INTRODUCTION TO VOLUME 8: REDUCTION

Adding two atoms of hydrogen to an organic molecule is a minimal modification, but one with profound significance in organic synthesis. Adding hydrogen to a planar functional group – an alkene or a ketone, or even an aromatic compound – provides a way of introducing three dimensional stereochemistry and is at the core of some of the most important asymmetric methods currently in use. Adding hydrogen across a C–O or C–N σ bond provides opportunities for bond cleavage that underlie the importance of benzyl protecting groups. Other reductive methods remove functional groups completely, allowing the versatile chemistry of oxygen and nitrogen-based functional groups to be utilized for the synthesis of unfunctionalised targets.

The synthetic organic chemistry of reduction that is covered in this volume is arranged primarily by functional group transformation, with subdivisions according to reagent type for the most important transformations. Thus, reductions of carbon–heteroatom double bonds (carbonyl groups and imines) take up about half of the volume, and are subdivided into chapters according to whether the reagent is, for example, a metal hydride, hydrogen, a dissolving metal, or an enzyme. A significant portion of the volume is devoted to C$=$C and C$\equiv$C bond reduction, with simple alkenes and alkynes being separated from aromatic C$=$C or enone C$=$C bonds, and further subdivisions being made for homogeneous and heterogeneous catalytic hydrogenation and other noncatalytic methods.

Although some of the topics covered in this volume provide updated coverage of the equivalent chapters from the 1991 edition of Comprehensive Organic Synthesis, other chapters and subdivisions have been introduced to reflect the great advances that have been made in those areas of chemistry in the past 20 years. These include chapters of hydrogenation and transfer hydrogenation of C$=$O bonds – an almost nonexistent area in 1991 – along with the huge advances made in biocatalysis.

Many of the chapters in the first section of the volume, which address the reduction of C$=$O and C$=$N bonds, are primarily concerned with stereochemical control, and these chapters survey the great progress made recently in the asymmetric synthesis of alcohols and amines and their derivatives by enantioselective reduction of ketones and imines. Methods covered include metal-catalysed transformations, developing organocatalytic methods, and also biocatalytic methods.

Reduction reactions capitalize on the careful investment in reactive functionality that drives a successful synthesis forward, and reductions provide many of the key methods for revealing important structural features in target molecules. This volume, with chapters written by leading practitioners of synthetic chemistry, presents the state of the art in this field.

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8.01 Reduction of C=O to CHOH by Metal Hydrides

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This chapter is a revision of the previous edition chapter by Nicholas Greeves, Vol. 8, pp 1–24, © 1991, Elsevier Ltd.

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Glossary

Chemoselective reduction The selective reduction of one functional group in the presence of other reducible groups, example reduction of aldehydes in the presence of ketones.
Hydrosilylation The addition of Si–H bonds across unsaturated bonds such as C=C and C=O.
LS-Selectride™ Commercial name used by Sigma–Aldrich for lithium trisiamylborohydride [$LiBH(CHMeCHMe_2)_3$]; a highly sterically bulky and very stereoselective reducing agent for ketones.
Oxazaborolidine Five-membered heterocyclic ring with O, B, and N hetero atoms, systematically is called 1,3,2-oxazaborolidine, which is made by reaction of borane with 1,2-amino alcohols. Enantiomeric derivatives are used as catalyst for the enantioselective reduction of ketones and some cycloaddition reactions. Most famous derivative is known as Corey–Bakshi–Shibata (CBS)-catalyst.
Stereoselective reduction The selective formation of one stereoisomer favorably over possible other(s) as a result of faster formation because of, for example, steric and chelative effects.

8.01.1 Introduction

The reduction of carbonyl functional groups to alcohols [(C=O) to CH–OH] is one of the most used reactions in the synthesis of organic molecules. This conversion (as described specifically here, C=O to CH–OH) is mostly used in reducing aldehydes and ketones to primary and secondary alcohols, respectively. Therefore, the scope of this chapter is limited to the use of metal hydrides in the reduction of aldehydes and ketones. Although there are fewer examples and it is carried out less frequently, the reduction of lactones to lactols (a reaction that converts a carboxylic acid derivative into the aldehyde oxidation state) is included within this scope.

Today, when we design a synthesis that includes such a reduction step, we have the luxury of choosing from a large selection of reducing agents and multiple reaction conditions associated with each reagent to accomplish this task conveniently, cleanly, and efficiently. A great portion of this selection of reducing agents is metal hydrides such as sodium borohydride ($NaBH_4$), lithium aluminum hydride (LAH), borane, and many of their derivatives and modified forms; a library of highly diversified reagents that come with varying degrees of capabilities and selectivities. This wide selection of metal hydride reducing agents was not always there and the reduction processes were not always done with such relative ease and exceptional control and expediency. To gain some appreciation of the enormous developments in the field of metal hydrides and their vast applications and versatility in organic synthesis, one has only to look back to the relatively short time before the discovery of these reagents. Before the discovery of metal hydrides the tools of reduction were very limited; the most practical methods for reducing aldehydes and ketones included less selective reduction methods such as catalytic hydrogenation as well as the reaction of metals like Zn, Fe, or Na/Hg with acids such as AcOH or HCl. Other conditions such as Na/EtOH or Zn/NaOH in EtOH were also used. Most of these methods were neither mild nor selective and as a result, their applications in reduction were limited in scope to simple substrates. Later the milder conditions of $Al(OR)_3$ where R is a secondary alkyl group (the Meerwein–Ponndorf–Verley (MPV) reduction) was developed.[1] All of these procedures became outdated and for the most part replaced after the discovery of borohydrides and aluminohydrides as reducing agents. It all started in 1939, when a pioneering study by Brown, Schlesinger, and Burg described the fast reduction aldehydes and ketones with diborane even at low temperatures.[2] This ground-breaking discovery marked the beginning of the era of the hydride reductions in organic chemistry. The discoveries of LAH ($LiAlH_4$)[3] and sodium borohydride ($NaBH_4$)[4] were announced soon after. These monumental discoveries have introduced a new method that revolutionized the tools of reduction in organic chemistry and participated in advancing the science of organic synthesis to great extent. The number of publications that describe applications of this rather 'simple' reaction in organic synthesis is very large. The author's 'selective and restricted' literature search has resulted in more than 2300 references on reduction of aldehydes and ketones alone from 1990 to present. That of course does not include reduction of other functional group such as imines, carboxylic acids, esters, lactones, amides, nitriles, epoxides, azides, and many more that can be reduced with these reagents.

It is safe to make a general statement that ALL metal hydrides can reduce ALL aldehydes and MOST ketones. In any case, the selection of one metal hydride reagent over the others may be determined by one of the following factors:

1. Chemoselectivity: The ability to target a specific group in the presence of other reducible groups.
2. Stereoselectivity: The ability to form preferentially one stereoisomer out of several possible.
3. Convenience: Ease of use, work up, and isolation of product.
4. Efficiency: To affect the maximum conversion and produce the highest yield.
5. Safety: In handling the reagent, carrying out of reaction, quenching and work up.

In this chapter, many of the metal hydride reagents and their use in the reduction of the C=O group of aldehydes, ketones (and lactones) into the corresponding CH–OH groups will be highlighted with emphasis on the scope using limited and selected literature examples. The selected examples illustrate the advancement in these reduction procedures and the selectivity of metal

hydride reagents from 1990 to present. However, this chapter is not intended to be a complete survey of all published metal hydride reductions of aldehydes and ketones.

8.01.2 Selectivity

The subjects of chemoselectivity and stereoselctivity of metal hydride reductions were thoroughly discussed in the first edition of this series, which includes a comprehensive discussion of the chemselectivity of reduction of enones, reduction of aldehydes versus ketones, reduction of ketones versus other carbonyl groups, reduction of quinones to hydroquinones, and reduction of α-haloketones.[5]

Improving the chemoselectivity of a certain chemical transformation has always been a main driving force behind the design and the discovery of better reagents that target specific functional group without affecting other groups with similar properties. As the demand on chemical transformation methodologies to selectively target one functional group of many in a complex molecule to undergo a specific transformation has grown, the design of chemical reagents and conditions that allow such demand to be realized has advanced and progressed. Tracking the development of hydride reagents from the beginning clearly shows the innovation that has characterized the field of metal hydride reductions. Research on borane led to the discovery of the metal hydride reagents, first among them being $NaBH_4$[4] and $LiAlH_4$.[3] These reagents considerably advanced the reduction method in terms of convenience and ease of carrying out a reduction procedure in organic synthesis. They also enhanced the scope and chemoselectivity of reductions, allowing application to structurally complex substrates and enabling a specific functional group to be reduced in the presence of other reducible functional groups. Continued research led to exceptional advancements in controlling the diastereoselectivity and enantioselectivity of reduction procedures.[6] The two reagents, $NaBH_4$ and LAH, may be thought of as the parent metal hydrides of all (or most) other hydrides. They represent two opposite extremes of reducing abilities; although $LiAlH_4$ is a very powerful nonselective reducing agent capable of reducing most reducible functional groups, $NaBH_4$ is mild and selective reducing agent that can reduce only aldehydes, ketones, and acid chlorides.[7] A systematic process of modification of these two reagents was initiated by the group of H. C. Brown. Substitutions of one or more of the hydrides and/or the use of different metal cations aimed to decrease the strength of LAH and increase that of $NaBH_4$, improving the selectivity and expanding the scope of the reductions.[6a] The result was the introduction of a host of reducing agents with varying strength, selectivity, solubility and other properties. Examples of modified reagents include $LiBHEt_3$ (Super-Hydride™), KBH*sec*-Bu_3BH (K-Selectride™), LiBH*sec*-Bu_3 (L-Selectride™), and $Li(Sia)_3BH$ (LS-Selectride™). Other research groups added to the library of modified reducing agents by introducing other modifications such as $NaCNBH_3$, acyloxyborohydrides, aminoborohydrides, and many more. In addition to $NaBH_4$ derivatives, borane, alane, and their derivatives (among them di-*iso*-butyl aluminum hydride or DIBAL, DIBAL-H) have added considerably to the utility and scope of selective hydride reagents.

The steric bulk of some of these reagents enhances the diastereoselectivity of the ketone reduction considerably.[6a] Structural modifications have been extended to include the design of enantioselective reagents for the reduction of pro-chiral ketones to enantiomerically enriched alcohols. Enantioselective reducing reagents such as 5-chlorodiisopinocampheylborane (also known as Ipc_2BCl or DIP-Cl) and oxazaborolidines and their catalytic use in borane reductions of prochiral ketones are two of many examples that added valuable tools for enantioselective reduction of ketones. Other modifications include additives, polymer support, solvent systems, etc., all adding to the versatility of the metal hydride reducing agents.

This chapter will explore the application of many of the common metal hydride reagents, their modifications in the reduction of aldehydes and ketones, emphasizing their scope and specific use, particularly their chemoselectivity and stereoselectivity. In addition to the reduction with traditional metal hydrides, hydrosilylation of aldehydes and ketones as well as catalytic enantioselective hydrosilylation has emerged as a very efficient and highly selective reduction method. Some of the recent developments in hydrosilylation will also be highlighted.

8.01.3 Reductions with Borohydrides

Borohydrides are the most commonly employed reagents for the reduction of aldehydes and ketones. The first discovered and most used member of this group is sodium borohydride ($NaBH_4$),[4] a very mild and selective reducing agent capable of only reducing aldehydes, ketones, and acid chlorides.[7] Because all four hydride atoms are used in the reduction process and because of its low molecular weight (37.83) and high hydride content, it has a very low cost per hydride equivalent, making it one of the most economical to use on large-scale reactions. It is convenient to handle and safer to use than many other hydride reagents; it can be weighed, transferred, and used in chemical reactions with ease. $NaBH_4$ dissolves in water but decomposes quickly under neutral or acidic conditions; caution should be exercised when mixing $NaBH_4$ with water under neutral or acidic conditions to avoid formation and accumulation of hydrogen gas particularly on large-scale reactions. Alkaline aqueous solutions of $NaBH_4$ are stable. $NaBH_4$ dissolves in MeOH (16.4 g per 100 g at 20 °C) but it reacts with MeOH to form $NaB(OMe)_3H$ which is a stronger reducing agent than $NaBH_4$.[8] It is less soluble in EtOH (4.0 g per 100 g at 20 °C) but reacts with it very slowly. The most commonly used solvents in $NaBH_4$ reactions are alcoholic solvents such as MeOH, EtOH, and *i*-PrOH in the presence or absence of water. It is

slightly soluble in lower ether solvents such as Et_2O and tetrahydrofuran (THF) but it dissolves more in diglyme (5.5 g per 100 g at 20 °C).[9] $NaBH_4$ reduces aldehydes and ketones rapidly and effectively to the corresponding alcohols.

$NaBH_4$ has been modified by replacing sodium with other cations such as lithium, potassium, zinc, and tetraalkylammonium cations.

1. Lithium borohydride ($LiBH_4$)[10]: This is more soluble than $NaBH_4$ in ether solvents such as Et_2O (4 g per 100 g) and THF (21 g per 100 g). It is also a stronger reducing agent than $NaBH_4$; in addition to reducing aldehydes, ketones, and acid chlorides; $LiBH_4$ also reduces esters, lactones, and epoxides, but it does not reduce acids, nitriles, or nitro compounds. $LiBH_4$ is not as widely used as $NaBH_4$ in reduction of aldehydes and ketones; but it is used frequently in reduction of other functional groups such as esters.
2. Potassium borohydride (KBH_4): It is a very similar in properties and selectivity to $NaBH_4$ and it usually sees similar applications to $NaBH_4$.
3. Zinc borohydride [$Zn(BH_4)_2$][11]: It is a very mild reducing agent; reduces aldehydes, ketones, and some imines. It is usually prepared *in situ* from reaction of $ZnCl_2$ with $NaBH_4$ in ether. It is most useful for selective reduction of α,β-unsaturated aldehydes and ketones. The chelation ability of the Zn atom enhances its diastereoselectivity in reduction of hydroxy or alkoxy ketones.
4. Tetraalkylammonium borohydrides are readily soluble in aprotic organic solvents and show lower reactivity as reducing agents than $NaBH_4$.[12] They are considerably more stable and easier to handle compared to other metal borohydrides, for example, tetrabutylammonium borohydride can be recrystallized from ethyl acetate.[13]

Another structural modification is to substitute one to three of the hydrogen atoms with different substituents. Based on the nature of the substituents, the strength of the reducing agent is increased or decreased. Substitution with electron-withdrawing groups such as cyano and acyloxy decreases the reducing ability of the reagent. For example, sodium cyanoborohydride ($NaBH_3CN$) is a much milder reducing agent than $NaBH_4$; it is stable in water and can reduce aldehydes and ketones only in acidic media. Sodium triacetoxyborohydride is a weaker reducing agent than $NaBH_4$ that was first introduced to selectively reduce aldehydes but not ketones. Although these two reagents have their applications in reduction of carbonyl groups, their properties made them ideal for reductive amination reactions, which will be discussed in Chapter 8.02. Tetraalkylammonium triacetoxyborohydrides have seen a large number of applications in the stereoselective reductions of β-hydroxy ketones, which will be discussed in Section 8.01.9 of this chapter. Substitution of the hydrides with electron donors increases the reducing power of the borohydride. Trialkoxy and trialkyl borohydrides are more powerful reducing agents than $NaBH_4$ or $LiBH_4$. The use of substituted borohydrides will be highlighted in Section 8.01.3.2.

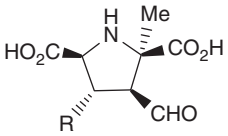
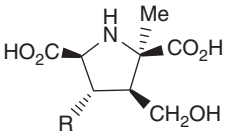
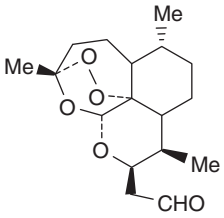
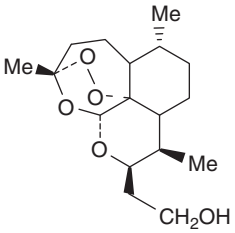
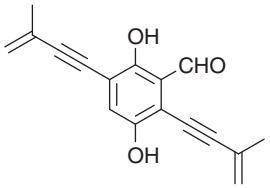
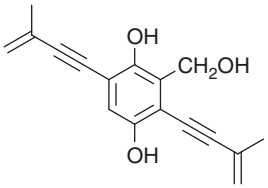
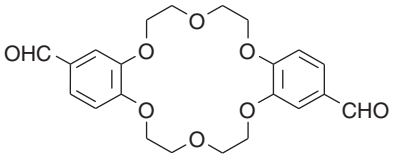
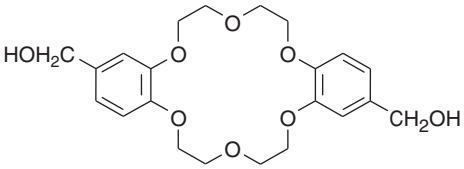
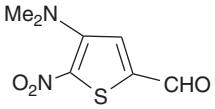
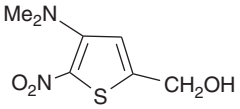
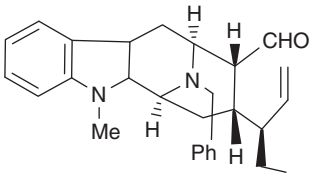
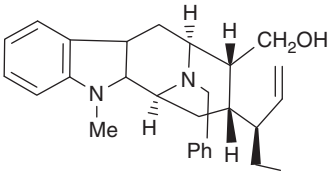
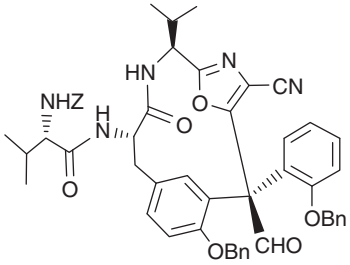
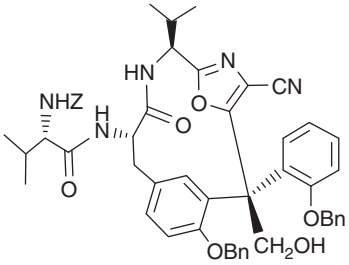
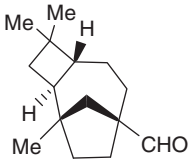
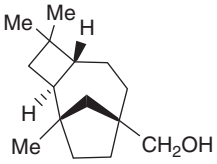
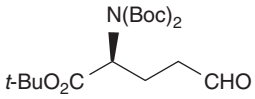
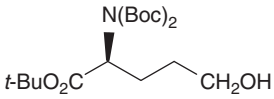
8.01.3.1 Reductions with Unsubstituted Borohydrides (MBH_4): [M = Na^+, Li^+, K^+, & Zn^{2+}]

The use of unsubstituted borohydrides [$NaBH_4$, KBH_4, $LiBH_4$, R_4NBH_4, and $Zn(BH_4)_2$] in the reduction of aldehydes and ketones is very common, but, $NaBH_4$ is by far the most used and most dominant in literature, judging by the number of reported examples and references describing its use compared to all others. The utility of these borohydrides in the reductions of aldehydes and ketones will be illustrated to demonstrate their scope and limitations and the wide applications in synthetic organic chemistry.

8.01.3.1.1 Reduction of aldehydes with unsubstituted borohydrides

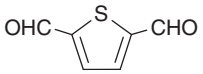
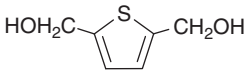
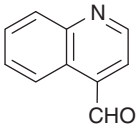
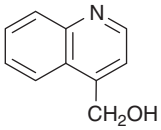
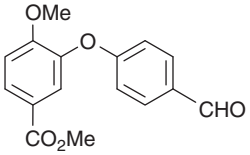
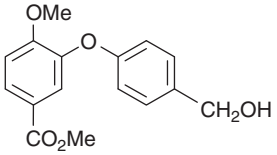
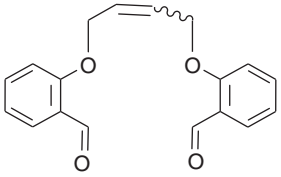
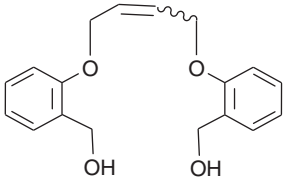
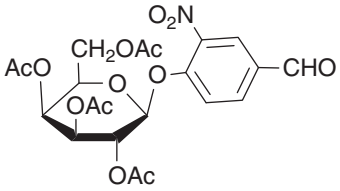
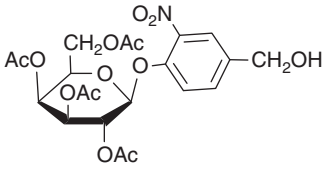
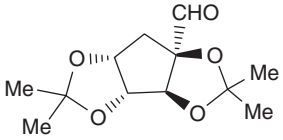
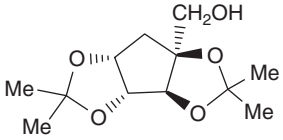
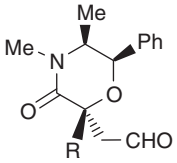
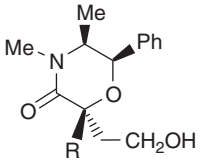
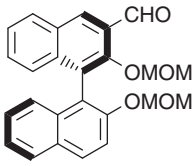
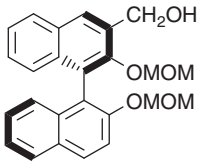
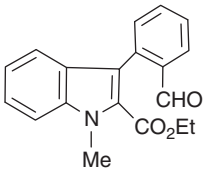
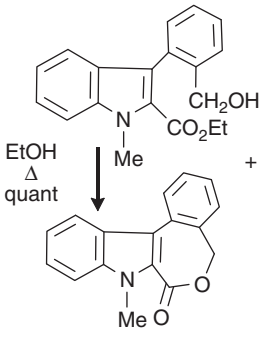
Aldehydes are less sterically hindered and are generally more reactive and can be reduced much faster and easier than ketones with nearly all of the metal hydride reducing agents. Brown et al. showed that $NaBH_4$ reduces benzaldehyde approximately 400 times faster than acetophenone.[14] As a result of their high reactivity, milder reagents such as $NaBH_4$, KBH_4, or $Zn(BH_4)_2$ are usually sufficient to carry out the aldehyde reduction but other stronger reagents may also be used. Except for the reduction of deuterated aldehydes (R-CDO) with borohydrides and the reduction of aldehydes (R-CHO) with borodeuterides, there is no stereochemical outcome or implication to the reduction of aldehydes to primary alcohols with unsubstituted borohydrides. Most aldehyde reductions are carried out at room temperature but lower temperatures may be needed to suppress side reactions or improve the chemoselectivity of the reaction. The reaction solvent is usually determined by the nature of the reducing agent, for example, most reactions with $NaBH_4$ are carried out in lower alcohols (MeOH, EtOH, *i*-PrOH) or a combination of an alcohol and water. Mixed solvents such as MeOH/THF are also used frequently with $NaBH_4$. Reactions with $LiBH_4$ and $Zn(BH_4)_2$ are carried out mostly in ether solvents such as Et_2O and THF. Other factors to consider in the selection of reducing agents are usually related to safety, ease of operation, best yield as well as ease of work up, and isolation of products. The combination of commercial availability as well as physical properties of $NaBH_4$ makes this reagent ideal for the majority of aldehyde reductions, because it meets most requirements of convenience and chemoselectivity. Table 1 illustrates the utility of unsubstituted borohydrides as mild and effective reducing agents for aldehyde reductions. Milder selective reducing agents are beneficial in targeting the intended functional groups in complex molecules. The representative examples in Table 1 show clearly that the reduction of aldehydes can be carried out conveniently and selectively in the presence of other reducible functional groups such as carboxylic acids, carboxylic esters, lactones, carboxamides, epoxides, cyano, and nitro functional groups. Most reactions afford the desired primary alcohols in good to excellent yields.

Table 1 Reduction of aldehydes with unsubstituted borohydrides

Entries	*Aldehyde*	*Alcohol*	*Conditions*	*Yield (%)*	*References*
1	 R = Me or substituted aryl		$NaBH_4$, MeOH	56–83	15
2			$NaBH_4$, MeOH, r.t., 1.5 h	95	16
3			$NaBH_4$, MeOH, –70 °C	86	17
4			$NaBH_4$, MeOH, r.t., 1 h	72	18
5			$NaBH_4$, THF/ H_2O, 0 °C	82	19
6			$NaBH_4$, MeOH, 1 h, r.t.	96	20
7	 *Z* = benzyloxycarbonyl		$NaBH_4$, MeOH/ THF, –10 °C	82	21
8			$NaBH_4$ MeOH, r.t., 24 h,	89	22
9			$NaBH_4$, MeOH, 45 min, 0 °C	95	23

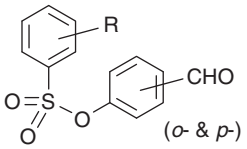
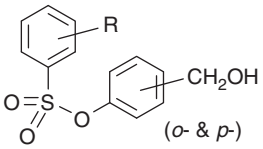
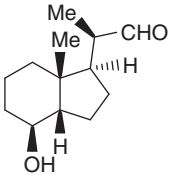
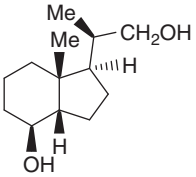
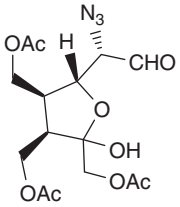
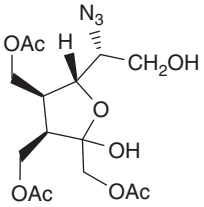
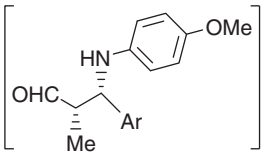
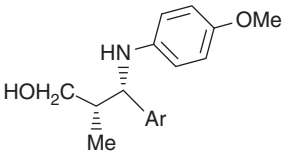
(*Continued*)

Table 1 Continued

Entries	*Aldehyde*	*Alcohol*	*Conditions*	*Yield (%)*	*References*
10			$NaBH_4$, EtOH,	98	24
11			$NaBH_4$, MeOH, 2 h	94	25
12			$NaBH_4$, MeOH, r.t.,	100	26
13			$NaBH_4$, MeOH, 0–5 °C	Yield: *Z*: 66 *E*: 68	27
14			$NaBH_4$, $CHCl_3$, *i*-PrOH, 2 h	73	28
15			$NaBH_4$, MeOH	85	29
16	 R = Me, Et, Pr, *i*-Pr		$NaBH_4$, EtOH	83–95	30
17			$NaBH_4$, MeOH/ THF, 0 °C	98	31
18			$NaBH_4$, EtOH, r.t.	Hydroxy ester: 80 Lactone: 20	32

(*Continued*)

Table 1 Continued

Entries	Aldehyde	Alcohol	Conditions	Yield (%)	References
19	 (*o*- & *p*-)	 (*o*- & *p*-)	$NaBH_4$, MeOH, 0–5 °C, 30 min–5 h	42–100	33
20			$NaBH_4$ MeOH, r.t., 30 min, $NaBH_4$	89	34
21			CH_2Cl_2, EtOH, −78 °C, 10 min	94	35
22	 Generated, *in situ*		$NaBH_4$, DMF, 0 °C, 10 min	57–89	36

8.01.3.1.2 Reduction of ketones with unsubstituted borohydrides

Ketones are generally reduced quickly and cleanly with $NaBH_4$ and most other borohydride reagents. Steric and electronic factors may affect the reduction rate. For example, sterically hindered ketones are reduced slower than nonsterically hindered ones and aromatic and conjugated ketones are reduced slower than aliphatic, nonconjugated, and saturated ketones. Unlike the reduction of aldehydes, the reduction of ketones may also display stereoselectivity or enantioselectivity. Other than symmetrical ketones, the reduction results in the formation of a new stereogenic center and the preference for one diastereomer will be determined by the steric and electronic factors associated with the substrate. The diastereoselectivity may also be affected by the ability of the reagent or an additive to chelate the carbonyl group during the reduction, which is a common feature of reductions with $Zn(BH_4)_4$ or Luche's reagent. Cyclic ketones are commonly reduced with greater diastereoselectivity than acylic ones. The use of chiral auxiliaries, chiral additives, and enantiomerically modified hydride reagents may induce enantioselectivity in the reduction, and these modifications are covered in Section 8.01.10 of this chapter.

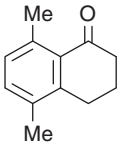
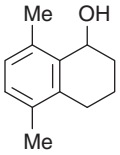
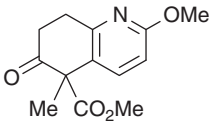
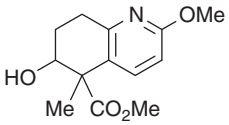
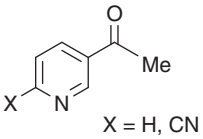
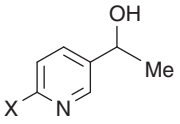
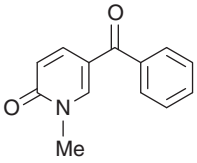
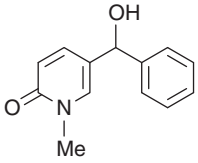
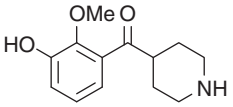
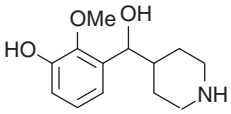
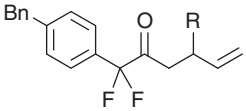
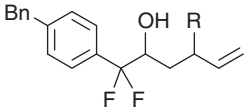
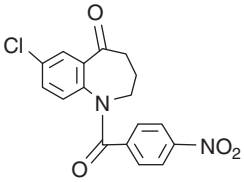
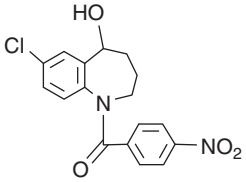
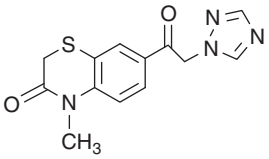
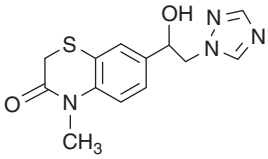
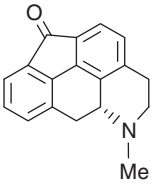
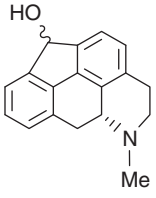
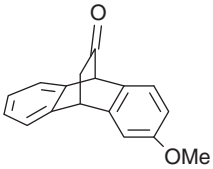
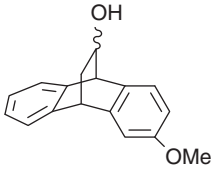
The representative examples in Table 2 illustrate the chemoselectivity of the borohydride reagents, selectively reducing the ketone functional group in the presence of other reducible groups. Some of the examples represent simple reductions where the stereochemistry is not a concern or has no impact on the synthesis and was not reported (Table 2, entries 1–13).

Saturated ketones are usually reduced faster than α,β-unsaturated ketones; the example in Table 2, entry 15 highlights a remarkable case of selective reduction from the total synthesis of two *Lycopodium* alkaloids reported by Paquette and coworkers.[51] A saturated ketone (cyclopentanone) is reduced selectively in the presence of an α,β-unsaturated ketone (cyclohexenone) with $NaBH_4$ in 1:1 $EtOH/CH_2Cl_2$ at 0 °C. Using the conditions developed by Ward and Rhee[80] ($NaBH_4$ in 1:1 $MeOH/CH_2Cl_2$ or 1:1 $EtOH/CH_2Cl_2$ at −78 °C) for chemoselective reductions not only was the cyclopentanone reduced chemoselectively, but also with complete stereoselectivity. This chemoselective procedure can also differentiate aldehydes from ketones and will be further highlighted in Section 8.01.6. Ward[52] used the same procedure for a similar reduction in the synthesis of (±)-allocyathin-B3; the reduction of the cyclohexanone was carried out selectively in the presence of α,β-unsaturated cyclopentanone, one of the six-step conversion sequence (Table 2, entry 16).

The reduction of a diketo taxane derivative was reported by Zamir and coworkers[53] (Table 2, entry 17) shows another selective reduction of the cyclohexanone with $NaBH_4$ in the presence of a cyclooctanone to give 7-epi-13-acetylbaccatin III exclusively in 82% yield.

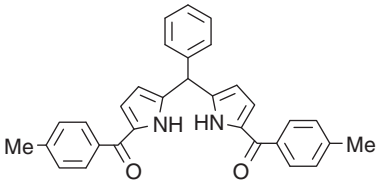
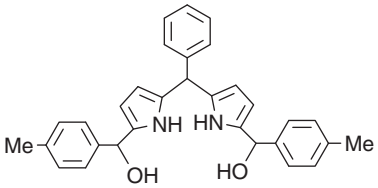
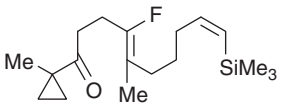
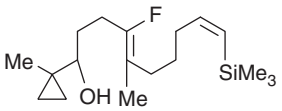
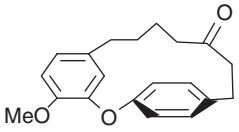
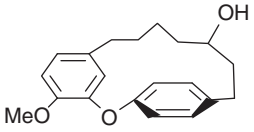
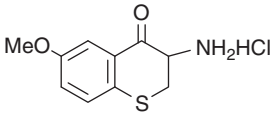
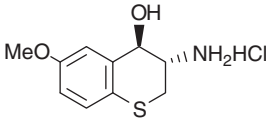
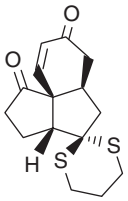
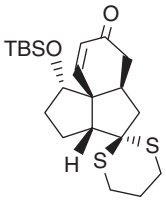
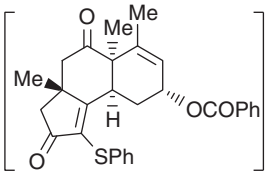
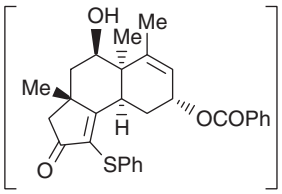
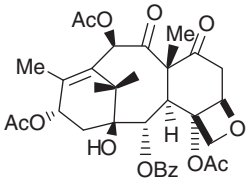
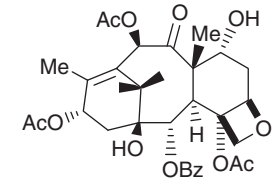
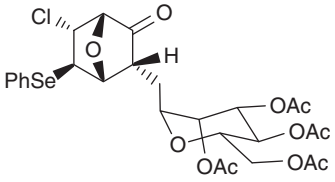
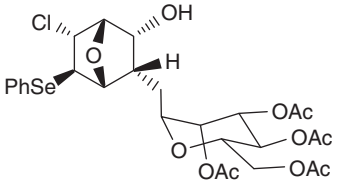
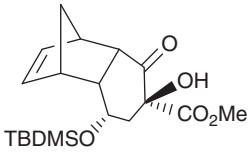
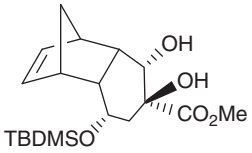
Sieburth and coworkers[71] observed a stereochemical temperature dependence in the reduction of a cyclooctanone derivative with $NaBH_4$ (Table 2, entry 35). The reduction was nonselective at 0 °C or above yielding two isomeric alcohols, but at −20 °C gives only a single product resulting from the approach of the hydride from the less-hindered face of the molecule.

Table 2 Reduction of ketones with unsubstituted borohydrides

Entries	*Ketone*	*Alcohol*	*Conditions*	*Yield (%)*	*References*
1			$NaBH_4$, EtOH, r.t., overnight	97	37
2			$NaBH_4$, EtOH, 0 °C	95.8	38
3			$NaBH_4$, MeOH	X=H, 91 X=CN, 64 r.t.	39
4			$NaBH_4$, EtOH, r.t., 1 h	No reported yield	40
5			$NaBH_4$, MeOH, 25–30 °C	71	41
6			$NaBH_4$, EtOH, r.t., 1 h	89	42
7			$NaBH_4$, MeOH	99	43
8			$NaBH_4$, MeOH, r.t., 1 h	79	44
9			$NaBH_4$ (1:1 H_2O, MeOH), r.t., 5 min	76 (45:55 mixture)	45
10			$NaBH_4$, MeOH, –43 °C	99 (*syn*:*anti* 46:54)	46

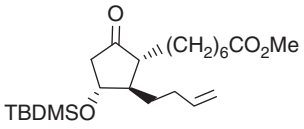
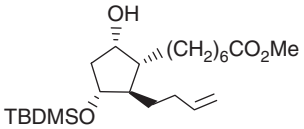
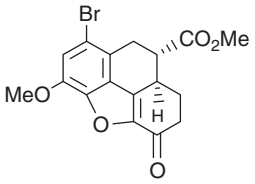
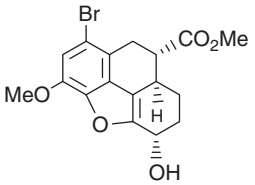
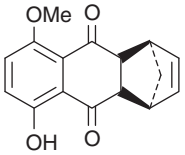
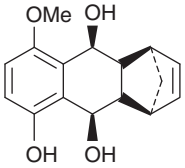
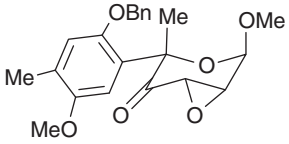
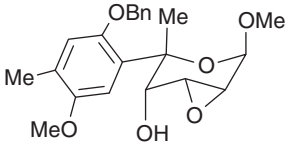
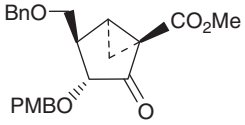
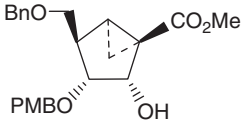
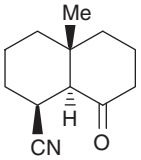
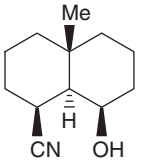
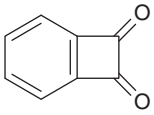
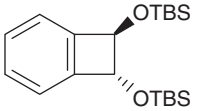
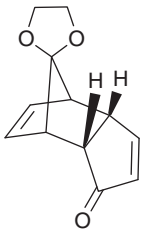
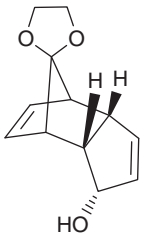
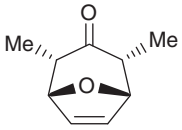
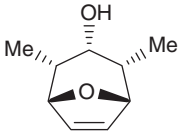
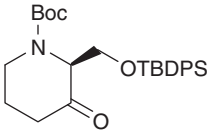
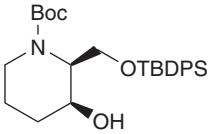
(*Continued*)

Table 2 Continued

Entries	Ketone	Alcohol	Conditions	Yield (%)	References
11			$NaBH_4$ (50 equivalents) THF, MeOH (2:1) 0 °C, 40 min	No reported yield (mixture of stereoisomers)	47
12			$NaBH_4$, MeOH, 0 °C, 15 min	92	48
13	 Acerogenin C	 Acerogenin A	$NaBH_4$, MeOH, 0 °C to r.t., 20 min	100	49
14			$NaBH_4$, CH_2Cl_2, *i*-PrOH (1/1), 35 °C; 10% aqueous HCl	73 (93:7 *trans:cis*)	50
15			1. $NaBH_4$, EtOH/CH_2C1_2 (1:1), 0 °C 2. TBSOTf, imidazole, CH_2C1_2, r.t.	91	51
16	 Not isolated	 Not isolated	$NaBH_4$, CH_2C1_2-MetOH (1:1), −78 °C, 14 h	56–61 For 6-step sequence	52
17		 7-*epi*-13-acetylbaccatin III	$NaBH_4$, MeOH, 4 °C, 2 h	82	53
18			$NaBH_4$ THF, MeOH, 0 °C, 5 min	79	54
19			$NaBH_4$, MeOH-THF, −15 °C	>92	55

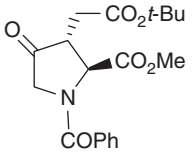
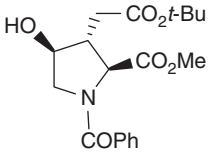
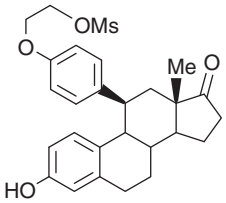
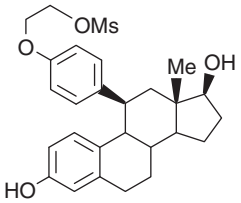
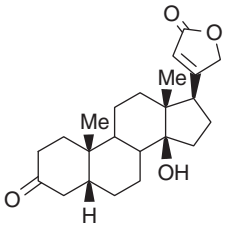
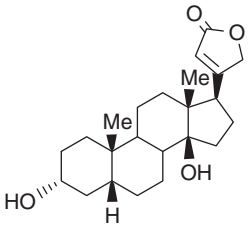
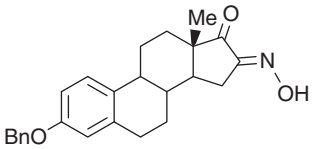
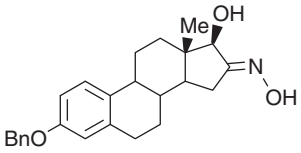
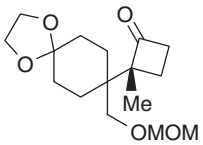
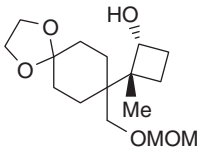
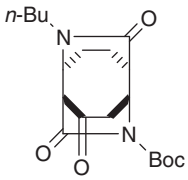
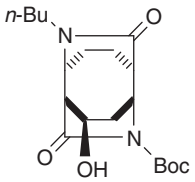
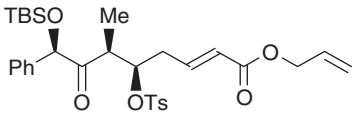
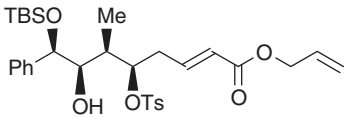
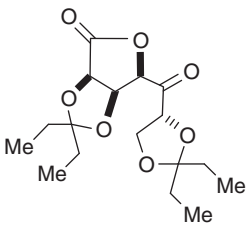
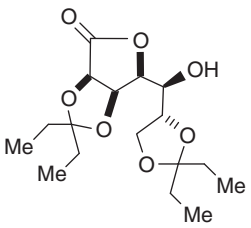
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Table 2 Continued

Entries	*Ketone*	*Alcohol*	*Conditions*	*Yield (%)*	*References*
20			$NaBH_4$, MeOH, 13 h at −40 °C; 12 h at −78 °C	61 (4:1 α:β)	56
21			$NaBH_4$, CH_2Cl_2-*i*-PrOH (3:1), r.t., 12 h	99	57
22			$NaBH_4$, THF, MeOH, −78 °C (2 h); 0 °C (1 h)	88 (<50% with LAH or DIBAL-H)	58
23			$NaBH_4$, *i*-PrOH, r.t., 24 h	100	59
24			$NaBH_4$, MeOH-CH_2Cl_2 (2:1), −20–0 °C; 30 min	91	60
25			$NaBH_4$, MeOH-THF (2:1), r.t.	100	61
26			$NaBH_4$, MeOH, 0 °C, 30 min, Then TBSOTf, Et_3N, −78 °C, 1.5 h, chromatography	58 *trans*:*cis* 6:1 in crude	62
27			$NaBH_4$ MeOH, 0–5 °C	80	63
28			$NaBH_4$, MeOH	98	64
29			$NaBH_4$, MeOH, 0 °C	88	65

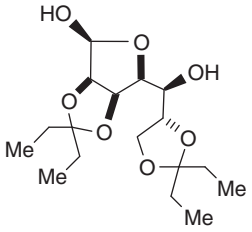
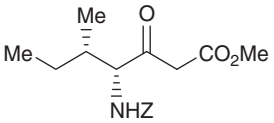
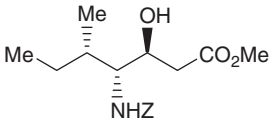
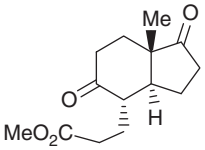
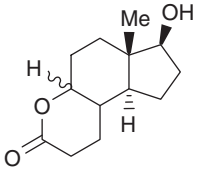
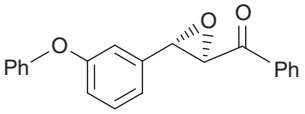
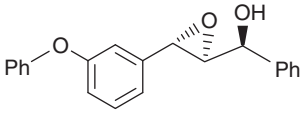
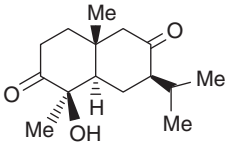
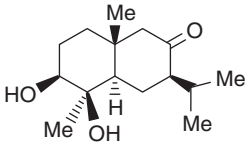
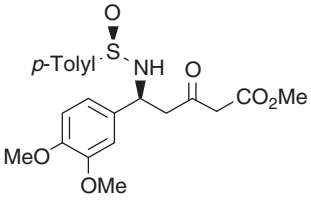
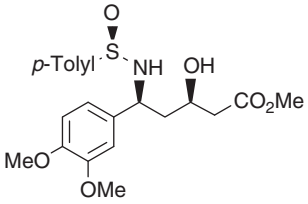
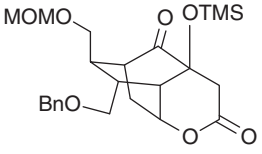
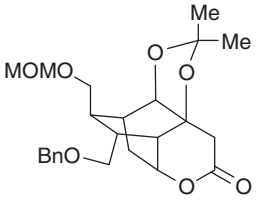
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Table 2 Continued

Entries	Ketone	Alcohol	Conditions	Yield (%)	References
30			1. $NaBH_4$, MeOH, 2. MsCl, Et_3N, CH_2Cl_2	91	66
31			$NaBH_4$, MeOH-THF (1:1), 0 °C, 1 h	88	67
32			$NaBH_4$, dioxane/ water, r.t.	92	68
33			$NaBH_4$, MeOH, CH_2Cl_2, 1% aqueous KOH, 20 min, r.t.; reflux, 40 min; AcOH	98	69
34			$NaBH_4$, MeOH, 3 h, r.t.	87	70
35			$NaBH_4$, MeOH, −20 °C, 5 min	>95% yield	71
36			$NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, 0 °C	96 20:1	72
37		 (**A**) Desired product	$Zn(BH_4)_2$ Et_2O, −50 °C, 60 h	65	73

(*Continued*)

Table 2 Continued

Entries	*Ketone*	*Alcohol*	*Conditions*	*Yield (%)*	*References*
			$NaBH_4$, $CeCl_3$, MeOH, −78 °C, 2 h	70	
		(**B**) Over reduction product			
38			KBH_4, MeOH, −30 to 0 °C	99 *dr*=11:1	74
39			KBH_4, MeOH, 0 °C, 30 min	85	75
40			$Zn(BH_4)_2$ (0.3 equivalent), Et_2O, 0 °C, 3 h	95	76
41			$Zn(BH_4)_2$, DME	70 (55:45 β:α)	77
42			$Zn(BH_4)_2$ (3.2 equivalents), −78 °C, 1 h	87 (50:6 *syn*:*anti*)	78
43			1. $Zn(BH_4)_2$ Et_2O, 0 °C 2. TBAF, THF, 0 °C 3. 2,2-DMP, PPTS, acetone, r.t.	73	79

Tius and coworkers[72] reported the reduction of a β-keto tosylate (Table 2, entry 36), a step in their synthesis of 1-aza-cryptophycin-1. The reduction with $NaBH(OAc)_3$ and $Me_4NBH(OAc)_3$ gave very low stereoselectivity; $LiBH_4$ gave the product in a better selectivity as a 6:1 mixture of diastereoisomers, but Luche reduction ($NaBH_4$, $CeCl_3$) took place with both high yield (96%) and high stereoselectivity (20:1).[72]

In the synthesis of the C(1)-C(15)-subunit of halichondrin B, Burke and coworkers[73] examined several reagents for the reduction of the intermediate ketone (Table 2, entry 37) to the desired alcohol (**A**) with (*S*)-configuration. Although the reduction with $Zn(BH_4)_2$ gave the desired product, the reaction proved inconvenient for large-scale applications. Other reducing agents such as $NaBH_4$, $LiBH_4$, and $LiBHsec\text{-}Bu_3$ gave unsatisfactory results. The best alternative to $Zn(BH_4)_2$ was to use $NaBH_4/CeCl_3{\cdot}7H_2O$, to form the overreduced product **B** exclusively then selectively oxidize it to the desired product **A**.

In the synthesis of Tamandarins A and B, Joullié and coworkers[74] found KBH_4 to be a better reagent for the diastereoselective reduction of the ketone in a γ-amino-β-ketoester (Table 2, entry 38) than other reagents. The reduction with KBH_4 at room

temperature gave 80% *de* in 8 min and was improved at −30–0 °C, to 91% *de* in 15 min. $NaBH_4$ gave only 85% *de* in 15 min at −78 °C.

Davis and Chao[78] reported the use of $Zn(BH_4)_2$ in the reduction of a *β*-(sulfinylamino)ketone (Table 2, entry 42), a key step in the synthesis of (−)-lasubine-II to produce the *syn*-product. Chelation control with $Zn(BH_4)_2$ at −78 °C gave a 50:6 *syn*:*anti* ratio of the *β*-amino alcohol in 87% yield.

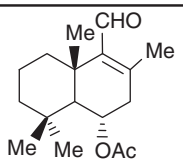
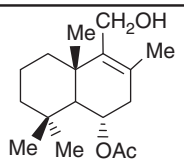
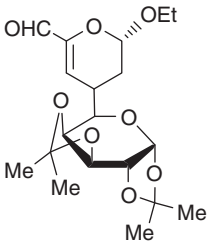
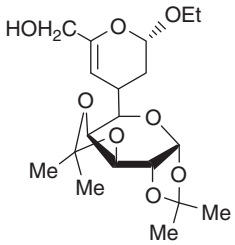
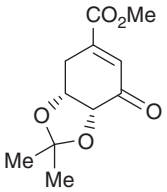
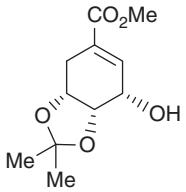
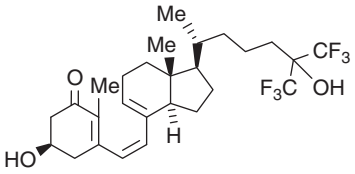
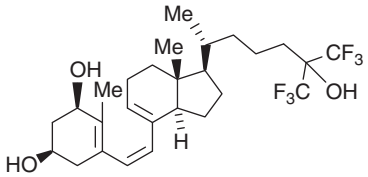
8.01.3.1.3 Reduction of α,β-unsaturated aldehydes and ketones

Sodium borohydride often reduces the carbonyl group of *α*,*β*-unsaturated aldehydes and ketones to give the corresponding allylic alcohols, particularly when the terminal carbon of the conjugated system is sterically hindered. Thus, in many reported cases, the reduction of *α*,*β*-unsaturated aldehydes and ketones proceeds in a 1,2-fashion without affecting the conjugated alkenes. However, in some reductions of *α*,*β*-unsaturated aldehydes and ketones with $NaBH_4$ the reduction of the conjugated C=C double bond may take place. In many examples of reduction of *α*,*β*-unsaturated aldehydes and ketones with $NaBH_4$, there is a tendency to form variable amounts of 1,4-reductions leading ultimately to saturated alcohols.[81]

Many alternative procedures may be used to suppress these 1,4-conjugate reductions. The most popular is the procedure developed by Luche.[82] Luche and coworkers studied the effects of addition of lanthanide salts on the reducing properties of $NaBH_4$. They found that the combination of some of these salts particularly $CeCl_3$, with $NaBH_4$ in alcoholic solvents, particularly methanol, is very effective in promoting selective 1,2-reductions of *α*,*β*-enals and enones[83] The best results were obtained from the combination of $NaBH_4$ and $CeCl_3$ in MeOH (see examples in Table 3, entries 7–13). The kinetics and effects of reagents ratios and solvent were thoroughly studied; the formation of alkoxyborohydrides and catalysis by $CeCl_3$ were involved in the reaction mechanism. The following observations were made:

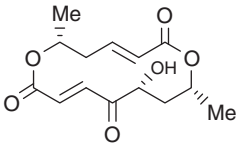
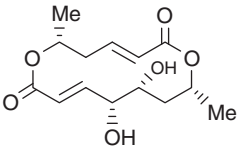
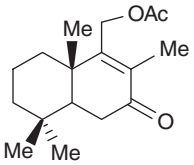
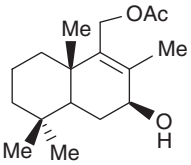
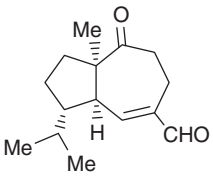
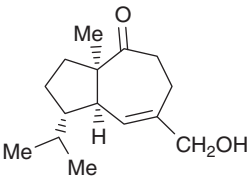
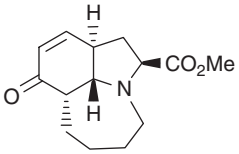
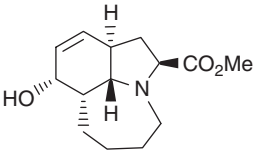
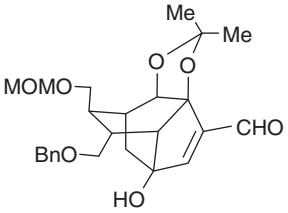
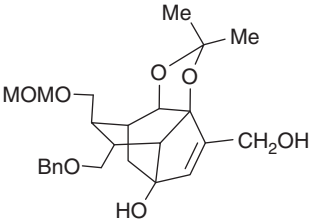
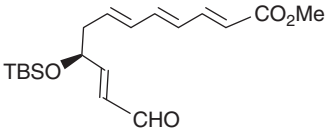
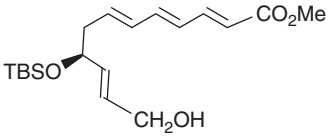
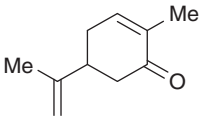
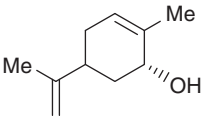
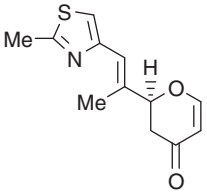
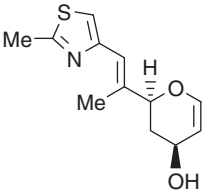
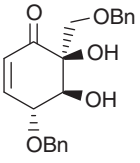
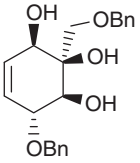
- One molar equivalent of $NaBH_4$ (i.e., 4-fold hydride excess) is required to reduce the *α*,*β*-enals or enones completely.
- Reductions with 1 equivalent of $NaBH_4$ and >0.5 equivalent of $CeCl_3$ in MeOH are faster than in other alcohols and provide highest selectivity.
- Addition of $NaBH_4$ to a solution of $CeCl_3$ in MeOH results in vigorous hydrogen evolution indicating a catalytic effect of Ce^{3+} in the reaction of MeOH with BH_4^-.

Table 3 Reduction of *α*,*β*-unsaturated aldehydes and ketones

Entries	Substrate	Product	Conditions	Yield (%)	References
1			$NaBH_4$, EtOH, −8 °C to r.t.	94	84
2			$NaBH_4$, MeOH, r.t., 15 min	89	85
3			$NaBH_4$, MeOH 0 °C to r.t. 30 min	98	86
4			$NaBH_4$, MeOH	66	87

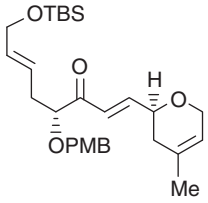
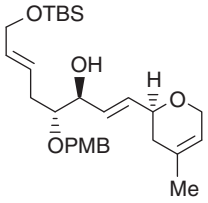
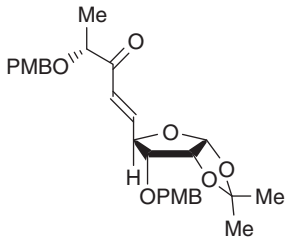
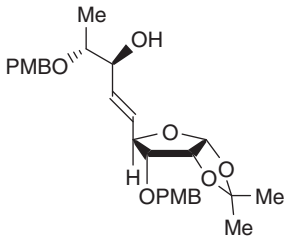
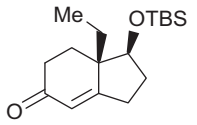
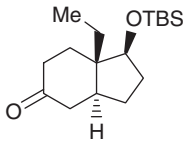
(*Continued*)

Table 3 Continued

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
5			$NaBH_4$, MeOH, −15 °C, 30 min	81	88
6			$NaBH_4$, EtOH, 0 °C to r.t. 30 min	96	89
7			$NaBH_4$, MeOH, $CeCl_3$, 0 °C	97	90
8			$NaBH_4$, $CeCl_3$ THF/ MeOH, 0 °C	71	91
9			$NaBH_4$, MeOH, $CeCl_3$, r.t.	89	79
10			$NaBH_4$, *i*-PrOH, $CeCl_3$, 0 °C	77	92
11			$NaBH_4$, $CeCl_3$ MeOH, 0 °C to r.t.	75	93
12			$NaBH_4$, $CeCl_3$ MeOH, 0 °C to r.t.	99	
13			$NaBH_4$, $CeCl_3{\cdot}7H_2O$ MeOH, −70 °C	100	55

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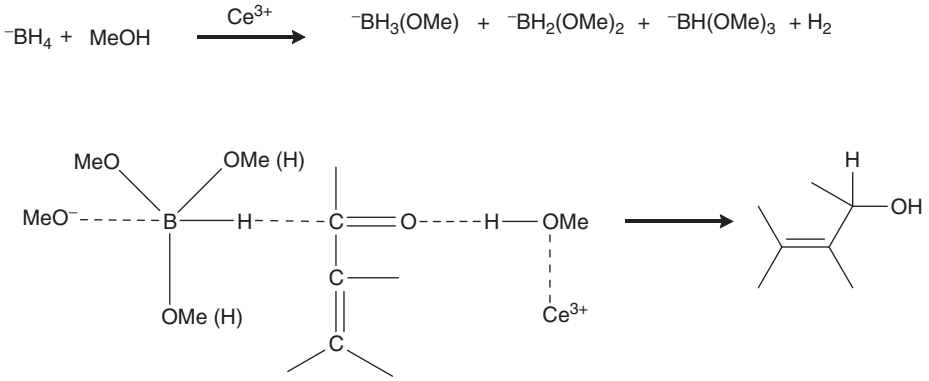
Table 3 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
14			$Zn(BH_4)_2$, Et_2O, 0 °C (10 min); r.t. (50 min)	77(>98:2 *dr*)	94
15			$Zn(BH_4)_2$ Et_2O, −40 °C, 6 h $NaBH_4$, EtOH	98 ≥98:2 95 47:53	95
16			DIBAL-H, *t*-BuCu, HMPA	91	96

- Based on the hard and soft acids and bases (HSAB) theory, alkoxyborohydrides such as $[BH_3(OMe)]^-$ are harder bases than BH_4^-; accordingly, $[BH_3(OMe)]^-$ is more likely to attack the hard C=O site of the conjugated enone system.

The authors proposed a mechanism (**Scheme 1**) to explain the regioselectivity and the above observations:

In the same study, Luche addressed another aspect of this reduction procedure; its effect on stereoselectivity. He referred to the study of Anh and coworkers[97] that suggested, based on HSAB theory, that the stereoselectivity of the reduction is related to the hardness of the hydride compound; the harder the reagent, the more favored the axial attack on cyclohexenones. With few exceptions, most enone reductions performed in the presence of Ce^{3+} yielded a greater preference for the equatorial alcohols in agreement with that prediction. The stereoselectivity is generally poor in open-chain enones, and in cyclopentenones. Most cyclic saturated ketones reduced with $NaBH_4/CeCl_3$ in MeOH are also attacked preferentially from the axial side.



Scheme 1 Mechanism reduction with Luche's reagent.

Another reagent that is used effectively for the selective 1,2-reduction of α,β-unsaturated aldehydes and ketones is $Zn(BH_4)_2$.[11,98] In one of the earlier demonstrations of the effectiveness of $Zn(BH_4)_2$ in this chemoselective reaction, Yoon and coworkers[99] showed that the reduction of 2-cyclohexenone with $Zn(BH_4)_2$ gave 96% 2-cyclohexenol and 4% of cyclohexanol. An added advantage of $Zn(BH_4)_2$ is the ability of Zn^{2+} to chelate with substituents such as –OH, –OR, and other hetero atoms, a property that may affect the stereochemical outcome of the reduction.

In addition to Luche's reagent and $Zn(BH_4)_2$, many other procedures demonstrate the regioselective reduction of α,β-unsaturated aldehydes and ketones to allylic alcohols; some of these procedures will be highlighted in Section 8.01.3.3.

The results in Table 3 show several reductions of α,β-unsaturated aldehydes and ketones. Some reactions were carried out chemoselectively with $NaBH_4$ alone giving the 1,2-reduction products (Table 3, entries 1–6). In all these cases, there were no reports of C=C reduction; producing only allylic alcohols in good to excellent yields. The following entries (Table 3, entries 7–15) show some recent applications of Luche's reagent and $Zn(BH_4)_2$ in the reduction of α,β-unsaturated aldehydes and ketones. In the synthesis of (+)-aphanamol I, Wender and Zhang[90] reported the use of Luche's reduction procedure to selectively reduce an α,β-unsaturated aldehyde in the presence of a saturated ketone in excellent yield (Table 3, entry 7). Wipf and coworkers[91] performed a selective 1,2-reduction with $NaBH_4/CeCl_3$ in the synthesis of (−)-tuberostemonine; not only was the chemoselective reduction accomplished in good yield (71%), but also with high diastereoselectivity (Table 3, entry 8). The reactions in Table 3, entries 9 and 10 show the chemoselective reductions of highly functionalized α,β-unsaturated aldehydes with Luche's reagent.[79,92] Luche's reagent was also utilized successfully in the highly chemoselective and diastereoselective reductions of the α,β-enones: *R*-(−)-carvone (Table 3, entry 11),[93] the intermediate in total synthesis of epothilones A & B[100] (Table 3, entry 12) and (−)-tonkinenin-A to (−)-uvarigranol-G3[55] (Table 3, entry 13). The reaction in Table 3, entry 14 shows a reduction of an intermediate ketone with $Zn(BH_4)_2$ in Crimmins and coworkers' synthesis of (−)-laulimalide.[94] The reduction was performed with excellent chemoselective 1,2-reduction of the α,β-unsaturated ketone and the chelation control of the Zn^{2+} gave the *anti*-diastereomer in >98:2 diastereomeric ratio. Another example of reduction of an enone using zinc borohydride (Table 3, entry 15) gave chelation control product as the major component in ≥98:2 ratio on 2 g scale. However, the selectivity was lower (9:1) on larger scale but was still better than $NaBH_4$ which gave an almost 50:50 mixture of the epimeric alcohols.[95]

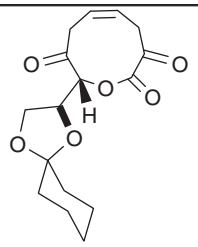
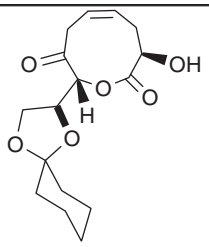
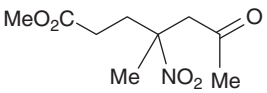
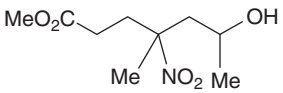
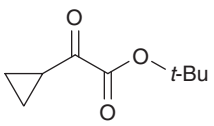
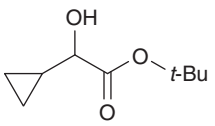
It is worth mentioning here that sometimes it is desirable to perform the opposite task, that is, to reduce the C=C double bond of the conjugated system. In the Corey and Huang's[96] synthesis of desogestrel, the C=C bond of an α,β-unsaturated ketone (Table 3, entry 16) was reduced with DIBAL-H in combination with an alkyl copper reagent such as MeCu or *t*-BuCu in HMPA as a solvent to effect selective 1,4-reduction in 91% yield. Other effective procedures for 1,4-reduction of α,β-unsaturated aldehydes and ketone via hydrosilylation[101] is highlighted in Section 8.01.11 (see examples in Table 30).

8.01.3.2 Reductions with Substituted Borohydrides

8.01.3.2.1 Cyanoborohydride

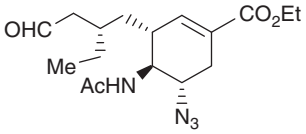
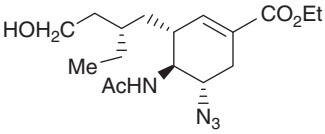
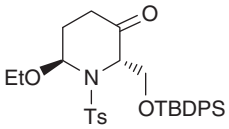
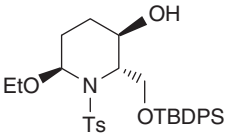
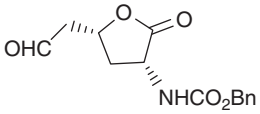
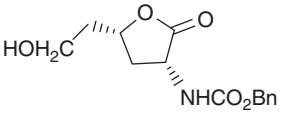
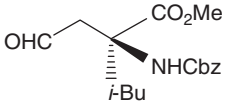
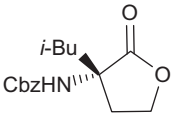
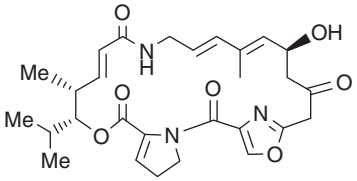
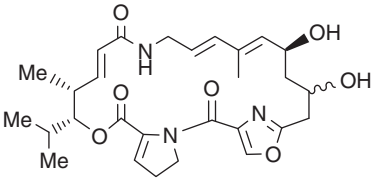
Sodium cyanoborohydride is a very mild reducing agent; it reduces aldehydes and ketones at low pH but it is nearly inactive at weakly acidic, neutral, and basic media toward aldehydes and ketones. $LiBH_3CN$ was first reported in 1951 by Wittig.[102] The reagent can be used effectively in the reduction of aldehydes and ketones at low pH, but the low pH requirement limits its use in acid sensitive substrates. However, what may appear to be a drawback gives it a great advantage and makes it ideal for another very important reduction–the reductive amination of aldehydes and ketones. Since early 1970s $NaBH_3CN$ has become one of the most widely used reagents in reductive amination of aldehydes and ketones;[103] this topic will be covered in Chapter 8.02 in this volume. However, to illustrate its use in the reduction of aldehydes and ketones, a few examples are highlighted in Table 4. The example in Table 4, entry 1 shows the reduction of a 9-membered-diketolactone. The object was to reduce both ketones selectively, but $LiBHsec\text{-}Bu_3$ at −130 °C gave a mixture of four possible diastereomers including only 60% of the desired isomer. A stepwise approach proved beneficial: the reduction of the α-ketolactone was achieved by using $NaBH_3CN$ with high stereoselectivity toward the desired *R*-isomer. The chemical yield of 43% includes a previous ring expansion step.[104]

Table 4 Reductions with sodium cyanoborohydride

Entries	Substrate	Product	Conditions	Yield (%)	References
1			$NaBH_3CN$, AcOH, 13 °C, 20 min	43 (*R*:*S*=95:5)	104
2			$NaBH_3CN$, MeOH, HCl	84 2:1 *dr*	105
3			$NaBH_3CN$, HCl/MeOH	75	106

(*Continued*)

Table 4 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
4			$NaBH_3CN$, EtOH, HCl	61	107
5			$NaBH_3CN$, AcOH, MeOH, 0 °C to r.t.	85	108
6			$NaBH_3CN$, MeOH, pH 4 1 h	89	109
7			$NaBH_3CN$, 2 N HCl, MeOH,	80	110
8			$NaBH_3CN$, MeOH/AcOH (1:1) r.t., 21 h	69 1:1 *syn/anti*	111

In the synthesis of 14,36-didehydro-pristinamycins-IIs (Table 4, entry 8), Ronan and coworkers[111] attempted the eduction of the intermediate ketone with $NaBH_4$ but that gave a complex mixture; the reduction with $NaBH_3CN$ in MeOH/AcOH (1/1–5/1 vol/vol) at room temperature proceeded selectively to reduce the carbonyl group and provide a separable 1:1 mixture of the diols in good yield.

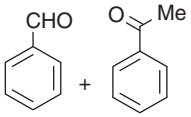
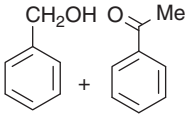
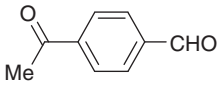
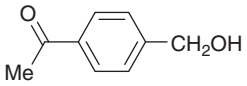
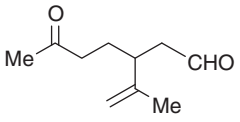
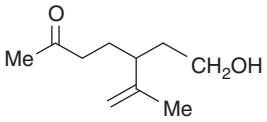
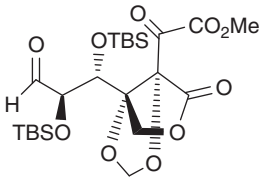
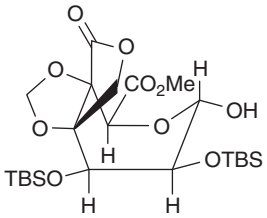
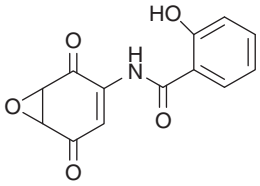
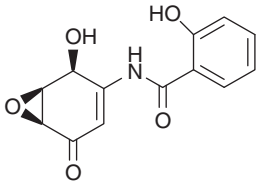
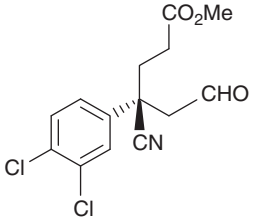
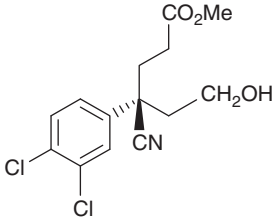
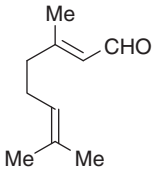
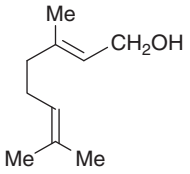
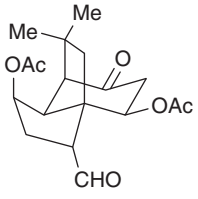
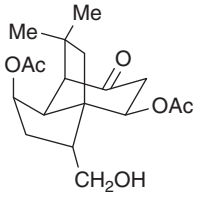
8.01.3.2.2 Triacetoxyborohydrides

Sodium triacetoxyborohydride $NaBH(OAc)_3$ is a mild reducing agent that exhibits remarkable selectivity. It reduces aldehydes and some cyclic ketones, but it does not reduce aromatic or sterically hindered ketones.[112] The steric and the electron-withdrawing effects of the three acetoxy groups stabilize the boron–hydrogen bond and are responsible for its mild reducing properties.[113] It is commercially available and also easily prepared by the reaction of $NaBH_4$ with excess acetic acid in benzene or toluene. Wartik and Pearson[114] were the first to report the synthesis of a sodium triacyloxyborohydride [triformatoborohydride ($NaBH(OOCH)_3$)] from the reaction of $NaBH_4$ and CO_2. Brown and Rao[115] postulated the existence of acyloxyborohydrides from $NaBH_4$ and carboxylic acids. Independently, Reetz[116] isolated a water-sensitive white solid from the reaction of $NaBH_4$ with AcOH in THF which was characterized as sodium monoacetoxyborohydride ($NaBH_3OAc$).

Triacetoxyborohydrides are used extensively in two very important reactions. The first is the selective reduction of *β*-hydroxyketones to form 1,3-*trans* (or *anti*) diols for which tetramethylammonium triacetoxyborohydride is usually the preferred reagent; this reaction will be thoroughly highlighted in Section 8.01.9. The second is the reductive amination of aldehydes and ketones;[117] this reaction will be highlighted in Chapter 8.02.

Several examples that show the use of triacetoxyborohydride in reduction of aldehydes and ketones are listed in Table 5. The pioneering work of Gribble and coworkers showed the utility of tetrabutylammonium triacetoxyborohydride in the selective reduction of aldehydes in the presence of ketones whether the keone is in another (entry 1) or the same molecule (entries 2 and 3). The chemoselective reduction of the oxoaldehyde reported by Vogel[118] with $NaBH(OAc)_3$ in THF at 20 °C, gave the hemiacetal product (Table 5, entry 4), a case of reverse selectivity in which the keto moiety activated by the *α*-carboxylic ester is reduced preferentially and the resulting alcohol forms a hemiacetal with the aldehyde. $NaBH(OAc)_3$, prepared from $NaBH_4$ and glacial AcOH in benzene, reduces *α*,*β*-unsaturated aldehydes regioselectively to allylic alcohols (Table 6, entry 7), but not *α*,*β*-unsaturated ketones under these conditions. Lee and Kim[119] used $NaBH(OAc)_3$ in THF for the selective reduction of the aldehyde group of the keto aldehyde (Table 5, entry 8) to produce the corresponding keto alcohol during the total synthesis of suberosenone.

Table 5 Reductions of aldehydes and ketones with triacetoxyborohydrides

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			Excess *n*-$Bu_4NBH(OAc)_3$ PhH, Δ	95 alcohol 96 ketone	112b,120
2			*n*-$Bu_4NBH(OAc)_3$ PhH, Δ	72	
3			*n*-$Bu_4NBH(OAc)_3$ PhH, Δ	77	
4			$NaBH(OAc)_3$ in THF (20 °C, 3 h)	98	118
5			$NaBH(OAc)_3$, r.t., 10 min;	86	121
6			$NaBH(OAc)_3$, AcOH, 20 °C, 2.5 h	72	122
7			$NaBH(OAc)_3$, benzene, AcOH, reflux, 3 h	92	123
8			$NaBH(OAc)_3$ (1.5 equivalents) THF	80	119

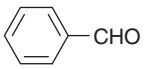
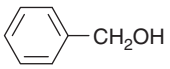
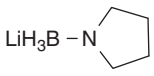
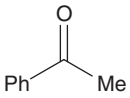
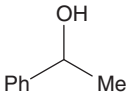
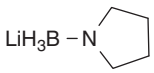
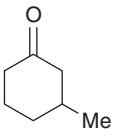
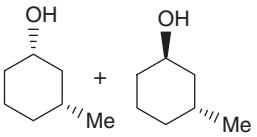
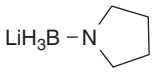
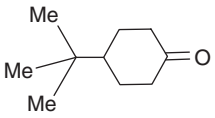
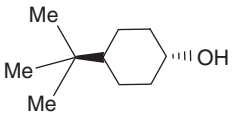
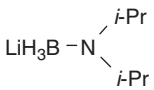
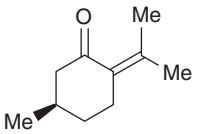
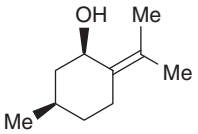
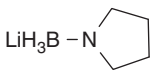
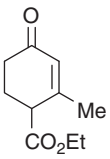
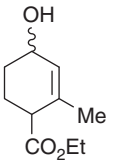
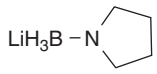
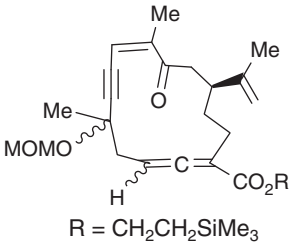
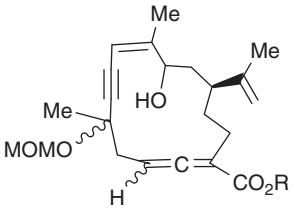
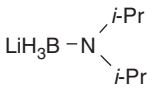
8.01.3.2.3 Lithium aminoborohydride

Lithium aminoborohydrides [LABs, ($LiBH_3NR_2$)] are powerful, selective, air-stable reducing agents. These reagent have similar reducing characteristics to LAH but they are safer alternative and more convenient to handle. The first synthesis of their close analogs sodium aminoborohydrides was reported in 1961.[126] Hutchins and coworkers[127] studied the properties of sodium (dimethylamino)borohydride and sodium (*tert*-buty1amino)borohydrid and concluded that they are effective reagents in the reduction of aldehydes, ketones, and esters to alcohols, and primary and tertiary, but not secondary, amides to amines in good to excellent yields. In spite of these promising results, no further work had appeared in the literature on the use of aminoborohydride

reducing agents until 1990. During their work on hydroboration of β,β-disubstituted enamines, Singaram and coworkers discovered and subsequently characterized lithium aminoborohydrides (LABs).[128] They are prepared in quantitative yields by the reaction of *n*-BuLi or MeLi with amine-borane complexes. LABs readily reduce aldehydes, ketones, carboxylic esters to the corresponding alcohols, whereas α,β-unsaturated aldehydes and ketones are reduced regioselectively to allylic alcohols. They also reduce tertiary amides, *N*-alkyl lactams, epoxides, azides, primary alkyl halides, methane sulfonates, and aryl nitriles. Most reductions are carried out in THF under either nitrogen or dry air at ambient temperature or at reflux and the products are easily isolable by simple acidic workup.

Table 6 contains several examples to highlight the use of LABs in the reduction of aldehydes and ketones. The reduction of aldehydes and ketones with LABs is fast with only 1 equivalent needed to complete conversion to the corresponding alcohols in 15–30 min at 0 °C. The Singaram group has explored the scope of reductions with LABs and reported on their applications in reduction of a wide variety of reducible functional groups.[129] Several of their results from the reduction of aldehydes and ketones are listed in Table 6 (entries 1–6).[124] The LABs were used also by other groups including the key step in the total synthesis of (−)-rubifolide by Marshall and Sehon[125] (Table 6, entry 7) in which the α,β-unsaturated enone was reduced with lithium diisopropylaminoborohydride to the allylic alcohol.

Table 6 Reduction of aldehydes and ketones with lithium aminoborohydrides (LABs)

Entries	Substrate	Product	Conditions	Yield (%)	References
1			 THF, 0 °C	98	124
2			 THF, 0 °C	98	
3			 THF, 0 °C, 30 min	95 *dr* 92:8	
4			 THF, 0 °C, 30 min	95	
5			 THF, 0 °C, 3 h	96	
6			 THF, 0 °C, 3 h	94	
7	 R = $CH_2CH_2SiMe_3$		 THF, –78 °C, 15 min	47	125

8.01.3.2.4 Trialkylborohydrides (Super-Hydride® and Selectrides®)

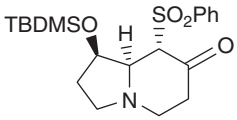
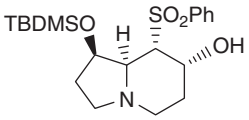
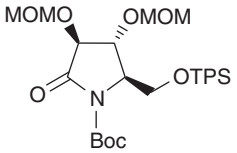
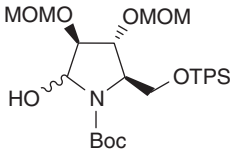
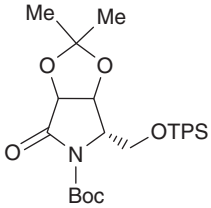
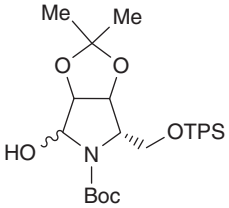
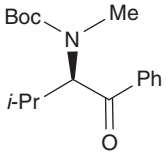
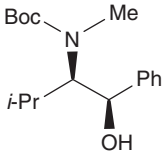
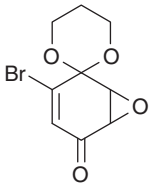
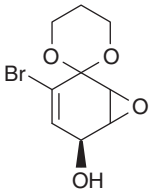
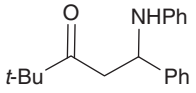
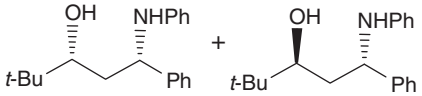
Substitution of the hydrides in borohydrides with alkyl groups increases the reducing power of the hydride reagent.[130] In addition, the increased steric bulk on the boron atom causes these reagents to exert significant steric interactions that increase with the

increase in the size of the alkyl groups. The result is effective face differentiation and preferred attack from the least hindered face of the carbonyl that usually increases the stereoselectivity and diatereoselectivity of the reaction. The effect is more noticeable in the reduction of the cyclic than acyclic ketones and is dependent on the size of the attached alkyl groups. Because of the selectivity and strength of trialkylborohydrides, their use is mostly relevant to prochiral ketones and they are rarely used for reduction of aldehydes.

8.01.3.2.4.1 Lithium triethylborohydride (Super-Hydride®)

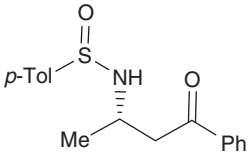
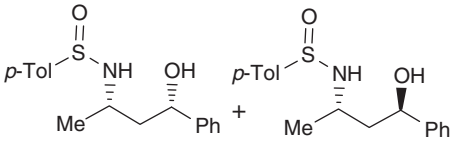
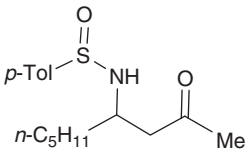
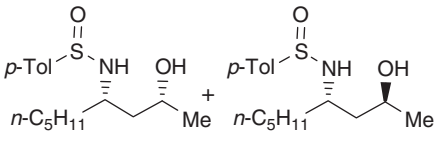
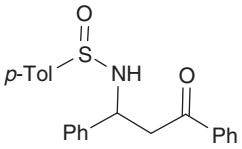
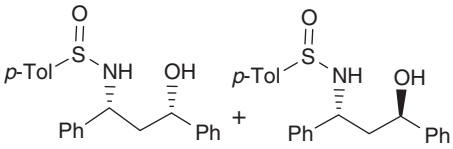
Lithium triethylborohydride ($LiBHEt_3$) is an exceptionally powerful and selective reducing agent; it is far more powerful than the unsubstituted $LiBH_4$ and even more powerful than LAH in many cases.[131] It is commonly known as Super-Hydride® (Super-Hydride® is a Sigma–Aldrich trade name for $LiBHEt_3$). The solvent of choice is THF and many reactions are carried out at 0 °C. This reagent is very effective in the nucleophilic displacements of halides, sulfonate esters, and selective opening of epoxides with hydride. Although $LiBHEt_3$ reduces aldehydes and ketones readily, it is not as commonly used as $NaBH_4$ for the reduction of aldehydes or simple ketones. It is however used in stereoselective and diastereoselective reductions of prochiral ketones where the stereochemical outcome is of high importance. For example, the reagent reduces norcamphor selectively to give 99:1 *endo*/*exo* ratio; and 2-methyl cyclohexanone to give 75:25 ratio of *cis*/*trans* cyclohexanols. The highlighted examples in **Table 7** show some of the applications of this versatile reagent in the stereoselective reductions of carbonyl groups. The reduction of the α-phenylsulfonylketone in **Table 7**, entry 1, with $LiBHEt_3$ was completely stereoselective affording the alcohol product in 70% isolated yield.[132] The examples in entries 2 and 3 show a rare reduction of a lactams to 2-hydroxypyrrolidines with $LiBHEt_3$ in high yields.[133,134]

Table 7 Reductions with $LiBHEt_3$ (Super Hydride™)

Entries	Substrate	Product	Conditions	Yield (%)	References
1			$LiBHEt_3$, THF, −78 °C	70	132
2			$LiBHEt_3$, THF, −78 °C	93	133
3			$LiBHEt_3$, THF, −78 °C, 30 min	>95% yield	134
4	 Several examples		$LiBHEt_3$, THF, −78 °C, 15 min $LiBHsec\text{-}Bu_3$ DIBAL-H, toluene, −78 °C	97 *dr*: 98:2 70 *dr*: >99:<1 *dr*: 60:40	135
5			$LiBHEt_3$, THF, −78 °C, 1 h	98	136
6			$LiBHEt_3$, THF, −78 °C, 2 h $Zn(BH_4)_2$, THF, 0 °C, 2 h	18:82 83:17	137

(*Continued*)

Table 7 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
7			$LiBHEt_3$ (5 equivalents), −78 °C, CH_2Cl_2 $Li(t\text{-}BuO)_3AlH$ (3 equivalents), Et_2O, −78 °C	73 99:1 61 1:9	138
8			$LiBHEt_3$ (5 equivalents), −78 °C, CH_2Cl_2	72 80:20	
9			$LiBHEt_3$ (5 equivalents), −78 °C, CH_2Cl_2 $Li(t\text{-}BuO)_3AlH$ (3 equivalents), Et_2O, −78 °C $Zn(BH_4)_2$ (5 equivalents), Et_2O, 0 °C	90 99:1 68 15:85 86 17:83	

The reduction of the Boc-protected aminoketones (Table 7, entry 4) with LiBH*sec*-Bu_3 gave the amino alcohols in excellent selectivity. However, the reaction was sluggish resulting in low conversion with increased steric hindrance on the substrate. Reductions of these ketones with DIBAL-H (toluene, −78 °C) or $Zn(BH_4)_2$ proceeded with poor selectivity to give mixtures of diastereomeric alcohols in ratios of 60:40 and 65:35, respectively. Better results[135] were obtained from $LiBHEt_3$, which gave consistently high yields even with hindered systems with slightly lower but still excellent stereoselectivity.

The epoxy ketone (Table 7, entry 5) was reduced in poor diastereoselectivity (1:1) with DIBAL-H or $Zn(BH_4)_2$ however, the reduction with $LiBHEt_3$ afforded the *syn*-epoxy alcohol in high yield; in this case[136] the ketone group was selectively reduced in the presence of the epoxide with $LiBHEt_3$ which is known to reduce epoxides.

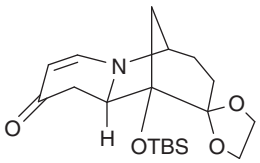
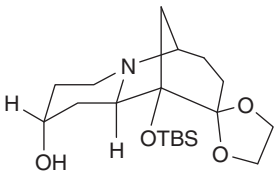
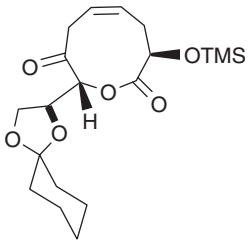
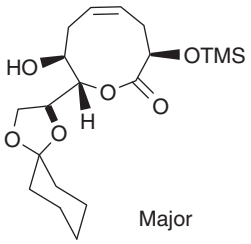
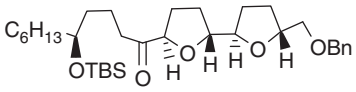
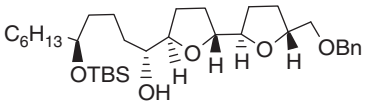
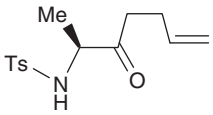
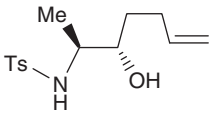
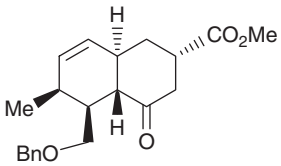
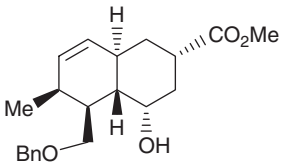
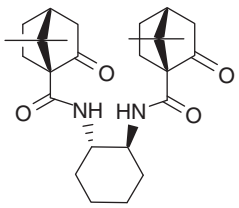
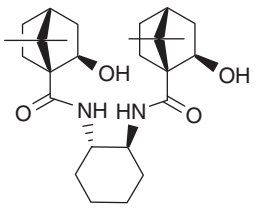
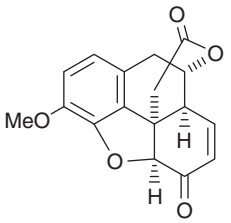
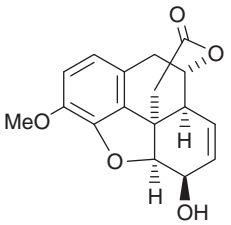
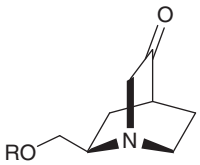
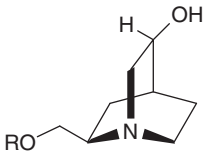
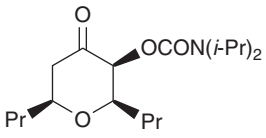
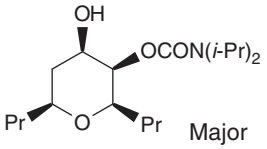
The reduction of *N*-aryl-*β*-amino ketones was studied by Pilli and coworkers[137] using $LiBHEt_3$ and $Zn(BH_4)_2$ (Table 7, entry 6); the highest *anti*-diastereoselectivity was obtained with $LiBHEt_3$ and the selectivity was dependent on of the bulkiness of the attached groups. The observed *anti*-selectivity was rationalized by external delivery of the hydride to the conformer with the least steric hindrance. However the reduction with $Zn(BH_4)_2$ favored the formation of the *syn*-diastereomers, which was rationalized by a chelated intermediate in which the Zn^{2+} ion coordinate both carbonyl and NH. Davis and coworkers[138] studied the reduction of the closely related *N*-sulfinyl *β*-amino ketones (Table 7, entries 7–9). The reductions with $LiBHEt_3$ gave consistently the *anti*-diastereomers in all derivatives but the selectivity was lower with alkyl versus aryl ketones. The formation of the *anti*-diastereomers was rationalized by a noncoordinated transition state. The use of $Li(t\text{-}BuO)_3AlH$ and $Zn(BH_4)_2$ gave the *syn*-diastereomers as the major products probably via coordinated TS.

8.01.3.2.4.2 Lithium and potassium tri-sec-butylborohydrides (LiBHsec-Bu$_3$) and (KBHsec-Bu$_3$): L- and K-Selectrides®

Substitution of three of the hyrides in BH_4^- with three sterically hindered *sec*-butyl groups produces very powerful hydride reducing agents similar to $LiBHEt_3$ in strength. However, the increased steric bulk provides a higher steric hindrance than that exerted by $LiBHEt_3$, and as a result the reagent may become more diastereoselective. There are two commercially available tri-*sec*-butylborohydrides, potassium tri-*sec*-butylborohydride (KBH*sec*-Bu_3) and lithium tri-*sec*-butylborohydride (LiBH*sec*-Bu_3), known commonly as K-Selectride® and L-Selectride®, respectively.[139] These reagents are a powerful reducing agent that reduces aldehydes and ketones to their corresponding alcohols, even at −78 °C. The use of such selective reducing agents in the reduction of aldehydes adds no advantage over simpler and more economical reagents such as $NaBH_4$. The selectrides provide more effective means for the stereoselective reduction of ketones compared to $NaBH_4$ and other reducing agents. The lithium derivative (LiBH*sec*-Bu_3) is more commonly used than the potassium derivative and other trialkylborohydrides. The examples listed in Table 8 (as well as some examples in Table 18, Section 8.01.8) show clearly the advantage of the selectrides as effective stereoselective and diastereoselective tools in the reduction of ketones. In some examples, the results from other reagents are highlighted for comparison.

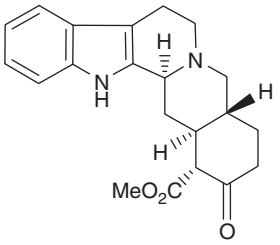
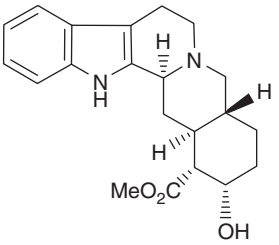
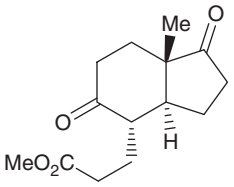
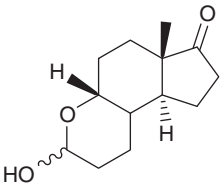
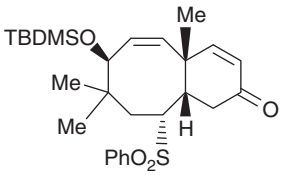
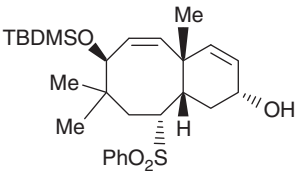
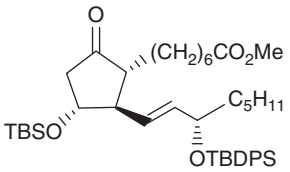
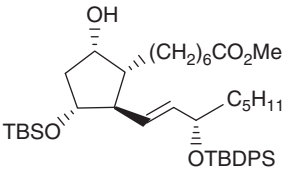
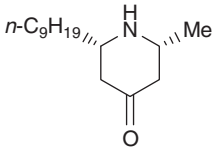
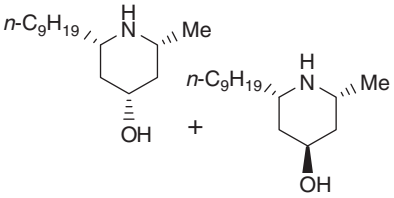
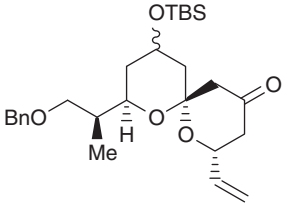
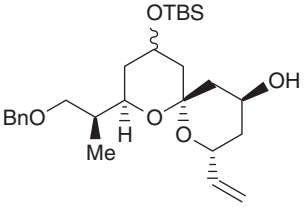
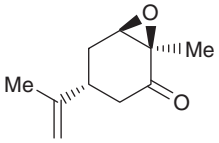
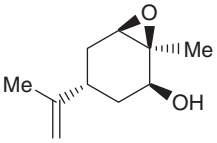
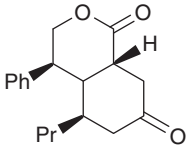
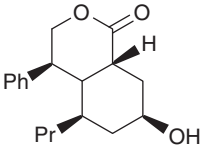
The entries in Table 8 represent examples of very effective stereoselctive reduction of cyclic and acyclic ketones. Weinreb and coworkers[140] reported an unusual reduction of an intermediate *α*,*β*-unsaturated ketone in the synthesis of phyllanthine (Table 8, entry 1). Although LiBH*sec*-Bu_3 does not usually perform 1,4-reduction of conjugated systems, the use of 2 equivalents of LiBH*sec*-Bu_3 affects both 1,4-reduction and stereoselective ketone reduction to give the saturated axial alcohol in excellent yield.

Table 8 Reductions with tri-*sec*-butylborohydrides (L- or K-Selectride®)

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			LiBH*sec*-Bu_3 (2 equivalents), THF, –78 °C	85	140
2		 Major	LiBH*sec*-Bu_3 1 M in THF	73 6:1 ratio at –78 °C 14:1 ratio at –130 °C	106
3			LiBH*sec*-Bu_3 (5 equivalents), THF, –110 °C to –60 °C, 1.5 h	77	141
4		 Major	LiBH*sec*-Bu_3 THF, –100 to –60 °C, 3 h	83 (85:15)	142
5			LiBH*sec*-Bu_3 THF, –78 °C, 10 min	88	143
6			LiBH*sec*-Bu_3, THF, –78 °C (1 h); r.t. (2 h)	95	144
7			LiBH*sec*-Bu_3 THF, –78 °C (2 h)	81	145
8		 R = trityl	LiBH*sec*-Bu_3 THF, –90 °C; –78 °C (2 h); to 0 °C (4 h)	91 (98:2)	146
9		 Major	$NaBH_4$, EtOH $Zn(BH_4)_2$, Et_2O LiBH*sec*-Bu_3	80 (9:1) 54 (9:1) 74 (99:1)	147

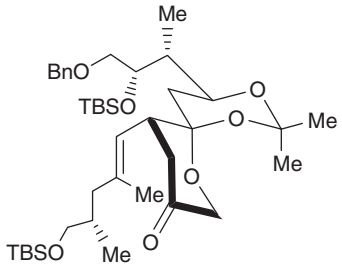
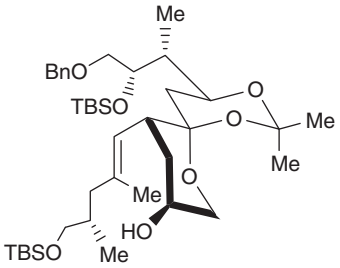
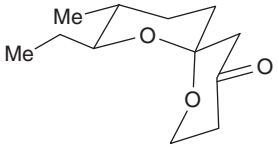
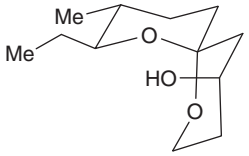
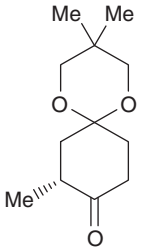
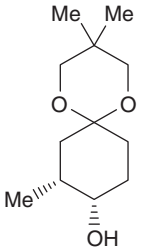
(*Continued*)

Table 8 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
10			LiBH*sec*-Bu_3, THF, –78 °C, 30 min	86, (>95% *de*)	148
11			LiBH*sec*-Bu_3, THF, –78 °C, 30 min	86	75
12			LiBH*sec*-Bu_3, THF, 0 °C, 14 h	87 (>94/6)	149
13			LiBH*sec*-Bu_3, THF, –78 °C	85	150
14			LiBH*sec*-Bu_3, THF, –78 °C $NaBH_4$, MeOH, 20 °C	95 (<2:>98) 95 (92:8)	151
15			LiBH*sec*-Bu_3, THF	76	152
16			LiBH*sec*-Bu_3, THF, –78 °C	96	153
17			KBH*sec*-Bu_3, THF, –78 °C, 80 min	54	154

(*Continued*)

Table 8 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
18			LiBH*sec*-Bu_3, THF, −78 °C, 2 h, then 0 °C overnight	84 (+10% SM)	155
19		 NaBH$_4$ yields a 1:1 mixture of axial and equatorial alcohols	LiBH*sec*-Bu_3, THF, −78 °C, 2 h, to 0 °C Then H_2O_2/NaOH	79	156
20			LiBH*sec*-Bu_3, THF, −78 °C, 2 h; H_2O_2, NaOH, H_2O, r.t., 16 h	99	157

Marko and Leroy[147] studied the reduction of the 4-pyranone (Table 8, entry 9) under 10 different reduction conditions, the highest selectivity (>99:1) was obtained from using LiBH*sec*-Bu_3 as the reducing agent.

Aubé and coworkers[148] reduced yohimbinone (Table 8, entry 10) to (+)-yohimbine (α-OH) in >95% *de* using LiBH*sec*-Bu_3. If the reduction is carried out with $NaBH_4$ it produces only β-yohimbine in good yield.

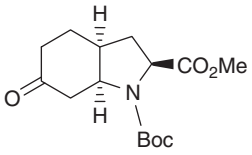
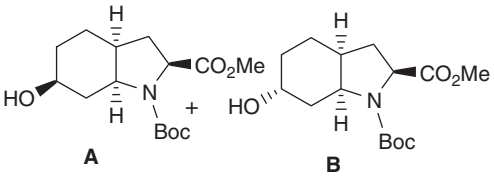
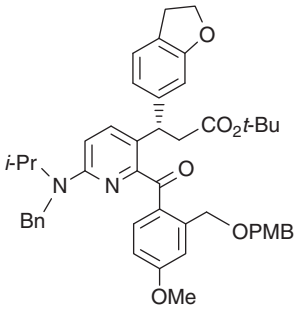
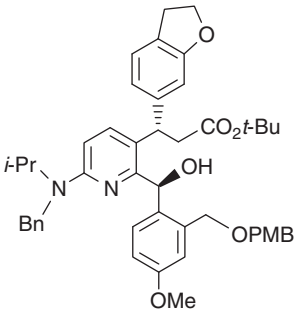
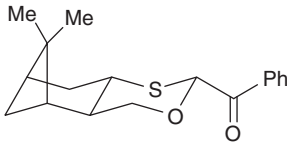
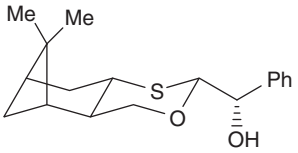
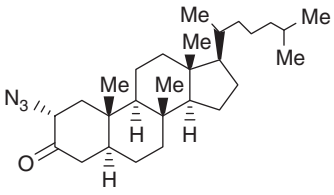
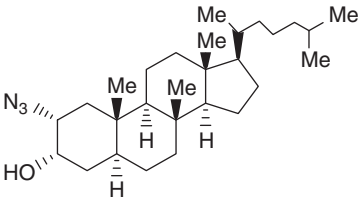
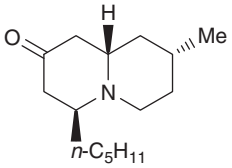
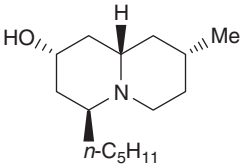
Rigby and coworkers[75] reported an interesting reduction of a diketoester (Table 8, entry 11) with LiBH*sec*-Bu_3 to produce a keto-lactol in excellent yield with complete control of stereochemistry; under these conditions, the cyclohexanone reduction occurred selectively without affecting the cyclopentanone.

The reduction of a 4-piperidinone was reported by Troin, Canet, and coworkers[151] in their synthesis of the alkaloid 241D and its epimer (Table 8, entry14). The reduction with LiBH*sec*-Bu_3 in THF at −78 °C gave the C-4 epimer exclusively in 96% yield; however, the reduction with $NaBH_4$ gave selectively the natural (−)-isomer of the alkaloid 241D.

8.01.3.2.4.3 Lithium trisiamylborohydride (LS-Selctride®) and potassium trisiamylborohydride (KS-Selctride®)

Further increase in the steric bulk of the alkyl groups in trialkylborohydrides led to the preparation of more highly selective trialkyl borohydrides, lithium trisiamylborohydride [LiBH(CHMeCHMe$_2$)$_3$ or LiBH(Sia)$_3$] commercially known as LS-Selectride® and potassium trisiamylborohydride [KBH(CHMeCHMe$_2$)$_3$ or KBH(Sia)$_3$] commercially known as KS-Selectride®. These reagents are similar to L- and K-Selectrides® in reactivity but exhibit even better diastereoselectivity in reduction of ketones. Some of the results from the early study by Brown and Krishnamurthy[158] revealed the remarkable stereoselective control exerted by lithium trisiamylborohydride. The reagent provides a superior means of synthesis of the thermodynamically less stable alcohols from unhindered cyclic ketones with previously unprecedented selectivity of >99%. For example, 4-*tert*-butylcyclohexanone was reduced to *cis*-4-*tert*-butylcyclohexanol in ≥99.5% isomeric purity and 3-methylcyclohexanone to the corresponding *trans*-carbinol in 99.6% isomeric purity. Moderately hindered ketones, such as 2-methylcyclopentanone and 2-methylcyclohexanone, were also rapidly converted into the corresponding *cis* alcohols in excellent isomeric purities (≥99.5%). However, the highly hindered camphor was reduced very slowly with LiBH(Sia)$_3$ at 0 °C (10%, 24 h); however, 80% conversion to 99.3% *exo* alcohol was achieved in 72 h at 25 °C, an indication of the unusually large steric effect of this reagent. Recent examples of reduction with Li(Sia)$_3$BH are listed in Table 9.

Table 9 Reductions with lithium trisiamylborohydride (LS-Selectrides)

Entries	Substrate	Product	Conditions	Yield (%)	References
1		 **A** **B**	$LiBH(Sia)_3$ THF, −78 °C, 2 h $NaBH_4$, $CeCl_3$ −23 °C, 6 h	7 **A** 56 **B** 91 **A** 3 **B**	159
2			$LiBH(Sia)_3$ THF, 0 °C, 5 h	84 5:1	160
3			$LiBH(Sia)_3$ Toluene/THF, −78 °C, 4 h, then r.t. overnight	82 ≥99:1	161
4			$LiBH(Sia)_3$ THF, −60 °C, 40 min then MeOH	82	162
5			$LiBH(Sia)_3$ THF, −78 °C	83	163

The example in Table 9, entry 1 shows a stereoselective ketone reduction with $LiBH(Sia)_3$ in 8:1 ratio and the desired alcohol was isolated in 56%. Although the isolated yield of the desired (*R*)-alcohol could not be improved, other reduction procedures such as Luche's reagent give predominantly the opposite stereochemistry and additional steps have to be carried out to invert the stereochemistry.[159]

The reduction of the ketone in Table 9, entry 2 with a variety of reducing agents gave no satisfactory results, for example, LiBH*sec*-Bu_3 afforded 60% yield and 3:1 ratio of diastereomers; both Li 9-BBN-H and BH_3.THF gave 80% yield and 2:1 diastereomeric ratio; $NaBH_4$ provided excellent yield of 96% but 1:1 mixture, whereas DIBAL-H reduced the *tert*-butyl ester. The reduction with $Li(Sia)_3BH$ gave 5:1 diasteromeric ratio in 84% which, after crystallization afforded the desired alcohol of 99.5% *de* purity in 66% yield.[160]

The bicyclic ketone in Table 9, entry 5 was reduced with $LiBH(Sia)_3$ in THF at −78 °C to give the corresponding alcohol in 83% yield as a single isomer in one of the steps in the total synthesis of (3*S*,4a*S*,6*R*,8*S*)-hyperaspine.[163]

8.01.3.3 Borohydride Modifications: Additives, Combinations, Solvents, and Polymer Support

The modification of borohydrides is not limited to the structural modifications mentioned earlier but has been extended to other changes such as addition of salts, particularly those of transition metals, addition of other reagents, changing solvent systems, and using polymer supported reagents. Many of these modifications can significantly alter and vary considerably the properties of sodium borohydride and its chemoselectivity.

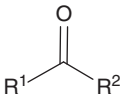
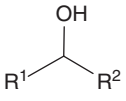
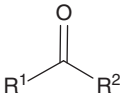
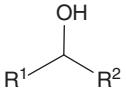
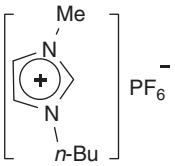
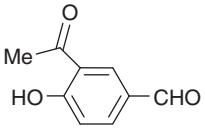
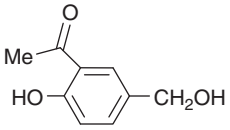
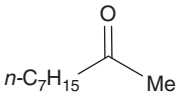
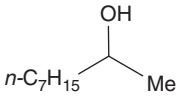
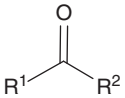
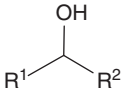
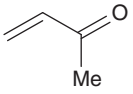
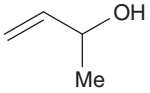
Some earlier studies have demonstrated that the usual reaction selectivity and reducing power of $NaBH_4$ can be substantially varied by addition of various metal salts. For example, in 1956 Brown and Rao[164] reported that addition of $AlCl_3$ to $NaBH_4$ resulted in the formation of a more powerful reducing agent than $NaBH_4$ by itself. They proposed the formation of $Al(BH_4)_3$ to explain the change in the reducing properties. They also mentioned that addition of other polyvalent metal halides such as $GaCl_3$ and $TiCl_4$ to $NaBH_4$ resulted in a similar increase of $NaBH_4$ reducing power. Since then, other salts were studied such as Co^{++} ($CoCl_2$),[165] Cu^{++},[166] Ni(0),[167] Sn^{4+} ($SnCl_4$),[168] and Ti^{4+} ($TiCl_4$).[169] Many of these combinations are capable of performing synthetically useful conversions including the reductions of acyl chlorides to aldehydes, olefins to saturated hydrocarbon and dehalogenation of aryl halides to arenes and hydroboration of alkenes.

The use of polymer-supported borohydrides is another form of borohydride modification. Gibson and Baily[170] reported the preparation and use of borohydride exchange resin (BER) in 1977. BER has been used for the regioselective reduction of carbonyl compounds in alcoholic solvents[171,172] and shows good chemoselectivity in reducing aldehydes in the presence of ketones[172] and reducing α,β-unsaturated aldehydes to allylic alcohols.[171]

This section highlights several reports since 1990 on the use of borohydrides in combination with metal salts, their use in different solvent systems and different polymer supported forms. The coverage is limited to the scope of this chapter and only to their use in the chemoselective reductions of aldehydes and ketones. Examples of the highlighted procedures are listed in **Table 10**.

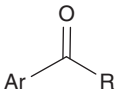
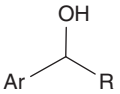
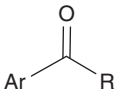
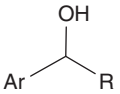
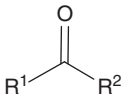
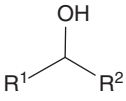
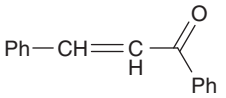
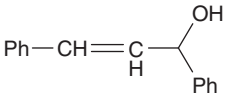
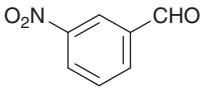
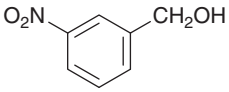
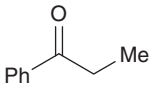
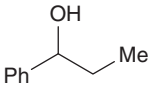
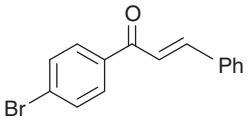
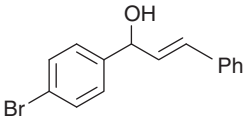
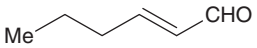
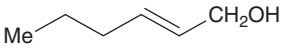
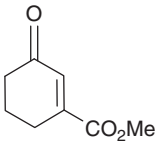
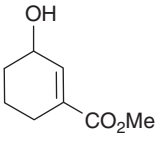
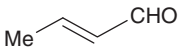
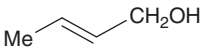
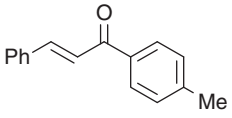
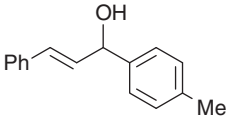
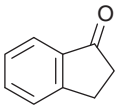
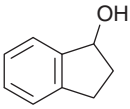
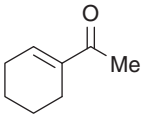
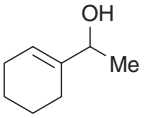
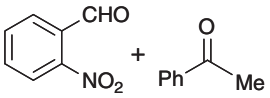
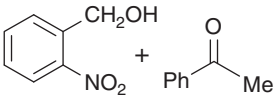
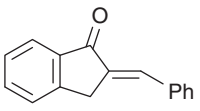
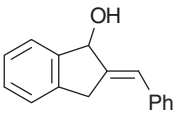
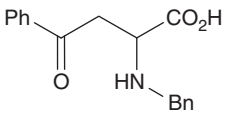
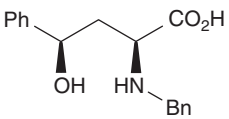
Hirano and coworkers[173] have developed a procedure for the reduction of aldehydes and ketones with an *in situ* generated reagent of silica gel-supported $NaBH_4$. The reduction of several aldehydes and ketones was carried out with this heterogenous reagent in hexane at 40 °C. Several examples of alicyclic, aliphatic, and aromatic ketones as well as aliphatic and aromatic aldehydes were reduced to the corresponding alcohols in excellent to quantitative yields (**Table 10**, entries 1 and 2).

Table 10 Borohydride reductions using additives, combinations, solvents, and polymer support

Entries	*Substrate*	*Product*		*Conditions*	*Yield (%)*	*References*
1	RCHO	RCH_2OH	R = C_5H_{11}, C_8H_{17}, Ph, 4-$NO_2C_6H_4$, 3,4-$(OCH_2O)C_6H_3$, *trans*-PhCH=CH	$NaBH_4$ silica gel, hexane 40 °C	91–100	173
2			For example, cyclopentanone, cyclohexanone, $PhCOCH_3$, PhCOPh, 2-hexanone			
3			For example, PhCHO, PhCOPh, PhCOCH(OH)Ph cyclohexanone	$NaBH_4$ 	55–90	174
4	RCHO	RCH_2OH	R = C_5H_{11}, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4	Sulfurated borohydride exchange resin (BER) MeOH, 25 °C, 4–45 min	80–93	175
5					90	
6	RCHO	RCH_2OH	For example, R = *n*-C_7H_{15}, 4-ClC_6H_4, PhCH=CH-	$NaBH_4$ in PEGDME, r.t.	88–98	176
7				$NaBH_4$ in PEGDME 60 °C, 8 h	98	
8			For example, PhCHO, PhCOMe, Py-CHO, c-hexanone	$NaBH_4$, $LiClO_4$ CH_3CN, r.t. 10–20 min	80–98	177
9				$NaBH_4$, $LiClO_4$ CH_3CN, r.t., 15 min	85	

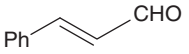
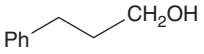
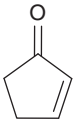
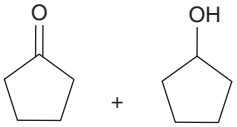
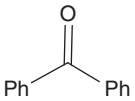
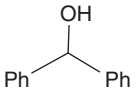
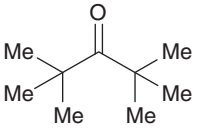
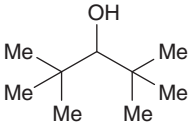
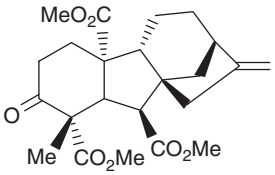
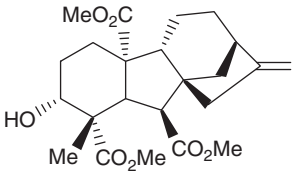
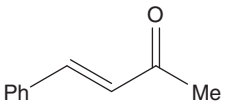
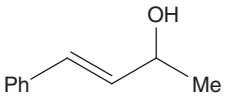
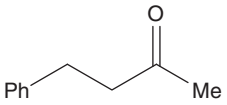
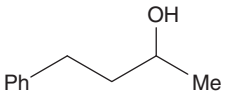
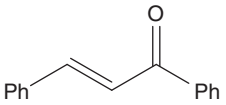
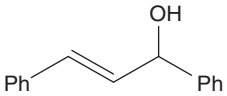
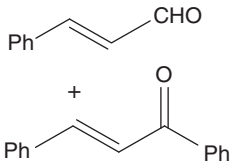
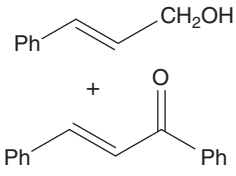
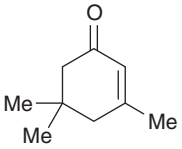
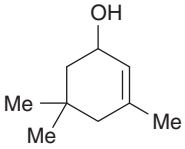
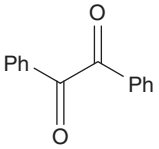
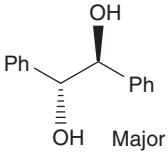
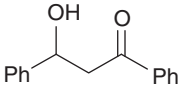
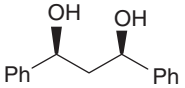
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Table 10 Continued

Entries	Substrate	Product		Conditions	Yield (%)	References
10			Ar=Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$ R=H, Me	Bu$_4$NBH$_4$ PhCH$_2$Cl, toluene, THF, 25 °C	82–94	178
11			Ar=Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$ R=H, Me	Bu$_4$NBH$_4$ I$_2$, toluene, THF, 0–25 °C	89–94	
12			20 examples (aldehydes & ketones)	NaBH$_4$, wet-THF polymer PTC 10–120 min	93–96	179
13				NaBH$_4$, wet-THF polymer PTC 10–120 min	95	
14			23 examples of aldehydes and ketones	PIBH or BIIBH MeOH, r.t., 10 min,	93–96	180
15				PIBH or BIIBH *i*-PrOH, reflux 1.2–1.5 h	95	
16				PIBH or BIIBH *i*-PrOH, reflux 2.5 h	92–93	
17				NaBH$_4$, $H_3PW_{12}O_{40}$ (0.5 mol%), MeOH	93	181
18				Zn(BH$_4$)$_2$ –silica gel, THF –5 to –10 °C	85	182
				7–8 h	80	
19				1. NaBH$_4$, InCl$_3$ (cat.) MeCN, 20 °C, 2 h 2. MeOH	93	183
20				NaBH$_4$, H_3BO_3 (1 equivalent each), 20 min NaBH$_4$ (1 equivalent), 20 min	>99 2	184
21				NaBH$_4$, H_3BO_3 (1 equivalent each), 10 min NaBH$_4$ (1 equivalent), 60 min	98 27	
22				[(Piperazine)-Zr(BH$_4$)$_2$Cl$_2$] Et$_2$O, 25 min	100	185
23				[(Piperazine)-Zr(BH$_4$)$_2$Cl$_2$] Et$_2$O, 5 h, r.t.	82	
24				NaBH$_4$, MnCl$_2$·4H$_2$O (cat.) MeOH, 20 °C,	77 >97:3	186

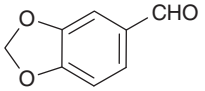
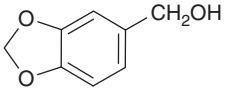
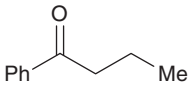
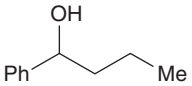
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Table 10 Continued

Entries	Substrate	Product		Conditions	Yield (%)	References
25				$BER-CuSO_4$, (5 equivalents) MeOH, r.t., 1 h	100	187
		 **A** + **B**		$BER-CuSO_4$, (2 equivalents) MeOH, r.t., 15 min	**A**: 85 **B**: 15	
26				$NaBH_4$ (5 equivalents) Amberlyst-15 (1 g $mmol^{-1}$ ketone), THF, 10 min	98	188
27				$NaBH_4$ (40 equivalents), Amberlyst-15 (6 g $mmol^{-1}$ ketone), THF, 7 min	98	
28				$NaBH_4$ (5 equivalents), Amberlyst-15 (3 g $mmol^{-1}$ ketone), THF, 4 min	98	
29				$NaBH_4$ (1.1 equivalents), MeOH	99	189
				$NaBH_4$ (3.5 equivalents), $CoCl_2$ (3 equivalents), aqueous sodium dodecyl sulfate (SDS) (0.1 M)	77	
				$NaBH_4$ (6 equivalents), $CoCl_2$ (3 equivalents), H_2O	97	
30			Examples of aldehydes, ketones & diketones	$NaBH_4$ (2 equivalents), THF-H_2O (3:0.1) Reflux, 12 min	92	190
31		 No ketone reduction		$NaBH_4$ (1 equivalent), THF-H_2O (3:0.1) r.t., 2 min	100	
32				$(i\text{-PrO})_2TiBH_4$ CH_2Cl_2, –20 °C, 5 min	97	191
33		 Major		$(i\text{-PrO})_2TiBH_4$ CH_2Cl_2, –20 °C, 15 min	94 (96:4)	192
34				$(i\text{-PrO})_2TiBH_4$ CH_2Cl_2, –20 °C, 5 min	95	

(*Continued*)

Table 10 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
35			$NaBH_4$ (9 equivalents), $NiCl_2$ (3 equivalents), THF, r.t., 5 min	86	193
36			$NaBH_4$ (9 equivalents), $NiCl_2$ (3 equivalents), THF, r.t., 15 min	89	

Howarth and coworkers[174] studied the use of ionic liquids as solvents for $NaBH_4$ reduction of aldehydes and ketones. Ionic liquids such as 1-butyl-3-methylimidazolium cation ([bmim]PF_6) and similar ionic liquids can solvate a wide range of organic and inorganic materials. They are highly polar but noncoordinating, and while they are immiscible with a wide range of organic solvents, it is possible to vary their immiscibility with water and other solvents by varying the counter ion. Their unique properties make them possible environmentally friendly alternatives to classical solvents. The study included six common carbonyl compounds (two aldehydes and four ketones), the isolated yield ranged from 55 to 90% (Table 10, entry 3).

The use of sulfurated BER in the chemoselective reduction of aldehydes was reported by Bandgar and Kamble.[175] The reductions of one aliphatic and 14 aromatic aldehydes were carried out in MeOH at 25 °C in 4–45 min and the isolated yields ranged from 80 to 93%. The examples included one selective reduction of an aldehyde in the presence of a ketone (Table 10, entries 5 and 6).

The use of $NaBH_4$ in polyethylene glycol dimethyl ethers (PEGDME) was reported by Tanemura and coworkers[176] as a mild condition for the chemoselective reduction of aldehydes. The reduction of aldehydes was complete at r.t. in 0.5–1.5 h, whereas ketones required heating to 60–100 °C and several hours (Table 10, entries 6–7). Several competitive reactions demonstrate that aldehydes are reduced in the presence of ketones.

The combination of $NaBH_4$ and solid $LiClO_4$ in aprotic solvent such as CH_3CN was reported by Saidi[177] as a mild and efficient reagent for the reduction of aldehydes and ketones. A group of 14 aldehydes and ketones (Table 10, entry 8) were all reduced in 10–20 min to produce the corresponding alcohols in 80–98%. (−)-Camphor needed 5 h and gave 69% yield as 2:1 *exo*/*endo* products. The reagent was also used for the reduction of several acid chlorides to primary alcohols and the 1,2-reduction of α,β-unsaturated aldehydes and ketones to allylic alcohols (Table 10, entry 9).

Periasamy and coworkers[178] used $PhCH_2Cl$ or I_2 to generate borane from tetrabutylammonium borohydride at 25 °C in toluene. The reagent combination can be used for reduction of aldehydes and ketones in good isolated yields of 82–94% (Table 10, entries 10–11) as well as hydroboration of alkenes.

Tamami and Mahdavi[179] reported the use of poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride resin as efficient polymeric phase transfer catalyst (polymer PTC) for the reduction of aldehydes and ketones by $NaBH_4$ in wet THF to give the corresponding alcohols in high yields under mild conditions (Table 10, entry 12). The presence of the polymer PTC in the reaction mixture caused rate acceleration particularly with aromatic ketones such as acetophenone; however, aldehydes still react faster than ketones. Competition reactions between aldehydes and ketones show promising results for selective reduction of aldehydes versus. ketones. The reduction of α,β-unsaturated aldehydes and ketones with this system also show clear preference for the regioselective 1,2-reduction resulting in the formation of the corresponding allylic alcohols (Table 10, entry 13).

Lakouraj and coworkers[180] developed linear polymer-supported borohydride reducing agents, 2,4-ionene borohydride (PIBH) and xylylene-ionene borohydride (PIIBH). These reagents are stable nonhygroscopic white powders, insoluble in most organic solvents such as Et_2O, THF, $CHCl_3$, *i*-PrOH, and *t*-BuOH, slightly soluble in MeOH and soluble in water. They reduce aldehydes, ketones, acid chlorides, and imines and the authors presented several examples of each category. Reductions of aldehydes and imines were best carried out in MeOH, whereas reductions of ketones were best done in *i*-PrOH or THF/MeOH. In addition, the reagents show promising results for the chemoselective reduction of aldehydes in the presence of ketones, some examples are highlighted in Table 10, entries 14–16.

Heydari and coworkers[181] described a procedure for reductive amination as well as selective reduction of α,β-unsaturated aldehydes and ketones using the combination of $NaBH_4$ and a catalytic amount (0.5 mol%) of $H_3PW_{12}O_{40}$ (12-tungstophosphoric acid) in MeOH (Table 10, entry 17).

Ranu[182] reported on the use of silica gel-supported zinc borohydride as effective reagent for the selective reduction of α,β-unsaturated aldehydes and ketones (Table 10, entry 18).

Ranu[183] also reported the use of the combination of sodium borohydride and a catalytic $InCl_3$ in acetonitrile as a chemoselective reducing system for the reduction of the C=C in a wide range of activated conjugated enones. One application is the reduction of chalcones to saturated alcohols after MeOH quench (Table 10, entry 19).

Cho, An, and coworkers[184] described a procedure for reduction of aldehydes and ketones using sodium borohydride activated by solid acids such as boric acid, benzoic acid, and *p*-toluenesulfonic acid monohydrate under solvent-free conditions.

The addition of acid shows no advantage with aldehydes but shows enhancement in yield and rate with ketones (Table 10, entries 20 and 21).

$Zr(BH_4)_4$ is an unstable borohydride derivative. Early work by Sorrell[194] introduced bis(cyclopentadieny1)chlorotetrahydroborato zirconium(IV), $[Cp_2Zr(Cl)BH_4]$, as a stabilized form that reduces aldehydes and ketones. However, the reagent was sluggish with α,β-unsaturated ketones and gave very poor stereoselectivity in reduction of cyclic ketones. The use of stabilized $Zr(BH_4)_4$ on cross-linked poly(4-vinylpyridine) [XP4-$Zr(BH_4)_4$] was reported in 1994[195] and was used for reduction of aldehydes such as benzaldehyde, cinnamaldehyde, and ketones such as acetophenone. Another stabilized form, zirconium borohydride piperazine complex abbreviated as $[(Ppyz)Zr(BH_4)_2Cl_2]$, was reported by Tajbakhsh.[185] The reagent reduces saturated and α,β-unsaturated aldehydes and ketones to alcohols and allylic alcohols, respectively. It also reduces aldehydes in the presence of ketones (Table 10, entries 22–23)

Berkes and coworkers[186] reported the use of the combination of $NaBH_4$ and $MnCl_2$ for the *syn*-selective reduction of 4-aryl-4-oxo-α-amino acids. Using $NaBH_4$ alone at low temperature was also *syn*-selective but in lower selectivity (up to 11:1). The authors stated that $MnCl_2$ serves as a chelating agent, increases the solubility of starting materials, accelerates the rate of reduction and increases the *syn*-selectivity. The preferred ratio of $MnCl_2$ to achieve high *syn*-diastereoselectivity is 20 mol%; a representative example is shown (Table 10, entry 24).

Yoon and Sim[187] reported on the use of BER with catalytic $CuSO_4$ in MeOH at r.t. in the reduction of aldehydes and ketones. Reduction with BER was applied to saturated aldehydes and ketones but was also applied to the 1,4-reduction of α,β-unsaturated aldehydes and ketones with variable results; enals and some enones formed allylic alcohols but some enones formed mixtures of allylic alcohols and mostly saturated ketones (Table 10, entry 25).

Tellado and coworkers[188] reported the use of the combination of $NaBH_4$ and amberlyst-15(H^+) in aprotic solvents as a powerful and practical reducing agent. This reagent combination is efficient as it reduced unreactive and hindered ketones in excellent yields and the work up is simple. Representative examples are highlighted in Table 10, entries 26–28.

Savelli and coworkers[189] investigated the use of $NaBH_4/CoCl_2$ in the reduction of α,β-unsaturated ketones with the goal of optimizing conditions to the selective preparation of the three possible reduction products; allylic alcohols, saturated ketones, and saturated alcohols. They also studied the effect of several reaction solvents including MeOH, H_2O, and the aqueous surfactants sodium dodecyl sulfate (SDS) or cetyltrialkylammonium bromide (CTABr). The study was successful in devising conditions for the selective formation of each one of the three products by changing the reaction conditions (Table 10, entry 29).

Zeynizadeh and Behyar[190] reported on the use of THF containing small amount of water as a solvent for $NaBH_4$ reductions. This reduction procedure can reduce aldehydes and ketones, 1,2-diketones, aldehydes in the presence of ketones and α,β-unsaturated aldehydes and ketones to allylic alcohols (Table 10, entries 30–31).

Chandrasekaran and coworkers[191] developed a reduction procedure using diisopropoxy-titanium(III) borohydride $[(i\text{-PrO})_2\text{-}TiBH_4]$ made from the combination of diisopropoxytitanium dichloride and benzyl triethylammonium borohydrides in a 1:2 ratio. The reagent reduces α,β-unsaturated aldehydes and ketones in CH_2Cl_2 at −20 °C to allylic alcohols (Table 10, entry 32). The use of this reagent was extended[192] to the reduction of α-hydroxyketones, 1,2-diketones, β-hydroxyketones, and 1,3-diketones to the corresponding diols in high stereoselectivity (Table 10, entries 33–34). The reductions with this reagent are highly selective and show better results than the combination of $NaBH_4/TiCl_3$.[196]

The use of Ni boride in THF was reported to reduce aldehydes and ketones, including α,β-unsaturated derivatives (Table 10, entries 35–36).[193]

8.01.4 Reductions with Aluminum Hydrides

LAH was first reported in 1947.[3] It is a very powerful reducing agent but not chemoselective. It reduces all kinds of carbonyl-containing compounds as well as epoxides, nitriles, and amides. The reports in this chapter will be limited to the use of LAH in the reduction of aldehydes and ketones. All four hydrides are used in the reduction. The best solvents for LAH reactions are anhydrous ethereal solvents such as diethyl ether (solubility: 35–40 g per 100 g) and THF (solubility: 13 g per 100 g). Water, alcohols, and other protic solvents are not suitable; LAH reacts violently in an exothermic reaction with these solvents with the evolution of large amounts of hydrogen which can be a fire hazard and very dangerous. The reaction of LAH with water is very exothermic ($\Delta H^\circ_{298} = -714$ kJ mol^{-1}) so the hydrogen can ignite spontaneously. Caution should be exercised when using LAH to avoid contact with water or alcohols and prevent this hazard. Direct quench of excess reagent with water or lower alcohols is not advisable for the same reasons; 10% aqueous NaOH or ammonium chloride may be better alternatives but still need to be done with cooling and extreme caution. Quenching excess LAH by slow addition of EtOAc while cooling is preferred, because no hydrogen gas is formed.[197]

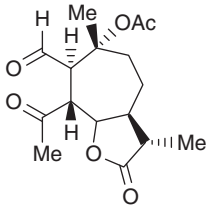
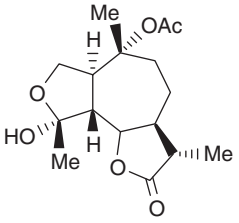
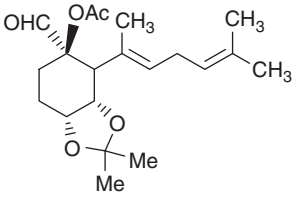
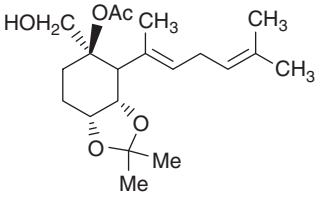
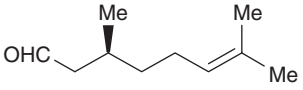
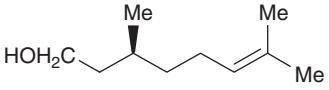
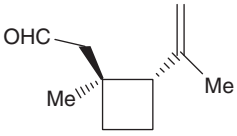
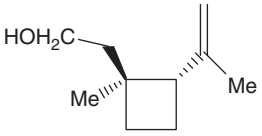
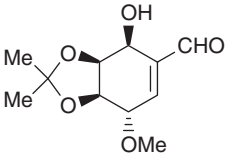
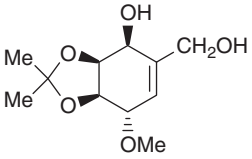
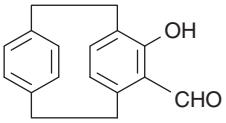
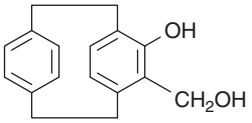
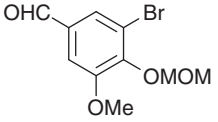
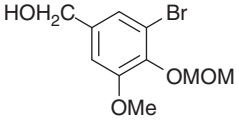
Sodium aluminum hydride (SAH): Cha and Brown[198] examined the properties of $NaAlH_4$ and compared its reducing power to that of $LiAlH_4$. They found the two regents very similar. $NaAlH_4$ reduces aldehydes and ketones rapidly and quantitatively; it also reduces most other functional groups and can replace LAH in most reactions with similar results. One of the few differences is that SAH reduces carboxylic acids, anhydrides, and epoxides slower than LAH. $NaAlH_4$ is soluble in ethers such as THF and 1,2-dimethoxyethane. The lower cost and ease of handling makes $NaAlH_4$ a valuable alternative to LAH, but there are far fewer reports on using $NaAlH_4$ compared to LAH. $NaAlH_4$ has recently been studied as a possible candidate for hydrogen storage in fuel-cells.[199]

8.01.4.1 Reductions with Unsubstituted Aluminum Hydrides

8.01.4.1.1 Reductions of aldehydes with LAH

The use of LAH in the reduction of aldehydes is somewhat limited compared to $NaBH_4$; the need for a mild reagent to carry out this task my preclude LAH as a proper choice. Its use is limited to simpler substrates that contain no competing reducible groups. However, there are still large numbers of reports where LAH is used in the reduction of aldehydes. The examples listed in Table 11 show several reports that illustrate the effective use of LAH in reduction of aldehydes; all highlighted examples show good results with high isolated yields. Some aldehyde reductions are very fast requiring only 10 min at 0 °C (Table 11, entry 4) and some can be relatively slow requiring 1.5 h at r.t. (Table 11, entry 6).

Table 11 Reductions of aldehydes with LAH

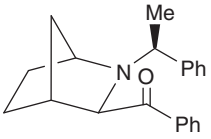
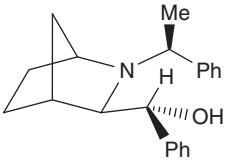
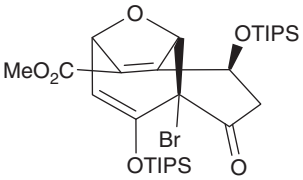
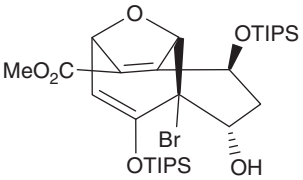
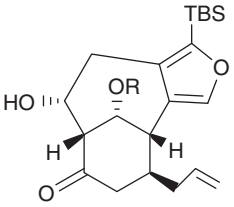
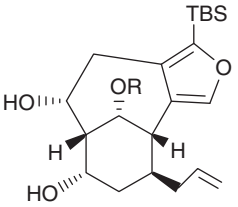
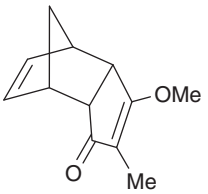
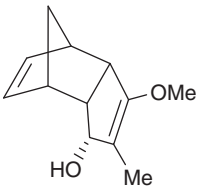
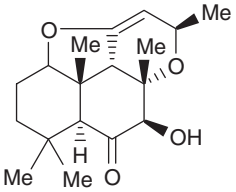
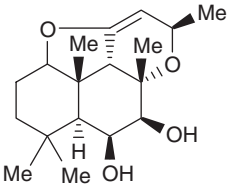
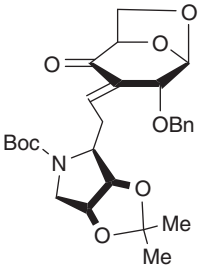
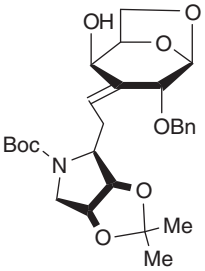
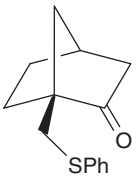
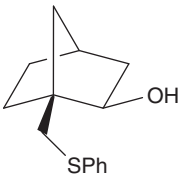
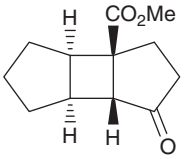
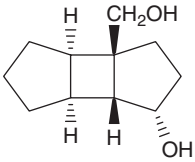
Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			$LiAlH_4$, THF, 0 °C, 3 h	95	200
2			$LiAlH_4$ (6 equivalents), Et_2O, 0 °C r.t., 1 h	71	201
3			$LiAlH_4$, Et_2O	96	202
4			$LiAlH_4$, Et_2O, 0 °C, 10 min	93	203
5			$LiAlH_4$, THF, 0 °C	93	204
6			$LiAlH_4$, Et_2O, r.t., 1.5 h	98	205
7			$LiAlH_4$	92	206

The reduction of the aldehyde intermediate in the synthesis of α-D-carbatalopyranose (Table 11, entry 5)[204] was not successful with $NaBH_4$ or $NaCNBH_3$ giving rise to complex mixtures of products. The best result was obtained from the reduction of the aldehyde with $LiAlH_4$ in THF at 0 °C to give the product diol in 93% yield.

8.01.4.2 Reduction of Ketones with LAH

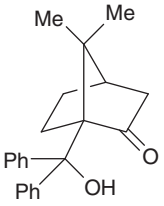
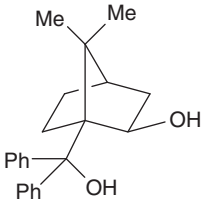
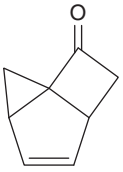
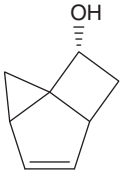
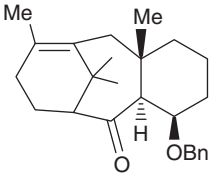
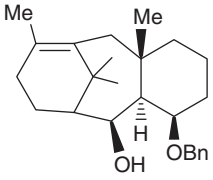
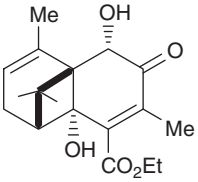
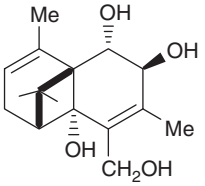
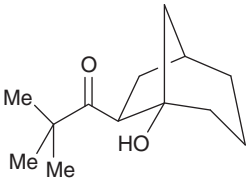
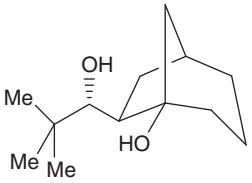
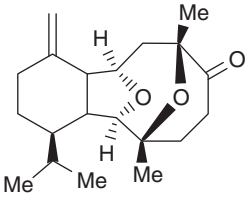
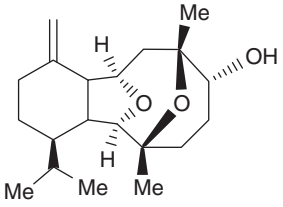
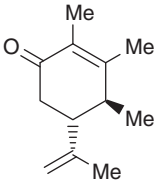
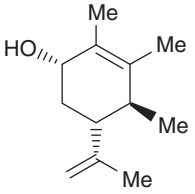
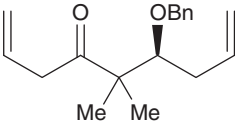
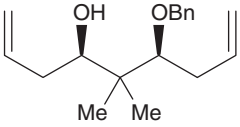
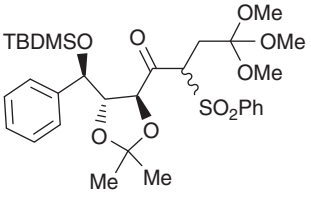
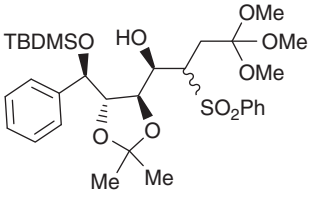
The use of LAH for reduction of ketones is more frequent than of aldehydes. Ketones, particularly aromatic and sterically hindered ketones, react with metal hydrides slower than aldehydes and consequently they may require stronger reagent to affect their reductions. The examples listed in Table 12 represent reports of LAH reductions of very diverse and highly functionalized ketones

Table 12 Reduction of ketones with LAH

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			$LiAlH_4$, THF, −78 °C (30 min), r.t. (1 h)	71 (80:20)	207
2			$LiAlH_4$, THF −78 °C, 1 h	82	208
3			$LiAlH_4$, Et_2O	90	209
4			$LiAlH_4$, Et_2O, reflux	65	210
5			$LiAlH_4$, Et_2O, −65 °C	80	211
6			$LiAlH_4$, THF, −78 °C, 3 h	89	212
7			$LiAlH_4$, Et_2O, 0 °C then r.t., 2 h	85 (*exo*) *exo* : *endo* 10:1	213
8			$LiAlH_4$, Et_2O, 0 °C (2 h); then r.t. (1 h) and reflux (3 h)	74 6:1	214

(*Continued*)

Table 12 Continued

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
9			$LiAlH_4$, THF, −78 °C, 30 min	95	215
10			$LiAlH_4$, THF, 0 °C to r.t. 2 h	95	216
11			$LiAlH_4$, THF 0 °C	~100	217
12			$LiAlH_4$ (excess), Et_2O	74	218
13			$LiAlH_4$, Et_2O 30 °C, 0.5 h	95	219
14			$LiAlH_4$, THF	79	220
15			$LiAlH_4$, Et_2O, −70 °C (2 h); r.t. (0.5 h)	83	221
16			$LiAlH_4$, Et_2O/THF −120 to −60 °C (18 h)	82	222
17			$LiAlH_4$, Et_2O, −78 °C, 2 h	96	223

with very demanding steric and stereochemical environments. In spite of being a very powerful reducing agent, LAH reduces many of these complicated structures with good chemoselectivity and synthetically practical levels of stereoselectivity in good to excellent yields. The clever use of the reagent and the careful tailoring of the reaction condition to produce the desired outcome are evident in most cases. For example the reduction of the benzoyl azabicyclononane derivative (Table 12, entry 1)[207] was unsuccessful with $NaBH_4$, progressing only 20% after 2 days at 20 °C; LAH reduced this ketone in good yield and good (4:1) stereoselectivity in a much shorter time. Also in the example highlighted in Table 12, entry 2, attempts to reduce the ketone with a variety of reagents were unsuccessful, however, LAH reduced the ketone at −78 °C giving the desired alcohol in 82% yield without affecting an ester group.[208]

Treatment of the sterically hindered enone in Table 12, entry 4 with LAH in refluxing Et_2O afforded the *endo*-allylic alcohol stereoselectively as a single product in 65% overall yield.[210]

The tricyclic ketone in entry 8 was reduced with LAH; the facial selectivity of the reduction was improved from 3:1 at r.t. to >6:1 by starting the reduction at 0 °C.[214] In the synthesis of taxa-4(20),11(12)-diene-2α,5α-diol, the reduction of the ketone in entry 11 with LAH proceeded with high stereoselectivity in nearly quantitative yield but unfortunately it was the wrong stereochemistry.[217] However, the reduction of the β-ketosulfone with LAH at −78 °C (entry 17) in the synthesis of (+)-goniofufurone was completely diastereoselective, unaffected by the configuration of the stereogenic center bearing the phenylsulphonyl group, and afforded the desired product in excellent yield.[223]

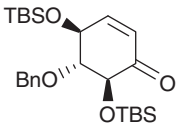
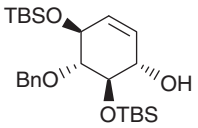
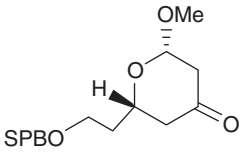
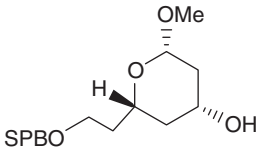
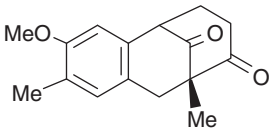
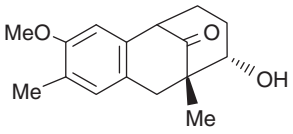
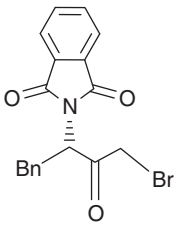
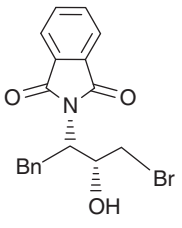
8.01.4.3 Reductions with Substituted $LiAlH_4$ and AlH_3

Similar to $NaBH_4$, LAH has also seen some modifications to alter its properties. Because it is already a very strong reducing agent, these modifications aimed to decrease its reducing power and increase its selectivity. The most common substituted aluminum hydrides are alkoxy aluminum hydrides. Some relatively common derivatives of $LiAlH_4$ are lithium tri *tert*-butoxy aluminum hydride ($Li(t\text{-}BuO)_3AlH$) and sodium bis(2-methoxyethoxy)aluminum hydride ($NaAlH_2(OCH_2CH_2OMe)_2$). The most commonly used related reagent, diisobutylaluminum hydride (DIBAL-H), is a derivative of alane (AlH_3); it is a very effective reducing agent which is widely utilized in the stereoselective reduction of ketones.

8.01.4.3.1 Lithium tri tert-butoxy aluminum hydride ($Li(t\text{-}BuO)_3AlH$) and sodium bis(2-methoxyethoxy)aluminum hydride ($NaAlH_2(OCH_2CH_2OMe)_2$)

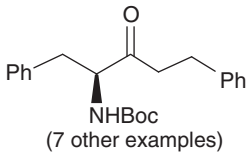
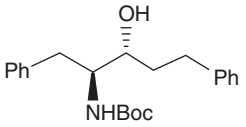
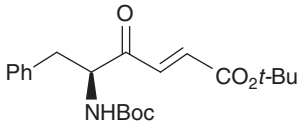
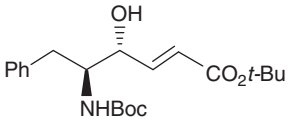
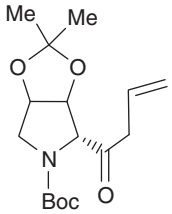
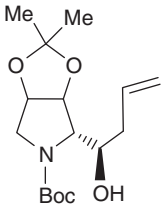
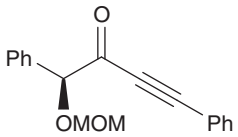
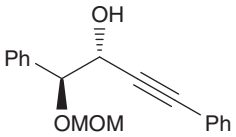
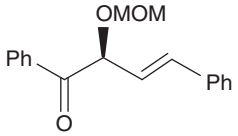
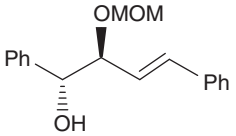
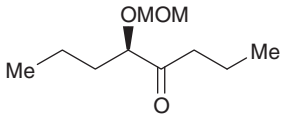
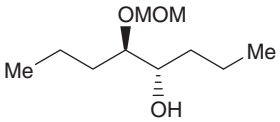
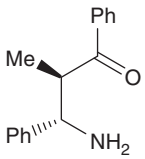
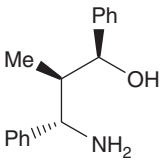
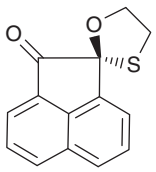
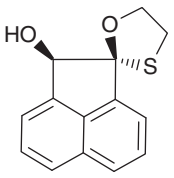
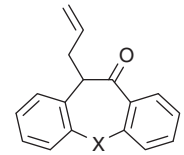
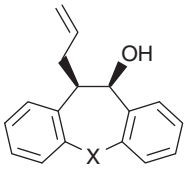
One of the mildest derivatives of LAH is lithium tri *tert*-butoxy aluminum hydride ($Li(t\text{-}BuO)_3AlH$). It is a very selective reducing agent with several unique applications in reduction.[224] Probably the most unique reaction is its ability to reduce acid chlorides[225] and Weinreb amides[226] to aldehydes. It reduces aldehydes and ketones effectively, but it is not commonly used in the reduction of aldehydes. However, because of its mildness and high steric demand, it is used frequently in the stereoselective reduction of ketones; some representative examples are listed in Table 13, entries 1–7. Many of the $Li(t\text{-}BuO)_3AlH$ reductions are carried out in

Table 13 Reductions with ($Li(t\text{-}BuO)_3AlH$) and ($NaAlH_2(OCH_2CH_2OMe)_2$)

Entries	Substrate	Product	Conditions	Yield (%)	References
1			$Li(t\text{-}BuO)_3AlH$, (2 equivalents), THF, −78 °C to r.t., 12 h	98	227
2			$Li(t\text{-}BuO)_3AlH$, THF, r.t., 3 h $LiBHsec\text{-}Bu_3$, THF, −78 °C to r.t. (3 h)	92 100:0 72 1:1	228
3			$Li(t\text{-}BuO)_3AlH$, THF, reflux	65	229
4			$Li(t\text{-}BuO)_3AlH$ (2 equivalents), THF, −20 °C, 30 min	60 >95:5	230

(*Continued*)

Table 13 Continued

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
5	 (7 other examples)		$Li(t\text{-}BuO)_3AlH$, EtOH, −78 °C	96 >95:5	231
6			$Li(t\text{-}BuO)_3AlH$, EtOH, −78 °C, 2 h	87 >95:5	232
7			$Li(t\text{-}BuO)_3AlH$, THF, −78 °C, 4 h	81 95:5	134
8			$NaAlH_2(OCH_2CH_2OMe)_2$, CH_2Cl_2, −78 °C	88 *anti*:*syn* 5:1	234
9				85 *anti*:*syn* 19:1	
10				85 *anti*:*syn* 11:1	
11			$NaAlH_2(OCH_2CH_2OMe)_2$, toluene, −78 °C	93	235
12		 Major	$NaAlH_2(OCH_2CH_2OMe)_2$ Et_2O, 0 °C	77 91:9	236
13	 X = O, S, CH_2, NMe		$NaAlH_2(OCH_2CH_2OMe)_2$, THF, −30 °C to r.t., 6 h	87–96	237

THF as in the reduction of a cyclic enone[227] (entry 1), a cyclic saturated ketone[228] (entry 2), a selective reduction of one of the ketones of a dione[229] (entry 3), and the reduction of an acyclic α-bromoketone[230] (entry 4); all these reductions were performed in very high stereoselectivity and excellent yields. Hoffman and coworkers[231] developed a highly stereoselective reduction of a series of α-carbamate-protected amino ketones using Li(*t*-BuO)$_3$AlH in ethanol at −78 °C (**Table 13**, entry 5). The choice of ethanol as a solvent in reduction with Li(*t*-BuO)$_3$AlH was unprecedented but proved effective; the yields were very high and the reduction was highly selective giving only one detectable diastereomer by NMR. The typical reduction in THF at −78 °C was nonselective giving a 1:1 mixture of two isomers. The selective formation of the *anti*-product may be rationalized by chelation control. A possible explanation for this outcome is that under these conditions, the interaction of the *tert*-butoxy groups with EtOH may result in formation of a different reducing species. It is also possible that the polar protic solvent may improve the chelation of the reagent with the α-carbamate-protected amino group. Luthman and coworkers[232] used this procedure successfully with similar results in the reduction of an α-Boc-protected amino ketone (**Table 13**, entry 6) to obtain almost exclusively the *anti*-product. However, Lei, Wei, and coworkers[134] studied the reduction of an α-Boc-protected amino ketone (**Table 13**, entry 7) and found the reduction with Li(*t*-BuO)$_3$AlH in THF at −78 °C to give better yield and higher selectivity than the reaction in EtOH at −78 °C.

Sodium bis(2-methoxyethoxy)aluminum hydride [NaAlH$_2$(OCH$_2$CH$_2$OMe)$_2$, also known as SMEAH, Vitiride or Red-Al] is another LAH derivative. It is, however, a very strong reducing agent, comparable in strength to LAH but unlike LAH it is nonpyrophoric, so it is somewhat easier and safer to use and handle.[233] As with many modified reagents, it is not commonly used in reduction of aldehydes, but widely used in the reduction of several other functional groups such as esters, lactams, lactones, acid chlorides, anhydrides, nitriles, imines, and oximes. It can be used in hydrocarbon solvents such as toluene and in ether solvents such as THF and Et$_2$O and in CH$_2$Cl$_2$. SMEAH is more bulky than LAH and it has been used to perform many stereoselective reductions of cyclic and acyclic ketones with high selectivity. Several examples of the use of NaAlH$_2$(OCH$_2$CH$_2$OMe)$_2$ in stereoselective reduction of ketones are listed in **Table 13**, entries 8–13. The stereoselectivity from reduction of acyclic ketone with NaAlH$_2$(OCH$_2$CH$_2$OMe)$_2$ is enhanced by the presence of chelating atoms or groups at the α- or β-positions. For example the reduction of ketones bearing an α-MOM group with NaAlH$_2$(OCH$_2$CH$_2$OMe)$_2$ gave the *anti*-products in high diastereomeric ratios ranging from 5 to 20:1 in good to excellent yields[234] (**Table 13**, entries 8–10). The reduction of the β-amino ketone[235] (**Table 13**, entry 11) was also very highly selective to give the *syn, anti*-product exclusively in 93% yield. In the absence of a chelating atom, the reaction proceeds to form the *syn*-product as in the case of the α-allyl ketone (**Table 13**, entry 13), which was reduced with NaAlH$_2$(OCH$_2$CH$_2$OMe)$_2$ to give the product with complete *syn*-diastereoselectivity in excellent yield.[237]

8.01.4.3.2 Diisobutylaluminum hydride [(i-Bu)$_2$AlH, DIBAL-H, DIBAL or DIBAH]

Diisobutylaluminum hydride (known commonly as DIBAL or DIBAL-H) is a very unique and versatile reducing agent. Unlike LAH and NaBH$_4$, it is Lewis acidic, so it reacts quickly with electron-rich functional groups and slowly with electron-poor ones. It is less reactive than LAH but more sterically hindered, thus it demonstrates increased chemo- and stereoselectivity compared to LAH. It is soluble in hydrocarbon solvents like toluene and CH$_2$Cl$_2$ and it is used in both regularly. It also dissolves in ethers such as Et$_2$O and THF, however mixing with ethers could be exothermic (because of its Lewis acidity) and it is advisable to cool the mixture before mixing. DIBAL-H is neither compatible with water nor alcoholic solvents. It reacts violently with water and alcohols producing hydrogen gas, so caution should be exercised to avoid contact with water or alcohols.[238]

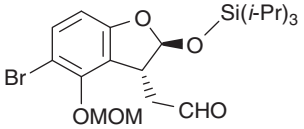
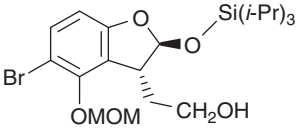
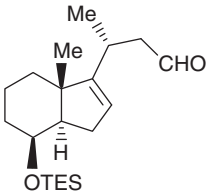
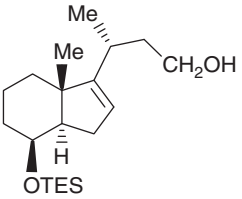
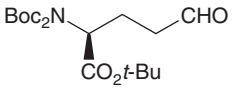
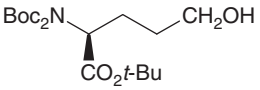
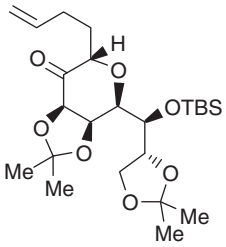
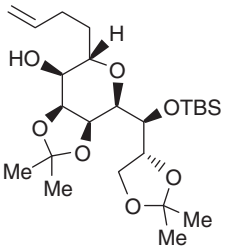
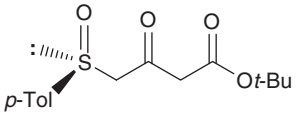
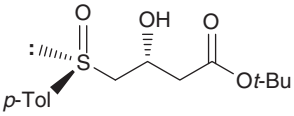
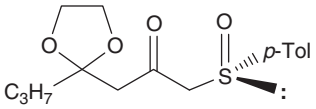
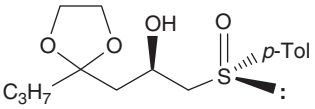
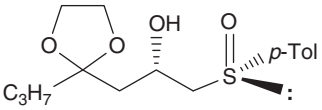
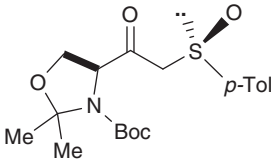
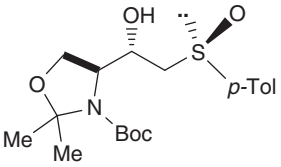
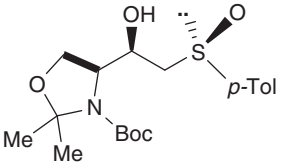
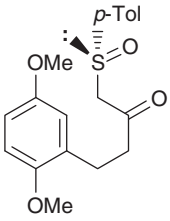
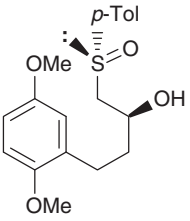
It was first reported by Ziegler,[239] and its early use in reduction was reported by Miller and coworkers.[240] Yoon and Gyoung[241] conducted a detailed study of the reducing properties of diisobutyl aluminum hydride with a wide variety of organic compounds with different reducible groups. It is a strong reducing agent and has become one of the most used aluminum reducing agents. Diisobutylaluminum hydride reduces aliphatic and aromatic aldehydes and ketones rapidly and quantitatively to the corresponding alcohols. It also reduces α,β-unsaturated aldehydes and ketones such as cinnamaldehyde, methyl vinyl ketone, and isophorone rapidly and cleanly to the corresponding allylic alcohols. It reduces other functional groups including acid chlorides, carboxylic esters, lactones, epoxides, nitriles, and tertiary amides.

Because of its selectivity and steric bulkiness, it is widely used in the stereoselective reduction of ketones and in the reduction of lactones to lactols. Most reaction are carried out at low temperature (−78 °C but can be as high as 0 °C). The solvents of choice are toluene and CH$_2$Cl$_2$ but Et$_2$O and THF are also used alone or in combination with toluene. Several representative examples are listed in **Table 14** for the reduction of aldehydes (entries 1–3) and ketones (entries 4–22).

The reduction of β-ketosulfoxides with DIBAL-H or DIBAL-H/ZnCl$_2$ has been established by Solladie and coworkers[258] as a reliable procedure for obtaining the corresponding alcohols with opposite stereoselectivity. DIBAL-H is able to coordinate to the sulfoxide group and deliver the hydride intramolecularly, but in the presence of ZnCl$_2$, chelation of Zn is favored and DIBAL-H delivers the hydride externally to the chelated species thus giving the opposite stereochemistry. The procedure has been used successfully in many reductions of β-ketosulfoxides with remarkable stereoselectivity (**Table 14**, entries 5–12).

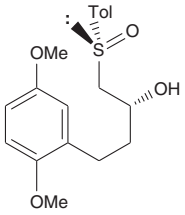
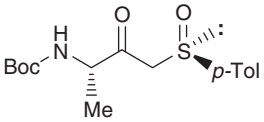
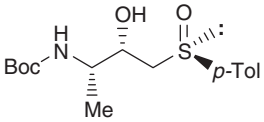
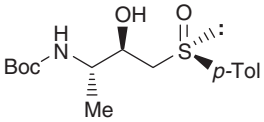
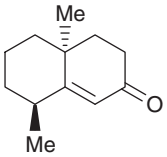
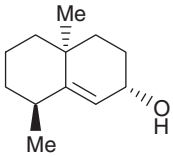
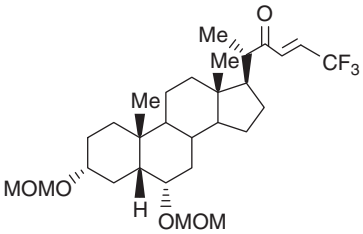
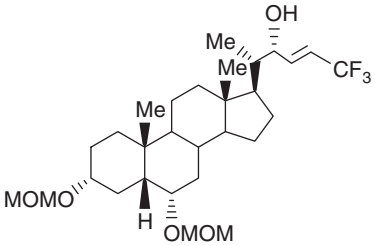
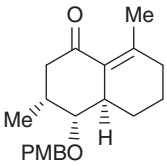
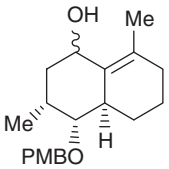
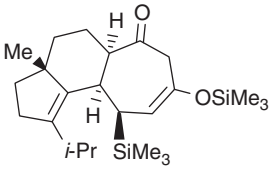
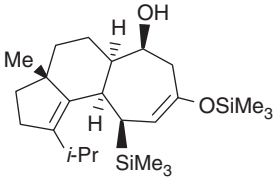
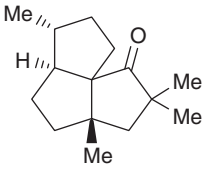
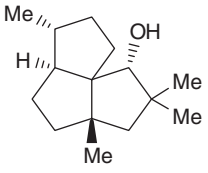
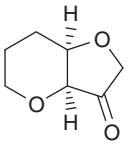
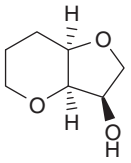
DIBAL-H is very effective in the regioselective reduction of α,β-unsaturated ketones to allylic alcohols (entries 13–15). The other examples in the table show the effective use of DIBAL-H as a selective reducing agent with high levels of stereocontrol.

Table 14 Reductions with $(i\text{-Bu})_2$AlH (DIBAL-H)

Entries	Substrate	Product	Conditions	Yield (%)	References
1			DIBAL-H, THF-hexane, −43 to 0 °C 1 h	94	242
2			DIBAL-H, CH_2Cl_2, −78 °C, 45 min	98	243
3			DIBAL-H, Et_2O, 0 °C; 1 h	80	244
4			DIBAL-H, Toluene/THF, −78 °C, 3 h	99	72
5			DIBAL-H, Toluene/THF, −75 °C, 45 min	67	245
6			DIBAL-H	78 (*de* >95)	246
			1. DIBAL-H ZnI_2,THF, −78 °C 2. Oxalic acid, THF, H_2O	77	
7			DIBAL-H (1.1 equivalents), THF, −78 °C,	>95% yield	247
8			DIBAL-H, $ZnCl_2$ (1 equivalent), THF, −78 °C	>95% yield	
9			DIBAL-H (1.1 equivalents), THF −78 °C, 3 h	89 (96:4)	248

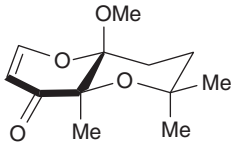
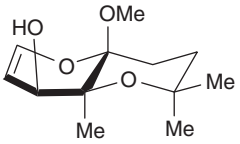
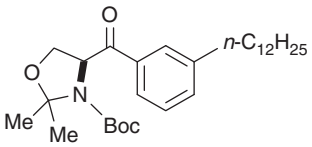
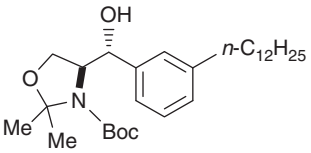
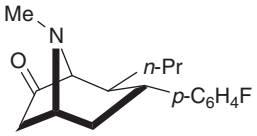
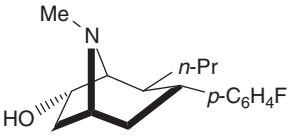
(*Continued*)

Table 14 Continued

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
10			DIBAL-H, $ZnBr_2$ (3 equivalents), Tol/THF −78 °C	98 (only isomer)	
11			DIBAL-H (5 equivalents), THF, −78 °C	99 (91:9)	249
12			DIBAL-H (3 equivalents), $ZnBr_2$ (1.1 equivalents), Tol/THF, −78 °C	98 (10:90)	
13			DIBAL-H, THF-DME, −78 °C, 5 min	>95% yield 96 *de*	250
14			DIBAL-H, THF, −78 °C, 30 min	85 (9:1) 69 isolated pure	251
15			DIBAL-H, THF, −98 °C, 1 h	93 (1:1)	160
16			DIBAL-H, Et_2O, −80 °C,	72	252
17		 Major	DIBAL-H, CH_2Cl_2, −78 to 25 °C, 20 h	88 (3.7:1)	253
18			DIBAL-H (1.5 equivalents), PhMe −78 °C, 5 min	63	254

(*Continued*)

Table 14 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
19			DIBAL-H (1 equivalent), PhMe, CH_2Cl_2, −78 °C	75	255
20			DIBAL-H, THF, 0 °C, 0.5 h	94 (26:1)	256a
			DIBAL, Toluene, r.t., 0.5 h	96 (93:7)	256b
21			DIBAL-H, CH_2Cl_2, 0 °C	No reported yield	257

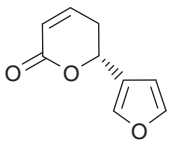
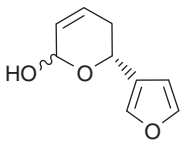
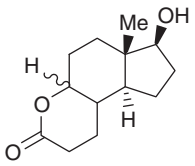
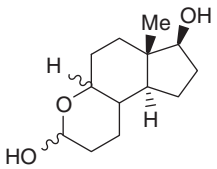
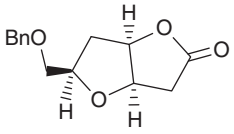
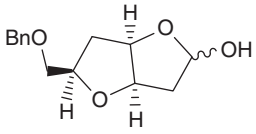
8.01.4.3.3 Reduction of lactones to lactols

Lactones, being cyclic esters, are normally reduced with strong reducing agents such as LAH or $LiBH_4$ to diols. The partial reduction of a lactone to a lactol (a cyclic hemiacetal) is more difficult since lactols are the equivalent of hydroxy aldehydes and aldehydes can be reduced with even the weakest of common reducing agents.

Diisobutylaluminum hydride (DIBAL-H) is usually the reagent of choice for the effective reduction of lactones to lactols; LiBH*sec*-Bu_3 is another reagent that is used similarly but rarely. Solvents such as toluene, CH_2Cl_2, and THF are used in this reduction at low temperature (−78 °C) in most cases. The examples listed in Table 15 highlight the reduction of several lactones to lactols during the synthesis of a wide variety of diverse natural and unnatural compounds including: total synthesis of (+)-estradiol[75] (entry 2), the enantioselective total synthesis of the nonisoprenoid sesquiterpene (−)-kumausallene[260] (entry 3), total synthesis of crispatenine[261] (entry 4), synthesis of bryostatins ABH-14[262] (entry 5), synthesis of the C1–C9 fragment of callipeltoside-A[265] (entry 8), synthesis of 2-deoxy-2-fuoropentoses[266] (entry 9), asymmetric total synthesis of (+)-quebrachamine[267] (entry 10), enantioselective synthesis of (−)-citreoviral[268] (entry 11), and the stereoselective synthesis of the enantiomeric samin-type of lignin[270] (entry 13).

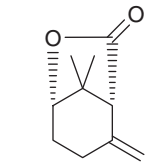
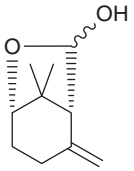
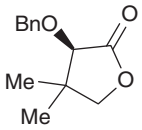
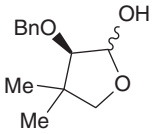
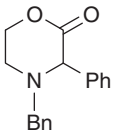
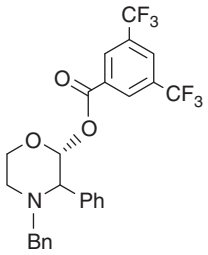
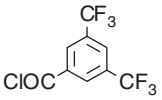
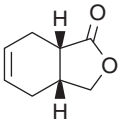
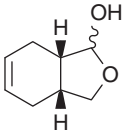
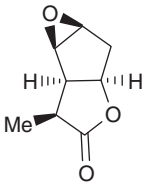
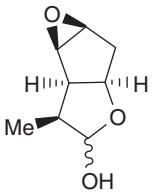
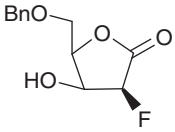
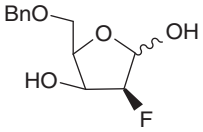
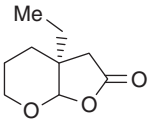
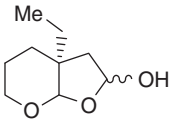
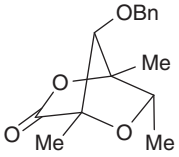
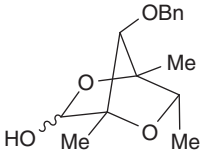
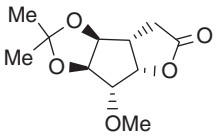
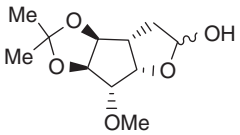
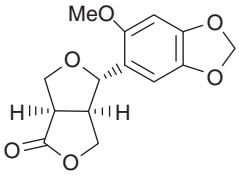
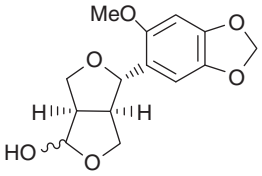
The reduction of the lactone, 3-(*S*)-phenyl-4-benzyl-2-morpholinone (Table 15, entry 6), a starting material in synthesis of the hNK-1 receptor antagonist L-742694, to the corresponding lactol was effectively accomplished using LiBH*sec*-Bu_3. The lithium salt of the lactol is trapped directly with a substituted benzoyl chloride to give the substituted benzoyl ester in 79% combined yield for the two steps.[263]

Table 15 Reduction of lactones to lactols

Entries	Lactone	Lactol	Conditions	Yield (%)	References
1			DIBAL-H, PhMe, CH_2Cl_2 −78 °C,	98	259
2			DIBAL-H, CH_2Cl_2, −78 °C	70	75
3			DIBAL-H, THF, −78 °C	99	260

(*Continued*)

Table 15 Continued

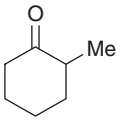
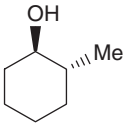
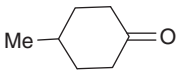
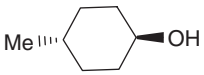
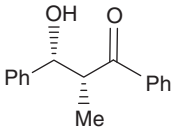
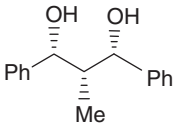
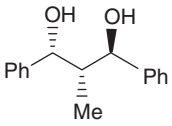
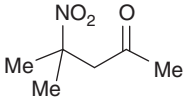
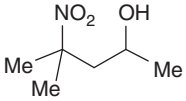
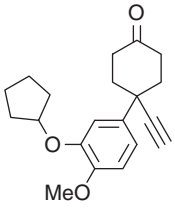
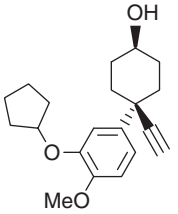
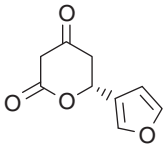
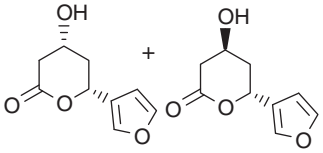
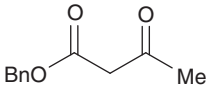
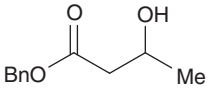
Entries	*Lactone*	*Lactol*	*Conditions*	*Yield (%)*	*References*
4	 (+)-Karahana lactone		DIBAL-H, toluene, –70 °C; 45 min	95	261
5			DIBAL-H, THF, –35 °C, 5 h, MeOH quench at –78 °C	88	262
6			LiBH*sec*-Bu_3 THF, –78 °C, 45 min; then 	79	263
7			DIBAL-H, (1.1 equivalents), Fast addition, toluene, –78 °C	92	264
8			DIBAL-H, toluene-CH_2Cl_2, –78 °C; 3 h	91	265
9			DIBAL-H, CH_2Cl_2, –78 °C; 1 h	68	266
10			DIBAL-H, Et_2O, –78 °C; 1 h Warm to r.t., then 1M HCl	79	267
11			DIBAL-H, hexane-CH_2Cl_2, –78 °C	69	268
12			DIBAL-H, CH_2Cl_2, –78 °C 40 min	84	269
13			DIBAL-H, Toluene –75 °C; 1 h	70	270

8.01.5 Reductions of Aldehydes and Ketones with Boranes

Borane (BH_3) is unstable in the monomeric form; it forms a more stable dimer, diborane (B_2H_6). The first report on the use of B_2H_6 in the reduction of organic compound came in 1939 with the pioneering publication of Brown, Schlesinger, and Burg that described the fast reduction aldehydes and ketones with diborane even at low temperatures.[2] It was this discovery that marked the beginning of the era of the hydride reductions in organic chemistry.

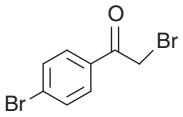
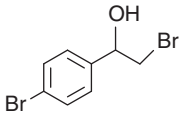
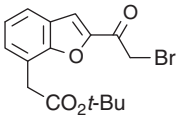
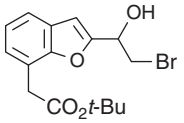
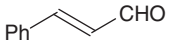
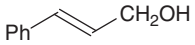
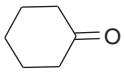
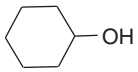
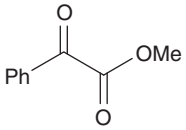
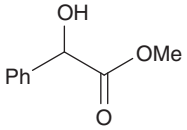
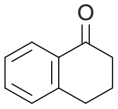
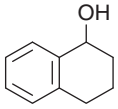
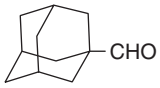
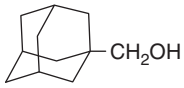
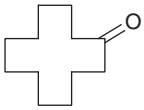
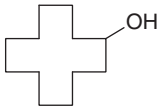
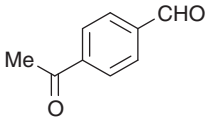
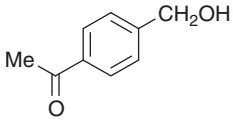
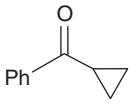
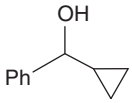
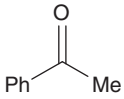
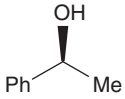
Due to the difficulty in handling diborane, several stable BH_3-Lewis base complexes with ethers, amines, and alkyl sulfides were developed, which made it easier and more convenient to use and handle borane in chemical reactions. The main use of boranes is for the hydroboration of alkenes, one of the most versatile and useful reactions in organic synthesis.[115,271] Borane also reduces aldehydes, ketones, lactones, epoxides, acids, tertiary amides, and nitriles but does not reduce esters. Borane has become more widely used in the reduction of prochiral ketones with the development of the remarkable catalytic oxazaborolidine asymmetric reductions (Section 8.01.10.2). It is not usually the reagent of choice in reducing aldehydes; there are much fewer reports on its use in the reductions of aldehydes compared to $NaBH_4$, particularly in the recent literature. There are however more applications of borane for the reduction of ketones. Several representative examples are listed in **Table 16**. Cha and coworkers[272] reduced several substituted cyclic ketones with BH_3-THF at reflux temperature to produce the thermodynamically more stable diastereomers. Although the reactions at 0 °C and 25 °C give mixtures of diastereomers regardless of time, the reactions at reflux are dependent on time. The stereoselectivity improves consistently with time to afford the thermodynamically more stable diastereomeric alcohols exclusively; the only exception is the norcamphor (**Table 16**, entries 1–2).

Table 16 Reduction of aldehydes and ketones with boranes and borane complexes

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			BH_3-THF, Reflux, 5 day	81 >99.5 *trans*	272
2			BH_3-THF, Reflux, 5 day	82 >99.5 *trans*	
3			BH_3-Me_2S, THF, 0 °C to r.t., 12 h at r.t.	81	273
4			$LiBH_4$, MeOH, 0 °C to r.t., 7 h at r.t.	95	
5			BH_3-THF (1.4 equivalents), THF, 20 °C, 3.5 h	86	105
6			BH_3-THF, −40 °C	80 96 *de*	274
7			BH_3-NH_3, −5 °C	90 *syn*:*anti* 3:1	275
8			$B_{10}H_{14}$ (0.3 equivalent), pyrrolidine (0.1 equivalent), $CeCl_3 \cdot 7H_2O$ (0.1 equivalent), MeOH, 50 °C, 1.5–2 h	98	276

(*Continued*)

Table 16 Continued

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
				92	
9			B_2H_6,THF, 0 °C, 30 min	80	277
10			$NH_3 \cdot BH_3$, H_2O, 20 min	94	278
11			$NH_3 \cdot BH_3$, H_2O, 1 h	91	
12			$NH_3 \cdot BH_3$, H_2O, 30 min	91	
13			$Me_2NH{\cdot}BH_3$ (2 equivalents), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol%), THF, 70 °C, 24 h	77	279
14			diMe-Imd-BH_3 **(1)** EtOAc, silica gel, 1 h	86	280
15			diMe-Imd-BH_3 **(1)** EtOAc, silica gel, 96 h	89	
16			diMe-Imd-BH_3 **(1)** EtOAc, silica gel, 1 h	82	
17			diMe-Imd-BH_3 **(1)** EtOAc, silica gel, 96 h	73	
18			**2** (10 mol%) catecholborane, 4Å MS, toluene, −48 °C 24 h	88 98 *ee*	281

The Lewis acidity and ability to chelate with substituents with electronegative atoms such as oxygen and nitrogen affect the stereochemical outcome of the reduction. Thus the reduction of (+)-(2*R*,3*R*)-3-hydroxy-2-methyl-1,3-diphenylpropan-1-one (Table 16, entries 3–4) with BH_3-Me_2S in THF reported by Badia and cowokers[273] gave the 1,3-*syn*-diol preferentially. The reaction was fast at reflux temperature but it showed poor stereoselectivity of 55/45; carrying out the reduction at room temperature was slower (12 h) but resulted in full stereoselectivity leading to the 1,3-*syn*-isomer as the only detectable product. However, the use of $NaBH_4$ in MeOH proceeded with low selectivity, whereas $LiBH_4$ gave the 1,3-*anti*-isomer cleanly. Also the reduction of a cyclic ketone intermediate from the synthesis of SB-222618 (Table 16, entry 6)[274] was more selective with borane-THF (96% *de*) than $LiBH_4$ (93% *de*) and $NaBH_4$ (85% *de*), whereas DIBAL-H was much less selective.

Yoon and coworkers[276] found the combination of decaborane and pyrrolidine in the presence of $CeCl_3{\cdot}7H_2O$ in methanol to be effective in the chemoselective reduction of ketones exemplified by the reduction of a β-ketoester and α-bromoketone (Table 16, entry 8). However, Bodor and coworkers[277] carried out the reduction of another α−bromoketone with diborane in THF in their synthesis of bufuralol analogs (Table 16, entry 9).

Ammonia-borane (NH_3-BH_3) is a thermally stable, water-soluble, and easily handeled solid. Zhang and coworkers[278] developed a procedure for the reduction of aldehydes and ketones to alcohols using ammonia-borane as a reducing agent in neat water

as a solvent. In addition to typical reduction of aldehydes and ketones, the procedure was applied successfully to the reduction of α,β-unsaturated aldehydes and ketones to allylic alcohols and α- and β-keto esters to hydroxy esters with better selectivity than $NaBH_4$. The reduction products are usually isolated in high yields via extraction with organic solvents such as EtOAc (Table 16, entries 10–12). Another stabilized borane, dimethylamine-borane ($Me_2NH.BH_3$) in combination with $[Ru(p\text{-cymene})Cl_2]_2$ catalyst was reported[279] as a reagent for the reduction of ketones, aldehydes, imines, oximes, nitriles, nitroarenes, and alkenes. The reductions of several ketones, including tetralone (Table 16, entry 13) were reported in good to excellent yields.

Curran and Taniguchi[280] studied the use of *N*-heterocyclic carbene boranes (NHC-boranes) such as 1,3-dimethylimidazol-2-ylidine trihydridoborane (diMe-Imd-BH_3, **1**, Figure 1) as hydride donors for the reduction of aldehydes and ketones, and discovered that the reactivity of simple carbonyl groups toward NHC-boranes can be boosted by adding silica gel. Earlier work had shown that imines are reduced but typical aldehydes or ketones are not sufficiently electrophilic to be reduced by diMe-Imd-BH_3. The diMe-Imd-BH_3 does not react with silica gel even after 48 h contact, so it was postulated that the role of the silica gel is to activate the carbonyl group and provide a proton for the product to complement the hydride from the NHC-borane.

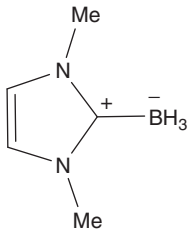


Figure 1 diMe-Imd-BH_3 (**1**). Reproduced from Taniguchi, T.; Curran, D. P. *Org. Lett.* **2012**, *14*, 4540–4543, with permission from ACS.

The reaction works well with aldehydes and aryl methyl ketones, but sterically hindered ketones react much slower. In a typical experiment, equimolar amounts of aldehyde or ketone and diMe-Imd-BH_3 are mixed in EtOAc (4 $mmol^{-1}$) with flash chromatography silica gel (1 g $mmol^{-1}$) and the mixture stirred at r.t. Several examples that show the reduction of aldehydes and ketones using this procedure as well as selective reduction of aldehyde in the presence of a ketone are highlighted in Table 16, entries 14–17.

A patented procedure by Li and Falck[281] describes a class of thiourea ligands that can be used as catalysts in a method for the enantioselective reduction of prochiral ketones with catecholborane to produce enetiomerically enriched secondary alcohols. There are many examples of catalysts and reductions listed in the patent; one of the examples is the enantioselective reduction of acetophenone in 88% yield and 98% *ee* using catecholborane and the thiourea derivative **2** (Table 16, entry 18) (Figure 2).

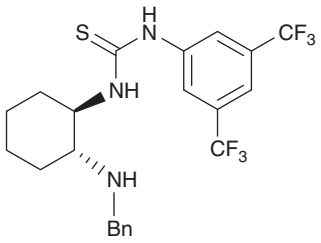


Figure 2 Thiourea derivative **2**.

8.01.6 Chemoselective Reductions of Aldehydes versus Ketones

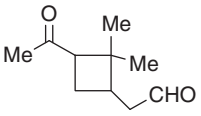
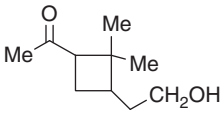
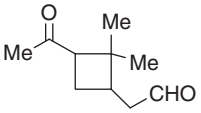
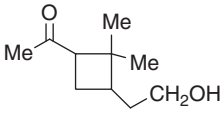
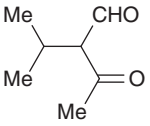
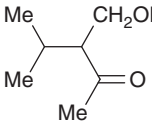
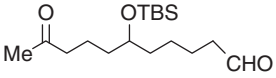
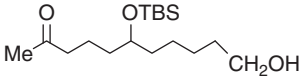
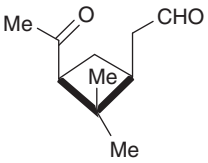
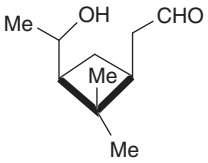
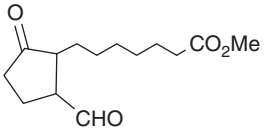
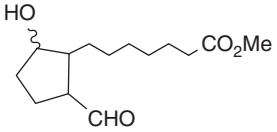
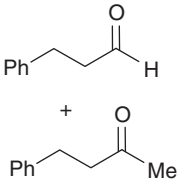
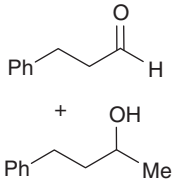
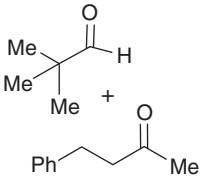
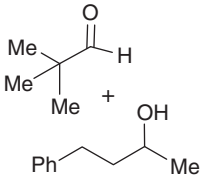
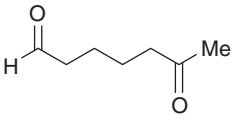
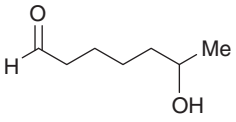
8.01.6.1 Selective Reduction of Aldehydes

Aldehydes are more reactive toward reduction with metal hydrides than ketones. Brown and coworkers[14] showed that $NaBH_4$ reduces benzaldehyde approximately 400 times faster than acetophenone. This higher reactivity of aldehydes prompted several research groups to study the selective reduction of aldehydes in the presence of ketones. As a result several reagents and conditions were developed to accomplish this task; some of the earlier reports include the use of the following reagents and reagent combinations: Bu_4NBH_3CN/HMPA/acid at 25 °C,[282] $NaBH(OAc)_3$,[112a] $Bu_4NBH(OAc)_3$,[112b] $LiBu_2$–9-BBN,[283] B-alkyl-9-BBN,[284] Bu_3SnH,[285] Et_4NBH_4 in CH_2Cl_2,[286] BER,[175] $NaBH(OAr)_3$,[287] $NaBH_4/CeCl_3$/DMSO,[288] and KPh_3BH.[289]

In 1988 Ward and Rhee[80b] developed a procedure for the selective aldehyde reductions using $NaBH_4$ in EtOH/CH_2Cl_2 solvent system at −78 °C. They determined the reactivity of carbonyl groups under these conditions to be in the order: aldehydes > conjugated aldehydes > ketones > conjugated enones. Typical aldehydes were reduced completely in 1 h at −78 °C with excess

sodium borohydride in 30% EtOH in CH_2C1_2. Various aldehydes were reduced selectively in the presence of enals, ketones, and enones. One of the examples is the reduction of the ketoaldehyde [2-(3-acetyl-2,2-dimethylcyclobutyl)acetaldehyde] in Table 17, entry 1, in which the ratio of aldehyde to ketone reduction was >97:3. The conditions also proved useful in the reduction of saturated ketones in the presence of α,β-enones[51] (see example in Table 2, entry 15).

Table 17 Chemoselective reductions: aldehydes versus ketones

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			Excess $NaBH_4$, 30% EtOH in CH_2Cl_2, −78 °C	>97	80b
2			$Zn(BH_4)_2$, THF, −10 °C, 5 min	100	290
3			$Zn(BH_4)_2$, THF, −10 °C, 5 min	100	
4			$NaBH(HFIP)_3$ (in THF, 3 equivalents), HFIP, 25 °C, 1.5 h	94	291
5			$CeCl_3$ (1 mol), $NaBH_4$ (1.5 mol), EtOH-H_2O (1:1.5), −15 °C	95 (78 isolated)	292
6			$CeCl_3$ (1 mol), $NaBH_4$ (1.5 mol), EtOH-H_2O (1:1.5), −15 °C	85 75 isolated	
7			1. Et_2AlSPh (1.1 equivalents), toluene, −78 °C 2. DIBAL-H, −78 °C	89	293
8				91	
9				69	

Ranu and Chakraborty[290] reported the use of zinc borohydride (prepared from $NaBH_4$ and $ZnCl_2$) in THF at −10 °C for the selective reduction of aldehydes to primary alcohols in the presence of ketones. For example, the aldehyde group of two ketoaldehydes (Table 17, entries 2 and 3) were reduced with high selectivity. Additional examples of competition reactions with mixed aldehydes and ketones have also demonstrated preferential reduction of aldehydes in the presence of ketones.

Toshima and coworkers[291] examined the use of sodium tris(hexafluoroisopropoxy)borohydride, [$NaBH[OCH(CF_3)_2]_3$ or $NaBH(HFIP)_3$] in the selective reduction of aldehydes over ketones. The reagent is prepared from the reaction of $NaBH_4$ with excess hexafluoroisopropanol (HFIP) in THF at 0 °C for 15 h, and the product is used as a 1 M solution in THF. The reagent shows very good selectivity for the reduction of aldehydes, whereas ketones alone or in mixtures with aldehydes were not reduced at all or reduced very slowly (Table 17, entry 4).

The use of Luche's reagent in the selective reduction of an α,β-unsaturated aldehyde in the presence of a ketone in Wender's synthesis of (+)-aphanamol-I[90] was highlighted in Section 8.01.3.1.3 (Table 4, entry 8). There are also many additional reagent combinations and modification that describe procedures for the selective reduction of aldehydes in the presence of ketones; some of these are highlighted in Section 8.01.3.3 and Table 10.

8.01.6.2 Selective Reduction of Ketones

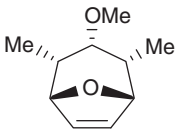
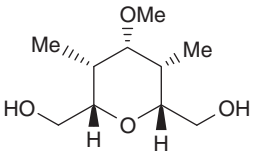
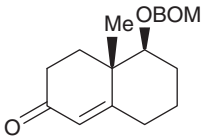
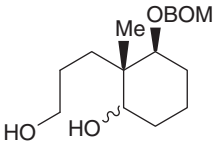
Because aldehydes are more reactive than ketones, it is possible to develop all the known procedures for the selective reduction of aldehydes in the presence of ketones. It is not surprising that the opposite selectivity is not common. The more common approach to reduce a ketone selectively in the presence of an aldehyde is to protect the aldehyde. However, there are a few reported procedures that were developed to accomplish this task without aldehyde protection. In 1979, Luche and Gemal[292] developed a modified reagent that was successful in reducing ketones in the presence of saturated aldehydes. It was postulated that the selectivity is a result of selective conversion of aldehydes to their hydrates under the reaction conditions. The best conditions are to reduce the ketoaldehyde (or equimolar mixture of an aldehyde and a ketone) in aqueous ethanol (1:1.5 EtOH-H_2O) in the presence of 1 mol of $CeCl_3$ and 1.5 mol of $NaBH_4$ at −15 °C. Under these conditions, the ketone is reduced selectively in high yield without, or with minimum, aldehyde reduction (see examples in Table 17, entries 5–6). The addition of $CeCl_3$ is essential to the success of the reaction because considerable aldehyde reduction occurs in its absence. Conjugated aldehydes are the exception and that was explained by slow hydrate formation.

A more recent procedure for the selective reduction of ketones over aldehydes was developed by Marko and coworkers.[293] They observed that when 1 equivalent of diethylaluminum benzenethiolate (Et_2AlSPh) was reacted with a mixture of hydrocinnamaldehyde and benzylacetone, only the aldehyde reacted to form the O,S-aluminum acetal and the ketone remained unreacted. Thus, an optimized procedure for selective reduction of ketones in the presence of aldehydes was devised in which a ketoaldehyde (or a mixture of aldehyde and ketone) is treated with 1.1 equivalents of Et_2AlSPh in toluene at −78 °C, and the subsequent reduction with DIBAL-H. The procedure was demonstrated successfully on several examples (Table 17, entries 7–9) and was applied to reduction of esters in the presence of aldehydes.

8.01.7 Direct Reductions of Aldehydes and Ketones Resulting from Oxidative Processes

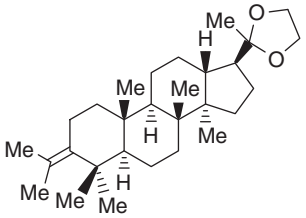
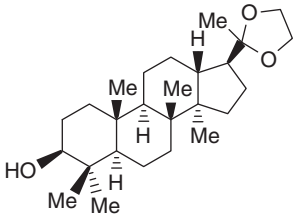
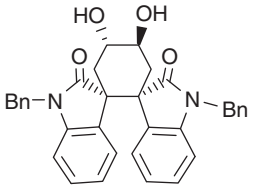
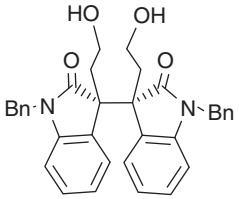
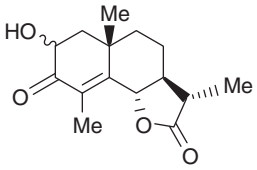
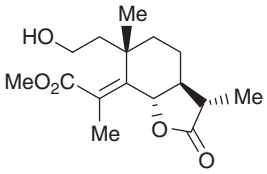
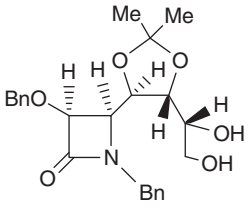
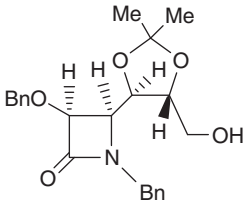
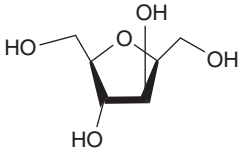
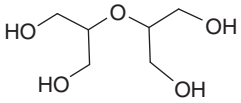
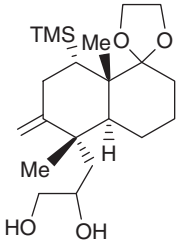
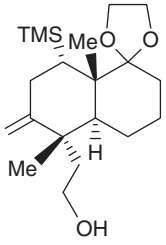
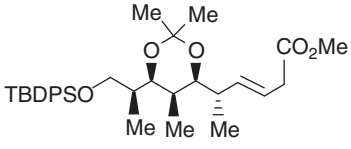
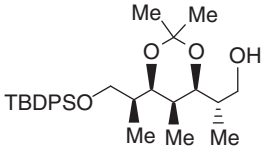
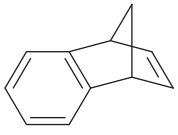
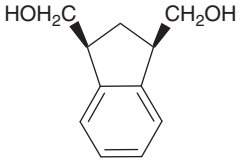
There are many reports in which olefinic groups (C=C), 1,2-diols (CHOH–CHOH) or α-hydroxycarbonyl compounds (CO–CHOH) are oxidatively cleaved then directly reduced to the corresponding alcohols. The C=C bonds are usually cleaved via ozonolysis or with $OsO_4/NaIO_4$, whereas the CHOH–CHOH and CO–CHOH bonds are cleaved via treatment with $NaIO_4$ or $Pb(OAc)_4$. Based on the location of the cleaved bond in the molecule the combined bond cleavage/reduction reactions may break into two molecules or may form diols or hydroxy acid intramolecularly. The aldehyde and/or ketone intermediate oxidation product(s) may be isolated or may be reduced directly after quick work up to afford the corresponding alcohol products. This synthetic strategy uses C=C, CHOH–CHOH and CO–CHOH bonds as latent moieties for introduction of alcohols late in a synthesis and for further structural elaboration and manipulation in complex syntheses. The choice of the metal hydride reducing agent is determined by the chemoelective outcome, but in most cases, either $NaBH_4$ or LAH was the reducing agent. There are many literature examples that exploit this strategy in organic synthesis; several illustrative examples are listed in Table 18.

Table 18 Direct reductions of aldehydes and ketones resulting from oxidative processes

Entries	Substrate	Product	Conditions	Yield (%)	References
1			1. O_3, CH_2Cl_2, MeOH (2:1.5), −60 °C 2. $NaBH_4$ (excess), −60 °C to r.t.	70	64
2			1. O_3, MeOH, −78 °C 2. $LiAlH_4$ THF −60 °C to r.t.	79	294

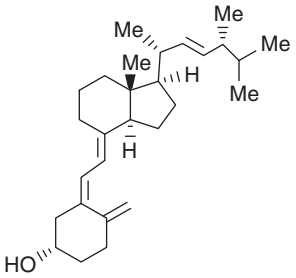
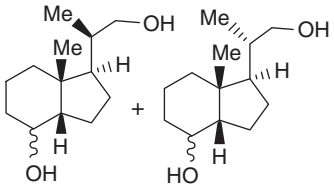
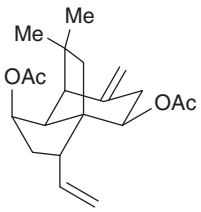
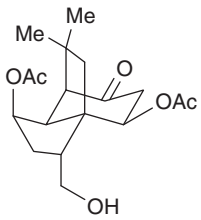
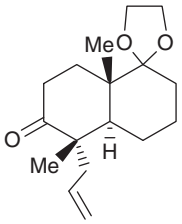
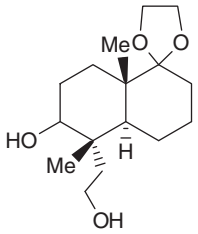
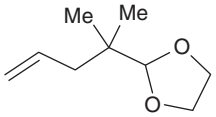
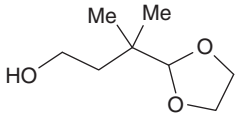
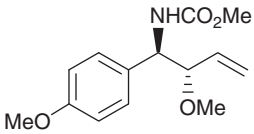
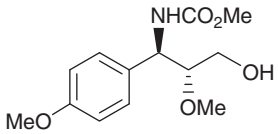
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Table 18 Continued

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
3			1. O_3, CH_2Cl_2, MeOH, −78 °C 2. $NaBH_4$, EtOH, 0 °C, 1 h; 25 °C, 1 h	95	48
4			1. $Pb(OAc)_4$, PhH 2. $NaBH_4$, MeOH	92	295
5			1. $Pb(OAc)_4$, MeOH, 0 °C (5 min); r.t. (25 min) 2. $NaBH_4$, MeOH, 0 °C (25 min)	67	296
6			1. $NaIO_4$, H_2O, MeOH 2. $NaBH_4$, MeOH	81	297
7			1. $NaIO_4$, H_2O, r.t. (dark) 2. $NaBH_4$, H_2O	96	298
8			1. $NaIO_4$, THF-H_2O (4:1), 23 °C, 30 min 2. $NaBH_4$,THF-EtOH (6:1), 0 °C, 20 min	94	299
9			1. O_3, MeOH, Py, then Me_2S 2. $NaBH_4$, MeOH	92	300
10			1. O_3, MeOH, $CHCl_3$ (1:1), −78 °C then Me_2S 2. $LiAlH_4$ THF, 0 °C, 48 h	70	301

(*Continued*)

Table 18 Continued

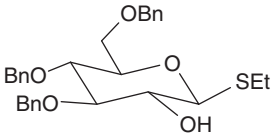
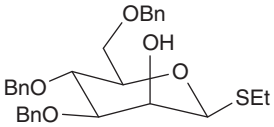
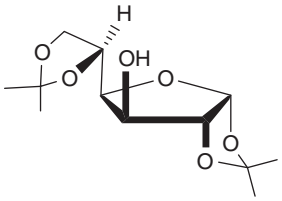
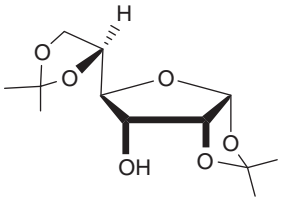
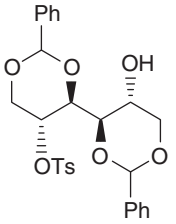
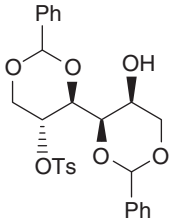
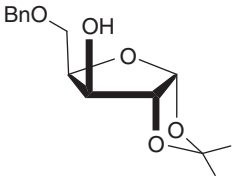
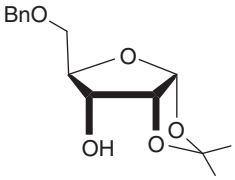
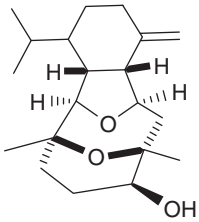
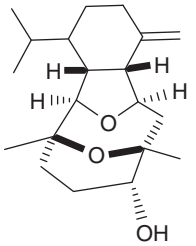
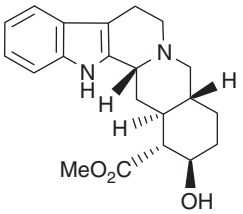
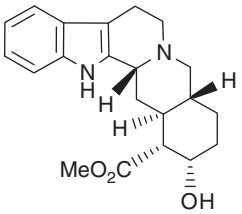
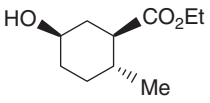
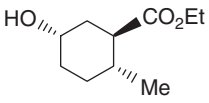
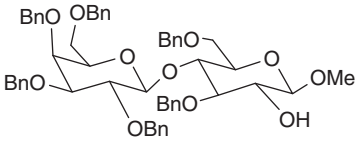
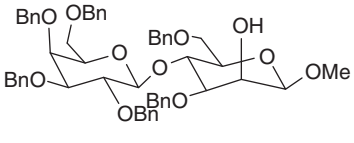
Entries	Substrate	Product	Conditions	Yield (%)	References
11			1. O_3, MeOH, Py, −78 °C then Me_2S 2. HCl-THF, 30 °C, 36 h 3. Chromatography 4. $NaBH_4$ MeOH, r.t., 20 min	67	34
12			1. O_3, CH_2Cl_2, −78 °C; Me_2S 2. $NaBH(OAc)_3$ (1.5 equivalents), THF	80	127
13			1. O_3, CH_2Cl_2, −78 °C 2. $LiAlH_4$ (3 equivalents), Et_2O, 0 to 25 °C, 1 h	65	302
14			1. OsO_4, $NaIO_4$, Et_2O–H_2O, r.t. 2. $NaBH_4$, MeOH, 0 °C	66	152
15			1. O_3, CH_2Cl_2, −78 °C 2. $NaBH_4$, CH_2Cl_2-MeOH, 0 °C	94	303

8.01.8 Inversion of the Stereochemistry of Secondary Hydroxy Groups

The inversion of the stereochemistry of chiral centers bearing secondary hydroxyl groups is a common process in organic synthesis. The most common procedure to accomplish this transformation is Mitsunobu reaction.[304] An alternative procedure for inversion of the stereochemistry of secondary hydroxyl group utilizes a two-step oxidation-reduction sequence. The secondary alcohol with the incorrect or undesired stereochemistry is oxidized to the corresponding ketone; the ketone is then reduced with the appropriate metal hydride reagent to form the secondary alcohol with the desired stereochemistry. The procedure is applicable to either absolute or relative stereochemistry; for example a racemic alcohol may be oxidized to the ketone then reduced enantioselectively to form one enantiomer. It can also be applied to converting one diastereomer into another. The oxidation product may be isolated and reduced in a separate step or may be reduced directly after work up. The procedure has been used in cases when the Mitsunobu reaction fails to affect the required inversion.[305] In other cases, it may be selected because it is easier to carry out compared to Mitsunobu reaction or because it affords better isolated yield. This oxidation-reduction sequence is more common in cyclic structures than acyclic ones, because it is easier to predict and control the reduction process in cyclic substrates. The selected examples in Table 19 show many cases of the inversion of secondary hydroxyl groups using this rather popular and effective procedure. In some examples (Table entries 1–7, and 9) the use of $NaBH_4$ was sufficient to afford the correct stereochemistry in high selectivity and yield. In some other cases (Table 10, entries 10, 12) $NaBH_4$ was nonselective.

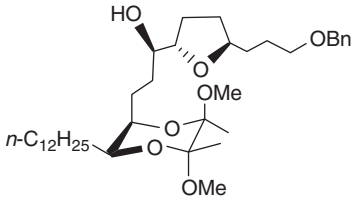
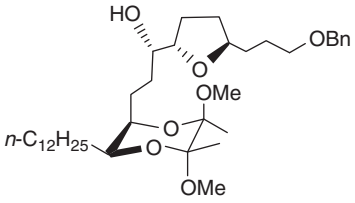
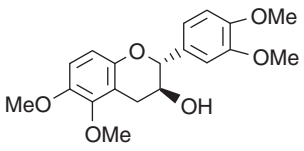
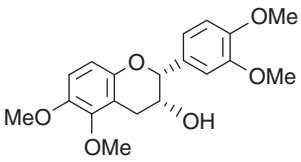
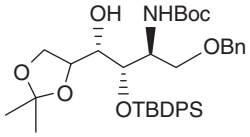
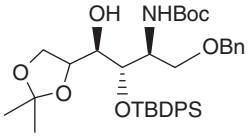
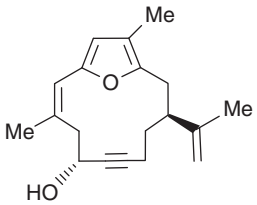
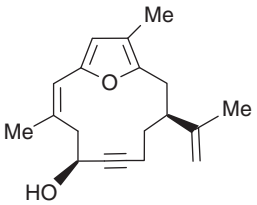
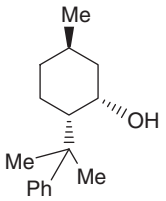
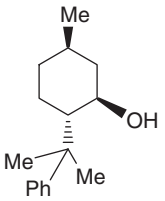
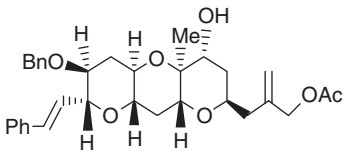
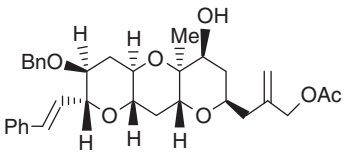
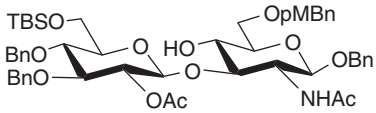
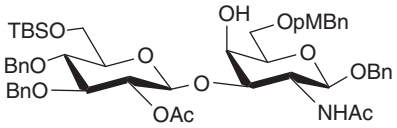
In the reduction of the ketone intermediate in the example in Table 19, entry 11, Kozikowski and coworkers[305] had to deal with a problem that may be encountered in the reduction of some enolizable ketones with LiBH*sec*-Bu_3 which in this case was the most selective reagent providing the desired alcohol in >200:1 selectivity. The yield, however, was only moderate even with the

Table 19 Inversion of the stereochemistry of secondary hydroxy groups

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			1. DMSO, Ac_2O, r.t., 72 h 2. $NaBH_4$, CH_2Cl_2, MeOH, 0 °C – r.t.	76	306
2			1. CrO_3, CH_2Cl_2, Ac_2O, pyr. 0 °C, 1 h 2. $NaBH_4$, EtOH, 0 °C, 30 min	80	307
3		 Contains about 14% isomer	1. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78–0 °C 2. $NaBH_4$, MeOH, 0 °C, 1 h	90	308
4			1. Swern oxidation 2. $NaBH_4$, MeOH	64	309
5			1. $(COCl)_2$, DMSO, TEA 2. $NaBH_4$, MeOH, 0 °C	42	310
6			1. Dess-Martin Oxidation 2. $NaBH_4$, MeOH	70	311
7			1. DMSO, Ac_2O, 16 h 2. $NaBH_4$, *i*-PrOH, 20 h	No reported yield	312
8			1. PCC, CH_2Cl_2, overnight 2. KBH*sec*-Bu_3, THF, –78 °C to –50 °C (4 h)	77	313
9			1. $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C 2. $NaBH_4$, CH_2Cl_2/MeOH (1:1), r.t., 4 h,	64	314

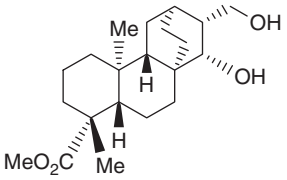
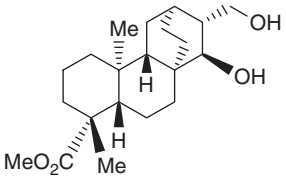
(*Continued*)

Table 19 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
10	 **A**	 **B**	1. DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C; NEt_3, −78 °C to rt 2. **Reduction** $NaBH_4$ $LiBHEt_3$ $LiBHsec\text{-}Bu_3$ (*R*)-CBS	80 ***B:A*** *ratio* 1:1 1:2 4:1 9:1	315
11			1. Dess-Martin periodinane, moist CH_2Cl_2, r.t. 2. $LiBHsec\text{-}Bu_3$ LiBr, THF, −78 °C; then H_2O_2	81 (≥200:1)	305
12	 **A**	 **B**	1. Tetrapropyl-ammonium perruthenate (TPAP), NMO, CH_3CN, r.t., 2 h	93	316
			2. **Reduction** $LiBHsec\text{-}Bu_3$, THF, −78 °C, 30 min	88 **B/A** 85:10	
			$NaBH_4$, $CeCl_3$, MeOH	85 only **A**	
			$NaBH_4$, MeOH	90 **B/A** 70:30	
			DIBAL-H, CH_2Cl_2	95 **B/A** 60:40	
			$Zn(BH_4)_2$, Et_2O	60 **B/A** 50:50	
13			1. MnO_2, CH_2Cl_2, r.t., overnight 2. $KBHsec\text{-}Bu_3$, THF, −78 °C, 15 min	99	125
14			1. CrO_3, py, CH_2Cl_2, 0 °C, 45 min 2. $LiBHsec\text{-}Bu_3$, THF, 4 h, 0 °C;	86	317
15			1. PCC, MS-4 Å, benzene, 80 °C 2. $LiBHsec\text{-}Bu_3$, THF, −78 °C; then MeOH	85	318
16	 OpMBn = *p*-methoxybenzyl		1. $(COCl)_2$, DMSO, Et_3N, −78 °C to −13 °C2 2. $K(sec\text{-}Bu)_3BH$, THF, −78 °C to −10 °C	88	319

(*Continued*)

Table 19 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
17			1. $NaBrO_3$, $NaHSO_3$, MeCN, H_2O, r.t., 2 h 2. $NaBH(OAc)_3$, AcOH, MeCN, 0 °C, 5 h	67	320

addition of excess reagent because of partial enolization of the ketone (19%). The alcohol was obtained in a pure form by applying oxidative work up with alkaline H_2O_2 to destroy the enolate. Addition of $CeCl_3$ to suppress the ketone enolization was only partially successful because of its insolubility in THF. On the other hand, the addition of 6 equivalents of the more THF-soluble LiBr resulted in better suppression of the enolization and consequently resulted in high conversion to the alcohol (11:1 alcohol/ketone). Thus, the addition of LiBr combined with the above mentioned oxidative workup has greatly improved the reaction to afford 81–82% yield of the pure alcohol reproducibly.

In the example in Table 19, entry 12, the reduction of the acyclic ketone intermediate with several hydride reagents including $NaBH_4$/MeOH and DIBAL-H/CH_2Cl_2, $Zn(BH_4)_2/Et_2O$ and $NaBH_4/CeCl_3$ gave unsatisfactory results. The reduction with LiBH*sec*-Bu_3 gave the best selectivity and good yield of the desired alcohol.[316]

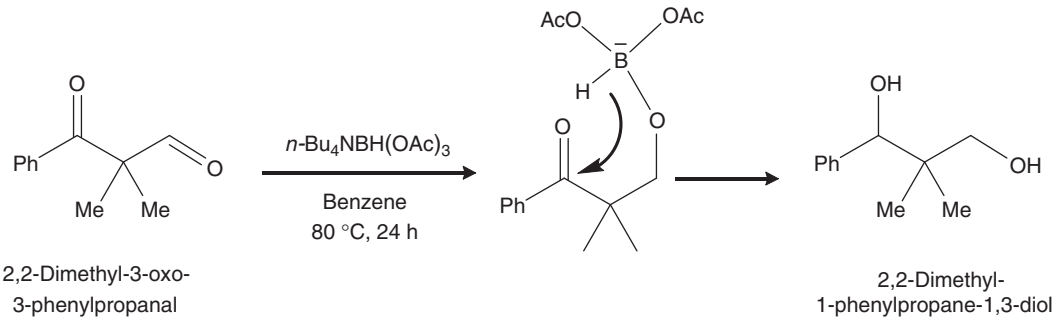
The undesired acetylenic alcohol (Table 19, entry 13) or a mixture of the two isomeric alcohols was oxidized with MnO_2 to the intermediate cyclic acetylenic ketone. The reduction of the ketone with KBH*sec*-Bu_3 gave the desired alcohol as a single diastereomer in 99% yield for the combined two steps.[130]

8.01.9 Reduction of β-Hydroxy Ketones

Reduction of *β*-hydroxy ketones with metal hydrides to produce 1,3-diols is a very important reaction that has been utilized extensively in the synthesis of natural and unnatural products. The hydroxyl group plays a pivotal role in directing the delivery of hydride from either face of the molecule based on the reaction conditions. In particular, a chiral center carryimg a hydroxyl function can exert very effective 1,3-chiral induction during the formation of the new stereogenic center in the reduction of the carbonyl group. It has become possible to form either 1,3-*syn* or 1,3-*anti*-diols with high selectivity by careful choice of reaction conditions, such that the reduction can proceed with or without chelation control based on the choice of reagents. Two main common procedures for the selective reduction of *β*-hydroxyketones leading to opposite stereochemistry will be highlighted in this section. Both reactions rely on chelation of the *β*-hydroxyketones to selectively form either 1,3-*anti* or 1,3-*syn*-diol. In the first reaction, triacetoxyborohydride delivers a hydride intramolecularly to give a 1,3-*anti*–diol, whereas in the second the hydride is delivered externally to form a 1,3-*syn*-diol.

8.01.9.1 Reduction of β-Hydroxyketones to 1,3-*anti*-Diols: Reduction with Triacetoxyborohydrides

During a study of the chemoselective reduction of aldehydes in the presence of ketones, Gribble and Nutaitis observed the reduction of 2,2-dimethyl-3-oxo-3-phenylpropanal to 2,2-dimethyl-1-phenylpropane-1,3-diol. Although most ketones were very slow to reduce or did not reduce at all under these conditions, the diol was obtained in 80% yield. They explained this result by intermolecular hydride delivery involving the hydroxyl group resulting from reduction of the aldehyde as shown in Scheme 2.[112b]

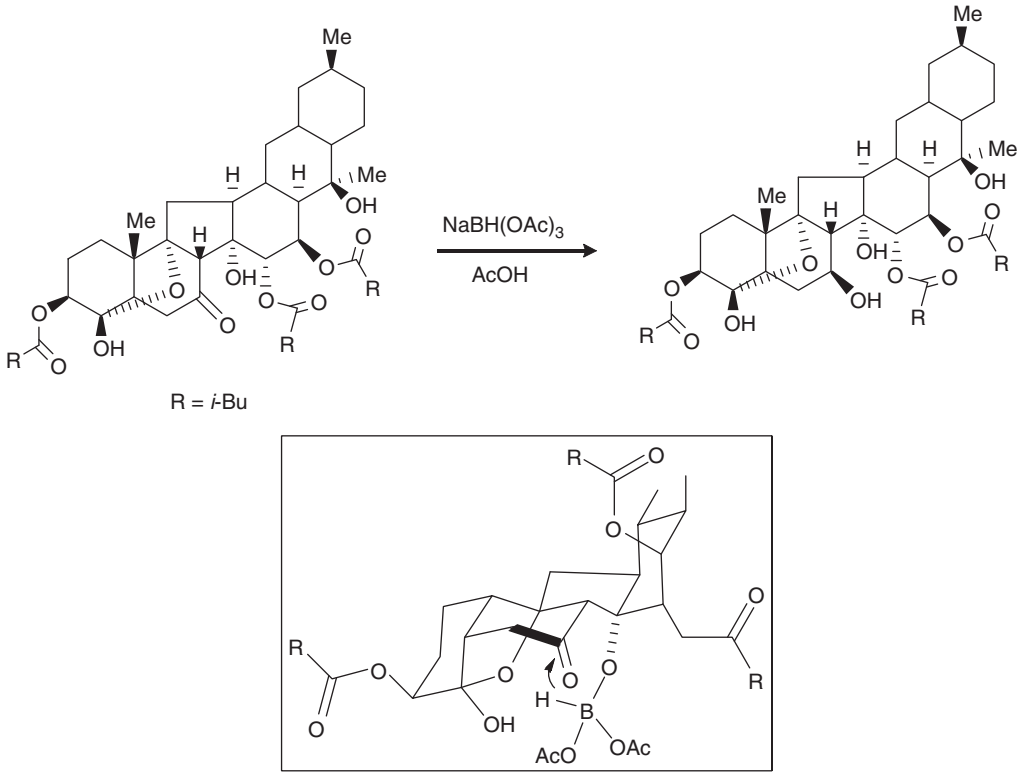


2,2-Dimethyl-3-oxo-3-phenylpropanal

2,2-Dimethyl-1-phenylpropane-1,3-diol

Scheme 2 *β*-OH-Directed reduction of ketones with triacetoxyborohydride (Gribble).

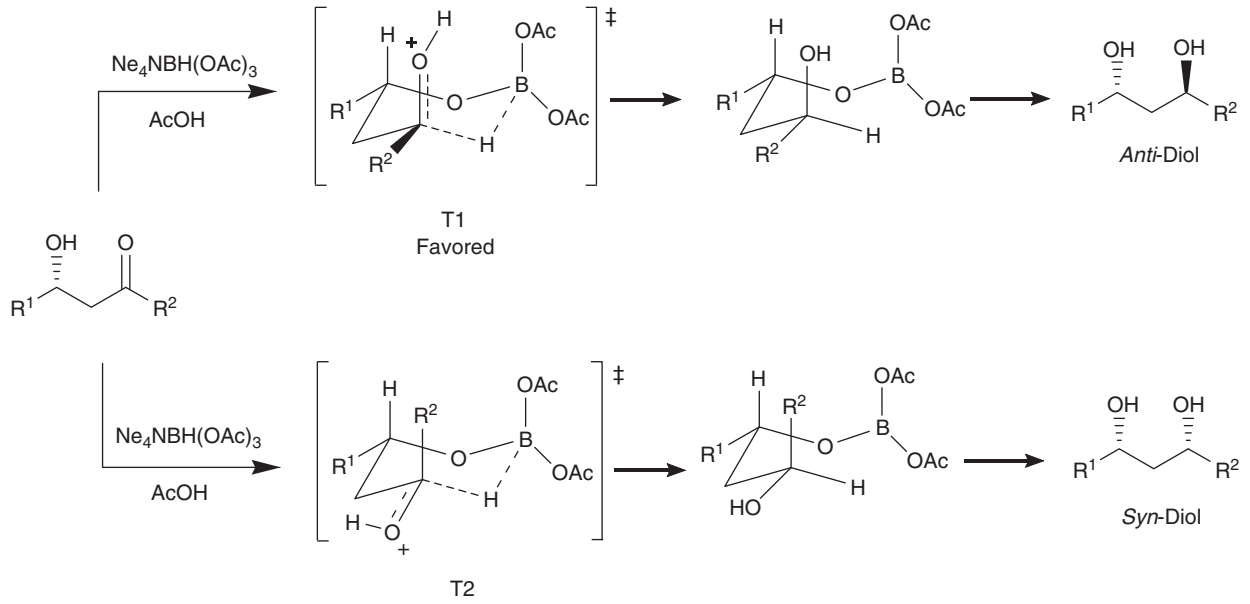
Saksena[321] independently revealed a similar reaction and observed an unusual reduction of a β-hydroxy ketone in the veratrum alkaloid germine, with $NaBH(OAc)_3$ in AcOH. Not only was the ketone reduced in high yield (92%), but the reduction has also proceeded with excellent stereoselectivity with the hydride delivered in an opposite manner to that obtained from $NaBH_4$ in EtOH. He explained the result by suggesting displacement of one of the acetoxy groups in $NaBH(OAc)_3$ by the β-alcohol followed by intramolecular delivery of the hydride to the ketone as illustrated in Scheme 3.



Scheme 3 β-OH-Directed reduction of ketones with triacetoxyborohydride (Saksena).

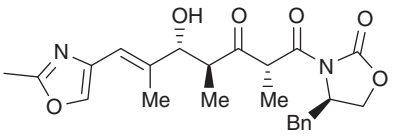
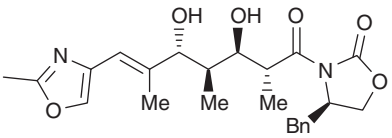
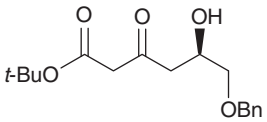
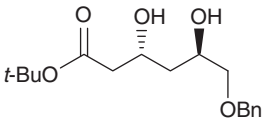
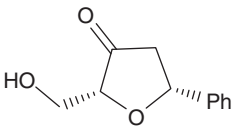
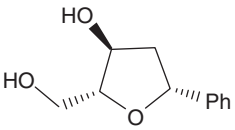
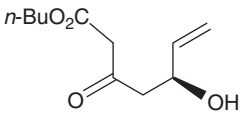
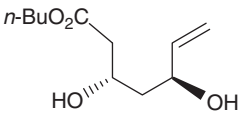
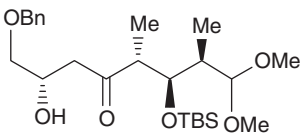
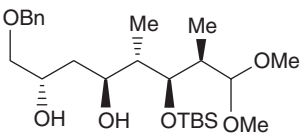
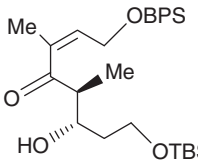
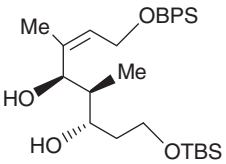
The reaction did not see many applications until Evans and coworkers[322] re-examined this reaction and extensively explored its scope and utility. Their efforts led to the development of a very powerful method for the stereoselective reduction of β-hydroxy ketones to 1,3-*anti*-diols using triacetoxyborohydrides. One of the most important developments that resulted from this study was the preparation and the full characterization of pure $NaBH(OAc)_3$ and $Me_4NBH(OAc)_3$. Before this work, the two reagents were never isolated in pure form and were prepared by adding $NaBH_4$ or Me_4NBH_4 to neat AcOH. Concerns that such reagent solutions might not be homogenous and impurities might lead to lower diastereoselectivities led to the development of pure reagents. The Evans group has also determined that the use of $Me_4NBH(OAc)_3$ gives better diastereoselectivity than $NaBH(OAc)_3$, and the presence of AcOH was necessary to enhance the reaction rate and increase selectivity. Thus, the best conditions to carry out this reaction are to use $Me_4NBH(OAc)_3$ as the reducing agent in 1:1 CH_3CN/AcOH solution at -40 °C. To rationalize the high degree of stereocontrol, Evans proposed the reaction mechanism illustrated in Scheme 4 in which the initial step is the displacement of one of the acetoxy groups by the β-hydroxy group. The resulting alkoxydiacetoxyborohydride is presumed to be a more reactive species (alkoxy substitution activates borohydrides). This intermediate delivers a hydride intramolecularly to the carbonyl group, via two possible cyclic chair-like 6-membered ring transition states (T1 and T2), each activated by acid catalysis. The 1,3-diaxial interactions between R^2 and OAc destabilize T2 to a greater extent than the analogous 1,3-diaxial interaction between HO^+ and OAc in T1. The hydride is delivered from the side of the hydroxyl group in T1 thus forming the 1,3-*anti*-diol.

The procedure is very practical, highly predictable, and it has become a widely used method. Literature applications are numerous; several representative examples from recent literature are listed in Table 20. The examples show the effectiveness and high stereoselectivity of this reduction procedure. The procedure is very mild and can be applied to highly functionalized substrates over a wide range of diverse cyclic and acyclic structures. A remarkable feature of this reaction is its ability to deliver very high level of diastereoselectivity in acyclic β-hydroxy ketones.



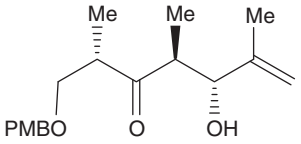
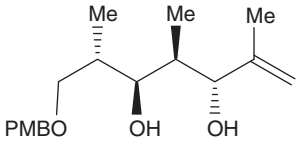
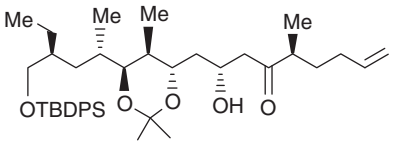
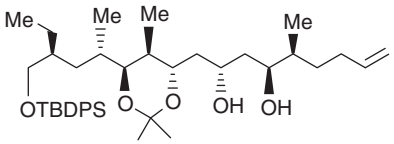
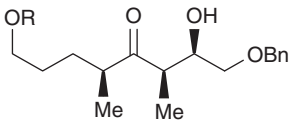
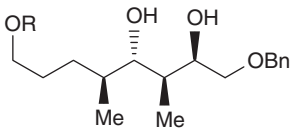
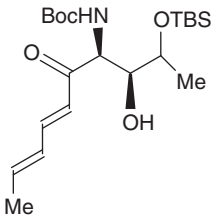
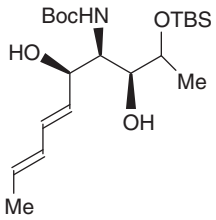
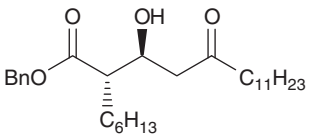
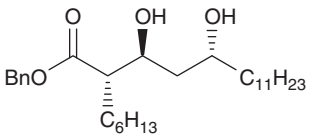
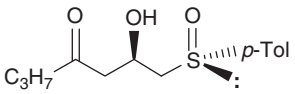
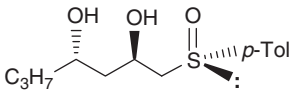
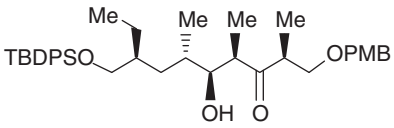
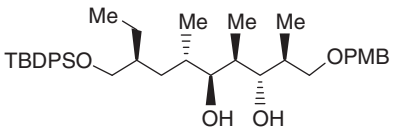
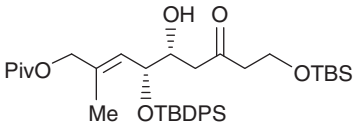
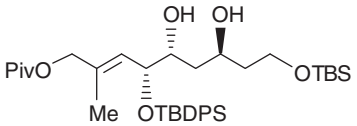
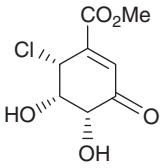
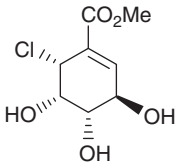
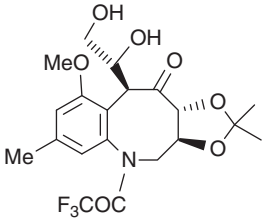
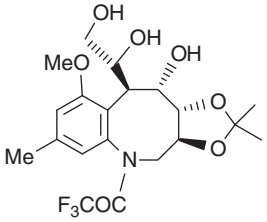
Scheme 4 Mechanism of reduction of β-hydroxy ketones with triacetoxyborohydrides (Evans).

Table 20 Stereoselective reduction of of β-hydroxy ketones with triacetoxyborohydrides

Entries	*β-Hydroxy ketone*	*Diol*	*Conditions*	*Yield (%)*	*References*
1			$Me_4NBH(OAc)_3$, AcOH, 0 °C to r.t.	81	323
2			$Me_4NBH(OAc)_3$, AcOH/MeCN, −35 °C	84 *dr* 94:6	324
3			$NaBH(OAc)_3$ MeCN, AcOH 0 °C, 1 h	94	325
4			$Me_4NHB(OAc)_3$ AcOH-MeCN, 1:1, 0 °C, 2 h	93	326
5			$Me_4NHB(OAc)_3$ AcOH-MeCN	97 >99:1	327
6			$Me_4NHB(OAc)_3$, AcOH-MeCN −20 °C, 16 h	98	328

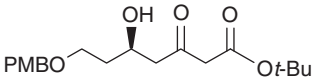
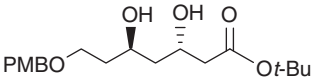
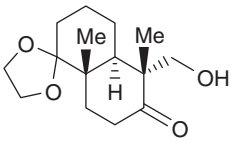
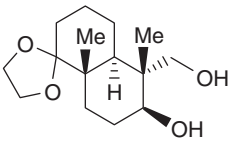
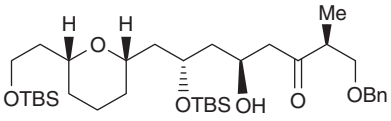
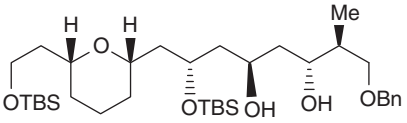
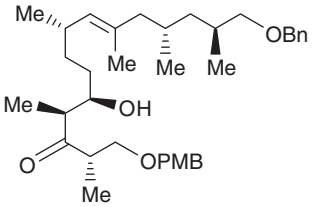
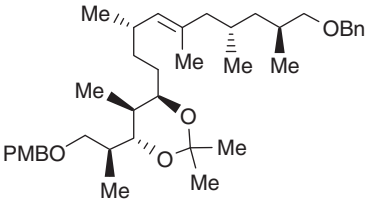
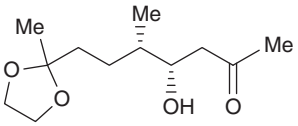
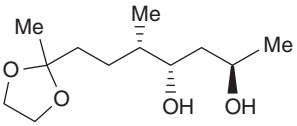
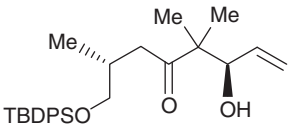
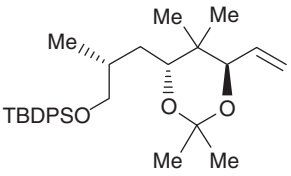
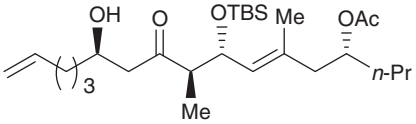
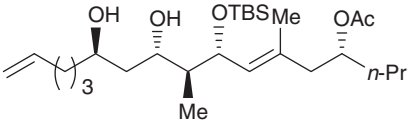
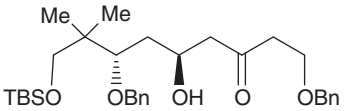
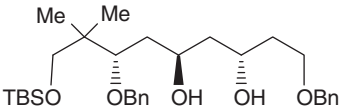
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Table 20 Continued

Entries	β-Hydroxy ketone	Diol	Conditions	Yield (%)	References
7			$Me_4NHB(OAc)_3$ AcOH-MeCN, −40 to −23 °C	94 >97 *ds*	329
8			$Me_4NHB(OAc)_3$ AcOH-MeCN	72	330
9	 R = *p*-Anisyl	 R = *p*-Anisyl	$Me_4NHB(OAc)_3$ AcOH-MeCN, −40 °C (15 min); −25 °C (72 h)	99	331
10			$Me_4NHB(OAc)_3$ AcOH-MeCN, −40 °C, 1 h; −20 to −10 °C, 5 h	93	332
11			$Me_4NBH(OAc)_3$ AcOH-MeCN (1:1), −40 °C, 24 h	99 (22:1)	333
12			$Me_4NBH(OAc)_3$ AcOH	97 (*de* >95)	246
13			$Me_4NBH(OAc)_3$ HOAc, MeCN, −25 to 0 °C, overnight	82	334
14			$Me_4NBH(OAc)_3$, AcOH/MeCN (1:1), −20 °C, 10 h	94 *dr* >95:5	335
15			$Me_4NBH(OAc)_3$, AcOH/MeCN	64	336
16			1. NaBH $(OAc)_3$, AcOH/THF (1:10), 0 °C, 30 min; 2. Aqueous NaOH, MeOH, r.t., 5 min,	85 (2 steps)	337

(*Continued*)

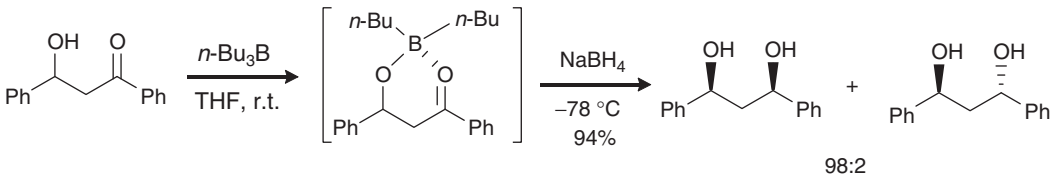
Table 20 Continued

Entries	β-Hydroxy ketone	Diol	Conditions	Yield (%)	References
17			$Me_4NBH(OAc)_3$, AcOH-MeCN −30 °C	86 *dr*: 8:1	338
18			$Me_4NBH(OAc)_3$, AcOH-MeCN −40 °C	95	339
19			1. $Me_4NBH(OAc)_3$, AcOH-MeCN −30 °C 2. PPTS, $Me_2C(OMe)_2$	90 Single isomer	340
20			1. $Me_4NBH(OAc)_3$, AcOH-MeCN −30 °C 2. PPTS, $Me_2C(OMe)_2$	75	341
21			$Me_4NBH(OAc)_3$, AcOH-MeCN −30 °C	91	342
22			1. $Me_4NBH(OAc)_3$, AcOH-MeCN −30 °C 2. PPTS, CH_2Cl_2, $Me_2C(OMe)_2$, r.t.	76	343
23			$Me_4NBH(OAc)_3$, AcOH, MeCN-THF −40 to −20 °C	91 *dr* 10:1	344
24			$Me_4NBH(OAc)_3$, AcOH, MeCN (1:1), −20 °C, 18 h	95	262

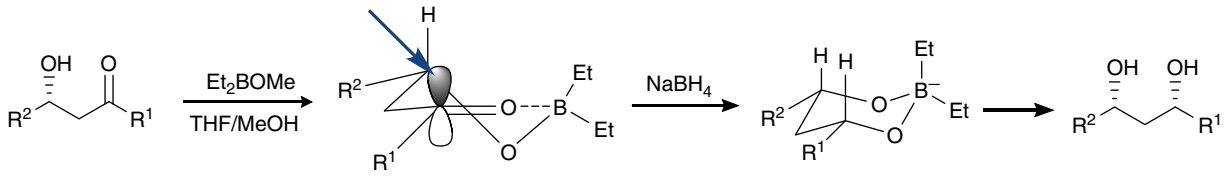
8.01.9.2 Reduction of β-Hydroxyketones to 1,3-*syn*-Diols: Reduction with Et_2BOCH_3-$NaBH_4$ (Prasad Reaction)

In 1980, Narasaka and Pai[345] reported a highly selective procedure for the reduction of *β*-hydroxy ketones to *syn*-1,3-diols by treatment of the hydroxy ketone with $(n\text{-Bu})_3B$ in THF at room temperature and subsequent reduction with $NaBH_4$ at −100 °C. They rationalized the result by proposing initial formation of a stable chelate complex between the *β*-hydroxy ketone and $(n\text{-Bu})_3B$ which determines the direction of hydride attack (Scheme 5).

In 1987, Prasad and coworkers[346] introduced alkoxy diethylboranes as better chelating agents with better selectivity in a diastereoselective procedure for the reduction of *β*-hydroxy ketones with $NaBH_4$ to form 1,3-*syn*-diols. They also determined that stoichiometric amounts of alkoxyboranes are not essential for high selectivity. The scope of the reaction covers aliphatic, benzylic, and allylic alcohols along with aliphatic or conjugated ketones. Although they listed several alkoxyborane derivatives, the use of methoxydiethylborane is the most common in THF/MeOH at −78 °C. The selectivity of the reaction was explained by a similar rationale (Scheme 6) to that given by Narasaka and Pai.



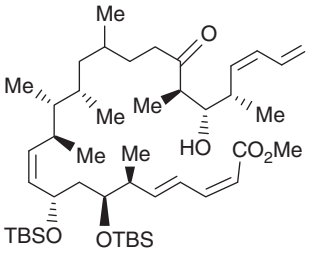
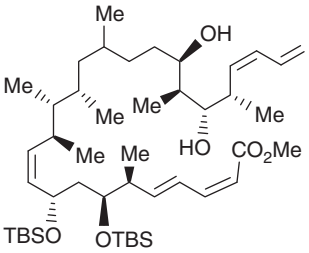
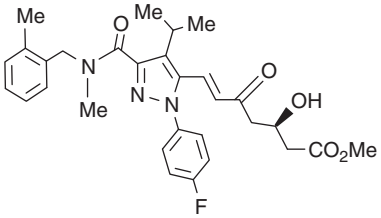
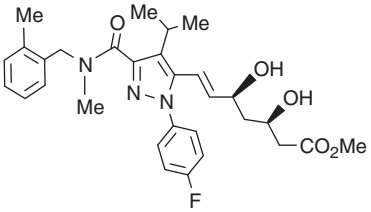
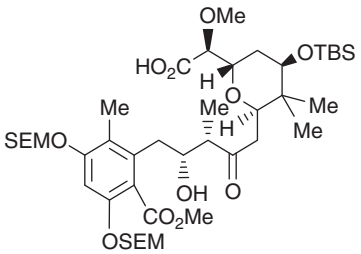
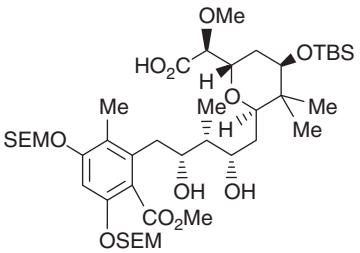
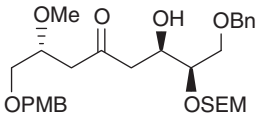
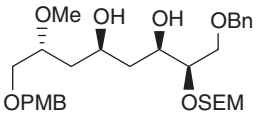
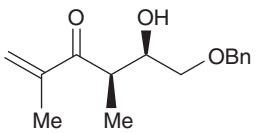
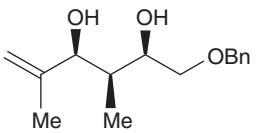
Scheme 5 *Syn*-selectivity in reduction of β-hydroxy ketones (Narasaka and Pai).



Scheme 6 *Syn*-selectivity in reduction of β-hydroxy ketones (Prasad).

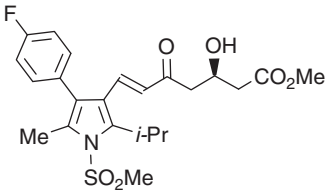
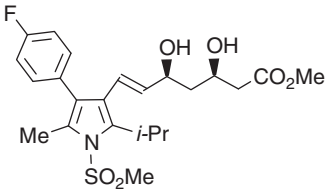
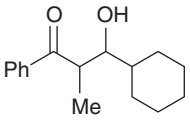
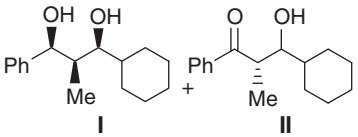
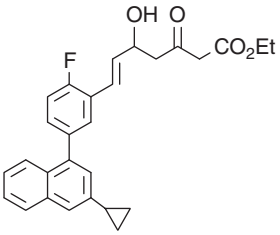
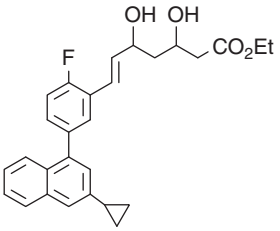
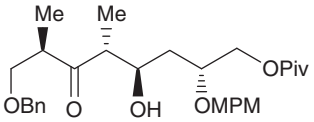
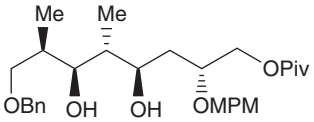
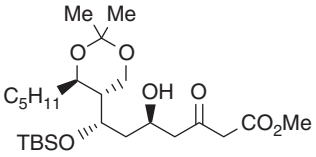
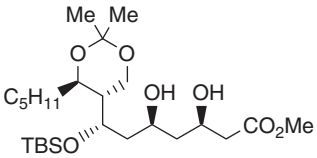
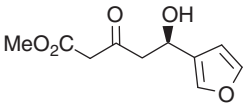
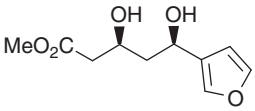
The procedure which is referred to sometimes as Prasad reduction, is widely used for the reduction of β-hydroxy ketones to 1,3-*syn*-diols. It is a remarkably selective and effective reduction procedure with very high levels of stereocontrol as evident from the examples in Table 21.

Table 21 Reduction of β-hydroxyketones with Et_2BOCH_3-$NaBH_4$ to 1,3-*syn*-diols

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			Et_2BOMe-THF, –78 °C, 1 h, $NaBH_4$, –78 °C, 6 h	87	347
2			Et_2BOMe-THF/MeOH, –78 °C, 1 h, $NaBH_4$, –78 °C, 2 h, then warm to r.t.	81	348
3			Et_2BOMe-THF/MeOH, –78 °C, 25 min, $NaBH_4$, –78 °C, 1 h, Then r.t. (30 min)	95 >20:1 *dr*	349
4			Et_2BOMe-THF/MeOH, –78 °C, 15 min, $NaBH_4$, –78 °C, 2 h	84	350
5			Et_2BOMe-THF/MeOH, –70 °C, 15 min, $NaBH_4$, –70 °C, 4 h	99 >500:1	351

(*Continued*)

Table 21 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
6			Et_2BOMe $NaBH_4$, THF: MeOH, −78 °C	89	352
7	 *syn*:*anti* = 65:35	 I II	Et_2BOMe (10 mol%), $NaBH_4$, THF: MeOH, −78 °C, 5 h	I: 63 II: 31	353
8			$NaBH_4$, Et_2BOMe, −78 °C	(±)-*syn* >98:2 *syn*:*anti*	354
9			Et_2BOMe, $NaBH_4$, MeOH/ THF (1/3), −78 °C	83	355
10			Et_2BOMe, $NaBH_4$, MeOH, −78 °C	>95, >98 *de*	356
11			Et_2BOMe $NaBH_4$, THF: MeOH, −70 °C, 5 h	>90 >95:5	259

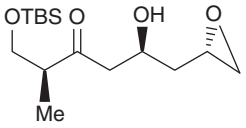
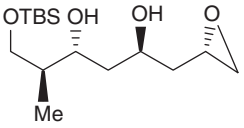
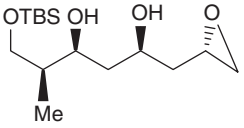
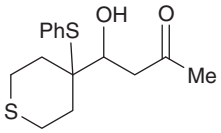
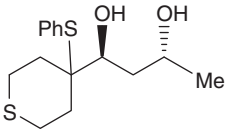
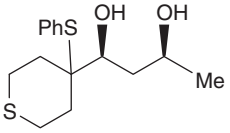
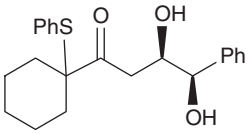
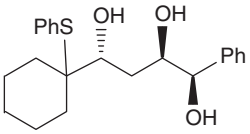
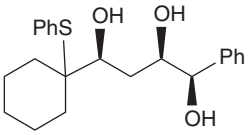
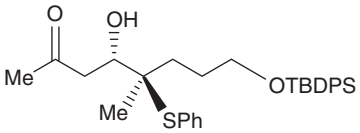
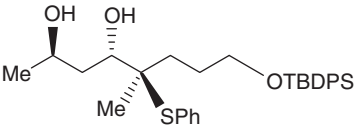
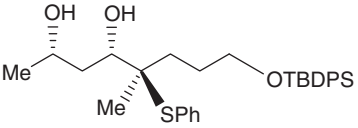
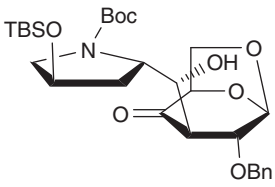
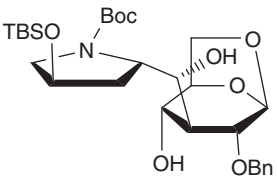
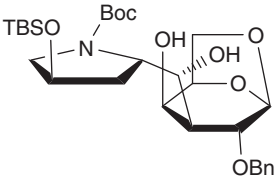
Evans and coworkers[351] used this procedure in the synthesis of polyol glycoside sub unit of cytovaricin; the reduction of a β-hydroxy ketone intermediate (Table 21, entry 5) with $MeOBEt_2/NaBH_4$ afforded the desired *syn*-diol with >100:1 facial selectivity.

In the example in entry 7, the β-hydroxy ketone has a chiral center at the α-position and consists of a 65:35 diastereomeric mixture. The reduction of this mixture was carried out using only 10 mol% of Et_2BOMe; under this modification, the *syn*-diasteromer was reduced selectively to give the pure *syn*-diol in 63% yield, whereas the pure *anti*-diasteromer was recovered unchanged in 31% yield. The authors explained the results by unfavorable *gauche* interactions in the chelate intermediate leading to the reduction of *anti*-diastereomer compared to that of the *syn*-diastereomer.[353]

8.01.9.3 Reduction of β-Hydroxyketones: Comparisons and Other Reagents

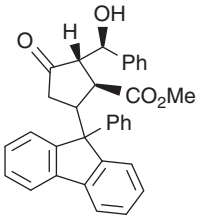
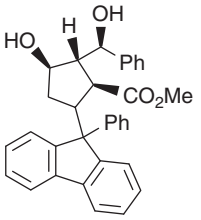
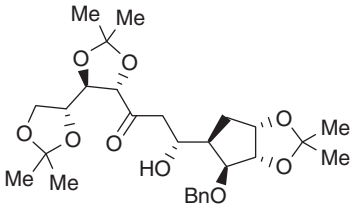
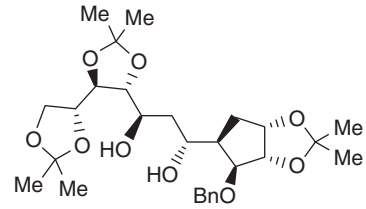
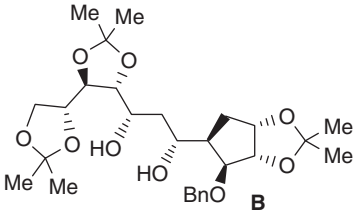
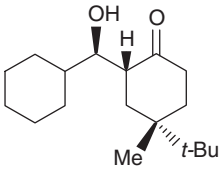
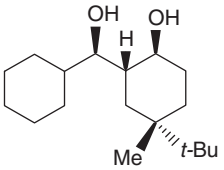
There are several studies that reported the reduction of same β-hydroxy ketone with two different conditions to prepare the two diasteromeric forms, *syn*- and *anti*-diols selectively either as a means of comparison or because both diastereomeric forms were needed. Representative examples of these studies are listed in Table 22. Some of the examples (entries 1–4) show comparisons between the above two procedures; the results show outstanding selectivity for the two procedures and a nearly complete reversal of stereoselectivity. In other studies the use of reducing agents other than the two procedures highlighted above was reported. The examples in entries 5–8 used other reagents including $NaBH_4$, DIBAL-H, and $LiBHsec\text{-}Bu_3$ to obtain the *syn*-diol from reductions of β-hydroxy ketones in excellent stereoselectivity.

Table 22 Reduction of β-hydroxyketones: comparisons and other reagents

Entries	Substrate	Product	Conditions	Yields (%)	References
1		 **A**	$Me_4NBH(OAc)_3$ CH_3CN, AcOH, 0 °C, 1 h	91 **A/B** = > 98:2	357
		 **B**	$NaBH_4$, Et_2BOMe, −78 °C, THF-MeOH, 2 h	98 **A/B** = 2 : > 98	
2			$Me_4NBH(OAc)_3$, AcOH/MeCN, −30 °C, 5 day	90 (*dr*: 96:4)	358
			Et_2BOMe, $NaBH_4$, THF: MeOH, −78 °C, 2 h	96 (*dr*: 97:3)	
3			$Me_4NBH(OAc)_3$, AcOH/MeCN, −20 °C, 7 day	75	359
			Et_2BOMe, $NaBH_4$, THF: MeOH, −78 °C, 8 h	74	
4			$Me_4NBH(OAc)_3$, AcOH/MeCN	85 > 98:2	360
			Et_2BOMe, $NaBH_4$	81 89:11	
5			$Me_4NBH(OAc)_3$ CH_3CN, AcOH, −40 °C, then −20 °C (20 h)	60 (Incl. aldol step)	361
			LiBH*sec*-Bu_3, THF, −78 °C	53	

(*Continued*)

Table 22 Continued

Entries	Substrate	Product	Conditions	Yields (%)	References
6			$NaBH_4$, THF: MeOH, −78 °C, 4 h	98	362
7		 **A**	$NaBH_4$ EtOH/H_2O	**A**: 28 **B**: 51	363
		 **B**	LiBH*sec*-Bu_3	**A**: 3 **B**: 97	
8			DIBAL-H THF, PhMe −78 °C, 1 h	67 92:8	364

8.01.10 Enantioselective Reductions of Ketones

8.01.10.1 5-Chlorodiisopinocampheylborane (Ipc_2BCl or DIP-Cl)

One of the pioneering borane reagents for asymmetric reductions of carbonyl compounds is *B*-pinan-3-yl-9-borabicyclo[3.3.l] nonane (Alpine–Borane, Figure 3) developed by Midland and coworkers.[365] This reagent is effective in reducing reactive non-hindered ketones such as acetylenic ketones, α-ketoesters, and deutrated aldehydes in high stereoselectivity; however, it is not as stereoselective with more hindered and less reactive ketones such as ethyl iso-propyl ketone and acetophenone. The poor stereoselectivity with unreactive ketones was explained by competitive formation of 9-BBN via dehydroboration which results in achiral reduction.[366]

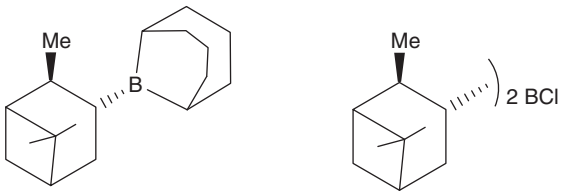
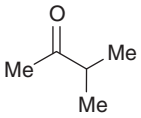
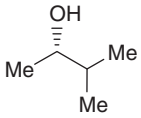
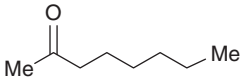
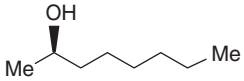
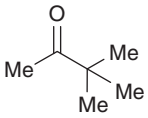
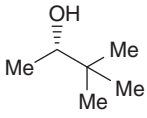
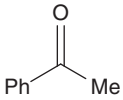
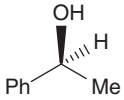
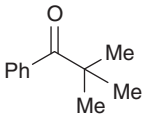
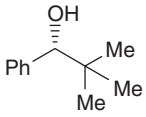
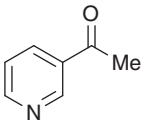
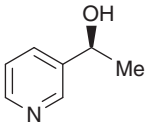
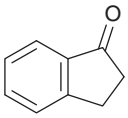
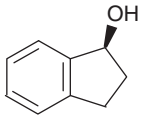
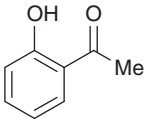
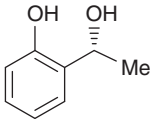
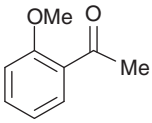
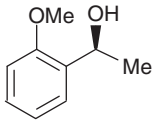
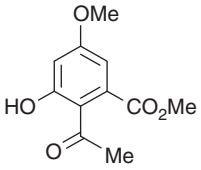
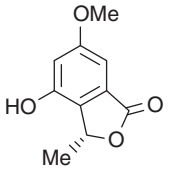
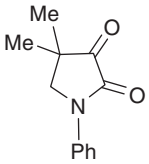
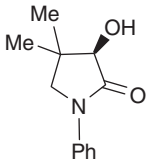


Figure 3 Alpine–Borane and Ipc_2BCl.

Brown and Ramachandran[367] introduced Ipc_2BCl or DIP-Cl (Figure 3) as a faster and more effective asymmetric reducing agent than Alpine–Borane. Replacement of the B–H bond in Ipc_2BH by B–Cl enhances the rate of reactions by increasing the Lewis acidity of the boron. The (−)-Ipc_2BCl enantiomer is prepared in high chemical and enantiomeric purities (99% *ee*) by hydroboration of (+)-α-pinene with $BH_3.SMe_2$ followed by treatment with dry HCl in diethyl ether. Alternatively, it is prepared by direct

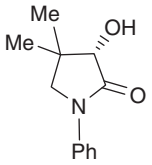
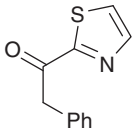
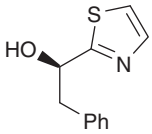
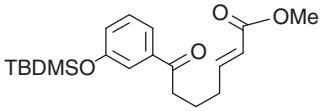
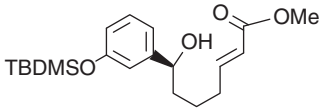
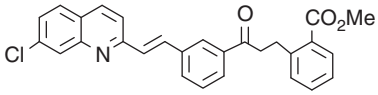
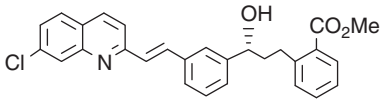
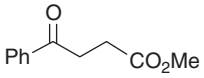
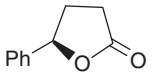
hydroboration of (+)-α-pinene with monochloroborane. Ipc_2BCl is very efficient in the enantioselective reduction of aromatic ketones, α-hindered, and perfluoroalkyl ketones. It is not similarly effective with alkyl ketones particularly where the steric differentiation is lacking (see examples in Table 23). Because both enantiomers of α-pinene are commercially available, either (−)-Ipc_2BCl or (+)-Ipc_2BCl can be produced and used in asymmetric reductions of prochiral ketones to produce both enantiomers of the corresponding secondary alcohol.[375]

Table 23 Reductions with 5-chlorodiisopinocampheylborane (Ipc_2BCl): DIP-Cl

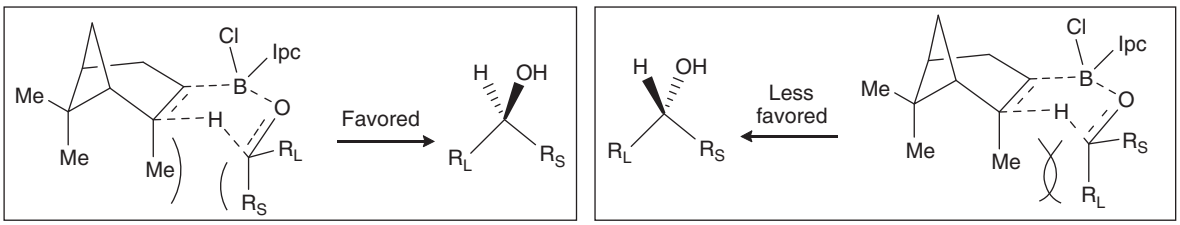
Entries	Substrate	Product	Conditions	Yield (%)	References
1			(−)-Ipc_2BCl, THF, −25 °C, 5 h	72 32 *ee*	367
2			(−)-Ipc_2BCl, THF, −25 °C, 3 h	62 7 *ee*	
3			(−)-Ipc_2BCl (neat), −25 °C, 12 day	50 93 *ee*	
4			(−)-Ipc_2BCl, THF, −25 °C, 5 h	72 98 *ee*	
5			(−)-Ipc_2BCl, THF, −25 °C, 12 day	60 79 *ee*	
6			(−)-Ipc_2BCl (2 equivalents) THF, −25 °C, 15 h	67 92 *ee*	
7			(−)-Ipc_2BCl, THF, −25 °C, 15 h	62 97 *ee*	
8			1. (−)-Ipc_2BCl, THF, −25 °C, HCl_g then r.t., (36 h) 2. NaOH, H_2O_2; HCl 3. NaOH, Me_2SO_4	90 *ee*	368
9			(−)-Ipc_2BCl, THF, −25 °C, 8 h	92 *ee*	
10			(+)-Ipc_2BCl, THF	73	369
11			(−)-Ipc_2BCl, THF −25 °C, 5 h, Recrystallization	71 85 *ee* 99 *ee*	370

(*Continued*)

Table 23 Continued

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
12			(+)-Ipc_2BCl, THF, −25 °C, 4 h; Recrystallization	65 64 *ee* 99 *ee*	
13			(+)-Ipc_2BCl, Et_2O 0 °C, 23 h	80 93 *ee*	371
14			(−)-Ipc_2BCl, THF, −25 °C	56	372
15			(−)-α-Pinene (70% *ee*, 4 equivalents) Me_4S-BH_2Cl, THF/hexane, $(i\text{-}Pr)_2NEt$ −20 °C, 3.5 h; to 0 °C over 1 h	87 99.5 *ee*	373
16			(−)-α-Pinene (87% *ee*), $NaBH_4$, BCl_3, DME, 0–22 °C, 48 h	70 97 *ee*	374

The mechanism of the ketone reduction is believed to proceed via a 6-membered, cyclic, 'boat-like' transition state (**Scheme 7**) similar to that proposed for Midland's Alpine–Borane.[367]



Scheme 7 Mechanism of reduction of ketones with Ipc_2BCl.

Several examples highlighting the use of Ipc_2-BCl in the enantioselective reduction of ketones are listed in **Table 23**. Although the reductions of aliphatic ketones with Ipc_2-BCl proceed with low enantioselectivity, the reduction of aromatic ketones affords consistently high chemical yield and predictable stereoselectivity (**Table 23**, entries 1–7).[367] The reduction of 2-hydroxy acetophenone versus 2-methoxyacetophenone was used to produce both enantiomeric forms of 2-(2-methoxyphenyl)ethanol in good yields and high enantioselectivity (**Table 23**, entries 8–9).[368] A similar enantioselective reduction of a 2-hydroxyacetophenone derivative was used in Danishefsky's synthesis of descarbamoylcalicheamicin (**Table 23**, entry 10).[369]

The enantioselctive reduction of the ketolactam, 4,4-dimethyl-1-phenylpyrrolidine-2,3-dione (**Table 23**, entries 11–12) to prepare the enantiomers of the alcohol product was accomplished by (−)- and (+)-Ipc_2BCl in THF at 25 °C; each enantiomer was obtained in good yield and 99% *ee* after one crystallization.[370]

The reduction of benzyl 2-thiazolyl ketone (**Table 23**, entry 13) is an intermediate step in the preparation of (*S*)-dolaphenine, the C-terminal unit of the anticancer compound dolastatin 10. Reductions with several reagents were unsatisfactory, the best result was obtained from (+)-Ipc2BCl in ether at 0 °C.[371]

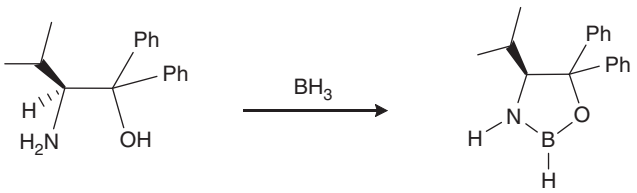
The use of Icp_2BCl is stoichiometic, and while (+)- and (−)-α-pinenes are commercially available in highly enantiopurity, the price of the high purity enantiomers may become a financial concern on large scale. It is nonetheless possible to use the economical lower enantiopurity (+)- and (−)-α-pinenes with remarkable enantiomeric amplification. Chemists at Merck[373] developed a large-scale process for the asymmetric synthesis of the leukotriene antagonist L-699,392 that included the enantioselective reduction of the intermediate ketone (**Table 23**, entry 15) with (−)-Ipc_2BCl. They observed very high asymmetric

amplification when Ipc_2BCl generated from 70% *ee* α-pinene reduced the ketone to obtain the alcohol in 95% *ee*. Another enantiomeric amplification was reported by Senanayake and coworkers[374] in the enantioselective synthesis of (*R*)-fluoxetine and its metabolite (*R*)-norfluoxetine. The enantioselective reduction of methyl 4-oxo-4-phenylbutanoate (Table 23, entry 16) was accomplished in 97% *ee* by using Ipc_2BCl generated from (−)-α-pinene with 87% *ee*.

8.01.10.2 Enantioselective Reduction of Ketones with Oxazaborolidines

Chiral oxazaborolidines have been used as enantioselective catalysts for the reduction of prochiral ketones as well as catalysts for other transformations in organic synthesis. The discussion in this chapter will be limited to their use as catalysts for the asymmetric reductions of prochiral ketones.

In 1981 Itsuno and coworkers[376] introduced a procedure for the asymmetric reduction of aromatic ketones using what were described as 'borane complexes' resulting from 2:1 mixtures of borane and enantiomeric aminoalcohols at 30 °C for 60 h. Most reductions were carried out in THF but C_6H_6, $CHCl_3$, and $MeOH/H_2O$ were also used to give excellent chemical yields but low and varying enantiomeric purities (7.3–60% *ee*). The nature of the borane complexes were not known but the authors observed the structural importance of the free hydroxy group in the amino alcohols because the use of methyl ethers considerably lowers the enantioselectivity of the reduction. Further studies by Itsuno[377] showed that the enantioselection of the aromatic ketone reduction was improved (94–100%) by the use of (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**3**, Scheme 8) with 2 equivalents of borane in THF at 30 °C for 2 h. The use of the (*S*)-amino alcohol gave the (*R*)-product and the (*R*)-amino alcohol gives (*S*)-product with the same degree of asymmetric induction.



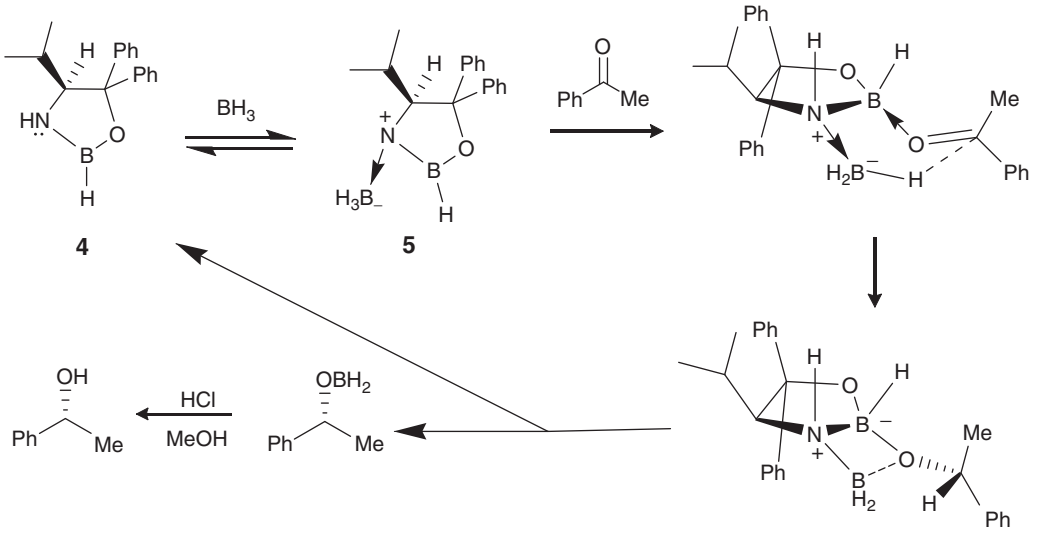
3 **4**

Itsuno oxazaborolidine

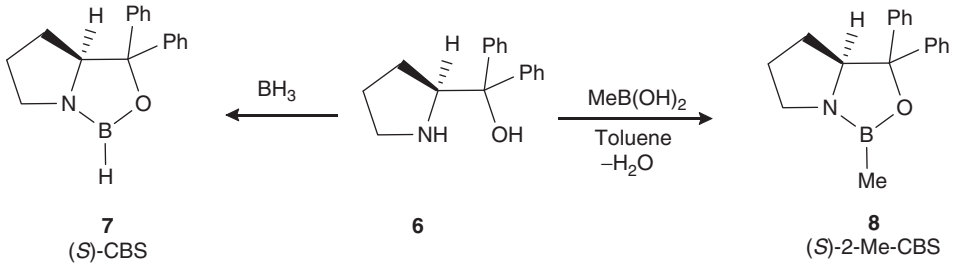
Scheme 8 Synthesis of Itsuno oxazaborolidine.

In realizing the potential of this novel asymmetric reduction of ketones, Corey's group further studied this reaction with the aim of understanding its mechanism and determining the exact structure of the borane complex reducing agent. Their successful studies[378] have determined the following important aspects of this reaction that made it more practical and predictable reduction procedure than many others.

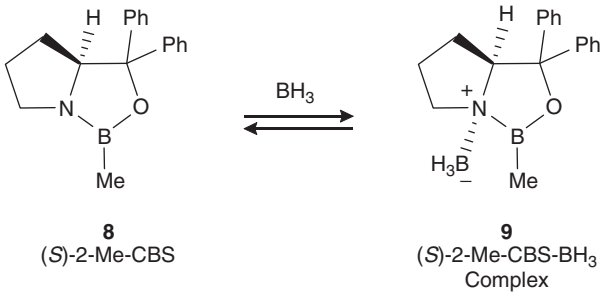
1. The amino alcohol, (*S*)-(−)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**3**) reacts initially with borane to form oxazaborolidine (**4**, Scheme 8, referred to as Itsuno's oxazaborolidine) which was isolated and characterized.
2. The roles of the oxazaborolidine and BH_3 in the reaction were identified. It was observed that the oxazaborolidine **4** alone does not reduce acetophenone even after several hours in THF at 23 °C. It was also observed that BH_3·THF alone reduced acetophenone relatively slowly at 23 °C. However, the combination of the oxazaborolidine with borane reduces aromatic ketone effectively with high enantioselectivity in < 1 min. Examination of the reaction kinetics added full understanding of the mechanistic rationale of the reaction and identified the role of the oxazaborolidine as a catalyst and the role of borane as stoichiometric reagent in the reduction procedure.[379] The role of the oxazaborolidine as a catalyst was confirmed by the reduction of acetophenone in 94% *ee* using BH_3-THF in the presence of 2.5–5 mol% of the oxazaborolidine **4**.
3. Based on the above findings, a mechanism for the catalytic process was proposed and supported by identification of key intermediates (Scheme 9).[379]
4. Once the reaction mechanism was understood, better oxazaborolidines were designed. The oxazaborolidine **7** derived from (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**6**) was prepared (Scheme 10) and determined to be a superior catalyst; it was named the Corey–Bakshi–Shibata (CBS)-catalyst. The next improvement introduced the B-methylated oxazaborolidine catalyst **8** (2-Me-CBS, Scheme 10)[380] which is easy to prepare (from (*S*)-diphenyl(pyrrolidin-2-yl)methanol and 1.1 equivalents of methylboronic acid in toluene) and exhibits better physical properties and air-stability than the CBS catalyst. Other substituted CBS catalysts were also prepared.[379]
5. The initial oxazaborolidine–borane addition complex intermediate (**9**, Scheme 11) was isolated and its structure was confirmed by single-crystal X-ray diffraction analysis.[381] Mathre and coworkers at Merck discovered that **9** can be isolated as a stable crystalline solid which is more stable than B-Me-CBS (**8**) and reported its single-crystal X-ray structure.[381a] Corey and coworkers also reported the preparation and single-crystal X-ray structure of the same borane complex **9**.[381b] The Merck group



Scheme 9 Mechanism of oxazaborolidine/borane reduction of ketones.



Scheme 10 Preparation of CBS oxazaborolidines.



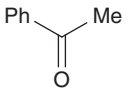
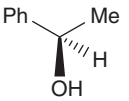
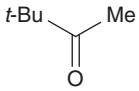
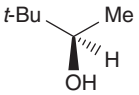
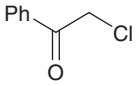
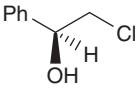
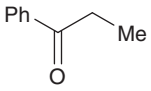
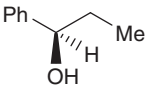
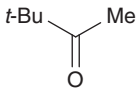
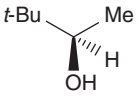
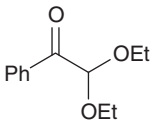
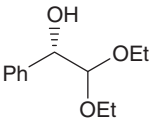
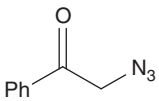
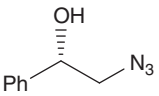
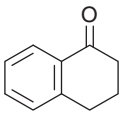
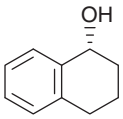
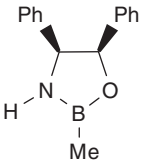
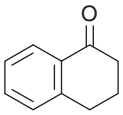
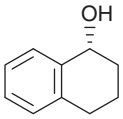
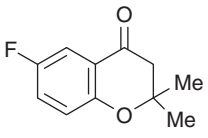
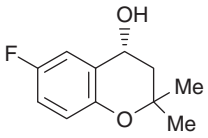
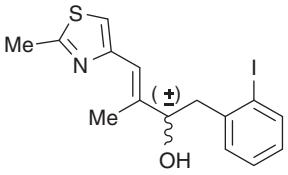
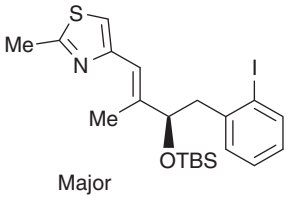
Scheme 11 Formation of the initial oxazaborolidine-BH_3 addition complex (9).

has used it as a stoichiometric reagent and as a catalyst with stoichiometric amounts of $BH_3.Me_2S$ to effect the enantioselective reduction of ketones in large-scale reactions (see Table 24, entry 18).

The utility of these oxazaborolidine catalysts was demonstrated by Corey's group and by many others; today, the CBS catalysts are used regularly in the asymmetric reduction of prochiral ketones with high levels of stereocontrol and accurate predictability of the stereochemical outcome. In addition to the above-mentioned oxazaborolidines, there are many other derivatives prepared by Corey and other research groups; a few examples are shown in Figure 4.[395,384,398–400]

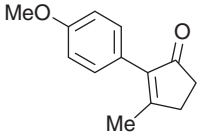
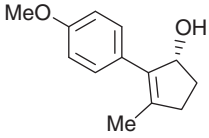
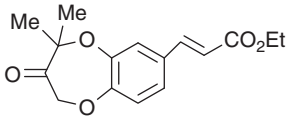
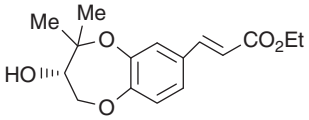
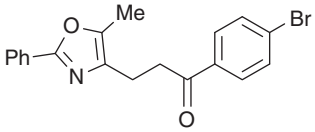
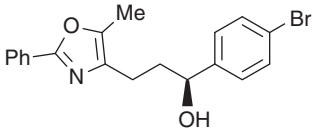
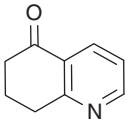
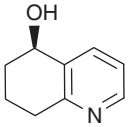
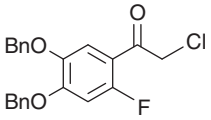
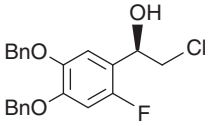
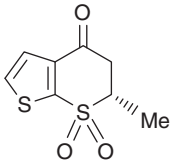
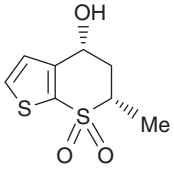
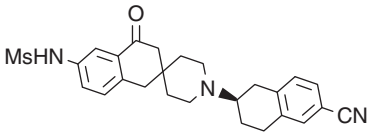
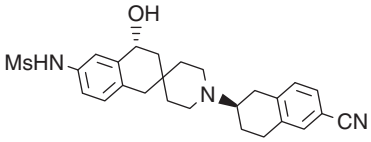
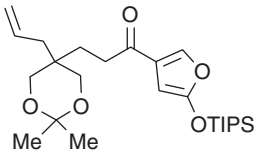
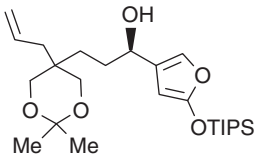
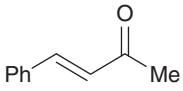
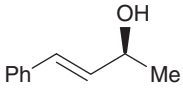
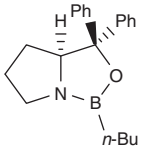
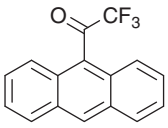
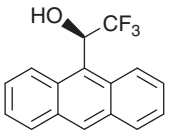
The vast applications of oxazaborolidine reductions are represented by many examples listed in Table 24 to highlight this highly effective and widely utilized procedure for the asymmetric reduction of prochiral ketones. Three of the early results from Corey's group using the CBS oxazaborolidine **7** are listed in entries 1–3, whereas two of the early results from **8** are highlighted in entries 4–5. An interesting example (Table 24, entry 12) is the conversion of the racemic alcohol, used by Danishefsky and

Table 24 Asymmetric reductions of ketones with oxazaborolidines/borane

Entries	Substrate	Product	Conditions	Yield (%)	References
1			(*S*)-CBS (0.1 equivalent) THF, BH_3 (1 equivalent), 1 min, 25 °C	>99.7	378
2			(*S*)-CBS (0.1 equivalent), THF, BH_3 (0.6 equivalent), 1 min, 25 °C	>99.7	
3			(*S*)-CBS (0.05 equivalent), THF, BH_3 (0.6 equivalent), 1 min, 25 °C	>99.7	
4			(*S*)-Me-CBS (0.1 equivalent), THF, $BH_3 \cdot THF$ (0.6 equivalent), −10 °C, 2 min	96.7 *ee*	380
5			(*S*)-Me-CBS (0.1 equivalent), THF, $BH_3 \cdot THF$ (0.6 equivalent), −10 °C, 2 min	97.3 *ee*	
7			(*S*)-Me-CBS (10 mol %) $BH_3 \cdot PhN(Et)_2$ (1 equivalent), THF, 25 °C	96 96 *ee*	382
8			(*S*)-CBS, 10 mol% $BH_3 \cdot SMe_2$ (1 equivalent) toluene/THF, 40 °C	92 100 *ee*	383
9			 BH_3-SMe_2 (0.7 equivalent), THF, 25 °C	>90 94 *ee*	384a
10			(*R*)-Me-CBS (5 mol%) $BH_3 \cdot PhNEt_2$ (1 equivalent) Toluene	≥99 *ee*	385
11			(*S*)-Me-CBS (0.1 equivalent) $BH_3 \cdot SMe_2$ (1 equivalent) Toluene, −20 °C	>99 95 *ee*	386
12		 Major	1. Swern oxidation 2. (*R*)-Me-CBS, $BH_3 \cdot SMe_2$; 3. TBSOTf, lutidine	92 (*S*: *R*=4:1)	387

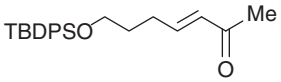
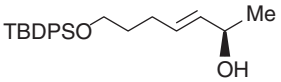
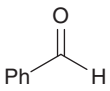
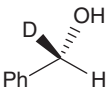
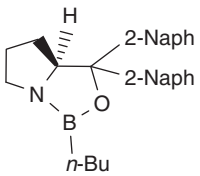
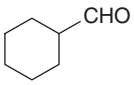
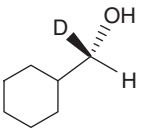
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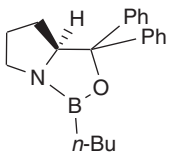
Table 24 Continued

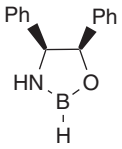
Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
13			(*S*)-Me-CBS $BH_3 \cdot SMe_2$	>95% yield 90 *ee*	388
14			(*R*)-Me-CBS (0.03 equivalent), $BH_3 \cdot Me_2S$ (0.6 equivalent), THF, 0 °C, 20 min	72, 78 *ee*	389
15			(*R*)-Me-CBS (0.05 equivalent), BH_3(1.7 equivalents), THF, 23 °C	>95 94 *ee*	390
16			(*S*)-Me-CBS (1 equivalent), $BH_3 \cdot SMe_2$ (1 equivalent), CH_2Cl_2, r.t.	88 >99 *ee*	391
17			(*R*)-Me-CBS (0.1 equivalent), $BH_3 \cdot THF$ (0.6 equivalent), THF/Tol., 10 min, r.t.	95 95 *ee*	392
18			(*S*)-Me-CBS-BH_3 (9) (1 equivalent), $BH_3 \cdot SMe_2$ (1 equivalent), CH_2Cl_2, –20 °C	96 99.4 *ee*	381a
19			*i*-PrOH, CH_2Cl_2, $BH_3 \cdot SMe_2$ (2.5 equivalents), –20 °C Then: (*S*)-Me-CBS-BH_3 (**9**) (0.1 equivalent), –20–15 °C	92 99 *ee*	393
20			(S)-Me-CBS (30 mol %) $BH_3 \cdot SMe_2$, neat (1 equivalent), –10 °C, 10 min Then: TBAF, 0 °C	100 97 *ee*	394
21				>95 92 *ee*	395
22			0.1 equivalent Catecholborane (1.5–2 equivalents), toluene, –78 °C, 15 h	95 94 *ee*	

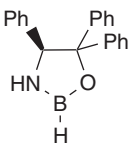
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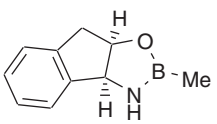
Table 24 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
23			Catecholborane (1.98 equivalents), (*S*)-Me-CBS (0.14 equivalent), toluene, −78 °C	94 88 *ee*	396
24			 (0.3 equivalent) D-catecholborane (1.5 equivalents), −126 °C, 3.5 h	95 *ee*	397
25				92 *ee*	


10[391]


11[392]


12[393]


13[394]

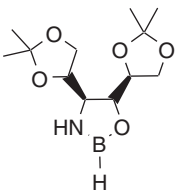

14[395]

Figure 4 Different oxazaborolidines.

coworkers[387] in the synthesis of 12,13-benzodesoxyepothilone-B. The racemic alcohol was oxidized to the ketone then reduced with (*R*)-2-Me-CBS to give a 4:1 mixture of *S*:*R* enantiomers.

Quallich and Woodall[390] studied the enantioselective reduction of an oxazole derivative (Table 24, entry 15). Typical reduction with 0.05 equivalent of oxazaborolidine catalyst and 0.7 equivalent of borane gave incomplete reaction (85:15 mixture of recovered ketone to product alcohol). They determined that excess borane (1.7 equivalents) was needed to compensate for the competitive coordination of the oxazole nitrogen with borane. A similar case with a nitrogen heterocyclic compound was reported by Bell and coworkers[391] (Table 24, entry 16). In this case, using the (*S*)-2-Me-CBS (**8**) stoichiometrically and excess borane to complex with the pyridine nitrogen gave the (*R*)-tetrahydroquinolinol in excellent yield and >99% *ee*.

As mentioned above, Mathre and coworkers[381a] isolated and used the initial borane addition complex (*S*)-2-Me-CBS-BH_3 (**9**). The ketosulfone (Table 24, entry 18), an intermediate in the synthesis of the carbonic anhydrase inhibitor MK-0507, was reduced with **9** (1 equivalent) and BH_3-SMe_2 (1 equivalent) to give the corresponding alcohol in 99.4% *ee*.

Shi and coworkers,[393] studied the reduction of the ketone in entry 19; originally required stoichiometric amounts of the (*S*)-Me-CBS-BH_3 (**9**) to give the product in >99% *ee*. Using catalytic amount of the oxazaborolidine the enantiomeric purity was only 90–92%. They found that addition of isopropanol to the reaction mixture improved the enantioselectivity of the catalytic system from 92 to 98%. The role of *i*-PrOH in the catalytic process was not clear but the reaction was scaled up to large-scale production.

Corey and Bakshi[395] found the use of the combination of B-*n*-Bu-CBS catalyst (**10**) and catecholborane to be superior to the use of Me-CBS catalyst/BH_3 combination with substrates containing functionalities which are sensitive to borane (e.g., olefins and amides) and with trifluoromethyl ketones. The B-*n*-Bu-CBS/catecholborane procedure performs with considerably enhanced enantioselectivity at low temperature in the reduction of substrates such as α,β-enones (Table 24, entry 21) and 9-anthryl trifluoromethyl ketone (Table 24, entry 22). Similarly, Ellman and Soures[396] used (*S*)-Me-CBS and catecholborane combination in the reduction of an α,β-enone intermediate in the synthesis of 3-substituted pipecolic acid (Table 24, entry 23).

Corey and Link[397] used another B-*n*-Bu-CBS catalyst made from (*S*)-(−)-2-(di-β-naphthylhydroxymethyl)pyrrolidine in combination with D-catecholborane to prepare chiral 1-deuterio primary alcohols from aldehydes in high enantioselectivity (Table 24, entries 24–25).

8.01.10.3 Enantioselective Reduction of Ketones with Sodium Borohydride, Catalyzed by Chiral (β-Oxoaldiminato)cobalt(II) Complexes

Mukaiyama, Yamada, and coworkers[401] developed a procedure for the enantioselective reduction of prochiral ketones and *N*-diphenylphosphinylimines with $NaBH_4$ in the presence of a chiral nonracemic Co(II) catalyst. The reaction requires the addition of small amounts of an alcohol or a combination of two alcohols to achieve the optimum yield and enantioselectivity.

Cobalt Catalysts: The cobalt catalysts are (β-ketoiminato)cobalt(II) complexes; several of these cobalt complexes were synthesized and tested with different ketones (Figure 5). The choice of one catalyst is based on a general matching pattern with the ketone substrates. For example, the cobalt complex **14** derived from 1,2-diphenylethylenediamine is effective for the reduction of sterically hindered aryl ketones. The complex **15** derived from 1,2-bis(3,5-dimethylphenyl)ethylenediamine matches better with cyclic aryl ketones that exhibit lower steric demands. The cobalt catalyst **16** derived from the bulky 1,2-bis(2,4,6-trimethylphenyl)-ethylenediamine matches well with acylic alkyl aryl ketones and complex **17** is best for reduction of 1,3-diketones.

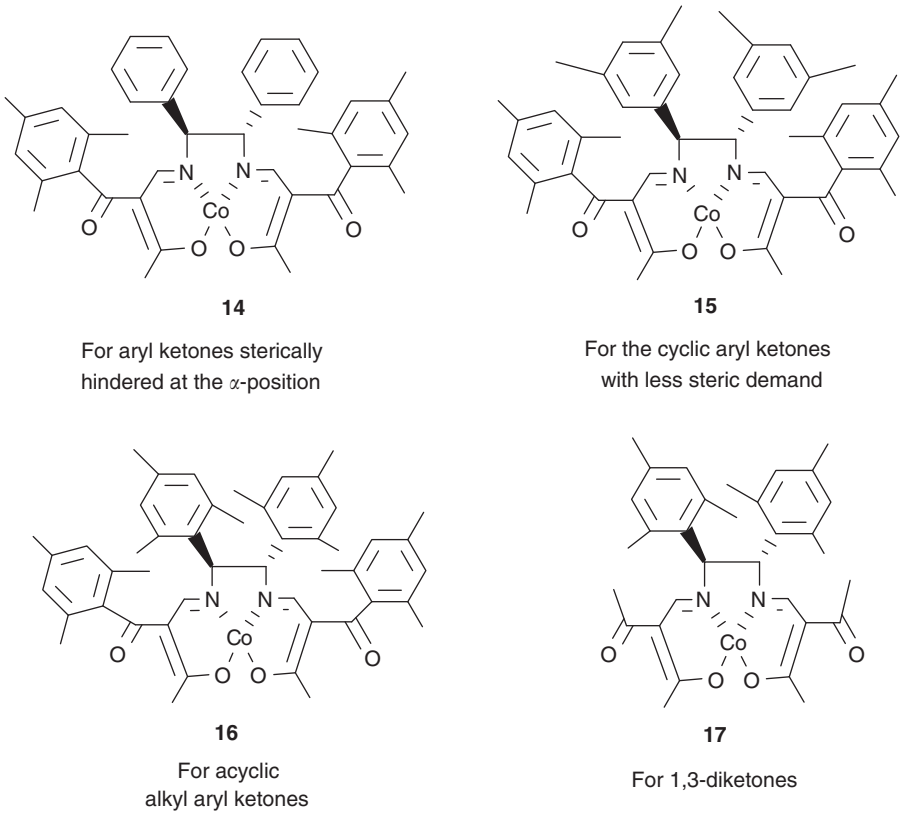


Figure 5 β-Ketoiminato cobalt(II) complex catalysts for enantioselective borohydride reductions. Reproduced from Yamada, T.; Nagata, T.; Sugi, K. D.; *et al. Chem. Eur. J.* **2003**, *9*, 4485–4509.

Role of alcohols in activating $NaBH_4$: In the absence of any alcohol, 6-methoxy-1-tetralone was reduced in <10% yield and in only 5% *ee*; the reduction was improved in the presence of ethanol to give the alcohol in 38% yield and 83% *ee* after 24 h. Both yield and enantioselectivity were greatly improved to 82% and 87% *ee*, respectively, when tetrahydrofurfuryl alcohol (THFA) was used. The best enantioselectivity (91% *ee*) was obtained when a combination of ethanol and THFA was used. The amount of H_2 evolution during the treatment of the borohydride with alcohols is nearly 2 M equivalents indicating that $NaBH_4$ reacted with 2 M equivalents of alcohols. It was postulated that $NaBH_4$ is modified with the two alcohol molecules to form the substituted form $NaBH_2(OEt)(OTHFA)$ (**18**, Figure 6).

The use of MeOH versus EtOH in combination with THFA was also studied and it was concluded that the ethanol-THFA combination is preferred for reduction of sterically less demanding ketones (primary alkyl or cyclopropyl ketone) and methanol-THFA combination is preferred for reduction of sterically hindered ketones (secondary alkyl ketone).

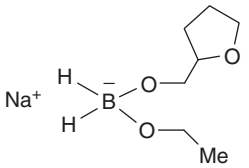
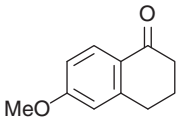
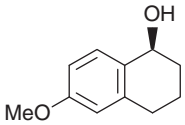
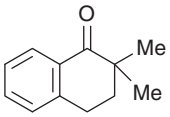
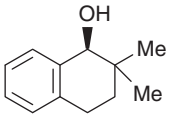
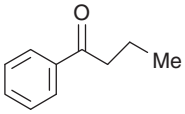
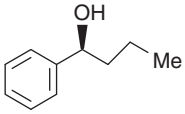
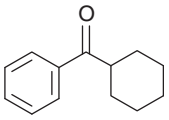
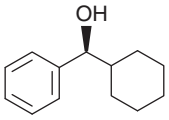
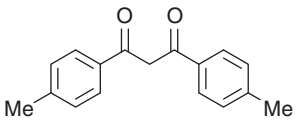
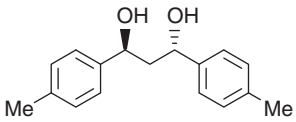
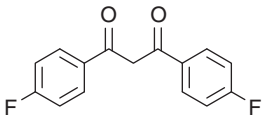
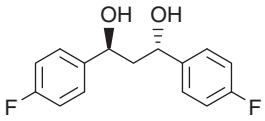
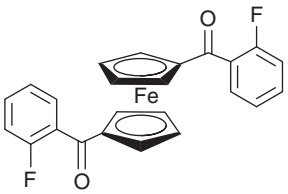
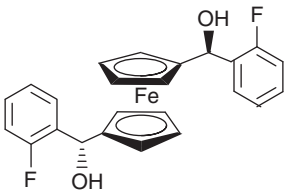
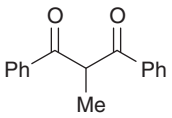
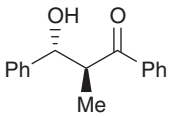


Figure 6 $NaBH_2(OEt)(OTHFA)$ (**18**). Reproduced from Yamada, T.; Nagata, T.; Sugi, K. D.; *et al. Chem. Eur. J.* **2003**, *9*, 4485–4509.

Thus using the modified borohydride **18** and 1 mol% of the Co catalyst **14**, the reduction of 6-methoxy-1-tetralone in $CHCl_3$ at −20 °C for 20 min gave a quantitative yield of the alcohol in 94% *ee* (Table 25, entry 1). Other examples of the enantioselective reductions of ketones are listed in Table 25, entries 2–4.

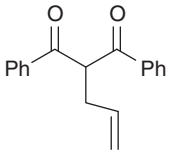
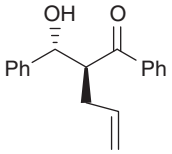
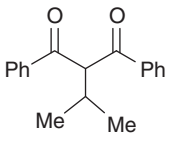
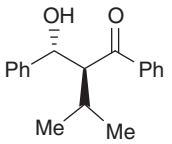
The scope of this innovative enantioselective reducing system was extended to include the reduction of other more complex classes of ketones.[402] Optimized procedures were devised for the reduction of 1,3-diaryl-1,3-diketones to prepare enantiomerically

Table 25 Enantioselective borohydride reduction catalyzed by chiral cobalt complexes

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			Co catalyst **15** (1 mol%) $NaBH_2(OEt)(OTHFA)$ $CHCl_3$, −20 °C, 20 min	>95% yield 94 *ee*	401
2			Co catalyst **14** (1 mol%) $NaBH_2(OMe)(OTHFA)$ $CHCl_3$, −20 °C, 12 h With Co catalyst **15** With Co catalyst **16**	>95% yield 91 *ee* 75 *ee* No Rxn	
3			Co catalyst **14** (1 mol%) $NaBH_2(OEt)(OTHFA)$ $CHCl_3$, −20 °C, 12 h With Co catalyst **15** With Co catalyst **16**	>95% yield 63 *ee* 87 *ee* 97 *ee*	
4			Co catalyst **14** (1 mol%) $NaBH_2(OEt)(OTHFA)$ $CHCl_3$, −20 °C, 12 h With Co catalyst **15** With Co catalyst **16** $NaBH_2(OMe)$ (OTHFA)	>95% yield 62 *ee* 65 *ee* 95 *ee*	402
5			Co catalyst **17** (5 mol%)	94 85:15 *dl:meso* 97 *ee*	
6			$NaBH_4$ (3 equivalents) EtOH (9 equivalents), THFA (42 equivalents), $CHCl_3$, 20 °C, 40–60 h	94 85:15 *dl:meso* 97 *ee*	
7			Co catalyst **17** (1.25 mol%) $NaBH_2(OEt)(OTHFA)$ (4 equivalents), Et_2O, 0 °C, 3 h	94 99:1 *dl:meso* >99 *ee*	
8			Co catalyst **17** (5 mol%) $NaBH_4$ (4 equivalents) EtOH (3 equivalents), THFA (14 equivalents), $CHCl_3$, 0 °C, 10 h	93 99 *ee* 99:1 *dr*	402

(*Continued*)

Table 25 Continued

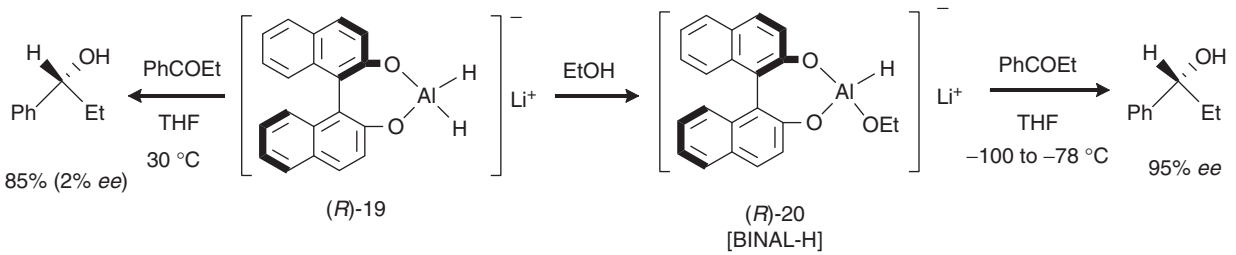
Entries	Substrate	Product	Conditions	Yield (%)	References
9			Co catalyst **17** (5 mol%) $NaBH_4$ (4 equivalents) EtOH (3 equivalents), THFA (14 equivalents), $CHCl_3$, 0 °C, 10 h	88 97 *ee* 99:1 *dr*	402
10				45 91 *ee* 99:1 *dr*	

pure C_2-symmetrical 1,3-diaryl-1,3-propanediols, reduction of 1,1′-diacylferrocene to enantiomerically pure 1,1′-ferrocenyldiols with high *dl* to *meso* selectivity and reduction of 2-substituted-1,3-diketones to *anti*-aldol compounds. The products of these reductions are extremely useful synthetic targets. The best performing catalyst for the reduction of 1,3-diaryl-1,3-diketones and 1,1′-diacylferrocene is catalyst **17**. Several of these compounds were reduced using the optimized procedure in excellent yield and high enantioselectivity; some representative examples are listed in Table 25, entries 5–7.

The reduction of 2-substituted-1,3-diketones to the corresponding aldol compounds is more complicated, because only one of the two carbonyls is reduced and there are four possible diastereomeric product because of the 2-substitution. The reaction was optimized using the symmetrical 1,3-diphenyl-2-methyl-1,3-propanedione and it was found that catalyst **17** was the most efficient catalyst for the enantioselective reduction of this diketone to the *anti*-aldol compound (2*S*,3*R*)-3-hydroxy-2-methyl-1,3-diphenylpropan-1-one in 93% yield of the *anti*-product of 99% diastereoselectivity and 99% *ee* (Table 25, entry 8). The catalytic enantioselective reduction was successfully applied to other 2-substituted-1,3-daryl-1,3-propanediones to form the corresponding enantiomerically enriched 2-substituted-1,3-diaryl-3-hydroxypropanones in good to high yield with excellent *anti*-selectivity and excellent enantioselectivity (Table 25, entries 9–10).

8.01.10.4 Enantioselective Reduction of Ketones with Binaphthol-Modified LAH (BINAL-H)

In 1984, Noyori and coworkers[403,404] reported a chiral reagent for the stereospecific reduction of prochiral aromatic ketones. The reagent was made from equimolar amounts of (*R*)- or (*S*)-2,2′-dihydroxy-l,1′-binaphthyl (binaphthol) and a simple alcohol. The initial design was to mix equimolar amounts of binaphthol and LAH in THF to form the C2-symmetric (*R*)- or (*S*)-**19**. However, this reagent was disappointing as it reduced acetophenone to 1-phenylethanol with only 2% *ee*. A much better reagent was obtained by replacing one of the remaining two hydrides in **19** (Scheme 12) with an alkoxide group such as ethoxy, so that only one hydride remains to form (*R*)- or (*S*)-**20**. The use of the binaphthol-modified aluminum hydride reagent (*R*)-**20** or (*S*)-**20** (known as BINAL-H) resulted in a remarkable increase in stereospecificity of the reduction of acetophenone to form 1-phenylethanol in 95% *ee*. The reagent provided excellent results in the reduction of aryl alkyl ketones and α-alkynyl ketones However, the enantioselectivity dropped severely when purely aliphatic ketones are employed as substrates. For example, the reductions of 2-octanone and benzyl methyl ketone with (*S*)-**20** gave the corresponding alcohols in low enantiomeric ratios (Table 26, entries 4–5).



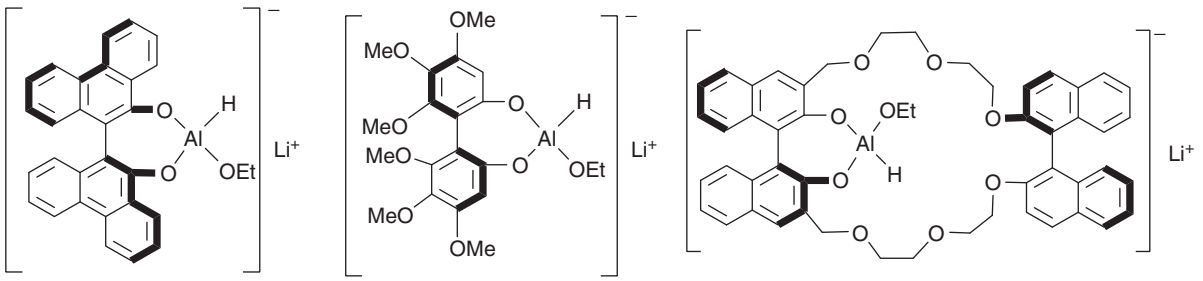
Scheme 12 Formation of BINAL-H and reduction of propiophenone.

Yamamoto[405] developed the BINAL-H derivative **21** (Figure 7) which behaved similarly to **20** and offered no improvement in the stereoselective reduction of aliphatic ketones. The stereoselective reduction of aliphatic ketones was improved to levels comparable to that obtained from reduction of aromatic ketones by two modifications of BINAL-H. The first is hexamethoxybiphenyl ligand **22** (Figure 7) developed by Meyers and coworkers;[406] this reagent reduced 2-octanone with high enantioselectivity of 88:12 *er* and benzyl ethyl ketone with even better 97:3 *er* (Table 26, entries 6–7). The second is the crown

Table 26 Reduction of ketones with BINAL-H reagents

Entries	*BINAL-H*	*Ketone*	*Product*	*Conditions*	*Yield (%)*	S : R *ratio*	*References*
1	(*R*)-20	PhCOMe	PhCH(OH)Me	100 °C (3 h); −78 °C (16 h)	61	3:97	404
2	(*S*)-20	Ph-CO-*n*-Pr	Ph-CH(OH)-*n*-Pr	100 °C (3 h); −78 °C (16 h)	78	>99:1	
3	(*S*)-20	I-Octyn-3-one	I-Octyn-3-ol	100 °C (1 h); −78 °C (2 h)	71	94:6	
4	(*S*)-20	2-Octanone	2-Octanol	100 °C (2 h); −78 °C (16 h)	67	62:38	
5	(*S*)-20	Benzyl methyl ketone	3-Phenyl-2-propanol	100 °C (2 h); −78 °C (16 h)	74	56:54	
6	(*S*)-22	2-Octanone	2-Octanol	100 °C (2 h); −78 °C (12 h)	76	88:12	405
7	(*S*)-22	Benzyl methyl ketone	3-Phenyl-2-propanol	100 °C (2 h); −78 °C (12 h)	72	97:3	
8	(*S,S*)-23	Benzyl methyl ketone	3-Phenyl-2-propanol	0 °C (24 h)	76	94:6	406
9	(*S,S*)-23	2-Hexanone	2-Hexanol	0 °C (24 h)	78	93:7	

2,2′-dihydroxy-l,1′-binaphthyl complex **23** (Figure 7) developed by Yamamoto[407] which also showed practical selectivity in the reduction of aliphatic ketones (Table 26, entries 8–9).

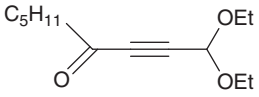
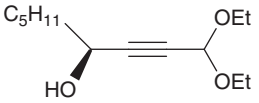
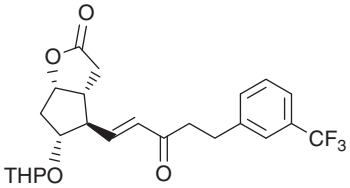
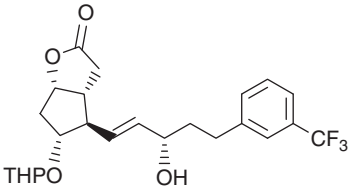
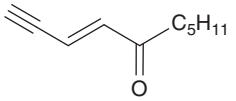
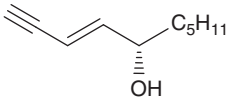
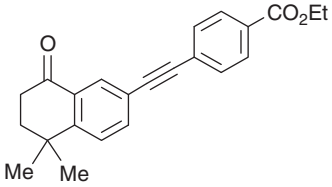
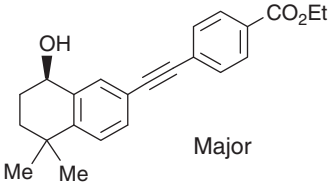


(*S*)-**21** (*S*)-**22** (*S,S*)-**23**

Figure 7 BINAL-H derivatives [(*S*)-**21**, (*S*)-**22** and (*S,S*)-**23**].

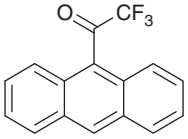
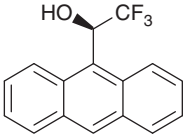
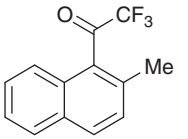
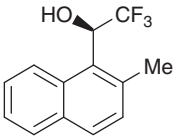
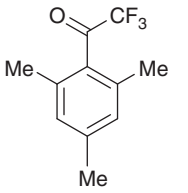
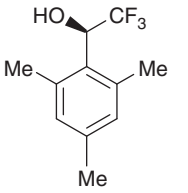
BINAL-H reductions have been used numerous times in organic synthesis with excellent stereoselectivity; some of these examples are listed in Table 27. In the stereoselective synthesis of the lipid peroxidation products 4-hydroxypent-2-enal, the

Table 27 Literature examples for the use of BINAL-H in ketone reductions

Entries	*Ketone*	*Product*	*Conditions*	*Yield (%)*	*References*
1			(*S*)-**20** THF, −78 °C	85 97 *ee*	408
2			(*S*)-**20**, THF	Only isomer No reported yield	409
3			(*S*)-**20** (3 equivalents), THF, −100 °C (1 h); −80 °C (1 h)	88 94 *ee*	410
4		 Major	(R)-**20** (5 equivalents) THF, −50 °C, 16 h	>95% yield *R*: 85 *S*: 15	411

(*Continued*)

Table 27 Continued

Entries	Ketone	Product	Conditions	Yield (%)	References
5			(*S*)-**20** (2.6 equivalents) THF, −20 °C, 22 h (*S*)-**20** (1.6 equivalents) THF, 25 °C, 3 h	90 98 *ee* 82 75 *ee*	412
6			(*S*)-**20** (2.5 equivalents) THF, −60 °C, 24 h	85 93 *ee*	
7			(*S*)-**20** (2.3 equivalents) THF, −60 °C, 24 h	69 97 *ee*	

intermediate acetylenic ketone (Table 27, entry 1) was reduced to the (*S*)-enantiomer in 85% yield and 97% *ee* using Noyori's reagent (S)-**20**.[408] Similar results[409–410] were reported for other unsaturated ketones (Table 27, entries 2–3) while the selectivity was lower in the reduction of the tetralone derivative at entry 4.[411]

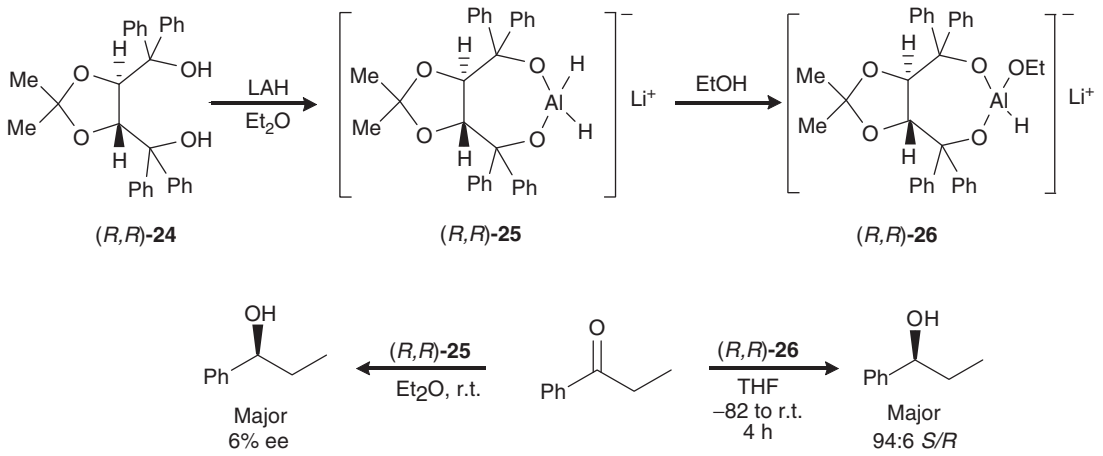
The enantioselective reduction of 9-antharyl trifluoromethyl ketone to the corresponding alcohol (Table 27, entry 2) was studied by Chong and Mar[412] They found the most common reagents used for the asymmetric reduction of alkyl aryl ketones to be unsuccessful. For example, reduction of the ketone with Itsuno's oxazaborolidine gave 75% yield of the (*R*)-alcohol in 13% *ee*, Corey's 'CBS' reagent gave only 16% yield of (*R*)-alcohol in 18% *ee*, whereas Brown's chlorodiisopinocampheylborane was very slow (<l0% reaction after 20 h at room temperature). However, using 2.6 equivalents of Noyori's (*S*)-BINAL-H reagent reduced this ketone and other 'hindered' aryl trifluoromethyl ketones in good to excellent enantioselectivity at −60 °C. The reduction was extremely slow requiring 3 days to reach 51% conversion, but the (*R*)-trifluoromethylcarbinol was obtained in 93% *ee* (Table 27, entry 2). Unlike other BINAL-H reductions that require very low temperatures, the yield was improved and the reaction time was much shorter without loss of enantioselectivity by carrying out the reduction at −20 °C. Other aryl trifluoromethyl ketones were reduced under similar conditions in good enantioselectivity (Table 27, entries 3–4). Corey[395] reported later the reduction of 9-anthryl trifluoromethyl ketone in 94% *ee* and >95% yield with a modified CBS-reducing agent (see Table 24, entry 22).

Although the BINAL-H reagents have demonstrated their effectiveness and high enantioselectivity in the reduction of pro-chiral ketones, their use has been limited in the recent years. The development of newer catalytic more efficient and economical procedures may have contributed to that. In addition, the reagents are usually used in excess (2–4 equivalents), most are expensive and commercially unavailable and most reductions are carried out at very low temperatures (−100 °C to −78 °C).

8.01.10.5 Enantioselective Reduction of Ketones with TADDOL-Modified LAH

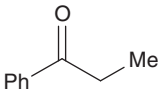
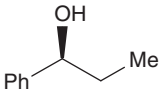
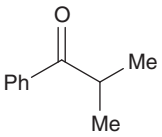
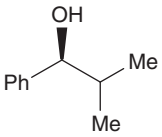
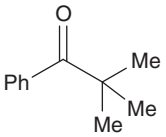
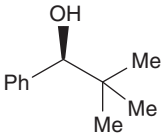
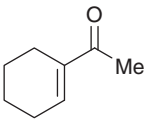
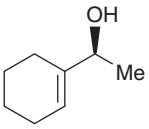
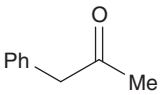
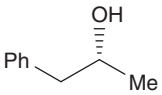
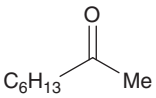
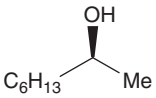
The use of tartaric acid or its derivatives as chiral auxiliaries has always been an attractive target in enantiomeric reactions because of the commercial availability of tartaric acid in both enantiomeric forms. Seebach and coworkers prepared tartaric acid derivatives known as $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs). They used these compounds as chiral auxiliaries (such as (*R*,*R*)-**24**) for enantioselective nucleophilic additions.[413] Beck and coworkers[414] investigated the enantioselective reduction of ketones with TADDOL-modified LAH. The first attempt using the C_2-symmetric dihydride (*R*,*R*)-**25** in reduction of propiophenone gave the secondary alcohol in 6% *ee*. However, the reagent was later remodeled after Noyori's BINAL-H reagent and modified by adding 1 equivalent of EtOH to form (*R*,*R*)-**26**; this reagent reduced propiophenone under optimized conditions to give the corresponding alcohol in 94:6 *er*. Several other TADDOL reagents were prepared but none was better than (*R*,*R*)-**26** (Scheme 13).

The enantioselctive reduction of several ketones was examined with (*R*,*R*)-**26**; the best results were obtained when the ketone was added to a solution of 2 equivalents of the reducing agent in THF at −78 °C and the mixture allowed to warm up to room temperature for over 4 h. Under these conditions, the enantioselectivity in the reduction of aryl alkyl ketones is excellent but decreases with increasing size of the alkyl group (Table 28, entries 1,3–4), moderate for acetylcyclohexene (Table 28, entry 5), and poor for 3-octanone (Table 28, entry 7). The selectivity is reversed with benzyl methyl ketone with moderate selectivity for the *R*-enantiomer (Table 28, entry 5). The authors have also attempted to make use of a known property[413] of TADDOLs inclusion compounds (clathrates) with chiral alcohols to enhance the enantiopurity of the low selectivity products. Addition of pentane to the crude product (still containing TADDOL) and stirring the resulting white precipitate with the supernatant liquid for 24 h,



Scheme 13 TADDOL-modified LAH and their use in reduction of propiophenone.

Table 28 Enantioselective reduction of ketones with LAH-TADDOLate [(*R,R*)-26][413]

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*(S):(R)*
1			(*R,R*)-**26** (2 equivalents), THF, –82 °C to r.t., 4 h	95	95:5
2			1. (*R,R*)-**26** (2 equivalents), THF, –82 °C to r.t., 4 h 2. enhancement via clathrate formation	43	98.5:1.5
3			(*R,R*)-**26** (2 equivalents), THF, –79 °C to r.t., 4 h	90	93:7
4			(*R,R*)-**26** (2 equivalents), THF, –72 °C to r.t., 4 h	89	77:23
5			(*R,R*)-**26** (2 equivalents), THF, –63 °C to r.t., 5 h	72	82:18
6			1. (*R,R*)-**26** (2 equivalents), THF, –82 °C to r.t., 4 h 2. Enhancement via clathrate formation	38	98.5:1.5
7			(*R,R*)-**26** (2 equivalents), THF, –74 °C to r.t., 5 h	82	21:79
8			1. (*R,R*)-**26** (2 equivalents), THF, –82 °C to r.t., 4 h 2. Enhancement via clathrate formation	25	11.5:88.5
9			(*R,R*)-**26** (2 equivalents), THF, –76 °C to r.t., 5 h	83	61:39

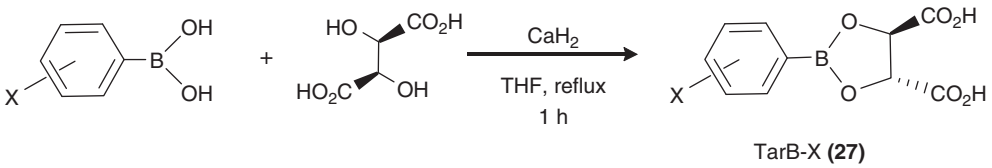
followed by filtration and heating in a bulb-to-bulb distillation apparatus afforded the alcohol product. This work-up procedure was applied to the crude product from reduction of acetophenone (entry 2) and acetylcyclohexene (entry 6) to give the corresponding alcohols in higher enantiopurity but considerably lower yield.

This procedure has seen very limited applications probably because it is stoichiometric and has limited scope.

8.01.10.6 Enantioselective Reduction of Ketones Mediated by L-TarB-NO_2

Singaram and coworkers[415] introduced a new class of enantioselective reducing reagents based on the tartaric acid scaffold. The reduction system consists of the combination of enantiomeric boronate esters, named collectively TarB-X and $LiBH_4$. TarB-X are prepared in high yields from the reaction of equimolar amounts of L-tartaric acid and arylboronic acids in THF at reflux

temperature in the presence of CaH_2 for water removal (Scheme 14). The TarB-X reagents are prone to hydrolysis and must be used in aprotic solvents. Reduction of acetophenone with the combination of the unsubstituted reagent **27** (X=H) and $LiBH_4$ in THF at r.t. gave 1-phenylethanol in 71% *ee*. After screening several substituted reagents, the 3-nitrophenyl reagent **27** (X=3-NO_2) named TarB-NO_2 emerged as a superior reagent as it reduced acetophenone with the highest enantioselectivity (99% *ee*). The study also showed that free carboxylic groups on TarB-NO_2 are necessary to achieve high enantioselectivities probably through the formation of acyloxyborohydrides with $LiBH_4$.

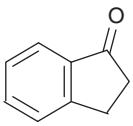
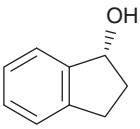
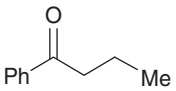
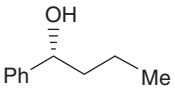
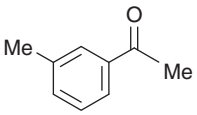
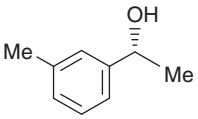
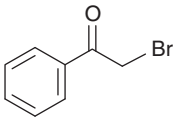
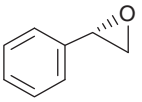
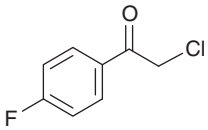
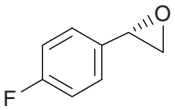
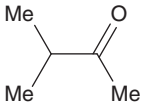
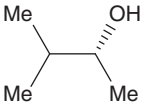
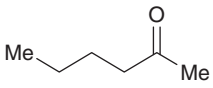
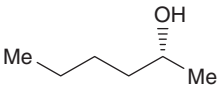


TarB-X **(27)**

Scheme 14 Preparation of tarB-X ligands.

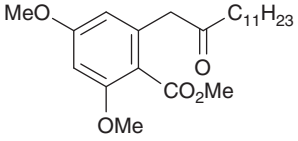
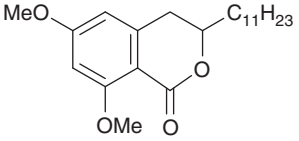
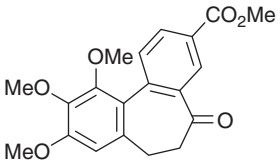
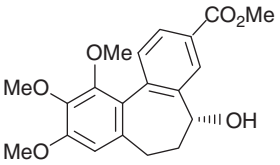
The optimized reduction conditions make use of L-TarB-NO_2 reagent (2 equivalents), $LiBH_4$ (1 equivalent) in THF at 25 °C. Even though the reagent is used in stoichiometric amounts, the boronic acid is recovered by a simple extraction with aqueous NaOH. Several ketones were reduced under these conditions in high enantioselectivity and excellent chemical yields. Although the use of $LiBH_4$ is ideal for this reduction system, it is both expensive and difficult to handle. Therefore, the economical and easier to handle $NaBH_4$, which is nearly insoluble in THF, was used in combination with TarB-NO_2 in a heterogenous mixture and was found to be as effective as the homogenous $LiBH_4$ reductions. In general, the reduction of aromatic and hindered ketones gave the corresponding alcohols in excellent enantioselectivity, whereas the reduction of aliphatic and α-haloketones gave the corresponding alcohols in moderate to high enantioselectivity. One of the limitations of TarB-NO_2 is in the reduction of α-substituted ketones (with amino, cyano, azido, thio, sulfonyl, alkoxy, and phenoxy) which proceed with poor to modest enantioselectivity.[416] Several examples from the Singaram's group study are listed in Table 29 to show the utility of TarB-NO_2/BH_4^- combination for

Table 29 Enantioselective reduction of ketones with TarB-NO_2

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			L-TarB-NO_2 (2 equivalents) $LiBH_4$ (1 equivalent), THF, 25 °C, 1.5 h	100 (GC) 99 *ee*	415b
2			L-TarB-NO_2 (2 equivalents), $LiBH_4$ (1 equivalent), THF, 25 °C, 0.5 h	100 (GC) 90 *ee*	
3			L-TarB-NO_2 (2 equivalents), $NaBH_4$ (1 equivalent), THF, 25 °C	79 98 *ee*	
4			1. L-TarB-NO_2 (2 equivalents), $NaBH_4$ (1 equivalent), THF, 25 °C 2. NaOH	80 94 *ee*	
5				87 86 *ee*	
6			L-TarB-NO_2 (2 equivalents), $NaBH_4$ (1 equivalent), THF, 25 °C	80 80 *ee*	
7				83 56 *ee*	

(*Continued*)

Table 29 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
8			L-TarB-NO_2 (2 equivalents) $LiBH_4$ (1 equivalent), THF, r.t., 2 h	82 80 *ee*	417
9			L-TarB-NO_2 (2 equivalents) $LiBH_4$ (2.1 equivalents), THF, 25 °C	91 *ee*	418

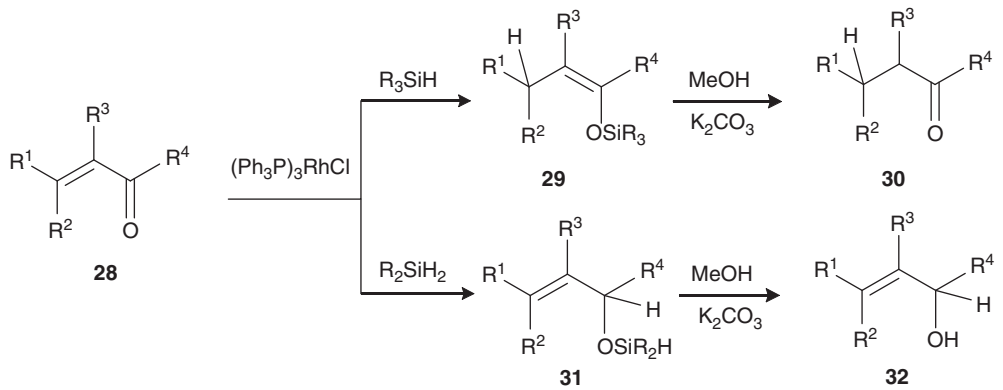
the enantioselective reductions of ketones (Table 29, entries 1–7). The reduction procedure proved very effective in Saeed's total synthesis of (3*R*)-3,4-dihydro-6,8-dimethoxy-3-undecyl-1*H*-[2]benzopyranone.[417] The key reduction of a ketoester intermediate (Table 29, entry 8) provided the product lactone in 80% *ee*; other reducing systems including diisocamphenylborane, Alpine–borane, and even enzymes were ineffective. In Wulff's enantioselective synthesis of (−)-(7*S*)-allocolchicine, (*S*)-methyl-CBS in equimolar amounts provided the corresponding alcohol in only 70% *ee* and kinetic resolution of the racemic alcohol was ineffective. The reduction with TarB-NO_2 and $LiBH_4$ gave the desired alcohol in 91% *ee* (Table 29, entry 9).[418]

8.01.11 Reduction with Silanes

8.01.11.1 Reductions of Aldehydes and Ketones via Hydrosilylation Reactions

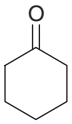
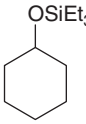
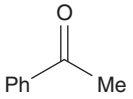
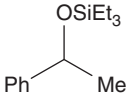
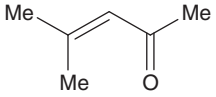
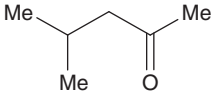
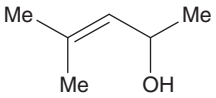
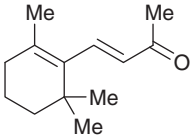
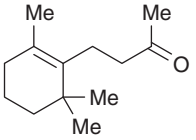
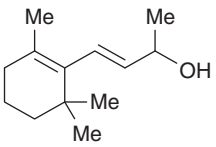
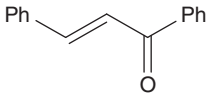
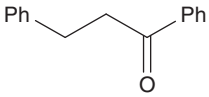
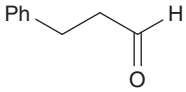
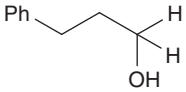
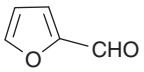
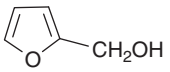
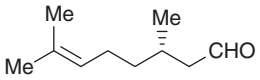
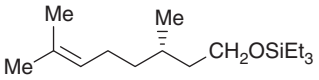
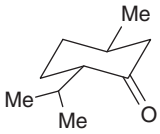
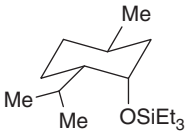
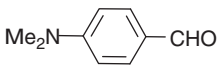
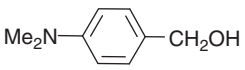
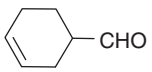
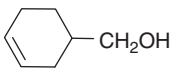
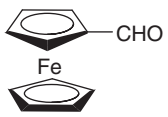
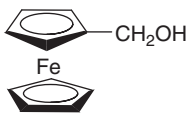
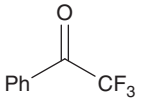
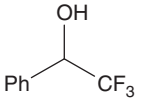
Hydrosilylation is the addition of Si–H bonds across unsaturated bonds such as C=C and C=O. The process is usually catalyzed by a metal ion in the presence of a hydrosilane. Rhodium was the first used metal in the Wilkinson's catalyst-mediated hydrosilylation of ketones in 1972. Since then, other metals such as iridium, rhenium, ruthenium, iron, nickel, and copper have been used as catalysts for hydrosilylation. Today, there is a wide selection of catalytic systems for hydrosilylation reactions that has expanded the scope of hydrosilylation to perform both chemoselective and stereoselective reductions of ketones and aldehydes.

In 1972, Ojima[419] reported a procedure for hydrosilylation of carbonyl compounds with triethylsilane catalyzed by Wilkinson's catalyst, $(Ph_3P)_3RhCl$. The procedure was applied to the reduction of cyclohexanone, acetophenone, and benzaldehyde and the products were isolated as the triethylsilyl ethers in high yields (Table 30, entries 1–2). It was also stated that α,β-unsaturated ketones and aldehydes were hydrosilylated via 1,4-addition to give silyl enol ethers, but no specific examples were mentioned. In a following publication in 1982, Ojima and Kogure[420] further studied the hydrosilylation of α,β-unsaturated ketones and aldehydes using the same catalyst to optimize the reaction conditions for regioselective hydrosilylation forming either the 1,4- or the 1,2-adducts, selectively. Remarkably, the type of hydrosilane determines the selectivity of the reaction for aliphatic α,β-unsaturated ketones and aldehydes (**28**, Scheme 15). The use of monohydrosilanes (R_3SiH) effects 1,4-addition to form the silyl enol ether **29** which up on methanolysis forms the saturated ketone **30**. However, the use of dihydro- or trihydrosilanes effects the selective 1,2-reduction of the carbonyl group to give the allylic alcohol **32** via allylic silyl ether **31** (see Scheme 15 and examples in Table 30, entries 3–4). Exceptions are aromatic enones such as chalcone or crotonophenone that are always reduced by exclusive 1,4



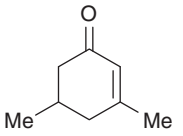
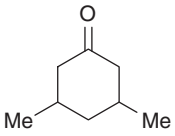
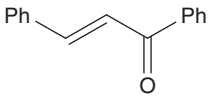
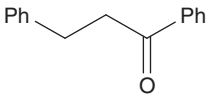
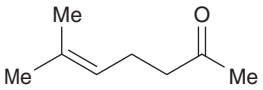
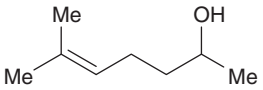
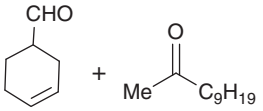
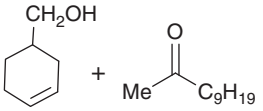
Scheme 15 Regioselective hydrosilylation of α,β-unsaturated aldehydes and ketones.

Table 30 Reductions of aldehydes and ketones via catalytic hydrosilylations

Entries	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			Et_3SiH, $(Ph_3P)_3RhCl$ r.t.	98	419
2				97	
3			1. Et_3SiH (1.1 equivalents) $(Ph_3P)_3RhCl$ (0.01 equivalent), 50 °C, 1 h 2. MeOH, K_2CO_3	95 99:1	420
			1. $PhSiH_3$ (1.1 equivalents) $(Ph_3P)_3RhCl$ (0.01 equivalent), r.t., 1 h 2. MeOH, K_2CO_3	95 1:99	
4			1. Et_3SiH (1.1 equivalents) $(Ph_3P)_3RhCl$ (0.01 equivalent), 50 °C, 2 h 2. MeOH, K_2CO_3	90 100:0	
			1. $PhSiH_3$ (1.1 equivalents) $(Ph_3P)_3RhCl$ (0.01 equivalent), r.t., 30 min 2. MeOH, K_2CO_3	97 0:100	
5			1. Et_3SiH or $PhSiH_3$ $(Ph_3P)_3RhCl$, 0–25 °C, 6–15 h 2. MeOH, K_2CO_3	100:0	
6			Cl_3SiH CH_2Cl_2/DMF (4:1) 0 °C, 4–6 h	98	421
7				81	
8			$Cl_2(PCy_3)_2Ru{=}CHPh$ (1 mol%) Et_3SiH (0.9 equivalent) 80 °C, 1 h	>85	422
9			$Cl_2(PCy_3)_2Ru{=}CHPh$ (1 mol%) Ph_2SiH_2 (0.9 equivalent) 50 °C, 3 h	80 3:1 a/e	
10			**33** (0.2 mol%) $PhSiH_3$ Toluene, r.t., 2 h; Then basic hydrolysis	89	423
11			**33** (0.2 mol%) $PhSiH_3$ Toluene, r.t., 4 h; Then basic hydrolysis	64	
12			$(dppe)_2Fe(H)_2$ (1 mol%) polymethylhydrosiloxane (PMHS) (2 equivalents) $NaB(OEt)_4$ (1 mol%) Toluene, 100 °C, 1–2 h Visible light; Then basic hydrolysis	90	424
13				75	

(*Continued*)

Table 30 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
14		 One isomer	$[(Ph_3P)CuH]_6$ (5 mol%) $PhSiH_3$ (1.5 equivalents) Toluene, r.t., 46 h	>95% yield	101
15			$[(Ph_3P)CuH]_6$ (5 mol%) $PhSiH_3$ (1.5 equivalents) Toluene, r.t., 10 min	96	
16			$[(Ph_3P)CuH]_6$ (3 mol%) PMHS (2.5 equivalents) Toluene, r.t., 22 h Then basic workup	78	425
17			$[(Ph_3P)CuH]_6$ (1.7 mol%) PMHS (2 equivalents) Toluene, 0 °C-r.t., 22 h Then basic workup	94	

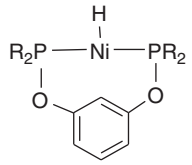
addition regardless of the kind of hydrosilane employed (Table 30, entry 5). The hydrosilylation of benzalacetone with triethylsilane or diphenylsilane gave a mixture of the 1,4 and 1,2 adducts, whereas cinnamaldehyde was reduced with normal regioselectivity.

Many reports described the use of other metal catalysts and their applications to the hydrosilylation of aldehydes and ketones. A few of these reports are highlighted in Table 30. However, the main advancements in hydrosilylation are in the enantiomeric reductions of prochiral ketones described below.

The hydrosilylation of aldehydes and ketones may be performed in the absence of metal catalysis as in the report by Kobayashi and coworkers[421] in which the combination of trichlorosilane and dimethylformamide was used to reduce aldehydes, ketones, and imines in good yields (Table 30, entries 6–7). The authors rationalized the outcome by proposing the generation of hypervalent hydrosilicates from the coordination of DMF to Cl_3SiH.

Lee and coworkers[422] reported the use of Grubbs' carbene complex $Cl_2(PCy_3)_2Ru{=}CHPh$ in a catalytic process for the hydrosilylation of carbonyl compounds under neat conditions. The reactions required heating at 50 °C or higher and the products were isolated as silyl ethers (Table 30, entries 8–9).

The use of nickel PCP-pincer hydride complexes, **33** and **34** (Figure 8) for the hydrosilylation of aldehydes and ketones was reported by Guan and coworkers.[423] Many aldehydes were hydrosilylated in good yields (Table 30, entries 10–11) but no examples of hydrosilylation of ketones were reported. The catalyst appeared to be inert toward alkene and alkynes.



33: R = *i*-Pr
34: R = *t*-Bu

Figure 8 Nickel PCP-pincer hydride complexes. Reproduced from Chakraborty, S.; Krause, J. A.; Guan, H. *Organometallics* **2009**, *28*, 582–586, with permission from ACS.

Darcel and coworkers[424] reported a catalytic procedure for the reduction of aldehydes and ketones using bis(diphenylphosphinoethane)iron dihydride complex $[(dppe)_2FeH_2]$ as a hydrosilylation precatalyst with polymethylhydrosiloxane (PMHS) as the silylating agent and sodium tetraethoxyborate $[NaB(OEt)_4]$ as a cocatalyst under irradiation byvisible light (Table 30, entries 12–13).

Lipshutz and coworkers[101] reported on the use of the Stryker's reagent $[(Ph_3P)CuH]_6$ as a catalyst for the hydrosilylation of α,β-unsaturated ketones with $PhSiH_3$ to effect their 1,4-reduction to the saturated ketones in excellent yields (Table 30, entries 14–15). A similar procedure[425] was applied effectively to the reduction of nonconjugated aldehydes and ketones (Table 30, entry 16). The reaction conditions also allow the selective reduction of aldehydes in the presence of ketones (Table 30, entry 17).

8.01.11.2 Enantioselective Reductions of Prochiral Ketones via Catalytic Hydrosilylation

The above examples demonstrate the utility of hydrosilylation as a general procedure for the chemoselective reductions of aldehydes and ketones. The emerging developments in this field have led to the study of the catalytic enantioselective hydrosilylation of prochiral ketones as an efficient procedure for the enantioselective reduction of ketones. The advancements in this field are result of the improved designs of chiral ligands. One of the most important classes of chiral ligands are the NHC developed in 1996 by Enders[426] and Herrmann.[427] These ligands were used in the design of efficient catalysts for enantioselective hydrosilylation of prochiral ketones.[428] Several recent reports have described the use of catalytic chiral nonracemic NHC metal complexes in enantioselective hydrosilylation and showed good promise for enantioselective reduction of ketones. The enantioselectivity is achieved at practical levels and the scope of reactions is expanding to include different kinds of ketones. Additionally, the alcohol products may be isolated as silyl ethers or as free alcohols. Some representative examples are highlighted below.

Andrus and coworkers[429] reported on the preparation of ruthenium complexes with bis-paracyclophane-NHC ligands that can be used for asymmetric hydrosilylation of ketones; one of these ligands (**35**) is illustrated in Figure 9. The optimized hydrosilylation reaction conditions include the use of the NHC ligand **35** (1.2 mol%) with ruthenium dichloride tris (triphenylphosphine) $[RuCl_2(PPh_3)]_3$ (0.5 mol%), silver triflate (1 mol%), and diphenylsilane (2.5 equivalents) in THF at room temperature. Following the reaction, the products are treated with aqueous HCl to cleave the silyl ethers. Under these conditions, several aryl alkyl ketones, with few exceptions, were reduced to the *S*-alcohols in high enantioselectivity (Table 31, entries 1–3).

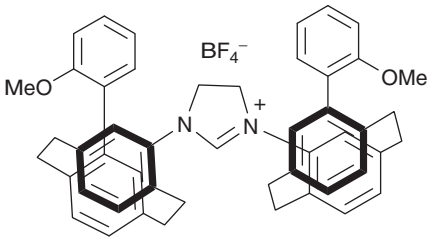
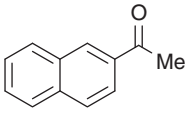
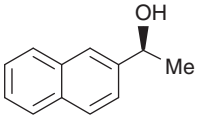
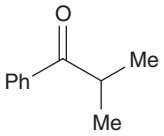
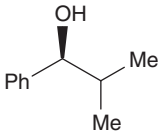
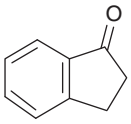
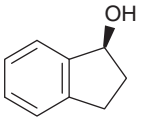
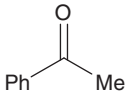
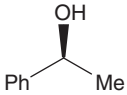
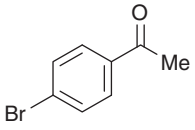
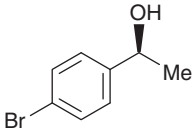


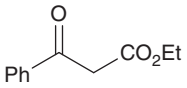
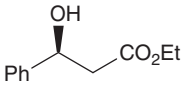
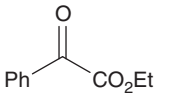
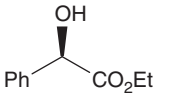
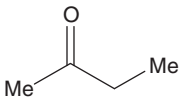
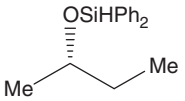
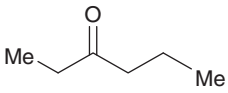
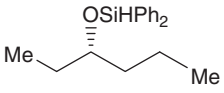
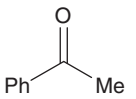
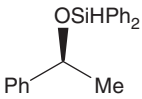
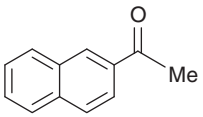
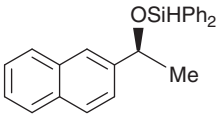
Figure 9 Bis-paracyclophane-NHC ligand (**35**). Reproduced from Song, C.; Ma, C.; Ma, Y.; *et al. Tetrahedron Lett.* **2005**, *46*, 3241–3244.

Table 31 Reductions of pro-chiral ketones via catalytic hydrosilylations

Entries	Substrate	Product	Conditions	Yield (%)	References
1			**35** (1.2 mol%) $[RuCl_2(PPh_3)]_3$ (0.5 mol%), CF_3SO_3Ag (1 mol%) Ph_2SiH_2 (2.5 equivalents), THF, r.t., 18–20 h, then H_2O, HCl	98 96 *ee*	429
2				95 93 *ee*	
3				80 93 *ee*	
4			(*R*)-**36** (2 mole %), Ph_2SiH_2 (2 equivalents), Toluene, r.t., 48 h, then 2 M HCl in MeOH	70 55 *ee*	430
5				86 92 *ee*	

(*Continued*)

Table 31 Continued

Entries	Substrate	Product	Conditions	Yield (%)	References
6				70 96 *ee*	
7				67 20 *ee*	
8			(*R,R,R,R*)-**37** (2 mol%) Ph_2SiH_2 (3 equivalents), *t*-BuOK (12 mol%), THF, r.t., 30 min	100 (69% isolated) 98:2 *er*	431
9			(*R,R,R,R*)-**37** (2 mol%) Ph_2SiH_2 (3 equivalents), *t*-BuOK (12 mol%) THF, r.t., 45 min	100 (77% isolated) 95:5 *er*	
10			(*R,R,R,R*)-**37** (2 mol%) Et_2SiH_2 (3 equivalents), *t*-BuOK (12 mol%) THF, r.t., 45 min	100 (90 isolated) 99:1 *er*	
11			(*R,R,R,R*)-37 (2 mol%) Et_2SiH_2 (3 equivalents), *t*-BuOK (12 mol%) THF, r.t., 45 min	100 (92 isolated) 99:1 *er*	

Shi and coworkers[430] developed a group of axially chiral bis(NHC) Pd(II) and Rh(III) complexes with a 1,1′-biphenyl scaffold. The Pd(II) complexes were used in oxidative kinetic resolution of secondary alcohols but the Rh(III) complexes such as (*R*)-**36** (Figure 10) were used as catalysts for the enantioselective hydrosilylation of ketones. The preferred conditions for the hydrosilylation of ketones are: (*R*)-**36** complex (2 mol%), Ph_2SiH_2 (2 equivalents), in toluene at room temperature for 48 h, then methanolysis with 2 M HCl in MeOH. Under these conditions, the hydrosilylation of aryl methyl ketones and the *β*-ketoester, ethyl benzoyl acetate, proceeded in good yields and moderate to excellent enantioselectivities, whereas sterically hindered 3,4-dihydronaphthalen-1(2H)-one and the *α*-ketoester, ethyl 2-oxo-2-phenylacetate, were reduced in moderate to poor enantioselectivity (Table 31, entries 4–7).

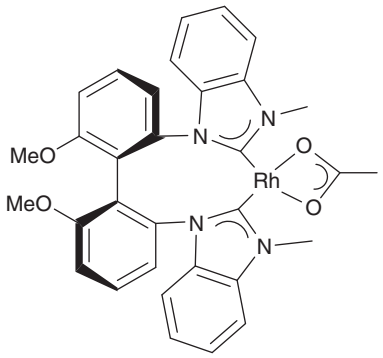


Figure 10 Rh(III) complexes with a 1,1′-biphenyl scaffold [(*R*)-**36**]. Reproduced from Liu, L.-J.; Wang, F.; Shi, M. *Organometallics* **2009**, *28*, 4416–4420, with permission from RSC.

The effectiveness of Cu catalysts in chemoselective hydrosilylation of conjugated and nonconjugated aldehydes and ketones was demonstrated in the previous section. Gawley and Albright[431] developed a very effective procedure for the hydrosilylation of prochiral ketone using the copper *N*-heterocyclic carbene complex ((*R,R,R,R*)-**37**, Figure 11).

The catalyst is air stable and displays a remarkable enantioselectivity in hydrosilylation of ketones. Not only it is very effective in the hydrosilylation of aryl alkyl ketones, but it also shows extraordinary selectivity with acyclic aliphatic ketones under mild conditions. The optimized conditions uses either Et_2SiH_2 (with less volatile ketones) or Ph_2SiH_2 (with volatile ketones), (3 equivalents); (*R,R,R,R*)-**37** (2 mol%), *t*-BuOK (12 mol%) in THF at room temperature. Some selected examples are highlighted

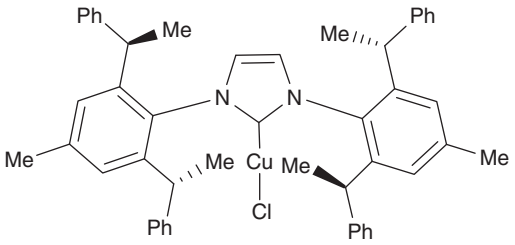


Figure 11 Gawley's enantioselective NHC–Cu catalyst [(*R,R,R,R*)-**37**]. Reproduced from Albright, A.; Gawley, R. E. *J. Am. Chem. Soc.* **2011**, *133*, 19680–19683, with permission from ACS.

in Table 31, entries 8–11. The most remarkable enatioselectivity is that obtained from hydrosilylation of 2-butanone and 3-hexanone to produce 2-butanol and 3-hexanol in 98:2 and 95:5 *er*, respectively (Table 31, entries 8 & 9). All alcohols are obtained in the (*S*)-configuration resulting from the addition of (*R,R,R,R*)-**37** to the *Re*-face of the ketone.

8.01.12 Conclusion

The recent advancements in the reductions of C=O to CH–OH by metal hydrides have grown exponentially on all fronts. Brown equated the discovery of metal hydrides with the discovery of a new continent that was waiting to be explored by generations of chemists.[6a] This review highlights only representative examples of the vast research done by generations of excellent hard working chemists all over the world in just one aspect of reduction exploring one part of the continent. Names of the lead scientists are quoted to emphasize their dedication in improving the tools available for reduction and in discovering new ones. There are more developments in reduction than can be captured by one review, but every development moves us a step higher in our understanding of the reduction process and, more importantly, provides the tools to advance the science of organic synthesis.

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8.02 Reduction of C═N to CH–NH by Metal Hydrides

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This chapter is a revision of the previous edition chapter by Robert O Hutchins, Marygail K Hutchins, Vol. 8, pp 25–78, © 1991, Elsevier Ltd.

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Glossary

Imines Compounds containing C═N bonds in which the nitrogen is attached to a hydrogen (C═NH) or to alkyl or aryl group (C═NR or C═NAr); these *N*-substituted derivatives are also named Schiff bases or azomethines. The carbon is attached to two groups from H, R, Ar in any combination.

***N*-sulfinyl imines (thiooxime S-oxides) [C═N-S(O)R]** Imine derivatives in which the nitrogen is attached to alkyl or aryl sulfinyl [S(O)R] groups, where R is alkyl or aryl. They are chiral molecules and can be obtained in both enantiomeric forms; used in enantioselective preparation of amines via reduction or nucleophilc addition to the carbon of the C═N bond followed by removal of the sulfinyl group with acid treatment.

Oximes Imine derivatives in which the nitrogen is attached to the OH group (C═N–OH). Generated by the condensation of hydroxylamine with aldehydes (aldoximes) or with ketones (ketoximes); may also be obtained from the reaction of isoamyl nitrite with carbanions.

Reductive amination The reaction of aldehydes or ketones with ammonia, primary amines, or secondary amines in the presence of reducing agents to form primary, secondary, or tertiary amines, respectively. Also named reductive alkylation (of amines).

Note

The first edition of *Comprehensive Organic Chemistry* contained a chapter with the same title as this one written by Robert O. Hutchins (Drexel University) and MaryGail K. Hutchins (ICI America).[1] They presented a comprehensive discussion of several very

important aspects of metal hydride reductions of imines and imine derivatives. Their presentation included very thorough discussions of the following topics:

1. Chemoselectivity of hydride reagents.
2. Stereoselectivity of cyclic derivatives of imines, emamines, and oximes.
3. Reductive amination with sodium cyanoborohydride.

This chapter discusses these topics as needed, but it concentrates on highlighting new developments that appeared in the literature from 1990 to the present with the help of representative examples. It expands the discussion on the topics of reductive amination, reduction of *N*-sulfinyl imines, and reduction of *N*-phsophinylimines that have seen the most advancement during this period.

8.02.1 Introduction

Nitrogen compounds in general and amines in particular are very important molecules in nature and in synthetic organic chemistry. Amines occupy a very special place in organic chemistry. They exist in many natural biologically important molecules such as amino acids, peptides, proteins (enzymes and glycoproteins), β-lactams, porphyrins, chlorophyll, nucleosides, nucleotides, DNA, RNA, alkaloids, and many others. They are also common features in many of the synthetic compounds used as medicines and commercial drugs. Amines are used as bases in many synthetic transformations, serve as key intermediates in organic synthesis, and are important building blocks in many of the common polymers such as nylons and other polyamides. Due to the importance of amines, there are numerous methods for their preparation. A general, more direct method is via alkylation of ammonia or primary or secondary amines with alkyl halides or sulfonates. This method may suffer from overalkylation when used with ammonia and primary amines. Other general methods include the reduction of nitrogen-containing functional groups such as nitro, cyano, azide, and carboxamide derivatives. The reduction of C═N bond in imines, *N*-alkyl imines, oximes, and other C═N derivatives is a superior method for the preparation of amines. The reduction of C═N compounds to the corresponding CH–NH products with metal hydrides is the subject of this chapter; many types of C═N derivatives will be included and their reductions to the saturated derivatives will be highlighted. There are three main types of C═N reductions:

- Reduction of preformed imines such as C═NH or C═NR (R═alkyl or aryl) similar to the reduction of C═O groups. Imines vary considerably in stability from unstable to very stable based on their substitution.
- Reductive amination reactions: reaction of aldehydes or ketones with ammonia or primary or secondary amines in the presence of a reducing agent. In these reactions, imines or iminium ions are the presumed intermediate and are reduced directly to the amine product.
- Reduction of C═N–X compounds where X is a heteroatom (O, S, P, etc.); examples are oximes, hydrazones, and *N*-sulfinyl imines. The heteroatom may remain or may be eliminated during or after the reduction. These C═N–X derivatives are generally more stable than alkyl or aryl imines and usually can be isolated and stored for long periods of times if needed. The X may also be a chiral nonracemic group such as sulfinyl group (S═O) that is capable of directing and promoting enantioselective reduction of the C═N bond.

The choice of the reducing agent depends on this classification and the complexity of the structures. For example, in the case of preformed imines or C═N–X compounds, the main requirement in selecting a reducing agent is its ability to chemoselectively reduce the C═N bond in the presence of other reducible groups. However, the choice of the reducing agent is more critical in reductive amination reactions since there will be competition between the intermediate imine and the carbonyl group of the aldehyde or ketone for the hydride addition. The reducing agent has to be able to reduce the imine selectively without affecting the carbonyl compound. Two main reduction procedures can be used in the reduction of C═N compounds: catalytic hydrogenation and metal hydrides. There are many applications and limitations for each category; most limitations are the result of structural complexity combined with nonselective reagents and reaction conditions. The discussion in this chapter will be limited to the use of metal hydrides in the reduction of various C═N compounds. It is not intended to be a survey of all reactions but it will highlight the different aspects of C═N reduction with various hydride reagents using illustrative examples to emphasize the scope and limitation of reactions and reagents.

8.02.2 Comparisons to Carbonyl Reductions

Replacing the oxygen of a carbonyl group with NH, NR, NAr, or NX (X═O, N, S, P, etc.) changes the properties of the group significantly. The C═N compounds are much more complicated; some exist as two stereoisomers and possess a wide range of

stabilities compared to carbonyl groups. *N*-substituted C═N compounds can exist as geometrical isomers which may affect their reactivity toward addition of nucleophiles and reduction and this may also affect the stereochemistry of the product. The nitrogen of the C═N group is basic and can be protonated much more easily than the oxygen of the carbonyl, which makes the C═N group more susceptible to attack by nucleophiles and hydrides than carbonyl compounds under acidic conditions. Although the diversity in different kinds of carbonyl (aldehydes, ketones, acids, esters, etc.) originates from the variations of two different substitutions on the carbon of the carbonyl group, the added substitution on the nitrogen of the C═N compounds renders them more diverse and more complicated. Substitution on nitrogen may determine their stability, basicity, and reactivity toward other reagents. For example, unsubstituted imines (C═NH), particularly aliphatic aldimines and ketimines, may not be stable enough to isolate and are prone to hydrolysis in the presence of water, but they can be stable in nonaqueous solutions. *N*-alkyl and *N*-aryl imines, known as Schiff bases[2] or azomethines, are stable enough to isolate and characterize. Other C═N derivatives, particularly those with heteroatom substituents on the nitrogen such as oximes, oxime ethers, oxime esters, hydrazones, substituted hydrazones, *N*-phosphinylimines, and *N*-sulfinyl imines, are more stable. These derivatives can be isolated, purified, and characterized and usually have good shelf life. Another structural difference from carbonyl groups is that the C═N bond can be part of a heterocyclic ring (endocyclic), either aromatic or nonaromatic. The C═N bonds that exist as part of aromatic rings (e.g., the C═N bond in pyridine) are very stable and are not easily reduced, whereas cyclic nonaromatic ones behave similar to acyclic compounds.

However, there are enough structural similarities with C═O that make the C═N group susceptible to reduction with metal hydride reagents. Mostly, the reduction of C═N groups to CH–NH with metal hydrides is similar to the reduction of C═O to CH–OH, using the same reagents such as $LiAlH_4$ (LAH), $NaBH_4$ (SBH), $NaBH_3CN$, BH_3, etc. The *N*-substituents can alter, sometimes substantially, the chemical properties of the C═N compound by varying the electrophilicity of the carbon atom and the nucleophilicity and basicity of the nitrogen. The *N*-substitution may also cause wide variations in reduction rates or, in some cases, prevention of reduction altogether. For example, although trialkylborohydrides rapidly reduce most carbonyls (even at −78 °C),[3] they do not reduce oximes and oxime ethers even in refluxing tetrahydrofuran (THF) (65 °C).[4]

Based on the author's own observation from searching the literature in the fields of C═O versus C═N reductions, it is clear that the discovery and early research on metal hydrides as reducing agents have been directed in most part toward the reduction of aldehydes, ketones, esters, and other carbonyl derivatives. Reduction of imines and imine derivatives has been lagging behind the carbonyls and usually comes to existence when exploring the scope and limitations of these reagents or when comparing new reagents or conditions with existing reagents or procedures. Many references still describe $NaBH_4$ as a selective reducing agent that can reduce aldehydes, ketones, and acid chlorides, even though it has been known for decades that it can also reduce many imines and imine derivatives. Most early efforts following the discovery of $LiAlH_4$ and $NaBH_4$ were directed toward exploring all the modifications to enhance the reactivity and selectivity of metal hydride reagents toward reduction of carbonyl compounds and improving their properties (*see* Chapter 8.01). However, there were a few scattered reports on reduction of imines in the late 1950s and early 1960s, particularly by Billman and coworkers.[5] The main advances in the reduction of imines with metal hydrides came in 1971 with the report of Borch and coworkers[6] on the reductive amination of aldehydes and ketones with $NaBH_3CN$. This major development changed the landscape and moved the reduction of C═N compounds to the center of hydride reduction activity. From this time on, based on the realization of the impact of this reaction on the synthesis of amines, more efforts were directed toward further development on reduction of imines and reductive amination reactions with metal hydrides.

8.02.3 Reduction of Imines and Iminium Ions with Metal Hydrides

8.02.3.1 Reduction of Preformed Imines and Iminium Ions with Metal Hydrides

8.02.3.1.1 Formation of imines

Imines are typically prepared by the condensation of ammonia or primary amines with aldehydes and ketones. The mechanism of imine formation will be further discussed in Section 8.02.3.2. Although this method of imine formation is reversible requiring long reaction times and the use of acid catalysts and dehydrating agents such as molecular sieves or azeotropic removal of water to drive the reaction to completion, it is still the most common method for preparation of imines. Aldimines and ketimines are the names given to imines derived from aldehydes and ketones, respectively. Another method of imine formation is the addition of metal alkyls or metal aryls (such as alkyl or aryl lithiums and Grignard reagents) to nitriles. The imine nitrogen in the crude product bears a metal cation [Li^+ or $(MgX)^+$]. A more recent procedure for preparation of imines is catalytic hydroamination of alkynes with ammonia or amines (see **Table 1**, entry 33). Many aliphatic imines (particularly R_2C═NH) display lower stability than the corresponding carbonyl derivatives and are usually prone to hydrolysis in the presence of water. These imines are best reduced directly and not isolated. Iminium ions (or salts) are derived from reaction of aldehydes or ketones with secondary amines and from protonation of imines (under acidic conditions). Iminium ions are more reactive toward reduction and nucleophilic attack than imines.

8.02.3.1.2 Reduction of imines

Some of the early studies of imine reductions with metal hydrides were reported by Billman and coworkers who prepared several kinds of imines and studied their reductions with hydrides to prepare secondary amines. Their studies showed that imines were reduced with LAH[5a] and with dimethylamine-borane in glacial AcOH[5b] effectively and in good yields. Triethylamine-borane in glacial AcOH reduced the imines, but the products were also acetylated to give the corresponding acetamides on prolonged heating at reflux.[5c] The reduction of imines has become more common in organic synthesis following the introduction of $NaBH_3CN$ in reductive amination reactions. Many imine reductions have been used either as part of the synthesis of complex molecules or as part of methodology studies. Several of these applications are listed in Table 1. The reduction of preformed imines can be advantageous and effective in eliminating or suppressing unwanted side reactions that may occur during reductive amination reactions.

Today there are more choices available of reagents and modified conditions for reduction of imines following the lead of carbonyl reductions. The most popular reagents in carbonyl reduction are also popular in imine reductions. Sodium borohydride is one of the most used reagents for reduction of imines because of its effectiveness and the ease of handling (Table 1, entries 1–18). $NaBH_3CN$ (Table 1, entries 19–24) and $NaBH(OAc)_3$ (Table 1, entries 44–50) are two effective reducing agents for reduction of imines and imine derivatives due to their stabilities in weakly acidic media, which favor reduction of imines. Other frequently used reducing agents are $LiAlH_4$ (Table 1, entries 31–39), $Zn(BH_4)_2$ (Table 1, entries 25–30), and borane (Table 1, entries 40–44). $CaH_2/ZnBr_2$ was also used for imine reduction (Table 1, entry 50). In general, these reagents reduce imines in a similar manner and with similar trends to the reduction of aldehydes and ketones.

Formation of 'NH-imines' from the addition of carbanions to nitriles, followed by reduction, provides a good method of preparing primary amines. The sequence has been applied to preparation of primary amines in many syntheses and studies; some examples are listed in Table 1 (entries 1–7, 29, 32). Oh and coworkers[7] prepared *E*-allylic amines in a one-pot procedure by addition of lithio-methylphosphonate to nitriles, followed by condensation with aldehydes and reduction of the resulting *E*-allylic imines with $NaBH_4$. The procedure was applied successfully to several examples (Table 1, entry 1). The reduction of a chiral pentaflurophenyl imine derivative (Table 1, entry 4) with $NaBH_4$ was highly diastereoselective giving the amino alcohol in >99% *ee* and 63% yield after chromatography.[10] The reduction of a chiral iminomagnesium intermediate (Table 1, entry 6) with $NaBH_4$ gave the amine product without loss of enantiomeric purity.[12] It was postulated that the iminomagnesium intermediate might adopt a chelated conformation, which forces the addition of the incoming hydride from the less hindered face leading to the observed *erythro* diastereomer.[12] A similar iminomagnesium intermediate (Table 1, entry 7) that has two competing chelating atoms (O and N) on either side probably favors chelation with nitrogen. Its reduction with $NaBH_4$ gave 79:21 *dr* in favor of the *threo* product.[13]

In the preparation of polydentate amine-oxime ligands,[17] the imines were reduced selectively with $NaBH_4$ in EtOH in the presence of oximes (Table 1, entry 12).

In the asymmetric synthesis of (*S*)-ornithine, Corey and Zhang[21] reported the reduction of both functional groups of a cyano imine (Table 1, entry 16) with $CoCl_2$-$NaBH_4$ in methanol at 55 °C to afford the diamine 78% yield.

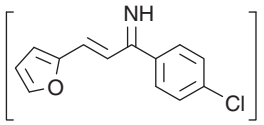
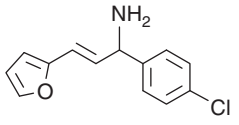
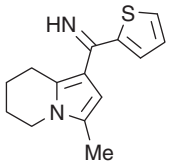
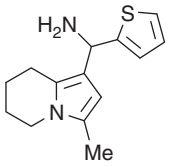
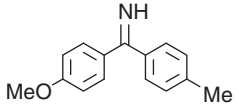
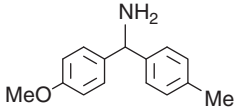
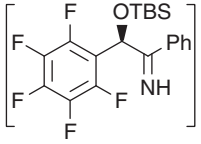
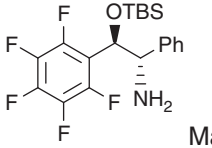
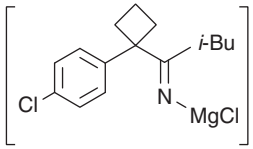
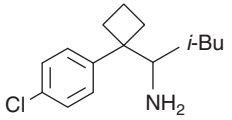
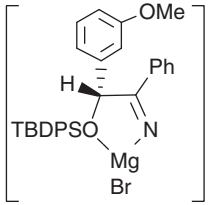
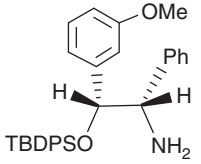
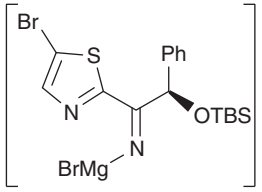
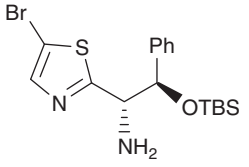
Some syntheses have taken advantage of the nucleophilicity of the product amines to affect secondary transformations from the initial reduction products. For example, the initial reduction products, (*S*)-*N*-(benzylidene)-*β*-aryl-*β*-chloroamines (Table 1, entry 17), were subsequently cyclized by an S_N2-type intramolecular nucleophilic substitution to the corresponding aziridines without racemization.[22] In another example (Table 1, entry 20), the 5-chloro amine reduction products cyclized spontaneously under the reaction conditions to provide *N*-alkylated 3,3-difluorinated piperidines.[24] The reduction of imino aldehydes (Table 1, entries 21 and 22) with $NaBH_3CN$ at pH 5 gave *N*-benzhydryl piperdines and *N*-benzhydryl pyrrolidine, respectively, most likely via reductive amination of the aldehydes with the initially formed amines.[25,26]

Ranu and coworkers[29] described the reduction of imines with $Zn(BH_4)_2$ supported on silica gel (Table 1, entries 25–27). The authors postulated that silica gel moderates the reactivity of zinc borohydride causing a slow but cleaner reaction compared to using zinc borohydride alone. Axial hydride attack is generally preferred in reduction of substituted cyclohexylimines (entry 26), whereas in the reduction of camphorimine, the *endo*-product was produced exclusively (entry 27). Kotsuki and coworkers[30] reported a procedure for the reduction of several imines with $Zn(BH_4)_2$ in diethyl ether. The imine derivatives were prepared either by condensation of amines with aldehydes and ketones or by addition of Grignard reagents to nitriles. In some cases, particularly aliphatic derivatives, the product amines formed borane complexes and were treated with 6N HCl to free the amines (Table 1, entries 28–29).

Doye and coworkers[33] studied the intermolecular hydroamination of alkynes with primary amines in the presence of dimethyltitanocene (Cp_2TiMe_2). The resulting imines were reduced with $LiAlH_4$ at 0 °C to give the amine products in good yields (Table 1, entry 33). In a study of 3-aza-Cope rearrangements by Stille and coworkers,[34] the imines resulting from the rearrangement were reduced with $LiAlH_4$ to provide the corresponding amines in good yields (Table 1, entries 34 and 35).

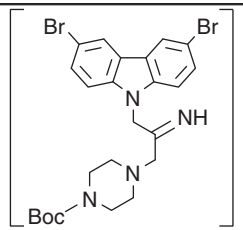
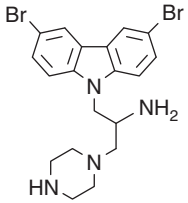
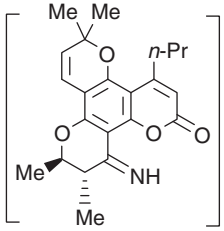
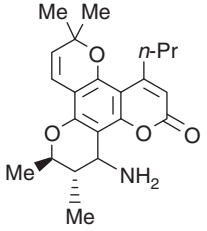
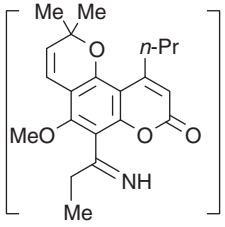
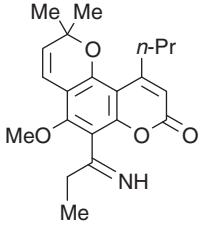
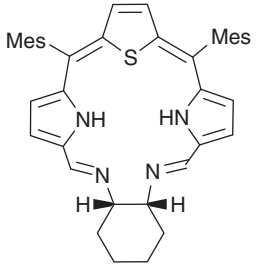
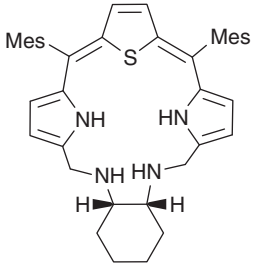
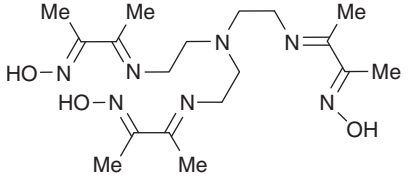
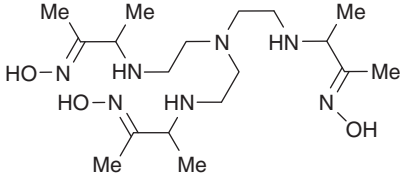
The reduction of various *N*-alkyl-*N*-(3-arylcyclobutylidene)amines with $LiAlH_4$ yielded *cis*-substituted cyclobutylamines as the only stereoisomers (Table 1, entry 38). The tetrachloro imine (Table 1, entry 39) could not be reduced with $LiAlH_4$ or $NaBH_4$, but was reduced with 1 equivalent of borane to provide the corresponding amine cleanly in high yield.[36] Lu and coworkers[37] found the combination of phthalic acid and BH_3.THF to be effective in the reduction of imines. Borane reduction of the imines without the diacid needed higher temperature and gave lower yield, whereas both $NaBH(OAc)_3$ and $NaBH_3CN$ did not reduce the imine. The procedure was applicable to other imines giving the amine products in yields ranging from 79% to 93% (Table 1, entries 40 and 41).

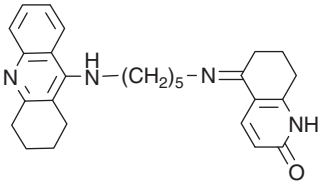
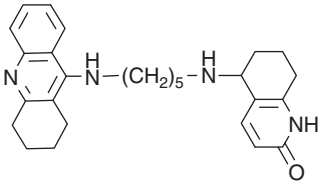
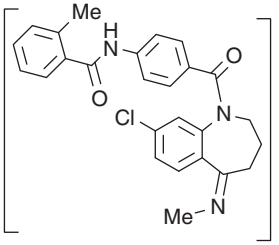
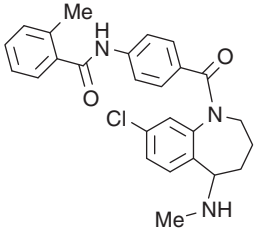
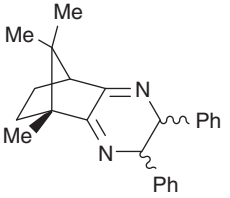
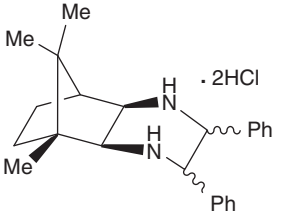
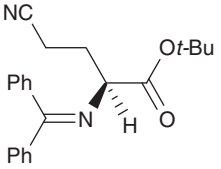
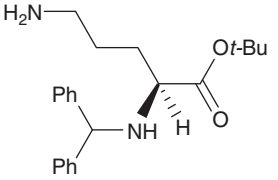
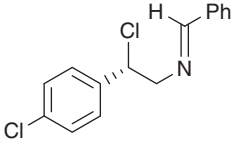
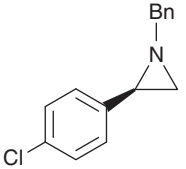
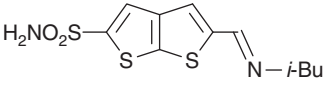
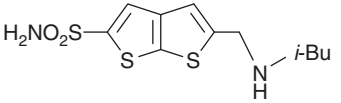
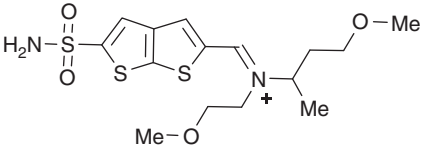
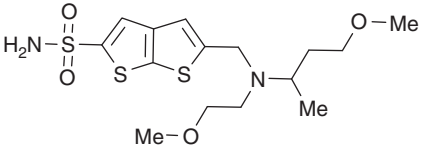
Table 1 Reduction of preformed imines with hydrides

Entry	*Substrate*	*Product*		*Conditions*	*Yield (%)*	*References*
1			8 Examples, 58–85%	1. $NaBH_4$, MeOH, –78 °C (1 h); r.t. (1 h) 2. H_3O^+ 3. NaOH	83	7
2				$NaBH_4$, MeOH r.t., 6 h	83	8
3				$NaBH_4$, MeOH, r.t. (1 h); Δ, 1 h	98	9
4			Major	$NaBH_4$, EtOH, 0 °C	63 90 *de*	10
5				$NaBH_4$ (1 equivalent), MeOH, 0–25 °C, 1 h	> 95	11
6				$NaBH_4$ Et_2O, MeOH overnight	91	12
7			Major	$NaBH_4$/EtOH-MeOH	73 *dr.* 79:21	13

(*Continued*)

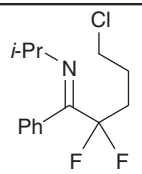
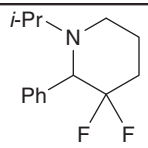
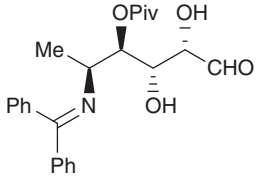
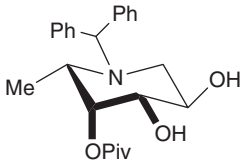
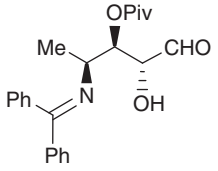
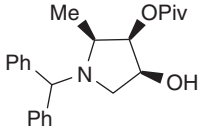
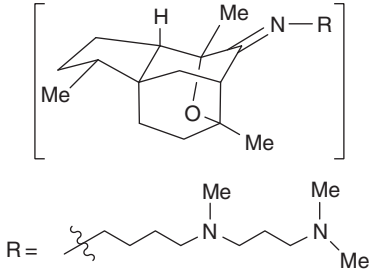
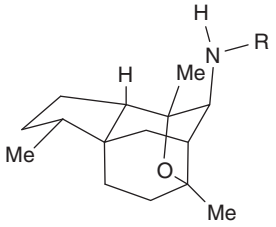
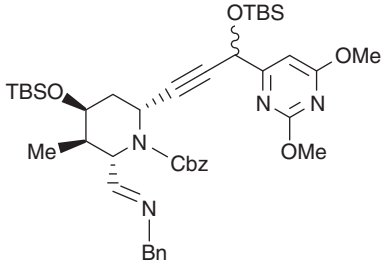
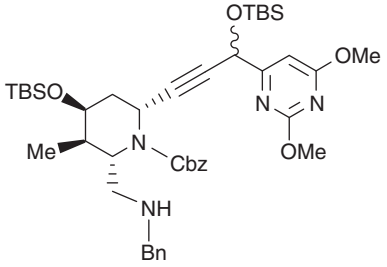
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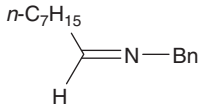
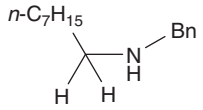
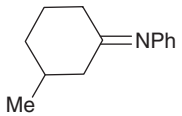
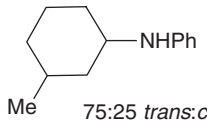
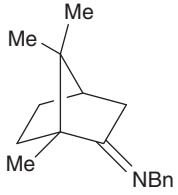
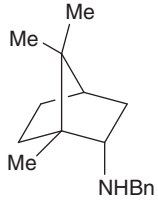
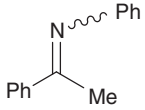
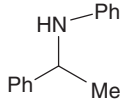
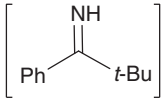
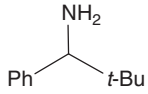
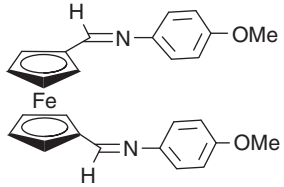
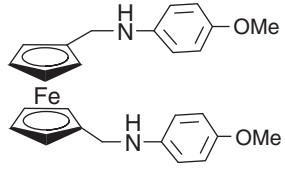
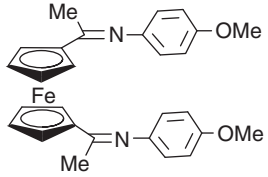
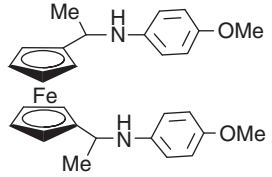
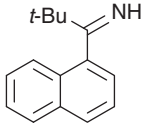
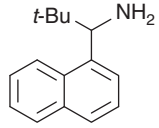
Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
8			$NaBH_4$, MeOH, r.t., 15 h then: TFA, CH_2Cl_2, r.t.	58	14
9			$NaBH_4$ (5 equivalents) MeOH, 0 °C, 2 h	53	15
10				98	
11			$NaBH_4$ THF/MeOH (7/3)	76	16
12			$NaBH_4$, EtOH r.t., 4 h	40	17

13			$NaBH_4$, MeOH, 4 h	52	18
14			$NaBH_4$, MeOH, r.t., overnight	78	19
15			1. $NaBH_4$, MeOH, r.t., 1 h; 2. HCl, MeOH	88	20
16			$NaBH_4$, $CoCl_2$, MeOH, 55 °C	78	21
17			$NaBH_4$ (1 equivalent) MeOH, reflux 3 h	93 98 *ee*	22
18			$NaBH_4$, MeOH-THF 0 °C, 2 h; r.t., 1 h	92	23
19			$NaBH_3CN$, MeOH, HCl 48 h	55	

(*Continued*)

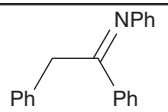
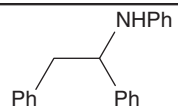
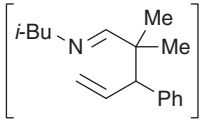
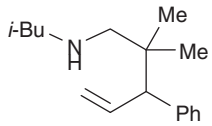
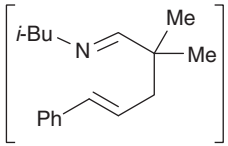
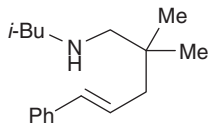
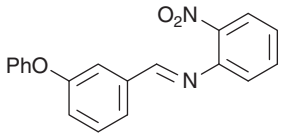
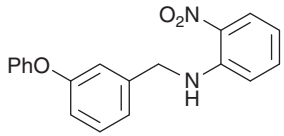
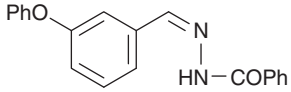
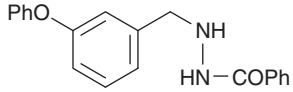
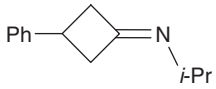
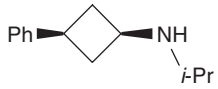
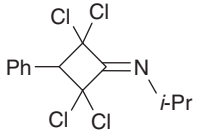
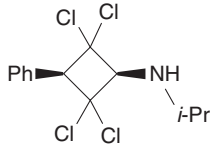
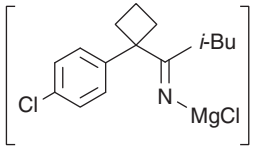
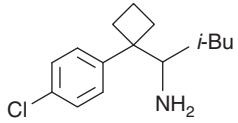
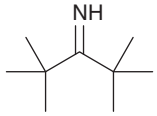
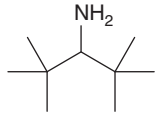
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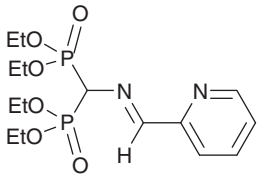
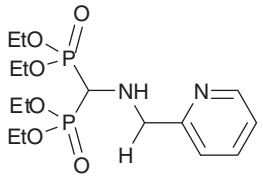
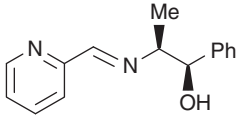
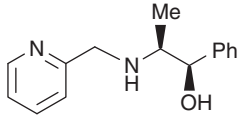
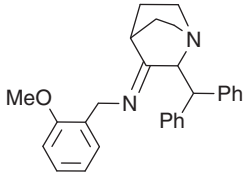
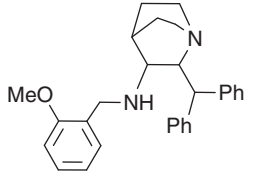
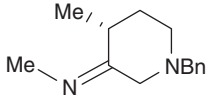
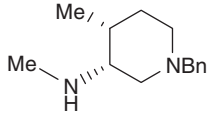
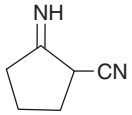
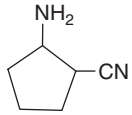
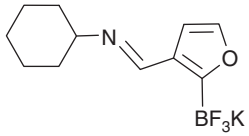
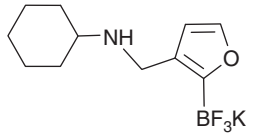
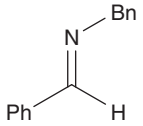
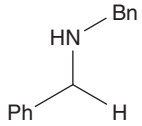
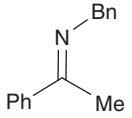
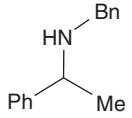
Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
20			$NaBH_3CN$ AcOH, MeOH, reflux, 4 h	70	24
21			$NaBH_3CN$ AcOH (pH 5), H_2O	75–80	25
22			$NaBH_3CN$ AcOH (pH 5), CH_3CN	51	26
23			$NaBH_3CN$ MeOH, HCl (pH 6), 36 h, r.t.	60	27
24			$NaBH_3CN$ PhMe, MeOH, AcOH 2 h, r.t.	68	28

25			$Zn(BH_4)_2$ on silica gel, THF, 8 h, r.t.	94	29
26		 75:25 *trans*:*cis*	$Zn(BH_4)_2$ on silica gel, THF, 8 h, r.t.	91	29
27			$Zn(BH_4)_2$ on silica gel, THF, 14 h, r.t.	85	29
28		 11 examples 27–98%	$Zn(BH_4)_2$ Et_2O, 0 °C to r.t.	97	30
29			$Zn(BH_4)_2$ Et_2O, 0 °C to r.t.	82	30
30			$NaBH_4$, EtOH or $LiAlH_4$–$AlCl_3$ THF	90	31
31			$LiAlH_4$–$AlCl_3$ THF	89	31
32			$LiAlH_4$, Et_2O 22 h	80	32

(*Continued*)

Table 1 Continued

Entry	Substrate	Product	Conditions	Yield (%)	References
33			$LiAlH_4$, THF 0 °C, 3 h	62	33
34			$LiAlH_4$, toluene THF, 0 °C, 6 h	76	34
35				56	34
36			$LiAlH_4$, THF 66 °C, 5 h	74	35
37			$LiAlH_4$, THF 66 °C, 5 h	97	35
38			$LiAlH_4$ (1.2 equivalents) Et_2O, r.t., 2 h	81	36
39			BH_3·Me_2S (1 equivalent), THF, 0 °C to r.t., 3 h	86	36
40			BH_3·THF, phthalic (or succinic) acid (1 equivalent), THF, –25 °C to –30 °C, 30–60 min	95	37
41				79	37

42			$NaBH(OAc)_3$ AcOH, CH_3CN, 0 °C, 1 h	40	38
43			$NaBH(OAc)_3$ (2 equivalents), DCE 48 h, r.t.	98	39
44			$NaBH(OAc)_3$ DCE, AcOH r.t., 4.5 h	86	40
45		 Major	$NaBH(OAc)_3$, toluene-EtOH AcOH, 13 h, 2 °C	92 86:14	41
46			$NaBH(OAc)_3$, AcOH, 3 h, r.t.	65	42
47			$NaBH(OAc)_3$ AcOH, MeCN, r.t.	87	43
48			$Pyr{\cdot}BH_3$ (4 equivalents), KHF_2 MeOH, r.t., 16 h	82	
49			CaH_2 (1.3 equivalents), $ZnBr_2$ (1.2 equivalents) $Ti(O\textit{i}\text{-}Pr)_4$ (0.05 equivalent) THF, 40 °C	86	44
50				91	

Some of the imine reductions were carried out in large-scale synthesis of amines. For example, a 3-amino-1-azabicyclo[2.2.2] octane derivative (Table 1, entry 44) was prepared effectively on a 1-mole scale by the reduction of the corresponding imine at 25 °C with $NaBH(OAc)_3$ to give the amine in 86% isolated yield. The isolated product has *cis*-stereochemistry, but no ratio of products was reported.[40] Another very practical and efficient synthesis is that of *cis*-*N*-benzyl-3-methylamino-4-methylpiperidine (Table 1, entry 45) developed by Ripin and coworkers.[41] The reaction was carried out on approximately 25 kg scale. The imine intermediate was reduced with $NaBH(OAc)_3$ to provide an excellent yield (92%) of the product, in 86:14 ratio in favor of the desired *cis*-diastereomer.

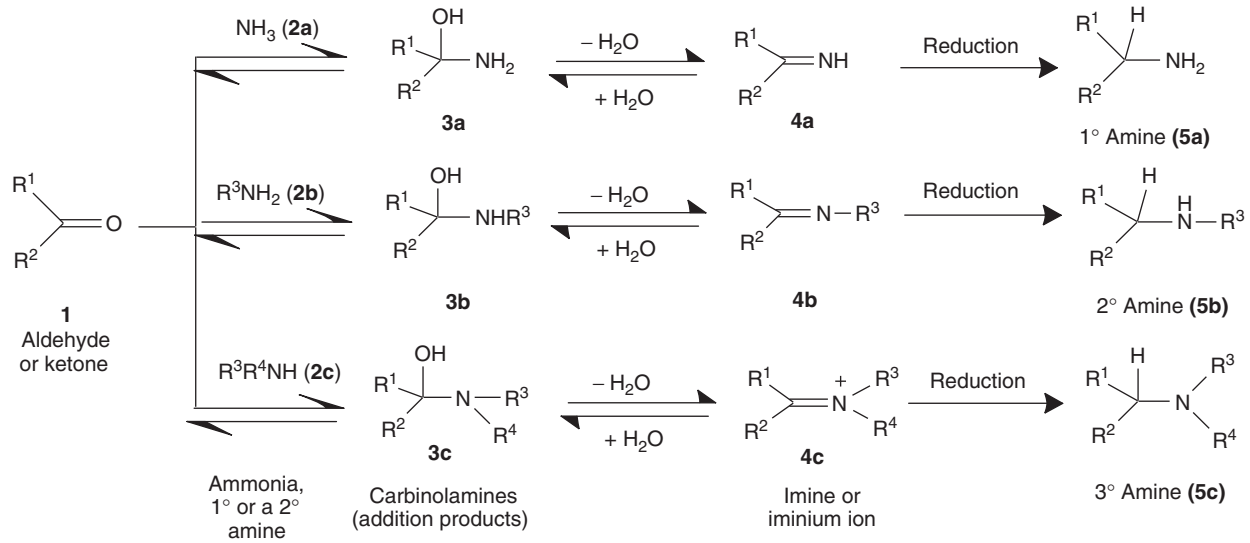
Molander and coworkers[43] studied the reductive amination of a variety of aldehyde-containing trifluoroborates via a stepwise procedure. The reduction of the intermediate imines and iminium salts was examined under several conditions. Although $NaBH(OAc)_3$ gave some promising results (Table 1, entry 47), it was not consistent in all cases. The use of borane-pyridine ($pyr.BH_3$) in the presence of KHF_2 proved very effective in the imine reductions (Table 1, entry 48).

Okamoto and coworkers[44] reported the use of CaH_2 as a reductive hydride source together with ZnX_2 (X═Br or Cl) and a catalytic amount of $Ti(Oi\text{-}Pr)_4$ in a procedure for reduction of imines. Aromatic and aliphatic aldimines and ketimine were reduced in high yield (Table 1, entries 49 and 50).

8.02.3.2 Reduction of *In Situ* Generated Imines and Iminium Salts with Metal Hydrides: Reductive Amination of Aldehydes and Ketones with Ammonia, Primary Amines, and Secondary Amines

The reductive amination of aldehydes and ketones is a cornerstone reaction and is one of the most useful and important tools in the synthesis of different kinds of amines. It is the reaction of aldehydes or ketones with ammonia, primary amines, or secondary amines in the presence of reducing agents to give primary, secondary, or tertiary amines, respectively.[45] The reaction is named either reductive alkylation (of amines) or reductive amination (of aldehydes or ketones). In this chapter, the term *reductive amination* (of aldehydes and ketones) will be used to describe this reaction. The reaction eliminates the need to preform imines; this is a significant and practical advantage particularly in the reaction of aldehydes and ketones with secondary amines. The formation of the corresponding iminium species is usually very slow and highly reversible and if forced it may form enamines rather than iminium ions when structurally possible. The majority of reductive amination of aldehydes and ketones with secondary amines provides the corresponding tertiary amines conveniently and effectively in reasonable times.

Generally, the reaction proceeds via initial nucleophilic addition of ammonia (**2a**) or an amine (**2b,c**) to the carbonyl group of an aldehyde or a ketone **1** (Scheme 1) to form intermediate carbinolamines **3a,b,c**. Dehydration of the carbinolamines under neutral or acidic conditions forms either an imine (**4a,b**) or an iminium ion (**4c**).[46] Reduction of **4a–c** produces the amine products **5a–c**. Tadanier and coworkers[47] presented some evidence suggesting a direct reduction of the carbinolamines (**3**) as a possible pathway leading to **5**. Other evidence has been presented to support the possibility of reduction of carbinolamines including the reduction of bis(methoxymethyl)amines to dimethylamines[48] and the reduction of methylols to *N*-methylamides with $NaBH_3CN$ in acidic media.[49]



Scheme 1 General reductive amination pathway.

The term *indirect* or *stepwise* reductive amination reaction describes the preformation of intermediate imines (from either ammonia or a primary amine and an aldehyde or a ketone) or sometimes enamine or iminum species (from secondary amines

and aldehydes or ketones) followed by reduction directly or in a separate step. The procedure is generally used to avoid any competing reduction of aldehydes or ketones or suppress other side or undesirable reactions. Examples of reduction of preformed imine were presented in the previous section (Table 1).

The term *direct* reductive amination reaction describes the procedure when the carbonyl compound (aldehyde or ketone) and either ammonia, ammonia source (such as NH_4OAc), a primary amine, or a secondary amine are mixed with the proper reducing agent in a proper solvent without prior formation of the intermediate imine or iminium salt to form the amine products. The direct reductive amination is the most convenient, and it is usually the method of choice to conduct this reaction. The choice of the reducing agent for direct reductive aminations is critical to the success of the reaction. The reducing agent must reduce imines (or iminium ions) selectively in the presence of aldehydes or ketones under the same reaction conditions. There are two main commonly used reduction procedures based on the nature of the reducing agents. The first and older method uses catalytic hydrogenation for reduction.[46b,50] The second, more recent method utilizes metal hydride reducing agents. The use of $NaCNBH_3$ was thoroughly discussed and its scope and limitations were highlighted with many examples in the previous edition of this volume by Hutchins and Hutchins.[1] Although it will also be highlighted here, more emphasis will be given to the use of $NaBH(OAc)_3$ in reductive amination of aldehydes and ketones. In addition, other procedures will be briefly highlighted with representive examples.

The early research of Billman and coworkers[5] on reduction of imines was mostly directed toward the reduction of preformed imines. Schellenberg[46b] reported one of the earlier significant studies of direct reductive amination procedure using a hydride reagent in 1963. In his study, Schellenberg mixed lysine with acetone in buffered aqueous solutions (AcOH–AcONa; pH 4.1–4.7) at 0 °C followed by addition of $NaBH_4$ over 30 min. Remarkably, a fast reaction provided N^6-isopropyl lysine in 50% yield. This occurred despite the fast rate of acetone reduction with $NaBH_4$, which led him to conclude that the reduced species was the 'Schiff base salt or tertiary iminium salt formed from the reactants,' which accounted for the rapid reduction under the weakly acidic conditions compared to the relatively slow reduction of isolated Schiff bases. He also concluded that the reduction of the Schiff base salts must be several orders of magnitude faster than the reduction of acetone under these conditions. He also obtained respectable yields of reductive amination products from several similar reactions including acetone+isobutylamine (63%), isobutyraldehyde+aniline (91%), benzaldehyde+aniline (83%), and piperidine+acetaldehyde (53%). The study also reported failed reactions between acetophenone and benzophenone and between piperidine and ketones. This study was very significant as it opened new possibilities for direct reductive amination reactions without preformation of imines. The major limitation of this procedure originated from the use of $NaBH_4$, which is a relatively strong reducing agent for that task since it reduces aldehydes and ketones effectively at a rate competitive with the reduction of imines.

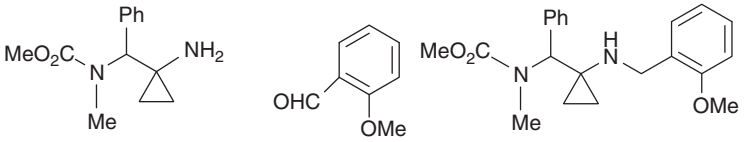
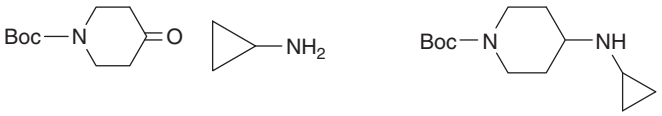
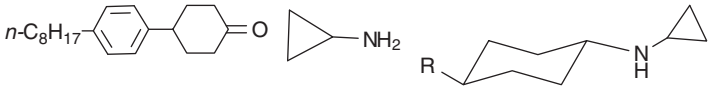
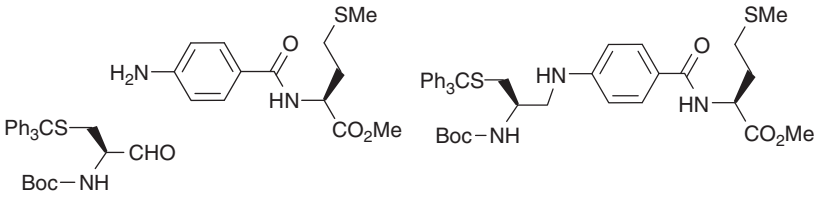
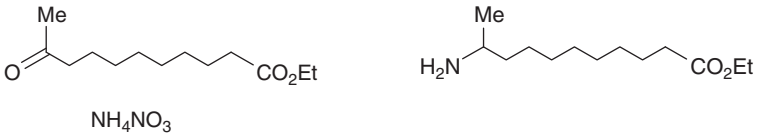
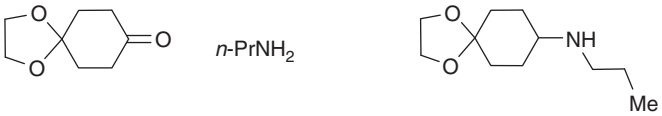
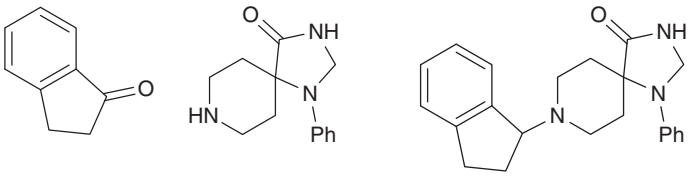
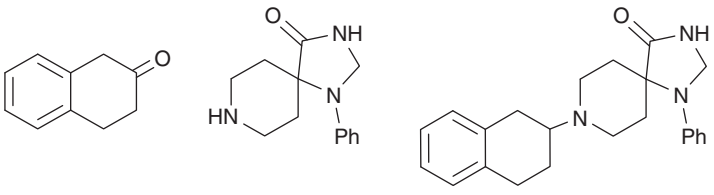
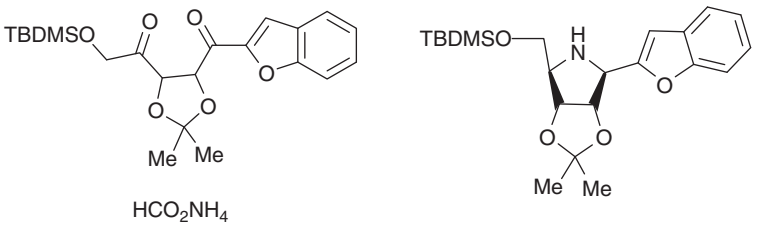
8.02.3.2.1 Reductive amination of aldehydes and ketones with amines using sodium cyanoborohydride

In 1971, Borch[6] reported a major advancement and the first practical and general procedure for direct reductive amination of aldehydes and ketones with a metal hydride in which he used the more selective sodium cyanoborohydride ($NaBH_3CN$) as the reducing agent. The success of $NaBH_3CN$ in reductive amination reactions is due to its different selectivities at different pH values, its stability in acid solutions (~pH 3), as well as its good solubility in hydroxylic solvents such as methanol and aqueous media. At pH 3–4, it reduces aldehydes and ketones effectively,[51] but this reduction becomes very slow under neutral or weakly acidic conditions (pH 6–8).[6,52] Conversely, at pH 6–8, the more basic imines are preferentially protonated and reduced at a much faster rate than aldehydes or ketones.[6] Therefore, by carrying out the reductive amination reaction under neutral to weakly acidic conditions (pH > 4), the reactants would be able to form imines or iminium ions without consumption of aldehydes or ketones via reduction and the formed imines or iminium salts are reduced as they form. This selectivity permits an efficient direct reductive amination procedure with a wide scope of applications to a large variety of substrates. The reductive amination is conveniently conducted by mixing the reactants with $NaBH_3CN$ usually in MeOH or MeOH/H_2O with or without AcOH or HCl and stirring the mixture at room temperature. Other solvents such as EtOH, MeCN, THF, and *N*,*N*-dimethyl formamide (DMF) may be used alone or in combination with H_2O and/or AcOH.

The introduction of $NaBH_3CN$ as a reducing agent for the selective reductive amination reactions was a monumental achievement that revolutionized an old reaction with a very limited scope under catalytic hydrogenation conditions to one of the most convenient and most used reactions for the synthesis of amines and in forming C–N bonds. Today there are more reagent choices and newer methodologies, but this discovery is credited with leading the way and establishing the requirements for a successful reductive amination reagent that is capable of differentiating aldehydes and ketones from their corresponding imines. It is that discovery that put reduction of imines in the middle of all of the new activities and led to further advancements in the field. Many publications document the very successful use of sodium cyanoborohydride in a wide scope of applications of reductive amination reactions.[52]

The procedure nonetheless suffers from some limitations such as the occasional requirement of a large excess of the amine,[6] sluggish reactions with aromatic ketones[6] and with weakly basic amines,[53] and the possibility of contamination of the product with cyanide.[54] The reagent is also highly toxic[55] and produces toxic by-products such as HCN and NaCN upon work-up, which may be a safety concern in large-scale reactions. However, the use of $NaBH_3CN$ in reductive amination reactions has continued to be widespread, and it remains one of the most effective reagents and popular reductive amination procedures in the literature. Several recent examples in the literature of reductive amination with cyanoborohydride are listed in Table 2.

Table 2 Reductive amination of aldehydes and ketones with $NaBH_3CN$

Entry	Reactants	Product	Conditions	Yield (%)	References
1			$NaBH_3CN$, AcOH, MeOH	40	56
2			$NaBH_3CN$, AcOH, MeOH r.t., 20 h	84	57
3		R = *n*-C_8H_{17}-C_6H_4-	$NaBH_3CN$ (4 equivalents) MeOH, 0 °C to r. t., 12 h	70 *cis:trans* 38:62	58
4			$NaCNBH_3$ MeOH, AcOH, r.t., 15 h	65	59
5			$NaCNBH_3$ NH_4NO_3 (5 equivalents) MeOH, r.t., 3 days	89	60
6			1. AcOH, 1,2-DCE, 0–5 °C, 0.5 h 2. $NaBH_3CN$ 1,2-DCE 20 °C, 8 h	94	61
7			1. $Ti(O\text{-}i\text{-}Pr)_4$,THF, r.t. 2. $NaBH_3CN$, THF/EtOH, r.t., 20 h	45	62
8			1. 4 Å molecular sieves, toluene, reflux 2. $NaBH_3CN$, THF/EtOH, r.t., 16 h	46	62
9			$NaBH_3CN$, MeOH, 3A-MS r.t., 18 h	39	63

8.02.3.2.2 Reductive amination of aldehydes and ketones with amines using sodium triacetoxyborohydride

Following the introduction of sodium cyanoborohydride for reductive amination reactions, some modifications and other reductive amination procedures were introduced in the 1980s and early 1990s, but these had limited applications. Examples include borane-pyridine,[53d] $Ti(OiPr)_4/NaBH_3CN$,[53c] borohydride exchange resin,[64] Zn/AcOH,[65] $NaBH_4/Mg(ClO_4)_2$,[66] Zn $(BH_4)_2/ZnCl_2$,[67] electrochemical reductive amination,[68] and many others.

The next major milestone came in 1989 when Abdel-Magid and coworkers introduced[69] a new procedure for reductive amination of aldehydes and ketones using sodium triacetoxyborohydride as the reducing agent, which has become one of the most used agent in carrying out reductive amination reactions with a large number of applications and literature reports. Sodium triacetoxyborohydride [$NaBH(OAc)_3$ or STAB-H][70] is a superior, convenient, and effective alternative reducing agent for reductive amination reactions. The selection of $NaBH(OAc)_3$ was based on the pioneering studies of Gribble on reductive alkylation of amines with sodium borohydride in neat liquid carboxylic acids.[71] It is a very mild selective reducing agent that reduces aldehydes but not most ketones.[70] The main exception is β-hydroxyketones, which are reduced in a relatively fast rate with high diastereoselectively to give 1,3-*anti*-diols[72] (*see* Chapter 8.01, Section 8.01.9.1). The steric and electron-withdrawing effects of the three acetoxy groups stabilize the boron–hydrogen bond and are responsible for its mild reducing properties.[73] It is commercially available as a hygroscopic white powder with a melting point of 116–120 °C,[70c] but it is also easily prepared by the reaction of $NaBH_4$ with excess acetic acid in benzene or toluene.[72b]

A comprehensive study of the scope and limitations of sodium triacetoxyborohydride in the direct reductive amination of aldehydes and ketones with ammonia and primary and secondary amines showed that the reagent performed very well in the study with typical cases of aldehydes and ketones with primary and secondary amines.[74] It was also used with great success in reductive amination reactions utilizing weakly basic amines[75] and reduction of preformed imines and enamines.[76] Studies comparing the use of sodium triacetoxyborohydride with $NaBH_3CN$ and other literature methods clearly showed it to be the reagent of choice in most cases.[76] The scope of the reactions includes all aldehydes and alicyclic, heterocyclic, bicyclic, and saturated acyclic ketones with primary and secondary amines. Limitations include most aromatic ketones, α,β-unsaturated ketones, sterically hindered aliphatic ketones, and sterically hindered amines. The reagent did not perform well in reductive amination of aldehydes and ketones with NH_4OAc, giving mostly secondary amines.[76] The majority of products were isolated by simple extraction and salt formation without the need for chromatographic purification. The most commonly used solvent is 1,2-dichloroethane (DCE), but other polar aprotic solvents such as THF and CH_3CN were also used with successful results.[76] Water reacts with sodium triacetoxyborohydride, and it was avoided as a solvent or cosolvent. The presence of small amounts can be tolerated, but additional amounts of $NaBH(OAc)_3$ are used. Reactions in methanol were not consistent, and in many cases, particularly with aldehydes, reduction of the carbonyl compound was competitive with reductive amination. However, MeOH has been used successfully as a solvent with $NaBH(OAc)_3$ in reductive amination reactions.[77,78] Higher alcohols such as EtOH and *i*-PrOH react slowly with $NaBH(OAc)_3$ and may be used as solvents. Another compatible solvent with $NaBH(OAc)_3$ is *N*,*N*-dimethylacetamide.[79]

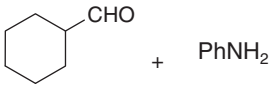
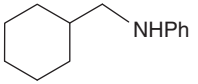
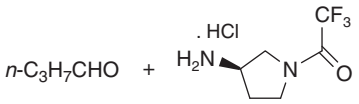
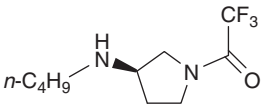
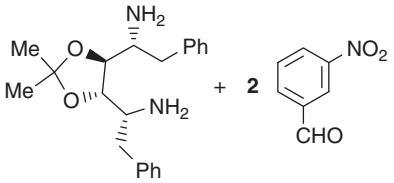
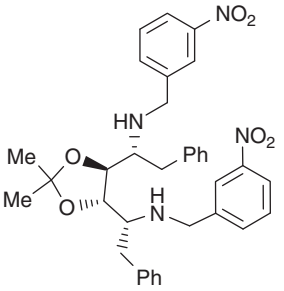
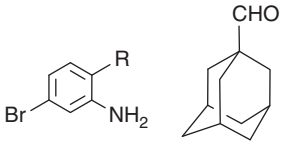
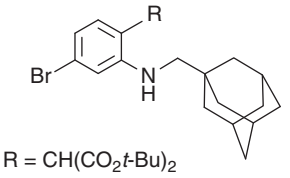
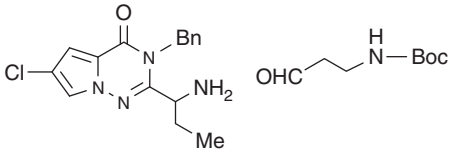
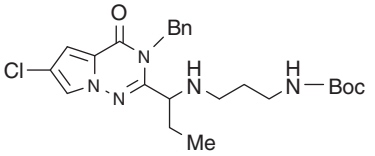
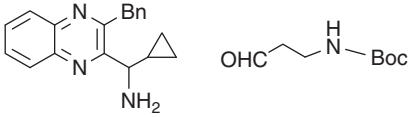
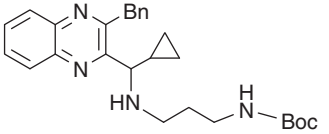
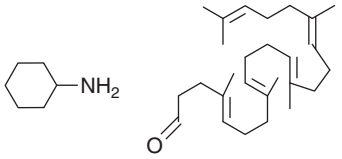
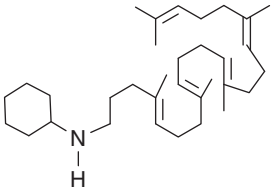
Since the introduction of this procedure, it has been applied to the synthesis of a large number of amine substrates and continues to be an outstanding reagent for reductive amination reactions. The utility of sodium triacetoxyborohydride as a reducing agent in reductive amination reactions is demonstrated by several examples listed in **Tables 3–6**.

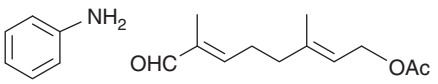
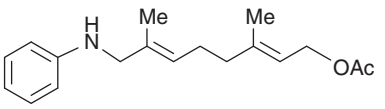
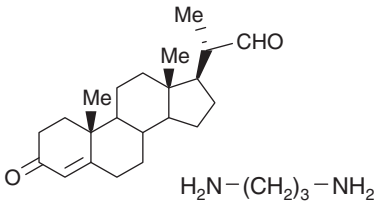
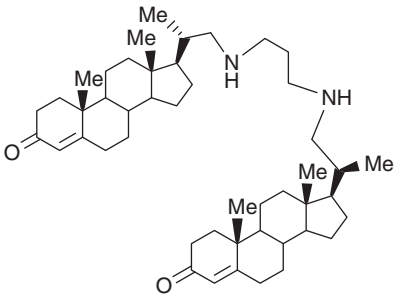
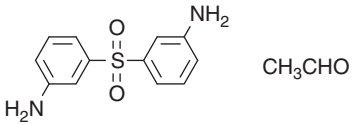
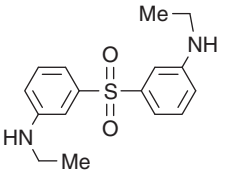
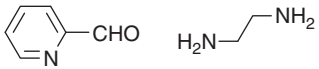
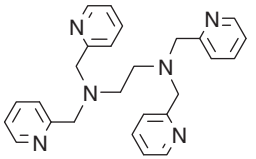
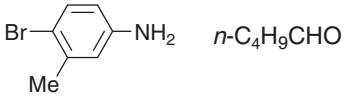
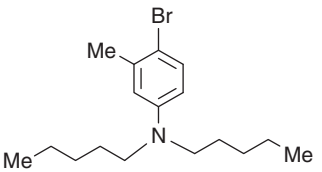
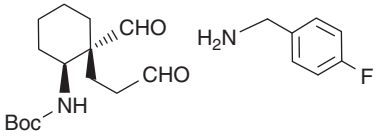
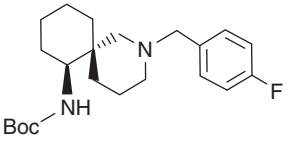
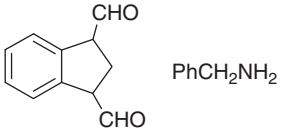
8.02.3.2.2.1 Reductive amination of aldehydes with primary and secondary amines using $NaBH(OAc)_3$

Despite the ability of $NaBH(OAc)_3$ to reduce aldehydes, reductive aminations with aldehydes occur very effectively. The reaction has the widest scope of applications with both aliphatic and aromatic aldehydes with nearly all kinds of primary and secondary amines. Most aldehyde reductive aminations do not require the use of acid activation. All aldehydes are reactive, and their main limitation to undergo reductive amination reactions arises primarily from the use of unreactive or sterically hindered amines. The absence of acids could be beneficial as it minimizes the chance of aldehyde reduction in some slow reactions.[76] Carboxylic acid salts of amines can be used directly in the reaction, but salts of stronger acids such as hydrochlorides and sulfates require the addition of approximately 1.1 equivalents of triethylamine. The reactions are fast, nearly complete within 20 min to 24 h. The mild reaction conditions and the easy work-up and isolation of products can tolerate the presence of a large variety of functionalities and allow the application of the reaction to a wide range of structurally complex aldehydes. There are numerous examples of this procedure; several representative applications are listed in **Table 3**.

Reductive aminations of aldehydes with primary amines are typically the fastest and highest yielding reactions. There are very few limitations with highly unreactive primary amines such as 2,4-dinitroaniline, particularly with aromatic aldehydes. Aldehydes and primary amines condense readily (completely or partially) to form imines in most solvents, particularly in methanol, THF, and DCE.[76] Several modifications have taken advantage of this property and mixed the two reactants for some time before addition of $NaBH(OAc)_3$ to minimize possible side reactions such as dialkylation and aldehyde reductions. Variable examples representing reductive amination of aldehydes with primary amines are listed in **Table 3** (entries 1–14). The yields from the represented examples range from 65% to 100%. The selected examples show the utility of the procedure and the tolerance and compatibility with other groups in highly functionalized substrates. Dialkylation of primary amines is a possible side reaction during the reductive amination of aldehydes, but it is rarely a problem in this procedure. If dialkylation is detected, it may be suppressed effectively by the addition of approximately 1–5% molar excess of the primary amine. In the examples in **Table 3** (entries 8 and 9), the procedure was modified by mixing the aldehyde with the primary amine in the first case[85] and with a diamine in the second[86] before adding the reducing agent. This modification is typically implemented to minimize side reactions and maximize the yields. Occasionally, however, the dialkylation of primary amines may be the desired outcome. In this case, the

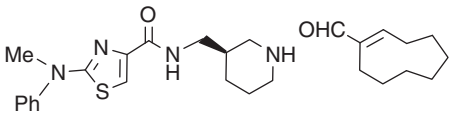
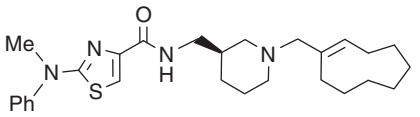
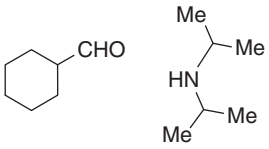
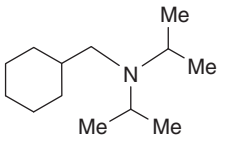
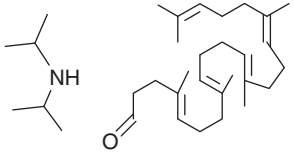
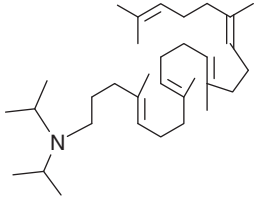
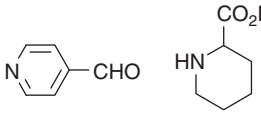
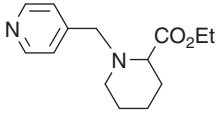
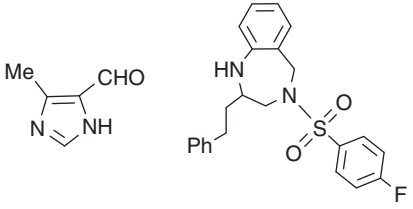
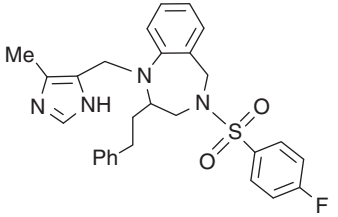
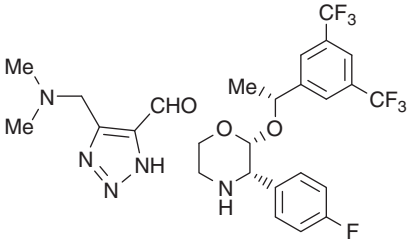
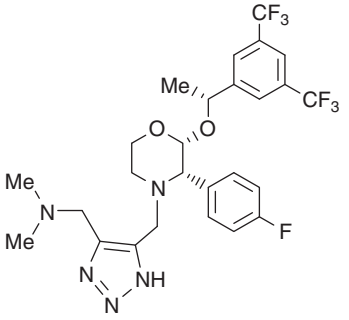
Table 3 Reductive amination of aldehydes with amines using $NaBH(OAc)_3$

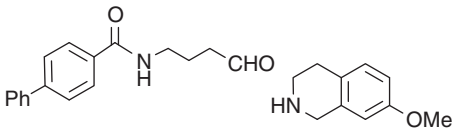
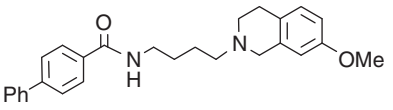
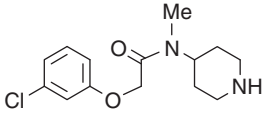
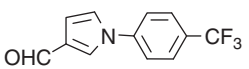
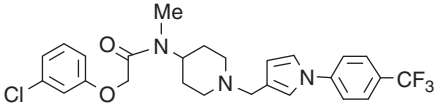
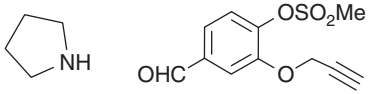
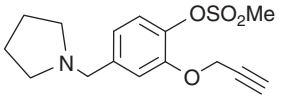
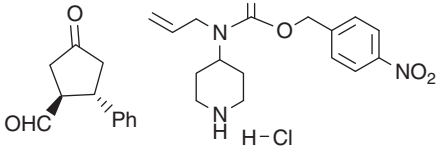
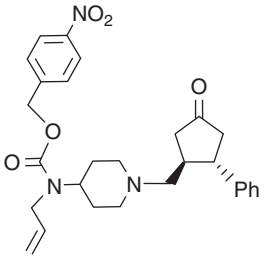
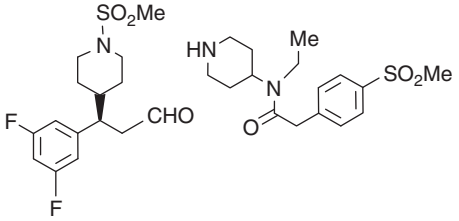
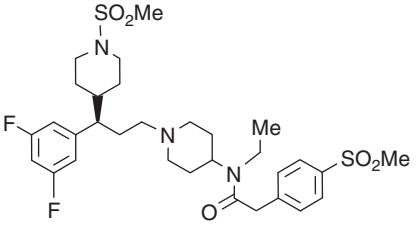
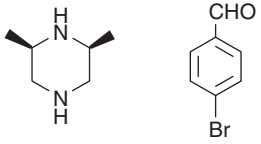
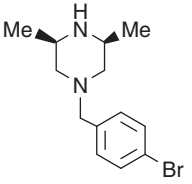
Entry	Reactants	Product	Conditions	Yield (%)	References
1			$NaBH(OAc)_3$ DCM, r.t., 24 h	83	76
2			$NaBH(OAc)_3$ TEA, DCM, AcOH r.t., 18 h	66	80
3			$NaBH(OAc)_3$ AcOH, r.t.	83	81
4		 R = $CH(CO_2t\text{-}Bu)_2$	$NaBH(OAc)_3$ AcOH, r.t., 30 min	>95	82
5			$NaBH(OAc)_3$ THF, AcOH r.t., overnight	92	83
6			Ald + amine in MeOH (20 min) Then: $NaBH(OAc)_3$ AcOH, r.t., 2 h	80	84
7			$NaBH(OAc)_3$ DCE, r.t., 1 h	94	76

8			ald. + amine + AcOH in DCE (10 min) then: $NaBH(OAc)_3$ r.t., 5 h	85	85
9			ald. + diamine + DCE (24 h) then: $NaBH(OAc)_3$ AcOH, 72 h	65	86
10			$NaBH(OAc)_3$ THF, r.t., 5 h	No yield	87
11			ald. + diamine + DCE (30 min) then: $NaBH(OAc)_3$ DCE, r.t., 24 h	58	88
12			$NaBH(OAc)_3$ MeOH, r.t., 3 h	95	78
13			$NaBH(OAc)_3$ DCE, r.t., 24 h	100	89
14			$NaBH(OAc)_3$ DCE, 0 °C to r.t.; 0.5–3 h	86	90

(*Continued*)

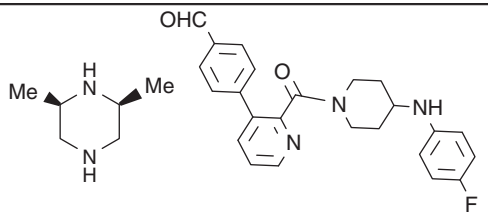
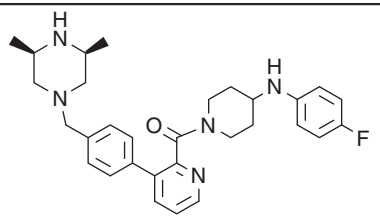
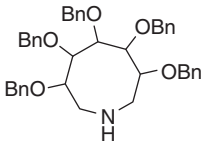
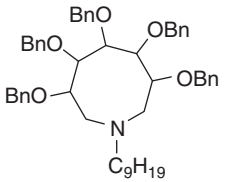
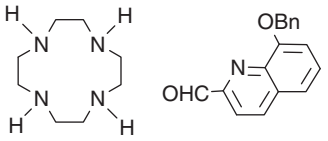
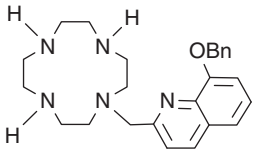
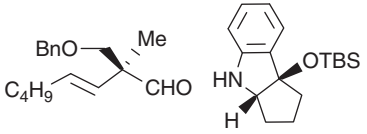
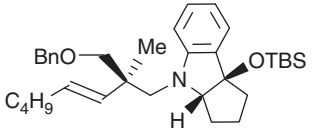
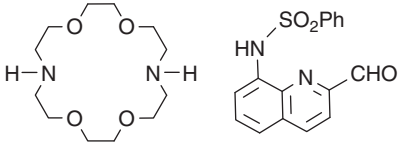
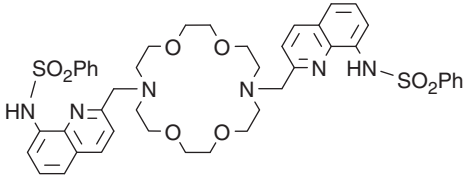
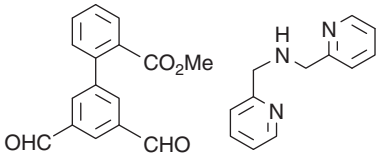
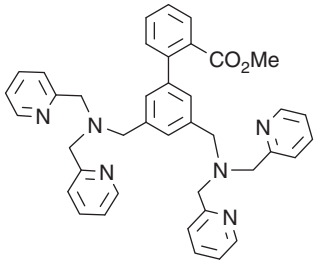
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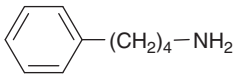
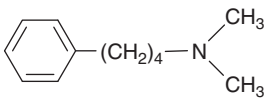
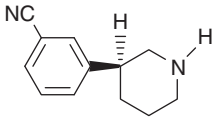
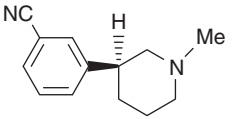
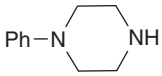
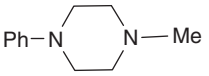
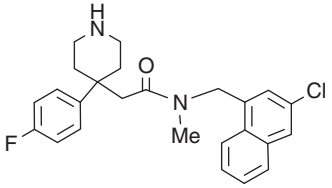
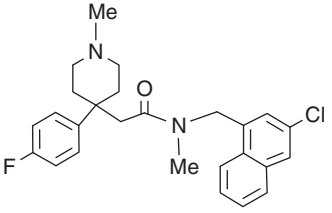
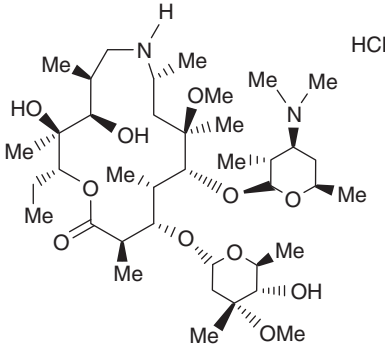
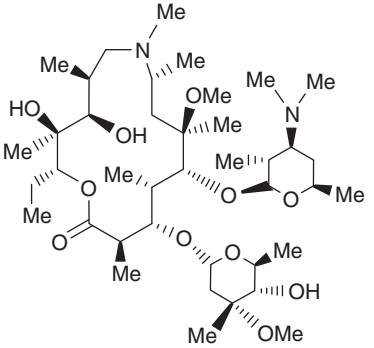
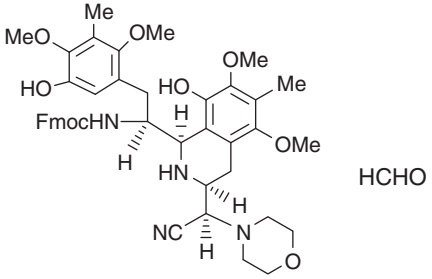
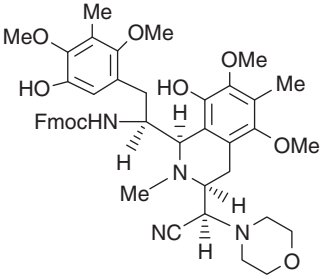
Entry	Reactants	Product	Conditions	Yield (%)	References
15			$NaBH(OAc)_3$ THF, AcOH, r.t., 16 h	76	91
16			$NaBH(OAc)_3$ DCE, AcOH, r.t., 3 h	41	76
17			$NaBH(OAc)_3$ DCE, r.t., 8 h	74	76
18			$NaBH(OAc)_3$ DCE, r.t., 1.5 h	90	76
19			$NaBH(OAc)_3$ DCE, r.t., 1.5 h	95	76
20			ald. + diamine DCE, AcOH, r.t., 30 min then: $NaBH(OAc)_3$	90	92
21			$NaBH(OAc)_3$ $MeCONMe_2$ (DMAC) 0 °C to –5 °C, 2 h	95	79

22			$NaBH(OAc)_3$ DCE, r.t., 16 h	83	93
23	 		$NaBH(OAc)_3$ DCE	79	94
24			$NaBH(OAc)_3$ DCE, r.t., 1.5 h	95	95
25			$NaBH(OAc)_3$ DIPEA, DCE r.t., 4 h	43	96
26			$NaBH(OAc)_3$ DCE, r.t., 2 h	68	97
27			$NaBH(OAc)_3$ DCE, 0 °C-r.t.	87	98

(*Continued*)

Table 3 Continued

Entry	Reactants	Product	Conditions	Yield (%)	References
28			$NaBH(OAc)_3$ DCE, r.t.	63	98
29	 C_8H_{17}-CHO		$NaBH(OAc)_3$, 1,2-DCE, r.t., 16 h	84	99
30			$NaBH(OAc)_3$ (2 equivalents) DCE, r.t., 15 h	61	100
31			$NaBH(OAc)_3$ $Sn(OTf)_2$ DCE, 0 °C	66	101
32			$NaBH(OAc)_3$ DCE, r.t., 5 h	85	102
33			$NaBH(OAc)_3$ DCE, 22 °C, 3 h	93	103

34		HCHO		$NaBH(OAc)_3$ DCE, r.t., 1 h	90	76
35		HCHO		$NaBH(OAc)_3$ DCE, r.t., 1 h	89	104
36		HCHO		$NaBH(OAc)_3$ DCE, r.t., 1 h	95	76
37		HCHO		$NaBH(OAc)_3$ CH_3CN, r.t., 2 h	85	105
38		HCHO		$NaBH(OAc)_3$ DCE, AcOH, r.t., 1 h	96	106
39		HCHO		$NaBH(OAc)_3$ CH_3CN, r.t.	94	107

amine is used as the limiting reagent with two (or more) aldehyde equivalents (Table 3, entries 11 and 12).[79,88] In other cases a primary amine reacts with dialdehydes to form cyclic compounds, as in the reaction of 1,5-dialdehydes with primary amines to form piperidine rings (Table 3, entries 13 and 14).[89,90]

The reductive amination of aldehydes with secondary amines follows a trend similar to the primary amines but can vary considerably based on the steric hindrance and structural features caused by a second substituent on the amine nitrogen. Several applications of reductive amination of aldehydes with secondary amines are listed in Table 3 (entries 15–32). In general, the reactions are slower than those with primary amines, and this may cause competing side reactions, namely aldehyde reduction, *N*-acetylation, and *N*-ethylation of amines. One example of a very slow reaction is the reductive amination of cyclohexane carboxaldehyde with diisopropylamine in the presence of AcOH, which afforded only 41% of the desired product and reduced 25% of the aldehyde. Carrying out the reaction without AcOH made it slower but much cleaner, giving the product in 74% isolated yield with only 5% aldehyde reduction (Table 3, entries 16 and 17).[76] The same hindered secondary amine gave much better result in the reductive amination of 1,1′,2′-tris-norsqualene aldehyde (Table 3, entry 18) with no added AcOH. The reaction was complete in 1.5 h and provided the product in 90% isolated yield with no detectable aldehyde reduction.[76] This is a much improved result compared to standard reduction with $NaBH_3CN$ giving only 4% product in the absence of AcOH and 45% in its presence.[132] The reductive amination of aromatic aldehydes with ethyl 2-carboxypiperidine (Table 3, entry 19) was also improved using $NaBH(OAc)_3$[76] when compared with other literature procedures.[54]

N,*N*-dimethylacetamide proved to be a better solvent in reductive amination with $NaBH(OAc)_3$ than DMF, which caused formylation of the starting secondary amine in the synthesis of a substance P antagonist (Table 3, entry 21). The final step in the convergent synthesis was a reductive amination step using $NaBH(OAc)_3$ in *N*,*N*-dimethylacetamide; the reaction was carried out on a 4.4 mol scale and gave the desired product in 95% isolated yield.[79]

Westaway and coworkers[98] reported the reductive amination of aldehydes with *cis*-2,6-dimethylpiperazine (Table 3, entries 27–28) in which the less hindered secondary amine of the piperazine reacted preferentially over the more hindered one. An interesting example of selective reductive amination of an aldehyde in the presence of a ketone is represented in Table 3 (entry 25).[96] In the total synthesis of madindoline A, Kobayashi and Hosokawa[101] attempted the reductive amination of a sterically hindered aldehyde with an acid-labile aromatic amine (Table 3, entry 31). In the presence of AcOH, the reductive amination failed and only aldehyde reduction occurred. They discovered a novel and effective combination of $Sn(OTf)_2$ (1.1 equivalents) and $NaBH(OAc)_3$ (1.5 equivalents) with 4A MS in dichloroethane at 0 °C to obtain the desired product in 66% yield.

The use of formalin as a source of formaldehyde in reductive amination reactions for the *N*-methylation of amines is a common reaction particularly with $NaCNBH_3$, which is stable in aqueous media and in MeOH. The use of paraformaldehyde is more compatible with $NaBH(OAc)_3$ than formalin, but the latter can also be used mostly on a small scale (10–20 mmol) with excess of the reducing agent. The reaction is generally not suitable for monomethylation of primary amines with any of the reagents and usually forms *N*,*N*-dimethyl amines in good yields (Table 3, entry 34).[76] Secondary amines, however, can be methylated only once; thus, it is a much easier reaction as in the *N*-methylation of 3-(3-cyanophenyl)piperidine to give the product in 89% isolated yield (Table 3, entry 35).[104] In addition, *N*-methylation of 1-phenylpiperazine with formalin and 4 equivalents of $NaBH(OAc)_3$ in DCE gave nearly quantitative yield of 4-methyl-1-phenylpiperazine (Table 3, entry 36).[76] Other reported reactions show a diversity of structures in which formalin was used in the *N*-methylation of several amines in the presence of $NaBH(OAc)_3$ (Table 3, entries 37–39).

8.02.3.2.2.2 Reductive amination of ketones with primary and secondary amines using $NABH(OAc)_3$

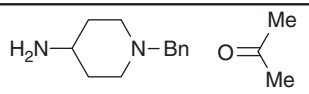
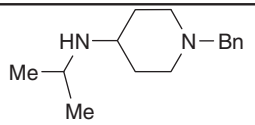
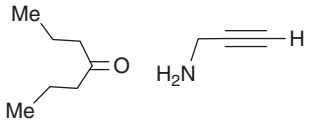
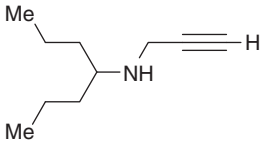
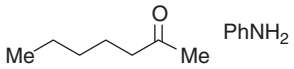
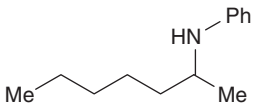
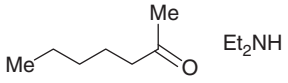
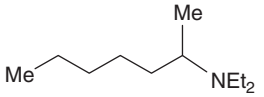
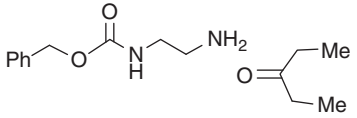
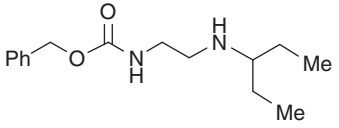
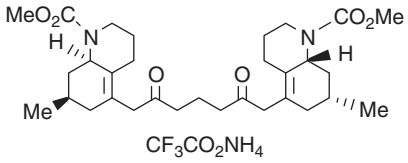
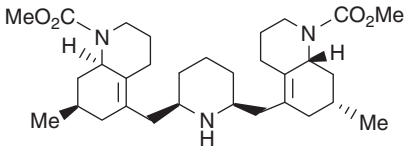
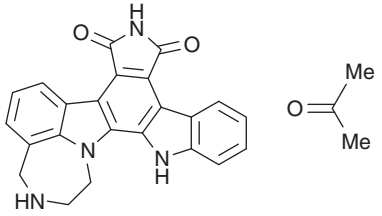
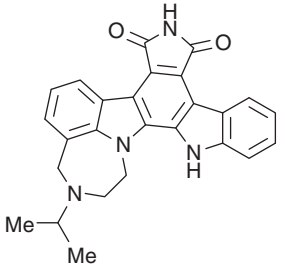
Except for *β*-hydroxy ketones,[72] the reduction of ketones with $NaBH(OAc)_3$ is very slow or does not occur at all.[70] However, ketimines are reduced with $NaBH(OAc)_3$ under neutral to weakly acidic conditions, which makes this reagent ideal for reductive amination of ketones. A systematic study[76] and numerous applications demonstrate the utility and the vast scope of this reagent in reductive amination of different kinds of ketones including saturated acyclic, alicyclic, heterocyclic, and bicyclic ketones with few limitations. Major limitations include most aromatic, *α*,*β*-unsaturated, and sterically hindered aliphatic ketones.

Examples of products obtained by reductive amination of several saturated acyclic ketones are shown in Table 4 (entries 1–7). Slow reactions with hindered secondary amines are accelerated by adding 1–2 equivalents of AcOH. Some of these slow reductive aminations (e.g., Table 4, entries 3 and 4) may be accompanied by side reactions including *N*-acetylation and *N*-ethylation of the starting amines. The *N*-acetylation is believed to be the result of nucleophilic attack by the amines on the triacetoxyborohydride.[53b,71b] The *N*-ethylation of amines is a known process with sodium borohydride in neat acetic acid and is believed to proceed through acetaldehyde formation under the reaction conditions.[71a] It is possible the AcOH that is added to accelerate the reaction could be the cause of these side reactions; in many cases, the use of trifluoroacetic acid instead of AcOH eliminates the formation of these side products.

An interesting example is the reductive amination of acetone with 1-benzyl-4-aminopiperidine (Table 4, entry 1),[108] which was carried out in methanol, a solvent that is not commonly used with $NaBH(OAc)_3$. The ketone and amine were mixed in MeOH for 12 h at r.t.; then the mixture was cooled to 5 °C for 30 min before addition of $NaBH(OAc)_3$ and the product was isolated in a very high yield of 95%. The reaction was scaled up to 2 kg in DCM and performed equally well to give an isolated yield of 96%. The reductive amination of a 1,5-diketone with ammonia (Table 4, entry 6) was first attempted using $NaBH_3CN$, but the reaction was very slow with some reduction of ketone. Ketone reduction was avoided by using $NaBH(OAc)_3$; however, the reductive amination was still slow, resulting in incomplete conversion to afford 28% yield of the piperidine and 50% recovered unreacted diketone.[110]

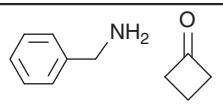
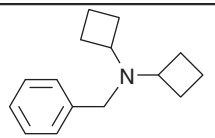
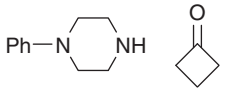
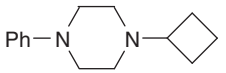
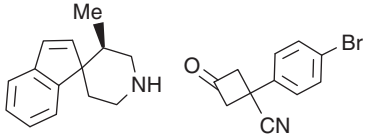
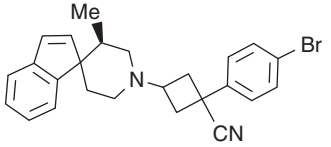
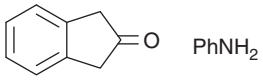
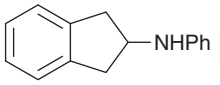
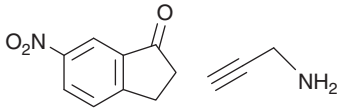
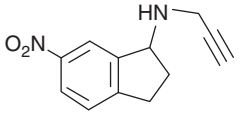
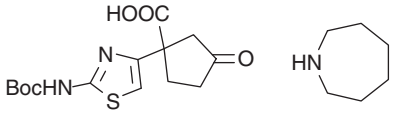
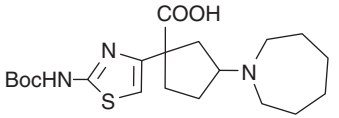
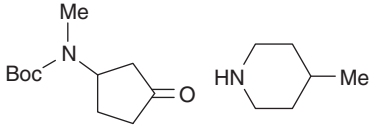
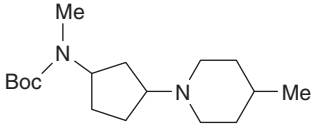
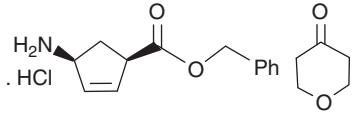
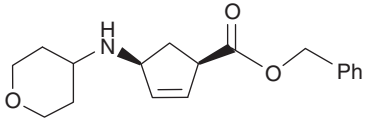
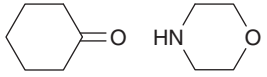
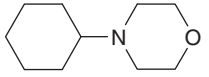
Most reported reductive aminations for saturated cycloalkanones are for cyclohexanone derivatives, but other cyclic ketones ranging in size from 4- to 12-membered rings give excellent yields in reductive amination reactions with primary and secondary

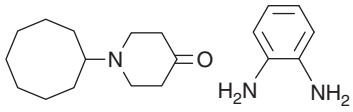
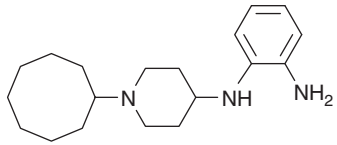
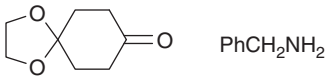
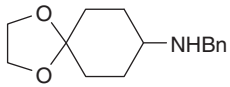
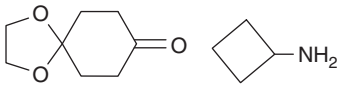
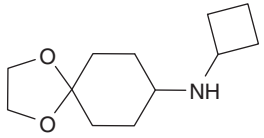
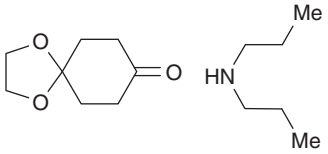
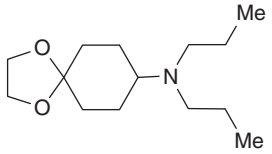
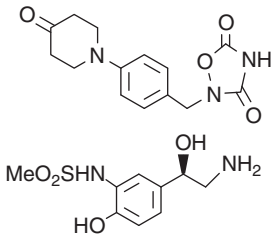
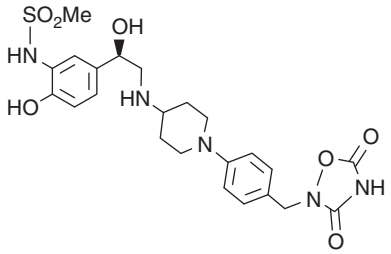
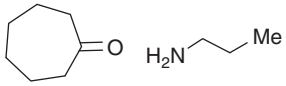
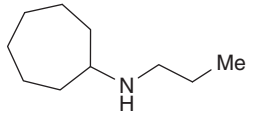
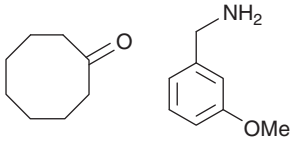
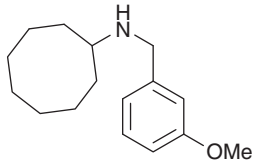
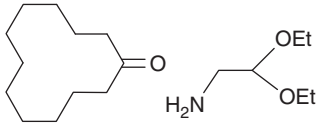
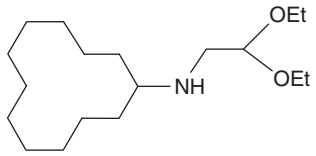
Table 4 Reductive amination of ketones with primary and secondary amines using $NaBH(OAc)_3$

Entry	*Substrates*	*Product*	*Conditions*	*Yield (%)*	*References*
1			1. Ketone + amine r.t., 12 h 2. MeOH, 5 °C 3. $NaBH(OAc)_3$ MeOH, 5 °C 4. r.t., 2 h; 5 °C	95	108
2			$NaBH(OAc)_3$ DCE, AcOH r.t., 12 h	84	76
3			$NaBH(OAc)_3$ DCE, AcOH r.t., 96 h	90	76
4			$NaBH(OAc)_3$ DCE, AcOH r.t., 192 h	44	76
5			$NaBH(OAc)_3$ CH_2Cl_2, r.t., 16 h	79	109
6			$NaBH(OAc)_3$ THF, 3A-MS, r.t.	28	110
7			$NaBH(OAc)_3$ DCE, AcOH	90	111

(*Continued*)

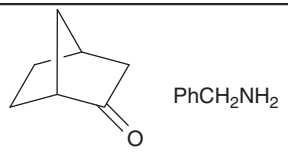
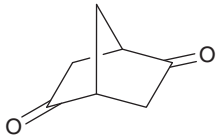
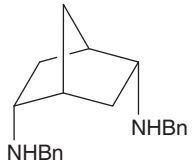
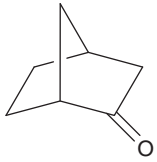
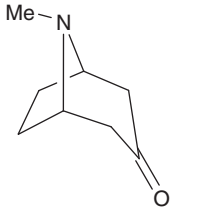
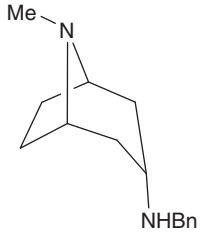
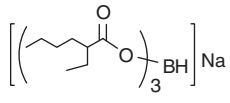
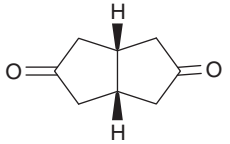
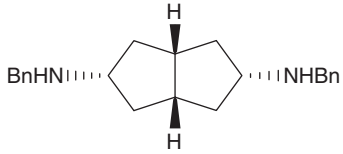
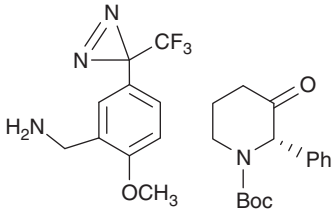
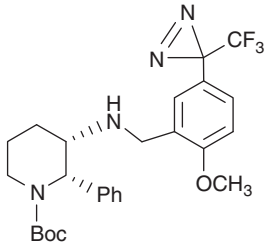
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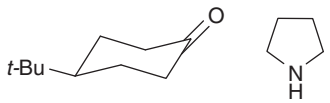
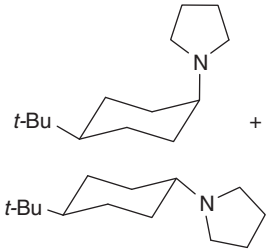
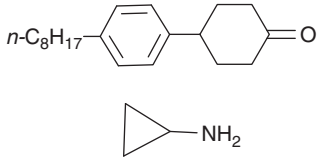
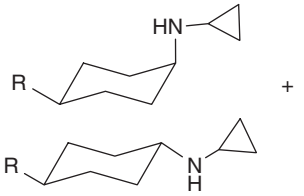
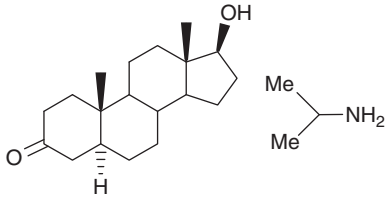
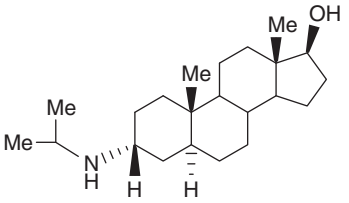
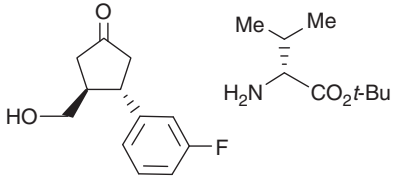
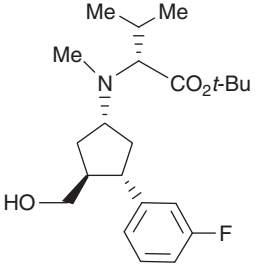
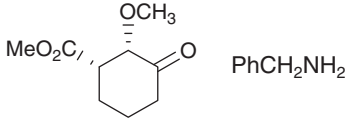
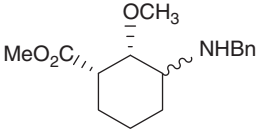
Entry	Substrates	Product	Conditions	Yield (%)	References
8			$NaBH(OAc)_3$ DCE, AcOH r.t., 1.5 h	98	76
9			$NaBH(OAc)_3$ DCE, r.t., 2 h	96	76
10			$NaBH(OAc)_3$ DCM, r.t., 24 h	99	112
11			$NaBH(OAc)_3$ DCE, AcOH r.t., 6 h	85	76
12			$NaBH(OAc)_3$ DCE, r.t., 50 h	69	113
13			$NaBH(OAc)_3$ THF, r.t., overnight	75	114
14			$NaBH(OAc)_3$ DCE, AcOH r.t., 16 h	35	115
15			$NaBH(OAc)_3$ DIEA, CH_2Cl_2, 4A MS, r.t., overnight	84	116
16			$NaBH(OAc)_3$ DCE, r.t., 2 h	96	76

17			$NaBH(OAc)_3$ DCE, r.t., overnight	81	117
18			$NaBH(OAc)_3$ DCE, AcOH r.t., 20 min	98	76
19			$NaBH(OAc)_3$ DCE, AcOH r.t., 25 min	98	76
20			$NaBH(OAc)_3$ DCE, AcOH	>95	118
21			$NaBH(OAc)_3$ DCE, AcOH r.t., 24 h	71	119
22			$NaBH(OAc)_3$ DCE, AcOH r.t., 3 h	88	76
23			$NaBH(OAc)_3$ DCE, AcOH r.t., 23 h	95	76
24			$NaBH(OAc)_3$ DCE, r.t., 24 h	88	76

(*Continued*)

Table 4 Continued

Entry	Substrates	Product	Conditions	Yield (%)	References
25			$NaBH(OAc)_3$ DCE, AcOH r.t., 6 h	95	76
26			$NaBH(OAc)_3$ CH_2Cl_2, AcOH r.t., 6 h	98	120
27			$NaBH(OAc)_3$ DCE, AcOH r.t., 96 h	76	76
28			$NaBH(OAc)_3$ DCE, AcOH r.t., 20 h	85 *endo:exo* 15:1	76
29		 CH_2Cl_2, r.t.		85 *endo:exo* >50:1	121
30			$NaBH(OAc)_3$ DCE, r.t.	96	122
31			$NaBH(OAc)_3$ DCE, r.t.	61	123

32			$NaBH(OAc)_3$ DCE, AcOH r.t., 10 min	98 *ax:eq* 71:29
33		 R = *n*-C_8H_{17}-C_6H_4-	$NaBH(OAc)_3$ CH_2Cl_2 r.t., 2 h	66 *cis:trans* 70:30
34		 Major	$NaBH(OAc)_3$ DCE, AcOH r.t., 24 h	99 α/β 75:25
35			$NaBH(OCOPr)_3$ CH_3CN, DIPEA 70 °C, 30 min then: HCHO-H_2O $NaBH(OAc)_3$ CH_3CN, r.t., 30 min	61
36			$NaBH(OAc)_3$ DCE, AcOH r.t.	99 1:1

32	76
33	58
34	76
35	124
36	125

amines (Table 4, entries 8–27). The reaction conditions vary largely based on the solubility and reactivity of the individual ketones and amines. Small-ring ketones are usually more reactive than larger ones, but all react efficiently. Cyclobutanone is as reactive as or more reactive than aldehydes; for example, reductive amination of cyclobutanone with benzylamine gave a mixture of *N*-cyclobutyl and *N*,*N*-dicyclobutyl benzylamines even when using excess benzylamine.[76] The only homogeneous reaction was achieved when using 2 equivalents of cyclobutanone to form *N*,*N*-dicyclobutyl benzylamine (Table 4, entry 8).[76] Reactions with secondary amines performed well since only one product is possible (Table 4, entry 9).[76] Most other cyclic ketones react more slowly, and the dialkylation of primary amines is not common. Reactions with cyclopentanones and cyclohexanones are usually complete in 1–24 h. Unusually fast reactions were observed with 4-substituted cyclohexanones such as cyclohexane-1,4-dione monoethylene ketal (Table 4, entries 18 and 19) and with 4-*tert*-butylcyclohexanone (Table 4, entry 32) where the reactions are complete in only 10–25 min.[76]

Bicyclic ketones such as norcamphor and tropinone are successfully reductively aminated with primary and secondary amines in good to excellent yields (Table 4, entries 25–30). The reactions are relatively slow, particularly with secondary amines, but show high levels of diastereoselectivity toward the *endo*-products. For example, the products from reductive amination of norcamphor with primary or secondary amines are exclusively *endo* (Table 4, entries 25–27), whereas those obtained from reductive amination of tropinone with primary amines show approximately 15:1 ratio of the *endo*- to *exo*-products (Table 4, entry 28). McGill and coworkers[121] reexamined the reductive amination of tropinone with benzylamine using $NaBH(OAc)_3$ and obtained a 12:1 ratio of *endo*:*exo*-product. Increasing the selectivity of the reaction by using the bulkier sodium tri-(2-ethylhexanoyl)borohydride led to the formation of the amine product in a >50:1 *endo*:*exo* ratio (Table 4, entry 29). The reductive amination of *cis*-bicyclo[3.3.0]octane-3,7-dione (Table 4, entry 30) gave the symmetric diamine product in 96% yield with slight contamination of two minor diastereomers.[122]

The reductive amination of Boc-protected 2-phenylpiperidin-3-one with a benzylamine derivative (Table 4, entry 31) using $NaBH(OAc)_3$ gave only the *syn*-product.[123] The reductive amination of 4-substituted cyclohexanones with $NaBH(OAc)_3$ usually gives approximately 70:30 mixture of *cis*:*trans* diastereomers (Table 4, entries 32 and 33),[58,76] and a similar result was obtained from a 3-ketosteroid (Table 4, entry 34).[76]

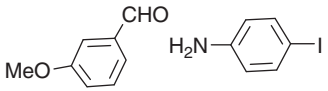
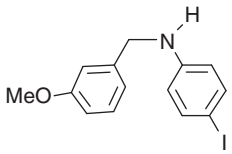
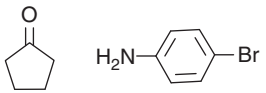
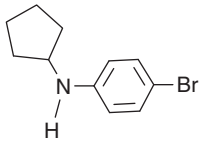
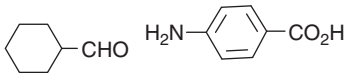
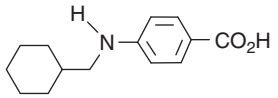
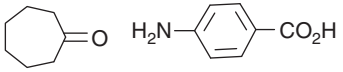
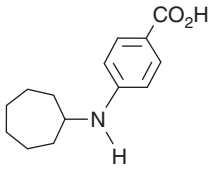
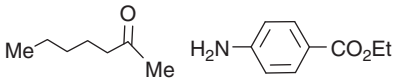
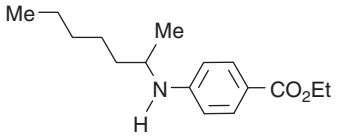
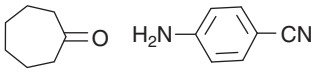
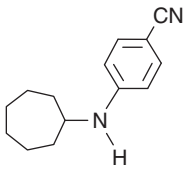
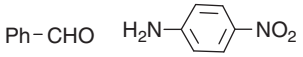
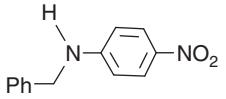
Conlon and coworkers[124] reported a practical and efficient diastereoselective synthesis of an anti-human immunodeficiency virus drug candidate (Table 4, entry 35). The key step in this synthesis is a unique hydroxy-directed reductive amination of (+)-*trans*-3-hydroxymethyl-4-(3-fluorophenyl)cyclopentanone with *tert*-butyl D-valinate to obtain the *trans*-product. The authors explained their result by a hydroxyl-directed reduction similar to that obtained from reduction of *β*-hydroxy ketones with triacetoxyborohydride. The selectivity of the reductive amination was improved from 1.9:1 ratio in DCE at r.t. to approximately 7:1 in favor of the desired *trans*-diasteromer by carrying out the reaction in dry acetonitrile, elevating the reaction temperature to 50 °C, and increasing the stoichiometric ratio of the amine. Further improvement was obtained by using sodium tripropoxyborohydride; the increased bulk of this hydride reagent and higher reaction temperature (70 °C) gave a 10:1 ratio favoring the *trans*-isomer. The reaction was carried out on approximately 4-mole scale, and the product was converted directly to the *N*-methyl derivative by a second reductive amination with formalin using $NaBH(OAc)_3$. This sequence provided the desired product in 61% isolated yield for the two reductive amination steps.

8.02.3.2.2.3 Reductive amination of aldehydes and ketones with weakly basic amines

Weakly basic amines are mostly aromatic amines that are both weak bases and poor nucleophiles. The pK_a values of represented amines (expressed as the pK_a of the protonated amines) range from 3.98 for *p*-chloroaniline to –4.26 for 2,4-dinitroaniline.[133] The use of these amines in the reductive amination of aldehydes and ketones results in sluggish, low-yielding reactions. Because of their poor nucleophilicity, imine formation with aldehydes and ketones is a slow process. $NaBH(OAc)_3$ is superior over other reagents in reductive amination of aldehydes and ketones with weakly basic amines.[75] Representative examples are listed in Table 5. Most *p*-mono-substituted anilines with substituents such as Cl, Br, CN, COOH, and NO_2 are used as regular amines to give the corresponding reductive amination products in very good isolated yields (Table 5, entries 1–9). Although these amines react slower than regular amines, they still show the same trend observed in all other reductive amination reactions. They react with both aldehydes and ketones, but aldehydes react faster and produce higher yields than ketones in all cases.[75,76]

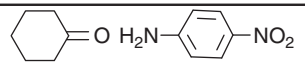
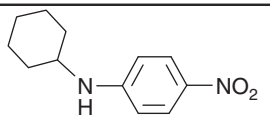
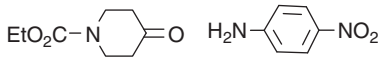
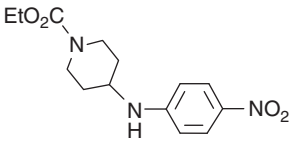
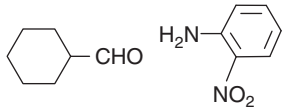
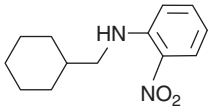
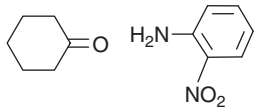
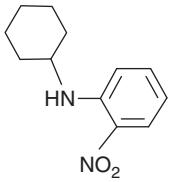
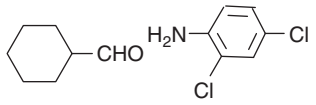
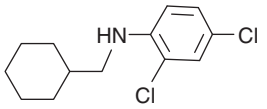
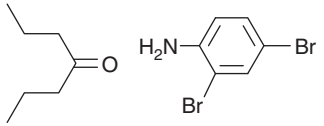
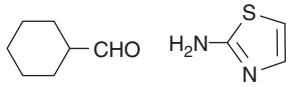
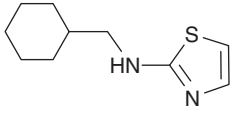
The less basic amines such as *o*-nitroaniline, 2,6-dibromoaniline, 2,4,6-trichloroaniline, 2-aminothiazole, 5H-dibenzo[b,f] azepine, and [60]fulleropyrrolidines react with aldehydes (Table 5, entries 10, 12, 14, 15, 17, and 19), but some of the reactions are noticeably slow. These reactions are also accompanied by approximately 10–30% aldehyde reduction and consequently the reactions are modified to use the amines as the limiting agents and up to 1.5 equivalents of aldehyde to compensate for this side reaction. The reactions with ketones are either very slow (Table 5, entry 11) or do not proceed at all (Table 5, entries 13, 16, and 18). Thus, although the reductive aminations of cyclohexane carboxaldehyde with *o*-nitroaniline (entry 10) and 2,4-dichloroaniline (entry 12) are fast and provide good to excellent yields, the corresponding reactions with ketones gave poor results. The reductive amination of cyclohexanone with *o*-nitroaniline (entry 11) progressed to only 30% conversion after 144 h, whereas 4-heptanone showed no reaction with 2,4-dibromoaniline after 24 h (entry 13). Interestingly, hexanal was reductively aminated successfully and effectively with 5H-dibenzo[b,f]azepine in the presence of $NaBH(OAc)_3$ (entry 15) to give high yield (82%) in 10 h, but the reaction of hexanal with the dihydro-derivative, 10,11-dihydro-5H-dibenzo[b,f]azepine, failed to give any product (entry 16). Li, Zhu, and coworkers[126] studied the reductive amination of aldehydes and ketones with the very weakly basic amine, [60]fulleropyrrolidines, to synthesize several *N*-alkylated derivatives. They observed that saturated aliphatic aldehydes were most reactive as they can reach nearly 100% conversion with no detectable side reactions. Thus, the reductive amination of dodecanal

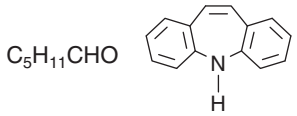
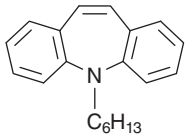
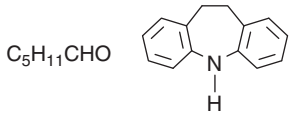
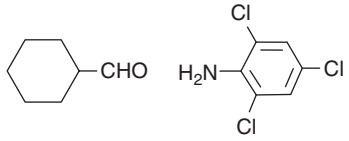
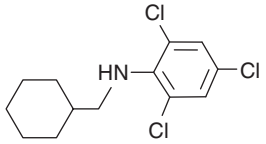
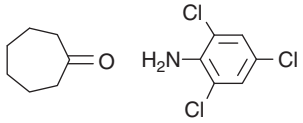
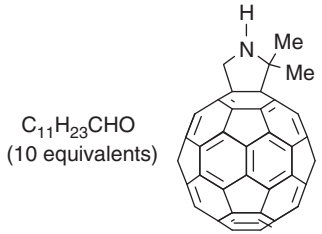
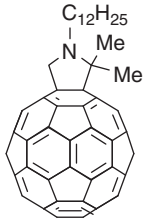
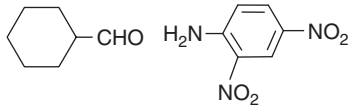
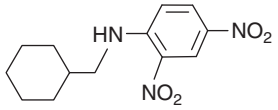
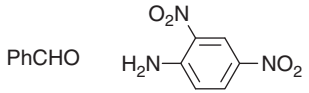
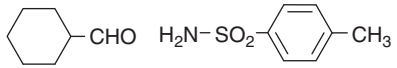
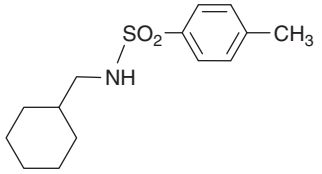
Table 5 Reductive amination of aldehydes and ketones with weakly basic amines

Entry	*Reactants*	*Product*	*Conditions*	*Yield (%)*	*References*
1			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 30 min	90	75
2			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 48 h	89	75
3			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 0.5 h	86	75
4			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 22 h	79	75
5			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 14 h	94	75
6			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 24 h	71	75
7			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 1.5 h	85	75

(*Continued*)

Table 5 Continued

Entry	*Reactants*	*Product*	*Conditions*	*Yield (%)*	*References*
8			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 23 h	66	75
9			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 18 h	60	75
10			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 1.5 h	66	75
11			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 144 h	30	75
12			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 40 min	96	75
13		No Reaction Recovered starting materials	$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 24 h	0	75
14			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 23 h	85	75

15			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 10 h	82	75
16		No Reaction Recovered starting materials	$NaBH(OAc)_3$ 1,2-DCE r.t., 24 h	0	75
17			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 48 h	58	75
18		No Reaction Unreacted starting materials	$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 24 h	0	75
19			$NaBH(OAc)_3$ (10 equivalents) 1,2-DCE, AcOH (10 equivalents) r.t., 2 h	95	126
20			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 96 h	61	75
21		No Reaction Recovered starting materials	$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 24 h	0	75
22			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 28 h	85	76

(10 equivalents) with [60]fulleropyrrolidines in the presence of AcOH and $NaBH(OAc)_3$ (10 equivalents each) gave the *n*-dodecyl derivative in 95% yield (Table 5, entry 19). Aromatic and α,β-unsaturated aldehydes reacted much more slowly and were accompanied by high levels (up to 38%) of *N*-ethylation of the amine. Attempted reductive aminations with ketones such as acetone and 3-pentanone failed.

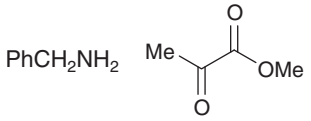
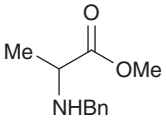
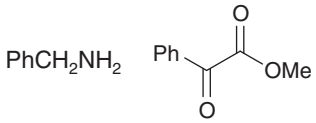
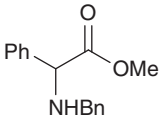
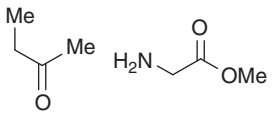
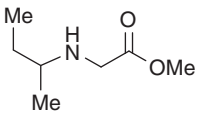
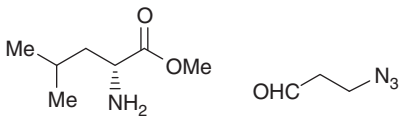
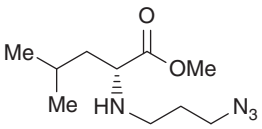
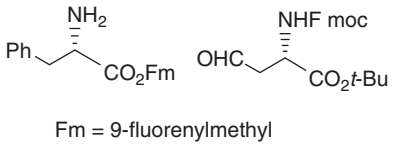
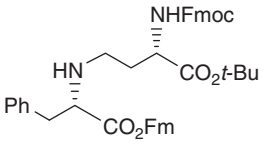
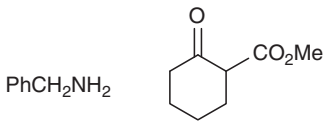
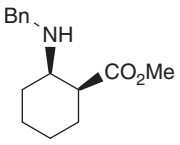
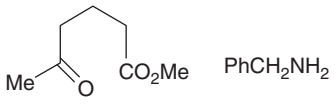
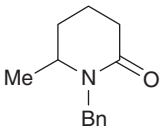
The nonbasic 2,4,6-trichloroaniline and 2,4-dinitroaniline are among the least reactive amines. The reductive amination of cyclohexane carboxaldehyde with these amines progressed very slowly and was accompanied by considerable aldehyde reduction. The reaction was carried out in the presence of 3–5 equivalents of AcOH and required occasional addition of excess aldehyde and $NaBH(OAc)_3$, up to 5 equivalents each, over 2–4 days to effect complete consumption of the amines. The amine products are highly nonbasic and do not form salts with strong acids such as HCl. They could be purified only by chromatography to give 58% and 61% yield, respectively (Table 5, entries 17 and 20). Aromatic aldehydes such as benzaldehyde could not be reductively aminated with 2,4-dinitroaniline (Table 5, entry 21).[75]

It is not common to use sulfonamides in reductive amination reactions, but aldehydes can be reductively aminated with *p*-toluenesulfonamide to give the corresponding *N*-alkyl sulfonamides in good isolated yields (Table 5, entry 22). However, this reaction fails with ketones.[76]

8.02.3.2.2.4 Reductive amination of keto acids, keto esters, amino acids, and amino esters

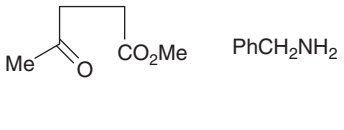
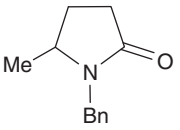
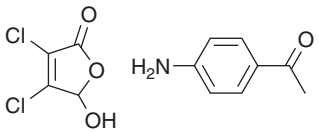
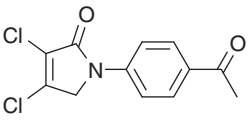
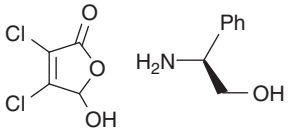
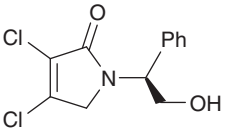
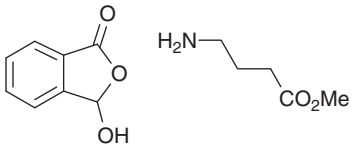
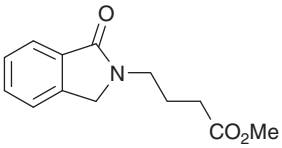
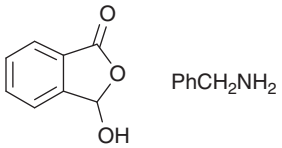
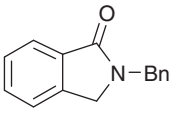
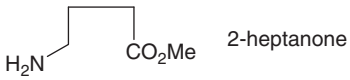
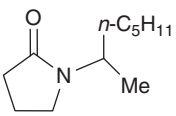
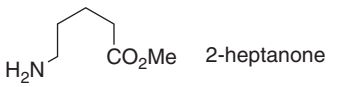
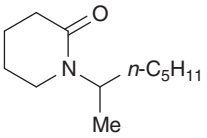
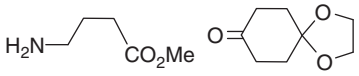
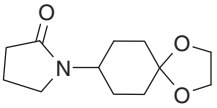
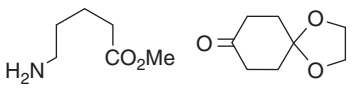
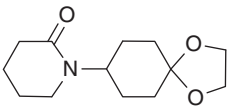
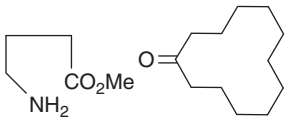
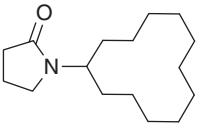
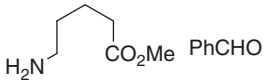
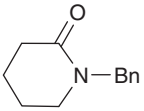
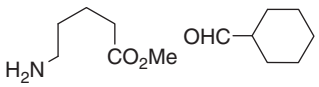
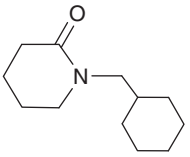
The reductive amination of α-keto esters with benzylamine (Table 6, entries 1 and 2) proceeds in good to excellent yields to afford the α-benzylamino esters.[76] Reactions involving other amines, such as aniline or morpholine, are not as efficient and are accompanied by variable amounts of ketone reductions. The electron-withdrawing effect of the α-esters activates the ketones toward nucleophilic additions compared to alkyl or aryl ketones. This effect explains the relative reactivity of methyl

Table 6 Reductive amination of keto acids, keto esters, amino acids, and amino esters

Entry	Reactants	Product	Conditions	Yield (%)	References
1			$NaBH(OAc)_3$ 1,2-DCE r.t., 30 min	90	76
2			$NaBH(OAc)_3$ 1,2-DCE r.t., 54 h	58	76
3			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t., 24 h	88	76
4			$NaBH(OAc)_3$ 1,2-DCE, AcOH r.t.	83	127
5	 Fm = 9-fluorenylmethyl		$NaBH(OAc)_3$ DMF r.t., 30 min	94	128
6			$NaBH(OAc)_3$ 1,2-DCE r.t., 24 h	85	129
7			$NaBH(OAc)_3$ 1,2-DCE 45 °C, 22 h	80	131

(*Continued*)

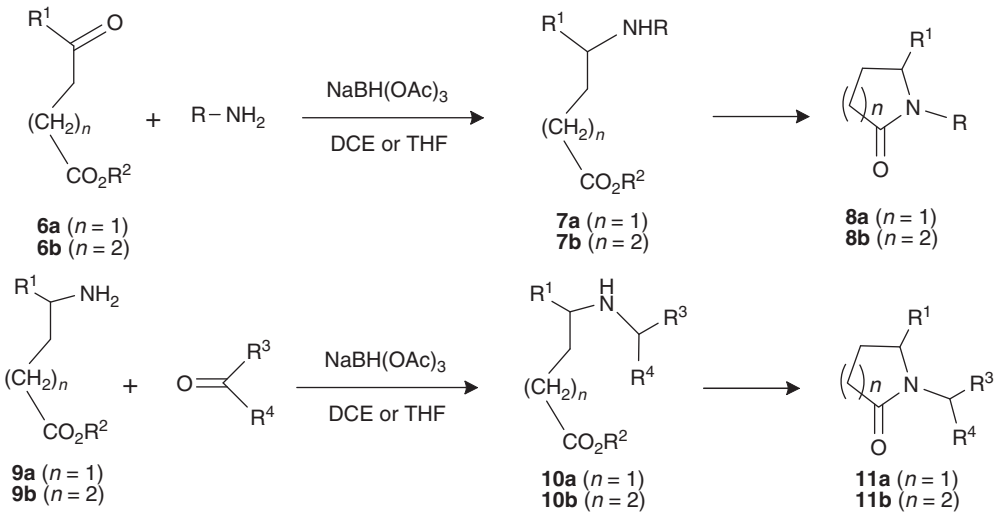
Table 6 Continued

Entry	Reactants	Product	Conditions	Yield (%)	References
8			$NaBH(OAc)_3$ 1,2-DCE 45 °C, 1.5 h	84	131
9			$NaBH(OAc)_3$ (3 equivalents) CH_2Cl_2-AcOH r.t., 24 h	68	130
10			$NaBH(OAc)_3$ $CHCl_3$–4 A MS AcOH (cat.) 24 h, r.t.	89	130
11			$NaBH(OAc)_3$ 1,2-DCE r.t., 48 h	70	131
12			$NaBH(OAc)_3$ 1,2-DCE r.t., 48 h	91	131
13			$NaBH(OAc)_3$ 1,2-DCE r.t., 90 h	96	131
14			$NaBH(OAc)_3$ THF r.t. (24 h); 55 °C (10 h)	55	131
15			$NaBH(OAc)_3$ 1,2-DCE r.t., 45 h	92	131
16			$NaBH(OAc)_3$ 1,2-DCE r.t. (4 h); 55 °C (24 h)	85	131
17			$NaBH(OAc)_3$ 1,2-DCE r.t., 120 h	91	131
18			$NaBH(OAc)_3$ 1,2-DCE 45 °C, 22 h	75	131
19			$NaBH(OAc)_3$ 1,2-DCE 45 °C, 22 h	68	131

benzoylformate (Table 6, entry 2) in reductive amination with $NaBH(OAc)_3$ compared to acetophenone, which is very unreactive in reductive aminations with $NaBH(OAc)_3$. Yet this activation makes these ketones prone to reduction by $NaBH(OAc)_3$, and this becomes a competing process in slow reductive amination reactions of this class of ketones. *N*-substituted *α*-amino esters may also be obtained from the reductive amination of aldehydes or ketones with *α*-amino esters (Table 6, entries 3–5). The reductive amination with amino esters is a faster higher yielding alternative to the use of *α*-keto esters in preparation of *N*-substituted *α*-amino esters. For example, Joullié and coworkers[127] used leucine methyl ester in the reductive amination of 4-azidobutanal with $NaBH(OAc)_3$ in DCE to obtain the corresponding *N*-alkyl derivative in good yield (Table 6, entry 4). This result was much improved over that obtained from using $NaBH_3CN$ or reaction with alkyl halides. Chorev and Han[128] developed a novel one-pot procedure to reduce *S*-ethyl thioesters to aldehydes with Et_3SiH and Pd-C followed by subsequent reductive amination of the resulting aldehydes with amino esters using $NaBH(OAc)_3$. For example, *tert*-butyl 2(*S*)-4-oxo-9-fluorenylmethoxycarbonylaminobutyrate was obtained using the Et_3SiH/Pd-C, and then reductively aminated with *L*-Phe-9-fluorenylmethyl ester using $NaBH(OAc)_3$ (Table 6, entry 5) to give the product in 93% yield. This is a noticeable improvement over $NaBH_3CN$, which gave 34% yield and 50% aldehyde reduction.[128]

The reductive amination of *β*-keto esters is a unique reaction that proceeds with control of the stereochemistry at both the *α*- and *β*-positions. There is a structural evidence of formation of enamines rather than imines as intermediates. The reduction usually favors the formation of one major diastereomer. The effect is most pronounced in reductive amination of cyclic *β*-keto esters such as methyl cyclohexanone-2-carboxylate, which gives almost exclusively the *cis*-product with benzylamine (Table 6, entry 6).[129]

The reductive amination of *γ*- and *δ*-keto esters or acids with primary amines is a special reaction in which the reductive amination products, *N*-alkyl *γ*- or *δ*-amino esters or acids, tend to cyclize to form the corresponding lactams (Scheme 2) under the reaction conditions.[131] The initial reductive amination step is usually fast; however, the cyclization to the lactam takes a longer time. The tandem reaction may be termed a 'reductive lactamization.' The reaction provides *N*-substituted *γ*-butyrolactams and *δ*-valerolactams under mild conditions. The reaction was studied for its scope and limitations, and it proved effective primarily for the formation of *γ*-butyrolactams and *δ*-valerolactams but not for other lactams.[131] Examples of these reactions are listed in Table 6 (entries 7–12). The reductive amination of methyl-5-oxohexanoate and methyl-4-oxopentanoate with benzylamine gave 1-benzyl-6-methylpiperidin-2-one (Table 6, entry 7) and 1-benzyl-5-methylpyrrolidin-2-one (Table 6, entry 8), respectively, in good yields.[131] The cyclization was accelerated by warming the reaction to 40–45 °C, but the formation of the *γ*-butyrolactam was much faster than that of the *δ*-valerolactam (1.5 h vs. 22 h). Zhang and coworkers[130] studied the reductive amination of mucochloric acid with different primary aromatic and aliphatic amines (Table 6, entries 9 and 10). The initial reductive amination products from these reactions cyclize to form the corresponding *γ*-butyrolactams. Similarly, the reductive amination of *o*-carboxybenzaldehyde with amines formed the corresponding *γ*-butyrolactams (Table 6, entries 11 and 12).[131] It is interesting to observe that the cyclization of the intermediate from reductive amination of *o*-carboxybenzaldehyde with 4-aminobutyrate occurs only with the carboxy group to form *γ*-butyrolactam rather than with the ester to form *δ*-valerolactam (Table 6, entry 11).



Scheme 2 Reductive amination-lactamization.

The reductive amination of aldehydes and ketones with *γ*- or *δ*-amino acids or esters forms similar products to those obtained from reductive amination of *γ*- and *δ*-keto acids or esters with amines (Scheme 2). Consequently, the reductive amination products also cyclize to the corresponding lactams under the reaction conditions.[131] Some representative examples are listed in Table 6 (entries 13–19). These reactions also have the same limitation as in the formation of *γ*-butyrolactams and *δ*-valerolactams only. Ketones are better candidates for this reaction as they form the corresponding lactams, slowly but cleanly (Table 6, entries

13–17). Although aldehydes give good yields of the expected lactams, they also tend to form *N,N*-dialkyl products up to 15–20%. The preformation of the imines and reduction with stronger hydride eliminates this undesired reaction.[131]

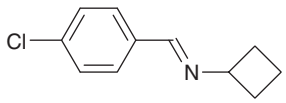
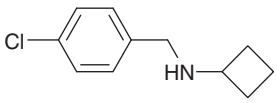
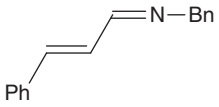
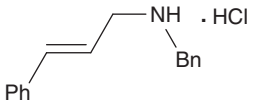
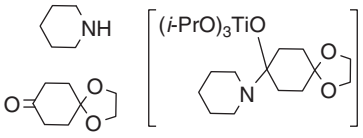
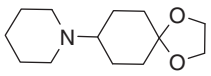
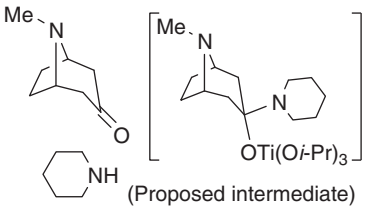
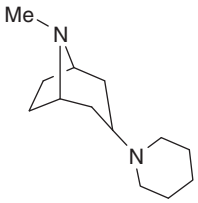
8.02.3.2.3 Miscellaneous reductive aminations and modified procedures

In addition to the two main reductive amination procedures using $NaBH_3CN$ and $NaBH(OAc)_3$, there are many other reagents and procedures that were introduced to improve the reductive amination reactions including modified reagents, modified procedures, use of different solvent systems, use of polymer-supported reagents, different catalysts, and additives. Some of these are highlighted in this section.

8.02.3.2.3.1 Stepwise (indirect) reductive amination of aldehydes and ketones with amines

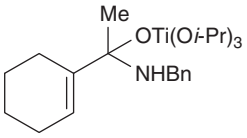
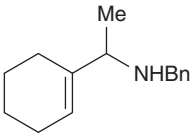
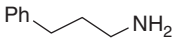
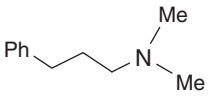
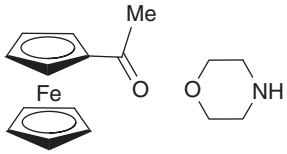
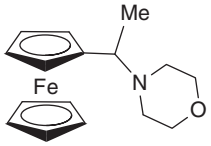
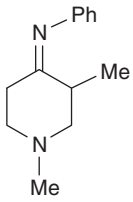
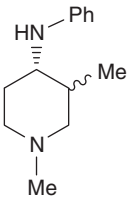
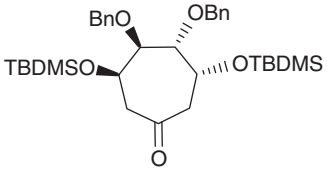
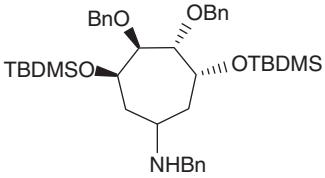
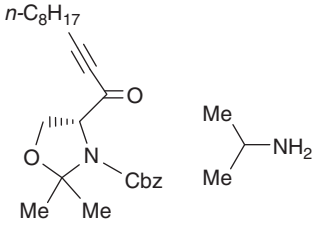
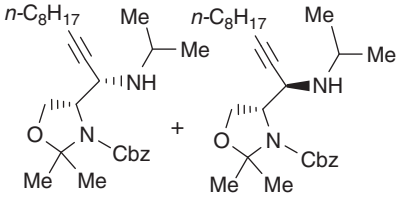
Reductive amination of aldehydes with primary amines is the easiest reductive amination procedure. However, there were some cases where the formation of significant amounts of dialkylation was observed. Typically, this undesired side reaction is suppressed by simply adding a slight excess of the primary amine, but that is not a general solution. Surprisingly, the dialkylation happens in some reactions even when excess amine was used or when the reaction was carried out with a 'preformed imine' and no excess aldehyde was present.[131] The problem of undesired dialkylation reactions was solved in these cases by conducting fast reductions of preformed imines to minimize the coexistence of product amines with unreacted imines. However, imine formations from carbonyl compounds and primary amines are reversible reactions that require long reaction times and the use of a dehydrating agent such as molecular sieves or the azeotropic removal of water to drive the reaction to completion. Studies were conducted to measure the relative rates of aldimine formation from aldehydes and primary amines in different solvents, namely THF, DCE, and MeOH without added catalysts or dehydrating agents.[76] In all the cases, aldimine formation in MeOH was consistently faster and gave nearly quantitative conversions relative to those carried out in THF or DCE. Once imine formation is complete, the reduction of the aldimine is carried out directly in methanol by adding $NaBH_4$ to give the corresponding secondary amines in high yields and in short reaction times. Thus, this stepwise (or indirect) one-pot procedure involving aldimine formation in methanol followed by *in situ* reduction with $NaBH_4$ is a very convenient and efficient alternative, but it is limited to aldehydes and primary amines (Table 7, entries 1 and 2).[76] Ketimine formation was much slower in all three solvents and never reached 100% conversion, but was still faster in methanol.

Table 7 Stepwise (*Indirect*) reductive aminations

Entry	Reactants	Product	Conditions	Yield (%)	References
1	 Prepared from *p*-ClC_6H_4CHO + cyclobutylamine in MeOH		$NaBH_4$-MeOH r. t., 10 min	98	76
2	 Prepared from cinnamaldehyde + benzylamine in MeOH		$NaBH_4$-MeOH r. t., 10 min then: HCl	85	76
3	 (proposed intermediate)		$Ti(O\text{-}i\text{-}Pr)_4$ 1 h, r. t. EtOH, $NaBH_3CN$ r.t., 20 h	49	53c
4	 (Proposed intermediate)		$Ti(O\text{-}i\text{-}Pr)_4$ 1 h, r. t. EtOH, $NaBH_3CN$ r.t., 20 h	58	53c
5			$Ti(O\text{-}i\text{-}Pr)_4$, 2–3 h, MeOH, $NaBH_4$ r.t. 5 min	90	76

(*Continued*)

Table 7 Continued

Entry	*Reactants*	*Product*	*Conditions*	*Yield (%)*	*References*
6	 Proposed intermediate		$Ti(O\textit{i}\text{-}Pr)_4$, 2–3 h, r.t. MeOH, $NaBH_4$ r.t., meoH, $NaBH_4$ 5 min	>95	76
7		 15 examples	$Ti(O\textit{i}\text{-}Pr)_4$, $(HCHO)_n$ diglyme, 60 °C (30 min); r.t. (30 min); $NaBH_4$, r.t., 5 h	88	135
8			$Ti(O\textit{i}\text{-}Pr)_4$, 25 °C (3–4 h); $NaBH_4$, EtOH 25 °C, 15 h	88	136
9	 from ketone + aniline + $Ti(O\textit{i}\text{-}Pr)_4$		$NaBH_4$, EtOH	75 *cis*:*trans* 70:30	137
10	 + $PhCH_2NH_2$		1. $Ti(O\textit{i}\text{-}Pr)_4$, 20 °C, 2 h 2. $NaBH_3CN$ (4 equivalents), EtOH, 20 °C, 12 h	72	138
11			$Ti(O\textit{i}\text{-}Pr)_4$, r.t., 6 h; EtOH, $NaBH_3CN$ r.t., 16 h	85 (9:7)	139

A very efficient stepwise reductive amination procedure was developed by Mattson and coworkers.[53c,134] In this procedure, the amine and the carbonyl compound are mixed in neat $Ti(O\textit{i}\text{-}Pr)_4$. The authors proposed the formation of a Ti-carbinol amine intermediate (Table 7, entries 3–6) rather than the usual imine or iminium ion based on the infrared spectra of the intermediates. Once the conversion is complete, the mixture is diluted with ethanol and reduced with $NaBH_3CN$. The procedure was applied to reductive amination of aldehydes and ketones with primary and secondary amines (Table 7, entries 3 and 4). This procedure was modified to use $NaBH_4$ in methanol (instead of $NaBH_3CN$/ethanol) with better results.[76,140] For example, the reductive amination of the unsaturated ketone 1-acetylcyclohexene with benzylamine, which was very slow with $NaBH(OAc)_3$, proceeded very fast under Mattson's modified conditions to give a quantitative yield of the reductive amination product (Table 7, entry 6). The reductive amination of tropinone with benzylamine using this procedure gave a near-quantitative yield of a 3:2 mixture of the *endo*- and *exo*-products (Table 7, entries 4 and 5). However, it gave approximately 15:1 ratio of the *endo*:*exo* products using $NaBH(OAc)_3$ (Table 4, entry 28). On the contrary, the reaction between tropinone and aniline using this modified system resulted in incomplete reactions. Mattson et al.[53c] reported a successful reductive amination of tropinone with piperidine in 58% yield, but

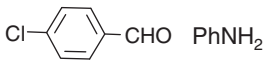
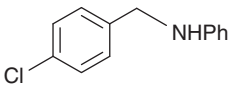
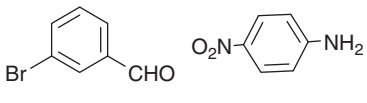
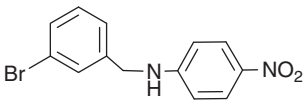
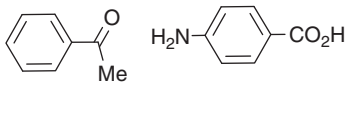
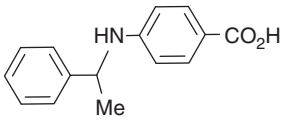
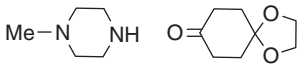
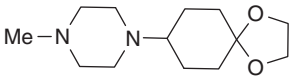
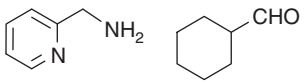
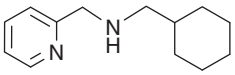
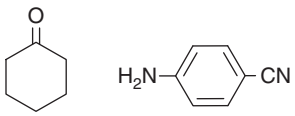
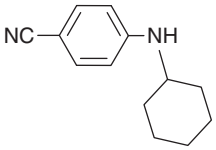
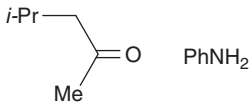
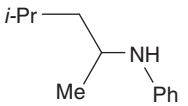
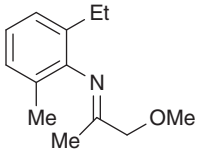
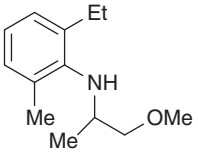
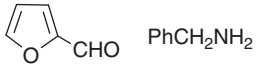
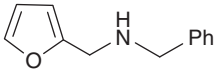
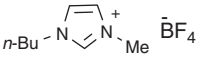
the stereochemistry of the product was not disclosed. The modified conditions gave the product with a 90% crude yield as a mixture of the *endo*- and *exo*-products in approximately 1:7 ratio in opposite selectivity to the reaction with primary amines. The pure *exo*-product was isolated as the oxalate salt in 66% yield (Table 7, entry 5).[76]

A similar modification ($Ti(Oi\text{-}Pr)_4$-$NaBH_4$ in diglyme at 60 °C or in ethanol at 25 °C) was reported for the reductive amination of formaldehyde with primary and secondary amines to prepare *N*,*N*-dimethyl and *N*-methyl amines, respectively (Table 7, entry 7).[135] This procedure was applied to the reductive amination of acetylferrocene with secondary amines to form *N*,*N*-dialkyl-1-ferrocenylethylamines (Table 7, entry 8).[136] Mattson's procedure and its modified versions were used in several successful reductive aminations; some examples are listed in Table 7 (entries 9–11).

8.02.3.2.3.2 Various recent reductive amination procedures

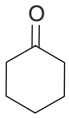
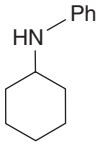
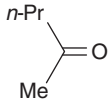
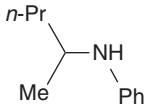
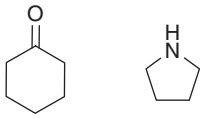
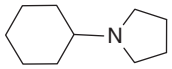
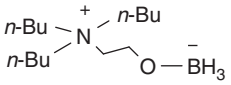
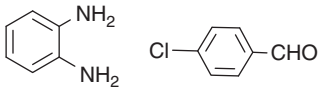
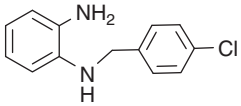
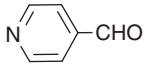
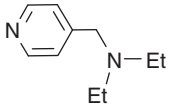
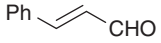
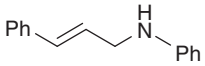
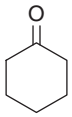
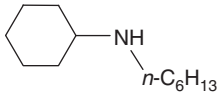
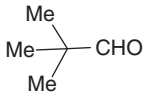
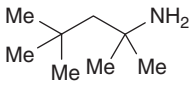
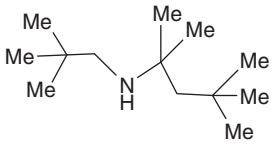
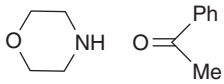
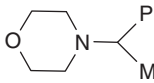
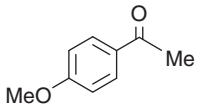
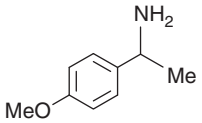
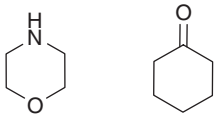
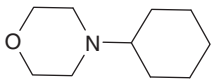
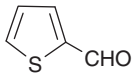
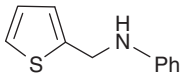
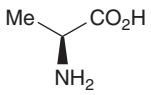
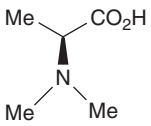
Varma and Dahiya[141] described the use of a solvent-free procedure to carry out reductive amination of carbonyl compounds using wet montmorillonite K-10 clay-supported $NaBH_4$ facilitated by microwave (MW) irradiation. The procedure entails *in situ* formation of the imines with the aid of MW irradiation before the addition of the reducing agent, $NaBH_4$-K-10 clay, and a small amount of water, then subjecting the mixture to MW-irradiation again for 30 s to reach 65 °C (Table 8, entry 1).

Table 8 Miscellaneous and modified reductive amination procedures

Entry	Reactants	Product	Conditions	Yield (%)	References
1			K-I0 clay + reactants MW-irradiation (2 min) $NaBH_4$-K-10 clay, H_2O MW-irradiation (30 s)	90	141
2			$B_{10}H_{14}$ (30 mol%) MeOH r.t., 30 min	94	142
3			$B_{10}H_{14}$ (30 mol%) MeOH r.t., 12 h	98	142
4			MP-$BH(OAc)_3$ THF, r.t., 16 h	85	143
5			MP-$BH(OAc)_3$ THF, r.t., 16 h	90	143
6			picoline-BH_3 MeOH-AcOH r.t., 6 h	73	144
7			picoline-BH_3 H_2O-AcOH r.t., 17 h	90	144
8			$NaBH_4$-H_3BO_3 (1:1) No solvent, r.t.	99	145
9			 H_2O $NaBH_4$, r.t., 2.5 h	80	146
10	Ph-$(CH_2)_2$-CHO $PhNH_2$	Ph–$(CH_2)_3$–NH-Ph	$NaBH_4$ CTAB-H_2O r.t., 8 h	84	147

(*Continued*)

Table 8 Continued

Entry	Reactants	Product	Conditions	Yield (%)	References
11			*N*-Me-piperidine/$Zn(BH_4)_2$, MeOH, pH 7 (with 10% HCl) r.t., 1.2 h	93	148
12	$PhNH_2$		*N*-Me-pyrrolidine/$Zn(BH_4)_2$, MeOH, pH 7 (with 10% HCl) r.t., 2 h	95	149
13			$NaBH_4$, SiO_2-Cl THF, r.t., 5 min	95	150
14	$PhNH_2$		$NaBH_4$, SiO_2-H_2SO_4 THF, r.t., 3 min	92	151
15			$NaBH_4$, Amberlyst 15 THF, r.t., 0.1 h	95	152
16	Ph-CHO+$PhNH_2$	Ph–(CH_2)–NH-Ph		92	153
17			$LiClO_4$-TMSCl CH_2Cl_2 40 °C, 15 min (Ppyz) $Zr(BH_4)_2Cl_2$ 3 h	90	154
18	 Et_2NH		$NaBH_4$, $H_3PW_{12}O_{40}$ (0.5 mol%), MeOH	87	155
19	 $PhNH_2$		$Cu(PPh_3)_2BH_4$ NH_2SO_3H MeOH, r.t., 2 h	84	156
20	 $Me(CH_2)_5NH_2$		$Cu(PPh_3)_2BH_4$ NH_2SO_3H MeOH, r.t., 4 h	87	156
21	 		$Ti(OiPr)_4$-THF r.t., 1 h then NH_3-BH_3 r.t., 10 h	90	157
22			$Ti(OiPr)_4$-THF r.t., 1 h then NH_3-BH_3 r.t., 8 h	84	157
23			$Ti(OiPr)_4$-THF r.t., 1 h then NH_3-BH_3 r.t., 10 h	83	157
24			poly-2,4-ionene borohydride i-PrOH pH 7 (with 10% HCl) reflux, 2 h	85	158
25	 $PhNH_2$		$NaBH_4$-CF_3CH_2OH 35–40 °C, 8 min	90	159
26	 $(HCHO)_n$		$NaBH_4$-CF_3CH_2OH reflux, 48 h	90	159

Yoon and coworkers[142] reported the use of decaborane ($B_{10}H_{14}$) as a reducing agent for indirect reductive amination of aldehydes and ketones. The procedure was applied to multiple examples and showed good results with poorly nucleophilic amines such as 4-nitroaniline and with aromatic ketones (Table 8, entries 2 and 3).

Bhattacharyya and coworkers[143] reported the use of a polymer-supported triacetoxyborohydride (named MP-triacetoxyborohydride) in reductive amination of aldehydes and ketones with primary and secondary amines. The reaction is carried out in THF, DMF, or other polar aprotic solvents and was applied to multiple examples (Table 8, entries 4 and 5).

Kikugawa and coworkers[144] developed a procedure for reductive amination using 2-picoline-borane (pic-BH_3) as a reducing agent. The reaction is carried out in MeOH, H_2O, or in the absence of solvents, may be activated by addition of AcOH, and was applied to a variety of substrates (Table 8, entries 6 and 7).

Cho and Kung[145] described a procedure for reductive amination of aldehydes and ketones using $NaBH_4$ activated by solid acids such as boric acid, benzoic acid, and *p*-toluenesulfonic acid monohydrate. The direct reductive aminations were carried out by grinding a 1:1:1:1 mixture of aldehyde, amine, sodium borohydride, and boric acid with an agate mortar and pestle at room temperature under solvent-free conditions but were accompanied by carbonyl reductions. Better results were obtained when the imines were preformed before reduction (Table 8, entry 8).

Nagaiah and coworkers[146] described the use of the combination of $NaBH_4$ and the ionic liquid 1-butyl-3-methyl imidazolium tetrafluoroborate and water in a procedure for reductive amination of aldehydes and ketones (Table 8, entry 9).

Alinezhad and coworkers described several procedures for reductive amination of aldehydes and ketones (Table 8, entries 10–15). The authors reported the use of $NaBH_4$ in micellar media[147] in which an aldehyde or a ketone is mixed with excess amine and aqueous solution of cetyl trimethylammonium bromide (CTAB) followed by the addition of $NaBH_4$ at r.t. (Table 8, entry 10). In another report, they described the use of the combination of $Zn(BH_4)_2$ and *N*-methylpeperidine[148] as a reducing system for reductive amination of aldehyde and ketones (Table 8, entry 11). A similar reagent *N*-methylpyrrolidine-$Zn(BH_4)_2$ was later introduced (Table 8, entry 12).[149] This group also reported a reducing combination of $NaBH_4$-silica chloride (SiO_2-Cl) in THF for reductive amination reactions[150] in which the carbonyl compound and amine are mixed in THF and treated with $NaBH_4$ and silica chloride (SiO_2-Cl) at room temperature (Table 8, entry 13). The combination of $NaBH_4$ and SiO_2-H_2SO_4 in THF or solvent-free conditions at room temperature was similarly used (Table 8, entry 14).[151] The use of $NaBH_4$-Amberlyst 15 (H^+ form) in THF or solvent-free conditions was also introduced (Table 8, entry 15).[152]

Mohanazadeh and coworkers[153] reported a procedure for reductive amination of aldehydes and ketones with amines using 2-(tributylamino)ethoxyborohydride. Mixing benzaldehyde and aniline with 2-(tributylamino)ethoxyborohydride and stirring the mixture for 30 min afforded the reductive amination product in 62% yield (Table 8, entry 16).

The use of zirconium borohydride piperazine complex (abbreviated (Ppyz)$Zr(BH_4)_2Cl_2$) in combination with $LiClO_4$ (5 mol%) and Me_3SiCl (1 equivalent) in CH_2Cl_2 was reported for reductive amination of aldehydes and ketones with amines by Heydari and coworkers.[154] The iminium species is preformed with $LiClO_4$ and Me_3SiCl in CH_2Cl_2 and then reduced with (Ppyz)$Zr(BH_4)_2Cl_2$ (Table 8, entry 17). Another report from this group[155] described a method for reductive amination of aldehydes and ketones using the combination of $NaBH_4$ and a catalytic amount (0.5 mol%) of $H_3PW_{12}O_{40}$ (12-tungstophosphoric acid) in MeOH (Table 8, entry 18).

Bhanage and coworkers[156] reported the development of a procedure for the direct reductive amination of aldehydes and ketones using the combination of bis(triphenylphosphine) copper(I) tetrahydroborate ($Cu(PPh_3)_2BH_4$) and sulfamic acid as a reducing agent (Table 8, entries 19 and 20).

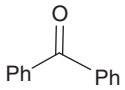
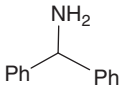
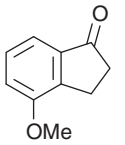
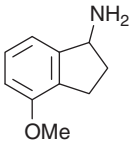
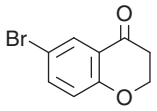
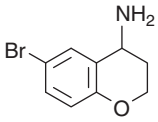
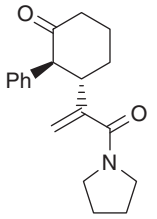
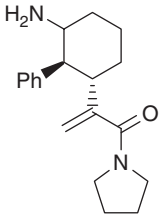
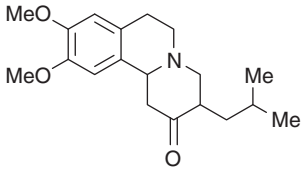
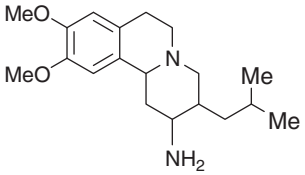
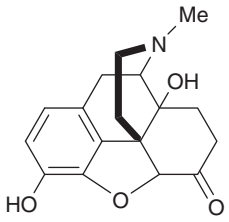
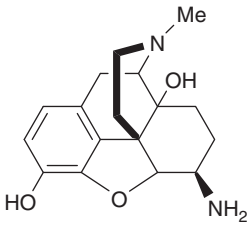
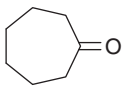
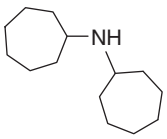
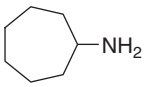
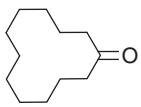
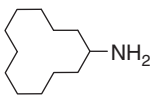
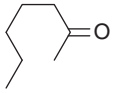
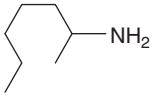
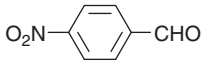
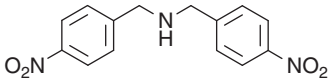
Ramachandran and coworkers[157] reported the use of ammonia borane (AB), a solid with remarkable thermal, hydrolytic, and air stability in reductive amination reactions. The reagent is used with Lewis acids such as $ZnCl_2$, $NiCl_2$, SiO_2, and $Ti(OiPr)_4$ in THF; the Lewis acid activates imine formation, and in its absence, aldehydes are reduced to alcohols. Typically the amine and carbonyl compounds are mixed with the Lewis acid in THF for 1 h at r.t. to allow imine or iminium ion formation before adding the reducing agent. Some examples of the procedure are listed in Table 8 (entries 21–23).

The use of poly-2,4-ionene-borohydride exchange resin was reported by Tajbakhsh and coworkers.[158] The reagent is stable and the procedure was applied to several typical reductive amination examples (Table 8, entry 24). They also developed another procedure[159] that uses $NaBH_4$ in CF_3CH_2OH as a reducing agent for reductive amination reactions. In addition to its application to typical reductive amination of aldehydes and ketones, the procedure was used for *N*-methylation of amines with paraformaldehyde (Table 8, entries 25 and 26).

8.02.3.2.4 Reductive amination of aldehydes and ketones with ammonia: Preparation of primary amines

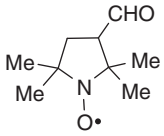
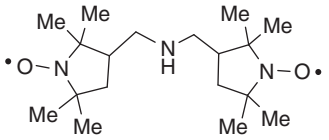
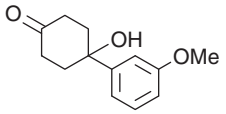
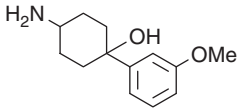
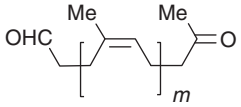
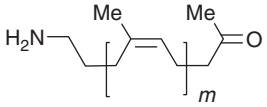
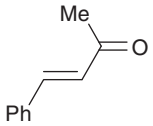
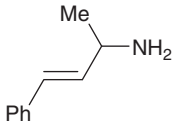
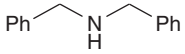
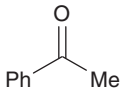
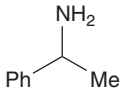
The reductive amination with ammonia is the most direct way to convert aldehydes and ketones to primary amines. Although it is widely used, it is a challenging task because the initial product, the primary amine, is a better nucleophile than ammonia and can react effectively with the carbonyl compound, being reduced to form dialkylamines. Formation of dialkylamines is common with both ketones and aldehydes. In order to suppress this overreaction, a large excess of ammonia (10 or more equivalents) is used. Ammonium acetate is very convenient, and it is the most commonly used source of ammonia or ammonia substitute in these reactions. One of the best reducing reagents to employ for this reaction is $NaBH_3CN$ since it is used in methanol or aqueous MeOH, a solvent that can effectively dissolve ammonium acetate. Several recent examples for the use of $NaBH_3CN$ are illustrated in Table 9 (entries 1–6).

Table 9 Preparation of primary amines via reductive amination of aldehydes and ketones with ammonia

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			$NaBH_3CN$ AcOH, MeOH, 25–30 °C, 18 h	85	160
2			$NaBH_3CN$ (1.2 equivalents)	66	160
3			NH_4OAc (15 equivalents), EtOH MW (130 °C) 2 min	95	160
4			$(NH_4)BH_3CN$ NH_4OAc, MeOH 3 A-MS, −78 °C (2 h); r.t. (10 h)	81	161
5			(a) NH_4OAc, MeOH, r.t., 24 h; (b) $NaCNBH_3$ r.t., 4 h	87	162
6			$CH_3CO_2NH_4$, $NaBH_3CN$, MeOH, r.t., 24 h chromatography to isolate the β-isomer	33–35	163
7			$NaBH(OAc)_3$ NH_4OAc (10 equivalents) Et_3N THF or 1,2-DCE r.t., 48 h	91	76
8			$NaBH(OAc)_3$ $CF_3CO_2NH_4$ (10 equivalents) THF, r.t., 4 h	95 (<5% 2°-amine)	164a
9			$NaBH(OAc)_3$ $CF_3CO_2NH_4$ (10 equivalents) THF, r.t., 1 h	95 (<5% 2°-amine)	164a
10			$NaBH(OAc)_3$ $CF_3CO_2NH_4$ (10 equivalents) THF, r.t., 3 h	98 (<2% 2°-amine)	164b
11			$NaBH(OAc)_3$ $CF_3CO_2NH_4$ (10 equivalents) THF, r.t., 1 h	95 (<5% 1°-amine)	164b

(*Continued*)

Table 9 Continued

Entry	Substrate	Product	Conditions	Yield (%)	References
12			$NaBH(OAc)_3$ $CF_3CO_2NH_4$, 3 A-MS THF, r.t., 36 h	65	165
13			$NaBH(OAc)_3$ $CF_3CO_2NH_4$ (1.4 equivalents) THF, r.t., overnight	41	166
14			$NaBH(OAc)_3$ NH_4OAc (30 equivalents), AcOH CH_2Cl_2, r.t., 24 h	86	167
15			1. $Ti(Oi\text{-}Pr)_4$, NH_3, EtOH 25 °C, 6 h 2. $NaBH_4$, 25 °C, 3 h	89	168
16	PhCHO		1. $Ti(Oi\text{-}Pr)_4$, NH_4Cl Et_3N, EtOH 25 °C, 6 h 2. $NaBH_4$, 25 °C, 3 h	76	168
17			$Ti(Oi\text{-}Pr)_4$, NH_4Cl Et_3N, EtOH r.t., 10 h then NH_3-BH_3, r.t., 8 h	85	157

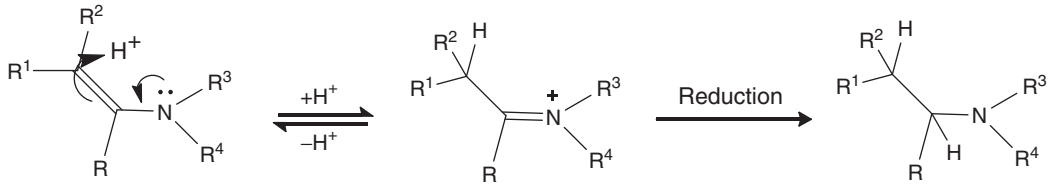
During the initial study to evaluate the scope of $NaBH(OAc)_3$ in reductive amination reactions, several attempts were made to develop a practical procedure for the synthesis of primary amines. The poor solubility of NH_4OAc in THF, CH_3CN, or DCE limits the use of this reagent in the preparation of primary amines. Even with the use of 10 or more equivalents of NH_4OAc, the reaction gave exclusively dialkylamines (Table 9, entry 7).[76] Although this may be used as a reliable procedure for preparation of symmetric dialkylamines, it did not provide the desired primary amines. After examining the solubility of a large number of commercially available ammonium salts, ammonium trifluoroacetate was identified as a good ammonia substitute in reductive amination reactions with $NaBH(OAc)_3$.[164] It is very soluble in THF and can be used effectively in reductive amination reactions. Cycloheptanone and cyclododecanone (Table 9, entries 8 and 9) gave the corresponding primary amines in excellent isolated yields as the major products with $<5\%$ of the dialkylamines.[165a] The study was expanded to include reactions with several ketones and aldehydes.[165b] Although the reaction was very effective in preparation of primary amines from ketones, aldehydes could produce only dialkylamines as the main products (Table 9, entry 11).

Other examples using $NaBH(OAc)_3$ were reported including the preparation of *N*,*N*-bis(1-ylooxy-2,2,5,5-tetramethylpyrrolidin-3-ylmethylene)amine from the reductive amination using ammonium trifluoroacetate (Table 9, entry 12).[165] Another use of $NaBH(OAc)_3$ $CF_3CO_2NH_4$ is the conversion of a ketone to the primary amine (Table 9, entry 13).[166] However, the most interesting result was obtained from carbonyl *cis*-1,4-oligoisoprene. The reductive amination of this ketoaldehyde with excess NH_4OAc and $NaBH(OAc)_3$ resulted in a selective formation of a primary amine from the aldehyde in 86% yield and no reaction with the ketone (Table 9, entry 14).[167] This is unusual, since most aldehyde reductive aminations produce only secondary amines.

Another procedure for the reductive amination of aldehydes and ketones with ammonia using a pretreatment with $Ti(Oi\text{-}Pr)_4$ in EtOH followed by reduction with $NaBH_4$ was reported.[168] Ketones gave primary amines, whereas aldehydes afforded the symmetric dialkylamines (Table 9, entries 15 and 16). A similar procedure reported the pretreatment of ketones with the combination of $Ti(Oi\text{-}Pr)_4$, NH_4Cl, and triethylamine in ethanol at ambient temperature and then used BH_3-NH_3 for reduction to obtain the desired primary amines in good yield. In this case also, the reaction of aldehydes resulted in the formation of secondary amines (Table 9, entry 17).[157]

8.02.3.2.5 Reduction of enamines

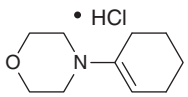
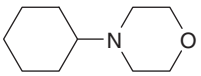
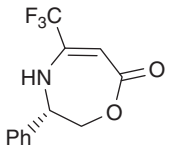
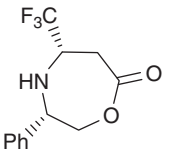
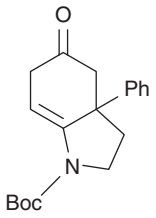
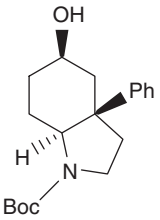
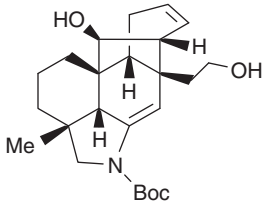
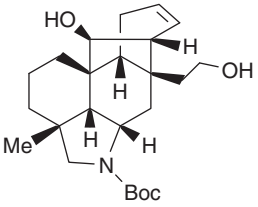
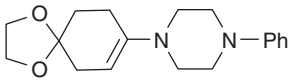
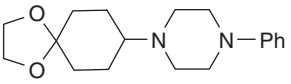
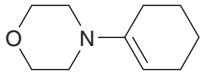
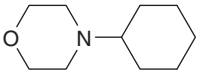
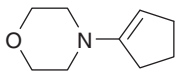
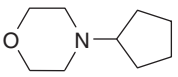
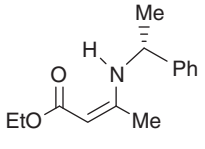
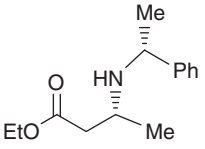
Enamines are obtained from the reaction of secondary amines with aldehydes and ketones containing at least one α-hydrogen. Although metal hydrides do not reduce C═C bonds, many can reduce enamines particularly under acid conditions. Under acid conditions, an enamine is protonated and rearranges into an iminium ion (Scheme 3), which is reduced with metal hydrides. Consequently, the best hydride reagents to reduce enamines are those that are stable under acid conditions such as $NaBH_3CN$ and $NaBH(OAc)_3$.



Scheme 3 Rearrangement and reduction of enamines under acidic conditions.

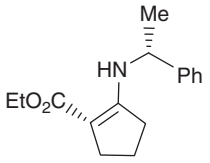
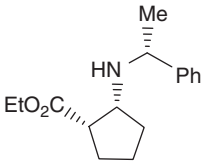
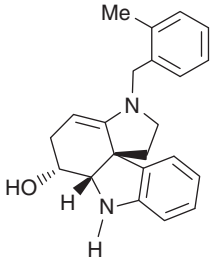
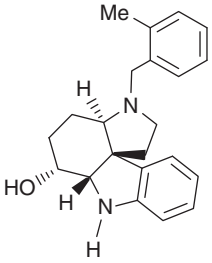
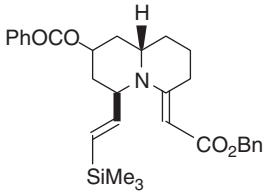
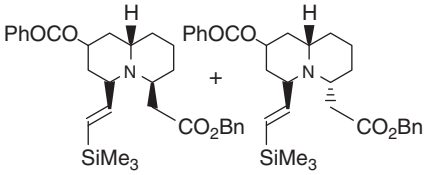
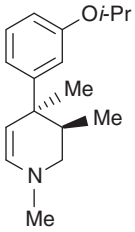
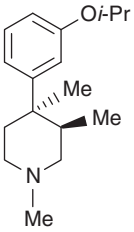
In their early studies of the reducing properties of $NaBH_3CN$, Borch and coworkers[6] obtained almost no reduction when they treated *N*-cyclohexenylmorpholine with $NaBH_3CN$ in MeOH-THF for 3 h. However, when they used the HCl salt of the enamine, they observed a quantitative and fast reduction of the enamine (Table 10, entry 1). Other enamines were also reduced in the presence of catalytic amounts of acid with initial pH of 5. Conjugated enamines reacted slower and required more acid to proceed. Other more recent examples are listed in Table 10 (entries 2–5). The reduction of a cyclic enamino ester (Table 10, entry 2)

Table 10 Reduction of enamines

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			$NaBH_3CN$ THF-MeOH (15:1) r.t., 15 min	80	6
2			$NaBH_3CN$ (1.2 equivalents), HCl (10 equivalents), CH_2Cl_2/dioxane (2:1), –78 °C to r.t., 96 h	74 97:3	169
3			$NaBH_3CN$, EtOH 20 °C, 84 h	62	170
4			$NaBH_3CN$, HCl MeOH-H_2O 0–20 °C	85	171
5			$NaBH_3CN$ THF-MeOH 25 °C, 0.5 h		172
6			$NaBH(OAc)_3$, AcOH (1 equivalent), 1,2-DCE, r.t., 10 min	99	76
7			$NaBH(OAc)_3$, AcOH (1 equivalent), 1,2-DCE, r.t., 20 min	99	76
8			$NaBH(OAc)_3$, AcOH (1 equivalent), 1,2-DCE, 0 °C, 1–3 h	61 *de*:58	173

(*Continued*)

Table 10 Continued

Entry	Substrate	Product	Conditions	Yield (%)	References
9				73 *de*:85	173
10			$NaBH(OAc)_3$, 1,2-DCE, −20 °C, 3 h (Part of combined 4-step sequence)	65	174
11			$NaBH_3CN$, MeOH, AcOH (pH 4) 0 °C, 1 h $NaBH(OAc)_3$, MeCN-AcOH, 0 °C, 4 h	77 1:2 72 10:1	175
12			$NaBH_4$, MeOH, 25 °C, 3 h	92	176

required more acid to compensate for the low bacisity of the enamine due to the electron-withdrawing effect of the CF_3 substitution but resulted in good isolated yield and very high diastereoselectivity.[169]

Sodium triacetoxyborohydride reduces enamines quickly and efficiently in DCE in the presence of AcOH to give the corresponding tertiary amines in high yields (Table 10, entries 6 and 7).[76] The reduction of several enantiomeric β-enamino esters with $NaBH(OAc)_3$ prepared from reaction of $NaBH_4$ and AcOH in acetonitrile provided the corresponding β-amino esters with good diastereo- and enantioselectivity (Table 10, entries 8 and 9).[173]

Hary and coworkers[175] studied the effects of iminum ion conformational preferences and the size of the reducing agent on the stereochemical outcome in the reduction of an enamine intermediate. The study was carried out within the context of model studies directed toward the synthesis of the quinolizidine alkaloid clavepictine A (Table 10, entry 11).[175] The reduction with $NaBH_3CN$ and $NaBH(OAc)_3$ shows opposite selectivities, but $NaBH(OAc)_3$ was more selective due to its steric bulk.

In a synthesis of opioid antagonists, an enamine intermediate (Table 10, entry 12) was reduced effectively with $NaBH_4$ in MeOH.[176]

8.02.4 Reductions of *N*-Heteroatom-Substituted Imines

8.02.4.1 Reduction of Oximes and Oxime Derivatives

8.02.4.1.1 Reduction of oximes, oxime ethers, and esters to primary amines

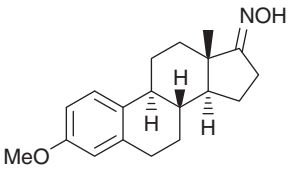
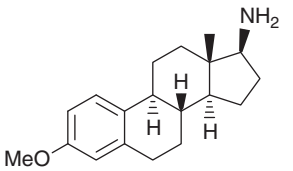
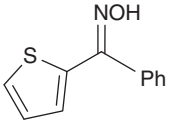
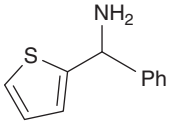
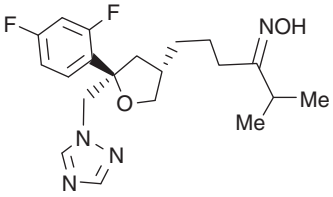
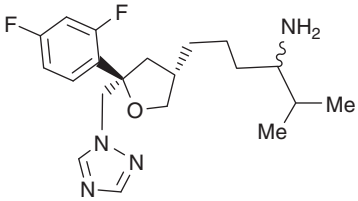
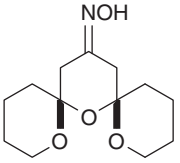
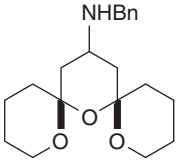
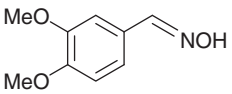
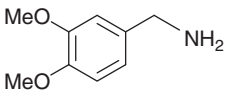
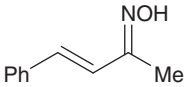
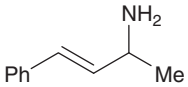
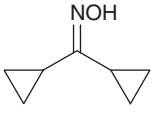
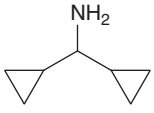
Oximes are generated by the condensation of hydroxylamine with aldehydes (aldoximes) or with ketones (ketoximes). They may also be obtained from the reaction of isoamyl nitrite with carbanions.

The reduction of oximes or oxime ethers and esters to primary amines is a useful synthetic transformation that is used as a substitute for direct reductive amination to convert ketones or aldehydes to primary amines. The reaction involves reduction of

C═N bond and reductive cleavage of N–O bond. Thus, the transformation requires the use of strong hydride reagents or reagent combinations. The most currently employed metal hydride reducing agents are reagents that are well tested and traditionally used and reagent combinations, reported in the 1970s, and 1980s for the same task. Sodium borohydride by itself is not typically used for this reduction but it has been successfully used in combination with transition metal salts. Such combinations include $NaBH_4$-MoO_3,[177] $NaBH_4$-$NiCl_2$,[177] $NaBH_4$-$ZrCl_4$,[178] and $NaBH_4$-$TiCl_3$.[179] Strong hydride reagents such as $LiAlH_4$[180] and [$NaAlH_2(OCH_2CH_2OMe)_2$][181] were also frequently used. Other reported reagents include borane (at high temperature)[182] and $NaBH_3CN$-$TiCl_3$.[183]

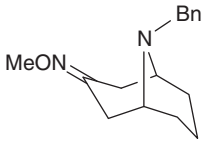
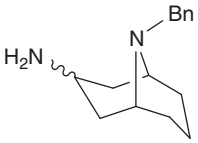
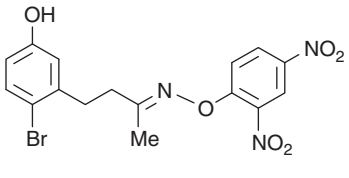
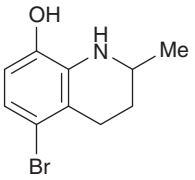
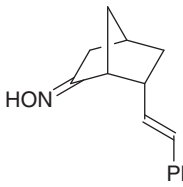
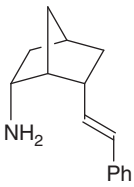
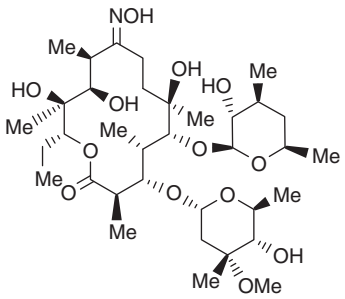
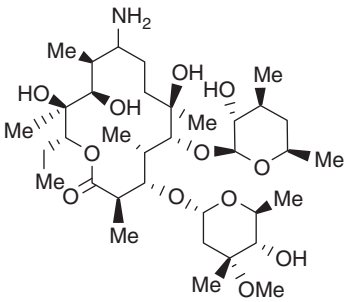
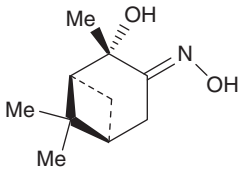
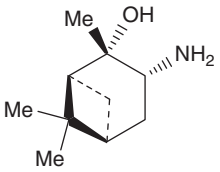
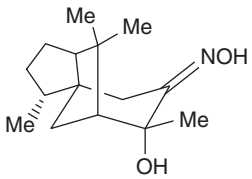
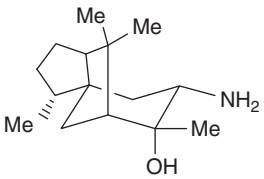
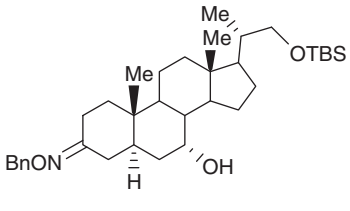
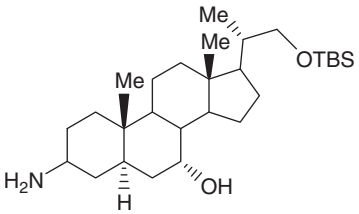
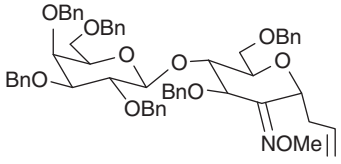
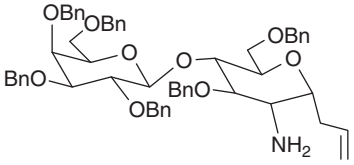
Several recent examples of reduction of oximes and oxime ethers to primary amines are listed in **Table 11**. Several combinations of $NaBH_4$ with transition metal salts were used effectively in the reduction of oximes to the corresponding primary amines. For example, the reduction of a steroidal ketoxime (**Table 11**, entry 1) with $NaBH_4$-MoO_3 in MeOH/THF gave exclusively the β-isomer.[184] $NaBH_4$-$TiCl_4$ combination in 1,2-dimethoxy ethane was reported to reduce an aromatic ketoxime (**Table 11**, entry 2).[185] The combination of $NaBH_4$-$NiCl_2$ in MeOH was used in the reduction of an aliphatic ketoxime (**Table 11**, entry 3)[186] and the polyspiroketal oxime derivative (**Table 11**, entry 4) to the corresponding primary amines; in the second case, the amine was directly reductively alkylated with benzaldehyde.[187] Several aldoximes and ketoximes were reduced effectively to the corresponding primary amines using a combination of amberlyst-15(H^+)-LiCl-$NaBH_4$ in THF at room temperature (**Table 11**, entries 5–7).[188] Borane in THF was reported to reduce oxime methyl ether to the primary amine when heated at reflux for 20 h (**Table 11**, entry 8).[189]

Table 11 Reduction of oximes, oxime ethers, and oxime esters to primary amines

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			$NaBH_4$, MoO_3 MeOH-THF 0–10 °C	86	184
2			$NaBH_4$, $TiCl_4$, DME 20 °C, 48 h	60	185
3			$NaBH_4$, $NiCl_2 \cdot 6\,H_2O$ MeOH –30 °C (30 min); r.t. (1.5 h)	89	186
4			1. $NaBH_4$, $NiCl_2$, MeOH 2. PhCHO, Ti(O*i*-Pr)$_4$, $NaBH_3CN$	61	187
5			Amberlyst-15(H^+) LiCl-$NaBH_4$ THF, r.t., 2 h	85	188
6			Amberlyst-15(H^+) LiCl-$NaBH_4$ THF, r.t., 2.5 h	75	188
7				80	188

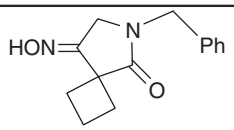
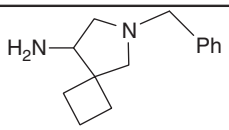
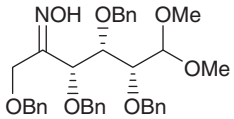
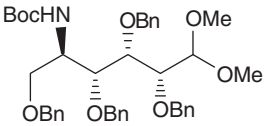
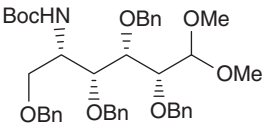
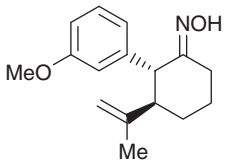
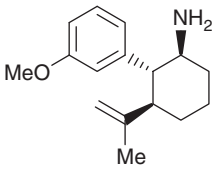
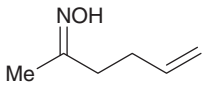
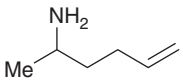
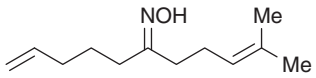
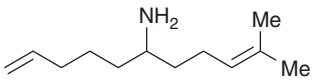
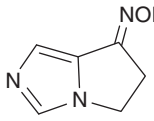
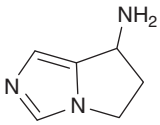
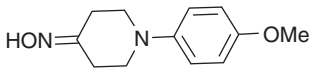
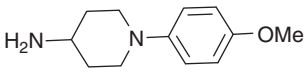
(*Continued*)

Table 11 Continued

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
8			BH_3-THF THF, reflux 20 h	90	189
9			$NaBH_3CN$, NaH dioxane –50 °C, 5 h	92	190
10			$NaCNBH_3$,$TiCl_3$, NH_4OAc, MeOH, 14 h then HCl/Et_2O	40	191
11			$NaBH_3CN$, $TiCl_3$	65	192
12			$LiAlH_4$, Et_2O reflux, 14 h	62	193
13			$LiAlH_4$, THF reflux, 18 h	56	194
14			$LiAlH_4$, Et_2O reflux, 16 h	95	195
15			$LiAlH_4$, THF 0 °C-r.t., 16 h	57	196

(*Continued*)

Table 11 Continued

Entry	Substrate	Product	Conditions	Yield (%)	References
16			$LiAlH_4$, THF, heat, 1 h	98	197
17		A:  + B: 	1. $LiAlH_4$, Et_2O; 2. $(Boc)_2O$, Et_3N, MeCN	A; 65 B: 15	198
18			$LiAlH_4$, THF, heat, 2 h	76	161
19			$LiAlH_4$, Et_2O Reflux, 3 h	63	199
20			$LiAlH_4$, Et_2O Reflux, overnight	99	199
21			$(i\text{-Bu})_2AlH$, toluene 7 h, 20 °C	65	200
22			$NaAlH_2(OCH_2CH_2OMe)_2$ toluene 140 °C, 2 h	89	201

The combination of $NaBH_3CN$-$TiCl_3$ reported in 1988 by Leeds[183] was applied in the reduction of a bicyclic ketoxime (Table 11, entry 10)[191] and a macrolide ketoxime (Table 11, entry 11).[192]

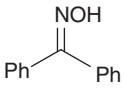
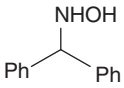
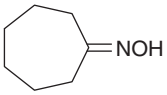
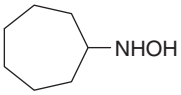
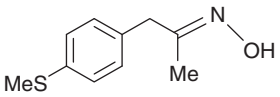
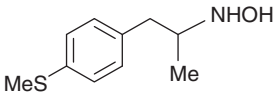
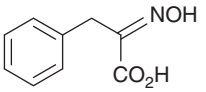
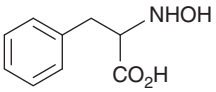
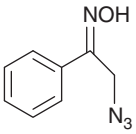
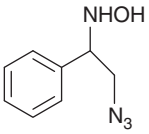
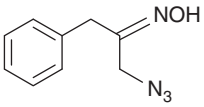
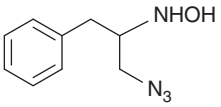
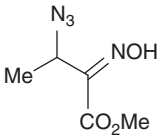
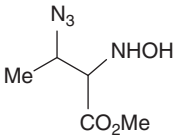
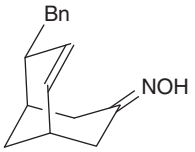
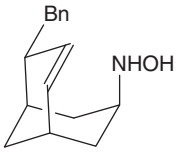
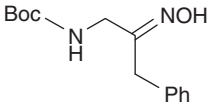
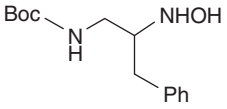
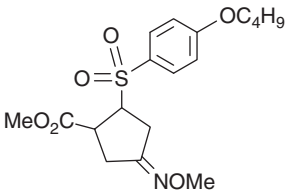
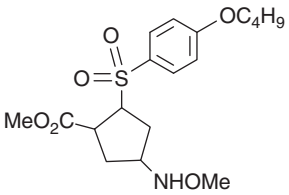
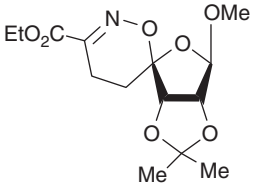
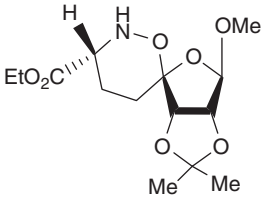
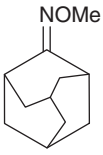
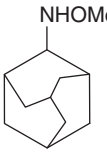
Large numbers of oximes and oxime derivatives are reduced with strong hydride reagents such as LAH (Table 11, entries 12–20), DIBAL-H (Table 11, entry 21), and $NaAlH_2(OCH_2CH_2OMe)_2$ (Table 11, entry 22) to give the corresponding primary amines with very good results.

8.02.4.1.2 Reduction of oximes to hydroxylamines and oxime ethers and esters to hydroxylamine ethers and esters

The reduction of oximes, oxime ethers, and oxime esters to hydroxylamines involves only the reduction of the C═N bond. That is reflected in the kind of reducing agents and conditions that are used for this reduction, which are typically milder than those used for the reduction of oximes to primary amines. Examples of reducing agents that were reported to reduce oximes (and derivatives) to hydroxylamines (and derivatives) include $NaBH_3CN$+HCl,[6,52a,b,202] $NaBH_3CN$+AcOH,[203] $NaBH_4$-AcOH,[73] BH_3-THF,[204] BH_3-pyridine+HCl,[205] and BH_3-NMe_3-HCl.[205b] Table 12 contains some recent examples from reduction of oximes to hydroxylamines and oxime ethers or esters to hydroxylamine ethers and esters. In many of the recent reports on reduction of C═N bonds of oximes and oxime derivatives, $NaBH_3CN$, in the presence of an acid, is one of the most commonly used and most effective reducing agents (Table 12, entries 1–12). Other reagents include BH_3-Py in MeOH (Table 12, entry 13)[217] and BH_3-THF (Table 12, entry 14).[217]

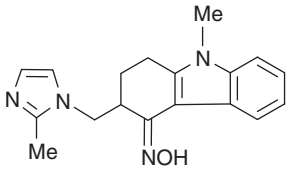
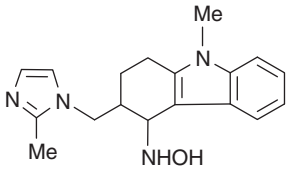
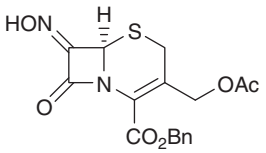
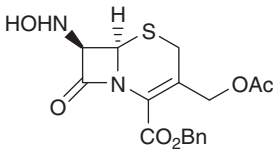
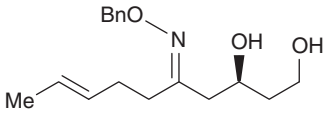
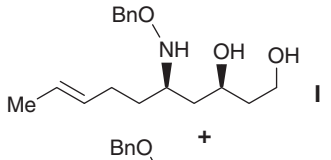
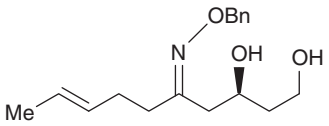
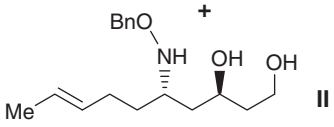
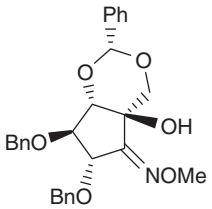
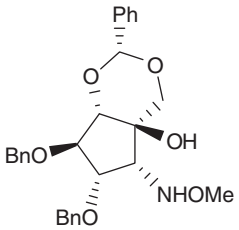
A clear difference in reactivity and selectivity was observed in the reduction of the *E*-oxime (Table 12, entry 15) and *Z*-oxime isomers of (*S*)-streptenol A. The *E*-oxime was generally reduced under milder conditions faster and smoother than the *Z*-oxime.[218]

Table 12 Reduction of oximes to hydroxylamines

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			$NaBH_3CN$, MeOH, HCl to pH 3 (methyl orange) 0 °C to r.t.; 4 h, r.t.	90	206
2			$NaBH_3CN$, MeOH, HCl to pH 3, r.t. (methyl orange)	65	207
3			$NaBH_3CN$, MeOH, HCl to pH 3, 20 °C 72 h	68	208
4			$NaBH_3CN$, AcOH, H_2O r.t., overnight	58	209
5			$NaBH_3CN$, MeOH, H_2O, HCl r.t., overnight	79	210
6			$NaBH_3CN$, AcOH r.t., 2 h	85	210
7			$NaBH_3CN$, AcOH r.t., 2 h	21	210
8			$NaBH_3CN$, EtOH 0 °C, 10 min; CF_3CO_2H 0 °C, 4 h	56	211
9			$NaBH_3CN$, THF, AcOH 0 °C, 2 h	74	212
10			$NaBH_3CN$, HCl MeOH 20 °C	71	213
11			$NaBH_3CN$, AcOH 20 °C, 24 h	80	214
12			$NaBH_3CN$, HCl, MeOH	77	215

(*Continued*)

Table 12 Continued

Entry	Substrate	Product	Conditions	Yield (%)	References
13			1. BH_3-Py, MeOH 0 °C, then r.t. (12 h) 2. HCl, 6 h 3. NaOH	28	216
14			BH_3-THF, THF, r.t.	40	217
15			$Me_4NBH(OAc)_3$ MeOH, AcOH –15 °C, 5 h $NaBH_3CN$ MeOH, AcOH –20 °C, 60 h	50 66:34 (I:II) 98 81:19 (I:II)	218
16			$Me_4NBH(OAc)_3$ MeOH, AcOH –15 °C, 5 h $NaBH_3CN$ MeOH, AcOH –20 °C, 108 h	50 30:70 (I:II) 92 50:50 (I:II)	218
17			LAH, MeONa, THF, –20 °C	67	219

$NaBH_3CN$ and $Me_4NBH(OAc)_3$ reduced the oxime ethers to hydroxylamine ethers under acid conditions with the *E*- and *Z*-oximes showing different selectivities (Table 12, entry 16).

$LiAlH_4$ was used to reduce a hydroxy oxime ether in the presence of MeONa at –20 °C (Table 12, entry 17).[219] The complete diastereoselectivity was explained either by complexation with the α-OH activated by MeONa or by attack on the less shielded upper side of the cyclopentanone ring.

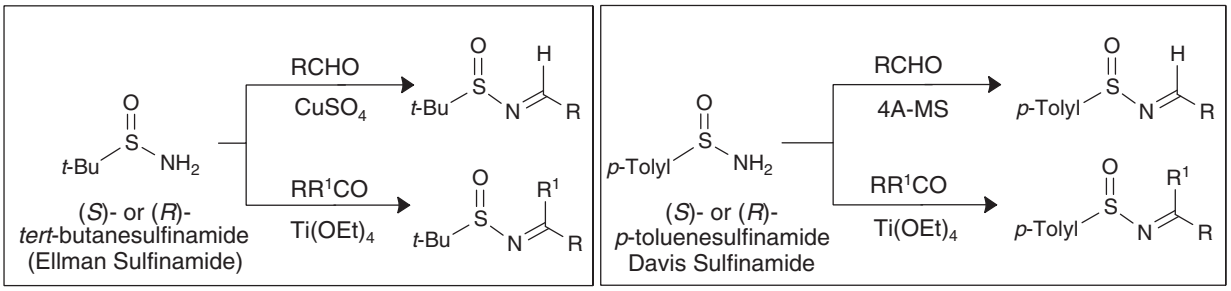
8.02.4.2 Reduction of *N*-sulfinyl Imines

N-sulfinyl imines are a family of imine derivatives in which the nitrogen of the C═N bond is attached to the SOR group, where R is alkyl or aryl. They are generally stable derivatives and can be purified and isolated. Several characteristic features of the sulfinyl group make it very useful, versatile, and most reliable in the synthesis of amines:

- The electron-withdrawing nature of the sulfinyl group activates imines toward nucleophilic addition to the carbon of the C═N bond. Typical nucleophiles include RMgX, R_2Zn, RLi, enolates, and hydrides.
- The sulfinyl group is chiral and has the characteristics of a good chiral auxiliary. During nucleophilic additions to the C═N bond, it exerts powerful and predictable stereo directing effects that result in high levels of asymmetric induction.
- The sulfinyl group can be cleaved relatively easily by acid treatment to obtain the corresponding amines.

Racemic *N*-sulfinyl imines were first prepared by Davis in 1974[220] by oxidation of *p*-toluenesulfenyl imines with *m*-CPBA. The enantiomeric synthesis was first reported by Cinquini and coworkers in 1977[221] by the reaction of metallo-ketimines with Andersen reagent (menthyl *p*-toluenesulfinate). A more practical procedure was developed by Davis in 1997[222] from the reaction of menthyl *p*-toluenesulfinate with LiHMDS and aldehydes. In 1997, Ellman and coworkers[223] reported the preparation of enantiomerically pure *tert*-butanesulfinamide and the preparation of chiral *N*-sulfinyl imines by direct condensation of *tert*-butanesulfinamide with aldehydes[223] and with ketones[224] using $CuSO_4$ and $Ti(OEt)_4$, respectively, as Lewis acid catalysts and water scavengers (Scheme 4). In

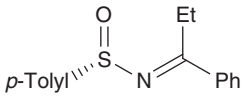
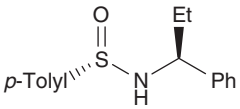
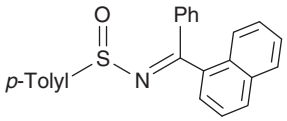
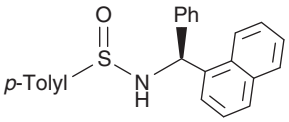
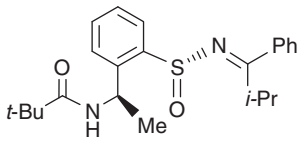
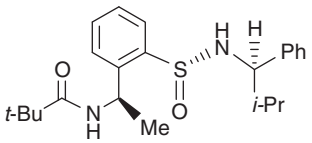
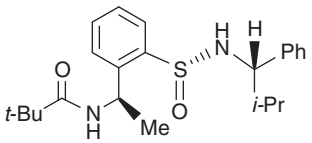
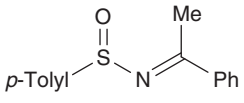
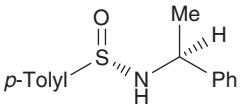
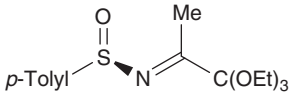
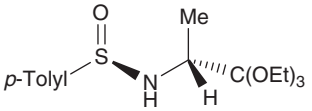
1999, Davis and coworkers[225] reported the preparation of *N*-*p*-toluenesulfinyl imines by direct condensation of *p*-toluenesulfinamide with aldehydes and ketones in the presence of 4 Å molecular sieves or $Ti(OEt)_4$, respectively (Scheme 4).



Scheme 4 Preparation of *N*-sulfinyl imines.

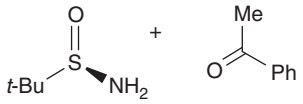
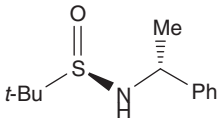
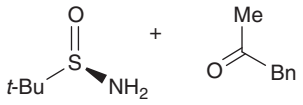
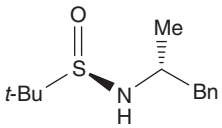
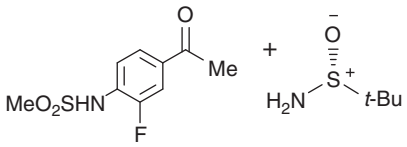
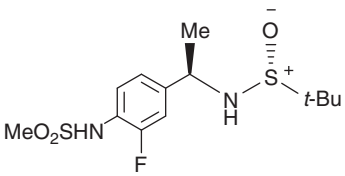
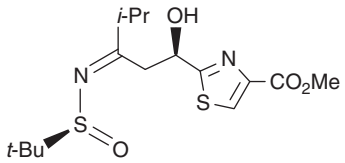
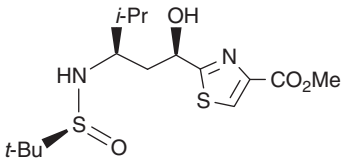
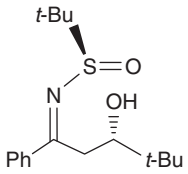
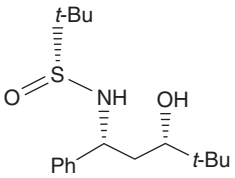
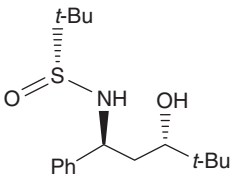
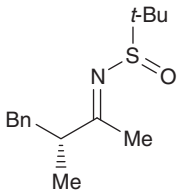
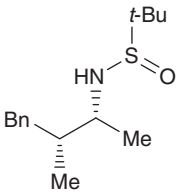
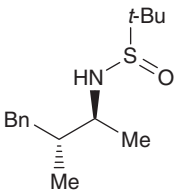
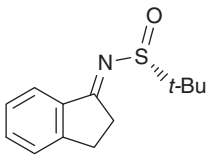
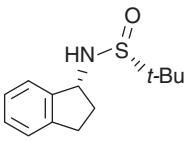
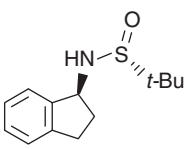
The development of these reliable and efficient procedures provided easy access to *N*-sulfinyl imines from aldehydes and ketones and contributed to the expansion of the utilization of these versatile building blocks in the synthesis of different classes of amines and amine derivatives.[226] The most important application that relates to the subject of this chapter is the reduction of *N*-sulfinyl ketimines to prepare enantiomerically enriched primary amines. The reduction of *N*-sulfinyl imines provides either *N*-sulfinyl amine derivatives or free amines after acid treatment. Many applications of reduction of *N*-sulfinyl ketimines in synthesis of amines are listed in Table 13.

Table 13 Reduction of *N*-sulfinyl imines

Entry	Substrate	Product	Conditions	Yield (%)	References
1		 Major	$NaBH_4$, EtOH r.t., 10–15 h $LiAlH_4$, Et_2O r.t., 10–15 h	90–100 1.9:1 *dr* 80–90 4:1 *dr*	227
2	 Racemic		[$LiAlH_3$(menthyloxy)] Et_2O, r.t., 4 h	81 93:7 *dr*	227
3		 	DIBAL-H, THF, –23 °C $ZnBr_2$; DIBAL-H, THF, r.t.	85 71 *de* 62 88 *de*	228
4	 (Racemic)	 (Racemic, *RR/SS*)	DIBAL-H, THF, – 23 °C, 0.5 h $ZnBr_2$; DIBAL-H, THF, r.t., 0.5 h	89 66 *de* 81 14 *de*	228
5		 Major	$LiAlH_4$, Et_2O, –40 °C, 1 h DIBAL-H, THF, –78 °C, 1 h 9-BBN, THF 0 °C, 12 h	86 3:1 *dr* 83 3.5:1 *dr* 95 Only product	229

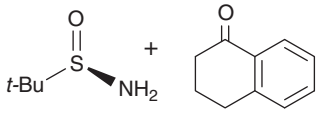
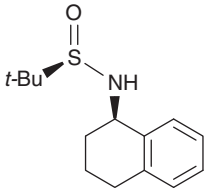
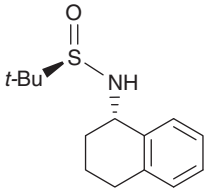
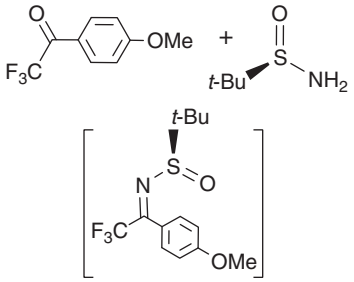
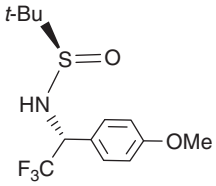
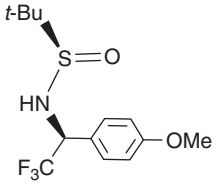
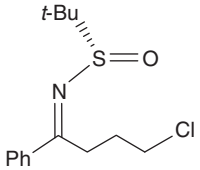
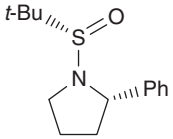
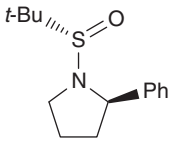
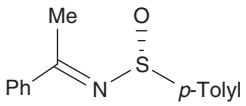
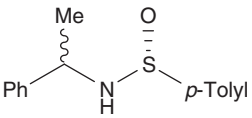
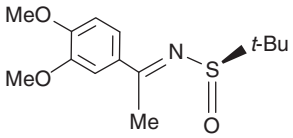
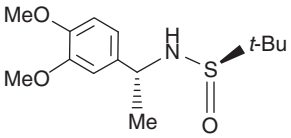
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Table 13 Continued

Entry	Substrate	Product	Conditions	Yield (%)	References
6			1. $Ti(OEt)_4$ (2 equivalents), THF, 60–70 °C 2. $NaBH_4$, –48 °C, 10 h	78 *dr*: 96:4	230
7			1. $Ti(OEt)_4$ (2 equivalents), THF, 60–70 °C 2. $NaBH_4$, –48 °C, 6 h	86 *dr*: 90:10	230
8			1. $Ti(OEt)_4$-THF, reflux, 16 h 2. $NaBH_4$, –20 °C, 16 h	53 *dr*: 99:1	231
9			$NaBH_4$, $Ti(OEt)_4$-THF –78 °C; Chromatography	88	232
10			Catecholborane (5 equivalents) THF, –10 °C, 20 h	89 96:4 *dr*	233
			$LiBHEt_3$ (2.5 equivalents) THF, –78 °C, 3 h	91 >99:1 *dr*	
11			$NaBH_4$, $Ti(OEt)_4$-THF –48 °C	86 96:4 *dr*	234
			$LiBHEt_3$ THF, –78 °C	89 96:4 *dr*	
12			$NaBH_4$, THF/H_2O –50 °C to r.t. (3 h)	96 *de*	235
			$LiBHEt_3$, THF, 0 °C to r.t. (3 h)	97 *de*	

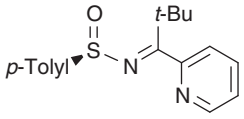
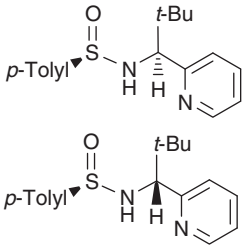
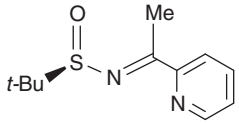
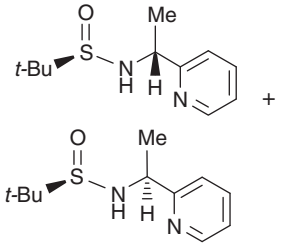
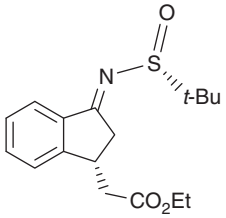
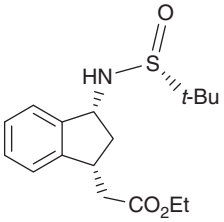
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Table 13 Continued

Entry	Substrate	Product	Conditions	Yield (%)	References
13			1. $Ti(OEt)_4$ (2 equivalents), THF, 75 °C, 7.5 h 2. $NaBH_4$, –48 °C, to r.t.	80 86:14 *dr*	236
			1. $Ti(OEt)_4$ (2 equivalents), THF, 75 °C, 7.5 h 2. $LiBHEt_3$, THF –48 °C, to r.t.	83 99:1 *dr*	
14			$Ti(Oi\text{-}Pr)_4$, Et_2O, reflux Then: $NaBH_4$, –78 °C, 3 h	78 *dr*: 95:5	237
15			$Ti(Oi\text{-}Pr)_4$, Et_2O, reflux Then: $Li(sec\text{-}Bu)_3BH$, –78 °C, 3 h	68 *dr*: 96:4	237
16			DIBAL-H, toluene –78 °C, 3 h; LHMDS, r.t., 1 h	92 99:1 *dr*	238
			$LiBHEt_3$, THF, –78 °C, 3 h; r.t., 1 h	94 1:99 *dr*	
17		 Stereochemistry of the major product was not specified	BH_3-THF, THF phthalic acid (1.1 equivalents) –30 °C, 15 min BH_3-THF, THF phthalic acid $Ti(OiPr)_4$, –30 °C	92 60:40 *dr* 90:10 *dr*	37
18			DIBAL-H (2.3 equivalents), THF –68 °C, 1.5 h $NaBH_4$ (4 equivalents), THF –40 °C, 120 h	87 *dr*: 98:2 90 *dr*: 93:7	239

(*Continued*)

Table 13 Continued

Entry	Substrate	Product	Conditions	Yield (%)	References
19			$NaBH_4$-MeOH 25 °C, 1 h	95 53:47 *dr*	240
			Li(*sec*-Bu)$_3$BH, THF 0 °C, 24 h	40 1:1 *dr*	
			DIBAL-H, THF −78 °C, 6 h	92 96:4 *dr*	
20			$NaBH_4$-MeOH 25 °C, 1 h	93 32:68 *dr*	241
			Li(*sec*-Bu)$_3$BH, THF −78 °C, 6 h	31 1:99 *dr*	
			DIBAL-H, THF −78 °C, 8 h	72 88:12 *dr*	
			9-BBN, THF, 25 °C, 11 h	50 99:1 *dr*	
21			$NaBH_4$, wet THF, −78 °C	80 >20:1 *dr*	242

Most reductions reported before 1999 were carried out using *p*-toluenesulfinyl imines. Annunziata and coworkers[227] reported one of the earliest studies on the reduction of sufinyl imines in 1982. They determined that the selectivity of the reduction was mainly dependent on the nature of the reducing species. LAH gave better selectivity than $NaBH_4$, but the best results (93:7 *dr*) were obtained with alkoxy-lithium aluminum hydrides (**Table 13**, entries 1 and 2). Wills and coworkers[228] showed that the addition of $ZnBr_2$ to DIBAL-H reduction of a sulfinyl imine (**Table 13**, entry 4) reverses the diastereoselectivity of the product. However, the effect was not general (**Table 13**, entry 5). Hua and coworkers[229] reduced (*R*)-(−)-[1-(triethoxymethyl)ethylidene]-*p*-toluenesulfinamide with various reducing agents (**Table 13**, entry 5). Both LAH and DIBAL-H gave diastereomeric mixtures in ratios close to 3:1, but 9-BBN yielded exclusively one diastereomer.

The introduction of *tert*-butanesulfinamide in 1997 as well as the studies of the reduction of *tert*-butanesulfinyl ketimines by the Ellman group starting in 1999[230] has expanded the utility and scope of *N*-sulfinyl imines for the preparation of chiral amines. The reduction of *N*-sulfinyl imines was also studied and applied to the synthesis of chiral amines by many other groups and has become a widely used reaction. In their first report on reduction of *N*-sulfinyl imines, Ellman and coworkers[230] described a stepwise procedure for chiral reductive amination of ketones with *tert*-butanesulfinamide. Several aromatic, aliphatic, and acyclic ketones were condensed with *tert*-butanesulfinamide in the presence of $Ti(OEt)_4$ to form *tert*-butanesulfinyl ketimines, which were reduced *in situ* with $NaBH_4$ to afford *tert*-butanesulfinyl-protected primary amines in high selectivity (**Table 13**, entries 6 and 7). The authors emphasized the role of $Ti(OEt)_4$ as a water scavenger, a catalyst for imine condensation, and a Lewis acid to enhance both reduction rate and diastereoselectivity. The procedure was later used as a key step in the synthesis of two TRPV1 antagonists (**Table 13**, entry 8).[231] In the synthesis of Tubulysin D,[232] the low-temperature reduction of a sulfinyl imine with $NaBH_4$ in the presence of $Ti(OEt)_4$ (**Table 13**, entry 9) was very selective and provided a desired 1,3-amino alcohol in 91:9 diastereomeric ratio. After chromatography, the product was isolated in diastereomerically pure form in 88% yield.

One useful aspect of diastereoselectivity that is applied frequently to the reduction of *N*-sulfinyl imines is the use of the same *N*-sulfinyl imine enantiomer to obtain the two possible diasteremeric products by changing the reducing agent. Thus, the reduction of *α*-hydroxy *N*-*tert*-butanesulfinyl imines was directed to provide *syn*- and *anti*-1,3-amino alcohols in very high diastereoselectivity based on the choice of the reducing agent. Ellman and coworkers[233] discovered that the use of catecholborane resulted in the selective formation of the *syn*-product, whereas $LiBHEt_3$ (Super-Hydride®) was highly selective for the *anti*-product (**Table 13**, entry 10). This method was applied effectively to a variety of aromatic and aliphatic substrates. The asymmetric synthesis of (6*R*,7*S*)-7-amino-7,8-dihydro-*α*-bisabolene[234] included the reduction of an intermediate *N*-sulfinyl imine with either $NaBH_4/Ti(OEt)_4$ or $LiBHsec\text{-}Bu_3$ (L-Selectride®) to afford the two diastereomeric products in high selectivity (**Table 13**, entry 11). The researchers at Amgen[235] reported the reduction of cyclic and acyclic *N*-*tert*-butanesulfinyl imines with $NaBH_4$ in wet THF and with $LiBHsec\text{-}Bu_3$ in dry THF to obtain opposing stereochemical outcomes (**Table 13**, entry 12). They explained the reversal of

selectivity by cyclic versus acyclic transition states. Ellman[236] revisited the original one-pot stepwise chiral reductive amination of ketones and expanded its scope by applying the selective reductions with either $NaBH_4$ or Li(*sec*-Bu)$_3$BH to obtain either stereoisomer using one common *N*-sulfinyl imine (Table 13, entry 13). Lu and coworkers[237] applied the one-pot stepwise reductive amination procedure with $NaBH_4$ or LiBH*sec*-Bu$_3$ to the preparation of either diastereomer of *N*-*tert*-butanesulfinyl α-trifluoromethyl amines in high diastereoselectivities (up to 99:1 *dr*). The *in situ* formation of *N*-sulfinyl imines was improved by using ether rather than THF as solvent and heating the mixture at reflux in the presence of Ti(O*i*-Pr)$_4$ (Table 13, entries 14 and 15).

Reddy and coworkers[238] devised a procedure for the asymmetric synthesis of either enantiomer of 2-substituted pyrrolidines from the same γ-chloro-*N*-*tert*-butanesulfinyl ketamine. Treatment with either LiBHEt$_3$ in THF at −78 °C to 23 °C or with DIBAL-H/LiHMDS in toluene at −78 °C to 0 °C gave either of the diastereomeric products. Subsequent cyclization gave the diastereomers of 2-substituted *N*-*tert*-butanesulfinyl pyrrolidines in high selectivity (Table 13, entry 16).

The reduction with borane and phthalic acid described by Lu and coworkers[37] (see Table 1, entries 40 and 41) was also applied to the reduction of an *N*-*p*-toluenesulfinyl ketimine to give 60:40 ratio of diasteremeric products (Table 13, entry 17). The selectivity increased to 90:10 with addition of Ti(OiPr)$_4$.

Rozwadowska and Grajewska[239] reported a synthesis of (*R*)-(+)-salsolidine 1 of high enantiomeric purity in which the key step was the reduction of a *N*-*tert*-butanesulfinyl ketamine with either $NaBH_4$ or DIBAL-H. Both reducing agents afforded the same desired product; however, the reduction with $NaBH_4$ was much slower than that with DIBAL-H but gave a better yield with slightly lower selectivity (Table 13, entry 18).

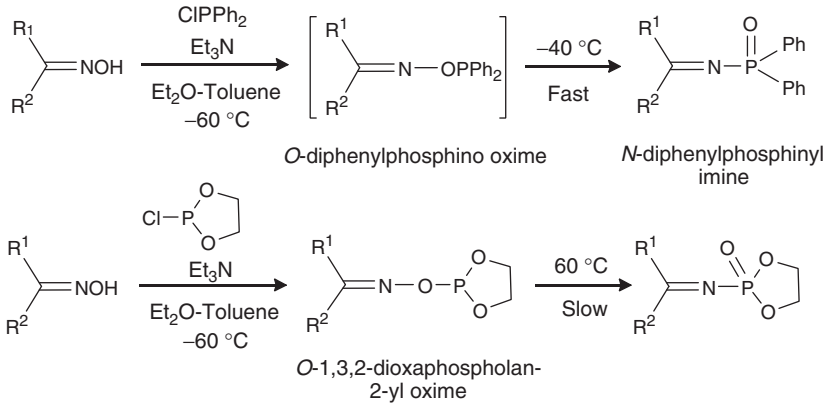
Chelucci and coworkers[240] described a procedure for the preparation of chiral-substituted 2-pyridylmethylamines via reduction of *N*-*p*-toluenesulfinyl imines. Generally, the reduction with LiBH*sec*-Bu$_3$ or DIBAL-H gave better selectivity than $NaBH_4$ particularly with large substituent (e.g., *t*-Bu) on the imino moiety (Table 13, entry 19). That trend was reversed in the reduction of the corresponding *N*-*tert*-butanesulfinyl imines[241] with the same reagents, which gave better selectivity with imines having smaller substituents (e.g., Me) on the imine moiety (Table 13, entry 20).

Fustero and coworkers[242] improved the product diastereomeric ratio in the reduction of an indanone sulfinyl imine (Table 13, entry 21) from 5:1 with $NaBH_4$-MeOH at 0 °C to exclusive formation of one diastereomer by carrying out the reaction in wet THF at −78 °C.

8.02.4.3 Reduction of *N*-phosphinylimines

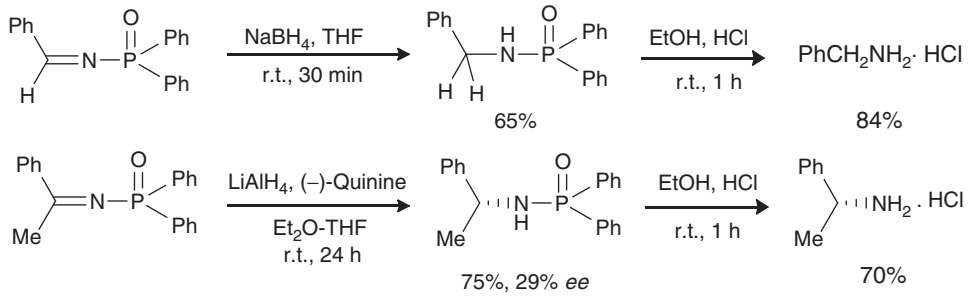
N-phosphinyl imines are imine derivatives in which the nitrogen of the C═N bond is attached to a P(O)R$_2$ group. R may be alkyl or aryl, but the most commonly used is the diphenylphosphinyl group. *N*-diphenylphosphinyl imines are stable derivatives and provide advantages similar to those described for *N*-sulfinyl imines. The *N*-diphenylphosphinyl group is highly electron withdrawing and greatly enhances the electrophilicity of the imine carbon so that they undergo faster reductions than ketones with most boron and aluminum hydride reagents, including those that are bulky.[243]

N-phosphinyl imines are prepared from the corresponding oximes. The reaction of oximes with ClPPh$_2$ at low temperature (−60 °C to −80 °C) in the presence of Et$_3$N produces unstable *O*-diphenylphosphino oxime intermediate. The intermediate undergoes free radical rearrangement at −40 °C to give *N*-diphenylphosphinyl imines (Scheme 5).[244] The corresponding intermediate from 2-chloro-1,3,2-dioxaphospholane is much more stable and rearranges slowly to *N*-phosphinyl imine upon heating to 60 °C (Scheme 5).[244]



Scheme 5 Preparation of *N*-phosphinyl imines.

A pioneering study of the reduction of *N*-phosphinyl imines was reported by Stec and Krzyzanowska.[244b] Reduction of *N*-benzylidene diphenylphosphinic amide with $NaBH_4$ in THF gave *N*-benzyl diphenylphosphinamide in 65% yield (Scheme 6). They also examined the asymmetric reduction of several prochiral *N*-diphenylphosphinyl imines using $LiAlH_4$ in the presence of an equimolar amount of (−)-quinine.[245] The reduction provided the corresponding (*R*)-*N*-diphenylphosphinyl amines in low



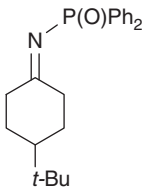
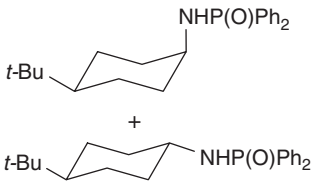
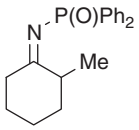
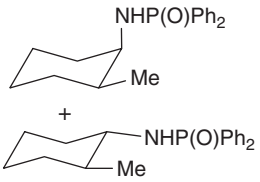
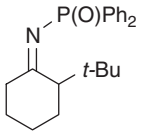
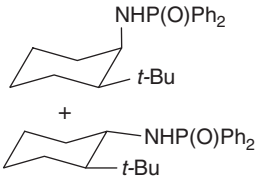
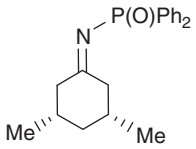
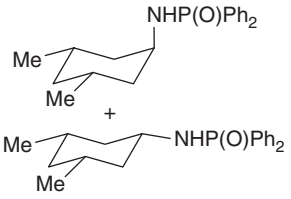
Scheme 6 Reduction of *N*-phosphinyl imines and cleavage of diphenylphosphinyl group.

8–34% *ee* (Scheme 6). The authors also reported that *N*-diphenylphosphinyl group is cleaved by treatment with HCl in benzene or ethanol to give the corresponding amine hydrochlorides without loss of enantiomeric purity.[244b,245]

Hutchins and coworkers[243,246,247] initiated several studies on the reductions of *N*-phosphinyl imines with hydride reagents. The studies addressed three different aspects of stereoselective reductions of *N*-phosphinyl imines as precursors to enantiomeric and diastereomeric amines.

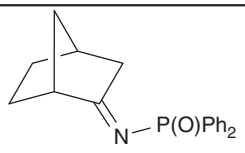
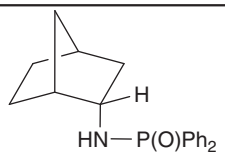
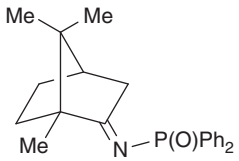
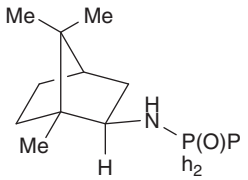
The first study[246,247] examined the diastereoselectivity in the reduction of cyclic *N*-diphenylphosphinyl imines bearing diastereotopic faces with bulky trialkylborohydrides. The reduction of cyclic *N*-diphenylphosphinyl imines showed, in general, parallel results to reduction of cyclic ketones[248] and *N*-alkyl imines.[249] The reduction of 2-, 3-, or 4-substituted *N*-diphenylphosphinyl cyclohexanone imines with Li(*sec*-Bu)$_3$BH gave consistently very high selectivity (>97%) toward the formation of the *axial N*-diphenylphosphinyl amines resulting from preferred *equatorial* approach by the bulky reagent (Table 14, entries 1–4). However, small, unhindered reagents such as $NaBH_4$ and $LiAlH_4$ showed poor selectivity (Table 14, entries 1–4). The only exception was observed in the reduction of 2-*tert*-butyl derivative with $NaBH_4$ (Table 14, entry 3), which gave the same high selectivity of >97:3 toward the formation of the axial amine as that obtained from Li(*sec*-Bu)$_3$BH. It was postulated that the 2-*tert*-butyl phosphinyl imine exists as a concave 'bowl-like' twist boat conformation that favors the attack from outside of the bowl by either small or bulky hydride reagents leading to the axial product (Figure 1).

Table 14 Diastereoselective reductions of cyclic *N*-diphenylphosphinyl imines[a]

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*
1			$NaBH_4$, THF r.t., 2 h Li(sec-Bu)$_3$BH THF, r.t., 2 h	65 26:74 (a/e) 64 >97:3 (a/e)
2			$NaBH_4$, THF r.t., 2 h Li(sec-Bu)$_3$BH THF, r.t., 2 h	63 50:50 (a/e) 64 >97:3 (a/e)
3			$NaBH_4$, THF r.t., 2 h Li(sec-Bu)$_3$BH THF, r.t., 2 h	63 >97:3 (a/e) 64 >97:3 (a/e)
4			$LiAlH_4$, THF r.t., 2 h Li(sec-Bu)$_3$BH THF, r.t., 2 h	63 35:56 (a/e) 64 >97:3 (a/e)

(*Continued*)

Table 14 Continued

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*
5			$NaBH_4$, THF r.t., 2 h	77 80 *endo*
			$Li(sec\text{-}Bu)_3BH$ THF, r.t., 2 h	68 >97 *endo*
6			$NaBH_4$, THF r.t., 2 h	70 90 *exo*
			$Li(sec\text{-}Bu)_3BH$	63 >97 *exo*
			THF, r.t., 2 h	

[a]All examples are from refs 247 and 248.

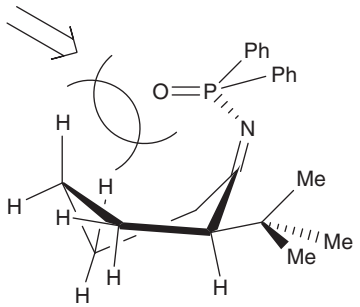
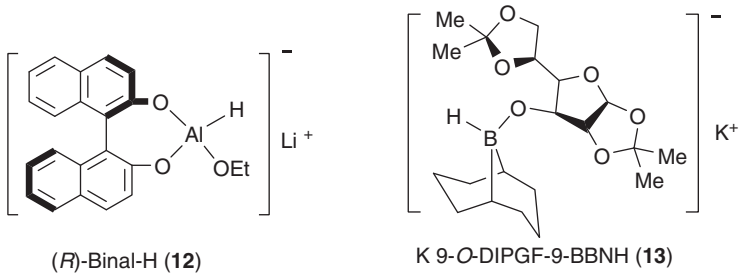


Figure 1 Proposed conformation of 2-*tert*-butyl *N*-diphenylphosphinyl cyclohexanone imine. Reproduced from Hutchins, R. O.; Zhu, Q.-C.; Adams, J.; *et al.* Diastereo- and Enantioselective Hydride Reductions of Ketone Phosphinyl Imines to Phosphinyl Amines. ACS Symposium Series. In *Reductions in Organic Synthesis: Recent Advances and Practical Applications*; Abdel-Magid, A. F., Ed.; American Chemical Society; Washington DC, **1996**, pp 127–137, with permission from ACS.

The reduction of norbornanone phosphinyl imine, which is more hindered on the *endo*- than the *exo*-face, is attacked predominantly from the *exo*-face. Both $NaBH_4$ and $Li(sec\text{-}Bu)_3BH$ reduce the imine to give the *endo*-product as the major product (Table 14, entry 5). The camphor phosphinyl imine, which is more hindered on the *exo*-face, is reduced by the two reagents to give predominantly the *exo*-product (Table 14, entry 6). In both bicyclic examples, $Li(sec\text{-}Bu)_3BH$ gave higher diastereoselectivity than that obtained from $NaBH_4$.

The second study examined the enantioselective reductions of *N*-phosphinyl ketimines and *α*-*N*-phosphinylimino esters with chiral hydride reagents for the synthesis of enantiomerically enriched primary amines and *α*-amino esters, respectively.[243,246] The group examined many chiral reducing agents, but most enantioselective reductions were carried out using two enantioselective reducing agents: Binal-H, (Noyori's reagent)[250] (**12**, Figure 2) and potassium 9-*O*-(1,2;5,6-di-*O*-isopropylidene-*α*-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (K 9-*O*-DIPGF-9-BBNH, Brown's reagent)[251](**13**, Figure 2).

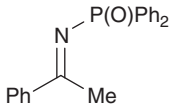
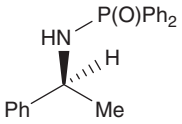
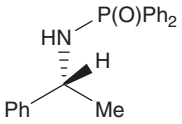
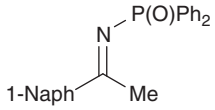
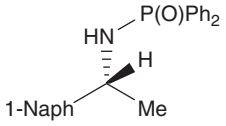
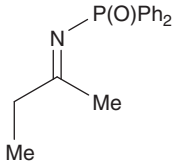
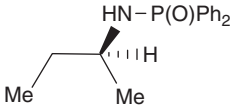
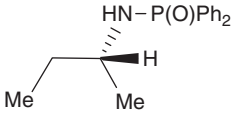
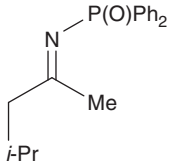
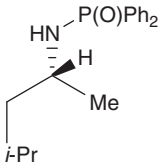
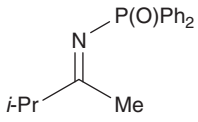
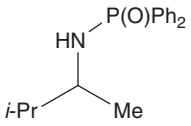
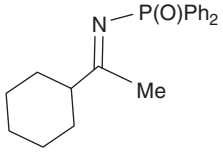
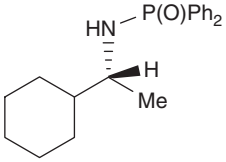
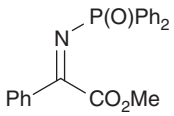
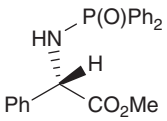
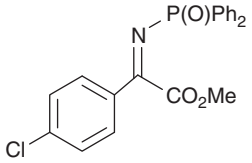
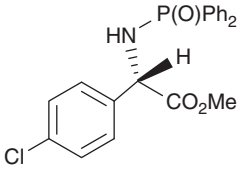
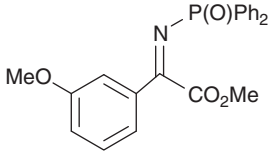
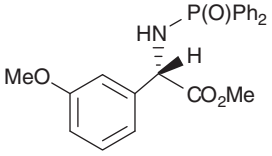


(*R*)-Binal-H (**12**) K 9-*O*-DIPGF-9-BBNH (**13**)

Figure 2 Chiral reducing agents for enantioselective reduction of *N*-phosphinyl imines.

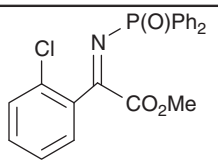
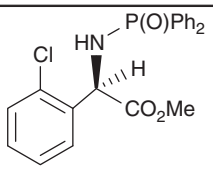
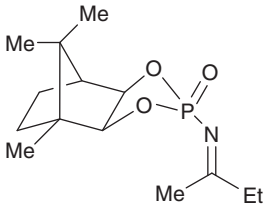
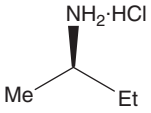
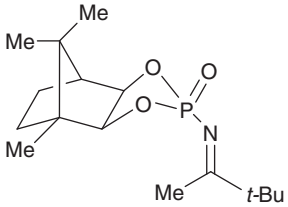
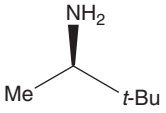
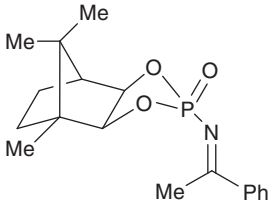
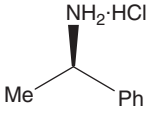
In general, the reduction of aryl alkyl imines with either reagent occurred with moderate to low enantioselectivity (Table 15, entries 1–4). However, reduction of dialkyl derivatives (Table 15, entries 5–9) gave better enantioselectivity particularly with

Table 15 Enantioselective reductions of *N*-diphenylphosphinyl imines

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			(*S*)-BINAL-H, THF –78 °C, 0.5 h	84 13 *ee*	243
2			K 9-*O*-DIPGF-9-BBNH THF, –78 °C, 1 h	54 15 *ee*	243
3			(*R*)-BINAL-H, THF –78 °C, 0.5 h	66 52 *ee*	243
4			K 9-*O*-DIPGF-9-BBNH THF, –100 °C, 0.5 h	82 77 *ee*	243
5			(*S*)-BINAL-H, THF –40 °C, 0.67 h	63 40 *ee*	243
6			K 9-*O*-DIPGF-9-BBNH THF, –78 °C, 2 h	56 61 *ee*	243
7			K 9-*O*-DIPGF-9-BBNH THF, –78 °C, 0.5 h	64 80 *ee*	243
8				66 68 *ee*	243
		(–)-Isomer, configuration unknown			
9				95 84 *ee*	243
10			(*R*)-BINAL-H, THF –80 °C, 2–3 h	64 77 *ee*	246
11				80 96 *ee*	246
12				64 93 *ee*	246

(*Continued*)

Table 15 Continued

Entry	Substrate	Product	Conditions	Yield (%)	References
13				68 90 *ee*	246
14			1. $NaBH_4$, THF r.t., 2 h 2. HCl, MeOH	72 87 *ee*	246
15			1. $NaBH_4$, THF r.t., 2 h 2. HCl, MeOH	65 76 *ee*	246
16			1. $NaBH_4$, THF r.t., 2 h 2. HCl, MeOH	75 28 *ee*	246

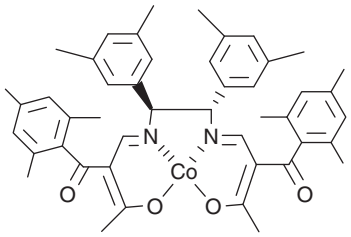
K 9-*O*-DIPGF-9-BBNH, which consistently afforded the *R* enantiomer predominately. The enantioselectivity obtained from the reductions of dialkyl *N*-diphenylphosphinyl imine derivatives with K 9-*O*-DIPGF-9-BBNH (50–84% *ee*) was still among the highest enantioselectivities obtained for reduction of prochiral aliphatic imine derivatives with hydride reagents. The enantioselective reduction of *N*-diphenylphosphinyl imines derived from *α*-keto aryl acetic esters[246] with (R)-BINAL-H gave good to excellent enantioselectivities with the *S*-enantiomers being the predominant products (Table 15, entries 10–12). The reverse enantioselectivity was observed in the reductions of *ortho*-substituted derivatives, which gave the *R*-enantiomers preferentially (Table 15, entry 13). The enantioselectivity obtained with the *meta*- and *para*-substituted derivatives and the observed reversal with the *ortho*-substituted derivatives were accounted for by assuming cyclic 6-membered ring transition states.

The third study examined the reduction of chiral nonracemic *N*-camphorylphosphinyl imines derived from camphordiol with achiral reagents.[246] The labile intermediate imines were not isolated but were reduced directly with $NaBH_4$ in THF and the products were treated with methanolic HCl to provide the amine salts (Table 15, entries 14–16). As in the previous study, the dialkyl derivatives were reduced in good stereoselectivity (78–87% *ee*), whereas the aryl derivatives were obtained in poor selectivity (26–29% *ee*).[246]

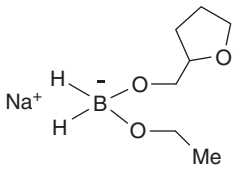
Other groups have also studied the enantioselective reduction of *N*-phosphinyl imines. Several of these studies used catalytic enantioselective hydrosilylation for the reduction of *N*-phosphinyl imines with very good outcomes. Yamada and coworkers[252] described the use of enantiomeric (*β*-oxoaldiminato)cobalt(II) complexes in reduction of ketones and imines (*see* Chapter 8.01, Section 8.01.10.3). They reported the reduction of several cyclic *N*-diphenylphosphinyl imines using the Co(II)-catalyst **14** and a modified $NaBH_4$ ($NaBH_2(OEt)(OTHFA$, **15**)) (Figure 3). The reductions were highly selective giving the corresponding *N*-diphenylphosphinyl imines in 77–99% *ee* (Table 16, entries 1 and 2).

Lipshutz and coworkers[253] described a novel procedure for asymmetric hydrosilylations of aryl *N*-phosphinyl ketimines using catalytic CuH and a ligand. The ligated CuH catalyst was prepared *in situ* from CuCl, NaOMe, and DTBM–SEGPHOS (**16**, Figure 4) in toluene at r.t. The reduction is carried out with 6% catalyst, tetramethyldisiloxane (TMDS) in the presence of 3.3 equivalents of *t*-BuOH. Improved enantioselectivity was achieved when they replaced the diphenylphosphinyl group on the imine nitrogen with di(3,5-dixylyl)phosphinyl group (Table 16, entries 3 and 4).

Toste and coworkers[254] developed a hydrosilylation procedure for enantioselective reduction of *N*-diphenylphosphinyl imines, *α*-*N*-diphenylphosphinyl imino esters, and *α*,*β*-unsaturated *N*-diphenylphosphinyl imines. The procedure employs a chiral



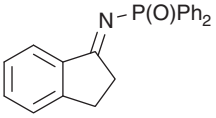
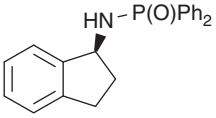
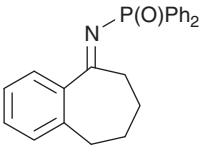
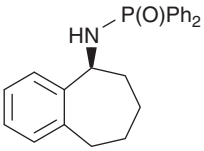
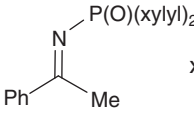
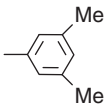
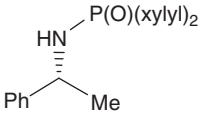
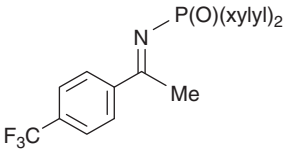
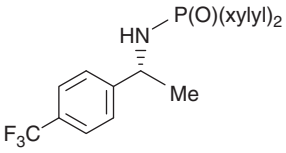
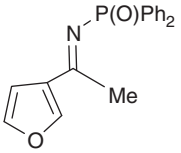
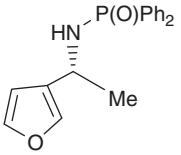
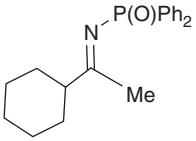
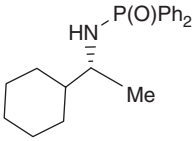
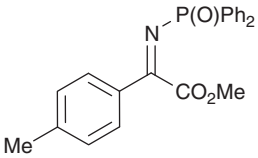
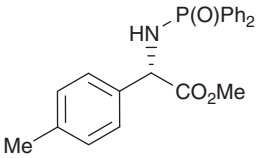
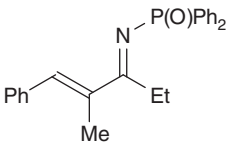
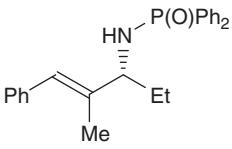
Co(II) catalyst **14**



$NaBH_2(OEt)(OTHFA)$ (**15**)

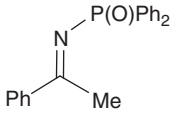
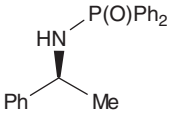
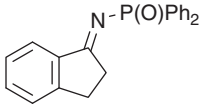
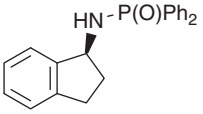
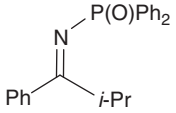
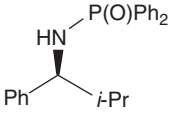
Figure 3 Cobalt catalyst for enantioselective hydrosilylation. Reproduced from Yamada, T.; Nagata, T.; Sugi, K. D.; *et al. Chem. Eur. J.* **2003**, *9*, 4485–4509.

Table 16 Enantioselective reduction of *N*-phosphinyl imines via hydrosilylation

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
1			Co catalyst **14** (1 mol%) $NaBH_2(OEt)(OTHFA)$ (**15**) (3 equivalents), $CHCl_3$, 0 °C, 4 h	86 91 *ee*	252
2				81 94 *ee*	252
3	 xylyl = 		CuCl (6%), NaOMe (6%), (*R*)-DTBM–SEGPHOS **16** (6%), ($Me_3SiOSiH_2Me$) (3 equivalents), *t*-BuOH (3.3 equivalents), toluene, r.t., 17 h	99 96 *ee*	253
4				94 97 *ee*	253
5			Re-complex **17** (3 mol%) Me_2PhSiH (2 equivalents), CH_2Cl_2, r.t.	76 99 *ee*	254
6				69 32 *ee*	254
7				89 99 *ee*	254
8				71 99 *ee*	254

(*Continued*)

Table 16 Continued

Entry	*Substrate*	*Product*	*Conditions*	*Yield (%)*	*References*
9			Diamine ligand **18** (5 mol%) $Zn(Et)_2$ (5 mol%) PMHS (3 equivalents) MeOH-THF (20:80) r.t., 12 h	88 97 *ee*	255
10				83 98 *ee*	255
11				74 55 *ee*	255

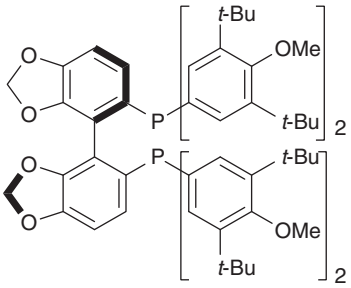


Figure 4 (*R*)-(–)-DTBM–SEGPHOS (**16**). Reproduced from Lipshutz, B. H.; Shimizu, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 2228–2230.

rhenium(V)-oxo complex (**17**, Figure 5) as a catalyst and Me_2PhSiH as the hydride source. Several *N*-diphenylphosphinyl imines were reduced under these conditions to the corresponding *N*-diphenylphosphinyl amines in good yields and mostly high selectivity (Table 16, entries 5–8).

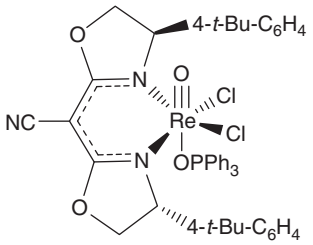


Figure 5 Cyanobis(oxazoline)Re(V)-oxo complex (**17**). Reproduced from Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462–12463, with permission from ACS.

Park and coworkers[255] described a highly enantioselective hydrosilylation procedure for the reduction of *N*-diphenylphosphinyl imines using chiral Zn/diamine catalysts. The combination of (*R,R*)-1,2-diphenyl-1,2-ethanediamine ligand (**18**, Figure 6), $Zn(Et)_2$, and polymethylhydrosiloxane (PMHS) is used for the reduction of several aryl *N*-diphenylphosphinyl imines in moderate to high enantioselectivity (Table 16, entries 9–11).

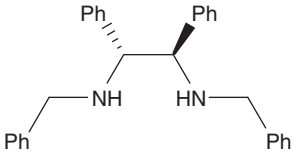
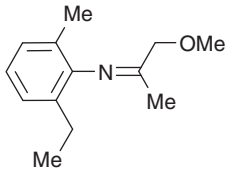
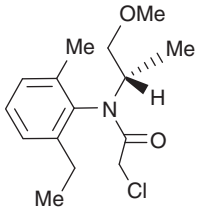
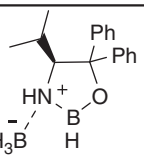
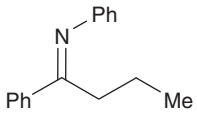
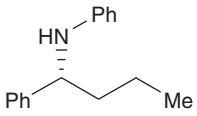
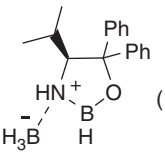
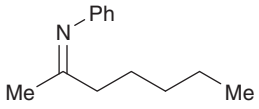
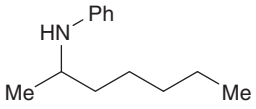
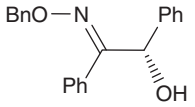
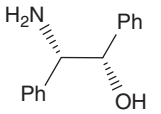
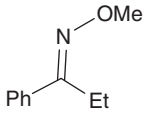
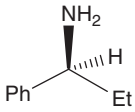
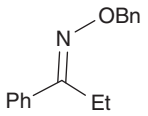
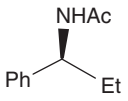
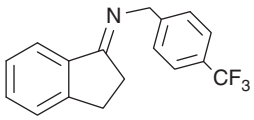
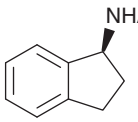
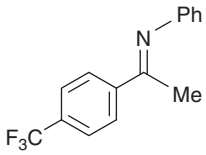
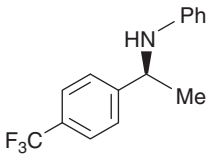
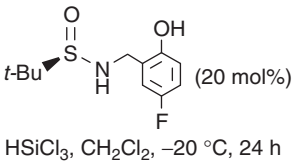
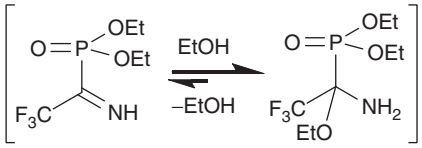
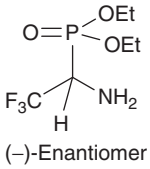


Figure 6 (*R,R*)-Dibenzyl-1,2-diphenyl-1,2-ethanediamine (**18**). Reproduced from Park, B.-M.; Mun, S.; Yun, J. *Adv. Synth. Catal.* **2006**, *348*, 1029–1032.

8.02.4.4 Other Enantioselective Reductions of Imines and Imine Derivatives

Enantioselective reduction of imines and imine derivatives is an expanding field. The advances in reduction of enantiomerically pure *N*-sulfinyl imines with achiral reducing agents have added very convenient methodology with wide scope to obtain chiral non-racemic amines, particularly primary amines (Section 8.02.4.2). Some recent advances in the enantioselective reduction of *N*-phosphinyl imines with metal hydrides and catalytic hydrosilylation (Section 8.02.4.3) show good promise as new tools in the synthesis of chiral amines. These developments reflect the importance of synthesis of chiral amines as synthetic targets using different reduction methodologies, which has been the topic of at least one recent comprehensive review.[256] In addition to these procedures, some recent miscellaneous examples are highlighted in this section with representative examples listed in Table 17.

Table 17 Miscellaneous enantioselective reduction of imines

Entry	Substrate	Product	Conditions	Yield (%)	References
1		 Metolachlor	 THF, 30 °C, 2 days Then: $ClCH_2COCl$, Na_2CO_3 benzene	87 62 *ee*	257
2			 (1 equivalent)	97 88 *ee*	258
3		 Absolute configuration unknown	THF, 30 °C, 22 h	87 18 *ee*	
4	 98% *ee*		$Na[AlH_2(OCH_2CH_2OCH_3)_2]$ THF, toluene –30 °C (2 h); reflux (3 h)	59 *syn*:*anti* 98:2 98 *ee*	259
5			(*R*,*S*)-**19** (1 equivalent), BH_3-THF (1.5 equivalents) THF, 0 °C, 48 h	76 92 *ee*	260
6			1. Spiroborate ester **20** (0.1 equivalent) BH_3 (stabilized with $NaBH_4$) (4 equivalents), dioxane, 0 °C, 36 h 2. Ac_2O, CH_2Cl_2, Et_3N, DMAP, r.t., 3 h	89 83 *ee* 77 97 *ee*	261
7					
8			 HSiCl$_3$, CH_2Cl_2, –20 °C, 24 h	93 92 *ee*	262
9		 (–)-Enantiomer	(*R*)-1-Me-CBS (5 mol%), catecholborane THF-toluene, –15 °C, 5 h	95 72 *ee*	263

Cho and coworkers[257] prepared the enantiomerically enriched herbicide metolachlor by the asymmetric reduction of the imine shown in Table 17 (entry 1) and subsequent chloroacetylation. Itsuno's oxazaborolidine-BH_3 complex gave the best enantioselectivity among several other tested chiral reducing reagents, but the selectivity was still moderate. In another study,[258] Cho examined several chiral reducing agents for the enantioselective reduction of *N*-phenyl aromatic ketimines to enantiomerically enriched *N*-phenyl secondary aromatic amines. Itsuno's oxazaborolidine-BH_3 complex provided the best enantioselectivity in these reductions (Table 17, entry 2). Aliphatic *N*-phenyl imines were reduced with low enantioselectivity under the same conditions (Table 17, entry 3).

Fujisawa and coworkers[259] studied the diastereoselective reduction of several diaryl *β*-benzyloxyimino alcohols. The reduction with either $LiAlH_4$ or $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ afforded the *syn*-isomer as a major product. Although LAH was more effective, it gave lower selectivity and caused racemization in some cases. $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ was sometimes less reactive and some reactions did not reach completion, but the diastereoselectivity was high (Table 17, entry 4).

Shane and coworkers[260] reported the first enatioselective reduction of oxime ethers using chiral spiroborate esters such as compound (*R,S*)-**19** (Figure 7). Prochiral aralkylketoxime ethers were reduced by BH_3-THF in the presence of (*R,S*)-**19** at 0–5 °C to give (*S*)-1-aralkylamines in high enantioselectivity up to 98% *ee* (Table 17, entry 5).

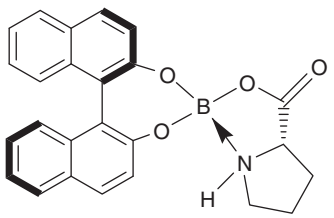


Figure 7 Chiral spiroborate ester (*R,S*)-**19**. Reproduced from Chu, Y.; Shan, Z.; Liu, D.; Sun, N. *J. Org. Chem.* **2006**, *71*, 3998–4001, with permission from ACS.

Ortiz-Marciales and coworkers[262] reported the use of other stable enantiopure spiroborate esters derived from chiral 1,2-amino alcohols as catalysts for the asymmetric reduction of oxime ethers. They developed a procedure for borane-based catalytic asymmetric reduction of oxime ethers to primary amines. Thus, the chiral spiroborate ester **20** (derived from 1,2-diphenylvalinol) (Figure 8) was used as a catalyst in combination with BH_3 stabilized by $NaBH_4$ in dioxane at 0 °C. The procedure was applied to the asymmetric reduction of several *O*-benzyl oxime ethers to afford primary amines with high enantioselectivity (Table 17, entries 6 and 7). The amine products were isolated as their *N*-acetyl derivatives.

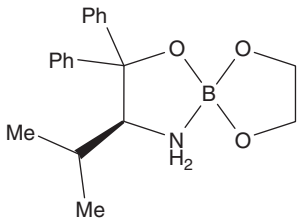


Figure 8 Chiral spiroborate ester (**20**) derived from 1,1-diphenylvalinol. Reproduced from Huang, X.; Ortiz-Marciales, M.; Huang, K.; *et al. Org. Lett.* **2007**, *9*, 1793–1795, with permission from ACS.

Sun and coworkers[262] reported the use of the enantiopure *N*-sulfinyl amine **21** (Figure 9) as the first example of *S*-chiral compound to be used as a catalyst for the enantioselective reduction of *N*-aryl ketimines with trichlorosilane. The reduction procedure was demonstrated by the enantioselective reduction of *N*-aryl aryl ketimines in high chemical yields and high enantioselectivity (Table 17, entry 8).

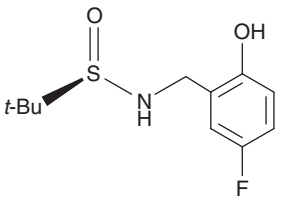


Figure 9 (*R*)-*N*-(5-Fluoro-2-hydroxybenzyl)-2-methylpropane-2-sulfinamide (**21**). Reproduced from Pei, D.; Wang, Z.; Wei, S.; Zhang, Y. Sun, J. *Org. Lett.* **2006**, *8*, 5913–5915, with permission from ACS.

Mikolajczyk and coworkers[263] reported a catalytic enantioselective reduction of *C*-phosphorylated NH-imines to afford enantiomerically enriched α-aminotrifluoroethylphosphonates. These molecules are precursors to α-aminophosphonic acids. The reduction was carried out using (*R*)-Me-CBS oxazaborolidine catalyst (5 mol%) with catecholborane at −15 °C. The enantioselectivity of the reduction was improved by adding one molar equivalent of EtOH, which adds to the C═N bond of the imine. The addition adduct exists as a major component in an equilibrium with the imine and thus serves as a slow release mechanism for the imine to limit its concentration and maintain a favorable catalyst/imine ratio during the course of the reduction (**Table 17**, entry a9).

8.02.5 Conclusion

Imines were discovered by Hugo Schiff in 1864[2] from condensation of aldehydes with aniline, a discovery still commemorated today in the term 'Schiff bases.' That discovery initiated substantial scientific discussion then, and led to the discovery of other important reactions and syntheses, which still inspire new developments. The first reductive amination of aldehydes and ketones using catalytic hydrogenation over a Ni catalyst was reported in 1921 by Georges Mignonac.[264] Today there are many options and various procedures for carrying out this transformation. Methods for reduction of C═N to CH–NH have advanced considerably since that early pioneering research, and this transformation has grown to be a cornerstone synthetic conversion in organic chemistry. It is a direct and effective way to synthesize many different kinds of amines. The period covered by this chapter has seen some great advances in the reduction of isolated C═N compounds and in the reductive amination of aldehydes and ketones using metal hydrides as well as other reduction methods. Many of these new methods have been highlighted with representative examples. The discussion in this chapter has emphasized new developments, such as reductive amination with $NaBH(OAc)_3$, enantioselective reduction of chiral *N*-sulfinyl imines, and the diastereo- and enantioselective reductions of *N*-phosphinyl imines.

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8.03 Reduction of C═N to CHNH by Hydride Delivery from C

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Glossary

Biomimetic reaction A human-designed chemical process that imitates the mode in which nature performs biochemical transformations.

Hantzsch ester (named after the German chemist Arthur Hantzsch) The 1,4-dihydropyridine resulting from the three-component coupling of an aldehyde (1 equivalent), ammonia (1 equivalent), and a dicarbonyl compound (2 equivalents), that easily oxidizes to its pyridine analog.

Hydrosilylation The addition of silicon hydrides across unsaturated bonds.

Organocatalysis A form of catalysis, whereby the rate of a chemical reaction is increased by a simple small molecule, referred to as an 'organocatalyst', containing only carbon, hydrogen, oxygen and maybe nitrogen, sulfur, or other nonmetallic elements.

Reductive amination A one-pot conversion of aldehydes or ketones to a primary or secondary amine without

isolation of the intermediate imine, in which a reducing agent coexists in the presence of the starting carbonyl compound.

Transfer hydrogenation The addition of a proton and a hydride, formally an equivalent of H_2, to a molecule, from a source other than hydrogen gas.

8.03.1 Introduction

8.03.1.1 Importance and Challenges of Imine Reduction

The reduction of imines is a powerful tool for the synthesis of amines; however, relatively few efficient and practical methods have been reported. When imines derived from unsymmetrical ketones are employed, a new chiral center is formed at the carbon connected to the nitrogen atom in the reduced product amine. The demand for enantiomerically pure amines to produce drug candidates, pharmaceuticals, agrochemicals, and other fine chemicals has motivated significant research effort in the field of asymmetric catalysis, particularly in the subject of reductive methods.

In contrast to the large number of asymmetric reduction protocols that are known for ketones,[1] only limited success has been achieved in the reduction of ketimines. Imines are less electrophilic than their carbonyl analogs, and consequently are poorer substrates for nucleophilic addition than aldehydes and ketones.[2] Several strategies can be envisaged for the activation of the imine before the attack of the hydride (Figure 1(a)). One valuable way to increase the reactivity of imines toward reduction is protonation of the basic imine nitrogen. Another useful strategy is the introduction of an aryl or an electron-withdrawing group on the nitrogen to increase the electrophilic nature of the imino group. Activating groups such as diphenylphosphinoyl, tosyl, aryl or substituted aryls, alkoxy, and benzyl groups have been used. In addition to the activating effect of these groups, the direct preparation of primary amines is not simple, because the corresponding imines are usually unstable compounds. For both reasons, *N*-substituted substrates are generally required and methods for the reduction of *N*-unprotected imines are rare.[3]

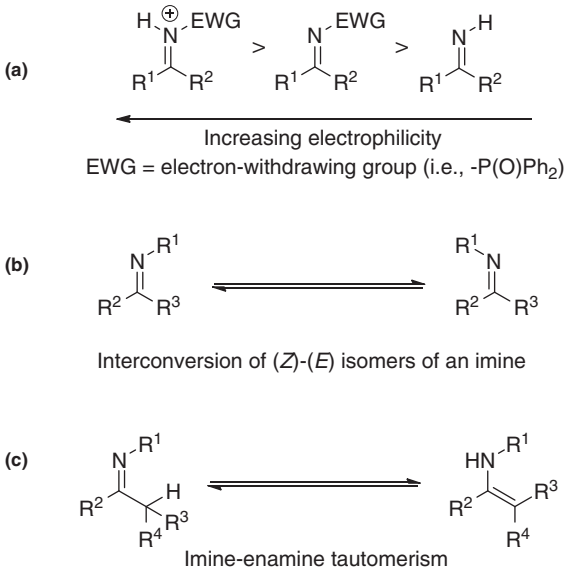


Figure 1 Challenges arising from imine reduction (a) strategies for imine activation, (b) and (c) isomer-interconversion events in imines.

A particular difficulty in the reduction of imines arises from the possible *cis–trans* isomerization of the C═N double bond in *N*-substituted aldimines and ketimines. The presence of *Z*- and *E*-isomers makes the stereochemistry of the reaction difficult to control because different geometrical isomers are reduced at different rates and with different selectivities. Two possible ways to circumvent this issue are (1) using cyclic imines (endocyclic imines) that can only exist as *cis* isomers or (2) using oximes as substrates, because *E*- and *Z*-isomers can usually be isolated and subjected to reduction separately. However none of these strategies offers a general solution. Moreover, the transformation is further complicated when the imine has at least one hydrogen in the α-position, because for those substrates tautomerization to the enamine is possible. These isomerization events translate into a loss in the selectivity of the reaction (Figure 1(b),(c)). In addition to these difficulties, most chiral Lewis acids are trapped by the basic nitrogen atoms of the imine substrates and of the reduced product amines, leading to retarded rates of reaction and limiting the potential for the design of catalytic strategies.

8.03.1.2 Alternative Methods to Hydrogenation and Metal-Hydride Reductions

In the search for a general method that meets all the synthetic challenges arising from the preparation of enantioenriched amines from imines, a range of different methods have been developed. Every method has strengths and weaknesses, but its appropriateness to solve the problem has to be evaluated for each particular case to select the most suitable solution for the specific target.

Among the alternative methods to asymmetric hydrogenation amenable today (Figure 2), catalytic transfer hydrogenation is an attractive strategy that was born out of academic interest and gradually evolved toward more practical applications.[4] In this strategy, a proton and a hydride, formally an equivalent of H_2, are abstracted from a donor organic molecule. The main advantage of this strategy is the avoidance of hazardous chemical handling (such as molecular hydrogen or metal hydrides). From the perspective of fundamental research, this means that screening experiments can be done in simple laboratory flasks. From the viewpoint of large scale processing, it permits reactions to be performed in standard rather than specialized costly reactors. Moreover, the use of reducing systems that allow high concentration of the reductant, as an alternative to hydrogen, can also be advantageous to avoid mass transfer limitations associated with the use of a gaseous reactant. When compared to catalytic hydrogenation reactions, the limitations of the transfer hydrogenation processes are usually related to lower turnover numbers. However, transfer hydrogenation procedures are in general operationally simple, the catalysts are less expensive and the final product quality, in terms of trace metal contamination, is higher. The first methods developed for transfer hydrogenation employed formic acid or 2-propanol as hydride sources. Acetone vapor and carbon dioxide have to be distilled off from the mixtures, in the 2-propanol and the formic acid systems respectively, in order to maintain a low rate of the reverse reaction and avoid the subsequent racemization of the product. Although good yields and selectivities have been reported for these methods, degassing limitations associated to scaled-up processes (the rate of gas disengagement is related to the ratio surface area to volume),[5] often result in reduced yields when moving from laboratory experiments to industrial scale.

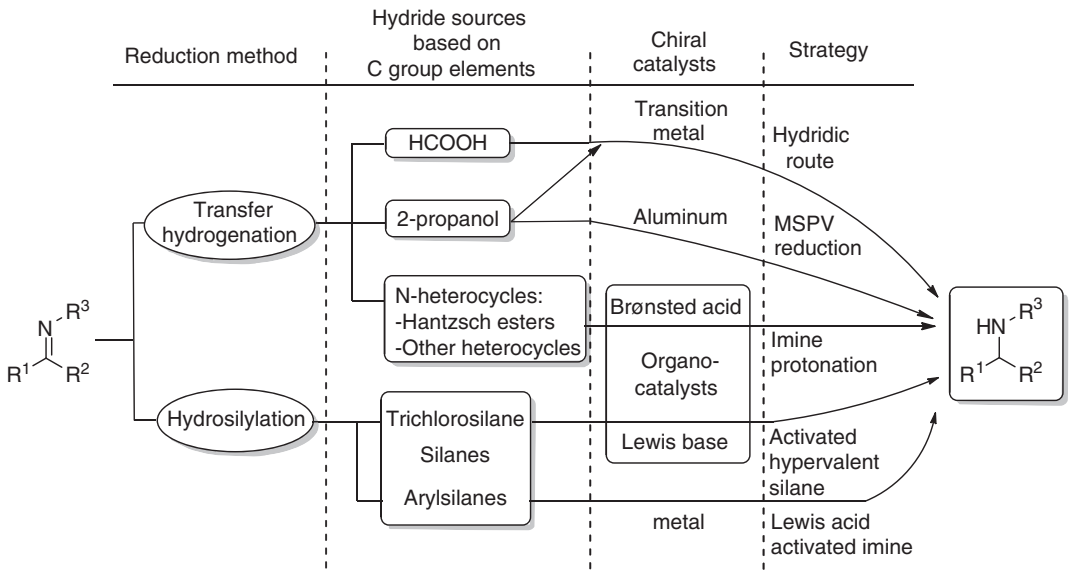


Figure 2 Outline of the reduction methods reviewed in the chapter (MSPV reduction, Meerwein–Schmidt–Ponndorf–Verley reduction).

Very importantly, some transfer hydrogenation strategies are compatible with organocatalysts, which have some inherent advantages: no metal leaching to the product, low cost and toxicity, and relatively inexpensive regeneration. The formidable development of organocatalysis has encouraged the search for novel alternative sources of hydride and provided new directions to asymmetric reductions. In this context, although asymmetric transfer hydrogenation has been extensively applied to the reduction of ketones for the synthesis of optically active secondary alcohols, the asymmetric reduction of imines via this strategy has been much less explored.

Imine groups can also be reduced catalytically to the corresponding amines via an indirect process, involving hydrosilylation followed by acid work-up. This transformation is a well known strategy that can be carried out without isolation of the intermediate organosilane. Transition metal-catalyzed asymmetric hydrosilylation employing inexpensive hydrosilanes such as polymethylhydrosiloxane (PMHS) provides an attractive route to chiral amines. Metal-free activation of trichlorosilane provides alternative mild and selective procedures for imine reduction.

8.03.1.3 Hydride Sources Based on Carbon (and Other Carbon Group Elements)

The traditional hydride sources for reduction protocols are stoichiometric metal hydrides (i.e., $NaBH_4$–CF_3CO_2H, $NaBH(OAc)_3$, $NaB(CN)H_3$, and $BH_3 \cdot Me_2S$) and molecular hydrogen. In addition, the use of silanes as efficient reagents for the reduction of

carbonyls and other C═X functional groups has been largely documented, and the discovery of new catalytic systems which allow the use of cheaper silanes such as PMHS has brought about a rebirth of hydrosilylation in the field of asymmetric reduction. Complementary to these hydride sources, 2-propanol and formic acid are the most used compounds in transfer hydrogenation reactions (see Sections 8.03.2.1 and 8.03.2.2). Additionally, further investigation in the organocatalysis field revealed new alternative classes of compounds that can also serve as formal hydrogen donors. There are two well recognized alternative sources of hydrogen: *N*-heterocycles (Hantzsch esters, employed in the Brønsted acid-catalyzed reduction; see Section 8.03.3.1) and trichlorosilane (employed in the Lewis base-catalyzed hydrosilylation reaction; see Section 8.03.4.2).

8.03.1.3.1 2-Propanol

Primary and secondary alcohols can be used as reducing agents, the generation of a strong C═O bond being the driving force for the loss of hydride (Figure 3(a)). Among the alcohols examined, 2-propanol has several advantages that make it a very convenient hydride source. These characteristics include high stability, nontoxicity, low cost, easy handling, and environmental friendliness. It dissolves many organic compounds, so it can be used as a solvent or cosolvent. In addition, the presence of 2-propanol does not affect the pH of the reaction mixture and therefore it avoids problems related to high acidity observed when formic acid is used as hydrogen donor. During the reduction process, 2-propanol is oxidized to acetone in a reversible reaction. This reversibility is a major problem in asymmetric transfer hydrogenation. Under kinetic control (at low conversions) the stereoselectivity may be high, but as the conversion increases, the rate of the reverse reaction becomes higher and the stereoselectivity drops under thermodynamic control. To shift the equilibrium toward the desired reduced product, two strategies can be followed: (1) operate under high dilution conditions, using 2-propanol as the solvent of the reaction and (2) remove the acetone by continuous distillation. Although acetone is readily removable at reduced pressures, this is an important technical difficulty when employing 2-propanol as a reducing agent, especially when the reaction has to be scaled up.

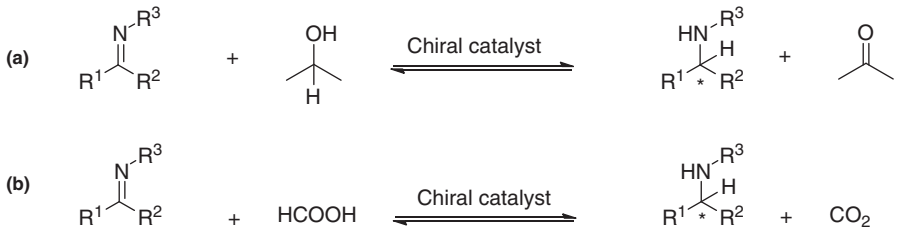


Figure 3 (a) 2-Propanol and (b) formic acid as hydride sources in imine reduction.

8.03.1.3.2 Formic acid

Another inexpensive reducing agent that has been frequently used in transfer hydrogenation processes is formic acid. It is most frequently used as an azeotropic 5:2 mixture of HCOOH and NEt_3. Deprotonated formic acid can decompose to provide a hydride with carbon dioxide evolution (Figure 3(b)). Due to the evolution of CO_2, the process has to be run in an open system. Theoretically, the use of formic acid should overcome the problems detected with 2-propanol related to the reversibility of the reaction. Because CO_2 gas is exergonically released in the process, the reaction should proceed irreversibly, under kinetic control, avoiding the reverse reaction and racemization, thus promoting better stereoselectivity and high conversion. The mixture formic acid/triethylamine is miscible with several solvents and allows operation under high substrate concentration. On the downside, there are several problems related to catalyst stability and inhibition in the presence of formic acid. However, in general nitrogen-containing functional groups are best catalytically reduced with $HCOOH/NEt_3$ than with 2-propanol as hydride donor.

8.03.1.3.3 N-Heterocycles

Hydrogen transfer from dihydroaromatic compounds to unsaturated bonds may occur, the driving force being the stabilization through aromatization of the hydride donor. For example, the hydride donating ability of cyclohexadienes is well documented. Research on heterocycles having such hydrogen-donating ability has attracted considerable attention in the last decade. A large number of studies using a variety of structurally different 1,4-dihydropyridines have been carried out on a variety of unsaturated substrates to develop efficient mimics of the cofactor NAD(P)H, which plays an important role in many biological redox processes (see Section 8.03.3.1.1). 1-Benzyl-1,4-dihydronicotinamide (BNAH), Hantzsch 1,4-dihydropyridine (Hantzsch esters, HEH), 10-methyl-9,10-dihydroacridine ($AcrH_2$) and many other 1,4-dihydropyridine derivatives have been used as NAD(P)H models to probe the mechanistic details of the hydride transfer[6] and to study their potential as alternative reducing agents (Figure 4). Although enzyme-controlled NADH reductions are catalytic in this cofactor, which is regenerated in the process, in general the 1,4-dihydropyridines have been studied as stoichiometric reducing reagents.[7]

In addition to 1,4-dihydropyridine derivatives, five-membered heterocycles such as 1,3-dimethyl-2-phenylbenzimidazoline (DMBI), 2-phenylbenzimidazoline (PBI) and 1-acetyl-2,3-dimethylimidazolidine (ADMI) (Figure 4) have been examined as hydride donors, but little application has been found for their use as selective reducing agents.[8] A remarkable exception is the use of benzothiazoline as reductant in the enantioselective Brønsted acid-catalyzed transfer hydrogenation of ketimines[9] and α-imino esters.[10]

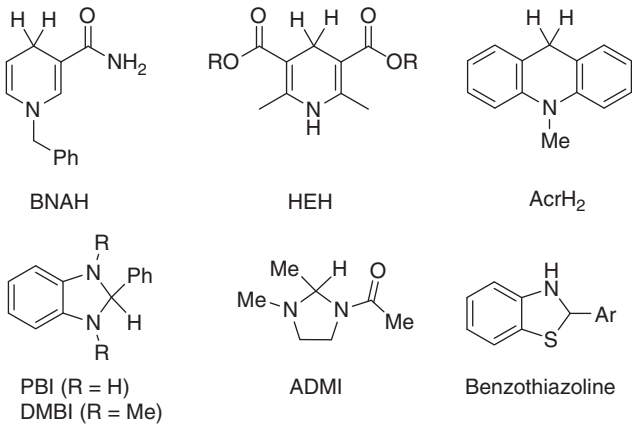


Figure 4 *N*-heterocyclic hydride donors.

Among all the *N*-heterocycles investigated, Hantzsch esters, which are easily prepared from condensation of an aldehyde with *β*-ketoesters, have been the most successful reductants and have been broadly employed in enantioselective organocatalytic[11] or metal-catalyzed[11b,12] transfer hydrogenation reactions of unsaturated bonds. Among the advantages of the Hantzsch ester-mediated reductive processes, the main features are mild and simple reaction conditions, availability and safe handling of the reducing agent, and high compatibility with organocatalysts. In contrast, the major weakness (especially regarding industrial applications) is the necessity of stoichiometric amounts of these reducing reagents along with the problematic removal of the oxidized pyridine byproduct. Moreover, lower yields and reaction rates have been reported for organocatalytic systems, compared to the well established reduction methods using metal catalysts and hydrogen gas. Details of the most synthetically useful protocols for the reduction of imine substrates will be described in Section 8.03.3.1.

8.03.1.3.4 Trichlorosilane

Among silanes, trichlorosilane is the most convenient reducing agent, because it grants access to metal-free organocatalytic processes. This inexpensive and relatively easy-to-handle reducing agent is a liquid material easily prepared in the silicon industry, and it is widely employed as raw material in the polysilicon manufacture on large scale reactions. Although the reduction with trichlorosilane may present some problems with regard to the generation of some halogen waste, it undeniably deserves consideration as an alternative organic reductant and as a viable tool for the synthesis of chiral nonracemic secondary amines. (see Section 8.03.4.1 for a summary of the recent advances in metal-catalyzed reduction of imines using silanes as reductants. (see Section 8.03.4.2 for organocatalytic hydrosilylation methods using trichlorosilane).

8.03.1.4 Activating Groups for the Reduction of Imines

Almost every method that has been developed so far for the reduction of acyclic and exocyclic imines has an unavoidable necessity for an *N*-activated imine. The most frequently used *N*-activating groups include phenyl, substituted phenyl, phosphinoyl, benzyl, or alkoxy group or hydrazones.[13] Unfortunately, these activating groups are often not useful and need to be removed following reduction to access the final useful amine. In the next subsections, a short overview is given of the methods for the preparation and removal of the activating group, as well as the synthetic utility in the context of the reduction methods discussed in this chapter (Figure 5).

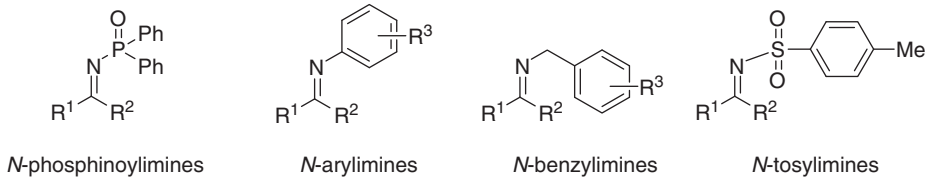


Figure 5 Most common *N*-activated imines.

8.03.1.4.1 N-Phosphinoylimines

Of the imine substrates examined to date, *N*-phosphinoylimines are advantageously reduced with high yields and enantioselectivities. *N*-phosphinoylimines are easily accessible, and acid-catalyzed removal of the phosphinoyl group is simple. In contrast to *N*–H imines (typically obtained as mixtures of *cis*/*trans* stereoisomers) the steric bulk of the phosphinoyl group importantly forces high *anti*-imine diastereoselectivity to occur during imine formation.

One of the benefits offered by this type of imines is the fact that in general, they can be isolated, purified, and stored.[14] The most widely used method to synthesize *N*-phosphinoylimines involves the conversion of a ketone to an oxime (or an aldehyde to an aldoxime), and treatment of the oxime with a tervalent phosphorus reagent. Oximes are easily prepared by refluxing an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride and pyridine. Solvent-free environmentally friendly procedures are also available.[15] Treatment of an oxime with chlorodiphenylphosphine at low temperature ($-45\ ^{\circ}C$) followed by warming to room temperature leads to the *N*-phosphinoylimine (51–75% yield from aryl alkyl ketones).[16] Dialkyl *N*-phosphinoylketimines are rare substrates for this strategy. Nguyen has studied their reduction and has reported yields of 35–60% for their synthesis.[17] Thiophenyl methyl *N*-phosphinoylimines have also been synthesized.[18]

After the *N*-phosphinoylimine is enantioselectively reduced, a nitrogen–phosphorus bond cleavage is required. Deprotection occurs under mild conditions, by treatment with a HCl solution in methanol for a few hours at room temperature or under reflux, thus providing the primary amine in high yield (80–98%) without racemization.[19]

8.03.1.4.2 N-Arylimines

Both transition metal-mediated hydrogenation and organocatalytic transfer hydrogenation (with Hantzsch esters or $HSiCl_3$ as hydride sources) have provided an extensive collection of highly efficient and stereoselective reductive protocols for the reduction of acyclic *N*-arylimines (see Sections 8.03.3 and 8.03.4). Organocatalysts, although more recently developed, have proved remarkably efficient when employed with sterically hindered acyclic dialkyl and aryl alkyl *N*-arylimines, notably expanding the substrate scope of this transformation beyond that of the transition-metal catalysts.

The typical procedure for the preparation of *N*-arylimines is accomplished by heating the corresponding ketone and an aniline derivative (1.0–1.2 equivalents) in anhydrous toluene at reflux or at 80 °C in the presence of $NaHCO_3$ and molecular sieves. In most cases the imines are isolated in good yields.[20] Alternatively, the synthesis can be carried out in the presence of an acid catalyst[21] and a water scavenger, or at reflux in a Dean–Stark apparatus. Condensation of acetophenone and aniline derivatives has been reported to proceed in a few minutes using microwave irradiation in the presence of molecular sieves.[22] *N*-Arylimines have been prepared also at room temperature by addition of $TiCl_4$ to a mixture of the ketone, aniline and Et_3N in dichloromethane.[23] Phenyl methyl *N*-phenylimine has been synthesized in high yield (92%) at room temperature by combination of the ketone, aniline, and 3 Å molecular sieves in benzene for 2 h.[24] Although good yields are generally obtained in the preparation of aryl methyl *N*-arylimines and alkyl methyl *N*-arylimines, lower yields (55–70%) result when the methyl group is replaced by larger alkyl groups. Purification of the *N*-arylimines is commonly performed by crystallization or distillation under reduced pressure and in some cases, by chromatography on deactivated silica.[23,25]

After reduction, the nitrogen–aryl bond oxidative cleavage generally provides the primary amine in good to high yield. Different reagents are applied depending on the aniline derivative employed. Procedures that use cerium(IV) ammonium nitrate,[26] iodobenzene diacetate,[27] periodic acid,[28] or trichloroisocyanuric acid[29] are known.

8.03.1.4.3 N-Benzylimines

N-Benzylimines form another class of substrates investigated in asymmetric reduction protocols. However, although many examples can be found in the literature examining the direct hydrogenation and the metal-catalyzed transfer hydrogenation of phenyl methyl *N*-benzylimine (with moderate to good enantioselectivity), these methods often do not provide an evaluation of the scope for other aryl methyl *N*-benzylimines.[30] In contrast to this, a highly enantioselective organocatalytic method for the reduction of various aryl methyl *N*-benzylimines with trichlorosilane has been reported.[31] The use of aryl alkyl *N*-benzylimines (alkyl other than methyl) is rare.

The preparation of *N*-benzylimines[31–32] can be performed from a ketone and benzylamine (1 equivalent) in toluene at reflux, in the presence of a water scavenger, in reactions often characterized by very long reaction times. The procedure is general for dialkyl- and aryl alkyl *N*-benzylimines (yields 50–80%).

After reduction, cleavage of the benzyl group can be achieved in good yield (80–95%) by mild hydrogenolysis with Pd heterogeneous catalyst.[33] Oxidative debenzylation with cerium(IV) ammonium nitrate in acetonitrile/water is also known to proceed with preservation of the enantiopurity.[34]

8.03.2 Imine Reduction by Transfer Hydrogenation from Formic Acid and 2-Propanol

Metal-catalyzed hydrogen-transfer processes have provided in the last decade a large number of highly selective reactions under mild conditions, using readily available solvents such as 2-propanol or formic acid instead of molecular hydrogen. Although the stereoselective reduction of ketones have been the subject of extensive studies,[35] the application to imine reduction for the synthesis of optically active amines has been less fully developed. There are two types of processes differentiated by their mechanism:[36] (1) the Meerwein–Schmidt–Ponndorf–Verley reduction (MSPV reduction) or direct hydrogen-transfer and (2) reduction through a hydridic route, with the formation of metal-hydride intermediate species.

In MSPV reduction, hydrogen transfer occurs through a six-centered transition state in which a metal coordinates to both substrate and the hydrogen source (generally a secondary alcohol). This mechanism is typically observed for metals that do not readily form hydrides (main group metals). Conversely, with metals such as Ru and Rh, which can easily form hydrides, different mechanisms are involved.

8.03.2.1 Transition Metal-Catalyzed Transfer Hydrogenation

In the early 1990s, Bäckvall et al. reported the first hydride transfer on imine substrates using [$RuCl_2$ (PPh_3)$_3$], K_2CO_3, and 2-propanol as the hydride source.[37] A few years later, Noyori reported the first asymmetric example of transfer hydrogenation on imine substrates with a chiral Ru(II) catalyst, with excellent yields and enantioselectivities and employing a formic acid/triethyl amine mixture as the hydrogen source.[38] Among the examples reported,[39] ruthenium,[20,39f,40] rhodium,[41] iridium,[42] and iron[43] complexes bearing chiral ligands such as diamines, diphosphines, and aminoalcohols[44] have been successfully used for the asymmetric transfer hydrogenation of *N*-alkyl,[38] *N*-benzyl,[38,45] *N*-aryl,[46] *N*-phosphinyl,[47] and *N*-sulfinylimines,[48] as well as in a few examples of endocyclic imines.[38,44,49] Some examples of iridium and ruthenium *N*-heterocyclic carbene[42,50] complexes have also been reported, although the methods are not asymmetric (*see* Volume 8, Chapter 8.02). Because 'Chapter 8.02' in this volume covers in detail the hydrogen-transfer reactions catalyzed by metal-hydride species, a complete evaluation of the mechanisms and progress of this strategy will not be included in the present section. An overview of significant achievements in imine reduction by transition metal-catalyzed transfer hydrogenation employing formic acid or 2-propanol can be found in Figure 6.[43–45,47,49b,c]

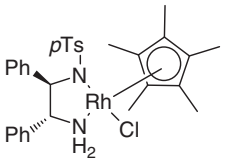
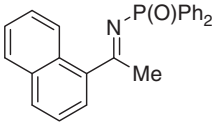
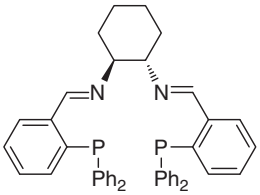
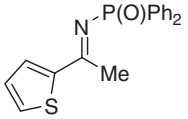
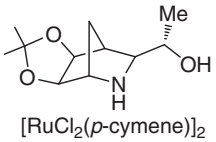
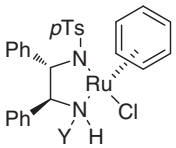
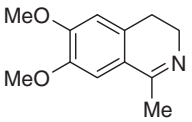
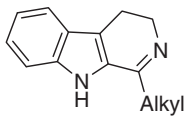
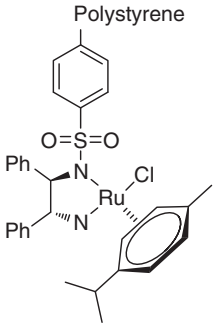
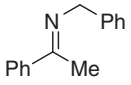
Catalyst (0.1–1 mol%)	Hydride source	Substrate	Solvent, additive temperature time	Product yield (%), *ee* (%)
	HCOOH/Et_3N (5:2)		CH_3CN 25 °C 3 h	(95, 99)
 $(Et_3NH)[Fe_3(CO)_{11}]$	2-Propanol		5 mol% KOH 45 °C 30 min	(68, 94)
 $[RuCl_2(p\text{-cymene})]_2$	2-Propanol		25 °C 10 min	Ar = Ph (80, 70) Ar = 2-Cl-C_6H_4 (83, 56)
 X = H	HCOOH/Et_3N (5:2)		28 °C 4 h	(82, 99)
X = Bn	HCOOH/Et_3N (5:2)		CH_3CN 25 °C 12 h	(70–88, >98)
 Polystyrene	HCOOH/Et_3N (5:2)		CH_2Cl_2 25 °C 48 h	(95, 84)

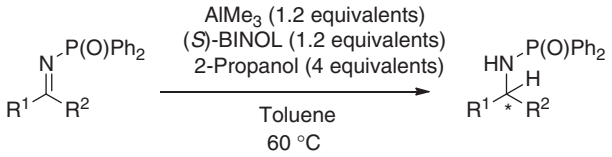
Figure 6 Representative examples of asymmetric transition-metal catalyzed transfer hydrogenation of different classes of imine substrates using formic acid or 2-propanol.

8.03.2.2 MSPV Reduction

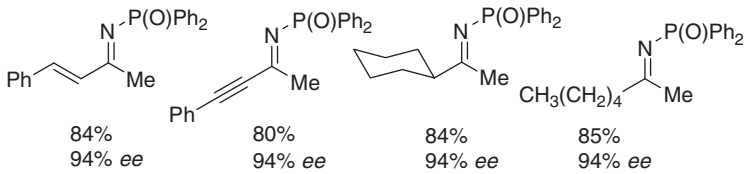
In line with the modern interest in efficient synthetic strategies that avoid the use of transition metals and metal hydrides, researchers have directed their goals toward more environmentally friendly reduction methods, sometimes also reconsidering methods that were disregarded in the past. One emblematic case is the aluminum-based MSPV reduction, which is a highly chemoselective reaction that uses an inexpensive and nontoxic metal and operates under fairly mild conditions. Furthermore, the reducing agent employed is a simple, benign, and low-cost secondary alcohol, most often 2-propanol. This reaction has been studied in more detail for the reduction of ketones,[36c,51] but its application to imine substrates has been inexplicably overlooked regardless of its potential for further asymmetric developments.

Reduction of carbonyls by aluminum ethoxide with ethanol was discovered in 1925 by Meerwein and Schmidt[52] and by Verley[53] independently; in 1926, Ponndorf[54] established an effective method using aluminum isopropoxide with isopropanol. Despite offering remarkably practical advantages, such as high chemoselectivity, easy removal of byproducts, and applicability to both laboratory and industrial scales,[51d] this methodology was largely supplanted in the late 1950s by methods utilizing metal hydrides such as lithium aluminum hydride and sodium borohydride. This was most likely due to the fact that the earliest MSPV protocols often required super-stoichiometric amounts of aluminum alkoxides to obtain satisfactory yields of the reduced product alcohol in reasonable reaction times. It was not until almost a century after its discovery that catalytic variants of this reduction protocol were realized.[51a,55] Equally, the catalytic protocols for the asymmetric MSPV reduction of ketones, avoiding the use of stoichiometric amounts of chiral alcohols as hydride source, were first described at the beginning of the twenty-first century.[51b,51d,56]

Regarding the asymmetric reduction of imines, Nguyen and coworkers have reported a highly enantioselective reduction of *N*-phosphinoyl ketimines based on a chiral complex formed *in situ* from enantiomerically pure 2,2′-dihydroxy-1,1′-binaphthyl (BINOL), $AlMe_3$, and 2-propanol (**Figure 7**).[17] A similar system had been used previously by the same authors for the asymmetric



R^1: Aryl	R^2: Alkyl	Yield (%)	*ee* (%)
Ph	Me	85	96
Ph	Et	85	95
Ph	Pr^n	84	94
Ph	Pr^i	79	96
1-Naphthyl	Me	80	98
2-Naphthyl	Me	84	96



Pentacoordinate aluminum species
in the six-membered transition state model

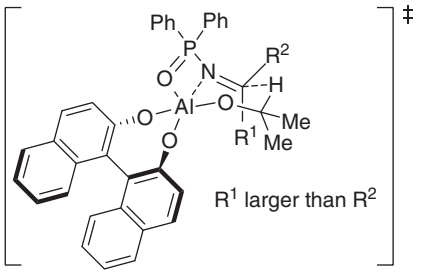


Figure 7 Asymmetric MSPV reduction of imines.

reduction of ketones.[51b] The procedure requires anhydrous conditions and inert atmosphere. A moderate temperature of 60 °C and 80 mM concentration of the imine in toluene is needed to achieve high conversion after 20 h. More diluted reaction mixtures or lower temperatures result in a significant drop in the yield. This reductive transformation can be performed with high yields on a variety of alkyl-aryl ketimines and more significantly, the very challenging α,β-unsaturated imines and dialkyl ketimines are also reduced with high levels of stereocontrol. This system is able to discriminate the subtle differences between nonbranched alkyl groups with very similar steric environment. Thus far, there is no other protocol that can accomplish the asymmetric reduction of acyclic aliphatic imines with this selectivity.

The choice of *N*-phosphinoyl-derived substrates seems to be crucial for this system, because the phosphinoyl moiety acts not only as a protecting group and as an activator, increasing the electrophilic nature of the imino group, but according to the authors, also plays a key role in the stabilization of a highly organized transition state. Based on phosphorus-31 nuclear magnetic resonance spectroscopy and equivalency studies, the hydride transfer is proposed to take place through a six-membered transition state in which the phosphorous atom in the *N*-phosphinoylimine also coordinates to the aluminum center (Figure 7).

Although this protocol still requires stoichiometric amounts of (*S*)-BINOL and $AlMe_3$, the authors provide a straightforward procedure by which the BINOL ligand can be extracted with 93% recovery from a gram-scale imine reduction and reused with analogous results. This method expands the value of the aluminum-based MSPV reduction and it complements the scope of the transition metal-based transfer hydrogenation in asymmetric imine reduction chemistry.

8.03.3 Imine Reduction by Transfer Hydrogenation with *N*-Heterocycles as Hydride Donors

8.03.3.1 Transfer Hydrogenation with Hantzsch Esters

8.03.3.1.1 Bioinspired foundations

In nature, redox processes are mediated by enzyme catalysts, oxidoreductases, assisted by cofactors such as NADH, NADPH, or $FADH_2$ (reduced nicotinamide adenine, adenine phosphate, or flavine dinucleotides respectively) (Figure 8). These essential cofactors serve as hydride sources in the very stereoselective biochemical reactions. Proposed mechanisms[57] for the biological synthesis of α-amino acids involve the protonation of an α-iminoester to generate a highly reactive iminium ion and subsequent hydride transfer from the NADH cofactor.

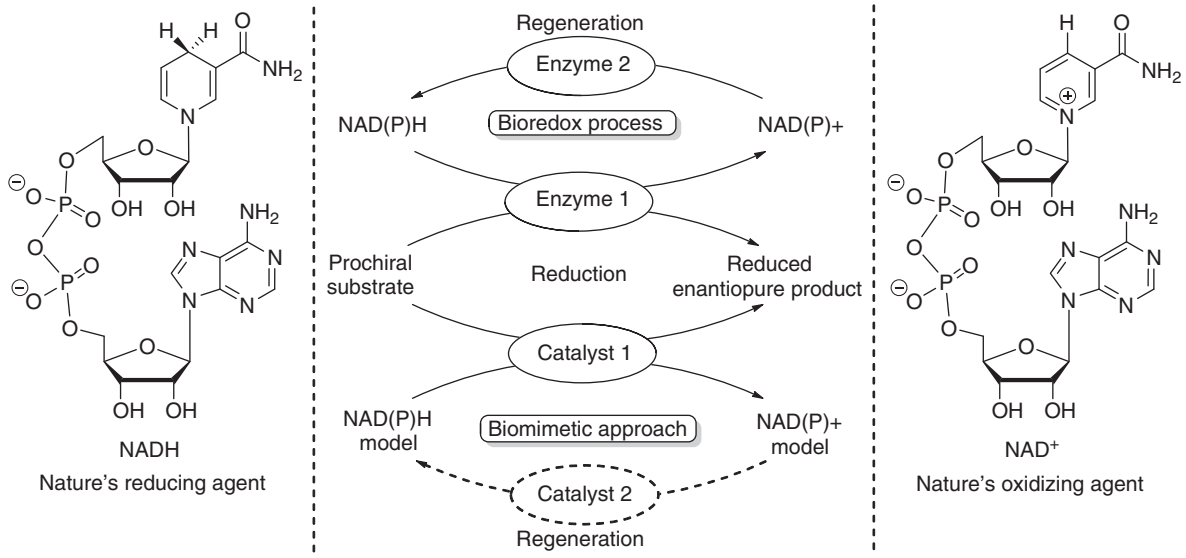


Figure 8 Redox process in nature and biomimetic approach.

Based on this mechanism, several research groups have been pursuing nonenzymatic biomimetic systems capable of inducing high levels of stereocontrol in the reduction of unsaturated compounds. Simplified models of the relevant coenzymes have been synthesized and studied with the aim of developing new useful oxidation or reduction reagents for synthetic purposes.[58] The most useful models described thus far possess a dihydropyridine ring as a common feature, mimicking the nicotinamide fragment in the coenzymes. The source of hydride in such systems is one of the two chemically equivalent hydrogens at the C4 position in the dihydropyridine ring.[59]

The utilization of Hantzsch esters as nicotinamide analogs (**1**–**4**, Figure 9), first reported in 1955 by Mauzerall and Westheimer,[60] has been the most successful bioinspired strategy for asymmetric transfer hydrogenation, allowing enantioselective

reduction of C═C, C═O, and C═N double bonds in the presence of organocatalysts or catalytic amounts of metal complexes.[11b,61] This field has been reviewed extensively.[11c–e,62]

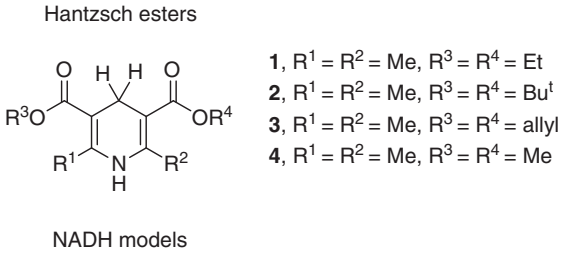


Figure 9 Hantzsch esters.

The first asymmetric example of imine reduction involving the use of an achiral Hantzsch ester was reported by Singh and Batra in 1989. By the use of α-amino acid hydrochlorides as catalysts, prochiral imines were reduced by a Hantzsch ester to afford amines with low enantioselectivities (up to 63% *ee*).[63] Additionally, metal-catalyzed reduction of imines using chiral nicotinamide analogs has been reported.[64] However, it was not until the discovery of the remarkable ability of chiral phosphoric acids to activate imines that other examples of asymmetric transfer hydrogenation of C═N bonds using Hantzsch esters as hydride donors were reported.

8.03.3.1.2 Brønsted acid-catalyzed reduction of imines by transfer hydrogenation from Hantzsch esters

8.03.3.1.2.1 C═N activation via asymmetric Brønsted acid catalysis

Highly recognized electrophilic activators of C═X bonds (X being O, NR, and CR) are metal-centered Lewis-acid catalysts. This activation is based on a decrease of the lowest unoccupied molecular orbital (LUMO) energy of the molecule to promote the attack of a nucleophile on the C═X bond. A huge library of chiral Lewis-acid catalysts has been developed over the years with different metals as the center element. Currently, strategies that circumvent the use of transition metals are highly desirable due to the increasing demand for environmentally friendly and inexpensive methods. If the metal center element is replaced by hydrogen, we enter the Brønsted acid catalysis field.

In contrast to chiral Lewis-acid catalysts, which are normally generated *in situ*, chiral Brønsted acids are used directly and in general they are stable toward moisture and oxygen. Furthermore, they are potentially recoverable and recyclable. On the downside, a weakness of chiral Brønsted acids is that usually higher catalyst loadings are required as compared to metal Lewis-acid-catalyzed processes. Nevertheless, the impressive development of this area has led to increasingly efficient chiral Brønsted acid catalysts and a promising future in industrial applications is foreseen.

Chiral Brønsted acids can activate C═X bonds through two different modes of activation: (1) via single or double hydrogen bonding interactions ('general acid catalysis') and (2) when the Brønsted acid is sufficiently strong, via protonation of the substrate ('specific acid catalysis'). The preference of one mechanism versus the other is determined by factors such as the pK_a of the catalyst in the reaction media, the rate of proton transfer to X (which is different for C═O, C═N, or C═C) and the stability of the reaction intermediates.[65]

Akiyama and Terada[66] revealed the potential of chiral BINOL-derived phosphoric acids as very efficient catalysts in enantioselective Mannich reactions of aldimines. Enantiopure phosphoric acid catalysts have since been applied to a wide range of asymmetric organic transformations.[67] Axially chiral phosphoric Brønsted acid catalysts have a rigid conformation with only one highly acidic proton and have proved effective for the activation of imine substrates. The incorporation of diverse aryl substituents in the positions adjacent to the bi-2-naphthol oxygen atoms (for example see **Figure 11**, compounds **5** and **6**) has a direct influence in the asymmetric induction. Both steric and electronic effects have been observed.

This protonation strategy is a valuable way to increase the reactivity of imines toward reduction. Imines are particularly sensitive to this type of activation because the nitrogen atom is intrinsically basic and because the generated iminium ions are stabilized through charge delocalization. On protonation, the imine substrate becomes a component of a chiral ion pair. Solvent effects are particularly important in this strategy, because effective chirality transfer requires that the chiral counteranion stays in close proximity, as a stereochemically well-defined ion pair. Furthermore, for this method to succeed, an efficient reducing agent is required (formally a source of hydride) that will not react as a base in the presence of an acid. As will be described in detail in the following Sections 8.03.3.1.2.2–8.03.3.1.2.7, the use of Brønsted acid organocatalysts in combination with dihydropyridines, such as Hantzsch esters, has proved to be a useful strategy to exploit the LUMO-lowering activation concept in biomimetic metal-free hydrogenations.

8.03.3.1.2.2 Reduction of acyclic imines

In 2005, Rueping et al. reported that diphenyl phosphate (DPP) and various other relatively strong Brønsted acids, i.e., camphor sulfonic acid (CSA) or trifluoroacetic acid (TFA) (**Figure 10**), were able to catalyze the metal-free hydrogen transfer of imines with Hantzsch dihydropyridine **1**, to afford various amines under mild reaction conditions.[68] This method was extended to the

asymmetric version, using a chiral phosphoric acid as an efficient Brønsted acid catalyst for the asymmetric transfer hydrogenation of *N*-aryl ketimines.[11a] In the presence of 20 mol% of **5**, various phenyl- or *p*-methoxyphenyl-protected aryl methyl ketimines underwent transfer hydrogenation with Hantzsch ester **1** in benzene at 60 °C to give the desired optically active amines in 46–91% yield (after 3 days of reaction) with moderate enantioselectivity (68–84% *ee*) (Figure 11). Good to excellent yields (80–98%) and enantioselectivities (80–93% *ee*) have been obtained in the reduction of *p*-methoxyphenyl-protected (*N*-PMP) aryl methyl ketimines, by utilizing 1 mol% of the more sterically hindered phosphoric acid **6** in the presence of Hantzsch ester **1** in toluene at 35 °C (reaction time 42–71 h).[39e] More importantly, 80% yield and 90% *ee* were achieved for an aliphatic ketimine, the isopropyl methyl ketimine.

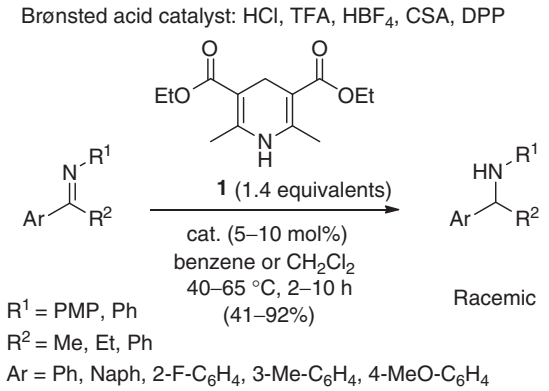


Figure 10 Brønsted acid-catalyzed transfer hydrogenation of imines from Hantzsch esters.

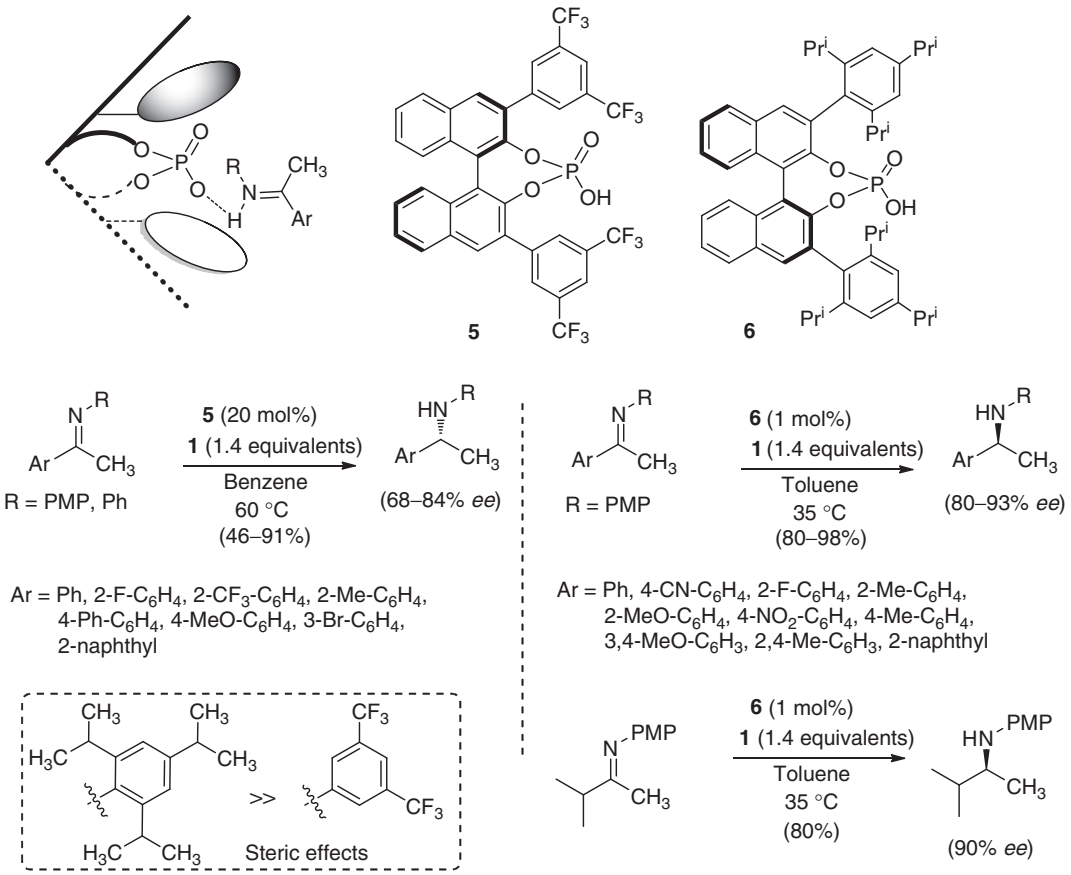


Figure 11 First examples of asymmetric Brønsted acid-catalyzed reduction of imines with Hantzsch esters.

In the accepted mechanism, activation of the imine is proposed to occur via protonation, generating an iminium ion strongly bound to the chiral catalyst counterion. It is supposed that the substituents on the 3,3′- positions of the 1,1′-binaphthyl system are not coplanar with the naphthyl groups and can effectively shield the phosphate region, leading to efficient asymmetric induction. In this iminium ion-catalyst interaction, the largest substituent of the imine would be located toward the less hindered sites of the catalyst. A model has been proposed in which there is an additional interaction by the Hantzsch ester complexation to the other phosphoric acid oxygen of the catalyst.[69] Hydride transfer from the Hantzsch ester to the activated imine yields a chiral enantio-enriched amine and a pyridinium ion. Proton transfer from the pyridinium ion to the chiral phosphate releases a Hantzsch pyridine and regenerates the catalyst (**Figure 12**).

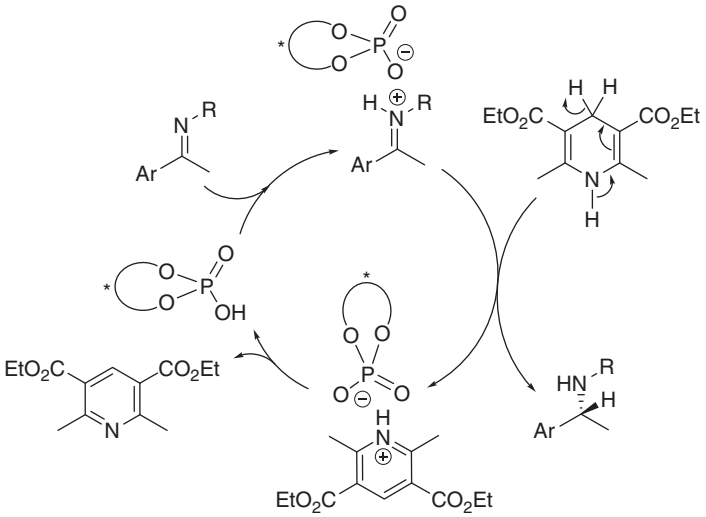
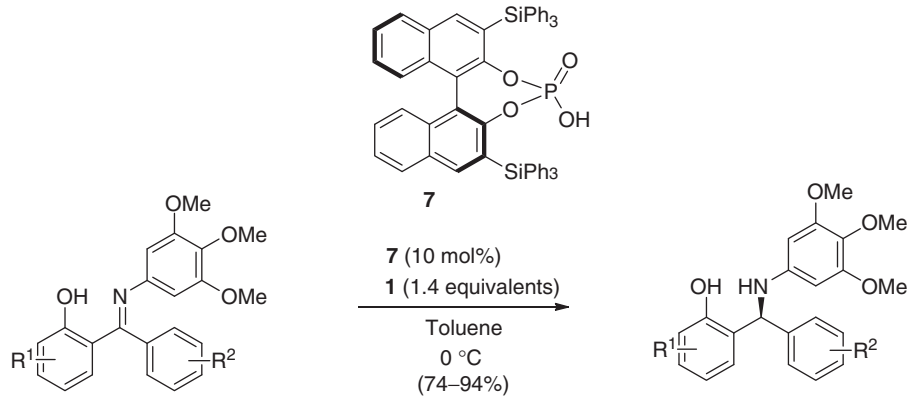


Figure 12 Accepted mechanism for the reduction of imines with Hantzsch esters catalyzed by phosphoric acids.

The asymmetric reduction of *N*-protected diaryl ketimines using Hantzsch dimethyl ester has been reported.[29] The reduction using BINOL-derived phosphoric acid **7** as catalyst was explored with diarylimine substrates bearing different *N*-aryl groups, showing a large influence of the identity of the protecting group on the enantioselectivity of the process (**Figure 13**). Although the imines derived from *ortho*-substituted anilines afforded very low enantioselectivities and the *para*-substituents did not appear to have an effect on the selectivity, the presence of *meta*-substituents greatly influenced the stereoselectivity of the reaction. The reduction of differently substituted *N*-(3,4,5-trimethoxyphenyl)-*ortho*-hydroxybenzophenone ketimines proceeded with good yields (74–94%) and enantioselectivities (80–91%) in toluene at 0 °C for 16 h, with a broad scope of substrates with substitution in different positions of both aromatic rings by electron-withdrawing and electron-donating groups. The presence of the *ortho*-hydroxyl group is critical to achieve reasonable reaction times and stereo-differentiate the two equally hindered aryl groups. The cleavage of the trimethoxyphenyl group in the reduced amines was achieved using trichloroisocyanuric acid in acidic



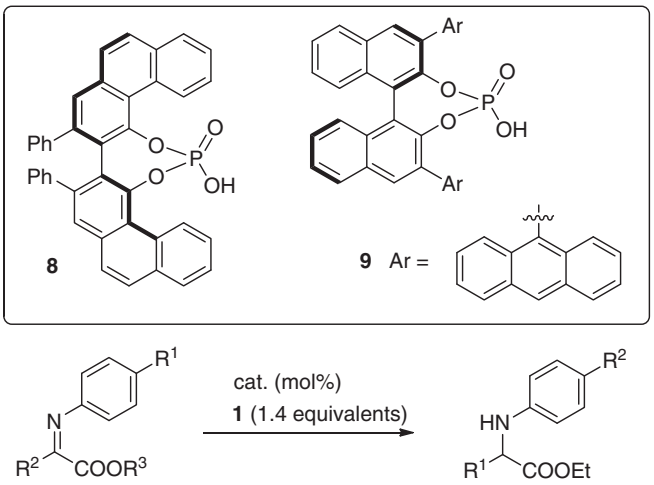
R^1 = H; R^2 = H, 4′-Me, 4′-Ph, 4′-Br, 4′-NO_2, 3′-Me, 3′-MeO, 3′-NO_2

R^1 = 5-Me, 5-OMe, 4-Me: R^2 = H, 4′-Cl

Figure 13 Asymmetric Brønsted acid-catalyzed reduction of diaryl *N*-aryl ketimines with Hantzsch esters.

acetonitrile/water at room temperature. The aminophenol was obtained in moderate yield (67%) preserving the enantiomeric purity. The removal of the protecting group was ineffective using cerium ammonium nitrate as oxidant.

A different type of imine substrate has been employed by Antilla and coworkers[70] for the direct enantioselective synthesis of protected α-amino acids using the Brønsted acid-catalyzed hydride reduction strategy. Using a VAPOL-derived phosphoric acid **8**, (VAPOL: 2,2′-Diphenyl-(4-biphenanthrol) a phosphoric acid bearing vaulted biaryl ligands, readily available α-alkyl and α-aryl substituted imino esters could be efficiently (85–98% yield) and selectively (94–99% *ee*) reduced to the related amines employing stoichiometric amounts of **1** (Figure 14). The use of nonpolar and noncoordinating solvents such as benzene and toluene ensured quantitative conversions after 20 h of reaction at 50 °C. The method was general for *N*-aryl imino esters derived from aromatic and aliphatic α-keto esters and substitution with electron-withdrawing and electron-donating groups in *para* position on the aryl in the imine carbon was well tolerated. Analogous substrates were reduced using a similar approach by You et al.[71] using the BINOL-derived phosphoric acid **9** bearing as substituents in the 3,3′ positions the large anthracenyl groups. The reactions, performed in toluene at 60 °C with 10 mol% of catalyst **9**, effectively reduced *N*-PMP protected aromatic α-imino esters in 48 h affording the corresponding *N*-PMP protected α-amino acids with good yield (46–95%) and high enantioselectivity (84–98% *ee*). Unlike Antilla's reduction of α-imino esters, You reports lower efficiency for alkyl substituted substrates. However, additional types of imines such as heteroaromatic imino esters (thienyl-derived substrate) and α-imino carboxamides were successfully reduced in



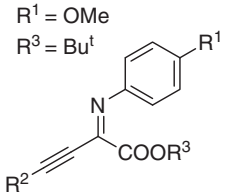
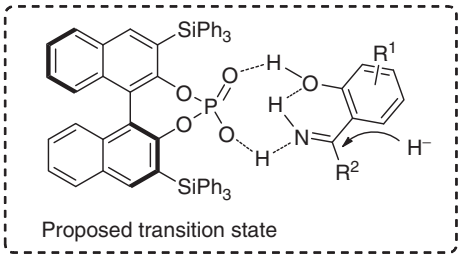
Catalyst	Temperature / time solvent (yield)	Imino ester substrates		Product *ee* (%)
8 10 mol%	50 °C, 20 h toluene (88–98%)	R^1 = OMe, H; R^3 = Et R^2 = Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, 3,5-F-C_6H_3, Me, $(CH_2)_5CH_3$, CH_2CH_2Ph		96–99
9 10 mol%	60 °C, 48 h toluene (78–88%)	R^1 = OMe; R^2 = Ph; R^3 = Et		92
			Me	33
			NH-Bu^t	96
	(82–94%)	R^1 = OMe; R^3 = Pr^i R^2 = Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 2-naphthyl		96–98
	(46–78%)	R^1 = OMe; R^3 = Pr^i R^2 = cyclohexyl, thienyl		84–88
9 1 mol%	r.t., 24 h Et_2O (27–64%)	R^1 = OMe R^3 = Bu^t 	R^2 = Ph	94
			4-Me-C_6H_4	95
			3-Me-C_6H_4	93
			4-Cl-C_6H_4	96
			3-F-C_6H_4	95
			1-naphthyl	83

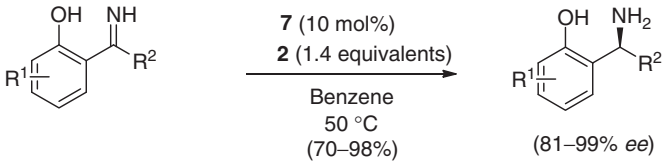
Figure 14 Asymmetric Brønsted acid-catalyzed reduction of *N*-aryl α-amino acids with Hantzsch esters.

the reaction conditions. In addition, the authors were able to perform a gram-scale reaction in which only 0.1 mol% of catalyst was needed to perform the asymmetric transfer hydrogenation with high stereocontrol.

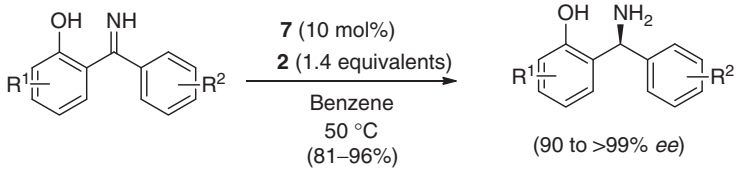
This method can be applied to the asymmetric transfer hydrogenation of *N*-PMP-substituted β,γ-alkynyl-α-imino esters[72] using 1 mol% of the chiral acid **9** and Hantzsch ester **1**, affording *trans* alkenyl α-amino esters with high enantioselectivity (83–96% *ee*) although with moderate yields (27–64%) (**Figure 14**). Both the carbon–carbon triple bond and the carbon–nitrogen double bond were reduced under these reaction conditions and mechanistic studies showed that the reduction of the alkyne occurs faster than that of the imine. Further reduction of the carbon–carbon double bond in the product does not take place under the reaction conditions.

The transfer hydrogenation of C═N bond described above are all limited to *N*-protected substrates. To prepare the truly useful enantiopure amines, the deprotection of the corresponding amines (see Section 8.03.1.4) requires an additional step accompanied by a loss in overall yield and lower atom economy, and it might sometimes require harsh conditions incompatible with the stability of the substrate. This limitation is overcome[3] in the transfer hydrogenation of unprotected imines employing phosphoric acids as catalysts. *Ortho*-Hydroxyaryl alkyl[3a] and *ortho*-hydroxybenzophenone *N*–H ketimines[3b] were reduced to the corresponding primary amines by Hantzsch di-*tert*-butyl ester **2** and 10 mol% of catalyst **7** in benzene at 50 °C (**Figure 15**). Substituents in the aromatic rings were tolerated independently of their electronic nature in both types of substrates, affording after 72 h of reaction, the corresponding amines with high yields and enantioselectivities. The authors propose that both the imine and the hydroxyl groups form hydrogen bonds with the phosphoric acid catalyst in the transition state.





R^1 = H, 3-Me, 4-F, 4-Me, 4-OMe, 4-NO_2, 5-Me, 5-Bu^t, 5-Br, 5-OMe, 5-NO_2, 6-OEt
R^2 = Me, Et, Pr^n, *n*-hexyl, Pr^i



R^1 = H, 3-Me, 4-Me, 4-Ph, 4-F, 5-Me, 5-Ph, 5-Br, 5-OMe, 5-NO_2, 5-Bz
R^2 = H, 4′-Me, 4′-Ph, 4′-Cl, 4′-OPh, 4′-NO_2, 4′-CO_2Me, 3′-Me, 3′-OMe, 3′-NO_2, 2-F, 3′,4′-$(CH)_4$

Figure 15 Asymmetric Brønsted acid-catalyzed reduction of *N*–H ketimines with Hantzsch esters.

8.03.3.1.2.3 Reduction of endocyclic imines

N-heteroaromatic compounds and related endocyclic imines are very challenging substrates, which have been also successfully reduced stereoselectively by Brønsted acid-catalyzed transfer hydrogenation with Hantzsch esters. This excellent behavior toward endocyclic imines importantly complements the metal catalyzed approaches. Even though a variety of chiral Rh, Ru, and Ir complexes have demonstrated to be highly efficient catalysts in the enantioselective transfer hydrogenation of olefins, ketones, and imines with 2-propanol or formic acid/triethyl amine, only a few examples[38,44,49] have been reported for the asymmetric reduction of *N*-heteroaromatic compounds and endocyclic imines.

Building their strategy on the Hantzsch ester-mediated hydrogenation of alkenes and imines, Rueping et al. led the research on the metal-free catalytic transfer hydrogenation of nitrogen heterocycles, by showing that 9-phenanthryl-substituted phosphoric acid **10** could effectively reduce quinolines.[73] In the reduction of 2-substituted quinolines, a proposed cascade-hydrogenation process including 1,4-hydride addition, isomerization, and 1,2-hydride addition afforded tetrahydroquinolines (in general, over 90% yield) with excellent enantioselectivities (88 to >99% *ee*). The reaction was performed in nonpolar solvents such as benzene, at 60 °C and in the presence of 2 mol% of **10** using Hantzsch ester **1** as the hydride source, with reaction times between 12 and 60 h (Figure 16). The mild reaction conditions and relatively low catalyst loading make this strategy valuable for the preparation of optically active tetrahydroquinolines. In fact, several biologically important tetrahydroquinoline alkaloids such as (+)-galipinine (91% *ee*) and (+)-cuspareine (90% *ee*) were synthesized applying this method from 2-methylquinoline, by alkylation followed by reduction and subsequent N-methylation.

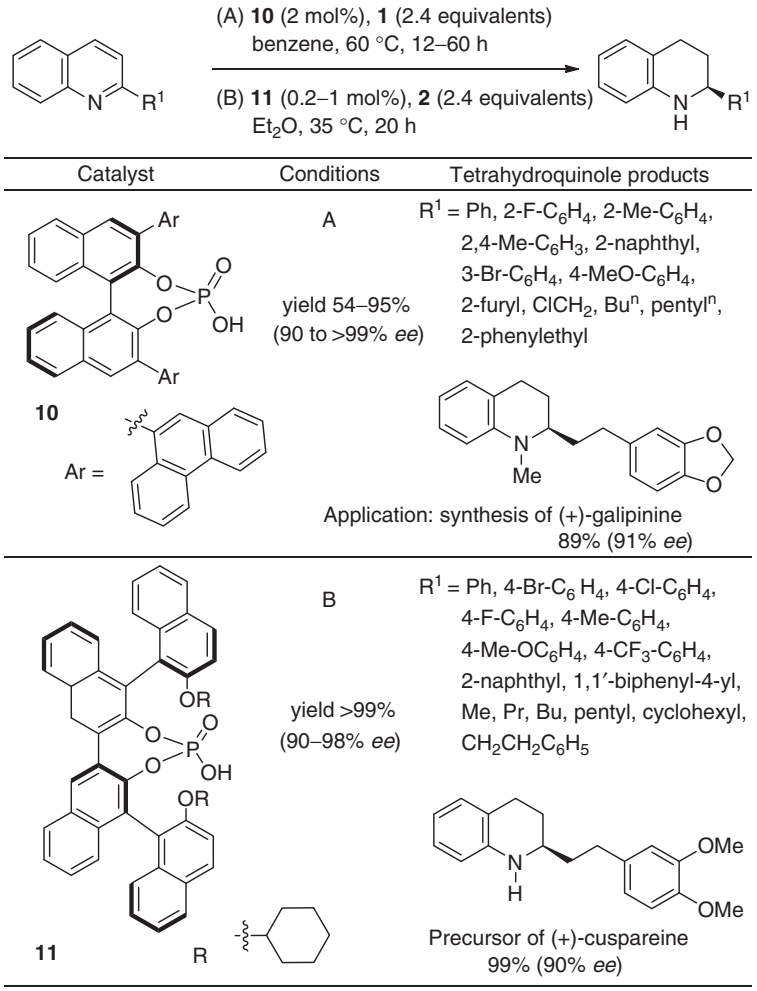


Figure 16 Asymmetric Brønsted acid-catalyzed reduction of 2-substituted quinolines with Hantzsch esters.

The asymmetric reduction of 2-substituted quinolines was also accomplished using double axially chiral phosphoric acids.[74] The substituents at the 3,3′-positions of BINOL are crucial for achieving high selectivity. The use of 3,3′-unsubstituted binol phosphate as a catalyst always conferred low or no enantioselectivity. The larger chiral pocket formed by **11** (Figure 16) proved to be beneficial for asymmetric induction in the transfer hydrogenation of 2-substituted quinolines in comparison to the chiral phosphoric acids based on the simple 3,3′-substituted BINOL scaffold. A broad collection of 2-aryl- and 2-alkyl-tetrahydroquinoline derivatives was prepared with excellent enantioselectivities (88–98% *ee*) and yields (up to 99%) using low catalyst loadings (0.2–1 mol %) and relatively short reaction times (20 h). Although the reaction conditions were optimized in diethyl ether at 35 °C, the method appears to tolerate diverse solvents (CH_2Cl_2, THF, benzene, and toluene) with no substantial variations in the yield and little effect on the enantioselectivity.

The reduction of 3-substituted quinolines was achieved by transfer hydrogenation and a cascade reaction in which a Brønsted acid-catalyzed protonation event is proposed to be the stereodetermining step.[75] Rueping et al. employed the sterically crowded

3,3-triphenylsilylsubstituted H_8-BINOL-phosphate **12** as a catalyst (5 mol%) in benzene in the presence of 2.4 equivalents of the allyl ester dihydropyridine **3** (Figure 17). Intriguingly, better enantiocontrol was attained at higher (60–70 °C) rather than lower (35–50 °C) temperatures. This method was suitable for the preparation of the fluoroquinolone antibiotic flumequine.[76]

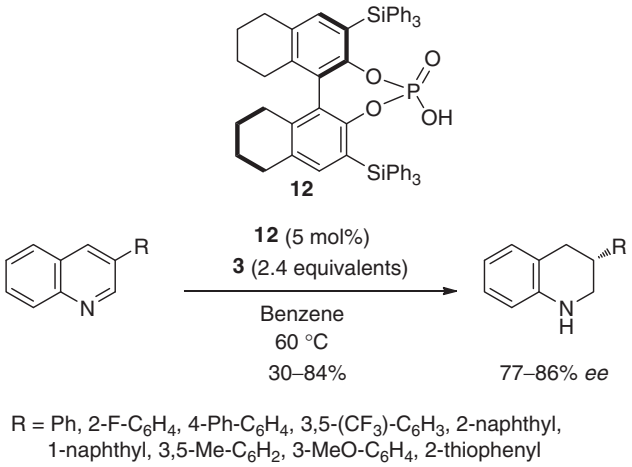


Figure 17 Asymmetric Brønsted acid-catalyzed reduction of 3-substituted quinolines with Hantzsch esters.

2,3-Disubstituted quinolines were also hydrogenated employing the methods of both Rueping[75] and Du[74] (Figure 18). Although better enantioselectivities were achieved in the reduction with H_8-BINOL-phosphate **12**, the double axially chiral phosphoric acid **11** produced higher levels of diastereoselectivity. Intriguingly, different configurations of the major isomer were obtained whether the substituents in the 2 and 3 positions were or were not connected through a ring.

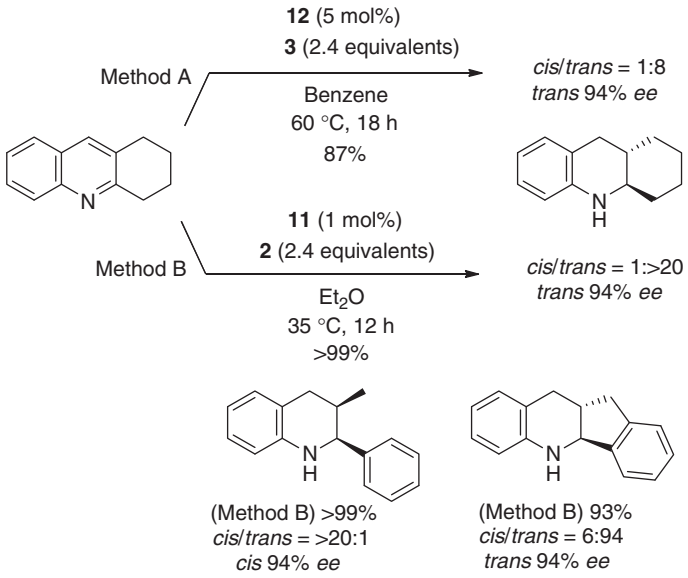


Figure 18 Asymmetric Brønsted acid-catalyzed reduction of 2,3-substituted quinolines with Hantzsch esters.

Enantioselective reduction of 4-substituted quinolines can be achieved using phosphoric acid **12**. The bulky triphenysilyl substituents in this octahydro-BINOL-derived catalyst were advantageous as well for stereoselectivity at the prochiral center in position 4, which is quite distant from the protonated nitrogen. Good yields (67–90%) and moderate enantioselectivities (72–83% *ee*) were observed for various 4-substituted alkyl- and aryl-tetrahydroquinolines (Figure 19).[77] Substrates containing a chlorine substituent were reduced more efficiently (81–98%) and with higher enantioselectivities (75–92% *ee*). These improved results were attributed to an enhancement of the electrophilic character of the imine by the electron-withdrawing chlorine.

The reduced heterocycles obtained from other heterocyclic substrates such as 3*H*-indoles, benzo-fused thiazines, quinoxazinones, quinoxalinones, oxazines, and pyridine derivatives are of interest as building blocks in the synthesis of many

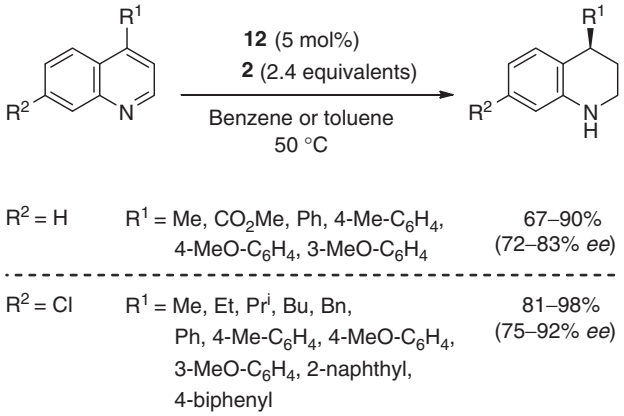


Figure 19 Asymmetric Brønsted acid-catalyzed reduction of 4-substituted quinolines with Hantzsch esters.

pharmaceuticals. The highly enantioselective synthesis of 2-aryl substituted indolines (97 to >99% *ee*) has been achieved[78] with 1 mol% of catalyst **9** and Hantzsch ester **1** in toluene at room temperature in excellent yields (84–99%) after 16 h of reaction. The same methodology provided modest yields (54–87%) and selectivities (70–90% *ee*) for the 2-alkyl substituted substrates (Figure 20).

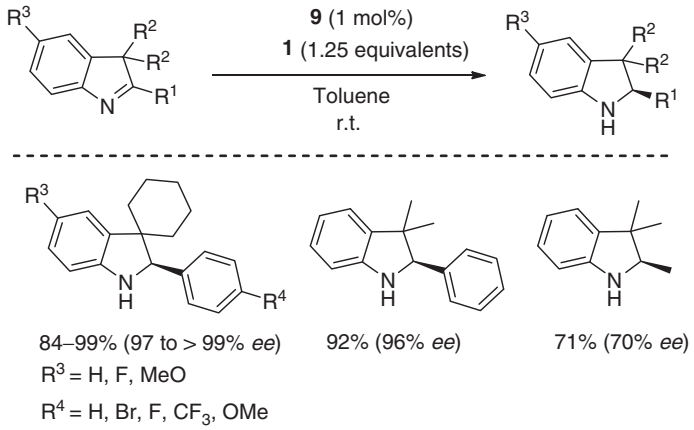


Figure 20 Asymmetric Brønsted acid-catalyzed reduction of 3-*H*-indoles with Hantzsch esters.

The asymmetric synthesis of tetrahydroquinoxalines and dihydroquinoxalinones[61d] was accomplished using catalyst **9** (5 mol%) with 2.4 equivalents of Hantzsch ester **1** as reducing agent. In the case of quinoxalines (Figure 21, X═NH) the reduction was carried out in chloroform at 35 °C, achieving excellent yields after 24 h of reaction (73–98%) and good enantioselectivities (80–98% *ee*). In the case of quinoxalinones (Figure 22, X═NH), the reactions were performed in THF at 50 °C attaining at similar reaction times lower yields (42–75%) but excellent enantioselection (up to 98% *ee*). With remarkably low (especially for organocatalysis) amounts of BINOL-derived catalyst **10** (0.1–1 mol%) the asymmetric reduction of benzoxazines, benzothiazines, and benzoxazinones was performed in $CHCl_3$ at room temperature.[79] Dihydrobenzoxazines were prepared in excellent yields (92–95%) and with excellent levels of enantiomeric purity (98 to >99% *ee*) (Figure 21, X═O). Benzoxazinones (Figure 22, X═O) underwent transfer hydrogenation with Hantzsch ester **1** to afford the corresponding reduced products with high performance (55–92% yield, 96 to >99% *ee*). The enantioselective hydrogenation of benzothiazines (50–87% yield, 93 to >99% *ee*) (Figure 21, X═S) makes evident one of the advantages of this organocatalytic approach compared to most late-transition metal catalysts, which are poisoned by sulfur-containing substrates.

The asymmetric reduction of bispyridyl systems has been investigated[80] using a Hantzsch dihydropyridine in the presence of BINOL-derived phosphoric acid catalysts **9** or **10**. 2- and 2,9-substituted 1,10-phenanthroline substrates bearing unbranched or nitrogen-containing alkyl groups in the 2- or 2,9-positions afforded, by reduction of the two pyridyl rings, chiral octahydrophenanthrolines in moderate yield (40–88%) and good enantioselectivity (78–99% *ee*). The method is not applicable to substrates with larger substituents (Figure 23).

The asymmetric reduction of substituted pyridine derivatives is a particularly challenging transformation that gives access to chiral piperidines, a core structural motif in many natural alkaloids. The method using 5 mol% of the anthracenyl-substituted binol phosphate catalyst **9** gave access to differently substituted hexahydroquinolinones.[81] To date there are no metal-catalyzed

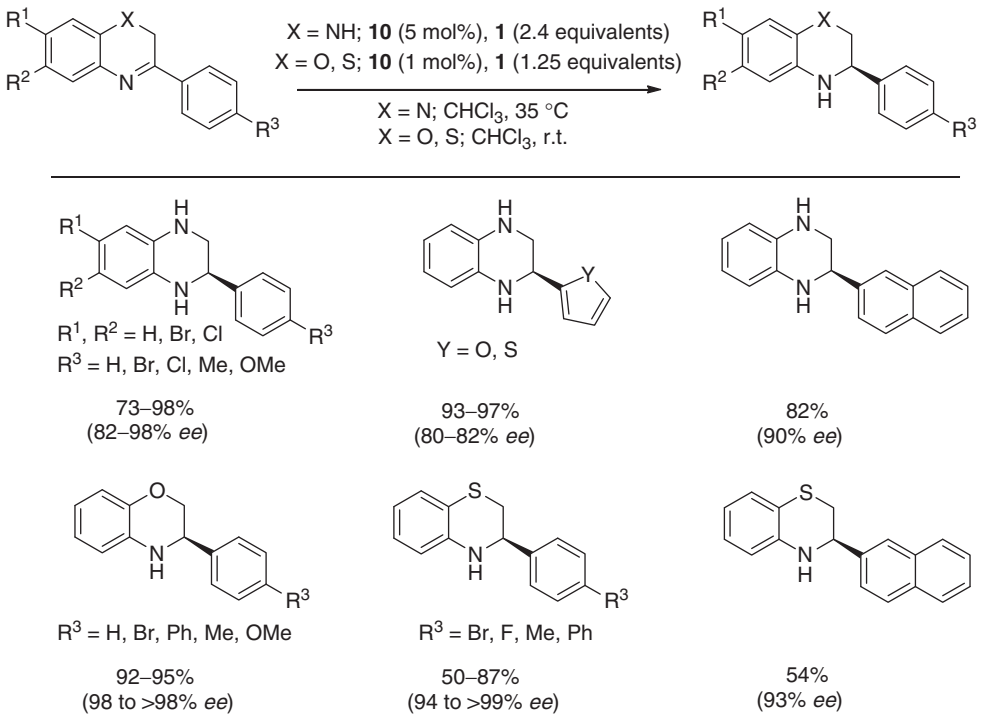


Figure 21 Asymmetric Brønsted acid-catalyzed reduction of quinoxalines, benzoxazines, and benzothiazines with Hantzsch esters.

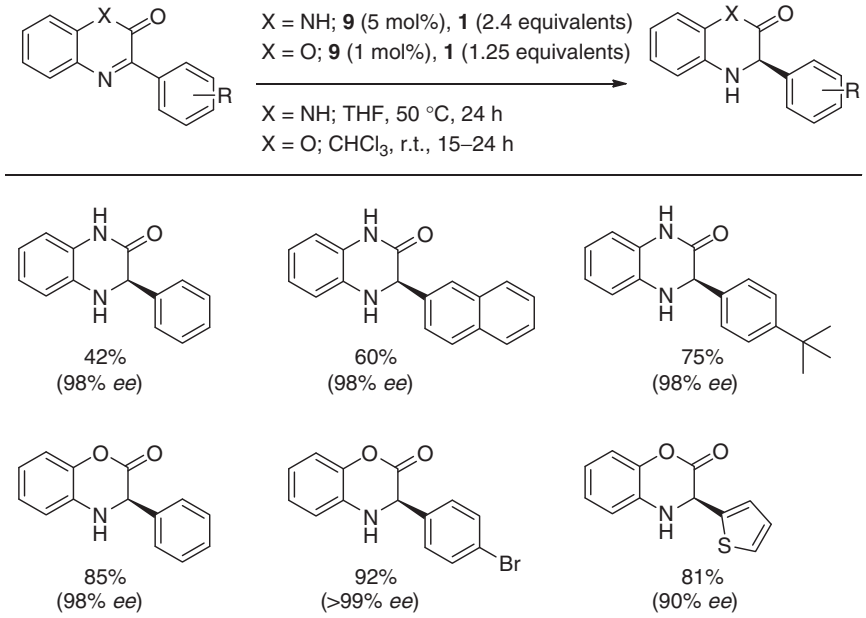


Figure 22 Asymmetric Brønsted acid-catalyzed reduction of quinoxalinones and benzoxazinones with Hantzsch esters.

methods to afford these compounds from pyridine reduction. Modest yields (47–84%) were obtained after 30–36 h of reactions performed in benzene at 50 °C (Figure 24). Other solvents such as toluene and dibutyl ether were compatible as well affording similar enantioselection. The application of diethyl ester **1** as the hydride source resulted in higher selectivity (84–92% *ee*) compared to other Hantzsch esters.

Seven-membered cyclic imines have been also subjected to asymmetric transfer hydrogenation. The asymmetric synthesis of benzodiazepinones by asymmetric reduction[82] has been performed employing catalyst **13** (5 mol%) and Hantzsch ester **3** (2 equivalents) in methyl *tert*-butyl ether (MTBE) as solvent at 50 °C (Figure 25). To afford complete conversion of the substrates,

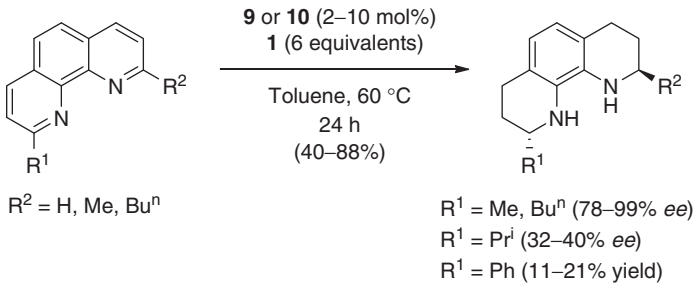


Figure 23 Asymmetric Brønsted acid-catalyzed reduction of phenanthrolines with Hantzsch esters.

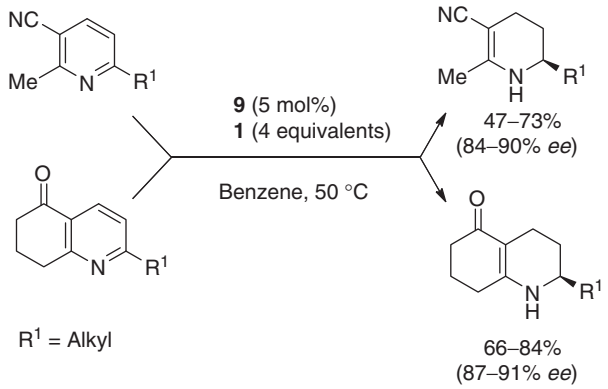
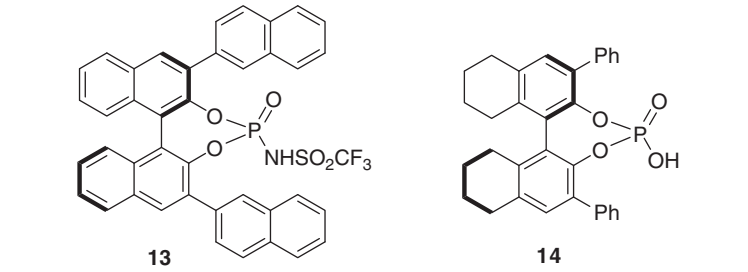


Figure 24 Asymmetric Brønsted acid-catalyzed reduction of pyridines with Hantzsch esters.

microwave irradiation was necessary. The reaction was general for substrates with different substitution in the benzene ring and phenyl, including halogen substituents and nitro functional groups, affording the benzodiazepinones in moderate to high yields (51–95%) and good enantioselectivities (83–99% *ee*). Dynamic kinetic hydrogenation of 2-methyl-2,4-diaryl-2,3-dihydrobenzo[*b*][1,4]diazepines catalyzed by H_8-BINOL derived phosphoric acid **14** (10 mol%) has been reported.[83] Allyl Hantzsch ester **3** appeared to be the optimal hydride source for this process, which was performed in $CHCl_3$ at $-10\ ^{\circ}C$ for a period of 2–5.5 days. Generally, the electronic nature of the aryl substituents did not affect the enantioselectivity, which was more influenced by the substituent's position. However, electronically poor aryl substituents were favorable to diastereoselectivity. In all cases, higher enantioselectivities were observed in the minor diastereomers. This protocol provides access to optically active 1,3-diamines bearing a quaternary stereocenter with good yields (63–97%), and moderate diastereomeric ratios (*syn–anti* 2/1–8/1) and enantioselectivities for the major (73–86% *ee*) and minor (75–94% *ee*) isomers (Figure 25).

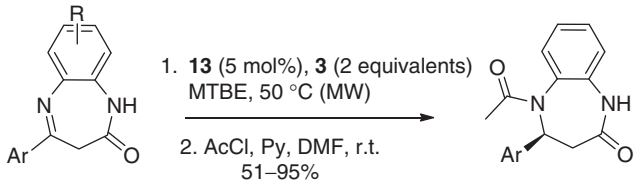
8.03.3.1.2.4 Brønsted acid catalysis in aqueous media

All the previously mentioned protocols based on Brønsted acid catalysis were performed in dry nonpolar aprotic, aromatic or chlorinated solvents. Such solvents have been used to mimic the hydrophobic effects present in the aqueous enzymatic processes. Water was avoided in the biomimetic systems, because it was assumed that the strong hydrogen-bond donor molecules of water would compete with the catalyst preventing the formation of the required chiral ion pair, resulting in a nonstereo discriminating activation of the substrate and consequently reduced selectivity. However, the use of water as solvent is highly desirable for economic and environmental reasons. A highly enantioselective Brønsted acid-catalyzed reduction protocol in aqueous solution has been described, making an unprecedented advance in this area.[84] The concept of hydrophobic hydration was used to explain the success of this approach. Molecules of water tend to aggregate minimizing their surface of contact. When there are nonpolar substances in water that have a tendency to form complexes, the proximate molecules of water reorient to assemble a net around this complex, thus causing an effect of increased concentration that can accelerate the reaction rate. To be able to exploit this effect, without weakening the chiral ion pair, two strategies were followed. First, increasing the nonpolar character of the ion-pair was accomplished using the sterically demanding catalyst **6**; and second, enhancing the ionic strength, hence the polarity of the media, was achieved by 'salting-out' with an inorganic salt such as NaCl that decreases the solubility of the chiral ion pair. Reactions were performed in brine at 50 °C in the presence of 2.4 equivalents of Hantzsch ester **2** and 2 mol% of catalyst **6**. The method provides access to 2-substituted tetrahydroquinolines or cyclic amines in good yields (60–96%) and high selectivity (83–97% *ee*) (Figure 26).



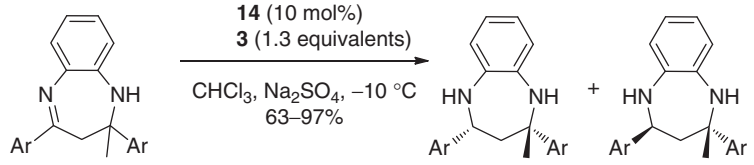
13 **14**

Asymmetric reduction by transfer hydrogenation



Ar = Ph, 4-NO_2-C_6H_4, 2-F-C_6H_4, 3,4-MeO-C_6H_3 (83–99% *ee*)
R = H, Me, Cl, Br

Dynamic kinetic asymmetric transfer hydrogenation

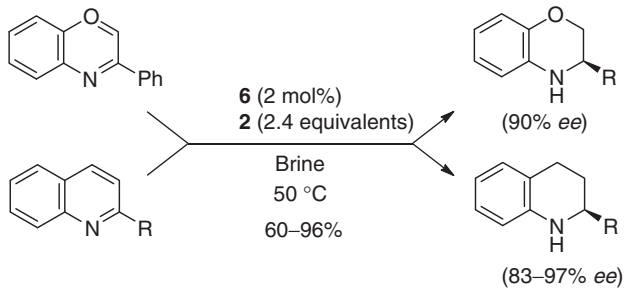


Racemic *syn* *anti*

Ar = 4-CF_3-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-Me-C_6H_4, 4-Ph-C_6H_4, 3-MeO-C_6H_4, 3-F-C_6H_4, 3-B-rC_6H_4, 2-naphthyl

syn/anti 2/1–8/1
syn (63–86% *ee*)
anti (81–94% *ee*)

Figure 25 Asymmetric Brønsted acid-catalyzed reduction of seven-membered cyclic imines with Hantzsch esters.



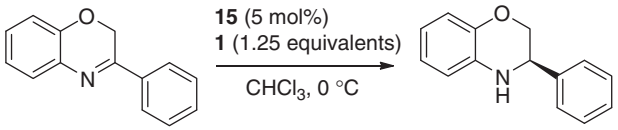
R = Ph, 3-F-C_6H_4, 3-Me-C_6H_4, 4-ethyl-C_6H_4, 2-naphthyl, 2-Br-C_6H_4, 4-CF_3-C_6H_4, 4-MeO-C_6H_4, 1,1′-biphenyl-4-yl, 2-furyl, 4-Cl-C_6H_4, 4-F-C_6H_4, 3,4,5-$(MeO)_3C_6H_2$

Figure 26 Asymmetric Brønsted acid-catalyzed reduction of quinolines with Hantzsch esters in aqueous solution.

8.03.3.1.2.5 Solid-supported Brønsted acid catalysis

Immobilization of chiral catalysts on solid supports suffers in general from problems related to inferior catalytic and stereoinductive ability compared to the homogenous catalysts, but offers advantages of easy separation and recovery with the possibility of recycling. A new method based on polymer-supported BINOL-phosphoric acid catalysts to perform asymmetric organocatalytic transfer hydrogenation has been reported.[85] Catalyst **15**, with bulky substituents in the 3,3′-positions and styrene groups as linkages for immobilization in the 6,6′-positions, was subjected to cross-linking radical copolymerization with styrene and

divinylbenzene and employed as a solid catalyst in the form of a polymer-stick. The performance of this catalyst was tested in the reduction of a benzoxazine in $CHCl_3$ where the reaction proceeded at room temperature to afford the product after 20 h in good yield (96%) and high enantioselectivity (96% *ee*) (Figure 27). The system provided similar efficiency in other solvents such as benzene, toluene, CH_2Cl_2, and dibutyl ether. The polymer-stick catalyst, once removed from the reaction mixture and washed, was successfully reused for 12 times preserving its original activity and selectivity. This approach opens opportunities for future practical applications and for the design of one-pot sequential transformations.



Catalyst removed, washed and reused after each run

run 1:97%	96% *ee*
run 4:96%	94% *ee*
run 8:86%	94% *ee*
run 12:91%	94% *ee*

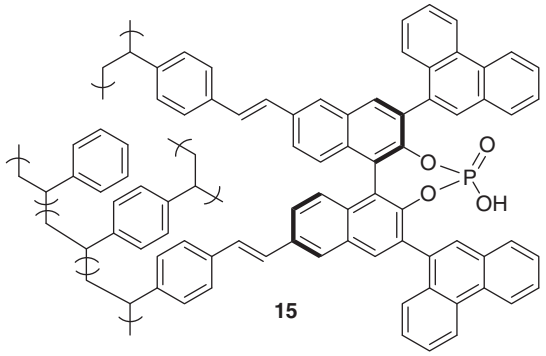


Figure 27 Asymmetric reduction of benzoxazines with a Hantzsch ester under solid-supported Brønsted acid catalysis.

8.03.3.1.2.6 Reduction with soluble polymer-supported Hantzsch esters

Another interesting technique for a more convenient application of transfer hydrogenation is the immobilization of the Hantzsch esters on solid supports. One main drawback of the use of Hantzsch esters in reductions is related to the generation of a large amount of a byproduct: one equivalent of the Hantzsch pyridine. Removal by recrystallization or typically by chromatography implies a practical problem for industrial application. Insoluble supported reducing agents, although appealing because of the highly simplified separation of the oxidized byproduct from the reaction mixture, have in general been characterized by low efficiency. However the use of soluble supported reducing agents that combine advantages of both homogeneous and heterogeneous systems have provided more promising results in the reduction of activated olefins. Regarding the transfer hydrogenation of imines, an efficient Brønsted acid-catalyzed reduction of ketimines using soluble polymer-supported Hantzsch ester **16** (Figure 28) as hydride source has been developed.[86] The reactions, performed in toluene at room temperature and using trichloroacetic acid as catalyst (10 mol%), afforded in 2 h the desired amines in high yields (84–94%) following a simple work-up procedure. Although still no asymmetric equivalent of this protocol has been reported, this is an encouraging advance toward the viability for practical applications of the transfer hydrogenation method using Hantzsch esters.

8.03.3.1.2.7 In situ regeneration of Hantzsch esters

The preceding sections focused on the selectivity and substrate scope of the hydride transfer reactions. Unfortunately, the utility of the transformations is limited by the complexity (and therefore cost) of the NADH models used to obtain good reaction performance; however, this problem can be overcome by the development of protocols for the efficient regeneration of the hydride donor.[87] A very attractive strategy that could overcome the problem of the undesired generation of stoichiometric quantities of Hantzsch pyridines has been devised by Zhou et al.[7] In a highly atom-economic process, catalytic amounts of a Hantzsch ester were employed for the chiral phosphoric acid-catalyzed hydrogenation of benzoxazinones, along with a Ru(II) catalyst for the *in situ* regeneration of the Hantzsch ester under hydrogen gas. In the optimized conditions 9-phenathryl-substituted BINOL-derived phosphate **17** (2 mol%), $[Ru(p\text{-cymene})I_2]_2$ (1.25 mol%) and ester **1** (10 mol%) were used, in a THF/CH_2Cl_2 mixture (1/3) at 50 °C and under hydrogen pressure (1000 psi) for 48 h, to afford a variety of dihydrobenzoxazinones in good yields (59–98%) and excellent enantioselectivities (92–99% *ee*) (Figure 29). This approach still has significant drawbacks for its practical use, such as elevated temperature combined with a high pressure of hydrogen gas. More importantly, a

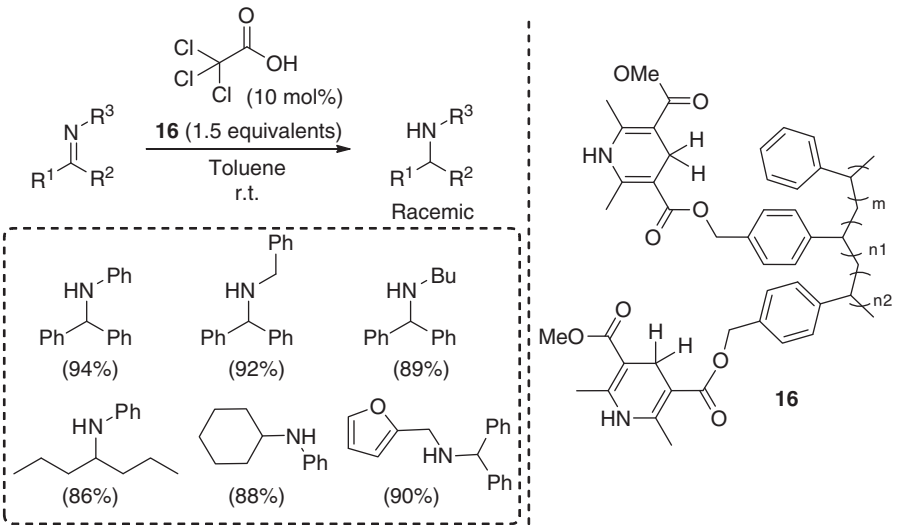


Figure 28 Brønsted acid-catalyzed reduction of *N*-protected ketimines with polymer-supported Hantzsch esters.

careful study of suitable substrates must be done before considering further applications, because only compounds that are inactive toward reduction under hydrogen gas in the presence of the metal catalyst will avoid a background reaction leading to racemic hydrogenated amines. Nevertheless, this strategy represents a promising avenue in the direction of maximizing the atom efficiency of the Hantzsch ester-mediated reductions.

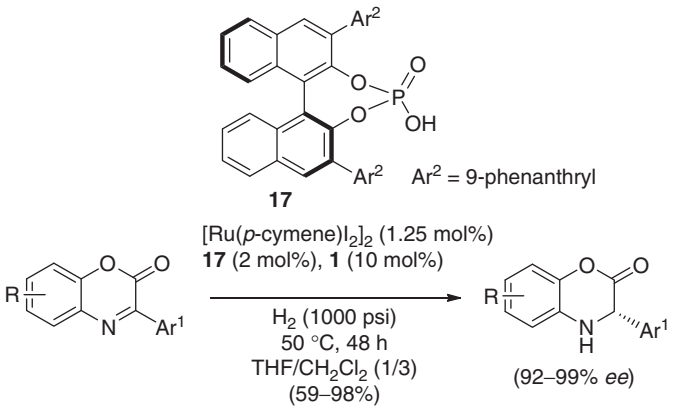


Figure 29 Asymmetric Brønsted acid-catalyzed reduction of benzoxazinones with *in situ* regeneration of Hantzsch esters.

8.03.3.1.3 Thiourea-catalyzed reduction of imines by transfer hydrogenation from Hantzsch esters

Urea and thiourea derivatives have been successfully employed in multiple diastereo- and enantioselective reactions and the versatility of these urea derivatives as general acids has been established by several research groups.[88] On the subject of imine reduction, a protocol for the thiourea-catalyzed transfer hydrogenation of aldimines with Hantzsch ester **1** as hydrogen source has been reported.[89] A variety of *ortho*-, *meta*-, and *para*-substituted aromatic aldimines, including electron-donating and electron-deficient substrates, were reduced in the presence of 3,3′,5,5′-tetratrifluoromethyl thiocarbanilide catalyst **18** in CH_2Cl_2 at room temperature, affording at 15 h of reaction the corresponding secondary amines in high yields (84–93%) (Figure 30). Moreover, aliphatic aldimines were also efficiently reduced under these conditions (80–87% yield). A catalyst loading of 1 mol% was used, although amounts as low as 0.1 mol% were also suitable at the expense of longer reaction times. At the present time, asymmetric versions of the imine reduction through urea- or thiourea-catalyzed transfer hydrogenation with Hantzsch 1,4-dihydropyridines have not been reported.

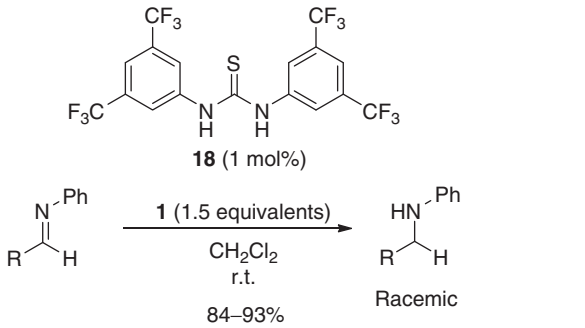


Figure 30 Thiourea-catalyzed reduction of *N*-aryl aldimines with Hantzsch esters.

8.03.3.1.4 Metal-catalyzed reduction of imines by transfer hydrogenation from Hantzsch esters

Hantzsch esters have been combined with metallic species for the asymmetric transfer hydrogenation reactions of other carbonyl compounds such as methyl phenylglyoxylate[12a] (with a chiral europium complex), methylbenzoylformate[90] (with magnesium salts) and α-ketoesters[11b] (with a chiral Cu(II)–bisoxazoline complex). A method for the enantioselective iridium-catalyzed transfer hydrogenation of quinolines with Hantzsch esters has been developed.[12b] $[Ir(COD)Cl]_2$/(*S*)-SegPhos/I_2 catalyzed the transfer hydrogenation of quinolines with moderate to good selectivity (68–87% *ee*) affording the optically active reduced products in good yields (43–98%) (Figure 31). The reactions were performed in a mixture of toluene/dioxane (1/1) at room temperature for 40–80 h, using 1 mol% of $[Ir(COD)Cl]_2$, 2.2 mol% of the ligand, 5 mol% of I_2, and 2 equivalents of Hantzsch ester 4 (Figure 31). 2-Alkyl substituted quinolines were reduced in good yields, although the enantioselectivity decreased as the length of the side chain increased. Electron-donating substituents in the 6-position resulted in low reactivity but 2-(2-arylethyl)-substituted quinolines afforded good conversions and enantioselectivities. The system appears to tolerate hydroxyl groups, although providing the reduced products with moderate enantiomeric excess. Curiously, a common type of substrate for this sort of transformation, the 2-aryl-substituted quinolones, were found unsuitable for this method, giving very low selectivity (10% *ee*).

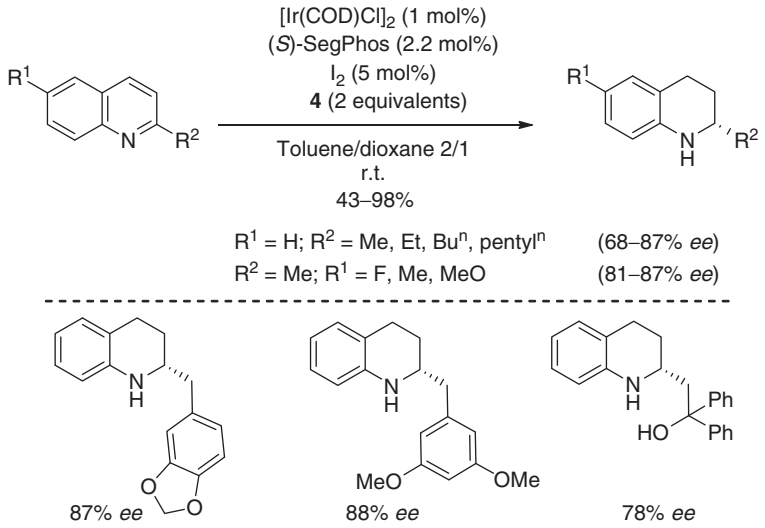


Figure 31 Asymmetric metal-catalyzed reduction of quinolines with Hantzsch esters.

8.03.3.2 Transfer Hydrogenation with Other *N*-Heterocycles

8.03.3.2.1 Benzothiazoline

Benzothiazoline was first used as a reducing reagent under Lewis-acid catalysis in the 1980s by Chikashita et al. for the reduction of carbonyl compounds. However, it was not until 2009 that it was applied as a hydride source in the transfer hydrogenation of ketimines by Zhou and Akiyama.[9] In this system, the driving force for the powerful hydride donating ability of benzothiazoline is

its transformation into a much more stable aromatic benzothiazole (Figure 32). In this first report, with the use of 2-naphthyl substituted benzothiazoline **19**, and under BINOL-derived phosphoric acid catalysis the reduction of a variety of aryl methyl *N*-aryl imines was performed with good efficiency (80–96% yield) and excellent stereocontrol (95–98% *ee*) (Figure 33). One example of aliphatic ketimine was provided, with comparable results. In the same way as in the Brønsted acid-catalyzed Hantzsch ester-mediated reductions, larger substituents in the 3,3′-positions of the BINOL scaffold promoted higher enantioselectivity. In the optimized conditions, acid **6** (R=2,4,6-Pr^i-C_6H_2) was employed as catalyst (2 mol%) in mesitylene at 50 °C for 26 h of reaction. The *in situ* generation of the benzothiazoline, by combination of 2-naphthalenecarbaldehyde (1.4 equivalents) and 2-aminothiophenol (1.4 equivalents), and the reduction of the ketimine in the same pot, affords comparable results (Figure 35).

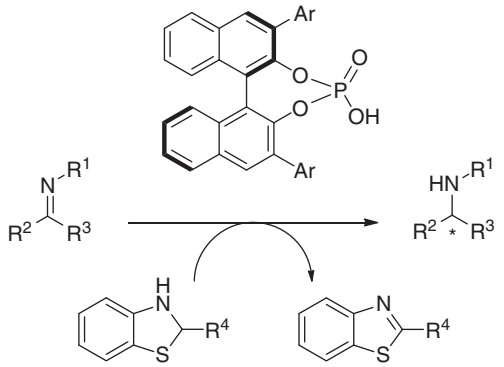


Figure 32 Benzothiazoline as hydride source in the reduction of ketimines.

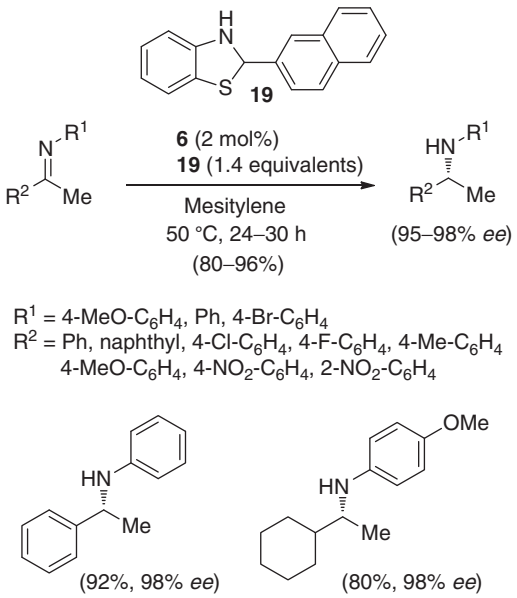


Figure 33 Asymmetric Brønsted acid-catalyzed reduction of aryl methyl *N*-aryl imines with benzothiazoline.

This method was then further extended to the asymmetric transfer hydrogenation of α-imino esters.[10] The same acid **6** was employed, with catalyst loadings as low as 0.5 mol%, but in this case the 2-phenyl substituted benzothiazoline **20** was the hydride source of choice. Methyl α-imino esters afforded the reduced products with higher enantioselectivity compared to the analogous ethyl esters. A range of α-imino esters bearing electron-withdrawing and electron-donating substituents were reduced with very high yield (90–99%) and enantioselectivity (93–99% *ee*) (Figure 34). *N*-*p*-Methoxyphenyl, *N*-phenyl, and *N*-*p*-chlorophenyl imino esters were equally suitable for this protocol. One example of an aliphatic α-imino ester was provided. Also in this case, a three component reaction with the *in situ* generation of the reducing agent could be performed (Figure 35). Furthermore, modification of the benzothiazoline by introduction of a hydroxyl group in the 2-phenyl substituent (benzothiazoline **21**) gave rise to a largely improved procedure, in which the oxidized benzothiazole by-product precipitates in the reaction media facilitating its removal by simple filtration (Figure 36). When comparing this approach with the Hantzsch ester-mediated reduction

protocols, the easy purification process and the *in situ* generation of benzothiazolines from inexpensive materials appear as major advantages from a practical point of view.

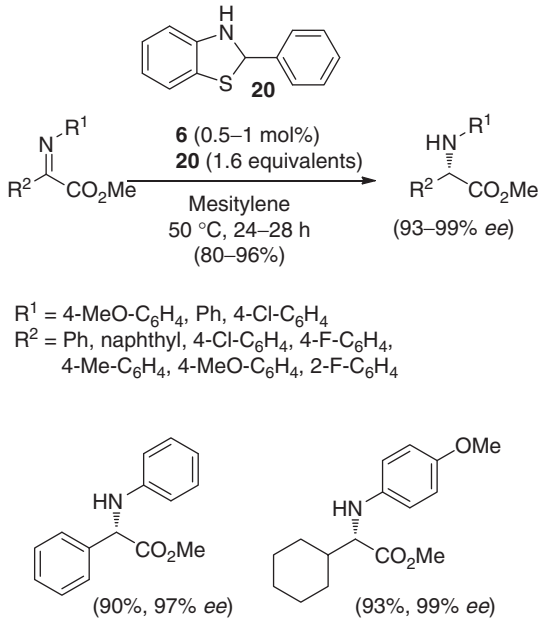


Figure 34 Asymmetric Brønsted acid-catalyzed reduction of *N*-aryl α-imino esters with benzothiazoline.

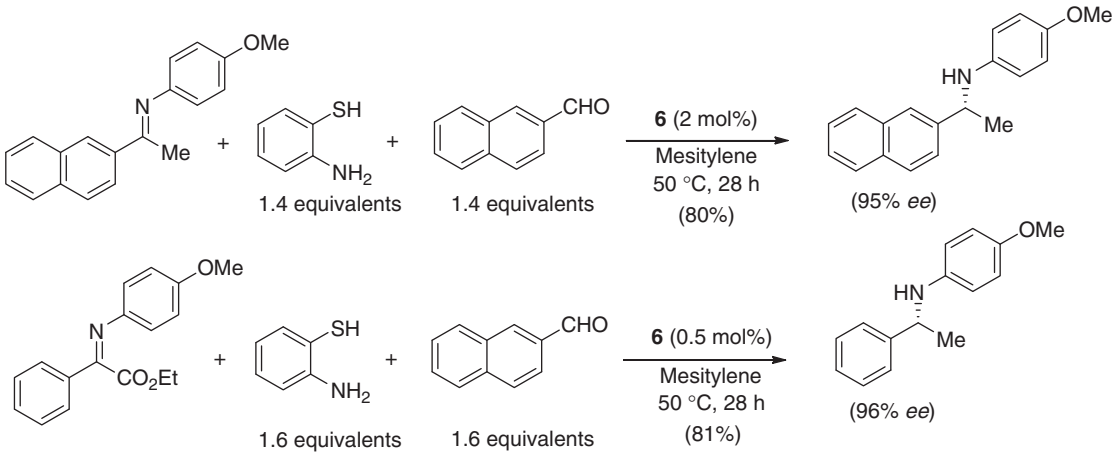


Figure 35 Asymmetric Brønsted acid-catalyzed reduction of *N*-aryl imines with *in situ* generation of benzothiazoline.

8.03.3.2.2 ADMI

Other five-membered ring heterocycles such as 2-phenylbenzimidazole and 1,3-dimethyl-2-phenylbenzimidazole have been used in the past as models to mimic nature's NADH system and have been tested in the reduction of unsaturated compounds. Only one example of a successful application of ADMI **22** in the nonasymmetric reduction of unsaturated aldehydes and imines has been reported.[8d] The presence of the electron-withdrawing acetyl group in the imidazolidine structure was crucial to achieve high reduction yields. In the optimized reactions, a variety of *N*-tosyl imines were reduced in refluxing acetonitrile–methanol affording, after 2–5 h, the amines in high yields (81–99%) (Figure 37). A different procedure was required for the reduction of *N*-phenyl imines where the reaction proceeded at room temperature in acetonitrile–methanol in the presence of 10 mol% of $Mg(ClO_4)_2$. The authors did not identify the oxidation path for the reducing agent, so the mechanism is still unclear in the present, and no asymmetric version of this method has been reported.

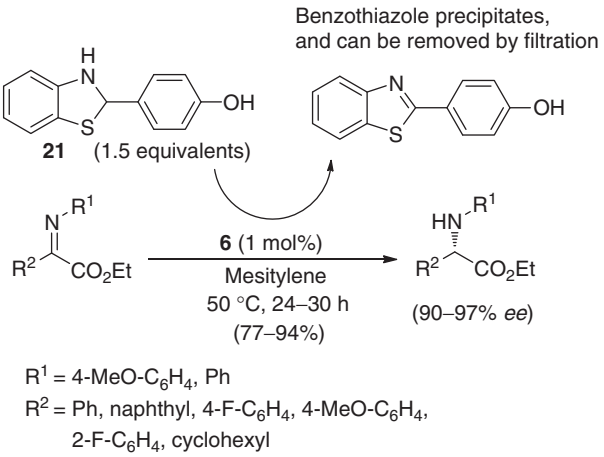


Figure 36 Benzothiazoline-mediated asymmetric Brønsted acid-catalyzed reduction of *N*-aryl imines with precipitation of benzothiazole.

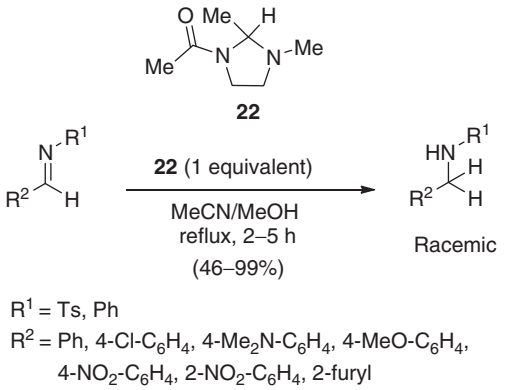


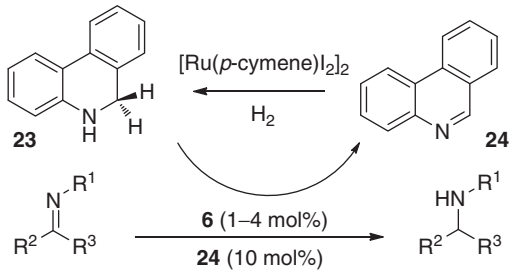
Figure 37 Reduction of *N*-tosyl imines with ADMI.

8.03.3.2.3 Dihydrophenanthridine

An innovative method in which 9,10-dihydrophenanthridine **23** is employed in the asymmetric reduction of benzoxazinones, benzoxazines, quinoxalines, and quinolines has been reported.[91] It has the exceptional feature of being combined with a regeneration process that allows the use of the reducing agent in catalytic quantities. A Ru(II) complex was found to be able to regenerate 9,10-dihydrophenanthridine using hydrogen gas under very mild conditions. The presence of 0.5 mol% of $[Ru(p\text{-cymene})I_2]_2$ and H_2 pressures as low as 1 atm were effective enough to allow the use of only 10 mol% of phenanthridine **24** to perform the asymmetric transfer hydrogenation using different classes of endocyclic imines under chiral Brønsted acid catalysis (acid **6**, 1–4 mol%) (Figure 38) at room temperature, affording good yields and excellent enantioselectivities.

The feasibility of this new strategy was first evaluated in the reduction of benzoxazinones, with the optimized conditions showed in Figure 38 (method A). This method is general for a variety of substrates regardless of the electronic properties of the substituents, affording the corresponding dihydrobenzoxazinones in good yields (77–96%) and high enantioselectivities (87–97% *ee*). Similar good results (95–99% yield, 87–97% *ee*) were obtained with benzoxazine compounds using a slightly modified protocol (method B). The dihydrophenanthridine-mediated asymmetric transfer hydrogenation was also applied to the reduction of aromatic quinoxalines and quinolines substrates. In the case of quinoxalines, only 10 mol% of phenanthridine (method C) was required for reduction of the two C═N bonds with good yield and enantiocontrol (93–99% yield, 85–95% *ee*) and the results were general for differently substituted substrates. In the case of quinolines, to achieve high conversions, the catalyst loading, the hydrogen pressure and the reaction temperature had to be increased (method D), but also in these conditions high stereocontrol was achieved (86–93% *ee*).

In the previously mentioned highly enantioselective Brønsted acid-catalyzed transfer hydrogenation methods employing Hantzsch esters (see Section 8.03.3.1.2.3.), at least 2 equivalents of the Hantzsch ester were required to reduce the two unsaturated double bonds present in these aromatic substrates, with the consequent generation of 2 equivalents of Hantzsch pyridine. The dihydrophenanthridine-mediated reduction overcomes difficult byproduct removal and offers a more atom-economic process. Although in this case the ultimate source of hydrogen is H_2, the role of dihydrophenanthridine as a mediator allows the use of a lower pressure of hydrogen gas, in contrast to the generally higher pressures (1000 psi) employed in metal-catalyzed direct



Method	**6** (mol%)	Ru(II) cat. (mol%)	H_2 (psi)	Solvent	Temperature	Time (h)
A	2	0.5	500	CH_2Cl_2	r.t.	48
B	1	1	50	CH_2Cl_2	r.t.	32
C	1	0.5	100	Benzene	r.t.	48
D	4	0.5	400	Benzene	40 °C	48

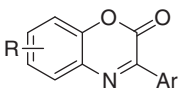
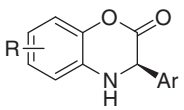
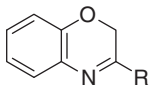
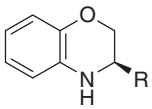
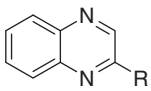
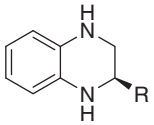
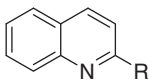
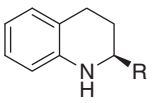
Substrate	Method	Substrate scope	Yield (%)	Product	*ee* (%)
	A	R = H, 6-Cl, 6-Me, 7-Me Ar = Ph, 4-MeO-C_6H_4, 3-F-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 3, 4-Me_2-C_6H_3, 2-thienyl	77–96		87–97
	B	R = Ph, 4-Me-C_6H_4, 4-Ph-C_6H_4, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 3-Br-C_6H_4, 3,4-Cl_2-C_6H_3, 2-naphthyl	95–99		87–97
	C	R = Ph, 4-Me-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 4-MeO-C_6H_4, 4-CF_3-C_6H_4, 3-F-C_6H_4, 3-Cl-C_6H_4, 2-naphthyl	93–99		85–95
	D	R = Ph, 4-Me-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 4-MeO-C_6H_4, 4-CF_3-C_6H_4, 4-Cl-C_6H_4, 2-naphthyl	64–98		86–93

Figure 38 Asymmetric Brønsted acid-catalyzed reduction of benzoxazinones, benzoxazines, quinoxalines, and quinolines by *in situ* generated dihydrophenanthridine.

hydrogenations. As a negative aspect, this method is not purely organocatalytic, facing the problems mentioned before for metal-catalyzed reactions, such as metal contamination of the products and high sensitivity of the catalyst to impurities. It is interesting to mention that opposite senses of enantioinduction were observed when comparing both methods (Hantzsch ester- and dihydrophenanthridine-mediated transfer hydrogenation), which can be translated into fundamental mechanistic differences. The 1,2-hydride transfer from dihydrophenanthridine to the Brønsted acid-activated imine originates certain steric demands in the transition state, different to the 1,4-hydride transfer from a Hantzsch ester, which determines the stereoselectivity of the reaction.

The strategy described above, together with the *in situ* regeneration of Hantzsch esters[7] (see Section 8.03.3.1.2.7), both conceived by Zhou et al., have supplied important information to the transfer hydrogenation technology area, where research efforts meet the challenges of how to overcome the problem of minimizing the amount of waste and energy.

8.03.4 Asymmetric Imine Reduction by Hydride Delivery from Silanes

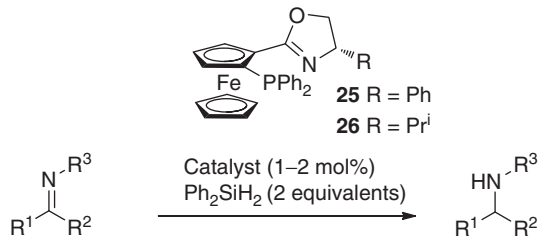
Silanes are normally too unreactive for a direct hydride transfer to unsaturated bonds, and the use of a catalyst is necessary to make this process possible. In the case of aryl- or alkylsilanes the reaction requires catalysis by Lewis acids or transition metal complexes, employing the well known LUMO-lowering activation strategy (see Section 8.03.4.1). In contrast, with the more Lewis acidic trichloro- or trialkoxysilanes an alternative metal-free activation can be accomplished through hypercoordinated silicon hydrides, which will act as Lewis acids themselves, coordinating to the substrate and delivering the hydride via an intramolecular process (see Section 8.03.4.2).

The position of silicon in the periodic table, directly beneath carbon, suggests a similar reactivity; however, this is only valid for those organosilanes that have four carbon atoms directly attached to the silicon. Even then, as a result of the lower electronegativity, most ligands on silicon compounds have a higher electron withdrawing power than the silicon atom, creating a partial positive charge on the central silicon atom. Silanes containing Si attached to halides or other heteroatoms also exhibit different reactivity. The most important difference between carbon and silicon, which explains the ability of trichlorosilane to act as a reducing reagent is that silicon can participate in hypervalent bonding by connection to five or six ligands. This hypervalency is often the result of chelation by a multidentate ligand possessing an electron-rich donor group.

8.03.4.1 Transition Metal-Catalyzed Hydrosilylation

Asymmetric hydrosilylation employing safe and inexpensive hydrosilanes such as PMHS provides an alternative and attractive route to access chiral amines. Homogeneous catalysts derived from transition metals such as Ti,[92] Rh,[93] Ru,[94] Cu,[95] Ir,[96] and Re[18] have been developed for the enantioselective hydrosilylation of imines from organosilanes. Again, reports on the reaction with C═N bonds are much less common than those for C═C and C═O bonds. Only limited examples have been reported with rhodium or ruthenium-chiral bisphosphine catalysts, and these reactions afforded amines with modest enantioselectivity.[97] Highly enantioselective reductions were developed with Ti, Cu, and Re, but either the synthesis of complex catalysts, the use of relatively harsh conditions, the addition of high quantities of additives or the use of unusually modified substrates was necessary. The design of metal catalysts that are efficient for both *N*-aryl and *N*-alkyl imine substrates, as well as aldimines and ketimines, and the development of more efficient and atom-economical methods remain as important goals for hydrosilylation research. This section reviews the most significant catalytic systems developed in the period 1987–2012, concentrating on those methods that complement the substrate scope offered by the methods described in previous sections.

As mentioned above, only a few enantioselective examples are known for ruthenium and iridium-based catalytic systems, and even fewer for rhodium-based catalysts. The use of Ru(II) and Ir(I) catalysts has been investigated[96] in combination with chiral ferrocenyl phosphinooxazoline ligands **25** and **26** for the reduction of cyclic 5-membered imines and *N*-methyl imines. However, although the catalysts effectively promoted hydrosilylation, the chiral amines were obtained with low yields and modest enantioselectivities (up to 89% *ee*) (Figure 39). When activated by silver triflate,[98] the Ru-based catalyst gave promising enantioselectivity



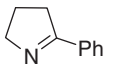
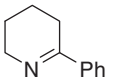
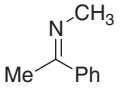
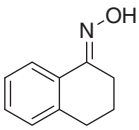
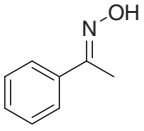
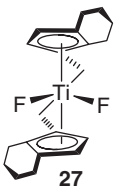
Substrate	Catalyst	Solvent, temperature, time	Amine yield, *ee*
	[$RuCl_2(PPh_3)$**25**]	Toluene, 0 °C, 40 h	60%, 88% *ee*
	$[Ir(COD)Cl]_2$; **25**	Et_2O, 0 °C, 20 h	>95%, 85% *ee*
	$[Rh(COD)Cl]_2$; **25**	Et_2O, 0 °C, 20 h	75%, 34% *ee*
	[$RuCl_2(PPh_3)$**25**]	Toluene, 0 °C, 50 h	10%, 25% *ee*
	$[Ir(COD)Cl]_2$; **25**	Et_2O, 0 °C, 100 h	18%, 7% *ee*
	[$RuCl_2(PPh_3)$**25**]	Toluene, 0 °C, 40 h	51%, 73% *ee*
	$[Ir(COD)Cl]_2$; **25**	Et_2O, 0 °C, 20 h	56%, 89% *ee*
	[$RuCl_2(PPh_3)$**25**] AgOTf	THF, r.t., 20 h	50%, 79% *ee*
	[$RuCl_2(PPh_3)$**26**] AgOTf	THF, r.t., 40 h	21%, 89% *ee*

Figure 39 Asymmetric reduction of *N*-aryl ketimines through hydrosilylation with ruthenium- and iridum-based catalysts.

in the reduction of some cyclic ketoximes (up to 89% *ee*), although the method was not general, offering lower selectivity for acyclic substrates (61–74% *ee*) and almost racemic material for aliphatic acyclic ketoximes (12% *ee*).

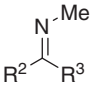
The Buchwald group first reported in 1996 a titanocene-catalyzed method[92a] for the enantioselective reduction of imines using the chiral C_2-symmetric difluorotitanocene precatalyst **27**. Catalyst loadings as low as 0.02 mol% were used and remarkably, the method (method A, Figure 40) was applied to unactivated imines, with methyl substituents on the nitrogen. Several aryl alkyl ketimines were reduced with high enantioselectivities (95–99% *ee*) and yields (88–95%). Reduction of cyclohexyl substituted *N*-methylketimines could also be achieved using this catalyst system (96%, 92% *ee*). Although the scope of imines provided by this method is very interesting, the use of the fairly expensive phenylsilane as stoichiometric reducing agent was required. Later on, and based on mechanistic studies, the same group was able to provide optimized conditions[92b] for this transformation, by the introduction of amine additives in the reaction media, which allowed the use of PMHS as convenient alternative to monomeric silanes. Although these procedures are very stereoselective and require small amounts of catalyst, the use of high quantities of reducing agents and additives offers low efficiency in terms of atom economy. Diverse methyl alkyl and methyl aryl *N*-alkyl imines were reduced in high yields and selectivities (92–97% yield and 91–99% *ee*) (method B, Figure 40). A slight modification of the protocol[92c] (method C, Figure 40) allowed the reduction of dialkyl *N*-aryl ketimines with excellent enantioselectivities (up to 99% *ee*). This method however, provided very low selectivity for alkyl aryl *N*-aryl ketimines.



27

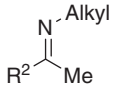


Method A 1. **27** (0.02–2.5 mol%), $PhSiH_3$ (1.5 equivalents)
pyrrolidine (4 mol%), MeOH (4 mol%), THF, r.t.
2. Imine, 35 °C 3. Acid work-up



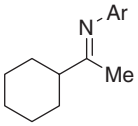
R^2	R^3	yield (%)	*ee* (%)
Me	Ph	95	99
Me	4-Cl-C_6H_4	85	99
$-(CH_2)_{10}CH_3$	Ph	88	95
Me	Cyclohexyl	96	92

Method B 1. **27** (0.05–5 mol%), $PhSiH_3$ (4 mol%)
piperidine (4 mol%), MeOH (4 mol%), THF, 60 °C
2. PMHS (9 equivalents), imine,
Bu^iNH_2 (2 equivalents, slow addition, 2.5 h), 65 °C



Alkyl = Bn, Pr^n
R^2 = Ph, 4-Cl-C_6H_4, cyclohexyl, hexyl
(92–97%, 91–99% *ee*)

Method C 1. **27** (2 mol%), $PhSiH_3$(8 mol%)
pyrrolidine (8 mol%), MeOH(8 mol%), toluene, 60 °C
2. PMHS (12 equivalents), imine,
Bu^iNH_2 (5.2 equivalents, slow addition, 13 h), 60 °C

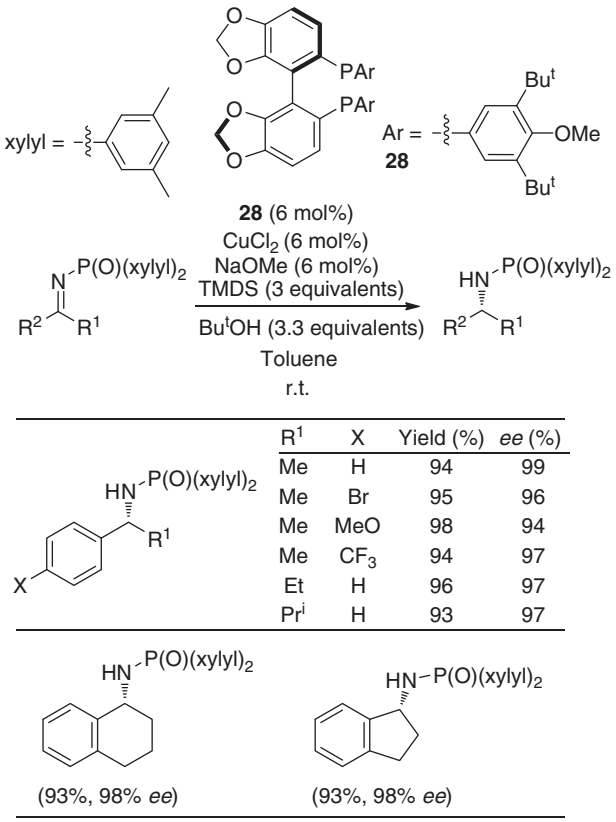


Ar = Ph, 4-MeO-C_6H_4, 4-Me-C_6H_4
(63–79%, 99% *ee*)

Figure 40 Asymmetric reduction of *N*-aryl ketimines through hydrosilylation with titanium-based catalysts.

A copper hydride catalyst has been used for the reduction of imines through hydrosilylation.[95] Aryl alkyl ketimines can be reduced enantioselectively using the 5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole ligand **28** (Figure 41) with copper chloride and a silane, such as tetramethyldisiloxane (TMDS), with high enantiomeric excess but limited to very specific substrates: *N*-xylylphosphinoyl imines. The use of these sterically hindered activating groups allowed high

enantioselectivity (94 to >99% *ee*) and yields were excellent for all substrates reported (93–99%). The process is economically attractive because both the catalyst and the reducing agent are inexpensive.



R^1	X	Yield (%)	*ee* (%)
Me	H	94	99
Me	Br	95	96
Me	MeO	98	94
Me	CF_3	94	97
Et	H	96	97
Pr^i	H	93	97

Figure 41 Asymmetric reduction of *N*-xylylphosphinoyl imines through hydrosilylation with copper-based catalysts.

In contrast to the commonly found low-oxidation state transition metal catalysts, the use of a highly efficient high oxidation state rhenium-oxo catalyst[18] **29** (Figure 42) has been described. Several aryl methyl *N*-phosphinoylimines were reduced with high enantioselectivities (>98% *ee*) and good yields. The method was also applied to the sterically more demanding phenyl *n*-propyl *N*-phosphinoylimine (68% yield, >99% *ee*). Aliphatic imines such as cyclohexyl methyl *N*-phosphinoylimine showed lower enantioselectivity (69% yield, 32% *ee*). The same catalyst was applicable to heteroaromatic derivatives, such as 3-furyl methyl *N*-phosphinoylimine (76% yield, 99% *ee*) and an indole-based *N*-phosphinoylimine (81% yield, 99% *ee*), and additionally, to aryl α-imino esters (95 to >99% *ee*). Particularly rare[17,92c] and interesting is the chemo- and enantioselective reduction of α,β-unsaturated imines to the corresponding allylic amines in good yields (48–71%) and enantioselectivities (74–99% *ee*).

A Zn-diamine catalyst in the presence of PMHS as reducing agent was reported[99] for the reduction of imines. One problem related to the use of Zn is the strong Zn–N bond formed between the metal and the imine (or the product amine), but this problem was avoided by employing diphenylphosphinoyl as activating group and methanol as cosolvent. Several diamine ligands were investigated, with the (*R,R*)-1,2-diphenyl-1,2-ethanediamine-derived ligand **30** giving highest enantioselectivity. Aryl methyl *N*-phosphinoylimines were reduced in good yields (77–86%) and high enantioselectivities (96–97%) (method A, Figure 43). Phenyl alkyl imines were also examined: phenyl ethyl *N*-phosphinoylimine was reduced with high enantioselectivity and good yield (82% yield, 96% *ee*) but phenyl *iso*-propyl *N*-phosphinoylimine, more sterically demanding, provided lower enantiomeric excess (74% yield, 55% *ee*). One heterocyclic substrate was also reduced, 2-furyl methyl *N*-phosphinoylimine with 96% *ee* (77% yield). This catalytic process offers some attractive features, such as the use of a non-precious metal and an inexpensive silane. Moreover, the easy modification of the chiral diamine ligands offers new possibilities for catalyst design. In fact, the modification of the diamine ligand (diamine **31**) has extended the scope to new substrates, such as α,β-unsaturated imines, dialkyl *N*-phosphinoylimines or tosylimines[100] (method B, Figure 43). A protocol with more sophisticated ligands, based on hexamine macrocycle **32** (readily available from diethyl zinc and *trans*-1,2-diaminocyclohexane), has been described[101] for the reduction of aryl alkyl and diaryl *N*-phosphinoylimines with good enantioselectivities (method C, Figure 43). Different *N*-substituted imines were investigated, and whereas *N*-*p*-methoxyphenyl substrates afforded lower enantioselectivities compared to *N*-phosphinoylimines, *N*-OH, and *N*-OBn substrates did not undergo hydrosilylation under the reaction conditions.

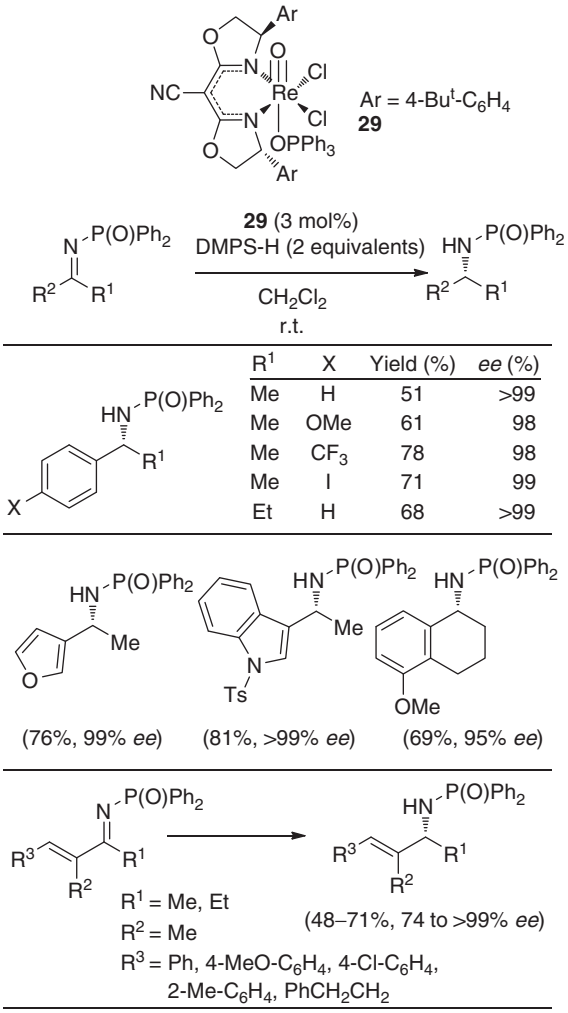


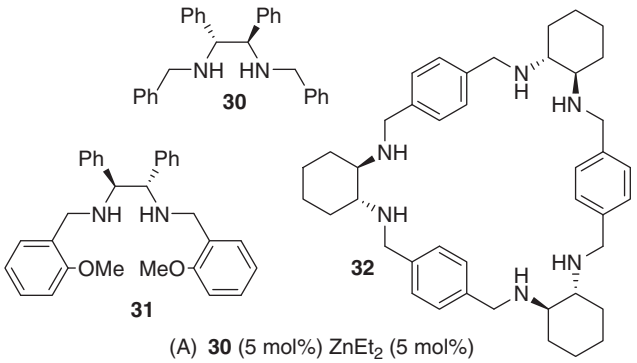
Figure 42 Asymmetric reduction of *N*-phosphinoyl ketimines through hydrosilylation with a rhenium-oxo catalyst.

8.03.4.2 Asymmetric Organocatalytic Reduction of Imines with Trichlorosilane

The simplest system within this strategy, with trichlorosilane as reductant and dimethylformamide (DMF) as a Lewis basic promoter, operates as a mild organocatalytic procedure for the effective reduction of unsaturated organic substrates.[102] Lewis base-activated trichlorosilane can effect, in different conditions, the reduction of ketones, aldehydes, and imines. Asymmetric hydrosilylation of imines activated by chiral Lewis bases has undergone very recent expansion[103] in parallel with the development of the Hantzsch esters as reducing agents for hydrogen transfer. The introduction of *N*-formylpyrrolidine derivatives and analogous organocatalysts, along with *S*-chiral sulfonamides, has made this strategy a promising alternative to transition-metal catalysis in the synthesis of chiral amines. However, a very limited number of highly enantioselective processes have been described and the substrate scope remains limited. Lewis base-catalyzed hydrosilylation is still worth further exploring in view of the economy of this method and the mild reaction conditions provided.

Because it was known that DMF (and other Lewis bases) could activate trichlorosilane for the reduction of imines to amines, it is not surprising that the first chiral catalysts designed for the asymmetric reduction of imines were formamides derived from naturally available amino acids. The first chiral catalyst[104] was introduced by Matsumura et al. for the reduction of ketones, and was later applied to the reduction of imines.[105] (*S*)-Proline derived anilide **33** and its naphthyl analog **34** proved to be suitable chiral promoters of the $HSiCl_3$-mediated reactions, offering moderate enantioselectivities (49–66% *ee*) in the reduction of aryl methyl *N*-arylimines with 10 mol% of catalyst (**Figure 44**). The formamide moiety was found to be crucial for the activation, because acetamide derivatives failed to catalyze the reaction. Since the disclosure of this report, several research groups have dedicated their efforts to the development of more efficient Lewis basic catalysts for the asymmetric reduction of imines, achieving a remarkable progress in only a few years.

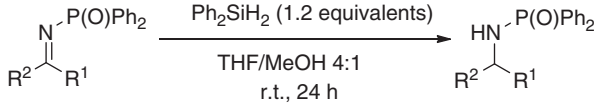
The use of *N*-methyl-(*S*)-valine-derived catalyst **35** by Malkov and Kočovský presented the first highly enantioselective example of this strategy.[106] The Lewis-basic formamide **35** (Sigamide) is the most valuable catalyst in an efficient protocol (85–92% *ee*) for



(A) **30** (5 mol%) $ZnEt_2$ (5 mol%)
PMHS (3 equivalents)

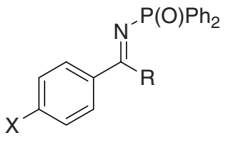
(B) **31** (5.5 mol%) $ZnEt_2$ (5 mol%)
PMHS (3 equivalents), 12 h

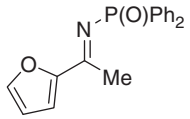
(C) **32** (2 mol%) $ZnEt_2$ (2 mol%)
Ph_2SiH_2 (1.2 equivalents)



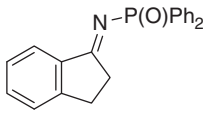
Method A

R	X	Yield (%)	*ee* (%)
Me	H	86	97(*S*)
Me	Br	77	97
Me	MeO	83	96
Et	H	82	96
Pr^i	H	74	55



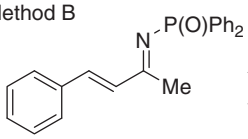


(77%, 96% *ee*)

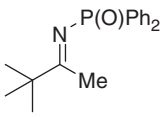


(83%, 98% *ee*)

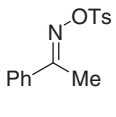
Method B



(91%, 95% *ee*)

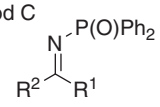


(89%, 93% *ee*)



(92%, 99% *ee*)

Method C

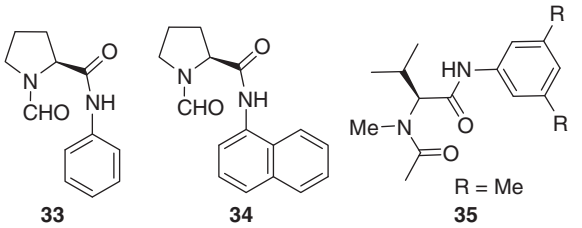


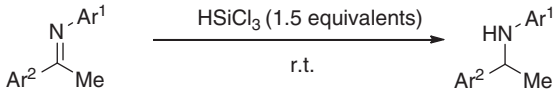
R^1	R^2	Yield (%)	*ee* (%)
Me	Ph	66	99(*S*)
Me	4-Me-C_6H_4	62	97(*S*)
Ph	4-Me-C_6H_4	35	61

*Unless specified, the absolute configuration was not determined.

Figure 43 Asymmetric reduction of *N*-phosphinoyl ketimines through hydrosilylation with zinc-based catalysts.

the reduction of several aryl methyl *N*-arylimines in toluene at room temperature (Figure 44). α-Imino esters and α,β-unsaturated imines may be reduced by lowering the temperature to −20 °C and employing catalyst **35**, although with moderate enantioselectivities (59–81% *ee*). The same group reported an extensive library of chiral *N*-formylated amino acids and studied the effect of structural variations on the stereoselectivity.[107] The main conclusions of their investigations were that (1) the *N*-methyl formamide moiety on the catalyst is crucial for the enantioselectivity, (2) important arene–arene interactions are involved, because both the anilide part of the catalyst and the *N*-aryl substituent of the substrate imine are crucial for the enantiodifferentiating process, (3) the anilide moiety of the catalyst must be a secondary amide, with an NH group, and (4) the nature of the amino acid side chain determines the configuration of the resulting product. In this report, they provide an exhaustive study on the scope and limitations for the *N*-arylimine reduction with catalyst **35**. A representative summary of results can be found in Figure 45. High yields and enantioselectivities (81–92% *ee*) were obtained for a variety of aryl methyl ketimines. Although good





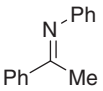
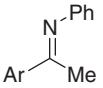
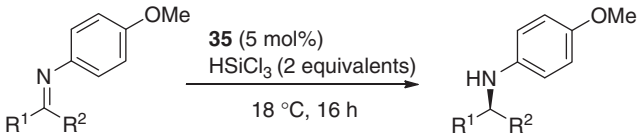
Imine substrates	Method	Yield, *ee*
	**33** (10 mol%), CH_2Cl_2, 24 h **34** (10 mol%), CH_2Cl_2, 24 h	91%, 55% *ee* (*R*) 52%, 66% *ee* (*R*)
	**35** (10 mol%), toluene, 16 h	81–90%, 85–92% *ee* (*S*)
Ar = Ph, 4-MeO-C_6H_4, 4-CF_3-C_6H_4, 2-Me-C_6H_4		

Figure 44 Asymmetric reduction of aryl methyl *N*-aryl imines with $HSiCl_3$ using *N*-formyl derivatives as catalysts.



R^1	R^2	Yield (%)	*ee* (%)
Me	2-naphthyl, PhCH=CH-, cyclohexyl, thiophenyl, 1-Me-2-indolyl, 2,5-Me_2-3-furyl	62–94	81–92
	Bu^t, Pr^i	63,83	39,62
	2-pyridyl, 2-thiazolyl, 2-furyl, 5-Me-2-furyl	78–88	7–56
Et, Pr^i	Ph	81,98	92,97
Bu^t, cyclohexyl	Ph	18,83	10,76
CH_2Cl	Ph, 4-Cl-C_6H_4, 4-F-C_6H_4 2-Cl-C_6H_4, 2-naphthyl 4-MeO-C_6H_4, 3-MeO-C_6H_4	54–98	91–96
CH_2CN	Ph	75	87
CH_2CO_2Et	Ph, 4-F-C_6H_4, 4-MeO-C_6H_4	80–98	88–90

Figure 45 Enantioselective reduction of dialkyl and aryl alkyl *N*-arylimines with $HSiCl_3$ using Sigamide as catalyst.

results were attained with a few substrates containing heteroaromatic groups such as thienyl or indole derivatives, the reaction was not general for heteroaromatic groups, because 2-pyridyl-, 2-thiazolyl-, or 2-furyl-derived ketimines afforded low enantioselection. Phenyl ketimines with alkyl groups other than methyl were also tolerated, obtaining good enantiomeric excess for ethyl- and *iso*-propyl-derived substrates (92–97% *ee*) whereas moderate to low enantioselectivities were observed for *tert*-butyl and cyclohexyl derivatives (10–76% *ee*). More importantly, the method was extended to the reduction of other classes of ketimines, such as α-chloro- and α-cyano imines, which facilitates the possibility of further transformations, such as cyclization to the corresponding aziridines. In addition to the noticeable efficiency of this catalyst, several strategies have been reported for the preparation of functionalized **35**, to facilitate the recovery and recycle of the catalyst. Examples of such strategies include soluble polymer supported catalysts,[108] attachment to fluorinated tags to enable filtration through a pad of fluorous silica,[109] immobilization onto gold nanoparticles,[110] and a dendron-anchored catalyst.[111]

Modified catalysts with a chiral amine coupled to the proline moiety have been prepared.[112] The *N*-formylprolinamide of (*R*)-α-methylamine **36** was a suitable catalyst for the reduction of phenyl methyl *N*-phenyl imine (75%, 81% *ee*) in the presence of hexamethylphosphoramide (HMPA) as an additive (**Figure 46**). C_2-symmetric tetraamides derived from (*S*)-proline have been also studied targeting higher stereoselective reductions. Sun et al.[113] found that catalyst **37** provided good to moderate yields and enantioselectivities for a variety of *N*-aryl ketimines; alkyl aryl-ketimines (up to 86% *ee*) and diarylketimines (up to 77% *ee*). This catalyst, expected to offer higher stereocontrol through extensive chelation with the reagent, did not provide any particular advantage over the previous catalysts.

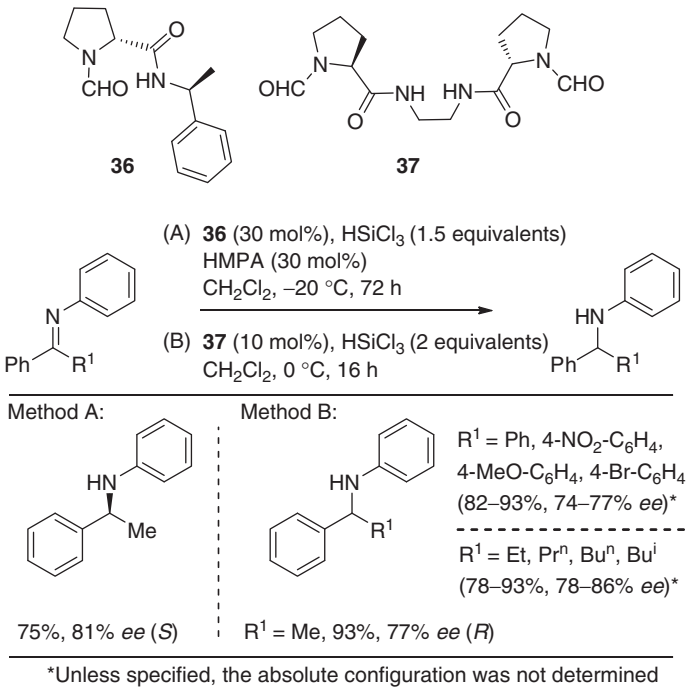


Figure 46 Enantioselective reduction of *N*-aryl imines with $HSiCl_3$ using *N*-formylprolinamide catalysts.

Shifting from the five-membered ring of the proline-derived catalysts to the six-membered ring pipecolinic derivative **38** or its piperazidine analog **39** improved the enantioselectivity.[114] A broad range of imines can be reduced with these types of catalyst[25a,b] with good yields and enantioselectivities (*ee* up to 99%), with a remarkable extension of the substrate scope of aromatic and aliphatic ketimines (**Figure 47**).

Replacement of the formamide moiety in the valine-derived catalysts by other amides results in a dramatic decrease in reactivity and enantioselectivity. However, replacement of the formyl group in the original proline-derived catalyst by the picolinic amide, combined with a sterically hindered tertiary hydroxyl group in place of the amide group of the proline, offered improved enantioselectivity and generated a new type of catalyst for the trichlorosilane-mediated reduction.[115] The first examples of picolinic amide derivatives, developed by Matsumura et al.[116] were however not very selective for the reduction of different aryl methyl *N*-phenyl imines (**Figure 48**, catalyst **40**). The enantiomeric excess could be slightly improved by the use of *N*-*p*-methoxyphenyl or *N*-benzyl ketimines.

Chiral picolinic amide-derivative **41**, prepared from commercially available (*S*)-picolinic acid and (1*S*, 2*R*)-ephedrine, was employed in the reduction of *N*-aryl ketimines.[117] Good enantioselectivities (up to 92% *ee*) and yields were obtained for various aryl methyl ketimines. Phenyl ethyl and cyclohexyl methyl *N*-*p*-methoxyphenyl imines were also reduced with modest

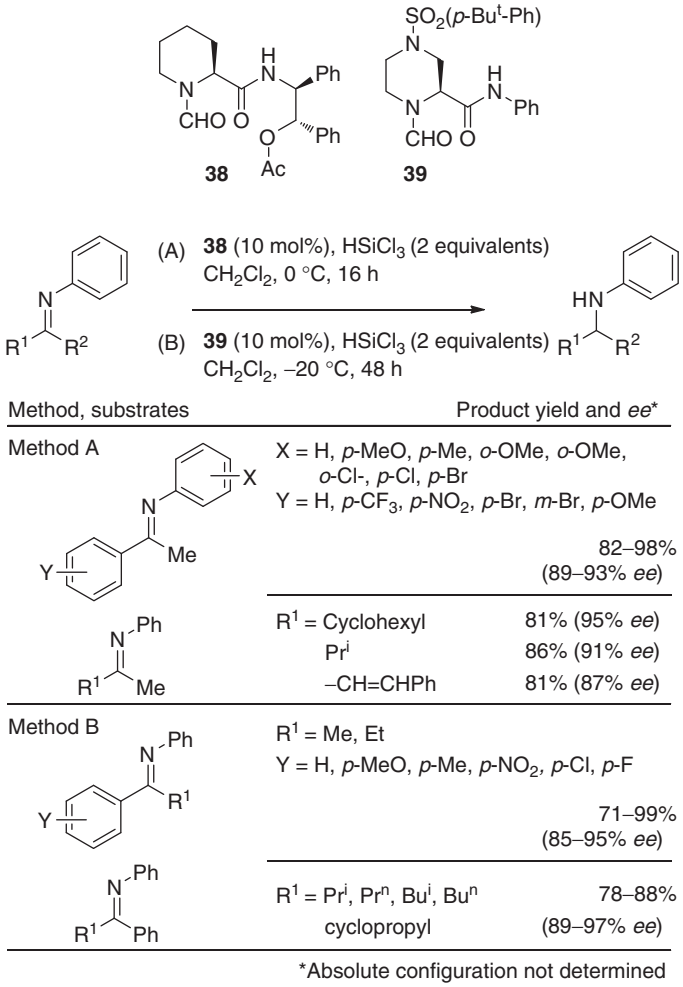


Figure 47 Enantioselective hydrosilylation of *N*-aryl imines with $HSiCl_3$ using pipecolinic or piperazidine derivatives as catalysts.

enantioselectivities (84 and 61% *ee*). Regarding cyclic *N*-*p*-methoxyphenyl imines, the authors reported mediocre enantioselectivity for 1-indanone (90% yield, 68% *ee*) but greatly increased stereoselectivity for 1-tetralone (85% yield, 95% *ee*) using organocatalyst **41**.

The scope of this type of Lewis basic pipecolinic acid-derivatives significantly expanded to α-imino esters,[118] benzoxazinones, quinoxalinones,[119] and benzodiazepinones.[120] Highly enantioselective hydrosilylation of α-imino esters was achieved with catalyst **42**, derived from *trans*-4-hydroxy-L-proline, and trichlorosilane. Several acid additives were employed, of which pentanoic acid proved to be the most effective (Figure 49). For substituted phenyl ethyl esters, substituents in *para* or *meta* positions showed equally high reactivities (90–97% yield) and enantioselectivities (86–93% *ee*), regardless of the electronic nature of the substituent. However, substitution at the *ortho* position of the phenyl group caused a significant drop in the enantiomeric excess.

Picolinic amide-derivative **41** promoted a highly enantioselective hydrosilylation of both benzoxazinones and quinoxalinones.[119] For 3-substituted phenylbenzoxazinones, electron donating and electron withdrawing substituents *para* or *meta* on the phenyl group were well tolerated affording various chiral dihydrobenzoxazinones in high yields (90–98%) and with high enantioselectivities (80–97% *ee*). Substitution in the *ortho* position of the phenyl group resulted in lower enantiomeric excess (Figure 50, R=2-MeO-C_6H_2, 48% *ee*). Two 3-alkylbenzoxazinones were evaluated (R=Me and R=$PhCH_2CH_2$) providing the desired products in good yields (86–96%) but poor selectivities (16–8% *ee*). Extension of this method to 3-aryl substituted quinoxalinones gives the corresponding dihydroquinoxalinones. Once again, unfavorable effects were observed with the *ortho* substitution on the phenyl group in position 3 (R^2=2-Cl-C_6H_4, 37% *ee*), whereas *para* and *meta* substituents presented generally good yields (89–98%) and enantioselectivity (89–94% *ee*). 3-Alkyl quinoxalinones (R^2=Me) generated the corresponding reduced product in good yield (95%) but very low enantiomeric excess (8% *ee*).

In addition to chiral formamide catalysts, it was shown that quinoline, isoquinoline, and pyridine-derived chiral oxazolines may be efficient promoters for the hydrosilylation of imines. In 2006 Malkov and Kočovský developed novel chiral Lewis bases, such as oxazolines containing isoquinoline fragments. The catalyst **43** was employed in reductions of aromatic ketones and imines with trichlorosilane, providing the products with good levels of enantioselectivity[121] (Figure 51). A few examples of aryl

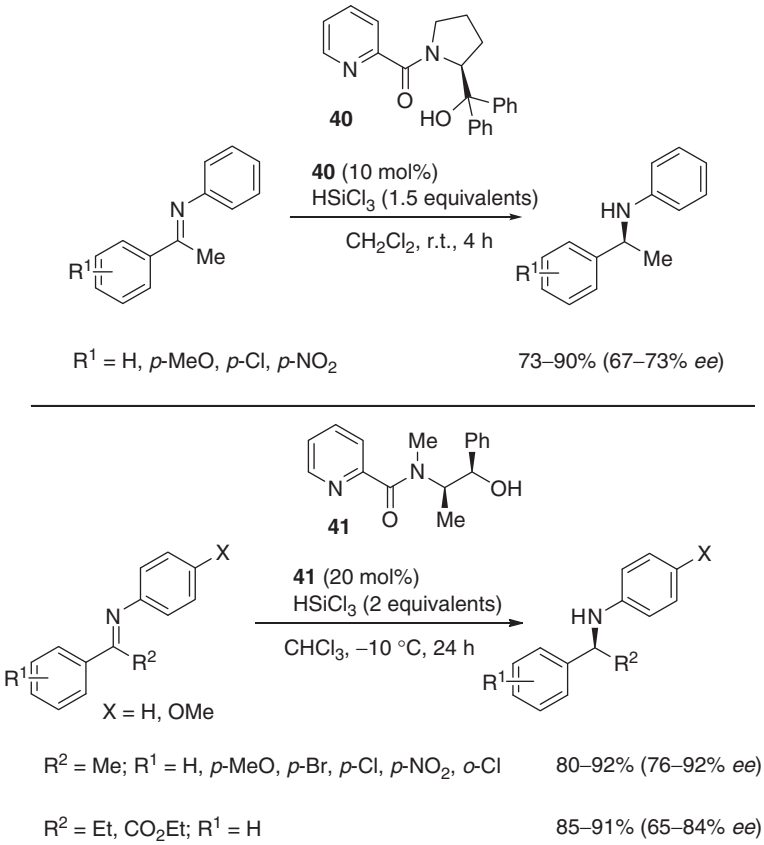


Figure 48 Enantioselective reduction of aryl alkyl ketimines with $HSiCl_3$ using picolinic amide-derivatives as catalysts.

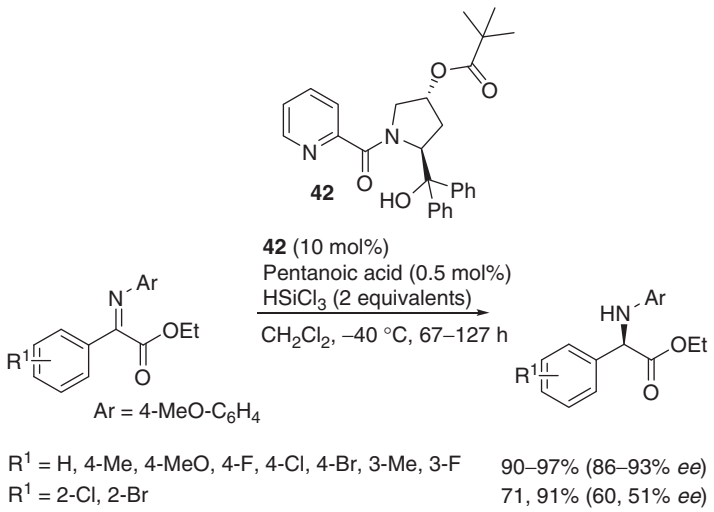


Figure 49 Enantioselective reduction of α-imino esters with $HSiCl_3$.

methyl *N*-aryl imines were reduced in the presence of **43** (20 mol%) and trichlorosilane (2 equivalents) in $CHCl_3$ at $-20\ ^{\circ}C$ for 24 h, affording the optically active amines in moderate yield (51–67%) and good enantiomeric excess (85–87% *ee*).

The *N*-methylated imidazole bifunctional catalyst **44** was found[25c] to be a very efficient catalyst for the reduction of a variety of *N*-*para*-methoxyphenyl imines, with a remarkably low catalyst loading (1 mol%) and short reaction times (4 h). In general, good yields (59–96%) and selectivities (73–87% *ee*) were observed (Figure 52). Reduction of *N*-phenyl imines was equally efficient.

In 2006, the first example of *S*-chiral compounds as highly effective organocatalysts for the asymmetric reduction of ketimines with trichlorosilane in high yield and enantioselectivity was reported.[122] Using catalyst **45** (20 mol%), the reduction of several

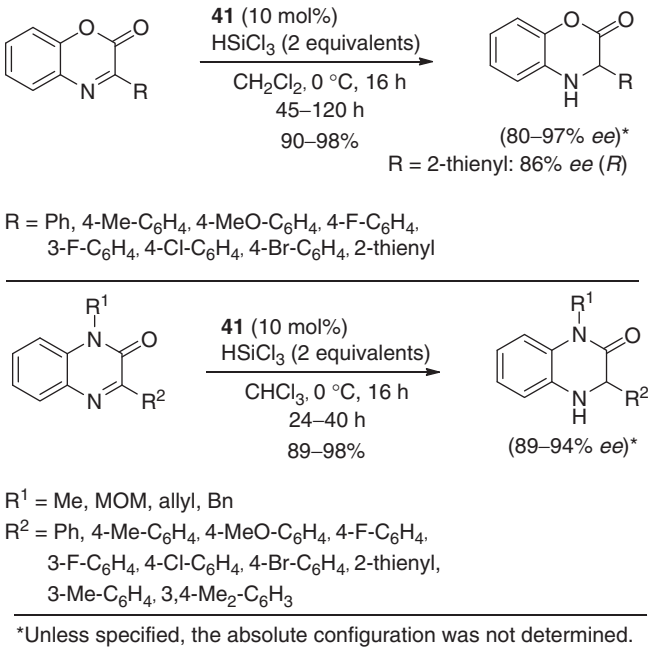
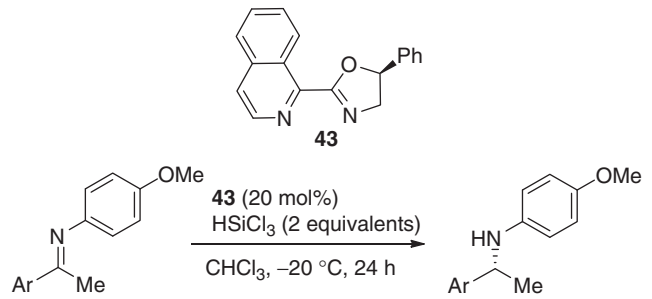


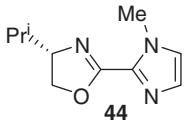
Figure 50 Enantioselective reduction of benzoxazinones and quinoxalinones with $HSiCl_3$.



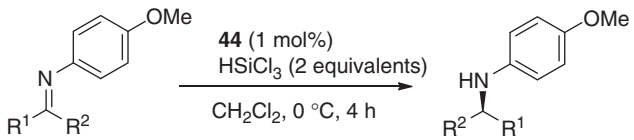
Ar	Yield (%)	*ee* (%)
Ph	60	85
2-Naphthyl	67	86
4-MeO-C_6H_4	51	87
4-CF_3-C_6H_4	65	87

Figure 51 Enantioselective reduction of ketimines with $HSiCl_3$ using an oxazoline-derived organocatalyst.

electron-deficient and electron-rich *N*-phenyl ketimines was performed in CH_2Cl_2 as solvent and at -20 °C for 24–48 h affording the products in high yield (92–98%) and enantioselectivity (90–93% *ee*). Notably, phenyl alkyl *N*-aryl ketimines with alkyl groups other than methyl (such as ethyl, propyl, butyl, or *iso*-butyl) were also good substrates for the reaction (82–94%, 86–93% *ee*) (Figure 53, method A). On the assumption that the mechanism would involve two molecules of Lewis base for the activation of $HSiCl_3$, a novel chiral bis-sulfinamide **46** was developed.[31,123] The authors reported remarkably high enantioselectivity (more than 99% *ee*) for the very uncommon *N*-benzylimine substrates. Two different methods were optimized, employing catalyst **46** (10 mol%) and $HSiCl_3$ (2 equivalents) at 0 °C for 24 h, differing in the solvent of choice, toluene or CCl_4 (Figure 53, methods B and C). A variety of aryl methyl *N*-benzylimines afforded the corresponding amines in good yield (80–98%) and enantioselectivity (91 to >99% *ee*). Phenyl ethyl *N*-benzylimine was also reduced with this system (80%, 89% *ee*) in toluene as solvent. In addition to *N*-benzyl substrates, the use of other *N*-alkyl substrates was reported to proceed with good yields and selectivities, which is unexpected and remarkable, because activated imines are generally required for this type of transformation (see Section 8.03.1 for discussion on imine activation). The system was applied to the reduction of aryl methyl *N*-propyl, *N*-*iso*-butyl, and *N*-allyl imines. Phenyl methyl *N*-propyl imine and phenyl methyl *N*-*iso*-butyl imine afforded, in CCl_4, slightly reduced yields (60 and 80% respectively) but high enantioselectivities (90 and 87% *ee*). Several *N*-allylimines were reduced in toluene providing good yields (65–97%) and enantioselectivities (83–97% *ee*) (Figure 53).

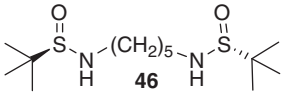


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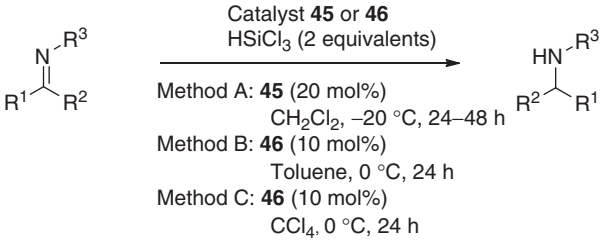


R^1	R^2	Yield (%)	*ee* (%)
Me	Ph	96	87
	4-CF_3-C_6H_4	72	82
	4-MeO-C_6H_4	81	85
	4-NO_2-C_6H_4	85	86
	1-Naphthyl	71	74
	2-Naphthyl	86	86
	Cyclohexyl	85	73
Et	Ph	95	83

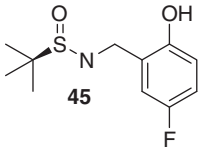
Figure 52 Enantioselective reduction of ketimines with $HSiCl_3$ using an imidazole-derived organocatalyst.



46



R^3	Method	R^1	R^2	Yield (%)	*ee* (%)*
Ph	A	Me	Ph	92	92 (*S*)
			4-CF_3-C_6H_4	93	92
			4-NO_2-C_6H_4	94	90
			4-OMe-C_6H_4	92	92
		Et	Ph	92	93
		Pr^n	Ph	87	91
		Bu^n	Ph	94	93
		Bu^t	Ph	82	86
Bn	B	Me	Ph	98	97 (*R*)
	B		4-F-C_6H_4	80	97
	B		4-NO_2-C_6H_4	80	>99
	C		4-OMe-C_6H_4	90	92
	B	Et	Ph	80	89
Allyl	B	Me	Ph	82	92
	B		2-Cl	75	97
	C		4-F	83	96
Pr^n	C	Me	Ph	60	90
Bu^i	C			80	87



45

*Absolute configuration not determined unless specified.

Figure 53 Enantioselective reduction of *N*-alkyl ketimines with $HSiCl_3$ using *S*-chiral sulfonamide catalysts.

The discovery of zinc, copper, and rhenium catalysts, as well as the use of newly designed chiral Lewis bases, which complement other organocatalytic methods, herald rapid developments in the area of the synthesis of chiral amines by asymmetric hydrosilylation of imines. A highly enantioselective catalytic system with broad scope remains elusive, but many of these methods have the advantage of inexpensive reducing reagents and mild reaction conditions.

8.03.5 Amine Synthesis from Reductive Amination of C═O

Reductive amination is an attractive one-pot conversion of aldehydes or ketones to a primary or secondary amines without isolation of the intermediate imine. In this process, a reductant coexists with the starting carbonyl compound. A particular advantage of this strategy is that it can potentially tolerate substrates that are normally not compatible with direct imine reduction due to their inherent instability (such as dialkyl imines). However, this transformation (asymmetric or nonasymmetric) is not trivial, and avoiding the reduction of the starting reagent ketone to alcohol is challenging. Not many efficient methods are known for the reductive amination of ketones, and very few of them are asymmetric. The authors will evaluate metal- and organocatalyzed transfer hydrogenation and hydrosilylation processes, where hydride delivery occurs from C (or Si) sources: namely, (1) formic acid or its derivatives, (2) Hantzsch esters or other *N*-heterocycles, and (3) trichlorosilane. Some of these procedures offer milder reaction conditions than catalytic hydrogenation with H_2, and the major advantage is chemoselectivity, due to the high tolerance to other reducible moieties such as cyano and nitro groups.

8.03.5.1 Reductive Amination with Hydride Delivery from Formic Acid or its Derivatives

The reaction with formic acid as reductant is known as the Leuckart–Wallach reaction. Varieties of this approach use ammonium formate, formamide, or mixtures of formamide/formic acid. It is a simple reaction, but has several problems such as the requirement of high temperatures (usually above 180 °C) and the concomitant formation of *N*-formyl derivatives that have to be hydrolyzed with acid. This makes the Leuckart–Wallach reaction incompatible with thermally unstable and acid-sensitive molecules. An improved and high yielding protocol to prepare racemic secondary and tertiary amines has been described by heating an aldehyde or a ketone with inexpensive solid ammonium formate in refluxing toluene or benzene (Figure 54(a)).[124] A milder procedure that requires lower temperature (50–70 °C) was described to proceed with high chemoselectivity in the reductive amination of simple ketones catalyzed by a $Cp^*Rh(III)$ complex using $HCOONH_4$ (Figure 54(b)). For example, in the reaction with acetophenone in methanol and 0.05 mol% of the catalyst, 1-phenyl ethyl amine was formed with over 96% selectivity and isolated with 90% yield. The method was also applied to the synthesis of α-amino acids from α-keto acids.[125]

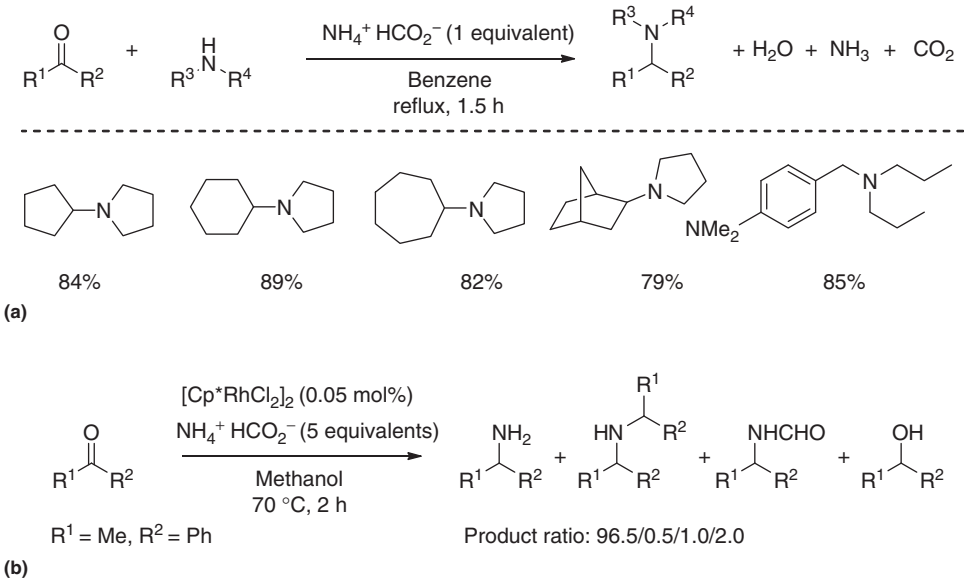


Figure 54 Leuckart–Wallach-type reductive amination of ketones.

An impressive variety of aliphatic and aromatic carbonyl compounds combined with aromatic or aliphatic amines (or with ammonium formate to form primary amines) in a mixture formic acid/triethyl amine/methanol underwent efficient reductive amination (71–98% yield) at 80 °C with the air-stable cyclometalated imido Ir(III) catalyst **47**.[126] This method gives amine products that are generally difficult to obtain by reduction of imines due to the instability of the starting imines, and holds a high potential for the design of chiral catalysts for an asymmetric version of the reductive amination reaction (Figure 55).

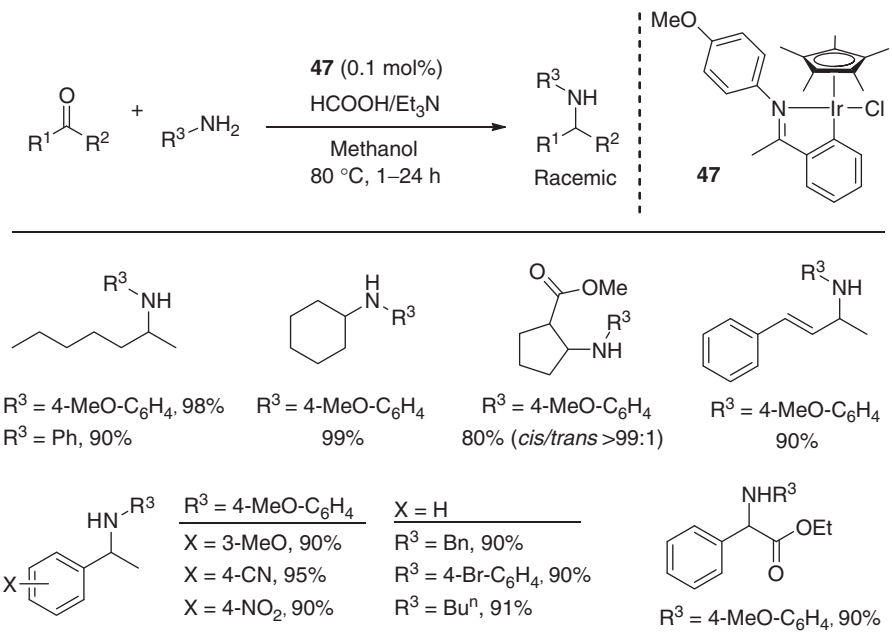
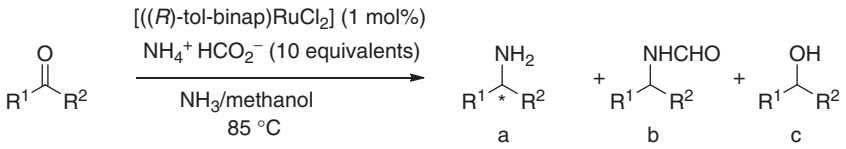


Figure 55 Iridium-catalyzed Leuckart–Wallach-type reductive amination of ketones.

An asymmetric synthesis of primary amines from ketones by reductive amination with ammonium formate as hydrogen donor was disclosed by Kadyrov and Reirmeier (Degussa AG).[127] 2-Propanol and formic acid were also investigated as hydride sources with inferior results. Various Rh, Ir, and Ru catalysts were tested, with ruthenium-derived catalysts affording higher enantioselectivities. Among the ligands screened, 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl was more selective. Acid additives enhanced the reactivity but diminished the stereoselectivity, and the addition of ammonia caused the opposite effects. The optimized method used ammonia/methanol as solvent, at temperatures between 60 and 85 °C, and 1 mol% of catalyst [((*R*)-tol-binap)$RuCl_2$]. The desired product was formed as a mixture of the free amine and the *N*-formylated product, which had to be hydrolyzed. With aromatic ketones good yields were obtained (69–93%) and high enantioselectivities (86–98% *ee*). The method was not valid for aliphatic ketones, which offered low yields and selectivities (Figure 56).



R^1	R^2	Time (h)	Ratio a:b:c	a, Yield (%) after hydrolysis	a, *ee* (%)*
Me	Ph	20	75:19:1	92	95
	3-Me-C_6H_4	24	38:39:0	74	89
	4-Me-C_6H_4	21	8:91:0	93	93
	4-MeO-C_6H_4	24	64:32:1	83	95
	4-Cl-C_6H_4	24	6:94:0	93	92
	4-Br-C_6H_4	48	10:90:0	56	91
	4-NO-C_6H_4	48	45:55:0	92	95
	1-Naphthyl	30	11:69:6	69	86
Et	Ph	21	22:78:0	89	95

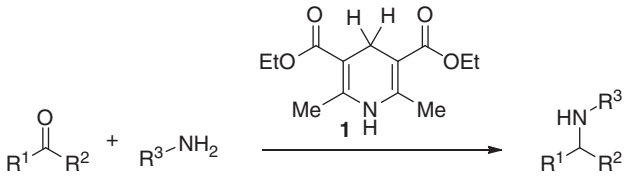
*Products a have the (*R*) configuration.

Figure 56 Enantioselective Leuckart–Wallach-type reductive amination of ketones.

8.03.5.2 Reductive Amination with Hydride Delivery from *N*-Heterocycles

The use of *N*-heterocycles as hydride donors has generated several procedures for the preparation of racemic as well as enantioenriched amines through reductive amination. Hantzsch ester-mediated transformations were achieved by several

strategies: hydrogen bond catalysis, Brønsted acid catalysis, and metal-based catalysis. An acid-free reaction, mediated by thiourea as organocatalyst, was reported for the reductive amination of aldehydes[128] and ketones.[129] The reaction was performed in toluene with Hantzsch ester **1** (1.5 equivalents), at 50 °C and in the presence of 5 Å molecular sieves, using catalytic quantities (0.1–1 mol%) of thiourea (method A, Figure 57). The reaction conditions were optimized in the reaction of acetophenone with equimolar amounts of *para*-anisidine and then applied to the reaction of less electron-rich amines or hindered anilines, with both aromatic and aliphatic ketones, with high efficiency (62–91% yield). The method also allowed the preparation of heteroaromatic amines such as furans, thiophenes and pyridines. The ability of *S*-benzyl isothiouronium chloride as catalyst in the reductive amination of aldehydes has been investigated.[130] Due to the enhanced acidity of the NH moieties, this catalyst was expected to provide better hydrogen bonding. The reactions were performed at room temperature in the heterogeneous conditions of the catalyst in CH_2Cl_2, allowing for its recovery by filtration. The procedure (method B, Figure 57) does not require the presence of molecular sieves, generally used to prevent the negative effect of water, and excellent yields (84–98%) were obtained with aromatic, aliphatic, heterocyclic, and cyclic aldehydes in combination with *para*-anisidine. However, aliphatic aldehydes required a slight increase of the temperature (70 °C) and a switch of solvent to toluene to obtain good yield. The presence of nitro, nitrile, carboxy, and hydroxy moieties was tolerated. The reaction of benzaldehyde with differently substituted anilines also proceeded with good yield. Highly convenient is the easy recovery of the *S*-benzyl isothiouronium catalyst by filtration and its reuse with the same efficiency. In addition to these organocatalytic approaches for the racemic reductive amination reaction with Hantzsch esters, one example of a homogeneous gold(I) catalyzed process is known. Gold catalysts, although pricey, usually function with very low catalyst loading and under mild reaction conditions. The reactions[131] were performed at room temperature in CH_2Cl_2, in the presence of Hantzsch ester **1** and with 1 mol% of $Ph_3PAuCl/AgOTf$, achieving high conversions within short reaction times (0.5–3 h) (method C, Figure 57). The method was successfully applied to the reaction of benzaldehyde with differently substituted anilines (in *ortho* and *para* positions) (89–95% yield), to the reaction of differently substituted aromatic aldehydes (in *ortho* and *para* positions) with aniline (89–96%), to the reaction of heteroaromatic aldehydes with aniline (87–95%), and finally to the reaction of aliphatic cyclic and acyclic ketones with aniline (87–94%).



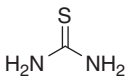
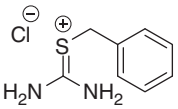
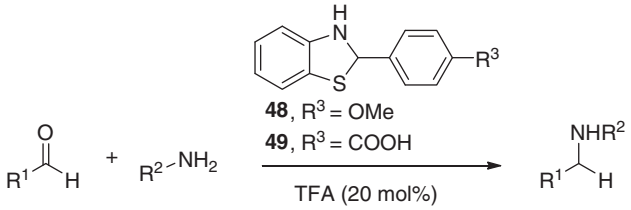
	Catalyst	Conditions	Substrates	Yield
Method A	 (10 mol%)	Toluene, 5 Å MS 50 °C **1** (1.5 equivalents) 48 h	R^1 = Me R^2 = Aryl, alkyl, heteroaryl R^3 = Aryl, pyridyl	62–91%
Method B	 (10 mol%)	CH_2Cl_2, r.t. **1** (1.5 equivalents) 12 h	R^1 = H R^2 = Ph R^3 = Aryl, Bn	92–99%
Method C	$Ph_3PAuCl/AgOTf$ (1 mol%)	CH_2Cl_2, r.t. **1** (2.5 equivalents) 0.5–3 h	R^1 = H, alkyl R^2 = Aryl, alkyl, heteroaryl R^3 = Aryl, Bn	89–96%

Figure 57 Reductive amination using Hantzsch esters in the synthesis of racemic amines.

An additional *N*-heterocyclic source of hydride has been used in nonasymmetric reductive amination, for the Brønsted acid-catalyzed reactions with benzothiazoline as reductant. A protocol[132] in which TFA (20 mol%) was used as catalyst (method A, Figure 58) in CH_2Cl_2 at room temperature was optimized for the reductive amination of aromatic aldehydes bearing electron-withdrawing, electron-donating, and bulky substituents with *para*-anisidine and using *para*-methoxyphenyl 2-substituted benzothiazoline **48** as hydride source. In general, good yields of the corresponding amines were achieved (90–99%) after 4–6 h of reaction. An aldimine derived from cinnamaldehyde underwent 1,2-reduction exclusively. In addition, heteroaromatic aldehydes and aliphatic aldehydes also gave similar yields with prolonged reaction times (up to 40 h). An improved protocol (method B, Figure 58) employing carboxyl-substituted benzothiazoline **49** in the presence of TFA as catalyst (20 mol%) and in

nonchlorinated solvents (acetonitrile) at room temperature was reported.[133] The method was applied to the reaction of several aromatic aldehydes and *para*-anisidine with good efficiency (79–91% yield). Remarkably, after the completion of the reaction (22 h), the excess of the carboxyl-substituted benzothiazoline and the corresponding oxidized product benzothiazole could be removed by simply washing with an aqueous 10% NaOH solution.



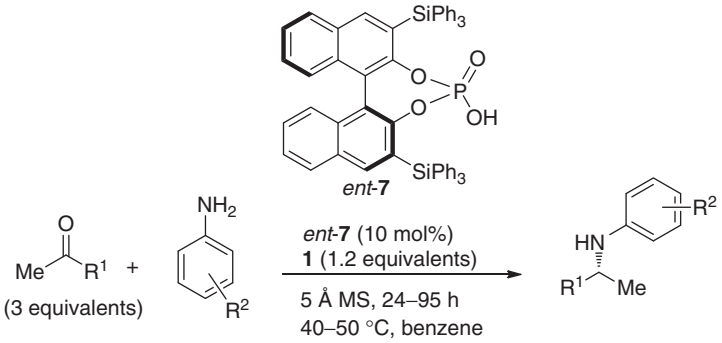
	Conditions	Substrates	Yield
Method A	CH_2Cl_2 r.t., 4–48 h **48** (1.2 equivalents)	R^1 = Aryl, heteroaryl R^2 = Aryl, alkyl	62–91%
Method B	CH_3CN, r.t., 22–26 h **49** (1.4 equivalents)	R^1 = Aryl R^2 = 4-MeO-C_6H_4	78–87%

Figure 58 Reductive amination using benzothiazolines in the synthesis of racemic amines.

Among the few Hantzsch ester-mediated reductive amination reactions in the literature, the first report of an intermolecular enantioselective process was described in 2006 by MacMillan et al.[134] A highly enantioselective organocatalytic protocol (Figure 59) was developed employing the BINOL-derived phosphoric acid *ent*-**7** (10 mol%), Hantzsch ester **1** (1.2 equivalents) and 5 Å molecular sieves in benzene at 40–50 °C in an excess of the ketone (3 equivalents). Highly stereoselective and efficient reductive amination of aromatic ketones (60–78%, 90–96% *ee*) and, remarkably, also of dialkyl ketones (49–75%, 81–94% *ee*) with *para*-anisidine was reported. Additionally, several aniline derivatives and heteroaromatic amines operated equally well for the reductive amination of aryl alkyl and dialkyl ketones. One single example of asymmetric Brønsted acid-catalyzed reductive amination was also reported by List et al.[39e] but proceeding through a sequential process, generating an imine from acetophenone followed by addition of a Hantzsch ester **1** and BINOL-derived catalyst **6** in the same pot.

List et al. discovered an alternative to this strategy where racemic α-branched aldehyde substrates[61a] can provide enantioenriched products on reductive amination via dynamic kinetic resolution. Under their reductive amination conditions, an α-branched aldehyde would undergo fast racemization in the presence of an amine and an acid, via imine/enamine tautomerization. In the presence of Hantzsch ester **2** and catalyst **6** (5 mol%) in benzene at 6 °C, one of the two imine enantiomers is reduced faster than the other, resulting in an almost enantiopure amine product. The efficient removal of water during the reaction seemed to be crucial, so the use of 5 Å molecular sieves was required. The generality of the method (method A, Figure 60) was demonstrated with a variety of 2-arylpropionaldehydes and *para*-anisidine (80–96% yield, 94–98% *ee*). Aliphatic aldehydes can also be employed with slightly lower enantioselectivity. Other anilines were also investigated, but the reaction was less efficient than with *para*-anisidine. In 2010, the same group extended this concept to the organocatalytic asymmetric reductive amination of α-branched ketones.[135] Substituted cyclohexanones were the preferred substrates for this transformation (method B, Figure 60). In the presence of Hantzsch ester **1** (1.4 equivalents), *para*-anisidine (1.1 equivalents), 5 Å molecular sieves and catalyst **6** in cyclohexane at 50 °C, a broad range of ketones formed the corresponding cyclohexylamines in good yields and diastereoselectivities and high enantioselectivities. 2-Alkyl-substituted substrates were more reactive, requiring only 1 mol% of catalyst, and more sterically hindered 2-substituted substrates required higher catalyst loadings (5–10 mol%). Although diastereoselectivities varied from modest to high (from 5:1 to 99:1 *dr*) depending on the substrate, the enantioselectivity was generally high (87–96% *ee*). When other cyclic ketones with different ring size were investigated, cyclopentanone derived substrates provided lower selectivity and cycloheptanone did not undergo reductive amination in the reaction conditions.

Also employing Hantzsch esters as reductants, the first example of a reductive amination of carbonyl compounds using a single nucleotide (adenosine 5′-diphosphate, ADP) has been reported for the asymmetric synthesis of different amines.[136] This combination of Hantzsch esters and ADP is an undeniably biomimetic model of the NADH-mediated biological processes. However, at the moment this method is restricted to the reductive amination of a small substrate scope of ketones. A variety of acetophenone derivatives were reacted with electron-rich and electron-poor primary amines. The reactions were performed in toluene, at 0 °C for 24 h, with 1.1 equivalents of Hantzsch ester **1** and 2 mol% of the catalyst **50**, affording the amines with high yield (85–96%) and good enantioselectivity (75–89% *ee*) (Figure 61). The investigation of other solvents (CH_2Cl_2, THF, benzene and others) led to lower stereoselectivity, and the use of different Hantzsch esters resulted in longer reaction times. Mononucleotides



R^1	R^2	Yield (%)	*ee* (%)
Aromatic: Ph, 4-MeO-C_6H_4, 4-Me-C_6H_4, 4-F-C_6H_4, 4-NO_2-C_6H_4, 4-Cl-C_6H_4, 2-F-C_6H_4, 3-F-C_6H_4, 2-naphthyl	4-MeO	60–87	90–96
Ph	Ph, 4-CF_3-C_6H_4	73–55	93–95
Aliphatic: Ethyl, hexyl, -CH_2CH_2Ph cyclohexyl, -CH_2OBz -$CH_2CH_2CH{=}CH_2$	4-MeO	49–75	81–94

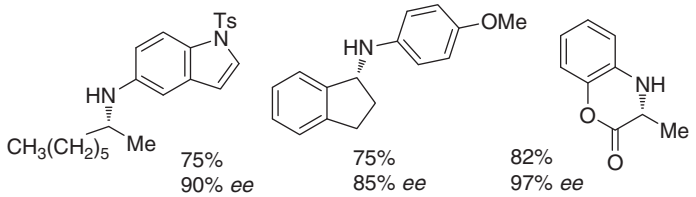
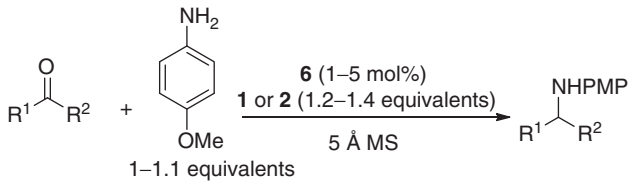


Figure 59 Enantioselective Brønsted acid-catalyzed organocatalytic reductive amination using Hantzsch esters.



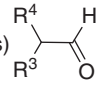
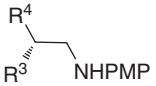
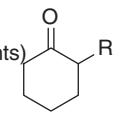
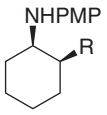
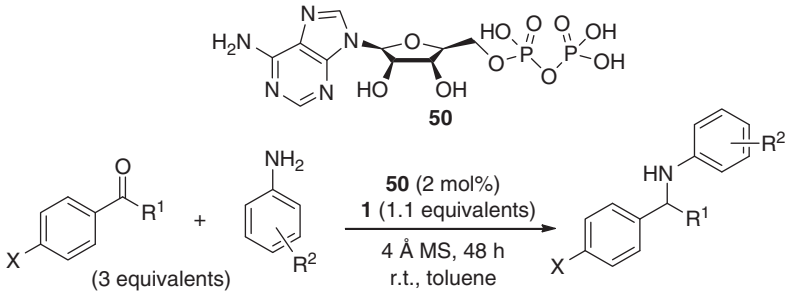
Method		Substrates	Yield (%)	Product, *ee*
A	**6** (5 mol%) **2** (1.2 equivalents) Benzene 6 °C, 72 h		40–96	 78–98% *ee*
	R^3 = Me, Et R^4 = Ph, 4-MeO-C_6H_4, CF_3, 1-naphthyl, 2-Naphthyl, 4-Br-C_6H_4, 2-F-C_6H_4, Bu^t, 3-F-C_6H_4, 2-thiophenyl, cyclohexyl			
B	**6** (1 mol%) **1** (1.2 equivalents) cyclohexane 50 °C, 72 h		63–92 *dr* 5:1 to >99:1	 87–96% *ee*
	R = Me, Et, Pr^n, Bn, Ph, Cl allyl, 1-cyclohexenyl, 2-thiophenyl			

Figure 60 Enantioselective organocatalytic reductive amination via dynamic kinetic resolution using Hantzsch esters.

are commercially available and this purely biomimetic approach could also be relevant for other scientific fields such as biochemistry.



R^1	X	R^2	Yield (%)	*ee* (%)
Me	H	H	96	82 (*R*)
Me	MeO	4-MeO	91	89
Me	Cl	4-MeO	96	88
Et	H	4-MeO	95	85
Bu^n	H	4-MeO	94	75

Figure 61 Enantioselective single nucleotide-catalyzed organocatalytic reductive amination using Hantzsch esters.

8.03.5.3 Reductive Amination with Hydride Delivery from Trichlorosilane

Additionally, organocatalytic protocols for the asymmetric reductive amination of ketones with trichlorosilane as hydride source have been developed. The reaction of acetophenone and anilines was first investigated by Benaglia et al.[115] They provided three examples of the reductive amination process for different substrates in CH_2Cl_2 or $CHCl_3$ at 0 °C or −20 °C in the presence of catalyst **51** (10 mol%) and 3 equivalents of $HSiCl_3$ (method A, Figure 62). In 2011, Jones et al.[137] developed a method employing a low loading of catalyst **52** (1 mol%) in CH_2Cl_2 at 0 °C and with 2 equivalents of trichlorosilane (method B, Figure 62).

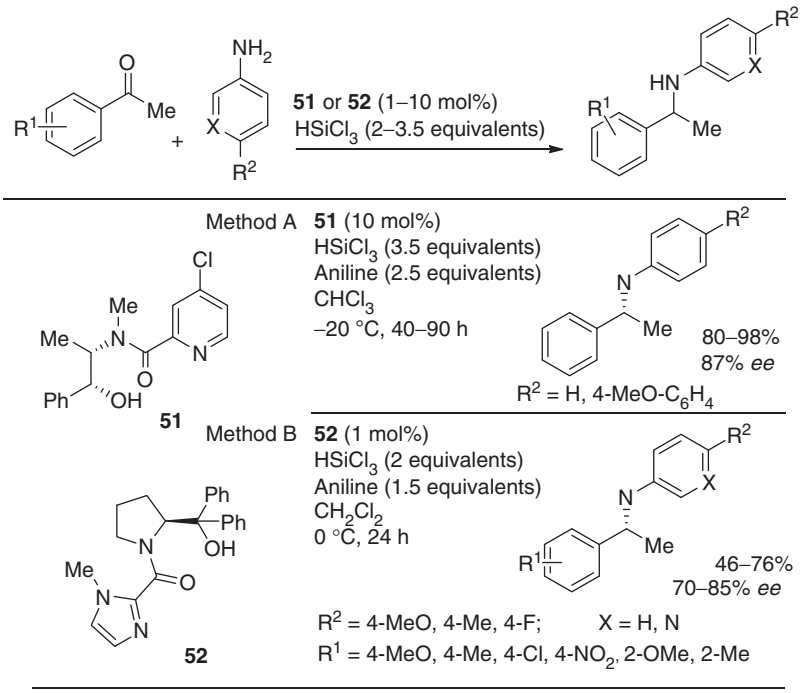


Figure 62 Enantioselective organocatalytic reductive amination using trichlorosilane.

Both electron-rich and electron-poor aryl methyl ketones with *para*-anisidine afforded the amines with good enantioselectivities (70–84% *ee*), although lower yields were attained with electron poor ketones. *Ortho*-substitution and sterically demanding substrates resulted in reduced enantioselectivity. Propiophenone afforded the amine in high enantioselectivity (85% *ee*) but low yield (15%). However, longer aliphatic chains (employing benzyl ketones or conjugated cinnamyl ketones) provided high yield (77–82%) but lower selectivity (0–15% *ee*). Various aromatic imines could also be used, such as *para*-methyl aniline or *para*-fluoro aniline with good results (65% yield, 81–84% *ee*), but 3-aminopyridine afforded the product with low enantiomeric excess (10% *ee*) although in good yield (58%).

The preliminary reports of organocatalytic asymmetric reductive amination provide very encouraging results, in terms of stereoselectivity and substrate scope, for the synthesis of optically active amines. This suggests that forthcoming advances will probably be focused on investigating new processes, built on the knowledge acquired from the parallel and fast development of the asymmetric reduction of imines using Hantzsch esters and trichlorosilane as reducing agents. Mild and environmentally friendly conditions stand as the most significant advantages of these methods, with the main challenges for the future being lowering the catalysts loadings and the reaction times, and the recycling of the catalyst and the reductant.

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8.04 Reduction of C═O to CHOH by Metal-Catalyzed Hydrogenation and Transfer Hydrogenation

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8.04.1 Introduction

Reduction of carbonyl compounds leads to alcohols, one of the most often encountered functional groups in organic synthesis. Although the transformation can be effected with various metal hydrides in stoichiometric quantities, hydrogenation with H_2 is preferred, a reaction which is clean, economic, and readily scalable. In the last two decades or so, hydrogenation with hydrogen sources other than H_2, that is, transfer hydrogenation (TH), has gained a great deal of significance, because of the easy availability of various hydrogen sources, operational simplicity, and avoidance of hazardous hydrogen gas. This chapter summarizes the major advances in carbonyl reduction via hydrogenation and TH made mainly in the two decades since 1990.

8.04.2 Hydrogenation of Carbonyl Groups with H_2

8.04.2.1 Hydrogenation of Functionalized Ketones

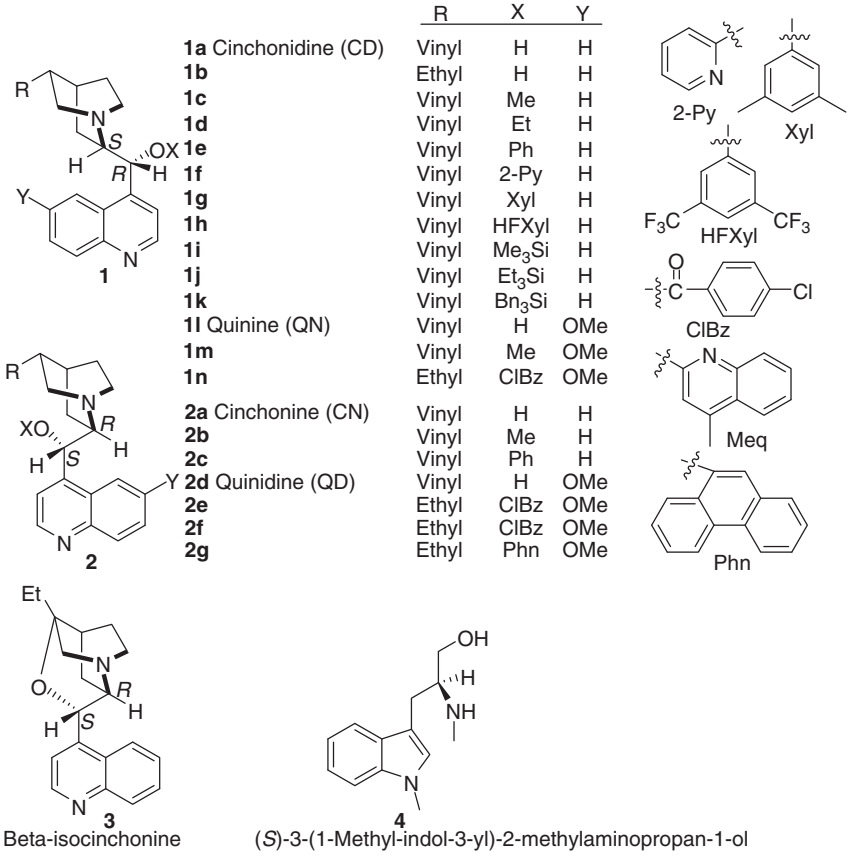
8.04.2.1.1 Hydrogenation of ketoesters

Catalytic asymmetric hydrogenation (AH) of α- or β-ketoesters is an efficient and economical method for preparing optically active α- or β-hydroxyl acids and their derivatives, important intermediates for pharmaceuticals and natural products. These ketoesters can be hydrogenated by using either heterogeneous or homogeneous catalysts.

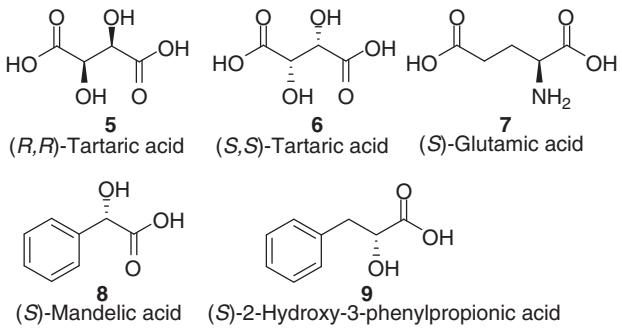
 doi:10.1016/B978-0-08-097742-3.00806-5

8.04.2.1.1.1 Heterogeneous hydrogenation of α- or β-ketoesters

The heterogeneous hydrogenation of α- or β-ketoesters has been widely explored since the 1960s. The catalysts initially used were PtO_2, Pd/C, $Pd/CaCO_3$, $Pd/BaSO_4$, and Raney nickel.[1–9] Among these catalysts, cinchona-modified Pt/Al_2O_3[10–12] and tartrate-modified Raney nickel[13,14] are the most successful for the hydrogenation of α- and β-ketoesters, respectively. These two catalysts have been most intensively studied in various enantioselective heterogeneous hydrogenation reactions, and have been exploited on an industrial scale.[9,15,16] The reduction of ethyl pyruvate to ethyl lactate has drawn particular attention, including studies carried out in batch reactors[17–20] as well as continuous measurements performed in fixed-bed reactors.[21–26] Schemes 1 and 2 show chiral molecules that were used for the modification of Pt (Cinchona alkaloids and derivatives) and Raney Ni (chiral acids), respectively. The main drive of recent studies into these two catalytic systems is to expand their field of use, elucidate the reaction mechanism, and understand the origin of enantioselectivity. It has been found that the two catalytic systems cannot be generally applied to enantioselective hydrogenation; that is, they only allow for high enantioselectivities for certain types of compounds. High *ee* values were initially achieved mainly in the hydrogenation of α-ketoesters using the Pt-cinchona catalyst and in that of β-ketoesters using the tartaric acid (TA) modified Ni catalyst in the presence of NaBr.[3,4,27–34] The minimal requirement for



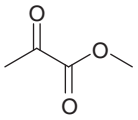
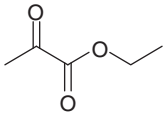
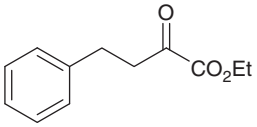
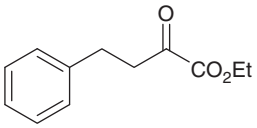
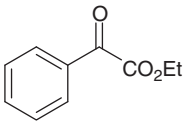
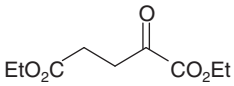
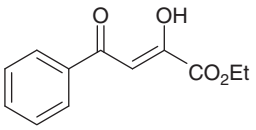
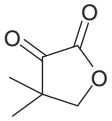
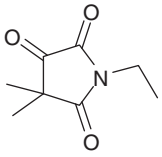
Scheme 1 Cinchona alkaloids and derivatives used for the modification of Pt.



Scheme 2 Chiral organic acids used for the modification of Raney nickel.

an efficient modifier for the hydrogenation of α-ketoesters appears to be a basic N atom, one or more stereogenic centers and an aromatic system, as evidenced by the modifiers **1**–**4**, which contain conjugated, flat aromatic rings (Scheme 1). Detailed study into the hydrogenation of ethyl pyruvate with a variety of cinchona derivatives has shown that cinchonidine or slightly altered derivatives as modifiers give ethyl (*R*)-lactate in the highest *ee*'s, whereas cinchonine derivatives afford the (*S*)-enantiomer, albeit in lower *ee*'s. Three structural elements in the cinchona molecule were identified to affect both the rate and enantioselectivity of the hydrogenation of α-ketoesters: an extended aromatic moiety, the substitution pattern of the quinuclidine (with the absolute configuration at C8 controlling the sense of asymmetric induction and *N*-alkylation resulting in racemate), and the substituent at C9 (with OH or MeO being optimal and larger groups reducing *ee* values). The choice of solvent has a significant effect on both *ee* and reaction rate as well. Thus, **1c**/acetic acid and **1b**/toluene are the most effective modifier/solvent combinations. Selected examples of AH of α-ketoesters showing the best *ee* values are presented in Table 1.[18,35–47] However, the reaction conditions have to be optimized for every single substrate. Toward the end, various strategies have been applied, including using special colloids, ultrasound, solvent mixtures, and additives. For the aliphatic α-ketoesters, AcOH in combination with MeO-**1b** or **1b** afforded the

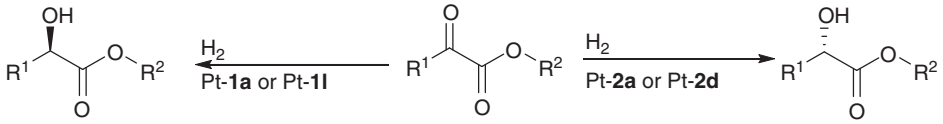
Table 1 Best *ee* values from the heterogeneous hydrogenation of α-ketoesters

Entries	*Substrate*	ee *(%)*	*Catalyst*	*Modifier*	*Solvent*	*Conditions*	*References*
1		98	Pt colloids	**1a**	AcOH	40 bar H_2, 25 °C	47
2		97	Pt/Al_2O_3 5%	MeO-**1b**	AcOH	10 bar H_2, 25 °C, ultrasound	42
3		96	Pt/Al_2O_3 5%	MeO-**1b**	AcOH	10 bar H_2, 25 °C, ultrasound	42
4		94	Pt/Al_2O_3 1%	**1b**	AcOH	5.8 bar H_2, 17 °C, dosing of modifier	18,39
5		98	Pt/Al_2O_3 5%	**1b**	AcOH /Toluene	25 bar H_2, 0 °C	41
6		96	Pt/Al_2O_3 5%	MeO-**1b**	AcOH	20 bar H_2, 20 °C	35
7		86	Pt/Al_2O_3 5%	**1b**	Toluene	60 bar H_2, 25 °C	37,40
8		60	Pt/Al_2O_3 5%	**1a**	AcOH	60 bar H_2, r.t.	46
9		92	Pt/Al_2O_3 5%	**1a**	Toluene	70 bar H_2, −13 °C	38
10		91	Pt/Al_2O_3 5%	**1a**	Toluene	70 bar H_2, 17 °C	38

best results in terms of both reaction rate and enantioselectivity. Both acidic and basic additives improve the enantioselectivity of the products. However, for the aromatic, conjugated, and cyclic substrates, the combination of **1b** and toluene was optimal. Bulky substituents on the ester moiety can cause a significant decrease in both the reduction rate and enantioselectivity.[48]

Further examples of the hydrogenation of pyruvate derivatives with Pt catalysts are presented in Table 2, where various modifiers are featured. There were some unexpected inversions of enantioselectivity.[3,5,30,49–75] Thus, the (*S*)-enantiomer was formed when very low concentrations of the alkaloid modifier were used, whereas at higher modifier concentrations, the (*R*)-enantiomer was formed under otherwise identical reaction conditions (entry 2, Table 2). Likewise, by using modifier **3** (Scheme 1), a significant solvent effect was observed in the hydrogenation of ethyl pyruvate: in toluene, unlike in AcOH, the expected (*R*)-ethyl lactate was produced in excess (entry 6, Table 2). The ability of modifier **3** to cause inversion was also demonstrated over

Table 2 Heterogeneous hydrogenation of α-ketoesters

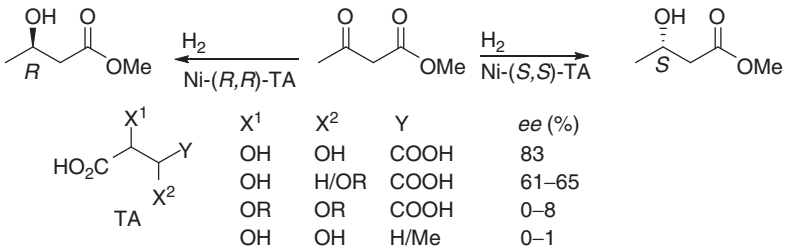


Entries	ee *(%)*	*Catalyst*[a]	*Solvent*	*Temperature (°C)*	*H_2 (bar)*	*R^1*	*R^2*	*Catalyst*	*Solvent*	ee *(%)*	*References*
1	70	Pt-**B/1a**	EtOH	24	70	Me	Me	Pt-**B/2a**	EtOH	65	50
2	20	Pt-**A/1b**/high	MeOAc	25	1	Me	Et	Pt-**A/1b**/low	MeOAc	8	76
3	18	Pt-**A/2g**	EtOH	20	100	Me	Et	Pt-**A/2g**	AcOH	4	53
4	11	Pt-**A/2f**	EtOH	20	100	Me	Et	Pt-**A/2f**	AcOH	13	53
5	37	Pt-**A/4**	Toluene	25	1	Me	Et	Pt-**A/4**	AcOH	9	54
6	48	Pt-**A/3**	Toluene	25	1	Me	Et	Pt-**A/3**	AcOH	50	57,60,63,64
7	27	Rh-**A/3**	Toluene	r.t.	10	Me	Et	Rh-**A/2a**	Toluene	41	30
8	74	Pt-**A/1a**	Toluene	r.t.	1	Me	Et	Pt-**A/1g**	Toluene	32	62
9	8	Pt-**A/2e**	DCM	r.t.	50	Me	Et	Pt-**A/2e**/low	DCM	32	70
10	20	Pt-**A/1m**	DCM	r.t.	50	Me	Et	Pt-**A/2e**/high	DCM	14	70
11	17	Pt-**B/2e**	Gas-phase	10	50	Me	Et	Pt-**B/2e**/low	Gas-phase	15	68
12	15	Pt-**B/1m**	Gas-phase	10	50	Me	Et	Pt-**B/1m**/high	Gas-phase	10	68
13	80	Pt-**A/1a**	THF	r.t.	1	Me	Et	Pt-**A/1i**	THF	28	66
14	80	Pt-**A/1a**	THF	r.t.	10	Me	Et	Pt-**A/1e**	THF	36	72
15	80	Pt-**A/1a**	THF	r.t.	10	Me	Et	Pt-**A/1j**	THF	20	66
16	80	Pt-**A/1a**	THF	r.t.	10	Me	Et	Pt-**A/1k**	THF	19	66
17	52	Pt-**A/1f**	THF	r.t.	10	Me	Et	Pt-**A/1e**	THF	36	72
18	15	Pt-**A/2a**	EtOH	0	60	Me	Et	Pt-**A/2a**	EtOH	26	69
19	50	Rh-**A/1a**	Toluene	r.t.	10	Pr^i	Et	Rh-**A/2a**	Toluene	43	30
20	29	Rh-**A/1l**	Toluene	r.t.	10	Pr^i	Et	Rh-**A/2d**	Toluene	19	30
21	33	Rh-**A/3**	Toluene	r.t.	10	Pr^i	Et	Rh-**A/2a**	Toluene	43	30
22	21	Rh-**A/3**	AcOH	r.t.	10	Pr^i	Et	–	–	–	30
23	50	Pt-**A/3**	Toluene	r.t.	1	Ph	Me	Pt-**A/2a**	Toluene	78	27,77,78
24	46	Pt-**A/3**	Toluene	r.t.	1	Ph	*Cy*-hexyl	–	–	–	77
25	50	Pt-**A/3**	Toluene	r.t.	1	Ph	Adamantyl	–	–	–	77
26	35	Pt-**A/3**	Toluene	r.t.	1	Ph	Decalyl	–	–	–	77
27	8	Pt-**A/3**	Toluene	r.t.	1	Ph	Ph	–	–	–	77
28	54	Pt-**A/3**	Toluene	r.t.	1	Ph	1-Naphthyl	–	–	–	77
29	20	Pt-**A/3**	Toluene	r.t.	1	Ph	2-Naphthyl	–	–	–	77
30	92	Pt-**A/1a**	Toluene	r.t.	10	3,5-$Me_2C_6H_3$	Et	Pt-**A/1e**	Toluene	52	79
31	87	Pt-**A/1a**	Toluene	r.t.	10	3,5-$F_2 \cdot C_6H_3$	Et	Pt-**A/1e**	Toluene	68	79
32	66	Pt-**A/1a**	Toluene	r.t.	10	3,5-$(CF_3)_2$ C_6H_3	Et	Pt-**A/1e**	Toluene	48	79
33	94	Pt-**A/1a**	Toluene	r.t.	10	3,5-$(MeO)_2$ C_6H_3	Et	Pt-**A/1e**	Toluene	73	79
34	95	Pt-**A/1a**	Toluene	r.t.	10	Ph	Bu^t	Pt-**A/1e**	Toluene	78	79
35	52	Pt-**A/1a**	EtOH	0	10	Ph	Et	Pt-**A/1e**	Toluene	15	69
36	86	Pt-**A/1a**	Toluene	r.t.	10	Ph	Et	Pt-**A/1f**	Toluene	31	79

[a]Pt-**A**=Pt/Al_2O_3; Pt-**B**=Pt/silica; Rh-**A**=Rh/Al_2O_3.
Abbreviation: DCM, dichloromethane.

the Rh/Al_2O_3 catalyst in the hydrogenation of α-ketoesters (entries 7, 19–22, Table 2). It has been pointed out that the change in adsorption mode of the chiral modifier may explain the inversion; but argument for the inversion being associated with changes in the reaction mechanism was raised as well. In the gas-phase (entries 11–12, Table 2) and in a continuous reaction (entry 18, Table 2), inversion was observed in the same reduction of ethyl pyruvate. The heterogeneous hydrogenation of phenylglyoxylic acid esters with cinchona-modified $Pt\text{-}Al_2O_3$ catalyst was significantly slower than that of ethyl pyruvate (entries 23–36, Table 2). Inversion of enantioselectivity was also reported in the hydrogenation in toluene over Pt-**A**/**3** catalyst, and especially over Pt-**A**/**1e** catalyst (entry 34, Table 2). It has been demonstrated that both electronic and steric factors on the ester moiety may play a role in determining the reaction rate and enantioselectivity. With aliphatic substituents (entries 23–26, Table 2), steric effects predominate, whereas with aromatic groups, electronic effects become more crucial in affecting the reaction rate and *ee* (entries 27–29, Table 2). For the hydrogenation of ketopantolactone, an inversion in the alcohol configuration was reported as well. Thus, in the presence of the chiral modifiers **1a**, **1c**, and **1d**, the hydrogenation afforded the expected (*R*)-enantiomer with excellent *ee*'s (e.g., entry 9, Table 1), whereas in the presence of a bulky substituent on C9 of the modifier (e.g., **1e**, **1i**, **1j**, Scheme 1), the (*S*)-enantiomer was formed in excess.

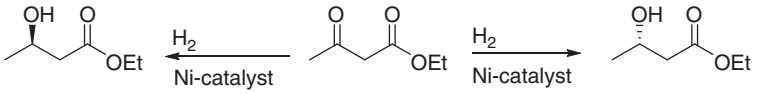
As mentioned in Section 8.04.2.1.1.1, heterogeneous hydrogenation of β-ketoesters is mainly successful with Ni catalysts. The preferred form of nickel is freshly prepared Raney Ni, and TA is currently the best modifier for the transformation (Scheme 3).[10–12,80,81–87] However, sodium bromide is an obligatory comodifier for high *ee*'s. It is noted that substituting more than one of the hydroxyl groups or one of the acid groups in TA leads to significant loss of enantioselectivity (Scheme 3).[83,86] Several other acids (**7**–**9**, Scheme 2), such as amino acids (**7**, Scheme 2), have been reported to afford low to medium *ee*'s.[86] The composition of the nickel–aluminum alloy, the impregnation procedure (concentration of TA and NaBr, pH of reaction solution, temperature, time, and ultrasound) as well as the reaction conditions (e.g., solvent, H_2 pressure, temperature, acid comodifier) are also crucial in obtaining good yield and enantioselectivity. Supported Ni or Ni powders can be modified and they often give better results.[86] The hydrogenation normally requires high catalyst loading, high temperature, and high hydrogen gas pressure to achieve good yields. However, *in situ* modification with TA/NaBr of a prehydrogenated metallic nickel powder yielded a catalyst that showed much higher activity and notably could be recycled at least 30 times with little loss of activity, giving products with 80–84% *ee*.[83,86]



X^1	X^2	Y	*ee* (%)
OH	OH	COOH	83
OH	H/OR	COOH	61–65
OR	OR	COOH	0–8
OH	OH	H/Me	0–1

Scheme 3 Heterogeneous hydrogenation of β-ketoesters with TA modified Ni catalysts.

Inversion of enantioselectivity in the heterogeneous hydrogenation of β-ketoesters has also been reported.[15,80,88] It was noted that the conditions of catalyst preparation are essential for achieving good *ee* values. For instance, the enantioselectivity of Ni catalysts modified with various amino acids was profoundly influenced by the temperature and solution pH applied during preparation of the chiral catalysts (Scheme 4).



Modification conditions:	Temperature <80 °C	Modifier = (*S*)-**7**	Temperature >80 °C
	pH < 10.5	(*S*)-**8**	pH > 10.5
	pH < 10.5	(*S*)-**9**	pH > 10.5

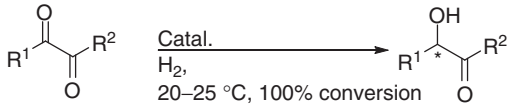
Scheme 4 Effect of catalyst modification conditions on the hydrogenation of ethyl acetoacetate with Ni-catalysts.

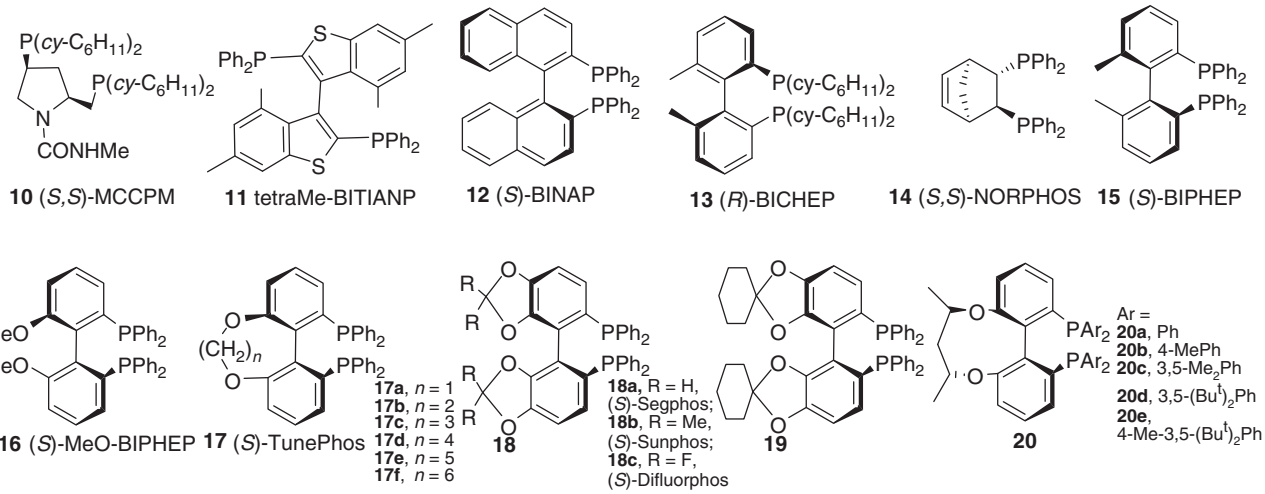
8.04.2.1.1.2 Homogeneous hydrogenation of α- or β-ketoesters

Homogeneous AH of ketoesters is performed mainly with ruthenium catalysts, although Rh-phosphine complexes were explored in earlier days.[89–92] Table 3 summarizes the enantioselectivities obtained for a few representative α-ketoesters with various catalysts. AH of methyl pyruvate with a rhodium complex prepared *in situ* from $[RhCl(COD)]_2$ and the pyrrolidine-derived diphosphine MCCPM (**10**) afforded methyl lactate in 87% *ee* (entry 1, Table 3),[93] and 2-oxo-4-phenylbutanoate was reduced with a Rh-Norphos (Rh-**14**) catalyst in high *ee* (entry 5, Table 3).[94] Ru-phosphine complexes have been much more widely used, as shown in Table 3. AH of methyl pyruvate using a neutral $[RuCl_2\text{-}(R)\text{-}12]$ complex gave the (*R*)-hydroxyl ketone in 83% *ee*.[95] Using

the ligand **11** possessing five-membered heteroaromatic rings (tetraMe-BITIANP), this ketone was reduced with Ru-**11** with better enantioselectivity (entry 2, Table 3).[96] A well-defined cationic complex [RuCl(*R*)-BINAP)(C_6H_6)]$^+$ (Ru-**12**) catalyzed the hydrogenation of methyl benzoylformate in 89% *ee* in the presence of HBF_4 (entry 3, Table 3).[97] However, significantly higher *ee* was obtained with a ruthenium complex of BICHEP (**13**), an electron-rich biaryl ligand (entry 4, Table 3).[98] A series of chiral biaryl

Table 3 Selected examples of homogeneous hydrogenation of α-ketoesters

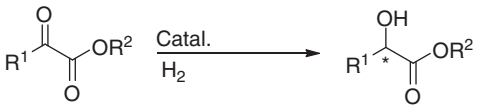


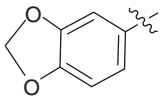
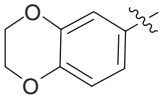
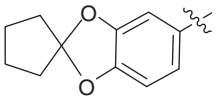


Entries	*R^1*	*R^2*	*Catalyst*	*H_2 (bar)*	*Solvent*	ee *(%)*	*Configuration*	*References*
1	Me	OMe	[RhCl(COD)]$_2$-**10**	20	THF	87	*R*	93
2	Me	OMe	Ru(II)-**11**	98	MeOH	88	*S*	96
3	Ph	OMe	Ru(II)-**12**	98	MeOH	89	*S*	95
4	Ph	OMe	Ru(II)-**13**	5	EtOH	>99	*S*	98
5	Ph(CH$_2$)$_2$	OEt	[Rh(nbd)Cl]$_2$-**14**	101	MeOH	96	*S*	94
6	Ph	NHCH$_2$Ph	Ru(II)-**13**	40	MeOH	96	*R*	98
7	Ph	OMe	Ru(OAc)$_2$-**17c**	5	MeOH	14	*S*	99
8	Ph	OMe	RuCl(C_6H_6)-**17c**	5	MeOH	95	*S*	99
9	Ph	OMe	RuCl(*p*-cymene)-**17c**	50	MeOH	94	*S*	99
10	Ph	OMe	RuCl$_2$(DMF)$_n$-**17a**	5	MeOH	91	*S*	99
11	Ph	OMe	RuCl$_2$(DMF)$_n$-**17b**	5	MeOH	93	*S*	99
12	Ph	OMe	RuCl$_2$(DMF)$_n$-**17c**	5	MeOH	97	*S*	99
13	Ph	OMe	RuCl$_2$(DMF)$_n$-**17d**	5	MeOH	93	*S*	99
14	Ph	OMe	RuCl$_2$(DMF)$_n$-**17e**	5	MeOH	93	*S*	99
15	Ph	OMe	RuCl$_2$(DMF)$_n$-**17f**	5	MeOH	92	*S*	99
16	Ph	OMe	(NH$_2$Me$_2$)RuCl-**17c**	5	MeOH	97	*S*	99
17	Ph	OEt	RuCl(C_6H_6)-**18b**	50	EtOH	85	*S*	100
18	Ph	OEt	RuCl(C_6H_6)-**18b**/$CeCl_3 \cdot 7H_2O$	50	EtOH	96	*S*	100
19	Ph	OEt	RuCl$_2$(DMF)$_n$-**18b**	50	EtOH	86	*S*	100
20	Ph	OEt	RuCl$_2$(DMF)$_n$-18b/$CeCl_3 \cdot 7H_2O$	50	EtOH	96	*S*	100
21	Ph	OEt	(NH$_2$Me$_2$)RuCl-**18b**	50	EtOH	89	*S*	100
22	Ph	OEt	(NH$_2$Me$_2$)RuCl-**18b**/$CeCl_3 \cdot 7H_2O$	50	EtOH	96	*S*	100
23	Ph	OEt	RuCl(C_6H_6)-**12**	50	EtOH	81	*S*	100
24	Ph	OEt	RuCl(C_6H_6)-**12**/$CeCl_3 \cdot 7H_2O$	50	EtOH	88	*S*	100
25	Ph	OEt	RuCl(C_6H_6)-**18a**	50	EtOH	85	*S*	100
26	Ph	OEt	RuCl(C_6H_6)-**18a**/$CeCl_3 \cdot 7H_2O$	50	EtOH	96	*S*	100
27	Ph	OEt	RuCl(C_6H_6)-**18c**	50	EtOH	71	*S*	100
28	Ph	OEt	RuCl(C_6H_6)-**18c**/$CeCl_3 \cdot 7H_2O$	50	EtOH	93	*S*	100
29	Ph	OEt	RuCl(C_6H_6)-**19**	50	EtOH	85	*S*	100
30	Ph	OEt	RuCl(C_6H_6)-**19**/$CeCl_3 \cdot 7H_2O$	50	EtOH	96	*S*	100
31	Ph	OMe	RuCl$_2$(DMF)$_n$-**20c**	5	MeOH	99	*S*	101

bisphosphines **17** (C_n-Tunephos, Table 3) in combination with Ru complexes have proved to be effective for the AH of α-aryl- and α-alkyl-substituted α-ketoesters (entries 7–16, Tables 3 and 4).[99] Up to 97% *ee* was achieved with both [$RuCl_2$-**17c**](DMF)$_n$ and [NH_2Me_2][RuCl-**17c**]$_2$(μ-Cl)$_3$] in the hydrogenation of methyl benzoylformate (entries 12, 16, Table 3), but [Ru(OAc)$_2$–**17c**] proved to be less effective (entry 7, Table 3). In the presence of a catalytic amount of $CeCl_3 \cdot 7H_2O$, [RuCl(C_6H_6)-**18b**]Cl was highly effective for the AH of aromatic α-ketoesters (entries 17–30, Tables 3 and 4), affording a variety of ethyl α-hydroxyl-α-aryl acetates in up to 98% *ee* with turnover number (TON) up to 10 000.[100] The addition of $CeCl_3 \cdot 7H_2O$ not only improves the enantioselectivity, but also enhances the stability of the catalyst (entries 18, 20, 22, 24, 26, 28, and 30 versus entries 17, 19, 21, 23, 25, 27, and 29, Table 3).[100] The series of ligands **20**, similar to **17a** with its phenyl ring modified, demonstrated better performance than **17** in the Ru(II)-catalyzed AH of α-ketoesters, for example, methyl benzoylformate, affording excellent *ee*'s in most cases (entry 31, Table 3).[101]

Table 4 Comparison of selected examples of AH of α-ketoesters



Entries	[$RuCl_2(C_6H_6)$-**18b**][a]				[$RuCl_2$-**17c**](DMF)$_n$[b]				[$RuCl_2$-**20c**](DMF)$_n$[c]
	R^1	R^2	ee (%)[d]	ee (%)[e]	R^1	R^2	Yield (%)	ee (%)[f]	ee (%)[g]
1	Ph	Et	85	96	4-F-Ph	Me	94	95	98
2	4-Me-C_6H_4	Et	87	96	3-F-Ph	Me	91	94	98
3	4-F-C_6H_4	Et	75	96	2-F-Ph	Me	90	85	N/A
4	4-Cl-C_6H_4	Et	75	96	4-Cl-Ph	Me	95[i]	93	98
5	4-Br-C_6H_4	Et	80	96	4-Br-Ph	Me	92[i]	92	96
6	4-MeO-C_6H_4	Et	89	89	4-Me-Ph	Me	89	96	99
7	2-Me-C_6H_4	Et	39	89	4-MeO-Ph	Me	90	96	98
8	2-Cl-C_6H_4	Et	29	78	3-MeO-Ph	Me	91	95	98
9	2-MeO-C_6H_4	Et	−16	95	Me	Me	70	96	N/A
10	3-Cl-C_6H_4	Et	74	95	Pr^i	Et	75[j]	96	N/A
11	2,4-Me_2-C_6H_3	Et	40	88	Bu^t	Et	90[j]	95	N/A
12	2,4,6-Me_3-C_6H_2	Et	N/D[h]	92	$Ph(CH_2)_2$	Et	94[j]	96	98
13	4-MeO-3,5-Bu^t_2-C_6H_2	Et	82	93	–	–	–	–	–
14	4-HO-3,5-Bu^t_2-C_6H_2	Et	83	94	–	–	–	–	–
15	2-Naphthyl	Et	91	98	–	–	–	–	–
16	1-Naphthyl	Et	40	90	–	–	–	–	–
17	2-Thienyl	Et	61	87	–	–	–	–	–
18		Et	79	93	–	–	–	–	–
19		Et	81	94	–	–	–	–	–
20		Et	85	94	–	–	–	–	–

[a]The reaction was carried out in EtOH with a substrate (1 mmol) concentration of 0.5 M in EtOH at 50 °C, 50 bar initial H_2 for 20 h, S/C = 100, full conversion was obtained for all reactions.[100]

[b]The reaction was carried out in MeOH at r.t., 5 bar initial H_2 for 20 h, S/C = 100, full conversion for all reactions.[99]

[c]The reaction was carried out in MeOH at r.t., 5 bar initial H_2 for 20 h, S/C = 100, full conversions for all reactions.[101]

[d]*ee* without additives, all the reactions run at 70 °C and *S* configuration for products.

[e]*ee* with $CeCl_3 \cdot 7H_2O$ as additive, *S* configuration for products.

[f]*S* configuration for products.

[g]*S* configuration for products.

[h]Conversion < 5%, *ee* was not determined.

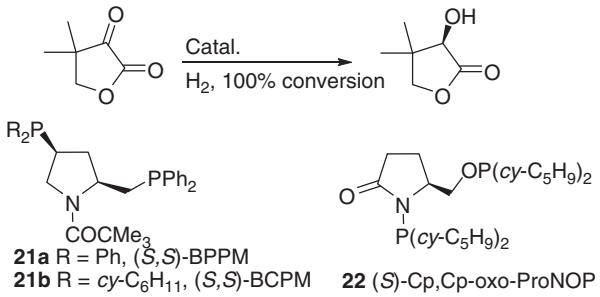
[i]The reaction run at 50 °C at 50 bar for 15 h.

[j]EtOH was used as a solvent.

In Table 4, the AH of a range of α-ketoesters with three of the most efficient Ru-diphosphine catalysts is presented. High enantioselectivities were obtained for α-aryl-substituted α-ketoesters with all three catalysts, with [$RuCl_2$–**20c**] performing the best.

Ketopantolactone is also reduced. A pyrrolidine-based phosphine ligand **21a**, when combined with a rhodium precursor, is an efficient catalyst for the AH, affording (*R*)-pantoyl lactone in 87% *ee* (entry 1, Table 5).[92,102,103] Bearing a cyclohexyl group on one of the phosphorus atoms, the catalyst Rh-**21b** gave a better enantioselectivity of 92% for the same reduction (entry 2, Table 5).[93,104] However, Rh-**22** produced a significantly higher *ee* of 99% and a high turnover frequency (TOF) of 3300 h^{-1} (entry 3, Table 5).[105]

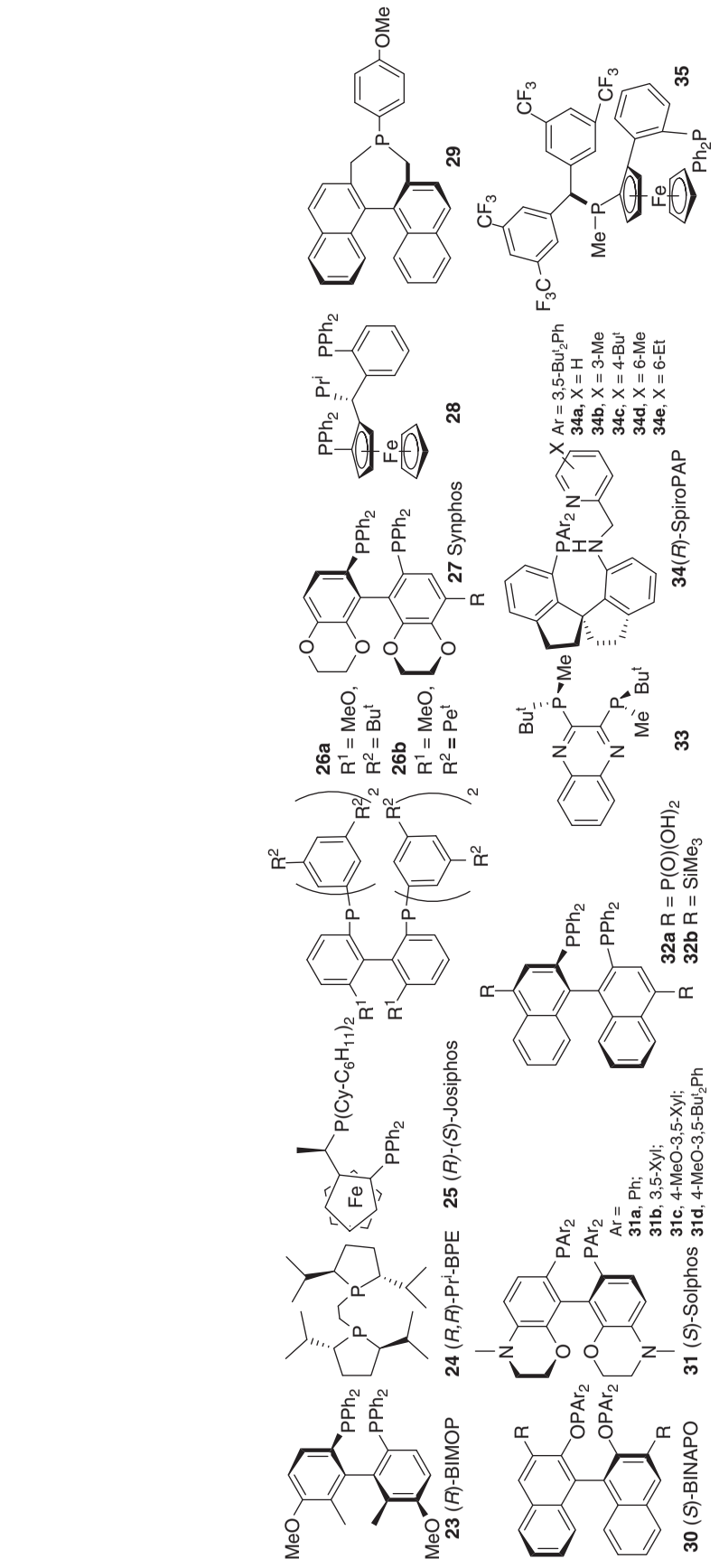
Table 5 Hydrogenation of ketopantolactone



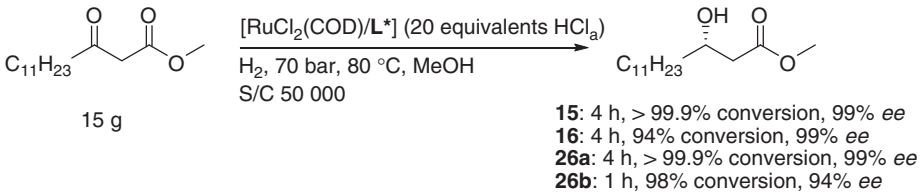
Entries	*Catalyst*	*Solvent*	*H_2 (bar)*	*Temperature (°C)*	ee *(%)*	*References*
1	[RhCl(COD)]$_2$-**21a**	Benzene	50	30	87	92,102,103
2	[RhCl(COD)]$_2$-**21b**	THF	50	50	92	104
3	[Rh(OCOCF$_3$)-**22**]$_2$	Toluene	1	r.t.	99	105

Although the first successful example of homogeneous hydrogenation of β-ketoesters was reported by using a Rh catalyst,[106] the AH of β-ketoesters catalyzed by ruthenium complexes with chiral phosphine ligands has been more extensively studied (Scheme 5).[107–115] Pioneered by Noyori and coworkers, the chiral ruthenium diphosphine complexes [RuX_2(diphosphine)] (X = Cl, or Br) and their analogues have become the most popular catalysts for this transformation, with many showing excellent enantioselectivity (>99% *ee*) and high activity (up to 10^6 ton) in the reduction of β-alkyl β-ketoesters.[113–118] In particular, halogen-containing RuX_2(**12**)$(DMF)_n$ display excellent catalytic performance in the hydrogenation of a wide range of β-ketoesters.[118] For example, hydrogenation of methyl 3-oxobutanoate catalyzed by such complexes gave (*R*)-methyl 3-hydroxybutanoate quantitatively with an excellent *ee*.[118] The reaction can be easily achieved with a substrate/catalyst (S/C) ratio of 10 000 in an alcohol medium. β-Ketoamides and thioesters can also be hydrogenated with high enantioselectivity by using the Ru–BINAP complexes as catalysts.[95,113] A range of chiral phosphine ligands have been explored for the hydrogenation of β-ketoesters; selected chiral phosphine ligands are shown in Scheme 5.[107,119–131] Thus, Ru-**11** [96] (Table 3) and Rh-**25**[111] (**25**, Scheme 5) are both outstanding for the AH of β-ketoesters, giving up to 99% *ee*. The bisphospholane ligand **24** (Scheme 5, *i*-PrBPE) is also highly effective when combined with $RuBr_2$.[110] Similarly, the BIPHEP (**15**) type diphosphines (**13**, **15**–**18**, **20** Tables 3; 23,26,27, and **31**, Scheme 5) demonstrated high *ee*'s in Ru(II) catalyzed hydrogenation of β-ketoesters. For example, methyl 3-oxotetradecanoate was hydrogenated to (*S*)-3-hydroxytetradecanoate with Ru-L* catalysts in excellent conversions and *ee*'s (Scheme 6).[117] On a larger scale, 200 g of the ketoesters were reduced completely in 4 h with >99% purity and >99% *ee*, and a multikilogram scale application has been undertaken in the industry.[117]

The extensive use of BINAP-type catalysts has prompted further studies into atropisomeric biaryldiphosphines.[110,132–157] In particular, the dihedral angle of ligand backbone is shown to play a critical role in the enantioselection of AH.[139,149,150] This parameter is geometrically related to the ligand bite angle.[134] The size of the dihedral angle determines the proximity of the pseudoequatorial aryl group and the chelating substrate around the metal, affecting the relative stability of the two diastereomeric transition states of the AH. A smaller angle leads to more efficient ligand-substrate interaction, providing better chiral discrimination.[139–142] β-Aryl β-ketoesters are one of the substrates which are not reduced with sufficient enantioselectivity with Ru-**12**. However, the selectivity is significantly improved by using diphosphine ligands of narrower dihedral angles.[118,133,139–143,147,149,150] Thus, the *ee* of the AH of trifluromethyl 4,4,4-trifluoroacetoacetate could be improved from 85 to 98% by using the diphosphine ligands ranging from (*R*)-BINAP ((*R*)-**12**), (*R*)-MeO-BIPHEP ((*R*)-**16**), (*R*)-SYNPHOS ((*R*)-**27**), (*R*)-SEGPHOS ((*R*)-**18a**), and (*R*)-DIFLUORPHOS ((*R*)-**18c**), the dihedral angles of which vary from 86.2 to 67.6°.[149,150] Similarly, a Ru-**31a** (Ph-Solphos) complex showed both high activity and high enantioselectivity for the hydrogenation of β-ketoesters, enabling complete conversion in EtOH at 80 °C within 20 h with S/C ratio up to 100 000 and *ee* up to 99%.[116] However, 4,4′-disubstitution on the original BINAP ligand also improves the enantioselectivity (**32**, Scheme 5), with up to 99.5% *ee* achieved in the hydrogenation of β-phenyl β-ketoesters.[151] Meanwhile, several excellent ligands of other types have been reported. The P-chirogenic phosphine ligands (e.g., **33**, Scheme 5)



Scheme 5 Chiral phosphine ligands.



Scheme 6 Homogeneous hydrogenation of β-alkyl β-ketoesters.

exhibit high enantioselectivity (up to 99.3% *ee*).[157–160] The spiro monophosphine ligand **34** (Scheme 6, spiroPAP) has been combined with iridium(I), resulting in the most efficient catalyst up to date for the hydrogenation of difficult β-aryl β-ketoesters.[155] The reduction afforded excellent *ee*'s (up to >99% *ee*) and remarkably high TONs (as high as 1 230 000) under mild reaction conditions (8 bar H_2 at r.t.).[155] Table 6 presents selected examples of AH of β-ketoesters catalyzed by the three most effective catalysts.

Table 6 Selected examples of AH of β-ketoesters



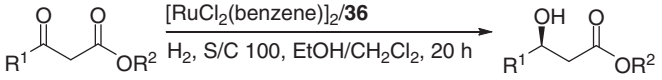
Entries	*[Ir(COD)Cl]$_2$-**34b**[a]*				*[RuCl$_2$(benzene)]$_2$-**31b**[b]*			*[RuCl$_2$-**20b**](DMF)$_n$[c]*		
	R^1	*R^2*	*Time (h)*	ee *(%)*	*R^1*	*R^2*	ee *(%)*	*R^1*	*R^2*	ee *(%)*
1	Ph	Et	1	98	Ph	Et	99.5	Ph	Et	98
2	4-Me-C_6H_4	Et	0.4	99.3	4-MeO-C_6H_4	Et	99.5	4-Cl-C_6H_4	Me	97
3	4-MeO-C_6H_4	Et	0.7	99.3	4-Cl-C_6H_4	Me	99.1	4-F-C_6H_4	Me	98
4	4-Cl-C_6H_4	Et	1	96	4-F-C_6H_4	Me	99.3	4-Cl-C_6H_4	Et	97
5	4-Br-C_6H_4	Et	0.8	99	4-CF_3-C_6H_4	Me	99.0	4-Br-C_6H_4	Me	96
6	3-Me-C_6H_4	Et	0.7	99.2	3-CF_3-C_6H_4	Me	98.4	4-Br-C_6H_4	Et	96
7	3-MeO-C_6H_4	Et	1.7	96	2-CF_3-C_6H_4	Me	97.8	4-Me-C_6H_4	Et	99
8	3-Br-C_6H_4	Et	1.7	95	2-Cl-C_6H_4	Me	99.6	2-Me-C_6H_4	Et	97
9	2-Me-C_6H_4	Et	1	99.8	–	–	–	2-MeO-C_6H_4	Et	95
10	2-MeO-C_6H_4	Et	0.8	99.5	–	–	–	Me	Me	99
11	2-Cl-C_6H_4	Et	4	99.3	–	–	–	Me	*i*-Pr	99

[a]Reaction conditions: 1.5 mmol scale in EtOH at r.t. with S/C = 1000, 8 bar H_2, substrate concentration = 2.1 M, base concentration = 0.02 M, 93–98% isolated yield were obtained.[156]

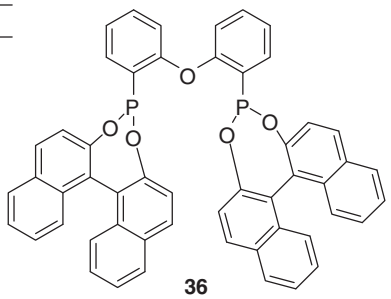
[b]Reaction conditions: 0.25 mmol scale in MeOH (1 ml) at r.t. with S/C = 100, 1400 psi H_2 for 20 h, >98% conversions were obtained in all reactions.[116]

[c]Reaction conditions: 0.021 mmol scale in MeOH or EtOH (16 ml) at 80 °C with S/C = 100, 50 bar H_2 for 12 h, full conversions obtained for all reactions.[157]

AH of β-ketoesters with Ru-diphosphonite **36** (Scheme 7) is also efficient.[161] Both β-alkyl and aryl β-ketoesters were reduced with high conversions and high enantioselectivities in all cases.



R^1	R^2	Temperature (°C)	H_2 (bar)	Conversion (%)	*ee* (%)
Me	Et	60	80	100	95
Me	Et	85	50	97	99
Et	Me	60	50	100	95
Et	Me	60	80	100	95
Pr^n	Et	90	50	100	97
Pr^n	Et	60	50	100	97
Ph	Et	60	50	100	93
Ph	Et	60	80	100	93
Ph	Et	85	50	100	97



Scheme 7 AH of β-ketoesters with Ru-diphosphonite catalyst.

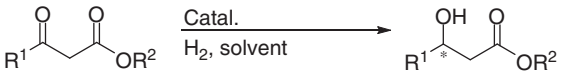
Hydrogenation of γ-ketoesters or *o*-acylbenzoic esters to provide the corresponding γ-lactones or *o*-phthalides with Ru diphosphine catalysts has also been reported. The AH afforded excellent *ee*'s (up to 99.5% *ee*).[114,115] In the presence of HCl, an *in situ* generated $RuCl_2$-BINAP system catalyzed the enantioselective hydrogenation of γ-ketoesters to γ-lactones in up to 99.5% *ee*.[162]

8.04.2.1.2 Hydrogenation of other functionalized ketones

8.04.2.1.2.1 Hydrogenation of bifunctional ketones

γ-Heterosubstituted β-hydroxyl esters are important building blocks in organic synthesis; hence efficient catalysts have been sought for the AH of the corresponding ketones. However, competitive interaction of the functional groups with the central metal tends to decrease the enantioselectivity, and the interaction depends on the steric and electronic nature of the coordinative groups. As a result, the AH may give low enantioselectivities. Heterogeneous hydrogenation of ethyl 4,4,4-trifluoro-3-oxobutanoate using Pt-**1c** (Scheme 1) as catalyst afforded 90% *ee* under 10 bar H_2 in AcOH.[4,163–165] Homogeneous Ru(II) catalysts are more effective, however (Table 7). For example, the ruthenium complexes with chiral biphenyl-type ligands (e.g., **16–18** in Table 3) have been shown to give high selectivities (entries 2–5, 7–8, 10–14, Table 7). Apart from the atropisomeric diphosphines such as **12** and **16–18**, the P-chiral phosphine **33** (Scheme 5) has also been demonstrated to be highly enantioselective; up to 99.2% *ee* was obtained (entry 9, Table 7).[157] In particular, Sunphos (**18b**, Table 3) combined with $[RuCl_2(p\text{-cymene})]_2$ forms a highly versatile catalyst for the AH of these ketones.[166] A wide range of γ-heterosubstituted β-ketoesters have been successfully hydrogenated to their corresponding γ-heterosubstituted β-hydroxyl esters, with excellent *ee*'s obtained with almost all of the substrates, as shown in Table 8. It is worth noting that ethyl 4-arylsulfonyl-3-hydroxybutyrate was prepared through AH for the first time. The reaction temperature, H_2 pressure and metal precursors could affect the enantioselectivity of the products.[166] However, perfluoro β-ketoesters are more difficult to reduce. The reported enantioselectivity is not significantly higher than 80% at present (entries 12–15, Table 7); the ligands **18c** and **35** are more effective.[149,150,167]

Table 7 AH of bifunctional ketones



Entries	R^1	R^2	Catalyst	Conditions	Yield (%)	ee (%)	Configuration	References
1	CH_2OTIPS	Et	$RuBr_2$-**12**	EtOH, r.t., 101 bar H_2, S/C 290, 86 h	100	95	*R*	95
2	CH_2OBn	Et	$RuBr_2$-(*R*)-**16**	EtOH, 80 °C, 8 bar H_2, S/C 3000, 48 h	100	98	*S*	147
3	CH_2OBn	Et	$RuCl_2$(benz)-**18b**	EtOH, 70 °C, 20 bar H_2, S/C 100, 16 h	100	98.2	–	166
4	CH_2OBn	Et	$RuCl_2$(benz)-**17c**	EtOH, 70 °C, 20 bar H_2, S/C 100, 16 h	100	98.7	–	166
5	CH_2OBn	Et	$RuCl_2$(*p*-cymene)-**18b**	EtOH, 70 °C, 20 bar H_2, S/C 100, 18 h	100	99.1	–	166
6	CH_2OMe	Me	$RuBr_2$-**24**	MeOH/H_2O, 35 °C, 4 bar H_2, S/C 500, 20 h	100	95.5	*R*	110
7	CH_2Cl	Et	$RuBr_2$-**18c**	EtOH, 110 °C, 10 bar H_2, S/C 100, 3 h	100	97	*R*	149,150
8	CH_2Cl	Et	(Me_2NH_2)[Ru-(*R*)-**18a**]Cl_3	EtOH, 90 °C, 30 bar H_2, S/C 2500, 2 h	100	98.5	*S*	139
9	CH_2Cl	Et	$RuCl_2(C_6H_6)$-**33**	EtOH/DCM, 50 °C, 20 bar H_2, S/C 50, 24 h	96	99.2	–	157
10	CH_2Cl	Et	$RuCl_2$(*p*-cymene)-**18b**	EtOH, 70 °C, 20 bar H_2, S/C 100, 18 h	100	95.5	–	166
11	CH_2Cl	Et	$RuCl_2$(*p*-cymene)-**18b**	EtOH, 90 °C, 20 bar H_2, S/C 100, 18 h	100	96.5	–	166
12	CF_3	Et	$RuBr_2$-**18a**	EtOH, 110 °C, 10 bar H_2, S/C 100, 1 h	100	59	*R*	150
13	CF_3	Et	$RuBr_2$-**18c**	EtOH, 110 °C, 10 bar H_2, S/C 100, 1 h	100	70	*R*	149,150
14	CF_2CF_3	Et	$RuBr_2$-(*R*)-**18c**	EtOH, 110 °C, 10 bar H_2, S/C 100, 1 h	100	81	*R*	149,150
15	CF_3	Pr^i	$RuBr_2$-**35**	Pr^iOH, 77 °C, 20 bar H_2, S/C 1000, 16 h	>99	77	*S*	167

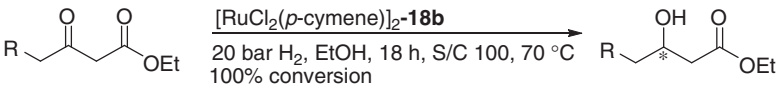
The Ru-**18b** catalyst has also been explored for the hydrogenation of ε-chloro substituted δ-ketal-β-ketoesters to give ε-chloro-substituted δ-ketal-β-hydroxyl esters. As shown in Scheme 8, high *ee*'s were observed for a range of ε-chloro hydroxyl esters and related alcohols.[168] Catalytic $CaCO_3$ plays a key role, maintaining a neutral medium for the AH and so preventing product decomposition.

Diastereoselective hydrogenation of β-ketoesters is also known. As illustrated in Scheme 9, AH of the *N*-Boc-protected (*S*)-γ-amino β-ketoesters with Ru-(*R*)-**12** afforded the *syn* alcohols (equation 1, Scheme 9).[169] AH of the *N*-Boc-protected (*S*)-δ-amino β-ketoester followed by cyclization yielded the *trans* lactone stereoselectively (equation 2, Scheme 9).[170] Hydrogenation of chiral α-keto amides has also been demonstrated. Using Rh-**37** as catalyst, the (*S,S*)-hydroxyl amide shown in equation 3 is preferentially produced (Scheme 9).[171,172]

8.04.2.1.2.2 Hydrogenation of α-substituted ketones

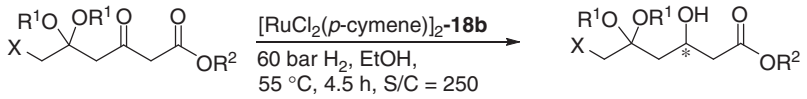
AH has been successfully applied to the reduction of diverse α-substituted ketones, for example, those bearing α-hydroxy, amino, and chloro groups.[95,129,139,173–181] Table 9 summarizes the results obtained with various homogeneous catalysts bearing phosphine or amine ligands and a heterogeneous nickel catalyst. α-Aminoacetophenone hydrochloride was reduced to the chiral amino

Table 8 AH of γ-heterosubstituted β-ketoesters



Entries	*R*	ee *(%)*	*References*
1	BnO	99.1	166
2[a]	BnO	98.8	166
3[b]	BnO	98.4	166
4	Bu^tO	97.9	166
5	Cl	95.5	166
6[c]	Cl	96.5	166
7	$PhCO_2$	97.7	166
8	AcO	99.0	166
9	TBSO	98.6	166
10	OH	88.6	166
11	4-Cl-C_6H_4-S	64.9	166
12	4-Cl-C_6H_4-SO_2	96.9	166
13	$PhSO_2$	98.2	166
14[d]	$PhSO_2$	98.1	166
15[e]	$PhSO_2$	97.3	166
16	4-Me-C_6H_4-SO_2	98.2	166
17	4-Br-C_6H_4-$PhSO_2$	97.5	166
18[f]	CbzNH	97.1	166
19[f]	FmocNH	97.2	166
20[f]	BocNH	98.0	166

[a] S/C = 2000.
[b] 50 g of substrate, [RuCl(benzene)-(*S*)-TolSunphos]Cl was used as catalyst, S/C = 3000.
[c] Reaction was run at 90 °C.
[d] S/C = 2000.
[e] S/C = 5000.
[f] [RuCl(benzene)-**18b**]Cl was used as catalyst.

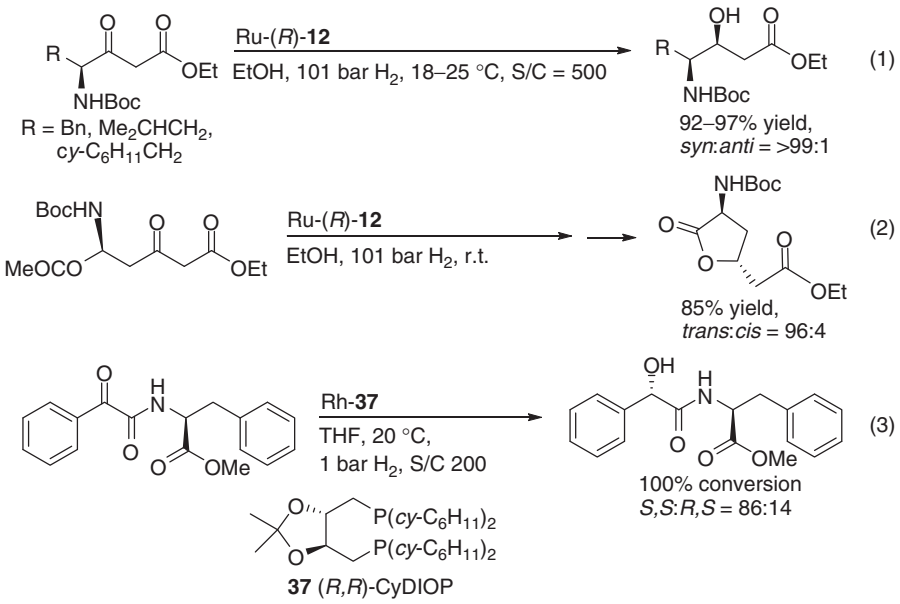


Entries	X	R^1	R^2	Yield (%)	*ee* (%)
1	Cl	Et	Me	97	99.2
2	H	$-(CH_2)_2-$	Me	79	99.3
3	Me	$-(CH_2)_2-$	Me	81	99.5
4	Cl	Et	Et	95	99.4
5[a]	Cl	Me	Me	91	99.2
6[b]	BnO	$-(CH_2)_2-$	Me	93	99.2
7[c]	BnO	$-(CH_2)_2-$	Et	91	99.2
8	BnO	$-(CH_2)_2-$	Bu^t	95	99.6

[a] MeOH as solvent.
[b] Reaction was run at 65 °C.
[c] Reaction was run at 75 °C, 10 h.

Scheme 8 Hydrogenation of ε-chloro-substituted δ-ketal-β-ketoesters.[169]

alcohol with 93% *ee* by using either Rh-**38**[176] or Rh-**39**[177] (Table 9) as catalyst. The Rh-**10** catalyst (Table 3) is effective for the hydrogenation of a series of α-amino and α-dialkylamino ketones (entries 3–8, Table 9); the AH afforded full conversions with up to 97% *ee* in 20 h at a S/C ratio of 1000 or 10 000.[173–175,178,190] Epinephrine hydrochloride could be prepared in 95% *ee* via hydrogenation using Rh-**40** at 40 °C under 51 bar H_2 pressure.[190] α-Dialkylamino ketones were hydrogenated with Ru-**12**[95,97,191] (Table 3) and Rh-**41**[182] (Table 9), and up to 99% *ee* was obtained (entries 9–13, Table 9). With the Rh-**22** catalyst, not only α- but also β- and γ-amino ketone hydrochlorides were effectively converted into the corresponding chiral alcohols in up to 97% *ee*.[190] The Ru-**17c** is particularly effective for the AH of α-phthalimide ketones in terms of enantioselectivity (entries 14–15, Table 9).[179] The hydrogenation of α- as well as β-hydroxyl ketones and β-amide ketones has also been achieved with ruthenium catalysts. Thus,



Scheme 9 Diastereoselective hydrogenation of bifunctional ketones.

chiral 1,2-diols with 92–98% *ee* were obtained by the Ru-**12**-catalyzed AH of hydroxyl ketones (entries 16–18, Table 9).[95,183] α-Chloroacetophenones with substitutents on the phenyl rings were hydrogenated to the chiral chlorohydrins using **42** (Table 9) as catalyst (entries 20–25, Table 9), which is well known for its activity in TH.[184,185] The AH afforded quantitative yield and consistently high enantioselectivities (93–96% *ee*). A large scale of 260 g substrate has been successfully reduced with S/C ratios up to 4000 demonstrated.

The AH of α-phosphono ketones[129,138,186,187,192,193] and sulfonyl ketones[129,138,142,187,188,194–197] has also been documented. Thus, Ru-**12** catalyzed the hydrogenation of β-keto phosphonates under mild conditions (1–4 bar H_2 and r.t.) to give the chiral β-hydroxyl phosphonates in up to 99% *ee* (entries 26–30, Table 9). In a similar manner, β-keto thiophosphonates were selectively reduced with Ru-**16** (entries 31–32, Table 9).[187] In the presence of iodine, Ru-**18b** catalyzed AH of aryl and alkyl sulfonyl ketones, furnishing chiral hydroxyl sulfones with excellent enantioselectivities (entries 33–41, Table 9).[188] It has been revealed that the *in situ*-generated HI promotes the enantioselectivity. Sulfonyl ketones have also been hydrogenated using the biferrocenyl diphosphine ligand **40** possessing only planar chirality combined with $[Rh(COD)_2]^+$, giving the corresponding optically active β-hydroxyl sulfones in excellent yield and good enantioselectivity (72–98% *ee*).[197] Heterogeneous hydrogenation of β-keto sulfones is possible but less effective, as shown by the AH with Ni-TA (entries 43–45, Table 9).[189]

In comparision with the AH of β-keto phosphonates, α-keto phosphonates are less studied and their reduction is mainly limited to the oxazaborolidine-catalyzed hydroboration. Heterogeneous hydrogenation of such phosphonates was reported recently.[192,198] The reduction was carried out over Pd/C in MeOH at 65 °C with a S/C ratio of 10, affording high yields. The same reduction can also be performed by using palladium immobilized in a chitosan matrix on a carbon carrier but appears to be slower than that with Pd/C. Homogeneous AH of α-keto phosphonates was revealed very recently. Following the screening of a series of diphosphine ligands, (*R*)-MeO-BIPHEP ((*R*)-**16**, Table 3) combined with $Pd(OCOCF_3)_2$ was shown to give the best, albeit moderate, enantioselectivity (Scheme 10).[192]

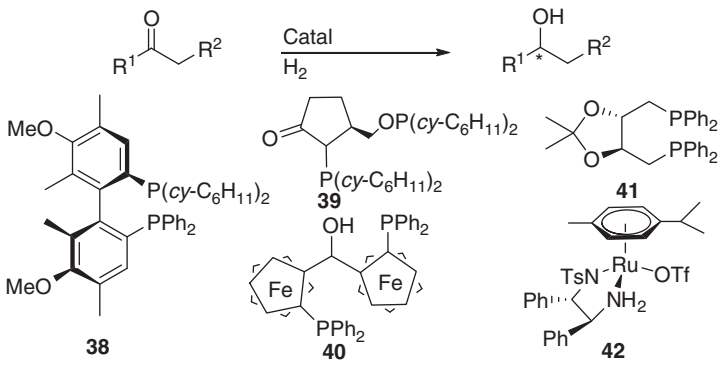
AH of aryglyoxal dialkyl acetals has met success with a Ru(II) catalyst containing a BINAP-type ligand and a chiral diamine (equation 1, Scheme 11).[199,200] The reduction afforded 92–98% *ee* and 95–98% yield in isopropanol (IPA) under mild conditions for several of these ketones. The same reduction with a chirally modified Pt/Al_2O_3 led to lower enantioselectivity (81–89% *ee*).[201]

AH of acylsilanes generates optically pure α-hydroxysilanes, key intermediates for stereo controlled C–C bond formation and rearrangements. Using a Ru-diphosphine/aminopyridine catalyst, a range of acylsilanes were hydrogenated to the corresponding chiral α-hydroxysilanes with high yields and enantioselectivities (equation 2, Scheme 11).[202]

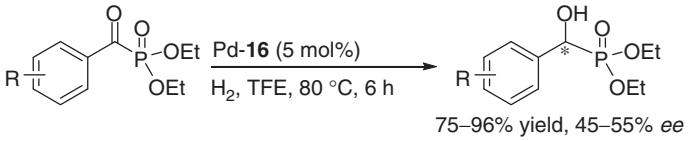
8.04.2.1.2.3 AH via dynamic kinetic resolution (DKR)

Hydrogenation of β-ketoesters containing an α-substituent produces four possible steteroisomeric hydroxyl esters. Given the α-carbon is configurationally labile and hence can be readily racemized, AH of the racemic compounds can afford a single stereoisomer selectively and with high yield.[97,181,,203–224] Successful AH involving such a DKR process is seen in the reduction of racemic 2-methoxycarbonylcyclopentanone with Ru-(*R*)-**12**, which produces the (*1R,2R*) product with a 99:1 *anti*:*syn* ratio and 92% *ee* (entry 1, Table 10).[205,206] Further examples with this and other Ru(II) catalysts are given in Table 10. Excellent stereoselectivities (up to 99% *ee*) were obtained with Ru-**11**[96] and Ru-**24**.[110]

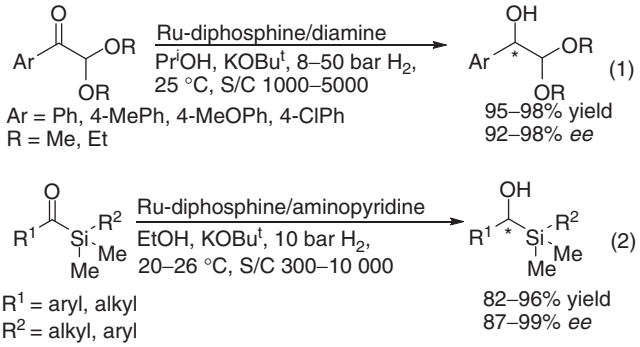
Table 9 AH of α-substituted ketones



Entries	*R^1*	*R^2*	*Catalyst*	*Conditions*	ee *(%)*	*Configuration*	*References*
1	Ph	$NH_2 \cdot HCl$	Rh-**38**	MeOH, 91 bar H_2, 50 °C, 168 h, S/C 1000	93	*R*	176
2	Ph	$NH_2 \cdot HCl$	Rh-**39**	MeOH, 51 bar H_2, r.t., 4.5 h, S/C 200	93	*S*	177
3	Ph	NHBn · HCl	Rh-**10**	MeOH, 20 bar H_2, 50 °C, 20 h, S/C 1000	93	*S*	178
4	Ph	NHBn · HCl	Rh-**10**	MeOH, 20 bar H_2, 50 °C, 20 h, S/C 10 000	91	*S*	178
5	Ph	NMeBn · HCl	Rh-**10**	MeOH, 5 bar H_2, 50 °C, 20 h, S/C 1000	91	*S*	178
6	Ph	NMeBn · HCl	Rh-**10**	MeOH, 20 bar H_2, 50 °C, 20 h S/C 10 000	88	*S*	178
7	Ph	$NEt_2 \cdot HCl$	Rh-**10**	MeOH, 20 bar H_2, 50 °C, 20 h, S/C 1000	97	*S*	178
8	Ph	$NEt_2 \cdot HCl$	Rh-**10**	MeOH, 20 bar H_2, 50 °C, 20 h S/C 10 000	96	*S*	178
9	Me	NMe_2	Ru-**12**	MeOH, 103 bar H_2, 30 °C, 12 h, S/C 780	99	*S*	95,97
10	Ph	NMe_2	Ru-**12**	MeOH, 101 bar H_2, r.t., 24 h, S/C 490	95	*S*	95,97
11	2-Naphthyl	NEt_2	Rh-**41**	Benzene, 70 bar H_2, 50 °C, 20 h, S/C 200	95	+	182
12	Ph	NEt_2	Rh-**41**	Benzene, 70 bar H_2, 50 °C, 20 h, S/C 200	93	+	182
13	4-Me-C_6H_4	NEt_2	Rh-**41**	Benzene, 70 bar H_2, 50 °C, 20 h, S/C 200	91	+	182
14	Me	2-Naphthyl	Ru-**17c**	EtOH, 101 bar H_2, 60 °C, 72 h, S/C 50	>99	*S*	179
15	4-Me-C_6H_4	2-Naphthyl	Ru-**17c**	EtOH, 101 bar H_2, 80 °C, 72 h, S/C 50	>99	*S*	179
16	Me	OH	Ru-**12**	EtOH, 94 bar H_2, r.t., 42 h, S/C 900	92	*R*	95,183
17	Pr^n	OH	Ru-**12**	EtOH, 94 bar H_2, r.t., 42 h, S/C 900	95	*R*	95,183
18	Me	CH_2OH	Ru-**12**	EtOH, 71 bar H_2, r.t., 42 h, S/C 900	98	*R*	95,183
19	Me	$CONMe_2$	Ru-**12**	EtOH, 64 bar H_2, r.t., 86 h, S/C 680	96	*S*	95,183
20	Ph	Cl	**42**	EtOH, 10 bar H_2, 30 °C, 15 h, S/C 1000	96	*R*	184,185
21	3-Me-C_6H_4	Cl	**42**	EtOH, 10 bar H_2, 30 °C, 15 h, S/C 1000	96	*R*	184,185
22	4-Me-C_6H_4	Cl	**42**	EtOH, 10 bar H_2, 30 °C, 15 h, S/C 1000	95	*R*	184,185
23	2-Cl-C_6H_4	Cl	**42**	EtOH, 10 bar H_2, 30 °C, 15 h, S/C 500	95	*R*	184,185
24	3-Cl-C_6H_4	Cl	**42**	EtOH, 10 bar H_2, 30 °C, 15 h, S/C 1000	94	*R*	184,185
25	4-Cl-C_6H_4	Cl	**42**	EtOH, 10 bar H_2, 30 °C, 15 h, S/C 1000	93	*R*	184,185
26	Me	$PO(OEt)_2$	Ru-(*R*)-**12**	MeOH, 4 bar H_2, 50 °C, 50 h, S/C 1187	96	*R*	186
27	Me	$PO(OMe)_2$	Ru-(*R*)-**12**	MeOH, 4 bar H_2, 50 °C, 72 h, S/C 1187	98	*R*	186
28	Ph	$PO(OMe)_2$	Ru-(*R*)-**12**	MeOH, 4 bar H_2, 60 °C, 160 h, S/C 1187	95	*R*	186
29	Ph	$PO(OEt)_2$	Ru-**27**	EtOH, 20 bar H_2, 50 °C, 24 h, S/C 100	>99	*S*	142
30	$Me(CH_2)_4$	$PO(OMe)_2$	Ru-**16**	MeOH, 4 bar H_2, r.t., 17 h, S/C 100	99	*S*	138
31	*n*-C_5H_{11}	$PS(OMe)_2$	Ru-**16**	MeOH, 101 bar H_2, r.t., 88 h, S/C 100	94	*S*	187
32	Pr^i	$PS(OMe)_2$	Ru-**16**	MeOH, 10 bar H_2, r.t., 70 h, S/C 100	93	*S*	187
33	Ph	SO_2Ph	Ru-**12**	EtOH, 1.1 bar H_2, 70 °C, 20 h, S/C 100	73	–	188
34	Ph	SO_2Ph	Ru-**18a**	EtOH, 1.1 bar H_2, 70 °C, 20 h, S/C 100	93	–	188
33	Ph	SO_2Ph	Ru-**18b**	EtOH, 1.1 bar H_2, 70 °C, 20 h, S/C 100	94.5	–	188
34	Ph	SO_2Ph	Ru-**19**	EtOH, 1.1 bar H_2, 70 °C, 20 h, S/C 100	95.2	–	188
35	Ph	SO_2Ph	Ru-**18b**	EtOH, 1.1 bar H_2, 70 °C, 20 h, I_2, S/C 100	99.2	–	188
36	4-F-C_6H_4	SO_2Ph	Ru-**18b**	EtOH, 1.1 bar H_2, 70 °C, 20 h, I_2, S/C 100	98.9	–	188
37	4-Cl-C_6H_4	SO_2Ph	Ru-**18b**	EtOH, 1.1 bar H_2, 70 °C, 20 h, I_2, S/C 100	98.7	–	188
38	4-Me-C_6H_4	SO_2Ph	Ru-**18b**	EtOH, 1.1 bar H_2, 70 °C, 20 h, I_2, S/C 100	99.4	–	188
39	4-MeO-C_6H_4	SO_2Ph	Ru-**18b**	EtOH, 1.1 bar H_2, 70 °C, 20 h, I_2, S/C 100	98.2	–	188
40	Me	SO_2Ph	Ru-**18b**	EtOH, 1.1 bar H_2, 70 °C, 20 h, I_2, S/C 100	99.4	–	188
41	*Cy*-C_6H_{11}	SO_2Ph	Ru-**18b**	EtOH, 1.1 bar H_2, 70 °C, 20 h, I_2, S/C 100	99.3	–	188
42	$(CH_2)_{10}Me$	SO_2Ph	Ru-**16**	MeOH, 4 bar H_2, 50 °C, 48 h, I_2, S/C 50	94	*S*	138
43	Et	SO_2Me	Ni-TA	THF–CH_3CO_2H, 98 bar H_2, 16 h 100 °C	71	*S*	189
44	*n*-C_5H_{11}	SO_2Me	Ni-TA	THF–CH_3CO_2H, 98 bar H_2, 16 h, 100 °C	69	*R*	189
45	*n*-C_8H_{17}	SO_2Me	Ni-TA	THF–CH_3CO_2H, 98 bar H_2, 16 h, 100 °C	67	*S*	189

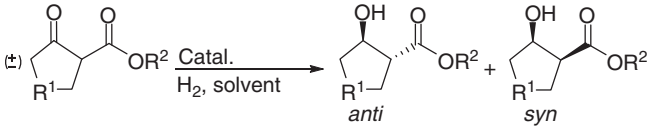


Scheme 10 Hydrogenation of α-keto phosphonates.



Scheme 11 AH of α-substituted ketones.

Table 10 Diastereoselective hydrogenation of cyclic β-ketoesters via DKR



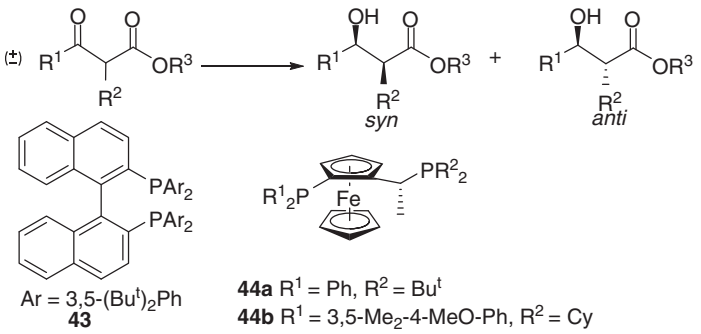
Entries	*R^1*	*R^2*	*Catalyst*	*Conditions*	anti:syn	ee *(%)*	*Configuration*	*References*
1	CH_2	Me	Ru-(*R*)-**12**	DCM, 101 bar H_2, 50 °C, 70 h, S/C 1170	99:1	92	1*R*, 2*R*	205
2	CH_2	Me	Ru-**12**	DCM, 98 bar H_2, 50 °C, 40 h, S/C 1170	99:1	95	1*S*, 2*S*	205,206
3	CH_2	Et	Ru-(*R*)-**12**	MeOH, 20 bar H_2, 80 °C, 2 h, S/C 100	97:3	94	1*R*, 2*R*	209
4	CH_2	Me	Ru-**11**	MeOH, 97 bar H_2, 70 °C, 2 h, S/C 1000	93:7	99	1*R*, 2*R*	96
5	CH_2	Me	Ru-**24**	MeOH-H_2O, 4 bar H_2, 35 °C, 20 h, S/C 500	96:4	98	1*S*, 2*S*	110
6	$(CH_2)_2$	Et	Ru-(*R*)-**12**	DCM, 101 bar H_2, 50 °C, 70 h, S/C 1170	95:5	90	1*R*, 2*R*	205
7	$(CH_2)_2$	Me	Ru-**12**	MeOH, 20 bar H_2, 80 °C, 2 h, S/C 100	74:26	91	1*S*, 2*S*	209
8	$(CH_2)_3$	Me	Ru-(*R*)-**12**	DCM, 101 bar H_2, 50 °C, 70 h, S/C 1170	93:7	93	1*R*, 2*R*	205

Several factors play important roles in the reduction, for example, nature of the substrates, method of preparation of Ru-**12**, reaction conditions including choice of solvent.[97,205,206,209] The DKR relies on catalyst-based intermolecular and substrate-based intramolecular asymmetric induction together with appropriate kinetic parameters.[207,208,212] A simulation analysis of DKR with a Ru-(*R*)-**12** complex in DCM revealed that the *R* substrate is reduced almost 10 times faster than the (*S*)-isomer and the equilibration between the enantiomeric substrates occurs 4.4 times faster than hydrogenation of the slow-reacting (*S*)-ketoester.[97,206]

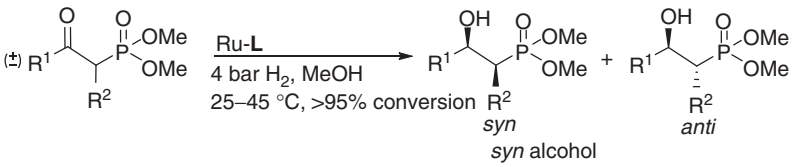
Other racemic substrates, such as α-amino, α-acylamino, α-amidomethyl-, α-chloro, and α-fluoro-subsituted β-ketoesters, have also been submitted to hydrogenation via DKR.[181,216–224] High enantioselectivities were obtained for the reduction of α-amino, α-acylamino, and α-amidomethyl substituted ketoesters (Table 11). The hydrogenation catalyzed with a sterically hindered ligand **43** combined with an Ru complex afforded almost perfect enantioselectivity for the desired chiral *syn* product (entry 5, Table 11).[97]

The MeO-BIPHEP ligand **16** (Table 3) allows Ru, Rh, and Ir complexes to be used for this transformation. Notably, $Ni(OAc)_2$ in combination with the chiral planar ferreocyl diphosphine ligands **44** (Table 11) has been shown to be effective as well, achieving good to excellent results in terms of stereoselectivity.[216–223] Hydrogenation of the α-chloro analogues with Ru-**12** yielded predominantly the *anti* chloro alcohols in up to 99% *ee*.[210] In a same manner, α-acylamino- or α-bromo-substituted β-keto phosphonates were hydrogenated with Ru-**12**, affording *syn* alcohols preferentially with up to 98% *ee* (Scheme 12).

Table 11 Stereoselective hydrogenation of α-substituted β-ketoesters via DKR



Entries	*R^1*	*R^2*	*R^3*	*Catalyst*	*Conditions*	syn:anti	ee *(%)*	*References*
1	Me	NHCOMe	Me	Ru-(*R*)-**12**	DCM, 101 bar H_2, 50 °C, 70 h, S/C 1170	99:1	98	205
2	Me	NHCOMe	Me	Ru-(*R*)-**12**	MeOH, 101 bar H_2, 80 °C, 2 h, S/C 100	74:26	95	209
3	Me	$NHCOCHMe_2$	Me	Ru-(*R*)-**12**	MeOH, 101 bar H_2, 80 °C, 2 h, S/C 100	74:26	95	209
4	Me	$CH_2NHCOPh$	Me	Ru-**12**	DCM, 98 bar H_2, 50 °C, 40 h, S/C 1170	94:6	97	205,206
5	Me	$CH_2NHCOPh$	Me	Ru-**43**	DCM/MeOH, 50 bar H_2, 50 °C, 40 h, S/C 1000	98:2	99	97
6	Cp	$NH_2 \cdot HCl$	Bn	Ru-**12**	Pr^nOH, 50 bar H_2, 50 °C, 48 h, S/C 26	98:2	95	220
7	Pr^n	$NH_2 \cdot HCl$	Bn	Ru-(*R*)-**16**	DCM, 50 bar H_2, 23 °C, 48 h, S/C 26	97:3	91	220
8	Ph	$NH_2 \cdot HCl$	Me	Rh-**44a**	AcOH/AcONa, 51 bar H_2, 23 °C, 1 h, S/C 33	94:6	84	216
9	Ph	$NH_2 \cdot HCl$	Me	Ir-**16**	AcOH/-Na, 4.5 bar H_2, 23 °C, 96 h, S/C 100	<1:99	92	217
10	Ph	$NH_2 \cdot HCl$	Me	Ni-**44b**	TFE/AcOH, 101 bar H_2, r.t., 24 h, S/C 20	<1:99	92	218



R^1	R^2	L	syn:anti	ee (%)	Configuration
Me	NHCOMe	(*R*)-**12**	97:3	>98	1*R*,2*R*
Ph	NHCOMe	(*R*)-**12**	98:2	95	1*R*,2*R*
Me	Br	**12**	90:10	98	1*S*,2*S*

Scheme 12 Stereoselective hydrogenation of α-substituted β-keto phosphonates via DKR.

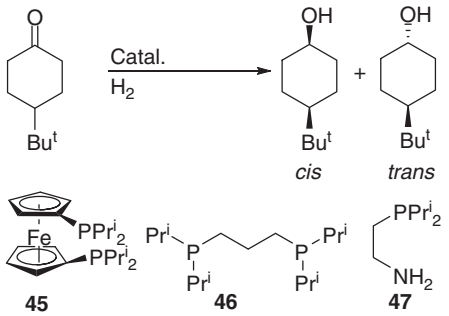
The stereoselective hydrogenation of configurationally unstable α-substituted β-keto carboxylates and phosphonates via DKR has been used for the synthesis of bioactive compounds. Industrial applications have taken place, for example, AH of methyl 2-benzamidomethyl-3-oxo-butanoate to give 2-acetoxyazetidinone, a key intermediate in the synthesis of carbapenems.

8.04.2.1.2.4 Diastereoselective hydrogenation of ketones

Diastereoselective hydrogenation of ketones over heterogeneous catalysts, such as platinum, rhodium, ruthenium, and Raney nickel, affords the corresponding alcohols under mild conditions.[225–231] Substituted cyclohexanones are the most frequently studied for this transformation, and it is well known that the stereoselectivity of the reaction varies with the reaction conditions.[226–231] The hydrogenation of 4-*tert*-butylcyclohexanone is particularly well studied to gain insight into the facial selectivity in the reduction of the C═O double bond. Among the heterogeneous catalysts, Raney Ni and clay-supported or metallic Rh catalysts show very high stereoselectivity (entries 1–4, **Table 12**).[227,228,230] With PtO_2 as catalyst, 3,3-dimethyl-5-phenylcyclohexanone was converted into the *trans* alcohol in pure form.[232,233]

Diastereoselective hydrogenation with homogeneous catalysts affords lower stereoselectivity than those with heterogeneous catalysts in general.[234–242] However, hydrogenation of the benchmark substrate with ruthenium diphosphine/diamine catalysts produces *cis*-4-*tert*-butylcyclohexanol with excellent selectivity, because of the active catalytic species, ruthenium hydride, approaching the carbonyl carbon preferentially from the less crowded equatorial side. It has been demonstrated that the stereoselectivity is mainly dependent on the combination of phosphine and diamine ligands. Thus, by using an *in situ*-generated Ru-catalyst from $[RuCl_2(PPh_3)_3]$, ethylenediamine (EDN), and KOH in IPA, hydrogenation of 4-*tert*-butylcyclohexanone afforded

Table 12 Diastereoselective hydrogenation of 4-*tert*-butylcyclohexanone



Entries	*Catalyst*	*Conditions*	*Ratio* (cis/trans)	*Yield (%)*	*References*
1	Raney Ni	EtOH, 1 bar H_2, r.t.	92:8	100	227
2	Rh/C	EtOH, 1 bar H_2, r.t.	94:6	100	227
3	Rh	THF, HCl(cat.), 25 °C, 1 bar H_2, 3 h	99.3:0.7	100	228
4	Rh/**41**/Clay	MeOH, 30 °C, 1 bar H_2, 24 h	99.8:0.2	100	230
5	Rh-**45**	MeOH, 25 °C, 2–4 bar H_2, S/C 500	14:86	–	234
6	Rh-**46**	MeOH, 25 °C, 1 bar H_2, S/C 200	11:89	100	235
7	Cu-$PhPMe_2$	Benzene/Bu^tOH/Bu^tONa, r.t., 1 bar H_2, S/C 20	25:75	96	236,237
8	Ru-PPh_3/EDN	Pr^iOH/KOH, 28 °C, 4 bar H_2, 80 h, S/C 10 000	98.3:1.7	>99	238
9	Ru-**47**/Bu^tOH	Pr^iOH, 50 °C, 10 bar H_2, 12 h, S/C 500 000	95:5	100	239

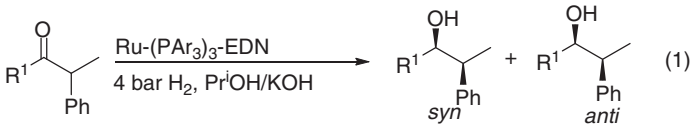
a 98.3:1.7 mixture of *cis* and *trans* alcohols (entry 8, Table 12).[235] The stereoselectivity of the reaction of other 4-substituted cyclohexanones is controlled similarly by the population of the equatorial and axial conformers, leading predominantly to the *cis* alcohols. Thus, hydrogenation of 3-methylcyclohexanone afforded quantitatively a 96:4 mixture of *trans* and *cis* alcohols. In a similar manner, 2-methyl and 2-isopropylcyclohexanone are hydrogenated to the corresponding *cis* alcohols with a 98:2 and >99.8:0.2 selectivity. The latter example represents the highest stereoselectivity observed in the reduction of this ketone. The selectivity is remarkably higher than the equilibrium equatorial/axial ratio of the starting ketone (74:26), indicating significant repulsive interactions between the axial substituent and the incoming ruthenium hydride. The five membered 2-methylcyclopentanone is reduced to the alcohol with a 99:1 *cis*/*trans* selectivity. Furthermore, very high TONs have been revealed recently for the hydrogenation of 4-substituted cyclohexanones by using an Ru-**47** complex (entry 9, Table 12); a S/C ratio as high as 500 000 was applied.[239] Other cyclic ketones were stereoselectively converted into the corresponding alcohols in a similar manner.[238]

Diastereoselective hydrogenation of acyclic substrates with Ru-PPh_3-EDN and related catalysts has also been explored.[243,244] For example, the hydrogenation of 1-phenylethyl ketones gave the *syn*-alcohols predominantly (equation 1, Scheme 13).[238] The stereoselectivity appears to be influenced by the electronic properties of the phosphine ligands, which affect the nucleophilicity of the ruthenium hydride species. When an enantiopure ketone is reduced, the diastereoselectivity is profoundly affected by the structure of the ruthenium complexes.[238] As shown in Scheme 13, hydrogenation of (*R*)-3-methylcyclohexanone with Ru-**12**-(*S*,*S*)-DPEN gave the alcohols with a *cis*/*trans* ratio of 3:97, whereas the reduction with Ru-(*R*)-**12**-(*S*)-DAIPEN afforded a product with a *cis*/*trans* ratio of 56:44 (equation 2, Scheme 13).[238]

Diastereoselective hydrogenation of *β*-hydroxyl ketones produces chiral 1,3-diols, a structure which frequently appears in bioactive compounds.[245–249] Ruthenium-catalyzed hydrogenation of *β*-hydroxyl ketones with high diastereoselectivity has been achieved (Table 13).[246,247] Thus, with a simple Ru-PPh_3 catalyst, a wide range of *β*-hydroxyl ketones have been converted into the *anti*-diols.[246,247] When a chiral catalyst is used, the diastereoselectivity can be controlled by the configuration of the catalyst.[245] Thus, while Ru-(*S*)-**16** affords the *trans*-diol in high diastereoselectivity, Ru-(*R*)-**16** gives the *syn*-diol predominantly.[245]

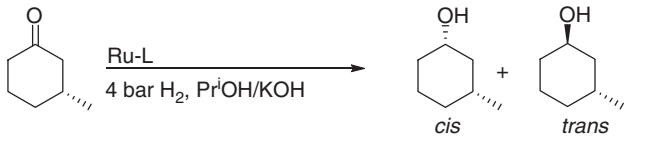
Ketones with other heteroatom substituents close to the carbonyl moieties have also been investigated. Hydrogenation with heterogeneous catalysts shows high diastereoselectivity.[250] For example, *α*-aminopropiophenone derivatives were hydrogenated with Pd/C under acidic conditions to give the *anti*-amino alcohol exclusively (equation 1, Scheme 14).[250] However, when $LiAlH_4$ was used as cocatalyst, the *syn*-amino alcohol was obtained predominantly. Hydrogenation of *α*-oxo *β*-tosylamino ester with Pd/C afforded the *syn*-amino alcohol in high diastereoselectivity; in contrast reduction with borohydride gave the *anti* product (equation 2, Scheme 14).[251]

Diastereoselective hydrogenation of the *α*-aminoketones with homogeneous catalysts has been less studied before 2000. However, the recently developed Ru(II) complex **49**, which contains a spirodiphosphine **48** and DPEN, enables the hydrogenation of acyclic *α*-substituted aliphatic ketones with almost perfect enantioselectivity and excellent *anti*/*syn* ratio.[181] As shown in Table 14, a variety of racemic acyclic *α*-*N*,*N*-dialkylamino-substituted aliphatic ketones can be hydrogenated under mild conditions, with complete conversions and remarkably high *ee*'s obtained in all the cases (entries 1–19, Table 14). The *α*-dialkylamino



(1)

R^1	Ar	Ratio (*syn*/*anti*)
Ph	Ph	98:2
Bu^n	Ph	93:7
Me	Ph	86:14
Me	4-$MeOC_6H_4$	96:4
Me	4-MeC_6H_4	95:5
Me	4-FC_6H_4	78:22

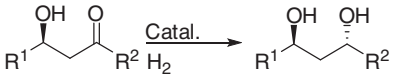


(2)

Ru-L	Ratio (*cis*/*trans*)
($RuCl_2$-**12**)$(DMF)_n$-(*S*,*S*)-DPEN	3:97
$RuCl_2$(*R*)-BINAP$(DMF)_n$-(*S*)-DAIPEN	56:44

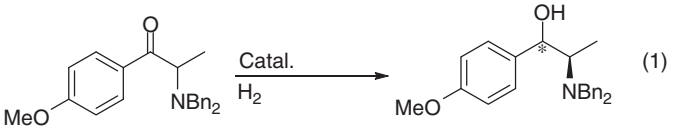
Scheme 13 Diastereoselective hydrogenation of ketones.

Table 13 Diastereoselective hydrogenation of β-hydroxyl ketones



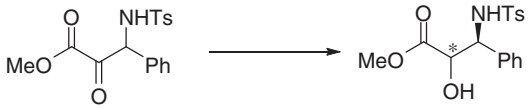
Entries	R^1	R^2	*Catalyst*	*Conditions*	de *(%)*	*Yield (%)*	*References*
1	Ph	Bu	Ru-PPh_3	MeOH, 10 bar H_2, 50 °C, 24 h, S/C 50	96	94	246
2	Ph	Me	Ru-PPh_3	MeOH, 10 bar H_2, 50 °C, 24 h, S/C 50	97	95	246
3	Pr	Bu	Ru-PPh_3	MeOH, 10 bar H_2, 50 °C, 24 h, S/C 50	97	95	246
4	Pr	Me	Ru-PPh_3	MeOH, 10 bar H_2, 50 °C, 24 h, S/C 50	98	94	247
5	Pr^i	Pr	Ru-PPh_3	MeOH, 10 bar H_2, 50 °C, 24 h, S/C 50	94	98	246
6	Pr	Bu	Ru-(*R*)-**16**	MeOH, 10 bar H_2, 50 °C, 24 h, S/C 50	98	100	245
7	Pr	Bu	Ru-(*S*)-**16**	MeOH, 10 bar H_2, 50 °C, 24 h, S/C 50	76[a]	100	245

[a] *syn*-1,3-diol is the main product.



(1)

Catalyst	Conditions	Yield (%)
Pd/C	HCl, EtOH, 1 bar H_2	96 *anti*
$LiAlH_4$/Pd/C	HCl, EtOH, 1 bar H_2	90 *syn*



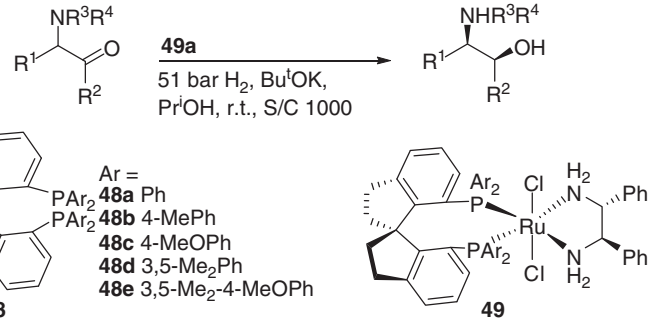
(2)

Catalyst	Conditions	Yield (%)
Pd/C	MeOH, 1 bar H_2	87 *syn, dr*>95:5
$NaBH_4$	THF, –10 °C	82, *anti, dr*>95:5

Scheme 14 Diastereoselective hydrogenation of ketones.

substrates impose significant influence on the diastereoselectivity. In general, the ketones with a small dialkylamino group, such as dimethylamino or pyrrolidinyl, provided high diastereoselectivities. In contrast, when a bulkier diethylamino group was introduced into the substrate, low diastereoselectivity resulted (entry 6, Table 14). High hydrogen pressure leads to a higher enantioselectivity and diastereoselectivity (e.g., compare to entry 1, 97:3 *anti*/*syn* ratio with 98% *ee* under 10 bar H_2). Comparison of the ligands shows that the substituents on the P-phenyls of the SDP ligands have no apparent effects on the enantioselectivity (98–99.9% *ee*), diastereoselectivity (98:2–99:1), or the reaction rates. The high efficiency of the catalysts is further demonstrated in an experiment with a lower catalyst loading (S/C = 10 000), giving identical *ee* and *dr* value of the product, albeit in a longer reaction time of 24 h. The catalysts are also viable for hydrogenation of racemic acyclic *α*-*N*-alkyl/arylamino aliphatic ketones, leading to chiral *β*–amino alcohols (entries 20–27, Table 14). A range of racemic *α*-*N*-alkyl/arylamino aliphatic ketones were converted into the corresponding amino alcohols in high enantioselectivities (>90% *ee*) and diastereoselectivities (>91:9 *anti*/*syn*).

Table 14 Diastereoselective hydrogenation of acyclic *α*-substituted aliphatic ketones



Entries	*R*[1]	*R*[2]	*R*[3],*R*[4]	*Time (h)*	anti/syn	ee *(%)*	*References*
1	Ph	Me	$(CH_2)_4$	5	>99:1	99.9	181
2	Ph	Me	$(CH_2)_5$	5	95:5	99	181
3	Ph	Me	$C_2H_4OC_2H_4$	5	96:4	99.9	181
4	Ph	Me	$C_2H_4N(Me)C_2H_4$	5	>99:1	99	181
5	Ph	Me	Me, Me	5	>99:1	99.9	181
6	Ph	Me	Et, Et	5	71:29[a]	99.9	181
7	Ph	Et	$(CH_2)_4$	5	96:4	99.3	181
8	4-MeO-C_6H_4	Me	$(CH_2)_4$	5	95:5	99.9	181
9	4-Cl-C_6H_4	Me	$(CH_2)_4$	5	>99:1	99	181
10	4-Br-C_6H_4	Me	$(CH_2)_4$	5	>99:1	99.2[b]	181
11	3-MeO-C_6H_4	Me	$(CH_2)_4$	5	95:5	98	181
12	3-Me-C_6H_4	Me	$(CH_2)_4$	5	>99:1	99.4	181
13	2-MeO-C_6H_4	Me	$(CH_2)_4$	5	99:1	99.6	181
14	2-Cl-C_6H_4	Me	$(CH_2)_4$	5	92:8	99.9	181
15	2-Br-C_6H_4	Me	$(CH_2)_4$	5	94:6	99.6	181
16	2,3-$(CH)_4C_6H_3$	Me	$(CH_2)_4$	5	>99:1	98	181
17	3,4-$(OCH_2O)C_6H_3$	Me	$C_2H_4OC_2H_4$	5	95:5	99	181
18	Me	Me	$(CH_2)_4$	5	97:3	97	181
19	Me	Et	$C_2H_4OC_2H_4$	5	89:11	93	181
20	Ph	Me	Ph, H	10	97:3	96	181
21	Ph	Me	Prⁱ, H	1	>99:1	99	181
22	Me	Me	Ph, H	2	>99:1	96	181
23	Me	Me	Bn, H	8	92:8	92	181
24	Me	Me	Cy-C_6H_{11}, H	2	99:1	96	181
25	Me	Et	Cy-C_6H_{11}, H	6	91:9	90	181
26	Et	Me	Ph, H	4	95:5	95	181
27	Et	Me	Bn, H	10	95:5	97	181

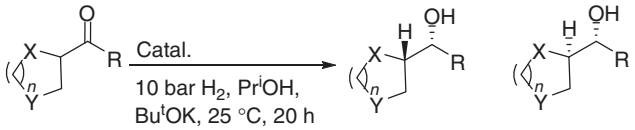
[a]57% *ee* was obtained for *syn* isomer.

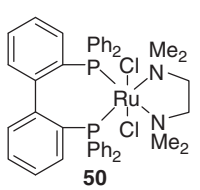
[b]The configuration of the product is (1*R*, 2*S*) determined by X-ray analysis.

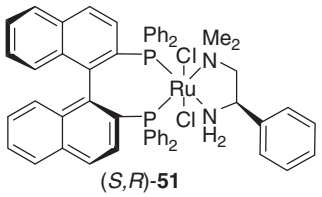
Diastereoselective hydrogenation of *α*-substituted heterocycloalkyl ketones has been demonstrated with the more common Ru(II) catalysts.[252] As shown in Table 15, hydrogenation of *α*-substituted heterocycloalkyl ketones with catalyst **50** in IPA in the presence of BuᵗOK afforded the *syn*-alcohols with >99:1 selectivity (entries 1–4, Table 15). The consistently high

diastereoselectivity appears to suggest that the stereoselection is primarily regulated by the structure of the catalyst not the internal stereocontrol of the substrates. Using the catalyst **51** (Table 15), enantioselective hydrogenation becomes possible.[252] A series of α-substituted heterocycloalkyl ketones have been converted into the alcohols in excellent diastereo- and enantioselectivities (entries 5–14, Table 15). In this case, however, the diastereoselectivity depends on the substituent in the cycloalkane.

Table 15 Diastereoselective hydrogenation of cyclic α-substituted ketones




50


(*S*,*R*)-**51**

Entries	*N*	*X*	*Y*	*R*	*Catalyst*	*S/C*	syn:anti	ee *(%)*	*References*
1	2	O	NBz	Ph	**50**	1 000	>99:1	–	252
2	2	O	NBz	Ph	**50**	5 000[a]	99:1	–	252
3	2	CH_2	NBoc	Ph	**50**	1 000	>99:1	–	252
4	2	CH_2	NBoc	Ph	**50**	5 000[a]	>99:1		252
5	2	O	NBz	Ph	**51**	5 000	>99:1	99	252
6	2	CH_2	NBoc	Ph	**51**	10 000	>99:1	>99	252
7	2	CH_2	NBoc	Ph	**51**	20 000	>99:1	>99	252
8	2	CH_2	NBoc	3-Cl-C_6H_4	**51**	5 000	>99:1	99	252
9	2	CH_2	NBoc	2-Thienyl	**51**	500	>99:1	99	252
10	2	NBoc	CH_2	Ph	**51**	1 000	1:>99	97	252
11	2	NBz	CH_2	Ph	**51**	200	1:>99	96	252
12	1	O	CH_2	Ph	**51**	500	95:5	99	252
13	1	CH_2	NBz	Ph	**51**	1 000	75:25	98	252
14	1	NBz	CH_2	Ph	**51**	1 000[b]	2:98	94	252

[a]Under 50 bar H_2.
[b]The mixture of PriOH/DCM (6/1) was used as solvent.

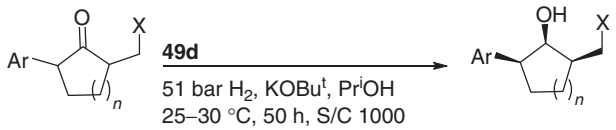
Hydrogenation of racemic α,α'-disubstituted cycloketones may be catalyzed by Ru catalyst **49d** (Table 16).[253] Proceeding via DKR, the AH affords chiral diols with three contiguous stereocenters in one pot. Good to excellent enantioselectivity has been achieved in most cases (91–99.9% *ee*). The substituent on the phenyl ring of the substrates has little effect on either reactivity or enantioselectivity. However, the ester group of the side chain plays a crucial role in determining the enantioselectivity (entries 13–17, Table 16).

8.04.2.1.3 Hydrogenation of diketones

AH of diketones is possible with both heterogeneous and homogeneous catalysts. Hydrogenation of 1,3-diketones with chirally modified Raney nickel catalyst Ni-**TA** to produce chiral diols was developed in the 1990s.[88,254–256] The reduction afforded diols with *ca.* 90% *ee* and has been applied to the synthesis of natural compounds.[257,258] Homogeneous hydrogenations of diketones are also well studied.[109,245,246,259–279] By using a quinine-NH_2Bn-Co(DMG)$_2$ (quinine-**52**) complex as catalyst,[259,280–282] the homogeneous hydrogenation of benzil furnished (*S*)-benzoin in 78% *ee* (equation 1, Scheme 15). Similar enantioselectivity was observed with the ligand **53**, when it was combined with Co(II) and quinine.[282] Hydrogenation of 2,3-butanedione with Ru-(*R*)-**12** afforded a 26:74 mixture of *anti*-1,2-diol and *meso*-isomer (equation 2, Scheme 15), with the *syn*-diol formed in 100% *ee*.[95]

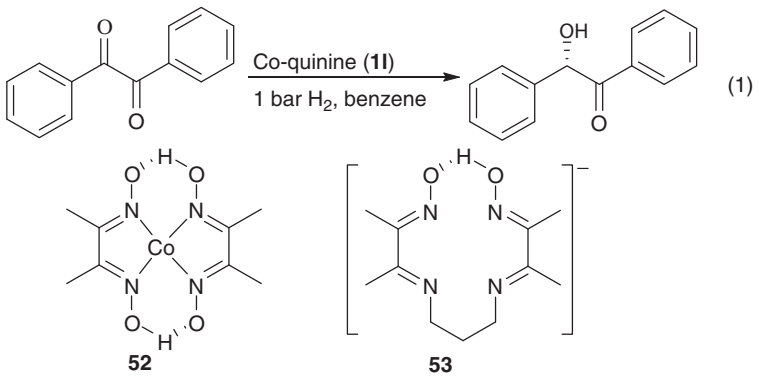
AH of 1,3-diketones appears more successful, with homogeneous hydrogenation showing excellent diastetero- and enantioselectivity (Table 17).[109,245,246,260–276] A series of diphosphine ligands has been investigated for this transformation, for example, **12**, **15**, **16**, **54–56**. For instance, Ru-**12** catalyzed hydrogenation of 2,4-pentanedione gives enantiomerically pure diol in 99% yield (entry 1, Table 17).[95,260] Methyl 3,5-dioxohexanoate was also hydrogenated with Ru-**12**, affording an 81:19 mixture of *anti* (78% *ee*) and *syn*-dihydroxy ester (entry 7, Table 17).[263] Enantioselective and diastereoselective hydrogenation of fluorinated diketones has also been explored with Ru catalysts, which show low activity and low to moderate selectivity.[275]

Table 16 AH of racemic α,α'-disubstituted cycloketones

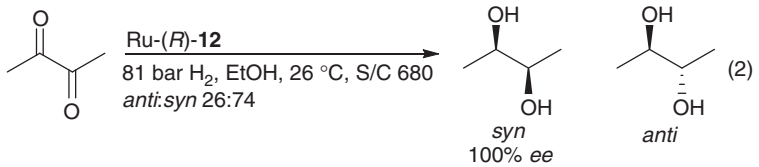


Entries	*Ar*	n	*X*	*Yield (%)*	ee *(%)*	*References*
1[a]	Ph	2	CO_2Me	98	98	253
2[b]	Ph	2	CO_2Me	97	98	253
3	4-Me-C_6H_4	2	CO_2Me	93	97	253
4	4-MeO-C_6H_4	2	CO_2Me	96	98	253
5	4-Cl-C_6H_4	2	CO_2Me	95	92	253
6	3-Me-C_6H_4	2	CO_2Me	96	98	253
7	2-Me-C_6H_4	2	CO_2Me	86	98	253
8	3,4-$(MeO)_2$-C_6H_3	2	CO_2Me	96	99.6	253
9	3,4-$(OCH_2O)C_6H_3$	2	CO_2Me	95	99.9	253
10	Ph	2	CH_2CO_2Me	93	91	253
11	Ph	1	CO_2Me	96	75	253
12	Ph	3	CO_2Me	92	96	253
13	Ph	2	H	99	73	253
14	Ph	2	Ph	99	27	253
15	Ph	2	$CONMe_2$	95	92	253
16	Ph	2	CONHBn	98	79	253
17	Ph	2	CH_2OBn	97	84	253

[a] *cis*-starting materials were used.
[b] *trans*-starting materials were used.



Catalyst	S/C	Temperature (°C)	Time (h)	Yield (%)	*ee* (%)
52-1l	10	−10	–	100	78
Co-**53-1l**	20	–	24	99	79

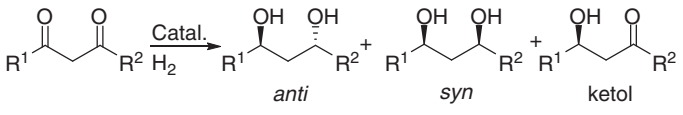


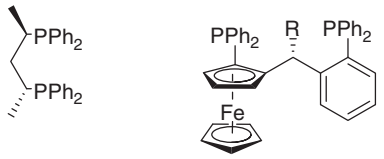
Scheme 15 AH of diketones.

8.04.2.2 Hydrogenation of Simple Ketones and Aldehydes

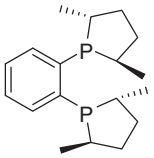
The reduction of simple ketones and aldehydes to alcohols is widely practiced in chemical synthesis. Although stoichiometric reducing agents are often used, the increasing demand for atom economy, clean synthesis, and straightforward work up procedures

Table 17 Hydrogenation of diketones





54 **55a** R = NMe_2 **55b** R = Me



56

Entries	R^1	R^2	*Catalyst*	*Conditions*	*Yield (%)*	anti/syn/*ketol*	ee *(%)*	*References*
1	Me	Me	Ru-(*R*)-**12**	EtOH, 73 bar H_2, 30 °C, S/C 2000	100	99/1/0	100	95,260
2	Me	Me	Ru-(*R*)-**15**	EtOH, 100 bar H_2, 50 °C, S/C 2000, 24 h	100	99/1/0	100	265
3	Me	Me	Ru-**54**	MeOH, 80 bar H_2, 80 °C, S/C 680, 16 h	100	75/25/0	97	264
4	Me	Pr^i	Ru-(*R*)-**12**	EtOH, 48 bar H_2, 50 °C, S/C 2000	92	97/3/0	98	95,260
5	Me	Ph	Ru-(*R*)-**12**	EtOH, 83 bar H_2, 26 °C, S/C 2000	98	94/6/0	94	95,260
6	Me	Ph	Ru-(*R*)-**12**	EtOH, 48 bar H_2, 50 °C, S/C 2000	89	2/0/98	98[a]	95,260
7	Me	CH_2CO_2Me	Ru-(*R*)-**12**	MeOH, 101 bar H_2, 25 °C, S/C 500, 48 h	100[b]	81/19/0	78	263
8	Ph	Ph	Ru-(*R*)-**15**	EtOH/DCM, 101 bar H_2, 40 °C, S/C 167, 64 h	70	94/6/0	87	266
9	CH_2Cl	CH_2Cl	Ru-(*R*)-**12**	EtOH, 85 bar H_2, 102 °C	–	–	94	261
10	Me	Ph	Ru-**55a**	EtOH/DCM, 51 bar H_2, 30 °C, S/C 200	100	–	100	277–279
11	Me	Ph	Ru-**55b**	EtOH/DCM, 51 bar H_2, 50 °C, S/C 200	100	–	92	277–279
12	Me	Me	Ru-**56**	MeOH, 70 bar H_2, 80 °C, S/C 50, 60 h	100	94/6/0	93	270
13	Pr^i	Pr^i	Ru-**56**	MeOH, 70 bar H_2, 80 °C, S/C 50, 70 h	100	96/4/0	97	270
14	C_6H_{11}	C_6H_{11}	Ru-**56**	MeOH, 70 bar H_2, 80 °C, S/C 50, 60 h	100	93/7/0	>95	270
15	Bn	Bn	Ru-**16**	MeOH, 30 bar H_2, r.t., S/C 50, 40 h	100	95/5/0	>95	270

[a] *ee* value of ketol.
[b] A mixture of diol and lactone.

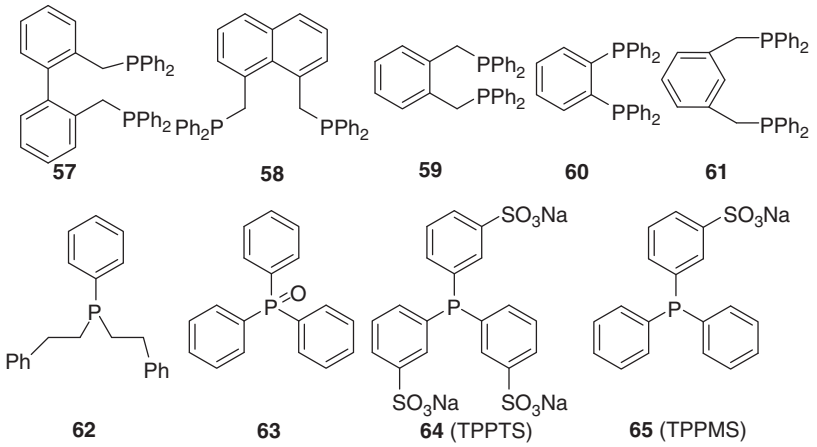
makes the use of molecular hydrogen more cost-effective and environmentally sound. Heterogeneous catalysts (e.g., Pt/C, Pd/C, Raney Ni) are well established for the reduction, and often represent the most economical method. However, where milder conditions, functional groups tolerance and selectivity are required, homogeneous catalysts are more advantageous.

8.04.2.2.1 Hydrogenation of aldehydes

Heterogeneous hydrogenation of aldehydes has been mainly focused on the carbonyl-selective hydrogenation of α,β-unsaturated aldehydes with group VIII metal catalysts.[236,366] An unsupported Pt/Zn/Fe catalyst was first explored for the hydrogenation of aldehydes, for example, cinnamaldehyde. The reduction provided cinnamyl alcohol with good conversion and selectivity.[283] Subsequent research into this reaction revealed that the catalyst activity and alcohol selectivity were highly affected by the metal, support, additives, and preparation conditions.[236,284–366] Pt was the most frequently used metal, and its catalytic properties were affected by the support, such as, alumina, graphite, Nylon, silica, and zeolites. For example, the selectivity was improved up to 95% at >90% conversion by adding 1–7 atom % of Ge to a Nylon-supported Pt catalyst for the hydrogenation of cinnamaldehyde.[286] A Pt/graphite catalyst which has large, faceted metal particles exhibited a higher selectivity than a catalyst which has small particles for the same reduction.[291] The amount of chlorine in a Co/SiO_2 catalyst can strongly affect both the activity and selectivity; thus cinnamyl alcohol was obtained from cinnamaldehyde with 96% selectivity at approximately a Cl/Co ratio of 0.2.[289,292] A Ru catalyst supported on nanometer scale carbon tubules showed much better selectivity than the alumina- or carbon-supported analogue, affording up to 92% selectivity at 80% conversion.[301] Up to 96% selectivity has been achieved with a polymer-supported Rh catalysts for the same hydrogenation.[304] Stabilized by phosphine ligands, Cu catalysts have been demonstrated to be highly selective for the reduction of α,β-unsaturated aldehydes and ketones.[236] Other metals, such as Au, Zn, Zr, Ce, and Ni have also been introduced to the hydrogenation.[344,353,356,359,,360,362,364,,366] In addition, bimetallic $Rh-Sn/SiO_2$ has been reported to be efficient catalyst for the hydrogenation of unsaturated aldehydes, the selectivity varying with the ratio of Rh/Sn.[319] A similar effect on selectivity was also observed in an $Fe-Ir/TiO_2$ system.[328] Extensive studies of the influence of support, preparation methods, size of particles, and metal precursors have been carried out.[345–348,351–354,356–358]

Homogeneous catalytic hydrogenation of aldehydes was first reported in the 1960s.[51,55,367–382] An *in situ*-prepared catalyst from $IrH_3(PPh_3)_3$ and acetic acid was demonstrated to be effective for the hydrogenation of *n*-butyraldehyde to *n*-butanol at 50 °C and 1 bar H_2 pressure.[367] The same catalyst could reduce a series of aldehydes under 10 bar H_2 without using any solvents.[368] TON

of up to 8000 were achieved for the hydrogenation of benzaldehyde. This catalyst afforded saturated alcohol for the hydrogenation of unsaturated aldehydes but did not work for ketones. $[Ir(COD)(OMe)]_2$ combined with a tertiary phosphine has been successfully applied to the hydrogenation of α,β-unsaturated aldehydes,[370] and it has been revealed that the selectivity depends on the solvent and ligands. Phosphines such as $PPhPr^i_2$, PPh_2Pr^i, and $PEtPh_2$ and especially $PCyPh_2$ were effective, affording over 95% selectivity. Other ligands and metal complexes, including those of Ru and Cu, have also been explored (**Scheme 16**).[55] The conversions and alcohol selectivities observed in the reduction of α,β-unsaturated aldehydes are summarized in **Table 18**.



Scheme 16 Ligands for hydrogenation of aldehydes.

Table 18 Hydrogenation of aldehydes with metal complexes

Entries	*Catalysts*	*Aldehydes*	*Conditions*	*Conversion (%)*	*Selectivity (%)*[a]	*References*
1	$IrH(CO)(PPh_3)_3$	Citral	50 bar H_2, 100 °C, Toluene, 5 h	3.1	70.5	55
2	$IrH(CO)(PPh_3)_3$	Cinnamaldehyde	50 bar H_2, 100 °C, Toluene, 3 h	11.4	35	55
3	$IrH(CO)(PPh_3)$/**57**	Citral	50 bar H_2, 100 °C, Toluene, 5 h	11.6	92.2	55
4	$IrH(CO)(PPh_3)$/**57**	Cinnamaldehyde	50 bar H_2, 100 °C, Toluene, 3 h	44.6	13.1	55
5	$IrH(CO)(PPh_3)$/**58**	Citral	50 bar H_2, 100 °C, Toluene, 5 h	19.3	95.8	55
6	$IrH(CO)(PPh_3)$/**58**	Cinnamaldehyde	50 bar H_2, 100 °C, Toluene, 3 h	20.6	77.4	55
7	$IrH(CO)(PPh_3)$/**59**	Citral	50 bar H_2, 100 °C, Toluene, 5 h	58.8	96.4	55
8	$IrH(CO)(PPh_3)$/**59**	Cinnamaldehyde	50 bar H_2, 100 °C, Toluene, 3 h	58.1	9.0	55
9	$IrH(CO)(PPh_3)$/**60**	Citral	50 bar H_2, 100 °C, Toluene, 5 h	7.7	61.2	55
10	$IrH(CO)(PPh_3)$/**60**	Cinnamaldehyde	50 bar H_2, 100 °C, Toluene, 3 h	27.3	19.3	55
11	IrHCl(CO)/**61**	Citral	50 bar H_2, 100 °C, Toluene, 5 h	13.9	42.5	55
12	IrHCl(CO)/**61**	Cinnamaldehyde	50 bar H_2, 100 °C, Toluene, 3 h	52	1.3	55
13	$RuCl_2(PPh_3)_3$	Citral	50 bar H_2, 70–80 °C, Toluene, S/C 1200	35	36	373
14	$RuCl_2(PPh_3)_3$	Cinnamaldehyde	50 bar H_2, 70–80 °C, Toluene, S/C 1600	40	62	373
15	$RuHCl(CO)(PPh_3)_3$/**58**	Citral	50 bar H_2, 70–80 °C, Toluene, S/C 1200	93	96	373
16	$RuHCl(CO)(PPh_3)_3$/**58**	Cinnamaldehyde	50 bar H_2, 70–80 °C, Toluene, S/C 1600	86	94	373
17	$RuH_2(CO)(PPh_3)_3$/**58**	Citral	50 bar H_2, 70–80 °C, Toluene, S/C 1200	64	>99	373
18	$RuH_2(CO)(PPh_3)_3$/**58**	Cinnamaldehyde	50 bar H_2, 70–80 °C, Toluene, S/C 1600	62	95	373
19	$RuCl_2(PPh_3)_3$/EDN	Citral	4 bar H_2, 28 °C, Pr^iOH/Toluene (6/1), S/C 500	92	100	373
20	$RuCl_2(PPh_3)_3$/EDN	Cinnamaldehyde	4 bar H_2, 28 °C, Pr^iOH/Toluene (6/1), S/C 500	88	100	373
21	$RuCl_2(PPh_3)_3$/EDN	Undecenal	4 bar H_2, 28 °C, Pr^iOH/Toluene (6/1), S/C 500	95	>99.5	373
22	$CuH(PPh_3)/PhPMe_2$	Citral	34 bar H_2, r.t., Bu^tOH/benzene, 15 h, S/C 20	90	92	237
23	$CuH(PPh_3)/PhPMe_2$	Cinnamaldehyde	5 bar H_2, r.t., Bu^tOH/benzene, 4 h, S/C 20	94	97	237

[a]Selectivity of allylic alcohol in total products.

A series of ruthenium complexes, including those containing phosphine and diamine ligands, has been explored for the hydrogenation of aldehydes.[55,307,372,375,375,377,383–410] For example, $[Ru(CO)_3(PPh_3)_2]$ was effective for the hydrogenation of propionaldehyde under 20 bar H_2 at 120 °C.[384] A wide range of aliphatic and aromatic aldehydes have been hydrogenated with $[RuCl_2(PPh_3)_3]$ at 70 °C under 10 bar H_2.[385] Related complexes such as $[RuHCl(CO)(PPh_3)_3]$, $[RuHCl(PPh_3)_3]$, and $[RuH_2(CO)(PPh_3)_3]$ are also efficient catalysts for the hydrogenation of both aliphatic and aromatic aldehydes.[388,390] $[RuHCl(CO)(PPh_3)_3]$ was most convenient to use, with which propionaldehyde was hydrogenated to the alcohol at 140 °C and 30 bar H_2 in 50 h at S/C

ratio of 50 000; TON of up to 32 000 were achieved.[389] Such ruthenium complexes can be combined with bidentate phosphines (**57–58**, Scheme 16), resulting in catalysts which showed good activity and selectivity for the hydrogenation of α,β-unsaturated aldehydes (entries 13–18, Table 18).[55,372,373] However, with Ru-**62** the C═C double bond was reduced selectively in the hydrogenation of α,β-unsaturated aldehydes.[372,373] Although the readily available $[RuCl_2(PPh_3)_3]$ catalyzes the hydrogenation of aldehydes, the substrate scope is limited and the selectivity is poor. However, by adding EDN as coligand, excellent chemoselectivities were achieved for the hydrogenation of α,β-unsaturated aldehydes to allylic alcohols (entries 19–21, Table 18).[396] A base, for example, KOH, is necessary to initiate the hydrogenation. It has been revealed that the diamine and KOH/IPA decelerates olefin hydrogenation, which in turn accelerates carbonyl hydrogenation.

In the presence of basic amines, $RhCl_3$-catalyzed hydrogenation of cinnamaldehyde under hydroformylation conditions (both CO and H_2 were used).[411] Only a small amount of hydrogenated products was obtained in the absence of CO or NEt_3, whereas increasing the concentration of NEt_3 led to increased catalytic activity and selectivity for cinnamyl alcohol.[412] However, primary and secondary amines were ineffective for the reduction. $[Rh_6(CO)_{16}]$-diamine has been applied to the hydrogenation of saturated and unsaturated aldehydes in water under hydroformylation conditions (CO and H_2 used).[413] Simple aldehydes can be reduced quantitatively in a few hours with S/C ratio of 300, with allylic alcohols obtained for the unsaturated aldehydes albeit in a longer reaction time. Cationic rhodium complexes, such as $[Rh(NBD)(PR_3)_2][ClO_4]$[414] and [Rh(COD)(DiPFc)][OTf] (DiPFc = diphenylphosphineferrocene),[234] were also used. In the case of the former, triethylphosphine and trimethyphosphine showed high activity, whereas the triphenylphosphine-based complex had little or no activity and the diphosphine (e.g., DPPE) inhibited the reduction completely. Benzaldehyde can be hydrogenated with [Rh(COD)(DiPFc)][OTf] under mild conditions; quantitative yield was obtained in 3 h at 25 °C under 4 bar H_2 with an S/C ratio of 500.[234] A wide range of saturated aldehydes have been reduced with this catalyst. It has also been immobilized on modified alumina, demonstrating high activity and selectivity.[415] Similarly, a polymer-immobilized rhodium carbonyl cluster showed good selectivity in the hydrogenation of a range of unsaturated aldehydes under hydroformylation conditions (CO and H_2 used).[304,416]

Water soluble Ru-**64** and Ru-**65** also showed good selectivity for the hydrogenation of α,β-unsaturated aldehydes in water, affording preferentially unsaturated alcohols.[394,395] A biphasic system was created and the hydrogenation (rate and selectivity) was independent of the organic solvent. However, using a water soluble Rh-**64** complex,[417] hydrogenation of α,β-unsaturated aldehydes took place at the C═C double bonds rather than the formyl group; saturated aldehydes were produced as the final product.[418] Further studies led to new rhodium complexes that are highly active and selective for aldehyde products in the hydrogenation of α,β-unsaturated aldehydes.[378,419]

Metal complexes such as those of copper and osmium have also been explored for the hydrogenation of aldehydes.[237,420–422] For instance, $[CuH(PPh_3)]/PPhMe_2$ catalyzed the hydrogenation of α,β-unsaturated aldehydes, showing good activity and selectivity for the allylic alcohols (entries 22–23, Table 18).[237] A Cu-1,4-bis(diphenylphosphino)butane (DPPB) catalyst was highly chemoselective, reducing a wide range of aldehydes into primary alcohols.[420] Results obtained with the osmium cluster $Os_3(CO)_{12}$ and its complexes bearing phosphines, for example, $Os_3(CO)_{12}/PPh_3$, $Os_3(CO)_{12}$/**63**, and $Os_3(CO)_{12}$/**65**, showed that good yields of allylic alcohols can be obtained by using a large excess of ligands.[421] Iron complexes have been used for the gas-phase hydrogenation of aldehydes.[422]

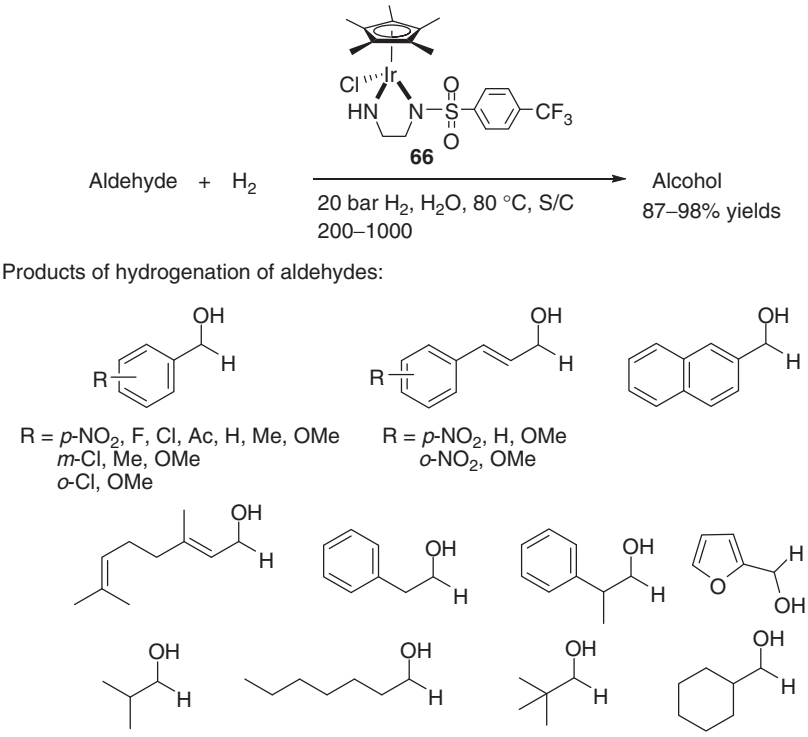
A diamine-ligated half-sandwich iridium complex **66** was shown to catalyze the hydrogenation of a wide range of aldehydes in neat water (Scheme 17).[423] Aromatic, aliphatic, heterocyclic, and α,β-unsaturated aldehydes were all viable substrates, and in the case where C═C and ketone C═O bonds coexist, only the formyl group was saturated. Interestingly, this catalyst is also highly active in TH of aldehydes with formate in water (*vide infra*).

AH of 1-deuterio benzaldehyde and its derivatives has been demonstrated with $Ru(OAc)_2$/(*R*)-**12** in the presence of 5 equivalents of HCl. This afforded 1-deuterio benzyl alcohols in up to 89% *ee*.[424] Racemic aldehydes and α-aryloxy aldehydes have been hydrogenated via DKR with ruthenium catalysts (Ru-48/DPEN). Excellent enantioselectivities and high yields were the feature of the transformation, together with a broad substrates scope.[425,426]

8.04.2.2.2 Hydrogenation of aryl ketones

Heterogeneous hydrogenation of ketones has been thoroughly investigated.[309,362,427–456] A wide range of supported catalysts based on Co, Rh, Ir, Pd, Pt, Ni, Ru, Os, Cu, Ag, Au, Re, and related multimetallic variants have been employed in this transformation.[427,428] The reaction can be carried out in either organic or aqueous solvents or under solvent-free conditions, with the selectivity (C═O reduction) levels depending both on the electronic and geometric structures of reactants and metal surfaces. Several factors affect the activity and selectivity of the catalyst, including the metal precursor, support, catalyst preparation, activation mode, and reaction conditions. Both metals and metal alloys can be used as active components with their electronic properties tunable by adding promoters. The support can be simple oxides, zeolites, mesoporous materials, clays, carbons, and so on. The nature of the support materials, such as porosity, pore size distribution, and reducibility, is an important parameter to consider in catalyst preparation. Selected examples of hydrogenation of aryl and related ketones are shown in Table 19.

Homogeneous hydrogenation of simple ketones has been challenging until recently.[76,234–237,457–470] A limited number of Rh and Ru complexes showed good catalytic activity toward ketones without functional groups adjacent to the carbonyl group. Thus, hydrogenation of acetophenone (ACP) with an $[RhCl_2(bipy)_2]Cl \cdot 2H_2O$ catalyst achieved >98% conversion, and the bipyridine-based complexes showed high activity under basic conditions.[76,460] The same reduction with the catalyst derived from $RhCl_3$ and PPh_3 gave good conversions, albeit requiring a large excess of KOH.[457] Cationic rhodium complexes with basic alkylphosphine ligands, for example, $[RhH(PPhMe_2)_2L_2][X]$ (X = PF_6 or ClO_4), [Rh(NBD)(DIPB)][ClO_4], and [Rh(COD)(DIPFC)][OTf], proved to



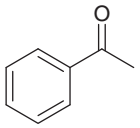
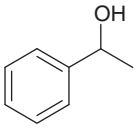
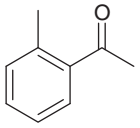
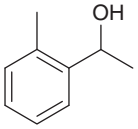
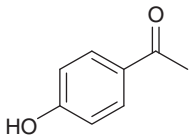
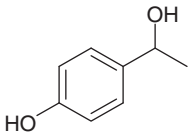
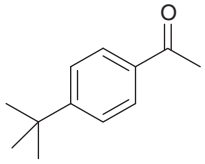
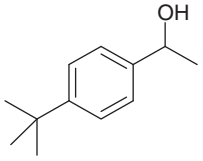
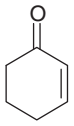
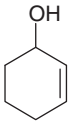
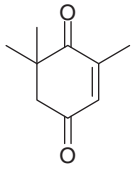
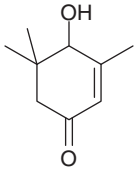
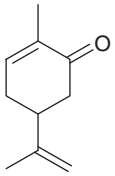
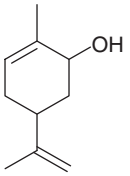
Scheme 17 Hydrogenation of aldehydes with an iridium catalyst in water.

be effective as well.[234,235,461] The basic ligands are expected to faciliate the oxidative addition of H_2.[466] The anionic ruthenium complex ($K_2[Ru_2H_4PPh_2(PPh_3)_3]\cdot 2O(CH_2CH_2OMe)_2$) was more active than the related neutral complexes, but the active catalytic species was later proposed to be a neutral ruthenium hydride $[RuH_4(PPh_3)_3]$.[458,462,464] A trinuclear ruthenium complex, [RuHCl(DPPB)]$_3$, was demonstrated to hydrogenate ACP under atmosphere pressure.[463] Notably, the hydrogenation of ketones with $[RuCl_2(PPh_3)_3]$ can be remarkably accelerated by the addition of a small amount of EDN and KOH. Thus, hydrogenation of ACP can be carried out quantitatively at 1 bar H_2 and r.t. in IPA with a high initial rate, and especially, S/C ratios as high as 10 000 and TOF up to 23 000 h^{-1} were reached under 51 bar H_2.[468] Cu and Ni complexes also showed good activity.[236,237,469,470]

AH of nonfunctionalized ketones with metal complexes had been less successful before the mid 1990s notwithstanding the pioneering work reported in the 1980s. A milestone was reached in 1995 with the discovery by Noyori and coworkers of remarkably highly active Ru-diphosphine-diamine catalysts.[396,468] By using Ru-**12**/DPEN/KOH, excellent yield and enantioselectivity has been achieved for the hydrogenation of a wide range of simple ketones. Studies show that the AH proceedes via a nonclassical metal–ligand cooperative mechanism with the NH group of the ligand acting to activate, position and protonate the carbonyl, whereas the hydride is being transferred, resulting in fast reaction rates, and high-level control of the enantioselectivity. This mechanism also explains why the catalyst is chemoselective toward C=O rather C=C/C≡C bond reduction. Numerous studies have since been launched, benefiting from the fact that the structure and property of the catalyst can be easily modified by changing the combination of chiral diphosphine and diamine ligands. As a result, a wide range of simple ketones have been reduced to the corresponding chiral alcohols in high yields and *ee*'s, using various Ru-diphosphine-diamine catalysts. Table 20 summarizes the results obtained. However, when combined with $[RuCl_2(PPh_3)_3]$, the C_2-symmetric ferrocenyl planar phosphinooxazoline ligands (**70–71**, Table 20), which do not possess the NH functional group, also give excellent enantioselectivities for a wide range of simple ketones (up to 99.7% *ee*), albeit with a low TON (entries 7–11, Table 20).[471] For example, the hydrogenation of 1-indanone and 1-tetralone afforded 99.5% and 99.7% *ee*'s, respectively, with quantitative conversions at 0 °C in 24 h at an S/C ratio of 100.[471] Phosphine-free catalysts have also been reported. The amino alcohol-substituted imidazo[1,5-*b*]pyridazine **72** (Table 20) in combination with $[Ir(COD)_2(OMe)]$ demonstrated almost perfect enantioselectivities for all the ketones tested (>99% *ee* in all cases) (entries 36–41, Table 20).[472]

Some of the catalysts show extraordinary activity and productivity, although in most of the cases the TON ranges from 10 to 1000. For example, using Ru-**67b**/DPEN, AH of ACP demonstrated a TON of 2.4 million with TOF=228 000 h^{-1}. The enantioselectivity of the product increased from 80 to 99% *ee* when DPEN was replaced with DAIPEN (entry 2, Table 20). Modification of the original Ru-diphosphine-diamine catalysts led to the ruthenabicyclic complexes **73** (Table 20), which are capable of AH of a wide range of ketones with excellent *ee*'s.[479] The catalysts exhibited high activity and a TOF up to 210 000 h^{-1} was achieved (entries 42–56, Table 20), with the substrate scope superior to one of the most efficient catalysts, Ru-**67b**/DAIPEN. Around the same time, an iridium catalyst bearing the tridentate spiro ligand **34b** was shown to exhibit unusually high activity in the hydrogenation of ACP, affording the chiral alcohol in 98% *ee* and a TON of 4.55 million (TOF=12 600 h^{-1}) (entries 12–14,

Table 19 Heterogeneous hydrogenation of ketones

Entries	*Ketones*	*Products*	*Catalyst*	*Selectivity (%)*	*Conversion (%)*	*References*
1			Ni/Y Ag/SiO_2 Pd/ZrO_2	74 94.8 –	70 – 80	452 309 438
2			Ni/SiO_2	90	25	455
3			Ni/Y	90	10	452
4			Ni/Y	90	8	452
5			Rh/SiO_2	0[a]	100	454
6			Pt/Al_2O_3	92	85	453
7			Pt/C	3[b]	100	456

[a]Saturated alcohol was obtained.
[b]Ring-saturated alcohol was obtained as main product.

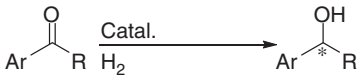
Table 20). This is the highest TON for hydrogenation reactions reported to date.[480] The catalyst also shows broad functional group tolerance. The coordinating pyridine moiety in the ligand is considered to play an important role in stabilizing the active catalyst.

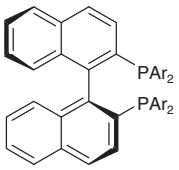
Most of the catalysts require the presence of a strong base for the AH to proceed. However, [RuH(η^1-BH_4)(**67b**)(DPEN)], prepared from the corresponding chloride complex and an excess of $NaBH_4$, showed excellent catalytic activity for the hydrogenation of ACPs in IPA, and required no base, although the AH was faster when $KOBu^t$ was added.[481,482] The catalyst allows for the hydrogenation of base-sensitive ketones, such as keto benzoates, giving high enantioselectivities. The role of the borohydride appears to be the provision of an active catalyst through dissociation.

A wide range of heteroaromatic ketones has also been hydrogenated to their corresponding chiral alcohols with excellent results (Table 21). The Ru-**67b**/DAIPEN catalyst shows excellent enantioselectivity in general.[483] For example, 2-acetyl furan and thiophene are hydrogenated to the desired alcohols in 99% *ee* without any notable effect from the hereoaromatic rings. The reduction of 3- and 4-pyridyl ketones leads to optically almost pure chiral alcohols, in 99.6% and 99.8% *ee*, respectively (entries 12 and 15, Table 21). However, the hydrogenation of 2-acetyl pyridine necessitated the addition of a catalytic amount of triisopropyl borate to complete the reduction. Ruthenium complexes containing ligands **48d**, **68b**, or **70b** show similar selectivity (entries 1, 5, 7, 9, 13, 14, and 16, Table 21).[125,131,471,475,484]

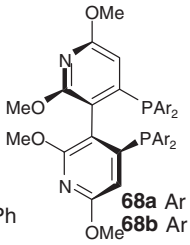
The synthesis of enantioenriched diarylmethanols by AH is difficult, as the products readily undergo hydrogenolysis to form diaryl methanes, and differentiating two similar aromatic rings is not easy. As shown in Table 22, Ru-**67b**/DAIPEN enables

Table 20 AH of aromatic ketones

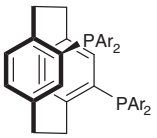




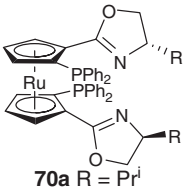
67a Ar = 4-MePh
67b Ar = 3,5-Me_2Ph



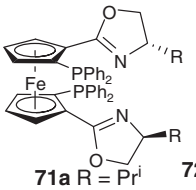
68a Ar = Ph
68b Ar = 3,5-Me_2Ph



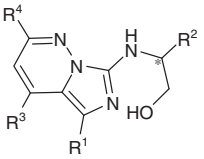
69a Ar = Ph
69b Ar = 3,5-Me_2Ph



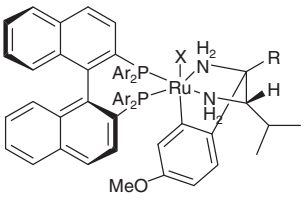
70a R = Pr^i
70b R = Bu^t



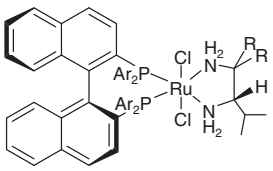
71a R = Pr^i
71b R = Bu^t



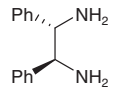
72a R^1 = Ph, R^2 = CH_2CHMe_2
R^3 = R^4 = Me
72b R^1 = Bu^t, R^2 = CH_2CHMe_2
R^3 = R^4 = Me



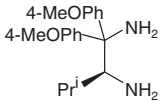
Ar = 3,5-Me_2Ph, R = 4-MeOPh
73a X = Cl; **73b** X = OTf



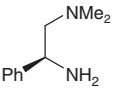
74 Ar = 3,5-Me_2Ph,
R = 4-MeOPh



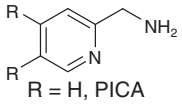
(*S,S*)-DPEN



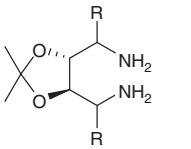
(*S*)-DAIPEN



(*S*)-DMAPEN



R = H, PICA
R = Bu^t, DTBPICA



R = H, (*S,S*)-IPBAN
R = Me, (*S,S*)-IPHAN

Entries	*Ar*	*R*	*Catalyst*	*Conditions*	*Yield (%)*	ee *(%)*	*Configuration*	*References*
1	Ph	Me	Ru-**12**/(*S,S*)-DPEN	Pr^iOH, $KOBu^t$, 30 °C, 45 bar H_2, 48 h, S/C 2 400 000	100	80	*R*	473
2	Ph	Me	Ru-**67b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 8 bar H_2, 60 h, S/C 100 000	97	99	*R*	474
3	Ph	Me	Ru-(*R*)-**67b**/(*R,R*)-DPEN	Pr^iOH, $KOBu^t$, 28 °C, 4 bar H_2, 60 h, S/C 100 000	98	99	*S*	474
4	Ph	Me	Ru-**48d**/(*R,R*)-DPEN	Pr^iOH, $KOBu^t$, 25 °C, 51 bar H_2, 1.5 h, S/C 5000	100	99	*S*	125,475
5	Ph	Me	Ru-**68b**/(*R,R*)-DPEN	Pr^iOH, $KOBu^t$, 25–28 °C, 34 bar H_2, 36 h, S/C 100 000	99.7	99.1	*S*	131,476
6	Ph	Me	Ru-**69b**/(*S,S*)-DPEN	Pr^iOH, $KOBu^t$, 20 °C, 8 bar H_2, 0.5 h, S/C 3000	100	99	*R*	477
7	Ph	Me	Ru-**70a**	Pr^iOH, $KOBu^t$, 25 °C, 10 bar H_2, 24 h, S/C 100	100	97.0	*R*	471
8	Ph	Me	Ru-**70a**	Pr^iOH, $KOBu^t$, 0 °C, 10 bar H_2, 24 h, S/C 100	100	99.1	*R*	471
9	Ph	Me	Ru-**70b**	Pr^iOH, $KOBu^t$, 25 °C, 10 bar H_2, 24 h, S/C 100	100	98.8	*R*	471
10	Ph	Me	Ru-**71a**	Pr^iOH, $KOBu^t$, 25 °C, 10 bar H_2, 24 h, S/C 100	100	96.8	*R*	471
11	Ph	Me	Ru-**71b**	Pr^iOH, $KOBu^t$, 25 °C, 10 bar H_2, 24 h, S/C 100	100	95.9	*R*	471
12	Ph	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, $<$0.33 h, S/C 5000	100	98	*S*	478
13	Ph	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 30 h, S/C 1 000 000	100	98	*S*	478
14	Ph	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 50 bar H_2, 15 days, S/C 5 000 000	91	98	*S*	478
15	Ph	Et	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.67 h, S/C 5000	$>$99	96	*S*	478
16	4-Me-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.83 h, S/C 5000	$>$99	98	*S*	478
17	4-MeO-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.67 h, S/C 5000	98	98	*S*	478
			Ru-**67b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 10 bar H_2, 1 h, S/C 2000	100	100	*R*	474
18	4-Cl-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.67 h, S/C 5000	96	97	*S*	478
			Ru-**57b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 8 bar H_2, 16 h, S/C 20 000	99.9	99	*R*	474
19	4-Br-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.67 h, S/C 5000	98	96	*S*	478
			Ru-**67b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 8 bar H_2, 5 h, S/C 20 000	99.9	99.6	*R*	474
20	3-Me-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.67 h, S/C 5000	96	98	*S*	478
			Ru-**67b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 8 bar H_2, 5 h, S/C 10 000	99.9	99.6	*R*	474
21	4-I-C_6H_4	Me	Ru-**67b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 8 bar H_2, 4 h, S/C 2000	99.7	99	*R*	474

(*Continued*)

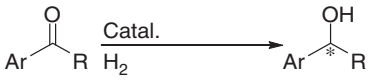
Table 20 Continued

Entries	Ar	R	Catalyst	Conditions	Yield (%)	ee (%)	Configuration	References
22	4-NO_2-C_6H_4	Me	Ru-**67b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 8 bar H_2, 15 h, S/C 2000	100	99.8	*R*	474
23	4-NH_2-C_6H_4	Me	Ru-**67b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 8 bar H_2, 4 h, S/C 2000	100	99	*R*	474
24	2-F-C_6H_4	Me	Ru-**67b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 8 bar H_2, 4 h, S/C 2000	100	97	*R*	474
25	Ph	CF_3	Ru-**67b**/(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 10 bar H_2, 16 h, S/C 11 000	100	96	*R*	474
26	3-MeO-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.83 h, S/C 5000	99	98	*S*	478
27	3-Br-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.83 h, S/C 5000	98	98	*S*	478
28	2-Me-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 3 h, S/C 5000	99	99.3	*S*	478
29	2-MeO-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.67 h, S/C 5000	99	99.6	*S*	478
30	2-Cl-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.58 h, S/C 5000	97	99	*S*	478
31	2-Br-C_6H_4	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 4 h, S/C 5000	97	98	*S*	478
32	2-Naphthyl	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 0.5 h, S/C 5000	97	96	*S*	478
33	3,5-$(CF_3)_2$-C_6H_3	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 1.5 h, S/C 5000	98	99.9	*S*	478
34	2-MeOCO-C_6H_4	Bu	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 1 h, S/C 5000	99	99	*S*	478
35	Cyclohexyl	Me	Ir-**34b**	EtOH, $KOBu^t$, r.t., 10 bar H_2, 4 h, S/C 1000	98	88	*S*	478
36	Ph	Et	Ir-**72a**	THF, $KOBu^t$, r.t., 10 bar H_2, 48 h, S/C 250	96	>99	–	472
37	Ph	Et	Ir-**72b**	THF, $KOBu^t$ u, r.t., 10 bar H_2, 48 h, S/C 250	96	>99	–	472
38	Ph	Bu^t	Ir-**72b**	THF, $KOBu^t$, r.t., 10 bar H_2, 48 h, S/C 250	>99	>99	–	472
39	Ph	Pr^i	Ir-**72b**	THF, $KOBu^t$, r.t., 10 bar H_2, 48 h, S/C 250	97	>99	–	472
40	Ph	Pr	Ir-**72b**	THF, $KOBu^t$, r.t., 10 bar H_2, 48 h, S/C 250	98	>99	–	472
41	4-MeO-C_6H_4	Et	Ir-**72b**	THF, $KOBu^t$, r.t., 10 bar H_2, 48 h, S/C 250	95	>99	–	472
42	Ph	Me	**73a**	MeOH, $KOBu^t$, 11–35 °C, 51 bar H_2, 0.75 h, S/C 10 000	>99	99	*R*	479
43	Ph	Me	**73a**	EtOH, $KOBu^t$, 11–35 °C, 51 bar H_2, 0.22 h, S/C 100 000	>99	>99	*R*	479
44	Ph	Me	**73a**	Pr^iOH, $KOBu^t$, 11–35 °C, 51 bar H_2, 0.42 h, S/C 100 000	>99	>99	*R*	479
45	Ph	Me	**73a**	EtOH/ Pr^iOH (1/1), $KOBu^t$, 11–35 °C, 51 bar H_2, 0.017 h, S/C 10 000	>99	>99	*R*	479
46	Ph	Me	**73a**	EtOH/ Pr^iOH (1/1), $KOBu^t$, 11–35 °C, 51 bar H_2, 0.1 h, S/C 100 000	>99	>99	*R*	479
47	Ph	Me	**73a**	EtOH/ Pr^iOH (1/1), $KOBu^t$, 11–35 °C, 7 bar H_2, 0.25 h, S/C 100 000	>99	>99	*R*	479
48	Ph	Me	**73a**	EtOH/ Pr^iOH (1/1), $KOBu^t$, 11–35 °C, 1 bar H_2, 24 h, S/C 10 000	>99	>99	*R*	479
49	Ph	Me	**73a**	EtOH/ Pr^iOH (1/1), DBU, 11–35 °C, 10 bar H_2, 0.13 h, S/C 10 000	>99	>99	*R*	479
50	Ph	Me	**73a**	Toluene, $KOBu^t$, 11–35 °C, 10 bar H_2, 2.5 h, S/C 2000	>99	>99	*R*	479
51	Ph	Me	**73a**	DCM, $KOBu^t$, 11–35 °C, 10 bar H_2, 2.5 h, S/C 2000	>99	>99	*R*	479
52	Ph	Me	**73b**	EtOH/ Pr^iOH (1/1), DBU, 11–35 °C, 10 bar H_2, 0.083 h, S/C 10 000	>99	>99	*R*	479
53	Ph	Me	**73b**	Toluene, DBU, 11–35 °C, 10 bar H_2, 2 h, S/C 4000	>99	>99	*R*	479
54	Ph	Me	**73b**	DCM, DBU, 11–35 °C, 10 bar H_2, 3 h, S/C 4000	>99	>99	*R*	479
55	Ph	Me	**74**	MeOH, $KOBu^t$, 11–35 °C, 51 bar H_2, 9 h, S/C 10 000	89	94	*R*	479
56	Ph	Me	**74**	Pr^iOH, $KOBu^t$, 11–35 °C, 51 bar H_2, 4 h, S/C 100 000	>99	98	*R*	479

efficient AH of *ortho*-substituted benzophenones, affording chiral diarylmethanols with good to excellent *ee*'s.[485] The ligand **68b** is also efficient for this transformation.[484] AH of aryl-pyridyl ketones has been investigated with Ru-**18b**/DAIPEN.[486] However, the catalyst only worked highly enantioselectively toward *ortho*-substituted aryl-pyridyl ketones. Thus, up to 99.5% *ee* was obtained for the hydrogenation of *ortho*-substituted ketones, whereas for the *para*- or *meta*-substituted analogues, much lower *ee*'s were obtained (entries 17–20, **Table 22**). Similar results were obtained with Ru-**68b**/DAIPEN.[484]

α-Tetralone and *α*-indanone are another class of ketones that are difficult to hydrogenate because the carbonyl group lies in a ring. Thus, AH of *α*-tetralone with Ru-**67b**/DAIPEN afforded only 82% *ee* along with lower activity (entry 1, **Table 23**).[487] However, by using the presynthesized ruthenabicyclic complexes **73–74** (**Table 20**), which are structurally similar to the Ru-**67b**/DAIPEN complexes, up to 97% *ee* was obtained for the same reduction.[479] Good results have also been achieved by using an Ir catalyst derived from the combination of an Ir precursor ([Ir(COD)BF_4]), ligand **12**, and $(2\text{-}Me_2NPh)_2PPh$.[488] The catalyst

Table 21 AH of heteroaromatic ketones



Entries	Ar	R	Catalyst	Conditions	Yield (%)	ee (%)	Configuration	References
1	2-Furyl	Me	Ru-**48d**/DPEN	Pr^iOH, $KOBu^t$, 20–25 °C, 51 bar H_2, 5 h, S/C 5000	99	98	*S*	125,475
2	2-Furyl	Me	Ru-**67b**/DAIPEN	Pr^iOH, $KOBu^t$, 25 °C, 8 bar H_2, 12 h, S/C 5000	>99	99	*S*	483
3	2-Furyl	Me	Ru-**67b**/DAIPEN	Pr^iOH, $KOBu^t$, 25 °C, 8 bar H_2, 12 h, S/C 40 000	93	99	*S*	483
4	2-Furyl	Me	Ru-**70b**	Pr^iOH, $KOBu^t$, 0 °C, 10 bar H_2, 24 h, S/C 100	100	91.9	*R*	471
5	2-Thienyl	Me	Ru-**48d**/DPEN	Pr^iOH, $KOBu^t$, 25 °C, 51 bar H_2, 5 h, S/C 5000	98	98	*S*	125,475
6	2-Thienyl	Me	Ru-**67b**/DAIPEN	Pr^iOH, $KOBu^t$, 30 °C, 8 bar H_2, 12 h, S/C 5000	>99	99	*S*	483
7	2-Thienyl	Me	Ru-**68b**/DPEN	Pr^iOH, $KOBu^t$, 25–28 °C, 24 bar H_2, 12 h, S/C 4000	>99.9	98.3	*S*	131,484
8	3-Thienyl	Me	Ru-**67b**/DAIPEN	Pr^iOH, $KOBu^t$, 30 °C, 8 bar H_2, 12 h, S/C 5000	>99	99.7	*S*	483
9	3-Thienyl	Me	Ru-**68b**/DPEN	Pr^iOH, $KOBu^t$, 25–28 °C, 24 bar H_2, 12 h, S/C 10 000	>99.9	99.0	*S*	131,484
10	2-Pyridyl	Me	Ru-**67b**/DAIPEN	Pr^iOH, $KOBu^t/B(OPr^i)_3$, 25 °C, 8 bar H_2, 3 h, S/C 2000	>99	96	*S*	483
11	2-Pyridyl	Pr^i	Ru-**67b**/DAIPEN	Pr^iOH, $KOBu^t$, 25 °C, 8 bar H_2, 12 h, S/C 2000	>99	94	*S*	483
12	3-Pyridyl	Me	Ru-**67b**/DAIPEN	Pr^iOH, $KOBu^t$, 25 °C, 8 bar H_2, 12 h, S/C 2000	>99	99.6	*S*	483
13	3-Pyridyl	Me	Ru-**68b**/DPEN	Pr^iOH, $KOBu^t$, 25–28 °C, 24 bar H_2, 24 h, S/C 4000	>99.9	97	*S*	131,484
14	3-Pyridyl	Me	Ru-**70b**	Pr^iOH, $KOBu^t$, 0 °C, 10 bar H_2, 24 h, S/C 100	100	95.1	*R*	471
15	4-Pyridyl	Me	Ru-**67b**/DAIPEN	Pr^iOH, $KOBu^t$, 25 °C, 8 bar H_2, 12 h, S/C 2000	>99	99.8	*S*	483
16	4-Pyridyl	Me	Ru-**68b**/DPEN	Pr^iOH, $KOBu^t$, 25–28 °C, 24 bar H_2, 24 h, S/C 4000	>99.9	97.9	*S*	131,484

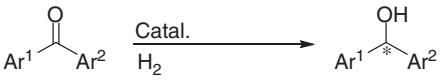
afforded 88% yield and 95% *ee* under 51–58 bar H_2 pressure at 90 °C in 75 h at S/C ratios of 190–230 (entry 2, Table 23). More interestingly, this difficult task can be addressed by replacing the conventional 1,2-diamine ligands with certain chiral 1,4-diamines, for example, 2,3-*O*-isopropylidenebutane-1,4-diamine (IPBAN) and 3,4-*O*-isopropylidenehexane-2,5-diamine (IPHAN) (Table 20). The AH of tetralone and its analogues with Ru-**67b**/IPHAN provides chiral 1-tetralols with up to 99% *ee* at S/C ratios as high as 55 000.[489] The use of phosphine ligands is not always necessary. Thus, ligand **75** (Table 23) combined with a Ru complex ($[Ru(\eta^3\text{-}CH_2CMe{=}CH_2)_2(COD)]$) exhibits excellent selectivity for the hydrogenation of α-tetralone (entry 10, Table 23),[490] and the tethered Ru complex **76** affords similar enantioselectivity under base-free conditions (entry 11, Table 23).[491]

8.04.2.2.3 Hydrogenation of unsaturated ketones

Hydrogenation of unsaturated ketones, whether conjugated or nonconjugated, is challenging because of competing reduction of unsaturated carbon–carbon bonds. Most heterogeneous and homogeneous catalysts preferentially saturate the C=C/C≡C multiple bonds over the C=O double bonds. This selectivity is thought to arise from the easier interaction of the metal center with an olefinic or acetylenic bond than with a carbonyl group. There are now catalysts which show excellent carbonyl selectivity. For instance, chromium-modified Raney nickel, Raney cobalt, or cobalt black shows good carbonyl selectivity, although the reduction is limited to tri- or *tetra*-substituted olefins.[78,492] Homogeneous catalysts have been much more successful. Thus, the $[RhCl_2(bpy)_2]Cl$ complex selectively hydrogenates ketones in the presence of olefins under basic conditions,[50,76] and $[CuH(PPh_3)_3\text{-}PMe_2Ph]$ catalyzes the hydrogenation of 4-cycloocten-1-one to afford the unsaturated alcohol.[77] Of more significant is the catalytic system formed by combining $[RuCl_2(PPh_3)_3]$ with a diamine, which shows excellent carbonyl selectivity over olefinic or acetylenic function in the presence of KOH.[396] The $[Ir(COD)_2(OMe)(PPh_2Et)]$ complex afforded allylic alcohol with 97% selectivity at 99% conversion in the hydrogenation of α,β-unsaturated ketones.[51,52]

AH of α,β-unsaturated ketones to generate chiral allylic alcohols is more challenging than the hydrogenation of simple ketones, since both the chemoselectivity and enantioselectivity need to be considered.[202,468,472,474,475,477,481,484,487,489,493–507] With established Ru-diphosphine/diamine catalysts,[468] α,β-unsaturated acyclic and cyclic ketones have been hydrogenated to the corresponding chiral allylic alcohols with high yield and high enantioselectivities.[202,475,481,484,489,494,496,498] Chalcones are frequently featured in these studies. Thus, by using Ru-**67a**-DMAPEN as catalysts, a range of chalcones have been reduced to their allylic alcohols (Table 24).[496] In order to suppress the concomitant reduction of C=C double bonds, the AH is carried out at 0 °C. Hydrogenation of 2-fluorophenyl and 2-furyl enones requires the addition of PPh_3 to eliminate the formation of saturated byproducts (entries 12 and 14, Table 24). PPh_3 may inhibit the coordination of the allylic alcohols to the metal center, which can trigger the isomerization of the product into saturated ketones. β,β-Disubstituted enones are more difficult to reduce, because of the steric hindrance at the β-position (entry17, Table 24). Ruthenium complexes containing diamines and other diphosphines, such as chiral TunesPhos (**20c**),[498] spiroPhos (**48d**),[475] Xyl-P-Phos (**68b**),[484] and PhanePhos (**69b**),[477] have also been explored for the hydrogenation of α,β-unsaturated ketones (entries 4–7,19,20, Table 24), although only a few samples were examined. It is worth noting that the Ru-**58b**/diamine catalytic system worked well for aliphatic α,β-unsaturated ketones, for example, mesityl oxide, 3-nonen-2-one, affording the corresponding allylic alcohols with >90% *ee* (entries 19, 20, Table 24). A copper catalyst

Table 22 AH of prochiral diaryl ketones



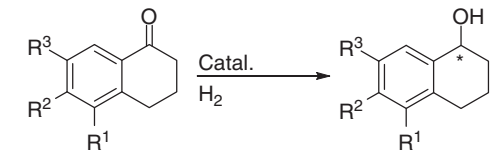
Entries	*Ar*^{1}	*Ar*^{2}	*Catalyst*	*Conditions*	*Yield (%)*	ee *(%)*	*Configuration*	*References*
1	Ph	2-MeO-C_6H_4	Ru-**67b**/DAIPEN	Pr^{i}OH, KOBu^t, 28 °C, 8 bar H_2, 15 h, S/C 2000	100	99	*S*	483
2	Ph	2-Me- C_6H_4	Ru-**67b**/DAIPEN	Pr^{i}OH, KOBu^t, 28 °C, 8 bar H_2, 11 h, S/C 2000	99	93	*S*	483
3	Ph	2-Me-C_6H_4	Ru-**68b**/DPEN	Pr^{i}OH, KOBu^t, 25–28 °C, 20 bar H_2, 12 h, S/C 2000	98.6	95.9	*R*	131,484
4	Ph	2-Me-C_6H_4	Ir-**72b**	THF, KOBu^t, r.t., 10 bar H_2, 48 h, S/C 250	70	>99	–	472
5	Ph	2-F-C_6H_4	Ru-**67b**/DAIPEN	Pr^{i}OH, KOBu^t, 28 °C, 8 bar H_2, 14 h, S/C 2000	99	97	*S*	483
6	Ph	2-F-C_6H_4	Ru-**68b**/DPEN	Pr^{i}OH, KOBu^t, 25–28 °C, 20 bar H_2, 15 h, S/C 2000	99.7	97.6	*R*	131,484
7	Ph	2-Cl-C_6H_4	Ru-**67b**/DAIPEN	Pr^{i}OH, KOBu^t, 35 °C, 8 bar H_2, 47 h, S/C 20 000	99	97	*S*	483
8	Ph	2-Cl-C_6H_4	Ru-**68b**/DPEN	Pr^{i}OH, KOBu^t, 25–28 °C, 20 bar H_2, 40 h, S/C 10 000	99.7	97.4	*R*	131,484
9	Ph	2-Br-C_6H_4	Ru-**67b**/DAIPEN	Pr^{i}OH, KOBu^t, 28 °C, 8 bar H_2, 13 h, S/C 2000	99	96	*S*	483
10	2-Me-C_6H_4	2-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	98.9	–	486
11	2-Me-C_6H_4	2-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 20 bar H_2, 48 h, S/C 10 000	100	98.8	–	486
12	2-MeO-C_6H_4	2-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	99.6	–	486
13	2-F-C_6H_4	2-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	98.9	–	486
14	2-Cl-C_6H_4	2-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	99.5	–	486
15	2-Br-C_6H_4	2-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	99.3	–	486
16	2-Br-4-Cl-C_6H_3	2-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	99.5	–	486
17	2-Me-C_6H_4	3-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	81.5	–	486
18	2-Me-C_6H_4	4-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	90.0	–	486
19	2-Me-C_6H_4	2-Pyrazine	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	84.4	–	486
20	4-Me-C_6H_4	2-Pyridyl	Ru-**18b**/DAIPEN	Pr^{i}OH, KOBu^t, 25 °C, 8 bar H_2, 16 h, S/C 200	100	30.4	–	486

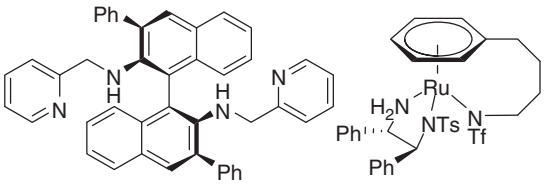
derived from Cu(II) and the monodentate binaphthophosphepine ligand **29**-CF_3 was also studied; however, low activity and enantioselectivity were obtained (entry 22, Table 24).[504]

AH of exocyclic α,β-unsaturated ketones and α-substituted α,β-unsaturated acyclic ketones gives rise to allylic alcohols which serve as key intermediates for the synthesis of chiral drugs and natural products. Iridium complexes bearing the spiro aminophosphine ligand **34** have been shown to be efficient for this reaction.[503,507] As shown in Table 25, Ir-**34a** allows for the hydrogenation of a number of α-arylmethylene cycloalkanones, affording chiral β-arylmethylene cyclohexanols in high yields and excellent enantioselectivities. Electron-donating or withdrawing groups on the phenyl ring of the ketones appear to impact little on both the yield and enantioselectivity. When the substrate with a five-membered ring or a seven-membered ring was subjected to the AH, the corresponding chiral β-arylmethylene cyclic alcohols were obtained in 97–98% yield with 93–96% *ee* slower (entries 14–17, Table 25). An α-alkylmethylene cyclohexanone was also reduced to the desired allylic alcohol in 91% *ee*, although the reaction was slower (entry 18, Table 25).

In a similar manner, α-substituted α,β-unsaturated acyclic ketones have been hydrogenated to the corresponding chiral allylic alcohols with Ir-**34a**, affording high yields (90–99%) and nearly perfect enantioselectivities (97–99.7%) (Table 26).[507] Thus, the reduction of (*E*)-3,4-diphenylbut-3-en-2-one showed 99.7% *ee* and TON as high as 100 000. For the α-aryl-substituted α,β-unsaturated acyclic ketones, most of the AH reactions completed in 15 min at r.t. under 6 bar H_2 pressure at a S/C ratio of 1000

Table 23 AH of tetralone derivatives





75 **76**

Entries	R^1	R^2	R^3	*Catalyst*	*Conditions*	*Yield (%)*	ee *(%)*	*Configuration*	*References*
1	H	H	H	Ru-**67b**/DPEN	Solvent (N/A), KOH, S/C 1000	81	82	*S*	487
2	H	H	H	Ir-(*R*)-**12**/(2-$Me_2NPh)_2PPh$	Dioxane/MeOH, 90 °C, 51–58 bar H_2, 75 h, S/C 190–230	88	95	*R*	488
3	H	H	H	Ru-**67b**/(*R*)-IPHAN	Pr^iOH, $KOBu^t$, 25 °C, 9 bar H_2, 8 h, S/C 3000	99.6	99	*R*	489
4	OMe	H	H	Ru-**67b**/(*R*)-IPHAN	Pr^iOH, $KOBu^t$, 25 °C, 9 bar H_2, 14 h, S/C 55 000	100	98	*R*	489
5	H	H	OMe	Ru-**67b**/(*R*)-IPHAN	Pr^iOH/Bu^tOH, $KOBu^t$, 25 °C, 9 bar H_2, 8 h, S/C 3300	100	99	*R*	489
6	H	OMe	H	Ru-**67b**/(*R*)-IPHAN	Pr^iOH, $KOBu^t$, 25 °C, 9 bar H_2, 13 h, S/C 1000	98	92	*R*	489
7	H	H	F	Ru-**67b**/(*R*)-IPHAN	Pr^iOH/Bu^tOH, $KOBu^t$, 25 °C, 9 bar H_2, 8 h, S/C 3000	100	98	*R*	489
8	H	H	H	**73**[a]	EtOH/Pr^iOH (1/1), $KOBu^t$, 5–30 °C, 10 bar H_2, 14 h, S/C 2000	>99	97	*S*	479
9	H	OMe	H	**74**[a]	Pr^iOH, $KOBu^t$, 5–30 °C, 10 bar H_2, 15 h, S/C 1000	42	90	*S*	479
10	H	H	H	Ru-**75**	Pr^iOH, $KOBu^t$, 25 °C, 51 bar H_2, 12–18 h, S/C 1000	>99	99	*R*	490
11	H	H	H	**76**	MeOH, 30 °C, 301 bar H_2, 24 h, S/C 100	>99	98	*S*	491

[a]Sunphos (**18b**) used as diphosphine ligand instead of XylBINAP (**67b**).

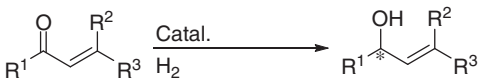
(entries 1–14, Table 26). However, AH of α-alkyl-substituted α,β-unsaturated acyclic ketones took slightly longer time to complete, but the *ee*'s remained high (entries 15–17, Table 26). Tetrasubstituted α,β-unsaturated acyclic ketones are viable as well, as shown by the high *ee*'s given in Table 26 (entries 19–20).

8.04.2.2.4 Hydrogenation of alkyl ketones

AH of simple alkyl ketones has been a difficult task for man-made catalysts, owing to the challenge of differentiating two similarly shaped sp^3-carbon groups connected to the carbonyl group. Up to date, the enantioselectivity still remains low and is generally lower than 80% *ee*. Using a Ni/TA/NaBr catalytic system, hydrogenation of alkan-2-ones achieved moderate selectivity (60–80% *ee*).[27,85–87,508–510] Polymer-supported metal catalysts have been explored as well.[27,509]

A great deal of effort has been made in homogeneous AH, but promising results were obtained in only a few cases. As shown in Table 27, various alkyl methyl ketones were hydrogenated to the chiral alcohols with moderate to high enantioselectivity by a rhodium catalyst ligated with the chiral diphosphine **77**.[511] The addition of 2,6-lutidine and KBr is crucial for high conversion and selectivity (entries 1–6, Table 27). Steric effect plays an important role in the enantioselection, with sterically less demanding groups leading to decreased selectivity. For example, hydrogenation of *tert*-butyl methyl ketone and *n*-butyl methyl ketone afforded 94% *ee* and 75% *ee*, respectively (entries 1 and 6, Table 27). In contrast to the AH of aryl ketones, a relatively high catalyst loading and long reaction time were necessary to achieve high conversion. However, *tert*-alkyl ketones can be reduced with the Ru-**67a**/PICA catalyst highly enantioselectively at low catalyst loading (entries 7–9, Table 27).[494] The catalyst can be readily synthesized by treating $[(RuCl_2–\mathbf{67a})(DMF)_n]$ with 1.2 equivalents of 1-(2-pyridyl)methanamine in DCM at 25 °C for 2 h. A wide range of bulky ketones have been reduced including the commercial synthesis of solifencin, an M3 receptor antagonist. In addition, cyclopropyl methyl ketone is hydrogenated to the corresponding chiral alcohol with 95% *ee* without cleavage of the cyclopropyl ring under the catalysis of Ru-**67b**/DAIPEN (entry 10, Table 27).[474] The analogues cyclohexyl methyl ketone afforded a lower *ee*, however (entry 11, Table 27). Good selectivity is also demonstrated by the ruthenabicyclic complex **73a**.[479] A ruthenium catalyst derived from $[RuCl_2(PPh_3)_3]$ and the ligand **78**, whereas showing good performance in the AH of simple aromatic ketones, was less effective for the hydrogenation of aliphatic ketones.[512] As shown in Table 27 (entries 14–16), AH of cyclohexyl methyl ketone gave 95% *ee*, but the other aliphatic ketones showed much lower *ee*'s.

Table 24 AH of α,β-unsaturated ketones



Entries	R^1	R^2	R^3	Catalyst	Conditions	Yield (%)[a]	ee (%)	References
1	Ph	H	Ph	Ru-**67a**/(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 0 °C, 8 bar H_2, 5 h, S/C 1000	99(1)	97	496
2	Ph	H	Ph	Ru-**67a**/(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 30 °C, 8 bar H_2, 1 h, S/C 1000	91(8)[b]	96	496
3	Ph	H	Ph	Ru-**67a**/(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 0 °C, 40 bar H_2, 3 h, S/C 10 000	99(1)	97	496
4	Ph	H	Ph	Ru-**20c**/(*S,S*)-DPEN	Pr^iOH, $KOBu^t$, 20–22 °C, 10 bar H_2, 4 h, S/C 10 000	>99.9	97.4	498
5	Me	H	Ph	Ru-**68b**/(*R,R*)-DPEN	Pr^iOH, K_2CO_3, 25–28 °C, 2.5 bar H_2, 15 h, S/C 10 000	>99.9	97.1	484
6	Me	H	Ph	Ru-**68b**/(*R,R*)-DPEN	Pr^iOH, $KOBu^t$, 25–28 °C, 3.5 bar H_2, 15 h, S/C 10 000	>99.9	97.0	484
7	Me	H	Ph	Ru-**48d**/(*S,S*)-DPEN	Pr^iOH, $KOBu^t$, 20–25 °C, 50 bar H_2, 3 h, S/C 5000	100	96	475
8	4-Me-C_6H_4	H	Ph	Ru-**67a**/(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 0 °C, 8 bar H_2, 4 h, S/C 1000	100(1)	98	496
9	4-F-C_6H_4	H	Ph	Ru-**67a**/(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 0 °C, 8 bar H_2, 3 h, S/C 1000	96(1)	96	496
10	4-CF_3-C_6H_4	H	Ph	Ru-**67a**(*R*)-DMAPEN	Pr^iOH/DMF(2:1), $KOBu^t$, 0 °C, 8 bar H_2, 2 h, S/C 1000	94(2)	92	496
11	4-MeO-C_6H_4	H	Ph	Ru-**67a**(*R*)-DMAPEN	Pr^iOH/DMF(1:1), $KOBu^t$, 0 °C, 8 bar H_2, 3 h, S/C 1000	96(2)	95	496
12	2-F-C_6H_4	H	Ph	Ru-**67a**/PPh_3(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 0 °C, 8 bar H_2, 15.5 h, S/C 1000	95(<1)	97	496
13	2-Naphthyl	H	Ph	Ru-**67a**(*R*)-DMAPEN	Pr^iOH/DMF(2:1), $KOBu^t$, 0 °C, 8 bar H_2, 5 h, S/C 1000	96(1)	95	496
14	2-Furyl	H	Ph	Ru-**67a**/PPh_3(*R*)-DMAPEN	Pr^iOH/DMF(2:1), $KOBu^t$, 0 °C, 8 bar H_2, 8 h, S/C 1000	98(<1)	92	496
15	Ph	H	4-Me-C_6H_4	Ru-**67a**(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 0 °C, 8 bar H_2, 13 h, S/C 1000	93(1)	97	496
16	Ph	H	4-Cl-C_6H_4	Ru-**67a**(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 0 °C, 8 bar H_2, 5 h, S/C 1000	99(<1)	97	496
17	Ph	Me	Ph	Ru-**67a**(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 0 °C, 51 bar H_2, 43 h, S/C 1000	97(<2)	89	496
18	Ph	H	Bu^t	Ru-**67a**(*R*)-DMAPEN	Pr^iOH, $KOBu^t$, 0 °C, 8 bar H_2, 8 h, S/C 1000	86(<1)[c]	97	496
19	Me	Me	Me	Ru-**68b**/(*R,R*)-DPEN	Pr^iOH, $KOBu^t$, 25–28 °C, 3.5 bar H_2, 16 h, S/C 12 000	99.1	90.3	484
20	Me	H	C_6H_{11}	Ru-**68b**/(*R,R*)-DPEN	Pr^iOH, K_2CO_3, 25–28 °C, 2.5 bar H_2, 15 h, S/C 2000	91.8	93.4	484
21	Me	H	Ph	Ru-**69b**/(*R,R*)-DPEN	Pr^iOH, K_2CO_3, 18–20 °C, 5.5–8.0 bar H_2, 0.5–2.5 h, S/C 3000	100	97	477
22	Me	H	Ph	Cu-**29**[d]	Pr^iOH, K_2CO_3, 30 °C, 51 bar H_2, 16 h, S/C 300	65	48	504
23	Me	H	Ph	Ru-**67b**(*S*)-DAIPEN	Pr^iOH, K_2CO_3, 28–30 °C, 81 bar H_2, 43 h, S/C 100 000	100	97	474
24	Me	H	Ph	Ru-**67b**(*S*)-DAIPEN	Pr^iOH, K_2CO_3, 28–30 °C, 10 bar H_2, 15 h, S/C 10 000	100	96	474
25	Pr^i	H	Ph	Ru-**67b**(*S*)-DAIPEN	Pr^iOH, K_2CO_3, 28–30 °C, 8 bar H_2, 20 h, S/C 2000	100	86	474
26	Me	H	C_5H_{11}	Ru-**67b**(*S*)-DAIPEN	Pr^iOH, K_2CO_3, 28–30 °C, 8 bar H_2, 15 h, S/C 2000	98	97	474
27	Me	Me	Me	Ru-**67b**(*S*)-DAIPEN	Pr^iOH, $KOBu^t$, 25–28 °C, 8 bar H_2, 16 h, S/C 10 000	100	93	474

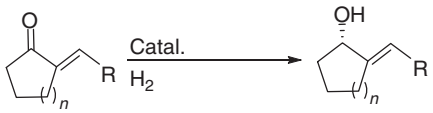
[a]Yield of saturated ketone is given in parentheses.
[b]The product contained saturated alcohol (9%).
[c]13% of starting ketone was recovered.
[d]The substituent on the phenyl ring of **29** was CF_3 instead of MeO.

8.04.2.3 Hydrogenation of CO_2

The fixation of CO_2 by hydrogenation is attractive because of its abundance and the potential of the products as a hydrogen source, for example, formic acid, methanol, and methane has been intensively investigated recently.[513–532] Both heterogeneous and homogeneous catalysts can be used to hydrogenate CO_2.[513–567] The former are preferable in terms of stability, separation, handling, and reuse. Although the latter often show outstanding activity and selectivity, the recovery and regeneration are problematic. Significant progress has been made in addressing these issues by immobilization of homogeneous catalysts, exploration of novel heterogeneous catalysts, and the use of nonconventional solvents. Well-designed catalysts and reaction media are important for achieving good conversions because of the high thermodynamic stability of CO_2.[524,527,528]

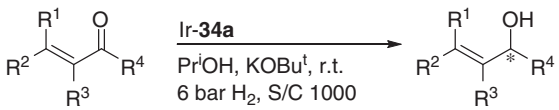
CO_2 can be hydrogenated to formic acid or its derivatives (**Scheme 18**). A number of ruthenium and rhodium complexes catalyze the reaction in water.[529,552] Water appears to be an ideal solvent for the hydrogenation. In the gas phase, the hydrogenation is endergonic with $\Delta Go_{298} = 33$ kJ mol^{-1}, whereas in the aqueous solution, the ΔGo_{298} becomes –4 kJ mol^{-1}. In the case of the latter, however, the hydrogenation is more complicated, as CO_2 is in equilibrium with hydrogen carbonate ($pK_1 = 6.35$) and carbonate ($pK_2 = 10.33$), both of which can be hydrogenated to formate. In addition, the product formic acid ionizes in water ($pK_a = 3.6$). Thus, CO_2 hydrogenation in water is pH-dependent. Most of the hydrogenation reactions have been run under basic conditions, enhancing the possibility of hydrogenating hydrogen carbonate instead of CO_2.

Table 25 AH of α-arylmethylene cycloalkanones



Entries	*R*	n	*Catalyst*	*Conditions*	*Yield (%)*	ee *(%)*	*References*
1	Ph	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	98	97	503
2	Ph	2	Ir-**34a**	Pr^iOH, $KOBu^t$, 30 °C, 50 bar H_2, 4 h, S/C 10 000	91	93	503
3	Ph	2	Ru-**48d**/(*S,S*)-DPEN	–	55	75	503
4	Ph	2	Ru-**67a**/(*R,R*)-DPEN	–	42	32	503
5	4-Me-C_6H_4	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	99	95	503
6	4-MeO-C_6H_4	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	99	96	503
7	4-Cl-C_6H_4	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	97	94	503
8	4-Br-C_6H_4	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	98	94	503
9	3-MeO-C_6H_4	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	98	97	503
10	2-MeO-C_6H_4	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	99	95	503
11	2-Furyl	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 1 h, S/C 2000	95	92	503
12	1-Naphthyl	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 1 h, S/C 2000	95	89	503
13	2-Naphthyl	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	98	93	503
14	Ph	1	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	98	96	503
15	4-MeO-C_6H_4	1	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	99	95	503
16	4-Br-C_6H_4	1	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	98	94	503
17	Ph	3	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 0.5 h, S/C 2000	97	93	503
18	Me	2	Ir-**34a**	Pr^iOH, $KOBu^t$, r.t., 6 bar H_2, 5 h, S/C 2000	66	91	503

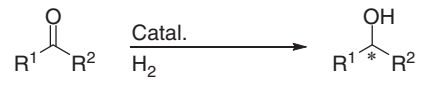
Table 26 AH of α-substituted α,β-unsaturated acyclic ketones

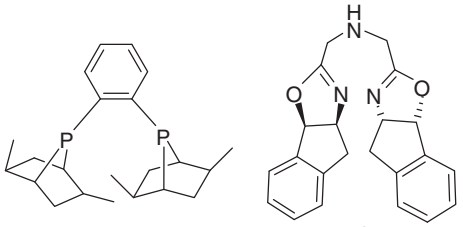


Entries	R^1	R^2	R^3	R^4	*Time (h)*	*Yield (%)*	ee *(%)*	*References*
1	H	Ph	Ph	Me	0.25	98	99.4	507
2	H	Ph	Ph	Me	10[a]	98	99.7	507
3	H	2-Cl-C_6H_4	Ph	Me	0.25	98	99.5	507
4	H	3-Me-C_6H_4	Ph	Me	0.25	98	99.6	507
5	H	4-Me-C_6H_4	Ph	Me	0.25	97	98	507
6	H	4-MeO-C_6H_4	Ph	Me	0.25	99	99	507
7	H	4-Cl-C_6H_4	Ph	Me	0.25	98	99	507
8	H	Ph	2-Cl-C_6H_4	Me	0.25	97	99.6	507
9	H	Ph	3-Me-C_6H_4	Me	0.25	98	97	507
10	H	Ph	4-Me-C_6H_4	Me	0.25	99	99.1	507
11	H	Ph	4-MeO-C_6H_4	Me	0.25	98	99.4	507
12	H	Ph	4-Cl-C_6H_4	Me	0.25	98	97	507
13	H	Ph	Ph	Et	0.25	98	99.7	507
14	H	Ph	Ph	Pr^i	0.25	98	98	507
15	H	Ph	Me	Me	0.25	99	99.1	507
16	H	Ph	Et	Me	0.25	99	99	507
17[b]	H	Me	Me	Me	0.5	90	99	507
18	H	$-(CH_2)_4-$		Me	12	98	99	507
19	Me	Ph	Me	Me	0.25	97	98	507
20[b]	Ph	$-(CH_2)_4-$		Me	1	96	97	507

[a] 5a bar H_2, S/C = 100 000.
[b] (*R*)-**34a** was used as ligand.

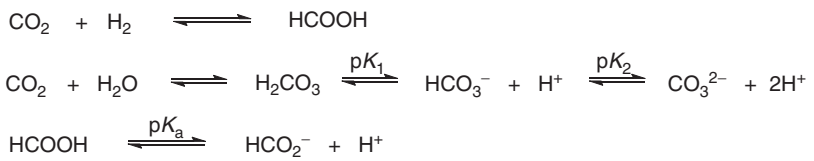
Table 27 AH of alkyl ketones





77 **78**

Entries	R^1	R^2	*Catalyst*	*Conditions*	*Yield (%)*	ee *(%)*	*Configuration*	*References*
1	Bu^t	Me	Rh-**77**	MeOH/2,6-lut/KBr, r.t., 30 bar H_2, 96 h, S/C 100	51	94	*S*	511
2	Cy	Me	Rh-**77**	MeOH/2,6-lut/KBr, r.t., 30 bar H_2, 106 h, S/C 100	90	92	*S*	511
3	Pr^i	Me	Rh-**77**	MeOH/2,6-lut/KBr, r.t., 30 bar H_2, 94 h, S/C 100	99	84	*S*	511
4	Bu^i	Me	Rh-**77**	MeOH/2,6-lut/KBr, r.t., 30 bar H_2, 756 h, S/C 100	66	85	*S*	511
5	$(CH_2)_2Ph$	Me	Rh-**77**	MeOH/2,6-lut/KBr, r.t., 30 bar H_2, 56 h, S/C 100	99	73	*S*	511
6	Bu^n	Me	Rh-**77**	MeOH/2,6-lut/KBr, r.t., 30 bar H_2, 48 h, S/C 100	96	75	*S*	511
7	Bu^t	Me	Ru-**67a**/PICA	EtOH, $KOBu^t$, 25 °C, 20 bar H_2, 24 h, S/C 100 000	96	98	*S*	494
8	Bu^t	$(CH_2)_7Me$	Ru-**67a**/PICA	EtOH, $KOBu^t$, 25 °C, 5 bar H_2, 5 h, S/C 2300	93	97	*R*	494
9	Bu^t	2-Thienyl	Ru-**67a**/PICA	EtOH, $KOBu^t$, 27 °C, 8 bar H_2, 5 h, S/C 2100	95	98	*R*	494
10	Cyclopropyl	Me	Ru-**67b**/ DAIPEN	Pr^iOH, $KOBu^t$, 28–30 °C, 10 bar H_2, 12 h, S/C 11 000	96	95	*R*	474
11	Cy	Me	Ru-**67b**/ DAIPEN	Pr^iOH, $KOBu^t$, 28 °C, 8 bar H_2, 20 h, S/C 10 000	99	85	*R*	474
12	Cy	Me	**73a**	Pr^iOH, $KOBu^t$, 5–30 °C, 10 bar H_2, 5 h, S/C 4000	96	90	*R*	479
13	Bu^t CH_2	Me	**73a**	Pr^iOH, $KOBu^t$, 5–30 °C, 10 bar H_2, 5 h, S/C 10 000	>99	77	*R*	479
14	Cy	Me	Ru-**78**	Pr^iOH, $KOBu^t$, r.t., 5 bar H_2, 15 h, S/C 100	>99	95	*R*	512
15	Pr^i	Me	Ru-**78**	Pr^iOH, $KOBu^t$, r.t., 5 bar H_2, 15 h, S/C 100	>99	65	*R*	512
16	Bu^t	Me	Ru-**78**	Pr^iOH, $KOBu^t$, r.t., 5 bar H_2, 15h, S/C 100	45	42	*R*	512

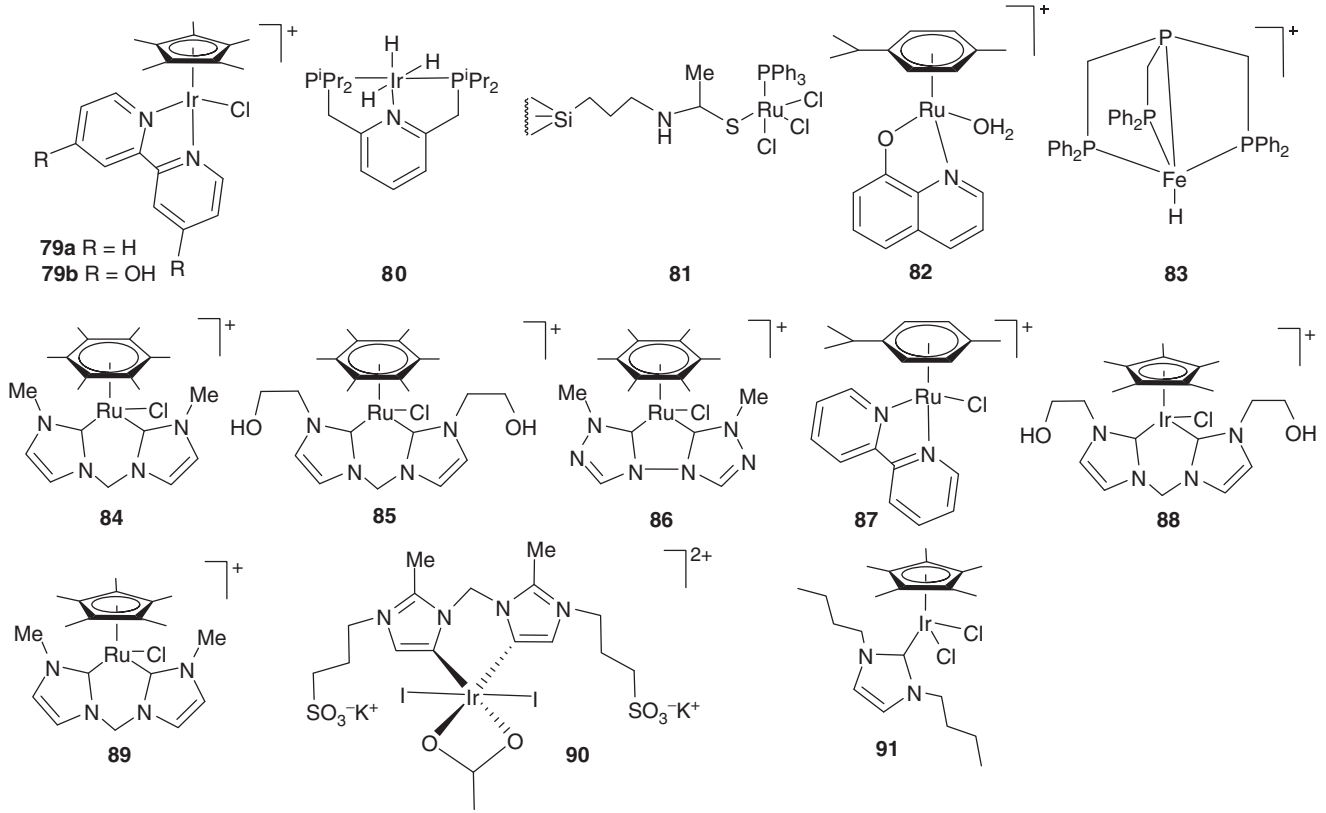


Scheme 18 Equilibria of CO_2 and its hydrogenated products.

Rhodium and ruthenium complexes dominated the scene, most containing phosphine ligands. Typical examples are [RhCl(**64**)$_3$] and [$RuCl_2$(**65**)$_2$]$_2$. In the hydrogenation reaction in water using [RhCl(**64**)$_3$], a TOF of 7260 h^{-1} was observed at a total pressure of 40 bar ($H_2/CO_2 = 1/1$) and 81 °C in the presence of $NHMe_2$,[568] whereas the Ru(II) catalyst afforded a TOF of 9600 h^{-1} at a total pressure of 95 bar ($H_2/CO_2 \sim 2/1$) and 80 °C in the presence of $NaHCO_3$.[554] Free formic acid can be produced by the hydrogenation of CO_2 in aqueous solutions of HCOONa with Rh-**64**.[569] High pressure, an appropriate concentration of HCOONa, and a 1:1 ratio of H_2/CO_2 were crucial for the production of free formic acid with high yield and concentration in the final reaction mixture. For instance, in a 0.5 M HCOONa solution, free formic acid was produced in a concentration of 0.13 M.

Recent studies have revealed a variety of other metal complexes capable of reducing CO_2 in aqueous media (Scheme 19 and Table 28).[513,529,540,544,546,552,569–582] A good example is seen in an Ir(III) complex **79b** bearing a dihydroxy-bipy ligand, which afforded a TON of 190 000 in 57 h with an initial TOF of 42 000 h^{-1} at a total pressure of 60 bar ($H_2/CO_2 = 1/1$) and 120 °C in an aqueous KOH (1 M) solution (entry 2, Table 28).[582] The analogues rhodium and ruthenium catalysts were less active, however. A kinetic study of the closely related Ru(II) and Ir(III) complexes suggests that the rate of hydrogenation is limited by hydride formation in the case of the former, but by hydride transfer to CO_2 in the case of the latter.[581]

The high catalytic activity of **79b** stems from the electron-rich nature of the bipy ligand, which is deprotonated during the reaction; the resulting oxyanion is a much stronger electron-donor than the hydroxyl group (σ_p^+: −2.3. vs. −0.91). There indeed



Scheme 19 Complexes exploited for hydrogenation of CO_2.

Table 28 Catalytic hydrogenation of CO_2 to formic acid and formates in water

Entries	*Catalyst*	*Additive*	*p(H2)/p(CO2) (bar)*	*Temperature (°C)*	*Time (h)*	*TON*	*TOF (h^{-1})*	*References*
1	**79a**	KOH	30/30	80	18	180	10	576
2	**79b**	KOH	30/30	120	57	190 000	42 000	582
3	**80**	KOH, THF	29/29	120	48	3 500 000	73 000	570,572
4	**81**	IL[a]	89/89	80	2	1 840	920	571
5	**82**	NEt_3	49/49	100	10	400	40	546
6	**83**	PP_3[b]	61/0	80	20	610	31	544
7	**84**	KOH	20/20	200	75	23 000	306	575
8	**85**	KOH	20/20	80	20	132	6.6	575
9	**86**	KOH	20/20	80	20	311	15.5	575
10	**87**	KOH	20/20	80	20	214	11	575
11	**88**	KOH	20/20	80	20	122	6	575
12	**88**	KOH	20/20	200	20	9 500	475	575
13	**89**	KOH	30/30	80	18	1 600	88	576
14	**90**	KOH	30/30	200	75	1.9×10^5	2 533	577
15	**91**	KOH	30/30	80	18	67	4	576

[a]IL = Ionic liquid (1,3-di-(*N*,*N*-dimethylaminoethyl)-2-methylimidazolium trifluoromethanesulfonate; methyl formate was the product.
[b]$PP_3 = P(CH_2CH_2PPh_2)_3$.

exists a correlation between the initial TOF and σ_p^+, and this is consistent with previous theoretical and experimental studies, which suggest that electron-rich ligands facilitate the hydrogenation.[583,584] The equilibrium shown in Scheme 18 also confers tunable solubility onto the catalyst: on completion of the hydrogenation, the solution turns acidic, rendering the ligand neutral and thus triggering the precipitation of the catalyst. Indeed the catalyst was shown to be recyclable by filtration, with iridium leaching <1 ppm in each run. The product HCO_2K was separated from the catalyst-free aqueous solution by evaporation of H_2O. Electron-rich *N*-heterocyclic carbenes (NHCs) are also effective in the ruthenium and iridium catalyzed hydrogenation (entries 7–9,11–15, Table 28).[575]

A more active catalyst is the tri-hydride iridium pincer complex **80** (Scheme 19) containing an electron-rich PNP ligand.[570] Under conditions similar to those employed for **79b**, this complex afforded HCOOK in aqueous KOH with a remarkable TOF of 73 000 h^{-1} and TON of 3 500 000 (entry 3, Table 28). These represent the highest values reported thus far for CO_2 hydrogenation, pointing to the potential of commercial production of formates via aqueous hydrogenation. The PNP ligand appears to undergo deprotonation during the catalysis, which is believed to facilitate the dissociation of formate from the iridium.

From both an eco-benign and economic point of view, iron is an appealing catalyst. Combining $Fe(BF_4)_2$ with the tetradentate ligand $P(CH_2CH_2PPh_2)_3$ (PP_3) under H_2 results in an active catalyst capable of promoting hydrogenation of CO_2, affording methyl formate in the presence of MeOH (entry 6, Table 28). The catalyst is most likely **83**, which has been isolated by subjecting $Fe(BF_4)_2$ and PP_3 to 10 bar H_2. The catalyst also enables the hydrogenation of bicarbonate into formate, furnishing 680 ton in 20 h at 60 bar H_2 and 80 °C.[544,572] Much earlier, it was shown that **83** can be readily formed by treating $Fe(BF_4)_2$ with PP_3 in the presence of HCOOH. Interestingly, **83** also catalyzes the decomposition of HCOOH into H_2 and CO_2, with the intermediate formato complex being isolable, and it reacts with H_2 to give a stable $[FeH(H_2)PP_3]^+$ complex. Ruthenium catalysts have also been explored for the hydrogenation of bicarbonates in aqueous media without addition of CO_2.[573] A $[RuH(HCO_3)(dppm)_2]$ complex was suggested to react with H_2, affording the corresponding formato complex, from which formate is generated.

Hydrogenation of CO_2 in the presence of NHR_2 (R = H or Me) under appropriate conditions generates a formamide, $HCONR_2$. This type of reaction was first discovered by using a heterogeneous catalyst, Raney Ni. Homogeneous catalysts have also been extensively studied.[513,517,527,529,531–567] DMF was produced with a high TON of up to 1200 in the reaction catalyzed by $[IrCl(CO)(PPh_3)_2]$, $[CoH(DPPE)_2]$, or $[CuCl(PPh_3)_3]$. The iridium complex was also effective for the formation of formamide. A ruthenium complex containing DPPE, $[RuCl_2(DPPE)_2]$, was found to be more effective (TON = 3400) than $[RuCl_2(PPh_3)_3]$ (TON = 2650) in hexane. When the hydrogenation was run in supercritical CO_2 ($scCO_2$) $RuCl_2(PPh_3)_4$ showed remarkable efficiency, with the TON up to 370 000. In the same reaction media, $[RuCl_2(DPPE)_2]$ gave even higher conversions; TON reached 740 000. An Ru catalyst ($[RuCl_2(PMe_2(CH_2)_2Si(OEt)_3)_3]$) immobilized on hybrid materials exhibited high activity for the formation of DMF in $scCO_2$ (TON = 110 800).[577] The catalyst is easily separated from the reaction mixture.

8.04.3 Transfer Hydrogenation of Carbonyl Groups

TH is the reduction of an unsaturated molecule by a hydrogen donor other than H_2 with the aid of a catalyst. This process is but one of several possible hydrogen transfer reactions classified by Braude and Linstead in 1954.[585] The reaction usually involves transfer of hydride and proton from a donor molecule to a substrate. IPA or the azeotropic mixture of formic acid and triethylamine are the donors that have been most often used. Primary alcohols (e.g., methanol, ethanol) and other secondary alcohols are rarely featured.

Extensive studies have been carried out of the reduction by TH of polar C═X (X═C, O, N) multiple bonds in the past two decades or so. The reactions can be effected by a variety of means including heterogeneous, homogeneous, and enzymatic catalysis. Catalytic hydrogen transfer was first demonstrated by Knoevenagel and Bergdolt in 1903, who observed that dimethyl 1,4-dihydroterephthalate disproportionates readily into dimethyl terephthalate and *cis*-hexahydroterephthalate under the catalysis of palladium black.[586] The reduction of ketones and aldehydes by TH, that is, the Meerwein–Ponndorf–Verley (MPV) reduction, first appeared in 1925.[587–589] In the following three decades, a great deal of progress was made in developing heterogeneous palladium and nickel catalysts for TH reactions. However, TH by transition metal complexes did not appear until the 1960s, when the modern homogeneous catalysis started. The initial studies centered on TH of ketones and aldehydes with iridium and ruthenium catalysts.[590–595] However, the reaction necessitated a high temperature of *c.* 200 °C in most cases and gave low TOFs. In early 1990s, base was found to accelerate the reaction.[596]

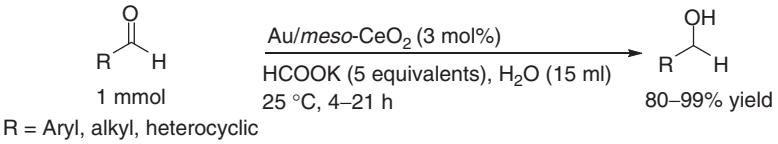
The asymmetric version of the reaction, asymmetric transfer hydrogenation (ATH), appeared first as enantioface discriminating reduction in the 1970s, when TH with $[RuCl_2(PPh_3)_3]$ in the presence of a chiral monophosphine or chiral hydrogen donor was explored.[597] Since then, a wide range of metal complexes coupled with various chiral phosphorus and nitrogen ligands were examined for the ATH of ketones and olefins.[598–602] However, the enantioselectivity was generally low before the 1990s, with few *ee* values exceeding 90%.[599,602]

The decades since 1995 have witnessed the most celebrated achievements in TH/ATH chemistry, highlighted by the advent of a number of highly active, selective, and productive catalytic systems.[398,598–601,603–615] Among the catalysts developed for ATH, the most important and significant are Ru(II) complexes containing monotosylated 1,2-diamines, discovered by Noyori et al. in 1995.[616] The application of these chiral ligands, represented by *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN), has led to the reduction of a number of aromatic ketones and imines with outstanding conversions and *ee*'s.[601,603,617–622] Following on from this discovery, a great number of related ligands and catalysts have been developed.[398,598–601,604–611,623–625]

8.04.3.1 Transfer Hydrogenation of Aldehydes

Catalytic TH of aldehydes can be challenging, because of inherent side reactions under basic conditions. The α-CH group is susceptible to deprotonation and can lead to aldol condensation, and possible decarbonylation under catalytic conditions may deactivate the catalyst through CO coordination. Thus, weakly basic conditions and a short reaction time may be necessary. Examples of highly efficient TH of aldehydes reactions are rare, however.[374,405,416,422,626–648]

Heterogeneous TH of aldehydes is less well known. Recently, supported gold nanoclusters were introduced for the TH of aldehydes.[642] The reduction was carried out in an aqueous HCOOK solution in air at room temperature, achieving high chemoselectivity. Thus, a range of aromatic, heterocyclic, aliphatic, and unsaturated aldehydes were hydrogenated to the corresponding primary alcohols in 4–21 h at S/C ratio of 33 (**Scheme 20**). The reduction was highly selective toward the formyl group and tolerated halo, ketone, and olefin groups substituted in the substrates. An intermolecular competitive reaction between benzaldehyde and ACP revealed that only benzyl alcohol was obtained as the product, with no reduction of ACP, whereas with styrene, >99% yield of benzyl alcohol was achieved and the reduction of styrene did not exceed 7%.[642] A larger scale reduction of benzaldehyde (10 mmol) was demonstrated, which afforded 96% in 19 h reaction time.

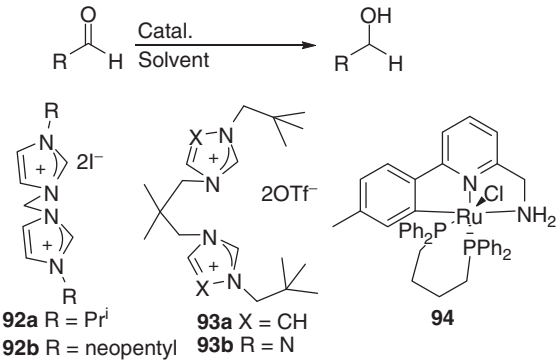


Scheme 20 Heterogeneous TH of aldehydes.

Despite the fact that a large number of homogeneous catalysts have been explored for the TH of ketones, only a few have been reported for aldehydes (**Table 29**).[629,635,636] The iridium complexes containing the NHC ligand **93** catalyzed the TH of benzaldehydes in IPA, achieving TOF values up to 3000 h^{-1}.[629] Recently, the terdentate CNN-ligated ruthenium complex **94** has been shown to be one of the most efficient catalysts for the TH of aldehydes. The reduction was carried out in IPA at 82 °C with an S/C ratio of 2000–10 000, affording TOF up to 5.0×10^5 h^{-1}.[636]

Transition metal-catalyzed TH of aldehydes can be carried out efficiently in water.[394,395] Joo and coworkers initially showed that unsaturated aldehydes were reduced to unsaturated alcohol by HCOONa with a ruthenium catalyst bearing the water-soluble TPPMS (**65**) (**Scheme 21**). The reduction was efficient, with most reactions complete in a few hours, including those involving multisubstituted aromatic aldehydes. For example, 2,6-dichlorobenzaldehyde was converted into the corresponding alcohol in 1.5 h without hydrodechlorination, and the reduction of α,β-unsaturated aldehydes was chemoselective, furnishing only unsaturated alcohols as the products. However, substrates containing an OH group, for example, 2-hydroxybenzaldehyde, did not react. Among the various catalysts tested, Ru(II)-**65** was the most efficient.[394,395,627] Subsequent work demonstrated TH as well as ATH of unsaturated carboxylic acids to saturated carboxylic acids by formate in water using a rhodium catalyst containing a water-soluble phosphine.[649]

Table 29 Homogeneous TH of aldehydes

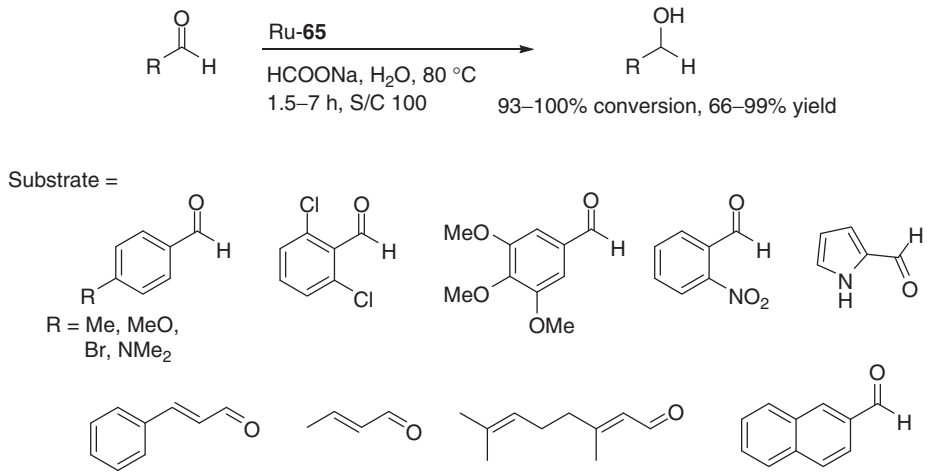


Entries	*R*	*Catalyst*	*Conditions*	*Yield (%)*	*TOF (h^{-1})*	*References*
1	4-Me-C_6H_4	Ir-**92**	Pr^iOH, K_2CO_3, reflux, 5 h, S/C 1000	98	200	629
2	4-Me-C_6H_4	Ir-**93a**	Pr^iOH, K_2CO_3, reflux, 0.75 h, S/C 1000	98	1300	629
3	4-Me-C_6H_4	Ir-**93b**	Pr^iOH, K_2CO_3, reflux, 1.5 h, S/C 1000	98	590	629
4	4-NO_2-C_6H_4	Ir-**93a**	Pr^iOH, K_2CO_3, reflux, 1 h, S/C 1000	98	1000	629
5	4-NO_2-C_6H_4	Ir-**93b**	Pr^iOH, K_2CO_3, reflux, 0.75 h, S/C 1000	98	1300	629
6	PhCHMe	Ir-**93a**	Pr^iOH, K_2CO_3, reflux, 0.5 h, S/C 1000	95	2000	629
7	PhCHMe	Ir-**93b**	Pr^iOH, K_2CO_3, reflux, 1 h, S/C 1000	98	1000	629
8	2-Naphthyl	Ir-**93a**	Pr^iOH, K_2CO_3, reflux, 0.3 h, S/C 1000	98	3000	629
9	2-Naphthyl	Ir-**93b**	Pr^iOH, K_2CO_3, reflux, 1 h, S/C 1000	95	1000	629
10[a]	Ph	**94**	Pr^iOH, K_2CO_3 (1 mol%), 82 °C, 1 min, S/C 2000	99	1.3×10^5	636
11[a]	Ph	**94**	Pr^iOH, K_2CO_3 (5 mol%), 82 °C, 0.5 min, S/C 2000	99	3.0×10^5	636
12[a]	Ph	**94**	Pr^iOH, K_2CO_3(10 mol%), 82 °C, 0.3 min, S/C 2000	99	5.0×10^5	636
13[a]	4-Me-C_6H_4	**94**	Pr^iOH, K_2CO_3 (1 mol%), 82 °C, 5 min, S/C 2000	99	3.0×10^4	636
14[a]	4-Me-C_6H_4	**94**	Pr^iOH, K_2CO_3 (5 mol%), 82 °C, 2 min, S/C 2000	99	8.0×10^4	636
15[a]	2,4-Me_2-C_6H_3	**94**	Pr^iOH, K_2CO_3 (1 mol%), 82 °C, 5 min, S/C 2000	99	3.6×10^4	636
16[a]	2,4-Me_2-C_6H_3	**94**	Pr^iOH, K_2CO_3 (5 mol%), 82 °C, 0.3 min, S/C 2000	98	4.5×10^5	636
17[a]	Bu^i	**94**	Pr^iOH, K_2CO_3 (5 mol%), 82 °C, 0.5 min, S/C 2000	98	2.4×10^5	636
18[a]	C_5H_{11}	**94**	Pr^iOH, K_2CO_3 (5 mol%), 82 °C, 0.5 min, S/C 2000	99	3.0×10^5	636
19[a]	C_5H_{11}	**94**	Pr^iOH, K_2CO_3 (10 mol%), 82 °C, 2 min, S/C 10 000	99	3.0×10^5	636
20[a]	Cy	**94**	Pr^iOH, K_2CO_3 (5 mol%), 82 °C, 5 min, S/C 10 000	99	2.0×10^5	636
21[a]	$PhCHMeCH_2$	**94**	Pr^iOH, K_2CO_3 (1 mol%), 82 °C, 5 min, S/C 2000	99	1.6×10^4	636
22[a]	$PhCHMeCH_2$	**94**	Pr^iOH, K_2CO_3 (5 mol%), 82 °C, 2 min, S/C 2000	99	9.0×10^4	636
23[a]	PhCHCH	**94**	Pr^iOH, K_2CO_3 (1 mol%), 82 °C, 2 min, S/C 2000	99	1.8×10^5	636
24[a]	PhCHCH	**94**	Pr^iOH, K_2CO_3 (2 mol%), 82 °C, 1 min, S/C 2000	99	2.0×10^5	636
25[a]	PhCHCH	**94**	Pr^iOH, K_2CO_3 (5 mol%), 82 °C, 0.5 min, S/C 2000	99	3.3×10^5	636
26[a]	PhCHCH	**94**	Pr^iOH, K_2CO_3(10 mol%), 82 °C, 0.5 min, S/C 2000	99	3.4×10^5	636
27[a]	MeCHCMe	**94**	Pr^iOH, K_2CO_3 (5 mol%), 82 °C, 0.5 min, S/C 2000	99	2.5×10^4	636

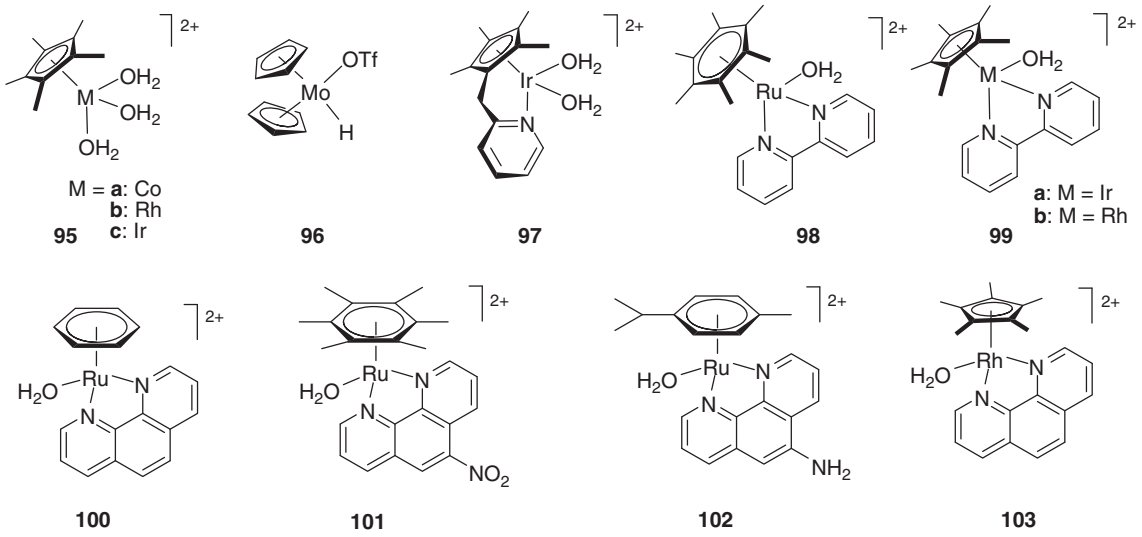
[a]TOF, turnover frequency at 50% conversion.

Recent research has revealed that ketones and aldehydes can be reduced by HCOONa or HCOOH in water with water-soluble half-sandwich complexes **95–103** (Scheme 22).[631,650–654] The reduction was solution pH-dependent, reminiscent of that in aqueous hydrogenation reactions.[627] Both water-soluble and insoluble substrates were reduced, and in the favored pH window, TOFs up to 525 h^{-1} were obtained with the Ir(III) catalyst **99a** and 153 h^{-1} with the Ru(II) catalyst **98**.[631,651,652] A water-soluble molybdocene monohydride, **96**, was also found to catalyze the TH of ketones and aldehydes in water, again with pH-dependent characteristics. Acetone could be converted into IPA in about 8 h at 40 °C in water, and the reduction of benzaldehyde under the same conditions was instantaneous.[655,656]

The half-sandwich catalysts above are unlikely to enable metal–ligand bifunctional catalysis.[604] This explains, to some degree, why the reduction rates are generally low. Accordingly, diamine ligands, having a $-NH_2$ functional group and so capable of activating a carbonyl substrate, are more effective. This is seen in the Ir(III)-catalyzed reduction of a wide range of aldehydes by HCOONa.[635] In particular, the catalyst **66** (Scheme 17) formed *in situ* from $[Cp^*IrCl_2]_2$ (Cp^* denotes pentamethylcyclopentadienyl) and the corresponding ligand afforded TOFs of up to 1.3×10^5 h^{-1} in the TH of aldehydes in neat water. In contrast, when carried out in IPA or the azeotropic HCOOH-NEt_3 mixture, a much slower reduction resulted. The catalyst works for aromatic, α,β-unsaturated and aliphatic aldehydes and for those bearing functional groups such as halo, acetyl, alkenyl and, nitro groups, and is highly chemoselective toward the formyl group. For example, 4-acetylbenzaldehyde was reduced only to



Scheme 21 TH of aldehydes by Ru-**65** with formate in water.



Scheme 22 Water-soluble complexes exploited for TH in aqueous media.

4-acetylphenylethanol, and the reduction of 4-acetylcinnamaldehyde took place without affecting the ketone and olefin double bonds. Selected examples are presented in Scheme 23.

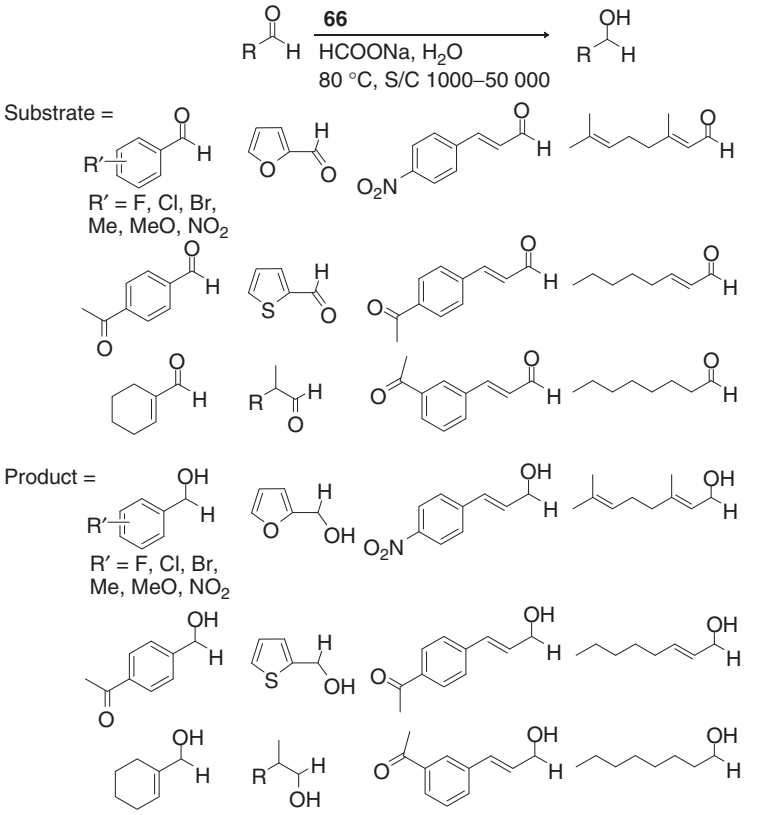
An interesting observation arising from the aldehyde reduction was the lack of reaction with water-soluble substrates under the conditions employed. For example, the water-soluble 4-carboxybenzaldehyde or its sodium salt could not be reduced; but its ester analogue, methyl 4-formyl benzoate, was reduced in a short time of 40 min with **66** at 80 °C at an S/C ratio of 5000. This suggests that the catalysis takes place *on* water rather than *in* water in these biphasic reactions.[629,657] As discussed in Section 8.04.2.2.1, **66** and its analogues also catalyze the hydrogenation of aldehydes in water.[658]

8.04.3.2 Transfer Hydrogenation of Ketones

8.04.3.2.1 Transfer hydrogenation of ketones in organic media

The first TH of carbonyl groups was carried out on heterogeneous aluminum alkoxides (MPV reduction), which also catalyzes the oxidation of secondary alcohols to ketones (Oppenauer oxidation). Subsequently, heterogeneous Pd, Ni, Mg, Cu, Au, Co, Zr and Ru catalysts have been explored for the TH of ketones.[602,659–676] Among these catalysts/metals, Mg and Ni are frequently used and have been extensively studied.[668,669,675]

Homogeneous TH has been extensively studied, drawing increasing attention in recent years.[3,121,123,124,126,127,398,600,604,607,610,639,677–709] Catalytic TH of ketones is usually carried out in azeotropic mixtures of formic acid/triethylamine or IPA under basic conditions.[619,710] The equilibrium between IPA and acetone sets a limit to the conversion of ketones in IPA, so the reduction



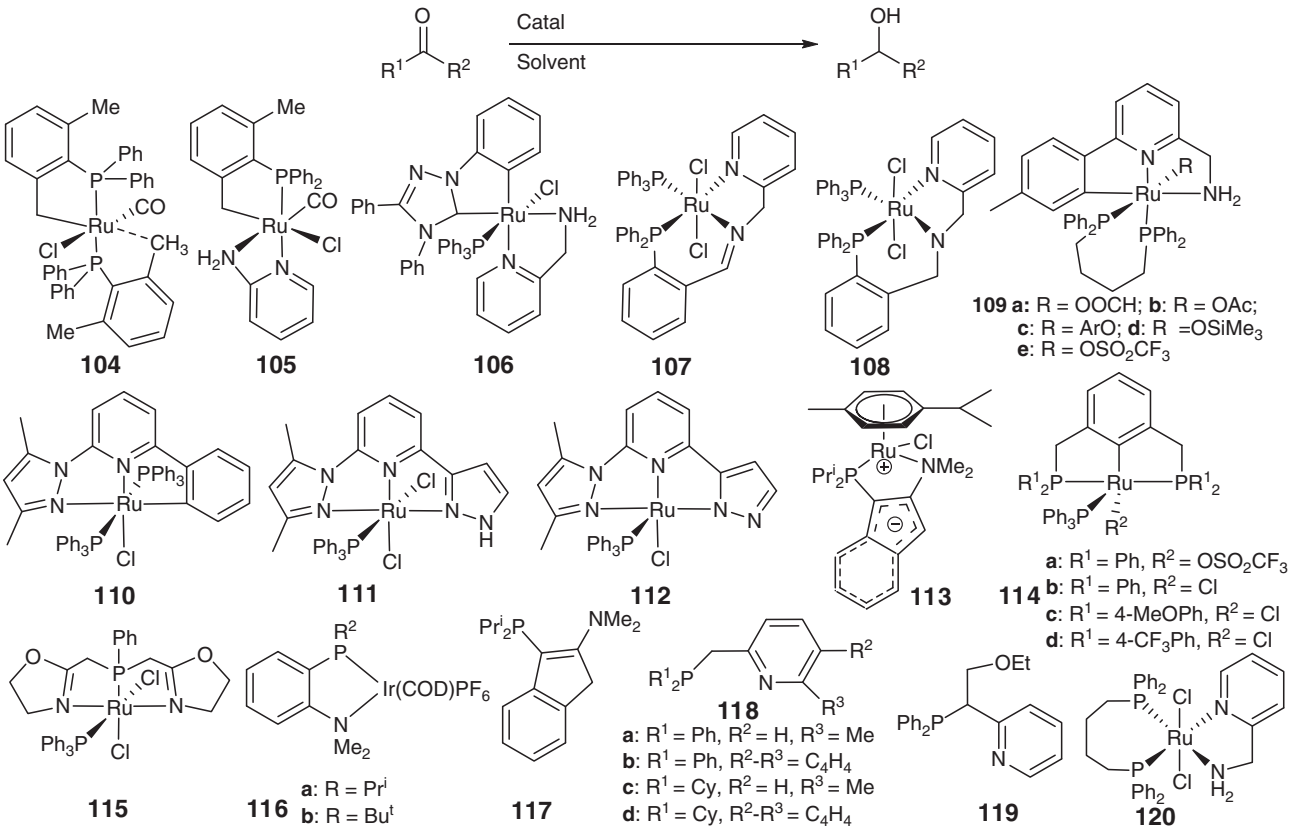
Scheme 23 TH of aldehydes by the catalyst **66** with formate in water.

is usually carried out with a low substrate concentration of about 0.1 M or by removing the acetone from the reaction mixture *in situ* to drive the equilibrium for a high product concentration.[600] In this context, using formic acid as hydrogen source, the reaction can reach complete conversion by releasing CO_2. Primary alcohols are not used as hydrogen donors in general, because of the unfavorable redox potential of the primary versus secondary alcohols. However, ethanol has been used as efficient reducing agent in TH with concomitant formation of ethyl acetate recently.[711–713]

In early studies, ruthenium complexes were shown to catalyze the TH of ketones.[596,714,715] Using $[RuCl_2(PPh_3)_3]$ as catalyst, the catalytic activity was found to increase significantly by addition of NaOH.[596] NaOH itself can affect the slow TH of ketones,[716] in a MPV manner.[676] However, the reaction rate and productivity remained low in general before the 2000s.

Highly active catalysts for the TH of ketones have been revealed only since 1995.[3,121,123,596,610,636,639,685,690–709,716–748] As shown in **Table 30**, a diverse series of Ru(II) complexes demonstrate high activity for the TH of ketones in IPA under basic conditions. Thus, TH of ACP with complex **104** (**Table 30**) went smoothly under basic conditions in refluxing IPA with a S/C ratio of 500, giving a TOF value of 300 h^{-1}.[718,749,750] Interestingly, considerable rate acceleration was observed when the same reduction was carried out when **104** was mixed *in situ* with 2-aminopyridine.[639] The TH of ACP was complete in 5 min at a S/C ratio of 2000 in the presence of a strong base, 1-(pyridin-2-yl)methanamine (Pyme) and TOF of 6.0×10^4 h^{-1} was achieved. However, without the base, **104**/Pyme was practically inactive. The aminopyridine ligand is crucial for the catalytic activity, as a much less active reduction was observed when using the related 2-(pyridine-2-yl)ethanamine as coligand for the same reduction (TOF of about 4000 h^{-1}).[639] The preformed catalyst **105** (**Table 30**) showed similar activity for the TH of ACP and TOF up to 6.3×10^4 h^{-1} was obtained.[639] Related ligands/catalysts (**94**, **105–120**) were subsequently introduced, with TOF up to 3.8×10^6 h^{-1} achieved.[636,639,685,692,702–704,706,708,717–731,736–748,750] For example, using the complex **120**, various ketones have been converted into their corresponding alcohols with high yield in very short reaction time, including aromatic ketones, cyclohexanone, unsaturated ketones, and diaryl ketones; TOF up to 4×10^5 h^{-1} was obtained. Replacing Pyme in **120** with EDN led to a lower TOF of about 103 h^{-1} under the same reaction conditions, reminiscent of the observations made with **104**.[639] Moreover, with the terdentate orthometalated CNN-pincer complexes **94** and **109**, still higher catalytic activity for the TH of ketones in IPA was observed. A wide range of ketones, including aryl alkyl, dialkyl, and diaryl ketones, were quantitatively and chemoselectively reduced to the corresponding alcohols within a minute or in a few minutes, using a low catalyst loading (0.005 mol%) and affording TOFs up to 3.8×10^6 h^{-1}.[636,639,685,719,721,726] However, replacing the NH_2 unit with NMe_2 in **94** resulted in much lower activity, indicating that fast catalytic TH is assisted by the NH_2 functional group.[639,702] The robust cyclometalated ligand that features the NH_2 group, together with the chelating diphosphine, significantly retarded the deactivation of catalyst, giving rise to the high activity and productivity observed. New developments on TH of ketones are still appearing. Other complexes,

Table 30 TH of ketones with high TOFs



Entries	*R^1*	*R^2*	*Catalyst*	*Conditions*	*Conversion (%)*	*TOF (h^{-1})*	*References*
1	Ph	Me	**104**	Pr^iOH, NaOH, reflux, S/C 500	–	300	639
2	Ph	Me	**104**/EDN	Pr^iOH, NaOH, reflux, S/C 500	–	2800	639
3	Ph	Me	**104**/Pyme	Pr^iOH, NaOH, reflux, S/C 2000	–	6.0×10^4	639
4	Ph	Me	**105**	Pr^iOH, NaOH, 82 °C, 5 min, S/C 2000	98	6.0×10^4	639
5	Bu^n	Me	**105**	Pr^iOH, NaOH, 82 °C, 10 min, S/C 2000	99	6.3×10^4	639
6	$CH_2CH(CH_2)_2$	Me	**105**	Pr^iOH, NaOH, 82 °C, 10 min, S/C 2000	95	3.0×10^4	639
7	$-(CH_2)_4-$		**105**	Pr^iOH, NaOH, 82 °C, 10 min, S/C 2000	99	3.4×10^4	639
8	$-(CH_2)_5-$		**105**	Pr^iOH, NaOH, 82 °C, 15 min, S/C 2000	99	1.9×10^4	639
9	Ph	Ph	**105**	Pr^iOH, NaOH, 82 °C, 5 min, S/C 2000	95	3.6×10^4	639
10	Ph	Me	**120**	Pr^iOH, NaOH, 82 °C, 1 min, S/C 2000	97	3.0×10^5	719
11	Ph	Ph	**120**	Pr^iOH, NaOH, 82 °C, 10 min, S/C 2000	98	8.0×10^4	719
12	$-(CH_2)_5-$		**120**	Pr^iOH, NaOH, 82 °C, 1 min, S/C 2000	99	4.0×10^5	719
13	$CH_2CH(CH_2)_2$	Me	**120**	Pr^iOH, NaOH, 82 °C, 10 min, S/C 2000	94	2.8×10^5	719
14	Ph	Me	**94**	Pr^iOH, NaOH, 82 °C, 5 min, S/C 20 000	98	1.1×10^6	708,721
15	3-Cl-C_6H_4	Me	**94**	Pr^iOH, NaOH, 82 °C, 1 min, S/C 20 000	99	2.5×10^6	61,78
16	4-Cl-C_6H_4	Ph	**94**	Pr^iOH, NaOH, 82 °C, 10 min, S/C 20 000	98	5.3×10^5	61,78
17	$-(CH_2)_5-$		**94**	Pr^iOH, NaOH, 82 °C, 2 min, S/C 20 000	97	1.5×10^6	61,78
18	Ph	Me	**106**	Pr^iOH, NaOH, 82 °C, 5 min, S/C 2000	99	1.1×10^5	720
19	Ph	Me	**107**	Pr^iOH, NaOH, 82 °C, 2 min, S/C 1000	98	1.85×10^5	704
20	Ph	Me	**108**	Pr^iOH, NaOH, 82 °C, 2 min, S/C 1000	98	1.9×10^5	704
21	Ph	Me	**109a**	Pr^iOH, NaOH, 82 °C, 2 min, S/C 20 000	97	1.4×10^6	685
22	Ph	Me	**109b**	Pr^iOH, NaOH, 82 °C, 2 min, S/C 20 000	97	1.8×10^6	685
23	3-Br-C_6H_4	Me	**109b**	Pr^iOH, NaOH, 82 °C, 0.5 min, S/C 20 000	99	3.8×10^6	685
24	2-Naphthyl	Me	**109b**	Pr^iOH, NaOH, 82 °C, 0.67 min, S/C 20 000	96	3.7×10^6	685
25	Ph	Me	**109c**[a]	Pr^iOH, NaOH, 82 °C, 5 min, S/C 20 000	98	1.1×10^6	685
26	Ph	Me	**109c**[b]	Pr^iOH, NaOH, 82 °C, 5 min, S/C 20 000	96	6.0×10^5	685
27	Ph	Me	**109c**[c]	Pr^iOH, NaOH, 82 °C, 5 min, S/C 20 000	98	8.7×10^5	685
28	Ph	Me	**109d**	Pr^iOH, NaOH, 82 °C, 5 min, S/C 20 000	98	9.4×10^5	685

(*Continued*)

Table 30 Continued

Entries	R^1	R^2	Catalyst	Conditions	Conversion (%)	TOF (h^{-1})	References
29	Ph	Me	**109e**	Pr^iOH, NaOH, 82 °C, 5 min, S/C 20 000	98	9.3×10^5	685
30	Ph	Me	**110**	Pr^iOH, KOH, 82 °C, 1 min, S/C 1000	98	5.88×10^4	692
31	3-Cl-C_6H_4	Me	**110**	Pr^iOH, KOH, 82 °C, 0.33 min, S/C 1000	99	1.78×10^5	692
32	3-Br-C_6H_4	Me	**110**	Pr^iOH, KOH, 82 °C, 0.33 min, S/C 1000	97	1.75×10^5	692
33	4-Cl-C_6H_4	Me	**110**	Pr^iOH, KOH, 82 °C, 0.33 min, S/C 1000	98	1.76×10^5	692
34	C_6H_{13}	Me	**110**	Pr^iOH, KOH, 82 °C, 0.33 min, S/C 1000	99	1.78×10^5	692
35	$-(CH_2)_4-$	110		Pr^iOH, KOH, 82 °C, 1 min, S/C 1000	98	5.88×10^4	692
36	$-(CH_2)_5-$		**110**	Pr^iOH, KOH, 82 °C, 1 min, S/C 1000	100	6.0×10^4	692
37	Ph	Me	**111**	Pr^iOH, KOH, 82 °C, 1 min, S/C 2000	95	1.1×10^5	746
38	2-Cl-C_6H_4	Me	**111**	Pr^iOH, KOH, 82 °C, 0.17 min, S/C 2000	96	6.9×10^5	746
39	2-Br-C_6H_4	Me	**111**	Pr^iOH, KOH, 82 °C, 0.17 min, S/C 2000	100	7.2×10^5	746
40	3-Br-C_6H_4	Me	**111**	Pr^iOH, KOH, 82 °C, 0.17 min, S/C 2000	99	7.1×10^5	746
41	4-Br-C_6H_4	Me	**111**	Pr^iOH, KOH, 82 °C, 0.17 min, S/C 2000	98	7.1×10^5	746
42	4-Me-C_6H_4	Me	**111**	Pr^iOH, KOH, 82 °C, 0.17 min, S/C 2000	96	6.9×10^5	746
43	Ph	Ph	**111**	Pr^iOH, KOH, 82 °C, 0.5 min, S/C 2000	98	2.4×10^5	746
44	Ph	Py	**111**	Pr^iOH, KOH, 82 °C, 15 min, S/C 500	95	1900	746
45	$-(CH_2)_4-$		**111**	Pr^iOH, KOH, 82 °C, 0.17 min, S/C 2000	98	7.1×10^5	746
46	$-(CH_2)_5-$		**111**	Pr^iOH, KOH, 82 °C, 0.17 min, S/C 2000	98	7.1×10^5	746
47	Ph	Me	**112**	Pr^iOH, KOH, 82 °C, 1 min, S/C 2000	95	1.1×10^5	746
48	Ph	Me	**113**	Pr^iOH, $KOBu^t$, 82 °C, 5 min, S/C 2000	98	1.8×10^5	737
49	Ph	Ph	**113**	Pr^iOH, $KOBu^t$, 82 °C, 5 min, S/C 2000	98	2.2×10^5	737
50	$-(CH_2)_5-$		**114a**	Pr^iOH, KOH, 82 °C, 1.3 h, S/C 10 000	>98	2.7×10^4	736
51	Ph	Me	**114a**	Pr^iOH, KOH, 82 °C, 0.5 h, S/C 1000	90	9000	736
52	$-(CH_2)_5-$		**114b**	Pr^iOH, KOH, 82 °C, 10 min, S/C 1000	98	3.4×10^4	736
53	$-(CH_2)_5-$		**114c**	Pr^iOH, KOH, 82 °C, 30 min, S/C 1000	96	0.8×10^4	736
54	$-(CH_2)_5-$		**114d**	Pr^iOH, KOH, 82 °C, 10 min, S/C 1000	98	3.6×10^4	736
55	$-(CH_2)_5-$		**115**	Pr^iOH, NaOH, 82 °C, 0.5 min, S/C 1000	94	1.1×10^5	734
56	Ph	Me	**115**	Pr^iOH, NaOH, 82 °C, 0.5 min, S/C 1000	59	7.0×10^4	734
57	Ph	Me	**116a**	Pr^iOH, $NaOBu^t$, 82 °C, 0.5 min, S/C 1000	35	4.2×10^4	738
58	Ph	Me	**116b**	Pr^iOH, $NaOBu^t$, 82 °C, 0.5 min, S/C 2000	43	1.0×10^5	738
59	Ph	Me	**116b**/$NaPF_6$	Pr^iOH, $NaOBu^t$, 82 °C, 0.5 min, S/C 1000	63	1.5×10^5	738
60	Ph	Me	Ir-**117**/PF_6	Pr^iOH, $NaOBu^t$, 82 °C, 0.5 min, S/C 1000	39	4.7×10^4	738
61	Ph	Me	Ir-**117**/BF_4	Pr^iOH, $NaOBu^t$, 82 °C, 0.5 min, S/C 1000	35	4.2×10^4	738
62	Ph	Me	Ir-**117**/OTf	Pr^iOH, $NaOBu^t$, 82 °C, 0.5 min, S/C 1000	30	3.6×10^4	738
63	Ph	Me	Ru-**118c**	Pr^iOH, NaOH, 82 °C, 1 min, S/C 1000	77	1.2×10^5	739
64	Ph	Ph	Ru-**118b**	Pr^iOH, NaOH, 82 °C, 1 min, S/C 1000	90	1.5×10^5	739
65	$-(CH_2)_5-$		Ru-**118a**	Pr^iOH, NaOH, 82 °C, 1 min, S/C 1000	99	2.7×10^5	739
66	Bu^n	Me	Ru-**118d**	Pr^iOH, NaOH, 82 °C, 1 min, S/C 1000	91	2.1×10^5	739
67	$-(CH_2)_5-$		Ru-**119**	Pr^iOH, NaOH, 82 °C, 0.5 min, S/C 1000	99	1.2×10^5	732

[a] Ar = 4-$NO_2C_6H_4$.
[b] Ar = 3-Me-4-FC_6H_3.
[c] Ar = $(3\text{-}NO_2C_6H_4)_2CH$.

such as **106**–**108** and **113** to Ru-**119** (Table 30), have also been explored and high catalytic activities were achieved in many cases. A new type of Ru-NNC, NNN complexes **110**–**112** were shown to be highly active and chemoselective for the TH of a very wide range of ketones.[692,746] In IPA under reflux conditions in the presence of strong base, TOFs up to 7×10^5 h^{-1} were observed.

8.04.3.2.2 Transfer hydrogenation of ketones in aqueous media

Organometallic catalysis in aqueous media has attracted interest since the 1970s.[394,395,627,649,657,751–754] In spite of well-documented studies of aqueous-phase hydrogenation, TH in water had been less developed until recently. In the 1980s, aqueous-organic biphasic TH of C═C and C═O double bonds with formate was reported.[657,752,754] Up to 76% conversion was obtained for aldehyde reduction with $RuCl_2(PPh_3)_3$ in 30 min at 90 °C; the reduction was less effective for ketones, however.[754]

Recent research has revealed that ketones and aldehydes can be reduced by HCOONa or HCOOH in water with water-soluble half-sandwich Ru(II) and Ir(III) complexes, for example, **95**, **98**, and **99** (Scheme 22).[631,650–654] The reduction was pH-dependent.[627] Both water-soluble and insoluble substrates were reduced, and in the favored pH window, TOFs up to 525 h^{-1} were obtained with the Ir(III) catalyst **99a** and 153 h^{-1} with the Ru(II) catalyst **98** (Table 31).[631,651,652] A water-soluble molybdocene monohydride, **96**, was also found to catalyze the TH of ketones and aldehydes in water, again with pH-dependent characteristics. Acetone was converted into IPA in about 8 h at 40 °C in water, as mentioned in Section 8.04.3.2.1.[655,656]

Table 31 TH of carbonyl compounds by HCOONa with **98**[a] and **99a**[b] in water

Substrate	*Catalyst*	*Time (h)*	*Yield (%)*	*TOF (h^{-1})*
Cyclohexanone	**98**, pH 4.0	4	99	98
2-Butanone		6	97	58
4′-SO_3Na-ACP		3	98	103
ACP		4	98	75
2-Trifluoro-ACP		4	99	153
α-Tetralone		13	97	21
Cyclohexanone	**99a**, pH 2.0	1	99	376
ACP		1	97	343
2-CF_3-ACP		1	99	525
Butanone		4	99	150
4′-SO_3Na-ACP		1	99	419
1-Tetralone		3	98	203

[a]0.32 mmol ketone, 0. 16 mol % **98**, 3 ml H_2O, 1.92 mol HCOONa, 70 °C, pH 4.0.[653]
[b]0.32 mmol substrates, 0.5 mol % **99a**, 3 ml H_2O, 0.32 mol HCOOH, 70 °C, pH 2.0.[632]

A series of water-soluble ruthenium-arene and rhodium complexes containing chelating 1,10-phenanthroline ligands have also been introduced (**100–103**, Scheme 22).[755–765] These complexes catalyze TH of ketones in aqueous solution using formic acid as hydrogen source, with **101** displaying the highest activity. For instance, TONs up to 164 were obtained in the reduction of ACP.[755] However, when the water-soluble ligand triphenylphosphine-3,3′,3′′-trisulfonic acid trisodium salt (TPPTS) (**64**) was used instead of phenanthroline, similar half-sandwich Ru(II) complexes displayed much reduced activities on going from IPA to water.[761] The trinuclear Ru complexes **125** (Scheme 24) are active catalysts for TH of ketones in water.[766] Compared to its mononuclear counterpart, **125** showed better catalytic performance. Kinetic analysis suggests that the two ruthenium centers in **125b** act cooperatively, with one activating the ketone, whereas the other bonds to the formate.[766]

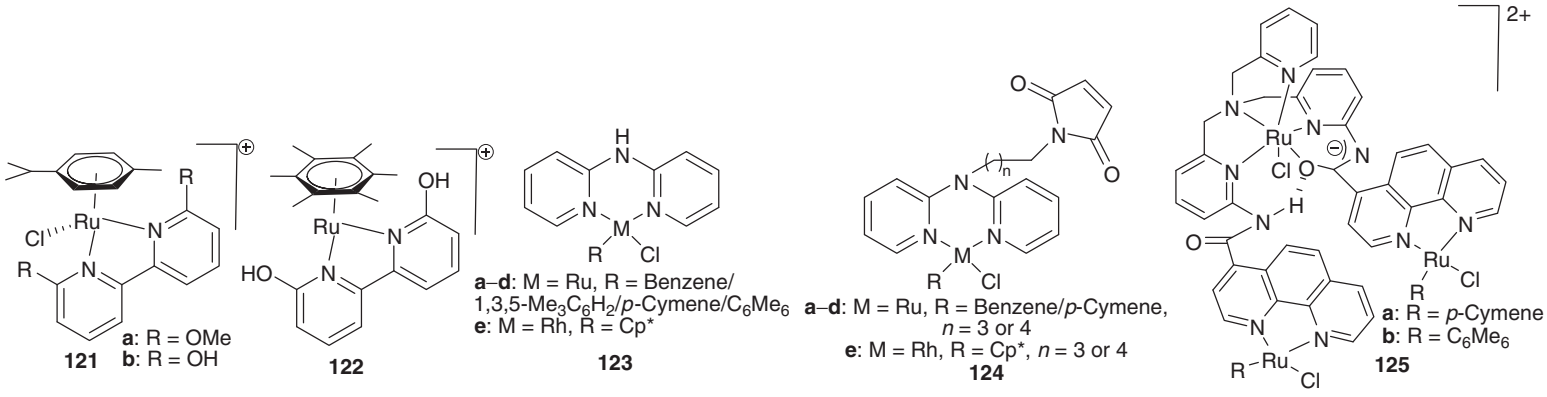
The bipyridine-type complexes of Ru(II) **121–124** have been studied (Scheme 24). [762–768] For instance, **121** catalyzed the TH of ketones in a mixture of MeOH/H_2O (10/90, v/v) at 85 °C with S/C ratio of 100, affording high conversions of aromatic ketones into the corresponding alcohols in 6 h.[767] The OH group in **121b** may engage in metal-ligand bifunctional activation of the substrate, although under the catalytic conditions it is likely to be deprotonated, having an estimated p*K*a~5. The arene ligand and the counteranion influence the catalytic activity.[762] The most active catalysts were the *p*-cymene species, and among these, the one containing the tosylate anion gave rise to the highest TOF values. However, the TH rate was highly dependent on the pH value of the reaction solution. A pH value of 4 was optimal for these complexes. Interestingly, these catalysts were also active for the reverse reaction, oxidation of alcohols in water.[762] The Ru(II) and Rh(III) complexes bearing dipyridylamine ligands (**123–124**) showed no advantages over the simple **98** and **99** in the TH of ketones in water.[764,768]

8.04.3.2.3 ATH of ketones in organic media

Although enzymes are well known to be highly enantioselective in ATH with nicotinamide adenine dinucleotide or nicotinamide adenine dinucleotide phosphate as the hydrogen donor, it took chemists several decades to develop chemical catalysts with selectivities approaching those of enzymes. The first ATH was reported by Doering and Young in 1950, who designed an asymmetric version of MPV reduction of ketones by using a achiral reagent and a chiral hydrogen source.[769] In the 1970s, the feasibility of ATH was demonstrated by using a chiral metal catalyst derived from combining [$RuCl(PPh_3)_3$] with a chiral monophosphine ligand.[597,770] Since then, several chiral catalytic systems for ATH have been developed, including those based on Ir,[771] Ru,[772] Rh,[773] and Sm,[774] though the enantioselectivity was generally low.

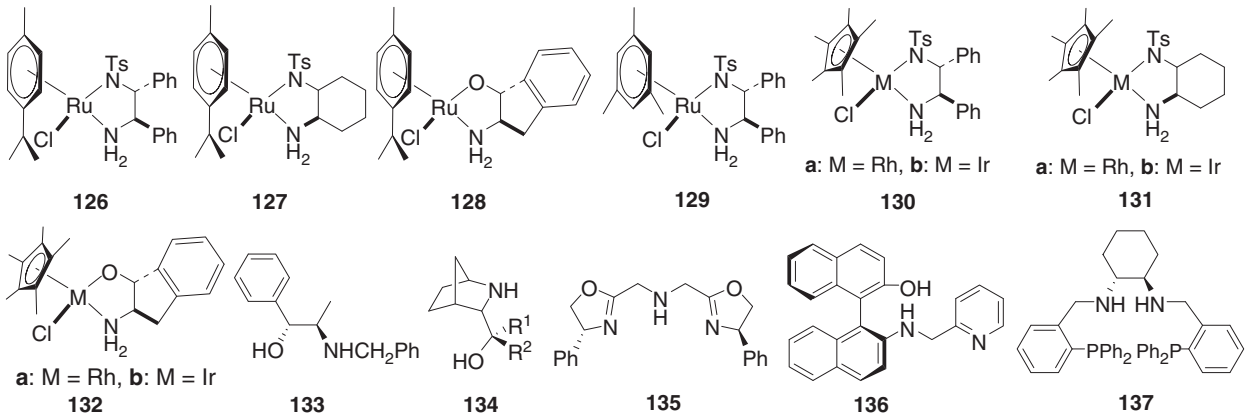
A significant breakthrough was seen in Ru(II) catalysts bearing monotosylated 1,2-diamines or amino alcohols, which were shown to be highly efficient and enantioselective for reduction of ketones with IPA or HCOOH/Et_3N azeotrope.[616,619,620] These Noyori-type catalysts, which have found broad applications [601,617,621,775,776] and operate via a novel metal-ligand bifunctional mechanism,[605,610,709,777,778] have since inspired intense research into ATH. The concept of bifunctional catalysis has also been extended into the design of catalysts for other chemical transformations,[604] and efforts have been made to immobilize the catalysts and develop more environmentally benign reaction conditions. New catalysts, which are more efficient or more economic and "greener," are being studied as well. Alongside the organometallic catalysts, bio-mimetic and organocatalytic ATH have emerged, providing new tools for organic synthesis and insight into natural processes. Various applications of the ATH have appeared, including industrial explorations.[3,123,124,398,598–601,605,607,609,639,681–684,686,687,689,693,779–789]

Bifunctional Ru, Rh, and Ir complexes have been most widely used (**126–130**, Scheme 25). These complexes are readily prepared by mixing commercially available metal precursors with ligands, such as monotosylated diamines, amino alcohols, PN ligands, and so on. The precatalysts can be isolated, or more conveniently used *in situ*. IPA and the azeotropic formic acid and triethylamine mixture are the most often used hydrogen sources. Conversion of the precatalyst into active catalyst requires the presence of base. Selected examples of the ATH of aryl ketones and functionalized variants catalyzed by these catalysts are presented in Table 32. Various functional groups, including acetal, tertiary amino, chloro, nitrile, ester, sulfide, sulfone, and CC



Scheme 24 Bipyridine-type complexes exploited for ATH.

multiple bonds are tolerated. Among those simple ketones, alkyl aryl, and alkyl hetaryl ketones have been highly enantioselectively converted into the corresponding chiral alcohols with high yields using **126** as catalyst (e.g., entries 1–20, Table 32); however, dialkyl ketones remained challenging until recently. The low *ee* obtained for such ketones in the ATH may be partly because of the lack of an unsaturated group interacting with the arene moiety of the catalyst in the transition state. Using **126** as catalyst, a series of α-chloro ketones, including heteroaryl ones, were reduced on a relatively large scale (10–43 g) at Pfizer and Eli Lilly.[790] Rhodium catalysts appear to be often more selective than the ruthenium analogues in the reduction of these α-chloro ketones (entries 30–31 versus 21–22, Table 32).



Scheme 25 Representative ATH catalysts/ligands.

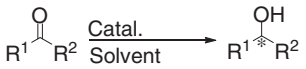
The complex **126** also catalyzed ATH of 1,2-diketones, giving the corresponding chiral diols with >99% *ee* in the azeotropic formic acid and triethylamine mixture.[775] Under the same reaction conditions, racemic benzoin was quantitatively transformed into chiral hydrobenzoin via DKR.[775] ATH of unsymmetrically substituted 1,2-diketones first took place at the less hindered carbonyl group; further reaction led to *anti*-1,2-diols.[84,791] Similarly, ATH of 1,3-diphenylpropane-1,3-dione afforded 1,3-diphenylpropane-1,3-diol with excellent selectivity ((+),(−)/*meso* 94:6; 99% *ee*) and yield (99%). However, alkyl-1,3-dione was not reduced under the same conditions.[48,800] Under controlled conditions with complex **126** as catalyst, the monoreduction of unsymmetrically substituted 1,3-diketones is feasible, occurring preferentially at the less hindered carbonyl group with excellent selectivity.[801] Furthermore, ethyl 3-oxo-3-phenylpropanaote and its aryl-ring-substituted derivatives were reduced by ATH either in IPA with a Ru(II)-ephedrine complex or formic acid with **126**, affording the corresponding 3-hydroxy esters with good to excellent *ee*'s.[57,607,802–804] However, aliphatic ketoesters displayed much lower selectivity. ATH of 2-acylarenecarboxylates and the related pyridine analogues in IPA with the hydrido species synthesized from complex **126** in the absence of base has been described, providing a convenient route to chiral alkylphthalides.[805] ATH of α,β-unsaturated ketones and sulfur-containing ketones is also feasible.[806–810]

Among the newly reported catalysts, the structurally rigid, tethered ruthenium, and rhodium catalysts originally developed by Wills and coworkers are of particular note.[811–821] The tether offers an additional element in controlling enantioselection and in stabilising the catalysts. For instance, the Ru complexes **138** and **139** are good ATH catalysts, generally providing faster reaction rate than the nontethered analogues for ketone reduction using HCOOH-Et_3N as hydrogen donor (Scheme 26).[811,812,814,817] The rhodium catalyst **142** affords a remarkably high enantioselectivity of 99.9% *ee* in tetralone reduction and is particularly good for ATH of α-substituted aromatic ketones.[815] Of further interest is the rhodium catalyst **143**, which represents one of the best ATH catalysts for aliphatic ketone reduction, providing a 87% *ee* in the reduction of cyclohexylmethyl ketone using HCOOH/Et_3N as hydrogen donor (Scheme 26).[816] These catalysts are also active in water without compromising enantioselectivity. New type ether-linked Ru catalysts, **140** and **145a**,**b**, have been developed very recently by Ikariya and Wills.[820,821] The catalysts showed excellent activity and selectivity for a wide range of ketones, affording up to >99% yield and >99% *ee* for alcohol products. Thus using **145**, an S/C ratio of as high as 40 000 has been achieved albeit at a higher temperature of 60 °C.[821] It is worth noting that the catalysts **145** are also highly active and selective for the AH of ketones in methanol.[821]

Amino acid derivates can act as ligands in ATH reactions as well (Scheme 27).[822–831] By changing the functional group on the same amino acid backbone, the resulting catalysts are shown to be enantioswitchable. For instance, the ligands **147** and **148** both gave *R* configured product in the reduction of ACP, indicating that the stereocentre in the amino acid backbone dictates the facial selection of ketone; having the same amino acid backbone, however, ligand **146** produced the *S* product (Scheme 27).[827,828] Using high throughput screening, Ru-**149** and Rh-**150** were identified as the best catalyst for the synthesis of a phenyl amino alcohol drug precursor for fluoxetine, and a thienyl amino alcohol precursor for duloxetine, (Scheme 27). The reduction afforded both of the alcohols with excellent enantioselectivities (>99% *ee*).[831]

Aliphatic ketones have been problematic, showing low *ee*'s in general. The Ru(II) catalyst formed from the Ru-cymene dimer and the bisphosphite ligand **151** gave high enantioselectivities for both aromatic and aliphatic ketones in IPA (Scheme 28).[832] In particular, aliphatic ketones were reduced with up to 99% *ee*.

Table 32 ATH of ketones in organic media

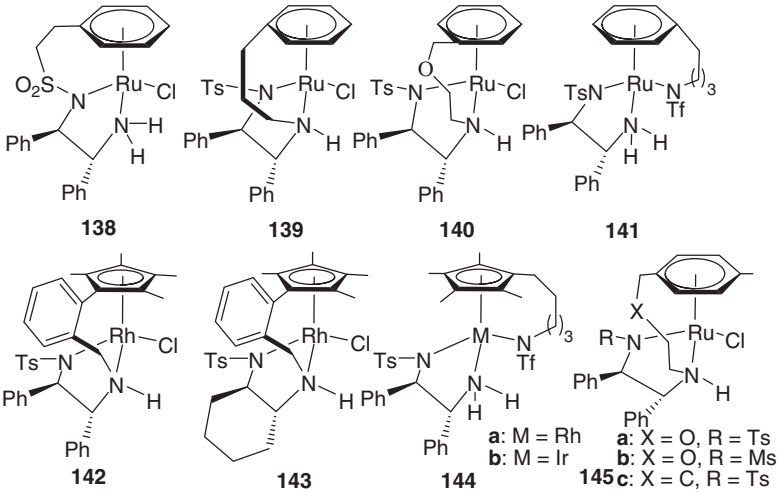


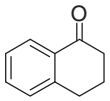
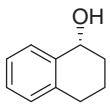
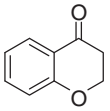
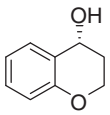
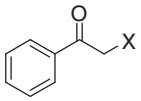
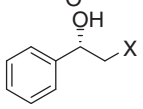
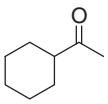
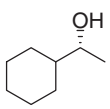
Entries	R^1	R^2	Catalyst	Conditions	Yield (%)	ee (%)	References
1	Ph	Me	**126**	Pr^iOH/KOH, r.t., 15 h, S/C 200	95	97	616
2	Ph	Et	**126**	Pr^iOH/KOH, r.t., 14 h, S/C 200	94	97	616
3	2-Me-C_6H_4	Me	**126**	Pr^iOH/KOH, r.t., 24 h, S/C 200	53	91	616
4	3-Cl-C_6H_4	Me	**126**	Pr^iOH/KOH, r.t., 2.5 h, S/C 200	98	98	616
5	4-Cl-C_6H_4	Me	**126**	Pr^iOH/KOH, r.t., 19 h, S/C 200	95	93	616
6	3-MeO-C_6H_4	Me	**126**	Pr^iOH/KOH, r.t., 16 h, S/C 200	96	96	616
7	4-MeO-C_6H_4	Me	**126**	Pr^iOH/KOH, r.t., 20 h, S/C 200	53	72	616
8	Ph	Me	**126**	F/T, 28 °C, 20 h, S/C 200	>99	98	619
9	Ph	Me	**126**	F/T, 60 °C, 1.5 h, S/C 200	>99	96	619
10	3-Cl-C_6H_4	Me	**126**	F/T, 28 °C, 21 h, S/C 200	>99	97	619
11	4-Cl-C_6H_4	Me	**126**	F/T, 28 °C, 24 h, S/C 200	>99	95	619
12	4-CN-C_6H_4	Me	**126**	F/T, 28 °C, 14 h, S/C 200	>99	90	619
13	3-MeO-C_6H_4	Me	**126**	F/T, 28 °C, 50 h, S/C 200	>99	98	619
14	4-MeO-C_6H_4	Me	**126**	F/T, 28 °C, 60 h, S/C 200	>99	97	619
15	Ph	Et	**126**	F/T, 28 °C, 60 h, S/C 200	96	97	619
16	1-Naphthyl	Me	**126**	F/T, 28 °C, 60 h, S/C 200	93	83	619
17	2-Naphthyl	Me	**126**	F/T, 28 °C, 22 h, S/C 200	>99	96	619
18	4-MeO-C_6H_4	4-CN-C_6H_4	**126**	F/T-THF, 28 °C, 60 h, S/C 200	54	66	619
19	1-Indanone		**126**	F/T, 28 °C, 48 h, S/C 200	>99	99	619
20	1-Tetralone		**126**	F/T, 28 °C, 48 h, S/C 200	>99	99	619
21	Ph	CH_2Cl	**126**	HCOOH/NEt_3 (1/1), 28 °C, S/C 1000, 24 h	36	91	792
22	2-Pyridyl	CH_2Cl	**126**	F/T, 28 °C, S/C 56	61	96	790
23	Ph	CH_2NMe_2	**126**	F/T, S/C 500	58	97	793
24[a]	PhCHCH	Me	**126**	F/T, S/C 200	75	30	794
25	Ph	Me	**128**	Pr^iOH/KOH, S/C 200	70	91	600,795
26	Ph	Me	**129**	F/T, S/C 200	>99	98	619
27	1-Tetralone		**129**	F/T, S/C 200	96	99	619
28	Ph	Me	**129**	Pr^iOH/KOH, S/C 200	95	97	619
29	PhC≡C	Me	**129**	Pr^iOH/KOH, S/C 200	>99	97	619
30	Ph	CH_2Cl	**130a**	F/T, EtOAc, 1 h, S/C 1000	99	97	792
31	Ph	CH_2Cl	**130a**	Pr^iOH, 14 h, S/C 100	94	98	792
32	Ph	CH_2Cl	**130b**	F/T, EtOAc, 4 h, S/C 1000	99	71	792
33	Ph	CH_2OTs	**130a**	F/T, EtOAc, 4 h, S/C 1000	97	95	796,797
34	2-Cl-C_6H_4	CH_2OTs	**130a**	F/T, EtOAc, 24 h, S/C 1000	42	62	796,797
35	3-Cl-C_6H_4	CH_2OTs	**130a**	F/T, EtOAc, 2 h, S/C 1000	99	93	796,797
36	2-MeO-C_6H_4	CH_2OTs	**130a**	F/T, EtOAc, 4 h, S/C 1000	99	85	796,797
37	Ph	Me	**131a**	Pr^iOH/KOH, 12 h, S/C 200	85	97	798
38	1-Naphthyl	Me	Ru-**133**	Pr^iOH/Bu^tOK, S/C 200	96	96	799
39	Ph	Me	Ru-**137**	Pr^iOH/KOH, r.t., S/C 200	93	93	622
40	Ph	Et	Ru-**137**	Pr^iOH/KOH, r.t., S/C 200	78	96	622

[a]The corresponding saturated alcohol was also formed in 25% yield.

Other catalysts have also been explored for the ATH reactions. Cyclometalated ruthenium complexes generated from [Ru(η^6-arene)Cl_2]$_2$ and simple chiral amines were shown to be active for ketone reduction, affording up to 89% *ee* for ACP.[833] Combining the PN ligand **156** with [$RuCl_2(PPh_3)_3$] led to an efficient Ru(II) catalyst for ATH of aryl ketones including α-stustituted ones; high conversion and enantioselectivity (up to 98% *ee*) were obtained in IPA at S/C=200 at room temperature in <30 min (**Scheme 29**).[834] A closely related catalyst afforded >99% *ee* in the ATH of *tert*-butyl methyl ketone. Notably, the catalyst works for both ATH and AH of ketones. However, the Ru(II)-PN complex **152**, which is active for AH, appears less efficient for ATH, and the related **153–155** complexes show similar activity for the ATH of ketones.[835] In similar ATH reactions, [IrCl(CO)$(PPh_3)_2$-**157**][836] and [$Ru_3(CO)_{12}$–**158**][837] demonstrated moderate to good enantioselectivities.

Highly active and productive TH catalysts are emerging, with TOF and TON approaching some of the best AH catalysts. As aforementioned (see **Tables 29**, **30**), some Ru(II) catalysts bearing tridentate CNN ligands have been shown to give high rates in achiral TH of ketones.[636,639,702,704,706,708,717–723,726–731,749,750] Asymmetric induction has been demonstrated with similar catalysts.[639,702,719,721,722,726,731] Thus, when a chiral CNN ligand was used, the resulting complex **159** was highly active and afforded good enantioselectivity (**Scheme 30**).[721] Recently the Ru(II) complex **160**, which bears a chiral phosphine ligand and



Catalyst	Substrate	Product		*ee* (%)
140 **142**				>99 99.9
140 **142** **145a**				>99 99.9 97
140,142,145a,b,c **140,142,145a** **140,142** **142,145a** **145a**			X=H X=Cl X=OPh X=OH X=CN	99,98,97,95,96 98,99.6,97 95,99 98,96 95
143				87

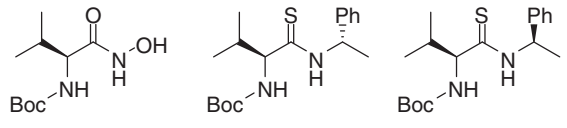
Conditions: HCOOH/Et_3N as hydrogen donor and solvent, S/C = 200.
30 °C (for **140**) or r.t. (for **142**, **143**); S/C 1000–40 000, 60 °C (for **145**).

Scheme 26 Tethered catalysts and their applications in ATH.

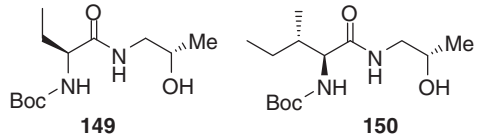
2-(aminomethyl)pyridine (ampy), was revealed to catalyze the ATH of ketones in IPA, affording up to 3×10^5 h^{-1} TOF and 94% *ee*.[719] The Ru complex **161** delivered high diastereoselectivity even when racemic pyme and a chiral phosphine ligand were used. TOF up to 7×10^4 h^{-1} and *ee*'s up to 99% were obtained for the ATH of ketones.[722] The analogues osmium complex is also effective, affording up to 5×10^5 h^{-1} TOF and 96% *ee*.[838] The ampy ligand in these catalysts seems to play a crucial role, aiding hydride generation and presumably enantioselective hydride transfer. Recently, highly active ruthenium complexes bearing unsymmetrical NNN ligands (**162–163**) were reported for ATH of ketones as well.[694,839] For instance, ATH with **162** afforded high yield with up to 97% *ee* in a few minutes in IPA at 30 °C at S/C ratio of 1000, with the TOF close to 4000 h^{-1}.[694] Using **163**, the ATH of ACP gave a TOF of 1.44×10^4 h^{-1} at 28 °C with 79% *ee*.[839]

Parallel to the quest for more efficient ATH catalysts, discovery of "greener" catalysts becomes another focal point. Iron, the active site of hydrogenases,[840–843] is cheaper and more abundant and environmental benign compared to the most commonly used ruthenium, rhodium, and iridium. However, the development of Fe catalysts for hydrogenation or TH lags far behind. Early in 1972, Noryori and coworkers reported that $Fe(CO)_5$ could selectively hydrogenate the C═C double bond of α,β-unsaturated ketones and aldehydes.[844] The iron carbonyl was also shown to be good catalyst for hydrogenation of imines.[845] Subsequent work demonstrated that iron carbonyls derived from $Fe_3(CO)_{12}$ catalyze TH of ketones with IPA as hydrogen donor, affording moderate to good yields.[846,847] Later, the nonclassic trihydride **164** was revealed to be effective catalyst for the selective reduction of unsaturated carbonyl compounds, using either IPA or cyclopentanol as hydrogen donor (Table 33).[848] The selectivity between the carbonyl group and C═C double bond were substrate dependent.

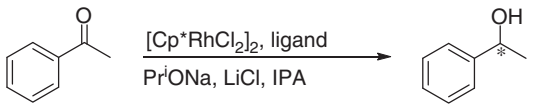
Significant progress has only been made in the past few years. Thus, iron-terpyridine-monophosphine[849] and iron-porphyrin[850] were found to catalyze the TH of ketones using IPA as hydrogen donor (Table 33). Both aromatic and aliphatic ketones were reduced with excellent yields. Suitable Fe precursors were $Fe_3(CO)_{12}$ and $FeCl_2$. The bifunctional iron complex **165** is



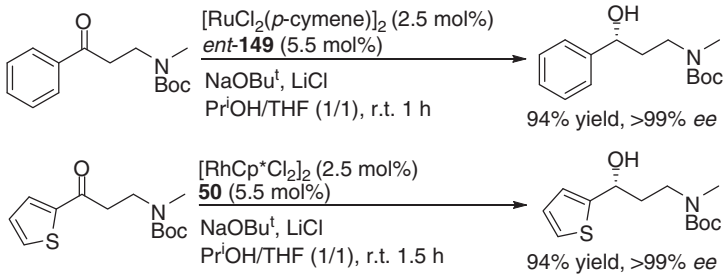
146 **147** **148**



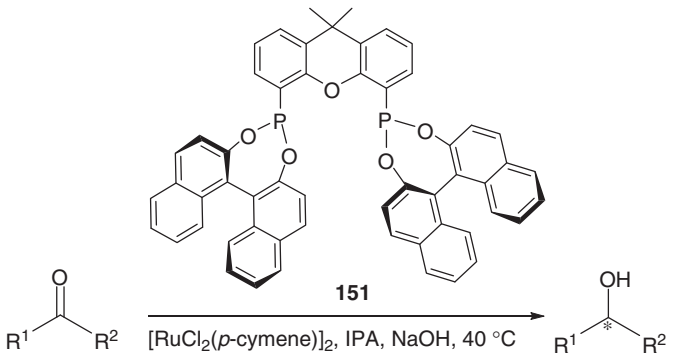
149 **150**



Ligand	*ee* (%)	Major product configuration
146	97	*S*
147	95	*R*
148	95	*R*



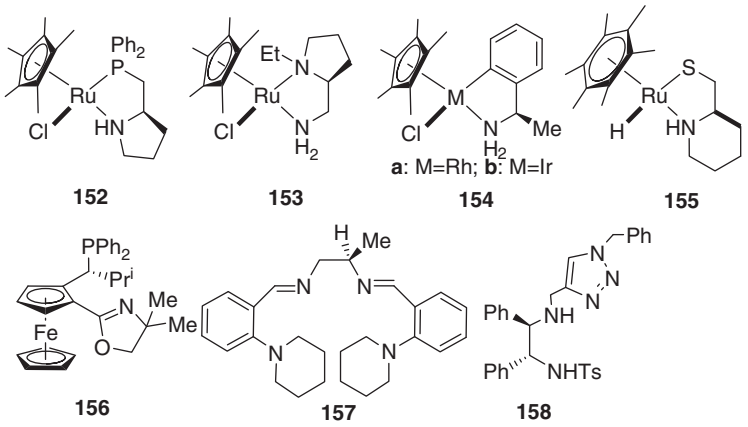
Scheme 27 Enantioswitchable amino acid ligands and their applications.



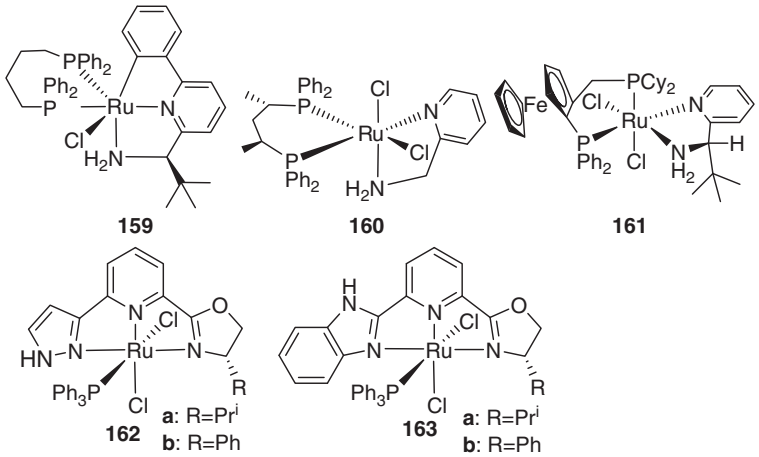
R^1	R^2	Conversion (%)	*ee* (%)
Ph	Me	93	98
o-ClC_6H_4	Me	90	99
cy-C_6H_{11}	Me	97	99
Pr^i	Me	99	99

Scheme 28 Ru-phosphite catalyst for the ATH of aromatic and aliphatic ketones.

capable of both hydrogenation and TH,[851] displaying high selectivity towards polar multiple bonds, such as carbonyl and imine groups. Bearing a hydride and an acidic hydrogen, this structurally well defined catalyst is analogous to the active Shvo's ruthenium catalyst[62,605,714,852] and has features reminiscent of diiron hydrogenases.[841–843]



Scheme 29 Ligands/catalysts for ATH in organic media.



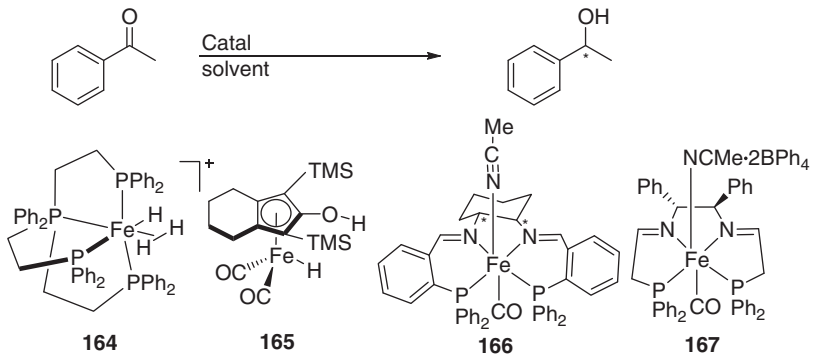
Scheme 30 Highly efficient catalysts for ATH.

The first iron catalyst for ATH was reported in 2004 by Gao and coworkers, who demonstrated that the complex $[Et_3NH]^+[HFe_3(CO)_{11}]^-$ together with the ligand **137**, originally developed by Gao and Noyori, could catalyze ATH of ketones in IPA, affording good yields and *ee*'s (Table 33).[853] Morris and coworkers reported the first well-defined iron ATH catalyst **166**, which afforded up to 907 h^{-1} TOF for ketone reduction, although the enantioselectivity was low.[854] The newly developed **167** achieved 83% *ee* for the ATH of ACP with 70% conversion in 8 h.[855–861] The enantioselectivity decreased to 12% *ee* with conversion rising to 90% in 30 h reaction time, indicative of dehydrogenation being involved (entries 7–8, Table 33). It has been proved that **167** reacts slowly with air in both the solid state and solution and a strong base is necessary for the reduction. Higher *ee*'s were observed with more sterically demanding ketones, for example, 1-phenylpropan-1-one (90% conversion, 94% *ee* in 25 min, S/C=1500), 2,2-dimethyl-1-phenylpropan-1-one (35% conversion, 99% *ee* in 200 min, S/C=500), and cyclobutyl phenyl ketone (95% conversion, 94% *ee* in 40 min, S/C 1000).

Recently, a novel P_2N_4 macrocyclic ligand **168** combined with $Fe_3(CO)_{12}$ complexes has been demonstrated as highly efficient and selective catalyst for ATH of a wide range of aromatic ketones.[862] The reduction was carried out in IPA at 65 °C with an S/C ratio of 200, affording up to 99% *ee* with good to excellent yields in a few hours in most cases. As shown in Table 34, aryl and heteroaryl ketones can all be reduced with excellent *ee*'s. The catalytic system worked more selectively for the more hindered aromatic ketones, with optically almost pure chiral alcohols obtained for these substrates (entries 20–26, Table 34). The remarkable efficiency of this Fe catalyst is also seen in the ATH using a low catalyst loading (S/C 1000–5000), where approximately identical enantioselectivities were achieved, with TOF up to 1940 h^{-1}.[862]

Some new strategies in asymmetric catalysis have also been adopted in ATH. For instance, an achiral ligand could be activated by a chiral ligand when both are coordinated to a metal (Scheme 31).[863] The Rh complex **169,** bearing a chirally activated achiral 2,2′-bis (diphenylphosphino)benzophenone ligand, gave virtually perfect enantiocontrol in the ATH of ketones, outperforming its enantiopure BINAP counterpart. In the reduction of 2-methyl ACP, complex **169** afford a 99% *ee*, whereas the BINAP complex only gave a 57% *ee*. The complex **170** contains a chiral-at-metal fragment, $[Ru(bipyridine)_2(bipyrimidine)]^{2+}$ bearing no chiral

Table 33 ATH of ketones with Fe-catalysts



164 **165** **166** **167**

Entries	*Catalyst*	*Conditions*	*Yield (%)*	ee *(%)*	*References*
1	$Fe_3(CO)_{12}$/terpy/PPh_3	IPA, 100 °C, 7 h, S/C 200	95	–	849
2	$Fe_3(CO)_{12}$/porphyrin	IPA, 100 °C, 7 h, S/C 200	94	–	850
3	**165**	IPA, 75 °C, 16 h, S/C 100	87	–	851
4	**165**	H_2, 25 °C, 20 h, S/C 50	83	–	851
5	$[Et_3NH][HFe_3(CO)_{11}]$-**137**	IPA, 82 °C, 7 h, S/C 100	92	56	853
6	**166**	IPA, 22 °C, 0.4 h, S/C 200	95	29	854
7	**167**	IPA, Bu^tOK, 22 °C, 8 h, S/C 6000	70	83	855
8	**167**	IPA, Bu^tOK, 22 °C, 30 h, S/C 6000	90	12	855

ligands. In the ATH of ketones, **170** afforded *ee*'s of up to 26%, with the chiral information being relayed through the bridging bipyrimidine.[864] Although the enantioselectivity is low, this 'chiral inorganic ligand' may lead to the design of new catalysts.

8.04.3.2.4 ATH of ketones in aqueous media

Water was considered an unsuitable solvent for reactions of sparingly soluble ketones. However, significant advances have been made since early 2000s. As with most other aqueous phase catalytic reactions, research into ATH of ketones in water started with the search for water-soluble catalysts. And as would be expected, this was achieved by synthesizing ligands that dissolve in water. However, recent studies have demonstrated that unmodified, water-insoluble ligands can deliver high activity and enantioselectivity for ketone reduction in water.[73,398,417,600,604–608,679,681,682,710,756–758,816,830,865–907] Scheme 32 shows examples of catalysts containing water-soluble and insoluble ligands that are effective in aqueous phase ATH.

8.04.3.2.4.1 ATH of simple ketones in water

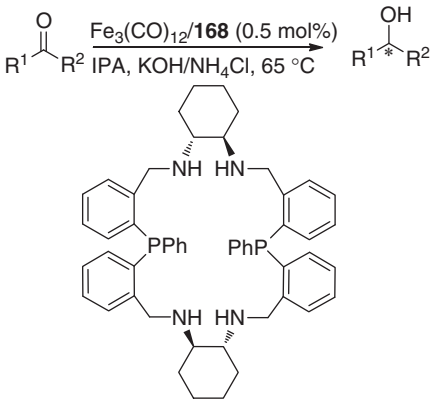
Williams, Blacker and coworkers were the first to explore the ATH of ketones with water-soluble Noyori–Ikariya type catalysts in 2001.[73,904] The reduction was performed using catalyst containing a sulfonated TsDPEN or TsCYDN ligand (**171** or **173**, Scheme 32) in IPA with water (up to 51%, v/v) added. The catalyst was *in situ* generated by reacting the ligand with $[RuCl_2(p\text{-cymene})]_2$ or $[Cp^*MCl_2]_2$ (M = Rh, Ir). Although good to excellent *ee*'s (up to 96%) were achieved, the reaction was generally sluggish under the chosen conditions. It was shown that the reaction went faster with increasing volume of water in the case of the Ir(III) catalysts. For example, the reduction of 3-fluoroacetophenone with the Ir-**173** catalyst gave an 82% conversion in 2.5 h when the water content was 34%, but a 94% conversion when the water level was increased to 51%. The enantioselectivities remained virtually unchanged, however, at 93–94% *ee*.

ATH of aromatic ketones by formate in neat water was demonstrated at about the same time, where a water-soluble catalyst was formed by combining $[RuCl_2(p\text{-cymene})]_2$ with a (*S*)-proline amide ligand (**174b**, Scheme 32).[903,905] The reduction was carried out with or without a surfactant, with better results obtained in its presence. As is seen from Scheme 33, the reaction afforded good conversions with moderate to good *ee*'s at 40 °C. These results represent the first examples of ATH in water with no organic cosolvents. Water-soluble Rh(III)–Schiff base complexes were later reported to catalyze similar reductions in aqueous formate solution, affording moderate to good reaction rates and *ee*'s.[902]

A highly water-soluble ligand **172a** was also developed.[901] ATH of ketones catalyzed by Ru-**172a** showed good activities and moderate to excellent enantioselectivities in the presence of a surfactant, sodium dodecyl sulfate (SDS). Moreover, the catalyst can be recycled twice without loss of enantioselectivity. Guanidinium has recently been used to modify the TsDPEN ligand, leading to a water-soluble cationic TsDPEN, which, when combined with $[Cp^*RhCl_2]_2$, permits the ATH of ketones as well as imines and ketoesters in water, with *ee*'s up to >99%.[908]

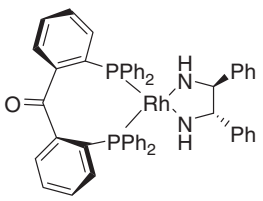
A common feature of these investigations is to make the catalysts soluble in water, and to circumvent the problem of low solubility of most organic substrates in water, surfactants are usually called upon. However, an investigation into the behavior of the water-soluble **187** (Scheme 32) and insoluble TsDPEN in ketone reduction by HCOONa in neat water revealed surprises.[874,909,910]

Table 34 ATH of ketones with macrocyclic Fe catalyst

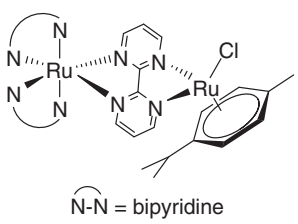


168

Entries	*R^1*	*R^2*	*Temperature (°C)*	*S/C*	*Time (h)*	*Conversion (%)*	ee *(%)*	*References*
1	Ph	Me	55	200	1	97	98	862
2	Ph	Me	75	1000	1	91	97	862
3	Ph	Me	75	2000	2	89	97	862
4	Ph	Me	75	5000	5	66	97	862
5	2-Me-C_6H_4	Me	75	200	2	64	99	862
6	3-Me-C_6H_4	Me	55	200	1	92	96	862
7	3-Me-C_6H_4	Me	75	1000	1	89	94	862
8	4-Me-C_6H_4	Me	75	200	0.5	94	96	862
9	4-Me-C_6H_4	Me	75	1000	1	89	94	862
10	2-Cl-C_6H_4	Me	75	200	2	92	97	862
11	3-Cl-C_6H_4	Me	55	200	0.5	98	95	862
12	3-Cl-C_6H_4	Me	75	1000	1	90	95	862
13	3-Cl-C_6H_4	Me	75	2000	3	95	95	862
14	4-Cl-C_6H_4	Me	65	200	0.5	99	97	862
15	4-Cl-C_6H_4	Me	75	2000	1	97	95	862
16	4-Cl-C_6H_4	Me	75	5000	12	80	93	862
17	3-MeO-C_6H_4	Me	75	200	0.5	86	93	862
18	2-NO_2-C_6H_4	Me	65	200	16	23	95	862
19	4-CN-C_6H_4	Me	65	200	3	99	95	862
20	Ph	Et	75	200	1	98	98	862
21	Ph	Et	75	1000	16	94	98	862
22	Ph	Pr^n	65	200	1	96	99	862
23	Ph	Pr^i	75	200	12	90	99	862
24	Ph	Bu^n	65	200	1	96	99	862
25	Ph	Cy	65	200	12	81	99	862
26	Bn	Me	65	200	12	95	99	862
27	2-Naphthyl	Me	55	200	1	93	96	862
28	3-Pyridyl	Me	50	200	2	99	90	862
29	2-Thienyl	Et	75	200	2	87	96	862
30	2-Thienyl	Pr^n	65	200	2	85	96	862

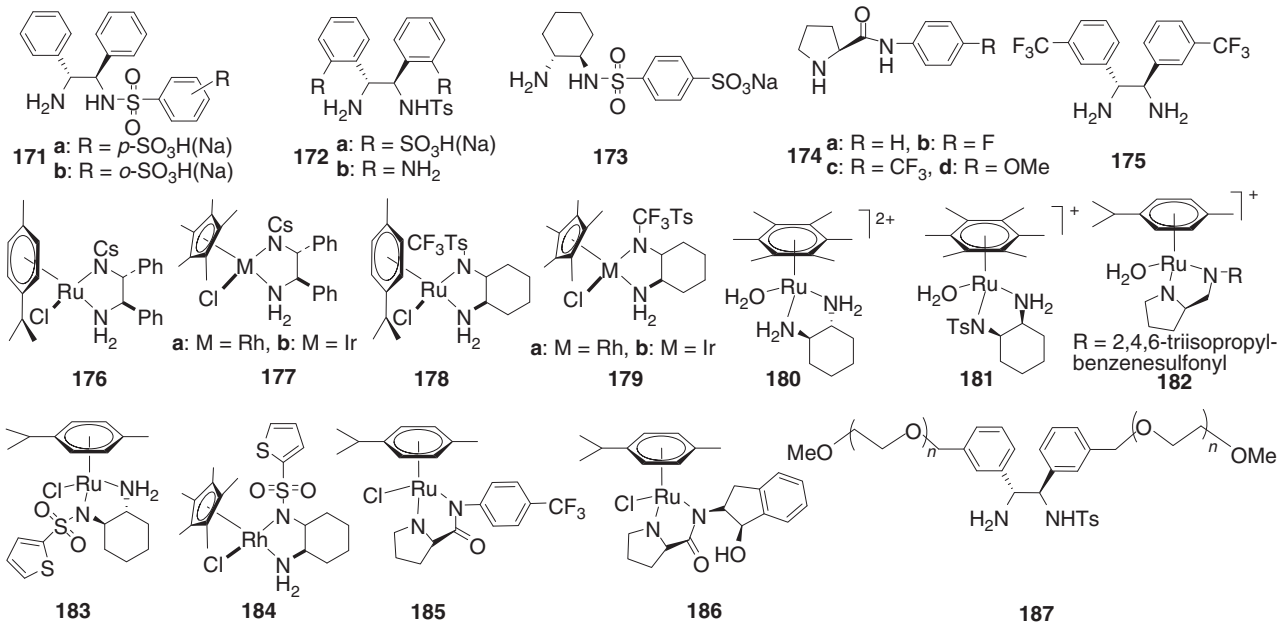


169

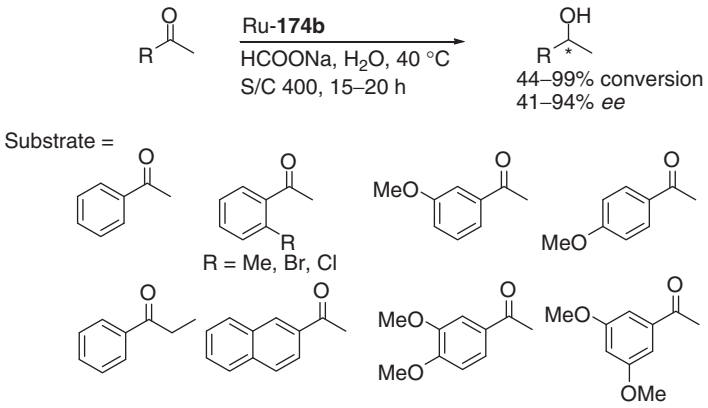


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Scheme 31 ATH catalysts featuring chirality relay.



Scheme 32 Representative ligands/catalysts for ATH in water.



Scheme 33 ATH of ketones by the catalyst Ru-**174b** with formate in water.

Although Ru-**187** was shown to be highly effective in neat water (see Section 8.04.3.2.5), the TsDPEN-containing **126** was equally good. Thus, using the precatalyst generated by reacting TsDPEN with $[RuCl_2(p\text{-cymene})]_2$, ACP was fully reduced into (*R*)-1-phenylethanol in 95% *ee* by HCOONa in water at 40 °C in 1 h at a S/C of 100. In comparison, the reaction run in the HCOOH-NEt_3 azeotropic mixture afforded a conversion of <2% in 1 h.[874] This initial finding has since been proved to be quite general; that is, water enables fast and enantioselective asymmetric reduction of unfunctionalized ketones by HCOONa with a range of metal–diamine catalysts. These catalysts can generally be prepared *in situ* by reacting an unmodified ligand with one of the metal dimers aforementioned without adding a base. They show varying solubilities in water, with those containing rhodium and iridium being more soluble than the ruthenium analogues. However, they display much higher solubility in ketones and alcohols. Hence, the reduction is often biphasic, with the catalysis probably taking place on water as mentioned in Section 8.04.3.1.

The performance of these catalysts in the ATH of the benchmark substrate ACP is shown in Table 35.[682,911] The monotosylated diamines, which have been shown to be successful ligands for ATH of ketones in IPA or the HCOOH-NEt_3 azeotropic mixture, can all be applied to the hydrogenation of ACP by HCOONa in water, with full conversions and up to 99% *ee*'s reached in short reaction times. In general, the ATH catalyzed by these catalysts in water is faster than in organic solvents, but with similar enantioselectivities. Under the given conditions, the Rh(III) catalysts appear to outperform both Ru(II) and Ir(III) in water in terms of catalytic activity and enantioselectivity, and the camphor-substituted **61** and **65** lead to the best enantioselectivity (Table 35). It is noted that the reaction with the Rh–diamine catalysts can be carried out effectively in the open air without degassing and/or inert gas protection throughout, thus making the reduction easier to operate than reactions catalyzed by most organometallic complexes (entries 21, 23, 29, and 32, Table 35).

Amino alcohol ligands were thought to be incompatible with formic acid as reductant in the past.[598,600] Table 35 shows that **128** and **132** do catalyze the hydrogenation of ACP by HCOONa in water; however, the reduction rates and enantioselectivities were much lower than those obtained with the diamines. The metal complexes containing (–)-ephedrine yielded better results than others in terms of rates and/or *ee*'s, and in general the iridium catalysts exhibited higher activity.[872,876,896] Terpene-based amino alcohol-Cr(II) complexes have also been explored, but only with limited success.[913,914]

The diamine-based catalysts have been applied to a range of ketones. Selected examples of simple ketones are shown in Scheme 34.[682,911] Unfunctionalized aromatic ketones and heterocyclic ketones are all viable substrates. The reduction is generally easy to perform, affording the chiral alcohols with high *ee*'s in a short reaction time for most of the substrates. S/C ratios of 100–10 000 have been demonstrated to be feasible.[710] Of particular note is the Rh-diamine catalyst **131a**,**179a**, which delivered high conversions for most of the ketones in a short reaction time and in most cases, the enantioselectivities were good to excellent, with *ee*'s up to 99% and TOFs close to 4000 h^{-1} in water in the open air.[873] The protocol works particularly well for some heteroaryl ketones. Thus, for instance, the reduction of 2-acetylfuran with **131a** was complete within 5 min, yielding (*R*)-1-(2-furyl)ethanol in 99% *ee*.

Amino acid-derived amides and hydroxamic acids have also been evaluated as ligands for ATH of ketones in aqueous media.[915,916] The catalysts were formed by treating a ligand with a Rh(III) or Ir(III) metal precursor, and the reduction was performed in water using HCOOLi as hydrogen source at 28 °C in the presence of 10 mol% SDS as surfactant, leading to high conversions (up to 99%) and enantioselectivities (up to 90% *ee*) for aryl ketones.[915] In related studies, the water-soluble Ru(II) complexes **182**, **185**, and **186** (Scheme 32) were applied to the aqueous reduction, affording good yields with *ee*'s up to 93%,[756–758] and a Ru(II)-prolinamide catalyst was explored for the reduction of more challenging aliphatic ketones in water; but only moderate enantioselectivities were obtained.[917]

The tethered complex **143** was shown to be effective in both organic and aqueous phase reduction of ketones.[816] Thus, ACP was reduced by HCOONa in water with **143** to give 100% conversion and 96% *ee* at 28 °C in 3 h, and in the case of 2-acetylfuran, the catalyst loading could be reduced to 0.01 mol% with an *ee* of 98% obtained. The catalyst even allows for the reduction of aliphatic ketones in water, albeit with slightly lower *ee*'s.

The PNNP ligand **137**, which is highly effective in ruthenium-catalyzed ATH of ketones in IPA,[622] could also be used for the aqueous-phase reduction when combined with $[IrHCl_2(COD)]_2$.[888,891] As shown in Scheme 35, the reduction of propiophenone

Table 35 ATH of Acp with various catalysts in aqueous media

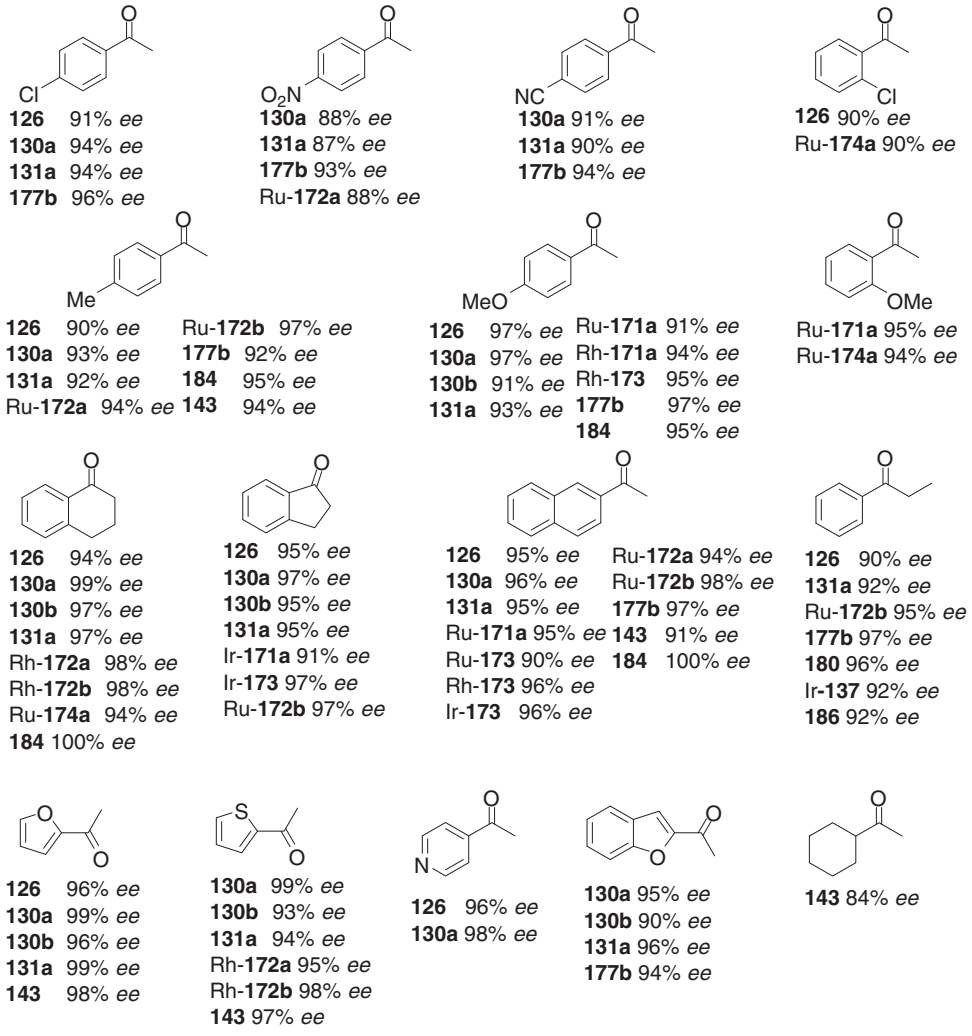
Entries	*Catalyst*	*[H]*[a]	*S/C*[b]	*Temperature (°C)*	*Time (h)*	*Conversion (%)*	ee *(%)*	*References*
1	Ru-**172a**	HCOONa	100	40	24	>99	95	901
2	Rh-**172a**	HCOONa	100	40	24	92	84	901
3	Ir-**172a**	HCOONa	100	40	24	10	58	901
4	Ru-**172b**	HCOONa	100	28	0.5	33	95	884
5	Rh-**172b**	HCOONa	100	28	0.5	97	97	884
6	Ir-**172b**	HCOONa	100	28	0.5	29	94	884
7	Ru-**174b**	HCOONa	400	40	18	98	69	903
8	**126**	HCOONa	100	40	1	99	95	874
9	**126**	F/T[c]	100	40	1.5	>99	97	710
10	**126**	F/T[c]	1 000	40	9	>99	96	710
11	**126**	F/T[c]	5 000	40	57	98	96	710
12	**126**	F/T[c]	10 000	40	110	98	94	710
13	**126**[d]	HCOONa	100	40	3	>99	96	883
14	**176**	HCOONa	100	40	2	99	97	890
15	**176**	HCOONa	1 000	40	20	95	96	890
16	**127**	HCOONa	100	40	2	99	85	873
17	**178**	HCOONa	100	40	2.5	>99	81	912
18	**128**	HCOONa	100	40	12	84	71	872
19	**128**	HCOONa	40	50	–	13	81	876
20	**130a**	HCOONa	100	40	0.5	99	97	906
21	**130a**[e]	HCOONa	100	40	0.5	99	97	906
22	**130b**	HCOONa	100	40	3.5	99	93	906
23	**130b**[e]	HCOONa	100	40	12	95	92	906
24	**177a**	HCOONa	100	40	0.7	99	99	890
25	**177a**	HCOONa	1 000	40	20	89	99	890
26	**177b**	HCOONa	100	40	0.7	99	97	890
27	**177b**	HCOONa	1 000	40	2.5	97	98	890
28	**131a**	HCOONa	100	40	0.25	>99	95	873
29	**131a**[e]	HCOONa	100	40	0.25	99	96	873
30	**131b**	HCOONa	100	40	3	99	93	873
31	**179a**	HCOONa	100	40	0.25	>99	94	912
32	**179a**[e]	HCOONa	100	40	0.25	>99	94	912
33	**179b**	HCOONa	100	40	1.5	>99	92	912
34	**132a**	HCOONa	100	40	20	92	55	872
35	**132b**	HCOONa	100	40	5	>99	27	872
36	**143**	HCOONa	200	28	3	100	96	816
37	**180**	HCOONa	100	60	2–5	>99	93	757
38	**182**	HCOONa	100	60	2–5	>99	44	757
39	**184**	HCOONa	100	40	0.5	100	93	885
40	**184**[f]	HCOONa	100	40	0.5	100	94	885
41	**184**[g]	HCOONa	100	40	0.5	100	94	885
42	**185**	HCOONa	20	30	12	100	67	875
43	**186**	HCOONa	20	30	40	100	84	875

[a]H] refers to hydrogen source.
[b]S/C is substrate to catalyst molar ratio.
[c]F/T = formic acid/triethylamine mixture.
[d]The reaction was carried out in PEG/H_2O.
[e]The reaction was carried out in open air without inert gas protection.
[f]In the presence of the surfactant cetyltrimethylammonium bromide.
[g]In the presence of the surfactant SDS.

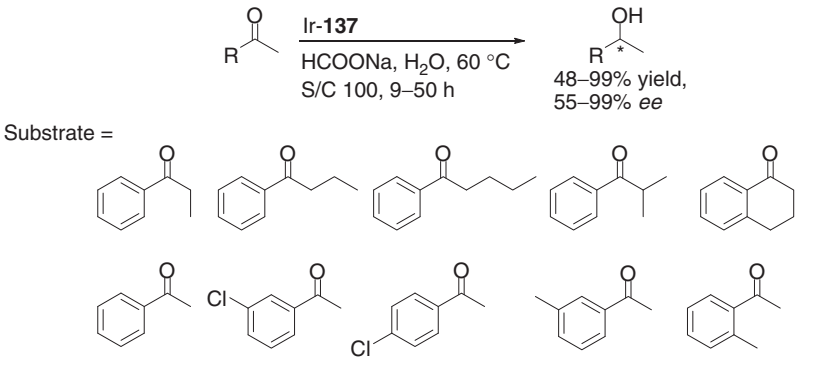
was completed in 9 h with 88% *ee* at 60 °C and an S/C ratio of 100 in the presence of a phase-transfer catalyst. The same reaction could be run without inert gas protection at a higher S/C ratio of 8000. In the latter case, the reaction afforded 80% isolated yield with 85% *ee* in 101 h. The reduction with the analogous Schiff base ligand led to a much reduced enantioselectivity (34% *ee* for propiophenone), indicating again the importance of the N–H moiety to the reduction.

8.04.3.2.4.2 ATH of functionalized ketones in water

Apart from the relatively simple ketones above, functionalized ketones have also been subjected to ATH in water. For instance, using the catalysts **130** or **177** under the conditions given in Table 35, ketones shown in Scheme 36 have been reduced with good enantioselectivities.

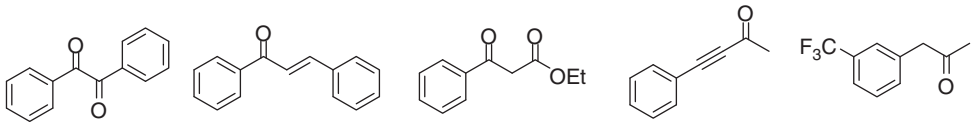


Scheme 34 Representative examples of ATH with metal-diamine catalysts in water.



Scheme 35 ATH of ketones by the Ir-**137** catalyst with formate in water.

Chiral α-hydroxy esters are useful building blocks in asymmetric synthesis.[890,918–920] ATH of α-ketoesters in water to produce these esters has been demonstrated with Ru(II) catalyst in the presence of a surfactant (Table 36).[920] Ru-**188**, generated from $[RuCl_2(p\text{-cymene})]_2$ and **188** which features a bulky tosyl variant, afforded good conversion and enantioselectivity. The less bulky ligands were less effective. There appear to be, however, some effects from the aryl group of the substrates. Thus, high *ee*'s were obtained with an electron-donating group on the aryl ring, whereas with electron-withdrawing substitutents, much lower *ee*



130a >99% *ee*
130b 97% *ee*

130a 93% *ee*
177b 92% *ee*

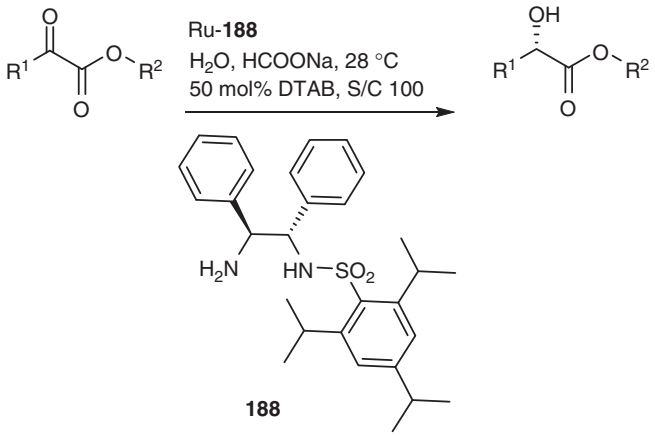
130a 80% *ee*

130a 92% *ee*
130b 85% *ee*

130a 98% *ee*
130b 95% *ee*

Scheme 36 Selected examples of ATH of functionalized ketones in water.

Table 36 ATH of ketoesters with a Ru(II) catalyst by formate in water



188

R^1	R^2	*Time (h)*	*Conversion (%)*	ee *(%)*	*References*
Ph	CH_3	1.5	100	90.9	920
2-Cl-C_6H_4	CH_3	1.5	100	75.5	920
4-Cl-C_6H_4	Et	1.5	100	69.9	920
4-MeO-C_6H_4	Et	2	100	90.1	920
2,4,6-Me_3-C_6H_2	Et	20	50	34.5	920
$Ph(CH_2)_2$	Et	1.5[a]	100	63.2	920
4-Me-C_6H_4	CH_3	1.5	100	99.2	920
2-MeO-C_6H_4	Et	2	100	33.0	920
Ph	Et	1.5	100	88.5	920
Ph	*i*-Pr	1.5	100	90.0	920
1-Naphthyl	Et	1.5	100	83.7	920
4-Me-C_6H_4	Et	1.5	100	91.1	920
2-Cl-C_6H_4	Et	1.5	100	78.6	920
2-Cl-C_6H_4	*i*-Pr	1.5	100	77.0	920

[a]S/C = 40.

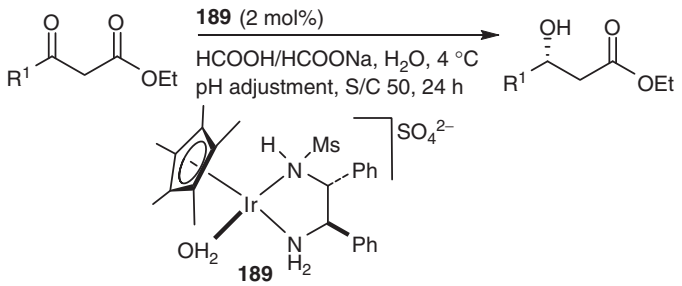
resulted. In addition, *ortho*-substitution erodes the *ee*. Surfactant was necessary, and dodecyl trimethyl ammonium bromide (DTAB) proved to be the best for conversion.

ATH of *β*-ketosters in water with Ir-**189** has been described (Table 37).[763] The catalyst can be readily prepared and is moisture and air stable. The reaction is conducted open to air and affords various *β*-hydroxy esters in high yield and selectivities. Interestingly, the yield and enantioselectivity do not vary significantly with pH under the conditions employed (e.g., entries 1–4, Table 37).

As with the ATH of *α*-ketoesters, catalytic reduction of *α*-substituted aryl ketones with high enantioselectivity is still challenging. An aqueous-phase ATH protocol has recently been reported, using Ir(III) catalysts **190–191**, which bear an electron-deficient perfluorinated sulfonamide ligand or -CF_3 substituent on the phenyl rings of the diamine ligands (Table 38).[921,922] A range of *α*-cyano aryl ketones were reduced by HCOOH in water at a relatively low catalyst loading. Electron-rich and -deficient groups at the *meta* and *para* positions of the aryl ring did not adversely affect the selectivity nor the conversion, and heteroaromatic ketones, such as furan and thiophene-containing ones, are viable substrates as well.

α-Nitro aryl ketones were also reduced efficiently by using either **190** or **191**, although a modest increase in catalyst loading was necessary to achieve full conversion.[921,922] Still interestingly, reduction of an *α*-chloro aryl ketone was shown to be feasible, affording high yield and *ee* (Table 38).[921] Such chiral chloro-alcohols are precursors to terminal epoxides. In contrast to the ATH

Table 37 ATH of β-ketosters with formate in water



Entries	*R^1*	*pH*	*Yield (%)*	ee *(%)*	*References*
1	Ph	8.0	96	96	763
2	Ph	3.5	98	92	763
3	Ph	5.0	98	96	763
4	Ph	10.0	97	96	763
5	4-F-C_6H_4	8.0	95	94	763
6	4-Cl-C_6H_4	8.0	94	92	763
7	4-Br-C_6H_4	8.0	96	94	763
8	4-I-C_6H_4	8.0	91	93	763
9	3-Cl-C_6H_4	8.0	92	93	763
10	2-Cl-C_6H_4	8.0	97	70	763
11	4-MeO-C_6H_4	8.0	97	95	763
12	4-NO_2-C_6H_4	8.0	99	87	763
13	2-Naphthyl	8.0	96	94	763
14	3-Pyridyl	8.0	77	73	763
15	2-Furyl	8.0	90	96	763

of ACPs, which performs well at neutral pH, ATH of these α-cyano and nitro ketones with catalyst **190** necessitates more acidic conditions, with the former preferentially reduced at pH 3.5 and the latter at 2.0.

A simpler catalytic system has appeared which enables efficient ATH of α-cyano aryl ketones as well as ketone esters and simple aryl ketones. Using **126** as catalyst, the reduction was performed in an emulsion formed by CH_2Cl_2 in aqueous HCOONa in the presence of a surfactant, tetrabutylammonium iodide (TBAI).[923,924] Table 39 shows the results obtained with α-cyano aryl ketones, and β-ketoesters and an amide. The system tolerates both solid and liquid substrates, affording excellent enantioselectivities in most cases. For example, ATH of β-keto amide (last entry, Table 39) afforded the corresponding chiral alcohol with 90% yield and 98% *ee* in 1 h, whereas the same reaction in the azeotropic HCOOH-NEt_3 mixture led to 93% yield and 86% *ee* in a longer time of 22 h.[925]

8.04.3.2.4.3 ATH of aliphatic ketones in water

Asymmetric reduction of aliphatic ketones with high enantioselectivities is challenging in either organic solvents or water. A novel diamine catalyst formed from the surfactant-like ligand **192** and $[Cp^*RhCl_2]_2$ has been demonstrated to be efficient.[926,927] As shown in Table 40, a wide range of aliphatic ketones were reduced to chiral alcohols with up to 95% *ee*. The reaction rate and enantioselectivity vary with the solvent, temperature, and the chain length of the aliphatic ketones. It has been observed that the catalyst forms metallomicelles in water, with the ATH taking place in the micelles. Synergistic effects between the metal-catalyst center and the hydrophobic microenvironment of the core in the metallomicelle led to the high enantioselectivity.

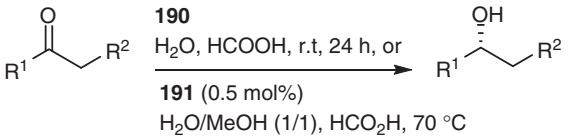
8.04.3.2.5 ATH of ketones with immobilized catalysts in water

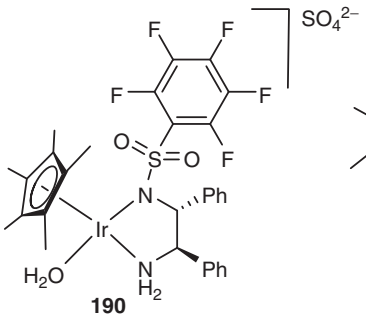
Catalyst separation is an important issue in homogeneous catalysis, and this can be addressed by using catalysts that bear water-soluble ligands or are immobilized on solids. The unmodified chiral diamine ligands presented above are soluble in common organic solvents but generally insoluble in water, and thus present a problem to catalyst separation and reuse for the aqueous-phase TH or ATH. This has been dealt with, with various degrees of success in recent studies, which are briefly summarized here.

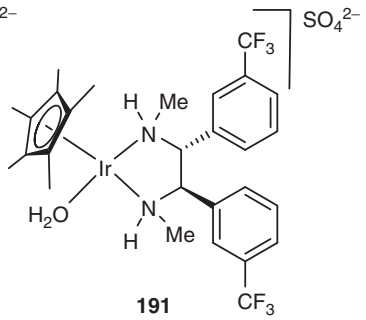
The half-sandwich catalysts of Sections 8.04.3.1–8.04.3.2 are often (partially) soluble in water but insoluble in nonpolar solvents. In this case, the product can be extracted with a nonpolar solvent such as diethyl ether without recourse to purpose-built water-soluble catalysts.[682,870,911] A good example is the reduction catalyzed by Ru-**174b** mentioned earlier, which could be reused up to 6 times without compromising *ee*'s.[905] Recently, a similar catalyst was also shown to be effective in the ATH of aromatic ketones and recyclable in water.[887]

For more practical and easier catalyst/product separation, highly water-soluble ligands or those that are supported on solid surfaces are desirable. As described in Section 8.04.3.2.4, Ru-**172** has been shown to be an efficient catalyst for ATH of ketones and

Table 38 ATH of α-substituted aryl ketones with HCOOH in water



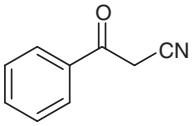
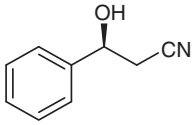
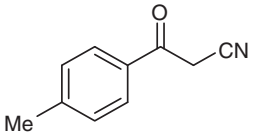
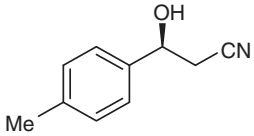
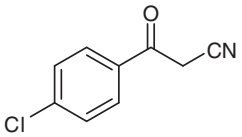
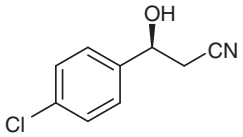
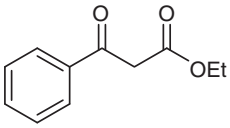
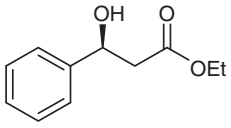
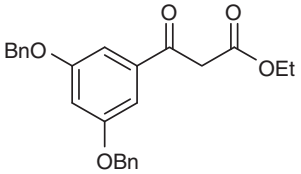
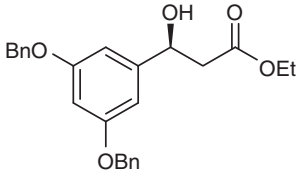
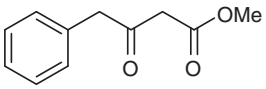
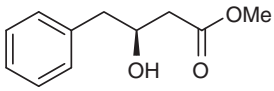
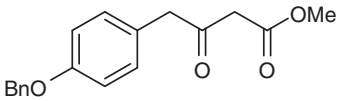
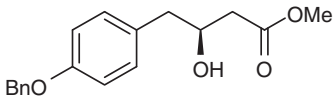
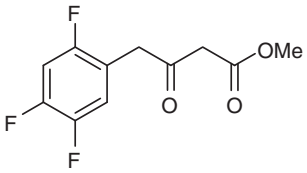
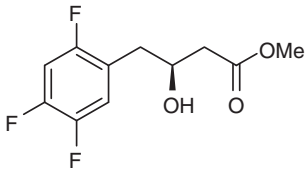
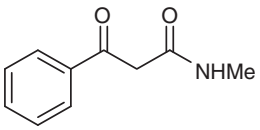
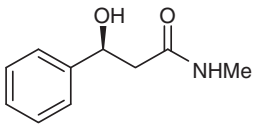




R^1	R^2	Catalyst	S/C	pH	Time (h)	Yield (%)	ee (%)	References
Ph	CN	**190**	400	3.5	24	96	94	921
Ph	CN	**190**	1000	3.5	24	83[a]	94	921
Ph	CN	**191**	200	–	12	96	95	922
3-Cl-C_6H_4	CN	**190**	400	3.5	24	90	90	921
3-MeO-C_6H_4	CN	**190**	400	3.5	24	96	95	921
3-MeO-C_6H_4	CN	**191**	200	–	15	91	97	922
4-MeO-C_6H_4	CN	**191**	200	–	20	90	90	922
2-MeO-C_6H_4	CN	**191**	200	–	24	90	99	922
4-F-C_6H_4	CN	**190**	400	3.5	24	95	91	921
4-F-C_6H_4	CN	**191**	200	–	18	85	87	922
4-Me-C_6H_4	CN	**190**	400	3.5	24	96	93	921
4-Me-C_6H_4	CN	**191**	200	–	18	93	92	922
2-Me-C_6H_4	CN	**191**	200	–	24	92	99	922
2-I-C_6H_4	CN	**191**	200	–	44	45	99	922
4-Br-C_6H_4	CN	**191**	200	–	18	87	90	922
3-NO_2-C_6H_4	CN	**191**	200	–	12	96	87	922
4-CN-C_6H_4	CN	**190**	400	3.5	24	97	86	921
2-Naphthyl[b]	CN	**190**	400	3.5	24	95	96	921
2-Naphthyl	CN	**191**	200	–	15	88	95	922
2-Furyl	CN	**190**	400	3.5	24	83	96	921
2-Thienyl	CN	**190**	400	3.5	24	94	92	921
1-Thienyl	CN	**191**	200	–	20	92	73	922
Ph	NO_2	**190**	200	2.0	24	94	93	921
Ph	NO_2	**191**	200	–	5	85	95	922
2-Me-C_6H_4	NO_2	**191**	200	–	18	51	99	922
4-But-C_6H_4	NO_2	**191**	200	–	8	77	92	922
4-But-C_6H_4	NO_2	**190**	200	2.0	24	92	99	921
3-Br-C_6H_4	NO_2	**190**	200	2.0	24	54	91	921
3-Cl-C_6H_4	NO_2	**190**	200	2.0	24	95	95	921
2-MeO-C_6H_4	NO_2	**190**	200	2.0	24	93	83	921
2-MeO-C_6H_4	NO_2	**191**	200	–	12	75	98	922
3-Br-C_6H_4	NO_2	**191**	200	–	15	35	94	922
3-Br-C_6H_4[c]	NO_2	**191**	200	–	3	78	93	922
3-Cl-C_6H_4[c]	NO_2	**191**	200	–	2	81	92	922
2-Naphthyl	NO_2	**191**	200	–	10	78	93	922
2-Naphthyl[b]	NO_2	**190**	200	2.0	24	53	93	921
2-Thienyl[c]	NO_2	**191**	200	–	9	50	76	922
Ph	Cl	**190**	400	3.5	24	93	91	921

[a]The reaction time was 72 h.
[b]10 mol% hexafluoroisopropanol was added.
[c]H_2O/HCOOH (1/1) mixture was used.

Table 39 ATH of α-functionalized ketones with catalyst **126** in emulsions[a]

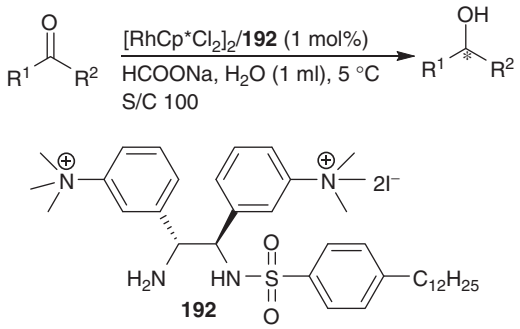
Substrates	*Products*	*Time (h)*	*Yield (%)*	ee *(%)*	*References*
		3.5	>99	99	923
		6.5	>99	94	923
		4	>99	95	923
		0.9	>99	97	923
		1.5	98	97	923
		1.5	98	48	923
		1.5	93	53	923
		0.9	95	72	923
		1	90	98	923

[a]Conditions: 1.0 mmol of substrate, 5 M HCOONa (20 ml), DCM (1 ml), TBAI (2.0 mmol), 40 °C, S/C = 100.

imines in water. Given the hydrophilic nature of **172**, the catalyst can be readily separated from the product by simple decanting.[901] The PEG-supported **187** represents an example of water-soluble polymeric ligands. As with its nonsupported counterpart, Ru-**187** is also highly effective for the ATH in water for a wide range of aromatic ketones, with results comparable to those obtained with **126**. The advantage in using Ru-**187** is that the product can be easily separated from the catalyst-containing aqueous phase. An example is seen in the reduction of ACP by HCOONa with Ru-**187** in water, where the product was extracted with diethyl ether.[900] An ICP analysis showed that 0.4 mol% of ruthenium leached into the organic phase. Remarkably, the PEG-immobilized catalyst could be reused 14 times with no loss in enantioselectivity, demonstrating its excellent recyclability and durability under aqueous conditions. In contrast, when carried out in HCOOH-NEt_3 without water, recycling was possible only for two runs without the rates and *ee*'s being eroded.[909]

A variety of diamine ligands have been immobilized though a substituent at one of the nitrogen atoms. Examples are found in Scheme 37, with their use in the reduction of the benchmark ACP given in Table 41. The PEG-supported **199** is effective and

Table 40 ATH of aliphatic ketones in water



Entries	*R^1*	*R^2*	*Time (h)*	*Conversion (%)*	ee *(%)/configuration*	*References*
1	Bu^n	CH_3	37	98	76/*S*	926,927
2	C_6H_{13}	CH_3	24	92	90/*S*	926,927
3	C_8H_{17}	CH_3	24	97	92/*S*	926,927
4[a]	C_9H_{19}	CH_3	48	97	92/*S*	926,927
5[a]	$C_{10}H_{21}$	CH_3	48	93	94/*S*	926,927
6[a]	$C_{11}H_{23}$	CH_3	48	74	94/*S*	926,927
7[b]	C_8H_{17}	Et	48	75	81/*S*	926,927
8[b]	C_8H_{17}	Pr^n	48	45	72/*S*	926,927
9	$Me_2(CH_2)_2$	CH_3	24	95	84/*S*	926,927
10	$Me_2(CH_2)_3$	CH_3	24	97	91/*S*	926,927
11	$Me_2C{=}CH(CH_2)_2$	CH_3	37	96	80/*S*	926,927
12[c]	$Me_2C{=}CH(CH_2)_2CH{=}CH(CH_2)_3$	CH_3	72	99	90(*Z*)/87(*E*)	926,927
13	Cy	CH_3	24	93	95/*S*	926,927
14	$PhCH_2CH_2$	CH_3	48	99	90/*S*	926,927
15	$Me_3COC(O)O(CH_2)_2$	CH_3	37	90	86	926,927
16	$Cl(CH_2)_4$	CH_3	24	96	83/*S*	926,927
17	Ph	CH_3	48	97	97/*R*	926,927
18[d]	Ph	CH_3	24	99	96/*R*	926,927

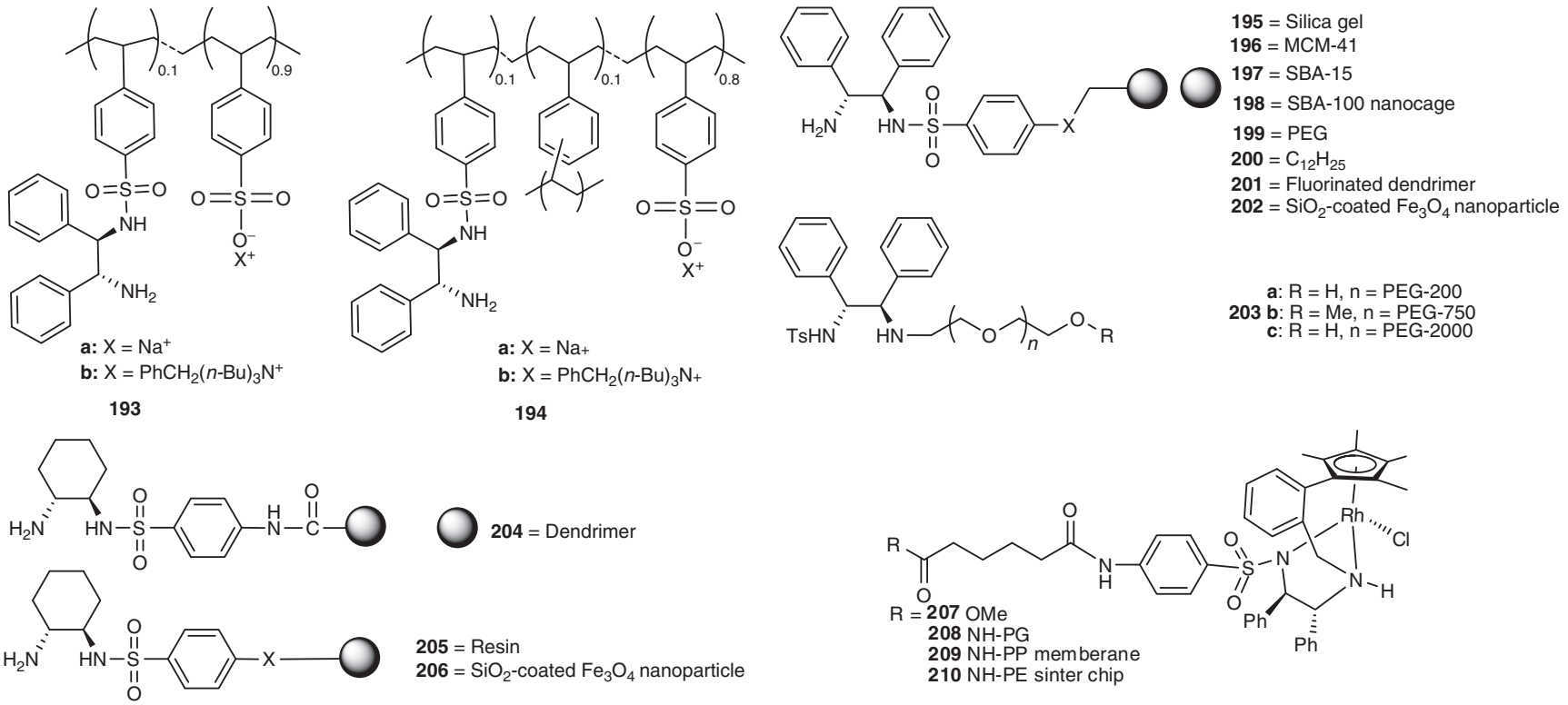
[a] 2 ml water was used for solid ketones.
[b] S/C = 50.
[c] *Z*/*E* ratio was 38.8:61.2.
[d] The reaction was carried out at 40 °C.

recyclable in Ru(II)-catalyzed ATH in water.[877,920,928–930] Similar results were obtained with the ligands **203**, in which the PEG chain is attached to the amino moiety (entries 13–15, Table 41).[930] Unlike **199**, the ligand **200** bears a long, lipophilic aliphatic chain. For ATH in micelles created by SDS, the aliphatic chain increases the solubility of the catalyst in water. Indeed, the catalyst works well for aryl ketones at room temperature, furnishing good to excellent conversion and *ee*. It is, however, less efficient with aliphatic ketones.[882]

The polystyrene-supported diamine **193** has been combined with $[RuCl_2(p\text{-cymene})]_2$ and $[Cp^*RhCl_2]_2$.[894,931–934] As shown in Table 41, ATH of ACP with Ru-**193** by HCOONa in water affords excellent enantioselectivity (entry 2, Table 41).[894] The cross-linked polymer **194** has also proved to be efficient for the reduction of ketones in water, and the catalyst can be recycled 5 times, giving about the same *ee* values in each run (entry 3, Table 41). These polymeric catalysts are also effective for ATH of imines in MeCN with the azeotropic $HCOOH/NEt_3$ as hydrogen source.[934] For these catalysts, the microenvironment within the polymer network appears to be important to stereoselection.

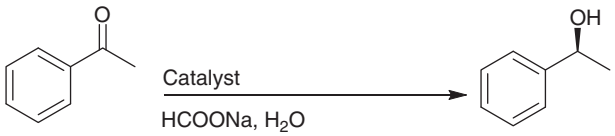
Dendrimer-supported ligands provide yet another example of recyclable catalysis. An Ru(II) catalyst, Ru-**201**, derived from the fluorinated dendritic ligand **201**, is shown to be viable for the asymmetric reduction of ketones, exhibiting remarkable recyclability (entry 10, Table 41).[924] In the ATH of ACP, excellent conversion and *ee*'s were obtained in the first 9 runs with no extension of reaction time, and the reaction still afforded 93% conversion and 91% *ee* in 18 h in the 24th run. Likewise, the first-generation, dendritic ligand **204** ligated to Rh(III) could be reused up to 6 times without enantioselectivity eroded (entry 16, Table 41).[892] The S/C ratio could be increased to 10 000/1.

Tethered Rh(III)-diamine catalysts have been immobilized on amine-functionalized hyperbranched polyglycerol (PG), polypropylene (PP), and polyethylene (PE) (**207–210**, Scheme 37).[939,940] The catalysts give excellent enantioselectivties in ATH of ketones in water. Using a HCOONa/HCOOH (1/1) mixture as hydrogen source, catalyst **210** can be used 7 times without loss of enantioselectivity in the reduction of ACP at 40 °C and a S/C ratio of 430. The reduction is faster in the presence of HCOOH.



Scheme 37 Immobilized ligands and catalysts for ATH in water.

Table 41 ATH of ACP with supported catalysts



Entries	*Catalyst*	*Conditions*	*Run*	*Time (h)*	*Conversion (%)*	ee *(%)*	*References*
1	Ru-**187**	ACP (1 mmol), H_2O (2 ml), 40 °C, S/C 100	1–14	1–8	>99–87	93–92	900
2	Ru-**193**	ACP (1 mmol), H_2O (2 ml), 40 °C, S/C 100	1	3	100	98	894
3	Ru-**194**	ACP (1 mmol), H_2O (2 ml), 40 °C, S/C 100	1–5	3	100	98–97	894
4	Ru-**195**	H_2O (2 ml), 40 °C, S/C 100, TBAB (4 mol%)	1–7	2–60	>99–60	96	899
5	Ru-**196**	ACP (0.4 mmol), H_2O (0.4 ml), 40 °C, SDS	1	22	>99	87	897
6	Ru-**197**	ACP (0.4 mmol), H_2O (0.4 ml), 40 °C, SDS	1–4	8–47	>99–43	92–94	897
7	Ru-**198**	ACP (0.1 mmol), H_2O (0.2 ml), 40 °C, S/C 100	1	2.5	>99	92	935
8	Ru-**199**	ACP (1 mmol), H_2O (2 ml), 40 °C, S/C 100	1–8	2–4	>99–96	97–95	877
9	Rh-**200**	H_2O (2.5 ml), 28 °C, SDS (10 mol%), S/C 100	1	17	97	97	882
10	Ru-**201**	H_2O (2 ml), 40 °C, TBAI (0.5 equivalent), S/C 100	1–26	4–24	>99–93	97–88	924
11	Rh-**202**	H_2O (2 ml), 40 °C, TBABr (0.4 equivalent), S/C 500	1–10	8	97–92	98–93	936
12	Ir-**202**	H_2O (2 ml), 40 °C, TBABr (0.4 equivalent), S/C 500	1–10	8	99–96	89–86	937
13	Ru-**203a**	H_2O (1 ml), 40 °C, PEG-200 (1.0 g), S/C 100	1–4	6	99–87	94–93	930
14	Ru-**203b**	H_2O (1 ml), 40 °C, PEG-750 (1.0 g), S/C 100	1–7	6–12	>99–80	94–93	930
15	Ru-**203c**	H_2O (1 ml), 40 °C, PEG-2000 (1.0 g), S/C 100	1–10	6	>99–85	94	930
16	Rh-**204**	ACP (0.4 mmol), H2O (1 ml), 40 °C, S/C 100	1–6	0.67–1.5	>99–85	96–94	892
17	Rh-**205**	H_2O (1 ml), 40 °C, S/C 100	1–3	–	98–31	84–80	938
18	Rh-**206**	H_2O (2 ml), 40 °C, TBABr (0.4 equivalent), S/C 500	1–10	8	>99–97	88–84	937
19	**207**	ACP (0.43 mmol), H_2O (1 ml), 40 °C, S/C 100	1	6	100	98	939
20	**208**	ACP (0.43 mmol), H_2O (1 ml), 40 °C, S/C 100	1	6	100	98	939
21	**209**	ACP (1 mmol), H_2O (40 ml), 50 °C, S/C 450	1	8	100	98	939
22[a]	**210**	ACP (1 mmol), H_2O (10 ml), 40 °C, S/C 430	1–7	4	82–59	98	939

[a]1:1 HCOONa/HCOOH.

Other catalysts which are soluble in ionic liquids or are immobilized on polymers and other materials have also been investigated for ATH.[682]

Inorganic supports have been explored as well, as seen in the ligands **195–198** and **202**.[884,892,895,897,899,931,935,938–948] These ligands are effective in both organic and aqueous media, with **195** being the most efficient. Although taking a long time to complete in recycled runs, even in the presence of a surfactant, the catalyst displayed excellent recyclability in terms of enantioselectivity–up to 11 recycles without loss of *ee*'s.[897,899]

Catalyst separation could be made easy with molecularly imprinted catalysts, with the potential benefit of enzyme-like shape selectivity. This is seen in an example where the catalyst **126** is immobilized on SiO_2 surface and imprinted onto hydrophobic organic polymer matrices with a chiral alcohol product, (*R*)-1-(*o*-flurophenyl)ethanol, as template.[949] The imprinted catalyst showed fine shape selectivity and good enantioselectivity (80% *ee*) in the ATH of *o*-fluoroacetophenone in water.

Magnetically recoverable catalysts have also been explored. The chiral ligands, such as TsDPEN and TsCYDN, were modified and attached to SiO_2-coated Fe_3O_4 nanoparticles (**202**, **206**, Scheme 37).[936,937] When combined with a rhodium or iridium precursor, the resulting catalyst exhibits high catalytic activities and enantioselectivities in the reduction of aromatic ketones, and it can be recovered easily via a small magnet and reused 10 times in the reduction of ACP in water without obviously losing the activity and enantioselectivity (entries 11–12, and 18, Table 41).

8.04.3.3 Transfer Hydrogenation of CO_2

CO_2 can be reduced under TH conditions, although this has been much less studied than using H_2. An example is seen in the NHC catalysts mentioned earlier (**84–86**, **88–91**, Scheme 19). Using the water-soluble Ir(III)-NHC complex, [IrI_2(OAc)(bis-NHC)] (**90**), CO_2 was reduced to formate in a mixture of H_2O/IPA (9:1, v/v), with up to 2700 ton obtained. The reaction was performed at 110 °C and 50 bar CO_2 in the presence of 0.5 M KOH.[577]

8.04.4 Concluding Remarks

Reduction of C═O to CHOH can be affected with catalytic hydrogenation using H_2 and with TH using a range of hydrogen sources, with the most popular being IPA and formic acid. Operating under different conditions, these two methods of reduction

are usually complementary. Various carbonyl compounds, including aryl ketones, alkyl ketones, ketoesters, unsaturated ketones, carbon dioxide, and aldehydes, have been reduced with high yields and high chemo and/or enantio-selectivities. Catalysts based on Rh, Ru, and Ir dominate the scene. To facilitate their recovery and reuse, water has been used as a solvent and heterogeneous catalysts have been developed. However, there are still challenges that remain to be addressed in this area of reduction chemistry, including, for example, enantioselective reduction of ketones bearing aliphatic or sensitive groups and minimization of the use of noble metal catalysts.

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8.05 Reduction of C═N to CHNH by Metal-Catalyzed Hydrogenation and Transfer Hydrogenation

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Glossary

ee Enantiomeric excess, defined as $100 \times |R - \%S|R + \%S)$, measure for the enantioselectivity of a catalyst.

s/c Substrate to catalyst ratio (mol%); measure for the potential catalyst productivity.

tof Turnover frequency (ton/reaction time, h^{-1}); measure for the catalytic activity.

ton Turnover number (mol product/mol catalyst); measure for the actual catalyst productivity.

8.05.1 Introduction

Chiral amines are important targets for synthetic chemists and attempts to prepare such compounds via enantioselective hydrogenation of an appropriate C═N function date back to 1941.[1] At first, only heterogeneous hydrogenation catalysts such as Pt black, Pd/C, or Raney nickel were applied. These classical hydrogenation catalysts were modified with chiral auxiliaries in the hope to achieve chiral induction, i.e., transfer of chirality from the auxiliary to the reactant. Only few substrates were studied and not surprisingly, enantioselectivities were low and not always reproducible.[2] The first reports on homogeneous Ru[3] and Rh[4,5] diphosphine complexes appeared in 1975, but useful enantioselectivities were reported only in 1984 by the Marko group.[6] As can

 doi:10.1016/B978-0-08-097742-3.00807-7

be seen from the compilation in Table 1, remarkable progress has been made in the 1990s and now, a variety of very selective catalysts are available for different types of C═N functions.[7–11] Moreover, the first industrial application was announced in 1996.[12,13]

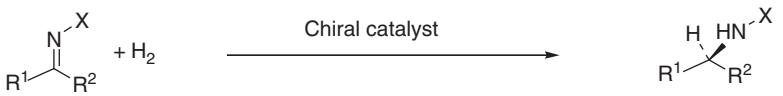
Table 1 Selected milestones for the enantioselective hydrogenation of C═N functions

Year	*Substrate*	*Catalyst*	*Chiral auxiliary*[a]	*ee (%)*	*Comment*	*References*
1941	Oxime	Pt black	Menthoxyacetic acid	3	First documented experiment	1
1958	Dioxime	Supported Pd	Silk fibroin	15	Chiral support	2
1975	Oxime	Ru complex	Diop	15	Homogeneous Ru catalyst	3
1975	Imine	Rh complex	Diop	22	Homogeneous Rh catalyst	4
1984	C═N–Alk	Rh complex	Bdpp	72	First useful *ee* value	6
1989	C═N–Alk	Rh complex	$Bdpp_{sulf}$	94	First very high *ee* value	7
1990	C═N–Ar	Ir complex	Bdpp	84	Homogeneous Ir catalyst	8
1992	Cyclic imine	Ti complex	Ebthi	99	Homogeneous Ti catalyst	9
1992	C═N–X	Rh complex	Duphos	96	Acyl hydrazone	10
1996	Cyclic imine	Ru complex	DpenTs	97	Transfer hydrogenation	11
1996	MEA imine	Ir complex	Josiphos	80	First industrial application	12

[a]For structures of ligands see **Figure 1**.

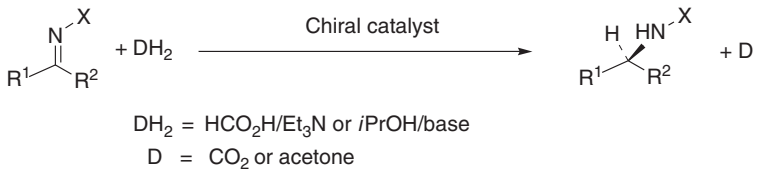
Despite this progress, the enantioselective hydrogenation of prochiral C═N groups such as imines, oximes, or hydrazones to obtain the corresponding chiral amines still represents a major challenge. Whereas many highly enantioselective catalysts have been developed for the asymmetric hydrogenation of alkenes and ketones bearing various functional groups, much fewer catalysts are effective for the hydrogenation of substrates with a C═N function. There are several reasons that might explain this situation. On one hand, the enantioselective hydrogenation of enamides and other C═C groups and later also of C═O compounds was so successful that most attention was directed to these substrates. On the other hand, C═N compounds have some chemical peculiarities that make their stereoselective reduction more complex than that of C═O and C═C compounds. Even though the preparation starting from the corresponding amine derivative and carbonyl compound is relatively simple, complete conversion is not always achieved and formation of trimers or oligomers can occur. In addition, the resulting C═N compounds are often sensitive to hydrolysis and because many of the homogeneous catalysts can complex with both the starting material and the reduction product, catalytic activity is often low. Further problems are the fact that imines can be in equilibrium with the corresponding enamine which can also be reduced but with different selectivity and the coexistence of *syn*/*anti* isomers which again might be reduced with different selectivity as shown for the Ru/binap-catalyzed hydrogenation of an oxime.[14] Generally, C═N substrates are prepared from the corresponding ketone and amino derivative and are hydrogenated as isolated and purified compounds. The purification of the imine is important, because the presence of traces of primary amines often negatively affects catalyst productivity. However, reductive amination where the C═N function is prepared *in situ* is attractive from an industrial point of view and indeed a number of successful examples have been reported. In general, the same metal precursor ligand combination identified for the isolated imine can be used but in many cases either the solvent has to be adapted or additives such as molecular sieves are necessary for good results.

A critical overview will be provided on the enantioselective hydrogenation (**Scheme 1**) and transfer hydrogenation (**Scheme 2**) of various C═N functions catalyzed by chiral organometallic catalysts. Because the net transformation is the same for both types of reduction, the results for the various substrate types will be summarized together. In all the tables, the use of a hydrogen donor is mentioned under 'reaction conditions,' whereas the pressure is given when H_2 was used. The discussions will be focused on catalysts which are able to reduce different C═N functions with synthetically useful *ee* values (usually >90%). The basis for this study is a comprehensive overview[15] which was updated covering the relevant literature up to June 2012 and several reviews that have recently been published.[16–23] Alternative reduction methods for C═N functions such as organocatalytic transfer hydrogenation, hydride reductions, hydrosilylation, and biocatalysis will be addressed briefly.



X = H, R_3, OH, $NHCOR_3$, SO_2R_3, $POPh_2$, CO_2R_3
$R_{1–3}$ = alkyl (het)aryl

Scheme 1



Scheme 2

8.05.2 Ligands and Catalysts

Most effective catalysts for the enantioselective (transfer) hydrogenation of C═N bonds are homogeneous complexes consisting of a central metal ion, one or more (chiral) ligands, and anions. There is always an interdependence between the nature of the C═N function and the most suitable catalyst. To get an effective catalyst for any specific substrate, not only the right metal but also the right ligand and (with somewhat lower priority) the right anion have to be chosen. Other reaction parameters are solvent, temperature, and hydrogen pressure, and sometimes additives are required for good performance. Experience has shown that low-valent Ir, Ru, Rh, and Pd complexes containing (bidentate) phosphorus and/or nitrogen ligands are the most effective and the most versatile hydrogenation catalysts. Not surprisingly, a majority of the past as well as of the current research is focused on this type of complexes. Complexes which are able to activate dihydrogen directly have somewhat different ligand requirements from transfer hydrogenation catalysts which formally transfer a hydrogen molecule from a suitable donor. For some applications, biscyclopentadienyl Ti and Zr complexes and recently some Pd diphosphine complexes have also shown very good enantioselectivity.

8.05.2.1 Chiral Ligands

A plethora of chiral ligands has been developed for enantioselective hydrogenation. However, relatively few have proved to be effective as well as practical and have been actually applied in catalytic studies.[24] For the reduction of C═N functions, the most effective and most frequently used ligands are depicted in **Figure 1**. The naming of a new ligand does not follow any rules. Quite common are names with a connection to a company or university such as duphos (DuPont) or to a person such as josiphos (Josephine Puleo, Solvias) or tangphos (Wenjun Tang, Penn State University). Also widespread are names related to a structural characteristic, for example, binap and abbreviations of chemical names such as 1,3-bisdiphenylphosphino pentane (bdpp). In this review the authors use the name given by the creator of the ligand using lower case letters only, except when a chemical group is specified as in MeO-biphep (**Figure 1**). For other ligands which have not been named, a bold number will be used with a short descriptor such as ferrocene P^N **L1**.

8.05.2.2 Metal Complexes (Figure 2)

8.05.2.2.1 Rh catalysts

Rhodium diphosphine catalysts can be easily prepared from a Rh precursor and a chiral ligand. The catalysts are either prepared *in situ* or applied as preformed and isolated complexes. In most cases, the *in situ* method is preferred because it offers greater flexibility but there are cases where preformed complexes are required, either because the ligand is not stable or because the performance is superior. The most common and commercially available Rh precursors are $[Rh(cod)Cl]_2$ and $[Rh(nbd)Cl]_2$ complexes for catalysts with a covalently bound anion and $[Rh(nbd)_2]BF_4$ for cationic catalysts. Preformed complexes are of the type [Rh(nbd)(diphosphine)]X (X = BF_4, OTf, SbF_6, and ClO_4). The catalytically active species are obtained by hydrogenation of the diene, a process that can take some time.[25] Cp^*Rh complexes with a tosylated diamine or an amino alcohol ligand are active transfer hydrogenation catalysts.

8.05.2.2.2 Ir catalysts

Among the various catalyst types investigated in recent years for the hydrogenation of imines, Ir diphosphine, and Ir phosphine oxazoline complexes have proved to be most versatile but monodentate phosphoramidites also give active catalysts. The Ir phosphine catalysts are usually generated *in situ* from commercially available $[Ir(cod)Cl]_2$ and a chiral diphosphine and often used in presence of iodide or iodine. Also common are preformed complexes of the type $[Ir(diphosphine)Cl]_2$ or [Ir(diphosphine)(cod)]BF_4 and some Ir(III) complexes like HBrIr(diphosphine)CH_3CO_2. The Ir/phox catalysts, [Ir(phox)(cod)]X, developed by Pfaltz are prepared starting from $[Ir(cod)Cl]_2$ and the P^N ligand, then the chloride is exchanged for a noncoordinating anion X. The best results have been reported when X = $B(3,5\text{-}(CF_3)_2C_6H_3)_4$ (BARF), which is a rather expensive anion and for this reason the recent report that cheaper methylaluminoxanes can also be used is of industrial interest.[26] As for Rh, the diene has to be removed to get the active Ir catalyst. Cp^*Ir complexes with a tosylated diamine or an amino alcohol ligand are active transfer hydrogenation catalysts.

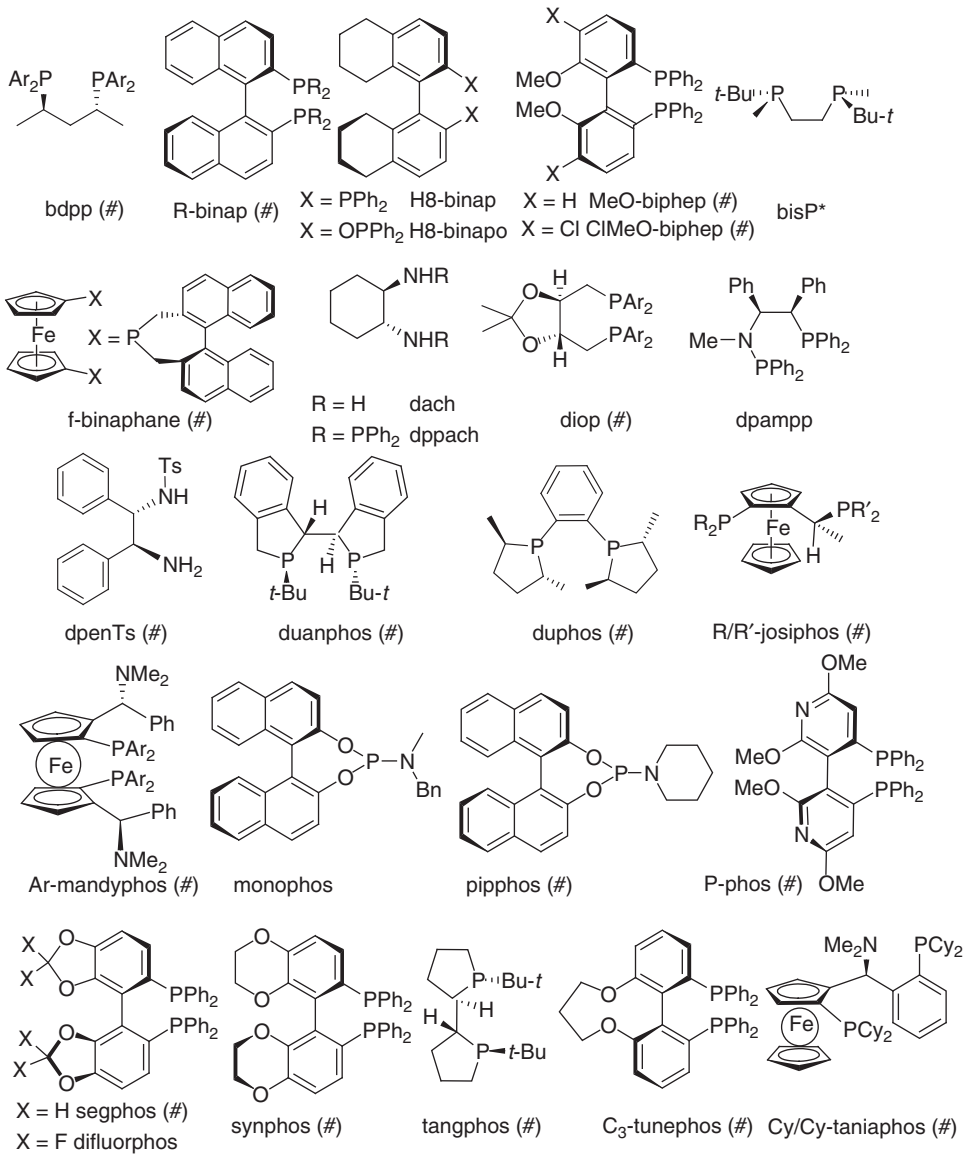


Figure 1 Structures of named ligands; ligands with (#) are available on technical scale.

8.05.2.2.3 Ru catalysts

For hydrogenation with H_2, Ru catalysts are usually applied as preformed complexes of the type Ru(diphosphine)X_2 (X=Cl and OAc) or Ru(diphosphine)(diamine)Cl_2. For transfer hydrogenations with HCOOH/NEt_3, areneRu(dpenSO_2R)Cl (arene=benzene or *p*-cymene) complexes introduced by Noyori are the catalysts of choice. It is also possible to prepare these Ru catalysts *in situ* from Ru(cod)Cl_2 or [Ru(cymene)$_2$Cl]$_2$ and the required sulfonylated diamine. The π-bound arene stays coordinated to the ruthenium atom throughout the reaction and its nature can have a strong effect on the catalytic performance. Recently, it was demonstrated that these complexes are also able to activate dihydrogen and several examples can be found in the Tables 3, 8, 12, and 13.

8.05.2.2.4 Pd catalysts

A recent development is the use of Pd diphosphine catalysts, especially for C═N–X functions and imines of α-keto esters. Applied are either complexes formed *in situ* from Pd$(CF_3CO_2)_2$ and a diphosphine or preformed Pd(diphosphine)$(CF_3CO_2)_2$ complexes.

8.05.2.2.5 Miscellaneous catalysts

The Ti-biscyclopentadienyl complex (ebthi)Ti can achieve remarkable enantioselectivities for the hydrogenation of cyclic imines. However, the authors consider their synthetic potential to be rather low because the ligands and complexes are difficult to prepare, the activation of the catalyst precursor is tricky and high catalyst loadings are needed.

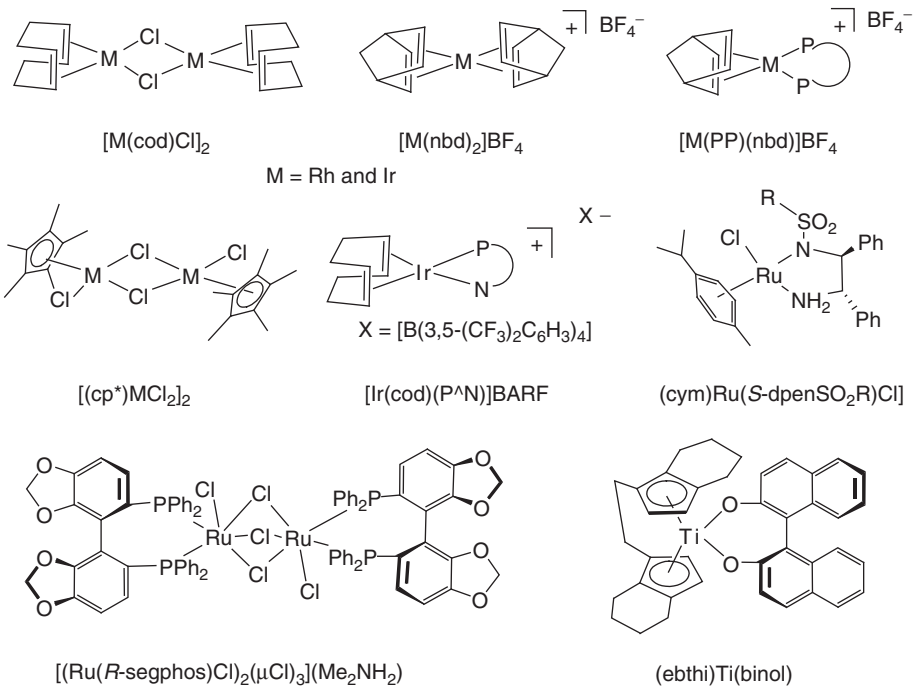


Figure 2 Structures and abbreviations of selected Rh, Ir, Ru, and Ti complexes.

8.05.3 Substrates and Transformations

The nature of the substituent directly attached to the nitrogen atom affects the properties (basicity, reduction potential, etc.) of the C═N function more than the substituents at the carbon atom. As a consequence, catalyst specificity can be very high. Two examples: Ir diphosphine catalysts that are very active for *N*-aryl imines were found to deactivate rapidly when applied for imines with aliphatic *N*-substituents,[8] titanocene-based catalysts are active only for *N*-alkyl imines but not for *N*-aryl imines.[27,28] Because quite different catalysts and/or reaction conditions are optimal for a particular substrate type and in order to facilitate the search for the optimal catalyst, the following substrate classes are distinguished (see **Figure 3**): *N*-aryl imines, *N*-alkyl imines, primary imines, endocyclic imines (including iminium derivatives), *N*-heteroarenes, and C═N–X compounds.

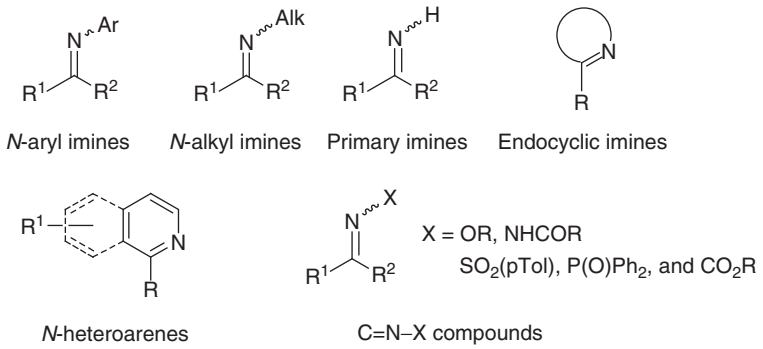


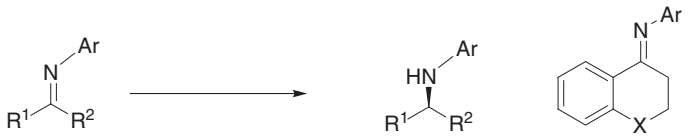
Figure 3 Substrate classes.

When assessing the results compiled in this overview, one has to keep in mind that their quality and relevance differ widely. Most new ligands have only been tested under standard conditions (usually with 1% catalyst) with selected model test substrates and results are usually optimized for enantioselectivity, whereas catalyst productivity (indicated by the required substrate to catalyst ratio, s/c) and catalyst activity (indicated by the necessary reaction time for high conversions) are only a first indication of the potential of a ligand. The decisive test, namely the application of a new ligand to 'real-world problems' will come later and tell about the scope and limitations of a given ligand (family) concerning activity and productivity, and tolerance to changes in the substrate structure and/or the presence of functional groups. Indeed, relatively few catalyst systems were optimized for synthetic or industrial application and representative examples are presented in Section 8.05.5.

8.05.3.1 *N*-Aryl Imines

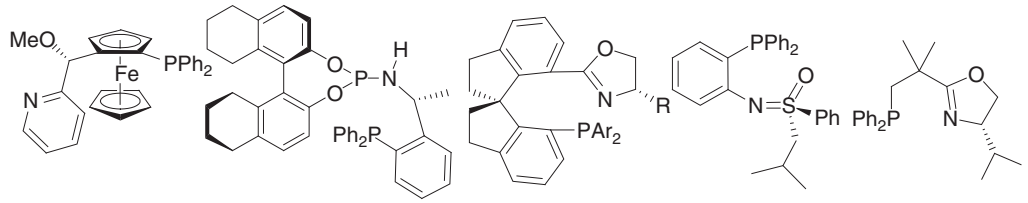
There is no doubt that the chiral switch to the enriched (*S*)-enantiomers of metolachlor, one of the major herbicides, was the driving force to develop suitable ligands and catalysts for the enantioselective hydrogenation of *N*-aryl imines (see Section 8.05.5).[13,29] Accordingly, much effort has been devoted to finding catalysts able to hydrogenate hindered *N*-aryl imines. Interestingly, it turned out that many Ir catalysts give higher enantioselectivities for 2,6-disubstituted *N*-aryl groups[8,30–32] and in some cases *ee* values >99% were achieved (Table 2, entry 2.1).

Table 2 Hydrogenation of *N*-aryl imines



S1, X = O and CH_2

Entry	R^1	R^2	Catalyst[a]	Reaction conditions[b]	ee (%)	References
2.1	Ar	Me	$[Ir(cod)Cl]_2$ and f-binaphane	s/c 100, 70 bar, r.t., 14–44 h	81–>99	31
2.2	Ar	Me	$[Ir(cod)_2]BARF$ and pipphos	s/c 50, 1–5 bar, r.t., 6–20 h	93–99	35
2.3	Ar	Me	[Ir(**L1**)(cod)]BARF	s/c 100, 10 bar, 25 °C, 2–6 h	84–99	34
2.4	Ar and Alk	Me	$[Ir(cod)Cl]_2$, **L2** and KI	s/c 100, 20 bar, r.t., 24 h	69–99	32
2.5	Ar	Me	[Ir(bisP*)(cod)]BARF	s/c 200, 1 bar, r.t.	69–99	33
2.6	Ar	Me	[Ir(duanphos)(cod)]BARF	s/c 100, 5 bar, r.t., 12 h	89–98	38
2.7	Ar and Alk	Me	$[(cp^*)Ir(dpenSO_2Ar)]binolPO_2$	s/c 100, 20 bar, r.t., 15–20 h	84–98	39
2.8	Ar	Me	[Ir(**L3**)(cod)]BARF	s/c 100, 1 bar, 10 °C, 20 h	90–97	40
2.9	Ar, Alk	Me, Et	$[(cp^*)Ir(dpenSO_2Ar)H]$	s/c 100, 5 bar, 35 °C, 15–24 h[c]	80–97	41
2.10	Ar	Me	$[Ir(cod)Cl]_2$, **L4** and I_2	s/c 100, 20 bar, r.t., 8 h	90–96	42
2.11	Ar	Me	$[Ir(cod)Cl]_2$, f-binaphane and I_2	s/c 100, 70 bar, r.t., 10 h[c)]	79–96	43
2.12	Ar	Me, Et	[Ir(**L5**)(cod)]BARF	s/c 200, 5–10 bar, −20 to 0 °C, 6–8 h	77–96	45
2.13	Ar and Alk	CH_2CO_2R	$[Rh(tangphos)(cod)]SbF_6$	s/c 100, 6 bar, 50–80 °C, 18–24 h	70–96	44
2.14	Ar	Me	$[Ir(cod)Cl]_2$, josiphos[d] and H^+/I^-	s/c 200, 30 bar, r.t.	96	46
2.15	**S1**		$Pd(CF_3CO_2)_2$ and C_4-tunephos	s/c 50, ~40 bar, r.t., 16 h	86–95	47
2.16	Ar and Alk	CO_2Et	$[Rh(tangphos)(cod)]BF_4$	s/c 100, 50 bar, 50 °C, 24 h	84–95	48
2.17	Ar and Alk	Rf[e]	$Pd(CF_3CO_2)_2$ and ClMeO-biphep	s/c 25, ~40 bar, r.t., 16 h	69–94	49



L1 **L2** **L3** **L4** **L5**

[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.
[c]*In situ* formation of imine (reductive amination).
[d]Ph/4-$CF_3C_6H_4$-josiphos.
[e](per)Fluorinated Alk.

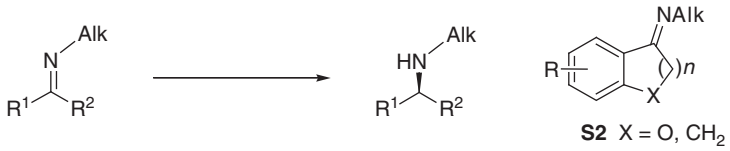
There are now a number of Ir diphosphines and Ir/P^N catalysts achieving medium to very high enantioselectivities for model substrates derived from (substituted) anilines and (substituted) acetophenones as well as some alkyl ketones. The results in Table 2 are sorted according to the best *ee* values reported. Enantioselectivities up to ≥99% *ee* and medium catalytic activities (entries 2.1–2.5) were observed for Ir complexes of f-binaphane, the monodentate pipphos, ferrocene P^N **L1**, the phosphine–phosphoramidite **L2**, and bisP*. Ir/pipphos achieved similar enantioselectivities in supercritical CO_2 with but the overall pressure of 250 bar makes this variant unattractive.[36] Ir/**L2** was applied to the synthesis of the intermediate of metolachlor and achieved up to 100 000 turnovers and 80% *ee* (80 bar, 100°, and 18 h).[32] A Pd/binap complex was also reported to achieve *ee* values up to 99%, but yields were low and not of synthetic relevance.[37] Duanphos, $dpenSO_2R$ (reductive amination) and the phosphine oxazoline **L3** (entries 2.6–2.9) led to *ee* values of 97–98%. In most cases, enantioselectivities for alkyl ketimines were slightly lower. Acceptable enantioselectivities of 94–96% were described for a number of other Ir complexes with phosphinosulfoxime **L4**, f-binaphane (reductive amination), phox **L5**, and josiphos (entries 2.10–2.12, and 2.14). Rh/tangphos was

successfully applied to the reduction of α- and β-imino esters (entries 2.13 and 2.16). The resulting products with Ar=4-MeOPh can be deprotected under mild conditions with cerium ammonium nitrate giving access to primary amines.[50] A Pd/C_4-tunephos catalyst was applied to the reduction of exocyclic *N*-aryl imines **S1** with good *ee* but low s/c values (entry 2.15). Fluorinated amines were obtained with a Pd/ClMeO-biphep catalyst with good enantioselectivity but low catalyst activity (entry 2.17). In several systematic studies it was shown that the effect of substituents at the Ar groups on enantioselectivity is often significant, but without a clear correlation between their position or nature.

8.05.3.2 *N*-Alkyl Imines

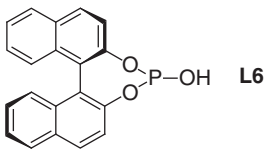
Until now, few acyclic *N*-alkyl imines or the corresponding amines are of practical synthetic or industrial importance. Most studies reported herein were carried out with model substrates, especially with the *N*-benzyl imine of acetophenone, substituted derivatives, and some analogs thereof (Table 3). One reason for this choice could be the easy preparation of a pure crystalline starting material, another one that synthetically useful chiral phenethyl amines can be obtained via hydrogenolysis of the benzyl group. Compared with *N*-aryl imines, *ee* values for *N*-alkyl imines are generally lower. Enantioselectivities of 97–98% can be achieved for the exocyclic C=N bonds in **S2** and **S3** with Ir/**L2** catalysts (entry 3.1) and with Ru/dpenTs acting as hydrogenation (entry 3.2) and as transfer hydrogenation catalyst (entry 3.4), respectively. The transfer hydrogenation of α-substituted exocyclic imines occurred with very high *cis* selectivity with up to 97% *ee* for five-membered rings (entry 3.4) but only with 50% *ee* for six-membered rings (Scheme 3).[53] An immobilized Ru/dpenTs complex achieved comparable results.[54] Imino esters were reduced with Ru/deguphos (entry 3.3, reductive amination) and simple acyclic imines with a Ru/dpenMs complex (entry 3.5). Somewhat lower enantioselectivities were obtained from Rh complexes with a sulfonated bddp ligand (entry 3.6), with two different Ir

Table 3 Hydrogenation of *N*-alkyl imines



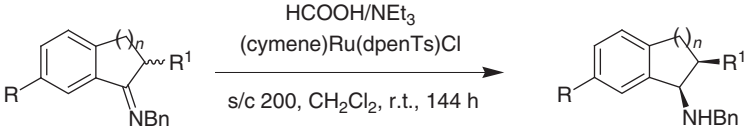
S2 X = O, CH_2

Entry	*R^1*	*R^2*	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
3.1	**S2**		[Ir(**L3**)(cod)] B_{ARF}	s/c 100, 1 bar, 10 °C, 20 h	95–98	39
3.2	**S2**		[(cym)Ru(dpenMs)]B_{ARF}	s/c 100–500, 50 bar, 40 °C, 10 h	92–98	51
3.3	Alk	CO_2H	[Rh(deguphos)(nbd)]BF_4	s/c 100–200, 60 bar, r.t., 2–24 h[c]	81–98	52
3.4	**S3** (R_1=H)		(cym)Ru(dpenTs)Cl	s/c 200, HCO_2H/Net_3, r.t., 144 h	92–97	53
3.5	(het)Ar	Me	[(cym)Ru(dpenMs)]B_{ARF}	s/c 100–500, 50 bar, 40 °C, 10 h	86–97	51
3.6	Ar	Me	$[Rh(cod)Cl]_2$, $bddp_{sulf}$,	s/c 100, 70 bar, 20 °C, 6 h	86–95	7
3.7	Ar	Me	$[Ir(cod)Cl]_2$, **L6**, PPh_3	s/c 100, 50 bar, r.t., 48 h	88–92	56
3.8	Ar	Me	[Ir(**L3**)(cod)]B_{ARF}	s/c 100, 1 bar, 10 °C, 20 h	88–92	55
3.9	Ar	Me	Ru(dppach)(dach)HCl	s/c 1500, 3 bar, 20 °C, 60 h	92	57
3.10	Alk	Alk	(ebthi)Ti(binol)	s/c 10–50, 65 °C, 140 bar, 8–48 h	53–92	28,58



L6

[a]For structures of named ligands see **Figure 1.**
[b]Reaction time for high conversion.
[c]*In situ* formation of imine (reductive amination).



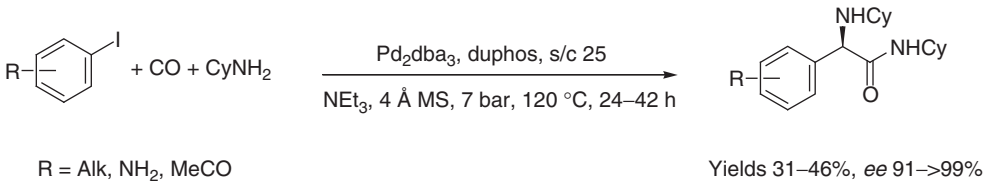
S3, R = H, Me; R^1 = Me, allyl

ee up to 97%

Scheme 3

catalysts (entries 3.7 and 3.8), and with a Ru diphosphine diamine complex (entry 3.9) with high s/c ratio. The (ebthi)Ti catalyst has been reported to hydrogenate *N*-alkyl imines of aliphatic ketones (entry 3.10) but very high pressures were required for good results.

An interesting domino reaction between aryl iodide, CO, and cyclohexylamine catalyzed by Pd/duphos was described (Scheme 4). The initial double carbonylation yields an α-keto amide which reacts with a second amine, leading eventually to the corresponding α-amino amide with high to very high enantioselectivities and respectable yields.[59]



Scheme 4

8.05.3.3 N–H Imines

Because N–H imines are very unstable, it was assumed that this was not a suitable substrate type for enantioselective catalysis. The first success was reported with a reductive amination approach where the C=N–H moiety is prepared *in situ*. Ru complexes with ClMeO-biphep as well as with tol-binap (Table 4, entries 4.1 and 4.2) gave excellent enantioselectivities and good to high yields of primary amines for the reaction of a variety of aryl methyl ketones with ammonium acetate or formiate. Another approach to prepare C=N–H compounds is the *in situ* preparation of aceto- and benzophenone N–H imines by the addition of Li or Mg organometallic compounds to the corresponding nitrile. Hydrogenation of the resulting benzophenone imines was possible with very high *ee* values with an Ir/monophos complex (entry 4.3) but the presence of a relatively bulky substituent in the *ortho* position and high pressures were required for good results. Ir/f-binaphane was reported to reduce acetophenone imines with good *ee* values but rather low s/c ratios (entry 4.4).

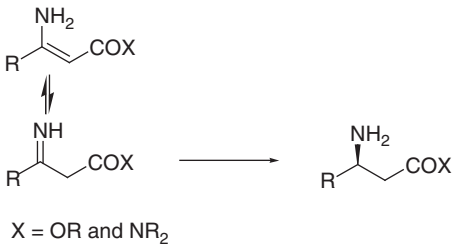
Table 4 Hydrogenation of C=N–H imines



Entry	*R^1*	*R^2*	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
4.1	Ar	CH_2CO_2R	(cym)Ru(ClMeO-biphep)Cl_2	s/c 100, 30 bar, 80 °C, 16 h[c]	96–99	60
4.2	Ar	Me, Et	Ru(tol-binap)Cl_2	s/c 100, 85 °C, 17–48 h[c]	89–95	61
4.3	2-XC_6H_4[d]	Ph	[Ir(cod)Cl]$_2$ and monophos	s/c 100, 100 bar, r.t., 36 h[e]	76–98	62
4.4	Ar	Alk	[Ir(cod)Cl]$_2$ and f-binaphane	s/c 20, 10 bar, r.t., 20 h[e]	86–94	63
4.5	R	CH_2CO_2R	Ru(segphos)$(AcO)_2$	s/c 100, 30 bar, 80 °C, 15–88 h	96–97	64
4.6	R	CH_2CO_2R	[Rh(cod)Cl]$_2$ and josiphos[f]	s/c 300, 6 bar, 50 °C, 16–20 h	93–96	65
4.7	R	CH_2CONR_2	[Rh(cod)Cl]$_2$ and josiphos[f]	s/c 300, 6 bar, 50 °C, 8 h	82–97	65

[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.
[c]*In situ* formation of C=N–H (reductive amination with RCO_2NH_4).
[d]X = Cl, Br, Me, and OMe.
[e]*In situ* formation of C=N–H via addition of R_2–M to Ar–CN.
[f]Ph/*t*Bu-josiphos.

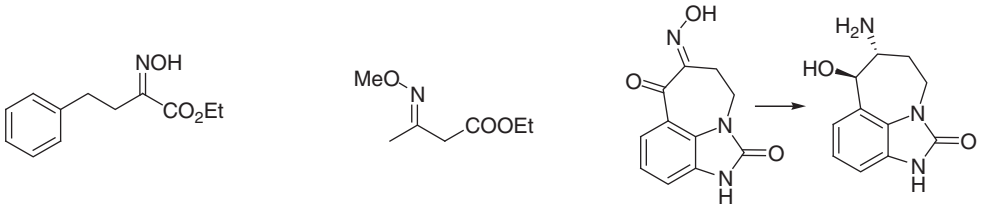
Of special interest was the unexpected finding that the hydrogenation of unprotected β-enamino acid derivatives is possible with high enantioselectivities. Although the reaction of the analogous acylated derivatives is a well-known transformation, this variant which does not require acylation/hydrolysis to get the β-amino acids has considerable synthetic and industrial potential. Very good enantioselectivities were achieved for several different primary β-imino esters with Ru/segphos (entry 4.5) and Rh/josiphos (entry 4.6) in trifluoroethanol. Rh/josiphos was also applied to β-imino amides (entry 4.7). Unfortunately, for both catalyst systems activity is an issue. Although the Rh/josiphos complexes gave high conversion at an s/c of 330 after 6–20 h, the Ru/segphos catalysts did not give full conversion even after 15–88 h at an s/c of 100 (in some cases 1000). Interestingly, deuteration experiments indicate that it is not the enamine C=C bond which is reduced but the tautomeric N–H imine (Scheme 5). In presence of $(Boc)_2O$, the hydrogenation with Rh/josiphos led directly to the *N*-protected β-amino acid derivatives with improved chemical yields and up to 99% *ee*.[66,67]



Scheme 5

8.05.3.4 C═N–X Functions (X═OR, NHCOAr, SO_2Ts, $POPh_2$, and COR)

Oxime derivatives were among the first C═N functions to be tried as substrates for enantioselective reduction. However, with *ee* values <30% both for modified heterogeneous catalysts[2] as well as homogeneous catalysts[3] the results were disappointing especially for α-keto acid derivatives giving access to α-amino acids. Besides the already mentioned hydrogenation of a simple oxime with Rh/binap (*ee* 30–66%),[14] there are now a few examples of synthetic relevance where reasonable enantioselectivities have been obtained[68–70] (see **Figure 4**), but this remains a very difficult transformation. An interesting variant is the hydrogenation of nitrones which can be carried out with an Ir/binap catalysts with *ee* values up to 86% but often low chemical yields.[71]



[Ir(dpampp)Cl]$_2$, BI_3
s/c 100, 48 bar, r.t., 46 h
yield 22%, *ee* 93%[68]

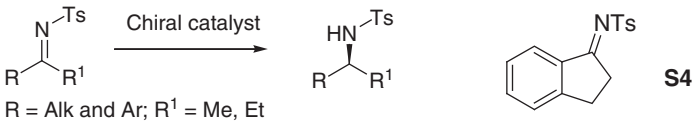
[Rh(cod)$_2$]BF_4, Ph/Cy-josiphos, HBF_4
s/c 150, 20 bar, 60 °C
yield 99%, *ee* 81%
feasibility study, Evonik[70]

[Rh(cod)(mandyphos)]BF_4
s/c 50, 50 bar, 40 °C
yield 95%, *ee* 93%, <2% *cis*
feasibility study, Intervet Int.[69]

Figure 4 Hydrogenation of functionalized oxime derivatives.

In contrast, very high enantioselectivities can be achieved for the hydrogenation of a variety of *N*-tosyl imines (**Table 5**) and cyclic analogs (**Table 6**). For *N*-tosyl imines, a Ru/dpenTs complex (transfer hydrogenation, entry 5.1) and Pd catalysts with tangphos and synphos ligands (entries 5.2–5.4) gave very high enantioselectivities but catalyst activities were rather low and high pressures were required. Endocyclic sulfonamides were accessed starting from substrates **S5** in very high enantioselectivities using either Ru/binap (entry 6.1) or Pd/tangphos (entry 6.3) or via transfer hydrogenation with Ru/dpenSO_2Ar (entry 6.2). Similar *ee* values were reported for the hydrogenation of **S6** and **S7** with Pd/josiphos catalysts (entries 6.4 and 6.5). Deuteration experiments have shown that it is indeed the C═N bond which is hydrogenated after isomerization. Sultams were prepared by reduction of **S8** and **S9** using either a Pd/f-binaphane (entry 6.6) or a (cp*)Rh/dpenSO_2Ar complex (transfer hydrogenation and entry 6.7). Both catalysts gave very high enantioselectivities but the Pd catalysts showed relatively low activity.

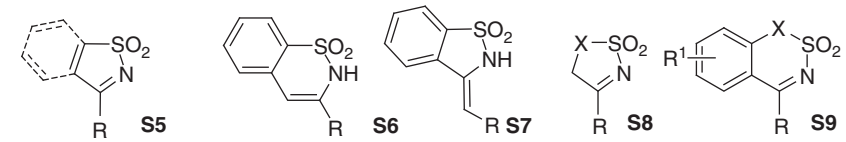
Table 5 Hydrogenation of *N*-tosylimines



Entry	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
5.1	(cp*)Rh(dpenTs)Cl	s/c 200, HCO_2H/NEt_3	83–99	72
5.2	Pd(tangphos)$(CF_3CO_2)_2$	s/c 100, 75 bar, 40 °C, 24 h	75–>99	73
5.3	Pd(tangphos)$(CF_3CO_2)_2$	s/c 100, 75 bar, 40 °C, 24 h[c]	98	73
5.4	Pd(synphos)$(CF_3CO_2)_2$	s/c 50, 40 bar, r.t., 12 h	88–97	73

[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.
[c]Substrate **S4**.

Table 6 Hydrogenation of endocyclic *N*-tosylimines and analogs

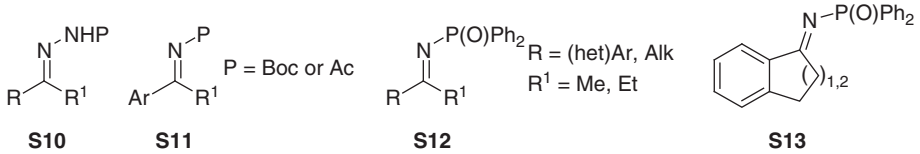


Entry	*Substrate*	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
6.1	**S5**	$Ru(cod)Cl_2$ and binap	s/c 100, 4 bar, 22 °C, 12 h	99	74
6.2	**S5**	$C_6H_6Ru(dpenSO_2Ar)Cl$	s/c 100, HCO_2H/NEt_3, 28 °C, 10 h	96	75
6.3	**S5**	$Pd(tangphos)(CF_3CO_2)_2$	s/c 100, 75 bar, 40 °C, 24 h	94	73
6.4	**S6**	$Pd(CF_3CO_2)_2$ and josiphos[c]	s/c 50, 28 bar, 70 °C, 16 h	95–98	76
6.5	**S7**	$Pd(CF_3CO_2)_2$ and josiphos[c]	s/c 50, 28 bar, 70 °C, 16 h	86–96	76
6.6	**S8**	$Pd(CF_3CO_2)_2$ and f-binaphane	s/c 50, 40–45 bar, r.t., 12 h	91–99	77,78
6.7	**S8, S9**	$(cp^*)Rh(dpenSO_2Ar)Cl$	s/c 200–1000, HCO_2H/NEt_3, r.t., 0.5 h	75–99	79

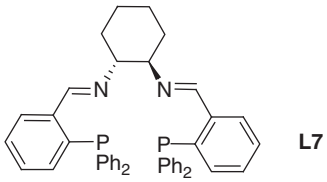
[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.
[c]Ph/*t*-Bu-josiphos.

Several other C═N–X functions are amenable to reduction with high selectivities (Table 7). That very impressive enantioselectivities were achieved with Rh/duphos for the hydrogenation of *N*-acylhydrazones **S10** (entries 7.1, 7.2) confirmed the hypothesis that the presence of a second coordinating group in the substrate is beneficial for getting high enantioselectivity. Although *ee* values were modest for acylhydrazones of alkyl ketones, good to very good enantioselectivities were achieved for those derived from aryl methyl ketones and α-keto esters. The resulting *N*-acylhydrazines can be reduced to the primary amine

Table 7 Hydrogenation of miscellaneous C═N–X functions



Entry	*Substrate (R/R1)*	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
7.1	**S10** (Ar/Me)	[Rh(duphos)(cod)]OTf	s/c 500, −10 to 20 °C, 4 bar, 2–36 h	88–97	10,80
7.2	**S10** (R/CO_2Et)	[Rh(duphos)(cod)]OTf	s/c 500, −10 to 20 °C, 4 bar, 2–36 h	83–91	10,80
7.3	**S10** (Ar/Me)	$[Rh(cod)_2]BF_4$ and josiphos[c]	s/c 50–100, 20 bar, 50 °C, 22–36 h	84–91	81
7.4	**S11** (R/Rf)[d]	[(Xyl-binap)Ir]BAR_F	s/c 30, 45 bar, r.t., 20 h	90–93	83
7.5	**S12**	$(cp^*)Rh(dpenTs)Cl$	s/c 50, HCO_2H/NEt_3, 20 °C, 2 h	86–>99	84
7.6	**S12**	$Pd(segphos)(CF_3CO_2)_2$	s/c 50, 70 bar, r.t., 8 h	87–99	85
7.7	**S12**	$[Rh(nbd)_2]BF_4$ and josiphos[e]	s/c 100–500, 70 bar, 60 °C, 1–21 h	62–99	86
7.8	**S12**	$[HFe_3(CO)_{11}]Et_3NH]$ and **L7**	s/c 100–300, *i*PrOH/KOH, 45 °C, 1 h[f]	87–98	87
7.9	**S13**	$[HFe_3(CO)_{11}]Et_3NH]$ and **L7**	s/c 100–300, *i*PrOH/KOH, 45 °C, 1 h[f]	90–94	87



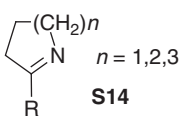
[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.
[c]Ph/*t*Bu-josiphos.
[d]Fluorinated alkyl.
[e]Cy/Cy-josiphos.
[f]Transfer hydrogenation.

using SmI_2, but an effective technical solution for the cleavage of the N–N bond to obtain the primary amine without racemization is still lacking. Good enantioselectivities were also obtained for the Rh/josiphos-catalyzed reduction of a butoxycarbonyl (Boc)-protected hydrazone (entry 7.3). An exocyclic *N*-Boc-hydrazone was reduced with up to 85% *ee* with a Rh/mandyphos catalyst albeit with a very low s/c ratio.[82] Fluorinated Boc or Ac-protected primary amines were obtained with good *ee* values but low s/c ratios with an Ir/binap catalyst (**S11**, entry 7.4). Phosphinylimines **S12** and **S13** have been shown to be suitable starting materials for a variety of chiral primary amines because the $P(O)Ph_2$ group can be easily removed hydrolytically. Very high enantioselectivities were observed for the transfer hydrogenation with Rh/dpenTs (entry 7.5) and for the hydrogenation with Pd/segphos and Rh/josiphos (entries 7.6, 7.7). Although s/c ratios for the transfer hydrogenation and the Pd/segphos catalyst were rather low, up to 500 turnovers can be obtained with Rh/josiphos. Of special interest are recent results with an *in situ* prepared Fe/**L6** complex which was shown to be quite active as transfer hydrogenation catalyst with *i*PrOH/KOH as reductant achieving *ee* values up to 98% (entries 7.8 and 7.9).

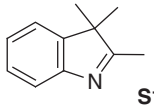
8.05.3.5 Endocyclic Imines

Cyclic imines do not have the problem of *syn*/*anti* isomerism; therefore, in principle higher enantioselectivities should be expected. Although this expectation is not generally met, it is the case for several cyclic model substrates where the (ebthi)Ti catalyst achieved up to 99% *ee* (Table 8, entry 8.1), whereas enantioselectivities for acyclic imines were $\leq$92% as described above.[9,28] It was also possible to selectively reduce one enantiomer of racemic disubstituted pyrrolines with very high selectivities.[88] Unfortunately, these very selective catalysts operate at rather low s/c ratios and, in addition, functional groups like esters, carboxylic acids, or nitriles are not tolerated. A related Zr complex exhibited similar properties as the (ebthi)Ti-catalyst but was more effective (s/c up to 1000).[89] Simple five- and six-membered endocyclic imines **S14** were hydrogenated in presence of Boc_2O with a Ru/dpenMs catalyst with excellent *ee* values (entry 8.2) and trimethylindoline **S15** was reduced in presence of Ir/josiphos with 95% *ee* (entry 8.2). Similar enantioselectivities were obtained in a screening with $[Ir(cod)Cl]_2$ and mixtures of monodentate phosphoramidites.[91] The reaction with Ir/josiphos was also carried out in ionic liquids with slightly lower enantioselectivities but similar catalyst activities.[92]

Table 8 Hydrogenation of endocyclic imines



S14



S15

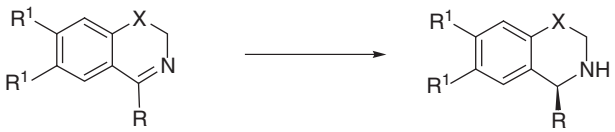
Entry	*Substrate*	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
8.1	**S14**	(ebthi)Ti(binol)	s/c 20–50, 5–140 bar, 45–65 °C, 8–48 h	98–99	9,28
8.2	**S14**	[(cym)Ru(dpenMs)]BARF	s/c 100, 50 bar, 40 °C, 10 h[c]	92–98	90
8.3	**S15**	$[Ir(cod)Cl]_2$, Xyl/Xyl-josiphos, and H^+/I^-	s/c 250, 40 bar, 30 °C, 47 h	95	46

[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.
[c]In presence of $(Boc)_2O$ to give Boc-protected amines.

Several bi- and tricyclic imines have been investigated as intermediates or model substrates for biologically active compounds (Tables 9 and 10; see also Section 8.05.5). They were reduced with good to very good enantioselectivities using a number of different catalytic systems. Interestingly, most reactions were reported not by catalyst specialists but by synthetic-organic chemists. This might be the reason that transfer hydrogenation was the preferred method because it seems to be more robust. Enantioselectivities up to 99% were described for variants of the Noyori type catalysis, i.e., the transfer hydrogenation using HCO_2H/NEt_3 as a reducing agent in presence of an arene Ru complex with $dpenSO_2Ar$ as chiral ligand (entries 9.2, 10.3 and 10.4). Using a sulfonated dpenTs allowed the reaction to be carried out in water with HCOONa as reducing agent (entries 9.6 and 10.1). Immobilized Ru/dpenTs complexes permitted recycling of the catalyst, but *ee* values were somewhat lower.[54,93] An analog where the cp^*-ring was tethered to the dpenTs gave a similar performance in the transfer hydrogenation.[94] Very good results were also described with $(cp^*)Rh(dpenTs)Cl$ (entry 9.3) which in presence of $AgSbF_6$ was also active and very selective for reduction using dihydrogen (entries 9.4 and 10.2). A dimeric Ir/f-binaphane complex (entry 9.1) and (ebthi)Ti (entry 9.5) achieved up to >99% *ee* with s/c ratios of 20–100. Benzoxazines were reduced with good *ee* values using an Ir/segphos complex (entry 9.7).

Tri- and tetracyclic iminium compounds for the synthesis of alkaloids were shown to be amenable to Ru/dpenTs-catalyzed transfer hydrogenation with 79–92% *ee* (Scheme 6).[101–103] Similar cyclic amines were obtained in good yields and up to 99% *ee* via *in situ* formed tricyclic iminium compounds.[104]

Table 9 Hydrogenation of dihydroisoquinolines and benzoxazines

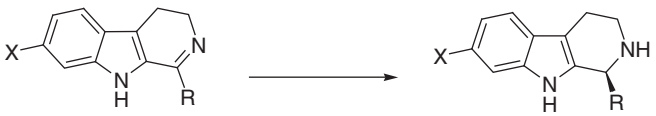


R = Ar, Alk; R^1 = H, OMe; X = CH_2, O

Entry	*X*	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
9.1	CH_2	{[Ir(f-binaphane)H]$_2$(μI$_3$)}I	s/c 100, 50 bar, r.t., 24 h	94–>99	95
9.2	CH_2	(cym)Ru(dpenTs)Cl	s/c 100–1000, HCO_2H/NEt_3, 28 °C, 12 h	84–99	11
9.3	CH_2	(cp*)Rh(dpenTs)Cl	s/c 200, HCO_2H/NEt_3, 20 °C, 0.15 h	83–99	96
9.4	CH_2	(cp*)Rh(dpenTs)Cl and $AgSbF_6$	s/c 100, 20 bar, r.t., 1–24 h	83–99	97
9.5	CH_2	(ebthi)Ti(binol)	s/c 20, 135 bar, 65 °C, 8–48 h	98	28
9.6	CH_2	[(cym)RuCl$_2$]$_2$ and dpenTs$_{sulf}$	s/c 100, HCOONa, 28 °C, 20 h	90–95	98
9.7	O	[Ir(cod)Cl]$_2$, segphos, and I_2	s/c 100, ~28 bar, r.t., 15 h	79–95	99

[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.

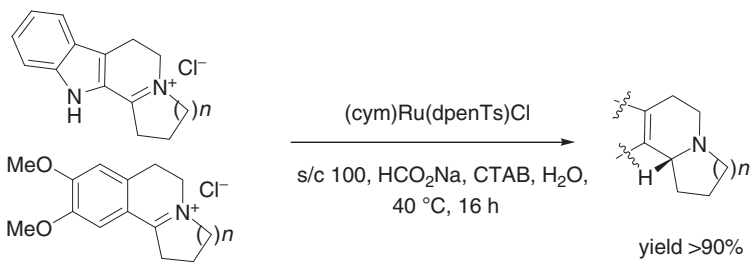
Table 10 Hydrogenation of tricyclic imines



X = H, Br, R = alkyl, (het)aryl

Entry	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
10.1	[(cymene)RuCl$_2$]$_2$ and dpenTs$_{sulf}$	s/c 500, HCOONa, 28 °C, 4–30 h	99	98
10.2	(cp*)Rh(dpenTs)Cl and $AgSbF_6$	s/c 100, 20 bar, r.t., 1–24 h	96–99	97
10.3	(cym)Ru(dpenTs)Cl	s/c 230, HCO_2H/NEt_3, r.t., 12 h	>98	100
10.4	(cym)Ru(dpenTs)Cl	s/c 200, HCO_2H/NEt_3, 28 °C, 5 h	96–97	11

[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.



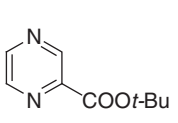
Scheme 6

8.05.3.6 Heteroaromatic Substrates

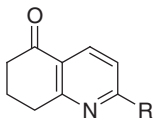
Until very recently, the homogeneous hydrogenation of heteroaromatic substrates was considered to be very difficult. Although this has changed for the partial hydrogenation of substituted quinolines, good results for pyridines or pyrazines are still rare, probably due to their more aromatic character.[23,105] There are a few exceptions as shown in Table 11. The Ir/josiphos-catalyzed hydrogenation of pyrazine amide **S16** occurred with up to 78% *ee* (entry 10.1) and very recently the Ir-catalyzed hydrogenation of pyridine derivatives **S17** with electron-withdrawing substituents 2-position using P-phos, MeO-biphep was reported with very

enantioselectivity and moderate-to-good activity (entries 11.2–11.4). Furthermore, *N*-iminium pyridine ylides were hydrogenated with up to 90% *ee* using Ir/phox complexes.[107]

Table 11 Hydrogenation of pyridine and pyrazine derivatives



S16



S17

Entry	*Substrate*	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
11.1	**S16**	$[Rh(nbd)Cl]_2$ and Ph/Cy-josiphos	s/c 50, 50 bar, 70 °C, 20 h	78	106
11.2	**S17**	$[Ir(cod)Cl]_2$, P-phos[c], and I_2	s/c 100–1000, ~50 bar, r.t., 20 h	81–99	108
11.3	**S17**	$[Ir(cod)Cl]_2$, MeO-biphep, and I_2	s/c 50, ~50 bar, 25 °C, 12 h	84–97	109

[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.
[c]Similar results for Ir/difluorphos.

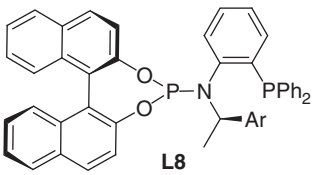
The enantioselective partial hydrogenation of quinoline derivatives to the corresponding tetrahydro derivatives is at the moment a very hot topic (Table 12). With few exceptions Ir diphosphine and Ru/dpenTs complexes are the catalysts of choice. Enantioselectivities depended mainly on the catalysts used and the nature of the substituent R at the hetero ring. Yields were good to quantitative at s/c ratios usually approximately 100, but in exceptional cases up to 50 000 (entry 12.7). Enantioselectivities up to 99% were reported for a Ru/dpenTs catalyst, an Ir/H8-binapo complex, and a $(cp^*)Ir/dpenSO_2R$ catalyst (entries 12.1–12.3). The latter complex could also be applied for transfer hydrogenation in water (entry 12.4). (Cym)Ru(dpenTs) also showed excellent stereoselectivity (*ee* > 99% and *dr* > 95/5) in the tandem asymmetric reduction of 2-(aroylmethyl)quinolines involving a transfer hydrogenation of an aromatic ketone and the hydrogenation of the quinoline.[116] Ir/**L8** and a number of Ir complexes with atropisomeric diphosphines such as MeO-biphep, P-phos, or **L9** achieved very high enantioselectivities for a variety of quinoline derivatives (entries 12.6–12.8). **Cat1**, an interesting variant of a Ru/dpenTs catalyst where a cp^*-ring is tethered to the dpenTs ligand and Ir/**L10** gave respectable enantioselectivities, the latter also has very good activities (entries 12.9 and 12.10). In addition

Table 12 Hydrogenation of quinolines

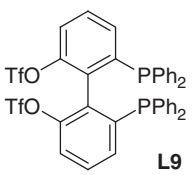


R = (subst)Alk, Ar; R^1 = H, Me, MeO, F

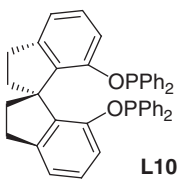
Entry	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
12.1	[(cym)Ru(dpenTs)]OTf	s/c 100–5000, 50 bar, 25 °C, 15–24 h	98–99	110,111
12.2	$[Ir(cod)Cl]_2$, H8-binapo, and I_2	s/c 50–100, 50 bar, r.t., 20 h	81–99	112,113
12.3	$[(cp^*)Ir(dpenSO_2R)]OTf$ and CF_3COH	s/c 100–1000, 50 bar, 0–25 °C, 24–60 h	79–99	114
12.4	$[(cp^*)Rh(dpenSO_2R)]OTf$	s/c 100, HCO_2Na/H_2O, 40 °C, 6–24 h	89–98	115
12.5	$[Ir(cod)Cl]_2$, **L8,** and I_2	s/c 100, 40 bar, r.t., 16–48 h	89–97	117
12.6	$[Ir(cod)Cl]_2$, MeO-biphep, and I_2	s/c 100, 50 bar, 25 °C, 18 h	75–96	118
12.7	$[Ir(cod)Cl]_2$, P-phos[c] and I_2	s/c 200–50 000, 50 bar, r.t., 20 h	89–95	108
12.8	$[Ir(cod)Cl]_2$, **L9**, I_2	s/c 1000–10 000, ~50 bar, r.t., 22 h	60–95	119
12.9	**Cat1**	s/c 200, HCO_2H/NEt_3, 28 °C, 48 h	81–94	120
12.10	$[Ir(cod)Cl]_2$, **L10**, and I_2	s/c 100–5000, 50 bar, r.t., 18 h	65–93	121



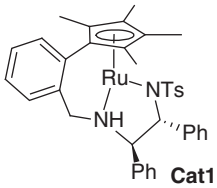
L8



L9



L10



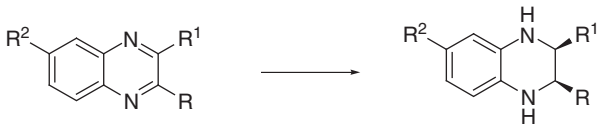
Cat1

[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.
[c]Similar results with ClMeO-biphep, difluorphos, and synphos.

to these results, a number of investigations were described where Ir diphosphine catalysts achieved enantioselectivities up to 92% but usually with moderate activities.[122–130]

Quinoxalines (Table 13) can be considered to be model substrates for the reduction of folic acid (see Section 8.05.5). Only a few successful catalysts have been described. Similar catalysts as for quinolines are useful and the best results were obtained with a Ru/dpenSO_2R and an Ir/H8-binapo catalyst, respectively, (entries 13.1 and 13.2) with good to very good catalytic activities and s/c ratios. The former catalyst was able to hydrogenate 2,3-dimethylquinolines with *ee* values up to 99%, but *cis*/*trans* ratios were only approximately 80:20.[131] The Ir complex with the monodentate pipphos and a dimeric Ir/difluorphos catalyst also achieved good enantioselectivities but with only moderate s/c ratios (entries 13.3 and 13.4).

Table 13 Hydrogenation of quinoxalines



R = (subst)Alk, Ar; R^1 = H, R; R^2 = H, Me, F

Entry	*Catalyst*[a]	*Reaction conditions*[b]	*ee (%)*	*References*
13.1	[(cym)Ru(dpenSO_2R)]BARF	s/c 100–1000, 50 bar, 40 °C, 20 h	89–99	131
13.2	$[Ir(cod)Cl]_2$, H8-binapo, and I_2	s/c 100–20 000, ~50 bar, −5 °C, 20 h	81–98	132
13.3	$[Ir(cod)Cl]_2$, pipphos, and HCl	s/c 50, 25 bar, 60 °C, 5–12 h	75–96	126
13.4	$\{[Ir(difluorphos)H]_2(\mu Cl_3)\}Cl$	s/c 100, 30–50 bar, 30 °C, 20 h	85–94	133

[a]For structures of named ligands see **Figure 1**.
[b]Reaction time for high conversion.

8.05.3.7 Conclusions Concerning Choice of Catalyst and Reaction Conditions

Unfortunately, there are no general recipes for choosing an optimal catalyst system for any of the substrate classes described in this chapter. The specific combination of all important process variables (metal, ligand, and reaction conditions) has to be adapted for an individual transformation. Nevertheless, existing results allow the identification of catalytic systems with an above average chance for success as summarized in Table 14.

Table 14 Successful catalyst systems

Metal/Anion	*Additives*	*Ligands*	*Substrate*
Ir/Cl and BARF	Iodide/acid, I_2, and Brønsted acid	f-Binaphane, various P^N ligands, duanphos, josiphos, phosphoramidites, binap and analogous biaryl diphosphines, and cp*/dpenTs	All substrate types
Rh/BF_4 and OTf	$AgSbF_6$	Tangphos, bdpp, josiphos, duphos, and cp*/dpenTs	Most substrate types
Ru/Cl and BARF	$AgSbF_6$	Cymene/dpenTs, benzene/dpenTs, binap, and analogous biaryl diphosphines	Most substrate types
Pd/CF_3CO_2	–	Tangphos, biaryl diphosphines, josiphos, and f-binaphane	C═NAr and C═NX
Ti/binol		Ebthi	Endocyclic C═N

In general, pressure does not affect enantioselectivities very much, but quite often quite high pressures are needed to achieve acceptable reaction times. For transfer hydrogenations, the preferred reducing system is an azeotropic mixture of HCOOH/Et_3N 5/2 in organic solvents and HCOONa in water. Temperatures are usually between room temperature (rt) and 50 °C with varying effect on enantioselectivity. Catalyst loadings vary greatly, depending on all components of the reaction system (and on the optimization efforts).

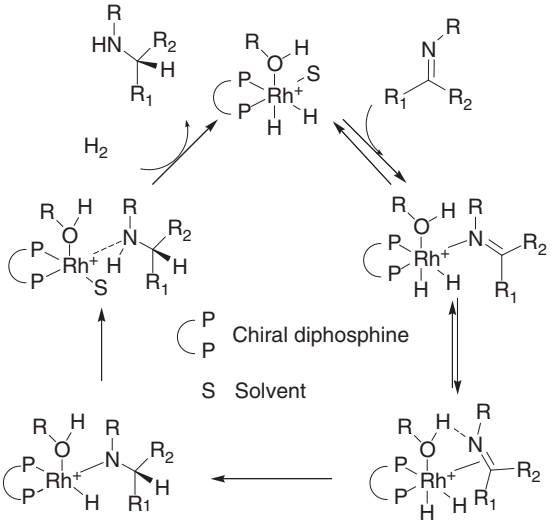
Many of the most active ligands are commercially available (indicated by (#) in Figure 1) in small quantities from Aldrich and Strem, and in larger quantities from Chiral Quest, Digital Specialty Chemicals, Dow, Johnson Matthey, Solvias, or Takasago. Most diphosphines should be handled with care. Especially, ligands with alkylphosphino groups are very air sensitive and in such cases either Schlenk technique or a glove box is required to get satisfactory results. An alternative is to use the preformed complexes, which are usually less sensitive and commercially available for selected ligands.

8.05.4 Mechanism and Stereochemistry

Most detailed mechanistic studies of homogeneous C═N hydrogenations were carried out using achiral metal complexes with monodentate ligands which are often quite different from the metal complexes effective for enantioselective reactions.[134] Furthermore, a generalization seems to be very difficult for two reasons. First, rather different catalyst types are effective and probably act by different mechanisms. Second, certain additives (especially iodide and acid/base) often significantly affect *ee* and rate but a promoter in one case can be a deactivator in another one. It is reasonably certain that most catalysts described in this review catalyze the addition of H_2 directly to the C═N bond and not to the tautomeric enamine C═C bond,[58,65,135] even though the C═C bond of enamines which cannot tautomerize can also be hydrogenated enantioselectively.[112] In many cases, the addition of Brønsted acids has been shown to be beneficial, probably due to an activation of the substrate.[136]

8.05.4.1 Rh Catalysts

Kinetic results for the Rh-catalyzed *N*-aryl imine hydrogenation led to the conclusion that in analogy to C═C hydrogenation, the so-called hydride route is preferred.[137,138] As depicted in **Scheme 7**, it is assumed that the imine is first η^1-coordinated via the nitrogen lone pair to a Rh^{III}-dihydride species. The isomerization to the π-coordinated intermediate thought to be necessary for reaction might be assisted by a bound alcohol molecule. After two H-transfer steps where the first determines the absolute configuration, a Rh^{I}–amine complex results which either directly or in a dissociative manner reacts with H_2 to recreate the Rh^{III}-dihydride.



Scheme 7

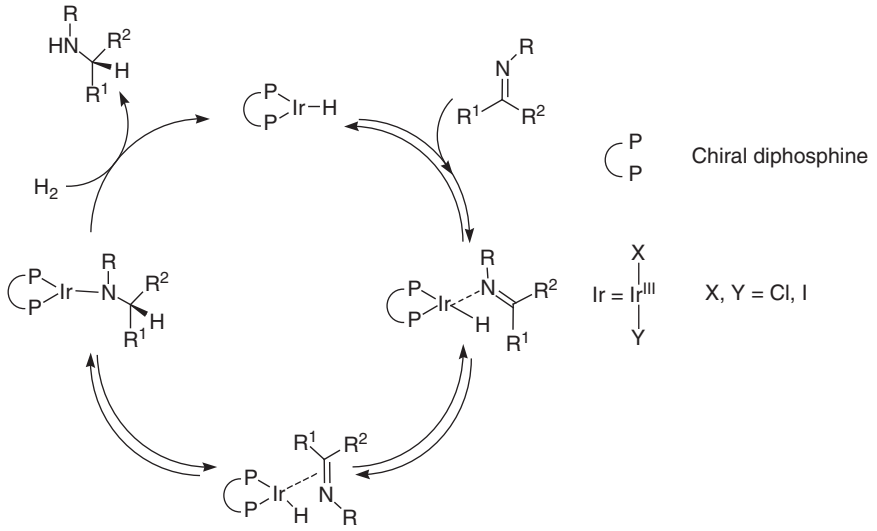
The Rh/duphos-catalyzed hydrogenation of acyl hydrazones was also studied in some detail.[80] The original idea to use these substrates was the creation of an additional stabilizing interaction between substrate and Rh center.[10] Such a secondary interaction is considered to be the major reason for the very high enantioselectivities observed for enamides, itaconates, or β-keto esters. Deuteration studies imply that the insertion of the C═N moiety into the Rh–H bond occurs irreversibly as proposed for the imine hydrogenation in the catalytic cycle depicted above.

A recent kinetic study[139] for the (cp*)Rh/dpenTs-catalyzed transfer hydrogenation of an endocyclic imine with NEt_3/HCOOC indicated that a similar sequence of steps occurs as suggested for the hydrogenation. The data show that a (cp*)Rh(dpenTs)–H species is likely to be the resting state of the catalytic cycle. It is suggested that the Rh hydride species is formed by the transfer of a hydride from formic acid reacting further by coordinating the C═N bond followed by insertion into the Rh–H bond and protonation to give the chiral amine.

8.05.4.2 Ir Catalysts

The Ir diphosphine-catalyzed hydrogenation of *N*-Aryl was studied in some detail.[140] Ir^{III} complexes of the type $[Ir(diphosphine)I_4]^-$, $[Ir(diphosphine)I_2]_2$, and $[Ir(diphosphine)I_3]_2$ were isolated and characterized. All three types of complexes were found to be catalytically active, suggesting the formation of the same active monomeric Ir species as for the *in situ* formed catalyst (from $[Ir(cod)Cl]_2$, diphosphine, and iodide) by splitting the iodo-bridge. Similar results have been reported for the

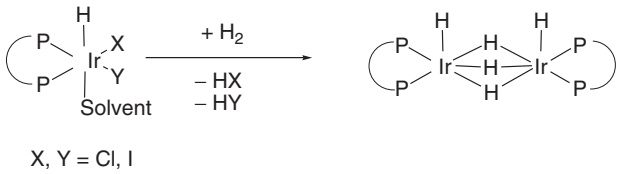
dimethylaniline imine/Ir/josiphos system[141,142] and a number of reaction intermediates were isolated. Based on these results, the catalytic cycle shown in Scheme 8 can be postulated.



Scheme 8

The proposed starting species is an Ir^{III}–H species that coordinates the imine via the lone pair in a η^1-manner (as proposed for the Rh-catalyzed reaction). A η^1,η^2-migration leads to two diastereomeric adducts with a π-coordinated imine that then inserts into the Ir–H bond to give the corresponding Ir amide complexes. The previous step is a simultaneous hydrogenolysis of the Ir–N and the formation of an Ir–H bond, presumably via heterolytic splitting of the dihydrogen bond. In contrast to Rh diphosphine-catalyzed hydrogenations, which most likely occur via Rh^I and Rh^{III} species, the cycle in Scheme 8 consists exclusively of Ir^{III} species, i.e., the halides X and Y stay on the Ir during the whole cycle. It is obvious that this simple catalytic cycle neither explains the mode of enantioselection nor the sometimes dramatic effects of additives such as the strong rate enhancement in presence of iodide and acids observed for the Ir/josiphos-catalyzed hydrogenation of *N*-aryl imines.[13]

Catalyst deactivation is often a serious problem, especially when hydrogenating relatively basic imines. Such a deactivation is indicated when the initial rate is high but then slows down significantly already at low conversion. In several studies[143–145] it was shown that the formation of triply hydrogen bridged species dinuclear species is the probable cause of deactivation for many Ir systems (Scheme 9). The catalytically inactive species are formed irreversibly; the formation is accelerated by base and by the absence of imine substrate. It has been shown that josiphos ligands are much less prone to deactivation than many other ligands and that the presence of iodide ions is often beneficial for the reaction.



Scheme 9

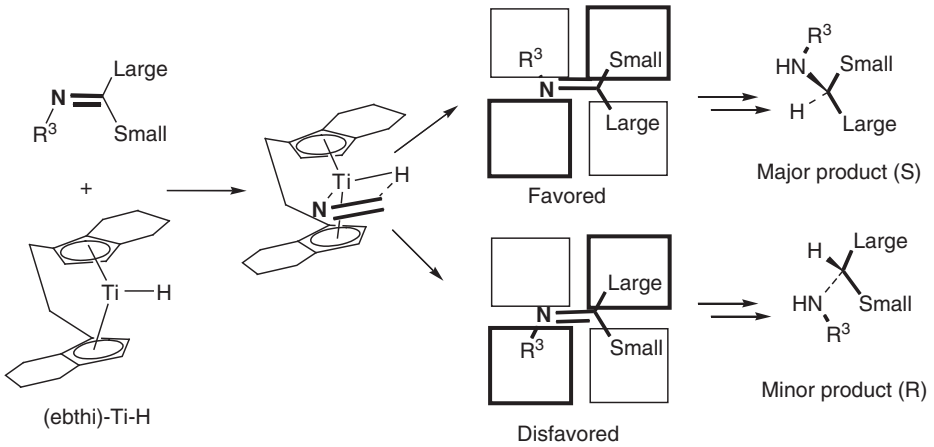
The reaction using Ir/phosphine oxazoline complexes has not yet been investigated mechanistically but a plausible stereochemical model was proposed for the Ir-catalyzed hydrogenation of *N*-aryl amines with spiro phosphine oxazoline **L2** (Table 2).[39] The prediction is based on the same stereochemical model developed for the (ebthi)Ti catalysts discussed in more detail below. For **L2** the hindered quadrants are occupied by the spiroindane backbone and by one of the PPh groups leading to the preferred coordination of the *N*-aryl imine where the large groups point toward the empty quadrants.

8.05.4.3 Ti Catalysts

For the Ti-catalyzed reactions a similar mechanism as for the Ir-catalyzed reactions was proposed.[9,28] The active catalyst is assumed to be the monohydride species (ebthi)Ti–H produced by reacting (ebthi)TiR_2 (R_2 = Cl_2 or binol) with *n*-BuLi and phenylsilane. Kinetic and deuterium-labeling studies are in agreement with the reaction sequence: (ebthi)Ti–H reacts with the imine via

a 1,2-insertion reaction to form two diastereomeric Ti amide complexes. Then this intermediate amide complex reacts via a σ bond metathesis reaction with dihydrogen as proposed for the Ir-catalyzed reaction to regenerate the titanium hydride and to form the two amine enantiomers. The reaction of the titanium amide complex with molecular hydrogen is proposed to be the rate determining step.

For most imine hydrogenations, the resulting absolute configuration of the major enantiomer cannot be predicted and must be discovered experimentally. An exception is the (ebthi)Ti catalyst where the absolute configuration of the major enantiomer can be predicted by a simple stereochemical model.[27,28,58] As schematically depicted in Scheme 10, two of the four quadrants (bold) are occupied by the six-membered ring of the tetrahydroindenyl ligand whereas the other two quadrants are much less crowded. It is assumed that the imine coordinates horizontally and for the antiisomer the preferred coordination can be easily predicted by simple steric arguments. For the *syn* isomer, the situation is more complicated because there might be a competition between R_3 and R_{large} for an empty quadrant, explaining the fact that noncyclic imines usually are hydrogenated with lower *ee* and that the enantioselectivity is pressure dependent.



Scheme 10

8.05.4.4 Ru Catalysts

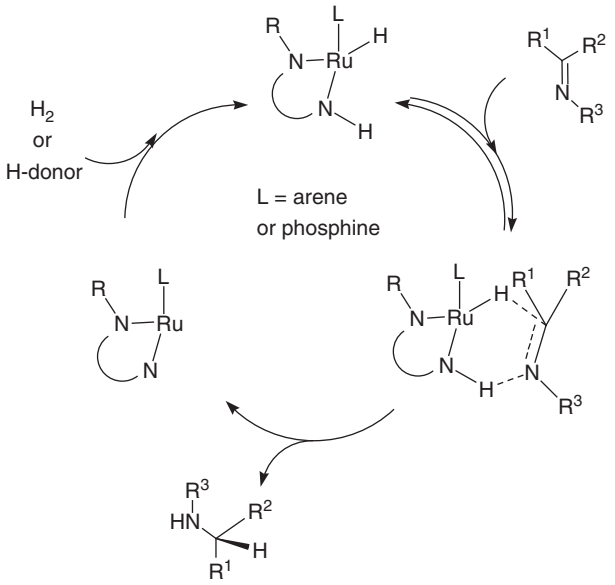
In two recent reviews, possible mechanisms are discussed for the reduction of polar C═X bonds both for reactions with dihydrogen as well as for transfer hydrogenations.[146,147] Just as for the hydrogenation of ketones, two rather different mechanisms seem likely to operate. The first is a classical inner-sphere mechanism as described above for Rh, Ir, and Ti complexes. This means that all reactants are coordinated to the metal center and bond breaking and bond making occurs in the first coordination sphere. It is quite likely that C═N reductions by Ru diphosphine complexes occur via a classical inner-sphere mechanism as discussed for Rh and Ir catalysts. The second type proposed for the enantioselective ketone reduction catalyzed by Ru diamine complexes is an outer-sphere variant where the ketone does not coordinate to the Ru center but interacts with a Ru–H and coordinated to the N–H group. Such a mechanism as depicted in Scheme 11 has been convincingly demonstrated for imine reductions using the achiral Shvo catalyst[134,146,147] and also for the hydrogenation of quinolines using [(cym)Ru(dpenTs)]OTf.[111] In this study, it was shown that the heteroarene reduction very likely happens in a stepwise fashion and that enantioselection occurs in the second 1,2-hydride addition to the dihydroquinoline intermediate as shown in Scheme 12. Furthermore, theoretical calculations indicated that C–H – π interactions between the arene ligand and the fused phenyl ring of the dihydroquinoline intermediate and participation of the OTf anion play an important role in the product determining transition state.

8.05.5 Synthetic and Industrial Applications

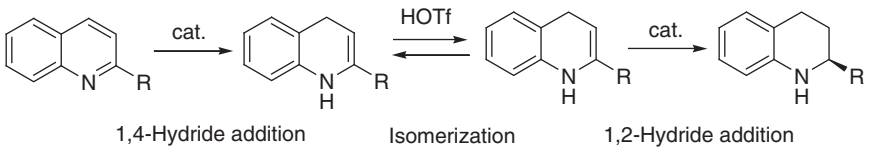
As already mentioned in the introduction, most reactions described in this review were carried out with model substrates. In this section, applications of asymmetric C═N reductions to the synthesis of molecules of industrial or biological interest are briefly summarize. There is little doubt that the (*S*)-metolachlor process is by far the most important application of any enantioselective catalyst and for this reason this reaction is described in more detail.

8.05.5.1 Production Process for (*S*)-Metolachlor (DUAL Magnum®)

Metolachlor is the active ingredient of DUAL, one of the most important grass herbicides for use in maize and a number of other crops. It is an *N*-chloroacetylated, *N*-alkoxyalkylated *ortho* disubstituted aniline. The commercial product was launched in 1976 as



Scheme 11



Scheme 12

a racemic mixture of four stereoisomers (Figure 5) in 1982 it was found that approximately 95% of the herbicidal activity of metolachlor was due to the two *(1′S)*-diastereomers. In 1997, after years of intensive research,[29] DUAL Magnum with a content of approximately 90% of the two *(1′S)*-diastereomers and with the same biological effect at approximately 65% of the use rate of the racemate was introduced into the market. Today, with a production volume of > 10 000 tons per year, this is by far the largest volume application of any homogeneous chiral catalyst.[148]

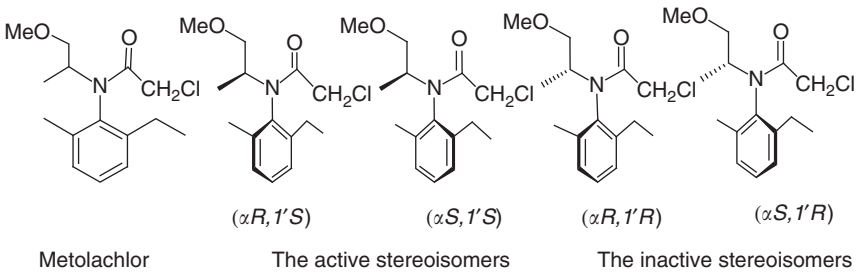
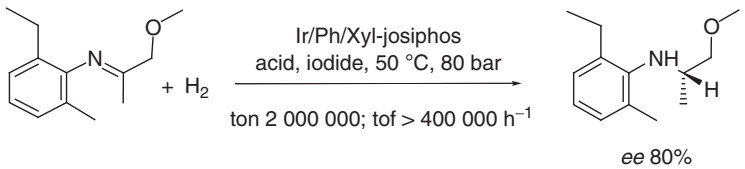


Figure 5 Structure of metolachlor and its individual stereoisomers.

Key step of the new process is the enantioselective hydrogenation of the distilled MEA imine (Scheme 13). The optimized process operates at 80 bar hydrogen and 50 °C with a catalyst generated *in situ* from $[Ir(cod)Cl]_2$ and Ph/Xyl-josiphos at an s/c

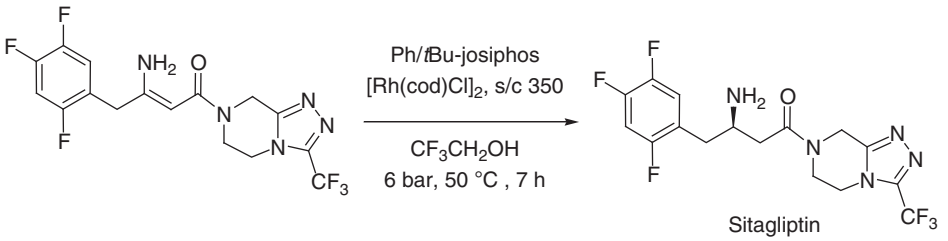


Scheme 13

ratio of 2 000 000. Complete conversion is reached within 3–4 h, initial turnover frequency exceeds 1 800 000 h^{-1} and enantioselectivity is approximately 80%. Key success factors of the new process were the novel, very active Ir/josiphos catalyst, the use of iodide and acid as additives and the high purity of MEA imine.[29] Alternative processes such as the direct reductive amination[149] as well as the application of immobilized josiphos[150] in order to avoid the distillation of the *N*-alkylated aniline were investigated. Although both catalyst systems reached respectable turnover numbers of 10 000–100 000, these variants were not competitive.

8.05.5.2 Production Process for Sitagliptin

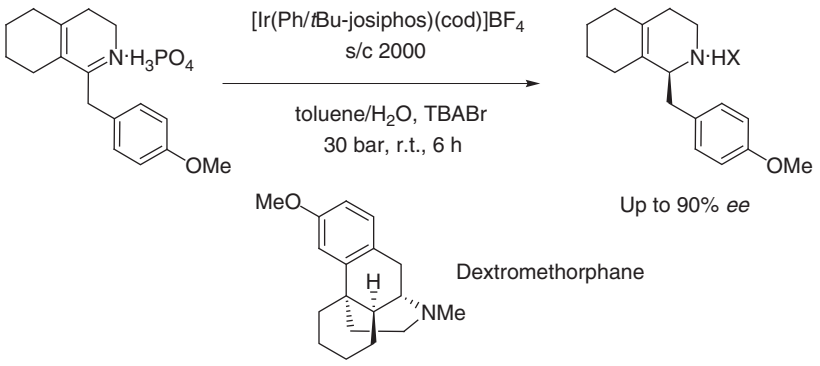
Merck has developed a manufacturing process for the manufacture of sitagliptin, a dipeptidyl peptidase-4 inhibitor for type 2 diabetes (Scheme 14). The reaction is carried out with a Rh/josiphos catalyst with up to 98% *ee* albeit with modest catalyst activities.[65,151] Key for success were the choice of the ligand, the solvent, and the presence of traces of ammonium chloride. Interestingly, deuteration experiments indicate that it is not the enamine C═C bond which is reduced but the tautomeric imine! The reaction is now carried out on a multiton scale.



Scheme 14

8.05.5.3 Pilot Process for Dextromethorphan

A pilot process for the preparation of dextromethorphan, a traditional antitussive agent, was developed using an Ir/josiphos catalyst in a two-phase system (toluene/water) (Scheme 15).[152] Important were ligand fine tuning, the choice of the phosphoric acid salt of the imine, the reaction medium, and the addition of base and iodide. Chemoselectivity with respect to C═C hydrogenation was high but catalyst productivity somewhat low for an economical technical application.

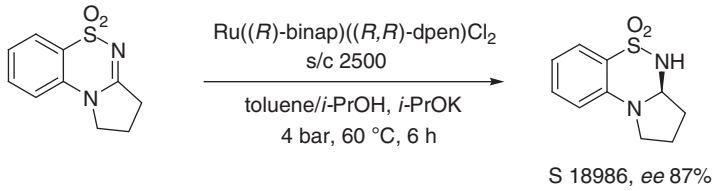


Scheme 15

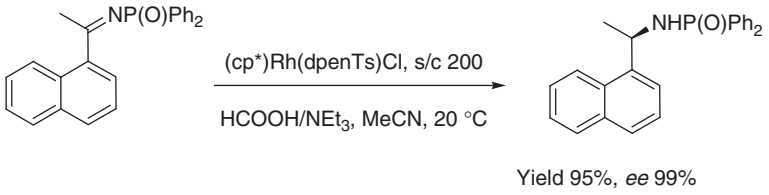
8.05.5.4 Industrial Feasibility Studies

Noyori's Ru/PP/NN catalyst system was successfully applied in a feasibility study for the hydrogenation of a sulfonylamidine, an intermediate for S 18986, an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor modulator (Scheme 16).[153] Considering that the substrate is an amidine, the catalytic activity is surprisingly high, but the *ee* is a modest 87%. A factorial experimental design was used to optimize reaction conditions showing the importance of the nature and amount of base.

The commercial viability of the CATHy™ catalysts based on a (cp^*)Rh complex were demonstrated for the reduction of phosphinylimines (Scheme 17).[154] The reaction with the 2-Np derivative was scaled up to multi-kilogram scale. Bubbling nitrogen through the reaction solution increased reaction rates significantly, due to the faster removal of CO_2.

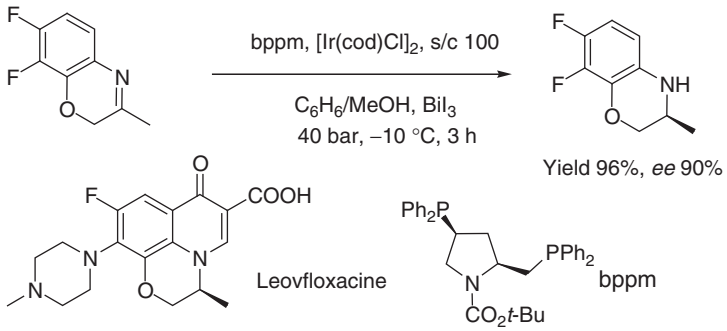


Scheme 16



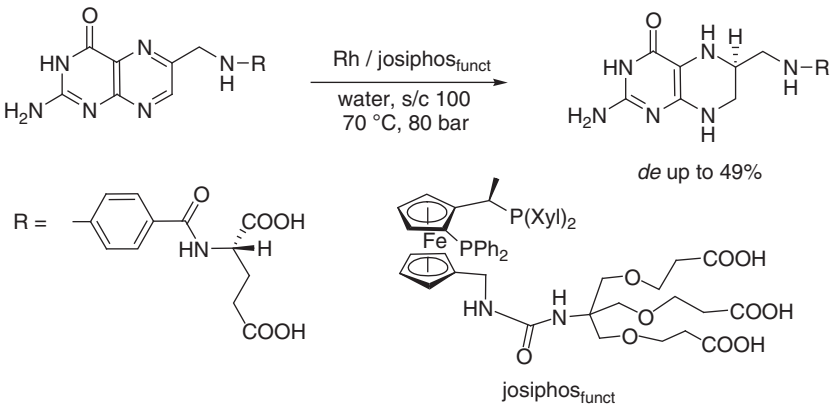
Scheme 17

Up to 90% *ee* was achieved for the hydrogenation of an intermediate of the antibiotic levofloxacin using Ir diphosphine complexes (Scheme 18).[155] Best results were obtained with bppm or a modified diop ligand in presence of bismuth iodide at low temperature.



Scheme 18

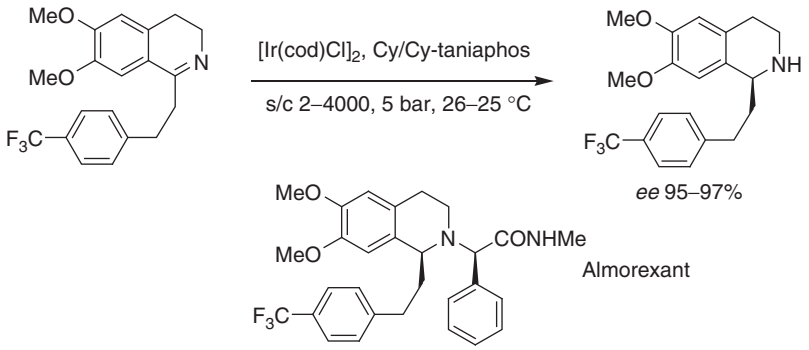
The hydrogenation of folic acid, formally a diastereoselective reaction depicted in Scheme 19, has been claimed to proceed with up to 90% *ee* with an Ir/bppm complex adsorbed on silica, a claim which had to be retracted later.[156] A major problem is the insolubility of folic acid in most organic solvents. Functionalized catalysts offer the opportunity to perform this reaction in water and it was shown that a Rh complex of the functionalized josiphos (josiphos$_{funct}$) can achieve diastereoselectivities up to 49%.[157] An alternative is the hydrogenation of the corresponding bismethyl ester which can be carried out in methanol. However, the best



Scheme 19

catalyst, $[Rh(cod)_2]BF_4$ – (*R*)-binap achieved diastereoselectivity of <44%.[158] Even though for both processes s/c ratios up to 1000 were possible, selectivity and activity are not sufficient for a technical application.

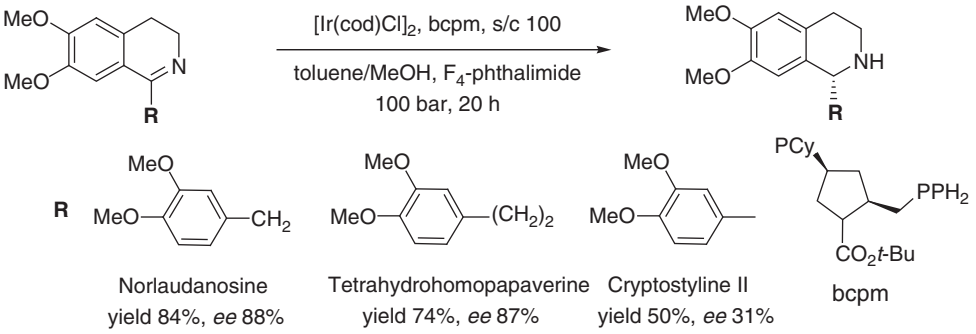
The Ir/taniaphos-catalyzed hydrogenation of a dihydroquinoline derivative was the key step of the synthesis of almorexant, an orexin antagonist for treating sleeping disorder (Scheme 20).[159] The process was carried out on pilot scale. At low temperatures, reasonable s/c ratios and very good *ee* values were obtained. Above 25 °C, catalyst deactivation was observed.



Scheme 20

8.05.5.5 Synthesis of Various Alkaloids

Several tetrahydroisoquinoline alkaloids such as salsoline, laudanosine, or cryptostyline were synthesized starting from the corresponding endocyclic dihydroisoquinolines. With very few exceptions,[28,160,161] Noyori's transfer hydrogenation catalyst was applied.[11,18,96,98,162–166] Here a few selected cases to illustrate scope and limitations of the methodology are described. First, results were reported for the synthesis of the closely related cryptostyline II, norlaudanosine, and tetrahydrohomopapaverine alkaloids (Scheme 21) using Ir diphosphine catalysts.[167] For norlaudanosine and tetrahydrohomopapaverine, good results (*ee* up to 88%) were achieved with an Ir/bcpm complex in presence of phthalimides, whereas low *ee* and yield were obtained for cryptostyline II.

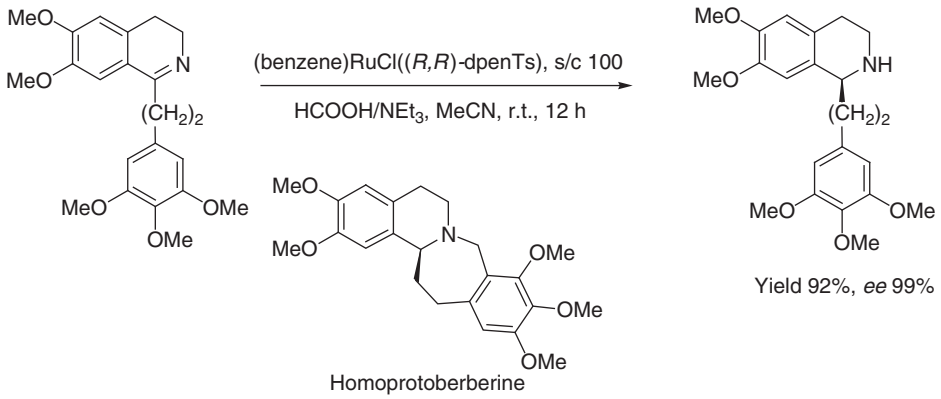


Scheme 21

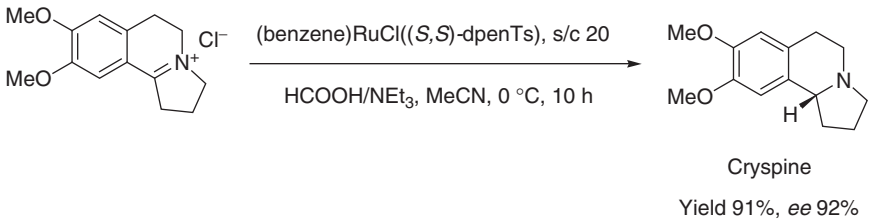
The synthesis of a homoprotoberberine alkaloid was achieved with very good yield and 99% *ee* using Noyori's transfer hydrogenation technology (Scheme 22).[163] The key step for the synthesis of cryspine A[101] (Scheme 23), harmicine,[102] and desbromoarborescidine[102] (Scheme 24) was also the transfer hydrogenation of tri and tetracyclic endocyclic iminium species which occurred in all cases with satisfactory yields and moderate-to-good enantioselectivities albeit at high catalyst loadings.

The key step in a recent synthesis of lennoxamine, an isoindolobenzazepine alkaloid, was the asymmetric reduction of a tetracyclic indolinium intermediate as depicted in Scheme 25.[168] Best results were reported for the Ru-catalyzed transfer hydrogenation using a novel proline-based tetrazole ligand. Similar enantioselectivities were obtained for the Rh and Ir-catalyzed hydrogenation but yields were somewhat lower.

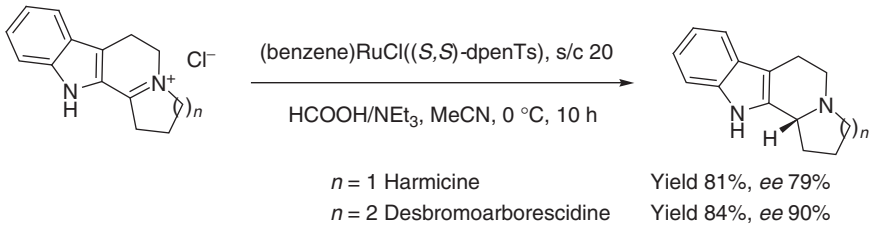
As a final example, all stereoisomers of emetine, an ipecacuanha alkaloid, were prepared via two consecutive asymmetric transfer hydrogenations under standard condition. In Scheme 26 the synthesis of the natural stereoisomer, (–)-emetine is shown.[169] The absolute configuration of the stereogenic centers is controlled by the choice of the appropriate dpenTs ligands. For the first reduction 2.5% catalyst was needed to give the desired tetrahydroquinolines in 93% yield and >99% *ee*. The second,



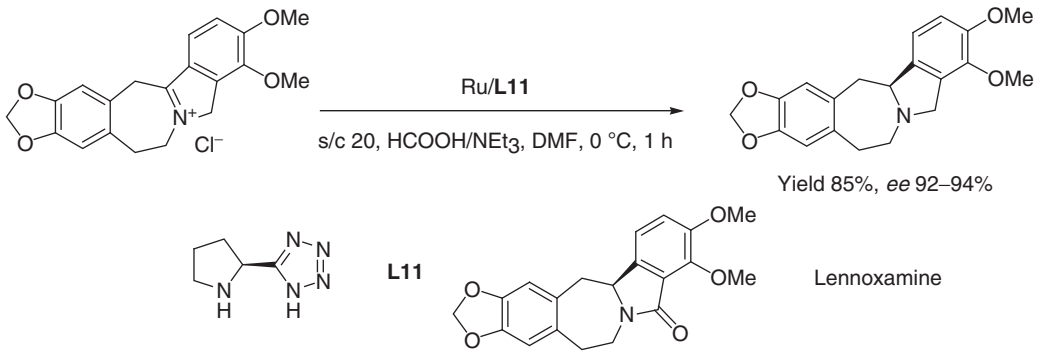
Scheme 22



Scheme 23

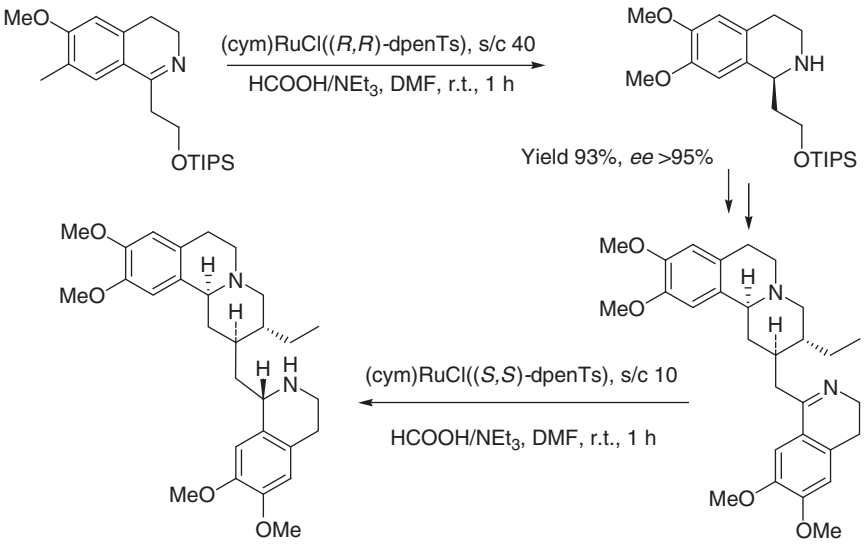


Scheme 24



Scheme 25

diastereomeric reduction required 10% catalyst and depending on the relative absolute configuration of catalyst and substrate, yields of 71–82% and diastereoselectivities of 81–>96% *de* were obtained.



(–)-Emitine, yield 71–82%, *de* 81–96%

Scheme 26

8.05.6 Alternative Reduction Systems

8.05.6.1 Organocatalytic Transfer Hydrogenation

A recent development is the application of organocatalysts for the asymmetric transfer hydrogenation of C═N functions.[170,171] The preferred catalysts are sterically hindered binol-derived phosphoric acids as catalysts and Hantzsch esters or benzothiazoles as hydride source. The method was successfully applied to the enantioselective reduction of imines as well as benzo-fused heterocycles, such as quinolines, benzoxazines, benzothiazines, benzoxazinones, quinoxalines, quinoxalinones, and a limited number of pyridines containing electron-withdrawing groups. Turnover frequencies of the organocatalytic C═N hydrogenations are still lower and reaction times longer than comparable metal-catalyzed hydrogenations. Furthermore, the hydrogen donors are rather expensive and cannot (yet) be recycled, leading to stoichiometric waste. Advantages are the mild and environmentally friendly conditions as well as excellent enantio- and chemoselectivity selectivity make this method a valuable approach to the small-scale synthesis of enantiopure amine building blocks.

8.05.6.2 Chiral Hydrides

Hydride reductions of C═N groups are well known in organic chemistry and it was therefore obvious to try to use chiral auxiliaries in order to render the reducing agent enantioselective.[172] Several chiral reducing agents starting from BH_3, $LiAlH_4$, or $NaBH_4$ and relatively cheap amino alcohols or diols have been developed for the reduction of imines and oxime derivatives.[173–175] Enantioselectivities are medium to high. Most effective chiral auxiliaries can be prepared in one or two steps from rather cheap starting materials like binol, amino acids, tartaric acid, or sugars and they can probably be recycled. A major drawback of most hydride reduction methods is the fact that stoichiometric or higher amounts of chiral material are needed and that the hydrolyzed borates and aluminates must be disposed of, which leads to increased costs for the reduction step. Chiral hydrides are at the moment useful on a laboratory scale but their potential for technical applications is medium-to-low (*see* Chapter 8.02).

8.05.6.3 Hydrosilylation

The situation for the hydrosilylation of C═N functions concerning ecology and economy is somewhat similar as for the hydride reduction, except that fewer effective catalytic systems have been developed.[176–178] Despite some recent progress with highly selective Ti[179] and Cu[180]-based catalysts using cheap polymethylhydrosiloxane as reducing agent and of organocatalysts able to activate trichlorosilene,[181,182] hydrosilylation will see its major applications in small-scale laboratory synthesis.

8.05.6.4 Biocatalysis

Chiral amines can also be produced using aminotransferases either by kinetic resolution of the racemic amine or by asymmetric synthesis from the corresponding prochiral ketone.[183] A variety of chiral amines can be obtained with high to very high enantioselectivities. Several transformations have been developed and were carried out on a 100 kg scale,[184] however, application to small-scale synthetic problems especially for more elaborate targets is not practical because the optimization of the enzyme and reactions condition are very time consuming. Alternative methods such as the asymmetric reductive acylation of ketoximes by enzyme–metal cocatalysis[185] or the use of artificial transfer hydrogenases consisting of an achiral metal complex combined with streptavidine[186] are still in an emerging state (*see* Chapter 8.08).

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8.06 Reduction of C═X to CH–XH by Dissolving Metals and Related Methods

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This chapter is a revision of the previous edition chapter by J. W. Huffman, Vol. 8, pp 107–127, © 1994, Elsevier Ltd.

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Glossary

Cram and *anti*-Cram product A model to describe chiral induction at carbonyl atoms during nucleophilic additions, which is based on steric considerations. According to 'Cram's rule,' the diastereomer is preferably formed that results from attack of the nucleophile from the least hindered side when the conformation of the C–C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent chiral center.

High and low overpotential Electrochemical term, which refers to the potential difference between the thermodynamically determined reduction potential of a half-reaction and the potential at which the redox process is experimentally observed. At an overpotential cathode, the potential is more negative, using more energy than thermodynamics require.

Intersystem crossing (ISC) A radiation-less process involving a transition between two electronic states with different spin multiplicity, for example radiation-less transition of a singlet to a triplet state or *vice versa*.

Moeller–Plessett (MP) perturbation theory It is one of several post-Hartree–Fock (HF) quantum mechanical methods used in computational chemistry, which improves HF by adding electron-correlation effects.

Proton-coupled electron transfer (PCET) Reaction mechanism common in redox reactions. The proton and electron start from different orbitals and are transferred to different orbitals in a concerted elementary step.

Supporting electrolyte A chemical species in electrochemistry, which is not electroactive (within the potential used) and which has an ionic strength and conductivity much larger than the electroactive species. Supporting electrolytes are used to increase the conductivity of the solution during electrochemical measurements, in particular when control of electrode potentials is required.

UHF/RHF theory Unrestricted Hartree–Fock method (UHF) is the most common molecular orbital method for open-shell systems used in quantum mechanical calculations, where the number of electrons of each spin is different. In contrast to the Restricted Hartree–Fock method (RHF) for closed-shell systems, which uses a single molecular orbital twice, once multiplied by the alpha spin function and once multiplied by the beta spin function in the Slater determinant, UHF uses different molecular orbitals for the alpha and beta electrons.

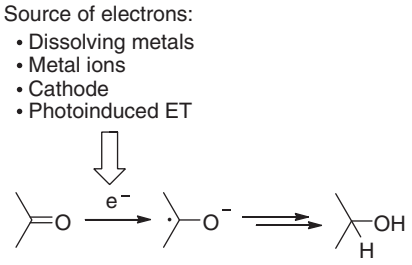
8.06.1 Introduction

Lithium, sodium, potassium, magnesium, calcium, mercury, and zinc are the most prominent examples of metals known for their ease by which they donate one or two electrons to molecules with an accessible, i.e., low lying, LUMO. This reductive electron transfer usually leads to formation of a radical anion in the initial step, which, depending on its nature, undergoes different subsequent reactions. Indeed, reduction of C═O and C═N double bonds by electron transfer in metal–alcohol,

 doi:10.1016/B978-0-08-097742-3.00808-9

metal–ammonia, and amalgam–water systems was for many decades the most important method, and the only viable alternative to catalytic hydrogenations, for transforming aldehydes, ketones, and imines to the corresponding alcohols and amines. Nowadays, dissolving metal reductions have largely been replaced by alternative, experimentally usually less challenging methods, such as complex hydrides or transfer hydrogenations,[1] which are based on the concepts of the Meerwein–Ponndorf–Verley reduction.[2] The reason why reductions of C═X bonds by electron transfer are still performed, however, is the fact that the stereoselectivity of these reactions is often complementary to hydride reductions and hydrogenations.

Reductions with electron transfer as a key step are not limited to dissolving metals, but can also be performed with other reagents, such as metal ions, for example Sm^{2+}, Cr^{3+}, etc., as well as through electrochemical reduction or by photoinduced ET (Scheme 1). In particular, radical cyclization cascades initiated by SmI_2 reduction of a carbonyl group have become a highly versatile tool to prepare complex molecular frameworks in one single step.[3]



Scheme 1

The previous edition of this book includes a survey on dissolving metals for the reduction of C═X systems, including historical developments, practical applications as well as mechanistic and stereochemical considerations that had been reported in the literature up to the mid-1980s. This chapter will therefore focus on important recent developments in this area since then, and readers interested in the earlier work are referred to the previous edition and literature cited in other reference series.[4]

In the first part of this survey, dissolving metal reductions of C═X to CH–XH will be presented, followed by reductions involving metal ions. Electrochemical reduction procedures and reductive photoinduced electron transfer will be treated in Sections 8.06.4 and 8.06.5 of this chapter. All sections will include mechanistic discussions, stereochemical considerations, and typical synthetic applications, with a strong bias on the reduction of the carbonyl moiety.

8.06.2 Reduction by Dissolving Metals

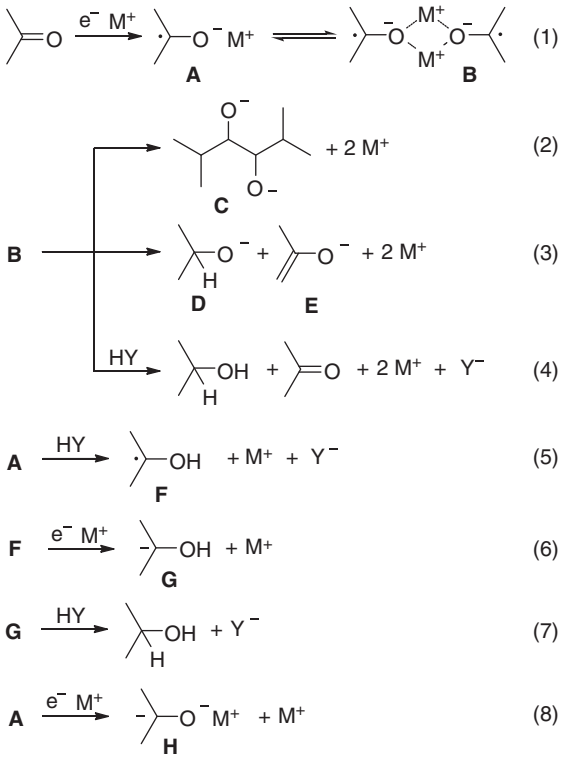
8.06.2.1 Reduction Mechanism

The majority of literature on the reduction of C═X double bonds by dissolving metals focuses on carbonyl reductions. Reductions by alkali metals in ammonia, NH_3, are usually carried out by one of two different methods. One procedure consists of direct reduction of the substrate, which is usually dissolved in an inert solvent, such as diethyl ether or tetrahydrofuran (THF), with the alkali metal dissolved in NH_3, under essentially aprotic conditions. The second method involves addition of an additive slightly more acidic than NH_3, such as ammonium chloride or an alcohol. Although the actual reducing species in either method are solvated electrons, the reaction outcome often varies and leads to different ratios of epimeric alcohols.

Most of the mechanistic discussions for the reduction of saturated carbonyl compounds by active metals are based on the House mechanism,[5] where transfer of an electron leads to formation of a ketyl radical **A**, which carries the negative charge on the more electronegative oxygen atom (Scheme 2). Ketyl radical complexes have been prepared and isolated by reducing aromatic ketones with Li or Na in THF in the absence or presence of hexamethylphosphoramide (HMPA).[6] The fate of **A** depends strongly on the reaction conditions, in particular the absence or presence of a proton donor HY.[7]

A exists in equilibrium with a dimeric (or higher) ketyl complex **B** (equation 1). The latter can either collapse into a pinacolate **C** (equation 2) or, if α-protons are available, undergoes disproportionation via hydrogen transfer to an alkoxide **D** and enolate **E** (equation 3).[8] In the presence of a proton source disproportionation leads to the alcohol and carbonyl compound (equation 4). Thus, these disproportionation pathways actually regenerate the initial carbonyl species, which is rereduced in a subsequent step. An alternative pathway, which is in accordance with the original House mechanism, involves protonation of the ketyl radical (either the monomer **A** or dimer **B**) to give hydroxyalkyl radical **F** (equation 5). A second reduction step leads to the hydroxy carbanion **G** (equation 6), which is subsequently protonated to the alcohol (equation 7).

There has been some controversy in the literature over whether formation of the dianion **H** through two-step reduction of the carbonyl compound is a possible pathway (e.g., equation 1 followed by equation 8). This mechanism, which has been initially proposed by House, could be of particular relevance in reactions in the absence of protons. But even when alcohols are added as a source of protons, it was speculated that the basicity of the ketyl radical **A** is not sufficiently high to accept a proton from an alcohol, and formation of dianions **H** should be the preferred process in reactions both with and without proton source.[9,10]



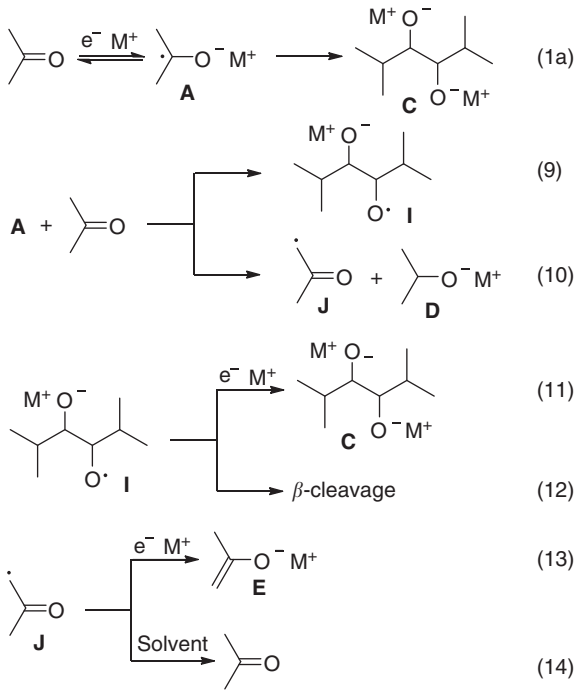
Scheme 2

However, there is meanwhile highly compelling evidence that reduction involving a dianion **H** is not possible with dissolving metals. In particular, it was found that (1) alkali metals are not sufficiently strong reducing agents to transfer two electrons to a carbonyl system, (2) dianions **H** cannot exist in alcoholic solvents,[8b] (3) carbonyl compounds react only with one, and not two equivalents of metal in ammonia,[11] and (4) ketyl radicals **A** are stable in the presence of excess metal.[7]

The extent to which each of the individual steps in Scheme 2 contribute to the actual reaction depends on a number of factors, in particular, structure of the carbonyl species, nature of the reducing metal and the availability of protons. In the absence of an added proton source, the major pathways for enolizable carbonyl compounds involve dimerization (equation 2) and disproportionation (equation 3). Nonenolizable substrates undergo dimerization to give pinacols, or may be trapped at the ketyl radical stage through reaction with the solvent involving radical pathways (not shown). In the absence of an added proton donor, pinacol formation is promoted when lithium is used as reducing metal.[7] In the presence of an added proton source, protonation of the ketyl radical **A** via equation 5 or the complex **B** via equation 4, followed by reduction to the desired alcohol, are processes that compete with dimerization and disproportionation. However, the competition between dimerization and reduction to the alcohol can be influenced by the acidity of the added proton source. Thus, if the desired reaction is indeed reduction of the carbonyl compound to the corresponding alcohol, the metal–ammonia reductions should be performed in the presence of the most practical proton donor (e.g., ammonium chloride or methanol), which favor the pathways shown in equations 4 and 5–8.[7]

Huffman et al. proposed an extended mechanism, which has been developed to accommodate experimental findings in the reduction of camphor in NH_3 in the absence of an added proton donor. Thus, in addition to isomeric pinacols, a dimeric α-hydroxycarbonyl product was also obtained in this reaction, which could only result from coupling of the ketone with a ketyl, followed by β-cleavage.[12] The most important difference, compared with the mechanism in Scheme 2, is therefore the suggestion that both ketone and ketyl must be present in the reaction system at the same time, which would be the case if the initial electron transfer is reversible (equation 9, Scheme 3). However, based on the redox properties of both reducing agent (e.g., metal) and reductant (e.g., the carbonyl species), this equilibrium should lie far to the right-hand side (=ketyl), which means that the initial ET should be an essentially irreversible process. It was, therefore, proposed that the simultaneous presence of ketyl radicals and ketones in the reaction system could result from 'micromixing effects,' where local concentrations of solvated electrons, e.g., $e^-(NH_3)_x$, become depleted so that not every ketone present in this local environment is immediately reduced. Coupling of the ketyl radical **A** with the ketone gives an alkoxyl radical I (equation 9), which can be either reduced to the pinacolate **C** (equation 11) or undergoes β-cleavage (equation 12).

Another adjustment of the proposed mechanism addresses the experimental findings that reductions of α-deuterium substituted carbonyl compounds not only resulted in a loss of isotope label, but also these reactions of undeuterated substrates performed in THF-d_8 gave products in which deuterium was incorporated at the carbon α to the newly formed C–OH moiety.[12] This suggests that some steps in these reactions could involve hydrogen transfer from the solvent. It was therefore proposed that



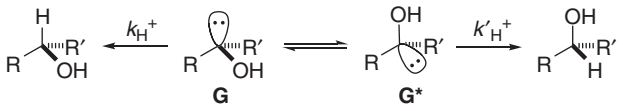
Scheme 3

formation of the disproportionation products, e.g., alkoxide **D** and enolate **E**, proceeds not only through the ionic mechanism in equation 3 (see Scheme 2), but could also involve a free radical pathway, where the ketyl radical **A** abstracts an α-hydrogen from the ketone to form α-keto radical **J** and alkoxide **D** (equation 10). Intermediate **J** can be reduced to the enolate **E** (equation 13) or can abstract a hydrogen atom from the solvent. It was suggested that ethers, such as THF, could act as source for hydrogen atoms, and possibly also NH_3.

8.06.2.2 Stereochemistry

As mentioned in Section 8.06.1, the fact that carbonyl reductions to alcohols with dissolving metals proceed with a considerable degree of stereocontrol, in particular in the case of cyclic substrates, which is often complementary to that in hydride reductions or hydrogenations, is one of the major reasons why dissolving metal reductions still have a place in the toolbox of synthetic methods. Therefore, the question of which step in the mechanism determines the stereochemical outcome has been the topic of a large number of investigations: is it the conformational equilibrium of the hydroxyalkyl radical **F** (or the ketyl radical **A**, respectively),[5] or does the stereochemistry of the product originate from the relative conformational stability of the hydroxyl carbanion **G**?[13]

The original rationale was based on the hypothesis that the stereochemistry of the reduction sequence in the presence of an added proton donor, e.g., electron transfer→H^+→electron transfer→H^+, is determined by the thermodynamic stability of the product, i.e., the more stable of the pair of epimeric alcohols is preferentially formed. According to this, the key step is protonation of the carbanion intermediate **G**, which has a definite tetrahedral configuration, but should undergo rapid inversion. Thus, it was proposed that protonation occurs at equal rates for both enantiomers ($k_H + = k'_{H^+}$), but the transition state energy differences for protonation correspond to the ground state energy differences of the isomeric hydroxyl carbanions **G** and **G*** (Scheme 4).

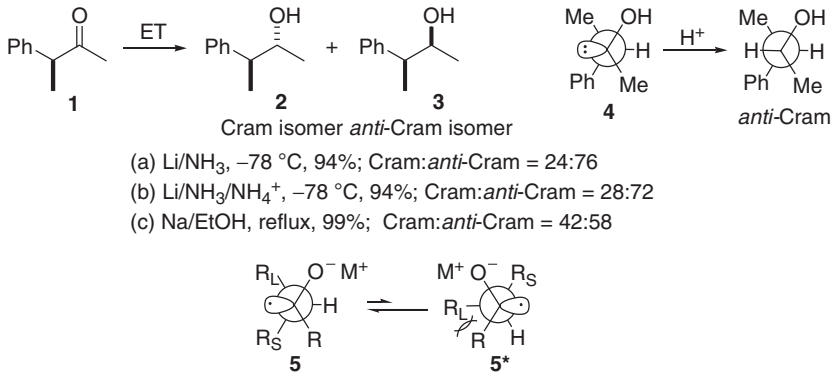


Scheme 4

Nonetheless, experimental data show that in many cases the thermodynamically less stable product is actually formed preferentially. In order to overcome this dilemma, it was therefore proposed that the observed products are the result of a kinetically controlled protonation of the carbanion **G**,[14] where in the majority of reactions the kinetic product is coincidentally also the thermodynamically preferred species. Another explanation proposes that the reaction is thermodynamically controlled in

those cases where the energy difference between the epimeric alcohols is large, whereas in reactions with small energy differences the relative rate of protonation of the epimeric carbanions **G** and **G*** determines the product distribution.[7]

Kinetic control of the protonation of the hydroxy carbanion **G** has been used to explain the stereochemical outcome of the ET-induced reduction of acyclic ketones possessing a chiral center α to the carbonyl group. Thus, reduction of **1** by dissolving metals under different conditions was found to give preferably the *anti*-Cram product **3** (Scheme 5), which is opposite to the selectivity of hydride reductions that favor formation of the Cram isomer **2**.[13]



Scheme 5

To explain the preferred formation of the *anti*-Cram isomer **3**, it was proposed that the intermediate hydroxy carbanion **4**, in which the bulkiness of the substituents decreases in the order OH > Me > negative charge, is protonated in the least sterically encumbered conformation, i.e., where OH and Ph are arranged *anti*. The observed variation in the stereoselectivity among the different reducing methods was attributed to different extents of carbanion pyramidalization.

However, the general problem arising from this stereochemical rationale results from the fact that inversion of carbanions carrying an oxygen substituent is much slower than in a pure alkyl carbanion. This becomes particularly relevant in reductions performed in protic solvents, where it is highly unlikely that protonation of the hydroxyl carbanion **G** (equation 7) occurs only after interconversion. It has therefore been generally accepted that the product ratio does not reflect the conformational equilibrium of the hydroxy carbanion itself, but is instead due to the ratio of the isomeric hydroxy carbanions formed during the reduction. The latter depends on the conformational equilibrium of the ketyl or hydroxylalkyl radical **A** and **F**, respectively. According to *ab initio* calculations using the UHF/RHF and MP2 theory by Houk et al., both ketyl and hydroxyketyl radicals are not planar species, but are slightly pyramidalized and undergo isomerization with low inversion barriers.[15] However, based on the finding that the computed stability of a hydroxycyclohexyl radical possessing an equatorial hydroxyl substituent was too high to account for the experimentally observed stereoselectivity in the reduction of cyclohexanone by dissolving metals, it is assumed that the stereoselectivity of these reductions is determined by the conformational equilibrium of the ketyl radical **A**. Thus, the preferred formation of the *anti*-Cram product **3** in the reduction shown in Scheme 5 results from reduction of the more stable ketyl radical **5**, in which the larger substituents at C1 and C2 are *anti*. It should be noted that the negative charge at the oxygen atom in ketyl radicals **A** is stabilized by the respective metal cation or by hydrogen bonding in the presence of a protic solvent.

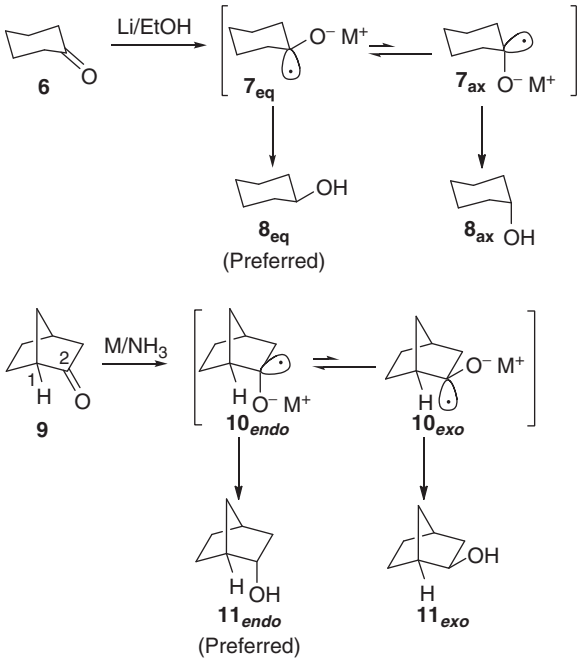
In the case of cyclic ketones it was found that reduction of cyclohexanones **6** with dissolving metals leads to preferred formation of the cyclohexanol isomer $\mathbf{8}_{eq}$ possessing an equatorial OH group (Scheme 6). This can be rationalized by a number of factors, such as a smaller 1,3-diaxial strain in the ketyl radical $\mathbf{7}_{eq}$ when the less voluminous singly occupied molecular orbital (SOMO) is axial. In addition to this, Houk et al. also proposed that induced dipole interactions, torsional strain, and destabilization by electron donation are responsible for a more favorable equatorial conformation of the ketyl radical.[15] However, the high *endo* selectivity of the reductions of bicyclo[2.2.1]heptan-2-ones **9**[14] can be explained by the ring constraints that result in a partial staggered conformation of the proton at C1 and the carbonyl group at C2. Formation of the pyramidalized ketyl radical $\mathbf{10}_{endo}$ with the unpaired electron being located in an equatorial SOMO is energetically more favorable than the isomeric structure $\mathbf{10}_{exo}$ with an axial SOMO.[15]

To conclude, the fact that the stereochemical outcome of dissolving metal reductions is governed by the equilibrium of ketyl radical inversion (where the negative charge is stabilized by either the metal counter ion or by hydrogen bonding, depending on the absence or presence of available protons), clearly shows that reaction conditions, in particular an added proton source, have no influence on the stereochemistry of the reduced product.

8.06.2.3 Synthetic Applications

8.06.2.3.1 Reductions with alkali metals and NH_3 in the absence or presence of an added proton source

Reductions that are carried out in the absence of an added proton donor use, apart from liquid NH_3, an ethereal cosolvent, typically diethyl ether, dimethyl ether, or THF. The most common metals Li, Na, and K, but Rb, Cs and alkaline earth metals have



Scheme 6

also been employed.[5,7,10,12,16] The reactions are typically performed by adding a solution of the carbonyl compound in ether to a solution of the alkali metal dissolved in liquid NH_3. The mixture is refluxed and, when the blue color has disappeared, quenched by addition of a proton source, such as an alcohol or ammonium chloride.[16] Other procedures follow an inverse order, where NH_3 is distilled into a solution of the carbonyl substrate in ether at −70 °C, followed by addition of the metal. The mixture is kept at this temperature until the blue color disappears, then quenched by addition of ammonium chloride and warmed to room temperature.[12] Excess metal can be destroyed by addition of solid ammonium chloride.[8] The latter procedure can also be used in reactions without the ethereal cosolvent.[12]

The reductions in the presence of an added proton donor are performed very similar to those without proton source. The carbonyl compound is dissolved in a mixture of anhydrous ether and alcohol, most commonly ethanol or *tert*-butanol, and the mixtures are stirred until the blue color disappears.[8,16]

8.06.2.3.2 Reductions with alkali metals in ethereal solvents in the absence of NH_3

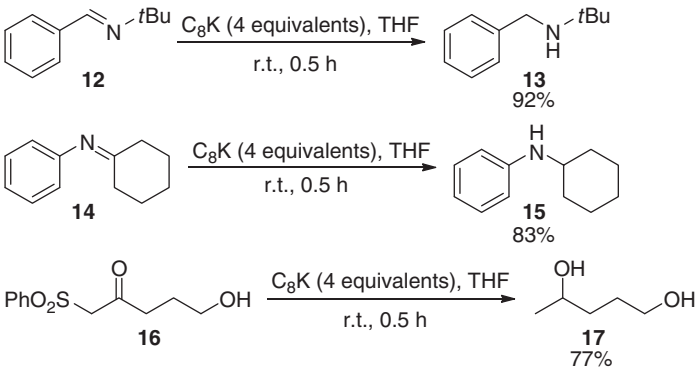
Highly efficient dissolving metal reductions can also be performed in ethereal solvents using sonication.[17] Huffman et al. demonstrated that reduction of (+)-camphor in the absence of NH_3 by the alkali metals Li, Na, and K in THF under sonication gave the same *endo*/*exo* product ratio as the reactions performed in NH_3, which strongly suggests that the reductions follow the same pathway in NH_3 and THF.[11] It should be noted that the reductions involving Li and Na gave a larger ratio of *endo* product, but also resulted in significant formation of pinacols.

Potassium graphite (C_8K), which can be prepared by melting K over graphite at 150–180 °C under an inert atmosphere, has been used to reduce carbonyl compounds and imines, for example **12** and **14**, to the corresponding alcohols and amines in anhydrous ethereal solvents under very mild conditions at room temperature (Scheme 7).[18] Although reduction of α,β-unsaturated ketones and esters under these conditions occurs regioselectively at the C═C double bond to give the saturated carbonyl product, ketones of type **17** possessing an α-sulfonyl group can be reduced to the alcohol with simultaneous cleavage of the C–S bond.

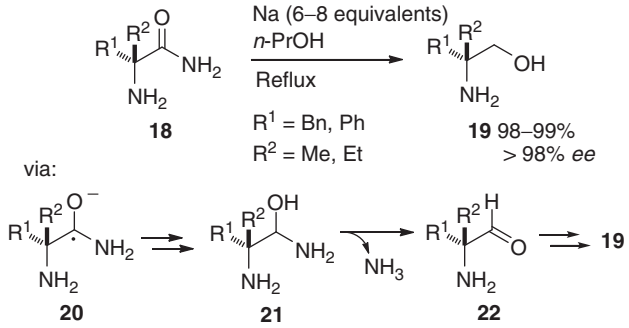
8.06.2.3.3 Reductions with alkali metals in alcohols

With the growing number of alternative procedures, reductions of carbonyl compounds by reducing metals in alcoholic solvents have become less important in organic synthesis. A major problem of reductions under these conditions results from the fact that alcoholates formed through reaction of the metal with the alcohol are strong bases, which could lead to enolization of substrates carrying protons α to the carbonyl group before the reduction. Thus, in the case of carbonyl compounds with a chiral center at the α position, scrambling of the stereocenter often occurs hand in hand with the actual reduction, so that stereoisomeric alcohols are obtained.

Reduction of nonenolizable amino acid amides **18** by liquid sodium metal in refluxing *n*-propanol has been used to prepare enantiomerically pure 2,2-disubstituted 2-amino alcohols **19** in good to excellent yield, and selected examples are given in Scheme 8.[19]



Scheme 7

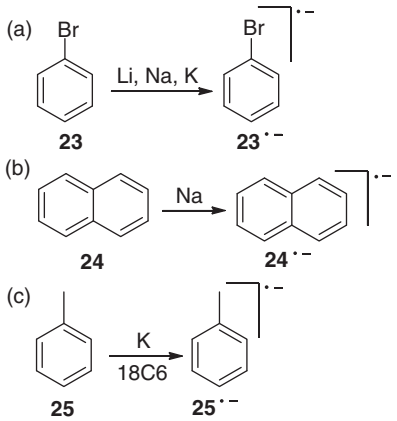


Scheme 8

The reaction is performed by dissolving the amino acid amide in the alcohol, adding an excess of sodium metal and heating to reflux in an inert atmosphere until the sodium is completely dissolved. Reduction occurs selectively at the amide moiety in **18** (via **20**) even in the presence of other functional groups, such as aromatic residues, C═C double bonds and thioethers. The reaction is believed to proceed through two different electron transfer processes, where the first two-electron reduction sequence leads to formation of the geminal amino alcohol **21**, which eliminates NH_3 to produce the aldehyde **22**. A second two-electron reduction process leads to the vicinal amino alcohol **19**.

8.06.2.3.4 Reductions with alkali metals in the presence of a mediator

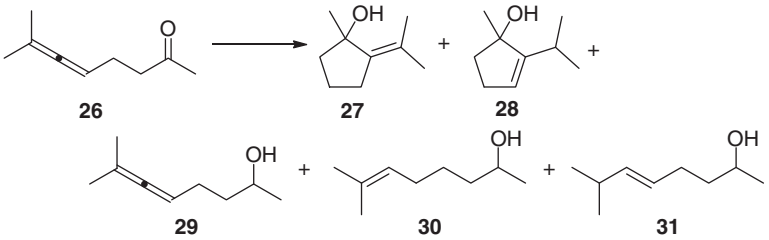
Although reductions with dissolving metals in NH_3 use the solvated electron to directly reduce the substrate, a number of procedures have been developed where metal reduction of an organic mediator, most commonly an aromatic species, produces first a radical anion, which transfers an electron to the carbonyl compound in a subsequent step. For example, reduction of bromobenzene (**23**) by Li, Na, and K leads to the corresponding bromobenzyl radical anion $\mathbf{23}^{\bullet -}$ (Scheme 9a), which readily reduces aromatic aldehydes to their ketyl radicals. Without the halogenated aromatic compound the reduction efficiency of this



Scheme 9

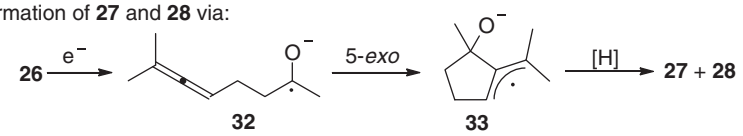
reaction is much lower. In the absence of solvent, this method is suitable for the reductive coupling of aromatic carbonyl compounds. However, dimerization is avoided when the reaction is performed in the presence of organic solvents, such as THF or dimethylformamide, DMF.[20]

Besides reduction of carbonyl compounds to alcohols, dissolving metal reductions have frequently been used to access ketyl radicals, which are trapped by subsequent intramolecular cyclization to π systems. Thus, sodium naphthalenide ($24^{\bullet -}$, Scheme 9b) reductions of allenic ketones of type **26** in THF has been used as initiating step to produce cyclic alcohols **27** and **28** (Scheme 10, entry a).[17] This reaction proceeds through the ketyl radical anion **32**, which undergoes 5-*exo* cyclization to the central carbon atom of the allenic moiety, followed by hydrogen abstraction. The reduction conditions using a mediator are considerably cleaner than the classical dissolving metal procedures using either Na in THF under sonication (entry b) or Li in liquid NH_3 in the presence of alcohol (entry c), which lead to considerable reduction of the allenic moiety without cyclization.



(a) Na naphthalenide (4 equivalents), THF, r.t., 5 h: 46%; **27**:**28** = 67:30:3 (unknown)
(b) Na (4 equivalents), THF, ultrasound, 4 h: 44%; **27**:**28**:**29** = 63:27:6:4 (unknown)
(c) Li (large excess), liquid NH_3, THF, *t*-BuOH: 66%; **27**:**28**:**30**:**31** = 23:39:21:9:5 (unknown):3 (unknown)

Formation of **27** and **28** via:



Scheme 10

The toluene radical anion ($25^{\bullet -}$, Scheme 9c) derived from reduction of toluene by K in the presence of 18-crown-6 (18C6) has been used to remove aliphatic isocyano groups reductively.[21]

8.06.2.3.5 Reduction by other metals

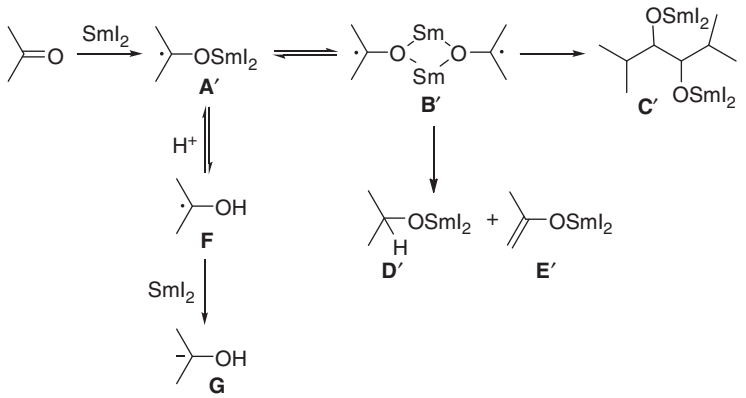
Metals other than the alkali and earth-alkali metals have also been used in carbonyl reductions. Wang et al. reported a procedure for the reduction of aromatic aldehydes using gallium in the presence of water or methanol and potassium hydroxide.[22] Although this study was aimed at optimizing the synthesis of pinacols, rather than reduction of the aldehyde to the respective primary alcohol (which occurs with yields less than 10%), the procedure provides an interesting mechanism for metal activation. Thus, it was proposed that the gallium surface is activated by base, which transforms the insoluble gallium oxide layer (Ga_2O_3) into a soluble mixed oxide ($KGaO_2$) to expose the free gallium metal surface for the reduction.

Lanthanoid metals have recently attracted some attention as reducing agents in organic synthesis. Metallic samarium in aqueous hydrochloric acid has been reported as highly efficient agent for the reduction of aliphatic acyclic and cyclic aldehydes and ketones, leading to the corresponding primary and secondary alcohols in excellent yields.[23] The reaction is performed under exclusion of oxygen by suspending the carbonyl compound in acidic THF and addition of usually 3 equivalents of freshly cut samarium metal at room temperature. Alternative methods that use samarium metal activated by amalgamation or through addition of various halogenated species often result in pinacol coupling as the dominant pathway.

Praseodymium metal, which can *in situ* be generated in THF in the presence of the carbonyl compound through reduction of praseodymium chloride by lithium naphthalenide (see Scheme 9b) under anhydrous conditions, can be used to reduce nonenolizable ketones and aldehydes to the corresponding alcohols in moderate to good yield. Reduction of enolizable carbonyl compounds leads to acyloins and 1,2-diketones.[24]

8.06.3 Reductions by Metal Ions

Samarium diiodide (SmI_2) has found widespread application as reducing agent in synthetic organic chemistry, in particular to promote reductive coupling of carbonyl compounds to C═C double bonds, which can be performed in either inter-[25] or intramolecular[26] fashion (the latter reactions often proceed with excellent stereoselectivities). The mechanism of the reduction of carbonyl compounds is closely related to that of dissolving metals and involves Sm-bound ketyl radicals **A′**, which undergo dimerization to **B′** (Scheme 11; Sm-bound intermediates are denoted with a prime to illustrate the chemical similarity with the



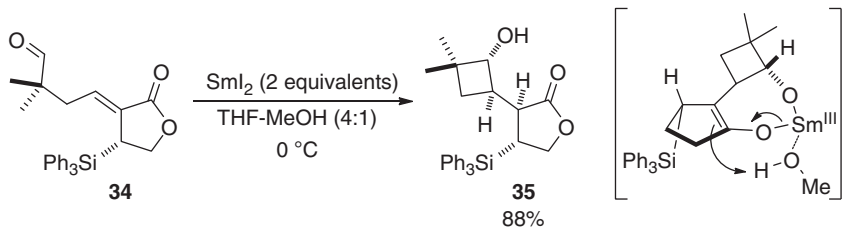
Scheme 11

species shown in Scheme 2). In the absence of protic solvents this dimer collapses to form either pinacolates **C′** or undergoes disproportionation to the samarium alkoxide **D′** and enolate **E′**. In the presence of a proton source the hydroxymethyl radical **F** is formed, which, after a second reduction/protonation step, ultimately yields the alcohol.

Aldehydes are selectively reduced in the presence of ketones by SmI_2.[27] SmI_2 is commonly generated *in situ* through reaction of samarium metal with either diiodomethane or diiodoethane. Although pure SmI_2 is air-sensitive and reactions are usually performed at low temperatures under strict exclusion of oxygen, solutions of the reagent may be manipulated on the benchtop without special precautions. The reaction of SmI_2 with water and alcohols is slow, and alcohols are, therefore, commonly used as cosolvents or proton sources in SmI_2 reductions, since immediate quenching of the negatively charged intermediates with a proton source were found to improve reaction yields.[28] Because SmI_2 can only transfer one electron, multiple equivalents must be used to accomplish two-electron reductions of organic substrates. In most cases, a stoichiometric amount of the reagent or slight excess is sufficient.

The drawback of reductions with SmI_2 is the required use of highly toxic HMPA to increase the reducing power of SmI_2 through complexation and displacement of iodide to the outer sphere. A considerable amount of effort has therefore been made to identify less problematic additives, such as tripyrrolidinophosphoric acid triamide,[29] ethers,[25] alcohols,[26d,e] and water,[26g] which have an accelerating effect on SmI_2-mediated reactions. Studies of the interactions between proton donors and SmI_2 revealed that additives should have enough affinity for Sm(II) to displace iodide, but should not saturate the coordination sphere, which would result in inhibition of substrate reduction.[30] Reductions of carbonyl compounds with SmI_2 in the presence of LiCl or LiBr gives pinacols through inner-sphere reductive coupling.[31] An atom efficient generation of Sm(II) triflate in acetonitrile, which provides a stable alternative to SmI_2, has been reported.[32]

SmI_2 reductions of acyclic ketones possessing a chiral center at the α-position lead, as with the reductions by dissolving metals, to preferred formation of the *anti*-Cram product (see Scheme 5).[13] Complexation of methanol at the samarium center in the 4-*exo* radical cyclization of lactone **34** controls protonation of the intermediate Sm(III) enolate, which occurs from the same face as the bulky triphenylsilyl group and leads to cyclobutanol **35** with complete diastereocontrol (Scheme 12).[33]



Scheme 12

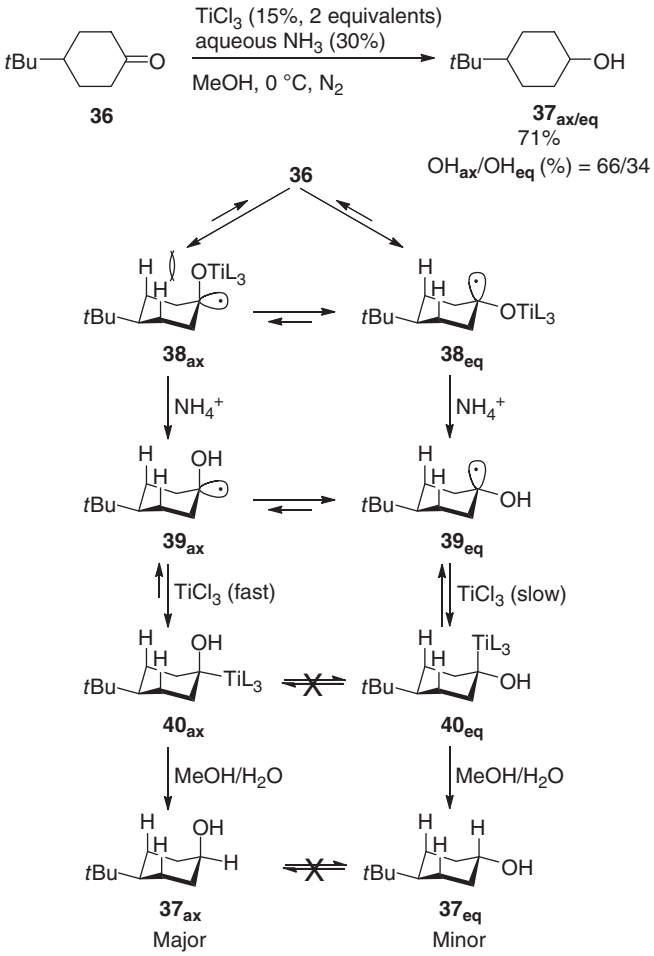
Although carbonyl–alkene couplings are believed to involve first formation of a ketyl radical, which undergoes addition to the alkene π system in a subsequent step, it was shown that reduction of substrates possessing both an isolated carbonyl group and an alkene moiety that is part of an α,β-unsaturated carbonyl π system occurs predominantly at the alkene moiety of the latter.[34]

A number of other transition metal ions also readily induce reduction of carbonyl compounds to the corresponding ketyl radical (under various conditions), but the majority of synthetic applications are aimed toward C–C coupling reactions, rather than direct reduction of the carbonyl group to the corresponding alcohol. Amongst those metal species are low-valent titanium

and vanadium compounds, which are usually generated *in situ* through reduction of Ti(IV) and V(III) species with a metal, for example Zn or Cu.[35]

Cadmium chloride–magnesium in THF/water can also be used for the reduction of ketones and aldehydes to the corresponding alcohols. In contrast to many other reagents, reduction of α,β-unsaturated carbonyl compounds occurs selectively at the alkene π system to yield allylic alcohols. Water is essential, which indicates that this reduction does not proceed through direct electron transfer from the metal to the carbonyl system. This is supported by the observation that hydrogen gas and metallic cadmium particles are generated. Thus, reduction in the presence of D_2O can be used to prepare deuterated alcohols.[36]

Reduction of aromatic and aliphatic cyclic ketones, for example the substituted cyclohexanone **36**, by $TiCl_3/NH_3$ in aqueous methanol leads to formation of the less thermodynamically stable axial alcohol $\mathbf{37_{ax}}$ (Scheme 13).[37] The stereochemical outcome is rationalized by a very fast reduction, where the intermediates do not interconvert. Since Ti(III) is not capable of reducing aliphatic carbonyl compounds, the reaction probably involves formation of a metal-bonded ketyl radical ($\mathbf{38_{ax/eq}}$) through an inner-sphere electron transfer following synergic carbonyl-Ti(III) Lewis acid complexation. It should be noted that in aqueous methanol the effective reductant is not $TiCl_3$ itself, but some other further identified monomeric or polymeric species abbreviated as TiL_3 in Scheme 13. Protonation by NH_4^+ leads to the respective isomeric hydroxymethylene radicals $\mathbf{39_{ax/eq}}$. The preferred formation of the thermodynamically less stable product with an axial OH group ($\mathbf{37_{ax}}$) has been rationalized by the relative rate of the second reduction step, where approach of the bulky TiL_3 occurs from the least hindered, equatorial face to give the transient intermediate $\mathbf{40_{ax}}$ as major isomer. Rapid protonation leads to the observed alcohols.



Scheme 13

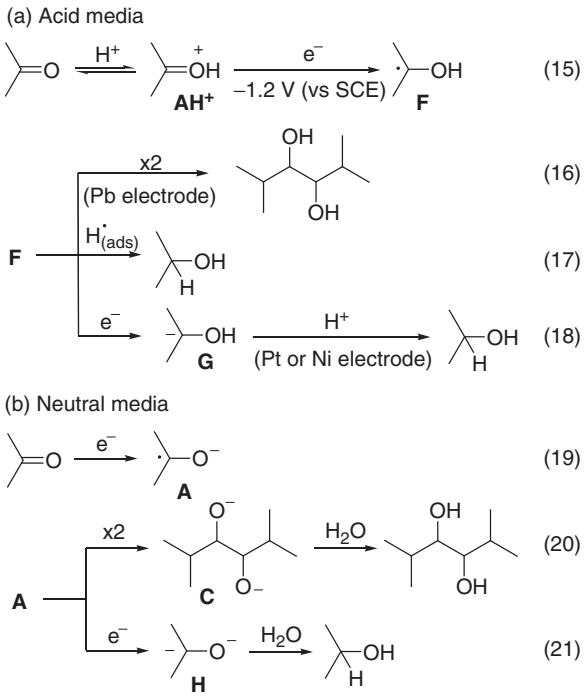
8.06.4 Electrochemical Reductions

8.06.4.1 Reduction Mechanism

Because the carbonyl function is a good electrophore, reduction of carbonyl compounds at the cathode can be readily performed.[38] These reductions could proceed through two, fundamentally different reaction mechanisms: either catalytic

hydrogenation through electrochemically generated hydrogen or through direct electroreduction of the carbonyl function. The reaction pathway can be directed by the conditions of the electrolysis, in particular electrode materials. Thus, catalytic hydrogenations are commonly performed in water–alcohol solutions at low overpotential electrodes (such as Pt, Ni, Cu, Fe), at which hydrogen is produced, which hydrogenates the π system in a subsequent step. Direct electroreductions, however, are usually performed at high-overpotential electrodes (such as Hg, Pb, Cd).[38]

The mechanism of direct electroreduction of carbonyl compounds at the cathode is outlined in Scheme 14. Under acidic conditions reduction of the protonated carbonyl group leads directly to the hydroxyalkyl radical (equation 15), which can be trapped by dimerization to pinacols when the reduction is performed at Pb electrodes (equation 16). With other electrode materials, reduction of the hydroxyalkyl radical to the alcohol is possible by hydrogen atoms adsorbed on the electrode surface (equation 17), or through a second stepwise electron/proton transfer process (equation 18). In a neutral environment, reduction of the carbonyl group leads initially to the ketyl radical **A**. The fate of this radical depends also on the electrode material. Besides dimerization to the pinacolate **C** (equation 20) a second reduction could also lead to a dianion intermediate **H** (equation 21), which is subsequently transformed to the respective alcohol using water as proton source. Although formation of a dianion **H** in dissolving metal reductions can be clearly excluded, the cathode potential can be adjusted to allow principally the reduction **A**→**H** under electrochemical conditions.



Scheme 14

The influence of pH, cathode material[39] and dipole moment of the carbonyl compound[40] on the electroreduction has been studied. Cyclic voltammetry experiments showed that cathodic reduction of aromatic ketones in the presence of acids leads to a cathodic wave that appears at more positive potentials than the original wave of the reactant in the absence of acid. This finding suggests cathodic reduction of a 1:1 hydrogen-bonded adduct between the carbonyl compound and the acid, which is formed in the double layer of the electrode, since the carbonyl compound becomes more basic near the electrode surface than in the bulk solution.[41] The factors controlling the ratio of dimerization/reduction in the electrochemical reduction of aromatic carbonyl compounds have been widely explored. For example, electroreduction of benzaldehyde to benzyl alcohol in acidic water–methanol mixtures depends on the cathode potential and a high rate generation of the intermediate hydroxyalkyl radical (i.e., high concentration), which can be achieved by electrode rotation, electrolyte flow rate, or ultrasound.[42] In fact, whether dimerization occurs in preference to reduction of the substrate to the corresponding alcohol depends also on the substrate itself. Thus, electroreductions performed in aqueous alcoholic solutions using an amalgamated Cu cathode lying on an anionic exchange membrane lead to formation of the pinacol in the case of acetophenone, whereas under identical conditions reduction of benzophenone gives the diphenylmethanol.[43] Under aprotic conditions (e.g., in DMF) and in the presence of bivalent transition metal cations, reductions of aromatic carbonyl compounds can be performed at potentials that are less negative than those required for the direct reduction of the ketone or aldehyde. It is possible that in the presence of metal ions a metal(I) or metal(0)–carbonyl complex is formed, which is subsequently reduced at the electrode. Other explanations propose reduction of

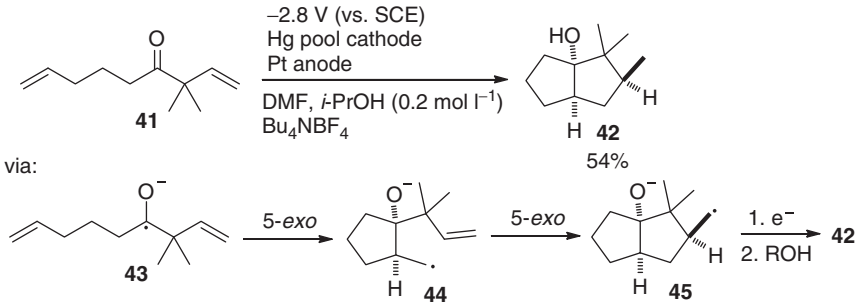
the carbonyl compound by a film of colloidal metal on the electrode surface. It was also observed that the degree of pinacol formation depends on the nature of these transition metal cations.[44]

The course of the electrochemical reduction of aromatic ketones using semiconducting *p*-Si or *p*-GaAs electrodes can be influenced by irradiation with UV–vis light. Thus, when electroreductions using such electrodes are performed under illumination, formation of the pinacol is the major pathway, in contrast to experiments in the absence of light. It appears that electronic excitation of both electrode and carbonyl compound is required to achieve a high degree of selectivity.[45]

Selective reduction of cyclohexanone to cyclohexanol without dimerization to pinacols can be obtained using a Ti/ceramic TiO_2 cathode in 50% methanolic sulfuric acid.[46] The mechanism of the reduction is suggested to involve electrogenerated Ti^{3+}, which chemically reduces the substrate, thereby regenerating Ti^{4+}. It was noted, however, that the selectivity strongly depends on the current density.

8.06.4.2 Synthetic Applications

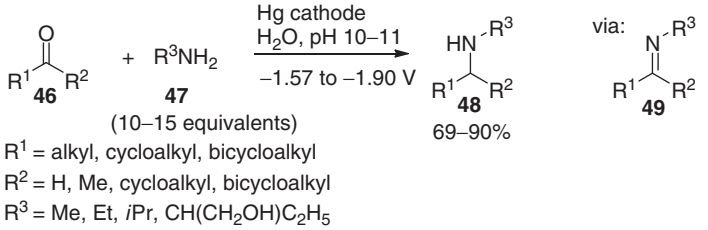
Electroreductions of carbonyl groups are most commonly used as the initiating step in cascade processes, where the intermediate ketyl or hydroxymethyl radical is trapped by intra- or intermolecular addition to a π bond. The example in Scheme 15 shows the tandem cyclization of the allyl pentenyl ketone **41** to the bicyclic alcohol **42**, which is initiated by reduction of the carbonyl group, followed by two consecutive 5-*exo* cyclizations, **43**→**44**→**45**, and a final second reduction step. The reaction is performed at a constant potential of -2.8 V (vs. SCE) in an undivided cell, using isopropanol as cosolvent and a tetraalkylammonium salt as supporting electrolyte.[47]



Scheme 15

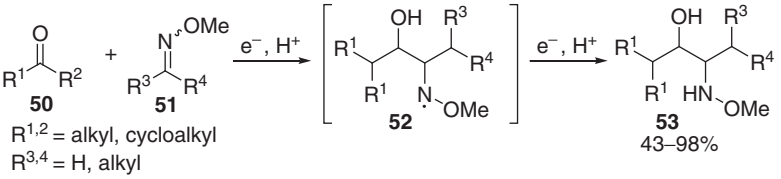
Aromatic ketones possessing an imino substituent in *ortho* position can be electroreductively cyclized to quinolones in acetonitrile at potentials of -2.15 to -2.60 V.[48] Electroreductive intermolecular cross-coupling of aromatic ketones with enol acetates or unsaturated silanes has been performed in divided cells using carbon rod or carbon fiber electrodes.[49]

Electroreduction of aliphatic, mono- and bicyclic aldehydes and ketones **46** in the presence of excess primary amines **47** at a mercury cathode in aqueous solution leads to formation of secondary amines **48** in good to excellent yields (Scheme 16).[50] The mechanism of this process involves first reaction of the carbonyl compound with the amine to form an imine **49**. Because of their lower reduction potential, compared with an aldehyde or ketone, imines are subsequently selectively reduced to the amine in the presence of the carbonyl compound through sequential electron/proton transfer steps.



Scheme 16

However, electroreduction of carbonyl groups in the presence of the more electron-rich oximes occurs selectively at the carbonyl moiety. This observation has been applied by Shono et al. to prepare α-amino alcohols through intermolecular reductive coupling of aliphatic and cyclic ketones **50** with excess oximes **51** (Scheme 17). These electroreductive couplings are usually conducted in alcoholic solvent in a divided cell, using a tin cathode and a carbon rod anode and can also be performed in an intramolecular fashion.[51]



Scheme 17

Different approaches have been used to perform stereoselective electroreductions. Thus, the stereoselective cathodic reduction of unhindered cyclic ketones, for example 4-*tert*-butylcyclohexanone, in alcoholic solvents can be influenced by the nature of the supporting electrolyte. For example, formation of the corresponding *cis*-alcohol (i.e., with an axial OH group) has been achieved in 98% yield in the presence of doubly charged electrolyte cations in the reaction mixture. This outcome has been explained by formation of ion pairs between the metal ion and the intermediate hydroxy carbanion.[52] Enantioselective cathodic reduction of prochiral ketones to the corresponding (*S*)-alcohols has been carried out in DMF/2-propanol mixtures at a mercury pool electrode in a divided cell, using tetrabutylammonium tetrafluoroborate as the supporting electrolyte and (–)-*N*,*N*′-dimethylquininium tetrafluoroborate[53a] or (1*R*,2*S*)-(–)-*N*,*N*′-dimethylephedrinium tetrafluoroborate[53b] as enantioselective inductor. Another approach to reduce ketones in a stereoselective fashion involves combination of specific enzymatic reactions with electrochemical methods. Thus, (*S*)-isomers of methylcyclohexanones can be electroenzymatically reduced to the corresponding (*S*,*S*)-methylcyclohexanols with high yields and excellent stereoselectivity by using methyl viologen as mediator fixed in an ion-exchange polymer (Nafion 117) layer-coated graphite felt electrode, in which the Nafion layer is coated with a thin layer of poly(acrylic acid) immobilized by NAD^+, diaphorase, and alcohol dehydrogenase.[54]

Cathodic reduction of chiral iron sandwich complexes **54–56** carrying carbonyl and oxime functions leads to formation of chiral alcohols and primary amines, respectively (Figure 1). The electroreductions, which are activated by the cationic organoiron moiety and result in regiospecific reduction of the functional group (while leaving the aromatic ring untouched), are performed under acidic conditions using a mercury electrode at potentials of -0.9 to -1.2 V versus SCE.[55]

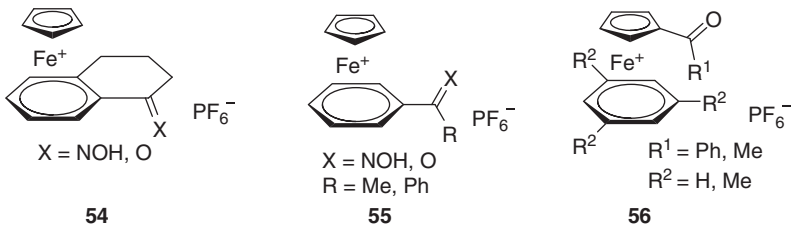


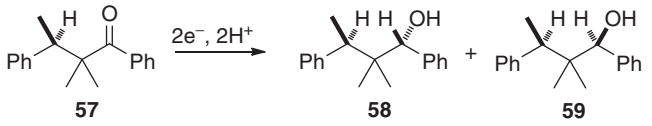
Figure 1 Chiral iron sandwich complexes **54–56** substituted with carbonyl and oxime groups.[55]

Racemic, open-chain prochiral ketones of type **57** possessing a chiral center in the β-position have been reduced at the mercury electrode to give a mixture of the isomeric secondary alcohols **58** and **59** with the latter being formed in excess. This is opposite to the stereochemical outcome of chemical reductions with hydrides, which occur in homogeneous solutions and not at a surface (Scheme 18).[56]

In fact, it was observed that the stereochemistry of the carbonyl reduction is influenced not only by the cathode material, but also the pH of the reaction system. Thus, the ketone **57** approaches the electrode surface from the least hindered site of the molecule, as shown in the example in Scheme 18, where the hydrogen atom at C-3 faces the electrode and not the bulkier methyl and phenyl substituents. The stereoselectivity of the reduction can be rationalized by retention of the tetrahedral configuration at the hydroxyalkyl and ketyl radical centers **60** and **62**, respectively, during the second electron-transfer step, since inversion of the configuration is hindered due to electrostatic repulsion between the electronegative oxygen and the cathode. This effect is amplified in the case of the ketyl radical intermediate **62**, where repulsion between the negatively charged oxygen and the cathode results in more favorable formation of **59**.

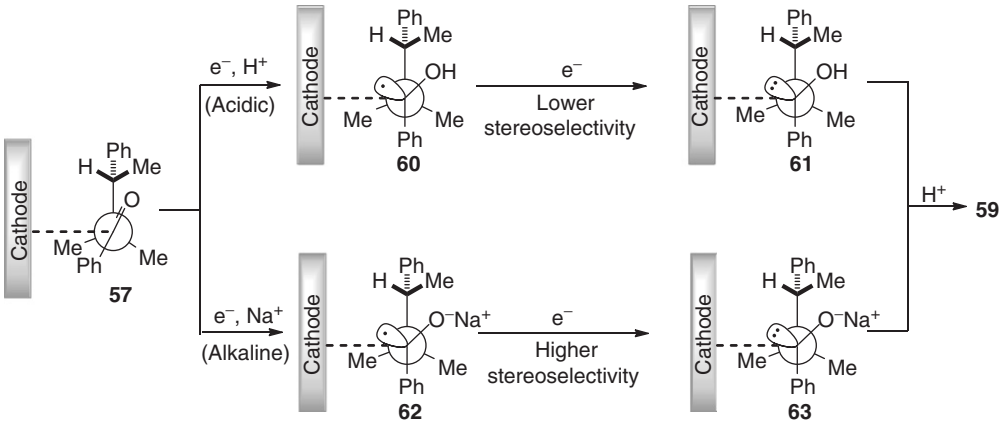
β-Ketosulfones **64** can be reduced in DMF at potentials of -0.9 to -1.2 V under weakly acidic conditions to alcohols with simultaneous scission of the C–S bond (Scheme 19).[57] Transfer of the first two electrons to **64** leads initially to loss of the sulfonyl moiety to give the desulfurized ketone **69**, which is subsequently reduced to the alcohol **70**. Under more acidic conditions formation of pinacols occurs preferably.

Electroreduction of aromatic α,β-unsaturated ketones leads usually to reduction of the conjugated C═C double bond in both aqueous and nonaqueous media to give the saturated, aromatic carbonyl compound, often in addition to other C–C coupling products.[46,58]

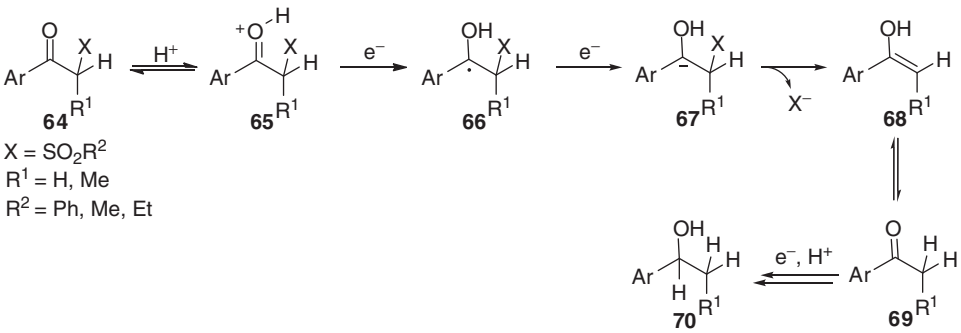


Electroreduction - acidic medium (0.5 M H_2SO_4): 92%; **58**/**59** = 0.76
alkaline medium (1 M NaOH): 100%; **58**/**59** = 0.64

Reduction with $LiAlH_4$ in ether: **58**/**59** = 3.55



Scheme 18



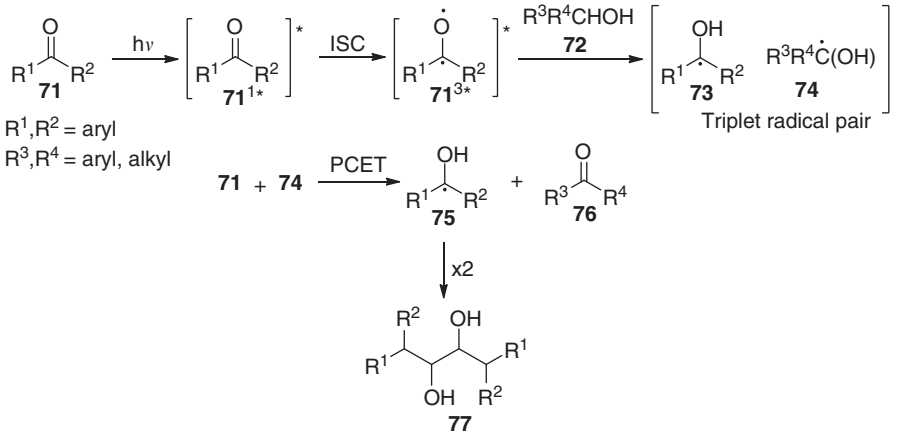
Scheme 19

8.06.5 Reductions by Photoinduced Electron Transfer

Photochemical reactions using semiconductor particles or organic dyes as photocatalysts or photosensitizers find increasing applications in organic synthesis, and some examples for photoinduced reductions of carbonyl compounds have been reported.

The photoreduction of aromatic ketones **71** by alcohols **72** has been intensively studied. Although this reaction does not lead to reduction of the ketone to the alcohol, but instead results in various dimeric coupling products, it will be discussed in this context since it sheds some interesting light into the redox chemistry of the intermediate hydroxymethyl radicals. In general, these reactions proceed through the electronically excited singlet ketone $\mathbf{71}^{1*}$, which undergo intersystem crossing (ISC) to the triplet $\mathbf{71}^{3*}$ (Scheme 20). Hydrogen abstraction from the alcohol **72** leads to a triplet radical pair $[\mathbf{73}\cdot\mathbf{74}]^3$, which, while trapped within the solvent cage, does not couple to a measurable extent to form a pinacol when $R^3=R^4=Ph$.[59] Once the radical pair becomes solvent-separated, it is proposed that transfer of a hydrogen atom from the hydroxymethyl radical **74** to the ground state ketone **71** leads to the hydroxymethyl radical **75**, which subsequently dimerizes to the pinacol **77**.

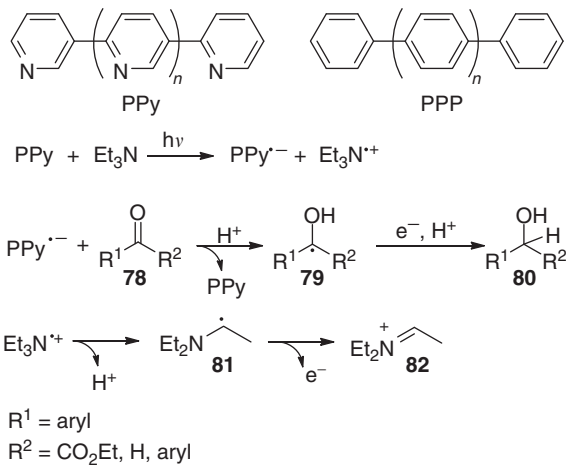
The question of why, in reactions where the substituents R^3 and R^4 in the carbonyl compound are not aromatic, the related cross-coupling between the two different hydroxymethyl radicals **73** and **74** to form mixed pinacols does not occur has been addressed in a number of studies. Lund et al. showed that the product distribution is actually strongly reflected by the exchange reaction between ground state ketone and the hydroxymethyl radical **74**, which in fact is not translocation of a hydrogen atom,



Scheme 20

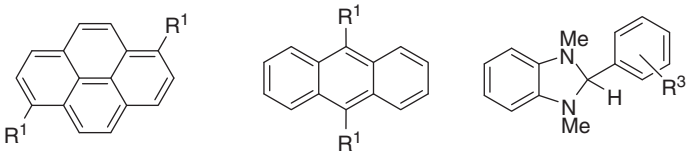
but proceeds via a proton-coupled electron transfer (PCET).[60] Knowledge of the redox properties of both ketone and hydroxymethyl radicals is therefore important for the prediction of the reaction outcome.

Electronically excited aliphatic amines are versatile reducing agents. These can be directly used either in direct photoreductions, but can also be applied in an indirect fashion, where they are used to activate a photocatalyst, which subsequently mediates the actual carbonyl reduction. Poly(pyridine-2,5-diyl), PPy, is an example for a heterogeneous and visible-light induced photocatalyst, which enables reduction of carbonyl compounds to alcohols in the presence of triethylamine as sacrificial electron donor (Scheme 21).[61] The reaction proceeds first by formation the catalytically active species $PPy^{\bullet -}$ through reductive electron transfer from excited triethylamine. $PPy^{\bullet -}$ subsequently reduces the carbonyl compound **78** in two successive steps to the corresponding alcohol **80**. These reactions are typically performed by irradiating a methanolic solution of triethylamine containing equimolar amounts of the respective carbonyl compound and catalytic amounts of PPy in Pyrex tubes at $\lambda > 400$ nm. In contrast to the majority of other methods, this photocatalytic reduction of carbonyl compounds yields the corresponding alcohol as the sole product with good to excellent yield and with no dimerization to pinacols. Although this outcome has been rationalized by suggesting that disproportionation (according to equation 4 in Scheme 2) does not occur in this reaction system, this may not be the correct explanation, since none of the carbonyl compounds studied was enolizable. This is further supported by the fact that pinacol formation was found to be the major pathway when poly(*p*-phenylene), PPP, was employed as photocatalyst. When PPy-catalyzed photoreductions are performed in aprotic solvents, reduction to the alcohol is also the exclusive pathway in anhydrous acetonitrile, although no reaction occurs in cyclohexane. This suggests that the more polar acetonitrile could contribute to stabilization of charge-separated states of the PPy assembly and/or resulting electron-transfer intermediates, which is not possible for the nonpolar cyclohexane. The likely proton source in the reactions in acetonitrile is the oxidized triethylamine, $Et_3N^{\bullet +}$.



Scheme 21

Formation of pinacols is also the major pathway in the photosensitized reduction of carbonyl compounds using electron-donating pyrenes **83** or anthracenes **84** in conjunction with benzimidazolines **85** as a sacrificial coreductant (Figure 2).[62]



83 $R^1 = NMe_2$, OMe

84 $R^1 = NMe_2$, OMe

85 R^2 = H, 4-OMe, 4-Me, 3,5-Cl_2, 2-OH

Figure 2 Pyrene (**83**) and anthracene (**84**) photosensitizer used for the photoreduction of carbonyl compounds in the presence of benzimidazolines (**85**) as coreductant.[62]

However, instead of dimerization the intermediately formed ketyl radical can be trapped through intramolecular cyclization to an alkene or alkyne.

In conclusion, this chapter shows that reduction of C═X bonds (X═O, N) by electron transfer is a highly versatile synthetic method to generate the corresponding radical anion $C^{\bullet}$–X^{-}, which can be further reduced to give alcohols or amines, or trapped through intra- or intermolecular coupling reactions. Of the various reducing agents, dissolving metals have the longest history. Dissolving metals, despite being experimentally more laborious than reductions involving hydrides or by transfer hydrogenation, are still used in synthetic applications, because the stereochemical outcome is often opposite to that obtained by reductions that do not proceed by electron transfer. Today, a number of alternative methods for the reduction of C═X bonds by electron transfer have been developed, and metal ions, in particular samarium(II) compounds, appear to be synthetically highly versatile. Electrochemical methods provide the advantage to perform reductions under 'reagent-free' conditions, since the reduction is performed at the cathode and can be directed into different pathways depending on electrode material and other conditions. The disadvantage of this method is that electrochemical equipment is not necessarily available in standard synthetic laboratories. Photoinduced electron transfer appears to be a promising and synthetically less challenging alternative to dissolving metal reductions, and a number of photocatalytic systems have been developed in recent years.

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8.07 Reduction of C=O to CHOH Using Enzymes and Microorganisms

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Glossary

Active pharmaceutical ingredient (API) The active compound in a pharmaceutical/drug product.

Enantiomeric excess (*ee*) A measure of the purity of the desired enantiomer of a chiral compound. For example, if the *R*-enantiomer is desired, then $ee = \frac{[R]-[S]}{[R]+[S]} \times 100$.

Ketoreductase (KRED)/alcohol dehydrogenase (ADH) A group of enzymes that facilitate the interconversion between alcohols and aldehydes or ketones.

Microorganism A single-cell or multicellular microscopic organism. They can include bacteria and yeast as well as other microscopic plants and animals.

Nicotinamide adenine dinucleotide (NADH) and its phosphorylated analog nicotinamide adenine dinucleotide phosphate (NADPH) – the reduced forms of the cofactors used by ketoreductases to transfer a hydride to a ketone and generate an alcohol. Both forms of the nicotinamide cofactor can be represented by the abbreviation NAD(P)H.

8.07.1 Using Ketoreductases for the Synthesis of Chiral Alcohols

The reduction of prochiral ketones to chiral alcohols is an excellent way to introduce enantioselectivity in the synthesis of a molecule. The enantioenriched alcohols produced can then be transformed into various other functional groups including halides, thiols, amines, azides, etc. without racemization (Figure 1).[1]

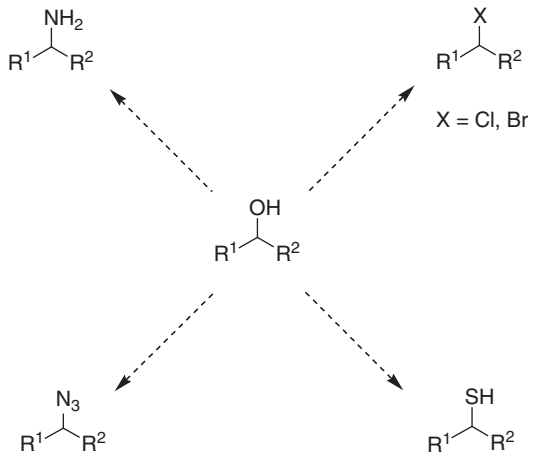


Figure 1 Routes to alternative products via chiral alcohols.

Ketoreductases (KREDs) can be used to generate chiral alcohols with good yields and excellent selectivities (often >99% *ee*). The enantiopure product obviates the need for an *ee* upgrade, which is often required with less selective metal-catalyzed transfer hydrogenation. The application of KREDs to the synthesis of chiral alcohols has met with such success over the past few years that

it is now often considered to be the preferred route to these useful intermediates. Approximately 30% of the reported industrial biotransformations employ KREDs.[2] This biocatalytic approach to synthesizing chiral alcohols is bolstered by an increasing industrial awareness and desire to develop greener, more sustainable processes with stable, predictable costs. However, this shift toward enzyme-catalyzed ketone reductions did not occur overnight. Advances in molecular biology techniques coupled with highthroughput screening enable the rapid generation of new enzymes via directed evolution that were capable of meeting the demands of today's industrial processes.

8.07.2 KRED Mechanism

Most KREDs/alcohol dehydrogenases (ADH) use either nicotinamide adenine dinucleotide (NADH) or nicotinamide adenine dinucleotide phosphate (NADPH) cofactors and catalyze the reduction of carbonyl groups or the oxidation of alcohols (Figure 2). The reaction starts with the binding of the NAD(P)H cofactor to the enzyme. Next, the ketone substrate is bound to the enzyme. Substrate binding is followed by hydride transfer from the cofactor to the ketone to produce an alcohol. The enzyme then releases the product alcohol. The oxidized cofactor must now be transformed back into the reduced form to be used again.

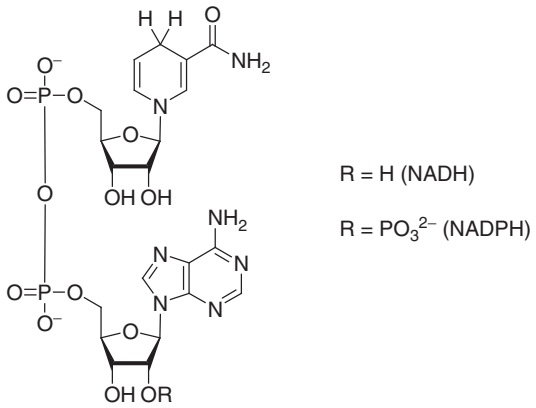


Figure 2 NADH and NADPH cofactors.

The chirality of the product produced is determined by the substrate face to which the hydride adds. If the hydride attacks the *re*-face of the substrate ketone, the (*S*)-alcohol product is obtained, and if it attacks the *si*-face, the (*R*)-alcohol product is obtained, as shown in Figure 3.[3] The equilibrium for this reaction lies far toward the reduction of substrate (half-reaction for NAD^+ reduction has a strongly negative reduction potential of -320 mV), so high conversions (>99%) are typically achieved.[4]

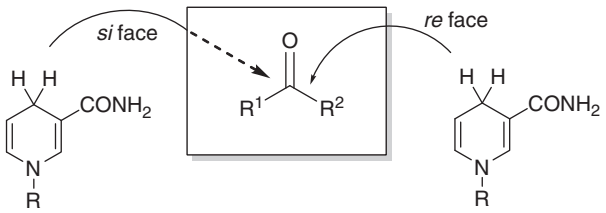


Figure 3 NAD(P)H hydride transfer to Form (*R*)- or (*S*)-alcohol product.

8.07.3 Whole-Cell Organisms for Ketone Reductions

The first enzyme-mediated ketone reductions were observed as a result of screening naturally occurring whole-cell microorganisms.[5] Dumas first described the reducing action of *Saccharomyces cerevisiae*, commonly referred to as baker's yeast, in 1874.[6] Baker's yeast has been used extensively at laboratory scale for the reduction of ketones. Its low cost and lack of toxicity (demonstrated by its use in the baking industry) make it an attractive option. An advantage of whole-cell biocatalysis, in addition to low cost, is the lack of need for an exogenous cofactor regeneration system, as the microbe contains all the enzymes necessary for cofactor regeneration.

The first industrial application of baker's yeast was applied to the synthesis of trimegestone (Figure 4), a steroidal progestin.[7] Excellent chemo-, regio-, and diastereoselectivity were obtained (99.5% *ee*). However, the authors noted that the application of

this whole-cell-mediated ketone reduction required high dilutions (2 g l^{-1} triketone substrate), which limited the utility of this method to very high-value substrates.

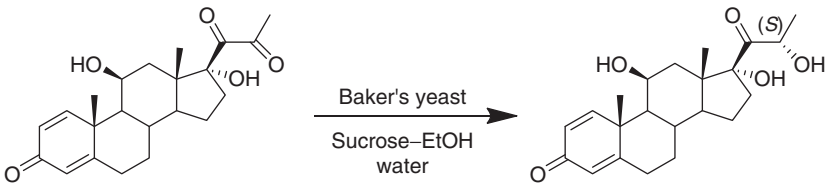


Figure 4 Synthesis of trimegestone via Baker's yeast ketone reduction.

Although the ability to reduce ketones with whole-cell catalysts is fairly commonplace, the productivity of the whole-cell-catalyzed process was clearly lacking. As demonstrated in the trimegestone example, the main drawback of whole-cell catalysis is low productivity due to the need to run in highly dilute media.[8] However, there are other drawbacks. Isolation of the desired product from the reaction media and away from the cells can be tedious and result in low yields. It is also possible to obtain mixtures of stereoisomeric products and undesired impurities due to the presence of multiple yeast reductases with different selectivities.[9] Genetic engineering techniques have been employed to improve the enantioselectivity of whole-cell bioreductions by knocking out the genes encoding for undesired reductase activity and upregulating the expression of the desired reductase. The rational design of engineered yeast strains was advanced with the sequencing of >12 million base pairs contained in yeast's nuclear deoxyribonucleic acid (DNA).[10,11] 6000 genes were identified, which led to a better understanding of individual gene functioning in baker's yeast-mediated ketone reductions and the division of yeast reductases into different families.[12] The identification of individual genes encoding for KREDs of interest allows gene knockout and gene overexpression techniques to eliminate undesired activity and enhance desired activity on a given substrate.[13] This enables access to products with higher enantioselectivity and stereospecificity than is possible using the wild-type organism. Sih et al. demonstrated altered stereoselectivity in the reduction of a keto ester using a yeast strain deficient in fatty acid synthase (Figure 5).[14]

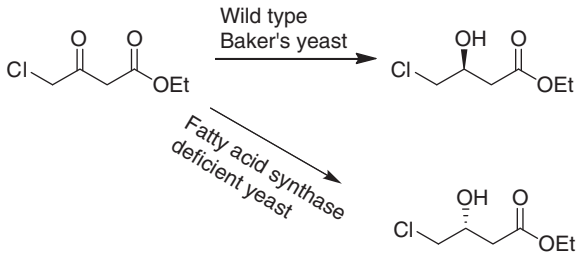


Figure 5 Engineered yeast strain deficient in fatty acid synthase demonstrating inversion of enantioselectivity.

8.07.4 Isolated Enzymes for Ketone Reductions

The most common way to overcome the drawbacks of whole-cell reaction systems is to use isolated enzymes. Isolated KREDs provide simple reaction systems with few reaction components. This is particularly important in the pharmaceutical industry, where isolated enzyme systems are amenable to the rapid process development timeline required to meet the demanding targets for material delivery to clinical trials. The use of recombinant DNA technology with high expression systems and protein engineering has made many isolated KREDs with high activity and a broad substrate range commercially available in kilogram quantities.[15] A number of suppliers provide screening kits containing KREDs that have been through rounds of directed evolution. The availability of these kits, along with the ability to purchase quality enzyme in bulk quantities has opened up biocatalytic ketone reductions to every chemist. These isolated enzyme systems have been used to deliver kilogram quantities of chiral intermediates successfully with excellent *ee* (>99%) and isolated yield (>90%).[16–18]

Efficient commercial chemical processes are characterized by high volumetric productivity. Substrate concentrations of >50 g l^{-1} are typically desired.[19] Additionally, many substrates tend to be very hydrophobic in nature, limiting their solubility in aqueous reaction systems. Therefore, industrial processes require enzyme tolerance to conditions that are typically not encountered by the wild-type enzyme. The enzymes need to withstand substrate and product concentrations that are often 100 times greater than what they would experience in the host organism. They need to be thermally stable and tolerant of solvents that are required to solubilize the substrate. Finally, they need to be able to provide robust, reproducible results. Advances in enzyme engineering, through directed evolution technologies, have enabled enzyme manufacturers to adapt their biocatalysts to these

nonnatural conditions. KRED technology has become such a successful method for the synthesis of chiral alcohols, that it is now the preferred method for the synthesis of chiral alcohols via ketone reduction.[20]

8.07.5 Cofactor Recycling

All KRED biocatalysis requires a hydride source either in the form of NADH or NADPH. Although whole-cell reaction systems can regenerate their own cofactor, isolated enzymes cannot. Because NAD(P)H cofactors are not readily available in bulk quantities at a cost that is amenable to use in stoichiometric amounts, the cofactor must be recycled *in situ* to facilitate catalytic use and enable practical isolated KRED processes. Various cofactor recycling systems have been developed to recycle the hydride source by oxidizing the $NAD(P)^+$ back to NAD(P)H. This regeneration of the hydride source also serves to drive reaction equilibrium toward the desired product. There are several ways to regenerate NAD(P)H that have enabled effective KRED use at large scale. These can be divided into two broad methods: the coenzyme approach and the cosubstrate approach.

The coenzyme approach relies on a second enzyme added to the reaction system whose sole purpose is to regenerate the oxidized form of the cofactor. A variety of coenzyme approaches have been employed. Formate dehydrogenase (FDH) has been used to recycle the nicotinamide cofactor NADH (Figure 6) by catalyzing the oxidation of formic acid to CO_2.[17,21–23] Formate is an inexpensive substrate for NADH regeneration, and the CO_2 byproduct can be easily separated from the desired product during isolation. Additionally, liberation of CO_2 drives the reaction equilibrium in the desired direction. The FDH system requires pH adjustment with acid as the reaction proceeds, which is attractive for base labile compounds.

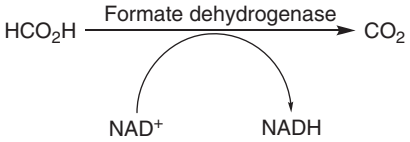


Figure 6 Recycling of NADH cofactor using FDH.

A FDH cofactor recycling system has been used by Pollard et al. to produce (*S*)-3,5-bis(trifluoromethyl)phenylethanol, a pharmaceutically important alcohol intermediate for the synthesis of NK-1 receptor antagonists, via asymmetric enzymatic ketone reduction (Figure 7).[18] An ADH from *Rhodococcus erythropolis* was used to produce the desired product with excellent *ee* (>99.9%) and conversion (>98%).

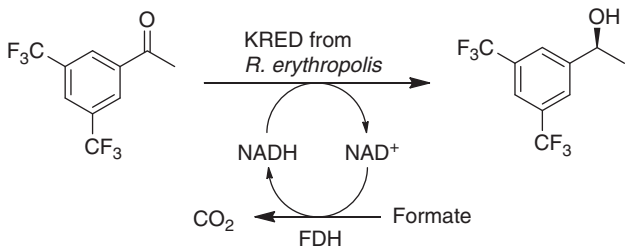


Figure 7 Ketone reduction to NK-1 receptor antagonist intermediate using FDH cofactor recycling.

A more general cofactor recycling system utilizes glucose dehydrogenase (GDH), shown in Figure 8.[19] GDH oxidizes glucose to gluconolactone, which then spontaneously hydrolyzes to give gluconic acid, driving the reaction equilibrium. Reaction pH must be controlled via base addition. The high activity and stability of GDH, combined with its ability to recycle both NADH and NADPH with high specific activity make it the coenzyme system of choice for the recycling of nicotinamide cofactors.

An alternative coenzyme system that is attractive but has not been often utilized uses phosphite dehydrogenase (PDH) for cofactor recycling.[24] PDH converts the reaction buffer from phosphite to phosphate with concurrent cofactor regeneration (Figure 9). The advantage of a PDH system is that there is no significant change in reaction pH, which is attractive for pH-sensitive compounds and simplifies the reaction protocol.

Perhaps the simplest approach to cofactor recycling is the cosubstrate approach. The most commonly employed cosubstrate approach uses isopropanol as an auxiliary substrate.[25,26] The same KRED that reduces the substrate ketone is also used to oxidize isopropanol to acetone, thereby concurrently regenerating the reduced cofactor (Figure 10). The reaction equilibrium can be driven by using a large molar excess of isopropanol, and by removing the acetone byproduct through distillation. One advantage of this approach is that there is no pH control necessary, as neither acid nor base are produced as byproducts. Additionally, this approach has economic advantages as it only requires a single enzyme to perform both the desired reduction and the recycling of the nicotinamide cofactor.

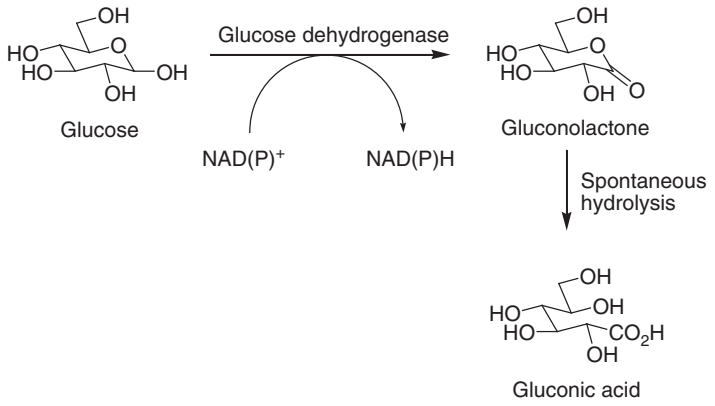


Figure 8 Recycling of NAD(P)H cofactor using GDH.

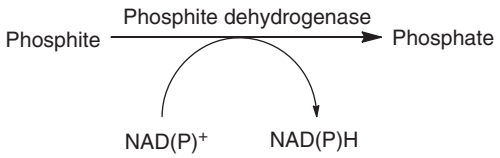


Figure 9 Recycling of NAD(P)H cofactor using PDH.

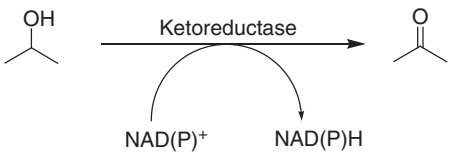


Figure 10 Recycling of NAD(P)H cofactor using isopropanol as an auxiliary substrate.

Savile et al. used the isopropanol cosubstrate approach to develop an efficient dynamic kinetic resolution for the synthesis of (*R*)-2-methylpentanol (Figure 11), an active pharmaceutical ingredient intermediate.[27] The process has been successfully scaled to 100 kg.

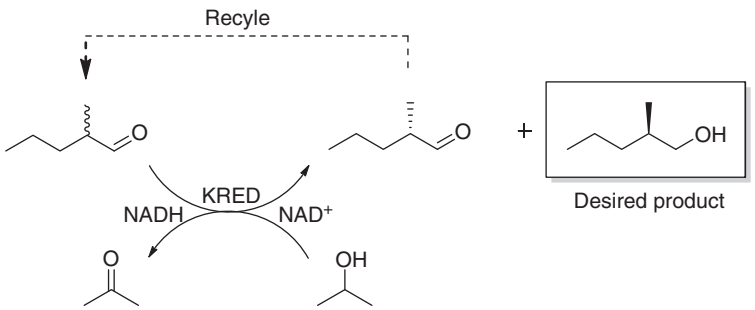


Figure 11 Isopropanol cosubstrate cofactor recycling demonstrated at 100 kg scale.

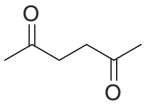
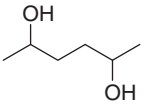
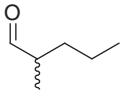
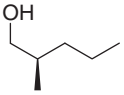
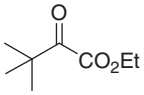
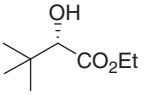
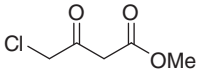
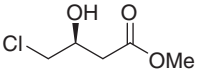
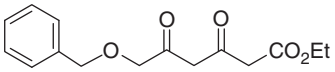
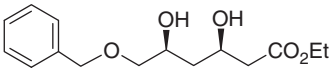
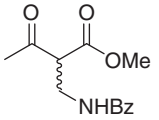
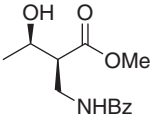
8.07.6 Substrate Range of KREDs

The purpose of this section is not to be comprehensive review of all enzymatic ketone reductions, as the list is quite extensive. Rather, this section is meant to highlight the range of substrates that KREDs are capable of reducing. KREDs have been used to reduce a wide variety of ketone substrates to industrially relevant chiral alcohol products. The products range from small chiral molecules to large, more elaborated intermediates. This chapter is arranged by the type of substrate ketone and in approximate order of substrate complexity and steric bulk.

8.07.6.1 Alkyl Ketones

KREDs are capable of reducing a wide range of alkyl ketones to their corresponding chiral alcohol products with high selectivity and productivity (Table 1).

Table 1 Examples of alkyl reductions by ketoreductases

Entry	Substrate	Product	Use	References
1			(S)-2-Butanol production using *Candida parapsilosis*	28
2			Hexane-2,5-diol used to make chiral phosphine ligands	29
3			(*R*)-2-Methylpentanol used in pharamaceuticals and liquid crystals	27
4			Chiral alcohol used in synthesis of a thrombin inhibitor	19
5			(*S*)-Ethyl-4-chloro-3-hydroxybutyrate used in atorvastatin synthesis	30
6			Advanced atorvastatin intermediate	31–33
7			Precursor on synthesis of carbapenem antibiotics	34

(*S*)-2-Butanol **1**, one of the smallest chiral alcohols, is produced on industrial scale using a carbonyl reductase from *Candida parapsilosis* in a biphasic reaction mixture.[28] The enzyme and NAD cofactor are dissolved in an aqueous buffer phase containing 100 mM triethanolamine at pH 7.0. This aqueous phase is then brought into contact with the organic phase, which consists of an immiscible alcohol (2-heptanol) and the substrate 2-butanone. The 2-heptanol serves as the cosubstrate needed for cofactor regeneration. The reaction can be run at $>100\ g\ l^{-1}$ of 2-butanone substrate, and the desired (*S*)-2-butanol product is obtained with >98% *ee* in 12 h.

Hexane-2,5-diol **2** is a starting material used in the synthesis of chiral phosphine ligands. Both the (*R*,*R*)- and (*S*,*S*)-enantiomers can be made efficiently via reduction of the prochiral diketone precursor using enantiocomplementary KREDs from *Lactobacillus* and baker's yeast, respectively.[29] Excellent enantioselectivity and diastereoselectivity was achieved (>99%), and yields greater than 95% were obtainable. A substrate-coupled cofactor regeneration approach with 2-propanol as the cosubstrate, combined with the use of continuous stirred tank reactor for *in situ* removal of the byproduct acetone, afforded high space-time yields of $>170\ g\ l^{-1}\ day^{-1}$ hexanediol.

(*R*)-2-Methylpentanol **3** is an important chiral intermediate used in the synthesis of a variety of products, including pharmaceuticals and liquid crystals. An evolved KRED was used to generate this chiral alcohol starting from the racemic 2-methylvaleraldehyde substrate.[27] The product was obtained in >98% *ee* at a high substrate loading of $220\ g\ l^{-1}$. Cofactor recycling was accomplished using a substrate-coupled approach with isopropanol, affording a cost-effective, green, and scalable process. The reaction was scaled to produce 100 kg of (*R*)-2-methylpentanol.

The reduction of ethyl trimethylpyruvate (entry 4) was carried out using KRED-101 from Biocatalytics (now Codexis, Inc.).[19] The chiral alcohol product is an important building block in the synthesis of a thrombin inhibitor. Greater than 99% *ee* was observed with quantitative conversion. Cofactor regeneration was accomplished using an enzyme-coupled approach with GDH, 1.3 M equivalents of glucose, and only $0.12\ g\ l^{-1}$ of NADP. This represents an extremely efficient 2000:1M ratio of substrate to cofactor. Up to $100\ g\ l^{-1}$ product alcohol concentration could be reached using a substrate-feeding strategy.

The reduction of prochiral alkyl ketoesters to their corresponding chiral alkyl β-hydroxyesters has been shown to produce useful intermediates for the synthesis of pharmaceuticals. The enantioselective reduction of 4-chloroacetoacetate (entry 5) yields an important building block for atorvastatin (Lipitor®).[30] The (*S*)-ethyl-4-chloro-3-hydroxybutyrate product is obtained in 96%

isolated yield and >99.5% *ee* using an evolved KRED and a GDH cofactor recycling system. 160 g l^{-1} of substrate could be converted in 8 h using only 0.57 g l^{-1} of KRED (0.36 wt%).

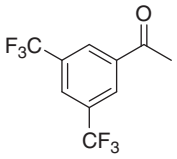
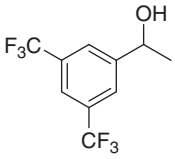
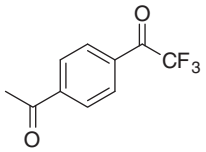
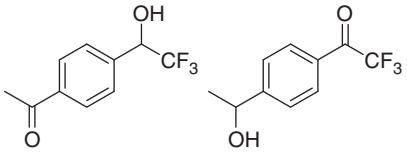
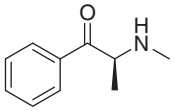
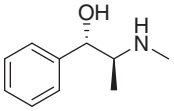
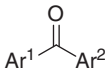
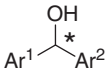
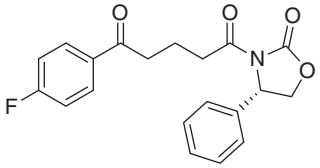
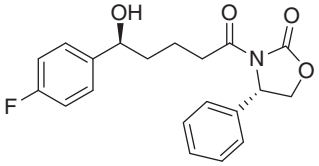
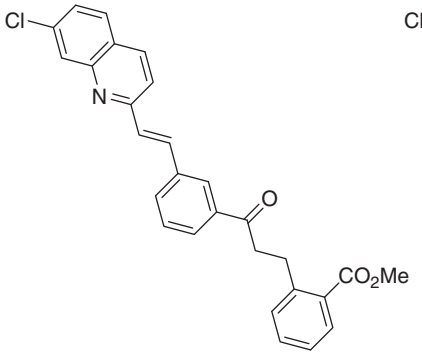
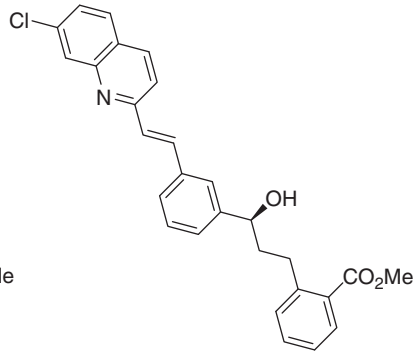
A more advanced intermediate to atorvastatin can be accessed via the diketone reduction of entry 6 using a KRED from *Acinetobacter* that was cloned and expressed in *Escherichia coli*.[31–33] Although a moderate substrate concentration (10 g l^{-1}) was demonstrated, >99% *ee* and diastereomeric excess was observed. NADPH cofactor recycling was accomplished using 2-propanol as a cosubstrate.

KREDs with the ability to reduce a racemic mixture of methyl-2-benzamidomethyl-3-oxobutyrate (entry 7) to 2*S*,3*R*-methyl-2-benzamidomethyl-3-hydroxybutyrate have been identified.[34] This single diastereomer product is a precursor in the synthesis of various carbapenem antibiotics. The substrate's chiral center, situated between two carbonyls, is easily epimerizable, enabling a dynamic kinetic resolution. An evolved KRED was capable of converting 250 g l^{-1} of substrate with >99% enantio- and diastereoselectivity. A cosubstrate approach with 2-propanol was used to regenerate the NADPH cofactor.

8.07.6.2 Aryl Ketones

Another common class of substrate reduced by KREDs is aryl ketones (Table 2). Aryl ketones can range from small acetophenone-like ketones to fairly large substrates, with bulk on both sides of the carbonyl being reduced. KREDs typically reduce substrates of this class with very high selectivity.

Table 2 Examples of aryl ketone reductions by ketoreductases

Entry	*Substrate*	*Product*	*Use*	*References*
1			Chiral (*S*)-3,5-bistrifluoro-methylphenyl ethanol for the synthesis of NK-1 receptor antagonists and aprepitant	18
2			Synthesis of fluorinated chiral intermediates	35
3			Reduction of MAK to active ingredients pseudoephedrine	36
4			Diaryl ketone reductions	37
5			Chiral alcohol intermediated in the synthesis of ezetimibe	52
6			Chiral alcohol intermediated in the synthesis of montelukast	53

The enzymatic reduction of bistrifluoroacetophenone **1** to the chiral alcohol has been used in the synthesis of (*S*)-3,5-bistrifluoromethylphenylethanol (a pharmaceutically important alcohol intermediate for the synthesis of NK-1 receptor antagonists) and (*R*)-3,5-bistrifluoromethylphenylethanol (used to make aprepitant/EMEND®).[18] The isolated enzyme ADH from *R. erythropolis* reduced the poorly water-soluble substrate to the (*S*)-enantiomer with excellent *ee* (>99.9%) and good conversion (>98%). The optimized process was demonstrated up to pilot scale and achieved a space-time yield of up to 260 g l^{-1} day^{-1}. The (*R*)-enantiomer was produced in >99% *ee* by KRED-101 from Biocatalytics, Inc. (now owned by Codexis, Inc.). A GDH cofactor recycling system was used in both cases even though KRED-101 was NADPH dependent, whereas the ADH from *R. erythropolis* was NADH dependent.

An excellent example of the exquisite selectivity that KREDs offer can be seen in the reduction of diketone **2**.[35] Commercially available KREDs were able to reduce selectively either the methyl ketone or the trifluoromethyl ketone. In the case of the trifluoromethyl hydroxy ketone product, both the (*R*)- and (*S*)-enantiomers could be obtained with excellent *ee* (>99%). As a result, costly and time-consuming protection/deprotection of the ketone moiety was avoided, and chiral hydroxyketones, chiral trifluoromethyl hydroxyketones, or chiral diols could be easily accessed. Fluorinated chiral intermediates such as these are routinely seen in the pharmaceutical industry, as the incorporation of fluorine allows chemists to alter the electronic properties, binding affinities, and bioavailability of their compounds.

The reduction of 1-phenyl-2-methylaminopropan-1-one (MAK) **3** to the active ingredient pseudoephedrine (SUDAFED®) has been accomplished using a KRED from *R. erythropolis* in an enzyme-coupled system with glucose and GDH.[36] Only the desired (*R*,*S*)-pseudoephedrine stereoisomer is produced enantioselectively and diastereoselectively from the racemic substrate MAK, leaving the (*R*)-enantiomer of the substrate unreacted.

A particularly good example of the selectivity of KREDs can be found in the enantioselective reduction of diaryl ketones **4** to diarylmethanols.[37] Diarylmethanols are important building blocks in the synthesis of pharmaceutically important molecules including antihistaminic, anesthetic, diuretic, antidepressive, antiarrhythmic, and anticholinergic compounds.[38–40] There are few examples of highly selective diaryl ketone reductions involving hydrogenation or Corey-Bakshi-Shibata reduction.[41–43] The highly enantioselective (>95% *ee*) reduction of select benzophenones has been demonstrated by using lithium aluminum hydride chiral amino alcohol complexes,[44,45] *B*-chlorodiisopinocamphenylborane,[46] oxazaborolidine,[47] and chiral diphosphine/diamine Ru complexes.[48] These types of chemically catalyzed diaryl ketone reductions rely on both electronic and steric effects to determine the degree of enantioselectivity (**Figure 12**). Their limitation lies in the fact that their substrates must either be highly electronically dissymmetric or have an *ortho*-substituted aryl group to achieve good selectivity.[49]

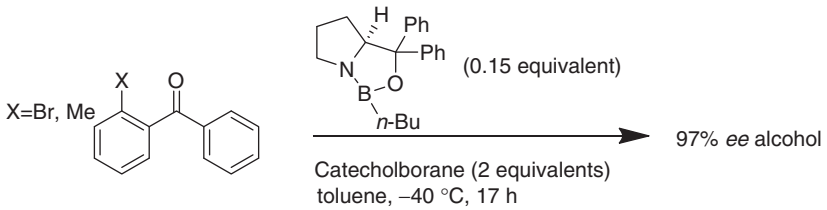


Figure 12 Chemically catalyzed diaryl ketone reductions require electronic dissymmetry or *ortho*-substitution for selectivity.

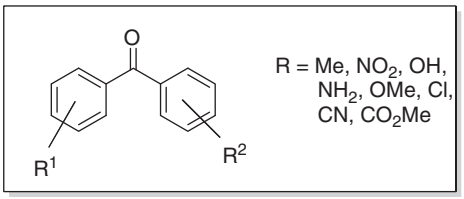
Truppo et al. screened a range of diaryl ketone substrates against commercially available KREDs, including *ortho*-, *meta*-, and *para*-substituted benzophenones as well as several benzoylpyridines. Aryl substitutions included electron-donating, electron-withdrawing, and halogen substituents (**Table 3**).

Generally, *ortho*-substituted substrates afforded greater alcohol product *ee* than their *meta*- and *para*-substituted counterparts. This trend was observed in methyl (**1**), hydroxyl (**6**), amino (**9**), and chloro-substituted (**12**) benzophenones. However, contrary to results obtained with most chemical catalyst reductions, *ortho*-substitution was not required for good selectivity. Nitro substitution at the *meta* (**4**) and *para* (**5**) positions and *m*-chloro (**13**) substitution provided excellent selectivity (97–99% *ee*), whereas *p*-methyl (**3**) substitution yielded 85% *ee* alcohol product. In comparison, the selective 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl/chiral diamine Ru-complex hydrogenation of *o*-methyl substituted benzophenone was achieved with high enantioselectivity (>93% *ee*), but the hydrogenation of the *p*-methyl-substituted counterpart resulted in 8% *ee* alcohol product.[48] Another trend observed for substrates with a single substitution on one of the phenyl rings was that electron-withdrawing groups generally provided for better selectivity than electron-donating groups. Nitro substitutions, for example, provided much higher enantioselectivity than hydroxy- or methoxy-substituted diaryl ketones. The enzymatic reduction of *p*-nitro-substituted benzophenone **5** produced 97% *ee* alcohol product compared with 81.8% *ee* achieved with diphenylzinc aryl addition with a chiral pyrrolidinylmethanol catalyst.[50] High selectivity was also observed in substrates with substituents on both phenyl rings (**15**,**16**).

A series of benzoylpyridine derivatives (**Figure 13**) also exhibited highly selective reduction to their diarylmethanol counterparts with the KRED enzymes. Of particular interest is the Cl-substituted benzoylpyridine **4**, which is a precursor of the histamine H1 antagonist (*S*)-carbinoxamine. The enantioselective enzymatic reduction of **4** achieves excellent selectivity (94% *ee*).

The final two aryl ketone entries (**5**,**6**) in **Table 2** represent higher molecular weight ketones that are reduced enantioselectively by KREDs. They also represent chiral alcohol intermediates to two large volume pharmaceutical products. Ketone **5** is reduced using an evolved KRED to a key chiral alcohol intermediate for the synthesis of ezetimibe (ZETIA®) with >99% *ee*.[16,51,52] Ketone

Table 3 Examples of diaryl ketone reductions of ketoreductases



Entry	R^1	R^2	*(R)-alcohol*		*(S)-alcohol*	
			ee	*KRED*	*ee*	*KRED*
1	*o*-CH_3	–	98	121	95	119
2	*m*-CH_3	–	72	121	–	–
3	*p*-CH_3	–	85	101	9	119
4	*m*-NO_2	–	34	111	>99	108
5	*p*-NO_2	–	96	128	97	119
6	*o*-OH	–	84	111	–	–
7	*m*-OH	–	61	112	13	119
8	*p*-OH	–	69	113	55	117
9	*o*-NH_2	–	91	101	64	114
10	*p*-NH_2	–	60	111	51	119
11	*p*-OMe	–	70	101	64	119
12	*o*-Cl	–	64	121	>99	118
13	*m*-Cl	–	39	111	>99	108
14	*p*-Cl	–	64	101	–	–
15	*m*-CN	*p*-Cl	84	112	90	108
16	*m*-CO_2Me	*p*-Cl	33	115	>99	108

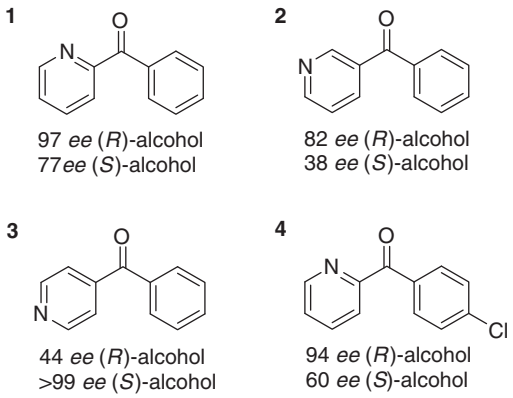


Figure 13 Benzoylpyridines selectively reduced by ketoreductases.

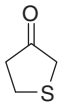
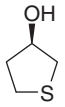
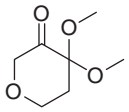
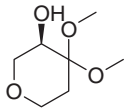
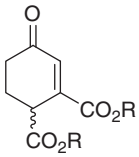
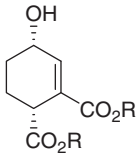
6 is reduced to a chiral alcohol intermediate used in the synthesis of montelukast (SINGULAIR®).[53] After identifying a KRED with perfect selectivity but poor activity, five rounds of directed evolution yielded an enzymatic process that can produce 100 g l^{-1} of product with >99.9% *ee* in 24 h with <4 wt% of catalyst. The KRED was also evolved to take advantage of the isopropanol substrate-coupled approach to cofactor regeneration.

8.07.6.3 Cyclic Ketones

KREDs have also been shown to be extremely selective in the reduction of a wide range of cyclic ketones, including five-, six-, and seven-membered rings, as well as bridged ring systems (Table 4).

(*R*)-Tetrahydrothiophene-3-ol **1** is a key starting material in the synthesis of the potent antibacterial prodrug sulopenem being developed by Pfizer. The original synthesis of the chiral alcohol was a five-step synthesis starting from L-aspartic acid. An alternative, one-step synthesis, was developed starting from the commodity chemical tetrahydrothiophene-3-one, in which a KRED was used to reduce the prochiral substrate to the desired product.[54,55] The initial KRED identified reduced the nearly

Table 4 Examples of cyclic ketone reductions by ketoreductases

Entry	*Substrate*	*Product*	*Use*	*References*
1			Chiral alcohol starting material in synthesis of antibacterial prodrug sulopenem	54,55
2			Chiral alcohol intermediate in the synthesis of a chemokine receptor antagonist	56
3			Dynamic kinetic reduction of a six-membered ring cyclic α,β-unsaturated ketone	57

spatially symmetrical ketone with only moderate selectivity (63% *ee*). After several rounds of directed evolution, a new enzyme variant enabled the desired product alcohol to be obtained in 99.3% *ee*. This process has been demonstrated at 100 kg scale.

The reduction of the six-membered ring cyclic ketone **2** to a chiral alcohol intermediate in the synthesis of a chemokine receptor antagonist was accomplished using KRED-101 (Codexis, Inc.).[56] 4,4-Dimethoxytetrahydro-2H-pyran-3-one was reduced to the (*R*)-α-hydroxyketal with excellent selectivity (>99% *ee*). The enzymatic system proved to be extremely productive, reducing 100 g l^{-1} of the substrate with only 0.1 g l^{-1} (0.1 wt%) KRED. A GDH cofactor recycle system was employed, and the reaction was demonstrated at 80 kg scale in the pilot-plant.

The dynamic kinetic reduction of six-membered ring cyclic α,β-unsaturated ketone **3** using a KRED enabled a facile method for obtaining the desired enantiopure material starting from racemic substrate.[57] In this way, two stereocenters were simultaneously set, as the second chiral center is epimerizable under the KRED reaction conditions. The alcohol product was produced with 99% *de cis* and 95% *ee* (*S*) at the COH. Cofactor recycling was accomplished using a substrate-coupled approach with isopropanol.

8.07.7 Summary

The availability of bulk quantities of KREDs, and the broad range of ketones that can be reduced with excellent enantioselectivity has made enzymatic ketone reduction one of the best choices for producing chiral alcohols from prochiral ketone substrates.[20] Enzymatic ketone reductions have largely supplanted chemocatalytic methods in pharmaceutical synthetic processes,[19] and have been used to deliver kilogram quantities of chiral intermediates economically with excellent *ee* (often >99%) and isolated yield (>90%).[16,19,58–60]

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8.08 A Reduction of C═N to CH–NH Using Enzymes and Microorganisms

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Glossary

Cofactor recycling *In situ* recycling of cofactors such as nicotinamide adenine dinucleotide reduced (NADH) and nicotinamide adenine dinucleotide (phosphate) reduced (NADPH) by the addition of auxiliary enzymes and reagents in order to allow for catalytic amounts of NADH, etc. to be used on large scale.

Directed evolution Enhancement of a characteristic of an enzyme (e.g., enantioselectivity, substrate specificity, and thermostability) by iterative rounds of random mutagenesis coupled with either screening or selection.

Flavoprotein Flavoproteins are proteins that contain a nucleic acid derivative of riboflavin: either flavin adenine dinucleotide or flavin mononucleotide.

NADH/NAD(P)H Nicotinamide cofactors involved in redox processes including the reduction of imines to amines catalyzed by imine reductases.

Protein engineering Alteration of properties of an enzyme by the rational/semirational mutation of specific amino acid residues within a protein.

Pyridoxal phosphate (PLP) PLP is an essential enzyme-bound cofactor involved in transaminase-catalyzed processes and other related reactions (e.g., racemases and decarboxylases).

8.08.1 Introduction

Enzymes have proved to be especially useful biocatalysts for the preparative synthesis of enantiomerically pure chiral amines and amino acids.[1] In particular, general methods have been developed based on the following biocatalyst classes: (1) hydrolases,[2] especially lipases, hydantoinases, acylases, proteases, and nitrilases (kinetic resolution, dynamic kinetic resolution, and desymmetrisation); (2) monoamine oxidases[3] (deracemisation and desymmetrisation); and (3) ammonia lyases[4] (asymmetric addition of ammonia to alkenes). These approaches are based on the hydrolysis/synthesis of the C–N bond of amides and related compounds (hydrolases), oxidation of C–N to C═N (monoamines oxidases) or the addition of NH_3 to C═C (ammonia lyases). This chapter provides an overview of an alternative approach based on the reduction of C═N bonds to CH–NH (Figure 1). This approach has only recently been explored as a biocatalytic route to chiral amines; however, although the field is relatively new there are some promising approaches that have begun to emerge. Including here are also the use of transaminases which although not catalyzing a reductive process to mediate a related transformation, namely the conversion of C═O into CH–NH via imine intermediates. The five basic enzyme classes discussed in this chapter are amino acid dehydrogenases (AaDHs), amine dehydrogenases, imine reductases, nitrile reductases (NReds), and transaminases (Figure 1).

8.08.2 AaDHs

AaDHs are a large family of enzymes that catalyze the reduction of α-keto acids to the corresponding α-amino acids using ammonia as the source of the amine group (Figure 2).[5] These enzymes use nicotinamide adenine dinucleotide reduced (NADH) as cofactor and as might be expected are predominantly L-selective. In order to use these enzymes on a preparative scale it is necessary to introduce cofactor recycling systems, for example, the use of formate/formate dehydrogenase or glucose/glucose dehydrogenase. A number of these processes have now been successfully operated on a large scale, for example, in the production of L-tert-leucine **1** using an engineered variant of L-leucine dehydrogenase.[6]

Paradisi et al. have reported the kinetic resolution of D/L-amino acids using both wild-type and engineered variants of L-phenylalanine dehydrogenase from *Bacillus sphaericus* combined with nicotinamide adenine dinucleotide oxidised (NAD^+). Using this approach they were able to prepare a range of enantiomerically pure D-amino acids. The cofactor NAD^+ was recycled

 doi:10.1016/B978-0-08-097742-3.00810-7

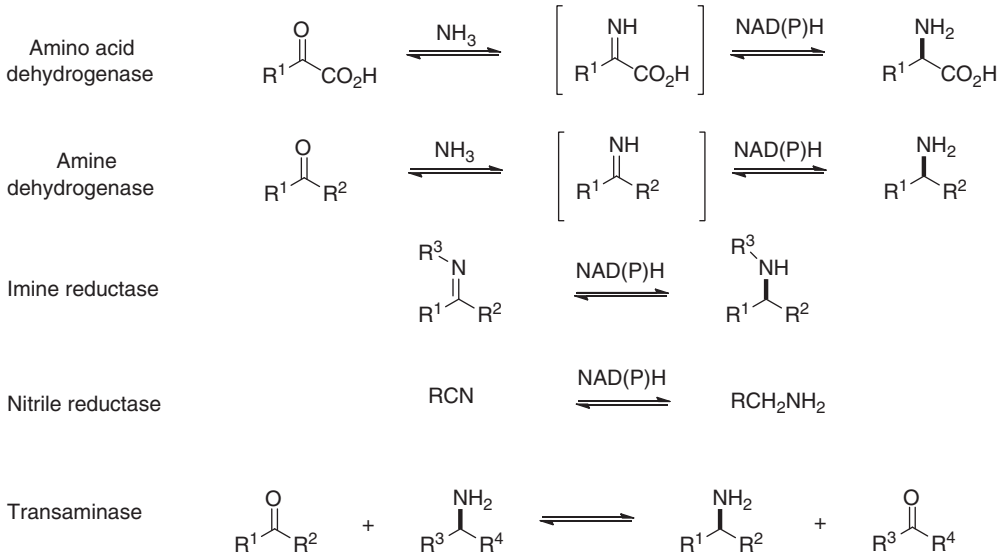


Figure 1 Biocatalytic approaches for the conversion of C═N into CHNH.

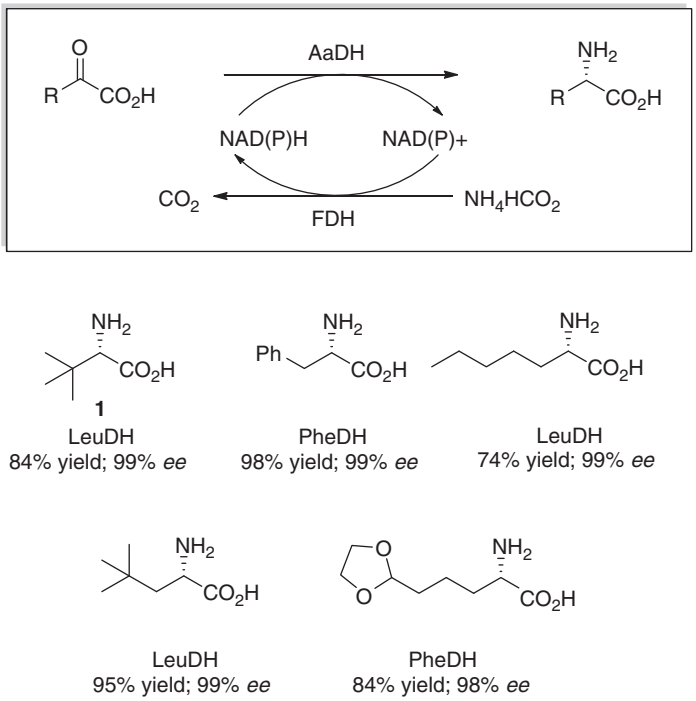


Figure 2 Reductive amination of keto acids using AaDH.

in situ by molecular oxygen with the assistance of the enzyme diaphorase.[7] Interestingly, a highly stereoselective D-AaDH has been developed by engineering of the enzyme *meso*-2,6-diaminopimelic acid dehydrogenase from *Corynebacterium glutamicum*.[8]

N-Methyl-L-AaDH (NMAADH) has been combined with L-lysine oxidase (EC 1.4.3.14), which catalyzes the oxidation of the ω-amino group of L-lysine. A one-pot, two-enzyme system was developed for the synthesis of several unnatural cyclic amino acids from the corresponding linear precursors.[9] L-lysine oxidase was initially used to convert the diamino acid **2** to the corresponding α-keto amino acid **3** which underwent spontaneous cyclization *in situ* to the imino acid **4** (Figure 3). Addition of NMAADH, resulted in reduction of the imine to afford the cyclic amino acid **5** in good yield and excellent optical purity.

The enzyme lysine cyclodeaminase, which catalyzes the oxidative cyclization of L-lysine to L-pipecolic acid, has been identified in the rapamycin gene cluster. Cloning of the gene and subsequent overexpression and purification of the enzyme (Figure 4)

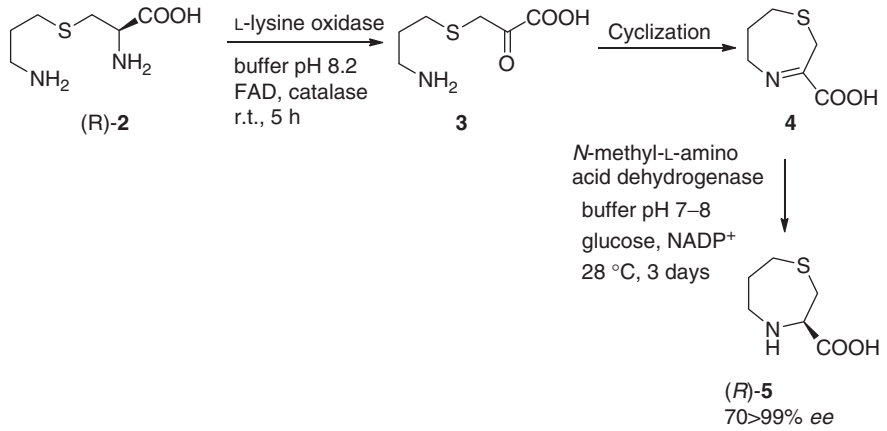


Figure 3 Use of L-lysine oxidase in combination with *N*-methyl AaDH for the conversion of (*R*)-**2** into cyclic amino acid (*R*)-**5**.

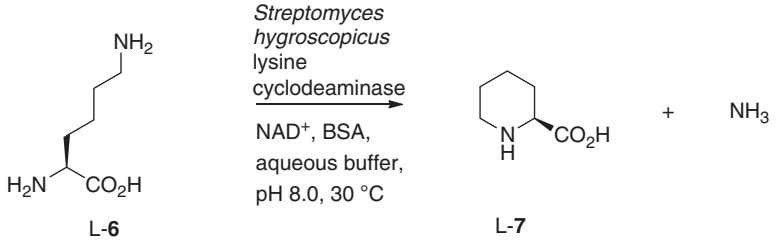


Figure 4 Conversion of L-lysine **6** into L-pipecolic acid **7** using a lysine cyclodeaminase obtained from *Streptomyces hygroscopicus*.

yielded a biocatalyst that was able to convert L-lysine **6** to L-pipecolic acid **7**. However, the enzyme displayed much lower activity toward L-ornithine 5 than L-lysine (13 mM^{-1} min^{-1}) and D-lysine was not active as a substrate.[10]

8.08.3 Amine Dehydrogenases

A recent report by the group of Bommarius at Georgia Tech describes a breakthrough in the quest to engineer AaDH enzymes, such that they lack the requirement for the carboxylic acid in the substrate. By analysis of the X-ray crystal structure of L-LeuDH they were able to identify active site residues that were associated with binding of the carboxylic acid group. Ultimately they were able to use this mutant for the conversion of 4-methyl-pentan-2-one into the corresponding amine in 98% *ee* (Figure 5).[11]

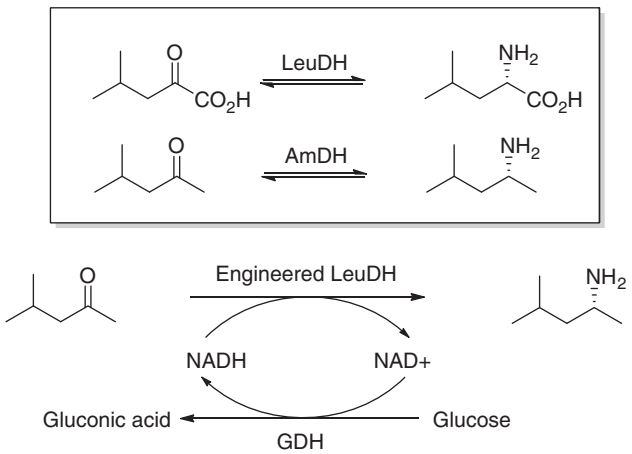


Figure 5 Reductive amination of ketones using an engineered LeuDH.

8.08.4 Imine Reductases

The asymmetric reduction of imines, both cyclic and acyclic, represents a potentially very attractive route to chiral amines. However, only a limited number of studies have been reported to date and hence this transformation is currently relatively unexplored, certainly by comparison with the related asymmetric reduction of ketones. Vaijayanthi et al. examined the reduction of a series of acyclic aryl imines **8** using the microorganism *Candida parapsilosis* ATCC 7330 (Figure 6). A range of different aryl substituents were found to be tolerated yielding (*R*)-secondary amines **9** in good yields (55–80%) and high *ee* (95–99%).[12]

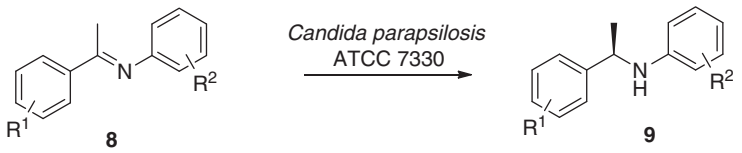


Figure 6 Asymmetric reduction of imines with *Candida parapsilosis*.

Stephens et al. have reported a novel method for screening for imine reductase activity in which a library of structurally different imines was assembled under dynamic combinatorial conditions. The library was screened against potential microorganisms which led to the discovery that the anaerobic bacterium *Acetobacterium woodii* possessed imine reductase activity.[13] The same group has recently reported the reduction of amides to amines. Washed cells of *Clostridium sporogenes* reduced benzamide (up to 20 mm) to benzylamine in yields up to 73% using H_2 as electron donor with less than 10 g biocatalyst per L over 24 h. Product formation exhibited complex kinetics, with a lag before benzylamine production began. Very little substrate was hydrolyzed since the maximum yield of benzoic acid was only 9% of the substrate added.[14]

The reduction of imines has also been reported using certain *Streptomyces* sp.[15,16] and indeed some attempts have been made to characterize the enzymes involved in these reductions; typically these systems catalyze the asymmetric reduction of 2-methyl-1-pyrroline **10** to the corresponding (*R*)- or (*S*)-2-methylpyrrolidine **11** employing nicotinamide adenine dinucleotide (phosphate) reduced (NADPH) as a cofactor (Figure 7). Some of these enzymes have been overexpressed in recombinant form together with partial characterization concerning their substrate specificity and other properties. The sequences of two enantiocomplementary imine reductases from *Streptomyces* sp. GF3587 and *Streptomyces* sp. GF3546 have been reported and they have been expressed recombinantly with some initial data reported concerning their properties.[17] Kinetic data and more in-depth substrate specificity studies have been described for an (*R*)-selective imine reductase from *Streptomyces* sp. GF3587.[16] In addition, a Δ1-piperidine-2-carboxylate/Δ1-pyrroline-2-carboxylate reductase (ΔPipC-Pyr2C-reductase) has been reported in several *Pseudomonas* strains and the enzyme from *Pseudomonas syringae* has been expressed recombinantly and also crystallized.[18]

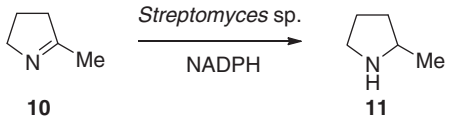


Figure 7 Reduction of 2-methyl pyrroline to 2-methyl pyrrolidine.

The asymmetric reduction of a series of β-carboline imines **12** to the corresponding amines **13** has been achieved using *Saccharomyces bayanus* (Figure 8). Moderate to good *ee*s were obtained across a broad range of C1-substituted substrates ranging from C_1 to C_{11} aliphatic substituents yielding (*S*)-configured amines. Interestingly, for C_{15} and higher aliphatic substituents together with aromatic groups there was an inversion of configuration yielding (*R*)-amine products.[19]

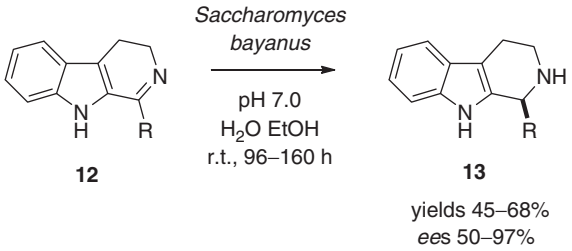


Figure 8 Asymmetric reduction of β-carboline imines **12** by *Saccharomyces bayanus*.

It is worth noting that the asymmetric reduction of an intermediate imine has previously been implicated as a key step in the biosynthesis of the β-carboline alkaloids eleagnine in the plant *Passiflora edulis*.[20]

8.08.5 Nitrile Reductases

NReds are relatively rare enzymes in nature and certainly they have not been exploited as biocatalysts in organic synthesis. Wilding et al. have reported the cloning, expression, and partial characterization of a NRed from the thermophilic organism *Geobacillus laustophilus* (Figure 9). The wild-type enzyme displays quite strict specificity for the natural substrate 7-cyano-7-deazaguanine **14**. Engineering of the enzyme resulted in the generation of some mutants that were able to reduce analogs of the natural substrate.[21]

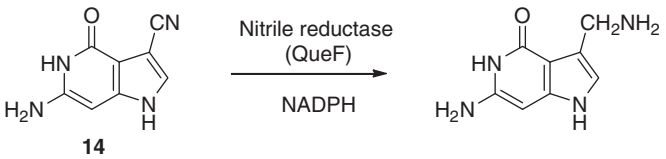


Figure 9 Reduction of 7-cyano-7-deazaguanine (preQ0) to 7-aminomethyl-7-deazaguanine (preQ1) catalyzed by aNRed.

8.08.6 Transaminases

Transaminases belong to one of the four families of B_6 (pyridoxal phosphate (PLP))-dependent enzymes that participate in the metabolism of amino acids. The four families are able to catalyze decarboxylations, replacements and eliminations, transaminations, and racemizations. PLP-dependent enzymes serve to labilize one of the three bonds (hydrogen[a], CO_2[b], R-group[c]) of the α-carbon atom of an amino acid substrate (Figure 10).[22]

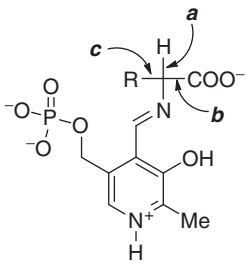


Figure 10 Transformations catalyzed by PLP-dependent enzymes.

The reaction mechanism and structural properties of transaminases have been studied in great detail.[23] The transamination reaction proceeds by a mechanism which involves two half reactions (Figure 11). In the first half of the reaction, an internal Schiff base between an active site lysine residue (via its ε-amino group) and the aldehyde group of a PLP bound to the enzyme (internal aldimine) is replaced by a Schiff base between the amino donor and the PLP, forming an external aldimine. The lysine residue that is released by this process serves as the base for the next step and catalyzes a 1,3-hydrogen shift involving the abstraction of the α-proton from the external aldimine and reprotonation to the imine of the coenzyme. Internal rearrangement proceeds through a quinoid intermediate yielding a ketimine stereoselectively. This intermediate is stabilized by a tyrosine, which hydrogen bonds with the phenolic oxygen of the PLP and the imine group of the internal/external aldimine. It is also stabilized by a carboxylate side chain from aspartate or glutamate, which forms an ion pair with the pyridine nitrogen of the cofactor. This causes a stabilization of the positive charge in the aromatic ring (forming an electron sink). Hydrolysis of the ketimine intermediate yields pyridoxamine 5′-phosphate (PMP) and releases the product ketone. Formation of a Michaelis-complex between the PMP bound to the enzyme and a different amino acceptor initiates the reverse second half of the reaction and regenerates the enzyme-bound PLP form.

The late 1990s saw the development of transaminase-mediated enzymatic resolution of racemic amines. Celgene developed transaminase technology for the enantioselective conversion of chiral amines into ketones.[24] Low molecular weight aldehydes, such as propionaldehyde, were used to accept the amino group (Figure 12). This process has been used on a 2.5 m^3 scale and has been demonstrated on several different aliphatic and aromatic amines. A disadvantage of this approach was the relatively low product concentrations attainable in an all aqueous reaction system with hydrophobic compounds. Another disadvantage was the significant inhibition of the transaminases by both the amine substrates and ketone products.

Shin and Kim[25] developed various methods aimed at increasing the product concentrations of transaminase-catalyzed amine resolutions, through the continuous removal of product ketone from the reactions. The application of an aqueous/organic two-phase system to the ω-transaminase-catalyzed resolution of racemic α-methylbenzylamine was found to be superior only to an aqueous system in product concentration obtained (Figure 13).

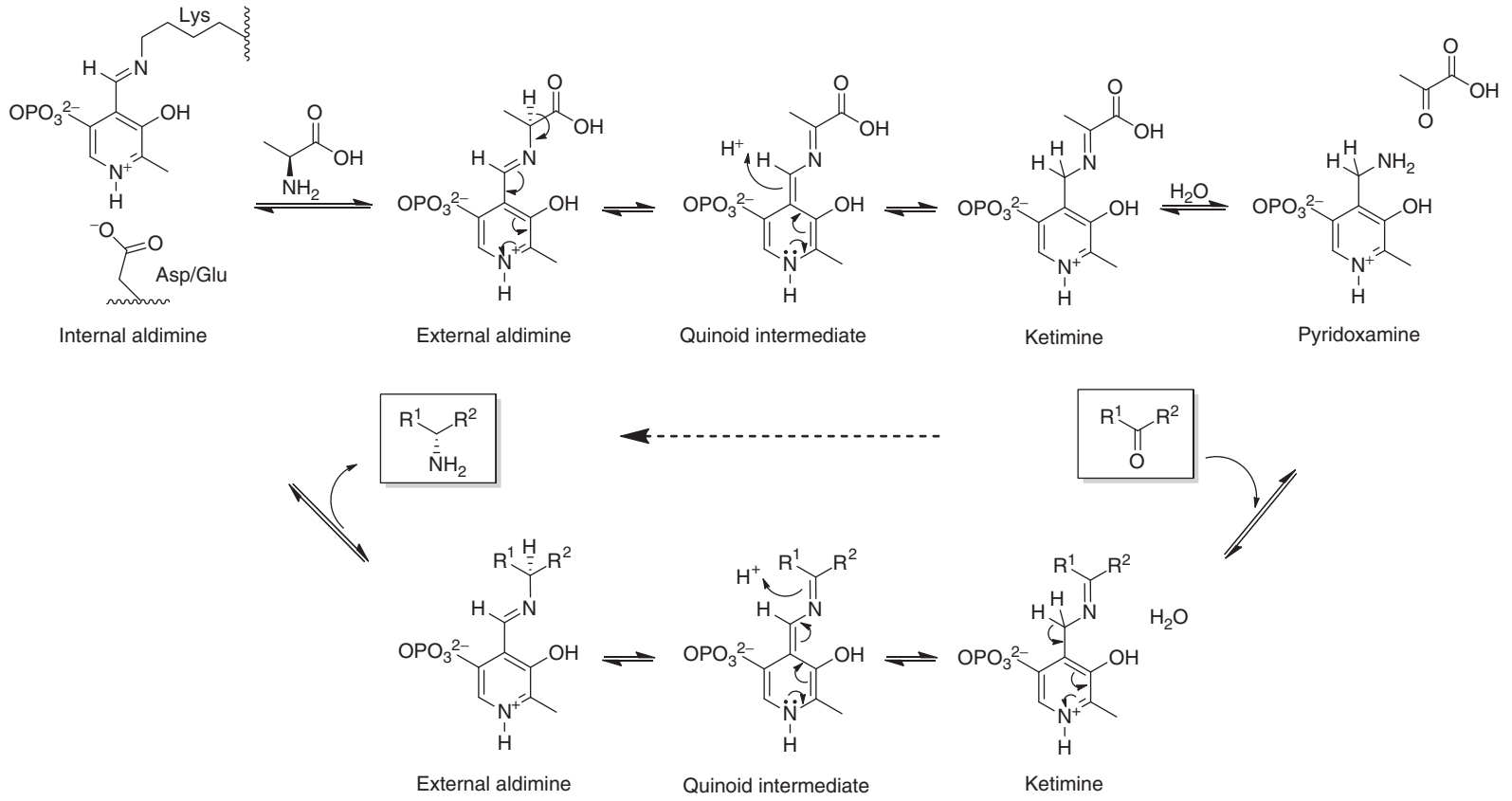


Figure 11 Transaminase mechanism (the amino acid above the first arrow has the *R*-configuration, but switches to *S* in the first Schiff base intermediates ('external aldimine')) now changed.

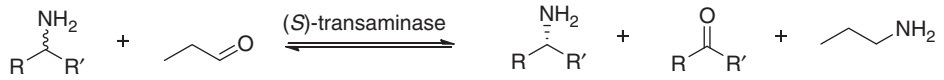


Figure 12 Transaminase-catalyzed resolution of amines using propionaldehyde as the amine-acceptor group.

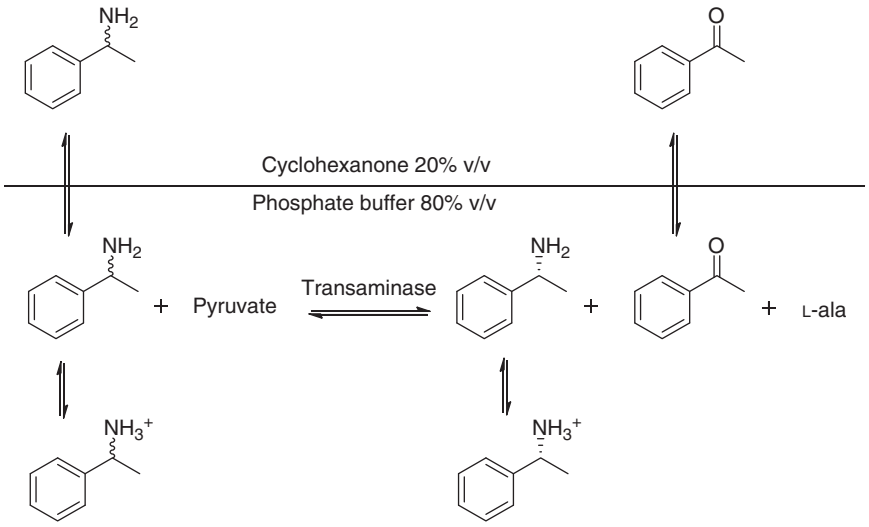


Figure 13 Aqueous/organic two-phase reaction system for the transaminase-catalyzed resolution of α-methylbenzylamine.

In 2008, Hanson et al.[26] identified an (*S*)-amine transaminase from *Bacillus megaterium* that was used for the preparation of (*R*)-1-cyclopropylethylamine and (*R*)-*sec*-butylamine by resolution of the racemic amines (Figure 14). In this example pyruvate was used as the amino group acceptor.

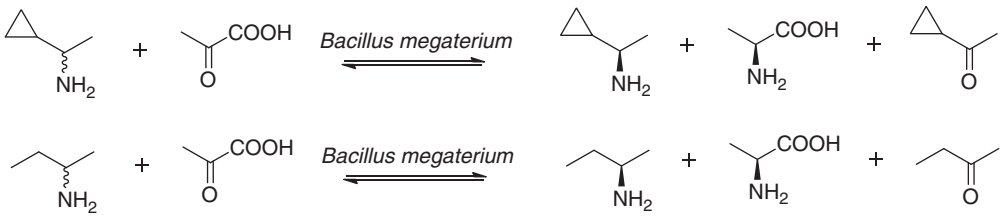


Figure 14 Transaminase-catalyzed resolution of 1-cyclopropylethylamine and *sec*-butylamine.

Hoehne et al.[27] have demonstrated a substrate protection strategy that enhances both the rate and enantioselectivity of transaminase-catalyzed kinetic resolution reactions. The ω-transaminase-catalyzed resolution of the pharmaceutically important synthetic intermediates 3-aminopyrrolidine and 3-aminopiperidine was improved by employing *N*-protecting groups (Figure 15). Reaction rates were improved by up to 50-fold, and product *ee* was improved from 86% to 99%.

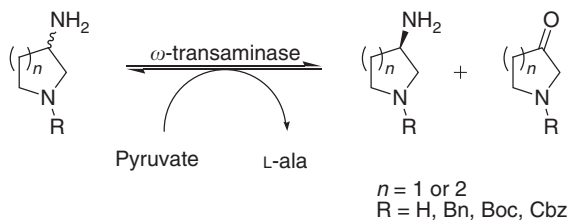


Figure 15 Protection strategy for increasing the rate and enantioselectivity of transaminase-catalyzed amine resolutions.

Recently, an alternative method for the resolution of racemic amines which uses amino acid oxidase (AAO) with catalytic quantities of pyruvate to regenerate the PLP cofactor has been developed.[28] AAO catalyzes the *in-situ* oxidation of alanine back to pyruvate in the presence of molecular oxygen (Figure 16). As a result, the AAO approach avoids the use of stoichiometric amounts

of pyruvate for the regeneration of PLP. This method serves to reduce the cost of the process (making O_2 the only reagent consumed in the cofactor regeneration) and also reduces transaminase inhibition due to high concentrations of pyruvate.

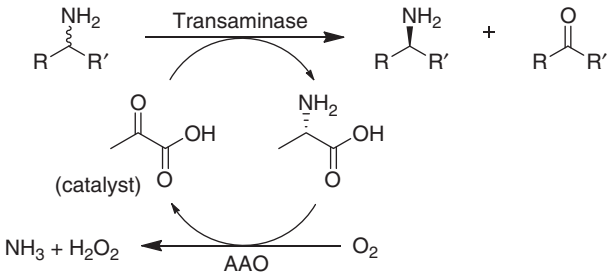


Figure 16 Use of catalytic pyruvate and AAO for the regeneration of PLP.

The enantioselective generation of chiral amines from prochiral ketones using transaminases has received lots of attention lately, and is now the preferred way of generating chiral amines in enantiomerically pure form at preparative scale. The first reported transaminase capable of transferring an amine to a substrate without a carboxylic acid group was a diamine-ketoglutaric transaminase identified in 1964.[29] However, it was not until the end of the 1980s that transaminase technology became an industrially viable option for the synthesis of chiral amines.

Researchers at Celgene developed both (*R*)- and (*S*)-selective transaminases that were active on a range of aliphatic and aromatic ketones and amines.[30] The synthetic approach started with a prochiral ketone substrate that served as an amino group acceptor and isopropylamine as the amino group donor (Figure 17). The product of the reaction was the desired chiral amine and acetone. The Celgene processes have been run successfully at 2.5 m^3 scale; however, poor equilibrium necessitates the use of excess reagents to drive the reactions to completion, and low product concentrations were obtained with hydrophobic substrates.

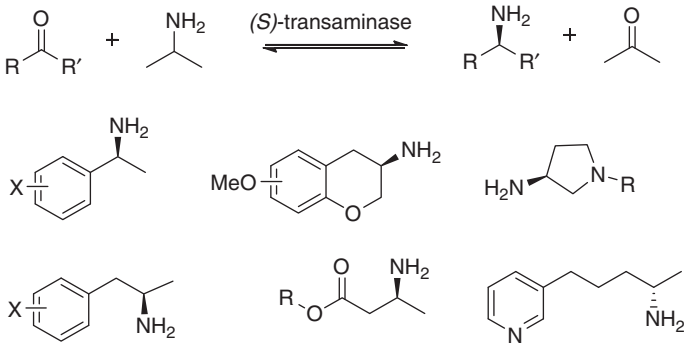


Figure 17 Transamination of ketones using isopropylamine as the amine-donor.

Using an (*S*)-selective ω-transaminase isolated from *Vibrio fluvialis*, Shin and Kim demonstrated the synthesis of aliphatic and aryl chiral amines using L-alanine as the amino group donor (Figure 18).[31,32]

Severe inhibition of the transaminase by both the amine and keto-acid reaction products, as well as extremely poor equilibrium conversion, were observed. Even with a large excess of amino group donor, reactions proceeded in $<2\%$ conversion. The continuous *in situ* removal of the inhibitory pyruvate product (Figure 19) via reduction using lactate dehydrogenase (LDH) boosted reaction yields to $>90\%$, but inhibition by the desired amine product still resulted in poor productivity.

In situ removal of pyruvate has also been accomplished using pyruvate decarboxylase (Figure 20).[33] A potential advantage of employing pyruvate decarboxylase over LDH is that it requires no cofactor recycling system (LDH is an NAD(P)H-dependent enzyme). However, a significant disadvantage is competitive inhibition of the transaminase by the aldehyde byproduct, which can also serve as a substrate for transamination.

An alternative method for alleviating inhibition by the coproduct pyruvate, developed by Truppo and Turner, uses catalytic alanine to regenerate the PLP cofactor coupled with an amino AaDH and ammonia for alanine recycling (Figure 21). AADH is an NADH-dependent enzyme and requires NADH regeneration using glucose dehydrogenase (GDH) and glucose. The constant removal and recycling of pyruvate back to alanine avoids inhibition by pyruvate, and allows for only catalytic amounts of alanine to be used. Therefore, the inexpensive cosubstrate ammonia becomes the substrate consumed in stoichiometric quantities for PLP cofactor regeneration.[34,35]

Thus far, the most economical approach for cofactor regeneration in transaminase-mediated amine synthesis has been the directed evolution of transaminases to accept and be active in high concentrations of isopropylamine.[36] Isopropylamine serves as the amine-group donor to regenerate the cofactor, and the acetone byproduct can be removed by vacuum distillation, driving the

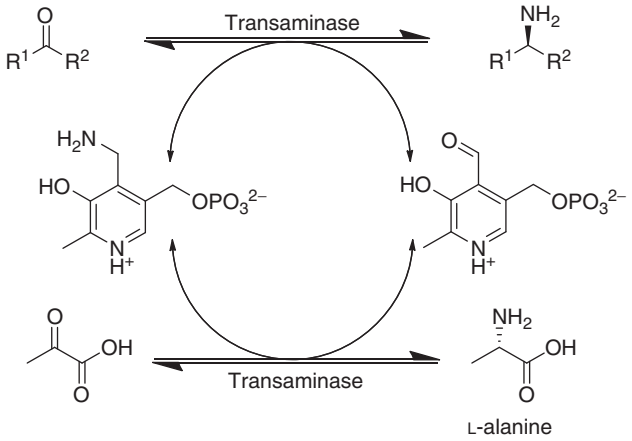


Figure 18 Enantioselective transamination of ketones to chiral amines using alanine as the ammonia source.

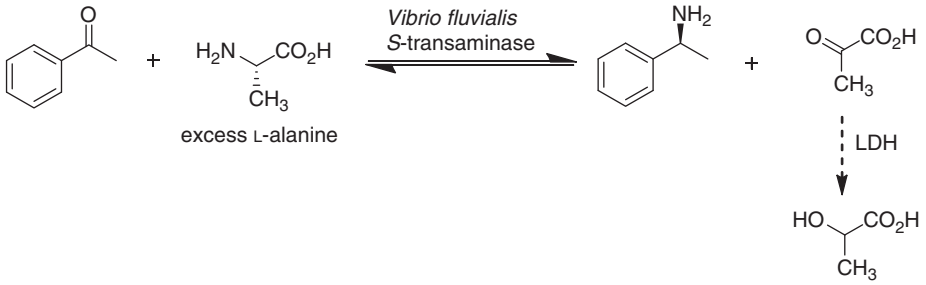


Figure 19 Transamination using L-alanine as the amine donor with removal of the inhibitory pyruvate product via reduction using LDH.

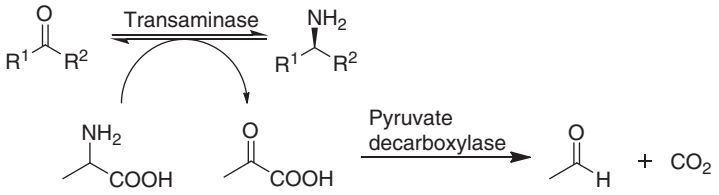


Figure 20 Removal of pyruvate with pyruvate decarboxylase.

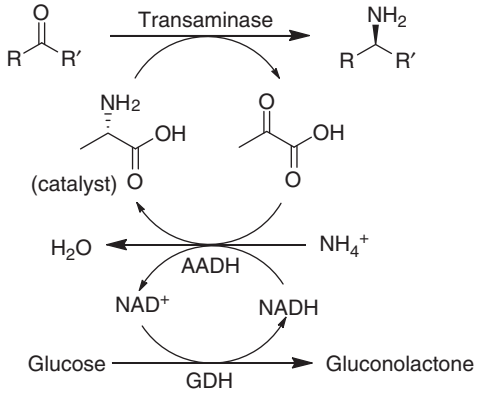


Figure 21 Use of catalytic alanine and AaDH for the regeneration of PLP.

reaction equilibrium toward the desired chiral amine product. This single enzyme system is proving itself to be the most cost-effective way to generate chiral amines, with volumetric productivities routinely exceeding 50 g l^{-1}. Most notably, Merck and Codexis have demonstrated the large-scale production of the antidiabetic compound sitagliptin (Januvia) using isopropylamine for the regeneration of the PLP cofactor (Figure 22) in which productivities >200 g l^{-1} have been reported.[37]

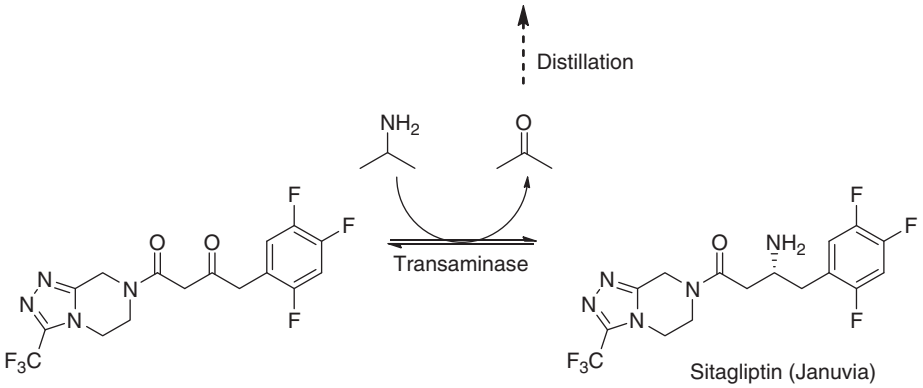


Figure 22 Transaminase-catalyzed synthesis of sitagliptin (Januvia) using isopropylamine as the amine donor.

Recently transaminases have been applied as biocatalytic components of cascade reactions, notably in the multienzyme conversion of alcohols into amines[38] and also in the cyclisztion of diketones to substituted piperidines.[39]

8.08.7 Conclusions and Future Prospects

The enantioselective reduction of C═N to CH–NH is an emerging area of biocatalysis which is certainly in its infancy when compared to the enantioselective reduction of C═O to CH–OH. Part of the reason for this difference is the lower stability of imines, particularly acyclic ones, although methods are now available for their generation *in situ* using amine oxidases. Undoubtedly new imine reductases/amine dehydrogenases will be discovered in the future and/or generated through protein engineering of existing sequences, thereby expanding the range of enzymes available for this synthetically important transformation.

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8.09 Reduction of *O,O*-, *N,O*-, and *S,O*-Acetals to Ethers

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Glossary

Acetal A functional group consisting of two ethers attached to the same carbon atom ($R_2C(OR)_2$); although the term acetal technically refers to such functional groups as derived from an aldehyde, by convention it is also used to describe 1,1-di-ethers formed from ketones (also known as ketals). It includes both cyclic and acyclic derivatives.

Benzylidene acetal The acetal formed from benzaldehyde with a diol. In the context of this chapter, this most often refers to the acetal formed between the C-4 and C-6 oxygen atoms of the pyranose form of a carbohydrate.

Dioxane A six-membered ring containing two oxygen atoms. For acetals, these are located at the 1- and 3-positions, and will usually feature a substituent (phenyl) at the 2-position. The five-membered ring equivalent of this acetal is called a dioxolane.

Oxocarbenium ion The representation of a carbenium ion (tervalent carbocation) adjacent to an ether (or alcohol) in which one of the lone pairs of the adjacent oxygen atom is used to form a double bond with the positively charged carbon, leading to the depiction as a carbonyl group in which the oxygen atom carries the formal positive charge.

Oxonium ion The positively charged species resulting from the formation of three covalent bonds from an oxygen atom. The simplest oxonium ion is H_3O^+; in this chapter, oxonium ion most commonly refers to the species formed from complexation of an (acetal) ether to a Lewis or Brønsted acid, and is not used to describe oxocarbenium ions.

8.09.1 Introduction

The formation of acetals and ketals from aldehydes and ketones represents one of the most fundamental transformations in organic chemistry. This process has many uses, of which the most common is the protection of a carbonyl group, or the corresponding diol, in a synthetic sequence. However, acetals offer significant synthetic opportunities beyond simple masking/unmasking of these functional groups; the selective reduction of the acetal to ether can provide a useful method to derivatize carbonyl groups, or to differentiate between two alcohol functional groups. The latter context is of great importance in the manipulation of carbohydrates, where selective deprotection of (benzylidene) acetals at the 2-, 3-, 4-, or 6-positions of pyranosides forms a cornerstone of carbohydrate chemistry.

At the time of the previous coverage of this field,[1] standard methods to achieve acetal reduction to ethers were limited mainly to ionic hydrogenation using powerful Lewis or Brønsted acids, or dissolving metal conditions. In the intervening years, significant progress has been made in several areas: first, in improving mechanistic understanding of the factors controlling the regioselectivity of selective reductions, mainly through a combination of kinetic measurements, and deuterium-labeling experiments. Second, the use of catalytic amounts of Lewis acids as promoters of acetal opening, in place of the traditional stoichiometric employment of acids such as aluminum(III) chloride or boron trifluoride, which has enabled reduction under much milder conditions. A wide range of Lewis acids, in particular metal triflate salts, have been shown suitable for this purpose. Finally, in the carbohydrate field, these advances in mechanistic understanding have enabled one-pot protection/reduction strategies that involve acetals as intermediates which are formed and cleaved without direct isolation. Alongside these advances, a plethora of methods have emerged for acetal reduction using transition metal catalysis, and also numerous techniques for the reduction of related thioacetals (*S,O*-), azaacetals (*N,O*-), aminals (*N,N*-), thioaminals (*N,S*-), and dithioacetals (*S,S*-).

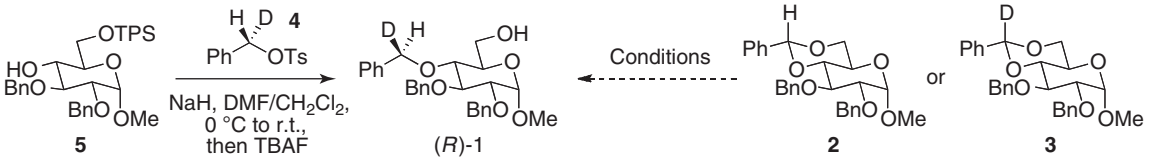
In light of these advances, this chapter is divided into two main sections. The first section discusses progress in mechanistic understanding, which informs about the selectivity of the many reduction methods that have been developed. A detailed analysis of work performed in this field is included, with a particular focus on carbohydrate benzylidene acetals, which represent a benchmark for the testing of acetal reduction methods. This is followed by a categorization of acetal reduction by acetal structure, and a discussion of methods that have emerged since the previous coverage of each structural variant. This section includes examples of applications in (noncarbohydrate) complex molecule synthesis, and also a more extensive report on reductions of the related *X,Y*-acetals as listed above.

8.09.2 Advances in Mechanistic Understanding

Acetal reduction is widely recognized to proceed via a range of mechanisms, with the reaction pathway depending on factors such as the nature of the acid promoter, hydride source, solvent, and reaction temperature. This mechanistic variation enables the tuning of acetal reduction to effect regioselective reductions, which are particularly important in the context of the reduction of carbohydrate *O*-4,6-acetals, as they result in selective deprotection at *O*-4 or *O*-6. Although detailed analysis of the mechanisms of many of these methods is as yet incomplete, substantial evidence has been gathered for a number of the most commonly used reaction conditions, with particularly important studies from the groups of Ellervik[2–6] and Hung.[7,8] This includes kinetic data, such as determination of the order of reaction with respect to the acid promoter, and primary and secondary kinetic isotope effects using deuterated acetals or hydride/deuteride sources. It also includes deuterium-labeling studies which permit unambiguous determination of the stereochemistry of the reduction. In this section, advances in mechanistic understanding of the reduction of carbohydrate acetals are described, which enable the rationalization of many of the methods for general acetal reduction detailed later in this chapter.

8.09.2.1 Reductions of *O*-4,6-Benzylidene Acetals to Give *O*-4 Benzyl Ethers/*O*-6 Hydroxyl

At least four mechanisms can be envisaged to operate for reductions which give *O*-4 benzyl ethers/*O*-6 hydroxyl groups, with others having been ruled out due to the wealth of mechanistic evidence that has now been gathered. Deuterium-labeling studies, in which the stereochemical course of the reaction can be monitored through the formation of benzyl ether products which are monodeuterated at the benzylic carbon ((*R*)-**1**, Scheme 1), have been particularly informative. For example, (*R*)-**1** could potentially be formed through the reaction of the nondeuterated acetal **2** and a deuteride source with inversion of configuration at the stereogenic center, or the reaction of deuterated acetal **3** and a hydride source with retention of configuration. Key to the interpretation of these experiments is the assignment of the stereochemistry of the monodeuterated benzyl ether products (i.e., (*R*)-**1** or (*S*)-**1**). The independent synthesis of these ethers through S_N2 reactions of enantioenriched, monodeuterated benzylic tosylates (**4**) with appropriate alcohols (**5**) has permitted unambiguous stereochemical characterization,[8] and therefore enables the secure assignment of the stereochemistry of acetal reductions. This confirmation of stereochemistry has led to a reinterpretation of several reaction mechanisms which had been proposed on the basis of a previous erroneous stereochemical assignment of (*R*)-**1** and (*S*)-**1** based on ^{1}H NMR NOE experiments.[5,7]

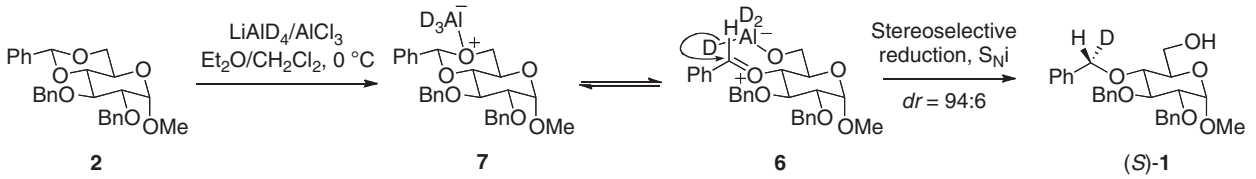


Scheme 1

8.09.2.1.1 Mechanism A: Strong hydridic Lewis acid

Acetal reduction using strong hydridic Lewis acids in noncoordinating solvents such as toluene or dichloromethane would be expected to proceed via full oxocarbenium ion formation, followed by hydride transfer. The use of AlD_3 as a deuteride source

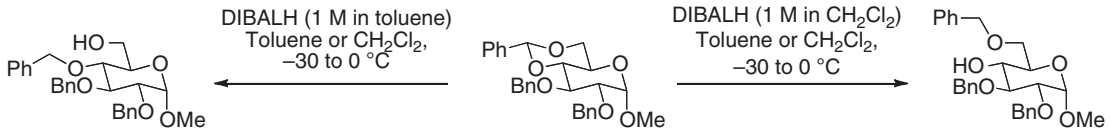
(generated *in situ* from $AlCl_3$ and $LiAlD_4$) has revealed this reaction to be highly stereoselective, with monodeuterated benzyl ether (*S*)-**1** formed from **2** with 94:6 *dr* (Scheme 2), revealing that hydride transfer occurs with retention of configuration.[8] An identical observation had previously been made using deuterated acetal **3** and $LiAlH_4/AlCl_3$.[5] The former result led to the proposal of an S_Ni-type process, which had not previously been widely considered for acetal reduction, where the formation of the *O*-4 oxocarbenium ion **6** (promoted by Lewis acid complexation at *O*-6 (**7**)), is followed by intramolecular hydride delivery; this is effectively a directed reduction of the *O*-4 oxocarbenium ion by the *O*-6 alkoxide–Lewis acid hydride complex. This mechanism may also have implications for reductions that employ nonhydridic Lewis acids and an external hydride source (see Section 8.09.2.4).



2 **7** **6** (*S*)-**1**

Scheme 2

A note of caution is included for reductions using diisobutylaluminum hydride (DIBALH), the regioselectivities of which show a remarkable dependence on the solvent in which the DIBALH is prepared, irrespective of the age of the reagent, 'and the bulk reaction solvent' (Scheme 3). For example, reaction of acetal **2** using 1 M DIBALH in toluene, with either toluene or dichloromethane as cosolvent, gives an ~8:1 ratio of 6-OH:4-OH products **1** and **8**. However, performing this reduction using 1 M DIBALH in dichloromethane leads to inversion of this selectivity, the ratio of 6-OH:4-OH now being ~1:8. The reasons for this reversal are not well understood.

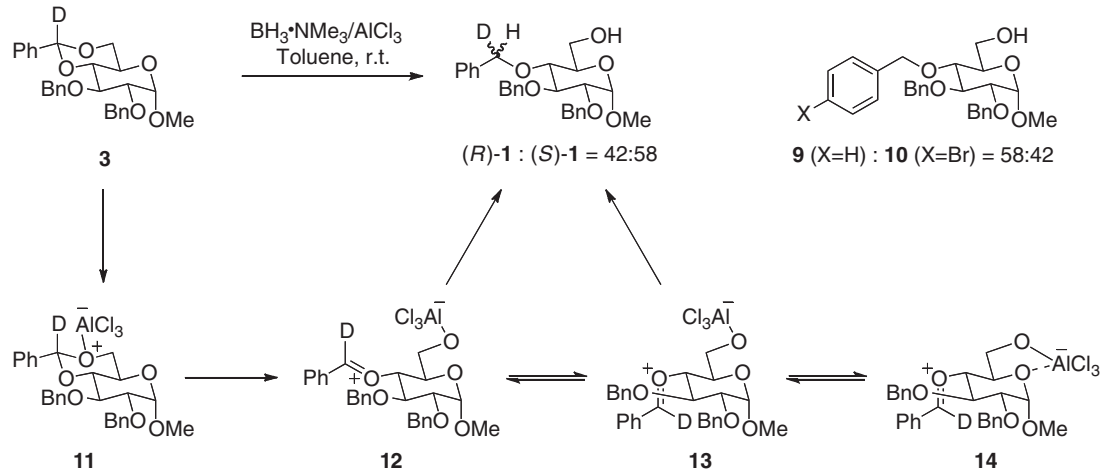


1 (*rr* ~ 8:1) **2** **8** (*rr* ~8:1)

Scheme 3

8.09.2.2 Mechanism B1: Strong Lewis Acid with Hydride Source in Noncoordinating Solvents

Another much-employed set of conditions also uses strong Lewis acids in noncoordinating solvents, but with an external hydride source such as $BH_3 \cdot NMe_3$.[9] This rapid reaction similarly leads to selective formation of the *O*-4 benzyl ether product, with the rate depending crucially on the absence of coordinating solvents (which reduce Lewis acidity). In contrast to Mechanism A, the reaction proceeds with low stereoselectivity, giving a 58:42 ratio of (*R*)-**1**:(*S*)-**1** from deuterated acetal **3** (Scheme 4).[5] This observation alone is strongly suggestive of the intermediacy of a free oxocarbenium ion, which is subject to a facially nonselective addition of hydride.



3 (*R*)-**1** : (*S*)-**1** = 42:58 **9** (X=H) : **10** (X=Br) = 58:42

11 **12** **13** **14**

Scheme 4

Additional mechanistic observations[5] include a moderate inverse secondary kinetic isotope effect, which would be consistent with a change in hybridization at the acetal carbon from sp^2 to sp^3 in the rate-determining step (as expected for a reaction proceeding via an oxocarbenium ion where hydride transfer is rate-determining), and a primary kinetic isotope effect for the reactions of $BH_3 \cdot NMe_3$ and $BD_3 \cdot NMe_3$ (which supports hydride transfer to the oxocarbenium ion as the rate-determining step). Finally, a competition experiment between the parent benzylidene acetal **2** and the equivalent *p*-bromobenzylidene acetal led to a 58:42 mixture of products in favor of benzyl ether **9** (Scheme 4). This similar proportion of products suggests that the formation of the oxocarbenium ion is fast, such that the electronic effect of the aryl ring is of low importance, compared with a slower, rate-determining, reduction step.

The mechanism is therefore thought to proceed via complexation of the highly reactive Lewis acid to the most basic/least hindered *O*-6 (**11**), followed by rapid ring opening to the oxocarbenium ion **12**. The absence of tight ion pair effects may allow rotation of this ion to other conformations (**12**↔**13**), and thus lead to nonstereoselective reduction. Indeed, the use of powerful Lewis acids with more than one coordination site may even induce the formation of complexes such as **14**, in which the ejected *O*-6 alkoxide is prevented from interacting with the oxocarbenium ion by complexation with the pyran oxygen, which 'ties back' the C-6 sidechain, and which could certainly contribute to nonstereoselective reduction.

8.09.2.3 Mechanism B2: Strong, Bulky Lewis Acid with Hydride Source

A variation of the above mechanism is proposed when the Lewis acid is particularly bulky, which under any conditions (i.e., coordinating or noncoordinating solvent) prevents activation of the *O*-4 oxygen (which would lead to *O*-6 oxocarbenium ion formation). In these cases, complexation at *O*-6 by necessity results in *O*-4 oxocarbenium ion formation and *O*-6 hydroxyl deprotection. Data on deuterium-labeling are not available for reactions using $PhBCl_2/Et_3SiH$,[10,11] or $Bu_2BOTf/BH_3 \cdot$ to hyperconjugation from (THF);[12,13] however, deuterium-labeling using $TMSOTf/Et_3SiD$ showed this reaction to be stereoselective in favor of hydride substitution with retention of configuration.[8] For reactions employing non-Lewis acidic hydride sources, the reasons for retention of configuration are not well understood, but may involve a stereoselective substrate-controlled reduction of the oxocarbenium ion. The particular distinction of these conditions is that even the use of triethylsilane as hydride source fails to overcome the usual preference for *O*-6 oxocarbenium ion formation, as is generally observed with bulky hydride sources (see Section 8.09.2.5.2 for further discussion).

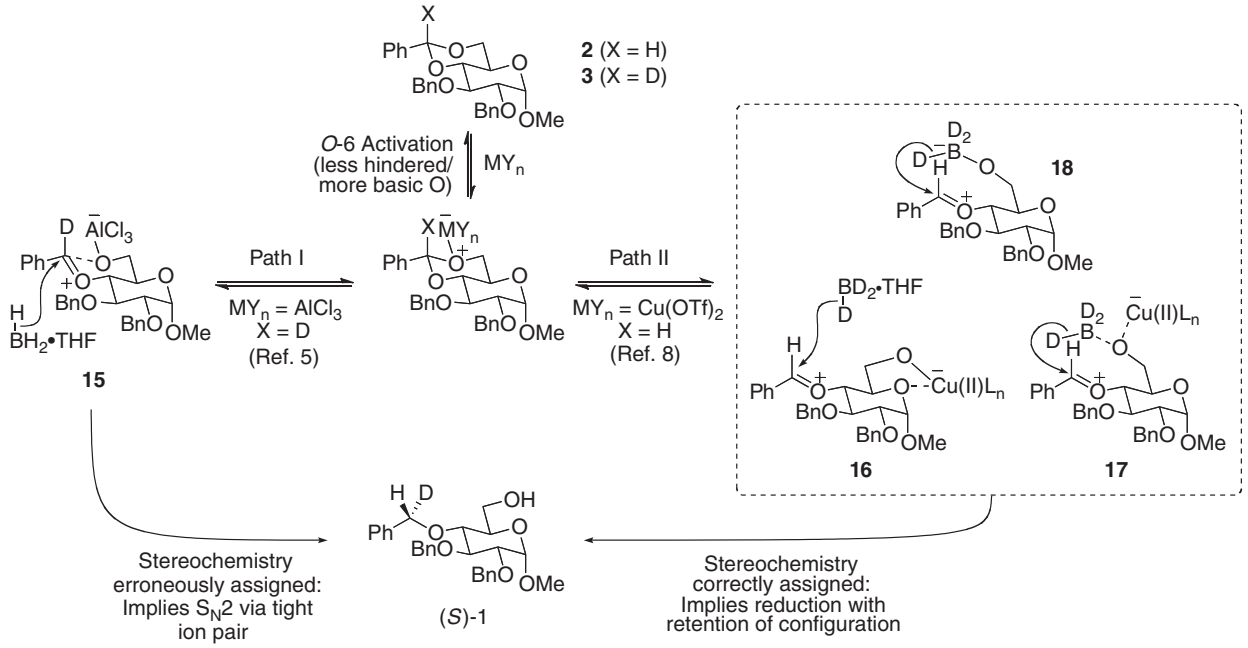
Caution should therefore be exercised with the interpretation of reductions promoted by bulky Lewis acids which lead to *O*-4-hydroxyl products, as the presence of adventitious water, leading to trace amounts of acid on reaction with the Lewis acid, presents a viable and more likely method for *O*-4 activation than complexation to a bulky Lewis acid promoter. Indeed, studies on the use of $Bu_2BOTf/BH_3 \cdot THF$ at $-78\ ^\circ C$ (conditions developed for the regioselective preparation of *O*-4 pathways mediated by (PMB) ethers from the *p*-methoxybenzylidene acetal) revealed the likely dependence of this reaction on trace acid: conducting the reaction using base-washed glassware in the presence of molecular sieves and *di-tert*-butyl-4-methylpyridine resulted in no reaction at $-78\ ^\circ C$.[13]

8.09.2.4 Mechanism C: Lewis Acid with Hydride Source in Coordinating Solvents

An interesting situation arises with the use of nonhydridic Lewis acids (such as $AlCl_3$, or metal triflate salts such as $Cu(OTf)_2$) and hydride sources such as $BH_3 \cdot THF$ in polar (coordinating) solvents. Here, the solvent plays an important role in deactivating the Lewis acid catalyst, such that these reactions proceed at a markedly slower rate to those in noncoordinating solvents. Although the overall result of these reactions is similar to that in noncoordinating solvents – i.e., the product 6-OH/4-O benzyl ether, arising from preferential coordination of the Lewis acid to the less-hindered and more basic *O*-6, the reduction is now stereoselective (compared with the rate-determining stereorandom reduction of the free oxocarbenium ion invoked in Mechanism B1).

Experiments using deuterated acetal **3** (Path I, Scheme 5)[5] initially implied that these reactions proceed with inversion of configuration at the acetal carbon, with the stereochemistry of the product being incorrectly assigned as (*S*)-**1** on the basis of an earlier stereochemical misassignment of (*R*/*S*)-**1** by ^1H NMR nOe analysis.[7] This reasonable interpretation led to the proposal of an S_N2-type mechanism, where the tempered acidity of the Lewis acid in coordinating solvents renders it insufficiently powerful to effect formation of a free oxocarbenium ion; instead, a tight ion pair **15** would explain the observed results. Further evidence for such a mechanism included an inverse secondary kinetic isotope effect for the acetal proton of 0.85, which could be interpreted as supporting an S_N2 mechanism due to the benefit of the smaller effective size of deuterium compared with hydrogen on the S_N2 transition state. Similarly, a moderate primary kinetic isotope effect of 2.4 for $BD_3/BH_3 \cdot THF$ was interpreted as implying B–H/D bond cleavage is not involved in the rate-determining step. However, caution should be exercised with these interpretations, as similar magnitudes of isotope effects had been observed in alane reductions (Mechanism A) and $AlCl_3/BH_3 \cdot NMe_3$ (Mechanism B1), which in both cases led to mechanistic hypotheses based on oxocarbenium ion formation. Competition experiments between **2** and the corresponding *p*-bromobenzylidene acetal led to a 73:27 ratio of benzyl ether products, which suggests that the development of positive charge at the acetal carbon is of some importance, as would be observed in the formation of a tight ion pair (but also an oxocarbenium ion). Subsequent to this work, the correction of the stereochemical assignment of the monodeuterated benzyl ether product from the reaction of **2** with $BD_3 \cdot THF$ and a variety of Lewis acids including $Cu(OTf)_2$ (which give

benzyl ether (*S*)-**1** via Path II, Scheme 5)[8] now suggests that the *O*-4 benzyl ether is formed with 'retention' of configuration in the reduction event.



Scheme 5

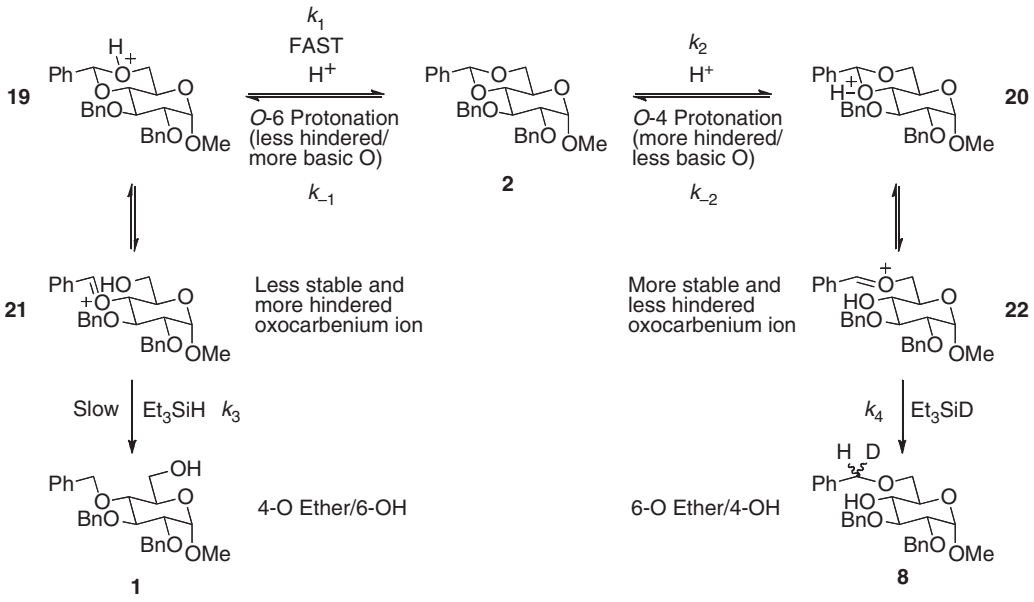
These developments lead toward two possible mechanistic explanations. The now-proven retentive reduction could be viewed as a stereoselective process in which hydride addition to one face of the oxocarbenium ion is sterically favored, which might be the case should the *O*-6 alkoxide rotate away from the tight ion pair to expose the *Si*-face (**16**, Scheme 5). However, this would contradict the $AlCl_3/BH_3 \cdot NMe_3$ reduction in which low stereoselectivity was observed, presumably due to the ability of the intermediate oxocarbenium ion to itself undergo rotation around the C–O-4 bond (see structure **13**, Scheme 4). A caveat to this is that the rate of reduction of the oxocarbenium ion with $BH_3 \cdot THF$ in THF may be much faster, with a relatively short-lived and therefore conformationally stable oxocarbenium ion **17**. However, a further possibility is that this reaction mirrors the reduction with alane (which is highly stereoselective), and follows a S_Ni-type pathway (*O*-6-directed reduction). The use of coordinating solvents likely makes the *O*-6 alkoxide–Lewis acid interaction weaker, potentially allowing it to complex another Lewis acidic species (i.e., the reducing agent, see **17**), or indeed for the metal cation to be substituted altogether (**18**). These latter complexes would direct the reductant to the *Si*-face of the oxocarbenium ion, with stereochemical erosion resulting from the aforementioned potential of the oxocarbenium ion to rotate (see **13**), exposing the re-face. Mechanistic data which have been interpreted to disfavor formation of a full free oxocarbenium ion might be explained by directed reduction some degree of interaction (i.e., ion pair complex) between a loosely bound alkoxide with the acetal carbon. Although the exact mechanism, therefore, remains the subject of some debate, the important point is that useful levels of regioselectivity can be obtained under the mild conditions employed in these reductions.

8.09.2.5 Reductions to Give *O*-4 Hydroxyl/*O*-6 Benzyl Ethers

The reduction of acetals to give *O*-4 hydroxyls can be achieved using two general principles: The combination of a silane-reducing agent with a wide range of (Brønsted or Lewis acid) activators in coordinating or noncoordinating solvents, or an activated borane reducing agent (derived from precursors such as $NaBH_3CN$ or $BH_3 \cdot NMe_3$) with Lewis acids in coordinating solvents. These conditions give rise to three mechanistic possibilities.

8.09.2.5.1 Mechanism D: Silane as hydride source with Brønsted or Lewis acid activator

With Brønsted or Lewis acids, activation is kinetically favored at *O*-6 (**19**, Scheme 6, illustrated for Brønsted acids) due to the greater accessibility and also basicity of this oxygen atom (fewer deactivating inductive effects/superior solvation of the conjugate acid). However, as Brønsted acids (temperature for acetals (TFA), TfOH) are relatively small, they are also able to effect protonation at *O*-4 (**20**). From either of these oxonium ions, acetal ring opening can occur to give the corresponding oxocarbenium



Scheme 6

ions **21** and **22**. Initially, these exist as tight ion pairs, but through C-5–C-6 bond rotation can convert to free oxocarbenium ions. The reverse of these processes permits the equilibration of **21** and **22**, and in this situation their relative reactivity, where the *O*-6 oxocarbenium ion **22** is less-hindered but more stable, and steric considerations of the hydride source, can dictate the outcome of the reaction. The latter factor is particularly important for reactions with bulky, relatively unreactive silane-reducing agents, for which the reduction of the *O*-4 oxocarbenium ion is sterically challenging (i.e., $k_3 < k_4$ ' $k_2 < k_1$), and these reactions therefore afford the 4-hydroxy/6-benzyl ether product **8** due to more rapid reduction by the silane of the *O*-6 oxocarbenium ion **22** in the equilibrating mixture.

For small Lewis acids ($BF_3 \cdot OEt_2$) in combination with bulky hydride sources, similar arguments apply. For example, a significant body of work has been carried out on the use of silanes in combination with metal triflate salts. These relatively strong Lewis acids are capable of promoting the formation of full oxocarbenium ions in inert solvents such as dichloromethane, leading to the formation of product **8**. Notably, the importance of steric factors for the hydride transfer step is underlined by the finding that 'small' silanes such as dimethylethylsilane react more rapidly than triethylsilane. The choice of solvent also has a marked affect on the rate of reaction, with polar solvents such as acetonitrile or nitromethane affording significantly shorter reaction times compared with dichloromethane – observations which again support a mechanism proceeding via an oxocarbenium ion intermediate.

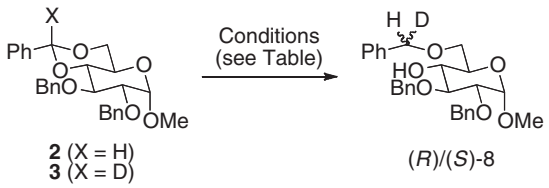
Deuterium-labeling studies provide a final convincing piece of evidence for the formation of the free oxocarbenium ion for both Brønsted and Lewis acid-mediated reactions (Table 1). Stereorandom reduction was observed for the reduction of acetal **2** using Et_3SiD with $Cu(OTf)_2$, $BF_3 \cdot OEt_2$, or trifluoroacetic acid as promoter (entries 1–3). For these triethylsilane reductions catalyzed by metal triflate salts, additional kinetic information such as kinetic isotope effects is not yet available to provide further support for oxocarbenium ion formation.

8.09.2.5.2 Mechanism E1: Borane as hydride source with Lewis acid activation

A distinct mechanism operates when seemingly stable borane–amine complexes are employed in acetal reductions, in combination with Lewis acids in coordinating solvents, leading to the formation of the 4-O benzyl ether/6-OH. Here, higher order kinetics with respect to the Lewis acid imply that a more involved mechanism is at bay than those described above. The abnormally high rate of reduction under these conditions suggests a 'decomplexing' role for the added Lewis acid; however, it is apparent from ^{11}B NMR experiments that the presence of the acetal is also crucial in enabling this decomplexation of the amine from the borane (no reaction is observed between $AlCl_3$ and $BH_3 \cdot NMe_3$ in THF in the absence of the acetal). Thermodynamic considerations suggest that $AlCl_3 \cdot THF$ is able to activate $BH_3 \cdot NMe_3$ (resulting in the formation of decomplexed and highly Lewis acidic BH_3), but not $BH_3 \cdot THF$; in a similar vein, $NaBH_3CN$ is known to be activated by Brønsted acids to give BH_2CN (Table 1, entry 6). Interactions (reactions) of this type lead to the *in situ* formation of powerful boron Lewis acids, which are able to form complexes with acetal oxygens.

Kinetic isotope effects measured for the borane–amine reduction revealed a strong primary isotope effect (4.9) and a normal secondary isotope effect (1.4), the latter being in contrast to mechanistic data presented earlier for the complementary opening to free 6-OH. The 2° kinetic isotope effect (kie), suggests that rehybridization (sp^3 to sp^2) is involved in the rate-determining step, which would be consistent with rate-determining formation of an oxocarbenium ion – a hypothesis supported by the comparison

Table 1 Deuterium-labeling studies for the ring opening of glucose-*O*-4,6-benzylidene acetals



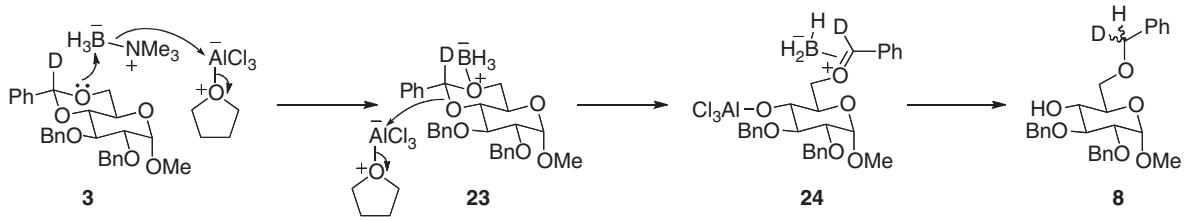
2 (X = H)
3 (X = D)

(*R*)/(*S*)-8

Entry	*Substrate*	*Reaction conditions*	*Ratio ((R)-8: (S)-8)*	*References*
1	2	1 mol% $Cu(OTf)_2$, Et_3SiD, MeCN, 0 °C→r.t.	52:48	8
2	2	$BF_3 \cdot OEt_2$ (2 equivalents), Et_3SiD, CH_2Cl_2, 0 °C→r.t.	51:49	8
3	2	CF_3CO_2H (5 equivalents), Et_3SiD, 0 °C→r.t.	53:47	8
4	3	$BH_3 \cdot NMe_3$, $AlCl_3$, THF	43:57	5
5	3	$BH_3 \cdot NMe_3$, $AlCl_3$, H_2O, THF	42:58	5
6	3	$NaBH_3CN$, HCl, Et_2O, THF	44:56	5

of benzylidene and *p*-bromobenzylidene acetals, which revealed a strong electronic preference for reduction of the (non-brominated) benzylidene acetal (87:13). The strong primary isotope effect was found to vary significantly with time, which renders interpretation difficult; these kinetics are potentially influenced by different dissociation constants for $BH_3 \cdot NMe_3$ and $BD_3 \cdot NMe_3$, and further by hydride/deuteride exchange between the two reagents.

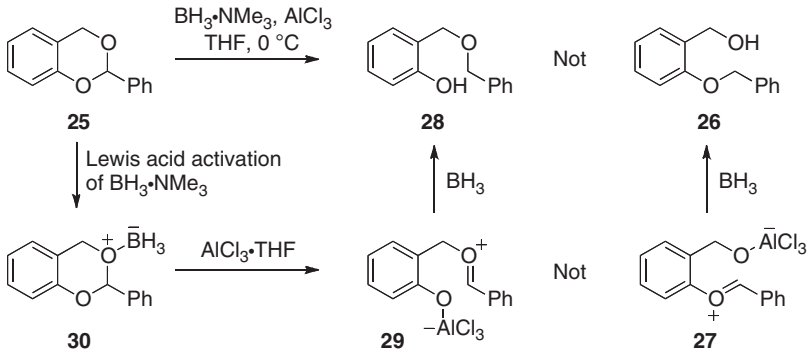
A mechanism proposed by Ellervik to account for these observations involves interaction of all three components in the initial stages of the reaction, with complexation of borane to the less-hindered *O*-6 being triggered by Lewis acid activation (**3**→**23**, Scheme 7). This event is followed by coordination of the second equivalent of Lewis acid at *O*-4 in a ring-opening process that leads to a free *O*-6 oxocarbenium ion (**24**). This undergoes nonstereoselective reduction (Table 1, entry 4) to give the *O*-6 benzyl ether **8**. The extension of this mechanistic hypothesis to Garegg's HCl/$NaBH_3CN$ conditions (which show an equivalent 2° kie of 1.4) would view a dual role for the Brønsted acid – as an activator for $NaBH_3CN$, generating highly reactive BH_2CN, and as a mediator of *O*-4 oxocarbenium ion formation.



3 **23** **24** **8**

Scheme 7

Additional support for this mechanism arises from a study of the ring opening of dioxane acetals **25** derived from *o*-phenoxybenzyl alcohols (Scheme 8). Despite the marked difference in Lewis basicity of the phenolic and benzylic oxygen atoms, where preferential Lewis acid complexation at the benzylic oxygen would be expected (reinforced by DFT calculations),



25 **28** **26**

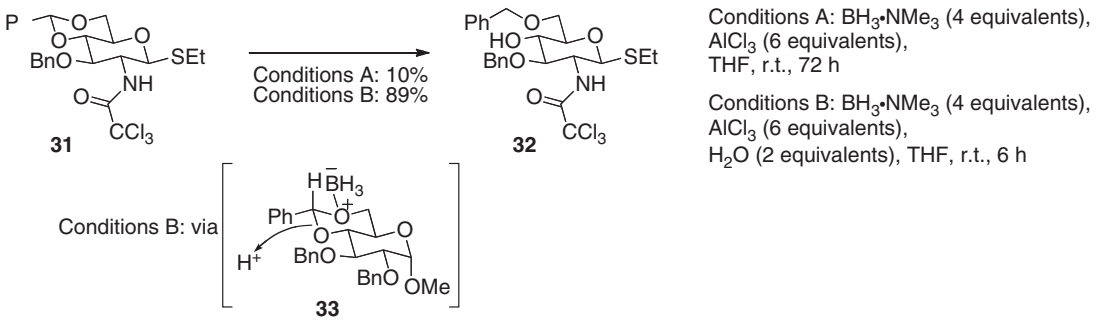
30 **29** **27**

Scheme 8

leading to the benzyl alcohol product **26** via oxocarbenium ion **27**, the observed outcome is instead the exclusive formation of phenol **28**. This implies the counter-intuitive formation of oxocarbenium ion **29**, which could be rationalized using the Lewis acid-activated borane mechanism outlined above – in effect, the borane serves as a protecting group for the more basic oxygen atom (**30**), which enables activation of the less basic oxygen by another (more powerful) Lewis acid. However, a note of caution is sounded for this general mechanistic hypothesis, as the influence of adventitious water may well be important in this process (see Mechanism E2).

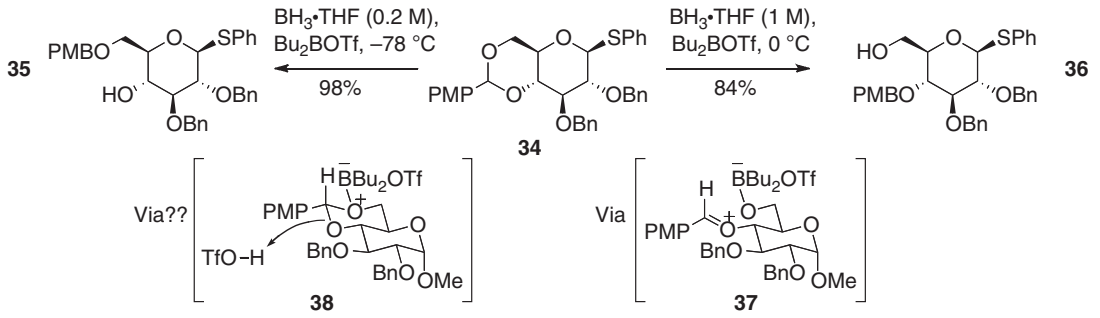
8.09.2.5.3 Mechanism E2: Borane as hydride source with Lewis acid activator in the presence of water

Studies on the influence of adventitious – or stoichiometric – amounts of water on Lewis acid-promoted acetal reduction have revealed an accelerating effect that has been associated with the production of small amounts of Brønsted acid, as the unhindered nature of proton sources leads to a rapid rate of protonation even at low concentration. Seminal work by Nifantiev revealed the influence of water on the rate of acetal ring opening.[14] For example, attempted reduction of acetal **31** using $BH_3 \cdot NMe_3/AlCl_3$ (Scheme 9) led to almost no reaction after a 72 h period (10% isolated yield of **32**). However, repeating this reaction in the presence of stoichiometric quantities of water gave an 89% yield of **32** in just 6 h. This result could be explained by a modification of Mechanism E1, in which the Brønsted acid formed from reaction of water with $AlCl_3$ is able to protonate *O*-4 much more rapidly than the Lewis acid is – leading to effective ring opening via **33** in spite of the presumed *O*-6 coordination to BH_3 – in effect, the borane acts to protect *O*-6 in this reaction, much as in Scheme 8. These observations have been supported by more detailed investigations into the influence of the ratio of $AlCl_3$ to H_2O, where acceleration was again observed at a ratio of 3:1, but at higher ratios (i.e., increased amounts of $AlCl_3$), slower reactions were seen.[3] Most intriguingly, no reaction was detected with equimolar quantities of $AlCl_3$ and H_2O. These findings were rationalized on the basis of the formation of different $H_2O/Al(III)$ complexes, with cationic $[AlCl_2(H_2O)_4]^+$ proposed as an activating species, but neutral $AlCl_3(H_2O)_3$ being a deactivated species.



Scheme 9

A similar observation has been made in the study of the temperature dependence of the reduction of various 4,6-*O*-benzylidene acetals with $BH_3 \cdot THF/Bu_2BOTf$ (Scheme 10).[13] In this work (which is discussed earlier in the context of Mechanism B2), reduction of acetals such as **34** led to complementary regioselectivity at –78 °C (giving the 4-OH product **35** in the presence of a dilute (0.2 M) solution of $BH_3 \cdot THF$) to reductions performed at 0 °C (which give the 6-OH product **36** using more concentrated (1 M) $BH_3 \cdot THF$ solution). The outcome of the latter reaction has been discussed in the context of Mechanism B2 in which the relatively bulky Lewis acid dictates the regioselectivity of ring opening (**37**). However, at –78 °C, it is unrealistic to propose *O*-4 activation by this Lewis acid. Instead, it is suggested that adventitious water leads to the formation of trace amounts of TfOH, which at –78 °C is able to mediate *O*-4 activation to give the *O*-6 oxocarbenium ion.[13] Notably, although not proposed by the authors, this reaction 'may' occur through Mechanism E1 with trace Brønsted acid activating (at *O*-4) the *O*-6–Bu_2BOTf



Scheme 10

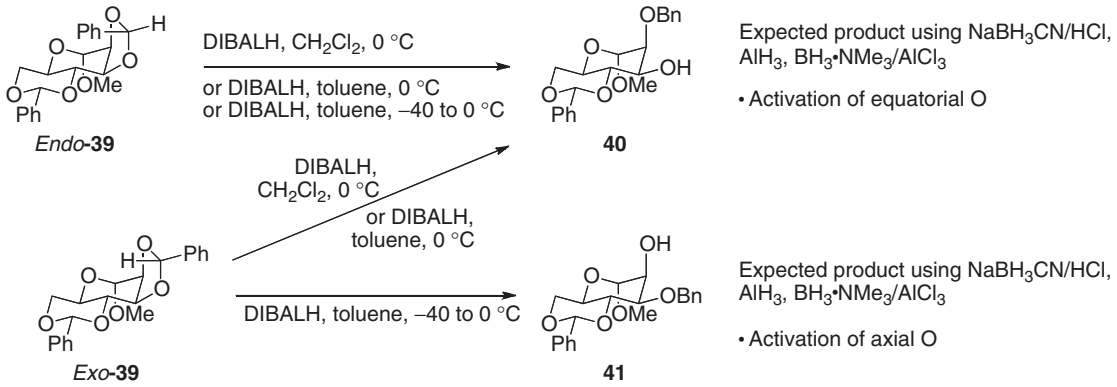
complex of the acetal (**38**). As mentioned previously, support for the role of the Brønsted acid in this reaction was obtained on conducting the reduction using base-washed glassware, in the presence of molecular sieves and acid scavenger (4,6-*di-tert*-butylpyridine), under which conditions no reaction was observed at −78 °C.

The conclusion of these studies is that unless reactions are performed under strictly anhydrous and acid-free conditions, PMB trace amounts of Brønsted acids must be considered in explaining the outcome of acetal reductions.

8.09.2.6 Mechanistic Aspects of Dioxolane Ring Opening

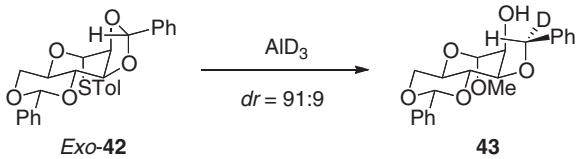
In addition to the detailed work carried out on 4,6-O-benzylidene acetals of carbohydrates (particularly glucose), a number of other mechanistic studies have contributed to the understanding of acetal reduction. Particularly relevant are studies of the selectivity of the reduction of 2,3-O-benzylidene acetals (dioxolanes), which in general exhibit higher reactivity compared with the corresponding carbohydrate 4,6-dioxanes, due to inferior stabilization of the acetal by anomeric effects.[6,9,14–17] The opening of these 1,3-dioxolanes features two aspects of interest from a mechanistic perspective: the exact mechanism of ring opening (in light of the above discussion on dioxanes), and the variation in regioselectivity of ring opening with the configuration of the acetal carbon. This latter behavior is well established to depend primarily on the accessibility of the two oxygen atoms, but is mentioned here in showing variation not only with acetal configuration but also with the nature of the solvent.

For example (Scheme 11), reduction of dioxolane *endo*-**39** with DIBALH in toluene or dichloromethane is selective for formation of the 2-O benzyl ether/3-OH product **40**,[18] a result which is typical of the reduction of such *endo*-dioxolanes under other conditions and which likely proceeds via selective activation of the equatorial oxygen of the dioxolane.[6,9,14–17] In contrast, reaction of *exo*-**39** with DIBALH shows strong solvent dependence: performing the reaction in dichloromethane also leads to the formation of **40**, which is the reverse of the usual selectivity observed with *exo*-dioxolanes, where the formation of the 2-OH/3-O benzyl ether **41** would be expected through activation of the axial dioxolane oxygen atom.[6,9,14–17] Indeed, reaction in toluene at −40 °C reverses this selectivity to give the expected product **41**. More surprising, however, is that an identical (DIBALH/toluene) reduction at 0 °C restores selectivity for the formation of **40**. The reasons for this behavior are not clear.



Scheme 11

Deuterium-labeling experiments have confirmed that the reduction of such carbohydrate dioxolanes with alane proceeds through Mechanism A (S_Ni mechanism); reaction of *exo*-**42** with AlD_3 (prepared from $AlCl_3$ and $LiAlD_4$) leads to a 91:9 ratio of monodeuterated 3-O benzyl ethers in favor of the retentive product (***R***)-**43** (Scheme 12).[8]

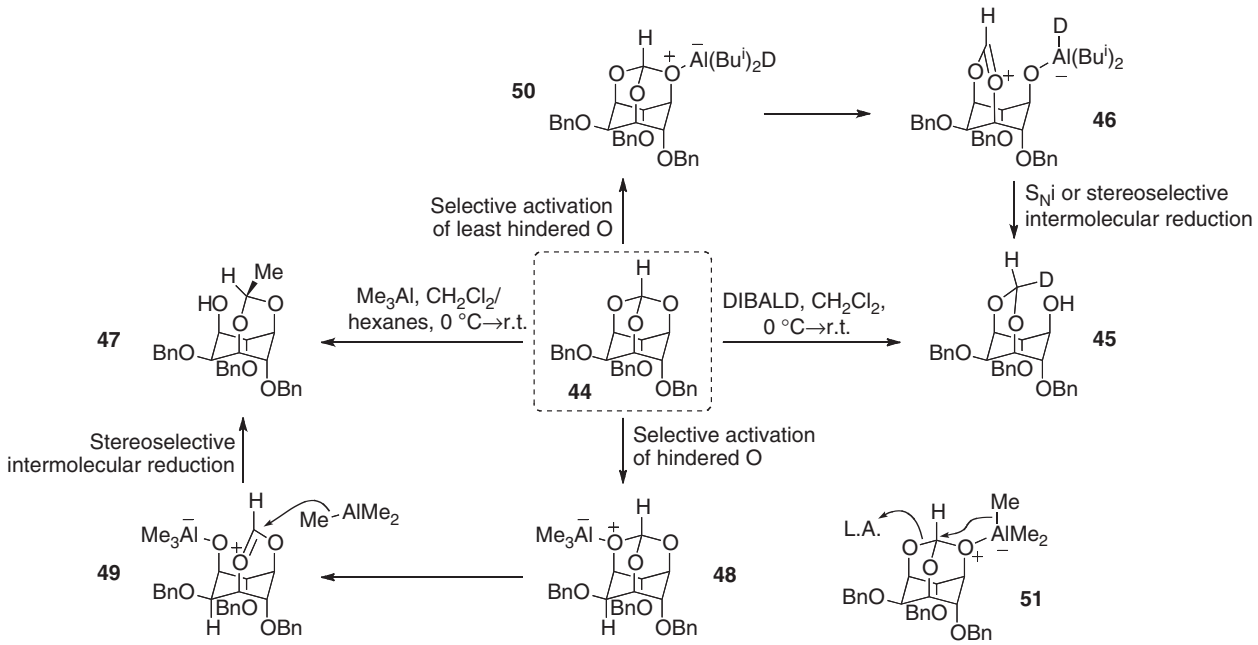


Scheme 12

8.09.2.7 Mechanistic Aspects of the Reduction of Inositol Orthoester Derivatives

A final branch of acetal reduction that has developed from a mechanistic perspective since previous coverage of the field lies in the closely related area of orthoester reduction. These reductions might well be expected to proceed with similar mechanisms to those

of acetals, and indeed employ identical reaction conditions in many cases. A particular substrate class that allows detailed probing of the mechanism of orthoester cleavage are orthoesters derived from inositols, which have been productively employed in the synthesis of inositol phosphate derivatives.[19] The use of an orthoester in this context allows the simultaneous protection of three of the hydroxyl groups of the inositol ring, and the selective reductive cleavage of this functional group provides a further avenue for hydroxyl differentiation. This principle is illustrated by reactions of orthoester **44** (**Scheme 13**), which on treatment with DIBALH undergoes selective orthoester ring opening to afford acetal **45**.[19,20] Deuterium-labeling experiments using DIBALD revealed this reaction to proceed with retention of configuration, which is immediately suggestive of an S_Ni-type mechanism (Mechanism A), but may also imply a stereoselective intermolecular reduction of the oxocarbenium ion **46** following a ring flip of the axial aluminum alkoxide to a pseudo-equatorial position. In contrast, treatment of **44** with trimethylaluminum leads to a complementary ring opening, with the formation of acetal **47**.[19,20] It is postulated that the smaller size of trimethylaluminum compared with DIBALH permits complexation to one of the more hindered oxygen atoms – possibly due to a directing effect by the adjacent benzyloxy substituent, or to the greater basicity of these oxygen atoms due to hyperconjugation from the adjacent axial C–H bond (i.e., $\sigma_{C-H} \rightarrow \sigma^*_{C-O}$ increases electron-density on the oxygen atom – the C–H bond is illustrated in oxonium ion **48**). Not only is the regiochemistry of this reaction different but also the stereoselectivity – the addition of methyl nucleophile now occurs with 'inversion', implying an intermolecular delivery to oxocarbenium ion **49**. In light of the mechanistic evidence presented for acetal reduction (Mechanism E), a different mechanistic possibility may be the activation of the more hindered oxygen atom by an acid, following complexation (protection) of the less-hindered oxygen by trimethylaluminum – in other words, the initial site of Lewis acid complexation is identical for both DIBALH/D (**50**) and trimethylaluminum (**51**). This complexation would equally enable an invertive mechanism for methyl delivery on steric grounds, either concerted (as shown) or stepwise via an oxocarbenium ion similar to **49**.



Scheme 13

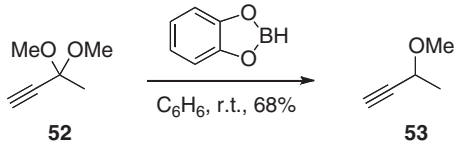
In summary, significant advances have been made in the mechanistic understanding of reductive acetal ring-opening processes. These developments provide a secure platform to interpret the many methods that have been developed for acetal reduction as will be described in the subsequent sections.

8.09.3 Selective Reductions

8.09.3.1 Acyclic Acetals

The reduction of acyclic acetals presents a particular challenge owing to the greater propensity of these substrates to undergo hydrolysis to the parent carbonyl under relatively mild conditions. Thus, the use of mild reducing agents is common for these substrates, such as silanes or even stannanes – reagents which see little use for more robust acetals. Other creative solutions to this challenge include the use of single-electron transfer strategies, and transfer hydrogenation.

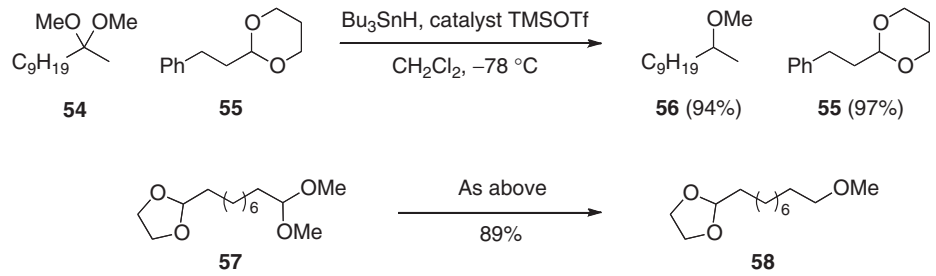
Although a number of boranes ($BH_3 \cdot THF$, $LiAlH_4$) are capable of effecting acetal reductions, problems can arise if additional functional groups are present that are also susceptible to reduction. In this vein, catecholborane achieves the selective reduction of acetals adjacent to unsaturated carbon–carbon multiple bonds (**52**→**53**, Scheme 14), where the use of other boranes gives rise to mixtures of the desired ether product, together with unwanted hydroboration/protodeboration (i.e., reduction of the multiple bond).[21] Notably, whereas heating is required to cleave cyclic acetals, the reaction proceeds at room temperature for acetals derived from propargylic or allylic carbonyl compounds. This is likely due to the stabilizing effects of the adjacent unsaturation on the transition state for acetal cleavage using this mild Lewis acid.



52 **53**

Scheme 14

The delicate nature of acyclic acetals is further underlined by an interesting report on the selective reduction of acyclic acetals in the presence of dioxanes or dioxolanes (Scheme 15).[22] Exposure of an equimolar mixture of cyclic acetal **54** and acyclic acetal **55** to a combination of tributyltin hydride and trimethylsilyl chloride led to rapid, highly selective reduction of the acyclic acetal to give ether **56** in excellent yield, with complete recovery of the cyclic counterpart. To further illustrate this chemoselectivity, a substrate **57** featuring both acyclic and cyclic acetals were also described, where reduction gave exclusively the ether **58**.

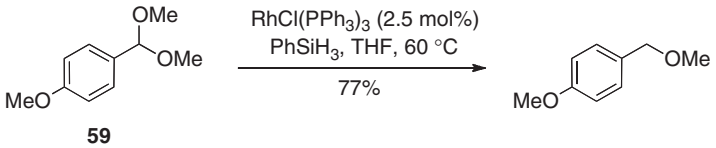


54 **55** **56** (94%) **55** (97%)

57 **58**

Scheme 15

Several other methods have been developed for the reduction of acyclic acetals and ketals, although in many cases the substrate scope of the examples reported is somewhat limited. Transition metal catalysis of this challenging process has produced some promising results, which have not been widely applied to date. For example, Wilkinson's catalyst can be used to catalyze the reduction of dimethyl acetal **59** (Scheme 16) using triphenylsilane as the reductant.[23] Although this is the only acyclic example described in this work, with the method mainly being applied to dioxanes and dioxolanes, the authors note that the 'more active' rhodium hydride complex $RhH(CO)(PPh_3)_3$ could also be employed (see also orthoesters, Section 8.09.3.5).

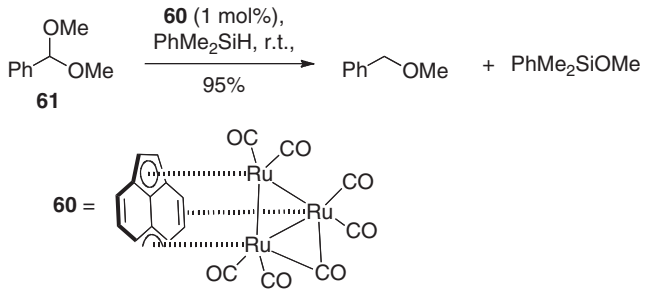


59

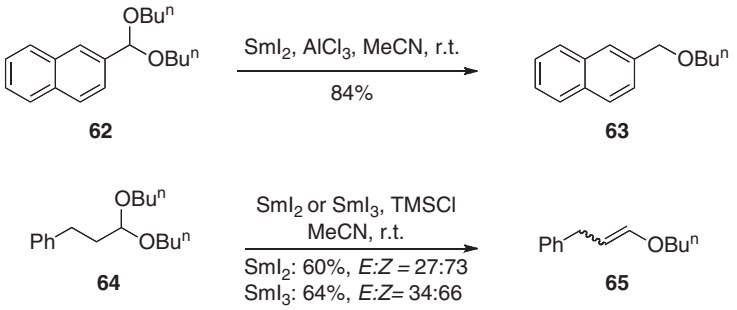
Scheme 16

In a similar vein, ruthenium complex **60** has been used as a catalyst to achieve the reduction of acyclic acetal **61** with phenyldimethylsilane (Scheme 17),[24] where the active ruthenium complex is prepared from oxidative addition into the Si–H bond. Although this reaction proceeded in very high yield, this complex also effects the hydrosilylation of aldehydes and ketones, and the polymerization of cyclic ethers; as such it is likely to be of limited use from a synthetic perspective.

Single-electron transfer agents have also been shown to be of some use in achieving the reduction of acyclic acetals (**62**→**63**, Scheme 18), although the reaction scope is limited to benzylic acetals and requires multiple equivalents of both the single-electron reductant (SmI_2) and Lewis acid promoter ($AlCl_3$).[25] The reaction is believed to proceed by samarium-mediated reduction of the oxonium ion or oxocarbenium ion arising from complexation of the acetal to the Lewis acid. Attempts to extend this methodology to the reduction of alkyl acetals led instead to elimination to the enol ether (**64**→**65**), a process that could be optimized by changing the metal halide from $AlCl_3$ to TMSCl.

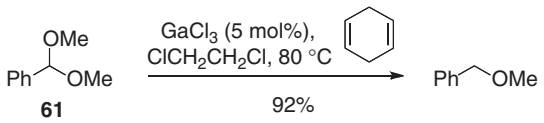


Scheme 17



Scheme 18

Finally, in work focused mainly on the partial reduction of dithioacetals to thioethers, gallium(III) chloride has been reported to reduce acyclic acetal **61** to the corresponding ether using 1,4-cyclohexadiene as an unusual stoichiometric reductant (Scheme 19).[26] The reduction did not proceed to completion at ambient temperature, but heating to 80 °C gave full conversion to the ether in excellent yield.



Scheme 19

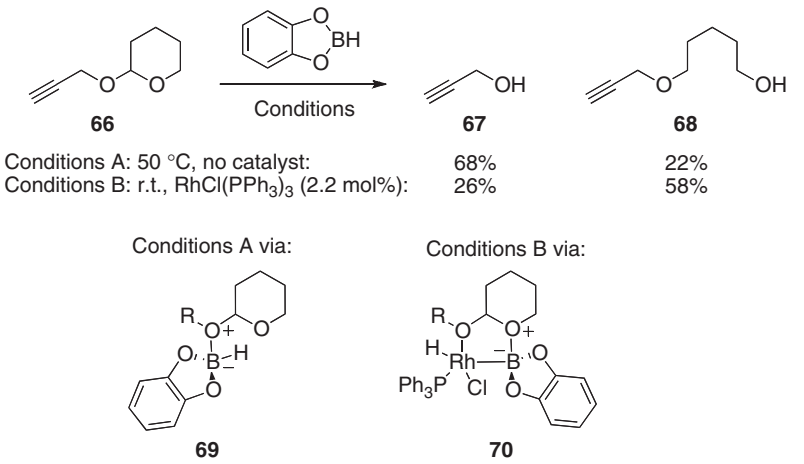
8.09.3.2 Furanosides and Pyranosides

Relatively few new methods have been developed for the reduction of furanyl or pyranyl ethers, most likely due to the significant challenge of selectively activating one of the two ether groups, and to the more standard use of the THP ring as an alcohol protecting group, where hydrolytic cleavage is usually employed. Although ionic hydrogenation does provide an attractive route from acetals into pyrans and furans, the alternative starting point of a lactol generally provides a more convenient synthetic entry point. The vast majority of these acetal reductions have employed triethylsilane as reductant, with boron trifluoride or trimethylsilyl triflate as activator.[1,27]

It has been shown that catecholborane can also be used for a moderately selective reduction of THP ethers. Reaction of THP ether **66** (Scheme 20) at 50 °C mainly delivers the product **67** resulting from cleavage of the exocyclic C–O bond (which is reduced to tetrahydro-2*H*-pyran).[21] In contrast, catecholborane in combination with catalytic Wilkinson's catalyst at ambient temperature effects a reversal in regioselectivity of the reduction, now favoring endocyclic C–O bond cleavage (**68**). An explanation of this switch in regioselectivity is proposed based on preliminary complexation of rhodium with the exocyclic oxygen atom, which orients attack by boron to the endocyclic oxygen, leading to preferential scission of the endocyclic C–O bond (compare **69** and **70**).

8.09.3.3 Dioxolanes and Dioxanes: Noncarbohydrate Examples

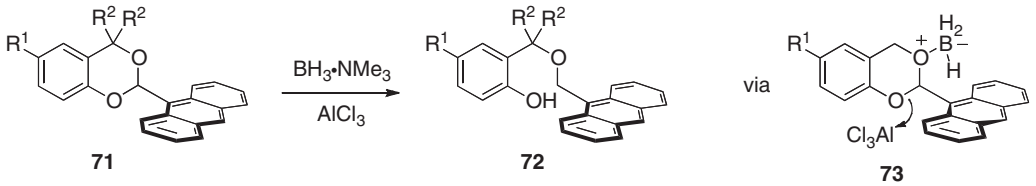
Almost without exception, methodology for the reduction of noncarbohydrate dioxolanes and dioxanes employs borane- or silane-reducing agents in combination with a Lewis acid activator. A typical example is found in the regioselective reductive ring



Scheme 20

opening of mixed phenolic/benzylic cyclic acetals (**71**, Table 2) using a combination of $BH_3 \cdot NMe_3$ and aluminum trichloride,[2] the Garegg conditions[9] which have been applied so successfully in the carbohydrate field. This particular class of substrate was targeted with a view to utilizing reduction products of type **72** as fluorescent probes.

Table 2 Regioselectivity in the ring opening of phenolic/benzylic acetal 71

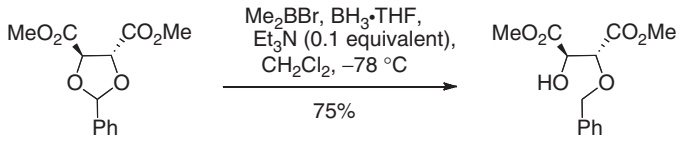


Entry	*R^1*	*R^2*	*Conditions*	*Products*
1	OMe	H	THF, 0 °C, 3 h	73%
2	H	H	THF, 0 °C, 3 h	83%
3	NO_2	H	THF, 0 °C, 3 h	No reaction
4	H	Me	THF, 0 °C, 3 h	No reaction
5	H	Me	Toluene, r.t., 5 min	Degradation

The somewhat surprising finding of this work was that the regioselectivity of dioxane ring opening, leading to the deprotection of the phenol rather than benzyl alcohol, suggests Lewis acid activation of the phenolic oxygen rather than the benzylic oxygen – the latter being the expected site of activation on the basis of Lewis basicity. The effect of steric and electronic parameters were investigated, with an electronically activating *p*-methoxy substituent on the aromatic ring being tolerated (entry 1), but the deactivating *p*-nitro functional group resulting in the return of starting material (entry 3). Introduction of a *gem*-dimethyl group at the benzylic position also led to no reaction (entries 4, 5), leading the authors to postulate that initial coordination of the more basic benzylic oxygen to a Lewis acid (namely activated borane) must be important/required, with $AlCl_3$ then activating the phenolic ether (**73**). More detailed analysis of this process, and its general importance in the acetal reduction field, is discussed in the mechanistic section of this chapter (see Section 8.09.2.5.2).

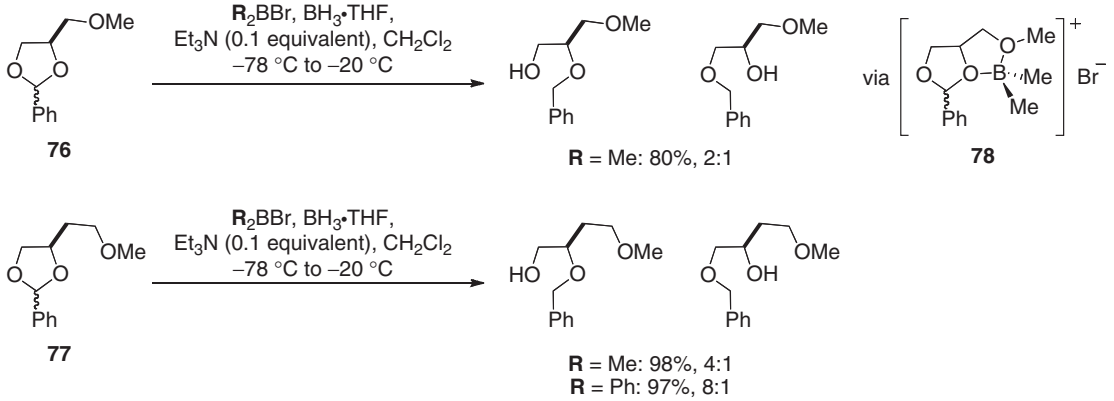
An alternative activator for borane-mediated reduction that is particularly effective for the reductive opening of benzylidene acetals is dimethylboron bromide. This reagent has seen significant use in noncarbohydrate settings, with various coreductants such as borane, DIBALH, or Super-Hydride.[28] Of the various boranes, $BH_3 \cdot THF$ gives superior results; in the reduction of tartrate-derived acetal **74** (Scheme 21), ester functional groups are tolerated under the reaction conditions, which give ether **75**. The mechanism of this reaction remains the subject of some uncertainty, owing to related results for acetal ring opening with concurrent nucleophilic substitution by organocuprate reagents, and may involve the intermediacy of an α-bromoether.[29]

For nonsymmetrical benzylidene acetals, there is a general preference for cleavage of the less-hindered C–O bond, through coordination of one of the more available oxygen atom lone pairs to the Lewis acidic Me_2BBr.[28] The exception to this are derivatives containing additional chelating groups such as **76** and **77** (Scheme 22), which show reduced levels of regioselectivity.



Scheme 21

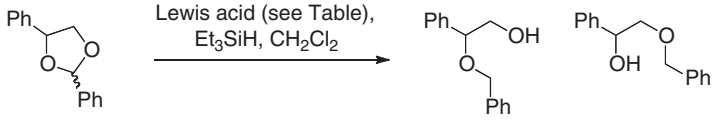
It is suggested that intramolecular chelation of the methoxy functional group (**78**) renders the more hindered oxygen atom somewhat more susceptible to C–O bond cleavage (although presumably this chelation also reduces the electron-withdrawing ability of the boron and therefore the reactivity of this complex). By switching the Lewis acid promoter to the more hindered Ph_2BBr, good selectivity for cleavage of the less-hindered oxygen atom can be restored.



Scheme 22

Silanes also offer opportunities for the regioselective cleavage of unsymmetrical benzylidene acetals. Building on a report of the use trifluoroacetic acid/triethylsilane to achieve selective the reduction of carbohydrate acetals,[30] a screen of a number of Brønsted and Lewis acids revealed that $EtAlCl_2$ greatly improves both the rate and regioselectivity of the reductive cleavage of more generalized acetal systems such as **79** (Table 3), to afford predominantly the primary alcohol **80**.[31]

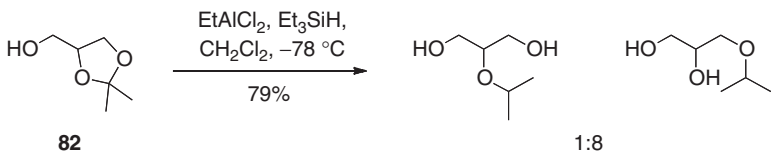
Table 3 Regioselective reductive ring opening of dioxolane 79



Entry	*Lewis acid*	*Temperature (°C), (time (h))*	*Yield (%), (conversion (%))*	*80:81*
1	$BF_3 \cdot OEt_2$	–78 (1)	12 (40)	6.5:1
2	TFA	0→r.t. (4)	19 (70)	1.5:1
3	TfOH	–78 (1)	38 (48)	7.5:1
4	$TiCl_4$	–78 (0.5)	77 (100)	2.4:1
5	$InCl_3$	0→r.t. (5)	10 (58)	6.0:1
6	DIBALH	0 (4)	70 (80)	1.6:1
7	$EtAlCl_2$	–78 (0.5)	77 (100)	10.1:1

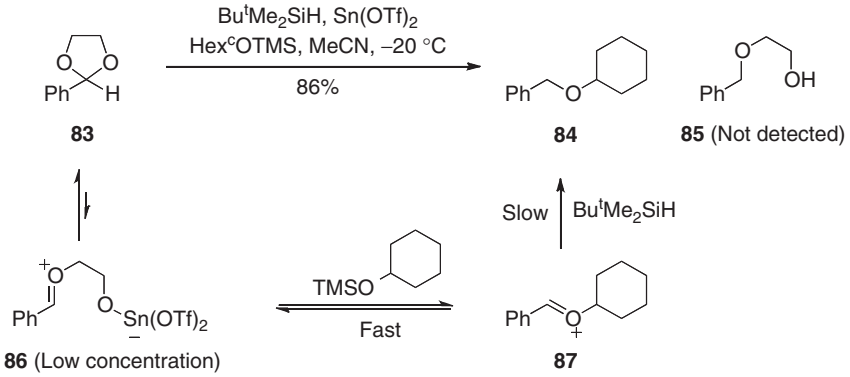
A number of nonsymmetrical acetals were evaluated, including more robust acetonides. Interestingly, glycerol-derived acetonide **82** (Scheme 23) underwent selective cleavage with opposite regioselectivity to the above example, presumably due to Lewis acid complexation by the free hydroxyl directing ketal cleavage in a similar manner to that observed with $Me_2BBr/BH_3 \cdot NMe_3$.[31]

An alternative silane-mediated method for the reduction of acetals has been developed which converts cyclic dioxolane acetals into what are effectively the products of acyclic acetal reduction, via a sequenced transacetalization/reduction using Lewis acid



Scheme 23

activation in combination with trimethylsilyl ethers and a hydrosilane (**83**→**84** Scheme 24).[32] Although substoichiometric TMSOTf could be employed as the Lewis acid activator,[33] stoichiometric amounts of $Sn(OTf)_2$ proved most effective, with the reaction being suitable for both aryl and alkyl acetals and ketals, and a decent selection of alcohol nucleophiles; a representative example is illustrated in Scheme 24. No products from direct reduction of the dioxolane acetals were obtained (**85**), which suggests that the rate of reduction of cyclic acetals is significantly slower than acyclic, presumably due to the greater reversibility of cyclic acetal ring opening arising from entropic effects. It is likely that a relatively rapid equilibrium is established which allows interconversion of the various acetals and their oxocarbenium ions (**86** and **87**); and that the nucleophilicity of the trimethylsilyl ether exceeds that of the silane-reducing agent, such that hydride transfer is the rate-limiting step.



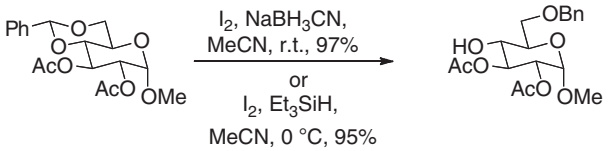
Scheme 24

Finally, a ruthenium-catalyzed reduction of cyclic acetals using triphenylsilane as the stoichiometric reductant has been reported which prepares ethers in good-to-excellent yields, although reactions times are long and varying levels of starting material are recovered.[23] This reaction has been discussed in the context of acyclic acetals (see Scheme 17, Section 8.09.3.1).

8.09.3.4 Dioxolanes and Dioxanes: Carbohydrate Examples

Advances in the selective reduction of carbohydrate acetals have been realized with the development of increasingly mild and selective reaction conditions which afford greater functional group tolerance than the classical procedures pioneered by Garegg, Lipták, and others. In many cases, a single activator such as a metal triflate salt is capable of leading to complementary reduction outcomes depending on the choice of reductant.

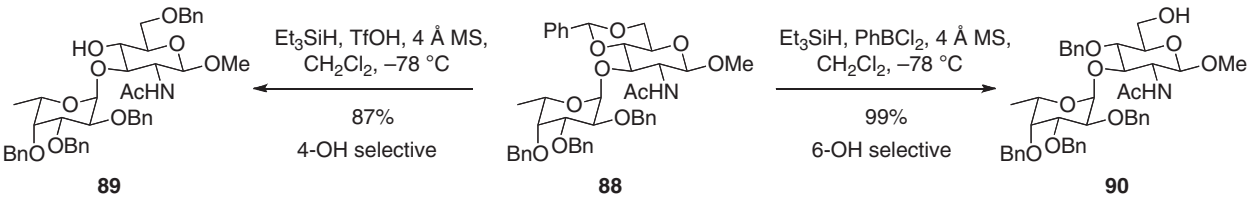
A number of Brønsted acids have been found to be effective activators of acetal ring opening. The use of hydrochloric acid in combination with cyanoborohydride (as pioneered by Garegg)[15] has found continued application, particularly in the one-pot derivatization of carbohydrates (see Scheme 33), but several other acids offer alternative means to activate the cyanoborohydride ion, presumably with the formation of H_2 and subsequent ring opening promoted by BH_2CN. For example, methanesulfonic acid offers a cheap alternative to trifluoromethanesulfonic acid, and has been shown to selectively deprotect the 4-hydroxyl of glucosamine *O*-4,6-benzylidene acetal.[34] More appealingly, the combination of iodine and sodium cyanoborohydride results in a similar outcome, with very high yields over a range of substrates.[35] The reaction shows high functional group compatibility and is generally complete in 20 min; a typical example is shown in Scheme 25. The reaction presumably proceeds via the *in situ* generation of BH_2CN and HI from the reaction of $NaBH_3CN$ with I_2, and follows Mechanism E1 (i.e., BH_2CN complexation at



Scheme 25

O-6, followed by acid-mediated ring opening through protonation at *O*-4). Notably, iodine has also been found to activate triethylsilane in an equivalent process, which again delivers 4-OH products in excellent yields and short reaction times.[36]

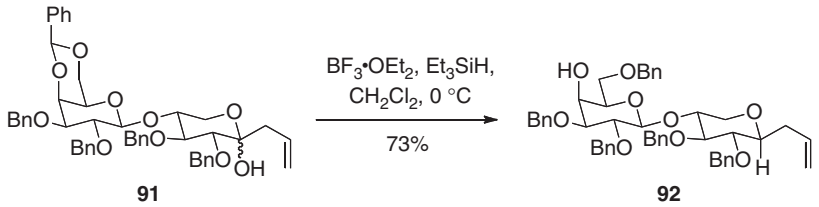
Although iodine likely activates triethylsilane through the controlled formation of triethylsilyl iodide, the use of Brønsted acids relies on the bulk of the silane to favor reduction of an *O*-6 oxocarbenium ion over the more hindered *O*-4 oxocarbenium ion, under conditions that allow equilibration of these species. Trifluoroacetic acid and trifluoromethanesulfonic acid have been shown to be suitable activators,[10,30] with reactions in dichloromethane proceeding at −78 °C. The latter method was also compatible with the use of a polystyrene-supported silane, which aids purification of the reduction product. An example that illustrates application to a moderately complex disaccharide is shown in Scheme 26 (**88**→**89**). These techniques have been applied in contemporary situations such as the deprotection of fluorous acetals,[37] and in one-pot protection/reduction/glycosylation sequences (see below).[38]



Scheme 26

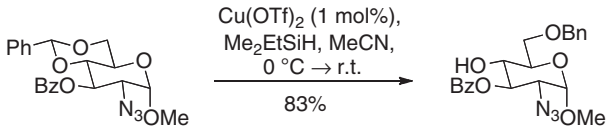
Impressively, the regioselectivity of benzylidene acetal ring opening using triethylsilane could be completely reversed by using $PhBCl_2$ as promoter (**88**→**90**).[10] This seemingly counter-intuitive result may well be explained by the presence of adventitious Brønsted acid (discussed earlier in 'Mechanism B2'). In any event, these mild and highly selective conditions represent an unusual but useful outcome for silane reduction.[11,37]

The use of silanes in combination with a wide range of Lewis acids offers an alternative, much-used method to achieve selective reduction of benzylidene acetals to the more hindered free hydroxyl. These reactions follow Mechanism D, where the regioselectivity is explained by the bulk of the silane reagent. Whether or not adventitious Brønsted acid is involved in these reactions, the outcome is consistent. The first example of this mode of activation involved the use of the classical Lewis acid $BF_3 \cdot OEt_2$, and was discovered in the context of the reduction of hemiketal **91** to pyran **92** (Scheme 27).[39] This serendipitous result proved to be quite general, and has been applied by several research groups, including in the context of challenging electron-deficient *p*-nitrobenzylidene acetals, which afford photolabile *p*-nitrobenzyl ether products,[11,40] and in flow chemistry, where yields of up to 100% are achieved through short reactant contact times.[41]



Scheme 27

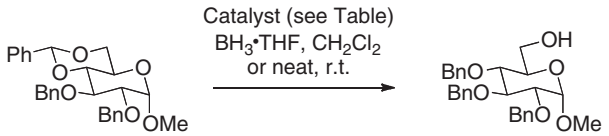
This discovery paved the way for a plethora of more contemporary Lewis acid-catalyzed processes. These are typified by the report of $Cu(OTf)_2$-catalyzed ring opening of benzylidene acetals, which proceeds at an impressive 1 mol% catalyst loading.[7] An example is shown in Scheme 28, where Me_2EtSiH (as opposed to Et_3SiH) is employed as reductant in a polar solvent (acetonitrile), which shortens reaction times to the order of 1 h. Of other metal triflate salts screened under these optimized conditions, only scandium(III), indium(III), and silver(I) triflates gave comparable results, with many proving ineffective.[42] A subsequent report revealed that iron(III) chloride is also capable of inducing this selective ring opening.[43]



Scheme 28

These Lewis acid catalysts are equally capable of directing highly selective reductions to the free 6-OH (or, more generally, deprotection of the least hindered hydroxyl) when combined with $BH_3 \cdot THF$. Representative examples for the reduction of the glucose-*O*-4,6-benzylidene acetal **2** are illustrated in Table 4, although the substrate scope extends to galactose and mannose derivatives, and functional group compatibility includes thioacetals, azides, and esters. The seminal paper in this field reported the use of the vanadium oxo catalyst $V(O)(OTf)_2$ at 15 mol% to achieve this reduction (entry 1),[44] but subsequent investigations revealed the catalyst scope not only to be much broader but also to enable reduction at lower catalyst loading; copper(II) triflate seems the catalyst of choice for most applications (entry 2).[7,42] Interestingly, reductions catalyzed by $Cu(OTf)_2$ can be accelerated using sonochemistry (reaction times 5–35 min), whereas maintaining excellent yields.[45] A stoichiometric variant has also been reported which employs inexpensive $CoCl_2$ as the Lewis acid (entry 8), which leads to exceptionally rapid reduction; the recovery of unreacted $CoCl_2$ from this reaction suggests that this metal salt could also be employed catalytically.[46]

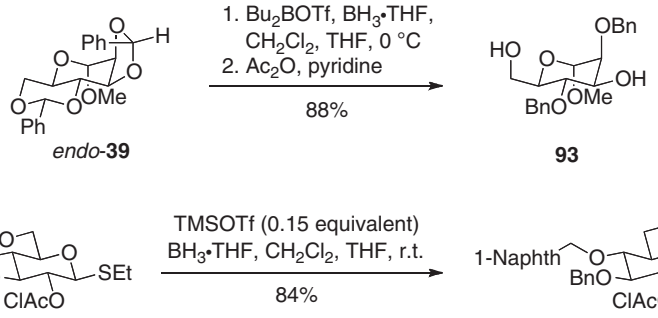
Table 4 Lewis acid-catalyzed reductive ring opening of glucose-*O*-4,6-benzylidene acetal 2 with $BH_3 \cdot THF$



2 **1**

Entry	*Catalyst*	*Mol %*	*Time (h)*	*Yield (%)*	*References*
1	$V(O)(OTf)_2$	15	3	94	42,44
2	$Cu(OTf)_2$	5	2.5	95	7,42
3	$Sc(OTf)_3$	15	5	94	42,44
4	$Yb(OTf)_3$	15	2	94	42
5	$In(OTf)_3$	15	2.5	82	42
6	$Zn(OTf)_2$	15	4	94	42
7	AgOTf	15	4	88	42
8	$CoCl_2$	3000	0.16	100	46

The use of boranes to achieve selective acetal ring opening is well-known in the context of the classical Garegg conditions ($AlCl_3$, $BH_3 \cdot NMe_3$).[9] However, many variants have been reported that allow tuning of the regioselectivity of the reduction, and which can avoid the use of particularly strong Lewis acids such as $AlCl_3$. For example, dibutylboron triflate, and (catalytic) trimethylsilyl triflate, have been shown to be effective activators toward 4-OH deprotection (Scheme 29), no doubt due to the bulk of the Lewis acid activator which permits coordination only at the less-hindered oxygen atom of the acetal (Mechanism B). Examples of these reactions include the simultaneous selective reduction of a dioxane and dioxolane with Bu_2BOTf promoter (*endo*-**41** → **93**); both sets of conditions appear to be widely applicable. The intriguing reversal of regioselectivity for reductions using $Bu_2BOTf/BH_3 \cdot THF$ at −78 °C has been discussed in the mechanistic section (Mechanism B2).[13]

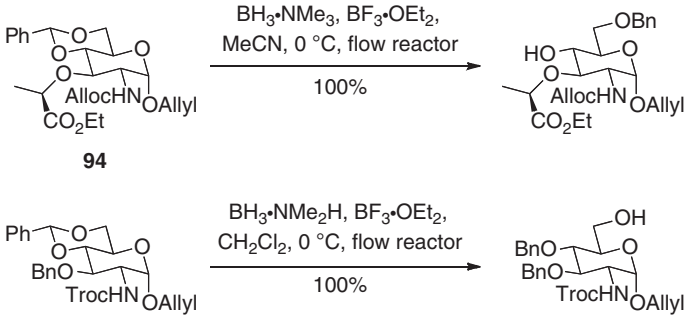


endo-**39** **93**

Scheme 29

Borane–amine complexes are popular in achieving selective reductions, but are also arguably the most perplexing from a mechanistic perspective. The combination of $BH_3 \cdot NMe_3/AlCl_3$ has been extensively discussed in the mechanistic section of this chapter, due to the intriguing reversal of selectivity (Scheme 30) on switching the reaction solvent from noncoordinating (toluene) to coordinating (THF),[5,9] and the accelerating effect of adding stoichiometric amounts of water to the latter reaction conditions.[14] The use of $BF_3 \cdot OEt_2$ with $BH_3 \cdot NMe_2H$ mirrors this selectivity, with reactions in dichloromethane resulting in

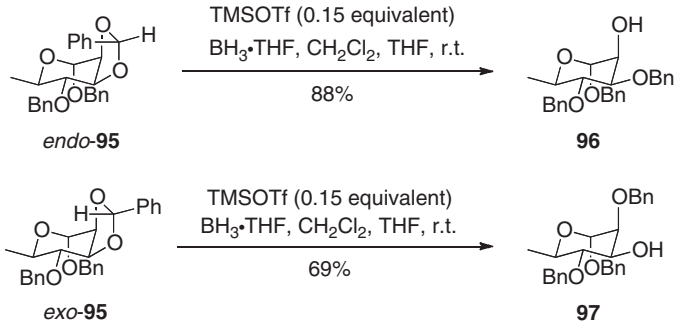
deprotection of the less-hindered *O*-6 position, but the use of the more polar acetonitrile as solvent leading to deprotection at *O*-4 (Scheme 30), presumably due to similar mechanistic arguments. The examples illustrated in Scheme 30 have been achieved using flow techniques, which due to short reactant contact times are able to tolerate the ester functional group of substrate **94**, and also result in exceptional yields.[41] A further variant on this reaction which uses dimethylboron bromide as promoter with $BH_3 \cdot NMe_3$ in dichloromethane/toluene to achieve selective *O*-6 deprotection, in the presence of acetyl groups, has also been reported.[47]



Scheme 30

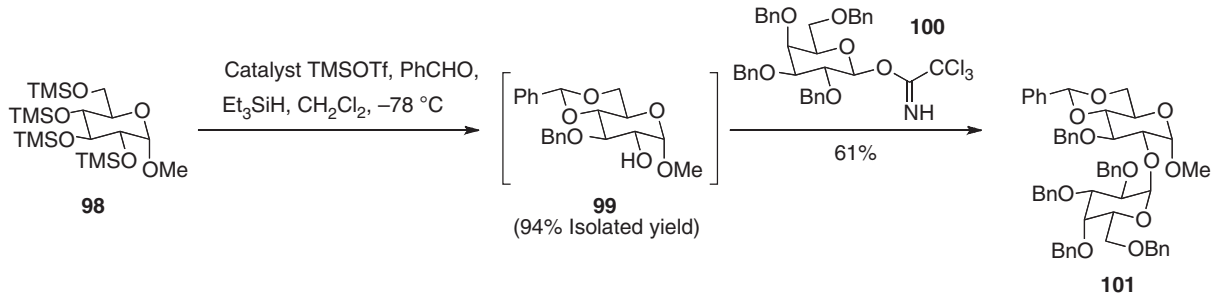
Finally, a review of carbohydrate applications would not be complete without mention of the use of Lewis acidic hydride sources such as alane[48] and DIBALH. The latter is most notable due to the complete switch in regioselectivity that can be achieved simply by varying the solvent in which the stock solution of DIBALH is prepared; reactions using DIBALH in dichloromethane lead to the free 4-hydroxy product, whereas reactions with DIBALH in toluene lead to the 6-hydroxy product.[18] This result is particularly remarkable given that the bulk solvent does not seem to influence the reaction outcome, and suggests the aggregation state of the DIBALH in these different solvents to be of importance. These results have been discussed in context of Mechanism A (Scheme 3).

The application of many of these methods to the reduction of carbohydrate dioxolanes has been reported. The dioxolane ring is more susceptible to reduction, as discussed in the mechanistic section above, and the outcome of reduction can be predicted based on the stereochemistry of the acetal carbon. A general rule of thumb with these systems (for *cis*-fused rings) is that the *endo*-dioxolane (*endo*-**95**, Scheme 31) undergoes cleavage via selective activation of the equatorial oxygen of the dioxolane, giving the axially deprotected alcohol **96** (illustrated for reduction with catalytic TMSOTf/$BH_3 \cdot$THF),[49] whereas the *exo*-dioxolane *exo*-**95** reacts through activation of the axial oxygen, leading to the equatorial alcohol product **97**.



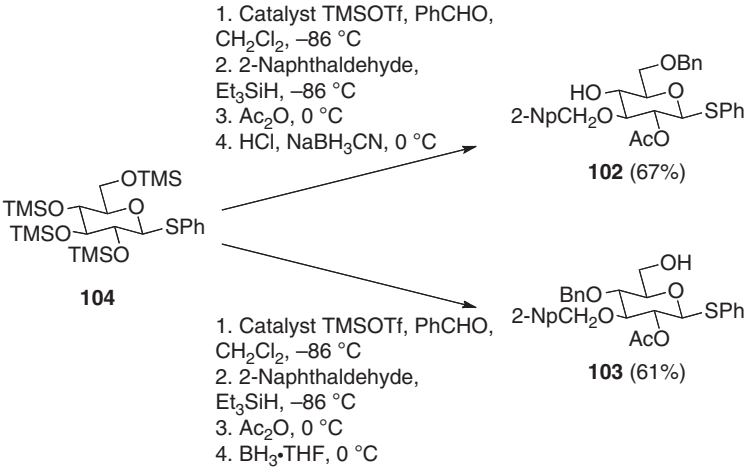
Scheme 31

The culmination of the improved levels of mechanistic understanding, and the selectivity that can be achieved in acetal reduction, has been the development of one-pot processes for the selective protection/derivatization of carbohydrates, pioneered by the groups of Hung[50,51,52] and Beau.[43,53] A general starting point for this one-pot manipulation of the carbohydrate is a per-silylated carbohydrate derivative, which is capable of undergoing desilylative acetalization under Lewis acidic conditions. For example, reaction of **98** (Scheme 32) with benzaldehyde, TMSOTf, and triethylsilane effects acetal formation and reduction in a single step, providing **99** as a single regioisomeric product.[50] This sequence can also be combined with an *in situ* Schmidt glycosylation, in this case also mediated by TMSOTf; for example, addition of trichloroacetimidate **100** to the reaction mixture directly and selectively provides disaccharide **101**. The concept of direct glycosylation has subsequently been extended to the synthesis of a wide range of di- and trisaccharides by other research groups,[38] and enables the automated and highly tuneable assembly of oligosaccharide motifs for a wide range of biological applications.[54]



Scheme 32

By carefully tuning the regio- and chemoselectivity of acetal manipulation, as well as that of other protecting groups, the complete differentiation of all four nonanomeric hydroxyl groups of the carbohydrate is possible.[51,52,55] This particularly impressive achievement is illustrated in Scheme 33 through selective access to either the 4-OH or 6-OH derivatives (**102** and **103**, respectively) from the same per-silylated starting material **104**. The compatibility of the thioacetal with these conditions is notable, as this enables subsequent use of the products in glycosylation chemistry.



Scheme 33

In conclusion, the veritable smörgåsbord of methods that are available for the selective reduction of carbohydrate acetals has secured the place of this protecting group in carbohydrate chemistry. Table 5 summarizes most of the methods and their selectivities as shown below (Table 5).[6]

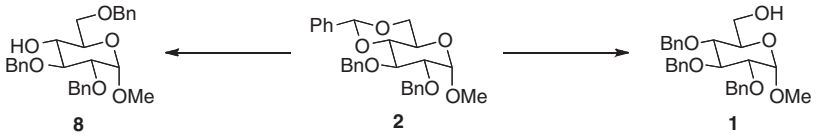
8.09.3.5 Orthoesters

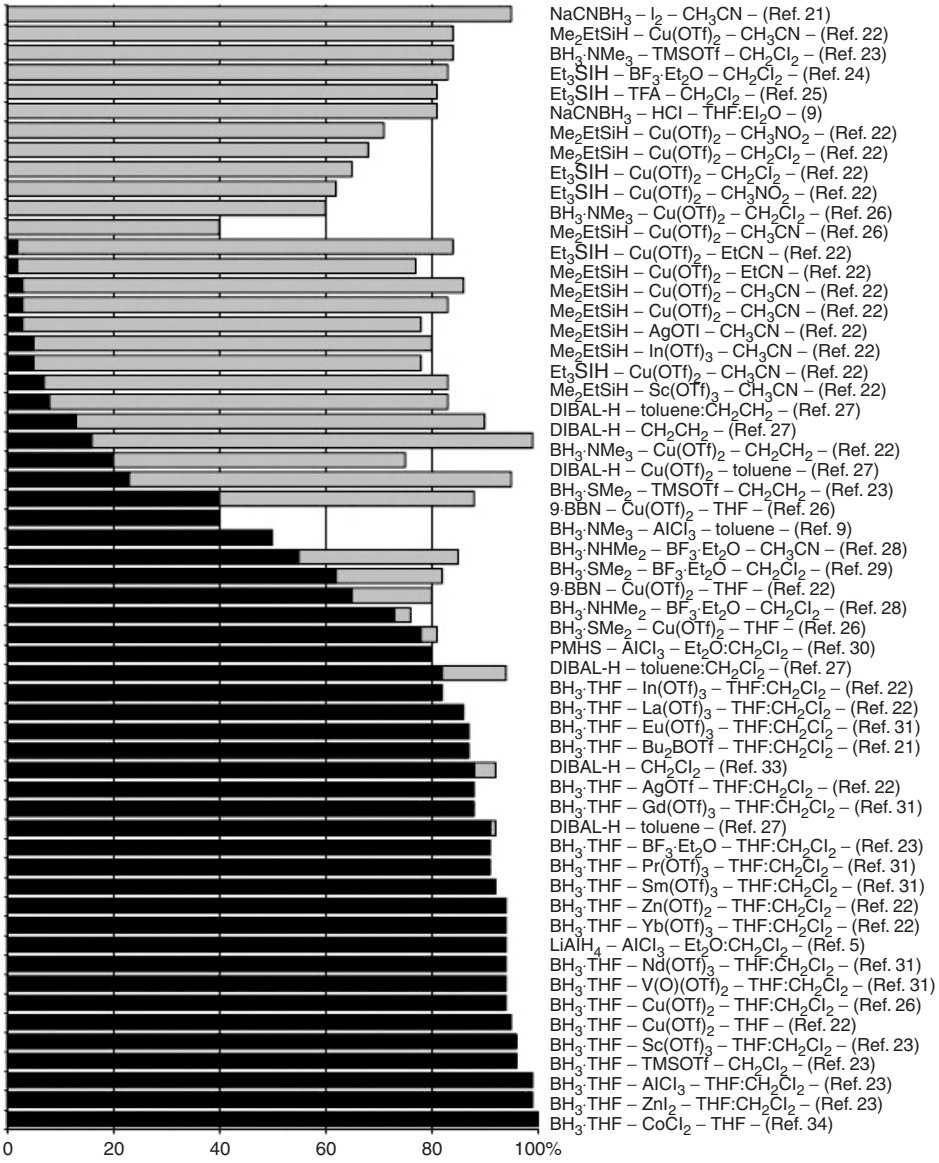
The selective reduction of orthoesters theoretically represents a useful synthetic process as it provides a tuneable entry to acetals or ethers – however, controlling the outcome of the reaction to selectively afford one of these products represents a challenge. An example of this issue is found in a report of a rhodium-catalyzed reduction of orthoesters using triphenylsilane.[23] With trimethyl orthobenzoate **105** as the substrate (Scheme 34), the predominant product obtained was the dimethyl acetal **61**, with a small proportion of methyl ether **106** observed spectroscopically. At higher catalyst loadings (>2 mol%), and in the absence of a phosphine ligand, poor selectivity for the acetal is observed.

An interesting tactic has been described to achieve the selective protection of the primary alcohol of diol **107** (Scheme 35) as a MOM ether via the selective reduction of an orthoester.[56] Conversion of **107** to the mixed orthoester **108** under acid-catalyzed conditions, followed by treatment with DIBALH at –78 °C, led to selective reduction to give the primary MOM ether **109** in a 23:1 ratio with isomer **110**. This result was not the desired outcome to the reaction, as literature precedent from the same research group,[57] and earlier reports,[58] suggested that these conditions should lead to deprotection of the primary alcohol. However, this result is easily rationalized through the influence of the adjacent PMP ether, which is likely able to chelate the aluminum and thus reverse the usual regioselectivity by directing ring opening to effect oxocarbenium ion formation at the less-hindered oxygen atom.

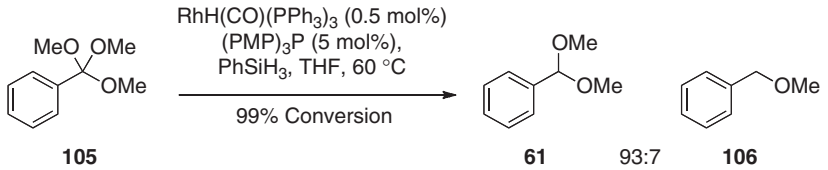
A creative method has been developed for the construction of glycoside linkages utilizing a highly regio- and stereoselective reduction of glycosidic orthoesters (Scheme 36).[59] The requisite spirocyclic orthoester starting materials (**111**, **112**) can be prepared from sugar lactones and glucose or galactose *O*-4,6 diols,[60] using the Noyori conditions for acetal formation

Table 5 Regioselective openings of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (2) to give methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (8, gray) or methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (1, black)

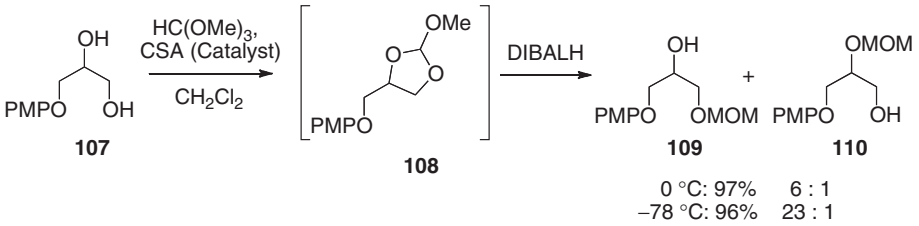




Source: Reproduced from Figure 2 in Ohlin, M.; Johnsson, R.; Ellervik, U. *Carbohydr. Res.* **2011**, *346*, 1358–1370.

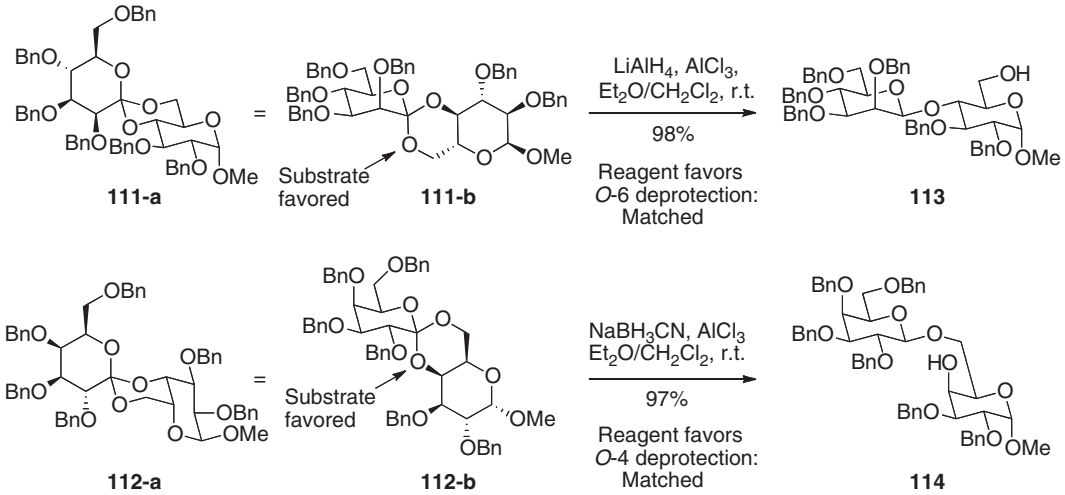


Scheme 34



Scheme 35

(i.e., reaction of the bistrimethylsilyl ethers and the lactone under the influence of trimethylsilyl triflate, in the presence of methoxytrimethylsilane).[33] As might be expected, the reaction of the carbohydrate diol with a given lactone delivers the orthoester that benefits from maximal anomeric effect stabilization. In the case of the glucose diol, this corresponds to an (*R*)-configuration of the orthoester at the anomeric carbon (**111**), whereas for the galactose diol, this affords the (*S*)-configured orthoester (**112**). The axial relationship of the former lactone ring oxygen with respect to the dioxane oxygens is apparent in depictions **111-a** and **112-a**.



Scheme 36

With a wide selection of glycosylidene orthoesters in hand, their selective reductions were studied. Here, a stark-matched/mismatched situation arises with respect to the intrinsic ring-opening preference of the orthoester and the choice of reduction conditions. From the well established carbohydrate precedent, it was known that *O*-6 dioxane deprotection would be favored by the classic Lipták conditions ($LiAlH_4/AlCl_3$),[16] whereas *O*-4 deprotection would be favored by Garegg-type conditions ($NaBH_3CN/AlCl_3$).[15] However, the orthoesters would favor cleavage of the axial dioxane C–O bond (with respect to the former lactone ring), as marked in conformation depictions **111-b** and **112-b**, due to the anomeric effect labializing the Lewis acid-complexed axial oxygen atom. This latter preference results in the exclusive formation of the *β*-glycoside from both sets of reaction conditions, but only when the bond being cleaved matches the reagent selectivity is productive reaction observed. In the case of the examples in Scheme 36, the axial dioxane oxygen in **111** corresponds with the reagent-preferred *O*-6 position, and high-yielding ring opening to **113** is observed under Lipták conditions; similarly, the dioxane oxygen in **112** corresponds with the reagent-preferred *O*-4 position, giving **114** under Garegg conditions. The use of mismatched substrate/reagent combinations result in complex mixtures/poor reactivity.

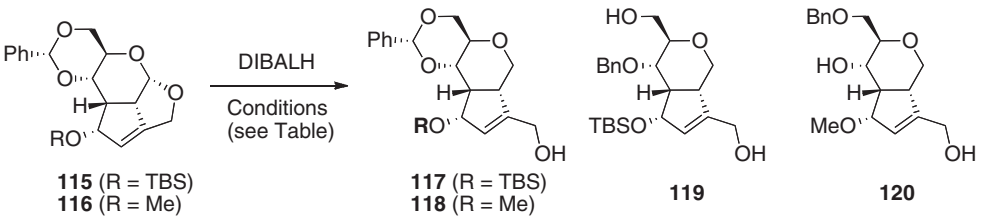
Further examples of orthoester reduction in the context of the selective reduction of inositol derivatives are discussed in the mechanistic section of this chapter (see Section 8.09.2).

8.09.3.6 Bicyclic Acetals and Spiroketals

The selectivity of cleavage of bicyclic acetals is generally controlled by loss of ring strain, with cleavage of five-membered rings often favored in this regard, or reactions that retain thermodynamically stable six-membered rings (this may also be kinetically favored where anomeric effects are important).

Interesting regioselectivity has been observed using DIBALH to achieve the reductive cleavage of perhydrofuro[2,3-b]pyran derivatives (**8**, **9**, Table 6).[61] Both **8** and **9** undergo preferential cleavage of the 5,6-fused glycosidic (nonbenzylidene) acetal

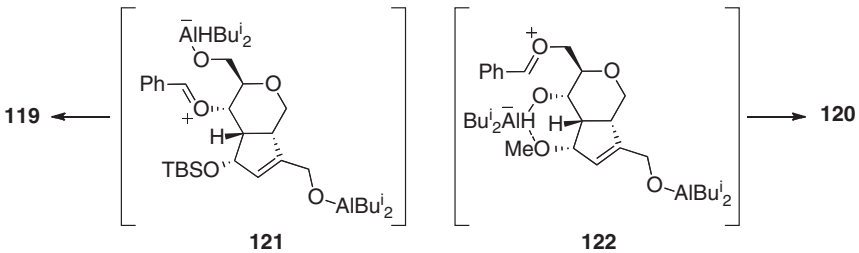
Table 6 Regioselective reductive ring opening of bicyclic acetals 115 and 116 with DIBALH



Entry	*Substrate*	*Conditions*	*117/118: 119: 120 (%)*
1	115	Toluene, −40 °C	57: 0: 0
2	115	CH_2Cl_2, −40 °C	79: 8: 0
3	116	CH_2Cl_2, −40 °C	32: 0: 34

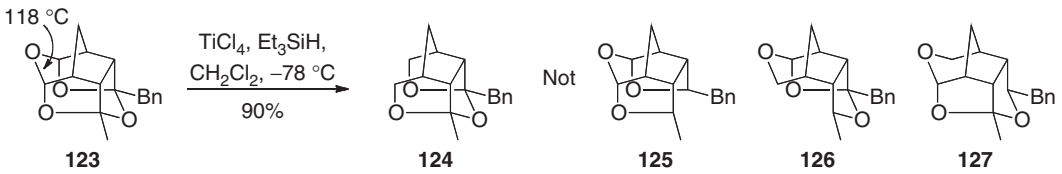
moiety, underlining the relative lability of five-membered ring acetals. This affords the expected five-membered ring cleavage as the major product, with varying amounts of double acetal cleavage; however, the nature of the alcohol protecting group influences the outcome of the benzylidene acetal reduction.

The expected ring opening is observed for acetal **115** (or **117**), where aluminum coordinates to the less-hindered oxygen, followed by ring opening and S_Ni-type reduction via oxocarbenium ion **121** (Scheme 37). The reversal of selectivity for the ring opening of **116** (or **118**) reflects chelation of aluminum by the proximal allylic methyl ether, which leads to selectivity for opening of the benzylidene acetal (to give oxocarbenium ion **122**) at the more hindered position.



Scheme 37

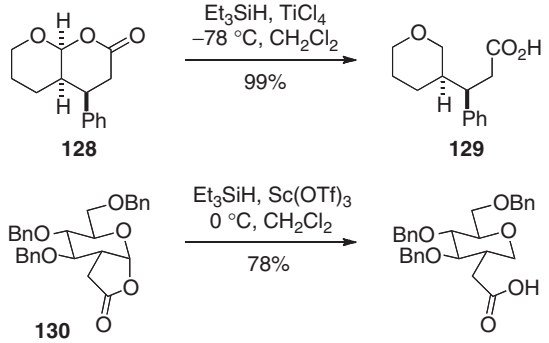
A more challenging ring opening is illustrated in Scheme 38.[62] Using classic acetal reduction conditions of titanium(IV) chloride with triethylsilane, the bridged tetraacetal **123** was selectively reduced to give solely bridged diacetal **124**. This selectivity was ascribed to stereoelectronic effects, specifically the rehybridization of the bridging oxygen that would be required to accommodate an unusually large bond angle of 117.5°, which leads to raising of the energy of the oxygen lone pairs through greater *p*-character. None of the alternative ring cleavage products **125**–**127** were observed, and **124** was isolated in an outstanding yield of 90%.



Scheme 38

Silanes have also been employed in the ring opening of bicyclic lactone-acetals (Scheme 39). The introduction of the carbonyl motif intrinsically biases the activation of these otherwise pseudosymmetrical acetals toward activation of the lactone, through Lewis acid complexation to the carbonyl. This leads to lactone ring opening, and subsequent reduction of the oxocarbenium ion leads to the cyclic ether product. Two examples are given; in the first, **128** was selectively reduced to the THP derivative **129** using Et_3SiH with $TiCl_4$ activation, a method which is also suited to the ring opening of pyranofuranone derivatives.[63,64] The second example illustrates the application of this methodology to the ring opening of a carbohydrate pyranofuranone **130** using

scandium(III) triflate as promoter – where, perhaps surprisingly, stoichiometric amounts of the Lewis acid were required. Both methods are well-suited to the addition of other nucleophiles (allylsilanes, sulfides, etc.), which occur with the expected axial delivery of nucleophile to the oxocarbenium ion.[65]

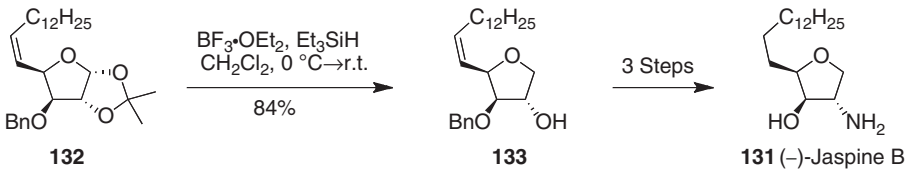


Scheme 39

8.09.3.6.1 Applications in synthesis

The ease with which bicyclic or spirocyclic acetals can be prepared from ketones and aldehydes, together with the stereocontrol exhibited in the reduction of cyclic oxocarbenium ions, renders acetal reduction a useful tactic for the synthesis of saturated oxacycles in total synthesis. A number of examples are described in this section to illustrate applications in complex molecular settings.

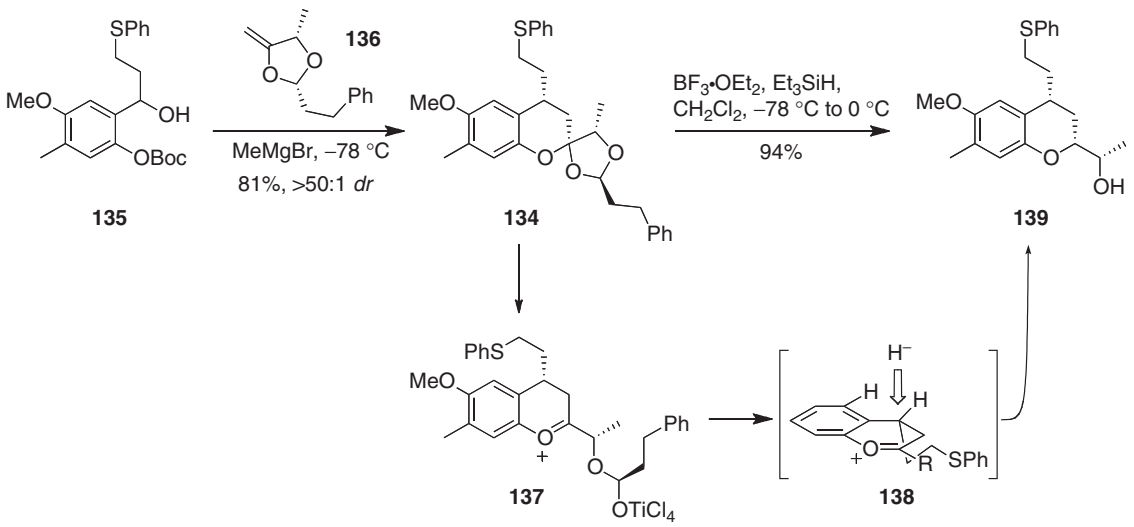
A relatively simple example which illustrates the value of carbohydrate starting materials as precursors to saturated oxacycles is illustrated by an anomeric deoxygenation strategy which formed a key step in a concise formal synthesis of (–)-jaspine B **131** (Scheme 40).[66] Beginning from glucose, acetonide **132** was prepared in three steps, from which reduction to the tetrahydrofuran **133** using $BF_3 \cdot OEt_2$ and Et_3SiH proceeded in excellent yield. **133** was then transformed in two further steps to an intermediate which corresponds to a formal total synthesis of jaspine B, being one step from the natural product.



Scheme 40

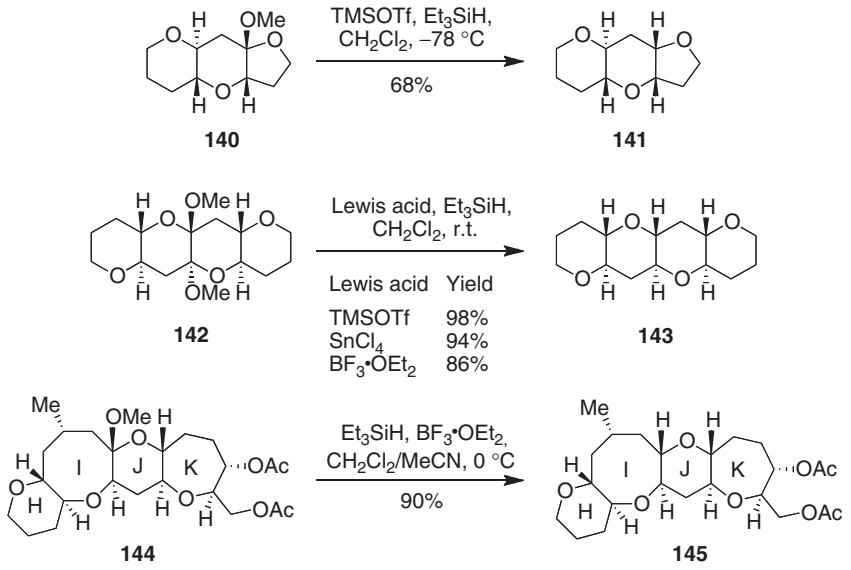
An elegant reductive cleavage of spiroketal **134** has been employed as a pivotal step in syntheses of *ent*-heliespirones A and C (Scheme 41).[67] **134** was prepared from benzyl alcohol **135** through a highly diastereoselective cycloaddition of enol ether **136** with the *o*-quinone methide generated on treatment of **135** with MeMgBr. The combination of $BF_3 \cdot OEt_2$ and Et_3SiH then effected cleavage of the dioxolane and spiroketal moieties, with the superior anomeric effect of the pyran ring (and, possibly, release of ring strain) controlling the selectivity of ring fission. Notably, the resultant oxocarbenium ion **137** underwent a highly selective hydride addition, mediated by the pseudoaxial disposition of the sulfide-containing sidechain (conformation **138**). The ring-opened dioxolane is actually a hemiacetal that fragments *in situ* to afford the tetrahydropyran alcohol product **139**, which was elaborated in four further steps to the heliespirones.

The polycyclic ether frameworks of the ladder polyether toxins (such as the brevetoxins and ciguatoxins) provide an ideal testing ground to investigate the stereocontrolled and selective reduction of complex, hindered ketals to fused-ring cyclic ethers. Three examples are illustrated in Scheme 42 which typify the field. In the first, tricycle **140** can be selectively deoxygenated using TMSOTf/triethylsilane, to give THF **141** in good yield (68%).[68] The reduction of the intermediate oxocarbenium ion proceeds with complete selectivity for the expected 5,6-*cis*-fused tetrahydrofuran product. However, when the ring junction at which reduction occurs is a bispyran, this selectivity is reversed, as demonstrated by the stereoselective double reduction of bisketal **142**, formed from a dehydrative cyclization of the corresponding bishydroxy diketone.[69] A range of Lewis acids were screened as promoter for the triethylsilane-mediated reduction of **142** (or other diastereomers), with all conditions delivering the *trans*-fused bispyran reduction product **143** as a single stereoisomer in excellent yield. This stereoselectivity can easily be rationalized through standard stereoelectronic arguments. Even more impressively, reduction of an 8,6-fused oxocane-tetrahydropyran ketal **144** has been achieved, using triethylsilane in combination with boron trifluoride.[70] Once again, the



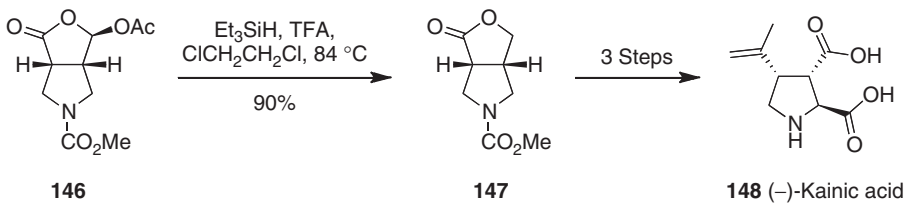
Scheme 41

reduction occurred with complete stereoselectivity for the *trans*-fused product **145**, which corresponds to the HIJK rings of ciguatoxin CTX1B.



Scheme 42

Finally, although not strictly a bicyclic acetal, an interesting reduction of the bicyclic lactone **146** has been achieved using closely related reduction conditions (Scheme 43). Reduction of **146**, perhaps unsurprisingly, was selective for cleavage of the exocyclic acetoxy C–O bond, leading to lactone **147**. This lactone was eventually transformed into the natural product (–)-kainic acid **148**.[71]

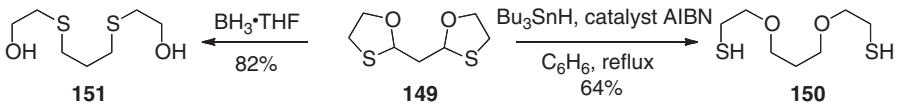


Scheme 43

8.09.3.7 Thioacetals and Azaacetals

The reduction of *X,Y*-acetals to 'X-' or 'Y-ethers' has advanced considerably since the previous coverage of this field.[1] A selection of examples are included in this section which illustrate not only the synthesis of ethers from *X,O*-acetals but also the synthesis of amines and thioethers from such derivatives, which can proceed under unique conditions compared with the parent ether synthesis.

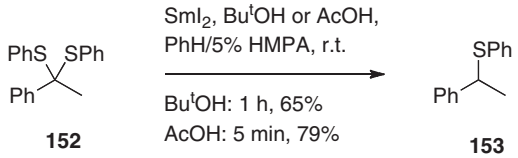
S,O-acetals (thioacetals) can be selectively reduced under several conditions. The superior radical-stabilizing ability of sulfur compared with oxygen permits the use of radical reactions to cleave these functional groups, and in this context Bu_3SnH (with AIBN as initiator) has been demonstrated to reduce the C–S bond in a number of sulfur-containing heterocycles, including dithianes, dithiolanes, oxathiolanes, and thiazolidines.[72] The less-toxic $(Me_3Si)_3SiH$ has also been used for similar reductive cleavage in dithianes[73] and oxathiolanes.[74] Selectivity between C–S and C–O bond cleavage can be observed based on the nature of the reducing agent;[75] bisthioacetal **149** (Scheme 44) undergoes C–S bond cleavage to dithiol **150** using Bu_3SnH/AIBN, but C–O scission is effected to give diol **151** using borane, presumably due to the greater oxophilicity of boron which preferentially activates oxygen, leading to thiocarbenium ion formation.



151 **149** **150**

Scheme 44

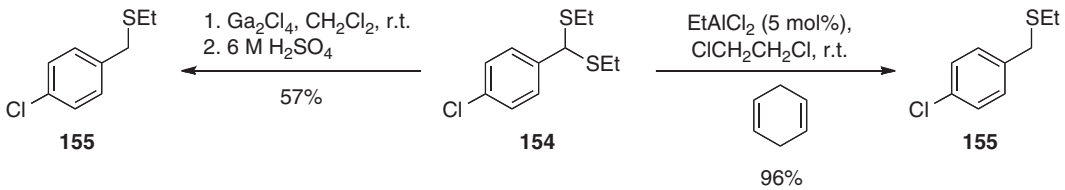
Samarium(II) iodide has been shown to be effective for the reduction of a number of acyclic dithioacetals and dithioketals to the corresponding thioether (**152–153**, Scheme 45). In contrast to the related reduction of *O,O*-acetals, $AlCl_3$ activation resulted in poor conversion, but the use of additives such as *tert*-butanol or acetic acid, in either THF or benzene/HMPA, were more effective. This protocol can suffer from the recovery of unreacted dithioacetal, even after prolonged exposure to the reaction conditions, and there appears to be no general trend between the type of substrate and the additive required to improve conversion.



152 **153**

Scheme 45

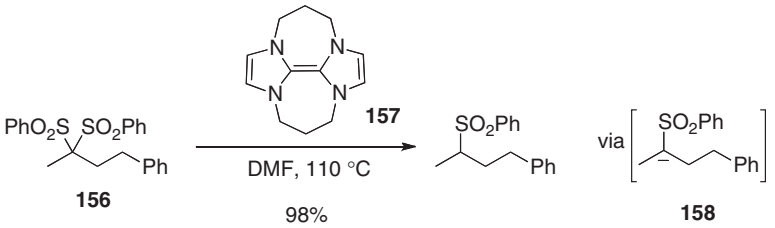
Two gallium-promoted methods for the selective reduction of dithioacetals to sulfides have been reported. The first involves the unusual use of stoichiometric gallium(II) chloride (Scheme 46),[76] which was able to reduce a wide range of (mostly acyclic) dithioacetals **154** to the corresponding thioether **155**. Strongly acidic conditions (6 M H_2SO_4) are required to protodemetallate the weakly polarized C–Ga bond contained in the initial product. Subsequently, a second method for the reduction of dithioacetals was developed using 1,4-cyclohexadiene as the hydride source, and either gallium(III) chloride or Et_2AlCl (illustrated) as a catalytic Lewis acid (see also Section 8.09.3.1).[26] This development represents a significant improvement over the stoichiometric gallium-mediated protocol, both from the perspective of reducing waste, and in that a separate hydrolysis step is not required. In both cases reductions of cyclic dithioacetals (dithianes) were less effective.



155 **154** **155**

Scheme 46

Finally, although strictly not a dithioacetal or ketal, a mild method has been developed for the selective reduction of 1,1-disulfones **156** (Scheme 47).[77] Although the reductive cleavage of sulfones typically uses dissolving metals (Li, Na, K), or equivalent single-electron transfer agents (e.g., lithium naphthalenide, SmI_2, or $LiAlH_4$/nickel compounds), here a neutral organic molecule (tetraazafulvalene **157**) can promote reduction through single-electron transfer under significantly less aggressive conditions, in excellent yield. A representative example is shown; overreduction is avoided through the 'protection' of the monosulfone (until work-up) as the carbanion **158**.

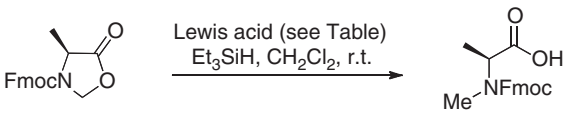


Scheme 47

N,O-Acetals (hemiaminal ethers), are generally more resistant toward reductive cleavage than their *O,O*-acetal relatives. This is not least due to the stability of the ammonium ion formed on complexation of the activating agent to the more basic nitrogen atom lone pair, which disfavors the usually-observed selectivity for ring cleavage via activation of the oxygen atom (leading to iminium ion formation). In many cases these motifs, especially azaketals, are thus inert to the typical reagents used for reduction of acetals. However, the combination of triethylsilane and Brønsted or oxophilic Lewis acids can be effective, and is the most widely applied method for hemiaminal ether reduction, with trifluoroacetic acid having been used quite extensively, as described in the previous coverage of the field.[1,78,79]

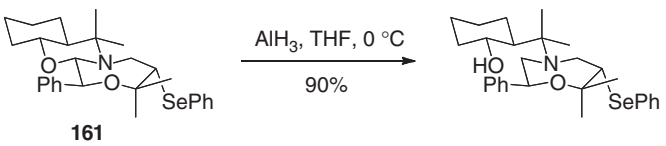
More recently, *N*-methylamino acids **159** have been prepared in good yield from 5-oxazolidinones **160** using a range of Lewis acid promoters, with $FeCl_3$, $AlCl_3$, and $ZnBr_2$ exhibiting comparable or increased reactivity compared with TFA or other Lewis acids (Table 7).[80] Notably, the protection of the amine functional group as a carbamate prevents it from sequestering the activator, and allows complexation of the Lewis acid to oxygen. That these conditions are milder than TFA is evidenced by the tolerance of a wide range of functional groups, including allyl and *tert*-butyl ethers, benzoates, and Boc carbamates, and the absence of epimerization under the reaction conditions.

Table 7 Lewis acid-promoted ring opening of oxazolidine 160 with triethylsilane



Entry	*Lewis acid*	*Time (h)*	*Yield (%)*
1	None	22	96
2	$AlCl_3$	4	90
3	$ZnCl_2$	72	72
4	$ZnBr_2$	24	95
5	$FeCl_3$	0.5	84
6	$CuCl_2$	72	12

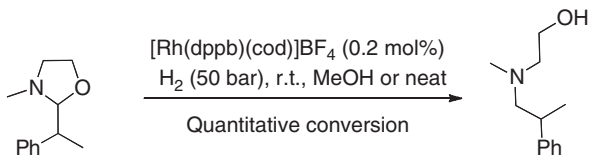
A further example which illustrates the importance of using an oxophilic Lewis acid to mediate ring opening is illustrated by the cleavage of the polycyclic *N,O*-acetal **161** (Scheme 48) in excellent yield and high selectivity using alane, conditions which tolerate a potentially delicate – but 'soft' – phenylselenyl ether.[81]



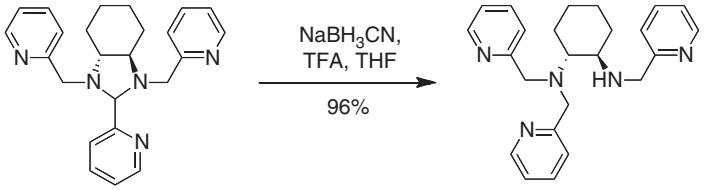
Scheme 48

A final example of azaacetal reduction which leads to benzylic amines is illustrated in Scheme 49, in which the rhodium catalyst [Rh(dppb)(cod)]BF_4 is able to promote selective and highly efficient hydrogenolysis of the C–N bond of 1,3-oxazolidine-*N,O*-acetals and ketals.[82] The method used low catalyst loadings and relatively mild conditions, and was effective for the reduction of a wide selection of benzylidene groups.

Reductions of *N,N*-acetals (aminals) to amines are often achieved through the use of an anionic borohydride reagent, in the presence or absence of a Brønsted acid. In light of the main focus of this review on reductions of acetals to ethers, a single example of the reductions of a C_2-symmetric aminal **162** is shown in Scheme 50, which uses the well established conditions of TFA/$NaBH_3CN$,[83,84,85] as were discussed in the previous coverage of the field.[1] Other methods include: AcOH/$NaBH_3CN$,[86] HCl/$NaBH_3CN$[87] and TCA/$NaBH_4$.[88]



Scheme 49

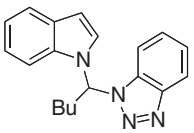
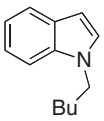
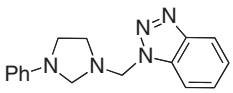
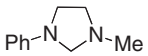
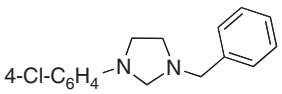
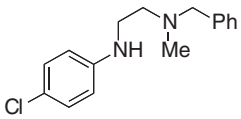
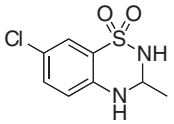
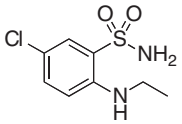
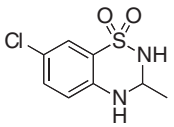
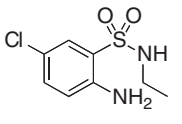
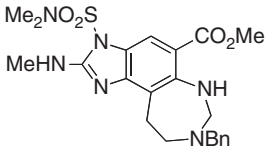
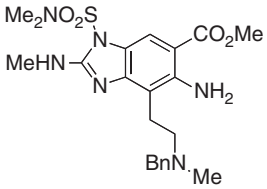
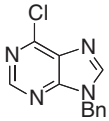
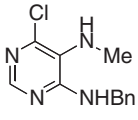


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Scheme 50

Several methods that address selective (nonsymmetric) reduction have been developed, which are summarized briefly in Table 8. The main use of these processes is the selective reduction of methylene aminals to afford *N*-methyl derivatives, although other substituted aminals have also been examined. The general direction of reduction proceeds via ejection of the superior

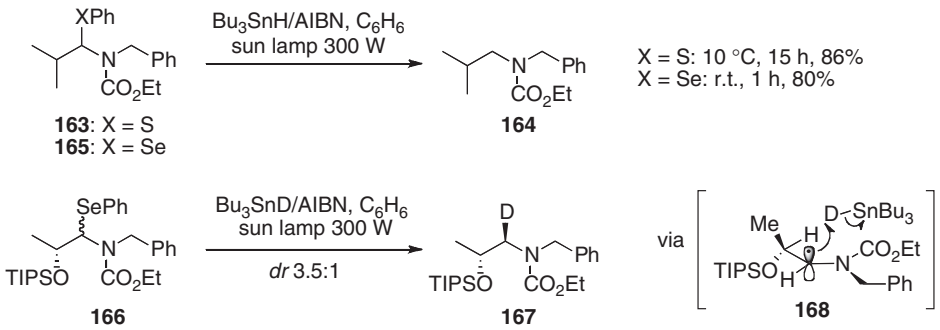
Table 8 Regioselective reductive ring opening of aminals

Entry	*Conditions*	*Substrate*	*Product*	*Yield (%)*	*References*
1	$LiAlH_4$			92	89
2	$NaBH_4$			96	90
3	$NaBH_4$			n.d.	91
4	$NaBH_3CN$, AcOH, r.t.			89	92
5	$NaBH_3CN$, EtOH, H_2O, 70 °C			65	92
6	$NaBH(OAc)_3$, $ClCH_2CH_2Cl$, reflux			83	93
7	$LiAlH_4$, −80 to 75 °C			77	94

Abbreviation: n.d., not determined.

nitrogen leaving group to generate the more stable iminium ion on ring opening, rather than being controlled by the relative basicity of the two nitrogen atoms. In entries 1–2, this is achieved through the preferential loss of a benzotriazole anion, which leads to *N*-methylation.[89,90] However, entry 3 results in a reversal of selectivity for imidazolidine cleavage through the generation of an aniline, rather than benzyl amine.[91] Related selectivity is exhibited in entries 4 and 5,[92] where cleavage of the sulfonyl aminal under acidic conditions proceeds through generation of an aniline iminium ion (via protonation of the sulfonamide nitrogen atom) whereas neutral conditions lead to complementary ring opening via the sulfonyl imine. Similarly, entries 6 and 7 illustrate remarkable selectivity for ring opening through cleavage of the C–N bond which releases the nitrogen atom which is better conjugated with its adjacent aromatic ring.[93,94]

The final class of *X,Y*-acetals covered in this chapter are *S,N*- and *Se,N*-acetals, which have received less attention due to their more specialist applications, but which are easily prepared by the reaction of imines with a chloroformate and the relevant heteroatom (S or Se) nucleophile. These acetals have been shown to undergo selective reductive cleavage of the C–S bond using either Raney nickel[95] or Bu_3SnH.[96] Under the latter conditions, the *S,N*-acetal **163** (Scheme 51) undergoes relatively slow cleavage to the amine **164**, requiring prolonged irradiation. This contrasts with the related *Se,N*-acetal **165**, which is susceptible to more rapid C–Se bond cleavage. Extending this investigation to chiral substrate **166** led to diastereoselective deuteration (**167**), which supports a stereochemical model based on $A_{1,3}$-strain (**168**).



Scheme 51

8.09.4 Conclusion

The arena of acetal and ketal reduction to ethers has expanded greatly through advances in understanding of the roles of both the activating and reducing agents, allowing highly regioselective transformations to be performed in a wide range of applications. The ongoing development of this field, through the emergence of catalysts which facilitate these transformations, and through applications in both the carbohydrate arena and natural product synthesis, has maintained its synthetic value. Further progress which leads to improved functional group tolerance and selective reductions under increasingly mild conditions are to be anticipated.

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8.10 Reduction of Carboxylic Acids and their Derivatives to Alcohols, Ethers, and Amines

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 doi:10.1016/B978-0-08-097742-3.00812-0

8.10.1 Introduction

The reduction of carboxylic acids and their derivatives represents one of the fundamental transformations used by synthetic chemists. The field is extremely well established with many classical reagents capable of carrying out rapid and efficient reductions. Reagents such as lithium aluminum hydride (LAH, $LiAlH_4$), diisobutylaluminum hydride (DIBAL), borane, and sodium borohydride have been used for many decades to reduce these groups, often with excellent chemoselectivity. These reagents are also commonly found in synthetic laboratories and their use is therefore ubiquitous in synthetic strategies. The ready availability of these reagents (and also oxidants) has perhaps led to their overuse and in turn spurned a growing concern for the redox efficiency in synthetic strategies. It is not surprising that the choice of reducing agent has become driven by efficiency and selectivity in complex, highly functionalized substrates. To this end many methods have appeared in the literature highlighting the different aspects of chemoselectivity in reducing carboxylic acids and their derivatives. This chapter seeks to give a comprehensive overview of the reductants available to reduce carboxylic acids and their derivatives to alcohols, amines, and ethers. This is done by grouping the different reducing methods within each functional group (e.g., carboxylic acids, esters, amides, etc.). The literature is awash with many variations on these themes as researchers have tweaked and tuned the reagents and methods to improve them. Unfortunately, many reports of new reagents highlight only the instances of chemoselectivity without showing the particular lack of chemoselectivity a reagent may have. This, coupled with a general sense of inertia in adopting newer methods, has meant that the classical reagents have essentially remained the preferred choice in the literature. This chapter places these newer developments in context, at the same time remaining true to the safe and well-established reagents that continue to be used very effectively.

8.10.2 Reduction of Carboxylic Acids to Alcohols

The reduction of carboxylic acids is most conveniently achieved with the boron and aluminum hydride reagents. Both are exceptionally versatile and effective; combined they account for approximately 97% of all carboxylic acid reductions in the literature (Reaxys® search June 2012). Hydrogenation reductions are more suited for industrial-scale operations owing to the general lack of chemoselectivity and high pressures and temperatures required. Electrochemical means are not practical for widespread use in synthetic laboratories, although some examples have been found in large-scale plants. Silanes tend to give silyl esters, rendering them unsuitable for general use as a reductant for carboxylic acids.

8.10.2.1 Hydrogenation

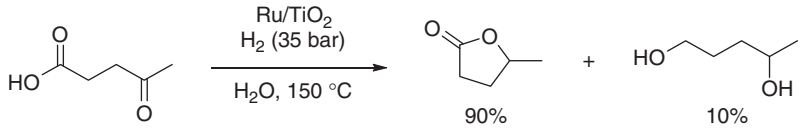
Although hydrogen represents an ideal reagent for the reduction of carboxylic acids to alcohols in terms of atom economy, the reality has been that the carboxyl group is very resistant to this form of reduction and high pressures and temperatures are frequently required, along with a suitable catalyst. Notwithstanding the fact that synthetic laboratories are infrequently equipped with equipment capable of reaching the high pressures required (often >150 bar; 1 bar $=100$ kPa), only very simple carboxylic acids are typically converted to alcohols since other reducible functional groups are usually intolerant of these conditions. Nevertheless, a number of different catalysts have been examined for the large-scale reduction of this functional group and include ruthenium dioxide (RuO_2),[1] rhenium heptaoxide (Re_2O_7),[2] and copper chromite ($Cu_2Cr_2O_5$)[3] (see **Table 1** for more details). Modifications emerging in the 1990s saw mixed metal catalysts such as Rh–Os (**Table 1**)[4] and Ru–Sn–Al_2O_3 (**Table 1**) being applied,[5] which succeeded in reducing the hydrogen pressure required, though in the latter example reaction temperatures still remained quite high. In an important study, Fuchikami et al. explored bimetallic catalysts based on Group 8 to 10 late-transition metals, and Group 6 or 7 early-transition metals,[6] reporting that a large number of combinations were successful, for example, Rh–Re, Rh–Mo, Rh–W, Ru–Re, Pd–Re, and Pt–Re (**Table 1**). It is interesting to note that these also include combinations of homogeneous and heterogeneous forms of the bimetallic catalysts. Two important points should be noted from this study: (1) the monometallic catalysts were completely inefficient or ineffective when used under the reaction conditions of 100 bar and up to 180 °C (also noted by others)[7,8] and (2) (perhaps the more surprising) that combinations of Rh–Re, Rh–Mo, and Ru–Re were excellent at selectively reducing a carboxylic acid in the presence of a methyl ester. A number of aliphatic examples gave yields of 80–90%. This feature of selective reduction has, however, not been applied in the synthetic literature most likely because the catalysts are very efficient at reducing carbon–carbon double bonds, including those of benzene. Nevertheless, homogeneous bimetallic catalysts comprising equimolar mixtures of $[Rh(acac)(CO)_2]$ and $[Mo(CO)_6]$ have also been shown to be excellent at reducing carboxylic acids (**Table 1**, entry 13) and lactones (see Section 8.10.6.1), and a heterogeneous combination of Rh–Re has been used to reduce carboxylic acids with α-chiral centers without racemization (60 bar, 270 °C).[9] Another method has demonstrated that platinum supported on titanium dioxide is also very effective at catalyzing the hydrogenolysis of a number of aliphatic carboxylic acids to alcohols.[10] The advantage of this method is that reduced pressures of hydrogen (as low as 5 bar) and lower temperatures (130 °C) are required to accomplish the reaction. Platinum itself cannot act as a suitable catalyst for this reaction[6] and so the titanium dioxide support is critical to its success (other conventional supports such as SiO_2, Al_2O_3, CeO_2, and ZrO_2 were also studied but only very poor conversions were noted). An additional equimolar amount of rhenium does significantly increase the rate of the reaction, but with a concomitant deleterious increase in alkane side product as a result of decarboxylation. As a side note, the researchers point out that this last observation may be of use since decarboxylation is the sole

product when a nitrogen atmosphere is used. Corma and coworkers have demonstrated in a similar fashion that ruthenium supported on titanium dioxide is also an effective catalyst system for the hydrogenolysis of carboxylic acids, although in their case they only looked at two examples of dicarboxylic acids and one example of a keto-acid both of which resulted in lactones being isolated (equation 1).[11]

Table 1 Some literature examples of heterogeneous reductions of carboxylic acids to alcohols

Entry	*Substrate*	*Catalyst*	*Pressure H_2 (bar)*	*Temperature (°C)*	*Yield (%)*	*Reference*
1	Acetic acid	RuO_2	700–950	147–170	88	1
2	Adipic acid	RuO_2	520–700	150–175	48	1
3	Hydroxyacetic acid	Ru/C	660–700	149–155	68	1
4	Trifluoroacetic acid	Re_2O_7	300	207	100	2
5	Caproic acid	Re_2O_7	188	200	93	2
6	Lactic acid	Re_2O_7	258	150	84	2
7	Decanoic acid	Rh–Os	25–100	100–120	85	4
8	Valeric acid	Ru–Sn–Al_2O_3	56	250	50	5
9	Caproic acid	Ru–Sn–Al_2O_3	56	250	45	5
10	Stearic acid	Ru–Sn–Al_2O_3	80	250	80	5
11	Pentadecanoic acid	Rh/Al_2O_3 + $W(CO)_6$	100	180	84	6
12	Benzoic acid	Rh/Al_2O_3 + $Mo(CO)_6$	100	150	99[a]	6
13	2-Ethylheptanoic acid	$Rh(acac)(CO)_2$/ $Mo(CO)_6$	150	190	95	8
14	Octadecanoic acid	Pt/TiO_2	20	130	75	10

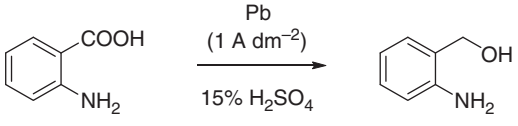
[a]Benzoic acid reduced to cyclohexylmethanol.



(1)

8.10.2.2 Electrochemical and Single Electron Reductions

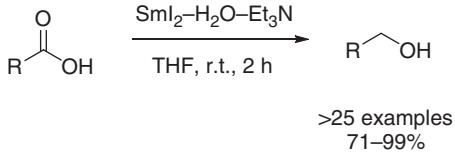
The electrochemical reduction of carboxylic acids is very limited as a practical method to achieve this transformation. Aromatic acids undergo reduction to benzyl alcohols when using cathodes of lead or mercury in solutions of sulfuric acid, but aliphatic carboxylic acids are unaffected.[12] Conjugated α,β-unsaturated carboxylic acids are reduced but only at the alkene functional group, leaving the aliphatic carboxylic acid unchanged (*see* Chapter 8.11). Oxalic acid is partially reduced to glyoxylic acid (oxoethanoic acid) in 87% yield in 10% sulfuric acid on lead or mercury cathodes.[13] The reason that the aldehyde is obtained in this case is due to the fact that the aldehyde exists in the fully hydrated geminal diol form in solution preventing further reduction. Likewise, salicylic acid and its analogs have been reduced to salicylaldehydes at pilot plant scale using a boric acid solution and a Hg–Cu cathode.[14] There are some advantages in reducing benzoic acid derivatives electrochemically, since amino and hydroxyl functional groups are tolerated (equation 2), as are aromatic halides, though not iodides. Unfortunately, the limited substrate scope and the unusual laboratory setup needed for these reactions makes them less obvious as a first choice for achieving this reduction. Dissolving metal reductions are not applicable to the formation of alcohols from carboxylic acids.



(2)

Samarium(II) iodide can be used to reduce carboxylic acids at room temperature within a few hours if combined with excess H_2O and triethylamine (equation 3). Although reductions using SmI_2–H_2O have been reported,[15] the addition of an amine is crucial for good yields.[16] This reductant is fairly powerful and will reduce aldehydes, ketones, esters, amides, nitriles, and aryl bromides. It will also partially dearomatize phenol and aniline moieties, slightly lowering the yields when using these substrates. α,β-Unsaturated carboxylic acids will also undergo complete reduction to the saturated alcohol. Nevertheless aryl fluoride-, chloride-, and trifluoromethyl-groups are tolerated, as are terminal alkenes, whereas internal alkenes are not isomerized. Steric

hindrance of the carboxylic acid is also not a determining factor in this method and the reduction is very general. In competitive experiments it could be shown that a primary amide or a nitrile group is much more rapidly reduced than the carboxylic acid, suggesting possible chemoselective reductions of these groups in the presence of a carboxylic acid. Chemoselective reduction of a carboxylic acid in the presence of an ester can be achieved if the *tert*-butyl ester is used.[16]



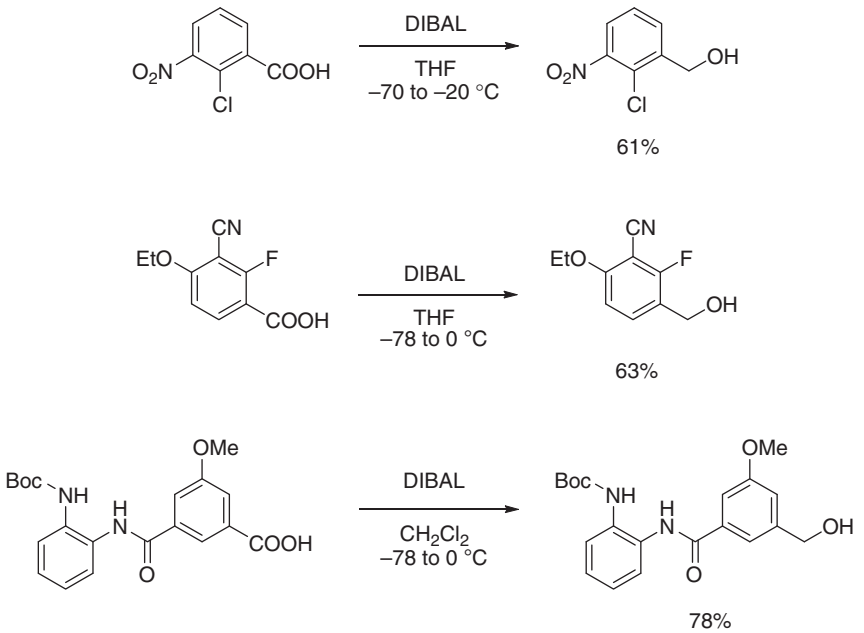
(3)

8.10.2.3 Reductions with Metal Hydride Reagents

Metal hydride reagents are by far the most popular methods for the reduction of carboxylic acids to alcohols. By sheer numbers, LAH accounts for 50% of all carboxylic acid reductions, whereas borane derivatives make up close to 40% (Reaxys® search June 2012). The following two sections divide these reagent classes and discuss them separately.

8.10.2.3.1 Aluminum hydride reagents

Aluminum hydride reagents tend to be extremely powerful reducing agents and therefore relatively unselective for reducible functional groups. LAH is the most powerful in this class of reducing agent and readily converts carboxylic acids and their salts to primary alcohols in diethyl ether or THF at low temperatures. All carbonyl and carboxylic acid derivatives are readily reduced, as are azides and nitro groups. The only exception is that LAH does not reduce alkenes and alkynes (unless an allylic alcohol is present), which does give it an advantage over the borane reagents in this respect (see Section 8.10.2.3.2). Although LAH can deliver up to four hydride equivalents, it is more common to use it in slight excess to ensure the reaction goes to completion rapidly. Carboxylic acids may, however, have problems with solubility in diethyl ether or THF causing the reaction to proceed slowly. In these cases it may be advisable either to form a derivative of the carboxylic acid (e.g., ester), or use sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®, Vitride®) which is soluble in toluene. Red-Al® effectively has the same selectivity profile as LAH, but has advantages related to safety and handling. Even so, problems with solubility are not that common and the synthetic community frequently chooses LAH over Red-Al® as the preferred aluminum hydride reagent for this reaction; a survey of the literature reveals that in the first decade of the 21st century LAH was over 40 times more likely to be employed than Red-Al® for the reduction of a carboxylic acid to an alcohol (Reaxys search, June 2012). This popularity of LAH stems from it being slightly cheaper and more well known to synthetically trained chemists. DIBAL is also a viable choice and offers a modicum of selectivity compared with other aluminum hydrides. This includes converting α,β-unsaturated carboxylic acids to allylic alcohols, something which is more of a challenge with LAH. DIBAL can also be used in the presence of nitriles and amides, but not esters, which are very rapidly reduced (**Scheme 1** contains some examples of DIBAL's chemoselectivity).

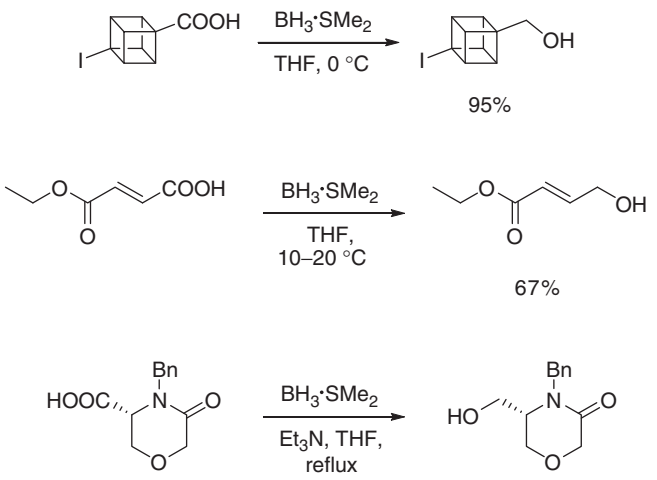


Scheme 1

Although not popular, alane (AlH_3) is also good for reducing carboxylic acids to alcohols and has the advantage that it can be used in the presence of halogen and nitro substituents and like DIBAL reduces α,β-unsaturated systems to the allylic alcohol.[17] As mentioned it has been rarely employed in the literature probably due to its inconvenient availability. This has changed though since Park and Marlett described a stable complex of alane with dimethylethylamine,[18] which is commercially available. Other derivatives such as alkoxyaluminum hydride complexes have been shown to reduce carboxylic acids, for example, $LiAlH(O\text{-}t\text{-}Bu)_3$ but have no advantage over the reagents already covered. Amino aluminum hydrides have also been explored, but more in the context of selective reductions to aldehydes (*see* Chapter 8.11).

8.10.2.3.2 Boron hydrides

Borane remains one of the more attractive choices to reduce carboxylic acids to alcohols owing to a number of important features,[19] chief amongst these being its greater chemoselectivity compared with the aluminum hydride reagents. For example, functional groups such as acid chlorides, esters, carboxylic acid salts, epoxides, halides, and nitro compounds are generally left untouched, or react very slowly under the mild reaction conditions needed to reduce carboxylic acids (room temperature; up to a few hours). Aldehydes, ketones, lactones (see Section 8.10.6.3), tertiary amides (see Section 8.10.7.3.2), and nitriles (see Section 8.10.8.3.2) are also readily reduced with borane, either as $BH_3 \cdot THF$ or $BH_3 \cdot SMe_2$. However, alkenes and alkynes also undergo rapid hydroboration (*see* Chapter 8.11) with borane and so these functional groups will not be tolerated if carboxylic acid reduction is required. The choice between using $BH_3 \cdot THF$ or $BH_3 \cdot SMe_2$ is in some respect up to the preference of the researcher as they are somewhat similar, although $BH_3 \cdot SMe_2$ is slightly less reactive. However, $BH_3 \cdot THF$ is commercially available as a 1 M solution in THF (higher concentrations cause THF to be cleaved), whereas $BH_3 \cdot SMe_2$ can be obtained in its undiluted form (though it is more typical to have 2–5 M solutions in THF). This means that higher concentrations of borane can be obtained in reactions, thus increasing the reaction rate. Alternatively, the addition of trimethyl borate[20] or boron trifluoride[21] has been shown to accelerate the rate of reaction and improve yields. **Scheme 2** gives some examples of borane reductions of carboxylic acids in the presence of other reducible groups.



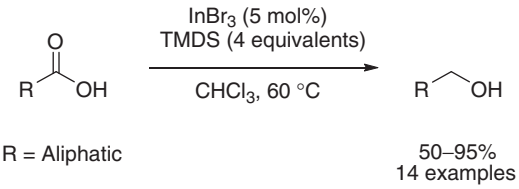
Scheme 2

Other borane derivatives are known and many are capable of reducing carboxylic acids to alcohols. Catecholborane, for instance, is effective at reducing both the free acid and its salt, but this derivative has hardly been used for this purpose in the literature.[22] Likewise, the borane complex with *N*,*N*-diphenylamine ($BH_3 \cdot HNPh_2$) which is a stable crystalline solid, reduces carboxylic acids to alcohols.[23,24] However, this and other amine derivatives are not typical choices for this transformation. Some derivatives such as 9-borobicyclo[3.3.1]nonane (9-BBN)[25] and thexylborane[26] will slowly reduce aliphatic carboxylic acids in the presence of aromatic acids, but again these are rarely employed in the literature. Nevertheless thexylborane and its derivatives have been exploited as selective reductants, converting carboxylic acids to aldehydes (*see* Chapter 8.11).

Sodium or lithium borohydride do not normally reduce carboxylic acids to alcohols unless coupled with powerful Lewis acids. The most commonly added Lewis acid is $BF_3 \cdot OEt_2$, which effectively generates borane *in situ*; its chemoselectivity thus being the same as borane. Likewise, iodine[27] and chlorotrimethylsilane[28] are also excellent at generating borane *in situ* from $NaBH_4$, often being used to reduce chiral amino acids to their respective amino alcohols without racemization. These methods of generating borane *in situ* are much more popular than using purchased borane derivatives owing to their lower expense. Finally, it has also been shown that carboxylic acids can be reduced to alcohols with sodium borohydride if they are first activated *in situ* via the formation of the hydroxybenzotriazole ester.[29] The reaction is reported to proceed well even in the presence of water.

8.10.2.4 Reductions with Silanes

Unlike the use of silanes for reducing esters and amides, the reduction of carboxylic acids with silanes usually proceeds with formation of a silyl ester.[30] Only one practical method has emerged, namely using tetramethyldisiloxane (TMDS) and indium bromide as a catalyst (equation 4), although this only works for aliphatic carboxylic acids.[31] These conditions will reduce ketones, aldehydes, amides, and esters, whereas amino- and nitro-containing compounds inhibit the reduction. The aromatic acids are not reduced, though if the solvent is changed to toluene, then diphenylmethane derivatives are obtained from deoxygenation of the starting material and subsequent coupling to toluene. It should also be noted that esters are reduced to ethers (see Section 8.10.5.4).



(4)

8.10.3 Reduction of Acyl Halides

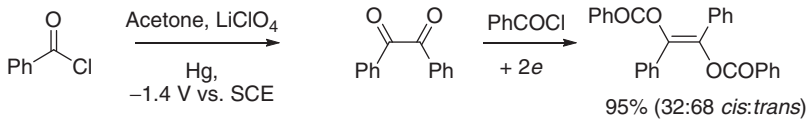
The reduction of acyl chlorides to alcohols is uncommon and acid bromides have only been reduced in a handful of cases. Although it is true that the acid chloride group is much more easily reduced than the carboxylic acid from which it is derived, the availability of standard methods for reducing carboxylic acids in the presence of other groups renders this method unattractive. However, should this method be required, simple metal hydrides are the most common choice for reductant.

8.10.3.1 Hydrogenation Reactions

The hydrogenolysis of acyl chlorides to alcohols should be relatively trivial since they are very reactive. As testimony to this, the classical Rosenmund reduction from the 1930s requires a poisoned $Pd/BaSO_4$ catalyst system to effect the partial reduction of an acid chloride to an aldehyde (*see* Chapter 8.11). The problem with complete reduction of an acid chloride with hydrogen is that the product alcohol is capable of reacting with any unreacted acid chloride, which can lead to significant ester side-products. For this reason and the availability of very mild hydride reagents (see Section 8.10.3.3), hydrogenolysis of acid chlorides is very poorly represented in the literature.

8.10.3.2 Electrochemical and Single Electron Reductions

The electrochemical reduction of acid chlorides does not give primary alcohols, but rather promotes the formation of acyloin esters and ene-diolate diesters. For example, the reduction of benzoyl chloride generates two benzoyl radicals which dimerize to give benzil (1,2-diphenylethane-1,2-dione) which is then further reduced and reacts with additional acid chlorides to give a stilbene derivative (**Scheme 3**).[32] Similar reactions occur with dissolving metal reductions and have been studied, for example, using lithium amalgam (Li/Hg).[33]



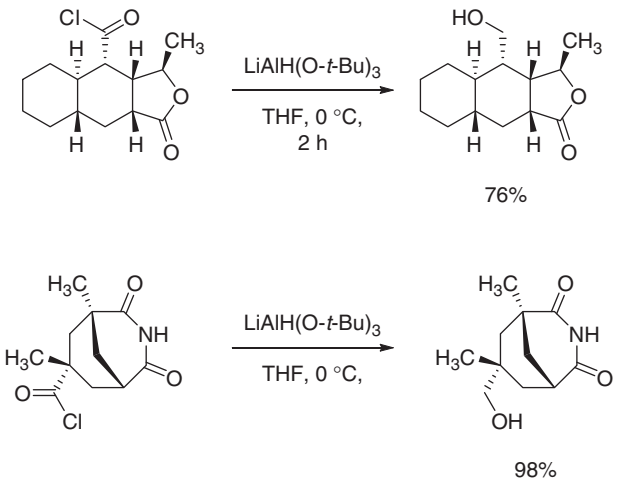
Scheme 3

8.10.3.3 Reductions with Metal Hydride Reagents

8.10.3.3.1 Aluminum hydride reagents

Essentially all the aluminum hydride reagents will reduce the highly reactive acid chloride group to an alcohol. However, achieving a selective reduction of an acid chloride in the presence of other reducible functional groups is not easily achieved with this class of reagent. The only success is with the very mild tri-*tert*-butoxyaluminum hydride, which can be used to fully reduce acid chlorides (including α,β-unsaturated acid chlorides) in the presence of esters, lactones, nitriles, β-lactams, amides, and imides (see **Scheme 4** for some examples). This method allows for the selective reduction of carboxylic acids to alcohols in the presence of these functional groups by first selectively converting the carboxylic acid to the acid chloride. Lithium tri-*tert*-butoxyaluminum

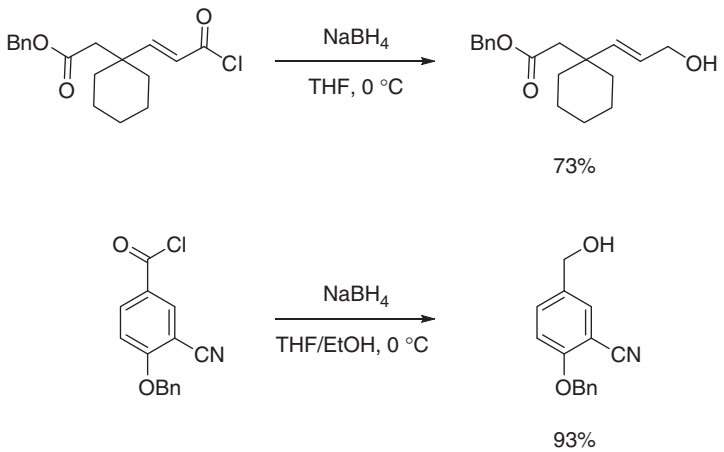
hydride is itself also mild enough to effect partial reduction and give the aldehyde product through careful control of conditions and stoichiometry (*see* Chapter 8.11).



Scheme 4

8.10.3.3.2 Boron hydrides

Sodium borohydride is very efficient at reducing an acid chloride to the primary alcohol and has been used quite extensively. The advantages over the aluminum hydrides are that $NaBH_4$ is readily available, easy to handle, and has a good degree of functional group tolerance (esters, lactones, amides, nitriles, etc.; see **Scheme 5** for some examples). A plethora of variations including $NaBH_4$–$TiCl_4$,[34] $NaBH_4$–alumina,[35] $Zn(BH_4)_2 \cdot TMEDA$,[36] and Bu_4NBH_4[37] have also been reported, though these are infrequently applied in the literature. The advantage of these modifications stems more from their solubility in other nonalcoholic solvents, for example, the more popular of these, Bu_4NBH_4, can be used in dichloromethane. Nevertheless sodium borohydride has itself been used in THF (**Scheme 5**). Lastly, it should be mentioned that borane and its derivatives react very slowly with acid chlorides and are therefore not generally used to achieve this transformation.



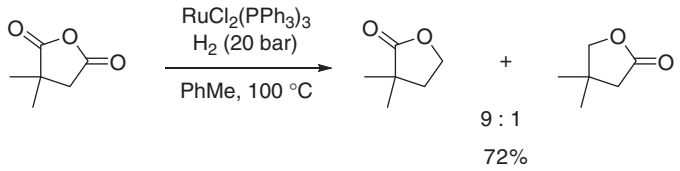
Scheme 5

8.10.4 Reduction of Anhydrides

The reduction of acyclic anhydrides is not common in the literature, though in these cases the more powerful lithium hydride reagents are used. Of greater interest is the selective reduction of cyclic anhydrides to lactones, which can be useful intermediates and so will be covered here. The most popular choice of reagent is sodium borohydride, but regioselectivity of the reduction is controlled by a number of different factors, including the choice of reagent, and so other reductants must be examined.

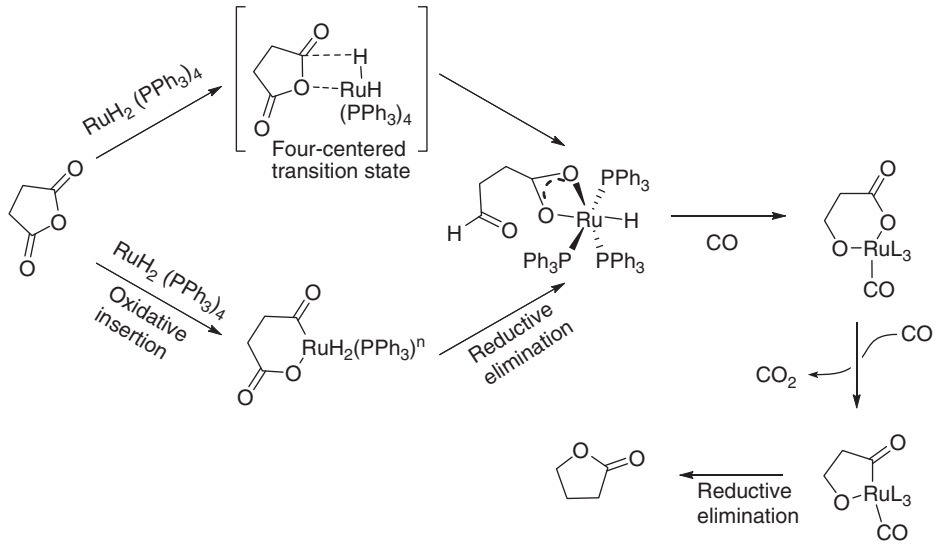
8.10.4.1 Hydrogenation

Although the hydrogenolysis of anhydrides does not suffer from the same problem as acid chlorides (see Section 8.10.3.1), there are few examples of acyclic anhydrides being used. More interest has been found in the selective hydrogenolysis of cyclic anhydrides such as succinic or phthalic anhydride to give the corresponding lactones. There are but a few examples of heterogeneous catalyzed reactions: for example, maleic anhydride has been converted to γ-butyrolactone in the vapor phase over a $ZnO–CuO–Al_2O_3$ catalyst at 425 °C with >95% conversion.[38] More commonly these reactions have been dominated by homogeneous ruthenium complexes, particularly dichlorotris(triphenylphosphine)ruthenium(II) [$RuCl_2(PPh_3)_3$]. First reported by Lyons in 1975,[39] Morand and Kayser showed in 1976 that this reagent preferentially catalyzed the hydrogenation of the less-hindered carbonyl group of the anhydride moiety (equation 5).[40] This selectivity is in contrast to that when using LAH, which gives a 19:1 ratio in favor of the more hindered carbonyl group being reduced (see Section 8.10.4.3). The reaction conditions still require high temperatures (100 °C) and pressures (20 bar) and thus specialized equipment.



(5)

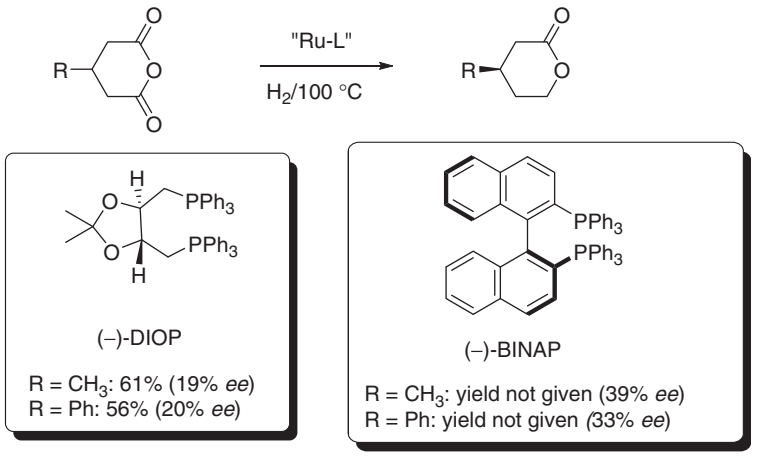
The mechanism of this reaction has been probed by conducting the reaction with a stoichiometric quantities of [$RuH_2(PPh_3)_4$] and various anhydrides (e.g., phthalic and succinic anhydrides).[41,42] The carboxylate complex that formed (Scheme 6) was postulated to occur via either a two-step, oxidative addition/reductive elimination mechanism, or a one-step, four-centered transition state. Treatment of this complex with dry hydrogen chloride, carbon monoxide, or hydrogen gas resulted in the lactone product being obtained. The authors suggest that the regioselectivity reported earlier must therefore be due to the initial ruthenium complex formation being driven by steric effects controlled by the bulky triphenylphosphine ligands.[43] There have been a few reports extending this method, particularly with the view of improving the yields which are very low. Reports by Wada and Hara suggest that the addition of *p*-toluenesulfonic acid dramatically improved the activity of the reaction giving better yields.[44] This modification has been applied to the synthesis of γ-butyrolactone from maleic anhydride.[45]



Scheme 6

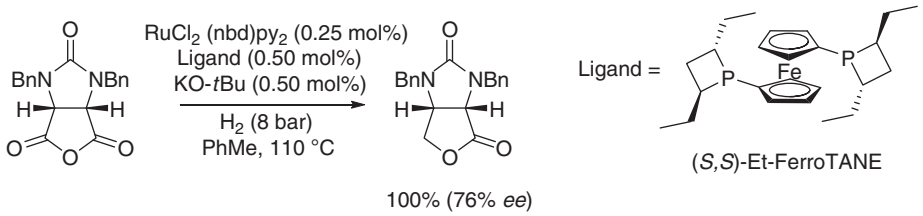
The development of this method to effect an enantioselective desymmetrization of mesocyclic anhydrides has been explored. Two reports by Ikariya and Yoshikawa appeared in the early-1980s using the chiral ligands (–)-DIOP ((–)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenyl-phosphino)butane)[46] and (–)-BINAP ((–)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl).[47] Although this work showed some promise, the results were disappointing and only moderate yields and low *ee*'s were obtained (Scheme 7).

This work subsequently received scant attention over the subsequent three decades, possibly because of the generally poor yields, which are attributed to water being formed in the reaction hydrolyzing the anhydride starting material. In 2011, Kitamura et al. reported using a desymmetrization method on a cyclic anhydride in order to synthesize a common target in the synthesis of biotin (vitamin B_7). The optimization was performed specifically for the intended target, but some features of this work may have



Scheme 7

application in related substrates. Perhaps the most important observation was that ligands with large bite angles gave the best results and that the inclusion of a base such as potassium *tert*-butoxide was very important for high yields. The study examined a number of chiral ligands known to have wide bite angles, finding that (–)-1,1′-bis((2*S*,4*S*)-2,4-diethylphosphotano)ferrocene to be the best (equation 6).



(6)

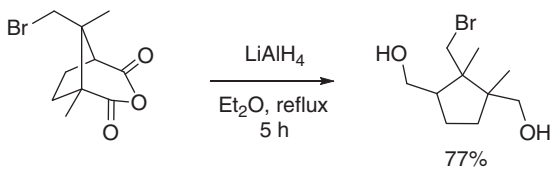
There is little work demonstrating the chemoselectivity of these reagents, though the low hydrogen pressures suggest that all the less active carboxylic acids should be stable (e.g., esters, amides, nitriles, etc.). Ketones and aldehydes would be reduced as would unsaturated aliphatic bonds.

8.10.4.2 Electrochemical and Single Electron Reductions

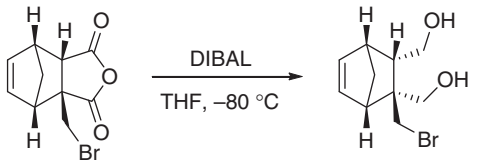
Cyclic anhydrides can give lactones via electrochemical or dissolving metal reduction. For example, electrochemical reduction of phthalic anhydride has given phthalide (2-benzofuran-1(3*H*)-one) on a lead cathode in 90% yield.[48] This particular reaction has also been accomplished with zinc in acetic acid.[49,50] In general though, these sorts of reductions are not frequently employed in synthetic schemes.

8.10.4.3 Reductions with Metal Hydrides

Relatively speaking, the complete reduction of cyclic anhydrides is very uncommon in the synthetic literature. It is readily achieved with the aluminum hydride reagents with LAH (equation 7) being by far the most popular choice. Red-Al® and DIBAL (equation 8) have likewise been used, though far less frequently. Lithium tri-*tert*-butoxyaluminum hydride is more commonly used to access the hydroxy lactone product.

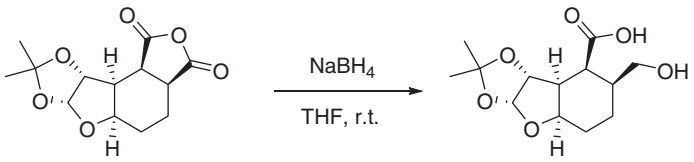


(7)

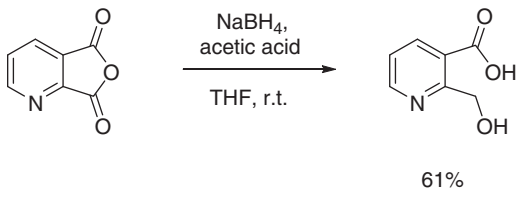


(8)

Borane can be used to fully reduce anhydrides to the alcohols, but this has rarely been applied in the literature. It is more usual to employ LAH in this case. Reduction of acyclic anhydrides with $NaBH_4$ can give the alcohol and carboxylate salt, thus for unsymmetrical anhydrides this is an inefficient method. For cyclic anhydrides this reaction can be considered a feature and has been reported in some cases, although it is more common to obtain the lactone. The important factor though is the regioselectivity of the opening, which is unfortunately not easy to predict as many factors can influence this (equations 9 and 10).



(9)



(10)

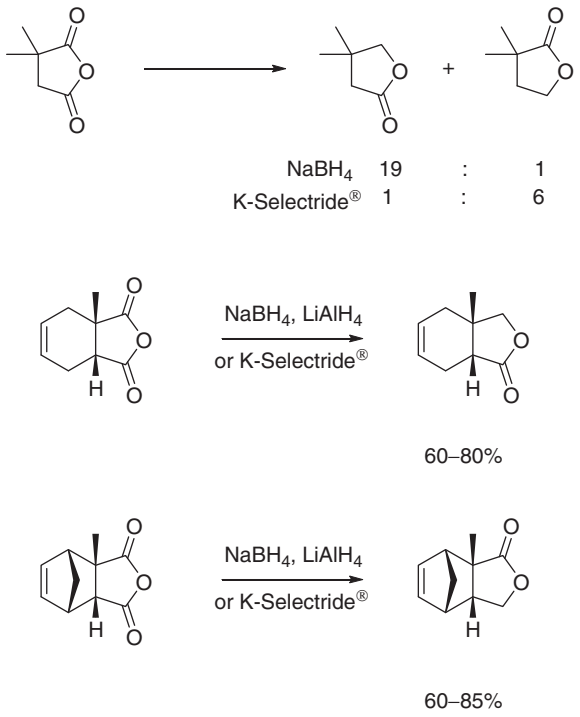
Of greater interest though is the reduction of cyclic anhydrides to γ- or δ-lactones, which can be readily achieved with LAH or sodium borohydride by careful control of the number of equivalents and temperature. The reaction works well, but as mentioned above the regioselective reduction of unsymmetrical cyclic anhydrides is difficult to predict. This has been extensively investigated by the group of Kayser and coworkers[51–55] such that some general rules can be applied for predicting the regioselectivity. Typically, reductions with $LiAlH_4$ and $NaBH_4$ result in the carbonyl with the greater degree of substitution on the α-carbon to be reduced preferentially. This can be reversed if a sterically encumbered reductant such as K-Selectride® is used. Unfortunately, there are many exceptions to this rule and other factors have been found to be important in explaining regioselectivity. The interplay between the electrophilicity of the two carbonyls, steric encumbrance to the trajectory of the hydride (i.e., the Bürgi–Dunitz angle), the effect of neighboring bonds coplanar to the carbonyl system (also referred to as the antiperiplanar effect), and chelation possibilities all come together in determining the outcome. Some examples are shown in Scheme 8.

8.10.5 Reduction of Carboxylic Esters

The metal hydrides are by far the most important class of reductant, accounting for approximately 90% of all reductions of carboxylic esters to alcohols. Hydrogenation comes in second place owing to it requiring specialized catalysts and reaction conditions more suited for industrial-scale applications. Importantly though, a number of nonmetal hydride methods have been reported since the 1990s, many of which are intriguing in terms of offering an alternative option to the classical reagents. For instance, one very important development has been the introduction of silanes as reducing agents, including examples of silanes being used to reduce esters to ethers.

8.10.5.1 Hydrogenation Reactions

Although the heterogeneously catalyzed hydrogenolysis of esters is slightly easier than that of carboxylic acids, the preference for reducing esters and not the carboxylic acids on an industrial scale has to do with the catalysts themselves being sensitive to acidic attack. Industrially, the reaction is very important for the production of what are termed fatty alcohols (long-chain aliphatic alcohols, both saturated and unsaturated), which are important components in the manufacture of many commercially important chemicals, for example, lubricants, surfactants, plasticizers, and thickeners in the food and cosmetic industries. One of the most important catalysts for this is copper chromite with reactions typically being run at 150–300 °C and hydrogen pressures of

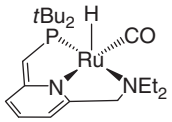
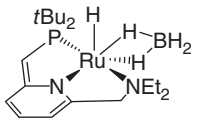
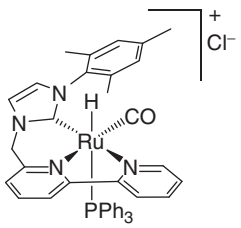
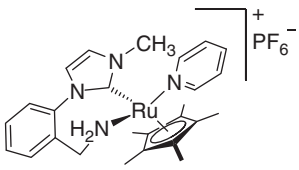
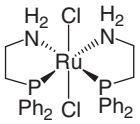
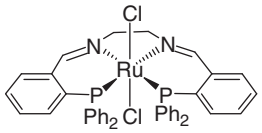
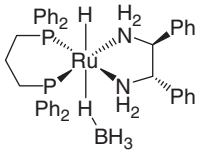
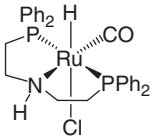


Scheme 8

250–300 bar.[56] Other metal combinations such as palladium–rhenium and rhodium–tin have also been used,[57] but a challenge for industrial hydrogenolysis has been to selectively reduce a fatty ester in the presence of unsaturation in the aliphatic chain. One of the earliest reports comes from Sauer and Adkins who demonstrated in 1937 that zinc chromite was effective at catalyzing the hydrogenolysis of butyl oleate to oleyl alcohol (*cis*-9-octadecen-1-ol). This process was however very inefficient, requiring 40% catalyst loading and a process temperature of 300 °C and pressure of 200 bar, yielding 65% of the theoretical yield of the alcohol. Further developments in the heterogeneous hydrogenolysis of fatty acids have come from many quarters owing to the industrial importance of this process, and have been extensively reviewed.[58,59]

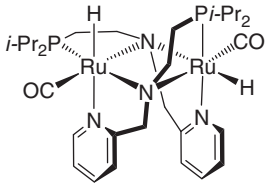
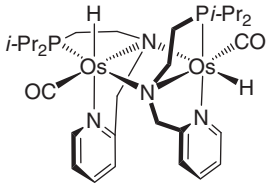
Homogeneous catalytic hydrogenation of esters has received much attention since the early 1980s. Grey et al. were one of the first groups to describe a ruthenium-based homogeneous catalyst ($2K^+[(Ph_3P)_3(Ph_2P)Ru_2H_4]^{2-} \cdot 2$(diglyme)) that could hydrogenate esters to alcohols.[60] However, this catalyst was only capable of reducing activated esters such as methyl trifluoroacetate to 2,2,2-trifluroethanol and methanol, although the catalyst did allow for much milder conditions than heterogeneous catalysis (90 °C, 62 bar). Matteoli using $[Ru(CO)_2(OAc)_2(PBu_3)_2]$[61] and Elsevier using $[Ru(acac)_3/MeC(CH_2PPh_2)_3]$[62] have reduced dimethyl oxalate to ethylene glycol, though Elsevier's use of the tridentate phosphine ligand was superior allowing milder conditions (100 °C and 70 bar H_2).[63] Elsevier and Theunissen then demonstrated that it was possible to use their ruthenium–tridentate system to catalyze the hydrogenation of aliphatic and aromatic esters, though this was only a preliminary communication and required the use of fluorinated alcoholic solvents.[64] Since the mid-2000s a number of patents[65–72] and articles have emerged reporting improved catalytic systems based on ruthenium[73–82] and osmium.[82,83] In one of the first reports, the group of Milstein demonstrated a PNN-type ruthenium pincer complex (**Table 2**, entry 1) that was capable of hydrogenating simple aromatic and aliphatic esters under relatively mild conditions (115 °C and 5.4 bar H_2 pressure).[73] In a further publication they showed that the analogous ruthenium hydrido borohydride pincer complex was also effective, though not as good as their first reported catalyst (**Table 2**, entry 2).[74] A slight improvement was made when the phosphine in the pincer complex was changed for an *N*-heterocyclic carbene (**Table 2**, entry 3); Morris et al. have also demonstrated an *N*-heterocyclic carbene–ruthenium complex that was efficient at hydrogenating methyl benzoate (**Table 2**, entry 4).[76] The industrial research group of Saudan reported their work on ester hydrogenolysis around the same time as Milstein, showing that Noyori-type[84] ruthenium complexes with bis-N,P-ligands appeared to be an excellent choice for designing efficient ruthenium hydrogenation catalysts that showed high activity (**Table 2**, entries 5 and 6).[77] One of their catalysts (**Table 2**, entry 6) was also shown to be suitable for the hydrogenation of esters that contained unsaturated carbon bonds. Not all alkenes were resistant, however, with conjugated and simple monosubstituted alkenes being rapidly reduced under the reaction conditions. The hydrogenation of esters that contain a chiral center was an aspect initially ignored; indeed Saudan's efficient bis-N,P-ligand ruthenium complex (**Table 2**, entry 5) was shown to often racemize chiral substrates. However, the industrial research group of Kuriyama developed a number of catalysts based on P,P and N,N-bidentate ligands that showed excellent tolerance for chiral ester substrates (**Table 2**, entry 7). Although this ruthenium borohydride complex has a chiral diamine, it was shown that either antipode of the

Table 2 Comparison of homogeneous hydrogenation catalysts reported in the literature[a]

Entry	Catalyst	References	Temp (Pressure)	TOF [a] (h^{-1})	Selected substrate	Comment
1	 Milstein	73	115 °C 5.4 bar	25	Ethyl benzoate	Few simple esters hydrogenated
2	 Milstein	74	110 °C 10 bar	16	Methyl benzoate	Few simple esters hydrogenated
3	 Milstein	75	135 °C 5.4 bar 110 °C 50 bar	48 240	Ethyl benzoate	Few simple esters hydrogenated
4	 Morris	76	25 °C 8 bar 50 °C 25 bar	209 838	Methyl benzoate	Only ester example
5	 Saudan	77	100 °C 50 bar 100 °C 10 bar	2200 235	Methyl benzoate	Various simple esters and lactones
6	 Saudan	77	100 °C 50 bar	1980 ~700	Methyl benzoate Various esters	Ignores isolated alkenes (not primary alkenes)
7	 Kuriyama	79,80	80 °C 50 bar	30 ~6	Methyl benzoate Various chiral esters	*N*-Boc, OTBS, and OBn groups stable
8	 Kuriyama	81	28 °C 40 bar 80 °C 45 bar	153 348	Methyl (*R*)-lactate Methyl *l*-menthoxy-acetate	Performed on large scale

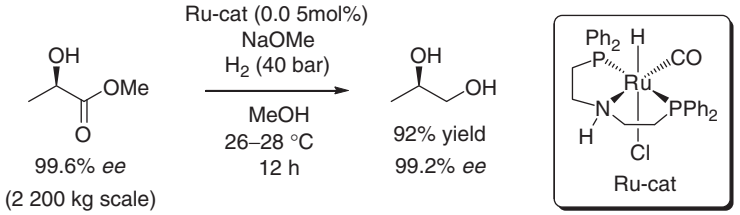
(*Continued*)

Table 2 Continued

Entry	Catalyst	References	Temp (Pressure)	TOF [a] (h^{-1})	Selected substrate	Comment
9	 Gusev	82	80 °C 50 bar	1470	Methyl benzoate	Few simple esters hydrogenated
10	 Gusev	82	100 °C 50 bar	~140	Various alkene-containing esters	Conjugated double bonds are hydrogenated

[a]The reader is reminded that directly comparing catalysts is somewhat difficult due to the different conditions under which they are tested. The TOF (turnover frequency) gives some degree of comparison but must be compared with the temperature and pressure of the reaction since these will have a dramatic effect on the TOF. TOF values have been calculated from the published data and so often do not reflect a particularly optimized procedure.

trans-diphenylethylenediamine ligand returned the same result, namely, the reduction of an ester without affecting the chiral center α or β to the ester carbonyl moiety. A disadvantage of this catalyst is that the activity is low, which prompted Kuriyama et al. to seek an improved catalyst by considering some mechanistic insights observed in the literature. It had been suggested that methanol produced in the reaction deactivated the catalyst by carbonylation of the metal.[77] Therefore, Kuriyama proposed that a tridentate ligand should be better able to replace any transient carbonyl ligand. Using this information they developed a PNP ruthenium complex (Table 2 entry 8), which shows much better activity, while still avoiding any racemization of chiral centers.[81] It was found that in this case the temperature of the reaction was important for some substrates and optimization was important to prevent racemization of the product. In demonstration of this, they described the large-scale (2.2 t) reduction of methyl (*R*)-lactate to (*R*)-1,2-propanediol with almost complete retention of the enantiomeric purity found in the starting material (equation 11). Even though low temperatures were required (less than 30 °C), the catalyst was still very active, reducing 2.2 t of methyl (*R*)-lactate with 0.05 mol % catalyst in 12 h with a 92% recovered yield.



(11)

Finally, Gusev et al. have synthesized interesting ruthenium and osmium dimers that are suitable catalysts for the reduction of esters.[82] The ruthenium dimer (Table 2, entry 9) appears to be comparable to the Saudan catalysts (Table 2, entries 5 and 6), though it should be mentioned that the Saudan catalyst requires the addition of catalytic amounts of base (NaOMe), whereas the Gusev catalysts operate under neutral conditions. Gusev et al. have been the first group to use osmium instead of ruthenium in these types of reactions, although these early results have not shown any advantage over using ruthenium-based catalysts. For example, in Table 2 entry 10, the osmium dimer analog of the ruthenium dimer just discussed has been shown to not catalyze the hydrogenation of isolated alkenes, but like Saudan's catalyst (entry 6) it also hydrogenates alkenes conjugated to the ester. The Saudan ruthenium catalyst is also more active. In another report, an osmium complex using a ligand similar to the Kuriyama ruthenium catalyst (Table 2, entry 8) has been used in the hydrogenation of triglycerides. Unfortunately, alkenes in seed oils are not tolerated by this catalyst and must be hydrogenated before the reduction of the fatty ester to the fatty alcohol.[83]

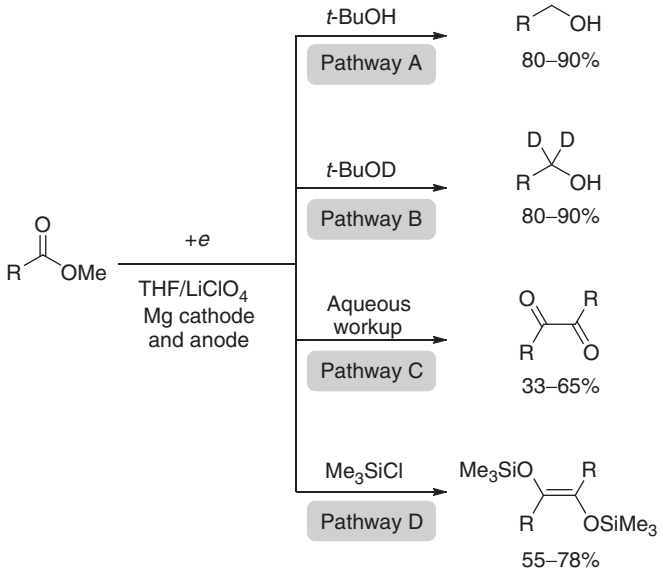
Although the use of homogeneous catalysis for the reduction of esters to alcohols has shown exciting results, little work has emerged on the chemoselectivity of these reagents. It has been mentioned that some catalysts will tolerate unconjugated double bonds, and that others will tolerate chiral centers, but no reports have emerged regarding catalysts that show chemoselectivity toward other reducible groups. These catalysts offer promising options for industrial-scale ester hydrogenation, but laboratory-scale

workers will likely default to hydride reductions since their reactivity and chemoselectivity are well known and understood. For the interested reader it should be noted that this process of hydrogenolysis of esters is only mildly exergonic (-5 kcal mol^{-1} for ethyl acetate) and so the reverse process, alcohol dehydrogenative coupling, is also feasible, particularly because the hydrogen formed in the reaction can be expelled in an open system. For more information *see* Chapter 8.11.

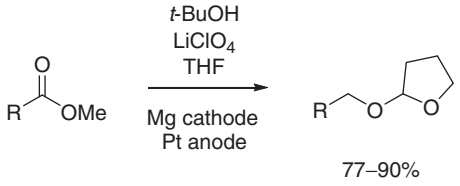
8.10.5.2 Electrochemical and Single Electron Reductions

The electrochemical reduction of aromatic esters can be accomplished at mercury, lead, or cadmium electrodes provided this is done under acid conditions.[85,86] Using this method, ethyl benzoate will give benzyl alcohol in 70% yield and phenyl benzoate reduced in almost quantitative yield. However, the electrochemical reduction of aliphatic esters is more difficult with these returning yields in the range of 31–36%. The solution to this problem has been reported by Shono and coworkers and involves the use of a sacrificial magnesium anode and cathode with *tert*-butanol as a proton source (Scheme 9, pathway A).[87] A variety of methyl esters have returned good yields (80–90%), with the reaction tolerating aromatic and heteroaromatic rings, isolated alkenes, and alcohols. Careful examination and experimentation by this group suggested that the electroreduction system involved alkali metal ions as the mediators, and that the electrogenerated alkali metal, Mg(0), was the active reductant in the reduction of aliphatic esters.[88] An application of this method was proposed to be the preparation of 1,1-dideuterated alcohols when using *t*-BuOD as the deuterium source (Scheme 9, pathway B). Without a proton source it was found that diketone products are obtained after an aqueous workup (Scheme 9, pathway C).[87,89] This has been suggested to occur through an intermediate magnesium chelate, similar to a pinacol coupling, which is insoluble in the reaction medium, thus preventing further reduction. If chlorotrimethylsilane (Me_3SiCl) is added to the reaction the bis(trimethylsilyloxy)alkene is obtained (Scheme 9, pathway D).[89]

Further work in this field by the same authors demonstrated that higher yields of the diketone, or better yet unsymmetrical diketones, could be obtained by first making a diester with ethylene glycol.[90] The ethylene backbone acted as a tether dramatically increasing the yields of unsymmetrical diketone obtained to approximately 80%. Another potentially important demonstration of this chemistry is that by changing the magnesium anode for a platinum one, the THF solvent is oxidized and reacts with the alkoxide intermediate of the reduced methyl ester giving an acetal (equation 12).[91] Only a small selection of esters have been reported, so functional group tolerance is unknown, but the synthetic use is intriguing since it allows the introduction of a protecting group on an alcohol obtained via reduction of an ester in one step.



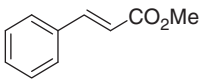
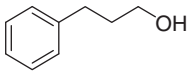
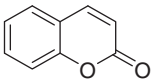
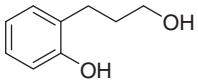
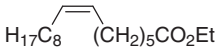
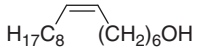
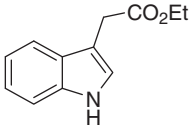
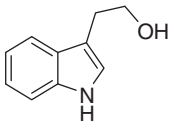
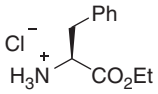
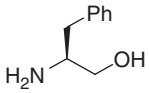
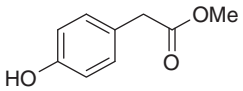
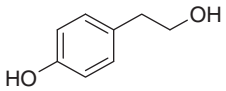
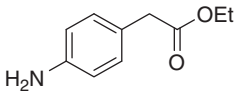
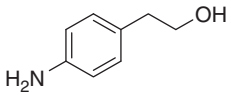
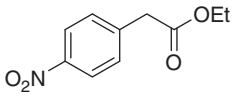
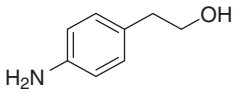
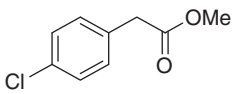
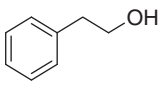
Scheme 9



(12)

Dissolving metal reduction using an alkali metal in an alcohol can reduce esters to primary alcohols. This is the classic Bouveault–Blanc reduction first described by these French chemists in 1903.[92,93] Historically, this method remained the favored choice for the reduction of aliphatic esters until the introduction of metal hydride reagents in the late 1940s. The original method called for the substrate to be added in ethanol to sodium metal while heating under reflux. Other alkali or alkali earth metals may be used, as can other alcoholic solvents. The reaction itself has a major drawback in being unpredictable owing to the need for very careful control of the reaction conditions, notwithstanding the fact that working with molten sodium and solvents under reflux presents a practical health hazard. Still the reaction has continued to find some use in the literature. A development in the 2000s has been the encapsulation of alkali metals in silica gel nanopores.[94,95] This produces a stable form of the alkali metal that can be conveniently handled in the open. In 2009, Bodnar and Vogt demonstrated that this stabilized form of sodium metal (abbreviated Na-SG) was very efficient in the Bouveault–Blanc reduction (Table 3).[96] The reaction is conducted at room temperature in THF and workup is through conventional aqueous means. The functional group tolerance for the Bouveault–Blanc reaction is conserved: aromatic esters give mixtures of products; cinnamate esters are fully reduced, whereas isolated double bonds are left untouched; aryl and aliphatic halides are reduced as are aryl nitro groups; aryl amino and hydroxyl groups are however tolerated by the reaction conditions.

Table 3 Selected examples of the Bouveault–Blanc reduction using Na-SG

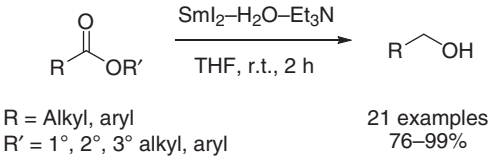
Entry	*Substrate*	*Product*	*Yield (%)*
1			95
2			77
3			99
4			95
5			27[a]
6			93
7			78
8			36
9			71

[a]Yield after recrystallization to 98% *ee*.

Other dissolving metal reactions of esters include the acyloin condensation (*see* Chapter 8.11) and deoxygenation (*see* Chapter 8.11). These are beyond the scope of this chapter.

Samarium(II) iodide has been shown to reduce esters to alcohols in high yields by Procter and coworkers when combining the reagent with an excess of water and amine additives (equation 13).[97] The SmI_2–H_2O–amine system is crucial to the success of the reaction which shows wide scope for aliphatic and aromatic esters, including sterically demanding substrates. Reductions are typically run at room temperature and are complete within a few hours. Triethylamine is usually the preferred choice of amine partner, but others do work; for example, pyrrolidine was found to be a better choice when reducing *tert*-butyl esters. Functional group tolerance has not been reported, but ketones, aldehydes, and carboxylic acids would be reduced; unsaturated esters and aryl bromides, although unreported, would almost certainly be fully reduced since they are reduced under similar conditions.[16]

Radical traps in the substrates (e.g., alkenes) could possibly complicate the reaction if only reduction is required, although radical cyclization may be a feature of a synthetic strategy.



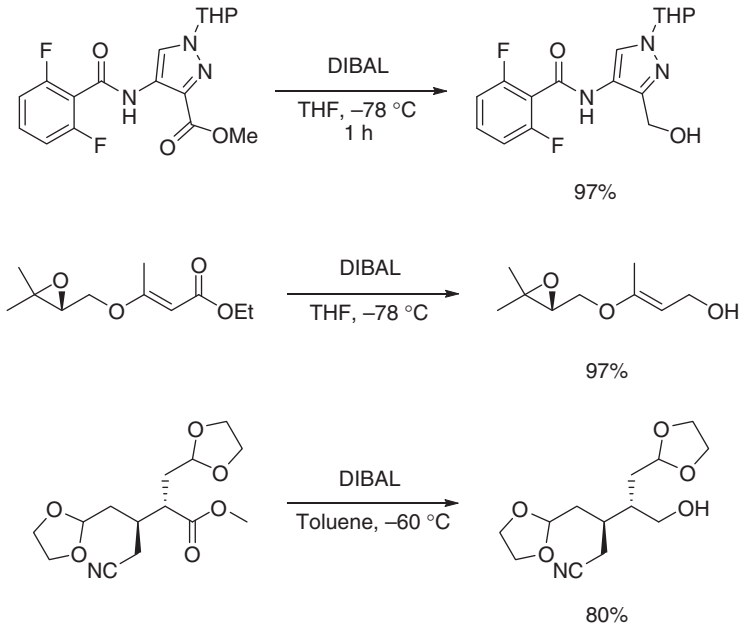
(13)

8.10.5.3 Reductions with Metal Hydride Reagents

The aluminum hydride reagents $LiAlH_4$ and DIBAL are the most common choice, together accounting for more than 70% of all reductions of esters to alcohols. This is followed by the boron hydride reagents sodium and lithium borohydride, which make up approximately 20% of these reductions. Lithium borohydride is an excellent choice, particularly regarding its chemoselectivity.

8.10.5.3.1 Aluminum hydrides

The popularity of using LAH to completely reduce carboxylic esters is unsurpassed. The advantages are that the reaction is quick, clean, and generally gives high yields of the desired alcohol. The disadvantages are generally associated with this reagent being a powerful reducing agent and thus its extreme lack of chemoselectivity. The use of other aluminum hydride reagents is also common, with DIBAL for example, finding extensive usage. In many respects DIBAL may be considered superior to $LiAlH_4$ in that it is more easily handled and compatible in a wider range of organic solvents (aliphatic and aromatic hydrocarbons, dichloromethane, and ethers, though the latter are cleaved at high temperatures). It also has more options for selective reductions compared to $LiAlH_4$, being for instance the preferred choice for reducing α,β-unsaturated esters to allylic alcohols. Esters have been selectively reduced with DIBAL in the presence of amides, epoxides, carbamates, and aryl halogens and nitro groups. DIBAL can also be used to selectively reduce a methyl ester in the presence of a *tert*-butyl ester in very high yield.[98] DIBAL is often used to selectively reduce esters to aldehydes, although this reaction is frequently temperamental (*see* Chapter 8.11). Scheme 10 contains some selected examples of DIBAL reductions of esters, highlighting some aspects of its chemoselectivity.

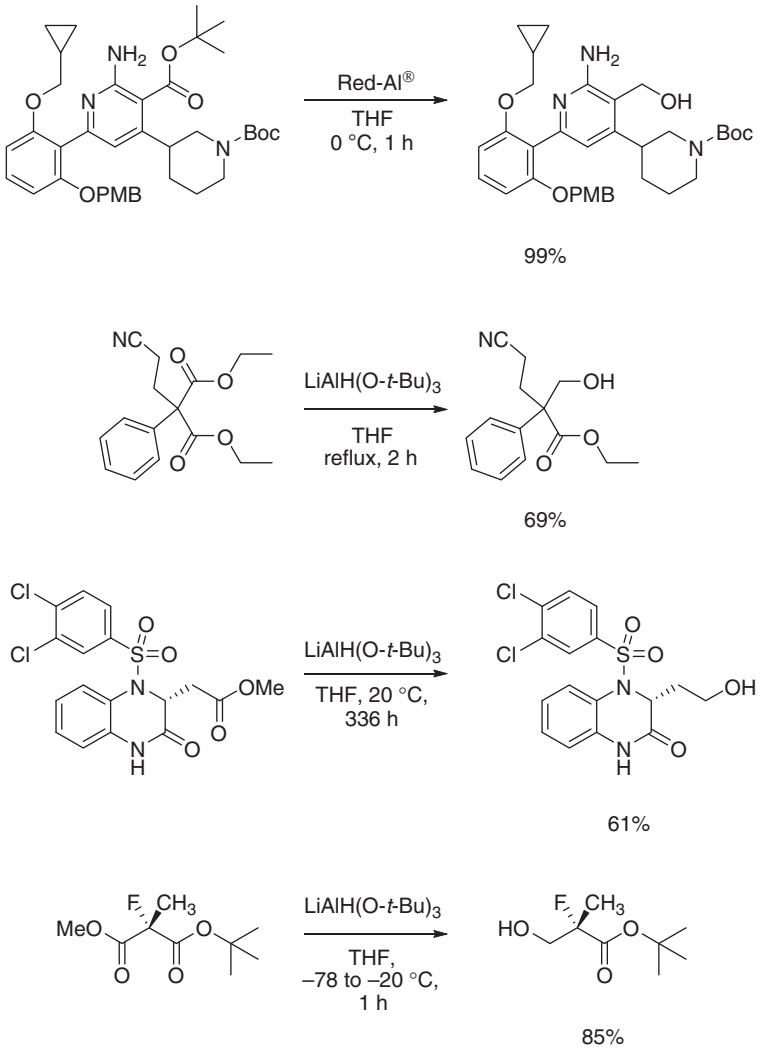


Scheme 10

Sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al®) will reduce esters to alcohols in toluene and ethereal solvents, though its reactivity is closer to that of $LiAlH_4$ than DIBAL. Many other aluminum hydride reagents have been reported incorporating different cations (Na^+, Ca^{2+}) and substituents on the aluminum center (-O-*i*-Butyl, -O-cyclohexyl, $-OCH_2CH_2O$-*i*-Pr, etc.). In practice their use has been extremely limited due to their exotic nature and lack of significant benefits over the standard reagents. However, lithium tri-*tert*-butoxyaluminum hydride ($LiAlH(O\text{-}t\text{-}Bu)_3$) has the following few advantages: it is a much milder reducing agent and is known to be better than DIBAL at selectively cleaving methyl esters in the presence of *tert*-butyl esters.[99]

Furthermore, it has also been shown to selectively monoreduce malonate esters (methyl or ethyl) to the corresponding β-hydroxy ester.[100] Owing to the mild reducing power of LiAlH(O-*t*-Bu)$_3$, aliphatic esters can be reduced in the presence of aromatic esters,[101] lactones,[102] amides, and nitriles. Some representative examples for LiAlH(O-*t*-Bu)$_3$ and Red-Al® can be seen in Scheme 11.

The reduction of esters to ethers using a combination of LAH and boron trifluoride has been reported, but is more of a curiosity than a practical method owing to the very poor yields obtained.[103,104] The better choice for such a transformation would be with silane reductions discussed later in Section 8.10.5.4.

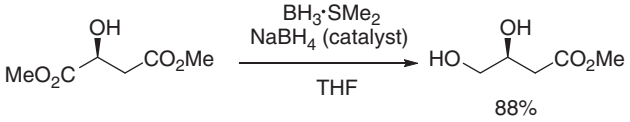


Scheme 11

8.10.5.3.2 Boron hydrides

In general, the borane reagents do not reduce carboxylic esters though prolonged reaction times and elevated temperatures (for esters of aromatic carboxylic acids) have been known to result in primary alcohols. It is, therefore, perhaps more instructive to observe that the boranes can be used to chemoselectively reduce a number of other groups in the presence of an ester, for example, carboxylic acids (see Section 8.10.2.3.2), amides (see Section 8.10.7.3.2), aldehydes, and ketones (*see* Chapter 8.11). Should one desire to use borane to reduce an ester, then a solution offered by Brown and coworkers is to use borane-dimethyl sulfide in refluxing THF such that the dimethyl sulfide is allowed to distill off during the reaction.[105] In this way aliphatic esters are reduced in approximately 30 min, whereas esters of aromatic carboxylic acids require 4–16 h; the yields are generally very good. In another important adaption, Saito et al. have shown that a catalytic amount of sodium borohydride with borane dimethyl sulfide is excellent at reducing esters with an α-hydroxyl group.[106] More importantly, the substrates can be diesters with only the α-hydroxy ester being reduced (equation 14). Interestingly, this combination of reductant and catalyst was found to be important in these systems since using either one or the other resulted in very poor results. This method has been applied numerous times in the

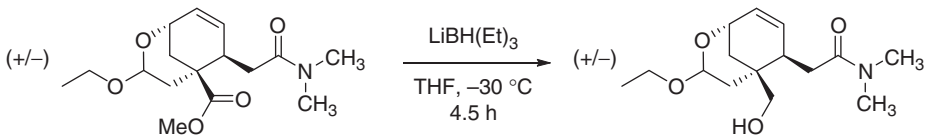
literature and the mechanism has also been investigated.[107] The various other borane derivatives (e.g., thexylborane, catecholborane, and 9-BBN) also behave similarly to that of borane dimethyl sulfide in the reduction of carboxylic esters and are therefore not recommended. As always it should be highlighted that borane will also add to olefinic bonds and so this should be considered in any synthetic strategy.



(14)

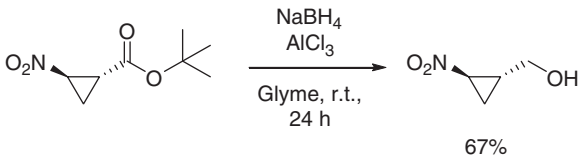
Sodium borohydride is inefficient as a reductant in these systems and only slowly reduces esters to alcohols at room temperature. However, if the ester has an α-oxygen substituent this changes and it is usually rapidly reduced to the primary alcohol.[108,109] It has also been shown that good yields can be obtained with sodium borohydride when heating the ester in *t*-BuOH or THF with concomitant slow addition of MeOH.[110] Better though are the borohydride salts that contain more Lewis-acidic salts such as $LiBH_4$, $Ca(BH_4)_2$, and $Mg(BH_4)_2$, which are much more effective and therefore recommended over the use of sodium borohydride. Fortunately, these can be generated *in situ* from sodium borohydride and an appropriate metal salt, or purchased separately if desired. Of the various options, lithium borohydride is certainly the preferred choice and has been extensively used in the literature. The most important point is that it is particularly useful in the chemoselective reduction of an ester in the presence of a carboxylic acid, amide, or nitrile functional group. Like sodium borohydride, lithium borohydride is also susceptible to activation under different solvent effects.[111] Thus in diethyl ether, lithium borohydride and 1 equivalent of methanol cleanly reduces esters, lactones, and epoxides in the presence of carboxylic acids, chloro, nitro, and carbamoyl groups. However, changing the solvent to THF or diglyme and adding 4 equivalents of methanol dropwise to the refluxing solution dramatically changes the reducing power, allowing lithium borohydride to reduce carboxylic acids, nitro, nitrile, and primary and tertiary amide groups. The yields of these reductions are not exceptional and are not advised as a general method. Examples of the reduction of esters with $LiBH_4$ can be seen in **Scheme 12**, highlighting the chemoselectivity of this reagent.

Many variations on the borohydride theme have been reportedly effective in ester reductions. These include reagents such as $NaBH_3(OH)$, $NaBH_2(SCH_2CH_2S)$, $NaBH(OMe)_3$, and $NaBH_3(NH\text{-}t\text{-}Bu)$, but their use in the literature has been limited by the fact that they offer no significant improvement over lithium borohydride or the aluminum hydrides mentioned in the previous section. The lithium aminoborohydrides ($LiBH_3NR^1R^2$) also reduce esters,[112] but their use in reducing tertiary amides to alcohols is more significant (see Section 8.10.7.3.2). It has also been claimed that the hindered borohydride reagents can selectively reduce unhindered esters in the presence of hindered ones, but this has routinely been achieved with lithium borohydride (**Scheme 12**). The alkyl substituted borohydride, lithium triethylborohydride ($LiBHEt_3$, Superhydride®), is also a powerful reductant and readily reduces esters to alcohols.[113] It is used with reasonable frequency, but lower reaction temperatures are usually recommended (−78 °C to −20 °C). Carboxylic acids, carbamates, amides, lactams, and nitriles are not reduced; tertiary amides can be reduced, but are frequently left intact at the low temperatures used (e.g., equation 15). Ireland and Thompson have also reported that methoxyethylmethyl (MEM) esters can be selectively cleaved with $LiBHEt_3$ in the presence of other esters.[114]



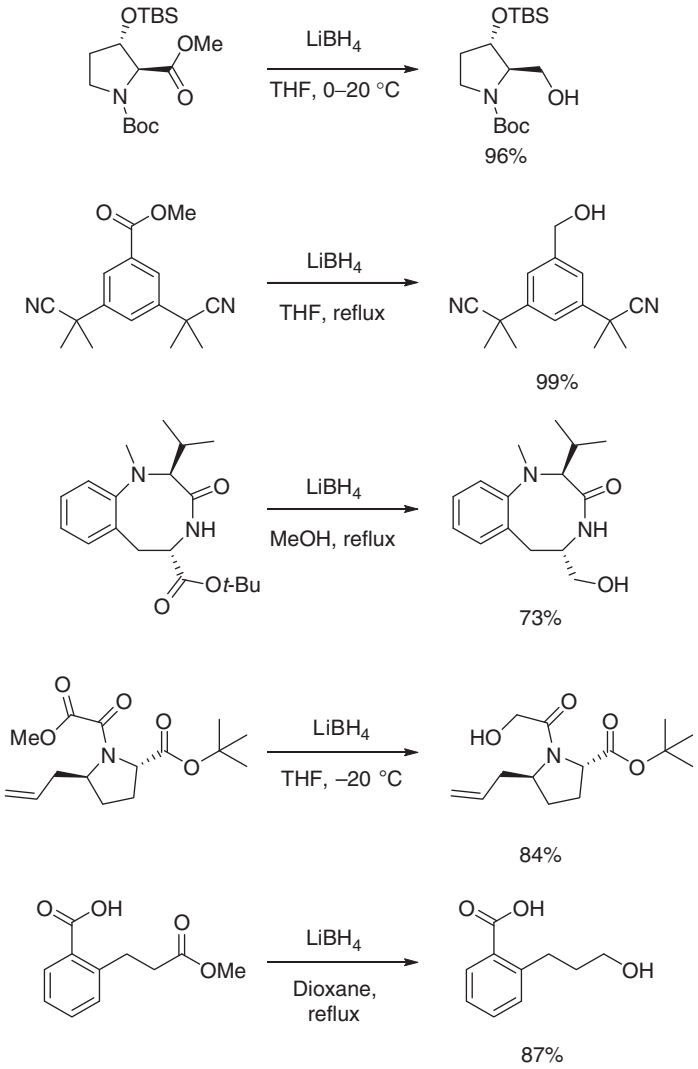
(15)

Borohydride reagents are also activated through the use of Lewis acids, particularly aluminum chloride.[115] The combination of $NaBH_4$ and $AlCl_3$ creates a reagent that sits somewhere between $LiBH_4$ and $LiAlH_4$ in terms of reducing ability (equation 16). Thus esters are readily reduced, as are carboxylic acids (though not their salts) and nitriles, but primary amides and nitro groups are not.



(16)

The reduction of esters to ethers using sodium borohydride and boron trifluoride has been reported.[116,117] However, as with the LAH variant of this reaction, the method is not general and has found only limited use. Higher yields are found when the carbon center α to the alcohol side of the ester is tertiary.



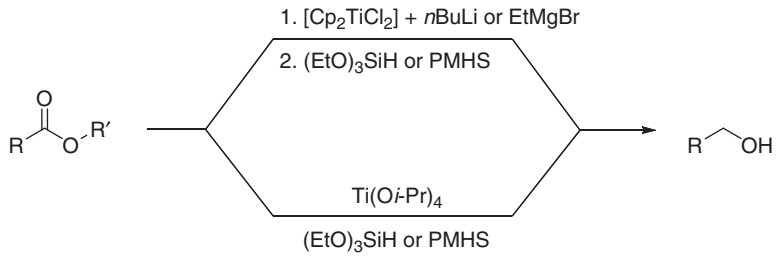
Scheme 12

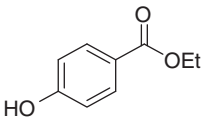
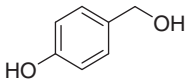
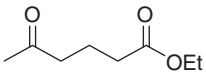
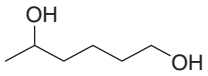
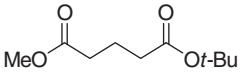
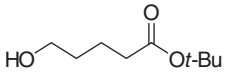
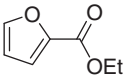
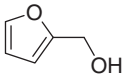
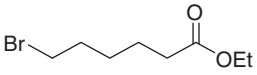
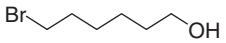
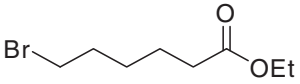
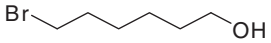
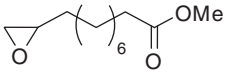
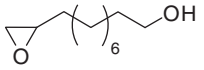
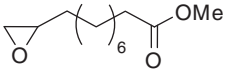
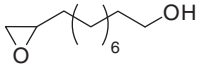
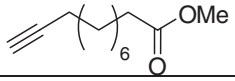
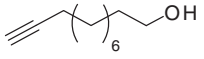
8.10.5.4 Reductions with Silanes

The reduction of esters by silanes has been an important emerging field since the 1990s, particularly since Buchwald and coworkers established that titanocene and titanium alkoxides were efficient catalysts for this reduction.[118–121] In general, the titanocene catalyst (generated *in situ* from dichlorotitanocene and *n*-butyllithium) is more active than the robust and air-stable titanium isopropoxide catalyst. Both triethoxysilane and polymethylhydrosiloxane (PMHS) have been used as hydride source with the latter having the obvious advantage of being very cost-effective and safe. However, when using PMHS, $Ti(O\textit{i}\text{-}Pr)_4$ must be used with 100% loading. Some representative examples can be seen in Table 4; the conditions are tolerant of various functional groups, though using $Ti(O\textit{i}\text{-}Pr)_4$ allows for greater selectivity, for example, with epoxides and halides. Ester chemoselectivity is also possible since *tert*-butyl esters are more slowly reduced than simple aliphatic ones (Table 4, entry 3). Ketones and aldehydes would be reduced, but there is no information regarding other functional groups such as nitriles (likely to be stable), amides, and carboxylic acids (likely to form silyl esters).

A number of variations on this theme have emerged. For example, the use of PMHS in the presence of catalytic amounts of tetrabutylammonium fluoride (TBAF) or benzyltrimethylammonium hydroxide (Triton® B) has been shown to reduce esters.[122] The yields of alcohols are good, but carboxylic acids, aldehydes, and ketones are all reduced. Mimoun has demonstrated that PMHS can be used as a reductant in the presence of 5 mol% of zinc hydride.[123] The zinc catalyst is itself conveniently synthesized *in situ* by the reduction of Zn(2-ethylhexanoate)$_2$ with $NaBH_4$. Reductions are typically complete in 4 h at 70 °C in diisopropyl ether; esters and lactones are reduced, as are ketones and aldehydes, though the reagent is very sensitive to steric environments. Epoxides are also reduced slowly, with terminal epoxides reacting much faster than their internal and/or more sterically hindered counterparts. Carboxylic acids, nitriles, lactams, and nitro compounds are essentially inert under these reaction conditions. Beller

Table 4 Titanium-catalyzed reductions of esters with silanes



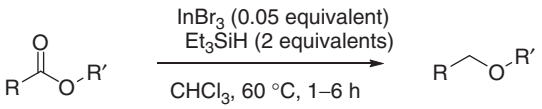
Entry	Substrate	Catalyst (loading)	Silane	Product	Yield (%)
1		Cp_2TiCl_2 + *n*BuLi (5 mol%)	$(EtO)_3SiH$		88
2		Cp_2TiCl_2 + *n*BuLi (5 mol%)	$(EtO)_3SiH$		78
3		Cp_2TiCl_2 + *n*BuLi (5 mol%)	$(EtO)_3SiH$		87
4		Cp_2TiCl_2 + EtMgBr (5 mol%)	PMHS		75
5		$Ti(Oi\text{-}Pr)_4$ (5 mol%)	$(EtO)_3SiH$		88
6		$Ti(Oi\text{-}Pr)_4$ (100 mol%)	PMHS		87
7		$Ti(Oi\text{-}Pr)_4$ (5 mol%)	$(EtO)_3SiH$		83
8		$Ti(Oi\text{-}Pr)_4$ (100 mol%)	PMHS		81
9		$Ti(Oi\text{-}Pr)_4$ (5 mol%)	$(EtO)_3SiH$		70

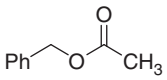
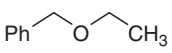
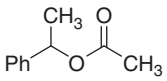
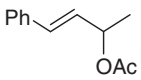
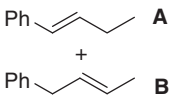
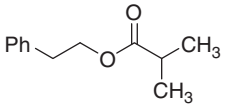
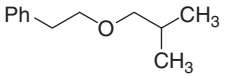
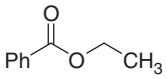
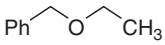
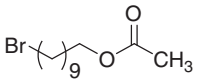
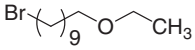
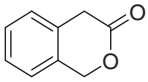
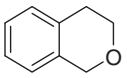
and coworkers have shown that $Zn(OAc)_2$ can also be used as a catalyst, although in this case the more expensive diethoxymethylsilane is needed (PMHS was unreactive) and the reactions typically required 24 h at 65 °C for completion.[124]

Nagashima et al. have reported using a triruthenium carbonyl cluster catalyst with ethyldimethylsilane which can reduce esters to alcohols or ethers in dioxane and tetrahydropyran, respectively.[125] However, mixtures of alcohol and ether products do occur except in some cases; methyl esters are more likely to give the alcohol product when using dioxane, whereas ethyl esters can be converted to ethers in tetrahydropyran. Lactones are selectively reduced to cyclic ethers, and carboxylic acids and amides to alcohols and amines, respectively. Similarly, the rhodium complexes $[RhCl(cod)]_2$ or $[RhCl(PPh_3)_3]$;[126] the molybdenum complexes $[MoO_2Cl_2]$[127] or $[MO_2(acac)_2]$;[128] or the iron complexes $[Fe_3(CO)_{12}]$[129] or $[(CpFe(CO)_2PCy_3)^+(BF_4)^-]$[130] have been reported to be effective in this reaction as well.

However, the reduction of esters to ethers is much rare. In reported methods, triethylsilane is used as the reductant in the presence of TMSOTf and $TiCl_4$[131] or $BF_3 \cdot OEt_2$.[132] However, a more synthetically useful procedure involves the use of indium bromide and triethylsilane as the hydride source.[133] Aliphatic esters are readily reduced, but those derived from aromatic acids are very sluggish in the reaction (**Table 5**, entry 5). Substituents on the benzylic position of benzyl esters or allylic esters undergo deacetoxylation of the substrate (**Table 5**, entries 2 and 3). This reagent does not react with thioesters and primary or secondary amides, whereas carboxylic acids are only moderately reduced under these conditions (using TMDS works more efficiently, see Section 8.10.2.4).[31] In one example a ketone resulted in a dimeric, symmetric ether product being obtained in good yield, suggesting that these groups would be unsuitable in this reaction.

Table 5 Reduction of esters using $InBr_3$–Et_3SiH



Entry	Substrate	Product	Yield (%)
1			69
2			76
3		 **A** + **B** 7:3 **A**:**B**	60
4			71
5			10
6			73
7			84

8.10.6 Reduction of Lactones

The reduction of lactones to alcohols proceeds in a similar fashion to that of esters. Of importance though is the selective reduction to cyclic ethers, which is possible with a number of different reagents. However, these transformations are not popular in the literature owing to a lack of an easy and general one-step method.

8.10.6.1 Hydrogenation Reactions

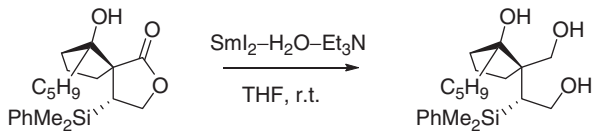
Simply put, the hydrogenation of lactones to diols can be achieved in the same ways described under the hydrogenation of esters (see Section 8.10.5.1).[134] However, unlike the catalytic hydrogenation of esters, the reduction of lactones with hydrogen can readily lead to cyclic ethers through judicious choice of catalyst and conditions. Much of the work in this area has been dominated by the need to add value to biomass-derived compounds such as lignocellulose (plant waste).[135] Thus, for example, a number of industrial procedures have used heterogeneous catalysis to convert γ-butyrolactone to tetrahydrofuran with transition metal combinations such as ruthenium–molybdenum–tin[136] or palladium–silver–rhenium.[137] γ-Butyrolactone is itself obtained from substrates such as maleic anhydride or succinic esters which are in turn derived from plant sugars. In other work the mechanism has been examined using a nickel–cobalt catalyst[138] and a CuO–ZnO catalyst,[139] and involves the initial formation of 1,4-butanediol before a dehydrogenative cyclization to THF and not, as might be thought, a direct reduction of the lactone to the ether. For this reason, it is not surprising that the conditions needed to reduce a lactone to a cyclic ether are even higher than those for the reduction of esters to alcohols.

γ-Valerolactone has been identified as an important biomass-derived platform chemical owing to it having a number of interesting properties (high boiling and flash points, low vapor pressure, less toxic than ethanol, and pleasant smelling).[140] It can also be converted to 2-methyltetrahydrofuran, which is an important renewable alternative to tetrahydrofuran. Work has focused on this task and homogeneous catalysis using ruthenium has taken central stage, though few reports exist. Horváth et al. demonstrated that γ-valerolactone could be converted to 2-methyltetrahydrofuran using $Ru(acac)_3$, PBu_3, and NH_4PF_6 (as cocatalyst) and 80 bar H_2 at 200 °C for up to 2 days.[141] These harsh conditions were examined by Klankermayer and Leitner who expanded on this study.[142] First, their findings demonstrated that the tridentate phosphine, 1,1,1-tris(diphenylphosphinomethyl)ethane

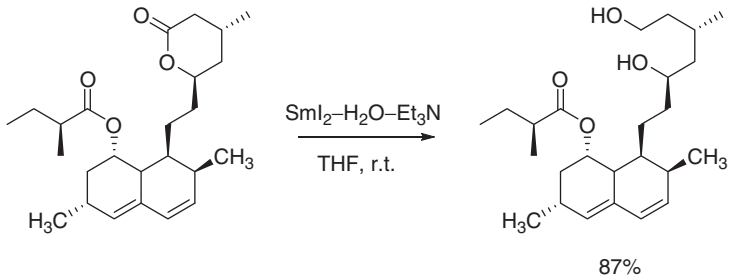
(triphos – which had already shown promise in reducing esters to alcohols)[62–64] was better suited than the monophosphine used by Horváth. They also demonstrated that the NH_4PF_6 cocatalyst was important in catalyzing the dehydration of the initial diol to 2-methyltetrahydrofuran, though in their case it was not that efficient. Through optimization they identified an acidic ionic liquid, 1-butyl-2-(4-sulfobutyl)imidazolium-*p*-toluenesulfonate, which in combination with NH_4PF_6 gave a 92% yield of cyclic ether when hydrogenating at 160 °C and 100 bar H_2. However, these conditions are not easily replicated in a normal synthetic laboratory. Therefore, notwithstanding the fact that chemoselectivity would likely be very poor, these processes are of more interest to ton-scale industrial reactions.

8.10.6.2 Electrochemical and Single Electron Reductions

The electrochemical and single electron reductions of esters (see Section 8.10.5.2) apply to lactones and result in diols. Importantly samarium(II) iodide when combined with excess water and amine (typically triethylamine) produces a powerful single electron reductant that will reduce lactones to diols.[143] Although this reagent combination is very powerful and will reduce aldehydes, ketones, carboxylic acids, esters, amides, and nitriles, it can be used to reduce difficult lactones (equation 17), which under conventional conditions only resulted in decomposition products. Furthermore, the reduction can be chemoselective and it has been shown that a lactone can be reduced in the presence of an ester in one example (equation 18).



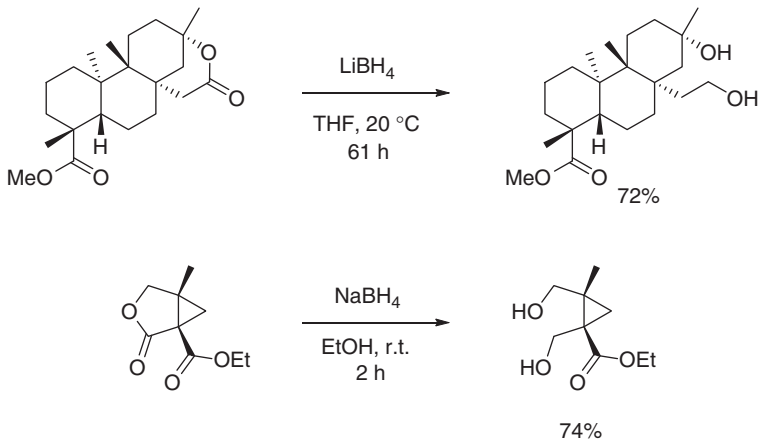
(17)



(18)

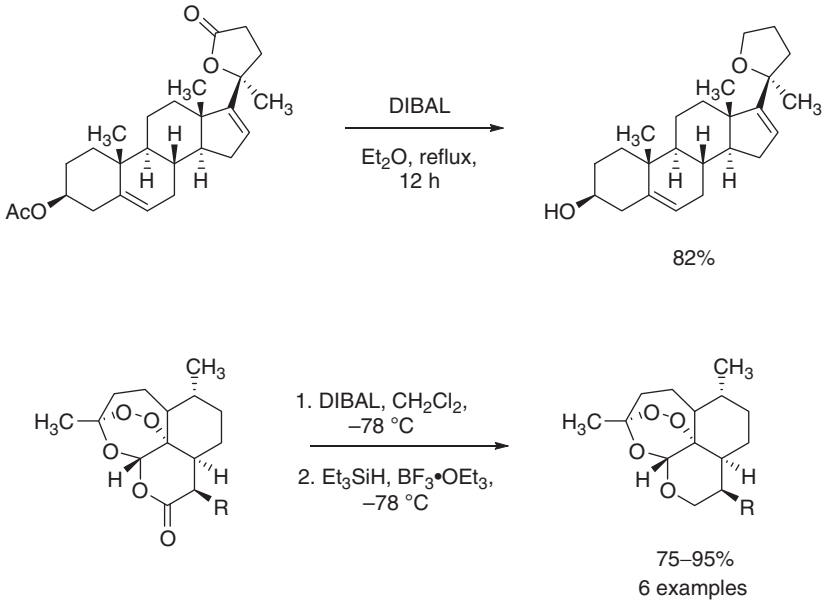
8.10.6.3 Reductions with Metal Hydride Reagents

The reduction of lactones to diols with metal hydride reagents can be achieved in much the same way as that already described for esters. Usually, the reduction of lactones is faster than esters and so it is sometimes possible to achieve chemoselective reduction in the presence of these groups (Scheme 13).



Scheme 13

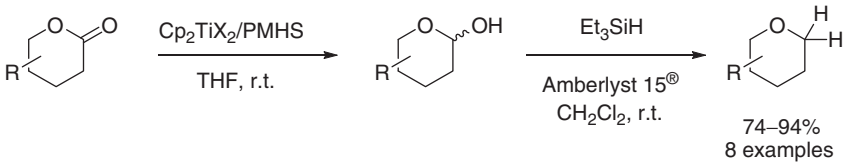
Lactones can also be reduced to cyclic ethers with $LiAlH_4$, DIBAL, or $NaBH_4$ with boron trifluoride provided there is greater substitution at the alcohol side of the lactone.[117] The yields and success of these reductions is thus variable. DIBAL has been more extensively used to partially reduce lactones to lactols (*see* Chapter 8.11), which are then further reduced to the cyclic ether using $BF_3 \cdot OEt_2$ and Et_3SiH.[144] Finally, one report demonstrated that crown lactones could be reduced to the crown ether using only $LiAlH_4$. Since this reaction does not normally work with lactones, the authors suggest that lithium cation complexation must be important in preventing the macrocyclic ring from opening[145] (Scheme 14).



Scheme 14

8.10.6.4 Reductions with Silanes

The methods discussed under reduction of esters apply equally to the reduction of lactones. No specific chemoselectivity has been reported between esters and lactones when using silane reductive methods, though in some cases the conversion to ethers is more readily achieved with lactones, for example, when using Nagashima's ruthenium carbonyl cluster catalyst.[125] Buchwald has shown that lactones can be partially reduced to lactols (*see* Chapter 8.11) and then subsequently reduced to ethers using triethylsilane and Amberlyst 15® ion-exchange resin (Scheme 15).[146] The procedure is fairly efficient at reducing a number of cyclic lactones in good-to-excellent yield comparing favorably (or better) to other popular two-step methods such as the abovementioned DIBAL reduction followed by treatment with $BF_3 \cdot OEt_2$ and Et_3SiH. These conditions will not tolerate carboxylic acids, amides, ketones, and aldehydes.



Scheme 15

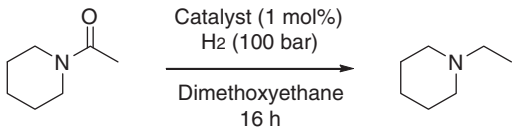
8.10.7 Reduction of Amides and Lactams

The reduction of amides more often results in the amine product being obtained, though a number of methods exist that favor the alcohol product formation under specific conditions (e.g., lithium aminoborohydride). Overall, the reduction of amides is complicated by the fact that primary, secondary, and tertiary amides all react differently depending on the conditions used. The metal hydride reagents once again dominate as the most commonly employed reagents ($LiAlH_4$ alone is used in just more than 50% of all amide reductions), whereas hydrogenation finds greater application within the industrial-scale procedures. Lactams are almost always reduced to the cyclic amine, except where an electron-withdrawing group is attached to the nitrogen atom. In this case the ring-opened reduced product is formed.

8.10.7.1 Hydrogenation Reactions

The hydrogenation of amides and lactams to amines is considered to be one of the most difficult reactions within the carboxylic acid derivatives. The reason for this is that much higher temperatures and pressures of hydrogen are needed (compared with the reduction of carboxylic acids and esters), and these reductions are prone to give mixtures of products. Primary carboxamides are for instance prone to give secondary amines; for example, when lauramide (dodecanamide) was hydrogenated using copper chromite as a catalyst at 250 °C under 300 bar of hydrogen it gave dodecylamine (48%) and didodecylamine (49%).[147] Other catalysts can be used, for example, Raney nickel, Raney cobalt, ruthenium on carbon, and rhenium oxide,[148] but the addition of ammonia to the reaction medium has been the main solution to reducing the mixtures of amines obtained.[149] In the mid-1990s Fuchikami et al. explored bimetallic catalysts based on Group 8 to 10 late transition metals, and Group 6 or 7 early transition metals in an extension of their study of these systems on carboxylic acids (see Section 8.10.2.1).[150] As in their earlier findings, the group demonstrated that bimetallic catalyst systems were particularly effective with combinations of rhodium–rhenium, rhodium–molybdenum, and ruthenium–rhenium being very effective (Table 6). It was interesting to note that these combinations worked with either homogeneous or heterogeneous catalyst precursors or with a combination of heterogeneous and homogeneous catalyst. It was also reported that no alcohol or hydrocarbon byproducts were observed. A number of simple amides were evaluated using their preferred catalysts system of $Rh_6(CO)_{16}$–$Re_2(CO)_{10}$ with generally good-to-excellent yield. Aromatic rings are not tolerated and are rather efficiently reduced to cyclohexyl groups. A primary carboxamide (*n*-hexylamide) requires an additive in the form of diethylamine to prevent the formation of dihexylamine; lactams are also efficiently reduced. Although not reported in this study, these conditions are unlikely to tolerate any other reducible groups owing to the harsh conditions employed.

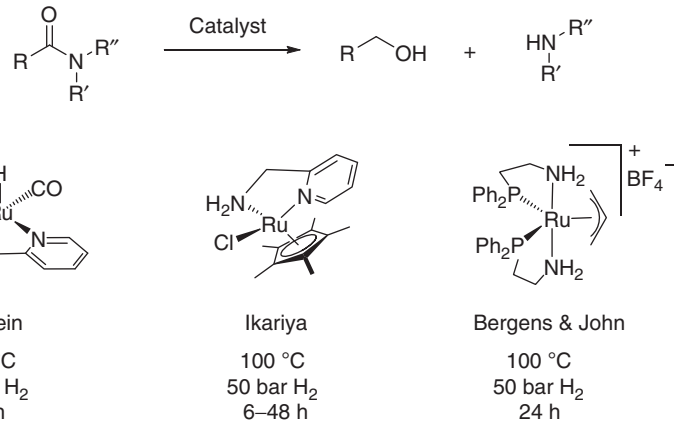
Table 6 Fuchikami's bimetallic hydrogenation of amides (selected results)



Entry	*Catalyst 1*	*Catalyst 2*	*Temp (°C)*	*Yield (%)*
1	$Rh_6(CO)_{16}$	$Re_2(CO)_{10}$	160	96
2	$Rh_6(CO)_{16}$	$W(CO)_6$	160	50
3	$Rh_6(CO)_{16}$	$Mo(CO)_6$	160	98
4	$Ru_3(CO)_{12}$	$Re_2(CO)_{10}$	160	96
5	Rh/C	Re/C	170	98
6	$Ru_3(CO)_{12}$	Re/ Al_2O_3	170	94

The Whyman group has examined this bimetallic reaction in greater detail and has reported some important observations. First, they have shown that the catalysts in these reactions are most certainly heterogeneous in nature since the homogeneous precursors generate the active heterogeneous catalytic species under the reaction conditions. Second and most important, the ratio of the metals used is critical to the performance of the catalyst; using a Mo:Rh = 0.55,[151] Mo:Ru = 0.50,[152] Re:Ru = 0.3 − 1.5,[153] or Re:Rh = 0.8[153] ratio allows for excellent yields of primary amine to be obtained without the addition of ammonia or amines. Having studied these combinations in detail, the authors have highlighted some of the key features and commonalities of each system,[153] that is, the synergistic behavior of each catalyst pair in promoting amide reduction, the high selectivities of these catalysts toward hydrogenation of the primary amide cyclohexylamide to cyclohexylamine, and their recyclability. Also noted was that the Ru/Mo, Rh/Mo, and Rh/Re combinations required significant initiation periods before catalysis began, whereas Ru/Re only required heating to the reaction temperature. However, catalysts using rhenium as the modifier required higher temperatures (150–160 °C) and pressures (50–100 bar) compared with those modified with molybdenum (130–140 °C, 20–100 bar).

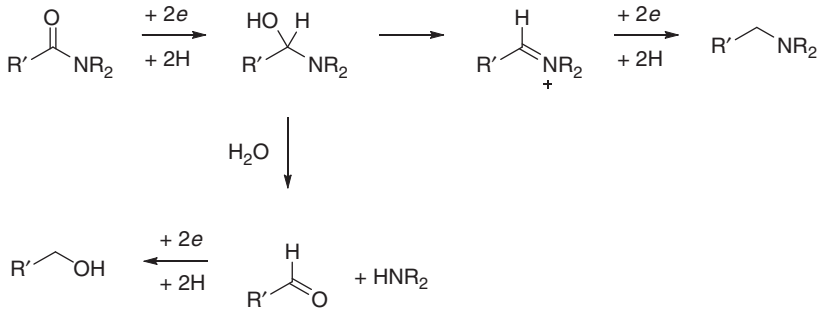
There have been very few reports on homogeneous catalysis of amide reductions with hydrogen. One of the earliest appeared in 2007 from Cole-Hamilton et al. and demonstrated that primary amides could be hydrogenated by a Ru-triphos catalyst system (triphos = 1,1,1-tris(diphenylphosphinomethyl)ethane) providing ammonia was present (140 °C, 40 bar H_2).[154] However, homogeneous catalysts have more often resulted in the cleavage of the C–N bond of the amide to give an amine and alcohol product. To this end, ruthenium catalysts by Milstein,[155] Ikariya,[156] and Bergens and John[157] have all demonstrated this ability on a number of different substrates (equation 19). It is important to note that aromatic rings are not reduced under these homogeneous conditions. The origin of the selectivity of C–N cleavage versus the conventional C–O cleavage more typically observed under heterogeneous conditions has been studied computationally by Cantillo using the Milstein catalyst.[158] It was found that the calculated energy barrier for C–N cleavage was 10 kcal mol^{-1} lower than that of C–O cleavage. This explained the unusual selectivity in these reactions since the temperatures were significantly lower than in the case of heterogeneous catalyzed one. Indeed this is further supported by the fact that in the heterogeneous reactions, lower temperatures are also associated with alcohol formation.[151–153]



(19)

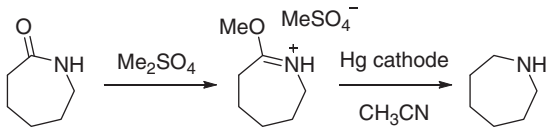
8.10.7.2 Electrochemical and Single Electron Reductions

The electrochemical reduction of amides, lactams, and imides is known and has been well-studied, although a number of different products can be obtained depending on many different factors (Scheme 16).[12] For example, early workers employed extreme conditions (50–90% sulfuric acid as solvent and analyte)[159,160] using a lead cathode in order to obtain amines. The strongly acidic conditions are needed to force the initially formed carbinolamine to form the iminium ion, which is then further reduced to the amine (Scheme 16). This process is fairly general for tertiary or secondary amides, though primary amides are more difficult to reduce since the intermediate iminium salt is less stable under the conditions employed. However, amides can also be electrochemically reduced to give an amine and an alcohol, that is, the N–C bond of the amide is cleaved. This is promoted when the solvent is an alcohol or amine and an appropriate electrolyte is used, for example, tetraalkylammonium[161] or alkali metal salts.[162] The cleavage may be stopped at the aldehyde stage, but yields are very low and not synthetically useful. Both aliphatic and aromatic amides have been cleaved in these ways, but the studies have not been extensive nor have they looked at complex structures. One interesting report has demonstrated a selective reductive cleavage of a primary amide in the presence of a lactone,[163] its success being owed to the general difficulty in reducing esters electrochemically (see Section 8.10.5.2). Others have also observed reductive cleavage of *N*,*N*-dimethyl amides under the same conditions that were developed for the electrochemical reduction of esters (i.e., magnesium anode and cathode and *tert*-butanol as the proton source).[87]



Scheme 16

The electrochemical reduction of phthalimides has also been studied extensively and various intermediate reduction products have been isolated by several authors.[164] For example, isoindolines can be synthesized by full reduction of phthalimides under strongly acidic conditions,[165] whereas hydroxyphthalimidines, phthalimidines, and phthalides have all been observed.[166] Finally, cyclic lactams have been reduced electrochemically to cyclic amines by first converting the amide functionality to the methyl imidate and then reducing over a mercury electrode (Scheme 17).[167]



Scheme 17

Dissolving metal reductions of amides have been reported to give amines, primary alcohols, and aldehydes.[168,169] However, none of these products is produced in any significant amount even when simple aliphatic amides have been used. Thus, little application of this method is found in the synthetic literature.

8.10.7.3 Reductions with Metal Hydride Reagents

8.10.7.3.1 Aluminum hydride reagents

LAH is extremely good at reducing primary, secondary, and tertiary amides to their corresponding amines. Tertiary amides are generally more conveniently reduced at 0 °C, but secondary and primary amides require the more forceful conditions of heating in THF under reflux. Yields are generally excellent and chiral centers α to the carbonyl carbon remain unracemized. The obvious disadvantage to using $LiAlH_4$ is that it is a powerful reductant and readily reduces almost all carbonyl-containing groups, except carbamates (CBz and Boc protecting groups can be stable to $LiAlH_4$ reductions). Lactams are also readily reduced by this popular choice of reagent with the six-membered piperidinone lactams being more readily reduced than the five-membered pyrrolidinone ones.[170] This fact has been, for example, exploited in the total synthesis of (–)-nakadomarin by Dixon and coworkers.[171] β-Lactams are however more difficult to reduce with $LiAlH_4$ and frequently result in bond cleavage and isolation of the substituted 3-aminopropanol. The preferred reagent for these reactions is monochloroalane (AlH_2Cl) prepared by allowing a 1:1 mixture of $LiAlH_4$ and $AlCl_3$ to react before the reduction reaction.[172] Importantly, AlH_2Cl also maintains the stereochemical integrity of the β-lactam rings. This reagent has also been used instead of $LiAlH_4$ for reducing amides, in general being slightly milder than $LiAlH_4$, thus tolerating nitro[173] and alkyl-halide[174] groups. Although AlH_2Cl is known to behave like a Lewis acidic reducing agent, reductively cleaving acetals to ethers, these groups are stable under the conditions needed to reduce β-lactams to azetidines.[175] Red-Al® (sodium bis(2-methoxyethoxy)aluminum hydride) also finds application in the reduction of amides and is useful in that it is soluble in aromatic solvents allowing higher reaction temperatures to be used. Other alkoxyaluminum hydride reagents can reduce amides, for example, $LiAlH(OMe)_3$, though these are infrequently used in the literature. Sterically hindered reagents such as $LiAlH(O\text{-}t\text{-}Bu)_3$ are also unsuitable. Likewise, DIBAL has been used to reduce amides to amines and can be useful for the reduction of unsaturated amides. The reductants such as DIBAL and Red-Al® are more typically used for the partial reduction of amides to aldehydes (*see* Chapter 8.11). **Scheme 18** contains a number of examples of aluminum hydride reductions of amides and lactams, highlighting the chemoselectivity of the various reagents.

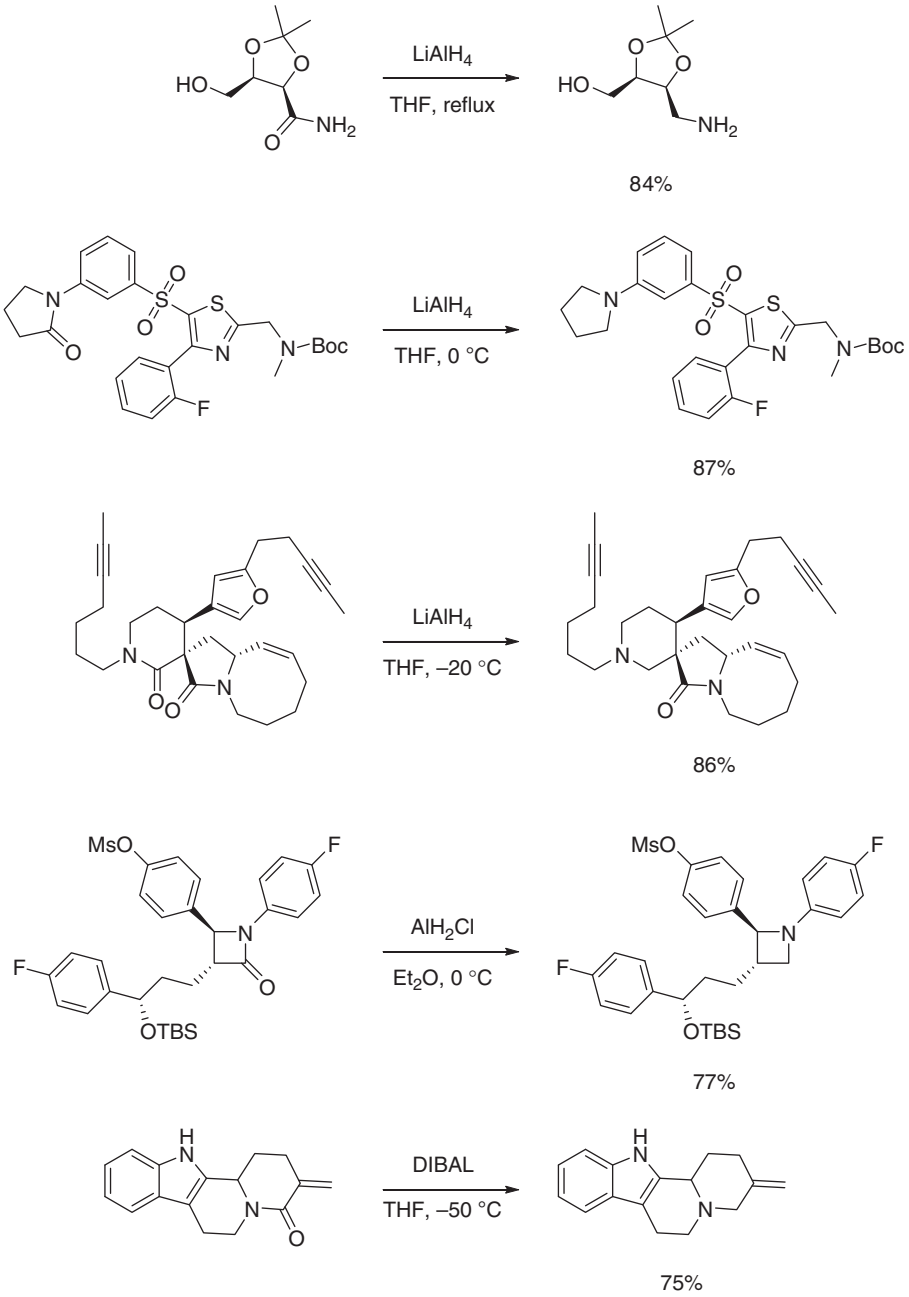
8.10.7.3.2 Boron hydrides

Boranes are very effective reagents for the reduction of amides to amines and have the advantage of being slightly more chemoselective than the aluminum hydrides (**Scheme 19**). For both $BH_3 \cdot THF$ and $BH_3 \cdot SMe_2$ their tolerance of ester groups makes them ideal choices for amide reduction especially where the ester is required to be intact. Other functional groups such as alkyl halides, carbamates, epoxides, and nitro groups are also tolerated, but the Achilles heel of the borane reagents remains their reactivity to unsaturated carbon–carbon bonds. It should also be noted that the initial product is the amino–boron adduct which needs to be cleaved on work-up. This is often not a problem with tertiary or aromatic amines, but primary and secondary aliphatic amines may require vigorous conditions to hydrolyze the adduct, for example, refluxing in 2 M HCl. Hall and coworkers have reported that a mild oxidative work-up with iodine can also be used, particularly in the context of solid-phase synthesis.[176] The reduction of lactams with boranes results in the cyclic amine except for β-lactams which are reduced to β-amino alcohols. In this case, the use of AlH_2Cl mentioned in the previous section is preferable. Since reduction of the five-membered γ-lactams proceeds slower than that of the six-membered δ-lactams, chemoselectivity can be obtained in systems that contain both these ring systems (see **Scheme 18** for a similar example with $LiAlH_4$).

In short, alkyl-substituted boranes are not suitable reagents for the reduction of amides to amines. Thexylborane and disiamylborane have been reported to give aldehydes from tertiary amides (*see* Chapter 8.11) and 9-BBN reduces tertiary amides to the tertiary amine without any advantage over borane.

The borohydride reagents are less reactive than the boranes and when used alone generally require more forcing conditions to reduce amides. The exception to this is when lactams have an electron-withdrawing group on the nitrogen atom (i.e., as a carbamate or sulfamate) in which case the lactam undergoes facile ring-opening reduction with sodium borohydride at room temperature (**Scheme 20**).

For tertiary amides the use of $NaBH_4$ in refluxing pyridine can give tertiary amines in moderate yield, whereas secondary and primary amides were not reduced (primary amides were found to give nitriles, albeit in low yields).[177] However, in a more practical general approach, $NaBH_4$ is frequently converted to borane *in situ* via the addition of a number of reagents. Sulfuric acid,[178] iodine,[27,179] and $BF_3 \cdot OEt_2$[21] are common additives in this regard and have been widely used. The advantages of these systems is that the cost is less than using purchased $BH_3 \cdot THF$ or $BH_3 \cdot SMe_2$ and is also considered to be safe in handling at larger scales. Other additives to sodium borohydride such as the acids HCl or $MeSO_3H$;[180] methylating agents such as MeI, Me_2SO_4, or MeOTs;[181] chlorotrimethylsilane[28] or transition-metal salts such as $CoCl_2$ or $NiCl_2$[182] have also been used but without advantage over the ones already mentioned and have therefore been infrequently reported. Sodium borohydride can also be used if the amide is initially converted to the Vilsmeier salt with $POCl_3$ and then reduced.[183] This procedure works with amides and lactams in the presence of esters, but has not been widely adopted in the literature. $LiBH_4$ can be used to reduce primary amides to amines or tertiary amides to alcohols through careful tuning of the solvent conditions;[111] the reactions are conducted in diglyme while slowly adding 4 equivalents of methanol. Secondary amides and carboxylate salts are resistant to reduction under these

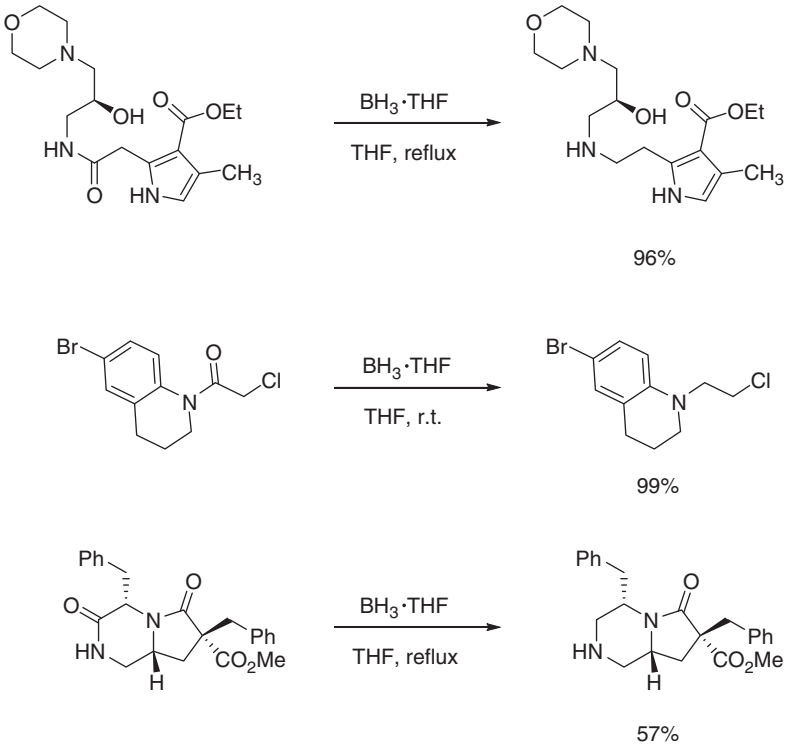


Scheme 18

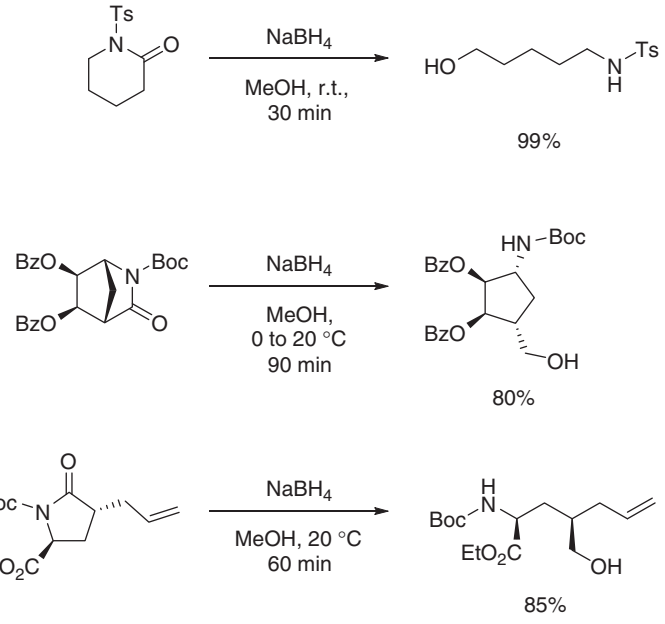
conditions, but esters are readily reduced (see Section 8.10.5.3.2). In practice though, this too has not been readily applied in the literature.

Many borohydride reagents that have been substituted by sulfur-, oxygen-, or nitrogen-containing ligands have been examined for their potential as amide reductants. The acyloxyborohydrides $NaBH_3(OAc)$ and $NaBH_3(O_2CCF_3)$ have been very successful in this regard and are used fairly frequently to reduce amide groups.[184] They are synthesized *in situ* from a 1:1 mixture of sodium borohydride and acetic or trifluoroacetic acids. Sodium acetoxyborohydride readily reduces primary and secondary amides to amines in refluxing dioxane, but tertiary amides are only poorly reduced unless sodium trifluoroacetoxyborohydride is used. Esters and *N*-Boc groups are resistant to reduction though other carbamates and nitriles can be reduced when $NaBH_3(O_2CCF_3)$ is used (**Scheme 21**).

An important class of reducing agents is the lithium aminoborohydrides ($LiBH_3NR^1R^2$) which reduce only tertiary amides to either alcohols or amines.[112] Primary and secondary amides are left untouched even in refluxing THF, otherwise other groups such as ketones, aldehydes, esters, azides, and epoxides are reduced. Choosing the course of the reduction of a tertiary amide to either

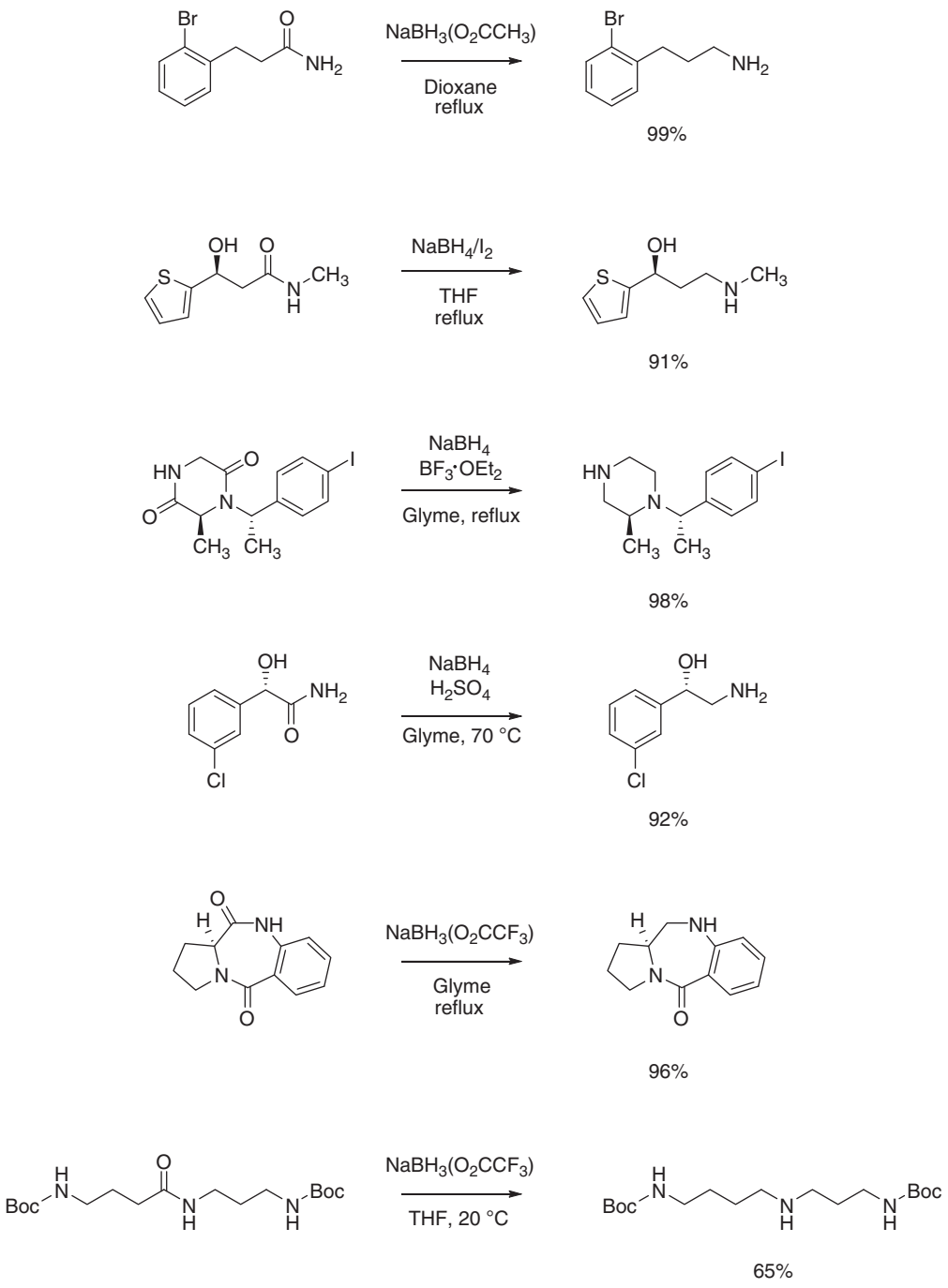


Scheme 19



Scheme 20

alcohol or amide resides in steric and electronic tuning of the reagent and substrate. Thus, unhindered tertiary amides (e.g., *N,N* dimethylamides) give the alcohol product, but more sterically demanding amides can be reduced to amines if a sterically demanding lithium aminoborohydride (e.g., $LiBH_3Ni\text{-}Pr_2$) were used (Schemes 22 and 23). These reagents have the advantages of the borohydrides (dry air stable and easy to handle) with the activity closer to that of the aluminum hydrides. Myers has used $LiBH_3NH_2$ to reductively cleave the pseudoephedrine chiral auxiliary from amido-substrates (Table 7).[185] It should be noted that alkyl halides can alkylate the amino group of the reagent giving a tertiary amine product.[186]



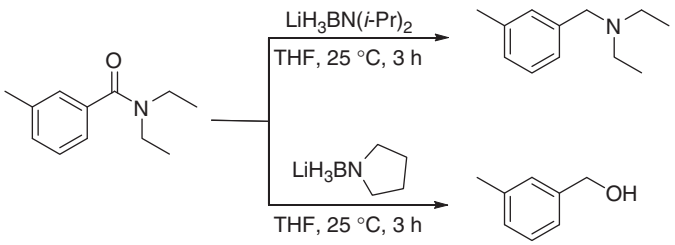
Scheme 21

Tertiary amines can also be reduced to alcohols with $LiBHEt_3$ (Super-Hydride®) and this is a frequent choice for such reductions. Primary and secondary amides are not reduced since the initial amide salt is stable and poorly electrophilic.

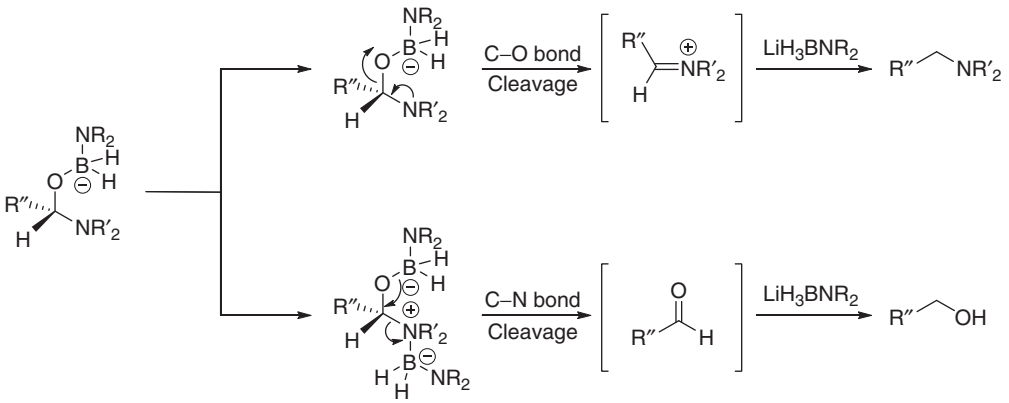
8.10.7.4 Reductions with Silanes

The reduction of amides to amines with silane reducing agents has been studied aggressively since the late 1990s. In general, these reductions often have the advantage of being chemoselective in that esters, epoxides, nitriles, and other sensitive functional groups are not reduced. The reduction of primary amides is however a challenge and frequently dehydration to the nitrile is observed.

An early study employed diphenylsilane (Ph_2SiH_2) in the presence of $[RhH(CO)(PPh_3)_2]$ as a catalyst to reduce tertiary amides to their corresponding amines at room temperature in THF. Lactams and imides are also fully reduced, but esters and epoxides are

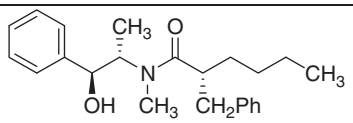
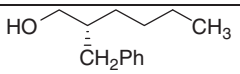
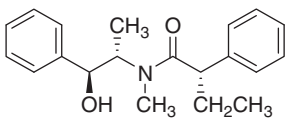
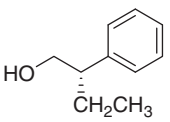
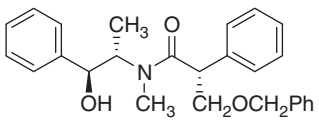
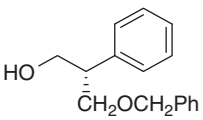
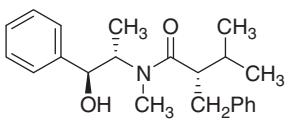
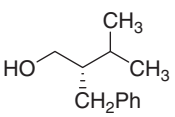
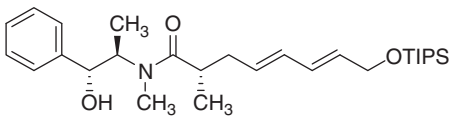
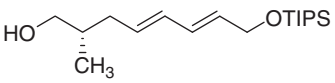


Scheme 22



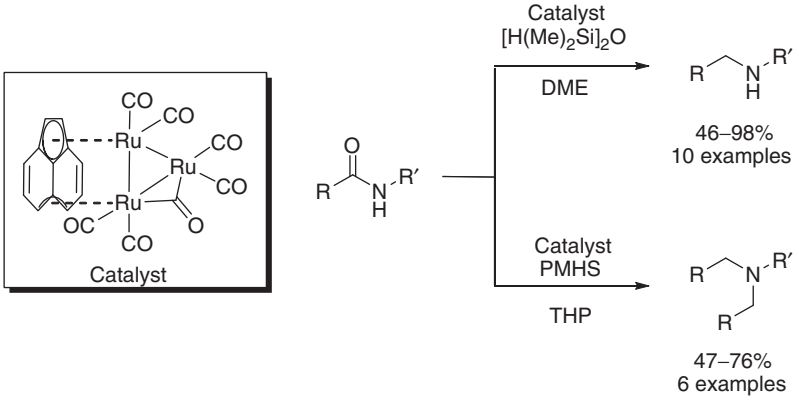
Scheme 23

Table 7 Use of lithium amino borohydride in the reduction of alkylated pseudoephedrine amides to primary alcohols

Entry[a]	*Substrate*	*Product*	*Yield (%)*
1			92
2			90
3			88
4			88
5			84

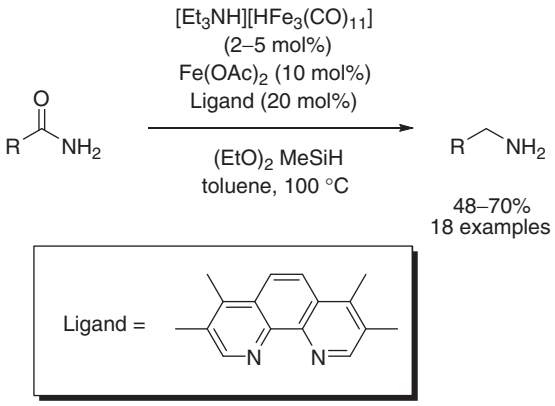
[a]Reactions run with 4–4.5 equivalents of lithium amino borohydride generated *in situ* at 0 °C.

not.[187] Others have shown that a wide range of transition metal catalysts can be used for this reaction, for example, $[Ru_3(CO)_{12}]$, $[Os_3(CO)_{12}]$, and $[Mn_2(CO)_{10}]$, cleanly affording tertiary and secondary amines (primary amines were obtained in moderate yields).[188] Indium,[189] iridium,[190] and molybdenum[191] catalysts have also been reported and are effective catalysts. Nagashima has extensively investigated this reaction showing that inclusion of an amine when using a ruthenium carbonyl cluster catalyst (Scheme 24) allowed tertiary amides to be reduced even in the presence of ketones.[192] Using the same catalyst secondary amides can be converted to amines with TMDS ($[H(Me)_2Si]_2O$). The cheaper PMHS results in tertiary amides in moderate-to-good yields (Scheme 24).



Scheme 24

Chloroplatinic acid ($H_2PtCl_6 \cdot 6H_2O$) has also been effective as a catalyst with either TMDS or PMHS,[193] interestingly without hydrosilylation of internal alkenes which is known to occur with other silanes and platinum catalysts (a terminal alkene did undergo hydrosilylation). The use of PHMS offers a useful way of purifying the product since the metal salt is absorbed onto an insoluble poly(siloxane) gel that forms during the reaction. This allows for simple filtration and evaporation for product isolation. The metal catalyst can then be recovered from the silicone resin. Likewise, iron complexes such as $[Fe_3CO_{12}]$ and $[Fe(CO)_5]$ can be used with PMHS or TMDS under thermal or photo-assisted conditions offering a more green approach to the reduction of amides.[129,194] Nitro groups are reduced to amines under these conditions, which then retards the reduction of the amide. Primary amides are not reduced, but rather undergo dehydration to nitriles, particularly with diethoxymethylsilane.[195] The solution is to use a mixture of two different iron catalysts in the presence of a phenanthroline ligand and diethoxymethylsilane as the reductant (Scheme 25).[196] Yields are moderate-to-good, with aliphatic primary amides giving slightly lower yields than the aromatic ones.

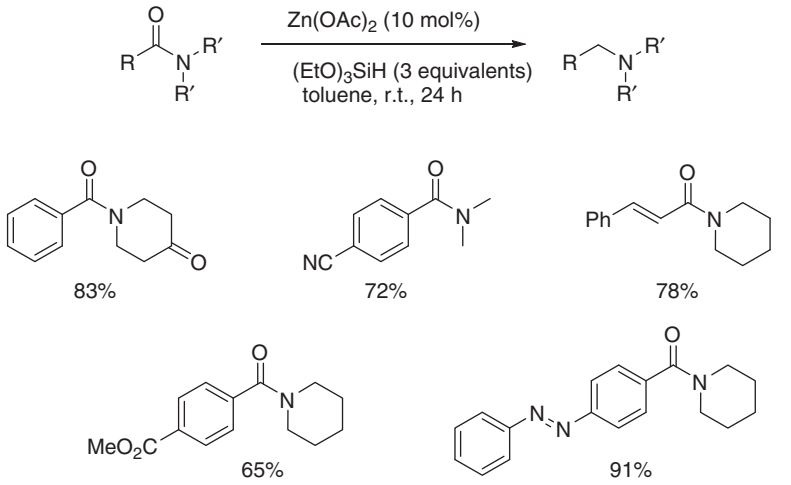


Scheme 25

Zinc acetate is another important catalyst in reducing tertiary amides, primarily due to it being cheaper and the conditions being milder.[197] Functional group tolerance includes esters, nitriles, nitro and diazo groups, alkenes, and ketones (Scheme 26).

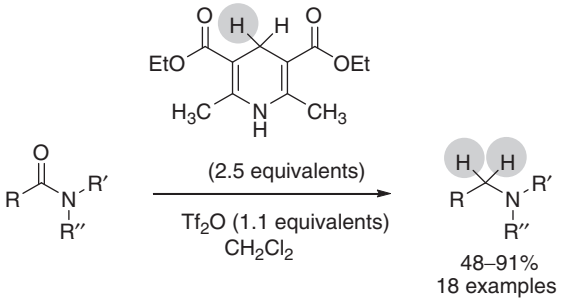
8.10.7.5 Hantzsch Ester Reduction

The Hantzsch Ester (HEH) is a readily available analog to the biological reductant nicotinamide adenine dinucleotide, which has found use in organic synthesis as a nonmetallic hydride donor. The hydride donated by HEH is however fairly weak and is more



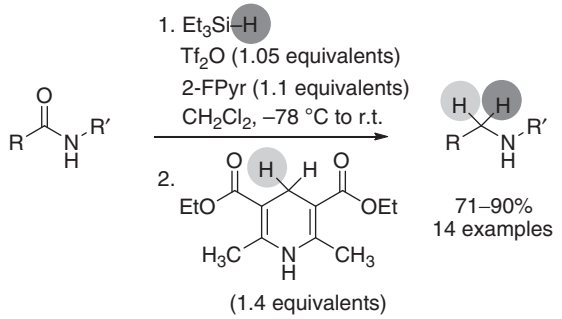
Scheme 26

typically used to reduce reactive systems such as imines and electrophilic olefins. Charette has demonstrated that tertiary amides can be activated by triflic anhydride and then successfully reduced with the HEH in good yields (Scheme 27).[198] Although the yields are variable depending on the substrate (steric hindrance is a negative factor), the reaction has a high degree of chemoselectivity similar to the silane reduction catalyzed by zinc acetate mentioned in the previous section. Thus, ketones, epoxides, esters, nitriles, alkenes, and alkynes are tolerated, making this one of the few highly chemoselective methods available.



Scheme 27

The reduction of primary and secondary amides are however not applicable to this method, giving a mixture of products. Rather it has been found that secondary amides can be reduced provided that they are first reduced to the imine with triethylsilane and triflic anhydride in the presence of 2-fluoropyridine (*see* Chapter 8.11) and then reduced again with the HEH (Scheme 28).[199] Yields are good-to-excellent and functional group tolerance is extensive (esters, nitriles, azides, alkenes, and alkynes).



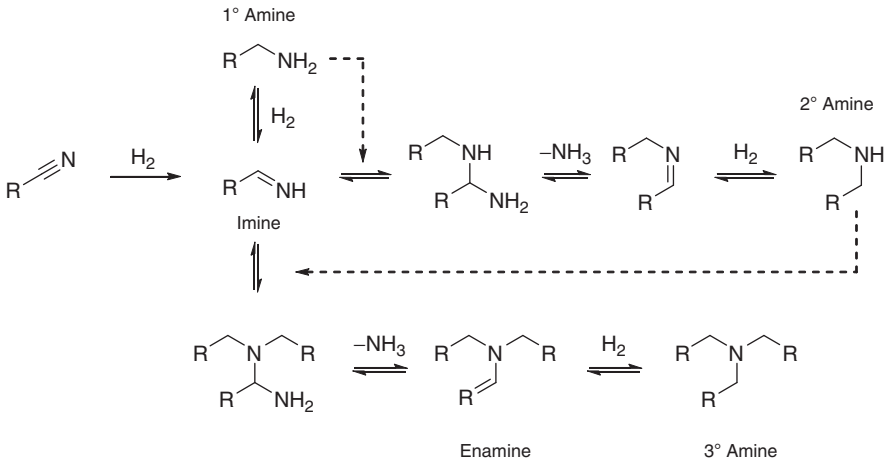
Scheme 28

8.10.8 Reduction of Nitriles

On the laboratory scale, hydrogen gas over Raney nickel is the reagent of choice for the reduction of nitriles because of its ready availability, chemoselectivity, and ease of use (barring the hazard it poses if it gets dry). Other readily available classical catalysts such as palladium on carbon or Adams' catalyst (PtO_2) are also popular. LAH is also extensively employed, but suffers from poor chemoselectivity; borane may therefore be a better choice if Raney nickel is unavailable. The silane reduction methods are not yet practical for general use.

8.10.8.1 Hydrogenation Reactions

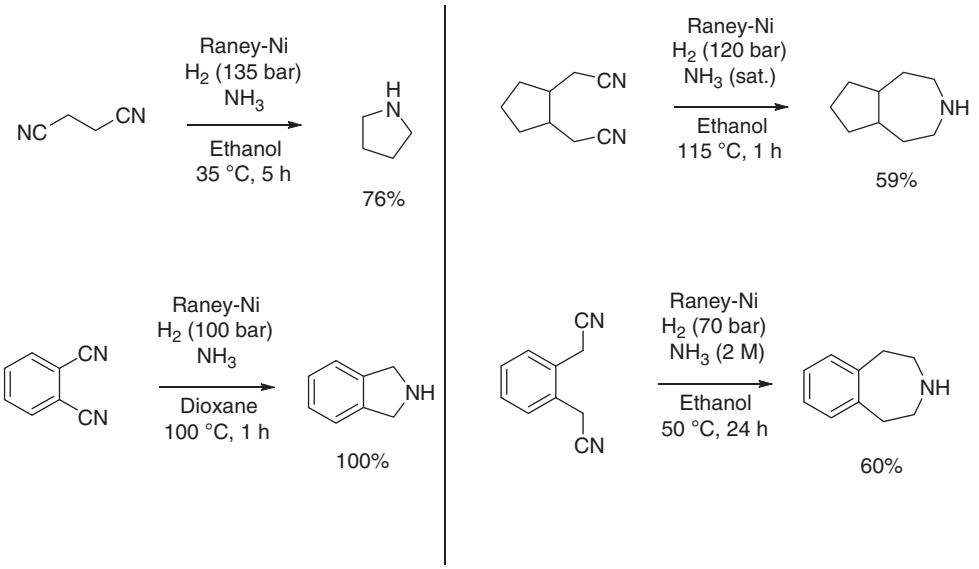
Considering the difficulty experienced in hydrogenating the various carboxylic acid derivatives mentioned in the previous sections, the hydrogenolysis of nitriles is much easier. As an example, heterogeneous catalysis in the gas phase is used industrially for the hydrogenation of adiponitrile to hexamethylene diamine, which is widely used in the synthesis of nylon. These catalysts are typically iron or nickel that has been doped with various elements such as phosphorus or silver. This process requires huge quantities of ammonia and very high temperatures (200 °C) to work, making it very unsuitable for laboratory work. The study of these mechanisms of hydrogenation on solid catalysts has been reviewed.[200] More commonly though are liquid-phase hydrogenations[201] where the reagent of choice is Raney nickel, although many other metals can be used. This reaction typically gives amines, though aromatic nitriles can give aldehydes under specific conditions (*see* Chapter 8.11). As in the hydrogenation of amides (see Section 8.10.7.1), the reaction is prone to giving mixtures of amines. This can be understood by looking at the simplified mechanism in **Scheme 29** (a more detailed treatment can be found in reference).[201] Essentially, the side products arise because the first intermediate is an imine that is prone to react with any nucleophiles that are present. Should this be the primary amine, then an aminal can be formed which on loss of ammonia gives a secondary imine that can then be reduced to the secondary amine. This secondary amine could now also react with the original imine in a similar way; if a β-hydrogen atom is present on the R-group, then an enamine can form and a tertiary amine side product can be observed.



Scheme 29

It is therefore not surprising that ammonia is an important component of the reaction since it minimizes the formation of secondary amines by shifting the transamination steps to occur with ammonia instead. Often using aqueous ammonium hydroxide is sufficient, though in some cases liquid ammonia is used.[202] With respect to the other reaction conditions: the temperature is generally less than 100 °C and hydrogen gas can be used at atmospheric pressure, though it is more common to increase this to 5 – 20 bar to improve the reaction rate, particularly with aromatic nitriles (50–100 bar). An important point should be made on the reduction of dinitriles, since these are prone to cyclize and result in cyclic amines (**Scheme 30**). The mechanism of this should be clear in that the transamination side reactions in **Scheme 29** can also occur intramolecularly. This reaction is however not typical of all dinitriles and is governed by the size of the ring formed (five- to seven-membered rings are more likely to form) and also whether the new ring will be part of a more stable bicyclic structure.

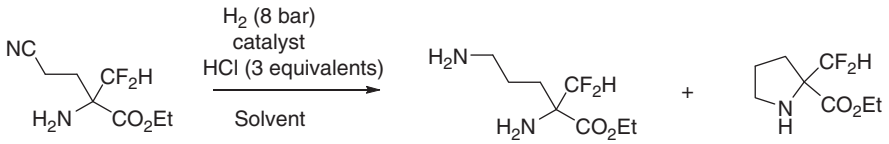
The use of Raney nickel to hydrogenate nitriles to amines is very common and accounts for approximately half of the hydrogenation procedures employed in the literature. The reason for this is the high chemoselectivity that this reaction enjoys, something not observed for the hydrogen reductions of other carboxylic acid derivatives which are themselves stable to the mild Raney nickel conditions employed here. Other groups stable to these conditions include aromatic rings, halides, ethers (including benzyl and silyl), benzylamines, sulfonamides, and sulfones. Imines, oximes, and ketones are however not stable and prone to



Scheme 30

coreduction. It should also be mentioned that transfer hydrogenation using Raney nickel and hydrazine under basic conditions has also been effective.[203,204] The use of formic acid as a hydrogen transfer reagent gives the aldehyde product (*see* Chapter 8.11).

Less common, but still effective as heterogeneous catalysts, are palladium (on charcoal), palladium hydroxide, and platinum oxide, and to a lesser extent rhodium. The palladium and platinum catalysts are more often used in the presence of an acid, which helps to minimize the formation of secondary amines. Hydrochloric acid and acetic acid are common choices, whereas using chloroform or dichloromethane as an additive allows for the *in situ* formation of HCl, which can be useful. The preferred choice of solid catalyst may not be trivial as can be exemplified by a report by Zhu et al. (equation 20).[205] This study on the reduction of an amino-nitrile revealed that cyclization was dependent on the catalyst used. Since the cyclized product was not wanted, their eventual solution was to form a Schiff base with the primary amine before hydrogenation with Raney cobalt.

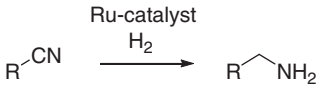


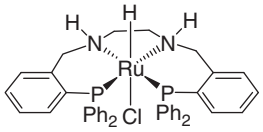
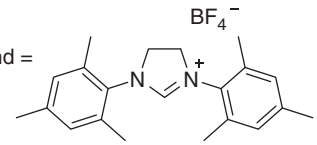
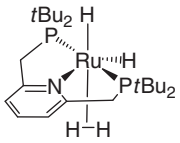
(20)

Catalyst	*Diamine (%)*	*Cyclized (%)*
Pd/C	2–5	95–98
Rh/C	41	49
Pt/C	71–81	19–29

Homogeneous catalysis has been less applied in this field, which is likely because it has not produced by any solutions that offer significant advantages over the heterogeneous ones. The reason for this may be due to the nitriles themselves preferring to coordinate to the metal through the nitrogen atom, rather than the π-system, which is necessary for reduction to occur. The imine and amine products would also deactivate the catalyst. Of the scarce reports, rhodium, iridium, and ruthenium have been examined with ruthenium being the most studied metal. One of the earliest reports (1979) on a homogeneous catalyst for nitrile hydrogenations looked at rhodium hydrido complexes.[206] The researchers reported that the $[RhH(PiPr_3)_3]$ complex was efficient at catalyzing the hydrogenation of a number of simple aliphatic nitriles to primary amines at room temperature and 1 bar hydrogen pressure in 20 h. Aromatic nitriles reacted much slower, but increasing the hydrogen pressure overcame this problem; olefins were unsurprisingly reduced. Importantly, only primary amines were observed, although the substrates studied were rather limited in scope and variety. The only report on iridium-based catalysis demonstrates poor selectivity for the primary amine products.[207] A number of ruthenium complexes have been synthesized and the conditions are summarized in **Table 8**. All of these complexes produced the primary amine selectively, but more work is needed to demonstrate a catalyst that is superior to the heterogeneous catalysts.

Table 8 Homogeneous ruthenium-based catalysts



Entry	Catalyst	Conditions	Yield (%)	Notes	Reference
1		H_2 (14 bar) KO*t*Bu/KH 20 °C 3 h	100 (conversion)	Only benzonitrile tested	208
2	[Ru(cod)methylallyl$_2$] Ligand = PPh_3	H_2 (50 bar) KO*t*Bu 80–140 °C 6 h	60–99	Various aromatic and heteroaromatic nitriles	209
3	[Ru(cod)methylallyl$_2$] Ligand = 	H_2 (50 bar) KO*t*Bu 80–140 °C 1–2 h	63–99	Various aromatic and heteroaromatic nitriles. Aryl methyl ester was tolerated	210
4	[Ru(cod)methylallyl$_2$] Ligand = 	H_2 (35 bar) KO*t*Bu 40–80 °C 1–16 h	12–88	Yields highly variable for aromatic and heteroaromatic substrates. One aliphatic substrate reacted poorly	211
5		H_2 (75 bar) H_2O 135 °C 24 h	59–96	Simple aromatic and aliphatic substrates. Inclusion of H_2O is essential	212

8.10.8.2 Electrochemical and Single Electron Reductions

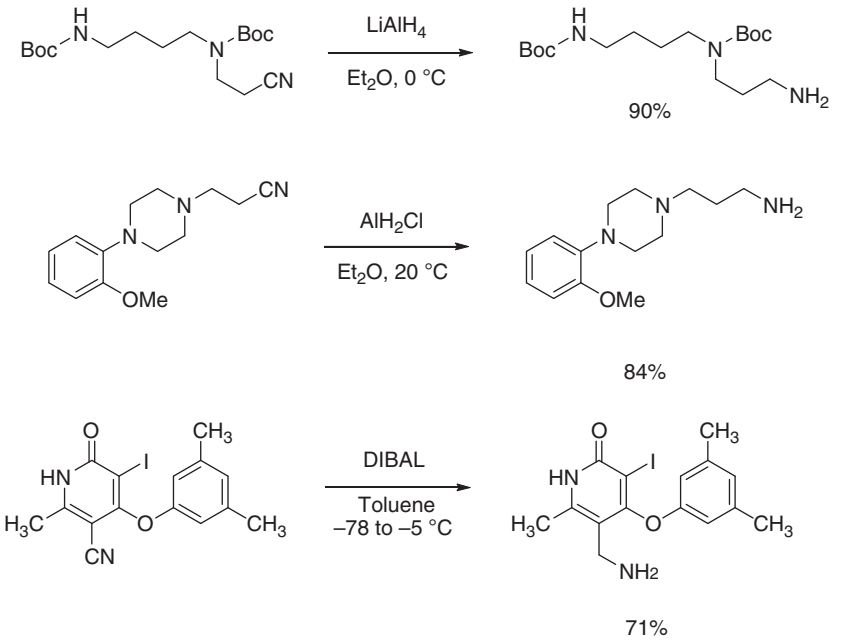
Reduction of the cyano group by electrochemical or dissolving metal reduction means is fraught with difficulties. More often than not the result is a decyanation reaction by fragmentation of a C–C bond. This has been reported using sodium in liquid ammonia,[213] Fe(acac)$_3$ and sodium,[214] potassium, and a crown ether,[215] and potassium on alumina.[216] Dissolving calcium in liquid ammonia has been shown to give better yields of the primary amine product of reduction, but these yields of simple aliphatic nitriles are nowhere near synthetic usefulness (30–63%).[217] Some reports have shown good yields of primary amines when using sodium in methanol,[218,219] but the capriciousness of this reaction suggests that LAH (see Section 8.10.8.3.1) or Raney nickel (see Section 8.10.8.1) be examined first as methods to reduce nitrile groups.

8.10.8.3 Reductions with Metal Hydride Reagents

8.10.8.3.1 Aluminum hydrides

LAH is the most popular choice for the reduction of nitriles to amines, the reduction being complete within a few hours in refluxing diethyl ether. However, this choice may not always be the best since yields are usually better with other aluminum hydride reagents such as AlH_3 and DIBAL, notwithstanding the fact that $LiAlH_4$ is a powerful reducing agent making chemoselective reduction somewhat of a challenge. The lower yields when using $LiAlH_4$ are often attributed to its basicity, which promotes α-deprotonation of alkyl nitriles. One excellent solution is to employ monochloroalane (AlH_2Cl), which is more Lewis acidic and can be easily generated before reduction from a 1:1 mixture of $LiAlH_4$ and $AlCl_3$.[173] The yields of these reductions are usually higher than when using only $LiAlH_4$. The reducing power of monochloroalane is slightly less than $LiAlH_4$ but will still reduce most functional groups. Alane (AlH_3, aluminum hydride) has also been used to reduce nitriles and has some chemoselective advantages over $LiAlH_4$ in that alkyl and aryl halides and nitro groups are only very slowly reduced.[17] DIBAL is also effective at reducing nitriles to amines, though it is more commonly used to convert them to aldehydes (*see* Chapter 8.11). Both DIBAL and AlH_3 are considered Lewis acidic reducing agents and so the reduction of alkyl nitriles is better with these reagents than with $LiAlH_4$, which may cause α-deprotonation. The alkoxy derivatives of aluminum hydrides, for example,

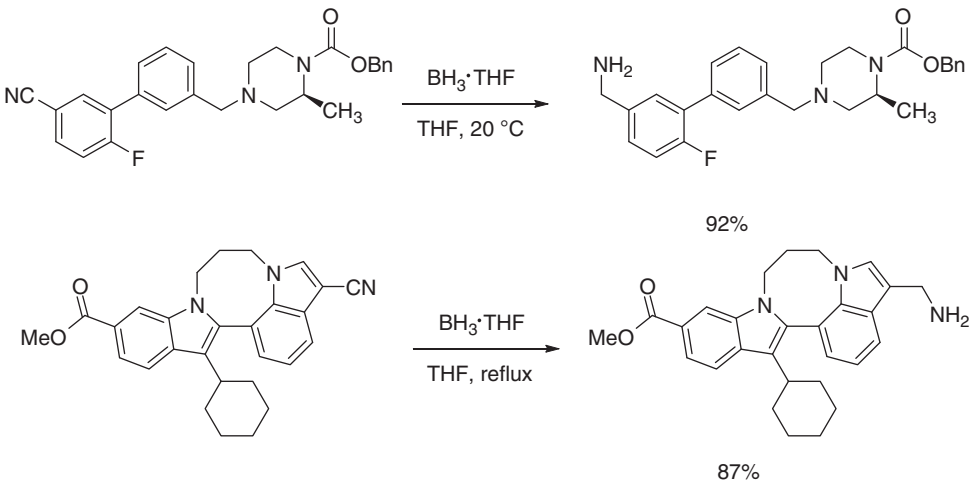
$LiAlH(OMe)_3$ and Red-Al®, can be used to reduce aromatic nitriles to amines, but aliphatic nitriles are often not efficiently reduced owing to the basicity of these reagents. Scheme 31 contains some representative examples of aluminum hydride reductions of nitriles.



Scheme 31

8.10.8.3.2 Boron hydrides

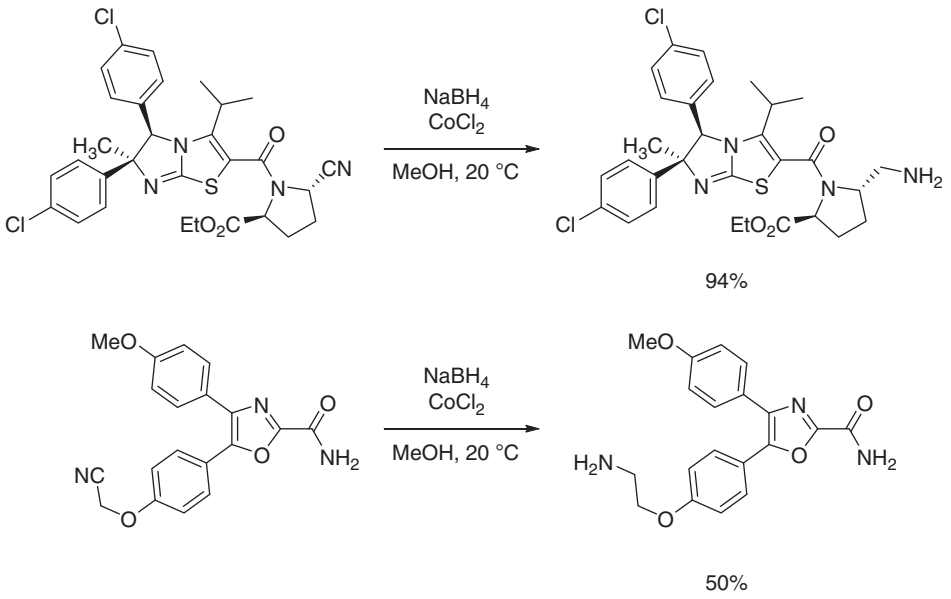
$BH_3 \cdot THF$ is good at reducing aromatic and aliphatic nitriles to amines, which are obtained after the intermediate borazine salts are hydrolyzed under acidic conditions. The yields are generally good, but importantly borane is more chemoselective than the aluminum hydrides, thus esters and carbamate groups can be tolerated in the reaction (Scheme 32). Carbon–carbon double bonds are however not compatible and will undergo borohydride addition reactions. $BH_3 \cdot SMe_2$ is slightly less popular in that it is most efficiently used at reflux with continuous removal of dimethyl sulfide. The alkoxy and alkyl borane derivatives such as catecholborane and thexylborane only slowly reduce nitrile groups and so they have found limited use.



Scheme 32

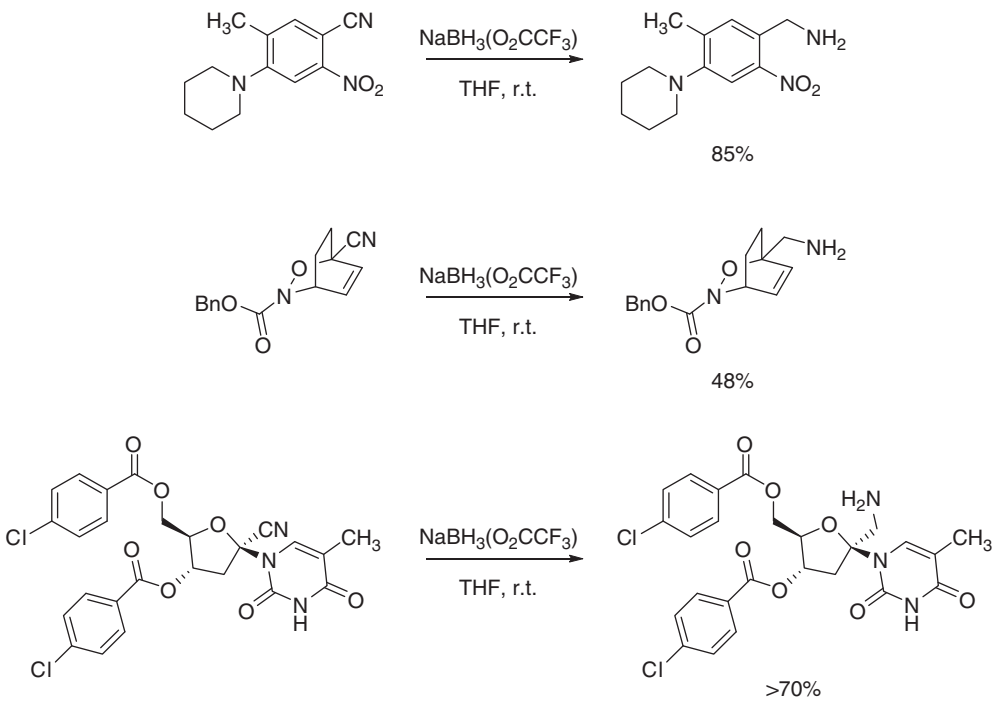
Sodium borohydride is not suitable for reducing nitriles to amines, but it can be used to generate borane *in situ* when treated with $BF_3 \cdot OEt_2$ or iodine, for example. More often though it is combined with cobalt(II) chloride (usually 20 mol%) forming insoluble cobalt boride which acts as a heterogeneous catalyst in these reductions.[182] This reagent also reduces amide, azide, and

nitro groups, but leaves esters untouched (*see* Scheme 33). Amides are also more slowly reduced than nitriles and so chemoselectivity can be achieved by running the reaction at temperatures slightly less than 20 °C. Many other transition metal salts are also suitable, with nickel(II) chloride being the second most popular choice after cobalt(II) chloride.



Scheme 33

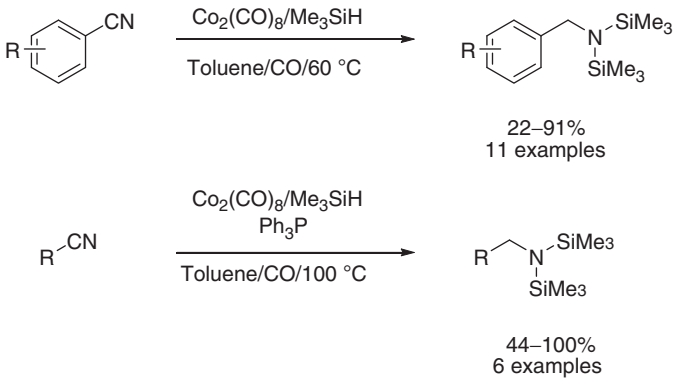
Another good reagent is sodium trifluoroacetoxyborohydride ($NaBH_3(O_2CCF_3)$), which is formed by adding 1 equivalent of trifluoroacetic acid to sodium borohydride.[220] This reagent is excellent at reducing nitriles to amines in the presence of esters and carbamates, but amide groups can be reduced (Scheme 34). It should also be mentioned that secondary amines have been synthesized from nitriles by alkylation of the nitrile with dialkoxycarbonium fluoroborates and then reduction of the nitrilium salt intermediate with sodium borohydride.[221]



Scheme 34

8.10.8.4 Reductions with Silanes

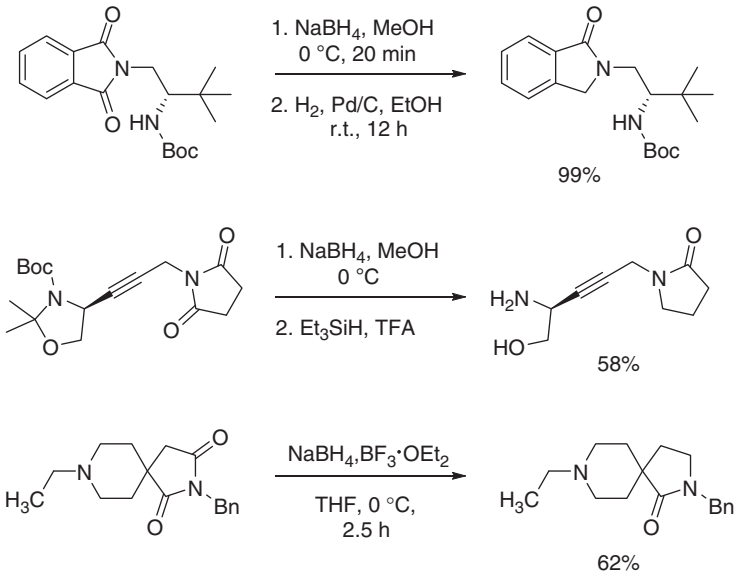
The reduction of nitriles with silanes is more of a challenge and few methods have emerged in the literature. One early report demonstrated that aromatic and aliphatic nitriles could be reduced with trimethylsilane in the presence of $[Co_2(CO)_8]$ as catalyst and an atmosphere of CO,[222] resulting in the *N*,*N*-disilylamine. Aromatic nitriles were more readily reduced at 60 °C, whereas aliphatic amines required higher temperatures (100 °C) and the addition of phosphorus ligands to stabilize the catalyst (Scheme 35). A ruthenium catalyst has also been employed in the presence of dimethylphenylsilane to reduce a small number of nitrile groups to the *N*,*N*-disilylamines,[223] though this method was more tuned to the synthesis of silyl imines via a mono-reduction of the cyano group.



Scheme 35

8.10.9 Reduction of Imides to Lactams

The monoreduction of imides and phthalimides is more commonly achieved via a two-step reduction procedure. First, sodium borohydride reduction of the imide gives the hydroxy lactam, which is then further reduced with triethylsilane in the presence of either trifluoroacetic acid or boron trifluoride. The *in situ* production of borane with sodium borohydride and boron trifluoride has also been applied, though this is rare. Scheme 36 gives some examples of these procedures.



Scheme 36

In a slightly unusual method, phthalimide has also been reduced to the isoindolinone using either CF_3COOH/SbF_5 or $AlCl_3$ in the presence of cyclohexane at elevated temperatures.[224] These superacidic conditions favor the cyclohexane acting as a reductant

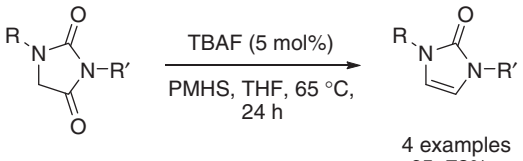
and hydrogen source. The reported yields are good (80%) and have been reproduced by others. Clemmensen reduction using tin or zinc metal in hydrochloric or acetic acid has also been used in a number of cases, but these yields are generally poor (40–50%). Reduction over Raney nickel and hydrogen gas is also applicable but the very high temperatures (180–200 °C) and pressures of hydrogen (200 bar) make it unsuitable for general use.

Finally, and perhaps most importantly, Beller has shown that PMHS can be used as a cheap reductant in the presence of catalytic amounts of TBAF.[225] Coincidently, this less expensive and nontoxic silane was reported to give the best result for a number of phthalimide substrates, without any overreduction to the amine (equation 21). Owing to the polymeric nature of PMHS, the reaction is also practically easy, requiring only filtration to remove the silane. The procedure appears to be scalable and has been demonstrated on a 100 mmol (12 g) scale. Furthermore, the same method reduces imidazolidinediones to imidazolones when run at 65 °C (equation 22).



10 examples
65–78%

(21)



4 examples
65–72%

(22)

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8.11 Reduction of Carboxylic Acids and their Derivatives to Aldehydes

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This chapter is a revision of the previous edition chapters by R.A. Johnstone and A.P. Davis, Vol. 8, pp 259–305, © 1991, Elsevier Ltd.

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8.11.1 Introduction

Aldehydes are certainly important functional groups in synthetic chemistry owing to their high reactivity and ease of modification. This is particularly evident if one considers their role in C–C and C–heteroatom bond forming reactions that are ubiquitous in synthetic chemistry. These advantages are also somewhat ironically a challenge in synthetic strategies, since this high reactivity needs to be protected or shielded in some form until needed. Thus the chemistry of aldehydes is often the chemistry of masking and unmasking them in a synthetic sequence, something which can notionally be achieved in three general ways: (1) hydrolysis of acetyls or other similarly protected intermediates; (2) oxidation of primary alcohols; and (3) partial reduction of carboxylic acid derivatives. It is this last approach that will be explored in greater detail in this chapter.

The complete reduction of carboxylic acid derivatives is generally a well-understood science with a few notable reagents being broadly applicable. However, the partial reduction of these functional groups is frequently less understood, almost certainly because of the (often) unpredictable nature of these reactions. For example, diisobutylaluminum hydride (DIBAL) is classically taught as 'the way' one should reduce carboxylic esters to aldehydes, but this reaction often fails and overreduction to the primary alcohol is commonplace. Thus it is not uncommon to see examples in the literature where researchers attempted a selective reduction of an ester to an aldehyde only to obtain the alcohol instead, thus requiring a second oxidation step. Although this may

 doi:10.1016/B978-0-08-097742-3.00813-2

not be problematic on the laboratory scale, there is a growing body of work that is concerned with syntheses that are more redox efficient[1]; treating a substrate to a full reduction followed by oxidation is a waste of energy and should be avoided as far as possible. It is because of the capricious behavior of the partial reduction of carboxylic acids that many different methods have become available in the literature. In this chapter these alternatives are explored, trying to highlight the advantages and disadvantages of the many varied methods available. As will be obvious by the contents section, the material will be divided up and discussed by functional group, making it easier for the reader to get to the section of interest. Within each section, the work will be further subdivided by general class of reducing reagents. In this regard, the aluminum hydrides, and to lesser extent boron hydrides, have dominated the methods used by chemists since the 1950s. Since the mid-1990s, the single-most important development in this area of research has been the introduction of silanes as hydride sources suitable for partial reduction reactions. Although silanes show much promise, their uptake in the literature has been slow, but this is likely to change as newer methods are adopted. Another emerging area is that of enzymatic reductions. These are however extremely rare in this context and have only been reported for the direct reduction of carboxylic acids to aldehydes. Overall, although it can be said that the partial reduction of carboxylic acids and their derivatives is a mature field, it still draws attention to its exploration and study.

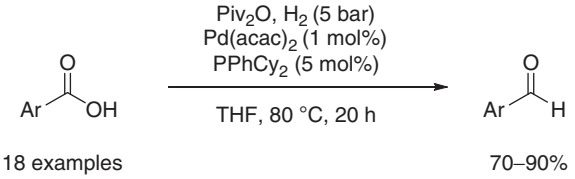
8.11.2 Carboxylic Acids

The authors begin by looking at the direct reduction of carboxylic acids to give aldehydes, a reaction that is considered nontrivial since the aldehyde product is much more susceptible to reduction than the starting material. This is not to say that it is an impossible task and indeed quite a few methods have emerged in the literature since the late-1960s. What is perhaps more interesting to note is that although quite a few excellent protocols exist for this transformation, there is a general lack of them being applied in multistep syntheses. It is likely that a number of reasons exist to explain this fact, particularly owing to the subtle nuances that come into play during synthetic planning and design. One reason for instance is that the carboxylic acid functional group's acidic proton can readily interfere in synthetic strategies. More often than not this group must be masked or protected as an ester or other derivative and then, when needed reduced (or indeed oxidized) to an aldehyde. Since many methods exist to transform carboxylic acid derivatives into aldehydes, it is unlikely that any synthetic design would opt for a two-step hydrolysis-reduction approach. Of course another reason may be that many researchers are simply unaware of the methods available for the direct reduction of carboxylic acids and thus avoid them in their planning.

8.11.2.1 H_2 as Reductant

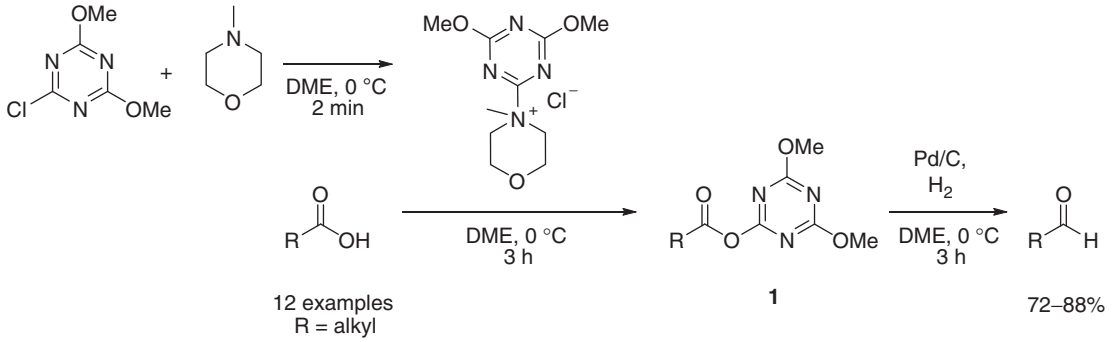
Hydrogen gas is considered first which, from an atom economy point of view, represents the most ideal method for this transformation. Since the 1970s, many patents have appeared demonstrating procedures employing heterogeneous catalysis that are of importance for industrial-scale transformations. The most successful of these appears to be a chromium-modified zirconium oxide (Cr/ZnO_2) catalyst invented by Yokoyama and Maki for the Mitsubishi Chemical Corporation.[2] Since 1988 their plant started with a capacity of 2000 t yr^{-1} of simple aromatic aldehydes from aromatic acids. Changing to chromium oxide (Cr_2O_3) as a catalyst they have also managed to produce aliphatic aldehydes such as undecanal and 10-undecylenic aldehyde. Yokoyama has written a good review on this chemistry and the reader interested in industrial heterogeneous catalysis for this reaction is encouraged to read it and the references cited therein.[3] These methods are however not suitable for laboratory-scale work since the reactions are performed in the gaseous phase at temperatures typically more than 350 °C. The method is also presumably only suited to simple aromatic and aliphatic carboxylic acids since the conditions are unlikely to be tolerated by highly functionalized compounds containing reducible groups.

Fortunately, suitable laboratory-scale solution-based methods have been reported. In 1998, Yamamoto et al. reported that an *in situ*-derived pivaloyl anhydride of a carboxylic acid could be hydrogenated using $Pd(PPh_3)_4$ as a catalyst.[4] The reaction gave excellent yields for aromatic, heteroaromatic, and aliphatic substrates, leaving isolated double bonds intact. The major drawback is the requirement of high pressures of hydrogen (at least 30 bar). However, Gooßen and coworkers fine-tuned the reaction through a careful study of both the palladium source and phosphine ligand. They found that by using palladium(II) acetylacetonate ($Pd(acac)_2$) and dicyclohexylphenylphosphine ($PPhCy_2$) as a ligand, the pressure could be reduced to 5 bar, making this method much more attractive for laboratory-scale reactions (equation 1). In their study, they only examine aromatic and heteroaromatic acids; functional groups such as esters, amides, nitriles, aryl-F, and CF_3 were left untouched, including a conjugated double bond from the reduction of cinnamic acid to cinnamaldehyde.



(1)

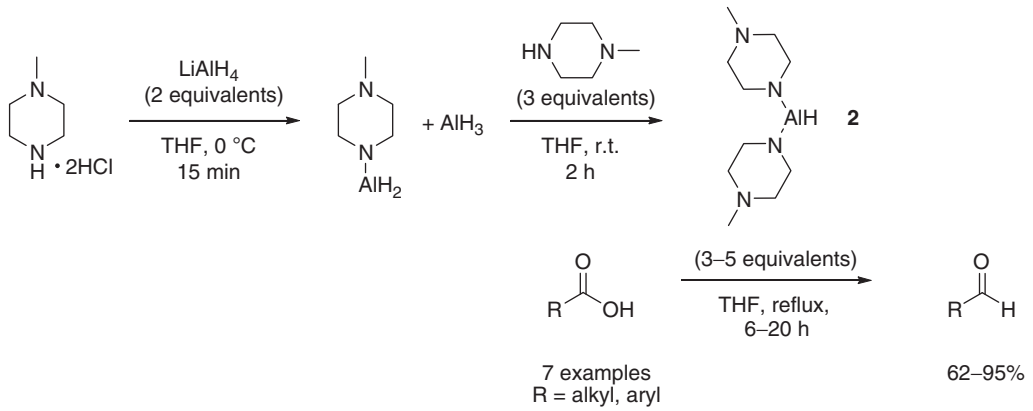
Another method developed earlier by Taddei et al.[5] relies on the similar principle of *in situ* activation of a carboxylic acid (Scheme 1). Here the triazine ester (**1**) is formed, which is rapidly reduced to the aldehyde using palladium on carbon and hydrogen gas at atmospheric pressure (the balloon method so loved by synthetic chemists can be used). The advantage of this method is that the byproducts are filtered and washed out of the reaction mixture, leaving the semipure aldehyde ready for further reactions. Unfortunately, this reaction is not without its problems and suffers from one major challenge: overreduction to the alcohol. This cannot be avoided in the case of aromatic acids, whereas for aliphatic acids the authors recommend careful optimization of the reaction time and temperature for each substrate. Obviously other nucleophilic functional groups would not be tolerated in this or the previous method and would need to be protected.



Scheme 1

8.11.2.2 Aluminum-H Reagents

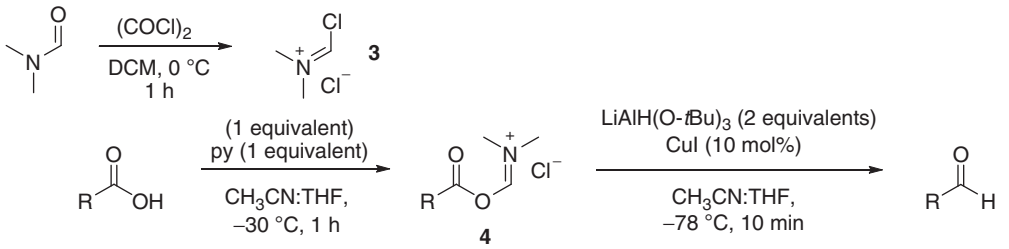
The parent aluminum hydrides such as alane (AlH_3) or lithium aluminum hydride (LAH; $LiAlH_4$) are far too reactive to accomplish the desired reduction of a carboxylic acid to an aldehyde. Nevertheless, it has been reported that careful control of reagent stoichiometry and reaction conditions can achieve this, but the practical difficulties and chance of overreduction make this an impractical choice. Modifying the aggressiveness of the parent alane has opened some opportunities for selective reduction, the most notable modification being that of diisobutylaluminum hydride (DIBAH, DIBAL, or DIBAL-H; diisobutylalane). In the early days of its discovery, Zakharkin and Khorlina reported that DIBAL could reduce carboxylic acids to aldehydes provided the reaction temperature was kept less than $-70\ ^{\circ}C$.[6] Unfortunately, this has not emerged as a practical synthetic protocol since yields average between 40% and 70% and the tendency toward overreduction and lack of functional group tolerance are less than satisfying. Attempts to improve the selectivity through modification of alanes with alcohols (e.g., lithium trimethoxyaluminum hydride or lithium tri-*tert*-butoxyaluminum hydride) did not result in a better reagent, either being, respectively, too reactive or unreactive to carboxylic acid reduction.[7] Modification of the alanes with a secondary amine however showed more promise. Many amine derivatives have been examined, and the best has been found to be *N*-methylpiperazine.[8] This reagent, bis(4-methylpiperazin-1-yl)aluminum hydride (**2**), conveniently reduces both aliphatic and aromatic acids to aldehydes. In 1984, Wiemer et al. were interested in applying this method to their work and improved on the synthesis of the reagent starting from the more readily available $LiAlH_4$ rather than AlH_3 (Scheme 2).[9] Further examination and expansion on this work by Cha and coworkers confirmed that *N*-methylpiperazine was the optimal amine for modification of the alane,[10,11] noting that bidentate amino versions showed no further improvement.[12] From a practical standpoint this method appears to favor substrates that do not have Lewis-basic components since others have mentioned failed reactions in these cases.[13–15] It should also be noted that 3–5 equivalents of the reagent are frequently required, thus making it unattractive from a reagent economy point of view.

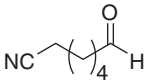
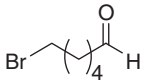
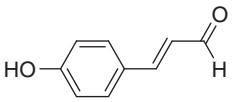
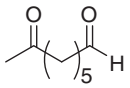
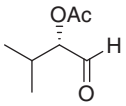
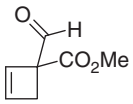
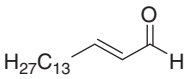
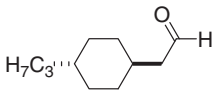
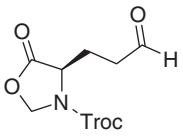
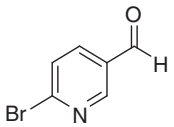
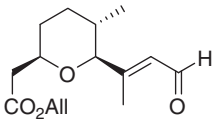
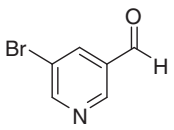


Scheme 2

The true test of any method comes from its use in the literature and here one of the most synthetically applied methods comes from the group of Fujisawa.[16] In the early-1980s they demonstrated a one-pot method involving the *in situ* activation of the carboxylic acid with the Vilsmeier reagent (**3**, Table 1), followed by reduction of this intermediate (**4**) with mild lithium tri-*tert*-butoxyaluminum hydride. The methodology has afforded good yields of aldehyde products; functional group tolerance includes alkenes (including those conjugated to the acid), esters, nitriles, alkyl halides, and heteroaromatic structures. If one considers the commercial availability of the reagents, practical ease of the synthesis and work-up, and tolerance for functional groups, it is not surprising that this method has found favor in the literature for converting carboxylic acids to aldehydes. Obviously one would be wary of performing such a reaction on an industrial scale, owing to the atom-uneconomical nature of the method, but for bench-scale synthetic procedures this is one of the tried-and-tested methods which should be seriously considered.

Table 1 Fujisawa reduction: examples are from the literature



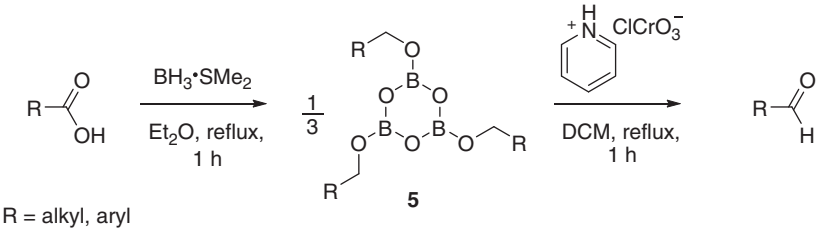
Product	*Yield (%)*	*Reference*	*Product*	*Yield (%)*	*Reference*
	80	16		73	16
	80	17		60	18
	Not reported	19		50	20
	94	21		72	22
	Not reported	23		50	24
	77	25		63	26

Others have developed similar *in situ* activation–reduction protocols; for example, Chandrasekhar et al. reduced an *in situ*-derived silyl ester with DIBAL returning yields of aldehyde in the range of 63–85% for some aromatic and aliphatic acids.[27] Also, Kangani et al. reported in 2006 that the formation of a Weinreb amide using the Deoxo–Fluor reagent allowed for the *in situ* reduction of this intermediate using DIBAL.[28] In this case, yields for simple alkyl and aryl acids were in the range of 73–91%. In this latter example it should be noted that the reagents are not cheap, giving the Fujisawa method the upper hand. Finally, in all three cases the researcher should pay careful attention to the obvious potential functional group incompatibilities and protect where necessary.

8.11.2.3 Boron-H Reagents

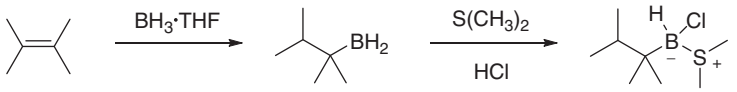
Perhaps the most applied method using a boron reagent involves a one-pot reduction oxidation sequence. In 1979, Brown et al. reported a rather simple method involving the addition of borane-dimethylsulfide ($BH_3 \cdot SMe_2$, BMS) to the carboxylic acid and then oxidizing the resulting boroxine intermediate (**5**) with pyridinium chlorochromate (PCC, Scheme 3).[29] The reaction works

well with both aromatic and aliphatic groups and appears to be limited only by the incompatibility of BMS for alkenes and alkynes and PCC's ability to oxidize free alcohols. The major drawback of this method is its inefficient redox approach that is problematic with the modern push to more efficient synthetic strategies (see Section 8.11.1).



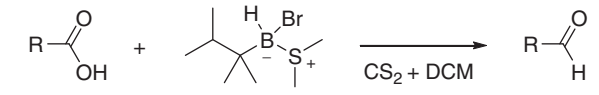
Scheme 3 Stepwise, one-pot borane reduction–PCC oxidation protocol.

The use of thexylborane (**6** in Scheme 4) was shown to be effective for the reduction of carboxylic acids to aldehydes by Brown and coworkers.[30] Later the same group revealed that modifying the reagent with HCl and dimethyl sulfide gave a thexylchloroborane–dimethyl sulfide complex (**7**) which was a more active and efficient reagent.[31,32] This reagent shows good tolerance to esters, epoxides, aromatic nitriles, and nitro compounds, although rapidly (15 min at room temperature) reducing aliphatic and alicyclic carboxylic acids to aldehydes. Reduction of aromatic acids was found to be very sluggish, needing at least 24 h at room temperature. It was however demonstrated that this could be considered a feature of the method by performing a chemoselective reduction of an aliphatic carboxylic acid in the presence of an aromatic one. There are a number of drawbacks to this protocol and these should be highlighted: (1) the reagent is not readily available from standard commercial sources and must therefore be synthesized; (2) obtaining the aldehyde product involves a complicated work-up procedure involving the formation of the bisulfite adduct and then conversion back to the aldehyde using formaldehyde; and finally (3) the reagent will also react with any alkene or alkyne functional groups. However, Cha has demonstrated that this last problem is solved by changing the reagent to the bromo derivative, i.e., thexylbromoborane–dimethyl sulfide complex (**8** in equation 2).[33–35]



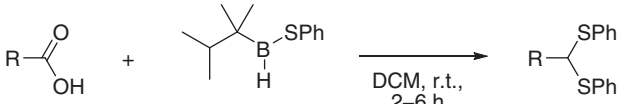
6 **7**

Scheme 4

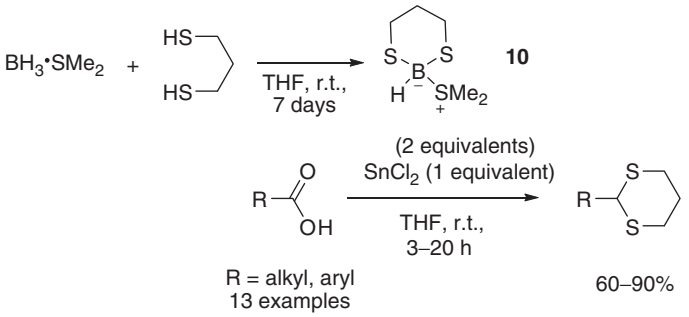


8 (2)

An interesting adaption in using boranes to reduce carboxylic acids warrants a small diversion from the topic. The reason is that the use of a thioborane has resulted in thioacetyl formation which is itself a masked aldehyde. Kim et al. have reported that thexylphenylthioborane (**9**) cleanly afforded the bisphenylthio acetal with carboxylic acids, although aromatic acids were again not suitable substrates (equation 3).[36] A further modification using the 1,3,2-dithiaborinane–dimethyl sulfide complex (**10**) returned cyclic dithioacetals in good yields when using tin(II) chloride as a Lewis-acid catalyst (Scheme 5 – the addition of $SnCl_2$ allowed alkene substrates).[37] It is somewhat surprising that although dithianes are classic umpolung reagents, this method has never been incorporated into any synthetic strategies. It should be noted though that the dithiaborinane reagent required to make cyclic thioacetals involves a lengthy preparation reaction lasting 7 days, though the reagent itself is stable and storable once synthesized.



9 (3)



Scheme 5

8.11.2.4 Electrochemical Approaches

The use of electrochemical approaches in organic synthesis is not common, more than likely due to the requirement of specialized equipment. Some electrochemical methods for the formation of aldehydes from carboxylic acids have been reported[38–41] but the yields do not warrant recommendation as a preferred method. One method for the reduction of α-amino acids to α-amino aldehydes effected by the electrochemical oxidation of triphenylphosphine may have significance for researchers interested in those compounds in particular.[42] In such a case, the reader is directed to a 2003 review on α-amino aldehydes by Jurczak et al.[43]

8.11.2.5 Enzymatic

Biological methods for functional group interconversion are not typical choices for most synthetic chemists since the enzymes are often fairly specialized and expensive. However, it is prudent to mention that there have been some preliminary reports on enzymes that reduce free carboxylic acids to aldehydes since they may have industrial appeal for large-scale batch reactor processes. The first reported isolation of a carboxylic acid reductase (Car) came from Gross and Zenk in 1969 isolated from *Neurospora crassa*.[44] Since then, others have found similar enzymes in other microorganisms such as *Clostridium thermoaceticum*,[45] *Clostridium formicoaceticum*,[46] and *Nocardia*[47] to name but a few. In 2008, Rosazza et al., after having cloned the gene responsible for the Car enzyme, demonstrated its application to some common organic carboxylic acids.[48] The enzyme exhibited substrate specificity (e.g., fumaric, maleic, and pyruvic acids were not reduced, whereas aconitic, malic, and α-ketoglutaric acids were rapidly reduced), suggesting that a carboxylic acid adjacent to an sp^2 carbon was not a substrate. In one case enantioselectivity was demonstrated, reducing D-tartaric acid whereas leaving L-tartaric acid. Along with the fact that isocitric acid was not reduced, whereas citric acid was, the enzyme has potential in enzymatic resolution processes.

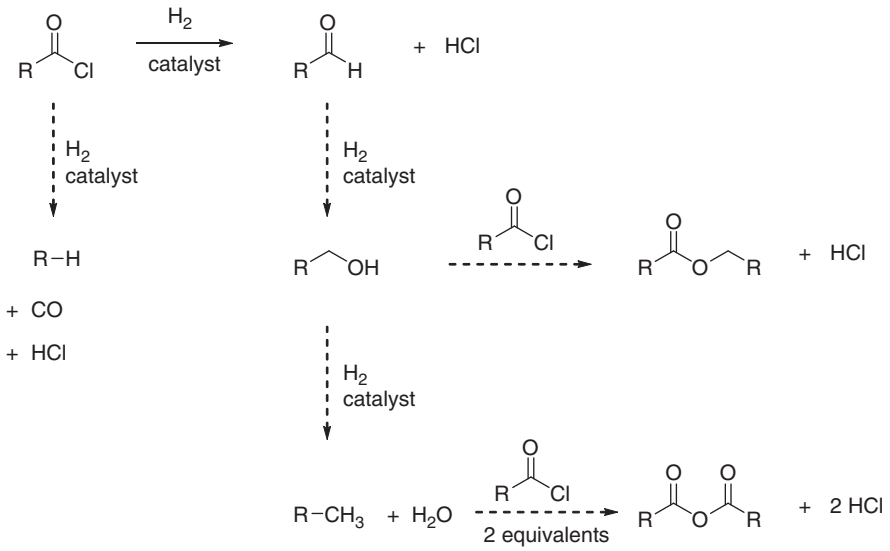
8.11.3 Acyl Chlorides

Before the development of the methods in Section 8.11.2, the reduction of acid chlorides to aldehydes represented the earliest convenient means for the overall conversion of carboxylic acid derivatives to aldehydes. These methods are perhaps less useful today with the advent of the direct procedures on the more stable acids, esters, and amides, but their inclusion here serves as a means to complement the range of options available to the synthetic chemist.

8.11.3.1 H_2 as Reductant

The earliest method to achieve this conversion was reported by Rosenmund in 1918,[49] and involves the passage of hydrogen gas through a toluene or xylene solution containing the substrate and catalyst while heating under reflux. The original catalyst system was palladium on barium sulfate and included a regulator in the form of a sulfur-containing compound. This last additive was needed to prevent overreduction to the alcohol, particularly in aromatic substrates. On a side note, it is perhaps interesting to observe that this was the first report of a modified hydrogenation catalyst system, predating Lindlar's well-known system by 35 years. The reaction produced hydrochloric acid which would be trapped by passing the gasses through water, allowing a convenient way to monitor the reaction via a titration. Although in many cases high yields are obtained, the reaction is susceptible to side reactions such as overreduction and decarbonylation (Scheme 6).

Later variants of the reaction used basic additives to trap the hydrochloric acid *in situ* and thus altered the procedure to a closed system, much improving the synthetic protocols. Four variations on this theme have been reported. The first is that of Rachlin et al. where the basic additive is sodium acetate. Although the advantage of operating in a closed system is achieved, the conditions required a hydrogen gas pressure of 50 psi.[50] The second method comes from Burgstahler et al. who showed that the sterically hindered base 2,6-dimethylpyridine could be used, allowing the reaction to proceed in THF at room temperature for aliphatic hydrocarbons, whereas aromatic acyl chlorides required higher temperatures using benzene as a solvent and Pd/C



Scheme 6

poisoned with quinoline-S as a catalyst (Table 2). The reactions were typically complete in 1–2 h; these conditions tolerate conjugated unsaturated alkene and aromatic chloride functional groups (entries 12, 13, and 15).

Table 2 Aldehydes prepared by 2,6-dimethylpyridine modification of the Rosenmund reduction[51]

Entry	*Product*	*Catalyst*	*Solvent*	*Yield (%)*
1	Dodecanal	10% Pd/C	THF	95
2	Octadecanal	10% Pd/C	THF	96
3	$OCH(CH_2)_4CHO$	10% Pd/C	THF	74
4	$OCH(CH_2)_8CHO$	10% Pd/C	THF	77
5	$MeCO(CH_2)_6CHO$	10% Pd/C	THF	85
6	*i*-$PrO_2C(CH_2)_2CHO$	10% Pd/C	THF	89
7	*i*-$PrO_2C(CH_2)_3CHO$	10% Pd/C	THF	89
8	3-Oxo-5-octanolide	10% Pd/C	THF	94
9	2-Ethylhexanal	10% Pd/C	THF	87
10	*c*-C_5H_9CHO	10% Pd/C	THF	78
11	Dehydroabietinal	10% Pd/C	THF	92
12	(*Z*)-$C_8H_{17}CH{=}CH(CH_2)_7CHO$	5% Pd–$BaSO_4$	THF	96
13	(*E*)-$PhCH{=}CHCHO$	5% Pd–$BaSO_4$	THF	84
14	Benzaldehyde	10% Pd/C–quinoline-S	C_6H_6	93[a]
15	4-Chlorobenzaldehyde	10% Pd/C–quinoline-S	C_6H_6	77[a]

[a]Reaction carried out at 40–50 °C.

The third, equally successful modification comes from Peters and van Bekkum who demonstrated that Hünig's base (diisopropylethylamine) allowed aliphatic as well as aromatic acid chlorides to be smoothly reduced to aldehydes at room temperature and atmospheric pressure of hydrogen over Pd/C. Using either acetone or ethyl acetate as solvent, no overreduction, nor reduction of aromatic nitro and chloro substituents, or double bonds in cinnamoyl chlorides was observed.[52,53]

Lastly, in a development aimed at the industrial preparation of 3,3-dimethylbutyraldehyde from 3,3-dimethylbutanoyl chloride, the group of Li et al. revealed that palladium nanoparticles supported on a silica substrate gave excellent conversions to product (>90%) after seven cycles of catalyst use.[54] The method is similar to the original Rosenmund conditions in that the hydrogen gas is bubbled through the reaction while heating the catalyst and substrate in a solution of cyclohexane at 80 °C. This work was not expanded into a study of other aldehydes and therefore it still remains to be seen whether the palladium nanoparticle approach is more general in scope.

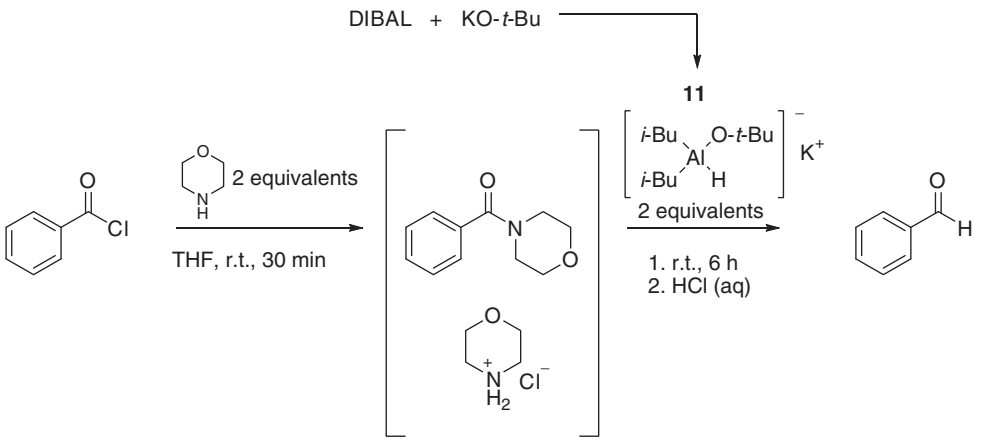
8.11.3.2 Aluminum-H

LAH is obviously an unsuitable choice to achieve this transformation since it is too powerful a reducing agent. Rather, it has been shown by Brown and McFarlin that moderating the reactivity of the aluminum hydride bond can be achieved by forming trialkoxy

derivatives.[55,56] More specifically, lithium tri-*tert*-butoxyaluminum hydride was shown to be able to selectively reduce acid chlorides to aldehydes in diglyme at low temperatures. Yields were variable in the samples studied, with aromatic substrates giving better yields (60–85%) than aliphatic ones (20–60%).[57] Almost 40 years later, Cha and Brown showed that using the sodium salt of tri-*tert*-butoxyaluminum hydride resulted in much improved yields. These reagents are said to tolerate oxides, acetals, esters, lactones, and nitriles.

In what can be considered a step-wise method, An and coworkers demonstrated in 2008 that potassium diisobutyl-*tert*-butoxyaluminum hydride (PDBBA, **11**) was very effective at reducing the *in situ*-derived amide of the acid chloride and morpholine (Table 3).[58] The reagent itself is readily prepared from DIBAL and potassium *tert*-butoxide and is most promising as a selective reductant (see reduction of esters, Section 8.11.4.1 and nitriles, Section 8.11.8.1). Two equivalents of the base and reducing reagent are required making the reaction somewhat atom-uneconomical but the yields quoted are excellent, albeit with simple substrates (Table 3). Although touted as being a method for partially reducing acid chlorides, this method is important for the reduction of *N*-morpholino amides to aldehydes (see Section 8.11.6.1).

Table 3 Aldehydes prepared from *in situ*-derived morpholino amides using PDBBA

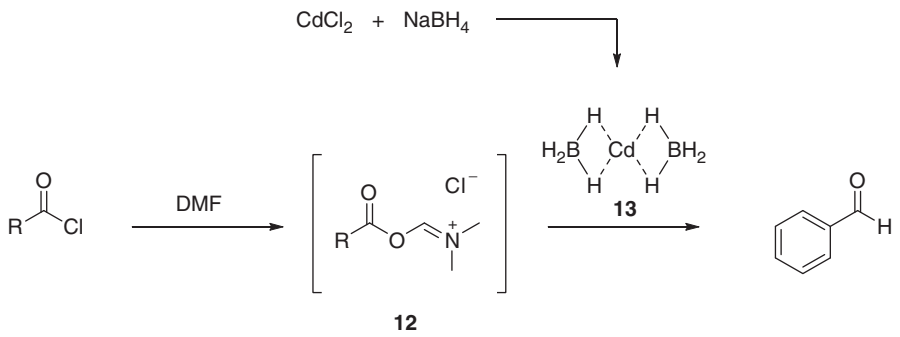


Entry	*Product*	*GC yield (%)*	*Isolated yield (%)*
1	Benzaldehyde	95	
2	4-Fluorobenzaldehyde	92	
3	3-Chlorobenzaldehyde	96	86
4	4-Chlorobenzaldehyde	94	
5	4-Bromobenzaldehyde	96	
6	4-Nitrobenzaldehyde	99	88
7	4-Methylbenzaldehyde	93	
8	4-Methoxybenzaldehyde	95	
9	2-Naphthaldehyde	96	83
10	2-Furfural	94	
11	Hexanaldehyde	97	
12	Undecanaldehyde	92	
13	Cinnamaldehyde	94	

8.11.3.3 Boron-H

Sodium borohydride is also too powerful a reductant for the partial reduction of acid chlorides, though a number of additives and procedural changes have opened the doors for its use. In one modification, sodium borohydride was mixed with cadmium chloride and dimethylformamide (Scheme 7). This combination proved to be effective at reducing acid chlorides to aldehydes in 5 min at 0 °C.[59,60] The reaction tolerates alkyl, aryl, and benzyl halides but yields are rarely more than 70%. The mechanism is attributed to two factors: a more stable (and therefore less reactive) hydride via a cadmium–borohydride complex (**13**) and a more active acyl–DMF complex (Scheme 7). It should be pointed out that the intermediate (**12**) is the same as that used by Fujisawa[16] in his method for the one-pot conversion of carboxylic acids to aldehydes (see Section 8.11.2.2).

This reaction was however prone to low yields caused by overreduction; picking up on this Babler and coworkers considered whether the overreduction could be due to the borane given off during workup. They proposed quenching with acid and ethyl vinyl ether, though this led to an acknowledged difficulty in the workup, although in this case the cadmium salt was shown to be no longer necessary.[61] In a second publication, Babler showed that the addition of pyridine successfully acted as a borane scavenger and allowed appreciable quantities of the aldehyde product to be obtained (70–80%).[62] It should be noted that at least



Scheme 7

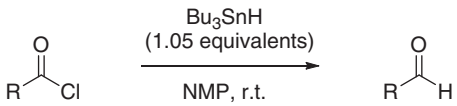
one report mentioned that they were unable to reproduce this reaction on their substrate.[63] Copper salts have also found application in moderating borohydride reactivity; Sorrell[64] and Fleet[65] independently reported that bis(triphenylphosphine)tetrahydroborato copper(I) was an efficient reductant at ambient temperatures furnishing good yields of aldehyde products. The reagent is readily prepared and air- and water-stable, with a disadvantage being that it would be impractical for large-scale use due to its high molecular weight. Changing the phosphine ligand to a phosphinite was not effective at reducing the molar mass of the reagent, hinting that the reagent was highly sensitive to changes in the ligands.[66]

Unlike the alkoxyaluminum hydrides, sodium trimethoxyborohydride is not an efficient reagent for the conversion of an acid chloride to an aldehyde.[67] The yields are low even at $-80\,^{\circ}C$, although it should be mentioned that at least one example has reported a yield of 85%.[68] Boranes in general are also not suitable, either reducing the acid chloride to the alcohol (e.g., diborane or borane dimethylsulfide) or reacting very slowly (e.g., thexylborane or thexyl-*sec*-butoxyborane).[69,70]

8.11.3.4 Miscellaneous

There are a number of other methods that have been developed that do not fit into the standard mold of typical reducing reagents and are mentioned here for completeness. Such examples include a whole family of metal carbonyl complex anions: $[Fe(CO)_4]^{2-}$;[71] $[HFe(CO)_4]^{-}$[72]; $[HCr(CO)_5]^{-}$[73]; $[HW(CO)_5]^{-}$[73]; and $[CpV(CO)_3H]^{-}$.[74] The use of tin hydrides has also been well studied and has undergone a revolution of sorts. In 1960, Kuivila demonstrated that tributyltin hydride could be used fairly effectively as a partial reductant of acid chlorides, though ester side products were common.[75] Twenty years later Guibe demonstrated that the addition of palladium dramatically improved the yields of the reaction.[76,77] Then in 2010, Hamze and Alami reported that the transition metal could be successfully eliminated if *N*-methyl-pyrrolidinone was used as a solvent.[78] The reaction tolerates alkenes, aromatic bromo, and nitro groups and is applicable to both aromatic and aliphatic substrates (**Table 4**). However, this method does suffer from the use of toxic tin reagents that are known to contaminate products, often frustrating purification processes.

Table 4 Transition-metal-free, tributyltin hydride reduction of acid chlorides



Entry	*Product*	*Yield (%)*	*Entry*	*Product*	*Yield (%)*
1	Benzaldehyde	87	9	4-Nitrobenzaldehyde	74
2	4-Methoxybenzaldehyde	81	10	4-Terephthalaldehyde	86
3	3,5-Dimethoxybenzaldehyde	60	11	2-Naphthaldehyde	90
4	4-Benzyloxybenzaldehyde	63	12	Thiophene-2-carbaldehyde	93
5	4-Allyloxybenzaldehyde	70	13	Cinnamaldehyde	85
6	4-Methylbenzaldehyde	80	14	Octanal	96
7	2-Methylbenzaldehyde	87	15	3,7-Dimethyloct-6-en-al	65
8	4-Bromobenzaldehyde	90			

In another alternative method, Jia and coworkers reported in 2007 that samarium(0) combined with tributylphosphine also acted as a suitable partial reductant of acid chlorides.[79] Here too, the method has been shown to tolerate esters, aromatic chlorides, and nitro groups and an alkene of cinnamaldehyde. Isolated yields are very good (generally more than 90%), though stoichiometric uses of samarium and phosphine reagent are likely to make this method less attractive in practice.

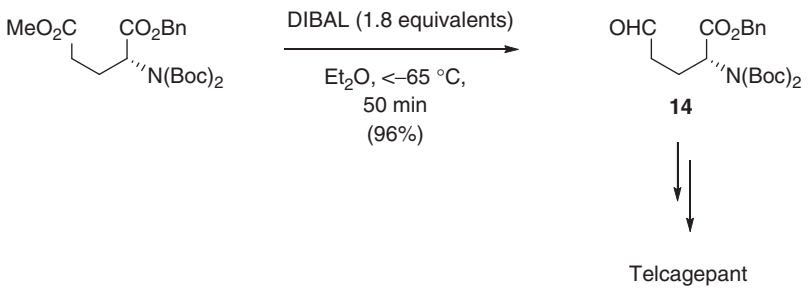
8.11.4 Carboxylic Acid Esters

The partial reduction of carboxylic acid esters has been a well-studied area in synthetic chemistry. This is because there is a very real need for reagents that can effect the transformation of an ester into an aldehyde. Between 1990 and 2011, there was an average of 300 reported reactions per year that involved the transformation of an ester to an aldehyde. Yet many of these were not achieved in one-step, requiring a step-wise reduction–oxidation protocol. Dunetz and Magano, in their 2012 review on carbonyl reductions in the pharmaceutical industry, commented that very few examples of large-scale direct reductions of esters to aldehydes have been reported.[80] More often the step-wise (and thus wasteful) process of reduction–oxidation is used. For the researcher working on a laboratory-scale reaction the reason for this is likely that the step-wise methods can often lead to higher overall yields and involve less experimentation with optimizing conditions to find the ideal reagent. Industrially this can be extremely wasteful, and so it is in the interest of laboratory-scale researchers to consider the redox inefficiencies in their work. There are indeed many available procedures to accomplish this task, and the literature continues to advance and mature with respect to the options available. Before 2000, the only way to partially reduce an ester to an aldehyde involved aluminum hydride reagents, which have been indeed fine-tuned over the years to give reagents more attractive than those developed in the 1960s. Since 2000, the application of silanes has come to the fore, and may possibly also have an important role to play in these reactions in the future. The aluminum hydrides are discussed first and then the silicon hydrides. It should be mentioned that boron hydrides have been found to be synthetically unsuitable for this transformation and will therefore not be covered; there are also no reported enzymatic methods that directly transform an ester to an aldehyde.

8.11.4.1 Aluminum-H

Without doubt, diisobutyl aluminum hydride (DIBAH, DIBAL, or DIBAL-H) is the first reagent that springs to mind when one considers a chemoselective reduction of an ester to an aldehyde. Of course the reason for this is not so much as its recognized efficacy in this reduction, but rather its notoriety at failing to give the desired aldehyde.[1] In a general literature search of DIBAL reductions of esters it was found that, of the approximately 6500 reactions surveyed, just over 2000 required a subsequent oxidation to the aldehyde. Even so, this reagent continues to be taught in undergraduate courses as being a classical and safe means of achieving this transformation. This reagent thus often results in synthetic schemes that are particularly redox inefficient, requiring reoxidation of the alcohol to the aldehyde.

Historically, DIBAL was first reported by the Russian chemists Zakharkin and Khorlina in 1962 as a means to selectively reduce esters to aldehydes (60–80% yield).[81] In this article it was noted that simple alkyl esters are preferred to aromatic ones, and temperatures less than $-70\ ^{\circ}C$ are also very important for high yields. The capriciousness of this reaction can also be gleaned from the fact that (as of early 2012) out of the 18 times it is mentioned in the journal *Organic Synthesis*, only five articles use it to expressly reduce an ester to an aldehyde. In all cases the authors and checkers note that very careful control of the number of equivalents and slow, cold addition to the ester including the direct monitoring of the reaction temperature is recommended. The aforementioned preference for simple alkyl esters has been exploited for chemoselectivity. For example, Burgey and coworkers have reported a large-scale synthesis of **14**, an early intermediate in the synthesis of telcagepant which was under development by Merck as a drug for the treatment of migraines (**Scheme 8**).[82]



Scheme 8

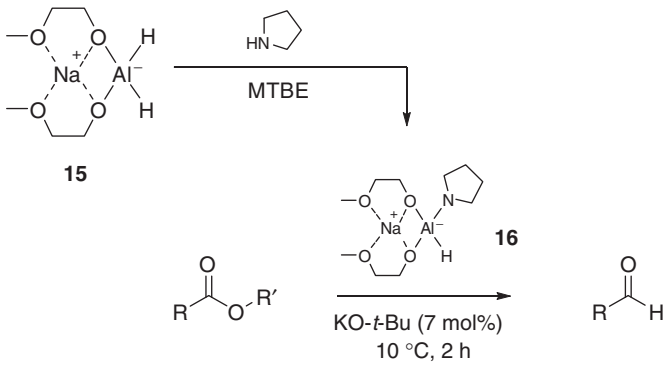
It should also be mentioned that DIBAL has been successfully used in the reduction of carboxybenzoyl derivatives of α-amino acid esters (methyl and ethyl) to give the protected α-amino aldehydes in moderate yields (33–64%) without any racemization.[83]

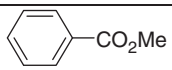
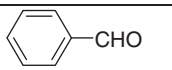
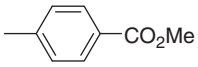
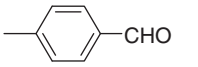
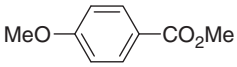
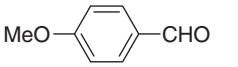
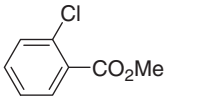
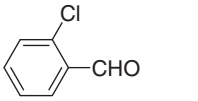
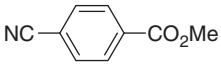
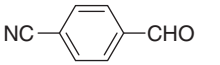
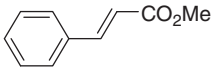
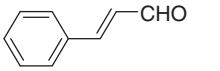
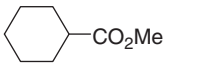
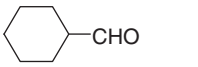
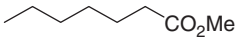
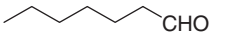
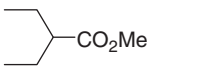
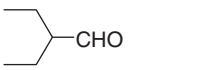
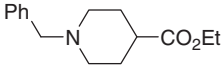
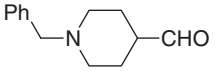
In an update to the practical method of using DIBAL, Jamison and Webb have demonstrated that a flow reactor protocol can be successfully used with aliphatic esters.[84] This observation, that is, that only aliphatic esters are successfully reduced to aldehydes with DIBAL in flow, was also independently reported at the same time by Alcázar and coworkers.[85] The obvious disadvantage this method is the requirement of specialized equipment, but the advantages may prove to be very important in process chemistry.

DIBAL is by far not the only aluminum hydride reagent to have been applied to the reduction of esters to aldehydes. Indeed quite a few modified aluminum reagents have been investigated. For example, Zakharkin and Khorlina, the same workers who first reported on DIBAL's chemoselectivity, also demonstrated that sodium aluminum hydride ($NaAlH_4$) could be employed to

partially reduce esters though without any advantage over DIBAL in terms of yields obtained.[86] One major disadvantage of this particular method was that the reagent and its reduction intermediates are insoluble at the low temperatures required. A solution to this problem was found by Vit in the form of modifying the reagent with two 2-methoxyethanol ligands, thus forming sodium bis(2-methoxyethoxy)aluminum dihydride (Vitride, SMEAH, Red-Al, **15**).[87] Although this popular reagent overcame the insolubility problems, even further improvement was found when 1 equivalent of *N*-methylpiperidine was added to give sodium bis(2-methoxyethoxy)-*N*-methylpiperidino aluminum hydride which was suitable for reducing aliphatic, aromatic, and α,β-unsaturated esters in moderate-to-good yields (50–85%).[88] Then in 2001, Abe and coworkers conducted a very careful study on optimizing the reaction conditions for large-scale production of *N*-benzyl-4-formylpiperidine.[89] They found that the addition of pyrrolidine to Red-Al gave sodium bis(2-methoxyethoxy)-*N*-pyrrolidino aluminum hydride (**16**) which resulted in the best yields. Furthermore, they found that the addition of 7 mol% of potassium *tert*-butoxide to the reaction mixture greatly increased the yield by suppressing byproduct formation (Table 5). Importantly the formation of the reagent is typically conducted at $-20\,^{\circ}C$ to $-5\,^{\circ}C$, whereas the reduction itself is run at approximately 10 °C, which is much more amenable to industrial reactors (Table 6).

Table 5 Partial reduction of alkyl esters using sodium bis(2-methoxyethoxy)-*N*-pyrrolidino aluminum hydride

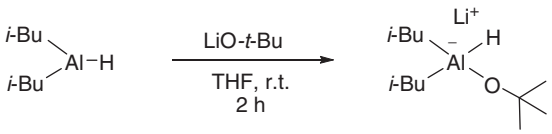


Entry	*Substrate*	*Product*	*Yield (%)*
1			93
2			97
3			100
4			98
5			85
6			39
7			97[a]
8			70[a]
9			58[a]
10			95

[a]These yields obtained from GC.

In 2007, An and coworkers released three papers demonstrating the applicability of lithium,[90] sodium,[91] and potassium[92] diisobutyl-*tert*-butoxyaluminum hydride on the partial reduction of esters. The reagent is conveniently made from DIBAL and

Table 6 Yields of aldehyde in the reduction of representative esters with LDBBA at 0 °C



Entry	*Compound*	*LDBBA equivalent*	*Time (h)*	*Yield of aldehyde (%)*
1	Ethyl benzoate	1.2	3	74
3	Isopropyl benzoate	1.3	3	89
4	*tert*-Butyl benzoate	3.0	3	63
6	Ethyl 4-fluorobenzoate	1.2	3	83
7	Methyl 3-chlorobenzoate	1.2	3	81
8	Ethyl 4-chlorobenzoate	1.2	3	83
9	Ethyl 2-bromobenzoate	1.2	3	85
10	Ethyl 4-bromobenzoate	1.2	3	83
11	Ethyl 4-nitrobenzoate	1.2	3	85
12	Ethyl 2-toluate	1.2	3	82
13	Ethyl 2-naphthoate	1.2	3	80
14	Ethyl 2-furoate	1.2	1	81
15	Ethyl caproate	1.2	1	87
16	Isopropyl caproate	1.3	1	98
17	Ethyl undecanoate	1.2	1	88
18	Ethyl cyclohexanecarboxylate	1.2	1	81

alkali-*tert*-butoxide, with the lithium counterion being marginally better for the reduction of esters to aldehydes. Importantly, aromatic esters give excellent yields and the reaction is conveniently run at 0 °C. A number of other authors have successfully applied this method to their synthetic schemes,[93–96] and one report demonstrated the application of the reagent to flow chemistry.[85] Potassium diisobutyl-*tert*-butoxyaluminum hydride (PDBBA) has already been mentioned as a method to reduce acid chlorides via an *in situ*-derived morpholine amide (see Section 8.11.3.2). This reagent is reportedly unable to reduce nitriles (though the sodium and lithium salts do),[97] but its reactivity to other functional groups such as carboxylic acids, epoxides, and aliphatic halides has not been reported.

Modification of aluminum hydride by amines has been reported by Mukaiyama in 1975 and has already been covered as a method for the reduction of carboxylic acids (see Section 8.11.2.2). They found that the diamino aluminum hydrides obtained from *N*-methylpiperazine and morpholine were most effective at partially reducing simple carboxylic esters to aldehydes.[98] The yields reported on the relatively small sample studied were good (56–86%), though the reagent is relatively unselective, reacting with carboxylic acids[8] and amides[99] as well. Little uptake of this method has occurred in the literature, probably due to the yields not being any better than those of DIBAL. The reaction does need to be heated in THF under reflux, which may interest the researcher whose substrate is only sparingly soluble under other conditions.

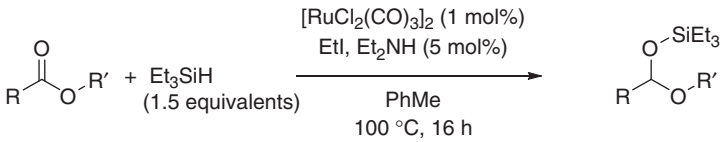
Finally, Brown and Weissman have demonstrated that lithium tri-*tert*-butoxyaluminohydride could selectively reduce phenyl esters of carboxylic acids to aldehydes in low-to-good yields (33–77%).[100] Other ester functional groups are reportedly unreactive as well as many other functional groups (other than acyl chlorides – see Section 8.11.3.2). This method has been applied to the synthesis of amino acid and peptide aldehydes.[101]

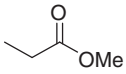
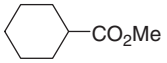
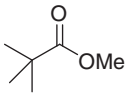
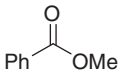
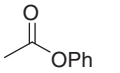
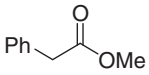
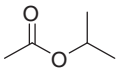
8.11.4.2 Silicon-H

Silanes have been known to be effective at completely reducing esters since the early 1980s. In the mid-1990s Buchwald reported a silane method for the selective reduction of lactones to lactols (see Section 8.11.5.3). However, the use of silanes for the partial reduction of esters to aldehydes remained elusive until the turn of the twenty-first century. A few methods have appeared over the last decade and the reader is encouraged to follow the developments in this field.

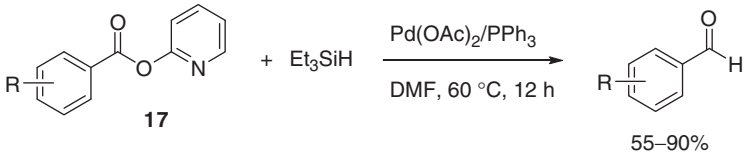
In the first example, hydrosilylation of esters using triethylsilane and 1 mol% of $Ru_3(CO)_{12}$ has been reported by Fuchikami et al. in 2001 to give alkyl silyl acetals in moderate-to-good yields (**Table 7**).[102] Mild hydrolysis of the silyl acetals with 1 M HCl in THF at room temperature releases the aldehydes in very good yield. The authors found that using 1 mol% $(RuCl_2(CO)_3)_2$ with 5 mol% of the cocatalysts diethylamine and ethyliodide gave comparable or slightly better results. The reaction must be performed at 100 °C for 16 h, but the intermediate silyl acetal can be considered as a protecting group for the aldehyde (*tert*-butyldimethylsilane and dimethylphenylsilane give similar yields of the silyl acetal product). The study was relatively limited in scope and only one example of a lactone (γ-butyrolactone) being reported (**Table 7**, entry 8); the yield for this was poor, suggesting this reagent is not suitable for these substrates. The authors report that the hydrolysis step typically returns greater than 90% of the aldehyde from the silyl acetal.

Table 7 Silane reduction of esters catalyzed by hexacarbonyltetrachlorodiruthenium(II)



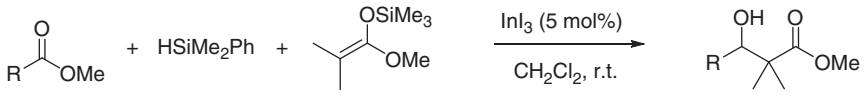
Entry	*Substrate*	*Yield (%)*	*Entry*	*Substrate*	*Yield (%)*
1		57	5		97
2		66	6		63
3		98	7		90
4		91	8		44

In 2006, Chatani and coworkers reported that 2-pyridynyl esters (**17**) could be selectively reduced to aldehydes using a palladium catalyst and triethylsilane as reductant (equation 4).[103] The reaction is important in that it tolerates a wide variety of functional groups, including aromatic fluoro, methoxy, ester, acetate, acetal, and aldehyde groups. Aromatic esters gave the best results with yields between 55% and 90%; one example of an α,β-unsaturated ester gave a 74% yield.



(4)

It is perhaps worth highlighting that Baba et al. have reported an interesting direct use of esters in the Mukaiyama aldol reaction via the *in situ* reduction of the ester using indium triiodide and dimethylphenylsilane as reductant (equation 5).[96] The catalyst was important as indium tribromide is known to reduce esters to ethers in the presence of triethylsilane.[104] The aldehydes themselves were not isolated in this study, but this may offer another route via the hydrosilylation method.

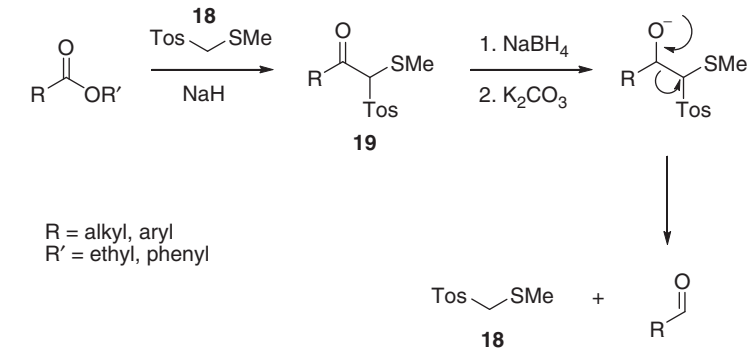


(5)

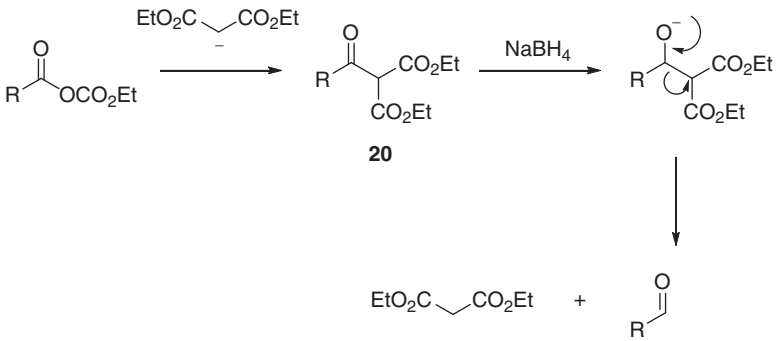
8.11.4.3 Miscellaneous

An unusual method for reducing carboxylic acid esters to aldehydes involves the formation of a C–C bond which is then cleaved in a reverse aldol fragmentation reaction. Thus esters are allowed to react with the anion of methyl(tosylmethyl)sulfane (**18**) forming ketones of the form (**19**). Although ethyl esters gave good-to-moderate yields, the best conversions were obtained when phenyl esters were used. Subsequent reduction of the ketone with sodium borohydride, followed by treatment by potassium carbonate afforded the aldehyde and methyl(tosylmethyl)sulfane (**18**) in near quantitative yields (**Scheme 9**).[105] The samples studied were however very small and only aromatic esters gave excellent results. A single example of an aliphatic ester required the addition of 5 mol% 18-crown-6 to obtain good yields.

A conceptually similar method involves the formation of an acylmalonate (**20**) which when reduced with sodium borohydride undergoes fragmentation under the alkaline reaction conditions to give the aldehyde and malonic ester (**Scheme 10**).[106] Neither of these reactions though has found application in synthetic schemes.



Scheme 9



Scheme 10

8.11.5 Lactones

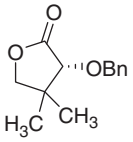
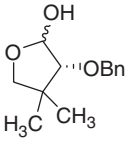
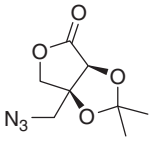
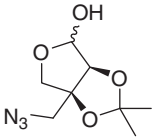
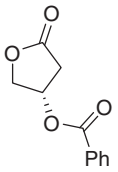
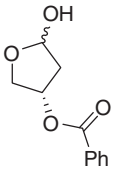
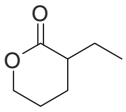
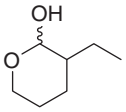
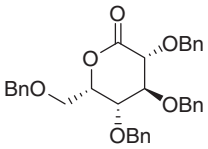
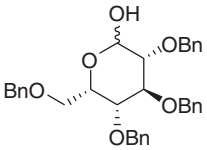
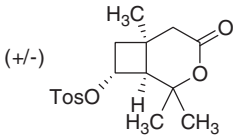
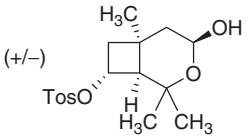
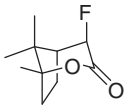
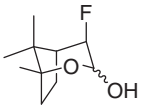
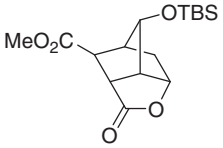
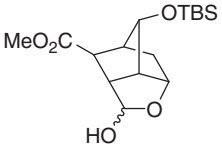
Lactones are mentioned separately since their reactivity is quite different than that of esters. This is exemplified by the partial reduction of a lactone to a lactol which is much easier than the ester equivalent owing to the greater stability of the lactol intermediate. This stability though is directly linked to the size of the lactol ring with five- to seven-membered lactols being very readily obtained in good yields. Lactones with larger rings are seldom selectively reduced and are very rare in the literature. These should be treated as esters and the methods in Section 8.11.4 explored. In general, the partial reduction of lactones to lactols is dominated by the aluminum hydride reagents, particularly that of DIBAL. Boron hydrides feature as well, but the introduction of silanes in the mid-1990s as selective reductants for lactones is perhaps the most important development in this chemistry in recent years.

8.11.5.1 Aluminum-H Reagents

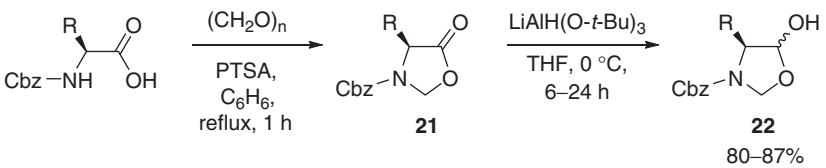
If one compares the reagent literature, comparatively little work has gone into the modification of aluminum hydride reagents for the selective reduction of lactones. This is unsurprising since the relative ease of partially reducing lactones means that the mainstays of this class of reagent, particularly diisobutyl aluminum hydride, have stood the test of time. This is not to say they are completely free of problems, but rather that unlike the selective partial reduction of esters, there is little reason to explore more exotic reagents to achieve this transformation. In principle, all the reagents used for the partial reduction of esters should be suitable for this transformation, but often the reports on these reagents fail to include lactones and so little information is available. The focus is on some of the more popular reagents that have been applied in the literature. In this regard it is fitting to start with mention of DIBAL, since it is excellent at converting lactones to lactols and is indeed the method of choice on the laboratory scale. A general search of the literature reveals that it has been used in just more than 60% of the reported conversions of γ-, δ-, and ε-lactones to their respective lactols (Table 8). Yields are usually excellent, though it should be highlighted that cryogenic temperatures are typically required (-78 °C to -60 °C).[107,108] The reagent can also be very selective and tolerates a wide variety of functional groups, for example, epoxides, halides, alkenes, ethers (including silyl), acetyls, azides, etc. Importantly, esters are often tolerated since the lactone is usually more electrophilic and thus stoichiometric control affords good yields of the lactol in the presence of the ester (Table 8, entries 3 and 8). Aldehydes and ketones would need to be protected.

LAH is also suitable, though success usually requires very careful control of the reagent stoichiometry. In these cases high yields of γ-lactols have been reported.[117] Other aluminum hydrides can be used, such as sodium bis(2-methoxyethoxy)ethoxyaluminum

Table 8 Selection of reductions using DIBAL as reported in the literature

Entry	*Substrate*	*Product*	*Yield (%)*	*Reference*
1			94	109
2			93	110
3			75	111
4			100	112
5			92	113
6			85	114
7			100	115
8			76	116

hydride which is Red-Al modified with an ethoxy ligand. This modified version of Red-Al is reported to reduce γ-lactones to lactols in excellent yields in less than 1 h at 0 °C. Without the ethoxide ligand, the reaction becomes uncontrollable and only poor yields are obtained.[88] $LiAlH(O\text{-}t\text{-}Bu)_3$ will also give lactols providing the reaction is carefully controlled.[118,119] As an example of this, Liu et al. reported in 2001 that chiral α-amino lactones **21** could be reduced to the corresponding lactols **22** with lithium tri-*tert*-butoxyaluminohydride in good yields and high optical purity (**Scheme 11**).[120] The authors comment that on these particular substrates, DIBAL and $NaBH_4$ reductions were ineffective.

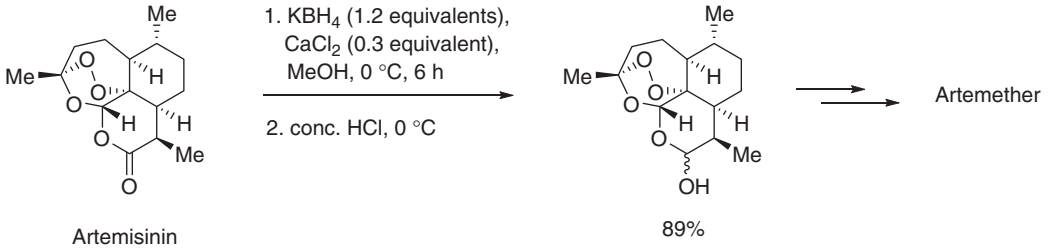


R = methyl, isopropyl, isobutyl, benzyl, phenyl

Scheme 11

8.11.5.2 Boron-H Reagents

Unlike the partial reduction of esters, where boron reagents have proved to be unsuitable choices, the partial reduction of lactones has proved to be facile with borohydride reagents. This fact is directly attributable to the stability of the lactol intermediate. Though not as popular at the aluminum hydrides, they have been shown to be very useful. For example, sodium borohydride has been used to partially reduce monosaccharide (aldonic) lactones when the reactions were conducted at a pH of 3–4.[121] Luche conditions ($CeCl_3 + NaBH_4$) have also been employed in a number of examples where sodium borohydride by itself was unsuccessful.[122,123] On an industrial scale, workers at Novartis used potassium borohydride in the reduction of a natural product (artemisinin) en route to artemether, a component of Coartem which is administered as an effective malarial treatment (Scheme 12).[124] The potassium salt was used as it is more easily manipulated on an industrial scale since it is less hygroscopic.



Scheme 12

In the borane series of reagents, both thexylborane[125] and disiamylborane[126] have been reported to partially reduce lactones to lactols. However, disiamylborane appears to be favored,[127] with it finding greater application in the reduction of aldonic lactones to aldoses.[128] The disadvantage of this reagent is that it must be synthesized just before the reaction as its shelf-life is limited (1 week in the refrigerator is reportedly satisfactory). It should also be reminded that borane reagents will not tolerate the presence of olefinic bonds.

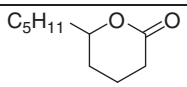
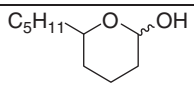
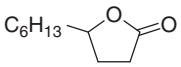
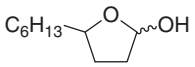
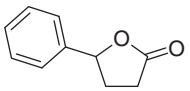
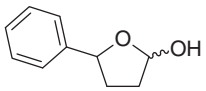
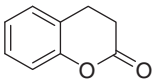
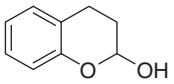
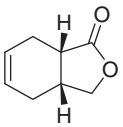
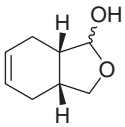
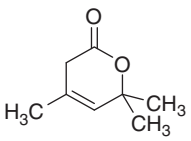
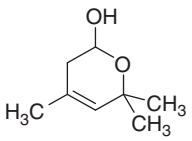
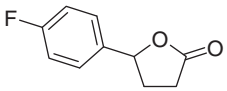
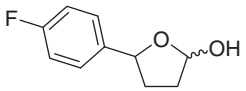
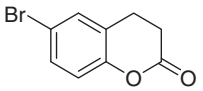
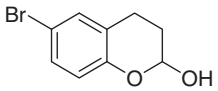
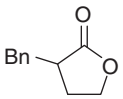
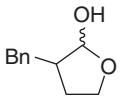
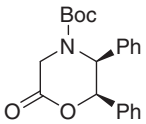
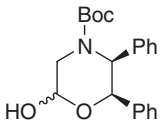
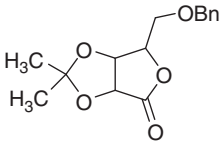
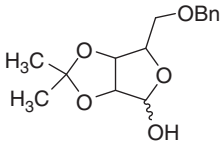
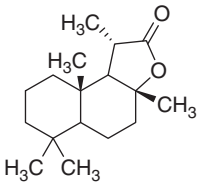
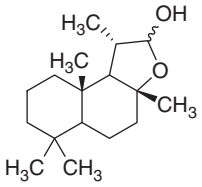
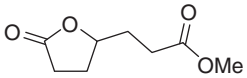
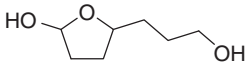
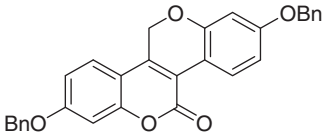
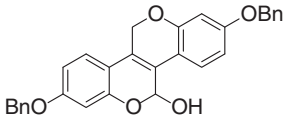
8.11.5.3 Silicon-H Reagents

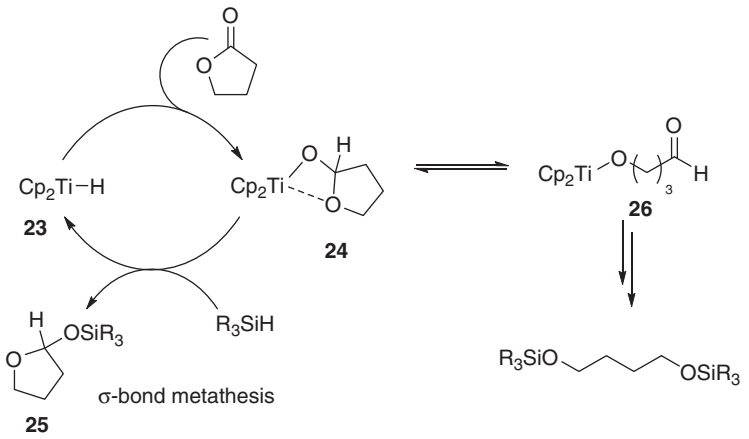
In an important development, Buchwald et al. reported in 1995 that a system employing a titanocene catalyst and polymethylhydrosiloxane (PMHS) as hydride source was very effective at converting lactones to lactols.[129] In a refinement to this study, they revealed that the best catalyst was either bis(η^5-cyclopentadienyl)difluoridotitanium (titanocene difluoride, Cp_2TiF_2) or di(4-chlorophenoxy)bis(η^5-cyclopentadienyl)titanium (titanocene di-*p*-chlorophenoxide, $Cp_2Ti(O\text{-}p\text{-}ClC_6H_4)_2$) both of which are air-stable, returning very good yields when γ- and δ-lactones were used as substrates (Table 9).[130] The reaction tolerates a wide range of functional groups, including some potentially reactive groups such as olefins (entries 5 and 6) and aryl halides (entries 7 and 8). A Boc-group is stable (entry 10) as well an acetyl (entry 11), and it was shown that a chiral center α to the carbonyl of the lactone is not epimerized during the reduction (entry 12). Carboxylic esters are unfortunately unsuitable and are fully reduced to the alcohol stage (entry 13). It should be noted that sterically hindered lactones also reacted poorly and returned high yields of the diol product.

The mechanism is proposed to involve a titanocene(III) hydride (**23**) which adds to the lactone carbonyl affording a titanium alkoxide (**24**, Scheme 13). A σ-bond metathesis reaction with the silane then regenerates the titanium hydride and yields the product silylated lactol (**25**), which is hydrolyzed on work-up with aqueous sodium hydroxide or tetrabutylammonium fluoride. The limitation to the reaction involves a competing reaction pathway with ring opening of the titanium alkoxide to form an alkoxy aldehyde complex (**26**), which on further hydrosilylation would give the fully silylated diol. This pathway is invoked when larger ring lactones are used as substrates, for example, ε-caprolactone gave only 1,6-hexanediol as the sole product.

Despite these rather small limitations this reaction has a number of significant advantages over the classical aluminum hydride methods, particularly for industrial chemistry. First, the reaction is run at ambient temperatures, negating the need for expensive cryogenic reactors. Second, the reaction uses air-stable and cheap reagents that are easily manipulated, particularly in the case of PMHS. Third, the reaction does not require environmentally unsound dichloromethane as a solvent (as is typical of DIBAL reductions). In a practical example of this, Depré and coworkers have described a large-scale synthesis of a bis-chromene lactol using this method (Table 9, entry 14).[131] Compared with the DIBAL method, they found the overall reproducible yield to be higher and the product purity better. Subsequent reactions also gave better yields and most importantly the waste streams from the PMHS method were up to 70% lower than the DIBAL method. It should be mentioned that the report by Fuchikami et al. (covered previously on Section 8.11.4.2 on the hydrosilylation of esters using triethylsilane and $Ru_3(CO)_{12}$ to give alkyl silyl acetals and thus aldehyde) has been shown to be poor at converting lactones to lactols.[102] Depré and coworkers also noted poor yields with this method in their study on the synthesis of the bis-chromene lactol already mentioned.[131]

Table 9 Lactone hydrosilylation using 2 mol% of either $Cp_2Ti(OR)_2$/TBAF (1) or Cp_2TiF_2 (2) as precatalysts

Entry	*Substrate*	*Product*	*Precatalyst*	*Yield (%)*
1			1 2	94 90
2			1 2	97 94
3			1 2	96 89
4			1	87
5			2	88
6			1 2	89 76
7			1 2	96 97
8			1	69
9			1 2	93 87
10			1	92
11			1	91
12			1	94
13			2	88
14			2	88[131]



Scheme 13 Mechanism of titanocene-catalyzed hydrosilylation of lactones.

8.11.6 Carboxylic Acid Amides

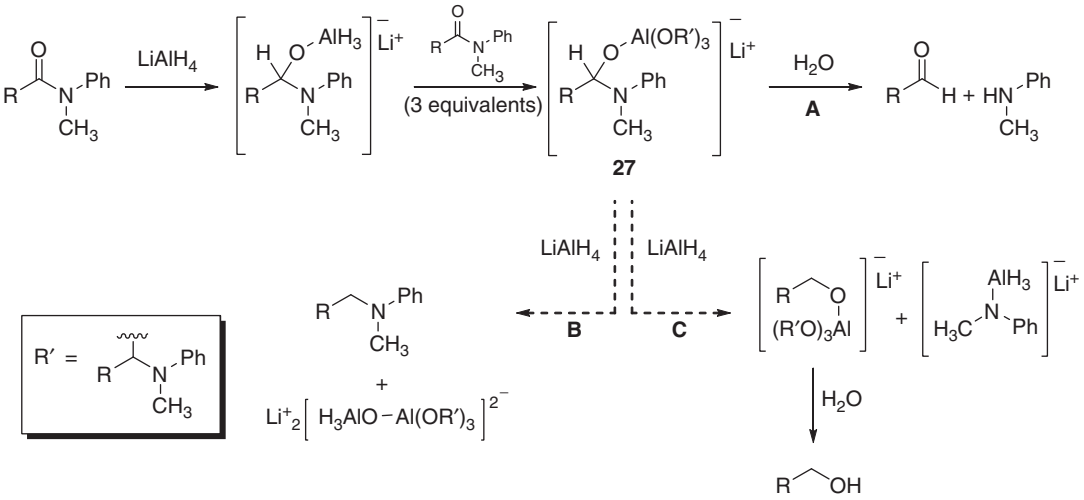
The reduction of amides to aldehydes has a long history going back to the earliest reports on the applications of LAH. Since then many different methods have emerged, though until recently they were all dominated by the derivatives of the aluminum hydride reagents. The application of silanes in the mid-1990s has allowed for a reinvigoration of the field which continues to grow and develop. It should be noted that the partial reduction of amides is controlled not just by the choice of reagent, but also the R-groups on the nitrogen atom; not all are suitable and depend on reagent choice. A few observations can however be made in this regard. First, tertiary amides are better substrates than their secondary or primary counterparts. Second, the use of Weinreb amides (*N*-methoxy-*N*-methyl amides) is extremely popular, followed by *N*-morpholino amides which often show similar reactivity. Amides where the nitrogen atom is bonded to electron-withdrawing groups (e.g., aryl) or is part of a heteroaromatic core are also often, though not exclusively, better reaction partners for partial reduction. Synthetically, the requirement for methods to partially reduce amides to aldehydes must come from the amide's stability in a number of reactions. Thus the amide becomes a masked aldehyde, suitably stable until required in a synthetic sequence. We begin again with the aluminum reagents which have dominated this field, and then introduce the silanes which are extremely promising as alternative reagents for the organic chemist. A couple of reagents are discussed under the title of other methods, not because they should not be considered, but rather that they do not fall under any major obvious grouping. There have been no enzymatic methods reported nor has catalytic hydrogenation been used to partially reduce an amide to an aldehyde.

8.11.6.1 Aluminum-H Reagents

Although it is more typical for LAH to be used to reduce amides to amines, it is equally possible to obtain aldehydes if careful reaction conditions and reagent stoichiometry are controlled. The early literature on using LAH focused on studying the features that promoted high yields of aldehyde product. The main finding was the importance of only 0.25 equivalent of LAH being used, otherwise the usual amine and, to a lesser extent, alcohol side-products are obtained. The mechanism has been discussed and can be seen in Scheme 14.[132] In order to get the best yield of aldehyde, it becomes critical that the reaction stops at intermediate (**27**). From a practical point of view, other than keeping the number of equivalents of LAH to 0.25, best results have been observed when the reducing agent is added slowly to the amide. Then during workup, hydrolysis of intermediate (**27**) results in the aldehyde product (route **A**). The side reactions represented by routes **B** and **C** are important and are controlled by steric and electronic effects. It is proposed that bulky amides stabilize intermediate (**27**) and thus reduce the reaction rate of routes **B** and **C** ultimately giving high yields of aldehyde product. Delocalization of the amide nitrogen lone pair away from the amide bond is also proposed to favor intermediate (**27**) and thus aromatic groups, especially with electron-withdrawing substituents, are more effective. When the amide nitrogen forms part of a pyrrole, indole, or carbazole system,[133] very good yields of aldehyde have been observed. However, electronic effects on the carbonyl-side of the amide bond had little or no effect on the reaction rate.

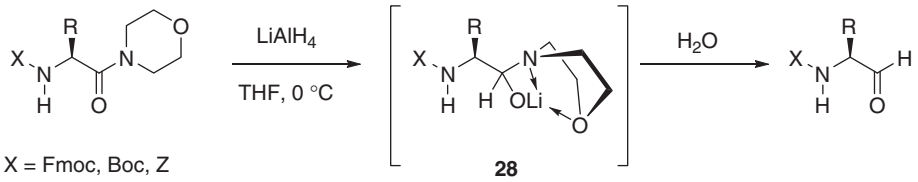
Delocalization of the amide nitrogen has been well explored in other systems. For instance, both acylated pyrazole[134] and imidazole[135] derivatives have been shown to be useful in this reaction. Unusually acyl aziridines are also reported to give very good yields of aldehydes,[136] even when an excess of $LiAlH_4$ was used,[137] but their expense makes them less attractive. Another very popular choice has been the use of Weinreb amides, which have been reduced to aldehydes with LAH in the presence of, for example, *tert*-butyl esters[138] and *N*-Boc groups.[139]

Another important group has been the *N*-morpholino amides. For example, Martinez and coworkers reported in 2000 that an *N*-morpholino derivative of protected amino acids could be reduced with excess LAH at 0 °C in 10–20 min.[140] The yields reported



Scheme 14

were comparable to those using the Weinreb amide method (43–75%), and likewise also preserved the stereochemical integrity of the amino aldehyde. The main side-product was the alcohol, which suggested a stable chelate intermediate (**28**, Scheme 15); the alcohol byproduct could not be reduced at lower temperatures and thus running the reduction at 0 °C was preferred.

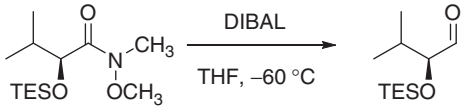


Scheme 15

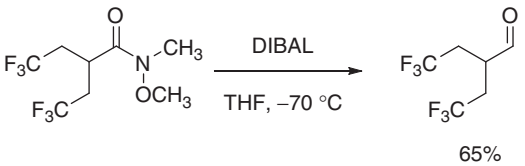
A report in 1969 by Zakharkin et al. suggested that the sodium aluminum hydride ($NaAlH_4$) partial reduction of dimethylamide derivatives gave better yields than the conventional LAH reduction.[141] This report has however been poorly cited in the literature and thus remains unconfirmed, possibly due to this reagent not normally being found in research laboratories.

The obvious problem with using lithium (or sodium) aluminum hydride to partially reduce amides is that of functional group tolerance since LAH is a powerful reducing agent. Ketones, aldehydes, and esters (except *tert*-butyl esters) are amongst the obvious groups that are incompatible and must be protected or masked before reduction of the amide. One should also note that the reduction of primary and secondary amides generally gives lower yields and could be considered wasteful since hydrogen gas will be produced from the valuable hydride.

Other aluminum hydride derivatives have also been widely studied and applied to the reduction of amide bonds to aldehydes. The most popular derivative is DIBAL and it has been shown to be generally better than LAH at this transformation, provided a tertiary amine is used.[142,143] The preference though appears to be to combine a Weinreb amide with DIBAL, a reaction first reported by Weinreb himself.[144] Two examples of this are shown in equations 6 [145] and 7 [146] and come from the industrial process literature. In all cases, cryogenic temperatures are important (− 78 to − 60 °C) to prevent overreduction to the alcohol, though an excess of the reagent is tolerated.



(6)



(7)

A number of authors have investigated the effect of modifying DIBAL to improve its selectivity in reductions. On the whole, the modifications have not been rapidly adopted by researchers, perhaps because the initial studies are often conducted on a very limited pool of substrates or because they are relatively recent methods. Three modifications will be mentioned, starting with one of the more recent ones already covered in Section 8.11.3.2 (Table 3) on the *in situ* reduction of acid chlorides. PDBBA, described by Choi et al. is reported to reduce *N*-morpholino amides to aldehydes in high yields.[58] The substrate scope is rather specific for the *N*-morpholino amide as low yields are observed for amides derived from diethylamine, dicyclohexylamine, pyrrole, and indole. This specificity is not observed for the lithium and sodium salts of this reagent, both of which reduce *N*,*N*-dimethylamides in excellent yields (Table 10), whereas PDBBA gave only trace quantities of aldehyde even after 24 h.[147] On the carboxylic acid side of the amide, the substrate scope appears to be reasonable, with aromatic, heteroaromatic, alkyl, and unsaturated amides being suitable substrates. It should be noted that esters will also be reduced by these reagents (see Section 8.11.4.1), but that a nitrile functional group is stable to PDBBA.[148] The advantage of this reagent is that it can be used at room temperature which may be of important significance to process chemists.

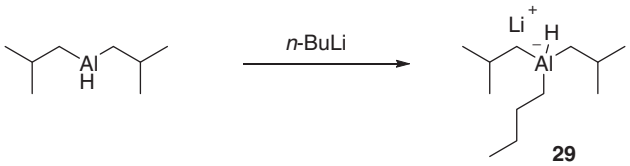
Table 10 Lithium diisobutyl-*t*-butoxyaluminum hydride reduction of *N*,*N*-dimethyl amides

Entry[a]	*Compound*	*GC Yield of aldehyde (%)*
1	*N*,*N*-Dimethyl benzamide	99
2	*N*,*N*-Dimethyl 4-chlorobenzamide	92
3	*N*,*N*-Dimethyl 4-methoxybenzamide	90
4	*N*,*N*-Dimethyl 3-toluamide	96
5	*N*,*N*-Dimethyl 3-nitrobenzamide	30
6	*N*,*N*-Dimethyl 2-naphthylamide	98
7	*N*,*N*-Dimethyl 2-furoamide	91
8	*N*,*N*-Dimethyl caproamide	89
9	*N*,*N*-Dimethyl dodecanoamide	99
10	*N*,*N*-Dimethyl cyclohexanecarboxamide	76
11	*N*,*N*-Dimethyl cinnamamide	29

[a]Reactions conducted for 1 h with 1.5 equivalents of hydride reagent.

Second, as already mentioned in Sections 8.11.2.2 and 8.11.4.1, another way that DIBAL has been modified is with an amino group. Woo et al. have reported that the reaction of DIBAL with lithium piperidide (formed by treating piperidine with *n*-butyllithium), resulted in lithium diisobutyl(piperidin-1-yl)aluminum hydride (LDBPA) that was capable of reducing *N*,*N*-dimethyl amides to aldehydes at 0 °C within 1 h.[149] Yields were generally more than 90%, except for two examples: *N*,*N*-dimethyl 3-nitrobenzamide and *N*,*N*-dimethyl cinnamamide which returned 30% of the aldehyde product. Comparing the results of this study and the previous one, PDBBA is more likely to emerge as the better reagent for this transformation.

Lastly, Kim and Ahn have reported that *n*-butyldiisobutylaluminum hydride (**29**, LiAlH(*i*-Bu)$_2$(*n*-Bu)), formed by the reaction of DIBAL with *n*-butyllithium (equation 8), could reduce tertiary amides to aldehydes with 1 equivalent of the reagent at room temperature (Table 11).[150] Primary or secondary amides were not reduced, even with excess reagent; carboxylic acids were also stable under the reaction conditions. Nitriles reacted slowly at room temperature, whereas esters, lactones, thiol esters, acid chlorides, and anhydrides were all reduced to the alcohol stage.

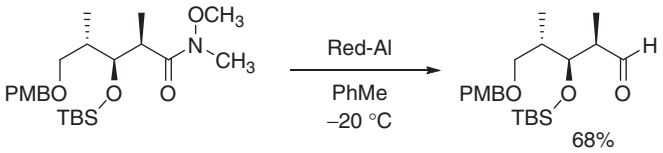


29 (8)

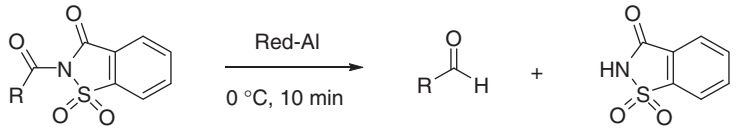
Table 11 Reduction of tertiary amides with *n*-butyldiisobutylaluminum hydride

Entry	*Compound*	*LiAlH(i-Bu)$_2$(n-Bu) equivalent*	*Time (h)*	*GC Yield of aldehyde (%)*
1	Benzamide	3	7	0
2	Caprylamide	3	7	0
3	*N*-*n*-Butylbenzamide	3	7	0
4	*N*-*n*-Butylcaprylamide	3	7	0
5	*N*,*N*-Diethylbenzamide	1	2	97
6	*N*,*N*-Diethylcaprylamide	1	1	99
7	*N*-Benzoylpiperidine	1	0.1	95
8	*N*-Capryloylpyrrolidine	1	1	98

Just as adding alkyl substituents to aluminum hydrides increases their reactivity, adding alkoxy substituents has a tempering effect. Though not widely used, sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) has been explored in the partial reduction of amides. More typically it is partnered with Weinreb amides, but other secondary amides are selectively reduced as well. Some cases of the reductive cleavage of nitrogen-based chiral directing groups to aldehydes are also reported, for example, a benzyl oxazolidinone[151] and an *N*-acyl proline derivative.[152] Simple alkyl, cycloalkyl, and aryl saccharin amides were reduced, including a simple cinnamamide. An example from Mickel and coworkers at Novartis describes a Red-Al reduction of a Weinreb amide as part of their large-scale study toward the C_{9-14} fragment of (+)-discodermolide (equation 9).[153] Important to note is that they found that this reagent was better than DIBAL and could be run at higher temperatures ($-20\ ^{\circ}C$ vs. $-78\ ^{\circ}C$ for DIBAL) resulting in less of the alcohol byproduct. Another slightly unusual example comes from the Red-Al reduction of amides derived from saccharin to aldehydes (equation 10), although the yields are not as high as some other methods (60–80%).[154]



(9)



(10)

Other aluminum alkoxide derivatives have been prepared, but only lithium triethoxyaluminum hydride has been shown by Brown and Tsukamoto to be particularly good at reducing a wide range of *N*,*N*-dimethylamides to aldehydes (isolated yields between 60% and 80%).[155] Other aluminum alkoxides were not as effective, giving lower yields.

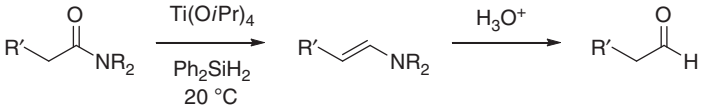
Modification by amines has also been studied, and the bis(4-methyl-1-piperazinyl)aluminum hydride reagent of Mukaiyama (already covered in Section 8.11.2.2) has been used to partially reduce a variety of tertiary amides.[99] The deactivation of the hydride by the amino groups is noticeable in that the amide needs to be refluxed with the reagent in THF. Aromatic acyl amides gave poor yields of aromatic aldehydes, whereas aliphatic tertiary amides resulted in favorable isolated yields of aldehyde products (70–80%).

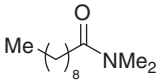
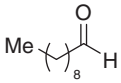
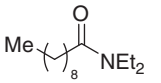
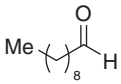
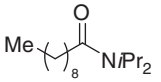
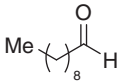
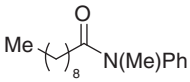
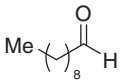
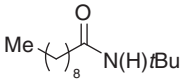
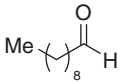
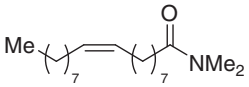
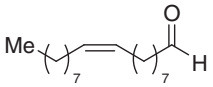
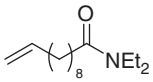
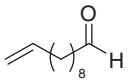
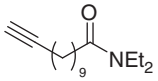
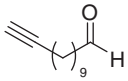
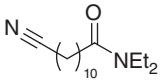
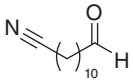
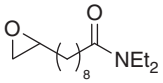
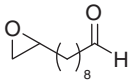
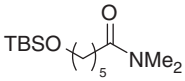
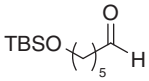
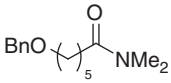
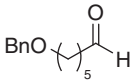
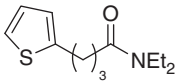
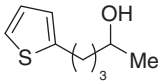
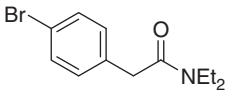
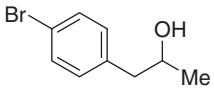
8.11.6.2 Silicon-H Reagents

Buchwald et al. reported the first example of using a silane as a reductant for the partial reduction of amides.[156] By drawing on their work demonstrating partial reductions of esters and lactones, the team at MIT could show that a combination of 1 equivalent of $Ti(OiPr)_4$ and 1.1 equivalents of Ph_2SiH_2 was efficient at partially reducing amides to their corresponding aldehyde. The reaction tolerated a wide range of functional groups, including nitriles, ethers (alkyl and silyl), epoxides, alkenes, and alkynes. Furthermore, the reaction appeared to be insensitive to the choice of amide group with tertiary and secondary amides being equally effective. Though the precise nature of the mechanism was not confirmed, it was known that the reaction proceeded via the enamine, which was hydrolyzed on work-up with 1 M HCl. This introduced a number of acknowledged limitations to the method, particularly the fact that only amides with α-hydrogen atoms were efficiently reduced. Lack of this in the substrate gave complex mixtures or mixtures of alcohol and aldehyde products. Furthermore, α-chiral amides would be completely epimerized and also the reactivity of the aldehyde products with α-(hetero)aryl groups meant these could not be isolated and were reacted *in situ* with methyl magnesium bromide (**Table 12**, entries 13 and 14).

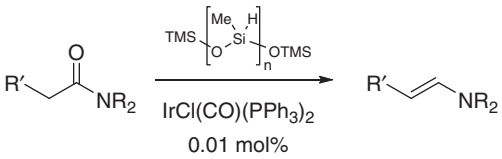
Although not promoted as a means of partially reducing amides to aldehydes, Nagashima et al. have reported a facile variation to the Buchwald method.[157] Their method has been explicitly touted as a means of synthesizing enamines from amides, but these could be in principle hydrolyzed in much the same way as Buchwald reported in his system. The Nagashima protocol involves using an iridium catalyst ($IrCl(CO)(PPh_3)_2$) with PMHS as the reductant (equation 11). The reactions are run in toluene at room temperature and typically take 30 min to reach completion. Besides the very low catalyst loading needed (0.01 mol%), the major advantage is that the product enamine can be isolated by filtration since the PMHS is insoluble and the iridium catalyst is adsorbed onto the polymer during the reaction. Importantly, this reaction tolerated a methyl ester, an alkyl bromide, and a ketone; presumably the functional groups mentioned by Buchwald are also tolerated.

Table 12 Diphenylsilane reduction of amides catalyzed by titanium isopropoxide



Entry	*Substrate*	*Product*	*Yield (%)*
1			74
2			90
3			78
4			83
5			90
6			86
7			90
8			71
9			80
10			50
11			87
12			81
13[a]			65
14[a]			80

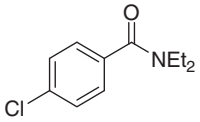
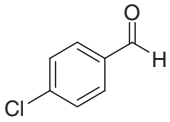
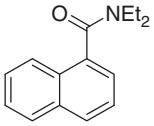
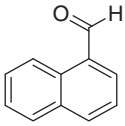
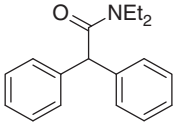
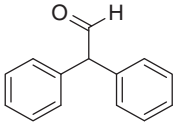
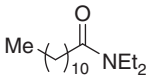
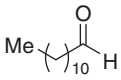
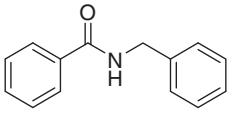
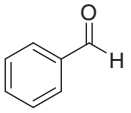
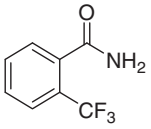
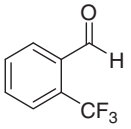
[a]These reactions were quenched with MeMgBr.



(11)

In another slight but important modification of the Buchwald method, Lemaire and coworkers reported that a 1,1,3,3-tetramethyldisiloxane/titanium(IV)isopropoxide reducing system extended the scope of the earlier method, allowing amides without α-hydrogen atoms to be reduced to aldehydes (Table 13).[158] The substrates reported did not include a wide variety of functional groups and so it may take time for other authors to apply this method. One observation was that secondary amides appear to be suitable substrates (entry 5), whereas a primary amide was essentially untouched after 24 h at room temperature (entry 6). The authors suggest that a single electron transfer process was taking place, invoking a Ti(III) species; this proposal was based on other studies conducted in their laboratory.

Table 13 Reduction of amides with TMDS/Ti(OiPr)^4

Entry[a]	*Substrate*	*Product*	*Yield (%)*
1			81
2			75
3			85
4			90
5			86
6			3

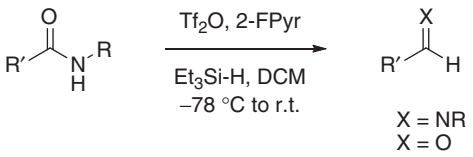
[a]Reactions conducted at room temperature for 24 h.

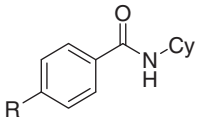
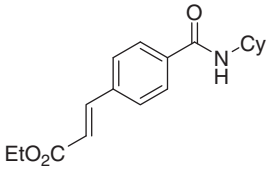
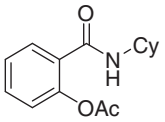
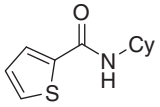
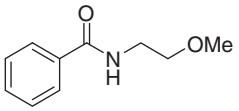
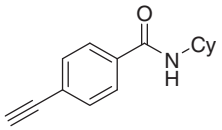
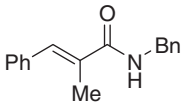
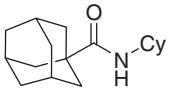
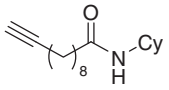
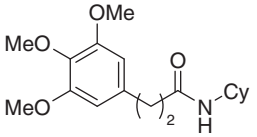
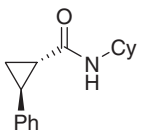
Charette et al. demonstrated that by activating the amide functional group with trifluoromethanesulfonic anhydride (triflic anhydride, Tf_2O), the resultant triflic imidate intermediate can then be easily reduced by very weak hydride donors (Table 14).[159] In this case, triethylsilane was found to be an excellent partner for this reaction. It was further found that the already good yields could be further improved by the addition of very weak bases. In their comprehensive study the authors reported that 2-fluoropyridine resulted in the best yields of aldehyde products. This unusual choice of base was crucial; for example, in one reaction, without any additional base the yield of the imine intermediate was 77%, but including a more conventional base such as pyridine resulted in a severely decreased yield.

8.11.6.3 Boron-H

Borane and borohydride reagents are in general very poor choices for the partial reduction of amides to aldehydes. Thexylborane reduction of amides is difficult to control and mixtures of aldehyde and alcohol are obtained. Disiamylborane has shown better success on simple tertiary amides,[126,160] but this has been poorly adopted by the literature. One report has investigated the use of lithium tri-*sec*-butylborohydride (L-Selectride) after the amide had been activated by ethyl triflate (EtOTf).[161] Although reasonable yields of product were reported, the reaction was never observed to go to completion. It should be noted that other hydride reducing agents were also examined, but without better results.

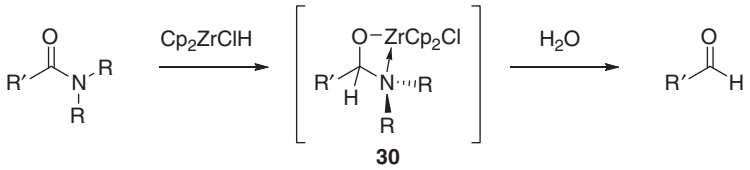
Table 14 Silane reduction of amides activated by trifluoromethanesulfonic anhydride



Entry	*Substrate*		*Yield imine (%)*	*Yield aldehyde (%)*
1		R = H	81	89
2		R = CN	88	89
3		R = NO_2	84	81
4		R = N_3	88	89
5		R = CO_2Me	95	90
6		R = CHO	81	84
7		R = $PO(OEt)_2$	65	64
8		R = $CONEt_2$	99	95
9			96	96
10			80	84
11			85	80
12			79	85
13			95	94
14			75	92
15			78	70
16			80	72
17			75	70
18			83	84

8.11.6.4 Other Methods

An unusual choice of metal hydride that has shown success in the partial reduction of amides is chloridobis(η^5-cyclopentadienyl)hydridozirconium (Cp_2ZrClH), commonly known as Schwartz's reagent. In 2000, Georg et al. communicated their findings that Cp_2ZrClH rather effectively gave the aldehyde product from a range of amide substrates (**Scheme 16**).[162] A more comprehensive study appeared later by the same group, building on their earlier findings and mechanistic proposals.[163] The only drawback to this method is the need for stoichiometric quantities of the reagent which will be prohibitively expensive for large-scale use. This said, the reagent has a number of key features that may interest the synthetic chemist. First, aromatic, heteroaromatic, and aliphatic amides are all efficiently reduced (yields are mostly more than 90%). The amide itself can be primary, secondary, or tertiary, though tertiary amides are reported to give slightly better yields. Weinreb amides are also suitable substrates, though not necessary for improved yields. Importantly, ester functional groups and *tert*-butylcarbamate groups are not reduced, and the reaction is fairly tolerant of conjugated alkenes. Alkynes are however not suitable, which is unsurprising since Schwartz's reagent is known to react with these functional groups. Another feature arises from the fact that the deuterated reagent, Cp_2ZrClD, is readily available allowing for deuterated aldehydes to be synthesized in excellent yields.[164] Practically the synthesis is reportedly trivial; the reagent and substrate are stirred at room temperature in THF for 15–30 min and then passed through a short plug of silica gel to purify the aldehyde.



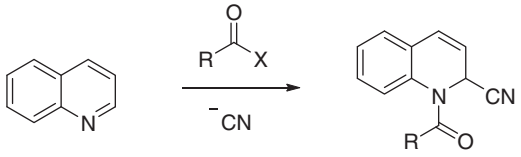
30

Scheme 16

The mechanism of the reaction has been proposed by Georg et al. in their publications and has been investigated by Philips and Zhao using density functional theory calculations.[165] These calculations suggest that the first step of the reaction is the coordination of the carbonyl oxygen with the zirconium atom. This is followed by the hydrogen atom of the Zr–H bond migrating to the carbonyl carbon to form the stable intermediate (**30**) via a four-centered transition state. The key to the success of this reaction is that under anhydrous conditions the cleavage of the carbon–oxygen single bond in (**30**), which would result in the formation of an iminium cation, is both kinetically and thermodynamically unfavorable. On addition of water, a strong hydrogen bond between the oxygen atom and H_2O is formed which assists the cleavage of the carbon–oxygen bond in (**30**) leading to a highly active iminium cation. Hydrolysis of the iminium cation then yields the aldehyde product. This study confirmed the mechanistic observations by Georg et al. that the source of the oxygen atom of the aldehyde was from the water and the hydrogen atom from Schwartz's reagent.

Next, it should be briefly mentioned that Kamochi and Kudo have reported a samarium(II) iodide procedure that is capable of reducing primary aromatic amides to substituted benzaldehydes in excellent yields.[166] Unfortunately the method is unsuitable for aliphatic amides, or for secondary/tertiary amides.

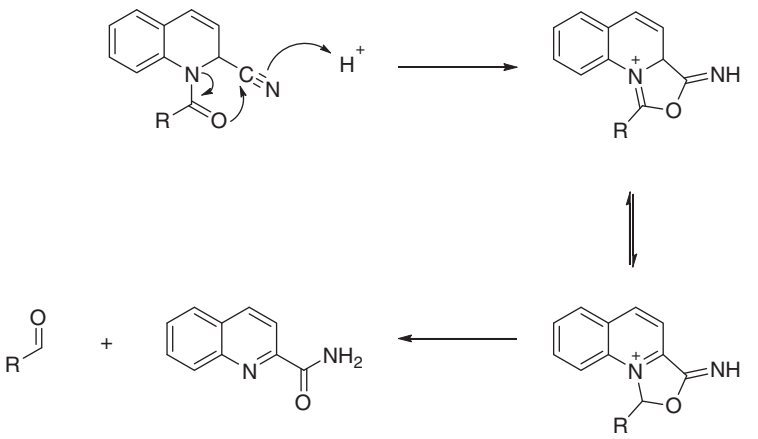
A rarely used method that will be covered lastly is the acid-catalyzed decomposition of Reissert compounds (e.g., **31**).[167] These are formed by the acylation of a C═N nitrogen, followed by the addition of a cyanide anion to the iminium intermediate. An example using quinoline is shown in equation 12. What is important though, in the context of obtaining aldehydes, is that these compounds can be induced to cleave under acidic conditions to give the desired aldehyde (**Scheme 17**).[168] The application of this method as a practical means of obtaining aldehydes is poorly represented in the literature, possibly because of the generally moderate yields obtained when forming the Reissert compound itself.[169,170] Yields of the aldehyde are usually excellent on decomposition with aqueous HCl or H_2SO_4, though aromatic aldehyde yields are usually superior.



(12)

31

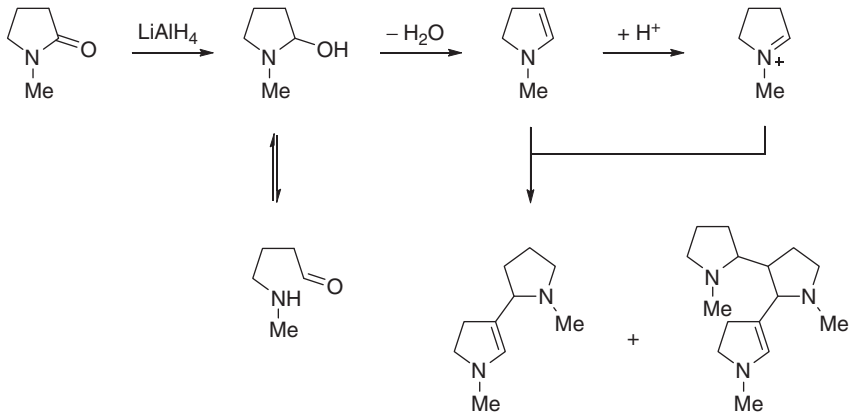
Single electron[171] and electrochemical[172] reduction of amides to aldehydes are also known methods, but the yields and selectivities obtained from these reactions are of little synthetic use and will not be discussed here.



Scheme 17

8.11.7 Lactams (Including Cyclic Imides)

There have not been many specific studies on the partial reduction of lactams to cyclic amino alcohols (hemi-aminals), partly owing to the relatively unstable nature of these products. One of the first records of this reduction was by Galinovsky et al. using stoichiometric quantities of LAH to reduce *N*-methyl pyrrolidinone.[173] This product, as well as that of *N*-methyl piperidinone, was susceptible to di- and trimerization confirming their instability (Scheme 18).[174]

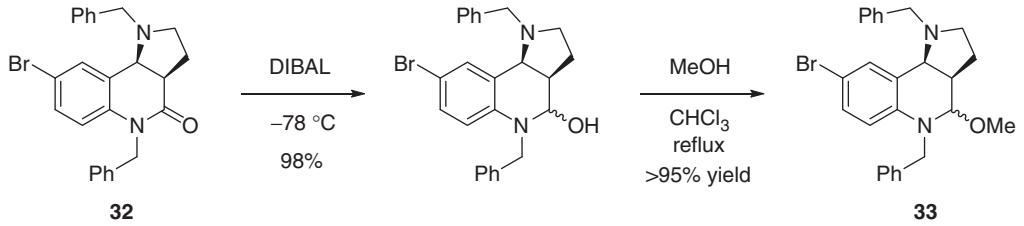


Scheme 18

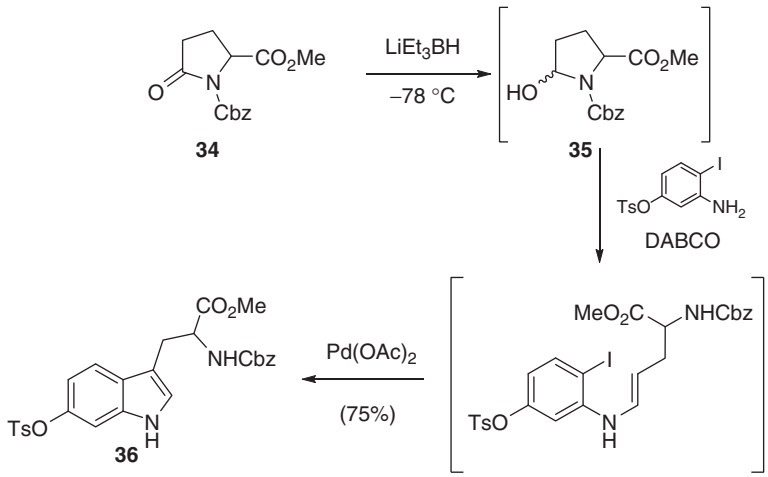
More often, the reduction of a lactam to the hemiaminal is immediately followed by a second reductive step in order to access the cyclic amine (see Section 8.10.7 in Chapter 8.10). Although in principle most of the methods described for the partial reduction of amides could be used, the reagents of choice have been DIBAL and Super-Hydride® (lithium triethylborohydride, $LiBH(Et)_3$). Two representative examples from the literature will be mentioned here to demonstrate their use on a practical level. This first comes from He and coworkers' formal total synthesis of martinellic acid. An early goal was the synthesis of the methoxy aminal (**33**) from the known lactam (**32**).[175] This was achieved in an exceptionally high yield by DIBAL reduction at $-78\ ^{\circ}C$, followed by heating the product in a mixture of methanol and chloroform (Scheme 19).

The second example comes from Baran et al. who describe a short, enantioselective synthesis of Stephacidin A, a structurally complex prenylated alkaloid.[176] The first step in their synthesis involved a selective reduction of pyroglutamate derivative **34** with Super-Hydride® ($LiBH(Et)_3$). The product, which is an aldehyde in its ring-opened form, was allowed to react immediately with an aniline derivative which was then ring-closed *in situ* using a Heck reaction to give a 75% yield of indole **36** (Scheme 20).

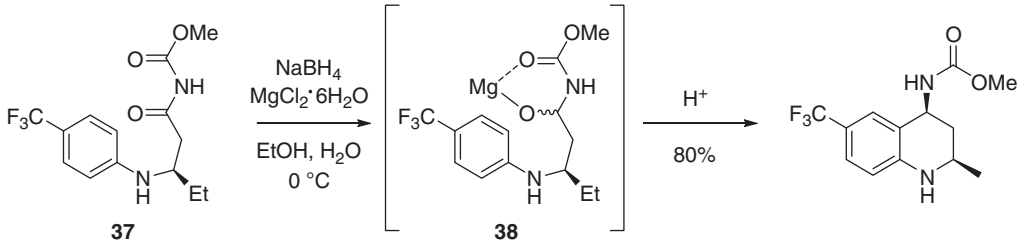
Partial reduction of imides to give hydroxy-lactams is however much more common and has been extensively used as a means of generating *N*-acyliminium ion precursors.[177,178] Unlike the partial reduction of amides and lactams, metal borohydrides have been successfully employed, and are most commonly used in the partial reduction of cyclic and acyclic imides. One example involves a synthesis of an intermediate of a compound used to treat cardiovascular disease. Here, the imide (**37**, Scheme 21) was partially reduced with sodium borohydride in the presence of magnesium chloride.[179] In this particular case, the magnesium salt was important to activate the imide and stabilize the intermediate (**38**) preventing overreduction (as was observed with other metal salts). Acid quench afforded the cyclized product via the *N*-acyliminium species.



Scheme 19

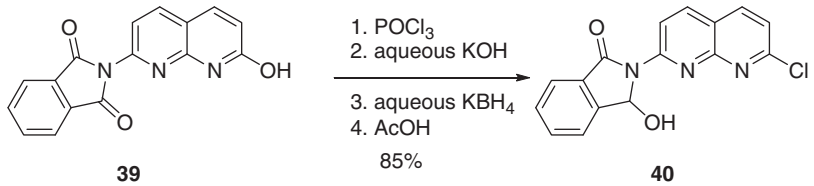


Scheme 20



Scheme 21

Another example typical of cyclic imide partial reduction comes from Stuk et al. where a succinimide intermediate (**39**) underwent a one-pot chlorination/reduction process (equation 13).[180] Potassium borohydride was successfully used to give high yields of the desired hydroxy lactam (**40**).



(13)

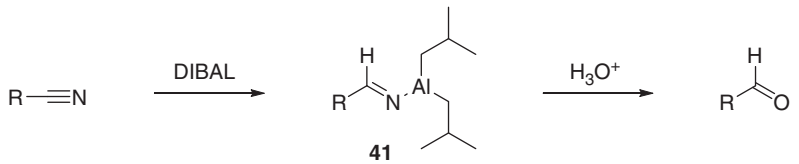
DIBAL,[181] Super-Hydride®,[182] and Red-Al® [183] have also been successfully employed in the literature.

8.11.8 Nitriles

The partial reduction of nitriles to aldehydes is quite a common feature in synthetic transformations. The stability of the nitrile makes it a good choice for unmasking as an aldehyde in a synthetic sequence. The range of applicable methods that can successfully accomplish this transformation is however somewhat limited. In the metal hydride class of compounds, DIBAL is almost exclusively used as the preferred method, though it has a distinct disadvantage of reacting with many other reducible functional groups. In the nonhydridic class of reagents, Raney nickel stands out as a superior method with excellent substrate functional group tolerance. It is therefore somewhat surprising that this method is not more frequently applied, though it should be noted that there has been a small increase in the number of reported reactions since 2000.

8.11.8.1 Metal Hydrides

Although a number of metal hydrides have been used to effect the reduction of a nitrile to an aldehyde, the most common choice in the literature has been DIBAL.[181] Indeed in almost three quarters of the literature-reported reactions of this type, DIBAL has been used as the preferred reagent. The reaction was first described by the discoverers of DIBAL, Zakharkin and Khorlina in 1957 and was enthusiastically adopted by the chemical community.[184] The reaction requires 1 equivalent of DIBAL which rapidly reduces the nitrile to a relatively stable aldimine intermediate (**41**) as shown in Scheme 22. This is then hydrolyzed under acidic conditions to release the desired aldehyde. Yields for this reaction are generally very good (50–90%), though aromatic nitriles are better substrates. The usual tolerance for functional groups is observed, thus organic halides (alkyl and aryl), ethers (including silyl ethers), acetals, alkenes, and carbamates are unaffected. Aldehydes, ketones, and carboxylic acids will be reduced; esters are also typically reduced by DIBAL, however good control can be had if a sterically hindered ester such as *tert*-butyl ester is used. In a report from 1994, Cha and coworkers recommended that the addition of dimethyl sulfide to DIBAL results in a reagent that gives slightly better yields than DIBAL itself,[185] though this has as yet not been adopted in the literature.



Scheme 22

Other variations on the metal-hydride theme are known. For example, LAH has been used and occasionally gives good yields,[186–189] though this reagent is seldom the first choice for this reaction. Lithium trialkoxyaluminum hydrides have also been explored by Brown and coworkers, with the favorite being lithium triethoxyaluminum hydride in diethyl ether.[190] The reagent is conveniently prepared *in situ* by reacting LAH with 1.5 equivalents of ethyl acetate at 0 °C for 30 min, before addition of the nitrile. The reduction itself is usually complete within 1 h at 0 °C and yields are generally good for aliphatic and aromatic substrates (58–96%). Since reductions of nitrile groups require powerful reducing agents, it is not surprising that this reagent is not tolerated by other groups such as ketones, aldehydes, esters, and carboxylic acids.

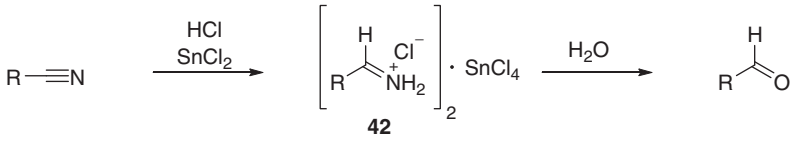
The sodium salts of all the reagents mentioned previously have been explored but have not demonstrated any performance gain over their lithium counterparts.[191–193] Thus, considering the readier availability of the lithium salts, these are not particularly attractive options. The more well-known reagent sodium bis(2-methoxyethoxy)aluminum dihydride (Red-Al®) gave only trace quantities of amines and is therefore unsuitable for this reaction.[194]

A number of other aluminum hydride derivatives have appeared in recent years and may find some application in this particular conversion. For instance, amino derivatives of LAH such as lithium tris-(dihexylamino)aluminum hydride (LTDHA)[195] and lithium *N*,*N*′-dimethylethylenediaminoaluminum hydride (LDMEDAH)[196] have been reported; these reagents give high yields of simple aromatic aldehydes from the nitrile, but do not react with aliphatic or heteroaromatic nitriles. This may be considered a feature for selective reduction of an aromatic nitrile in the presence of an aliphatic one. An and coworkers have shown that their DIBAL derivatives, lithium diisobutyl(piperidin-1-yl)aluminum hydride (LDBPA),[197] lithium diisobutyl-*iso*-propoxyaluminum hydride (LDBIPA),[148] and lithium diisobutyl-*tert*-butoxyaluminum hydride (LDBBA)[148] are similarly effective, giving high yields of aromatic aldehydes between 0 °C and room temperature, whereas aliphatic nitriles are unaffected. Lastly, catecolalane (1,3,2-benzodioxaluminole) was said to reduce aliphatic and aromatic nitriles to aldehydes in high yield at room temperature,[198] but the only reference to its use in the literature reported failure on their substrate.[199]

Borohydrides or boranes are inefficient choices: disiamylborane[126] and thexylborane[125] react very slowly with nitriles and give very low yields of aldehyde products. The only boron reagent reported to efficiently partially reduce nitriles is potassium 9-*sec*-amyl-9-boratabicyclo[3.3.1]nonane,[200] though it has a number of disadvantages. First, it is rather esoteric and not readily available; second, it only slowly reduces simple aromatic nitriles (24 h at room temperature); and third, the products require a complicated isolation procedure involving the bisulfite adduct.

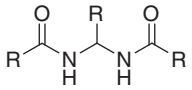
8.11.8.2 Other Methods

The classic nonhydridic method for partial reduction of nitriles to aldehydes is the Stephen reduction (Scheme 23). First reported by Stephen in 1925, the reaction involves the use of a reagent system prepared from tin(II) chloride and anhydrous hydrochloric acid in ether.[201] The mechanism involves the addition of HCl to the nitrile group followed by reduction of this by $SnCl_2$. The initial complex is the aldimine stannic chloride (**42**) which is easily hydrolyzed to the aldehyde. Although the reaction is generally considered to be anhydrous, it has been noted that a small amount of water is beneficial.[202] The reaction is most successful on aromatic nitriles and still finds application in the modern literature,[203,204] though its use has dramatically declined since the 1980s. Aliphatic nitriles have undergone careful study in the Stephen reduction and it has been found that the major source of low yields is trimerization of the intermediates to give compounds of the type (**43**) (Figure 1).[205]



42

Scheme 23



43

Figure 1 Stephen reduction aliphatic trimerization product.

Although Raney nickel is commonly used to reduce nitriles to amines (see Section 8.10.8.1 in Chapter 8.10) under alkaline or hydrogenation conditions, it has also been used to selectively reduce nitrile groups to aldehydes under acidic conditions. This area has been recently reviewed,[206] and is well represented in the literature. Three slightly modified procedures have been studied; they are: Raney nickel and sodium hypophosphite in aqueous acetic acid-pyridine solution;[207] Raney nickel with aqueous formic acid;[208] and a Raney (Ni/Al) alloy and formic acid.[209] The advantages of these systems is that the selectivity for a nitrile group is high, with olefins, ketones, esters, aldehydes, amides, halo compounds, and carboxylic acids being inert (some examples from the literature can be found in Table 15). Surprisingly, examples containing sulfur atoms are not uncommon (such as entry 3 in Table 15), showing a level of selectivity for a functional group well known to be excised by Raney nickel reductions. It should also be noted that this method is only applicable to aromatic nitriles since aliphatic nitriles are overreduced under these conditions. The solution has been found and involves adding a trapping reagent to remove the aldehyde (or imine) from the reaction. Semicarbazide hydrochloride is one such example, which when added to the reduction of aliphatic nitriles gives the corresponding aldehyde semicarbazone in reasonable yields.[218] The obvious disadvantage of this method is that the aldehydes must then be obtained via hydrolysis of the semicarbazone. A better trapping agent is *N*,*N*′-diphenylethylenediamine which forms a tetrahydroimidazole derivative which is more easily hydrolyzed to the aldehyde.[218]

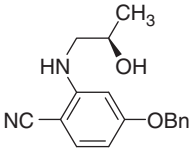
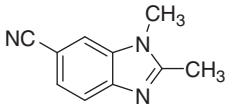
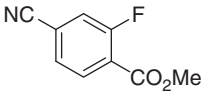
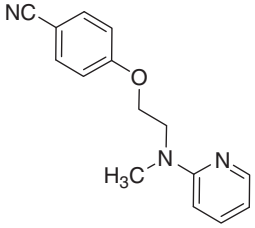
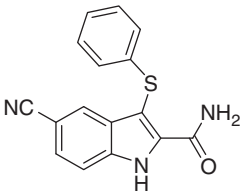
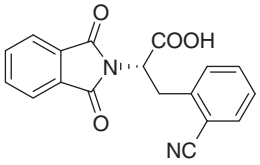
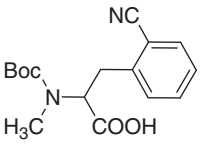
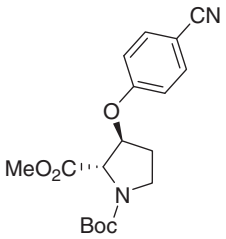
8.11.9 Other Derivatives

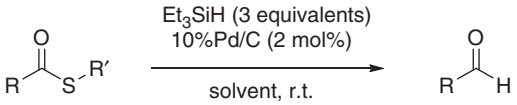
Other than the most common carboxylic acid derivatives, a number of lesser exploited derivatives have also undergone selective reduction to aldehydes. Since these have been less explored they will be briefly discussed here.

8.11.9.1 Thioesters

The most important way of partially reducing thioesters to aldehydes comes from reports by Fukuyama et al. in which they demonstrated that these could be conveniently reduced to aldehydes using triethylsilane and palladium on carbon (equation 14).[219–221] The importance of this reaction is that a large number of functional groups are tolerated under these neutral reaction conditions, including ester, acetal, silyloxy, sulfide, amide, and β-lactam groups. Olefins are the only groups which are also reduced under these conditions, but Evans has reported that this can be mitigated by employing Lindlar's catalyst and using an excess of a terminal auxiliary alkene such as 1-hexene.[222–224] Various solvents can be used, though acetone appears to be favored (the reaction rate is generally faster in polar solvents). Likewise various groups on the sulfur atom are also tolerated but in practice the more bulky this group the slower the reaction. For this reason ethylthiol esters are most conveniently exploited by this reagent.

Table 15 Examples of Raney nickel reductions. In each case only the nitrile group was reduced to the aldehyde

Entry	Substrate	Yield (%)	Reference	Entry	Substrate	Yield (%)	Reference
1		90	210	5		79	211
2		70	212	6		82	213
3		60	214	7		78	215
4		97	216	8		78	217

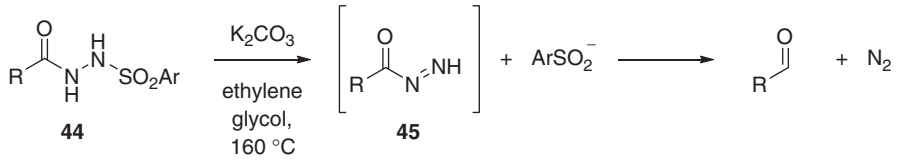


(14)

Of the other methods that exist, the use of DIBAL is the next most popular choice of reagent.[225,226] In this regard it is very similarly employed as with the reduction of carboxylic acid esters and requires low temperatures and careful control of the number of equivalents added (2 equivalents are required). Functional group tolerance is not as wide as the Fukuyama method and groups reducible by DIBAL would need to be protected or avoided. Yields are however generally excellent. Lastly, Raney nickel can also be employed, though the yields are somewhat lower and long reaction times in refluxing solvent are needed.[227]

8.11.9.2 Acyl Hydrazides

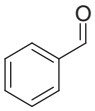
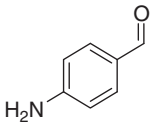
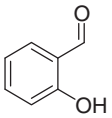
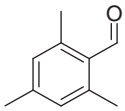
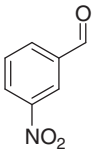
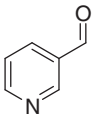
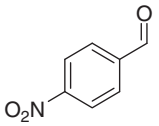
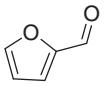
A classic method that still finds application in the literature is the McFadyen–Stevens aldehyde synthesis. This involves the base decomposition of an arenesulfonylhydrazide (**44**) to give a putative acylimide (**45**) which eliminates nitrogen to give the aldehyde (Scheme 24).[228] The classical method uses either a phenyl or toluyl arene and decomposition is initiated by base (potassium carbonate) while heating to 160 °C in ethylene glycol for approximately 2 min. Yields are better with electron-rich aromatics which give approximately 80% of the product, whereas electron-poor aromatics give poorer yields of approximately 40–50%. Aliphatic substrates are unsuitable using this particular procedure, which is probably due to the aldehyde product being unstable under the reaction conditions.



Scheme 24

Successful attempts to improve the yield and scope of this reaction have been examined, with an early report demonstrating that the reaction requires a heterogeneous environment to be successful.[229] Thus, the original procedure reported by McFadyen and Stevens was shown to work because the base was itself insoluble in the reaction solvent and provided a surface for the reaction. Indeed homogeneous reactions of this type (i.e., using a preformed sodium salt of the hydrazide) completely failed to give any product. It was found however that the inclusion of finely powdered glass further improved the yields of the original procedure by approximately 10%, except in one case (entry 2, **Table 16**).[229]

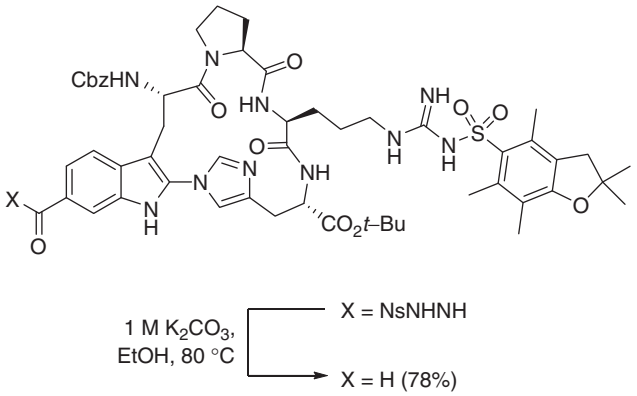
Table 16 McFadyen–Stevens synthesis using powdered glass

Entry[a]	*Product*	*Time (min)*	*Yield (%)*[b]	*Entry*[a]	*Product*	*Time (min)*	*Yield (%)*[b]
1		4	81 (73)	5		3	36
2		3	38 (55)	6		3	38
3		3	52 (42)	7		3	64 (36)
4		4	15 (0)	8		3	64

[a]Reactions conducted in ethylene glycol at 160 °C using 1.1 equivalents of Na_2CO_3 and powdered glass.
[b]Yields in brackets are those obtained without powdered glass.

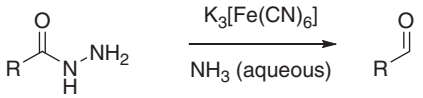
In another attempt at improving the reaction, the steric bulk of the sulfonyl aryl group was increased by using the 2,4,6-triisopropylphenyl group.[230] Although this did allow the reaction to be conducted at lower temperatures (methanol, reflux, 15–60 min), the yields were lower. A better aryl derivative has been found by Braslau and coworkers as part of their investigations into using acyl hydrazines as precursors to acyl radicals.[231] They reported that the 2-nitrobenzenesulfonyl (nosyl) group gave yields similar to that of the classic McFadyen–Stevens procedure, while allowing the reaction to be conducted at much lower temperatures (80 °C, EtOH, 2.5 h). This method has been employed by Castle et al. in their total synthesis of the antimitotic bicyclic peptide celogentin C.[232] A fairly late-stage target for the group was obtained using the Braslau variation in 78% yield (equation 15), although due to the subsequent synthetic reaction failing the final total synthesis did not employ this intermediate.

The production of aliphatic aldehydes by the classical McFadyen–Stevens method has not been possible. However, Nair and Schechter have shown that volatile aliphatic aldehydes can be obtained if the tosylhydrazide salts of (44) are heated under a vacuum and the aldehydes collected with a cold trap.[233] Simple volatile aldehydes can then be obtained in 60–85% yield.



(15)

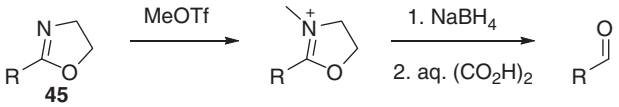
Another procedure that has found limited application in the literature is the conversion of a primary acyl hydrazide to an aldehyde (equation 16). Although this reaction appears to be a partial reduction of the starting material to an aldehyde, the overall reaction is an oxidation with potassium ferricyanide ($K_3[Fe(CN)_6]$). Originally reported by Kalb and Groß in 1926,[234] this reaction was seemingly ignored until the late 1990s.[235] The method is somewhat limited in that only simple aromatic aldehydes have been synthesized this way, but it does offer a tangential approach to aldehyde synthesis via an oxidative method. The acyl hydrazide can be readily obtained by heating hydrazine with an ester, but this functional group is likely to be problematic since it is an excellent nucleophile. Therefore the oxidative cleavage reaction would need to be done immediately following the hydrazide formation.



(16)

8.11.9.3 Cyclic Carboxylic Acid Derivatives

Oxazolines (**45**, 4,5-dihydrooxazoles) are important functional groups in organic chemistry, particularly in the role they play as chiral auxiliaries in organolithium reactions.[236] There exists only one practical method for their conversion to aldehydes: quaternization of the oxazoline with methyl iodide[237] or methyl triflate[238] to give the iminium salt followed by facile reduction to the oxazolidine and then hydrolysis to the aldehyde with oxalic acid (Scheme 25). Sodium borohydride is the more popular reducing agent, though in one case sodium trimethoxyborohydride has also been used.[239] Yields for this type of reaction are variable and typically in the range of 40–75%.

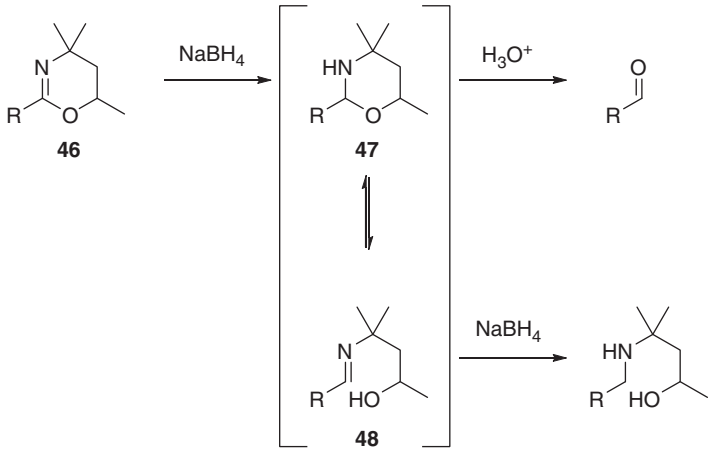


Scheme 25

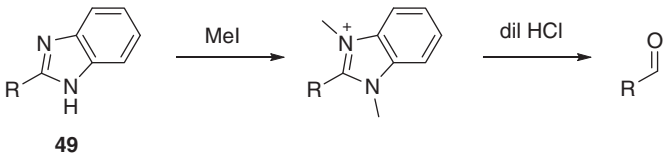
5,6-Dihydro-4*H*-1,3-oxazines (**46**) have also been successfully reduced to aldehydes.[240] This is somewhat easier to accomplish compared with oxazolines since they are much easier to reduce and do not require the quaternization step. Sodium borohydride is used to achieve the selective reduction, but the temperature must be kept between -35 °C and -45 °C and the pH kept between 5 and 8. The low temperature is the key since higher temperatures allow for a side-reaction in which the tautomeric form (**48**) of the aminol product (**47**) is further reduced resulting in amino alcohol products (Scheme 26). Hydrolysis of the aminol is readily achieved with 90% acetic acid or aqueous oxalic acid.

The sulfur analogs, dihydro-1,3-thiazines, are also similarly reduced with sodium borohydride in yields of 66–84%.[241] Lastly, benzimidazoles (**49**) have been shown by Craig et al. to undergo partial reduction and hydrolysis to aldehydes after quaternization with methyl iodide (Scheme 27).[242] Once again sodium borohydride is the preferred reductant and hydrolysis occurs with dilute hydrochloric acid. Yields are approximately 70%.

All of the above methods can be considered to be relatively mild since sodium borohydride is used and weak acidic conditions are needed for hydrolysis. Groups sensitive to these reagents should be carefully considered in any synthetic plan.



Scheme 26



Scheme 27

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8.12 Reduction of C═X to CH_2

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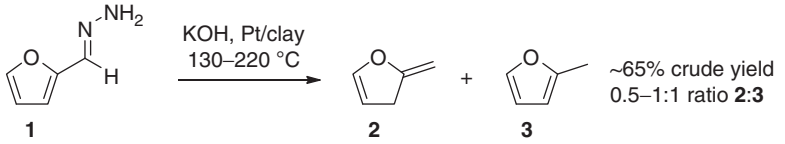
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8.12.1 Reduction of C═X to CH_2

8.12.1.1 Wolff–Kishner and Related Reductions

8.12.1.1.1 Introduction

The deoxygenation of the carbonyl group of an aldehyde or ketone using hydrazine or its equivalents under basic reaction conditions is commonly referred to as the Wolff–Kishner reduction. In the vast majority of cases the reduction substrate is an aldehyde or ketone although the use of imines[1,2] and oximes[3] is not unknown. The originally reported procedures,[4,5] which involved the use of sealed tubes or the addition of the preformed hydrazone or semicarbazone to hot potassium hydroxide containing platinized porous plate, have generally been superseded by a plethora of milder, and operationally simpler methods. An example of the Kishner reduction of 2-furyl hydrazone,[6] which has recently been reinvestigated,[7] is shown (equation 1). Addition of the hydrazone **1** to hot platinized clay in the presence of potassium hydroxide gave a mixture of 2-methylene-2,3-dihydrofuran **2** and 2-methyl furan **3**. The formation of mixtures of products from the reduction of α,β-unsaturated hydrazones is common and will be discussed further below (see Section 8.12.1.1.3.3.3).



1 **2** **3** (1)

The use of high-boiling solvents such as ethylene glycol and diethylene glycol in tandem with hydrazine hydrate and base (the Huang–Minlon modification)[8] is the most popular method for Wolff–Kishner reduction. Addition of the base subsequent to hydrazone formation can give improved yields of product and is a popular modification of the Huang–Minlon procedure. The use of anhydrous hydrazine with glycol solvents under strictly anhydrous conditions (Barton modification)[9] has been used for the reduction of highly hindered aldehydes and ketones, as has the use of acid catalysis in the hydrazone forming step (Nagata modification).[10] All of the above procedures generally require the use of high temperatures (>180 °C). Lower temperature variants of the Wolff–Kishner reduction have been developed. In the Henbest procedure[11] the hydrazone is heated with potassium *tert*-butoxide in toluene at reflux, whereas the Cram modification[12] requires the slow addition of the preformed hydrazine to potassium *tert*-butoxide in dimethyl sulfoxide at ambient temperature. Neither the Cram nor the Henbest procedures have been widely used most probably because of the need to preform the hydrazone. Recently, Myers[13] has championed the use of silylated hydrazones (specifically *tert*-butyldimethylsilyl (TBS)-protected hydrazones) in the low-temperature Cram-type Wolff–Kishner reduction, one of the advantages of this procedure being that the slow addition of the preformed hydrazone to the base is not required. All of the above procedures require the use of strong base and hence are incompatible with certain substrates. Additionally, if the substrate is an α-heteroatom-substituted aldehyde or ketone then generally elimination of the heteroatom occurs to give an unsaturated product (Kishner–Leonard elimination). Furthermore, the reduction of α,β-unsaturated aldehydes and ketones often leads to mixtures of unsaturated products. The reduction of tosylhydrazones with hydride reagents (Caglioti reaction)[14,15] is the equivalent of the Wolff–Kishner reduction and generally proceeds under milder reaction conditions. A large number of reducing agents have been used[16,17] and conditions can generally be found which prevent Kishner–Leonard elimination or which allow α,β-unsaturated substrates to be reduced with reliable transposition of the enone double bond. The following Sections 8.12.1.1.2–8.12.1.1.6 will cover the mechanism of the Wolff–Kishner reduction followed by a full discussion of the above procedures. A number of useful reviews[18–20] and summaries of the Wolff–Kishner reduction have been published.[13,21,22] Examples will generally be taken from the literature published since the first edition of *Comprehensive Organic Synthesis* and as far as possible contain experimental procedures.[23]

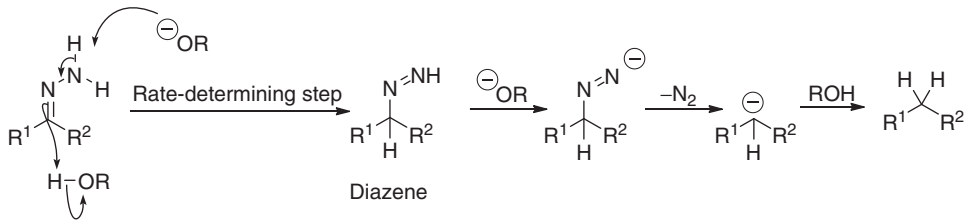
8.12.1.1.2 Mechanism

The mechanism of the Wolff–Kishner reaction has been widely studied most notably by Szmant.[24] It is proposed that in protic solvents, the rate-determining step involves tautomerism of the hydrazone into the corresponding diazene (**Scheme 1**). Loss of nitrogen from the deprotonated diazene gives a carbanion that is rapidly protonated by solvent. Evidence for the post rate-determining formation of such anions has recently been provided by Taber.[25,26] This anionic mechanism for nitrogen extrusion is in contrast with the radical mechanism for nitrogen extrusion found in some of the modified Wolff–Kishner procedures.[27–29] The proposed anionic mechanism readily accounts for both the Kishner–Leonard elimination found with α-heteroatom-substituted aldehydes and ketones (see Section 8.12.1.1.4.3), as well as the frequent formation of mixtures of alkene products from the reduction of α,β-unsaturated aldehydes and ketones.

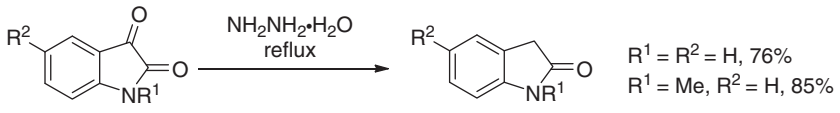
8.12.1.1.3 Modified procedures

8.12.1.1.3.1 Huang–Minlon modification

Wolff–Kishner reactions generally require a high temperature to proceed and high-boiling point solvents such as ethylene- and triethylene glycol are now generally used, although with certain substrates, for example, 1,2-dicarbonyl compounds, reduced reaction temperatures can be used. In certain highly favorable cases the use of added base is not required. For example, a number of isatin derivatives have been reduced on heating at reflux with hydrazine hydrate (equation 2).[30]



Scheme 1



(2)

The most widely used procedure for the Wolff–Kishner reduction is that discovered by Huang–Minlon (Table 1).[8] In this procedure, hydrazine hydrate is mixed with the carbonyl compound to be reduced in ethylene glycol or triethylene glycol in the presence of sodium or potassium hydroxide. The mixture is heated and, once hydrazone formation is judged complete, excess hydrazine and water are distilled from the reaction mixture allowing the temperature of the reaction to rise and the loss of nitrogen to occur. Although Huang–Minlon was not the first to use ethylene glycol or triethylene glycol, the use of these solvents along with hydrazine hydrate (and sometimes with pure hydrazine) is generally now referred to as the Huang–Minlon modification. A recent kilogram-scale Wolff–Kishner reduction has been reported including a useful discussion of the hazards and safety considerations when using large quantities of hydrazine (entry 1).[22] A kilogram-scale preparation of 2,2,6,6-tetramethylpiperidine has been recently reported from the Schlosser group (entry 2)[31] in which the substrate was premixed with hydrazine hydrate followed by continuous slow addition to hot potassium hydroxide in diethylene glycol with the product distilling from the reaction mixture. The usual solvents used in the Wolff–Kishner reduction and in the Huang–Minlon procedure are ethylene-, diethylene-, and triethylene glycol. However, these high-boiling point solvents can be difficult to fully remove from product. The use of triethanolamine as solvent overcomes this problem as it can be readily removed by acid extraction. The preparation of docosanedoic acid is representative (entry 3).[32] The Huang–Minlon procedure is also applicable to aminals (entry 4),[33] some hindered carbonyl groups (entry 5),[34] and to an unusual bridged amide (entry 6).[35] The example in entry 7 demonstrates the formation of mixtures of alkene products from the Wolff–Kishner reduction of α,β-unsaturated ketones.[36] Silyl ethers are cleaved under the reaction conditions (entry 5).[34]

8.12.1.1.3.2 Barton and Nagata modifications – sterically hindered substrates

The Huang–Minlon modification can fail with highly hindered aldehydes and ketones. Two procedures have been developed that frequently overcome these problems.

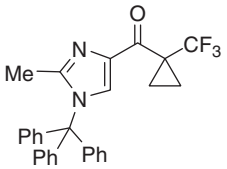
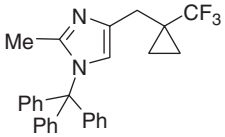
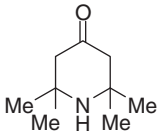
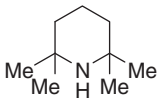
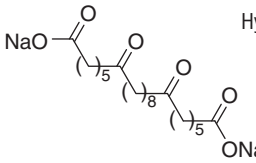
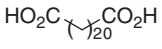
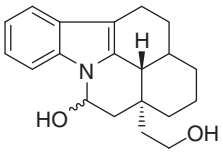
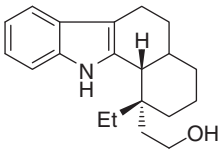
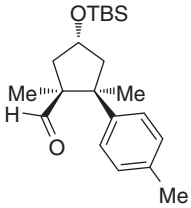
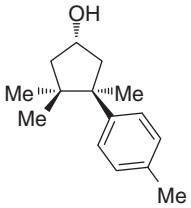
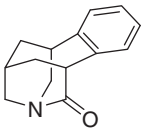
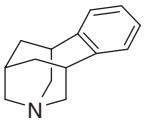
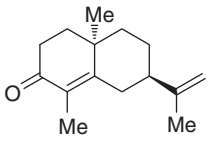
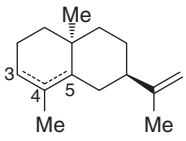
8.12.1.1.3.2.1 Barton modification

The difficulty encountered in the Wolff–Kishner reduction of sterically hindered aldehydes and ketones can arise from problems with initial formation of the hydrazone. Barton reported a modification of the Huang–Minlon procedure that used strictly anhydrous conditions, namely anhydrous hydrazine and sodium in diethylene glycol. The procedure was initially developed for the reduction of hindered steroid substrates and the use of anhydrous hydrazine is known as the Barton modification.[9] The use of anhydrous hydrazine in the Wolff–Kishner reduction of a range of sterically hindered aldehydes and ketones are collected in Table 2. This procedure has been used to deoxygenate a sterically hindered diketone (entry 1).[9] A major drawback of this method is the requirement to use or prepare anhydrous hydrazine with the attendant explosion and fire risks. Indeed, Wolff–Kishner reduction of the ketone in entry 3 on one occasion resulted in the reaction mixture catching fire; previous attempted use of the Nagata modification (see Section 8.12.1.1.3.2.2) for deoxygenation had failed.[37] The example in entry 4 shows how distal alkenes can undergo isomerism under the hot basic reaction conditions.[38] Silyl ethers are not stable to Wolff–Kishner reduction; however, a trimethylsilyl ethyl ether can survive the harsh reaction conditions (entry 5).[39] Not surprisingly esters are labile under Wolff–Kishner conditions (entry 1).

8.12.1.1.3.2.2 Nagata modification

Nagata addressed the difficulty of preparing hydrazones from highly hindered aldehydes and ketones by the simple expedient of adding an acid cocatalyst either in the form of hydrazine dihydrochloride or by the addition of *p*-toluenesulfonic acid coupled with the use of hydrazine hydrate followed by the usual Huang–Minlon procedure (Table 3).[10] The advantage of this procedure is that it avoids the use of hazardous anhydrous hydrazine, although occasionally both anhydrous hydrazine and acid are used in concert (entry 1).[42] A number of other examples using highly hindered ketones are shown (entries 2–4). Interestingly, a phenolic methyl ether undergoes partial demethylation (entry 4) under the hot basic reaction conditions.[43]

Table 1 Wolff–Kishner reduction using the Huang–Minlon procedure

Entry	*Substrate*	*Conditions*[a,b]	*Products*	*Yield (%)*	*References*
1		Hydrazine hydrate, H_2O, KOH, diethylene glycol, 155 °C		85	22
2		Hydrazine hydrate, KOH diethylene glycol, 210 °C		83	31
3		Hydrazine hydrate, KOH, triethanolamine to mixture, 140 °C		62	32
4		Hydrazine hydrate, KOH, ethylene glycol		53	33
5		Hydrazine hydrate, diethylene glycol, then NaOH, 180 °C		95	34
6		Hydrazine, ethylene glycol, then KOH, 200 °C		64–85	35
7		Hydrazine hydrate, KOH, triethylene glycol, 210 °C		71[c]	36

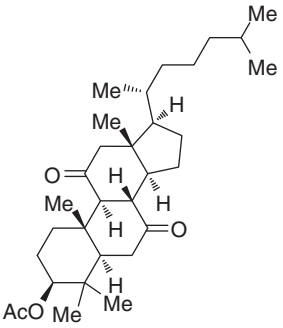
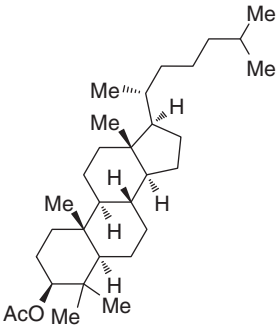
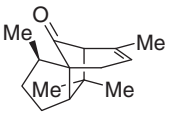
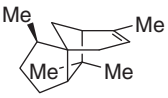
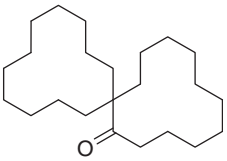
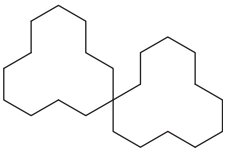
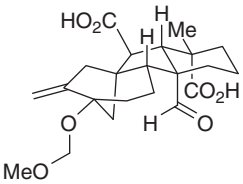
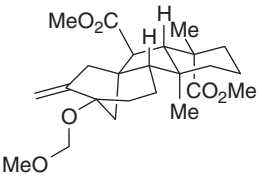
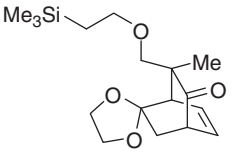
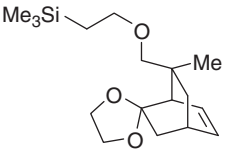
[a]The degree of hydration and concentration of hydrazine hydrate varies in the examples (see specific references for details).
[b]The experimental procedures vary among the examples and the temperature given is the final temperature that the reaction mixture attained.
[c]The product consisted of a mixture of three compounds: the $\Delta^{3,4}$, 5βH and $\Delta^{3,4}$, 5αH regioisomers, and the $\Delta^{4,5}$ regioisomer.

8.12.1.1.3.3 Lower temperature modifications – Cram, Myers, and Henbest

8.12.1.1.3.3.1 Cram modification

The previously discussed procedures for the Wolff–Kishner reduction generally require relatively high temperatures. In 1962, Cram reported a low-temperature modification of the Wolff–Kishner reduction in which preformed hydrazones could be reduced at ambient temperature by slow addition to a solution of potassium *tert*-butoxide in dimethyl sulfoxide.[12] The drawback of this method is the requirement of isolating the hydrazones and consequently this method has not been widely used in synthesis; attempted isolation and purification of hydrazones frequently results in azine formation with azines not usually being reduced under Wolff–Kishner conditions (see Section 8.12.1.1.4.1). Cram also found that slow addition of the hydrazone to the base in dimethyl sulfoxide was a necessity to avoid formation of significant quantities of the corresponding azine. It was later shown that use of specific protic cosolvents resulted in increased reaction rates under Cram reducing conditions.[46] Some low-temperature Wolff–Kishner reductions of preformed hydrazones are shown in Table 4.

Table 2 Wolff–Kishner reduction using anhydrous hydrazine on hindered ketones

Entry	Substrate	Conditions[a]	Products	Yield (%)	References
1		1. NH_2NH_2 (anhydrous), Na, diethylene glycol, 210 °C 2. Acetylation		69	9
2		NH_2NH_2 (anhydrous), KOH, diethylene glycol, 215 °C		52	40,41
3		NH_2NH_2 (anhydrous), Na, ethylene glycol, 210 °C		36	37
4		1. NH_2NH_2 (anhydrous), ethylene glycol then NaOH, 174 °C 2. CH_2N_2		53[b]	38
5		NH_2NH_2 (anhydrous), Na, diethylene glycol, 190 °C		71	39

[a]The experimental procedures vary among the examples and the temperature given is the final temperature that the reaction mixture attained.
[b]The product was formed as a mixture with the corresponding *endo*-cyclic alkene –> 5.5:1 mixture of *exo*:*endo*-cyclic alkenes.

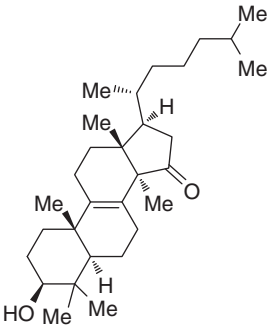
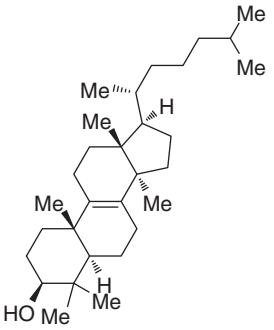
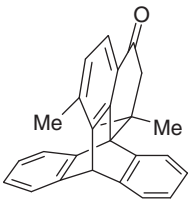
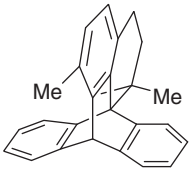
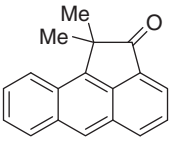
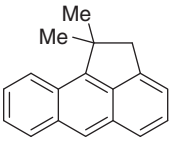
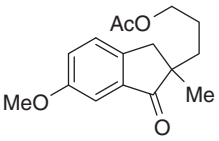
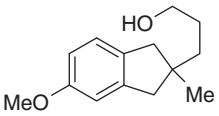
8.12.1.1.3.3.2 Myers modification

The drawbacks of the original Cram procedure[12] have recently been addressed by Myers who utilized 1,2-bis(TBS)hydrazine for the preparation of *N*-*tert*-butyldimethylsilylhydrazones.[13] Myers showed that a wide range of *N*-*tert*-butyldimethylsilylhydrazones could be readily prepared by the reaction of aldehydes and ketones with 1,2-bis(TBS)hydrazine in the presence of scandium(III) triflate generally at ambient temperature with very low amounts of the corresponding azine (~ 1–2%) being formed. The silylated hydrazones have long-term stability if stored at − 20 °C under an inert atmosphere and can be handled in air. Reduction of the crude silylated hydrazones under modified Cram conditions (*t*-BuOK, dimethyl sulfoxide, *t*-BuOH) occurs with high efficiency. This procedure has yet to be widely used but shows great promise because of its operational simplicity and high efficiency. Reduction of the hindered steroidal ketone (**Table 5**, entry 2) by treatment of the corresponding *N*-silylated hydrazone with *t*-BuOK in *t*-BuOH/DMSO at 100 °C gave the product in 96%, whereas the Huang–Minlon procedure gave the product in 79% yield along with numerous byproducts.[13] The Myers protocol has also been applied to a highly hindered aldehyde (entry 3) which gave the corresponding alkane in 38% yield.[50]

8.12.1.1.3.3.3 Henbest modification

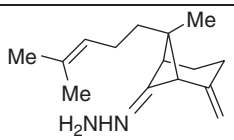
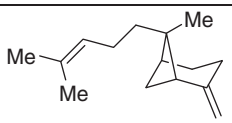
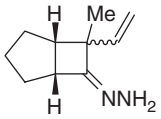
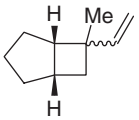
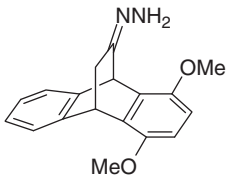
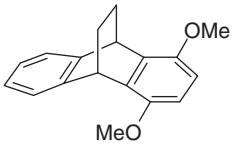
In the Henbest modification of the Wolff–Kishner reduction, hydrazones, or semicarbazones are treated with potassium *tert*-butoxide in toluene at reflux (**Table 6**).[11] The use of semicarbazones can avoid the problems of azine formation that frequently occur during hydrazone formation (see Section 8.12.1.1.4.1). Azine formation was problematic with the aldehyde in entry 1, whereas semicarbazone formation was successful;[51] semicarbazones are converted to hydrazones under the subsequent basic reaction conditions. Henbest found that these conditions frequently reduced the amount of Kishner–Leonard elimination product

Table 3 Wolff–Kishner reduction – Nagata modification

Entry	Substrate	Conditions[a]	Products	Yield (%)	References
1		NH_2NH_2 (anhydrous), $NH_2NH_2 \cdot HCl$,triethylene glycol, 135 °C then KOH, 210 °C		72	42
2		Hydrazine hydrate, $NH_2NH_2 \cdot 2HCl$, triethylene glycol, 130 °C then KOH, 210 °C		98	44
3		Hydrazine hydrate, $NH_2NH_2 \cdot 2HCl$, triethylene glycol, 130 °C then KOH, 210 °C		92	45
4		Hydrazine hydrate, $NH_2NH_2 \cdot 2HCl$, diethylene glycol, 130 °C then KOH, 210 °C		75[b]	43

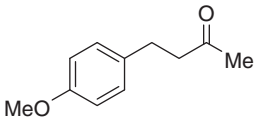
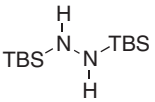
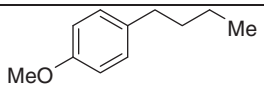
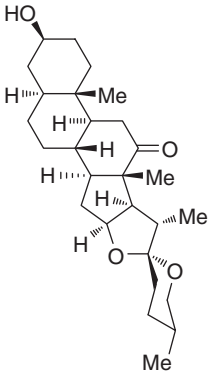
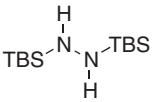
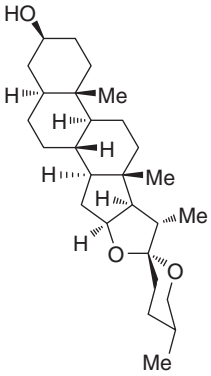
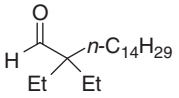
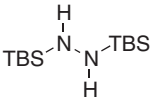
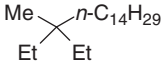
[a]The degree of hydration and concentration of hydrazine hydrate varies in the examples (see specific references for details).
[b]Also isolated was 16% of the reduced and *O*-demethylated product.

Table 4 Wolff–Kishner reduction of preformed hydrazones – Cram modification

Entry	Substrate	Conditions	Products	Yield (%)	References
1		*t*-BuOK, DMSO, r.t.		64	47
2		*t*-BuOK, DMSO, r.t.		56	48
3		*t*-BuOK, DMSO r.t.–80 °C		96	49

(entry 2)[52] particularly with α-amino ketone substrates and also minimized double-bond isomerization when reducing α,β-unsaturated carbonyl derivatives (entry 3).[36] A further benefit of the Henbest modification is that hydrolysis of various substrates is reduced as the reaction is effectively conducted under nonhydroxylic conditions. Under Huang–Minlon conditions the substrate in entry 4 underwent lactam hydrolysis, which was avoided under the Henbest conditions.[53]

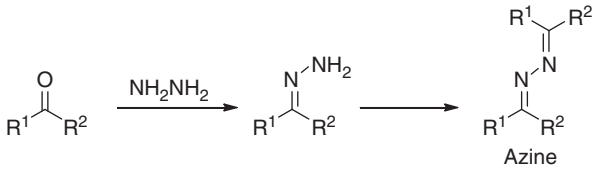
Table 5 Wolff–Kishner reduction – Myers modification

Entry	Substrate	Conditions	Products	Yield (%)	References
1		 $Sc(OTf)_3$, then *t*-BuOK, *t*-BuOH, DMSO, 23 °C		94	13
2		 $Sc(OTf)_3$, then *t*-BuOK, *t*-BuOH, DMSO, 100 °C		96	13
3		 $Sc(OTf)_3$, then *t*-BuOK, *t*-BuOH, DMSO, 80 °C		38	50

8.12.1.1.4 Scope and limitations

8.12.1.1.4.1 Azine formation

One issue with the Wolff–Kishner reduction is the production of azines during hydrazone formation (equation 3). This is particularly problematic if the hydrazone is isolated,[11] although various methods to suppress azine formation have been reported.[13] Isolation and purification of hydrazones should therefore be avoided whenever possible. A method for the hydrolysis of azines to the parent ketone has been reported.[48]

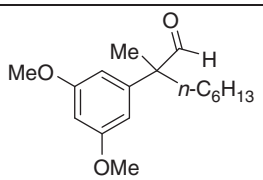
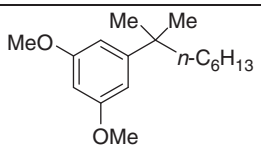
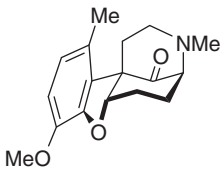
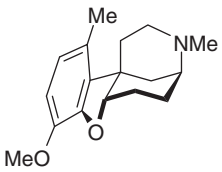
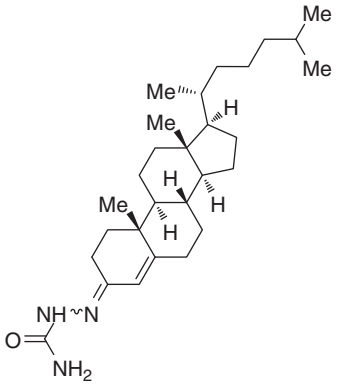
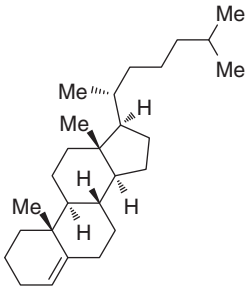
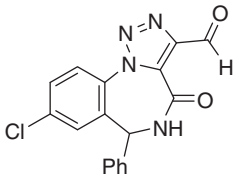
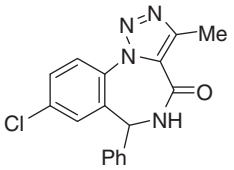


(3)

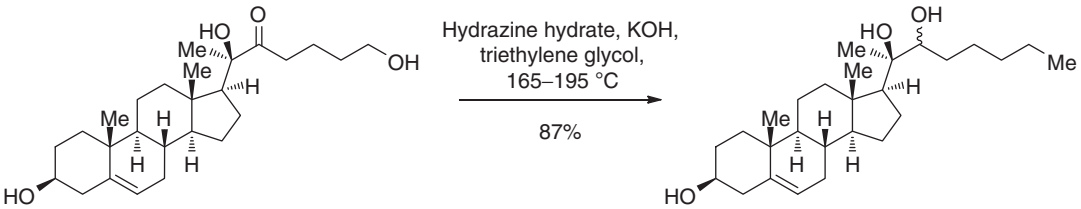
8.12.1.1.4.2 Base-mediated side reactions

All of the above Wolff–Kishner modifications, and the original procedure itself, require strongly basic reaction conditions frequently at high temperature. It is therefore no surprise that base sensitive functionality is generally not compatible with the Wolff–Kishner reduction. As can be seen from some of the examples above, esters are hydrolyzed under the reaction conditions (Section 8.12.1.1.3.3.1, **Table 2**, entry 1; Section 8.12.1.1.3.3.3, **Table 3**, entry 4) and amides and lactams are frequently also attacked, although less so with the Henbest modification; nitriles are also sometimes hydrolyzed.[54] There are number of reports of aryl methyl ethers undergoing demethylation under the high temperature basic Wolff–Kishner reduction conditions (**Table 3**, entry 4).[43,55] Furthermore, silyl groups and base-labile protecting groups generally do not survive (**Table 1**, entry 5). The reduction of the carbonyl-containing substrate to the corresponding alcohol can occur if hydrazone formation is slow. For example, the steroidal ketone in equation 4 gave the corresponding butyl-substituted secondary alcohol under Huang–Minlon conditions.[56] A plausible mechanism for this reaction involves intramolecular hydride transfer (Meerwein–Ponndorf–Verley-type reduction) to give the terminal aldehyde, which undergoes Wolff–Kishner reduction. A similar reaction within a bicyclo[3.3.1] system has also been observed.[57]

Table 6 Wolff–Kishner reduction – Henbest modification

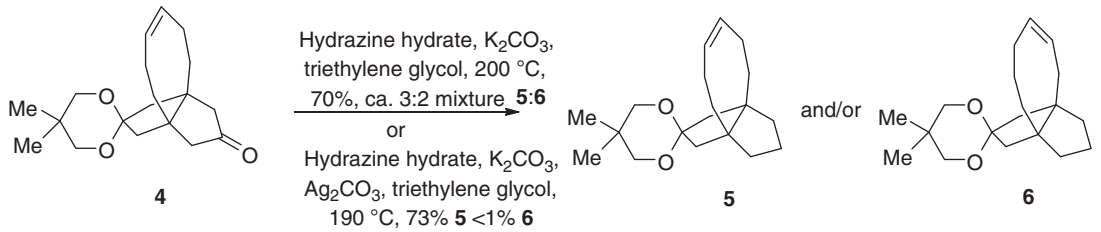
Entry	Substrate	Conditions	Products	Yield (%)	References
1		1. $NH_2CONHNH_2 \cdot HCl$, MeOH, water 2. *t*-BuOK, xylene, reflux		85	51
2		1. hydrazine, EtOH 2. *t*-BuOK, toluene, reflux		36	52
3		*t*-BuOK, toluene, reflux		81[a]	11
4		1. Hydrazine hydrate, EtOH 2. *t*-BuOK, toluene, reflux		91	53

[a]Product contained <10% of the regioisomeric alkene.



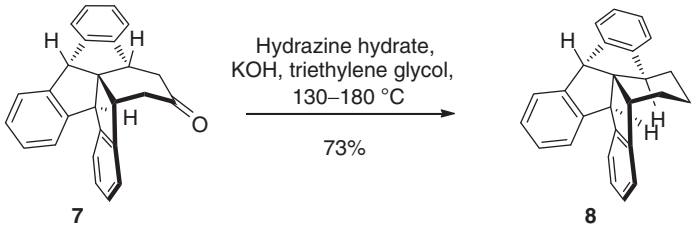
(4)

One of the major side reactions in Wolff–Kishner reductions is the isomerism of isolated double bonds (Table 2, entry 4) as well as isomerism of enones in the reduction of α,β-unsaturated aldehydes and ketones (Table 1, entry 7). In a general approach to polyquinanes, reduction of the ketone **4** under Huang–Minlon conditions with potassium carbonate as base gave a 70% yield of a mixture of alkene isomers **5** and **6** (equation 5).[58] However, addition of silver carbonate to the reaction mixture effectively prevented the alkene isomerization. This method of suppressing alkene isomerization does not appear to have been explored by others.



(5)

Under the basic reaction conditions of the Wolff–Kishner reduction, epimerization of certain substrates can occur. In the example shown in equation 6, Wolff–Kishner reduction of the *cis,cis,cis,trans*-fenestrane **7** gave the *cis,cis,cis,cis*-fenestrane **8** where epimerization of one of the benzylic stereocenters had occurred.[59] The authors demonstrated that the hydrazone of ketone **7** could be formed without epimerization, however, even low-temperature reduction of the hydrazone (Cram modification) gave the *cis,cis,cis,cis*-fenestrane **8**.

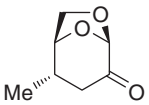
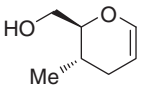
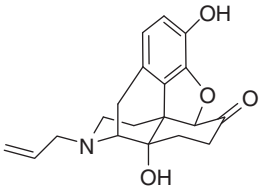
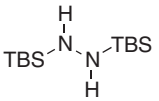
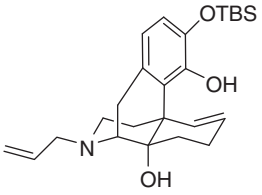
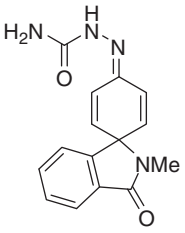
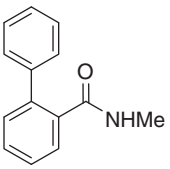
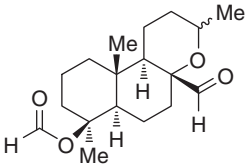
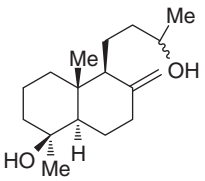
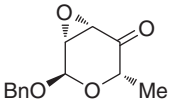
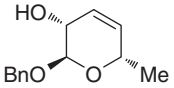


7 **8** (6)

8.12.1.1.4.3 Kishner–Leonard elimination

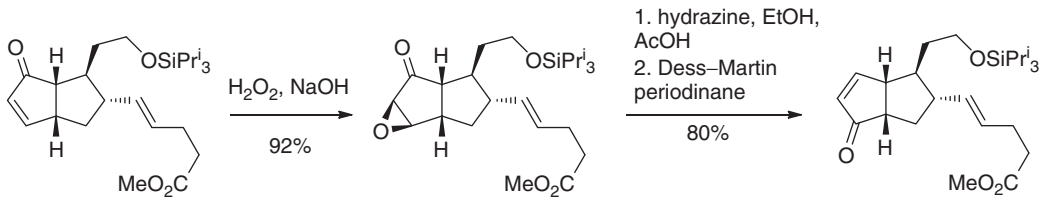
Aldehydes and ketones which carry an α-heteroatom generally undergo elimination, to a greater or lesser extent, under basic Wolff–Kishner reaction conditions to give the corresponding alkene (Table 7; *see* Chapter 8.31). Leonard reported that the extent of elimination observed depended on the nature of the leaving group and steric environment of the α-substituent.[60] This has been developed into a useful synthetic reaction for the formation of enol ethers (entry 1).[61] Similar eliminations occur using the Myers conditions, in this case *in situ* silyl-protection of the phenol group occurred (entry 2).[13] A homo-Kishner–Leonard elimination has also been reported (entry 3).[62,63]

Table 7 Eliminations of α-substituents

Entry	Substrate	Conditions[a]	Products	Yield (%)	References
1		1. Hydrazine hydrate, EtOH 2. NaH, DMSO, r.t.		68	61
2		 $Sc(OTf)_3$, then *t*-BuOK, *t*-BuOH, DMSO, 100 °C		81	13
3		*t*-BuOK, toluene, reflux		94	62
4		Hydrazine hydrate, KOH, triethylene glycol, 160 °C		95	64
5		Hydrazine hydrate, MeOH, then AcOH, 0 °C–r.t.		67	65

[a]The degree of hydration and concentration of hydrazine hydrate varies in the examples (see specific references for details).

Treatment of epoxy-ketones with hydrazine in methanol-containing acetic acid results in the formation of allylic alcohols (entry 5).[65] Synthetically this reaction (the Wharton rearrangement) provides a method for allylic alcohol or enone transposition. A recent example of an enone transposition is shown in Scheme 2.[66]



Scheme 2

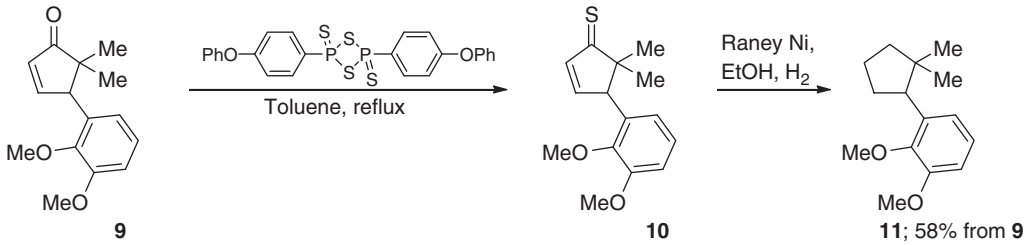
In a related transformation to the Kishner–Leonard elimination an α-cyclopropyl ketone bearing a γ-electron-withdrawing group underwent cyclopropyl cleavage under both Huang–Minlon and Cram conditions;[67] complete removal of two carbons of a cyclopropane has also been observed[68] as has cleavage of other strained rings.[69] However, α-cyclopropyl ketones which do not carry a γ-electron-withdrawing group may be reduced without cyclopropyl cleavage (Table 1, entry 1).[22,70,71] The formation of a cyclopropane under the basic reaction conditions has also been reported.[72]

8.12.1.1.4.4 Other side reactions

Certain α,β-unsaturated aldehydes and ketones can form pyrazolines in the presence of hydrazine which on heating yield cyclopropanes;[73] nevertheless, some α,β-unsaturated aldehydes undergo standard Wolff–Kishner reduction.[74,75] The use of semicarbazones in the place of hydrazones can result in good yields for the Wolff–Kishner reduction of α,β-unsaturated aldehydes and ketones substrates. Related to the above issues of pyrazoline formation, it is generally the case that substrates which react with hydrazine to give stable heterocycles (e.g., the formation of pyrazoles from β-diketones) generally do not undergo Wolff–Kishner reduction although there are exceptions.[76]

Other reported side reactions include: reduction of α-haloketones to ketones,[75] disproportionation of alkenes to acetylenes and alkanes,[77] and elimination of an allylic alcohol or ether to give a diene.[78] Generally aromatic nitro compounds do not survive Wolff–Kishner reduction as they are readily reduced by hydrazine.[79] Frequently aromatic halides do not survive high temperature Wolff–Kishner reduction.[80]

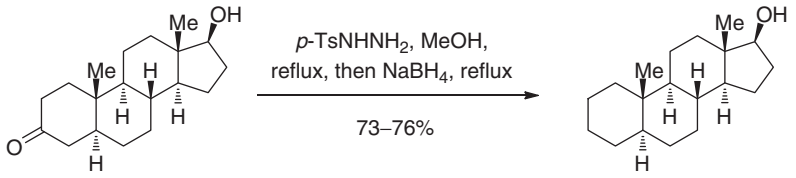
Despite the numerous procedures that have been developed for the Wolff–Kishner reduction there are still many reports of difficulties when trying to reduce sterically hindered or electronically deactivated substrates, as well as problems associated with the reduction of base sensitive substrates. The sterically hindered cyclopentenone **9** did not undergo Wolff–Kishner reduction, and neither was it possible to form the corresponding ethylene dithioketal. Ultimately reduction of the thione **10** with Raney nickel under an atmosphere of hydrogen gave the cyclopentane **11** (Scheme 3).[81]



Scheme 3

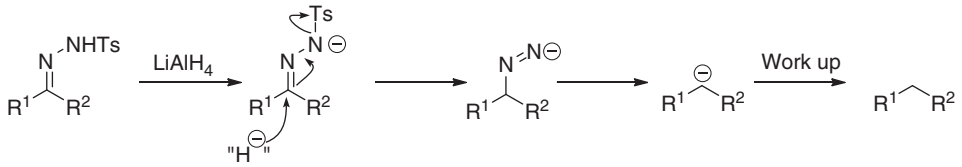
8.12.1.1.5 Reduction with modified hydrazones

The conversion of aldehydes and ketones into the corresponding tosylhydrazones followed by reduction with an appropriate hydride source allows deoxygenation of the carbonyl group (equation 7).[82] The initial report of this transformation came from the group of Caglioti who reduced tosylhydrazones with either lithium aluminum hydride[14] or sodium borohydride.[14] Since the original report a number of related procedures have been developed including the use of sodium cyanoborohydride, catechol-borane, or diisobutylaluminum hydride as the reducing reagents in various solvents. These modifications will be discussed after a brief overview of the mechanism of the reaction.



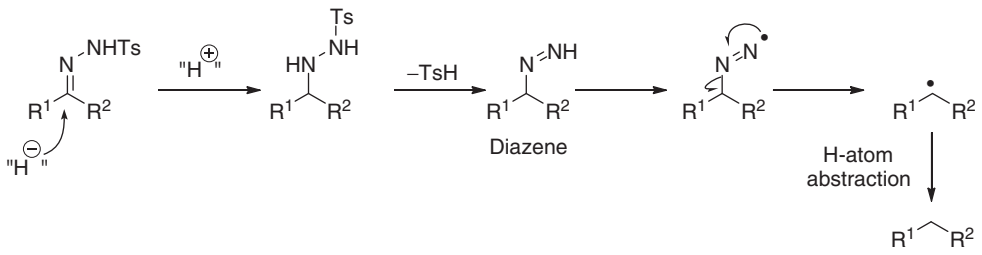
(7)

The mechanism of the reduction of tosylhydrazones with various sources of hydride has been widely studied. Reduction of tosylhydrazones with lithium aluminum hydride is in keeping with the following mechanism (Scheme 4).[83] *N*-Deprotonation of the tosylhydrazone followed by hydride addition to the carbon–nitrogen double bond with concomitant loss of the sulfinic acid anion gives the diazene anion. Loss of nitrogen leads to a carbanion that is protonated up on work up. Owing to the basic nature of lithium aluminum hydride, alkenes are frequently formed as byproducts in the reduction of tosylhydrazones by Shapiro-type processes, sometimes as the sole product.[84] Owing to the aggressive reducing power of lithium aluminum hydride and the relatively frequent formation of alkene byproducts, the use of lithium aluminum hydride to reduce aldehydes and ketones to methyl/methylene groups via tosylhydrazones is now only used infrequently.

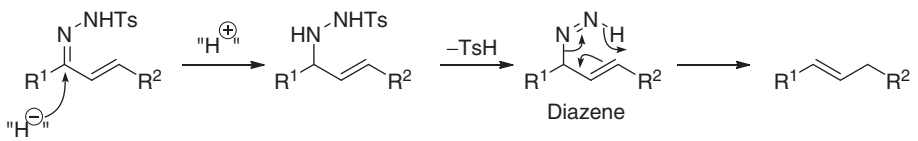


Scheme 4

With milder reducing agents (e.g., $NaCNBH_3$, $NaBH_4$, catecholborane) there is good evidence, at least under some reaction conditions, for a radical mechanism for the loss of nitrogen (Scheme 5).[27–29] Reduction of the tosylhydrazone (or the corresponding iminium ion) occurs first to give the corresponding tosylhydrazide,[85,86] which can be isolated and characterized in certain instances.[87] Elimination of toluenesulfinic acid gives a diazene, which decomposes to give product most probably by a radical mechanism; in the reduction of tosylhydrazones derived from α,β-unsaturated aldehydes and ketones loss of nitrogen can occur via a pericyclic reaction (retro-group transfer reaction – Scheme 6).[88] In the classical Wolff–Kishner reduction and the many modifications discussed in Section 8.12.1.1.2, the reaction mechanism is ionic in nature. The radical and pericyclic mechanistic pathways available with the reduction of tosylhydrazones greatly expand the scope of Wolff–Kishner process most notably in that α-oxygenated substrates can be reduced with high efficiency and α-stereocentres are generally not compromised. Moreover, the reduction of α,β-unsaturated tosylhydrazones frequently occurs with complete transposition of the enone alkene. These reactions will be discussed in Sections 8.12.1.1.5.1–8.12.1.1.5.4.



Scheme 5

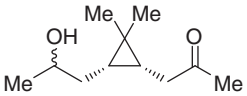
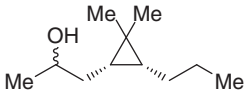
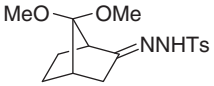
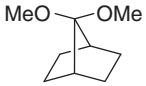
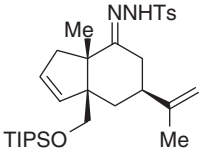
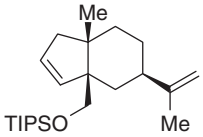


Scheme 6

8.12.1.1.5.1 Reduction with lithium aluminum hydride or diisobutylaluminum hydride

As noted above, the original procedure of Caglioti using lithium aluminum hydride is now only used infrequently. A relatively recent example comes from the reduction of the ketone-derived tosylhydrazone in Table 8, entry 1, with lithium aluminum

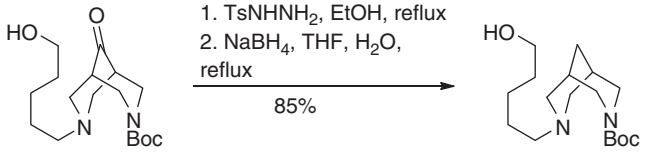
Table 8 Eliminations of α-substituents

Entry	Substrate	Conditions	Products	Yield (%)	References
1		1. $TsNHNH_2$, EtOH, reflux 2. $LiAlH_4$, THF, reflux		42	89
2		DIBAL-H, CH_2Cl_2, 0 °C		66	90
3		DIBAL-H, CH_2Cl_2, 0 °C		77	91

hydride which gave the propyl-substituted cyclopropane in 42% yield.[89] Diisobutylaluminum hydride has also been used to reduce tosylhydrazones.[90] The use of diisobutylaluminum hydride to reduce an acetal-containing hydrazone yielded product with the acetal retained (entry 2).[90] Recently as part of the total synthesis of (+)-cyperolone, the hindered tosylhydrazone in entry 3 was reduced with diisobutylaluminum hydride to give the corresponding [4.3.0]-bicyclic alkene.[91] Diisobutylaluminum hydride also reduces α,β-unsaturated tosylhydrazones with double-bond transposition.[90] The reduction of α,β-unsaturated tosylhydrazones with lithium aluminum hydride results in mixtures of alkene products in keeping with the anionic mechanism outlined above (**Scheme 4**).

8.12.1.1.5.2 Reduction with sodium borohydride

The use of sodium borohydride in hydroxylic solvents to reduce tosylhydrazones is still a relatively popular method. An example is shown in equation 8 where reduction of a [3.3.1]-bicyclic ketone was achieved in good yield without loss of the Boc protecting group.[92]



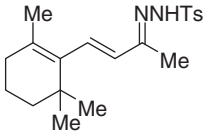
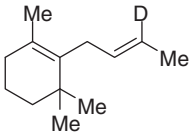
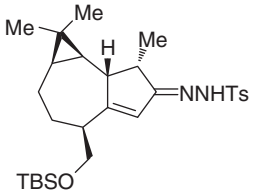
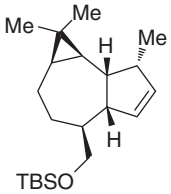
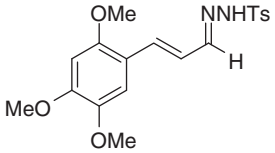
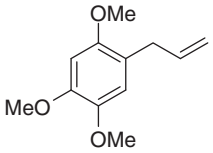
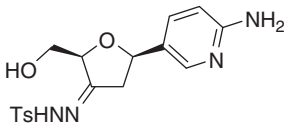
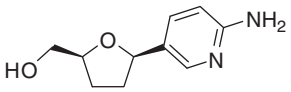
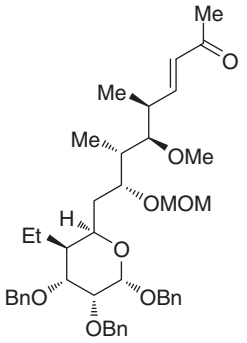
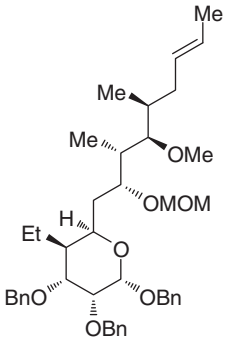
(8)

The reduction of α,β-unsaturated tosylhydrazones as well as aromatic aldehydes and ketones in methanol does not result in simple reduction of the original carbonyl group. Rather, the corresponding diazo compound is formed, which yields pyrazoles or gives methyl ethers via a Bamford–Stevens reaction.[93,94] Hutchins demonstrated that these limitations could be overcome by conducting the reduction using acetic acid as solvent.[95] It is likely that the use of acid serves both to avoid *N*-deprotonation of the tosylhydrazone and promote iminium ion formation and hence increase the rate of tosylhydrazone reduction (**Scheme 5**). As can be seen from the examples in **Table 9** aldehydes and ketones, including those with α-heteroatoms, are good substrates for the reaction with α,β-unsaturated substrates giving deoxygenated products with enone double-bond transposition. These conditions also constitute a useful method for introducing deuterium atoms regioselectively (**Table 9**, entry 1).[95] In the example in entry 2, reduction of the tosylhydrazone takes place from the less hindered lower face of the substrate resulting in diazene formation on the upper face and hence delivery of hydrogen to the angular position from the upper face.[96] Acyclic α,β-unsaturated ketones also undergo reduction with faithful transposition of the enone double bond (entry 5).[97]

8.12.1.1.5.3 Reduction with sodium cyanoborohydride

Sodium cyanoborohydride is a mild reducing agent which reduces iminium ions under acidic conditions (pH 3.8 is optimum, at pH < 1 $NaCNBH_3$ is not stable).[100] The reaction of relatively unhindered aldehydes and ketones with tosylhydrazone and sodium cyanoborohydride in a *N*,*N*-dimethylformamide (DMF):sulfolane mixture followed by heating at 100 °C with *p*-toluenesulfonic acid is a reliable and well-used method for the deoxygenation of aldehydes and ketones.[101] The mild reaction conditions render the reaction highly chemoselective, with esters, amides, nitriles, nitro groups, chlorides, and acetals surviving intact; primary bromides, primary iodides, and α-thioketones are reduced.[101] With more hindered substrates, it is necessary to preform the hydrazone and excess reducing agent and a slightly higher reaction temperature is used, sometimes with *p*-toluenesulfonic acid replaced by concentrated hydrochloric acid. The reduction of aryl ketones is generally inefficient with this procedure.[16,101] **Table 10** collects some recent examples. As in Section 8.12.1.1.5.2, substrates with α-oxygenation are tolerated, and α,β-unsaturated ketones react with enone double-bond transposition. In entry 2 selective reduction of a less hindered ketone is possible

Table 9 Reduction ketones and tosylhydrazones with sodium borohydride or sodium triacetoxyborohydride in acetic acid

	Substrate	*Conditions*	*Products*	*Yield (%)*	*References*
1		$NaBD_4$, AcOH, 70 °C		75	95
2		$NaBH_4$, AcOH, r.t.–70 °C		51	96
3		$NaBH_4$, AcOH, 10–120 °C		43	98
4		$Na(AcO)_3BH$, AcOH, MeCN, 0 °C		86	99
5		1. $TsNHNH_2$, MeOH, 25 °C 2. $NaBH_4$, AcOH, 25 °C		68	97

although a one-pot method was required in order to prevent isolation of the corresponding meso compound.[59] α-Stereocenters are generally not compromised (entries 3 and 4).[102,103]

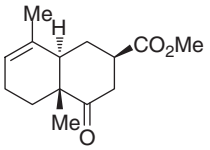
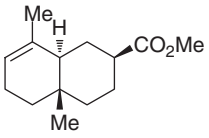
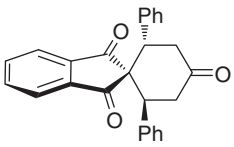
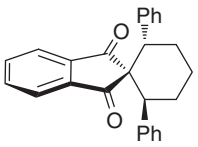
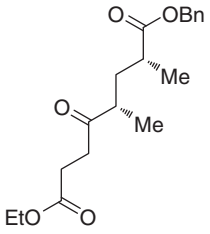
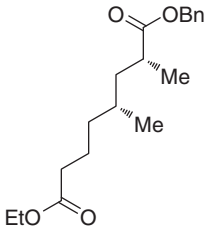
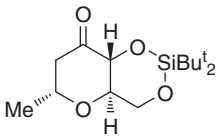
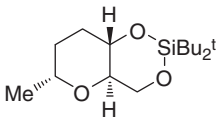
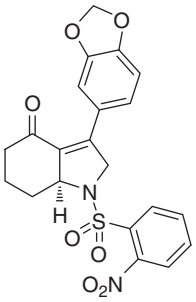
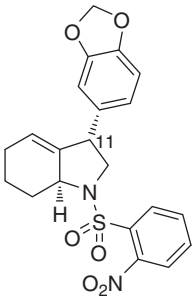
8.12.1.1.5.3.1 Nair three-step procedure

While attempting the deoxygenation of ketones in sugar substrates, Nair found that the reduction of the xylose-derived tosylhydrazone **12** with sodium cyanoborohydride in DMF/sulfolane with or without *p*-toluenesulfonic acid gave multiple products.[87] In a tetrahydrofuran (THF)/methanol mixture (maintained at pH 3.8), reduction of the tosylhydrazone **12** with sodium cyanoborohydride gave the corresponding tosylhydrazide **13** in good yield (Scheme 7). Subsequent treatment of the tosylhydrazide **13** with sodium acetate gave the deoxy sugar **14** in good overall yield. This three-step procedure is now widely used for the reduction of ketones bearing α-oxy stereocenters. Generally the acidity of the reduction mixture is maintained at approximately pH 3.8 by the addition of methanolic HCl as needed using methyl orange, or bromocresol green as indicator. Examples of the three-step procedure are collected in Table 11.

8.12.1.1.5.3.2 Other methods using sodium cyanoborohydride

A number of other procedures using sodium cyanoborohydride either in protic solvents or with a Lewis acid additive, typically zinc(II) chloride,[109] have been used to deoxygenate aldehydes and ketones. Some recent examples are collected in Table 12. Noteworthy examples include the double-bond transposition from the α,β-unsaturated ketone in entry 1;[110] the deoxygenation of the ketone in entry 2 that was low-yielding using transfer hydrogenolysis (see Section 8.12.1.4);[111] the retention of the *N*-Boc group and the α-stereocenter in entry 3;[112] the reduction of a highly hindered ketone (entries 4 and 5);[113,114] and the stability of a silyloxy group to the reaction conditions (entry 5).[114]

Table 10 Reduction of tosylhydrazones with sodium cyanoborohydride in DMF/sulfolane

Entry	Substrate	Conditions	Products	Yield (%)	References
1		1. $TsNHNH_2$, AcOH, r.t. 2. $NaCNBH_3$, DMF, sulfolane, TsOH, 110 °C		65	104
2		$TsNHNH_2$, $NaCNBH_3$, TsOH, DMF, sulfolane, 110 °C		32	59
3		1. $TsNHNH_2$, MeOH, 40 °C 2. $NaCNBH_3$, DMF, sulfolane, TsOH, 120 °C		65	102
4		1. $TsNHNH_2$, MeOH, TsOH, 4 Å sieves, r.t. 2. $NaCNBH_3$, DMF, sulfolane, TsOH, 140 °C		46	103
5		1. $TsNHNH_2$, TsOH, EtOH 2. $NaCNBH_3$, DMF, sulfolane, HCl, 100 °C		64[a]	105

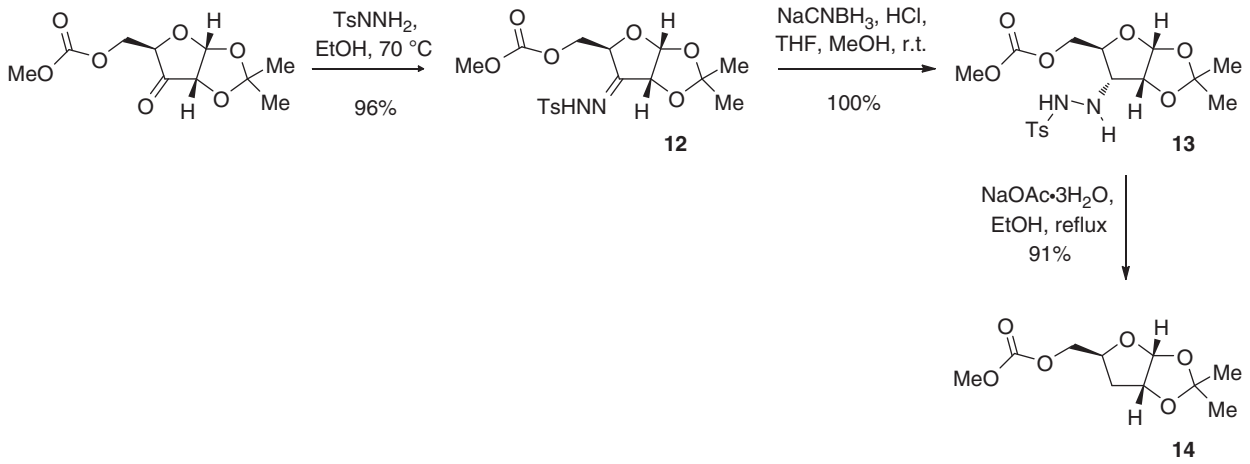
[a]Six percent of the C-11 epimer was also isolated.

An interesting radical rearrangement was recently reported by Toyota (Scheme 8).[115] Here, treatment of the tosylhydrazone **15** results in reductive rearrangement to give **19**. The reaction most likely proceeds by formation of diazene **16**, which yields *C*-centered radical **17**. Homoallyl–homoallyl radical rearrangement of **17** gives the [2.2.2]-bicyclic radical **18** which undergoes reduction to give **19**, most likely via hydrogen atom abstraction from diazene **16**. This homoallyl—homoallyl radical rearrangement was recently used by Nicolaou in a synthesis of platencin.[116]

8.12.1.1.5.4 Reduction with catecholborane

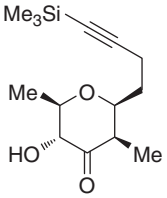
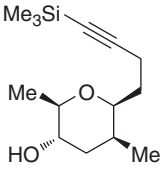
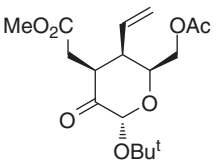
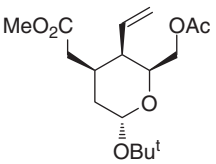
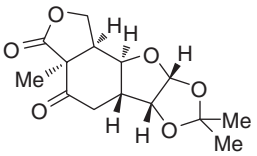
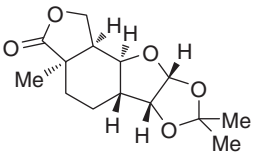
The deoxygenation of aldehydes and ketones via the corresponding tosylhydrazones may also be achieved efficiently using catecholborane (and some other boranes) followed by treatment with sodium acetate[17] or tetrabutylammonium acetate.[117] This procedure also offers a good method to reduce α,β-unsaturated aldehydes and ketones with enone double-bond transposition.[118] The mechanism for this reduction probably involves hydroboration of the C═N of the tosylhydrazone followed by formation of a boron 'ate' complex on addition of sodium acetate, which promotes diazene formation. Loss of nitrogen gives the product (Scheme 9).

A number of recent examples of the catecholborane reduction are collected in Table 13. Noteworthy is the resilience of an *N*-Boc protecting group to the reaction conditions (entry 1)[119] and the reduction of a highly hindered aldehyde in the presence of a diene (entry 2).[120] Attempted standard Wolff–Kishner reduction of the substrate shown in entry 3 resulted in epimerization of the stereocenters under the basic reaction conditions, whereas use of tosylhydrazone method gave the deoxygenated product in good yield.[121] A large scale reduction of a steroidal α,β-unsaturated ketone gave the product with double-bond transposition in good overall yield (entry 4).[122] Here hydroboration of the intermediate α,β-unsaturated tosylhydrazone occurs on the lower face



Scheme 7

Table 11 Nair three-step procedure

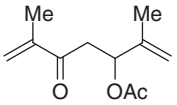
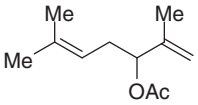
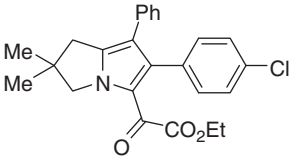
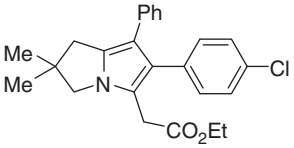
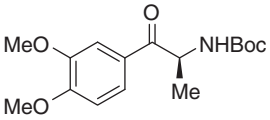
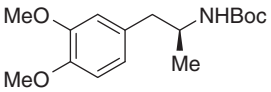
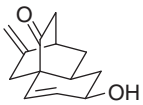
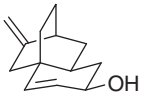
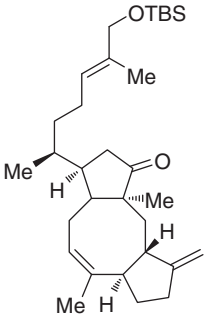
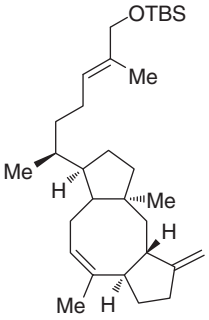
Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		1. $TsNHNH_2$, MeOH, r.t. 2. $NaCNBH_3$, THF, MeOH, HCl, 0 °C 3. $NaOAc \cdot 3H_2O$, EtOH, 75 °C		80	106
2		1. $TsNHNH_2$, EtOH, 73 °C 2. $NaCNBH_3$, THF, MeOH, HCl 3. $NaOAc \cdot 3H_2O$, EtOH, 72 °C		57	107
3		1. $TsNHNH_2$, EtOH, reflux 2. $NaCNBH_3$, THF, MeOH, HCl 3. $NaOAc \cdot 3H_2O$, EtOH, reflux		80	108

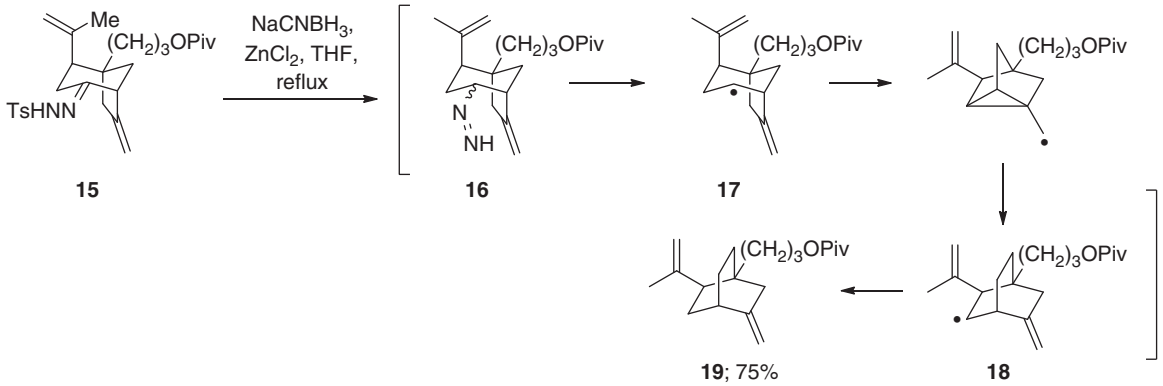
of the steroid ultimately to give the diazene on the top face of the molecule, which after retro-ene elimination gives the corresponding alkene in 74–80% yield. The synthesis of allenes is also possible (entry 5).[123] Particularly noteworthy is the reduction of the acyclic ketone (entry 7) which provides the product in >20:1 *dr* providing an excellent method for 1,4-stereocontrol.[124]

8.12.1.1.5.5 Scope and limitations

The mild reaction conditions for the formation and reduction of tosylhydrazones especially with sodium borohydrides and catecholborane mean that these modified Wolff–Kishner reductions have significantly improved functional group tolerance compared with the standard Wolff–Kishner procedures. As can be seen from the examples above, numerous reducible or base sensitive functional groups are compatible with the tosylhydrazone method including esters, lactones, carbamates, silyl ethers, sulfones, etc. The formation and reduction of tosylhydrazones generally does not compromise α-stereocenters; however, there are reports of epimerization of α-stereocenters during hydrazone formation.[126,127] Generally tosylhydrazone formation is a relatively simple process of mixing tosylhydrazine with the carbonyl compound commonly in alcoholic solvent with or without acid catalysis, although a number of other methods have been used (**Tables 8–13**). The formation of azines is generally not a problem although their formation has occasionally been reported;[128] however, using acetic acid as reaction solvent can overcome this problem. Reduction of α-cyclopropyl tosylhydrazones[71,129] with borohydride or boranes results in opening of the cyclopropyl ring in keeping with the radical mechanism outlined in **Scheme 5**. The reduction of tosylhydrazones is a mild method for the deoxygenation of aldehyde and ketones, but the reduction of tosylhydrazones is not always effective and other methods such as

Table 12 Reduction with sodium cyanoborohydride in protic solvents or with Lewis acid additives

Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		$TsNHNH_2$, AcOH, r.t., then $NaCNBH_3$, 70 °C		72	110
2		$TsNHNH_2$, EtOH, reflux, then $NaCNBH_3$, reflux		90	111
3		1. $TsNHNH_2$, $CHCl_3$, reflux 2. $NaCNBH_3$, $ZnCl_2$, MeOH, reflux		82	112
4		1. $TsNHNH_2$, TsOH, THF, reflux 2. $NaCNBH_3$, $ZnCl_2$, EtOH, reflux		90	113
5		1. $TsNHNH_2$, $(CO_2H)_2$, EtOH, r.t. 2. $NaCNBH_3$, $ZnCl_2$, MeOH, 90 °C (sealed tube)		55	114

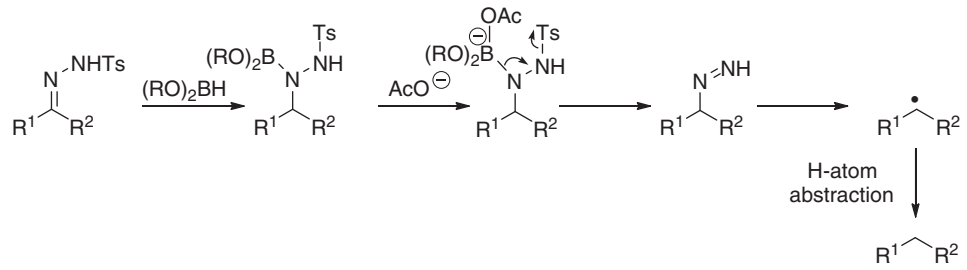


Scheme 8

hydrogenolysis of C–S bonds (*see* Chapter 8.28) and deoxygenation of alcohols (e.g., with the Barton–McCombie reaction; *see* Chapter 8.27) are frequently used when more direct reduction of C═X to CH_2 is ineffective.

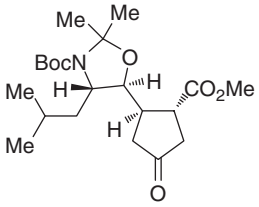
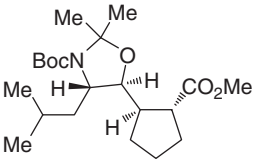
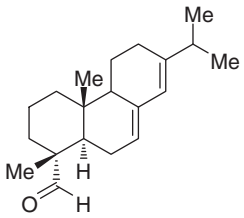
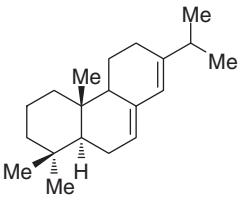
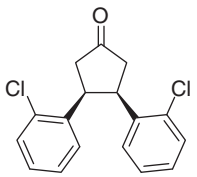
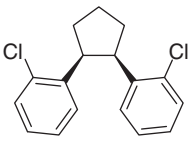
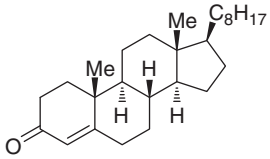
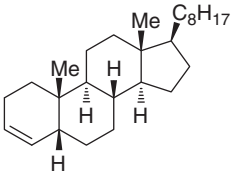
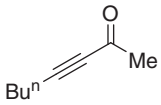
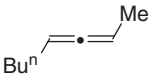
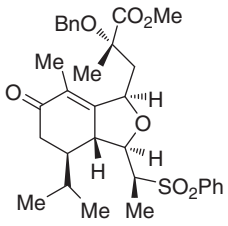
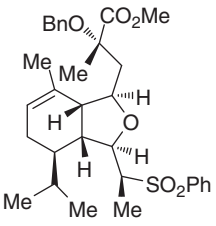
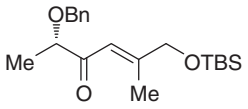
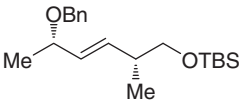
8.12.1.1.6 Overview of Wolff–Kishner methods

Owing to the plethora of Wolff–Kishner methods available, initial method selection may not be obvious. The Huang–Minlon procedure is still very popular but if the substrate has base sensitive functionality, including epimerizable stereocenters or α-heteroatoms then one of the tosylhydrazone methods should be selected. For base stable, hindered substrates the Huang–Minlon modification is a good starting point followed by the Nagata procedure and the Barton procedure noting the



Scheme 9

Table 13 Reduction with catecholborane

Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		1. $TsNHNH_2$, Na_2SO_4, MeOH, reflux 2. Catecholborane, $CHCl_3$, 0 °C–r.t. then $NaOAc \cdot 3H_2O$, reflux		67	119
2		1. $TsNHNH_2$, EtOH, 25 °C 2. Catecholborane, $CHCl_3$, 25 °C, then $NaOAc \cdot 3H_2O$, reflux		57	120
3		1. $TsNHNH_2$, MeOH, reflux 2. Catecholborane, $CHCl_3$, 25 °C, then $NaOAc \cdot 3H_2O$, reflux		54	121
4		1. $TsNHNH_2$, EtOH, reflux 2. Catecholborane, $CHCl_3$, 0 °C, then $NaOAc \cdot 3H_2O$, reflux		75–80	122
5		1. $TsNHNH_2$, EtOH, reflux 2. Catecholborane, $CHCl_3$, r.t. then $NaOAc \cdot 3H_2O$, heat		64	123
6		1. $TsNHNH_2$, EtOH, reflux 2. Catecholborane, $CHCl_3$, 0 °C–r.t., then $NaOAc \cdot 3H_2O$, 0 °C–reflux		77	125
7		1. $TsNHNH_2$, $Ti(OPr^i)_4$, r.t. 2. Catecholborane, $CHCl_3$, SiO_2, –42 °C–r.t., then $NaOAc \cdot 3H_2O$, reflux		66	124

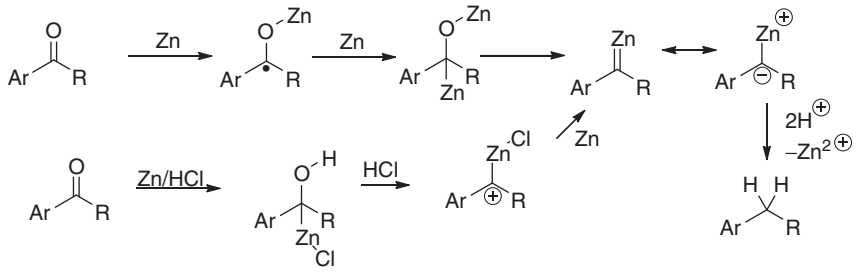
attendant risk of using anhydrous hydrazine. With less base-stable substrates, the Henbest and Myers procedures are sensible starting points along with the tosylhydrazones methods. With α,β-unsaturated aldehydes and ketones the Henbest procedures should minimize double-bond migration and the tosylhydrazone methods with sodium borohydrides or catecholborane will maximize enone double-bond transposition. α,β-Unsaturated tosylhydrazones that are able to adopt an *s-cis* conformation generally give products in higher yield than from substrates that are constrained to an *s-trans* geometry; the use of catecholborane is recommended as the first method to try with α,β-unsaturated tosylhydrazones. With α-heteroatoms a useful starting point would be to use Nair's three-step procedure. It should be also remembered that α-cyclopropyl aldehydes and ketones will likely undergo ring opening under tosylhydrazone method but may survive standard Wolff–Kishner reduction with hydrazine and base.

8.12.1.2 Clemmensen and Related Reductions

Zinc metal is a widely used reagent for the reduction of numerous functional groups. In 1913, Clemmensen reported that the deoxygenation of aldehydes and ketones could be readily achieved on heating the substrate with zinc/mercury amalgam in aqueous hydrochloric acid containing an organic solvent.[130] A number of modifications have been published since the original disclosure of Clemmensen most notably the use of anhydrous conditions at lower temperatures. The Clemmensen reduction is most commonly used to deoxygenate ketones adjacent to aromatic rings, which, in conjunction with Friedel–Crafts acylation, accomplishes a transformation equivalent to Friedel–Crafts alkylation. A number of reviews[20,131,132] and useful overviews[21,133] have been published on the subject. In general recent reports and experimentally defined procedures of the use of the Clemmensen reduction in synthesis will be covered in this section.

8.12.1.2.1 Mechanism

The mechanism of the Clemmensen reduction has been widely studied.[131,132,134–136] The exact mechanism of the reaction has not been completely elucidated although it is known that alcohols are not intermediates except in certain specific cases; the product distribution in the Clemmensen reduction is also highly dependent on the reaction conditions. Zinc carbenes have been implicated as intermediates as shown by the formation of cyclopropanes during Clemmensen reduction in the presence of added styrene,[133,134] although the exact mechanism for the formation of the zinc carbene is likely condition dependent. Plausible mechanisms are shown in Scheme 10.



Scheme 10

8.12.1.2.2 Reduction using zinc/mercury amalgam

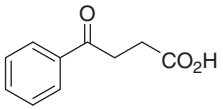
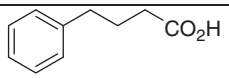
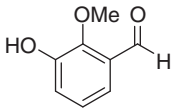
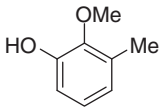
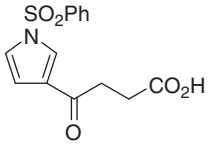
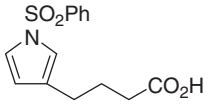
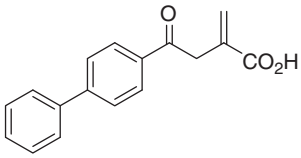
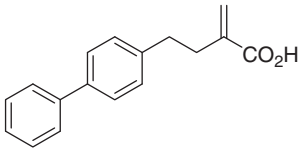
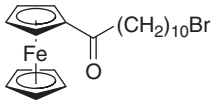
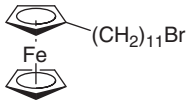
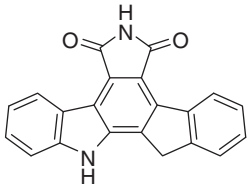
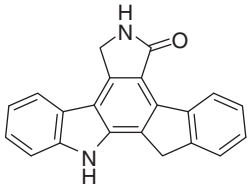
As noted in Section 8.12.1.2, the classical procedure for the Clemmensen reduction involves heating the substrate with zinc/mercury amalgam and concentrated hydrochloric acid in toluene or another organic solvent at reflux. A number of examples are depicted in Table 14. Noteworthy is the survival of an α,β-unsaturated acid under Clemmensen conditions (entry 4).[76] The low-yielding reduction of the ketobromide in entry 5[137] is probably because of reduction of the bromide by zinc metal. Reduction of a phthalimide derivative is unusual (entry 6).[138]

8.12.1.2.3 Modified zinc procedures

8.12.1.2.3.1 Zinc dust and hydrochloric acid

A drawback of the original Clemmensen procedure is the necessity of using zinc/mercury amalgam with its attendant toxicity issues. Recent procedures frequently use zinc dust in place of the amalgam. A number of examples are shown in Table 15. Reduction of aryl ketones occurs in good yields (entries 1 and 2)[143,144] as does the selective reduction of a tricarbonyl substrate (entry 3).[145] The use of acetals as substrates is effective (entry 4).[146] The use of chlorotrimethylsilane and *iso*-propanol at low temperature is effective for the deoxygenation of dialkyl ketones (entry 5) and aldehydes.[147] The use of zinc dust and aluminum trichloride hexahydrate as a means for deoxygenating ketones has also been reported.[148]

Table 14 Reduction with zinc/mercury amalgam

Entry	Substrate	Conditions	Products	Yield (%)	References
1		Zn/Hg, HCl, H_2O, toluene, reflux		82–89	139
2		Zn/Hg, HCl, H_2O, EtOH, reflux, reflux		60–67	140
3		Zn/Hg, HCl, H_2O, toluene, reflux		71	141,142
4		Zn/Hg, HCl, H_2O, toluene, reflux		52	76
5		Zn/Hg, 47% HBr, EtOH, reflux[a]		26	137
6		Zn/Hg, HCl(g), EtOH, reflux		50[b]	138

[a]Zn/Hg amalgam prepared from $HgBr_2$, Zn, and HBr.
[b]The product was a 4:1 mixture of the lactam shown and the lactam formed by reduction of the other imide carbonyl group.

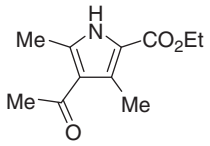
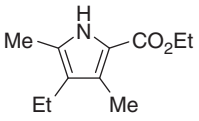
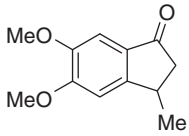
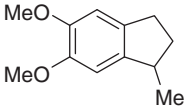
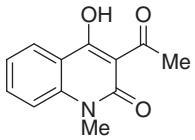
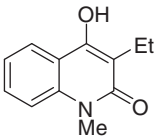
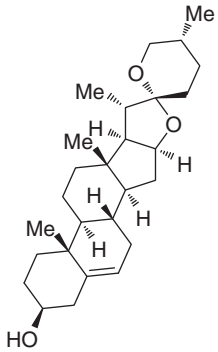
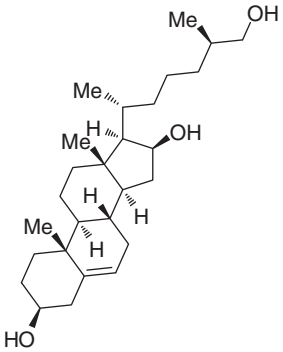
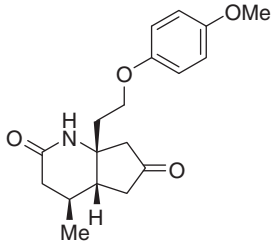
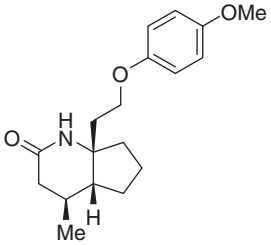
8.12.1.2.3.2 Zinc dust and hydrogen chloride: Yamamura's procedure

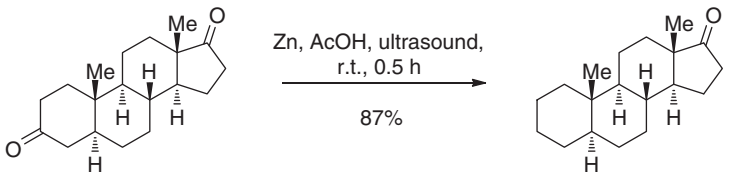
The original Clemmensen procedure not only required the use of zinc/mercury amalgam and hydrochloric acid but also high temperatures, which meant that the functional group tolerance was relatively limited. Moreover, nonaromatic substrates were frequently reduced inefficiently. One of the major procedural advances was reported in the 1960s from the group of Yamamura.[149–152] Yamamura reported two procedures for the deoxygenation of ketones: one using zinc and hydrogen chloride gas in an organic solvent at ambient temperature or below, and the other involving using acetic anhydride as solvent (**Table 16**). These procedures can be used to remove a sterically less hindered ketone oxygen in a diketone substrate, although the rate of reduction of hindered ketones depends on whether or not freshly activated zinc is used.[150] Low-temperature reduction of a range of dialkyl ketones is shown in **Table 16**. As can be seen in entry 2[153] α-stereocenters can be compromised under the acidic reaction conditions. It is not always necessary to use hydrogen chloride gas as the addition of chlorotrimethylsilane to a known quantity of water can provide anhydrous hydrogen chloride. The example in entry 6 demonstrates the introduction of deuterium atoms using D_2O and chlorotrimethylsilane;[154] enol formation has clearly occurred under the reaction conditions.

8.12.1.2.3.3 Other methods

The Clemmensen reaction may be promoted by ultrasound.[159,160] This would appear to be a good method to initiate heterogenous Clemmensen reductions that take place on the surface of the zinc metal. In one study the use of nonactivated zinc dust in acetic acid at room temperature with ultrasonic irradiation allowed reduction of a less hindered ketone from a diketone substrate in good yield (equation 9).[160]

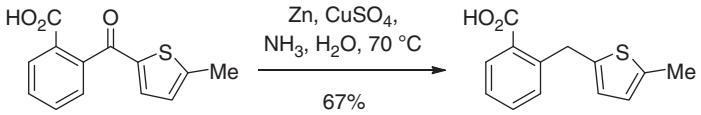
Table 15 Reduction with zinc dust

Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		Zn, EtOH, HCl, 70 °C		92	143
2		Zn, toluene, H_2O, HCl, reflux		75	144
3		Zn, EtOH, AcOH, HCl, 80 °C–reflux		75	145
4		Zn, EtOH, HCl, reflux		85	146
5		Zn, Me_3SiCl, Pr^iOH, CH_2Cl_2, 0 °C		77	147



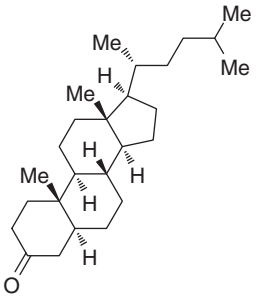
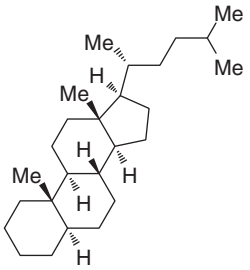
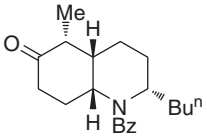
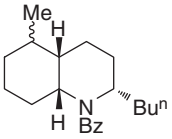
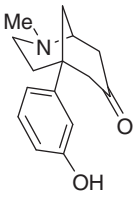
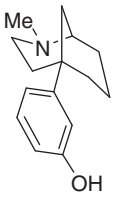
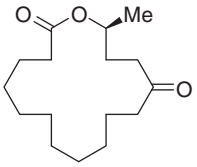
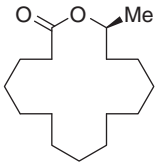
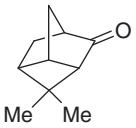
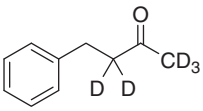
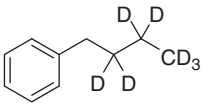
(9)

An unusual Clemmensen-type reduction has been reported using zinc/copper couple in aqueous ammonia (equation 10)[161] and the reduction of electron-rich aromatic aldehydes and ketones to methylene groups using zinc and aqueous sodium hydroxide has also been reported.[162] These Clemmensen reductions under basic conditions are complementary to the deoxygenation of aldehydes and ketones under acidic conditions.



(10)

Table 16 Reduction with zinc and hydrogen chloride gas

Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		Zn, HCl(g), Et_2O, –20–0 °C		76–77	155
2		Zn, HCl(g), Et_2O, –20 °C		57	153
3		Zn, HCl(g), Et_2O, 0 °C		66	156
4		Zn, HCl(g), Et_2O, 0 °C		86	157
a		Zn, HCl(g), Et_2O, 0 °C		86	158
6		Zn, D_2O, Me_3SiCl, THF, 0 °C		72[a]	154

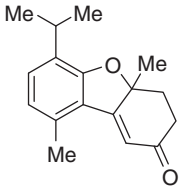
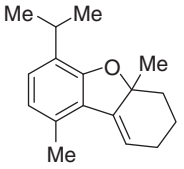
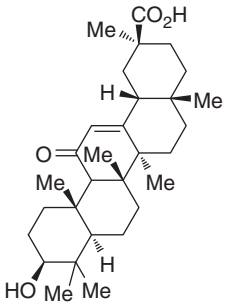
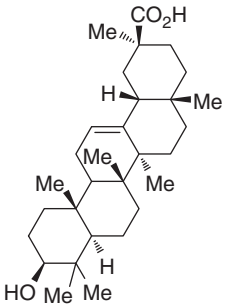
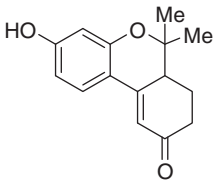
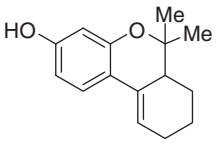
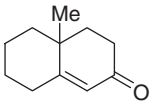
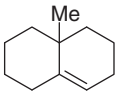
[a]Product contained 72% d_7, 24% d_6, and 4% d_5 species.

8.12.1.2.4 Substrate scope

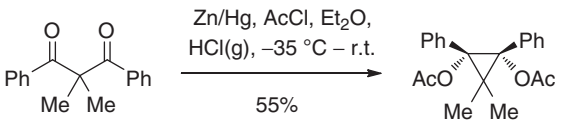
Owing to the reducing reaction conditions and acidic nature of the Clemmensen reduction functional group compatibility is limited. It is to be expected that readily reducible functional groups, e.g., nitro, bromo, iodo, certain alkenes, α-oxy ketones would be incompatible with the reaction conditions. In general α-heteroatom-substituted ketones undergo reductive loss of the heteroatom. The Clemmensen reduction of α,β-unsaturated ketones can lead to deoxygenation of the ketone carbonyl group (Table 17). The more usual course of Clemmensen reduction of α,β-unsaturated ketones is to give rearranged products[152] as well as McMurray and pinacol coupling, reduction of the alkene, reduction of the alkene and carbonyl group.[163,164] The rearranged products most likely arise from cyclopropanol intermediates, which can be trapped in certain instances.[165]

Both 1,3-diketones and 1,4-diketones have a tendency to give products arising from nonstandard reduction under Clemmensen reaction conditions. 1,3-Diketones generally give products of rearrangement via the corresponding cyclopropanes which, again can be trapped in certain cases.[164] A recent example is shown in equation 11.[170] The standard reduction of 1,3-dicarbonyl compounds can be high yielding when formation of the cyclopropane is disfavored.[171]

Table 17 Reduction of α,β-unsaturated ketones without rearrangement

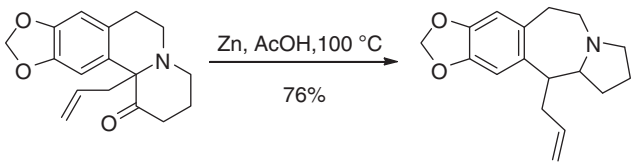
Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		Zn/Hg, HCl, toluene, reflux		50	166
2		Zn/Hg, HCl, dioxane, r.t.		77	167
3		Zn/Hg, HCl, toluene, reflux		59	168
4		Zn/Hg, HCl, H_2O, reflux		60[a]	169

[a]30–40% of McMurray coupled product was also isolated.



(11)

With 1,4-diketones a range of products are possible including normal reduction of both ketones, carbon–carbon bond cleavage and cyclobutane formation; which pathway is the major pathway depends on both the steric and electronic environments of the carbonyl groups.[164] The reduction of α-heteroatom-substituted ketones generally results in loss of the α-substituent.[152] Cyclic α-amino ketones undergo rearrangement under Clemmensen reaction conditions and this reaction has been widely studied by Leonard[172] who also found that cyclic α-thioketones undergo the same rearrangement.[173] This reaction has been used in the synthesis of cephalotaxine (equation 12).[174]



(12)

8.12.1.2.5 Other side reactions

A number of common side products can be formed during the Clemmensen reaction. These include products arising from pinacol and McMurray reactions (Table 17, entry 4), reduction of the ketone carbonyl to a secondary alcohols, and the formation of alkenes, which has been developed into a useful synthetic transformation.[175]

8.12.1.3 Ionic Hydrogenation and Related Procedures

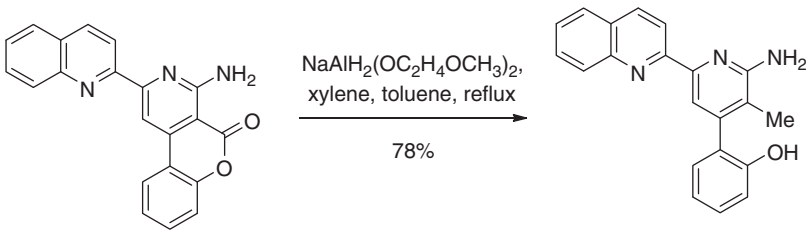
Exposure of aldehydes and ketones to a hydride donor and a Brønsted or Lewis acid is a well-used method for the deoxygenation of aldehydes and ketones. A generic mechanism for such transformations is shown in Scheme 11. Activation of the carbonyl group by a Brønsted or Lewis acid occurs first followed by hydride attack. Loss of the carbonyl oxygen atom gives a carbenium ion that is attacked by hydride to give the deoxygenated product. A large number of reagents have been reported for this transformation; however, the vast majority of these require R^1 or R^2 to be a cation-stabilizing group. Practically, therefore, these methods are generally applicable only to aromatic aldehydes and ketones although there are exceptions.



Scheme 11

8.12.1.3.1 Use of metal hydrides

The deoxygenation of aromatic ketones using lithium aluminum hydride is possible although generally requires an electron-rich substrate.[176] Sodium bis(2-methoxyethoxy)aluminum hydride in hot xylene can also be used to deoxygenate electron-rich aromatic aldehydes and ketones.[177,178] This method has been used in the synthesis of the tetracyclic ring system of streptanigrin (equation 13).[179] Here, reduction of the δ-lactone to the methyl-substituted pyridine is facilitated by the electron-donating amino group.



(13)

8.12.1.3.1.1 Use of metal hydrides and Lewis or Brønsted acids

A much more common method for the deoxygenation of aromatic aldehydes and ketones involves the use of a hydride source in conjunction with a Lewis or Brønsted acid. A vast number of hydride/acid combinations have been used; only the most popular combinations are covered.

8.12.1.3.1.1.1 Lithium aluminum hydride and aluminum trichloride

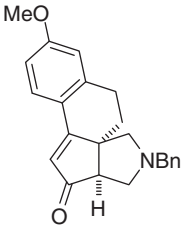
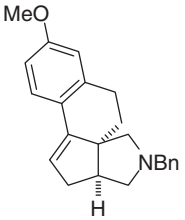
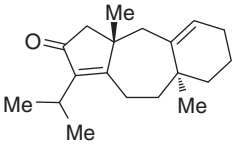
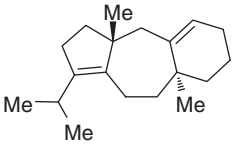
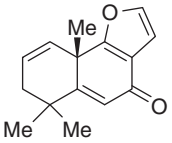
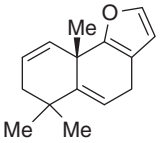
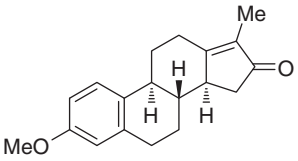
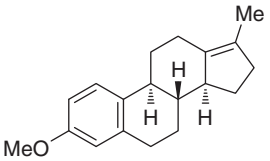
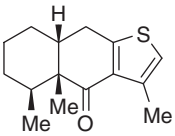
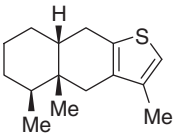
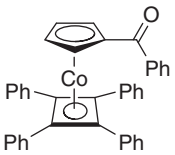
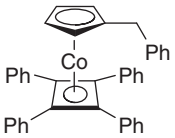
The combination of lithium aluminum hydride and aluminum trichloride generates alane, dichloroaluminum hydride, and chloroaluminum dihydride depending on stoichiometry. These reagents are able to readily deoxygenate electron-rich aromatic aldehydes and ketones and some α,β-unsaturated ketones.[180–182] Deoxygenation with these reagent combinations occurs under much milder conditions than with the hydride reagent alone and is still a popular method. Table 18 contains some recent examples including deoxygenation of α,β-unsaturated ketones; reduction of the alkene in preference to the ketone with α,β-unsaturated ketones has also been reported.[183] Interestingly a phenolic methyl ether survives these conditions (entry 1)[184] as does an acid-sensitive furan (entry 3).[185] With the substrate in entry 2, Wolff–Kishner reduction, including using the Henbest modification, resulted in deoxygenation with migration of the enone double bond into the seven-membered ring.[186] With the example in entry 4 the ratio of lithium aluminum hydride to aluminum trichloride was crucial to avoid complete reduction of both the alkene and ketone of the enone.[187]

Sodium borohydride/aluminum trichloride has also been used to deoxygenate alkyl aryl ketones including aryl chlorides;[190–192] electron-deficient aryl ketones do not undergo deoxygenation with lithium aluminum hydride.

8.12.1.3.1.1.2 *tert*-Butylamine-borane complex and aluminum trichloride

Another popular method for the deoxygenation of aldehydes and ketones is the combination of aluminum chloride and *tert*-butylamine-borane complex (Table 19).[193] This reagent combination will deoxygenate electron-poor aryl ketones (entry 1).[193] Nitro groups can survive this reducing system (entry 3) although they can also suffer reduction.[194] The reagent system is tolerant of a pyrrole NH (entry 4)[195] and amides can also survive unscathed (entry 5).[196] Some esters are readily reduced by the reagent combination.[196] The ester in entry 1 undergoes partial reduction under the reaction conditions.

Table 18 Reduction with lithium aluminum hydride/aluminum trichloride

Entry	Substrate	Conditions[a]	Products	Yield (%)	References
1		1.0 $LiAlH_4$, 2.2 $AlCl_3$, Et_2O, 0° C, then add substrate, r.t.		95	184
2		1.0 $LiAlH_4$, 2.0 $AlCl_3$, Et_2O, 0° C, then add substrate, reflux		88	186
3		1.0 $LiAlH_4$, 2.0 $AlCl_3$, Et_2O, 0° C, use supernatant, add substrate, r.t.		87	185
4		1.0 $LiAlH_4$, 4.0 $AlCl_3$, Et_2O, 0 °C, use supernatant, –10 °C		95[b]	187
5		1.0 $LiAlH_4$, 2.0 $AlCl_3$, Et_2O, r.t.		79	188
6		1.0 $LiAlH_4$, 1.0 $AlCl_3$, Et_2O, r.t.		98	189

[a]The relative molar ratios of $LiAlH_4$:$AlCl_3$ are given.
[b]Formed as a 20:1 mixture with fully reduced enone.

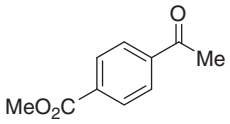
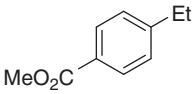
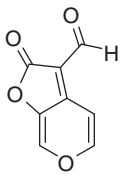
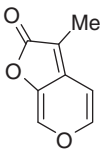
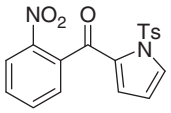
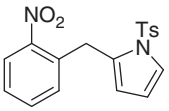
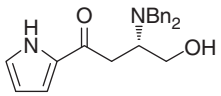
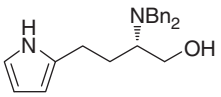
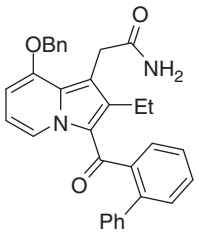
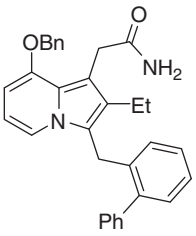
8.12.1.3.1.1.3 Sodium cyanoborohydride and zinc iodide

Sodium cyanoborohydride and zinc(II) iodide is a mild reagent combination widely used for the reduction of electron-rich aryl ketones (**Table 20**).[198] With this reagent combination esters are generally tolerated (entries 2–4)[199–201] although unhindered esters may suffer some reduction (entry 1). With the example in entry 3 the initially formed product was isolated as a tertiary amine/borane complex that required heating in ethanol at reflux to release the free tertiary amine. In general silyl- and Boc-protecting groups are tolerated (entry 4)[201] and α-stereocenters are not compromised.[202]

8.12.1.3.1.1.4 Triethylsilane and sodium cyanoborohydride

By far the most popular method for the complete ionic hydrogenation of aryl aldehydes and ketones is the use of triethylsilane in combination with trifluoroacetic acid.[203–205] Reduction of aromatic aldehydes and ketones to the corresponding methyl/methylene compounds generally occurs at room temperature in a few hours, with electron deficient aryl ketones requiring significantly longer reaction times; electron deficient aryl aldehydes do not undergo complete deoxygenation under these conditions. Aromatic aldehydes with two electron-donating groups give Friedel–Crafts products predominantly.[204] The mild reaction conditions are compatible with other reducible functional groups such as nitro, cyano, carboxylic acid, esters, etc. Phenyl cyclopropyl ketone undergoes deoxygenation and rearrangement[204] but not all phenyl cyclopropyl ketones rearrange.[206] There is good evidence that these reactions proceed via carbenium ion intermediates, and relative rate constants for reduction of a range of

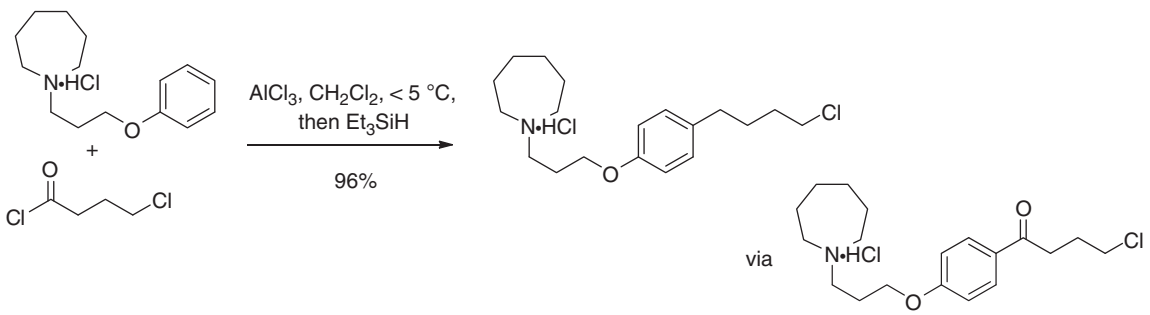
Table 19 Reduction with aluminum trichloride and *tert*-butylamine-borane complex

Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		$Bu^tNH_2 \cdot BH_3$, $AlCl_3$, CH_2Cl_2, 0 °C		58[a]	193
2		$Bu^tNH_2 \cdot BH_3$, $AlCl_3$, CH_2Cl_2, reflux		83	197
3		$Bu^tNH_2 \cdot BH_3$, $AlCl_3$, CH_2Cl_2, 0 °C–r.t.		65–70	194
4		$Bu^tNH_2 \cdot BH_3$, $AlCl_3$, CH_2Cl_2, 0 °C		44	195
5		$Bu^tNH_2 \cdot BH_3$, $AlCl_3$, CH_2Cl_2, 0 °C		60	196

[a]Also isolated was methyl 4-(1-hydroxyethyl)benzoate (7%) and (4-ethylphenyl)methanol (16%).

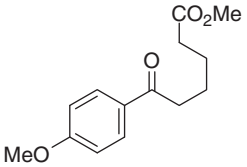
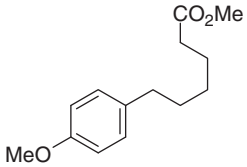
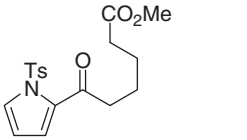
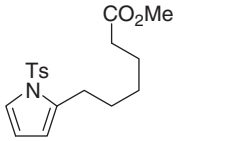
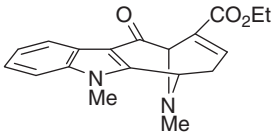
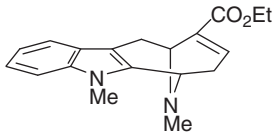
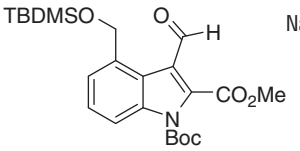
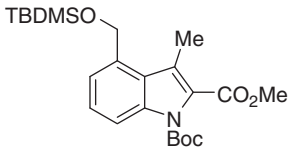
ketones have been established.[207] The use of this method for ionic hydrogenation of aryl ketones, in conjunction with initial Friedel–Crafts acylation provides a very popular method for overall Friedel–Crafts alkylation of an aromatic ring. A number of examples are shown in **Table 21**. The mildness of the reaction conditions is clear: a strained nitrogen–nitrogen double bond is not reduced (entry 2),[208] esters, amides, indoles, and imides survive intact (entries 3–5).[209–211] α-Stereocenters are generally not compromised (entry 5).[211] Rearrangements are rare but can occur under the reaction conditions as shown in the deoxygenation of the substrate in entry 6.[212]

Friedel–Crafts acylation/reduction has been telescoped into a single flask reaction. Thus, Friedel–Crafts acylation of the azepine shown in equation 14 with 4-chlorobutyryl chloride and aluminum trichloride in dichloromethane followed by addition of triethysilane gave the chlorobutane product in 96% yield on a 750 g scale.[213] A large scale Friedel–Crafts acylation/*in situ* carbonyl deoxygenation using 1,1,3,3-tetramethyldisiloxane has also been reported (equation 15).[214]

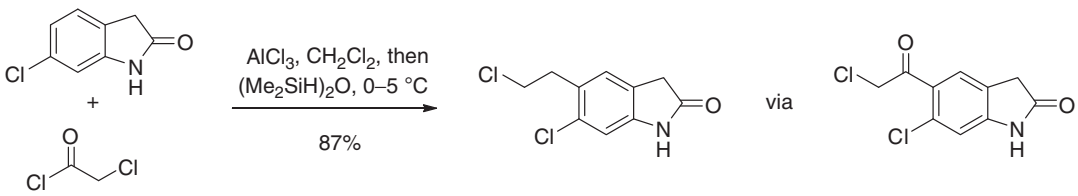


(14)

Table 20 Reduction with sodium cyanoborohydride and zinc iodide

Entry	Substrate	Reduction Solvent	Products	Yield (%)	References
1		$NaCNBH_3$, ZnI_2, $ClCH_2CH_2Cl$, r.t.		61[a]	198
2		$NaCNBH_3$, ZnI_2, $ClCH_2CH_2Cl$, 80 °C		78	199
3		$NaCNBH_3$, ZnI_2, $ClCH_2CH_2Cl$, reflux, then ethanol, reflux		73	200
4		$NaCNBH_3$, ZnI_2, $ClCH_2CH_2Cl$, reflux		63	201

[a]Also isolated was 6-(4-methoxyphenyl)hexan-1-ol (10%).

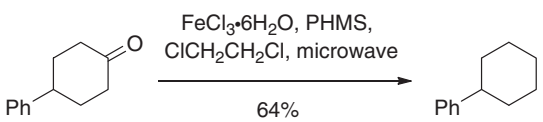


(15)

8.12.1.3.1.1.5 Ionic hydrogenation of dialkyl ketones

The majority of the above methods are applicable to aromatic aldehydes and ketones and it is unusual for ionic hydrogenation to be applied to dialkyl ketones. The use of triethylsilane and boron trifluoride gas will not only reduce electron–poor aryl aldehydes and ketones, but also dialkyl ketones.[215,216] The drawback of this method is the need for gaseous boron trifluoride. Recently, the use of triethylsilane, butylsilane, diethylsilane, or polymethylhydrosiloxane in the presence of substoichiometric quantities of tris(pentafluorophenyl)borane has been shown to reduce aliphatic aldehydes and ketones to alkanes[217–219] and as well as reducing α,β-unsaturated ketones without double-bond migration (**Table 22**). Moreover the use of silanes and tris(pentafluorophenyl)borane can directly reduce carboxylic acids, acid chlorides, and esters to the corresponding methyl group.[217,218]

The use of cheap iron(III) chloride trihydrate and polymethylhydrosiloxane under microwave irradiation has recently been shown to deoxygenate both aromatic and aliphatic aldehydes and ketones. An example is shown in equation 16.[220] The above methods are relatively new and will likely see increased use in the future.



(16)

8.12.1.3.2 Side reactions

In general the main side reaction observed in ionic hydrogenation is incomplete reduction with the corresponding alcohols frequently being isolated. Given that these reactions proceed by carbenium ion intermediates, Friedel–Crafts reactions can occur as can rearrangement reactions (**Table 20**, entry 6). An example of a high-yielding intramolecular Friedel–Crafts reaction under these conditions is shown in equation 17.[221]

Table 21 Reduction with triethylsilane and trifluoroacetic acid

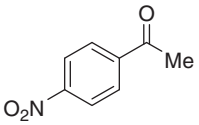
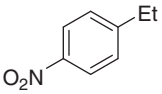
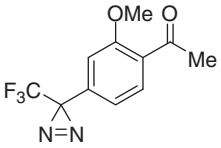
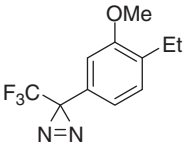
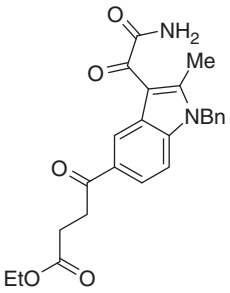
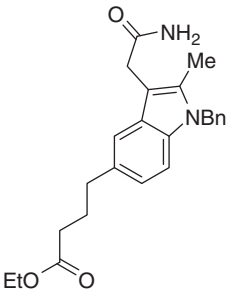
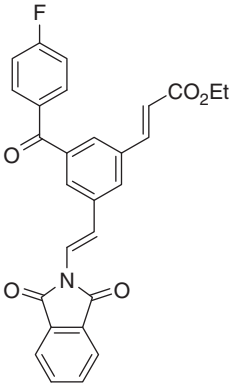
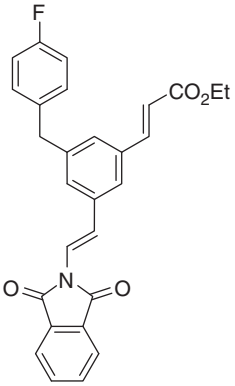
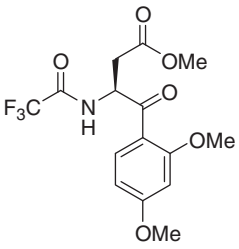
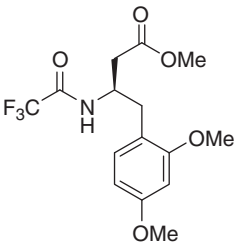
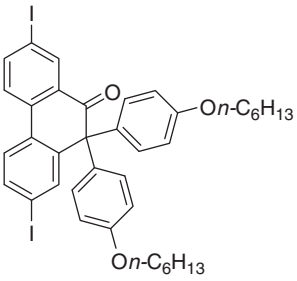
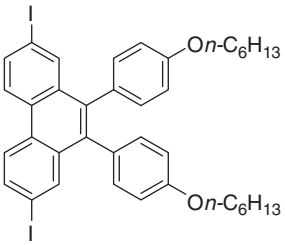
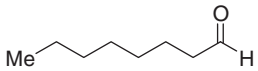
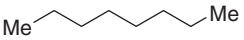
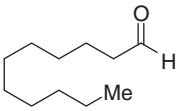
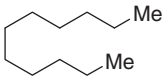
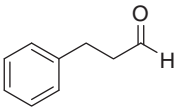
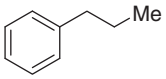
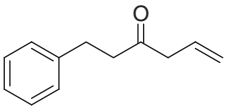
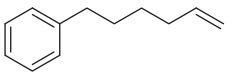
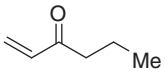
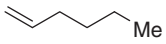
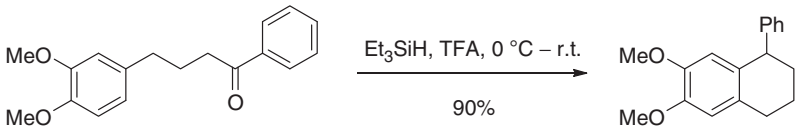
Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		TFA, Et_3SiH, r.t.		96	204
2		TFA, Et_3SiH, r.t.		96	208
3		TFA, Et_3SiH, $ClCH_2CH_2Cl_2$, reflux		63	209
4		TFA, Et_3SiH, 10–15 °C		83	210
5		TFA, Et_3SiH, CH_2Cl_2, r.t.		79	211
6		TFA, Et_3SiH, 80 °C, 3 h		80	212

Table 22 Reduction with silanes and tris(pentafluorophenyl)borane

Entry	Substrate	Conditions	Products	Yield (%)	References
1		$BuSiH_3$, or Et_2SiH,$(C_6F_5)_3B$, CH_2Cl_2, r.t.		79–81	217
2		Et_3SiH, $(C_6F_5)_3B$, CH_2Cl_2, r.t.		95	218
3		Polymethylhydrosiloxane,$(C_6F_5)_3B$, CH_2Cl_2, r.t.		90	219
4		Polymethylhydrosiloxane,$(C_6F_5)_3B$, CH_2Cl_2, r.t.		88	219
5		$BuSiH_3$		84	217



(17)

8.12.1.4 Transition Metal-Catalyzed Hydrogenation

Deoxygenation of aromatic aldehydes and ketones by transition metal-catalyzed hydrogenolysis has been widely used. Simple catalysts such as platinum oxide or palladium on carbon, frequently in the presence of an acid additive, have been used for this transformation although platinum catalysts are known to be able to hydrogenate aromatic rings. These reactions proceed via the corresponding alcohol. The direct hydrogenolysis of various aromatic imine derivatives to methylene is also successful.[222] A set of recent reactions is collected in **Table 23**. Reduction of the aldehyde in entry 1 was successfully conducted on a 5 kg scale.[223] Successful removal of the carbonyl group of the ketone in entry 2 was achieved by hydrogenolysis; ionic hydrogenation resulted in cyclization (equation 17).[221] Unsurprisingly, reduction of alkenes occurs during hydrogenolysis of ketones (entry 4).[224] Selective hydrogenolysis of an aromatic ketone is possible in the presence of a dialkyl ketone (entry 5).[219] Aromatic halides generally suffer reduction (entry 6).[225] Under extended reaction conditions, rearrangement of aromatic side chains can occur as was experienced with the substrate in entry 7 during the 7–10 day reduction period.[226]

Transfer hydrogenation is also applicable to the reductive deoxygenation of aromatic aldehydes and ketones. The first catalyst system involved the use of Pd/C, iron(III) chloride, and acetic anhydride with cyclohexene or limonene as hydrogen donors.[229,230] More usual conditions for transfer hydrogenation, namely ammonium formate as the hydrogen donor with palladium on carbon as catalyst have also been used to deoxygenate aromatic aldehydes and ketones.[231] A few examples are shown in **Table 24**. Reduction of the ketone shown in entry 4 resulted in the product being formed in low yield along with dehydrohalogenated products.[111] The desired product could be formed in high yield by reduction of the corresponding tosylhydrazone (**Table 12**, entry 2).

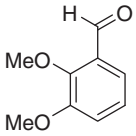
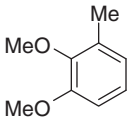
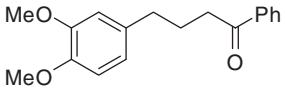
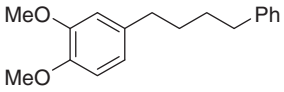
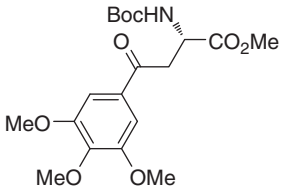
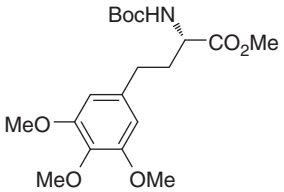
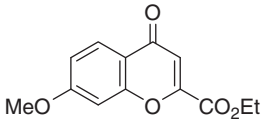
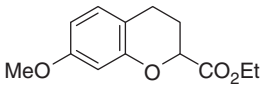
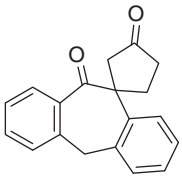
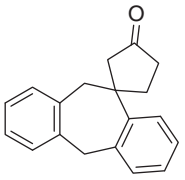
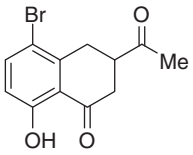
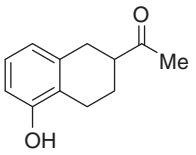
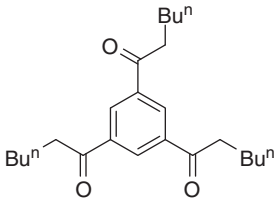
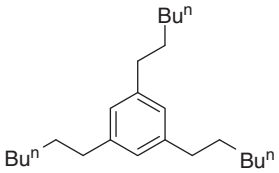
8.12.1.4.1 Side reactions

Functional groups which are readily reduced by transition metal-catalyzed hydrogenation/hydrogenolysis will likely be reduced under the conditions discussed in Section 8.12.1.4. As noted above aromatic halides are frequently reactive under the reaction conditions with dehalogenated products being isolated. Decarbonylation of aromatic aldehydes has been reported.[230]

8.12.1.5 Other methods

Other methods for the deoxygenation of aldehydes and ketones include the use of lithium in ammonia,[232–234] the use of palladium(II) chloride with sodium borohydride[235] or polymethylhydrosiloxane,[236] iodine and hypophosphorous acid,[237] supercritical *iso*-propanol,[238] and Raney nickel/aluminum alloy in water.[239]

Table 23 Transition metal-catalyzed hydrogenation

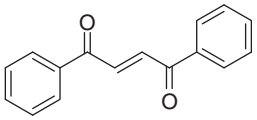
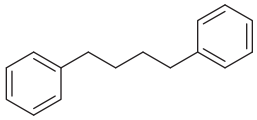
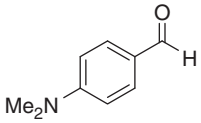
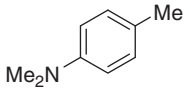
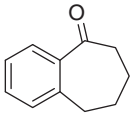
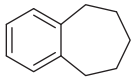
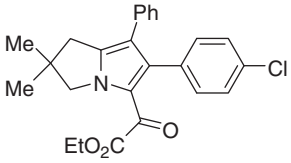
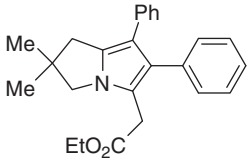
Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		H_2, Pd/C, EtOAc, r.t.		>95	223
2		H_2, Pd/C, THF, r.t.		92	221
3		H_2, Pd/C, EtOH, r.t.		91	227
4		H_2, Pd/C, AcOH, r.t.		72	224
5		H_2, Pd/C, THF, AcOH, r.t.		88	228
6		H_2, PtO_2, EtOH, r.t.		60[a]	225
7		H_2, Pd/C, AcOH, H_2SO_4, r.t.		72	226

[a]A small amount of the benzylic alcohol was also isolated.

8.12.1.6 Overview

Numerous methods exist for the reduction of C═X to CH_2 in aldehydes, ketones, imines, and related compounds. The methods discussed in Section 8.12.1.2 are the most commonly used namely: the Wolff–Kishner reduction (see Section 8.12.1.1) and related tosylhydrazone method, the Clemmensen reduction, ionic hydrogenation (see Section 8.12.1.3), and transition metal-catalyzed hydrogenolysis (see Section 8.12.1.4). All of these methods have various advantages and disadvantages with respect to individual substrates. All of the methods work with aromatic aldehydes and ketones. Electron-rich aromatic substrates are generally more readily reduced than electron-poor aromatic substrates in the Clemmensen reduction and with ionic and transition metal-catalyzed hydrogenolysis. Alkyl aldehydes and dialkyl ketones do not undergo transition metal-catalyzed hydrogenolysis and have only recently been deoxygenated under ionic hydrogenation conditions with the substrate scope and functional group tolerance yet to be fully investigated; α,β-unsaturated ketones undergo deoxygenation frequently with good efficiently using lithium aluminum hydride and aluminum trichloride. The deoxygenation of alkyl aldehydes and dialkyl ketones is possible using the Clemmensen reduction and variants. The most versatile method for the deoxygenation of most types of aldehydes and ketones is the Wolff–Kishner reduction and tosylhydrazone variants. Conditions can generally be found that will deoxygenate most types of aldehyde and ketone and α,β-unsaturated aldehydes and ketones can readily be reduced, with faithful transposition of the enone double bond, using one of the many tosylhydrazone methods. Even with the numerous methods and variants discussed above it

Table 24 Transition metal-catalyzed transfer hydrogenation

Entry	*Substrate*	*Conditions*	*Products*	*Yield (%)*	*References*
1		Pd/C, $FeCl_3$, limonene, reflux		68	229
2		Pd/C, $FeCl_3$, cyclohexene		75	230
3		Pd/C, AcOH, NH_4HCO_2, 110 °C		54	231
4		Pd/C, AcOH, NH_4HCO_2, 110 °C		32[a]	111

[a]A number of other products were also isolated.

is not always possible to directly reduce C═X to CH_2. Other methods, including the reduction of C–S sigma bonds using Raney–Nickel and the deoxygenation of the corresponding alcohols are frequently used.

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8.13 Recent Developments in the Reduction of Nitro and Nitroso Compounds

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8.13.1 Introduction

Nitro compounds are among the most versatile and useful building blocks in synthetic organic chemistry.[1,2] The reduction of nitro compounds is an important transformation particularly in the contemporary fine chemical industry. Pharmaceuticals, dyes, and agricultural chemicals are synthesized with nitro compounds as precursors.[1–3] Not surprisingly, the search for new, mild, and selective reduction methods for nitro compounds is still an active area of research. Several reviews and previous book chapters have covered the continuous progress in this field.[1–7] The reduction of nitroso compounds, however, has been by far less exploited. Recent developments in this field are limited to a few examples and traditional methods for the reduction of nitroso compounds are still widely used.[8] Synthetic studies around this chemical motif are nowadays focused more commonly on the electrophilic nature of the nitroso group and its role in addition reactions like the nitroso/Diels–Alder and aldol transformations.[9] This chapter highlights only the most recent and outstanding contributions in the reduction of nitro and nitroso compounds since 2000.

8.13.1.1 Reduction of Aromatic Nitro and Nitroso Compounds to Anilines

The synthetic reduction of nitroarenes to anilines occurs through the formation of different intermediates, such as nitroso compounds and *N*-hydroxylamines. This kind of transformation has a remarkable importance in both academia and industry and, therefore, a number of methods have been developed to accomplish it.[2,6] The hydrogenation of simple aromatic nitro compounds under heterogeneous conditions possesses few limitations and represents the best choice in simple cases. Nevertheless, most of these conventional protocols fail in terms of chemoselectivity.[10] The selective reduction of aromatic nitro compounds is more challenging when other functional groups such as alkene, halide, aldehyde, ester, or nitrile are present in the molecule. The latest achievements in this field are noteworthy and briefly reviewed in this section. Some reports involving the direct reduction of nitroso compounds are also highlighted.

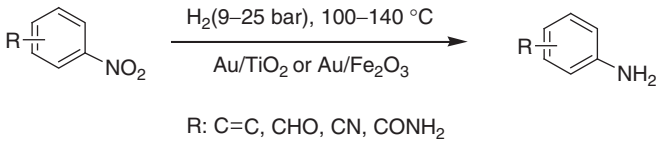
8.13.1.1.1 Catalytic hydrogenation

The synthesis of anilines through the heterogeneous catalytic hydrogenation of aromatic nitro compounds employing transition metal catalysts, such as palladium, platinum, ruthenium, and nickel, is well described.[7–12] Work-up procedures are generally simple, that is, filtration to remove the catalyst and concentration of the filtrate to isolate the product. In general, these processes are considered environmentally benign due to their operational simplicity and generation of minimal quantities of waste product. However, the chemoselective reduction of the nitro group by means of conventional heterogeneous catalytic hydrogenation in the presence of other reducible functional groups is difficult.

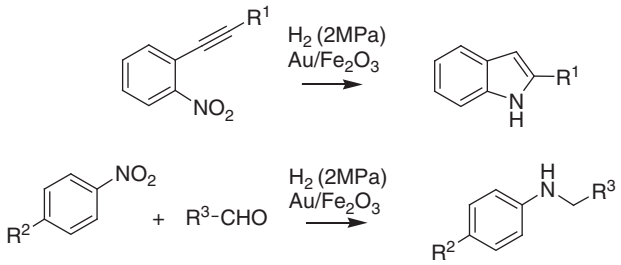
Catalytic systems based on Au, Ag, and Cu have been developed to overcome the chemoselective issue in the catalytic hydrogenation of aromatic nitro compounds.[13–19] Corma and Serna were the first to report the use of gold nanoparticles supported on TiO_2 or Fe_2O_3 as new and highly chemoselective catalysts for the reduction of aromatic nitro compounds under a hydrogen atmosphere and in the presence of vinyl, carbonyl, nitrile, and amide groups (**Scheme 1**). These results highlighted the potential of gold-catalyzed reactions and opened up a new avenue in the synthesis of anilines from nitroarenes.[13] Gold nanoparticles supported on Fe_2O_3 are also able to catalyze under hydrogenation conditions the synthesis of indoles from

(2-nitroaryl)alkynes through a one-pot hydrogenation/hydroamination sequence and aniline derivatives from nitroarenes by means of a hydrogenation/reductive amination protocol (Scheme 2).[20]

Corma and Serna



Scheme 1 Hydrogenation of aromatic nitro compounds catalyzed by gold nanoparticles.



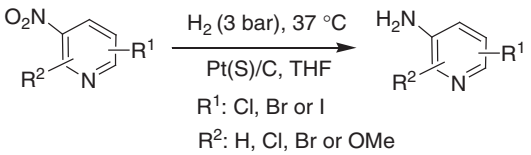
Scheme 2 One-pot synthesis of aniline derivatives from nitroarenes.

The catalytic properties of heterogeneous catalysts can be tuned through both modification of the surface structure of the support and the particle size of the metal.[10–22] Following this principle Nagashima et al. used polysiloxane gels as carriers of platinum species.[21] The resulting complexes are able to catalyze the chemoselective reduction of functionalized nitroarenes under a hydrogen atmosphere. The novel catalysts can be easily prepared and reused with retention of the catalytic activity. Platinum and palladium nanoparticles supported on carbon nanofibers have been used by Motoyoma et al. for the efficient catalyzed hydrogenation of nitroarenes carrying a wide range of other reducible functional groups, e.g., halide, nitrile, ketone, ester, amide, benzyl ethers.[22] In addition, platinum nanoparticles on a highly porous ionic copolymer were successfully employed as a catalyst for the chemoselective reduction of nitroarenes at room temperature and under an atmospheric pressure of hydrogen.[23]

Nishihara et al. reported the catalytic properties of bimetallic nanoparticles in a dendrimer cage.[24] The system carries rhodium and iron at the active core and was employed for the catalytic hydrogenation of nitroarenes. Chemoselective reduction of nitroarenes has also been performed using a ligand-free heterogeneous nanocrystalline magnesium oxide-stabilized palladium(0) catalyst under a hydrogen atmosphere. The conditions tolerate a wide range of functional groups.[25]

Ionic liquids have been recently reported as an excellent media for the selective reduction of halonitrobenzenes to haloni-troanilines under heterogeneous conditions and using standard catalysts like Raney nickel, Pt/C, and Pd/C. According to Xu et al., fine-tuning of the catalytic properties can be performed through the proper selection of the cation and anion of the ionic liquid.[26]

Sulfide-mediated reductions constitute another alternative to achieve the desired chemoselectivity in the nitroarene conversion into anilines. These methods are widely used in the industry.[7] The chemoselective catalytic hydrogenation of nitro groups in the presence of activated heteroaryl halides has been reported. The use of a sulfided platinum catalyst (Pt(S)/C) led to the hydrogenation of the nitro compounds with minimum hydrodehalogenation (Scheme 3).[27]



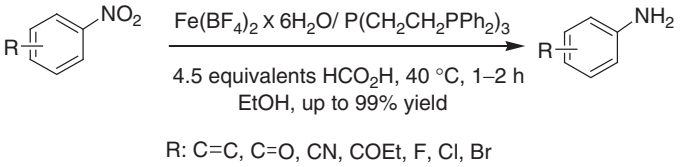
Scheme 3 Chemoselective hydrogenation of aromatic nitro compounds mediated by a sulfided platinum catalyst.

8.13.1.1.2 Catalytic transfer hydrogenations

Despite the recent outstanding achievements in the chemoselective catalytic conversion of nitroarenes into anilines by tuning the properties of heterogeneous catalytic systems, yet more active, more accessible, and selective catalysts are highly sought after by industry. Catalytic transfer hydrogenations (CTHs) represent a safer and greener choice to consider. The handling of hazardous

hydrogen is then avoided and high-pressure equipments are no longer needed. Usually alcohols, hydrocarbons, hydrazines, or organic acids and their salts are employed as the hydrogen source with a wide range of metal-based catalysts.[28–30]

Beller et al. reported the use of the first well-defined iron complex as an effective catalyst for the reduction of nitroarenes to anilines using formic acid as the reducing agent.[31] The novel transfer reduction is compatible with other reducible functional groups such as vinyl, ketone, nitrile, ester, or halide groups (Scheme 4). Previously, similar transformations had been performed employing formates as hydrogen donors but, however, with other metal-based catalytic systems.[19,32–34] The use of iron has several advantages such as its low cost, high abundance, and low toxicity relative to other precious metals. Before Beller's report, iron-mediated transfer hydrogenations were only known using toxic hydrazine or derivatives as hydrogen donors.[35,36] Shortly afterwards, the same group reported the use of iron–phenanthroline complexes supported on carbon, with hydrazine monohydrate as the hydrogen source, also for the chemoselective reduction of nitroarenes to anilines in excellent yields.[37]

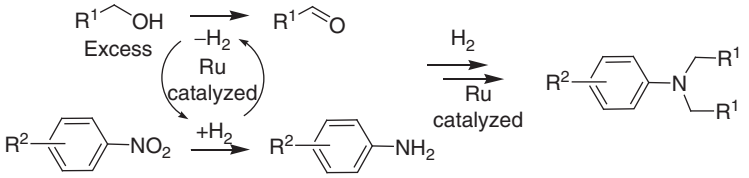


Scheme 4 CTHs catalyzed by an iron complex and with formic acid as the reducing agent.

Solid supports have been used for the development of more eco-friendly CTHs. Hydrazine hydrate supported by a macroporous weak acidic resin was prepared and employed as a hydrogen donor for the synthesis of functionalized anilines from nitroarenes.[38] Iron oxide-hydroxide served as the catalyst. The new protocol avoids the release of the toxic hydrazine hydrate, simplifies the purification procedure, and may be applicable to other systems. Hydrazine hydrate included into faujasite zeolites have also been reported as an effective system for CTHs.[39] However, alumina-supported hydrazine and catalytic iron(III) species were employed by Varma et al. for the chemoselective reduction of nitroarenes under solvent-free conditions and with microwave assistance.[40]

A variety of methods for the CTHs on aromatic nitro compounds take advantage of nonnoble metals as catalysts. Copper nanoparticles and ammonium formate in ethylene glycol at 120 °C are effective in the synthesis of functionalized anilines from nitroarenes.[41] These conditions are compatible with a wide range of reducible groups. The chemoselectivity is even better than other methods including noble metal nanoparticles as catalysts. The low cost of copper nanoparticles compared to that of other noble metal nanoparticles constitutes an additional advantage.

The one-pot synthesis of tertiary amines from nitroarenes and primary alcohols has been accomplished by means of a hydrogen-borrowing strategy (Scheme 5).[42] The hydrogen released by oxidation of the alcohol is transferred for the reduction of the nitro group to the aniline. This is followed by imine formation with the resulting aldehyde and a subsequent reduction in a cascade reaction. The whole process is catalyzed by ruthenium complexes in moderate-to-good overall yields. An excess of the alcohol is necessary for acceptable yields. Under the optimal conditions other reducible functional groups remain intact conferring a high degree of chemoselectivity to the method. A hydrogen-borrowing strategy, also catalyzed by ruthenium species, allowing the synthesis of secondary amines from benzonitriles and alcohols or nitroarenes and alcohols was reported by Deng et al.[43]

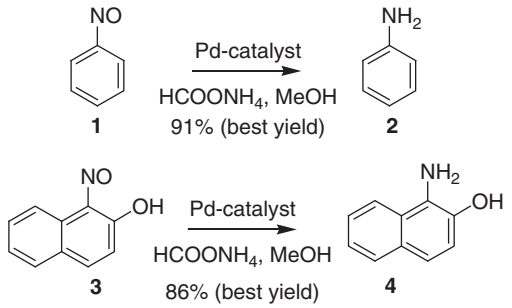


Scheme 5 Synthesis of tertiary amines from nitroarenes and primary alcohols.

The chemoselective reduction of nitro and nitroso compounds was achieved by means of a palladium-based mesoporous silicate molecular sieve catalyst and with ammonium formate as the source of hydrogen.[44] The conversion of aromatic nitroso amines to aromatic amines occurred in excellent yields is shown in Scheme 6.

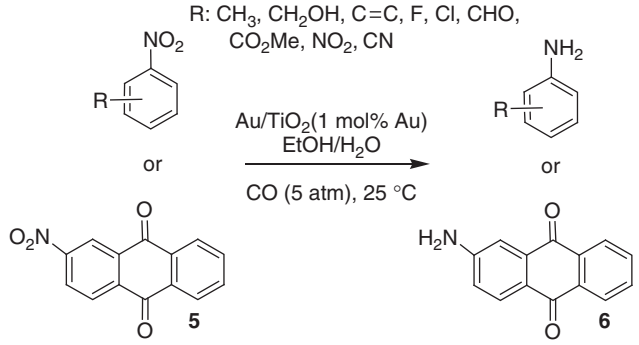
8.13.1.1.3 Carbon monoxide and water

The selective reduction of nitroaromatic compounds to anilines using cheap and readily available carbon monoxide and water as the hydrogen source stands as an attractive alternative to direct hydrogenation and is one with great industrial potential. Much research effort has been devoted to this area.[4,45] A highly chemoselective gold-catalyzed method for the conversion of nitro compounds into amines has been reported (Scheme 7).[46] The reaction proceeds at room temperature, low operational pressure, and in short reaction times (most of the examples were complete within the 2 h). Carbon monoxide and water served as the



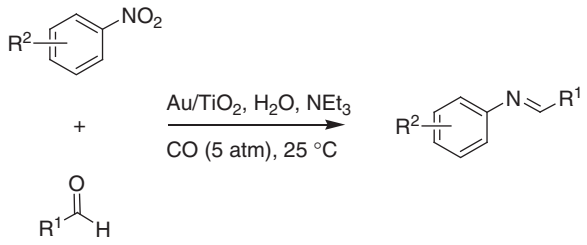
Scheme 6 Conversion of nitroso amines to aromatic amines mediated by ammonium formate and palladium as a catalyst.

hydrogen source. Very small gold nanoparticles supported on TiO_2 transpired to be the best catalyst among those tested. Nitroarenes bearing other functional groups such as halide, vinyl, nitrile, phenyl, carbonyl, ester, or other nitro group were submitted to the reduction conditions. A good level of chemoselectivity was achieved. Nitroanilines were obtained when dinitro compounds were tried under the optimized reduction conditions. The reaction proceeds efficiently even when only water is used as the solvent, thus it represents a clean and sustainable alternative for the synthesis of anilines.



Scheme 7 Carbon monoxide and water in the gold-catalyzed reduction of nitroarenes.

The same catalyst system (in the presence of carbon monoxide and water as hydrogen donor) was also effective in the one-pot synthesis of imines from nitroarenes in the presence of a wide range of aldehydes (Scheme 8).[47] The system presents a high activity under mild reaction conditions and offers a high degree of chemoselectivity. Gold nanoparticles supported on iron hydroxide species together with carbon monoxide and water as the hydrogen source have also been used for the chemoselective reduction of aromatic compounds, but under harsh conditions ($T \geq 100$ °C).[48]



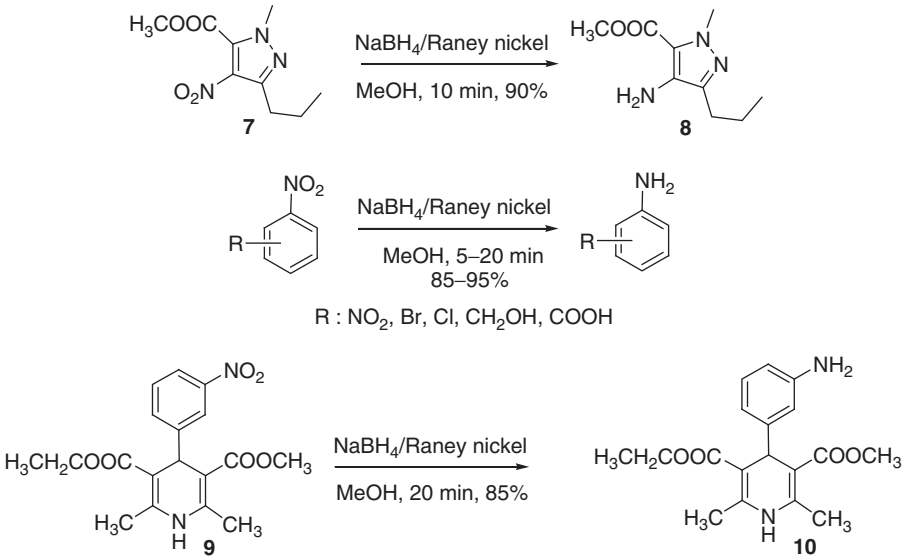
Scheme 8 One-pot synthesis of imines from nitroarenes in the presence of aldehydes and gold nanoparticles.

Good levels of chemoselectivity for the reduction of nitroaromatic compounds were achieved using silver nanoparticles supported on hydrotalcite.[49] In some cases, the chemoselectivity is superior to that of previous reports. The catalyst was reused without any loss of activity.

8.13.1.1.4 Borohydrides

The metal-catalyzed reduction of aromatic nitro compounds with sodium borohydride is a conventional and widely used protocol.[6] Recently, Litvic et al. were first to report the use of a sodium borohydride–Raney nickel system for the large-scale production of functionalized anilines and some heterocyclic aryl amines.[50] The method was easily scaled up and used for the

large-scale synthesis of **10** (Scheme 9). Aromatic and heteroaromatic nitro compounds can also be reduced to anilines by the combination of zirconium tetrachloride and sodium borohydride under mild reaction conditions.[51]

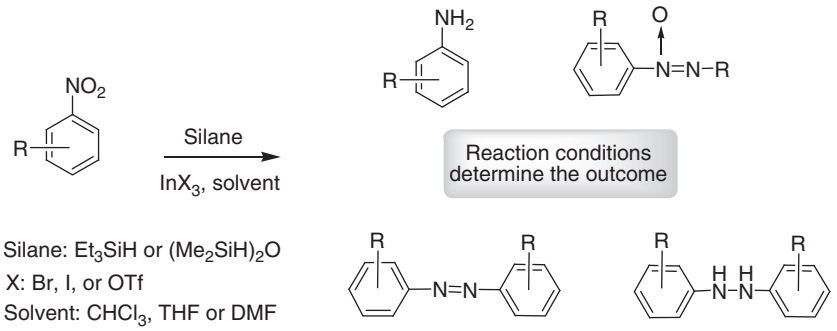


Scheme 9 Sodium borohydride–Raney nickel system in the reduction of nitroarenes.

The reduction of nitroarenes into anilines with a nickel boride–silica system was performed by Rahman and Jonnalagadda.[52] In most of the reactions studied, short reaction times and quantitative conversions were achieved by the use of 5% Ni-SiO_2 and $NaBH_4$ under mild reaction conditions. The simplicity of the method and the use of nonexpensive materials without the need for additives are significant advantages.

8.13.1.1.5 Organosilanes

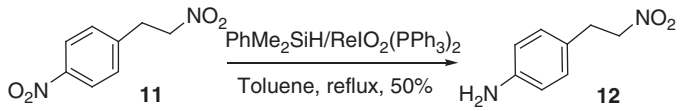
The potential of hydrosilylation for the reduction of nitroarenes has not yet been fully exploited. The relatively low cost and toxicity of silyl hydrides makes them an interesting target for the development of industrially relevant catalytic methodologies. Some recent advances are noteworthy. For example, Sakai et al. reported the selective reduction of aromatic nitro compounds using various indium salts and hydrosilanes.[53] Both the reaction conditions and the catalytic systems employed determine the outcome of the reaction. Following this strategy nitroarenes are selectively converted into anilines, azoxybenzenes, diphenylhydrazines, or azocompounds (Scheme 10).



Scheme 10 Indium salts in the catalytic reduction of nitroarenes under the presence of organosilanes.

Polymethylhydrosiloxane (PMHS) in the presence nanoparticles from palladium(II) acetate and aqueous potassium fluoride has been used by Rahaim and Maleczka, Jr. for the reduction of aromatic nitro groups in high yields.[54,55] A great variety of silanes were screened and most of them were efficient for the catalytic conversion of 2-nitrotoluene to 2-aminotoluene, the model system chosen for the study.[54] The use of PMHS brings several advantages: It is readily available, inexpensive, and relatively stable to air and moisture compared to other silicon hydrides. Several functionalized nitroarenes were selectively reduced; nevertheless, the method failed with aromatic nitrobromo or nitrochloro compounds.

Beller et al. reported the use of organosilanes for the selective iron-catalyzed reduction of nitroarenes to anilines.[56] The novel hydrosilylation protocol is based on $FeBr_2$-PPh_3 and $PhSiH_3$. Differently functionalized anilines were reduced employing this method and a broad spectrum of functional groups was tolerated. Shortly afterwards, another iron-silane-based catalytic system was reported for the chemoselective reduction of aromatic nitro compounds.[57] The catalytic systems $PhMe_2SiH/ReIO_2(PPh_3)_2$ and $PhMe_2SiH/ReOCl_3(PPh_3)_2$ were developed by Fernandes et al. for the same purpose. Remarkably, the selective reduction of an aromatic nitro group in the presence of an aliphatic nitro functional group was performed leading to the formation of the functionalized nitro aliphatic aniline **12** (Scheme 11).[58]

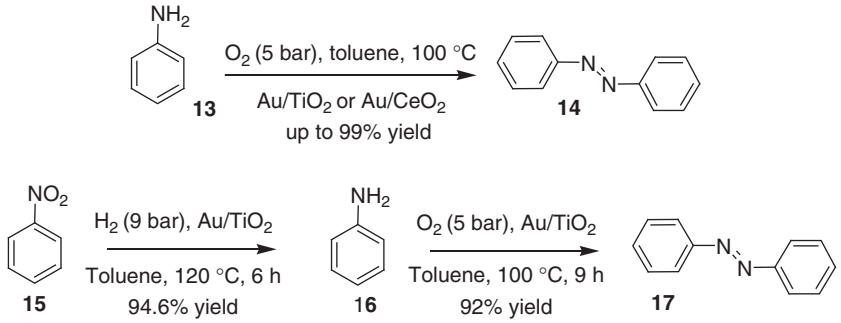


Scheme 11 Selective reduction of an aromatic nitro group in the presence of an aliphatic nitro functional group.

8.13.1.2 Reduction of Aromatic Nitro and Nitroso Compounds to Azocompounds

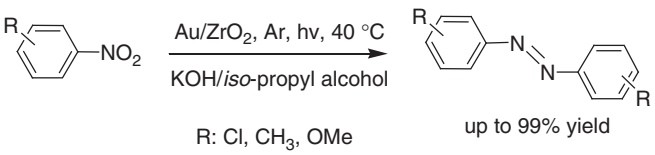
Aromatic azocompounds are widely exploited in chemical industry as organic dyes, indicators, food additives, therapeutic agents, and radical reaction initiators.[5] Despite the numerous methods that have been reported for their synthesis, there are still significant challenges to be solved. The formation of diazonium salts from anilines with subsequent nucleophilic attack by electron-rich arenes is perhaps the most popular method for the preparation of asymmetric azocompounds and a common laboratory practical experiment for undergraduate students. Nevertheless, this process requires large amounts of nitrite salts to promote formation of the diazonium salts and, therefore, generates equivalent quantities of undesirable inorganic waste. However, other known processes for the preparation of aromatic azocompounds include stoichiometric amounts of environmentally unfriendly oxidants like lead, mercury, iron, or manganese salts, which are a great disadvantage in the industry.[5]

The catalytic aerobic oxidation of aniline to azobenzene was recently reported.[59] Gold nanoparticles supported on titanium dioxide (Au/TiO_2) or nanocrystalline ceria (CeO_2) and under dioxygen atmosphere (5 bar) allowed the clean conversion of aniline into the corresponding azo-derivative **14**. Remarkably, the one-pot synthesis of azobenzenes from nitro compounds was also achieved. Initially, gold nanoparticles on titanium dioxide catalyzed the selective reduction of nitrobenzene to aniline under hydrogen atmosphere. After flushing out the hydrogen and switching to the oxidation conditions (5 bar of oxygen pressure) aniline was converted into azobenzene in excellent overall yields as highlighted in Scheme 12.



Scheme 12 Azobenzene from aniline through a two-step reductive–oxidative sequence.

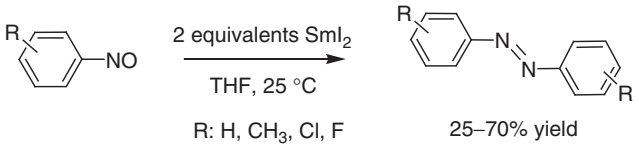
Gold nanoparticles supported on zirconia (ZrO_2) powder enabled the photocatalytic reduction of nitroarenes to the corresponding azobenzenes (Scheme 13).[60] The conversion proceeded after illumination with visible or ultraviolet light and in the presence of the photocatalyst at 40 °C. The new catalytic system for the nitroarene reduction to aromatic azocompounds offers a greener alternative and suggests a potential use of solar energy for this important transformation.



Scheme 13 Gold nanoparticles on zirconia as a catalyst in the conversion of nitroarenes to azocompounds under ultraviolet light.

The catalytic hydrogenation of nitroarenes to render the corresponding azo aromatic compounds was reported by Lu et al.[61] The chemoselective conversion is catalyzed by worm-like palladium nanoparticles and remarkably, the catalytic system was validated for the preparation of both symmetrical and unsymmetrical aromatic azocompounds.

The reduction of nitrosobenzenes to azoarenes mediated by SmI_2 was recently reported.[62] The extent of the reduction was controlled by the amount of SmI_2 employed. A large excess of this reagent led to the formation of the corresponding anilines. Under the optimized conditions the azocompounds were synthesized in low-to-moderate yields as shown in Scheme 14.

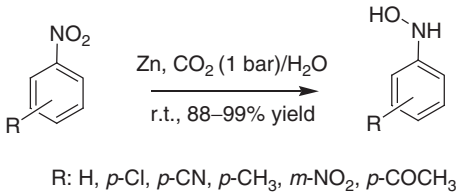


Scheme 14 Samarium(II) iodide-based reduction of nitroso compounds to azocompounds.

8.13.1.3 Reduction of Aromatic Nitro Compounds to Hydroxylamines

N-Arylhydroxylamines are important building blocks in synthetic organic chemistry.[63–65] They also show a broad spectrum of biological activities.[66–68] The conventional protocol for the preparation of *N*-arylhydroxylamines involves the reduction of nitroarenes by the action of metals under acidic conditions. Often, the control of the reaction to avoid overreduction products is problematic and more selective methods for the synthesis of these compounds are highly desirable.

Carbon dioxide and water (CO_2/H_2O) have been employed in the selective conversion of nitroarenes into *N*-arylhydroxylamines.[69] It is well known that high-pressure systems based on carbon dioxide and water can reach low pH values. Accordingly, Jiang et al. reported the chemoselective reduction of nitroarenes in the presence of zinc (dust) and CO_2/H_2O as an environmentally friendly alternative to conventional corrosive and strong acids. The reductions are performed under mild reaction conditions, i.e., 25 °C and $P(CO_2)=1$ bar. Nitroarenes bearing other reducible functional groups are chemoselectively reduced to the corresponding *N*-arylhydroxylamines in excellent yields as highlighted in Scheme 15.



Scheme 15 Chemoselective conversion of nitroarenes into *N*-arylhydroxylamines catalyzed by zinc (dust).

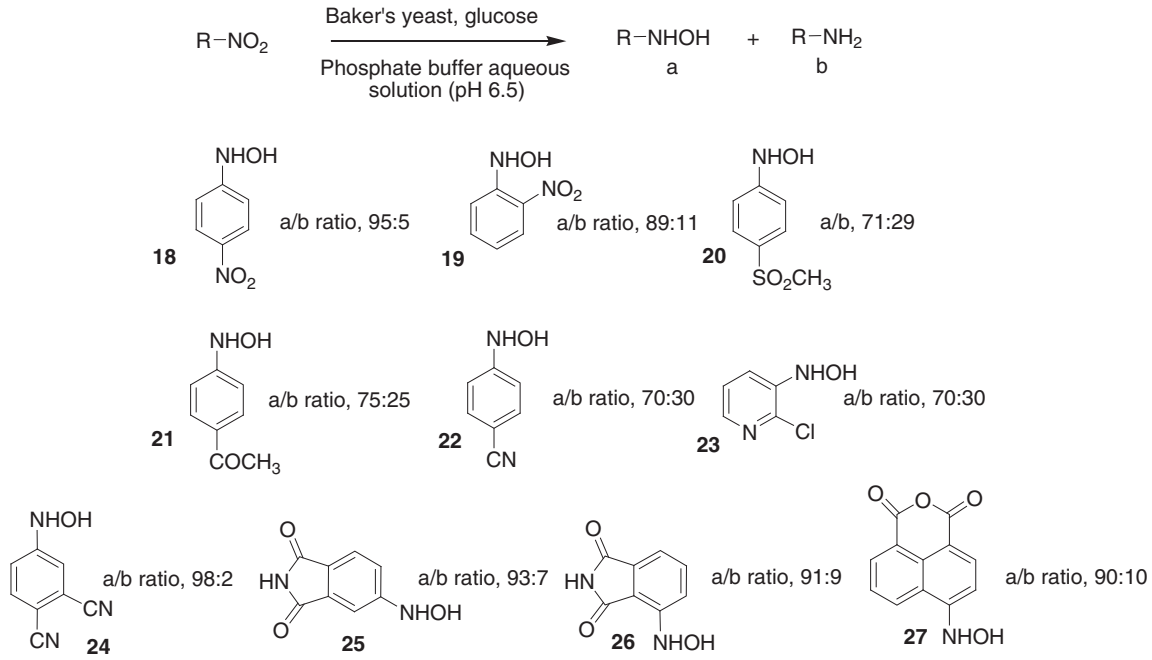
The preparation of *N*-arylhydroxylamines through the chemoselective biocatalyzed reduction of aromatic nitro compounds possessing electron-withdrawing groups was reported by Cui et al.[70] (Scheme 16). Baker's yeast was employed as a biocatalyst under mild reaction conditions. The procedure is environmentally friendly, efficient, and simple, though limited by the long reaction time or substrate scope. Shortly afterwards, the same group reported the use of cells from a grape (*Vitis vinifera* L.) in the biocatalyzed selective reduction of aromatic nitro compounds into *N*-arylhydroxylamines.[71]

Yasuda et al. reported the highly efficient synthesis of *N*-arylhydroxylamines by the catalytic hydrogenation of nitroarenes using platinum supported on silica (Pt/SiO_2) as a catalyst, at room temperature and under hydrogen atmosphere ($p=1$ bar).[72] Small amounts of additives were employed to promote the reduction of the aromatic nitro compounds while inhibiting overreduction to anilines. A wide range of functionalized nitroarenes possessing other reducible groups was converted into the corresponding *N*-arylhydroxylamines. Alternatively, colloidal platinum supported on carbon was employed as an efficient catalyst to achieve the same overall transformation.[73] The protocol is additive free, but the scope was only validated for nitroarenes possessing electron-withdrawing groups.

Ultrasound-assisted selective reduction of nitroarenes to the corresponding *N*-arylhydroxylamines has been reported.[74] The ultrasonic hydrogen transfer system is based on zinc, ammonium formate, and acetonitrile ($Zn/HCOONH_4/CH_3CN$). The conversions are achieved in short reaction times, in excellent yields, and under mild reaction conditions. Aromatic nitro compounds possessing either a nitrile or halide group were chemoselectively converted into the corresponding *N*-arylhydroxylamines without affecting the other functional groups.

8.13.1.4 Reduction of Aliphatic Nitro Compounds

Historically, most of the research into the reduction of nitro compounds has been focused on the conversion of nitroarenes into anilines. However, like their aromatic counterparts, aliphatic nitro compounds can be reduced to amines, hydroxylamines, or

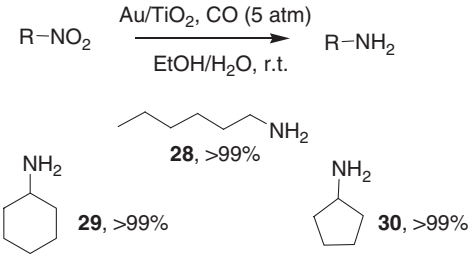


Scheme 16 Biocatalytic reduction of aromatic nitro compounds to *N*-arylhydroxylamines.

oximes,[6] but there are a limited number of methods to accomplish these transformations. Furthermore, only a handful of reports have appeared over the past years detailing new protocols for these important reactions.

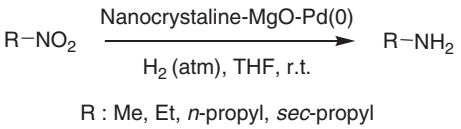
8.13.1.4.1 Reduction of nitroalkanes to amines, hydroxylamines, or oximes

The almost quantitative reduction of aliphatic nitro compounds through a gold-catalyzed reaction with carbon monoxide and water as hydrogen donor was described by Cao et al.[46] (Scheme 17). The reaction is performed at room temperature and proceeds under a carbon monoxide atmosphere. Although the scope of the method for the synthesis of aliphatic amines was not extensively investigated, the protocol constitutes an environmental friendly and highly efficient alternative to existing methods.



Scheme 17 Gold-catalyzed reduction of aliphatic nitro compounds to amines.

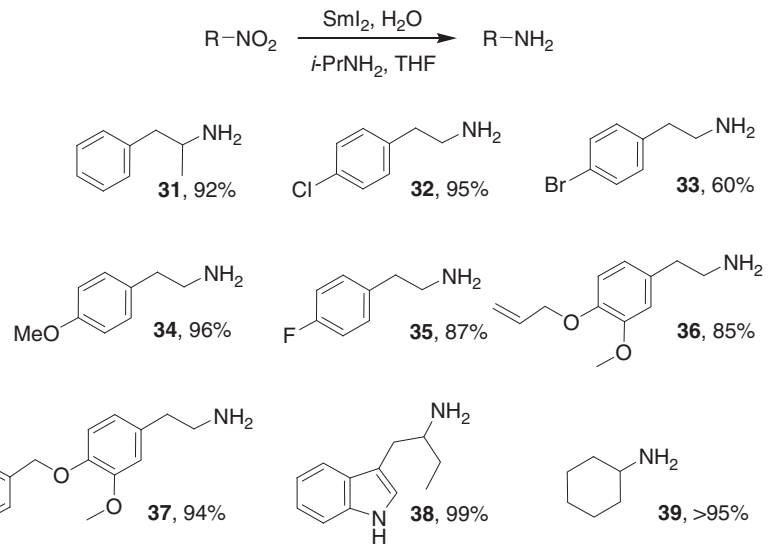
Kantam et al. reported the use of a nanocrystalline magnesium oxide-stabilized palladium(II) catalyst for the selective hydrogenation of aliphatic nitro compounds into amines at room temperature with hydrogen at atmospheric pressure as highlighted in Scheme 18.[75] The catalyst was recovered and reused several times without significant loss of catalytic activity.



Scheme 18 Palladium and magnesium oxide under the presence of hydrogen at atmospheric pressure mediate the reduction of aliphatic nitro compounds to amines.

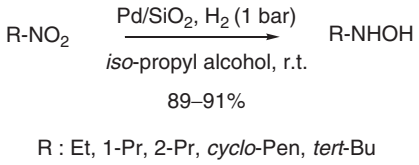
The samarium-mediated reduction of nitroalkanes to amines in the presence of a tertiary amine and water was reported by Hilmersson et al.[76] A broad range of primary amines were synthesized in moderate-to-excellent yields (Scheme 19). The selective

single electron reduction proceeded instantaneously and the work-up of the reaction was made shortly after the reagents were mixed together. Although some chemoselectivity limitations were attached to this method (like in the example **33** wherein the hydrodehalogenated product was also observed), in many cases the reactions were efficient, selective, and fast.



Scheme 19 Water and samarium(II) iodide in the reduction of nitroalkanes to amines.

There are only a small number of methods for the partial reduction of nitroalkanes to *N*-monosubstituted hydroxylamines.[6] The selective hydrogenation of aliphatic nitro species has been performed with a reusable and commercially available silica-supported palladium catalyst[77] (Scheme 20). The high-yielding method is applicable to the reduction of sterically hindered aliphatic nitro compounds. In addition, the reductions are performed under hydrogen at atmospheric pressure.



Scheme 20 Silica-supported palladium catalyst for the reduction of aliphatic nitro compounds to *N*-monosubstituted hydroxylamines.

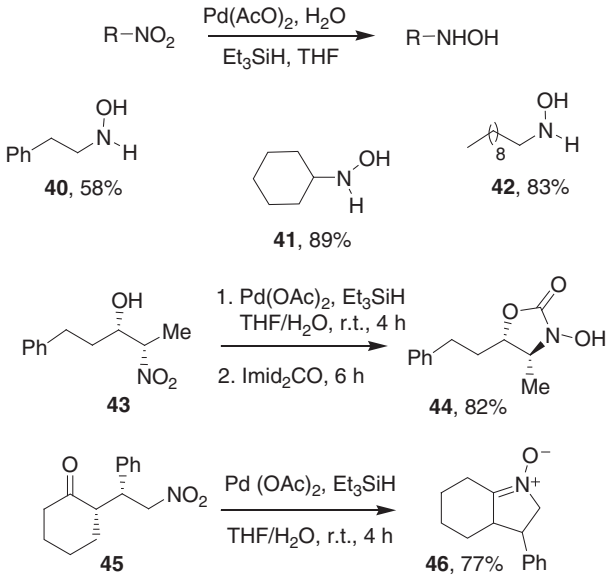
Aliphatic nitro compounds were reduced by the action of $Pd(OAc)_2$ and Et_3SiH to afford the desirable hydroxylamines in moderate-to-good overall yields as described by Maleczka, Jr. et al. (Scheme 21).[78] The reactivity of the silane was crucial for the outcome of this palladium-catalyzed hydrosilylation. When the reduction was performed in the presence of a fluoride salt and PMHS, the hydroxylamine **40** was obtained in low yields, most likely due to competing side reactions with the reactive silane. However, the performance of the reaction was improved in the absence of the fluoride source.

The conversion of primary nitroalkanes into oximes has been traditionally accomplished by the use of reagents like Bu_3SnH, $SnCl_2$, $Se/BaBH_4$, or CS_2.[45,79–86] More recently, Carreira et al. established a novel reductive protocol for the synthesis of optically active aldoximes starting from chiral nitroalkanes. The scope of the method is very broad, i.e., nitroalkanes including aromatic, heteroaromatic, branched, and linear aliphatic moieties were successfully converted. Furthermore, no racemization was observed when enantiomerically enriched substrates were employed[87] (Scheme 22).

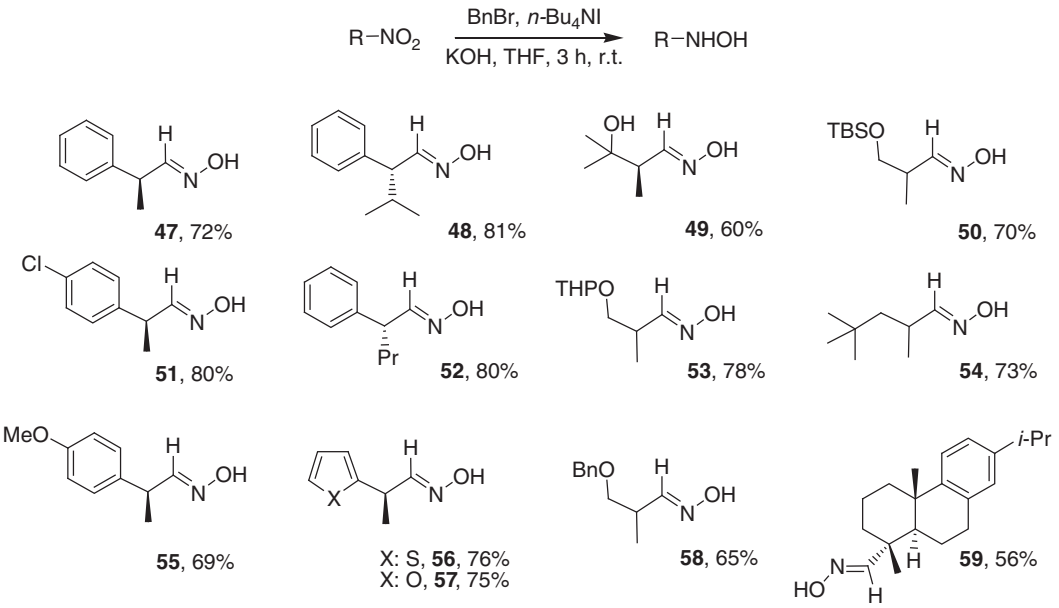
8.13.1.4.2 Reduction of nitroalkanes to alkanes

The nitro group is not usually present in targets of biological relevance. Nevertheless, several and important C–C bond forming reactions are facilitated by nitro compounds. Indeed, the transformation of the nitro group into other functional groups is very often an important step in a synthetic design. The conversion of nitroalkanes into the corresponding alkanes by reductive removal of the nitro group is, however, less common. Nevertheless, this kind of transformation can be strategically very important in synthetic organic chemistry, as exemplified by Dixon et al. in the total synthesis of the complex alkaloid natural products (–)-nakadomarin (**62**) and (+)-manzamine A (**65**)[88,89] (Scheme 23).

Despite this and other related transformations, recent developments in the reductive cleavage of nitroalkanes leading to the formation of the respective alkanes, since the pioneering studies of Ono and co-workers, are limited. Traditional methods for the



Scheme 21 Palladium(II) acetate and triethylsilane in the conversion of aliphatic nitro compounds to *N*-hydroxylamines.

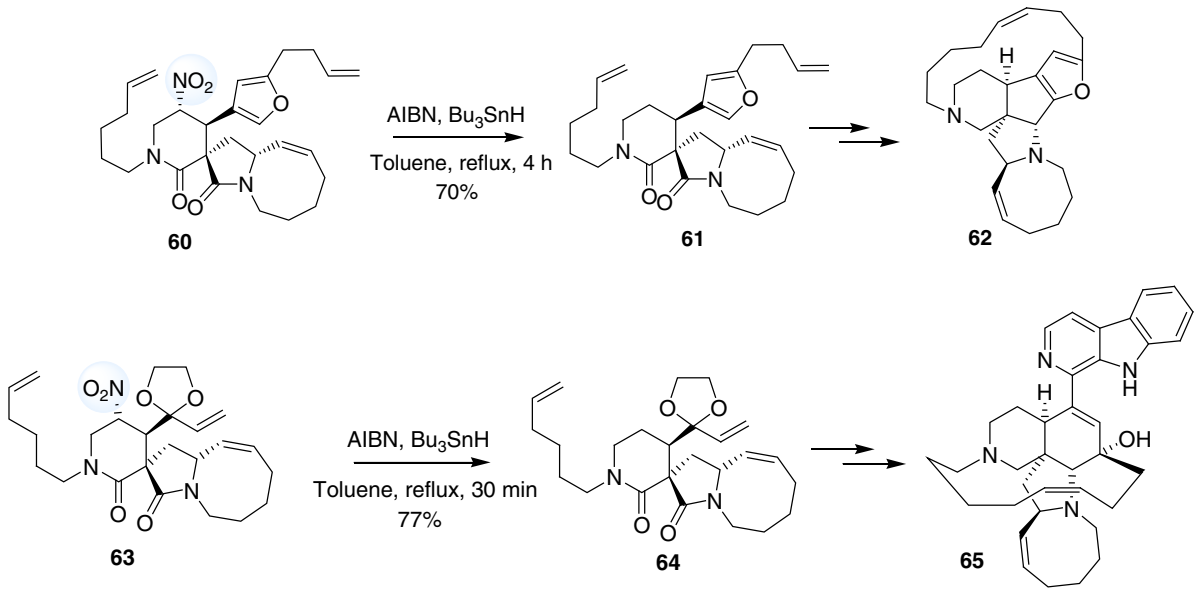


Scheme 22 Carreira's protocol for the synthesis of aldoximes from nitro compounds.

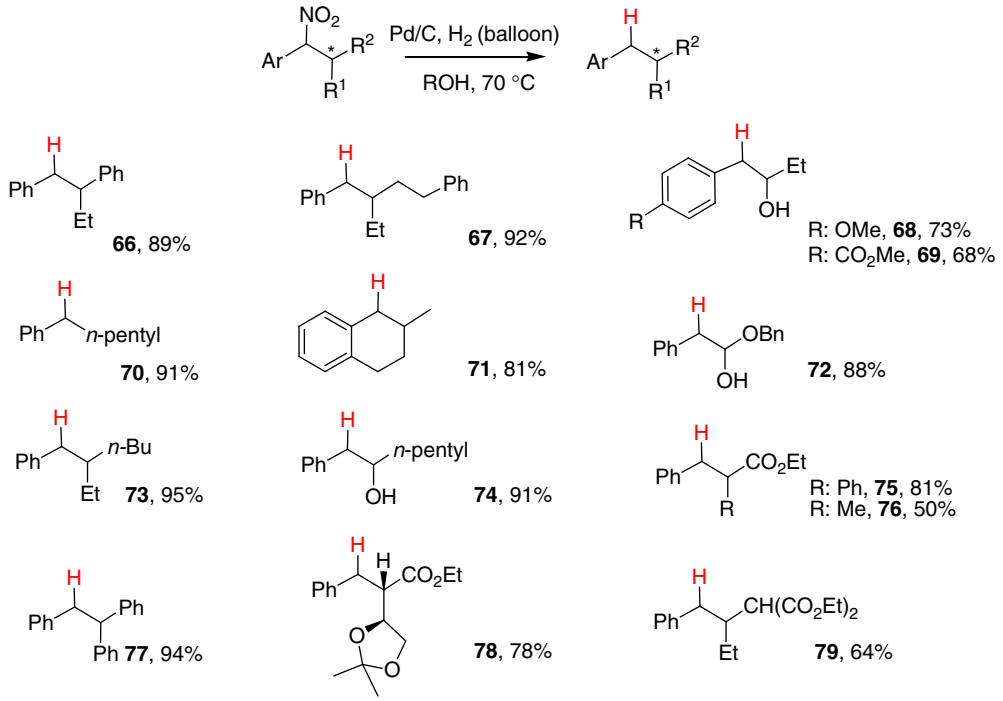
reduction of nitroalkanes to alkanes normally employ stoichiometric quantities of toxic, environmentally unfriendly reagents.[90–96] Nowadays, an environmentally friendlier modification of the Ono procedure stands as the alternative of choice.[97] According to this method, catalytic amounts of Bu_3SnH and stoichiometric (0.5 equivalent) $PhSiH_3$ are used for the reductive cleavage of nitroalkanes in yields ranging from good to moderate. In some cases, and depending on the nature of the substrate, sodium methanethiolate can be efficiently used for the denitration of tertiary nitro compounds. Obviously, the nucleophilicity of this reagent is a drawback of the method.[98] More recently, Carreira et al. reported the reduction of benzylic nitroalkanes to the respective alkanes in good-to-excellent yields by the action of H_2/Pd. Unfortunately, the scope of the method is restricted to benzylic nitroalkanes as highlighted in Scheme 24.[99]

8.13.1.4.3 Reduction of nitroalkenes

The reduction of α,β-unsaturated nitroalkenes can lead to the formation of amines, *N*-substituted hydroxylamines, oximes, or ketones.[6] Despite the scope of these transformations, only a few reports in this area of research have been published over the past few years.[76,100–102]



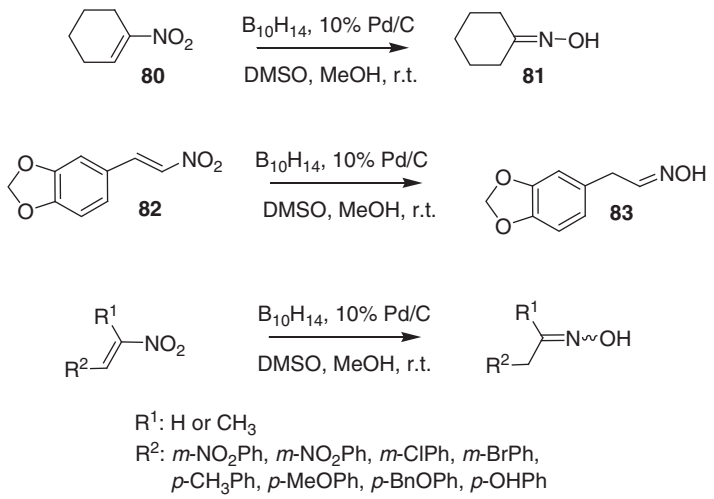
Scheme 23 Removal of the nitro group in the Dixon's synthesis of the structurally complex alkaloids (–)-nakadomarin (**62**) and (+)-manzamine A (**65**) AIBN, azobisisobutyronitrile.



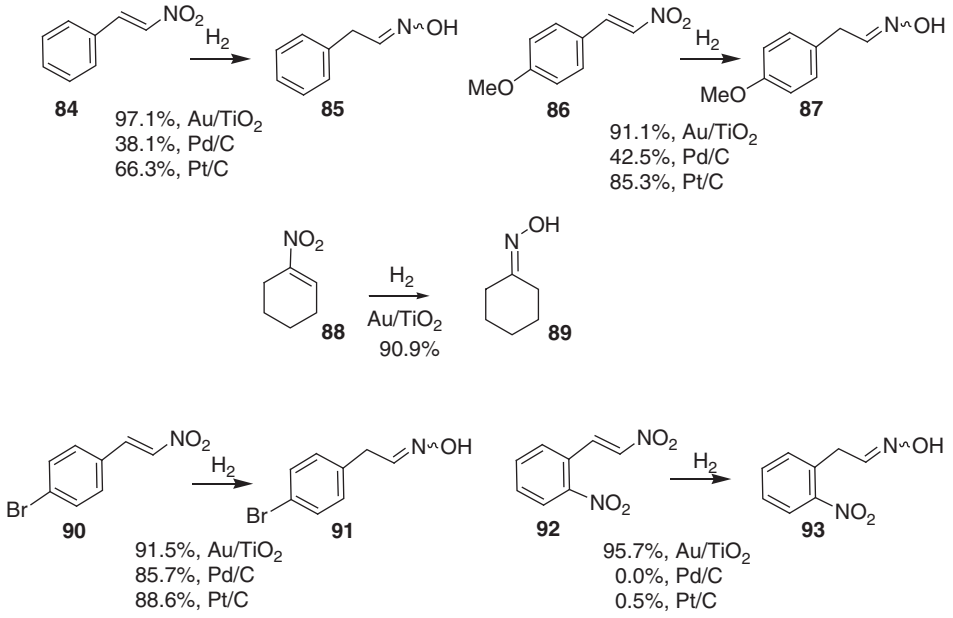
Scheme 24 Carreira's protocol for the reduction of benzylic nitro compounds to alkanes.

The synthesis of oximes through the CTH of conjugated nitroalkenes was reported by Yoon et al.[100] Decaborane served as the hydrogen donor in the presence of dimethyl sulfoxide (DMSO) and 10% Pd/C under mild reaction conditions and methanol as a solvent. The method offers a good level of chemoselectivity since other reducible functional groups were tolerated under the reduction conditions (Scheme 25). Interestingly, the presence of DMSO was important for the outcome of the reaction.

The high-yielding gold-catalyzed hydrogenation of α,β-unsaturated nitroalkenes to afford oximes was published by Corma et al.[101] The new protocol features the use of gold nanoparticles supported on TiO_2 under a hydrogen atmosphere. The excellent performance of this method is proved by its level of chemoselectivity, wherein other more conventional catalysts such as Pd/C and Pt/C failed. This is best exemplified in the synthesis of oxime **93** (Scheme 26). The scope of this chemistry extends also to aliphatic nitroalkenes such as 1-nitro-1-cyclohexene (**88**).



Scheme 25 CTHs in the synthesis of oximes from conjugated nitroalkenes.



Scheme 26 Gold-catalyzed hydrogenation of α,β-unsaturated nitroalkenes to afford oximes.

A samarium-based reductive system useful for the reduction of nitroalkanes and highlighted in the previous section is also extendable to the reduction of conjugate nitroalkenes to amines.[76] The nitro functional group and the double bond are both reduced but overall yields range from low to moderate. Finally, the biocatalytic conversion of (*E*)-2-nitro-1-phenyl-1-propene and its homolog (*E*)-2-nitro-1-phenyl-1-butene into their corresponding amines and under anaerobic conditions was recently reported by Stephens et al.[102]

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8.14 Reduction of N=N, N–N, N–O, and O–O Bonds

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Glossary

Annulation Elaboration of a cyclic structure by two successive reactions.

Biocatalytic Catalysis with an enzyme or a microorganism.

Chemoselective A reaction in which a functional group is transformed in the presence of another functional group.

Dipolar Structure or reaction involving a molecule possessing both a positive and a negative charge.

Electrolysis Chemical transformation induced by an electric current.

Ligation Elaboration of a chemical bond between two molecular entities under mild conditions and without any external reagents.

Radical pathway Mechanism involving intermediates devoid of any electric charges.
Redox process A reaction in which one entity is oxidized and another simultaneously reduced.
Reductive cleavage Cleavage of a chemical bond in reductive conditions.
Surrogate A functional or structural group equivalent.

8.14.1 Introduction

This chapter will cover the principal methods for heteroatom–heteroatom bond reduction or related cleavage. It follows the chapter in the preceding edition of *Comprehensive Organic Synthesis*.[1] Consequently, most of the methods and references included within this chapter have been published since 1991.

The reduction of N═N, N–N, N–O, and O–O bonds is often incorporated into strategies for the introduction of amine or hydroxyl functional groups in various substrates, and is involved in several important synthetic sequences, such as nucleophilic additions to oximes or hydrazones followed by nitrogen–oxygen or nitrogen–nitrogen bond cleavage. Furthermore, these reactions are often employed after heterocycloadditions such as hetero Diels–Alder reactions or dipolar cycloadditions. As a result, there are many methods available for each reaction. The purpose of this chapter is to highlight the most important and the most recent methods for such reductions, with applications in the total synthesis of natural products.

8.14.2 Reduction of N═N Bonds

This section addresses nitrogen–nitrogen double bonds such as azo and azoxy compounds, as well as triple-bonded nitrogen-containing compounds such as azides.

8.14.2.1 Reduction of Azides to Amines

The azido function is a very important functional group in organic synthesis. As azides are easily prepared by S_N2 displacement of halides or sulfonates, they have been widely used for various synthetic transformations.[2] The conversion of azides into primary amines is indeed one of the methods of choice for amine synthesis (Figure 1). Furthermore, azides are precursors to other reactive species such as nitrenes, which undergo rearrangement[3] or insertion[4] reactions.

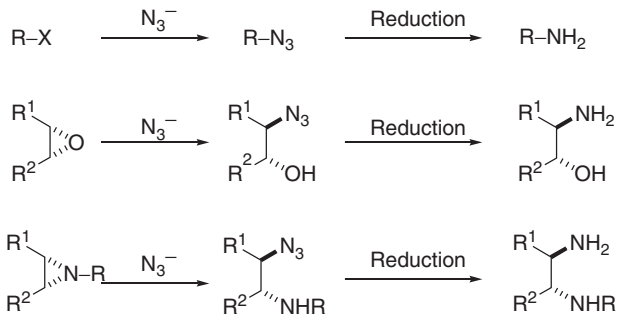


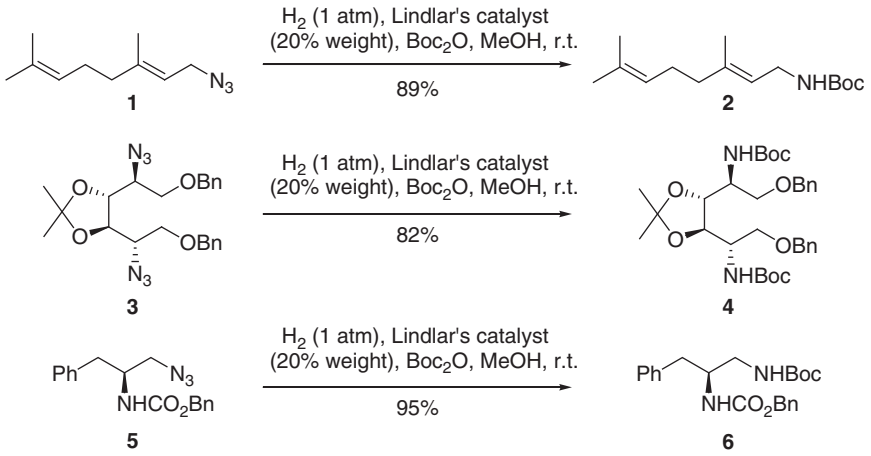
Figure 1 Examples of amine synthesis via azides.

Various reducing reagents are available for this reaction. Recent developments have focused on the discrimination between aromatic and aliphatic azides, compatibility with other functional groups, and direct access to protected amines, as well as the environmental issues of the reaction.

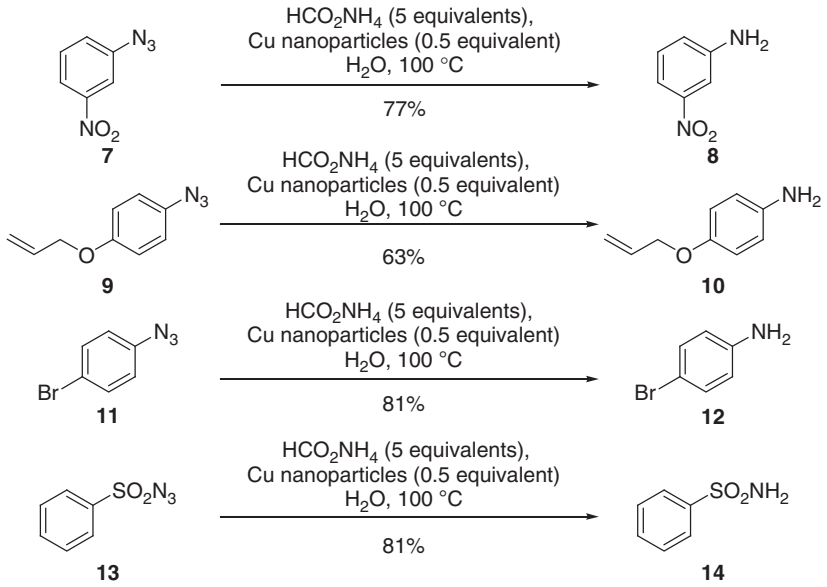
8.14.2.1.1 Reduction by hydrogenation

Catalytic hydrogenation is a simple method for azide reduction, Pd/C being the most widely used catalyst. In a recent development, Lindlar's catalyst was introduced for chemoselective reductions[5]: the reaction is compatible with alkenes, benzyl ethers, and benzyl carbamates. Moreover, the reaction can be performed in the presence of Boc anhydride, thus leading directly to Boc-protected amines (Scheme 1).

Transfer hydrogenation is also a simple and efficient method for azide reduction. Thus, aromatic azides as well as sulfonyl azides are reduced with ammonium formate in water in the presence of copper nanoparticles.[6] This environment-friendly protocol allows chemoselective reductions: aromatic halides, cyanides, carbonyl, carboxyl, or nitro groups are not reduced under these conditions (Scheme 2).



Scheme 1 Chemoselective hydrogenation of azides using Lindlar's catalyst. Reproduced from Reddy, P. G.; Pratap, T. V.; Kumar, G. D. K.; Mohanty, S. K.; Baskaran, S. *Eur. J. Org. Chem.* **2002**, 3740–3743.



Scheme 2 Chemoselective transfer hydrogenation of aromatic and sulfonyl azides. Reproduced from Ahammed, S.; Saha, A.; Ranu, B. C. *J. Org. Chem.* **2011**, *76*, 7235–7239, with permission from ACS.

8.14.2.1.2 Reduction with low-valent metals

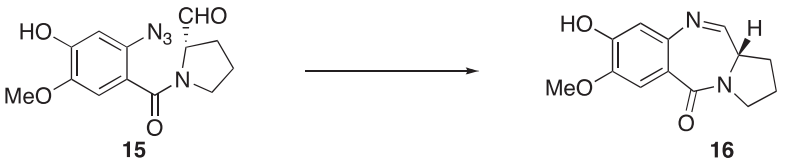
A wide array of low-valent metals can reduce aryl and/or alkyl azides to the corresponding amines, although most of these methods are not totally chemoselective. Thus, iron salts such as $FeSO_4$[7] in the presence of an amine, or $FeCl_3/Me_2N–NH_2$,[8] cleanly reduce aryl and alkyl azides under very mild conditions that are applicable to the synthesis of complex natural products (Scheme 3).

Iron salts in the presence of zinc powder also reduce azides. This reagent is very general since alkyl, aryl, aroyl, and sulfonyl azides are reduced in good yields.[9]

The combination of a trivalent metallic salt and excess sodium iodide has been reported to reduce a great variety of azides efficiently. Thus, cerium chloride heptahydrate in the presence of sodium iodide reduces alkyl azides at 100 °C (Scheme 4).[10] Room temperature reduction can be achieved using aluminum or gadolinium triflates instead of cerium chloride; however, only aryl azides are reduced under these conditions, the reaction being highly chemoselective (Scheme 5).[11] The mechanism is believed to proceed via a nitrene intermediate.

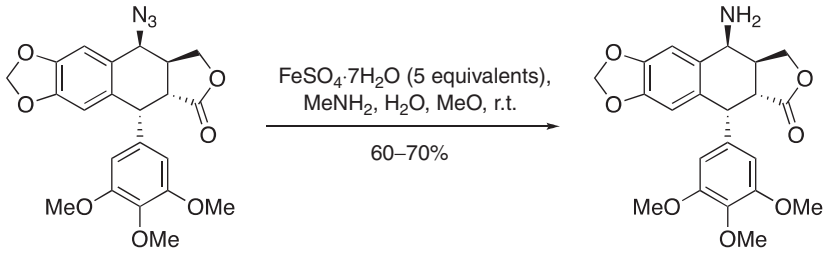
The closely related chlorotrimethylsilane/sodium azide reagent also reduces azides to amines in high yields. Although both alkyl and aryl azides are reduced, other functions such as aromatic nitro groups and esters are left untouched.[12]

A very practical and simple method for azide reduction uses indium powder in the presence of a proton donor (HCl or NH_4Cl) in EtOH or aqueous tetrahydrofuran (THF).[13] A wide array of alkyl and aryl azides are reduced in high yields, and the conditions are compatible with many functional groups, except for aromatic nitro groups (Scheme 6, Table 1).



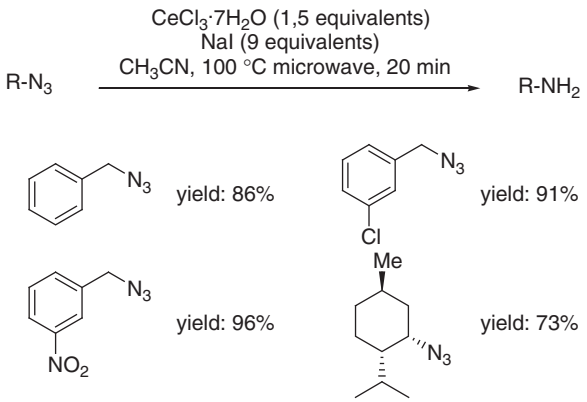
15 **16**

Conditions	Yield	Reference
$FeSO_4{\cdot}7H_2O$ (5 equivalents), NH_3, H_2O, CH_2Cl_2, r.t.	70%	7
$FeCl_3{\cdot}6H_2O$ (0.04 equivalent), $H_2N\text{-}NMe_2$ (1 equivalent), MeOH, r.t.	72%	8

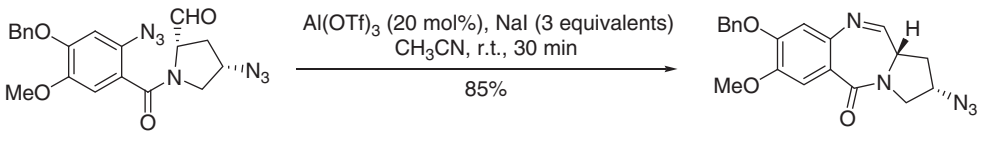


17 **18**

Scheme 3 Reduction of azides with iron salts/amine system. Reproduced from Kamal, A.; Laxma, E.; Arifuddin, M. *Tetrahedron Lett.* **2000**, *41*, 7743–7746, and Kamal, A.; Reddy, B. S. N. *Chem. Lett.* **1998**, 593–594.

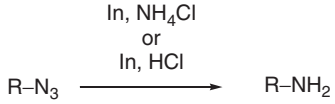


Scheme 4 Reduction of alkyl azides with $CeCl_3$/NaI. Reproduced from Bartoli, G.; Di Antonio, G.; Giovannini, R.; *et al. E. J. Org. Chem.* **2008**, *73*, 1919–1924, with permission from ACS.



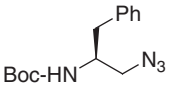
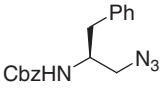
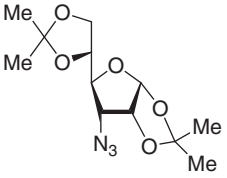
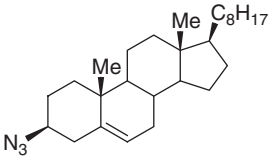
19 **20**

Scheme 5 Chemoselective reduction of an aromatic azide with $Al(OTf)_3$/NaI. Reproduced from Kamal, A.; Markandeya, N.; Shankaraiah, N.; *et al. Chem. Eur. J.* **2009**, *15*, 7215–7224.



Scheme 6 Reduction of azides with In/proton donor.

Table 1 Reduction of azides with In/proton donor

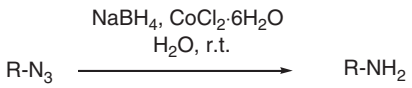
R–N_3	*Conditions*	*Yield (%)*	*Reference*
p-Cl–C_6H_4–N_3	HCl, aqueous THF, r.t.	68	13b
o-HO_2C–C_6H_4–N_3	NH_4Cl, EtOH, reflux	96	13a
$PhCH_2$–N_3	HCl, aqueous THF, r.t.	85	13b
$PhCH_2$–N_3	NH_4Cl, EtOH, reflux	95	13a
n-C_8H_{17}–N_3	HCl, aqueous THF, r.t.	80	13b
n-C_8H_{17}–N_3	NH_4Cl, EtOH, reflux	89	13a
	NH_4Cl, EtOH, reflux	92	13a
	NH_4Cl, EtOH, reflux	91	13a
	NH_4Cl, EtOH, reflux	91	13a
	NH_4Cl, EtOH, reflux	94	13a

Source: Reproduced from Vidyasagar Reddy, G.; Venkat Rao, G.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 3937–3938, and Lee, J. G.; Choi, K. I.; Koh, H. Y.; *et al. Synthesis* **2001**, 81–84.

Samarium diiodide[14] or samarium/iodine[15] cleanly reduce alkyl, aryl, and aroyl azides, probably through a radical mechanism. Numerous functional groups are compatible with the reaction conditions, except for sulfonamides.

8.14.2.1.3 Reduction with metal hydrides

Azides are easily reduced with various metal hydride reagents such as $LiAlH_4$ or borohydrides such as $Zn(BH_4)_2$,[16] $NaBH_4/CuSO_4$,[17] $LiB(Me_2N)BH_3$ (alkyl azides),[18] $NaBH_4/CoCl_2$,[19] or $MePh_3PBH_4$,[20] the latter reagent reducing aryl azides only. The $NaBH_4/CoCl_2$ system is highly chemoselective and can be used in water (Scheme 7, Table 2).



Scheme 7 Reduction of azides with $NaBH_4/CoCl_2$ in water.

The reduction of azides may be accomplished with boranes, although the reaction rate depends on the nature of the borane reagent. A systematic study revealed that $ClBH_2$/DMS was the best reagent for azide reduction.[21] The reaction is compatible with the presence of alkenes, which was not the case for BH_3/THF. Halides, esters, nitriles, and nitro groups were also compatible with the reduction conditions (Scheme 8).

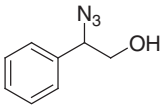
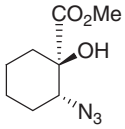
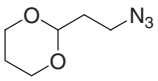
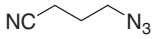
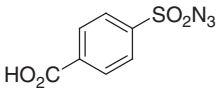
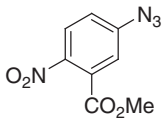
8.14.2.1.4 Radical-mediated reductions

The addition of radicals to azides has recently emerged as a powerful tool for azide reduction, Bu_3SnH being by far the best reagent for azide reduction. The reaction proceeds through a stannylaminyl radical which is reduced to the corresponding amine (Scheme 9).

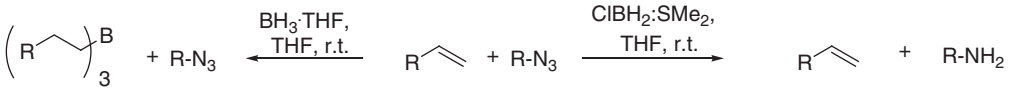
As for carbon-centered radicals, nitrogen-centered radicals obtained by reduction of azides with tin hydride may be used for radical cyclizations. This was recently applied to the synthesis of guanidines from *β*-azido *N*-acyl cyanamide **21** through a cascade radical process (Scheme 10).[22]

As Bu_3SnH has to be used in excess, alternative methods have been investigated: the Ph_3SiH/catalytic Bu_3SnH[23] or Bu_3GeH.[24] A tin-free method for radical reduction of aryl, akyl aroyl, and sulfonyl azides using triethylsilane and indium chloride has been reported in 2006.[25] The mechanism is believed to involve an intermediate indium-aminyl radical (Scheme 11, Table 3).

Table 2 Reduction of azides with $NaBH_4/CoCl_2$ in water

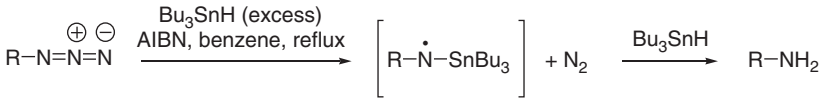
R–N_3	*Yield (%)*	*R–N_3*	*Yield (%)*
	97		95
	92		98
	97		92
PhCO-N_3	96		

Source: Reproduced from Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Synthesis* **2000**, 646–650, with permission from Thieme.

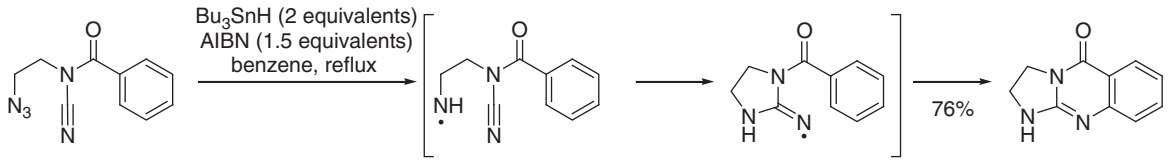


R = alkyl, aryl

Scheme 8 Chemoselectivity of the reduction of azides with boranes.

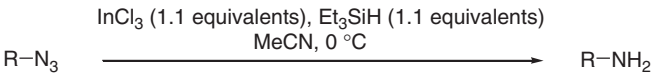


Scheme 9 Radical reduction of azides with Bu_3SnH.



21 **22**

Scheme 10 Radical cascade initiated by radical reduction of an azide. Reproduced from Larraufie, M.-H.; Ollivier, C.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem. Int. Ed.* **2010**, *49*, 2178–2181.



Scheme 11 Reduction of azides with $InCl_3/Et_3SiH$.

8.14.2.1.5 Reduction with phosphorus and sulfur reagents

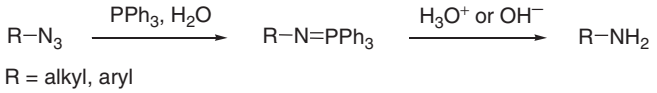
The Staudinger reduction of azides involves the conversion of azides into amines by treatment with a phosphine and water. The reaction proceeds through the formation of an iminophosphorane intermediate which is hydrolyzed. This reaction has a great importance in organic synthesis and has found numerous applications.[26] The most often used phosphines are

Table 3 Reduction of azides with $InCl_3/Et_3SiH$

R–N_3	*Yield (%)*	*R–N_3*	*Yield (%)*
p-MeO–C_6H_4–N_3	96	*p*-NC–C_6H_4–N_3	97
p-I–C_6H_4–N_3	88	*p*-O_2N–C_6H_4–N_3	99
1-naphthyl–N_3	70	$Ph(CH_2)_2$–N_3	55
$PhSO_2$–N_3	82	PhCO–N_3	75

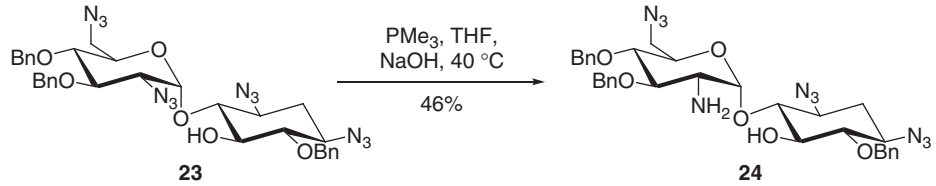
Source: Reproduced from Benati, L.; Bencivenni, G.; Leardini, R.; *et al. Org. Lett.* **2006**, *8*, 2499–2502, with permission from ACS.

triphenylphosphine and tributyphosphine (Scheme 12). The main drawback to this reaction is the acidic or basic conditions required for the hydrolysis of the iminophosphorane intermediate.



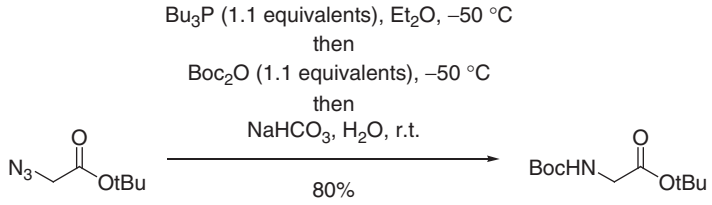
Scheme 12 The Staudinger reduction of azides.

The regioselectivity of the Staudinger reaction with polyazides was investigated after the observation that the reduction of the tetrazide **23** with trimethylphosphine was regioselective.[27] The selectivity was explained in terms of electronic effects, the azido function next to the anomeric center being the most electrophilic (Scheme 13).



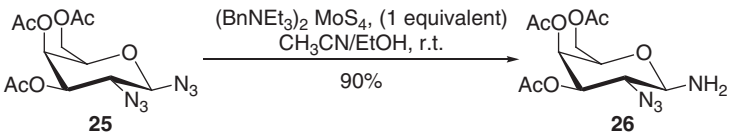
Scheme 13 Regioselective Staudinger reaction with PMe_3. Reproduced from Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773–10778, with permission from ACS.

The intermediate iminophosphorane can be further functionalized before hydrolysis by electrophilic addition to the nitrogen atom. This was applied to the synthesis of carbamates such as *N*-Boc carbamate from azides in a one-pot procedure (Scheme 14).[28]



Scheme 14 One-pot reduction of azides to Boc carbamates. Reproduced from Afonso, C. A. M. *Tetrahedron Lett.* **1995**, *36*, 8857–8858.

Sulfur nucleophiles react readily with azides to give amines after nitrogen extrusion and hydrolysis of the nitrogen–sulfur bond. Benzyl trimethylammonium tetrathiomolybdate selectively reduces aromatic azides to amines, whereas aliphatic azides are reduced to imines.[29] Interestingly, the same reagent reduces anomeric azides selectively in glucopyranosyl azide substrates (Scheme 15).[30]

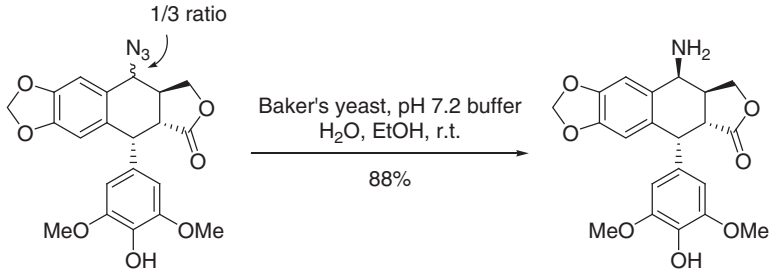


Scheme 15 Regioselective azide reduction with tetrathiomolybdate. Reproduced from Sridhar, P. R.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2003**, *68*, 5261–5264, with permission from ACS.

Other sulfur-based reagents have been designed for azide reduction, such as sodium thiophosphate (alkyl and aryl azide reduction),[31] hexamethyldisilathiane/MeOH (aryl azide reduction),[32] or tin bis(1,2-benzenedithiolate)/$NaBH_4$ (alkyl and aryl azide reduction),[33] this last reagent system giving very high yields.

8.14.2.1.6 Enzymatic reductions

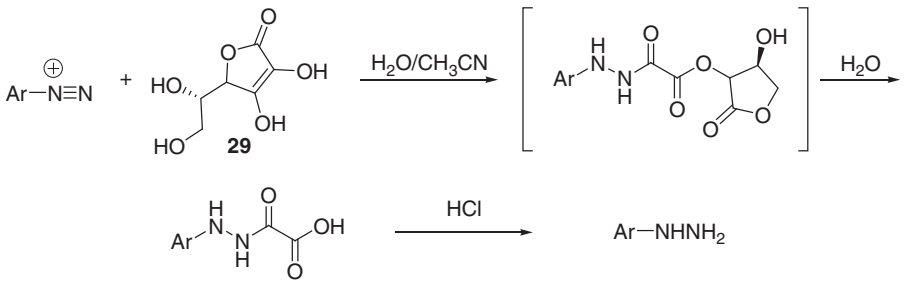
As for other functions, azides can be reduced to amines using biocatalytic methods. Baker's yeast reduces aromatic, benzylic, and allylic azides in high yields.[34] This method was applied to the stereoselective synthesis of the podophyllotoxin analog **28** (Scheme 16).[35]



Scheme 16 Selective azide reduction with Baker's yeast. Reproduced from Kamal, A.; Laxminarayana, B.; Gayatri, N. L. *Tetrahedron Lett.* **1997**, *38*, 6871–6874.

8.14.2.2 Reduction of Diazonium Salts to Hydrazines

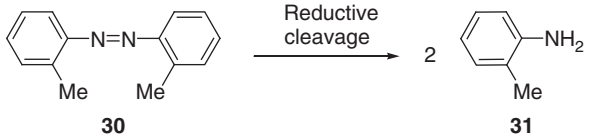
Arylhydrazines are essential compounds for heterocycle sythesis as they can lead to pyrazoles or indoles (Fischer synthesis). The classical method for the synthesis of arylhydrazines is the reduction of readily accessible aryldiazonium salts. The synthesis of hydrazines has been the subject of a review.[36] Diazonium salts are classically reduced to hydrazines with Sn/HCl, tin(II) chloride or sodium sulfite. A metal-free method for diazonium salt reduction with ascorbic acid **29** has been described. The reduction involves the formation of an oxamic acid, which is easily hydrolyzed (Scheme 17).



Scheme 17 Reduction of diazonium salts to hydrazines with ascorbic acid. Reproduced from Browne, D. L.; Baxendale, I. R.; Ley, S. V. *Tetrahedron* **2011**, *67*, 10296–10303.

8.14.2.3 Reduction of Azo and Azoxy Compounds to Amines

Reductive cleavage of symmetrical or unsymmetrical azo- and azoxyarenes to amines can be performed either by transfer hydrogenation with ammonium formate and palladium[37] or zinc,[38] LiDTBB/$NiCl_2$,[39] or hydrazine hydrate.[40] A recent method describes a mild and efficient reductive cleavage of azoarenes by ruthenium-catalyzed transfer hydrogenation.[41] In all cases, reductive cleavage was compatible with other functional groups, except for nitro groups. Comparison for all methods in the reduction of azo-bis(2-toluene) **30** is presented (Scheme 18, Table 4).



Scheme 18 Reductive cleavage of azoarenes to amines.

Table 4 Reductive cleavage of azoarenes to amines

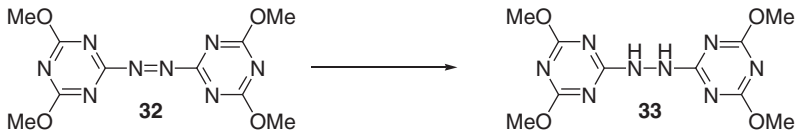
Conditions	*Yield (%)*	*Reference*
HCO_2NH_4, 10% Pd/C, MeOH, r.t.	96	37
HCO_2NH_4, Zn, MeOH, r.t.	94	38
Hydrazine hydrate, EtOH, reflux	94	40
$RuCl_2$(*p*-cymene)$_2$ (2.5%), 2,2′:6′,2″-terpyridine (5%), KOH, (15%), *i*PrOH, 100 °C	92	41

Source: Reproduced from Abiraj, K.; Srinivasa, G. R.; Gowda, D. C. *Can. J. Chem.* **2005**, *83*, 517–520; Gowda, S.; Abiraj, K.; Gowda, D. C. *Tetrahedron Lett.* **2002**, *43*, 1329–1331; Pasha, M. A.; Nanjundaswamy, H. M. *Synth. Commun.* **2005**, *35*, 897–900, and Jagadeesh, R. V.; Wienhöfer, G.; Westerhaus, F. A.; *et al. Chem. Eur. J.* **2011**, *17*, 14375–14379.

The reagent LiDTBB/$NiCl_2$ also reduces azoxy compounds to amines, extended reaction times being necessary.

8.14.2.4 Reduction of Azo and Azoxy Compounds to Hydrazines

Azo derivatives are reduced to hydrazines using milder reducing reagents than those for the reductive cleavage. Indeed, the reduction of azodiesters occurs during the important Mitsunobu reaction. Specific reduction of azo compounds is accomplished by treatment with hydrazines: hydrazine, alkylhydrazine, or hydrazobenzene can be employed for the reduction of alkyl, aryl, heteroaryl, or acyl azo derivatives (Scheme 19).[42]



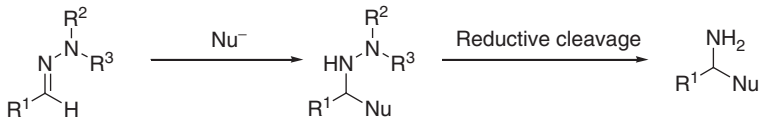
H_2N–NH_2 (0.5 equivalent), EtOH, r.t.: 93%
PhNH–NH_2 (1 equivalent), CH_3CN, r.t.: 94%
PhNH–NHPh (1 equivalent), EtOH or CH_3CN, r.t., 94%

Scheme 19 Reduction of azo compounds with hydrazines. Reproduced from Koppes, W. M.; Moran, J. S.; Oxley, J. C.; Smith, J. L. *Tetrahedron Lett.* **2008**, *49*, 3234–3237.

8.14.3 Reduction of N–N Single Bonds

8.14.3.1 Reductive Cleavage of Hydrazines to Amines

Reductive cleavage of hydrazines to amines is an important reaction for amine synthesis. Indeed, a standard protocol for enantioselective amine synthesis is the addition of carbon nucleophiles to chiral hydrazones followed by reductive cleavage to the amine (Scheme 20).

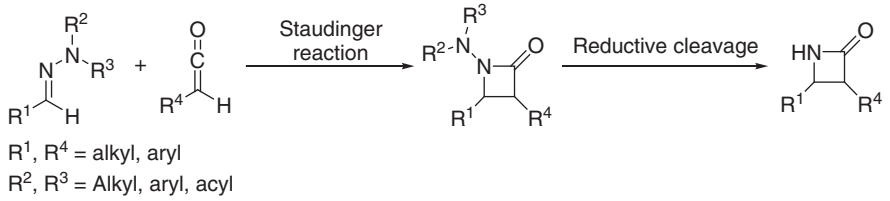


R^1 = alkyl, aryl
R^2, R^3 = Alkyl, aryl, acyl
Nu = carbon nucleophile

Scheme 20 General scheme for amine synthesis via addition of nucleophiles to hydrazones.

Hydrazones are also common precursors to biologically active β-lactams by Staudinger cycloaddition followed by N–N bond cleavage (Scheme 21).

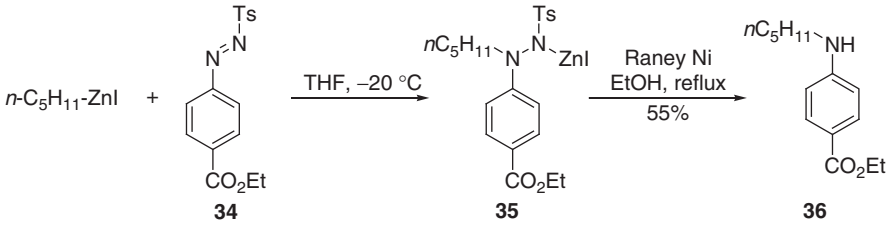
Methods for the reductive cleavage of hydrazines must therefore be compatible with other functional groups, and be applicable to alkyl- or arylhydrazines as well as hydrazides (acylhydrazines). Besides the traditional hydrogenolytic or reductive conditions, some nonreductive conditions based on carbanion-assisted elimination have been reported.



Scheme 21 Synthesis of β-lactams by Staudinger reaction of hydrazones.

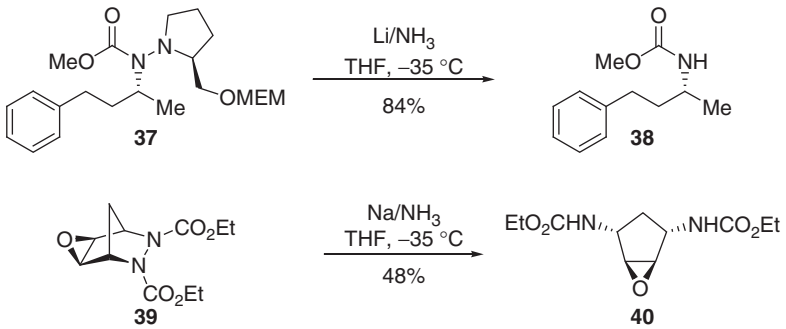
8.14.3.1.1 Reduction under hydrogenolytic conditions

Hydrogenolysis of hydrazines to amines is easily accomplished using various catalysts: Pd/C,[43] platinum oxide,[44] or Raney Ni[45] are popular catalysts that have been widely used in the synthesis of optically amines. In a recent study, *N*-sulfonyl hydrazines were obtained by addition of organozinc reagent to arylazo tosylates, and were cleaved with Raney Ni (Scheme 22).[45]



Scheme 22 Reductive cleavage of a hydrazine with Raney Ni. Reproduced from Sinha, P.; Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 3741–3744, with permission from ACS.

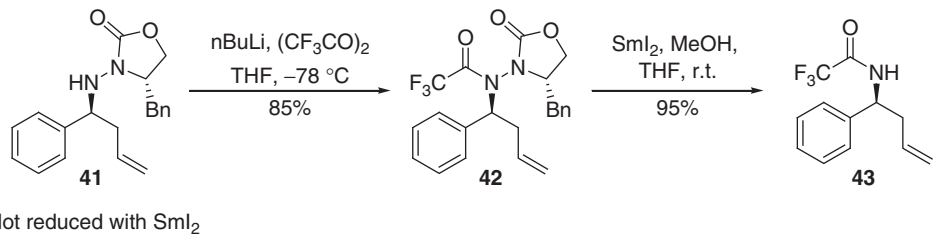
Hydrogenolysis under dissolving metal conditions has been found to be suitable for the reduction of *N*-acylhydrazines, for which traditional hydrogenolytic conditions often fail.[46] These conditions are applicable to cyclic or acyclic hydrazines and hydrazides (Scheme 23).



Scheme 23 Reductive cleavage of hydrazides under dissolving metal conditions. Reproduced from Denmark, S. E.; Nicaise, O.; Edwards, J. P. *J. Org. Chem.* **1990**, *55*, 6219–6223, and Bournaud, C.; Chung, F.; Pérez Luna, A.; *et al. Synthesis* **2009**, 869–887.

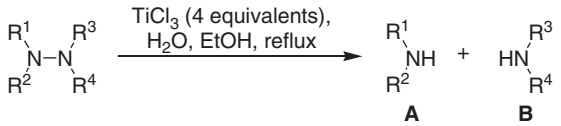
8.14.3.1.2 Reduction with metal reagents

Efficient reductive cleavage of hydrazines to amines can be achieved with samarium diiodide, provided that the hydrazine is activated with an acyl group.[47] The *N*-trifluoroacetyl group has been recommended as a very efficient activator. Coordination of fluorine to samarium is believed to be responsible for higher reaction rates (Scheme 24).[48]



Scheme 24 Reductive cleavage of *N*-trifluoroacetyl hydrazines with samarium(II) iodide. Reproduced from Ding, H.; Friestad, G. K. *Org. Lett.* **2004**, *6*, 637–640, with permission from ACS.

A very general, chemoselective, and high-yielding method for the reduction of N–N bonds in hydrazines has been reported using aqueous $TiCl_3$.[49] This reaction can be carried out under basic or neutral conditions and is applicable to the reduction of diversely substituted alkyl-, aryl-, or acyl-hydrazines (Scheme 25, Table 5).



Scheme 25 Reductive cleavage of a hydrazine with aqueous $TiCl_3$.

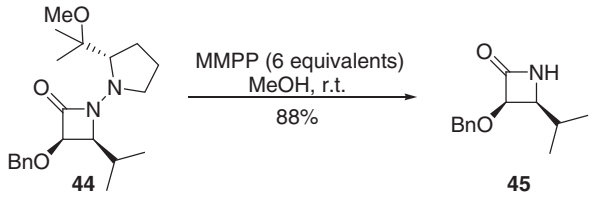
Table 5 Reductive cleavage of hydrazine with aqueous $TiCl_3$

R^1	R^2	R^3	R^4	Yield of **A** (%)	Yield of **B** (%)
Ph	H	H	H	90	Not given
Ph	Ph	H	H	84	Not given
Ph	Ac	H	H	82	Not given
Ph	H	Ph	H	78	78
Ph	H	Allyl	H	74	70
Ph	Me	Ph	H	82	85
Ph	H	CO_2Bn	H	75	73
$-(CH_2)_4-$		H	H	74	Not given
Ph	Bn	Ph	Bn	77	77

Source: Reproduced from Zhang, Y.; Tang, Q.; Luo, M. *Org. Biomol. Chem.* **2011**, *9*, 4977–4982, with permission from RSC.

8.14.3.1.3 Nonreductive conditions

Various nonreductive conditions for the cleavage of N–N bonds of hydrazines are available. These methods generally enjoy high functional group tolerance. Indeed, oxidative cleavage of tetrasubstituted *N*-acyl hydrazines is readily achieved using magnesium monoperoxyphthalate (MMPP). It allows reduction of highly sensitive substrates such as the *β*-lactam **44** (Scheme 26).[50]



Scheme 26 Oxidative cleavage of a tetrasusbstituted hydrazide. Reproduced from Fernandez, R.; Ferrete, A.; Llera, J. M.; *et al. Chem. Eur. J.* **2004**, *10*, 737–740.

Carbanion-assisted cleavage involves *N*,*N*′-diacyl hydrazines: nitrogen alkylation with a bromoester or a bromoketone, followed by basic treatment, smoothly afford the amine (or its carbamate derivative) after an elimination reaction.[51] This method is especially suited for substrates containing C=C multiple bonds (Scheme 27).

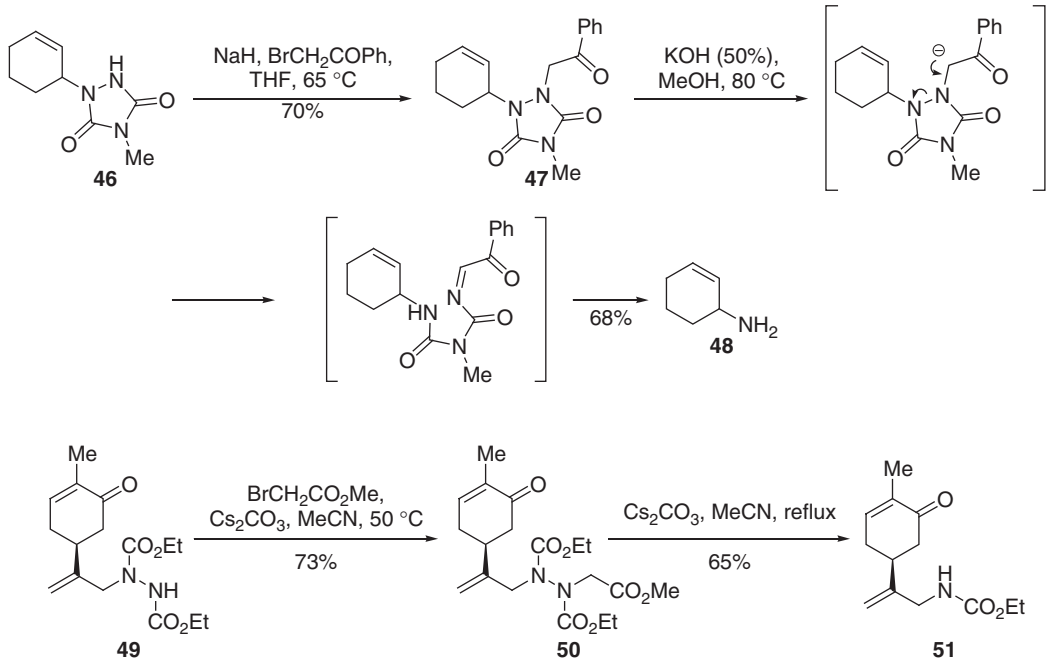
Cleavage of N–N bonds by elimination may also be performed under acidic conditions: thus, fragmentation of the *N*-trimethylsilylmethyl hydrazine **52** under mild acid conditions cleanly afforded the corresponding amine **53**. Basic conditions induced *β*-elimination of the secondary hydroxyl group (Scheme 28).[52]

N,*N*-Disubstituted hydrazines can be deaminated under various nonreductive conditions: photochemical activation,[53] copper salts (for Boc-substituted arylhydrazines such as **54**, Scheme 29),[54] or by naphthol amination (Scheme 30).[55]

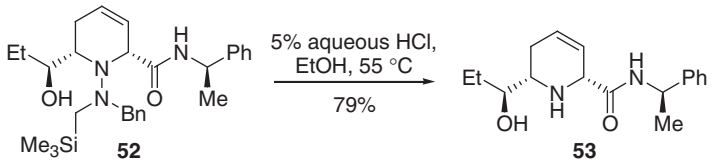
Besides carbanion-assisted elimination, radical cleavage of nitrogen–nitrogen bonds has been developed as an efficient method for the generation of nitrogen-centered radicals.[56] On addition of a radical such as Bu_3Sn to the thiocarbazone **60**, the intermediate **61** undergoes N–N bond scission to give a nitrogen-centered radical **62**, which can be used in radical-mediated polycyclizations (Scheme 31). This method has found many applications in alkaloid synthesis.[57]

8.14.4 Reduction of N–O Bonds

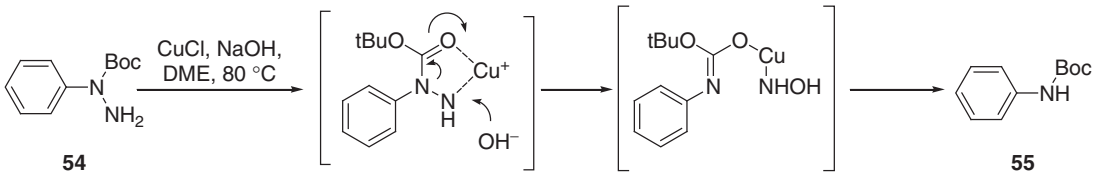
This section will mainly cover the reduction of single N–O bonds. This includes oxime reduction, the reductive cleavage of cyclic and acyclic hydroxylamines, as well as the deoxygenation of nitrones and *N*-oxides. Reduction of nitro and nitroso derivatives will be covered in a separate section.



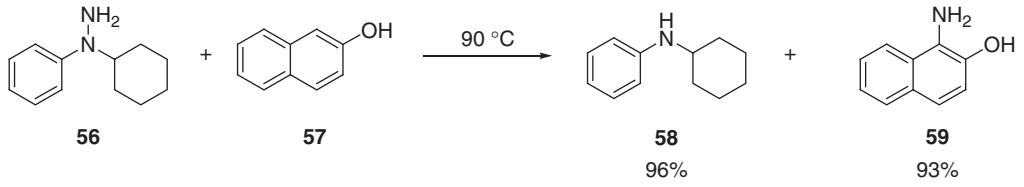
Scheme 27 Cleavage of the N–N bond in hydrazides by carbanion-assisted elimination. Reproduced from Adam, W.; Pastor, A.; Wirth, T. *Org. Lett.* **2000**, *2*, 1295–1297, and Magnus, P.; Garizi, N.; Seibert, K. A.; Ornholt, A. *Org. Lett.* **2009**, *11*, 5646–5648.



Scheme 28 Cleavage of the N–N bond by silicon-mediated elimination. Reproduced from Touré, B. B.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 8429–8436, with permission from ACS.



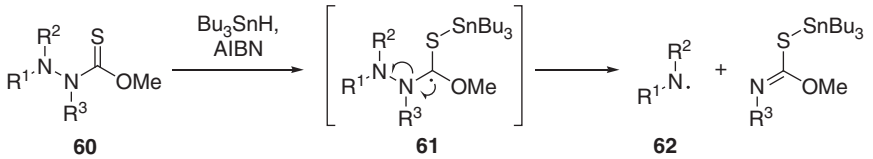
Scheme 29 Deamination of *N*-Boc arylhydrazines with copper(I) salts. Reproduced from Lim, Y.-K.; Pang, S.-J.; Paik, S.; Cho, G.-G. *Bull. Korean Chem. Soc.* **2003**, *24*, 543–544.



Scheme 30 Deamination of *N,N*-disubstituted hydrazines with 2-naphthol. Reproduced from Tang, Q.; Zhang, C.; Luo, M. *J. Am. Chem. Soc.* **2008**, *130*, 5840–5841, with permission from ACS.

8.14.4.1 Cleavage of the N–O Bond of Oximes

Cleavage of the N–O bond of oximes yields the corresponding imines. Primary imines are highly prone to hydrolysis to afford ketones unless they are highly substituted. The corresponding enamines may also be obtained by isomerization of the imines (Figure 2).



Scheme 31 Radical cleavage of N–N bonds.

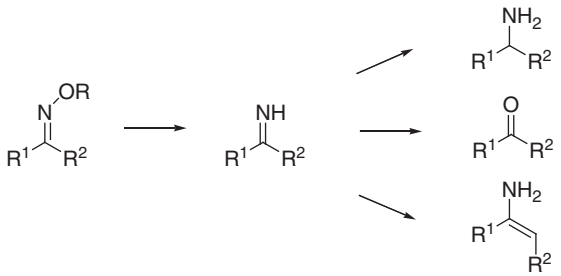


Figure 2 General scheme for oxime reductions.

4,5-Dihydroisoxazoles that are obtained from [3 + 2] cycloadditions between nitrile oxides or nitronates and alkenes are of special interest for the stereoselective construction of β-hydroxy ketones, 1,3-amino alcohols, or 1,3-diols in the context of total synthesis of natural products (Figure 3).

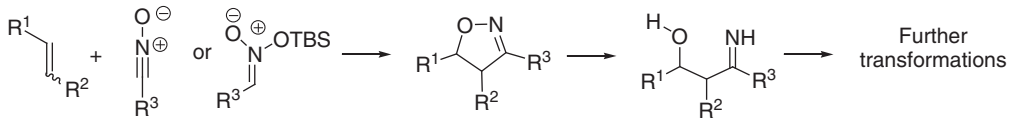
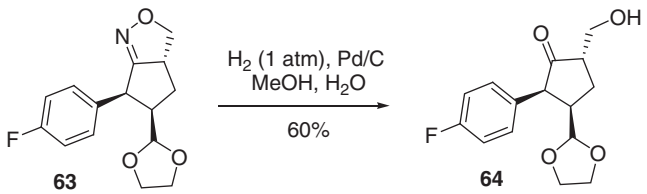


Figure 3 General scheme of isoxazoline formation and reduction.

8.14.4.1.1 Reduction by hydrogenation

Catalytic hydrogenation has been widely employed to achieve this N–O bond reduction with Pd/C[58] or Raney Ni in the presence of $B(OH)_3$ to avoid epimerization (when necessary). These conditions are suitable for acyclic or cyclic oximes such as isoxazoline **63** (Scheme 32) or **70** (Scheme 33).[59]



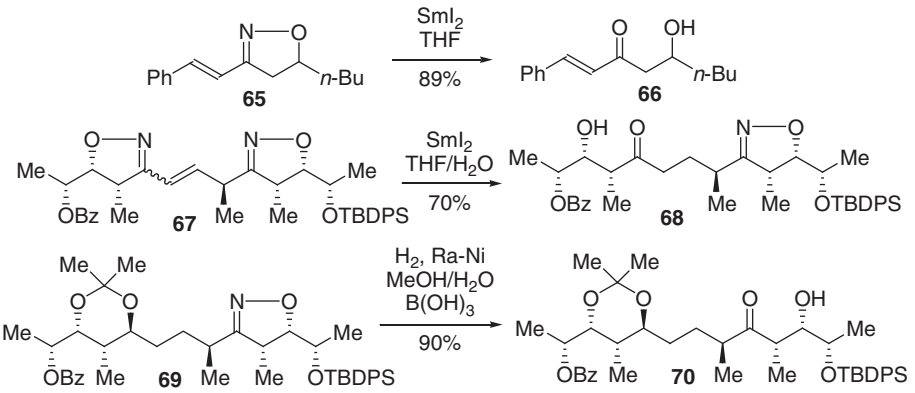
Scheme 32 Reduction of an isoxazoline by catalytic hydrogenation.

8.14.4.1.2 Reduction with low-valent metals

Low-valent metals that are able to transfer an electron to the N–O bond are also reagents of choice to achieve the reductive cleavage of the N–O bond.

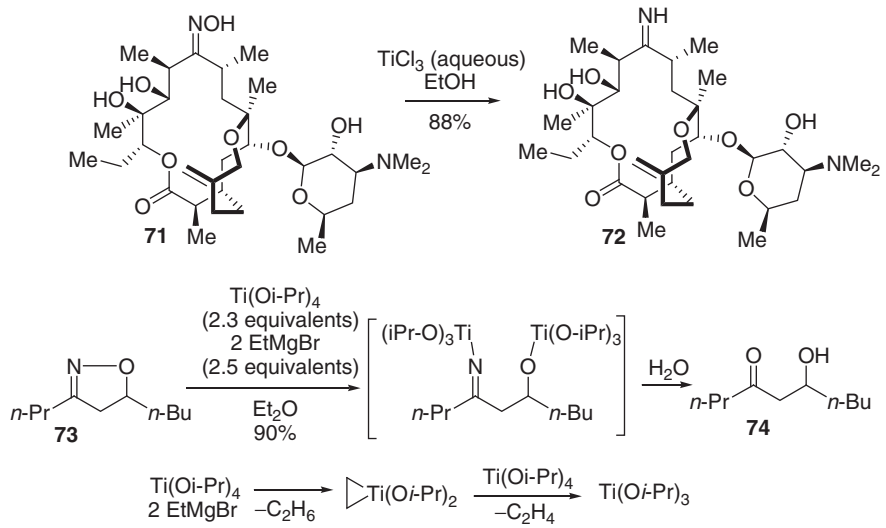
SmI_2 proved to be useful to achieve such a process as demonstrated with compound **65**.[60] In fact, SmI_2 is able to reduce 3-alkenyl isoxazolines at a higher rate than 3-alkyl isoxazolines. Therefore, the chemoselective cleavage of the left-hand isoxazolidine of **67** can be achieved. The addition of water in the reaction media resulted in the concomitant reduction of the double bond.[61] After further transformation the second isoxazolidine was reduced with Raney Ni (Scheme 33).

Titanium(III) is also efficient in the reduction of the N–O bond of oximes since erythromycin-derived oxime **71** was converted into imine **72** with aqueous $TiCl_3$.[62] More conveniently, the titanium(III) species could be generated by *in-situ* reduction of



Scheme 33 Reduction of isoxazolines with SmI_2.

titanium(IV) isopropoxide in the Kulinkovich conditions with ethylmagnesium bromide through the formation of a titanium(II) intermediate that disproportionates with titanium(IV) (Scheme 34).[63]



Scheme 34 Reduction of oximes and isoxazolines with titanium(III) reagents.

A large excess of zinc in acetic acid allows the recovery of imine **75** with concomitant reduction of the nitro group to an amine.[64] Al/Cu couple[65] prepared *in situ* from aluminum dust and $CuCl_2$ as well as iron powder[66] with ammonium chloride are efficient to induce the N–O bond cleavage in oxazolidines such as **77** and **79** (Scheme 35).

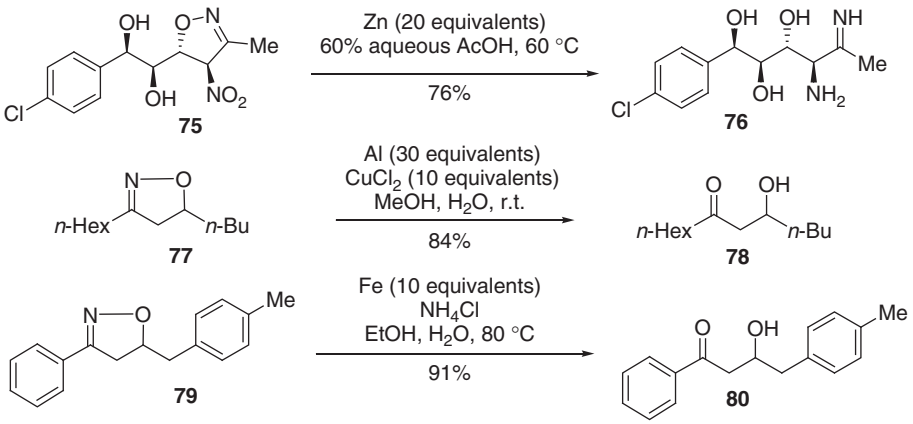
Iron powder has also been employed in combination with acetic anhydride to reduce oximes into enamides.[67] In those conditions, electron transfer from metallic iron to the formed oxime acetate results in the cleavage of the N–O bond. The resulting iminyl radical is then reduced by a second electron transfer to an iminyl anion, which is acetylated to yield the desired enamide (Scheme 36).

Metal carbonyl complexes such as $Fe(CO)_5$,[68] $Mo(CO)_6$,[69] and $Ru_3(CO)_{12}$[70] also efficiently induce N–O bond reductive cleavage in both oximes and isoxazolidines (Scheme 37).

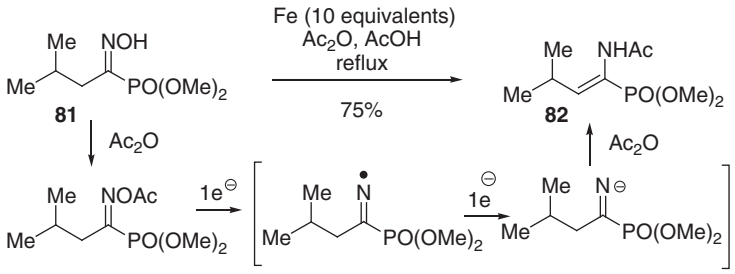
8.14.4.1.3 Radical reactions

Homolytic N–O bond cleavage of oximes could generate an iminyl radical, which could further add to a C═C bond. This radical process could be achieved by the addition of a tin radical, generated from tin hydride and AIBN, to the carbonyl group.[71] Fragmentation of the resulting radical yields the iminyl radical **88**, which could deliver the complex substrate **89** from **87**. Alternatively, the same iminyl radical **87** could be produced by single electron transfer from nickel in acetic acid and isopropanol (Scheme 38).[72]

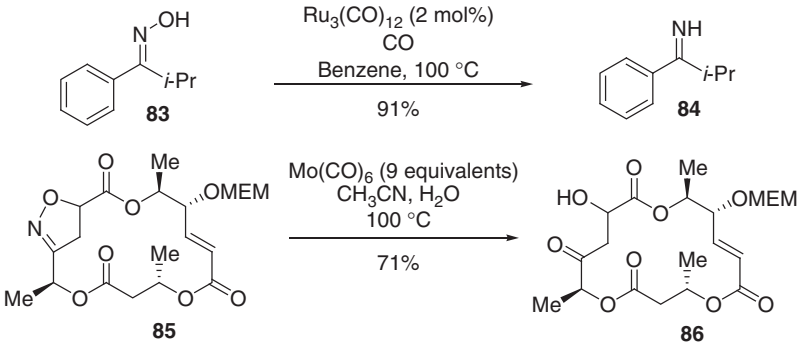
Thermal homolytic cleavage of the N–O bond of *O*-phenyl oximes also efficiently generates iminyl radicals that may add to double bonds to produce cyclic imines such as **91**.[73]



Scheme 35 Reduction of isoxazolidines with (0)-valent metals.



Scheme 36 Reduction of oximes to enamides with iron/acetic anhydride.



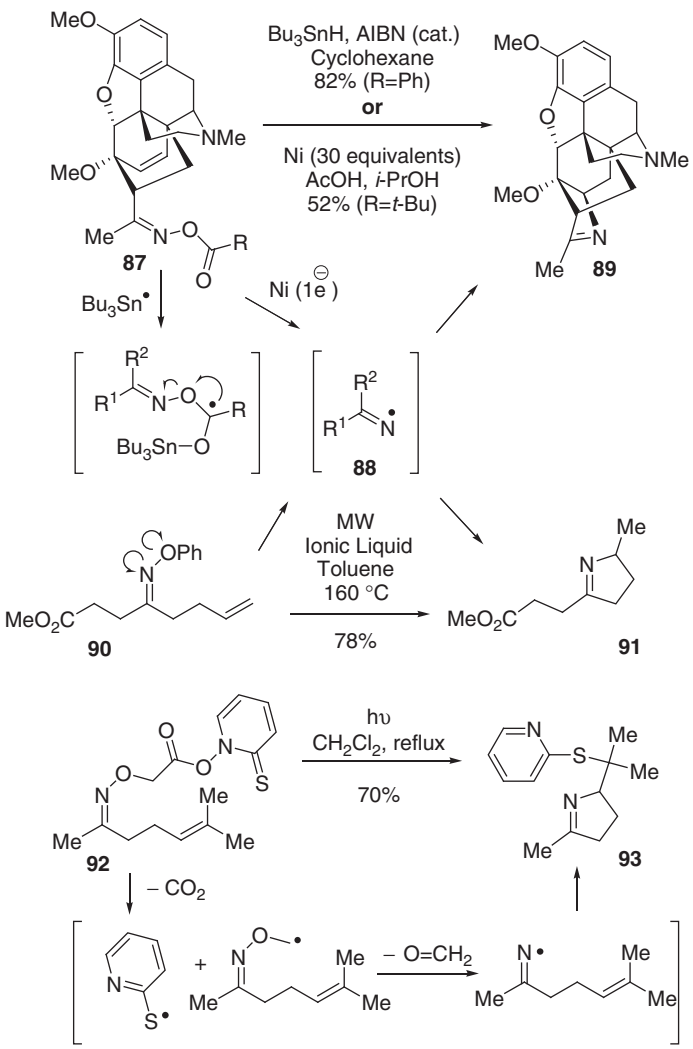
Scheme 37 Reduction of oximes and isoxazolidines with metal carbonyl complexes.

Irradiation with a 500 W tungsten lamp of esters of *N*-hydroxy-2-thiopyridone such as **92** results in the release of CO_2, formaldehyde and iminyl radical that gives the cyclic imine **93** (Scheme 38).[74]

8.14.4.1.4 Metal-catalyzed reactions

The oxidative addition of palladium to the N–O bond of oxime esters is the cornerstone of the amination of aromatic C–H bonds. Thus, treatment of oxime acetate **94** with a catalytic amount of palladium(0) results in the formation of indole **97** through intermediate **96** that would regenerate the active Pd(0) catalyst after reductive elimination.[75]

By a similar process isoquinoline **99** could be accessed by an amino-Heck reaction from oxime ester **98**,[76] whereas phenanthridine **102** could be obtained from the palladium-catalyzed coupling between oxime **100** and a benzyne intermediate derived from **101**.[77] Copper-catalyzed Chan-Lam type coupling between oxime ester **103** and boronic acid **104** delivers the aryl imine **105** (Scheme 39).[78]



Scheme 38 Generation of iminyl radicals from oxime derivatives.

8.14.4.1.5 Nucleophilic substitution

In the Beckmann rearrangement, activation of the hydroxyl of oxime results in migration of one of the substituents of the oxime with simultaneous cleavage of the N–O bond. The resulting nitrilium ion is intercepted by water to form amide **107** (Scheme 40).[79]

It is possible to achieve substitution at the oxime nitrogen center in the presence of a nucleophile to create a C–N bond without migration of one of the substituents of the oxime. For instance, β-(3-MeO-C_6H_4)-ketoxime **108** was converted to quinolines[80] **110** and **111** in the presence of a catalytic amount of $n$$Bu_4ReO_4$, whereas azaspiranic imine **112** was obtained from β-(4-HO)C_6H_4-ketoxime **109** (Scheme 41).[81]

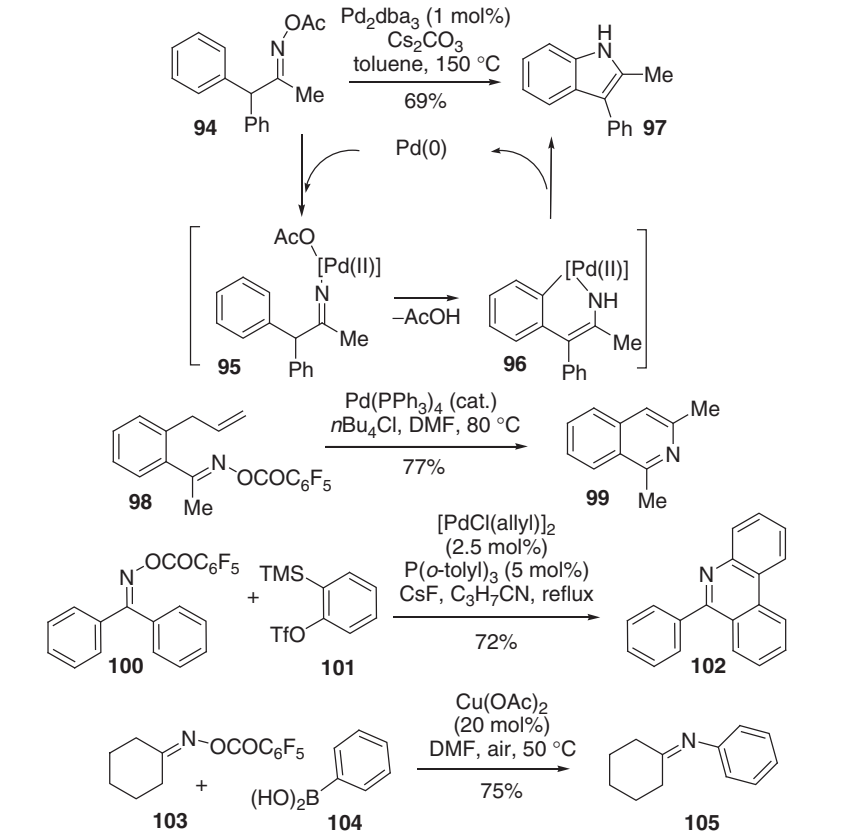
An analogous reaction involves the treatment of *O*-methylsulfonyl oxime **113** with 1,7-diazabicyclo-[5.4.0]-undecene (DBU) to give the cyclic imine **114** via an intramolecular S_N2 reaction (Scheme 41).[82]

8.14.4.1.6 Elimination reactions

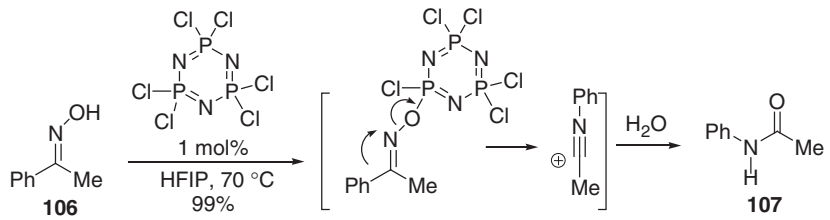
An alternative way to cleave the N–O bond of oximes relies on an elimination reaction induced by a base. Under microwave heating conditions, DBU abstracts the C-3 proton of the cyclic aldoxime **115** to give the β-hydroxy nitrile **116**.[83] The elimination could also be triggered by the addition of lithium methoxide to a ketone α to the C═N bond of isoxazoline **117** to deliver the β-hydroxy nitrile **118** (Scheme 42).[84]

8.14.4.2 Cleavage of the N–O Bond of Isoxazoles

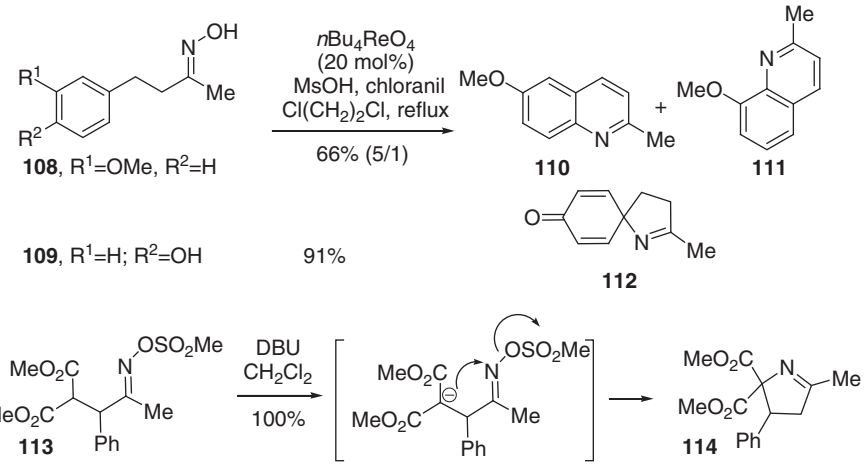
Isoxazoles are aromatic heterocycles containing an N–O bond. The weakness of this bond allows the ring opening of these heterocycles under reductive conditions. Isoxazoles are commonly used as enaminoketone or β-diketone surrogates (Figure 4).



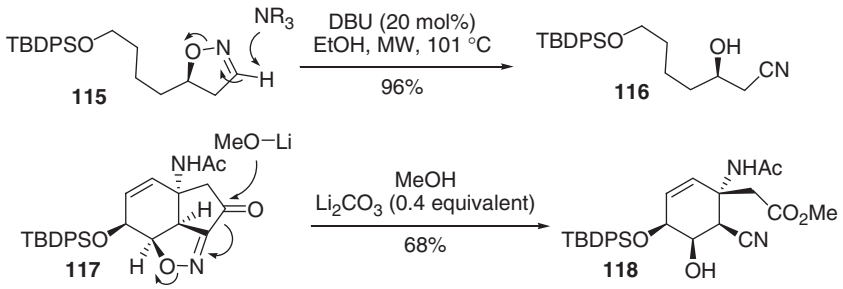
Scheme 39 Palladium-catalyzed reactions of oximes involving insertion into the N–O bond.



Scheme 40 The Beckmann rearrangement of oximes.



Scheme 41 Nucleophilic substitutions at the nitrogen center of oximes.



Scheme 42 Cleavage of N–O bond in isoxazolines via elimination.

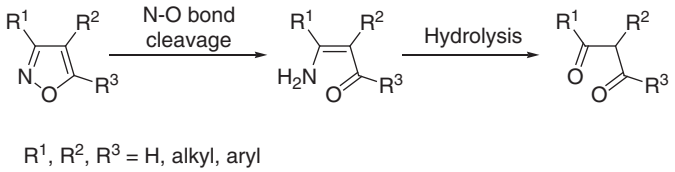
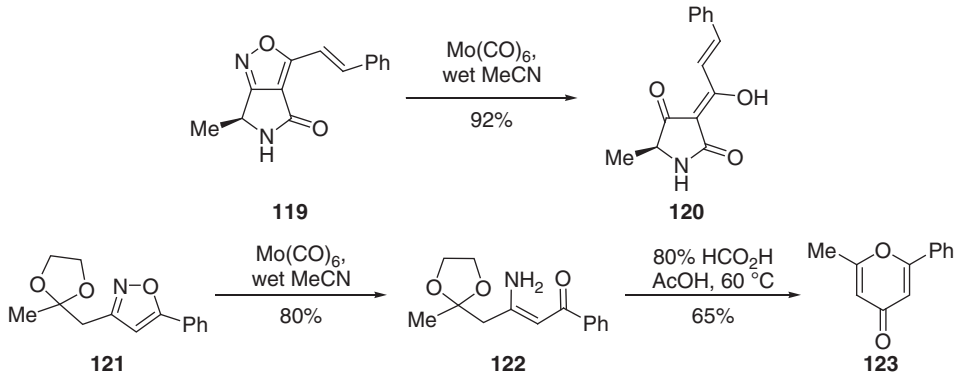


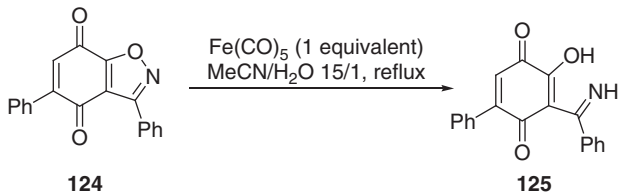
Figure 4 Isoxazoles as precursors to enaminoketones and β-diketones.

The most common methods for N–O bond cleavage in isoxazoles are hydrogenation with palladium or platinum catalysts or with Raney Ni. Recent developments have shown that $Mo(CO)_6$ efficiently cleaves the N–O bond in isoxazoles. This was applied to the synthesis of tetramic acid **120**,[85] or in the synthesis of pyran-4-ones such as **123**[86] (Scheme 43).



Scheme 43 Reduction of isoxazoles with $Mo(CO)_6$. Reproduced from Jones, R. C. F.; Pillainayagam, T. A. *Synlett* **2004**, 2815–2817, and Li, C.-S.; Lacasse, E. *Tetrahedron Lett.* **2002**, *43*, 3565–3568.

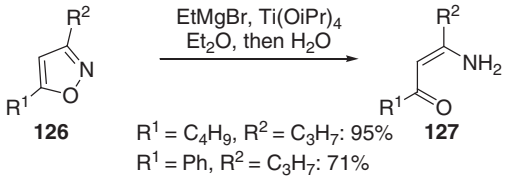
$Fe(CO)_5$ efficiently cleaves the N–O bond of fused isoxazolo-1,4-quinones to give the corresponding imines.[87] All the common reducing reagents failed to open the isoxazole ring of **124** (Scheme 44).



Scheme 44 Reduction of isoxazoles with $Fe(CO)_5$. Reproduced from Ben Hamadi, N.; Msaddek, M. *Het. Commun.* **2006**, *12*, 457–462.

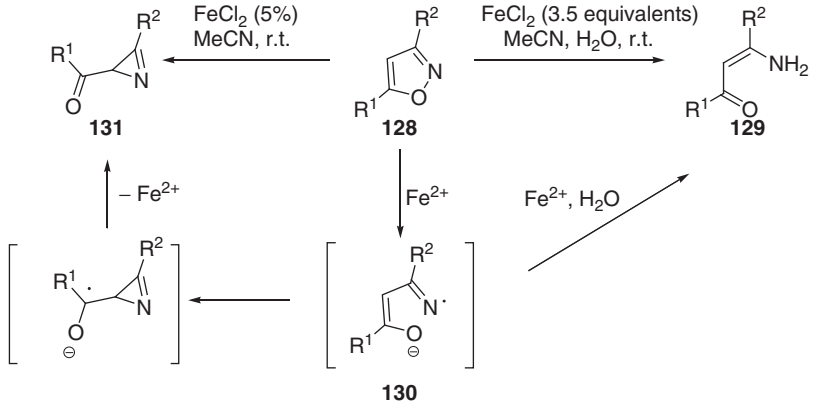
As with isoxazolines, isoxazoles may be cleaved using low-valent titanium obtained from the Kulinkovich reaction.[61] This procedure affords enaminoketones from 2,4-substituted isoxazoles (Scheme 45).

Isoxazoles can also be reduced to 2-azirines via a radical N–O bond scission. Interestingly, the same reagent, iron dichloride, can lead either to 2-carboxy azirines or to enaminoketones, depending on the stoichiometry; in the presence of a catalytic amount



Scheme 45 Reduction of isoxazoles with low-valent titanium. Reproduced from Fader, L. D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2485–2488, with permission from ACS.

of $FeCl_2$, single-electron transfer leads to the azirine **131** via the anion radical **130**, whereas excess iron dichloride reduces the radical to give the enaminoketone **129** (Scheme 46).[88]



Scheme 46 Reduction of isoxazoles to azirines or enaminoketones with $FeCl_2$. Reproduced from Auricchio, S.; Bini, A.; Pastomerlo, E.; Truscello, A. M. *Tetrahedron* **1997**, *53*, 10911–10920.

8.14.4.3 Reductive Cleavage of Hydroxylamines

This section refers to the N–O bond cleavage in acyclic and cyclic hydroxylamines. Cyclic hydroxylamine derivatives include isoxazolidines (products of nitrone cycloadditions), and dihydrooxazines (nitroso Diels–Alder cycloadducts), whereas acylic hydroxylamines usually arise from nucleophilic addition to oximes, nitroso aldol additions or the addition of carbon radical to TEMPO (Figure 5).

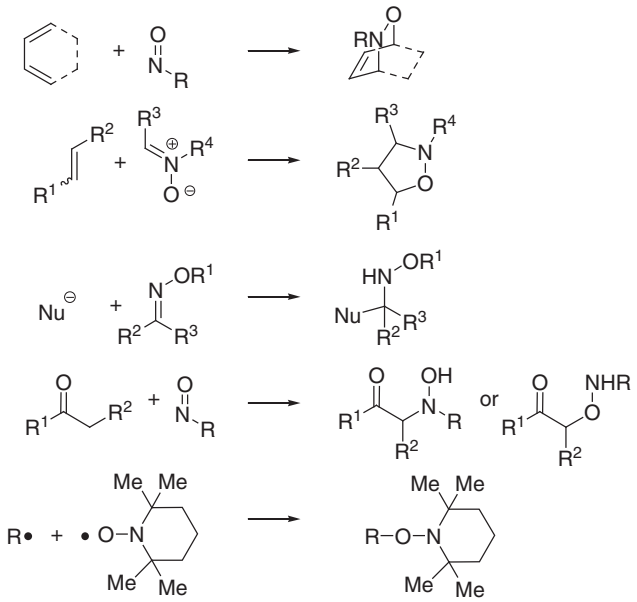
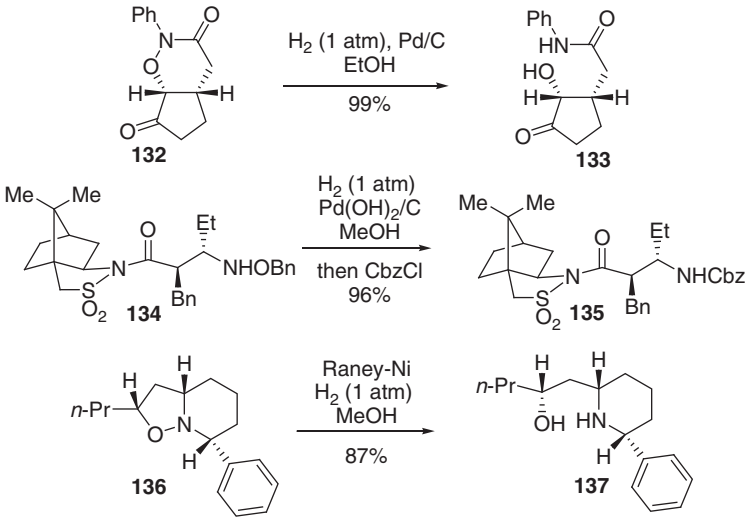


Figure 5 General scheme for acyclic and cyclic hydroxylamine synthesis.

8.14.4.3.1 Reduction by hydrogenation

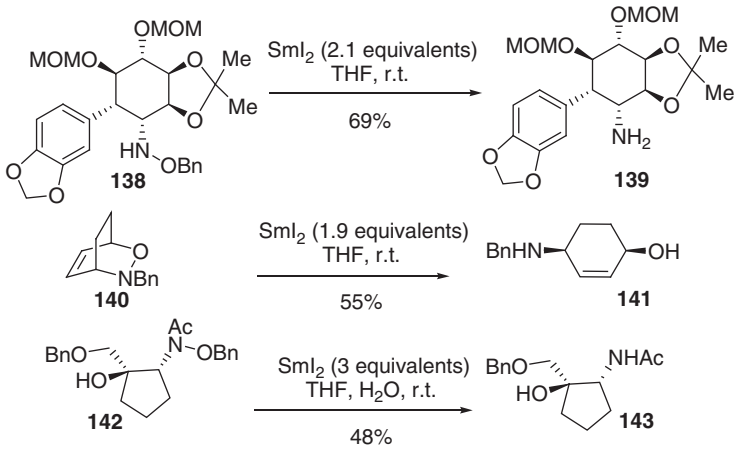
The reduction of the N–O bond of cyclic and acyclic hydroxylamines could be efficiently achieved via hydrogenation with Pd[89,90] or Raney-Ni[91] catalysts as in compounds **132**, **134**, and **136**. These conditions are usually not compatible with other unsaturation or benzyl protecting groups (Scheme 47).



Scheme 47 Examples of reductive cleavage of hydroxylamines by hydrogenation. Reproduced from Schmidt, V. A.; Alexanian, E. J. *Chem. Sci.* **2012**, *3*, 1672–1674; Miyabe, H.; Fujii, K.; Naito, T. *Org. Biomol. Chem.* **2003**, *1*, 381–383, and Vincent, G.; Guillot, R.; Kouklovsky, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 1350–1353.

8.14.4.3.2 Reduction with low-valent metals

SmI_2 is well recognized as a mild and highly functional group-tolerant method for the cleavage of the N–O bond through single electron transfer.[92,93] The reaction is usually run at room temperature and is compatible with double bonds and benzyl ethers, and applies to both acyclic and cyclic hydroxylamines (Scheme 48).

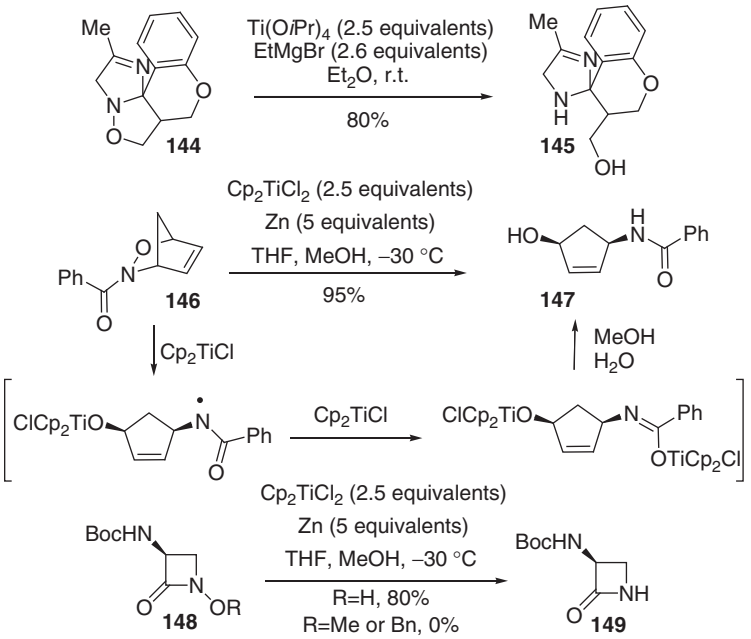


Scheme 48 Reductive cleavage of hydroxylamines with SmI_2.

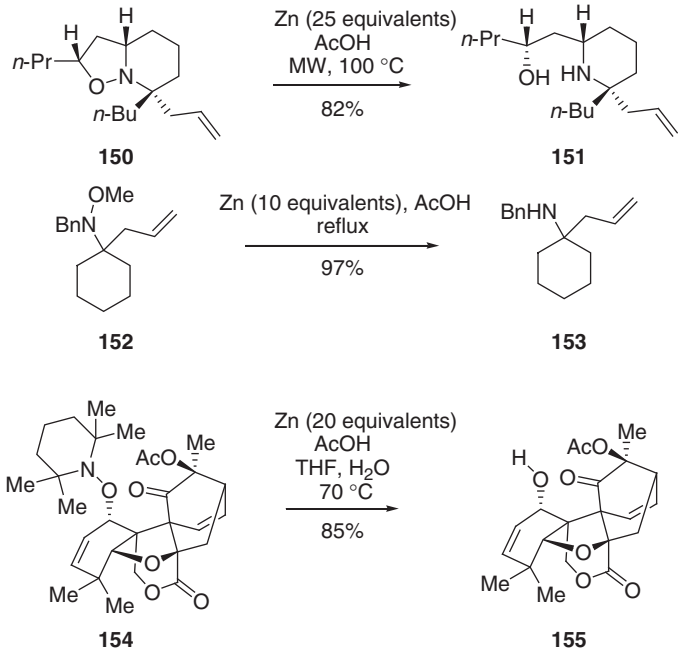
Low-valent titanium(III) species generated *in situ* from reduction of titanium(IV) with a Grignard reagent[94] are also able to induce the reduction of hydroxylamines. Hydroxylamides are reduced with a titanium(III) reagent that arises from reduction of Cp_2TiCl_2 with zinc (Scheme 49).[95]

Employing excess Zn in acetic acid is a widely used method to cleave the N–O bond of cyclic and acyclic[96] hydroxylamines and the particularly hindered adducts of carbon-centered radicals with TEMPO.[97] This method requires heating and a large excess of zinc but is efficient and displays compatibility with double bonds and benzyl protecting groups (Scheme 50).

Indium metal has also been reported to achieve chemoselective N–O bond reduction of *N,N*-disubstituted hydroxylamines and isoxazolidines in the presence of double bonds or (interestingly) acid labile protecting groups such as MOM, which would not have survived the Zn/AcOH conditions (Scheme 51).



Scheme 49 Reduction of hydroxylamines with low-valent titanium.



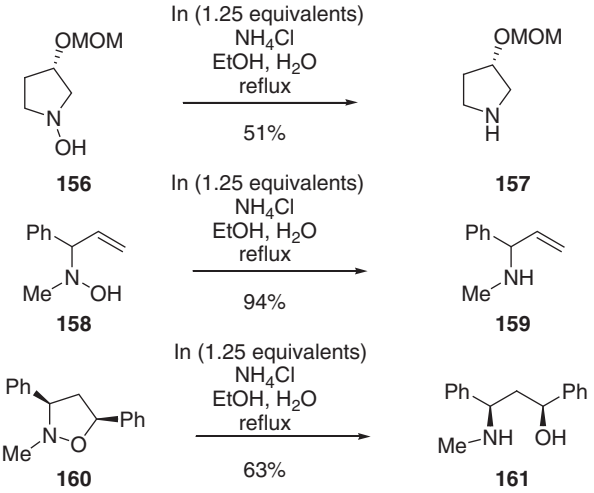
Scheme 50 Reductive cleavage of hydroxylamines with zinc/acetic acid.

Lithium in stoichiometric amounts with catalytic 4,4′-di-*tert*-butylbiphenyl (DTBB) is able to promote the dealkoxylation of hydroxylamides (Scheme 52).[98]

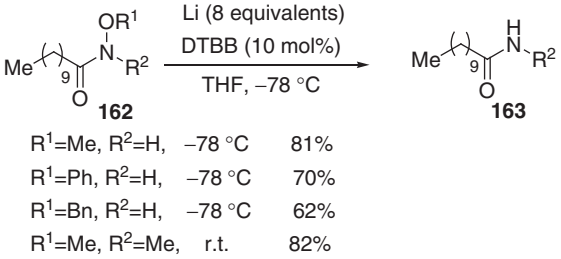
Ni/Al alloy (Scheme 54),[99] Al(Hg), and Na(Hg)[100] are also efficient methods to induce the reductive cleavage of the N–O bond (Scheme 53).

$Mo(CO)_6$ is a method of choice for the opening of cyclic hydroxylamines presumably via the insertion of the molybdenum into the N–O bond (Scheme 54).[101,102]

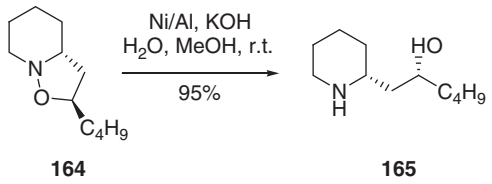
Ruthenium(III) chloride could be reduced *in situ* with a Zn/Cu system to reduce *N*-hydroxy and alkoxy amides into amides, presumably via ruthenium(II) intermediate **172**. α,β-Unsaturation is compatible with this reductive system (Scheme 55).



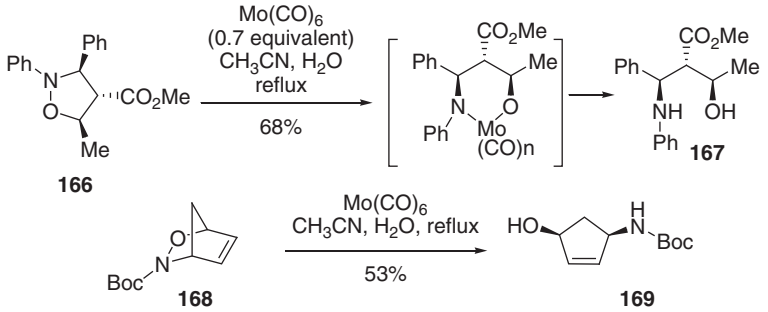
Scheme 51 Reductive cleavage of hydroxylamines with In/NH_4Cl.



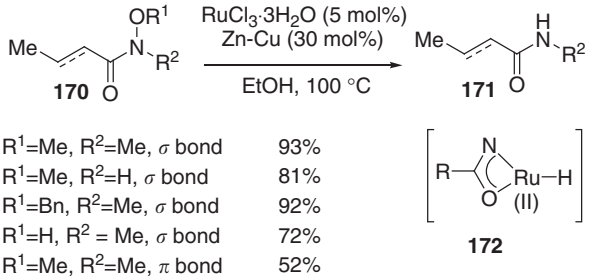
Scheme 52 Reductive cleavage of hydroxylamides with Li/DTBB.



Scheme 53 Reductive cleavage of an isoxazolidine wit Ni/Al alloy.



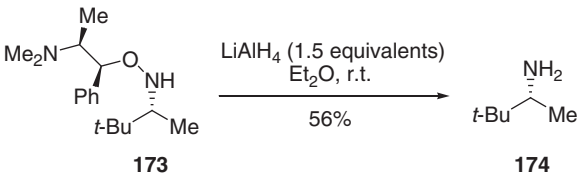
Scheme 54 Ring-opening of cyclic hydroxylamines with $Mo(CO)_6$.



Scheme 55 Reduction of hydroxylamides with $RuCl_3$/Zn–Cu.

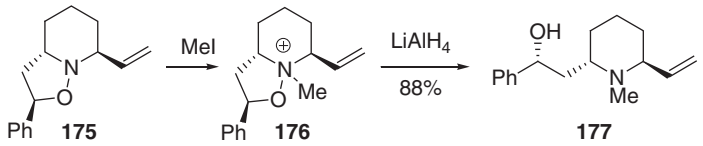
8.14.4.3.3 Hydride reduction

Reduction of alkoxyamines into amines can be achieved with metal hydrides such as lithium aluminum hydride, as demonstrated by the reduction of hydroxylamine **173** (Scheme 56).[103]



Scheme 56 Reduction of an alkoxyamine with $LiAlH_4$.

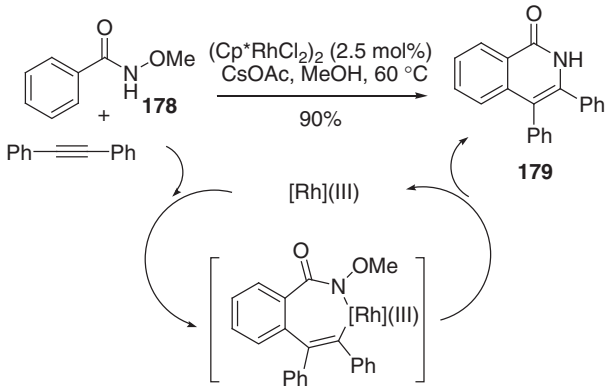
In the case of cyclic hydroxylamines, preliminary formation of the alkoxyammonium salt by alkylation of the nitrogen facilitates the reduction of the N–O bond by lithium aluminum hydride (Scheme 57).[104]



Scheme 57 N–O bond cleavage of a bicyclic isoxazoline via the ammonium salt.

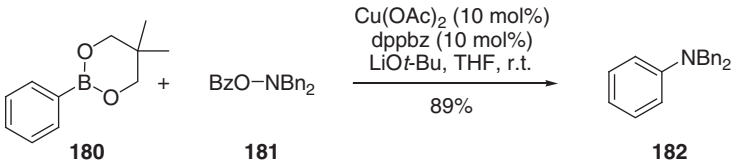
8.14.4.3.4 Metal-catalyzed reactions

A number of metal-catalyzed C–N bond-forming reactions make use of hydroxylamine derivatives as sources of nitrogen. These procedures involve a redox process where the cleavage of the N–O bond allows the reoxidation of the metal catalyst with a concomitant reductive elimination step forming the C–N bond. Isoquinolones such as **179** are obtained thus from the Rh(III) annulations of benzalkoxyamide **178** with alkynes (Scheme 58).[105]



Scheme 58 Rhodium-catalyzed annulation of hydroxylamides wuth alkynes.

The Chan-Lam type coupling between arylboronic acids such as **180** and *O*-Bz hydroxylamines **181** catalyzed by copper(II) acetate delivers arylamines without the addition of external oxidants (Scheme 59).[106]

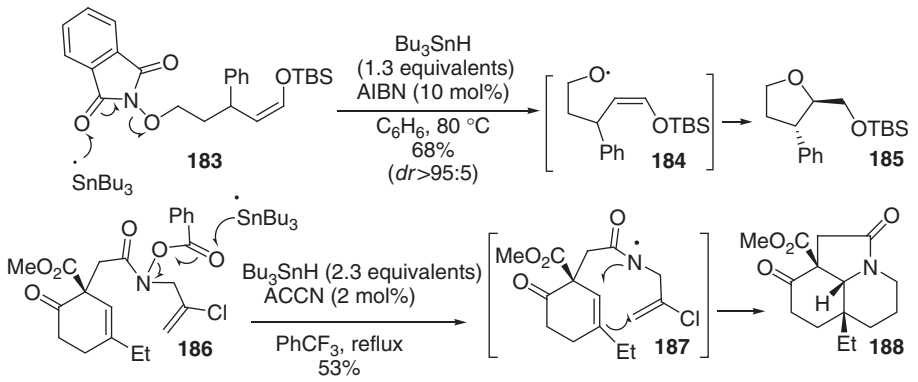


Scheme 59 Copper-catalyzed arene amination with hydroxylamines.

8.14.4.3.5 Radical reactions

Oxygen-centered radicals as well as nitrogen-centered radicals can be generated from the reduction of the N–O bond of hydroxylamines. These radical species can then be engaged in the synthesis of various heterocycles.

Treatment of the *N*-alkoxyphthalimide **183** with tin hydride and azobis(isobutyronitrile) (AIBN) resulted in the oxygen-centered radical **184** that cyclized stereoselectively onto tetrahydrofuran **185**.[107] Alternatively, the amidyl radical **187** was formed from the reaction of hydroxamic benzoate **186** with tin hydride and azobis(cyclohexanecarbonitrile) (ACCN) (Scheme 60).[108]

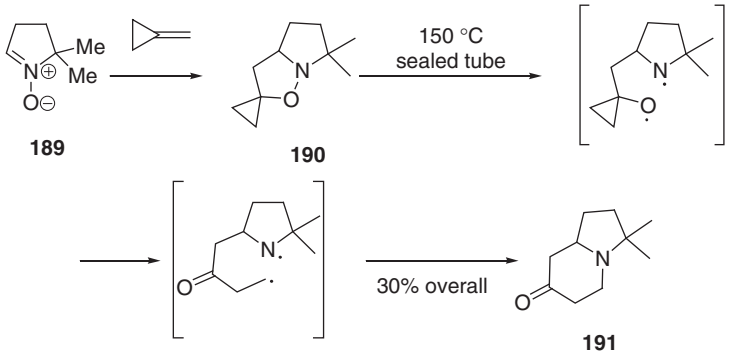


Scheme 60 Radical-mediated cleavage of N–O bonds in hydroxylamines.

8.14.4.3.6 Nonreductive cleavage

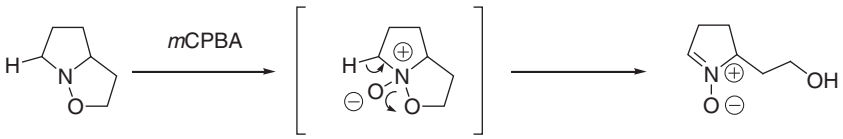
The nonreductive cleavage of N–O bonds is a convenient alternative to cleavage using reducing reagents. It is mainly employed when sensitive functional groups such as double bonds are present in the substrate.

Like N–N bonds, N–O bonds are relatively weak and can be easily cleaved to radicals by simple heating. This property has been especially exploited in the thermal cleavage of isoxazolidines. For instance, compound **190**, obtained by dipolar addition of the nitrone **189** with methylene cyclopropane, undergoes homolytic cleavage and radical rearrangement to give the indolizidine **191** (Scheme 61).[109]



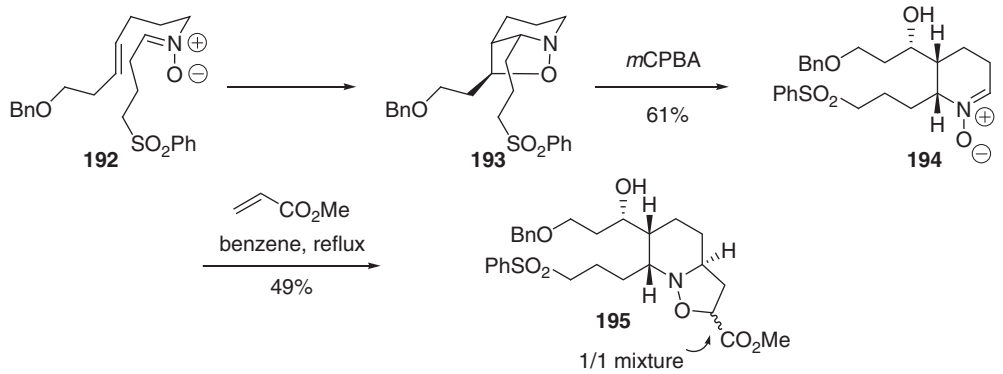
Scheme 61 Thermal N–O bond cleavage in isoxazolidines. Reproduced from Brandi, A.; Cordero, F. M.; De Sarlo, F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1–8, with permission from ACS.

The oxidative cleavage of isoxazolidine to nitrones and alcohols is a well-known reaction which has found numerous applications in alkaloid synthesis.[110] Nitrogen oxidation in isoxazolidines (generally using *meta*-chloroperoxybenzoic acid (*m*CPBA)) give a transient *N*-oxide which undergoes N–O bond cleavage to give a nitrone (Scheme 62). The fragmentation is generally regioselective, and has been applied to mono-, bi-, and tricyclic isoxazolidines.[111]



Scheme 62 General scheme for the oxidative cleavage of isoxazolidines. Reproduced from Baskaran, S.; Aurich, H. G.; Biesemeier, F.; Harms, K. *Tetrahedron* **1998**, *54*, 122249–122264.

This reaction has been applied for sequential nitrone cycloadditions in alkaloid synthesis. In an approach to the synthesis of gephyrotoxin, nitrone **192** underwent intramolecular dipolar cycloaddition to give the bicyclic isoxazolidine **193**. Oxidative cleavage allows the formation of a cyclic nitrone **194** which undergoes a second dipolar cycloaddition (Scheme 63).[112]



Scheme 63 Sequential nitrone cycloaddition with an oxidative cleavage of an isoxazolidine. Reproduced from Holmes, A. B.; Hughes, A. B.; Smith, A. L. *J. Chem. Soc. Perkin Trans. 1* **1993**, 633–643, with permission from RSC.

The camphor-derived oxazoline *N*-oxide **196** undergoes highly regio- and stereoselective dipolar cycloadditions with various dipolarophiles.[113] Although the N–O bond in cycloadduct **197** was resistant to almost all reducing reagents, treatment with *m*CPBA smoothly afforded the nitrone **200** which was further hydrolyzed. The reactions were highly chemoselective, as illustrated in an approach to the synthesis of tetrahydrolipstatin (Scheme 64).[114]

Oxidative cleavage has been also applied to the tranformation of TEMPO adducts. However, oxidation of *O*-alkyl TEMPO derivatives does not give rise to nitrones as with other substrates, owing to the absence of hydrogen atoms α to the nitrogen; instead, hydrogen abstraction occurs α to the oxygen, leading to a carbonyl derivative (Scheme 65).[115]

A related mechanism was invoked to explain the *in situ* cleavage of isoxazolidines obtained by intramolecular dipolar cycloaddition of silylnitronates (Scheme 66).[116] Fragmentation was induced by desilylation with TBAF. *In situ* oxidation of the intermediate nitroso derivative gave finally a nitro alcohol.

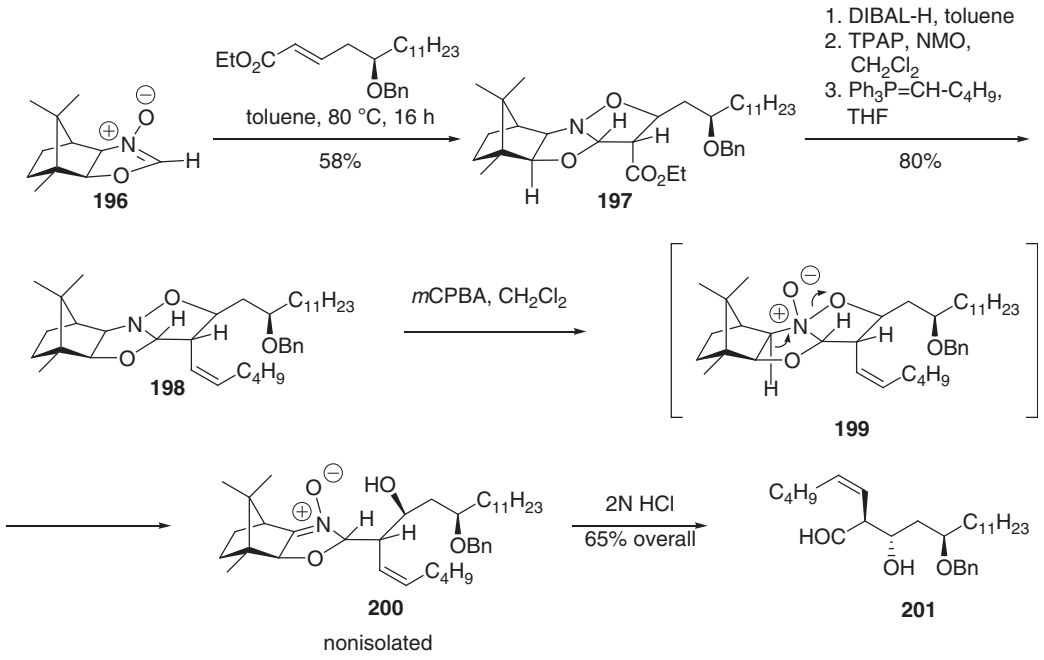
N–O Bond cleavage in heterocyclic systems by nitrogen activation may be achieved by ways other than oxidation. Thus, the nitroso Diels–Alder between the α-acetoxynitroso **207** and cyclohexadiene did not afford the expected bicyclic product but the amino alcohol **208** after nitrogen protection.[117] A mechanism involving the fragmentation of a heteroatom-substituted enamine was suggested (Scheme 67).

This observation paved the way for a new mild and efficient method for N–O bond cleavage in mono- and bicyclic dihydrooxazines. Treatment of the dihydrooxazine hydrochloride with dithiolane-2-carboxaldehyde **209** gave cleanly the corresponding amino alcohol according to a similar mechanism (Scheme 68).[118]

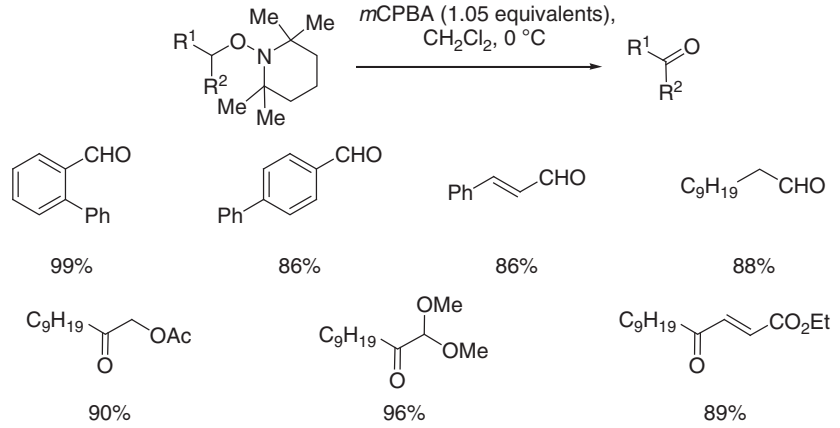
In an analogous fashion, activation of cyclic and acyclic *N*-arylhydroxylamines by Lewis acids in a protic solvent may result in the cleavage of N–O bonds; this was applied to the ring-opening of nitroso Diels–Alder cycloadducts using $In(OTf)_3$ in methanol,[119] and to the reduction of nitroso aldol adducts with $CuSO_4$.[120]

Redox processes are convenient methods for the mild cleavage of N–O bonds. However, they do not lead to amino alcohols but to aminocarbonyl or aminocarboxyl derivatives through alcohol oxidation.

Dihydrooxazines arising from nitroso Diels–Alder reactions are transformed into γ-aminoaldehydes after nitrogen quaternization and basic treatment (Scheme 69).[121] The reaction is compatible with the presence of ethers or enol ethers and is applied to a saturated structure such as **212**.



Scheme 64 Oxidative cleavage of a bicyclic isoxazolidine. Reproduced from Dirat, O.; Kouklovsky, C.; Langlois, Y. *Org. Lett.* **1999**, *1*, 753–755, with permission from ACS.



Scheme 65 Oxidative cleavage of TEMPO adducts. Reproduced from Inokuchi, T.; Kawafuchi, H. *Tetrahedron* **2004**, *60*, 11969–11975.

The redox process has also been applied to the direct synthesis of β-amino acids by nitrone cycloaddition with the cyclohexanone-derived acrylate **215**. Hydrolysis of the chiral auxiliary gives the isoxazolidine **217**, which undergoes decarboxylative redox process leading to the amino acids under extremely mild conditions (Scheme 70, Table 6).[122]

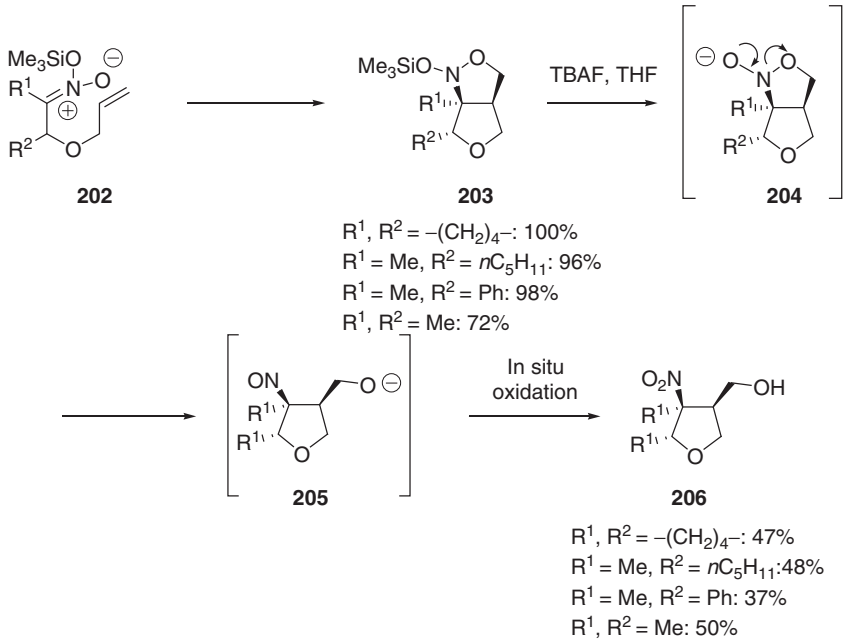
This very efficient redox process is the cornerstone of a new method for amide-forming ligation: reaction between a ketoacid and a hydroxylamine affords an amide. The mechanism involves the formation of a nitrone and subsequent decarboxylation (Scheme 71).[123]

N–O Bond cleavage by β-elimination has been applied to the transformation of Weinreb amide to secondary amides. Addition of Bu_3SnLi to a Weinreb amide followed by Brook rearrangement gives rise to the intermediate **220**, which undergoes spontaneaous elimination (Scheme 72).[124]

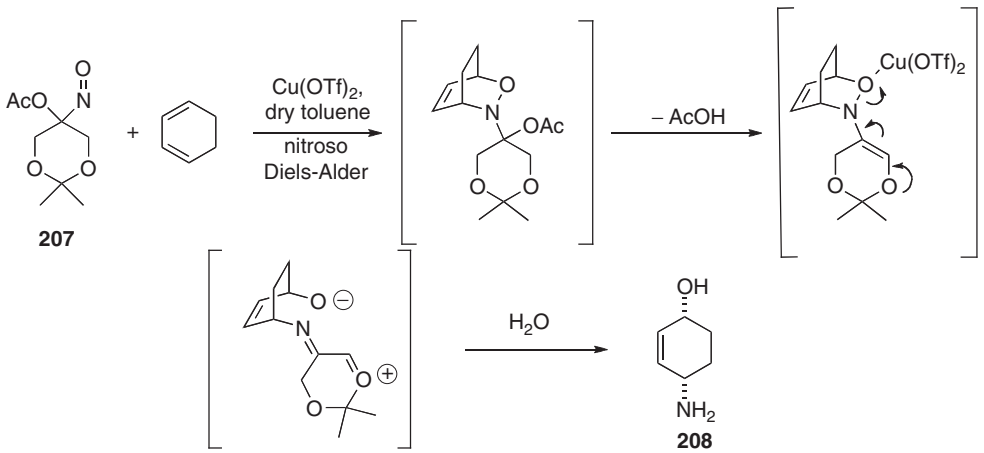
Finally, an unexpected N–O bond cleavage in a Weinreb amide occurred during a nucleophilic addition: treatment of the amide **221** with *n*-octyllithium resulted in the formation of the NH amide instead of ketone formation.[125] Deprotonation and formaldehyde extrusion is proposed to explain the formation of the amide **223** (Scheme 73).

8.14.4.4 Deoxygenation of Amine *N*-oxides and Nitrones

Amine *N*-oxides include the oxides of aliphatic and aromatic amines such as pyridines (Figure 6).



Scheme 66 Fluoride-mediated fragmentation of *N*-silyloxy isoxazolidines. Reproduced from Roger, P.-Y.; Durand, A.-C.; Rodriguez, J.; Dulcère, J.-P. *Org. Lett.* **2004**, *6*, 2027–2029, with permission from ACS.



Scheme 67 *In situ* N–O bond cleavage of a nitroso Diels–Alder cycloadduct. Reproduced from Calvet, G.; Dussaussois, M.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2004**, *6*, 2449–2451, with permission from ACS.

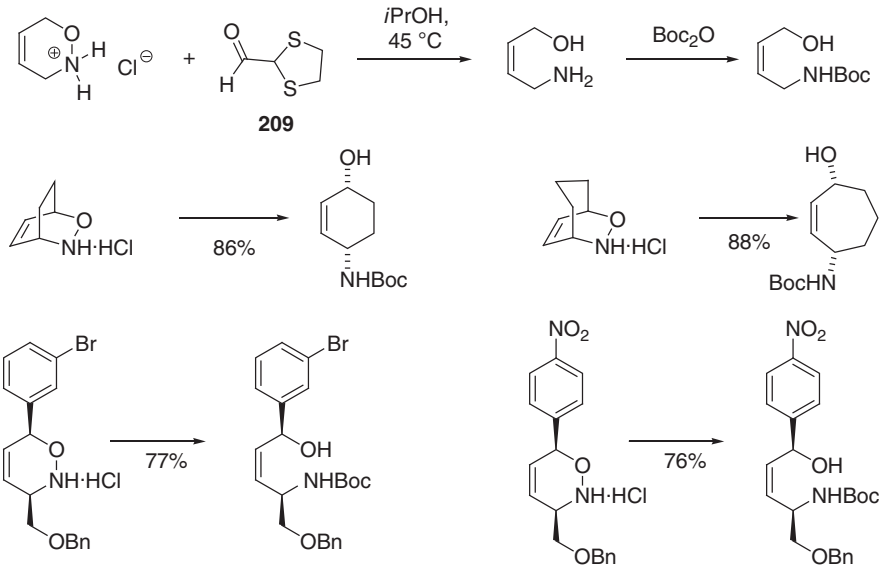
Many methods for this reaction have been reported, most of them being applied to the deoxygenation of pyridine *N*-oxides. A publication of 2010 lists almost all the available methods.[126] Reagents for amine *N*-oxide reduction include metal hydrides, low-valent metals, phosphorus or sulfur reagents, or acylating reagents.

Recent developments have focused on the use of low-valent metals, although these methods have been often restricted to the deoxygenation of pyridine *N*-oxides. Several systems based on indium metal have thus been reported: In/NH_4Cl,[127] In/$CoCl_2 \cdot 6H_2O$,[128] In/Cp_2TiCl_2,[129] or In/PivCl.[130] The first reagent system presents the advantages of simplicity, great functional group tolerance, and is efficient for the deoxygenation of both pyridine and amine *N*-oxides (Schemes 74 and 75).

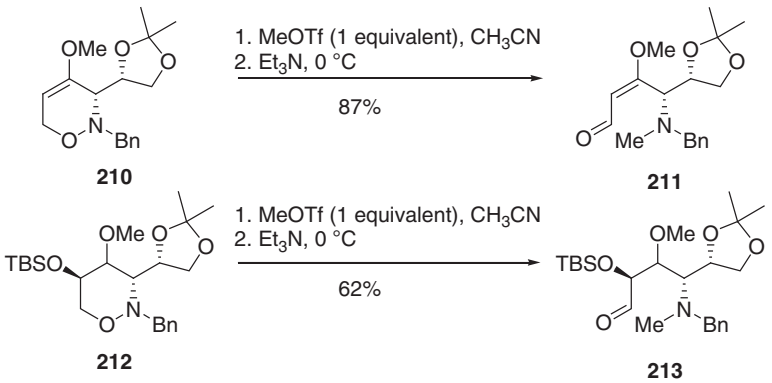
A related reagent system uses gallium metal in water. This reducing reagent cleanly deoxygenates pyridine *N*-oxides but fails to reduce amine *N*-oxides.[131] Molybdenum derivatives are also efficient for the deoxygenation of various amine oxides. Although the MoO_2Cl_2/silane system reduces pyridine *N*-oxides,[132] $Mo(CO)_6$ efficiently deoxygenates amine and pyridine *N*-oxides (Scheme 76).[133]

Ruthenium salts such as ruthenium(III) chloride may also be used for the reduction of amine *N*-oxides. Moreover, this reaction has been extended to the deoxygenation of nitrones or azoxybenzenes (Scheme 77).[134]

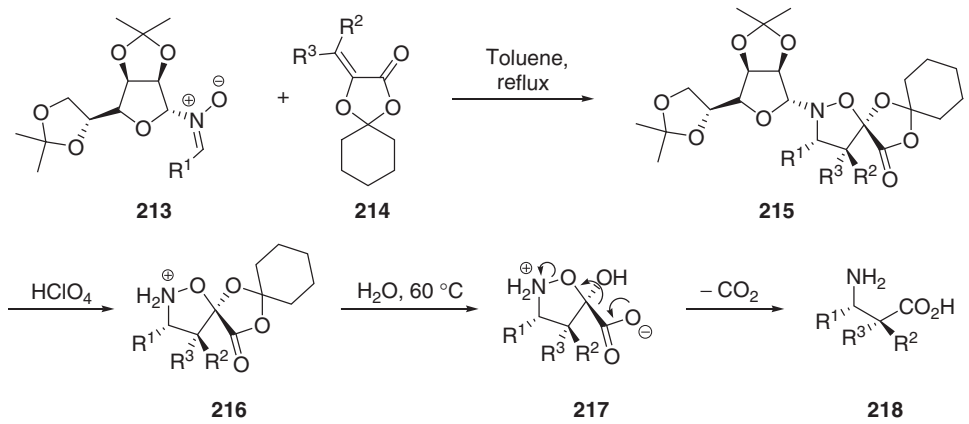
The use of copper or zinc salts allows more general and practical reactions. Although copper(I) iodide in THF is efficient for the deoxygenation of amine *N*-oxides, the deoxygenation of aromatic substrates requires the addition of a metal (Zn or Al).[135]



Scheme 68 N–O bond cleavage of dihydrooxazines by condensation with dithiolane-2-carboxaldehyde. Reproduced from Galvani, G.; Calvet, G.; Blanchard, N.; Kouklovsky, C. *Org. Biomol. Chem.* **2008**, *6*, 1063–1070, with permission from ACS.



Scheme 69 N–O bond cleavage in dihydrooxazines by redox process. Reproduced from Al-Harrasi, A.; Reissig, H.-U. *Synlett* **2005**, 1152–1154, with permission from Thieme.

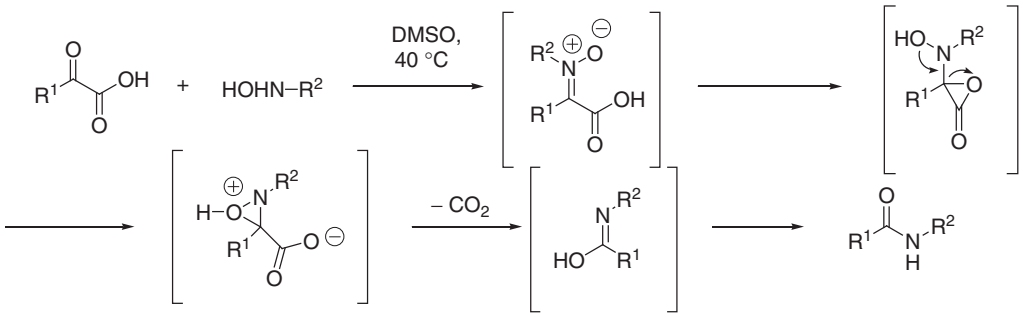


Scheme 70 Synthesis of β-amino acids by redox N–O cleavage of isoxazolines. Reproduced from Yu, S.; Ishida, H.; Juarez-Garcia, E. M.; Bode, J. W. *Chem. Sci.* **2010**, *1*, 637–641, with permission from ACS.

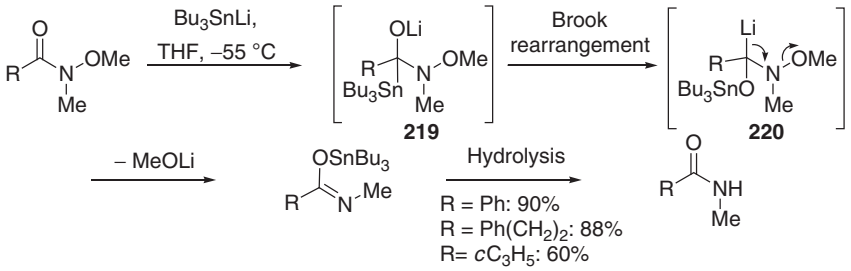
Table 6 Synthesis of β-amino acids by redox N–O cleavage of isoxazolines

R^1	R^2	R^3	Yield **215** (%)	Yield **216** (%)	Yield **218** (%)
*i*Pr	H	H	93	73	100
Bn	H	H	96	58	92
$PhS(CH_2)_2$–	H	H	71	71	70
H	*i*Pr	H	85	92	100
H	H	*i*Pr	91	94	100
H	Bn	H	88	90	90
*i*Pr	Me	H	42	98	100
*i*Bu	H	Et	59	93	100

Source: Reproduced from Yu, S.; Ishida, H.; Juarez-Garcia, E. M.; Bode, J. W. *Chem. Sci.* **2010**, *1*, 637–641, with permission from RSC.



Scheme 71 Protein ligation by reaction of hydroxylamines with ketoacids. Reproduced from Pusterla, I.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 513–516.



Scheme 72 N–O bond cleavage in Weinreb amide by Brook rearrangement and β-elimination. Reproduced from Paleo, M. R.; Calaza, M. I.; Grana, P.; Sardina, F. J. *Org. Lett.* **2004**, *6*, 1061–1063, with permission from ACS.

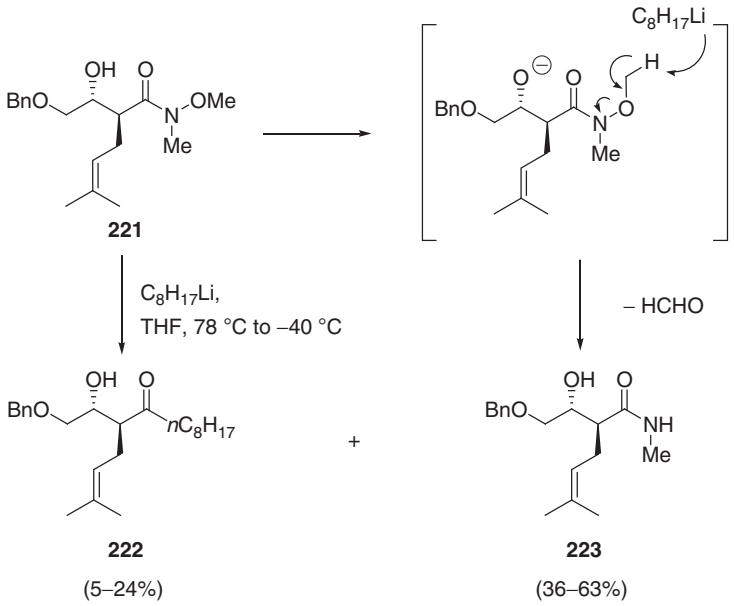
Copper(II) or zinc(II) triflates deoxygenate aromatic *N*-oxides, nitrones, and azoxybenzenes efficiently; generally, better yields are obtained with zinc triflate (Schemes 78 and 79).[136]

Besides metallic reagents, phosphorus and sulfur reagents are well known for the deoxygenation of *N*-oxides. A recent example shows the use of PBr_3 for the deoxygenation of an imidazolone *N*-oxide in the synthesis of the biologically active compound **225** (Scheme 80).[137]

Finally, as for the cleavage of hydroxylamines, the Brook rearrangement has proved to be an efficient tool for the deoxygenation of nitrones and pyridine *N*-oxides; addition of trimethylsilyllithium to the carbon–nitrogen bond followed by oxygen migration and β-elimination cleanly provides the deoxygenated product. The reaction is performed at low temperature in good yields (Scheme 81).[138]

8.14.5 Reduction of O–O Bonds

The cleavage of the O–O bond of hydroxyperoxides and disubstituted peroxides allows access to alcohols, diols, ethers, or ketones. Synthetically, peroxides are commonly obtained by interception of radicals by oxygen, the addition of peroxyl radical to double bonds, the addition of hydroperoxides to enones or the cycloaddition of singlet oxygen to dienes or alkenes. Ozonolysis of alkenes delivers ozonides that may be further transformed to aldehydes (Figure 7).



Scheme 73 Anionic cleavage of a Weinreb amide. Reproduced from Labeeuw, O.; Phansavath, P.; Genêt, J.-P. *Tetrahedron Lett.* **2004**, *45*, 7107–7110.

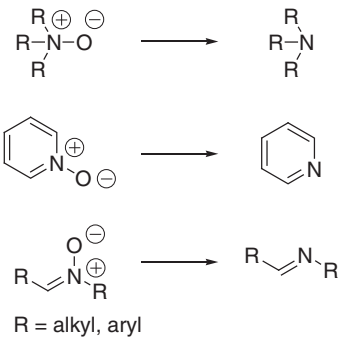
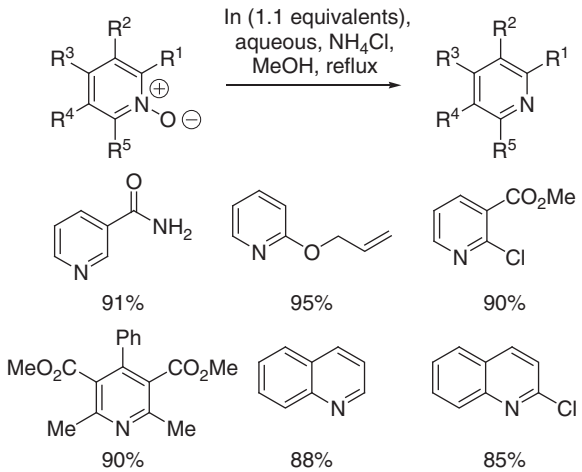
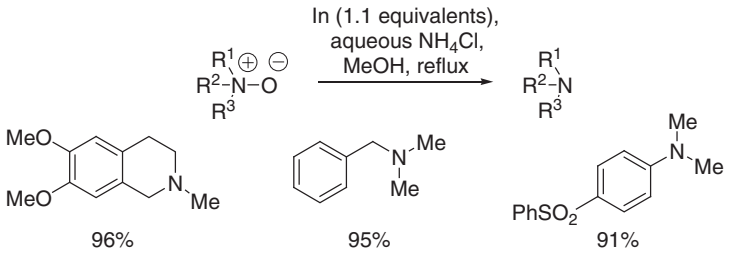


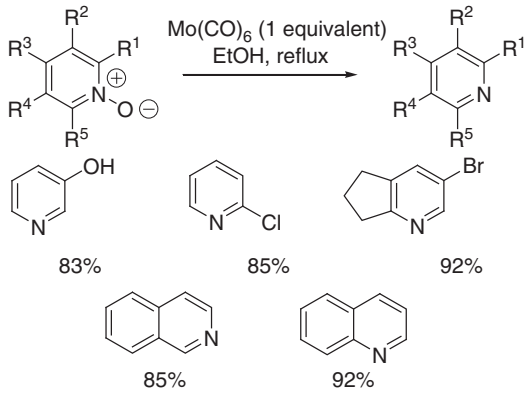
Figure 6 Substrates for the deoxygenation of amine *N*-oxides and nitrones.



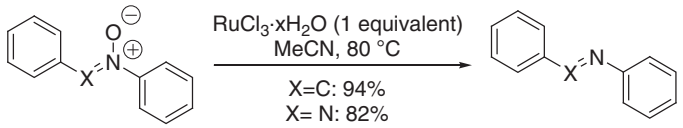
Scheme 74 Deoxygenation of pyridine *N*-oxides with In/NH_4Cl. Reproduced from Yadav, J. S.; Subba Reddy, B. V.; Muralidhar Reddy, M. *Tetrahedron Lett.* **2000**, *41*, 2663–2665.



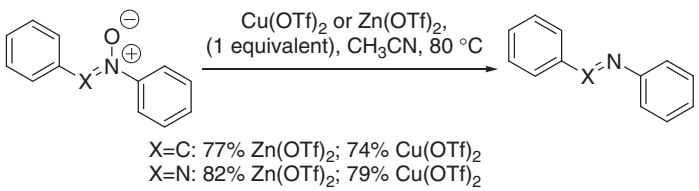
Scheme 75 Deoxygenation of amine *N*-oxides with In/NH_4Cl. Reproduced from Yadav, J. S.; Subba Reddy, B. V.; Muralidhar Reddy, M. *Tetrahedron Lett.* **2000**, *41*, 2663–2665.



Scheme 76 Deoxygenation of pyridine *N*-oxides with $Mo(CO)_6$. Reproduced from Yoo, B. W.; Choi, J. W.; Yoon, C. M. *Tetrahedron Lett.* **2006**, *47*, 125–126.



Scheme 77 Deoxygenation of nitrones and azoxybenzenes with $RuCl_3$. Reproduced from Kumar, S.; Saini, A.; Sandhu, J. S. *Tetrahedron Lett.* **2005**, *46*, 8737–8739.



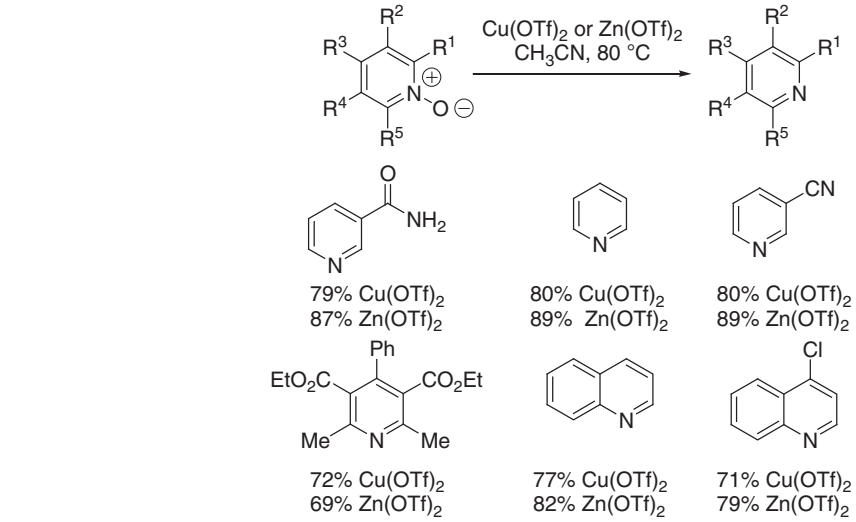
Scheme 78 Deoxygenation of nitrones and azoxybenzenes with $Zn(OTf)_2$ or $Cu(OTf)_2$. Reproduced from Saini, A.; Kumar, S.; Sandhu, J. S. *Synlett* **2006**, 395–398, with permission from Thieme.

8.14.5.1 Reduction with Sulfur or Phosphorus Compounds

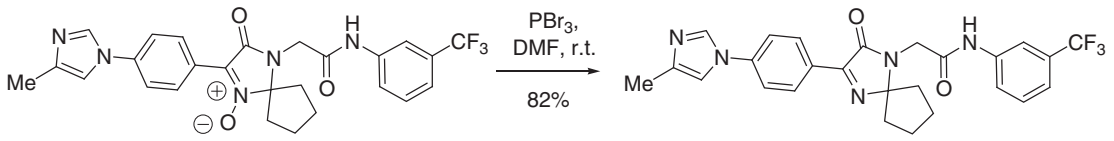
Sulfides, thioureas, and phosphines are widely employed to reduce peroxides and ozonides under very mild conditions. These conditions are compatible with a wider range of functional groups than for hydrogenation or reduction with low-valent metals or hydrides.

Thiourea can efficiently reduce peroxide **229** under mild conditions and in high yields. This method is widely employed to achieve O–O bond reduction.[139] The sulfur atom of methionine is able to cleave the O–O bond of dioxetane **231**,[140] whereas dimethyl sulfide can reduce hydroperoxide **235** (Scheme 82).[141]

Dimethyl sulfide[142] and triphenylphosphine[143] are amongst the most popular reagents to reduce the ozonides that arise from the ozonolysis of alkenes (Scheme 83).

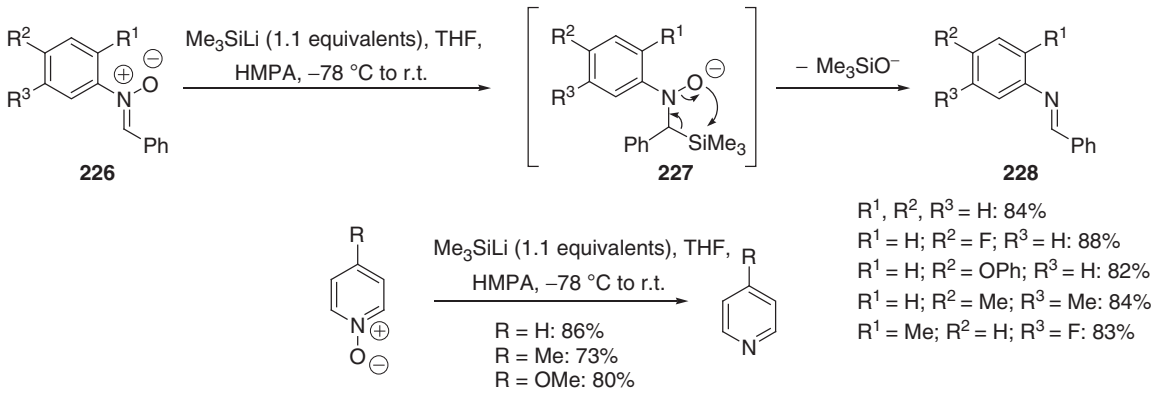


Scheme 79 Deoxygenation of heteroarenes with $Zn(OTf)_2$ or $Cu(OTf)_2$. Reproduced from Saini, A.; Kumar, S.; Sandhu, J. S. *Synlett* **2006**, 395–398, with permission from Thieme.



224 **225**

Scheme 80 Deoxygenation of an imidazolone *N*-oxide with PBr_3. Reproduced from Zhao, H.; Wang, R.; Chen, P.; *et al. Org. Lett.* **2012**, *14*, 1872–1875, with permission from ACS.



226 **227** **228**

Scheme 81 Deoxygenation of nitrones and pyridine *N*-oxides by the Brook rearrangement. Reproduced from Hwu, J. R.; Tseng, W. N.; Patel, H. V.; *et al. J. Org. Chem.* **1999**, *64*, 2211–2218, with permission from ACS.

During the opening of the O–O bond by phosphines, insertion of the phosphorus atom into the O–O linkage leads to the zwitterionic species **239** that may be hydrolyzed to the *syn* diol **240** and phosphine oxide.[144] During this process, the presence of a stabilizing group adjacent to the O–P bond may allow the formation of a carbocation that can furnish the rearrangement product **242** and S_N1 products **243** and **244**.

In the case of a sufficiently flexible zwitterion such as **246**, an S_N2 reaction can occur to deliver cyclic ether **247** (Scheme 84).[145]

One of the drawbacks of the reduction of peroxides with a stoichiometric amount of phosphine is the formation of a phosphine oxide that may be difficult to separate from the desired products. Therefore a method catalytic in triphenylphosphine has been developed.[146] The triphenylphosphine is regenerated by reduction of the triphenylphosphine oxide by a titanium hydride generated from titanium alkoxide and siloxane (Scheme 85).

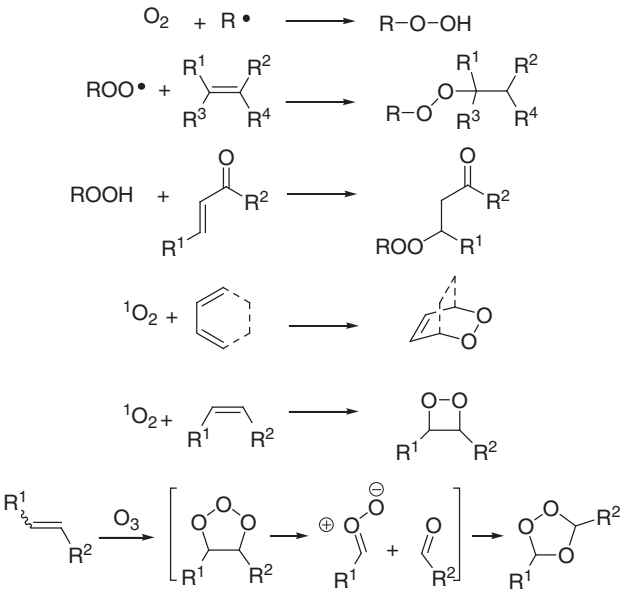
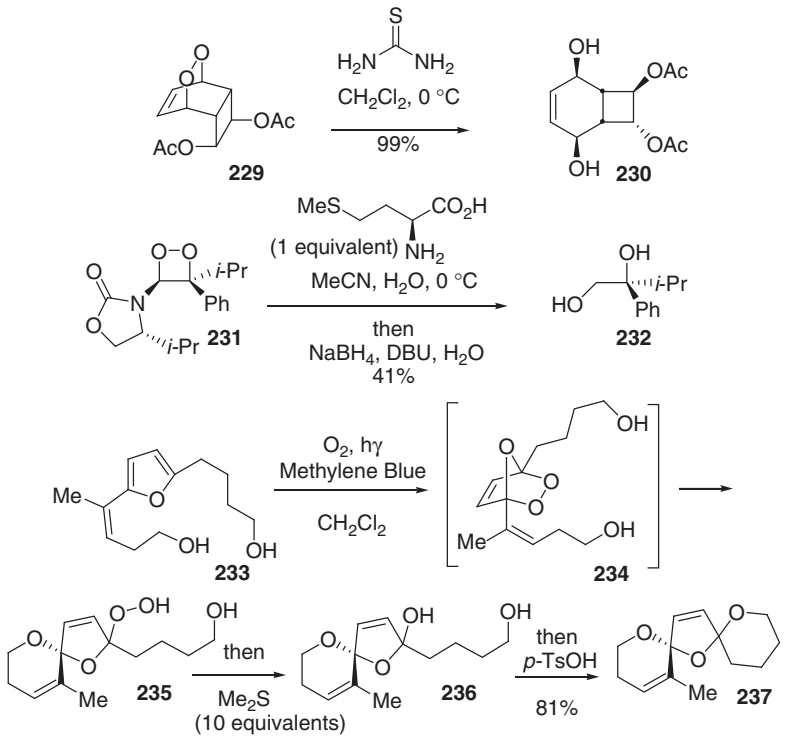
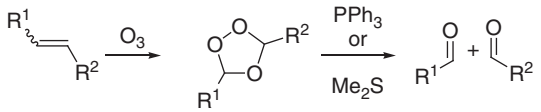


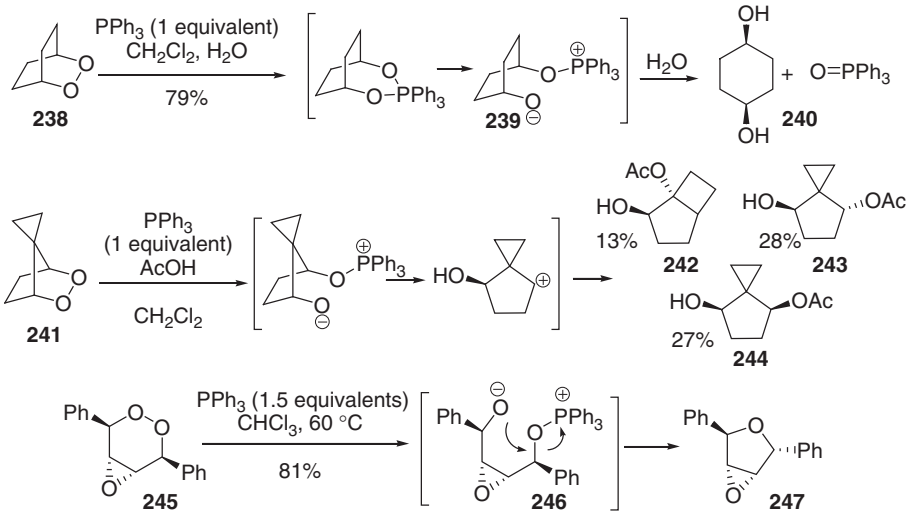
Figure 7 Examples of synthesis of O–O bond-containing compounds.



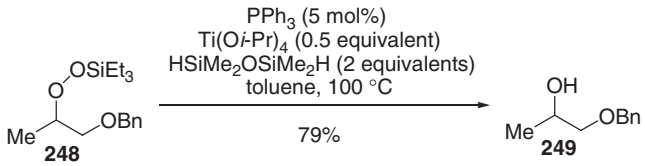
Scheme 82 Reduction of O–O bonds with sulfur-containing compounds.



Scheme 83 Reduction of ozonides with PPh_3 or Me_2S.



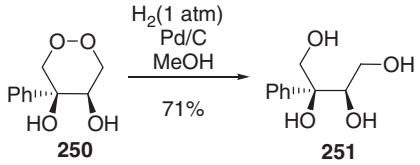
Scheme 84 Reduction of O–O bonds with phosphorus-containing compounds.



Scheme 85 Reduction of O–O bonds with a catalytic amount of PPh_3.

8.14.5.2 Reduction by Hydrogenation

As for the reduction of N–O bonds, hydrogenation over palladium on charcoal is one of the most popular methods to achieve the reductive opening of the O–O linkage as demonstrated in the synthesis of tetraol derivative **251**.[147] However, it is incompatible with the presence of double bonds or benzyl ethers (Scheme 86).



Scheme 86 Reduction of O–O bonds by hydrogenation.

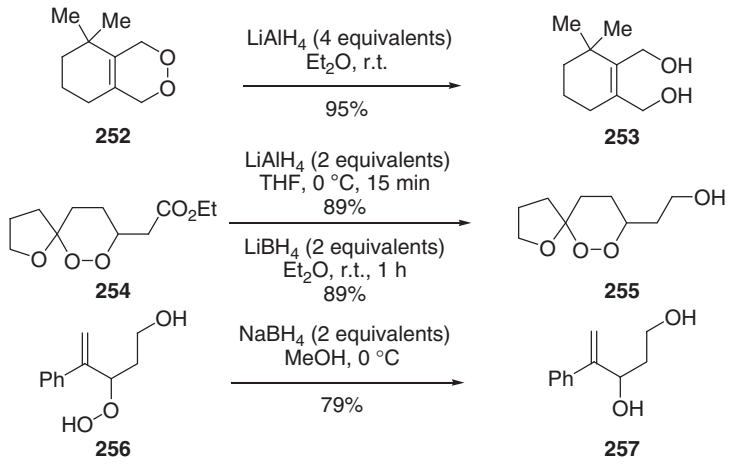
8.14.5.3 Reduction with Hydrides

Lithium aluminum hydride is able to reduce dialkyl perodide **252** efficiently into diol **253**.[148] However, it is possible to control the conditions to achieve the chemoselective reduction of an ester over the peroxy bond in **254**.[149] Hydroperoxide **256** could be reduced to alcohol **257** with the less reactive hydride $NaBH_4$ (Scheme 87).[150]

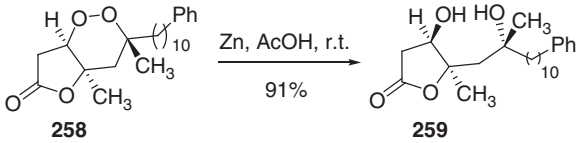
8.14.5.4 Reduction with Low-Valent Metals

Zinc in acetic acid is able to cleave O–O bonds as in **258** at room temperature, in contrast with N–O bonds for which heating is required (Scheme 88).[151]

Alternatively, reduction with magnesium in methanol offers mild conditions for acid-sensitive substrates like peroxyacetal **260**. The hindered dialkyl peroxide **262** is also reduced efficiently in these conditions, in contrast with Me_2S or PPh_3 that are unable to

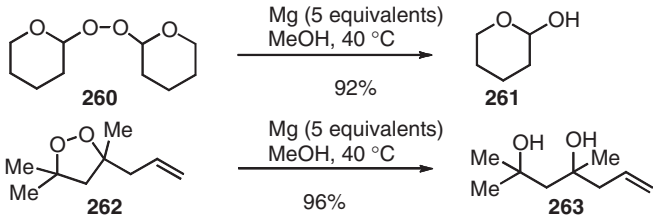


Scheme 87 Reduction of O–O bonds with hydrides.



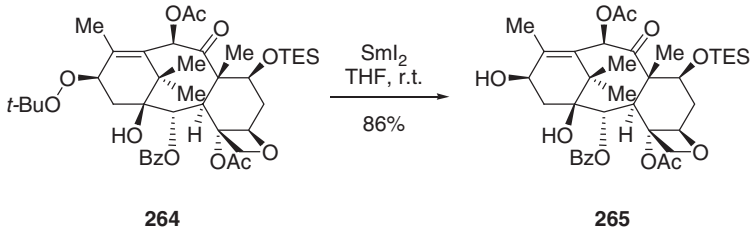
Scheme 88 Reduction of O–O bonds with Zn/AcOH.

achieve this reduction (Scheme 89). Double bonds or benzyl ethers or benzylamines are compatible with magnesium and zinc reductive conditions.



Scheme 89 Reduction of O–O bonds with Mg/MeOH.

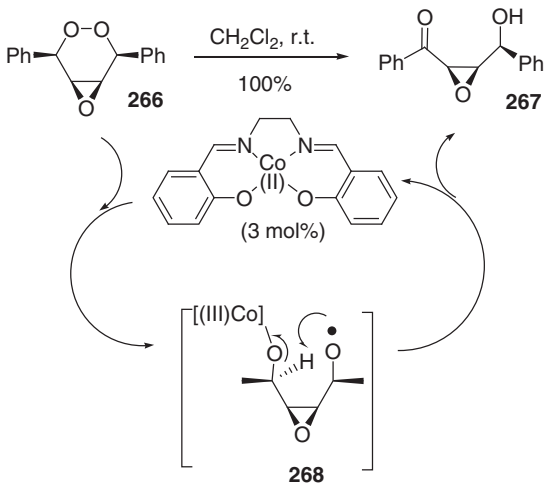
Although less commonly employed than for N–O bonds, SmI_2 is also able to induce the cleavage of O–O bonds. Very interestingly, the dialkyl peroxide **264** is transformed chemoselectively into taxol derivative **265** in the presence of several sensitive functional or protecting groups, whereas several hydride reagents were unselective and Me_2S or PPh_3 were unsuccessful (Scheme 90).



Scheme 90 Reduction of O–O bonds with SmI_2.

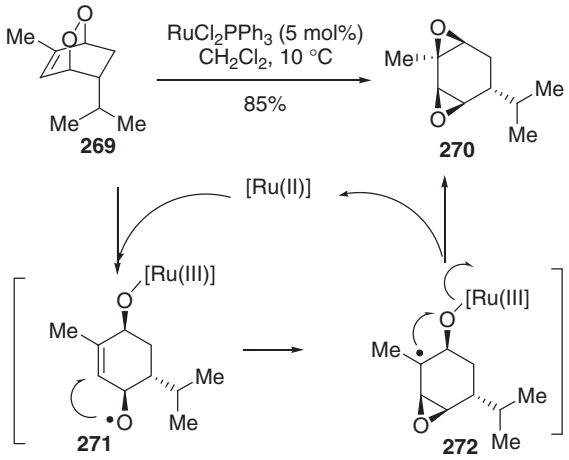
The reaction of peroxide **266** with a cobalt(II) catalyst led to the 1,4-hydroxyl ketone **267**.[152] Single electron transfer from cobalt(II) to the oxygen led to intermediate **268** that contains an O–Co(III) bond and an oxygen-centered radical that undergoes a

1,5 hydrogen abstraction to lead to **267** and the regenerated Co(II) catalyst (Scheme 91). Asymmetric ring opening of *meso* peroxides can be achieved with chiral cobalt catalysts.



Scheme 91 Cleavage of O–O bonds with a Co(II) catalyst.

In a similar manner, the treatment of bicyclic peroxide **269** with a Ru(II) catalyst deliver the bis-epoxide **270** via an oxygen-centered radical **271** that adds to the double bond to form the first epoxide. Addition of the resulting carbon radical **272** to the Ru(III)-O bond delivers the second epoxide with regeneration of the Ru(II) catalyst (Scheme 92).[153]



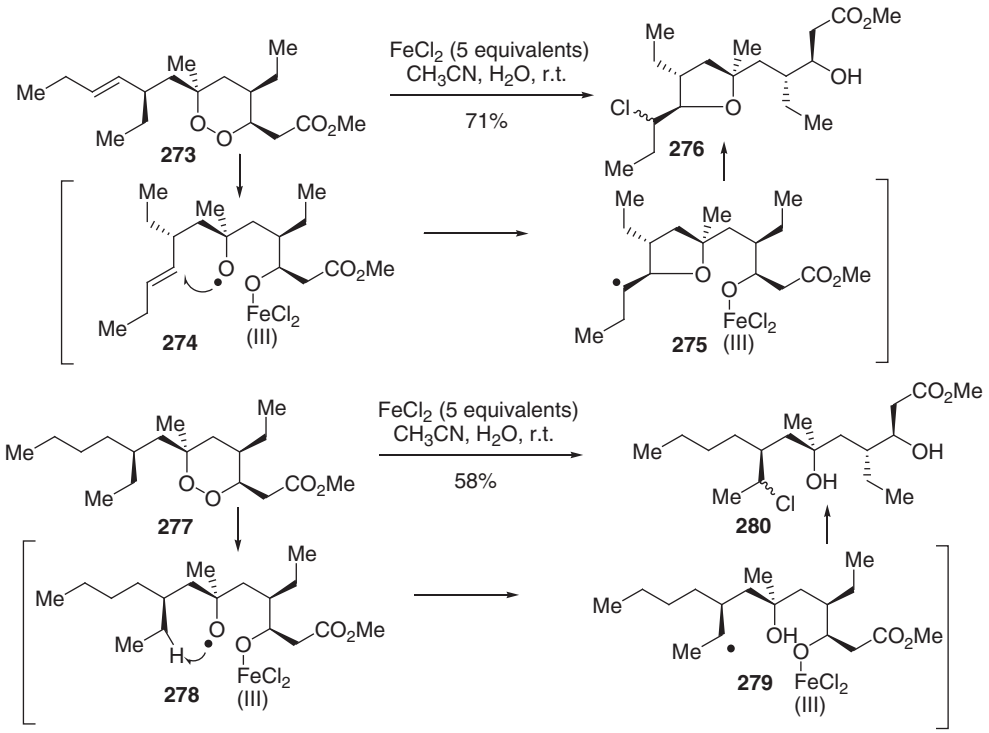
Scheme 92 Cleavage of O–O bonds with a Ru(II) catalyst.

Reduction of the endoperoxide of the antimalaria drug artemisinin by Fe(II)-heme accounts for the biological activity of this natural product. In fact, iron(II) salts are able to reduce O–O bonds. Interestingly, the reaction of plakortin **273** with $FeCl_2$ leads to the one electron reduction of the O–O bond with the formation of an oxygen anion linked to Fe(III) and an oxygen radical that adds to the double bond in proximity to deliver tetrahydrofuran **276**.

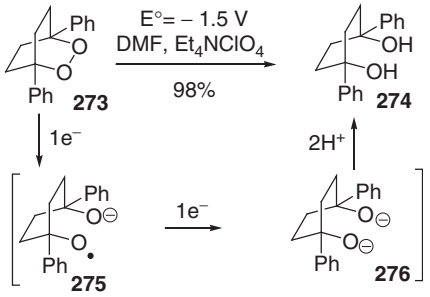
With dihydroplakortin **277**, 1,5 hydrogen shift from the oxygen-centered radical **278** leads to carbon radical **279** that evolves to the chlorodiol **280** (Scheme 93).[154]

8.14.5.5 Electrochemical Reduction

Reduction of O–O bonds can also be achieved with via electrochemistry. Electrolysis of **273** at a constant potential of -1.5 V afforded the diol **274**.[155] Electron transfer at the electrode led to dissociation of the O–O bond and to radical anion **275**. A second electron transfer at the electrode delivers diol **274** (Scheme 94).



Scheme 93 Cleavage of O–O bonds with $FeCl_2$.



Scheme 94 Electrochemical reduction of O–O bonds.

8.14.5.6 Homolytic Cleavage

Acyl peroxides are commonly used as radical initiators since the weak O–O bond can undergo homolytic cleavage under mild heating to generate two acyloxy radicals. Loss of carbon dioxide results in the formation of the more stable carbon radical that can promote radical chain reactions (Figure 8).[156]

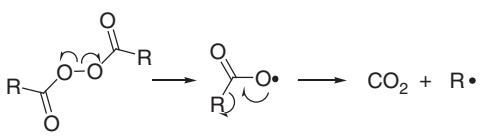
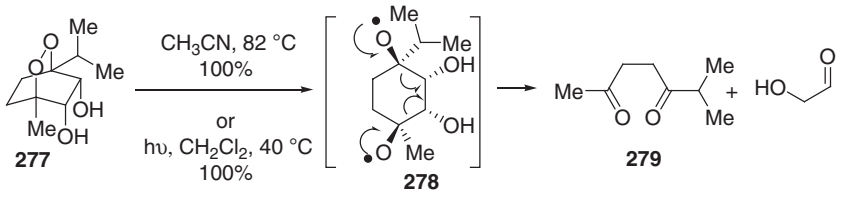


Figure 8 Homolytic cleavage of O–O bonds for the generation of radical promoters.

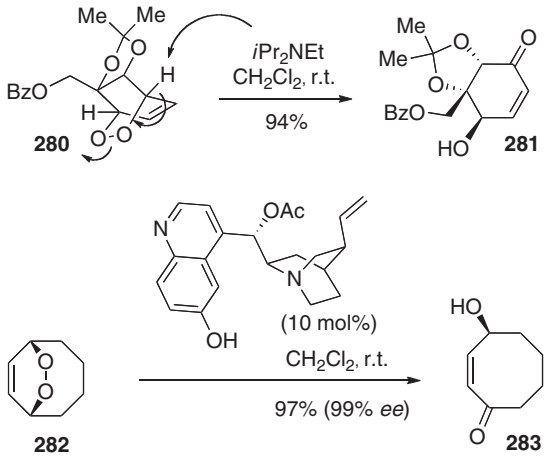
Mild heating or photolysis of the dioxabicyclo[2.2.2]octanediol **277** involves the homolytic cleavage of the O–O linkage with formation of the bi-radical species **278** followed by β-scission to generate the 1,4-diketone **279** (Scheme 95).[157]



Scheme 95 Homolytic cleavage of O–O bonds for the generation of 1,4-diketones.

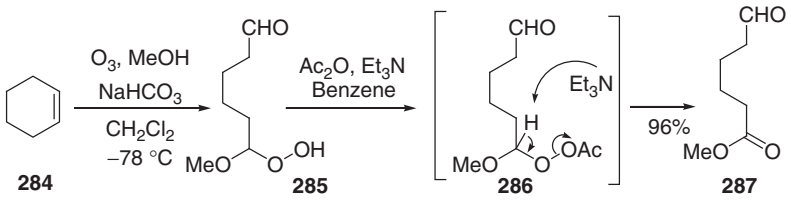
8.14.5.7 Elimination Reactions

Endoperoxides may react with weak bases such as tertiary amines to induce the formation of 4-hydroxyenones via abstraction of one of the protons α to the peroxide with subsequent opening of the O–O bond. Usually the hindered base deprotonates the more accessible proton as in compound **280**.[158] Interestingly, it is possible to desymmetrize bicyclic endoperoxides such as **282** into highly enantioenriched 4-hydroxyenones **283** with the use of a catalytic amount of a cinchona alkaloid-derived tertiary amine (Scheme 96).[159]



Scheme 96 Cleavage of O–O bonds via elimination.

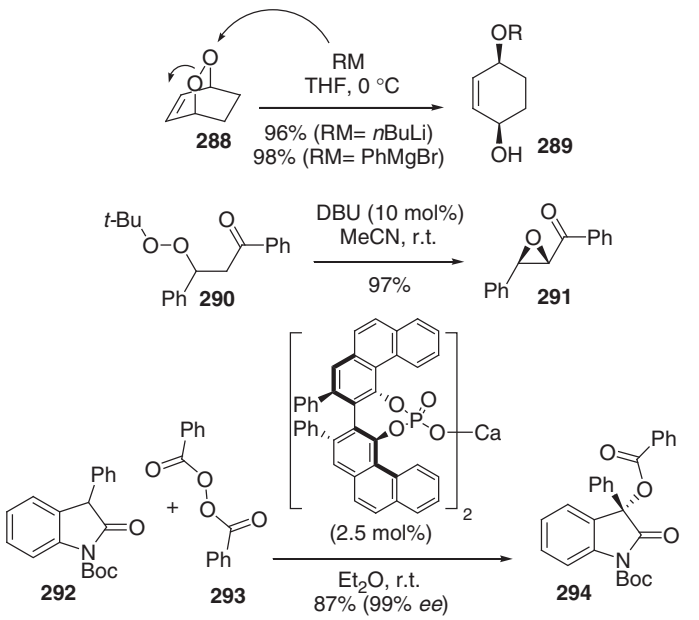
In the ozonolysis of cyclohexene, two terminal different functional groups can be obtained. Ozonolysis with methanol affords α-methoxy hydroperoxide **285**, which after treatment with acetic anhydride and triethylamine delivers aldehyde-ester **287** with elimination of acetic acid (Scheme 97).[160]



Scheme 97 Conversion of α-methoxy hydroperoxides into esters.

8.14.5.8 Nucleophilic Substitutions

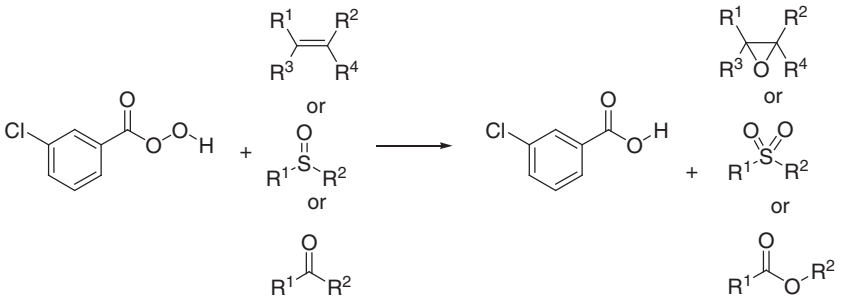
In contrast to the elimination reaction described earlier, the use of a strong nucleophile such as organolithium and Grignard reagents results in the direct attack of the peroxide linkage to give hydroxyl ethers such as **289**.[161] Enolate derivatives could also attack the O–O bond directly to yield epoxide **291**.[162] Enantioselective introduction of an oxygen-based functional groups with peroxides to enol derivatives is possible with a chiral catalyst as in **294** (Scheme 98).[163]



Scheme 98 Cleavage of O–O bonds via nucleophilic substitution.

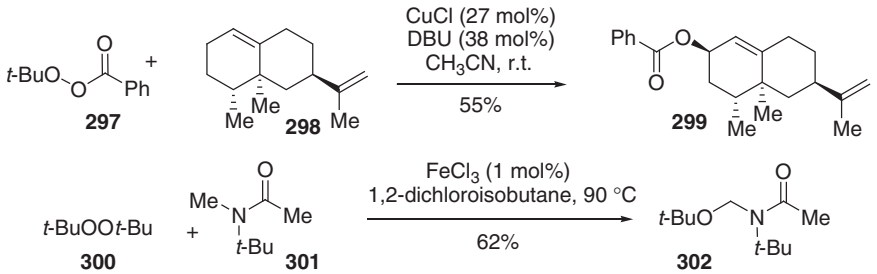
8.14.5.9 Oxidative Reactions with Peroxides

Several O–O bond-containing reagents are known to realize oxidative reaction via the transfer of one of their oxygens. *m*CPBA is a very popular reagent for the oxidation of alkenes into epoxides, sulfoxides into sulfones, or Baeyer–Villiger oxidations with recovery of the corresponding benzoic acid (Scheme 99).



Scheme 99 Oxidative reactions with *m*CPBA.

Addition of one of the oxygen atoms of a peroxide reagent to activated C–H bonds with a copper or iron catalyst proceeds via a radical pathway to deliver compounds **299**[164] and **302** (Scheme 100).[165]



Scheme 100 Oxidation of C–H bonds with peroxides.

In conclusion, the development of modern methods for heteroatom–heteroatom bond cleavage has contributed to solve the crucial issue of chemoselectivity in the reactions of highly functionalized substrates. Compounds bearing functional groups such as azides, oximes, hydrazines, or peroxides may be now routinely used as substrates for various chemical transformations en route to the synthesis of complex synthetic targets.

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8.15 Reduction of S=O and SO_2 to S, S–X to S–H, and P=O to P

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Glossary

Enantiomeric excess The excess of one enantiomer over the other in a mixture. It is used as one of the indicators of the success of an asymmetric synthesis. As a representative, for example, a mixture of two enantiomers in 86:14 ratio corresponds to an enantiomeric excess of 72% (72% *ee*). *Ee* values are ranging from 0% (racemic mixture) to 100% (enantiopure compound).

Ionic liquid A salt comprising an organic cation (such as an imidazolium or a pyridinium ion) and an inorganic or organic anion (e.g., C^-, Br^-, PF_6^-, or BF_4^-), which is liquid around room temperature. It offers a greener alternative to the classical solvents.

Resolution Any process leading to the separation of enantiomers, in general from a racemic mixture. A kinetic resolution is defined as a process where the two enantiomers are transformed to products at different rates. If the kinetic resolution is efficient, one enantiomer is converted into the desired product, while the other is recovered unchanged.

Sulfurane A common name for any hypervalent sulfur compound, of general formula SR_n (n=4 or 6). The valence of the sulfur atom has been expanded beyond the normal octet to a dectet or dodecet, respectively. The term σ-sulfurane is limited to the pentacoordinated SR4 species, the sulfur center possessing

four ligands and one lone pair of electrons. Such compounds adopt a trigonal bipyramidal structure, in which the lone pair always lies in an equatorial position.

Turnover frequency An additional way to quantify the catalyst activity in organometallic catalysis. The turnover frequency (TOF) – borrowed from enzyme catalysis – is related to the turnover number (TON) factor, but it includes a time factor. For example, the transformation of 20 mmol of substrate to the product using a catalyst loading of 0.1 mmol (TON of 200) in 2 h corresponds to a TOF of 100 h^{-1}. For most industrial applications, the TOF is in the range 10^{-2}–10^{2} s^{-1}.

Turnover number A measure of the catalyst activity in organometallic catalysis. The turnover number (TON) – originating from the field of enzymatic catalysis – corresponds to the number of moles of substrate that a mole of catalyst can convert before becoming inactivated. For example, the full transformation of 20 mmol of substrate to the desired product using a catalyst loading of 0.1 mmol corresponds to a TON of 200 (20/0.1). For industrial applications, the TON is in the range 10^{6}–10^{7}.

8.15.1 Introduction

This chapter describes procedures for the reduction of sulfur- and phosphorus-centered functional groups. It updates the review of Still published in the previous edition of Comprehensive Organic Synthesis, which included references as recent as 1989.[1] The material has been organized on the basis of the nature of the substrate and the type of reducing agent, rather than on the mechanism of the process.

The first section is dedicated to the reduction of S=O and related functional groups, most attention being paid to sulfoxides. Methods for the reduction of sulfones and sulfonic acid derivatives are then described. A brief paragraph also concerns sulfilimines and sulfoximines, the nitrogen analogs of sulfoxides and sulfones, respectively. Next comes the transformation of S–X compounds into the parent S–H derivatives, thus covering the reactivity of disulfides, thioesters, and thiocyanates. The final part focuses on the reduction of P=O containing compounds and deals mainly with the conversion of phosphine oxides into phosphines.

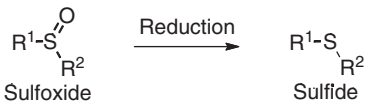
Firouzabadi published in 2008 a monograph dedicated to the reduction of various oxygenated organosulfur compounds.[2] Kudzin surveyed in 2007 reductive applications of the trifluoroacetic-sodium iodide system, and various sulfur-containing compounds were involved.[3] Kukushkin gave an overview of the reduction of coordinated sulfoxide ligands and metal-ion mediated processes in 1995.[4] In contrast, no specific review for the reduction in the phosphorus series has been published.

8.15.2 Reduction of S=O and Related Functional Groups

8.15.2.1 Reduction of Sulfoxides

8.15.2.1.1 General considerations

The reduction of sulfoxides into their corresponding sulfides is an important organic and biological reaction (equation 1). Simple reductive cleavage of the polarized S–O bond (deoxygenation) leading to the analogous thioether will be covered in this section. Other reductive pathways leading to a reduced sulfur center with modification of the carbon chains, such as, for example, the Pummerer rearrangement, will not be included. Furthermore reduction of other chalcogenide species (selenoxides and telluroxides) is excluded.



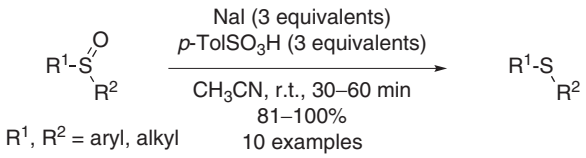
(1)

Most efforts in the area during the last 20 years focused on the development of mild and general procedures which tolerate the presence of various sensitive and/or reducible functional groups. A wide range of simple substrates is generally tested, including diaryl ($R^1=R^2=$aryl), aryl–alkyl ($R^1=$aryl, $R^2=$alkyl), and dialkyl ($R^1=R^2=$alkyl) structures. The scope of the process is examined through variation of electronic and steric properties of the precursors. Even if optimization of the protocols is generally performed with diphenyl ($R^1=R^2=$Ph) or phenyl methyl ($R^1=$Ph, $R^2=$Me) sulfoxides, deoxygenation of the dibenzyl compound ($R^1=R^2=$Bn) serves often as a diagnosis of efficiency, since most methods either fail completely, or only provide poor yields of dibenzyl sulfide. Suggested mechanisms generally involve covalent bond formation between the oxygen atom of the substrate and various electrophilic reagents or activation with a Lewis acid or an oxophilic transition metal complex. The following step often involves mainly an intra- or intermolecular nucleophilic reduction or a single electron transfer to the low-lying σ^* orbital of the S–O bond initiated by metal complexes with low ionization potentials.

Finally, we classify the various reported procedures according to the nature of the reducing agents involved. This classification is necessarily arbitrary in places with certain reducing systems, especially those involving *d*-block transition metal complexes with a coreagent.

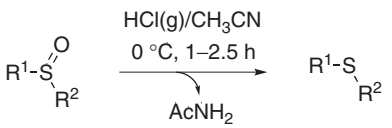
8.15.2.1.2 Reduction with halide ions in acidic medium

The use of halide ions (bromide or iodide) in an acidic medium is a convenient means for the reduction of sulfoxides into their corresponding sulfides. Protonation of the sulfoxide, giving rise to a reactive hydroxysulfonium salt, is undoubtedly the initial step of the reaction. Drabowicz described a general process involving a sodium iodide–sulfonic acid system (equation 2).[5] The reduction is instantaneous (<1 min) with trifluoromethanesulfonic or chlorosulfonic acids as activator. Longer reaction times are required with *p*-toluenesulfonic acid, but do not exceed 1 h. A solid-state protocol with the same reagents has also been developed.[6]



(2)

The group of García Ruano unexpectedly discovered that reduction could also be carried out simply in an HCl(g) saturated solution of acetonitrile (equation 3).[7] The mechanistic proposal, in agreement with the isolation of acetamide from the reaction media, suggests an initial nucleophilic attack of the sulfinyl oxygen atom on the protonated nitrile group.



R^1	R^2	Yield
p-Tol	Me	85%
Ph	Ph	91%
Bu	Bu	82%

(3)

Tetrabutylammonium iodide[8] and bromide[9] are both used in a trifluoroacetic acid solution to reduce the methionine sulfoxide residues of peptides. Significant improvements were observed with the addition of a sulfide or thiol (dimethyl sulfide, thioanisole, ethane-1,2-dithiol) as halogen scavenger.

Various solvent-free conditions involving supported acids were also reported. Silica chloride (SiO_2-Cl), prepared by treatment of silica gel with thionyl chloride, was also described as an efficient heterogeneous system.[10] For example, diphenyl sulfoxide (diluted in CH_2Cl_2) was converted into the parent sulfide in a 91% yield in less than 5 min. Sulfuric acid–silica gel (H_2SO_4–silica) is an alternative reagent, benzyl DABCO bromide being used as the halide source.[11]

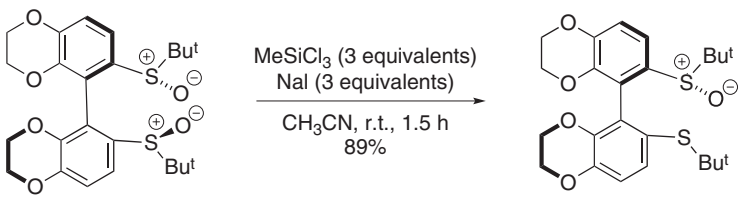
8.15.2.1.3 Reduction with silicon reagents

8.15.2.1.3.1 Reduction with silyl hydrides

Protocols of high synthetic value have emerged during the last 5 years, with the use of silyl hydrides in the presence of a catalytic amount of a metal complex. Most contributions arise from independent work of Fernandes and Enthaler. These processes are inspired by deoxygenation reactions performed in nature by enzymes such as dimethyl sulfoxide, biotin sulfoxide, and methionine sulfoxide reductases. Among the silyl hydrides tested, phenylsilane ($PhSiH_3$) is the most commonly encountered. Inexpensive polymethylhydrosiloxane (PMHS) is also an alternative reagent but is less efficient (requiring higher loading and temperature). Numerous oxophilic metal complexes have been used as efficient catalysts, including molybdenum[12] [MoO_2Cl_2, $MoO_2Cl_2(H_2O)_2$, $Mo_2(OBu^t)_6$], rhenium[13] [$ReIO_2(PPh_3)_2$, $HReO_4$], zinc[14] [$Zn(OTf)_2$], and copper[15] [$Cu(acac)_2$] based reagents. Catalytic systems composed of $[Fe_2(CO)_9]$[16] or an iron(II) complex[17] containing an *N*-heterocyclic carbene ligand have recently shown excellent performances. An highly efficient and heterogeneous process involving hydroxyapatite-supported gold nanoparticles (AuHAP) was also reported, with remarkable turnover frequencies and numbers (TOF of 200 h^{-1} and TON of 10,000 with diphenyl sulfoxide as substrate).[18] Inert conditions are generally not required and green protocols using water as solvent were also reported. Representative examples with the optimized conditions are collected in **Table 1**. Mechanistic suggestions have been proposed but need to be confirmed.

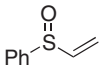
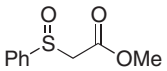
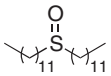
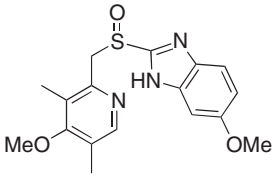
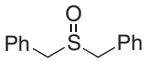
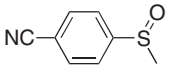
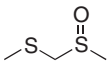
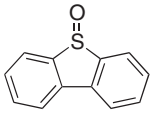
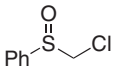
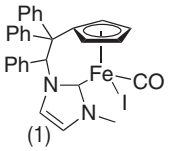
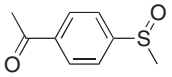
8.15.2.1.3.2 Reduction with halosilanes and related compounds

$MeSiCl_3$ is an attractive electrophilic silane for the reduction of sulfoxides. Zhou recently exploited this reagent with an axially chiral bis-sulfoxide (equation 4).[19] It is noteworthy that semi or full reduction of the sulfinyl moieties can be controlled by adjusting the loading of the reductive system.



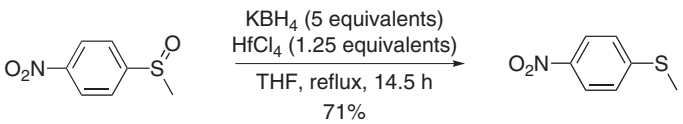
(4)

Table 1 Reduction of sulfoxides with silyl hydrides, in the presence of a metal catalyst

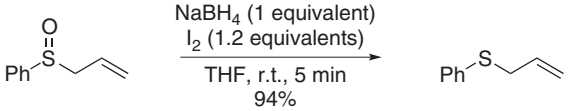
Sulfoxide	*Silane (equivalent)*	*Catalyst (mol%)*	*Conditions*	*Yield (%)*	*References*
	$PhSiH_3$ (1)	MoO_2Cl_2 (5)	THF, reflux, 2 h	92	12a
	PMHS (0.3)	$MoO_2Cl_2(H_2O)_2$ (5)	MeOH, reflux, 20 h	90	12a
	$PhSiH_3$ (1)	$Mo_2(OBu^t)_6$ (1)	THF, r.t., 1 h	83	12b
	$PhSiH_3$ (1)	$ReIO_2(PPh_3)_2$ (5)	CH_2Cl_2, r.t., 3 h	51	13a
	$PhSiH_3$ (1.20)	$HReO_4$ (5)	THF, r.t., 1.5 h	92	13b
	$PhSiH_3$ (1.1)	$Zn(OTf)_2$ (5)	Toluene, 100 °C, 24 h	95	14
	Ph_2SiH_2 (1.1)	$Cu(acac)_2$ (5)	Toluene, 100 °C, 12 h	86	15
	$PhSiH_3$ (1)	$Fe_2(CO)_9$ (5)	Toluene, 100 °C, 24 h	97	16
	$PhSiH_3$ (2)	 (1)	$AgBF_4$ (1 mol%), toluene, 100 °C, 6 h	96	17
	Me_2PhSiH (1)	AuHAP (1.6 Au)	1,4-Dioxane, 30 °C, 6 h, Ar	92	18

8.15.2.1.4 Reduction with boron reagents

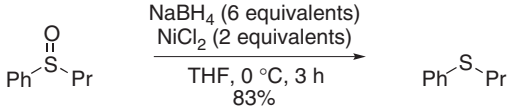
Boron derivatives have been frequently used to reduce sulfoxides to sulfides. Boron hydrides, such as sodium or potassium borohydride, are the most popular reagents. However, their reactivity has to be enhanced by carrying out the reaction in the presence of additives. For example, $KBH_4/HfCl_4$,[20] $NaBH_4/I_2$,[21] and $NaBH_4/NiCl_2$[22] combinations have been used as efficient reducing systems (equations 5–7). In the latter case, a nickel boride is probably the active species involved in the process. A heterogeneous protocol with $NaBH_4/CoCl_2 \cdot 6H_2O$ and moist alumina was also described but a high substrate dependency was observed (equation 8).[23]



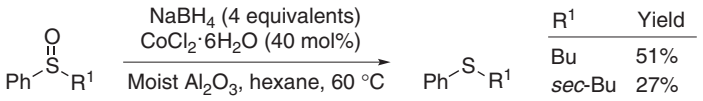
(5)



(6)

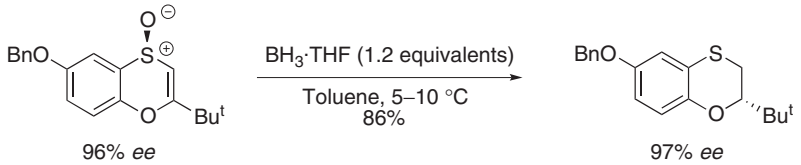


(7)



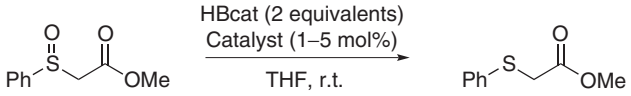
(8)

Borane species are also efficient reagents. A nice synthetic application of $BH_3 \cdot THF$ complex is reported starting with an enantiopure vinylic sulfoxide (equation 9).[24] Reduction of both the alkene moiety and the sulfur center occurred, thus furnishing a 2-substituted-1,4-dihydrobenzoxathiin. Furthermore, the configuration of the asymmetric carbon generated was totally controlled, as a result of a remarkable instance of asymmetric induction by the sulfinyl group. The transfer of the borane from THF to the sulfoxide is probably the rate-determining step of the reaction.



(9)

A gentle, efficient, and selective approach for the deoxygenation of sulfoxides to their corresponding sulfides with catecholborane (HBcat) has also been described, side-products being dihydrogen and the diboron compound catBOBcat (equation 10).[25] Although deoxygenation of bulky or electron-withdrawing sulfoxides is slow, the reaction can be greatly accelerated with the use of an excess of catecholborane or by employing transition metal catalysts such as rhodium[25] [$RhCl(PPh_3)_3$], rhenium[13b,26] [$HReO_4$, $ReIO_2(PPh_3)_2$, Re_2O_7, $MeReO_3$], or molybdenum[27] [$MoO_2Cl_2(H_2O)_2$] complexes. Reactions proceeded in this case cleanly with low catalyst loadings (1–5 mol%) and are remarkably rapid with the oxo-rhenium species. Representative results obtained for the reduction of the sulfinyl ester are collected in **Table 2**. It is noteworthy that reactions performed with a sulfoxide incorporating an alkene or alkyne moiety showed perfect chemoselectivity in favor of the sulfur center, without detection of hydroboration products. DFT calculations were performed with the system based on $ReIO_2(PPh_3)_2$ and a catalytic cycle was suggested.

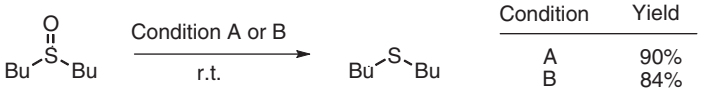


(10)

Table 2 Reduction with HBcat in the presence of an oxo-metal catalyst according to equation 10

Catalyst (mol%)	*Time*	*Yield (%)*	*References*
$HReO_4$ (5)	5 min	98	13b
$ReIO_2(PPh_3)_2$ (1)	5 min	90	26
Re_2O_7 (1)	5 min	91	26
$MeReO_3$ (1)	5 min	91	26
$MoO_2Cl_2(H_2O)_2$ (5)	16 h	85	27

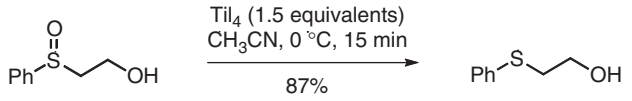
Dibromoborane dimethyl sulfide[28] ($Br_2BH \cdot SMe_2$) and boron triiodide-*N*,*N*-diethylaniline[29] [$I_3B \cdot NEt_2Ph$] complexes are also suitable reagents to induce an efficient deoxygenation of sulfoxides under mild conditions (equation 11).



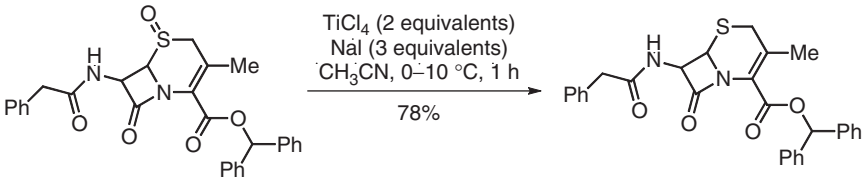
(11)

8.15.2.1.5 Reduction with titanium reagents

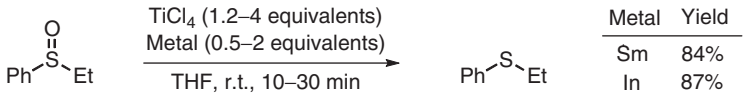
TiI_4 was shown to be an excellent reagent for the deoxygenation of sulfoxides, as depicted in equation 12 with a β-hydroxy sulfoxide.[30] The parent and more common chloro derivative $TiCl_4$ is an alternative (equation 13). The addition of sodium iodide[31] or metals such as samarium[32] or indium[33] is, however, required, generating a reactive low-valent titanium intermediate (equation 14).



(12)

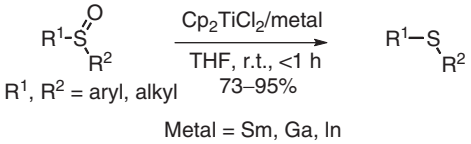


(13)



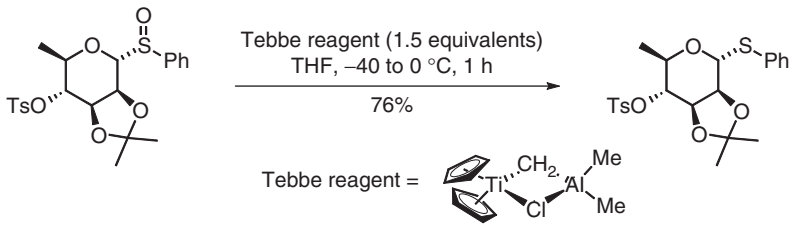
(14)

Bis(cyclopentadienyl)titanium dichloride (Cp_2TiCl_2) has also received particular attention for redox pathways (equation 15). The presence of metallic additives such as samarium,[34] gallium,[35] or indium[36] powder is again crucial to generate the Ti^{II} or Ti^{III} active species *in situ*.



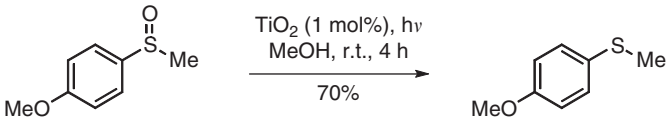
(15)

Simple treatment of sulfoxides with $Cp_2Ti(CO)_2$ can also furnish the corresponding thioethers.[37] For example, a stoichiometric amount of this reagent furnished dibenzyl sulfide in 93% yield after 6 h of reaction in refluxing THF. More recently, Nicolaou reported a very nice protocol mediated by titanocene–methylidene complex [$Cp_2Ti{=}CH_2$] generated *in situ* from Tebbe reagent (equation 16).[38] A wide range of diaryl, aryl–alkyl, and dialkyl sulfoxides was readily reduced (<3 h) in good to excellent yields at low temperatures (–40 to 0 °C). Functional tolerance is remarkably broad, including, for example, compatibility with epoxides, phosphine oxides, ketones, and also various acetal, silyl, benzyl, THP, and tosyl protective groups. An exception for chemoselectivity concerns, however, carbonyl group of aldehydes, amides, and esters, for which methylenation could not be avoided. The protocol was successfully applied to highly functionalized sulfoxide-containing sugars, as exemplified in equation 16. Petasis reagent Cp_2TiMe_2 was also successfully employed as another source of [$Cp_2Ti{=}CH_2$], despite longer reaction times and a higher temperature (12 h, 60 °C).[38] Mechanistic investigations revealed that [$Cp_2Ti{=}CH_2$] is the active Ti^{IV} species, which then initiates an unprecedented carbene reduction process.



(16)

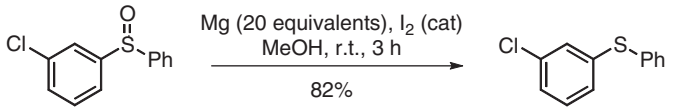
Srinivasan also described an original photodeoxygenation route.[39] Irradiation with a UV lamp ($\lambda = 366$ nm) of a suspension of titanium dioxide (TiO_2) in the presence of sulfoxides furnished the desired thioethers in fairly good yields (equation 17). The proposed mechanism involves the transfer of one electron from the conduction band of the semiconductor to the sulfinyl group.



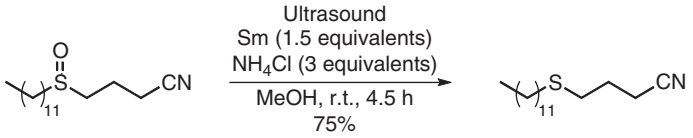
(17)

8.15.2.1.6 Reduction with stoichiometric metal reagents

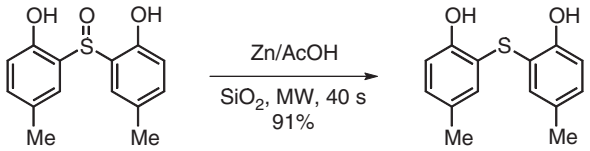
Use of magnesium metal in methanol solution is another reducing method for the reduction of sulfoxides into sulfides. A significant acceleration of the reaction rate is observed with the introduction of 1–2 crystals of iodine (equation 18).[40] A previous report also mentioned the beneficial effect of a catalytic amount of mercuric chloride.[41] Efficient conversions were observed with diaryl, 1-alkenyl-aryl, and benzyl-aryl substrates at r.t. in less than 3 h. In contrast, sulfoxides possessing an alkyl group are almost inert under the same conditions. A single electron transfer from Mg to the substrate is proposed for this transformation. A more general procedure involving the use of lanthanide metal (Sm) in methanolic ammonium chloride and promoted by ultrasound was also described (equation 19).[42] Finally, it was shown that microwave irradiation is particularly efficient with the Zn–AcOH system under solvent-free conditions (equation 20).[43]



(18)

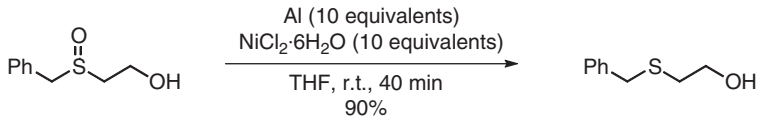


(19)



(20)

Another efficient and highly chemoselective electron transfer process was also described with the $Al/NiCl_2 \cdot 6H_2O$ bimetallic combination in THF (equation 21).[44] A chemoselective reduction is exemplified below with a substrate possessing a hydroxy function.



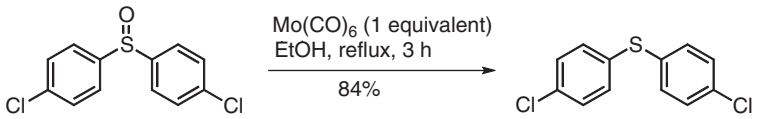
(21)

Other metal–metal salt binary systems have been investigated. Most encountered combinations involve a zinc or indium powder with molybdenum(V) or tungsten(VI) chlorides.[45] Complete conversions were reached in THF at r.t. in less than half an hour, with both aryl and alkyl substrates. Recently, low-valent niobium complexes generated *in situ* from $NbCl_5$ and zinc dust have been successfully used in a substoichiometric amount (0.5 equivalent).[46] An original precedent is offered with the gallium–$MoCl_5$ system, ultrasonic irradiation being necessary for the reaction to go to completion in a reasonable time.[47] Results obtained for the reduction of diphenyl sulfoxide are collected in **Table 3**.

Table 3 Reduction of diphenyl sulfoxide with a metal–metal salt binary system

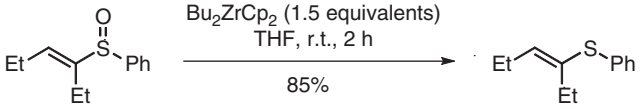
Metal (equivalents)	*Metal ion (equivalent)*	*Conditions*	*Yield (%)*	*References*
Zn (3)	$MoCl_5$ (1)	THF, r.t., 15 min	95	45a
Zn (3)	WCl_6 (0.8)	THF, r.t., 10 min	96	45b
Zn (5)	$NbCl_5$ (0.5)	THF/benzene (1/1), 23 °C, 4.5 h	97	46
In (4)	$MoCl_5$ (2)	THF, r.t., 5 min	92	45c
In (4)	WCl_6 (2)	THF, r.t., 5 min	92	45d
Ga (4)	$MoCl_5$ (2)	THF, r.t., 10 min	92	47

Metal carbonyl $Mo(CO)_6$ is a convenient reagent for the deoxygenation of sulfoxides in refluxing ethanol (equation 22).[48]



(22)

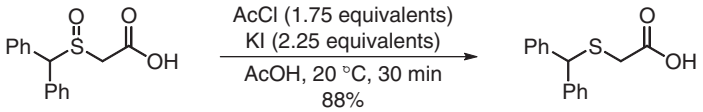
Marek unexpectedly discovered that organozirconium derivative Bu_2ZrCp_2 can also provide a mild deoxygenation of sulfoxides, with concomitant formation of insoluble polymers $[Cp_2Zr{=}O]_n$.[49] Diaryl, aryl–alkyl, and aryl–vinyl substrates were reduced cleanly and efficiently in less than 2 h at r.t. in THF solution. With aryl–vinyl derivatives, configuration of the alkene was retained during the reaction as exemplified with a trisubstituted-vinyl sulfoxide (equation 23). No stereochemical modification occurred when a substrate possessing two stereogenic carbons was tested.



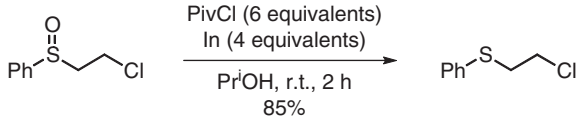
(23)

8.15.2.1.7 Reduction with carbonyl and triflic derivatives

The reductive system based on the use of acetyl chloride and an alkali metal iodide is well-documented in the literature, since the pioneering work of Allenmark. The acyl reagent reacts with the sulfinyl oxygen to generate a sulfonium salt, which is more reactive than the sulfoxide precursor toward reducing agents. Various modafinil derivatives, with potential analeptic properties, bearing a labile benzydryl unit and reducible carbonyl functions, were efficiently converted into their corresponding sulfides using a carefully adapted protocol.[50] For example, 30 g of modafinil acid were reduced in an excellent 88% yield (equation 24). An alternative procedure was also described using pivaloyl chloride in the presence of indium (equation 25).[51]

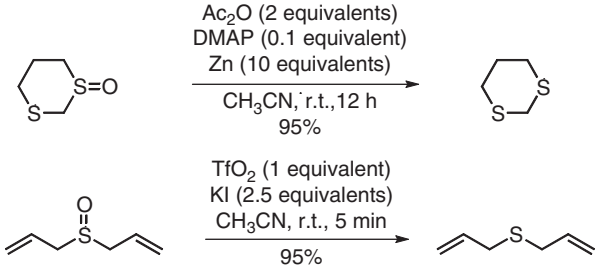


(24)



(25)

Acetic[52] and triflic[53] anhydrides are also suitable sulfoxide activators (Scheme 1). Under the conditions described, competing Pummerer rearrangement products were not detected. The association of oxalyl chloride with tetrabutylammonium iodide is also an efficient approach, a prominent application of which being reported with macrocyclic sulfoxide oligomers.[54] Another protocol inspired by the Swern oxidation was also reported with the oxalyl chloride–triethylamine system.[55] Reduction is effective at low temperature (−78 °C) but in accordance with the mechanistic proposal, the methodology is restricted to α-hydrogen containing sulfoxides.

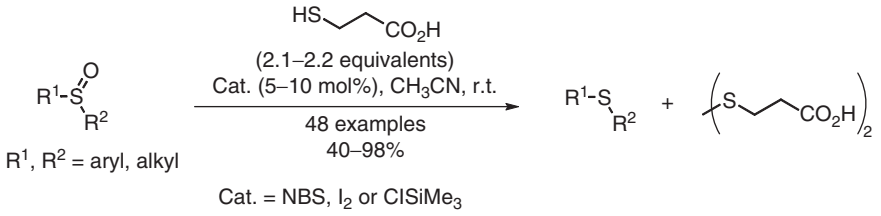


Scheme 1

8.15.2.1.8 Reduction with sulfur compounds

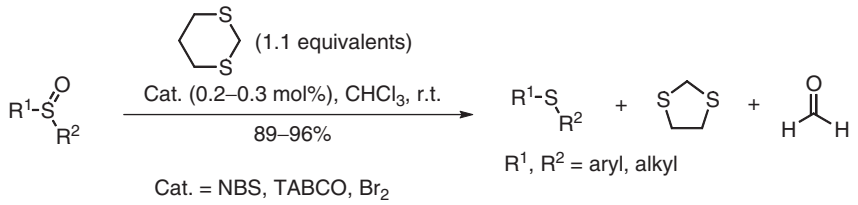
Sulfur-containing compounds have also been applied to the reduction of sulfoxides into their corresponding sulfides. Karimi developed an efficient protocol based on the use of 3-sulfanylpropionic acid (2.1–2.2 equivalents) in acetonitrile as solvent

(equation 26).[56] Introduction of a catalytic amount (5–20 mol%) of *N*-bromosuccinimide (NBS), iodine, and, to a lesser extent, chlorotrimethylsilane strongly accelerates the rate of the process. Interesting features include the mild conditions required (r.t.), reasonably short reaction times and a simple procedure. Moreover, the disulfide by-product possessing two carboxy groups can be easily extracted into the aqueous layer with a basic workup. Recent theoretical studies provided a mechanistic framework for these reductions mediated by thiols that appear in fact to be complicated.[57] A sulfurane intermediate is probably formed in the early steps of the process. *N*-Methyl sulfanylacetamide was also used alone but in large excess (20 equivalents) at the end of a solid-phase synthesis of a nucleopeptide possessing a methionine residue.[58]



(26)

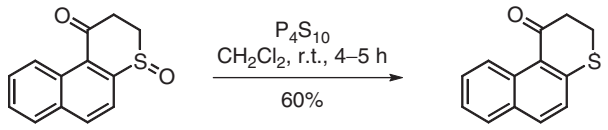
1,3-Dithiane was also successfully employed as an alternative sulfur reagent for the reduction of sulfoxide compounds (equation 27). The addition of an electrophilic bromine source is required and the best results were obtained with 20 mol% of *N*-bromosuccinimide (NBS), 2,4,4,6-tetrabromo-2,5-cyclohexanedione (TABCO), or Br_2.[59] According to the mechanism suggested by the authors and fully supported by additional experiments, formaldehyde and 1,2-dithiacyclopentane are formed as by-products. Removal of this cyclic disulfide is quite straightforward due to a spontaneous conversion into a polymeric derivative on concentration of the reaction mixture.



(27)

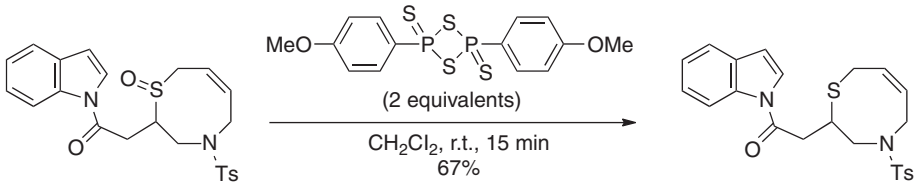
8.15.2.1.9 Reduction with phosphorus compounds

Reduction of sulfoxides to sulfides can also be performed with phosphorus reagents, the thermodynamic driving force being the formation of a very strong P=O bond. Use of P_4S_{10} is a well-established methodology, as exemplified in a review dedicated to the applications of this reagent.[60] The reduction of the sulfinyl group is faster than the thionation of a C=O (equation 28).[61] The reduction mechanism was suggested to involve a Wittig-like intermediate. Elemental sulfur and the phosphorus oxide species are the two side-products produced in stoichiometric amounts.

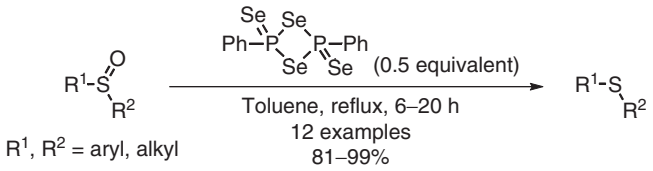


(28)

Lawesson's reagent (LR), another classical thionating agent for carbonyl compounds, has a similar reducing activity toward sulfoxides (equation 29).[62] Quantitative conversion into the corresponding sulfides is observed within 5–60 min in THF or CH_2Cl_2 at r.t. Remarkable chemoselectivity for the sulfinyl center is observed with a sulfoxide possessing an ester function, even when the reaction is carried out at much higher temperatures (refluxing THF or xylenes). In contrast, the temperature has to be controlled for substrates bearing an amide group to observe exclusive sulfoxide reduction. More recently, the selenium counterpart of LR, Woolins' reagent, was also successfully employed but the reaction has to be carried in refluxing toluene (equation 30).[63] During the reaction, the suspension of the reagent in toluene gradually disappears and a yellow solution is formed along with a gray elemental selenium precipitate. A mechanism of the reaction has been proposed according to ^{31}P and ^{77}Se NMR observations.

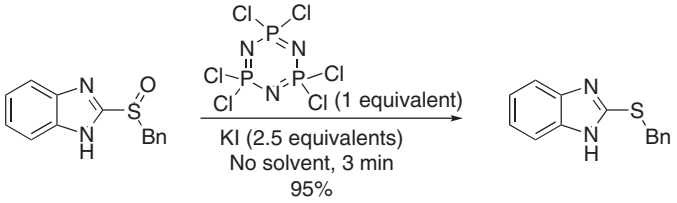


(29)



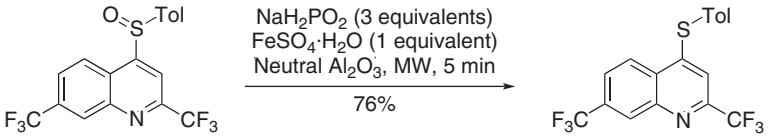
(30)

A precedent involving the phosphazene reagent TAPC (1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride) has also been described (equation 31).[64] The reaction is carried out at r.t. under solvent-free conditions in the presence of an excess of potassium iodide (2.5 equivalents).



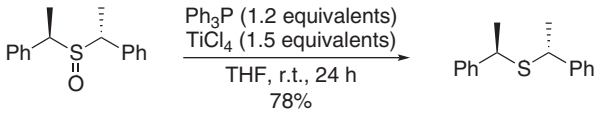
(31)

Reduction of a variety of sulfoxides on neutral alumina was also described using sodium hypophosphite (NaH_2PO_2, 3 equivalents) in combination with $FeSO_4$ (1 equivalent) under microwave activation (equation 32).[65] Irradiation exposure in the range of 3–5 min affords the targeted sulfides in yields above 60%.

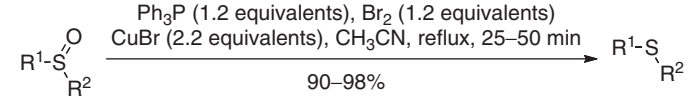


(32)

The deoxygenation of sulfoxides proceeds smoothly in the presence of Ph_3P (1.2 equivalents)/$TiCl_4$ (1.5 equivalents) combination in THF at r.t. (equation 33).[66] Another efficient Ph_3P-based system requiring the use of Br_2 and CuBr in refluxing acetonitrile was also reported (equation 34).[67] Association with a catalytic amount of commercial rhenium complex $ReOCl_2(PPh_3)_2$ (0.05 equivalent) was also particularly efficient in dichloromethane (equation 35).[68] Aryl sulfoxides were cleanly converted into their corresponding sulfide within 1 h at r.t. In contrast, alkyl species were distinctly more robust and an elevation of the temperature to 40 °C (refluxing CH_2Cl_2) is necessary. The molybdenum(VI) oxo-peroxo complex $MoO(O)_2(phox)_2$ (5 mol%) associated to PPh_3 (1.5 equivalents) was also found to be an extremely fast, efficient, and highly chemoselective catalytic system.[69] The reduction of diphenyl sulfoxide in 1,2-dichloroethane is instantaneous at r.t. and the turnover frequency (TOF) value above 1200 h^{-1}.

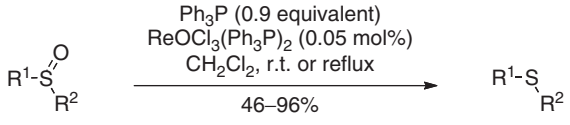


(33)



R^1, R^2 = aryl, alkyl (16 examples)

(34)

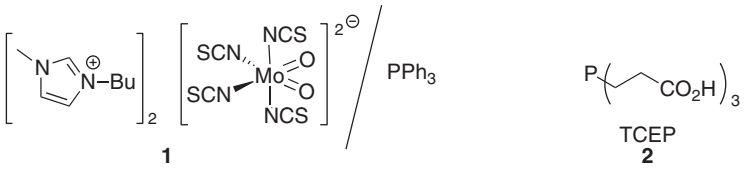


R^1, R^2 = aryl, alkyl (7 examples)

(35)

A reusable and efficient heterogeneous molybdate catalyst **1**, immobilized in [Bmim]PF_6 ionic liquid, was also reported with PPh_3 as reducing agent (**Figure 1**).[70] No loss of catalytic activity was observed after eight cycles with diphenyl sulfoxide as the model substrate. It was also described that triphenylphosphite $(PhO)_3P$ is an excellent promoter under dioxomolybdenum(VI)

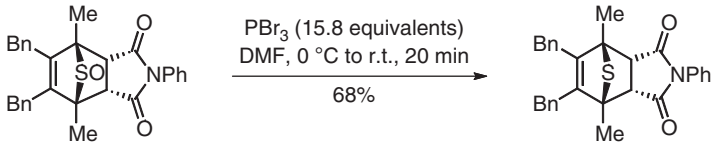
catalysis.[71] A protocol with tris(2-carboxyethyl)phosphine **2** (TCEP) was also mentioned in a 1,4-dioxane–water mixture at reflux (Figure 1).[72] In most of the cases, the addition of iodine (0.5–0.55 equivalent) was beneficial.



1 **2**

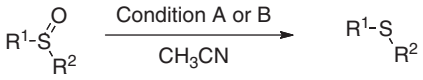
Figure 1 Phosphine-based systems for the reduction of sulfoxides.

Phosphorus(III) halides are also appropriate reducing agents. For example, the highly sensitive sulfinyl bridge of bicyclo[2.2.1]hept-5-ene cycloadducts is cleanly deoxygenated with PBr_3 in a DMF solution at 0 °C to afford the corresponding bridged thioethers (equation 36).[73]



(36)

It was also mentioned that Silphos [PCl_{3-n} $(SiO_2)_n$], readily prepared by treatment of PCl_3 with silica gel, is an efficient and heterogeneous phosphorus reducing reagent (equation 37).[74] The deoxygenation was carried out in the presence of molecular iodine (0.3 equivalent) in refluxing acetonitrile. The parent solid supported reagent derived from $PSCl_3$ was also developed, the reaction occurring this time cleanly and efficiently at r.t.[75]

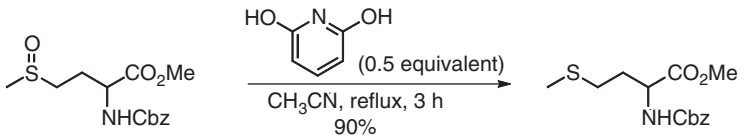


Condition A: [PCl_{3-n} $(SiO_2)_n$], I_2 (0.3 equivalent), reflux, 15 min
88–100% (14 examples)
Condition B: Silica-$PSCl_3$, r.t., 2–8 h
88–94% (11 examples)

(37)

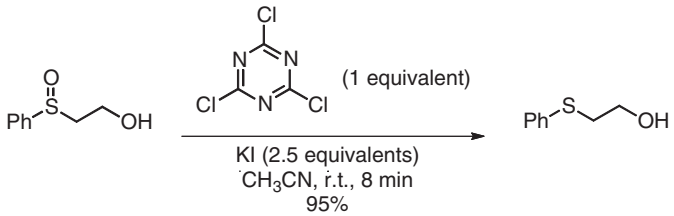
8.15.2.1.10 Reduction with other organic compounds

2,6-Dihydroxypyridine or its hydrochloride salt was also reported as an excellent deoxygenation promoter of sulfoxides.[76] Examination of the stoichiometry of the reaction indicates that the reagent is able to reduce approximately 4 equivalents of the sulfinyl compound in refluxing acetonitrile. Completion was reached in less than 5 h with the four dialkyl substrates investigated, including a methionine derivative incorporating ester and carbamate groups (equation 38). In contrast, the process is much slower in the diaryl series, a yield of only 24% being obtained after 14 h of reaction with diphenyl sulfoxide.



(38)

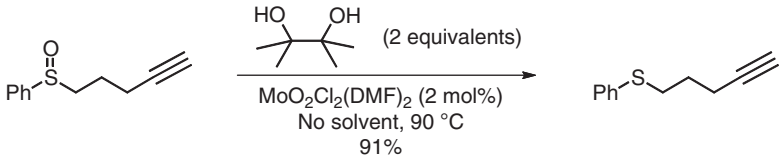
Cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) was also successfully employed in combination with potassium iodide (equation 39).[77] Reduction proceeds efficiently at r.t. in an acetonitrile solution.



(39)

Pinacol was also disclosed very recently as an environmentally benign reducing agent for sulfoxides assisted by readily available dichlorodioxomolybdenum(VI) complexes as catalyst (equation 40).[78] Interesting features include the high functional

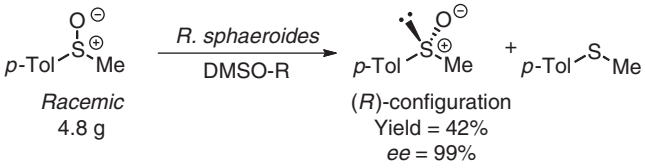
group tolerance, compatibility with solvent-free conditions, ease of scale-up (one example carried out with 9.4 g of substrate), clean reactions and easy purification of the products, acetone and water being the only by-products of this reaction.



(40)

8.15.2.1.11 Reduction with enzymes

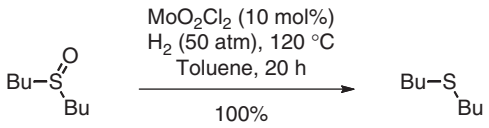
Particular attention has also been paid to enzymatic approaches involving DMSO reductases. This approach was successfully exploited to access enantiopure products, through the kinetic resolution of racemic sulfoxides.[79] Employing intact cells of *Rhodobacter sphaeroides* f. sp. *denitrificans*, Abo described a nice preparative example involving aryl methyl sulfoxides and carried it out up to a 4.8 g scale (equation 41).[79c] (*S*)-Enantiomers are exclusively deoxygenated, whereas enantiomerically pure (*R*)-isomers were recovered in good yield. Extension to a wider range of substrates was then described with an unprecedented electrochemical enzymatic system using a glassy carbon electrode and *N*,*N*-dimethyl-4,4-bipyridinium (methyl viologen) as the mediator.[80]



(41)

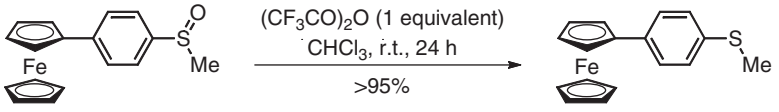
8.15.2.1.12 Miscellaneous

Very recently, oxo-rhenium and -molybdenum complexes, $ReCH_3O_3$, $ReIO_2(PPh_3)_2$, and MoO_2Cl_2, using dihydrogen as reducing agent have also been used to perform the conversion of sulfoxides to sulfides (equation 42).[81] DFT calculations were carried out in the molybdenum series and indicated that activation of H_2 proceeds through addition to the Mo=O bond, followed by hydride migration to yield a water complex.



(42)

The reduction of sulfoxides was also described using ferrocene in the presence of trifluoroacetic anhydride.[82] Quantitative yields were obtained with diaryl compounds, whereas disappointing results were obtained with aryl–methyl derivatives (<34% yield), as a result of a competing Pummerer reaction. However, this approach was successfully applied to a unique methyl sulfoxide possessing a ferrocenyl–aryl moiety (equation 43). A through-bond electron transfer is probably involved in this case.

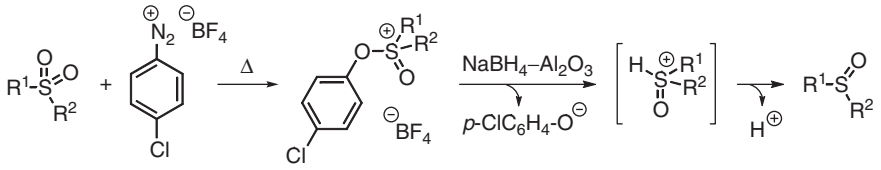


(43)

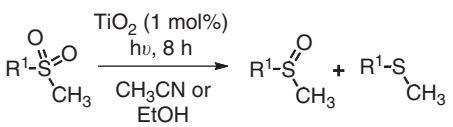
8.15.2.2 Reduction of Sulfones

In spite of a stronger S–O bond in sulfones (112 kcal mol^{-1}) compared to the corresponding sulfoxides (87 kcal mol^{-1}),[83] the reduction can take place, though activation of one of the two sulfone oxygen atoms is generally required. In this context, only two examples have been described for the conversion of sulfones to sulfoxides. Thus, after activation through the formation of an (aryloxy)sulfoxonium salt, diaryl sulfoxides were obtained by hydride reduction with $NaBH_4$–Al_2O_3 (Scheme 2).[84]

Titanium dioxide has been shown to react as an effective photocatalyst in the reduction of alkyl aryl sulfones, leading to sulfoxides as the major products. However, the reduction of dialkyl sulfones furnished sulfides selectively (equation 44).[85]



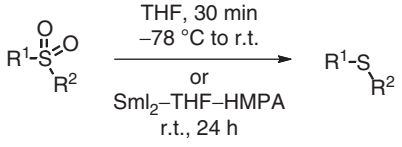
Scheme 2



R^1	Sulfone	Sulfoxide	Sulfide
Ph	2%	89%	9%
p-Et-C_6H_4	2%	89%	8%
Me	7%	2%	80%

(44)

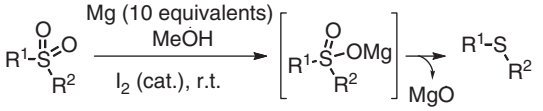
In most of the cases, reduction of sulfones affords the corresponding sulfides. Powerful reducing agents, such as $LiAlH_4$ or $(Bu^i)_2AlH$, and harsh reaction conditions are nevertheless often required. The reactivity can be enhanced using the $LiAlH_4$–$TiCl_4$ system[86] as exemplified in equation 45 and high reproducible yields were reached in a relatively short time (30 min). In comparison, significantly lower yields were obtained with the SmI_2–THF–HMPA combination.[87]



R^1	R^2	$LiAlH_4$–$TiCl_4$	SmI_2–HMPA
Ph	Me	93%	18%
Ph	Ph	80%	23%
p-Me-C_6H_4	Me	81%	<5%
p-MeO-C_6H_4	Me	91%	<5%
p-F-C_6H_4	Me	73%	<5%

(45)

A very efficient reduction of dibenzothiophene sulfone derivatives can be achieved using a large excess of methylmagnesium bromide.[88] A sulfurane intermediate was proposed, resulting from the nucleophilic attack of the Grignard reagent on the sulfur atom. The magnesium–methanol system provided a convenient, mild, and inexpensive method for the deoxygenation of diaryl sulfoxides, via a single electron transfer from Mg to the sulfone (Scheme 3).[40]



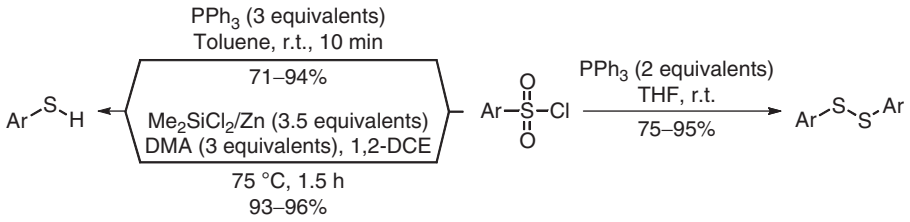
R^1	R^2	Time (h)	Yield
Ph	Ph	1.5	82%
p-MeO-C_6H_4	Ph	3	83%
p-Br-C_6H_4	Ph	2.5	75%
p-Cl-C_6H_4	Ph	3	80%
Ph-CH_2	Ph	3	83%
Ph	*n*-Pr	24	0%

Scheme 3

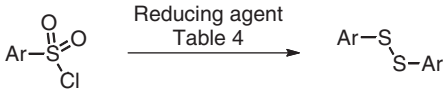
8.15.2.3 Reduction of Sulfonic and Sulfinic Acids and Their Derivatives

The reductive coupling of sulfonyl chlorides to the corresponding thiols or disulfides constitutes an important synthetic method because sulfonyl chlorides are easily prepared by chlorosulfonation. The Me_2SiCl_2/Zn/*N*,*N*-dimethylacetamide system, described by Kobayashi,[89] was developed for an efficient synthesis of aromatic thiols. Based on earlier work of Oae and Togo,[90] simpler procedures using tris(2-carboxyethyl)phosphine (TCEP) as reducing reagent have been reported.[72] Two groups described simultaneously but independently that PPh_3 is able to reduce efficiently arenesulfonyl chlorides. With 3 equivalents of phosphine, the corresponding thiophenols[91] were isolated, whereas disulfides were obtained when only 2 equivalents were employed (Scheme 4).[92] The concomitant formation of triphenylphosphine oxide suggested the transient formation of an arenesulfenyl chloride (ArSCl).[93]

A plethora of efficient systems has been developed to induce reductive dimerization of sulfonyl chlorides into disulfides (equation 46). A comparison of reported methods is given in Table 4 on selected examples: WCl_6/NaI or Zn;[45b] $(PipH)_2WS_4$;[94] Samarium;[103] Sm/$TiCl_4$;[95] Sm/$NiCl_2$/KI;[96] Sm/Cp_2TiCl_2;[97] SmI_2/THF/HMPA;[98] $TiCl_4$/Al;[99] $ZrCl_4$/NaI;[100] BI_3/$PhNEt_2$;[29] Silphos/I_2;[74] $ZrOCl_2 \cdot 8H_2O$/NaI;[101] $MoCl_5$/NaI or Zn;[45a] $NaBH_2Se_3$.[102] The use of $(PipH)_2WS_4$ was also successfully extended to the reduction of sulfinyl chlorides (ArSOCl), sulfinic acids ($ArSO_2H$), and thiosulfonates ($ArSO_2$–SAr). In contrast, sulfoxides, sulfones, and sulfonic acids remained unaffected under similar conditions.[94]



Scheme 4



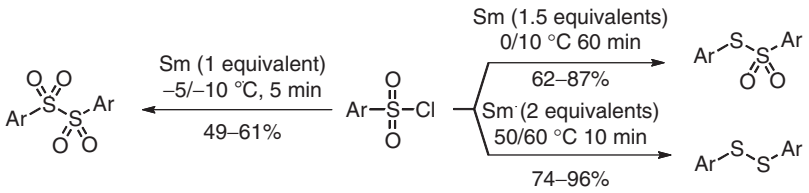
(46)

Table 4 Comparison of reductive coupling reactions of sulfonyl chlorides

Disulfide yield % (time, h)

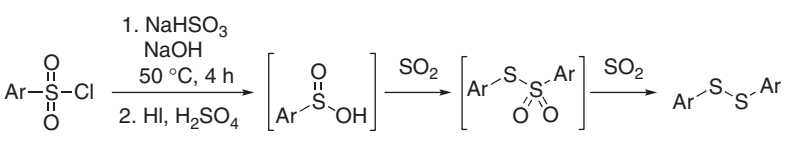
Reducing agent	*Conditions*	*Ar=Ph*	*Ar=p-Tol*	*Ar=p-Br–C6 H4*
WCl_6/NaI	CH_3CN, r.t.	97 (16)	94 (17)	85 (14)
$(PipH)_2WS_4$	DMF, r.t.	78 (2)	69 (2)	53 (2)
Sm/Cp_2TiCl_2	THF	83 (5)	86 (5)	80 (5)
$Sm/NiCl_2$/KI	HMPA, 60 °C	70 (3)	62 (3)	68 (3)
Sm	DMF, 50 °C	93 (10 min)	95 (10 min)	96 (10 min)
$Sm/TiCl_4$	THF, 60 °C	65 (2)	62 (2)	77 (2)
SmI_2/HMPA	THF, 60 °C	73 (0.5)	65 (0.5)	72 (0.5)
$TiCl_4$/Al	Et_2O, Δ	63 (4)	53 (5)	–
$MoCl_5$/Zn	CH_3CN, Δ	93 (10 min)	92 (20 min)	90 (25 min)
$ZrCl_4$/NaI	CH_3CN, Δ	97 (3 min)	94 (5 min)	96 (3 min)
$ZrOCl_2 \cdot 8H_2O$/NaI	H_2O, 90 °C	93 (0.5)	94 (1)	94 (1.33)
Silphos/I_2	CH_3CN, Δ	96 (10)	92 (10)	88 (12)
$NaBH_2Se_3$	CH_3CN, Δ	88 (3)	67 (4)	50 (2)
BI_3/$PhNEt_2$	C_6H_6, 80 °C	92 (2.5)	74 (3)	94 (3)

Interestingly, metallic samarium, without any activation, can reduce arenesulfonyl chlorides into diaryl disulfones, diaryl thiosulfonates, or diaryl sulfides. The selectivity of the reaction is simply controlled by the reaction temperature (Scheme 5).[103]



Scheme 5

An industrial process described also the reduction of arenesulfonyl chlorides into the corresponding disulfides via the analogous sulfinic acids and thiosulfonates, using SO_2 in the presence of an iodo catalyst (Scheme 6).[104]

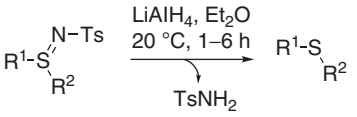


Ar	Yield
4-F-C_6H_4	95%
4-Br-C_6H_4	67%
4-Me-C_6H_4	95%
4-MeO-C_6H_4	84%
3-NO_2-C_6H_4	75%

Scheme 6

8.15.2.4 Reduction of Sulfilimines and Sulfoximines

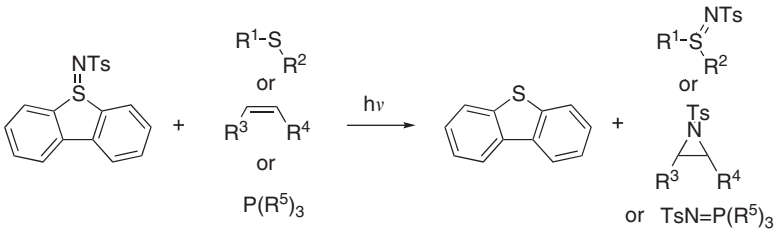
The nitrogen analogs of sulfoxides and sulfones, named, respectively, as sulfilimines and sulfoximines, have received increasing attention in synthesis. Their reduction remains surprisingly neglected. The most representative example consists in the reaction of *N*-(4-tosyl)sulfilimines with $LiAlH_4$ to afford the corresponding sulfides in excellent yields (equation 47).[105] The mechanism involves a nucleophilic attack of the hydride on the sulfinyl nitrogen atom to form a σ-sulfurane intermediate, followed by pseudorotation in which the hydride is placed in an equatorial position. Then, the ligand coupling furnishes the thioether with 4-toluenesulfonamide as side-product.



R^1	R^2	Yield
Ph	Ph	94%
p-MeO-C_6H_4	CH_3	86%
p-Me-C_6H_4	CH_3	83%
p-Me-C_6H_4	*p*-MeO-C_6H_4	92%
p-Br-C_6H_4	*p*-MeO-C_6H_4	93%

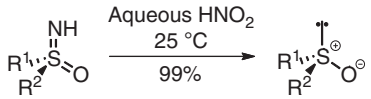
(47)

The photolysis of dibenzothiophene *N*-substituted sulfilimines as nitrene source, in the presence of trapping reagents (sulfides, olefins, or phosphines) allowed the synthesis of the corresponding imino-transfer compounds and dibenzothiophene in quantitative yield (Scheme 7).[106]



Scheme 7

The best method for the conversion of sulfoximines to sulfoxides is still the de-imination reaction described in 1972 by Cram et al.[107] The use of aqueous nitrous acid allowed a stereospecific reaction with retention of configuration (equation 48). To the best of our knowledge, deoxygenating processes leading to sulfilimines have not been reported yet.



(48)

8.15.3 Reduction of S–X to S–H

The most encountered substrates leading after reduction to thiols are disulfides, thioesters, and thiocyanates (equation 49). Because thiols are prone to oxidation into disulfides (even just under air), the reduction of a disulfide back to the desired thiol represents a useful reaction. Thioesters and thiocyanates are among the most readily available sulfur derivatives. They can be obtained by nucleophilic substitution or Mitsunobu reaction from halides or alcohols and a sulfur nucleophile (a thioacid, its salt or potassium thiocyanate). Some of the most recent and efficient methods for the reduction of these compounds will be given hereafter.

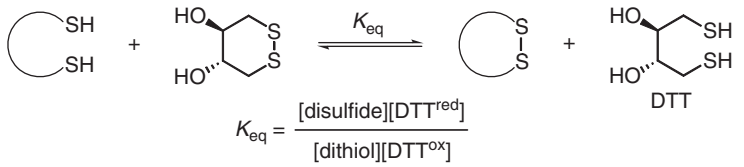


(49)

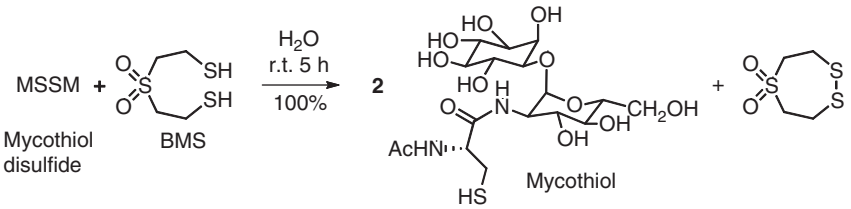
8.15.3.1 Reduction of Disulfides

Various reagents have already been used for the conversion of disulfides into thiols, thus including metal hydrides [$NaBH_4$, $Li(Bu^tO)_3AlH$, $K(Pr^iO)_3AlH$, KPh_3AlH], hydrazine, thiourea *S*,*S*-dioxide (formamidine sulfinic acid), aluminum in liquid ammonia, or biomimetic-reducing systems such as 1-benzyl-1,4-dihydronicotinamide (BNAH).[1] More recently, dithiols have received increasing attention, owing to their high conformational propensity to form cyclic disulfides by oxidation. Particular interest in the area concerns water-soluble species, within mind further biological applications. A high rate of reduction depends on the choice of pK_a value. Dithiothreitol (DTT, Cleland's reagent) is one of the more strongly reducing dithiols. However, its high cost has stimulated research toward the synthesis and evaluation of alternative dithiols.[108] Comparison with DTT is measured

with the calculation of the equilibrium constant of the thiol/disulfide exchange depicted in Scheme 8. As an efficient dithiol example, bis(2-mercaptoethyl)sulfone (BMS) was used to reduce mycothiol disulfide (MSSM) into mycothiol (equation 50).[109]

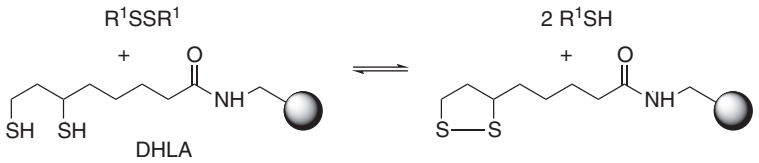


Scheme 8



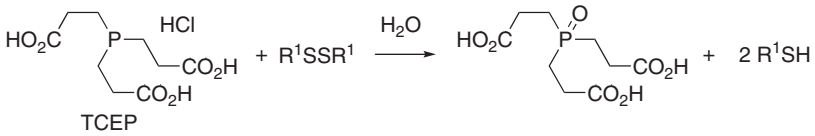
(50)

Another interesting precedent involves the α-dihydrolipoic acid (DHLA), which was supported on a resin and used as a totally recyclable reducing agent (equation 51).[110]



(51)

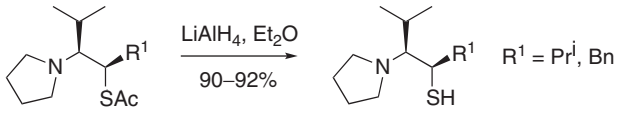
The ability of trialkylphosphines to reduce disulfide bonds in biochemical systems (peptides, proteins) has been known for many years. Some disadvantages, such as the low water-solubility and their unpleasant odor, were avoided with the discovery of tris(2-carboxyethyl)phosphine (TCEP).[111] This reagent is odorless, stable, and reduces rapidly and efficiently disulfides in water over a wide pH range (equation 52).



(52)

8.15.3.2 Reduction of Thioesters

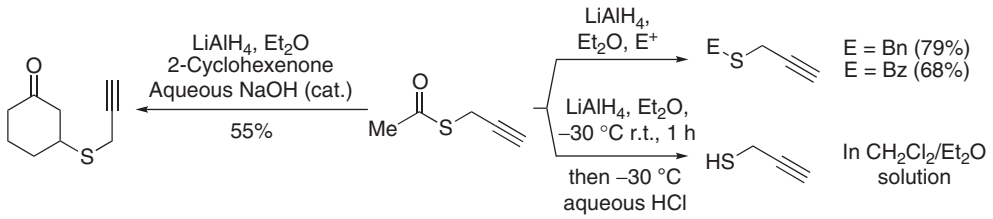
Thioesters can be deprotected by acidic or basic hydrolysis to give thiols, but, due to the sensitivity of some substrates under these conditions, alternative reductive methods can be employed. Many examples involve the reduction of thioacetates with $LiAlH_4$ leading, after hydrolysis, to thiols. Often encountered substrates are 2-aminoethyl thioesters, which are obtained from 2-aminoalcohols[112] or aziridines[113] and thioacids. Reduction affords 2-aminothiols and a representative example is given in equation 53.[112b]



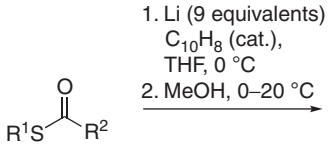
(53)

Propargylthiol is a challenging mercaptan due to its high volatility and instability. A convenient procedure for the preparation of propargylsulfanyl derivatives was described and consists in the reduction of propargyl thioacetate with $LiAlH_4$ (Scheme 9).[114] After acidification of the reaction mixture and dilution with dichloromethane, the solution of propargylthiol in CH_2Cl_2/Et_2O can be stored in the freezer for several weeks. Reaction with a Michael acceptor (i.e., 2-cyclohexenone), in the presence of a catalytic amount of a base, led to the 1,4-addition product. Otherwise, the lithium propargylthiolate can be trapped with an electrophile such as benzyl bromide and benzoyl chloride to give the corresponding sulfide and thioester, respectively.

The treatment of thioesters derived from benzoic and pivalic acids with an excess of lithium and a catalytic amount of naphthalene led, after methanolysis, to the corresponding thiols (equation 54).[115]



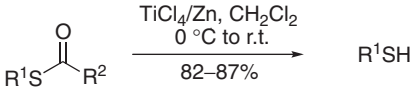
Scheme 9



R^1	R^2	Yield
n-$C_{10}H_{21}$	Bu^t	82%
n-$C_{10}H_{21}$	Ph	94%
c-C_6H_{11}	Bu^t	23%

(54)

Lee described a clean transformation of thioesters into thiols, using the titanium(IV) chloride/zinc system (equation 55). The reaction is chemoselective, as other functional groups such as an ester, an aldehyde, or a thioamide are unaffected. Although the mechanism of the reaction was not well-established, a reduction via a low-valent titanium species is probably involved in the process.[116]

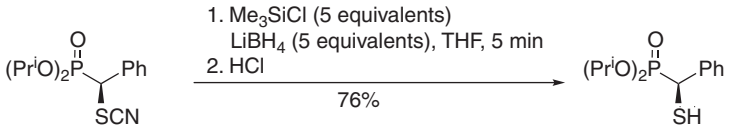


(55)

R^1 = *n*-C_5H_{11}, Ph, 2-MeCO-C_6H_4, 2-MeO_2C-C_6H_4, $CH_2CH_2CO_2Me$
R^2 = Me, Ph, *n*-C_5H_{11}

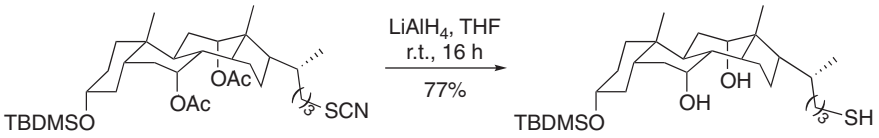
8.15.3.3 Reduction of Thiocyanates

Standard reducing agents for thiocyanates include sodium dithionite ($N_2S_2O_4$), dithiothreitol, phosphinic acid (H_3PO_2), sodium borohydride ($NaBH_4$), and tributyltin hydride (Bu_3SnH).[1] The classical conditions with hydride sources $NaBH_4$ in EtOH or $LiBH_4$ in THF have been applied to enantiopure α-thiocyanatophosphonates in order to prepare the corresponding α-sulfanylphosphonates. However, partial racemization was observed, as a result of a prototropic equilibrium between the thiolate and the α-phosphonylated carbanion.[117] This unwanted epimerization was suppressed by adding trimethylsilyl chloride at the beginning of the sequence (to ensure an immediate quench of the thiolate). Hence, after acidic hydrolysis, the desired thiols were obtained in good yields with total preservation of the enantiomeric excess (Scheme 10). Another beneficial effect of Me_3SiCl is the dramatic acceleration of the process, complete conversion being reached within minutes (instead of several hours without).



Scheme 10

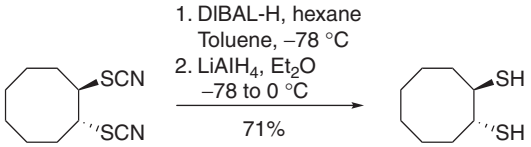
For substrates combining thiocyanate and acetate functions, the reduction with $LiAlH_4$ led to the products with free thiol and alcohol groups (equation 56).[118]



(56)

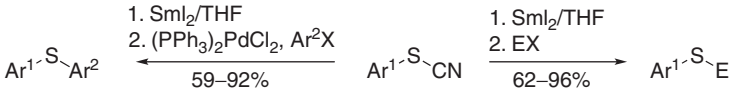
During the reduction of the *trans*-1,2-di(thiocyanato)cyclooctane with $LiAlH_4$ or $NaBH_4$, the episulfide was produced. The formation of this unwanted side-product was suppressed by sequential treatment of the substrate with DIBAL-H and then $LiAlH_4$. The desired dithiol was produced in 71% yield (Scheme 11).[119] Alternatively, this target was obtained in 79% yield through the reduction of *trans*-1,2-trithiocarbonate cyclooctane with $LiAlH_4$.

Still developed an efficient method to transform thiocyanates directly into sulfides using samarium diiodide as a single-electron transfer reagent. Two equivalents of SmI_2 are necessary to reduce the thiocyanate to the presumed samarium(III) sulfide species (R^1SSmI_2). This intermediate can be trapped with electrophiles via alkylation, acylation,[120] or arylation using a palladium-catalyzed



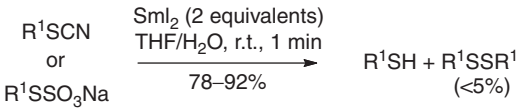
Scheme 11

cross-coupling reaction with aryl halides[121] (Scheme 12). More complex thiols, such as 5,6-dihydroxy-3-sulfanylindole, have been prepared according to this approach.[122]



Scheme 12

Samarium diiodide was also used to reduce thiocyanates with long alkyl chains into the corresponding thiols (equation 57).[123] To increase the reducing power of SmI_2, water was added as a cosolvent to the solution of SmI_2 in THF. Moreover, this procedure cleanly led to the thiol, with only a small amount of disulfide by-product. It was also successfully applied in the sodium alkylthiosulfate series.

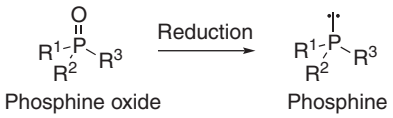


(57)

8.15.4 Reduction of P=O Compounds

8.15.4.1 General Considerations

Although any specific review dealing with the reduction of P=O compounds was published recently, this important reaction is sometimes mentioned in reviews dealing with the synthesis of phosphorus compounds.[124] The most encountered cases involve the reduction of phosphine oxides into the corresponding phosphines (equation 58). We selected here the most efficient methods developed between 1988 and 2012.[1] This includes some reducing agents (e.g., $PhSiH_3$, Cl_3SiH), which were already employed for this purpose, but are still used under optimized reaction conditions, as well as some new systems, which have been developed more recently.



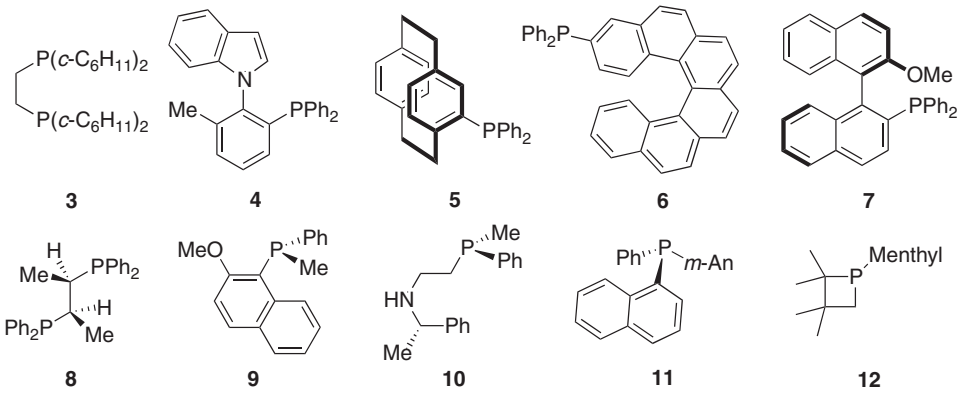
(58)

Phosphines constitute one of the most important classes of compounds in organic synthesis and in particular in catalysis as metal ligands.[125] They are often prepared by reduction of phosphine oxides. The choice of appropriate reagents and conditions for this transformation is particularly crucial, considering compatibility with other functional groups present in the precursor and air-stability of the final phosphine. Particular substrates are secondary phosphine oxides and methods applicable in these cases will be pointed out. Due to the large application of chiral phosphines in asymmetric catalysis, an essential point is the reduction of the *P*-stereogenic enantiopure phosphine oxide precursors with either a total inversion or a complete retention of the configuration at phosphorus.[126] (The reduction of a *P*-chiral phosphine oxide to the corresponding phosphine entails the removal of the highest priority group from phosphorus. For this reason, a reduction that takes place with retention at phosphorus leads to a phosphine

having the opposite stereochemical descriptor (*R* or *S*) from that of phosphine oxide.) It is noteworthy that phosphines, which are prone to oxidation on contact with air, are generally isolated as their borane adducts.[127]

8.15.4.2 Reduction with Silyl Hydrides

Almost 50 years after the first study,[128] the reduction of phosphine oxides with trichlorosilane ($HSiCl_3$), without or in the presence of a base (usually a tertiary amine), is still a widely used method to prepare phosphines. Many structures are accessible by this approach[129–152] and we have selected some examples, which are given in Figure 2 and Table 5. When optically active substrates having a *P*-chirogenic center are concerned, the reduction with $HSiCl_3$ affords, in most of the cases, phosphines with inversion of configuration at the heteroatom.[132,140,146] An exception concerns phosphetane **12**, which was produced with retention of configuration. This is in full agreement with the literature precedents involving four-membered phosphine oxides.[153]



3 **4** **5** **6** **7**

8 **9** **10** **11** **12**

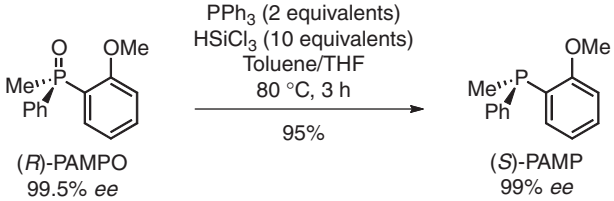
Figure 2 Phosphines prepared by reduction with $HSiCl_3$.

Table 5 Synthesis of phosphines (Figure 2) by reduction with $HSiCl_3$

Phosphine	*$HSiCl_3$ (equivalents)*	*Reaction condition*	*Yield (%)*	*References*
3	10	NEt_3, xylene, 155 °C	81	142
4	6	NEt_3, xylene, 130 °C	98	145
5	1.4	NEt_3, toluene, 100 °C	86	150
6	12	NEt_3, xylene, 120 °C	73	151
7	4	NEt_3, toluene, 120 °C	86	152
8	20	NEt_3, xylene, 130 °C	95	134
9	4	NEt_3, benzene, r.t.	72[a]	132
10	4.2	NEt_3, toluene, 130 °C	Not given[a]	140
11	3	Pyridine, benzene, reflux	95[a]	146
12	2	NEt_3, benzene, 25 °C	67[b]	130

[a]Inversion of configuration.
[b]Retention of configuration.

In 2004, Yu and Spencer published a new protocol to reduce phosphine oxides with retention of configuration, by using $HSiCl_3$–Ph_3P combination.[154] The method is complementary to that employing the $HSiCl_3$–Et_3N system, which leads to products with inverted configurations. As an example, (*S*)-PAMP was efficiently prepared by this method in 95% yield (equation 59). BINAP derivatives, known to be difficult to reduce, have been obtained in excellent yields (83–96%). Two equivalents of triphenylphosphine are used in the reaction and are recovered at the end as the corresponding phosphine oxide, which is difficult to separate from the product. Simplification of the purification was possible using triethylphosphite [$(EtO)_3P$] as the oxygen acceptor, even if a larger excess is required.



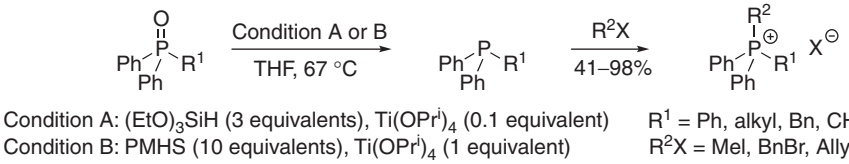
(*R*)-PAMPO
99.5% *ee*

(*S*)-PAMP
99% *ee*

(59)

The reduction of phosphine oxides by triethoxysilane or polymethylhydrosiloxane (PMHS), catalyzed by titanium(IV) isopropoxide [$Ti(OPr^i)_4$], provides an efficient method for the synthesis of phosphines (Scheme 13).[155] In most of the cases, subsequent *P*-alkylation was performed and the product was isolated as its phosphonium salt. The authors demonstrated that starting with an enantiopure *P*-chirogenic phosphine oxide, the expected phosphonium salt was produced with retention of stereochemistry at phosphorus. In contrast, use of the $HSiCl_3$–NEt_3 system led to the product with inversion of configuration.

The $Ti(OPr^i)_4$–PMHS system was also efficiently used for the reduction of various phosphine oxides (Figure 3). A series of diphosphines **13** derived from pinene, with two diphenylphosphanyl, dicycloxexylphosphanyl, or mixed diphenylphosphanyl/dicyclohexyl–phosphanyl functions were obtained by this method.[156] Hamada obtained from chiral xanthene-based diphosphine oxides, the corresponding optically pure diphosphine **14**. The reduction proceeds with complete retention of the phosphorus configuration.[157]



Scheme 13

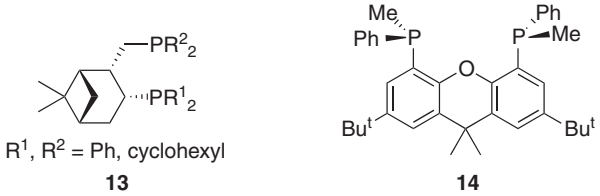
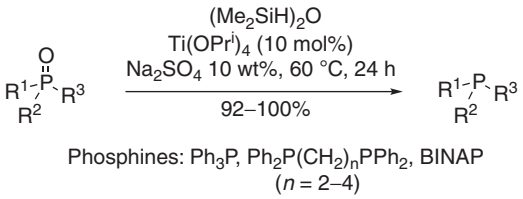


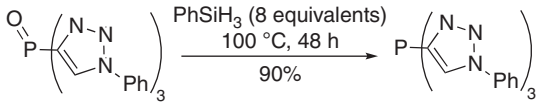
Figure 3 Phosphines prepared by reduction with the $Ti(OPr^i)_4$–PMHS system.

Lemaire studied the mechanism of the reduction of phosphine oxides by titanium(IV) isopropoxide–tetramethyldisiloxane system [$Ti(OPr^i)_4$–TMDS] and proved by electron spin resonance (ESR) spectroscopy that the process involves a single electron transfer. The reaction conditions were strongly improved by the use of a drying agent, thus furnishing phosphines or diphosphines in high yields (equation 60).[158] Unsymmetrical secondary phosphine oxides could be quantitatively reduced by the same system and the resulting phosphines were isolated as their protected borane form.[159] Very recently, the related $InBr_3$–TMDS system was used to reduce tertiary and secondary aliphatic or aromatic phosphine oxides.[160] In the cases of *P*-allyl and *P*-vinyl substrates, concomitant reduction of the double bond was also observed. The reduction of diphenylphosphinic acid was achieved under the same conditions, leading after protection with BH_3 to diphenylphosphine borane.



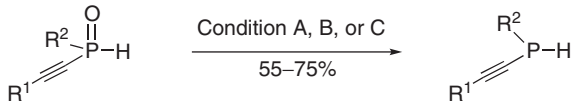
(60)

Phenylsilane ($PhSiH_3$) and diphenylsilane (Ph_2SiH_2) were also used as reducing agents for various phosphine oxides.[161] By using phenylsilane, Pietrusiewicz obtained *P*-chirogenic phosphabicyclic phosphines with complete retention of configuration at phosphorus.[162] As a recent example, a triazole phosphine oxide obtained by a Huisgen 1,3-dipolar cycloaddition has been reduced with an excess of $PhSiH_3$ affording the corresponding phosphine in 90% yield (equation 61).[163]



(61)

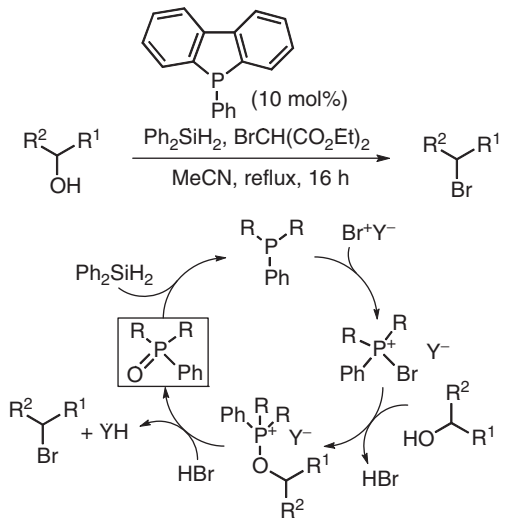
Gaumont synthesized nonstabilized secondary *P*-ethynyl phosphines bearing noncrowded substituents by reduction of the corresponding oxide precursors. *P*-alkyl derivatives were reduced with phenylsilane, whereas for the *P*-phenyl derivatives a $PhSiH_3$–$PhSiCl_3$ reducing mixture or pure $PhSiHCl_2$ was preferred (Scheme 14).[164]



Condition A (for R^2 = Et, Pr^i, Bu^t, R^1 = H or Ph): $PhSiH_3$, THF reflux or tetraglyme 70 °C, 1 h
Condition B (for R^2 = Ph, R^1 = H or Ph): $PhSiH_3/PhSiCl_3$ (3/1), THF or tetraglyme 30 °C, 0.5 h
Condition C (for $R^2 = R^1$ = Ph): Ph_2SiCl_2, THF, r.t., 15 min

Scheme 14

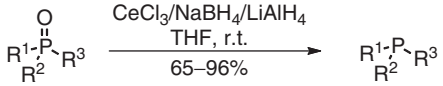
Very recently, van Delft described the application of phosphines in a catalytic Appel reaction, which involves the conversion of alcohols into bromides or chlorides (Scheme 15).[165] The phosphole catalyst is regenerated *in situ* by the reduction with Ph_2SiH_2 of the phosphorus oxide formed during the catalytic cycle.



Scheme 15

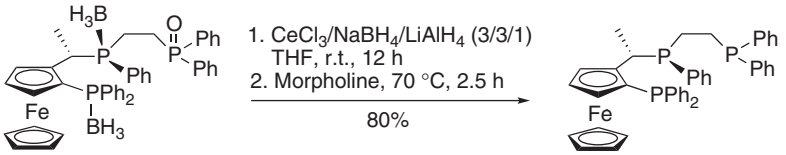
8.15.4.3 Reduction with Aluminum Hydrides

In 1985, Imamoto described the lithium aluminum hydride–cerium(III) chloride[166] ($LiAlH_4$–$CeCl_3$) system as a powerful reducing agent of phosphine oxides. Better efficiency is observed compared to $LiAlH_4$ alone.[167] The protocol is especially suitable for sterically crowded substrates. However, in the case of optically active *P*-chirogenic phosphine oxides, racemization occurred. Several years later, the same author brought a solution to this problem with the new system $LiAlH_4$–$NaBH_4$–$CeCl_3$, which enables direct transformation of phosphine oxides into phosphine boranes.[168] Control experiments indicated that the reaction did not take place without the cerium partner. It probably activates the phosphine oxide by coordination, thus allowing the deoxygenation with $LiAlH_4$ to proceed readily. The presence of $NaBH_4$ facilitates the phosphine–borane formation. Optically active phosphine oxides can be converted in this way into their corresponding phosphines with retention of configuration, after removal of the BH_3 by treatment with an amine (morpholine or diethylamine). The reaction is quite general, as both tertiary and secondary phosphine oxides can be prepared (equation 62).[168a]



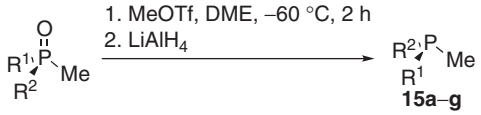
R^1 = aryl; R^2 = aryl, alkyl; R^3 = H, alkyl (62)

An example of a nice application of this method is the reduction of the P=O function of a diastereomerically pure ferrocenyl phosphine oxide/diphosphine-borane substrate to obtain the triphosphine derivative.[169] Although the results were unsatisfactory with $HSiCl_3/NEt_3$ or Si_2Cl_6, the $CeCl_3$–$NaBH_4$–$LiAlH_4$ mixture afforded a clean reduction with retention of configuration at all stereocentres (Scheme 16).



Scheme 16

An alternative and complementary method, also developed by Imamoto, involves the use of the methyl triflate–lithium aluminum hydride system (MeOTf–$LiAlH_4$). After treatment with MeOTf followed by reaction with $LiAlH_4$, optically pure *P*-chirogenic phosphine oxides can be efficiently reduced into phosphines, with inversion of configuration at the phosphorus atom (Scheme 17).[170] The yields and the *ee* values of some selected products are given in Table 6. It is noteworthy that at higher temperatures, partial epimerization occurred (e.g., at 0 °C **15a** was obtained in 72% *ee*). It was supposed that the phosphine oxide is methylated by methyl triflate, and the resulting phosphonium salt is subjected to hydride attack from the backside of the methoxy group.



Scheme 17

Table 6 Reduction of enantiomerically pure phosphine oxides

Product	R^1	R^2	*Yield (%)*	*% ee (configuration)*
15a	1-Naphthyl	Ph	90	98 (*S*)
15b	Ph	*o*-MeO-C_6H_4	85[a]	98 (*R*)
15c	*c*-C_6H_{11}	*o*-MeO-C_6H_4	74[a]	95 (*R*)
15d	*c*-C_6H_{11}	1-Naphthyl	81[a]	88 (*R*)
15e	Ph	*o*-Pr^i-C_6H_4	97[a]	98 (*R*)
15f	$(CH_2)_2Ph$	Bu^t	55[a]	97 (*R*)
15g	$(CH_2)_2Ph$	*c*-C_6H_{11}	96[a]	92 (*R*)

[a]Isolated as the phosphine–borane adducts.

The MeOTf–$LiAlH_4$ system proved its efficiency in many other cases. Figure 4 shows two representative examples, with chiral phospholanes **16** prepared by Fiaud,[171] and the fluorous BINAP **17** by Nakamura.[172]

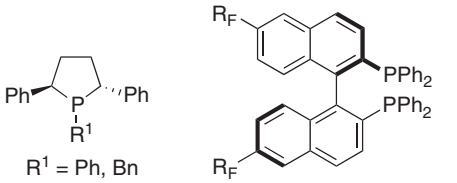
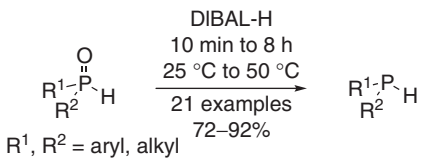


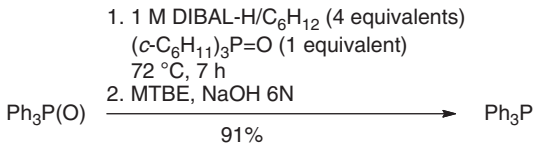
Figure 4 Phosphines prepared by reduction with the MeOTf–$LiAlH_4$ system.

Busacca et al. found that diisobutylaluminum hydride (DIBAL-H) is a very efficient reducing agent for secondary phosphine oxides (equation 63).[173] The reaction is extremely broad in scope, operationally simple, can be performed at moderate temperatures, and provides secondary phosphines in high yields and purities.



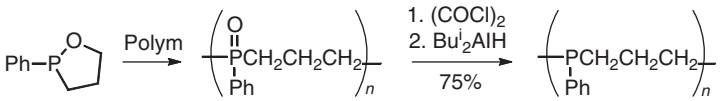
(63)

In 2008, the same authors published a detailed study of the reduction of tertiary phosphine oxides by DIBAL-H.[174] Significant solvent effects were reported, and hindered aliphatic ethers such as methyl tert-butyl ether (MTBE) provide the best conversions at ambient temperature, whereas in some common ethereal solvents such as THF, the reaction was ineffective. It was also showed that tetraisobutyldialuminoxane (TIBAO), generated *in situ*, is the source of the reduction inhibition. To prevent this competing pathway, tricyclohexylphosphine oxide $(c\text{-}C_6H_{11})_3P{=}O$, which is more sterically hindered than the substrate, was added before addition of DIBAL-H, to trap TIBAO and ensure full conversion. The scope and limitation of this reduction have been determined by using a large variety of substrates. For example, the reduction of triphenylphosphine oxide under these conditions is given below (Scheme 18). Steric, rather than electronic, effects are the most important parameters for the DIBAL-H reduction of tertiary phosphine oxides.



Scheme 18

One particular example deals with the reduction of a poly(phosphine oxide), which was prepared by a ring-opening polymerization from 2-phenyl-1,2-oxaphospholane. The reaction was carried out in one-pot and two steps: addition of oxalyl chloride leading to a dichlorophosphorane polymer intermediate and treatment with diisobutylaluminum hydride (Scheme 19).[175] The transformation took place with complete conversion and afforded cleanly the desired polyphosphine in good yield.

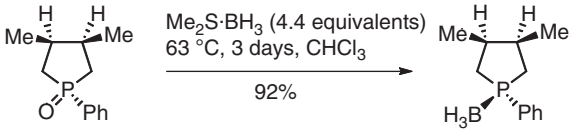


Scheme 19

Noteworthy is the use of alane derivatives ($AlHCl_2$), which are the reagents of choice for chemoselective reduction of vinyl or ethynyl phosphonates $[(R^1O)_2P(O)R^2]$ and phosphinates $[(R^1O)P(O)R^2R^3]$ into the corresponding primary (PR^1H_2) or secondary (PR^1R^2H) phosphines, the unsaturation remaining intact.[176]

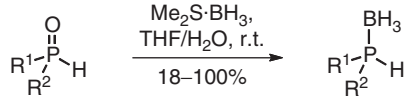
8.15.4.4 Reduction with Boron Hydrides

Cyclic phosphine oxides, such as phosphole 1-oxides, can be transformed into their corresponding phosphine-boranes by reaction with a borane complex in one-pot synthesis (equation 64).[177]



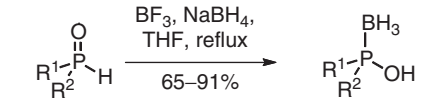
(64)

Pietrusiewicz converted secondary phosphine oxides to secondary phosphine-boranes by treatment with $BH_3 \cdot SMe_2$, under mild conditions (equation 65).[178] The addition of a small amount of water was found to be important to avoid the competitive formation of phosphinous acid-boranes. By switching to BF_3 in the presence of $NaBH_4$, phosphinous acid-boranes were obtained this time selectively (equation 66).[179]



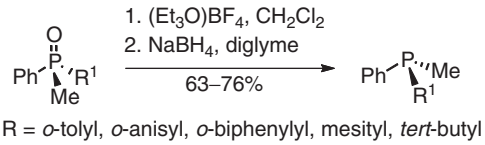
R^1, R^2 = aryl, alkyl

(65)



(66)

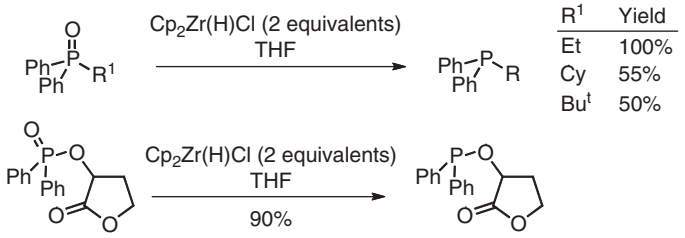
Phosphine oxides can also be converted directly to phosphine-boranes by alkylation with Meerwein's salt followed by reduction with sodium borohydride (Scheme 20).[180] The reaction is stereospecific and occurs with inversion of configuration at phosphorus.



Scheme 20

8.15.4.5 Reduction with Other Hydrides

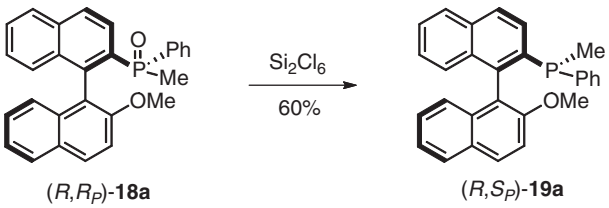
A less common hydride for phosphine oxides reduction, the Schwartz reagent $Cp_2Zr(H)Cl$, was reported by Majoral.[181] Diphenylethyl phosphine was obtained in quantitative yield. However, with more bulky substituents on phosphorus (cyclohexyl or *tert*-butyl), yields were moderate (Scheme 21). Noteworthy is the clean reduction of a phosphinate to the corresponding phosphinite in 90% yield.



Scheme 21

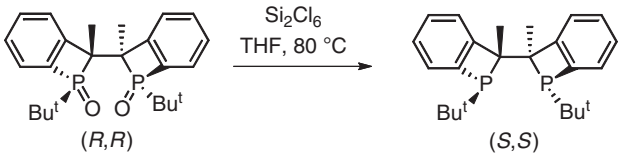
8.15.4.6 Reduction with Low-Valent Metals

To reduce *P*-stereogenic binaphthyl monophosphine oxide, Gilheany tested several commonly used reagents such as $HSiCl_3/NEt_3$, $LiAlH_4$/MeOTf, and Si_2Cl_6.[182] The best result in terms of yield and selectivity was obtained with Si_2Cl_6 (equation 67). However, it was noticed that the reduction of the (R,R_P)-**18a** diastereoisomer took place with complete inversion of the phosphorus configuration to afford diastereomerically pure phosphine (R,S_P)-**19a**. In comparison, the (R,S_P)-**18b** epimer suffered of a partial epimerization at phosphorus, and a mixture of phosphines (R,R_P)-**19b** and (R,S_P)-**19a** in a 86:14 ratio was isolated.



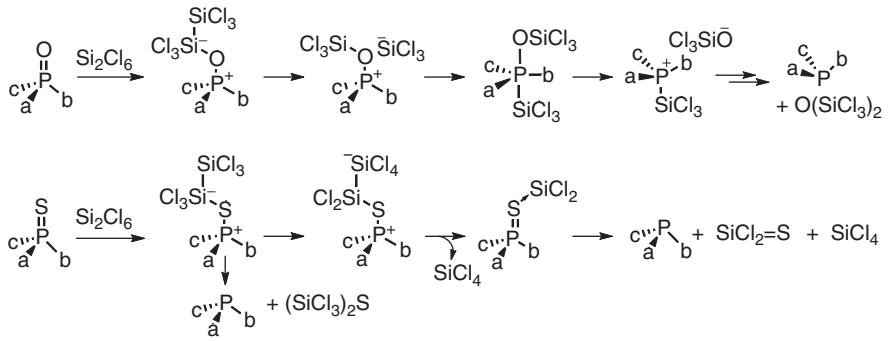
(67)

Imamoto attempted the reduction of a highly strained *P*-stereogenic diphosphine oxide into the corresponding optically active diphosphine using $PhSiH_3$, $HSi(OEt)_3$, $HSiCl_3/NEt_3$, $LiAlH_4$/MeOTf, and Si_2Cl_6 as reducing reagents.[183] Only the use of Si_2Cl_6 enabled the formation of the desired product; however, the yield was not given (equation 68). Even if this methodology generally proceeds with inversion of configuration, the authors assumed that the product was produced with retention of configuration (see phosphetane **12** in Section 8.15.2.1.3.1, Table 5, Figure 2).



(68)

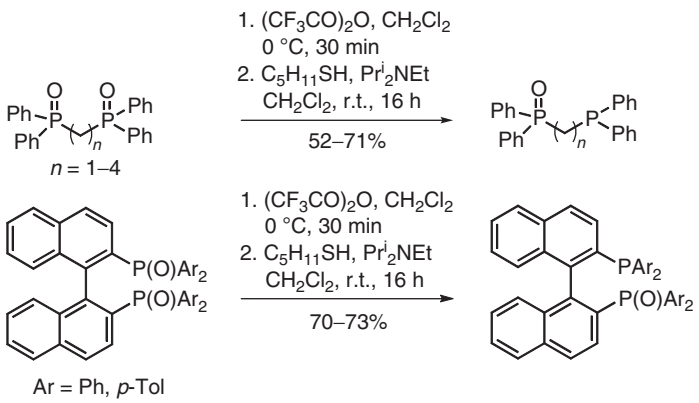
A very recent theoretical study[184] on the reduction of *P*-stereogenic enantiopure phosphine oxides and sulfides by chlorosilane explains the stereoselectivities observed experimentally[128b,185] in this reaction: inversion for the P=O and retention for the P=S derivatives. A phosphorane intermediate may be involved in the phosphine oxide reduction, although a donor stabilized $SiCl_2$ is proposed in the phosphine sulfide case (Scheme 22).



Scheme 22

8.15.4.7 Reduction with Nonmetallic Reagents

Jenkins developed a selective monoreduction of bis-phosphine oxides into phosphine–phosphine oxides. The transformation takes place under mild reaction conditions using triflic anhydride and pentane-1-thiol.[186] Two mechanisms are proposed, which involve initial formation of a phosphonium anhydride and attack of the thiol at one phosphorus atom, leading to the desired product together with dipentyl disulfide. The procedure was successful for four 1,*n*-diphenylphosphine oxides ($n = 1–4$) and two BINAP diarylphosphine oxides (Scheme 23). It can be applied also to monophosphine oxides. For example, Ph_3PO furnished Ph_3P in 47% yield.

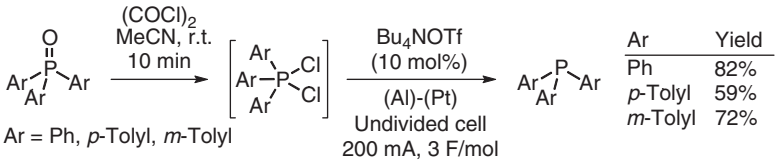


Scheme 23

8.15.4.8 Electrochemical Reduction

In many reactions, for example, the Wittig or Mitsunobu reactions, triphenylphosphine is a reagent used in stoichiometric amount (or in excess), and is converted into triphenylphosphine oxide. In the general context of the treatment and recycling of

phosphorus waste, various procedures for the reduction of Ph_3PO to Ph_3P have been reported.[187] An electrochemical one-pot procedure has been developed in 2011 as a promising environmentally benign alternative method.[188] Transformation of triarylphosphine oxide to triarylphosphine dichloride by treatment with oxalyl chloride and subsequent electroreduction takes place in an undivided cell fitted with an aluminum sacrificial anode and a platinum cathode. Al^{3+}, which is generated at the anode, would react as a Lewis acid to afford tetra-coordinate chlorotriarylphosphonium species (Scheme 24). Subsequent two-electron reduction at the cathode gives the desired triarylphosphine. Yields are moderate to good. The triphenylphosphine dichloride intermediate can also be reduced with a combination of aluminum–catalytic metal salt.[189] In another version, direct reductive transformation of Ph_3PO to Ph_3P was performed by electrolysis with TMSCl in a CH_3CN–Bu_4NBr–(Zn anode)–(Pt cathode) electrolysis system.[190] A mechanism involving the formation of a silylated-phosphorus radical is proposed.



Scheme 24

8.15.5 Conclusion

As illustrated in this chapter, the deoxygenation of sulfoxides into their corresponding sulfides has received much attention between 1989 and 2012. Most efforts focused on the development of efficient and general procedures fulfilling if possible the maximum of the following criteria: mild conditions, short reaction times, high functional group tolerance, use of inexpensive and common laboratory reagents, and simple workup. Consequently, there are many options available to synthetic chemists. It is, however, important to mention that most reactions were exemplified on quite simple substrates. Chemoselectivity was generally examined with bifunctional species and very few studies involved compounds possessing stereochemical informations (chirality or double bonds with a fixed configuration). In this context, of note is the contribution from the group of Nicolaou, in which sophisticated carbohydrate sulfoxides were subjected to reduction in the presence of a titanocene reagent.[38] Successful versions proceeding with silyl hydrides,[12–18] boranes,[25–27] or triphenylphosphine[68–70] in the presence of a catalytic amount of transition metal complexes have also recently emerged. Results achieved with dihydrogen are particularly attractive for further industrial applications, even if still in its infancy.[81] One promising direction to take for the future is probably toward the improvement of the catalytic versions, with full understanding of the mechanisms. Other essential considerations will probably also be toward green chemistry, with the use of unusual reaction media, recyclable catalytic systems and ultimately the development of continuous flow processes.

For additional comments concerning other sulfur species treated in this review, it is also fair to say that the reduction of sulfones remains an underdeveloped field and elaboration of new protocols is still of high demand. The reduction of sulfonic and sulfinic acid derivatives is also a challenging problem and reduction of the halide species is the most encountered process.

The section dealing with phosphorus compounds represents the first specific review on the reduction of the P=O function. The important number of studies published on this subject illustrates the growing interest for phosphorus(III) derivatives, mainly ascribed to their wide applications as ligands for transition metal catalysis or as organocatalysts. As the success of a catalyzed reaction strongly depends on the identification of the appropriate ligand, a large variety of phosphine ligands have been prepared and, in many cases, the synthesis involved the reduction of a phosphine oxide precursor. Thus, in the phosphorus series, problems are often encountered to reduce a particular substrate with commonly used reagents. This encouraged chemists to search more selective, milder, and more efficient reducing systems for this purpose. To consider are the particular P=O containing substrates with hindered substituents about the phosphorus atom (reactivity problems), with double or triple carbon–carbon bonds (selectivity problems), secondary phosphine oxides (product stability), and enantiopure *P*-stereogenic compounds (stereoselectivity problems). As we already pointed out, the air-stability of the resulting phosphine is also a specific aspect in this chemistry. Many procedures using common reducing agents such as silyl (e.g., Cl_3SiH, $PhSiH_3$) or aluminum (e.g., $LiAlH_4$, DIBAL-H) hydrides, low-valent metals (e.g., Si_2Cl_6), or nonmetallic reagents (TFAA/thiol) were successfully employed even in some problematic cases, after optimization of the reaction conditions. In the case of optically active substrates, Imamoto brought important contributions with the development of two general and efficient reducing systems, mediated, respectively, by the $LiAlH_4$–$NaBH_4$–$CeCl_3$ and MeOTf–$LiAlH_4$ combinations.[168,170] These systems enabled the reduction of *P*-stereogenic enantiopure phosphine oxides, with either total retention or inversion of the configuration at phosphorus. In the secondary phosphine oxides series, Pietrusiewicz proposed a standard borane reagent ($BH_3 \cdot SMe_2$) and mild conditions for the direct conversion into phosphine-boranes,[178] which are attractive reagents for hydrophosphination and C–P cross-coupling reactions. Efforts in phosphine recycling were reported by Tanaka, with the development of environmentally benign electrochemical routes.[188–190]

The various procedures, existing in the literature and revealed in this review, showed that a reasonable variety of phosphine structures are now accessible by the reduction of phosphine oxides. A challenge would be the *in situ* generation of a phosphine ligand by reduction of the P=O precursor in asymmetric metal-catalyzed reactions.[191] Doubtless, creative chemists will continue to develop novel and improved variants of all these reduction processes.

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8.16 Heterogeneous Hydrogenation of C=C and C≡C Bonds

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This chapter is a revision of the previous edition chapter by S. Siegel, Vol. 8, pp 417–442, © 1991, Elsevier Ltd.

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Glossary

Heterogeneous reaction A reaction composed of materials in two or more different physical states.

Hydrogenation A reaction in which hydrogen is added to an unsaturated compound, to give a reduced or saturated product.

Hydrogenolysis A reaction where a carbon–carbon or carbon–heteroatom bond is cleaved by hydrogen.

Metal black Finely divided powder of metal in its elemental oxidation state.

Semihydrogenation A controlled hydrogenation of multiply unsaturated compounds, in which hydrogenation is stopped prior to the fully saturated compound (e.g., hydrogenation of an alkyne to an alkene).

8.16.1 Introduction

The catalytic hydrogenation of olefins is one of the most useful and used synthetic transformations in both academic and industrial chemistry (*see* Chapters 8.17, 8.18, and 8.20).[1–9] Heterogeneous hydrogenation offers many practical benefits over the homogeneous counterpart, particularly in reaction work-up and catalyst removal, and has thus formed a key step in many industrial processes. However, the choice of catalyst and reaction conditions can seem bewildering to those unfamiliar

 doi:10.1016/B978-0-08-097742-3.00818-1

with the area. Considering the extensive literature on catalytic hydrogenation it could be thought that a simple series of guidelines exist for the choice of reaction conditions for a particular class of compounds. Unfortunately, this is not the case and it is far more useful for the synthetic chemist to simply treat the catalyst as an organic reagent with specific reactivity toward certain functional groups. Herein, the authors will attempt to provide a guide to this vast area of chemical research.

8.16.1.1 General

A wide range of heterogeneous hydrogenation catalysts have been developed and studied. These range from base metals (e.g., copper and nickel) to precious transition metals (e.g., platinum and palladium). The catalysts can be found in a wide variety of physical forms, but are most commonly either used as a finely divided powder of the metal (referred to as a metal black) or as a dispersion of the metal on an inorganic support. A support offers the advantage of a highly dispersed catalyst without the cost of a finely divided powder and so is most common for high cost catalysts. In the simplest sense, the support can be viewed as nothing more than a means to prevent catalyst aggregation and ensure high surface area. The method of catalyst preparation is usually secondary to the inherent reactivity of the metal catalyst; however, this assumes the method used has prepared 'active' catalyst.

Unfortunately no clear set of guidelines or rules have been reported for catalyst selection, although general reactivity of a metal toward a particular functional group can be used as a starting point (Table 1) (*see* Chapters 8.01, 8.02, 8.06, 8.19, 8.20, 8.21, 8.22, 8.26, 8.27, 8.28, 8.29, 8.30, and 8.32). The best option is still to check the primary literature for hydrogenation conditions for the exact or related hydrogenation to be carried out. This is particularly useful when wishing to carry out a selective hydrogenation of a bifunctional molecule. In this case the catalyst must offer preferential reactivity to one functional group of an adsorbed substrate. This selectivity arises as a result of the relative rates of reduction for both functional groups as a proportion of the catalyst active sites occupied by that functional group. Regardless of the rate of reduction, no reduction will occur if the functional group cannot occupy an active site due to preferential adsorption by another functional group, solvent, or poison.

Table 1 General reactivity of metals for the hydrogenation of functional groups

	Catalyst	*Pressure (bar)*	*Temperature (°C)*	*Reaction conditions*
$R_2C{=}CR_2 \rightarrow HR_2C\text{-}CHR_2$	Pt, Pd, Ni	1–100	5–100	
$R_2C{\equiv}CR \rightarrow H\,R_2C{=}CHR$	Pd	1–3	5–50	
$R_2C{=}O \rightarrow R_2CH\text{-}OH$	Pt, Ni, Ru	1–10	50–150	
Ar → R (saturated)	Rh, Pt, Ru, Ni	3–100	20–100	
$RCN \rightarrow RCH_2NH_2$	Ni	20–40	20–100	NH_3
$RCN \rightarrow RCH_2NH_2$	Pt, Pd	1–10	20–100	HCl
$ArNO_2 \rightarrow ArNH_2$	Pt, Pd, Ni	1–5	5–50	
ArX → ArH	Pd	1–10	50–100	Basic
$ArCH_2X \rightarrow ArCH_3$	Pd	1–10	20–100	Basic
$ArCH_2Y \rightarrow ArCH_3$	Pd	1–10	20–100	Acidic

Notes: X = Halide; Y = OR, NR_2.

Adsorption is strongly influenced by steric hindrance, thus any suitably designed bifunctional compound can be selectively hydrogenated at the least sterically hindered functional group.

The activity and selectivity of a heterogeneous hydrogenation are influenced by the following factors in approximate order of importance: catalytic metal > modifier, doping elements > reaction medium (polarity), and support > catalyst structure (morphology and active site location).

For academic research (and small-scale hydrogenation), Aldrich Chemical Co., Strem and Fluka provide a large range of heterogeneous hydrogenation catalysts, but the exact catalyst types are not specified and so reproduction on large scale can be problematic. For large-scale hydrogenation and development work, exact catalyst type and insight can be gained from BASF Catalysts, Degussa, and Johnson Matthey.

8.16.1.2 Reaction Processes

Heterogeneous catalysts can be divided into two types: fixed-bed processes and slurry or fluidized-bed processes. Fixed-bed processes use a stationary catalyst with large particle size in the form of beads, spheres, cylinders, or granules which can be readily suspended in gas or liquid over which the reactants are passed. Fixed-bed reactors are generally found in industrial settings where they are used for continuous processes where the large size and cost of the reactor and reaction development can be offset.

Slurry processes tend to be those used on small scale and in academic environments as the ability to fine tune the system is practically simple. The catalyst, concentration, temperature, and reactants can be easily varied without significant upheaval. Laboratory experiments can be easily scaled to industrial processes.

8.16.1.3 Inherent Metal Reactivity

The choice of metal catalyst primarily dictates the reactivity and selectivity of the hydrogenation. Metals have an inherent base reactivity and selectivity toward particular functional groups (Table 1).

'Platinum' catalysts are highly active for the hydrogenation of C=C, C≡C, C=N, and C=O bonds. Chemoselective hydrogenations can often be carried out in the presence of aryl halides, allylic and benzylic alcohols, and carbon–halogen bonds. In contrast to palladium, double-bond isomerization and migration is rarely observed.

'Palladium' is the metal of choice for the hydrogenolysis of C–O, C–N, N–N, N–O, and O–O bonds. Palladium catalysts show good activity for the hydrogenation of C≡C, C=C, C=O, and C=N bonds and olefins conjugated to an aromatic group. However, palladium catalysts have a high propensity to catalyze double-bond isomerization and migration reactions.

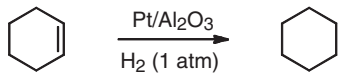
'Rhodium' is highly active for the hydrogenation of aromatic rings, under mild reaction conditions, alkenes, and alkynes.

'Nickel', and most commonly Raney nickel, shows good activity for the hydrogenation of alkenes, alkynes, and C=O bonds. The chemoselective hydrogenation of nonconjugated dienes has been achieved with nickel catalysts.

8.16.1.4 Metal Dispersion

Metal concentration (and so dispersion on a support) has a great influence on the rate of hydrogenation. The lower the metal concentration, the higher the specific rate of reduction (rate per unit weight of metal) (Table 2).[10] The gains in economy and metal efficiency are offset by the cost of catalyst production and so a loading of <5% metal is most practical. Base metals are generally much less active and so are routinely used at much higher metal loading (up to 100%).

Table 2 Specific rates of Pt-catalyzed hydrogenation of cyclohexene



Pt/Al_2O_3 loading (%)	*Specific rate*
1.11	76
0.72	96
0.52	113
0.39	121

The crystalline size of the dispersed metal can also have an effect on the specific rate of hydrogenation. Particle sizes of <10 Å have shown a decreased specific activity compared with larger metal particle (obtained at higher metal loading).[11] The morphology of a supported catalyst can influence both rate and selectivity of hydrogenation. The degree of internal mass transport is directly proportional to the porosity of a catalyst and the particle size will influence the degree of catalyst dispersion in solution and the aggregation of gas bubbles on the catalyst. Catalyst particle morphology is particularly important in fixed-bed reactors.

8.16.1.5 The Support

Base metals are routinely used in nonsupported form, whereas noble metals are most commonly used in supported form. The support of noble metals makes a more efficient and economical catalyst and aids in the recovery of the metal.

The support can interact with the substrate by altering the polarity or acidity of the reaction site and thus can affect the reactivity of the metal catalyst. For example, in the reduction of alkynes to alkenes, the use of $BaSO_4$ as support greatly reduces the likelihood of overreduction to the alkane (see Section 8.16.3).

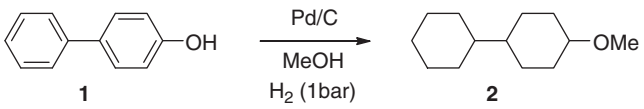
In the majority of cases when complete reduction is required, and in the absence of additional functional groups susceptible to hydrogenation or hydrogenolysis, the influence of the support is negligible. However, Blaser reports that catalyst activity decreases in the following order with the most commonly used supports; C (activated carbon) > Al_2O_3 > $CaCO_3$ > $BaSO_4$.[12]

8.16.1.6 Reaction Medium: Solvent

With the exception of liquid substrates, hydrogenations are usually carried out in an organic solvent. Frequently used reaction solvents include alcohols, ethyl acetate, acetic acid, hydrocarbons, ethers, water, and dichloromethane. Solvent molecules may

enter the catalytic cycle reversibly or irreversibly and thus offer the simplest means of 'tuning' the reactivity and selectivity of a heterogeneous hydrogenation as the number of solvent molecules is usually in vast excess when compared with the number of active catalyst sites. Solvent polarity has been shown to be highly influential.[13–17] The solvent can alter the chemical nature of the reaction by influencing the rate and position of the adsorption and desorption equilibrium of substrate and product and even the rate of the actual surface reaction. These affects can be significant if the solvent has a strongly coordinating group. Solvent also affects the solubility of hydrogen and rate of diffusion (viscosity).[10]

Solvents can also react with the substrate or product to give unexpected results such as in the hydrogenation of 4-phenylphenol **1** using palladium on carbon in methanol (Scheme 1).[18] In this case, the phenol is hydrogenated to cyclohexanone which then reacts with methanol to give the methyl ketal which is reduced to the methyl ether **2** by hydrogenolysis.



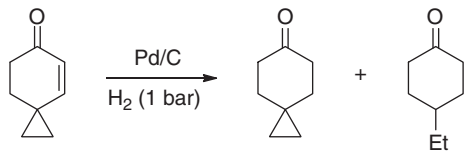
1 **2**

Scheme 1

8.16.1.7 Acids and Bases; Hydrogenolysis

The addition of acids and bases to the reaction solvent (or as the reaction solvent) can have a marked effect on the outcome of a hydrogenation. These can interact with the substrate, the product, an intermediate or the catalyst itself. The pH of the reaction can also have an effect on the diastereoselectivity.[19] Protonation or deprotonation of the substrate or product has been shown to affect the relative rates of adsorption and desorption.[13]

Of most significance is the influence of acids and bases on hydrogenolysis. Hydrogenolysis is the one of the most common side reactions within hydrogenations. A general rule of thumb is that apolar solvents favor hydrogenation and polar solvents favor hydrogenolysis.[3,4] Hydrogenolysis is also favored in acidic media.[20] For example, in the hydrogenation of enone **3** using palladium on carbon, competing hydrogenolysis of the cyclopropane, to give ketone **5** can be suppressed by the addition of base to give the spirocyclic ketone **4** as the majority hydrogenation product (Scheme 2).



3 **4** **5**

	Yield (%)	
Solvent	**4**	**5**
Aqueous EtOH (50%)	23	77
Hexane	68	32
Aqueous EtOH (85%) NaOH (0.1 M)	84	16

Scheme 2

8.16.1.8 Modifiers

Catalyst modifiers can strongly influence the rate and selectivity of heterogeneous hydrogenations. Along with altering the electronic and aggregation properties of the metal catalyst, modifiers can act as poisons to block either specific reaction sites (selectivity) or the catalytic sites at large (rate). See Sections 8.16.2 and 8.16.3 for a further discussion.

8.16.1.9 Temperature

Temperature can affect the rate and selectivity of the hydrogenation and also catalyst lifetime. Increasing temperature leads to higher rates of adsorption, desorption, and catalyst deactivation which can cause a decrease in rate and give unexpected selectivity.[21] Satisfactory levels of hydrogenation are usually obtained at room temperature and this is often a good starting point from which to work.

8.16.1.10 Hydrogen Pressure

In sufficiently agitated vessels, the concentration of hydrogen in the reaction solvent is directly related to hydrogen pressure. The rate of hydrogenation is thus generally increased at elevated hydrogen pressure. However, some metals (palladium notably) will form metal hydrides at elevated hydrogen pressures which can alter the reaction outcome.

8.16.1.11 Catalyst Prereduction

Prereduction of the catalyst is usually unnecessary, but is worth resorting to if a reported or an expected hydrogenation fails. Prereduction is done by treating the catalyst in the reaction solvent with hydrogen. Prereduction eliminates any induction period and allows for a more precise measurement of hydrogen uptake by the substrate. Catalyst prereduction is particularly useful for suppressing dehydrogenative side reactions,[22] but has been shown to be detrimental in other cases.[23,24]

8.16.1.12 Practical Considerations and Safety

Catalysts that in isolation are very safe to handle may catalyze the combustion of hydrogen or volatile organic solvents. For this reason it is recommended that hydrogenation catalysts are treated in the same way as any other pyrophoric reagent (e.g., solid $LiAlH_4$) and used and stored under inert conditions wherever possible. If using compounds that are easily dehydrogenated (e.g., cyclohexene, low carbon number alcohols) extra care should be taken as these materials are prone to ignition. The addition of solvent to a catalyst (under an inert atmosphere) is advised where possible.

Finely dispersed metal catalysts on activated carbon are pyrophoric when dry (particularly Pt/C, Pd/C) and can undergo dust explosions (in the same manner as activated carbon alone). Unused noble-metal catalysts should also be treated as pyrophoric, and be handled with increased care after use as any adsorbed hydrogen may ignite when the catalyst is dried. If the reaction conditions suit, wetting of the catalyst will reduce the risk of ignition.

Base metal dispersions can be highly pyrophoric (e.g., Raney-Ni) and are best kept wet and treated with due care.

Hydrogenations at atmospheric pressure are easily done in standard laboratory glassware, however if elevated pressure is to be used a suitable reaction vessel will be required. High-pressure reactors are often referred to as autoclaves and, unhelpfully, bombs. These can be made of toughened glass (<10 bar) or stainless steel. A number of commercial reactors are available and these are highly recommended for reactions at elevated pressure. Commercial reactors often include an agitation device, but a magnetic stirrer bar and external magnetic stirrer can be used if the reactor is of reasonable size. The use of a pressure release valve (pop-valve) is recommended for all hydrogenations at elevated pressure.

Heterogeneous hydrogenations are best carried out in shaken vessels as this greatly increases the specific rate of hydrogenation by ensuring that dissolution of hydrogen in the reaction solvent is most efficient. Poor hydrogen dissolution can render this process rate limiting.[10,25–28] Continuous-flow, bench-top hydrogenation reactors (e.g., H-cube) can also be used for small-scale hydrogenations. Hydrogen is produced *in situ* by the electrolysis of water and the catalyst is contained within a disposable cartridge leading to fewer safety concerns; however the operational temperature and pressure is limited. A high hydrogen:substrate ratio can be maintained and generally results in a more efficient hydrogenation.

8.16.2 Hydrogenation of Alkenes

The alkene bond is among the easiest of functional groups to hydrogenate, unless highly substituted or hindered. The hydrogenation of mono- and disubstituted alkenes is usually rapid over a wide variety of metal catalysts. The heat of hydrogenation is also greater for these alkenes compared with more substituted alkenes (Table 3).[29]

Table 3 Heat of hydrogenation ethylene derivatives (82 °C)

$CH_2=CH_2$	+	H_2	→	CH_3CH_3	$+137$ kJ mol^{-1}
$CH_3CH=CH_2$	+	H_2	→	$CH_3CH_2CH_3$	$+126$ kJ mol^{-1}
cis-$CH_3CH=CHCH_3$	+	H_2	→	$CH_3CH_2CH_2CH_3$	$+120$ kJ mol^{-1}
trans-$CH_3CH=CHCH_3$	+	H_2	→	$CH_3CH_2CH_2CH_3$	$+116$ kJ mol^{-1}
$(CH_3)_2C=CHCH_3$	+	H_2	→	$(CH_3)_2CHCH_2CH_3$	$+113$ kJ mol^{-1}
$(CH_3)_2C=C(CH_3)_2$	+	H_2	→	$(CH_3)_2CHCH(CH_3)_2$	$+111$ kJ mol^{-1}

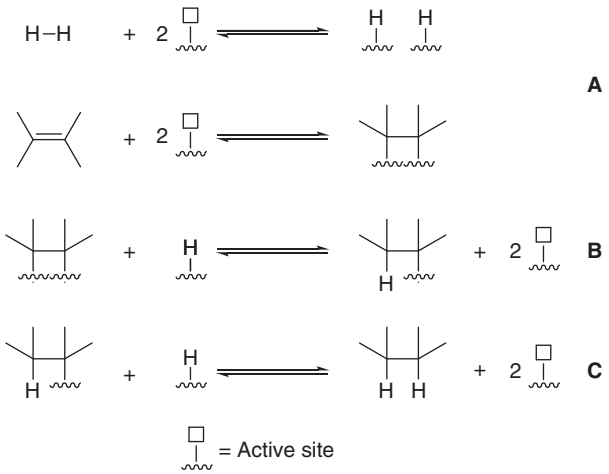
Isolated alkenes are particularly suited to heterogeneous hydrogenation as the complication of chemoselectivity is not present and catalyst reactivity and isomerization become the major points for consideration. Historically, palladium has been most widely applied in the heterogeneous hydrogenation of alkenes, although platinum, rhodium, and Raney nickel have also been extensively used. As a general guide the activity of the most commonly used metals decreases in the order Pt > Pd > Rh > Ru ≫ Ni (at equal metal loading).

Although electronic factors have a considerable influence on adsorption, the effect on the rate of hydrogenation appears to be minimal.[30] Steric factors exhibit the dominant effect in determining the rate of hydrogenation for both base metals and supported noble-metal catalysts.[10,31–33]

8.16.2.1 Mechanism

The mechanism of heterogeneous olefin hydrogenation was first formalized by Horiuti and Polanyi[34,35] and although this mechanism ignores the morphology of the metal surface at the catalytically active site,[15,16,36–42] it is still the most readily applied mechanism for the synthetic organic chemist.[1,28,43–45] Horiuti and Polanyi recognized that both the substrate and hydrogen must be

adsorbed onto the metal surface during hydrogenation and that the addition of both hydrogen atoms was not concerted. They proposed a series of elementary steps to describe hydrogenation, all of which are reversible (Scheme 3). Hydrogen is dissociatively adsorbed at an active site and the alkene is adsorbed at two adjacent active sites to give a diadsorbed species (Scheme 3, A). A hydrogen atom adds to one olefinic carbon to give a monoadsorbed species (Scheme 3, B). This is followed by the addition of a second hydrogen atom and the product is desorbed (Scheme 3, C). The final desorption is virtually irreversible, but can be observed in an exchange reaction between D_2 and alkanes and will be strongly influenced by the presence of other coordinating groups.



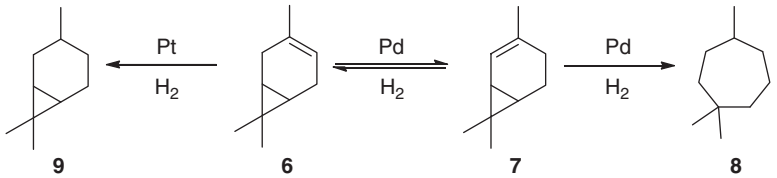
Scheme 3

8.16.2.2 Double-Bond Isomerization

Double-bond isomerization (*cis–trans* and regiochemical isomerization) can occur during hydrogenation due to the reversibly of the initial addition of a hydrogen atom to the adsorbed substrate (Scheme 3, B).[1,4,5] If the monoadsorbed species undergoes conformational change before reversion to the diadsorbed species, isomerization can occur. If the monoadsorbed species reverts to a different diadsorbed species (by abstraction of a different hydrogen to that which was added initially), double-bond migration will occur. The extent of isomerization is related to the rate at which the monoadsorbed species undergoes the reverse reaction to the diadsorbed species and the rate of addition of the second hydrogen atom. An alternative mechanism for isomerization proposes a metal–allyl intermediate that is generated by hydrogen atom abstraction α to the diabsorbed species.[46–48]

In general, the use of lower hydrogen pressures, and thus lower amounts of adsorbed hydrogen, favors isomerization processes.[47,48] Metals differ in their inherent ability to promote isomerization in the following order of decreasing activity Pd $\gg$ Rh, Ru, Pt > Os > Ir.[49] Active forms of Raney nickel show similar levels of isomerization to rhodium, but older (aged) Raney nickel and P-2 nickel are less active for isomerization.[50] Platinum is often the metal of choice if isomerization is to be minimized and palladium if isomerization is wanted or acceptable.[3,4]

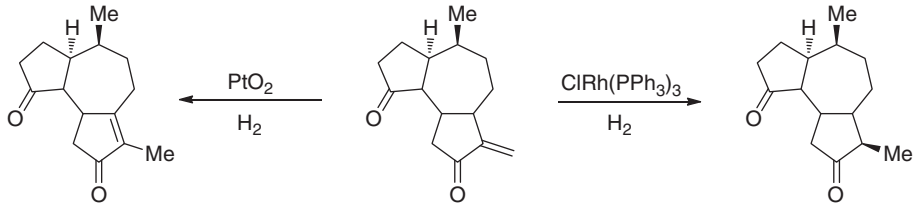
Double-bond migration can lead to the formation of functional groups susceptible to hydrogenolysis in compounds that appeared resistant to hydrogenolysis. Carene **6** contains a nonconjugated cyclopropane, but on attempted hydrogenation with palladium black, double-bond migration occurs and hydrogenation is accompanied by hydrogenolysis to give the ring-expanded product **8**. The use of platinum gives carane **9** as the major reaction product (Scheme 4).



Scheme 4

Although platinum usually offers a solution to problematic alkene isomerizations during hydrogenation, it is not always effective. The hydrogenation of coronopilin **10** with platinum oxide gives the isomerization product isocoronopilin **11** (Scheme 5). Hydrogenation to dihydrocoronopilin **12** can be achieved in a homogeneous fashion using Wilkinson's catalyst.[51]

For substrates that are particularly sensitive to hydrogenolysis or isomerization, Rh and Ru catalysts can offer the optimal reactivity for hydrogenation. Rh/Al_2O_3 is the catalyst of choice for the hydrogenation of chloroalkenes.[52] The hydrogenation of a



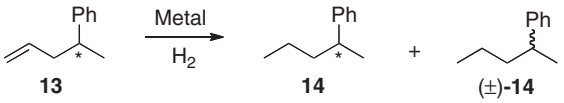
11 **10** **12**

Scheme 5

dihydrobenzofuran was only successful with Rh/Al_2O_3.[53] However, other metal catalysts have been reported to give selective hydrogenation. Ni (P-1) has been used for the selective hydrogenation of allylic alcohols, ethers, and esters.[54] Surprisingly, palladium reduced with borohydride was shown to be selective for the hydrogenation of vinyl- and allyloxy compounds.[55]

Racemization of enantioenriched alkenes has been observed and is particularly relevant when using palladium. Double-bond migration is usually the cause of racemization and the extent of double-bond migration directly correlates with the loss of enantiopurity of the substrate. The hydrogenation of enantioenriched 3-phenyl-1-butene **13** in ethanol using palladium on calcium carbonate gave a significant decrease in enantiopurity when compared with those observed for the hydrogenation using Raney nickel or platinum oxide (Table 4).[56] Similarly, but to a much greater degree, the hydrogenation of enantioenriched 3-methyl-1-hexene and 3,7-dimethyl-1-octene using palladium proceeded with extensive racemization (32–63%). This could be reduced by the addition of base or use of high hydrogen pressure.[57]

Table 4 Catalyst propensity for racemization



13 **14** **(±)-14**

Metal	*Amount of racemization (%)*
$Pd/CaCO_3$	9.1–11.3
PtO_2	3.5
Raney-Ni	1.1–2.5

8.16.2.3 Apparent *anti*-Addition of H_2

With few exceptions, the *syn*-addition of both hydrogen atoms to the alkene is observed in heterogeneous hydrogenation. For example, the hydrogenation of diastereomeric alkenes (*E*)- and (*Z*)-2,3-diphenyl-2-butene, with palladium on carbon in AcOH, gives the racemic and *meso*-isomers of 2,3-diphenylbutane, respectively.[47] However, apparent *anti*-addition of H_2 can be observed if alkene isomerization occurs under the hydrogenation conditions.[44,47] The hydrogenation of 1,2-dimethylcyclohexene **15** with various noble metals gives a mixture of *cis*-**16** and *trans*-1,2-dimethylcyclohexane **17** (Table 5). The *trans*-diastereoisomer **17** arises from double-bond migration to give the trisubstituted alkene **18** which then undergoes *syn*-hydrogenation. The ratio of diastereoisomers presumably reflects the tendency of the metal to catalyze double-bond migration (Scheme 6).[44,47,58]

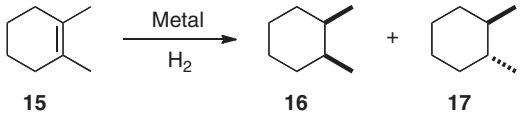
8.16.2.4 Isolated Alkenes

In the most general terms, less substituted or sterically unencumbered isolated alkenes are hydrogenated more easily. The relative rates of the P-2 nickel-catalyzed[50] (Scheme 7) and silica-supported platinum (Scheme 8) hydrogenation of various alkenes demonstrate this nicely. Ring strain can also lead to increased rates of hydrogenation.[50]

The rate of hydrogenation is thus clearly related to the degree of alkene substitution in the following order $H_2C{=}CHR^1 > H_2C{=}CR^1R^2 > cis\text{-}R^1CH{=}CHR^2 > trans\text{-}R^1CH{=}CHR^2 > R^1R^2C{=}CHR^3 \gg R^1R^2C{=}CR^3R^4$ with variation of the substituents having only a secondary effect.[59]

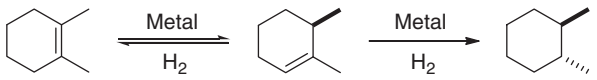
The steric hindrance about an alkene can also affect the diastereoselectivity of hydrogenation as adsorption will preferentially occur to the least hindered face of the alkene. This often means that the preference for one diastereoisomer in a hydrogenation can be predicted. The hydrogenation of norbornene **19** with D_2 using palladium, platinum, and rhodium all gave the *exo*-isomer **20** exclusively (Scheme 9).[5] However substituents at C-7 can have a direct effect on the diastereoselectivity of the hydrogenation.

Table 5 Effect of catalyst choice on *syn*- and apparent *anti*-addition of H_2 to 1,2-dimethylcyclohexene



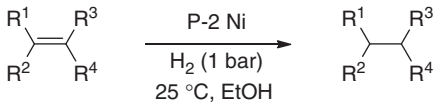
15 **16** **17**

Metal	*Conditions*	*Yield (%)*	
		*cis-**16***	*trans-**17***
Pt (PtO_2)	1 bar, AcOH	82	18
Pt (PtO_2)	300 bar, AcOH	96	4
Pt black	1 bar, ^{t}BuOH	79.1	20.9
Pd black	1 bar, ^{t}BuOH	26.4	73.6
Os black	1 bar, ^{t}BuOH	98.6	1.4
Ir black	1 bar, ^{t}BuOH	98.9	1.1

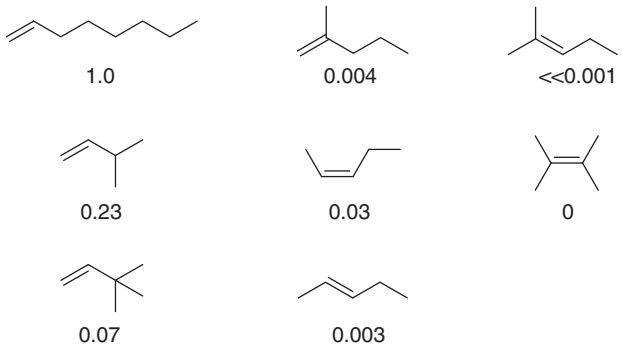


15 **18** **17**

Scheme 6



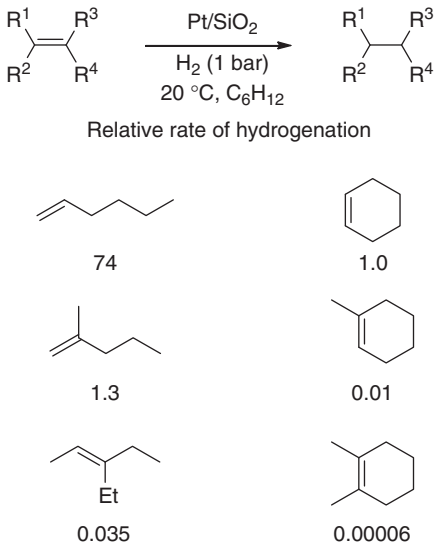
Relative rate of hydrogenation



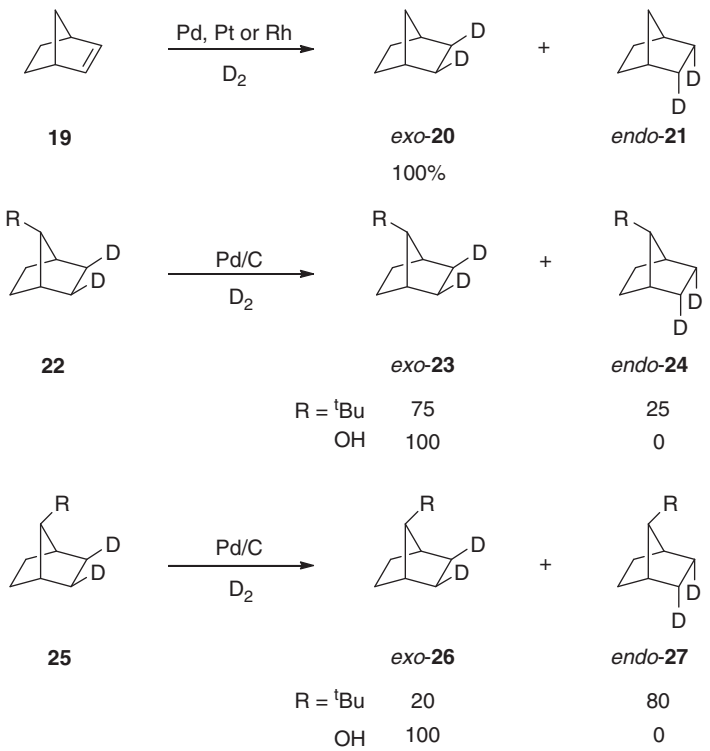
Scheme 7

A C-7 *anti*-*tert*-butyl group **22** gives an increase in the *endo*-isomer **24**, whereas an *anti*-hydroxyl group has no effect giving *exo*-isomer **23**. The substituent effects are increased when *syn*-C-7 **25** substituents are used.[60] Now the *tert*-butyl group gives the *endo*-isomer **26** as the major hydrogenation product, but a hydroxyl group still gives the *exo*-isomer **27** exclusively. Presumably the hydroxyl group can coordinate to the metal surface and hence direct alkene adsorption to favor *exo*-addition of D_2.

At first glance, it can appear that the choice of metal catalyst for the hydrogenation of an isolated alkene can come down to palladium versus platinum (Scheme 10). In the most general terms, platinum offers the best reactivity and lowest levels of alkene isomerization, but this reactivity can cause overreduction of other groups and rapid increases in reaction temperature. Palladium offers a good balance of reactivity and cost versus the high propensity to catalyze alkene isomerization. The rate of hydrogenation using platinum catalysts tends to be an order of magnitude faster for alkyl alkenes and even the most resistant of alkenes can be hydrogenated at elevated temperature and hydrogen pressure.[61,62] Monosubstituted alkenes are hydrogenated most rapidly over platinum oxide and the addition of a second alkyl substituent has little effect on the rate of hydrogenation. With 1,1-disubstituted alkenes, the nature of the substituents has a marked effect on the rate of hydrogenation. Dialkyl or monoaryl 1,1-distubstitued alkenes show similar reactivity, but 1,1-diaryl alkenes are significantly less reactive. Trisubstituted alkenes show a similar trend in



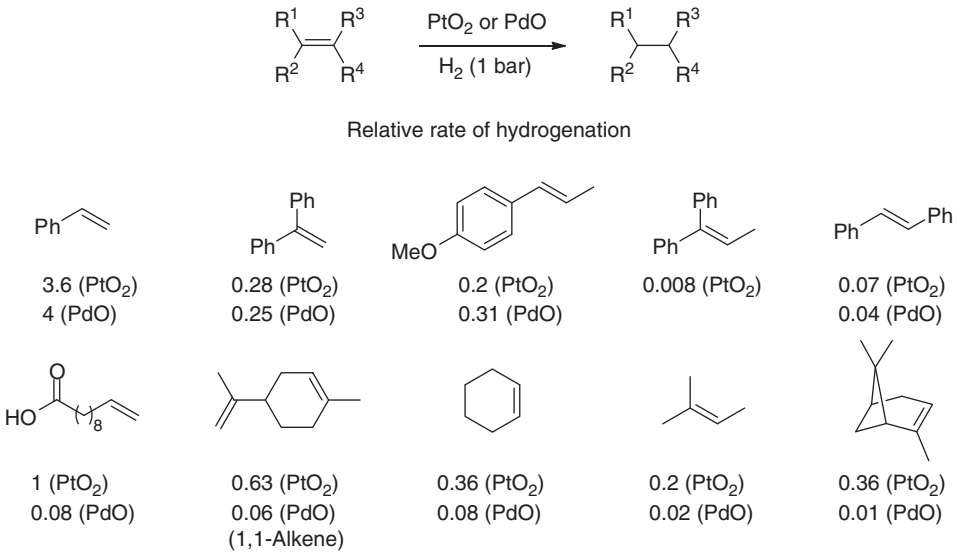
Scheme 8



Scheme 9

reactivity. The rate of hydrogenation of strained alkenes is significantly faster than the analogous nonstrained alkenes. In the case of aryl-substituted alkenes, palladium shows very similar activity to platinum.[63,64]

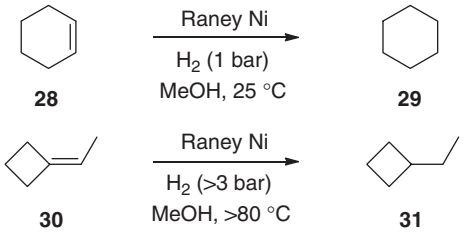
Phenyl substitution on the alkene has been shown to increase the rate of hydrogenation in contradiction to the general rule of thumb that increasing substitution decreases the rate of hydrogenation. The competitive hydrogenation of α-phenylstilbene and 3-ethyl-2-pentene over palladium and platinum catalysts showed selective hydrogenation of the triaryl alkene.[65] The rate of hydrogenation was also much faster on palladium than platinum. Raney nickel showed similar activity for phenyl-substituted alkenes.[66]



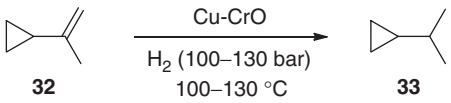
Scheme 10

Nickel catalysts are effective for the reduction of alkyl-substituted alkenes, although higher catalyst loadings than with platinum or palladium are needed.[38,61] Raney nickel has been used for the hydrogenation of cyclohexene **28** at atmospheric pressure, but elevated hydrogen pressure and reaction temperature were required to hydrogenate the trisubstituted alkene **30** (Scheme 11).[38,67,68]

Copper–chromium oxide has been used for the hydrogenation of alkenes that are susceptible to double-bond migration or hydrogenolysis, albeit at high pressure and temperature. For example, the hydrogenation of isopropenylcyclopropane **32** was accomplished without hydrogenolysis of the vinyl cyclopropane (Scheme 12).[69]



Scheme 11

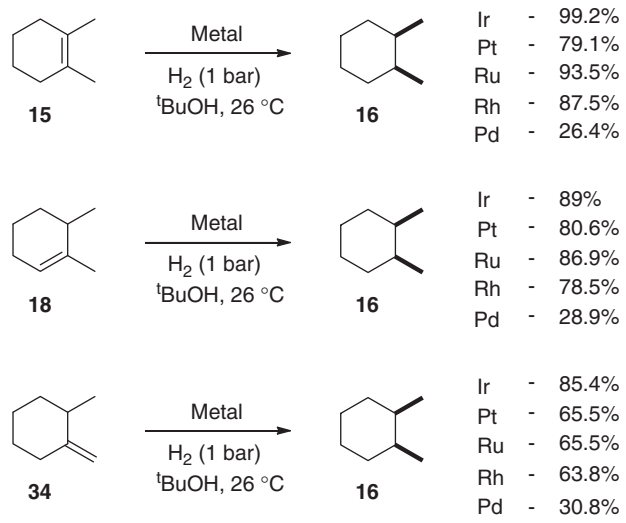


Scheme 12

The stereochemical outcome of the hydrogenation of monosubstituted cyclohexene derivatives proceeds to give the thermodynamically favored equatorial conformer of the substituted cyclohexane. However, predicting the product stereochemistry in the hydrogenation of disubstituted cyclohexenes is nontrivial.[70,71] The adsorbed alkene is in equilibrium with the two states associated with the addition of the first hydrogen atom. The preferred geometry of the adsorbed species favor eclipsing bonds around the original (now adsorbed) alkene leading to a boat-like transition-state structure.[70,71] This model has been used to successfully predict the hydrogenated stereochemistry of 1,4- and 2,3-disubstituted cyclohexenes, but should be applied with caution.[70,72] In the most general sense, dialkyl-substituted cyclohexenes tend to give high proportions of the *cis*-dialkylcyclohexane, except where palladium catalysts are used.

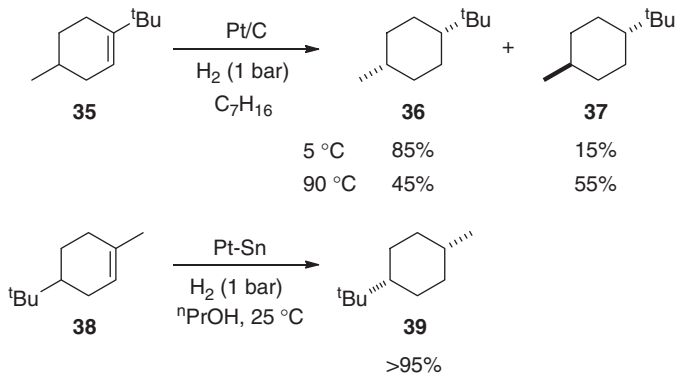
All the three regioisomeric alkenes, **15**, **18**, and **34**, showed preferential hydrogenation to the *cis*-isomer **16** except when palladium black was used (Scheme 13).[73] The higher proportion of *trans*-1,2-dimethylcyclohexane can be accounted for by double-bond migration.

Platinum-catalyzed hydrogenation of 1-*tert*-butyl-4-methyl-1-cyclohexene **35** and 1-methyl-4-*tert*-butyl-1-cyclohexene **38** showed a preference for the *cis*-cyclohexane **36** in both cases, but with a higher selectivity observed for the latter alkene



Scheme 13

38 (Scheme 14). In the case of 1-*tert*-butyl-4-methyl-1-cyclohexene **25**, the stereoselectivity could be reversed to favor the *trans*-cyclohexane **37** by carrying out the hydrogenation at higher temperature over platinum on carbon.[74–77]



Scheme 14

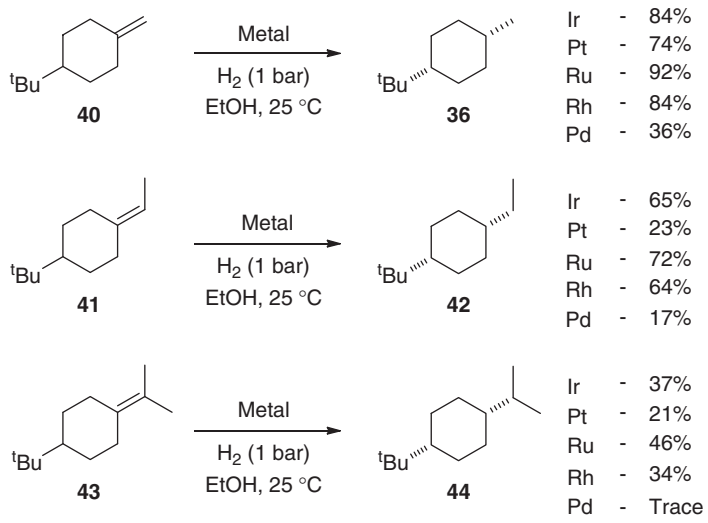
This situation becomes more complicated when an *exo*-alkylidene is hydrogenated. In these cases, increasing the size of the alkylidene group leads to decreased selectivity for formation of the *cis*-isomers **36**, **43** and **45** (Scheme 15), and in contrast to 1-methyl-4-*tert*-butyl-1-cyclohexene **38**, increased hydrogen pressure led to lower levels of selectivity.[78–80]

In contrast, Raney nickel can be used to give excellent selectivity of the *cis*-isomer **36**, but the catalyst must be aged or treated with carbon monoxide before hydrogenation (Scheme 16).[81–83] The increased stereoselectivity for the *cis*-isomer **36** of the aged Raney nickel was attributed to carbon monoxide abstraction from the solvent (ethanol) during the ageing process and a decreased propensity for the aged catalyst to catalyze double-bond migration into the ring. Fresh Raney nickel gave the *trans*-isomer **37** preferentially.

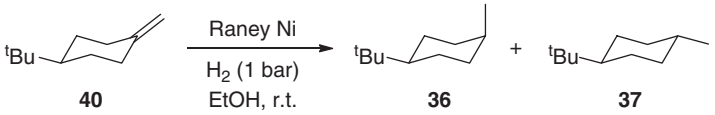
The hydrogenation of α-pinene **46** and β-pinene **45** proceeds with addition of hydrogen from the same face as the methylene bridge (not the isopropylidene bridge face) in both cases to give *cis*-pinane **47**. However, excellent diastereoselectivity can only be achieved with α-pinene **46** at high pressure using platinum on carbon (Scheme 17).[84,85] The use of palladium catalyzes rapid isomerization to α-pinene. Raney nickel has been shown to give high levels of stereoselectivity in the reduction of α-pinene, albeit at high temperature and pressure.[86]

The introduction of heteroatoms to cyclohexene leads to markedly different hydrogenation stereoselectivity. Hydrogenation of the six-membered cyclic acetals **49** proceeded with good-to-excellent levels of stereoselectivity for the *cis*-product **50** with most metal catalysts tested (Scheme 18). Platinum and palladium gave similar levels of the *cis*-isomer. Little variation in stereoselectivity was observed when the steric requirements of the substituent were increased.[87–89]

In contrast to the *O*-heterocycles, *N*-heterocycles give less predictable results. Hydrogenation of the two isomeric methylenepiperidines **51** and **54** showed unique reactivity (Scheme 19). *N*-Methyl-6-methyl-4-methylenepiperidine **51** gave the *cis*-piperidine **52** with all metal catalysts tested. In contrast, *N*-methyl-6-methyl-3-methylenepiperidine **54** gave the *cis*-piperidine **53** when hydrogenated with Raney nickel or palladium and the *trans*-piperidine **55** when hydrogenated over platinum, rhodium, or ruthenium catalysts.[90]

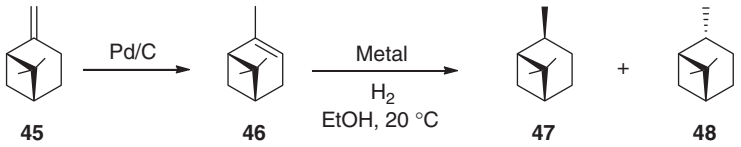


Scheme 15



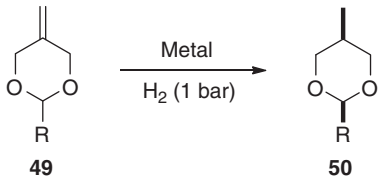
Fresh Raney Ni	23%	77%
Aged Raney Ni (40 days, EtOH)	95%	5%
Raney Ni pre-treated with CO	98%	2%

Scheme 16



Pt/C (100 atm)	98.5	1.5
Pt/C (1 atm)	90.0	10.0
PtO_2 (1 atm)	93.5	6.5
Pd/C (1 atm)	74.0	26.0

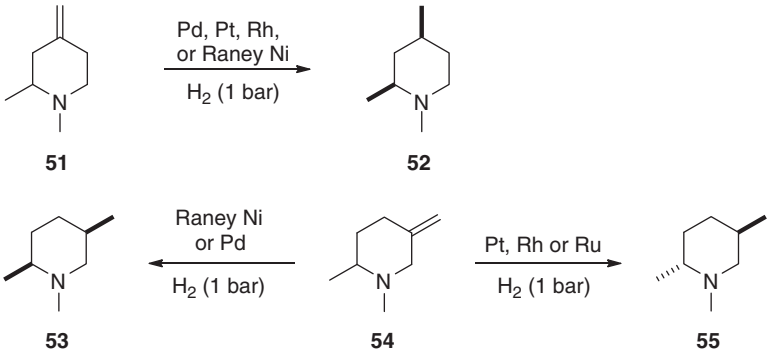
Scheme 17



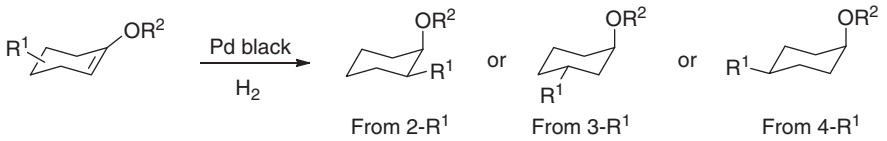
R =	Me	tBu
Pt	96%	98%
Pd	90%	97%
Rh	87%	92%
Ru	88%	98%
Raney Ni	89%	89%

Scheme 18

The use of 1-alkoxylcyclohexanes gives the axial/equatorial stereoisomer (axial OR, equatorial R) predominantly irrespective of the position of the alkyl substituent on the ring. This suggests that the stereochemical controlling step involves reductive elimination of the most stable alkyl intermediate which is adsorbed onto the metal at the carbon atom bearing the alkoxy substituent (Scheme 20).[5,73,91]

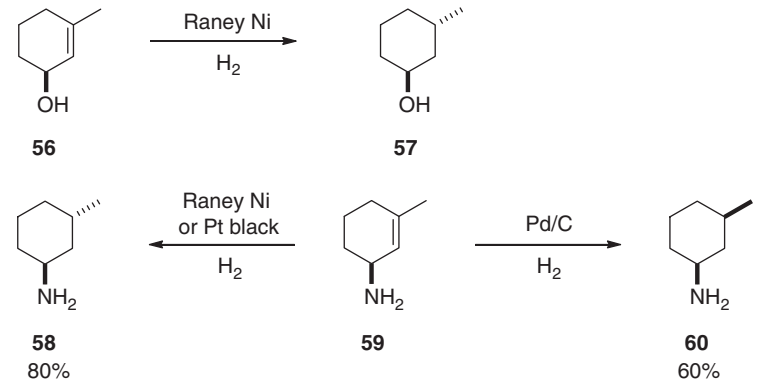


Scheme 19



Scheme 20

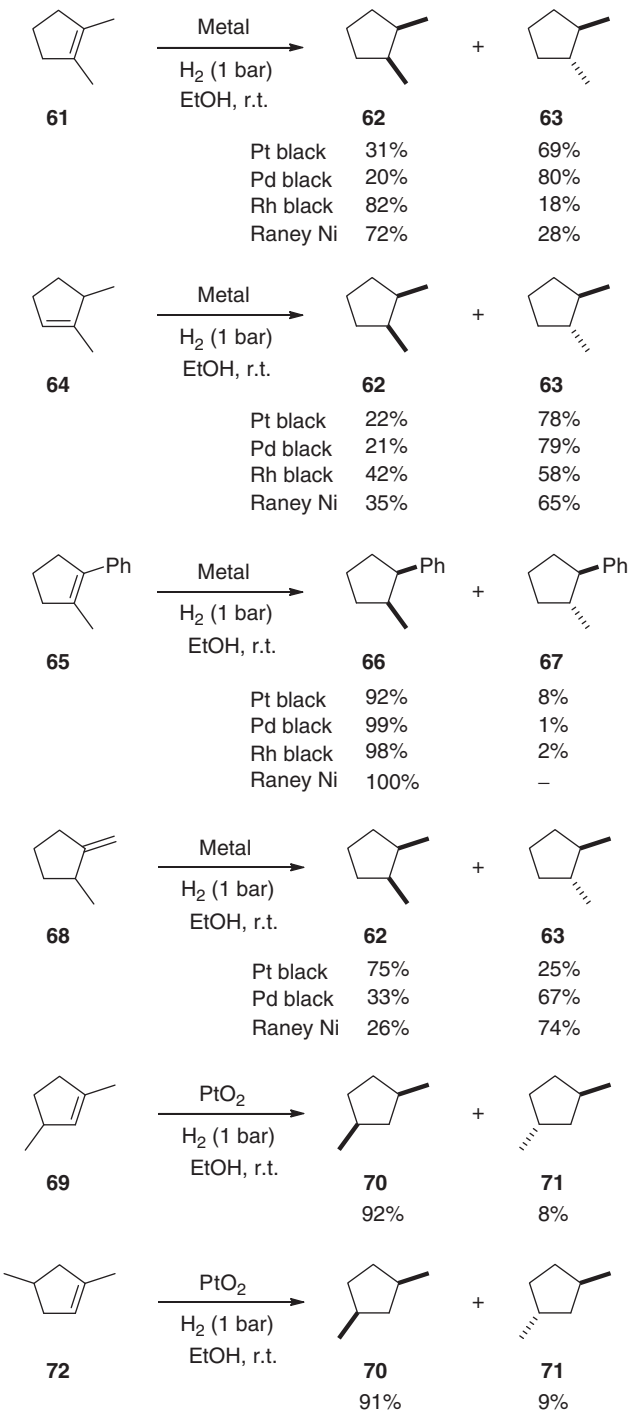
The addition of polar/coordinating groups to a cyclohexene can direct hydrogenation so as to add hydrogen from the same face as the polar group. This is attributed to preferential adsorption to the metal on the same face as the polar group. Methylcyclohexenol **56** was selectivity hydrogenated to the *trans*-cyclohexane **57** using Raney nickel (Scheme 21).[92] The same selectivity, for the *trans*-cyclohexane **58**, was observed for the hydrogenation of aminocyclohexene **59** when Raney nickel or platinum catalysts were used. However, hydrogenation using palladium on carbon gave the *cis*-cyclohexane **60** (Scheme 21).[93,94] The *trans*-selectivity was attributed to high levels of alkene isomerization resulting from the use of a palladium catalyst.



Scheme 21

The general selectivity for hydrogenation to the *cis*-isomer of cyclic alkenes is not observed for cyclopentenes (Scheme 22). Hydrogenation of dialkyl-substituted cyclopentenes gives the *trans*-cyclopentane preferentially. The 1,2-dimethyl-1-cyclopentene **61** showed only moderate selectivity for the *cis*-isomer, even when a rhodium catalyst was used. The high proportion of *trans*-cyclopentane **63** has been attributed to alkene isomerization by the metal catalyst. Support for this is seen in the hydrogenation of 1,2-dimethyl-2-cyclopentene **64** which gives very similar results to the double-bond isomer **61**, suggesting that the *trans*-cyclopentane **63** is a result of hydrogenation of the double-bond migration product. The introduction of a phenyl substituent reverses the selectivity of hydrogenation toward the *cis*-product. Hydrogenation of 1-phenyl-2-dimethyl-1-cyclopentene **65** gave excellent selectivity for the *cis*-cyclopentane **66** with all the metal catalysts tested. Selective hydrogenation to the *cis*-cyclopentane was also observed for the methylidene cyclopentane **68** and the two 1,3-dimethyl-cyclopentenes **69** and **72**. Interestingly, very similar levels of stereoselectivity were achieved for both of the double-bond isomers **69** and **72** to give the *trans*-cyclopentane **70**, suggesting rapid double-bond isomerization between the two cyclopentenes under hydrogenation conditions.[95–98]

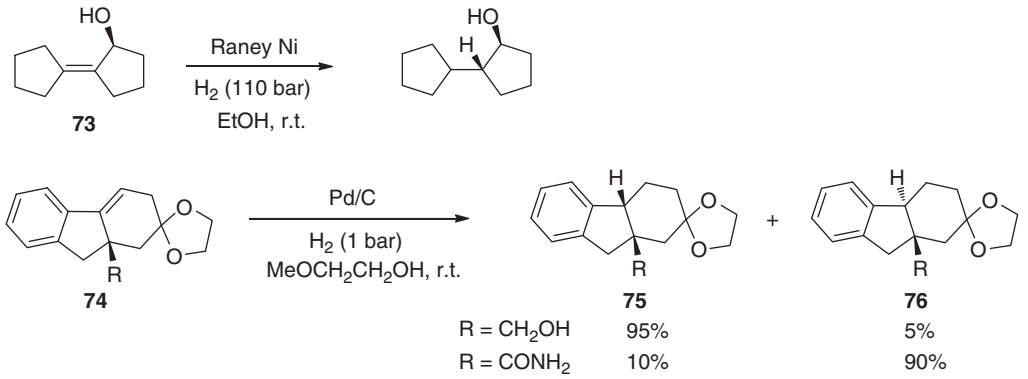
Selective hydrogenation to the *trans*-cyclopentane can be achieved by the use of a suitable directing group on the cyclopentene (Scheme 23).[99–104] Hydrogenation of alkene **73** bearing an adjacent alcohol gave almost exclusively the *trans*-product when Raney



Scheme 22

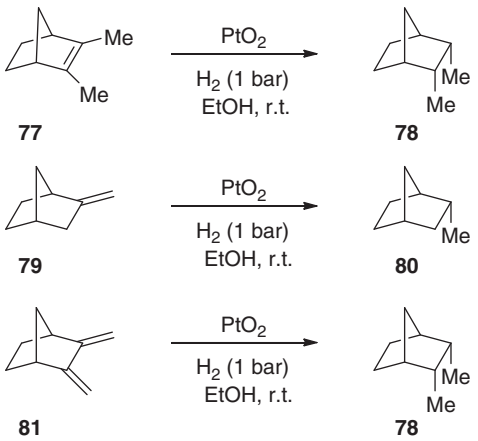
nickel was used as the catalyst.[99] The use of other metal catalysts (Pt, Pd, Ru, and Rh) also gave the *trans*-isomer, but with lower selectivity (81–92%).[100] Raney nickel also showed good activity and selectivity in the hydrogenation of related substrates, however palladium catalyzed double-bond migration to give the carbonyl product.[100,101] The amount of *cis*-product could be favored by using metals which catalyze alkene isomerization (Ni < Ru < Pt < Rh < Pd in this case).

The tetracycle **74** was used to evaluate the directing group ability of various functional groups.[105] The free alcohol was found to have the greatest directing effect to give the *cis*-isomer **75**, whereas an amide gave selectivity for the *trans*-isomer **76** (Scheme 23). The ability to direct hydrogenation to give the *cis*-isomer followed the order (*cis*-isomer %): CH_2OH (95) > CHO (93) > CN (75) > CH=NOH (65) > CO_2Na (55) > CO_2Li (23) > CO_2H (18) > CO_2Me (15) > COMe (14) > $CONH_2$ (10). It was not apparent that this order could be correlated to a single electronic or steric effect.[106]



Scheme 23

The hydrogenation of norbornenes **77**, **79**, and **81** usually proceeds to give the *endo*-product **78** and **80** (*endo-syn* product) when platinum catalysts are used (Scheme 24), *syn*-addition of hydrogen to the *exo*-face of the alkene gives the *endo*-norbonane **78** and **80**.[107,108] Greater than 95% selectivity for the *endo*-product was observed for norbornenes bearing both endocyclic and exocyclic alkenes in methanol or acetic acid. Any limited alkene isomerization therefore presumably has no effect on diastereoselectivity, with both endo- and exocyclic isomers being hydrogenated with the same high diastereoselectivity.

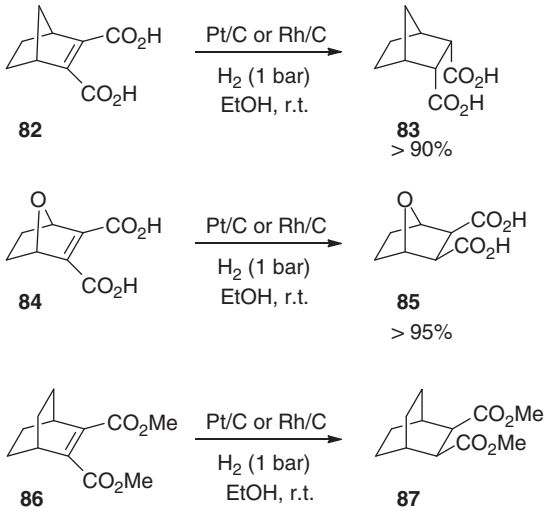


Scheme 24

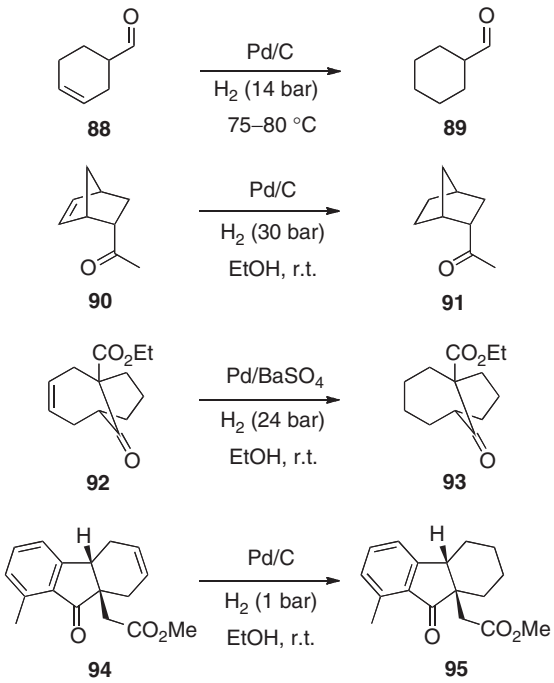
Norbornenes bearing ester or carboxylic acid substitution at the alkene show slightly reduced *endo*-selectivity in hydrogenations over platinum. This has been accounted for by isomerization of the adsorbed alkene to give an enolate after addition of the first hydrogen atom.[107,108] The hydrogenation of the diacid norbornene derivative **82** gave the *endo*-norbornene **83** with a selectivity of 90% (Scheme 25). In contrast, substitution of the methylene bridge for oxygen causes a complete reversal in hydrogenation selectivity. Hydrogenation of bicycle **84** gave the *exo*-alkane **85** almost exclusively (Scheme 25).[109] The addition of an extra CH_2 group to the bridge also reverses the selectivity of hydrogenation to give the *exo*-[2.2.2]-bicycle **87** as the only product when either platinum or rhodium catalysts were used (Scheme 25).[110–112]

8.16.2.5 Chemoselective Hydrogenation: Introduction

The chemoselective reduction of alkenes with remote carbonyl groups can usually be accomplished with most metal catalysts, unless the alkene is strongly deactivated (sterically or electronically). Palladium catalysts appear to be the most general and widely used metal catalysts for the chemoselective reduction of alkenes in the presence of carbonyl groups (Scheme 26). However, these reductions can require careful monitoring (hydrogen uptake or reaction progress) and optimization to avoid reduction of the carbonyl group. 3-Cyclohexene carboxaldehyde **88** was chemoselectively hydrogenated at the alkene using palladium on carbon to give cyclohexanecarboxaldehyde **89**, but 14 bar hydrogen pressure and careful temperature control were needed to ensure minimal reduction of the aldehyde.[113] Alkenes bearing distant ketones have also been chemoselectively hydrogenated. The strained norbornene[114] **90** required elevated pressure to ensure good chemoselectivity and the 1,3-dicarbonyl[115] **92** required the use of a 'poisoned' palladium catalyst ($Pd/BaSO_4$). The aryl ketone-substituted cyclohexene **94** was reduced at atmospheric pressure and temperature.[116]

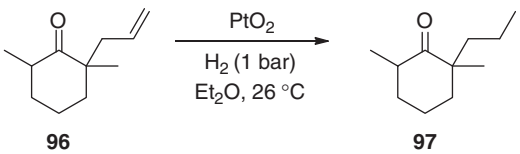


Scheme 25



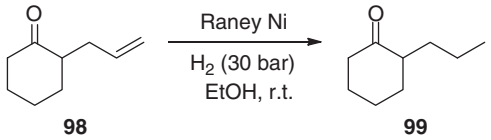
Scheme 26

Platinum oxide has been used successfully used to catalyze the hydrogenation of the terminal alkene **96** which has a remote ketone (Scheme 27).[117] Overreduction to the corresponding alcohol was not observed and the hydrogenation proceeded well at room temperature and atmospheric pressure. However, the relatively high reactivity of platinum catalysts increases the likelihood of concurrent carbonyl reduction.



Scheme 27

Raney nickel has also been used for the chemoselective hydrogenation of an alkene bearing a remote ketone, however, in contrast to when using a platinum catalyst, elevated hydrogen pressure and strict monitoring of the hydrogen uptake by the reaction were needed to prevent overreduction (Scheme 28).[118]

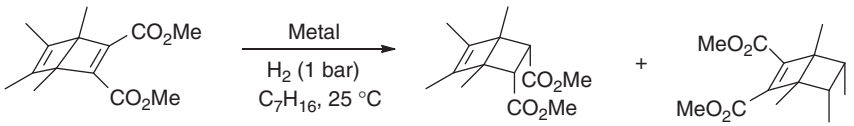


98 **99**

Scheme 28

8.16.2.6 Chemoselective Hydrogenation; Nonconjugated Dienes

Selective hydrogenation of nonconjugated dienes can usually be accomplished if the individual alkenes are significantly differentiated by steric or electronic factors. Hydrogenation of the [2.2.0]-bicyclohexadiene **100**, which has two tetrasubstituted alkenes, did not proceed beyond the dihydro-products **101** and **102**, however only Raney nickel gave good selectivity for reduction at the ester-substituted alkene to give alkene **101** (Scheme 29).[119] In all cases, the hydrogenation proceeded to give the *endo*-products, of both dimethyl alkene and diester alkene hydrogenation. Surprisingly, palladium on carbon was the most selective noble metal used, showing good selectivity for hydrogenation at the ester-substituted alkene.

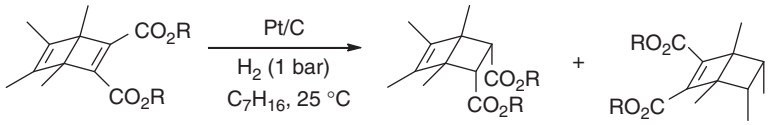


100 **101** **102**

Pt/C	42%	58%
Pd/C	85%	15%
Rh/C	52%	48%
Ru/C	66%	34%
Raney Ni	100%	0%

Scheme 29

However, increasing the steric demands of the ester substituent (from methyl to *tert*-butyl) was used to give selective hydrogenation at the dimethyl alkene (Scheme 30).[119]



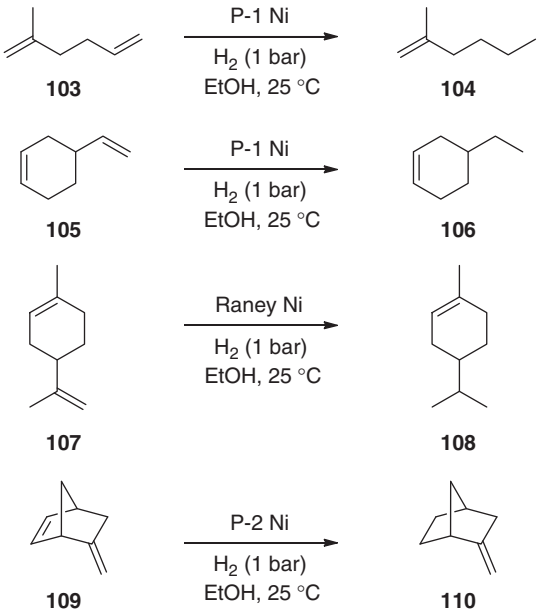
R = Me	42%	58%
^{t}Bu	5%	95%

Scheme 30

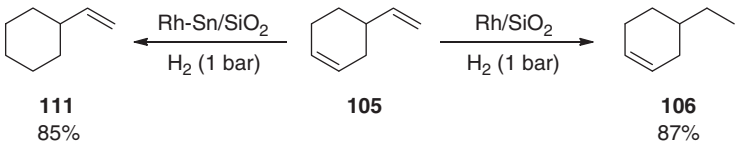
High chemoselectivity for the hydrogenation of a single alkene of a diene using nickel catalysts has also been reported for less exotic dienes (Scheme 31).[38,50,120,121] Selective hydrogenation of the terminal (monosubstituted) alkene of 2-methyl-1,5-hexadiene **103** was achieved using P-1 nickel under mild hydrogenation conditions, and without alkene isomerization of either the starting diene or product. P-1 nickel was also used for the selective hydrogenation of the terminal alkene of 4-vinylcyclohexene **106**.[120,136] Similarly, the 1,1-disubstituted alkene of limonene **107** was selectively hydrogenated over Raney nickel without racemization.[121] Ring strain increases the reactivity of an endocyclic alkene. The hydrogenation of norbornene derivative **109** with P-2 nickel was chemoselective for the 1,2-disubstituted *endo*-cyclic alkene, not the 1,1-disubstituted *exo*-methylidene, to give the *exo*-methylidene norbornene derivative **110**.[50]

The selective hydrogenation of either alkene of 4-vinylcyclohexene **105** has been reported using rhodium catalysts (Scheme 32).[122] Silica-supported rhodium selectively hydrogenated the terminal alkene to give 4-ethylcyclohexene **106**, whereas tin-doped rhodium on silica hydrogenated the cyclic alkene to give vinylcyclohexane **111**.

Copper catalysts have found use for the selective monohydrogenation of dienes, although usually under forcing reaction conditions. The selective hydrogenation of the allylic alcohol of geraniol **112** to citronellol **113** was achieved using copper at high

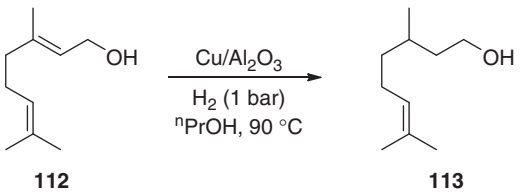


Scheme 31



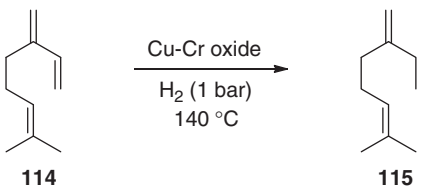
Scheme 32

temperature (Scheme 33). A copper catalyst (Cu/Al_2O_3) was highly chemoselective and avoided the production of menthol, as seen using other metal catalysts and forcing reaction conditions.[123]



Scheme 33

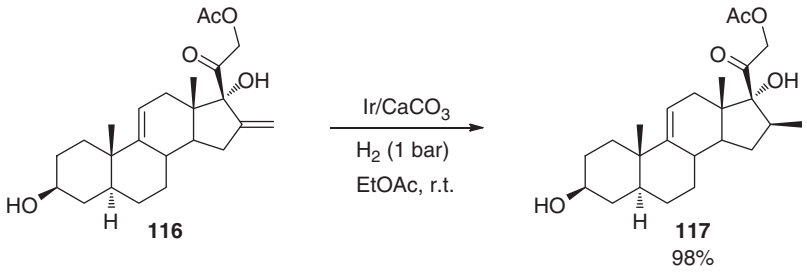
Triene **114** was chemoselectively hydrogenated at the monosubstituted alkene to give diene **115** using copper–chromium oxide, again at high temperature. Surprisingly, alkene isomerization of the triene or diene, both of which bear *exo*-methylene groups, did not occur under the hydrogenation conditions (Scheme 34).[124]



Scheme 34

Iridium on calcium carbonate has been used for the selective hydrogenation of the steroidal alcohol **116** (Scheme 35).[92] The use of an iridium catalyst minimized the amount of alkene isomerization at both the cyclic and terminal alkene and overreduction

at the carbonyl groups. Unsurprisingly, the 1,1-disubstituted alkene was chemoselectively hydrogenated in preference to the cyclic trisubstituted alkene.

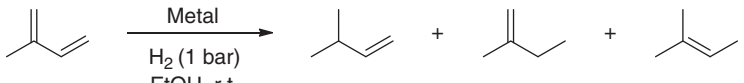


Scheme 35

8.16.2.7 Chemoselective Hydrogenation; Conjugated Dienes

The hydrogenation of conjugated dienes is generally undertaken with the aim of forming a monoene product. The selective semihydrogenation is possible as conjugated dienes are generally more reactive than simple alkenes or unconjugated dienes. However, it is rarely possible to hydrogenate selectively to a single regioisomeric monoene. Hydrogenation can occur by 1,2 or 1,4-addition of hydrogen and is usually accompanied by alkene isomerization. Using palladium catalysts this can be attributed to a greater preference for an η^4- over an η^2-adsorption mode. The addition of additives and poisons to the semihydrogenation of dienes has been shown to improve selectivities in a similar manner to that shown in the semihydrogenation of alkynes (see Section 8.16.3). Due to the industrial importance and simplified theoretical modeling, the vast majority of studies have been conducted using 1,3-butadiene, isoprene, 1,3-cyclooctadene, and other simple conjugated dienes.[125–128]

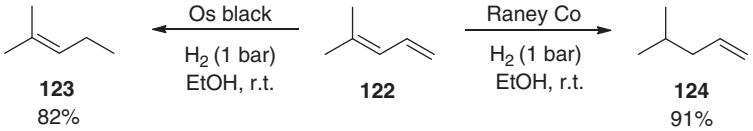
The hydrogenation of isoprene **118** over platinum black, palladium black, or Raney nickel gave a mixture of three alkene products, **119**, **120**, and **121** (Scheme 36).[129] The selective hydrogenation to a specific alkene has not been reported with any degree of selectivity and overhydrogenation to the alkane was observed with platinum black.



118		119	120	121
	Pt black	7	26	15
	Pd black	25	30	40
	Raney Ni	16	40	40

Scheme 36

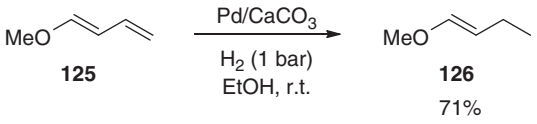
The hydrogenation of 4-methyl-1,3-pentadiene **122** could be achieved with good selectivity to give the terminal alkene **124** (Scheme 37). Raney cobalt and cobalt black (produced by reduction of cobalt oxide with hydrogen) were found to be the best catalysts, with all other noble metals and Raney nickel giving a mixture of monoene products. Osmium black was the exception to this, giving the trisubstituted alkene **123** as the major hydrogenation product. Interestingly osmium and cobalt showed good selectivity for a different alkene within the diene (Scheme 37).[130]



Scheme 37

Electronically differentiating the alkenes of a 1,3-diene, has been shown to not increase the regioselectivity of 1,3-diene hydrogenation.[131] *trans*-1-Methoxy-1,3-butadiene **125** could only be selectively hydrogenated using palladium supported on calcium carbonate to give the *trans*-alkene **126** as the major hydrogenation product (71%) (Scheme 38). Interestingly, the uptake of hydrogen nearly ceased after 50% (equivalent with respect to diene). Nickel and platinum catalysts gave a mixture of 1,4-, 1,3-, and 2,3-addition of hydrogen along with significant amounts of overhydrogenation to the alkane.

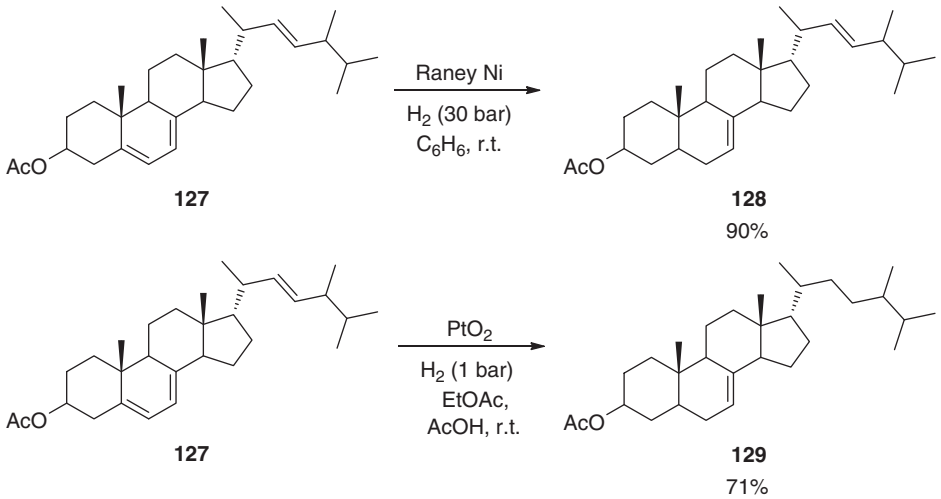
The regioselective monohydrogenation of cyclopentadiene and cyclooctadienes has also been reported.[132–136] Cyclopentadiene appears more difficult to monohydrogenate than the cyclooctadienes, with 1,3-cyclooctadiene giving much higher selectivity



Scheme 38

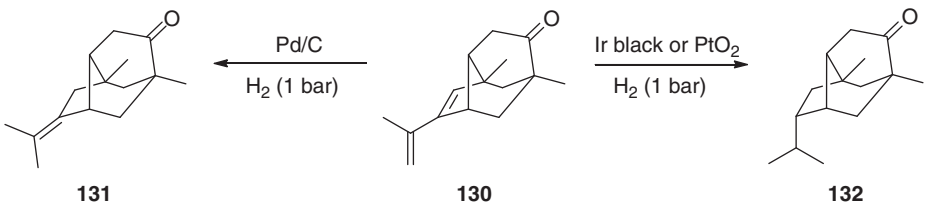
for monohydrogenation to cyclooctene. A series of modifiers have been used to attenuate the metal catalysts' reactivity and give good selectivity for hydrogenation to the monoenes.[137,138]

Few synthetically orientated examples of regioselective monohydrogenation of 1,3-dienes have been reported. Raney nickel and platinum oxide have been used for the selective reduction of steroidal polyene **127** (Scheme 39). When Raney nickel was used for the selective monohydrogenation of **127**, strict monitoring of the hydrogen uptake had to be done to ensure hydrogenation was stopped after 1 equivalent of hydrogen.[139] Quick separation of the catalysts and diene product **128** were needed to prevent overhydrogenation. In the case of platinum oxide, prereduction of the catalyst, in the reaction solvent, was needed and the monoreduction of the diene was accompanied by reduction of the isolated alkene in the side-chain to give the monoene **129**.[140]



Scheme 39

The use of iridium black or platinum oxide as catalyst for the hydrogenation of diene **130** proceeded without reduction of the ketone but was unselective for monoene reduction, giving the alkane **132** as the *endo*-isomer exclusively. Palladium on charcoal did give monoreduction to the alkene **131**, but with the addition of hydrogen in a 1,4 fashion. Presumably the tetrasubstituted alkene is a result of alkene isomerization (Scheme 40).[141,142]

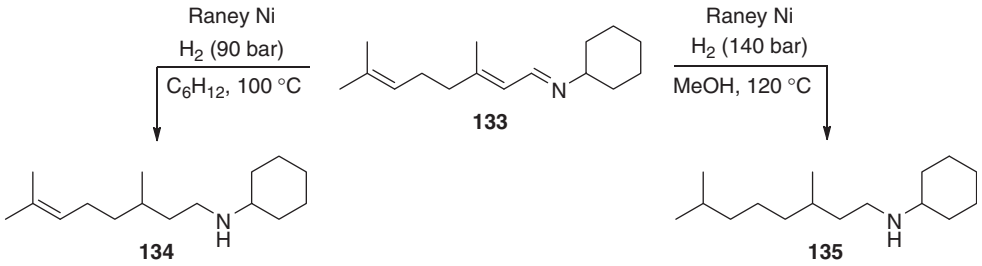


Scheme 40

The selective reduction of the α,β-unsaturated imine **133** bearing a remote alkene was achieved using Raney nickel (Scheme 41).[143] However, specific reaction conditions, including the use of cyclohexane as the reaction solvent, were needed to give the alkene **134** selectively. At higher hydrogen pressures or in polar solvents, complete reduction to the alkane **135** was observed.

8.16.2.8 Chemoselective Hydrogenation; Alkene Hydrogenation in the Presence of Other Reducible Functional Groups

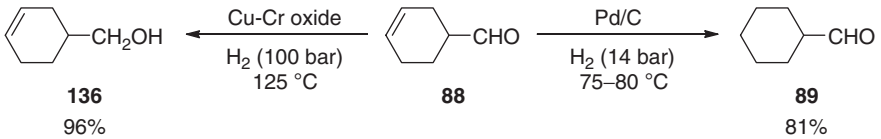
The chemoselective hydrogenation of alkenes in the presence of a carbonyl is usually achieved without difficulty. The hydrogenation of C═C over C═O is thermodynamically favored, and also kinetically favored when the correct catalyst is chosen. Palladium catalysts are usually the best choice for selective hydrogenation due to their low activity for the hydrogenation of



Scheme 41

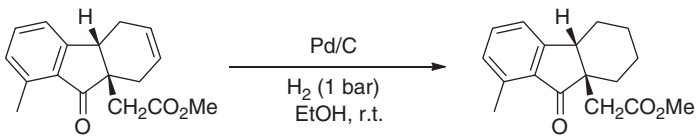
aliphatic carbonyl groups. Platinum and nickel catalysts are sometimes used when side reactions such as double-bond isomerization or hydrogenolysis may occur over palladium catalysts. Copper and rhodium heterogeneous catalysts have also proven to be effective in certain instances for the selective hydrogenation of alkenes in the presence of carbonyl functionalities. Due to the greater difficulty in selectively hydrogenating a carbonyl group in the presence of an alkene, the focus of most research is on this issue; however there are still many examples in which the selective reduction of the alkenic double bond is demonstrated.

The selective hydrogenation of 3-cyclohexene-1-carboxaldehyde **88** to the corresponding saturated aldehyde **89** was achieved over a palladium on carbon catalyst in high yield, with minimal overhydrogenation to the saturated alcohol (Scheme 42).[113] In contrast, hydrogenation of **88** over a copper–chromium oxide catalyst resulted in the selective hydrogenation to the unsaturated alcohol **136** (Scheme 42).[144] Citronellal has been selectivity hydrogenated to the saturated aldehyde over palladium on barium sulfate or platinum oxide,[145,146] whereas hydrogenation over chromium promoted Raney nickel[147] or lead-poisoned ruthenium oxide[148] led to the selective hydrogenation of the aldehyde to give citronellol in excellent yield.



Scheme 42

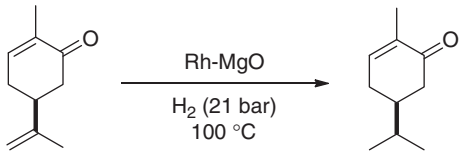
There are numerous examples of the selective hydrogenation of unsaturated ketones to saturated ketones using palladium, platinum,[117] and nickel[118] catalysts. The selective hydrogenation of 4-acetylcyclohexene (methyl ketone derivative of **88**) was readily achieved by reaction over a palladium on carbon catalyst, with no reduction of the ketone observed.[149] Hydrogenation of the tetrahydrofluorenone derivative **94** over palladium on carbon gave the reduced product **95** in high yield with no reduction of the keto-, ester-, or aromatic functionalities observed (Scheme 43). Hydrogen absorption was reported to cease after the absorption of 1 equivalent of hydrogen.[116]



Scheme 43

When a molecule contains both an isolated alkene and an enone or enal, the α,β-unsaturated system is usually hydrogenated preferentially, however the selective hydrogenation of the isopropenyl group of carvone **137** has been achieved.[150] Hydrogenation over a rhodium–magnesium oxide catalyst resulted in 92% selectivity for carvotanacetone **138**, however the yield of the reaction was not reported (Scheme 44). The selectivity appeared to be highly dependent on the choice of support material, as lower selectivities were observed for rhodium catalysts supported on either silica and titanium oxide.

α,β-Unsaturated aldehydes and ketones are also readily hydrogenated to the corresponding saturated aldehydes and ketones, usually without great difficulty. Palladium is the metal of choice for the preparation of highly chemoselective catalysts. The intrinsic selectivity of palladium catalysts is attributed to their propensity to coordinate enones and enals by an η^4-adsorption mode, favoring 1,4-addition rather than 1,2-addition, and hence the selective formation of unsaturated aldehydes and ketones. However if an aryl, or vinylogous aryl carbonyl such as cinnamaldehyde is hydrogenated, overhydrogenation to the saturated

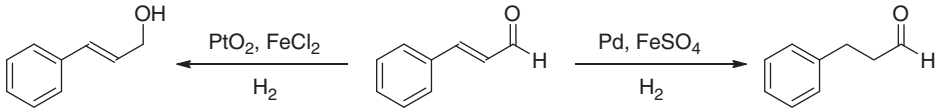


137 **138**

92% Selectivity

Scheme 44

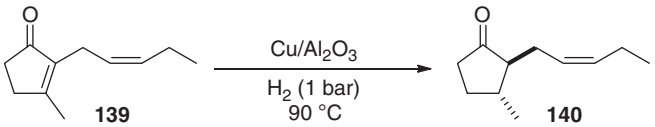
alcohol and subsequent hydrogenolysis to the alkane may occur over certain palladium catalysts.[151] By judicious choice of catalyst support and solvent, numerous conditions have been developed to chemoselectively hydrogenate cinnamaldehyde to 3-phenylpropionaldehyde. Palladium on alumina in ethanol or palladium on kieselguhr in acetic acid have been reported to give 3-phenylpropionaldehyde in quantitative yield at room temperature and atmospheric hydrogen pressure.[152] The simple addition of iron salts, such as ferrous sulfate, in a 1:1 ratio with respect to palladium is also effective in the selective hydrogenation of cinnamaldehyde.[153] Interestingly, in contrast, the addition of iron salts to platinum oxide has been used for the selective hydrogenation of cinnamaldehyde to cinnamyl alcohol[154] (Scheme 45). Modification of palladium catalysts by the addition of small quantities of potassium acetate also diminishes the rate of carbonyl reduction in related α,β-unsaturated aldehydes.[155]



Scheme 45

Recent studies into the selective heterogeneous hydrogenation of cinnamaldehyde and related α,β-unsaturated aldehydes have focused on the replacement of volatile organic solvents for the purpose of improved industrial applications. The immobilization of palladium nanoparticles on ionic liquid modified silica gels produced a catalyst which was highly active for the chemoselective alkene hydrogenation of cinnamaldehyde, with no loss in activity on recycling the catalyst up to nine times.[156] Imidazolium ionic liquids have also been used with a palladium on carbon catalyst for the hydrogenation of cinnamaldehyde and the related ester, benzyl cinnamate.[157] High yields and selectivities were observed for the preparation of the saturated aldehyde and ester, with no hydrogenolysis of the benzyl group observed in the latter case.

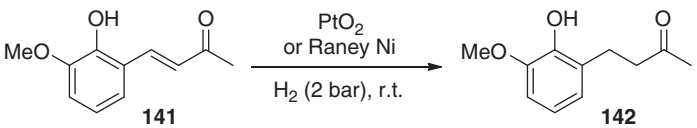
Hydrogenation of α,β-unsaturated ketones to the corresponding saturated ketones is readily achieved due to the low tendency of aliphatic ketones to undergo hydrogenation to the corresponding alcohols. The hydrogenation of usually challenging double bonds can be achieved under mild conditions when the double bond is conjugated with a carbonyl group, as demonstrated by the Cu/Al_2O_3-catalyzed hydrogenation of *cis*-jasmone **139**.[158] Here, the tetrasubstituted double bond of the enone was hydrogenated whereas the ketone functionality and the isolated disubstituted alkene were conserved (Scheme 46).



139 **140**

Scheme 46

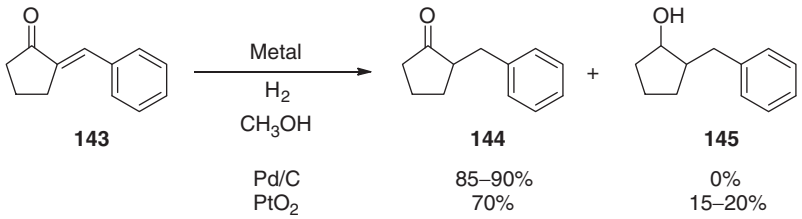
Platinum oxide and Raney nickel were both found to be suitable catalysts for the quantitative hydrogenation of 4-(2-hydroxy-3-methoxyphenyl)-3-buten-2-one **141** to the corresponding butanone **142**, but only when small quantities of catalyst were used (Scheme 47). When the loading of platinum oxide was increased from 0.5 to 1 wt.%, or similarly when the loading of Raney nickel was increased to 10–15 wt.%, overhydrogenation took place.[159] Mannich and Merz found that the hydrogenation of the related 4-hydroxy-3-methoxy derivative over palladium on carbon resulted in significant overhydrogenation, with up to 30% of the butanol product formed.[160]



141 **142**

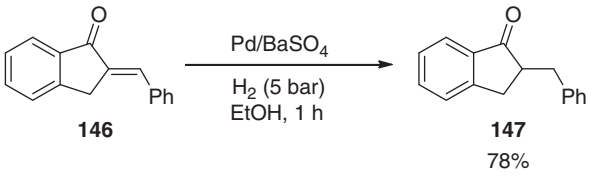
Scheme 47

Palladium catalysts however are generally the best choice for the selective hydrogenation of α,β-unsaturated ketones to the corresponding saturated ketones. Hydrogenation of aliphatic α,β-unsaturated ketones presents no problem over palladium due to the intrinsic chemoselectivity for 1,4-addition over 1,2-addition.[161] The hydrogenation of 2-benzylidenecyclopentanone **143** over palladium on carbon in methanol proceeded with the uptake of just 1 equivalent of hydrogen to give benzylcyclopentanone **144** in 85–90% yield (Scheme 48). Hydrogenation of **143** over platinum oxide however resulted in a yield of 70% of **144** and 15–20% overhydrogenation to 2-benzylcyclopentanol **145**.[162]



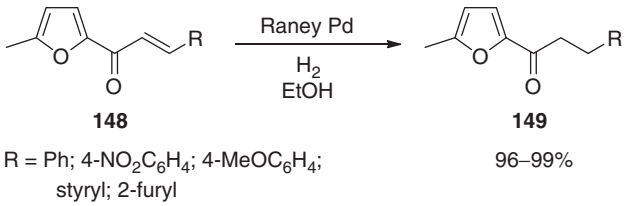
Scheme 48

In keeping with the trends noted for aryl aldehydes however, the hydrogenation of aryl ketones can lead to overhydrogenation to benzyl alcohols and hydrogenolysis to hydrocarbons. Nevertheless, there are still many examples in which this substrate class has been successfully hydrogenated selectively to give the saturated ketone. 2-Benzyliden-1-indanone **146** was hydrogenated selectivity and in good yield to the corresponding saturated ketone **147**. The reaction was stopped after the absorption of 1 equivalent of hydrogen to give the product, with no overhydrogenation to the benzyl alcohol reported (Scheme 49).[163]



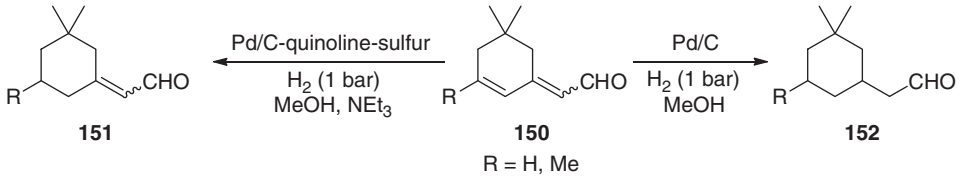
Scheme 49

A range of furan-conjugated enones **148** were hydrogenated over Raney palladium to give the saturated ketones **149** in excellent yield with no reduction of the ketone or furan ring observed (Scheme 50).[164]



Scheme 50

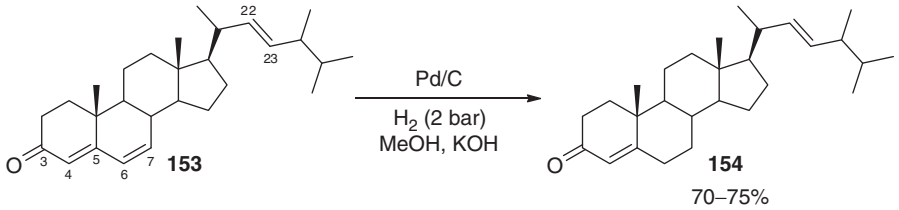
A greater challenge is presented in the selective hydrogenation of conjugated polyunsaturated aldehydes or ketones. The hydrogenation of the α,β,γ,δ-unsaturated aldehyde **150** over palladium on charcoal in methanol gave the fully saturated aldehyde **152**. Selective partial hydrogenation to the α,β-unsaturated aldehyde **151** was achieved in methanol over a palladium on carbon catalyst poisoned with quinoline and sulfur with added triethylamine. The pheromone, 3,3-dimethlcyclohexylideneacetaldehyde **151** (R=H) was produced in quantitative yield when hydrogenation was stopped after the addition of 1 equivalent of hydrogen (Scheme 51).[165]



Scheme 51

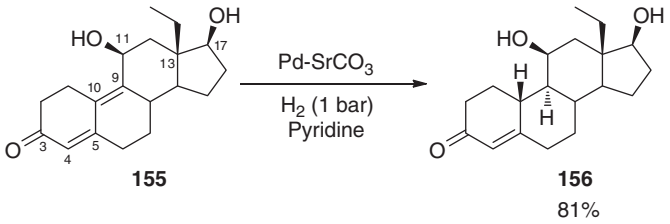
Palladium catalysts have been widely applied for the selective partial hydrogenation of 3-oxo-4-ene, 1,4-diene, and 4,6-diene steroids.[166] Ergosta-4,6,22-trien-3-one **153** was selectively hydrogenated to the 4,22-dien-3-one derivative **154** by reaction over

palladium on carbon in methanol containing a small quantity of potassium hydroxide. Optimum yields were obtained when the catalyst was prepared by prereduction. After the absorption of 1 equivalent of hydrogen the reaction was stopped to give **154** in 70–75% yield (Scheme 52).[167]



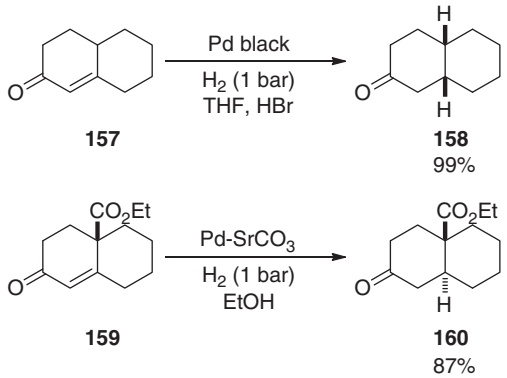
Scheme 52

In steroidal structures, such as ergosta-4,6,22-trien-3-one **153** the γ,δ-double bond of the dienone is often selectively hydrogenated over palladium catalysts. In 13β-ethyl-11β-hydroxygona-4,9-dien-3-one **155**, unlike in **153**, the γ,δ-double bond of the dienone is tetrasubstituted, however hydrogenation over palladium on strontium carbonate still gave the α,β-unsaturated enone **156** selectively and in high yield. It was suggested that the 9α,10α-isomer was initially formed after *syn*-addition of hydrogen, but was followed by isomerization to the naturally occurring 9α,10β-isomer (Scheme 53).[168]



Scheme 53

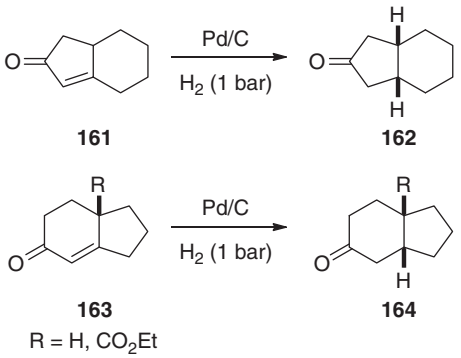
The stereochemistry of the hydrogenation of steroids and related polycyclic structures has been extensively investigated.[16,169–172] In the hydrogenation of the simple bicyclic enone **157** over palladium catalysts, hydrogenation of the alkenic double bond leads to the formation of *cis*- and *trans*-2-decalone. The stereoselectivity of the reduction is highly dependent on the solvent, and it was found that increasing the polarity of aprotic solvents led to an increased preference for the *cis*-2-decalone product **158**.[173] The addition of hydrobromic acid in tetrahydrofuran gave **158** in quantitative yield, with no overreduction to the alcoholic product (Scheme 54).[16] Many steroids possess a substituent at the C-10 position on the AB ring juncture. Substitution of decalenone **157** at the ring juncture with CH_3 or CH_2OH had little effect on the stereoselectivity of the hydrogenation, and the *cis*-product was still obtained in good yield.[172,174] Unlike the parent system however, when a methyl group was placed at the C-10 position, the solvent of choice proved to be 4-methoxypyridine (87% selectivity for the *cis*-product), whereas use of strong acid in tetrahydrofuran led to only 75–79% selectivity. Pyridine and 4-methoxypyridine are excellent solvents for steroids, and they are commonly used for selective hydrogenations, which can be performed at high concentrations. Rather than their basic properties, it has been suggested that it is the nucleophilic nature of pyridine derivatives which determines the selectivities often observed.[16] Interestingly however, when an ester



Scheme 54

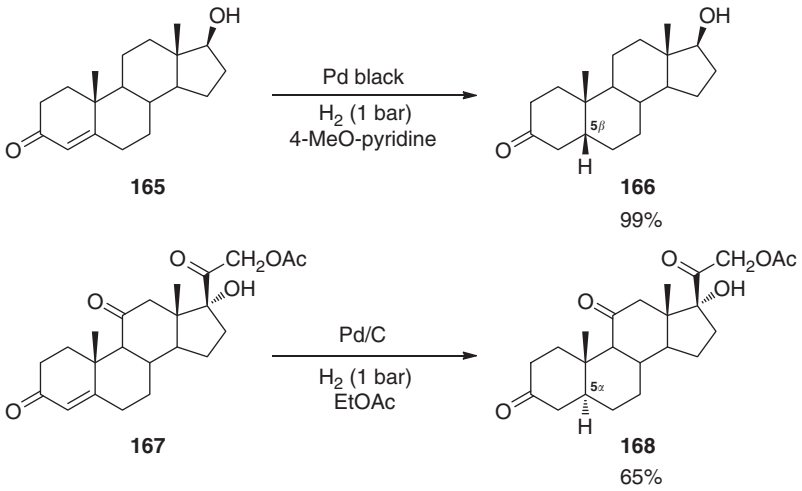
group was placed at the C-10 position of a decalenone system **159**, a reverse in stereoselectivity was reported, and the *trans*-fused ring product **160** was formed in 87% yield (Scheme 54).[175]

The hydrogenation of tetrahydroindanones **161** and **163** over palladium on charcoal resulted in the stereoselective formation of *cis*-ketones **162** and **164** in quantitative yield whether in neutral, acidic, or basic media (Scheme 55).[176] In contrast to the decalenone system however, an ester substituent at the ring juncture has no effect on the stereoselectivity of the reaction, and the *cis*-fused ring system is still formed by hydrogenation over palladium on charcoal under neutral, acidic, or basic conditions.[177]



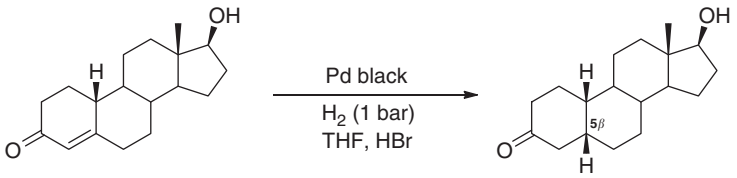
Scheme 55

The stereoselectivity in the hydrogenation of steroids tends to follow the same trends observed with the simple decalenone system. Testosterone **165**, which possesses a β-methyl group at the C-10 position, undergoes hydrogenation over palladium to give a 99% yield of the 5β *cis*-ring fused product **166** when carried out in 4-methoxypyridine (Scheme 56). When pyridine was used as solvent, a yield of only 90% of the 5β product was obtained.[16] It is well known in the hydrogenation of steroids that seemingly remote functionality can have a stark effect on the stereoselectivity of the hydrogenation. The hydrogenation of cortisone acetate **167** over palladium on charcoal results in the selective formation of the 5α *trans*-ring fused product **168** in good yield (Scheme 56).[178] Although cortisone acetate possesses a β-methyl group at the C-10 position, it seems that the added functionality at C-11, C-17, or C-20 directs the stereoselectivity of the hydrogenation. A number of thorough investigations have been conducted to elucidate the origin of stereoselectivity in the hydrogenation of substituted steroids.[16,170–172]



Scheme 56

In contrast to the usual steroids which possess a 10β-methyl group, 19-norsteroids lack this substitution, and when hydrogenated display a decreased stereoselectivity for 5β-ketones. As with the hydrogenation of decalenone **157** (Scheme 53), the most highly stereoselective hydrogenations of 19-norsteroids are generally achieved in tetrahydrofuran in the presence of hydrobromic acid. Thus, 19-nortestosterone **169** was hydrogenated to the corresponding 5β-ketone **170** in 99% yield over palladium black in tetrahydrofuran and hydrobromic acid (Scheme 57).[16] It is worth noting that the hydrogenation of testosterone **165** under these conditions gave a reduced yield of 78%,[170] compared with 99% selectivity observed in 4-methoxypyridine.



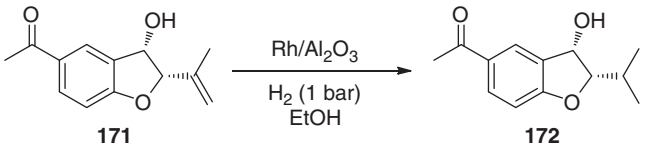
169 **170** 99%

Scheme 57

8.16.2.9 Chemoselective Hydrogenation; Hydrogenations in the Presence of Groups Prone to Hydrogenolysis

The hydrogenation of alkenes in the presence of reducible functionalities such as vinyl and allyl ethers; benzyl ethers, esters, and amines; epoxides, sulfides, and carbon–halogen bonds can present issues of chemoselectivity (*see* Chapters 8.26, 8.27, 8.28, 8.29, 8.30, and 8.32).

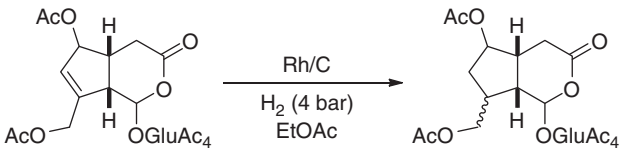
In general, the hydrogenation of allylic functionalities such as allyl ethers and allyl acetates can be accomplished using ruthenium and rhodium catalysts. The use of palladium tends to lead to increased levels of hydrogenolysis through the formation of π-allyl complexes.[179] A classic example is the hydrogenation of toxol **171**, which over palladium or platinum catalysts led to a complex mixture of products, presumably due to hydrogenolysis of either the allyl phenol ether or benzyl alcohol, or hydrogenation of the aryl ketone. When hydrogenation was performed over rhodium on alumina, hydrogen uptake stopped after a molar equivalent, and dihydrotoxol **172** was obtained in good yield (Scheme 58).[180,181]



171 **172** 77%

Scheme 58

The hydrogenation of diacetate **173** over platinum oxide or palladium on carbon in ethyl acetate, ethanol, acetic acid, dioxane, or water gave products with extensive hydrogenolysis of the allylic acetate groups. Hydrogenation at 4 bar over a rhodium-on-carbon catalyst, however, gave **174** in 95% yield as a 1:1 mixture of diastereoisomers. At 1 bar of hydrogen, a 1:4 ratio of diastereoisomers was formed, from which the major diastereoisomer was crystallized in a yield of 75% (Scheme 59).[182]

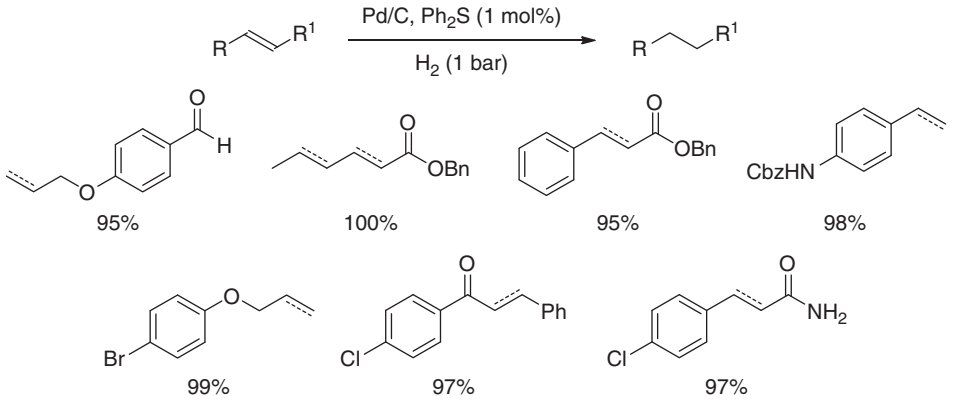


173 **174** 95%

Scheme 59

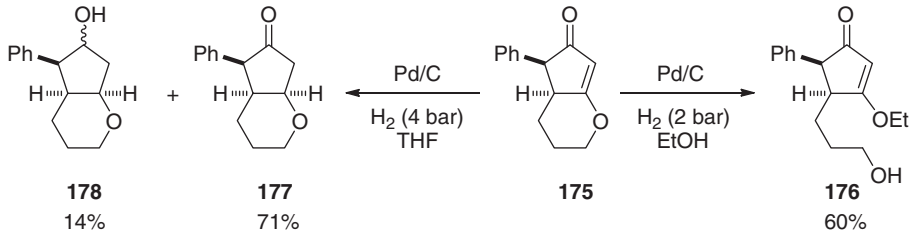
Contrary to the extensive hydrogenolysis observed in hydrogenations over most palladium catalysts, specially prepared or poisoned palladium catalysts have been used effectively for the hydrogenation of alkenes in the presence of hydrogenolysable functional groups. Palladium chloride reduced with sodium borohydride produces a catalyst over which the successful hydrogenation of a range of allyl and vinyl alcohols, ethers, esters, amines, and amides was achieved with no hydrogenolysis of the carbon–heteroatom bond observed.[183] Nitrile groups were also conserved, but it was noted that substrates containing epoxides were slowly opened to give alcohol products. A palladium on carbon–ethylenediamine complex catalyst has been developed which shows good chemoselectivity for the hydrogenation of alkenes in the presence of *O*-benzyl and *N*-Cbz groups and epoxides.[184–186] After pretreating the catalyst with ethylenediamine, the hydrogenolysis of phenolic benzyl ethers was suppressed, however the hydrogenolysis of benzyl esters was still rapid. A range of allyl epoxides were demonstrated with limited ring opening to the alcohol reported, although perhaps notably no allyl epoxides were included in the substrate scope. In addition, the catalyst system was shown to be an effective catalyst for hydrogenation of aryl ketones to the corresponding secondary alcohols, which could limit substrate scope with respect to the hydrogenation of alkenes.[187] Sajiki has shown that the addition of diphenylsulfide to palladium on carbon produces a highly selective catalyst for the hydrogenation of alkenes, alkynes, and azides.[188,189] Excellent

yields were reported for the hydrogenation of alkenes in the presence of aromatic carbonyls, aromatic halides, cyano groups, benzyl esters, and *N*-Cbz protecting groups, with no hydrogenolysis of the carbon–heteroatom bonds observed (Scheme 60).



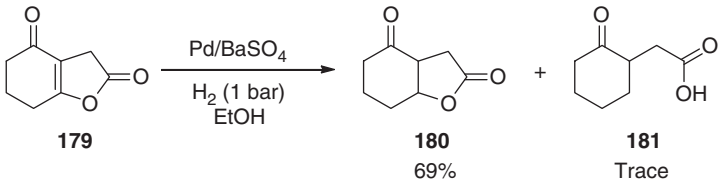
Scheme 60

In general, palladium, ruthenium, and rhodium catalysts are of use for the hydrogenation of enol ethers.[190] For the hydrogenation of simple enol ethers, such as ethyl 4-methyl-1-cyclohexenyl ether, hydrogenolysis was favored over platinum catalysts and suppressed by ruthenium and palladium catalysts.[191] The hydrogenation of the vinylogous ester **175** over palladium on carbon in ethanol, however, led exclusively to the transesterification product **176**.[192] When the solvent was switched to tetrahydrofuran, hydrogenation took place to predominately form the dihydro product **177**, with some overhydrogenation to alcohol **178** also observed (Scheme 61).



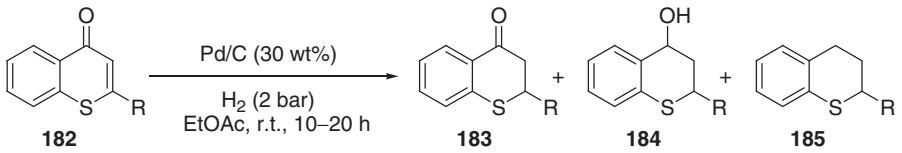
Scheme 61

The enol lactone **179** was hydrogenated in good yield over palladium on barium sulfate in ethanol to give the saturated lactone **180**.[193] The reaction was stopped after the absorption of 1 equivalent of hydrogen, however it was noted that a small quantity of the hydrogenolysis product **181** was formed, and this affected the isolated yield of the reaction due to the need for purification (Scheme 62).



Scheme 62

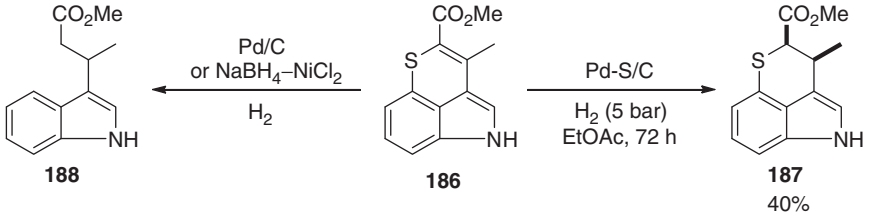
Alkenic substrates that contain sulfide groups can be expected to be reduced slowly as sulfides bind strongly to the heterogeneous surface and thus act as a catalyst poison. Satisfactory hydrogenations generally require a high catalyst loading and long reaction times. Palladium on carbon is the most common catalyst used.[194] The hydrogenation of the vinylogous thioesters of thiochromone **182** to the corresponding thiochromanones **183** was achieved over palladium on carbon (30 wt.%) after 10–20 h of reaction time (Scheme 63).[195] The selectivity of the hydrogenation was reported to be highly dependent on substrate structure, with good yields and excellent chemoselectivity observed for 2-alkyl-substituted derivatives. 2-Aryl derivatives however showed much lower selectivity and overhydrogenation of the aryl ketone to the benzyl alcohol **184** and subsequent hydrogenolysis to the saturated hydrocarbon **185** was observed. It should be noted that the reduction of **182** with Zn/AcOH, Li/liquid NH_3, Wilkinson's catalyst, diimide, and cyclohexene/palladium on carbon failed to give the expected product **183**.



R =	183	184	185
Me	65	0	0
Et	62	0	0
Ph	45	18	31
p-ClC_6H_4	10	25	40
p-$MeOC_6H_4$	0	0	66

Scheme 63

A highly chemoselective hydrogenation of a complex vinyl sulfide was reported in the synthesis of the antibiotic chuangxinmycin.[196] Dehydrochuangxinmycin methyl ester **186** was anticipated to be a challenging substrate for hydrogenation due to the tetrasubstituted olefin which may be further deactivated by conjugative electron release from the indolic nitrogen. The vinyl sulfide would also act as a poison to the catalyst and the compound may be susceptible to hydrogenolysis. Numerous conditions using homogenous and heterogeneous catalysts did indeed fail, however a sulfided palladium catalyst proved to be highly chemoselective in the hydrogenation of **186** to give chuangxinmycin methyl ester **187** in good yield (Scheme 64). Hydrogenation over sodium borohydride reduced nickel chloride or palladium on carbon gave only the desulfurized hydrogenolysis product **188**.[197]



Scheme 64

Extensive hydrogenolysis can occur in the hydrogenation of chloroalkenes over palladium and platinum catalysts to form hydrocarbons and HCl, whereas reaction over supported rhodium catalysts has proven somewhat better.[198] Hydrogenation over rhodium on alumina gave excellent yields for alkenes with remote alkyl chloride functionalities; however vinyl and allyl chlorides gave lower yields of only 42–58%. Carbon–fluorine bonds (sp^3) are usually stable under hydrogenation conditions, and hydrogenolysis is generally not observed unless high temperatures are used.[199,200] However, allylic, vinylic, and benzylic carbon–fluorine bonds are readily hydrogenolyzed over various catalysts. The most selective catalyst for the hydrogenation of vinyl fluorides was reported to be palladium on carbon in ether, whereas platinum and rhodium catalysts favored hydrogenolysis of the carbon–fluorine bond to give saturated hydrocarbons.[201]

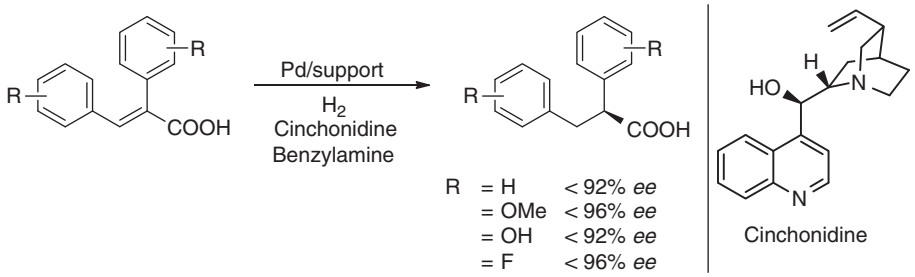
8.16.2.10 Enantioselective Hydrogenations

The modification of a metal surface by the adsorption of a chiral organic molecule had led to the development of enantioselective heterogeneous hydrogenation catalysts (*see* Chapter 8.17). Palladium catalysts modified by cinchona, vinca, or ephedra alkaloids are the best catalysts for the hydrogenation of α-functionalized olefins. The source of enantioselectivity is generally accepted to arise from a strong substrate–modifier interaction, in conjunction with a modifier–catalyst surface interaction, and thus unfunctionalized olefins are not suitable substrates. The catalytic systems developed are generally very specific with respect to the substrate–chiral modifier interactions, nevertheless good-to-excellent *ee* have been achieved for the hydrogenation of α,β-unsaturated acids, esters and ketones, and pyrone derivatives.[202–205]

8.16.2.10.1 α,β-Unsaturated acids and esters

In 1964 Beamer reported that the hydrogenation of methylcinnamic acid over a silica-supported palladium catalyst in the presence of a cinchona alkaloid resulted in a slight *ee* of (+)-dihydro-α-methylcinnamic acid.[206] The methodology was later developed, in the main by Nitta, to achieve an *ee* of more than 90% in the case of diaryl-substituted acids (Scheme 65). In order to obtain good enantioselectivities, a relatively high loading of cinchona alkaloid is generally required. This observation is often attributed to the weak adsorption of cinchona alkaloids on palladium. A stoichiometric amount of an achiral amine such as benzylamine is usually added to the reaction, which results in a faster and more enantioselective reaction. A study has suggested that added benzylamine has little effect on the cinchona alkaloid–substrate complex, but effectively dissociates the cinchona alkaloid–product complex resulting in the preferential formation of a benzylamine–product complex, releasing the cinchona

alkaloid and leading to a more efficient catalytic cycle. The increased enantioselectivity is explained by both the blocking of unselective catalyst sites by benzylamine, and by an increase in the electron density of the catalyst surface. This results in a preference for π-bound (rather than *N*-bound) cinchona alkaloid, leading to a better stereochemically defined surface.[207]



Scheme 65

A study by Baiker concluded that the enantioselectivity of the reaction was heavily affected by the structure of the substrate.[208] The differences in enantioselectivity were explained as an artefact of double-bond migration, a process common on palladium catalysts (Figure 1). The lowest enantioselectivities were observed when the substrate contained a terminal double bond which could migrate to a more stable internal double bond. Intermediate enantioselectivities were observed for substrates containing internal double bonds, and the best enantioselectivities were observed when migration was not possible. Further developments, particularly from Szöllösi and Sugimura, have extended the substrate scope to include substituted heteroaromatics,[209,210] unsaturated *N*-acetylamino acids,[211] and *s*-alkyl-substituted derivatives[212] in good-to-excellent *ee*. However, *n*-alkyl derivates still invariably result in poor-to-moderate *ee*, especially when located at the β-position (with respect to the carboxylic acid).[213]

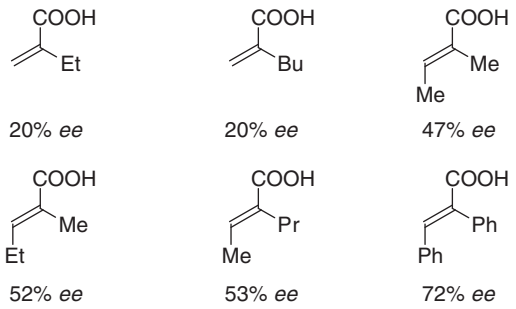
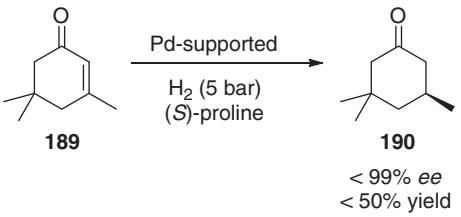


Figure 1 Enantioselectivities achieved in the asymmetric catalytic heterogeneous hydrogenation of various α,β-unsaturated carboxylic acids.

Mechanistic studies consistently propose that the enantioselection of the reaction is determined by an acid–base interaction between substrate and modifier, and accordingly esterification of the substrate results in a reduction in enantioselectivity.[214,215] The palladium–cinchona alkaloid system is moderately effective however when extra functionality is introduced at the α-position of the double bond. Examples include the hydrogenation of an enamine (24% *ee*),[216] ethyl 2-acetoxyacrylate (50% *ee*),[217] and an *N*-acetyl dehydroamino ester (up to 33% *ee*).[218]

8.16.2.10.2 Unsaturated ketones

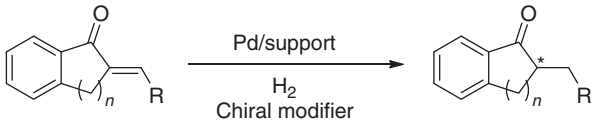
Much of the work on enantioselective heterogeneous hydrogenation of α,β-unsaturated ketones is related to the proline-directed reduction of isophorone **189**.[219–221] Excellent enantioselectivities have been achieved (up to 99%), however stoichiometric amounts of proline were required and the reaction gave yields of less than 50% (Scheme 66).



Scheme 66

In Tungler's original work it was suggested that proline acts as a chiral auxiliary that reacts to form an imine which is hydrogenated diastereoselectivity. It is now generally accepted however that isophorone undergoes racemic hydrogenation, and the observed enantioselectivity is the result of a secondary kinetic resolution of the hydrogenated product.[222] This theory accounts for the observed maximum yield of 50% and the need for stoichiometric amounts of proline. It was originally proposed that the kinetic resolution occurred in solution; however, subsequent studies have reported that enantioselectivities are dependent on catalyst choice suggesting that enantiodifferentiation may take place on the catalyst surface.[223–225] An enantioselective heterogeneous hydrogenation of isophorone has been achieved by tethering chiral sulfide ligands to palladium nanoparticles. The ligands used were derived from proline and at a loading of 0.05 mol%, up to 14% *ee* could be achieved, indicating that a truly enantioselective hydrogenation is taking place and not a kinetic resolution.[226]

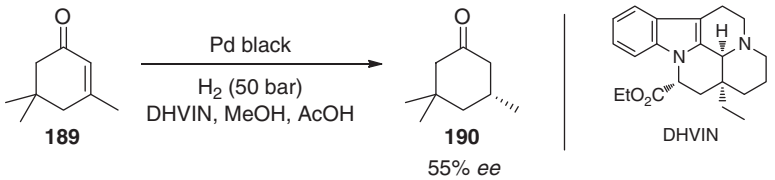
For 'true' enantioselective heterogeneous hydrogenation of unsaturated ketones, the best reported *ee* are generally approximately 50%. Cinchonidine modified palladium black has been used for the enantioselective hydrogenation of an exocyclic alkenone, 2-benzylidene-1-benzosuberone, with 54% *ee* (Scheme 67).[227] (–)-Ephedrine has also been used as a chiral modifier for palladium on carbon in the enantioselective hydrogenation of structurally related exocyclic α,β-unsaturated indanone and tetralone derivatives in 19–36% *ee* (Scheme 67).[228]



n	R	Chiral modifier	*ee*
3	Ph	Cinchonidine	54%
1, 2	H, *i*-Pr, Ph	(–)-Ephedrine	19–36%

Scheme 67

The enantioselective hydrogenation of isophorone **189** over palladium black has also been achieved by the addition of a vinca alkaloid, (–)-dihydro-apovincaminic acid ethyl ester (DHVIN), resulting in *ee* of up to 55% (Scheme 68).[229,230] The addition of a weak acid was used to improve the enantioselectivity of the reaction, and it was therefore suggested that enantioselection may arise from the interaction of the keto function of isophorone with the protonated aliphatic nitrogen of DHVIN.

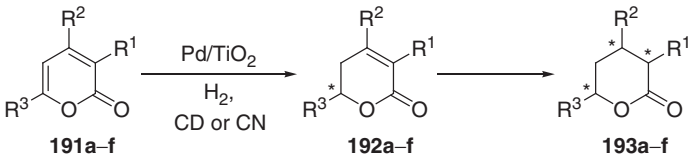


Scheme 68

8.16.2.10.3 Pyrone derivatives

The enantioselective hydrogenation of 4-hydroxy, 4-methoxy, and 4-methyl derivatives of 2-pyrone has been achieved on cinchona alkaloid modified, titanium oxide-supported palladium catalysts (Table 6).[231,232] Partial hydrogenation of the 4-hydroxy pyrone derivative **191a** to the corresponding dihydropyrone **192a** was accomplished in 85% *ee*, using cinchonidine as the chiral modifier. The hydrogenation was slow, and was complicated by a competitive hydrogenation of the quinoline ring of cinchonidine, leading to decreasing enantioselectivity over the course of the reaction. Continuous addition of chiral modifier suppressed this problem, and higher enantioselectivities could be maintained for the course of the reaction. Mechanistic studies using *O*- and *N*-alkylated cinchonidine derivatives and in the presence of acid and base, led the authors to suggest that enantioselection arose from the formation of a thermodynamically favored bidentate substrate–modifier complex. An acid–base interaction between the quinuclidine nitrogen of the modifier and the phenolic group of the substrate, and a hydrogen bond between the hydroxy group of the modifier and the carbonyl of the substrate were cited as the probable governing factors.[233] Alkylation of the acidic 4-hydroxy group of the substrate led to a faster rate of reaction with no competitive hydrogenation of the cinchona alkaloid modifier. Excellent enantioselectivities (85–94% *ee*) were observed for 4- and 6-substituted pyrone derivatives (Table 6, **192b,c,** and **e**), however substitution in the 3-position led to a slight decrease in enantioselectivity (75% *ee*, Table 6, **191d**). The 4-methyl-substituted pyrone derivative **191f** was also readily hydrogenated, however hydrogenation could not be stopped after a single uptake of hydrogen, and the fully hydrogenated tetrahydropyrone derivative **193f** was formed with 99% *de*. The lack of selectivity for partial hydrogenation of the 4-methyl-substituted pyrone derivative **192f** was attributed to the missing stabilization imparted in the other examples by the methoxy or hydroxy group.

Table 6



Entry	*Modifier*	R^1	R^2	R^3	*ee (%)*
191a	CD	H	OH	Me	85 (*S*)
191b	CN	H	OMe	Me	94 (*R*)
191c	CN	H	OEt	Me	85 (*R*)
191d	CN	Me	OMe	Me	75 (*R*)
191e	CN	H	OMe	$Ph(CH)_2$	89 (*R*)
191f	CN	H	Me	Me	–

Abbreviations: CD, cinchonidine; CN, cinchonine.

8.16.3 Hydrogenation of Alkynes

8.16.3.1 General

The heterogeneous hydrogenation of alkynes is usually performed with the aim of semihydrogenation to produce the corresponding *cis*-alkene (*see* Chapters 8.17 and 8.18). Complete hydrogenation to give the alkane product is achievable by judicious choice of catalyst based on the same considerations taken in the hydrogenation of alkenes; however, chemoselective semihydrogenation to the unsaturated alkene product is of greater practical and academic interest. In achieving selective semihydrogenation of alkynes, overhydrogenation must be suppressed in addition to *cis–trans* and positional isomerization of the double bond. Oligomerization processes can also operate, however this is only an important consideration in the hydrogenation of acetylene, as with increasing substitution of the alkyne, the selectivity of oligomer formation is substantially reduced due to increased sterics.[234]

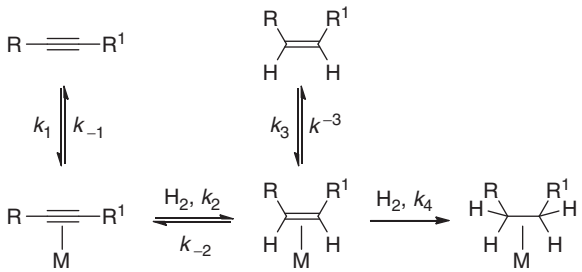
The following issues of selectivity will be addressed within this section:

1. Chemoselective semihydrogenation of alkynes to alkenes.
2. Stereoselectivity of semihydrogenation.
3. Regioselective hydrogenation of one alkyne in the presence of another alkyne.
4. Selective hydrogenation of alkynes in the presence of other reducible functional groups.

The chemo-, stereo-, and regioselectivity of alkyne semihydrogenation is dictated by the correct choice of metal, catalyst support material and morphology, and the addition of modifiers (either other metals or organic molecules). In depth mechanistic discussions will not be covered, but a number of excellent resources exist on this subject.[44,235–238]

8.16.3.2 Catalyst Composition

Sabatier and Senderens were the first to report that the semihydrogenation of acetylene over palladium and nickel catalysts proceeded selectivity to produce ethene, whereas hydrogenation over a platinum catalyst occurred unselectively.[239] Iron, rhodium, platinum, and nickel catalysts have since been successfully used as catalysts for the semihydrogenation of alkynes, however palladium has remained the catalyst of choice, both in terms of chemo- and stereoselectivity.[6,11,235,240] In general, the selectivity in the hydrogenation of hydrocarbons with multiple unsaturation can be described by the 'rake' diagram (**Scheme 69**).[241]



Scheme 69

The selective semihydrogenation of the alkyne to alkene can be achieved if either $k_2 \gg k_4$ (kinetic selectivity), or if $k_1/k_{-1} \gg k_3/k_{-3}$. In the latter case, the strong adsorption of the alkyne results in a low concentration of adsorbed intermediate alkene, and hence prevents further hydrogenation to the fully reduced alkane. Over palladium catalysts, the rate of hydrogenation of alkenes and alkynes are of the same order of magnitude, with alkenes generally exhibiting faster rates (i.e., k_4 is generally greater than k_2).[242] The observed selectivity however can be attributed to the fact that alkynes are adsorbed much more strongly than alkenes on palladium, and thus the reactive sites are monopolized by the adsorbed alkyne.[242,243] The morphology of the catalyst, as well as the addition of catalyst poisons and modifiers can perturb the relative kinetics and binding energies involved, and thus selective semihydrogenation can be achieved by judicious choice of conditions.[244,245]

Common materials used to support palladium include alumina, silica, calcium carbonate, barium sulfate, pumice, carbon, and aluminosilicates (zeolites).[7] The supporting material not only immobilizes the catalyst to allow for easy handling on a small scale, but can also have a pronounced effect on the morphology of the catalyst and subsequently the catalytic activity.[246] The effect of particle size is an important consideration in heterogeneous catalysis. Changing the dispersion of the metal (or the nature of the support) can lead to structural and electronic changes in the catalyst, and these in turn affect the activity and selectivity exhibited by the catalyst.[247] Large particles possess extended planes of terraced atoms with high coordination numbers (few free coordination sites), whereas small particles have a higher density of atoms with low coordination numbers typical of stepped regions and corners. In addition, the chemisorption bands of bulk metal compared with small particles have been shown to be significantly different, with small particles appearing to be electron deficient,[248] resulting in an increase in the chemisorption of electron-rich substrates such as alkynes. The result of these changes has not been categorically agreed on, with various studies reaching conflicting conclusions. The greater affinity for adsorption of alkynes over alkenes displayed by small particles have led some to conclude this is a source of increased selectivity, however other studies have suggested that the addition of beneficial additives work by the blocking of stepped and corner sites (characteristic of small particles), increasing the terraced palladium surface and resulting in fewer unwanted side reactions.[7,249]

The location and in particular the accessibility of the metal particle within the support is also of great importance. On conversion of alkyne to alkene, a concentration gradient is produced between the layer immediately in contact with the metal and the bulk solution.[27,250] If the rate of hydrogenation is faster than the rate of desorption and diffusion of alkene away from the surface, or the rate at which the active site is replenished with alkyne and hydrogen, overhydrogenation or double bond isomerization can take place. These rates can be highly dependent on temperature, pressure, and choice of solvent.[11] In highly porous catalysts through which diffusion is slow, the alkyne:alkene concentration ratio within the catalyst pores can be significantly lower than in the bulk solution, and so overhydrogenation can occur.[251] High selectivities have been reported using highly porous supports, however lower activities are also generally observed, which may partly explain the high selectivity.[252] In general however, high selectivities are more consistently observed with nonporous supports such as calcium carbonate and barium sulfate.

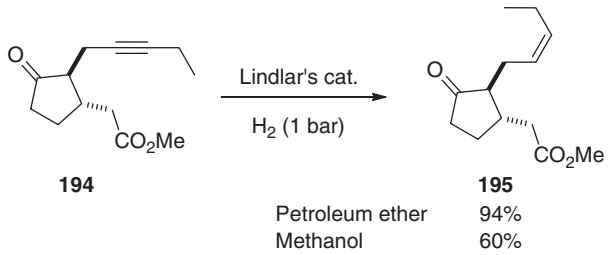
The addition of a second metal to the catalyst either through alloying, reaction with an organometallic precursor or a metal salt may improve selectivity by changing the electronic or structural properties of the palladium catalyst.[244,253] A change in the electronic nature of the catalyst may alter the relative affinities of adsorption of alkyne, alkene, and hydrogen. Alternatively, the blocking of unselective catalyst sites or reorganization of the reactive site may be achieved. The addition of numerous metals including Pb, Zn, Cd, Zr, Au, Ag, Cu, Fe, Hg, Bi, Ge, Sn, and B to palladium and platinum has been widely utilized to produce catalysts with high selectivities for alkyne semihydrogenation.[254] The doping of alumina-supported palladium with potassium also showed an increased selectivity for the semihydrogenation of acetylene. This was attributed to an electron-transfer process from potassium to palladium resulting in increased electron density on palladium, and hence a lower affinity for the binding of ethene.[255] The high activity and selectivity of a pumice-supported palladium catalyst has also been attributed to the presence of surface bound alkali metal ions extruded during the thermal treatment of the catalyst.[256]

The addition of organic additives to improve selectivity is also a common feature in the semihydrogenation of alkynes. Traditionally, nitrogen bases such as quinoline, pyridine, ammonia, piperidine, and ethylenediamine (EDA) are used, although sulfurous compounds, such as dimethyl sulfoxide,[257] have also been shown to improve selectivity. A simple explanation for the selectivity is that the added amine has an intermediate binding affinity for the catalyst, and hence binds in preference to the alkene, but can be displaced by the alkyne, leading to selective semihydrogenation.[258] A more general explanation however is that the nucleophilic additive is able to increase electron density on palladium, leading to a decreased adsorption affinity for the alkene intermediate.[259] In addition, it has been suggested that the Pd–H bond is amphipolar in nature and can react as either $Pd^{\delta+}$–$H^{\delta-}$ or $Pd^{\delta-}$–$H^{\delta+}$. It has been shown that on unmodified Pd/C, $Pd^{\delta-}$–$H^{\delta+}$ dominates, however on the addition of quinoline, the $Pd^{\delta+}$–$H^{\delta-}$ species is preferred. As alkynes are more electrophilic than alkenes, it has been suggested that the increased nucleophilicity of the Pd–H bond in the presence of an amine base is a possible source of the increased selectivity for semihydrogenation.[260,261] In contrast, the addition of electron accepting molecules such as thiophene leads to a decrease in selectivity.[262] It is essential that the additive chosen cannot itself be hydrogenated under the reaction conditions, as this can lead to a reduction in selectivity over time.

8.16.3.3 Semihydrogenation of Internal Alkynes

The semihydrogenation of isolated, internal alkynes is usually performed over poisoned palladium catalysts, and often proceeds without great difficulty, with selectivity for the *cis*-alkene typically >95%. Unpoisoned palladium usually does not give high

selectivity due to overhydrogenation and *cis–trans* isomerization.[263] In 1952, Lindlar developed a calcium carbonate-supported palladium catalyst poisoned with lead acetate, which used in the presence of quinoline formed a highly selective catalyst for the semihydrogenation of alkynes.[264,265] Lindlar's catalyst is still commonly used today, in addition to a number of similar partially poisoned palladium catalysts such as $Pd/BaSO_4$ with either quinoline or pyridine. These catalysts are often also erroneously referred to as Lindlar's catalyst.[266,267] The hydrogenation of internal alkynes is frequently reported to cease after the addition of 1 equivalent of hydrogen, however this is not always the case and overhydrogenation can occur. In addition, the hydrogenation of terminal alkynes invariably results in hydrogenation to the fully reduced product. Nonetheless, Lindlar's catalyst shows good substrate scope and is still a good first port of call for a synthetic organic chemist. The Lindlar catalyst displays the highest activity and selectivity when used in aprotic solvents such as cyclohexane or petroleum ether. This activity is demonstrated by comparison of the semihydrogenation of methyl dehydrojasmonate **194** over Lindlar's catalyst in either petroleum ether[268] or methanol[269] (Scheme 70). In methanol, a catalyst loading two orders of magnitude higher was required to give a yield of just 60%, whereas in petroleum ether, and lower catalyst loading, 94% yield was achieved. The semihydrogenation of methyl dehydrojasmonate **194** to produce methyl jasmonate **195** in 98% yield has also been reported in the presence of palladium on barium sulfate in pyridine solution. Hydrogen uptake was reported to cease completely after the absorption of 1 equivalent.[270] Polar, protic solvents have been successfully used however for the hydrogenation of particularly polar substrates.[271]



Scheme 70

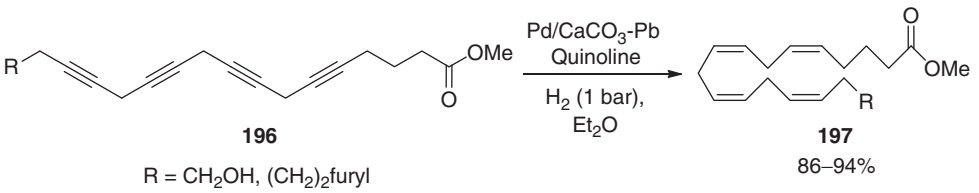
The semihydrogenation of alkynes in the presence of other reducible functional groups is not usually problematic due to the relatively strong and preferential adsorption of the alkyne on the catalyst. As demonstrated by the semihydrogenation of methyl dehydrojasmonate **194** over either Lindlar's catalyst,[271] or $Pd/BaSO_4$,[270] ketone and ester functionalities remain untouched under the conditions of hydrogenation. Nitrile groups are also well tolerated, as demonstrated in the synthesis of 11-deoxyprostaglandins.[272]

The hydrogenation of terminal alkynes over Lindlar's catalyst however is difficult to control, and overhydrogenation to give alkanes is generally observed.[263] Other palladium catalysts such as $Pd–SrCO_3$[273] or Pdc,[274] and nickel catalysts such as Nic[275] and nickel boride modified with copper[276] have been reported to selectivity semihydrogenate terminal alkynes, however these methods either require reaction termination after the absorption of 1 equivalent of hydrogen, or suffer from narrow substrate scope. Recent advances have been made with a number of highly selective procedures for the semihydrogenation of terminal alkynes. A preparatively simple palladium catalyst supported on borohydride exchange resin in the presence of caesium iodide and ethanol was capable of the hydrogenation of terminal and internal alkynes with no overhydrogenation to the alkane.[277] Palladium nanoparticle-based catalysts such as a colloidal palladium nanoparticle-tetrabutylammonium borohydride catalyst, and a silica-supported palladium nanoparticle catalyst used with dimethyl sulfoxide have also proved to be highly selective for the semihydrogenation of internal and terminal alkynes.[257,278] Sajiki has developed a heterogeneous Pd(0)-polyethyleneimine complex which is effective for the partial hydrogenation of alkynes. The selectivity for semihydrogenation is excellent for internal alkynes but slightly reduced for terminal ones, although good functional group tolerance has been demonstrated.[279,280] Sajiki has also recently reported a simple preparative method for a novel boron nitride-supported palladium catalyst, which in the presence of diethylenetriamine forms an efficient and highly selective catalyst for the semihydrogenation of terminal and internal alkynes. A variety of reducible groups were tolerated including esters, benzyl-, and silyl ethers, Cbz- and unprotected anilines, nitroarenes, and triazole groups. In addition, catalyst recycling was demonstrated with no observed loss in activity.[281]

The selective semihydrogenation of multiple alkyne functionalities is usually not an issue, as long as they not conjugated, as demonstrated in the recent synthesis of anandamide analogs, in which tetrayne **196** was hydrogenated over Lindlar's catalyst to produce tetraene **197** in 94% yield (Scheme 71).[282]

When both internal and terminal alkynes are present, the terminal alkyne will be preferentially hydrogenated before hydrogenation of the internal alkyne commences.[246] By interrupting the hydrogenation after the addition of 1 mol of hydrogen, the enyne product can be isolated. The reverse selectivity may be achieved if the terminal alkyne is protected with a sterically demanding or deactivating group.[246,283]

The hydrogenation of conjugated polyynes and enynes over Lindlar and other palladium catalysts generally proceeds with lower selectivity. Overhydrogenation to the fully reduced products and *cis–trans* isomerization are common problems.[284] Many groups have found that a procedure using superstoichiometric amounts of activated zinc powder is a mild alternative which



196

R = CH_2OH, $(CH_2)_2$furyl

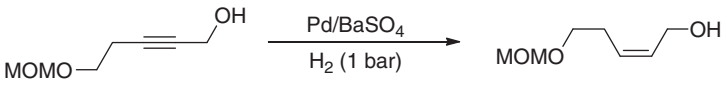
197

86–94%

Scheme 71

results in the *cis*-selective semihydrogenation of polyenynes.[285] A variety of techniques for the activation of zinc have been reported including treatment with copper acetate and silver nitrate,[286,287] potassium cyanide,[288] and dibromoethane and lithium dibromocuprate.[289] Although superstoichiometric amounts of zinc are required, it is suggested that the reduction process occurs on the surface of zinc particles due to the high diastereoselectivity of the process in producing the *cis*-alkene product. Isolated alkyne bonds remain unaffected by the process, and various functional groups are tolerated such as alcohols, ethers, esters, and ketones.

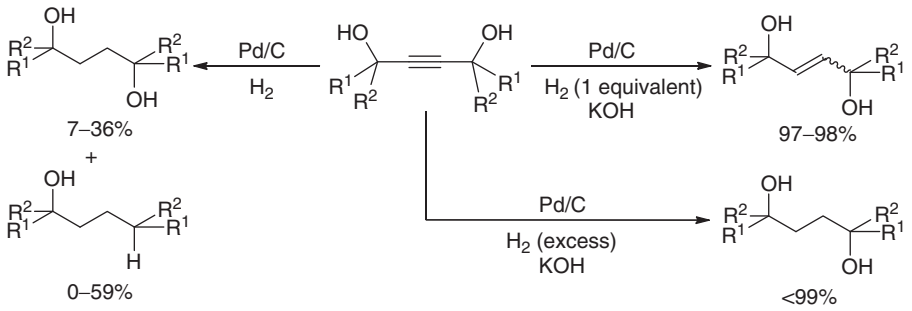
Hydrogenolysis of reducible functional groups is also a potential side reaction in the hydrogenation of alkynes over palladium catalysts. The hydrogenolysis of functional groups adjacent to the alkyne can present selectivity issues when the resulting allylic product is susceptible to reduction.[290–292] Hydrogenation of propargylic alcohols and ethers usually proceeds without difficultly, as demonstrated by the selective hydrogenation of 5-(methoxymethoxy)-2-pentyn-1-ol **198** over a palladium on barium sulfate catalyst in the synthesis of Gephyrotoxin (Scheme 72).[293]



198 **199**

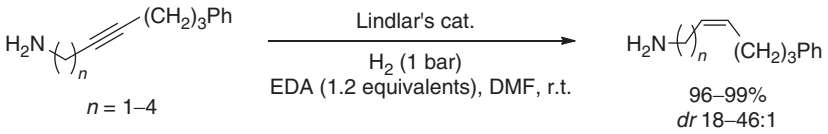
Scheme 72

However, the hydrogenation of tertiary propargylic alcohols can result in significant hydrogenolysis of the C–O bond. This problem is particularly prevalent in the hydrogenation of 1,4-acetylenic glycols. The hydrogenolysis of tertiary alcohols requires protonation of the alcohol, and so can be suppressed by the addition of small quantities of base.[294] The addition of potassium hydroxide to the hydrogenation of acetylenic glycols resulted in high yields of olefinic and saturated glycols by interrupting the hydrogenation after the uptake of 1 or 2 equivalents of hydrogen, respectively. By comparison, the hydrogenation in the absence of base resulted in low yields of the saturated diols in addition to varying amounts of hydrogenolysis products (Scheme 73).[295] However, care should be taken as large quantities of alkali may promote *cis–trans* double bond.[296] Another technique to suppress hydrogenolysis and *cis–trans* isomerization is to perform the reaction at low temperature.[297,298]



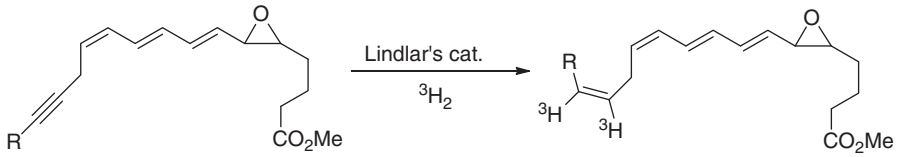
Scheme 73

Hydrogenolysis may also be a side-reaction in the hydrogenation of propargylic amines.[299] Solutions to the problem include the hydrogenation of the acetylenic amines as hydrochlorides over platinum oxide,[300] or by hydrogenation over W-2 Raney nickel in the presence of potassium hydroxide.[301] In both cases however, full reduction to the alkyl amine product was achieved. Recent research has demonstrated that the addition of EDA to Lindlar's catalyst results in a highly selective catalyst for the semihydrogenation of primary aminoalkynes, with little overreduction (even after extended reaction times) and only a low level of *cis–trans* isomerization (Scheme 74).[302] Alonso and Yus have also reported the use of nickel nanoparticles ($NiCl_2$-Li-DTBB) in the transfer semihydrogenation of a number of internal and terminal alkynes.[303] Secondary and tertiary amines and benzylic ethers were well tolerated under the conditions leading to high yields and selectivities for the *cis*-alkene product, however, stoichiometric amounts of nickel are required.



Scheme 74

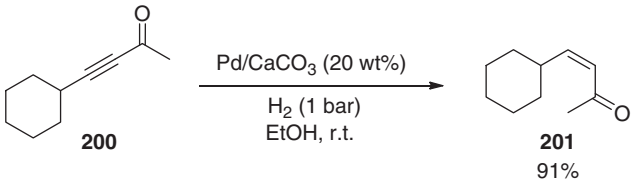
The semihydrogenation of nonadjacent acetylenic epoxides proceeds without complication by hydrogenation over Lindlar's catalyst.[304] When the resulting epoxide is allylic however, hydrogenolysis has been observed.[290] The semihydrogenation of a remote alkyne in the presence of an allylic epoxide has been completed by reaction over Lindlar's catalyst with no observed hydrogenolysis reported (Scheme 75).[305] The low yield of this isotope labeling experiment was not commented on; however it may be accounted for by the small scale on which it was carried out.



Scheme 75

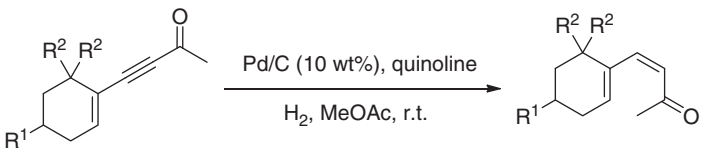
Propargylic cyclopropanes are also easily hydrogenated over Lindlar's catalyst in high yield and diastereoselectivity for the *cis*-alkene, with no hydrogenolysis or rearrangement of the cyclopropane ring observed.[306]

Hydrogenation of the α,β-ynone, 4-cyclohexyl-3-butyn-2-one, **200** to the corresponding *cis*-enone **201** was achieved by hydrogenation over a palladium on calcium carbonate catalyst (Scheme 76).[307] It was found that *cis–trans* isomerization of the product was significant unless a relatively fast rate of hydrogenation was attained. For this reason, the less active Lindlar catalyst proved unsuitable, and a relatively high loading of the more active palladium on calcium carbonate (20 wt%) was required. The acyclic α,β-ynones,3-decyn-2-one and 3-heptyn-2-one, were also converted to the corresponding *cis*-enones in good yield under similar conditions.[308] The semihydrogenation of α,β-ynamides to the corresponding α,β-enamides has also been achieved without complication and in excellent yield by hydrogenation over lead-doped palladium on calcium carbonate ($Pd/CaCO_3$-Pb) in the presence of quinoline.[309]



Scheme 76

Selective hydrogenation of more highly conjugated systems however often proves much more difficult. In contrast to the previous example, the hydrogenation of the closely related enynones **202a** and **202b** over quinoline-poisoned palladium on carbon resulted in formation of the semihydrogenated products **203a** and **203b** in 38% and 7% yield, respectively, after isolation via their semicarbazones (Scheme 77).[310]

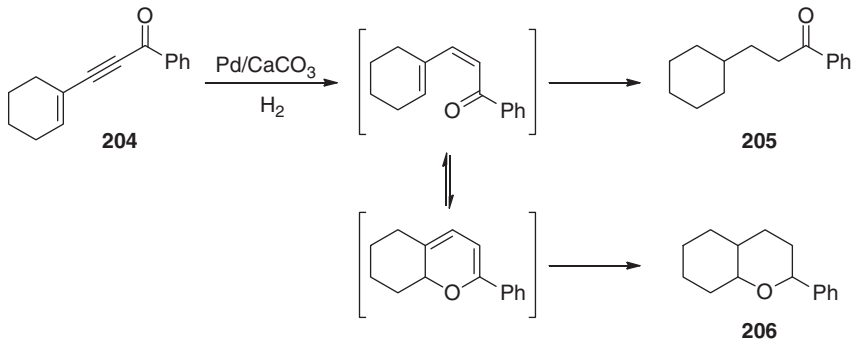


202a: R^1 = H; R^2 = Me
202b: R^1 = Me; R^2 = H

203a: 38%
203b: 7%

Scheme 77

The hydrogenation of 1-phenyl-3-(cyclohexen-1-yl)-2-propynone **204** under similar conditions led to none of the expected dienone, but a complex mixture of fully saturated products **205** and **206** (Scheme 78).[311] Although the expected intermediates were not isolated, some evidence was collected in support of the mechanism. In addition, the sigmatropic rearrangement to form pyran derivatives has been observed in another attempted semihydrogenation of similar enynone derivatives.[312–314] In contrast however, Eschenmoser found that when the triple bond is located at the terminal position of the enynone system, and rearrangement to the pyran derivative is not possible, excellent conversion to the expected dienone is observed by hydrogenation over Lindlar's catalyst.[315]



Scheme 78

8.16.4 Useful Notes

Common catalysts pseudonyms:
Adam's catalyst – $PtO_2 \cdot H_2O$
Pearlman's catalyst – $Pd(OH)_2/C$
Lindlar's catalyst – $Pd/CaCO_3$ poisoned with $Pb(OAc)_2$ and quinoline

Pressure conversions:
1 bar = 0.987 atm
1 bar = 14.5038 psi
1 bar = 100 kPa
1 bar = 750.06 Torr (mm Hg)

Inherent metal reactivity:
Pt > Rh > Pd > Ru, Os > Ni
'Platinum' catalysts are the 'most active' and rarely catalyze isomerization reactions.
'Palladium' is the metal of choice for 'hydrogenolysis' and 'isomerization' reactions and the hydrogenation of olefins conjugated to an aromatic group.
'Rhodium' is highly active for the hydrogenation of alkenes and alkynes.
'Nickel', and most commonly Raney nickel, shows good activity for the chemoselective hydrogenation of 'nonconjugated dienes'.

Alkene reactivity:
Monosubstituted > 1,1-disubstituted > 1,2-disubstituted > trisubstituted > tetrasubstituted
Note: Pd catalysts show increased activity toward aryl-substituted alkenes.

Inherent Metal Ability to Catalyze Double-bond Isomerization:
Pd ≫ Rh, Ru, Pt > Os > Ir
Palladium is the metal of choice when alkene isomerization is needed or will not alter the outcome of the hydrogenation.
Functional group compatibility for alkene hydrogenation using various metal catalysts.

Metal	*Functional group*				
	C═C	*C≡C*	*C≡N*	*C═O*	*Ar-Hal*
Pd	✓	✓/×	✓	✓	✓
Pt	✓/×	×	✓	✓/×	✓
Ru	✓	✓	–	✓	–
Rh	✓/×	✓/×	–	✓/×	–
Ni	✓	×	×	✓/×	✓

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8.17 Homogeneous Catalytic Hydrogenation of C=C and C≡C

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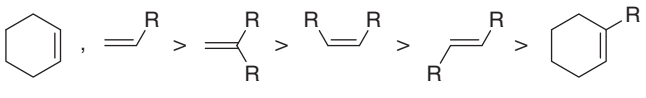
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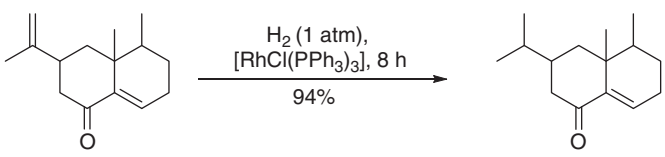
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8.17.1 Hydrogenation of Nonconjugated C=C

A wide variety of metals and derived complexes have been investigated for the hydrogenation of alkenes. Some provide useful rates and turnover numbers (substrate:catalyst ratio).[1,2] The most commonly used catalyst system for the reduction of a wide variety of nonconjugated alkenes is Wilkinson's catalyst {chlorotris(triphenylphosphine)rhodium(I), $[RhCl(PPh_3)_3]$} and extensive reviews have been published.[2–4] The hydrogenation conditions are mild. The presence of small amounts of impurities, such as oxygen or peroxides, can increase the reaction rate,[5,6] larger amounts of impurities cause the formation of rhodium metal.[7,8]

Wilkinson's catalyst will selectively hydrogenate alkenes in the presence of other reducible functional groups, such as aldehydes and nitro groups. The rate of hydrogenation reflects the coordination ability of the alkene (equation 1) and allows a more reactive alkene to be reduced preferentially,[9] as illustrated by the reduction of eremophilone **1**.[10] Tetrasubstituted alkenes are not easily reduced.

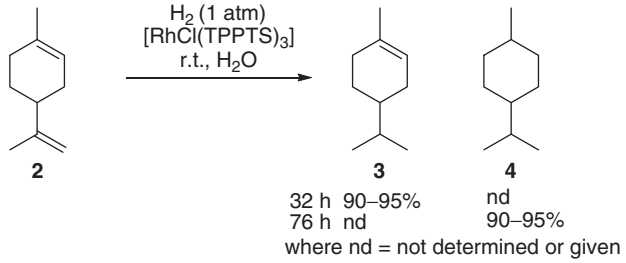




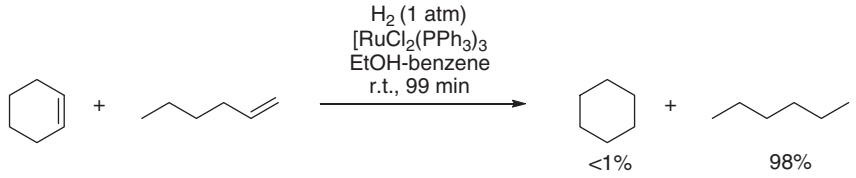
1

Labeling experiments have shown that, with Wilkinson's catalyst, the addition of hydrogen is *syn*.[11–15]

A water-soluble version of Wilkinson's catalyst ($RhCl(TPPTS)_3$, where TPPTS = triphenyltriphosphine *m*-trisulfonate) has been used to reduce alkenes under mild conditions. When more than one alkene is present in the substrate, selectivity can be achieved by the amount of hydrogen, as illustrated by the reduction of **2** to **3** in 32 h and to **4** in 76 h.[16]

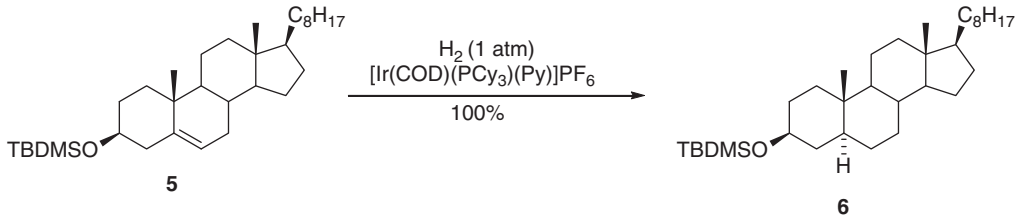


The ruthenium complexes $[RuCl_2(PPh_3)_3]$ and $[RuHCl(PPh_3)_3]$ provide efficient catalysts for the hydrogenation of terminal alkenes in the presence of methanol, ethanol, or triethylamine (equation 2).[17–20] The cyclopentadienone ruthenium carbonyl complexes, $[(\eta^4\text{-}Ph_4C_4CO)(CO)_2Ru_2]_2$ and $[(\eta^4\text{-}Ph_2Me_2C_4CO)(CO)_2Ru]_2$, also provide efficient catalytic systems for alkene reductions.[21]



(2)

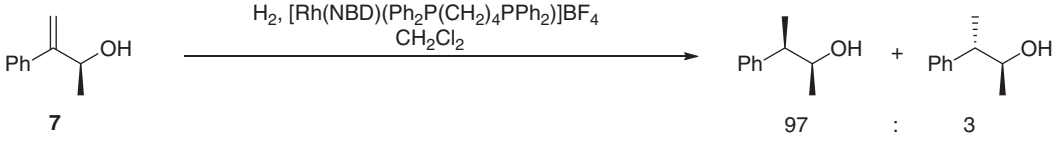
The iridium complex, often called Vaska's complex $[IrCl(CO)(PPh_3)_2]$, and derivatives can be used to reduce alkenes with similar steric demands as Wilkinson's catalyst; that is, terminal alkenes > *cis*-alkenes > *trans*-alkenes.[22–30] The catalyst is activated by UV radiation.[26] Noncoordinating solvents have to be used.[31,32] The cationic iridium complexes of the type $[Ir(COD)(PR_3)(Py)]PF_6$, also called Crabtree catalysts, are highly efficient for the hydrogenation of hindered alkenes.[33,34] The complex (R = C_6H_{11}) readily hydrogenates sterically congested steroid alkenes without reducing carbonyl groups, carbon–halogen bonds and cyclopropane rings. For example, **5** is reduced to **6**.[35]



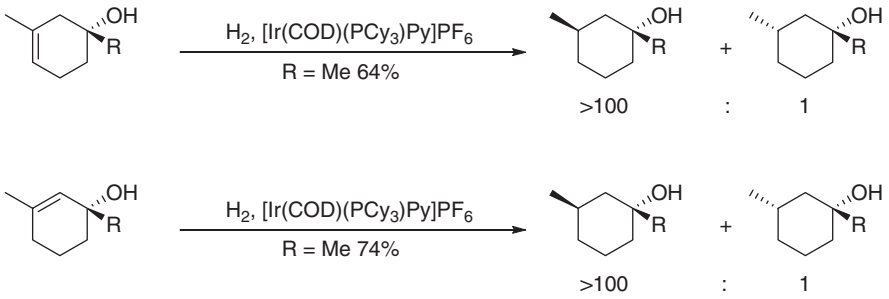
Asymmetric reductions of nonconjugated alkenes have been achieved with a variety of catalyst systems (see Section 8.17.5.5).

8.17.1.1 Hydrogenation of Allylic and Homoallylic Alcohols

The oxygen atom in an allylic or homoallylic alcohol can be complex to the metal in the catalyst and direct the stereochemical course of the reduction.[36] Wilkinson- and Crabtree-type catalysts can provide high diastereoselectivity. Modifications to these systems have led to a wealth of chiral catalysts (see Section 8.17.5.4). An example of high diastereoselectivity is provided by the reduction of the allylic alcohol **7**,[37,38] although a relatively high hydrogen pressure (44 atm) is required to achieve this selectivity.[39] With cyclic substrates, the *trans*-product is dominant.[38]



Iridium catalysts also provide high selectivity, especially with cyclic substrates.[38,40–46]



Hydrogenations of cyclic unsaturated ethers give lower selectivities than the corresponding allylic and homoallylic alcohols.[42]

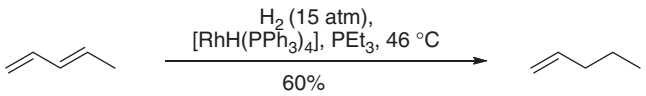
8.17.2 Hydrogenation of Conjugated Alkenes

8.17.2.1 Dienes, Trienes, and Polyenes to Saturated Hydrocarbons

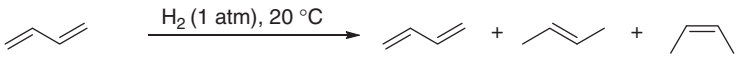
Dienes can be reduced to saturated alkenes by the use of Wilkinson's catalyst [$RhCl(PPh_3)_3$] under 60 atm of hydrogen. Sterically unhindered dienes will react at lower pressures but the reaction tends to be slow.[12] Dienes and trienes are hydrogenated in an aqueous–organic two-phase system using {[RhCl(1,5-hexadiene)]$_2$} and a phase transfer catalyst.[47] Polybutadiene can be reduced in the presence of Wilkinson's catalyst at low hydrogen pressures,[48] whereas polyenes can be hydrogenated in the presence of transition metal salts or soluble complexes, such as acetylacetonate, often called Ziegler catalysts.[2,49]

8.17.2.2 Dienes and Trienes to Alkenes by 1,2-Reduction

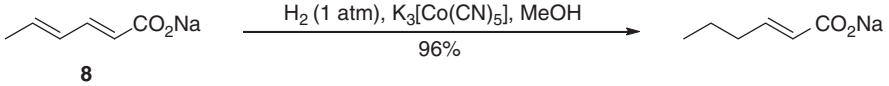
The hydrogenation of conjugated dienes can present a problem with homogeneous catalytic systems as stable diene- or allylmetal complexes can be formed.[50] 1,3-Dienes can be reduced to the corresponding terminal alkene in the presence of [$RhH(PPh_3)_4$] and [$Rh(CO)_2(PPh_3)_2$]·$2C_6H_6$ in cyclohexane under 15 atm of hydrogen.[51]



The same catalyst systems can be used for the reduction of 1,3-cyclooctadiene to cyclooctene.[51] 1,3- and 1,5-Cyclooctadiene can be hydrogenated to cyclooctene in the presence of zirconium(III) chelated to [$(Ph_3P)_2CH_2$].[52] In contrast, 1,4- and 1,5-cyclooctadiene can be hydrogenated to the mono alkene with iridium catalysts.[53,54] The reduction of dienes to monoalkenes can be achieved with a variety of other transition metal complexes, including ones based on Pd,[55–57] Ru,[54,58–60] Ni,[61] Mo,[62,63] Ir,[64] Ziegler catalyst,[65–67] and Co.[68,69] In some cases, the reaction conditions are important, as exemplified by the use of potassium pentacyanocobaltate(II), from $CoCl_2$ and KCN, which can provide high selectivities for 1- or 2-butene depending upon a number of factors including the CN:Co ratio. The system can also be used in the reductions of isoprene and 1-phenyl-1,3-butadiene,[70–72] and the sodium salt of sorbic acid **8**.[73]



Solvent	CN/CO	Yield (%)	Yield (%)	Yield (%)
H_2O	4.8	16	81	2
H_2O	6.0	95	4	1
Glycerol-MeOH	5.0	9	87	4
Glycerol-MeOH	5.7	50	9	41



8

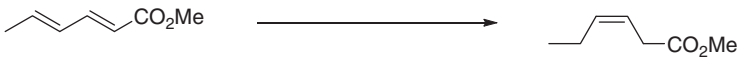
Cyclic dienes, such as 1,3-cyclohexadiene, are reduced more rapidly to the monoalkene with [$Co(CN)_2$(bipyridine)] than with the $K_3[Co(CN)_5]$ system.[74]

Wilkinson's catalyst can be used in the reduction of allenes to monoalkenes with the 2-*cis*-alkene being the predominant product.[75]

The Schrock–Osborn family of catalyst precursors, $[Rh(NBD)L_n]^+A^-$, can be used to reduce cyclic dienes to the monoene. With acyclic dienes, 1,2- or 1,4-addition of hydrogen can occur, and the pathway followed depends upon the ligand, L.[76]

8.17.2.3 Dienes to Alkenes by 1,4-Reduction

Chromium complexes provide excellent catalysts for the 1,4-reductions of 2,3:4,5-dienoate esters, and conjugated dienes such as isoprene.[77–91] The reduction of sorbic acid in a 1,4-manner can also be achieved by the use of ruthenium complexes containing Cp^*Ru.[92]



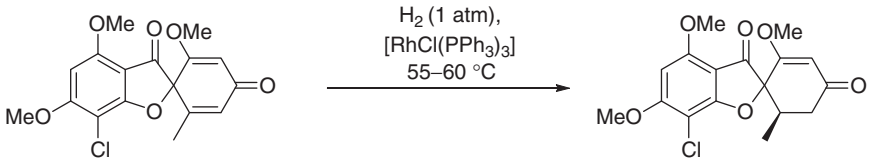
Catalyst	H_2 (atm)	Temp (°C)	Time (h)	Yield (%)
$Cr(CO)_3(C_6H_6)$	48	160	8	94
$Cr(CO)_3(MeO_2CC_6H_5)$	48	150	2	99
$Cr(CO)_3(^cC_7H_8)$	30	120	1	98
$Cr(CO_3)(ClC_6H_5)$	30	150	2	96

As noted in Section 8.17.2.2, the Schrock–Osborn family of catalyst precursors, $[Rh(NBD)L_n]^+A^-$, can be used to reduce acyclic dienes to the monoene by 1,2- or 1,4-addition depending upon the ligand, L.[76]

The use of $K_3[Co(CN)_5H]$ under phase transfer conditions and 1 atm. H_2 reduces 1,3-dienes to the monoene with the *trans*-product predominating.[93]

8.17.2.4 Hydrogenation of C=C Bonds Conjugated with Aromatic Rings, CN, CO, CO_2R, and so on

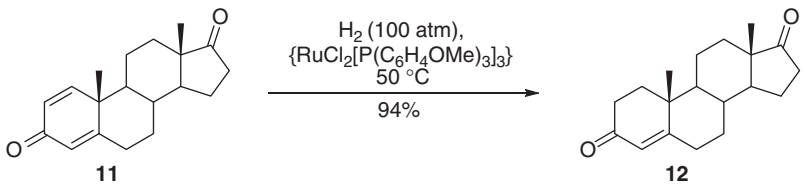
Wilkinson's catalyst $[RhCl(PPh_3)_3]$ affords a good catalytic system for the hydrogenation of alkenes conjugated with aromatic groups, including furans, thiophenes and heterocycles, carboxylic acids, esters, lactones, amides, nitriles, aldehydes, ketones, and nitro compounds.[10,11,41,42] In the last case, the nitro group is not reduced.[94] With aldehydes, decarbonylation can sometimes occur.[94,95] The presence of electron-withdrawing groups increases the rate of hydrogenation of the alkene with the order $CN > CO_2Me > Ph >$ alkyl, as illustrated by the reduction of dehydrogriseofulvin **9** to griseofulvin **10**.[10]



9 **10**

The air-stable complexes $[RhL(CO)(PPh_3)_2]ClO_4$ (where L=an unsaturated nitrile) allows the reduction of unsaturated carbonyl compounds under mild conditions.[28,96]

The use of $[RuCl_2(PPh_3)_2]$ in the hydrogenation of conjugated enones provides the saturated ketone as product.[17,18] As an example, reduction of 1,4-androstadiene-3,17-dione **11** in the presence of a close analog of this complex gives the 4-ene-3, 17-dione **12** in high yield (equation 3).[97]



11 **12** (3)

Crabtree's catalyst can be used in the hydrogenation of conjugated enones to ketones without affecting other functionality, such as a halogen, in the substrate.[35] Chromium-based catalysts, such as $[Cr(arene)(CO)_3]$, where arene is ethyl benzoate or naphthalene, are also efficient for the hydrogenation of acyclic enones to ketones. Isolated alkenes are not reduced.[98,99] The cobalt system, $K_3[Co(CN)_5H]$, under hydrogen and phase transfer conditions can be used to reduce α,β-unsaturated ketones to the saturated ketone.[93]

8.17.2.5 Transfer Hydrogenation of Conjugated C=C

As an alternative to hydrogen gas (equation 3), $[RuCl_2(PPh_3)_2]$ can be used for the reduction of conjugated enones to saturated ketones in the presence of a hydrogen donor, such as benzyl alcohol or formic acid.[100–102] $Pd(OAc)_2$ in the presence of $P(Bu^t)_3$ has been used successfully for the reductions of alkenes under transfer hydrogenation conditions with formic acid.[103]

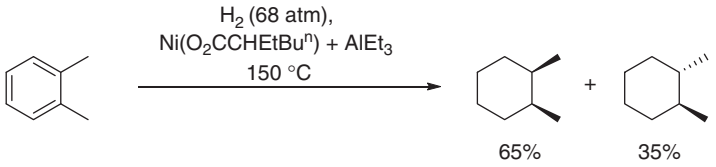
8.17.3 Hydrogenation of Aromatic and Heteroaromatic Rings

8.17.3.1 Hydrogenation of Carbocyclic Aromatic Compounds

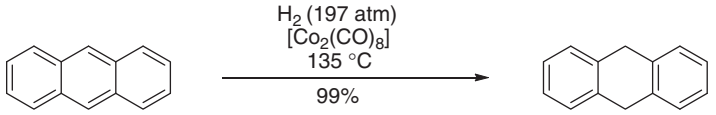
This type of hydrogenation reaction is dominated by heterogeneous catalysts. Even with some of the homogeneous examples, there is still some doubt about the nature of the active catalyst, as small amounts of metal(0) can be formed in the reaction mixture.[104–106]

Phenyl groups can be hydrogenated to the cyclohexane derivative by $\{[\eta^6\text{-}C_6Me_6)RuCl_2]_2\}$ in the presence of Na_2CO_3 and hydrogen (50 atm) at 50 °C. Conjugated alkenes, such as those of styrenes, are reduced along with the aryl group, but carbonyl groups are not.[107] Other ruthenium complexes can also be used to accomplish the transformation, such as $[(\eta^6\text{-}C_6Me_6)RuHCl(PPh_3)]$[108] and $[(\eta^6\text{-}C_6Me_6)(\eta^4\text{-}C_6Me_6)Ru]$, where *p*-xylene gives *cis*-1,4-dimethylcyclohexane. The rate of hydrogenation decreases with the size of the alkyl substituent.[109,110]

Nickel- or cobalt-based Ziegler catalysts allow the efficient hydrogenation of aromatic compounds.[111–114] With these systems, *o*-xylene gives a mixture of *cis*- and *trans*-1,2-dimethylcyclohexane with the former as the major product. Whereas phenol, dimethyl phthalate, and dimethyl terephthalate are reduced in high yield, the presence of a nitro group stops reduction from occurring. Naphthalene is hydrogenated to tetralin with this catalyst system.[112]



The rhodium complex $\{[RhCl(COD)]_2\}$ in the presence of a phase transfer catalyst will reduce aromatic hydrocarbons in a hydrogen atmosphere.[115] $\{[(\eta^5\text{-}C_5Me_5)RhCl_2]_2\}$ is an effective catalyst for the reduction of aryl groups but does not reduce a carbonyl group.[116] Substituted benzenes can be reduced under mild conditions with $\{Co(C_3H_5)[P(OMe)_3]_3\}$ as the catalyst precursor. An ester group is not affected. With this system benzene is more easily reduced than cyclohexene. Hydrocarbon polyaromatics are fully hydrogenated by the use of $\{Co(C_3H_5)[P(OMe)_3]_3\}$.[69,117–119] The partial hydrogenation of polyaromatic compounds, such as anthracene, 9-methylanthracene, and 9-trifluoroacetylanthracene to the 1,2,3,4-tetrahydroanthrocene derivative, can be accomplished with $[Rh(DPPE)(arene)]^+$[115] and ruthenium hydride complexes with triphenylphosphine ligands.[120–124] Partial hydrogenation of polyaromatics can also be achieved with $[Co_2(CO)_8]$ under carbon monoxide and hydrogen but an isolated benzene nucleus will not reduce.[125–127]



A list of metal complexes that have been claimed to generate catalysts for the hydrogenation of carbocyclic aromatic rings is given in Table 1.[104]

8.17.3.2 Hydrogenations of Heteroaromatic Compounds

For the hydrogenation of heteroaromatic compounds, heterogeneous catalysts still predominate. The work with homogeneous catalytic systems has been dominated by the reduction of heteroaromatics for fossil fuel treatment.[104]

Pyridine can be reduced to piperidine in the presence of the nickel Ziegler catalyst,[111,112] $\{[RhCl(COD)]_2\}$ with a phase transfer catalyst,[146] $[Rh(NCMe)_3(Cp^*)]^{2+}$,[147] or $[RhCl_3(Py)_3]$ with $NaBH_4$.[148] Polyaromatic heterocycles are hydrogenated in the presence of $[RhCl(PPh_3)_3]$,[149] $[RuHCl(PPh_3)_3]$, or $\{Ru[(C_6H_4)(PPh_2)_2]H_2(PPh_3)_2\}^-$ amongst other ruthenium complexes to give the products where the heterocycle is reduced but benzene nuclei are not.[120,150–153] For the reduction of quinolone, the cationic rhodium complex $[Rh(PPh_3)_2(COD)]^+$ gave the most active catalytic system.[154]

Sulfur heteroaromatics, such as thiophene and benzothiophenes, can be reduced by a number of homogeneous catalytic systems including $[RuCl_2(PPh_3)_3]$,[154] $[RuHCl(PPh_3)_3]$,[154] $RuH_2(\eta^2\text{-}H_2)(PCy_3)_2]$,[155] $RhCl(PPh_3)_3]$,[154] $\{[Rh(MeCN)_2(Cp^*)]BF4\}$,[147] $\{[Rh(PPh_3)_2(COD)]PF_6\}$,[154,156] $\{[Ir(PPh_3)_2(COD)]PF_6\}$,[154,157,158] and $\{[Ru(MeCN)_3(triphos)](SO_3CF_3)_2\}$.[150,159,160]

Table 1 Homogeneous catalyst precursors for the hydrogenation of aromatic hydrocarbons

Metal complex	*Substrate*	*References*
$[Ru(\eta^6\text{-}C_{10}H_{14})(\eta^2\text{-triphos})Cl]PF_6$	Benzenes[a]	128
$RuH_2(H_2)_2(PCy_3)_2$	Benzenes, polyaromatics	129
$[Ru_3(\eta^6\text{-}C_6Me_6)_2(\eta^6\text{-}C_6H_6)(\mu^3\text{-}O)(\mu^2\text{-}OH)(\mu^2\text{-}H)_2]BF_4$	Benzenes[a]	130
$RuCl_2(PTA)(\eta^6\text{-}C_{10}H_{14})$; $RuCl(PTA)_2(\eta^6\text{-}C_{10}H_{14})$	Benzenes	131
$Ru(\eta^6\text{-}C_6Me_6)(\eta^4\text{-}C_6Me_6)$	Benzenes	110,132
$[Ru(\eta^6\text{-}C_6Me_6)2(\mu\text{-}H)_2(\mu\text{-}Cl)]Cl_2$	Benzenes	107
$Ru(H)_3(PPh_3)_3$; $Ru(H)_2(H_2)(PPh_3)_3$	Anthracenes	121,124
$Ru_4H_4(\eta^6\text{-}C_6Me_6)$; $Ru_2Cl_4(\eta^6\text{-}C_6Me_6)$	Benzenes[a]	133–136
Ziegler-type	Benzenes, polyaromatics	111,112,137,138
$Co(\eta^3\text{-}C_3H_5)[P(OR)_3]$	Benzenes, polyaromatics	117–119,139,140
$Co(Cy_2PC_8H_{11}(\eta^5\text{-}C_8H_{13})$	Benzene	141
$Ni(\eta^6\text{-}MeC_6H_5)(C_6F_5)_2$	Benzene	142
$[Cp^*RhCl_2]_2$[b]	Benzenes, anthracene	107
$RhH[P(OPR^i)_3]_2(\mu\text{-}H)_3Rh[P(OPr^i)_3]_2$	Benzenes	143
$Rh(acac)[P(OPh)_3]_2$	Benzenes	144
$RhH[P(NC_4H_4)_3]_4$; $RhH(CO)[P(NC_4H_4)_3]_4$	Benzenes	145
$[Rh(diphos)(MeOH)_2]BF_4$	Anthracenes	115
$[RhCl(diene)]_2{}^+(NR_4)X$	Benzenes[c], naphthalene	146

[a]Liquid biphasic catalyst.
[b]Where Cp* denotes 1,2,3,4,5-pentamethylcyclopentadienyl.
[c]Phase transfer catalyst.

Many of the recent catalytic systems that have been developed for the hydrogenation of heteroaromatic compounds not only reduce the unsaturation, but also provide asymmetric induction (see Section 8.17.5.2.2.1).

8.17.4 Hydrogenation of C≡C Bonds

8.17.4.1 Reduction of C≡C Bonds to Saturated Hydrocarbons

Wilkinson's catalyst and $[Rh(OAc)(PPh_3)_3]$ can be used for the reduction of alkynes to alkanes or alkenes.[12,161] 1-Arylalkynes are hydrogenated to the corresponding aryalkanes in the presence of the titanium catalyst $[Ti(Cp)_2(CO)_2]$; terminal alkylalkynes are reduced to the alkene.[162] The electron-rich titanium complexes, $[(Cp)_2Ti(PhC{\equiv}CPh)(PMe_3)]$, $[(MeCp)_2Ti(PhC{\equiv}CPh)(PMe_3)]$, and $[(Cp)(Cp^*Ti(PhC{\equiv}CPh]$, are competent catalyst precursors for the hydrogenation of alkynes to alkanes under mild conditions.[163]

8.17.4.2 Reduction of Terminal C≡C Bonds to Alkenes

Wilkinson's catalyst in benzene with 2,2,2-trifluoroethanol or phenol as cosolvent provides a system for the reduction of alkynes to alkenes.[12,164] The rate of the alkyne reduction is faster than that of an alkene. 1-Alkynes can be hydrogenated to 1-alkenes in the presence of $[Rh(COD)(PPh_3)(Py)]PF_6$ and a benzoate salt.[165,166] Other catalyst precursors based on Rh and Co are given in Table 2. Although the Schrock–Osborn rhodium catalysts are widely used for the reduction of alkynes to *cis*-alkenes, their use with terminal alkynes is less successful, as the acidic nature of the substrate can lead to catalyst decomposition.[167] Terminal alkynes can be hydrogenated to the alkene in the presence of $\{[\eta^5\text{-}C_5H_5)Fe(\mu^3\text{-}CO)]_4\}$ even when alkenes or internal alkynes are present in the substrate.[168]

The iron(II) complexes, $\{[(Ph_2PCH_2CH_2)_3P]FeH(N_2)\}BPh_4$ and $\{[(Ph_2PCH_2CH_2)_3P]FeH(H_2)\}BPh_4$, provide catalysts for the reduction of terminal alkynes to alkenes.[169] With $\{[(\eta^5\text{-}C_5H_5)Fe(\mu^3\text{-}CO)]_4\}$ this occurs even when alkenes or internal alkynes are present in the substrate.[168] Ruthenium carbonyl clusters have been demonstrated to allow the hydrogenation of terminal alkynes to the alkene. However, the activities tend to be low and this can lead to isomerization of the hydrogenation product.[50] The mononuclear catalysts $\{RuH(\eta^2\text{-}H_2)[P(CH_2CH_2PPh_2)_3]\}$ and $\{[RuH(COD)(PMe_2Ph)_3]PF_6\}$ provide a catalyst system competent for the reduction of 1-alkynes to the corresponding alkene.[168,170,171]

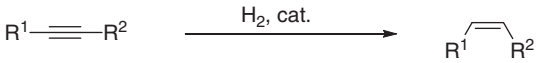
8.17.4.3 Reduction of C≡C Bonds to *cis*-Alkenes

For the reduction of alkynes to *Z*-alkenes, palladium or nickel catalysts are usually used,[50] and the Lindlar system (Pb-poisoned $Pd/CaCO_3$) is well known.[179,180] Although a large number of homogeneous catalysts have been reported (for examples, see Table 3), few have been investigated in depth.[50]

Table 2 Catalyst systems for the reduction of alkynes to alkenes

Catalyst precursor	*References*
$[Rh(COD)(PPh_3)(Py)]PF_6$	165,166
$[Rh_2(\eta\text{-}X)(CO)(Ph_2YCH_2YPh_2)_2]^+$ (where X=Cl or Br, Y=P or As)	172
$[RuH(PMe_2Ph)_5]PF_6$	172
$[CoH(CO)(PBu^n_3)_3$	173,174
$\{CoCl[P(OEt)_3]_n\}$ (where n=3,4)	2
$\{[\eta^5\text{-}C_5H_5)Fe(\mu^3\text{-}CO)]_4\}$	168
$\{[(Ph_2PCH_2CH_2)_3P]FeH(N_2)\}BPh_4$	
$\{[(Ph_2PCH_2CH_2)_3P]FeH(H_2)\}BPh_4$	169,175,176
$\{[\eta^5\text{-}C_5H_5)Fe(\mu^3\text{-}CO)]_4\}$	168
$\{[RuH(COD)PMe_2Ph)_3]PF_6\}$	170
$\{RuH(\eta^2\text{-}H_2)[P(CH_2CH_2PPh_2]_3\}$	171
$[OsH(Cl)(CO)(PR_3)_2]$ (where PR_3 is $PMeBu^i_2$ or PPr^i_3	177
$\{Ir(COD)[\eta^2\text{-}P(^iPr)CH_2CH_2OMe]BF_4\}$	178

Table 3 Reductions of alkynes to *cis*-alkenes



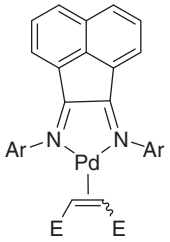
Catalyst precursor	*Yield (%)*	*References*
$[(MeO_2CC_6H_4)Cr(CO)_3]$	100	98,99
$[CoH(CO)(PBu_3^n)_3$	–	2,174,181
$\{[Co(CO)_2(PR_3)]_3\}$ where R=Ph or *n*-Bu	–	181,182
$[Rh(diene)L_n]PF_6$ where diene=norbornadiene, COD; L= a tertiary phosphine; n=2 or 3	>95	167,183
$[RuH(PMe_2Ph)_5]PF_6$	–	172
$[RuCl_2(PPh_3)_3$	–	2
$[Pd_5(PPh)_2(PPh_3)_2]$	–	144
$[(Cp)_2Mo_2(CO)_4]$	–	184
$[Ni_2(COD)_2(\mu\text{-}\eta^2\text{-}RC{\equiv}CR)]$	–	185
$[Ni_4(RNC)_4(\mu_3\text{-}\eta^2\text{-}RC{\equiv}CR)_3]$	–	186
$[(Cp)_2Ti(PhC{\equiv}CPh(PMe_3)]$	–	163

One of the most selective catalysts for the reduction of alkynes to *cis*-alkenes is derived from chromium tricarbonyl compounds.[187] A wide range of alkynes can be reduced but isolated alkenes are not touched; isomerization or overreduction of the resultant alkene also does not occur. For the mononuclear systems, $\{[RuH(PMe_2Ph)_5]PF_6\}$ is particularly effective for the hydrogenation although a large excess of the ligand PMe_2Ph does have to be present to avoid catalyst deactivation.[172] The need for excess ligand loading can be reduced by using the catalyst precursor $\{[RuH(COD)PMe_2Ph)_3]PF_6\}$, which under hydrogen reacts to give the complex $[RuH(PMe_2Ph)_3(solvent)_2]^+$, an active catalyst for the hydrogenation of alkynes and alkenes.[170] The addition of 1–2 equivalents of PMe_2Ph suppresses the alkene reactivity.

Ruthenium carbonyl clusters can be used in the hydrogenation of alkynes to *Z*-alkenes. Compared to the mononuclear systems, the reaction rates tend to be low and this can lead to significant amounts of isomerization of the initial product.[50]

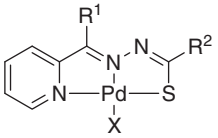
The Schrock–Osborn rhodium catalyst systems, $[Rh(NBD)L_n]^+$, where L is a ligand, are perhaps the most widely applied for the reduction of alkynes to *cis*-alkenes in coordinating solvents.[167] The addition of acid can produce a highly selective hydrogenation catalytic system. This also allows for other precursors, such as $[Rh(OAc)(PPh_3)_3]$ or $[Rh_2(OAc)_4/PPh_3]$ to be used.[188,189]

The selectivity and reactivity problems associated with the Lindlar catalyst system have led to the use of Pd(II),[190,191] or Pd(0),[192,193] where the metal is mononuclear.[50] Thus, the catalyst precursors **13** can be used in the hydrogenation of alkynes to *cis*-alkenes to give high yields and selectivity.[193,194] Another system that also provides for good catalysts, although at a slower rate, is based on the thiosemicarbazonates **14**.[190]



where Ar = 4-$MeOC_6H_4$
or 3,5-$(CF_3)_2C_6H_3$
E = CO_2Me (*trans*)
or C(=O)OC(=O)

13



where R^1 = Me or Ph
R^2 = NH_2 or Ph
X = Cl or OAc

14

In the presence of $\{[(\eta^5\text{-}C_5H_5)Fe(\mu^3\text{-}CO)]_4\}$ internal alkynes are slowly reduced to the *cis*-alkenes. Aryl nitro groups and terminal alkenes and alkynes are also hydrogenated.[181]

8.17.4.4 Reduction of C≡C Bonds to *trans*-Alkenes

The ruthenium complex $\{[Cp^*Ru(\eta^4\text{-}MeCH{=}CH{=}CHCO_2H)][CF_3SO_3]\}$ is one of the few homogeneous systems that affords *trans*-alkenes from the hydrogenation of alkynes.[195] This selectivity has been attributed to the involvement of a dimeric ruthenium complex.

The rhodium complex $\{RhH_2[OC(=O)OH](PPr^i_3)_2\}$ does provide a catalyst for the hydrogenation of alkynes, such as diphenylacetylene and dimethyl acetylenedicarboxylate to the *trans*-alkene product.[196] This complex also isomerizes *cis*-stilbene to *trans*-stilbene. Although diphenylacetylene is hydrogenated to *trans*-stilbene in the presence of $[RhCl_3(Py)_3]$, DMF, and $NaBH_4$, dimethyl acetylenedicarboxylate and butyn-1,4-diol afford the *cis*-products.[197]

8.17.5 Homogeneous Asymmetric Hydrogenation of C=C Bonds Using Chiral Catalysts

8.17.5.1 Chiral Catalysts

Many of the chiral catalysts described in this section are derivatives of systems that were first developed for achiral hydrogenations. Obviously, reduction to the alkane is usually required to generate the new stereogenic center(s). The asymmetric hydrogenation of a carbon–carbon double bond was the first transformation to achieve enantioselectivities approaching those of an enzymatic transformation.[198] Today, asymmetric hydrogenations of carbon–carbon double bonds are performed at an industrial scale.[199–201] There is also a large number of catalyst systems available that have been developed to perform an asymmetric hydrogenation on a wide range of substrate classes.[1,202–204] Often the choice of which catalyst system to use comes down to availability and its tolerance to other functional groups within the substrate.

For larger scale reactions, catalyst systems are often optimized to achieve high enantioselectivity, while being economical through low catalyst usage and relatively fast reaction rates.[205] Comparison with literature precedent or experimental screening is usually used to determine which type of catalyst system is to be used in a specific application. Many catalysts, when first developed, are tried with 'standard' substrates.[206] Most of the catalyst systems described later are the best currently available in that class for the asymmetric hydrogenation of a substrate class. To be cost effective in an asymmetric hydrogenation at scale, the criteria of a turnover number (TON = mol product/mol catalyst) or substrate/catalyst ratio of >1000 for high-value products and $>50\,000$ for less-value products, with catalyst reuse increasing the productivity, have been suggested. In addition, the turnover frequency [TOF = mol product/mol catalyst/reaction time (h^{-1})] should be $>500\ h^{-1}$ for smaller scale products and $>10\,000\ h^{-1}$ for larger scale. The TOF is a factor indicating production capacity and throughput.[199]

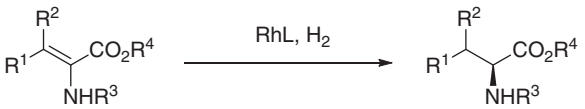
As with achiral hydrogenations, there can be advantages with some of the catalysts mentioned in the following sections by the use of supercritical solvents.[207] An example is in the use of a rhodium DuPhos system for the reduction of β,β-disubstituted enamides where sCO_2 are solvent led to higher enantioselectivities than when a conventional solvent was used.[208]

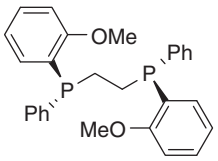
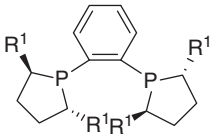
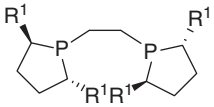
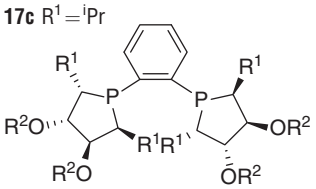
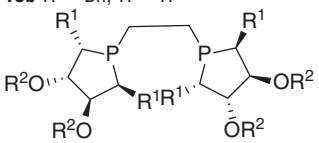
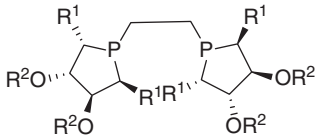
8.17.5.2 Asymmetric Hydrogenation of Enamides and Related Substrates

8.17.5.2.1 Hydrogenation of didehydroamino acid derivatives

In general, the most efficient asymmetric hydrogenation systems for didehydroamino acid derivatives are based on cationic rhodium(I) complexes with a chiral phosphorus-based ligands, a diene (cycloocta-1,5-diene or norbornadiene), and a non-associating counterion, such as perchlorate, tetrafluoroborate, trimethanesulfonate, or hexafluorophosphate. The reductions are typically run in an alcohol or halogenated solvent with hydrogen gas. The approach has found favor because other functional groups, such as aldehydes, ketones, imines, oximes, nitro groups, and even some types of alkenes are unreactive toward the catalysts. The reductions of didehydroamino acid derivatives with some classes of ligands are summarized in Table 4.

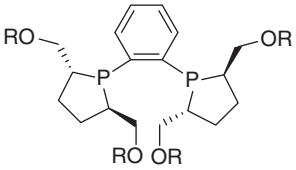
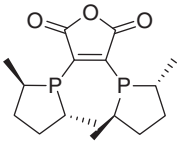
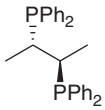
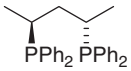
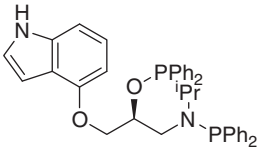
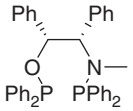
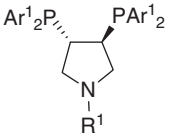
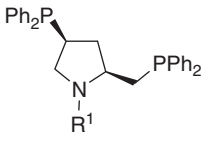
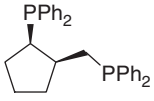
Table 4 Didehydroamino acid derivative reductions



Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
	–	95	209
15 (*R,R*)-Dipamp			
	91–100	95.0–98.2	210–212
16 (*S,S*)-DuPhos			
16a R^1 = Me			
16b R^1 = Et	100	97.8–99.5	199,210,213–215
16c R^1 = ^{i}Pr	100	95.1–99.8	213
	100	97.2–98.6	212
17 (*S,S*)-BPE			
17a R^1 = Me			
17b R^1 = Et	100	98.1	213
17c R^1 = ^{i}Pr	100	97.7	213
	100	97–99	216,217
18 RoPhos			
18a R^1 = Me, R^2 = H			
18b R^1 = Bn, R^2 = H	–	96.0	218
	–	96.8–98.4	218
19 RoPhos-type			
19a R^1 = Me, R^2 = ^{t}Bu			
			
19 RoPhos-type			
19a R^1 = Me, R^2 = ^{t}Bu			

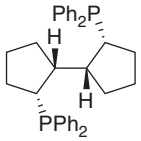
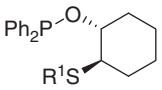
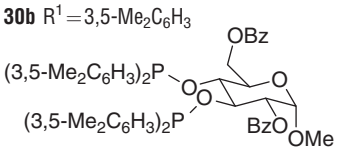
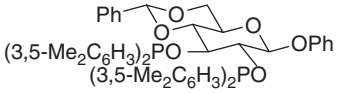
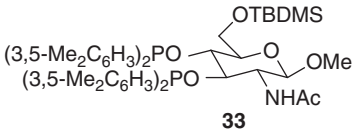
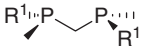
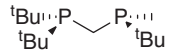
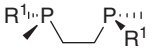
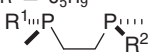
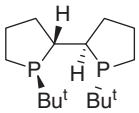
(*Continued*)

Table 4 Continued

Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
19b R^1 = Me, R^2 = Bn	–	97.5	218
 **20** BasPhos **20a** R = H	100	95.7–98.9	219
 **21** MalPhos	100	98.6	220
 **22** (*S,S*)-Chiraphos	100	98–100	221,222
 **23** (*S,S*)-SkewPhos	100	98	223
 **24** (*S*)-Pindophos	–	95	224
 **25** (1*R*,2*S*)-DPAMPP	100	95.7	225
 **26** **26a** Ar^1 = Ph, R^1 = Bn DeguPhos, PyrPhos or DegPhos	–	>99	199
26b Ar^1 = Ph, R^1 = Bz (Bz-PyrPhos)	–	>95	226
 **27** **27a** R^1 = Boc (2*S*,4*S*)-BPPM	91	96.0–98.5	227,228
 **28** (*R,R*)-PPCP	100	96	229

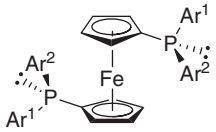
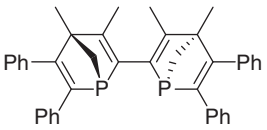
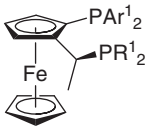
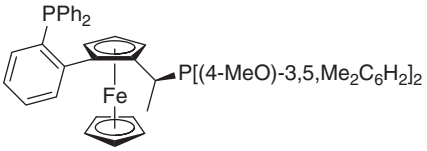
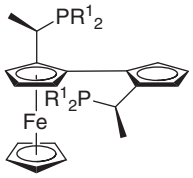
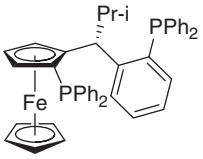
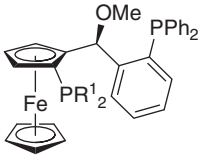
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Table 4 Continued

Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
 **29** (*R,R*)-BICP	100	96.8–99.0	230
 **30** **30a** R^1 = ^{t}Bu	100	94–98	231
30b R^1 = 3,5-$Me_2C_6H_3$	100	92–97	231
 **31** Carbophos	–	96–97	232
 **32**	–	97–99	232
 **33**	–	98.3	232
 **34** MiniPhos **34a** R^1 = ^{t}Bu	100	95–99	233,234
34b R^1 = ^{c}C_6H_{11}	100	98.9–99.1	234
34c R^1 = ^{i}Pr	100	98	234
 **35** TrichickenfootPhos, (*S*)-TCFP	100	99	235
 **36** (*S,S*)-BisP* **36a** R^1 = ^{t}Bu	100	95.9–99.9	233,236,237
36b R^1 = Ad	100	98.6–99.9	233,236,237
36c R^1 = ^{c}C_5H_9	100	95	233
 **37** (*S,S*)-Unsymmetrical BisP* **37a** R^1 = Ad, R^2 = ^{t}Bu	100	96.2–99.2	236
37b R^1 = Ad, R^2 = ^{c}C_6H_{11}	100	96.1–98.2	238
 **38** (1*S*,1*S′*,2*R*,2*R′*)-TangPhos	–	99	239

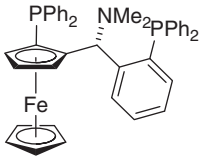
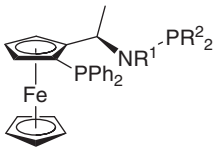
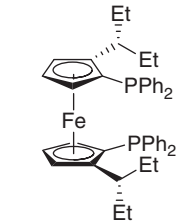
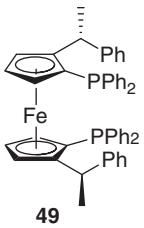
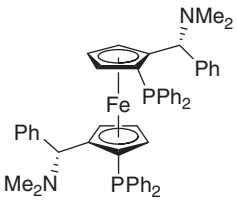
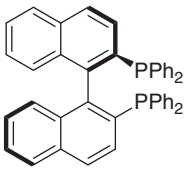
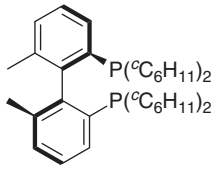
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Table 4 Continued

Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
 **39**	100	98.2–98.5	240
39a Ar^1 = 1-Naph, Ar^2 = Ph			
39b Ar^1 = 2-$MeOC_6H_4$, Ar^2 = Ph	99–100	95.4–97	240,241
39c Ar^1 = 9-Anth, Ar^2 = Ph	100	95.5–98.7	240
 **40** (*S,S*)-BIPNOR	100	98	242,243
	100	96	244
41 (*R*)-(*S*)-JosiPhos			
41a Ar^1 = Ph, R^1 = Cy			
 **42** WalPhos	>99	95	245
	95	95	246
43 (*R,R*)-(*S,S*)-TRAP			
43a R^1 = Ph (PhTRAP)			
43b R^1 = Et (EtTRAP)	–	96	247
 **44**	100	96.6	248,249
	100	95–99	249–251
45 TaniaPhos (2nd generation)			
45a R^1 = Ph			
45b R^1 = 3,5-$Me_2C_6H_3$	100	99	250

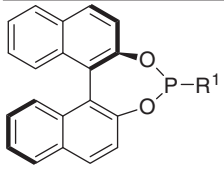
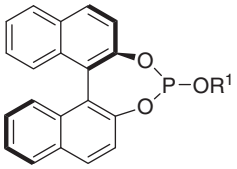
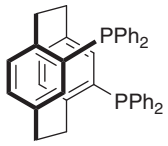
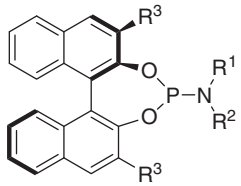
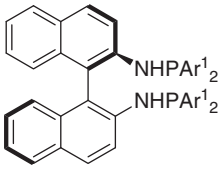
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Table 4 Continued

Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
 **46** TaniaPhos	100	95	251
 **47** BoPhoz **47a** R^1 = Me, R^2 = Ph	96–100	95–99.5	215,252
47b R^1 = H, R^2 = Ph	>95	97.2	252
 **48** (*S,S*)-FerroPhos	100	95.7–98.9	253
 **49**	100	97.3–98.3	254
 **50** FerriPhos	–	95.5–99	255
 **51** (*R*)-BINAP	96–100	96–97	256,257
 **52** (*R*)-BICHEP	100	97–99	258

(*Continued*)

Table 4 Continued

Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
	100	95.2–96.8	259
53a R^1 = Me			
	100	96.4	259
54a R^1 = CH_2Bu^t			
	–	97–99.6	260
55 (*R*)-PhanePhos			
	100	95–99	261,262
56(*R*)-Phosphoramidites, MonoPhos ligand family			
56a R^1 = R^2 = Me, R^3 = H, MonoPhos			
56b R^1, R^2 = -[$(CH_2)_2$]O, R^3 = H, MorfPhos	100	98–99	262
56c R^1, R^2 = -$(CH_2)_5$-, R^3 = H, PipPhos	100	99	262,263
	100	95.2–99	264
57a Ar^1 = Ph, (*R*)-BDPAB			
57b Ar^1 = 3,5-$Me_2C_6H_3$, (*R*)-Xyl-BDPAB	100	96–99	259

[a]Only one enantiomer of the ligand is shown, although some of the examples may be with the antipode.

The most common methods to prepare didehydroamino acids and ester substrates are an Erlenmeyer reaction, from *N*-protected glycine and an aldehyde,[265,266] or a Heck reaction.[267,268]

As substrates for asymmetric hydrogenations the *Z*-isomers of didehydroamino acids, in general, are reduced with higher enantioselectivities than the corresponding *E*-isomers. DuPhos **16**[213,269–271] and the related ethane-bridged BPE **17**[270,272] have demonstrated excellent levels of stereoinduction with either *Z*- or *E*-didehydroamino acids and esters to provide α-amino acids and esters with the same absolute stereochemistry regardless of the alkene geometry. β-Branched and β,β-disubstituted substrates are also tolerated.[212]

Despite early beliefs that a chiral center was required on phosphorus itself, some of the most successful catalyst systems for reductions of didehydroamino acid derivatives employ asymmetric carbon centers, often with the stereogenic center being adjacent to the phosphorus. The synthesis of such ligands is sometimes difficult, but the stability of the ligands, and their widespread commercial availability, easily overcome this limitation.

Conjugated diene-type didehydroamino ester reductions, such as with DuPhos as the ligand, resulted in the production of γ,δ-unsaturated amino esters.[210] Only the enamide unsaturation is reduced. In addition, these ligands perform equally well for

N-tert-butoxycarbonyl and *N*-benzyloxycarbonyl-protected didehydroamino acids, permitting mild protecting-group removal after reduction.[213,214]

Carbohydrate-based O–P ligands are another type of ligand class for the reduction of didehydroamino esters with high degrees of asymmetric induction that have a carbon backbone as the source of chirality. The product *ee* is dependent upon the protection of the nonphosphorylated hydroxy groups and the position of the phosphorus moieties, with 2,3-substitution giving the best results.[232]

The early discovery of the bidentate *P*-chiral ligand Dipamp **15** for rhodium to catalyze the asymmetric hydrogenation of didehydro amino acids and esters[209,273] has subsequently led to many improvements. Although Dipamp has been used at manufacturing scale, its use is still somewhat limited by the difficult synthetic sequence and by the inherent instability of the free ligand to racemization above ambient temperature. The fact that trialkylphosphines are not prone to racemization at normal working temperatures has led to the development of MiniPhos **34**[234], BisP* **36**,[237,238] trichickenfootphos (TCFP) **35**,[235] and TangPhos **38**.[239]

A series of ligands based on chiral phosphines with a ferrocene backbone, such as BoPhoz **47**, provide good to high degrees of asymmetric induction for the preparation of phenylalanine derivatives.[215,252] Subtle differences in the phosphorus substituents can result in large variations in the selectivity of the reaction.[240]

Rh(BINAP)-based catalysts can reduce didehydroamino acids with good enantioselectivities but, in general, they are inferior to other ligand classes for these substrates.[256,257] Better selectivity is observed with other ligands whose chirality arises from atropisomerism, such as PhanePhos **55**,[260] BICHEP **52**,[258] and the aminophosphine Xyl-BDPAB **57**.[259]

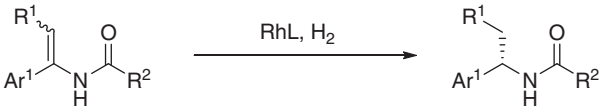
The MonoPhos™ family of ligands **56** provides high enantioselectivities with didehydroamino acid derivatives.[261,274] The reduction can also be faster than with bidentate ligands, such as DuPhos **16**.[275] The best ligand from this class for general usage for the preparation of α-amino acids is PipPhos **56c**.[262]

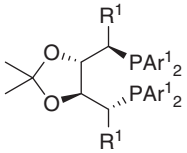
With the monodentate phosphonite **53** or phosphite **54** ligands, β,β-disubstituted didehydroamino esters can be reduced efficiently to the corresponding amino esters.[276]

8.17.5.2.2 Asymmetric hydrogenations of enamides

In many ways, the reduction of enamides (Table 5) is an extension of those described earlier for didehydroamino acid derivatives, as the metal usually forms a complex with the amide oxygen. As with didehydroamino acid derivative asymmetric hydrogenations, enamides can cause problems with some catalyst systems when the substrate is the *Z*-isomer or a mixture of *E*- and *Z*-isomers. Disubstitution at the β-position is still problematic. The ligands that have been used for the asymmetric reduction of enamides are summarized in Table 5.

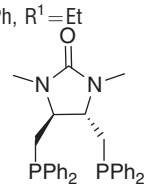
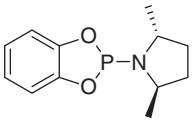
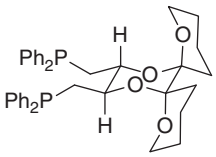
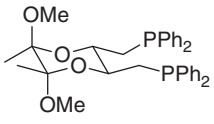
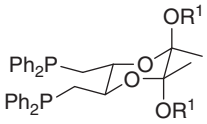
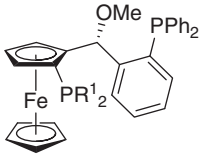
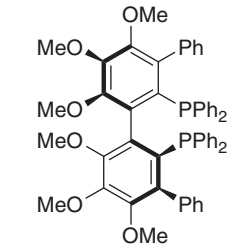
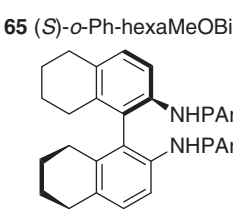
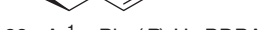
Table 5 Asymmetric enamide reductions



Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
16a	100	95.6–96.9	277
17a	100	95–98.3	277
18c R^1=Et, R^2=H	100	95–99	217
36a	100	96–99	278
38	–	97–99	239
45a	100	95–97	250
53b R^1=^{t}Bu and **54b** R^1= Me	100	95–97.2	279
53b and **54c** R^1=Bn	100	97.4	279
53b and **54d** R^1=(*S*)-CHMePh	100	96.8	279
54e R^1=(*R*)-CHMePh	100	97	280
56b	100	97–99	262
56c	100	96–99	262
	99–100	97.7–99.0	281,282
58 (*R,S,S,R*)-DIOP*			
58a Ar^1 = Ph, R^1 = Me			
58b Ar^1=4-MeOC$_6$H$_4$, R^1=Me	100	96–98	282

(*Continued*)

Table 5 Continued

Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
58c Ar^1 = Ph, R^1 = Et 	100 100	98–99 97.8–99	282 283
59 (*S,S*)-BDPMI or (*S,S*)-MeBDPMI 	100	97–99	284
60 	>99	97–98	285
61(*R,R,R,R*)-SK-Phos 	99	97	285
(*S,S,S,S*)-**62** 	>99	98	285
(*R,R,R,R*)-**63a** R^1 = Me 	>99 100	95–98 96–97	285 250
64a R^1 = Ph 	100 100	92–95 96–99	250 286
64b R^1 = 3,5-$Me_2C_6H_3$ 	100	96.8–99	287
65 (*S*)-*o*-Ph-hexaMeOBiPHEP 			
66a Ar^1 = Ph, (*R*)-H_8-BDPAB			

[a]Only one enantiomer of the ligand is shown, although some of the examples may be with the antipode.

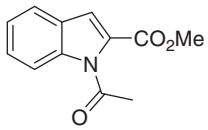
There are a few examples where the α-aryl group in the substrate can be replaced by an alkyl substituent, albeit a bulky one, and still obtain good asymmetric induction. A class of ligands that induces high selectivity with isomeric mixtures of aryl enamides is BDPMI **59**.[283] DuPhos **16** performs well giving slightly higher *ee*s than seen with BICP **29**.[271,277] SK-Phos **61** is good with acyclic examples,[285] as is DIOP* **58**.[281,282] The use of ferrocene-based ligands for the reduction of aryl enamides is limited, but one of the better systems is the TRAP ligands **43**.[246,250] Aryl enamide reductions with Rh(BDPAB) (Rh-**57**) and the H_8-analog **66** show variations in *ee* dependent upon the reaction temperature and solvent. Higher *ee*s, in general, are seen with the H_8-ligands.[288]

The MonoPhos family of ligands can also reduce enamides, with PipPhos **56c** and MorfPhos **56b** providing general utility. The *ee*s are higher with the *Z*-substrates.[262] Monodentate phosphites can also be used to reduce aryl-substituted enamides.[279] The use of two different phosphite ligands can enhance the selectivity and rate, and the second ligand can be a phosphonite.

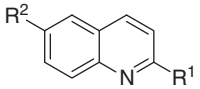
8.17.5.2.2.1 Asymmetric reductions of aromatic heterocycles

This topic has been reviewed.[289] Most of the examples, to date, of asymmetric aromatic heterocyclic reductions are with nitrogen heterocycles. As noted before (see Section 8.17.3.2), there has been limited success for the achiral reduction of these aromatic systems. However, the asymmetric reductions are showing promise not only in allowing the hydrogenation to proceed, but also for enantiofacial selectivity.

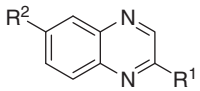
An indole derivative **67** can be reduced to the indoline with an Rh catalyst derived from PipPhos **56c**. Although the yield of the reduced product is quantitative, the *ee* is 74%.[290] For 6-membered *N*-heterocycles, quinolones **68** and **69** are reduced by the same catalyst system but in higher *ee* (76–89%), although in some cases the chemical yield may be lower.[291,292] A solvent effect is observed and piperidine hydrochloride needs to be added.



67

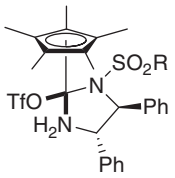


68

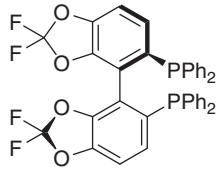


69

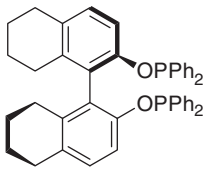
Iridium complexes, such as **70**[293] and one derived from DifluoroPhos[294] **71** give slightly higher *ee*s. Iridium catalysts derived from (*R*)-H_8-BINAPO **72** with iodine as an additive give similar results.[295]



70



71



72

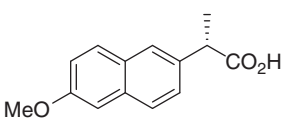
8.17.5.3 Asymmetric Hydrogenation of Acrylic Acids and Esters

The majority of catalysts used to perform the reduction of α,β-unsaturated acids are based on Rh or Ru and require a free carboxylate to control binding to the metal (**Table 6**). Esters of α,β-unsaturated acids act more like unfunctionalized alkenes, where Ir-based systems have enjoyed some success (see Section 8.17.5.5).[296–300]

The BINAP family of ligands provided the first success for the reduction of α,β-unsaturated acids. This has led to the majority of the ligand systems used to perform this reduction being based on hindered biaryl systems. One catalyst based on a ferrocene system has been successful with tetrasubstituted alkenes.

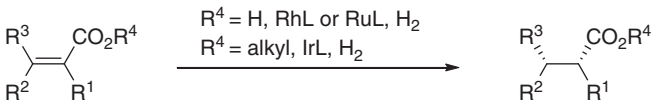
Catalysts based on ferrocene-bridged ligands **78** are capable of reducing 2-arylenoic acids when 3,3-disubstitution is also present.[305] When the two β-substituents are not identical, higher selectivities are seen with the *E*-isomer.[308]

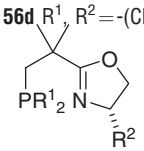
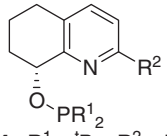
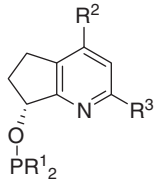
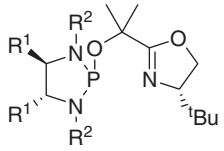
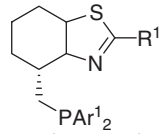
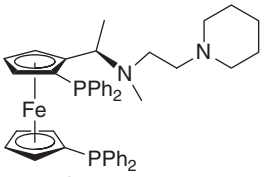
α,β-Unsaturated acids can be hydrogenated with Ru(BINAP) (Ru-**51**) catalyst systems with reasonable degrees of asymmetric induction. The synthesis of naproxen **82** exemplifies the reduction of α,β-unsaturated acids.[302,309,310] The P-Phos ligand system **81** induces slightly higher *ee*s than BINAP **51**, as does the TunaPhos-type ligand **79**.[306,307] Use of the H_8-BINAP system **80**, however, leads to even higher selectivities although trisubstituted alkenes were reduced in lower *ee*.[301]



82

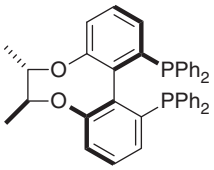
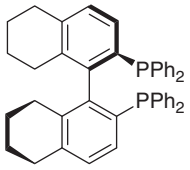
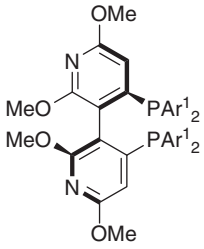
Table 6 Reductions of α,β-unsaturated acids and esters



Ligand structure[a]	*Metal*	*Conversion or yield (%)*	ee *(%)*	*References*
51	Ru	92–100	96–97	301,302
56d R^1, R^2 = -$(CH_2)_5$-, R^3 = Me	Rh	98–100	95–99	303
	Ir	>99	95	298
				
73 NeoPhox				
73a R^1 = Ph, R^2 = ^{t}Bu				
	Ir	>99	99	300
74a R^1 = ^{t}Bu, R^2 = H				
	Ir	99–100	94–99	297,300
75a R^1 = ^{t}Bu, R^2 = Me, R^3 = 2,4,6-$Me_3C_6H_2$				
	Ir	>99	97	299
76a R^1 = Ph, R^2 = 4-$MeOC_6H_4$				
76b R^1 = Ph, R^2 = 4-^{t}BuC_6H_4	Ir	>99	98	299
76c R^1 = -$(CH_2)_2$-, R^2 = 4-MeC_6H_4	Ir	>99	96	299
	Ir	99	95	304
77a Ar^1 = Ph, R^1 = H				
77b Ar^1 = Ph, R^1 = Ph	Ir	>99	98	304
77c Ar^1 = 2-Tol, R^1 = Ph	Ir	>99	98	304
	Rh	100	96.7–98.4	305
78				

(*Continued*)

Table 6 Continued

Ligand structure[a]	*Metal*	*Conversion or yield (%)*	ee *(%)*	*References*
 **79**	Ru	–	96	306
 **80** (*R*)-H_8-BINAP	Ru	100	95–97	301
 **81a** Ar^1 = Ph, (*R*)-P-Phos	Ru	92	97	307

[a]Only one enantiomer of the ligand is shown, although some of the examples may be with the antipode.

The use of phosphoramidites **56** with Rh does allow trisubstituted examples to be reduced even with hindered R^1 groups, such as isopropyl. The reactivity and stereoselectivity is enhanced by the addition of a phosphine ligand to the system.[303]

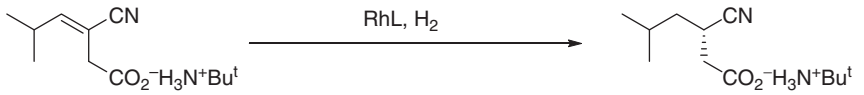
The presence of two carboxylate groups helps to achieve high degrees of asymmetric induction with a wide range of asymmetric hydrogenation catalysts. They can be used as either the free dicarboxylic acids, as homo or mixed diesters, or as monoesters (Table 7). There are a few examples where amides (X or Y=N) have been used as substrates.

β-Substituted itaconates are generally prepared via the Stobbe condensation, which leads to a mixture of *Z*- and *E*-isomers. These mixtures can be hydrogenated with remarkably high enantioselectivity using rhodium catalysts based on DuPhos **16** or BPE **17**. Screening showed that the best general ligand was Et-DuPhos **17b** for the system with the monomethyl ester **85** (R^1X=MeO, R^2Y=HO, R^3=H) in MeOH in the presence of NaOMe.[271,312] The amide **85** ($R^1X=H_2N$, R^2Y=HO, R^3=H) is reduced by Et-DuPhos in high yield although chloride has to be excluded rigorously.[311] The FerroTANE ligands **83** can also be used to reduce amido itaconates.[317] The *P*-chiral ligands have not been widely applied to the reduction of itaconates. However, TangPhos **38** provides high selectivities with aryl-substituted itaconates.[313]

Ferrocene-based ligands have enjoyed considerable application for the reductions of unsubstituted itaconates. Thus, JosiPhos **41** can be used in the rhodium-catalyzed reduction of itaconates to succinates with high asymmetric induction.[244] The TRAP family **43** can be used for the reduction of dimethyl itaconate **85** ($R^1X=R^2Y$=MeO, R^3=H); EtTRAP **43b** induces high selectivity as do some other analogs. The use of tetra- and trisubstituted itaconates as substrates led to lower *ee*s.[314]

Rh(BICHEP) (Rh-**52**) gives good ees during the reduction of itaconic acid to 2-methylsuccinic acid.[258] In addition to the itaconates themselves,[261] trisubstituted alkenes in the itaconate system can be hydrogenated with good selectivity through the use of phosphoramidite **56** and phosphite **54** ligands.[262,316]

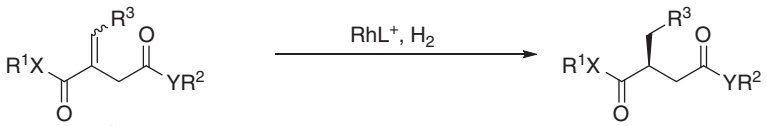
The asymmetric hydrogenation of the *tert*-butylammonium salt of 3-cyano-5-methylhex-3-enoate with Me-DuPhos **16a** as ligand gave the precursor to (*S*)-(+)-3-(aminomethyl)-5-methylhexanoic acid (pregabalin) with 97.7% *ee* (equation 4).[235,319] Trichickenfoot Phos (TCFP) **35** was developed specifically for this transformation and leads to higher *ee* and TON.[235] Attempted hydrogenation of the free acid was unsuccessful due to competing coordination of the nitrile that prevented alkene coordination to the metal.



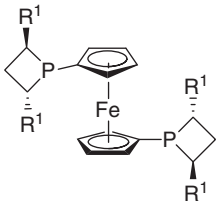
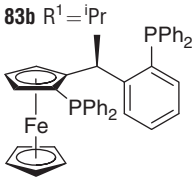
(*R*,*R*)-Me-DuPhos **16a** 97.7% *ee*
(*S*)-TCFP **35** 99% *ee*

(4)

Table 7 Asymmetric hydrogenations of itaconate derivatives



85

Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
17b	98–100	97–99	311,312
18a	100	96–98	217
18b	100	>99	217
18d R^1=Me, R^2=Bn	–	97.5–98	218
19b	–	96.7–99.1	218
20c R=Bn	100	95.9	219
20b R=Me	100	96.9–97.9	219
34a	100	99.9	233
36a	100	98.6	233
38	100	95–99	313
41a	100	98.5–99	244
43b	100	96	314
44	100	97.9	248
45a	100	98	250,251
46[b]	95	98	249
47a	>95	97.4–99	252
52	100	96–99	258
54d	100	99.2	315
54b	100	98	262
54c	99–100	99	262,316
54e R^1=^{i}Pr	>99	96–97	316
56a	>99	97	261
64a	100	95	250
	100	96–99	317
83 (*R,R*)-FerroTANE **83a** R^1 = Et			
83b R^1=^{i}Pr	100	97	317
	100	96	251
84			

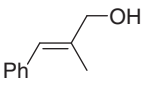
[a]Only one enantiomer of the ligand is shown, although some of the examples may be with the antipode.
[b]The structure of TaniaPhos **46** has been corrected since this publication.

8.17.5.4 Asymmetric Hydrogenation of Allylic Alcohols

There are relatively few examples of this class of asymmetric hydrogenation, despite its importance in industrial applications. Perhaps this is due to the early success with BINAP. Although the hydroxyl group in an allyl alcohol can be considered a ligand, some of the successful systems have been developed for the reduction of 'unfunctionalized' alkenes (see Section 8.17.5.5). The allylic alcohol **86** has become a standard substrate (Table 8).

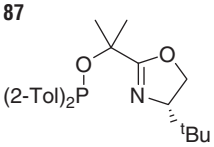
The reduction of geraniol **89** shows that high levels of enantioselectivity can be achieved.[322] In addition, the regioselectivity is high with the alkene of the allylic alcohol being reduced selectively; only 1.5% of dihydrocitronellol **90** was formed.[199,310,323]

Table 8 Reduction of the allylic alcohol **86** with Ir-Phox systems



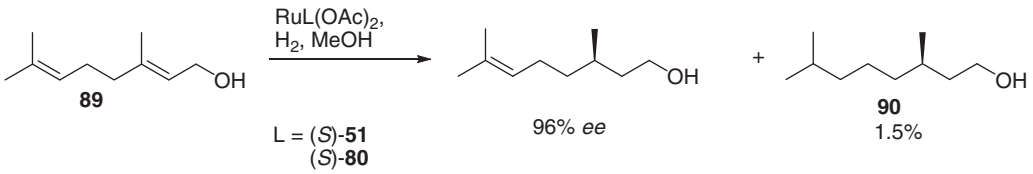
86

Ligand structure[a]	*Conversion (%)*	ee *(%)*	*References*
73b R^1=2-Tol, R^2=^{t}Bu	>99	96	298
74b R^1=Me, R^2=H	>99	97	300
75b R^1=Ph, R^2=Me, R^3=2-Naph	99	95	297
75c R^1=2-Tol, R^2=H, R^3=2,4,6-$Me_3C_6H_2$	95	97	297
77a	>99	99	304
77b	>99	99	304
87	95–99[a]	98–99[b]	320
	>99	97	321

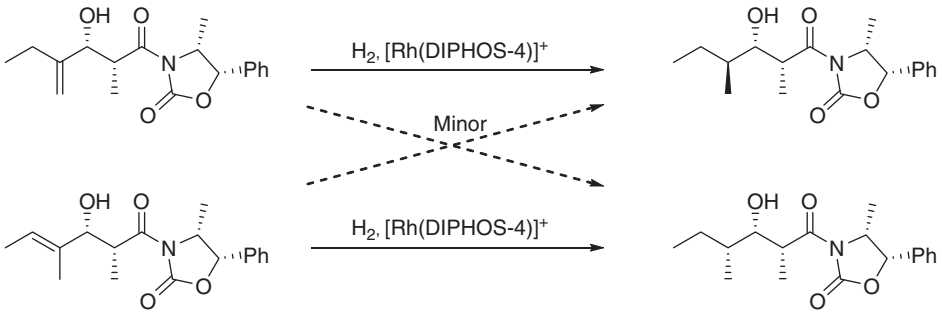


88 SimplePhox

[a]Only one enantiomer of the ligand is shown, although some of the examples may be with the antipode.
[b]Also with the allylic acetate rather than the allylic alcohol.



The presence of a stereogenic center in the substrate allows control of the hydrogenation of allyl alcohols with rhodium catalysts such as that derived from [Rh(NBD)(DIPHOS-4)]BF_4 and (DIPHOS-4 is 1,4-bis(diphenylphosphino)butane). The hydrogen is directed by the hydroxyl group.[39] In this example, the oxazolidinone does not control the stereochemical outcome of the reaction.

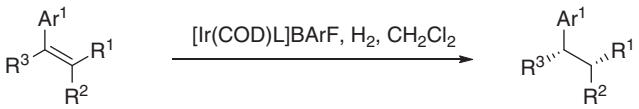


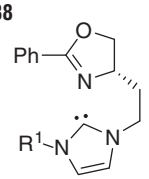
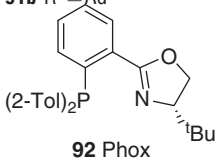
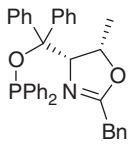
Reductions in the presence of Crabtree's iridium complex also can be directed by a hydroxyl group.[44]

8.17.5.5 Asymmetric Hydrogenation of Simple Alkenes

The hydrogenations of simple alkenes, defined to include aryl-substituted alkenes, have been reviewed.[324] The key to the success for the reduction of nonfunctionalized alkenes is the use of a noncoordinating counterion.[325] The most common is the BArF anion {[tetra[3,5-bis(trifluoromethyl)phenyl]]borate}.[326] Whereas Rh and Ru require a coordinating atom in a functional group of the substrate to allow asymmetric induction, this is not available in an isolated or nonfunctionalized alkene; Ir is the metal of choice.[325,327] Examples of catalyst systems that have been used with Ir for the hydrogenation of unfunctionalized alkenes are given in Table 9.

Table 9 Asymmetric hydrogenations of nonfunctionalized alkenes



Ligand structure[a]	*Conversion or yield (%)*	ee *(%)*	*References*
73a	>99	97	298
73b	>99	96	321
73c R^1=3,5-$Me_2C_6H_3$, R^2=^{t}Bu	>99	96–98	298
74b	>99	96	300
74c R^1=2-Tol, R^2=9-Anth	99–100	97–99	297,328
74d R^1=2-Tol, R^2=2,4,6-$Me_3C_6H_2$	100	99	297
75b	100	98	297,300
75c	>99	98	300
75d R^1=Ph, R^2=Me, R^3=9-Anth	100	95–98	297,300
75e R^1=2-Tol. R^2=Me, R^3=2,4,6-Anth	100	99	297
75f R^1=2-Tol, R^2=Me, R^3=3,5-(^{t}Bu)$_2$–4-$MeOC_6H_2$	100	97–99	297,300
75g R^1=2-Tol, R^2=Me, R^3=3,5-(^{t}Bu)$_2$–4-$MeOC_6H_2$	100	96–99	297,300
75h R^1=2-Tol, R^2=Me, R^3=Anth	>99	97–99	297,300
75i R^1=^{t}Bu, R^2=Me, R^3=3,5-(^{t}Bu)$_2$–4-$MeOC_6H_2$	>99	95	297
76a	>99	>99	299
77a	>99	98	304
77b	99	98–99	304
87	>99	96–99	320
88	>99	95–96	321
	99	97–98	329
91a R^1 = 2,6-(^{i}Pr)$_2C_6H_3$			
91b R^1=Ad	99	96–98	330
	95–99	95–98	331
92 Phox			
	100	97–99	332
93 ThrePhox			

[a]Only one enantiomer of the ligand is shown, although some of the examples may be with the antipode.

The iridium complex of the Phox ligand **29** gives high selectivity with aryl-substituted alkenes.[331] The BArF counterion provides better conversions and *ee*s.[325] The Phox-family of ligands has been further refined with different cores, including bicyclic systems. This allows the reduction of hindered alkenes and some cyclic examples.

8.17.6 Summary

Most of the methods for the reductions of alkenes, alkynes, and aromatic compounds with a homogeneous catalyst system are well established. In many cases, Rh is the metal of choice. The catalysts developed by Wilkinson, Schrock/Osborn, and Crabtree (the latter being based on Ir) have seen widespread application. For aromatic compounds, ruthenium, nickel, and cobalt are also very

useful. Although heterocycles can be hydrogenated in the presence of these metals, there are relatively few examples until recently when attempts have been made to control the stereoselectivity.

Asymmetric hydrogenations have become very important. The use of chiral ligands with the catalyst systems developed for nonchiral reductions have seen a plethora of ligands being developed. For the hydrogenation of didehydroamino acid derivatives, Rh-DuPhos has broad applicability and gives high enantioselectivities. The same catalyst system can also be used for the reductions of enamides to give chiral amides. Other ligand families that have wide applicability are the ones based on a ferrocene backbone and monodentate ligands derived from BINOL. The reduction of unfunctionalized alkenes is still somewhat problematic. The Phox-family provides the widest application and enantioselectivities.

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8.18 Reduction of C=C and C≡C by Noncatalytic Chemical Methods

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8.18.1 Introduction

The purpose of this update is to inform the reader of key developments since the original review concerning the noncatalytic reduction of C=C and C≡C bonds. As organic synthesis has made great strides in the past two decades, stoichiometric reductions discussed here often play a niche role and therefore have not seen extensive subsequent development. It is worthwhile placing the stoichiometric reductions into context with respect to catalytic methods, especially heterogeneous catalytic hydrogenation methods. Heterogeneous catalytic methods can present the synthetic chemist chemoselectivity problems in a complex molecule, for example, with alkene hydrogenation and hydrogenolysis at susceptible benzylic centers. A further problem observed in heterogeneous reductions can be hydride migration. It is often when such synthetic issues are observed that the chemist turns to some of the stoichiometric reductions discussed in this review, such as *cis*-diazene (diimide) or dissolving metal reductions. This review seeks to highlight key work in recent decades and convince workers that these stoichiometric methods may be good starting points when planning a C=C or C≡C reduction in a complex molecule.

8.18.2 Diimide

As alluded to in the original review, arylsulfonyl hydrazides constitute a major class of diimide precursors. Benzene- and toluenesulfonyl hydrazide **1–2** continue as popular choices, even though high temperatures are often required for diimide formation (Figure 1). A milder diimide source is triisopropylhydrazide **3**, whereby the bulky *ortho*-groups surrounding the hydrazide moiety assist in diimide formation. A major development in this class of diimide precursor since the original review has been the report that 2-nitrobenzenesulfonyl hydrazide (NBSH) **4** acts as a particularly mild precursor to diimide.[1]

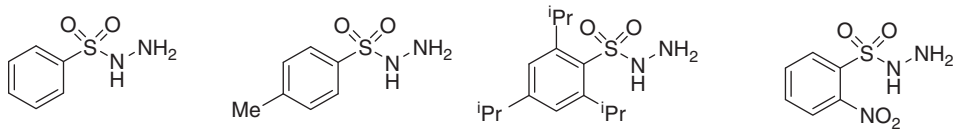
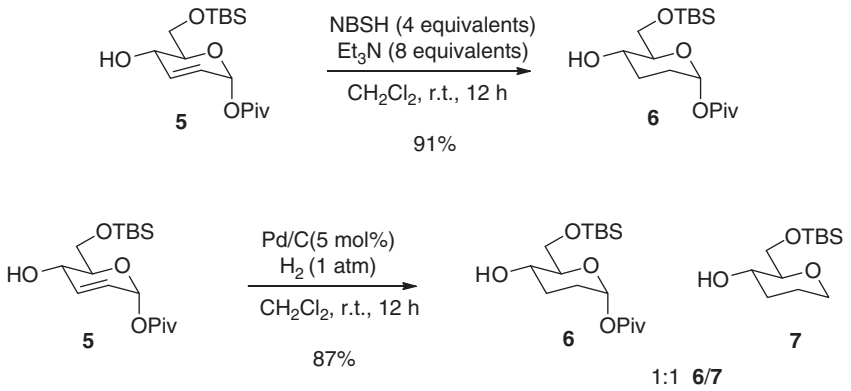


Figure 1 Sulfonylhydrazide diimide precursors.

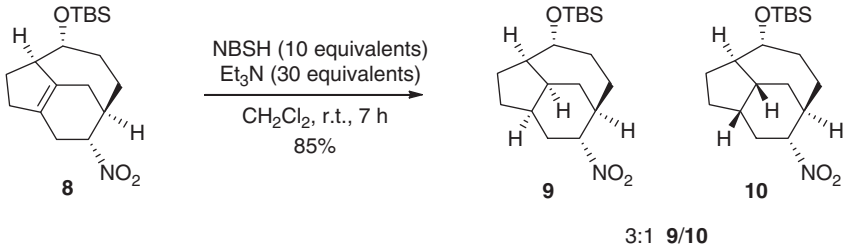
The authors of this report state this to be the first use of the NBSH reagent to effect a diimide-mediated alkene reduction, even though Hünig had previously demonstrated that diimide was a decomposition product of NBSH.[2] The initial synthetic application of NBSH as a diimide precursor was to reduce pyran **5** to **6**, which cleanly occurred in the presence of a twofold excess of triethylamine (Scheme 1), with a clean reaction reported. As is often the case, synthetic workers turn to diimide as an olefin reductant after more familiar transition metal-catalyzed hydrogenations, either homogeneous or heterogeneous, result in deleterious side reactions. This example from O'Doherty is no exception. It is worthwhile juxtaposing this diimide reaction with their application of a heterogeneous hydrogenation catalyst to exemplify the niche value of diimide. While effecting olefin reduction, the use of Pd/C and H_2 led to reductive cleavage of the pivalate group via a palladium π-allyl complex, forming **7** (Scheme 1).

The O'Doherty group has subsequently used this strategy to good effect in a series of elegant reports concerning saccharide manipulations.[3] This synthetic work has in turn helped to bring the NBSH/diimide reduction strategy to the attention of target-oriented synthetic groups. NBSH has now been used to good effect in some recent complex natural product syntheses and model studies. A good example comes from the Chen laboratory.[4] During their total synthesis of echinopines A and B, fused bicyclic olefin **8** was reduced by the NBSH/Et_3N combination in an excellent yield of 85% (Scheme 2). This example is noteworthy for

 doi:10.1016/B978-0-08-097742-3.00820-X

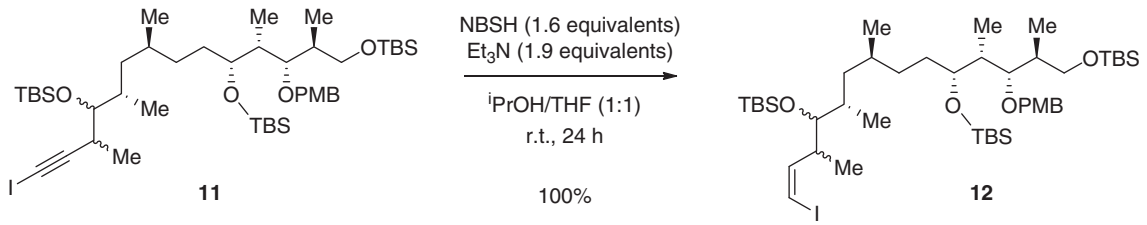


Scheme 1 Diimide reduction of sensitive unsaturated pyrans.



Scheme 2 NBSH generation of diimide and reduction of a tetrasubstituted alkene.

two reasons. First, the reactivity of diimide is understood to be highly sensitive to the olefin's steric environment, to the extent that synthetic workers may not even contemplate diimide as a useful reductant in instances presented by highly substituted alkenes. This example clearly displays that high levels of substitution can be accommodated. It should also be mentioned on balance that olefin **8** may be strained, raising the reactivity. Second, this reduction once again displays the excellent chemoselectivity offered by diimide-reductions, with the nitro group left unscathed by this transformation (Scheme 3).

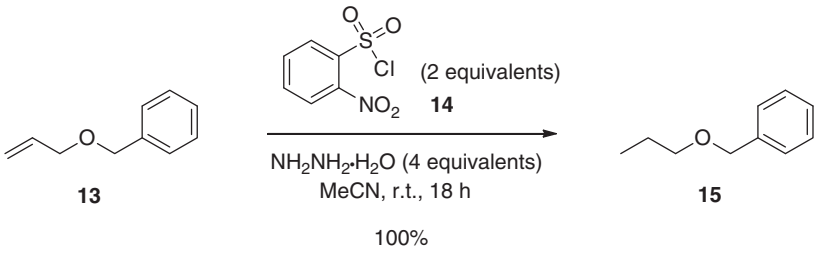


Scheme 3 Partial iodoalkyne reduction.

A further example of the utility of this strategy is seen with the reduction shown in Scheme 3.[5] Most recently, Gennari has utilized NBSH to perform the selective partial reduction of 1-iodoalkyne **11** to *Z*-iodoalkene **12**. This example demonstrates the exquisite chemoselectivity and mild nature of this reaction as the potentially reduction-sensitive para-methoxybenzyl group and C–I bond are unaffected. Similar NBSH-mediated reductions of iodoalkynes en route to polyketide natural products have been reported by Curran[6] and Maier.[7]

Further notable usage of NBSH has been reported during a templated synthesis of a multiple ring rotaxane[8] and on solid-supported olefin substrates.[9]

O'Doherty's rationale for examining 2-nitrobenzenesulfonyl hydrazide had been the potential of an improved leaving group in the form of 2-nitrobenzenesulfenate group. In addition, Myers had reported a practical synthesis of NBSH.[10] This report had also highlighted the sensitivity of the reagent with a clear statement that NBSH was robust if stored at $-30\,^{\circ}C$. The requirement for low temperature storage may lead to diminished practicality for this reagent. In this context Carbery has reported that the NBSH reagent can be formed in the presence of the olefin substrate, thus obviating isolation of NBSH (Scheme 4).[11] A range of substrates possessing functional groups that may be expected to be sensitive to more traditional heterogeneous hydrogenation protocols were compatible with this procedure. For example, benzyl ethers, benzyloxy carbamates, sulfides, and nitro groups are all

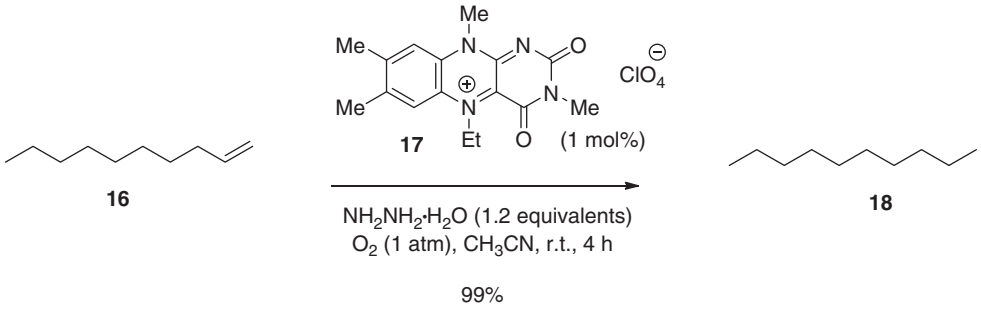


Scheme 4 One-pot NBSH synthesis, alkene reduction.

inconsequential with this one-pot NBSH protocol. Scheme 4 demonstrates this simple protocol with the reduction of ether **13** to ether **15**. Hydrazine hydrate is added to a MeCN solution of sulfonyl chloride **14** and olefin substrate, with **4** formed during the reaction before alkene hydrogenation.

The authors noted that no alkene reduction was observed when either 3-nitrobenzenesulfonyl- or 4-nitrobenzenesulfonyl chlorides were used under identical conditions to those discussed in Scheme 4. This suggests a more complex role for the nitro group other than simple electronic activation of the sulfenate leaving group.

The second major development in the chemistry of diimide reduction of alkenes and alkynes has been the use of flavin organocatalysts to generate diimide under aerobic conditions. Iamada and Naota reported this elegant transformation in 2005. The execution of an alkene reduction performed under an oxygen atmosphere is arguably a counterintuitive reaction and is a quite stunning method.[12] Scheme 5 exemplifies this reaction with the high-yielding reduction of 1-decene **16**. The flavin catalyst used in this synthetic chemistry was originally designed as a biomimetic oxidation model for riboflavin flavoenzyme cofactor by Bruice.[13]



Scheme 5 Flavin-organocatalysis for diimide production from hydrazine.

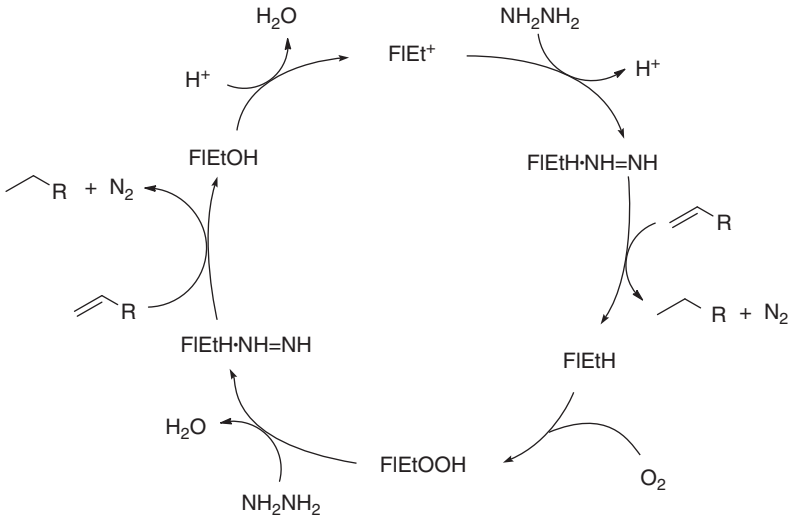
Low loadings of flavinium perchlorate organocatalyst **17** allow the formation of diimide from hydrazine hydrate before subsequent alkene reduction. The reaction requires oxygen to recycle the catalyst and the authors suggest the following cycle of flavinium catalyst **17** (Scheme 6). Key to the proposed mechanism is the 'protection' of highly reactive diimide by some form of complexation to the catalyst. The mechanism proceeds through aerobic and anaerobic subcycles, with diimide being generated from both of these subcycles.

A subsequent full study offered further extensive mechanistic examination and substrate scope studies.[14] The same workers have also described neutral flavins in this diimide-generating protocol and state that these neutral catalysts are more robust than those from their original report.[15]

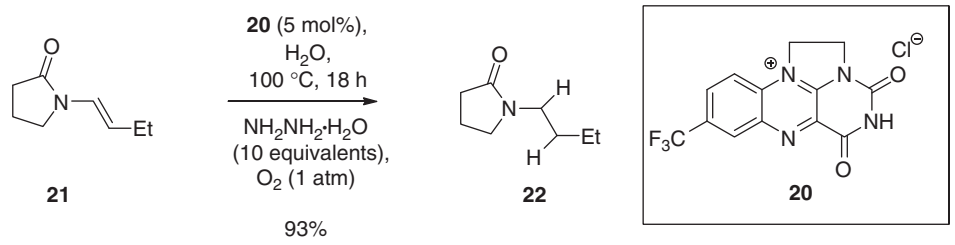
Subsequently, Minaard has reported that catalysts structurally similar to the perchlorate salt discussed earlier, yet simpler to access, are effective for the diimide reduction of alkenes. The catalysts are formed in one step from riboflavin (vitamin B_2) and display similar efficiency to the Imada and Naota system.[16]

Generally speaking, it is understood that diimide will preferentially reduce electronically unbiased olefins. However, Carbery has demonstrated that ethylene-bridged flavinium catalyst **20** is effective in the diimide-mediated reduction of enamides. For example, *N*-vinyl oxazolidinone **21** is hydrogenated to **22** in excellent yield. This reaction, which proceeds under thermal, aqueous conditions, is the first report of a diimide reduction of an electron-rich olefin, with the authors commenting that this system offers an alternative to *N*-alkylations using alkylating agents (Scheme 7).[17]

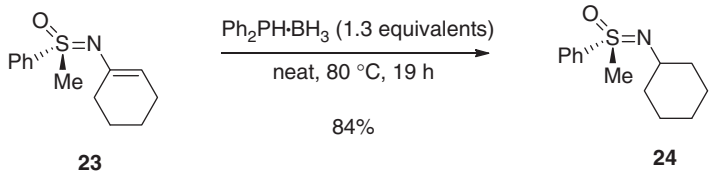
The reagent diimide transfers two hydrogen atoms simultaneously to an alkene from heteroatoms. In this regard, other combinations of bonded heteroatoms may facilitate a reductive double-hydrogen transfer to an alkene. In this respect, there has been a single report of a phosphine–borane complex reducing the C=C bond of chiral *N*-vinylsulfoximine **23** to sulfoximine **24** (Scheme 8).[18] Once again, relatively forcing conditions are required for an enamide. The synthetic usage of amine–borane and phosphine–borane complexes, including reductions, has been reviewed by Manners and coworkers.[19]



Scheme 6 Flavin-catalyzed diimide generation.



Scheme 7 Enamide reduction by diimide.



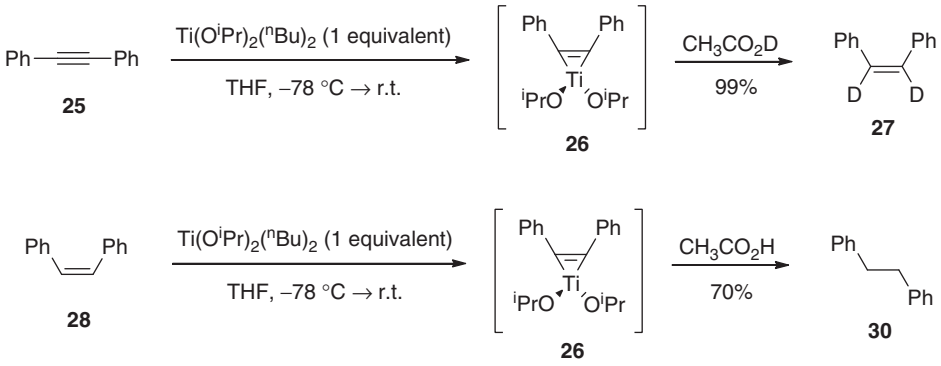
Scheme 8 Enamide reduction by mediated by a phosphine–borane complex.

8.18.3 Dissolving Metal Reductions

A computational study of dissolving metal reductions of alkynes has recently been published.[20] This work utilizes the polarizable continuum regime to model the liquid ammonia reaction medium. This largely supports the generally accepted mechanism for 'Birch' reduction of alkynes with the likelihood that *trans*-selectivity of the reduction is as a result of selective protonation of an intermediate *trans*-vinyl anion.

8.18.4 Low-Valent Metal Reductions

Since the original review there has been some significant work in this area. Low-valent, *in situ* formed, Ti-complexes have been demonstrated to be particularly useful for the *Z*-selective reduction of alkynes to alkenes by Eisch[21] and Tsuji.[22] Scheme 9 demonstrates the formation of Ti(II)–alkyne complex **26**, in this instance from diphenylacetylene **25**, which can form labeled *cis*-stilbene **27** in excellent yield after work up with deuterated acetic acid. Both the Eisch and Tsuji reports were equally effective for this alkyne reduction, providing an excellent and robust reduction of alkynes via low-valent Ti-complexes. In addition, Eisch also demonstrated this strategy to be effective for C=C bond reduction as seen by the reduction of *cis*-stilbene **28** to bibenzyl **30** in



Scheme 9 Low-valent Ti-alkyne complexes for alkyne and alkene reduction.

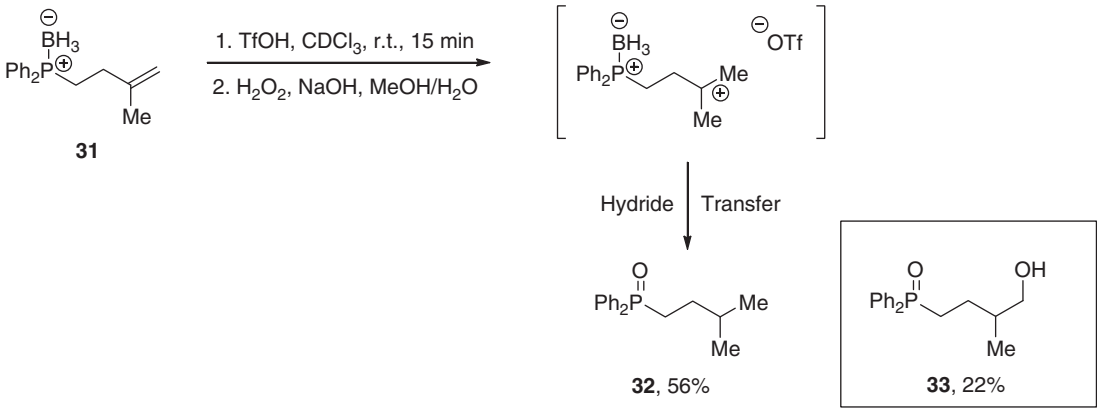
70% yield. However, it should be noted that the remaining mass balance was observed to be isomerized starting material, i.e., *trans*-stilbene.

This method has also been applied to solid phase-supported alkene substrates with excellent chemoselectivity.[23] Further substrates seen to be effectively reduced include fluorous silylacetylenes.[24] Low-valent vanadium complexes have also been reported for the reduction of multiple carbon–carbon bonds.[25]

8.18.5 Ionic Hydrogenation

The stepwise generation of a carbenium ion from an alkene through protonation followed by a subsequent hydride reduction of this carbenium ion is termed ionic hydrogenation. Many examples of this reaction exist, and were discussed at length in the original review. In particular, ionic hydrogenations are often associated with trialkylsilane-mediated reductions. This update section now looks to bring to the reader's attention developments in this general area.

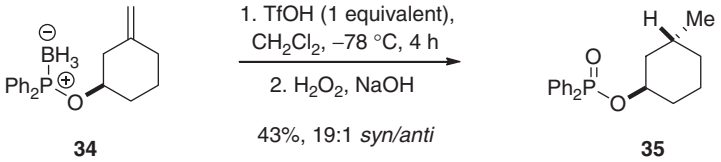
Vedejs has recently demonstrated the *in situ* formation of tertiary carbenium ion salt **32** though the protonation of the 1,1′-alkene moiety of the phosphine–borane complex **31**. These workers in turn observed that an intramolecular hydride delivery occurred, leading to reduction of **32** (Scheme 10). This sequence effects an intramolecular ionic hydrogenation. The facility of this process should be noted as this was faster than the originally intended, and competing, hydroboration reaction. This intramolecular hydroboration ultimately forms **33**, after oxidative work-up (Scheme 10).[26]



Scheme 10 Internal hydride delivery in ionic hydrogenation reactions.

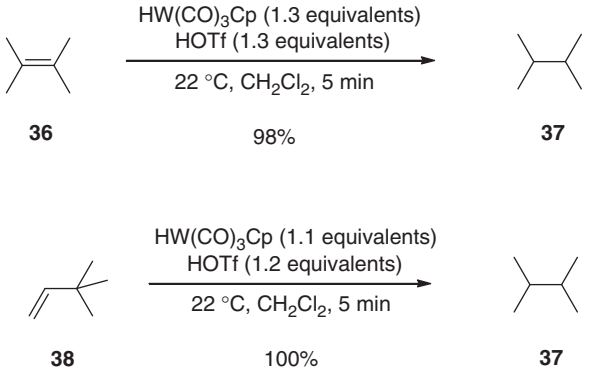
The same laboratory has in turn conducted further mechanistic work, improving their protocol and also performing ionic hydrogenations with hydrides derived from phosphinite boranes. For example, triflic acid-mediated protonation of **34**, before internal hydride delivery, forms **35** again after oxidative work-up (Scheme 11).[27] Excellent diastereoselectivity is obtainable from these processes, again demonstrated in Scheme 11.

Bullock has reported extensively on the use of transition metal hydride-mediated ionic hydrogenation of highly substituted alkenes.[28] Metal hydrides such as $HW(CO)_3Cp$ and $HMo(CO)_3Cp$ are shown to be particularly effective. The reactions proceed through a familiar sequence of olefin protonation, forming a carbenium ion before subsequent hydride delivery. The reactions benefit from rapid reaction times, with 5 min being representative. However, in many instances Wagner–Meerwein alkyl shifts of



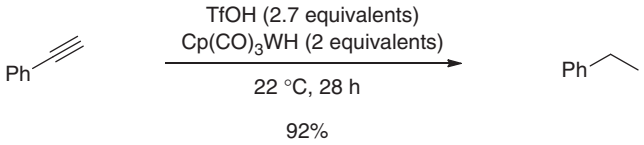
Scheme 11 Intramolecular phosphinite-controlled ionic hydrogenations.

intermediate carbenium ions may lead to synthetic complications. Both of these scenarios are highlighted in Scheme 12. Accordingly, **37** can be accessed through the rapid ionic hydrogenation of either tetrasubstituted alkene **36** or monosubstituted alkene **38**. With such methods, a niche is available for the reduction of hindered, highly substituted alkenes which may not be amenable to more traditional catalytic hydrogenation protocols. Additionally, synthetic opportunities may be offered by the incorporation of such reductive migratory transformations, as exemplified by **38**→**37**, into target syntheses at the design stage.



Scheme 12 Mo- and W-hydride complexes in ionic hydrogenation reactions.

In a similar fashion, Bullock has also reported the ionic hydrogenation of alkynes has been accomplished by using TfOH in conjunction with a tungsten hydride complex (Scheme 13).[29] For example, phenylacetylene **38** has formed ethylbenzene **39** in excellent yield, formally proceeding through a vinyl–carbenium intermediate. Therefore, this process may be expected to be less facile than the analogous alkene reduction discussed earlier in this chapter, and this is indeed borne out as gauged by a comparison of the respective reaction times (e.g., Schemes 12 and 13).

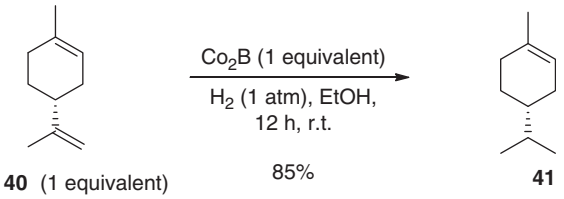


Scheme 13 Ionic hydrogenation of alkynes.

Alkene ionic hydrogenation has traditionally become indelibly linked to the use of silanes (e.g., Et_3SiH) as the reductant, as highlighted in the original review. In the timescale of this review, Olah has reported that the simple addition of ammonium fluoride to the reaction can markedly improve product isolation. This observation was rationalized by the formation of the volatile silyl fluoride, Et_3SiF.[30]

8.18.6 Modified Hydride Reagents

The ability to tune the reactivity of simple hydride reductants, such as $LiAlH_4$ and $NaBH_4$, by the addition of transition metal salts is an important strategy in alkene and alkyne reduction chemistry, as discussed in some length in the original review article. There has been significant work since, including mechanistic work on cobalt-modified hydride systems in alkene reductions. Ganem has studied the cobalt-modified protocol in more detail and has suggested that mixing $CoCl_2$ and $NaBH_4$ forms a stoichiometric amount of a cobalt boride, and it is this species that mediates the hydrogenation of alkenes utilizing the dissolved hydrogen generated from this mixture, e.g., the regioselective reduction of limonene **40** to **41** (Scheme 14).[31] This finding was supported by performing crucial control experiments with respect to the original $CoCl_2/NaBH_4$ alkene reduction report from Chung.[32] Ganem has, in turn, extensively reviewed this area.[33]



Scheme 14 Stoichiometric cobalt boride-mediated alkene hydrogenation.

In a similar fashion, a complex nickel reductant reagent was reported.[34] Tributyltin hydride has been demonstrated to be effective for C=C bond reduction in nitroolefins, without reducing the nitro group.[35] Organolanthanide hydride complexes have seen use as stoichiometric alkene reductants.[36] Of relevance to the previous area of chemistry, an excellent review concerning SmI_2-mediated reduction chemistry has appeared in the literature since the original report.[37]

A reagent that has attracted some synthetic usage for the reduction of ynones to enones has been the mixture of diisobutylaluminum hydride and hexamethylphosphoric triamide.[38] Alkynes have been reduced to *Z*-alkenes by the Stryker reagent, $[(Ph_3P)CuH]_6$, with distinct reactivity trends observed. Terminal alkynes are seen to react fastest, being reduced at room temperature, whereas internal alkynes require elevated temperatures.[39]

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8.19 Partial Reduction of Benzenoid Aromatic Rings by Dissolving Metals and by Other Methods

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Glossary

Benkeser reduction A variation on the Birch reduction in which a low molecular weight amine is used as solvent in place of liquid ammonia.

Benzoyl CoA An enzyme that is capable of effecting Birch-type reductions in biological systems.

Birch reduction The partial reduction of a benzenoid aromatic compound using an alkali metal in liquid ammonia.

Hydrogenolysis The reductive cleavage of a single bond, most commonly C–O, but also C–N and C–C.

Na-SG(I) Sodium adsorbed onto silica gel – one of a number of reagents in this general class that show varying levels of reducing ability.

8.19.1 Introduction

The partial reduction of readily available aromatic compounds to give cyclohexadiene and, occasionally, cyclohexene derivatives is of importance to organic synthesis. In particular, the potential to functionalize the cyclohexa-1,4-dienes produced in the Birch reduction in an asymmetric sense has broadened the appeal of these transformations, and this can be seen in the wealth of compounds that are routinely accessed by such partial reductions of aromatic compounds. The Birch reduction[1–3] is still the de facto method for the production of cyclohexa-1,4-dienes, although a number of other methods have also been used. Although a number of reviews of the Birch reduction have been cited, it would be remiss of the authors not to highlight a personal account of the development of this reaction.[4]

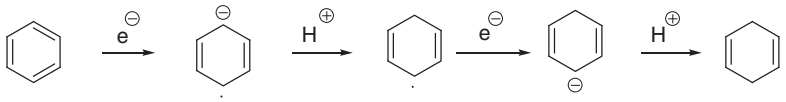
The cyclohexa-1,4-dienes produced have been elaborated in a number of ways, including synthetic sequences in which the six-membered ring is retained intact, as well as being transformed or oxidatively cleaved to give 1,3-dicarbonyl derivatives.[5]

This chapter continues the coverage in the previous edition of this reference work,[6] although the focus has shifted slightly to include applications of the chemistry, which reflects the maturity of the field.

8.19.2 The Birch Reduction

The Birch reduction reaction is the reduction of aromatic compounds using an alkali metal in liquid ammonia as solvent. A proton donor, usually an alcohol such as ethanol or *tert*-butyl alcohol, is added, although alkylating agents, which result in trapping of the intermediate anions, can be used instead. As a synthetic strategy, the Birch reduction provides a link between highly robust aromatic carbocycles and cyclic/acyclic nonaromatic compounds, often with sensitive functionality. It is, therefore, common to take an aromatic ring through multiple synthetic steps before carrying out a Birch reduction to unveil the more sensitive functionality. In recent years, the introduction of absolute stereochemistry during a Birch reduction, generally by alkylation of the intermediate anion, has been demonstrated as a powerful approach, whereas various methods for the formation and desymmetrization of cyclohexa-1,4-diene derivatives have also been reported. These are discussed in the relevant sections.

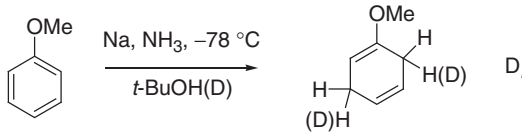
The mechanism of the Birch reduction reaction has been long accepted, with initial formation of a radical anion **1** being followed by protonation to give cyclohexadienyl radical **2**, reduction to cyclohexadienyl anion **3** and a second protonation to give cyclohexadiene **4** (Scheme 1). This reaction features in most good organic chemistry textbooks, but still causes confusion and controversy almost 70 years after it was first proposed.



Scheme 1

Zimmerman has had a long-standing interest in the mechanism of this reaction, and has recently reviewed his efforts, synthetic and computational, in this area.[7] A brief summary of the conclusions reached will be presented.

Although it might appear esoteric, one aspect of concern is the site of initial protonation in the case of substituted benzene derivatives. In the case of anisole, Birch initially proposed that the first protonation occurred *meta* to the methoxy group. However, based on computational evidence Zimmerman proposed *ortho* protonation. Actually, determining the outcome is far from straightforward. Based on the fact that radical anions such as **1** are much less basic than carbanions **3**, Zimmerman devised an elegant experiment using a proton source that is deuterated to a small extent. The initial protonation should be far more selective for protonation rather than deuteration, and the experimental result (equation 1) demonstrates that *ortho* protonation does indeed occur.

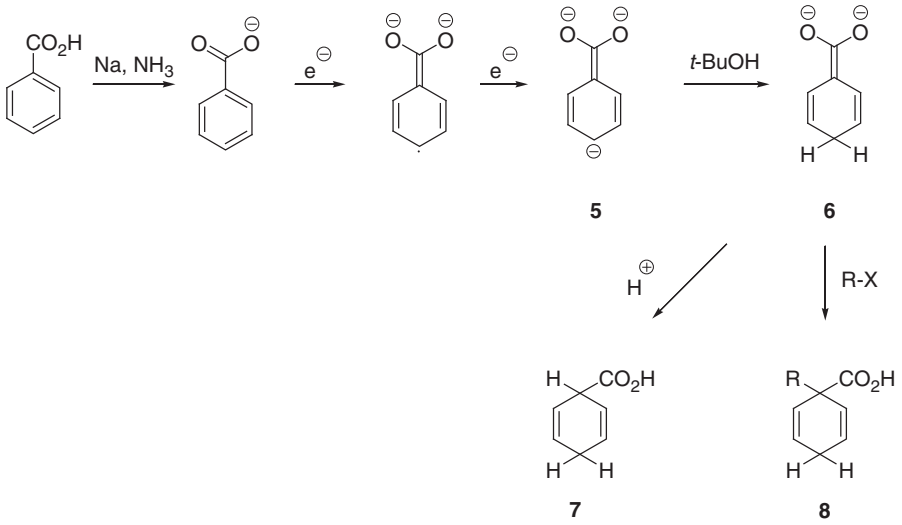


$D_m/D_o = 7.0$ (1)

With benzoic acid, the mechanism involves two sequential one-electron reductions to generate the trianion **5**. Protonation of this gives enediolate **6**, which can then be either protonated or alkylated to give products **7** or **8** (Scheme 2). In the absence of a proton source, the trianion **5** can also be alkylated, and examples of this are discussed below.

8.19.2.1 Experimental Procedures

Despite the use of liquid ammonia as solvent, Birch reductions are actually relatively straightforward to carry out. In most cases either lithium or sodium can be used with similar results, although in some cases (aromatic ketones and aromatic esters)



Scheme 2

potassium is advantageous in order to ensure reduction of the aromatic ring without reduction of other functional groups. The typical procedure involves condensation of liquid ammonia into a mixture of the substrate, a proton source, and a cosolvent. Alcohols such as ethanol and *tert*-butyl alcohol are typically used as proton sources, although they may not be necessary in the case of Birch reductions with alkylation. Diethyl ether and tetrahydrofuran are commonly used as cosolvents, although again the use of a cosolvent is not mandatory. The metal is then added in small portions until a permanent blue color persists for 10 min or more. For Birch reduction reactions with *in situ* alkylation, it may be convenient to quench an excess of metal with piperylene before addition of the electrophile. However, this is not necessary for simple reactions in which a large excess of the electrophile can be used (e.g., iodomethane).

Although, as noted above, the use of potassium often gives superior results, the resulting potassium enolates tend to give unselective alkylation (C– vs. O–). In these cases, it is then necessary to add lithium salts to form the lithium enolate before alkylation. These aspects are discussed in more detail in the relevant Sections 8.19.3.7.1, 8.19.3.8 and 8.19.3.9.

8.19.2.2 Scope and Limitations

Most aromatic compounds undergo Birch reduction to some extent, including benzenoid, fused benzenoid, and polycyclic compounds. In general, the polycyclic aromatic compounds are more readily reduced than simple benzenoid compounds. The presence of electron-withdrawing and electron-donating substituents on an aromatic ring alters the rate of reaction, with those possessing electron-withdrawing substituents reacting faster.

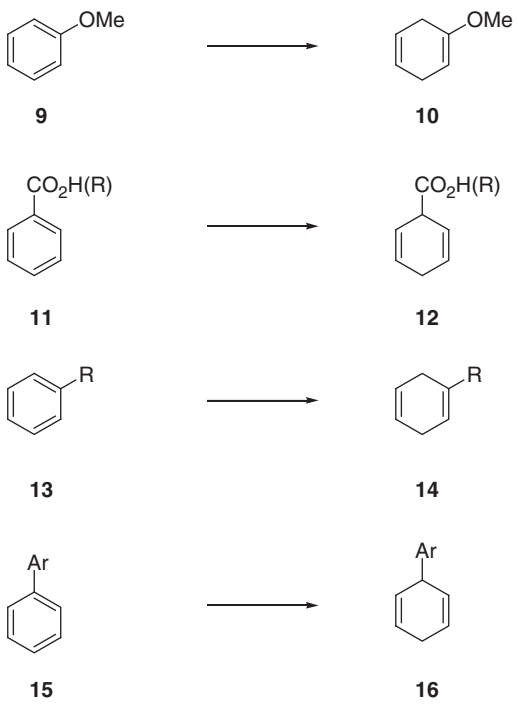
Alkyl-substituted benzene derivatives react more slowly than benzene itself, and dialkylbenzene derivatives react very slowly indeed. Nevertheless, these reactions do work and high yields of the reduced products can be obtained. In the corresponding chapter 'Comprehensive Organic Synthesis,' Mander made note of one limitation – 2,3-dialkylanisole derivatives are reduced extremely slowly and only then with vast excesses of the metal. In one case mentioned, a 2,3,4-trialkylanisole compound was entirely resistant to Birch reduction.

8.19.2.2.1 Substituent effects

The regiochemical outcome of the Birch reduction reaction depends on the nature of substituents on the aromatic ring, and is well established. Groups such as alkyl or alkoxy are invariably located on the double bonds in the products, as in **10** and **14**, whereas electron-withdrawing groups such as carbonyls are located on an sp^3 carbon as in **12**. There have been an increasing number of applications of biaryl compounds in Birch reductions, particularly with alkylation, and the regiochemical outcome of these reactions is as in structure **16** (Scheme 3). Examples of each of these reaction classes are presented in the sections below.

8.19.2.2.2 Secondary reactions

Benzenoid aromatic rings are not the only functional groups to be reduced by alkali metals in liquid ammonia. A number of other reactions are common, including cleavage of benzylic (and occasionally other) C–O bonds, benzylic C–N bonds, and occasionally even benzylic C–C bonds. These reactions can sometimes be carried out selectively without reduction of a benzenoid aromatic ring. For completeness, a number of examples have been included in Section 8.19.3.12 in which the benzenoid ring is not reduced. Furthermore, the potential of Birch reduction chemistry in the partial reduction of heterocyclic systems has been explored, and this is the subject of separate chapters in this volume (*see* Chapters 8.21 and 8.22).



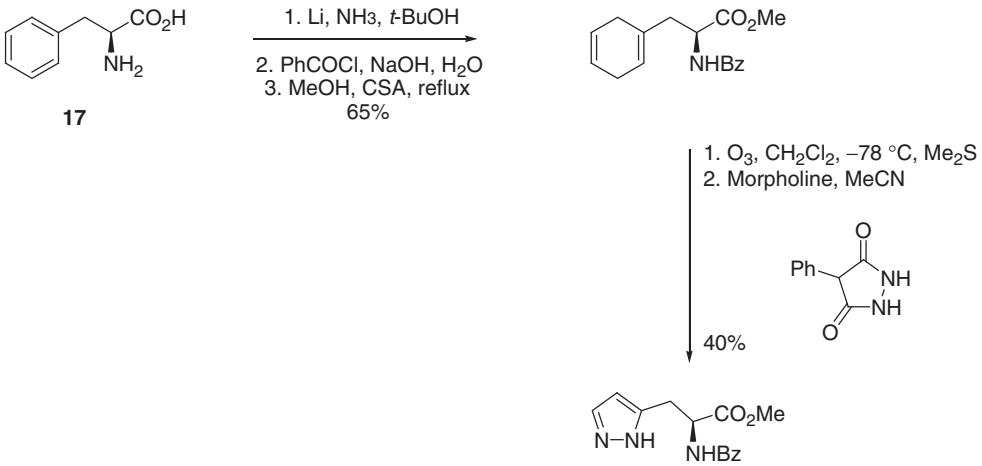
Scheme 3

8.19.3 Survey of Birch Reductions

The discussion of Birch reductions will follow the headings used in the corresponding chapter in the previous edition, albeit with some changes to reflect the developments in the field. However, some general methods have been applied to more than one class of aromatic compound, and in this case the examples that illustrate general methods are grouped together in a single section.

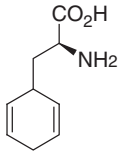
8.19.3.1 Benzenoid Hydrocarbons and Ethers

A number of syntheses have been reported in which a Birch reduction of an aromatic compound is followed by ozonolysis to unveil a 1,3-dicarbonyl compound. This approach is particularly useful starting from L-phenylalanine (**17**). In this case, a range of bisnucleophiles was added after the ozonolysis step to give useful heterocyclic amino acids (e.g., Scheme 4).[8] The same process has been applied to L-phenylglycine, although in this case heterocycles are also formed which include the amino acid's nitrogen atom.[9]



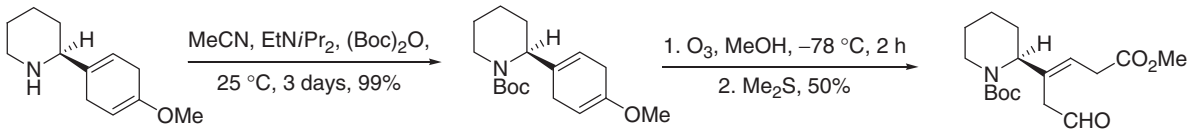
Scheme 4

The regiochemical outcome of this reaction is as expected, and Birch reductions generally only give one regioisomer of the product. It is therefore surprising that L-phenylalanine gives a small amount of the 1,4-dihydro isomer **18** in addition to the expected product.[10] The expected Birch reduction isomer of L-phenylalanine methyl ester has been used in the construction of chiral ligands.[11]



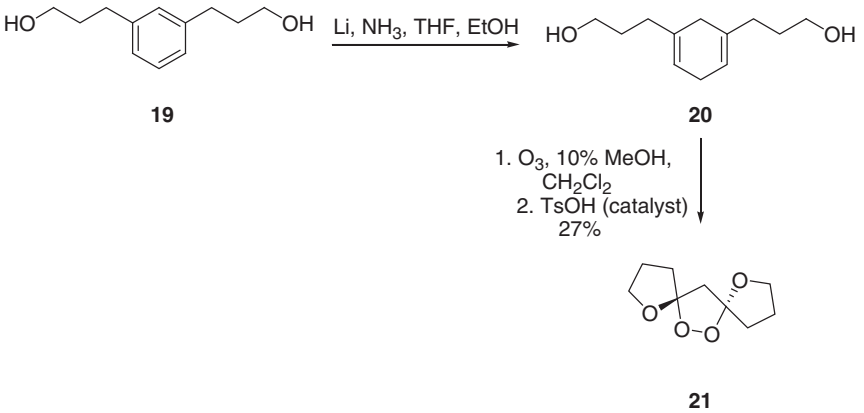
18

With an electron-donating substituent such as methoxy on the benzene ring, it is possible to cleave only the more electron-rich double bond. This has the advantage of forming a trisubstituted double bond in a stereoselective manner, for example, as shown in Scheme 5.[12]



Scheme 5

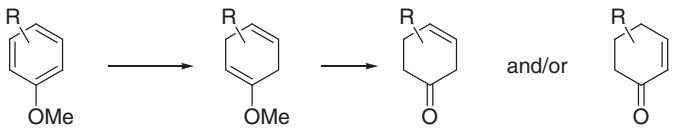
One further example of the combination of Birch reduction/ozonolysis features trapping of the intermediate ozonide to give a tricyclic peroxide **21** in 27% overall yield (Scheme 6).[13]



19 **20** **21**

Scheme 6

One of the most common applications of the Birch reduction in target synthesis is the reduction of an anisole of general structure **22** to give a diene **23**. This can then be hydrolyzed to give either the β,γ-enone **24** or, more commonly, the α,β-enone **25** (Scheme 7).

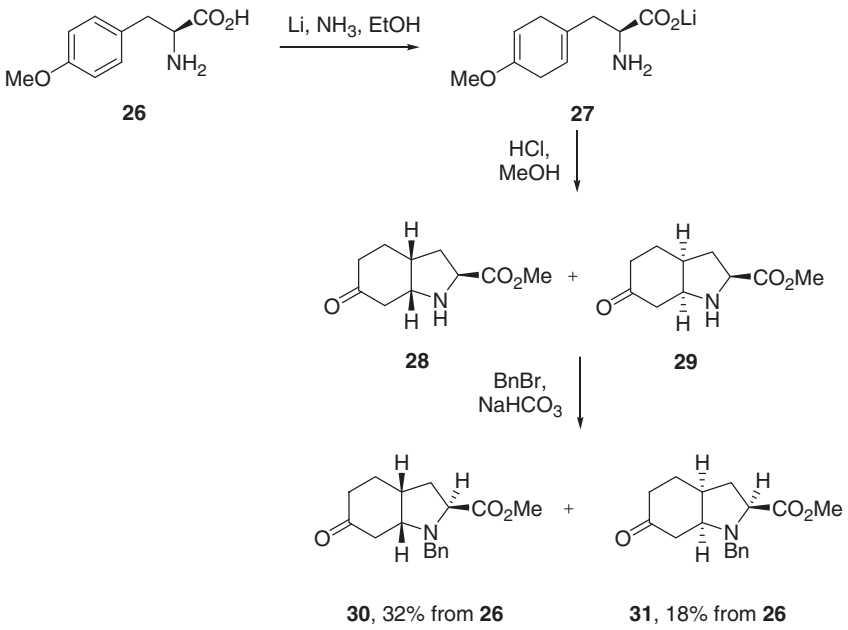


22 **23** **24** **25**

Scheme 7

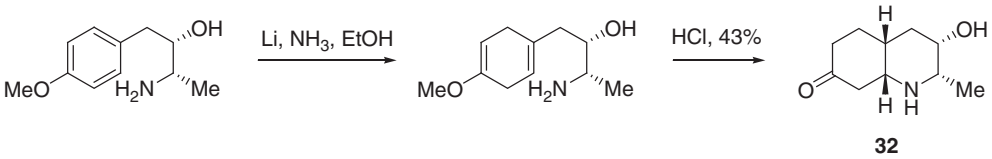
There have been numerous applications of approach reported over the past 20 years, particularly in the field of steroid chemistry, both preparatively to prepare 19-norsteroids[14] and analytically.[15]

Bonjoch has developed a range of methods centered around the Birch reduction of tyrosine derivatives. In the total synthesis of two aeruginosin natural products, reduction of *O*-methyltyrosine **26** was followed by esterification/enol ether hydrolysis/cyclization to give a mixture of stereoisomers **28** and **29**. *N*-Benzylation then gave a mixture of compounds **30** and **31**, although the former could be isomerized to give the latter using methanol/HCl (Scheme 8).[16]



Scheme 8

An essentially identical approach was used to prepare decahydroquinoline derivatives including compound **32** (Scheme 9) along with 17% of a diastereomeric product.[17]



Scheme 9

In such cyclizations, the nitrogen need not be the nucleophile. For example, Birch reduction of benzylic amine **33** gave diene **34** in which the benzylic amine was not cleaved. Formation of amide **35** was then followed by cyclization to give compound **36**. Several more steps then furnished the tricyclic compound **37** containing the core of the madangamine alkaloids (Scheme 10).[18]

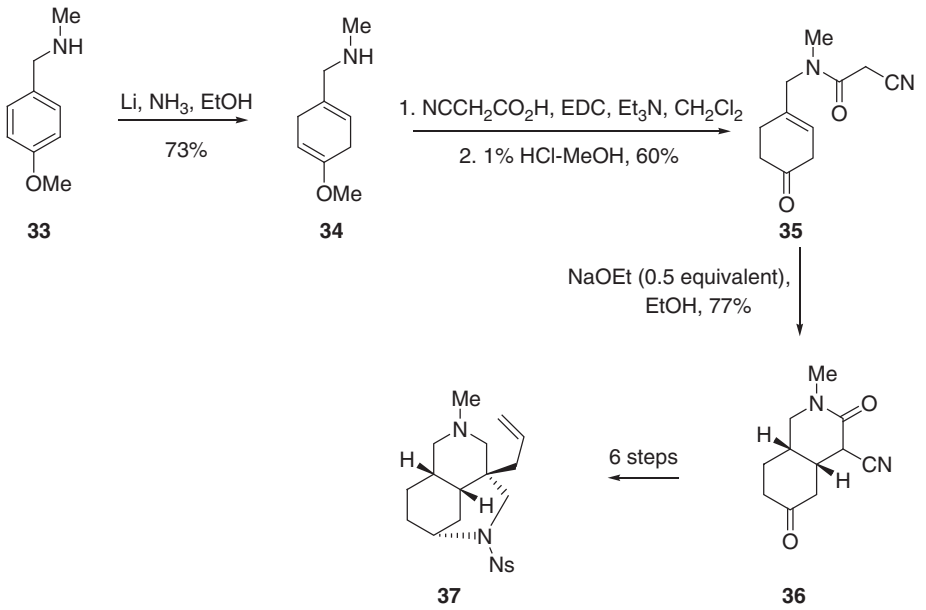
Corey and Lee have shown that it is possible to directly alkylate next to the methoxy group in the diene products (e.g., **38**) produced from such Birch reductions (Scheme 11). In this case the product **39** was elaborated to provide rapid access to pentacyclic triterpenes.[19]

8.19.3.1.1 Intramolecular protonation of Birch intermediates

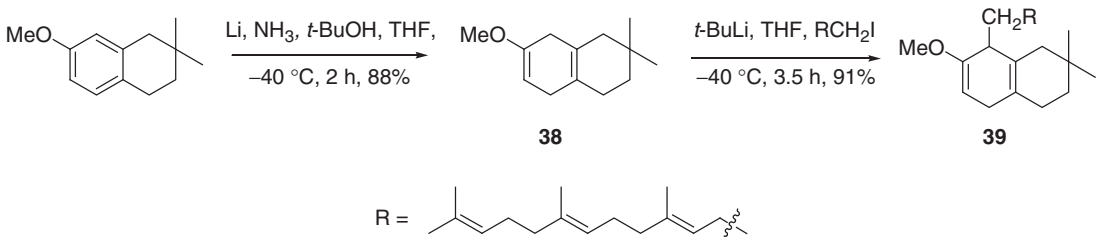
The previous review[6] identified a number of Birch reduction reactions in which the first protonation appears to be intramolecular. Since this is the rate-determining step,[7] it is unsurprising that the possibility of intramolecular protonation aids the reaction. Although the authors are confident that intramolecular protonation plays a role in some of the Birch reductions described herein, no examples were identified in which this is a clear and unambiguous factor.

8.19.3.2 Alkyl- and Alkoxy-naphthalenes

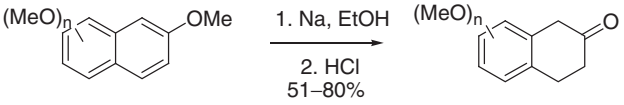
A range of other di- and trimethoxy naphthalenes have also been subjected to Birch reduction. In the cases where methoxy groups are present on each ring, the ring with a single methoxy group in the 2-position is selectively reduced (equation 2).[20]



Scheme 10



Scheme 11



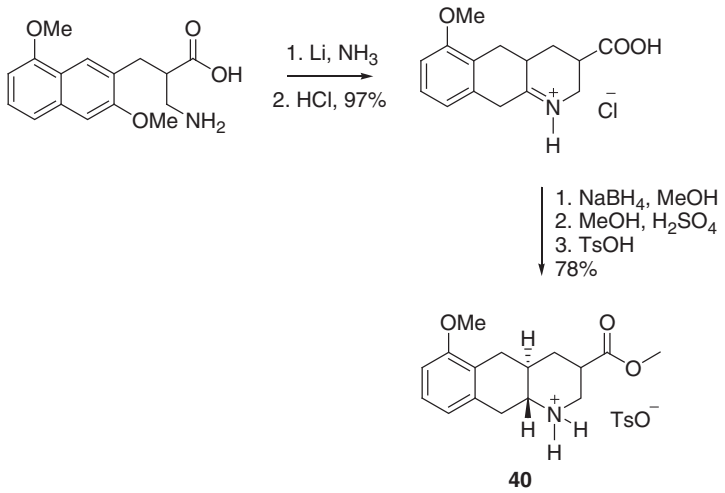
(2)

n = 1, 2; various substitution patterns

A highly efficient sequential Birch reduction/reductive amination has been reported as a route to benzoquinoline derivative **40** (Scheme 12).[21]

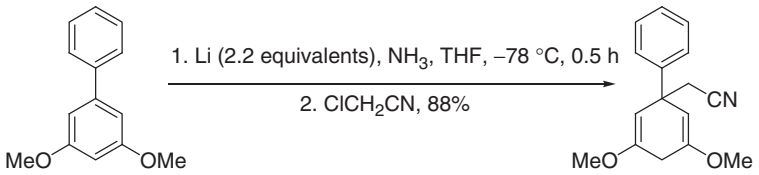
8.19.3.3 Biphenyls, Fluorenes, and Fused Polycyclic Hydrocarbons

Birch reduction of biaryls is a well-established process. Combining this reaction with alkylation, as is common with benzoic acid derivatives, is a relatively recent addition to the synthetic chemist's arsenal. Landais has reported a broad range of examples, many of which work extremely well. In general, reduction of the more electron-rich aryl ring is observed, with the 3-arylcyclohexa-1,4-diene regioisomer being formed (equation 3). Methoxy substituents in the *ortho* and *para* positions were reductively cleaved under these conditions (see Section 8.19.3.12.1). However, it was possible to retain an oxygen substituent in these positions by use of the corresponding phenol, which was deprotonated before reduction (equation 4).[22]

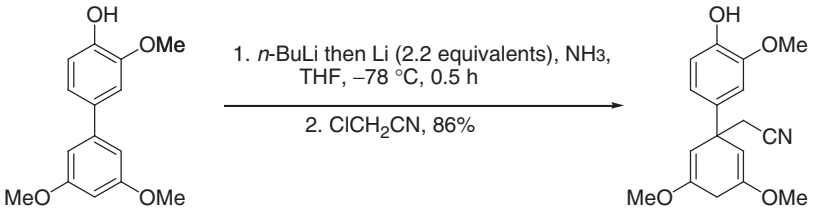


40

Scheme 12



(3)

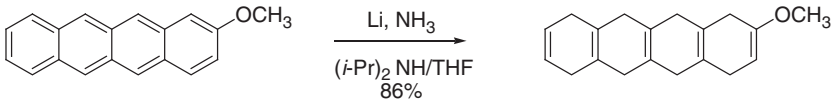


(4)

This method has also been used for the Birch reduction of biarylsulfonamides such as **41**, again with deprotonation. Three simple elaborations were required to convert the product **42** into compound **43** containing the core of the aspidospermine alkaloids (Scheme 13).[23]

Larger polycyclic aromatic hydrocarbons also undergo Birch reduction, giving a range of useful products. For example, crystals of compound **44**, prepared from anthracene by Birch reduction followed by epoxidation/solvolysis (Scheme 14), exhibits dimorphism.[24]

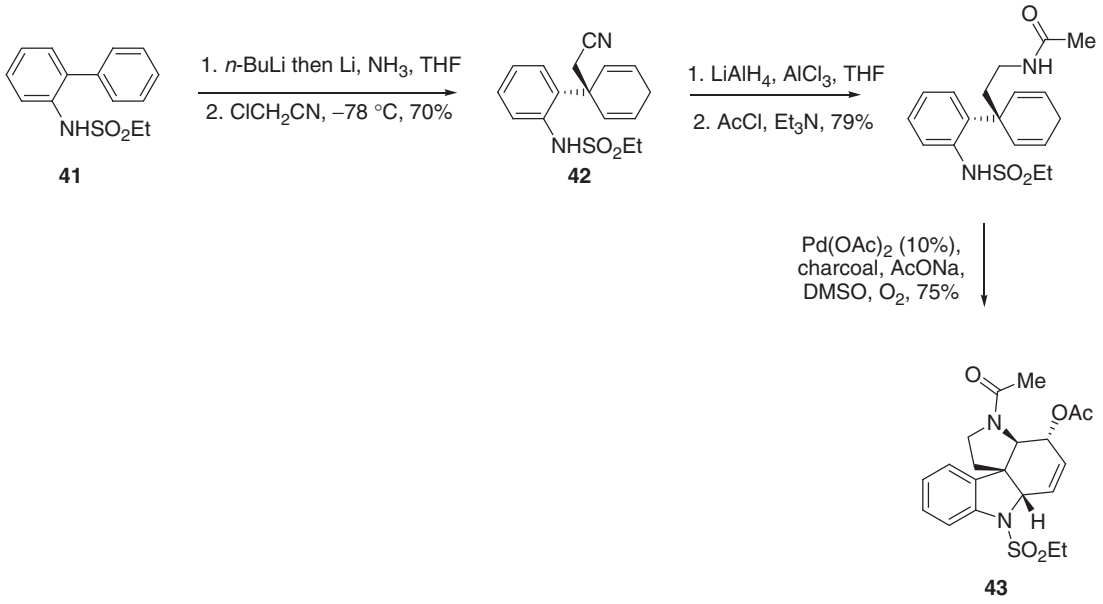
Even more rings can be reduced simultaneously, for example equation 5.[25] The same authors have previously reported an identical approach for a methoxyanthracene derivative.[26]



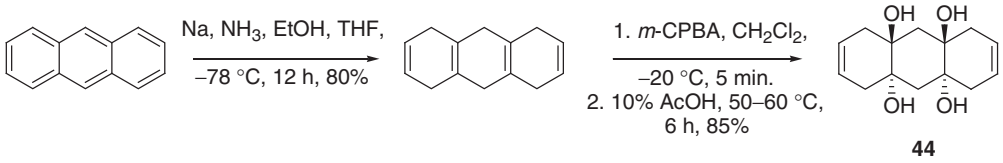
(5)

The Birch reduction of pyrene gives a mixture of two regioisomeric products **45** and **46**. Deprotonation and reaction with 1,4-dibromobutane then gave a mixture of spirocyclic compounds from which the major isomer was separated after selective epoxidation of the minor isomer (Scheme 15).[27] The reduction of pyrenes possessing an alkyl chain spanning the ring system gives reductive dimerization products.[28]

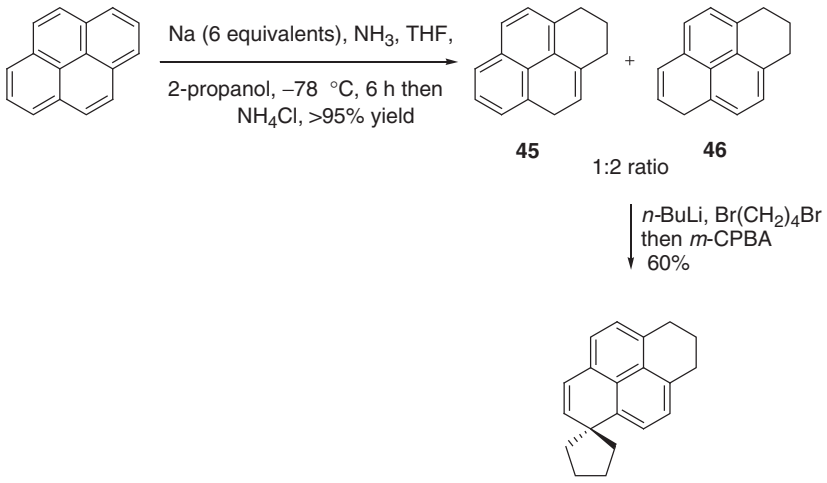
The ultimate 'biphenyl' is hexaphenylbenzene (**47**). This undergoes a facile Birch reduction at the central ring to give only two of the possible eight stereoisomers of the product (equation 6). In fact, **48** and **49** are, according to calculations, the least stable of the possible stereoisomers.[29]



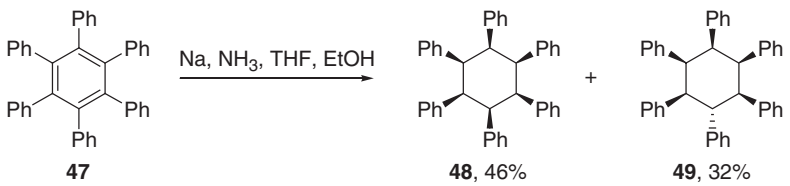
Scheme 13



Scheme 14



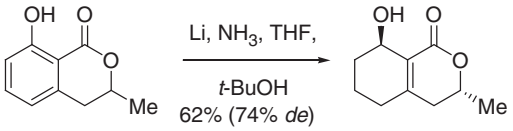
Scheme 15



(6)

8.19.3.4 Phenols

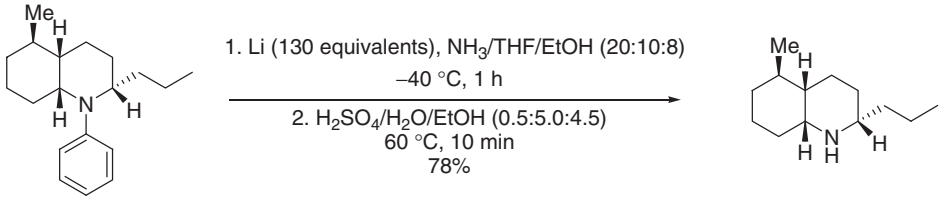
Generally, phenols are resistant to Birch reduction, since they will form the corresponding phenoxide anion. In this case it is believed that the lactone carbonyl provides stabilization for the intermediate radical dianion, allowing the formation of the product **50** with moderate stereocontrol (equation 7).[30]



50 (7)

8.19.3.5 Aromatic Amines

The Birch reduction of anilines is not widely used to access the cyclohexa-1,4-dienes, since these are enamines that are readily hydrolyzed. However, this does constitute a highly effective removal of a *N*-phenyl group, making this an effective protecting group. This approach has been used numerous times, with the example shown in equation 8 being representative.[31]

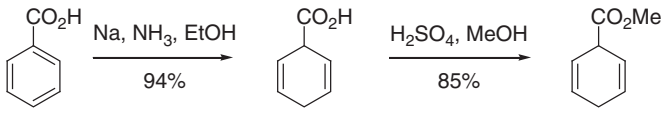


(8)

8.19.3.6 Carboxylic Acids

Benzoic acid derivatives readily undergo Birch reduction. Most commonly this is combined with alkylation at the *ipso* position (see Section 8.19.3.6.1) although there are examples of the Birch reduction of benzoic acid derivatives without alkylation.

1,4-Dihydrobenzoic acid **51** is a well-described compound which undergoes ready esterification in high yield and without adventitious oxidation to give compound **52** (Scheme 16).[32] This then permits alkylation reactions to be carried out with more sensitive electrophiles, broadening the scope of Birch reduction/alkylation chemistry.

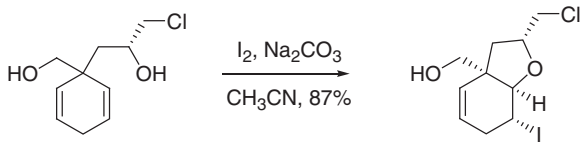


51 **52**

Scheme 16

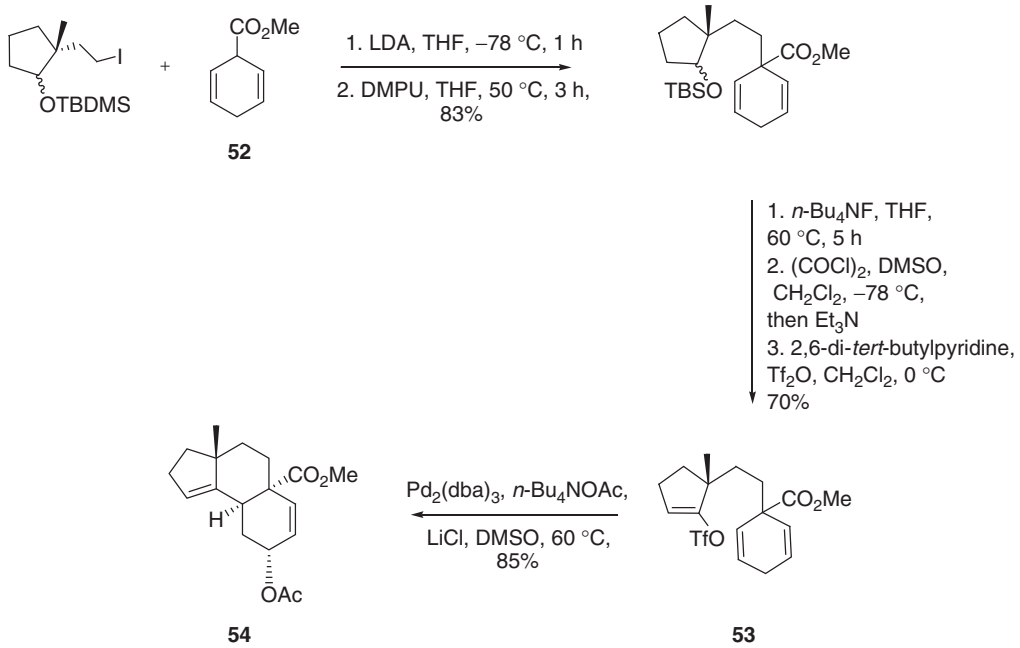
Compound **52** could then be alkylated as shown in Scheme 17, followed by elaboration to the triflate **53** and a highly diastereoselective Heck reaction to give the tricyclic compound **54**.[33]

A number of examples have been reported in which the cyclohexa-1,4-diene formed by Birch reduction then undergoes a desymmetrization reaction. For example, the Elliott group has reported alkylation of compound **52** with epoxides followed by reduction to give diols such as **55**. Iodocyclization of this compound then gave the bicyclic product **56** in high yield and with complete diastereocontrol (equation 9).[34]

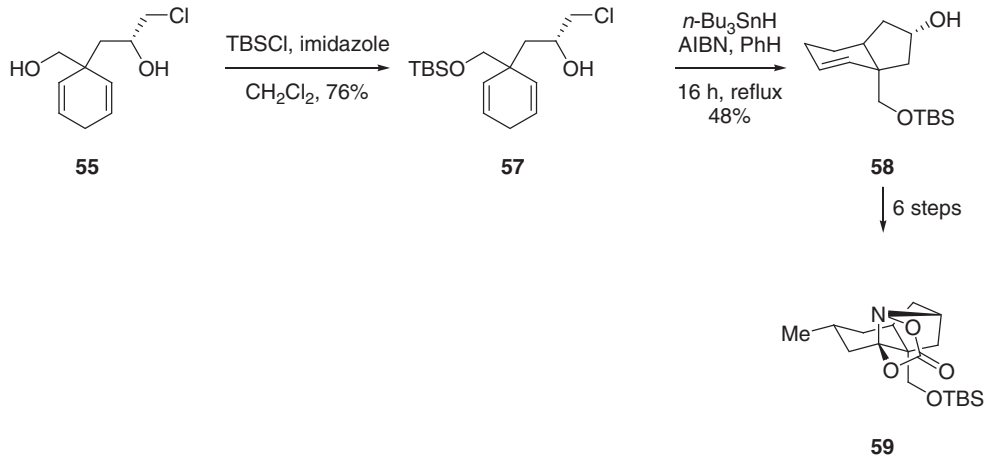


55 **56** (9)

The same diol, **55**, was used as a precursor to a substrate **57** for a free-radical cyclization. This gave compound **58** as the major component of a 2:1 mixture. A further six steps were required to form compound **59** which is closely related to the tetracyclic core of the alkaloid lycoposerramine A (Scheme 18).[35]

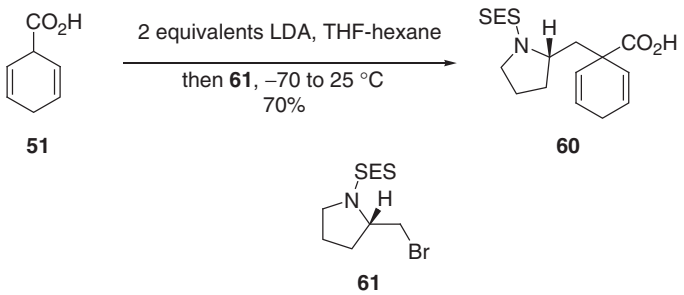


Scheme 17



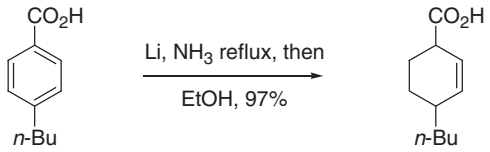
Scheme 18

Although formation of the ester **52** is convenient, it is not actually necessary for alkylation. For example, the dianion derived from compound **51** provided compound **60** directly (equation 10).[36]



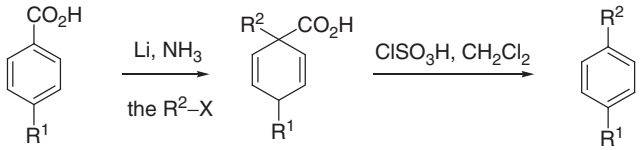
(10)

Although the 1,4-dihydrobenzoic acid derivatives are generally produced in Birch reduction reactions, the absence of a proton donor can lead to the formation initially of the 3,4-dihydrobenzoic acid derivative followed by further reduction to the 1,4,5,6-tetrahydrobenzoic acid **63**, for example, equation 11.[37]



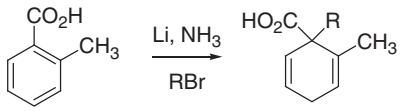
62 **63** (11)

The Birch reduction/alkylation of benzoic acid derivatives is now such a general and reliable reaction, so that for a substituted benzoic acid, a new substituent can be introduced in a single defined position. Decarboxylation under strongly acidic conditions (more correctly, dehydration and decarbonylation) then regenerates the aromatic nucleus in a process that is overall an *ipso* electrophilic substitution (**Scheme 19**).[38] The reaction works well for *ortho*- and *para*-substituted benzoic acids, but not for *meta*-substituted benzoic acids due to competing lactonization. Several examples with naphthoic acids were also reported. Others have reported alternative conditions for the oxidative decarboxylation of the Birch reduction/alkylation products.[39]



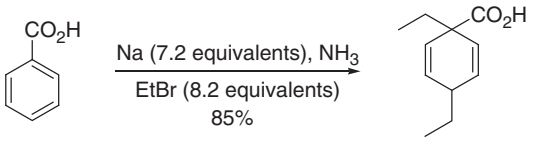
Scheme 19

Rather surprisingly, relatively few simple alkyl-substituted benzoic acids have been subjected to Birch reduction. However, there is no fundamental problem with these reactions (equation 12).[40]



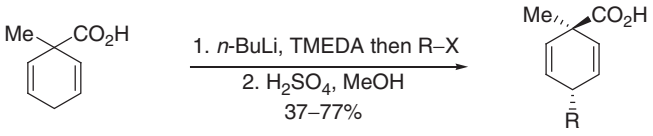
R = Me, 98%
R = Et, 73%
R= *i*-Pr, 98% (12)

When a large excess of the metal and alkylating agent is used, it is possible to obtain double-alkylation products. The reaction works well with primary and secondary alkyl bromides but not with allyl bromide. Good results are obtained with 3-methoxybenzoic acid derivatives, but also with simpler compounds including benzoic acid itself (equation 13).[41]



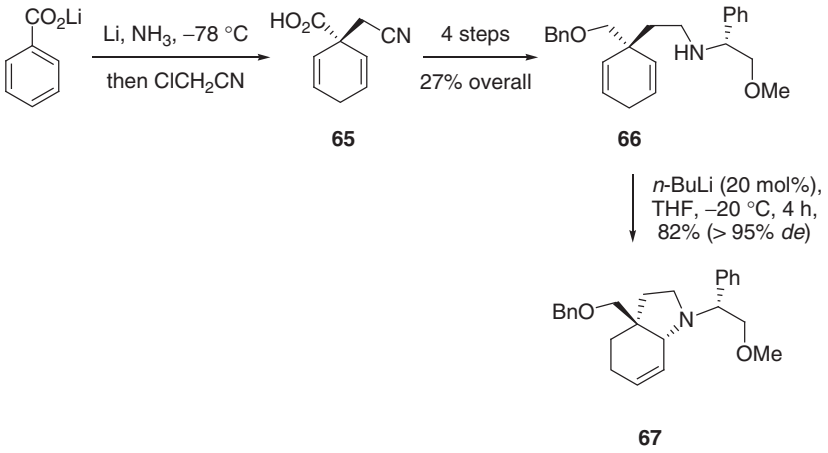
(13)

The stereochemistry of this reaction was not disclosed, but such reactions tend to be unselective.[42] However, it is possible to deprotonate and alkylate stereoselectively at the 4-position of 1-methylcyclohexa-2,5-diene-1-carboxylic acid **64** with *n*-BuLi in conjunction with *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA). Generally, good yields were obtained with primary alkyl halides, although in some cases double-alkylation products were obtained. Unfortunately, only modest yields were obtained using methyl electrophiles (equation 14).[43]



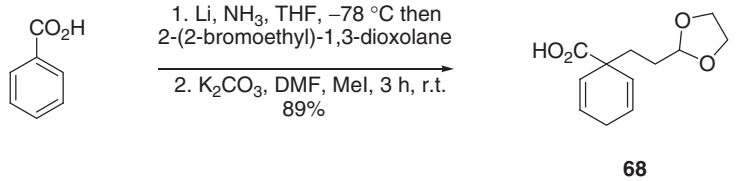
64 (14)

The Birch reduction/alkylation of benzoic acid is very general, and the apparently harsh reaction conditions do not preclude the use of sensitive electrophiles. Landais and coworkers have used chloroacetonitrile in a sequence in which the Birch reduction product **65** is transformed into a chiral amino alcohol derivative **66**, which then undergoes a novel diastereoselective cyclization to give compounds such as **67** (Scheme 20).[44]



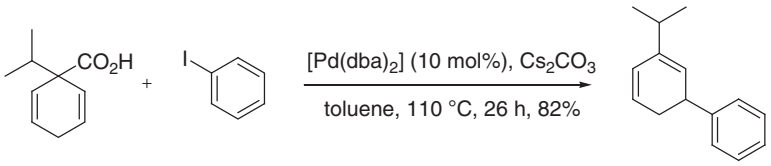
Scheme 20

Even with 2-(2-bromoethyl)-1,3-dioxolane, only 2.5 equivalents of the electrophile are needed, and the product **68** is obtained in extremely high yield after esterification (equation 15).[45]



(15)

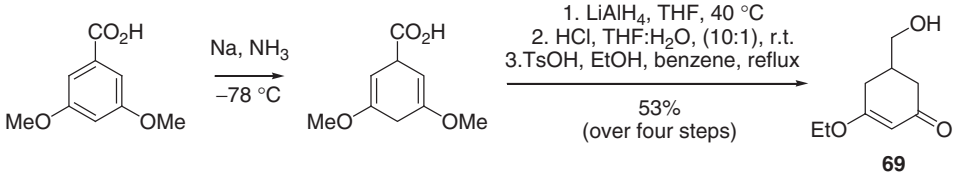
One further novel transformation of Birch reduction/alkylation products derived from benzoic acid is shown in equation 16. The decarboxylation/arylation is entirely stereospecific, with the phenyl being delivered to the same side as the carboxylic acid.[46]



(16)

8.19.3.6.1 Methoxybenzoic acids

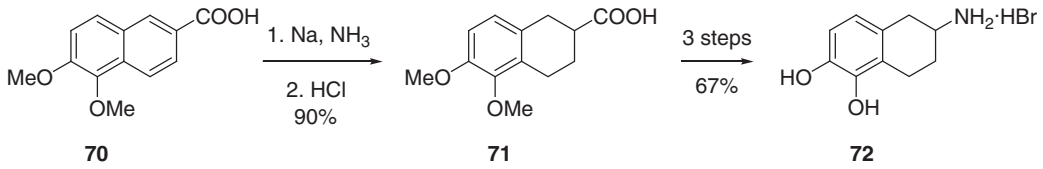
Methoxybenzoic acids are useful substrates in Birch reduction, since they provide access to cyclohexanone derivatives after hydrolysis of the resulting enol ether. During the period of coverage of this review, only a few examples of such Birch reductions have been reported, with the one shown in Scheme 21 being typical. The methoxy groups are located on the double bonds in the product, so that hydrolysis gives a dicarbonyl compound which in this case is elaborated to provide compound **69**.[47]



Scheme 21

8.19.3.6.2 Naphthoic acids and related compounds

2-Amino-1,2,3,4-tetrahydronaphthalenes are of interest as potential agonists for the dopamine receptor. Two representative compounds hydroxylated at the 5,6- and 6,7-positions have been prepared by Birch reduction of the corresponding naphthoic acid followed by Curtius rearrangement, for example the conversion of **70** into **72** via **71** (Scheme 22).[48,49]



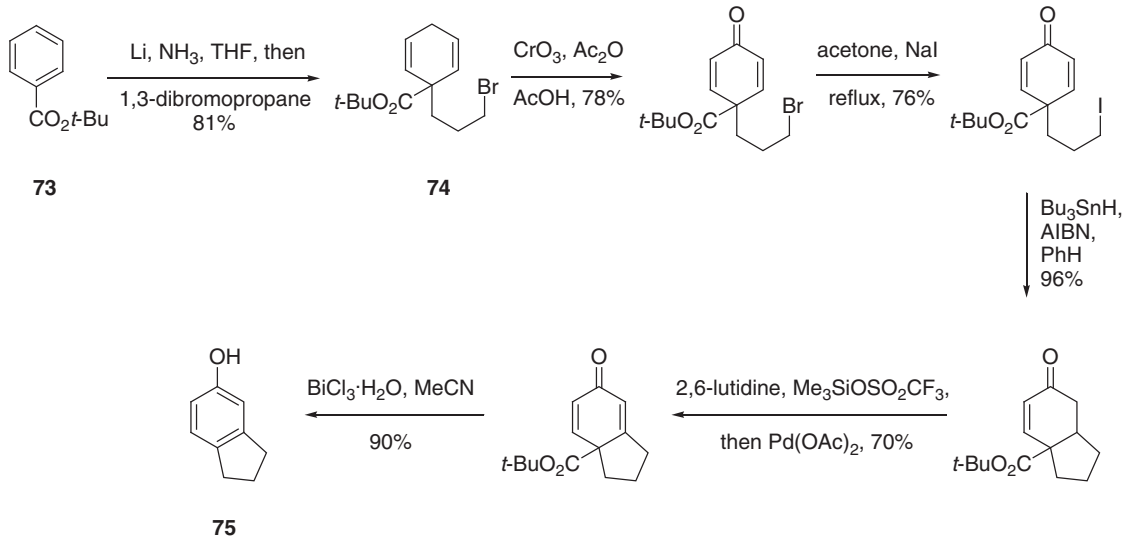
70 **71** **72**

Scheme 22

8.19.3.7 Aromatic Carboxylic Esters

The Birch reduction of carboxylic esters has been carried out far less frequently than those of the corresponding carboxylic acids. However, these reactions do work well, with lithium generally being the metal of choice.

For example, a simple Birch reduction/alkylation of *t*-butyl benzoate **73** with 1,3-dibromopropane proceeded in high yield (Scheme 23), with the product **74** subsequently being oxidized at the doubly allylic position. This then underwent free-radical cyclization, Saegusa oxidation, and decarboxylation with concomitant rearomatization to give compound **75**. A range of 1,3-dihaloalkanes were used, giving a number of fused aromatic products.[50] Birch reduction/alkylation of carboxylic esters with 1,2-dibromoethane also works well.[51]



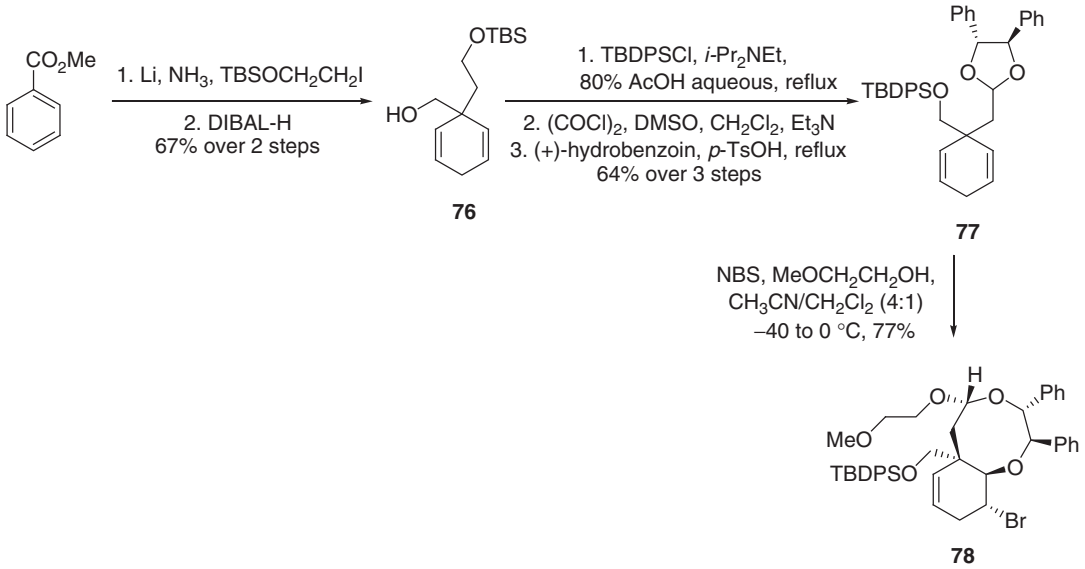
73 **74** **75**

Scheme 23

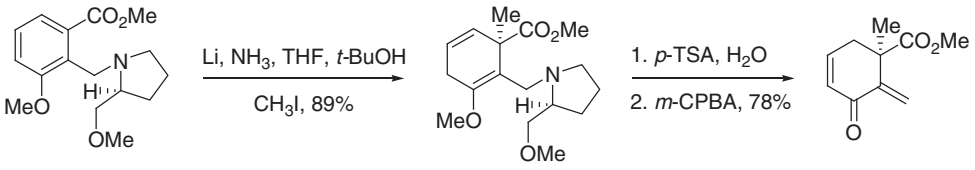
Fujioka, Kita, and coworkers have reported a number of applications of chiral acetals for the desymmetrization of cyclohexa-1,4-dienes. Birch reduction/alkylation of methyl benzoate gave compound **76** as shown in Scheme 24. Three further steps were required to form the acetal **77**, which underwent bromocyclization with opening of the acetal to give compound **78** with good stereoselectivity.[52]

Schultz's group has reported a wide range of applications of the asymmetric Birch reduction/alkylation of aromatic amides, as discussed in Section 8.19.3.8. An alternative approach using the same proline-derived chiral auxiliaries is shown in Scheme 25. After the initial Birch reduction/alkylation to give compound **79**, enol ether hydrolysis and oxidation permits removal of the chiral auxiliary.[53]

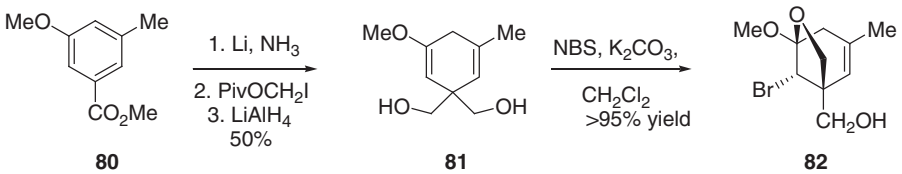
Desymmetrization strategies have already been discussed in the context of benzoic acid Birch reductions. An alternative approach is to ensure that the two double bonds are sufficiently different to permit selective reaction as shown in the Birch reduction of ester **80** followed by reaction with iodomethyl pivalate. After reduction to the diol **81**, bromocyclization gave the ketal **82** (Scheme 26).[54]



Scheme 24

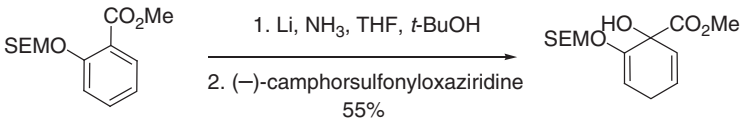


Scheme 25



Scheme 26

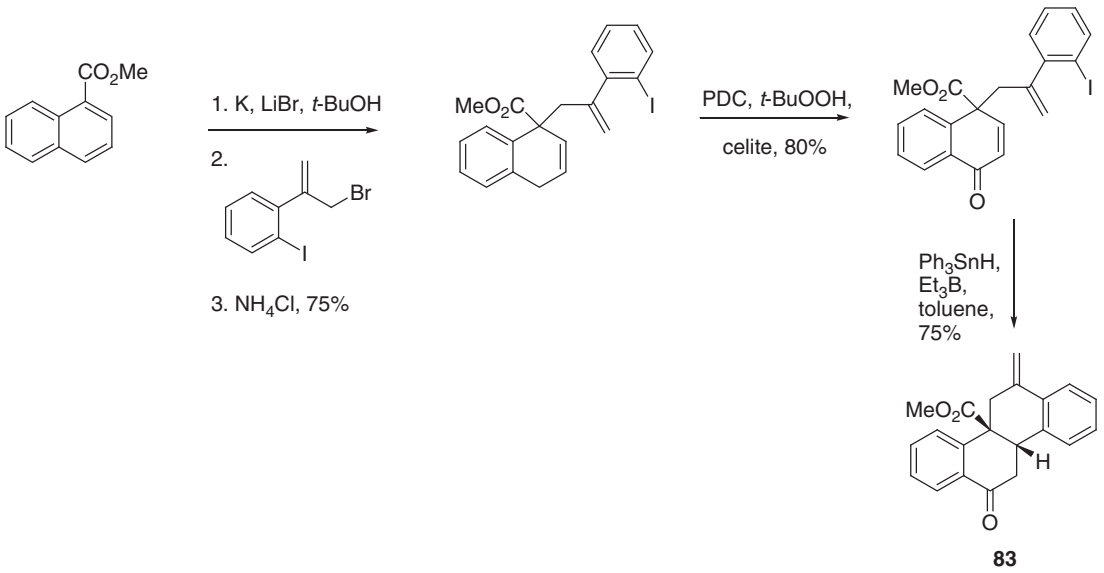
Although alkylation of the most common form of derivatization of the enolate produced in a Birch reduction of a benzoate ester, Snider, building on earlier work by Schultz,[55] has shown that it is possible to directly oxidize such anions. However, despite the use of a chiral oxaziridine reagent, the level of enantioselectivity was described as low (equation 17).[56]



(17)

8.19.3.7.1 Naphthoic acid esters

Birch reductions of naphthalenecarboxylic acid esters also work well, with the example shown in Scheme 27 showing the potential of these reactions in target synthesis. In this case, potassium was used in the Birch reduction, although lithium bromide was added, presumably to aid the alkylation. After the initial Birch reduction, allylic oxidation was followed by free-radical cyclization to give compound **83** containing the hydrochrysene core (Scheme 27).[57]

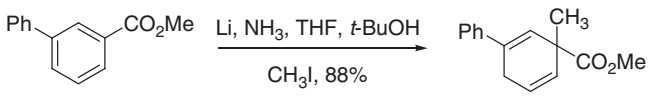


83

Scheme 27

8.19.3.7.2 Biphenylcarboxylic acid esters

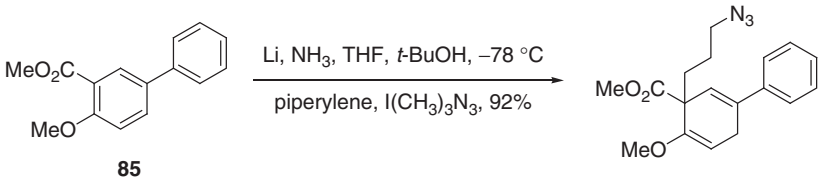
The Birch reduction/alkylation reactions of biphenyls were discussed in Section 8.19.3.3. Alkylation generally takes place *ipso* to the nonreduced aryl ring. However, introduction of a carbonyl group on one of the rings overrides this selectivity. As expected, the ring bearing the carbonyl substituent is reduced, and alkylation takes place *ipso* to the carbonyl. With simple derivatives such as esters of 3-phenylbenzoic acid, the reaction therefore gives the alkylated products **84** (equation 18).[58]



(18)

84

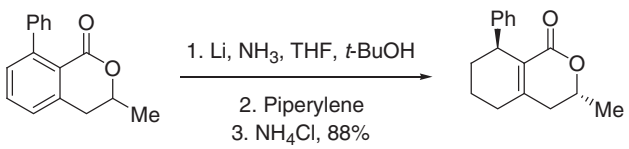
Following on from this work, the same authors prepared the core of the alkaloid vindoline with a key step being the Birch reduction/alkylation of a biphenyl compound **85** as shown in equation 19.[59]



(19)

85

With biphenylcarboxylic ester **86**, reduction to the cyclohexene **87** is observed. In this case, *t*-BuOH is essential for high levels of stereocontrol to be obtained (equation 20), with the product **87** resulting from further reduction of the intial diene. However, the stereoselectivity of the corresponding Birch reduction/alkylation did not depend on the alcohol used.[60,61]



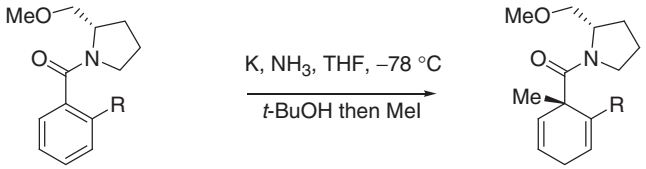
(20)

86 **87**

8.19.3.8 Aromatic Amides

Much of the work in this section relates to the ground-breaking work of Schultz in developing methods for the asymmetric Birch reduction. This work has been reviewed.[62]

In their earlier work, Schultz and Green reported the preparation and Birch reduction/methylation of a broad range of 2-alkylbenzamides **88** derived from prolinol. In all cases, high levels of diastereocontrol were observed in the formation of products **89** (equation 21).[63]

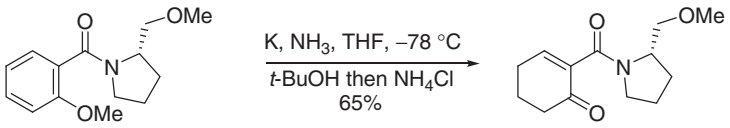


88 **89**

10 examples, 62–88% yield, 90–96% *de*

(21)

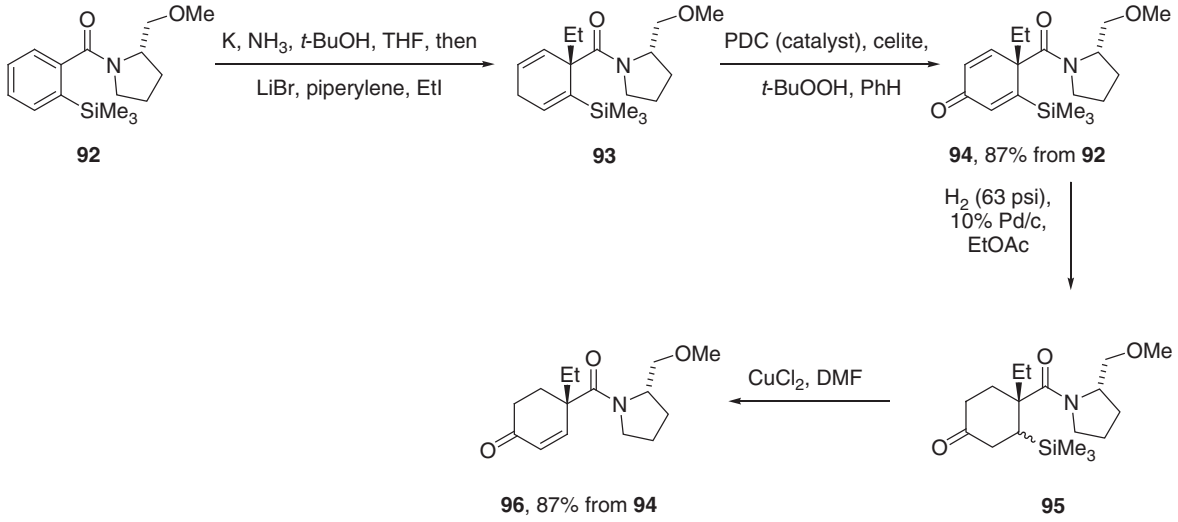
Much work has been carried out on the 2-methoxybenzamides, which provide ready access to various cyclohexenone derivatives. When the Birch reduction is carried out without alkylation, cyclohexenone **91** was produced in good yield (equation 22). This compound was then subject to a range of diastereoselective conjugate addition reactions.[64]



90 **91**

(22)

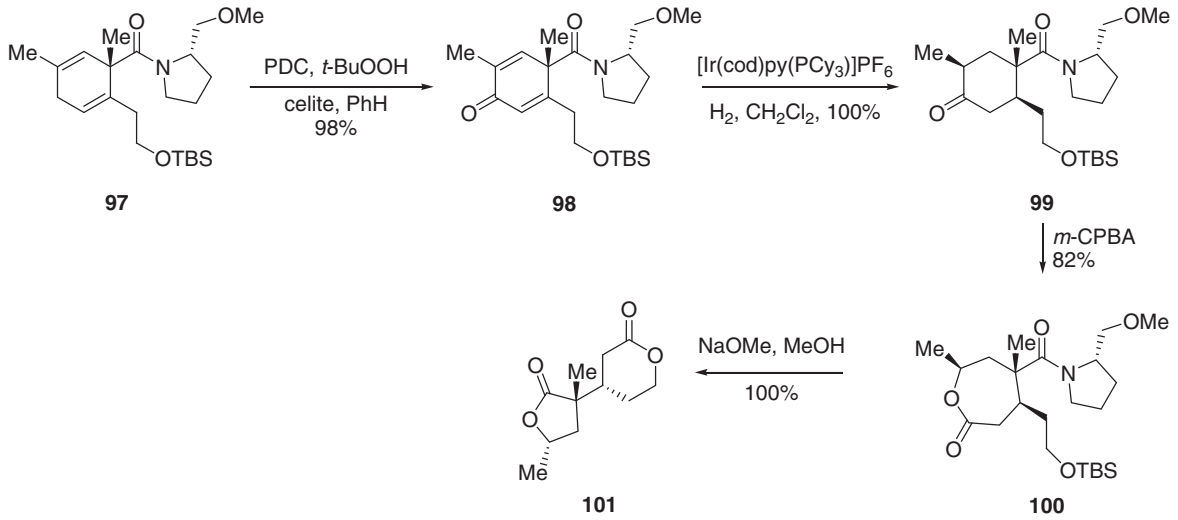
Other cyclohexenones can be accessed by a related approach starting with the 2-silylbenzamide **92**. For example, Birch reduction/alkylation of compound **92** was followed by allylic oxidation and hydrogenation to give compound **94**. Oxidative elimination of the trimethylsilyl group then gave the enone **96** (Scheme 28). In this case, only modest diastereoselectivity was observed with methyl as the alkyl group. All other groups (four examples) gave essentially complete stereocontrol.[65]



92 **93** **94**, 87% from **92** **95** **96**, 87% from **94**

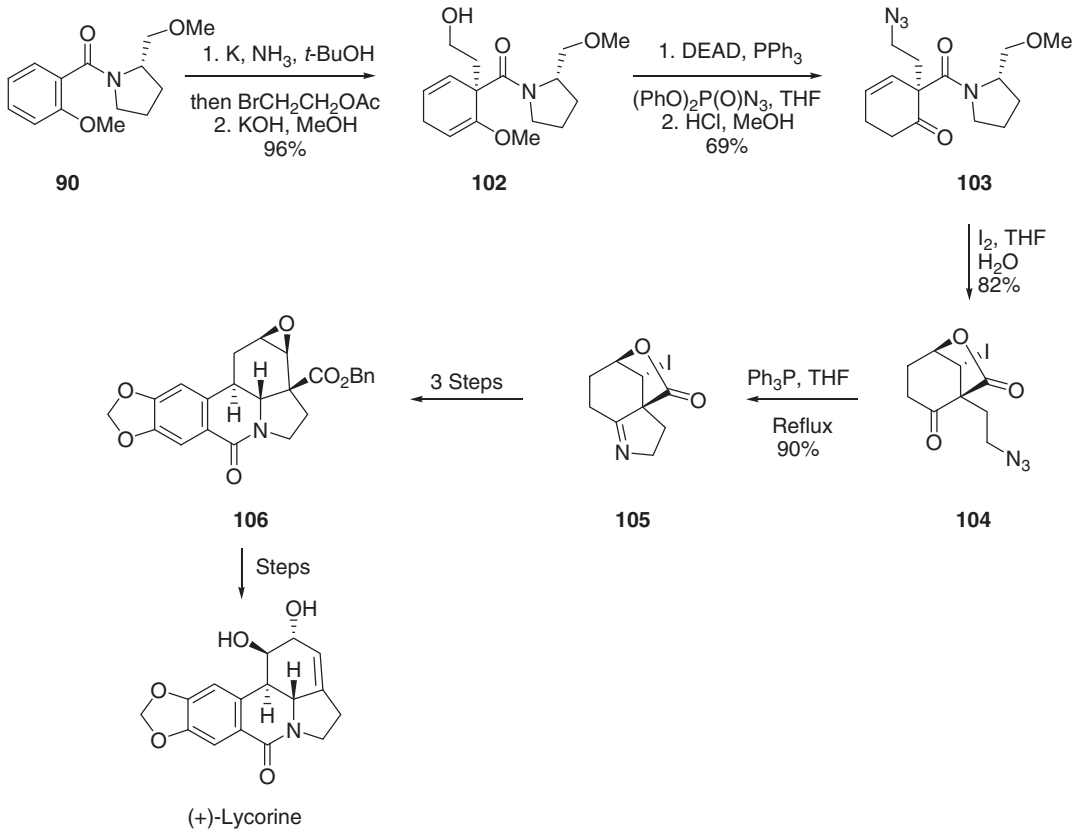
Scheme 28

The cyclohexa-1,4-diene framework is synthetically flexible, so that the products of these transformations can be converted into a wide range of compounds, not necessarily even containing a six-membered carbocyclic ring. For example, a four-step sequence is required to convert the immediate Birch reduction product **97** into the bislactone **101** (Scheme 29).[66] Elaboration of a compound similar to **100** gave a highly functionalized intermediate related to the core of the *Melodinus* alkaloids,[67] as well as total syntheses of the fruit fly pheromone (+)-epianastrephin[68] and the alkaloid (+)-apovincamine.[69] A related approach using a trimethylsilyl-substituted benzamide was used in the total synthesis of (–)-eburnamonine and (–)-aspidospermidine.[70]



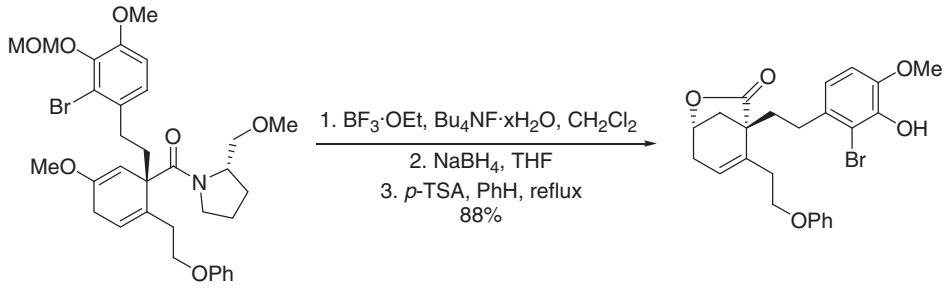
Scheme 29

The key feature of the Schultz asymmetric Birch reduction/alkylation reaction is the highly stereocontrolled incorporation of a quaternary stereogenic center. Nevertheless, the ease of elaboration of the products means that it may still be efficient to use the method for targets lacking such a stereochemical feature. For example, compound **103** was easily prepared from compound **90** in four steps, the first of which is a highly stereoselective Birch reduction/alkylation. A further five steps were required to produce compound **106**, which was subsequently transformed into (+)-lycorine (**Scheme 30**). A photochemical decarboxylation was used late in the sequence to remove the benzyl ester.[71]



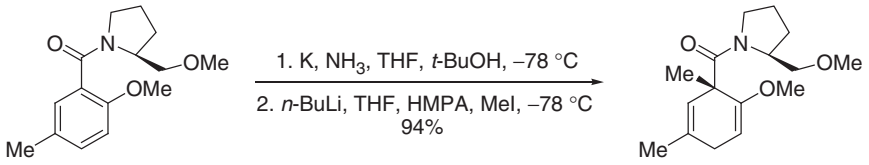
Scheme 30

A similar strategy was used in the total synthesis of (+)-cepharamine. Compound **107** was prepared by stereoselective Birch reduction/alkylation. Hydrolysis of the enol ether and sodium borohydride reduction produced a 1:1 mixture of diastereomeric alcohols. However, on treatment with acid, both diastereoisomers gave the same lactone **108** (equation 23).[72]



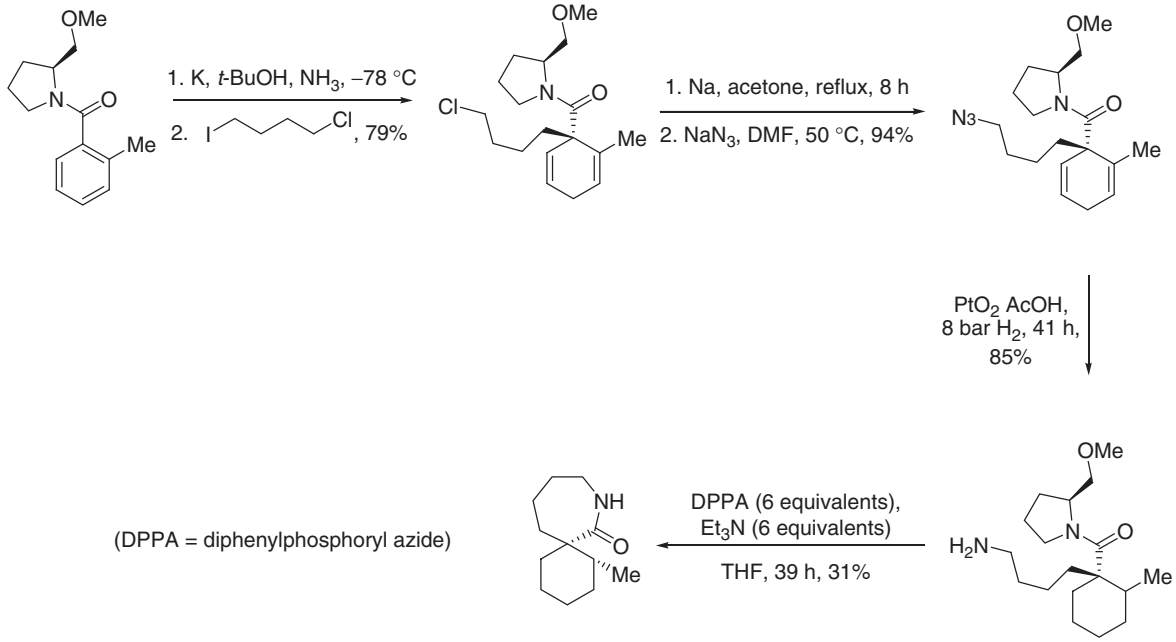
107 **108** (23)

Others have used this chemistry. Rather unusually, Magnus and coworkers chose to separate the Birch reduction and alkylation steps during their work on taxane diterpenes, but obtained compound **110** in extremely high yield in this way (equation 24).[73]



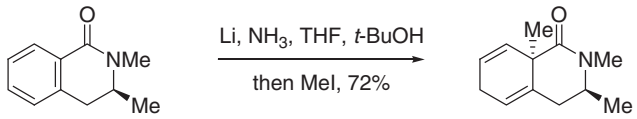
109 **110** (24)

Other functional groups can be introduced during the alkylation step, so that the products can be elaborated into a range of useful compounds, for example, bicyclic lactams (**Scheme 31**).[74] Although in this case the azide group was introduced in a subsequent step, Schultz and coworkers have shown that an electrophile containing an azide is tolerated in the Birch reduction/alkylation step.[75] Other examples of the tolerance of Birch reduction/alkylation to an azide group have already been noted.



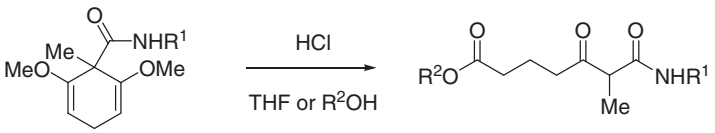
Scheme 31

Other work from the group of Schultz includes the diastereoselective Birch reduction/alkylation of 3,4-dihydroisoquinolin-1-ones **111** (equation 25) derived from (1*R*,2*S*)-ephedrine. In this case, lithium was used, although the authors made no comment on the choice of metal.[76] This chemistry has been applied to the synthesis of a range of ligands for opioid receptors.[77]



111 (25)

The Birch reduction of secondary 2,6-dimethoxybenzamides works well. The corresponding Birch reductions with alkylation fail, and a series of compounds **112** were therefore prepared by amide formation from the methyl ester. These compounds undergo ready hydrolysis to give compounds **113** in good yield (equation 26).[78]

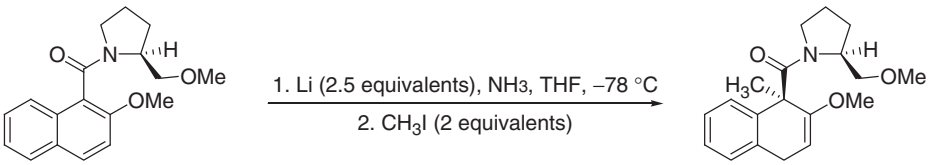


112 **113** (26)

42–98% (9 examples), R^1 = alkyl, phenyl, R^2 = H, Me, Et

8.19.3.8.1 Naphthoic acid amides

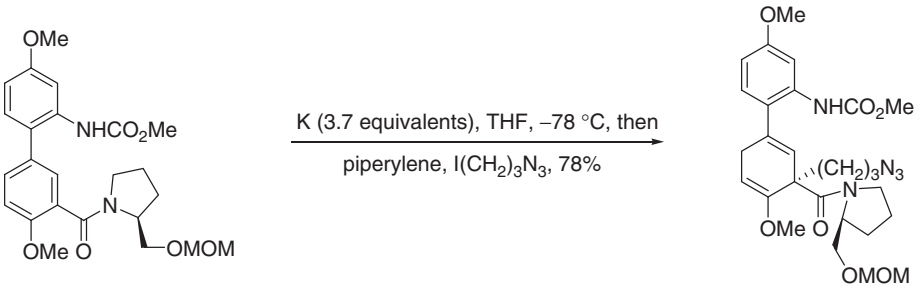
The Schultz diastereroselective Birch reduction/alkylation, which is discussed in Section 8.19.3.8, also give high levels of stereocontrol with naphthalene carboxamides as shown in equation 27. Yields were in excess of 50% for a range of examples, but were not individually reported.[79]



(27)

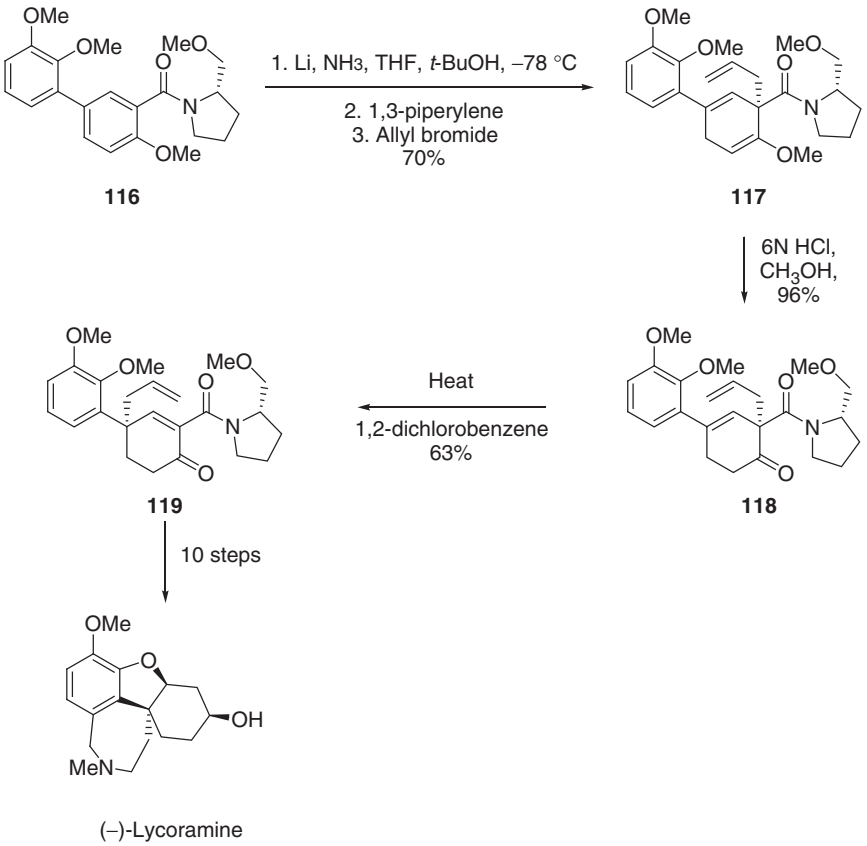
8.19.3.8.2 Biphenylcarboxylic acid amides

Casimiro-Garcia and Schultz have reported the diastereoselective Birch reduction/alkylation of compound **114** to give compound **115** in high yield and with excellent stereocontrol (equation 28). It proved critical to carry out this reaction with no added proton donor – substantially lower yields were obtained when *t*-BuOH was used.[80] The tolerance of both of these reactions to the azide group is noteworthy. Many more examples of the Birch reduction/alkylation of chiral amides are discussed in Section 8.19.3.8.



114 **115** (28)

Malachowski and coworkers have developed[81,82] an elegant combination of the Birch reduction/allylation and Cope rearrangement that allows the transposition of the initially formed quaternary stereogenic center. For example, compound **117** was formed as a single diastereoisomer in good yield. After hydrolysis of the enol ether, Cope rearrangement gave compound **119** (Scheme 32) which was subsequently converted into (–)-lycoramine.[83] The 3,4-dimethoxy analog of compound **119** was converted into (+)-mesembrine.[84]

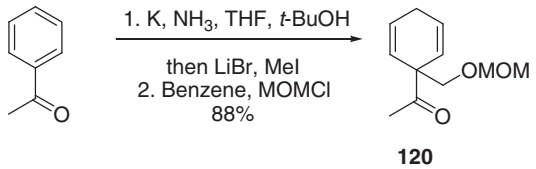


Scheme 32

8.19.3.9 Aromatic Ketones

8.19.3.9.1 Acetophenones

The standard conditions for the Birch reduction/alkylation of aromatic ketones require the use of potassium as metal in order to avoid reduction of the ketone, but successful alkylation requires the lithium enolate, so that lithium bromide is added, generally after removal of the ammonia solvent. In some cases, even this gives a significant amount of the *O*-alkylated product. In these cases, removal of the ammonia can be followed by addition of benzene or toluene before addition of the alkylating agent. For example, with chloromethyl methyl ether, the addition of the nonpolar cosolvent increased the yield of compound **120** from 37% to 88% (equation 29).[85]

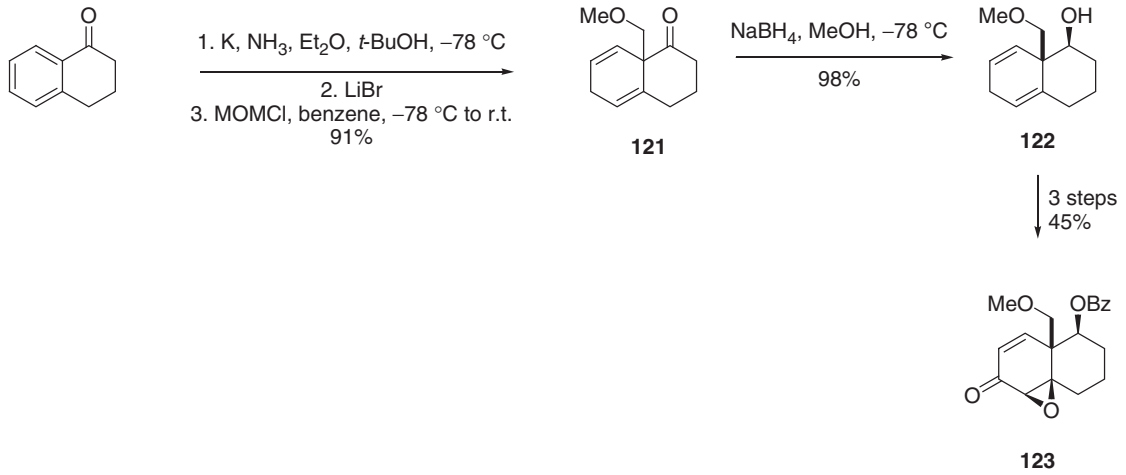


120 (29)

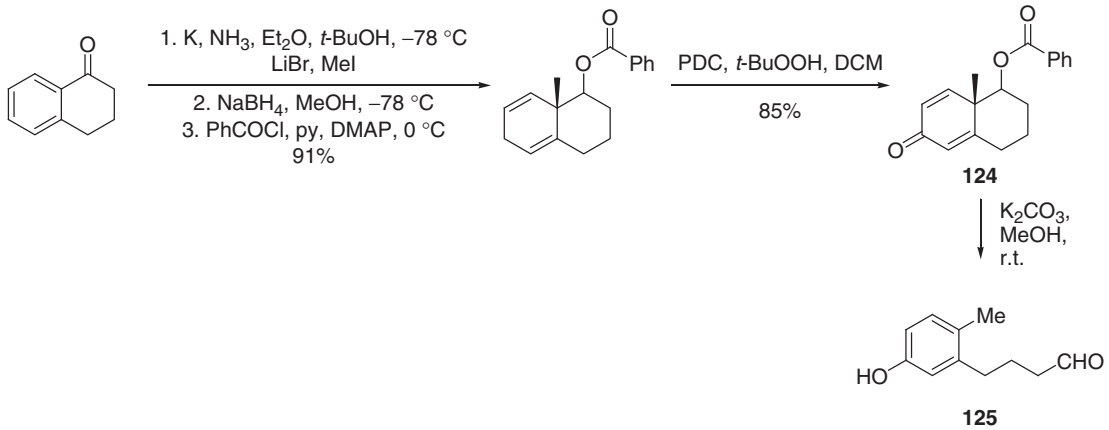
8.19.3.9.2 1-Tetralones and 1-indanones

The above mentioned method was used in the synthesis of compound **123** as a precursor to the cardiotonic steroid ouabain. Birch reduction/alkylation provided compound **121**, which then underwent a diastereoselective reduction to give **122** followed by routine transformations to give the target compound **123** (Scheme 33).[86] Not surprisingly, the Birch reduction/alkylation products are unstable, and are readily oxidized back to the tetralones with loss of the alkyl group.[87]

During the course of the above work, the authors observed an unsurprising fragmentation reaction that results in the Birch reduction product regaining aromaticity. This was subsequently extended to provide access to aromatic compounds with difficult-to-access substitution patterns. One example of this is shown in Scheme 34, in which the Birch reduction of 1-tetralone is followed by elaboration to give the benzoate ester **124**. On hydrolysis of the ester, this gives the butyraldehyde **125**.[88]



Scheme 33



Scheme 34

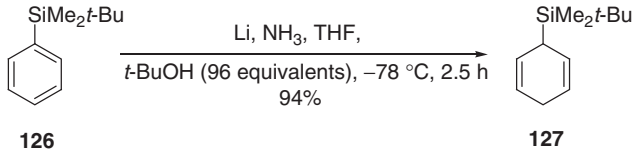
8.19.3.9.3 Acetylnaphthalenes and hydrophenanthrenones

No new examples were found within the period of coverage of the chapter.

8.19.3.10 Aryl- and Benzylsilanes

8.19.3.10.1 Arylsilanes

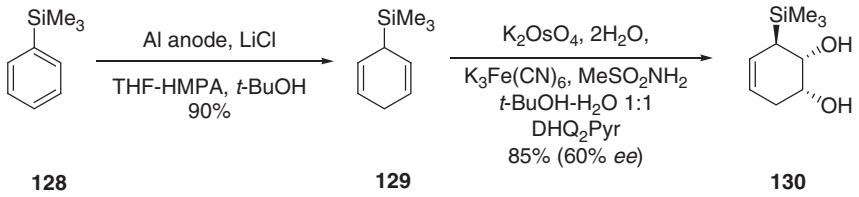
Silyl groups are generally tolerated in Birch reduction reactions. In such cases, the silyl group in the product will be located on a sp^3-hybridized carbon atom in the absence of other directing effects. For example, the Birch reduction of arylsilane **126** gives diene **127** in almost quantitative yield (equation 30).[89]



126 **127** (30)

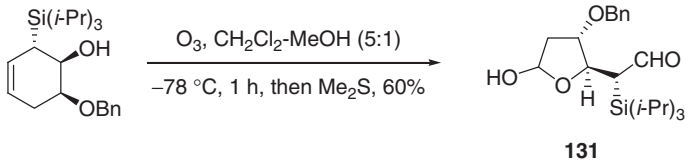
This reaction has been most widely used by the group of Landais, using asymmetric dihydroxylation of alkenes to effect the desymmetrization of cyclohexadienes. In much of their work, an electrochemical Birch reduction was used, as shown in Scheme 35. Dihydroxylation then gave the versatile silyl diol **130**.[90]

These compounds are extremely versatile synthetic intermediates that have been elaborated in a number of ways. The formation of lactol **131** (equation 31)[91] and carbocyclic sugar analog **132** (Scheme 36)[92] are representative of this work.[93]



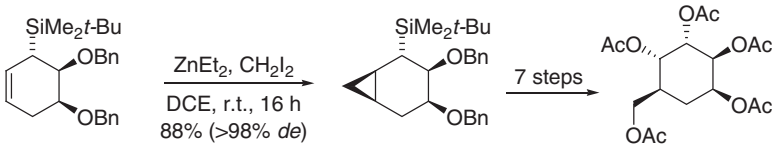
128 **129** **130**

Scheme 35



(31)

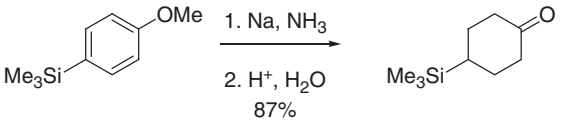
131



132

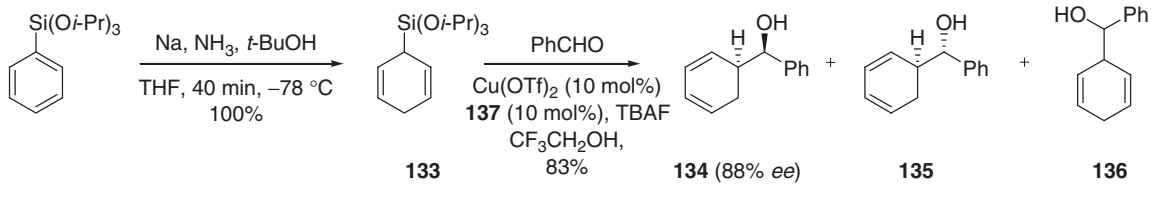
Scheme 36

In the example shown in equation 32, the regiochemical outcome of the Birch reduction is unclear since the product is only obtained after hydrolysis. It is notable in this case that further reduction has clearly taken place, since the product is a ketone rather than an enone.[94]



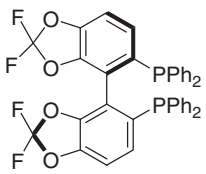
(32)

Aryltrialkoxysilanes are readily reduced under typical Birch conditions without cleavage of the Si–O bond. For example, compound **133** was produced in quantitative yield in this manner. These allylsilanes are versatile intermediates and can be desymmetrized as shown with high levels of diastereoselectivity and enantioselectivity (**Scheme 37**).[95]



133 **134** (88% *ee*) **135** **136**

90:8:2 **134**:**135**:**136**

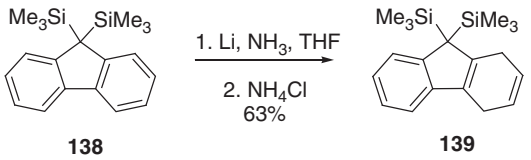


137

Scheme 37

8.19.3.10.2 Benzylsilanes

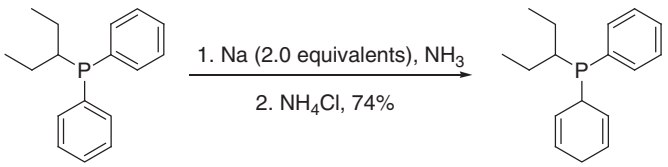
The Birch reduction of fluorene is unselective, with a mixture of regioisomers being formed. In contrast, the Birch reduction of 9,9-bis(trimethylsilyl)fluorene (**138**) is much more selective, with only the 1,4-dihydro derivative **139** being formed (equation 33). It is suggested that this is a result of the bulky silyl groups directing initial protonation to the 4-position, whereas it appears that in the case of fluorene itself, protonation takes place at both the 2- and 4-positions.[96]



138 **139** (33)

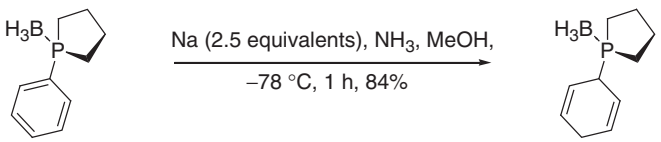
8.19.3.11 Arylphosphines

The Birch reduction of arylphosphines is a reasonably modern development, although it is well established that aryl groups can be cleaved from phosphorus under Birch reduction conditions. The successful partial Birch reduction of diarylalkylphosphines such as **140** has now been reported, using only two equivalents of sodium followed by hydrolysis with solid ammonium chloride (equation 34). The enantiomers of product **141** were subsequently separated.[97]



140 **141** (34)

Phosphine–borane complexes also undergo Birch reduction (equation 35) in high yield, with sodium generally giving superior results (less P–Ph bond cleavage) than lithium.[98]



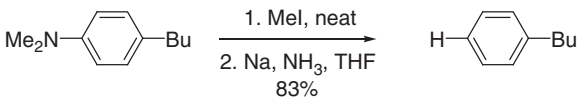
(35)

In both of these cases, the phosphorus in the product is on a sp^3 carbon.

8.19.3.12 Hydrogenolysis During Birch Reductions

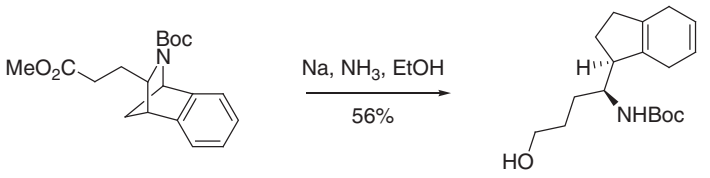
8.19.3.12.1 Hydrogenolysis of nuclear substituents

Benzylic amines are generally resistant to Birch reduction conditions, whereas the Birch reduction of aniline derivatives is most commonly used as a method a C–N bond cleavage to the aryl ring, thus constituting a robust protecting group for amines. Unfortunately, this effectively results in the destruction of the benzene ring. However, the benefits of an amine as an activating group on a benzene ring have prompted MacMillan and coworkers to investigate the reductive removal of amino groups from aromatic rings without concomitant reduction of the aromatic nucleus. This can be readily accomplished by quaternization of the amine before dissolving-metal reduction (equation 36).[99]



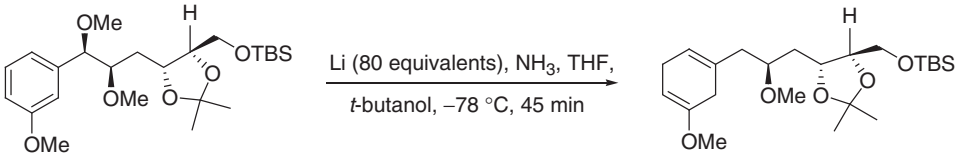
(36)

The benzylic carbamate **142** was readily cleaved during Birch reduction to give product **143**, although it seems likely that strain relief is a factor in this outcome (equation 37).[100]



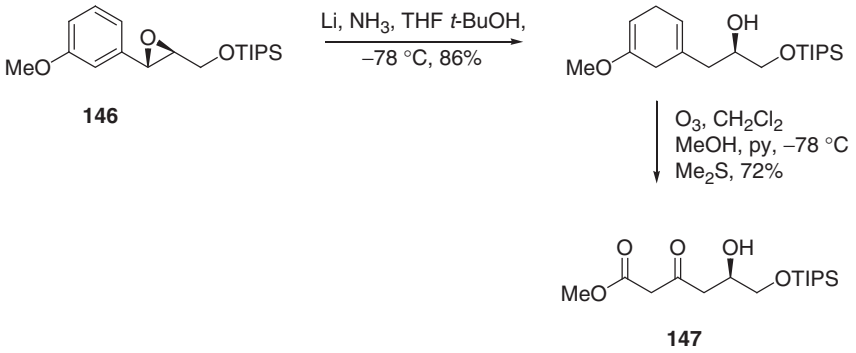
142 **143** (37)

The ease of introduction of chiral 1,2-diols, combined with the facile cleavage of benzylic C–O bonds makes the sacrificial introduction of an extra hydroxyl group an extremely attractive strategy. For example, during the synthesis of a key phorboxazole fragment, compound **144** underwent Birch reduction with selective loss of one methoxy group to give compound **145** (equation 38).[101]



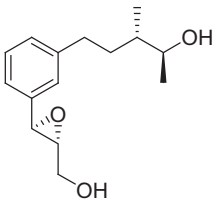
144 **145** (38)

A similar example comes from the group of Evans, reporting the formation of β-ketoester **147** in two steps from epoxide **146**. In this case, the epoxide was cleaved at the benzylic position during the Birch reduction (**Scheme 38**).[102] In a closely related example, compound **148** was reduced first with cleavage at the benzylic epoxide position (K and NH_3) and subsequently at the aromatic ring (Li and NH_3) as a one-pot protocol failed.[103]



146 **147**

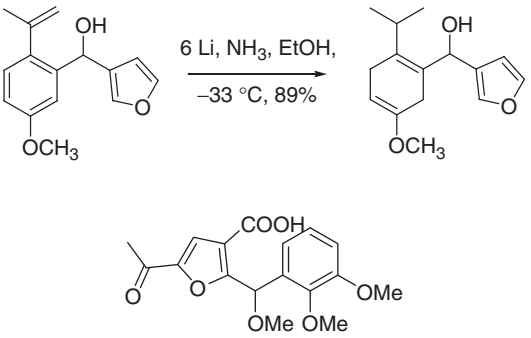
Scheme 38



148

In the case of a doubly benzylic oxygen substituent, C–O bond cleavage is by far the more favorable pathway. The example shown in equation 39 demonstrates the potential for regioselectivity in Birch reduction reactions. In this case, the OH is removed

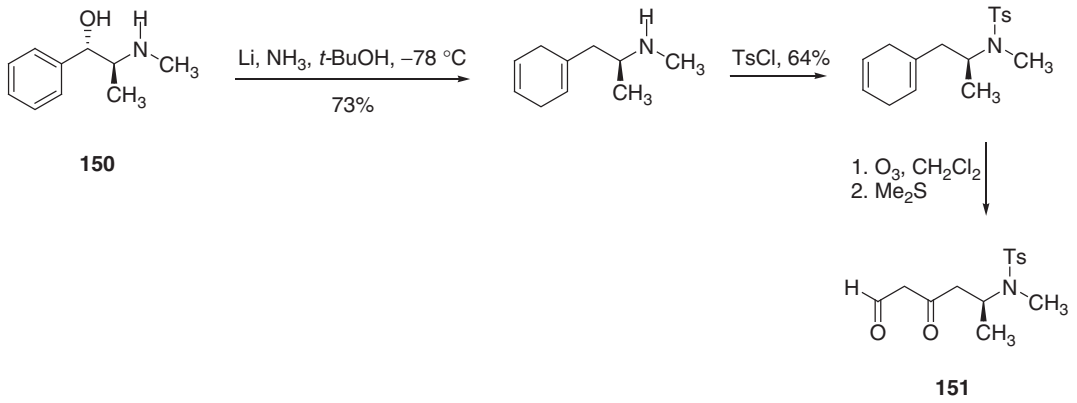
and the benzene ring reduced in the presence of the furan.[104] In a related example, the doubly benzylic C–O bond in compound **149** is cleaved selectively.[105]



(39)

149

Birch reduction conditions are used in the deoxygenation of ephedrine in the illicit manufacture of methamphetamine. In this case, reduction of the aromatic ring is not desirable.[106] However, in target synthesis this can be a useful goal, and Birch reduction of (–)-ephedrine **150** was followed by tosylation and ozonolysis to give keto-aldehyde **151** (Scheme 39). This was then used as a precursor to a range of heterocyclic amines, an approach that has already been discussed in Section 8.19.3.1.[107]

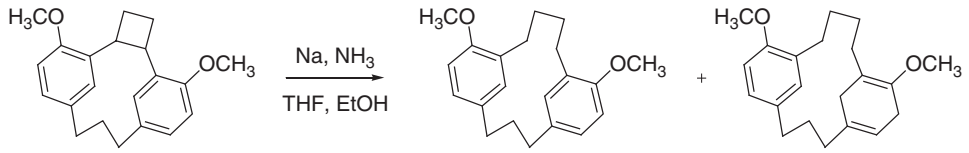


150

151

Scheme 39

Although benzylic hydrogenolysis to cleave C–O bonds is common during Birch reduction reactions, it is also possible to cleave benzylic C–C bonds in some cases. This is particularly common in cyclobutane systems, where the cyclobutane cleavage generally precedes Birch reduction. For example, in the case of compound **152**, the Birch reduction product **154** is the minor product with the major product **153** arising solely from cyclobutane cleavage (equation 40).[108]



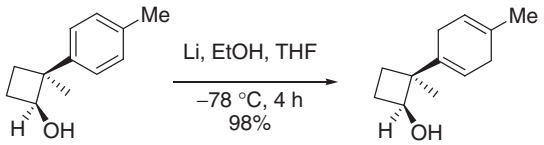
(40)

152

153, 62%

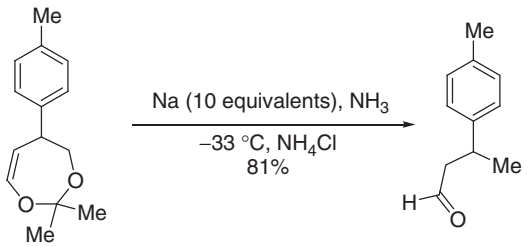
154, 26%

However, in the case of compound **155**, the cyclobutane is retained, presumably due to initial formation of the alkoxide (equation 41).[109]



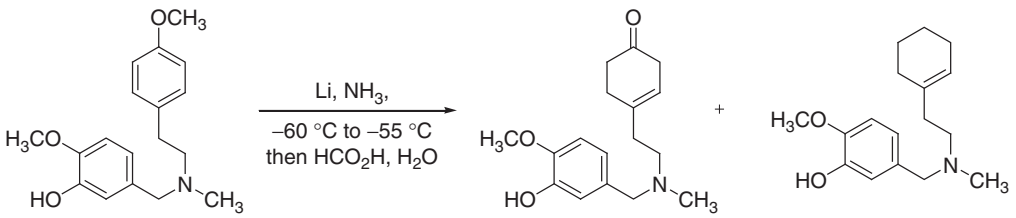
155 (41)

Even more surprisingly, homobenzylic C–O bonds can be cleaved in preference to Birch reduction in some instances. For example, compound **156** is readily reduced to give the aldehyde **157** in high yield (equation 42). Considerable evidence was presented for a mechanism in which removal of the benzylic C–H leads to an E1cb elimination followed by reduction.[110]



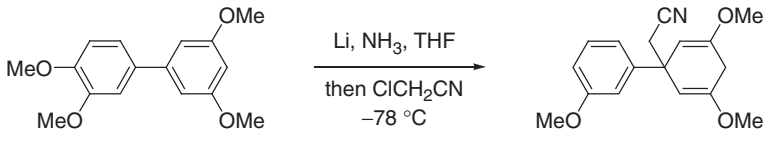
156 **157** (42)

Overreduction has been observed during the Birch reduction of anisole derivatives. For example, after careful hydrolysis the Birch reduction of compound **158** gave compound **160** (11%) in addition to the expected product **159** (equation 43).[111]



158 **159**, 74% **160**, 11% (43)

Such overreduction is relatively uncommon, as shown by the large number of anisole derivatives that have been used in Birch reduction. One exception to this is methoxy groups *para* to an activating substituent as in the case of compound **161** (equation 44). Only the Birch reduction product **162**, with loss of one methoxy group, was obtained, but a similar amount of starting material was recovered in which the methoxy group was retained.[22]

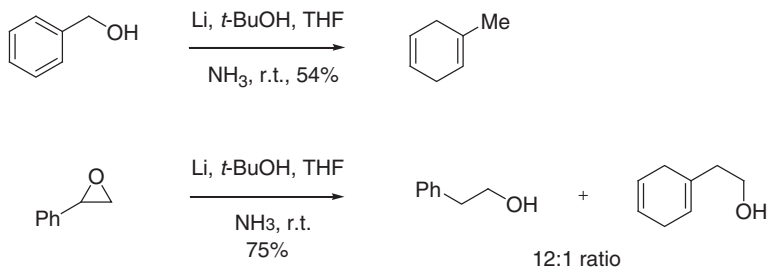


161 **162** (44)

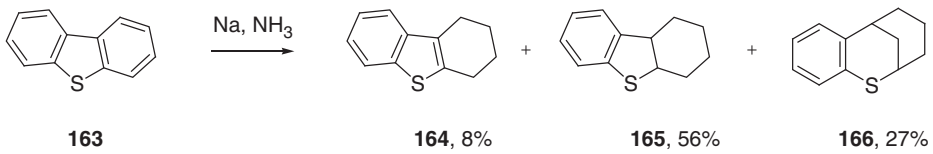
78% of a 1:1 mixture of **161** and **162**

Birch reductions are generally carried out at low temperature so that liquid ammonia is used as a solvent/cosolvent. However, it is possible to use other solvents and simply 'infusing' them under an atmosphere of ammonia. The reductions of benzyl alcohol and styrene oxide (**Scheme 40**) are representative.[112]

The cleavage of C–S bonds has also been described under Birch reduction conditions. The Birch reduction of dibenzothiophene **163** gives three products, **164–166**, all of which are formed by initial Birch reduction followed by C–S bond cleavage and recyclization (equation 45).[113]



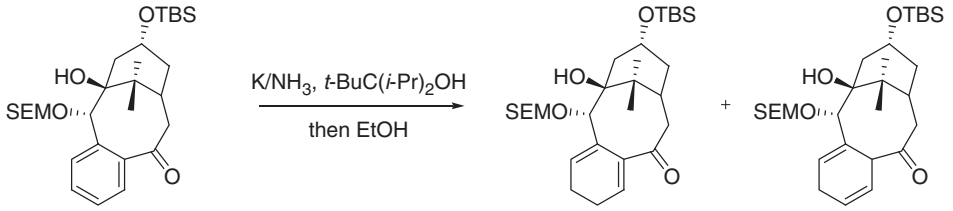
Scheme 40



163 **164**, 8% **165**, 56% **166**, 27% (45)

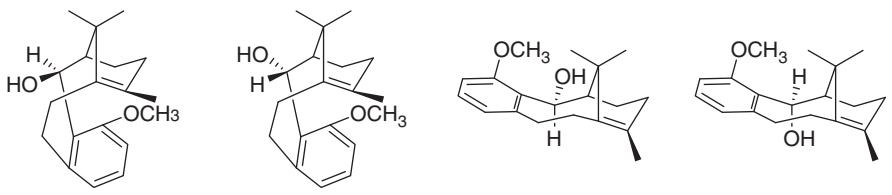
8.19.3.12.2 Protocols for the retention of benzylic substituents

Although benzylic ethers are generally cleaved under Birch-reduction conditions, this can be suppressed by judicious choice of the ether. For example, 2-(trimethylsilyl)ethoxymethyl ether **167** gave a high yield of the isomerized and normal Birch reduction products **168** and **169** (equation 46), whereas protection of the diol as a di-*tert*-butylsilylene derivative gave mainly the products of benzylic C–O bond cleavage.[114]



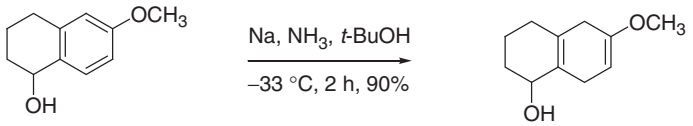
167 **168**, 68% **169**, 13% (46)

For deoxygenation to take place, the C–O bond must overlap with the π-system. Thus, in the case of compounds **170–173**, which include two pairs of separable conformational isomers, only compounds **170** and **173** undergo deoxygenation (>75% yield). Even with an excess of lithium (25 equivalents) this was the preferred process, with the aromatic rings remaining.[115] The other two isomers gave complex mixtures of products.



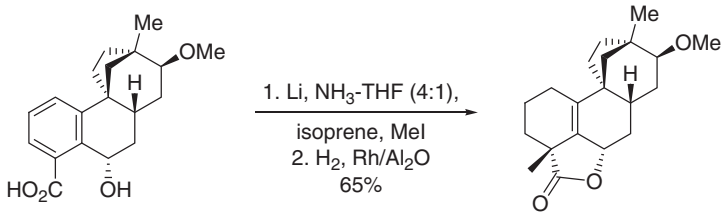
170 **171** **172** **173**

It is not entirely clear why a benzylic oxygen is sometimes retained during a Birch reduction, whereas in other cases reductive removal of the oxygen is preferred. For example, compound **174** is not dissimilar to compounds **170–173** above, and yet here the Birch reduction is the preferred pathway (equation 47).[116]



174 (47)

A particularly extreme example of this is found in Overman's synthesis of scopadulcic acid B, in which compound **175**, containing a benzylic alcohol, undergoes Birch reduction/alkylation with concomitant lactonization to give (after a further reduction) compound **176** (equation 48).[117]



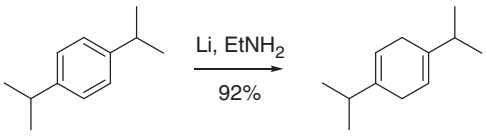
175 176 (48)

8.19.4 Further Methods for the Reduction of Aromatic Rings

It is testament to the broad scope of the Birch reduction that very few other methods are used for the partial reduction of carbocyclic aromatic rings. Very few of the methods described below have been widely applied.

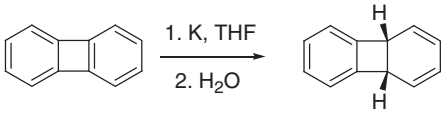
8.19.4.1 Birch-type Reductions in Solvents Other than Ammonia

The use of liquid ammonia as solvent is often perceived to be a disadvantage of the Birch reduction. The Benkeser reduction, using a low molecular weight amine as solvent, with lithium as the reducing agent, has been used, although overreduction is common and this reaction appears to have fallen out of favor. Rather surprisingly, a conventional Birch reduction was reported to lead to significant overreduction of 1,4-diisopropylbenzene **177**, and in this case the Benkeser reduction (equation 49) was reported to give superior results.[118]



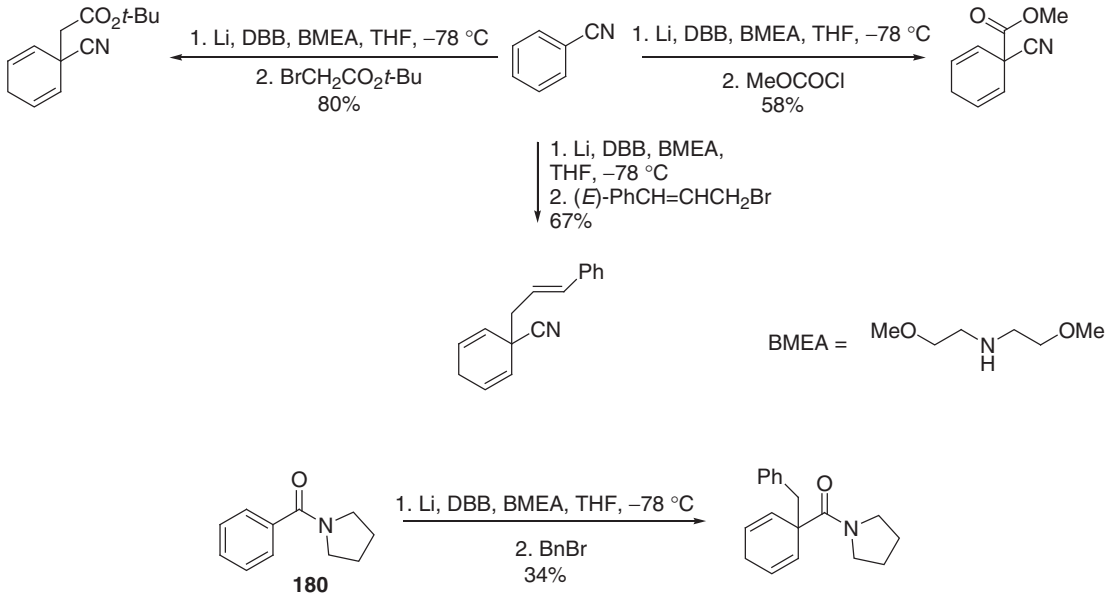
177 (49)

In some cases, ammonia (or an amine) is not needed. However, these reports tend to feature unusual substrates. In the case of biphenylene **178**, the conjugated reduction product **179** can be isolated (equation 50), although it undergoes ready electrocyclic ring-opening if heated. The tolerance of this procedure for the cyclobutane ring is noteworthy bearing in mind the example highlighted above (equation 40).[119]



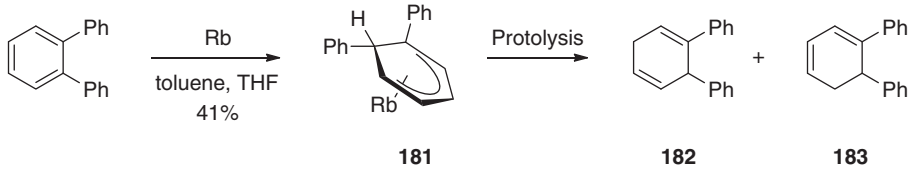
178 179 (50)

A number of alternative protocols have been reported in more recent years. For example, the use of finely powdered lithium and di-*tert*-butylbiphenyl (DBB) in tetrahydrofuran (THF) has been shown to facilitate the reductive alkylation of benzonitrile and benzamide **180** (Scheme 41). The intermediate LiDBB is prepared *in situ* by rapid stirring of a mixture of lithium wire and DBB in a Schlenk tube.[120]



Scheme 41

Not only can rubidium be used for Birch-type reductions but also a cyclopentadienylrubidium intermediate be isolated from the reaction. Addition of 1,2-diphenylbenzene to a suspension of rubidium in toluene/THF gave the rubidium complex **181**, which was characterized crystallographically. Protolysis of this complex gave a mixture of products **182** and **183** (Scheme 42).[121]



181 **182** **183**

Scheme 42

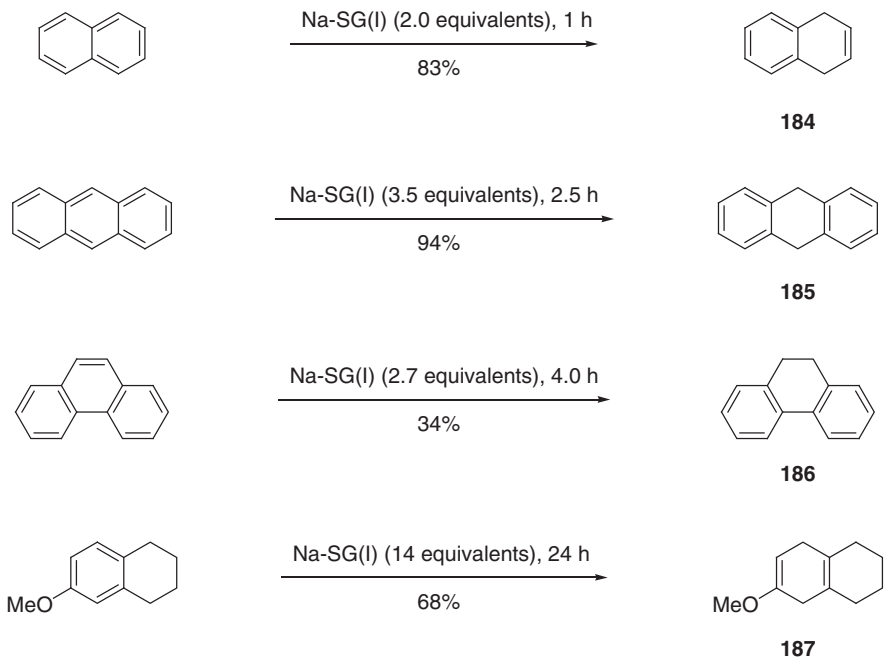
One important development is the absorption of alkali metals onto silica gel. Liquid alkali metals or their alloys have been absorbed onto amorphous silica gel at levels of up to 60 mol% using three distinct preparations. These have been denoted M-silica gel (SG) stages 0, I, and II. A stage 0 preparation, Na_2K-SG(0), can be prepared by shaking a liquid Na_2K alloy with silica gel for a few minutes, and is a loose black powder that is air and moisture sensitive. Heating this to 150 °C forms a stage I powder, which can also be formed directly by heating sodium and silica gel to 165 °C. The stage I powders are much less sensitive to air. Further heating (400 °C) forms a more stable stage II powder which is a slightly less powerful reducing agent than the stage 0 and stage I powders, but still reacts rapidly with water.[122] Na–SG(I) has been applied in the Birch reduction of polycyclic aromatic hydrocarbons, forming the dihydronaphthalene, anthracene, and phenanthrene derivatives **184–186** in moderate to excellent yield (Scheme 43). Tetrahydrofuran is used as solvent, in some cases with the addition of one equivalent of ethylenediamine. Simple aromatic hydrocarbons and ethers are reduced much less effectively, with the exception of compound **187**.[123] The yields are improved slightly by the use of Na_2K–SG(I) although this does not appear to extend the scope of the process.[124]

8.19.4.2 Electrochemical Methods

In many respects the Birch reduction is an ideal candidate for electrochemical development. However, only a very limited number of examples have been reported. One recent example uses ultrasound to assist the reduction process under high mass-transport conditions. Using a platinum disc working electrode and a magnesium foil counter electrode, with KI as electrolyte in liquid ammonia, anisole was reduced to give 2,5-dihydroanisole in 95% yield.[125]

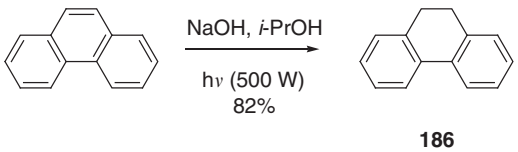
8.19.4.3 Photochemical Methods

Sodium hydroxide is a particularly attractive electron-source for Birch-type reductions. Photolysis of an isopropanol solution of phenanthrene and sodium hydroxide gave the reduction product **186** in high yield (equation 51). Reduction of various



Scheme 43

naphthalenes was also observed, but mixtures of the dihydro- and tetrahydronaphthalenes were obtained. Benzoic acid could be reduced by this method, albeit in modest yield.[126]



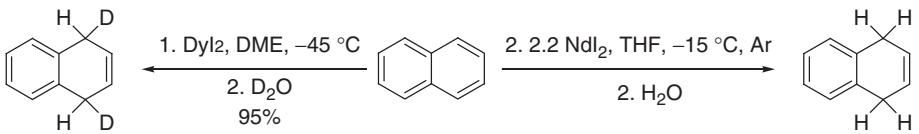
(51)

8.19.4.4 Reductive Silylations

No new examples were found.

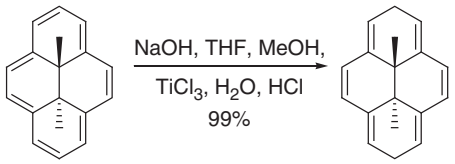
8.19.4.5 Transition or Lanthanide Metal-Mediated Procedures

Neodymium iodide in THF solution is capable of reducing naphthalene to 1,4-dihydronaphthalene, although the yield for this reaction was not reported.[127] Earlier, an analogous reaction was reported using dysprosium iodide in dimethoxyethane (Scheme 44).[128] In this case the intermediate complex $(C_{10}H_8)DyI(DME)_2$ was characterized crystallographically.



Scheme 44

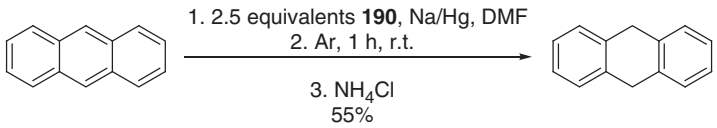
Titanium(III) chloride in acidic solution is not a sufficiently strong reducing agent to effect Birch-type reductions. However, the reducing power increases significantly with increasing pH, and addition of an acidic solution of $TiCl_3$ into a strongly basic solution of *trans*-10ab,10c-dimethyl-10b,10c-dihydropyrene **188** permits the quantitative reduction of this compound to give product **189** (equation 52).[129] Anthracene and substituted anthracenes can also be reduced by this method.[130]

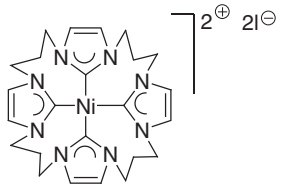


(52)

188 **189**

The reduction of nickel(II) complex **190** with sodium amalgam in DMF gives a species that is formally nickel(0). This compound was able to reduce anthracene as shown in equation 53. A number of other functional groups could be reduced by this system, including sulfonamides and benzylic epoxides.[131]

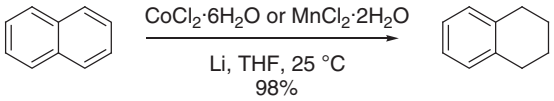




(53)

190

Cobalt nanoparticles, prepared *in situ* from cobalt(II) chloride and lithium sand in THF, have also been used to reduce polycyclic aromatic hydrocarbons. In the reaction of naphthalene, which is representative, the tetrahydronaphthalene **191** is obtained in near-quantitative yield (equation 54). Manganese nanoparticles, prepared in the same way, mediate the same reactions in comparable, and occasionally lower, yield.[132] An earlier report from the same group used nickel(II) chloride in a similar manner.[133]



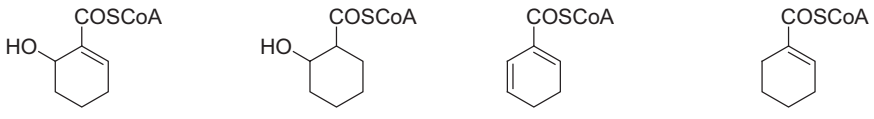
(54)

191

Finally, a study appeared comparing the reducing power of SmI_2 and YbI_2, both in water with triethylamine. Of the two, SmI_2 was considerably better, reducing a range of compounds including phenanthrene, naphthalene, and biphenyl that were not reduced by YbI_2. However, YbI_2 was effective for the reduction of anthracene.[134]

8.19.4.6 Biological Birch Reductions

Anoxic metabolism of many aromatic compounds occurs *via* the reduction of benzoyl coenzyme A by benzoyl CoA reductase. The details of this enzyme have been investigated, and the major reduction products isolated are **192** and **193**, presumably formed by further reaction of compounds **194** and **195** which were isolated in smaller quantities.[135] This reaction appears to proceed by a Birch-like mechanism with simultaneous protonation of the benzoyl CoA and delivery of the first electron.[136]



192 **193** **194** **195**

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8.20 Partial Reduction of Enones, Styrenes, and Related Systems

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Glossary

Baker's yeast *Saccharomyces cerevisiae* is a species of yeast, which is perhaps the most useful yeast.
DFT calculation Density Functional Theory calculation.
Hantzsch ester A 1,4-dihydropyridine dicarboxylate, which is an organic hydride donor.
NHC *N*-heterocyclic carbene, a persistent carbene is a type of diaminocarbenes $(R_2N)_2C$, in which 'R's can be bridged so that the carbon with unfilled orbitals is part of a heterocycle.
Old yellow enzyme An old yellow enzyme is called NADPH dehydrogenase, which uses flavin as a prosthetic group.
Spiro compound A bicyclic organic compound with rings connected through just one atom.

8.20.1 Introduction

Various types of conjugate reductions of α,β-unsaturated carbonyls have been extensively studied for many years because they afford complex and useful carbonyl compounds. In addition, asymmetric carbon–carbon bond formation reactions employing the enolate intermediates have been developed. These partial reductions can be applied to syntheses of complex organic molecules such as natural products and biologically active agents because of high chemoselectivity.

The previous edition of Comprehensive Organic Synthesis described this field in 1991.[1] Therefore, this discussion will focus on reductions reported during the 15-year period leading up to 2013. In addition, 1,2-reductions of α,β-unsaturated carbonyl compounds are presented here even though they do not involve reduction of C=C and C≡C bonds because of their close relationship with 1,2-reductions of α,β-unsaturated carbonyl compounds.

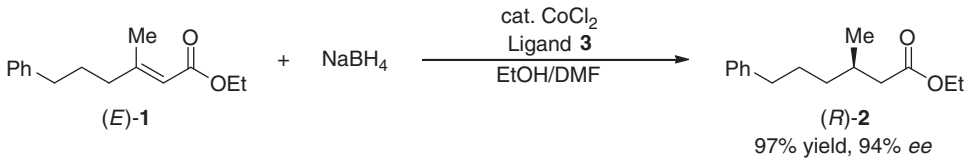
8.20.2 Transition Metal-Catalyzed Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds Using Metal Hydrides

Transition metal-catalyzed hydrometallation of α,β-unsaturated carbonyl compounds has some advantages in terms of high chemoselectivity, compatibility with various functional groups, and mild conditions. Diverse transition metals including Co, Ni, Cu, Mo, Pd, Rh, and Pt work as effective catalysts, and hydroboranes and hydrosilanes are mainly used as metal hydrides.

8.20.2.1 Cobalt-Catalyzed Conjugate Reduction

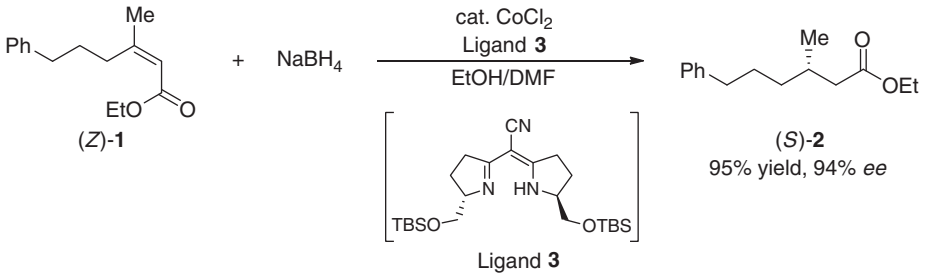
The combination of a cobalt catalyst and semicorrins, chiral C_2-symmetric chelate ligands, promotes asymmetric conjugate reduction of α,β-unsaturated carbonyl compounds using metal hydrides. In 1989, Pfaltz and coworkers reported the first example, in which the reduction of α,β-unsaturated ester (*E*)-**1** using sodium borohydride afforded the desired ester (*R*)-**2** in 97% yield with

excellent enantioselectivity (equation 1). In contrast, the (*Z*)-isomer was subjected to the reaction conditions to give the ester (*S*)-**2** in 95% yield with excellent enantioselectivity (equation 2).[2,3] The α,β-unsaturated carboxamides (*E*)- and (*Z*)-**4** also gave the corresponding amides (*R*)- and (*S*)-**5**, respectively, in high yields with high enantioselectivities (equations 3 and 4).[4] Tertiary amides like α,β-unsaturated *N*,*N*-dimethylamides were not applicable. The chiral aza(bisoxazoline) **8** is a highly efficient ligand in cobalt-catalyzed conjugate reduction of α,β-unsaturated esters and amides (equation 5).[5]



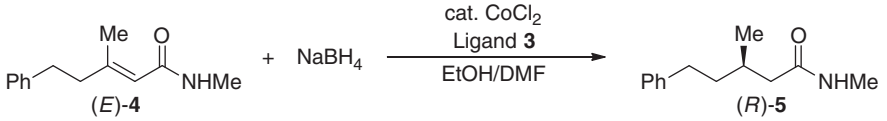
(*E*)-**1** (*R*)-**2**
97% yield, 94% *ee*

(1)



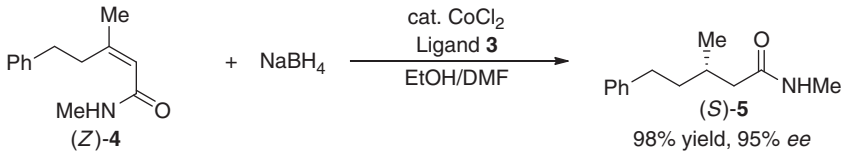
(*Z*)-**1** (*S*)-**2**
95% yield, 94% *ee*
Ligand **3**

(2)



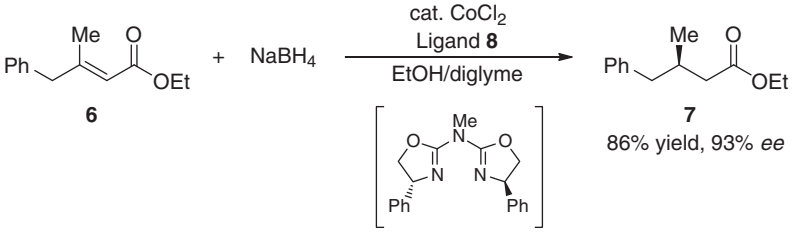
(*E*)-**4** (*R*)-**5**
95% yield, 97% *ee*

(3)



(*Z*)-**4** (*S*)-**5**
98% yield, 95% *ee*

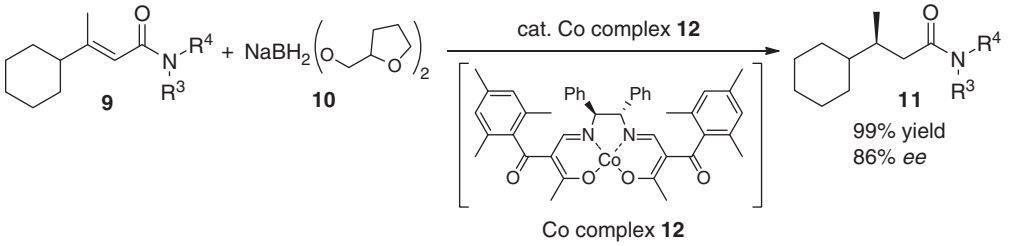
(4)



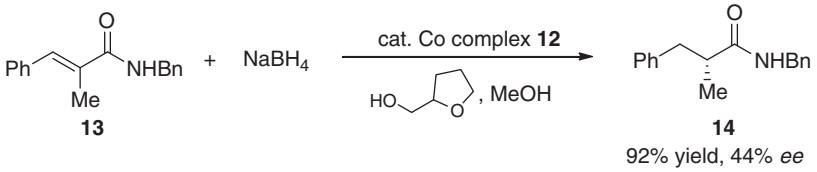
6 **7**
86% yield, 93% *ee*
Ligand **8**

(5)

The optically active aldiminato cobalt complex **12** catalyzed the asymmetric conjugate reduction of β,β-disubstituted α,β-unsaturated carboxamides **9** to the corresponding amides **11** in high yields with high enantioselectivities (equation 6). Pre-modified borohydride **10** prepared from $NaBH_4$ with tetrahydrofurfuryl alcohol worked as an efficient hydride donor.[6] The chiral cobalt complex **12** promoted the conjugate reduction of α-substituted α,β-unsaturated carboxamide **13** which was followed by enantioselective protonation to afford optically active α-substituted carboxamide **14** in high yield with moderate enantioselectivity (equation 7).[7]

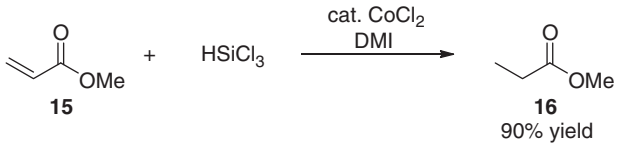


(6)

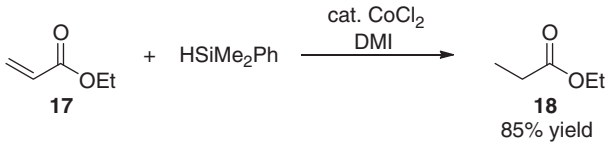


(7)

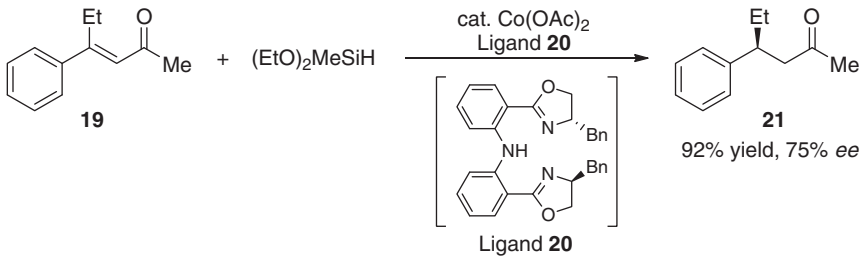
The cobalt-catalyzed conjugate reduction of α,β-unsaturated esters using trichlorosilane or dimethylphenylsilane was reported to give saturated esters **16** and **18** in high yields (equations 8 and 9).[8] The combination of $Co(OAc)_2$ catalyst, tridentate *N,N,N*-type ligand **20**, and $(EtO)_2MeSiH$ was effective in the conjugate reduction of α,β-unsaturated ketone **19** to afford the ketone **21** in 92% yield with moderate enantioselectivity (equation 10).[9]



(8)

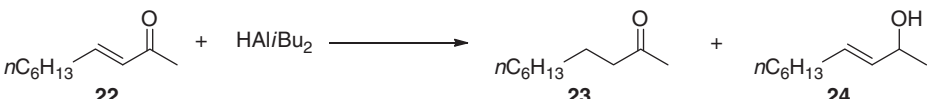


(9)



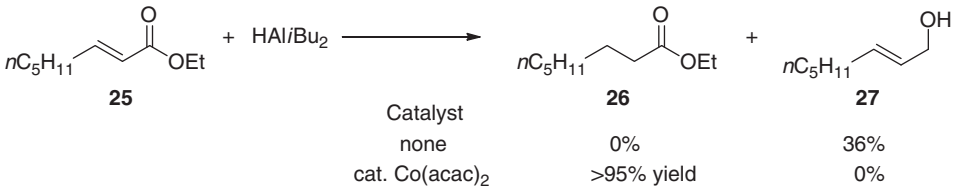
(10)

Diisobutylaluminum hydride is also a useful hydride source. In the absence of a cobalt catalyst, α,β-unsaturated ketone **22** and ester **25** were reduced in 1,2-reducing fashion to afford the corresponding allylic alcohols **24** and **27**. The combination of $Co(acac)_2$ catalyst and $HAliBu_2$ is essential for conjugate reduction, giving ketone **23** and ester **26** exclusively (equations 11 and 12).[10]



Catalyst	**23**	**24**
none	0%	90%
cat. $Co(acac)_2$	96%	0%

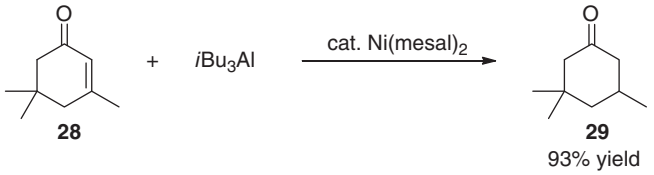
(11)



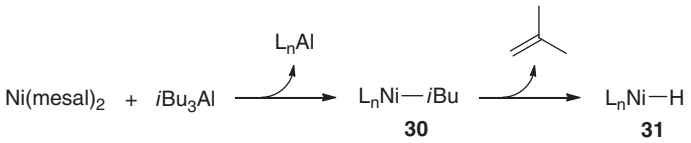
(12)

8.20.2.2 Nickel-Catalyzed Conjugate Reduction

In 1982, Caporusso and coworkers reported cobalt-catalyzed conjugate reduction using trialkylalane as a hydride source. In the presence of a catalytic amount of bis(*N*-methylsalicylaldimine)nickel, $Ni(mesal)_2$, the treatment of α,β-unsaturated ketone **28** with triisobutylaluminum gave saturated ketone **29** in 93% yield (equation 13). In this reducing system, β-hydride elimination from isobutylnickel produced by transmetalation between $Ni(mesal)_2$ and iBu_3Al affords nickel hydride which promotes conjugate reduction of the enone **28** (Scheme 1).[11]

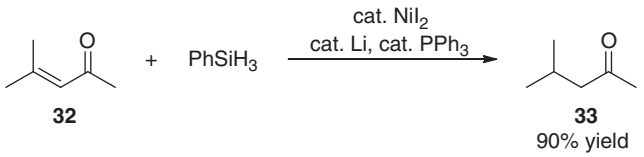


(13)



Scheme 1 Reproduced from Caporusso, A. M.; Giacomelli, G.; Lardicci, L. *J. Org. Chem.* **1982**, *47*, 4640–4644.

A Ni(0) catalyst, generated with the assistance of ultrasound, promoted the conjugate reduction of α,β-unsaturated ketone **32** with $PhSiH_3$ to give the corresponding saturated ketone **33** (equation 14). Diverse unsaturated ketones and nitriles were also susceptible to this 1,4-reducing system.[12]

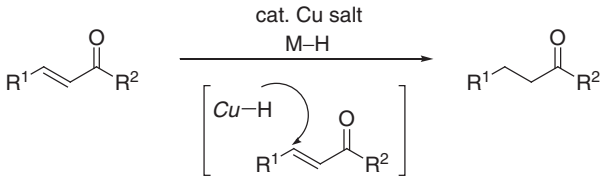


(14)

8.20.2.3 Copper-Catalyzed Conjugate Reduction

8.20.2.3.1 Conventional conjugate reduction

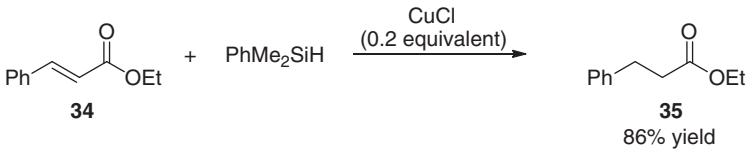
Copper hydride reagents are effective for the stereoselective and chemoselective conjugate reduction of α,β-unsaturated carbonyl compounds. In the early stages, a stoichiometric amount of copper hydrides were used.[1] For the past 20 years, the combination systems of a catalytic amount of a copper salt and a stoichiometric amount of a metal hydride (M-H) have been developed (equation 15).[13,14]



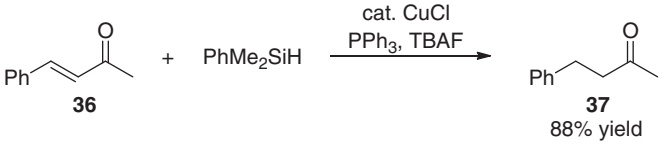
(15)

In 1997, Hosomi and coworkers reported that the combination of CuCl and hydrosilane for the conjugate reduction of α,β-unsaturated esters. The unsaturated ester **34** was treated with stoichiometric amount of CuCl and $PhMe_2SiH$ to give the corresponding saturated ester **35** in 96% yield. It is notable that a catalytic amount of CuCl was effective to afford 85% yield

(equation 16).[15] Hiyama also reported the reduction of enone **36** with $PhMe_2SiH$ in the presence of a catalytic amount of CuCl/PPh_3/tetrabutylammonium fluoride (TBAF) (equation 17).[16]

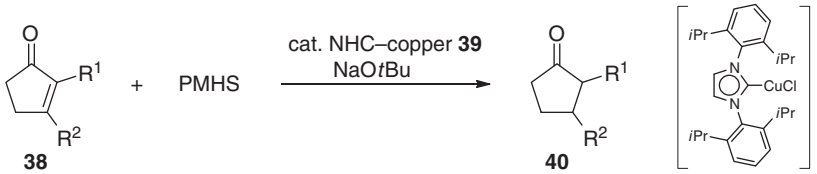


(16)



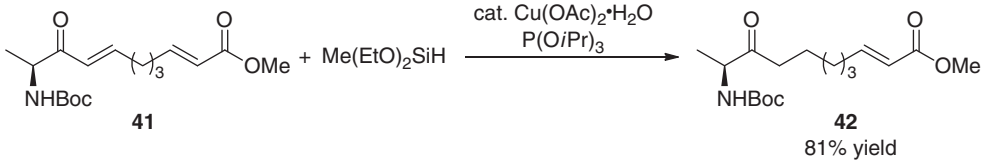
(17)

Buchwald and coworkers reported an N-heterocyclic carbene (NHC)–copper(I) complex **39**-catalyzed reaction using polymethylhydrosiloxane (PMHS), in which tri- and tetrasubstituted α,β-unsaturated esters and cyclic enones **38** were effectively reduced (equation 18).[17]



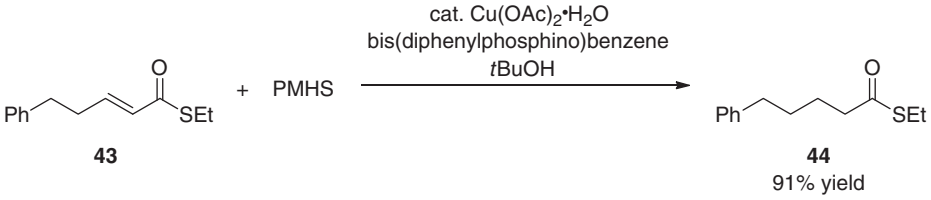
(18)

Conjugate reduction of the chiral α,β-unsaturated amino ketone **41** has been developed by the use of the combination of $Cu(OAc)_2 \cdot H_2O$ and triisopropyl phosphite, in which chiral-saturated α-amino ketone **42** was obtained without epimerization of the amino group (equation 19).[18]



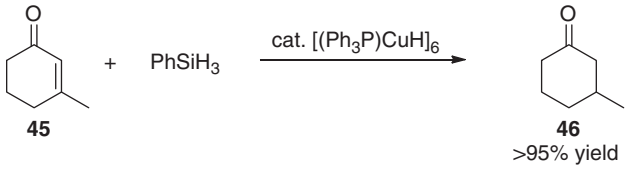
(19)

The α,β-unsaturated thioester **43** was reduced by PMHS in a conjugate fashion with a bis(diphenylphosphino)benzene ligated copper catalyst (equation 20).[19]

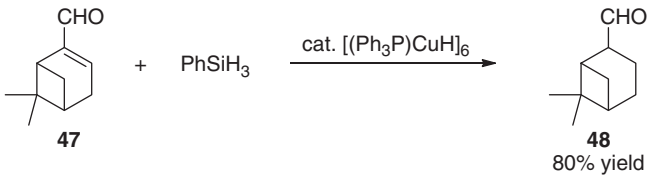


(20)

Stryker's reagent $[(Ph_3P)CuH]_6$ is an effective catalyst in 1,4-reductions of enones and enals. The enone **45** and the enal **47** reacted with $PhSiH_3$ in the presence of a catalytic amount of $[(Ph_3P)CuH]_6$ to give the saturated ketone **46** and aldehyde **48** in high yields (equations 21 and 22).[20]



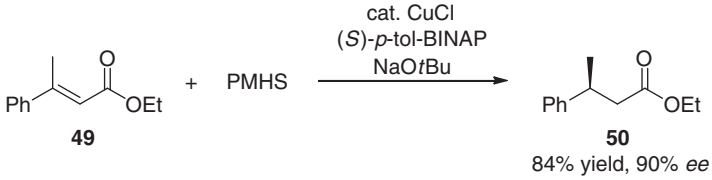
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(22)

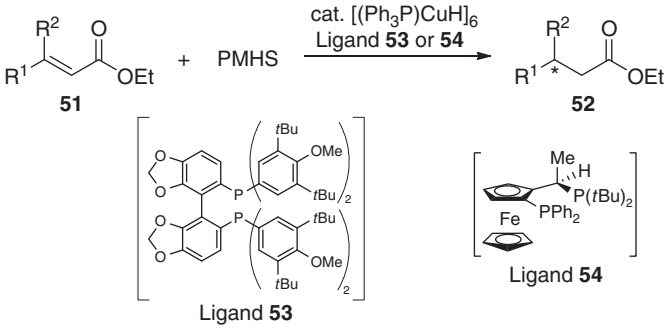
8.20.2.3.2 Asymmetric conjugate reduction of α,β-unsaturated esters

In 1999, Buchwald and coworkers reported the first example of asymmetric conjugate reduction of α,β-unsaturated esters using copper hydride species. The combination of CuCl, (*S*)-*p*-tol-BINAP, and NaO*t*Bu catalyzed the reduction of unsaturated ester **49** with PMHS to give the corresponding saturated ester **50** in 84% yield with high enantioselectivity (equation 23). In this reaction system, a chiral phosphine-ligated copper hydride is supposed to be an active catalyst. Various types of α,β-unsaturated esters were applicable to afford high yields and high enantioselectivities.[21]



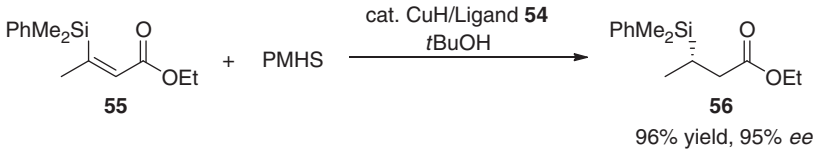
(23)

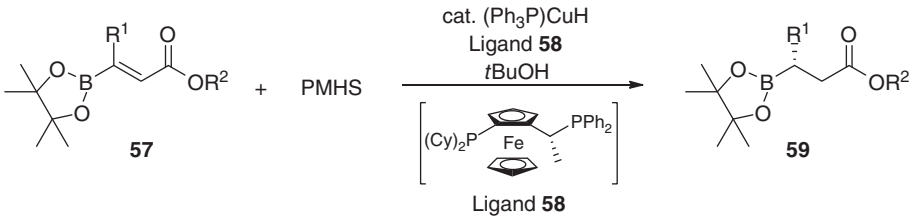
Lipshutz and coworkers reported that ligands in the SEGPHOS and JOSIPHOS families of nonracemic bis-phosphines **53** and **54** were effective in CuH-catalyzed asymmetric 1,4-reduction of α,β-unsaturated esters **51** (equation 24).[22–25] Chiral ferrocene-based phosphine–phosphoramidite ligands were also found to be efficient.[26] Water was applicable as a solvent by the addition of DL-α-tocopherol methoxypolyethylene glycol succinate-750-M as a surfactant, which dramatically increased the yield and enantioselectivity.[27]



(24)

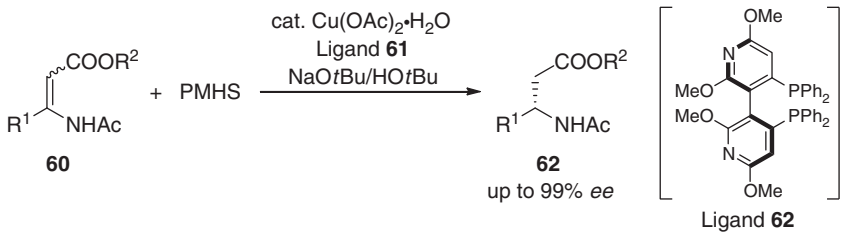
β-Metallo-α,β-unsaturated esters are suitable substrates for CuH-catalyzed 1,4-reduction. Synthesis of the chiral silane **56** possessing an ester moiety at γ-position of a silyl group was achieved by using the combination of ligand **54**-CuH catalyst (equation 25).[28] Hall and coworkers developed the effective synthetic method for chiral secondary boronic esters **59** shown in equation 26.[29]





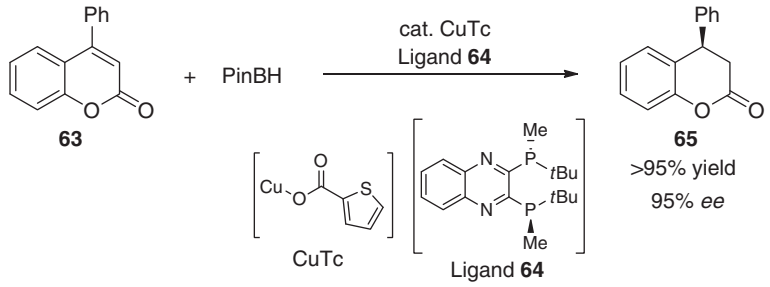
(26)

The β-(acylamino)acrylates **60** are also good substrates for CuH-catalyzed asymmetric 1,4-reduction. Employing ligand **61** gives the β-amino acid derivatives **62** with high enantioselectivity (equation 27).[30]



(27)

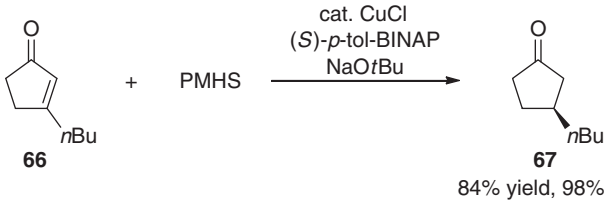
A borane is also an effective hydride source in CuH-catalyzed system. A copper hydride complex prepared from copper(I) thiophene-1-carboxylate (CuTc) and ligand **64** *in situ* promoted the asymmetric 1,4-reduction of ester **63** using pinacolborane (PinBH) to afford the corresponding saturated ester **65** in quantitative yield with 95% *ee* (equation 28).[31]



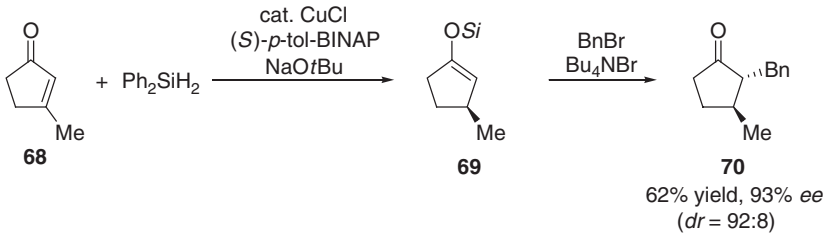
(28)

8.20.2.3.3 Asymmetric conjugate reduction of α,β-unsaturated ketones

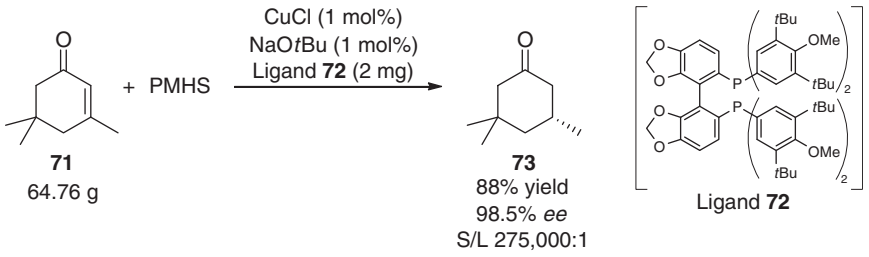
The CuH-catalyzed system is highly effective for the asymmetric conjugate reduction of α,β-unsaturated ketones, too. The asymmetric 1,4-reduction of unsaturated ketone **66** using PMHS was promoted by a catalytic amount of CuCl, (*S*)-*p*-tol-BINAP, and NaO*t*Bu to afford saturated ketone **67** in 84% yield with 98% *ee* (equation 29).[32] The optically active silyl enolate **69** generated in this system was alkylated using benzyl bromide and tetrabutylammonium bromide to give the corresponding ketone **70** with high enantio- and diastereoselectivities (Scheme 2).[33] The combination of $[(Ph_3P)CuH]_6$ and ligand **72** showed high substrate-to-ligand (S/L) ratios (up to 275,000:1) in the asymmetric 1,4-reductions of β-substituted cycloalkenones **71** (equation 30).[34] More inexpensive copper sources such as $Cu(OAc)_2 \cdot H_2O$ and copper-in-charcoal (Cu/C) could be used.[35]



(29)

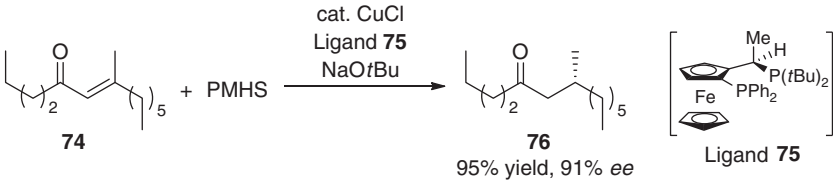


Scheme 2 Reproduced from Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129–1131.



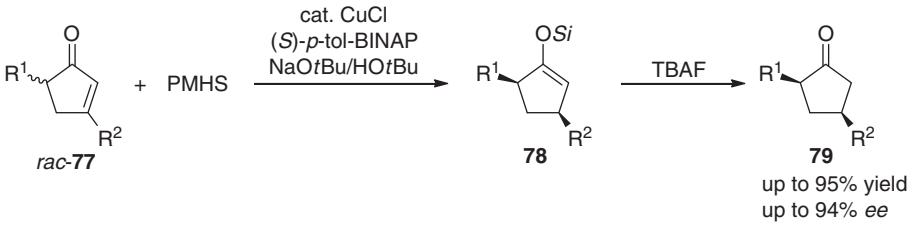
(30)

Lipshutz and coworkers achieved CuH-catalyzed asymmetric conjugate reduction of acyclic enones by the use of a chiral ferrocene bis-phosphine ligand. This is the first example of asymmetric 1,4-reduction of prochiral acyclic unsaturated ketones, in which the enone **74** was reduced to the corresponding ketone **76** in 95% yield with high enantioselectivity (equation 31).[36]

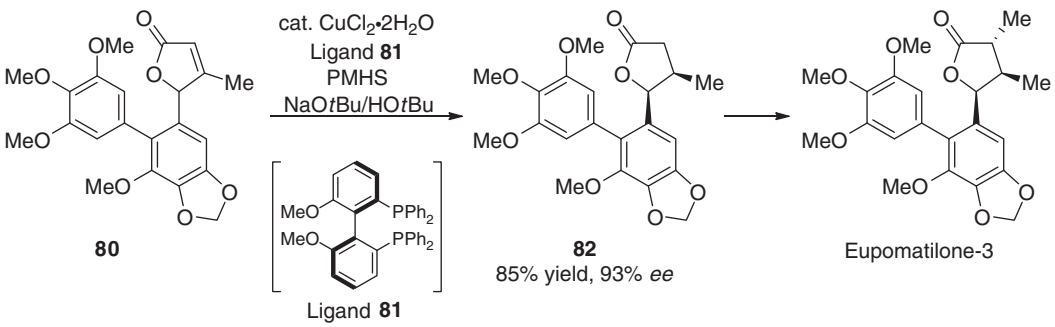


(31)

Dynamic kinetic resolution of 3,5-dialkylcyclopentenones was achieved by the catalytic system of CuCl and (*S*)-*p*-tol-BINAP in the presence of NaO*t*Bu and *tert*-butyl alcohol. Under these basic conditions, the rapid racemization of the starting ketone **77** occurs by keto-enol tautomerization, but the product ketone **79** avoids epimerization, being masked as silyl enol ether **78** (Scheme 3).[37] Similar kinetic resolution of α,β-unsaturated lactones was also successful by the use of a chiral copper complex generated from $CuCl_2$ and ligand **81**. It contributed to the first asymmetric total synthesis of eupomatilone-3 (Scheme 4).[38]



Scheme 3 Reproduced from Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892–2893.

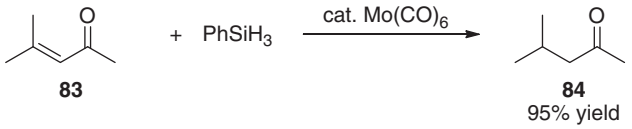


Scheme 4 Reproduced from Rainka, M. P.; Milne, J. E.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 6177–6180.

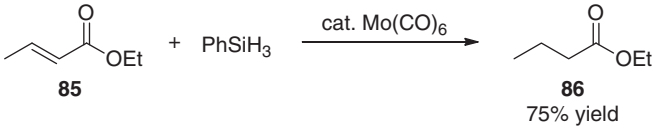
8.20.2.4 Molybdenum-Catalyzed Conjugate Reduction

Keinan reported a molybdenum-catalyzed system using hydrosilane, in which Michael acceptors including α,β-unsaturated ketones, carboxylic acids, carboxylic esters, and amides underwent 1,4-reduction. The α,β-unsaturated ketone **83** was treated with $PhSiH_3$ and a catalytic amount of $Mo(CO)_6$ to give the corresponding saturated ketone **84** in 95% yield (equation 32). $PhSiH_3$ showed the highest effect, and the reactivity of silanes was observed in the order of $PhSiH_3 > Ph_2SiH_2 > Me(EtO)_2SiH >$ PMHS, $PhMe_2SiH$, Et_3SiH. Among the hexacarbonyl complexes of group 6 metals, Cr, Mo, and W, $Mo(CO)_6$ was the most effective catalyst. α,β-Unsaturated ester **85** and amide **87**, which have in general lower reactivity than α,β-unsaturated ketones, were

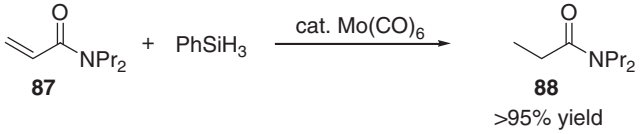
applicable to this system (equations 33 and 34). In the reduction of carboxylic acid **89**, $Mo(CO)_6$ catalyst did not suffer from an acidic proton and gave the product **90** in quantitative yield (equation 35).[39] Molybdenum oxadiene complex **92** realized higher turnover frequency than $Mo(CO)_6$ although the scope of the substrates was limited (equation 36).[40]



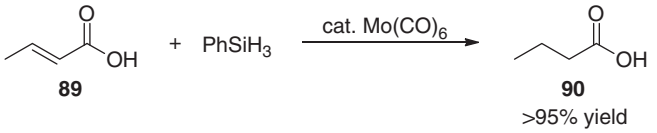
83 **84** 95% yield (32)



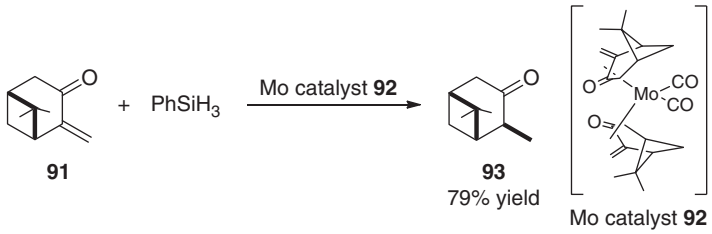
85 **86** 75% yield (33)



87 **88** >95% yield (34)



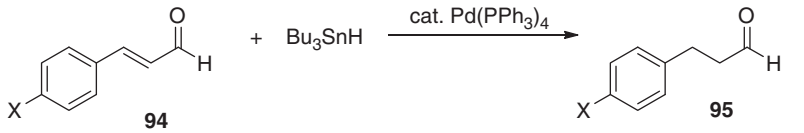
89 **90** >95% yield (35)



91 **93** 79% yield Mo catalyst **92** (36)

8.20.2.5 Palladium-Catalyzed Conjugate Reduction

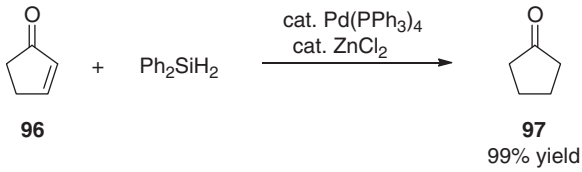
In the palladium-catalyzed conjugate reduction of α,β-unsaturated carbonyl compounds, various metal hydrides have been used as hydride sources. As to tin hydrides, in 1982, Keinan and coworkers found that the combination with $Pd(PPh_3)_4$ catalyst and tributyltin hydride was effective for 1,4-reduction of α,β-unsaturated ketones and aldehydes. This reducing system was quite sensitive to the electron density at the double bond as demonstrated in equation 37.[41]



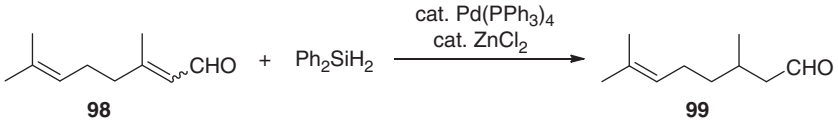
94 **95**

X = H >95% yield
NO_2 98%
NMe_2 0% (37)

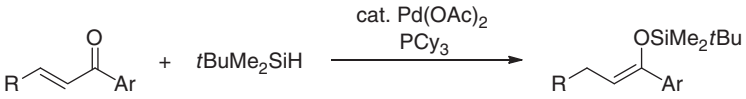
In 1985, the first example of Pd-catalyzed conjugate reduction of enones using hydrosilanes was reported, in which addition of a catalytic amount of $ZnCl_2$ was crucial for high yield and $HPd(SiR_3)$ produced by oxidative addition of the hydrosilane to palladium(0) is a key intermediate. No reduction of α,β-unsaturated ketone **1** using $Pd(PPh_3)_4$ catalyst and Ph_2SiH_2 occurred without $ZnCl_2$ (equation 38). The α,β-unsaturated aldehyde **98** was also reduced to give the corresponding aldehyde **99** in 96% yield (equation 39).[42] However, the combination of $Pd(OAc)_2$ and PCy_3 using tBuMe$_2$SiH required no additive to promote the conjugate reduction of α,β-unsaturated ketone **100** to (*Z*)-silyl enol ether selectively (equation 40).[43] In this reaction system, formation of an oxapalladacycle intermediate would occur by oxidative cyclization of the α,β-unsaturated ketone with palladium(0) and competitive oxidative addition of the hydrosilane to palladium(0) should be relatively slow.



96 **97** 99% yield (38)

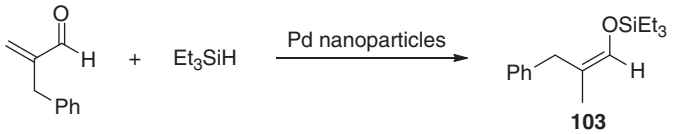


98 **99** 96% yield (39)

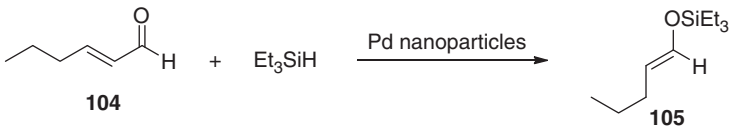


100 **101** (40)

Palladium nanoparticles prepared from $PdCl_2$ and $P(Cy)_3$ accelerated the conjugate reduction of α,β-unsaturated aldehydes using triethylsilane to give the corresponding silyl enol ethers stereoselectively. α-Benzyl acrolein **102**, a 2-substituted enal, was reduced to the silyl enol ether **103** in 84% yield with high *Z*-selectively (equation 41). In addition, the conjugate reduction of (*E*)-hex-2-enal **104**, a 3-substituted enal, took place to give the silyl enol ether **105** with high *E*-selectively (equation 42).[44]



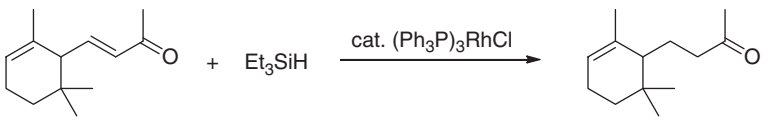
102 **103** 84% yield (*Z*/*E* = >50:1) (41)



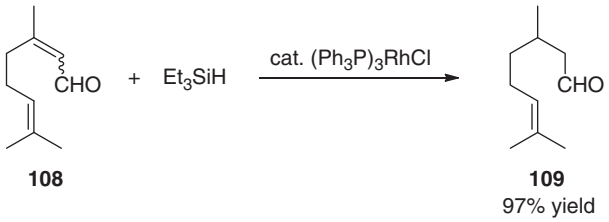
104 **105** 94% yield (*Z*/*E* = <1:50) (42)

8.20.2.6 Rhodium-Catalyzed Conjugate Reduction

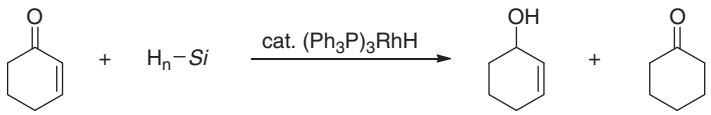
In 1972, it was reported that the combination of a rhodium complex and a hydrosilane promoted the conjugate reduction of α,β-unsaturated carbonyl compounds for the first time. Ojima and coworkers accomplished $(Ph_3P)_3RhCl$-catalyzed 1,4-reduction of α,β-unsaturated terpene carbonyl compounds using triethylsilane. α-Ionone **106** and citral **108** gave the corresponding ketone **107** and aldehyde **109** in high yields, respectively (equations 43 and 44).[45] Rh and Co–Rh carbonyl clusters were reported to have higher catalytic ability than $(Ph_3P)_3RhCl$.[46] Dirhodium(II) tetrakis(perfluorobutyrate) complex also showed an excellent turnover frequency.[47] In a reducing system using $(Ph_3P)_4RhH$ as a catalyst, the mode of 1,4-reduction or 1,2-reduction depends strongly on the choice of hydrosilanes as shown in equation 45.[48]



106 **107** 96% yield (43)



108 **109** 97% yield (44)

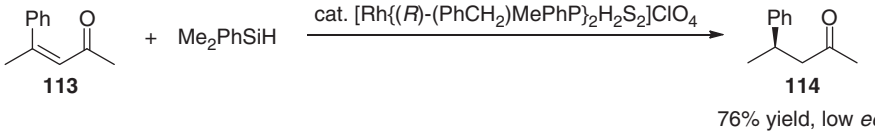


110

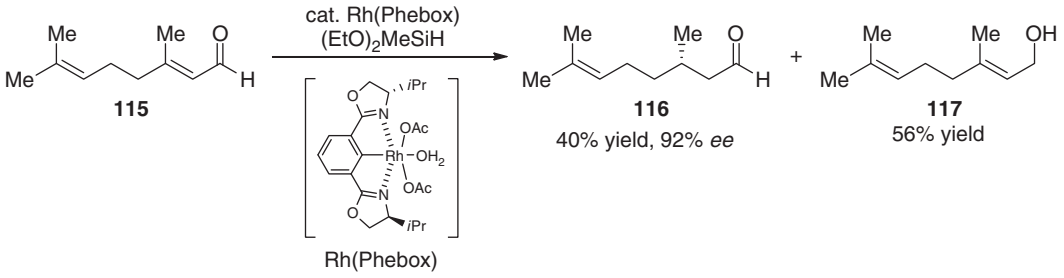
H_n-Si	**111**	**112**
Ph_2SiH_2	83%	0%
Me_2PhSiH	0%	84%

(45)

Asymmetric conjugate reduction of α,β-unsaturated ketone **113** using a chiral phosphine–Rh complex and hydrosilane was reported by Kumada and coworkers in 1975, although the enantioselectivity was low (equation 46).[49] Employment of chiral Rh(Phebox) catalyst improved the enantioselectivity by Nishiyama and coworkers in 2006. When α,β-unsaturated aldehyde **115** was treated with Rh(Phebox) and $(EtO)_2MeSiH$, 1,4-reduction took place to give the corresponding aldehyde **116** in 40% yield and high enantioselectivity, along with 56% yield of 1,2-reduction product **117** (equation 47).[50]



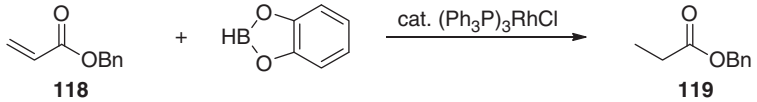
113 **114** 76% yield, low *ee* (46)



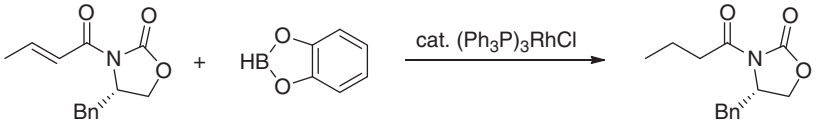
115 **116** 40% yield, 92% *ee* **117** 56% yield (47)

Rh(Phebox)

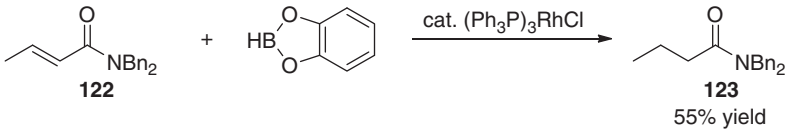
In addition to hydrosilanes, catecholborane also serves as an effective hydride source. A catalytic amount of $(Ph_3P)_3RhCl$ accelerated 1,4-reduction of α,β-unsaturated ester **118**, carbonate **120**, and amide **122** using catecholborane to give the corresponding saturated carbonyl compounds **119**, **121**, and **123** in high yields, respectively (equations 48–50).[51]



118 **119** 82% yield (48)



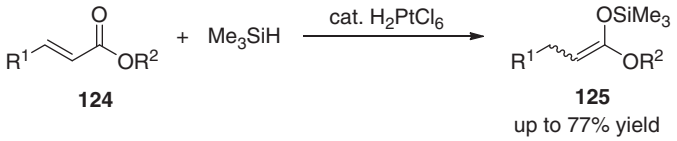
120 **121** 70% yield (49)



(50)

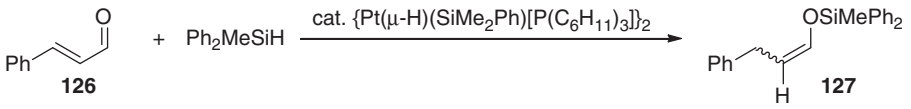
8.20.2.7 Platinum-Catalyzed Conjugate Reduction

The combination of a platinum catalyst and a hydrosilane promoted 1,4-reduction of α,β-unsaturated compounds to afford the corresponding silyl enol ethers. In 1974, the first example was reported, in which a catalytic amount of H_2PtCl_6 promoted the conjugated addition of α,β-unsaturated esters **124** with Me_3SiH to afford the ketene silyl acetals **125** (equation 51).[52]

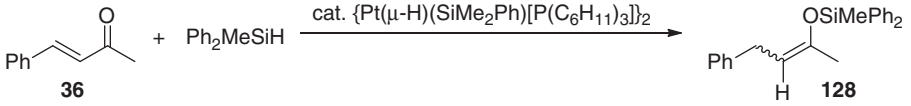


(51)

The α,β-unsaturated aldehyde **126** and ketone **36** were treated with Ph_2MeSiH in the presence of a catalytic amount of $\{Pt(\mu\text{-}H)(SiMe_2Ph)[P(C_6H_{11})_3]\}_2$ giving silyl enol ethers **127** and **128**, respectively (equations 52 and 53).[53] Rumin reported that the chloro-bridged platinum(II) complex dichlorobis(2,4,6-trimethylpyridine)platinum was also effective for similar reactions.[54]

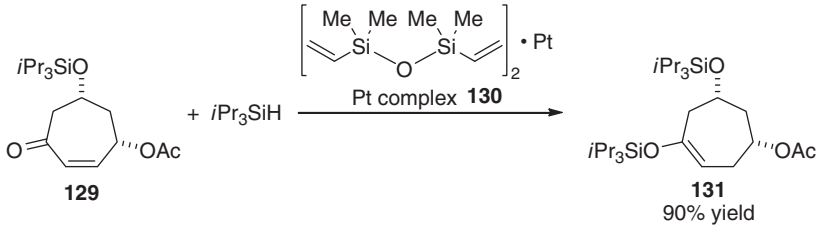


(52)

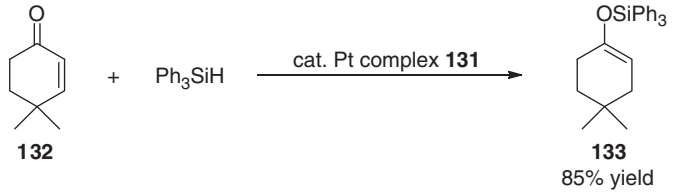


(53)

The platinum divinyltetramethyldisiloxane complex was reported to be effective for hydrosilylation of enones using the bulkier triisopropylsilyl and triphenylsilyl hydrides (equations 54 and 55). Other silyl hydrides such as triethylsilyl, *tert*-butyldimethylsilyl (TBDMS), dimethylphenylsilyl, and triethoxysilyl hydrides were applicable.[55] Generally, the form of Pt complex **130** is colloidal. Thus, exposing **130** to silane releases the active Pt(0) species, which catalyzes the addition of silane to the enone providing the hydrosilylated product.



(54)



(55)

8.20.3 Transfer Hydrogenation Using Organic Hydride Donors

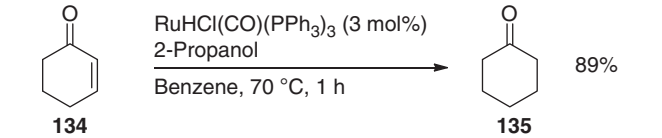
8.20.3.1 Transfer Hydrogenation with Transition Metal Catalysts

Since the second half of the twentieth century, attention was paid to the hydrogenation of unsaturated carbonyl compounds avoiding hazardous H_2, and new protocols were invented using simple organic molecules such as formic acid, ammonium salts,

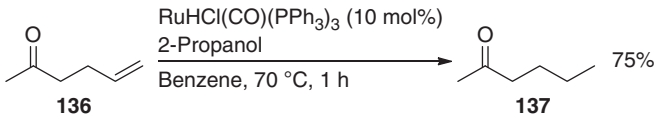
water, alcohols, and Hantzsch esters. These are 1. readily available, 2. easy to handle, and 3. easy to eliminate the byproducts. In most cases, they were employed with catalytic amount of transition metals or in the presence of various low-valent metals. This section will summarize the recent reports.

Generally, the most widely accepted strategy for reduction of double bonds of enones is the Ru-catalyzed hydride transfer from alcohols.[56] However, this reaction system often causes over reduction of enones to give saturated alcohols because of harsh reaction conditions.[57] To overcome this problem, the reaction conditions should be milder and new catalyst system would be desirable.

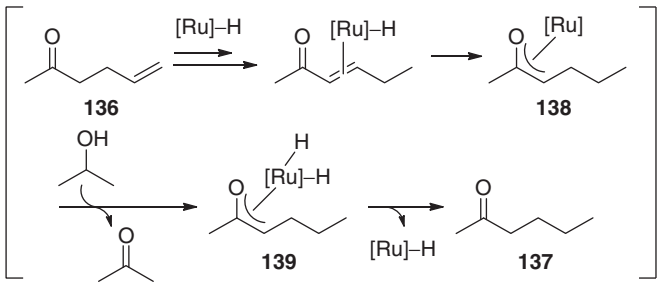
Ryu and coworkers reported the highly selective reduction of unsaturated cyclic ketone **134** using a $RuHCl(CO)(PPh_3)_3$ catalyst and 2-propanol as a hydride source under mild conditions (equation 56).[58] The Ru species was not considered to be suitable for transfer hydrogenation because it showed quite low reducing power for an aldehyde or ketone.[59] The targeted reduction of enones proceeded smoothly for various unsaturated ketones. Interestingly, this system was applicable to γ,δ-unsaturated ketone **136** to afford saturated ketone **137** even though the catalyst loaded needed to be increased (equation 57). This reaction involves isomerization of γ,δ-unsaturated ketones **136** to α,β-unsaturated ones **138** to afford π-oxyallyl intermediates **138**. This species reacts with 2-propanol to give ruthenium dihydro complex **139** followed by reductive elimination to give the product **137** (Scheme 5).



(56)

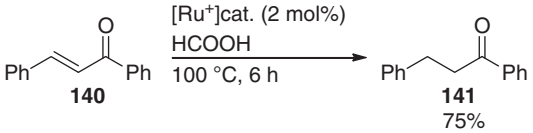


(57)



Scheme 5 Reproduced from Doi, T.; Fukuyama, T.; Horiguchi, J.; Okamura, T.; Ryu, I. *Synlett* **2006**, 721–724, and Watanabe, Y.; Ohta, T.; Tsuji, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2441–2444.

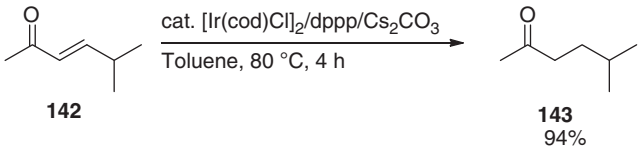
Bhattacharjee and a coworker also reported Ru-catalyzed transfer hydrogenation of enone **140** using formic acid as a hydride source giving the product **141** in which cationic Ru complex, $Ru[(PPh_3)_2(CH_3CN)_3Cl]^+[BPh_4]^-$, worked as an effective catalyst (equation 58).[60] On the contrary, 2-propanol as a hydride source caused over reduction to give the mixture of saturated ketones and alcohols.



(58)

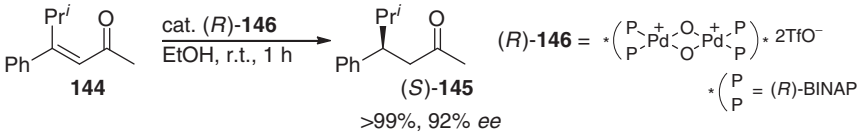
$[Ru^+] = [Ru(PPh_3)_2(CH_3CN)_3Cl]^+[BPh_4]^-$

Iridium complex-catalyzed transfer hydrogenation using 2-propanol was reported by Ishii.[61] The $[Ir(cod)Cl]_2$/dppp/Cs_2CO_3 system smoothly reduced unsaturated ketone **142** to the corresponding saturated ketone **143**. The reaction mechanism was not fully discussed although it was implied that an Ir–H complex generated *in situ* played an important role (equation 59).

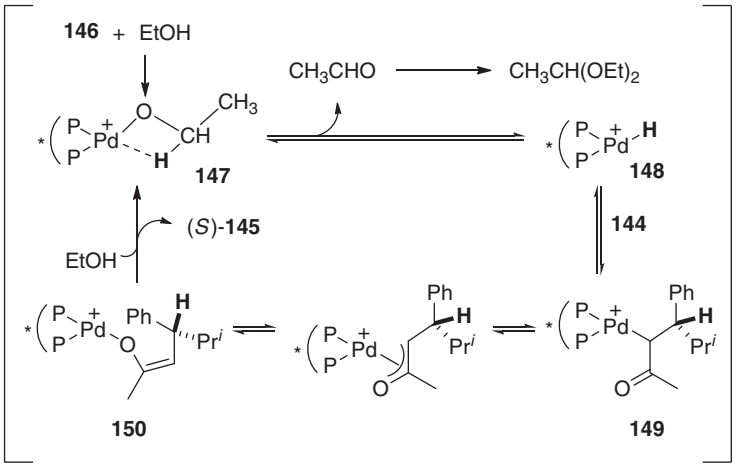


(59)

In 2006, a catalytic asymmetric conjugate reduction of α,β-unsaturated carbonyl compounds was reported by Sodeoka and coworkers employing an environmentally benign hydride source, such as ethanol.[62] The enone **144** is smoothly reduced at ambient temperature in the presence of chiral Pd–phosphine complex (*R*)-**146** (equation 60). The chiral Pd–phosphine complex (*R*)-**146** reacts with ethanol to generate Pd complex **147** followed by elimination of acetoaldehyde affording reactive cationic Pd–H complex **148** (Scheme 1). The hydropalladation takes place with the double bond of the ketone **144** to give Pd enolate **149**, which isomerizes to Pd enolate **150** followed by protonation with ethanol, giving ketone (*S*)-**145** quantitatively with 92% *ee* (Scheme 6).

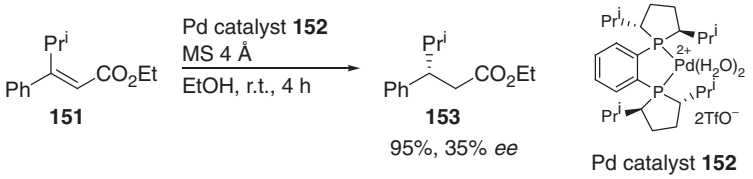


(60)

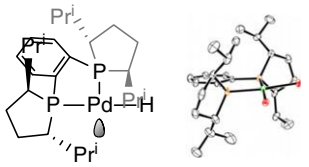


Scheme 6 Reproduced from Tsuchiya, Y.; Hamashima, Y.; Sodeoka, M. *Org. Lett.* **2006**, *8*, 4851–4854.

Later, Pd–Pr^i–DUPHOS catalyst **152** with MS 4 Å was found to show much higher reactivity for partial reduction of enone **151** to obtain the product **153** (equation 61).[63] Investigation of the reaction mechanism unveiled the fact that the electron-rich phosphine ligand enhanced the nucleophilicity of the Pd–H intermediate **154**. MS 4 Å worked as a weak base as well as dehydrating agent, promoting the formation of the Pd–ethoxide complex and acetal formation in a manner similar to early stages of Scheme 6. X-ray analysis of Pd–H species **154** gave significant insight into the mechanism of enantioselection (Figure 1).



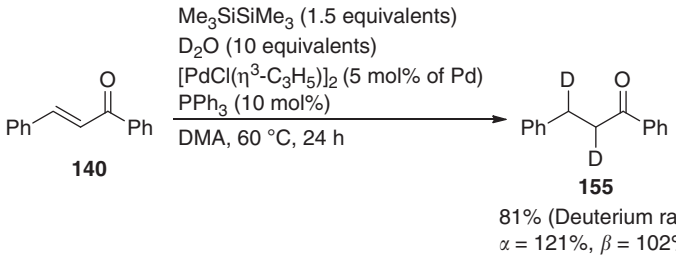
(61)



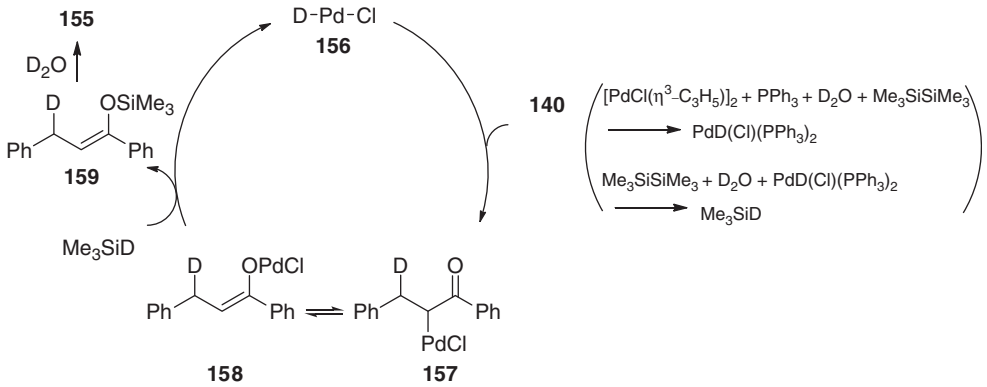
154

Figure 1 X-ray analysis of Pd–H species **154**. Reproduced from Monguchi, D.; Beemelmanns, C.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Organomet. Chem.* **2008**, *693*, 867–873.

Hayashi and Shirakawa found that conjugate reduction of enone **140** by hexamethyldisilane and D_2O in the presence of a Pd catalyst afforded α,β-dideuterio saturated ketone **155** (equation 62).[64] A plausible mechanism is shown in Scheme 7. Pd complex **156**, which is generated from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ with D_2O and hexamethyldisilane, reacts with unsaturated ketone **140** to generate Pd enolate **157** or **158**.[65] The enolate species undergoes silylation with Me_3SiD, which comes from hexamethyldisilane and D-Pd Cl **156**, giving silyl enolate **159**, which is quenched with D_2O to return the product **155**.

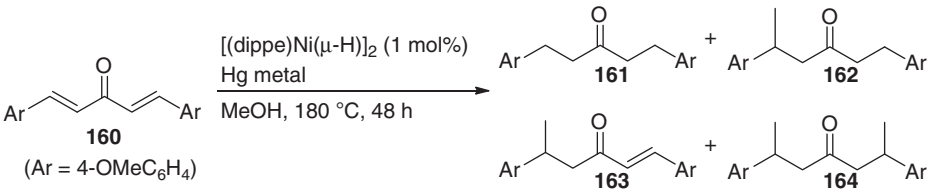


(62)



Scheme 7 Reproduced from Shirakawa, E.; Otsuka, H.; Hayashi, T. *Chem. Commun.* **2005**, 5885–5886.

García and coworkers reported Ni-catalyzed hydrogenation of C=C double bonds of unsaturated diketone **160** with methanol to afford the mixtures of saturated diketone **161** and partially methylated or reduced diketones **162–164** (equation 63).[66] They added a drop of mercury to the reaction medium in order to confirm the existence of nickel(0) nanoparticles and observed a decrease in the formation of partially methylated products **162–164**. This result indicated that the reaction involved not only a homogenous process for reduction but also a heterogenous process for methylation.

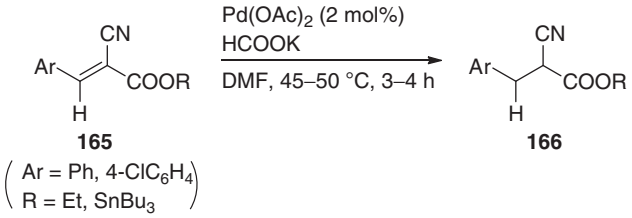


(63)

		Yield (%)			
Conversion (%)	Hg (drops)	**161**	**162**	**163**	**164**
100	0	0	18	76	6
100	3	54	6	40	0

In 1978, Heck and coworkers reported that ammonium formate acted as a useful reducing agent for enones in the presence of a palladium catalyst.[67] A similar reaction was achieved by Cacchi et al., in which potassium formate (HCOOK) was used with $Pd(OAc)_2$ as catalyst.[68] A more practical reaction system employing ammonium formate/Pd-C(10%) under reflux in methanol completed the reduction in 5 min,[69] and allowed coexistence of nonconjugated olefins in α,β-unsaturated carbonyl compounds.[70]

Chemoselective 1,4-reduction of unsaturated cyano esters **165** was reported using the $Pd(OAc)_2$/HCOOK system affording saturated cyano esters **166**. With conjugated cyano esters, it was difficult to leave the cyano group intact. Because the cyano moiety is easily reduced,[71] the key was to choose mild enough reductive conditions to reduce only the conjugated olefin moiety (equation 64).[72]

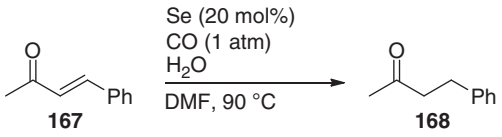


(64)

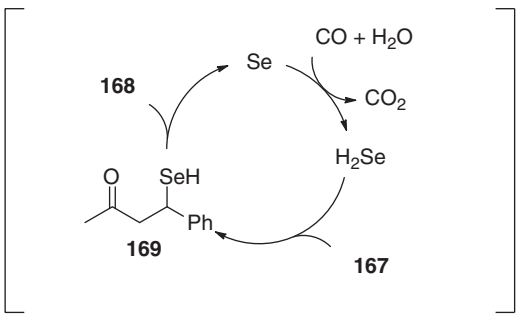
8.20.3.2 Transfer Hydrogenation Without Transition Metal Catalysts

Selenium hydride generated by reduction of elemental selenium with CO, H_2O, and strong base[73] or MSeH (M = Li or Na)[74] was reported to show highly selective reductive power toward the C=C double bond of enones. However, the methods required stoichiometric toxic sources of selenium.

Lu and coworkers developed the practical 1,4-reduction of enone **167** using CO, H_2O, and a catalytic amount of selenium under atmospheric pressure without base (equation 65).[75] In the reaction course, generated selenium hydride adds to enone **167** to obtain intermediate **169**, which is converted into the product **168** (Scheme 8).

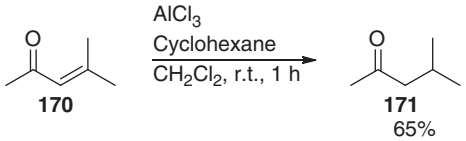


(65)

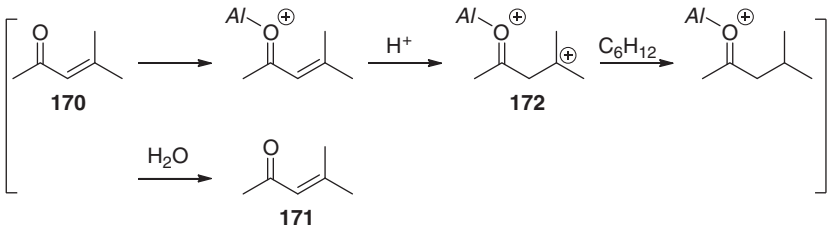


Scheme 8 Reproduced from Tian, F.; Lu, S. *Synlett* **2004**, 1953–1956.

Koltunov et al. has studied the reduction of conjugated enone **170** in the presence of excess aluminum halides and cyclohexane as a hydride donor (equation 66).[76] They argued that *O,C*-dicationic intermediate **172** which comes from protonation of $AlCl_3$-activated enone **170** has enough power to abstract hydride from cyclohexane (Scheme 9). This fact was supported by a theoretical calculation of the dicationic reaction intermediate.



(66)

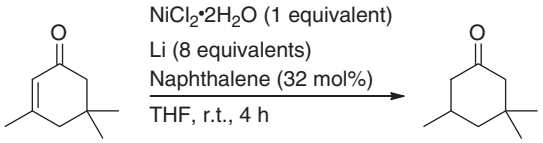


Scheme 9 Reproduced from Koltunov, K. Y.; Repinskaya, I. B.; Borodkin, G. I. *Russ. J. Org. Chem.* **2001**, *37*, 1534–1541.

This reduction protocol was applicable to unsaturated amides[77] and was improved by using HUSY-Zeolite instead of Lewis acid, which was applied to various α,β-unsaturated carbonyl compounds.[78]

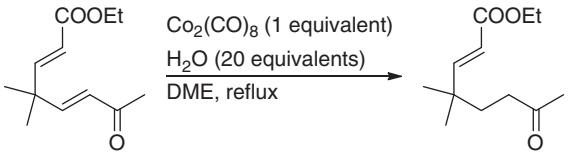
8.20.3.3 Transfer Hydrogenation Using Low-Valent Metals

Yus and coworkers have vigorously investigated a useful reduction system using $NiCl_2$, Li metal, and small amounts of arenes.[79] The reaction mechanism is not fully understood, but generation of Ni(0) was visually detected by the change of color of the reaction mixture to black. The hydride source was considered as molecular H_2 from reduction of H_2O on the metal surface. The reduction of cyclic ketone **173** proceeded smoothly affording saturated ketone **174** (equation 67).[80]



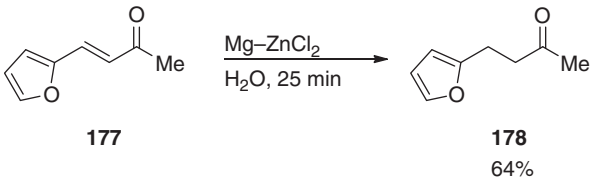
(67)

Lee et al. found that reductive Pauson–Khand reaction (PKR) was also effective for 1,4-reduction of several cyclic or acyclic unsaturated ketones using stoichiometric $Co_2(CO)_8$ and excess amount of water, in which $CoH(CO)_4$ was assumed to a reducing agent.[81] This $Co_2(CO)_8$–water system showed chemoselective reduction of the unsaturated ketone of the molecule **175** (which has both unsaturated ketone and unsaturated ester moieties) to give saturated ketone **176** (equation 68). Similar Pauson–Khand-type reductive protocols using isopropanol as a solvent, a hydride donor,[82] and CF_3COOH as a promoter were investigated.[83]



(68)

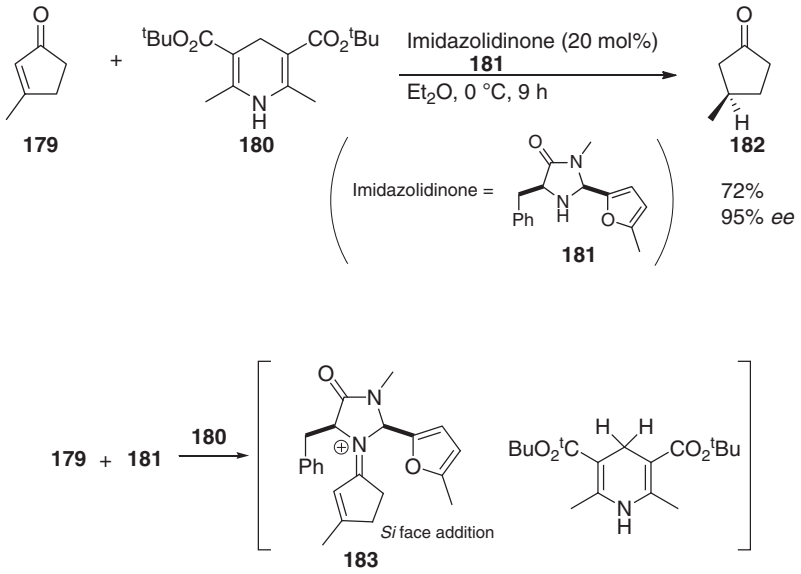
Boruah and coworkers found a facile and selective 1,4-reduction of enone **177** which was promoted by Mg–$ZnCl_2$ in aqueous medium (equation 69).[84] It was predicted that low-valent Zn metal generated from $ZnCl_2$ and Mg metal played an important role in the reduction but the details of the reaction mechanism were ambiguous.



(69)

8.20.3.4 Transfer Hydrogenation Using Hantzsch Esters

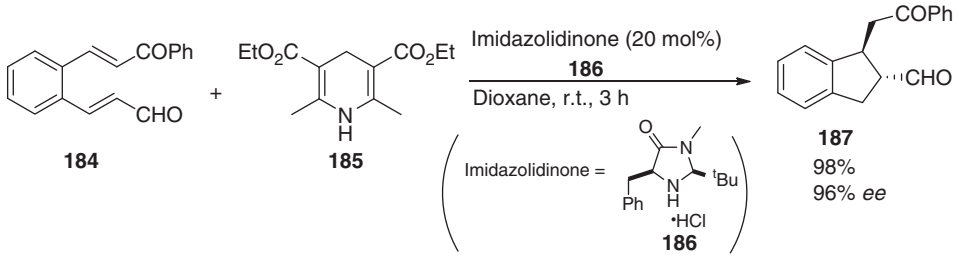
MacMillan and coworkers employed Hantzsch ester **180**[85] as a hydride donor for enantioselective 1,4-reduction of cyclic enone **179** to give enantio pure ketone **182** with an organocatalyst **181** (equation 70).[86] The selective 1,4-reduction was caused by Hantzsch ester **180** *Si* face addition to *cis*-iminium species **183** (Scheme 10).



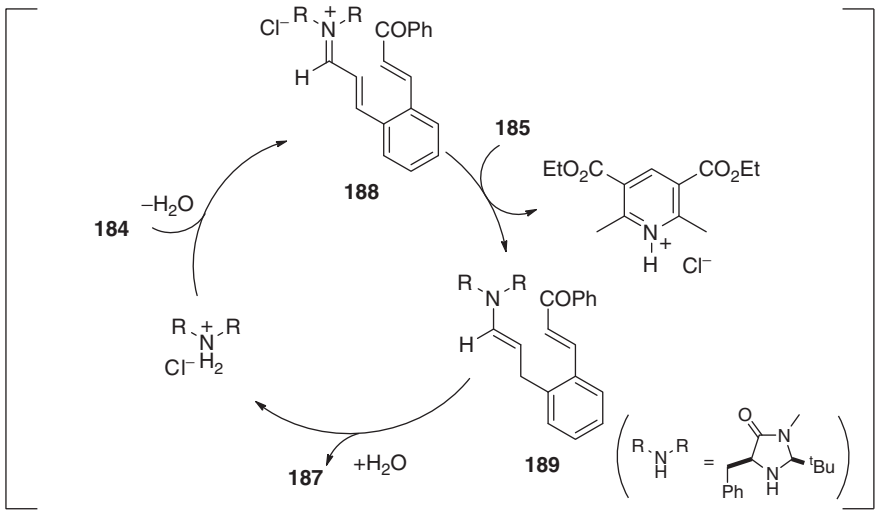
(70)

Scheme 10 Reproduced from Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662–12663.

The same type of transfer hydrogenation was investigated by List and coworkers,[87] which was further applied to the tandem intramolecular reductive Michael cyclization (equation 71).[88] The activation of enal moiety of the molecule **184** with imidazolidinone **186** initiated the reaction to afford iminium cation **188**, which was converted into enamine **189** by transfer hydrogenation from Hantzsch ester **185**. The enamine **189** added to the intramolecular conjugated olefin to give a cyclic product and regenerate ammonium salt **186** (Scheme 11).

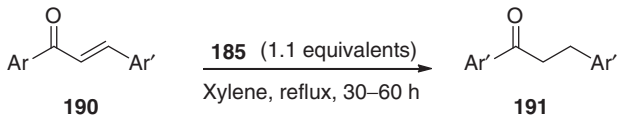


(71)



Scheme 11 Reproduced from Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036–15037.

The group of Liu and Fu has developed noncatalyzed selective hydrogen transfer from Hantzsch ester **185** to acyclic enones **190**, which proceeded under reflux for a long period in xylene (equation 72).[89] An electron transfer mechanism was proposed from the experimental result that the addition of *m*-dinitrobenzene, a strong electron acceptor, depressed the reduction process.

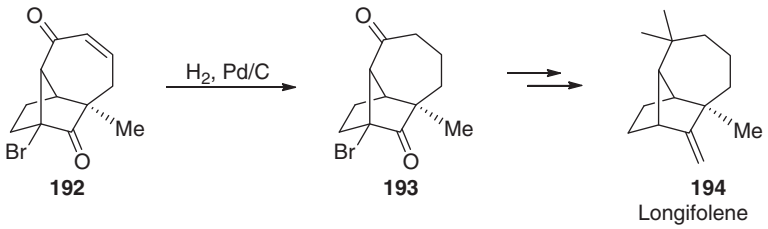


(72)

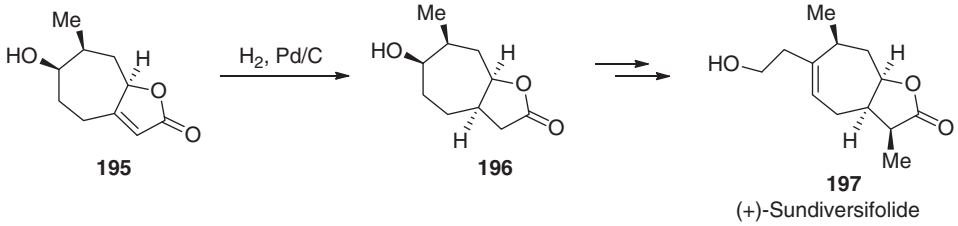
This reduction was improved by adding a catalytic amount of $TiCl_4$ which completed the reduction very rapidly without heating.[90]

8.20.4 Hydrogenation by Heterogenous Catalyst

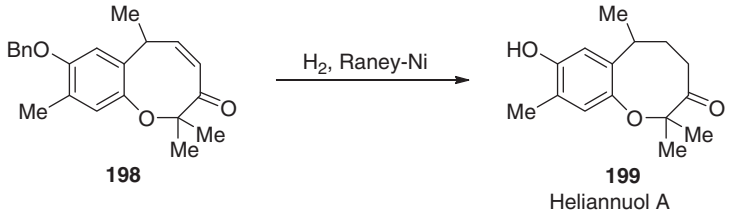
Hydrogenation of α,β-unsaturated carbonyl compounds using heterogenous catalysts such as Pd/C, Pt/C, Raney-Ni, platinum, and PtO_2 has been developed since early twentieth century, and this field has been extensively reviewed.[1] In the total synthesis of longifolene (**194**), enone **192** possessing bromo and keto moieties underwent 1,4-reduction in the presence of Pd/C under a hydrogen atmosphere to give the key intermediate **193** selectively (equation 73).[91] Stereoselective 1,4-reduction of enone **195** with Pd/C was employed for the synthesis of (+)-sundiversifolide (**197**) (equation 74).[92] Raney-Ni was also applicable to the reduction of enone **198** into Heliannuol A (**199**) in a 1,4-fashion along with deprotection of benzyl group (equation 75).[93]



(73)



(74)



(75)

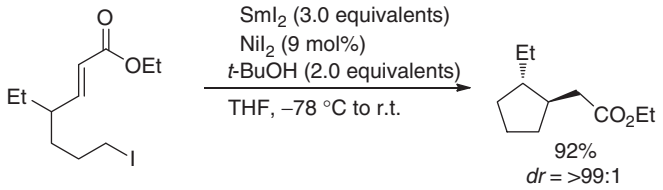
8.20.5 Electron Transfer Reductions

8.20.5.1 Samarium Diiodide-Mediated Reductions

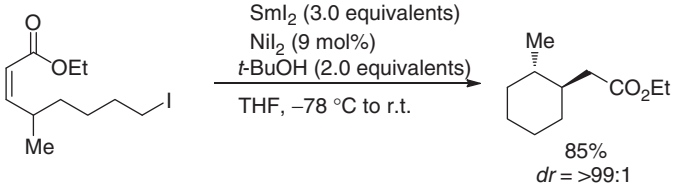
Samarium(II) diiodide (SmI_2) continues to prove an incredibly versatile reagent in organic reductions[94] because it is a very mild reagent with a reduction potential that is easily manipulated via the addition of an appropriate cosolvent[95] or catalyst.[96] Furthermore, SmI_2 is highly tolerant to a wide range of functional groups despite its strong reducing ability, and thus it provides an excellent alternative to more traditional reductive coupling methods. This chapter is focused mainly on the recent development of the SmI_2-mediated reductive cyclizations and other types of novel reactions.

8.20.5.1.1 Cyclization via alkyl radical intermediates

The SmI_2-mediated cyclization using alkyl halides onto intramolecular α,β-unsaturated carbonyl moieties is one of the most powerful protocols for the synthesis of functionalized carbocycles, although examples have been strictly limitted.[97] Molander and coworkers have established more general methods for radical cyclization of **200** and **202**, iodo-α,β-unsaturated esters, in the presence of NiI_2 catalyst, which gave five- and six-membered carbocyclic compounds **201** and **203** (equations 76 and 77).[98]

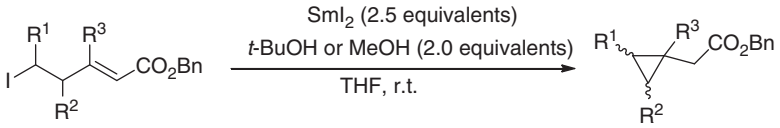


200 **201** (76)



202 **203** (77)

It is noteworthy that carbocyclic compounds were obtained with an excellent diastereoselectivity. Cyclopropane rings could be also synthesized by SmI_2-mediated cyclization of δ-halo-α,β-unsaturated esters **204** in high yields, although the diastereoselectivity was moderate (equation 78).[99]

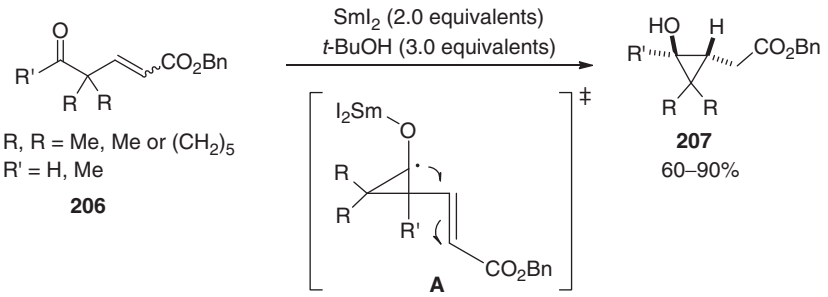


204 **205** (78)

8.20.5.1.2 Cyclization via ketyl radical intermediates

The samarium(II)-mediated reductive coupling of unsaturated aldehydes or ketones is a particularly powerful cyclization protocol which allows construction of a variety of cyclic alcohols with varying ring sizes under mild conditions.

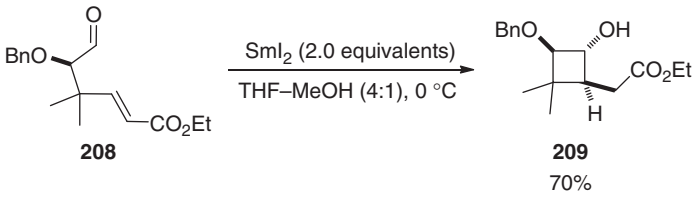
Guibé and coworkers have achieved the preparation of cyclopropanols by 3-*exo*-trig cyclization of δ-oxo-α,β-unsaturated esters **206**.[100] Since reactions proceeded via transition state **A**, *anti*-cyclopropanols **207** were produced with complete diastereocontrol, irrespective of *E* or *Z* configuration of the double bond in the starting olefins (**Scheme 12**).



206 **A** **207**

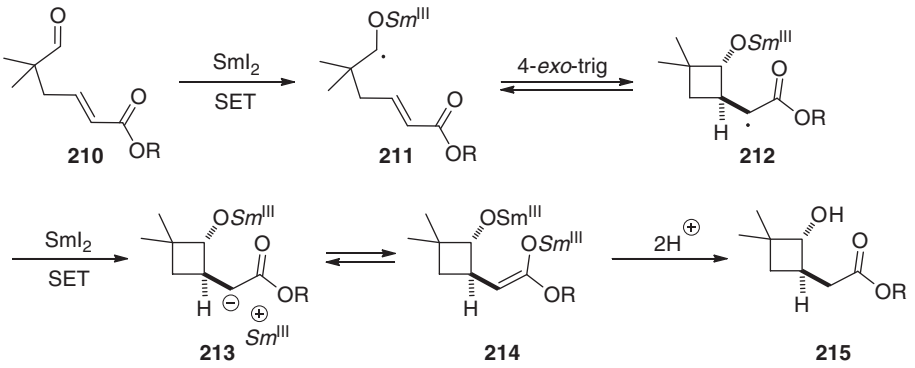
Scheme 12 Reproduced from Villar, H.; Guibé, F. *Tetrahedron Lett.* **2002**, *43*, 9517–9520; Bezzenine-Lafollée, S.; Guibé, F.; Villar, H.; Zriba, R. *Tetrahedron* **2004**, *60*, 6931–6944; Zriba, R.; Bezzenine-Lafollée, S.; Guibé, F.; Magnier-Bouvier, C. *Synlett* **2005**, 2362–2366, and Zriba, R.; Bezzenine-Lafollée, S.; Guibé, F.; Magnier-Bouvier, C. *Tetrahedron Lett.* **2007**, *48*, 8234–8237.

SmI_2-mediated 4-*exo*-trig ketyl-olefin cyclization of γ,δ-unsaturated aldehydes has been reported by Weinges and coworkers for the first time although the report contained only a single cyclization reaction using substrate **208** (equation 79).[101] In 1999, using a similar reaction system, various functionalized cyclobutanols were synthesized with moderate to excellent diastereoselectivity.[102]



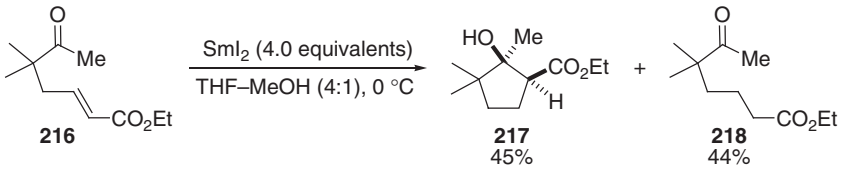
(79)

The reaction proceeds via a 'carbonyl first pathway'. The first equivalent of SmI_2 reduces aldehyde **210** to the ketyl radical **211**. A reversible 4-*exo*-trig cyclization then takes place forming the cyclobutylmethyl radical **212**. The second equivalent of SmI_2 then reduces radical **213** to the samarium enolate **214**. Finally, samarium enolate **213**/**214** is protonated *in situ*, generating the product **215** (Scheme 13).

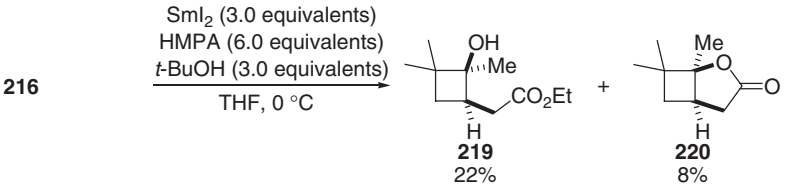


Scheme 13 Reproduced from Weinges, K.; Schmidbauer, S. B.; Schick, H. *Chem. Ber.* **1994**, *127*, 1305–1309.

Unlike the reactions using γ,δ-unsaturated aldehydes, the reaction using ketone substrate **216** gave a mixture of *syn*-cyclopentanol **217** and acyclic reduction product **218** when treated with SmI_2 in tetrahydrofuran (THF)–MeOH (equation 80). However, employing hexamethylphosphoramide (HMPA) as an additive and *t*-BuOH as a proton source led to cyclobutanol products **219** and **220** in moderate yields without generating cyclopentanol products (equation 81).[103]



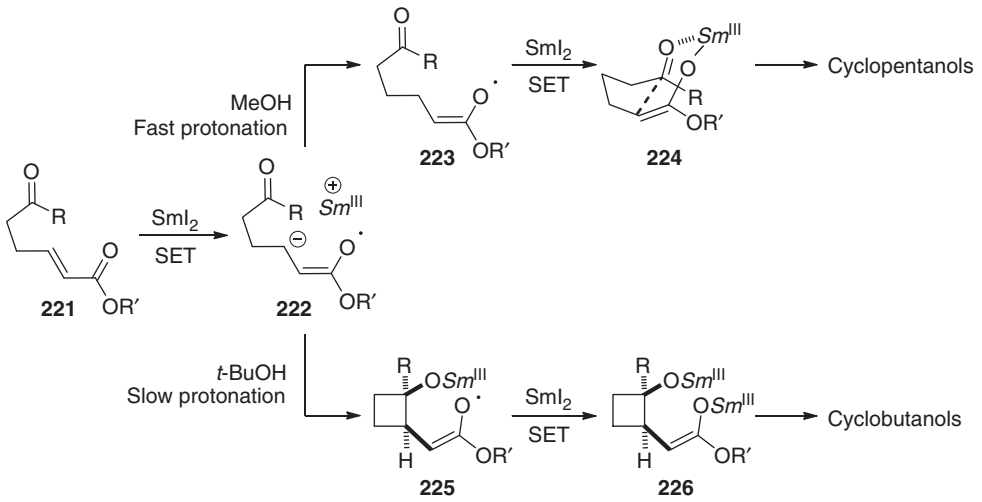
(80)



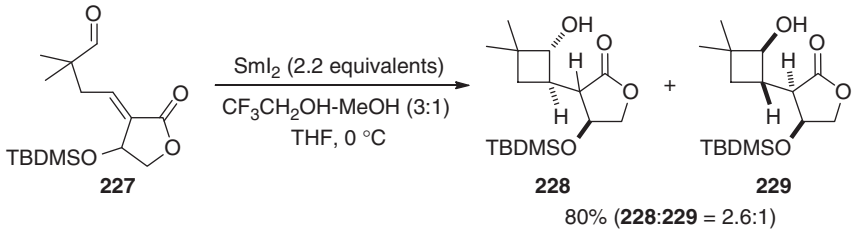
(81)

The mechanism for the cyclization of γ,δ-unsaturated ketones differs from their aldehyde counterparts and proceeds through an 'alkene first' mechanism. The first equivalent of SmI_2 reduces the electron-deficient alkene **221** to radical anion **222**. In the presence of MeOH cosolvent, the resulting anion is quickly protonated to give radical **223**. The second equivalent of SmI_2 reduces the radical **223** to samarium enolate **224**, which undergoes a diastereoselective aldol cyclization aided by chelation to samarium to give cyclopentanol products. However, when the bulky proton donor of *t*-BuOH is employed as a cosolvent, slow protonation of radical **222** allows a 4-*exo*-trig anionic (or radical) cyclization to give the cyclobutane ring **225**. A follow-up reduction with a second equivalent of SmI_2 generates a samarium enolate **226**, which is then protonated by the alcohol cosolvent (Scheme 14).[104]

Stereocontrol in 4-*exo*-trig cyclization by the introduction of a siloxy group was investigated although the diastereoselectivity was moderate (equation 82).[105]

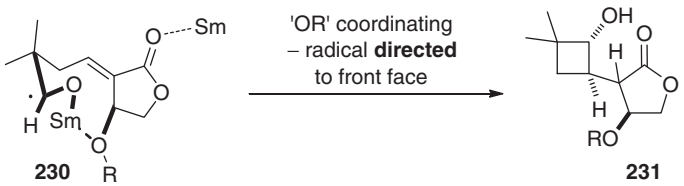


Scheme 14 Reproduced from Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811–4814.

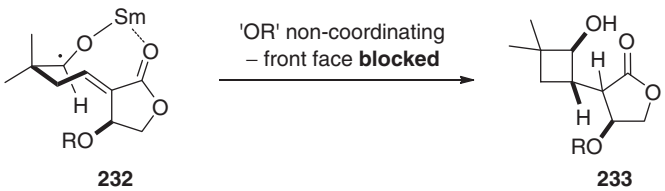


(82)

There are two possible roles for derivatized hydroxyl (OR) group. First, if the substituent works as a directing group, the samarium(III) radical anion might be delivered to the same face of the alkene (equation 83). The other is a steric blocking effect, forcing radical attack on the opposite face of the olefin (equation 84). Although a bulky TBDMS group was not expected to coordinate to a samarium center, it played as both 'directing'- and 'blocking'-roles.



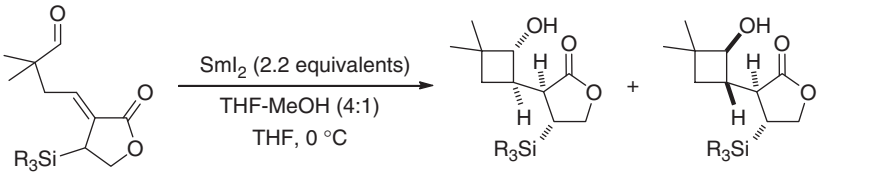
(83)



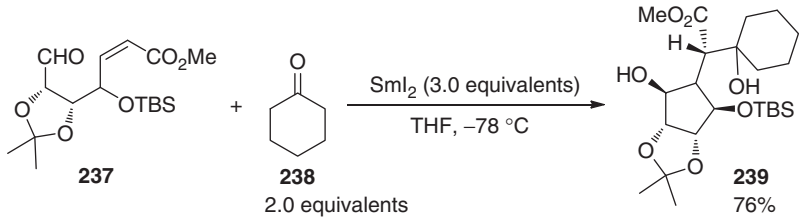
(84)

Replacement of the alkylsiloxy group by phenylsiloxy ones improved stereoselectivity.[106] This is the first example of a silicon substituent directing the stereochemical course of a cyclization reaction mediated by SmI_2. The employment of $SiPh_3$ group led to the complete diastereoselectivity (Scheme 15).

A SmI_2-mediated tandem radical cyclization of **237** and successive carbonyl addition with **238** gave highly functionalized and densely oxygenated bicyclic compound **239** in a good yield (equation 85).[107]

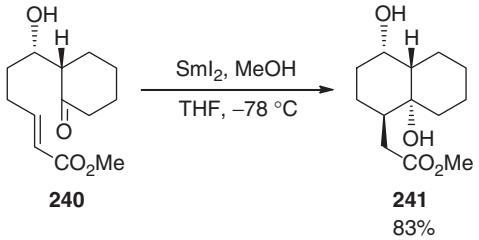


Scheme 15 Reproduced from Harb, H. Y.; Collins, K. D.; Alture, J. V. G.; *et al. Org. Lett.* **2010**, *12*, 5446–5449.

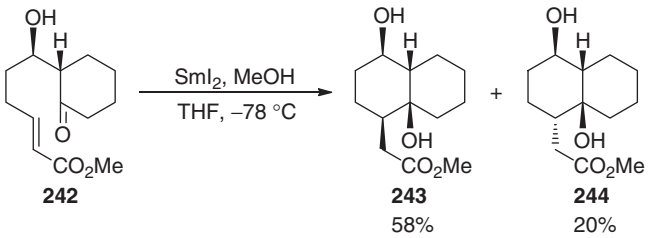


(85)

By treating the *anti*-hydroxyketone **240** and the *syn*-hydroxyketone **242** with SmI_2, the ketone–olefin coupling cyclizations took place to give the *trans*-decalin diol **241** and the epimeric mixtures of the *cis*-decalin diols **243** and **244**, respectively (equations 86 and 87).[108] The *β*-hydroxy group worked as a directing group toward SmI_2 to give the products with moderate to excellent stereoselectivities.

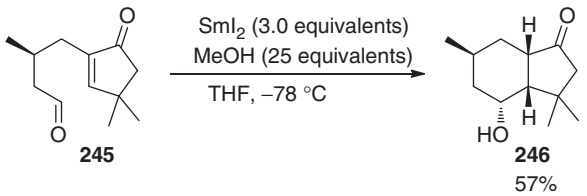


(86)

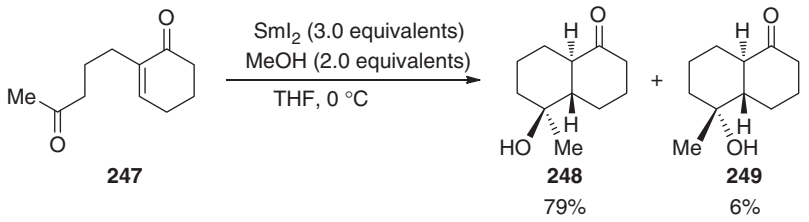


(87)

Enone-aldehyde **245** or -ketone **247** were efficiently cyclized with SmI_2 in an intramolecular 6-*endo*-trig manner, providing the corresponding hydrindane **246** or perhydronaphthalenones **248** and **249**, respectively (equations 88 and 89).[109] The diastereoselectivity of reactions was highly adjustable by additives such as MeOH.

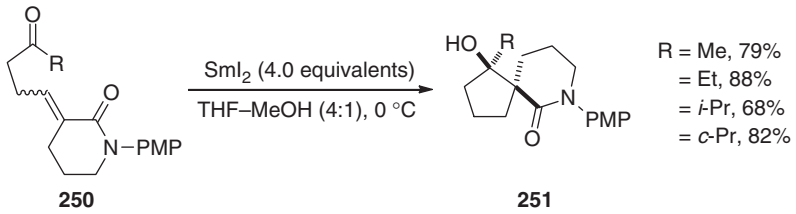


(88)



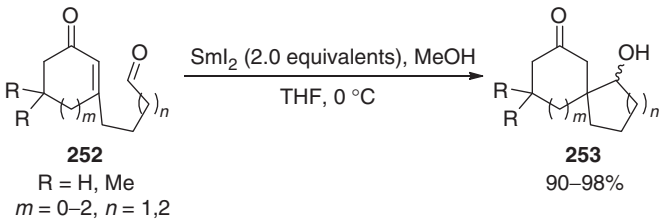
(89)

The SmI_2-mediated reductive cyclization is also useful for the synthesis of spiro compounds. For example, γ,δ-unsaturated ketones **250** bearing a lactam moiety generated various protected spirolactams **251** in moderate to high yields with complete diastereocontrol (**Scheme 16**).[110]



Scheme 16 Reproduced from Guazzelli, G.; Duffy, L. A.; Procter, D. J. *Org. Lett.* **2008**, *10*, 4291–4294.

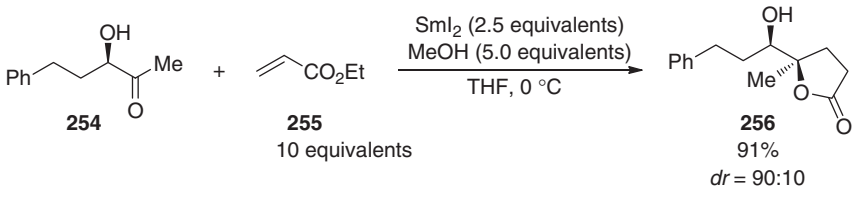
Various spirocyclic γ-hydroxyketones **252** were prepared by SmI_2-mediated reductive cyclization of enone-aldehydes **253** (**Scheme 17**). The ring size of the spiro compounds could be easily controlled either by using different cyclic enones or by altering the length of the side chain.[111]



Scheme 17 Reproduced from Hsu, D.-S.; Hsu, C.-W. *Tetrahedron Lett.* **2012**, *53*, 2185–2188.

8.20.5.1.3 Intermolecular ketone–olefin coupling

Although much research has been directed toward SmI_2-mediated intermolecular ketone–olefin coupling reactions, there have been few reports for stereoselective ones. In 1994, Matsuda and coworkers achieved stereoselective intermolecular coupling of α-hydroxy ketone **254** with α,β-unsaturated ester **255**.[112] The presence of an α-hydroxy group was crucial, and coupling product **256** was given with high diastereoselectivity (equation 90).



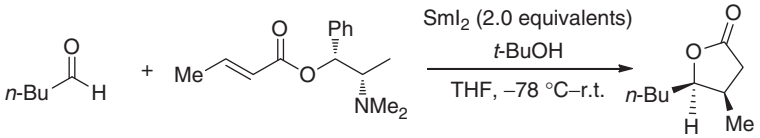
(90)

8.20.5.1.4 Asymmetric synthesis of γ-butyrolactones

Surprisingly, only a limited number of examples of SmI_2-mediated asymmetric reactions are known. A formal one is the formation of chiral γ-butyrolactones from aldehydes or ketones and α,β-unsaturated esters.

The reaction of aldehyde **257** with α,β-unsaturated ester **258**, which carries a chiral auxiliary, is one of the most facile and effective approaches, pioneered by Fukuzawa et al. in 1997 (equation 91).[113] Chelation control by the samarium atom plays an

important role in the asymmetric induction since the addition of HMPA resulted in production of a completely racemic mixture of the butyrolactone (the result was not shown in this chapter).



257 **258** **259**

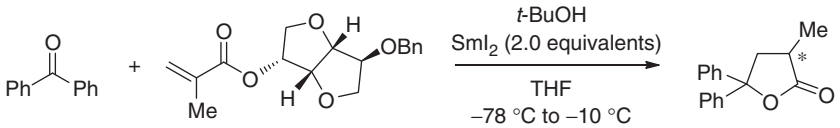
57%, *cis*:*trans* = 97:3
96% *ee* (*cis* isomer) (91)

Enantioselective synthesis of α,γ-substituted γ-butyrolactones was also reported. The sole use of a chiral proton source **262** in the reaction of benzophenone **260** with α,β-unsaturated ester **261** gave the desired product **263** in a high yield although the enantioselectivity was moderate (equation 92).[114] However, the reaction using α,β-unsaturated ester **258**, which has a chiral auxiliary, provided **263** as the opposite enantiomer (equations 93 and 94).[115] The results indicate that the chiral auxiliary of the α,β-unsaturated ester strongly controlled the enantioselectivity of the reaction, and the chirality of the proton source was not a determining factor.



260 **261** **262** (–)-**263**

90%
39% *ee* (92)



260 **264** (+)-**263**

55%
79% *ee* (93)

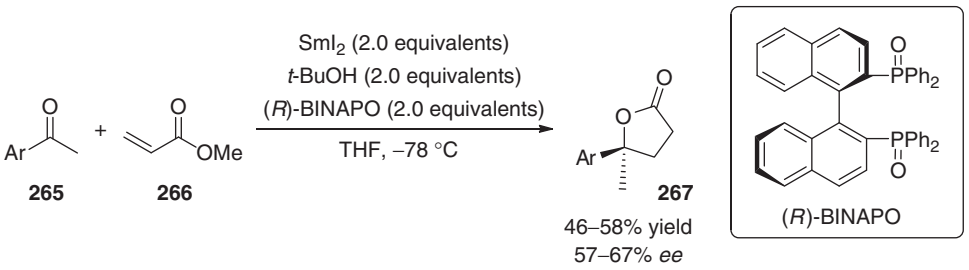


260 **264** **262** (+)-**263**

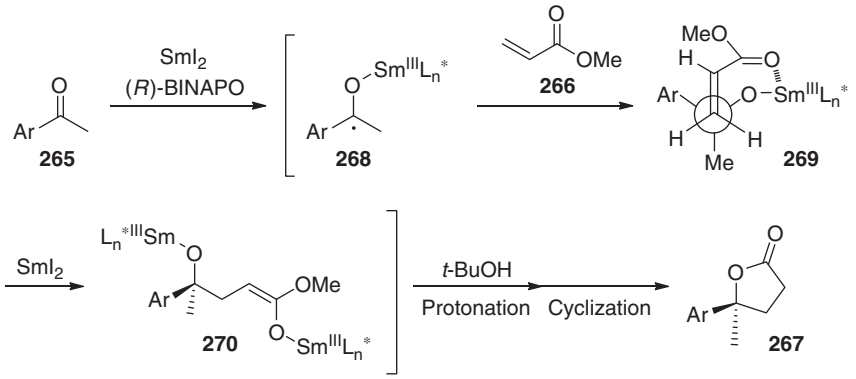
66%
95% *ee* (94)

Enantioselective synthesis of γ-butyrolactones utilizing chiral ligand control has been also reported, although yields and stereoselectivity were moderate (**Scheme 18**).[116]

The proposed reaction mechanism is shown in **Scheme 19**. First, chiral ketyl radical **268** is generated by SmI_2 and (*R*)-BINAPO. The ketylsamarium intermediate **268** can be trapped by methyl acrylate **266** through medium ring cyclic chelate **269** to form new carbon–carbon bond. Then, the protonation of the resulting samarium enolate **270** is followed by cyclization to give the chiral γ-butyrolactone **267**.



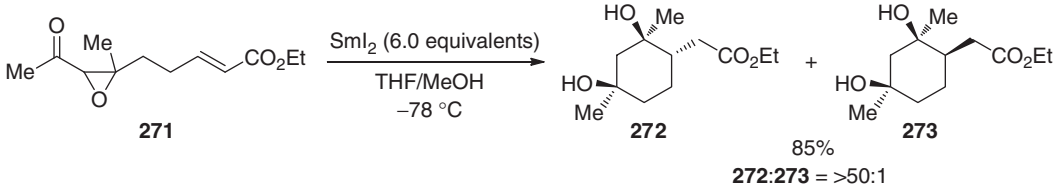
Scheme 18 Reproduced from Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501–4504.



Scheme 19 Reproduced from Mikami, K.; Yamaoka, M. *Tetrahedron Lett.* **1998**, *39*, 4501–4504.

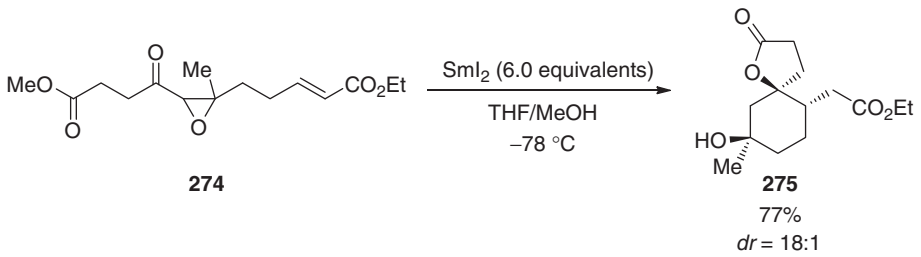
8.20.5.1.5 Domino epoxide ring-opening/ketyl olefin coupling reactions

Molander and coworkers have reported domino reactions including an epoxide ring-opening and a ketyl radical olefin cyclization, which led to *cis*-1,3-cyclopentanediol **272** with excellent diastereoselectivity (equation 95).[117]



(95)

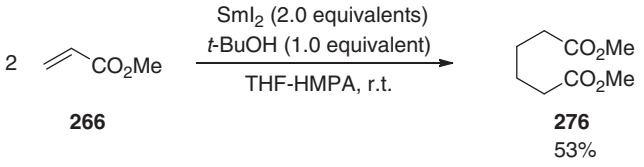
This reaction system was expanded to the synthesis of spirolactone **275** by using α,β-epoxy ketones **274**, which have an ester moiety (equation 96).[118]



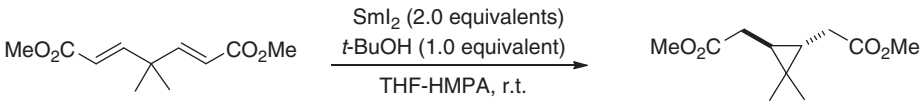
(96)

8.20.5.1.6 Hydrodimerization

In the absence of coupling partners, α,β-unsaturated esters **266** and **277** readily underwent hydrodimerization under the SmI_2-mediated reduction conditions.[119] Both intra- or intermolecular hydrodimerizations proceeded to give the corresponding products **276** and **278** in moderate to good yields (equations 97 and 98).

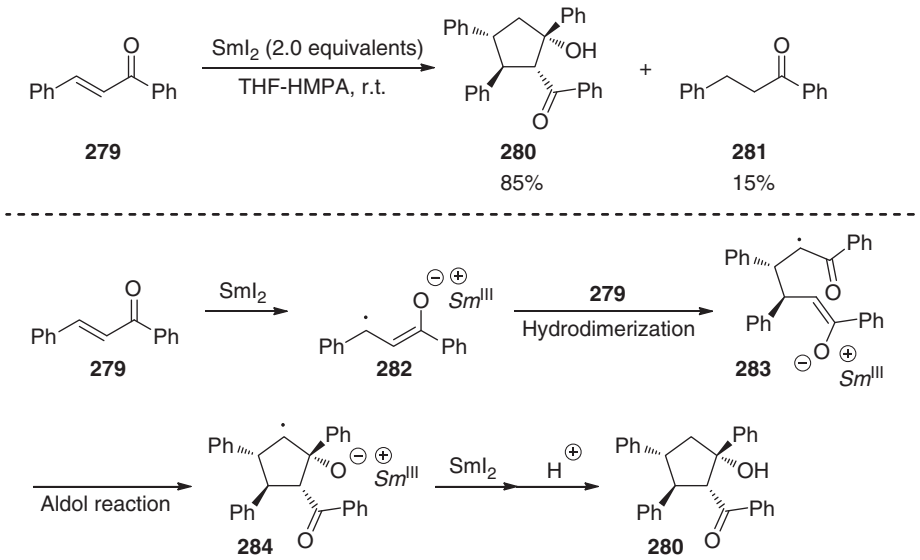


266 **276** 53% (97)



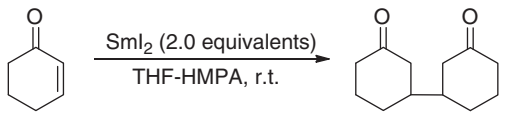
277 **278** 80% *dr* = 7:1 (98)

When acyclic α,β-unsaturated ketones such as *trans*-chalcone **279** were treated with SmI_2, cyclopentanol **280** and 1,4-reduction product **281** were obtained. Cyclopentanol **280** is obtained via hydrodimerization of samarium(III) radical anion **282** with **279** followed by an intramolecular aldol reaction of the resulting hydrodimerized intermediate **283** (**Scheme 20**).[120]



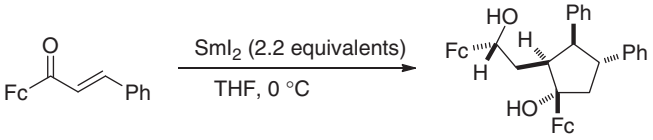
Scheme 20 Reproduced from Cabrera, A.; Rosas, N.; Alvarez, C.; *et al. Polyhedron* **1996**, *17*, 2971–2973, and Cabrera, A.; Le Lagadec, R.; Sharma, P.; *et al. J. Chem. Soc., Perkin Trans. 1*, **1998**, 3609–3617.

The reaction using cyclic ketone **285**, however, gave only hydrodimerized product **286** (equation 99).[120b,121]



285 **286** 87% (99)

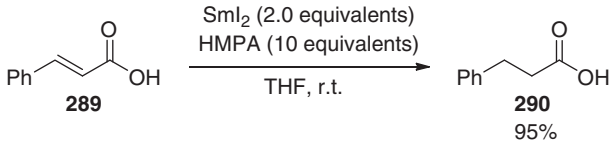
Further reduction of the product in the tandem reaction of α,β-unsaturated ketone **287**, which has a ferrocene unit, gave the corresponding cyclopentanediol **288** without any effect on ferocene moiety (equation 100).[122]



287 Fc = ferrocenyl **288** 92% *dr* = 86:14 (100)

8.20.5.1.7 Conjugate reduction of α,β-unsaturated carbonyl compounds

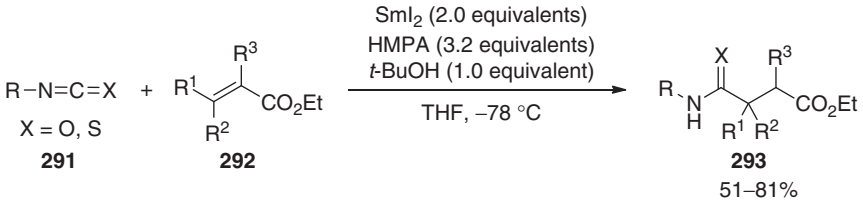
In the presence of HMPA as an additive, SmI_2-mediated conjugate reductions of various α,β-unsaturated carbonyl compounds could occur. For example, cinnamic acid **289** was reduced to hydrocinnamic acid **290** smoothly (equation 101).[123]



(101)

8.20.5.1.8 Coupling reaction of isocyanates or isothiocyanates with α,β-unsaturated esters

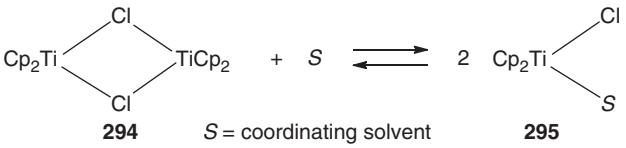
Isocyanates and isothiocyanates **291** are very reactive compounds whose coupling with α,β-unsaturated esters **292** may be mediated by SmI_2.[124] Various thioamides and amides **293** were obtained in good yields (equation 102).



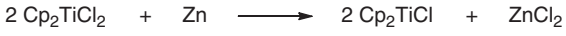
(102)

8.20.5.2 Cp_2TiCl-Mediated Reductions

In 1972, Cp_2TiCl was first reported by Green et al.[125] The reagent, sometimes called Nugent's reagent, exists as a chloride-bridged dimer **294** in its solid state, but dissociates to a monomeric species **295** in the presence of donor solvents, such as THF to afford a loosely solvated 'transition-metal-centered-radical' (Scheme 21). Cp_2TiCl can be isolated stably,[126] but it is often prepared from Cp_2TiCl_2 and powdered zinc *in situ* (equation 103).

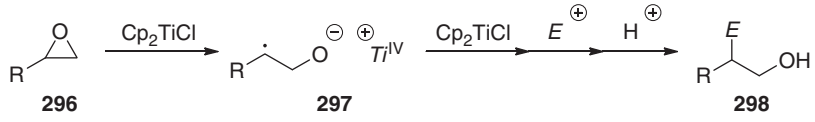


Scheme 21 Reproduced from Manzer, L. *Inorg. Synth.* **1982**, *21*, 84–86.



(103)

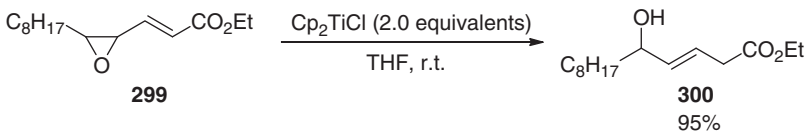
The reagent has very mild reactivity and is mainly used as a single-electron reductant in coupling reactions of epoxides **296** (Scheme 22).[127]



Scheme 22 Reproduced from Gold, H. J. *Synlett* **1999**, *1*, 159; Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771–2788; Li, J. J. *Tetrahedron* **2001**, *57*, 1–24; Gansäuer, A.; Narayan, S. *Adv. Synth. Catal.* **2002**, *344*, 465–475, and Gansäuer, A.; Lauterbach, T.; Narayan, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 5556–5573.

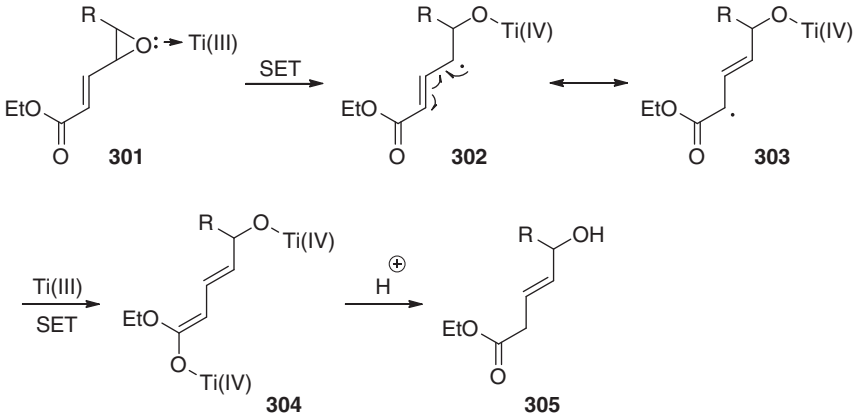
8.20.5.2.1 Selective reductions

The Cp_2TiCl-mediated reduction of vinyl epoxide **299** gave *E*-allylic alcohol **300** in high yield (equation 104).[128]



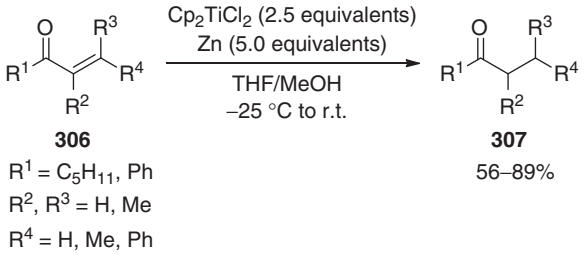
(104)

Titanium(III) species are known to homolytically cleave epoxide **301** to produce radical **302** which is stabilized by resonance of the ester carbonyl. Then, a second equivalent of Cp_2TiCl reduces the intermediate **303** to give titanium enolate **304**. Finally, **304** is protonated to give *E*-allylic alcohol **305** (Scheme 23).



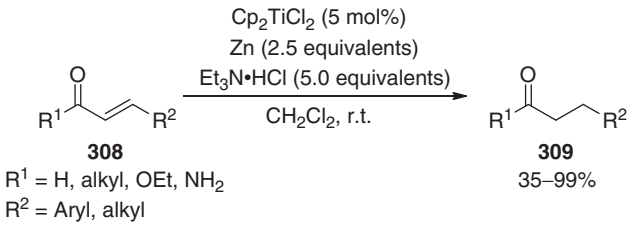
Scheme 23 Reproduced from Yadav, J. S.; Shekharam, T.; Srinivas, D. *Tetrahedron Lett.* **1992**, *33*, 7973–7976.

Conjugate reduction of α,β-unsaturated ketones by Cp_2TiCl was also successful (Scheme 24).[129]



Scheme 24 Reproduced from Moisan, L.; Hardouin, C.; Rousseau, B.; Doris, E. *Tetrahedron Lett.* **2002**, *43*, 2013–2015.

In 2010, a catalytic single-electron transfer (SET)-type process using Cp_2TiCl that can enable the conjugate reduction of carbonyl derivatives **308** was reported (Scheme 25).[130] Various carbonyl compounds were applicable to this reaction system. It is noteworthy that selective 1,4-reduction of α,β-unsaturated aldehydes was also successful.

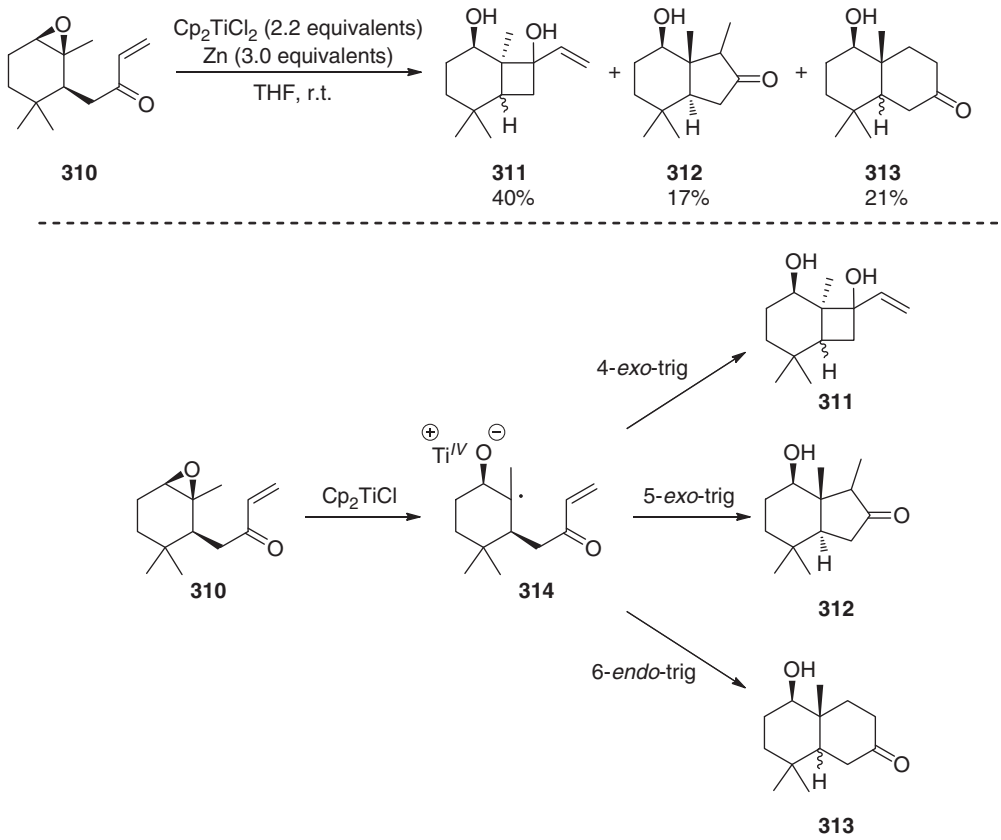


Scheme 25 Reproduced from Kosal, A. D.; Ashfeld, B. L. *Org. Lett.* **2010**, *12*, 44–47.

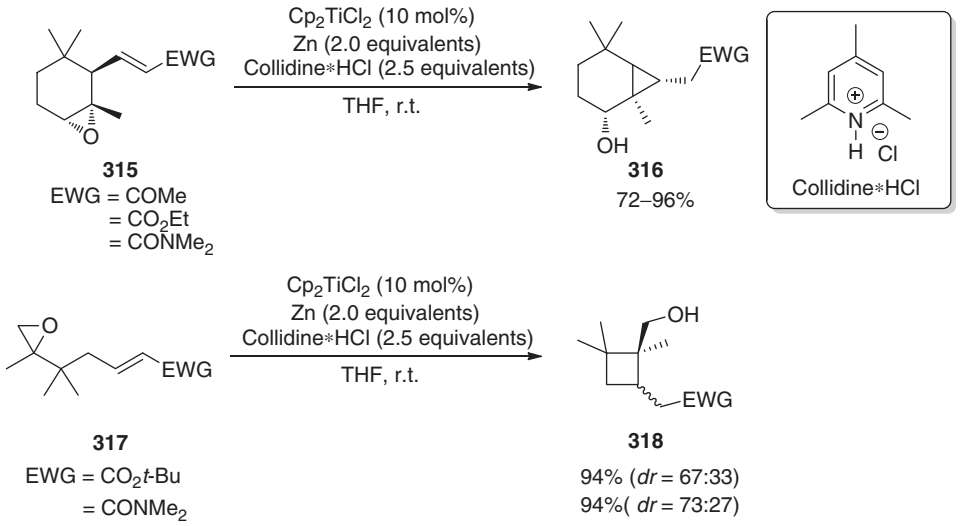
8.20.5.2.2 Intramolecular reductive couplings

Intramolecular reductive coupling using unsaturated epoxyketone **310** has been reported by Fernández–Mateos.[131] Various sized cyclic products **311–313** were obtained by the 4-*exo*-, 5-*exo*-, or 6-*endo*-trig cyclization of radical intermediate **314** although yields and selectivity were moderate (Scheme 26).

Around the same time as Fernández–Mateos's report, 3-*exo* and 4-*exo* cyclizations of unsaturated epoxyketones **315** and **317** catalyzed by Cp_2TiCl_2 were achieved (Scheme 27).[132] Collidine hydrochloride had an important role to restore catalytic ability of Cp_2TiCl_2. Reactions proceeded smoothly to give desired coupling products in high to excellent yields.



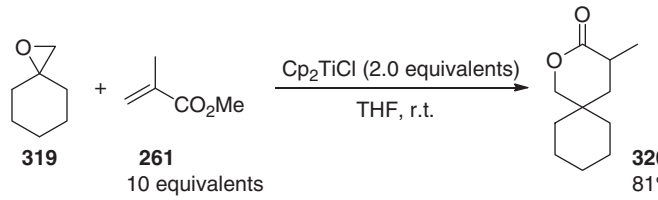
Scheme 26 Reproduced from Fernández-Mateos, A.; Mateos Burón, L.; Rabanedo Clemente, R.; Ramos Silva, A. I.; González, R. *Synlett* **2004**, 2553–2557.



Scheme 27 Reproduced from Gansäuer, A.; Lauterbach, T.; Geich-Gimbel, D. *Chem. Eur. J.* **2004**, *10*, 4983–4990.

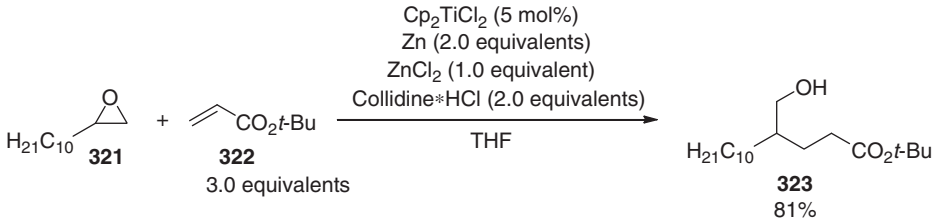
8.20.5.2.3 Intermolecular reductive couplings

RajanBabu and Nugent have reported Cp_2TiCl-mediated intermolecular reductive couplings of epoxide **319** with α,β-unsaturated ester **261**, furnishing spirolactone **320** (equation 105).[133] To achieve good yield, large excess amounts of the unsaturated ester was required.

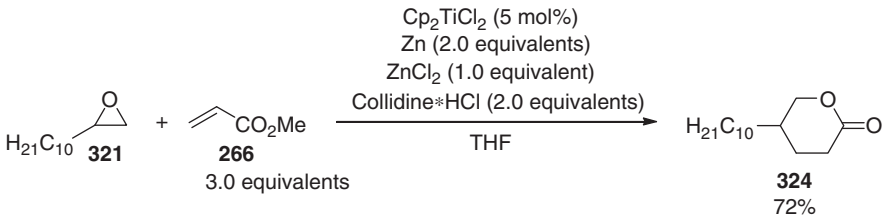


(105)

Cp_2TiCl_2-catalyzed reductive couplings occurred effectively by the employment of an appropriate proton source such as collidine hydrochloride.[134] By choice of the alkoxy moiety of the ester, different types of coupling products could be obtained. For example, while the reaction using *tert*-butyl acrylate **322** gave δ-hydroxyester **323**, that of methyl acrylate **266** produced the corresponding lactone **325** (equations 106 and 107).

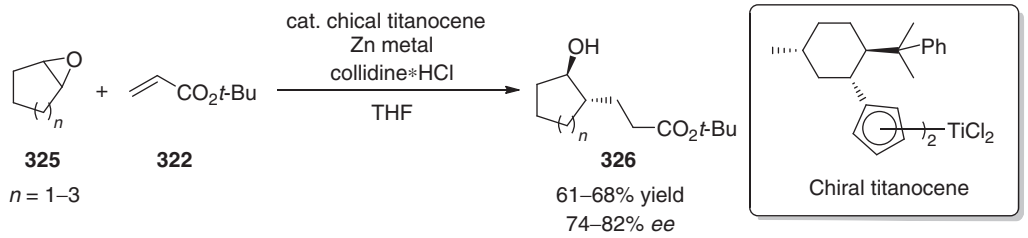


(106)



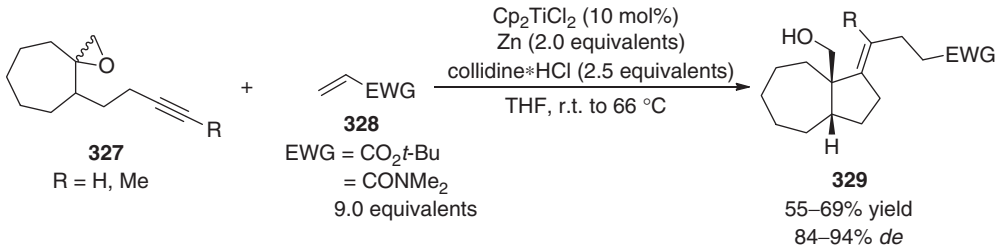
(107)

In 1999, the titanocene-catalyzed enantioselective reaction using epoxides was reported.[135] This is the first example of a transition metal-catalyzed enantioselective radical cyclization using epoxides, such as **325** (**Scheme 28**).



Scheme 28 Reproduced from Friedrich, J.; Dolg, M.; Gansäuer, A.; Geich-Gimbel, D.; Lauterbach, T. *J. Am. Chem. Soc.* **2005**, *127*, 7071–7077.

Tandem reactions including intramolecular reductive cyclizations of epoxides bearing an alkyne moiety and successive intermolecular radical coupling with α,β-unsaturated carbonyl compounds have been reported.[136] The synthesis of tetrasubstituted alkenes **329** was accomplished by this kind of transformation stereoselectively (**Scheme 29**).

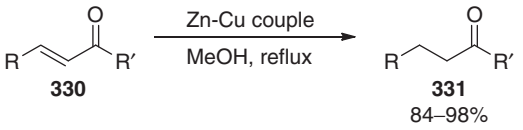


Scheme 29 Reproduced from Gausäuer, A.; Pierobon, M.; Bluhm, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3206–3208.

8.20.5.3 Other Metal-Mediated Reductions

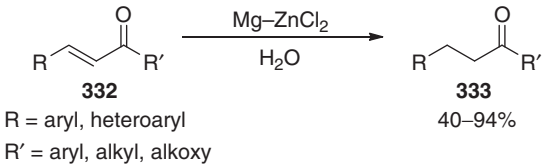
8.20.5.3.1 Zinc-mediated reductions

Zinc metal is one of the most popular reducing reagents in organic synthesis. However, activation procedures are required in almost cases since the surface of commercially available zinc metal is sometimes oxidized. The procedure using Zn–Cu couple under methanol reflux achieved selective 1,4-reduction of α,β-unsaturated carbonyl compounds.[137] This reaction system reduced various α,β-unsaturated carbonyl compounds **330** to give the corresponding saturated carbonyl compounds **331** in quite high yields (equation 108).



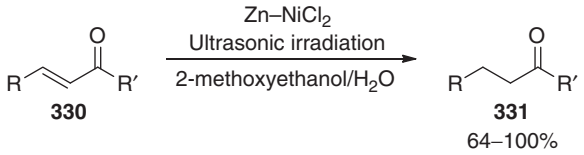
(108)

Boruah and coworkers reported Mg–$ZnCl_2$-mediated selective reduction of α,β-unsaturated carbonyl compounds **332** in aqueous medium.[84] This method provides the *in situ* generation and utilization of an activated form of zinc in aqueous medium (Scheme 30).

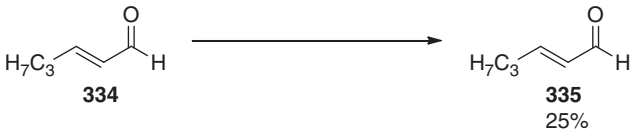


Scheme 30 Reproduced from Saikia, A.; Barthakur, M. G.; Boruah, R. C. *Synlett* **2005**, 523–525.

Another reduction system has been reported by using Zn–$NiCl_2$ (equation 109).[138] It is remarkable that selective 1,4-reduction of α,β-unsaturated aldehyde **334** was successful although the yield was low (equation 110). Some model experiments presume that the first step probably involves the generation of low-valent nickel on the surface of zinc.

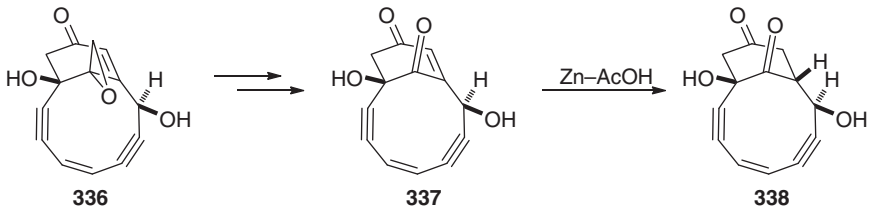


(109)



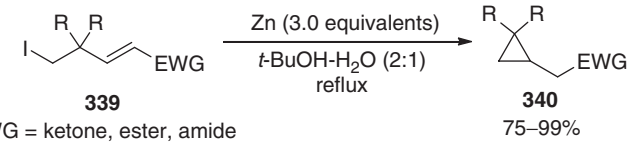
(110)

Danishefsky has achieved total synthesis of core analogs of calicheamicin–esperamin, which have DNA cleavage properties.[139] Selective 1,4-reduction using Zn activated by AcOH was employed in one step of the preparation of **338** (Scheme 31).



Scheme 31 Reproduced from Mantlo, N. B.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 2781–2783.

Zinc was also activated by *t*-BuOH, and 3-*exo*-trig cyclization using 2-iodoethyl-substituted olefins **319** occurred smoothly (Schemes 31 and 32).[140]

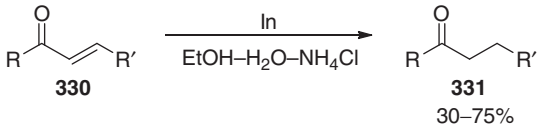


Scheme 32 Reproduced from Sakuma, D.; Togo, H. *Synlett* **2004**, 2501–2504.

8.20.5.3.2 Indium-mediated reductions

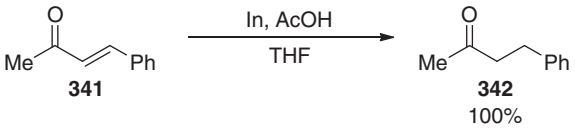
Indium metal has also a potential as a reducing reagent because indium resembles magnesium and zinc in several respects including low first ionization potential. In spite of the fact, there are a few examples of indium metal employed as a reductant, but α,β-unsaturated carbonyl compounds could be reduced readily because of their high activity.

Reductions of various α,β-unsaturated carbonyl compounds proceeded to give the corresponding saturated carbonyl compounds in moderate to good yields (equation 111).[141]

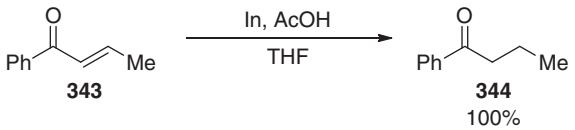


(111)

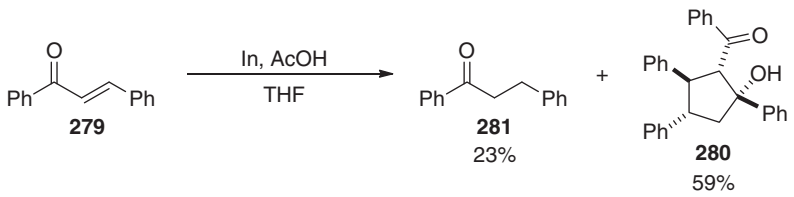
A similar reaction using indium metal assisted by the addition of acetic acid has been reported by Moody et al.[142] Although benzalacetone **341** and *E*-1-phenyl-2-buten-1-one **334** were reduced quantitatively, a considerable amount of dimerized product **280** was obtained along with 23% yield of the desired ketone **281** in the reaction of *trans*-chalcone **279** (equations 112–114). From these results, the indium-mediated reduction includes SET since such 'dimers' have been noted previously in the reduction of chalcone using samarium diiodide,[120b] zinc,[143] or electrochemistry.[144,120b]



(112)



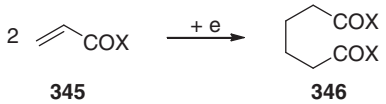
(113)



(114)

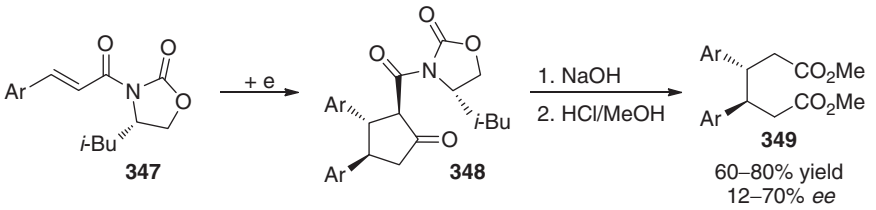
8.20.5.4 Electroreductive Hydrodimerizations

Electroreduction is one of the most clean reductive methods since no metal salt is generated during the course of the reaction. It is mainly employed in hydrodimerization of acyclic acid derivatives, and in particular, electroreductive hydrocoupling of α,β-unsaturated compounds **345** is well-known as a practical method for the synthesis of adipic acid derivatives **346** (equation 115).[145]



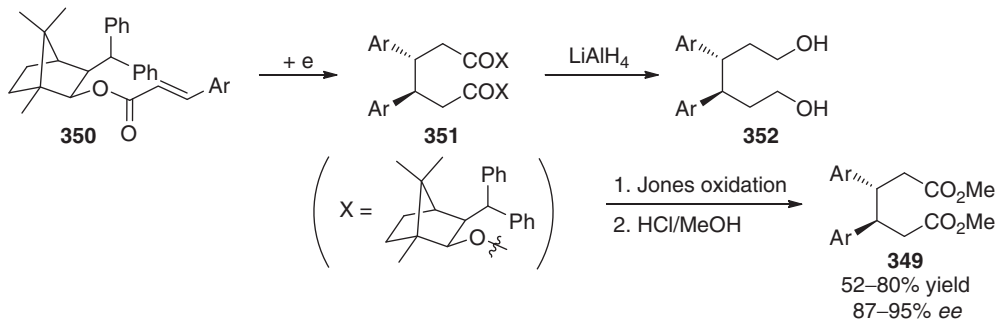
(115)

In 1994, Kise has reported electroreductive intermolecular hydrocouplings of chiral *N*-*trans*-cinnamoyl-2-oxazolidiones **347**.[146] Coupling products **348** could be easily transformed to DL-3,4-diaryladipic acid derivatives **349** (Scheme 33). The enantioselectivity, however, was low to moderate.



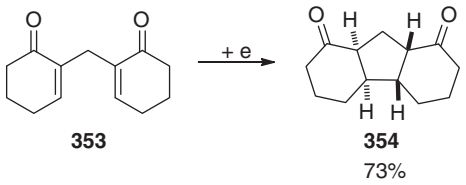
Scheme 33 Reproduced from Kise, N.; Echigo, M.; Shono, T. *Tetrahedron Lett.* **1994**, *35*, 1897–1900; Utley, J. H. P.; Güllü, M.; Motevalli, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1961–1970, and Kise, N.; Mashiba, S.; Ueda, N. *J. Org. Chem.* **1998**, *63*, 7931–7938.

The selectivity was improved by the employment of [(*1R*)-exo]-3-exo-(diphenylmethyl)borneol as a chiral auxiliary (Scheme 34).[147]



Scheme 34 Reproduced from Kise, N.; Iwasaki, K.; Tokieda, N.; Ueda, N. *Org. Lett.* **2001**, *3*, 3241–3244, and Kise, N.; Iitaka, S.; Iwasaki, K.; Ueda, N. *J. Org. Chem.* **2002**, *67*, 8305–8315.

Intramolecular electroreductive hydrodimerization could also occur. For example, α,β-unsaturated ketone **353** gave tricycle product **354** in 73% yield as a single isomer (equation 116).[121]



(116)

8.20.6 Reductive Aldol Reaction via 1,4-Reduction of Enones

Various important types of reactions have been developed since the discovery of the aldol reaction nearly 150 years ago, because aldol products (β-hydroxy carbonyl compounds) can be excellent building blocks for natural products, drugs, and agrichemicals, etc.[148] The reductive coupling of α,β-unsaturated carbonyl compounds with aldehydes or ketones, termed the 'reductive aldol reaction', has been the topic of intensive investigation. The reaction outline is generation of an enolate nucleophile via 1,4-reduction of an enone followed by reaction with carbonyl compounds.

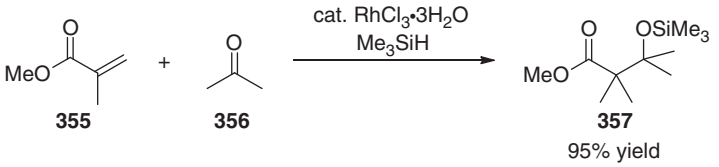
8.20.6.1 Transition Metal-Catalyzed Reaction with a Stoichiometric Metal Hydride Source

The combination of a transition metal catalyst and a metal hydride are quite effective in 1,4-reduction of enones. Since various carbonyl compounds such as aldehydes and ketones are compatible with the 1,4-reduction conditions, reductive aldol reactions promoted by various transition metal catalysts (Rh, Cu, Co, Ni, Pd, and Ir) have been studied strenuously.

8.20.6.1.1 Rhodium complex-catalyzed reductive aldol reaction

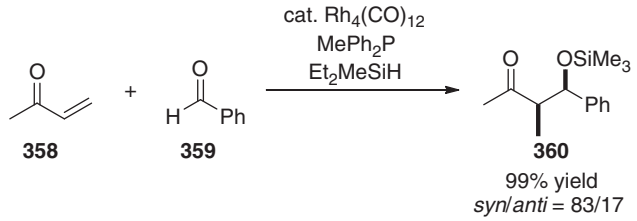
Revis and coworkers reported the $RhCl_3$-catalyzed reductive aldol reaction of α,β-unsaturated esters with ketones using trimethylsilane as a reducing reagent. The reaction of methyl methacrylate (**355**), acetone (**356**), and trimethylsilane with a catalytic

amount of $RhCl_3 \cdot 3H_2O$ took place at room temperature to give the corresponding aldol product **357** in 95% yield (equation 117).[149]



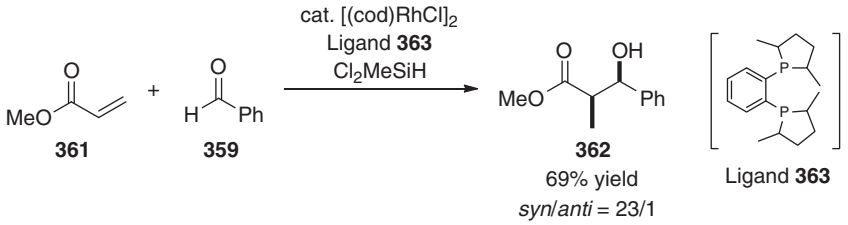
(117)

The reaction of methyl vinyl ketone (**358**), benzaldehyde (**359**), and diethylmethylsilane in the presence of $Rh_4(CO)_{12}$ catalyst and $MePh_2P$ gave the corresponding aldol product **360** in 99% yield with moderate *syn*-selectivity (equation 118).[150]



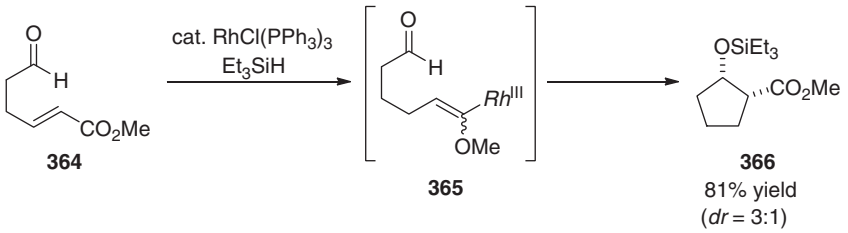
(118)

The combination of $[(cod)RhCl]_2$ and diphosphine ligand **363** catalyzed the reaction of methyl acrylate (**361**) with benzaldehyde (**359**) in the presence of Cl_2MeSiH to afford the aldol product **362** with higher *syn*-selectivity in 69% yield (equation 119).[151] Mechanistic studies employing *in situ* NMR analysis implicated silyl enol ethers as reactive intermediates.[152]



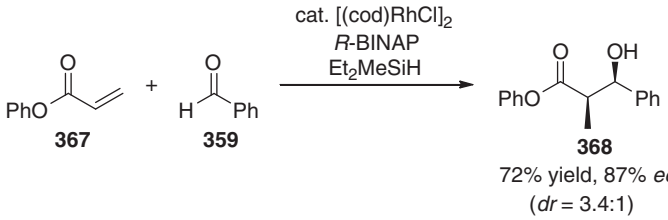
(119)

A rhodium(I) catalyst is also effective for tandem hydrosilylation-intramolecular aldol sequence. The treatment of (*E*)-6-oxo-2-hexenoate (**364**) with triethylsilane in the presence of Wilkinson's catalyst afforded the silylated cyclopentanol **366** in 81% yield with moderate diastereoselectivity (equation 120).[153]



(120)

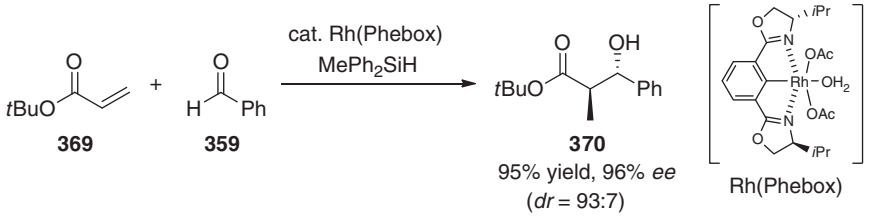
The first enantioselective reductive aldol reaction was achieved by Morken and coworkers. The reaction between phenyl acrylate (**367**), benzaldehyde (**359**), and Et_2MeSiH was catalyzed by Rh–*R*–BINAP to afford aldol product **368** in high enantioselectivity and moderate diastereoselectivity (equation 121).[154]



(121)

Chiral 2,6-bis(2-oxazolinyl)phenyl skeleton (Phebox) as a C_2-symmetric N–C–N ligand exhibited high efficiency for *anti*-selectivity and enantioselectivity. Nishiyama and coworkers reported that a catalytic amount of Rh(Phebox) complex accelerated

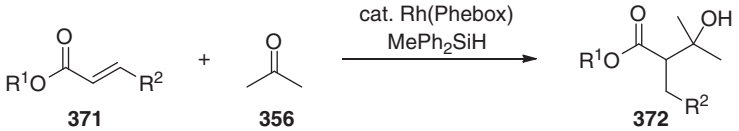
the reductive aldol reaction of *tert*-butyl acrylate (**369**) with benzaldehyde (**359**) in the presence of $MePh_2SiH$ to give the *anti*-aldol product **370** in 95% yield with high enantioselectivity (equation 5).[155] Wu and coworkers carried out density functional theory calculations (B3LYP) to reveal the mechanism and stereochemistry of Rh(Phebox)-catalyzed asymmetric reductive aldol reaction (equation 122).[156]



369 **359** **370**
95% yield, 96% *ee*
(*dr* = 93:7)
Rh(Phebox)

(122)

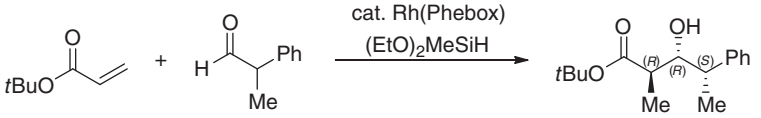
The Rh(Phebox) also catalyzed the enantioselective reductive aldol reaction of acetone (**356**) with cinnamates and crotonates **371** as acceptors to give the corresponding products **372** with high enantioselectivities (equation 123).[157]



371
R^2 = Me, Aryl
356
372
up to 98% *ee*

(123)

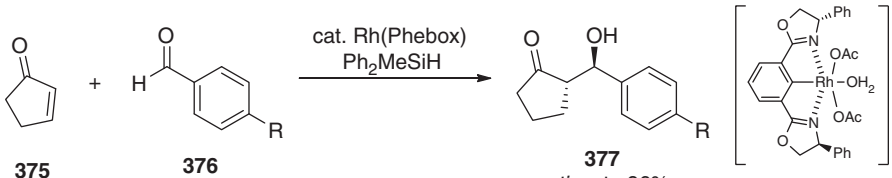
In asymmetric synthesis of stereotriads by reductive aldol reaction of 2-phenylpropionaldehyde (**369**) with acrylate derivatives **373**, Rh(Phebox) led to high *α,β-anti* diastereoselectivity and high enantioselectivity (equation 124).[158]



369 **373** **374**
83% yield, 99% *ee*
(*dr* = 88:12 (others))

(124)

α,β-Unsaturated ketones were also applicable and the reductive coupling reaction of cyclopent-2-enone (**375**) and aromatic aldehydes **376** was achieved by Rh(Phebox) catalyst with diphenylmethylsilane as a hydride donor to give the corresponding *β*-hydroxyketones **377** in high *anti*-selectivity with high enantioselectivity (equation 125). The reactions using other ketones such as six-membered cyclic ketones and acyclic ketones were also successful.[159]

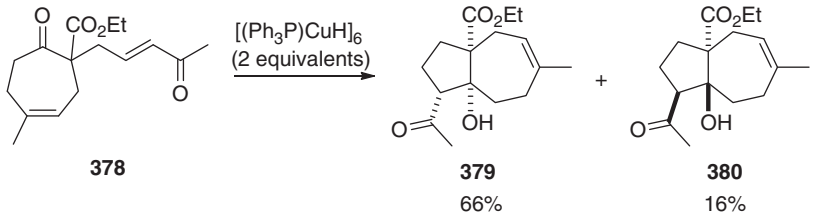


375 **376** **377**
anti up to 96%
ee up to 93%
Rh(Phebox)

(125)

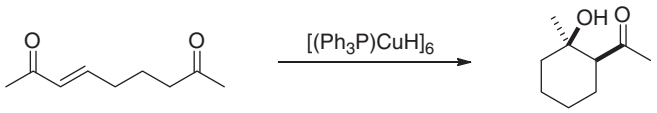
8.20.6.1.2 Copper complex-catalyzed reductive aldol reaction

A tandem reaction of conjugate reduction and intramolecular aldol cyclization using Stryker's reagent ($[(Ph_3P)CuH]_6$)[160] produced diastereomers **379** and **380** in 66% and 16% yields, respectively, from the ketoester **378** (equation 126).[161] Acyclic diketone **381** was also applicable to give the corresponding cyclic compound **382** in 80% yield with high stereoselectivity (equation 127).[162] This method was applied to the total synthesis of iphionane sesquiterpenoid lucinone. The treatment of substrate **383** with $[(Ph_3P)CuH]_6$ proceeded as anticipated to afford stereoselectively a quantitative yield of alcohol **384**, in which four of five stereocenters in lucinone (**385**) have been installed (**Scheme 35**).[163]



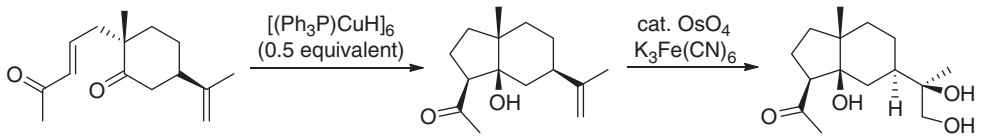
378 **379** 66% **380** 16%

(126)



381 **382** 80%

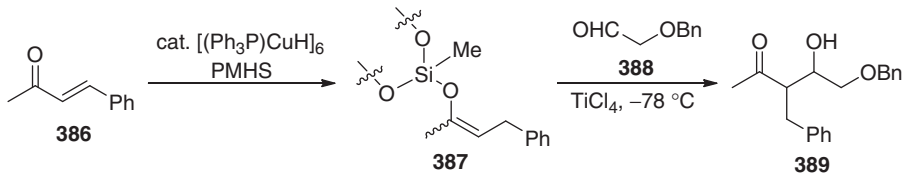
(127)



383 **384** 99% **385** Lucinone

Scheme 35 Reproduced from Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. *Tetrahedron Lett.* **2001**, *42*, 4091–4093.

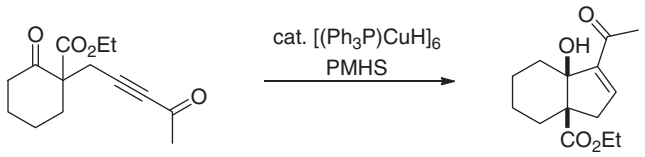
1,4-Reduction of enone **386** with a catalytic amount of $[(Ph_3P)CuH]_6$ and PMHS as a reducing reagent followed by aldol reaction of aldehyde **388** was reported. Without the isolation of silyl enolate intermediate **387**, the successive aldol reaction with **388** was promoted by the addition of $TiCl_4$ to give the corresponding product **389** in 83% yield (Scheme 36).[164]



386 **387** **389**

Scheme 36 Reproduced from Lipshutz, B. H.; Chrisman, W.; Noson, K.; *et al. Tetrahedron* **2000**, *56*, 2779–2788.

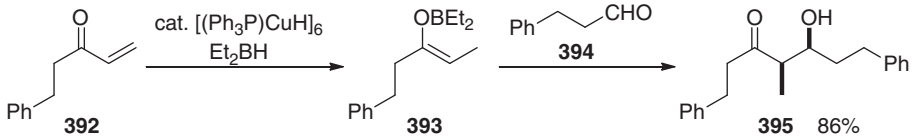
Alkynones were also applicable in $[(Ph_3P)CuH]_6$-catalyzed reductive aldol reactions using PMHS. In the intramolecular reaction using alkynone **390**, successive aldol reaction took place without Lewis acid assistance to afford the product **391** diastereoselectively (equation 128).[165]



390 **391** 56%

(128)

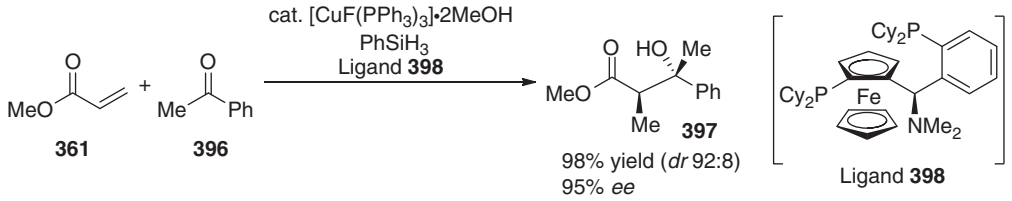
In the $[(Ph_3P)CuH]_6$-catalyzed reductive aldol reaction, the use of a dialkylborane instead of PMHS gives the corresponding *syn* aldol product selectively. The 1,4-hydroboration of acyclic enone **392** using Cu catalyst and Et_2BH gave (*Z*)-boron enolate **393**. The aldol reaction of enolate **393** with aldehyde **394** afforded *syn* aldol product **395** in 86% yield (Scheme 37).[166]



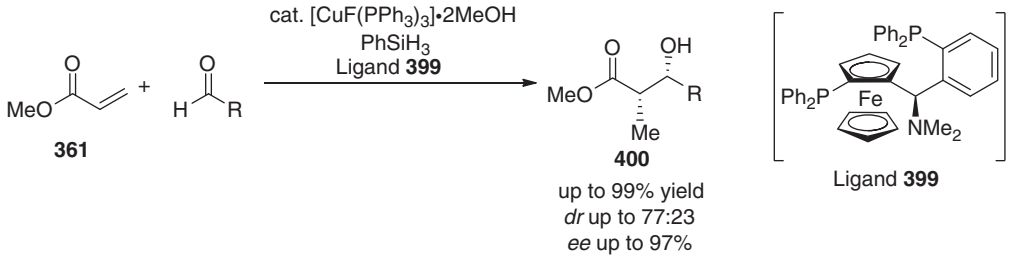
392 **393** **395** 86%

Scheme 37 Reproduced from Lipshutz, B. H.; Papa, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 4580–4582.

Riant and coworkers reported highly diastereo- and enantioselective copper-catalyzed reductive aldol reactions of ketones with methyl acrylate. The ligand **398**, which contains a 1,5-diphosphane unit and hence is capable of forming an eight-membered chelate ring with a metal, is the most effective. The reaction of methyl acrylate (**361**) with acetophenone (**396**) using a catalytic amount of $[CuF(PPh_3)_3] \cdot 2MeOH$, ligand **398**, and stoichiometric quantity of phenylsilane gave *β*-hydroxyester **397** in 98% yield, 95% *ee* (equation 129).[167] The diastereo- and enantioselective reductive aldol reaction using aldehydes was also developed, in which ligand **399** showed high selectivity (equation 130).[168]

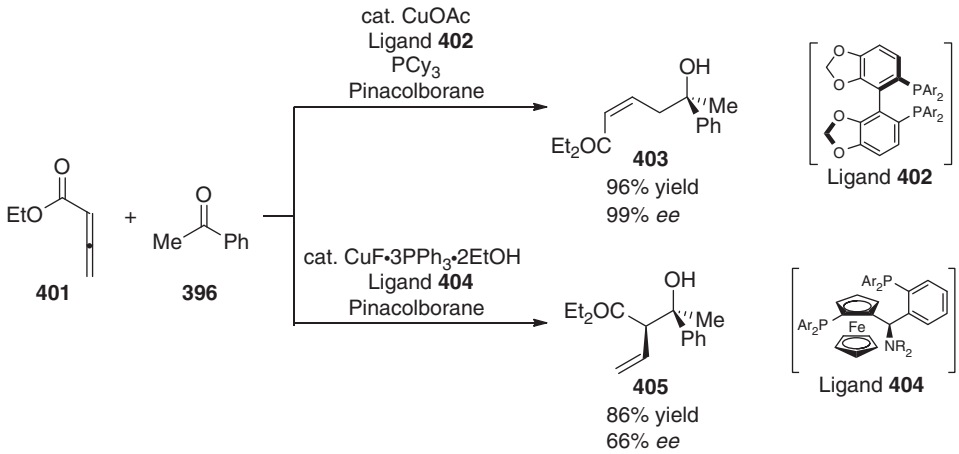


(129)



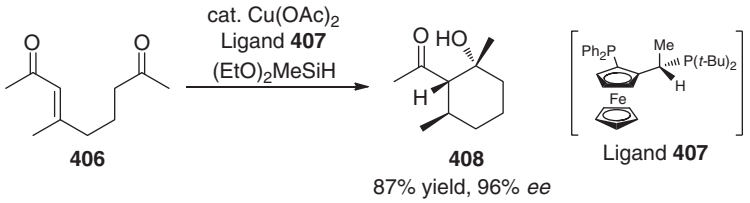
(130)

A catalytic asymmetric reductive aldol reaction of allenic esters with ketones was developed by Shibasaki and coworkers (**Scheme 38**). Two distinct constitutional isomers were selectively produced depending on the reaction conditions. A combination of CuOAc–**402**–PCy_3 as a catalyst system accelerated the reaction of allenic ester **401** with acetophenone (**396**) to predominantly give *γ-cis*-product **403** in high yield with excellent enantioselectivity. The reaction was also applicable to both aromatic and aliphatic ketones, including unsaturated ketones. However, a CuF–**404** complex produced *α*-aldol product **405** diastereo- and enantioselectively. The new Taniaphos derivative **404**, containing di(3,5-xylyl)phosphine and morpholine units, produced optimum results in the *α*-selective reaction.[169]



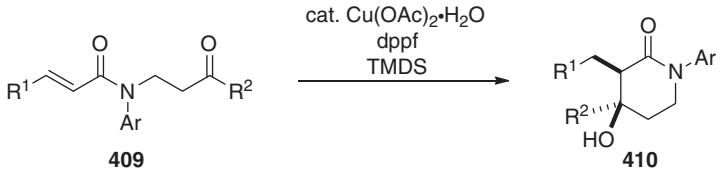
Scheme 38 Reproduced from Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440–14441, and Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403–1407.

The intramolecular reductive aldol reaction of *β,β*-disubstituted-*α,β*-unsaturated ketones bearing a ketone function was promoted by CuH ligated by ligand **407** in the presence of diethoxymethylsilane to give single diastereomer **408** in 87% yield with 96% *ee,* in which three newly adjacent chiral centers were created (equation 131).[170]

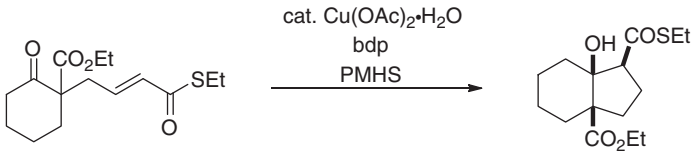


(131)

Several enantio- or diastereoselective reductive aldol cyclizations were reported. The reaction of α,β-unsaturated amides **409** with a ketone moiety using a Cu(II)-catalyst, dppf, and 1,1,3,3-tetramethylhydroxysilane (TMDS) produced 4-hydroxypiperidin-2-ones **410** in highly diastereoselective fashion (equation 132).[171] Keto-enethioate **411** also gave cyclization product **412** in 81% yield diastereoselectively, in which the combination of $Cu(OAc)_2$, 1,2-bis(diphenylphosphino)benzene (bdp), and PMHS was effective (equation 133).[19]

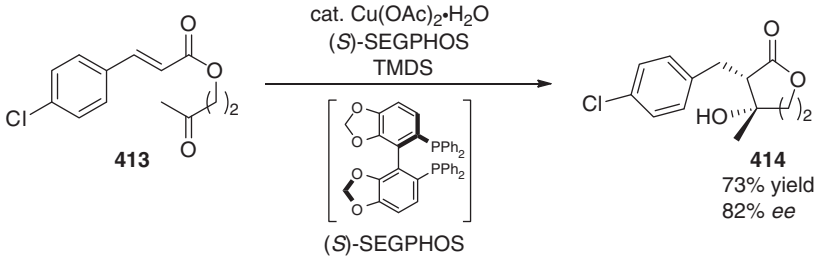


(132)



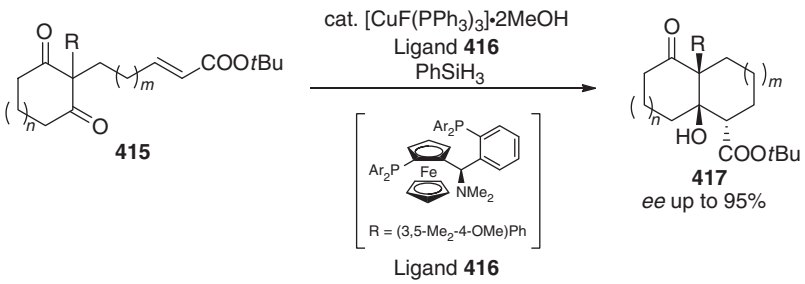
(133)

Copper bisphosphine complexes prepared from $Cu(OAc)_2 \cdot H_2O$ and (*S*)-SEGPHOS catalyzed the intramolecular reductive aldol reaction of α,β-unsaturated esters bearing ketone moiety **413**, affording five- and six-membered β-hydroxylactones **414** in high stereoselectivites (equation 134).[172]

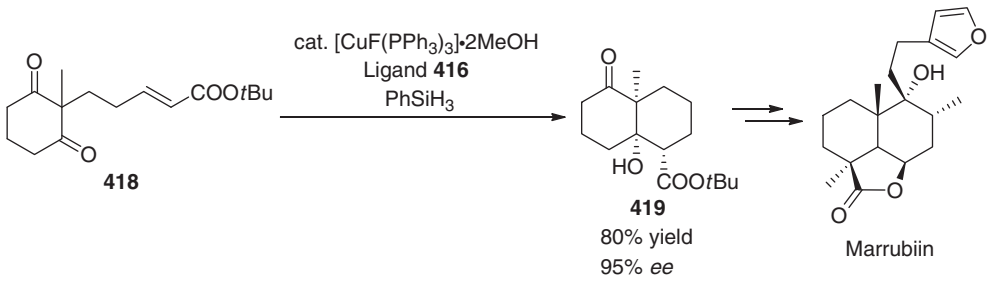


(134)

The reaction of diketo-esters **415** smoothly produced ring-fused compounds **417** stereoselectively (equation 135). This method was used for the synthesis of the key intermediate of marrubiin, a natural diterpene extracted from *Marrubium vulgare* L. (Scheme 39).[173]

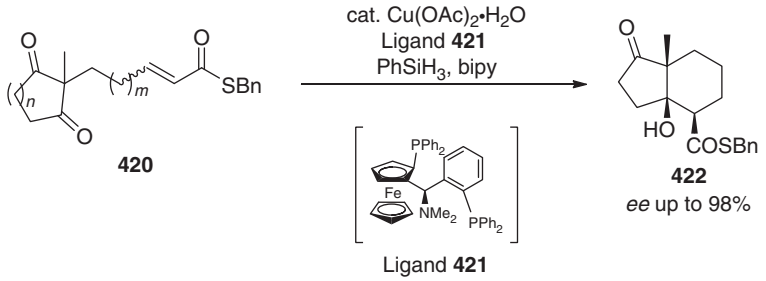


(135)



Scheme 39 Reproduced from Deschamp, J.; Hermant, T.; Riant, O. *Tetrahedron* **2012**, *68*, 3457–3467.

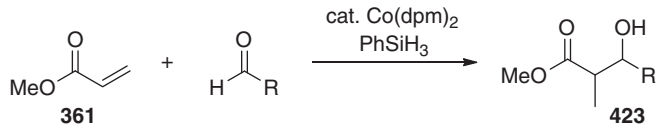
Reductive aldol cyclizations using diverse α,β-unsaturated thioesters with ketones **420** were also achieved by a similar catalyst system (equation 136).[174]



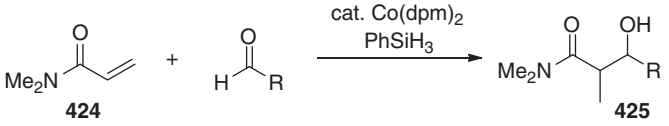
(136)

8.20.6.1.3 Cobalt complex-catalyzed reductive aldol reaction

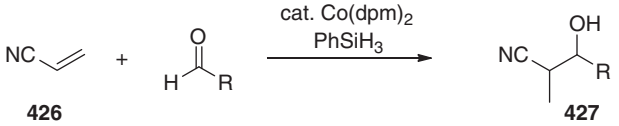
A catalytic amount of bis(dipivaloylmethanato)cobalt(II) {Co(dpm)$_2$} catalyzed the reductive aldol reaction of aldehydes with either methyl acrylate **361**, acrylamide **424**, or acrylonitrile (**426**) using phenylsilane as a reducing reagent, but with poor regioselectivity (equations 137–139).[175]



(137)

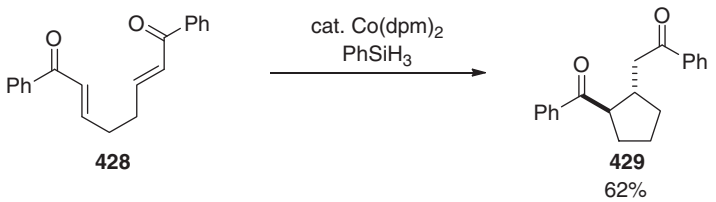


(138)

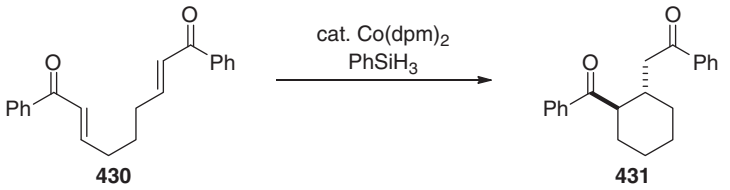


(139)

Krische and coworkers found that the combination of Co(dpm)$_2$ catalyst and phenylsilane accelerated highly diastereoselective inatramolecular version of the addition. This reaction system exhibited high level of *anti*-diastereoselectivety, and is viable for both five- and six-membered ring formations (equations 140 and 141).[176]

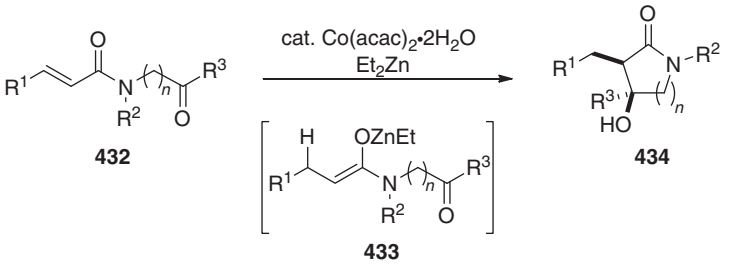


(140)



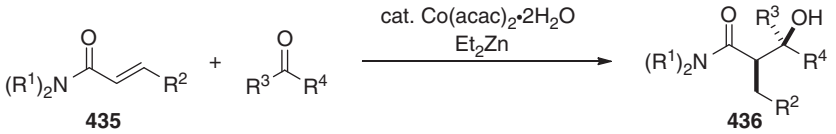
430 **431** 73% (141)

In the presence of diethylzinc as a stoichiometric reductant, $Co(acac)_2$ catalyst accelerated diastereoselective reductive aldol cyclizations of α,β-unsaturated amides **432** possessing a keto moiety, in which zinc enolate **433** was a key intermediate (equation 142).[177]

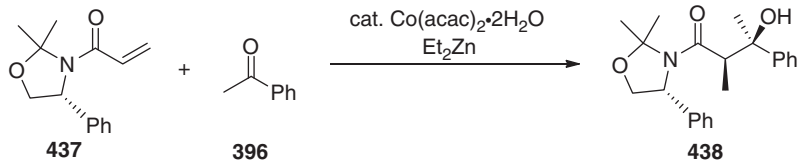


432 **433** **434** (142)

The intermolecular reaction of α,β-unsaturated amides **434** with ketones under similar conditions also took place to afford the corresponding β-hydroxy amides **436** with high diastereoselectivities (equation 143).[178] The use of a readily available oxazolidine as a chiral auxiliary imparted high levels of asymmetric induction (equation 144).[179]



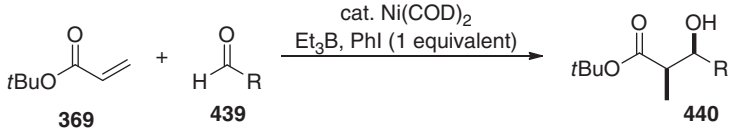
435 **436** (143)



437 **396** **438** 73% yield *dr* = 11:1 (144)

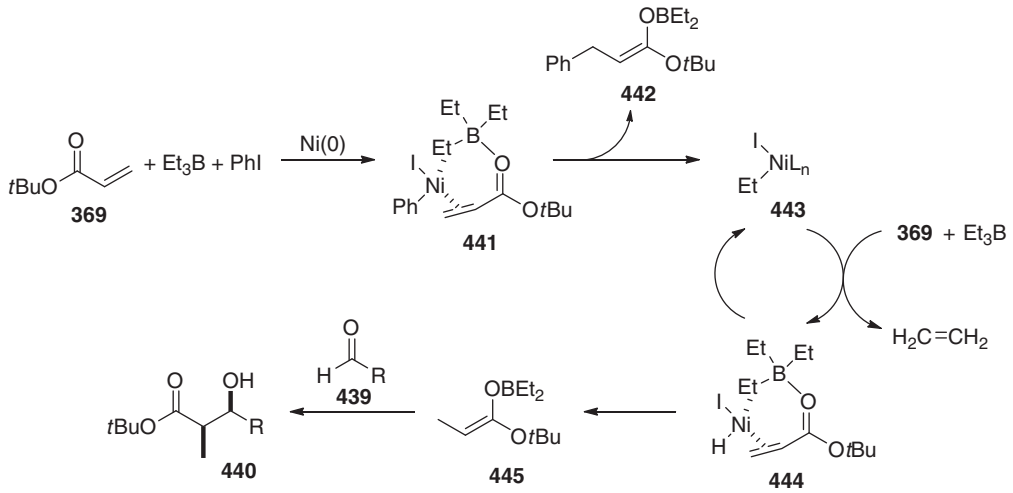
8.20.6.1.4 Nickel complex-catalyzed reductive aldol reaction

In nickel-catalyzed reductive aldol reactions, the general metal hydride sources are alkyl metals. The reaction of acrylate **369** with aldehydes **439** was accelerated by a nickel catalyst in the presence of Et_3B and iodobenzene (equation 145). Iodobenzene was required for the generation of nickel hydride as the actual reducing reagent (Scheme 40). Oxidative addition of PhI to Ni(0) and coordination of acrylate **369** and Et_3B will afford intermediate **441**. Reorganization of the intermediate to an ethyl(iodo)-nickel species **443** and boron enolate **442** may proceed by a migratory insertion and transmetalation sequence. The resulting ethyl(iodo)nickel species **443** then loses ethylene to generate nickel hydride–Et_3B–**369** complex **444**. Reorganization of **444** to boron enolate **445** is accompanied by the regeneration of ethyl(iodo)nickel species **443**. *Syn* aldol addition of **445** with aldehyde **439** then provides compound **440**.[180]



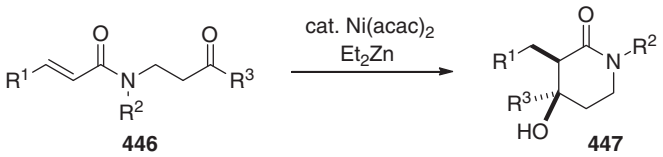
369 **439** **440** (145)

The combination of diethylzinc and $Ni(acac)_2$ catalyst effectively achieved the reductive aldol cyclization of substrates containing an α,β-unsaturated carbonyl moiety tethered to a ketone through either amide **446** or ester **448** (equations 146 and 147).

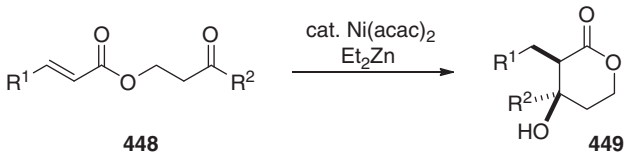


Scheme 40 Reproduced from Chrovian, C. C.; Montgomery, J. *Org. Lett.* **2007**, *9*, 537–540.

In these reactions, diethylzinc acts as a stoichiometric hydride source, formally delivering a hydride to the β-position of the α,β-unsaturated carbonyl component of the cyclization precursor, leading to the formation of β-hydroxylactams **447** and β-hydroxylactones **449** with good to high levels of diastereoselection.[181]

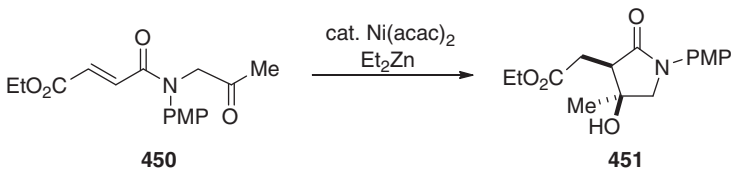


(146)

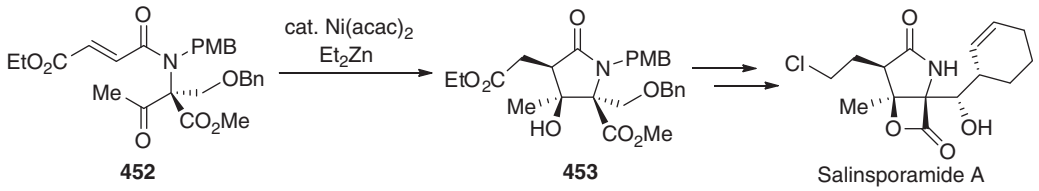


(147)

The sequential nickel-catalyzed reductive aldol cyclization–lactonization reaction of substrate **450** using Et_2Zn as a reducing reagent gave β-hydroxy-γ-lactam **451** diastereoselectively (equation 148). This reaction system was applied to a short formal synthesis of salinsporamide A, a potent 20S proteasome inhibitor and anti-cancer compound (**Scheme 41**).[182]



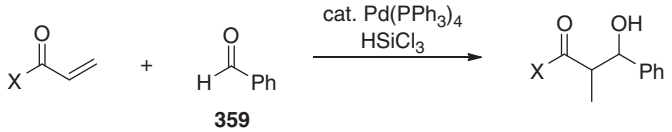
(148)



Scheme 41 Reproduced from Margalef, I. V.; Rupnicki, L.; Lam, H. W. *Tetrahedron* **2008**, *64*, 7896–7901.

8.20.6.1.5 Palladium complex-catalyzed reductive aldol reaction

$Pd(PPh_3)_4$ catalyzed reductive aldol reactions of *tert*-butyl acrylate with aromatic aldehydes using trichlorosilane produce the corresponding product **454** with moderate *syn*-selectivity. In contrast, the reductive aldol reaction using *N*,*N*-dimethylacrylamide afforded *anti*-**455** in moderate selectivity (equation 149).[183]

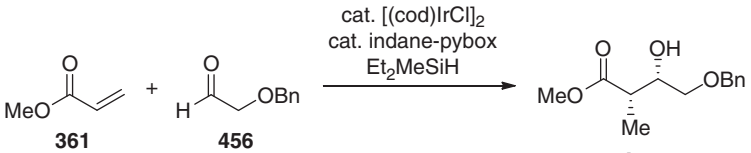


X = O*t*Bu (**454**) 37% yield, *syn*/*anti* = 72:28
NMe_2 (**455**) 87% yield, *syn*/*anti* = 32:68

(149)

8.20.6.1.6 Iridium complex-catalyzed reductive aldol reaction

A catalytic amount of $[(cod)IrCl]_2$ and indane-pybox converted Et_2MeSiH, methyl acrylate, and different aldehydes to the corresponding reductive aldol adducts with high enantio- and diastereocontrol. This reaction system was effectively applied to a large scale synthesis. The reaction using methyl acrylate (**361**) and α-benzyloxy acetoaldehyde (**456**) was carried out in a 35 mmol scale with 1 mol% of Ir catalyst and 3 mol% of ligand to give the corresponding product **457** in 59% yield, 96% *ee* (equation 150).[184]

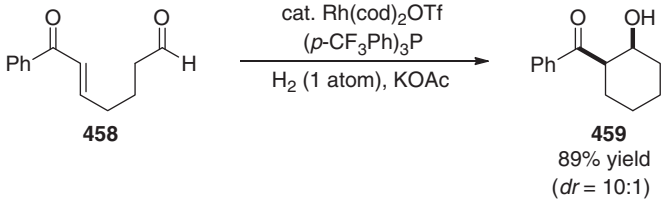


59%, 96% *ee*
(9.5:1 = *syn*/*anti*)
[35 mmol scale]

(150)

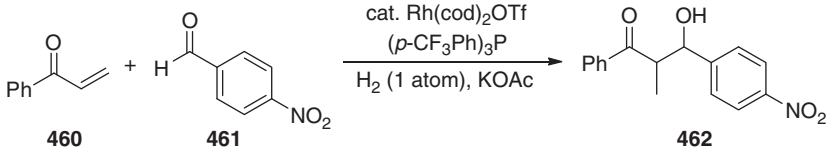
8.20.6.2 Hydrogenative Reductive Aldol Reaction

The conjugate reduction of enones under hydrogenation conditions is well-known as a convenient, mild, and chemoselective reaction.[1,185] The reductive generation of enolates from enones under hydrogenative conditions is a mild and atom economical means of enolate generation, which lead to the aldol products. In 2002, Krische and coworkers reported the first reductive aldol reaction under hydrogenative conditions, which is a catalytic protocol for the reductive generation of transition metal enolates using elemental hydrogen as terminal reductant. The combination of $Rh(cod)_2OTf$ and $(p\text{-}CF_3Ph)_3P$ catalyzed the reductive aldol cyclization of enone bearing formyl group **458** in the presence of a catalytic amount of KOAc as a base under 1 atom of dihydrogen to afford *syn*-aldol cycloreduction product **459** in 89% yield (equation 151). The intermolecular reaction between the enone **460** and the aldehyde **461** also proceeded to give the product **462** in 92% yield with moderate diastereoselectivity (equation 152).[186]



89% yield
(*dr* = 10:1)

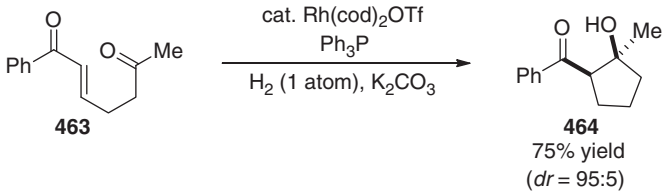
(151)



92% yield

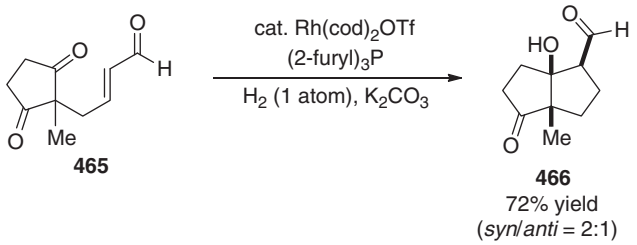
(152)

In the $Rh(cod)_2OTf$-catalyzed reductive aldol cyclization using ketone partner **463**, Ph_3P as a ligand and K_2CO_3 as a base was effective to give the corresponding cyclic product **464** in 75% yield with high diastereoselectivity (equation 153).[187]



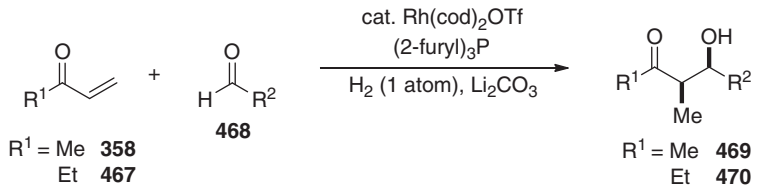
(153)

The intramolecular reductive aldol reaction of keto-enal **465** was also achieved by the Rh catalyst, which is the first catalytic cross-aldolization of metallo-aldehyde enolates with ketone acceptors (equation 154).[188]

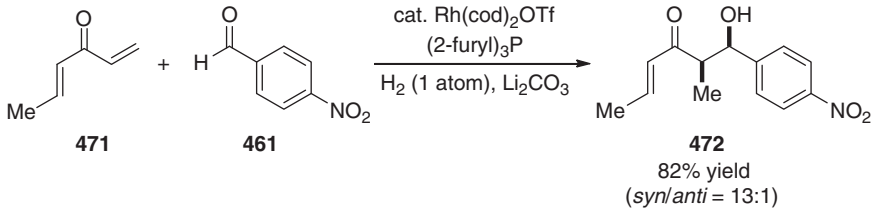


(154)

A tri(2-furyl)phosphine-ligated rhodium catalyst enabled the formation of aldol products **469** and **470** with high levels of *syn*-diastereoselectivity via the catalytic hydrogenation of methyl vinyl ketone (**358**) and ethyl vinyl ketone (**467**), respectively, in the presence of various aldehydes (equation 155). In this reaction system, tri(2-furyl)phosphine was found to contribute to the increase of diastereoselectivity.[189] The divinyl ketone **471** was also a feasible substrate to give *syn*-diastereoselective aldol product **472** (equation 156).[190]

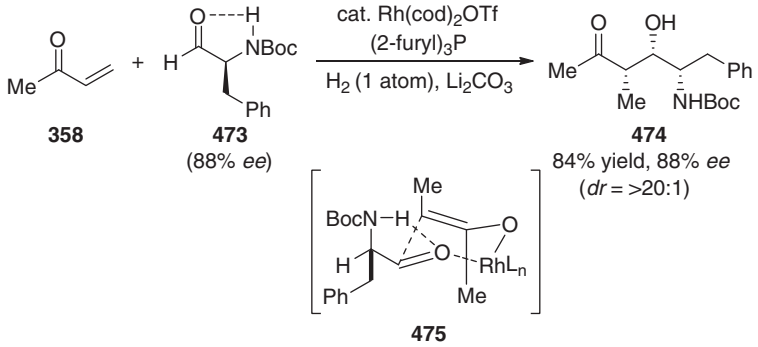


(155)



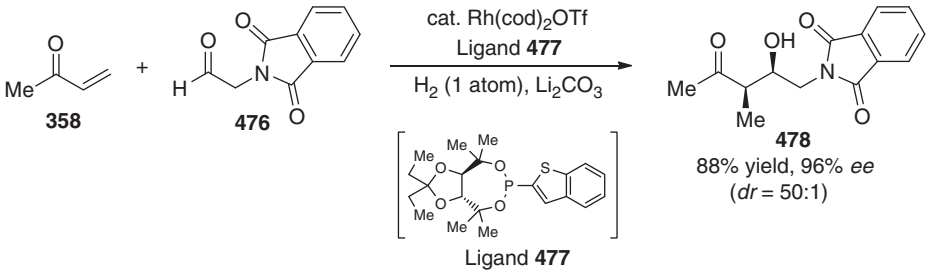
(156)

Rhodium-catalyzed hydrogenation of methyl vinyl ketone and ethyl vinyl ketone in the presence of *N*-Boc-α-aminoaldehydes resulted in reductive C=C coupling to afford aldol products. In this reaction system, asymmetric induction using *N*-Boc-L-phenylalaninal **473** was achieved to give the product **474** in 85% yield, 88% *ee* (equation 157).[191] In transition state **475**, Boc-protected α-amino aldehyde **473** incorporates an internal hydrogen-bond donor in the form of the carbamate N–H to lead high diastereoselectivity.



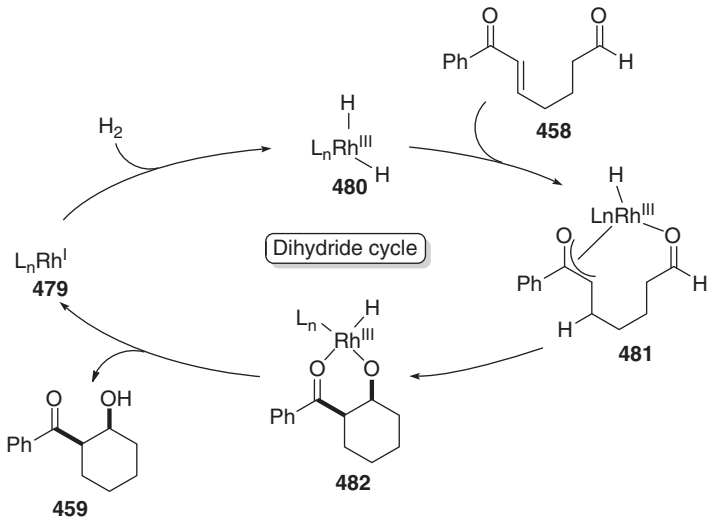
(157)

Hydrogenation of methyl vinyl ketone (**358**) in the presence of aldehyde **476** using cationic rhodium catalysts modified by ligand **477** produced aldol adduct **478** with excellent control of relative and absolute stereochemistry (equation 158). This was the first enantioselective reductive aldol coupling of vinyl ketones.[192]



(158)

Given the effect of basic additives, there are two plausible mechanisms, namely dihydride or monohydride based catalytic cycles.[193] The dihydride catalytic cycle involves four steps: 1. oxidative addition of $L_nRh(I)$ **479** to elemental hydrogen to afford $L_nRh(III)H_2$ **480**, 2. hydrometalation to enone **458** giving Rh–enolate intermediate **481**, 3. addition to the pendent aldehyde to form Rh–aldolate **482**, and 4. oxygen–hydrogen reductive elimination to afford the aldol product **459** along with $L_nRh(I)$ **479** to complete the catalytic cycle (**Scheme 42**).

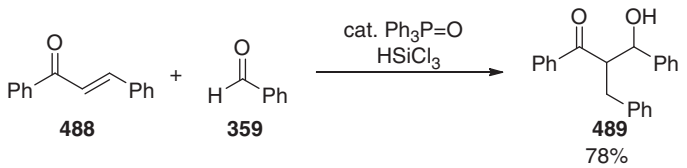


Scheme 42 Reproduced from Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953–3958, and Han, S. B.; Hassan, A.; Krische, M. J. *Synthesis* **2008**, (40), 2669–2679.

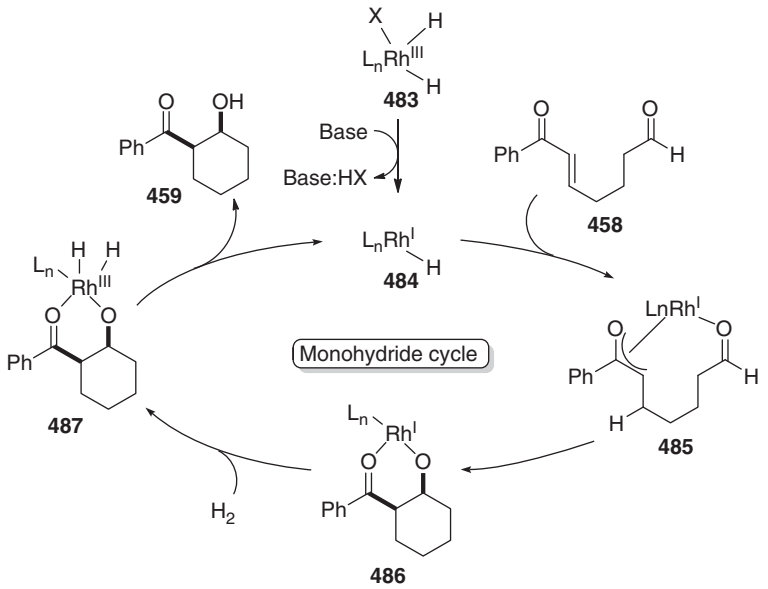
In monohydride catalytic cycle, a base abstracts a proton from dihydride Rh(III) **483** to afford monohydride Rh(I) **484** as an active catalyst. The catalytic cycle consists of four steps: 1. hydrometalation to enone **458** giving Rh–enolate intermediate **485**, 2. addition to the pendent aldehyde to form Rh–aldolate **486**, 3. generation of dihydride Rh–enolate **487** by oxidative addition of hydrogen to Rh–aldolate **486**, and (4) oxygen–hydrogen reductive elimination to afford the aldol product **459** along with monohydride Rh(I) **484** to complete the catalytic cycle (**Scheme 43**).

8.20.6.3 Lewis Base-Catalyzed Reductive Aldol Reaction

The combination of a phosphine oxide base catalyst and trichlorosilane as a reductant effectively mediates reductive aldol reactions between α,β-unsaturated ketones and carbonyl compounds including aldehydes and ketones. Ph_3PO catalyzed the 1,4-reduction of α,β-unsaturated ketone **488** with trichlorosilane and the aldol reaction of the resulting silyl enolate with aldehyde **359** with low diastereoselectivity (equation 159).[194]

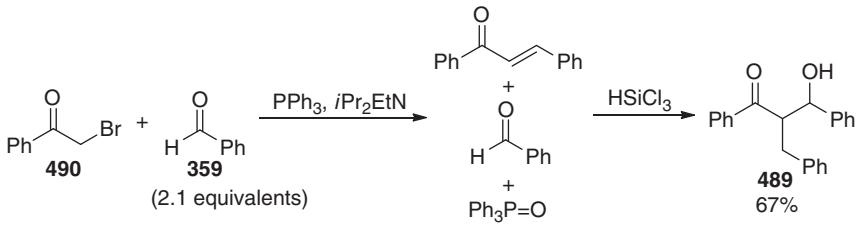


(159)



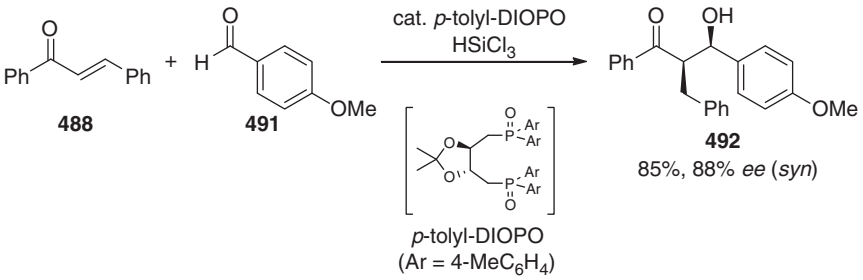
Scheme 43 Reproduced from Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953–3958, and Han, S. B.; Hassan, A.; Krische, M. J. *Synthesis* **2008**, (40), 2669–2679.

A tandem one-pot Wittig/reductive aldol reaction procedure was developed. The byproduct of the Wittig reaction, Ph_3PO, accelerated the subsequent reductive aldol reaction of the produced enone with aldehyde **359** using trichlorosilane (equation 160).[195]



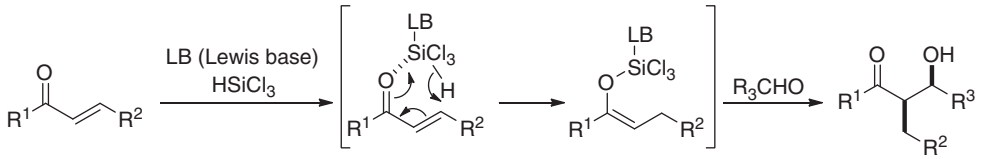
(160)

The *p*-tolyl-substituted DIOPO (*p*-tolyl-DIOPO), which was prepared from an optically pure tartaric acid-derived diiodide and a secondary phosphine oxide, was effective for the reductive aldol reaction of chalcone (**488**) and aldehyde **491** with trichlorosilane (equation 161).[196]



(161)

Scheme 44 illustrates the mechanism of Lewis base-catalyzed reductive aldol reaction using trichlorosilane. First, the accelerated conjugate reduction with a highly coordinated trichlorosilane proceeds via a six-membered transition state with an enone in an s-*cis* conformation to give the (*Z*)-trichlorosilyl enolate exclusively. Next, aldol reaction of the highly coordinated silyl enolate with an aldehyde proceeds with high *syn*-selectivity through a chair-like cyclic transition state.

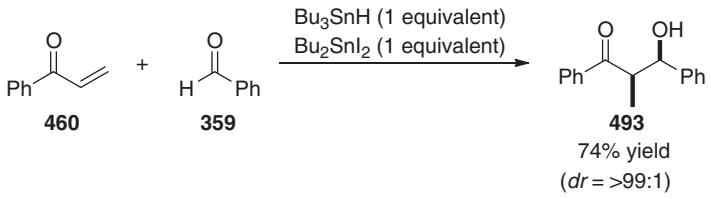


Scheme 44 Reproduced from Ohmaru, Y.; Sato, N.; Mizutani, M.; *et al. Org. Biomol. Chem.* **2012**, *10*, 4562–4570, and Sugiura, M.; Sato, N.; Sonoda, Y.; Kotani, S.; Nakajima, M. *Chem. Asian J.* **2010**, *5*, 478–481.

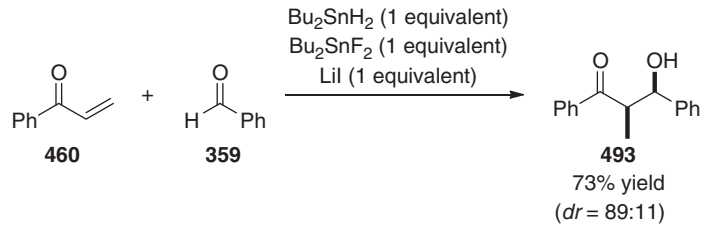
8.20.6.4 Main-Group Metal-Mediated Reductive Aldol Reaction

8.20.6.4.1 Tin hydride mediated reductive aldol reaction

Organotin hydrides appear to act as soft Lewis acids leading to 1,4-addition of enones in the presence of aldehydes and ketones.[197] The resulting tin enolates can be expected to show pronounced reactivity toward aldehydes.[198] Baba and Shibata reported a tin hydride-mediated reductive aldol reaction. The mixture of phenyl vinyl ketone (**460**) and benzaldehyde (**359**) was treated with Bu_3SnH and Bu_2SnI_2 to give the *syn*-selective aldol product **493** in high yield with high diastereoselectivity (equation 162).[199] Bu_2SnIH generated by the combination of Bu_2SnH_2, $BuSnF_2$, and LiI also showed high effect for reductive aldol reactions (equation 163).[200]

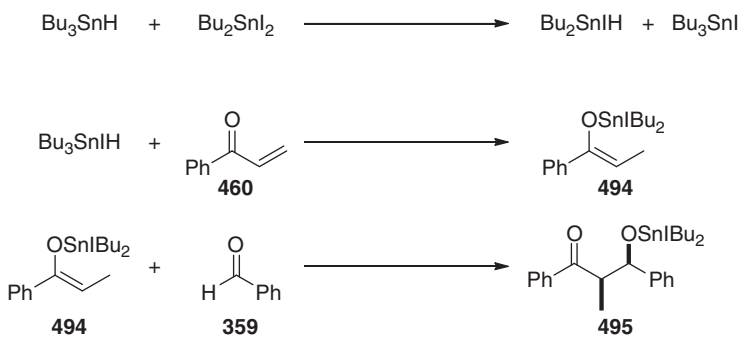


(162)



(163)

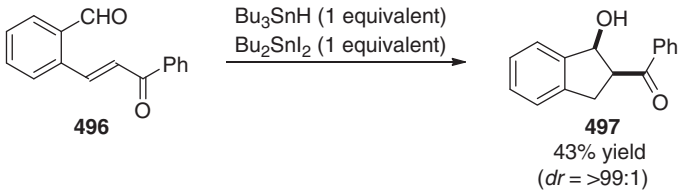
An actual reductant is Bu_2SnIH generated from redistribution between Bu_3SnH and Bu_2SnI_2 (**Scheme 45**). The complete formation of the Bu_2SnIH species was spectroscopically confirmed by ^1H, ^{13}C, and ^{119}Sn NMR. The selective 1,4-reduction of ketone **460** takes place with Bu_2SnIH to produce tin enolate **494**. The aldol reaction of tin enolate **494** with aldehyde **359** occurs to give tin aldolate **495** *syn*-selectively.



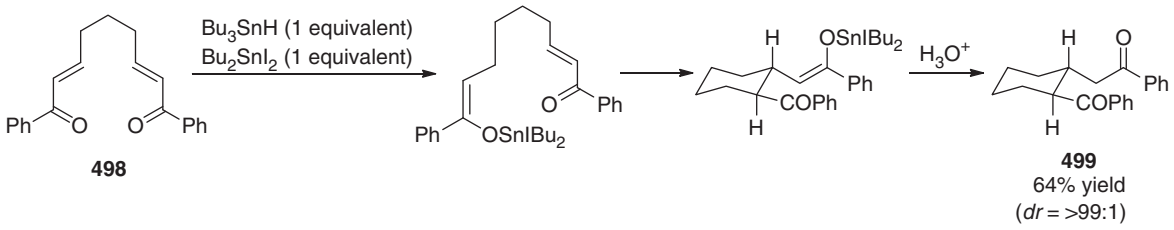
Scheme 45 Reproduced from Kawakami, T.; Miyatake, M.; Shibata, I.; Baba, A. *J. Org. Chem.* **1996**, *61*, 376–379.

By using Bu_2SnIH generated *in situ*, carbocycle **497** was synthesized from formyl substituted enone **496**, in which the enone-selective reduction was followed by a diastereoselective intramolecular aldol reaction (equation 164). An intramolecular reductive

Micheal reaction of dienone compound **498** in the presence of Bu_2SnIH occurred to give the corresponding product **499** with excellent diastereoselectivity (equation 165).[201]

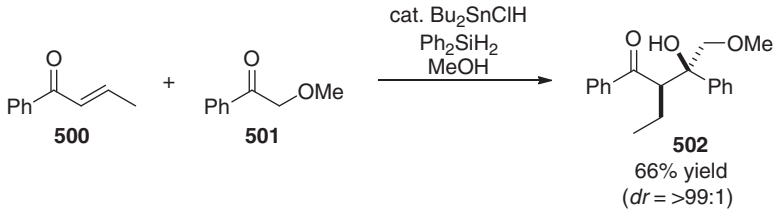


(164)



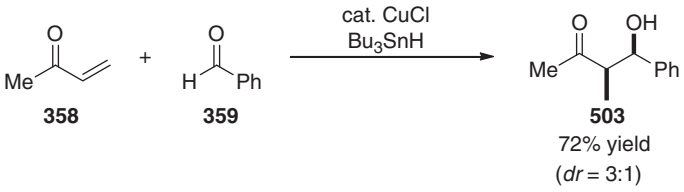
(165)

A catalytic amount of halogenotin hydride in the presence of silyl hydride accelerates diastereoselective reductive aldol reaction of enones to ketones, in which MeOH as an additive plays an important role in both steps of trapping of tin aldolate and of regeneration of Bu_2SnClH. Bu_2SnClH catalyzed the reaction of enone **500** with ketone **501** in the presence of Ph_2SiH_2 and MeOH to afford the aldol product **502** in 66% yield with excellent diastereoselectivity (equation 166).[202]



(166)

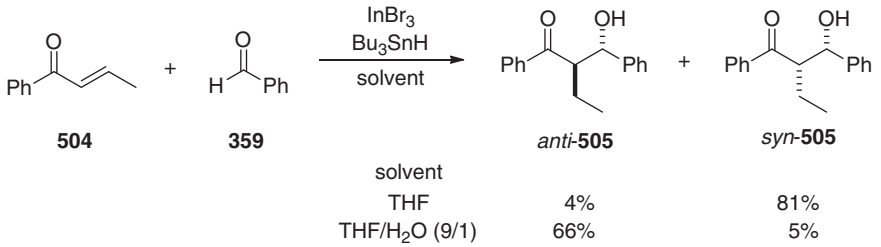
In the reductive aldol reaction using tin hydride, copper(I) chloride works as a radical initiator. The reaction between methyl vinyl ketone (**358**), benzaldehyde (**359**), and Bu_3SnH in the presence of a catalytic amount of CuCl gave the aldol adduct **503** in 72% yield with moderate diastereoselectivity (equation 167).[203]



(167)

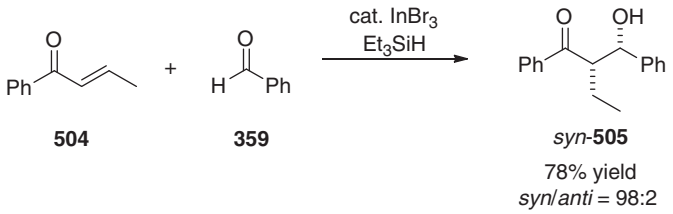
8.20.6.4.2 Indium hydride mediated reductive aldol reaction

The potential of indium hydrides in the field of organic syntheses has been intensively studied in this decade.[204] A stoichiometric amount of dichloroindium hydride generated by the transmetallation between tributyltin hydride and indium trichloride predominantly reduced α,β-unsaturated ketone **504** in a conjugate manner, even in the presence of aldehyde **359** (equation 168). Under anhydrous conditions, the subsequent aldol reactions between the resulting enolates and the remaining aldehyde **359** proceeded with high *anti*-selectivity. The stereochemistry was dramatically changed to *syn*-selectivity by the use of water and methanol as an additive and solvent, respectively.[205]



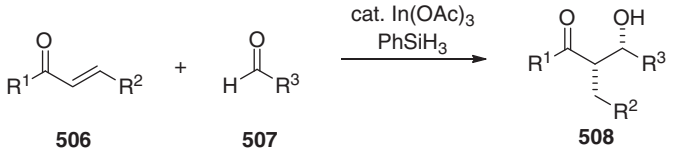
(168)

A catalytic amount of $InBr_3$ accelerated the diastereoselective reductive aldol reaction by using a stoichiometric amount of Et_3SiH, where $HInBr_2$ generated via the transmetalation between $InBr_3$ and Et_3SiH is an active reducing reagent. The reaction among enone **504**, aldehyde **359**, and Et_3SiH took place in the presence of $InBr_3$ catalyst to give the corresponding aldol product *syn*-**505** diastereoselectively in 78% yield (equation 169).[206]



(169)

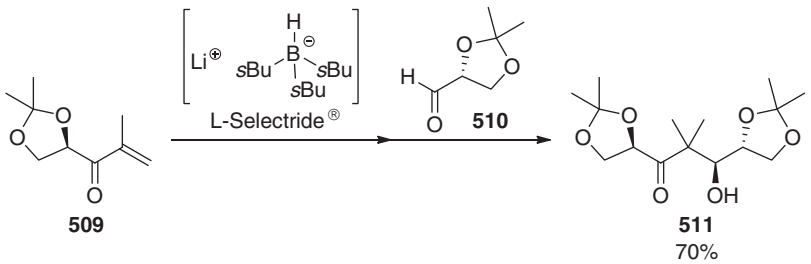
The combination of $In(OAc)_3$ catalyst and $PhSiH_3$ is also effective in the diastereoselective reductive aldol reaction of enones with aldehydes (equation 170).[207]



(170)

8.20.6.4.3 Boron hydride mediated reductive aldol reaction

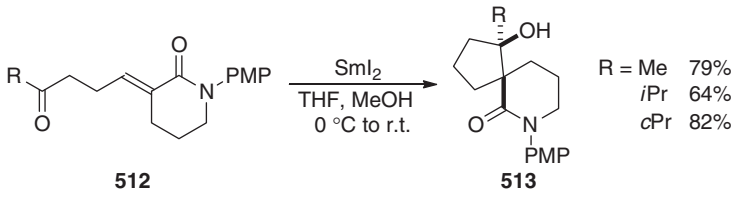
L-Selectride® ($LiBH(sBu)_3$) reduction of chiral enone **509**, which was derived from β-hydroxy carbonyl compound, gave the enolate intermediate. It reacted with optically active α-alkoxy aldehyde **510** to give the aldol product **511** with excellent diastereoselectivity (equation 171). α,α-Dimethyl-β-hydroxy ketones produced by this reaction system are inherent to a variety of biologically active natural products.[208]



(171)

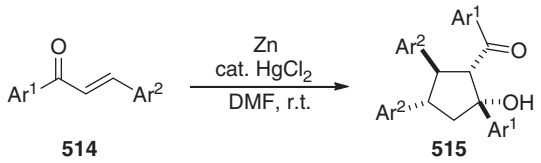
8.20.6.5 Electron Transfer Reductive Aldol Reaction

Samarium(II) iodide is a one-electron reducing agent with widespread utility in organic synthesis. Unsaturated keto-lactam **512** underwent sequential conjugate reduction–aldol cyclization on treatment with SmI_2 to give *syn*-spirocyclic piperidinone **513** containing vicinal, fully substituted stereocenters with complete diastereocontrol (equation 172).[110]



512 513 (172)

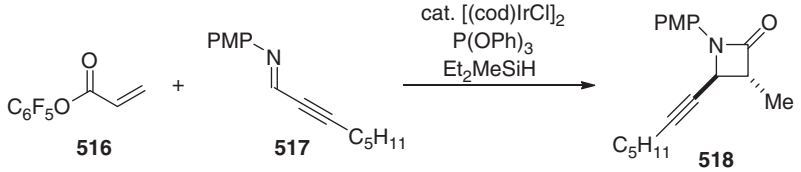
The combination of zinc and a catalytic amount of $HgCl_2$ mediated reductive dimerization and cyclization of chalcone derivatives **514** in dimethylformamide (DMF) at room temperature to give the cyclopentanol products **515** in good yields. The reaction is regio- and stereoselective to produce 3,4-*trans*-diarylcyclopentanols (equation 173).[209]



514 515 (173)

8.20.6.6 Reductive Mannich-Type Reaction

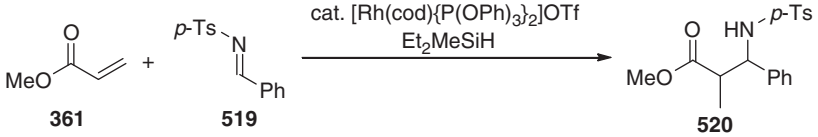
Iridium complex $[(cod)IrCl]_2$ catalyzed the reductive coupling of the acrylate **516** with the imine **517** in the presence of Et_2MeSiH to give the *trans*-*β*-lactam **518** in 58% yield with high diastereoselectivity (equation 174). The mechanism includes a reductive Mannich addition followed by cyclization. Various types of imines were applicable to this reaction system.[210]



516 517 518 (174)

58% yield
(*trans*/*cis* = >20:1)

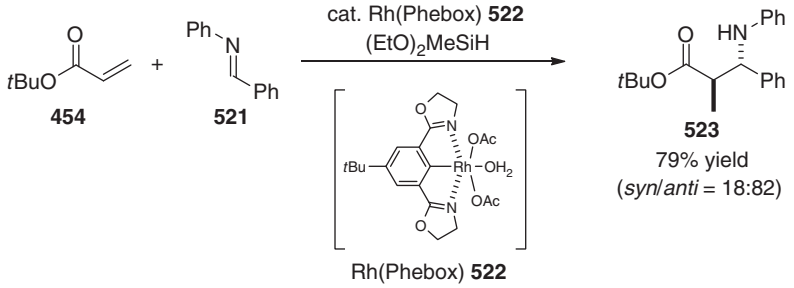
The reaction of methyl acrylate **361** and aldimine **519** in the presence of a catalytic amount of $[Rh(cod)\{P(OPh)_3\}_2]OTf$ and a stoichiometric amount of Et_2MeSiH occurred to give the *β*-amino ester **520** in 96% yield with moderate diastereoselectivity (equation 175).[211]



361 519 520 (175)

96% yield
(*syn*/*anti* = 32:68)

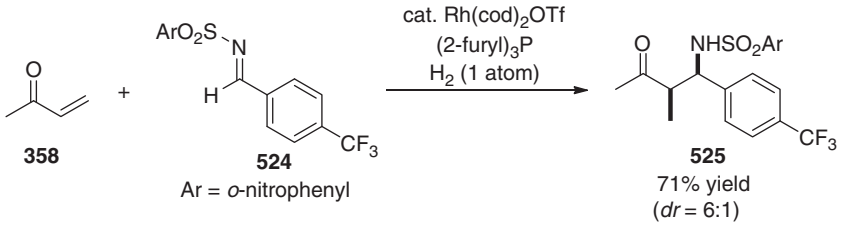
Rh(Phebox) catalyst **522** also promoted the conjugate reduction of *tert*-butyl acrylate **454**, which was followed by Mannich-type reaction toward aldimine **521** with high yield and high *anti*-selectivity (equation 176). This reaction was also successful with various *α*,*β*-unsaturated esters such as acrylates, crotonates, and cinnamates.[212]



454 521 Rh(Phebox) **522** 523 (176)

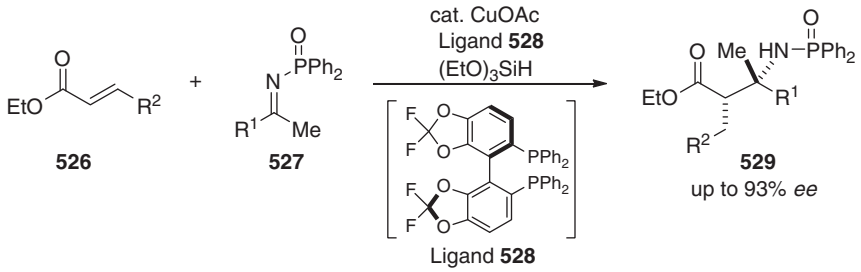
79% yield
(*syn*/*anti* = 18:82)

Catalytic hydrogenation of vinyl ketone **358** in the presence of *N*-(*o*-nitrophenylsufonyl)imine **524** at ambient pressure with the combination catalyst of $Rh(cod)_2OTf$ and tri(2-furyl)phosphine enabled the formation of Mannich products with *syn*-diastereoselectivity (equation 177).[213]



(177)

Shibasaki and coworkers developed catalytic asymmetric reductive Mannich reaction of ketimines via asymmetric 1,4-reduction of α,β-unsaturated esters with a copper hydride catalyst. The combination of CuOAc and ligand **528** promoted the reductive Mannich reaction of ketamine **527** with enoate **526** in the presence of $(EtO)_3SiH$ to afford β-amino ester **529** with high enantioselectivity (equation 178).[214]



(178)

8.20.6.7 Reductive α-Acylation of Enones

The coupling reaction of enolate nucleophiles with acylating reagents is a general synthetic method for 1,3-diketones. The treatment of benzalacetone (**386**) and benzoyl chloride (**530**) with Et_2Zn in the presence of $RhCl(PPh_3)_3$ afforded 1,3-diketone **531** effectively (equation 179). In this reaction system, $RhCl(PPh_3)_3$ reacts with Et_2Zn to give a rhodium hydride complex through the elimination of ethylene from an ethyl rhodium complex. The 1,4-reduction of an enone with the resulting rhodium hydride affords a rhodium enolate. Finally, the coupling of the rhodium enolate with an acyl chloride produces a 1,3-diketone.[215]

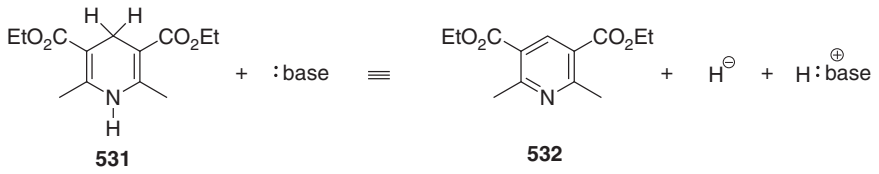


(179)

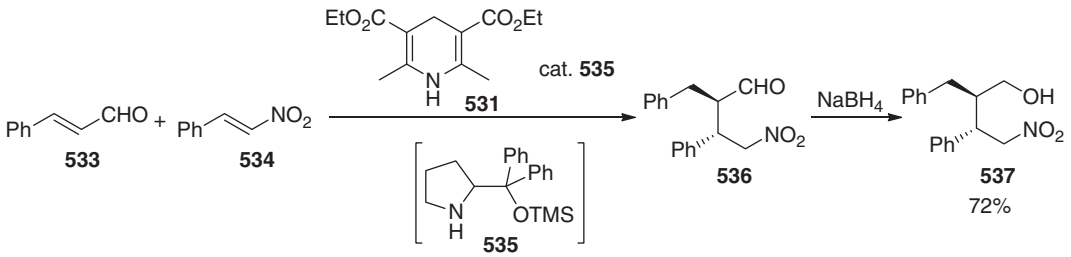
8.20.6.8 Organocatalyst-Promoted Reactions

8.20.6.8.1 Organocatalyst-promoted reductive nitro aldol reaction

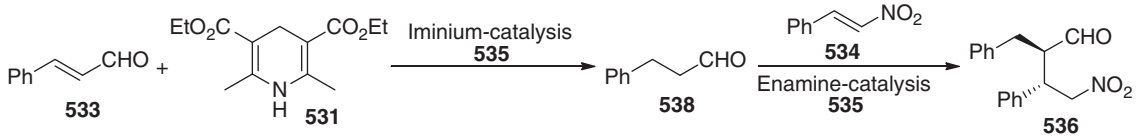
1,4-Dihydropyridines **531**, which are known as Hantzsch esters, are commonly known as synthetic analogs of nicotinamide adenine dinucleotide, reduced form (NADH). Hantzsch esters **531** work as hydride sources illustrated in equation 180. Diphenylprolinol–TMS–ether **535** catalyzed a one-pot multi-component domino reaction between α,β-unsaturated aldehyde **533**, nitroalkene **534**, and Hantzsch ester **531** and gave the domino product **536**. The reduction of **536** with $NaBH_4$ afforded nitro alcohol **537** in 70% yield (Scheme 46). In this reaction, catalyst **535** participates in both iminium and enamine catalysis. As an iminium catalyst, **535** accelerates the 1,4-reduction of **533** with **531** to give saturated aldehyde **538**. Subsequently, aldehyde **538** can serve as a substrate for the formation of an enamine which adds to nitroalkene **534** to provide the domino product **536** (Scheme 47).[216]



(180)



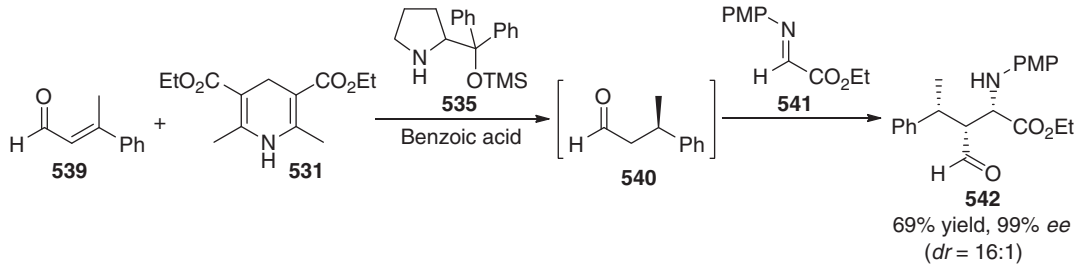
Scheme 46 Reproduced from Rueping, M.; Haack, K.; Ieawsuwan, W.; *et al. Chem. Commun.* **2011**, *47*, 3828–3830.



Scheme 47 Reproduced from Rueping, M.; Haack, K.; Ieawsuwan, W.; *et al. Chem. Commun.* **2011**, *47*, 3828–3830.

8.20.6.8.2 Organocatalyst-promoted reductive Mannich-type reaction

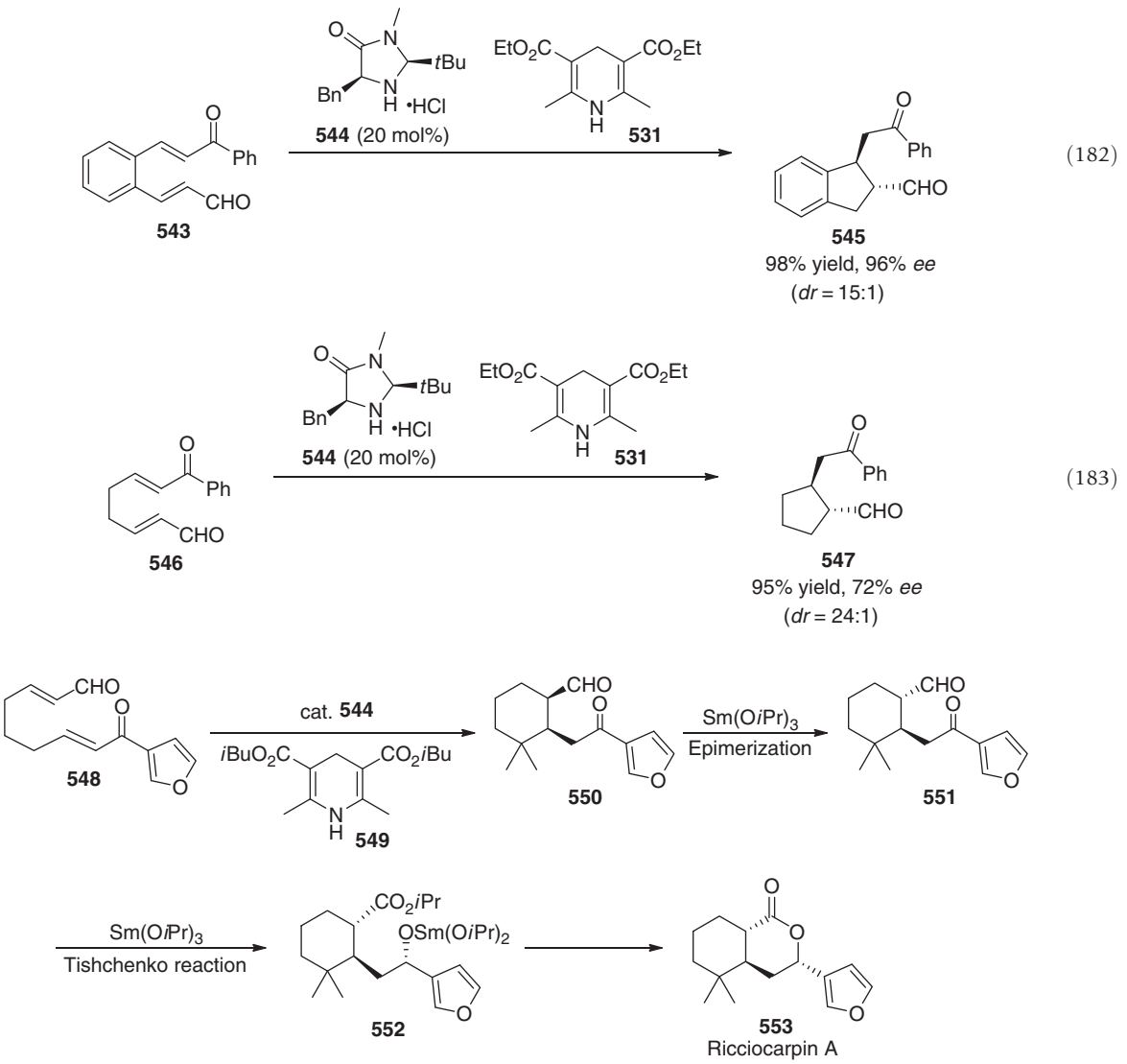
Chiral pyrolidine **535** accelerated direct asymmetric reductive Mannich-type reaction between enal **539**, Hantzsch ester **531**, and aldimine **541** to give the product **542** in 69% yield with high diastereoselectivity and excellent enantioselectivity (equations 181 and 182). In this reaction system, **535** acts as an iminium catalyst to accelerate the 1,4-reduction of **539** with **531** to give saturated aldehyde **540**. Aldehyde **540** can serve as a substrate for the formation of an enamine, which adds to **541** to provide the domino product **542**.[217]



(181)

8.20.6.8.3 Organocatalyst-promoted reductive Michael cyclization

A highly regio-, diastereo-, and enantioselective organocatalytic tandem conjugate reduction – Michael cyclization of the compound bearing enal and enone moieties was achieved by the use of an imidazolidinone catalyst along with a Hantzsch ester. Substrate **543** was treated with a catalytic amount of imidazolidinone **544** and a stoichiometric amount of Hantzsch ester **531** to give keto aldehyde **545** in 98% yield with excellent enantioselectivity and high diastereoselectivity (equation 182). The tether between the enal and the Michael acceptor moiety is not limited to a benzene ring. The cyclization of aliphatic enal **546** with catalyst **544** also afforded a cyclic compound **547** in high yield with high selectivity (equation 183).[218] List and coworkers accomplished a total synthesis of (+)-ricciocarpin A by the combination of this reductive Michael reaction and a Tishchenko reaction (Scheme 48).[219]



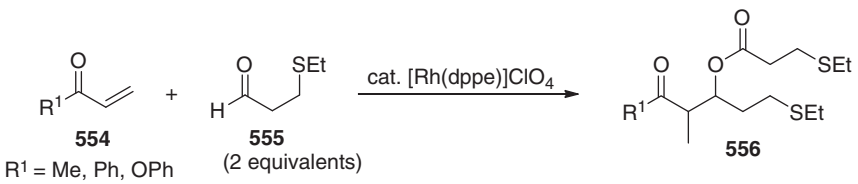
(182)

(183)

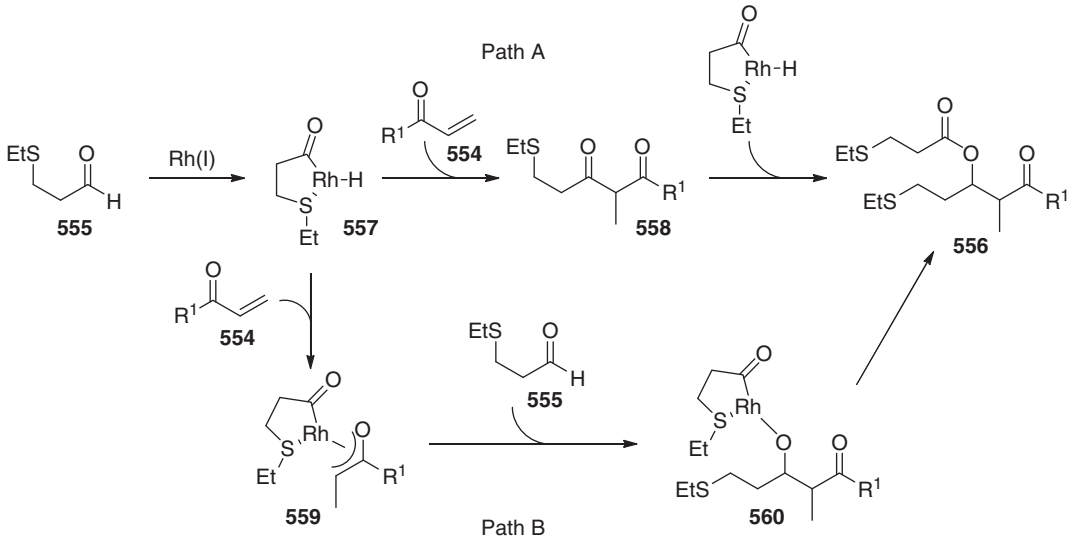
Scheme 48 Reproduced from Michrowska, A.; List, B. *Nat. Chem.* **2009**, *1*, 225–228.

8.20.6.9 Aldehyde as a Hydride Source: Rhodium Complex-Catalyzed Reductive Aldol Reaction

Willis and coworkers developed rhodium-catalyzed reductive aldol reactions using aldehydes as stoichiometric reductants. A treatment of unsaturated ketones and esters **554** with 2 equivalents of β-sulfide-substituted aldehyde **555** in the presence of a catalytic amount of $[Rh(dppe)]ClO_4$ produced ester **556** effectively (equation 184). There are two potential mechanisms (Scheme 49). Both commence with the oxidative addition of Rh(I) into the aldehyde C–H bond to generate a chelated acyl rhodium hydride **557**. Path A continues with the addition of the rhodium acyl across unsaturated carbonyl compound **554** in the manner of a hydroacylation reaction to generate the ketone **558**. Tishchenko-like reduction of ketone **558**, involving a second equivalent of acyl rhodium **557**, then affords ester **556**. Path B involves conjugate addition of the rhodium hydride present in intermediate **557** to unsaturated carbonyl compound **554** to produce rhodium enolate **559**. Addition of the enolate to a further equivalent of the starting aldehyde delivers aldolate **560**, which reductively eliminates Rh(I) to provide the final esterified aldol adduct **556**.[220]



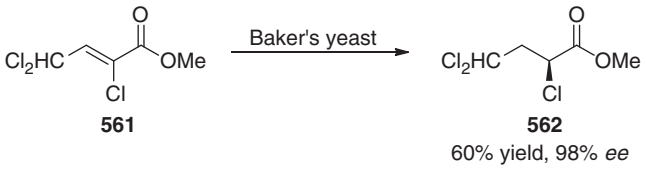
(184)



Scheme 49 Reproduced from Willis, M. C.; Woodward, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 18012–18013.

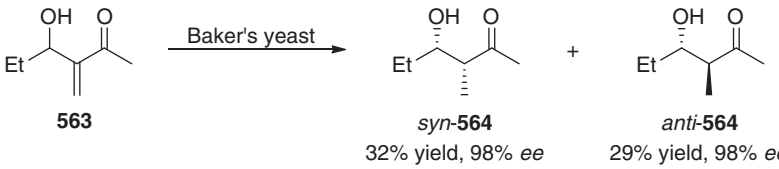
8.20.7 Biochemical Reductions

Many reports of the microbiological reduction of α,β-unsaturated carbonyl compounds were published by the latter part of the twentieth century. Early works were organized in previous review.[1] Asymmetric conjugate reductions of α,β-unsaturated carbonyl compounds using baker's yeast have been reported since 1987. Takeda and Utaki described the first report of asymmetric reaction of α,β-unsaturated esters. α-Chloro-α,β-unsaturated ester **561** was treated with baker's yeast to afford the corresponding α-chloroester **562** in 60% yield with 98% *ee* (equation 185).[221]

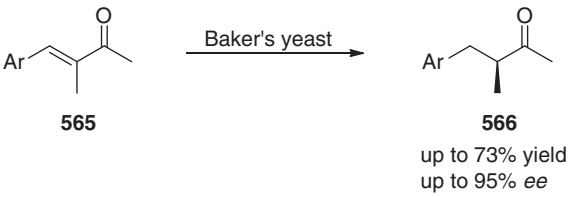


(185)

α-Alkyl-α,β-unsaturated ketone **563** was subjected to asymmetric reduction in the presence of baker's yeast to give *syn*- and *anti*-**564** in 32% and 29% yields with high enantioselectivities (equation 186).[222] Various β-aryl-α-methyl-α,β-unsaturated ketones **565** were also applicable to give moderate yields and high enantioselectivities (equation 187).[223] Cheng and Zhang studied the hydrogen transfer mechanism of cofactor reduction and recycling processes in the yeast reduction of α,β-unsaturated ketone by using quantitative isotope tracing close to natural abundance measured by ^{2}H NMR.[224]



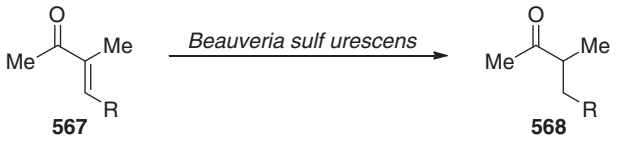
(186)



(187)

There are other types of bacterially mediated α,β-unsaturated carbonyl compounds. The 1,4-reduction of α,β-unsaturated methyl ketones **567** by *Beauveria sulfurescens* took place effectively (equation 188).[225] This reducing system was affected by the

steric factor of R group at the β-position. *Nicotiana tabacum*,[226] *Euglena gracilis Z*,[227] *Medicago sativa*,[228] and *Synechococcus* sp. PCC 7942[229] also promoted 1,4-reduction of enones in a moderate chemoselectivity.

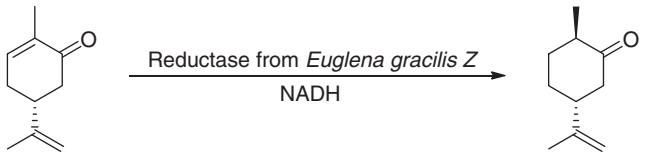


567 **568**

R = Et 90%
*n*Pr 92%
*n*Bu 0%

(188)

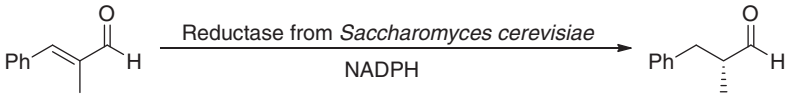
A reductase catalyzes the conjugate reduction of α,β-unsaturated carbonyl compounds using NADH or NADPH. The reductase from *Euglena gracilis Z* reduced α,β-unsaturated ketone **569** to give the corresponding ketone **570** in moderate yield and enantioselectively (equation 189).[230]



569 **570**

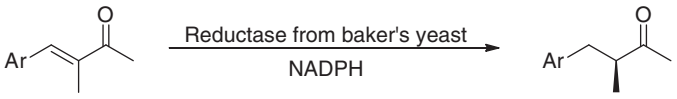
(189)

There are some reductases, such as those from *Saccharomyces cerevisiae* (equation 190),[231] baker's yeast (equation 191),[232] *Nicotiana tabacum* (equation 192),[233] *Astasia longa*,[234] and *Gluconobacter oxydans*,[235] which catalyze conjugate reduction of enones.



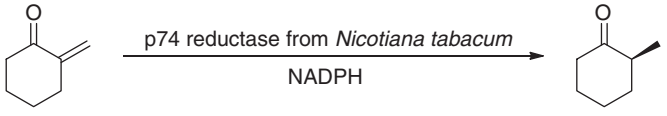
571 **572**

(190)



573 **574**
up to 99% *ee*

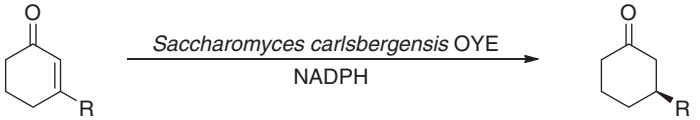
(191)



575 **576**
97% *ee*

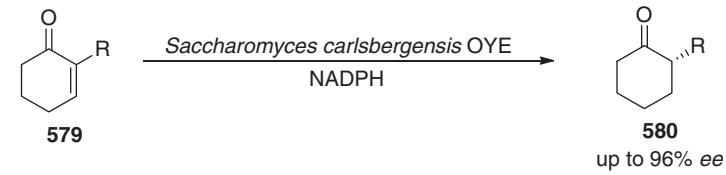
(192)

The 'old yellow enzyme' (OYE) family works as a catalyst of the conjugate reduction of α,β-unsaturated carbonyl compounds. Stewart and coworkers reported *Saccharomyces carlsbergensis* old yellow enzyme-catalyzed asymmetric conjugate reduction of cyclic unsaturated ketones in the presence of NADPH (equations 193–194).[236]



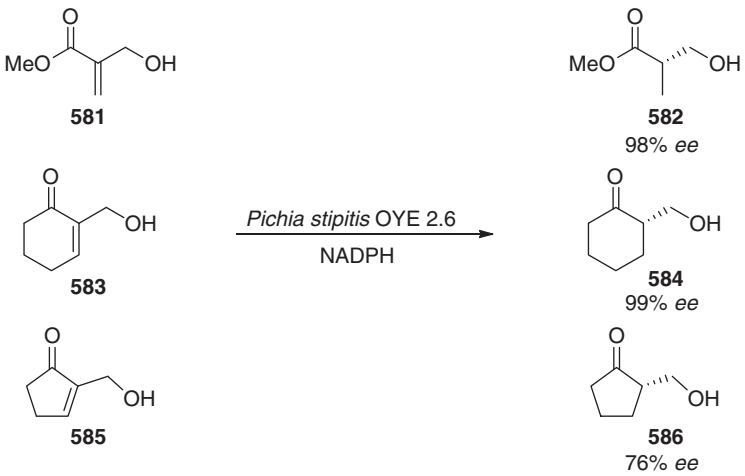
577 **578**
up to 94% *ee*

(193)



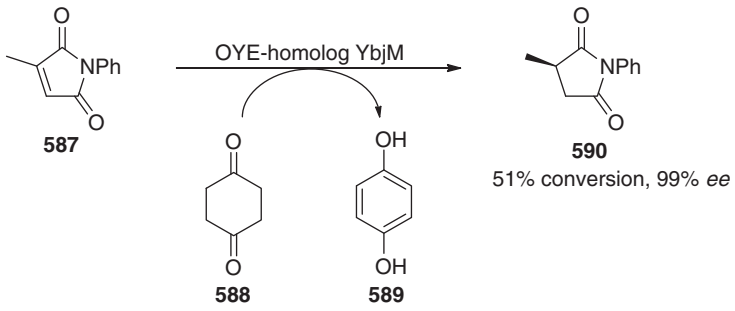
579 **580** up to 96% *ee* (194)

The asymmetric conjugate reduction of Baylis–Hillman adducts was accomplished by using *Pichia stipitis* OYE 2.6. Different types of substrates **581**, **583**, and **585** were applicable to this reducing system, affording the corresponding products in high yields with high enantioselectivities (Scheme 50).[237]



Scheme 50 Reproduced from Walton, A. Z.; Conerly, W. C.; Pompeu, Y.; Sullivan, B.; Stewart, J. D. *ACS Catal.* **2011**, *1*, 989–993.

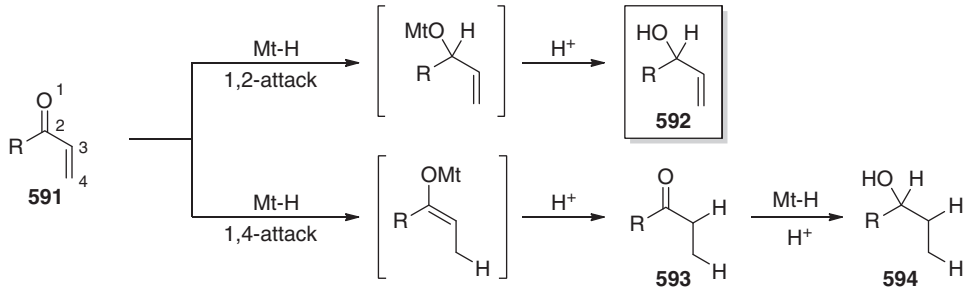
OYE-homolog YqjM-catalyzed asymmetric conjugate reduction of α,β-unsaturated carbonyl compounds using cyclohexane-1,4-dione (**588**) as a hydride donor instead of NADPH was reported by Faber and coworkers, although the scope of substrate was narrow. Unsaturated amide **587** was treated with OYE-homolog YbjM in the presence of **588** to afford product **590** with high enantioselectivity along with a coproduct, hydroquinone (**589**) (Scheme 51).[238]



Scheme 51 Reproduced from Stueckler, C.; Reiter, T. C.; Baudendistel, N.; Faber, K. *Tetrahedron* **2010**, *66*, 663–667.

8.20.8 1,2-Reduction of Enones

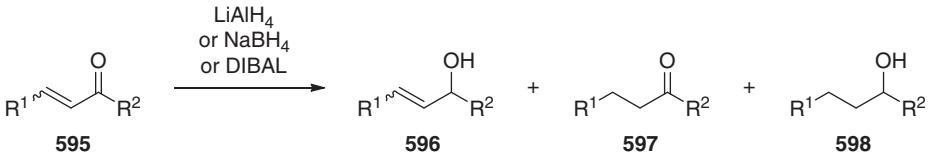
There are some synthetic problems often encountered in the reduction of enone **591** with hydride reagents. In addition to affording the corresponding allylic alcohols **592**, the reductions are often accompanied by such side reactions as concomitant reduction of the double bonds leading to saturated alcohols **594** or, less commonly, reduction to enols, which eventually give the saturated ketones **593**. Such divergence in reduction products has been attributed to competing 1,2 vs. 1,4 attack by hydride, but predictions concerning the mode of attack for a particular substrate are difficult (Scheme 52).



Scheme 52

8.20.8.1 Classical Reagents for 1,2-Reduction of Enones

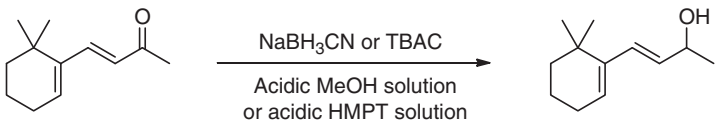
Classical reagents such as 1. $LiAlH_4$,[239] 2. $NaBH_4$,[239,240] and 3. DIBAL[241] (diisobutylaluminum hydride) sometimes used in 1,2-reduction of enones **595**. These reducing reagents are commercially available and common system not only for the reduction of enones in 1,2-manner but also for the carbonyl reduction. However, the competitive 1,4-reduction often takes place (equation 195).



(195)

8.20.8.2 Reaction of Enones with $NaBH_3CN$

The reduction of a variety of conjugated ketones **599** with $NaBH_3CN$ or TBAC (tetrabutylammonium cyanoborohydride) in acidic MeOH containing 2N HCl or acidic HMPT containing sulfuric acid has been reported. This system mainly promotes 1,2-hydride attack as shown here, which proceeds in chemoselective manner (equation 196).[242]

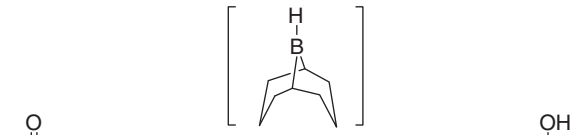


88% ($NaBH_3CN$/MeOH)
60% ($NaBH_3CN$/HMPT)
63% (TBAC/HMPT)

(196)

8.20.8.3 Reaction of Enones with 9-BBN

The boron reagent 9-borabicyclo[3.3.1]nonane (9-BBN) is an exceptionally stable bicyclic dialkylborane which hydroborates olefins with very high regio- and stereoselectivity, far greater than those observed with borane and other dialkylboranes. By the use of 9-BBN, cyclic enone **601** is converted to 2-cyclohexenol **602** in a 100% regioselective manner. Furthermore, the present reaction can tolerate the presence of a large variety of functional groups, which is a major advantage of 9-BBN over other reagents such as l $LiAlH_4$, $NaBH_4$, and DIBAL (equation 197).[243]

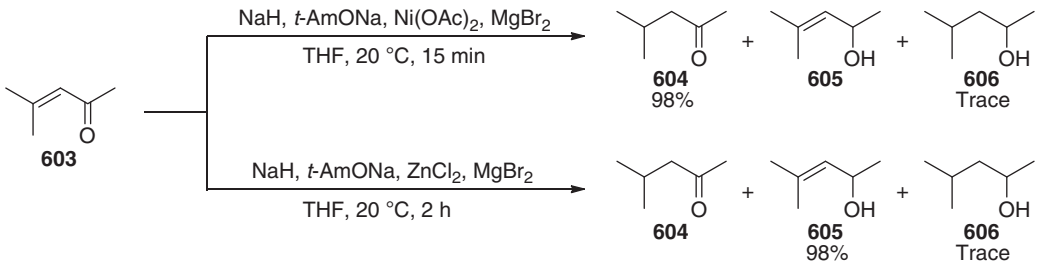


84%

(197)

8.20.8.4 Reaction of Enones with NaH–*t*AmONA–$ZnCl_2$–$MgBr_2$

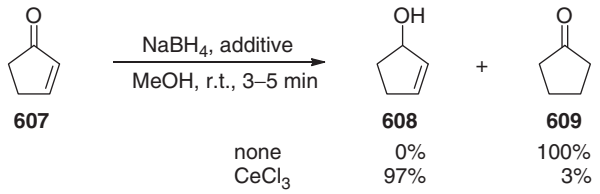
Complex reducing reagents NaH–RONa–MX_n (MCRA) and NaH–RONa–MX_n–$MgBr_2$ (MCRA–$MgBr_2$) are very efficient reagents for the regioselective reduction of α,β-unsaturated ketones in THF. The use of NiCRA–$MgBr_2$ (MX_n=$Ni(OAc)_2$) exhibit a 100% regioselectivity for the conjugate reduction of α,β-unsaturated ketones **603**, whereas under the same conditions ZnCRA–$MgBr_2$ (MX_n=$ZnCl_2$) are effective reagents for the regioselective 1,2 reduction of' enones **603** (Scheme 53).[244]



Scheme 53 Reproduced from Denis, C.; Laignel, B.; Plusquellec, D.; Marouille, J.-Y. L.; Botrel, A. *Tetrahedron Lett.* **1996**, *37*, 53–56.

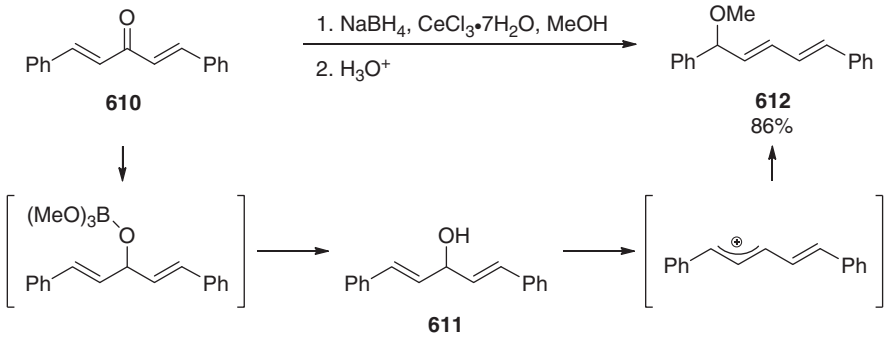
8.20.8.5 Luche Reduction of Enones

In 1978, Luche found that the use of lanthanide halides was highly effective in promoting the formation of 1,2-reduced products. Indeed, the combination of $NaBH_4$ and $CeCl_3$ gave allylic alcohol **608** from enone **607** in a chemoselective manner (equation 198). The reactions may be conducted at room temperature, without special exclusion of air or moisture, and excellent yields of products are obtained within 5 min.[245]



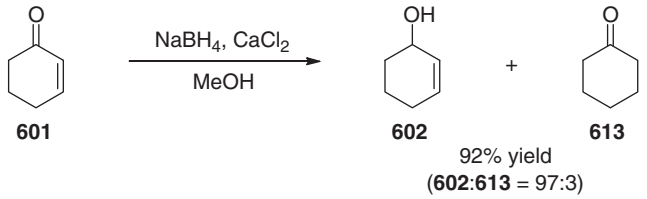
(198)

To prepare allylic alcohol **611**, the reduction of dibenzylideneacetone **610** with $NaBH_4$ in the presence of $CeC1_3 \cdot 7H_2O$ using MeOH as solvent was carried out. After acidic work up and chromatographic purification, only the dienyl methyl ether **612** was isolated with no alcohol **611**. It is interesting to note that the process is completely regio- and stereoselective and only the conjugated *E,E*-isomer of dienyl ether **612** was formed (Scheme 54).[246]



Scheme 54 Reproduced from Barluenga, J.; Fañanás, F. J.; Sanz, R.; García, F.; García, N. *Tetrahedron Lett.* **1999**, *40*, 4735–4736.

Oshima and Utimoto found that the employment of a $CaCl_2$–$NaBH_4$ system instead of a $CeCl_3$–$NaBH_4$ one was applicable to the selective 1,2-reduction of enones (equation 199).[247]

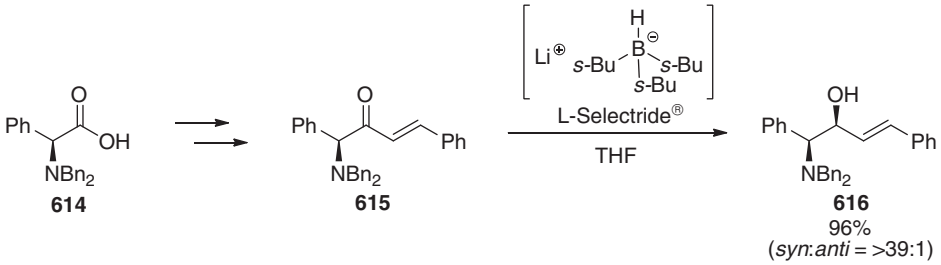


(199)

8.20.8.6 Reaction of Enones with L-Selectride

L-Selectride® ($LiBH(s\text{-}Bu)_3$) can selectively reduce enones in a 1,4- or 1,2-fashion. The greater steric hindrance of the bulky substituents of L-Selectride® prefers the vacant site of enones and induces regio- and stereoselective reduction of enones.

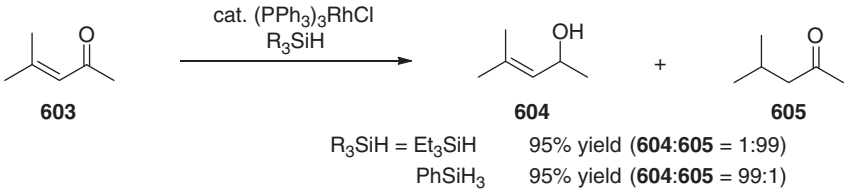
In the example shown in Scheme 55, treatment of α′-amino enone **615**, which was prepared from **614**, with L-Selectride® provided the β-amino-α-hydroxy compounds *syn*- and *anti*-**616** in high yield and high diastereoselectivity (Scheme 55).[248]



Scheme 55 Reproduced from Chung, S.-K.; Kang, D.-H. *Tetrahedron: Asymmetry* **1997**, *8*, 3027–3030; Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194–2200; Babu, K. G.; Yadav, V. K. *Indian J. Chem.* **2007**, *46B*, 1001–1003; Ganem, B. *J. Org. Chem.* **1975**, *40*, 146–147, and Crisp, G. T.; Scott, J. C. *Synthesis* **1985**, 335–337.

8.20.8.7 Reaction of Enones with Hydrosilane Catalyzed by Transition Metal

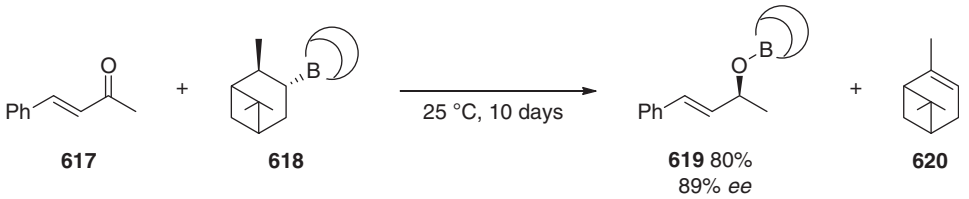
Highly regioselective reduction of the α,β-unsaturated carbonyl compound **603** to the corresponding saturated carbonyl **605** was achieved using monohydrosilane (Et_3SiH) catalyzed by tris(tripheny1phosphine)chlororhodium (Wilkinson's catalyst) followed by the methanolysis of the resulting adducts. Interestingly, the change of hydrosilane to trihydrosilane ($PhSiH_3$) gave the allylic alcohol **604** as the predominant product (equation 200). The selectivity of 1,4-addition of a monohydrosilane as well as that of 1,2 addition of a trihydrosilane is considerably influenced by the substituent(s) on silicon and also by the structure of the substrate.[249]



(200)

8.20.8.8 Reaction of Enones with Chiral Borane Reagents

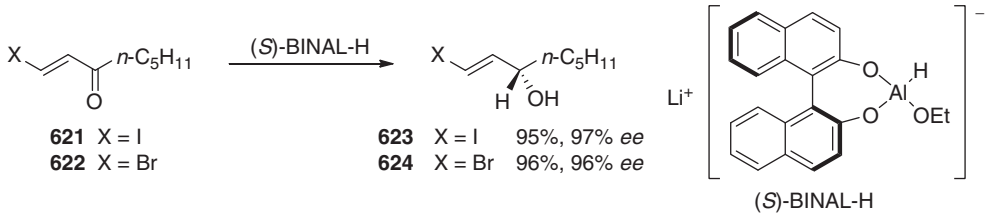
The chiral trialkylborane B-(3-pinanyl)-9-borabicyclo[3.3.l]nonane **618** (Midland's reagent) was employed to achieve an asymmetric reduction of ketones. This system was effective in the reduction of *trans*-4-phenyl-3-buten-2-one **617**, achieving an excellent optical induction using long reaction times (equation 201).[250]



(201)

8.20.8.9 Reaction of Enones with $LiAlH_4$ and Chiral Sources

The binaphthol-modified lithium aluminum hydride reagents (BINAL-Hs), which were devised through rational stereochemical engineering, offer promise of an asymmetric reduction of carbonyl functions.[251] The reduction of simple prochiral alkenyl ketones **621** and **622** with (*S*)-BINAL-H proceeds smoothly at low temperature to form the allylic alcohols **623** and **624** in high enantiomeric excess (equation 202). The chiral ligand can be recovered from the reaction mixture in high yield (>90%) in reusable form without racemization.[251e]



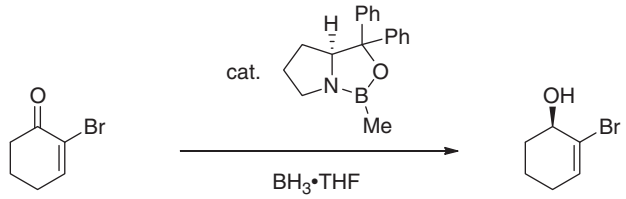
621 X = I
622 X = Br

623 X = I 95%, 97% *ee*
624 X = Br 96%, 96% *ee*

(202)

8.20.8.10 Corey–Bakshi–Shibata (CBS) Reduction of Enones

The Corey–Itsuno reduction, also known as the Corey–Bakshi–Shibata (CBS) reduction, in which an achiral ketone is enantioselectively reduced to produce the corresponding chiral alcohol, is widely used even in industry.[252] The application of CBS reduction into enones is also a good candidate for asymmetric synthesis of allylic alcohols. Indeed, α-bromo cyclic enone **625** was transformed into allylic alcohol **626** with high enantioselectivity (equation 203).[252c]



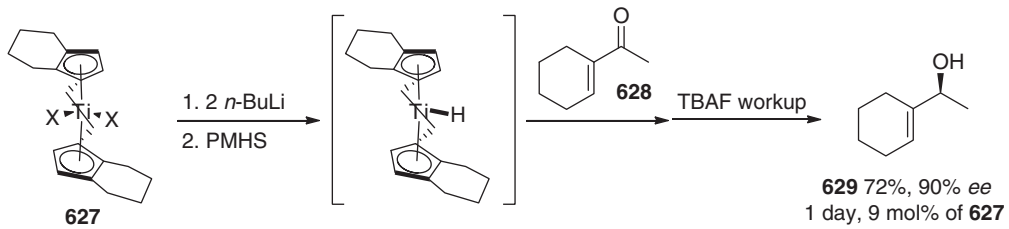
625

626
91% *ee*

(203)

8.20.8.11 Reaction of Enones with Hydrosilanes Catalyzed by Transition Metal Complex

Buchwald has developed the asymmetric hydrosilylation of aromatic ketones with an early transition metal catalyst to afford alcohols with excellent enantioselectivity.[253] In this procedure, complex **627** was used as the precatalyst. This method was also applied to enones. Although the hydrosilylation of 1-acetyl-1-cyclohexene **628** also proceeds with good enantioselectivity, a small amount of reduction of the olefin moiety occurred (**Scheme 56**).[253a]

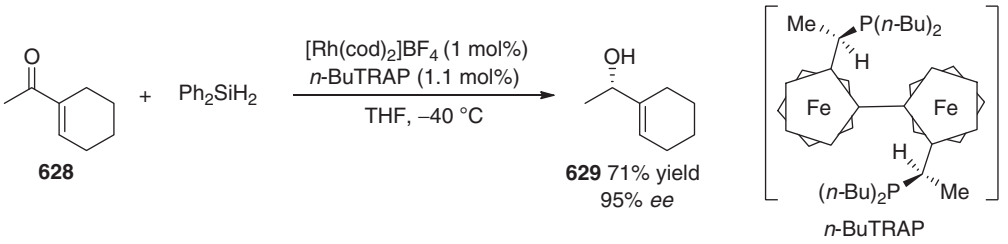


627
X = 1,1'- binaphthyl-2,2'-diolate

629 72%, 90% *ee*
1 day, 9 mol% of **627**

Scheme 56 Reproduced from Carter, M. B.; Schiøtt, B.; Gutiérrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11667–11670.

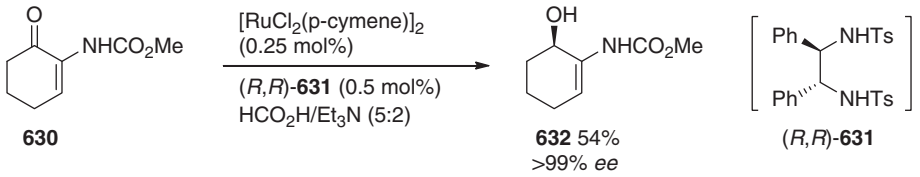
The combination of rhodium catalyst and *trans*-chelating chiral dienophile ligands bearing flexible *P*-alkyl substituents (AlkylTRAPs) worked well for asymmetric hydrosilylation of simple ketones. Reaction of 1-acetylcyclohexene **628** also gave allylic alcohols **629** with 95% *ee* accompanied by a trace amount of the 1,4-reduction product (<1% by GLC) (equation 204).[254]



(204)

8.20.8.12 Asymmetric Hydrogen-Transfer Reduction

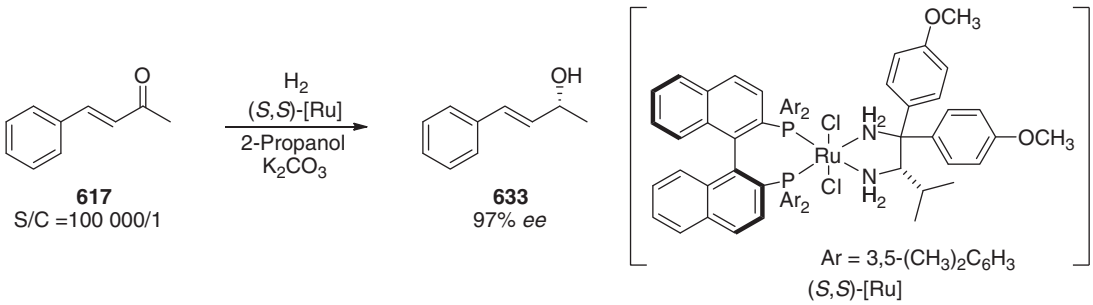
Asymmetric reduction of cyclic enone catalyzed by transition metal has been developed by the use of formic acid and triethylamine as a hydride donor. The α-substituted cyclohex-2-en-1-one **630** was selectively reduced to allylic alcohols **632** by 1,2-reduction process with very high enantioselectivities (99% *ee*) and modest yields (equation 205).[255]



(205)

8.20.8.13 Hydrogenation of Enones Catalyzed by Transition Metal Complex

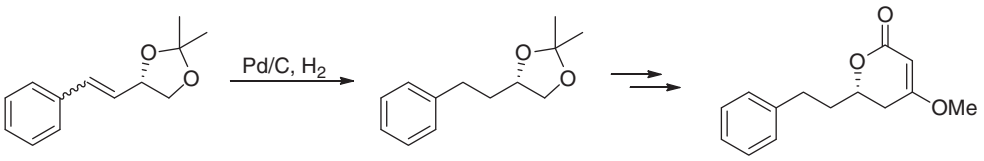
Noyori has achieved highly enantioselective hydrogenation of simple enones by the development of the XylBINAP/DAIPEN–ruthenium catalyst and by the use of K_2CO_3, a weak base cocatalyst, in place of conventional KOH or $(CH_3)_3COK$. Thus, reaction of benzalacetone **617** (100 g) in 2-propanol (150 mL) containing the (*S*)-XylBINAP/(S)–DAIPEN–ruthenium catalyst (8.3 mg) and K_2CO_3 (9.4 g) under 80 atm of H_2 [S/C (= substrate/catalyst) = 100 000/1, 2.7 M solution) gave the *R* alcohol **633** in 97% *ee*. In addition, the absence of any trace of C=C reduction products is noteworthy (equation 206).[256]



(206)

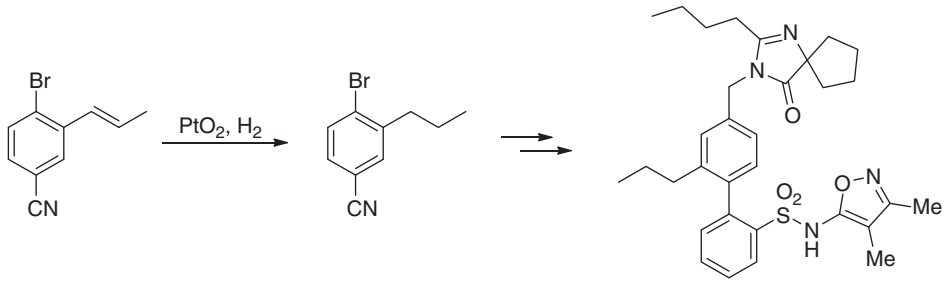
8.20.9 Partial Reduction of Styrene Derivatives

Partial reduction of styrene derivatives is an effective synthetic method of alkylated arenes because styrene derivatives are easily prepared by cross-coupling, Wittig reaction, etc. Only selected examples are listed in this chapter because many previous reviews have described this field fully.[1,257] Various types of reducing system such as hydrogenation, transfer hydrogenation, SET, and the combination of NHC catalyst (equations 207–213) have been used. Hydrogenations using Pd–C and PtO_2 are often applied to the synthesis of complex organic compounds (equations 207 and 208).[258,259] Homogenous catalysts such as Wilkinson's catalyst are also effective for hydrogenation (equation 209).[260] Transfer hydrogenation using homogenous and heterogenous catalysts have been developed (equations 210 and 211).[261] Hydrazine is also used as a hydrogen source (equation 212).[262] SmI_2 reduced styrene derivatives via SET (equation 213).[263]



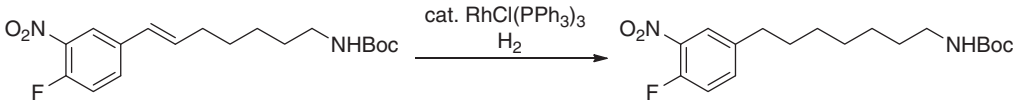
(207)

(*S*)-(+)-Dihydrokavain

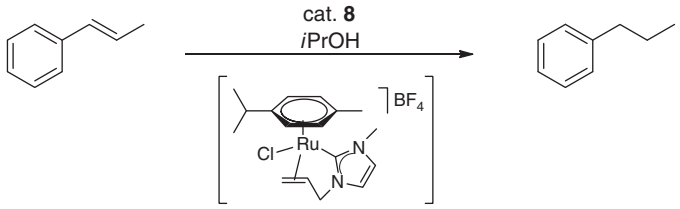


(208)

Irbesartan derivative

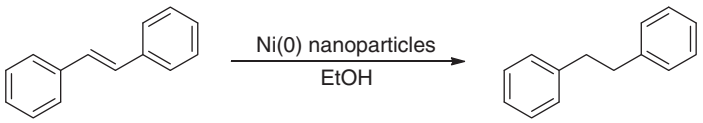


(209)

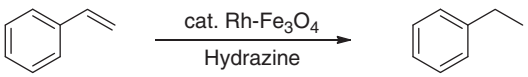


(210)

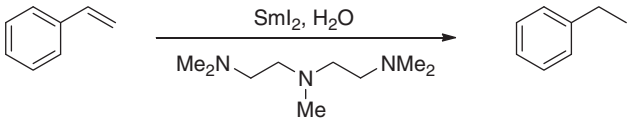
Catalyst **8**



(211)



(212)



(213)

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8.21 Partial and Complete Reduction of Pyridine and their Benzo Analogs

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This chapter is a revision of the previous edition chapter by James G. Keay, Vol. 8, pp 579–602, © 1991, Elsevier Ltd.

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Glossary

Atropisomers Stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The word atropisomer is derived from Greek–a, meaning not and tropos, meaning turn.

Chemoselective A reaction in which a functional group is transformed in the presence of another functional group.

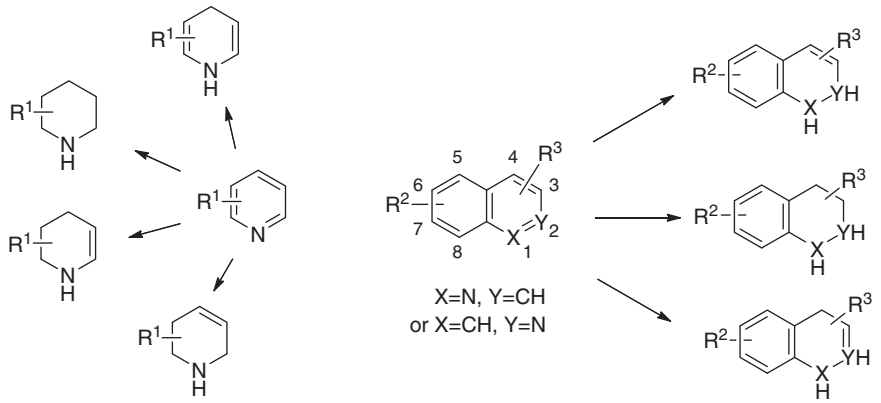
Epimerization In an optically active compound that contains two or more stereogenic centers, a process in which only one of these centers is altered by some reaction to form an epimer.

Frustrated lewis pairs A frustrated Lewis pair is a compound or mixture containing a Lewis acid and a Lewis base that, because of steric hindrance, cannot combine to form an adduct.

Heterogeneous catalysis A chemical process in which the catalyst is in a separate phase.
Homogeneous catalysis Catalysis occurring within a single phase, usually a gas or liquid.
Organocatalysis The term organocatalysis describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound.
Regioselective The preference of one direction of chemical bond making or breaking over all other possible directions.
Stereoselective The preferential formation in a chemical reaction of one stereoisomer over another. When the stereoisomers are enantiomers, the phenomenon is called enantioselectivity and is quantitatively expressed by the enantiomeric excess; when they are diastereomers, it is called diastereoselectivity and is quantitatively expressed by the diastereoisomeric excess.
Tautomerization The isomerization by which tautomers are interconverted.

8.21.1 Introduction

The reduction of pyridines and their benzo analogs continues to attract considerable attention as the corresponding saturated or partially saturated heterocycles are useful and versatile building blocks for the preparation of biologically active targets and new materials. This chapter covers the most relevant advances in this field after the publication of the first edition of *Comprehensive Organic Synthesis* in 1991 and includes both stoichiometric chemical reductions and organo- and metal-catalyzed processes with focus on pyridine, quinoline, and isoquinoline derivatives, in either their free base, their ammonium, or their *N*-oxide forms. Only reactions involving formal addition of H_2 or hydride reagents for the reduction of the pyridine moiety will be considered and discussed here. As depicted in Scheme 1, various reduced products can be obtained depending on the reaction conditions and substitution patterns, and the aim of this chapter is to provide the reader with a thorough critical comparison of the reported methods that allow a selective and efficient access to the desired saturated or partially saturated *N*-heterocyclic compounds. Reduction of pyridine benzo analogs bearing more than one aromatic ring, such as acridines or phenantridines, and reductive alkylation reactions are outside the scope of this review.



Scheme 1

8.21.2 Stoichiometric Chemical Reductions

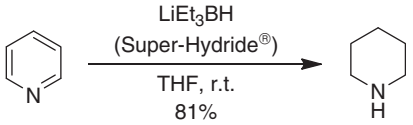
Historically, chemical reduction of pyridines and benzo analogs with hydrides or through single electron transfer reaction pathways has been very much studied. This particular area has been thoroughly reviewed in the first edition of this book,[1] and for this reason we will only present, in the context of this second edition, the most significant advances in the field. This update will be focused on borohydride-mediated reductions, reductions mediated by other kinds of hydride sources, and, finally, reductions involving single electron transfer processes. Notably, the asymmetric reduction of pyridines and benzo analogs involving Hantzsch esters as reducing agent will be reviewed distinctively in Section 8.21.4.

8.21.2.1 Borohydride-Mediated Reductions

Among the different classes of hydride sources allowing the reduction of pyridines, quinolines, and isoquinolines, borohydrides are certainly the most employed.

8.21.2.1.1 Pyridines and pyridinium salts

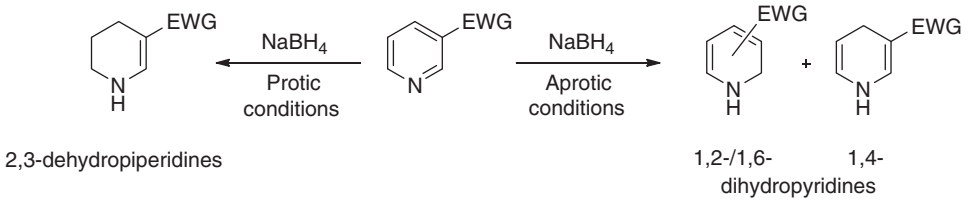
Although it has long been considered that, unless an electron-withdrawing group is present at the 3-position of the ring, a pyridine moiety cannot be effectively reduced with borohydrides, Caroll et al. demonstrated the peculiar behavior of lithium triethylborohydride (Super-Hydride®).[2] This rather electron-rich reagent displays a high reduction capacity allowing, at room temperature, the complete reduction of pyridine itself into saturated piperidine (Scheme 2).



Scheme 2

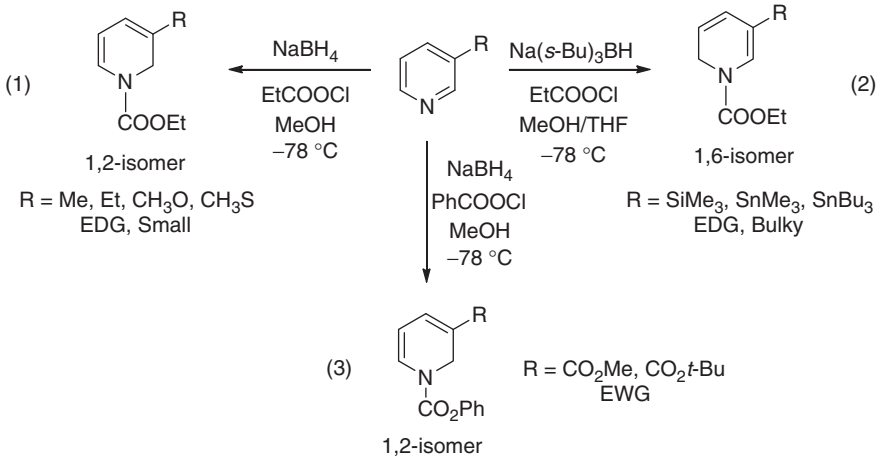
Additionally, Super-Hydride® is very efficient for the complete reduction of 3,5-disubstituted pyridines, though poorly capable of reducing 2,6- or 3,4-lutidines.

Pyridines bearing an electron-withdrawing group at the 3-position are routinely partially reduced with sodium borohydride or sodium cyanoborohydride. Whereas protic reaction media tend to favor the selective formation of the 2,3-dehydropiperidines, aprotic reaction conditions often lead to mixtures of 1,2-, 1,4-, and 1,6-dihydropyridine isomers (Scheme 3).[1]



Scheme 3

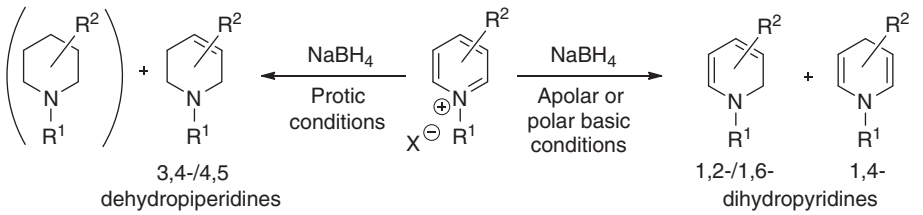
The selective 1,2-, 1,4-, or 1,6-monoreduction of the pyridine nucleus is, therefore, particularly challenging. This issue was partially addressed by Fowler et al. and Sundberg et al. in the case of the pyridines possessing an electron-donating group at the 3-position, for which the low temperature reduction in the presence of ethyl chloroformate and the appropriate borohydride source allows either a selective 1,2- or 1,6-hydride transfer (Scheme 4, equations 1 and 2).[1,3] This method could later be extended to pyridines possessing, in the same position, an electron-withdrawing group.[4] For such scaffolds, selective 1,2-monoreduction is achieved with phenylchloroformate with sodium borohydride in methanol at low temperature (Scheme 4, equation 3).



Scheme 4

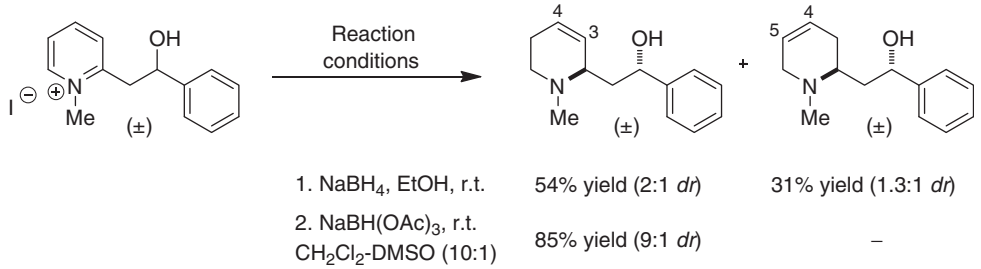
Pyridinium salts are more reactive than their pyridine parents such that their reduction does not necessitate the presence of an electron-withdrawing group at the 3-position. Consequently, sodium borohydride promotes the reduction of pyridinium salts typically (depending of the presence of a proton source in the reaction medium) leading to mixtures of dihydropyridines isomers or mixtures of dehydropiperidines and, occasionally, piperidines (Scheme 5).[1]

Whereas in acidic reduction conditions, 3-substituted pyridinium salts preferentially form 3,4-dehydropiperidines,[1] in the case of 2-substituted pyridinium salts, mixtures of 3,4- and 4,5-dehydropiperidines can be obtained. The presence of a suitably



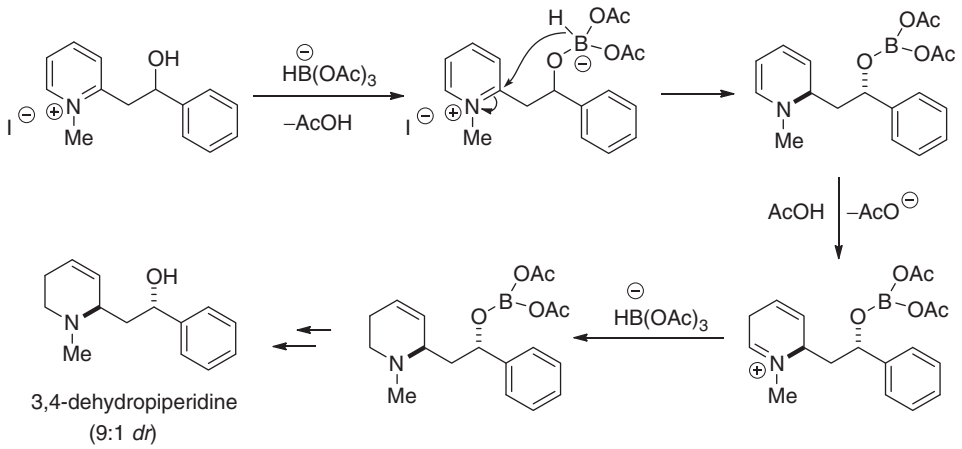
Scheme 5

positioned hydroxyl group in conjunction with a weaker hydride source such as sodium triacetoxyborohydride may greatly influence the outcome of the reduction. Indeed, as reported by Lebreton, Mathé-Allainmat et al., the latter reaction conditions are accountable for the sole formation of 3,4-dehydropiperidines (Scheme 6).[5]



Scheme 6

As discussed by the authors, this total selectivity in favor of the 3,4-dehydropiperidine isomer is the direct result of an initial regioselective 1,2-reduction of the pyridine core promoted by an intramolecular hydride delivery. The use in this process of triacetoxyborohydride is decisive since sodium borohydride is sufficiently reactive to induce to some extent an intermolecular 1,6-hydride transfer and, therefore, leads competitively to the 4,5-dehydro isomer (Scheme 7).

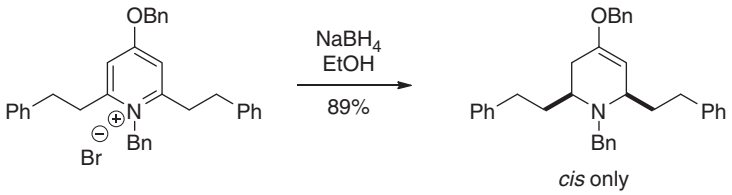


Scheme 7

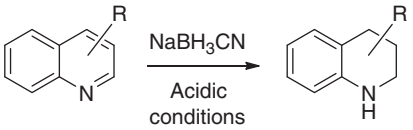
The presence of such a hydroxyl directing group is also an opportunity to induce good diastereoselectivity in the reduction process. Furthermore, total diastereoselectivity in favor of the *cis* dehydropiperidine isomer is evident when performing the sodium borohydride/EtOH reduction of 2,6-disubstituted pyridinium salts (Scheme 8).[6]

8.21.2.1.2 Quinolines

Although quinolines can be reduced by sodium borohydride in ethanol, mixtures of 1,2,3,4-tetrahydroquinolines and 1,2-dihydroquinolines are often obtained in the absence of a proton source. For this reason, borohydride reductions of these heterocyclic compounds are usually performed in acidic conditions using sodium cyanoborohydride, allowing the formation uniquely of the corresponding 1,2,3,4-tetrahydroisoquinolines (Scheme 9).[1]



Scheme 8



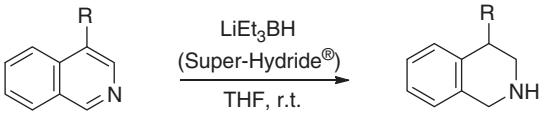
Scheme 9

Alternatively, it has been demonstrated that the preparation of 1,2,3,4-tetra-hydroisoquinolines from quinolines can also be promoted under Lewis acidic conditions with reducing systems such as sodium borohydride–nickel(II)chloride,[7] sodium cyanoborohydride–boron trifluoride etherate,[8] or zinc borohydride.[9]

8.21.2.1.3 Isoquinolines and isoquinolinium salts

In protic reaction conditions, isoquinolines behave like quinolines and lead specifically to tetrahydroisoquinolines with sodium cyanoborohydride.[1]

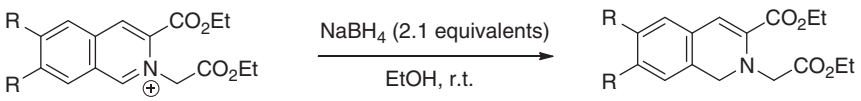
Alternatively, the same transformation was described by Caroll et al. under aprotic conditions using lithium triethylborohydride (Super-Hydride®).[2] Although poorly efficient for the reduction of quinolines, this reducing agent promotes, in good to excellent yields, the reduction of 4-substituted isoquinolines to the corresponding tetrahydroisoquinolines (Scheme 10).



R = H, Me, Et, $CH{=}CH_2$, $CH_2{-}CH{=}CH_2$, Ph Yield = 74–93%

Scheme 10

On reaction with sodium borohydride, isoquinolinium salts typically produce 1,2-dihydroisoquinolines regioselectively in anhydrous dimethylformamide or pyridine and tetrahydroisoquinolines in protic conditions.[1] However, it has been shown that the presence of an electron-withdrawing group at the 3-position of the heterocyclic ring favors the selective 1,2-monoreduction, even in protic conditions (Scheme 11).[10]



R = H, OMe

R = H, Yield = 81%
R = OMe, Yield = 89%

Scheme 11

8.21.2.2 Other Reducing Agents

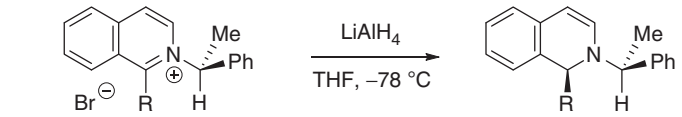
In this particular section, we will report some recent advances in the reduction of pyridines and benzo analogs involving the use of other kinds of reducing agents. For a more comprehensive approach, the discussion will be organized by reagent types.

8.21.2.2.1 Aluminum hydrides

Aluminum hydrides and alkoxyaluminum hydrides are usually not the best hydride sources for the reduction of pyridines or pyridinium salts since their use often leads to complex mixtures of reduced products. However, this kind of powerful hydride

donor is particularly adequate for the selective 1,2 monoreduction of *N*-carbonylpyridinium, quinolinium, and isoquinolinium salts when the reaction is conducted at low temperature.[1,11]

In this context, Marazano et al. reported that 1-substituted isoquinolinium salts bearing a chiral auxiliary on the nitrogen atom lead, in good to excellent yields, to the corresponding 1,2-dihydroisoquinolines with remarkable diastereoselectivities using lithium aluminum hydride at −78 °C (Scheme 12).[12]



R = Me, Ph, 3-(MeO)-C_6H_4, 4-(MeO)-C_6H_4, 3,4-$(MeO)_2$-C_6H_3

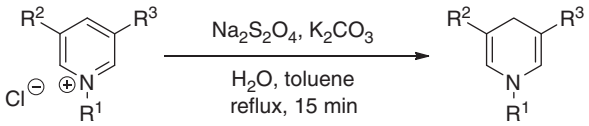
Yield = 25–93%
74–84% *de*

Scheme 12

8.21.2.2.2 Sodium dithionite

Although the aptitude of sodium dithionite to reduce pyridinium salts regioselectively to the corresponding 1,4-dihydropyridines is well established, it was considered in the past to be limited to substrates bearing electron-withdrawing groups at the 3- or 3,5-positions.[1,13]

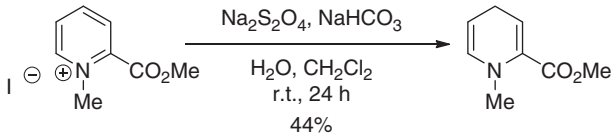
Marazano et al. succeeded in extending the scope of this method to 3- and 3,5-alkylated pyridinium salts demonstrating the determining role of hydrophobic interactions. Whereas *N*-methylpyridinium chloride is completely degraded on reaction with sodium dithionite, increasing the hydrophobicity of the *N*-substituent allows selective 1,4-monoreduction to take place. Using a *N*-benzyl moiety, unsubstituted, 3- and 3,5-dimethylsubstituted pyridinium salts lead in good yield to the corresponding 1,4-dihydropyridines (Scheme 13).[14a] Later, this work was extended to the selective 1,4-reduction of 3-arylsubstituted pyridinium salts.[14b]



R^1	R^2	R^3	Yield (%)
CH_3	H	H	–
$C_{12}H_{25}$	H	H	80
CH_2Ph	H	H	80
CH_2Ph	CH_3	H	80
CH_2Ph	CH_3	CH_3	80

Scheme 13

Additionally, the sodium dithionite-mediated reduction of pyridinium salts bearing an electron-withdrawing group at the 2-position was reported by Lavilla et al. (Scheme 14).[15]

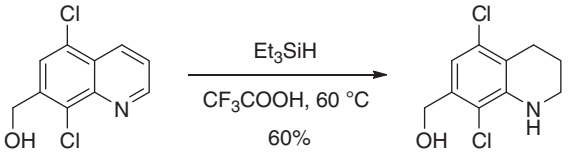


Scheme 14

8.21.2.2.3 Silanes

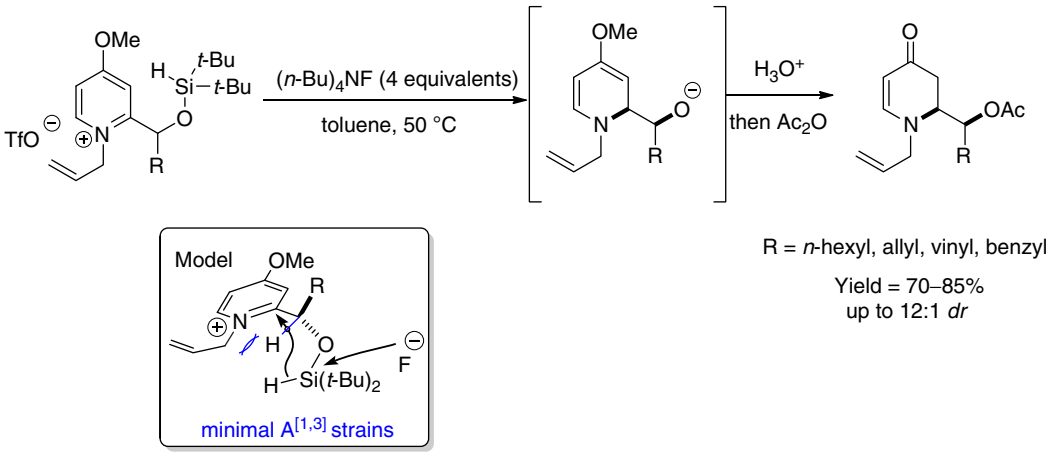
The use of silanes as hydride donors has found some applications in the reduction of quinolines and pyridinium salts.

As an alternative to borohydride-mediated, Griffith et al. reported that the preparation of a 1,2,3,4-tetrahydroquinoline from a quinoline can be accomplished using triethylsilane in trifluoroacetic acid at 60 °C (Scheme 15).[16]



Scheme 15

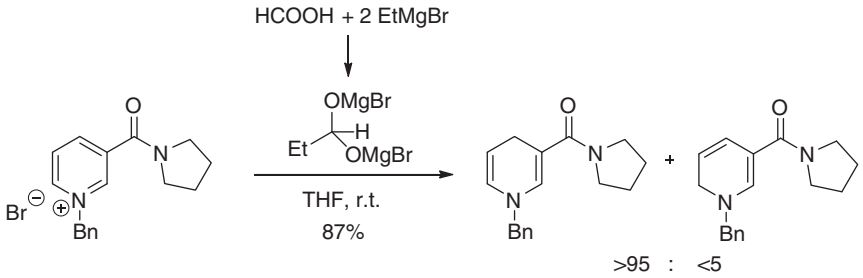
However, the great potential of this kind of hydride source for the selective reduction of pyridinium moieties has been established by Donohoe et al.[17] On reaction with a fluoride source, *N*-allylpyridinium salts possessing an oxygen-tethered silane residue undergo a regioselective intramolecular 1,2-monoreduction step. As a direct benefit of such an approach, good diastereoselectivities can be obtained due to the necessity of minimalizing $A^{[1,3]}$ allylic strains (Scheme 16).



Scheme 16

8.21.2.2.4 Magnesium diolate

The reduction of pyridinium salts with formic acid and its salt, referred to as Lukes reduction, usually necessitates elevated temperature.[1] To circumvent this problem, the use of a magnesium diolate, prepared by addition of ethyl Grignard reagent onto formic acid, has been described. This uncommon reducing agent allows the selective 1,4-monoreduction of *N*-nicotinamide pyridinium salts in tetrahydrofuran (THF) (Scheme 17).[18]



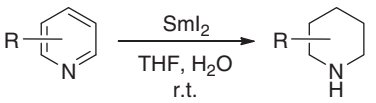
Scheme 17

8.21.2.3 Single Electron Transfer Reductions

Birch-type reduction and electrochemical-mediated reduction of pyridines, pyridinium salts, and benzo analogs usually suffer from several drawbacks such as dimerization of intermediate radical species or reduction of substituents. Even if dimerization processes can be suppressed in protic conditions, mixtures of products are commonly observed.[1] Recent results show that electron-deficient pyridines bearing several electron-withdrawing groups usually give better results. However, a specific substitution pattern is crucial to stabilize intermediary species which, therefore, limits the scope of such methods.[19,20]

As an alternative to alkali metals, the reduction of pyridines through single electron transfer can be realized using samarium(II) iodide in the presence of water. In such reaction conditions, alkyl- or aryl-substituted pyridines afford the corresponding

piperidines in good to excellent yields (Scheme 18). Notably, in this reaction conditions, halogenated pyridines afford dehalogenated piperidines.[21a]



R	Yield (%)
2-Me	89
3-Me	95
4-Me	92
2-Ph	96

Scheme 18

Although lower yields are obtained, the analogous reduction of pyridines is possible with samarium metal in 20% hydrochloric acid. Nevertheless, these latter reaction conditions are particularly adequate for the complete reduction of the *N*-heterocyclic ring of quinolines and isoquinolines.[21b] Indium metal in the presence of ammonium chloride in refluxing aqueous ethanol is also a way to reduce quinolines and isoquinolines to the corresponding tetrahydro compounds.[22]

8.21.3 Transition Metal-Catalyzed Reductions

8.21.3.1 Heterogeneous Catalysis

Saturation of the pyridine ring is most commonly achieved by heterogeneous catalytic hydrogenation in the presence of platinum, palladium, nickel, or rhodium catalysts. Complete reduction to the piperidine normally occurs and hydrogenation of pyridines, quinolines, and isoquinolines usually affords the corresponding saturated heterocycles in an efficient manner.

8.21.3.1.1 Racemic reductions

8.21.3.1.1.1 Heterogeneous catalytic hydrogenation

8.21.3.1.1.1.1 Pyridines and pyridinium salts

The heterogeneous catalytic hydrogenation of pyridine derivatives is usually carried out in acidic media since protonation activates the pyridines toward hydrogenation and suppresses catalyst poisoning by the resulting piperidines. Among the catalysts used for the hydrogenation of pyridines, although Rh/C is effective, platinum oxide (Adam's catalyst) and palladium on carbon are most frequently employed and are particularly efficient under low hydrogen pressure (Scheme 19).[23] Reducible functionalities such as alkyne, cyano, nitro, or halide groups are reduced before the pyridine ring, whereas more resistant groups like carboxylic acid, ester, amide, or carbamate remain unaffected. Partial ring reduction may occur with pyridines containing an electron-withdrawing group such as an ester, since the partially hydrogenated product is stabilized by the conjugation of the lone pair of electrons on the nitrogen atom with the C=C bond and the carbonyl group. In the case of aryl-3-pyridyl-methanol derivatives, one-pot deoxygenation and heteroaromatic ring saturation occurs in the presence of Pd/C affording cleanly 3-(substituted benzyl) piperidines in good yields.

An efficient Pd/C catalytic hydrogenation of 4-pyridinecarboxamides to 4-piperidinecarboxamide hydrochlorides under mild conditions has been developed in the presence of $ClCH_2CHCl_2$.[24] This method involves the catalytic hydrodechlorination of $ClCH_2CHCl_2$ with release of HCl allowing the *in situ* formation of the corresponding 4-pyridinecarboxamide hydrochloride, which undergoes hydrogenation more readily than the initial 4-pyridinecarboxamide (Scheme 20).

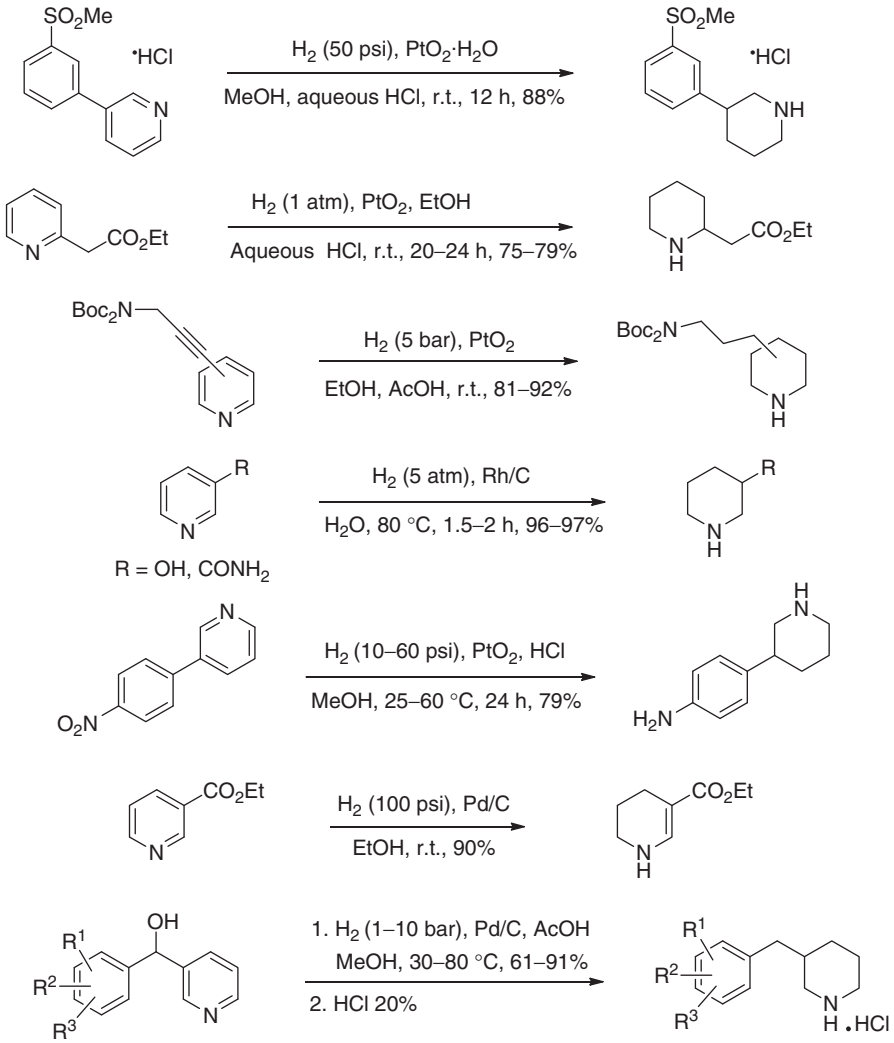
Pyridines-bearing pyrazole or indole moieties are selectively hydrogenated into the piperidine derivatives using PtO_2 either in acidic media or through prior conversion of the free base into the hydrochloride salt (Scheme 21).[25]

The heterogeneous catalytic hydrogenation of 4-(4-fluorobenzyl)pyridine using rhodium, platinum, and palladium catalysts allows the synthesis of the valuable pharmaceutical intermediate 4-(4-fluorobenzyl)piperidine without hydrodefluorination by conducting the reaction at an atmospheric pressure of hydrogen and at room temperature, whereas ruthenium catalyst is inactive under these conditions (Scheme 22).[26]

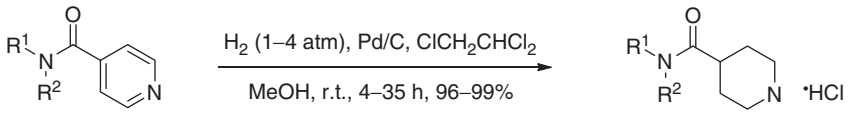
In addition to these standard procedures, microwave-assisted hydrogenation of functionalized pyridines has been reported.[27] Substrates that would require 24–48 h to be reduced under standard conditions undergo complete reduction in less than 1 h of exposure to hydrogen and microwave irradiation. However, hydrogenation of functionalized pyridines has also been carried out conveniently and efficiently under continuous flow conditions in a dedicated high-pressure reactor.[28]

Ruthenium,[29] rhodium,[30] iridium,[31] and palladium nanoparticles[32] show high activity in the reduction of pyridines and/or quinolines into the corresponding saturated heterocycles. Nanoheterogeneous catalytic hydrogenation has also been performed using reusable surfactant-stabilized aqueous rhodium(0) colloidal suspensions[33] or subnanometer palladium clusters.[34]

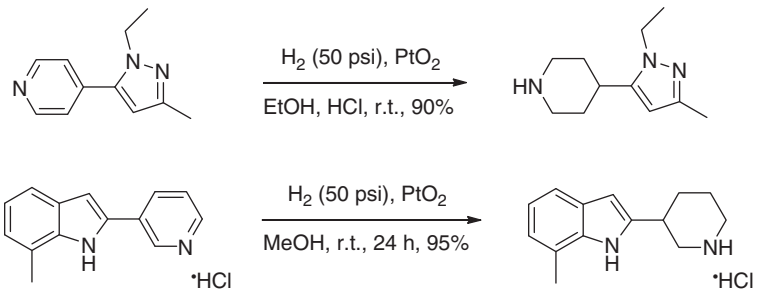
Partial reduction of bipyridines usually involves activation of one of the pyridine rings before the catalytic hydrogenation. Selective reduction of one heteroaromatic ring of the bipyridine may be initiated through selective *N*-alkylation of the less hindered pyridine nitrogen. Hydrogenation of the corresponding activated benzyl salt with Pd/C or PtO_2 in the presence of



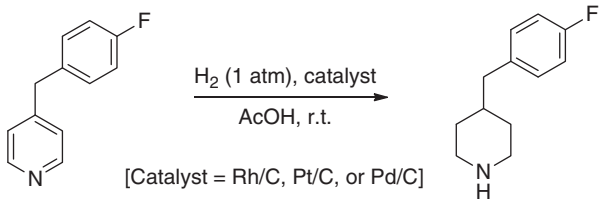
Scheme 19



Scheme 20

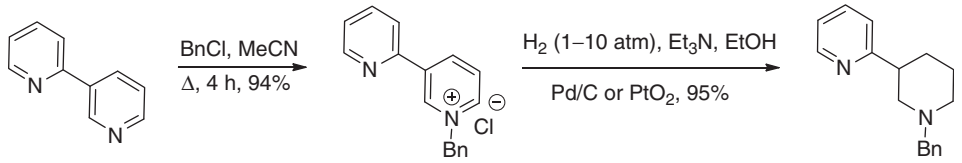


Scheme 21



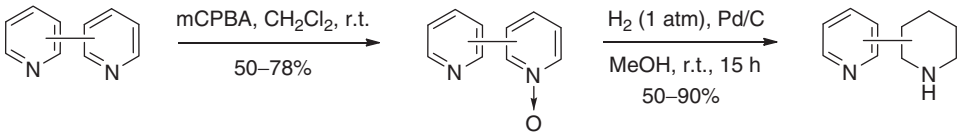
Scheme 22

triethylamine then affords the corresponding pyridyl piperidine in good yield. Although very efficient, this method nevertheless requires a further debenzylation step (Scheme 23).[35]



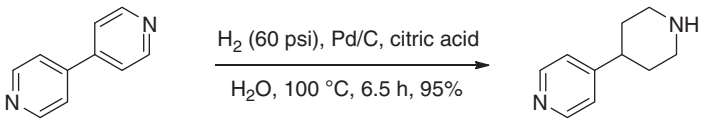
Scheme 23

The regioselective reduction of bipyridines may also be achieved through selective *N*-oxidation of the less hindered pyridine nitrogen. The Pd/C-catalyzed hydrogenation of the corresponding *N*-oxo derivative then occurs selectively on the activated *N*-oxide ring. The *N*-oxide is simultaneously reduced, avoiding an additional deprotection step (Scheme 24).[36]



Scheme 24

A more convenient and efficient method for the partial reduction of 4,4′-bipyridine involves direct hydrogenation with Pd/C by using citric acid as promoter. Under hydrogenation conditions of 100 °C and 60 psi of hydrogen pressure, a high yield of the pyridyl piperidine is obtained with less than 2% of over reduction to bipiperidine (Scheme 25).[37]



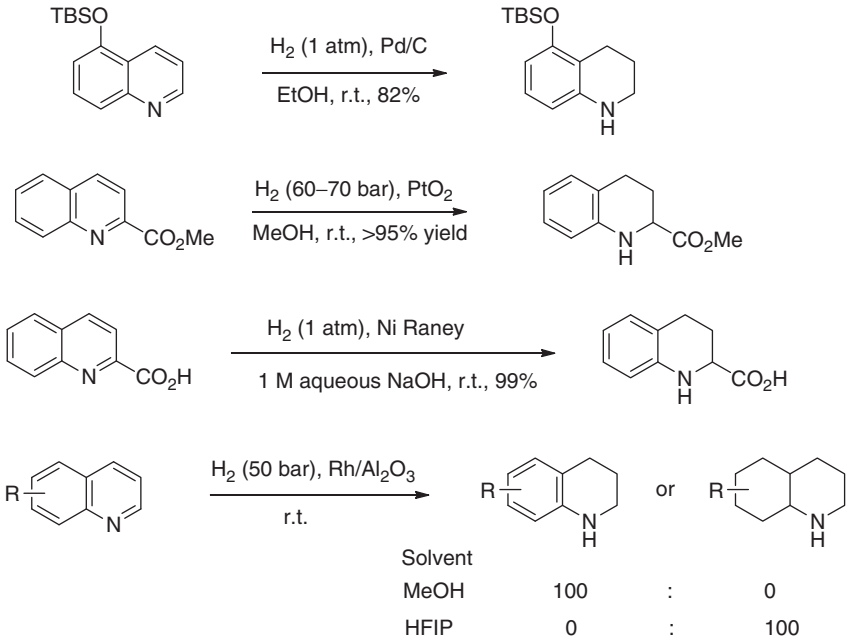
Scheme 25

8.21.3.1.1.1.2 Quinolines

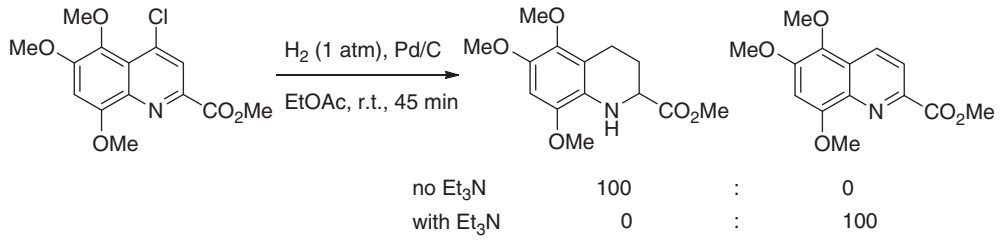
Catalytic hydrogenation of quinolines under neutral and weakly acidic conditions (e.g., in MeOH or acetic acid) occurs preferentially and rapidly in the pyridine ring yielding the corresponding 1,2,3,4-tetrahydroquinolines,[38] although over reduction to the *cis*- and *trans*-decahydroquinolines can be achieved on extended reaction times or on forcing the reaction conditions. The selectivity is reversed in favor of the formation of 5,6,7,8-tetrahydroquinolines when hydrogenation is performed in strongly acidic medium (e.g., CF_3CO_2H or 12 *N* HCl).[39] 1,2,3,4-Tetrahydroquinolines are commonly efficiently obtained with either Pd/C, PtO_2, or Raney Ni (Scheme 26). Solvent-dependent regioselective hydrogenation of substituted quinolines has been reported in the presence of Rh/Al_2O_3. By conducting the reaction in methanol, the 1,2,3,4-tetrahydroquinoline derivatives are selectively obtained, whereas in hexafluoroisopropanol (HFIP) the decahydro compounds are formed, avoiding the use of more forcing conditions.[16d]

Quinolines bearing a halogen atom usually undergo concomitant saturation of the pyridine ring and hydrogenolysis of the C–halogen bond. However, selective cleavage of a C–Cl bond can be achieved by conducting the reaction in the presence of a base such as Et_3N to avoid over reduction (Scheme 27).[40]

Cao et al. have reported the unusual chemoselective hydrogenation of quinoline compounds using supported gold catalysts.[41] They demonstrated that gold nanoparticles supported on TiO_2 could catalyze, under mild reaction conditions, the chemoselective hydrogenation of functionalized quinolines to the corresponding 1,2,3,4-tetrahydroquinolines, leaving intact a variety of valuable

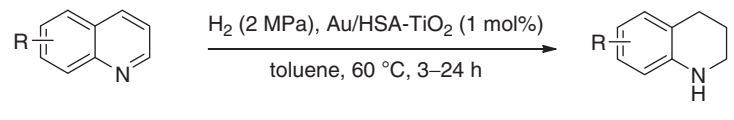


Scheme 26



Scheme 27

functional groups including halogens, ketones, and olefins (Scheme 28). The Au/HSA-TiO_2 catalyst allowed higher conversions and selectivities compared with other noble metals (Pd, Pt, and Ru) with identical particle size supported on HSA-TiO_2.



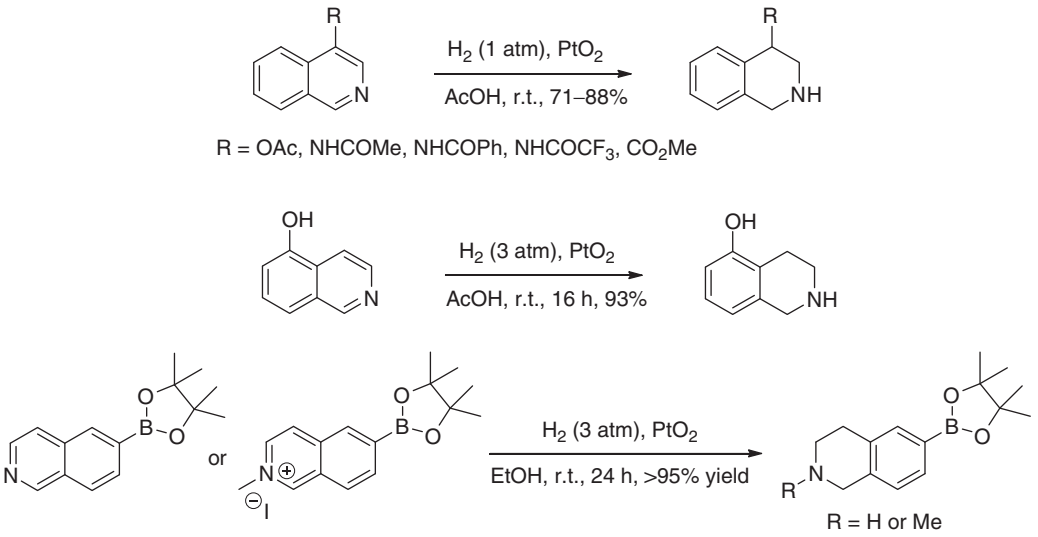
R = H, 6-MeO, 8-NH_2, 8-OH, 5-(Cl)-8-(OH), 6-F, 6-Cl, 6-CH_3C=O, 7-CH=CH_2

Scheme 28

Finally, the catalytic hydrogenation of organic compounds using the $NiCl_2$-Li-naphthalene or the $NiCl_2$-Li-(polymer-supported naphthalene) combination under an atmosphere of hydrogen (1 atm)[42] has been efficiently applied to the reduction of quinoline to the corresponding 1,2,3,4-tetrahydroquinoline. Using these conditions, isoquinoline *N*-oxide and pyridine *N*-oxide afford the corresponding deoxygenated compounds.

8.21.3.1.1.1.3 Isoquinolines and isoquinolinium salts

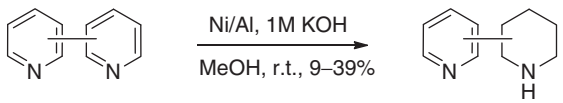
Isoquinolines are conveniently hydrogenated over Adam's catalyst under a low pressure of hydrogen to afford the corresponding saturated heterocycles (Scheme 29).[43] Variously substituted 1,2,3,4-tetrahydroisoquinolines can be readily prepared in high yields starting from either the free base or the *N*-alkyl pyridinium compound.



Scheme 29

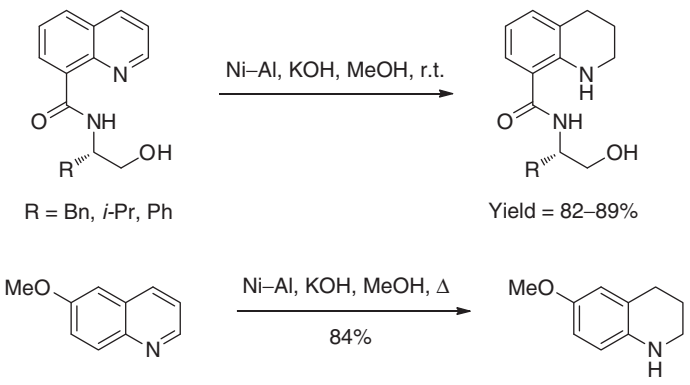
8.21.3.1.1.2 Heterogeneous catalytic transfer hydrogenation

Another method for the saturation of pyridine and quinoline rings relies on transfer hydrogenation reactions. Using nickel–aluminum alloy in potassium hydroxide solution, bipyridines are reduced to piperidinylpyridines in modest yields (Scheme 30).[44] The reduction is selective and depends on the substitution of the ring, 3-substituted rings being reduced in preference to 4- and 2-substituted compounds. Reduction of the symmetrical 2,2′- and 4,4′-bipyridines also affords the corresponding piperidinylpyridines, whereas 3,3′-bipyridines are much less reactive.



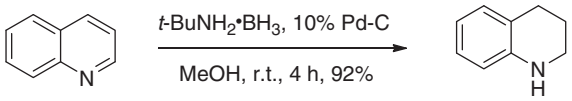
Scheme 30

Although moderate yields are observed for the Ni/Al alloy reduction of bipyridines, this method can be efficiently used for the preparation of 1,2,3,4-tetrahydroquinolines from the corresponding quinolines (Scheme 31).[45]



Scheme 31

Other efficient hydrogen-transfer conditions capable of reducing quinoline are provided by palladium-catalyzed methanolysis of borane–amine adducts.[46] Thus, the use of *tert*-butylamine borane allows this transformation in higher yield and under milder conditions than with the previously reported pyridine–borane/acetic acid system (Scheme 32).



Scheme 32

A general and mild procedure has been developed for the reduction of pyridine *N*-oxides by a transfer hydrogenation reaction using ammonium formate as the hydrogen source, in the presence of palladium on carbon (**Table 1**).[47] A variety of pyridine, quinoline, and isoquinoline *N*-oxides are efficiently converted into their piperidine derivatives in good to excellent yields and several reducible functionalities such as methoxycarbonyl, carboxyl, amino, hydroxyl, and amide are unaffected with this system; although when a chlorine atom is present, dehalogenation cannot be avoided.

Partial reduction occurs in the case of an *N*-oxide bearing a carboxylate group in the 3-position, and the conjugated enamidoester is obtained instead of the piperidine ring (entry x).[48] The HCO_2NH_4/Pd-C system is not limited to pyridine *N*-oxides and bisquinolines can be reduced as well into the corresponding biquinolyls (entry xi).[49] Closely related to this system, a simple procedure using deuterated ammonium formate and Pd/C allows the preparation of highly deuterated, substituted piperidines and tetrahydroquinolines.[50]

8.21.3.1.2 Diastereoselective reductions

8.21.3.1.2.1 Pyridines and pyridinium salts

In the case of substituted pyridines, catalytic hydrogenation yields predominantly the *cis*-substituted diastereomers and with some exceptions, high diastereoselectivities are commonly observed (**Scheme 33**).[51]

Chiral pyridine derivatives undergo diastereoselective reduction with diastereomeric excesses reaching up to 99%. The PtO_2-catalyzed hydrogenation of pyridines or *N*-alkylpyridiniums is a common method for the stereoselective synthesis of chiral-substituted piperidines,[52] which are important building blocks and fragments of many biologically active compounds like (–)-myrionidine[52a] or 1-*epi*-lentiginosine[52b] (**Scheme 34**).

However, the catalytic hydrogenation of a pyridine ring bearing a prochiral function such as a carbonyl group allows the formation of the corresponding piperidine with high diastereoselectivity. Thus, concomitant reduction of the carbonyl and pyridyl groups in the presence of a quinoline moiety using PtO_2 under acidic conditions delivers diastereoselectively the pentafluorosulfanyl analog of mefloquine.[53] Moreover, 2,2′-biquinoline can be reduced to the corresponding octahydrobiquinoline with a moderate *dr* (3:1 mixture of the *meso* and racemic forms) (**Scheme 35**).[54]

The asymmetric hydrogenation (AH) of auxiliary-substituted pyridines with achiral heterogeneous catalysts was first studied with nicotinic acid derivatives covalently bound to various chiral auxiliaries using Pd-, Rh-, and Ru-supported catalysts and showed moderate diastereoselectivities (up to 31% *dr*, **Scheme 36**).[55]

An efficient auxiliary-based method for the asymmetric reduction of substituted pyridines using standard achiral heterogeneous hydrogenation catalysts has subsequently been developed by Glorius et al.[56] The hydrogenation of 2-oxazolidinone-substituted pyridines under a high pressure of hydrogen (100 bar) using platinum-, rhodium-, and palladium-based catalysts directly affords the corresponding piperidines in good yields and with high enantiomeric excesses (up to 98%) through traceless cleavage of the chiral auxiliary under the reaction conditions (**Scheme 37**).

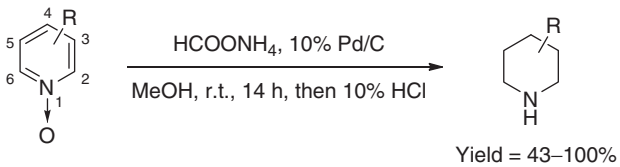
A plausible mechanism accounting for the observed selectivities involves a protonated intermediate that is rigidified by a strong H-bond between the pyridinium and the oxazolidinone moiety. The R group on the oxazolidinone shields the top face, whereas the bottom face is accessible for adsorption to the heterogeneous catalyst. The hydrogen atoms transfer leading to the stereoselective formation of an aminal-type structure (**Scheme 38**). This compound can then dissociate into the corresponding oxazolidinone and iminium, which is in equilibrium with the respective enaminium salt. Hydrogenation of the resulting C═N or C═C bond would result in the formation of the piperidine compounds.

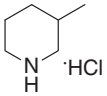
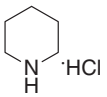
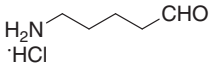
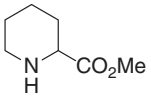
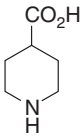
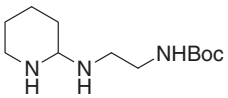
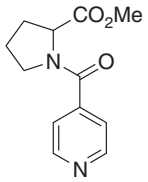
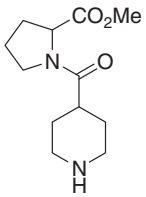
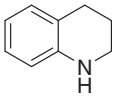
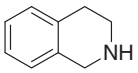
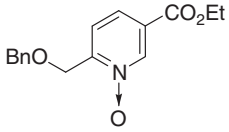
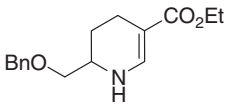
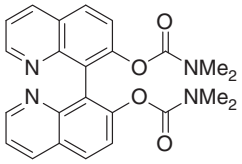
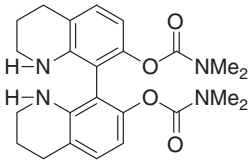
This method was applied to the total synthesis of (+)-coniine and of the macrocyclic spermidine alkaloid (–)-isooncinotine (**Scheme 39**).[57]

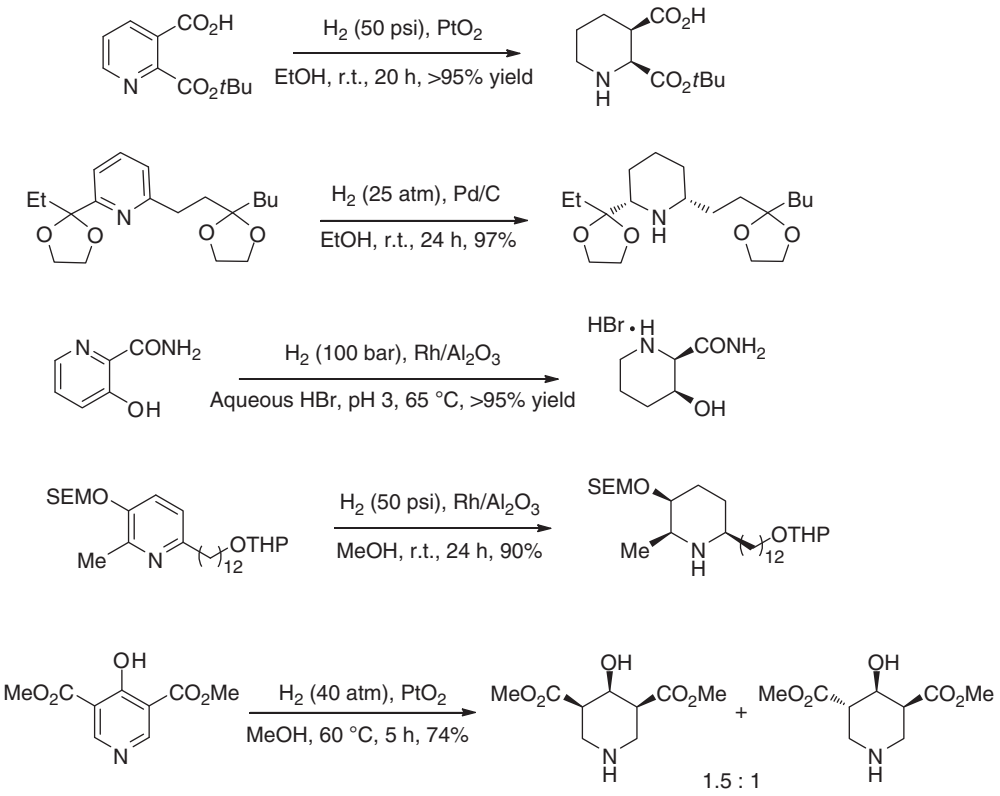
8.21.3.1.2.2 Quinolines

Enantiomerically pure decahydroquinolines can be prepared in two steps via stereoselective hydrogenation of substituted quinolines.[58] In the first step, the highly regioselective PtO_2-catalyzed hydrogenation of the carbocyclic ring of the quinoline occurs using trifluoroacetic acid as a solvent under 20 bar of hydrogen pressure. Under these conditions, the corresponding 5,6,7,8-tetrahydroquinolines are formed with *dr* up to 89:11 (**Scheme 40**). In a second hydrogenation step, the completely saturated decahydroquinolines are obtained in high yields using Rh/C as a catalyst in acetic acid at 150 bar of hydrogen. The reduction is highly *cis*-selective and the diastereomeric ratio of the products depends on the *dr* of the starting material. High *ee*s are observed for the major diastereomer (97%–99% *ee*), although the minor diastereomer is obtained in only moderate *ee*. This method is particularly attractive since in addition to the formation of 1,2,3,4-tetrahydroquinolines, stereocenters in the 5-, 6-, 7-, and 8-positions of the decahydroquinoline ring system can be efficiently controlled.

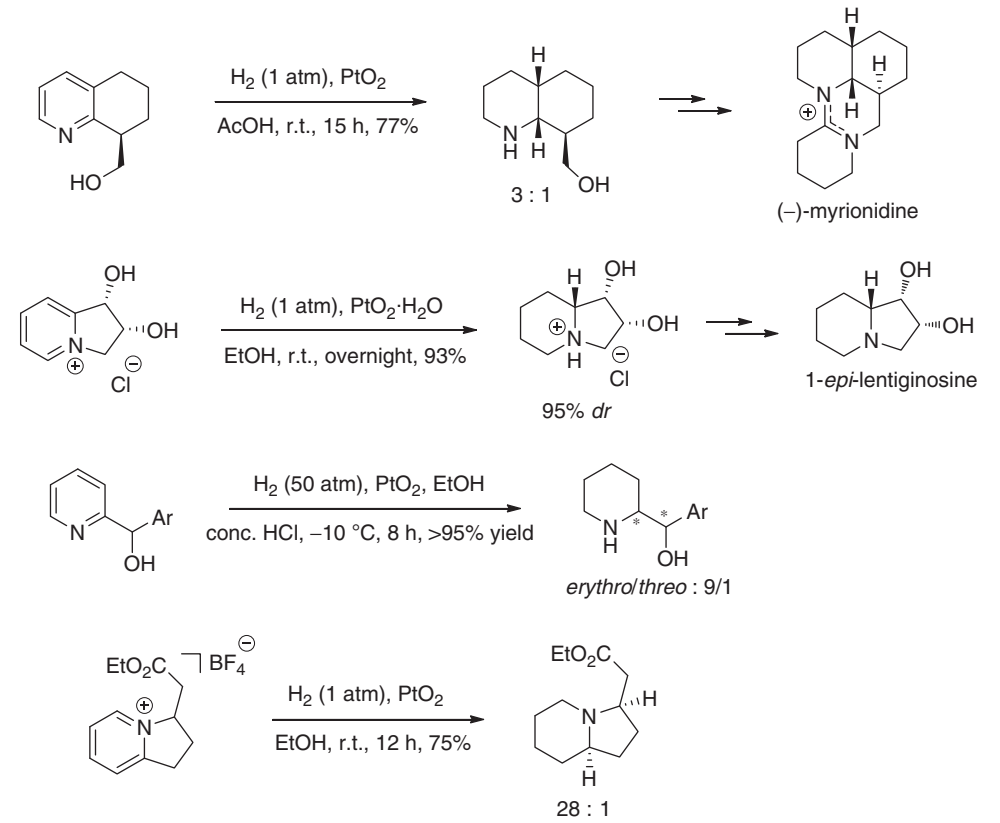
Table 1 Reduction of pyridine *N*-oxides with $HCOONH_4$/Pd-C system



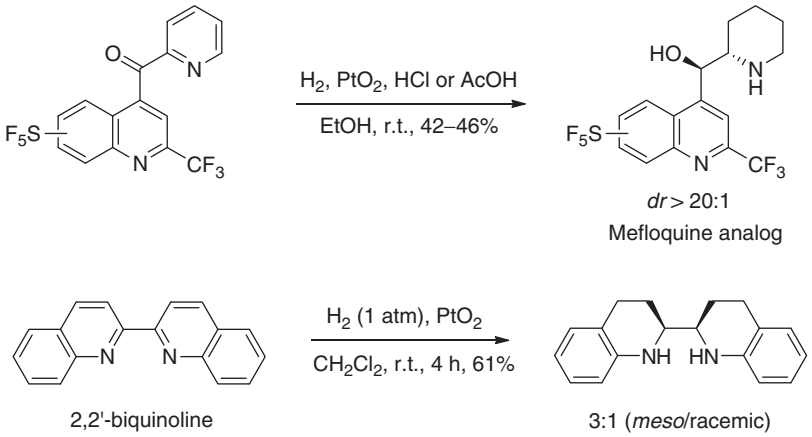
Entry	*R/Substrate*	*Product*	*Yield (%)*	*References*
i	3-CH_3		100	47
ii	2-Cl		100	47
iii	2-OH		98	47
iv	2-CO_2CH_3		84	47
v	4-CO_2H		99	47
vi	2-$NH(CH_2)_2NHBoc$		85	47
vii			84	47
viii	Quinoline *N*-oxide		87	47
ix	Isoquinoline *N*-oxide		84	47
x			76	48
xi			98	49



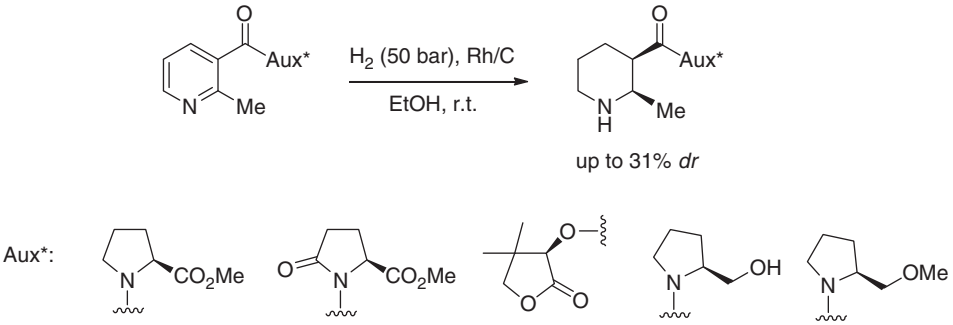
Scheme 33



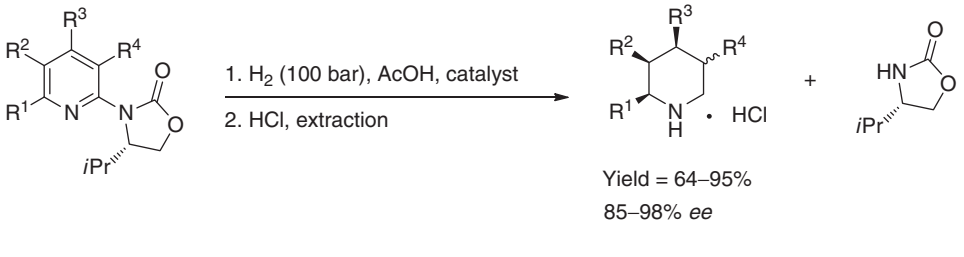
Scheme 34



Scheme 35



Scheme 36



Scheme 37

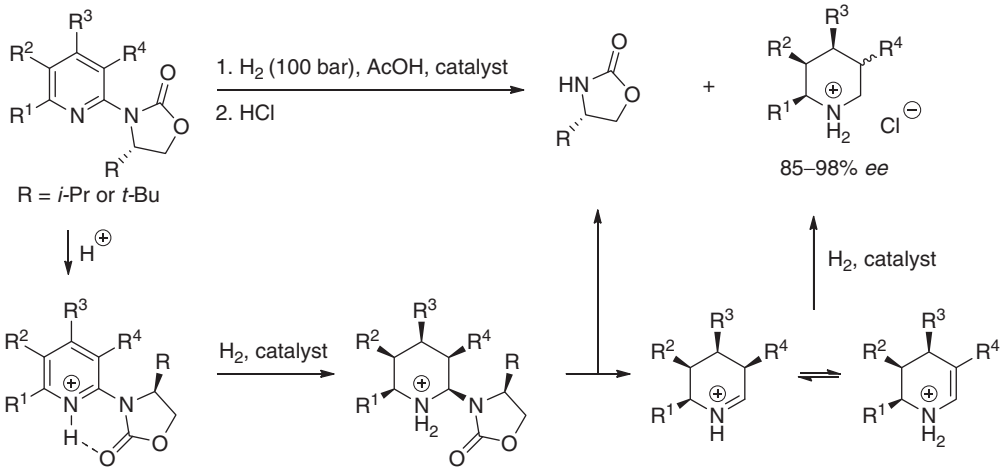
8.21.3.2 Homogeneous Catalysis

8.21.3.2.1 Racemic reductions

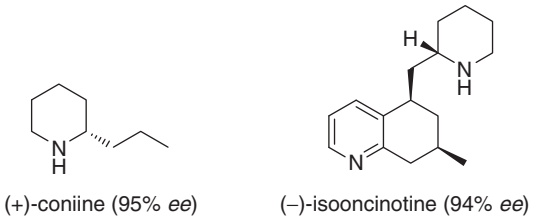
As pointed out in Section 8.21.3.1, the heterogeneous catalytic reduction of pyridines and benzo analogs using platinum group catalysts (Ru, Rh, Pd, Ir, and Pt) has been well documented in the literature. In sharp contrast, homogeneous catalytic systems for the reduction of such *N*-heteroaromatic compounds have been much less explored.

8.21.3.2.1.1 Pyridines

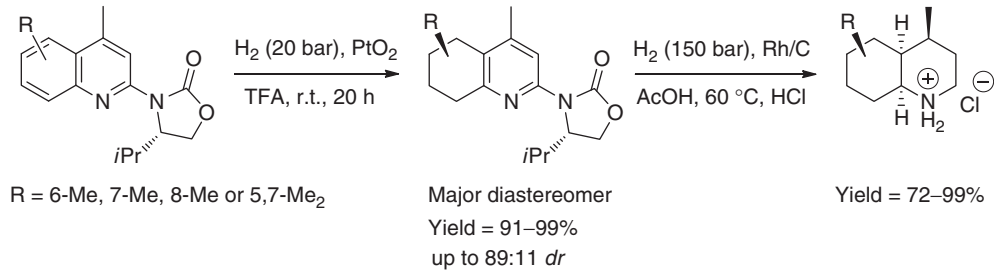
Harrod, Samuel et al. described the first example of titanocene-catalyzed homogeneous hydrosilylation/transfer hydrogenation of pyridine derivatives.[59] In a typical reaction protocol using 10 mol% of Cp_2TiMe_2 as catalyst in the presence of 2 equivalents of $H_2SiMePh$, simple pyridine and substituted pyridines give the corresponding *N*-silyl-dihydropyridine or



Scheme 38



Scheme 39



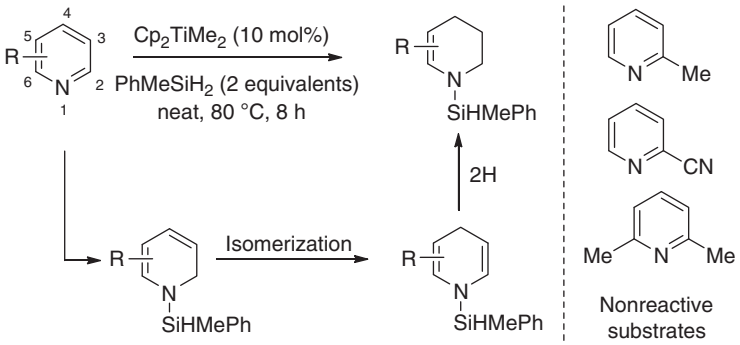
Scheme 40

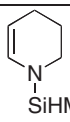
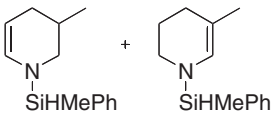
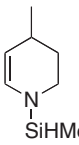
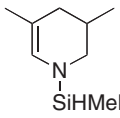
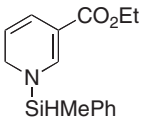
N-silyl-tetrahydropyridine products in good to excellent yields ranging from 70% to 100%, depending on the substitution patterns. Compounds with a methyl group in the 3-, 4-, and 3,5-positions provide *N*-silyl-tetrahydropyridines through a sequence involving a hydrosilylation/isomerization process producing 1,4-addition products followed by concomitant hydrogen transfer from Si–H catalyzed by Cp_2TiMe_2. Conversely, reaction of a pyridine bearing an ester group in the 3-position gives exclusively the 1,6-hydrosilylation product in quantitative yield, whereas pyridines with substituents in the 2- and/or 6-positions are unreactive under the above-mentioned reaction conditions (Table 2).

Nikonov et al. reported a cationic Ru-catalyzed hydrosilylation of pyridines using $HSiMe_2Ph$ as reducing agent.[60] The special feature of this process compared with conventional reduction methods (which usually give mixtures of 1,2- and 1,4-dehydropyridines[61]) is highlighted by the selective formation of *N*-silyl-1,4-dehydropyridines under mild conditions. More particularly, pyridine derivatives bearing methyl or chloride substituents in the 3- and/or 5-positions provide the corresponding *N*-silyl-1,4-dihydropyridines with high selectivity and in good to excellent conversions ranging from 82% to 100% (Table 3).

Although this catalytic system provides selective 1,4-monoreduction products, this protocol cannot be generalized. Indeed, reaction of 2-bromopyridine leads to a 1/4 mixture of pyridine and silylated 1,4-dihydropyridine with low overall conversion, which suggests that the 2-bromopyridine initially undergoes dehalogenation before hydrosilylation. Pyridines bearing a carbonyl group in the 3-position were also not good substrates for this transformation, since a mixture of partially reduced *N*-silylated

Table 2 Ti-Catalyzed hydrosilylation/transfer hydrogenation of pyridines with $PhMeSiH_2$



Entry	*R*	*Product*	*Yield (%)*
i	H		94
ii	3-Me		85 (3:2)
iii	4-Me		83
iv	3,5-diMe		70
v	3-CO_2Et		100

pyridines was obtained. In addition, as depicted in Table 3, the reaction does not work for 2-, 4-, and/or 6-substituted pyridines, which demonstrates that the steric accessibility of the nitrogen center is crucial for the success of this process.

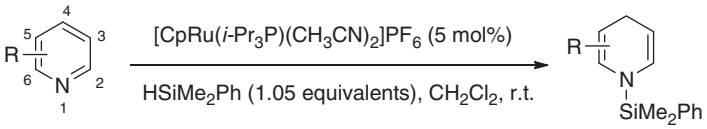
A plausible mechanism accounting for the observed 1,4-selectivity has been proposed by the authors. Reaction of cationic $[CpRu(i\text{-}Pr_3P)(CH_3CN)_2]PF_6$ with $HSiMe_2Ph$ gives σ-silane Ru-complex **A**, which then undergoes nucleophilic abstraction of the silylium ion by the pyridine substrate to form neutral ruthenium hydride complex **B**. A subsequent 1,4-hydride transfer furnishes the *N*-silyl-1,4-dihydropyridine and Ru complex **C**, which can bind another molecule of silane and restart the catalytic cycle (Scheme 41).

Zhou et al. reported the $[Ru(p\text{-cymene})I_2]_2$ catalyzed selective 1,4-reduction of diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate resulting in the formation of the corresponding Hantzsch ester under high hydrogen pressure (1000 psi) (Scheme 42).[62] Although a moderate conversion of 69% was obtained, this protocol has been successfully employed for the *in situ* regeneration of the reducing Hantzsch dihydropyridine from the Hantzsch pyridine under H_2 for biomimetic AH in the presence of Brønsted acid (*vide infra*).[62]

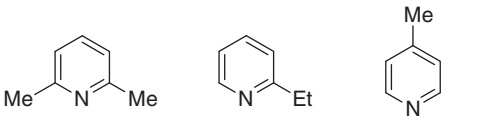
8.21.3.2.1.2 Quinolines

Harrod, Samuel et al. have extended the use of their titanocene/$H_2SiMePh$ catalytic system for the homogeneous hydrosilylation/transfer hydrogenation reactions of simple quinoline.[59] Using the above-mentioned optimized conditions employed for the reduction of pyridine derivatives, a 3/1 mixture of the corresponding 1,2,3,4-tetrahydroquinoline and 1,4-dihydroquinoline was obtained in 74% yield (Scheme 43).

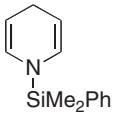
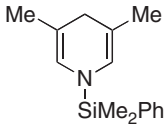
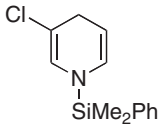
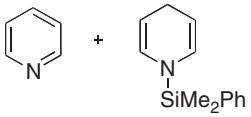
Table 3 Ru-catalyzed hydrosilylation of pyridines with $HSiMe_2Ph$

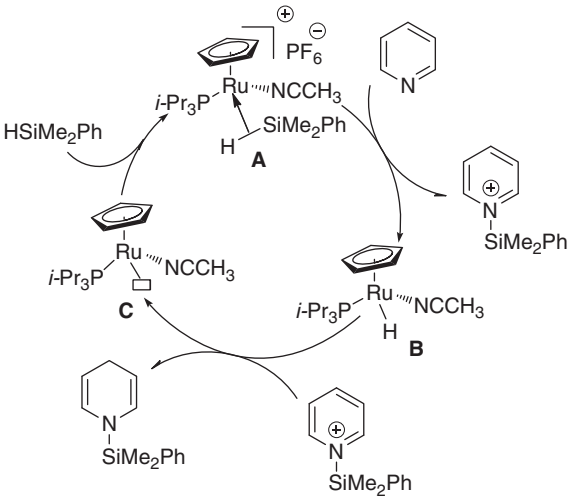


Nonreactive substrates:



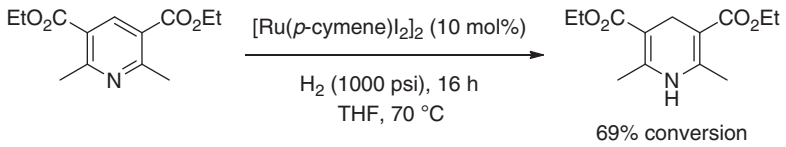
24 h Conversion 0% | 3 h Conversion 0% | 24 h Conversion 0%

Entry	*R*	*Product*	*Conversion (%)*
i	H		86
ii	3,5-diMe		82
iii	5-Cl		100
iv	2-Br		47 (1:4)

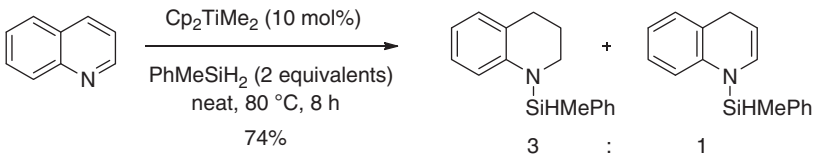


Scheme 41

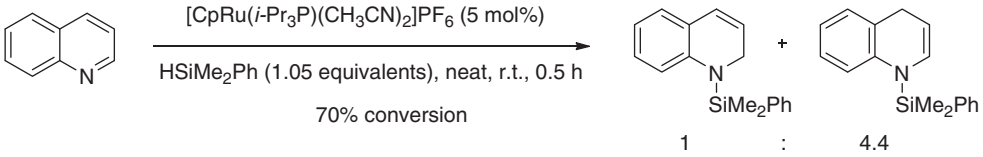
Similary, the catalytic system $[CpRu(i\text{-}Pr_3P)(CH_3CN)_2]PF_6/HSiM_2Ph$, which has been successfully used for the selective 1,4-hydrosilylation of pyridines by Nikonov et al., proved to be also effective using quinoline as substrate.[60] Under solvent-free conditions, a 1/4.4 mixture of *N*-silyl-1,2-dihydroquinoline and *N*-silyl-1,4-dihydroquinoline was obtained with a moderate conversion of 70% (Scheme 44).



Scheme 42



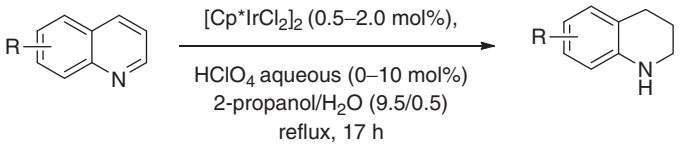
Scheme 43



Scheme 44

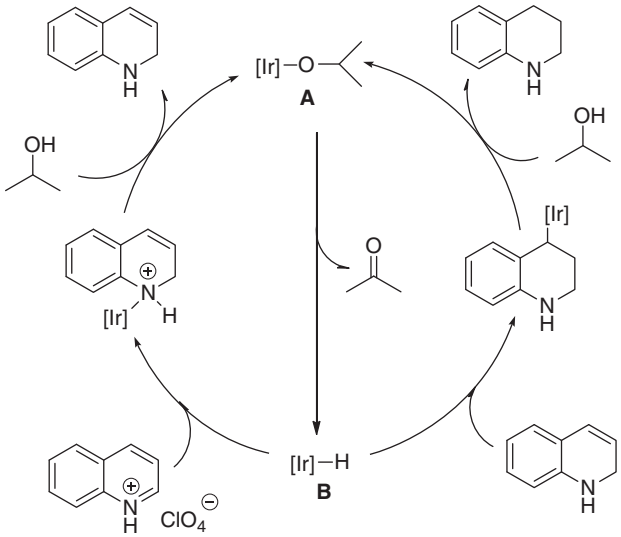
An efficient method for the homogeneous transfer hydrogenation of substituted quinoline derivatives catalyzed by CpIr complexes using 2-propanol as hydrogen source has been developed by Fujita, Yamaguchi et al.[63] The use of $HClO_4$ as additive and a small amount of water not only greatly accelerated the reaction rate but also completely suppressed the formation of the undesired *N*-isopropyl-1,2,3,4-tetrahydroquinoline byproducts. This process accommodates the use of various electron-donating and electron-withdrawing functional groups on the phenyl ring providing the 1,2,3,4-tetrahydroquinoline compounds in good to excellent yields ranging from 64% to 93%. However, isoquinoline and pyridine derivatives do not react under such conditions probably because of catalyst poisoning due to the higher basicity of these compounds (Table 4).

Table 4 Ir-catalyzed asymmetric transfer hydrogenation of quinolines



Entry	*R*	*Ir Cat (mol%)*	*Yield (%)*
i	H	0.5	93
ii	2-Me	1.0	91
iii	3-Me	1.0	98
iv	4-Me	1.0	87
v	6-Me	1.0	95
vi	6-NO_2	2.0	94
vii	6-Cl	1.0	78
viii	6-COOH	2.0	64
ix	6-OMe	1.0	79

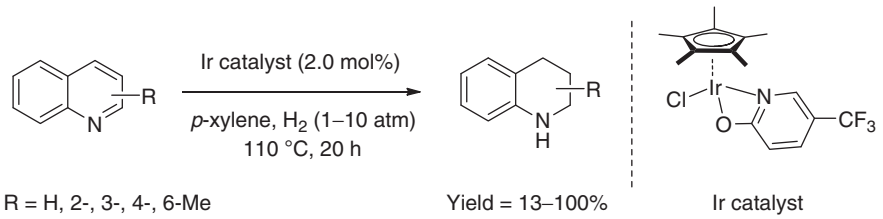
A plausible mechanism accounting for the regio- and chemoselective transfer hydrogenation of quinolines has been proposed by the authors (Scheme 45). In the first step, the dimeric Cp*iridium dichloride complex is converted into alkoxide complex **A**. *β*-Elimination then yields active iridium monohydride species **B** and acetone. Subsequent 1,2-hydride transfer into the C=N double bond of the quinolinium salt generated *in situ* from the reaction with $HClO_4$ followed by protonolysis gives the corresponding 1,2-dihydroquinoline and regenerated alkoxide complex **A**. After insertion of the C–C double bond of the



Scheme 45

1,2-dihydroquinoline into the iridium hydride bond followed by a novel protonolysis, the product is released and the alkoxide complex **A** is formed again, closing the catalytic cycle.

Fujita, Yamaguchi et al. also reported that Cρ*Ir complexes containing 2-pyridonate as functional ligand were effective catalysts for the hydrogenation of quinoline derivatives.[64] The introduction of an electron-withdrawing group such as trifluoromethyl in the 5-position of the pyridonate ligand was found to be essential for attaining high catalytic activity. Under low hydrogen pressure, 2- and 6-methyl-substituted quinolines were converted to the corresponding 1,2,3,4-tetrahydroquinolines in quantitative yields, whereas quinolines bearing a methyl group in the 3- or 4-positions provided significantly lower yields, 58% and 13%, respectively. These low yields are probably due to the much lower reactivity of a trisubstituted double bond toward hydrogenation in this system (Scheme 46).

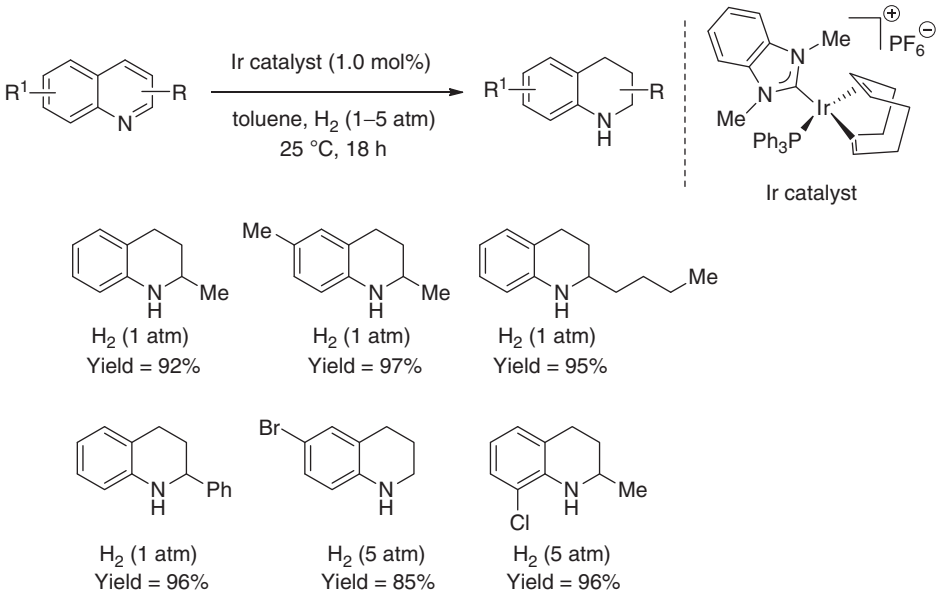


Scheme 46

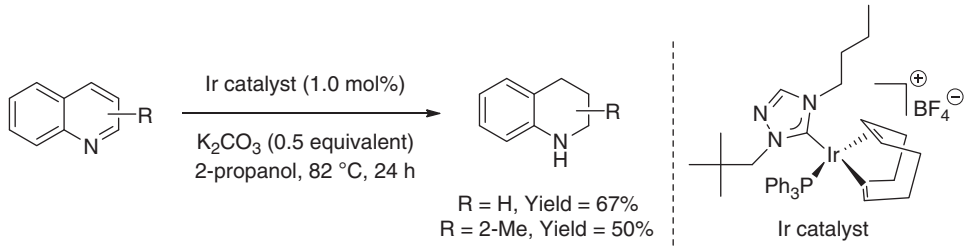
Crabtree, Eisenstein et al. disclosed that iridium catalysts containing *N*-heterocyclic carbenes (NHCs) as ancillary ligands were highly effective for the reduction of quinoline derivatives under very mild reaction conditions.[65] The complex featuring a benzimidazole NHC ligand comprising methyl wingtips provide the best catalytic activity. It should be noted that the addition of a catalytic amount of iodine did not improve the reaction outcome, which is in contrast to the case of some earlier catalysts. Further, the use of 1 mol% of triphenylphosphine greatly increased the reaction rate. In addition, this catalytic system proved to be both air and moisture stable and worked efficiently under low temperature and low hydrogen pressure (1–5 atm). Various quinoline derivatives with alkyl, aryl, and halogen substituents at the 2-, 6-, and 8-positions were smoothly reduced to the corresponding 1,2,3,4-tetrahydroquinolines in excellent yields (Scheme 47).

Crabtree et al. reported that a similar iridium NHC-based complex could be effective for the transfer hydrogenation reaction of quinolines using 2-propanol or HCOOH as hydrogen sources, thereby avoiding the use of high pressure of hydrogen, which is usually required by conventional hydrogenation.[66] Quinoline and 2-methylquinoline were completely reduced to the corresponding 1,2,3,4-tetrahydroquinolines in 67% and 50% yields, respectively. However, this protocol is rather very limited in substrate scope since only two examples were reported (Scheme 48).

The same group has shown that quinoline derivatives could be selectively reduced to the corresponding 1,2-dihydroquinolines through cationic $[Rh(COD)(PPh_3)_2]PF_6$ catalyzed hydrosilylation reaction with phenylsilane as hydride source in nonpolar solvents.[66] This protocol constitutes a complementary method to the use of the iridium NHC-based complex previously reported by the same authors (*vide supra*). In particular, a complete regioselective 1,2-reduction of quinoline derivatives, provides, in this

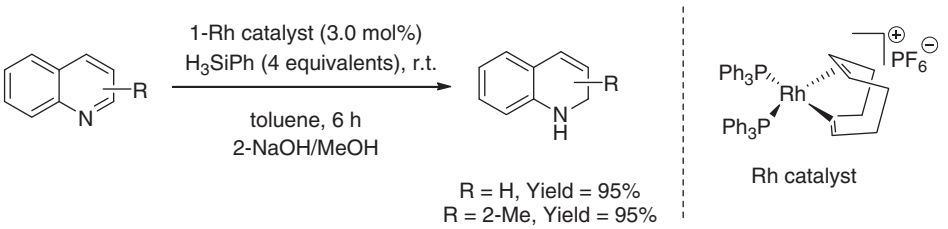


Scheme 47



Scheme 48

case, the corresponding dihydroquinolines, in excellent yields of approximately 95%. However, the substrate scope of this reaction is also very limited (Scheme 49).



Scheme 49

8.21.3.2.2 Enantioselective reductions

Until the mid-2000s, AH of heteroaromatic compounds such as pyridines and their benzo analogs was seldom documented in the literature, even if such a transformation is regarded as one of the most efficient and straightforward approaches to build up saturated or partially saturated enantiomerically pure cyclic amines, which are structural components of numerous biologically active natural products, drugs, and pharmaceuticals. There are three main reasons that may account for this situation. First, high temperatures and pressures are usually required for the reduction of nitrogen-based heteroaromatic compounds because of their high stability, which adversely affect the enantioselectivity. Second, the difficulty in achieving high activity and/or enantioselectivity may be ascribed to the lack of a secondary coordinating group to assist interaction between the substrate and the central metal atom as it is the case for the hydrogenation of ketones, imines, and olefins.[67] Third, the basic nitrogen atom can bind to the metal center to deactivate the catalyst or can simply serve as an achiral ligand. Despite these challenges, significant progress in the

development of transition-metal-catalyzed AH of pyridines and their benzo analogs has been made in the last past decade.[56b,68] To circumvent the problems mentioned above, three main strategies based on catalyst activation, substrate activation, and dual activation have been reported in the literature (Figure 1). Catalyst activation involves the use of additives and the development of more effective ligands by fine-tuning of their steric and electronic properties to form more active catalytic systems. Substrate activation consists in increasing the substrate reactivity toward hydrogenation by the introduction of activators next to or on the nitrogen atom, which results in partial destruction of the substrate aromaticity and alternatively serves as a secondary coordination site to the catalyst. Finally, dual activation involves the combination of the two strategies.

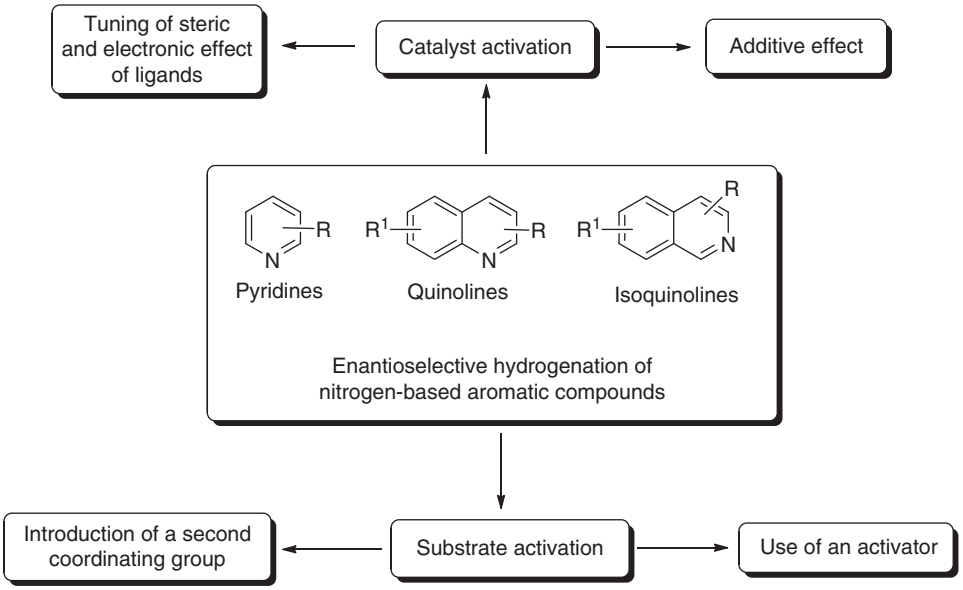


Figure 1

8.21.3.2.2.1 Pyridines and pyridinium salt

Chiral piperidines constitute one of the most common substructures in many biologically active natural products and represent important targets for pharmaceutical research, with thousands of them mentioned as drug candidates in clinical and preclinical studies. Consequently, impressive efforts have been directed toward the development of general methods and strategies for the enantioselective synthesis of piperidine derivatives over the past decades. Among them, AH of pyridine derivatives is undoubtedly one of the most direct and effective approaches to obtain optically active piperidines. However, until now, there are only limited reports about AH of pyridine derivatives.

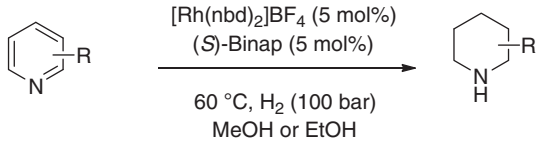
The first example of rhodium-catalyzed enantioselective hydrogenation of 2- or 3-carboxylic pyridine derivatives has been described by Studer et al.[69] Only poor results were obtained in terms of both conversion and selectivity under high hydrogen pressure (100 bar) and high catalyst loading (5 mol%) (Table 5). However, although the selectivity of the reaction was low (up to 26% *ee*), these disappointing results, which have been attributed to the deactivation and/or poisoning of the catalyst by the pyridine or piperidine ring, clearly demonstrated the feasibility of developing an asymmetric version.

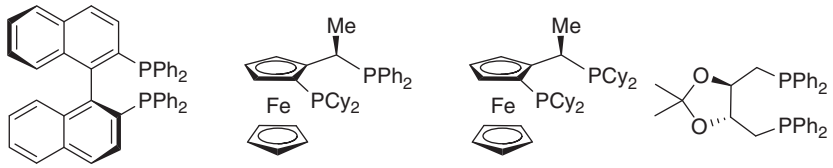
Charette et al. reported the first highly enantioselective iridium-catalyzed AH of *N*-benzoyliminopyridinium ylide derivatives.[70] Among various 2-methyl-pyridines and pyridinium salts, only *N*-benzoyliminopyridinium ylide, which activates the substrate and offers a secondary coordinating group, was reduced under hydrogen pressure (500 psi) with almost complete conversion but with only 13% enantioselectivity using $[Ir(COD)Cl]_2$/BINAP/I_2 catalytic system (Scheme 50).

A wide range of 2-substituted *N*-benzoyliminopyridinium ylides were successfully hydrogenated using a cationic iridium complex derived from phosphino oxazoline ligands at r.t. under 400 psi of H_2 to give the corresponding piperidine derivatives in excellent yields (85–98%) and variable enantioselectivities (54–97% *ee*). 2,3- or 2,5-Disubstituted *N*-benzoyliminopyridinium ylides were not suitable substrates for this transformation since only moderate selectivity were achieved. The use of an equimolar amount of iodine with respect to the iridium(I) catalyst is a key factor for attaining high catalytic activity. It was suggested that the role of iodine in this reaction is to oxidize the initial iridium(I) complex to the more active iridium(III) precatalyst. It is also noteworthy to mention that depending on the substrates, small amounts of remaining tetrahydropyridine derivatives, which can be further fully hydrogenated using Pd/C, were obtained (Table 6). This dual activation strategy of both substrates and catalysts is a successful example of efficient AH of pyridine derivatives.

Zhou et al. have extended their $[Ir(COD)Cl]_2$/diphosphines/I_2 catalytic system, which had been previously employed for the AH of quinoline derivatives (*vide infra*), to the enantioselective partial reduction of pyridine derivatives.[71] A variety of 2-alkyl and

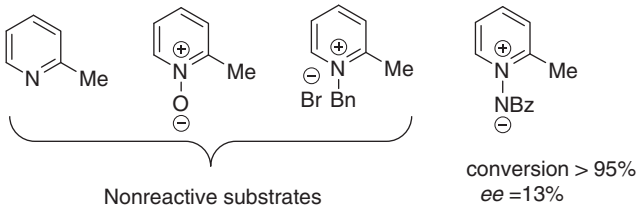
Table 5 Rh-catalyzed AH of pyridines





(*S*)-Binap (*R*,*S*)-Cy_2PF-PPh_2 (*R*,*S*)-Cy_2PF-PCy_2 (*R*,*R*)-Diop

Entry	*R*	*Ligand*	*Solvent*	*Yield (%)*	ee *(%)*
i	2-COOH	(*R*,*R*)-Diop	EtOH	14	26
ii	2-COOEt	(*R*)-Binap	EtOH	96	25
iii	3-COOH	(*R*,*S*)-Cy_2PF-PPh_2	MeOH	8	17
iv	3-COOEt	(*R*,*S*)-Cy_2PF-PPh_2	MeOH	45	12



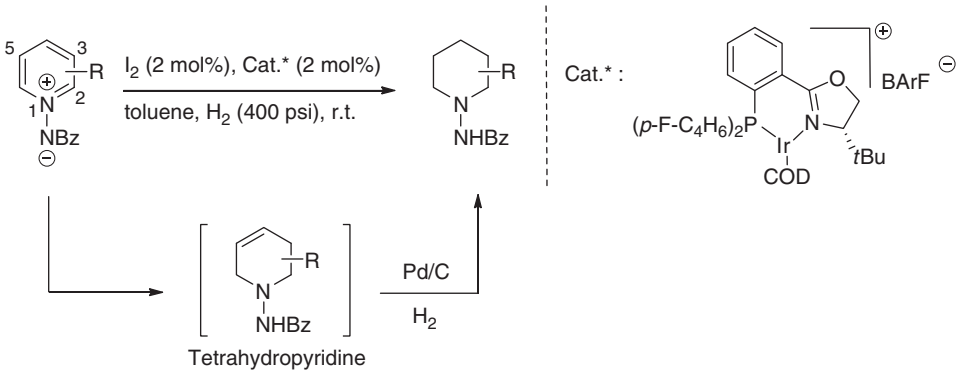
Scheme 50

2-phenyl substituted 7,8-dihydro-quinolin-5-(6H)-ones were hydrogenated to the corresponding hexahydroquinolines with moderate to good yields (57–98%) and good to excellent enantioselectivities (84–97% *ee*) using (*S*)-MeO-BiPhep as ligand (Table 7). However, a major drawback of this study lies in the use of highly toxic benzene as solvent to achieve high *ee*. A plausible explanation that may account for the good reactivity of 7,8-dihydro-quinolin-5-(6H)-one derivatives toward hydrogenation reactions is the presence of a strong electron-withdrawing carbonyl group at the 5-position. The authors suggested that such strong electron-withdrawing group considerably reduces the basicity of the products and thereby suppresses the catalyst deactivation. It may also contribute to the stabilization of the unreacted double bond of the tetrahydropyridine products. Based on this finding, trisubstituted substrates bearing other electron-withdrawing groups were also tested. However, compounds with an ester or a sulfonyl group were completely unreactive, whereas the cyano-substituted pyridine derivative provided good enantioselectivity (85% *ee*) but only 21% conversion.

Two years after the pioneering work of Zhou group regarding the AH of pyridine derivatives, Xu et al. found that electron-deficient diphosphine ligands such as P-Phos and DifluorPhos were more effective for this transformation compared with the electron-rich MeO-BiPhep ligand (Scheme 51).[72] Indeed, various 2-alkyl and 2-phenyl trisubstituted pyridines were hydrogenated at low catalyst loading (S/C ratio up to 1000) to give the corresponding piperidine derivatives in excellent yields (up to 99%) and with excellent enantioselectivity (up to 98% *ee*) in less toxic solvents including dichloromethane and 1,2-dichloroethane. Similar to quinolines, no reaction occurs in the absence of I_2 and after several trials it was found that 15–20% fold excess of iodine with respect to the iridium(I) catalyst is necessary for attaining high catalytic activity.

Zhou et al. reported a highly efficient iridium-catalyzed enantioselective hydrogenation of 2-substituted *N*-benzylpyridinium salts to give chiral 2-substituted *N*-benzylpiperidines.[73] The key to developing such successful catalytic process was to design more reactive *N*-benzyl-pyridinium bromide compounds that simultaneously greatly enhance the reactivity of the substrates and prevented deactivation of the catalyst by effectively eliminating coordination of the substrate to the metal center. AH of diverse 2-arylsubstituted pyridinium bromide salts using 1 mol% of $[Ir(COD)Cl]_2$/(*R*)-SynPhos as catalyst in a 1:1 mixture of PhMe/CH_2Cl_2 at 28 °C under 600 psi of hydrogen pressure provided the corresponding reduced products in excellent yields (82–99%) and with good to excellent enantioselectivities (84–93% *ee*) (Table 8). However, only moderate selectivities were obtained for the

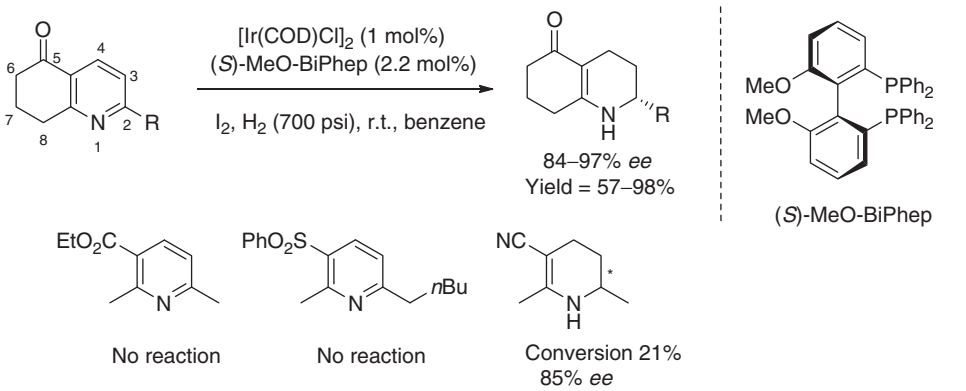
Table 6 Ir-catalyzed AH of substituted *N*-benzoyliminopyridium ylides



Entry	*R*	*Yield (%)*	ee *(%)*
i	2-Me	98	90
ii	2-Et	96	94
iii	2-*n*-Pr	98	97
iv	2-Bn	97	84
v	2-CH_2OBn	85	85
vi	2-$(CH_2)_3OBn$	88	92
vii	2,3-Me_2	91 [>95/5][a]	54
viii	2,5-Me_2	92 [57/43][a]	86/84

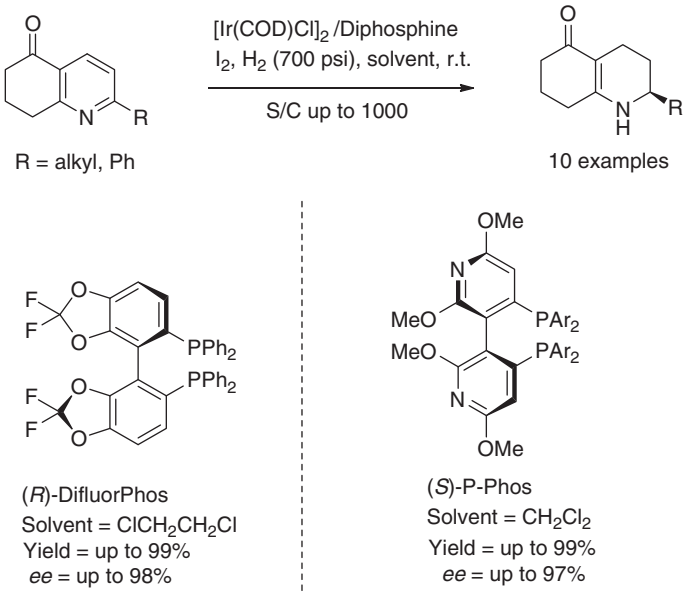
[a]Diastereomeric ratios are shown in brackets.

Table 7 Ir-catalyzed AH of trisubstituted pyridines



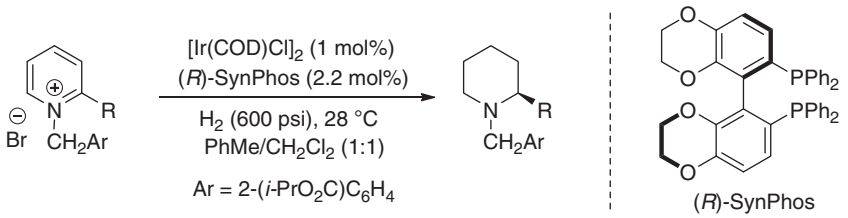
Entry	*R*	*Yield (%)*	ee *(%)*
i	Me	80	90
ii	*n*-Pr	91	94
iii	*n*-pent	98	97
iv	*i*-Pr	87	84
v	Bn	95	85
vi	Ph	57	92
vii	Phenethyl	76	92

hydrogenation of 2-alkylsubstituted pyridinium bromide salts with this catalytic system (up to 65% *ee*). Notably and in sharp contrast to isoquinolines, no base was used in this process. It was suggested that the stoichiometric amount of hydrogen bromide generated *in situ* had a beneficial effect on the stereochemical outcome of the reaction by inhibiting the coordination ability of the desired product through the formation of its piperidine hydrogen bromide salt.



Scheme 51

Table 8 Ir-catalyzed AH of 2-substituted pyridinium salts



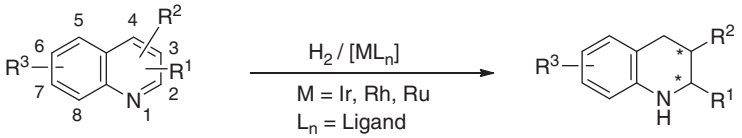
Entry	*R*	*Yield (%)*	ee *(%)*
i	Ph	99	90
ii	4-FC_6H_4	99	93
iii	4-$CF_3C_6H_4$	96	93
iv	4-MeC_6H_4	99	89
v	4-$MeOC_6H_4$	99	92
vi	3-$MeOC_6H_4$	93	92
vii	2-MeC_6H_4	82	78
viii	Bn	99	59
ix	*i*-Pr	60	65

8.21.3.2.2.2 Quinolines and quinolinium salts

Tetrahydroquinoline derivatives serve as leading therapeutic agents in pharmaceutical and agrochemical industry. Direct AH of readily available quinoline derivatives is an atom-economical and straightforward route to enantiomerically enriched tetrahydroquinoline derivatives, which are important core scaffolds found in numerous natural products and biologically active molecules.

Zhou and coworkers reported the first example of highly efficient enantioselective hydrogenation of quinolines using an iridium/MeO-BiPhep/I_2 catalytic system.[74] Since this significant breakthrough, exciting advances have been achieved in this field, with activation of catalysts and/or substrates. As a result, numerous highly efficient catalytic systems based on Ir, Rh, and Ru complexes have been successfully developed (**Scheme 52**).

A wide variety of chiral ligands has been used, including bidentate phosphorus ligands, especially atropisomeric biaryl diphosphines, diphosphonite ligands, phosphine–phosphoramidite ligands as well as other phosphorus-containing ligands such as N,P-ligands, S,P-ligands, and monodentate phosphine ligands. Chiral diamine ligands have also been shown to be highly

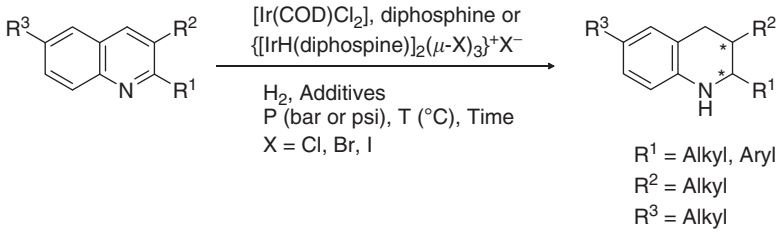


Scheme 52

effective for this transformation.[68] Finally, although hydrogen gas (H_2) is by far the most widely employed hydrogen source for the enantioselective reduction of quinolines, other hydrogen donors such as Hantzsch esters, water/silane mixture, or HCOOH/Et_3N system have been successfully used. Nowadays, this reaction has become a benchmark for testing newly developed ligands.

8.21.3.2.2.2.1 Chiral bidentate phosphorus ligands

The enantioselective hydrogenation reaction of quinoline derivatives has been extensively studied.[56b,68c,75] As far as transition-metal-catalyzed hydrogenation of 2-substituted alkyl- and aryl quinolines with chiral bidentate phosphorus ligands is concerned, several parameters have been considered such as the influence of the catalysts, the role of the additives and the reaction conditions. The hydrogenations have been carried out either by using *in situ* generated chiral iridium catalysts prepared by mixing [Ir(COD)Cl_2] and the chiral ligands or the preformed Ir(III) complexes $\{[IrH(diphospine)]_2(\mu\text{-}X)_3\}^+X^-$ (X=Br, Cl, I) (Scheme 53).[76]



Scheme 53

Zhou et al. first reported the iridium-promoted AH of a range of quinoline derivatives with high functional group tolerance and substrate scope.[74,77] The preliminary studies started with (*R*)-MeO-Biphep as chiral ligand. Excellent yields up to 94% and enantioselectivities up to 96% were obtained. A strong solvent dependence and a crucial role of additives (n-Bu_4NI, BiI_3, phthalimide, benzylamine, KI, NIS, and MeI) were demonstrated, toluene and iodine being, respectively, the most efficient for this transformation. The hydrogenation reaction cannot efficiently occur in the absence of additives such as iodine (Scheme 54).

Since this pioneer report, the catalytic AH of 2-alkyl-substituted quinoline derivatives has been successfully described with high yield and enantioselectivity using atropisomeric electronically rich or deficient bidentate diphosphines such as P-Phos,[78,79] PQ-Phos,[80] SynPhos, and DifluorPhos,[81,82] 6,6′-didodecyltetrahydroxyBinap,[83] Cl-MeO-Biphep,[84] MeO-PEG supported ligand,[85] C3* TunePhos,[86] OTf-BiPhep,[87] and CF_3O-BiPhep.[88] Some selected examples are summarized in Table 9.

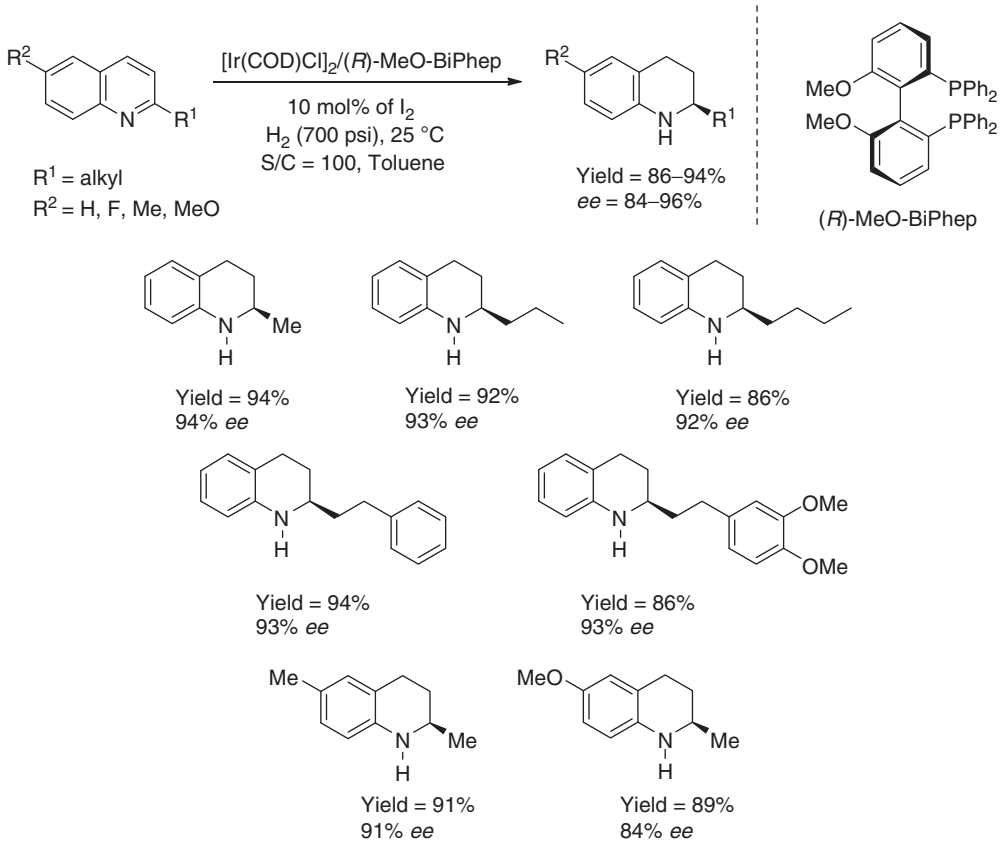
2-Alkyl-substituted quinolines were efficiently hydrogenated regardless of the substitution of the alkyl side chain. Investigations of the scope of the reaction[89,90] showed that several functional groups such as alcohols, esters, ketones, amides, and sulfones were tolerated for the hydrogenation reaction. The electronic properties and steric hindrance of the substrate did not significantly influence the stereochemical outcome of the reaction since *ee* up to 96% could be obtained (Table 10).

This strategy was successfully used for the total synthesis of tetrahydroquinoline alkaloids yielding (*R*)-galipinine, (*R*)-angustureine, and (*R*)-flumequine with high levels of enantioselectivity (Scheme 55).[91]

The role of additives has been studied in the hydrogenation reaction of 2-methylquinoline. No transformation takes place in the absence of additives. Excellent conversions were obtained for most of the additives considered (TClA, NBS, NIS, DCDMH, DBDMH, and BCDMH) with enantioselectivities ranging from 89% to 92% (Table 11). The best enantioselectivity was obtained with iodine, which activates the catalyst as shown in the mechanism proposed below.

Iridium-catalyzed hydrogenation of 2-alkyl quinolines using Brønsted acid-promoted substrate activation was reported in THF under the same reaction conditions with lower enantioselectivities ranging from 7% to 86% using piperidine triflate (Table 12).

A plausible mechanism involves the oxidative addition of I_2 to the Ir(I) species A, followed by a subsequent heterolytic cleavage of H_2 leading to the formation of the catalytic active iridium (III) hydrido iodo chloro complex **B** with concomitant release of HI. Coordination of the quinoline substrate to the active Ir(III) species **B** followed by 1,4 hydride transfer affords the intermediate **D**. Further heterolytic cleavage of H_2 with **D** through **E** regenerated the Ir(III) species **B** and gives the enamine **F** which, through acid (HI) catalyzed tautomerization gives the imine **G**. Coordination of imine **G** with the Ir(III) hydride species **B** provides intermediate **H**. Subsequent diastereoselective 1,2-hydride transfer then provides the chiral 1,2,3,4 tetrahydroquinoline **I**



Scheme 54

via σ bond metathesis with another molecule of H_2 from **J** and the Ir(III) hydride species **B**, which completes the catalytic cycle (Scheme 56).

Alternatively, strategies based on substrate activation with ClCOOR[77] or HX[92] were developed to explore a system aiming at performing the enantioselective hydrogenation of a variety of nitrogen-containing aromatic compounds (Scheme 57).

Various activating agents such as $ClCO_2Bn$, $ClCO_2Me$, $ClCO_2Et$, $ClCO_2Ph$, and $BrCO_2CH_3$ have been examined. Benzyl chloroformate was selected considering the easy deprotection of the corresponding Cbz protecting group. No influence of the substrate concentration or of Li_2CO_3 was observed. Good yields and asymmetric inductions were obtained for the hydrogenation reaction (Scheme 58).

Challenging 2,3-alkyl substituted quinoline derivatives were successfully hydrogenated with iridium catalysts containing atropisomeric diphosphines such as SegPhos, SynPhos, DuPhos, Binap, and MeO-Biphep. Decreasing the pressure to 40 psi, whereas increasing the temperature to 70 °C led to the *syn* 1,2,3,4-tetrahydroquinolines with a significant improvement of the asymmetric induction (Table 13).[89]

A possible mechanism of the iridium-promoted AH of 2,3-disubstituted quinolines involves the isomerization of an enamine to the C═N bond through a dynamic kinetic resolution process (Scheme 59).

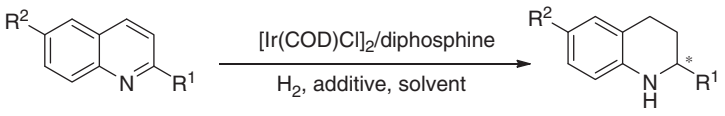
Interestingly, quinoline *N*-oxide could be hydrogenated under 50 atm of hydrogen in THF with complete conversion resulting in a 9:1 ratio of (*R*)-2-methyl-1,2,3,4-tetrahydroquinoline and 2-methylquinoline (Scheme 60).[86]

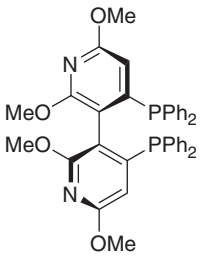
The AH of 2-aryl quinolines catalyzed by iridium complexes bearing atropisomeric diphosphines has been less studied, and only a few examples have been reported so far, with moderate to good enantioselectivities up to 80%. Numerous atropisomeric ligands have been tested for this transformation including MeO-BiPhep, SegPhos, MeO-PEG-supported ligand, and PQ-Phos family of ligands (Table 14).

Alternatively to the *in situ* generated chiral iridium catalysts, well-defined cationic dinuclear triply halogen-bridged iridium complexes $\{[IrH((S)\text{-Diphosphine})]_2(\mu\text{-}X)_3\}^+X^-$ **A-F** were used for the enantioselective hydrogenation of 2-phenylquinoline.[92] Excellent enantioselectivities up to 91% were obtained when DifluorPhos was used as chiral ligand. The results demonstrated an unexpected performance of chloro and bromo-iridium catalysts compared with the corresponding iodo-iridium complexes (Table 15).

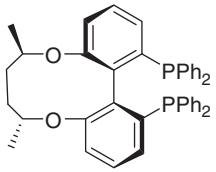
Based on these results, a series of arylquinolinium salts (HCl, HBr and HI salts) were hydrogenated for the first time to the corresponding tetrahydroquinolines with enantioselectivies ranging from 62% to 92% (Scheme 61). The hydrogenation of

Table 9 Iridium-mediated AH of 2-substituted quinolines

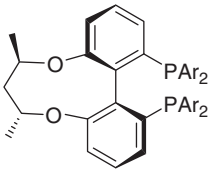




(*R*)-P-Phos

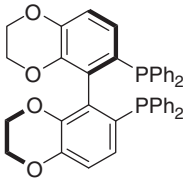


(*S*,*R*,*R*)-PQ-Phos

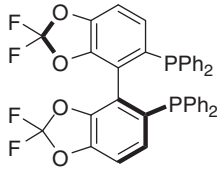


Ar = 3,5-(*t*-Bu)$_2$-4-MeO-C$_6$H$_2$

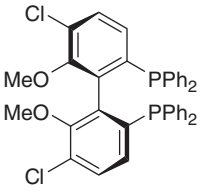
(*S*,*S*,*S*) -C$_3$*-TunePhos



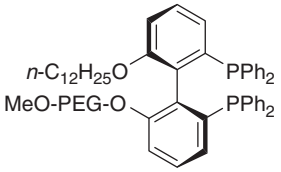
(*R*)-SynPhos



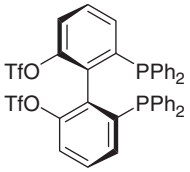
(*S*)-DifluorPhos



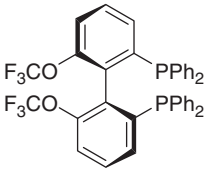
(*S*)-Cl-MeO-BiPhep



(*S*)-MeO-PEG-supported ligand



(*S*)-TfO-BiPhep



(*S*)-CF$_3$O-BiPhep

Entry	*Diphosphine*	*R*^{1}	*R*^{2}	*Conditions*	*Conversion (%)*	ee *(%)*	*References*
i	(*R*)-P-Phos	Et	H	H_2 (700 psi), I_2, r.t., DMPEG/Hexane, 20 h	99	90 (*S*)	78
ii	(*S*,*R*,*R*)-PQ-Phos	Me	H	H_2 (700 psi), I_2, r.t., Toluene, 20 h	99.9	91 (*S*)	80
iii	(*R*)-SynPhos	Me	H	H_2 (50 bar), HI, 30 °C, THF, 24 h	100	90 (*S*)	81
iv	(*S*)-DifluorPhos	Me	F	H_2 (50 bar), I_2, 30 °C, Toluene, 24 h	95	92 (*S*)	81
v	(*R*)-P-Phos	C_5H_{11}	H	H_2 (700 psi), I_2, r.t., THF, 20 h	91	97 (*R*)	84
vi	(*S*)-Cl-MeO-BiPhep	Me	OMe	H_2 (700 psi), I_2, r.t., THF, 20 h	89	94 (*R*)	84
vii	(*S*)-MeO-PEG supported ligand	Et	H	H_2 (600 psi), I_2, r.t., Toluene, 24 h	93[a]	91 (*S*)	85
viii	C_3*-TunePhos	Me	Me	H_2 (20 atm), I_2, r.t., Toluene, 24 h	95	92 (*S*)	86
ix	(*S*)-OTf-BiPhep	*n*-Pr	H	H_2 (700 psi), I_2, r.t., THF	97[a]	94 (*R*)	87
x	(*S*)-CF_3O-BiPhep	*n*-Pr	H	H_2 (700 psi), I_2, r.t., THF, 22 h	97[a]	90 (*R*)	88

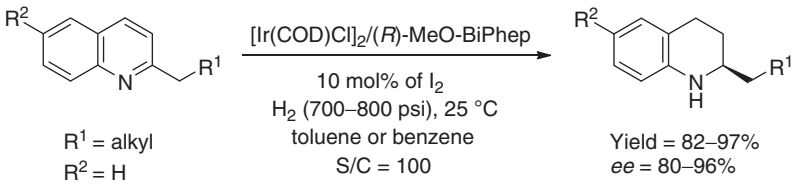
[a]Isolated yield.

para- and *meta*-substituted phenyl derivatives of HCl or HBr quinolinium salts proceeded with better enantioselectivies than that of the corresponding *ortho*-substituted derivatives (Scheme 61).

The HBr quinolinium salts of 2-methylquinoline were reduced using the same reaction conditions with high enantioselectivities up to 94% (Scheme 62).

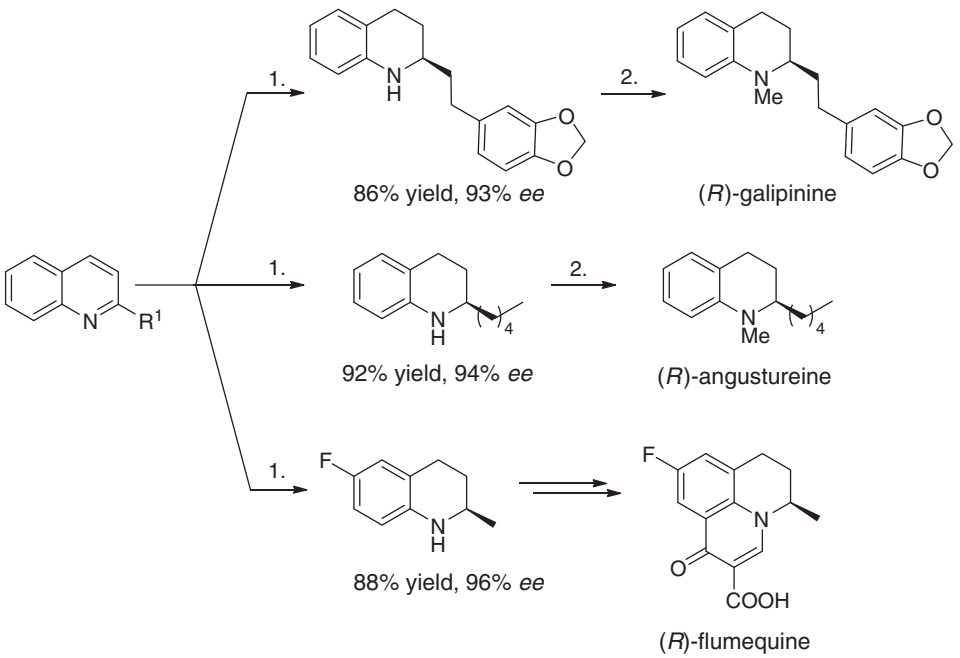
AH of quinolines typically involves the use of hydrogen gas as the reducing agent in conjunction with iridium catalysts containing chiral phosphorus ligands and iodine as additive. Zhou et al. have found that dehydroaromatization of 1,4-dihydropyridines (Hantzsch esters) catalyzed by a catalytic amount of [Ir(COD)Cl]$_2$/*rac*-MeO-BiPhep in the presence of iodine could be used to efficiently *in situ* generate hydrogen gas.[93] Inspired by this result, they subsequently reported the AH of 2-substituted quinoline derivatives using the optimal [Ir(COD)Cl]$_2$/(*S*)-SegPhos/I_2 catalytic system in the presence of 2 equivalents of Hantzsch ester as hydrogen source (Scheme 63). However, although this protocol avoids the use of handling high pressure of hydrogen gas, the corresponding 2-alkyl tetrahydroquinolines were obtained in lower yields (43–98%) and enantiomeric excesses (66–88%) compared with traditional methods cited above using H_2. Moreover, it should be noted that 2-phenylsubstituted quinoline which is a more challenging substrate is not suitable for this process (90% yield, 10% *ee*).

Table 10 Iridium-promoted AH of 2-substituted quinolines



Entry	*R^1*	*R^2*	*Yield (%)*	ee *(%)*
i	$C(OH)Me_2$	H	87[a]	94
ii	$C(OH)(c\text{-}C_5H_{10})$	H	89[a]	92
iii	$C(OH)Ph_2$	H	94[a]	91
iv	OH	H	83[a]	75
v	OCOMe	H	90[a]	87
vi	COPh	H	91[b]	96
vii	COMe	H	93[b]	90
viii	CO(*o*-MeOPh)	H	78[b]	95
ix	CO(*o*-MePh)	H	97[b]	96
x	CO(*p*-CF_3Ph)	H	90[b]	95
xi	COPh	Me	82[b]	94
xii	COPh	F	92[b]	96
xiii	CO_2Et	H	93[b]	92
xiv	$CONEt_2$	H	98[b]	80
xv	SO_2Ph	H	97[b]	90
xvi	COOMe	H	88[a]	66

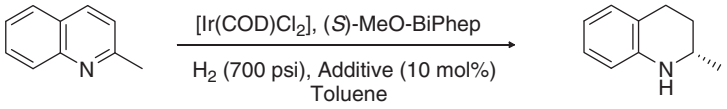
[a]Reaction in toluene.
[b]Reaction in benzene.



1. $[Ir(COD)Cl]_2$ (0.5 mol%), (*R*)-MeO-Biphep (1.1 mol%), H_2 (700 psi), I_2 (10 mol%)
2. HCHO, $NaBH_3CN$, MeCN, 96%

Scheme 55

Table 11 Influence of the additives



Yield = 5–95%

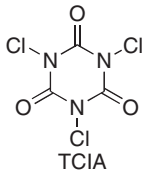
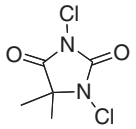
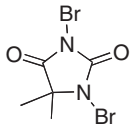
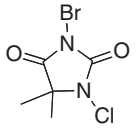
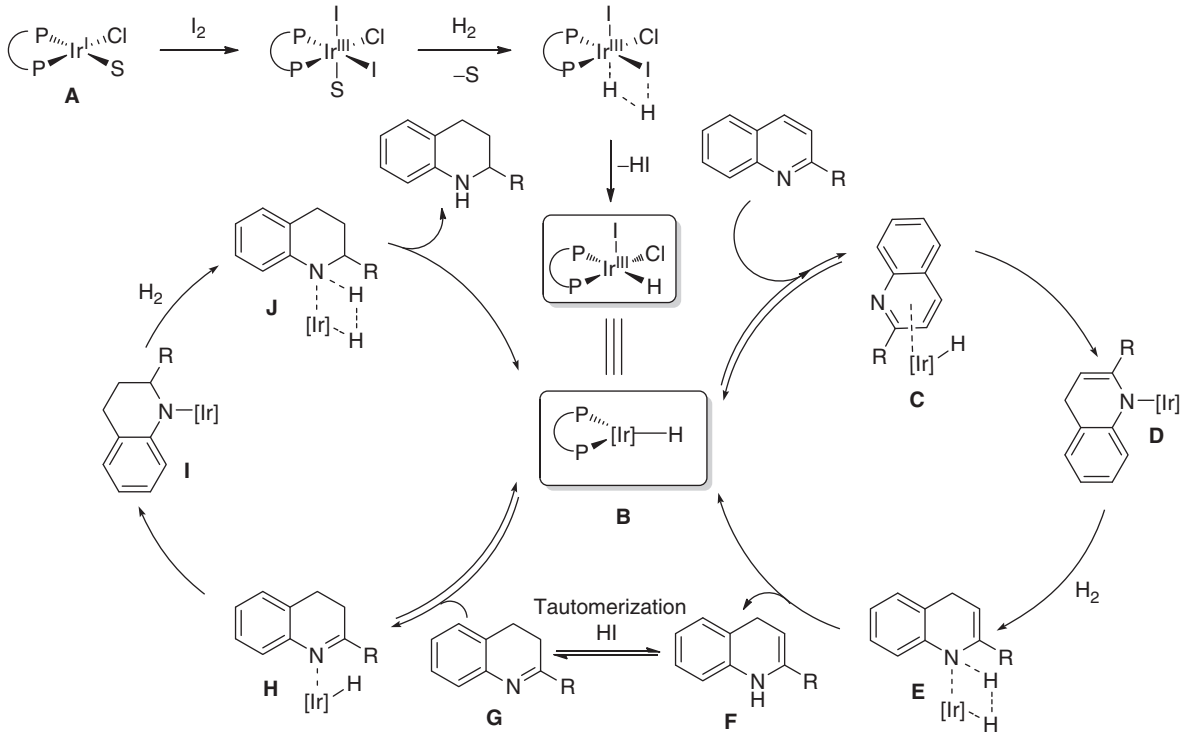
Entry	*Additive*	*Yield (%)*	ee *(%)*
i	 TCIA	>95	89
ii	NBS	95	91
iii	NIS	95	92
iv	 DCDMH	>95	91
v	 DBDMH	95	92
vi	 BCDMH	>95	92
vii	IBr	>95	93
viii	ICl	>95	93
ix	KI	15	2
x	None	>5	–
xi	I_2	>95	94

Table 12 Influence of the Brønsted acid

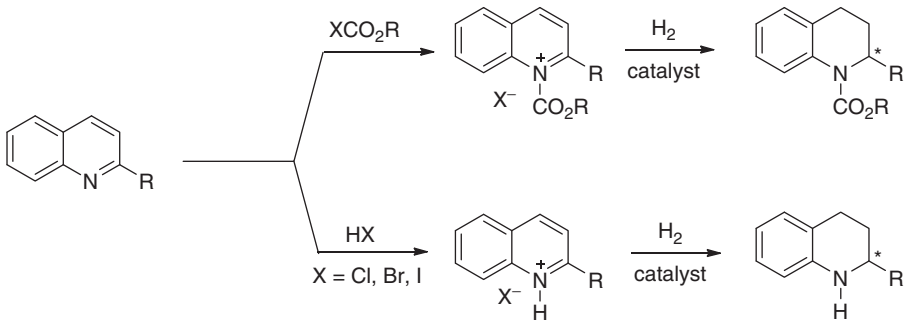
Entry	*Additive*	*Yield (%)*	ee *(%)*
i	TfOH	>95	79
ii	TFA	95	71
iii	TsOH · H_2O	95	74
iv	$PhCO_2H$	>95	49
v	HCl · piperidine	95	75
vi	TfOH · piperidine	>95	86
xi	AgOTf	11	7

The same group disclosed the first AH of quinolines under mild autoclave-free reaction condition using the same $[Ir(COD)Cl]_2$/(*S*)-SegPhos/I_2 catalytic system with a 1/3 mixture of water and triethylsilane as hydrogen source.[94] The key feature of this process lies in the *in situ* formation of metal–hydride bonds through the reaction of readily available metal–silyl compounds with water due to the high oxophilicity of silicon compounds (Scheme 64).

Various quinoline derivatives could be hydrogenated in good yields and up to 93% *ee*. This new protocol, using a 1/3 mixture of water/triethylsilane as hydrogen source, competes favorably with the best known methods (Scheme 65). Here again,



Scheme 56



Scheme 57

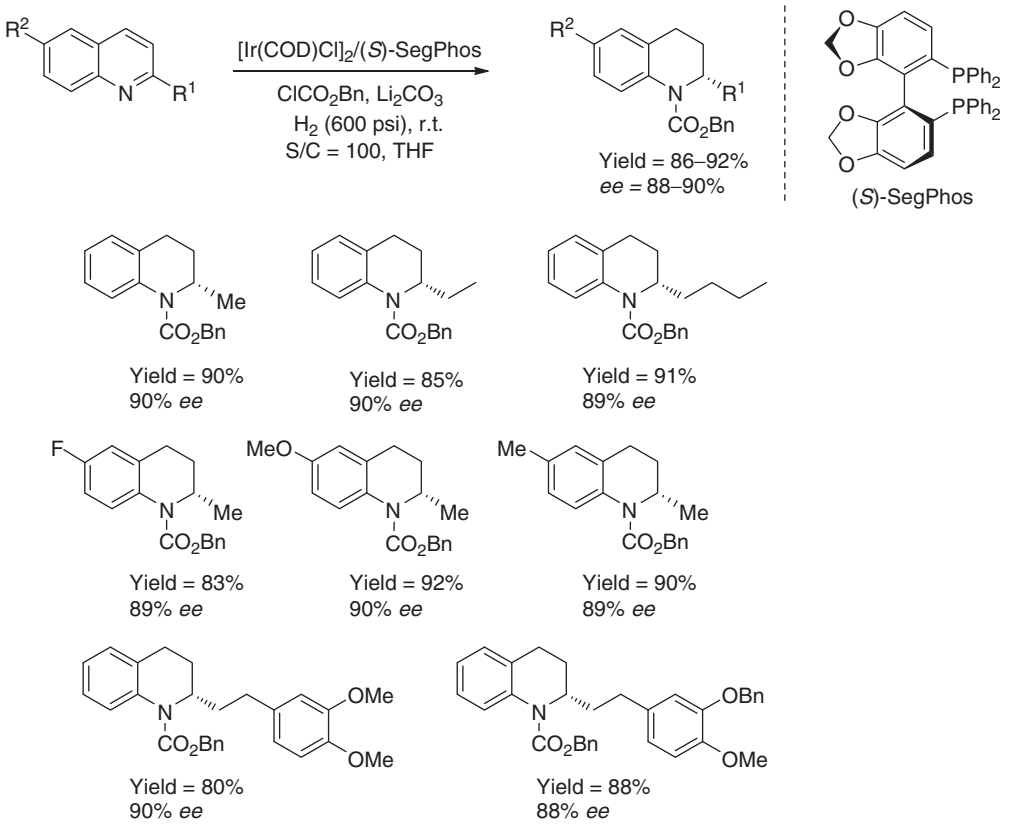
2-arylquinoline substrates such as 2-phenyl quinoline proved not to be suitable partners for this reaction since only 57% *ee* was obtained under optimized reaction conditions. This process was successfully applied to the asymmetric synthesis of three naturally occurring tetrahydroquinoline alkaloids (–)-galipinine, (–)-cuspareine, and (–)-angustrureine.

8.21.3.2.2.2.2 Other chiral phosphorus-containing ligands

The chiral diphosphonite H_8-BINAPO catalyzed the highly enantioselective hydrogenation of quinoline derivatives with excellent yields and *ee* up to 96% (Scheme 66).[95] The phosphonite-type ligands are easily accessible. Better enantioselectivities up to 97% have been obtained using DMPEG/hexane as a solvent. However, the recycling of the catalyst was not successful. A chiral phosphonite derived from BINOL bearing an achiral diphenyl ether backbone was also very efficient for the same transformation.[96]

Chiral dendritic catalysts derived from Binap[97] promoted the AH of quinoline derivatives. Excellent catalytic activities were observed with TON up to 43 000 and TOF up to 3450 h^{-1} demonstrating the importance of the dendritic wedges in the course of the reaction (Scheme 67).

Alternatively, the chiral diphosphinite derived from (*R*)-1,1′-spirobiindane-7,7′-diol promoted the hydrogenation of quinoline derivatives with S/C ratio up to 5000 and enantioselectivity of 94%. The reaction proceeded smoothly in poly(ethylene glycol)dimethylether/hexane biphasic solvent system.[98] The recyclability of the phosphonite spiro complex was studied with



Scheme 58

2-methylquinoline. The first run was comparable with the results obtained in THF in terms of enantioselectivity and conversion. Although the conversion dropped to 40% after 4 runs, the enantioselectivity was maintained up to 86% (Scheme 68).

The iridium complexes of sulfoximine-based naphthalene-bridged P,N ligands were used to hydrogenate quinolines with *ee* ranging from 64% to 87%.[99] Iodine had a negative effect on the stereochemical course and yield of the hydrogenation reaction. Therefore, it was carried out in the absence of iodine under 45 atm of hydrogen pressure at 60 °C in toluene (Scheme 69).

AHs of 2-quinolines and 2,6-substituted quinolines were successfully performed using the combination $[Ir(COD)Cl]_2$/Pip-Phos/tri-(*o*-tolyl)-phosphine/piperidine HCl.[100] Additives such as tri-(*o*-tolyl)-phosphine and/or chloride salts played a crucial role in the stereochemical outcome of the reaction (Scheme 70).

Excellent results were obtained with mixed phosphine–phosphoramidite ligands leading to conversions from 78% to 96% and *ee* up to 97% (Scheme 71).[101]

A library of modular iridium (*P-OP*) complexes was used for the AH of heteroaromatic compounds with *ee* up to 92% for the reduction of 2-methylquinoline.[102]

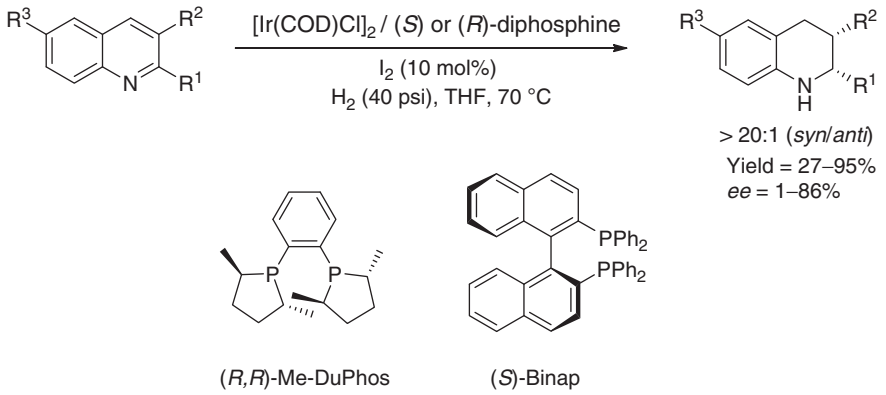
Chiral ferrocenyloxazoline–derived (N,P) and (S,P) ligands, easily synthesized from amino acids, catalyzed the AH of quinolines with *ee* up to 92% *ee*.[103] The role of the planar chirality is crucial for the reaction (Scheme 72).

8.21.3.2.2.2.3 Chiral diamine ligands

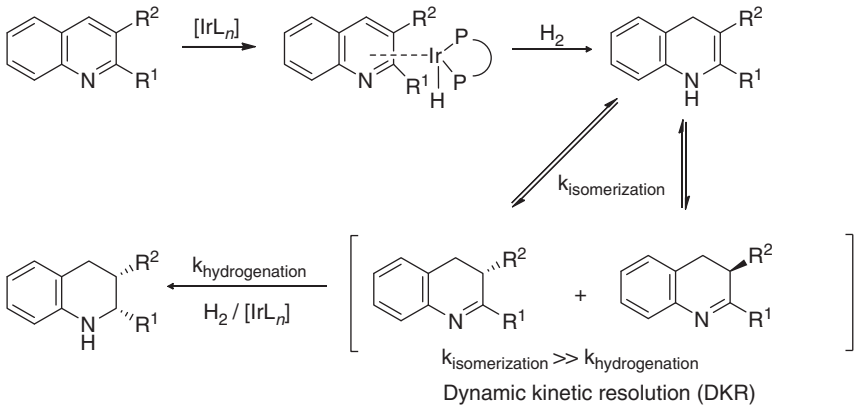
In comparison with most of the chiral phosphorus ligands, which can be readily oxidized by oxygen, chiral diamine ligands are more easily available and are known to be more air stable. However, despite these obvious advantages, only a limited number of truly efficient catalysts bearing chiral diamine ligands have been reported so far in the literature for the AH of quinolines.

Noyori et al. found that under slightly acidic conditions chiral η^6-arene/*N*-TsDPEN- Ruthenium(II) complexes can be made to effect both asymmetric transfer hydrogenation and AH of simple ketones.[104] Inspired by this significant breakthrough, Chan, Fan et al. reported the first phosphine-free chiral cationic Ru(*p*-cymene)(OTf)(*N*-TsDPEN) catalyst exhibiting unprecedented reactivity and high selectivity in the hydrogenation of quinoline derivatives in neat ionic liquid.[105] In this transformation, a wide variety of 2-alkyl substituted quinolines reacted smoothly in $[BMIM]PF_6$ (BMIM = 1-*n*-butyl-3-methylimidazolium) to give the corresponding 2-alkyl substituted tetrahydroquinolines in high yields (87–97%) and almost perfect enantiomeric excesses ranging from 96% to 99% using 1 mol% of catalyst at 25 °C under 50 atm of hydrogen pressure (Table 16). Interestingly, this catalytic system allows selective reduction of the heterocyclic ring over C=O bonds as illustrated by the hydrogenation of the quinoline derivative bearing an acetyl group at the 6 position (Table 16, entry x). The choice of the counterion is essential since catalysts

Table 13 Iridium-catalyzed AH of 2,3-substituted quinolines



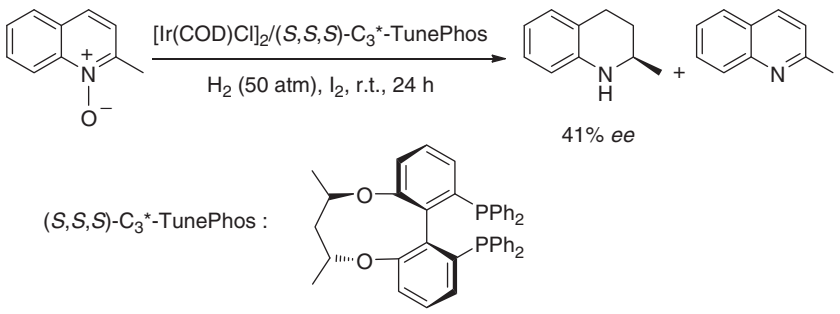
Entry	*Ligand*	R^1	R^2	R^3	*Yield (%)*	ee *(%)*
i	(*S*)-SegPhos	Me	Me	H	95	72
ii	(*S*)-SynPhos	Me	Me	H	93	70
iii	(*R,R*)-Me-DuPhos	Me	Me	H	27	1
iv	(*S*)-Binap	Me	Me	H	95	60
v	(*S*)-MeO-Biphep	Me	Me	H	92	73
vi	(*S*)-MeO-Biphep	*i*-Pr	Me	H	94	86
vii	(*S*)-MeO-Biphep	3-Butenyl	Me	H	90	83
viii	(*S*)-MeO-Biphep	Benzyl	Me	H	98	81
ix	(*S*)-MeO-Biphep	Et	Me	Me	91	84
x	(*S*)-MeO-Biphep	Et	Me	F	89	83
xi	(*S*)-MeO-Biphep	Et	Me	MeO	76	85
xii	(*S*)-MeO-Biphep	$(CH_2)_4$	H	H	96	39
xiii	(*S*)-MeO-Biphep	Ph	Me	H	90	38



Scheme 59

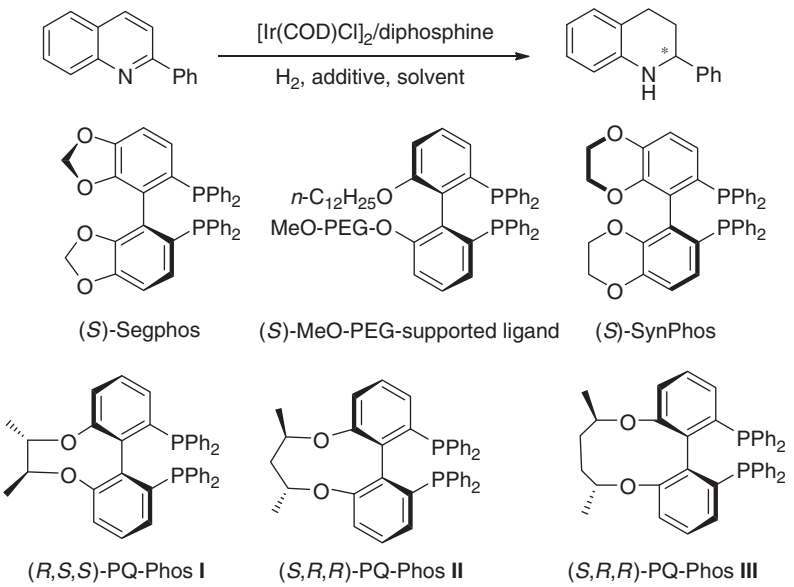
bearing chloride counterion instead of triflate yielded no product. Moreover, while catalysts decomposed in methanol within a week, the use of an ionic liquid solvent greatly enhanced the catalyst stability: after exposure to air for 30 days, the Ru catalyst solution can be reused 6 times without any loss of catalytic activity (95–91% yield, 98–99% *ee*). The authors postulated that such high stability was probably due to both very low solubility of oxygen in said ionic liquid and the solvation effect of $[BMIM]PF_6$ toward the cationic Ru(*p*-cymene)(OTf)(*N*-TsDPEN) catalyst. It is noteworthy to mention that this is one of the best catalytic systems for the reduction of quinolines reported so far.

A plausible ionic mechanism that involves a stepwise H^+/H^- transfer process outside the coordination sphere was proposed on the basis of experimental studies. Cationic Ru complex **A** accommodates an H_2 molecule to form Ru η^2-H_2 complex **B**, which after proton transfer with basic 2-methylquinoline gives rise to active ruthenium hydride species **C** and the corresponding activated quinolinium. The latter is then reduced through a 1,4-hydride transfer to provide the enamine and regenerates cationic



Scheme 60 Hydrogenation of 2-aryl-substituted quinoline derivatives.

Table 14 Iridium-mediated AH of phenylquinoline



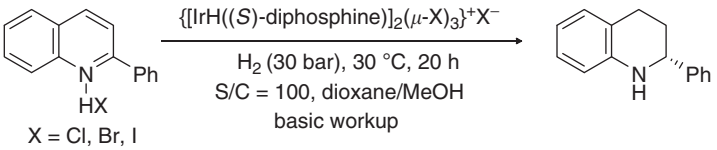
Entry	*Ligand*	*Conditions*	*Yield (%)*	ee *(%)*	*References*
i	(*R*)-MeO-BiPhep	H_2 (700 psi), I_2, r.t., Toluene	95	72 (*S*)	74
ii	(*S*)-SegPhos	H_2 (600 psi), r.t., $ClCO_2Bn$, Li_2CO_3 Toluene, r.t.	41	80 (*R*)	77
iii	(*S*)-MeO-PEG-supported ligand	H_2 (600 psi), I_2, r.t., Toluene	96	72 (*R*)	85
iv	(*S*)-SynPhos	H_2 (50 bar), I_2, 30 °C, THF	92[a]	66 (*R*)	81
v	(*R*)-SegPhos	H_2 (700 psi), I_2, r.t., THF, $TfOH \cdot NC_5H_{11}$	67	78 (*S*)	91
vi	(*R,S,S*)-PQ-Phos **I**	H_2 (600 psi), I_2, r.t., Toluene	100[a]	53 (*S*)	80
vii	(*S,S,R*)-PQ-Phos **II**	H_2 (600 psi), I_2, r.t., Toluene	100[a]	70 (*R*)	80
viii	(*S,S,R*)-PQ-Phos **III**	H_2 (600 psi), I_2, r.t., Toluene	100[a]	64 (*R*)	80

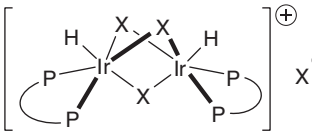
[a]Conversion determined by ^1H NMR.

Ru complex **A**, which can then start a second catalytic cycle after reaction with H_2 leading to complex **B**. Protonation of the enamine gives active RuH species **C** and the corresponding activated iminium cation. Subsequent diastereoselective 1,2-hydride transfer then provides the chiral tetrahydroquinoline (Scheme 73).

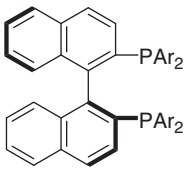
The same group has extended the use of this cationic Ru(*p*-cymene)(OTf)(*N*-TsDPEN) catalyst to the asymmetric synthesis of more challenging 2-aryl-substituted quinoline derivatives.[106] A wide variety of 2-aryl tetrahydroquinolines were obtained in good to excellent enantioselectivities (85–97% *ee*) with high yields (90–97%) (Table 17). The steric and electronic properties of the substituents on the 2-phenyl group of the substrates have a significant impact on the catalytic activity. Introduction of a substituent at the 2-position of the phenyl ring gives lower selectivities probably due to steric hindrance between the substrate and the catalyst. A similar trend was observed with substrates bearing electron-withdrawing groups whatever the position of the substituent on the phenyl ring. Finally, it is important to note that these *ee* values obtained are the highest reported so far for the AH of 2-aryl-substituted quinoline derivatives.

Table 15 Hydrogenation reaction with preformed Ir(III) catalysts

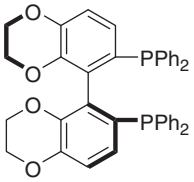




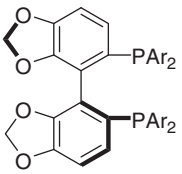
(*S*)-**A**: L = (*S*)-Binap
(*S*)-**B**: L = (*S*)-*p*-Tol-Binap
(*S*)-**C**: L = (*S*)-SynPhos
(*S*)-**D**: L = (*S*)-SegPhos
(*S*)-**E**: L = (*S*)-DTBM-SegPhos
(*S*)-**F**: L = (*S*)-DifluorPhos



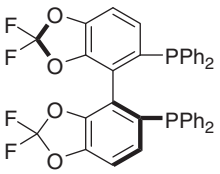
(*S*)-Binap, Ar = Ph
(*S*)-*p*-Tol-Binap,
Ar = 4-MeC$_6$H$_4$



(*S*)-SynPhos



(*S*)-SegPhos, Ar = Ph
(*S*)-DTBM-SegPhos,
Ar = 3,5-(*t*-Bu)$_2$-4-(OMe)-C$_6$H$_2$



(*S*)-Difluorphos

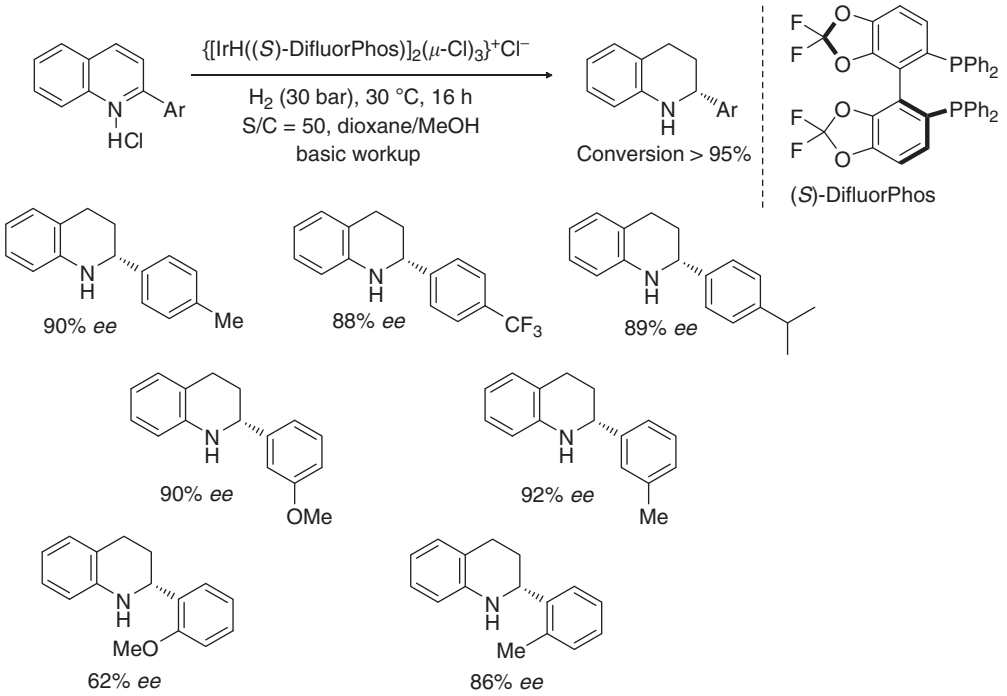
Entry	*Catalyst*	*X*	*Solvent*	*Conversion (%)*	ee *(%)*
i	(*S*)-**A**-Cl	Cl	THF	>95	72
ii	(*S*)-**A**-Br	Br	THF	95	70
iii	(*S*)-**A**-I	I	THF	76	1
iv	(*S*)-**A**-Cl	Cl	Toluene	66	72
v	(*S*)-**A**-Cl	Cl	Dioxane	>95	72
vi	(*S*)-**A**-Cl	Cl	MeOH	44	39
vii	(*S*)-**A**-Cl	Cl	Dioxane/MeOH	>95	73
viii	(*S*)-**B**-Cl	Cl	Dioxane/MeOH	43	68
ix	(*S*)-**C**-Cl	Cl	Dioxane/MeOH	62	78
x	(*S*)-**D**-Cl	Cl	Dioxane/MeOH	>95	79
xi	(*S*)-**E**-Cl	Cl	Dioxane/MeOH	52	24
xii	(*S*)-**F**-Cl	Cl	Dioxane/MeOH	38	91
xiii	(*S*)-**F**-Br	Br	Dioxane/MeOH	>95	91
xiv	(*S*)-**F**-Br	Cl	Dioxane/MeOH	>95	91
xv	(*S*)-**F**-Br	Cl	Dioxane/MeOH	>95	91

The above catalytic system was also employed for the AH of 2,3-substituted quinolines, for which only limited examples have been reported so far. As can be seen in **Scheme 74**, acyclic compounds reacted smoothly to give the corresponding reduced products with almost no diastereoselectivities but with excellent enantioselectivities up to 98% for the *syn* adduct and up to 86% for the *anti* adduct (**Scheme 74**). For cyclic compounds, excellent diastereoselectivities (up to 95/5 *dr*) in favor of the *syn* adduct were achieved, but the enantioselectivity significantly dropped from 95% *ee* to 17% *ee* when the ring is smaller.[106]

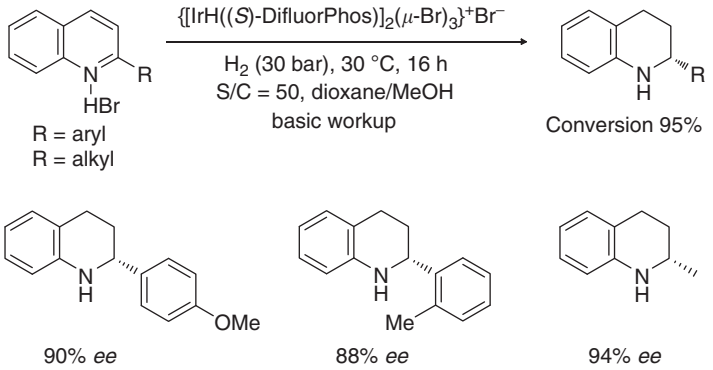
Finally, it should be mentioned that 3-substituted, 4-substituted, and 2,4-disubstituted quinoline derivatives, which are known to be even more challenging substrates and for which no successful transition-metal-catalyzed AH has been reported so far, were not good partners for this transformation (**Scheme 75**).[106]

Subsequently, it was found that the same Ru(*p*-cymene)(OTf)(*N*-TsDPEN) catalyst can be used under more friendly solvent-free or highly concentrated conditions for the AH of quinolines.[107] Using *i*-PrOH as a solvent in the presence of 0.1 mol% of TfOH as an additive, a wide range of 2-alkyl tetrahydroquinoline derivatives were obtained with excellent enantioselectivities (up to 97% *ee*) and yields (up to 99%) at a remarkably low catalyst loading (0.1–0.02 mol%) compared to traditional methods that typically employ 1 mol% of catalyst.

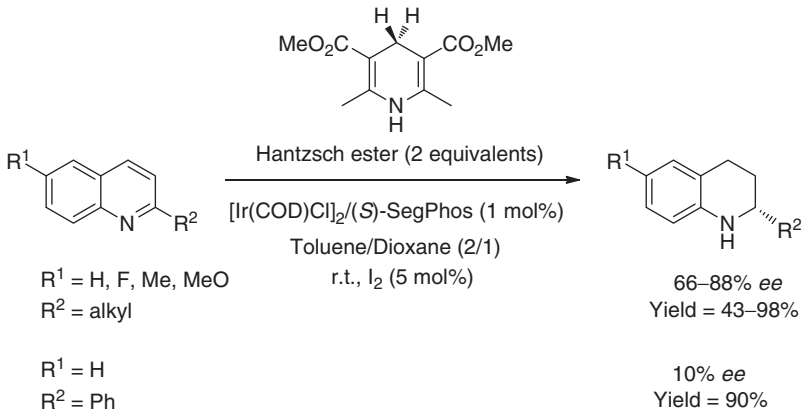
Fan et al. discovered that the phosphine-free Ru(*p*-cymene)(*N*-TsDPEN) catalyst could be efficiently used for the tandem asymmetric reduction of 2-(aroylmethyl)-quinolines (**Table 18**).[108] The reaction involves sequential one-pot asymmetric transfer



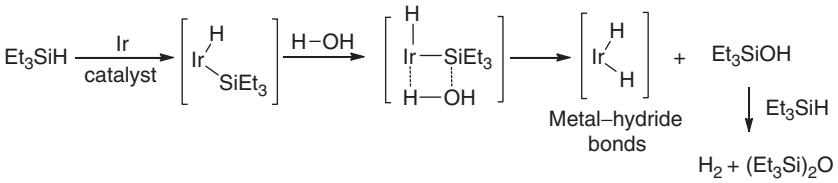
Scheme 61



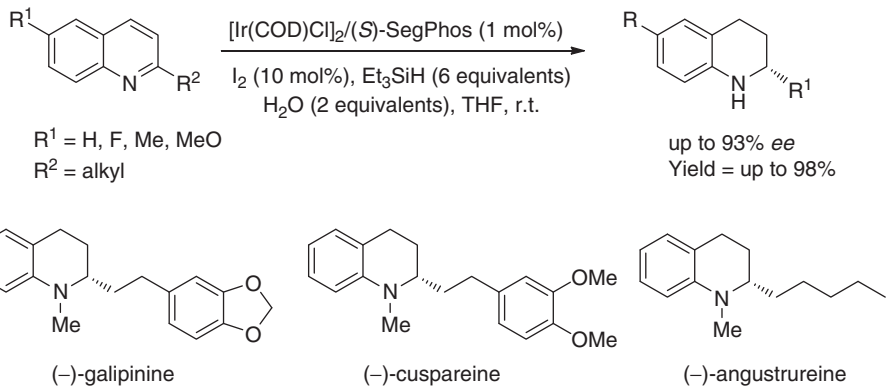
Scheme 62



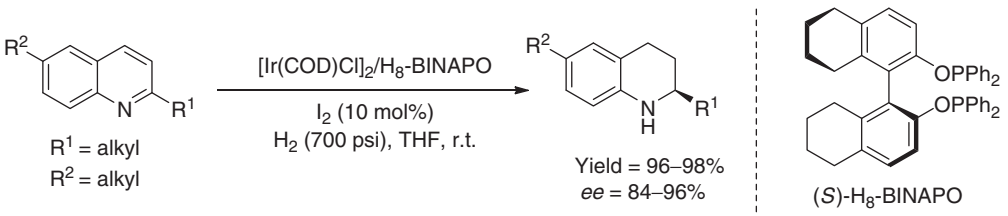
Scheme 63



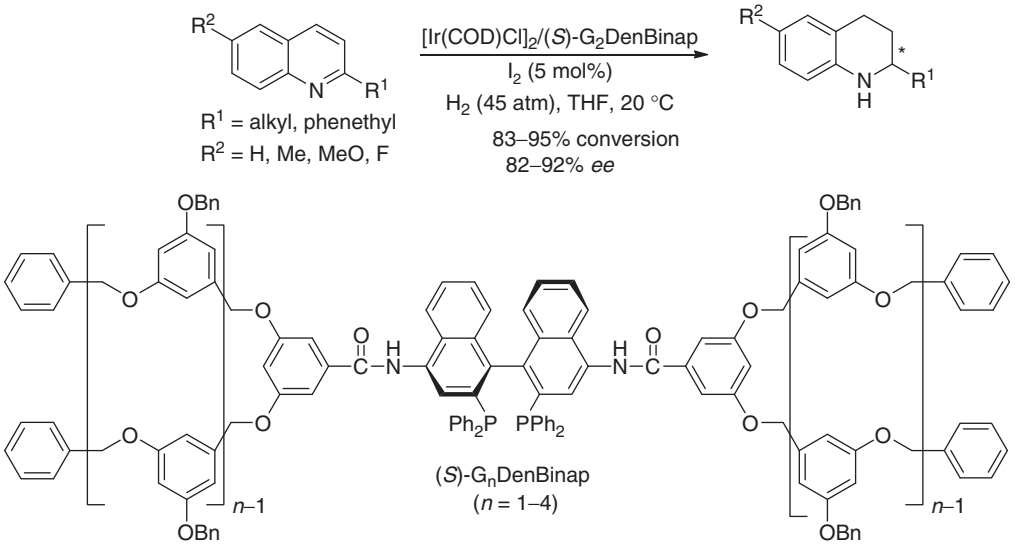
Scheme 64



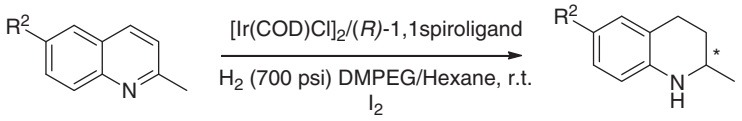
Scheme 65



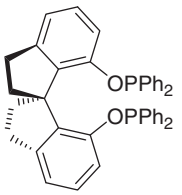
Scheme 66



Scheme 67

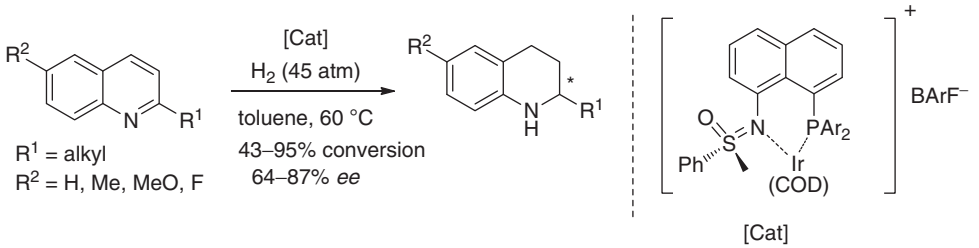


(*R*)-1,1-spiroligand :

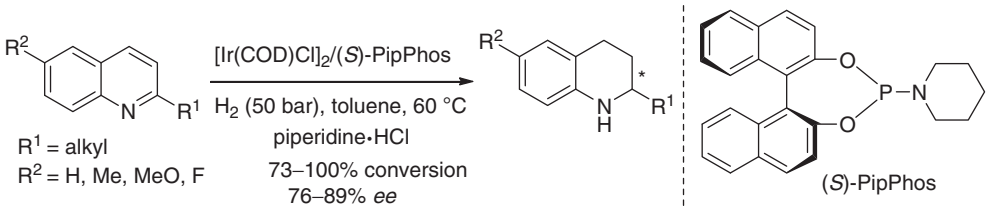


Run	1	2	3	4	5
Conversion (%)	>99	75	62	43	40
ee (%)	92	91	90	89	86

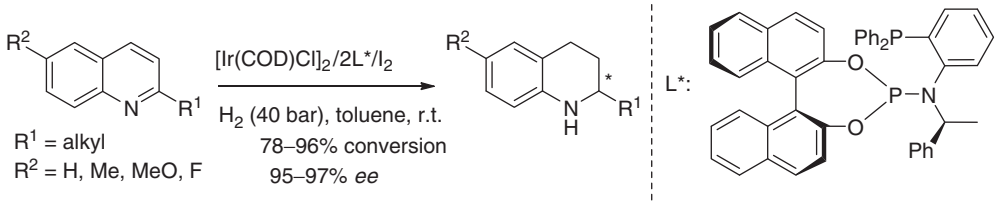
Scheme 68



Scheme 69



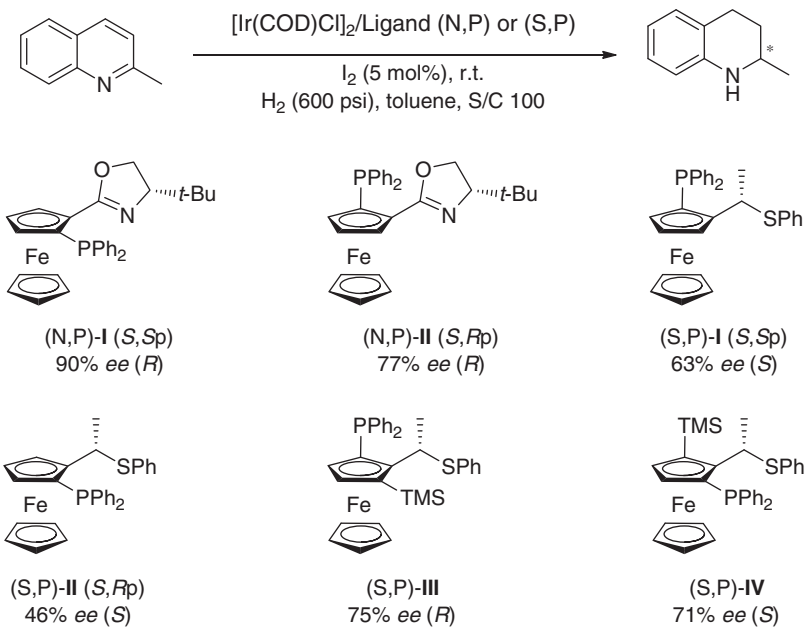
Scheme 70



Scheme 71

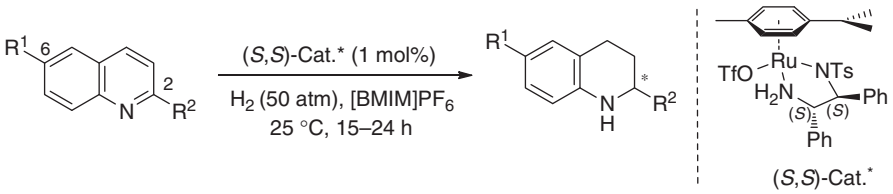
hydrogenation (ATH) of aromatic ketones followed by AH of quinolines providing the corresponding tetrahydroquinoline derivatives in almost perfect enantioselectivities (99% *ee*) and with moderate to good diastereoselectivities (88/12 to 95/5). In the first step, the C═O bond of the substrates is smoothly reduced at 25 °C using 1 mol% of Ru(*p*-cymene)(*N*-TsDPEN) catalyst (*R*,*R*)-**A** in EtOH, which served both as solvent and hydrogen source, to give the corresponding alcohols. Further addition of 10 mol% of TfOH to the reaction mixture allowed *in situ* generation of cationic Ru(*p*-cymene)(OTf)(*N*-TsDPEN) catalyst (*R*,*R*)-**B**, which, under 50 atm of hydrogen pressure, reduces the heteroaromatic ring. It should be mentioned that introducing a substituent at the *ortho* position of the phenyl ring of the aryl ketones led to relatively moderate yields and diastereoselectivities.

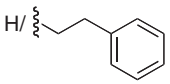
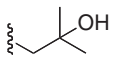
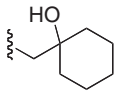
Fan, Xu et al. developed a related phosphine-free iridium catalyst for the enantioselective hydrogenation of 2,6-disubstituted quinolines (Scheme 76).[109] A wide variety of 2,6-alkyl quinoline derivatives were hydrogenated to give the corresponding reduced products in high yields (up to 99%) and remarkably high enantioselectivities (up to 99% *ee*). Interestingly, the reaction can be



Scheme 72

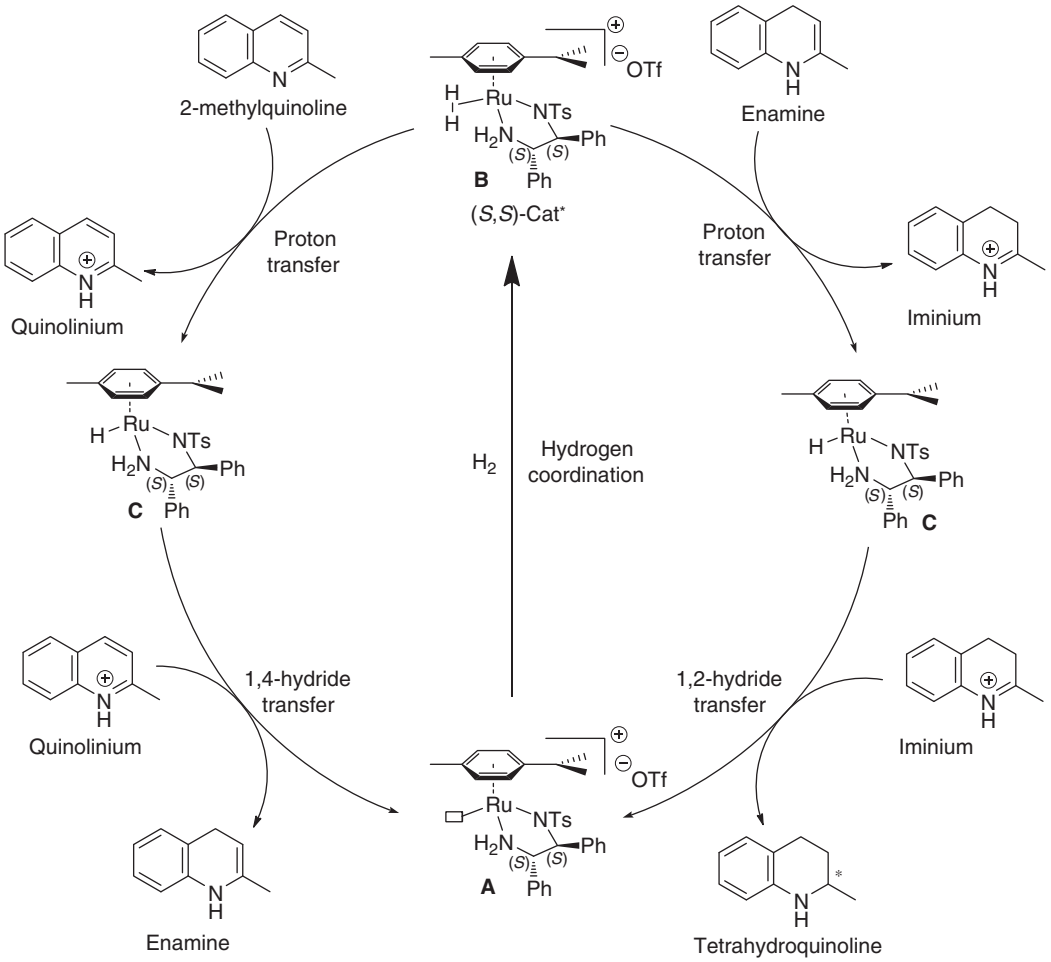
Table 16 Ru-catalyzed AH of 2,6-alkyl substituted quinolines



Entry	*R^1/R^2*	*Yield (%)*	ee *(%)*
i	H/Me	96	99
ii	H/Et	95	98
iii	H/*n*-Pr	95	99
iv	H/*n*-Pentyl	97	98
v	H/ 	96	97
vi	H/ 	92	99
vii	H/ 	93	99
viii	MeO/Me	91	99
ix	F/Me	92	98
x	CH_3CO/Me	87	96

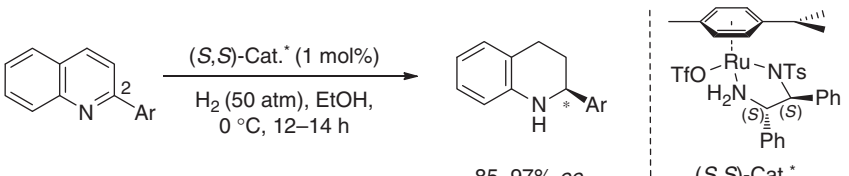
carried out in undegassed methanol with no need for inert gas protection, although still providing similar results in terms of both reactivity and selectivity. However, this catalytic system that compares favorably to the best cationic Ru(*p*-cymene)(OTf)(*N*-TsDPEN) catalyst for the reduction of 2-alkyl-substituted quinolines, provided only moderate enantioselectivity for the hydrogenation of 2-phenylquinoline (79% *ee* vs. 92% *ee*, respectively).

Rueping et al. reported the first iridium-catalyzed AH of 2,6-substituted quinolines using Brønsted acid through kinetic discrimination (Scheme 77).[110] A variety of 2,6-substituted quinoline derivatives can be smoothly transformed into the

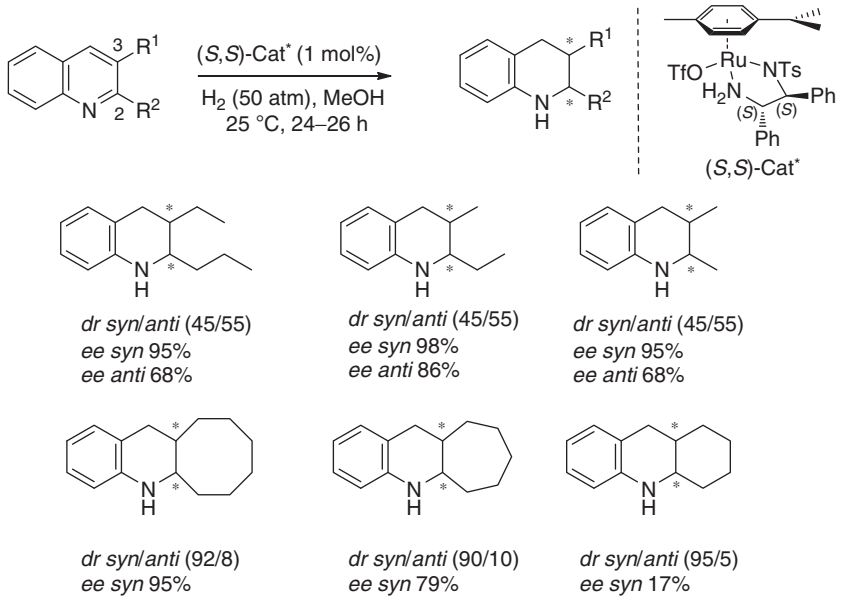


Scheme 73

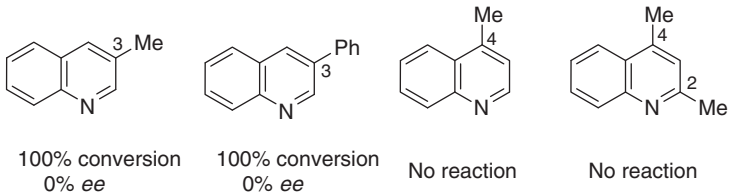
Table 17 Ru-catalyzed AH of 2-aryl substituted quinolines



Entry	*Ar*	*Yield (%)*	ee *(%)*
i	Phenyl	94	92
ii	2-Methylphenyl	95	85
iii	2-Naphthyl	95	88
iv	3-CF_3-phenyl	91	87
v	4-Methoxyphenyl	92	92
vi	4-Acetamidophenyl	92	91
vii	4-Aminophenyl	90	97
viii	4-Bromophenyl	95	86
ix	4-Chlorophenyl	90	85
x	2-Furyl	93	86
xi	2-Thienyl	80	92

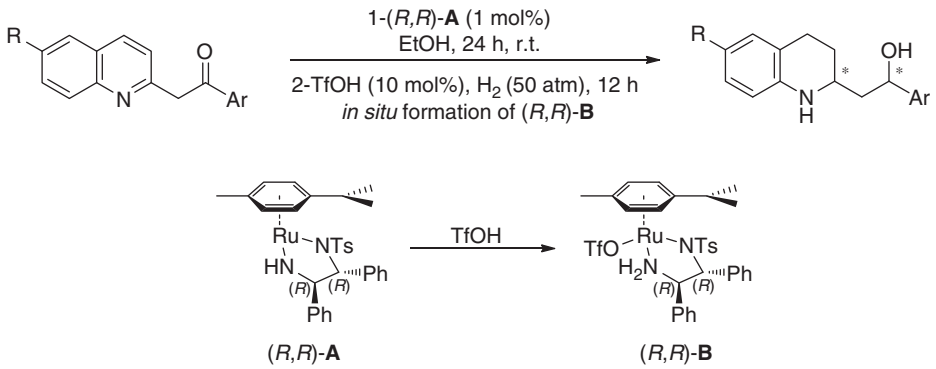


Scheme 74

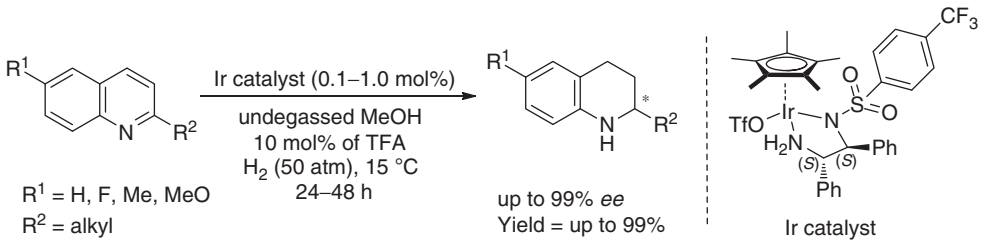


Scheme 75

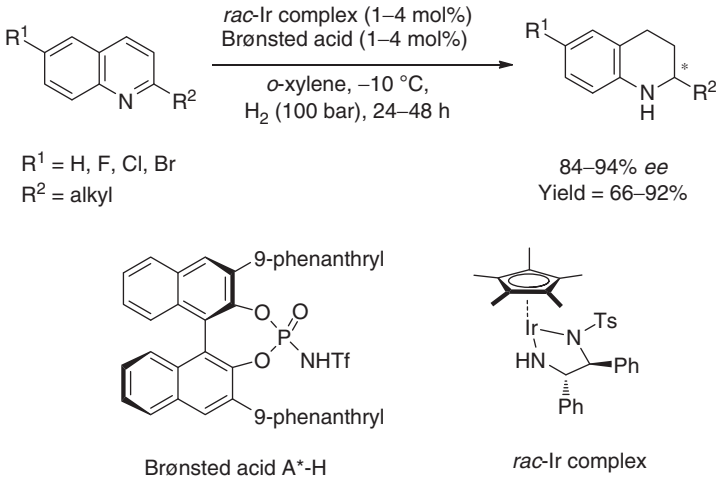
Table 18 Ru-catalyzed tandem ATH/AH reactions of 2-(aroylmethyl)-quinolines



Entry	*R/Ar*	*Yield (%)*	dr *(%)*	ee *(%)*
i	H/Ph	94	>95:5	>99
ii	H/*o*-MeOC$_6$H$_4$	80	88:12	99
iii	H/*o*-FC$_6$H$_4$	79	88:12	>99
iv	H/*m*-MeOC$_6$H$_4$	94	93:7	99
v	H/*m*-FC$_6$H$_4$	88	91:9	>99
vi	H/*p*-MeC$_6$H$_4$	95	94:6	>99
vii	MeO/Ph	94	95:5	>99
viii	F/Ph	89	95:5	>99



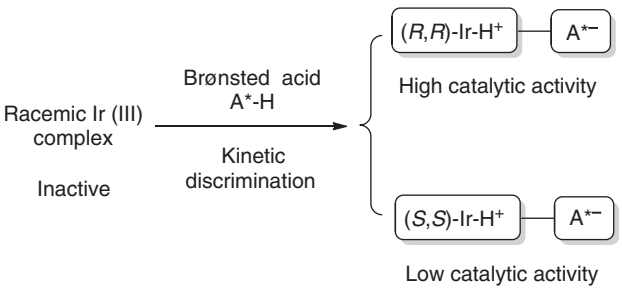
Scheme 76



Scheme 77

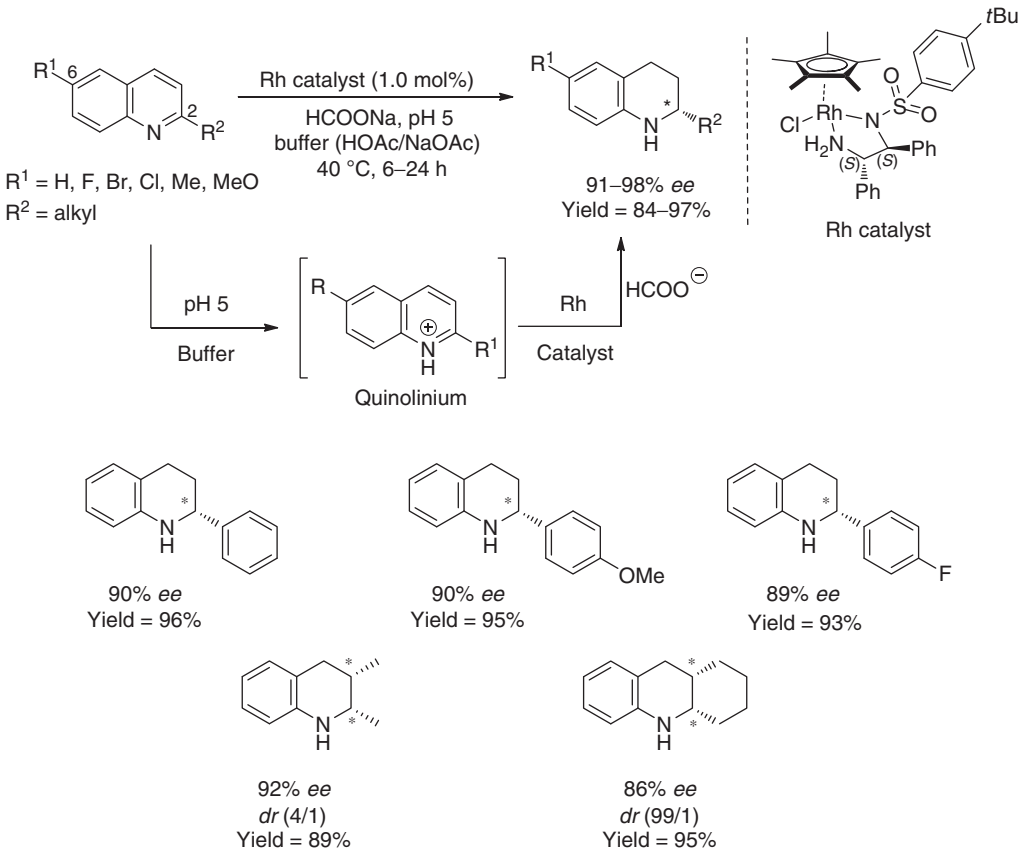
corresponding tetrahydroquinolines in good yields and enantioselectivities up to 94% using a combination of an achiral Cp*Ir (TsDPEN) complex and a chiral *N*-triflylphosphoramide bearing a 9-phenanthryl substituent in the 3,3′ position as Brønsted acid. The use of apolar and nonprotic solvents, which are known to be beneficial in chiral ion-pair catalysis, and the use of high hydrogen pressure are crucial for attaining high catalytic activity.

The success of this new protocol relies on the fact that protonation of the racemic Cp*Ir(TsDPEN) complex by a chiral Brønsted acid resulted in the formation of two different diastereoisomeric iridium complexes, which possess remarkable different properties with regard to both reactivity and selectivity (Scheme 78).



Scheme 78

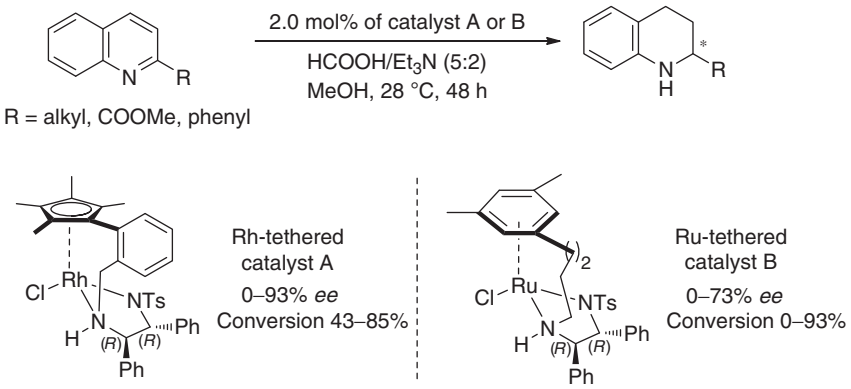
In addition to chiral ruthenium and iridium diamine-based catalysts, the group of Xiao et al. reported the first examples of rhodium-catalyzed asymmetric transfer hydrogenation of quinolines in an acidic aqueous media using HCOONa as hydride source (Scheme 79).[111] In this transformation, Cp*Rh(Cl)(*t*-BuTsDPEN) was used as an efficient catalyst for the reduction of a broad range of substrates including 2-alkyl, 2-aryl, 2,6-disubstituted, and 2,3-disubstituted quinolines, giving the corresponding hydrogenated products in high yields and with excellent enantioselectivities. For 2-alkyl-substituted quinolines, the pH value of the reaction medium needs to be adjusted to 5 using a HOAc/NaOAc buffer to achieve high catalytic activity, whereas for the less basic 2-aryl-substituted quinolines, a lower pH value of 4 in conjunction with higher catalyst loading (2 mol%) is required.



Scheme 79

Notably, the generality of this catalytic system was demonstrated through the successful hydrogenation of 2,3-disubstituted quinoline derivatives giving the corresponding reduced products in moderate to excellent diastereoselectivities and good enantioselectivities. The key factor for the success of this hydrogenation process lies in the high concentration of both formate and protonated quinolines at pH 5, which are the required conditions for high reaction rates when an ionic mechanism is involved.

Finally, the Wills group investigated the use of tethered Rh and Ru/TsDPEN complexes for the asymmetric transfer hydrogenation of 2-substituted quinolines in methanol using a solution of formic acid/triethylamine as hydrogen donor.[112] Both catalytic systems provide poor catalytic activity compared with other chiral ruthenium, iridium, and rhodium diamine based complexes since incomplete conversions and moderate to good enantioselectivities were obtained with all substrates even with higher catalyst loading of 2 mol% (Scheme 80).



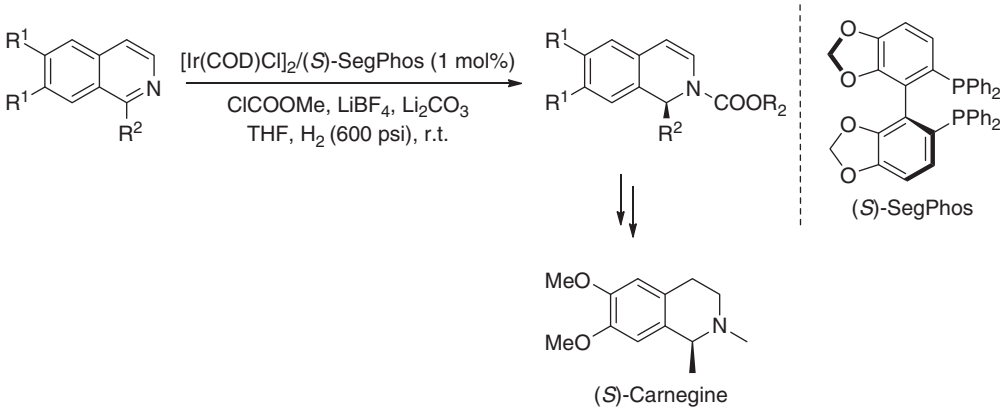
Scheme 80

8.21.3.2.2.3 Isoquinolines and isoquinolinium salts

The AH of isoquinoline derivatives proved to be a challenging task since almost no catalytic activity was obtained under the standard reaction conditions employed for the AH of quinolines. This lack of reactivity is most likely due to the presence of the more basic nitrogen atom of the isoquinoline substrate and of the corresponding reduced product, which probably deactivates the catalyst by binding more strongly to the metal center than does quinoline. Consequently, only two examples of AH of isoquinoline derivatives have been reported so far.

Zhou and coworkers described the first enantioselective hydrogenation of 1-substituted isoquinolines with enantiomeric excesses ranging from 10% to 83%, using 1 mol% of $[Ir(COD)Cl]_2$/(*S*)-SegPhos as catalyst (Table 19). The activation of the substrate by chloroformates to form isoquinolinium salts and the use of Li_2CO_3 as a base to neutralize the hydrogen chloride generated *in situ* during the course of the reaction were crucial in obtaining high yields and moderate to good selectivities.[113] The addition of a stoichiometric amount of a lithium salt such as $LiBF_4$ significantly improved the enantioselectivity of the reaction (76% *ee* vs. 83% *ee* for the 1-methylisoquinoline). It is worth noting that compared to quinolines, which are fully hydrogenated to tetrahydroquinolines, the complete saturation of the heteroaromatic ring of isoquinolines under the optimized reaction conditions was more difficult because only partially hydrogenated 1,2-dihydroisoquinoline products were obtained in moderate to good yields using methylchloroformate as activator (44–87%) (Table 19). This method was successfully applied to a short asymmetric synthesis of (*S*)-carnegine, a naturally occurring tetrahydroisoquinoline alkaloid, in three steps from a cheap and readily available isoquinoline precursor.

Table 19 Ir-catalyzed AH of activated 2-substituted Isoquinolines

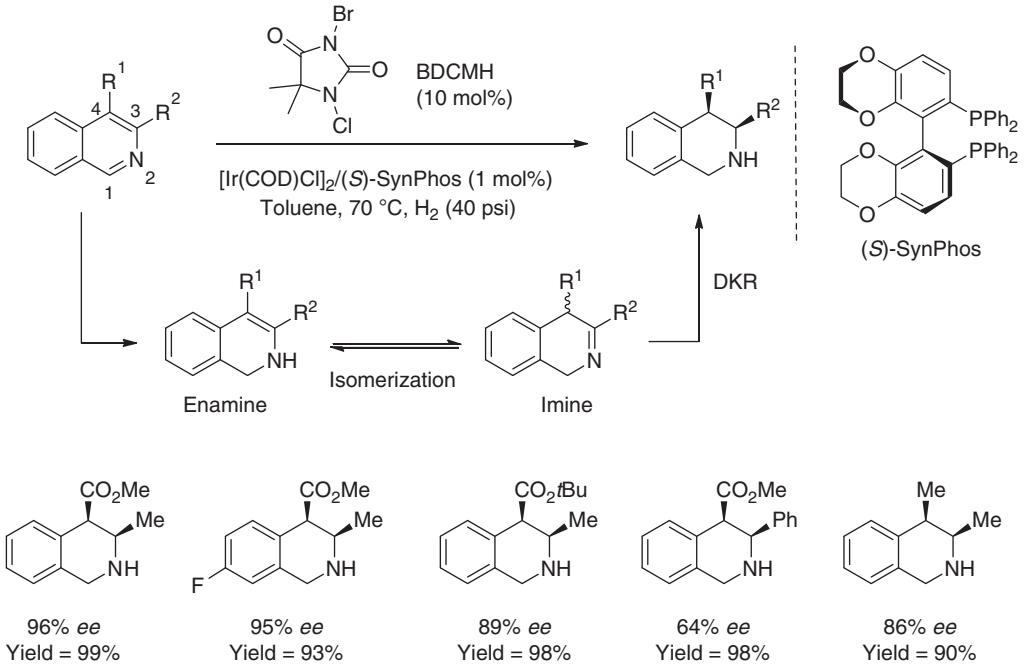


Entry	*R^1/R^2*	*Yield (%)*	ee *(%)*
i	H/Me	85	83
ii	H/Ph	57	82
iii	MeO/Me	44	63
iv	H/Et	85	62
v	H/*n*-Bu	87	63
vi	H/Bn	83	10

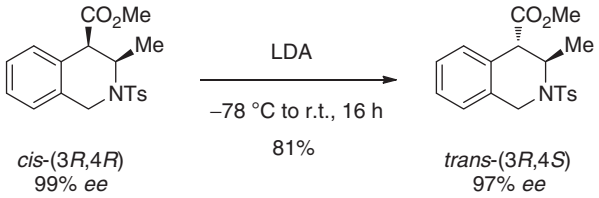
Zhou et al. reported a highly efficient iridium-catalyzed enantioselective hydrogenation of 3,4-disubstituted isoquinolines based on the catalyst activation strategy (Scheme 81).[114] A wide variety of 3,4-disubstituted isoquinolines were hydrogenated to give exclusively the corresponding chiral *cis*-3,4-disubstituted tetrahydroisoquinoline derivatives in excellent yields (up to 98%) with good to high *ee* values (up to 96% *ee*) as can be seen in some representative examples depicted in Scheme 81. Additionally, it was found that the presence of an ester function that can potentially act as a second coordinating group is not essential for achieving satisfactory results albeit slightly lower *ee* were obtained in this case.

Mechanistic studies based on ^1H nuclear magnetic resonance (NMR) experiments demonstrated that this transformation involves a stepwise reduction. 1,2-Hydride addition to the less sterically hindered 1,2-C=N bond provides the enamine intermediate, which after a rapid acid-catalyzed enamine–imine tautomerization followed by a diastereoselective hydrogenation through a dynamic kinetic resolution process gives exclusively the corresponding chiral *cis*-3,4-disubstituted tetrahydroisoquinoline. As a result, a slight decrease in enantioselectivity was observed for isoquinolines bearing bulky substituents either at the C_4 position or at the C_3 position, presumably because the isomerization of the imine to the enamine intermediate became slower.

Interestingly, the chiral *cis*-disubstituted products were easily converted to the corresponding *trans*-disubstituted compounds, which are otherwise difficult to obtain through direct AH, in good yield and without significant loss of selectivity by epimerization with lithium di*iso*propylamide (LDA) (Scheme 82).



Scheme 81



Scheme 82

This section has focused on recent advances made in AH of pyridines and their benzo analogs. Three main strategies based on catalyst activation, substrate activation, and dual activation have been successfully developed to tackle this long-standing problem. Among the large number of highly efficient catalytic systems that have been developed for such transformation, iridium catalysts containing chiral phosphorus ligands in combination with iodine as additive under hydrogen gas pressure are by far the most widely catalytic systems employed. Other hydrogen donors such as Hantzsch esters or a 1/3 mixture of water/triethylsilane can also be used as alternative H_2 sources. Of foremost interest is the use of Noyori's metal complexes of type [MX(η^6-arene)(*N*-TsDPEN)] (M = Ru, Rh and X = Cl, OTf) or [MXCp*(*N*-TsDPEN)] (M = Rh, Ir and X = Cl, OTf) in conjunction of either H_2 or a formic acid/triethylamine azeotrope mixture as hydrogen donors. These kinds of catalytic systems, which are known to be highly efficient for asymmetric transfer hydrogenation of ketones and imines, have also been introduced and provide spectacular results in terms of efficiency and selectivity. However, although some exciting results have been obtained, it is clear from the examples reported so far that AH of isoquinoline and pyridine derivatives is still far from being a mature field and is still in its infancy compared with AH of quinolines, for which a large number of highly efficient catalytic systems has been reported. Therefore, the development of new strategies and the design of more efficient chiral catalysts to reach a wider substrate scope, high reaction efficiency, and enantioselectivity are still highly desirable for the enantioselective hydrogenation of isoquinoline and pyridine derivatives.

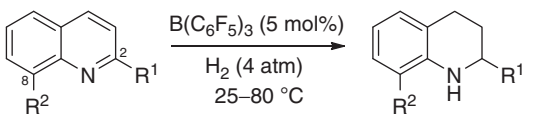
8.21.4 Organocatalyzed Reductions

8.21.4.1 Organocatalytic Metal-Free Hydrogenations

Since the discovery in 2006 that 'frustrated Lewis pairs' FLPs (i.e., combinations of Lewis acids and bases in which steric demands prevent the formation of classical Lewis acid–base adducts) could realize the heterolytic cleavage of hydrogen at room

temperature, the metal-free hydrogenation of a large variety of unsaturated systems including imines, enamines, and silyl enol ethers has been described.[115]

This strategy has also been successfully applied for the reduction of quinolines using electron-poor borane organocatalysts. The hydrogenation of these *N*-heterocycles catalyzed by *tris*(penta-fluorophenyl)borane leads to the corresponding tetrahydroisoquinolines in good yields if a substituent is present on either position 2 or 8.[116] Quinoline itself is not reduced under these reaction conditions probably because of the formation of a catalytically inactive stable complex between quinoline and tris(pentafluorophenyl)borane (Scheme 83).

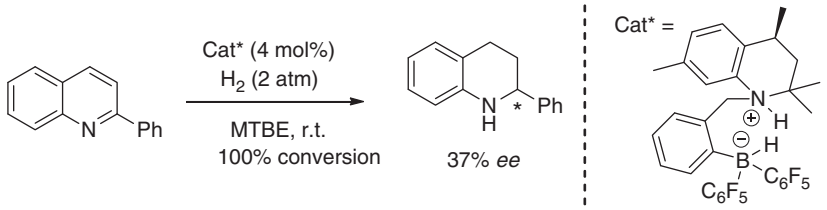


R^1	R^2	Yield (%)
Ph	H	80
Me	H	74
H	Me	88
H	H	–

Scheme 83

Subsequently, mesityl-*bis*(1,2,5,6-tetrafluorophenyl)borane proved to be a more efficient organocatalyst for this transformation. In addition to the notable advantage that this borane is relatively stable toward moisture, it catalyzes the hydrogenation of a larger scope of quinolines, including some that are not substituted neither at position 2 nor 8.[117]

Although in its infancy, the use of a chiral FLP organocatalyst in the metal-free AH of 2-phenylquinoline has been reported (Scheme 84).



Scheme 84

8.21.4.2 Organocatalytic Biomimetic Asymmetric Reductions

The biomimetic enantioselective Brønsted acid organocatalyzed transfer hydrogenation of numerous unsaturated system including C═C, C═N, and C═O bonds has been developed using dihydropyridine Hantzsch esters as hydride donors.[118] Since 2006, this field of research has led to some remarkable achievements in the context of the enantioselective reduction of pyridines and quinolines.

8.21.4.2.1 Pyridines

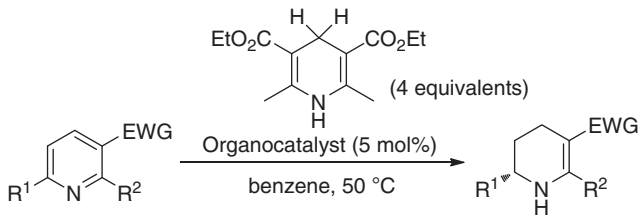
In the presence of 5 mol% of anthracenyl-substituted binol phosphoric acid and Hantzsch ester, several 2,3,6-trisubstituted pyridines are reduced to the corresponding tetrahydropyridines in good to average yields and high enantiomeric excesses. Notably, an electron-withdrawing group at the position 3 is required since it allows a better stabilization of the resulting tetrahydropyridine products, whereas the substrate scope only includes 6-alkyl-substituted pyridine systems (Scheme 85).[119]

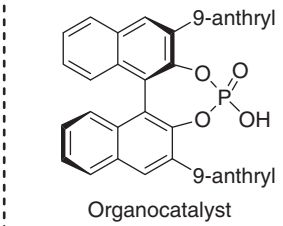
8.21.4.2.2 Quinolines

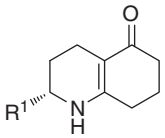
Analogously, Rueping et al. reported that the reduction of 2-substituted quinolines leads to the corresponding tetrahydroquinolines in good yields and enantioselectivities whatever the aryl, heteroaryl, or alkyl nature of the two substituents. Importantly, significantly better enantioselectivities are observed starting from 2-aryl quinolines (Table 20).[120]

Notably, this method could be applied to the highly diastereoselective asymmetric preparation of quinolizidine skeletons from aryl-3-quinolinylbutanones. Following a two-step reaction sequence, the biomimetic asymmetric reduction affords the enantiomerically enriched intermediary aromatic enamines that are subsequently diastereoselectively saturated by catalytic hydrogenation employing iridium nanoparticles stabilized on carbon nanotubes (Table 21).[121]

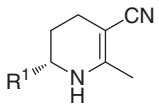
Through catalyst design, Du et al. introduced the catalytic use of a double axially chiral phosphoric acid which allows, in conjunction with the di(*t*-Bu)-Hantzsch ester in diethyl ether, the realization of a similar biomimetic reduction of 2-quinolines into the corresponding tetrahydroquinolines with catalyst loading as low as 0.2 mol%. Notably, this catalyst induces slightly better enantioselectivities starting from 2-alkyl quinolines and could be successfully used for the reduction of 2,3-disubstituted quinolines in high enantioselectivities and high diastereoselectivities (Scheme 86).[122]







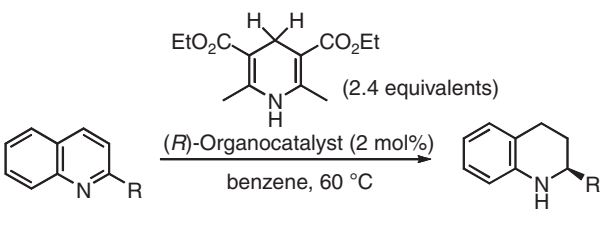
R^1	Yield (%)	*ee* (%)
n-butyl	72	91
n-pentyl	84	91
2-phenylethyl	66	92

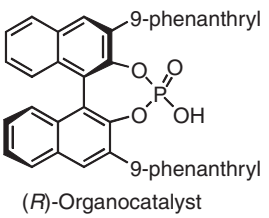


R^1	Yield (%)	*ee* (%)
n-butyl	55	84
n-pentyl	73	90
2-phenylethyl	47	86

Scheme 85

Table 20 Biomimetic chiral phosphoric acid catalyzed reduction of 2-substituted quinolines



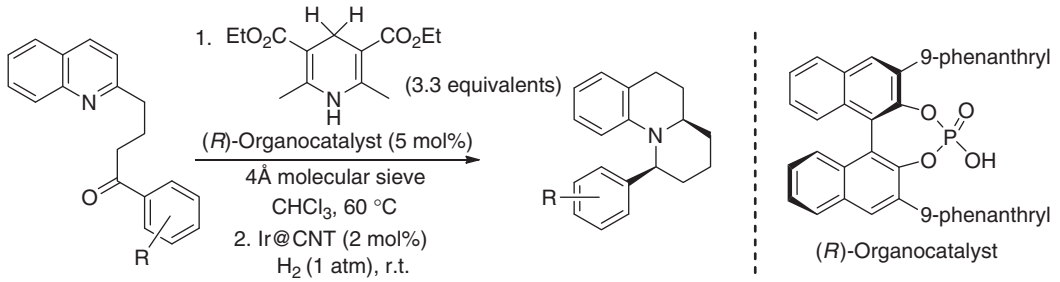


Entry	*R*	*Yield (%)*	ee *(%)*
i	C_6H_5	96	97
ii	2-F-C_6H_4	93	98
iii	2-Me-C_6H_4	54	91
iv	2,4-$(Me)_2$-C_6H_3	65	97
v	2-Naphthyl	93	>99
vi	3-Br-C_6H_4	92	98
vii	4-CF_3-C_6H_4	91	>99
viii	4-C_6H_5-C_6H_4	91	>99
ix	4-MeO-C_6H_4	90	98
x	2-Furyl	93	91
xi	CH_2Cl	91	88
xii	*n*-Bu	91	87
xiii	*n*-Pent	88	90
xiv	$(CH_2)_2Ph$	90	90

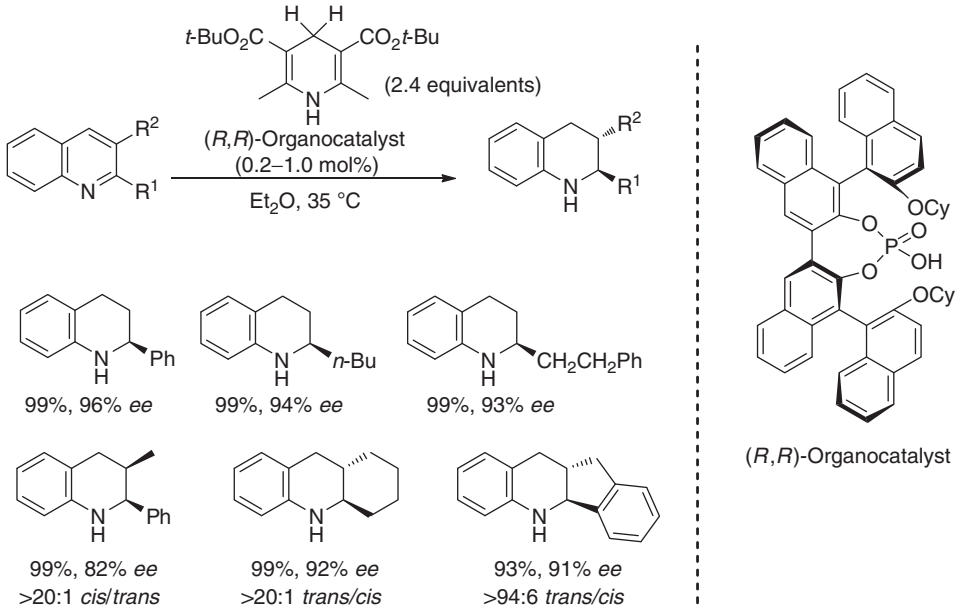
Since then, the organocatalyzed transfer hydrogenation of 2-substituted quinolines has also been developed in aqueous solvent,[123] or with polymer-supported/microporous chiral Brønsted acid organocatalysts.[124] Through a similar reaction mechanism, in which gold behaves as a proton surrogate, it is worth mentioning that chiral gold(I) phosphate complexes in the presence of Hantzsch esters catalyze the reduction of 2-aryl quinolines into the corresponding tetrahydroquinolines, in comparable yields and enantioselectivities, with catalyst loadings as low as 0.01%.[125]

The reduction of 3-aryl-substituted quinolines has also been studied. Rueping et al. demonstrated it to be much more challenging than that of 2-substituted quinolines. Nevertheless, through the proper choice of a much-hindered organocatalyst and a modified Hantzsch ester, respectable yields and enantioselectivities could be obtained (Table 22).[126]

Table 21 Biomimetic chiral phosphoric acid catalyzed preparation of quinolizidine scaffolds



Entry	*R*	*Yield (%)*	dr *(syn/anti)*	ee *(%)*
i	H	78	>98:2	93
ii	4-Me	79	>98:2	91
iii	4-MeO	70	>98:2	90
iv	3,4-Me_2	67	>98:2	93
v	3,4-$(MeO)_2$	73	>98:2	86
vi	4-F	80	>98:2	86
vii	4-Cl	73	>98:2	89



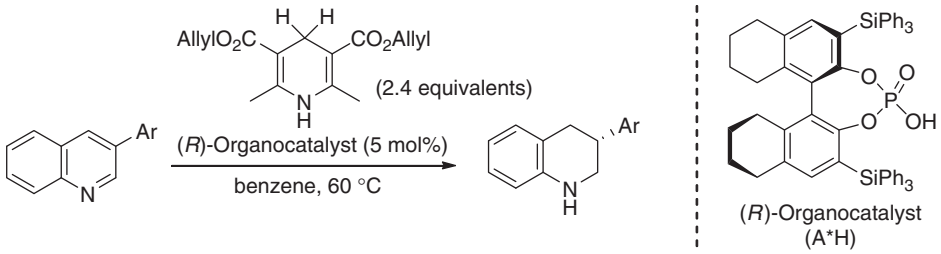
Scheme 86

It is important to notice that, in this case, chiral induction arises from a diastereoselective proton transfer, whereas in the case of 2-substituted quinolines a diastereoselective 1,2-hydride transfer takes place (Scheme 87).

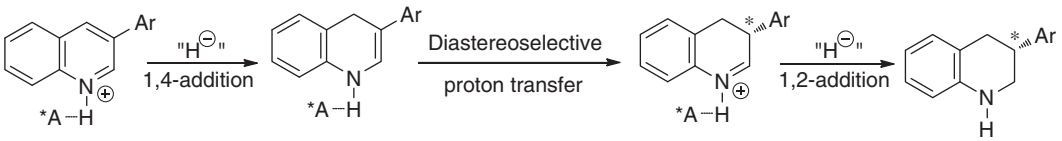
4-Substituted quinolines also undergo similar biomimetic reductions.[127] Because the stereocenter created during the reduction process is far away from the nitrogen protonated by the organocatalyst, a very hindered chiral Brønsted acid has to be employed in association with a very bulky di(*t*-Bu)-Hantzsch ester. In such reaction conditions, 4-alkyl and 4-aryl substituted tetrahydroquinolines are obtained from their quinoline parents in good to excellent yields and *ee*s. A chlorine atom at the position 7 often induces better reactivities and enantioselectivities (Table 23).

Finally, the Hantzsch ester reducing partner could be successfully replaced by 9,10-dihydrophenanthridine (DHPD) in the context of the biomimetic chiral phosphoric acid catalyzed reduction of 2-arylquinolines. As a direct benefit of such new NAD(P)H model, under milder reaction conditions DHPD could be employed in catalytic quantities, although its generation and regeneration being mediated by catalytic ruthenium hydrogenation of phenanthridine. The resulting sustainable relay catalytic system, which thus involves two different catalysts, allows the preparation of a variety of 2-aryl tetrahydroquinolines in yields and enantioselectivities comparable to those obtained with Hantzsch esters. Notably, a reversal of enantioselectivity is obtained while

Table 22 Biomimetic chiral phosphoric acid catalyzed reduction of 3-substituted quinolines

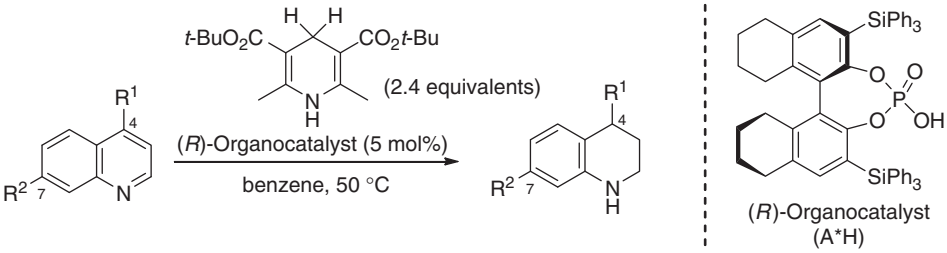


Entry	*Ar*	*Yield (%)*	ee *(%)*
i	C_6H_5	76	84
ii	4-C_6H_5-C_6H_4	58	82
iii	3,5-$(CF_3)_2$-C_6H_3	30	80
iv	2-Naphthyl	64	83
v	1-Naphthyl	84	77
vi	3,5-(*t*-Bu)$_2$–4-(MeO)-C_6H_2	35	77
vii	2-F-C_6H_4	77	85
viii	3-MeO-C_6H_4	67	85
ix	3,5-$(CH_3)_2$-C_6H_3	59	80
x	2-Thienyl	50	86



Scheme 87

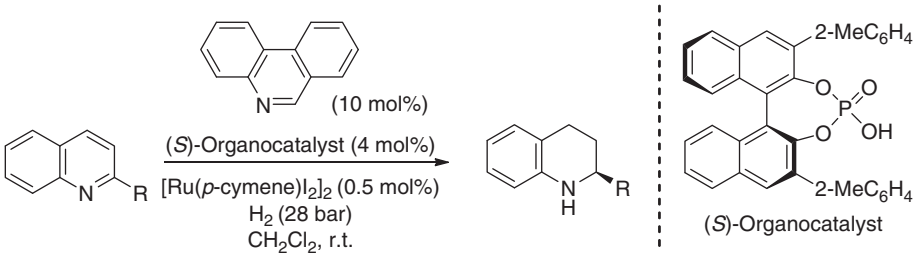
Table 23 Biomimetic chiral phosphoric acid catalyzed reduction of 4-substituted quinolines



Entry	*R^1*	*R^2*	*Yield (%)*	ee *(%)*
i	Me	H	67	73
ii	Me	Cl	85	85
iii	*i*-Pr	Cl	81	90
iv	*n*-Bu	Cl	82	84
v	Ph	H	84	81
vi	Ph	Cl	96	92
vii	3-MeO-C_6H_4	H	80	82
viii	3-MeO-C_6H_4	Cl	92	92
ix	4-Me-C_6H_4	H	77	83
x	4-Me-C_6H_4	Cl	92	91

using DHPD as hydride source and the success of this metalloorganocatalytic approach relies on the poor ability of the ruthenium complex to directly hydrogenate the quinoline scaffold (Table 24).[128]

Table 24 DHPD-mediated biomimetic chiral phosphoric acid catalyzed reduction of 2-arylquinolines



Entry	*R*	*Yield (%)*	ee *(%)*
i	Ph	95	91
ii	4-MeC_6H_4	96	90
iii	4-$MeOC_6H_4$	98	86
iv	4-FC_6H_4	96	90
v	4-ClC_6H_4	94	91
vi	4-BrC_6H_4	90	93
vii	4-$CF_3C_6H_4$	64	92
viii	2-Naphthyl	92	91

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8.22 Partial and Complete Reduction of Pyrroles, Furans, Thiophenes, and their Benzo Analogs, Heterocycles Containing More Than One Heteroatom

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Glossary

Arene An aromatic compound, usually a hydrocarbon.
Birch reduction A general term for the reduction of an organic compound (usually an arene) with sodium in liquid ammonia solvent.
Enantiopure A single enantiomer of a compound.
Heterogeneous catalyst A catalytic reaction in which the phase of the catalyst differs from that of the reactants.
Homogeneous catalyst A catalytic reaction in which the phase of the catalyst is the same as that of the reactants.
Ionic hydrogenation The reduction of a compound by the sequential addition of H^+ and then H^-.

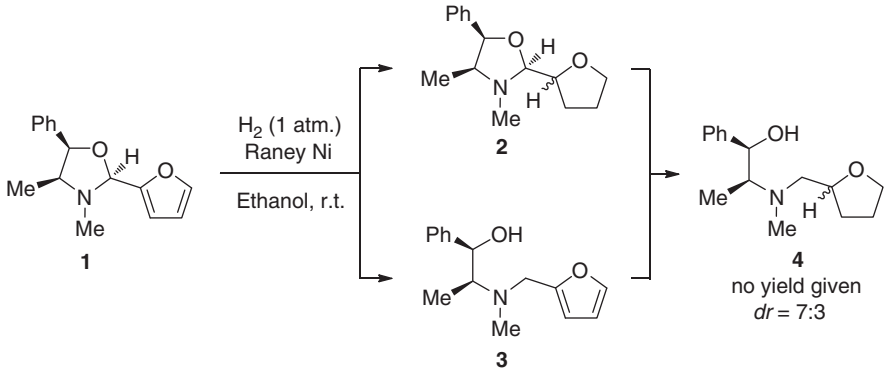
8.22.1 Reduction of Furans

8.22.1.1 Catalytic Hydrogenation

Although the history of the catalytic hydrogenation of furans goes back to the early 1950s, it suffered for a long time from some major drawbacks such as low catalyst activity, harsh conditions, ring opening of the furan skeleton, poor functional group tolerance, and a lack of methods for the enantioselective reduction of the aromatic ring. Thus, in the past two decades studies have focused on finding new methods to cope with these challenges. To increase the activity of palladium catalysts for the hydrogenation of furans Shirai and Arai investigated a hydrogen-permeating membrane, which can be used as an alternative to the standard coadsorbing catalysts used previously.[1] The authors found that this type of catalyst shows a significant and enhanced

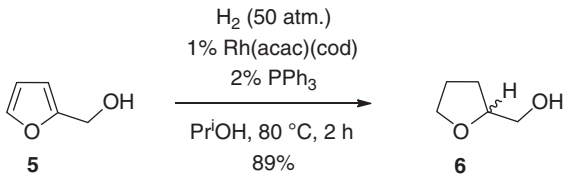
 doi:10.1016/B978-0-08-097742-3.00824-7

activity that can be explained by the larger amounts of hydrogen atoms on the active site of the catalyst, as well as the higher reactivity of the hydrogen atoms that pass through the membrane. A further increase of the reaction rate can be achieved by the choice of a suitable catalyst. The hydrogenation of oxazolidine-substituted furan **1**, for instance, could only be accomplished by the use of Raney nickel, whereas all attempts to hydrogenate the furan in the presence of platinum, palladium, or palladium on charcoal failed (Scheme 1).[2] Unfortunately, the use of Raney nickel does not just reduce the aromatic ring to yield the desired tetrahydrofuran (THF) **2**, but also formed the ring-opened compounds **3** and **4** in a ratio of 1.5:1:1. This hydrogenolysis prohibited the selective formation of **2**, but prolonged reaction times led to the selective formation of THF **4** in a diastereomeric ratio of 7:3.



Scheme 1

Although the ring opening of heterocycles was a long-standing problem encountered while carrying out catalytic hydrogenations, the introduction of rhodium and ruthenium catalysts enabled a selective reduction of furans without breaking the C–O bond. Ito and coworkers investigated the use of commercially available rhodium catalysts in the presence of phosphine ligands and identified the combination of Rh(acac)(cod) and triphenylphosphine as being especially effective for the hydrogenation of furans and other heteroaromatic compounds.[3] However, the reaction required elevated temperatures (80 °C in isopropanol) and 50 atm of hydrogen pressure to proceed to completion. By employing these conditions furan **5** was hydrogenated to yield THF **6** in 89% yield (equation 1). It is noteworthy, that a directing group (e.g., the primary alcohol) is not essential, as other heterocycles can be reduced which do not bear a coordinating heteroatom.

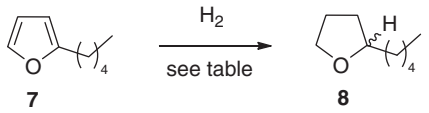


(1)

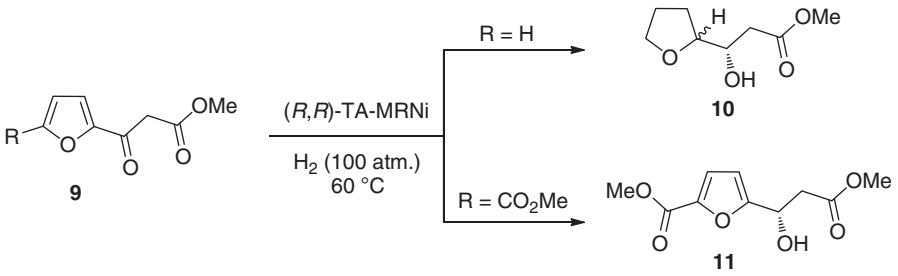
Sajiki and coworkers also showed that rhodium on carbon (Rh/C) was an effective catalyst for the hydrogenation of heteroaromatic compounds.[4] The higher activity compared with Pt/C, Pd/C, or Ir/C, in addition to the feasibility of performing this heterogeneous hydrogenation in water, makes Rh/C an interesting catalyst for the reduction of furans. With 10% Rh/C in water and at 80 °C furan **7** can be converted into THF **8** in 90% yield after a short reaction time of 30 min (Table 1). Owing to the insolubility of furan **7** in water, a hydrogen pressure of 5 atm was necessary. Changing to isopropanol as a solvent, the reduced heterocycles **8** were formed after 24 h in 90% yield, and only 1 atm of hydrogen and a temperature of 60 °C were required. In addition to Rh/C a less expensive ruthenium catalyst was also effective for the reduction, although again a pressure of 5 atm was mandatory in order to produce the THF. A great benefit of both heterogeneous catalysts compared with alternative hydrogenation catalysts is the possibility for recycling of the metal. Both catalysts can be simply filtered off after complete conversion and reused for further reactions without a notable decrease in their catalytic activity.

In 1999, Sugimura and coworkers reported their studies on the reduction of furyl ketones using modified Raney nickel and illustrated two challenges that were still to be solved: the chemoselective and the enantioselective reduction of heteroaromatics.[5] By employing tartaric acid-modified Raney nickel (Ta-MRNi) for the hydrogenation of furyl ketone **9** (R=H) they observed a simultaneous reduction of the aromatic ring and the ketone to obtain THF **10** (Scheme 2). Interestingly, the ketone was reduced enantioselectively (*ee*=77%), whereas reduction of the furan produced the newly formed stereogenic center without any selectivity. When the same conditions were applied to the electron-deficient furan **9** (R=CO_2Me) no hydrogenation of the aromatic ring took place and the secondary alcohol **11** was obtained as the only product with an *ee* of 69%.

Table 1 Complete hydrogenation of furan **7** applying different conditions



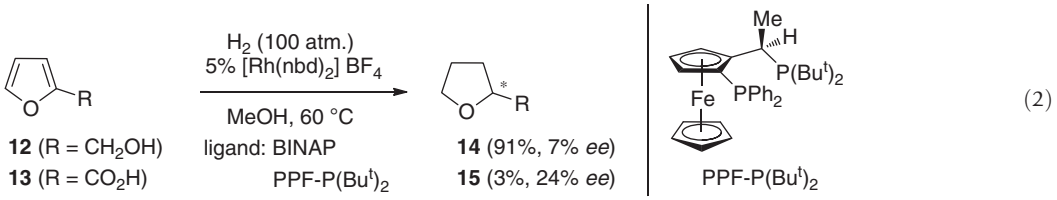
Entry	*Catalyst*	*H_2 pressure(atm)*	*Solvent*	*Temperature (°C)*	*Time (h)*	*Yield (%)*
i	10% Rh/C (10 wt %)	5	H_2O	80	0.5	90
ii	10% Rh/C (10 wt %)	1	Pr^iOH	60	24	90
iii	10% Ru/C (10 wt %)	5	Pr^iOH	60	12	89



(TA-MRNi = Tartaric acid modified Raney nickel)

Scheme 2

The first enantioselective hydrogenation of a furan was accomplished by Studer and coworkers in the year 2000, although the enantioselectivities were poor.[6] A catalyst screening exercise revealed that $[Rh(nbd)_2]BF_4$ (nbd = norbornadiene) was superior to other Rh, Ru, Ir, and Pt complexes in terms of both activity and stability, whereas ligand screening was not enlightening; various diphosphine ligands were examined for the hydrogenation of furans **12** and **13** (equation 2). Regarding the enantioselectivity, the best choice for hydroxymethyl furan **12** was 2,2′-binaphthyldiphenyldiphosphine (binap) affording THF **14** in 91% yield and 7% *ee*, whereas the ferrocenyl diphosphine PPF-$P(Bu^t)_2$ was the best ligand for the hydrogenation of 2-furoic acid **13** delivering the reduced heterocycles **15** in an *ee* of 24%, but only in 3% yield.

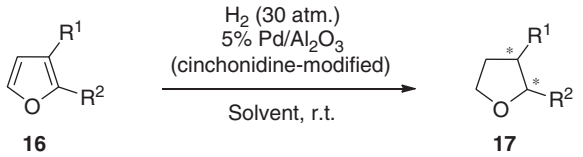


(2)

The use of cinchonidine-modified palladium on alumina showed a slightly higher level of enantioselectivity in the hydrogenation of furoic acids as described by Baiker et al.[7] In contrast to the rhodium catalyst employed by Studer (equation 2), the use of this heterogeneous catalyst did not just enable the reaction to be performed at room temperature and with a lower hydrogen pressure, it also afforded THF **17** in nearly quantitative yield and with an increased *ee* of 32% (entry i, **Table 2**). Hydrogenation of 3-furoic acid afforded a reduced heterocycle in quantitative yield and with 23% *ee* (entry ii). However, by applying the same conditions to disubstituted furoic acids the THFs were obtained in a very poor yield and with enantioselectivities of 22% and 15%, respectively (entries iii and iv). Unsurprisingly, the hydrogenation of the latter two aromatic compounds led to exclusive formation of the *cis*-THFs. The potential of Baiker's conditions are hampered by a competing reduction of the quinoline moiety of cinchonidine demanding an addition of small portions of the chiral amine as the reaction proceeds. Spectroscopic studies and *ab initio* calculations revealed that hydrogen bonding between the protonated tertiary amine and the secondary alcohol of cinchonidine with two molecules of the furoic acid is important.[8] The enantioselectivity itself arises from the adsorption of this chiral complex on the palladium and a face-selective hydrogenation of the electron-rich furan ring. An alternative complex consisting of one molecule of cinchonidine and one molecule of furoic acid is also feasible in solution, but it is less favored due to its rigid structure.

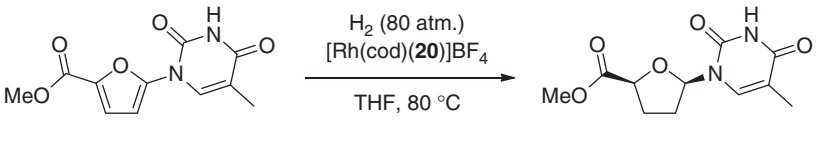
In the synthesis of 2′,3′-dideoxynucleoside analogs, Albert and coworkers wanted to prepare the dideoxyribofuranoside core via an asymmetric hydrogenation of 2,5-disubstituted furan **18** (**Scheme 3**).[9] The cationic rhodium complex $[Rh(cod)_2]BF_4$ (10 mol%) in combination with the diphospholane ligand (*R*,*R*)-Pr^i-butphane (**20**) afforded the reduced heterocycle **19** in 98%

Table 2 Enantioselective hydrogenation of furoic acids

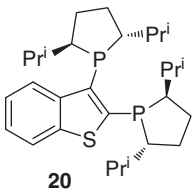


16 **17**

Entry	R^1	R^2	*Solvent*	*Yield (%)*	ee *(%)*	cis:trans
i	H	CO_2H	Toluene	95	32	–
ii	CO_2H	H	Pr^iOH	100	23	–
iii	CO_2H	Me	Pr^iOH	2	22	100:0
iv	Me	CO_2H	Pr^iOH	6	15	100:0



18 **19**



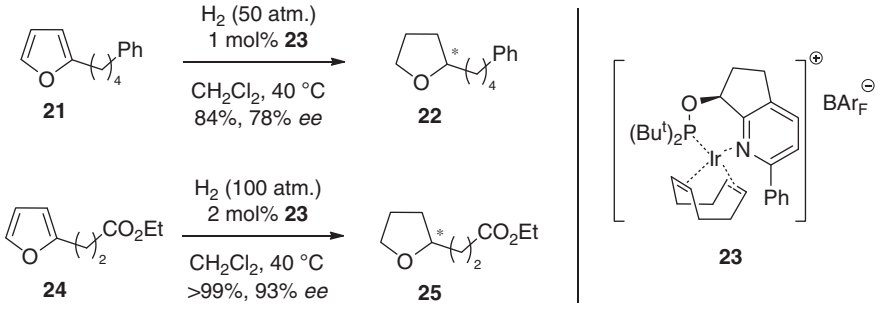
20

mol%	Yield (%)	*ee* (%)	*de* (%)
30	68	23	99
10	98	72	99
1	67	58	99

Scheme 3

yield and with 72% *ee*, without affecting the double bond of the nucleobase or the benzothiophene moiety of the ligand. An increased, or lower, catalyst loading gave **19** in slightly lower yields and enantioselectivities. Interestingly, changing the solvent from THF to a protic polar solvent such as methanol, or the addition of a base, resulted in the formation of the other enantiomer.

Until the year 2006, all of the asymmetric hydrogenations of furans required a coordinating group (e.g., carboxylic acid or ester) to direct the catalyst and to achieve reasonable enantioselectivities. From work concerning the hydrogenation of double bonds it was known that in contrast to rhodium and ruthenium catalysts, iridium complexes do not necessarily need such a polar group, as shown by Pfaltz and coworkers.[10] In his studies reducing purely alkyl substituted double bonds, Pfaltz also applied their optimized conditions to the hydrogenation of furans **21** and **24** (Scheme 4). By using the iridium phosphinite complex **23** hydrogenation of furan **21** produced THF **22** in 84% yield and with 78% *ee* without reducing the phenyl ring. An even better result was achieved in the case of furan **24**, which afforded **25** in quantitative yield and with an *ee* of 93%.

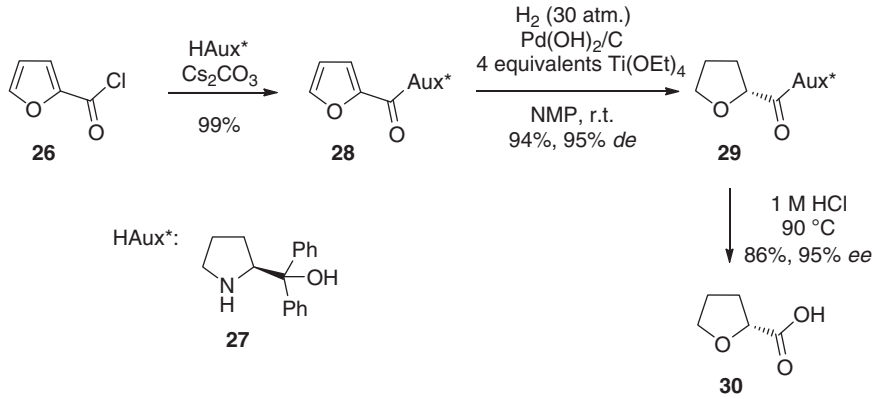


21 **22** **24** **25** **23**

Scheme 4

In addition to the employment of modified heterogeneous catalysts or chiral ligands, chiral auxiliaries can also be used to enable the selective hydrogenation of furans. Sebek et al. investigated various chiral furoic acid derivatives and revealed that amide **28**, derived from furoic acid chloride **26** and prolinol derivative **27**, in *N*-methyl pyrrolidinone (NMP) gave the highest diastereoselectivity while using palladium hydroxide on carbon as the heterogeneous catalyst (Scheme 5).[11] Addition of Lewis

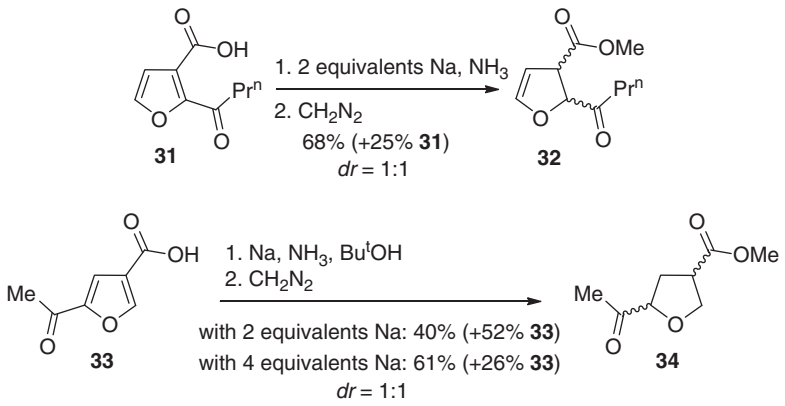
acids such as $Ti(OEt)_4$ to complex the furan oxygen and the amide group led to a rigid conformation and resulted in higher selectivities. Subsequent removal of the auxiliary by treatment with hydrochloric acid afforded (*R*)-THF-2-carboxylic acid (**30**) in 95% *ee*.



Scheme 5

8.22.1.2 Dissolving Metals

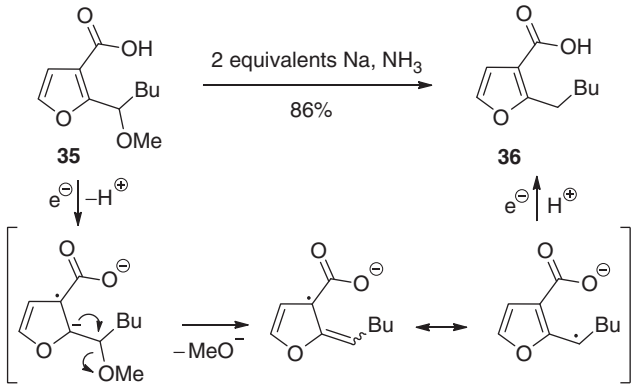
In 1975, the research groups of A.J. Birch[12] and T. Masamune[13] independently reported the first high-yielding partial reduction of furans by dissolving sodium or lithium in liquid ammonia, although a carboxylic acid in the 2-position was crucial to stabilize the resulting anion and to avoid opening of the furan ring. Although in most cases the Birch reduction of furans leads to the formation of dihydrofurans, complete reduction to the THF was reported by Kinoshita and coworkers.[14] Whereas 2-acyl-3-furoic acid **31** gave the expected dihydrofuran **32**, 5-acyl-3-furoic acid **33** afforded the THF **34**; albeit incomplete conversion was observed in both reductions and the products were obtained as 1:1 diastereomeric mixtures (Scheme 6).



Scheme 6

The authors assumed that the reduction of furan **33** initially formed the corresponding 2,3-dihydrofuran. A subsequent transfer of two more electrons to this α,β-unsaturated ketone resulted in the formation of the fully reduced heterocycle. The selective formation of both heterocycles clearly shows that conjugated ketones can survive the conditions for Birch reduction of furoic acids (presumably they are protected as their enolates during reduction). Furthermore, Kinoshita pointed out that alkoxy groups at the furan core or in a benzylic position will undergo reductive deoxygenation as shown in Scheme 7.[15] Thus, addition of 2 equivalents of sodium to furan **35** in liquid ammonia led to an elimination of methanol and furan **36** was obtained in 86% yield. By using 4 equivalents of sodium, a consecutive reduction to the 2,5-dihydrofuran derivatives could be achieved.

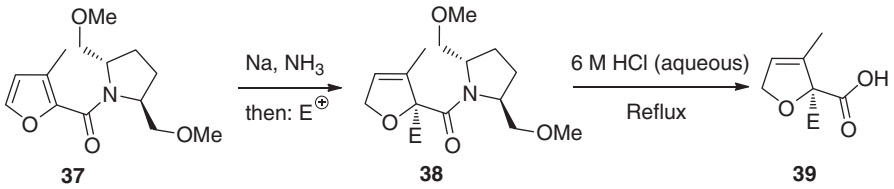
For the first two decades after its development, applications of the Birch reduction of furans were scarce, most likely due to the formation of racemic mixtures and *cis*/*trans*-mixtures in the cases of furans bearing more than one substituent. Neither the employment of a chiral proton source to quench the Birch reduction[16] nor the assistance of (*S*)-methoxymethyl pyrrolidine as a chiral auxiliary[17–19] led to a significant selectivity (3% *ee* and 22% *de*, respectively). A breakthrough was made by Donohoe and



Scheme 7

coworkers in 1998 by introducing (*S,S*)-bismethoxymethyl pyrrolidine as a powerful C_2-symmetric auxiliary.[18] The chiral furoic acid derivative **37** was reduced under standard Birch conditions and the resulting enolate trapped with various electrophiles (Table 3).[19] Linear alkyl halides afforded the dihydrofuran **38** with a high level of stereochemical control (*dr* = 30:1) and good-to-excellent yields (entries i–iv), whereas quenching with ammonium chloride as a proton source led to the formation of a 10:1-mixture of diastereoisomers (entry v). Removal of the chiral auxiliary by heating in hydrochloric acid delivered the carboxylic acids **39** with very good enantioselectivities (≥94%). Surprisingly, amide **38** (with E = H, entry v) did not undergo smooth hydrolysis and prolonged reaction time eventually led to decomposition of the dihydrofuran.

Table 3 Stereoselective Birch reduction of furoic acid derivative **37**



Entry	E^+	*E*	*Yield (**38**) (%)*	dr *(**38**)*	*Yield (**39**) (%)*	ee *(**39**) (%)*
i	MeI	Me	98	30:1	86[a]	96
ii	EtI	Et	74	30:1	74	>96
iii	BnBr	Bn	57	30:1	80[a]	>96
iv	Bu^iI	Bu^i	68	30:1	68	94
v	NH_4Cl	H	65	10:1	–	–

[a]2 M HCl (aqueous) was used for hydrolysis.

The authors proposed a mechanism that involves the formation of the (*E*)-enolate, in which the bulky auxiliary avoids clashing with the methyl group on the dihydrofuran ring (Figure 1).[18,19] In this intermediate the methoxymethyl group pointing upwards is closer to the α-carbon of the enolate than the side arm pointing down, the attack of the electrophile should be preferable from the lower face. Alternatively, the reaction could also proceed via a *Z*-enolate. Assuming that the nitrogen of the enolate is planar, rotation around the C–N bond would be necessary to avoid a steric clash with the methyl group. Again one side arm of the pyrrolidine shields the enolate more than the other, and therefore the electrophile will again approach from the *re*-side leading to

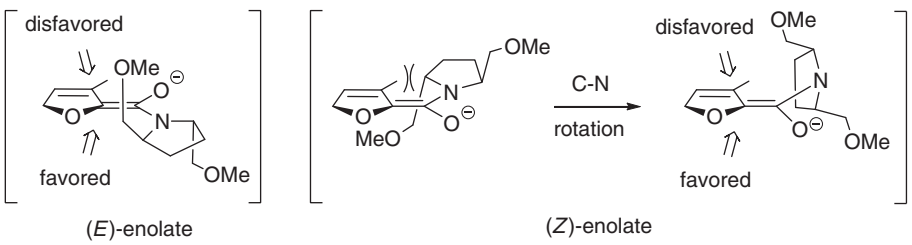
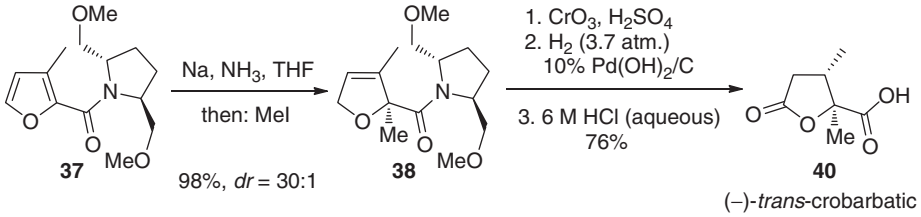


Figure 1 Explaining the observed diastereoselectivity.

the same diastereoisomer as indicated in the case of the (*E*)-enolate. As the rotation around the C–N bond results in a reduced overlap of the lone pair at nitrogen and the π-system, the authors assumed that a reaction pathway involving the (*E*)-enolate was more likely.

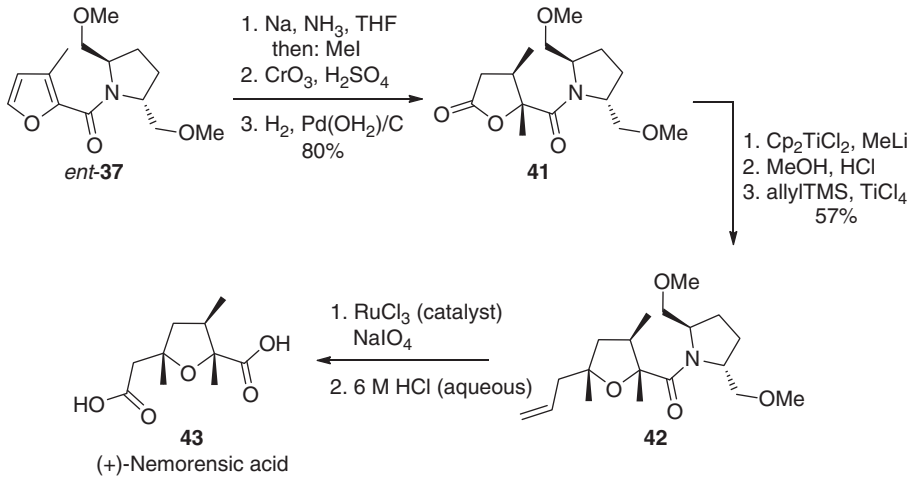
The high selectivity of the Birch reduction/alkylation sequence makes it a useful tool in organic synthesis as first shown by Donohoe et al. in the synthesis of (–)-*cis*-crobarbatic acid (**40**, Scheme 8).[20] Birch reduction of the readily available amide **37** and



Scheme 8

subsequent alkylation gave dihydrofuran **38** in nearly quantitative yield and with a *dr* of 30:1. Oxidation to the 2-furanone, stereoselective hydrogenation of the double bond and removal of the auxiliary afforded the natural product in only five steps and with an excellent overall yield of 66%. In an analogous manner, (–)-*trans*-crobarbatic acid was synthesized in 40% overall yield.

The stereoselective Birch reduction was also applied to the total synthesis of (+)-nemorensic acid (**43**, Scheme 9).[21,22] The same conditions that were used in the synthesis of the crobarbatic acids gave γ-lactone **41** starting from furan derivative *ent*-**37**. Olefination of the lactone carbonyl, followed by formation of the acetal and then allylation in the presence of titanium tetrachloride led to the THF **42** with high diastereoselectivity. Oxidative cleavage of the alkene and removal of the auxiliary afforded (+)-nemorensic acid (**43**) in nine steps and in 25% overall yield.

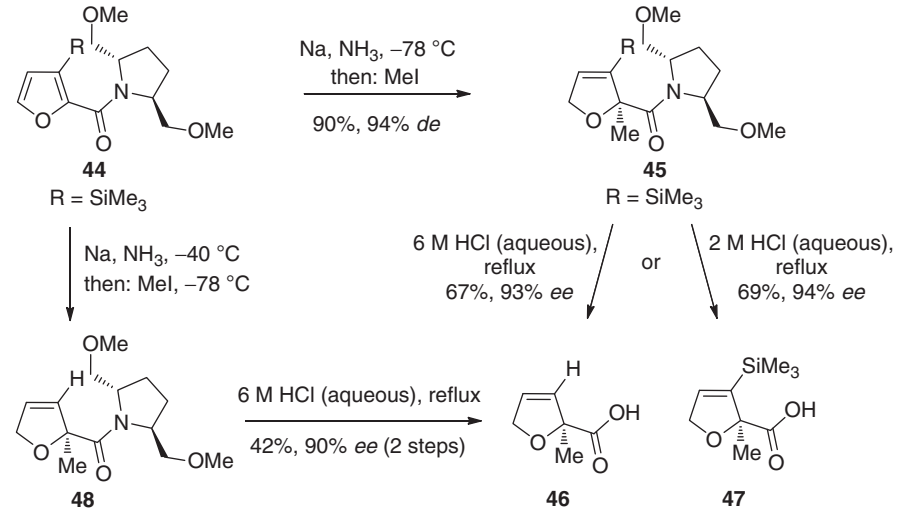


Scheme 9

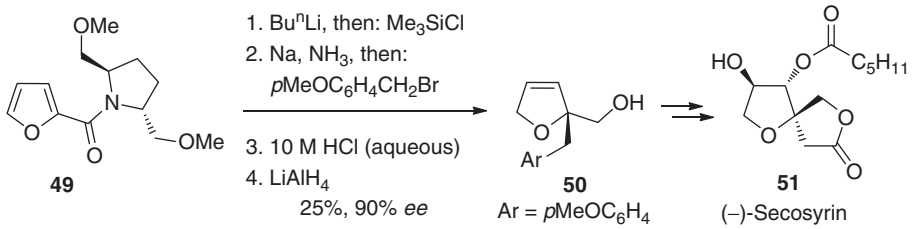
Although high levels of selectivity were achieved with furan **37** the stereoselectivity of the Birch reduction was limited to furan derivatives with a methyl group at the 3-position of the heterocycle because furans without a 3-substituent gave nearly no *de* (Figure 1). In order to broaden the scope of the Birch reduction/alkylation sequence, Donohoe and coworkers also investigated modifiable substituents in the 3-position, so that the functionality on the furan could be either transformed to synthetically more useful groups or removed afterwards.[23,24] Scheme 10 illustrates the studies on the reduction of 3-trimethylsilyl furoic acid derivative **44**. Birch reduction at -78 °C and subsequent trapping of the anion with iodomethane afforded dihydrofuran **45** in 90% yield and with a *de* of 94%, which is similar to the selectivity obtained with a 3-methyl furan (see Table 3, entry 1). Cleavage of the amide bond with 6 M HCl gave the desilylated acid **46**, whereas milder conditions (2 M HCl) resulted in the formation of silylated dihydrofuran **47**. Remarkably, the conditions for the Birch reduction could be tailored so that the silyl group was cleaved during the reduction step (see formation of **48**). Subsequent cleavage of the auxiliary furnished acid **46** in 42% yield (over two steps), although with a slightly lower *ee* of 90%. As a partial reduction without a substituent in the 3-position produced the dihydrofuran with little selectivity (*dr* = 59:41),[19] the authors assumed that the aromatic heterocycle was first reduced and then the *C*-3 silyl group removed either via an attack of sodium amide and consecutive protonation or via a Brook type migration.[23]

The effectiveness of the Birch reduction of 3-silyl furoic acid derivatives was demonstrated in a concise 11-step synthesis of secosyrin (**51**, Scheme 11).[25] Silylation of furoic amide **49**, which is readily available in one step, and consecutive partial reduction

gave the dihydrofuran, which was desilylated and hydrolyzed in the same step. Reduction of the acid afforded alcohol **50** with an *ee* of 90%. As the same authors had also described a synthesis of racemic secosyrin (**51**), preparation of **50** represented a formal synthesis of (–)-secosyrin.

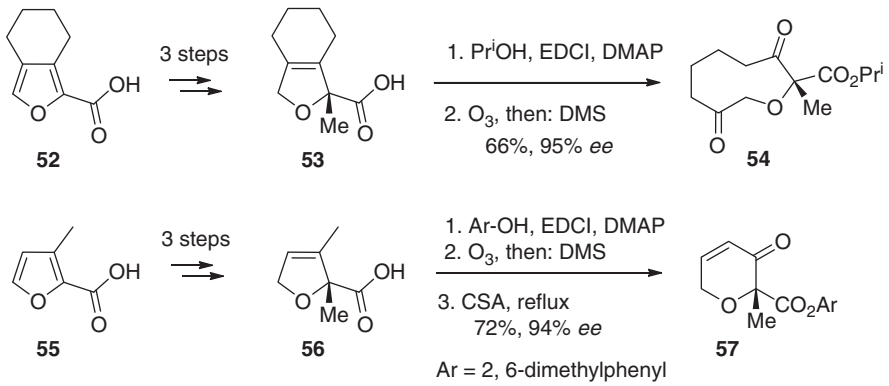


Scheme 10



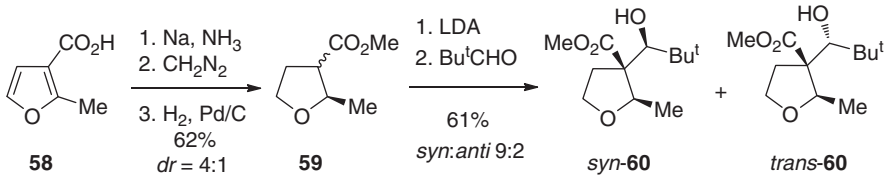
Scheme 11

The stereoselective partial reduction of furans furnishes chiral dihydrofurans in the first instance, but other chiral heterocycles are also accessible by some consecutive transformations. Two synthetically useful examples are shown in Scheme 12.[26,27] Both dihydrofurans **53** and **56**, which were prepared by stereoselective Birch reductions starting from furans **52** and **55**, were esterified and subsequently ring opened via ozonolysis. Whereas the tetrasubstituted alkene arising from **52** gave diketone **54**, in the latter case oxidative cleavage and treatment with acid gave dihydropyranone **57**.



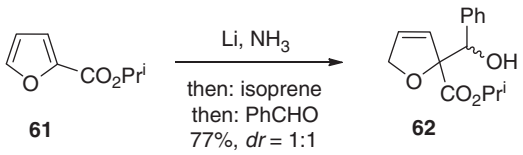
Scheme 12

In all of the Birch reductions described earlier, the intermediate enolate anion reacted with an alkyl halide to furnish the corresponding alkylated dihydrofurans. However, trapping of the anion with an aldehyde *in situ* was undeveloped, although Quayle and coworkers had reported a partial reduction of furoic acid **58** followed by esterification and hydrogenation to obtain THF **59** (Scheme 13).[28] Subsequent aldol reaction afforded secondary alcohol **60** as a 9:2 diastereomeric mixture. A similar multistep procedure for a subsequent conjugate addition was reported by the same authors.[29]



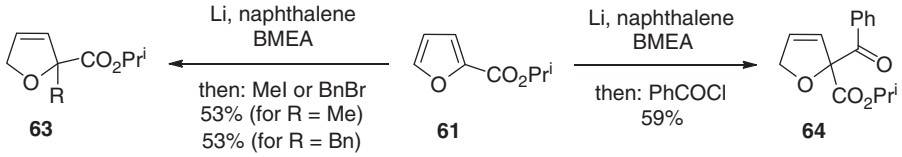
Scheme 13

The first partial reduction of a furan and subsequent trapping of the intermediate enolate anion with a carbonyl was accomplished by Donohoe et al. in 2000.[30] To obtain high yields, it was crucial that after complete reduction to the dihydrofuranoyl anion, any excess of electrons was quenched by the addition of isoprene, before the addition of the aldehyde. Thus, starting from furan derivative **61**, a reductive aldol reaction with benzaldehyde afforded alcohol **62**, albeit as a 1:1 diastereomeric mixture (Scheme 14). The lack of stereoselectivity can probably be attributed to the formation of a 1:1-mixture of *E*/*Z*-enolates.



Scheme 14

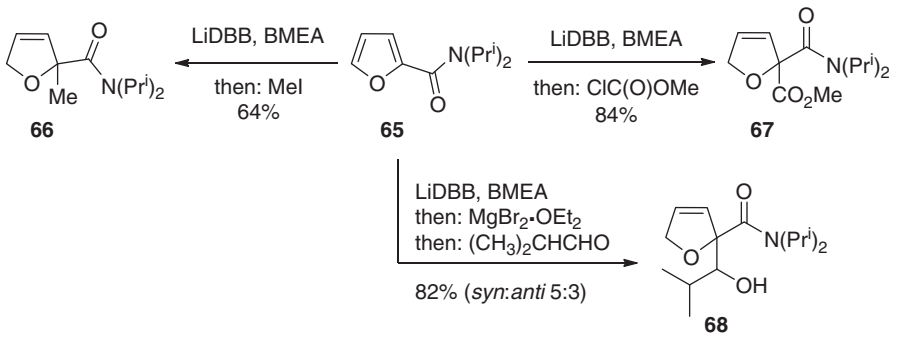
Unfortunately, the reductive aldol reaction shown in Scheme 14 only works with nonenolizable aldehydes as compounds with a hydrogen alpha to the carbonyl simply protonate the enolate faster than undergoing nucleophilic addition. To overcome this problematic side reaction and also to make the Birch reduction more user-friendly Donohoe and coworkers developed a partial reduction of heteroaromatics that still employs alkali metals, but under ammonia-free conditions.[31] By using lithium in combination with naphthalene as an electron carrier and with bis(methoxyethyl)amine (BMEA) as a proton source, it was possible to reduce and alkylate furoic ester **61** without the use of ammonia, and also to trap the intermediate anion with an acid chloride to obtain *β*-ketoester **64** (Scheme 15).



Scheme 15

As the yield of the alkylated dihydrofuran **63** was lower in the case of lithium naphthalene promoted reduction compared with the traditional Birch reduction in ammonia, further studies were carried out to investigate alternative electron carriers. During these studies it was found out that substituting naphthalene with di-*tert*-butylbiphenyl (DBB) increased the yields significantly.[32] Starting from furoic amide **65**, methylated dihydrofuran **66** was obtained in 64% yield, whereas quenching the anion with methyl chloroformate afforded ester **67** in 84% yield (Scheme 16). Additionally, the use of LiDBB also enabled reductive aldol reactions with enolizable carbonyls such as isobutyraldehyde, which was not possible when using ammonia as a solvent. Under these conditions furan **65** was converted into aldol product **68** in 82% yield, whereas addition of anhydrous magnesium bromide led to a transmetallation of the enolate counter ion before the aldol reaction and as a result to an increase in the diastereoselectivity (5:3).[33]

To gain an insight into the mechanism of the ammonia-free Birch reduction, Donohoe and Compton carried out electrochemical studies mimicking typical reducing conditions (anhydrous and at low temperature).[34] By comparing the partial reduction of various activated furans, they discovered that monoactivated furans undergo a reduction only in the presence of a proton source (such as BMEA) to protonate the rather unstable dianionic intermediate, whereas the same conditions applied to furoic 2,5-diesters resulted in a more stable dianion which furnished the reduced heterocycle without the requirement for a weak acid.

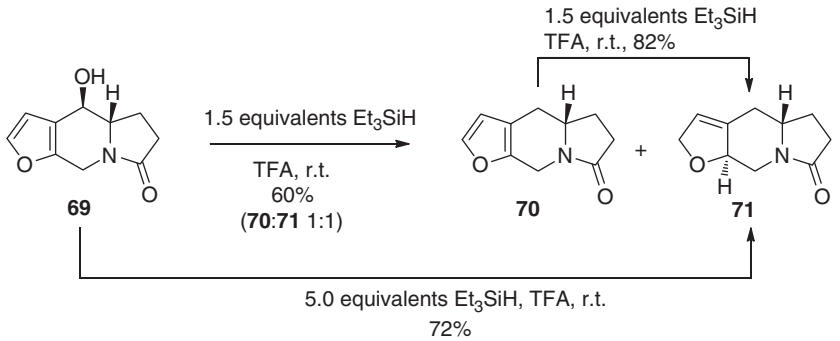


Scheme 16

8.22.1.3 Miscellaneous Reductions

Although the hydrogenation and use of dissolved metals are the two most frequently applied methods for the reduction of furans, there are two more strategies that are worth mentioning and that do not fit into either of these two categories.

During their studies on the synthesis of octahydrofuro[*f*]indolizines, Daïch and coworkers investigated a reduction of the furan ring by employing a silane in the presence of trifluoroacetic acid (TFA).[35] Addition of 1.5 equivalents of triethylsilane to furan **69** in pure TFA furnished the deoxygenated tricycle **70** in 30% yield together with the dihydrofuran **71** (Scheme 17). Reduction of furan **70** under the same conditions afforded dihydrofuran **71** as a single diastereoisomer in 82%. By treatment of alcohol **69** with 5 equivalents of the silane in TFA and a prolonged reaction time (8 h vs.1 h), dihydrofuran **71** was obtained as the only product and again as a single isomer.



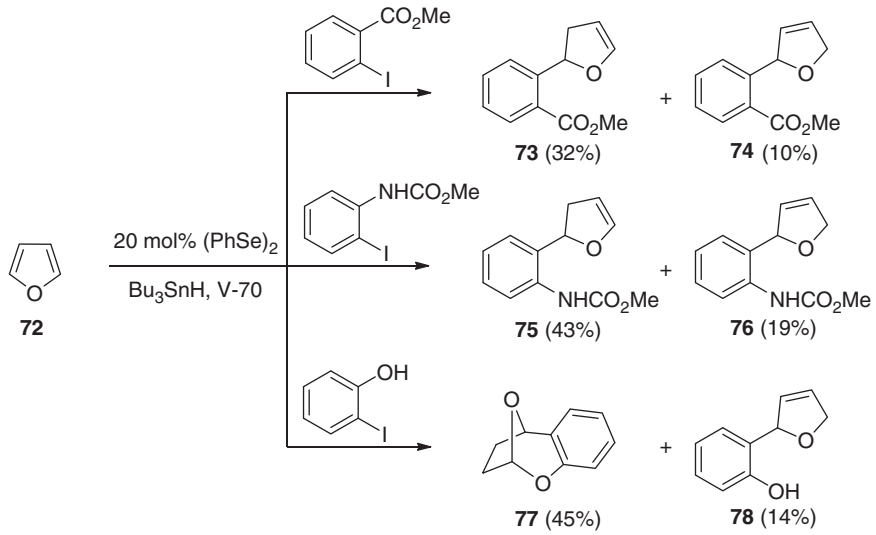
Scheme 17

A unique method for preparing 2,5-dihydrofurans and their 2,3-isomers by employing a selenol-catalyzed aryl radical addition to furan was described by Crich and Patel.[36] In the presence of tributyltin hydride and catalytic amounts of diphenyl diselenide and 2,2′azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) aryl iodides were converted into the corresponding aryl radicals, which added to the 2-position of furan **72** (Scheme 18). The resulting allylic radical was quenched by *in situ* formed PhSeH and produced mixtures of two dihydrofurans, where the 2,3-isomers **73** and **75** were the major products. In the case of *ortho*-iodophenol, only the 2,5-dihydrofuran **77** was obtained because the 2,3-isomer underwent a spontaneous cyclization to the tetrahydrobenzoxepin **78** in 45% yield.

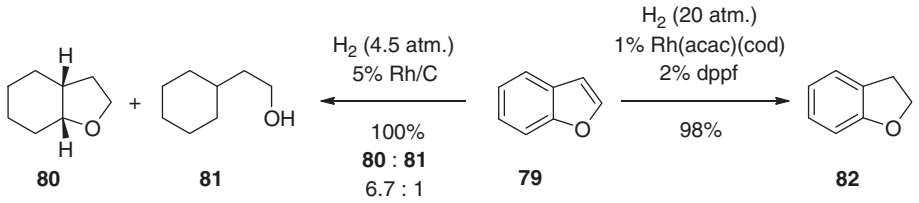
8.22.2 Reduction of Benzofurans

8.22.2.1 Catalytic Hydrogenation

Catalytic hydrogenations of benzofurans employing heterogeneous metal catalysts based on Pt, Pd, and Rh have been known for some time. However, from the early 1990s developments have focused on the establishment of suitable homogeneous catalysts as well as an expansion of the method to encompass the synthesis of chiral dihydrobenzofurans. The advantage using soluble rhodium catalysts in the presence of phosphine ligands versus rhodium on carbon is shown in Scheme 19. Although the hydrogenation of benzofuran (**79**) with Rh/C produced the two overreduced compounds **80** and **81**,[37] homogeneous conditions with Rh(acac)(cod) as a catalyst and 1,1′-bis(diphenylphosphino)ferrocene (dppf) as a ligand afford dihydrofuran **82** selectively and in almost quantitative yield.[3]

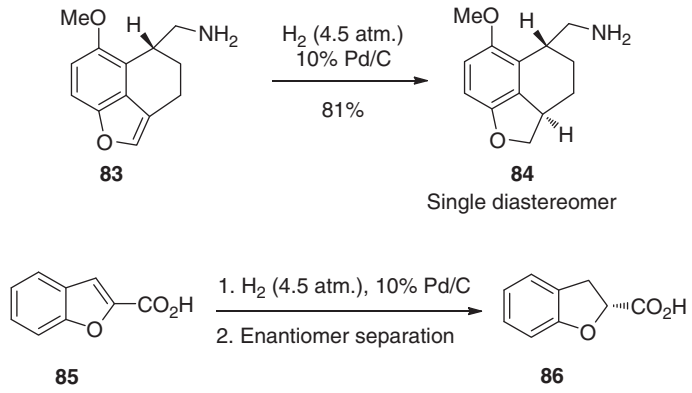


Scheme 18



Scheme 19

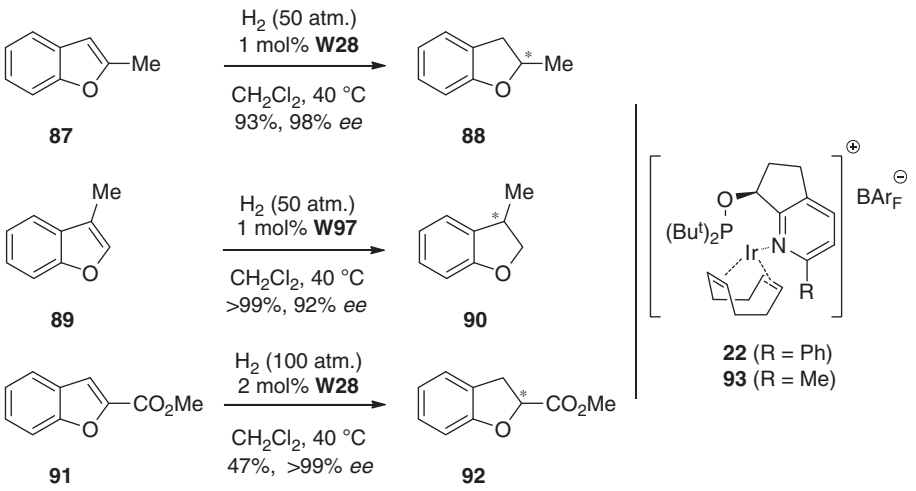
However, palladium on carbon seems to be superior to Rh/C as a heterogeneous catalyst for the selective reduction of benzofurans as demonstrated by Nichols and coworkers.[38] During their studies on the synthesis of 5-$HT_{2A/2C}$ receptor ligands, benzofuran **83** was reduced to the dihydrobenzofuran **84**, which was obtained as a single diastereoisomer in 81% yield (Scheme 20). To obtain enantiomerically pure dihydrofuran **86**, Chu and coworkers also applied a heterogeneous hydrogenation over Pd/C on benzofuran **85**,[39] however, due to the lack of any stereoselective methods for this reduction, the two enantiomers needed to be separated in a second step.



Scheme 20

The first asymmetric hydrogenation of a benzofuran was accomplished by Baiker and coworkers.[7,8] During their studies to find a heterogeneous catalyst for the stereoselective reduction of furoic acids, benzofuran **85** was hydrogenated in the presence of cinchonidine-modified palladium over alumina, and it furnished the dihydrofuran **86** with an *ee* of 50%, albeit in just 29% yield. Interestingly, the hydrogenation of 2- or 3-furoic acid gave nearly quantitative yields, but lower enantioselectivities (see Table 2).

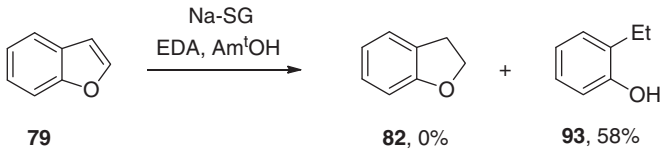
In 2006, Pfaltz and coworkers reported the use of a novel iridium phosphinite for the reduction of unfunctionalized double bonds.[10] To investigate the scope of this new hydrogenation catalyst, furans were reduced to their corresponding THFs (see Scheme 4), whereas the hydrogenation of benzofurans resulted in the formation of dihydrobenzofurans (Scheme 21). Both electron-rich (**87** and **89**) as well as electron-deficient benzofurans (**91**) furnished the dihydrobenzofurans **88**, **90**, and **92** with enantioselectivities of up to 99%. When reducing methyl-substituted compounds **87** and **89**, the chiral products were formed in excellent yields, whereas hydrogenation of the benzofuran carboxylic ester **91** proceeded only sluggishly and gave **92** in only 47% yield.



Scheme 21

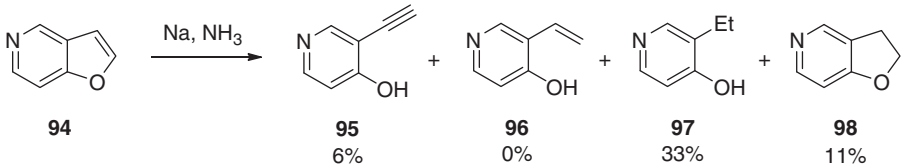
8.22.2.2 Dissolving Metals

As benzofurans are prone to undergo ring opening of the heterocycle, examples of reduction of this type of aromatics by using dissolving metals are rather scarce. In 2009 Costanzo et al. introduced a user-friendly ammonia-free reduction of aromatic compounds, which employs sodium encapsulated into silica gel.[40] Besides avoiding the use of toxic ammonia, these conditions have the advantage that sodium stabilized in silica gel (Na–SG) is easier to handle, more air stable, and reduces heteroaromatic compounds such as indoles, quinolines, and isoquinolines selectively. Despite the promising high-yielding reduction of nitrogen-containing heterocycles, an analogous reduction of benzofuran **79** in the presence of ethylenediamine (EDA) and *tert*-amyl alcohol (Am^tOH) did not lead to the dihydrobenzofuran **82**, but to phenol **93** (Scheme 22). It was shown that when the same conditions were applied to dihydrofuran **82**; they also cleaved the C–O bond affording phenol **93**.



Scheme 22

Yamaguchi and coworkers investigated the reduction of furopyridines with sodium in liquid ammonia.[41] Compared with benzofurans the nitrogen atom lowers the electron density of the aromatic compound and, therefore reduction should proceed more easily. Regardless of the position of the nitrogen in the six-membered ring, reduction of the furopyridines always led to the formation of complex product mixtures (Scheme 23). In the case of furo[3,2-*c*]pyridine **94**, the 2,3-dihydroisomer **98** was isolated in 11% yield together with the ring-opened compounds **95**–**97**.

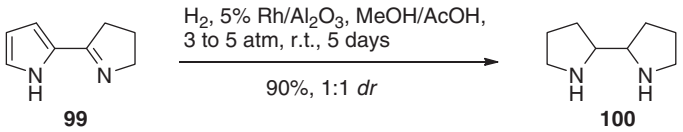


Scheme 23

8.22.3 Reduction of Pyrroles

8.22.3.1 Catalytic Hydrogenation

Reduction of the pyrrole nucleus typically requires relatively harsh conditions[42] (pressure and/or temperature) and the use of a protic acid, often as the solvent, to remove the basic amine product and thereby eliminate the problem of catalyst poisoning. A number of precious metals, such as platinum, palladium, rhodium, and ruthenium, have been used as catalysts to facilitate both the complete and partial reduction of pyrroles.[43] Hirama and Masamune's reduction of pyrrole **99** during the synthesis of 2,2′-bipyrrolidine **100**, which can serve as an auxiliary or ligand for metals, is representative of these hydrogenation conditions (equation 3).[44]

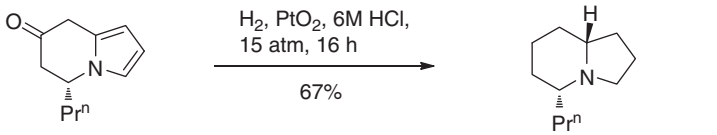


99 **100** (3)

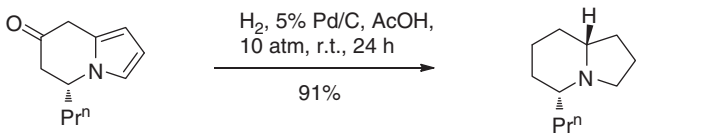
Since its discovery, a number of research groups have investigated and developed catalytic hydrogenations during total syntheses toward pyrrolidine-containing natural products.

8.22.3.1.1 Indolizidine alkaloids

Due to their scarcity and biological activity, the indolizidine alkaloids have proved to be popular synthetic targets. Central to many of these approaches has been a catalytic hydrogenation of a bicyclic pyrrole intermediate that contains a bridgehead nitrogen. During their synthesis of (–)-indolizidine 167B **101**, Jefford et al. used Adams' PtO_2 catalyst, albeit in a stoichiometric amount, to fully hydrogenate bicyclic pyrrole **102** and afford **101** in 67% yield, following neutralization with Na_2CO_3 (equation 4).[45] Note that the ketone in **102** is completely reduced under these conditions. The nicotinic inhibitor (–)-indolizidine 167B has also been prepared in an analogous manner by the Pellet-Rostaing and Lemaire group, using catalytic Pd/C to convert **103** to **101** in an excellent 91% yield (equation 5).[46] Both of these hydrogenations proceeded with complete diastereocontrol.

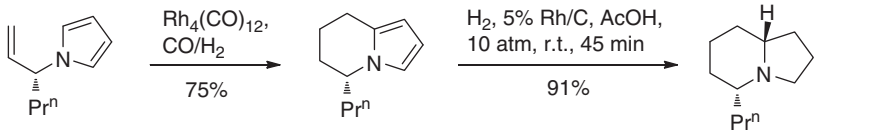


102 (–)-Indolizidine 167B **101** (4)



103 (–)-Indolizidine 167B **101** (5)

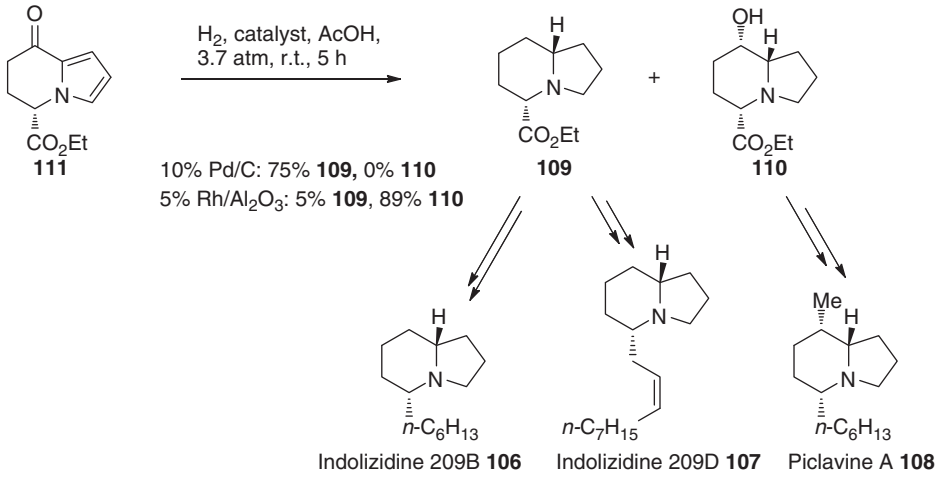
Lazzaroni and Settambolo adopted similar tactics with Rh/C to reduce diastereoselectively 5,6,7,8-tetrahydroindolizine **104**, which was prepared by a rhodium-catalyzed hydroformylation of *N*-propene protected pyrrole **105** (Scheme 24).[47]



105 **104** (–)-Indolizidine 167B **101**

Scheme 24

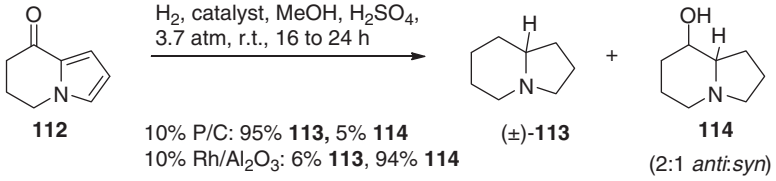
The very closely related indolizidines 209B **106** and 209D **107**, as well as piclavine A **108**, have all been synthesized by Jefford and coworkers from the structurally related intermediates **109** and **110**, accessed via a hydrogenation of bicyclic pyrrole **111** (Scheme 25).[48] The choice of catalyst proved to be the key to controlling the extent of reduction; Pd/C delivered fully reduced ethyl (5*S*,8a*R*)-indolizidine-5-carboxylate **109** in 75% yield with complete diastereoselectivity, whereas Rh/Al_2O_3 gave predominantly 8-hydroxyindolizidine **110**.



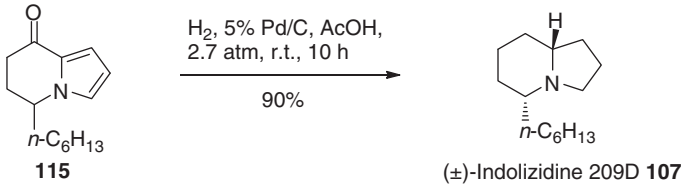
Scheme 25

Taylor et al. also reported this type of catalyst-derived control when hydrogenating indolizine derivative **112** (Scheme 26).[49]

Smith et al. hydrogenated a bicyclic pyrrole intermediate **115**, similar to Jefford, except with the *n*-hexyl side chain preinstalled, using Pd/C to generate (±)-indolizidine 209D **107** with high diastereoselectivity (equation 6).[50]



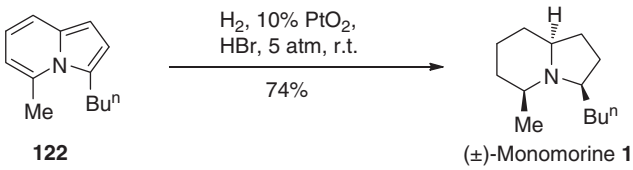
Scheme 26



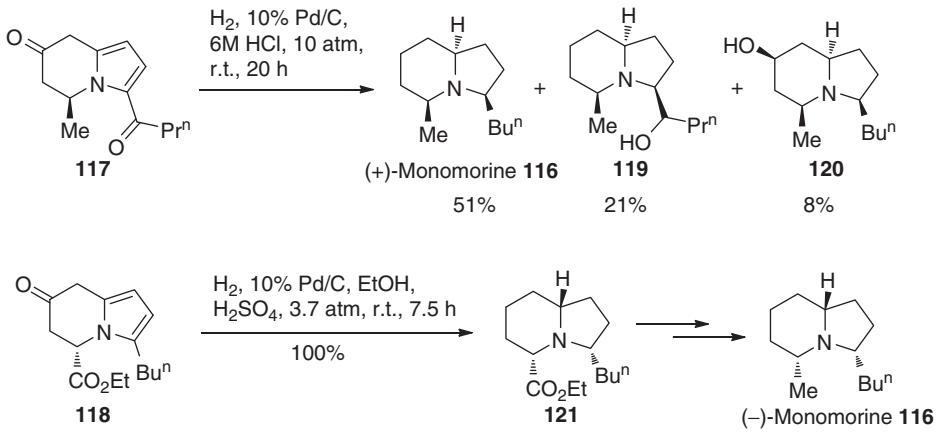
(6)

Natural (+)-monomorine **116** and unnatural (–)-monomorine have both been synthesized by the group of Jefford, exploiting Pd/C-catalyzed hydrogenations of pyrrole intermediates **117** and **118**, respectively (Scheme 27).[45,51] The reduction of **117** generated (+)-monomorine **116** in 51% yield, together with isomeric indolizinols **119** and **120** that were resistant to further hydrogenation. A slightly modified route to (–)-monomorine **116** obviated this problem, as fully reduced indolizidine **121** was obtained in quantitative yield. In both cases the hydrogenation proceeded in a completely *cis*-selective manner, with facial selectivity directed by the preexisting stereogenic center.

In 2001, Gevorgyan and coworkers found that PtO_2 effected a complete hydrogenation of indolizine **122** to furnish (±)-monomorine **116** as the last step in their synthesis (equation 7).[52]



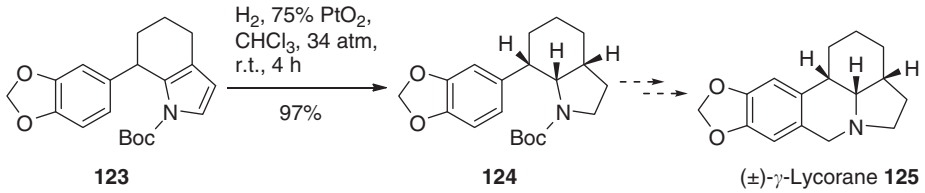
(7)



Scheme 27

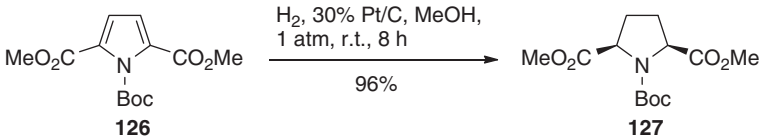
8.22.3.1.2 Miscellaneous alkaloid syntheses

Transition metal-mediated hydrogenations have not been restricted to the synthesis of the indolizidine skeleton. Angle and Boyce used substoichiometric quantities of PtO_2 to effect a chemo- and diastereoselective hydrogenation of the *C*-7 substituted tetrahydroindole **123** to afford exclusively *cis*-fused octahydroindole **124**, which was subsequently converted into (±)-γ-lycorane **125** (Scheme 28).[53] Note that the pendent carbocyclic ring was not affected and that a protic acid was not required due to the effect of the *N*-carbamate protecting group.



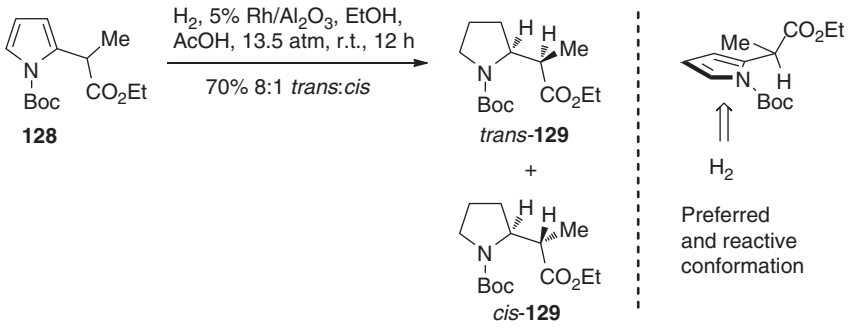
Scheme 28

Further examples of the use of *N*-protecting groups for pyrrole hydrogenation come from the groups of Chênevert and Gilchrist. Chênevert and coworkers reduced the symmetrical *N*-Boc pyrrole **126** to predominantly *cis*-pyrrolidine **127** in the presence of Pt/C under relatively mild conditions (equation 8).[54] The carbamate group ties up the basic lone pair on nitrogen such that an acid is not required, as well as making the pyrrole ring electron deficient (in combination with the two ester substituents) and therefore more susceptible to hydrogenation at atmospheric pressure. During their synthesis of carbapenam derivatives, Gilchrist et al. developed a diastereoselective hydrogenation of 2-substituted *N*-Boc pyrrole **128** wherein the substituent bore an α-stereogenic center (Scheme 29).[55] Despite the carbamate protecting group, reduction over Rh/Al_2O_3 did not occur without the addition of acetic acid. The selectivity of this reduction is consistent with a conformation of the substituted pyrrole **128** whereby the methyl group lies in the same plane as the ring and hydrogenation takes place from the less hindered face. Molecular modeling calculations made on analogous indole substrates corroborate this as a minimum energy conformation.[56]

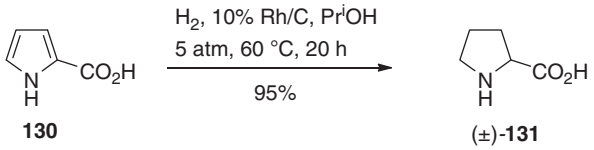


(8)

Through careful substrate selection, Sajiki and coworkers demonstrated that hydrogenation of unprotected pyrrole-2-carboxylic acid **130** over Rh/C proceeded in an excellent 95% yield without the need for an additional protic acid; the carboxylic acid moiety proving sufficient to suppress catalyst poisoning (equation 9).[4]

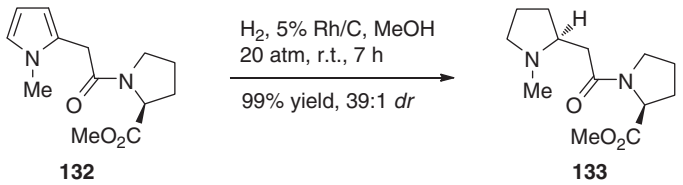


Scheme 29



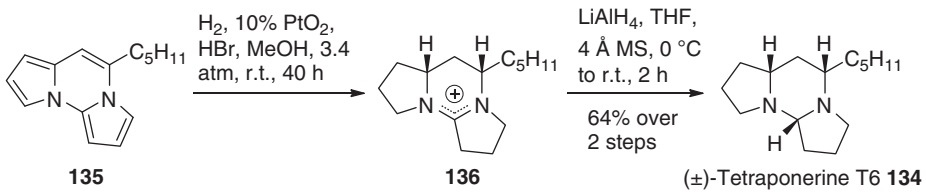
(9)

The group of Tungler investigated the effects of a range of catalytic metals (Rh/C, Rh/Al_2O_3, Ru/C, and Pd/C), temperature, and solvents on the acid-free diastereoselective hydrogenation of chiral pyrrole derivative **132** (equation 10).[57] Rhodium was found to be the optimum metal, with the nature of the support exerting no influence on the diastereoselectivity. Other factors that increased the level of stereoselectivity included lowering the temperature and raising the hydrogen pressure, whereas changing the solvent (methanol, ethyl acetate, or dichloromethane) had little affect (although the use of methanol resulted in much greater conversion).



(10)

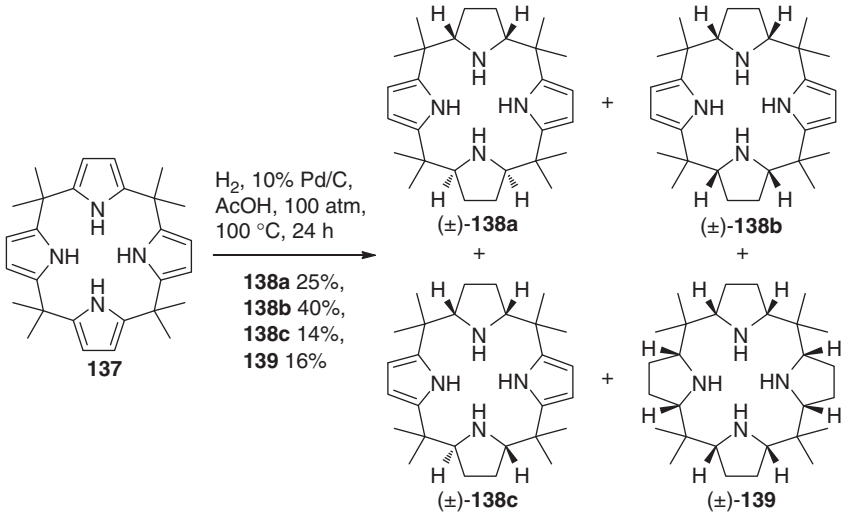
Elsewhere, during a synthesis of (±)-tetraponerine T6 **134** Gevorgyan et al. performed a highly diastereoselective reduction of pyrimidine derivative **135** using catalytic PtO_2 under acidic conditions (Scheme 30).[58,59] The subsequent *cis*-addition of hydride to amidinium salt **136** occurs from the *β*-face and proceeds through a favorable 'chair-like' transition state.



Scheme 30

8.22.3.1.2.1 Calix[4]pyrroles

With the excellent metal-binding affinities of calixpyrroles well established,[60] Neier et al. investigated the properties of some reduced analogs of *meso*-octamethylporphyrinogen.[61,62] Hydrogenation of calix[4]pyrrole **137** over catalytic Pd/C afforded predominantly the partially reduced alternating pyrrolidine–pyrrole **138** as a mixture of three possible diastereoisomers **138a–c**, with small amounts of the fully saturated macrocycle **139** (Scheme 31). Despite an extensive screen of catalysts and acidic media, forcing reaction conditions were required to effect the desired hydrogenation (100 atm of hydrogen pressure at 100 °C in acetic acid). Partially reduced intermediate **138** could be converted into fully saturated **139** in 23% yield by resubjecting it to the reaction conditions. Macrocyle **139** proved to be a strong base and smoothly formed metal complexes with Ni(II), Cu(II), and Pd(II) salts.

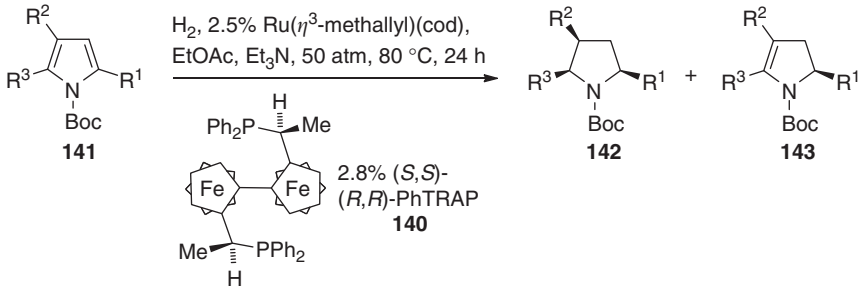


Scheme 31

8.22.3.1.3 Enantioselective hydrogenation

It has already been highlighted that chiral pyrrolidine skeletons are present in a number of natural products and biologically active molecules. However, there are few examples whereby optically active pyrrolidines can be accessed directly from simple achiral pyrroles. Kuwano et al. reported the first successful enantioselective reduction of *N*-protected pyrroles.[63] Using a Ru(η^3-methallyl)$_2$(cod)-(*S*,*S*)-(*R*,*R*)-PhTRAP catalyst system based on chiral ligand **140**, 2,3,5-trisubstituted *N*-Boc pyrroles **141** were hydrogenated to afford either pyrrolidines **142** or 4,5-dihydropyrrolidines **143** in high yields and up to 99.7% *ee* (Table 4). Due to the lack of dihydropyrrole regioisomers, the authors proposed that hydrogenation proceeded in a stepwise manner via two consecutive 1,2-additions of hydrogen across the two carbon–carbon double bonds. In the case of pyrrole-2-carboxylate **142i** the first step reduced the less hindered alkene and thus the second hydrogenation was enantiodetermining. However, in the case of

Table 4 Ruthenium-mediated enantioselective hydrogenation of *N*-protected pyrroles



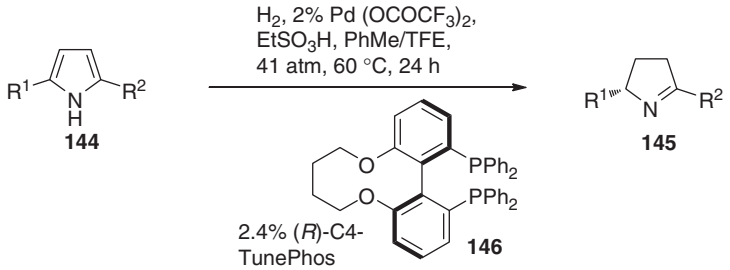
Entry	R^1	R^2	R^3	***142** yield (%)*[a] (ee (%))[b]
i	CO_2Me	H	H	92 (79)
ii	Me	Me	CO_2Me	52 (11)[c]
iii	Me	CO_2Me	Me	91 (74)
iv	CO_2Me	Me	Me	85 (96)
v	CO_2Me		$-(CH_2)_4-$	8 (91)[d]
vi	Ph	Pr^n	Me	96 (93)
vii	Ph	Ph	Ph	>99 (99.7)
viii	*p*-FC_6H_4	Ph	Ph	99 (99.3)
ix	*p*-$MeOC_4H_6$	Ph	Ph	96 (98)
x	Ph	Ph	*p*-$CF_3C_6H_4$	>99 (99.6)
xi	Ph	Ph	*p*-$MeOC_4H_6$	97 (99.2)

[a]Isolated yields.
[b]Determined by chiral GC or HPLC analysis.
[c]Isolated as a mixture, **143** obtained in an additional 42% yield and 75% *ee*.
[d]Isolated as a mixture, **143** obtained in an additional 70% yield and 95% *ee*.

the multisubstituted pyrroles **142ii** to **142xi**, it is the other double bond that is less hindered and hence reduced first. It follows that this must be the enantiodiscriminating step, with the subsequent reduction of **143** proceeding under substrate control so as to produce the all *cis*-diastereoisomer **142**. Note that if the second step was also catalyst controlled then *trans*-2,5-substituted pyrrolidines would have been expected.

In 2011, Zhou and Fan described the first asymmetric hydrogenation of simple unprotected pyrroles **144** to generate chiral 1-pyrrolines **145**.[64] Using $Pd(OCOCF_3)_2$ with (*R*)-C4-TunePhos **146** (a chiral bidentate phosphine), as well as a strong Brønsted acid and a reasonably high pressure of hydrogen, a range of 2-alkyl-5-aryl-disubstituted pyrroles **144** were hydrogenated in good-to-excellent yields and with up to 92% *ee* (Table 5).

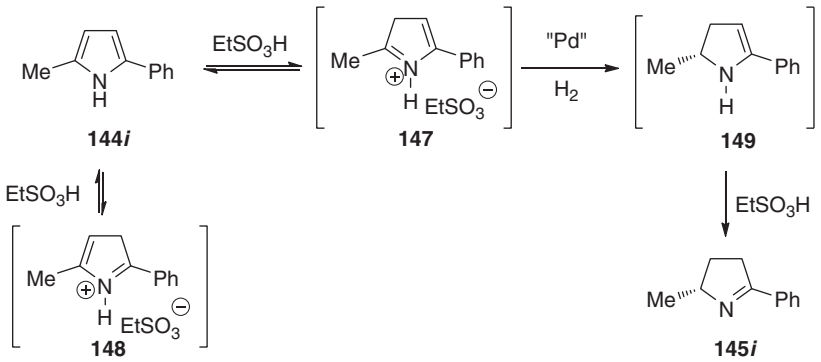
Table 5 Palladium-mediated enantioselective hydrogenation of unprotected pyrroles



Entry	R^1	R^2	*Yield (%)*[a]	ee *(%)*[b]
i	Me	Ph	80	92
ii	Pr^n	Ph	87	81
iii	Bu^i	Ph	80	86
iv	Bn	Ph	90	80
v	Me	*p*-MeC_6H_4	65	81
vi	Me	*p*-$CF_3C_6H_4$	79	89
vii	Me	1-Naphthyl	73	90

[a]Isolated yields.
[b]Determined by chiral HPLC analysis.

The authors proposed a mechanism to explain the observed regiochemical outcome (Scheme 32). According to this mechanism, the pyrrole is initially protonated by the Brønsted acid to form one of two possible regioisomeric iminium salts **147** and **148**. Density functional theory has shown the C=N bond in intermediate **148** to be better conjugated with the phenyl ring and this compound was calculated to be 1.4 kcal mol^{-1} (ΔG° in CH_2Cl_2) more stable than iminium ion **147**, which is thus more susceptible to subsequent hydrogenation, giving intermediate enamine **149**. In the presence of acid this enamine then isomerizes to the more stable 1-pyrroline **145**.

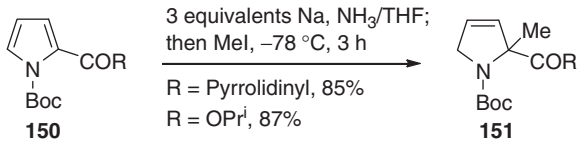


Scheme 32

8.22.3.2 Dissolving Metals

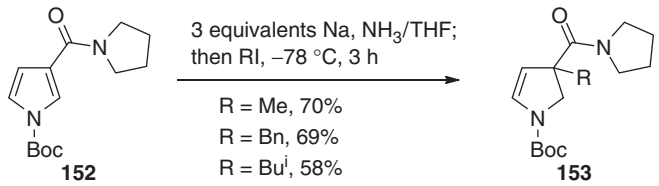
8.22.3.2.1 Birch reduction

The partial reduction of pyrroles to 3-pyrrolines is a fundamentally difficult reaction to accomplish as the high electron density of these heterocycles inhibits the addition of an electron. Moreover, an unprotected pyrrole nucleus contains an acidic hydrogen atom ($pK_a \approx 17$) that could easily be deprotonated under classical Birch conditions (sodium or lithium in liquid ammonia) and the resulting anion would be even more resistant to reduction. At the beginning of their work in this field, Donohoe and coworkers addressed these problems by employing an electron-withdrawing *N*-carbamate protecting group in the partial reduction of C-2 substituted electron-deficient pyrroles **150** (Scheme 33).[65] Both amide and ester substituents were amenable to reductive alkylation with Na in NH_3/THF at $-78\ ^\circ C$ followed by quenching with excess methyl iodide.



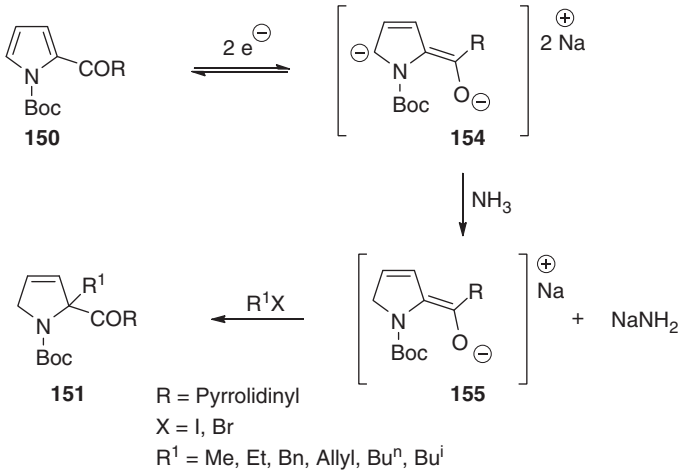
Scheme 33

The reduction of C-3 substituted pyrroles **152** was also possible under the same reaction conditions, albeit in slightly lower yields compared with the C-2 analogs (Scheme 34).[66]



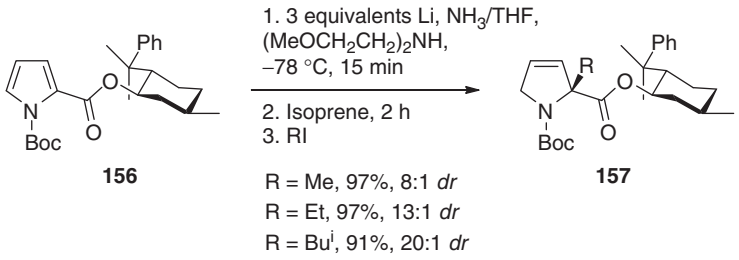
Scheme 34

It was proposed that the reaction proceeded via the mechanism shown in Scheme 35, whereby an intermediate dianion **154** was initially formed which was sufficiently basic to deprotonate NH_3, leading to enolate **155** that can be quenched by an external electrophile.[67]

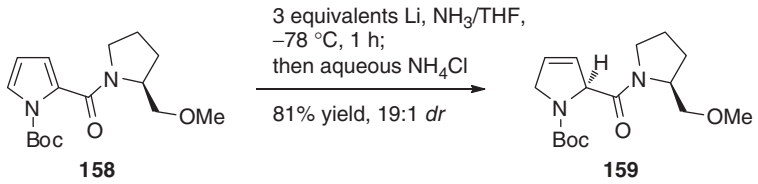


Scheme 35

Two subsequent separate reports from the groups of Donohoe and Schäfer described how, through the use of chiral auxiliaries, the Birch reduction of electron-deficient pyrroles could be quenched in a diastereoselective manner, with alkyl halides (Scheme 36) and aqueous ammonium chloride (equation 11), respectively.[68,69] Using (–)-8-phenylmenthol as an auxiliary, Donohoe and coworkers observed that the diastereoselectivity of reductive alkylation increased with the steric bulk of the electrophile.

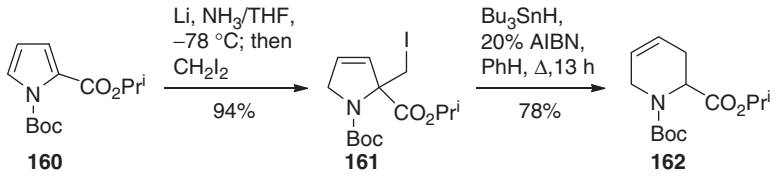


Scheme 36



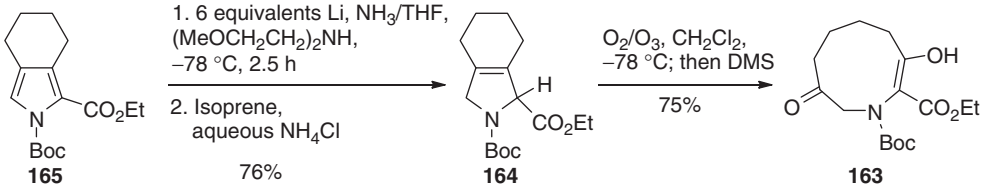
(11)

The potential utility of the 3-pyrroline skeleton obtained from reductive alkylation of C-2 substituted pyrroles **160** has also been demonstrated. Donohoe et al. have shown that α-iodomethyl pyrroline **161**, obtained by quenching the enolate from Birch reduction with diiodomethane, can undergo radical ring expansion to furnish tetrahydropyridines **162** in very good yields (Scheme 37).[70]



Scheme 37

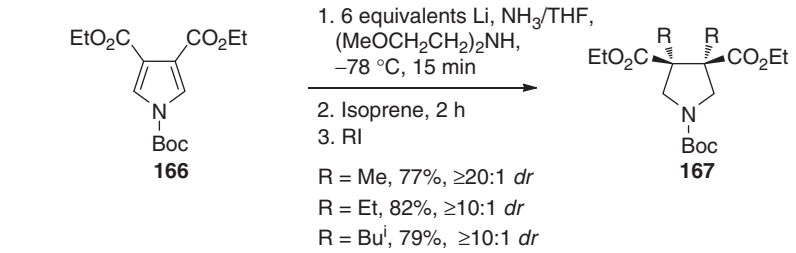
The same group has also accessed nine-membered nitrogen-containing rings **163** via ozonolysis of annulated 3-pyrroline **164** (Scheme 38).[26]



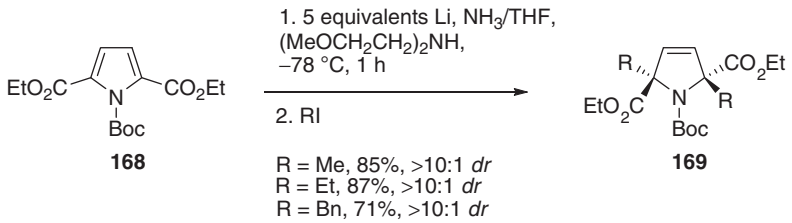
Scheme 38

Donohoe extended the Birch method to the generation of pyrrolidines via a double reductive alkylation of pyrroles adorned with multiple electron-withdrawing groups. 3,4-Disubstituted pyrrole **166** was treated with 6 equivalents of Li in NH_3/THF and quenched with a range of alkyl iodides to afford 3,4-disubstituted pyrrolidines **167** in a *cis*:*trans* ratio of $\geq$10:1 in each case (Scheme 39).[71] Interestingly, when the regioisomeric 2,5-disubstituted pyrrole **168** was exposed to very similar reaction conditions the predominant diastereoisomer was found to be *trans*-pyrrolidine **169** (Scheme 40).[72]

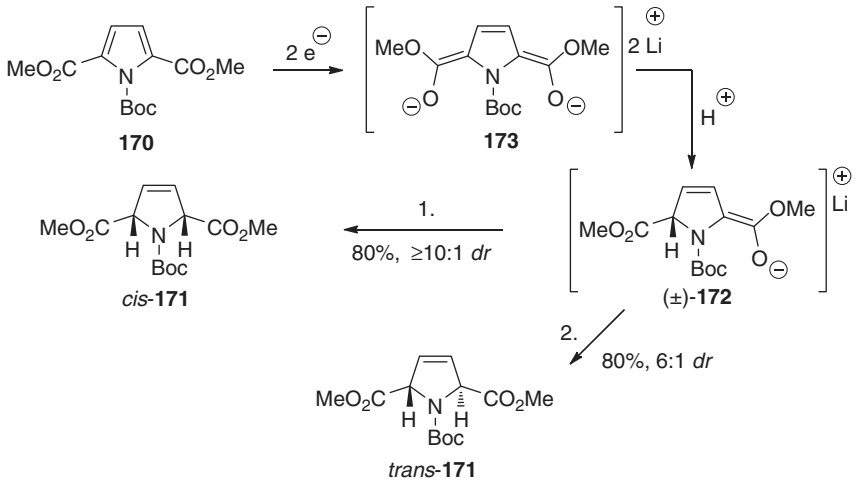
By varying the reaction conditions, Donohoe and coworkers were able to develop the partial reduction of 2,5-disubstituted pyrroles **170** into a diastereoselective process.[73] Using Li in NH_3/THF and quenching with aqueous NH_4Cl afforded *trans*-2,5-dihydropyrrole **171** in a 6:1 excess, whereas 'ammonia-free' conditions of Li and catalytic di-*tert*-butyl biphenyl (DBB) in THF followed by protonation with bulky 2,6-di-*tert*-butylphenol gave exclusively the *cis*-diastereoisomer (Scheme 41). The reversal in facial selectivity during protonation of mono-enolate **172** was partly rationalized by the relative size difference between NH_3/NH_4Cl and the sterically hindered phenol; although more in-depth analysis of the relative geometries and aggregation states of enolate **172** under the two respective reaction conditions is required to give a definitive explanation.



Scheme 39



Scheme 40



1. Li, catalyst DBB, THF, –78 °C; then 2,6-di-*tert*-butylphenol
2. Li, NH_3/THF, –78 °C; then aqueous NH_4Cl

Scheme 41

With a diastereoselective reduction of pyrrole **170** in hand, a number of polyhydroxylated pyrrolidine and pyrrolizidine natural products were synthesized in relatively short sequences (Figure 2).[73–75]

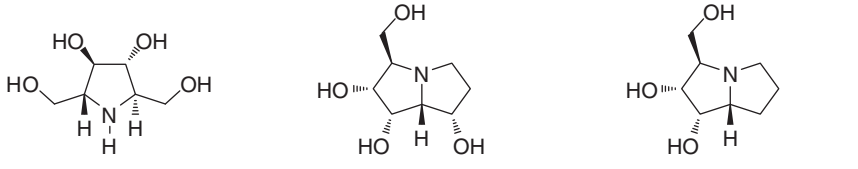
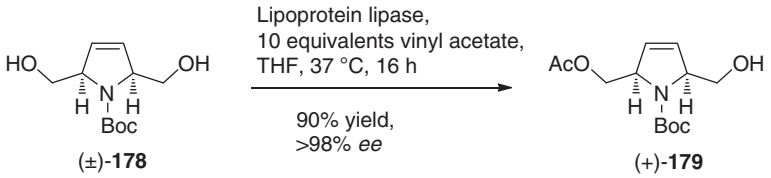


Figure 2 Polyhydroxylated pyrrolidine and pyrrolizidine natural products.

In an extension of this work, an enzymatic desymmetrization of *cis*-2,5-disubstituted pyrroline **178** (which was derived from *cis*-**171** by reduction), led to the corresponding monoacetylated compound **179** in high yield and *ee* (equation 12).[76]



(±)-**178** (+)-**179** (12)

Access to this intermediate in an enantiopure form enabled Donohoe et al. to complete efficient syntheses of the glycosidase inhibitor (+)-DGDP **180** and bicyclic pyrrolidine (–)-7-epialexine **181** (Figure 3).[77,78]

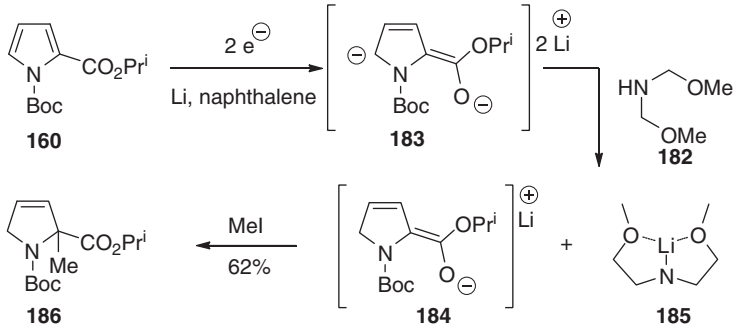


(+)-DGDP **180** (–)-7-Epialexine **181**

Figure 3 Polyhydroxylated pyrrolidine natural products.

8.22.3.2.1.1 Ammonia-free reduction

Identifying a suitable alternative electron carrier, such as naphthalene or DBB, enabled Donohoe and coworkers to perform dissolving metal reductions in the absence of ammonia, when it was not required as a proton source in a particular reaction mechanism.[72] This has the benefit of making the partial reduction more practicable[79] and offers the opportunity to quench reduction reactions with sensitive electrophiles that would otherwise react with NH_3 itself. A similar set of substituted pyrroles to those used in the Birch reduction proved amenable to partial reduction and reductive alkylation in the first iteration of the 'ammonia-free' method. These reaction conditions typically comprised 5 equivalents of Li, 5 equivalents of naphthalene, and 5 equivalents of bis(2-methoxyethyl)amine (BMEA) **182** in THF at −78 °C, followed by quenching with an appropriate electrophile (Scheme 42).[31]

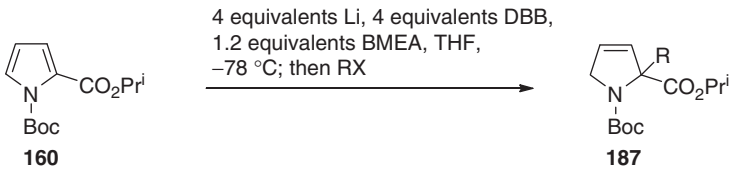


Scheme 42

Addition of the secondary amine **182** is key to the success of the reaction. Mechanistically, the dianion **183** that is formed after transfer of two electrons from lithium is highly unstable but basic enough to deprotonate NH_3 in the Birch reduction, thus generating enolate **184** which can subsequently be alkylated. It follows that in the absence of ammonia an alternative proton source is required. The lithium-bound anion **185** that is generated following deprotonation of **182** by **183** is less basic and nucleophilic than $LiNH_2$ which means that it is less aggressive toward both starting material and product. In addition, **182** is not sufficiently acidic to protonate the enolate **184**, so it will not compete with the chosen electrophilic quench thus allowing an excess of amine **182** to be used in the reaction.

A drawback with the 'ammonia-free' conditions employing naphthalene, in comparison to the Birch reduction, was the reduced reaction yield. Donohoe et al. addressed this issue by substituting naphthalene for the bulkier electron transfer agent, DBB, which facilitated reductions with a variety of electrophiles in yields that rivaled those achieved in NH_3 (Table 6).[32] Using 4 equivalents of Li, 4 equivalents of DBB, and 1.2 equivalents of BMEA at −78 °C, a range of electrophiles were used to quench the reduction, including a number that are not tolerated under standard Birch conditions, such as diphenyl disulfide (Table 6, entry ii). The improvement in reaction yield is attributed to two factors: the bulkier DBB should disfavor deleterious radical coupling reactions in solution, whereas LiDBB has a lower (i.e., more negative) reduction potential than naphthalene and is thus a more powerful reducing agent.[34]

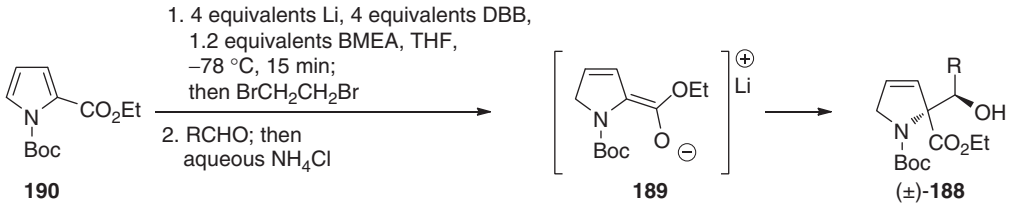
Table 6 Ammonia-free reduction; comparing naphthalene and DBB as electron transfer agents



Entry	*RX*	*R*	*Napthalene yield (%)*	*DBB yield (%)*
i	BnBr	Bn	59	80
ii	PhSSPh	SPh	–	52
iii	$BrCH_2CO_2Bu^t$	$CH_2CO_2Bu^t$	–	76
iv	PhCOCl	COPh	–	67

The introduction of Donohoe's 'ammonia-free' method also enabled reductive aldol reactions with enolizable aldehydes to occur in good yield. In comparison, under Birch conditions only nonenolizable aldehydes were tolerated (e.g., benzaldehyde) and the products **188** were formed as a 1:1 mixture of *syn* and *anti* diastereoisomers.[30] When LiDBB was employed, not only were a range of enolizable aldehydes compatible, but an inherent preference for the antiisomer was revealed (Table 7).[33,80] This selectivity could be enhanced by transmetallating the lithium enolate **189** with $MgBr_2{\cdot}OEt_2$ before addition of the aldehyde (Table 7, entry v).

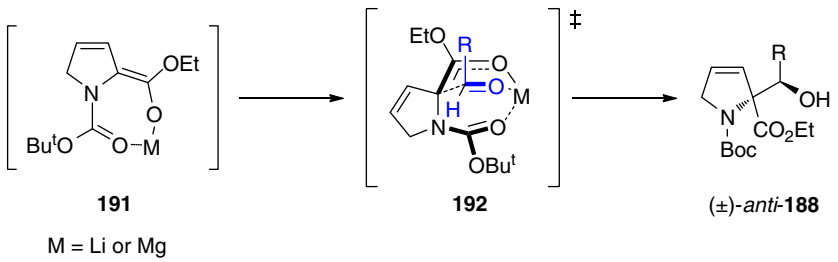
Table 7 Ammonia-free reductive aldol reaction



Entry	*R*	*Combined yield (%)*	dr *(anti:syn)*
i	Me	69	1.8:1
ii	Pr^i	74	8.0:1
iii	Bu^t	71	5.3:1
iv	Ph	73	1.8:1
v[a]	Pr^i	72	>20:1

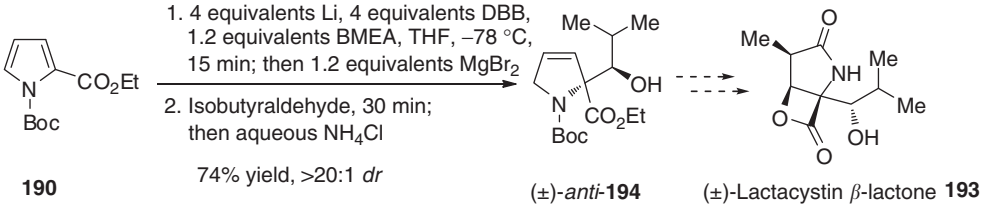
[a] $MgBr_2 \cdot OEt_2$ added before RCHO addition.

It was proposed that the metal (Li or Mg) retains its chelation to the carbonyl of the Boc group **191** throughout the aldol reaction (Scheme 43). Under kinetic control, this three-coordinate binding of the metal forces a boat-like conformation **192** to be adopted, wherein the 'R' group of the aldehyde and the pyrroline ring are kept furthest apart by the aldehyde taking up a pseudo axial position; resulting in the formation of *anti* aldol product **188**.

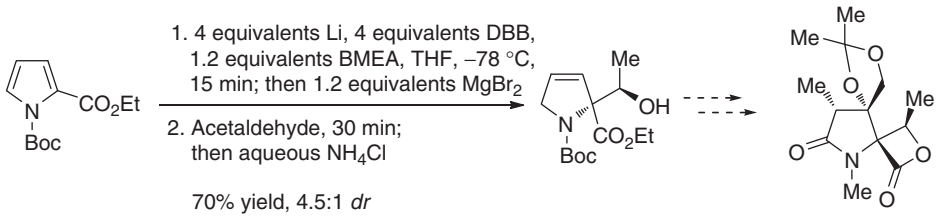


Scheme 43

This highly *trans*-selective reductive aldol reaction was showcased in Donohoe's total synthesis of (±)-lactacystin β-lactone **193** (Scheme 44).[81,82] It was also used to construct the pyrrolidinone core of KSM-2690 B **195**, wherein pyrrole **190** was subjected to a LiDBB-mediated reductive aldol reaction with acetaldehyde to furnish pyrroline **196** in 70% yield and 4.5:1 *anti*:*syn* selectivity (Scheme 45).[83]

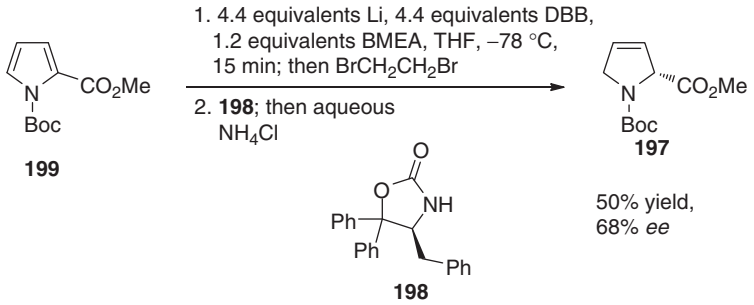


Scheme 44



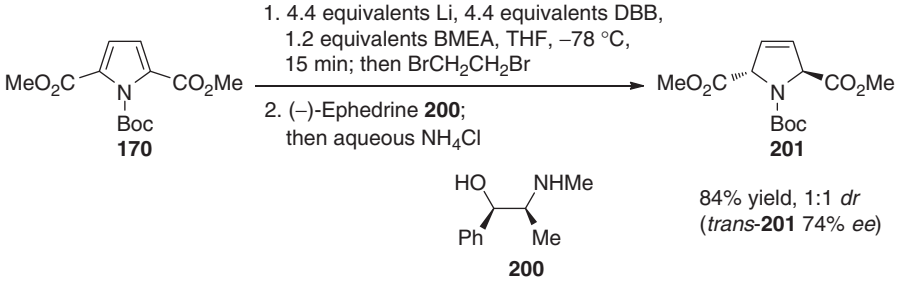
Scheme 45

The high level of geometrical control displayed toward formation of the *Z*-lithium enolate during the 'ammonia-free' partial reduction of pyrroles enabled Donohoe and coworkers to develop an enantioselective protonation protocol, allowing access to enantioenriched pyrroline systems **197** (maximum 68% *ee*) through the use of amino acid-derived oxazolidinones **198** (equation 13).[84]



(13)

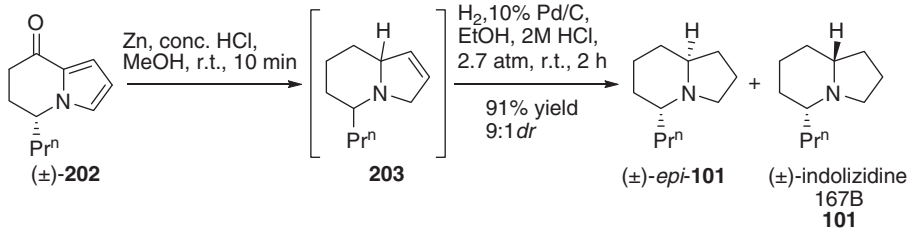
2,5-Disubstituted pyrrole **170** was also subjected to a chiral protonation strategy. Quenching with (–)-ephedrine **200** furnished pyrroline **201** in 84% yield, as a 1:1 mixture of the *cis*- and *trans*-diastereoisomers, with *trans*-**201** obtained in 74% *ee* (which could be amplified to >94% *ee* following a single recrystallization) (equation 14).[85]



(14)

8.22.3.2.2 Knorr–Rabe reduction

Unlike the Birch reduction of electron-rich pyrroles, which does not occur readily, the partial reduction of pyrroles to 2,5-dihydropyrroles using Zn/HCl is precedented.[86] Smith et al. employed the Knorr–Rabe reaction to reduce bicyclic α-ketopyrrole **202** to the corresponding hexahydroindolizidine **203** during a diastereoselective synthesis of (±)-*epi*-indolizidine 167B (Scheme 46).[87] From the common ketopyrrole intermediate **202**, it is noteworthy that Smith obtained a 9:1 ratio of epimers, with the major diastereoisomer *epi*-**101** opposite to that generated by catalytic hydrogenation (see Section 8.22.4.1.1).

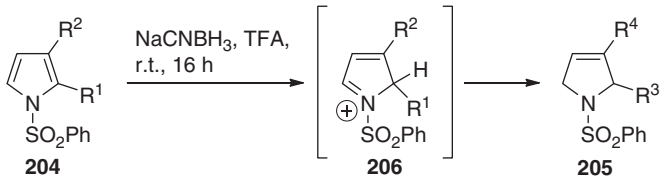


Scheme 46

8.22.3.3 Ionic Hydrogenation

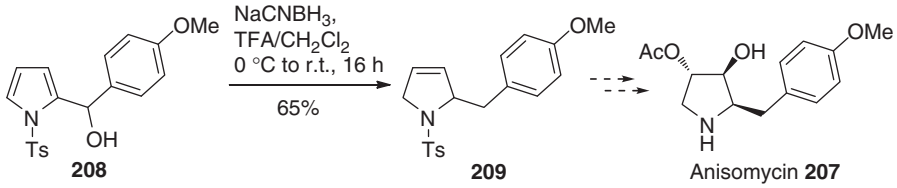
High levels of π-electron density in the ring system mean that pyrroles are extremely resistant to reduction via nucleophilic hydride sources. However, there are a few examples where this transformation has been accomplished under acidic conditions, whereby the pyrrole is initially protonated and then the resulting iminium intermediate reduced. Ketcha et al. were the first to report this type of reduction, using $NaCNBH_3$ in TFA to partially reduce a range of *N*-sulfonylated pyrroles **204** to the corresponding 2,5-dihydropyrroles **205** (Table 8).[88] Partial reduction was observed, as the α-pyrrolenium ion **206**, resulting from protonation of the pyrrole at C-2, is predominant with respect to protonation at C-3 (which would be expected to lead to complete reduction).

Table 8 Acid-mediated reduction of pyrroles using sodium cyanoborohydride

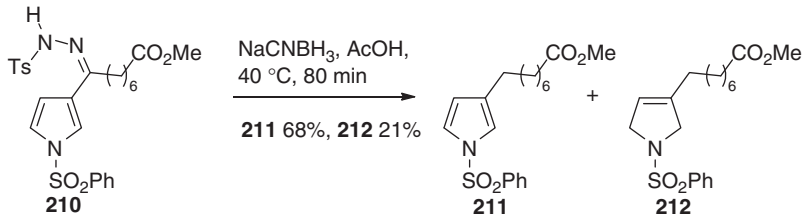


Entry	R^1	R^2	R^3	R^4	*Yield (%)*
i	H	H	H	H	75
ii	COMe	H	Et	H	76
iii	COEt	H	Pr^n	H	73
iv	H	COMe	H	Et	68
v	H	COPh	H	Bn	97
vi	Et	H	Et	H	72

Smith and coworkers used a modified version of Ketcha's procedure during their formal synthesis of the pyrrolidine alkaloid anisomycin **207** (Scheme 47).[89] Treatment of pyrrole **208** with $NaCNBH_3$ in TFA and dichloromethane as a cosolvent led to 2,5-dihydropyrrole **209** and the corresponding fully reduced pyrrolidine in a 2:1 ratio and a combined yield of 97%. Elsewhere, a similar reductive process was observed by Darbre and coworkers as a side reaction to a desired selective C=N bond reduction of tosylhydrazone **210** (equation 15).[90]



Scheme 47



(15)

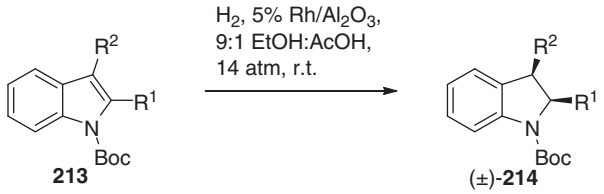
8.22.4 Reduction of Indoles

8.22.4.1 Catalytic Hydrogenation

The transition metal-catalyzed hydrogenation of indole is party to similar issues as pyrroles; namely an electron-rich aromatic ring that necessitates quite forceful reduction conditions (i.e., high pressures and temperatures). This can be circumvented by the presence of a strong acid, which initially protonates the indole, thereby interrupting the aromaticity of the heteroarene nucleus, and the resulting iminium ion can be reduced using milder methods. However, the addition of acid can result in polymerization, as indole is also a good nucleophile. A final point to consider with indoles is how to control the site of hydrogenation (i.e., pyrrole or benzo-fused ring) and the degree to which this occurs (i.e., partial or complete reduction). It is fair to say that methods for reducing the heterocyclic nucleus outnumber those for selective carbocyclic reduction.

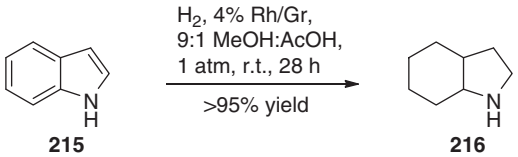
Gilchrist and Graham investigated the Rh-catalyzed hydrogenation of a range of *N*-Boc indoles **213** substituted at C-2 and C-3.[91] Using typical conditions of 5% Rh/Al_2O_3 in EtOH/AcOH under 14 atm of H_2 pressure, the corresponding *N*-Boc-*cis*-2,3-dihydroindoles **214** were generally obtained in high yield (Table 9). Interestingly, substrates bearing an acyl substituent at C-2 or an electron-withdrawing group at C-3 were found to inhibit reduction (entries iv and vi).

Table 9 Rhodium-catalyzed hydrogenation of *N*-Boc indoles



Entry	R^1	R^2	*Yield (%)*
i	H	H	84
ii	Me	Me	84
iii	Ph	H	99
iv	$-CO(CH_2)_3-$		–
v	CO_2Me	Me	84
vi	Me	CO_2Et	17

Savoia et al. used rhodium on graphite to catalyze the complete hydrogenation of indole **215** to octahydro-1*H*-indole **216** in quantitative yield (equation 16).[92] The reduction proceeded under very mild conditions, room temperature and 1 atm H_2 pressure, in 9:1 MeOH:AcOH (<5% conversion in neat MeOH). Partially hydrogenated indoline was observed if the reaction was stopped prematurely (<28 h).



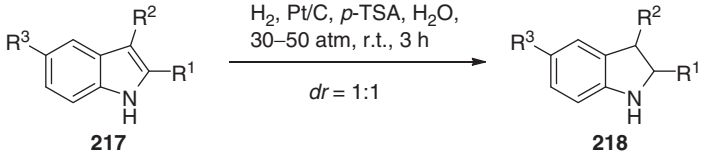
(16)

Another catalyst system to reduce indole to fully saturated octahydro-1*H*-indole **216** has been developed by Sánchez-Delgado and coworkers.[93] Ru nanoparticles immobilized on poly(4-vinylpyridine) were synthesized by reducing $RuCl_3.3H_2O$ with $NaBH_4$ in the presence of the basic support, which itself helped to prevent catalyst poisoning via potential irreversible adsorption of either

the substrate or its reduced product onto the catalyst surface. Elsewhere, Bianchini et al. successfully employed a homogeneous system to reduce indole to indoline.[94] In the presence of triflic acid, both Rh(III) and Ru(II) catalysts modified with the tripodal polyphosphine ligand $MeC(CH_2PPh_3)_3$ (triphos) were able to promote the hydrogenation at 60 °C and 30 atm of H_2 pressure.

Török and coworkers reported a Brønsted acid-induced heterogeneous catalytic hydrogenation of unprotected indoles **217** that works under mild conditions (i.e., low hydrogen pressure, at room temperature, with short reaction times and water as the solvent, Table 10).[95] Water was chosen for its increased nucleophilicity relative to alcoholic solvents, as this was required to lower the acidity of the reaction medium and thus reduce the propensity for indole to polymerize. In addition, once protonation of indole occurred, the resulting iminium ion was solvated by water, which also helped to prevent nucleophilic attack by another indole molecule.

Table 10 Platinum-catalyzed hydrogenation of indoles in water



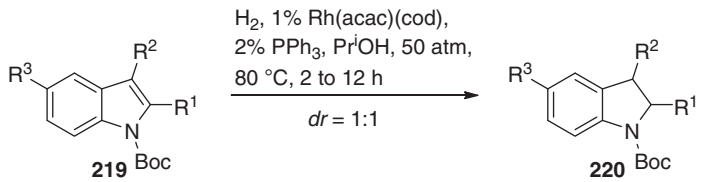
217 **218**

Entry	R^1	R^2	R^3	*Yield (%)*
i	H	H	H	94
ii	H	H	OMe	96
iii	H	H	F	93
iv	H	H	CO_2Me	84
v		$-(CH_2)_4-$	H	86

8.22.4.1.1 Enantioselective hydrogenation

In the pursuit of an asymmetric reduction of substituted indoles it had been rationalized that homogeneous hydrogenation conditions would offer the best opportunity for imparting selectivity. A significant advancement was made toward this goal by Ito and coworkers in 2000, when they demonstrated that the rhodium complex generated *in situ* from Rh(acac)(cod) and 2 equivalents of PPh_3 was an effective catalyst for the hydrogenation of a range of *N*-Boc protected C-2 substituted indoles **219** (Table 11).[3] It is noteworthy that C-3 substituted indole **219iv** was very resistant to reduction (entry iv).

Table 11 Rhodium-catalyzed hydrogenation of *N*-Boc indoles

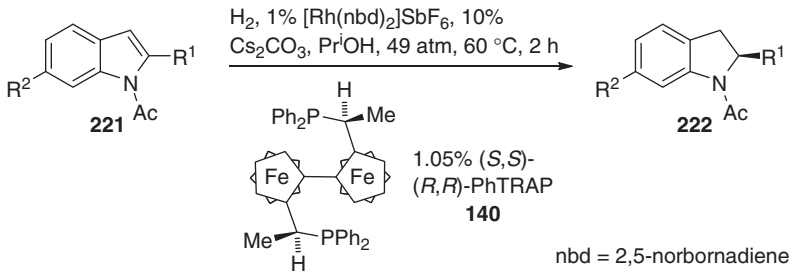


219 **220**

Entry	R^1	R^2	R^3	*Yield (%)*
i	Ph	H	H	98
ii	CO_2Me	H	H	85
iii	H	H	CO_2Me	95
iv	H	Me	H	7

In short order following these studies, Kuwano et al. reported an asymmetric variant employing the chiral bisphosphine ligand (*S*,*S*)-(*R*,*R*)-PhTRAP **140**.[3] Using 1 mol% of the $[Rh(nbd)_2]SbF_6$-PhTRAP-base catalyst, a variety of C-2 substituted indoles **221** were converted into the corresponding indolines **222** in high yield and with up to 95% *ee* (Table 12). The addition of a base was necessary in order to achieve high enantioselectivity and catalytic activity.

Table 12 Rhodium-catalyzed asymmetric hydrogenation of C-2 substituted *N*-Ac indoles

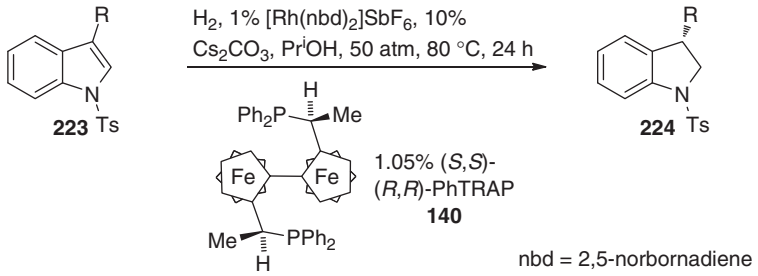


Entry	*R^1*	*R^2*	*Yield (%)*	ee *(%)*[a]
i	Bu^i	H	91	91
ii	Ph	H	91	87
iii	CO_2Me	H	95	95
iv	Bu	CF_3	83	92
v	Bu	OMe	86	94

[a]Determined by HPLC analysis.

In an extension of this work, Kuwano used the same catalyst system to efficiently reduce a number of C-3 substituted *N*-tosyl protected indoles **223** to the analogous indolines **224** in high yields and levels of enantiocontrol (95–98% *ee*) (Table 13).[96,97] As indoles bearing a group at C-3 are much less susceptible to hydrogenation, the activity of this system was attributed to the *trans*-chelating chiral bisphosphine ligand **140**, which was found to be essential for hydrogentaion as well as imparting enantioselectivity. Silyl ether, ester, and carbamate groups (entries iii to v) were all tolerated under these conditions.

Table 13 Rhodium-catalyzed asymmetric hydrogenation of C-3 substituted *N*-Ts indoles

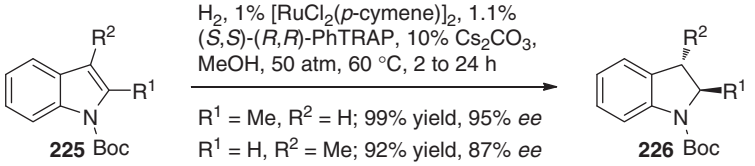


Entry	*R*	*Yield (%)*	ee *(%)*[a]
i	Pr^i	94	97
ii	Ph	93	96
iii	CH_2CH_2OTBS	94	98
iv	$CH_2CH_2CO_2Bu^t$	93	97
v	CH_2CH_2NHBoc	71	95

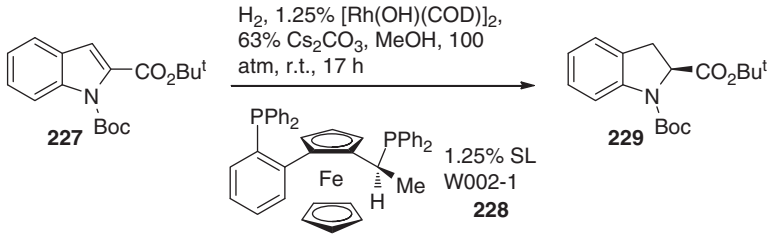
[a]Determined by HPLC analysis.

In 2004, the group of Kuwano reported an improved catalyst system that was able to tolerate the more synthetically useful *N*-Boc protected indoles, affording similarly excellent levels of enantioselectivity in the product indolines.[98] By changing the catalyst precursor from $[Rh(nbd)_2]SbF_6$ to $[RuCl_2(p\text{-cymene})]_2$, this new catalyst system was able to efficiently reduce both C-2 and C-3 monosubstituted indoles **225** in high yields and enantioselectivities to produce *N*-Boc indolines **226** (Scheme 48).

Following that discovery, Agbossou-Niedercorn et al. showed that *N*-Boc protected indole **227** can be hydrogenated using a catalyst system based on Rh and a chiral Walphos ligand (SL W002–1 **228**) to furnish indoline **229** in good conversion and enantioselectivity (equation 17).[99]

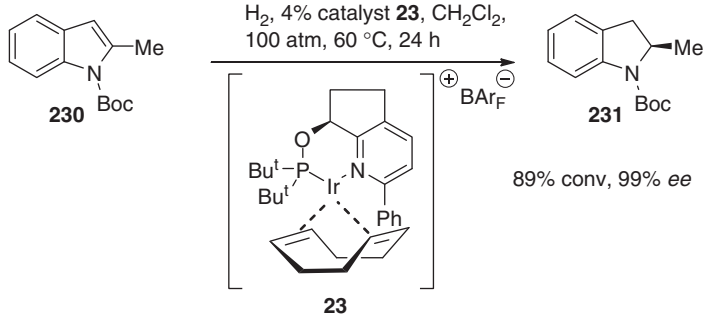


Scheme 48



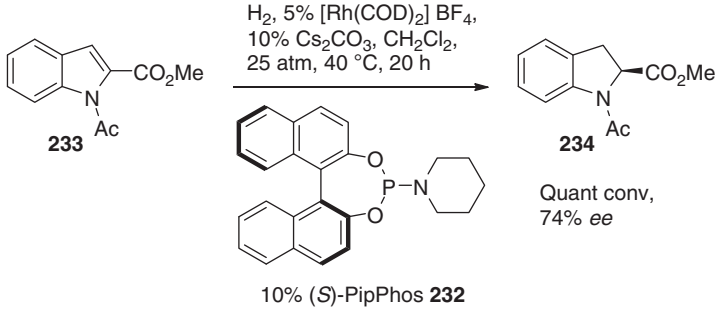
(17)

Pfaltz and Baeza developed an iridium-based catalyst system that effected asymmetric hydrogenation of substituted indoles with yields and enantioselectivities in the same range as those reported by Kuwano for the Rh and Ru complexes with PhTRAP.[100] For example, at 60° C and 100 atm H_2 pressure, subjection of indole **230** to the cationic Ir complex **23** led to (*R*)-2-methylindoline **231** in 89% conversion and with 99% *ee* (equation 18).



(18)

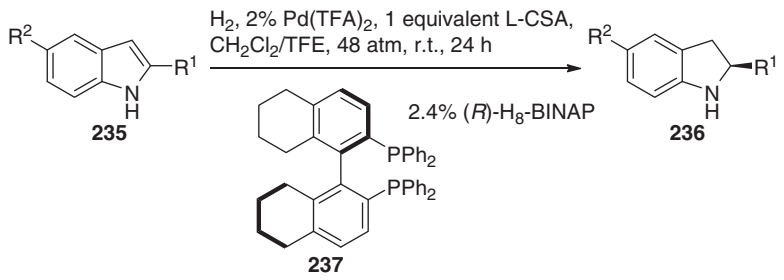
In 2010, Feringa and de Vries reported the asymmetric hydrogenation of C-2 substituted *N*-protected indoles using rhodium-based catalysts with monodentate phosphoramidite ligands.[101] In the presence of 5 mol% $[Rh(COD)_2]BF_4$, 10 mol% PipPhos **232** and 10 mol% Cs_2CO_3, *N*-acetyl-indole-2-carboxylate **233** was converted to the corresponding indoline **234** in quantitative conversion and 74% *ee* (equation 19). The use of a phosphoramidite has the advantage of being easy to prepare, air stable, and inexpensive compared with most bidentate ligands.



(19)

Zhou and Zhang reported the first asymmetric hydrogenation of unprotected indoles in 2010.[102] For example, 2-methylindole **235** was reduced to 2,3-dihydroindole **236** in 88% yield and 91% *ee* by incorporating the more classical approach of adding a Brønsted acid to activate the indole toward hydrogenation (i.e., through initial formation of the iminium salt) with a chiral Pd complex ($Pd(OCOCF_3)_2$/H8-BINAP) (entry i, Table 14). Substrates bearing a substituent at the C-5 position displayed slightly lower levels of enantioselectivity (entries v and vi).

Table 14 Palladium-catalyzed asymmetric hydrogenation of C-2 substituted indoles

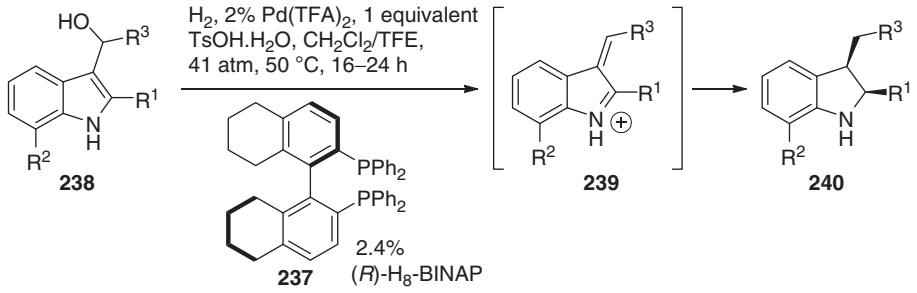


Entry	*R^1*	*R^2*	*Yield (%)*	ee *(%)*[a]
i	Me	H	88	91
ii	Bu^n	H	82	93
iii	Cyclohexyl	H	90	95
iv	Bn	H	99	95
v	Me	F	84	88
vi	Me	Me	81	84

[a]Determined by HPLC analysis.

By adopting an alternative activation strategy for indole hydrogenation, Zhou et al. were able to prepare chiral 2,3-disubstituted indolines.[103] Racemic 3-(α-hydroxyalkyl)indoles **238** were readily dehydrated in the presence of a Brønsted acid to form vinylogous iminium intermediate **239** that was hydrogenated by the chiral $Pd(TFA)_2$/H8-BINAP catalyst to afford indolines **240** in excellent yields and enantioselectivities (Table 15). Key to the success of this strategy was the identification of a catalyst system that tolerated water, as one mole is liberated during the reaction.

Table 15 Dehydration-asymmetric hydrogenation of 3-(α-hydroxyalkyl)indoles



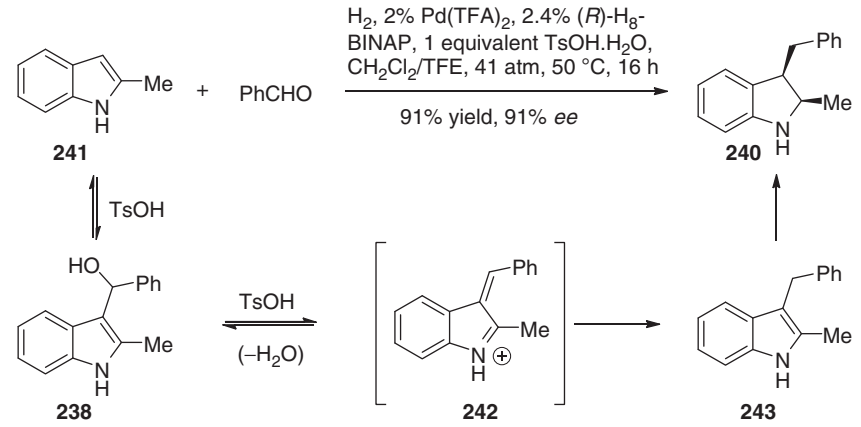
Entry	*R^1*	*R^2*	*R^3*	*Yield (%)*	ee *(%)*[a]
i	Me	H	Ph	96	91
ii	Me	H	Cyclohexyl	95	94
iii	Bu^n	H	Ph	94	94
iv	Me	Me	Ph	84	97
v	Me	Me	Pr^i	98	97

[a]Determined by HPLC analysis.

Zhou and coworkers then developed a tandem Brønsted acid-mediated reductive alkylation/asymmetric hydrogenation of 2-substituted indoles **241** and aldehydes to combine the synthesis of key intermediate 3-(α-hydroxyalkyl)indoles **238** with their subsequent reduction to chiral indolines **240** (Scheme 49).[104] Use of this procedure enabled rapid access to synthetically useful chiral building blocks in one step from commercially available materials.

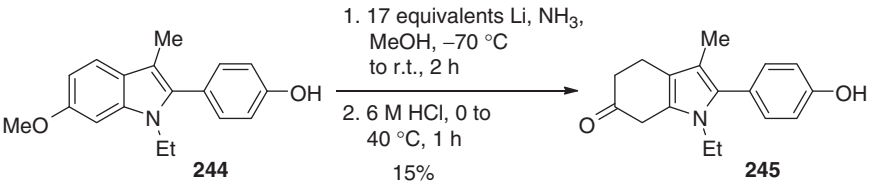
8.22.4.2 Dissolving Metals

The Birch reduction of indoles has been shown to be an effective method of accessing saturated indoline skeletons (see first edition of Comprehensive Organic Synthesis (COS)).



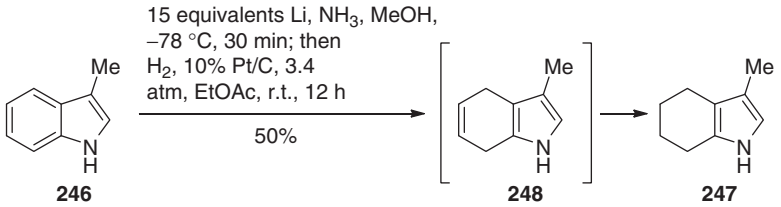
Scheme 49

It has been well documented that chemoselective reduction can be achieved through the presence or absence of a proton source.[105] In 1991, Schiller et al. exploited this by performing a Birch reduction in methanol and obtaining selective saturation of the benzene ring of antiestrogenic 2-phenylindole **244** during the synthesis of indolone **245** (Scheme 50).[106] If the alcohol had been omitted then typically the pyrrole ring would have been reduced.[105]



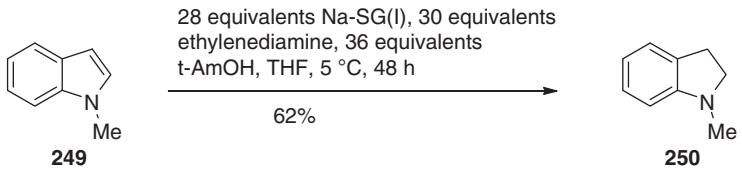
Scheme 50

Van Vranken and McComas employed a sequential Birch reduction-hydrogenation protocol to fully reduce the benzo-fused ring of 3-methylindole (skatole) **246** to tetrahydroskatole **247** (equation 20).[107] A metal-catalyzed hydrogenation (10% Pt/C) was found to be an essential second step, as Birch reduction of **246** typically led to a 2:1 mixture of dihydro- and tetrahydroskatole **248** and **247**.



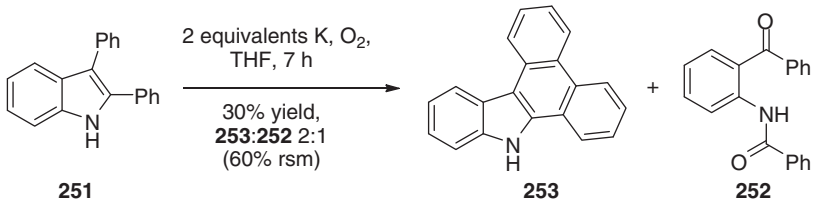
(20)

An ammonia-free protocol was developed by Vogt et al. whereby stage I sodium was encapsulated in silica gel, Na–SG(I), and shown to reduce a range of aromatic systems including *N*-methylindole **249** (equation 21).[40] The reduction took 48 h, but it afforded *N*-methyl indoline **250** in 62% yield, which compared very favorably to the 15% yield obtained under classical Birch conditions.[108] This encapsulation method reduces the danger associated with handling alkali metals, whereas retaining their reducing power, as well as obviating the requirement for NH_3 and cryogenic temperatures.



(21)

Elsewhere, very little has been reported over the last quarter of a century on the reduction of indoles with dissolved metals other than Li and Na. This was exemplified when Kamat and coworkers treated indole **251** with potassium superoxide in THF a mixture of products was isolated, including ring cleaved adduct **252**, but no indoline was obtained (equation 22).[109]



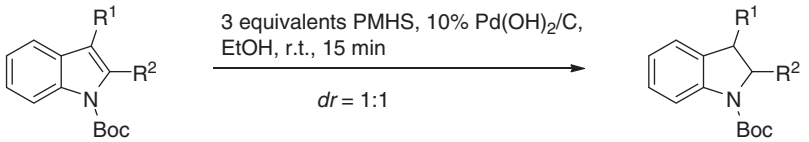
251 **253** **252** (22)

8.22.4.3 Ionic Hydrogenation

The main group metal hydride salts such as $LiAlH_4$ and $NaBH_4$ have previously been shown to effect hydride-mediated reduction of indoles (see first edition of COS). The groups of Chandrasekhar and Zhang in 2007 and 2009, respectively, have developed milder alternative reduction protocols that avoid the use of these reactive metal hydride sources.

Chandrasekhar and coworkers employed siloxanes as a safer option to $NaBH_4$ for the reduction of 2- and 3-substituted *N*-Boc-indoles **254** to the corresponding indolines **255** in excellent yields (Table 16).[110] Polymethylhydrosiloxane (PMHS), an inexpensive, air and moisture stable compound, was used as an efficient reducing agent in the presence of catalytic $Pd(OH)_2/C$ at room temperature and with short reaction times. It is noteworthy that esters were inert to the reductive conditions, whereas aldehydes were efficiently reduced to the corresponding alcohols (entries v and vi, Table 16).

Table 16 Reduction of indoles using polymethylhydrosiloxane

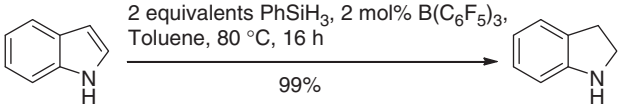


254 **255**

Entry	R^1	R^2	*Yield (%)*
i	H	H	96
ii	Me	H	92
iii	H	Me	90
iv	CH_2OTBS	H	88
v	H	CO_2Me	88
vi	CHO	H	85[a]

[a] R^1 reduced to the corresponding primary alcohol.

A metal-free process was exploited by Zhang and Tan to reduce indole **215** to indoline **256**, using phenylhydrosilane and catalytic $B(C_6F_5)_3$ in toluene at 80 °C (equation 23).[111] Lewis acidic $B(C_6F_5)_3$ extracts a hydride from the hydrosilane to form a hydridoborate ion, which serves as an efficient and easy-to-handle reducing agent.

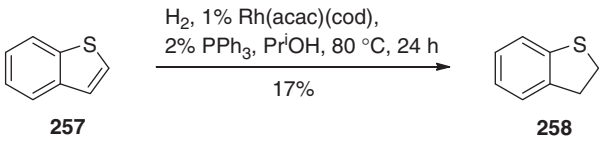


215 **256** (23)

8.22.5 Reduction of Thiophenes and Benzothiophenes

There has been little reported on the reduction of thiophenes and benzothiophenes since 1987. For older examples the reader is directed toward the first edition of this volume.

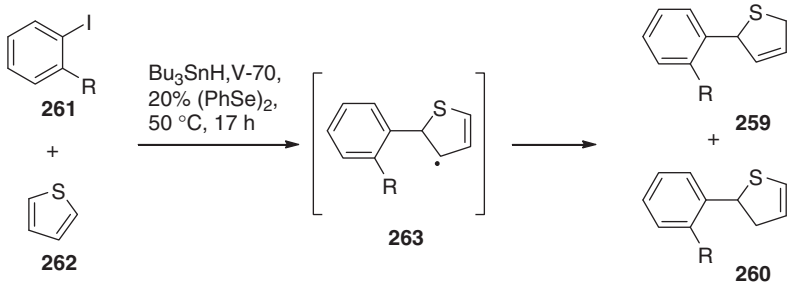
Perhaps the greatest problem associated with the attempted catalytic hydrogenation of sulfur-containing heteroaromatic rings is that sulfur is an excellent poison for transition metals. Another issue is the high degree of aromaticity of the thiophene ring. Despite these problems, Kuwano et al. were able to effect a selective reduction of benzothiophene **257**, albeit in a low yield of 17%, using a rhodium complex generated *in situ* from Rh(acac)(cod) and 2 equivalents of triphenylphosphine (equation 24).[3]



257 258 (24)

Elsewhere, Crich and Patel reported a dearomatizing aryl radical addition to thiophene.[36] In the presence of catalytic diphenyl diselenide, tributyltin hydride, and 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (V-70) promote the addition of aryl iodides to thiophene in moderate-to-good yields (Table 17). A mixture of the 2-substituted 2,5-dihydro **259** and 2,3-dihydrothiophenes **260** were isolated, but **259** predominated in all cases. Note the diphenyl diselenide is reduced *in situ* to benzeneselenol, and it is the Se–H bond that traps the alkyl radical.

Table 17 Dearomatizing aryl radical addition to thiophenes



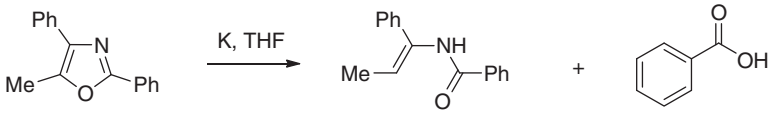
Entry	*R*	*Yield of **259** (%)*	*Yield of **260** (%)*
i	$NHCO_2Me$	31	11
ii	CO_2Me	35	15
iii	OH	32	4[a]

[a]Product isolated had cyclized to give a 2,3,4,5-tetrahydro-2,5-epithio-1-benzoxepin.

8.22.6 Reduction of Heterocyclic Rings Containing Two or More Heteroatoms

8.22.6.1 Reduction of Heterocycles Containing Both Nitrogen and Oxygen Atoms

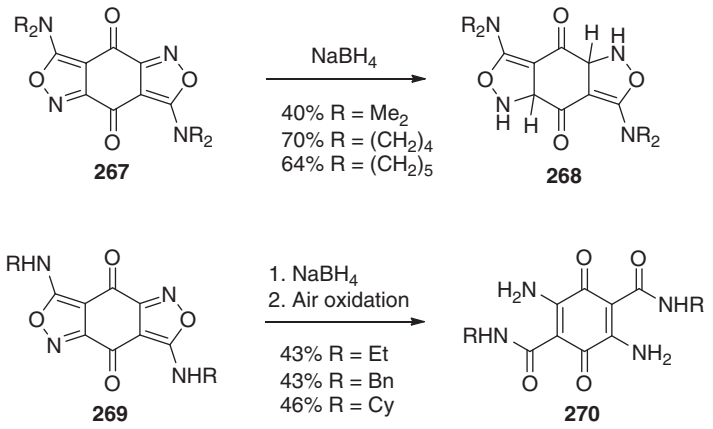
Regardless of whether the two heteroatoms are directly bound to each other or not, heterocycles containing a nitrogen and an oxygen atom are very prone to ring opening during reduction. To date, there has been no reduction of this type of aromatic compound by dissolving metals either in liquid ammonia or under ammonia-free conditions. Equation 25 illustrates the problematic reduction of oxazole **264** employing potassium as a metal.[109] Depending on the nature of the substituents on the heterocycle, the enamide **265**, benzoic acid **266**, and other degradation products were isolated in varying yields.



264 **265**, 37% **266**, 4% (25)

The high level of sensitivity of isoxazoles was demonstrated by Neidlein and coworkers during their investigations on the reduction of amino-substituted benzodiisoxazol-4,8-diones **267** (Scheme 51).[112] Whereas hydrogenation over Pd/C or reductive conditions employing zinc led to cleavage of the isoxazole ring and formation of hydroquinone derivatives, the use of sodium borohydride afforded isoxazolines **268** in moderate-to-good yields. When applying the same conditions to monoalkylamino-substituted isoxazoles **269**, the reduction did not result in formation of the oxazolines, but ring opened benzoquinones **270** were obtained after consecutive air oxidation.

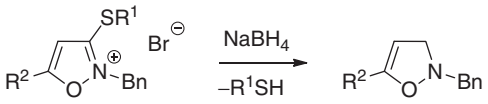
To enable a reduction of aromatic heterocycles with sodium borohydride or other hydride sources one double bond of the aromatic compound needs to be highly polarized. This can either be achieved by using electron-withdrawing groups attached to the ring (see Scheme 51) or by quaternization of the nitrogen atom to afford (is)oxazolium salts. In an early example, Jeon and Kim treated *N*-alkylated isoxazolium and thiazolium salts with sodium borohydride at room temperature.[113] Whereas the



Scheme 51

thiazolium salts resulted in ring cleavage of the heterocycle, reduction of the *N,O*-heterocycles **271** produced the desulfurized isoxazolines **272** selectively in very good yields (Table 18).

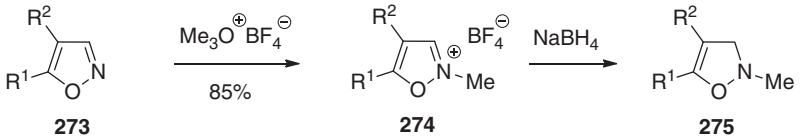
Table 18 Reduction of isoxazolium salts by sodium borohydride



Entry	R^1	R^2	*Yield (%)*
i	*o*-$BrC_6H_4CH_2$	Ph	92
ii	$CH_2{=}CHCH_2$	Ph	100
iii	EtO_2CCH_2	Ph	82
iv	*o*-$BrC_6H_4CH_2$	*p*-ClC_6H_4	94
v	*o*-$BrC_6H_4CH_2$	*o*-ClC_6H_4	87

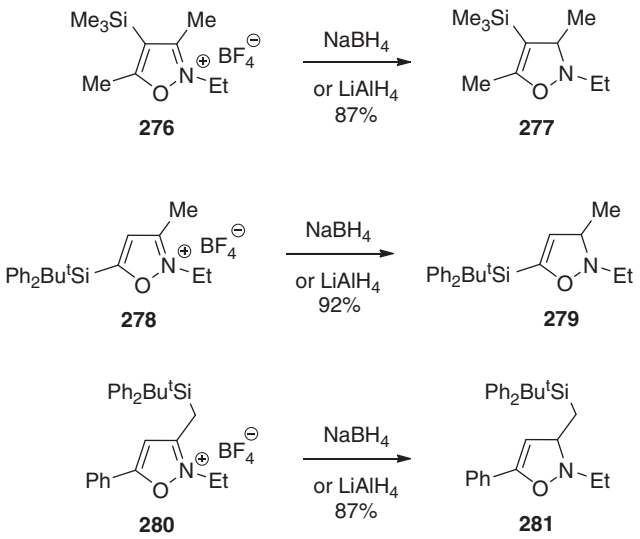
A similar tandem *N*-quaternization/reduction sequence of 4,5-disubstituted isoxazoles without the requirement of a sulfur being present on the heterocycle, was reported by Domínguez and coworkers.[114] Methylated isoxazolines **275** were obtained in excellent yields by alkylating bisarylated isoxazole **273** with Meerwein's salt (Me_3OBF_4) and subsequent addition of sodium borohydride to isoxazolinium salt **274** (Table 19). The same sequence was applied a few years later to various bis- and tri-substituted isoxazoles by Knaus et al. in their studies on the synthesis of novel cyclooxygenase-2-inhibitors, delivering the reduced heterocycle in moderate-to-good yields (50–76%).[115]

Table 19 Tandem *N*-quaternization/reduction sequence to produce isoxazolines **275**



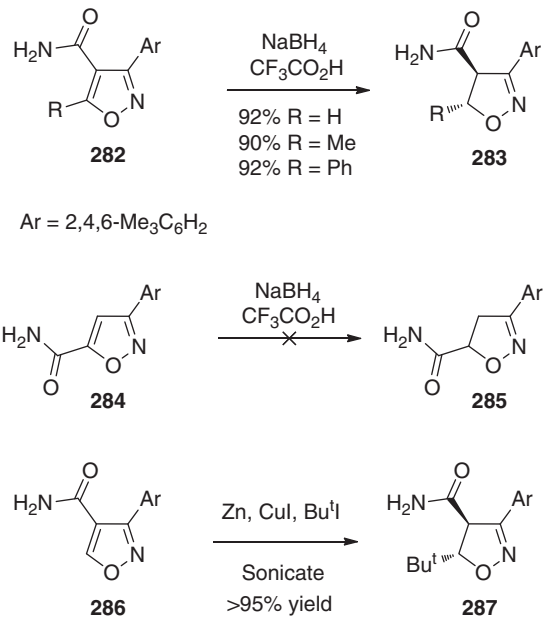
Entry	R^1	R^2	*Yield of **274** (%)*	*Yield of **275** (%)*
i	Ph	Ph	85	84
ii	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	94	64
iii	3,4-$(MeO)_2C_6H_3$	Ph	96	90
iv	2,3,4-$(MeO)_3C_6H_2$	3,4-$(MeO)_2C_6H_3$	99	93

In 2009 the scope of this reduction sequence was extended to encompass the synthesis of alkyl- and silyl-substituted isoxazolines.[116] González-Nogal et al. reported on the synthesis of a series of differently functionalized isoxazolinium salts and their reduction with sodium borohydride. Surprisingly, the authors found out that reduction with lithium aluminum hydride afforded the reduced heterocycles in the same yield as in the case of borohydride, whereas previous studies had revealed decomposition or much lower yields under these conditions.[114] Thus, both hydride sources were used to reduce fully substituted isoxazoles (e.g., **276**) as well as less substituted analogs (e.g., **278**) and benzylic silanes (**280**) to produce 4-isoxazolines **277**, **279**, and **281** (Scheme 52).



Scheme 52

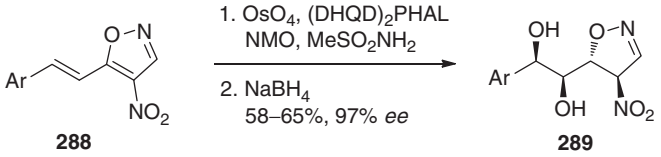
Crystallographic and computational studies carried out by Easton et al. revealed an interesting effect when placing an electron-withdrawing group at different positions on the isoxazole core.[117] An electron-withdrawing group in the 4-position enhanced the C4–C5 bond polarity and made its reactivity similar to that of a Michael acceptor. Thus, a suitable substituent on the 4-position enabled reduction of the aromatic heterocycle without prior activation through quaternization of nitrogen. Treatment of amide **282** with *in situ* prepared sodium trifluoroacetoxyborohydride led to smooth conversion to isoxazolines **283**, whereas the same conditions applied to isoxazole **284** bearing an electron-withdrawing substituent at the 5-position led to no conversion (Scheme 53).[118]



Scheme 53

Another utilization of the polarization of aromatic systems was demonstrated by the same group when treating C4–activated isoxazoles (such as **286**) with zinc dust and a cuprate. Under sonication a conjugate addition of the alkyl group took place via a radical mechanism leading to the alkylated isoxazolines **287**. In the case of bulky alkyl groups (e.g., *tert*-butyl, adamantyl, or isopropyl) the reduced heterocycle was obtained stereoselectively as the *trans*-isomer.[118]

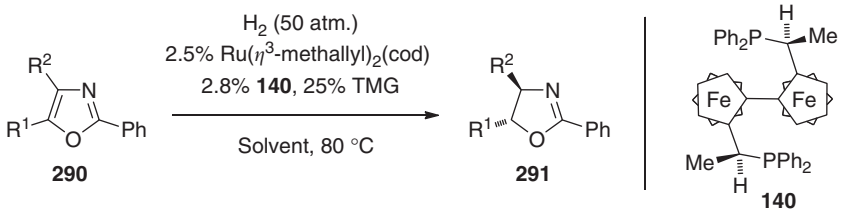
In addition to esters and amides, Adamo and Nagabelli showed that nitro groups are also suitable activating groups for the isoxazole ring. In a one-pot procedure starting from styryl isoxazoles **288**, a Sharpless dihydroxylation, followed by reduction with sodium borohydride, was carried out and furnished the reduced heterocycles **289** in 58–65% yield and with excellent enantioselectivity (Scheme 54).[119]



Scheme 54

A powerful route to access oxazolines with excellent enantioselectivities was reported by Kuwano and coworkers by developing an asymmetric hydrogenation of various aromatic heterocycles to obtain oxazolines and imidazolines.[120] The use of Ru(η^3-methallyl)$_2$(cod) in combination with the chiral bisphosphine ligand (*S*,*S*)-(*R*,*R*)-PhTRAP **140** and with *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) provided an ideal catalyst for the first successful hydrogenation of heterocycles containing more than one heteroatom, without any overreduced or ring opened side products. Table 20 shows a selection of differently substituted oxazoles **290**, which were all hydrogenated in very good yields and with high stereoselectivity. Remarkably, both 4- and 5-substituted oxazoles gave nearly the same selectivity, whereas 4,5-disubstituted heterocycles led to no conversion at all, probably due to steric reasons. The authors assumed that the enantiofacial selectivity of the hydrogenation arises from steric interactions between the ligand and the substituent at C4 or C5, rather than from the electronic properties of the double bond.

Table 20 Enantioselective hydrogenation of oxazoles **290**



Entry	R^1	R^2	*Solvent*	*Yield (%)*	ee *(%)*
i	H	Ph	Bu^{i}OH	>99	98
ii	H	*p*-FC$_6$H$_4$	Bu^{i}OH	92	97
iii	H	Me	Bu^{i}OH	88	91
iv	H	*c*-C$_6$H$_{11}$	Bu^{i}OH	91	88
v	Ph	H	Bu^{i}OH	>99	95
vi[a]	*p*-FC$_6$H$_4$	H	Toluene	>99	93
vii[a]	Me	H	Toluene	85	86
viii[a]	*c*-C$_6$H$_{11}$	H	Toluene	99	72

[a]Reactions were conducted in the absence of TMG.

The utility of this highly enantioselective hydrogenation was demonstrated by the synthesis of chiral amino alcohols that were obtained from acidic hydrolysis of the corresponding oxazolines.

8.22.6.2 Reduction of Heterocycles Containing Two or More Nitrogen Atoms

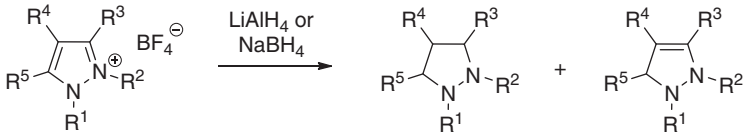
8.22.6.2.1 Reduction of five-membered heterocycles containing two nitrogen atoms

Due to the weak strength of the C–N bond in aromatic heterocycles containing two nitrogen atoms, all attempts to reduce either imidazoles or pyrazoles via single electron transfer resulted in ring cleavage of the heterocycle. During their studies on the

reduction of imidazoles and isoxazoles through the action of potassium in THF, Muneer and coworkers could only isolate ring opened amides (e.g., equation 25).[109]

Similar to *N,O*-heterocyclic compounds, pyrazoles can be activated by quaternization of one nitrogen atom and subsequent treatment with metal hydrides. González-Nogal et al. investigated the reduction of pyrazolium salts by lithium aluminum hydride and sodium borohydride, where the reactivity of the aromatic compound was further increased through an electron-withdrawing group at the 4-position.[121] Remarkably, the use of lithium aluminum hydride gave the pyrazolidine **293** selectively in all the cases, whereas sodium borohydride also afforded partially reduced 3-pyrazoline **294** in some cases (entries i and vi, Table 21). In general, nucleophilic attack of hydride onto the aromatic compounds gave good yields of the reduced heterocycles and the fully reduced pyrazolidine **293** was formed with excellent diastereoselectivities in most cases. The low yield from the brominated pyrazolium salt (entry iii) can be rationalized by a competing hydrogenolysis of the C–Br bond when $LiAlH_4$ was employed as a reducing agent.

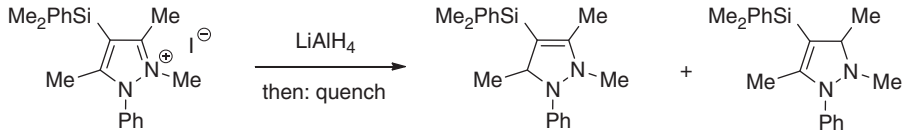
Table 21 Reduction of pyrazolium salts through hydride transfer



292 **293** **294**

Entry	*R*[1]	*R*[2]	*R*[3]	*R*[4]	*R*[5]	*Hydride source*	*Yield of **293** (%)*	*Yield of **294** (%)*
i	Ph	Et	NO_2	Me	H	$LiAlH_4$	77	~
ii	Ph	Et	NO_2	Me	H	$NaBH_4$	36	37
iii	Ph	Et	Br	Me	Ph	$LiAlH_4$	26	~
iv	Ph	Et	Br	Me	Ph	$NaBH_4$	80	~
v	Me	Me	CO_2Et	Me	Me	$LiAlH_4$	62	~
vi	Me	Me	CO_2Et	Me	Me	$NaBH_4$	43	25

Based on these initial results, the same authors then continued their studies onto the reduction of silylated pyrazolium salts.[116] By replacing the electron-withdrawing group (R^4 in Table 20) by a trialkylsilyl group, the reactivity of the salt is decreased drastically and sodium borohydride was not powerful enough to reduce the heterocycle. However, partial or complete reduction could be accomplished with lithium aluminum hydride as a hydride source. Interestingly, the outcome of the reduction depended strongly on the nature of the counter ion. Although tetrafluoroborate salts gave complex product mixtures in which the silyl group was cleaved from the heterocycle, the same conditions applied to iodide salt **295** resulted in the formation of 3-pyrazoline **296** and its regioisomer **297** (Scheme 55). The product obtained was strongly dependent on the hydrolysis conditions used after reduction. Addition of water gave the kinetic product **296**, which resulted from attack of the hydride at C-5, whereas quenching with a saturated solution of ammonium chloride furnished a 1:1-mixture of both isomers. Moreover, the kinetic product **296** isomerized to the thermodynamically more stable pyrazoline **297** when left standing at room temperature for several days.



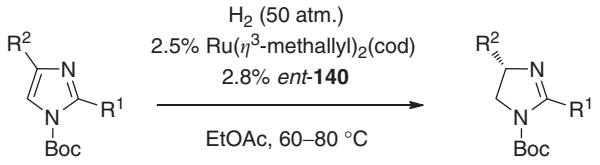
295 **296** **297**

	296	**297**
with H_2O:	86%	0%
with NH_4Cl:	42%	42%

Scheme 55

In 2011, Kuwano and coworkers developed conditions for the highly enantioselective hydrogenation of oxazoles and imidazoles.[120] Although the homogeneous catalyst formed *in situ* from Ru(η^3-methallyl)$_2$(cod) and the chiral bisphosphine ligand (*R,R*)-(*S,S*)-PhTRAP *ent*-**140** (Table 20) was not suitable for the hydrogenation of 4,5-disubstituted imidazoles, a variety of Boc-protected imidazoles **298** with only one substituent were reduced to the corresponding imidazolines **299** (Table 22). Whereas various alkyl substituents at the 4-position (R^2) were tolerated, the presence of a phenyl group (R^1) seemed to be crucial to obtain high yields and enantioselectivities.

Table 22 Enantioselective hydrogenation of imidazoles

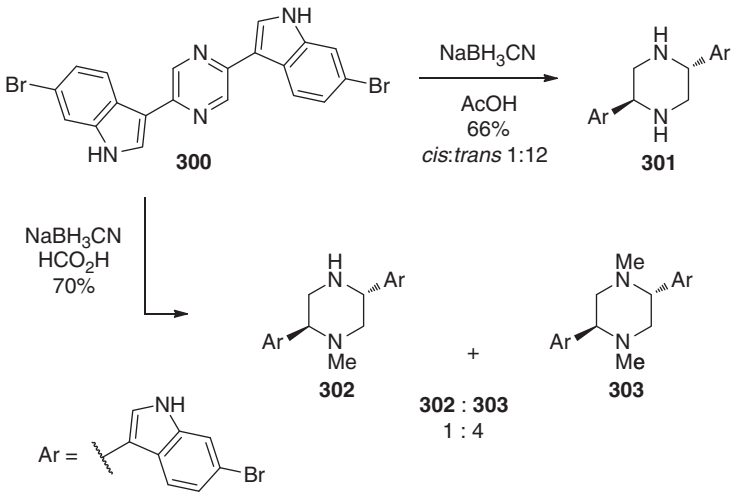


298 **299**

Entry	R^1	R^2	*Yield (%)*	ee *(%)*
i	Ph	Me	97	97
ii	Ph	*c*-C_6H_{11}	97	97
iii	Ph	CF_3	89	99
iv	Et	Me	35	86

8.22.6.2.2 Reduction of six-membered heterocycles containing two nitrogen atoms

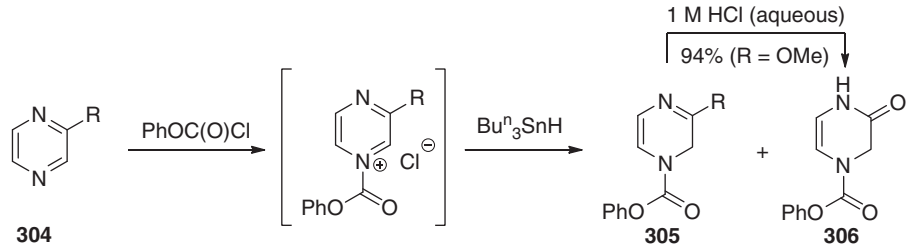
Since 1987 there have been no major improvements in methods for the partial or complete reductions of pyridazines, which is surprising because most of the known reduction conditions result in cleavage of the six-membered ring. However, new methods for the reduction of pyrimidines, pyrazines, as well as their benzo-analogs have been devised. The electrochemical reduction of 2-hydroxy-3-phenyl-6-methylpyrazine, a heterocycle that arises from the degradation of β-lactam antibiotics, was investigated by Nuñez-Vergara and coworkers.[122] This two electron and two or three proton process was strongly dependent on the pH of the reaction mixture. In a second study on the reduction of an unsubstituted pyrazine at a silver electrode, Irish et al. found that this electrochemical reduction is irreversible, even when the potential was switched to positive values.[123] A more practical, non-electrochemical reduction of pyrazines was reported by Horne and coworkers in their synthesis of the bisindolylpiperazines dragmacidin A–C.[124] Treatment of pyrazine **300** with sodium cyanoborohydride in acetic acid furnished *cis*- and *trans*-dragmacidin C (**301**) as a 1:12-mixture in 66% yield (Scheme 56). Replacing the acetic acid by formic acid led to reduction of the heterocycle and to reductive alkylation of one or both nitrogen atoms to afford dragmacidin A (**302**) and dragmacidin B (**303**) in 70% yield.



Scheme 56

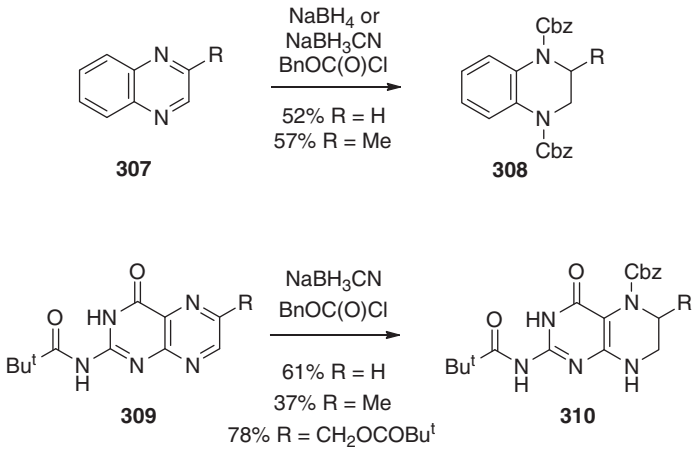
Whereas conditions for the reduction of pyrazine **300** resulted in an exhaustive reduction of the aromatic heterocycle, Williams et al. found that tributyltin hydride (in the presence of a chloroformate) provoked a partial reduction of the pyrazine ring.[125] The chloroformate activates 3-substituted pyrazine **304** and subsequent reduction resulted selectively in the formation of 1,2-dihydro pyrazine **305** (Table 23). The 1,6-dihydro isomer was not detected and calculations showed that it would be higher in energy than the corresponding 1,2-dihydro heterocycle. However, a heteroatomic substituent on C-3 was crucial in order to obtain **305**, as alkyl and aryl groups at this position gave no conversion at all. Surprisingly, reduction of 3-chloro pyrazine afforded no dihydropyrazine, but oxopiperidine **306**. This is probably due to hydrolysis of the imidoyl chloride during aqueous work-up. The same oxopiperidine was obtained by mild acidic hydrolysis of the 1,2-dihydro pyrazine **305** (R=OMe).

Table 23 Regioselective partial reduction of pyrazines with tributyltin hydride



Entry	*R*	*Yield of **305** (%)*	*Yield of **306** (%)*
i	OMe	90	0
ii	OBu^t	94	0
iii	OBn	81	0
iv	SEt	65	0
v	Cl	0	46

In 1992, Joule et al. had showed that borohydrides effectively reduced quinoxalines and pteridines in the presence of benzyl chloroformate.[126] Interestingly, the 2-substituted benzopyrazines **307** (R=H or Me) gave selectively the bisacylated tetrahydropyrazines **308** by using either sodium borohydride or sodium cyanoborohydride (Scheme 57), whereas more complex sulfur-containing substituents at the 2-position led to mono-acylated products. Additionally, pteridines **309** were reduced under the same conditions to furnish their tetrahydro derivatives **310** in moderate-to-good yields. During this transformation the double bond of the pyrimidine ring was not affected.

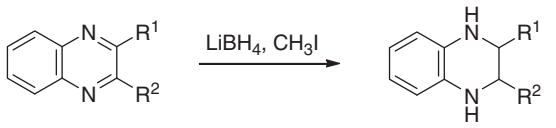


Scheme 57

For many years the reduction of quinoxalines seemed to be an unreliable transformation giving varied results and in many cases the outcome depended on prior activation of the arene through quaternization of the nitrogen atom, leading to alkylated or acylated heterocycles.[127] However, Salvatore and Gavin showed that the use of borane in THF gave superior yields compared with the use of sodium borohydride.[128] Nevertheless, the preparation of borane *in situ* from iodomethane and lithium borohydride seemed to be essential in order to achieve high yields. Thus, during the reduction of quinoxalines **311**, tetrahydroquinoxalines **312** were produced in excellent yields, and alkyl, phenyl, and heteroaromatic substituents were all tolerated (Table 24). In the case of disubstituted pyrazines (entries iii and vi), only the *cis*-diastereoisomer was detected. Sodium borohydride in ethanol or acetic acid could also be used for the reduction, but the yields were lower in general.

In addition to reduction via hydride transfer onto the heterocycle, it is also possible to reduce quinoxalines by the use of metals. Treatment of the aromatic heterocycle with zinc in the presence of acetic anhydride resulted in the formation of the corresponding reduced heterocycle, although in this case at least one nitrogen was acylated.[129] The use of indium, however,

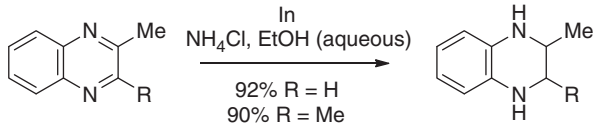
Table 24 Reduction of quinoxalines **311** with *in situ*-prepared borane



311 **312**

Entry	R^1	R^2	*Yield (%)*
i	H	H	91
ii	Me	H	99
iii	Me	Me	88
iv	Ph	H	81
v	2-Thienyl	H	90
vi	Ph	Ph	81

effected a direct reduction of benzo-fused pyrazine **313** to the tetrahydro derivative **314** (Scheme 58).[130] Although the heterocycles **314** were obtained in high yields, the disubstituted derivative was formed as a 2:1-mixture of *cis*/*trans*-isomers.

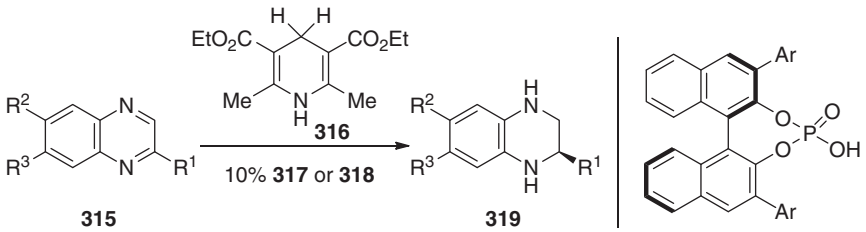


313 **314**
cis:*trans* 2:1
(for R = Me)

Scheme 58

All reductions of quinoxalines employing either metals or metal hydrides led to racemic tetrahydroquinoxalines, and no enantioselective method for this transformation was known until 2010, when Rueping and coworkers reported the first highly enantioselective reduction of quinoxalines.[131] In this case the heterocycle was reduced by a transfer hydrogenation using Hantzsch ester **316** as a hydrogen source and chiral phosphoric acids **317** and **318** as catalysts (Table 25). Under these conditions, a variety

Table 25 Reduction of quinoxalines **315** through transfer hydrogenation



315 **319**

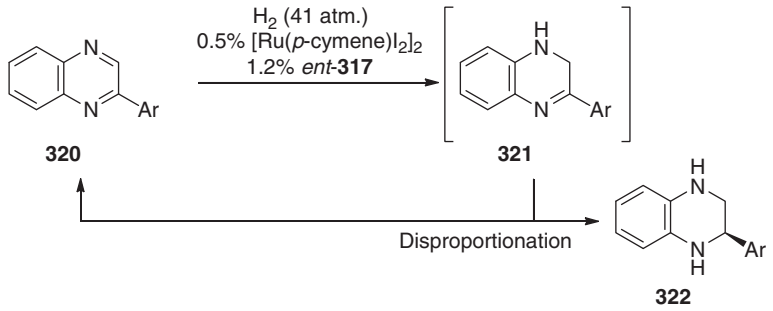
317 (Ar = Anthracenyl)
318 (Ar = 2,4,6-(Pr^i)$_3$-phenyl)

Entry	R^1	R^2	R^3	*Catalyst*	*Yield(%)*	ee *(%)*
i	Ph	H	H	**317**	98	90
ii	*p*-BrC_6H_4	H	H	**317**	88	96
iii	*m*-BrC_6H_4	H	H	**318**	91	86
iv	Ph	Br	H	**318**	95	92
v	Ph	H	Br	**317**	94	82
vi	Ph	Cl	Cl	**318**	93	98
vii	2-Furyl	H	H	**318**	93	82

of differently substituted quinoxalines **315** were reduced to their tetrahydro derivatives **319** in excellent yields and with up to 98% *ee*, although an aryl group at the 2-position was necessary in these cases.

In 2011, Zhou and Fan reported a highly enantioselective and ideal atom-economical reduction of quinoxalines.[132] The first step of this process is a ruthenium-catalyzed hydrogenation of quinoxaline **320** in the presence of $[Ru(p\text{-cymene})I_2]_2$ resulting in formation of the dihydroquinoxaline **321** (Table 26). Subsequently, this intermediate interacted with an added chiral phosphoric acid *ent*-**317** provoking a self-transfer hydrogenation of the dihydroquinoxaline **321**. This disproportionation led to one molecule of the parent quinoxaline **320** and one molecule of tetrahydroquinoxaline **322**. The slow metal-catalyzed hydrogenation of **321** under these conditions allowed disproportionation of the dihydroquinoxaline, and therefore formation of the tetrahydro derivatives, with excellent enantioselectivities. Computational studies provided further evidence for this interesting self-transfer hydrogenation mechanism.

Table 26 Enantioselective self-transfer hydrogenation to furnish tetrahydroquinoxalines **322**

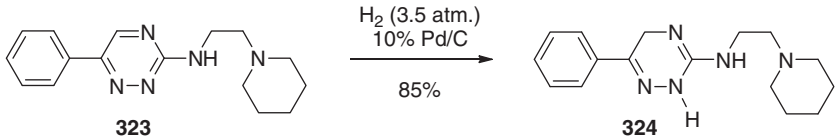


Entry	*Ar*	*Yield of **322** (%)*	ee *(%)*
i	Ph	96	90
ii	*p*-MeC_6H_4	98	83
iii	*p*-FC_6H_4	98	89
iv	*p*-$CF_3C_6H_4$	95	86
v	*m*-BrC_6H_4	97	94
vi	2-Naphthyl	98	94

Surprisingly, Zhou and Fan obtained the same enantiomer of tetrahydroquinoxaline **322** as observed by Rueping during his investigations using Hantzsch's ester (see Table 25), although the two groups used opposite enantiomers of catalyst **317**. Zhou rationalized this reversal of enantioselectivity by invoking the steric demands of the two different hydride transfers. Whereas a Hantzsch ester transfers its hydride in a 1,4-pathway, the dihydroquinoxaline **321** delivers the hydride in a 1,2-fashion and therefore the reduction proceeds via a different transition state.[132]

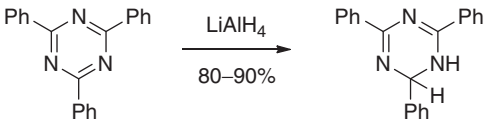
8.22.6.2.3 Reduction of heterocycles containing three nitrogen atoms

The reduction of aromatic compounds containing three heteroatoms is not a well-studied process. Amongst the heterocycles containing three nitrogen atoms a 1,2,4-triazine and its 1,3,5-isomer have been successfully reduced, although these reactions were not investigated intensively. An early example was reported by Wermuth and coworkers during their studies on aminopyridazines as potential acetyl cholinesterase inhibitors.[133] Catalytic hydrogenation of triazine **323** over palladium on carbon furnished the dihydrotriazine **324** selectively and interestingly, no overreduced heterocycle was obtained (equation 26).



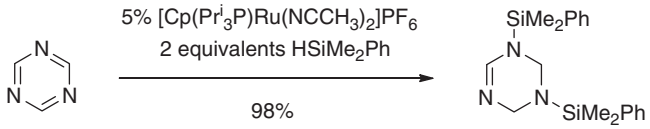
(26)

During studies toward the synthesis of 1,2-dihydrotriazinyl-*N*-oxy radicals Rey and coworkers treated triphenyltriazine **325** with lithium aluminum hydride to furnish dihydrotriazine **326** (equation 27).[134] The hydride transfer was very efficient and the 1,2-dihydroisomer was obtained as the only reduced heterocyclic product.



325 **326** (27)

In 2011 Nikonov et al. published their studies on the hydrosilylation of pyridines by employing a cationic ruthenium complex in the presence of a silane.[135] During their investigations, triazine **327** was also treated with 5% of $[Cp(Pr^i_3P)Ru(NCCH_3)_2]PF_6$ and 2 equivalents of $HSiMe_2Ph$ (equation 28). After 3.5 h complete conversion was observed and the silylated 1,2,3,4-tetrahydrotriazine **328** was obtained in high yield.



327 **328** (28)

References

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8.23 Hydrozirconation of Alkenes and Alkynes

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 doi:10.1016/B978-0-08-097742-3.00825-9

Glossary

Alkenylzirconocene A zirconocene compound with an alkenyl group, the product of hydrozirconation of alkynes.
Alkylzirconocene A zirconocene compound with an alkyl group, the product of hydrozirconation of alkenes.
Elimination A reverse process of addition reaction to unsaturated bonds.
Hydrozirconation A process in which 1,2-addition of H and Zr to unsaturated bonds occurs.
Schwartz reagent Complex Cp_2ZrHCl.
Transmetalation A process in which a metal moiety of organometallic compounds is replaced with other metals.

Hydrometalation, in the form of hydroboration, hydroalumination, and hydrozirconation, of alkenes and alkynes is one of the most powerful methods to synthesize functionalized alkanes and functionalized stereodefined alkenes. Hydrometalation is the addition reaction of H and M to alkenes and alkynes to produce metalated species that can be converted into various functionalized compounds. In the case of hydrozirconation, Cp_2ZrHCl (Schwartz reagent) has been used. The alkyl or alkenylzirconium complexes prepared from hydrozirconation of unsaturated carbon–carbon double or triple bonds subsequently react with electrophiles to form various C–C(X) or C═C(X) bonds, or undergo transmetalation to give more reactive M–C bonds. This very broad chemistry has been developed since the early 1970s. This chapter gives a general introduction to the hydrozirconation of alkene and alkyne derivatives,[1,2] but places special emphasis on synthetic applications of hydrozirconation that appeared after 1996. Several excellent reviews cover applications reported before 1996.[1,3,4]

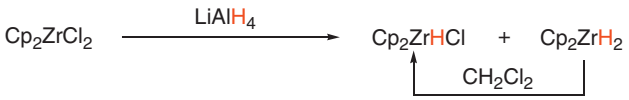
8.23.1 General Introduction

Transformations of alkenes or alkynes play a fundamental role in organic synthesis. Zirconium has an empty d-orbital that interacts with π-orbitals of alkenes and alkynes, and this interaction forms the first step of the hydrozirconation reaction. The resulting unstable π complex is rapidly converted to a σ complex by hydrogen migration of H–Zr to the unsaturated C–C double or triple bonds in an intramolecular manner. These alkyl or alkenyl sigma zirconium complexes can be subsequently used to construct a variety of new bonds with electrophiles, and allow various transformations by a combination of hydrometalation with transmetalation.

Hydrozirconation is one of the most reliable methods to convert alkenes or alkynes into organometallic reagents, and has found increasing application in organic synthesis.

8.23.2 Hydrozirconation Reagents: Schwartz Reagent Related and Others

Hydrozirconation can be historically traced back to the year 1970, when Cp_2ZrHCl was synthesized first by Wailes and coworkers and later used for hydrozirconation of alkenes and alkynes.[5,6] Hydrozirconation became very popular with the synthetic applications developed by Schwartz and coworkers, as hydrozirconation was found to be very valuable for the formation of functionalized alkanes and stereodefined functionalized alkenes under mild conditions with high yield and high regioselectivity.[1–4] For this reason the reagent Cp_2ZrHCl got started to be called the 'Schwartz reagent.' The compound Cp_2ZrHCl can be easily prepared by reduction of Cp_2ZrCl_2 with various hydride sources such as $LiAlH_4$, $LiAlH(O^tBu)_3$, $NaAlH_2(OCH_2CH_2OCH_3)_2$, or $^iBu_2AlH$.[5–7] The possible by-product Cp_2ZrH_2 can be converted into the desired product by a simple treatment with CH_2Cl_2 (Scheme 1). The yield was usually very high but the purity was not good enough. Therefore, these reaction conditions were carefully optimized in later patented work.[8] The reagent is relatively stable under dry air for several weeks.



Scheme 1

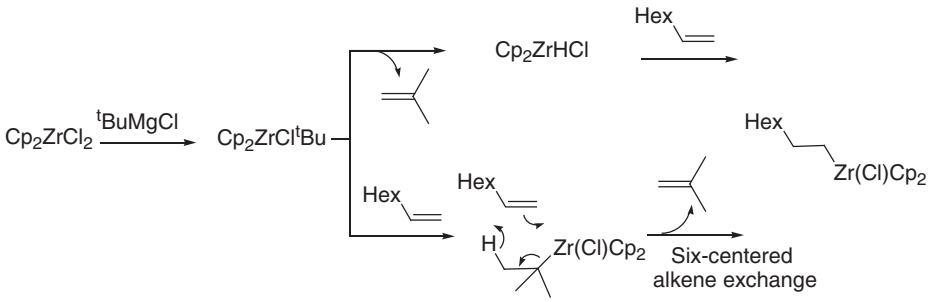
To make it more practicable, a number of modifications have been made to the generation process and the structure of the original Schwartz reagent.

8.23.2.1 Modification of the Generation Process of the Schwartz Reagent

An attractive alternative is the *in situ* synthesized Schwartz reagent, which was extensively studied by several groups including Negishi and coworkers when their synthesis required fresh Cp_2ZrHCl for hydrozirconation. Commercially available Cp_2ZrHCl slowly decomposes once opened to air. Repurification is not easy because of its poor solubility in organic solvents. To avoid this

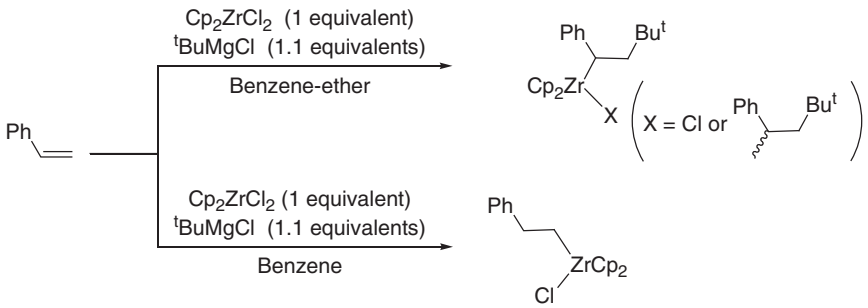
problem, freshly generated Cp_2ZrHCl is needed. The reagent immediately reacts with a substrate to give the hydrozirconation product.

The *in situ* generation of Cp_2ZrHCl can be achieved through a facile elimination, the reverse of hydrozirconation. Negishi and coworkers investigated the reaction of Cp_2ZrCl_2 with 1 equivalent of alkyl metal reagents. Simply mixing monosubstituted alkenes with 1 equivalent of Cp_2ZrCl_2 and 1.1 equivalents of ^{t}BuMgCl in benzene–ether (5:l) at room temperature gave the corresponding monoalkylzirconium derivatives in excellent yields.[9] The reaction was proposed to proceed by a transmetalation–elimination–hydrozirconation mechanism, or alternatively transmetalation and then a six-centered alkene exchange mechanism (**Scheme 2**).



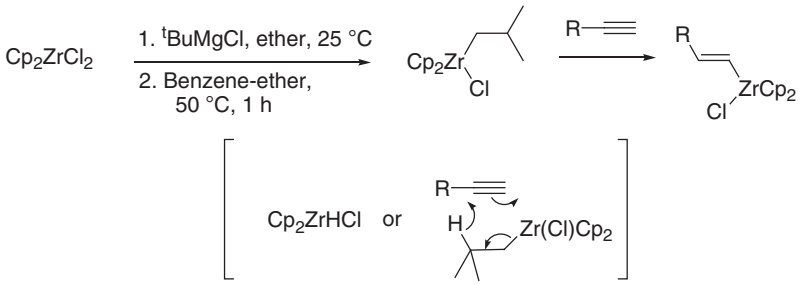
Scheme 2

However, when the same set of conditions was used for conjugated alkenes, such as styrene, 1,3-butadiene, and isoprene, a novel *tert*-butylzirconation reaction proceeded (**Scheme 3**). To overcome this limitation, the reaction was carried out in a different way. Reagents Cp_2ZrCl_2 and *t*-BuMgCl were premixed in benzene in the absence of ether and then added with styrene. Hydrozirconation was found to be the major course of the reaction, the reason for which remains to be clarified.



Scheme 3

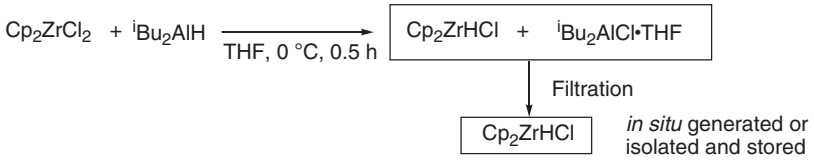
This success of alkene hydrozirconation using Cp_2ZrCl^tBu as a Schwartz reagent precursor was then applied to alkynes, especially terminal alkynes for simplicity. The result, however, was not satisfying. Hydrozirconation of 1-octyne, for example, gave a mixture of 1-octene and *n*-octane after hydrolysis. The reaction conditions were optimized again (**Scheme 4**). Complex Cp_2ZrCl_2 was treated with 1 equivalent of ^{t}BuMgCl in ether at 25 °C and then at 50 °C for 1 h in benzene–ether (5:1) apparently to form the Cp_2ZrCl^iBu complex. The premixed reagent was applied to the alkyne to produce the desired (*E*)-l-octenylzirconocene chloride in 90% yield. In this case, Cp_2ZrCl^iBu (not Cp_2ZrCl^tBu) was described as the Schwartz reagent precursor.[10] Hydrozirconation might occur via Cp_2ZrHCl complex or a concerted six-centered process for hydrocarbon ligand exchange.



Scheme 4

Cp_2ZrCl^iBu has been employed with various monosubstituted alkenes. In some sluggish cases, the reaction could be remarkably accelerated by a catalytic amount of Lewis acidic metal compounds, most notably $AlCl_3$, Me_3SiI, and Pd complexes such as Li_2PdCl_4 and $Pd(PPh_3)_2Cl_2$.[11]

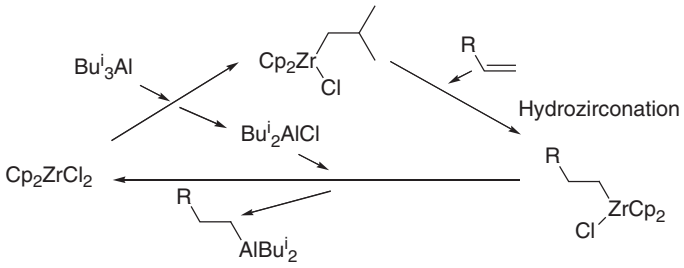
A combination of Cp_2ZrCl_2 and diisobutylaluminum hydride (DIBAL-H) provides a convenient and genuine equivalent to Cp_2ZrHCl, or even more than that. It represents one of the most practical methods for the *in situ* formation of Cp_2ZrHCl, which can be used especially for the conversion of terminal alkynes to alkenyl iodides, which are important as synthetic building blocks. The reaction of Cp_2ZrCl_2 with DIBAL-H was studied in detail by Negishi and coworkers. DIBAL-H was slowly added into a tetrahydrofuran (THF) solution of Cp_2ZrCl_2 at 0 °C to form, monitored by nuclear magnetic resonance (NMR) spectroscopy, a 1:1 mixture of Cp_2ZrHCl and $^iBu_2AlCl$–THF cleanly. The mixture could be conveniently separated by filtration to leave fresh Cp_2ZrHCl. This could also be stored and used (Scheme 5).[12]



Scheme 5

Hydrozirconation of alkenes with *in situ* generated Cp_2ZrHCl produces alkylzirconocene chlorides. A stoichiometric amount of zirconium is needed in those processes. Interestingly, in a previous report on Zr-catalyzed hydroalumination with $^iBu_3Al$ and a catalytic amount of Cp_2ZrCl_2 by Negishi et al., the reaction was proposed to involve hydrozirconation.[13] Complex Cp_2ZrCl_2 reacts with $^iBu_3Al$ to produce Cp_2ZrCl^iBu.

This convenient and genuine equivalent to Cp_2ZrHCl hydrozirconates monosubstituted alkenes smoothly (Scheme 6). The product alkylzirconocene complex undergoes transmetalation with $^iBu_2AlCl$ to give Cp_2ZrCl_2 complex and alkylaluminum compounds.



Scheme 6

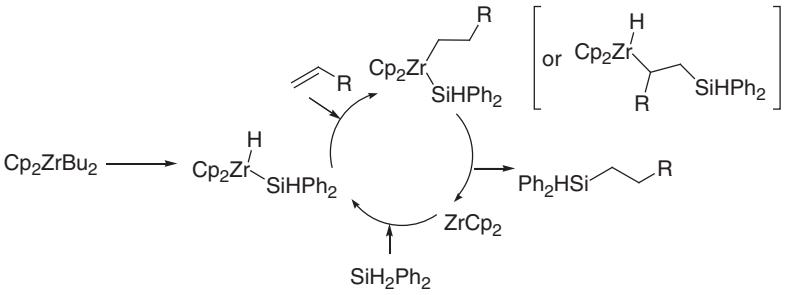
Takahashi et al. developed a highly regioselective Zr-catalyzed hydrosilation reaction of alkenes. Catalytic amounts of Cp_2ZrBu_2 (known as the Negishi reagent), *in situ* generated from the reaction of Cp_2ZrCl_2 with 2 equivalents of *n*-BuLi, was added to a mixture of alkenes and SiH_2Ph to give the desired hydrosilation products in an anti-Markovnikov manner.[14] The authors presumed the reaction proceeded via hydrozirconation (or silylzirconation) of the alkene with $Cp_2ZrH(SiHPh_2)$ and subsequent formation of C–Si (or C–H) bond by reductive elimination (Scheme 7). Moreover, Takahashi et al. proposed an alternative route involving the five-membered intermediates as shown in Scheme 7.[14c]

However, in sharp contrast to the above reaction, the catalytic system of Cp_2ZrCl_2 with 3 equivalents of *n*-BuLi promoted hydrosilation of styrene derivatives in the Markovnikov addition manner.[15] As described by Takahashi et al., the change in regioselectivity was likely due to the different active zirconium species.

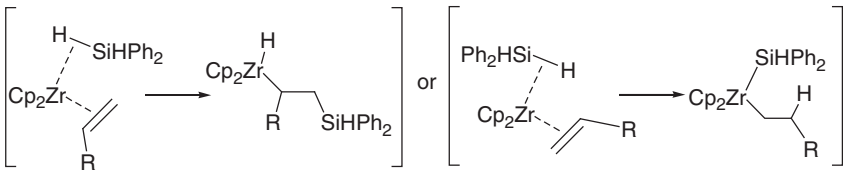
Reaction of Cp_2ZrCl_2 with the hydrogen sources such as Red-Al,[16] $LiEt_3BH$,[17] etc. provides fresh Cp_2ZrHCl that can be used for hydrozirconation directly. Scheme 8 shows one interesting intramolecular hydrozirconation reaction. $NaBEt_3H$ was used as a hydrogen source.[18] Reaction of the monochloro compound with equimolar amounts of sodium triethylborohydride, in THF and at room temperature, afforded the hydride complex (Scheme 8). In addition, the allyl group was isomerized to a 1-propene group via intramolecular hydrozirconation and elimination.

Replacing one hydride of Cp_2ZrH_2 by a halogen atom or other anions *in situ* is also a frequently used method. Complex Cp_2ZrH_2 is readily available and air stable, but not effective for addition to alkenes or alkynes. As shown in Table 1, it readily reacts with CH_2Cl_2, CH_2Br_2, MEM-I, and TMSOTf, etc. *in situ* to give the desired monohydride zirconocenes.[19]

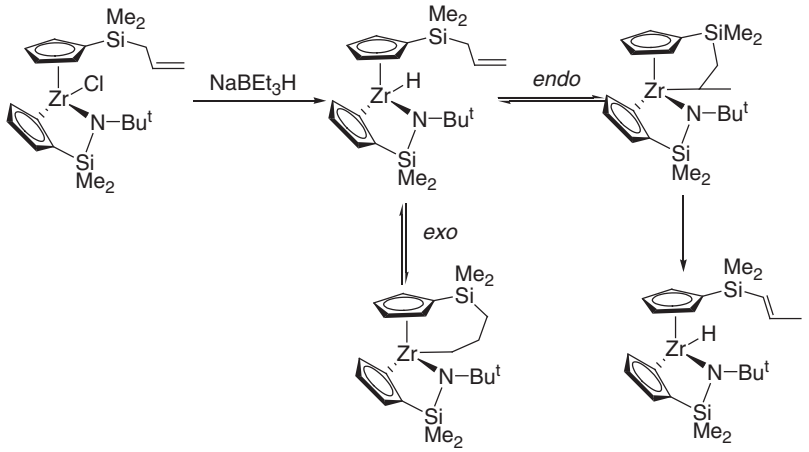
It should be noted that *in situ* formed Schwartz reagents could provide internal trapping products (Scheme 9). Treatment of 4-octene with a combination of zirconocene dihydride and TMSOTf gave, after bromination with Br_2, a mixture of 1-bromooctane and 4-bromooctane in a 1:1.8 ratio. In contrast, independently prepared $Cp_2ZrH(OTf)$ did not give any internal trapping product. Furthermore, no 2- or 3-brominated octanes were detected in either reactions.



Two five-membered intermediates

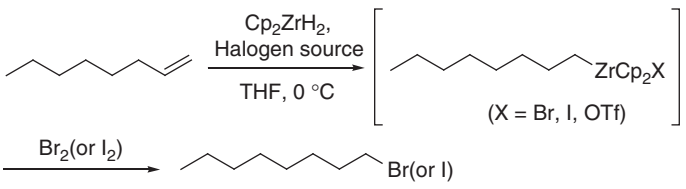


Scheme 7

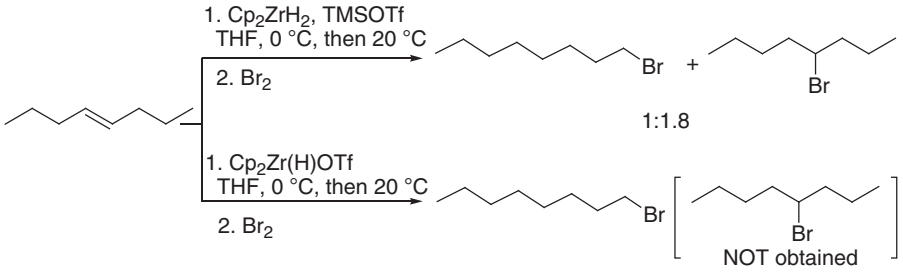


Scheme 8

Table 1 Hydrozirconation and halogenation of 1-octene with Cp_2ZrH_2



Entry	*Halogen source*	*Yield (%)*
1	$C_2H_2Br_2$	90
2	$C_2H_2I_2$	70
3	$C_2H_3OCH_2Br$	82
4	I_2	49
5	MeOTf	63
6	TMSOTf	93



Scheme 9

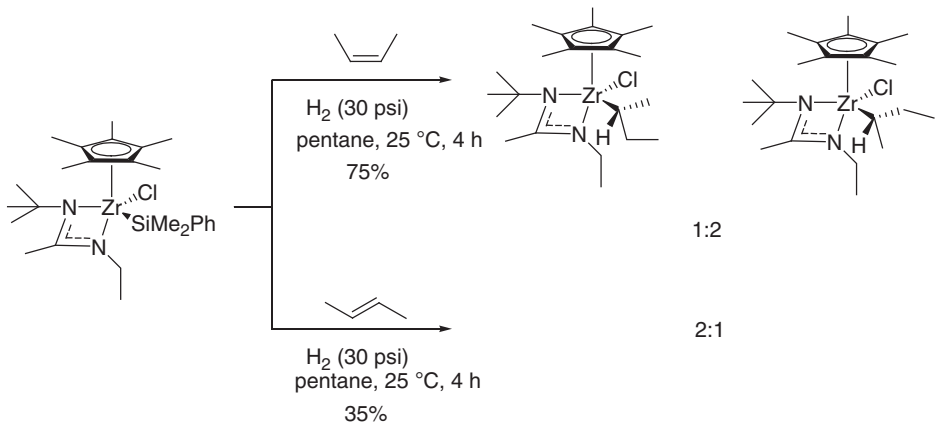
8.23.2.2 Structure Modification of Schwartz Reagent

To find out good alternatives to the Schwartz reagent, a variety of Zr–H-centered complexes have been developed by replacing the chloride or the Cp ligand. The effects of different ligands on reactivities and selectivities in hydrozirconation have also been extensively studied.

Several derivatives of Cp_2ZrHCl have been reported, such as [$(Me_2Si)(C_5H_4)ZrHC1$], [$(Me_5C_5)ZrHCl$], [$(MeC_5H_4ZrHCl$], [$(MeC_5H_4)HfHCl$].[20] For example, $(MeCp)_2ZrHCl$ was found to show alkene hydrozirconation 6–7 times faster than Cp_2ZrHCl, probably due to the better solubility of $(MeCp)_2ZrHCl$ than Cp_2ZrHCl.[20e]

Complex $(SiO_2)ZrH_2$ was designed as a hard ligand containing analog of Cp_2ZrHCl. The reactivity was very different, and the hydrozirconation of alkenes and alkynes was always followed by insertion reactions.[21]

Hydrozirconation of internal alkenes specifically gives the primary alkylzirconocene complex, due to facile Zr–H eliminations/reinsertions that allow the Cp_2ZrCl moiety to 'chain-walk' to the least sterically hindered terminal position of the alkyl chain. To overcome this regioselectivity, a cyclopentadienyl/amidinate ligand containing zirconium complex was prepared. On treating with H_2, the complex could be applied for hydrozirconation of the internal alkenes (**Scheme 10**). Another interesting point of this system is that this hydrozirconation is asymmetric.[22]

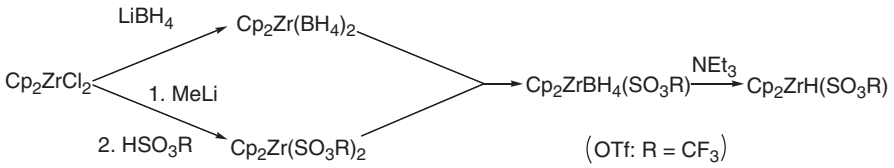


Scheme 10

Exchange of the chloride ligand for other anions is a straightforward way for optimizing the performances of the original Schwartz reagent. Compared with introduction of substituents to the Cp ligand, Cl ligand exchange is more convenient. The anions affect the electronic properties of the hydride and the alkyl groups greatly through the σ-bond to Zr. This dramatically increases the possibilities for controlling the hydrozirconation reaction. For this purpose, a variety of anions, such as Br,[23] OSO_2R,[24,25] OR,[26] have been tested.

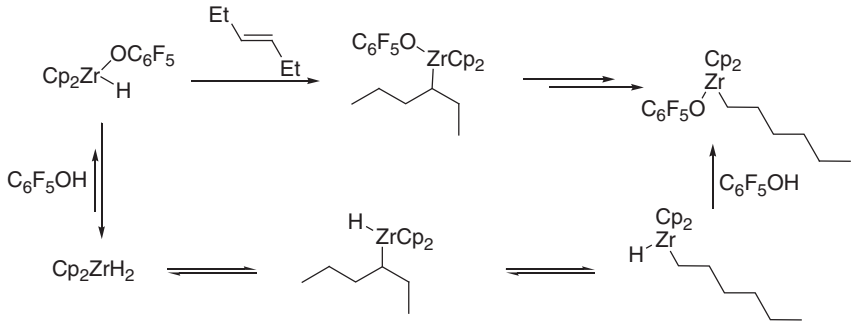
An attractive alternative to Schwartz reagent $Cp_2ZrH(OSO_2CF_3)$ was synthesized (**Scheme 11**). With the help of the sulfonate anion, this complex could be dissolved in THF. From this solution, large off-white needles were obtained. The solid-state structure showed a defined dimeric arrangement, where two hydrides bridge between two zirconocene triflate moieties. This soluble reagent was suitable for NMR studies. The hydrozirconation reaction could be monitored by NMR if needed. Moreover, this well-defined and easily accessible hydrozirconation reagent is very reactive. Monosubstituted alkenes and terminal alkynes were stoichiometrically converted into alkyl and alkenylzirconocene triflates within seconds at room temperature.[25]

Compared with the chloride, the sulfonate is a weaker coordinating anion. Alkylzirconocene sulfonate is highly prone to undergo β–hydride elimination. In Schaper et al.'s attempts,[26] Lewis basic alkoxide ligand was employed more which was supposed to stabilize the zirconocene complex after hydrozirconation. However, synthesis of the zirconocene alkoxide complexes



Scheme 11

$Cp_2ZrH(OR)$ was cumbersome due to fast disproportionation to Cp_2ZrH_2 and $Cp_2Zr(OR)_2$. In one special example, addition of C_6F_5OH to Cp_2ZrH_2 in the presence of excess 1-hexene in C_6D_6 yielded a dark solution after heating for 1.5 h at 70 °C (Scheme 12). The only species present in its ^1H NMR spectrum were $Cp_2Zr(^nHex)OC_6F_5$ and $Cp_2Zr(OC_6F_5)_2$ (6%). Hydrozirconation with $Cp_2ZrH(OC_6F_5)$ can thus be achieved on a reasonable time scale by preparing it *in situ* from commercially available precursors.

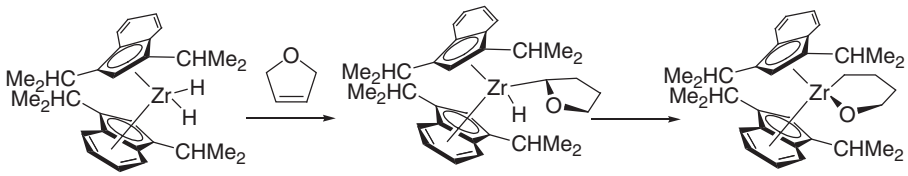


Scheme 12

It should be noted that several analogs of $Cp_2ZrH(OR)$ were successfully synthesized. One is bis(indenyl)ZrH(OR) by Chirik et al.[27] Another is $(C_5Me_5)_2ZrH(OR)$ by Marks and by Stephan, independently.[28,29] It is most likely the bulky indenyl or Cp^* ligand that made the complexes less prone to disproportionate dihydride and dialkoxide complexes.

8.23.2.3 Other Reagents

During the preparation of Cp_2ZrHCl by reduction of Cp_2ZrCl_2 with various hydride sources, by-product Cp_2ZrH_2 was unavoidably formed. Although Cp_2ZrH_2 was reactive toward insertion into unsaturated carbon bonds, this reagent cannot be conveniently handled and the hydrozirconation was usually uncontrollable. However, several analogs of Cp_2ZrH_2 with more bulky indenyl or pentamethylcyclopentadienyl ligand,[27,30] or hafnium and titanium complexes,[31] have been reported to show good activity for hydrometalation. For example, the bis(indenyl)zirconium dihydride derivative reacted with dihydrofuran at −78 °C followed by warming to ambient temperature to give the zirconocene alkyl hydride complex, where the zirconium has migrated to the carbon next to the oxygen atom.[27a] This complex gradually converted into the product of THF scission via C–O bond cleavage under mild conditions (Scheme 13).

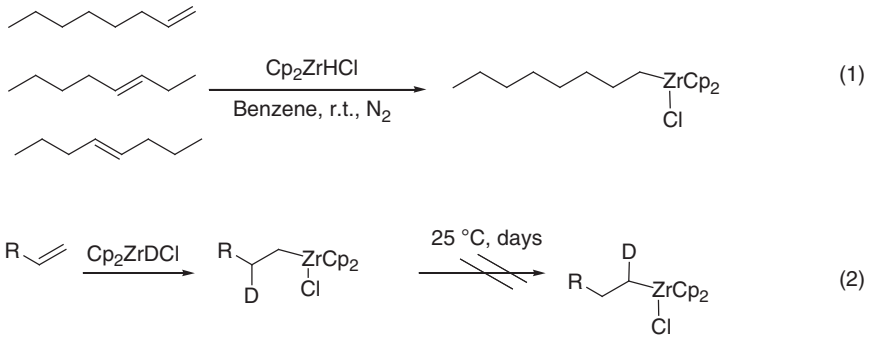


Scheme 13

8.23.3 Hydrozirconation of Alkene

Addition of Schwartz reagent Cp_2ZrHCl to an alkene gives an alkyl zirconocene σ-complex quantitatively. No further alkene insertion reaction was observed even with an excess of alkene. The alkylzirconocene complex can be rapidly isomerized. Even when a mixture of double bond regioisomers of octene was treated with Cp_2ZrHCl, only the primary alkylzirconocene complex

was finally obtained under mild conditions[32] (Scheme 14, equation 1). This isomerization is likely due to the combination of β-hydride elimination and hydrozirconation. However, there is no such evidence for such rearrangement.[33] When a monosubstituted alkene reacted with Cp_2ZrDCl, the generated β-D alkylzirconocene showed a single peak in the $\{^1H\}^2H$ NMR spectrum. No change was observed over the course of 1 week at 296 K, which indicated no isomerization to α-D alkylzirconocene occurred (Scheme 14, equation 2). Likewise, a mixture of $Cp_2Zr(CH_2CH_2CH_3)Cl$ and $^{13}CH_2CHCH_3$ in benzene-d6 did not undergo isotopic rearrangement at 296 K over the course of 1 week.



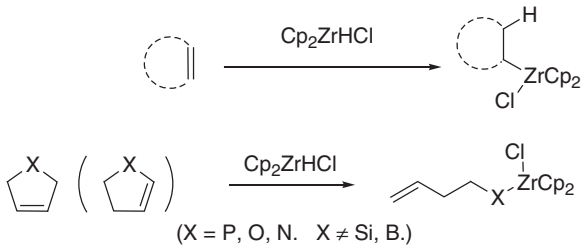
Scheme 14

The regioselectivity is tightly related to the steric hindrance of the bulky 'Cp_2Zr' moiety, and the least sterically hindered terminal alkylzirconocene complex is usually the major product. For example, a monosubstituted alkene can be hydrozirconated to give a linear alkyl zirconocene complex in high selectivity following the anti-Markovnikov and the *cis* addition rule (Scheme 15). The branched regioisomer is not favored in this process due to the large steric repulsion between the Cp and the substituent attached to the alkene.



Scheme 15

Reaction of cyclic alkenes with Cp_2ZrHCl theoretically poses no issues of selectivity since all carbons are equal, and the zirconocene moiety can move freely on the alkyl ring. However, in cases of heterocycles, the situation is very different. For example, five-membered phospholene and dihydrofuran and pyrroline gave the corresponding ring-opening products by Cp_2ZrHCl (Scheme 16). However, Si or B containing cyclopentene was not suitable for the ring-opening reaction.[34] The double bonds of these rings were moved from the β to the α position relative to Si and B in the presence of a catalytic amount of Cp_2ZrHCl.



Scheme 16

The resulting alkylmetal complex is air sensitive and thermally unstable. The reaction has to be carried out in an inert atmosphere. The reactivity of the alkylzirconocene complex is remarkably decreased by the steric hindrance of the bulky zirconocene moiety. Therefore, only with a limited number of electrophiles, in particular small ones, can the reaction take place smoothly. However, probably due to this low reactivity, the complex has good functional group tolerance. Furthermore, to obtain

higher or diverse reactivity in subsequent reactions, transmetalation can be employed to produce widespread synthetic applications.

8.23.3.1 Hydrozirconation of General Alkenes

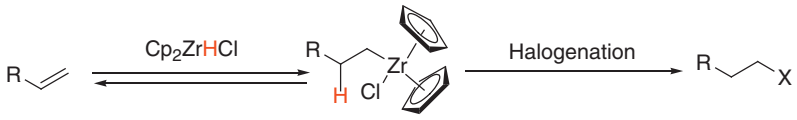
Hydrozirconation of linear alkenes with Cp_2ZrHCl readily gives primary alkylzirconocene complexes. Due to the very bulky zirconocene moiety, these react with small molecules such as halogens, oxygen, carbon monoxide, etc. as mentioned in Section 8.23.3. This provides reliable protocols for the formation of the corresponding alkyl halides and primary alcohols.

8.23.3.1.1 Transformation by halogenation and other heteroatom

8.23.3.1.1.1 Halogenation

Halogenation of alkylzirconocene complexes provides a reliable method for synthesis of alkyl halides, which are general building blocks in organic synthesis. Although direct halogenation of alkenes is the most straightforward way, there are some fundamental problems. The reaction is very poorly efficient and poorly regioselective.

Alkenes are more commonly used as alkyl bromide precursors. Alkene derivatives are found in a large number of natural products, and easily obtained as fine chemicals (Scheme 17). Hydrobromination of alkenes gives alkyl bromides in Markovnikov manner, whereas a combination of hydrozirconation and halogenation generally gives anti-Markovnikov addition products. This protocol is so reliable that this method is used for many synthetic applications, especially in total synthesis. These applications will be introduced in the following sections.



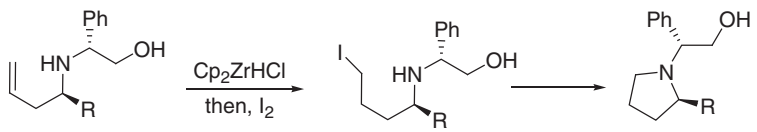
Scheme 17

Schwartz et al. investigated halogenation of the alkylzirconocene after hydrozirconation.[32] They reported that a benzene solution of a mixture of the alkylzirconocene with Br_2, I_2, or $PhIC1_2$ gave alkyl halides, as shown in Table 2.

Table 2 Hydrozirconation and halogenation of alkenes

Entry	*Olefin*	*Halogen*	*Product*	*Yield (%)*
1	1-Octene or 4-octene	Br_2	1-Bromooctane	96
2	1-Octene or 4-octene	I_2	1-Iodooctane	91
3	1-Octene or 4-octene	$PhICl_2$	1-Chlorooctane	65
4	2-Methyl-2-butane	Br_2	1-Bromo-3-methylbutene	100
5	Cyclohexene	Br_2	Bromocyclohexane	95

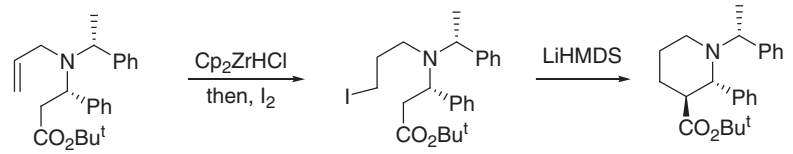
This method has very broad application for the synthesis of alkyl halides. The hydrozirconation and the sequential generation of an electrophilic site displays remarkable chemoselectivity.[35] For example, synthesis of pyrrolidine derivatives by the hydrozirconation–iodination of alkene moiety is shown in Scheme 18. Hydrozirconation and iodination gave an iodo compound. Subsequent intramolecular *N*-alkylation gave the desired pyrrolidine derivative successfully.[36]



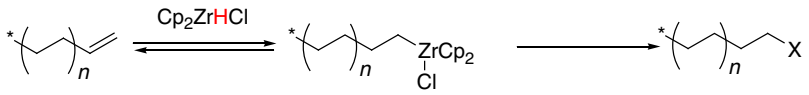
Scheme 18

Szymoniak et al. reported a straightforward route to the enantiomerically pure piperidine esters which are present in a broad range of biologically active compounds (Scheme 19).[37] The synthetic route involved hydrozirconation of an alkene and sequential halogenation, followed by cyclization.

Not only the simple alkenes, but also macromolecular alkenes can undergo hydrozirconation efficiently. This latter reaction could be applied to the synthesis of functionalized polymers. Tang et al. reported that 1,2-polybutadiene was treated with Schwartz reagent Cp_2ZrHCl to give zirconocene substituted polymer, which was followed by anti-Markovnikov halogenation to give the reactive polymer (Scheme 20).[38] The reactive polymer was converted into various functional polymers after



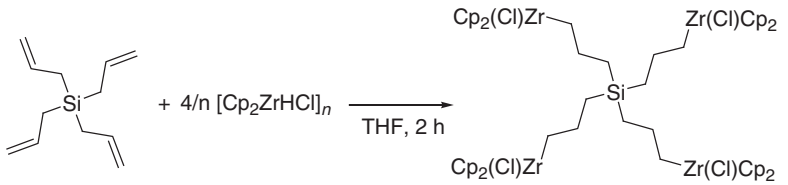
Scheme 19



Scheme 20

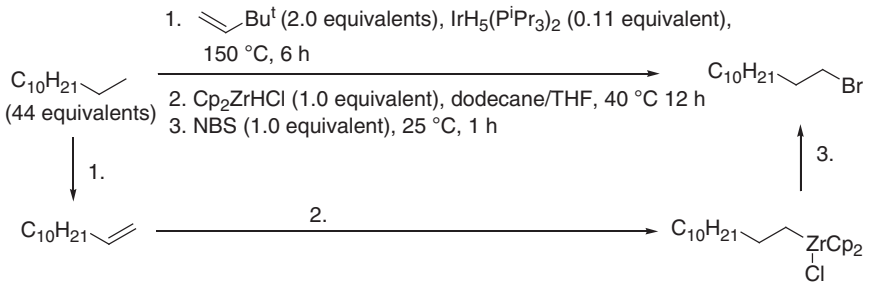
macromolecular substitution reactions with nucleophiles (amines, phenols, alcohols, carbanions, carboxylates, and azide, including macromolecular ones).

Hydrozirconation by the Schwartz reagent usually gives quantitative yield, which makes it quite useful even in polyalkenes such as highly branched three-dimensional molecules. Meijboom et al. have utilized Schwartz reagent to functionalize a series of organic dendrimers to new organometallic dendrimers (Scheme 21).[39] The reaction of $[Cp_2ZrHCl]_n$ with $Si(CH_2CH{=}CH_2)_4$ resulted in the all-insertion product $Si[(CH_2)_3(Cp_2ZrCl)]_4$ as a yellow oil.



Scheme 21

Another interesting example follows. Although direct halogenation of an alkane is difficult to achieve in one step, a similar job can be done by a combination of dehydrogenation and hydrozirconation and halogenation in this order.[40] Kuninobu et al. demonstrated that *n*-dodecane could be treated with a catalytic amount of iridium complex $IrH_5(P^iPr_3)_2$ and 3,3-dimethyl-1-butene (hydrogen acceptor) to give 1-dodecene, which was then subjected to hydrozirconation and bromination successively to give 1-bromododecane in 57% yield as a single product (Scheme 22). No other bromine regioisomers or polybromoalkanes were formed.



Scheme 22

8.23.3.1.1.2 Oxidation reactions

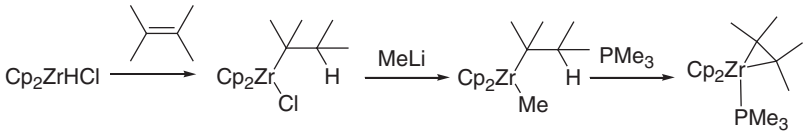
Schwarz et al. reported oxidation of alkylzirconium compounds in good yields, by various peroxides and oxygen.[41] Several years later, Gibson reported that hydrozirconation of internal alkenes followed by oxidation with anhydrous *t*-butyl hydroperoxide generated primary alcohols in good yields and with high purity.[42] For example, hydrozirconation of 1-octene followed by oxidation with 1 equivalent of 70% *tert*-butyl hydroperoxide in THF at 40 °C gave 1-octanol in 76% yield (Table 3). Various internal or cyclic alkenes were employed in this reaction, and all of them gave good yields of primary or cyclic alcohols.

Table 3 Hydrozirconation and oxidation reactions of alkenes

Entry	*Olefin*	*Cp_2ZrHCl (equivalent)*	*Time (h)*	*Yield (%)*
1	1-Octene	1.0	4	76
2	*trans*-4-Octene	1.5	24	73
3	Cyclohexene	1.5	24	63
4	7-Tetradecene	1.5	72	70
5	15-Triacontene	2.0	96	68

8.23.3.1.2 β–H abstraction

Thermal decomposition of zirconocene derivatives containing one or more β–H atoms has been widely utilized in various useful transformations. Alkylzirconocene chloride does not show this type of reactivity, but replacing the chlorine atoms with alkyl groups led to dialkylzirconocenes.[43] Thus, hydrozirconation of an alkene followed by methylation gave a dialkylzirconocene complex (Scheme 23). This underwent β–H abstraction to give a zirconacyclopropane complex in the presence of PMe_3. A similar reaction was also found in the case of alkynes.

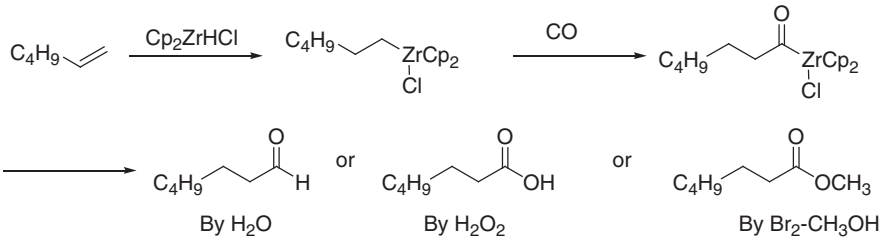


Scheme 23

8.23.3.1.3 Insertion with unsaturated bonds

8.23.3.1.3.1 Insertion of carbon monoxide into the carbon–zirconium bond

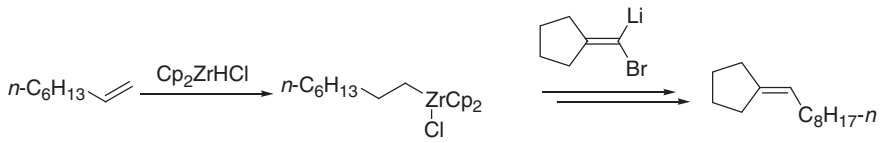
Schwartz et al. described that alkylzirconium compounds are versatile intermediates for organic synthesis. The Zr–C bonds were able to react with a variety of electrophilic reagents (Scheme 24). In one example they reported, the hexylzirconocene chloride underwent a clean and high yielding insertion of CO into the Zr–C bond to produce the first example of a zirconium-acyl complex[44] that was readily converted into aldehyde, carboxylic acid, or ester under different conditions.



Scheme 24

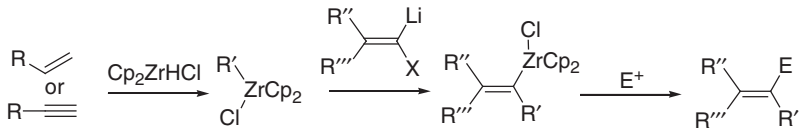
8.23.3.1.3.2 Insertion of vinyl carbenoid into alkylzirconocenes

Insertion of components with carbenoid properties (CO, RNC) into carbon–metal bonds is highly valuable. Insertion of CO into the Zr–C bond can accomplish the transformation of simple alkenes and CO into aldehydes, carboxylic acids, and so on. A particularly interesting elaboration method, the insertion of 1,1′-haloorganolithium species into *n*-octylzirconocene chloride described by Negishi et al., provided useful access to substituted olefins (Scheme 25).[45]



Scheme 25

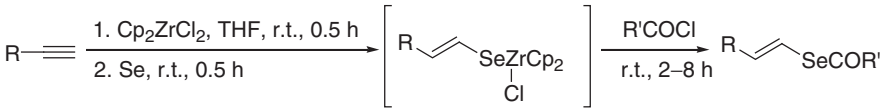
Subsequently, Whitby et al. reported insertion of 1-halo-1-lithio-1-alkenes into alkyl- or alkenylzirconocene chloride by extending to a much broader scope.[46] The reaction provides easy access to many structures including terminal (3*E*)- and (3*Z*)-1,3-dienes and (3*E*,5*E*)- and (3*Z*,5*E*)-1,3,5-trienes, and internal (*E*,*Z*)-dienes, (*E*,*Z*,*E*)-trienes, and (1*E*,3*Z*)- 1,3-dien-5-ynes, as shown in Scheme 26.



Scheme 26

8.23.3.1.3.3 Insertion of elemental selenium into Csp^2–Zr bond

Huang et al. demonstrated insertion of elemental selenium into the Zr–C double bond of alkenylzirconocene complexes.[47] The alkenylzirconocene complexes were generated *in situ* by hydrozirconation of terminal alkynes with Cp_2ZrHCl reagent (Scheme 27). The tandem reactions proceeded smoothly in THF at room temperature. The final products, a series of *(E)*-vinylic selenol esters, were obtained in good yields.



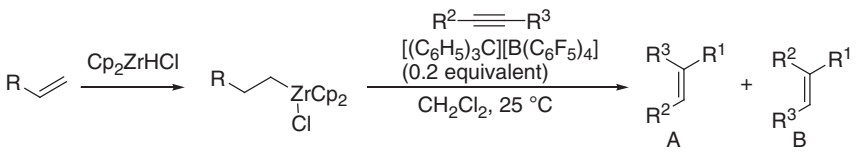
Scheme 27

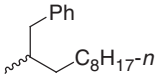
8.23.3.1.3.4 Alkylzirconation of alkynes

Alkylzirconocene chloride reacted with alkynes in the presence of $[(C_6H_5)_3C][B(C_6F_5)_4]$ as an initiator to afford di- or tri-substituted alkenes smoothly.[48] In particular, unsymmetrical alkynes gave the alkylzirconation products with high regioselectivity. The regioselectivity was sensitive to the steric effect of the substituents of alkynes. The major isomer resulted from alkyl transfer to the sterically more congested side of the C–C triple bond.

For example, hydrozirconating 1-hexene gave hexylzirconocene chloride.[49] This complex reacted with a dialkyl-substituted alkyne to give alkenes in 68% yield after hydrolysis (Table 4). The regioselectivity was very high at 96:4 and the major one had the hexyl group attached to the same side as the larger alkyl group of the alkyne, although two alkyl substituents were electronically comparable (entry 1). When a diarylacetylene was employed in entry 2, the hexyl group was *cis* to the *o*-chlorophenyl group. The ratio of the isomers was 96:4. Entries 3–6 show the variation of alkylzirconiums and alkynes in good yields of 73–96% and with high regioselectivity.

Table 4 Reaction of alkylzirconocene chloride with alkynes

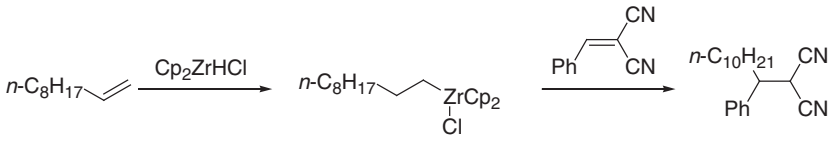


Entry	*R*	*R*^{2}	*R*^{3}	*Time (h)*	*Yield (%)*[a] *(A:B)*
1	*n*-C_4H_9	*n*-C_4H_9		7	68 (96:4)
2	*n*-C_4H_9	C_6H_5	*o*-C_6H_4Cl	7	75 (96:4)
3	*n*-C_4H_9	*n*-C_4H_9	*o*-C_6H_4OMe	0.25	96 (97:3)
4	*n*-C_4H_9	*n*-C_4H_9	*o*-C_6H_4Me	2	73 (>98:<2)
5	$C_6H_5(CH_2)_2$	C_6H_5	*o*-C_6H_4OMe	1.5	88 (94:6)
6[b]	$OTBDPS(CH_2)_4$	C_6H_5	*o*-C_6H_4OMe	1.5	88 (95:5)

[a]Gas chromatography yield.
[b]TBDPS is equal to *t*-butyldiphenylsilyl.

8.23.3.1.3.5 Direct alkylzirconation of alkenes

Direct addition of the organometallic compounds to activated alkenes provides useful C–C bond-forming methods in organic synthesis. However, alkylzirconocene derivatives, which are readily available by hydrozirconating alkenes, usually cannot react with alkenes. Takahashi et al. reported the direct addition of alkylzirconocene to activated alkenes.[50] The study was started from an alkene with two electron-withdrawing CN groups such as benzylidenemalononitrile. Addition of *in situ* formed decylzirconocene chloride to benzylidenemalononitrile gave the desired product in 86% yield (Scheme 28). This reaction was then applied to a variety of zirconium complexes and activated alkenes successfully.



Scheme 28

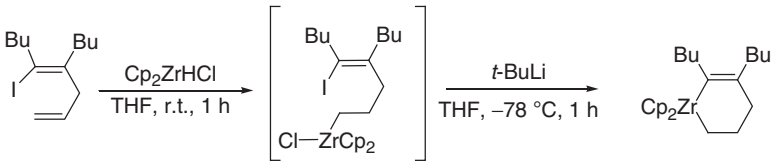
8.23.3.1.4 Transmetalation

8.23.3.1.4.1 Zirconium and aluminum exchange

Transmetalation of Zr to Al was studied by Schwartz when they tried to use alkylzirconocene complex for carbon–carbon bond formation reactions. The reaction worked well. The *in situ* generated alkylzirconocene reacted with $AlCl_3$ conveniently and was followed by addition of acid chloride to give a variety of ketones in good yields.[51]

8.23.3.1.4.2 Transmetalation with Li

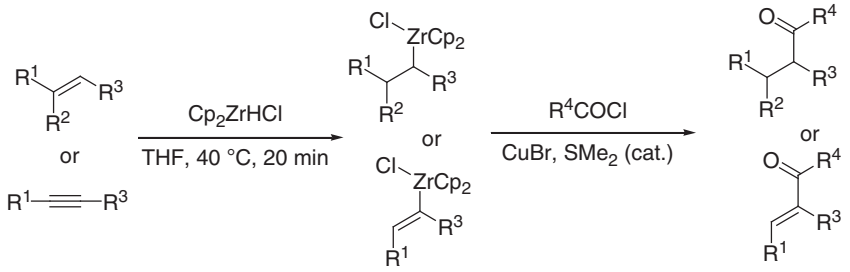
Addition of Cp_2ZrHCl to C═C double bonds provides a very useful method to afford Zr–C bonds. Thus formed Zr–C bond can be applied for organic synthesis, and the Zr–Cl remains inert. Interestingly, Xi et al., due to their research interest in active metallacycles,[52] converted Zr–Cl into Zr–C via an intramolecular transmetalation to form six-membered metallacycles. In one case, 1-iodo-1,4-pentadiene derivative was treated with Cp_2ZrHCl in THF at room temperature for 1 h to give an intermediate. The *in situ* generated pale yellow solution of the intermediate was treated with 2 equivalents of *t*-BuLi at −78 °C to form a six-membered metallacycle without isolation, the structure of which was supported by a series of further reactions (Scheme 29).



Scheme 29

8.23.3.1.4.3 Replacing Zr with Cu

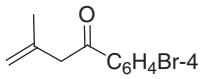
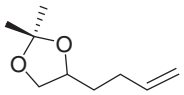
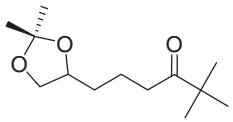
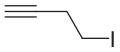
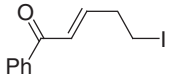
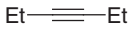
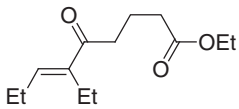
Hydrozirconation of alkene and alkyne produces alkyl and alkenylzirconocene complexes, respectively. Reaction of those zirconocene reagents with acyl chlorides gave a very straightforward route to ketone derivatives. However, the reaction needed to be carried out in the presence of copper catalyst CuBr dimethyl sulfide complex, as described by Wipf and Smitrovich (Scheme 30).[53]



Scheme 30

Reaction scope was found to be very broad since the starting material alkenes or alkynes and especially the acyl chloride can tolerate various functional groups. As shown in Table 5, alkenes and alkynes could be terminal or internal, or with functional groups (entries 6 and 7). Acyl chloride derivatives with a wide variety of functional groups (entries 2, 5, and 8) and even with sterically hindered substituents (entry 6) were applicable in this process. All cases gave moderate to high yields of the ketone products. There were, however, unavoidably contaminated by the products from further reactions of ketone with organometallic reagents.

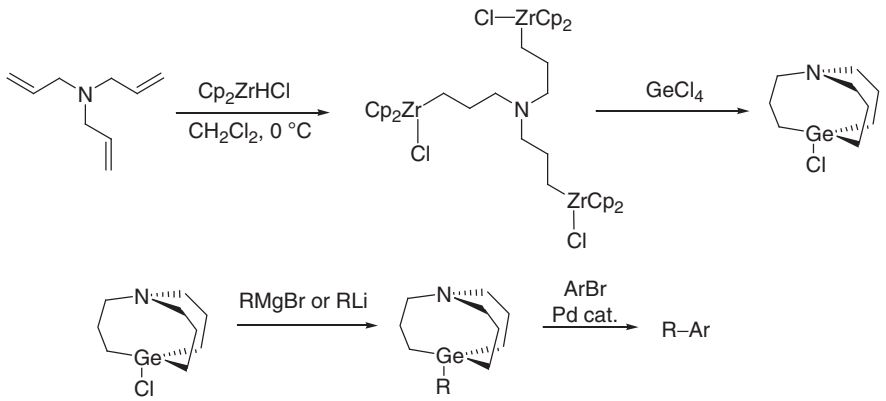
Table 5 Reaction of hydrozirconated alkenes or alkynes with acyl chloride in the presence of CuBr

Entry	*Alkene or alkyne*	*Carbonyl chloride*	*Product*	*Yield (%)*[a]
1	1-hexene	PhCOCl	*n*-hexylCOPh	83
2		4-BrC_6H_4COCl		51
3	Cyclohexene	PhCOCl	*c*-$C_6H_{11}COPh$	69
4	Cyclohexene	EtCOCl	*c*-$C_6H_{11}COEt$	90
5	Cyclohexene	$ClCOC_3H_6CO_2Me$	*c*-$C_6H_{11}COC_3H_6CO_2Me$	78
6		Me_3CCOCl		77
7		PhCOCl		79
8		$ClCOC_2H_4CO_2Et$		46

[a]Isolated yield.

8.23.3.1.4.4 Replacing Zr with Ge

Transmetalation of zirconium to germanium has been studied by Daran et al.[54] This process has been utilized for the synthesis of 1-aza-5-germa-5-organobicyclo[3,3,3]undecanes and organogermanium dendrimers (Scheme 31). Hydrozirconation of triallyl amine gave a trizirconocene complex, which was treated with $GeCl_4$ to afford 1-aza-5-germa-5-chlorobicyclo[3,3,3]undecanes in excellent yield. The product reacted with Grignard or lithium reagents to give a variety of 5-organo-substituted compounds that could be used for Pd-catalyzed cross-coupling partners.

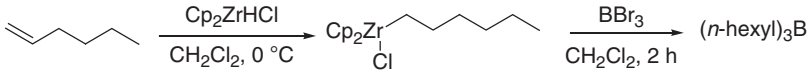


Scheme 31

8.23.3.1.4.5 Synthesis of organoboranes from alkylzirconocenes

Linking the hydrozirconation to boron chemistry is very promising due to the rapid development of boron chemistry. Alkylzirconocene chloride has been found to undergo transmetalation from Zr to B smoothly. Compared with direct hydroboration, this

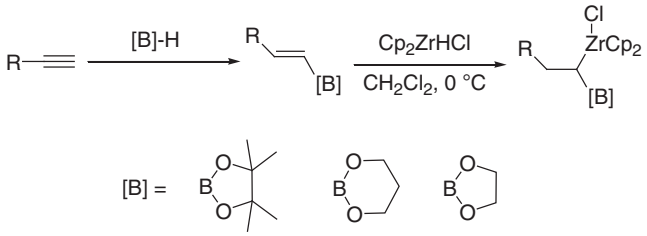
two-step process from alkene is more selective, as the isomerization of hydrozirconation is more facile than hydroboration.[55] In a representative example, 1-hexylzirconocene chloride, generated from addition of 1-hexene with Cp_2ZrHCl, reacted with BBr_3 in CH_2Cl_2 to give trihexylborane in quantitative yield (Scheme 32).



Scheme 32

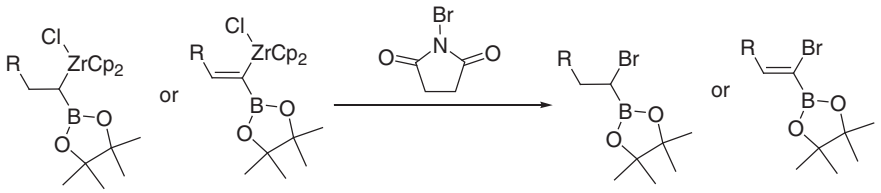
8.23.3.2 Hydrozirconation of Alkenylboronates

Hydrozirconation of unsaturated boronates affords the corresponding borazirconocene 1,l-alkanes and l,l-alkenes selectively. The C–Zr and C–B bonds can be possibly functionalized successively or simultaneously. This feature can be utilized for exploring novel methods in organic synthesis.[56] For example, Srebnik et al. reported that hydrozirconation of various alkenylboronate derivatives occurred smoothly in dichloromethane to give the expected *gem*-borazirconocenes (Scheme 33).[57]



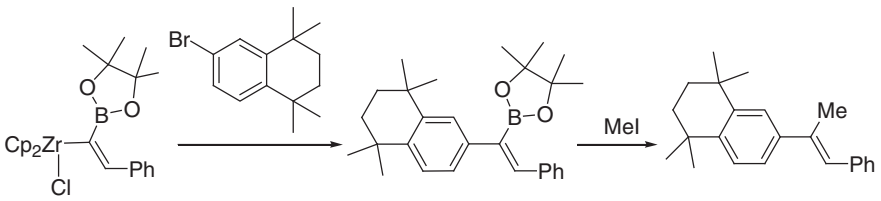
Scheme 33

Organozirconium compounds are more reactive toward electrophiles than organoboranes. For example, both *gem*-borazirconocene alkyl and *gem*-borazirconocene alkenyl derivatives reacted with *N*-bromosuccinimide to give α-haloalkyl and α-haloalkeny1 boronic esters, respectively (Scheme 34). However, hydrolysis or amination of the Zr–C of both *gem*-borazirconocene alkane and *gem*-borazirconocene alkene derivatives could give novel boron compounds.[58] This method provides a very useful class of boron intermediates for organic synthesis.



Scheme 34

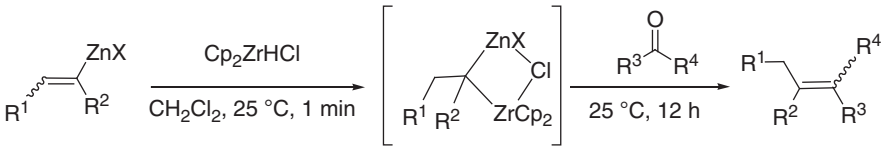
Carbon–carbon bond formation has been the major target of both organoboron chemistry and organozirconium chemistry. Therefore, use of conveniently prepared *gem*-borazirconocene alkene derivatives for C–C bond forming reactions is predictably very attractive.[59] In one example shown in Scheme 35, the C–Zr bond of *gem*-borazirconocene alkene reacted with aryl halides in the presence of copper(I) or palladium(0) catalysts to give coupling products in high yield. The C–B bond was then smoothly coupled with iodomethane to provide the product Temarotene.[60]



Scheme 35

8.23.3.3 Hydrozirconation of Alkenylzinc Derivatives

Alkenylzinc compounds could be easily prepared from zinc halide and alkenylmetal reagents. Hydrozirconation of those alkenylzinc compounds gave zinc and zirconium heterobimetallic products that have special usage in organic synthesis. The reaction of the products with aldehydes and ketones gave (*E*)-disubstituted olefins selectively or an *E*/*Z* mixture of stereoisomers, respectively.[61] Furthermore, these new zinc and zirconium 1,l-bimetallic reagents showed a good functional group compatibility (Scheme 36).

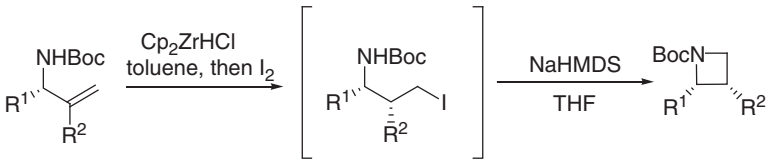


Scheme 36

Developing asymmetric hydrozirconation of alkenes for the synthesis of optically pure compounds has very important synthetic potential. This research field is just opening and only few examples have been reported. Szymoniak et al. demonstrated that hydrozirconation proceeded with high diastereofacial selectivity, which makes the construction of optically pure compounds possible.[62]

In some example reactions, Boc-protected chiral allylic amines were subjected to an asymmetric variant of the hydrozirconation reaction to form optically pure 2,3-disubstituted azetidines (Table 6). A typical reaction was carried out by using a simple amine with methyl and benzyl groups. Treatment of the hydrozirconated intermediate with iodine afforded the corresponding iodocarbamate. Subsequent addition of NaHMDS in THF gave *N*-heterocyclobutane with excellent diastereoselectivity (*dr* 95:5) in 65% isolated yield. The reaction was then applied to a variety of allylic amines to give *cis*-2,3-disubstituted azetidines in 65–80% yields. These reactions proceeded with high diastereoselectivity except with R^1 = *i*-Pr or Ph (entries 3 and 4). The lack of stereoselectivity in these cases is not entirely clear at present, but might be due to steric reasons.

Table 6 Synthesis of optically pure azetidines via hydrozirconation of chiral allylic amines



Entry	R^1	R^2	*dr*[a]	*Yield (%)*
1	Bn	Bu	96:4	75
2	Bn	Me	95:5	65
3	*i*-Pr	Me	50:50	68
4	Ph	Me	73:27	80
5	CH_2OTBS	Me	92:8	65

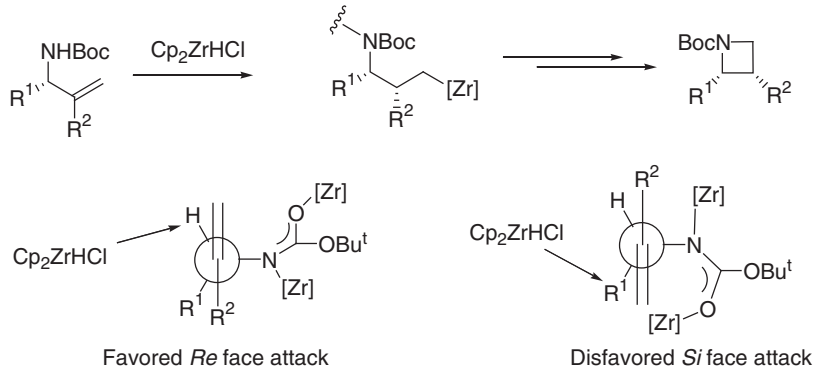
[a]Determined by proton NMR of the reaction mixture.

In the conformation of Boc-protected chiral allylic amines, the large Zr-coordinated *N*-Boc fragment was located in a pseudoaxial orientation with respect to the double C=C bond. The selectivity may thus be rationalized by a more favorable accessibility of the *re* face than the *si* face as shown in the Scheme 37.

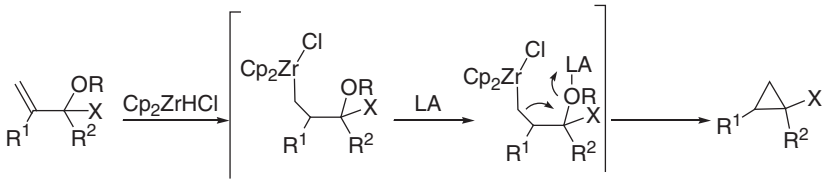
The same group reported diastereoselective synthesis of di- and trisubstituted cyclopropanes from allylic ethers and acetals.[63] This reaction involved a hydrozirconation followed by the Lewis acid-promoted deoxygenative ring formation (Scheme 38).

This type of reaction was then applied to a diastereoselective synthesis of pyrrolidines from readily available chiral *N*-allyl oxazolidines, which proceeded via a tandem hydrozirconation-stereoselective Lewis acid-mediated cyclization sequence (Scheme 39).[64]

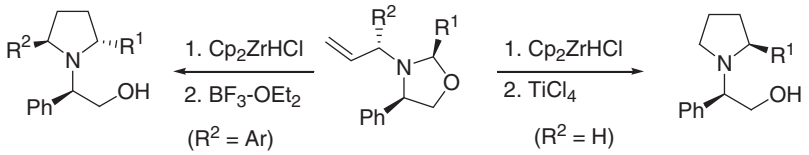
To achieve the ring-closure step, several Lewis acids were tested after hydrozirconation. Lewis acids such as BF_3-OEt_2, TMSOTf, $AlCl_3$, and Me_3Al gave good yield of pyrrolidine at 20 °C but with moderate diastereoselectivity of 2:1 to 3:1. The level of stereoselectivity increased to 6:1 when $ZnCl_2$ was used. The best diastereoselectivity of 10:1 was obtained in the presence of $TiCl_4$. Various oxazolidines were then tested for this reaction (Table 7). Oxazolidines bearing phenyl or substituted phenyl groups (entries 1–3) as well as heteroaromatic groups (entry 4) on the C3 atom afforded the corresponding pyrrolidines in moderate to



Scheme 37

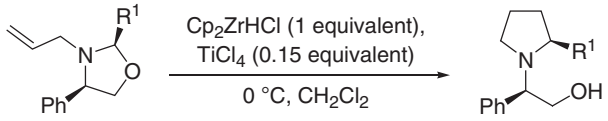


Scheme 38



Scheme 39

Table 7 Tandem hydrozirconation and $TiCl_4$-promoted cyclization of N-allyl oxazolidines



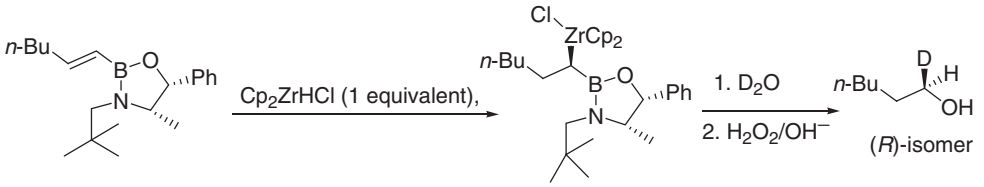
Entry	*R^1*	*Dr*	*Yield (%)*[a]
1	Ph	10:1	62
2	2-BrC_6H_4	7.4:1	53
3	2-$MeOC_6H_4$	4:1	62
4	3-Furyl	>12:1	43
5	*n*-C_5H_{11}	5.5:1	52
6	*i*-Pr	7:1	49

[a]Combined NMR yield of isomers.

good yields. The reaction also worked with oxazolidines bearing C2-alkyl substituents *n*-C_5H_{11} and *i*-Pr. It should be noted that when using oxazolidines with an *R*-substituted *N*-allyl chain, the reaction with $TiCl_4$ led to nonstereoselective reactions. However, BF_3-OEt_2 gave 2,5-disubstituted pyrrolidines as *trans* isomers with complete selectivity.

As described in Section 8.23.3.2 hydrozirconation of unsaturated boronates afforded the corresponding borazirconocene 1,l-alkanes and l,l-alkenes selectively. By using this method, optically active compounds could be synthesized by employing optically active ligands on boron. Hydrozirconation of l-alkenyloxazaborolidines provided a bimetallic complex, which cleaved the C–Zr

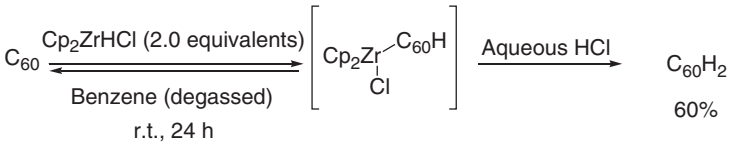
bond with D_2O and oxidized the C–B bond with H_2O_2 successively to give optically active 1-deuteroalcohols in excellent enantiomeric purities (Scheme 40).[65]



Scheme 40

8.23.3.4 Others

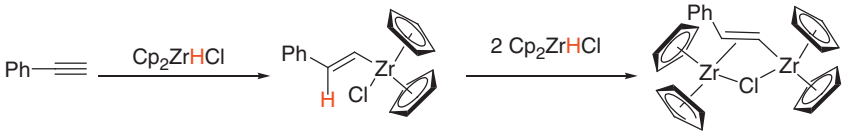
Hydrozirconation of the C=C double bond of fullerene C_{60} has been conducted by treating fullerene with 2 equivalents of Cp_2ZrHCl for 24 h at r.t. Without separating the C_{60}-zirconocene complexes, hydrolysis of the reaction mixture gave the crude product, which was contaminated by starting material and other overhydrogenated products. After purification by preparative high-performance liquid chromatography, pure $C_{60}H_2$ was obtained in 60% yield (Scheme 41).[66] Furthermore, the C_{60}–zirconocene complexes were isolated by Chiang and Canteenwala due to their interest in fullerene–metallocene complexes.



Scheme 41

8.23.4 Hydrozirconation of Alkyne

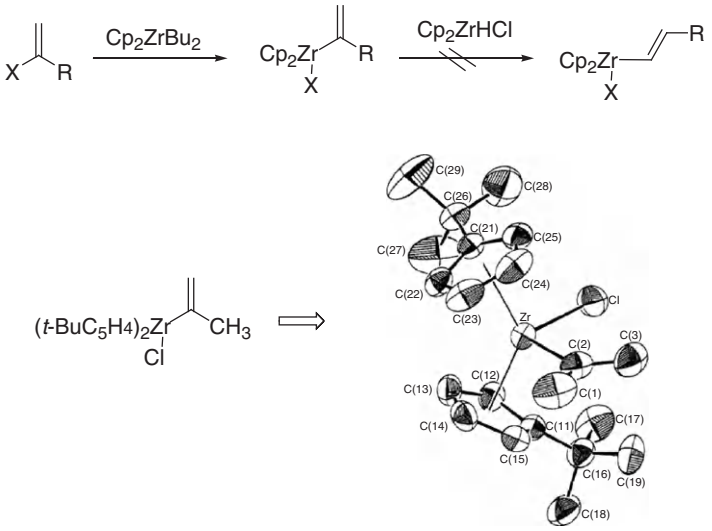
Addition of Schwartz reagent Cp_2ZrHCl to an equal amount of alkyne gave an alkenylzirconocene σ-complex. No further alkyne insertion reaction was observed even with an excess of alkyne. However, when Schwartz reagent Cp_2ZrHCl was used in excessive, the extra Cp_2ZrHCl reacted with the alkenylzirconocene complex to give a chlorine-bridged bis(zirconocene) complex, and others (Scheme 42).[67]



Scheme 42

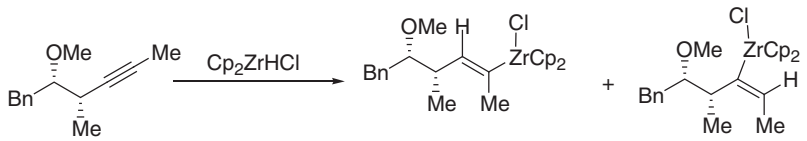
Controlling the regioselectivity of hydrozirconation of unsymmetrical alkynes is a critical aspect of the study. In the cases of terminal alkyl- and arylalkynes, zirconocene usually added *cis* to the C–H bond and *trans* to the alkyl and aryl groups in the alkenylzirconocene complexes. According to explanation of Schwartz, the origin of the high regioselectivity is the isomerization of alkenylzirconocene chloride. If the alkenylzirconocene with the opposite regioselectivity produced, immediate isomerization with an excess of Cp_2ZrHCl occurred to give exclusively the major isomer. Takahashi et al. prepared alkenylzirconocene with the opposite regiochemistry by oxidative addition of alkenyl halide to zirconocene and isolated the zirconium complex for the first time (Scheme 43). They found it was very stable and the structure was verified by X-ray analysis.[68] In addition, they tried the isomerization reaction in the presence of additional Cp_2ZrHCl, However, it did not isomerize to the alkenylzirconocene with the usual regiochemistry. An alternative explanation is needed for the high regioselectivity.

In the cases of internal alkynes, regioselectivity can be well controlled only when the sizes of two substituents are quite different and one is very small, such as methyl, ethyl, etc. The amount of Schwartz reagent, reaction temperature, solvent, and time, are all factors that are important to control the regioselectivity.[69] Panek et al. reported[69c] that quantitative conversion of alkyne to the



Scheme 43

desired hydrozirconated product was achieved in THF or benzene at 50 °C with reaction times ranging from 1 to 4 h (Scheme 44). Changing even one aspect of conditions led to formation of the other regioisomer.



Scheme 44

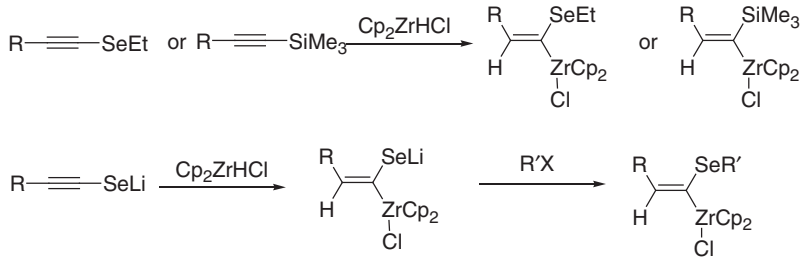
Hydrozirconation of alkynes with Cp_2ZrHCl generally proceeds in THF or CH_2Cl_2 solvent. In a report by Cai et al., ionic liquids were also suitable for hydrozirconation.[70]

An alkenylzirconocene complex allows introduction of various substituents at the olefin. Schwartz et al. demonstrated that Cp_2ZrHCl reacted with terminal alkynes to give (*E*)-vinylzirconium complexes $Cp_2ZrCl(CH{=}CHR)$ with *cis* stereochemistry and very high regioselectivity.[71]

8.23.4.1 Hydrozirconation of Various Alkynes

8.23.4.1.1 Alkynes attached with Si and Se and P groups

Hydrozirconation of alkynylselenides and the alkynylsilanes with commercially available Cp_2ZrHCl gave (*E*)-α-selenylvinylzirconium and (*E*)-α-silylvinylzirconium complexes in high yields (Scheme 45). In subsequent reaction with acyl halides via Zr–Cu transmetalation, α-seleno- or α-silyl-substituted α,β-unsaturated ketones could be synthesized in high yields.[72]

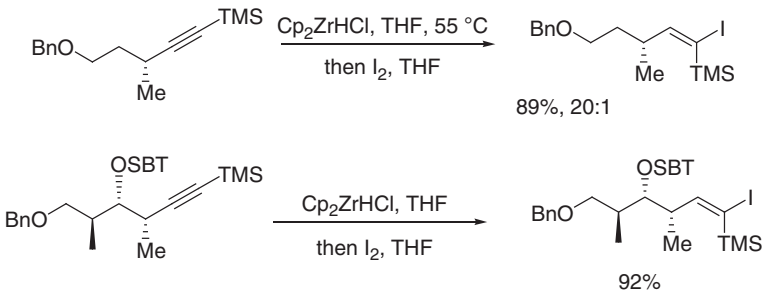


Scheme 45

However, lithium alkynylselenolate anions reacted with Cp_2ZrHCl to give the 1,1′-zirconated vinylselenolate complexes, which by treatment with an alkyl halide afforded the 1,1′-zirconated vinyl alkylselenide complexes.[73,74]

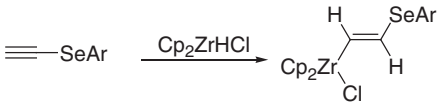
Reaction of unsymmetrical alkynes bearing a trimethylsilyl (TMS) group on one side of triple bond with Cp_2ZrHCl was not completely selective under these conditions. The ratio of two regioisomers after iodination was 20:1.[75]

As for other TMS alkynes, however, hydrozirconation proceeded with complete regioselectivity.[76] As shown in Scheme 46, silylacetylene reacted with Schwartz reagent and iodine in that order to afford the geminal iodovinylsilane as a single regio- and stereoisomer in 92% yield. The product, after simple purification, could be used for further coupling reactions. The origin of different selectivity for these two examples is not clear.



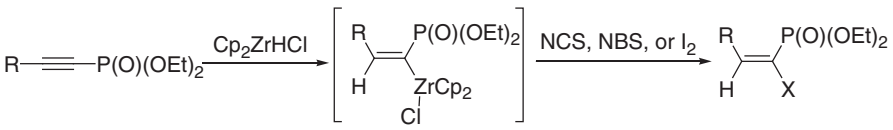
Scheme 46

It should be noted that terminal arylselenoethynes reacted with Cp_2ZrHCl smoothly. The zirconocene moiety was added to the β position of the Se group selectively (Scheme 47).[77]



Scheme 47

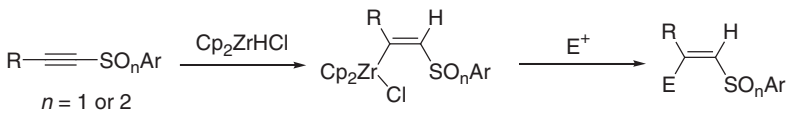
Hydrozirconation of 1-alkenylphosphonates with 1.0 equivalent of Cp_2ZrHCl in THF for 15 min at room temperature gave a clear solution of α-phosphonovinyl zirconocene,[78] (Scheme 48) which, without separation, could be halogenated to afford α-halovinylphosphonates in good yields.



Scheme 48

8.23.4.1.2 Hydrozirconation of 1-alkynyl sulfoxides or sulfones

To make hydrozirconation of alkynes more useful, introduction of functional groups to alkynes is important, since the hydrozirconation of a heteroatom-substituted alkyne provides a convenient approach to an alkenylic intermediate with two functional groups. In the contributions of Huang et al., the hydrozirconation reaction of 1-alkynyl sulfoxides or sulfones with Cp_2ZrHCl in THF at room temperature predominantly gave *Z*-β-zirconated vinyl sulfoxides or sulfones with excellent regioselectivity (Scheme 49).[79] Furthermore, the Zr–C bond of the latter ones could be easily functionalized under variety of conditions.



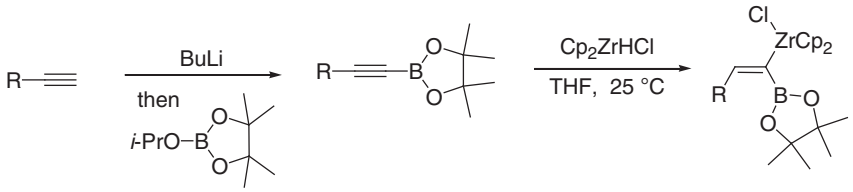
Scheme 49

8.23.4.1.3 Hydrozirconation of 1-alkynylzinc derivatives

Geminal organobismetallic alkene derivatives have been applied as an efficient and useful alternative to prepare functionalized olefins. Knochel et al. reported that addition of Cp_2ZrHCl to alkynylzinc bromide in CH_2Cl_2 gave 1,l-dimetalloalkenes of zinc and zirconium.[61] The subsequent reaction with aldehydes gave allene derivatives in good yields.

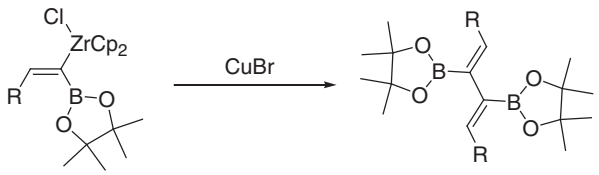
8.23.4.1.4 Synthesis of gem-borazirconocene

Hydrozirconation of 1-alkynyl dioxaborolanes with Cp_2ZrHCl affords *gem*-borazirconocene alkene derivatives. These can be used for synthesis of stereodefined compounds. For example, starting 1-alkynyl dioxaborolanes could be readily synthesized by the reaction of lithiated terminal alkynes, and followed by treatment with 2-isopropoxy-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane.[80] (Scheme 50) Reaction of the alkynes with Cp_2ZrHCl gave *gem*-borazirconocene alkene derivatives selectively.



Scheme 50

The Zr–C bond in this framework was found to be very reactive. The 1,l-bimetalloalkenes was treated with CuBr to give the homocoupled (1*E*,3*E*)-2,3-dibora-1,3-butadienes in good yields (62–67%) (Scheme 51).[81]



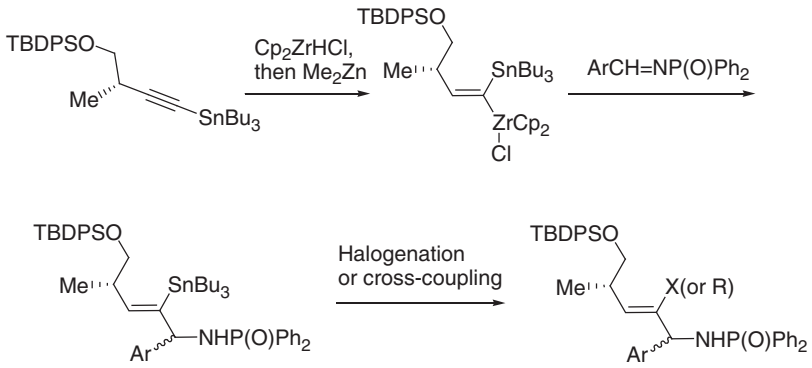
Scheme 51

8.23.4.1.5 Sn and Te functionalized alkynes and hydrozirconation

Application of 1,1-bimetalloalkenes composed of two different C–M bonds for the synthesis of substituted alkenes attracts increasing attention. Hydrozirconation of functionalized alkynes provides a convenient access to 1,1-bimetalloalkenes. Addition of Cp_2ZrHCl with acetylenic tellurides was found to give 1,1-bimetalloalkenes of tellurium and zirconium in good yields.[82]

In the case of tin, hydrozirconation of alkynylstannanes produced (*Z*)-*α*-stannylvinylzirconocenes cleanly.[83] Moreover, treatment of the product with aryltellurenyl iodides transmetalated Zr to Te to give (*E*)-*α*-aryltellurenylvinylstannanes in good to high yields.

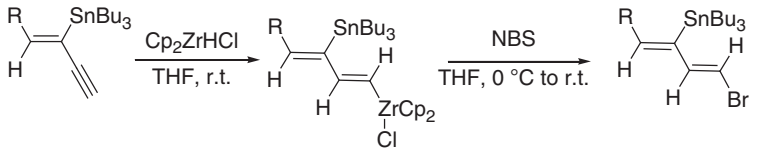
The 1,1-bimetalloalkenes of tin and zirconium can be used synthetically in a special way based on Sn and Zr chemistry.[84–86] Wipf et al. reported multicomponent reactions, in which hydrozirconation of alkynylstannanes gave Zr/Sn 1,1-bimetalloalkene[87] (Scheme 52) followed by transmetalation to Zn/Sn complex. The reaction mixture was treated with an electron-poor aldimine,



Scheme 52

and no regioisomeric addition products were detected in this case. The $SnBu_3$ moiety of alkenylstannane was converted into halogens (I, F) and a variety of organic groups by Stille coupling reactions.

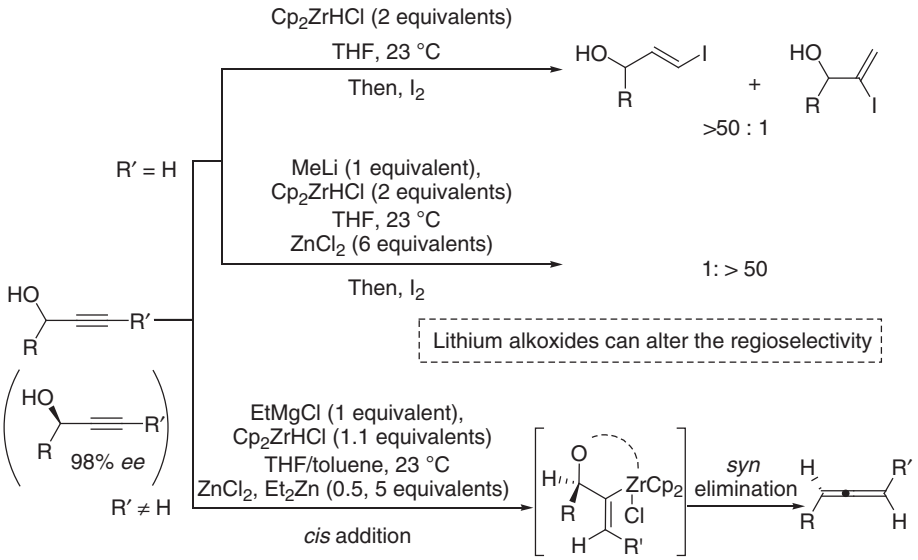
Efficient control of both regio- and stereoselectivity during the synthesis of 1,3-dienes containing metal or heteroatom functional groups is very attractive. A highly stereoselective and general route to difunctionalized 1,3-dienes containing tin and halogen has been developed by hydrozirconation of (*Z*)-3-(tributylstannyl)alk-3-en-1-ynes and bromination in this order (Scheme 53).[88]



Scheme 53

8.23.4.1.6 Directed hydrozirconation of propargylic alcohols

Hydrozirconation of propargylic alcohols provided, after iodination, the terminal vinyl iodide as a single regioisomer.[89] This regioselectivity is due to stereo effect of the substituent of alkynes and the zirconocene moiety during the hydrozirconation. In a sharp contrast, addition of MeLi before Cp_2ZrHCl to the propargylic alcohols, followed by treatment with 6 equivalents of $ZnCl_2$ and iodine in this order gave only the internal vinyl iodide. There is a big difference in regioselectivity from the standard hydrozirconation conditions (Scheme 54). In an extended study of such reactions, when internal propargylic alcohols were treated under similar reaction conditions, substantial quantities of disubstituted allenes were isolated in addition to branched allylic alcohols.[90] However, enantiomerically pure alcohols (98% *ee*) gave the allene in good yields and excellent enantioselectivity, under two optimized complementary sets of conditions. The conversion of the central chirality of the alcohols to axial chirality of allenes is consistent with a *cis* addition of Zr–H to the alkyne followed by a *syn* elimination of Cp_2ZrO.



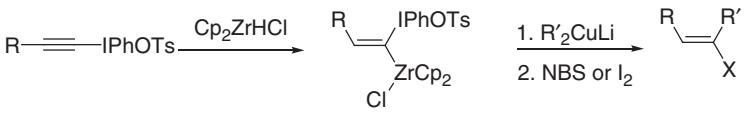
Scheme 54

8.23.4.1.7 Hydrozirconation of alkynyliodonium salts

Prompted by the use of alkynyl- and alkenyl(phenyl)iodonium salts in organic synthesis, Huang et al. demonstrated the hydrozirconation of alkynyliodonium salts (Scheme 55). The reaction underwent with good regioselectivity.[91] The zirconocene moiety attacked the α position of the iodonium salts. Reactions of alkenyliodonium salts with R_2CuLi proceeded with retention of the stereochemistry of the C=C bond.

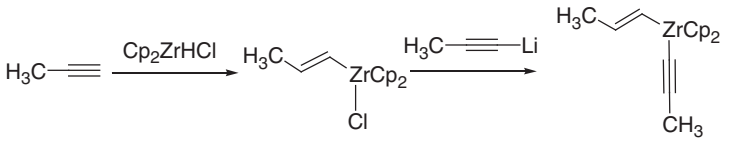
8.23.4.2 Chlorine Abstraction Reactions

Replacing the Cl atom of the alkenylzirconocene chloride with other ligands gives zirconocene derivatives bearing different σ-ligands. For example,[92] propyne was hydrozirconated by Cp_2ZrHCl in toluene at ambient temperature to afford the



Scheme 55

(*trans*-1-propenyl)zirconocene chloride complex in 74% yield. It was followed by treatment with propynyllithium to give an alkenyl-alkynylzirconocene complex in >90% yield, described by Erker et al. (Scheme 56). The subsequent coupling reaction between the two σ-ligands occurred by instantaneous addition of $B(C_6F_5)_3$ at room temperature.



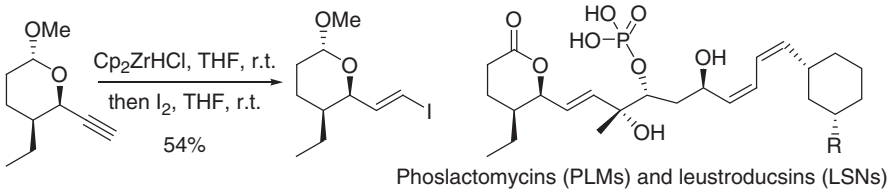
Scheme 56

8.23.4.3 Conversion of Zirconocene Moiety to Halogens and Other Metals

8.23.4.3.1 Halogenation reactions

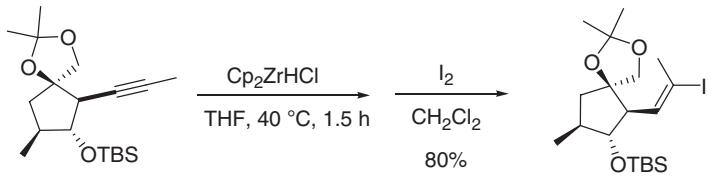
Addition of Cp_2ZrHCl to alkynes and subsequent halogenation affords alkenyl halides. This process has been commonly used in the total synthesis, since the C=C double bond is common to a number of natural products and medicinal drugs.

For example,[93] during the synthesis of a family of natural products phoslactomycins and leustroducsins, the conversion of a terminal alkyne into an alkenyl iodide was needed (Scheme 57). This reaction was done by hydrozirconation with Schwartz reagent followed by iodinolysis. The alkenyl iodide was obtained in the yield of 54%.



Scheme 57

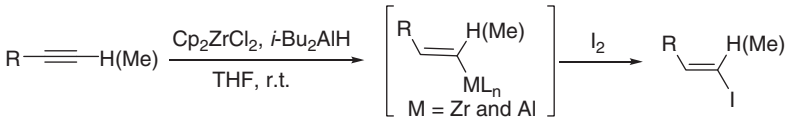
In another case,[94] one step in the enantioselective total synthesis of the jatrophane diterpene was the conversion of an alkyne into a vinyl iodide (Scheme 58). This process was accomplished by a hydrozirconation–iodination sequence. The desired iodovinyl product was provided as a single double bond isomer through hydrozirconation of the alkyne and subsequent exposure of the intermediate vinyl zirconium species to iodine. Moreover, the hydrozirconation could be carried out in THF or benzene solvent.

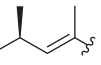


Scheme 58

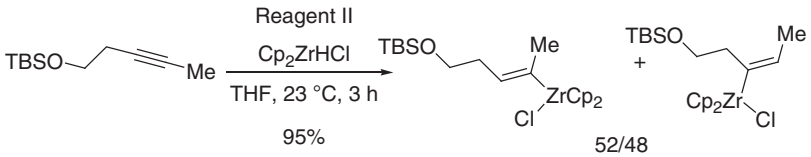
The tandem process of hydrozirconation and iodination of alkynes was modified by Negishi et al. by using a combination of Cp_2ZrCl_2 and diisobutylaluminum hydride instead of preformed Cp_2ZrHCl.[12,95] The reagent was convenient and satisfactory for both terminal and internal alkynes as shown in Table 8. In particular, 2-alkynes were converted into the corresponding iodoalkenes with high regioselectivity (≥98%) under such mild conditions. Hydrozirconation of 2-alkynes with the *in situ* generated Cp_2ZrHCl, as described in Scheme 5, could not give the comparable regioselectivity. The ratio of two regioisomers, in one case shown in Scheme 59, was 52:48. These results indicate that the combination of Cp_2ZrCl_2 and diisobutylaluminum hydride is not a genuine equivalent to Cp_2ZrHCl.

Table 8 Reaction of Cp_2ZrCl_2 /*i*-Bu_2AlH with alkynes and iodonation



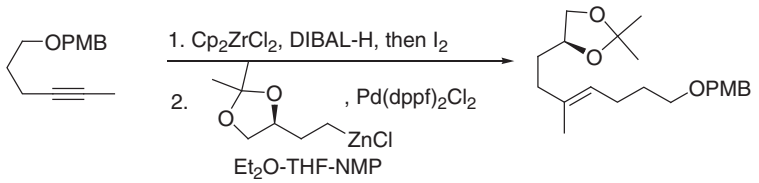
R[a]	*H or Me*	*Yield (%)*[b]	*R*[a]	*H or Me*	*Yield (%)*[b]
n-Hex	H	91	(*E*)-n-HexCH=CH	H	95
$HOCH_2$	H	83	(*E*)-TBSOCH=CH	H	79
HOC_2H_4	H	85	(*E*)-TBSO 	H	87
$TBSOCH_2$	H	92	$TBSOCH_2$	Me	82
TBSOCH(Pr)	H	93	$TBSOC_2H_4$	Me	74
$TBSOCH_2CHMe$	H	90	All isolated products were isomerically ≥98% pure by ^1H and ^{13}C NMR spectroscopy.		
$PhMe_2Si$	H	81			

[a]TBSO: tert-butyldimethylsiloxy.
[b]Isolated yield.



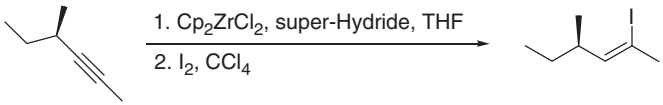
Scheme 59

Negishi et al. applied the Cp_2ZrCl_2 and *i*-Bu_2AlH reagent for hydrozirconation of an internal alkyne in Scheme 60. The reaction proceeded with high regioselectivity in this case. Subsequent iodination afforded in excellent yield the corresponding (*E*)-iodoalkene, which was coupled with an alkylzinc halide in the presence of a palladium catalyst to afford trisubstituted alkenes successfully. Such a sequence is very useful in organic synthesis.[96]



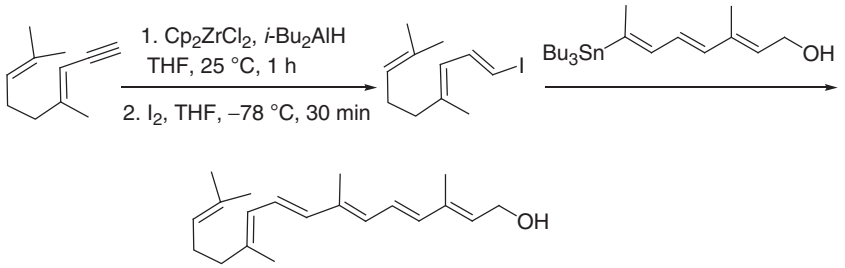
Scheme 60

In Hoye's synthesis of the side chain of scyphostatin, the first step is a stereoselective hydrozirconation/iodination of a chiral alkyne (Scheme 61). The hydrozirconation was carried out by use of a combination of Cp_2ZrCl_2 and superhydride. The reaction worked well and the vinyl iodide was synthesized in high yield with high selectivity.[97,98]



Scheme 61

Linear polyalkenes exist widely in natural products. Their synthesis attracts considerable attention.[99] Hydrozirconation of terminal alkynes using Cp_2ZrCl_2 and DIBAL-H gave an alkenylzirconocene intermediate which was trapped with iodine to afford iodide in 73% yield.[100] Stille cross-coupling reaction of the iodoalkene and stannane afforded the hexaenol compound in 58% yield, (Scheme 62) which was used for the synthesis of the C_{40}-symmetrical fully conjugated carotenoids.

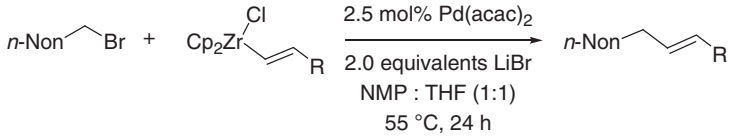


Scheme 62

8.23.4.3.2 Transmetalation

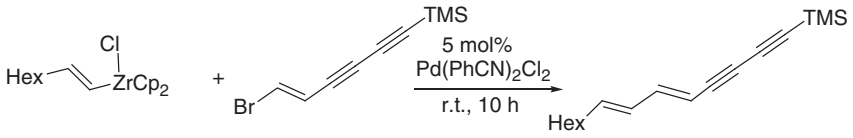
8.23.4.3.2.1 Pd

Application of alkenylzirconocene chloride to Pd-catalyzed cross-coupling reactions provides a protocol for the stereospecific synthesis of alkenes. Fu et al. reported $Pd(acac)_2$ catalyzed zirconium Negishi cross-coupling reactions of functionalized alkyl halides or tosylates with organozirconium reagents. They were generated *in situ* from hydrozirconation of alkenes or alkynes with Cp_2ZrHCl.[101] One special advantage of the current process was claimed to be its 'ligandless' nature (Scheme 63). Such a ligandless process is attractive from the standpoints of atom economy, simplicity, and ease of purification. Reaction conditions were optimized by employing 1-bromodecane and an alkenylzirconium reagent as coupling partners. Palladium complexes such as $Pd(acac)_2$, $PdBr_2$, and $Pd_2(dba)_3$ gave nearly quantitative yields of products, whereas nickel complexes $NiBr_2$ and $Ni(cod)_2$ were only modestly efficient under these conditions. For the lithium salt, both LiBr and LiI were good enough for this reaction. Reaction had a broad scope, a range of functionalized alkyl bromides and alkenylzirconium reagents resulted in generally good yields of the products.



Scheme 63

Coupling reactions of 1-octenylzirconocene with a 1,3-diyne functionalized vinyl bromide, in the presence of $Pd(PhCN)_2Cl_2$ as catalyst, gave the conjugated diene–diyne product effectively (Scheme 64).[102]



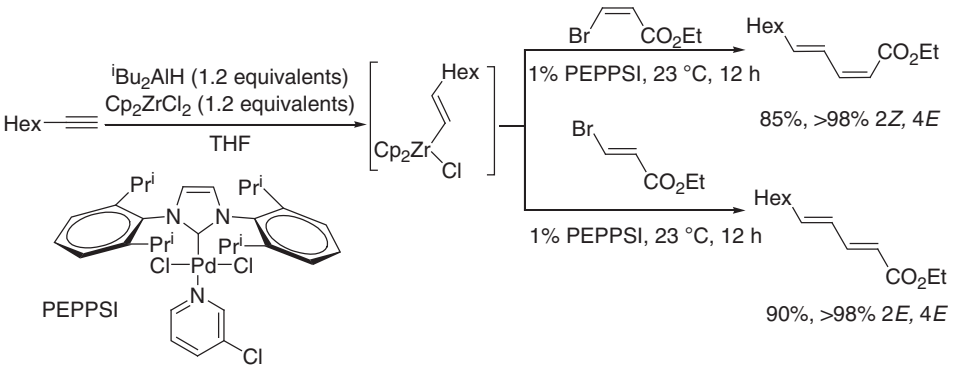
Scheme 64

The alkenylzirconocene chloride, generated *in situ* from reaction of 1-octyne with Cp_2ZrCl_2 and DIBAL-H, was subjected to Negishi coupling directly to afford butadiene compounds of ≥98% isomeric purity in ≥85% yields.[103] (Scheme 65) Furthermore, transmetalation of alkenyl-Zr to alkenyl-Zn, in addition to the use of bidentate phosphines and other critical factors, led to high turn over numbers.[104]

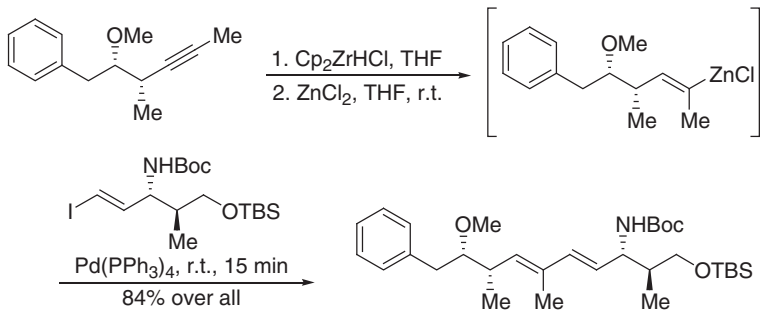
This hydrozirconation and Pd-catalyzed coupling sequence is also applicable to internal alkynes attached to very complicated frameworks. Unsymmetrical alkynes reacted with Cp_2ZrHCl to give the corresponding alkenylzirconocenes with high regio and stereoselectivity (Scheme 66). Quantitative conversion of the alkenylzirconocene to vinyl zinc intermediates followed by Negishi-type coupling, with branched (*E*)- and (*Z*)-vinyl halides catalyzed with $Pd(PPh_3)_4$, gave the diene product in 84% overall yield from acetylene.[105]

In other cases as shown in Schemes 67,[106] 1-phenyl-1-propyne was first treated with Cp_2ZrHCl and then with $Pd(PPh_3)_4$ catalyst and MeI to give tri-substituted alkenes readily. Similarly, [^{11}C]methyl iodide gave several ^{11}C-labeled α,α-dimethyl-substituted alkenes.

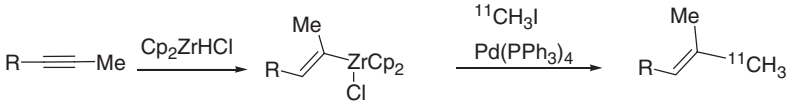
Alkenylzirconocenes underwent cross-coupling with (*E*)-α-iodovinyl sulfones, in the presence of Pd catalyst, (Scheme 68) to give a series of 1,3-dien-2-ylsulfones with complete stereoselectivity.[107] Similar coupling reactions were reported some years ago by using (*E*)-1-halo-2-arylselenoethylene analogs of Se or Sn.[108,109]



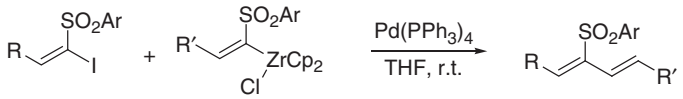
Scheme 65



Scheme 66

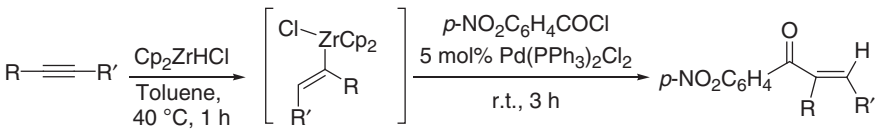


Scheme 67



Scheme 68

Reaction of alkenylzirconocenes with acyl chlorides in the presence of $Pd(PPh_3)_2Cl_2$ as catalyst gave α,β-unsaturated ketones in high yields.[110] The several steps were carried out in a 'one-pot' fashion, which is very applicable in organic synthesis (Scheme 69).

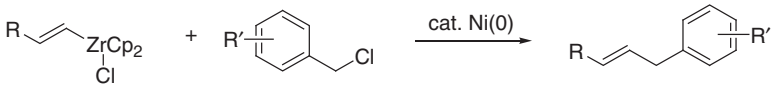


Scheme 69

8.23.4.3.2.2 Ni

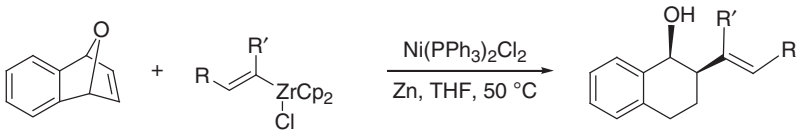
Nickel-catalyzed reaction of alkenylzirconium derivatives with aryl halides was initially reported by Negishi et al.[111] Although the reaction was limited in alkenyl–aryl framework formation, a variety of functional groups on both partners could be tolerated. This obvious advantage made this type Negishi coupling very useful.[112,113]

Alkenylzirconocene reacted with a variety of benzyl chlorides to give coupling products in good to high yields under the influence of Ni(0) catalyst.[114] When Pd(0) catalyst was used instead, the reaction needed longer time or higher temperature to give comparable results (Scheme 70).



Scheme 70

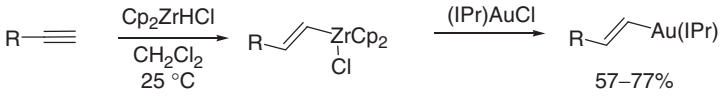
Stereocontrolled synthesis of cyclic and acyclic compounds, in particular those with multiple stereocenters, is very attractive. In this regard, the transition metal promoted ring-opening addition reaction of bicyclic alkenes has been described as a very efficient method. Cheng et al. employed alkenylzirconium reagents for the coupling reaction,[115] and a highly regio- and stereoselective ring-opening addition of alkenylzirconium reagents to bicyclic alkenes catalyzed by nickel complexes was thereby achieved (Scheme 71). Precursors of alkenylzirconium reagents could be a variety of terminal or internal alkynes bearing alkyl or aryl substituents.



Scheme 71

8.23.4.3.2.3 Au

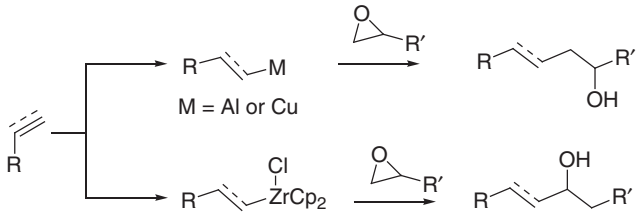
Stereodefined alkenylgold(I) complexes receive increasing attention due to rapidly developing homogeneous gold(I) catalysis in organic synthesis. Stereoselective synthesis of (*E*)-alkenylgold compounds through hydrozirconation and transmetalation sequence was reported by Blum et al. (Scheme 72). The advantages of hydrozirconation, high regio- and stereoselectivity and the tolerant of ester and halide functional groups, were well reflected in the (*E*)-alkenylgold products.[116]



Scheme 72

8.23.4.3.2.4 Ag

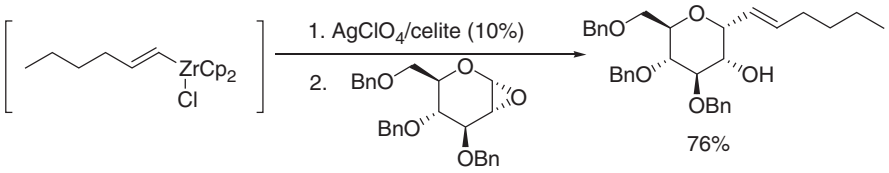
Reaction of epoxides with metal reagents proceeds with C–O bond cleavage and C–C bond formation. This method could be used for the synthesis of alcohols, in particular where stereoselectivity is required.[117] Reaction of an alkenylzirconocene chloride with epoxides in the presence of Lewis acid additives was investigated by Wipf et al. (Scheme 73).[117a] Among the metal reagents tested,



Scheme 73

addition of $AgClO_4$ led to a rapid conversion of the alkenylzirconocene to the secondary alcohols in excellent yields. In the absence of $AgClO_4$, however, no reaction between epoxides and organozirconocenes was detected at all. This special performance of $AgClO_4$ is likely due to the strong Cl abstraction from Cp_2ZrRCl. A $Cp_2RZr(+)$ species produced thereby is able to react toward the epoxide by cleaving the C–O bond and forming the C–C bond successively. Furthermore, this stereospecific access to secondary alcohols is also obviously different from the other ones as shown in the Scheme 72.

This tandem reaction was then used for the stereoselective synthesis of side chain-substituted *C*-glycosides.[118] Alkenylzirconocenes, the functionalized nucleophiles derived from readily available terminal alkynes, were treated with $AgClO_4$ and 1,2-anhydrosugars in this order to give *C*-glycoside in good yield (Scheme 74).



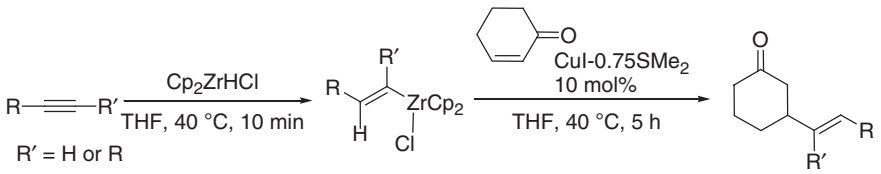
Scheme 74

8.23.4.3.2.5 B

Migration of organic groups from zirconium to boron was reported as a facile route to organoboranes in particular with complete retention of regio- and stereochemistry. One of the greatest advantages of organozirconium complexes is just such regio- and stereospecific preparative methods, and hydrozirconation of alkenes and alkynes provides very practical access to alkyl and alkenylzirconocenes. The alkenylzirconocenes reacted with various haloboranes smoothly to give the desired organoboranes, which were systematically investigated by Cole et al.[119]

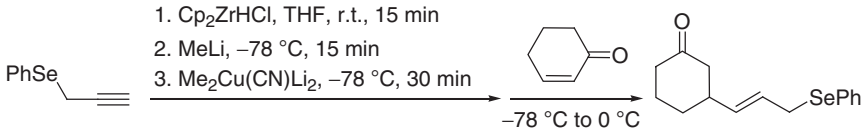
8.23.4.3.2.6 Cu

Activation of alkenylzirconocenes toward 1,4-addition to α,β-unsaturated ketones was achieved by $Me_2Cu(CN)Li_2$, or simple Cu(I) salts such as $CuBrSMe_2$ or CuCN, stoichiometrically or catalytically. However, when 10 mol% CuI–0.75 SMe_2 was used, 1,4-addition of alkenylzirconocenes to α,β-unsaturated ketones and aldehydes was greatly facilitated.[120] For example, (Scheme 75) the starting alkyne (R = *n*-Bu, R^1 = H) gave the adduct with cyclohex-2-enone in 81% yield in the presence of 10 mol% CuI–0.75 SMe_2, but only in 20% yield in the presence of CuBr–SMe_2.[121]



Scheme 75

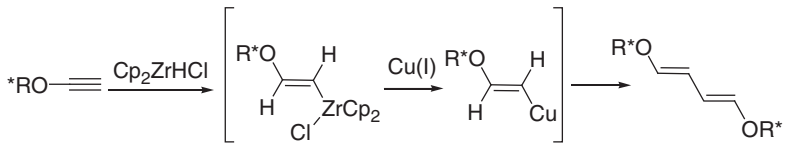
When the starting alkynes were attached to a phenylseleno group,[122] as shown in Scheme 76, conjugate addition to enones of vinylic organocuprates obtained via transmetalation of vinylzirconates worked well. The β-side chain of the products could be further functionalized using methods based on organoselenium chemistry.



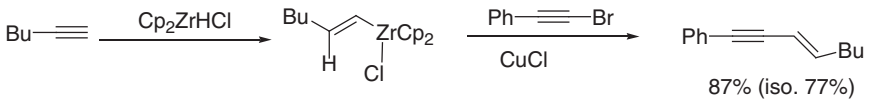
Scheme 76

In a special case as shown in Scheme 77, alkoxyethyne went through a sequence of hydrozirconation and transmetalation with Cu to give (*E,E*)-1,4-dialkoxy-1,3-butadiene on heating.[123] This process was then utilized to make a set of chiral dialkoxybutadienes.[124–126]

Phenylethynyl bromide reacted with alkenylzirconium compounds, prepared by hydrozirconation of l-hexyne, in the presence of CuCl to give substituted enynes in 87% yield (Scheme 78).[127]

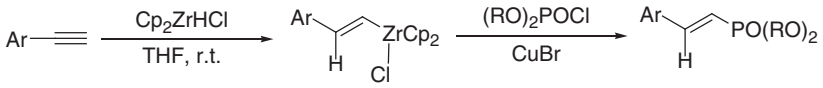


Scheme 77



Scheme 78

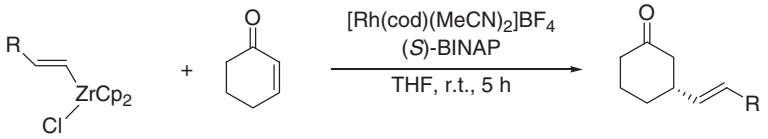
(*E*)-Arylvinylic Zr(IV) complexes reacted with dialkyl chlorophosphates in the presence of CuBr to afford (*E*)-2-arylvinylphosphonates in good to excellent yields.[128] However, the starting aliphatic acetylenes such as 1-heptyne barely reacted under similar conditions (**Scheme 79**).



Scheme 79

8.23.4.3.2.7 Rh

1,4-Addition of these alkenylzirconium reagents to α,β-unsaturated ketones has been achieved by using $Ni(acac)_2$ or copper reagents. However, an asymmetric version of the catalytic 1,4-addition of the alkenylzirconium reagents has been reported by Oi and Inoue et al.[129] In that report, (**Scheme 80**) highly enantioselective 1,4-addition of alkenylzirconocene chlorides to conjugated enones were accomplished by using a catalytic amount of a chiral rhodium complex. The *in situ* generated (*E*)-1-hexenylzirconocene chloride reacted with cyclohexenone in the presence of a catalytic amount of the rhodium(I) complex ($[Rh(cod)(MeCN)_2]BF_4$) (5 mol %) and (*S*)-BINAP (5 mol %) to give 1,4-adduct in good yield of 96% with an excellent *ee* of 96%.



Scheme 80

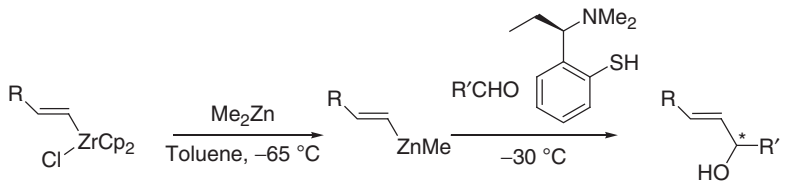
The reaction could be applied to either cyclic or acyclic enones, and either alkyl or aryl starting alkynes, with enantioselectivity up to 99% *ee*. The reaction was performed under neutral, anhydrous, and extremely mild reaction conditions. Therefore, this new method provides a facile and useful synthetic route to optically active β-(*E*)-alkenyl ketones.

8.23.4.3.2.8 Zn

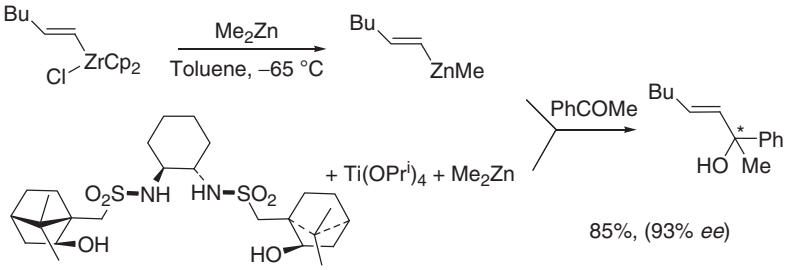
An *in situ* hydrozirconation–transmetalation–aldehyde addition process, by Wipf et al., serves as a convenient method for the generation of allylic alcohols.[130,131] A high-yielding protocol for the *in situ* transmetalation of alkenylzirconocenes to alkylzinc species[132] was performed and this reaction succeeded in developing a catalytic asymmetric protocol for subsequent additions to aldehydes.[133]

Hydrozirconation of alkynes and subsequent transmetalation to dimethylzinc gave alkenylzinc species.[134] In the presence of 10 mol% of a chiral thiobenzylamine ligand, (**Scheme 81**) the alkenylzincs reacted with aldehydes to (*E*)-allylic alcohols in up to 99% *ee*. To enhance the enantioselectivity and substrate scope of this process, a chiral β-amino thiol scaffold was evaluated in the addition reaction. Amino thiols tended to provide the highest *ee*, in part due to the higher affinity of sulfur for zinc over zirconium. A class of valine-based thiol ligands was identified to be effective for the formation of enantiomerically enriched allylic alcohols in terms of low ligand loading and high % *ee*.

According to the reports by Walsh et al.,[135] the catalyst was prepared in a separate reaction vessel by combining diaminocyclohexane ligand with $Ti(O^iPr)_4$. The reaction of 1-hexenylzinc with ketone in the presence of the catalyst proceeded to give 85% yield of alcohol with good enantioselectivity (93% *ee*) (**Scheme 82**). When the chiral ligand was used instead of the diaminocyclopentane-derived ligand, the observed 85% *ee* was slightly less than the diaminocyclohexane analog.



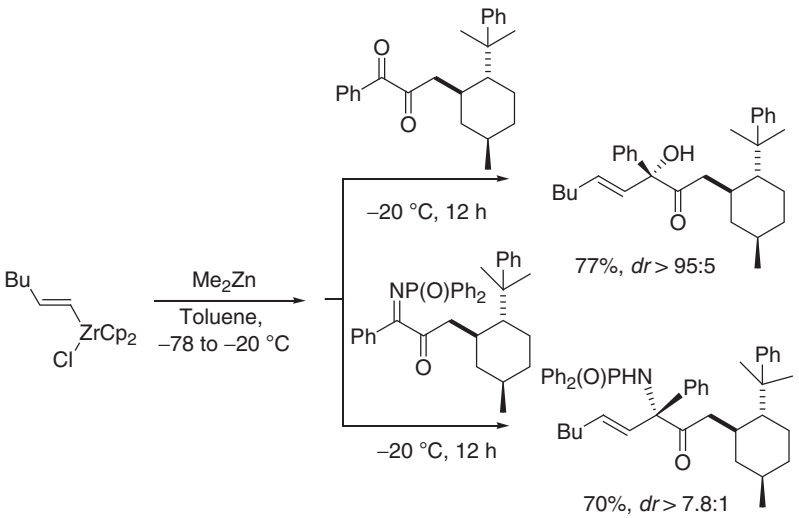
Scheme 81



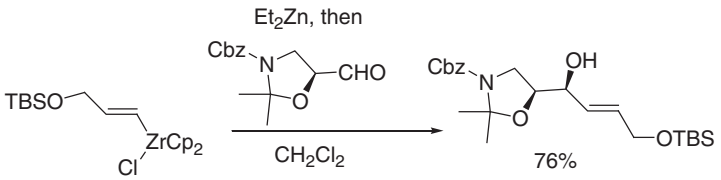
Scheme 82

Instead of the addition of chiral ligands, an 8-phenylmenthol moiety was introduced to the ketoester as a chiral auxiliary.[136] The chiral auxiliary led to the *si*-face attack to give good diastereoselectivity (Scheme 83). Replacing the C═O bond of the ketoester with a C═N bond produced the corresponding amine in comparable yield and with slightly lower diastereoselectivity.

Alkenylzirconocenes underwent transmetalation with Et_2Zn to afford vinylzinc nucleophiles. These reacted with Cbz-protected (*S*)-isoserinal acetonide to form a secondary alcohol with high *syn* diastereoselectivity (Scheme 84).[137]

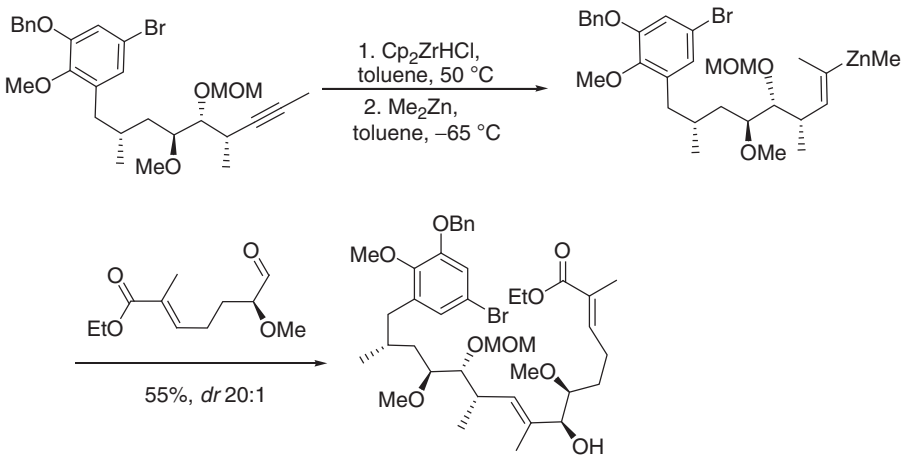


Scheme 83



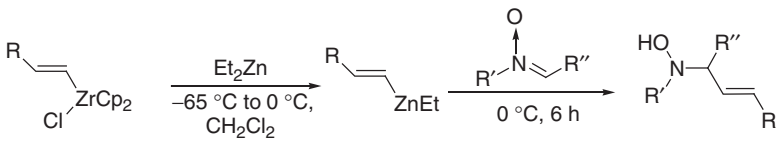
Scheme 84

Those reactions starting from 1-alkynes resulted in good to excellent enantioselectivities. With regard to internal alkynes, excellent levels of regioselectivity (>20:1) during hydrozirconation of 2-alkynes have been achieved under elevated temperature and use of 2 equivalents of Cp_2ZrHCl (Scheme 85). Accordingly, hydrozirconation was followed by transmetalation and addition to aldehyde. The product allylic alcohol was obtained in 55% yield.[138] Although analysis of the crude reaction mixtures showed partial epimerization at C10, the two diastereomers could be separated by chromatography.



Scheme 85

Beside the C=O bond, the C=N bond of nitrones could also react with the Zn reagent. (*E*)-Vinylzinc species were synthesized by hydrozirconation of alkynes followed by transmetalation.[139] In a 'one-pot' method, the Zn reagents were added readily onto nitrones to give secondary *N*-hydroxylamines in good yields (Scheme 86). The starting alkynes were limited to alkylacetylenes. Internal alkynes such as 3-hexyne were not efficient for this reaction. The yield of the corresponding product was only 30%.



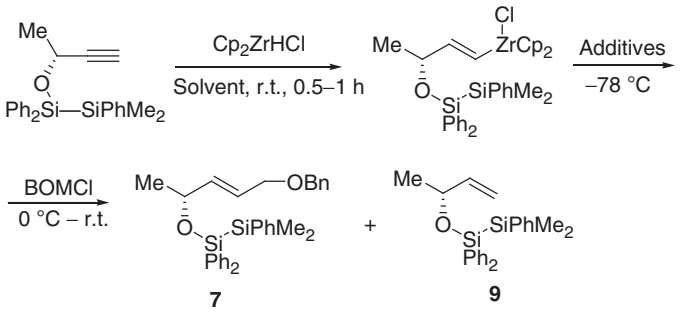
Scheme 86

Tanino et al. explored the alkylation reaction of the alkenylzirconocene intermediates (Table 9).[140] Although direct addition of BOMCl to the reaction mixture gave none of the desired products (entry 1), Lipshutz method, the combined use of methyllithium and cyano(2-thyenyl) copper lithium, promoted an alkylation reaction of an alkenylzirconocene species through a mixed cuprate but gave a low yield of 13% in the reaction with BOMCl (entry 2). In the presence of hexamethylphosphoramide (HMPA), the yield was slightly improved to 29% (entry 3). Wipf's method gave a better result in this reaction. Treatment of the alkenylzirconocene species with dimethylzinc followed by the addition of BOMCl afforded the desired optically pure disilanyl ether in 30% yield, along with 61% of the allyl ether (entry 4). In the addition with HMPA, the yield was improved to 48% (entry 5). Finally they found that addition of molecular sieves 4 A (MS4A) was remarkably effective in this particular reaction and gave the best result of 70% (entry 6).

A convenient diastereoselective synthesis of both D-*erythro*- and L-*threo*-sphingosine derivatives was reported, by reaction of L-serine-derived aldehyde and alkenylzirconocene and $ZnBr_2$ or Et_2Zn (Scheme 87). L-Serine-derived aldehyde was treated with 1-alkenylzirconocene chlorides in the presence of $ZnBr_2$ in THF at r.t. to give the natural *erythro*- (*anti*-) isomers with high diastereoselectivity (*anti*/*syn*=12–20:1). In sharp contrast, reaction with 1-alkenyl-ethylzinc and Et_2Zn in CH_2Cl_2 gave the unnatural *threo*- (*syn*-) isomers predominantly (*anti*/*syn*=1:12–15).[141]

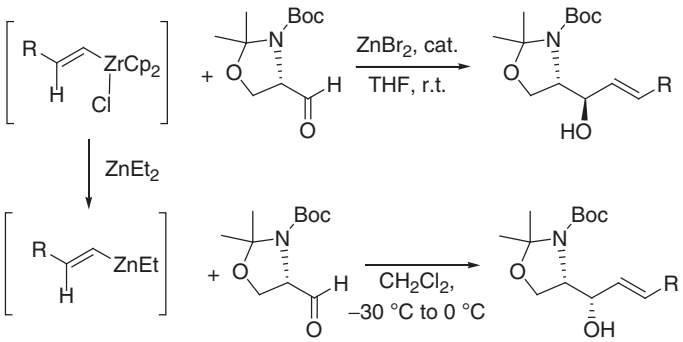
Transmetalation of alkenylzirconocene to zinc followed by addition of aldimines gave solely amine products. The reactions were carried in THF solvent and greatly accelerated by microwave irradiation.[142] In CH_2Cl_2 solvent, however, formation of amino cyclopropanes was observed by Wipf et al., which proceeded via three-component condensation of organozirconocenes, aldimines, and dihalomethanes with good stereoselectivity (Scheme 88). The reaction was expected to undergo via zinc carbenoid intermediate formed from adducts and dichloromethane, followed by Simmons–Smith-type cyclopropanation.[143] To improve the yield, 5 equivalents of CH_2I_2 was added to the reaction mixture to give the desired amino cyclopropane in good yields. Under

Table 9 Coupling of alkenylzirconocene derivatives with benzyl chloromethyl ether (BOMCl)

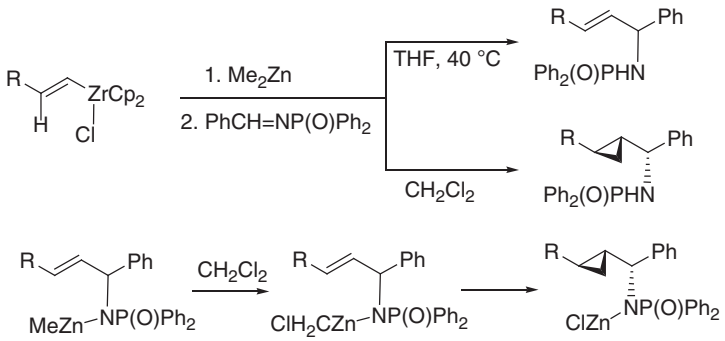


Entry	*Additives*	*Solvent*	*Yield*[a] *of* ***7***	*Yield*[a] *of* ***9***
1	None	THF	0	85
2	MeLi, (2-Th)Cu(CN)Li	THF	13	57
3	MeLi, (2-Th)Cu(CN)Li, HMPA	THF	29	–
4	Me_2Zn	CH_2Cl_2	30	61
5	Me_2Zn, HMPA	CH_2Cl_2	48	47
6	Me_2Zn MS4 Å	CH_2Cl_2	70	14

[a]NMR yield (%).



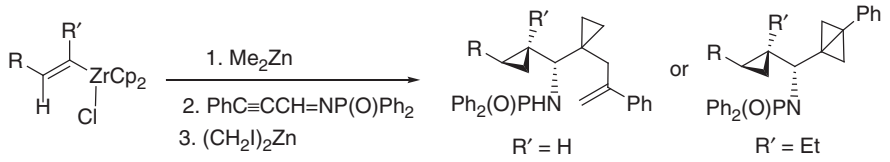
Scheme 87



Scheme 88

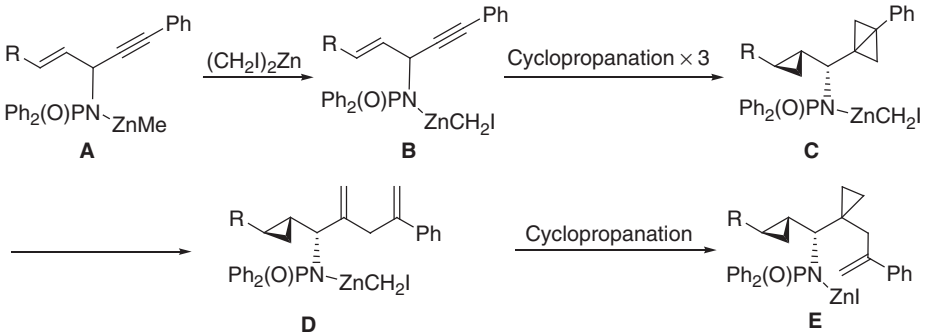
these optimized conditions, functionalized terminal and internal alkynes were converted into amino cyclopropanes in moderate to high yields and with excellent diastereoselectivity.

Furthermore, an extension of this amino cyclopropane reaction toward alkynyl imine gave *C,C*-dicyclopropylmethylamine derivatives, when terminal alkynes were treated with Cp_2ZrHCl, Me_2Zn, alkynyl imine, and $(CH_2I)_2Zn$, in this order (Scheme 89). A series of alkynes and alkynylimines were applicable in this reaction. Interestingly, when internal alkynes were used, the rare bicyclobutane derivatives could be obtained. The bicyclobutane products also gave an important hint on the mechanism.



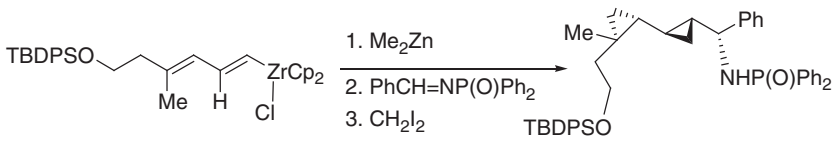
Scheme 89

The cascade process includes several carbon–carbon bond forming and cleavage steps (Scheme 90). On transmetalation of the alkenylzirconocene to dimethylzinc, addition to the imine proceeds to give **A**. Ligand exchange of **A** with $(CH_2I)_2Zn$ affords the zinc carbenoid **B,** which undergoes triple cyclopropanation at the allylic alkene as well as the alkyne moiety to give the bicyclo[1.1.0]butane **C**. Intermediate **C** undergoes a double σ-bond insertion with carbenes to give diene **D**. A final cyclopropanation of the allylic amine affords **E**.[144]



Scheme 90

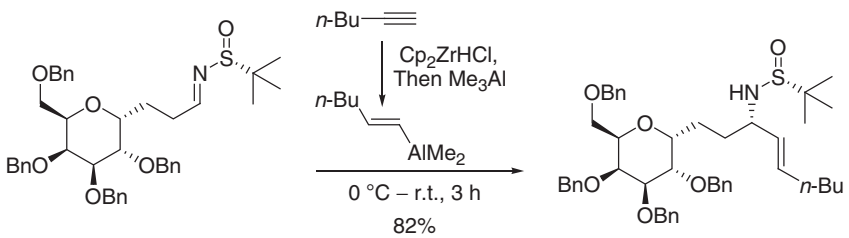
Moreover, another extension of the aminocyclopropane reaction toward dienylzirconocene gave bicyclopropylmethylamine derivatives (Scheme 91). The second cyclopropanation required more forcing conditions and an excess of diiodomethane.[145]



Scheme 91

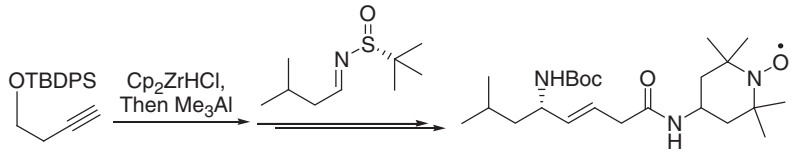
8.23.4.3.2.9 Al

Hydrozirconation/transmetalation to aluminum has been described by Schwartz et al.[146] To apply this in organic synthesis, Wipf et al. investigated the reactions of alkenylzirconium with trimethylaluminum, and the subsequent addition to electrophiles.[147] One of the key reactions in a concise synthesis of an α-C-galactosylceramide analog of KRN7000 is a diastereoselective alkenylalane addition to an *N-tert*-butanesulfinylimine, as shown in Scheme 92. In a typical procedure, 1-hexyne was treated with Cp_2ZrHCl in CH_2Cl_2 at r.t. to form the alkenylzirconocene complex. Subsequently, addition of Me_3Al followed by the reaction of the resulting alkenylaluminum compound with the starting material at 0 °C and warming to at r.t. for 3 h generated the desired allylic amine product in 82% yield as a single diastereomer.



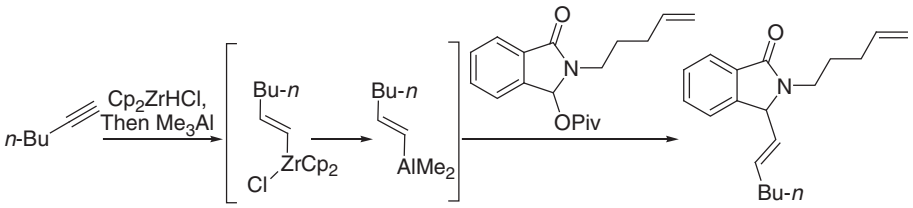
Scheme 92

In a similar procedure, an efficient and scalable one-pot method has been developed for asymmetric synthesis of 4-amino-TEMPO (4-AT) derivative (Scheme 93).[148]



Scheme 93

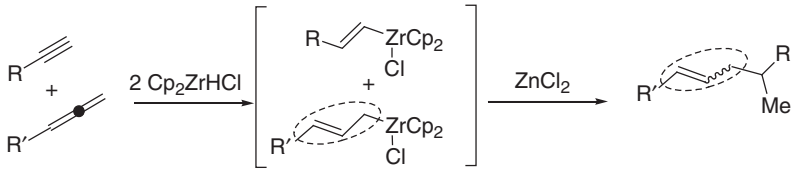
Coupling of the *in situ* generated alkenylzirconocene with an sp^3 C has been accomplished via transmetalation of Zr to Al.[149] Hydrozirconation of 1-hexyne with Cp_2ZrHCl was first carried out in CH_2Cl_2. Addition of trimethylaluminum activated the *in situ* generated alkenylzirconocene and allowed the displacement of the pivaloate in 55% yield to afford the diene product (Scheme 94).



Scheme 94

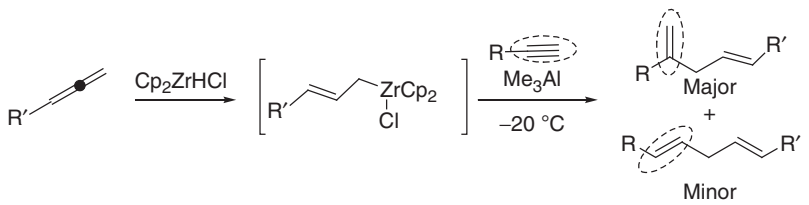
8.23.5 Hydrozirconation of Allene Derivatives

Allene derivatives are hydrozirconated with Cp_2ZrHCl to give allylzirconocenes selectively, whereas alkynes give alkenylzirconocenes. Both of them are useful protocols in organic synthesis (Scheme 95). Predictably, a mixture of allene and alkyne gave the corresponding mixture of allylzirconocene and alkenylzirconocene. When an equimolar mixture of allylzirconocenes and alkenylzirconocenes was added with $ZnCl_2$, the α-adducts were obtained as the sole products. Under the same conditions this unusual regioselectivity proved applicable to a wide range of starting allene/alkyne combinations, described by Suzuki et al.[150]



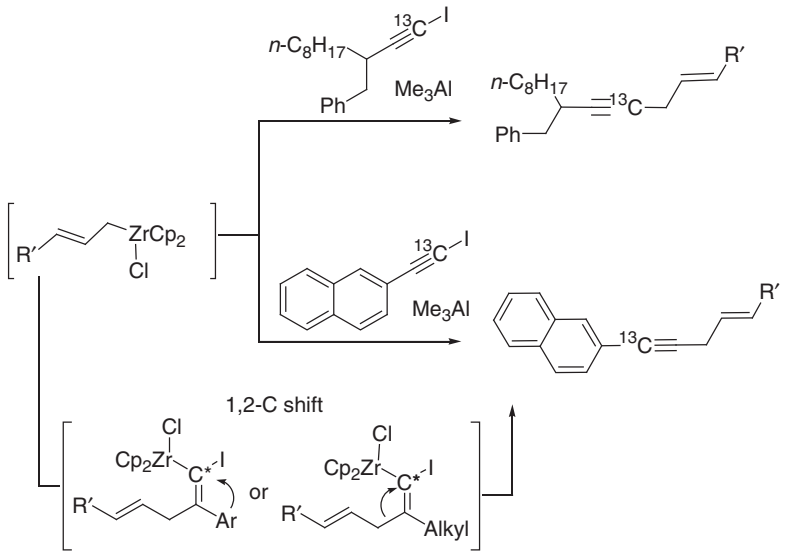
Scheme 95

Allylzirconocenes, generated from allene derivatives by hydrozirconation with Cp_2ZrHCl, were mixed with ethynylbenzene. No reaction occurred at this stage or even after the temperature was raised.[151] Me_3Al was added at −78 °C and the temperature was allowed to rise to −20 °C. A regioisomeric mixture of heptadienes was obtained in 93% combined yield with the ratio of 13:1 (Scheme 96).



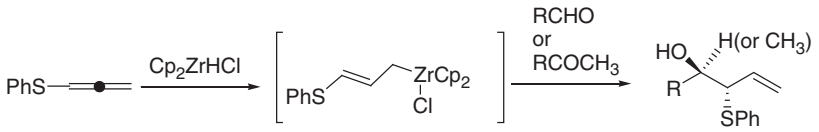
Scheme 96

However, allylzirconocenes reacted with 1-iodoalkynes to give the cross-coupled product 1,4-enynes in good yield.[152] Although either phenyl- or alkyl-substituted 1-iodoalkynes gave the same type of coupling products, the mechanisms are different (**Scheme 97**). When ^{13}C-labeled alkynes were employed for the reaction, the corresponding products clearly showed the difference between the alkyl- and aryl-substituted iodoalkynes. In the alkyl case, the allyl group directly attached to the ^{13}C position, whereas in the aryl case, two sp carbons completely switched their positions during the reaction, with the 2-naphthyl group connected to the ^{13}C. Possibly, the reaction proceeds via an alkylidene carbenoid intermediate, and 1,2- allyl or naphthyl shift gives the corresponding final product.



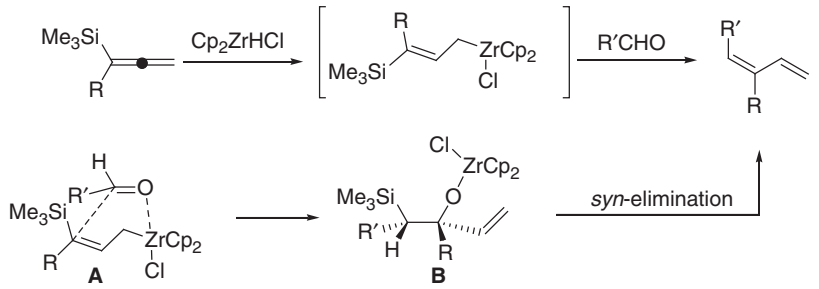
Scheme 97

Hydrozirconation of an allenyl sulfide gave the corresponding γ-thio-substituted allylzirconocene chloride quantitatively (**Scheme 98**). Application of these complexes to the addition with aldehydes and ketones resulted in antialkenyl β-sulfenyl alcohols with high regio- and stereoselectivity.[153]



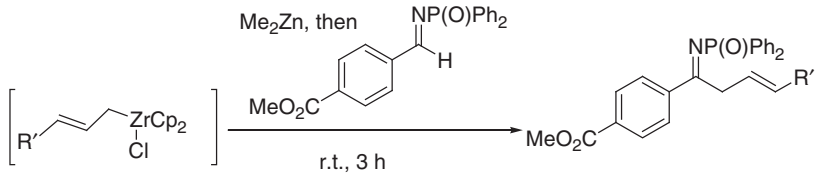
Scheme 98

TMS-substituted terminal allenes reacted with Cp_2ZrHCl to give γ-TMS-substituted allylzirconocenes (**Scheme 99**). These were treated with aldehydes to give, unexpectedly, 3-substituted terminal butadienes with *E* configuration as the major products.[154] Carbon–carbon bond at the γ-position of allylzirconocenes gave B probably via the chair-like transition state A. This was followed immediately by the Peterson olefination in a *syn* manner, which led to the formation of terminal butadiene in one step.



Scheme 99

Treatment of an allylzirconocene with dimethylzinc and an aldimine led to the (*E*)-vinylsilane in 78% yield (R^1 = TMS) (Scheme 100).[155] This reaction was then applied to variety of alkyl or aryl terminal allenes, even functionalized ones, to give good yields of the amino derivatives. However, extending this method toward chiral auxiliary-controlled addition to *N*-*tert*-butanesulfinylimines was not successful.



Scheme 100

8.23.6 Summary

Hydrozirconation of alkenes and alkynes is a very strong and convenient method providing alkyl- or alkenylzirconocene derivatives. These alkyl- or alkenylzirconocene derivatives can be converted into various useful organic compounds. Development of the combination with other synthetic method expands the area of hydrozirconation in organic synthesis continuously.

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8.24 Hydrometallation of C=C and C≡C Bonds. Group 3

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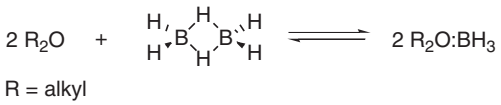
Glossary

Alkylalanes Alkylaluminum compounds.
Allylboration An addition of the allyl-B bond to the C–O or other multiple bond.
Borolanes, borinanes, and borepanes 5-7-Membered saturated boraheterocycles.
Boronates Esters of boronic acids, for example, alkylboronic acids, $RB(OH)_2$.
Desymmetrization Transformation of a symmetric prochiral compound into a chiral product.
Ditopic and polytopic boranes Boranes having two and more identical B–H groups in a molecule.
Frustrated Lewis pair A molecule containing a Lewis acid and Lewis base that cannot combine to form an adduct due to steric hindrance.
Iterative reactions The repeating reactions of the reactive group, followed by deprotection and the reaction of another group.
π-Stacking Attractive noncovalent interactions between aromatic rings.

8.24.1 Hydroboration of C=C and C≡C Bonds

8.24.1.1 General Considerations

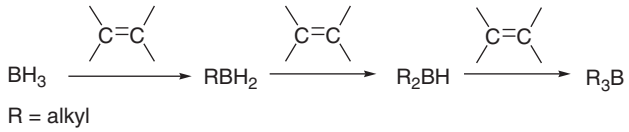
Previous information on this subject appears in books and reviews.[1–13] Hydroboration is the addition of a boron–hydrogen bond across a carbon–carbon multiple bond to give an organoborane. Although diborane reacts sluggishly with olefins in the gas phase, the reaction in ether solvents proceeds with remarkable ease, attributed to the formation of weak, highly reactive borane–ether complexes (equation 1).



(1)

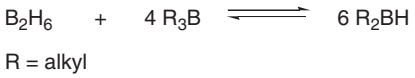
Hydroboration of olefins with borane, discovered in 1956 by Brown and Subba Rao,[14] may be conveniently carried out in diglyme or with commercially available 1 M borane–tetrahydrofuran solution. Diethyl ether can also be used, but low solubility of diborane in this solvent requires either external generation of the reagent or the use of more stable borane complexes. Such complexes formed with organic sulfides and certain hindered tertiary amines are also highly reactive and can be used in non-etheral solutions, for example, dichloromethane (DCM). Borane complexes with dimethyl sulfide, 1,4-oxathiane, pyridine, and several other tertiary amines are commercially available hydroborating reagents.

Hydroboration of olefins with the trifunctional borane molecule leads to mono-, di-, and trialkylboranes depending on the stoichiometry and structure (Scheme 1).



Scheme 1

Borane addition to terminal and unhindered disubstituted double bonds affords trialkylboranes. The addition to trisubstituted and hindered disubstituted bonds produces monoalkylboranes, and further reaction is slow. Tetrasubstituted olefins produce monoalkylboranes; further reaction is very slow and requires a large excess of olefin. Less stable unhindered mono- and dialkylboranes can be generated from lithium alkylborohydrides,[3,15] by the reduction of alkylhalogenoboranes[3,16] or by the redistribution reaction[17,18] (equation 2).

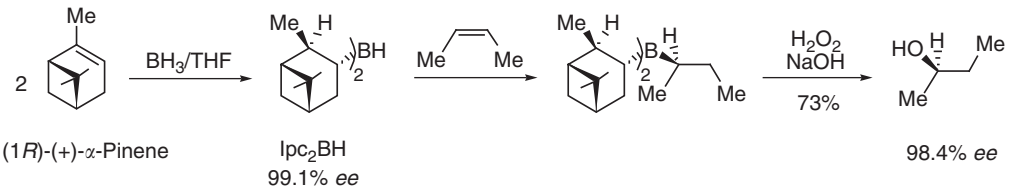


(2)

Alkyl- and dialkylboranes, alkoxyhydroboranes, halogenohydroboranes, and other organylhydroboranes are important hydroborating agents, and several of them are commercially available.

Basic features of the hydroboration reaction are the *cis*-addition of the boron–hydrogen bond, proceeding from the less-hindered side of a multiple bond and placing the boron atom at the less-substituted carbon atom[19] (Scheme 2).

Diisopinocampheylborane (Ipc_2BH) is a highly enantioselective hydroborating agent, which reacts with (*Z*)-2-butene generating a new stereogenic center of 98.4% *ee*. This transformation, reported in 1961 by Brown and Zweifel[20] using Ipc_2BH of lower enantiomeric purity, was the first highly selective asymmetric synthesis.



Scheme 2

Alkynes undergo hydroboration producing alkenylboranes,[4] which may be isolated or react further, depending on the reactivity of the hydroborating agent, stoichiometry, and the alkyne structure. Terminal alkynes react with borane affording predominantly 1,1-diborylated alkanes.[5]

Many functional groups are tolerated, for example, alkyl halides, NO_2, RCOCl, $RCONH_2$, RCOOR, epoxide, CN, and COOH. Consequently, hydroboration provides a variety of organoboranes, and their transformations are convenient methods for the formation of C–H, C–O, C–X, and C–C bonds, widely used in organic synthesis.[4–6]

In 1985, Maennig and Noeth[21] reported the hydroboration of olefins and alkynes with catecholborane (CatBH) catalyzed by $Rh(PPh_3)_3Cl$, initiating catalytic hydroboration, which expanded the reaction scope.[8–12] The selectivity of catalytic hydroboration is often complementary to the uncatalyzed reaction, less-reactive hydroborating agents react under mild conditions, and the catalyzed asymmetric reaction requires only a catalytic amount of a nonracemic ligand instead of a stoichiometric amount of a nonracemic reagent.[10,21–24]

Many functional groups are also tolerated in catalyzed hydroborations, and the reaction provides ready access to various organoboranes.

The important Suzuki–Miyaura cross-coupling reaction,[25–29] which has many industrial applications, requires a wide range of organoboranes. Many of them, such as alkyl- and alkenylboranes, their functional derivatives, and masked organoborane reagents,[30,31] are available by hydroboration. The reaction is also a powerful tool for the preparation of boron-doped π-conjugated macromolecules for optoelectronic devices.[32] It is also used for the synthesis of frustrated ion pairs,[33] an emerging group of important compounds, new ceramic materials,[34] and a range of natural products, for example, the early application to the synthesis of monensine,[35] the first synthesis of (+)-lanosterol via the carbocation–olefin cyclization route,[36] and the present approach to maitotoxin.[37]

8.24.1.2 Mechanism

The *cis*-addition and *anti*-Markovnikov regioselectivity of the hydroboration reaction were originally accounted for in terms of a simple four-centered transition state model **1** (Figure 1) serving as a useful working hypothesis.[38] Participation of the p orbital of boron removes the symmetry constraint, for the concerted thermal [2 + 2] addition, and the reaction is considered pseudopericyclic with little or no cyclic four-electron conjugation. The gas phase reaction of ethylene with borane monomer proceeds with low activation energy of ~2–3 kcal mol^{-o}.[39] Earlier theoretical calculations pointed to the formation of a loose π-complex reorganizing to the transition structure with little or no activation energy.[40–44]

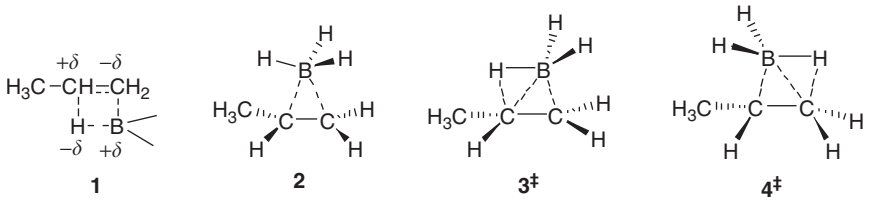


Figure 1 Proposed transition states for the borane addition to 1-propene. Reproduced from Oyola, Y.; Singleton, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 3130–3131, with permission from ACS.

Terminal alkenes undergo hydroboration with borane/THF producing organoboranes, which after oxidation give a mixture of 1- and 2-alkanols in a ratio of ~94:6. This ratio is the result of the three-step reaction (Scheme 1). The regioselectivity of steps 2 and 3, that is, hydroboration with mono- and dialkylboranes, is much higher. Consequently, the regioselectivity of the first step must be lower. Indeed, in a recent study[45] hydroboration–oxidation of perdeuterated 1-propene with BH_3/THF (1:100 equivalents) produced 1- and 2-propanol-d_6 in a ratio of 90.0:10.0 (±0.1). According to the transition state theory, this ratio corresponds to $\Delta G^{\ddagger} = 1.1–1.3$ kcal mol^{-1} for the transition states leading to products. The authors of the study undertook extensive calculations, using advanced theoretical methods and located the transition state structures $3^{\ddagger}$ and $4^{\ddagger}$ of the borane addition to 1-propene from the precursor complex **2** (Figure 1).

However, all the methods employed predicted energetic preference for $3^{\ddagger}$, resulting in much higher regioselectivity than the experimental result. Consequently, taking into account the considerable excess of energy available from the enthalpically barrierless formation of **2** (–11.0 kcal mol^{-1}), and quite small barriers for the formation of products from **2**, direct dynamic

trajectories of low selectivity to the products, faster than thermal equilibration with solvent, have been considered. To explain the experimental regioselectivity, and assumed non-TST behavior, the following three-stage mechanism has been proposed: a 'direct-trajectory' stage, with low selectivity; an Rice-Ramsperger-Kassel-Marcus (RRKM) stage, with medium selectivity; and a thermally equilibrated stage developing over several picoseconds.[45] In another theoretical study of the reaction, the competition between direct and indirect process was treated by an extension of a unified statistical model that does not involve running trajectories.[46] The RRKM – Master Equation model was also proposed as an alternative interpretation preserving a statistical reaction model.[47]

Experimental results for hydroboration with borane/THF and $BH_3 \cdot SMe_2$ established the dissociation of the borane complex to the free monomer and its reaction with an olefin as a general mechanism for borane–Lewis base complexes.

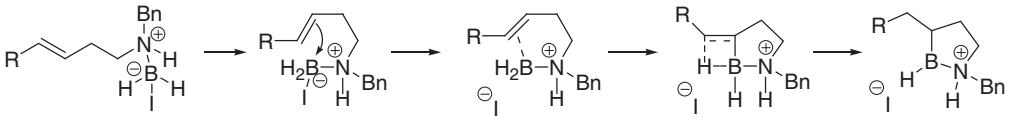
Hydroboration with dialkylboranes, which exist as dimers in solution, depends on the reagent and the substrate used. The reaction of moderately hindered alkenes with dialkylborane dimers, such as $[9\text{-BBN}]_2$, $[Ipc_2BH]_2$, $[Chx_2BH]_2$, and [3,6-dimethylborepane]$_2$, can be described by the three half-order kinetics, indicating that the rate-determining step is the olefin hydroboration by a monomer.[48–55] Hydroboration of bulky internal olefins with these reagents exhibits complex kinetics.

In contrast, hydroboration with $[Sia_2BH]_2$ exhibits the second-order kinetics regardless of alkene reactivity, indicating an associative mechanism involving a direct reaction of the dimer with an olefin.[48]

The reactions of 1-hexyne with $H_2BBr \cdot SMe_2$, 1-octene, and 4-octene with $HBBr_2 \cdot SMe_2$, $HBCl_2 \cdot SMe_2$ in a noncoordinating solvent, DCM, proceed by the dissociative mechanism.[51–53]

Controlling factors in these reactions are the complexing Lewis base and its amount in the reaction medium. Thus, the above-mentioned alkenes react with $H_2BCl \cdot THF$ in THF by a direct attack on the complex.[54]

A recent study demonstrates that homoallylic amines complexed with monoiodoborane undergo highly regioselective intramolecular hydroboration by a direct transfer of the complexed group to the double bond via an S_Ni-like displacement (Scheme 3).[55]



Scheme 3

8.24.1.3 Hydroborating Agents

8.24.1.3.1 Borane

A commercially available 1 M borane solution in THF is widely used and its reactivity has been described.[56] The reagent is stabilized with a small amount of sodium borohydride or better with Bu^{t}Me*i*PrN (NIMBA),[57] which is also used to stabilize BD_3/THF.[58]

The reagent can be prepared in concentrations of ~2 M by absorbing gaseous diborane in THF, conveniently generated from sodium borohydride and boron trifluoride etherate in diglyme. The procedure has been adapted for a small-scale reaction.[59] Other methods for its generation are known.[60,61]

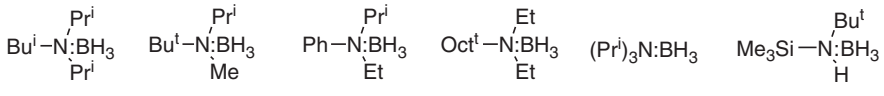
Although borane/THF is an excellent, highly reactive reagent, it is limited to one solvent, 1–2 M concentration, and has to be stabilized.

Borane-dimethyl sulfide complex (BMS) is free of these inconveniences and its scope is wider.[62] The commercially available complex is a pure 1:1 adduct, ~10 M in BH_3, stable indefinitely at room temperature, and soluble in ethers, DCM, benzene, and ether solvents. A disadvantage is an unpleasant odor of highly volatile and flammable dimethyl sulfide, which is insoluble in water. To circumvent this inconvenience, borane complexes with various less volatile sulfides, such as 1,4-oxathiane,[63] diisoamyl sulfide and dodecylmethyl sulfide,[64,65] (perfluorooctyl)ethyl methyl sulfide[66] (which can be recycled), borate esters of hydroxydialkyl sulfides[67] (which are water soluble), and polymeric sulfides,[68] have been developed.

Borane complexes with unhindered tertiary amines are more stable and require elevated temperatures for dissociation enabling hydroboration with the liberated borane. Slow release of borane can be advantageous, as in the transformation of cyclododeca-1,5,9-triene into tricyclic organoborane, involving intramolecular hydroboration of the intermediates.[69] However, organoboranes may undergo thermal isomerization at elevated temperatures. In contrast, certain hindered tertiary alkylamines and trimethylsilylamines of intermediate steric requirements form less stable, reactive borane complexes, whereas very hindered amines, for example, 2,2,6,6-tetramethylpiperidine, do not complex borane at room temperature. *N*,*N*-Dialkylanilines and pyridine, which are less basic than trialkylamines, are also used as borane carriers.[70]

Many reactive borane–amine complexes have been prepared and tested as hydroborating and reducing agents. Among them, such reagents as the complexes **5**–**10** shown in Figure 2 are highly reactive and hydroborate 1-octene in THF at room temperature in less than 1 h.[71–74]

Borane–amine complexes are soluble in various solvents, for example, THF, dimethoxyethane (DME), benzene, DCM, hexanes, and pentane. The reagents are environmentally benign since the amines can be recovered and recycled. Trimethylsilylamines hydrolyze readily to the corresponding amines. Complexes **5**, **7**, and **10** have been used for the synthesis of representative mono- and dialkylboranes. Their hydroboration characteristics are generally comparable to borane/THF. Unusual reactivity of **5** was



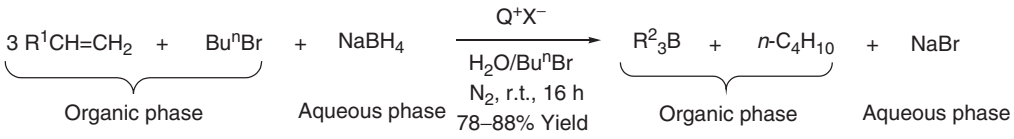
5 Liquid | **6** Liquid | **7** Liquid | **8** Liquid | **9** Solid | **10** Solid

Figure 2 Borane complexes with hindered amines.

observed in DCM, making possible selective hydroboration of internal olefins in the presence of less-hindered terminal olefins.[75] Borane–amine and borane–phosphine complexes have been reviewed.[76]

In situ generated borane is often used as a convenient hydroborating agent. Among several methods for the preparation of diborane, the reaction of sodium borohydride with boron trifluoride etherate in dyglyme was used for the *in situ* reaction in early hydroborations. Boron trifluoride etherate can be replaced with iodine,[77–78] sulfonates, sulfates, and alkyl halides.[79]

Diborane is also conveniently generated from quaternary ammonium borohydrides, which react with iodine or benzyl chloride in toluene,[80] methyl iodide, ethyl bromide, or 1,2-dichloroethane (DCE) in DCM,[81] or chlorotrimethylsilane in DCM.[82] In an ongoing search for a practical, low-cost, safe, and environmentally benign procedure, borane generated *in situ* from sodium borohydride and 1-bromobutane was used for hydroboration of olefins under phase-transfer catalysis conditions[83] (equation 3).



(3)

R^1 = Bu^n; *n*-C_6H_{13}; *n*-C_8H_{17}; Ph; 4-MeC_6H_4; 4-BrC_6H_4; 4-ClC_6H_4; 4-FC_6H_4; R^2 = $R^1CH_2CH_2$

Q^+X^- = $(C_8H_{17})_3N^+MeCl^-$; $C_{16}H_{33}P^+Bu_3Br^-$; $Bu_4N^+Cl^-(Br^-)$; $Bu_4P^+Cl^-(Br^-)$; $(C_6H_{13})_4N^+Cl^-$

Internal olefins, such as cyclohexene, norbornene, 7-tetradecene, 1-methylcyclohexene, and α-pinene, were also transformed into corresponding organoboranes in 78–90% yield.

8.24.1.3.2 Aminoboranes

Generally, aminoboranes are not active hydroborating agents. However, pyrrolylborane/THF, readily available by reaction of pyrrol with borane/THF, hydroborates unhindered alkenes and alkynes at room temperatures producing pyrrolyl(dialkyl)- and pyrrolyl(alkenyl)boranes, respectively.[84,85] The regioselectivity of the addition to 1-octene is 99:1, styrene 86.4:13.5, and 1-phenylpropyne 62:38. Isoprene and 1,5-cyclooctadiene undergo cyclic hydroboration with pyrazolyl- and other azolylboranes. The latter diene reacts with carbazolylborane producing 3-carbazolyl-9-borabicyclo[4.2.1]nonane.[86]

8.24.1.3.3 Borohydrides

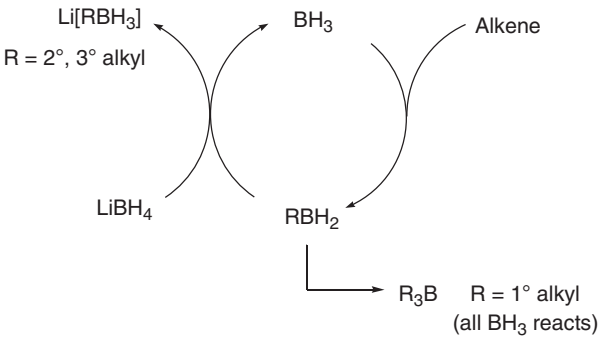
Zinc borohydride reacts with terminal alkenes in refluxing THF affording trialkylboron species.[87] At the molar ratio 1:2, dialkyl boron species are obtained. The reactivity difference of terminal/internal olefins is 6.5:1, enabling selective hydroboration of skipped terminal–internal dienes at the terminal double bond. Terminal alkynes react as far as the dialkylborane stage. Workup of the reaction products is simplified since no organic side products are formed from the reagent, as is the case with organylhydroborane reagents.

Lithium borohydride does not hydroborate simple unhindered alkenes but reacts slowly with 2,3-dimethyl-2-butene in THF at 60 °C.[88] In the presence of a small amount of borane the reaction is complete in 6 h at room temperature. The reactivity order of olefins in this reaction is tetramethylethylene > cyclohexene >> 1-hexene (unreactive), which is opposite to the order in hydroboration with borane/THF. The reversed reactivity is the result of the redistribution reaction of lithium borohydride with the intermediate alkylborane formed in the initial hydroboration of an olefin with the small amount of added borane. Terminal olefins react fast, utilizing all the borane, to give trialkylboranes, which do not react with lithium borohydride. Hindered olefins produce mono- or dialkylboranes in the initial reaction with borane, which are transformed into lithium alkylborohydrides with the regeneration of borane[88] (**Scheme 4**).

The hydroboration of substituted alkenes with lithium or sodium borohydride in the presence of a small amount of titanium tetrachloride or chlorotrimethylsilane, generating the initial borane, also proceeds according to **Scheme 4**.

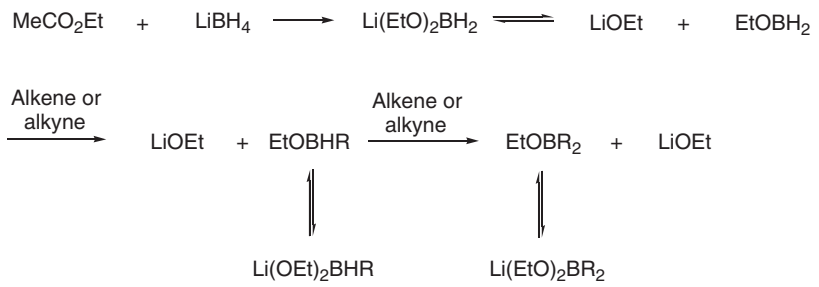
A tandem reduction–hydroboration of olefins was achieved with calcium and lithium borohydrides in the presence of ethyl acetate in the molar ratio 1:1:1 at reflux in THF in 5–7 h.[89] The relative reactivity of terminal/internal alkenes, 9:1 for the calcium reagent, was taken advantage of in selective hydroboration of (*Z*)-1,11-hexadecadiene.

The reduction–hydroboration of alkenes with lithium borohydride/ethyl acetate affords dialkylborinates, whereas alkynes give rise either to vinylboronates or vinylborinates, depending on the structure and reactivity of the alkyne and the stoichiometry.[90] The regioselectivity of the addition to terminal alkenes is similar to borane/THF but with phenylacetylene and phenylpropyne the



Scheme 4

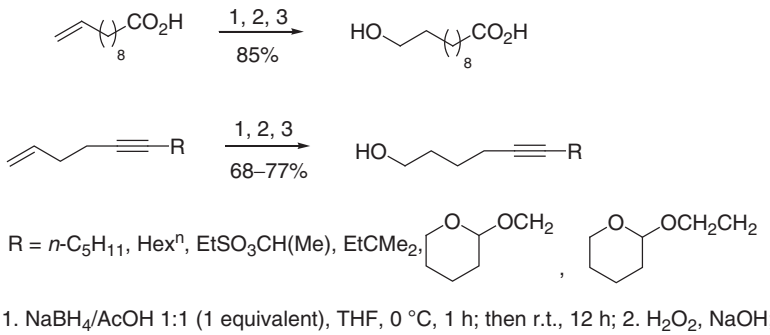
boron atom is preferentially placed in the α-position to the phenyl ring. The following reactivity differences as compared to borane/THF have been observed. Thus, with an excess of alkene the reaction proceeds cleanly to the second stage and stops there, whereas with borane trialkylborane is formed. Hydroboration of alkynes with borane leads to large amounts of 1,1-diboranyl-substituted products. Reduction–hydroboration of internal alkynes goes as far as the second stage, whereas terminal alkynes react to the first stage. The proposed reaction course is shown in Scheme 5.



Scheme 5

Lithium triethylborohydride (Superhydride®) hydroborates arylalkenes to give lithium (1-arylalkyl)triethylborates, the Markovinikov addition products, which can be transformed into mixed (1-arylalkyl)diethylboranes by treatment with methanesulfonic or hydrochloric acid.[91]

Lithium acetoxyborohydride[92,93] conveniently generated from sodium borohydride and acetic acid or mercuric acetate in THF hydroborates *in situ* one equivalent of mono-, di-, or trisubstituted C=C bonds.[94] The reaction is slow and takes several hours at room temperature. Hydroboration of 1-alkenes in 1:1 M ratio produces a mixture of mono- and dialkylboranes. Functional groups such as ester, amide, alkyl halide, tosylate, or methanosulfonate are tolerated.[95] An interesting result is the hydroboration of unprotected 10-undecenoic acid (Scheme 6). In contrast, the carboxylic group is readily reduced with borane/THF. Under the same conditions 2,4-enynes undergo hydroboration of the double bond (Scheme 6).[94,96]



1. $NaBH_4$/AcOH 1:1 (1 equivalent), THF, 0 °C, 1 h; then r.t., 12 h; 2. H_2O_2, NaOH; 3. H^+.

Scheme 6

Sodium malonyloxyborohydride, prepared from a 1:1 mixture of malonic acid and sodium borohydride in dry THF, hydroborates terminal alkenes at 60 °C in ~5 h with high regioselectivity (98:2), and unusual formation of monoalkylboron species, even at the 2:1 alkene/reagent ratio.[97]

8.24.1.3.4 Monoalkyl- and monoarylboranes

Representative monoalkyl and monoaryl hydroborating agents are presented in Figure 3. Hydroboration of terminal alkenes with borane complexes proceeds rapidly past the monoalkylborane stage. Only for certain highly hindered alkenes such as 2,3-dimethyl-2-butene or 2,4,4-trimethyl-2-pentene can the reaction be controlled to achieve the synthesis of the corresponding monoalkylboranes, thexylborane $ThxBH_2$[98] and DIBborane.[99] Monoisopinocampheylborane, $IpcBH_2$, and $ThxBH_2$ are well-established reagents, and their reactions have been reviewed.[98,100]

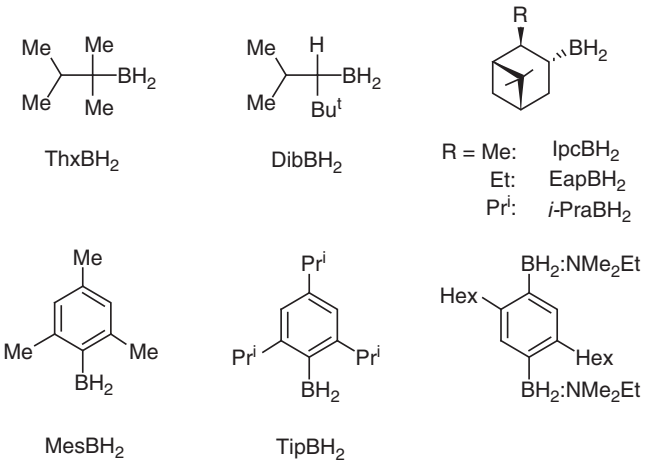
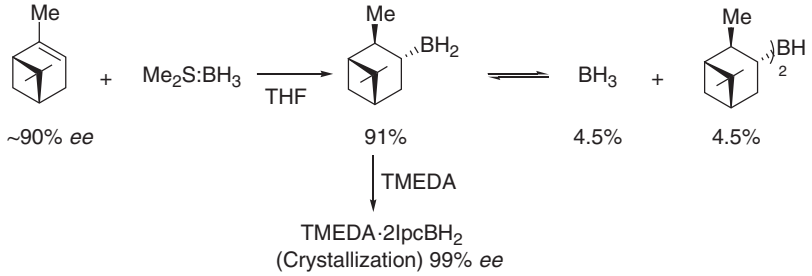


Figure 3 Monoalkylboranes and monoarylboranes.

$ThxBH_2$ must be prepared freshly before use since it has a tendency to undergo dehydroboration and isomerization. When treated with tetramethylethylenediamine (TMEDA), a stable $2ThxBH_2$–TMEDA complex is formed. It hydroborates internal olefins with displacement of 2,3-dimethyl-2-butene to give the corresponding 2:1 monoalkylborane–TMEDA complex. Free monoalkylboranes are liberated by treatment of the complex with boron trifluoride etherate. Chiral reagents, $IpcBH_2$, $EapBH_2$, and *i*-$PraBH_2$, which are more selective than $ThxBH_2$, have been prepared by hydroboration of the corresponding olefins with BMS.[101,102] Thus, TMEDA · $2IpcBH_2$ precipitates from the equilibrium mixture obtained by the reaction of α-pinene with BMS in a 1.2:1 M ratio (Scheme 7).



Scheme 7

The complex prepared from α-pinene, ~90% *ee*, can be upgraded by crystallization to 99% *ee*. Alternatively, the enantiomeric purity of α-pinene can be upgraded by crystallization at low temperature.[103] The 1:1 $IpcBH_2 \cdot DMAP$ complex is prepared in the same way, or by hydroboration with $DMAP \cdot BH_3$, catalyzed by iodine.[104] The complex prepared from α-pinene, ~90% *ee*, is upgraded to 99% *ee* after two crystallizations from methanol in 45% yield. It can be readily transformed into $K[IpcBF_3]$, a potential precursor of $IpcBF_2$, a chiral Lewis acid. A frequently used procedure for the preparation of $IpcBH_2$ starts with Ipc_2BH, 99% *ee*, readily available from α-pinene, ~90% *ee*, by hydroboration–crystallization. Ipc_2BH treated with TMEDA affords TMEDA · $2IpcBH_2$, displacing α-pinene.[105]

An alternative general approach to monoalkylboranes is the reduction of alkylboronic esters with lithium tetrahydroaluminate producing lithium monoalkylborohydrides in excellent yield. Treatment with a stoichiometric amount of ethereal solution of hydrogen chloride, chlorotrimethylsilane, or methyl iodide liberates the monoalkylborane[15] (Scheme 8).

Lithium monoalkylborohydrides are stable and can be stored over long periods, whereas simple monoalkylboranes are not stable and must be used within 1–2 h. In contrast, Bu^tBH_2 is remarkably more stable and no change in its solution in THF after 1 week is detected. An interesting feature of simple monoalkylboranes is their ability to react cleanly with one equivalent of internal olefins. $MeBH_2$ and Bu^tBH_2 can also cleanly monohydroborate 2-methyl-2-pentene, whereas only $MeBH_2$ can monohydroborate 1-hexene. Mixed trialkylboranes $R^1R^2R^3B$ have been prepared by stepwise hydroboration of two different olefins.[15]



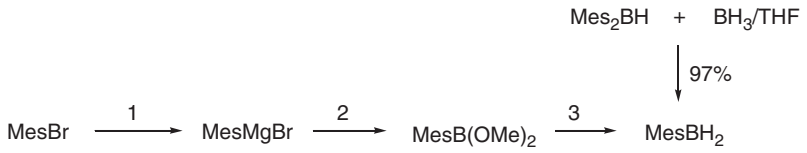
R = Me, Pr^i, Bu^n, Bu^s, Bu^t

1. $LiAlH_4$, Et_2O, pentane; 2. HCl/Et_2O, THF.

Scheme 8

The opposite approach, the stepwise reduction–hydroboration starting with R^1BBr_2, also leads to $R^1R^2R^3B$.[16] Such mixed trialkylboranes can also be prepared via hydroboration with mesitylborane and substitution of the mesityl group with an R^3 group.[106]

Sterically hindered arylboranes, for example, 2,4,6-trimethylphenylborane, mesitylborane, $MesBH_2$,[106] and 2,4,6-triisopropylborane, $TipBH_2$,[107] are readily available from the corresponding boronic esters. Mesitylborane can also be prepared from commercially available dimesitylborane by the redistribution reaction with borane/THF[106] (Scheme 9).

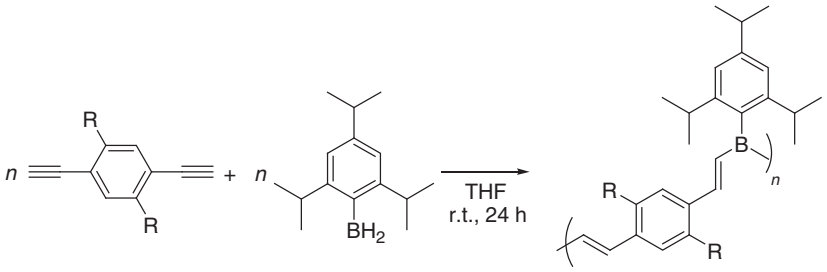


1. Mg, THF, 98%; 2. $B(OMe)_3$, 73%; 3. 1. $LiAlH_4$, 2. Me_3SiCl, 3. Crystallization, 73%.

Scheme 9

Mesitylborane, which is similar in reactivity to thexylborane, has a few important advantages.[106] Thus, it is a crystalline (m.p. 46 °C), stable borane, and does not undergo dehydroboration, isomerization, or redistribution after 24 h at room temperature. A 16% loss of the hydride activity in THF after 7 days was observed; however, pure crystalline $MesBH_2$ was recovered in 75% after 2 weeks. The reagent can sequentially hydroborate two different 1-alkenes, something that cannot be achieved with thexylborane, requiring a more hindered olefin in the first step. The regioselectivity of mesitylborane, ~99% in each step, is even higher than that of thexylborane.

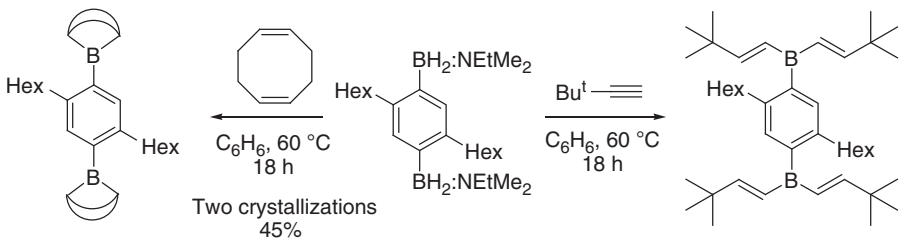
Hydroboration–polymerization of aromatic dynes is an important practical application of arylboranes, leading to electron-deficient π-conjugated organoboron polymers, optoelectronic materials that emit a blue-to-green light[108–109] (equation 4).



(4)

R = H, Me, OMe

Ditopic boranes containing two BH_2 groups are emerging reagents for the synthesis of new organoboron polymers. The reagent complexed with *N*-ethyldimethylamine (Scheme 10) has been prepared in the same way as $MesBH_2$. The uncomplexed form is not stable; however, even when complexed with an unhindered amine, which is a relatively strong Lewis base, it hydroborates terminal acetylenes and internal olefins.[110]



Scheme 10

8.24.1.3.5 Dialkylboranes

Hydroboration of certain moderately hindered alkenes with borane can be halted at the dialkylborane, which can be used for hydroboration of less-hindered alkenes. Unhindered dialkylboranes can be generated in other ways. Representative reagents are presented in Figure 4.

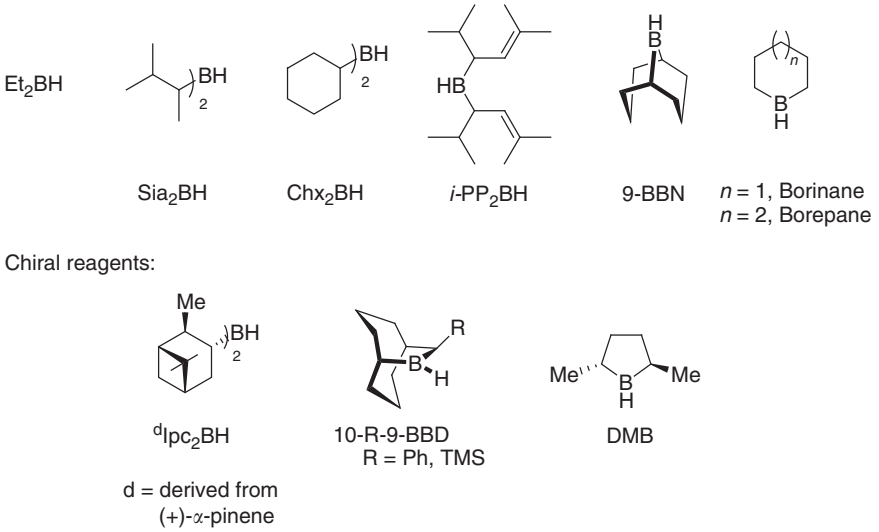


Figure 4 Dialkylboranes.

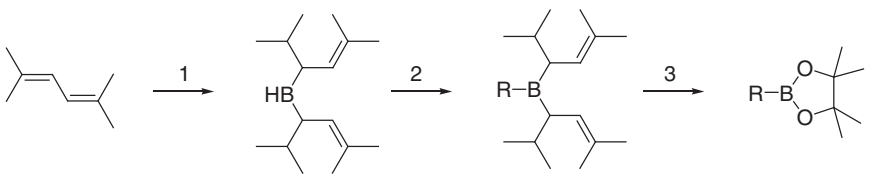
With the exception of a few highly hindered cases, dialkylboranes exist as dimers in solution. However, for convenience of presentation monomeric structures are shown.

Diethylborane is readily generated from BMS and triethylborane. In the presence of dimethyl sulfide, it is stable for prolonged periods when kept at 0–5 °C. The reagent is highly reactive and hydroborates alkenes and alkynes even at low temperature.

Bis(3-methyl-2-butyl)borane, Sia_2BH, prepared from 2-methyl-2-butene, was the first widely used reagent more selective than borane. Its limited stability requires its use when freshly prepared. The selectivity of Sia_2BH is governed by steric interactions and is higher than borane and monoalkylboranes (Table 4). The reagent discriminates well between terminal and internal double bonds of dienes. In contrast to borane, the monohydroboration of terminal alkynes with Sia_2BH is readily achieved, making possible a conversion of enynes to dienes. Hydroboration with Sia_2BH has been reviewed.[111,112]

Dicyclohexylborane, Chx_2BH[113,114] (Figure 4), readily prepared by the hydroboration of cyclohexene with borane complexes, is a solid, sparingly soluble in diethyl ether and tetrahydrofuran, and can be isolated or used as a slurry. Its selectivity is slightly lower as compared to Sia_2BH, but it is more stable, less prone to disproportionation, and often substitutes for Sia_2BH. Its synthetic applications have been reviewed.[115]

Bis(isopropylprenyl)borane, *i*-PP_2BH, generated *in situ*, has been introduced to provide convenient access to alkyl- and alkenylboronic acids.[116] Its unique feature is the nonoxidative, one-pot transformation of the hydroboration product into boronates (Scheme 11).

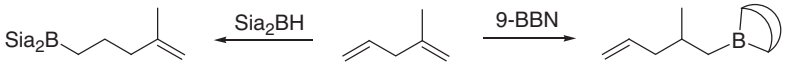


1. BH_3/THF or $NaBH_4$, diglyme; 2. Alkene or alkyne (1 equivalent);
3. 1. H_2O, 0.5 h, r.t., 2. $HCHO_{aq}$ (1 equivalent), 24 h, r.t., 3. Pinacol (1.1 equivalents).

Scheme 11

Other diols can also be used in the final step. The hydroboration product is an allylic organoborane, reacting with water and aldehydes. Consequently, both groups are removed under mild conditions at room temperature, the first one with water and the second one with formaldehyde. 1-Alkynes undergo monohydroboration with high (99%) *anti*-Markovnikov regioselectivity. Acetal, carbonate, and acetate groups and OBn, OMEM, and OTf protecting groups are tolerated.[116,117] Noteworthy is the direct conversion of alkenyl organoborane products into potassium alkenyltrifluoroborates.[117]

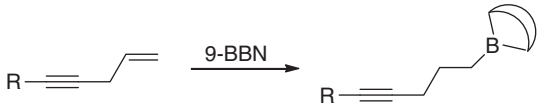
9-Borabicyclo[3.3.1]nonane, 9-BBN, is commercially available and can be readily prepared by hydroboration of 1,5-cyclooctadiene.[118] It is the most versatile hydroborating agent, described in monographs and reviews.[119,120] Recently, polymer-supported 9-BBN has been reported.[121] 9-BBN is a stable, solid dimer, and its thermal stability enables hydroboration at 30–80 °C. Most alkenes react at these temperatures in 1 h, even tetrasubstituted alkenes that fail to react with Sia_2BH. The reagent is also more sensitive to electronic effects than Sia_2BH. Thus, the difference in reactivity between 4-trifluoromethylstyrene and 4-methoxystyrene is 1.5 for Sia_2BH and 67 for 9-BBN.[122] The difference is also demonstrated in the selective hydroboration of 2-methyl-1,4-pentadiene (Scheme 12).



Scheme 12

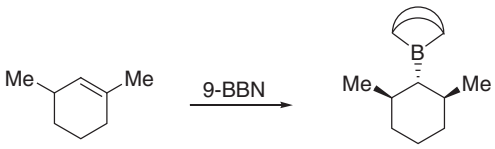
The relatively slow rate of reduction of many functional groups with 9-BBN makes possible hydroboration of functionalized alkenes. Vinylic, allylic, and isolated derivatives react with remarkable regioselectivity (Table 6) (Section 8.24.1.4.4.1).

Unlike most dialkylboranes, 9-BBN reacts with alkenes faster than with the corresponding alkynes, enabling selective hydroboration of enynes (equation 5).



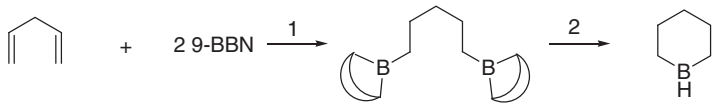
(5)

9-BBN is also a highly stereoselective reagent. For example, the hydroboration of 1,3-dimethylcyclopentene and 1,3-dimethylcyclohexene affords none of the *cis*-1,2-isomer that is formed in significant amounts when Sia_2BH is used (equation 6). B-Alkyl-9-BBN derivatives are valuable substrates for the Suzuki–Miyaura cross-coupling and other transformations.



(6)

Simple dialkylboranes can be generated by the redistribution reaction,[17] reduction of dialkylhalogenoboranes,[16] or conveniently from stable lithium dialkylborohydrides,[123–125] similarly to monoalkylboranes. They are unstable, readily disproportionate, and must be used freshly prepared. In contrast, borinanes and borepanes do not disproportionate readily and can be prepared by hydroboration of 1,4-pentadiene and 1,5-hexadiene with 9-BBN, respectively, followed by redistribution with borane[126] (Scheme 13). Their 3,5- and 3,6-dimethyl derivatives are formed directly by the hydroboration with borane. Trialkylboranes obtained from these reagents and internal alkenes are useful in free-radical reactions.[127]

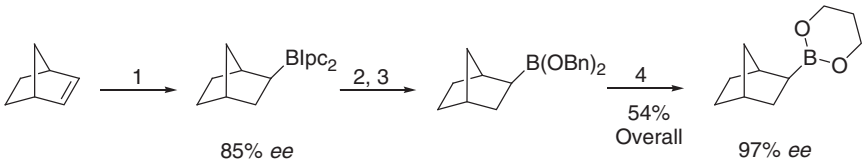


1. *n*-hexane, 25 °C, 6 h; 2. BH_3:SMe_2, 25 °C, 24 h.

Scheme 13

The most enantioselective chiral dialkylborane hydroborating agents are presented in Figure 4. Diisopinocamphenylborane, Ipc_2BH, is an important, widely used asymmetric hydroborating agent, readily available in high enantiomeric purity, 99% *ee* from α-pinene (~90% *ee*) by hydroboration/crystallization.[128] Its synthetic applications have been extensively reviewed,[19,129,130] and theoretical models, accounting for the observed enantioselectivity, have been proposed.[131] It is the reagent of choice for the hydroboration of (*Z*)-disubstituted olefins, achieving 98.4% *ee* in the reaction with (*Z*)-2-butene (Scheme 2) and even higher with cycloalkenes and heterocyclic olefins. The selectivity of its reactions with (*E*)-alkenes and other more hindered olefins is much lower due to slow reaction accompanied by dehydroboration. This produces α-pinene and $IpcBH_2$, which is more reactive and hydroborates faster with the opposite enantioselectivity, lowering the enantiomeric excess of the product. In spite of this inconvenience, enantiomerically pure transformed products, for example, boronic acids, can be obtained by crystallization of either the intermediates or products[132] (Scheme 14).

The enantioselectivity of the hydroboration of simple 1,1-disubstituted alkenes with Ipc_2BH is also low. Apparently, the reagent does not differentiate enough between similar alkyl groups. However, when the substituents differ more in steric

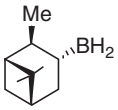
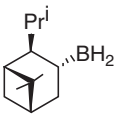
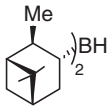
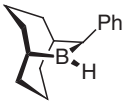
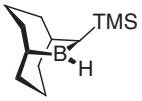
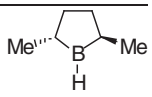


1. $^{d}Ipc_2BH$, Et_2O, 25 °C, 24 h; 2. PhCHO (1.8 equivalents), r.t., 6 h; 3. $BF_3{\cdot}Et_2O$ (1 mol%), r.t., 30 h; 4. 1,3-propanediol.

Scheme 14

requirements high selectivity can be achieved.[133] The comparison of the enantioselectivities obtained in the hydroboration of four classes of alkenes with selected chiral reagents is presented in Table 1.

Table 1 Asymmetric hydroboration of representative prochiral alkenes with mono- and dialkylboranes in diethyl ether[a]

Alkene class	*Monoalkylboranes*		*Dialkylboranes*			
Alkene	 IpcBH$_2$[b]	 *i*-PraBH$_2$[b]	 Ipc$_2$BH[c,e]	 10-Ph-9-BBD[d]	 10-TMS-9-BBD[d]	 DMB[e]
	1.5[b]	8[b]	21[c,e]	28[d]	40[d]	–
	24	38	99.1[e] 98.4	32	84	97.6[e]
	73	76	14[e]	96	95	99.5
	53	80	15[e]	74	–	97.6

[a]Values expressed as % *ee*.
[b]1998MoleculesOnline29.
[c]1964JACS1076; 1988ACR287.
[d]2008JACS9218.
[e]1985JACS4549.

Other chiral dialkylboranes derived from terpenes, such as 2- and 3-carene, limonene, longifolene, and a chloroborane prepared from nopol methyl ether, are no more selective. Certain derivatives may be useful in asymmetric synthesis, for example, *B*-allyl-2-diisocaranylborane is a highly enantioselective allylborating reagent,[134] and asymmetric hydroboration with the above-mentioned chloroborane is influenced by electronic effects.[135]

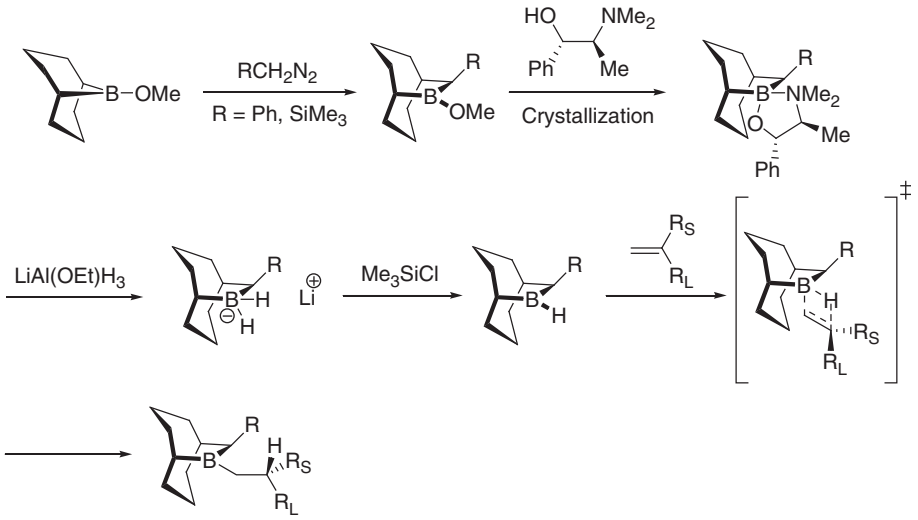
Trans-2,5-Dimethylborolane (DMB) (Figure 4) exhibits high enantioselectivity (>97%) in the hydroboration of olefins, except 1,1-disubstituted alkenes (Table 1). However, its lengthy synthesis involving two resolutions detracts from practical applications.[136,137]

Over recent years 10-TMS- and 10-Ph-9-borabicyclo[3.3.2]decanes (9-BBD) (Figure 4) have emerged as convenient enantioselective hydroborating agents, and their *B*-allyl and *B*-allenyl derivatives as valuable reagents for asymmetric synthesis.[125,138–140] Hydroboration of 1,1-disubstituted alkenes with 10-Ph-9-BBD and 10-TMS-9-BBD and their synthesis is presented in Scheme 15.

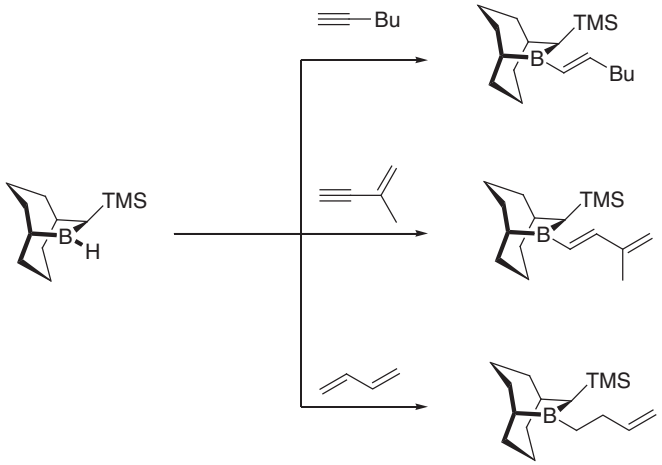
A quantum-mechanical study of alkene hydroboration with 10-R-9-BBD (R=Ph, TMS, and also *t*Bu, $SnMe_3$) showed that the 10-R group and its conformation is more important than the exact borabicyclo boat/chair ring conformation originally proposed.[125,141]

Unlike 9-BBN, 10-R-9-BBD monohydroborates 1-alkynes cleanly. The reactivity order 1-alkynes ≈ 1-alkenes > 1,1-disubstituted alkenes > 1,2-disubstituted alkene (cyclohexene) makes possible selective monohydroboration of isopropenylacetylene at the triple bond, and of 1-butene in the presence of cyclohexene. The 1,2-addition to 1,3-butadiene affords the *B*-homoallyl product (Scheme 16). Different diastereomers are obtained from (*E*)- and (*Z*)-2-butene.[138]

10-Ph-9-BBD is dimeric in solution, whereas the more hindered 10-TMS-9-BBD is a 3:1 monomer/dimer equilibrium, and both give 1:1 adducts with pyridine.



Scheme 15



Scheme 16

An advantage of these reagents is a moderate-to-high enantioselectivity in the hydroboration of 1,1-disubstituted alkenes, for example, 78% and 92% *ee* with 2-methylstyrene and 2,3,3-trimethyl-1-butene, respectively,[125] something not achieved by other dialkylboranes (Table 1).

8.24.1.3.6 Diarylboranes

Among diarylboranes (Figure 5) dimesitylborane, Mes_2BH, a solid dimer existing in an equilibrium with the monomer in solution,[142] is an established, commercially available, hydroborating agent.[7,143] It can be prepared by the reduction of dimesitylfluoroborane with lithium tetrahydroaluminate. Although sparingly soluble in diethyl ether, a slurry is used for hydroboration. Unhindered olefins react very slowly: even with 1-alkenes, 8 h at 25 °C is required to complete the reaction. In contrast, both terminal and internal alkynes react much faster with high regioselectivity. Consequently, the reagent is well suited for selective hydroboration of alkynes in the presence of olefins.

Bis(pentafluorophenyl)borane, $(C_6F_5)_2BH$, is a highly electrophilic borane with unique properties.[144,145] It may be conveniently prepared by the redistribution of tris(pentafluorophenyl)borane with borane-dimethylsulfide[146,147] (equation 7) or generated *in situ* from BMS, C_6F_5MgBr, and chlorotrimethylsilane.[148] Earlier syntheses are more labor intensive.

$$2\ (C_6F_5)_3B{\cdot}OEt_2 \ +\ BH_3{\cdot}SMe_2 \xrightarrow[54\%]{\text{Petroleum ether, r.t.}} 3\ (C_6F_5)_2BH \qquad (7)$$

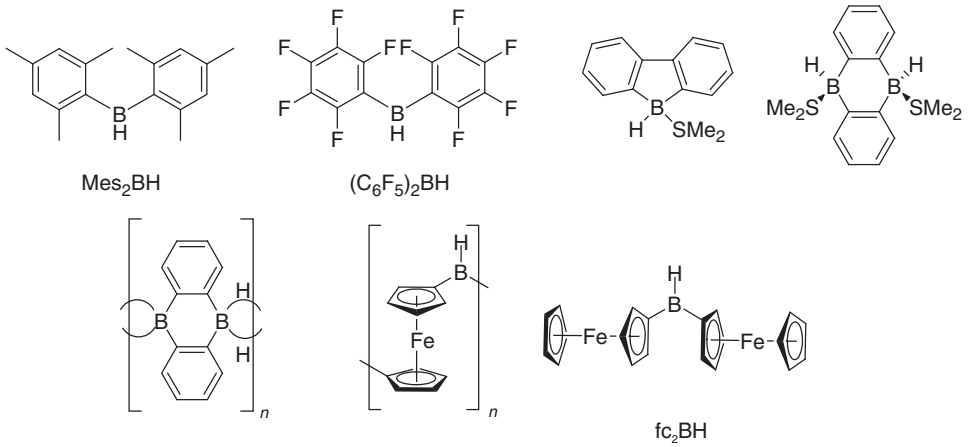


Figure 5 Diarylboranes.

$(C_6F_5)_2BH$ is a solid dimer existing in solution in an equilibrium with a significant amount of monomer, which is the active hydroborating agent.[144,145] Although it is only sparingly soluble in benzene or toluene at room temperature, these are the solvents of choice, since it reacts with donor solvents. Chlorinated solvents can also be used. The high reactivity of $(C_6F_5)_2BH$ makes possible rapid hydroboration of all types of C=C bonds. Regioselectivity is comparable to common dialkylboranes, and functional groups such as esters, alkyl bromides, or trimethylsilyl are tolerated. The hydroboration of representative olefins is presented in Table 2.

Table 2 Hydroboration of olefins with $(C_6F_5)_2BH$ in benzene at room temperature[a,144]

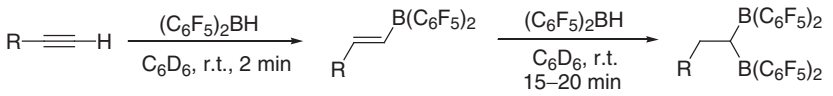
Olefin	*Product*[b]	
	Kinetic	*Thermodynamic*
$H_2C{=}CH_2$	$EtB(C_6F_5)_2$	
Ph	Ph, $B(C_6F_5)_2$	$(Ph)_2BC_6F_5$ + $B(C_6F_5)_3$
	$B(C_6F_5)_2$	$B(C_6F_5)_2$
n	$B(C_6F_5)_2$, n	$B(C_6F_5)_2$, n
n = 1, 2	n = 1, 2	n = 1, 2
Me		Me, $B(C_6F_5)_2$ + Me, $B(C_6F_5)_2$
		50% + 50%

[a]Organoboranes were not isolated but completely characterized by ^1H, ^{13}C, ^{11}B, and ^{19}F nuclear magnetic resonance (NMR).
[b]~5% of 2-boryl product present.

A characteristic feature of the hydroboration products is the tendency of the kinetic product to isomerize to the thermodynamically more stable product via dehydroboration/rehydroboration, which may occur at room temperature, depending on the structure. The hindered tertiary kinetic product formed from 2,3-dimethyl-2-butene undergoes isomerization to the primary product even at –30 °C, and (–)-*trans*-myrtanol is obtained by hydroboration–oxidation of (–)-*β*-pinene, whereas *cis*-myrtanol is produced with borane/THF. In contrast, the hydroboration product of 1-naphthylcyclohexene is stable, probably due to the stabilizing interaction of both aromatic groups. 4-Bromobutene, 4-pentenoic acid ester, and 1,1,4,4-tetraphenyl-1,3-butadiene afford the *anti*-Markovnikov addition products, whereas (*E*)-1-bromopropene reacts with C–Br bond cleavage.

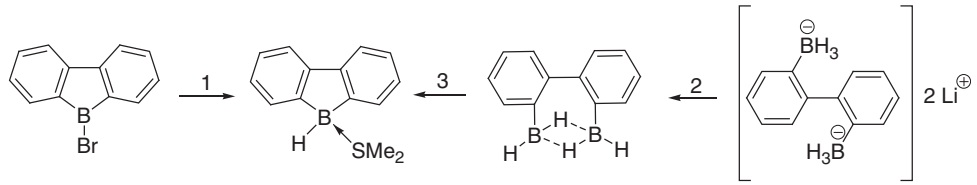
Generally, trialkylboranes undergo isomerization at temperatures above 150 °C, and only rarely at room temperature. Apparently, the highly electrophilic boron atom of the $(C_6F_5)_2B$ group facilitates the migration.

Internal alkynes undergo monohydroboration, surprisingly with no selectivity in the case of 1-trimethylsilylhexyne and 1-trimethylsilylphenylacetylene. Terminal alkynes are cleanly monohydroborated in ~2 min to give (*E*)-1,2-disubstituted alkenylboranes and 2–4% of the regioisomer. The hydroboration with the second equivalent of $(C_6F_5)_2BH$ proceeds at a slower rate only after the first equivalent is used, reaching completion in ~20 min, and affording the *gem*-diboryl products (Scheme 17).



Scheme 17

9-*H*-9-Borafluorene provides access to new boron-containing π-conjugated polymers.[149] It is a cyclic diarylborane with a tendency toward ring-opening oligomerization, though the adduct with dimethyl sulfide is stable. The reagent has been prepared by the reduction of 9-bromo-9-boraphenantrene and also from lithium (2,2′-biphenylborohydride) (Scheme 18). High yields have been achieved for mono- and dihydroboration of *tert*-butylacetylene with this complex.

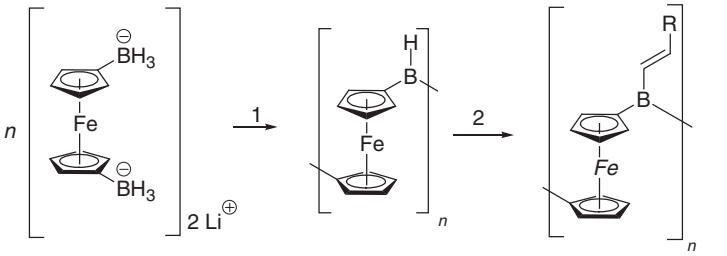


1. Et_3SiH, r.t., 2. Me_2S; 2. Me_3SiCl, Et_2O, –78 °C to r.t.; 3. Me_2S, C_6D_6, r.t.

Scheme 18

8.24.1.3.7 Ditopic and polytopic boranes

Hydroboration–polymerization of (hetero)aromatic diynes with mesitylborane, leading to π-conjugated boron-containing polymers, is a two-step reaction. In the first step, $MesBH_2$ is the hydroborating agent, and the reaction product, MesB(H)R, becomes the reagent in the second step.[108,109,150–152] The electronic and steric effects in both steps are not identical with different reagents, affecting the properties of the polymeric product, for example, polydispersity. In a search for hydroborating agents free from this disadvantage, ditopic and polytopic diarylboranes have been prepared. Thus, mono- and ditopic lithium ferrocenylhydroborates treated with chlorotrimethylsilane generate the corresponding boranes $fcBH_2$ and H_2B-fc-BH_2, which can be trapped as adducts with Me_2S or $EtNMe_2$. In diethyl ether, no stable adducts are formed, and dismutation leads to fc_2BH and the polytopic polymeric borane [–fcBH-]$_n$ respectively. The reagents monohydroborate terminal alkynes[153] (Scheme 19).



1. Me_3SiCl (excess), Et_2O; 2. Phenylacetylene (excess), toluene, 50 °C
or tert-butylacetylene (excess), hexane, 35 °C

Scheme 19

The hydroboration–polymerization approach to boron-containing metallapolymers complements approaches by other methods.[32]

9,10-Dihydro-9,10-diboraantracene (Figure 5) has been introduced as a ditopic hydroborating agent also leading to π-conjugated polymers,[154,155] and the polymeric reagent (Figure 5) has been obtained by the reduction of the monomeric dibromo precursor. It possesses an unprecedented polymeric solid-state structure and exhibits high reactivity toward terminal alkynes, for example, *tert*-butylacetylene is hydroborated in less than 1 min. The hydroboration of aryl diynes affords alkenylborane

polymers. The monomeric adduct (Figure 5) also hydroborates terminal alkynes, and the reaction of *tert*-butylacetylene with the Me_2S adduct proceeds rapidly, essentially in quantitative yield.

8.24.1.3.8 Monohaloboranes

Monohaloborane complexes with dimethyl sulfide, monochloroborane – dimethyl sulfide (MCBS), monobromoborane – dimethyl sulfide (MBBS), and monoiodoborane – dimethyl sulfide (MIBS), are conveniently prepared by the redistribution reaction of dimethyl sulfide complexes with borane and boron trihalides (equation 8).

$$2\ BH_3{\cdot}SMe_2 + BX_3{\cdot}SMe_2 \longrightarrow 3\ H_2BX{\cdot}SMe_2 \quad (8)$$

X = Cl (MCBS); Br (MBBS); I (MIBS)

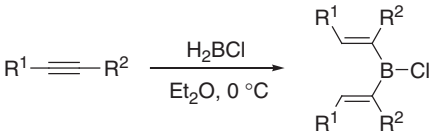
Their applications in synthesis has been reviewed.[6,156–158] The reagents are liquids, stable over prolonged periods, existing in equilibrium with small amounts of BMS and $H_2BX \cdot SMe_2$, which do not interfere in the majority of applications. The reactivity toward alkenes decreases in the order MCBS > MBBS > MIBS. Unhindered olefins react with MCBS in less than 2 h at room temperature, and hydroboration with MIBS requires gentle warming. Various solvents can be used, and the dialkylbromoboranes products complex with dimethyl sulfide whereas dialkylchloroboranes and dialkyliodoboranes are uncomplexed. The regioselectivity of the reaction with unsymmetrically substituted olefins is high: >99% for terminal alkenes and 96:4 for styrene (Table 4).

Monochloroborane solution in diethyl ether, although of limited stability, has synthetic applications.[156,157] Solutions in more strongly complexing THF are much less reactive.

The 0.2 M monochloroborane complex with 1,4-dioxane, stable for prolonged periods, is the reagent of choice among ethereal complexes.[158] Mono-, di-, and certain trisubstituted olefins undergo hydroboration to the corresponding dialkylchloroboranes within 0.5 h at room temperature in DCM. More hindered olefins react rapidly to the monoalkyl stage, and further reaction proceeds slowly. The regioselectivity of the reaction with 1-alkenes is >99.5%, and styrene affords a 95:5 mixture of primary/secondary products.

Monochloroborane–diethyl ether complex hydroborates α,ω-dienes producing *B*-chloroboraheterocycles with five- to eight-membered rings.[159] Pure *B*-chloroborinane, *B*-chloro-3,5-dimethylborinane, and *B*-chloroborepane have been isolated and found applications in the synthesis of pheromones.[160] Medium ring boraheterocycles could not be prepared in this way, but they have been obtained by the ring enlargement of the properly substituted boraheterocycles.[161]

The monohydroboration of alkynes with monochloroborane affords dialkenylchloroboranes (equation 9). Internal alkynes react in the stoichiometric ratio, whereas terminal alkynes must be used in an excess to minimize undesired dihydroboration.[162]



(9)

R^1 = alkyl, phenyl; R^2 = H or R^1.

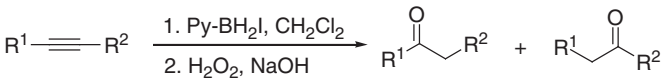
The pyridine–iodoborane complex $PyBH_2I$ is a convenient reagent, easy to generate from commercially available pyridine–borane complex by the addition of 50 mol% iodine in DCM.[163] Hydroboration of 1-alkenes is fast at room temperature affording monoalkyliodoboranes complexed to pyridine. Further reaction with the second equivalent of 1-alkene is slow. The reactivity difference enables a direct approach to boronic acids not possible when the more reactive borane/THF is used. Functional groups, such as OBn, OTBS, ester, amide, and amine, are tolerated.

Hydroboration–oxidation of (*E*)-β-methylstyrene with $Py \cdot BH_2I$ affords 1-phenyl-1-propanol and 1-phenyl-2-propanol, in a ratio of 94:6. The regioselectivity is higher than reported for $H_2BI \cdot SMe_2$ (78:22[164]) or borane/THF. Monoalkyliodoboranes obtained from 1-dodecene and trisubstituted alkenes are cleanly transformed into the corresponding potassium trifluoroborates, which are important synthetic intermediates. The regioselectivity of the monohydroboration of internal alkynes with $PyBH_2I$ is presented in Table 3.[163]

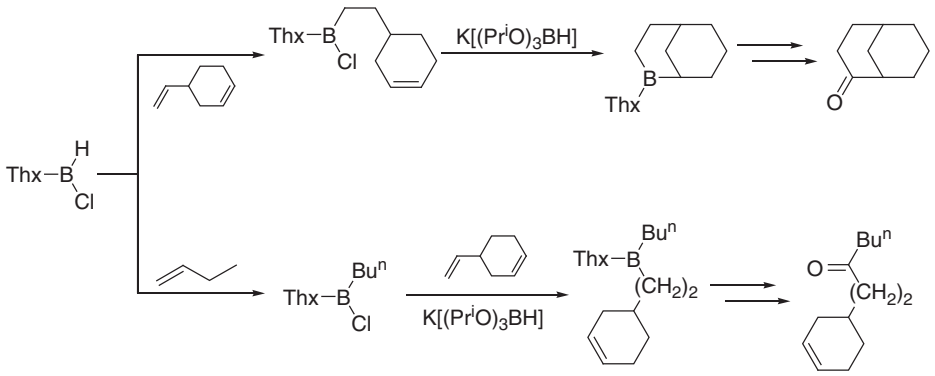
The high reactivity of $PyBH_2I$ may be due to the good leaving ability of the iodide anion enabling easier interaction between the boron atom and the double bond compared with borane–pyridine complex, which is unreactive at room temperature. A few mechanistic variants have been considered.[163]

Among alkylhaloboranes, 2,3,3-trimethyl-2-butylchloroborane, thexylchloroborane, ThxBHCl, is a valuable hydroborating and reducing agent, and its synthetic applications have been reviewed.[165] It can be prepared by the hydroboration of 2,3-dimethyl-2-butene with monochloroborane or from thexylborane and hydrogen chloride. The reagent rapidly disproportionates in diethyl ether but its complex with dimethyl sulfide is stable at room temperature. It readily hydroborates unhindered alkenes producing the corresponding alkyl thexylchloroboranes, which may be transformed into mixed dialkylthexylboranes by the reduction–hydroboration. The stepwise hydroboration enables flexibility in the product structure available from the same precursor[166] (Scheme 20).

Table 3 Hydroboration of internal alkynes with $PyBH_2I$



R^1	R^2		$R^1COCH_2R^2$	$R^1CH_2COR^2$	Yield (%)
Ph	Me		94	6	64
4-$CF_3C_6H_4$	Me		95	5	
4-$MeOC_6H_4$	Me		33	77	
Me	C_5H_{11}		60	40	61
Me	*c*-C_6H_{11}		75	25	64
Ph	Me	$H_2BI{:}SMe_2$	97	3	46



Scheme 20

More hindered alkenes react slowly, and the reaction is accomplished by redistribution. Thexylchloroborane is one of the most selective hydroborating agents (Table 4). Similarly to other halogenoboranes, it is more sensitive to electronic effects than dialkylboranes, due to its higher Lewis acidity. Noteworthy is its relative reactivity toward *Z*- and *E*-alkenes of the order *Z*/*E* 100:1.[167]

8.24.1.3.9 Dihaloboranes

Dihaloborane–dimethyl sulfide complexes DCBS, DBBS, and DIBS may be prepared by the redistribution reaction of BMS with boron trihalide–dimethyl sulfide complexes (equation 10).

$$BH_3{\cdot}SMe_2 + 2\ BX_3{\cdot}SMe_2 \longrightarrow 3\ HBX_2{\cdot}SMe_2 \quad X = Cl\ (DCBS);\ Br\ (DBBS);\ I\ (DIBS) \tag{10}$$

Their synthetic applications have been reviewed,[157,168,169] and the chloro and bromo reagents are commercially available.

Dichloroborane complexes with dimethyl sulfide and diethyl ether are so strong that direct hydroboration does not proceed, and the addition of a decomplexing agent, such as boron trichloride, is necessary for hydroboration. Dichloroborane-1,4-dioxane complex is readily prepared as a pure, stable 6.3 M liquid by passing diborane into a solution of boron trichloride in 1,4-dioxane or from sodium borohydride and boron trichloride in 1,4-dioxane in the presence of 3% vol triglyme.[158]

The reagent is somewhat more reactive than the above-mentioned complexes and exhibits remarkable selectivity hydroborating 1,1-disubstituted alkenes preferentially to 1-alkenes.

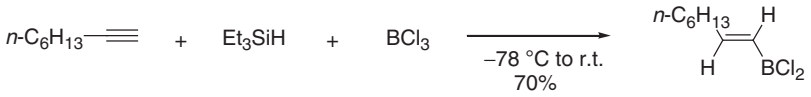
Moderately hindered olefins undergo hydroboration very slowly and incompletely even after 4 days, and the reaction proceeds with disproportionation. The reactivity difference of the reagent toward terminal and internal double bonds makes possible the selective hydroboration of limonene at the isopropenyl group.[158]

Alternatively, dichloroborane, conveniently generated by the reduction of boron trichloride with trimethyl- or triethylsilane, can be used *in situ* in a noncomplexing solvent, for example, DCM or without solvent, for the hydroboration of olefins and acetylenes.[170–172] The uncomplexed reagent is highly reactive at low temperature[173] (equation 11). Dihydroboration of 1-alkynes affords 1,1-bis(dichloroboryl)alkanes.

Table 4 Directing effects in hydroboration of representative alkenes and alkynes

Hydroborating agent	*Isomer distribution (%)* $Bu^nCH=CH_2$		$Et(Me)C=CH_2$		(*Z*)-$Pr^iCH=CHMe$		$PhCH=CH_2$		$PhC\equiv CMe$		$PhC\equiv CH$	
	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
BH_3/THF[a]	6	94	1	99	43	57	19	81	74	26[i]		
Sia_2BH[b]	1	99			3	97	2	98	19	81[i]		
9-BBN[c]	0.1	99.9	0.2	99.8	0.2	99.8	2	98	65	35[i]		
$H_2BCl_2 \cdot OEt_2$[d]	0.5	99.5	0.1	99.9	40	60	4	96	73	27		
$HBBr_2 \cdot SMe_2$[e,f]	0.4	99.6	0.8	99.2			1	99	64	36[i]		
$ThxBHCl \cdot SMe_2$[g]	0.6	99.4		99.9	3	97	1	99	3	97[j]	3	97
CatBH[h]	2	98 (6:94)[k]					8	92 (15:85)[k]	27	73	9	91
Mes_2BH[i]	6	94					1	99	2	98		
$(i\text{-PP})_2BH$[l]	4	96 (1-octene)					2	98	17	83	1	99
$(C_6F_5)_2BH$[m]							4	96				>98
PinBH[n]									15	85	4	96

[a]1960JACS4708.
[b]1961JACS1241.
[c]1974JACS7765.
[d]1976JACS1785.
[e]1980JOC384.
[f]1986JOC895.
[g]1982JOC863.
[h]1975JACS5249.
[i]1983TL1433.
[j]1993TL5113 and 1:99 with ThxBHBr.
[k]1996JOC3224.
[l]2003AC3399.
[m]1998OM5429 and 1995AC809.
[n]1992JOC3482.



(11)

This stepwise reduction–hydroboration protocol, employing *in situ* generated dichloroborane, has been applied to the one-pot asymmetric synthesis of the spiroketal[171] (R=Me), a major glandular component of the cucumber fly, *Dacys cucumis*, and other spiroketals (**Scheme 21**).

The remarkable accelerating effect of an ether solvent in the reduction of $IpcBCl_2$ with Me_3SiH makes possible fast and clean reaction. However, in the next step leading to mixed trialkylborane, the reduction with Me_3SiH is not successful and lithium tetrahydridoaluminate is used.

In contrast to DCBS, DBBS and DIBS hydroborate alkenes directly, without a decomplexing agent. The regioselectivity of DBBS is high, approaching that of 9-BBN (**Table 4**). Synthetically important is the selective monohydroboration of 1-haloalkynes placing the boron atom at the terminal position.[174,175] The reactivity of DBBS toward 1,1-disubstituted alkenes and internal alkynes is much higher than that of 9-BBN and Sia_2BH. The relative reactivity of DBBS toward representative alkenes and alkynes is as follows: 1-hexene (100), 2-methyl-1-pentene (2050), (*Z*)-3-hexene (42), 1-hexyne (234), and 3-hexyne (4885). Consequently, selective monohydroboration of dienes and enynes with these reagents can be achieved.

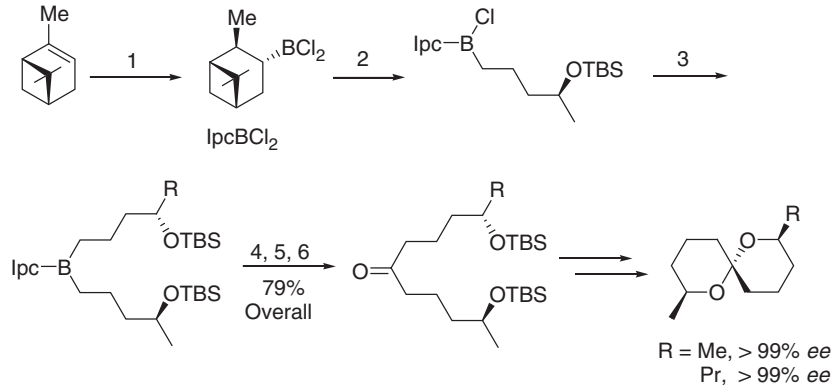
Alkyl and alkenyldihaloboranes are versatile synthetic intermediates in carbon-heteroatom and carbon–carbon bond formation. For example, hydroboration of 1-haloalkyne with DBBS or Ipc_2BH is the first step in a highly stereo- and regioselective synthesis of trisubstituted alkenes via a tandem Negishi–Suzuki coupling[175] (**Scheme 22**).

The complex HBI_2:NEt_2Ph, prepared by the reaction of H_3B:NEt_2Ph with iodine, hydroborates 1-alkenes faster than internal olefins and alkynes. Consequently, selective monohydroboration of 4-vinylcyclohexene and 1,4-enynes at the terminal double bond has been achieved.[176]

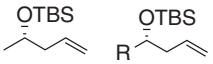
8.24.1.3.10 Dialkoxyboranes and diaryloxyboranes

Simple dialkoxyboranes are not stable and readily disproportionate. However, certain 1,2-diols and phenols, such as catechol, 1,8-dihydroxynaphthalene, pinacol, and its chiral derivative react with borane affording the corresponding 1,3,2-dioxaborolane or 1,3,2-dioxaborinane derivatives (**Figure 6**).

CatBH is a well-established, commercially available reagent and its synthesis and applications have been reviewed.[177–180] It is less reactive than dialkylboranes, and elevated temperatures are required for hydroboration of alkenes (~100 °C) and alkynes

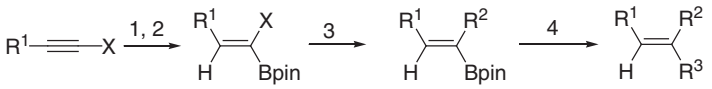


1. BCl_3, Me_3SiH, *n*-pentane, –78 °C, 10 min to >r.t.; 2. **11**, Me_3SiH, *n*-pentane, Et_2O, 0 °C, < 2 min; 3. **12**, $LiAlH_4$, Et_2O, 0 °C to >r.t., 30 min, evaporation of volatiles; 4. Pr^iCHO, Et_2O, 0 °C, 1 h, evaporation of volatiles; 5. DCME, Et_3COLi, THF, –10 °C to >r.t., 2.5 h; 6. H_2O_2, NaOAc, EtOH, 70 °C, 2 h.



11 **12**

Scheme 21



X = I, Br

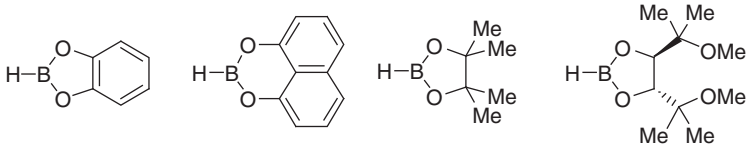
R^1 = Bu^n, Bu^t, Hex^n, 

R^2 = Bu^n, Hex^n, Ph, (*E*)-*n*-$C_6H_{13}CH{=}CHCH_2$, 4-$MeOC_6H_4$.

R^3 = Ph, 1-Hexen-1-yl, 1-Octen-1yl, Isopropenyl, 4-MeC_6H_4, 4-ClC_6H_4.

1. HBY_2, Y = Br, Ipc; 2. Pinacol; 3. R^2ZnBr, $Pd(Bu^t_3P)_2$ (1 mol%), THF, r.t., 2–12 h; 4. R^3X, TBAF, $PdCl_2$(DPEphos) (1 mol%), THF, reflux, overnight, 45–73% overall.

Scheme 22



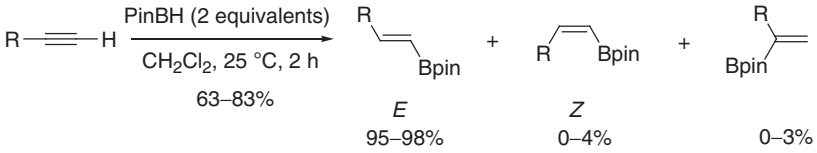
CatBH **13** PinBH **14**

Figure 6 Dialkoxyboranes and diaryloxyboranes.

(~70 °C). However, when the reaction is catalyzed with *N*,*N*-dimethylacetamide (10–20 mol%), it proceeds efficiently with mono-, di-, tri-, and tetrasubstituted olefins at room temperature in DCM using two equivalents of CatBH.[181] The reaction with 1-dodecene is also completed in the presence of 1 mol% *N*,*N*-dimethylacetamide. The regioselectivity of the addition, 94:6, is the same as observed with borane/THF for 1-alkenes, though lower than that obtained in the uncatalyzed hydroboration of 1-hexene (98:2) (Table 4). Analysis of the organoborane product obtained in the catalyzed reaction revealed the expected *B*-dodecylcatecholborane and also a significant amount of tridodecylborane. Despite this observation, *B*-alkylcatecholboranes prepared in this way from internal alkenes and used as intermediates in the radical hydroallylation of alkenes afford products in up to 89% yield.[182] The hydroboration of 1-alkynes with an excess of CatBH can also be accelerated with borane-*N*,*N*-dimethylaniline adduct.[183] A stoichiometric hydroboration of alkynes with CatBH, 1:1, which can be generated *in situ*, proceeds in the presence of a catalytic amount of dialkylborane, for example, dicyclohexylborane in THF at room temperature.[184]

The reagent **13** (Figure 6) is more reactive than CatBH in the hydroboration catalyzed by $Rh(Ph_3P)_3Cl$ and reacts with cyclohexene at room temperature in 4 min, whereas CatBH takes 90 min.[185]

Although *B*-alkyl- and *B*-alkenylcatecholboranes are important synthetic intermediates, they are water sensitive and difficult to purify by column chromatography. *B*-Alkyl- and alkenylpinacolboranes are free from these inconveniences. Pinacolborane, PinBH, is commercially available, and is easy to prepare by the addition of BMS to a solution of pinacol in dry DCM.[186] It is stable in the solution for at least 2 weeks at 25 °C or can be isolated by distillation. The monohydroboration of alkynes with PinBH proceeds at room temperature, with higher regioselectivity than with CatBH, and several functional groups are tolerated (equation 12).



(12)

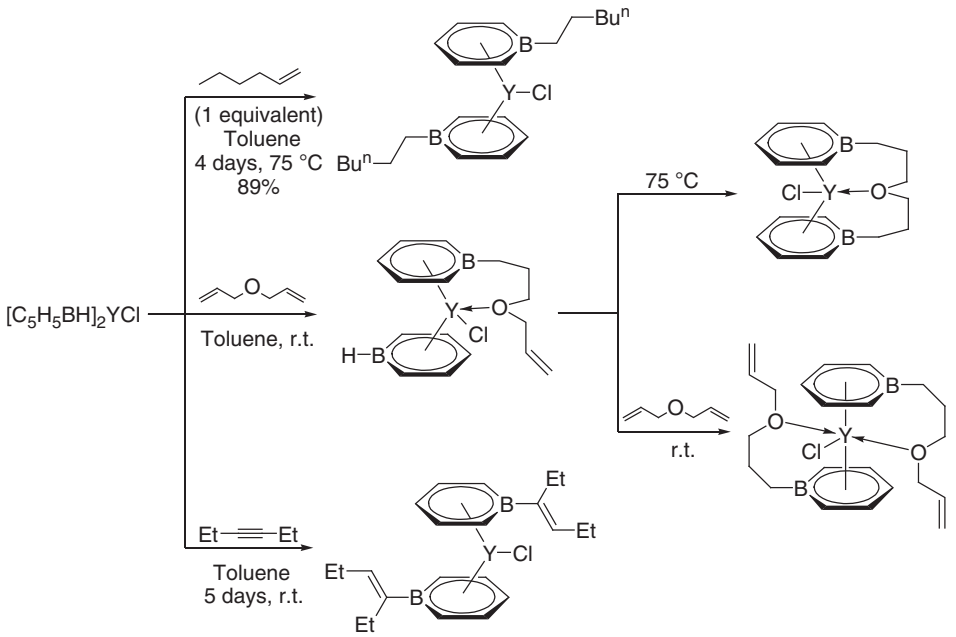
R = Hex^n, $X(CH_2)_3$ (X = Cl, I, CN, ButOOC), Ph, 1-cyclohexenyl.

Hydroboration of unhindered alkenes requires longer reaction time and warming, for example, 48 h at 50 °C for 1-decene. When less than two equivalents of PinBH is used the reaction is incomplete, and under neat conditions a mixture of isomers is obtained.[186] The monohydroboration of 1-alkynes with a stoichiometric amount of PinBH in the presence of a catalytic amount of dicyclohexylborane proceeds at room temperature under neat conditions, whereas internal alkynes give unsatisfactory results.[187]

The chiral reagent **14** (Figure 6) provides access to chiral alkenylboronates. 1-Heptyne is hydroborated in 12 h at 90 °C, phenylacetylene at 120 °C, protected propargylic alcohol at 120 °C, and its $(CH_2)_2$ homolog at 135 °C, under neat conditions.[188]

8.24.1.3.11 Boratabenzene and borazine

The 1-*H*-boratabenzene complexes with rare-earth metals hydroborate unactivated simple alkenes and alkynes with the *anti*-Markovnikov selectivity[189] (Scheme 23).



Scheme 23

The reaction with diallylether proceeds stepwise, with the second step taking place at a much slower rate.

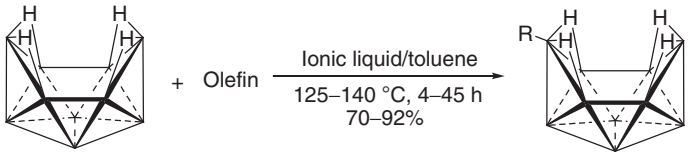
1-*H*-Boratabenzene–rhodium, zirconium, and lithium complexes do not hydroborate the tested compounds under the same conditions. However, the hydroboration products obtained with the rare-earth metal complexes undergo boratabenzene ligand redistribution providing access to the corresponding transition metal complexes. Studies on this interesting hydroboration reaction and its products are still in the early stages.

Borazine, isoelectronic with benzene, but highly water sensitive, is a slow-reacting trifunctional hydroborating agent, and not widely used. Nevertheless, borazine provides access to boron nitrides and other ceramics, and polymeric materials. Alkynes react with borazine to produce alkenylborazines.[190] The reaction with alkenes is catalyzed by $(Ph_3P)_3RhH(CO)$ and was used for the synthesis of boron-modified silicon carbide ceramics from diethylborazine and poly(vinylsiloxanes).[191] Polymer-derived SiC–B–N ceramics were obtained from borazine derivatives and 2,4,6-trimethyl-2,4,6-trivinylcyclotrisilazane.[192]

8.24.1.3.12 Polyhedral boranes

Hydroboration of alkenes and alkynes with certain higher boranes provides access to the corresponding alkyl and alkenyl derivatives. Thus, the polyhedral hydride *arachno*-6,9-$(Me_2S)_2$-$B_{10}H_{12}$ reacts with α- and β-pinene to produce the optically active 6-(α-pinanyl)- and 6-(myrtanyl)-$B_{10}H_{13}$, respectively.[193] Other olefins were also used and the products were transformed into *nido*-6-R-$B_{10}H_{13}$.[194] The titanium-catalyzed hydroboration of olefins with commercially available decaborane is a well-established reaction that is also useful in the monohydroboration of dienes, providing precursors for the synthesis of poly(organodecaboranes).[34]

Recently, convenient access to 6-R-$B_{10}H_{13}$ by ionic liquid-promoted hydroboration of olefins and functional derivatives with decaborane has been developed[195] (equation 13).



(13)

Olefin: 1-alkenes, styrene, allyl-X (X = Ph, TMS, *n*-PrO, BnO, pinB, OH (55% yield))
norbornene, cyclooctene, 1,7-octadiene, $H_2C{=}CH(CH_2)_4X$ (X = Br, OAc)
$H_2C{=}CH(CH)_2COOMe$
Ionic liquid: [bmim]Cl, $[bmpy]BF_4$

Olefins used in excess were hydroborated with decaborane in a ~1 M biphasic mixture containing ~20 mol% of the ionic liquid. The regioselectivity of the reaction is high as indicated by ^1H NMR and GC/MS, which shows almost exclusive *anti*-Markovnikov addition. A number of ionic liquids such as [bmim]X (X=Cl, Br, I, OAc, BF_4), [bmpy]Cl, and $[bmpy]BF_4$ can be used, whereas no reaction has been observed when the anions are PF_6 or OTf. The reactivity of olefins is influenced by the ionic liquid used. Strained olefins, for example, *cis*-cyclooctene, react at a higher rate than cyclohexene, which reacts very slowly. A possible reaction mechanism, based on experimental and computational studies, has been proposed.[196] In the first step, decaborane, which is a monoprotic Brønsted acid, dissociates in the presence of ionic liquid. The $B_{10}H_{13}^-$ anion thus formed rearranges to the more electrophilic $B_{10}H_{13}^-$ structure, which hydroborates an olefin, producing the 6-R-$B_{10}H_{12}^-$ anion. Finally, the anion is protonated with HCl and [bmim]Cl is regenerated.

6-Aza-*nido*-decaboranes RNB_9H_{11} (R=H, Ph, 4-C_6H_4Me, and 4-C_6H_4Cl) hydroborate olefins and alkynes such as 2,3-dimethyl-2-butene, 3-hexyne, or trimethylsilylethene in benzene at reflux, via the 9-BH vertex, providing the 1,2-addition products, $RNB_9H_{10}R$.[197]

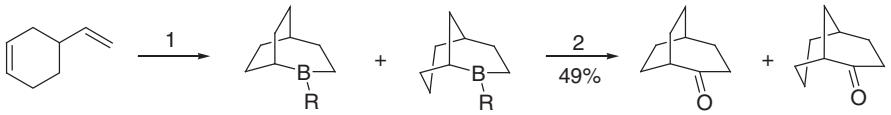
8.24.1.4 Hydroboration of Olefins, Acetylenes, and Derivatives

8.24.1.4.1 Olefins and dienes

Hydroboration of alkenes and dienes has been reviewed.[1,2,5–7] Basic characteristics of the reaction and representative hydroborating agents are described in Sections 8.24.1.1–8.24.1.3. Directing effects in the hydroboroation of representative alkenes and alkynes are presented in **Table 4**. The reagents currently known require a comment on their reactivity. Borane and the majority of substituted boranes exist as dimers in nonpolar solvents. Only for 10-TMS-9-BBN in $CDCl_3$,[198] Mes_2BH in benzene-d_6 and toluene-d_8,[142] and $(C_6F_5)_2BH$ in C_6D_6[144] have the monomer–dimer equilibria been observed. The exceptionally hindered Thx_2BH[199] and Tip_2BH[200] are monomeric in solution. CatBH and PinBH, stabilized by electron donation from oxygen to boron, are also monomeric.[201] Extensive experimental and theoretical studies indicate that complexes of monomeric boranes with weak Lewis bases generally deliver the monomer to an alkene.[48,202] Weak Lewis bases facilitate dissociation of dimers and increase the reactivity of the reagent. The addition of weak Lewis bases to the hydroboration with 9-BBN results in a ~10-fold increase in reaction rate, and diborane reacts with alkenes in weakly complexing ethereal solvents. In contrast, monomeric $(C_6F_5)_2BH$ in equilibrium with its dimer is highly reactive without any Lewis base complexation.[144] The reagent hydroborates ethylene dissolved in benzene at room temperature in 1 h at 1 atm. The rate of reaction with styrene is much higher than with 9-BBN. It also reacts rapidly with 1-(naphth-1-yl)cyclohexene, though arylcyclohexenes react slowly even with monoalkylboranes. As described in Section 8.24.1.3.6, its kinetic hydroboration products isomerize to thermodynamic products even at −30 °C. Its synthetic

application is demonstrated in the hydroboration–oxidation of *β*-pinene producing *trans*-myrtanol at room temperature, whereas *cis*-myrtanol is obtained when borane/THF is used.

The hydroboration with $MesBH_2$ and $ThxBH_2$ reveals synthetically useful differences.[107] Thus, $ThxBH_2$ is of limited stability and has to be freshly prepared at low temperatures and used immediately. It hydroborates unhindered olefins in a stepwise manner, although the reaction with two slightly hindered olefins results in the displacement of tetramethylethylene, limiting its scope. Mesitylborane is stable, and as a monoarylborane cannot undergo retrohydroboration. It hydroborates alkenes stepwise with high regioselectivity and without displacement of the aromatic group, even on the addition of two secondary alkyl groups. Both reagents are difunctional hydroborating agents and can achieve cyclic hydroboration of dienes. The reaction of $MesBH_2$ with 4-vinylcyclohexene followed by the cyanoborate process, replacing the boron with a carbonyl group, provides a single ketone cleanly, whereas using thexylborane a mixture of two isomeric ketones is obtained[107] (Scheme 24).



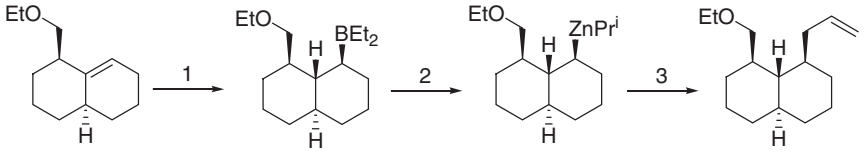
1. $MesBH_2$ or $ThxBH_2$, THF; 2. NaCN, TFAA, H_2O_2, NaOH.

Scheme 24

However, limonene undergoes cyclic hydroboration with$ThxBH_2$ but not with $MesBH_2$, indicating subtle differences in reactivity toward a less-reactive trisubstituted double bond in the second step. Consequently, both reagents are complementary in their synthetic applications.

The synthetic potential of hydroboration has been considerably expanded by the boron–zinc exchange of alkyl and alkenylboranes, providing convenient access to more reactive organozinc compounds.[203] Several functional groups, such as halogen, amide, ester, ether, nitrile, and nitro, are tolerated. The method can be applied to prepare primary, secondary, and benzylic zinc reagents.

The boron–zinc exchange of diastereomerically pure organoboranes proceeds with the retention of configuration[204] (Scheme 25).



1. Et_2BH (3 equivalents), Me_2S, CH_2Cl_2, 25 °C, 48 h; 2. Volatiles removed, $Pr^i{}_2Zn$ (3 equivalents), Et_2O, 25 °C, 5 h, 80% exchange; 3. Volatiles removed, THF, –78 °C, CuCN·2LiCl (0.7 equivalent), 1.5 h, allyl bromide (3 equivalents), –78 °C, 1 h, then r.t. overnight.

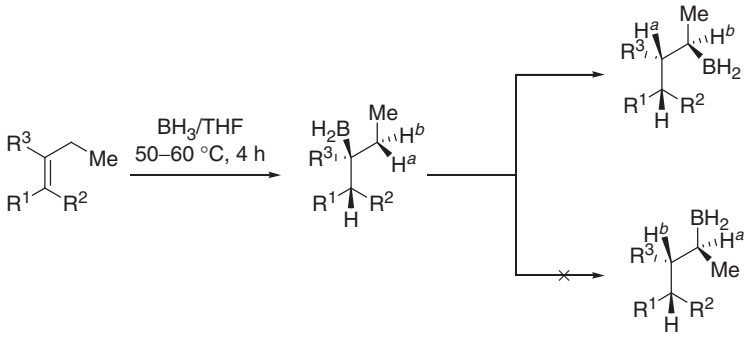
Scheme 25

Organoboranes obtained by hydroboration with more sterically demanding 9-BBN, $ThxBH_2$, or CatBH also undergo this exchange. The mechanism of this reaction, studied by theoretical methods for trimethylborane and dimethylzinc, involves a four-membered cyclic C–B–C–Zn intermediate, followed by the second intermediate featuring a linear C–B–Zn–C arrangement.[205]

The preparation of alkylmagnesium reagents from alkenes via hydroboration and boron–magnesium exchange has also been reported.[206]

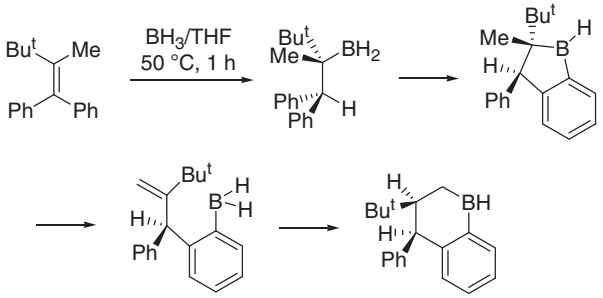
Further progress in the hydroboration–thermal isomerization of organoboranes has been achieved. Thus, it is known that internal alkylboranes heated at 100–150 °C undergo migration of the boron atom to the terminal position in the alkyl chain, and large-scale application to the synthesis of linear α-olefins has been considered.[207] A mixture of *E*/*Z* stilbenes or stilbenoids can be transformed into *E*-isomers by hydroboration with 9-BBN followed by isomerization at 150 °C and elimination of 9-BBN. The transformation has been applied to the synthesis of resveratrol.[208] Certain hindered or strained organoboranes undergo isomerization even at room temperature or on gentle warming. A detailed study revealed a highly regio- and stereoselective boron migration at ~50 °C in acyclic and cyclic organoboranes, obtained by hydroboration of tetrasubstituted double bonds[209] (Scheme 26).

The reaction is a formal stereoselective allylic C–H activation and can generate three adjacent stereocenters, for example, from *E*- or *Z*-diphenyl-3-hexene. Hydroboration–thermolysis, under mild conditions, of tri- and tetra-substituted double bonds



Scheme 26 Reproduced from Bromm, L. O.; Laaziri, H.; Lhermitte, F.; Harms, K.; Knochel, P. *J. Am. Chem. Soc.* **2000**, *122*, 10218–10219, with permission from ACS.

containing an aryl substituent makes possible a diastereoselective remote C–H activation of the suitably located aryl ring via the cyclic five-membered transition state[210] (Scheme 27).



Scheme 27

Other phenyl-substituted alkenes, cyclic and bicyclic olefins, for example, *exo*,*exo*-2-ethyl-3-phenyl-norbornene, also undergo the reaction,[210–212] which allows the generation of three adjacent stereocenters.

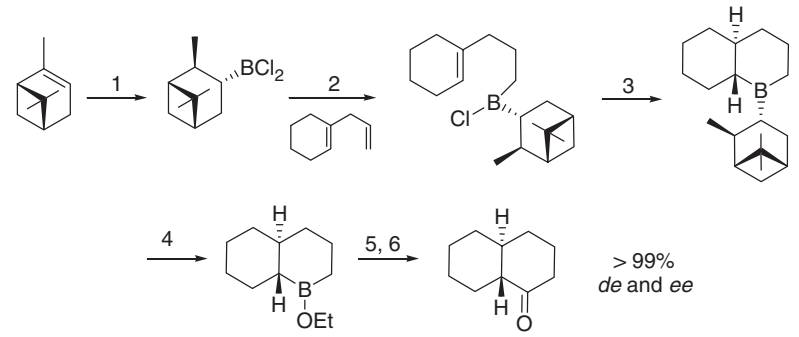
A study of the relative effectiveness of 2-organylapoisopinocampheylboranes for the asymmetric hydroboration of representative prochiral alkenes has been aimed at optimizing the steric fit between the reagent and olefin.[102] A series of enantiomerically pure $IpcBH_2$ homologs with the following R groups of increasing steric bulk replacing the 2-methyl group, R=Et, Pr^n, Bu^i, Pr^i, and Ph, has been prepared. The results clearly demonstrate that enantioselectivity of the reaction increases with the increasing steric bulk of the R group, but only for trisubstituted double bonds. The dramatically lowered optical induction when R=Ph is intriguing and raises the question of whether the phenyl group is exerting a strong steric or electronic effect, or both.

With these $IpcBH_2$ homologs in hand, the asymmetric cyclic hydroboration of dienes has been undertaken.[213] Two approaches are possible, either the direct hydroboration or the stepwise hydroboration–hydridation–hydroboration with IpcBHX (X=Cl, Br). Thus, reaction of $IpcBH_2$ with 1-allylcyclohexene, followed by transformation of the product organoborane into ketone, affords (9*R*,10*S*)-1-decalone with moderate enantioselectivity (54% *ee*). In the second approach, hydroboration of the diene with IpcBHCl, generated *in situ* by the reduction of $IpcBCl_2$, proceeds selectively at the terminal double bond. Reduction of the B–Cl bond and subsequent cyclic hydroboration provides the bicyclic organoborane, which is further transformed into (9*R*,10*S*)-1-decalone, >99% *de*, >99% *ee* (Scheme 28).

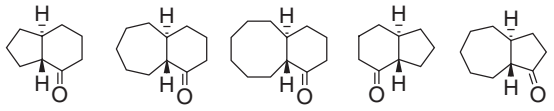
In the same way, aliphatic terminal *E*-1,4-dienes have been transformed into monocyclic organoboranes, and further into the corresponding secondary alcohols, 51–84% *ee*.

The *in situ* generated IpcBHBr reacts with representative prochiral alkenes in *n*-pentane at lower temperatures than possible with $IpcBH_2$ or IpcBHCl. It is remarkable that the α-pinene-derived reagent hydroborates alkenes in a relatively short time (4–6 h), usually in higher enantioselectivities than previously achieved (Scheme 29).[214] The hydroboration of cycloalka-1,3-dienes with Ipc_2BH provides *B*-(cycloalk-2-enyl)diisopinocampheylboranes of high enantiomeric purity.[215]

B-Alkylcatecholboronates, readily available by hydroboration of alkenes with CatBH, are convenient precursors of alkyl radicals.[216] A range of free-radical reactions leading to functional derivatives (e.g., alkyl nitroxides,[217,218] sulfides,[218] azides,[219] and silanes[220]) and to carbon–carbon bond formation (vinylation, allylation, alkynylation, alkylation,[221] cyanidation,[222] and others) have been developed.[223] Full utilization of the alkene precursor in these reactions is an advantage when compared with free-radical reactions of trialkylboranes. In several cases, the use of *B*-alkyl derivatives of the reagent, obtained from

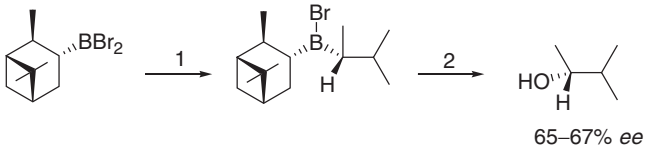


Also prepared:



1. Me_3SiH, BCl_3, pentane, –78 °C; 2. Me_3SiH, Et_2O, –5 °C; 3. $LiAlH_4$ (0.25 equivalent), –25 °C; 4. MeCHO, 0 °C, 5 h; 5. DCME, Bu^tOLi, Et_2O, 0 °C; 6. H_2O_2, AcONa, THF, 24 °C, 1 h; 40–50 °C, 1 h.

Scheme 28



1. 2-methyl-2-butene, Me_3SiH, *n*-pentane, –78 °C, 4–6 h; 2. H_2O_2, NaOH.

Scheme 29

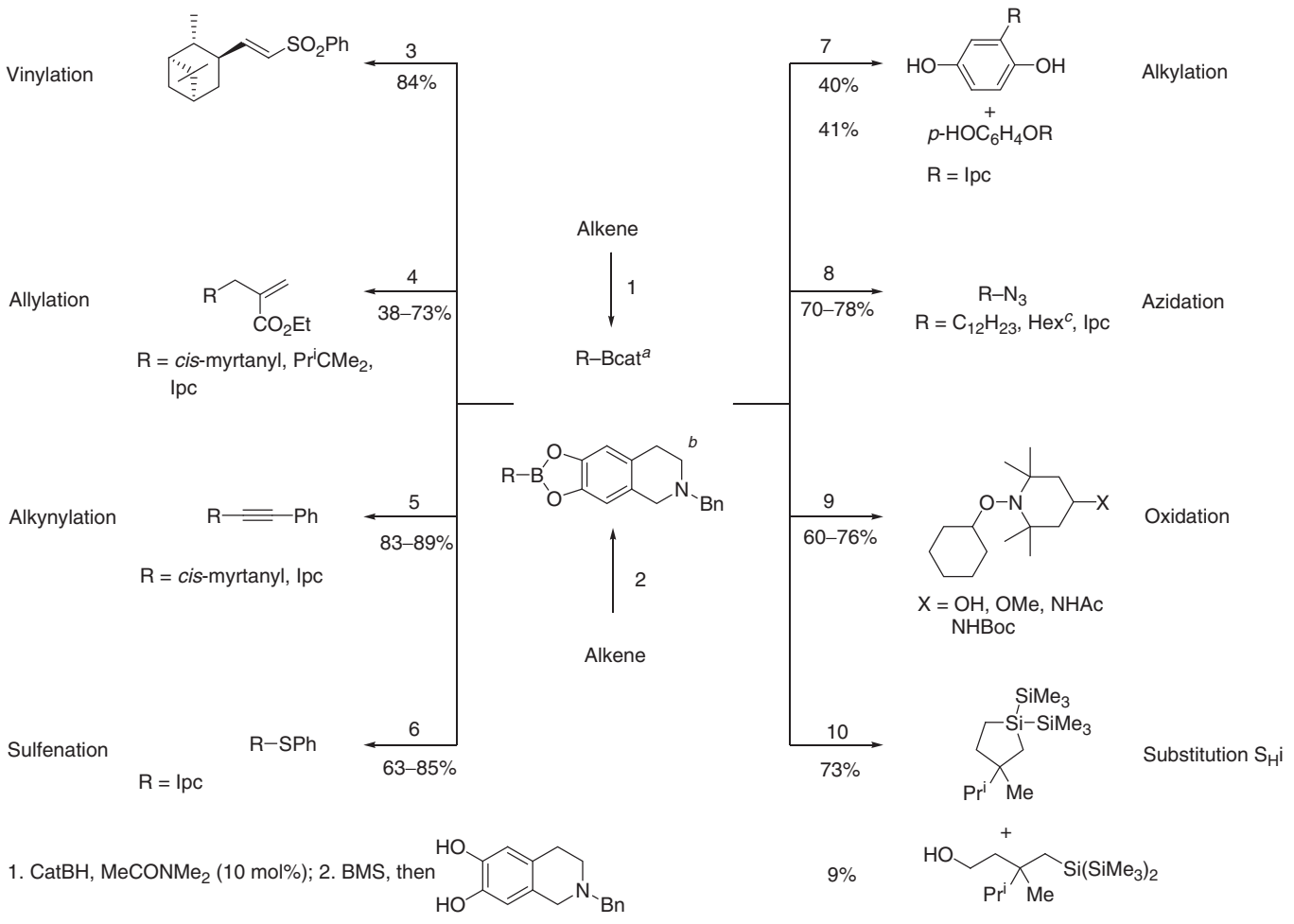
N-benzyltetrahydroisoquinolone analog of catechol, facilitates product isolation.[221] Selected examples of the above-mentioned reactions are presented in Scheme 30.

8.24.1.4.2 Allenes

Hydroboration of allenes is a convenient method for the synthesis of versatile allylic organoboranes, which find application in the allylboration of aldehydes, and in other transformations. Dialkylboranes react with monosubstituted allenes to give (*E*)-allylic organoboranes, and allylboration of aldehydes provides *anti*-homoallylic alcohols.[224–226] A characteristic feature of allylic organoboranes is the ability to undergo 1,3-boratropic shift, similarly to other allylmetals[227,228] (Scheme 31).

The equilibrium is influenced by temperature, the substituents at the boron atom, and those at the allylic group. Its rate decreases in the order: allyldialkylboranes > allylborinates > allylboronates > allyldiaminoboranes. Although allyldialkylboranes readily isomerize at room temperature, they can be used at low temperatures without the loss of configurational integrity. Hydroboration of terminal allenes with dialkylboranes initially affords (*Z*)-allylic organoborane, which is the kinetic product, readily undergoing 1,3-boratropic shift at room temperature to the more stable (*E*)-isomer, which is the thermodynamic product.[140,229,230] Fortunately, among the dialkylborane hydroborating agents, 10-TMS-9-BBD reacts with allenes producing unusually stable (*Z*)-allylic organoboranes, due to the interaction of the 10-TBS group with the π-allylic C–H bonds in the transition state, raising the barrier of the 1,3-boratropic shift.[140,231] Consequently, the allylboration of aldehydes with these organoboranes affords *syn*-homoallylic alcohols with high enantioselectivity when enantiomerically pure 10-TBS-9-BBD is used[231] (Table 5).

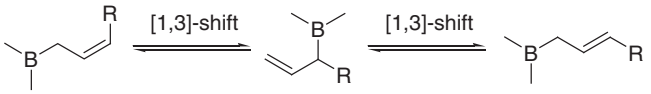
Hydroboration of heterosubstituted allenes provides access to functionalized allylic organoboranes, expanding their versatility. When the second functional group is the boryl group, double allylboration of two different aldehydes is possible[232,233] (Scheme 32).



[a]8. $PhSO_2N_3$ (3 equivalents), DTBHN, DMF, 80 °C; 9. 4-oxo-TEMPO, DMPU, r.t.; 10. Ph—≡—SO_2Ph, DTBHN, C_6H_6.

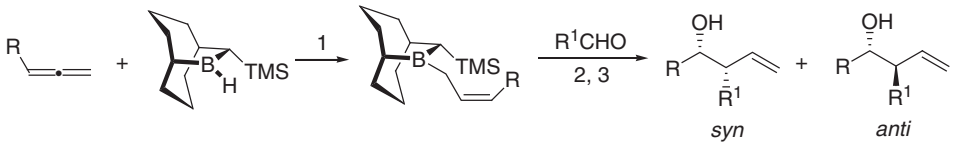
[b]3–5. O_2 (initial), CH_2Cl_2, DMF; 3. PhO_2S ⟋ SO_2Ph ; 4. SO_2Ph ⟋ CO_2Et ; 5. Ph—≡—SO_2Ph; 6. PhS-SO_2Ph, $Bu^tON{=}NOBu^t$ (initial), CH_2Cl_2, 40 °C; 7. DMPU, CH_2Cl_2, r.t.

Scheme 30



Scheme 31

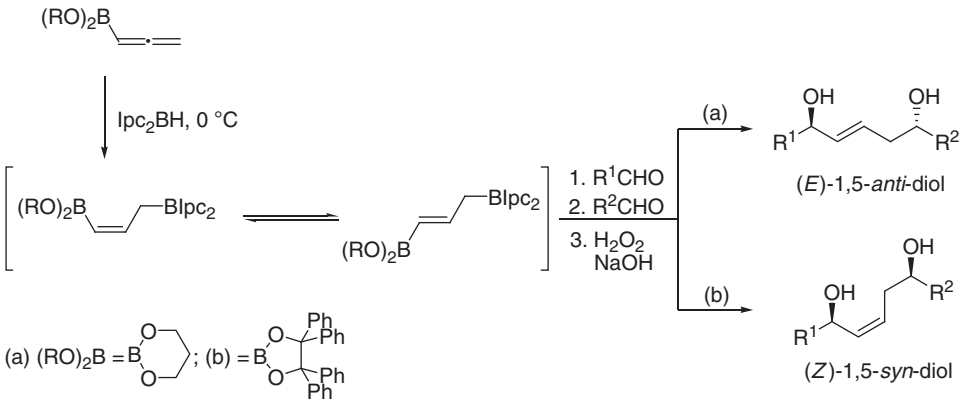
Table 5 Asymmetric allylboration of aldehydes with B-allylic-10-TMS-9-BBD



1. 1.3 equivalents, CH_2Cl_2, 0 °C, 12 h; 2. –40 °C, 12 h; 3. $HO(CH_2)_2NH_2$.

R	*R*[1]	*% Yield*	syn/anti	*% ee*
Ph	Ph	74	94:6	93
Ph	$PhCH_2CH_2$	60	93:7	92
$SiMe_2Ph$	Ph	70	90:10	86
$SiMe_2Ph$	$PhCH_2CH_2$	71	90:10	89
Bu[t][a]	Ph		99:1	93

[a]Hydroboration, 0 °C, 2–6 h.



Scheme 32

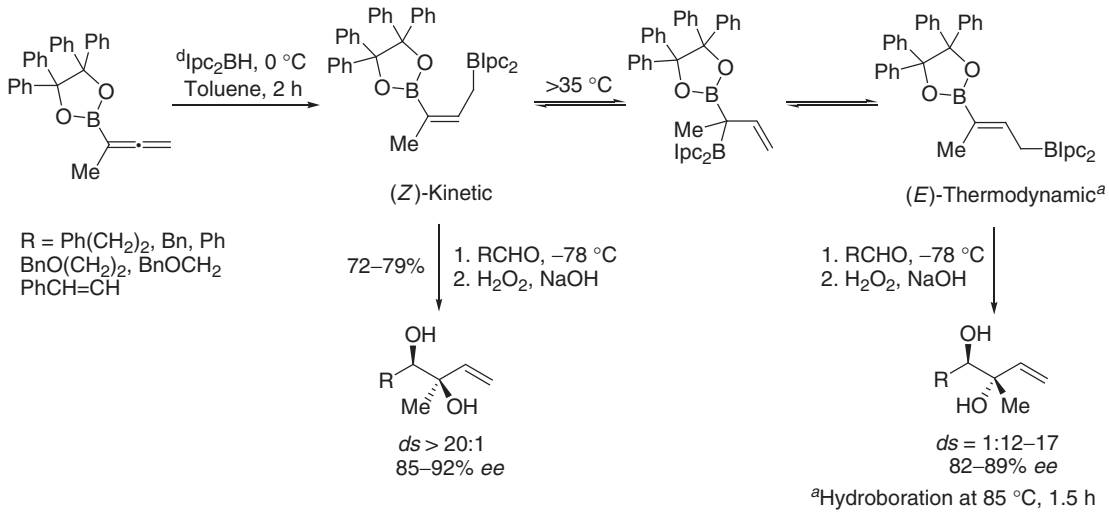
The different stereochemistry of the products is due to the stereochemical course of the second allylboration, which depends on the steric requirements of the boronate group. The kinetically controlled hydroboration of allenyltrifluoroborate, a smaller boron group, with 10-TMS-9-BBD followed by double allylboration provides (*E*)-1,5-*syn*-diols.[234]

Kinetically controlled (*Z*)-allylorganoboranes can also be obtained by the hydroboration of allenylboronates with Ipc_2BH at lower temperatures. Warming up the reaction mixture results in the formation of (*E*)-isomers. Consequently, isomeric allylboration products can be obtained from the same precursor under carefully controlled conditions[232] (**Scheme 33**).

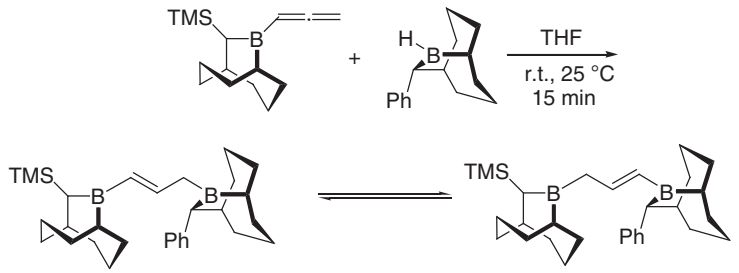
The hydroboration of (*S*)-*B*-allenyl-10-TMS-9-BBD with (*S*)-10-Ph-9-BBD provides a mixed allylic reagent suitable for the sequential asymmetric tandem allylboration of a ketone followed by an aldehyde[140] (**Scheme 34**).

The 10-phenyl-substituted allylic part of the reagent is more reactive than the TMS-part, and adds to ketones. The allylic TMS-part of the intermediate then reacts with aldehydes to give *anti*-1,3-diols.

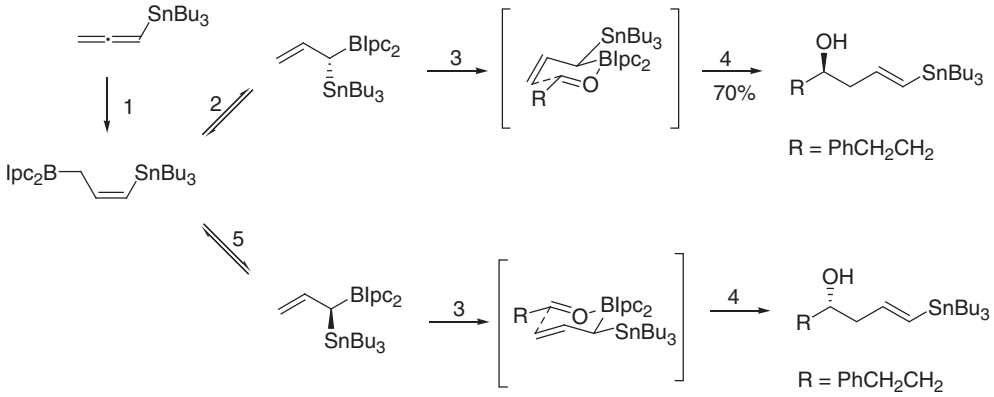
The hydroboration of tributylstannylallene with Ipc_2BH is highly temperature dependent, and the kinetic product is α-stannylallylic organoborane. When the reaction is carried out at −40 °C, then warmed to −20 °C, and followed by allylboration, (*E*)-δ-stannyl homoallylic alcohols are obtained[235] (**Scheme 35**). The high asymmetric induction exerted by the $^dIpc_2B$ group in the 1,3-boratropic shift of (*Z*)-allylic organoborane to $^dIpc_2$-α-stannylallylborane, and its stability up to −20 °C, is remarkable.



Scheme 33



Scheme 34

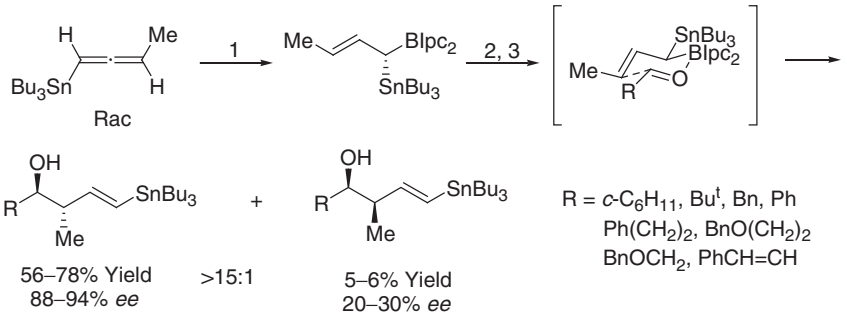


1. [d]Ipc_2BH, Et_2O, –40 °C; 2. to –20 °C, 5 h; 3. $Ph(CH_2)_2CHO$ (0.7 equivalent), –78 °C, 8 h; 4. H_2O_2, $NaHCO_3$; 5. 0 °C.

Scheme 35

The α-position of the stannyl group to the boron atom may be favored by the interaction of the C–Sn bond with the p orbital on boron. In contrast, hydroboration–allylboration of dimethylphenylsilylallene with Ipc_2BH proceeds via (*Z*)- or (*E*)-γ-silylallylboranes, depending on temperature, to give *syn*- and *anti*-β-hydroxyallylsilanes, respectively.[236]

Kinetic resolution of racemic 1,3-dimethylallenylboronate by hydroboration with [d]Ipc_2BH has been achieved. The kinetic (*Z*)-product is stable at −25 °C and allylboration provides (*E*)-2-methyl-1,2-*syn*-pentenediols, *syn*/*anti* ≥ 10:1, 63–75% yield, 90–94% *ee*. After heating the kinetic product at 95 °C for 1.5 h, the thermodynamic (*E*) product is formed and allylboration provides (*E*)-2-methyl-1,2-*anti*-pentenediols, *anti*/*syn* ≥ 6:1, 52–89% yield, 87–92% *ee*.[237] In contrast, the hydroboration of racemic 3-methylallenylstannane with [d]Ipc_2BH takes the enantioconvergent course, and both enantiomers are converted predominantly into the enantioenriched (*S*)-1-stannylcrotylborane[238] (Scheme 36).



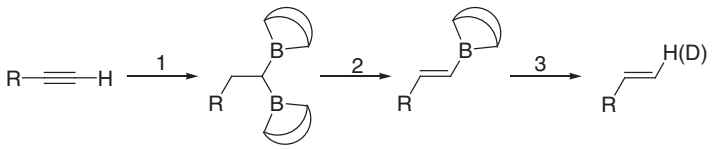
1. $^{d}Ipc_2BH$ (1 equivalent), 0 °C; 2. RCHO (1 equivalent), –78 °C; 3. H_2O_2, $NaHCO_3$.

Scheme 36

The preferential formation of (*S*)-α-stannylallylic organoborane is based on stereospecific suprafacial 1,3-boratropic shifts of the kinetic hydroboration products derived from both enantiomers, and not on the asymmetric induction exerted by the Ipc_2B group as in the hydroboration of monosubstituted stannylallene (Scheme 35).

8.24.1.4.3 Alkynes and enynes

The hydroboration of alkynes has been extensively reviewed,[2,4,6] and examples of directing effects are presented in Table 4. Monosubstituted alkynes undergo selective monohydroboration at the terminal position with hindered dialkylboranes, dimesitylborane, $(C_6F_5)_2BH$, dichloro- and dibromoboranes, catecholoborane, and PinBH to give (*E*)-alkenylorganoboranes with high selectivity. The reaction of 1-alkynes with 9-BBN in a 1:1 ratio does not cleanly stop at the monohydroboration stage, also affording the *gem*-disubstituted dihydroboration product. A large excess of alkyne is required to partially suppress the dihydroboration. To circumvent the inconvenience, and since *B*-alkenyl-9-BBN derivatives are important synthetic intermediates, an alternative synthesis via dihydroboration–dehydroboration has been developed[239] (Scheme 37).



R = Me, Bn, TMS.
1. 9-BBN, THF; 2. PhCHO; 3. AcOH or AcOD.

Scheme 37

Dimesitylborane, a highly hindered and sterically demanding reagent, monohydroborates the terminal alkynes cleanly in 5 min at 25 °C. The *in situ* generated dichloroborane also reacts rapidly at much lower temperatures. A recently developed dichloroborane-1,4-dioxane complex is a stable reagent hydroborating terminal and internal alkynes to give alkenyldichloroboranes, which hydrolyze to alkenylboronic acids.[240]

CatBH reacts rapidly with alkynes at 70 °C without a solvent providing the water-sensitive monohydroboration products in high yields and selectivity. PinBH is less reactive and hydroboration in DCM requires two equivalents of the reagent and long reaction times at 50 °C. The *E*-alkenylboronates, produced with 98% selectivity, are water-stable. In the presence of a catalytic amount of dicyclohexylborane, under neat conditions the reaction proceeds in a 1:1 M ratio at room temperature.

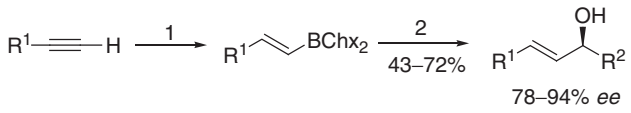
Alkenylorganoboranes undergo the boron–zinc exchange, and the transformation has been used for the catalytic enantioselective syntheses of allylic alcohols by the reaction with aldehydes. Recently, the zinc-free catalytic enantioselective synthesis of secondary allylic alcohols from terminal alkynes and aldehydes via 1-alkenylboronates or 1-alkenyldialkylboranes has been developed[241] (Scheme 38).

Monohydroboration of conjugated enynes with CatBH, PinBH, Chx_2BH, and Ipc_2BH provides convenient access to dienylorganoboranes, which are building blocks in the Diels–Alder and other cycloaddition reactions, recently reviewed.[242]

1,3-(Butadien-1-yl)boronates are frequently used reagents producing allylic organoboranes as the Diels–Alder adducts, which are reactive intermediates for further transformations[243] (Scheme 39).

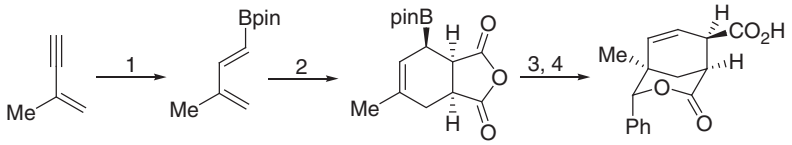
Boronated heterodienes can be prepared by the hydroboration of propiolaldehyde diethyl acetal with Ipc_2BH, followed by liberation of α-pinene with acetaldehyde, hydrolysis, and esterification of boronic acid with pinacol[244] (Scheme 40).

Functionalized (*E*)-1-alkenylboronic acids including 1-alkoxyboronic derivatives have also been prepared by hydroboration of functionalized terminal and internal alkynes with Ipc_2BH, followed by the liberation of α-pinene and hydrolysis. Terminal alkynes undergo dihydroboration with unhindered and moderately hindered boranes placing both boron groups at the terminal carbon.



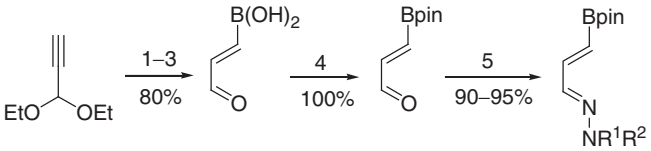
R^1 = C_6H_{13}, Bu^iCH_2, $BnCH_2$, Pr^c, $CH_2CH_2CH_2X$ (X = Cl, CN, CON⟨⟩).
R^2 = Hex^c-1-yl, CH_2=CMe, Ph, 1-Naph, 4-ClC_6H_4, 4-MeC_6H_4.
1. Chx_2BH (1.5 equivalents), THF; 2. R^2CHO, cat (5 mol%), $Ti(OPr^i)_4$ (3 equivalents) reflux, 2–3 h; cat = (*R*)-3-(3,5-$Ph_2C_6H_3$)-H_8-BINOL.

Scheme 38



1. pinBH; 2. Maleic anhydride, toluene, 80 °C, 3 h; 3. PhCHO, 0 °C to r.t., 1 h; 4. H_2O, 60 °C, 0.5 h.

Scheme 39



R^1 = H, Me.
R^2 = Me, Ph, 4-$CF_3C_6H_4$, 4-$MeOC_6H_4$, Ac, Boc.
1. Ipc_2BH, THF, 0 °C, 1 h; then r.t., 1 h; 2. MeCHO (10–20 equivalents), 0 °C; then reflux (45 °C), 12 h; 3. H_2O (75 equivalents), 0 °C, 3 h; 4. Dry pinacol (1 equivalent), THF; 5. $HN_2NR^1R^2$ (1 equivalent), CH_2Cl_2, $MgSO_4$ (1.3 equivalents), reflux, 2 h.

Scheme 40

The regioselectivity of monohydroboration of internal alkynes depends on the electronic and steric effects of substituents and the selectivity of the hydroborating agent. The addition of bulky disubstituted boranes, such as Chx_2BH, Mes_2BH, and Sia_2BH, is controlled mainly by steric effects, and the boron atom is preferentially placed at the less-hindered side of the triple bond. When the difference in steric requirements of substituents is large, as between a tertiary and primary group, the selectivity is high, for example, >95% for 4,4-dimethyl-2-pentyne. In the reaction with 2-hexyne only the highly sterically demanding Mes_2BH achieves 90% selectivity. The electronic effect of the phenyl group affects the addition, increasing the amount of product with the boron atom at the phenyl-substituted carbon atom. The regioselectivity of the addition of representative hydroborating agents to 1-phenylpropyne is shown in Table 4. Symmetrically substituted internal alkynes are cleanly monohydroborated by dialkylboranes or PinBH and the products are convenient intermediates for various transformations.

8.24.1.4.3.1 Functionalized olefins

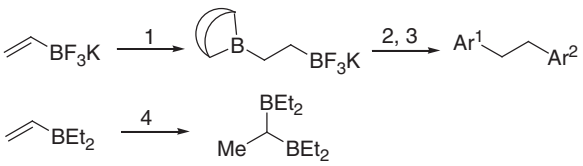
In vinyl derivatives, an electron-donating substituent directs boron to the β-position, whereas an electron-withdrawing substituent favors the α-position. The regioselectivity of hydroboration of functionalized olefins and alkynes also depends on steric effects of substituents and the structure of hydroborating agents (Table 6). The highly selective *anti*-Markovnikov addition of bulky dialkyl- or diarylboranes, for example, Chx_2BH, Sia_2BH, and Mes_2BH, is controlled by steric factors, even with multiple bonds substituted with strongly electron-withdrawing perfluoroalkyl groups. Dichloro- and dibromoborane are more sensitive to electronic effects, and undergo the Markovnikov addition to fluoroalkenes[245,246] (Table 6), and even tertiary alcohols have been obtained.[247] Noteworthy is the opposite regioselectivity in the hydroboration of vinyltrifluoroborates and vinylboranes providing 1,2-dibora and 1,1-dibora products, respectively. The 1,2-product with two different boryl groups is suitable for tandem transformations, for example, the Suzuki–Miyaura cross-coupling[248] (Scheme 41).

A rare substrate sensitivity to the hydroborating agent has been observed in the reaction with ring-monosubstituted trifluoromethyl and fluorostyrenes.[249] The attempted hydroboration with BMS in diethyl ether and also with BH_3/THF, 9-BBN, Chx_2BH, H_2BCl, $HBCl_2$, and $HBCl_2 \cdot SMe_2$ results in the olefin polymerization and quantitative recovery of the reagent. However,

Table 6 Directing effects in the hydroboration of representative functionalized alkenes

Reagent	*Isomer distribution (%)*													
	Cl		OAc		$SiMe_3$		2-Furyl		3-Pyridyl		BF_3K		BEt_2	
BH_3/THF[a]	40	60	35	65	60	40[d]	16	84[e]	50	50[e]				
Sia_2BH[b]	5	95	2	98	5	95[f]	0	100[e]	17	83[e]				
9-BBN[c]	1.1	98.9	2.4	97.6		100[d]	3	97[e]	8	92[e]		>99[h]	Et_2BH[l]	
$(i\text{-PP})_2BH$[g]			7	93		99								
	C_6F_{13}		C_6F_{13}		C_6F_{13}		CF_3		C_6F_5		C_6F_5		R_F C=CH R	R_F HC=CH R
BH_3/THF					83[i]	17	71[i,j]	29	79[i,j]	21				
Sia_2BH					40	60			6	94	1[i]	99		
Chx_2BH	1[i]	99	3[i]	97	5	95	6	94i	15	85				
9-BBN									8	92				
Cl_2BH	1	99	50	50	99	1	98	2	92	8	6	94	≥99[k]	≥97[k]
Br_2BH					99	1	97	3	94	6				

[a] 1964JACS1801.
[b] 1964JACS1791.
[c] 1981JOC3987.
[d] 1980JOC3571.
[e] 1983JOC1433.
[f] 1978JOM*156* C12.
[g] 2003AC3399.
[h] 2009OL2369.
[i] 2002CC386.
[j] 1999AC2052.
[k] 2001OL3769.
[l] 1997Coll.Czech.Chem.Commun.1254.
R_F = CF_3, C_6F_{13}, C_6F_5; R = *n*-alkyl.



1. 9-BBN, THF; 2. $Pd(OAc)_2$, DavePhos, KF, Ar^1X;
3. RuPhos, K_2CO_3, toluene/H_2O, Ar^2X; 4. $HBEt_2$, THF.

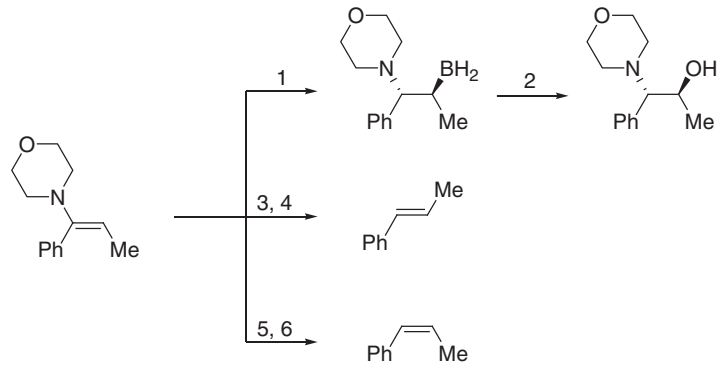
Scheme 41

the *anti*-Markovnikov hydroboration has been achieved with $H_2BI \cdot SMe_2$, whereas the Markovnikov product is obtained by catalytic hydroboration with PinBH.[250]

Acyclic β-substituted organoboranes are prone to elimination in polar solvents and in the presence of base. Nonpolar solvents and lower reaction temperatures decrease the rate of elimination. In cyclic systems, the organoboranes are relatively more stable under neutral conditions. For example, the β-substituted organoboranes are the intermediates in asymmetric hydroboration–oxidation of unsaturated heterocycles at low temperatures.[251,252]

The hydroboration of enamines leads to the corresponding β-amino alcohols and makes possible a simple conversion of aldehydes and ketones into (*E*) or (*Z*) alkenes (Scheme 42).[253]

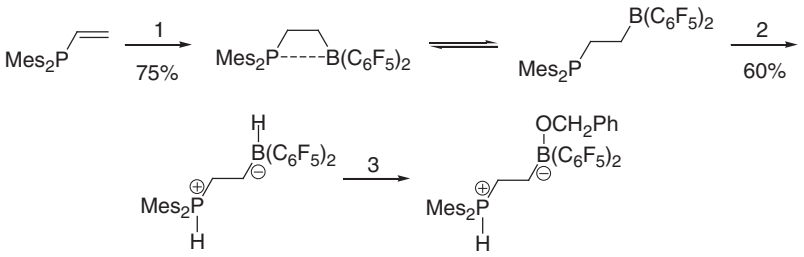
As described in Section 8.24.1.3.6, $(C_6F_5)_2BH$ is a highly reactive hydroborating agent of similar selectivity to dialkylboranes. It reacts with enamines and vinylphosphanes, placing the boron atom in the β-position to nitrogen or phosphorous. The addition products contain the Lewis acidic boryl group and basic amino or phosphino groups. When these groups are bulky, adduct formation



1. BMS, THF, 25 °C, 1 h; 2. Et_3NO; 3. BMS, THF; 4. MeOH; 5. 9-BBN, THF; 6. MeOH.

Scheme 42

is prevented by steric hindrance and the products are frustrated Lewis pairs[254–258] (Scheme 43).[255] The seminal discovery of the reversible metal-free dihydrogen cleavage by *p*-$Mes_2PC_6F_4B(C_6F_5)_2$, opened this rapidly growing field.[33]



1. $(C_6F_5)_2BH$, pentane, r.t.; 2. H_2 (1.5 bar), pentane, r.t., 15 min; 3. PhCHO, THF, r.t.

Scheme 43

Equilibria between the cyclic and acyclic structure of the pair obtained from dimesitylvinylphosphane and from other precursors are observed. The DFT-calculated structure of the cyclic pair, shown in Scheme 43, features π-stacking stabilization between one *P*-mesityl ring and one *B*-pentafluorophenyl ring in the four-membered cyclic structure. The highly cooperative reactivity of the pair enables dihydrogen cleavage at room temperature in 15 min.[255] The pair also reacts with aldehydes, carbon dioxide, other carbonyl compounds, and terminal acetylenes by the deprotonation and/or addition.[259]

A strong electronic effect is observed in the hydroboration of alkenyl- and alkynylphosphanes containing the $(C_6F_5)_2P$ group. The regioselectivity of the reaction with $(C_6F_5)_2BH$ is reversed as compared to the corresponding compounds with the Mes_2P group. Consequently, the boron is placed in α-position to the phosphoryl group, and the 1,1-disubstituted-type frustrated Lewis pair is obtained[259] (Scheme 44).

The interaction of a strongly acidic boryl group with a weakly basic phosphoryl group is weak in these pairs despite the close proximity of the groups. In contrast to the pair shown in Scheme 43, the 1,1-disubstituted pairs do not deprotonate terminal acetylenes, Nevertheless, they add to the C=C, C≡C, C=O, and C=N bonds.

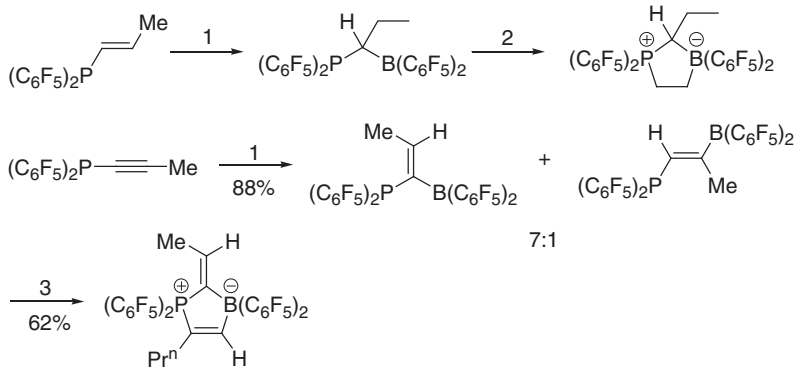
The reaction of a conjugated dienamine, 1,6-diamino-1,6-diphenyl-1,3,5-hexatriene, with $(C_6F_5)_2BH$ takes a course combining the strong Lewis acidity of the reagent and its hydroborating potential. Thus, the stable dienamine is tautomerized with two equivalents of the reagent to give a mixture of stereomeric diimine adducts, followed by slow hydroboration of the remaining carbon–carbon double bond[260] (Scheme 45).

The hydroboration of 1-alkynylphosphonates can be controlled to place the boron atom either on C1 or C2 of the triple bond by control of the reaction conditions. Initial hydroboration occurs on C1 (kinetic product), which can be isomerized to the B–C2 product (thermodynamic) by heating or catalytically.

The hydroboration of 2-butenyl derivatives places the boron predominantly at C2 and is often followed by the elimination and rehydroboration at the terminal position. However, the protection of 2-butenol with the tert-butyl or THP group prevents the elimination. The stability of β-functionalized organoboranes also depends on the steric requirements of the hydroborating agent.

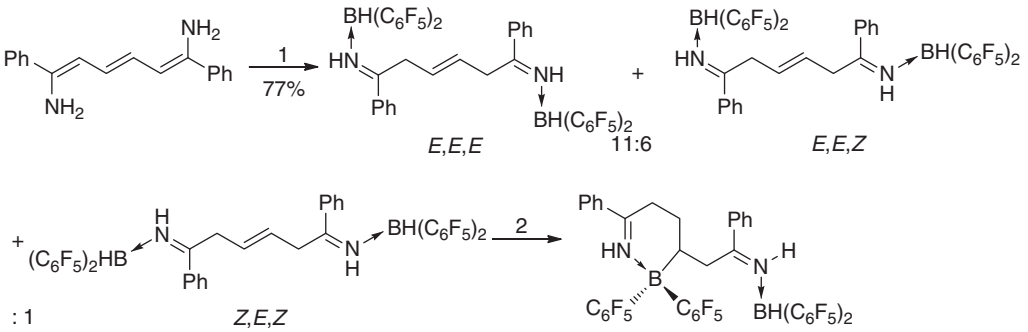
For example, 1,4-dihydronaphthalene-1,4-epoxide reacts with borane and 9-BBN producing the corresponding homoallylic alcohol, whereas Sia_2BH provides the addition product to the double bond[261] (Scheme 46).

1,3-Butadiene monoepoxide and monoaziridine undergo stereoselective intramolecular oxygen- and nitrogen-directed 1,4-borane addition with the double bond shift, producing (*Z*)-2-butenol and (*Z*)-2-butenylamine, respectively,[262,263] and the



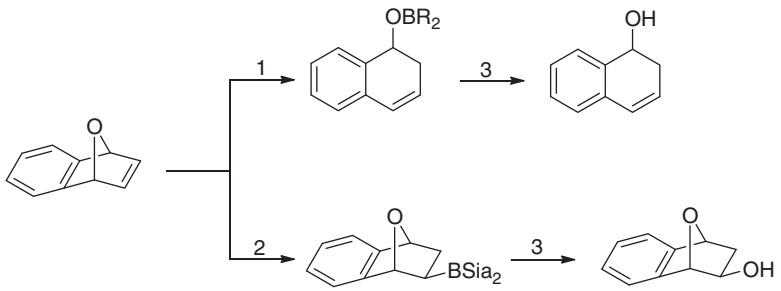
1. $(C_6F_5)_2BH$, *n*-pentane, –78 °C to r.t., 2 h; 2. $H_2C{=}CH_2$; 3. 1-pentyne, *n*-pentane, r.t., 12 h.

Scheme 44



1. $(C_6F_5)_2BH$ (2 equivalents), toluene, r.t., 7 min; 2. r.t., overnight.

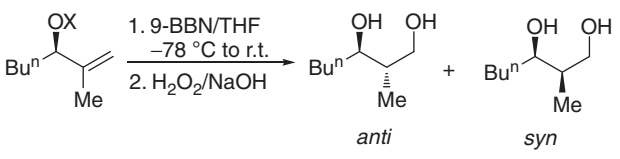
Scheme 45



1. BH_3/THF or 9-BBN, THF; 2. Sia_2BH, THF; 3. H_2O_2, NaOH.

Scheme 46

atom-directed addition reactions have been reviewed.[264] The substrate-controlled hydroboration of allylic alcohol derivatives leads to *anti*-diastereoselectivity[265] (equation 14).



X	*anti*	*syn*
H	11	1
Ac	7.5	1
THP	3.7	1
Bu^tMe_2Si	9.0	1
Bu^tOOC	15.4	1

(14)

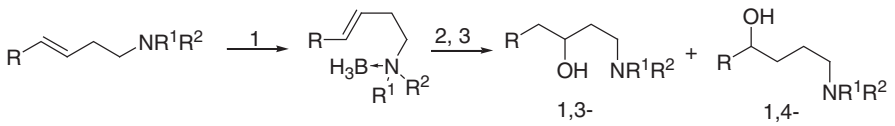
The *anti*-Markovnikov hydroboration product predominates in the borane addition to 3,4-dialkoxy-1-alkenes; however, a significant amount of the Markovnikov *anti*,*anti* product is also formed.[266]

Hydroboration of allyl ketones with Ipc_2BH enantioselectively provides 1,4-diols via the intramolecular reduction.[267] Cyclic allylic alcohols and ketenes give *trans*-1,2-substituted products.

Similarly, the Boc-protected allylic amines possessing an internal disubstituted double bond are regio- and stereoselectively hydroborated with borane/THF to give predominantly 1,2-aminoalcohols, *anti*/*syn* 16:1 for *Z*-isomer, and 4.8:1 for *E*-isomer.[268]

The intramolecular hydroboration of homoallylic amines, alcohols, and phosphines with iodine- or TfOH-activated borane is a highly regioselective alternative to the above-mentioned hydroborations directed by functional groups.[269] The reaction with homoallylic amines is presented in Table 7.

Table 7 Iodine-activated hydroboration of homoallylic amines with borane/THF



Conformer	*R*	*R*^{1}	*R*^{2}	*1,3-/1,4-*	*Yield (%)*
	H	H	H	1:1	69[a]
	H	H	Bn	1:3	90
E	Me	H	Me	43:1	85[a]
Z	Me	H	Bn	>20:1	87
Z	Et	$(CH_2)_4$		>30:1	92
E	Et	H	Bn	10:1	82
E	Ph	H	Bn	2:1	82

[a]Catalytic activation with 10 mol% I_2.

1. BH_3/THF; 2. I_2 (50 mol%), CH_2Cl_2, r.t.; 3. NaOOH.

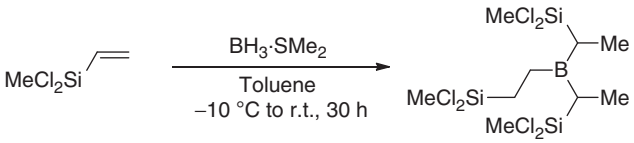
The regioselectivity of the addition to amines with phenyl-substituted and terminal double bonds is lower than other amines presented in Table 7. The TfOH-activated hydroboration of 2-allylic piperidines gives the expected 1,3-amino alcohols with diastereoselectivity 4–7:1 *dr*,[55] in accordance with the intramolecular process. Bis-homoallylic amines react in the same way, selectively producing 1,4-amino alcohols.[269] The proposed mechanism involves the formation of a tethered olefin π-complex ion pair, leading to the fused bicyclic four-center transition state with subsequent ion pair recombination[55,268–270] (Scheme 3).

In contrast to homoallylic amines, the iodine-activated hydroboration of allylic amines is less selective than hydroboration with borane/THF, which provides primarily 1,2-aminoalcohols from *N*-protected amines with electron-withdrawing substituents at nitrogen.[271]

Oxygen-directed intramolecular hydroboration of homoallylic alcohols with $BH_3 \cdot SMe_2$ activated by TfOH proceeds regioselectively to give a mixture of 1,3- and 1,4-diols in a 20–82:1 ratio.[271] (*E*)-4-Phenyl-3-butenol is practically unreactive under the same conditions.

Homoallylic phosphine boranes also undergo intramolecular hydroboration by activation with triflic acid selectively providing 1,3-phosphinoboranes, for example, diphenyl(4-phenyl-3-butenyl)phosphine is transformed into a mixture of 1,3 and 1,4 products in a 97:13 ratio.[272] Diphenyl-3-butenyl phosphine gives a 3:1 mixture of the primary and secondary products, whereas the intermolecular hydroboration with borane/THF affords the primary product as the major regioisomer, in a ratio of 7.3:1.

Hydroboration of unsaturated silanes has been reviewed.[273] The directive effect of silicon, favoring the placement of boron in the α-position, may be attributed to the stabilizing interaction between the empty p orbital of boron and the C–Si bond. Consequently, the hydroboration of vinyltrimethylsilane with borane/THF in the 3:1 M ratio is nonselective and a 1:1 mixture of primary and secondary alcohols is obtained.[274] Dichloro(methyl)vinylsilane has been cleanly transformed into primary/secondary silylated trialkylborane[275] (equation 15).



(15)

In the first two steps of the reaction boron is placed in a position α to silicon, and in the last step the regioselectivity with the bulky dialkylborane is opposite. Sterically demanding dialkylboranes hydroborate vinylsilanes, and boron is preferentially placed

in the primary position, 100% for vinyl-TMS/9-BBN. Selectivity in the addition to 1-alkenylsilanes depends on both reacting substrates[274,276] (Figure 7).

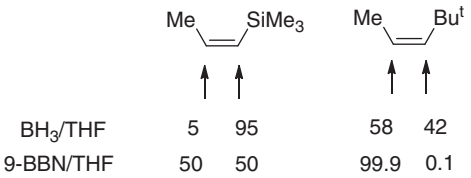


Figure 7 Directing effects of the trimethylsilyl and *tert*-butyl groups in hydroboration with borane and 9-BBN.

The C–$SiMe_3$ bond is longer than the C–CBu^t bond, making its steric effect weaker than the *tert*-butyl group, and acting against the stabilizing boron–silicon electronic interactions. Consequently, the selectivity of 9-BBN, depending mainly on steric interactions, is insufficient for high selectivity.

Among diorganoboranes, $(C_6F_5)_2BH$ reacts with vinylsilanes to give *β*-silylorganoboranes, which readily isomerize to *α*-silyl isomers at room temperature or when heated.[277]

The hydroboration products of allylic and homoallylic silanes with $(C_6F_5)_2BH$ also undergo isomerization to terminal *gem*-silylorganoboranes, despite the terminal position of the boryl group in the initial product.[277]

1-Alkenyltrimethylsilylanes are transformed into 1,1-trimethylsilylalkylboronates by the hydroboration with dibromoborane-dimethyl sulfide and dichloroborane-1,4-dioxane, followed by treatment with propan-1,3-diol.[278,279] Allylic and homoallylic trimethylsilanes have also been transformed into the corresponding 3- and 4-silylated boronic acid by hydroboration with dichloroborane followed by hydrolysis.[280]

Achiral carbosilane, crystallizing in chiral crystals, has been obtained by the hydroboration–oxidation of $Si(C_6H_4$–4-$SiMe_3Allyl)_4$. Other allylic carbosilanes of this type have been transformed into the corresponding terminal boronic acids.[281]

Enantioselectivity in the hydroboration of 2-methylpropen-1-ylsilanes (TMS, Me_2PhSi, and Et_3Si) with $IpcBH_2$ is 24, 24, and 48% *ee*, respectively, whereas 75% *ee* has been achieved in the reaction of Ipc_2BH with diisopropenyldimethylsilane.[282] This is relatively high selectivity when compared with ~20% *ee* achieved by this reagent with 2-methyl-1-butene.

Generally, aldehydes and ketones must be protected in hydroboration with borane/THF to avoid the competitive carbonyl reduction. However, selective hydroboration of unconjugated alkynyl aldehydes and ketones with a less-reactive dicyclohexylborane has been achieved.[283] Similarly, unconjugated ketones with terminal mono- and disubstituted double bonds, 2-acetyl-5-norbornene, and 11-undecenal undergo selective hydroboration with this reagent.[284]

Desymmetrization of functionalized alkenes and dienes with chiral hydroborating agents is an efficient strategy in natural products synthesis[285] and has been applied in the asymmetric synthesis of (+)-boureganic acid,[286] pteridic acid A,[287] cytotoxic agent Crocacin C,[288] tropinone derivatives,[289] and polycyclic polypropenoate fragments.[290]

Hydroborations influenced by remote functionalization have been observed (Figure 8).

In the first example, the second double bond affects the selectivity of addition. The Markovnikov addition in the second and third examples is directed by diene and oxygen, respectively. The lack of reactivity of the dienyne subunit toward CatBH and PinBH/$Cp_2Zr(H)Cl$ is unusual, since other dienyne compounds react with these reagents.[291,292] However, it reacts with Sia_2BH, Chx_2BH, and $(i\text{-}PP)_2BH$.

8.24.1.4.3.2 Functionalized alkynes

The monohydroboration of heterosubstituted alkynes provides functionalized alkenyl boranes, which are versatile synthetic intermediates that have been used in the synthesis of *E*- and *Z*-alkenes, trisubstituted olefins, and *Z*-alkenylboranes.[293,294] Alkenylboranes, functionalized with zinc at the double bond, are available by zinc insertion into the carbon–halogen bond or by the boron-to-zinc transmetalation. These bifunctional organoboranes are well suited for tandem transformations of great synthetic potential.

Thus, the hydroboration of 1-iodoalkynes followed by the reaction with zinc dust generates the 1,1-bimetallic reagent, used for the synthesis of *α*-hydroxyketones[295] (Scheme 47).

Transmetalation enables a flexible approach to the desired reagent and makes possible a one-pot synthesis by the introduction of an alkyl group and generation of *E*-alkenylzinc intermediate in one step,[296] and the stereoselective addition to aldehydes gives trisubstituted allylic alcohols (Scheme 48).

Similar methods have been applied for the highly stereo- and regioselective synthesis of trisubstituted alkenes. When the alkynyl derivative is an alkynylborane, the hydroboration product is 1,1-diborylalkene. The boryl groups of different structure differ in reactivity making possible a selective transmetalation with dialkylzinc, followed by tandem transformations,[297] for example, the stereoselective addition to aldehydes, transformation to conjugated aldehydes, or Suzuki–Miyaura cross-coupling with alkyl/aryl halides. A one-pot procedure is shown in Scheme 49.

Diastereoselective aziridination and cyclopropanation of 2-pinB-substituted allylic alcohols has been achieved.[298,299]

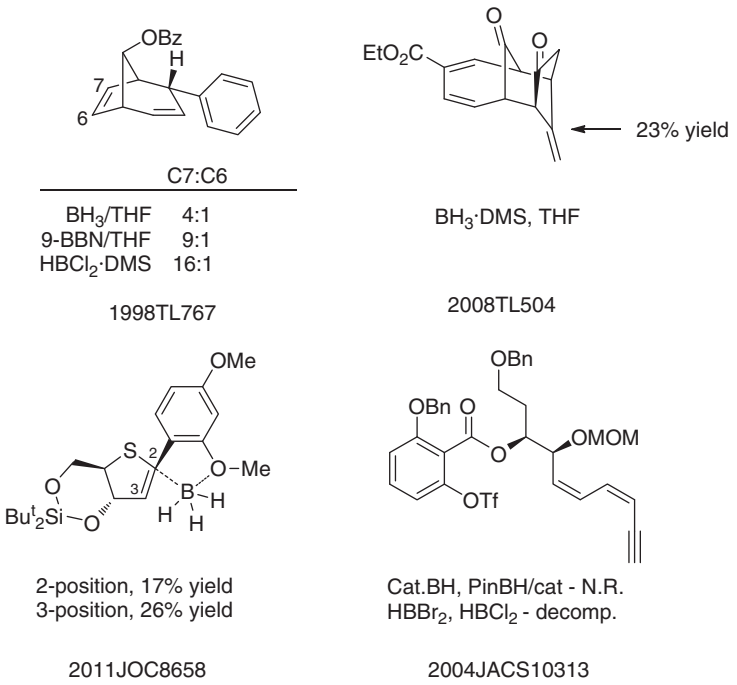
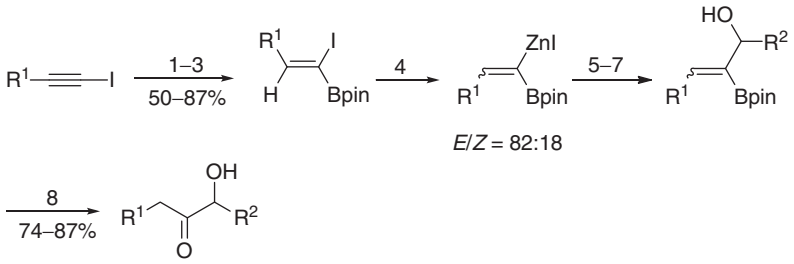
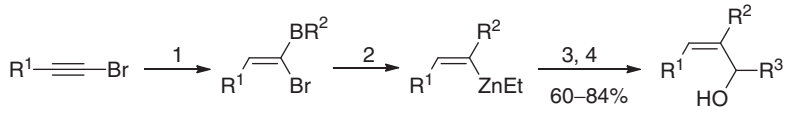


Figure 8 Hydroboration influenced by remote functionalization.



1. $HBBr_2·SMe_2$; 2. NaOH, H_2O; 3. Pinacol; 4. Zinc dust, DMA; 5. CuCN·2LiCl; 6. R^2CHO, $BF_3·OEt_2$; 6. H^+, H_2O; 8. H_2O_2, NaOH.

Scheme 47

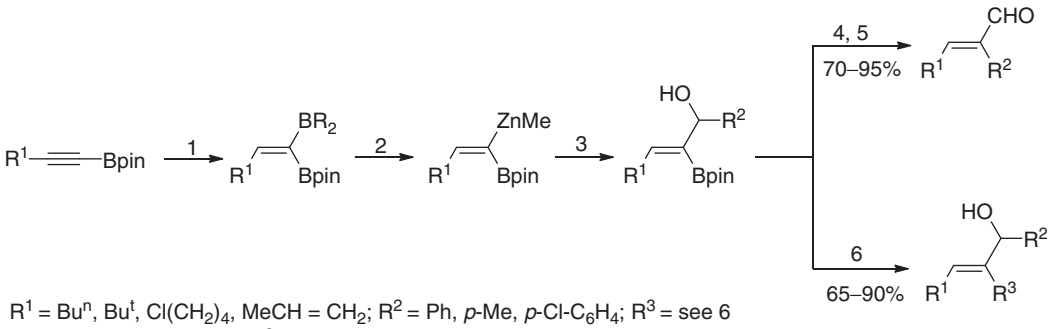


R^1 = Bu^n, $BnOCH_2$; $(CH_2)_2OTBS$; R^2 = Et, Hex^c.
R^3 = H, *p*-Cl-, *p*-Me, *o*-$MeOC_6H_4$.
1. Et_2BH or Chx_2BH; 2. Et_2Zn (3 equivalents); 3. R^3CHO; 4. H^+.

Scheme 48

Ethynyl amides undergo monohydroboration with CatBH providing the corresponding *E*-alkenylboronates, whereas *N*,*N*-methylphenylethynylamine reacts with decomposition.[300]

Internal ynamides are convenient precursors of *β*-hydroxyenamines, enaminocyclopropanes, and 1,3-amino alcohols.[301] A one-pot enantioselective synthesis of *E*-trisubstituted *β*-hydroxyenamines, which can be hydrogenated to the corresponding 1,3-amino alcohols, is shown in Scheme 50.



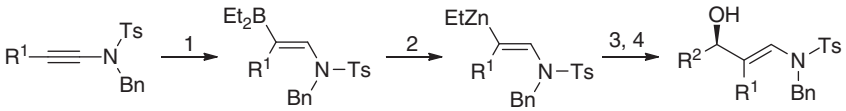
R^1 = Bu^n, Bu^t, $Cl(CH_2)_4$, MeCH = CH_2; R^2 = Ph, *p*-Me, *p*-Cl-C_6H_4; R^3 = see 6

1. Chx_2BH; 2. Me_2Zn; 3. R^2CHO; 4. H^+; 5. NBS; 6. $Pd(OAc)_2$ (5 mol%), PhI, 2-iodo-2-cyclohexenone,



, Bu^n—≡—Br.

Scheme 49

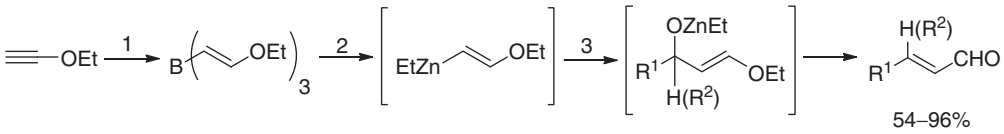


R^1,R^2 = Ph, Pr^i; Ph, cyclohexyl; Ph, Ph; Bu^n, Pr^i; Bu^n, Ph. 91–96% *ee*

1. 1 M Et_2BH, toluene, 20 °C, 20 min; 2. 2 M Et_2Zn, toluene, –78 °C, 20 min;
3. (–)-*exo*-3-morpholinoisoborneol (5 mol%); 4. R^2CHO, 0 °C, 12 h.

Scheme 50

The hydroboration of ethoxyacetylene followed by the boron–zinc transmetalation provides a convenient one-pot synthesis of α,β-unsaturated aldehydes and ketones[302] (**Scheme 51**).



54–96%

R^1,R^2 = $(CH_2)_5$; Ph; H,Bn; H,Ph; H,cyclohexyl.

1. $BH_3{\cdot}SMe_2$; 2.Et_2Zn, –78 °C; 2. R^1CHO or R^1R^2CO.

Scheme 51

Saturated aldehydes may be obtained by the Suzuki–Miyaura cross-coupling of the tris(2-ethoxyvinyl)borane intermediate with aryl iodides or bromides.[303]

Directive effects in the hydroboration of 1-trialkylsilylpropyne with 9-BBN are presented in **Figure 9**.[304] The dihydroboration product decreases with the increasing bulk of the silyl substituent. No geminal dibora products are formed.

1-Trimethylsilyl-1-alkynes have been hydroborated with borane/THF,[305,306] Chx_2BH,[307] and 9-BBN[304,308,309] under various conditions. Generally, 1-silyl-1-alkinylboranes are formed by 1,2-*cis*-addition. However, in some cases mixtures of regio- and stereoisomers or carboranes[305,310,311] are obtained.

The hydroboration product of 1,2-bis(trimethylsilyl)ethyne with 9-BBN undergoes isomerization of the initially formed *Z*-isomer into the more stable *E*-isomer after several days at room temperature.[312] The σ–π delocalization leading to a boracyclopropyl intermediate has been suggested to explain the *E*/*Z* isomerization. Alternatively, in the reaction of Et_2BH with $Me_2ClSiC{\equiv}CBu^n$, the mixture of *E*/*Z* products is possibly formed by dihydroboration–retrohydroboration. The *gem*-silyl-1-alkenylorganoboranes with the functionalized silyl group have been used as new synthons for the formation of five-membered heterocycles.[313]

The hydroboration of 1-trimethylgermyl-1-alkynes with Chx_2BH and $HBCl_2 \cdot SMe_2/BCl_3$ gives 1-trimethylgermyl-1-alkenylboranes, which have been transformed into *Z*-trimethylgermylalkenes and 1-trimethylgermyl-1-alkenylboronates.[314] 1-Selenyl- and 1-telluryl-1-alkynes react similarly.[315]

Propargylic derivatives react with bulky dialkylboranes, placing the boron atom at the terminal position providing γ-functionalized *E*-1-alkenylorganoboranes. For example, a flexible one-pot three-component process that can be directed toward either

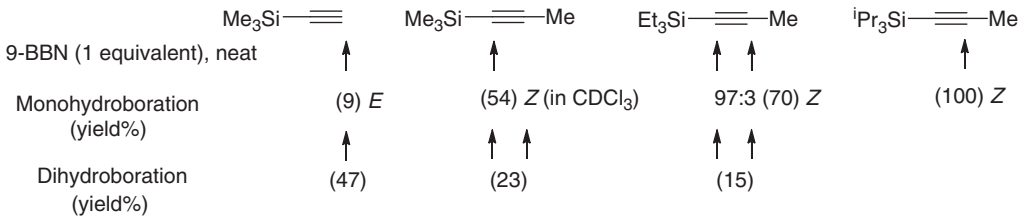
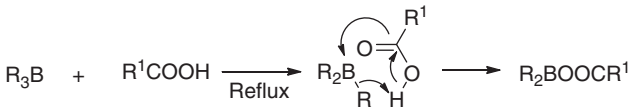


Figure 9 Regioselectivity of hydroboration of alkynylsilanes with 9-BBN.

the synthesis of *E*-homoallylic alcohols or antihomoallylic alcohols is based on the hydroboration of propargyl chloride with dialkylboranes.[316]

8.24.1.5 Protodeboration of Organoboranes

Protonolysis of organoboranes has been reviewed.[317] Simple trialkylboranes are relatively stable toward protonolysis by treatment with alcohols, water, aqueous bases, and mineral acids, except hydrogen fluoride.[318] However, organoboranes obtained by the hydroboration of alkenes and alkynes with $(C_6F_5)_2BH$ are sensitive to the standard basic oxidation conditions and produce significant amounts of hydrocarbons in addition to alcohols or carbonyl compounds. In contrast to mineral acids, carboxylic acids react with trialkylboranes, removing the first alkyl group rapidly, the second slowly, and the third very slowly at elevated temperatures. The relative rates are 1:0.052:~0.[319] Acetic acid and propionic acid at reflux temperatures are most often used. The reaction proceeds with retention of configuration of the alkyl group via a cyclic, six-membered transition state (equation 16). The mechanism is based on isotopic and kinetic studies.[319]



(16)

R = alkyl; R^1 = Me, Et.

The decreasing rate of removal of the second and third groups can be attributed to the decreased Lewis acidity on boron by the mesomeric effect of acyloxy groups substituting alkyl groups. The reactivity of alkyl groups decreases in the order primary > secondary > tertiary, which can be taken advantage of in selective protonolysis of a primary group in mixed trialkylboranes.[213] Products sensitive to the action of hot carboxylic acids may be affected. For example, protonolysis of Diels–Alder adducts of vinylic organoboranes with 2,3-dimethyl-1,3-butadiene gives a mixture of isomeric dimethylcyclohexenes.[173] Selective monohydroboration–protonolysis of (+)-limonene proceeds with racemization by protonation of the endocyclic double bond in refluxing propionic acid.[319]

Pivalic acid accelerates the rate of reaction of trialkylboranes with water and alcohols, which proceeds under mild conditions and can be controlled to give dialkylboronic acids and esters in excellent yields.[320]

The reduction of alkenes to alkanes under mild, acid-free conditions has been achieved by hydroboration with an excess of CatBH followed by treatment with methanol in the presence of air as a radical initiator[321] (**Table 8**).

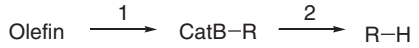
As shown in **Table 8**, primary, secondary, and tertiary groups undergo the reaction, with highest yields for the primary groups. Rearrangement in the reaction of 2-carene is consistent with the involvement of a free radical. The proposed mechanism of the reduction of the intermediate *B*-alkylcatecholborane with catechol is presented in **Scheme 52**.[322]

As mentioned above, protonolysis of the third group of trialkylboranes is very slow. Protodeboration of diarylalkyl- and dialkylarylboronic esters with propionic acid at 130 °C is also very slow and the conversion is low. Hydrofluoric acid reacts at room temperature to give a mixture of products. However, a dramatic acceleration of the protodeboronation has been achieved for alkyldiarylboronic esters with calcium fluoride and a controlled amount of water in 1,4-dioxane, and also for dialkylarylboronic esters with tetrabutylammonium fluoride ($TBAF \cdot 3H_2O$) in toluene or *n*-pentane. The reaction proceeds at 30–45 °C with retention of configuration[323] (**Table 9**).

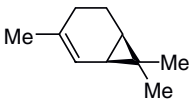
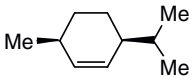
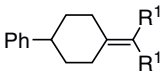
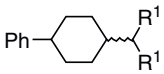
Deuterodeboronation of the esters presented in **Table 9** proceeds with the same high selectivity when deuterium oxide is used instead of water. The proposed reaction mechanism is shown in **Scheme 53**.[323] The amount of water is crucial for the reaction, and a particular application may need optimization of conditions as demonstrated in the enantioselective synthesis of (+)-sertraline and (+)-indantraline.[324]

Allylic and alkenyl organoboranes are more readily protonolyzed than alkylboranes, and it is often sufficient to use water or alcohols.[317] Thus, allylic organoboranes are hydrolyzed with water at room temperature, the reaction proceeding with complete 1,3-allylic shift. The reaction has been used in the final step of a convenient contrathermodynamic isomerization of olefins by the metalation–transmetalation–hydrolysis sequence. (+)-α-Pinene, (+)-2-carene, and (–)-thujene have been transformed into

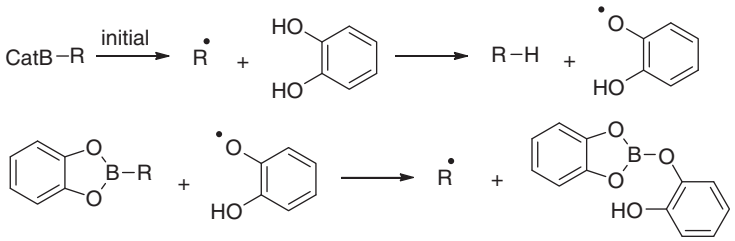
Table 8 Reduction of B-alkylcatecholboronates with catechol



1. CatBH (2 equivalents), $MeCONMe_2$ (0.1 equivalent), CH_2Cl_2, reflux, 5 h;
2. MeOH (4 equivalents), air (0.3 equivalent of O_2), CH_2Cl_2, reflux, 90 min.

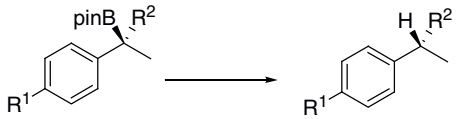
Olefin	R^1	*Yield*[a] (%)	*Product*	
1-Octene		90	*n*-Octane	
β-Pinene		96	*cis*/*trans*-Pinane 9:1	
Cyclohexene		94	Cyclohexane	
		75 (56)[b]		
	H	61		1:1
	Me	87 (71)[b]		
β-Sitosterol PMB ether[c]		61	3-β-Cholestanol PMB ether	

[a]GC yields.
[b]Isolated yields.
[c]PMB = *p*-methoxybenzyl ether.



Scheme 52

Table 9 Protodeboronation of tertiary pinacolatoboronates

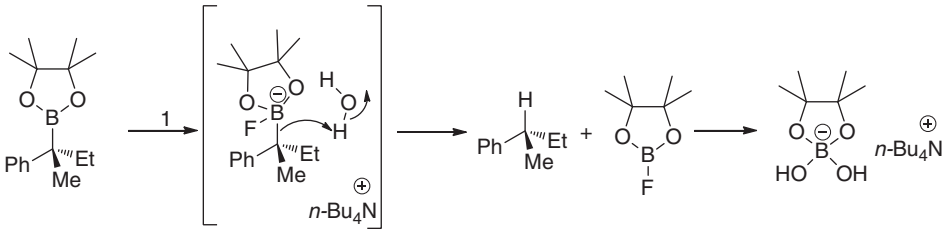


Procedure A, R^2 = aryl; CaF_2 (1.5 equivalents), H_2O (1.1 equivalents), 1,4-dioxane.
Procedure B, R^2 = alkyl; TBAF·$3H_2O$ (1.5 equivalents), *n*-pentane.

Boronic ester			*Procedure/Temperature (°C)*	*Product*		
R^1	R^2	er		*Yield (%)*	er	es *(%)*
H	*p*-ClC_6H_4	99.7:0.3	A/30	82	97.3:2.7	98
OMe	Ph	98.3:1.7	A/65	99	98.1:1.9	99
H	2-Furyl	99.0:1.0	A/35	99	97.9:2.1	98
H	Et	99.7:0.3	B/45	97	98.8:1.2	99
OMe	Et	99.9:0.1	B/45	90	99.8:0.2	99
H	Pr^i	99.5:0.5	B/45	96	99.2:0.8	99
H	Allyl	99.6:0.4	B/45	98	99.5:0.5	99

optically pure (+)-β-pinene,[325,326] (+)-3(10)-carene, and (+)-sabinene,[327] respectively, and deuterium has been stereoselectively incorporated into the 3-position of β-pinene.[328]

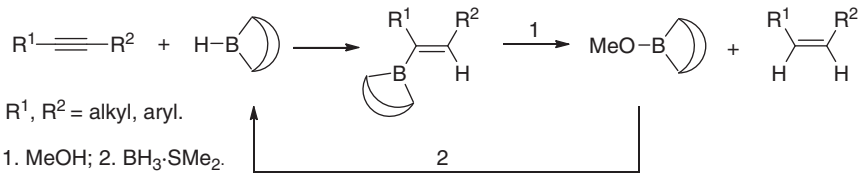
Alkenylorganoboranes are protonolyzed by carboxylic acids at room temperature. Monohydroboration–protonolysis of internal acetylenes provides convenient access to stereochemically pure *Z*-alkenes. It is also possible to carry the transformation



1. n-$Bu_4NF{\cdot}3H_2O$ (1.5 equivalents), THF.

Scheme 53

under neutral conditions using methanol. If the reaction is slowed by steric hindrance, a catalytic amount of pivalic acid is helpful. The method allows for recycling of the hydroborating agent in larger scale applications[329] (Scheme 54). Alkenylboranes can also be transformed into alkenes under basic conditions by treatment with aqueous sodium hydroxide.[330]



R^1, R^2 = alkyl, aryl.

1. MeOH; 2. $BH_3{\cdot}SMe_2$.

Scheme 54

8.24.1.6 Catalytic Hydroboration

8.24.1.6.1 Introduction

Hydroboration of alkenes and alkynes with borane, alkyl-, and haloboranes is usually a fast reaction. In contrast, the reaction with alkoxy- and aminoboranes is slow and proceeds at elevated temperatures. The products, particulary boronic esters, are important synthetic intermediates. Consequently, catalysts providing access to the esters under mild conditions are desirable. In 1985, Maennig and Noeth[21] reported the rhodium-catalyzed hydroboration of alkenes, 1-hexyne, and unsaturated ketones at room temperature, proceeding with opposite chemoselectivity to the uncatalyzed reaction with 9-BBN. The discovery prompted intensive further studies also revealing differences in the regio- and stereoselectivity of the uncatalyzed and catalyzed reaction (Scheme 55).

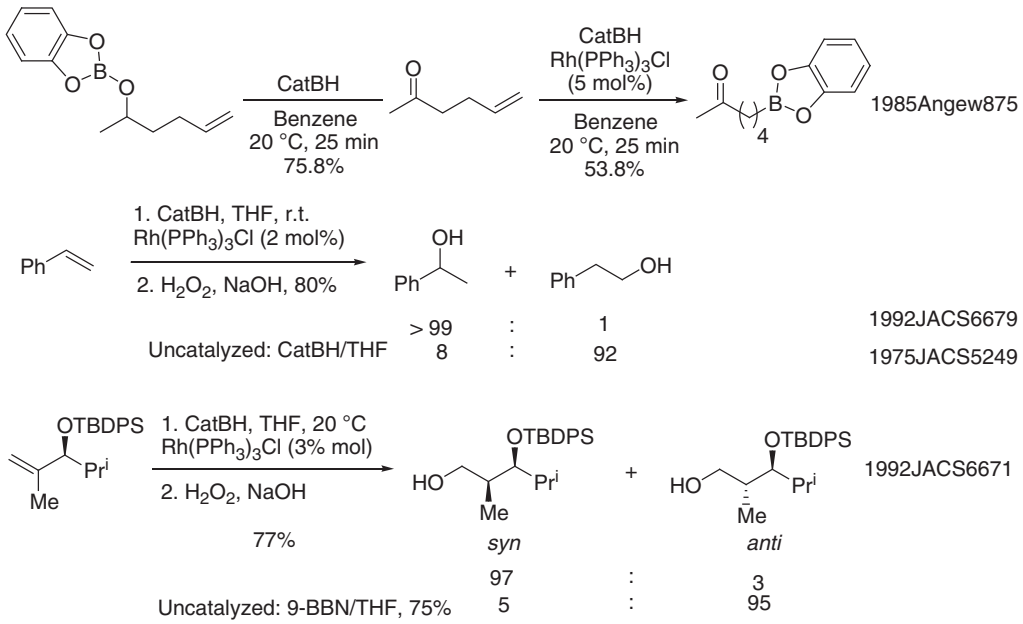
Several catalysts have been developed, and chiral catalysts make possible the asymmetric hydroboration with achiral hydroborating agents. The fast-growing field is constantly expanding the hydroboration scope, and the recently introduced copper-catalyzed hydroboration of double and triple bonds creates new synthetic possibilities.[331] Catalytic hydroboration has been extensively reviewed.[8–11,180,332–334]

8.24.1.6.2 Olefins and derivatives

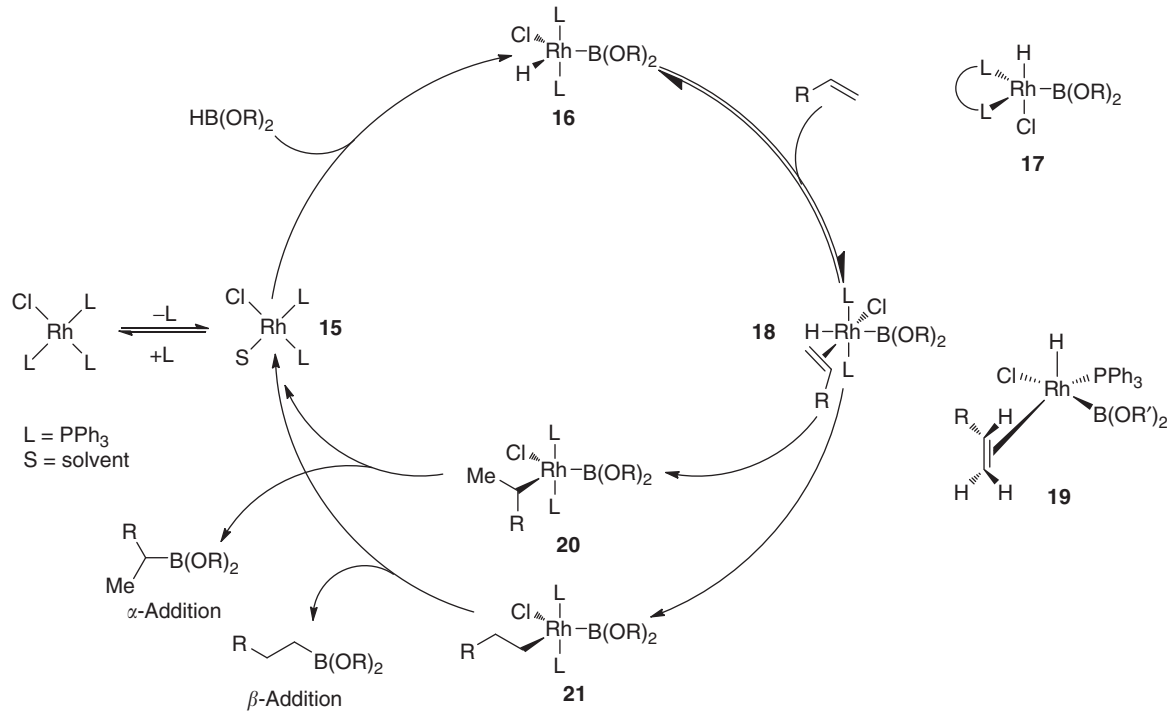
8.24.1.6.2.1 Mechanism of rhodium-catalyzed hydroboration

Rhodium catalysts are the most often used in catalytic hydroboration, and the addition mechanism of dialkoxyboranes to olefins has been studied since the discovery of the reaction. In spite of this, its pathways depending on electronic and steric factors of the substrates, the catalyst ligands, and the reaction conditions are still investigated. The possible steps leading from 1-alkene to the addition products in the presence of $Rh(PPh_3)_3Cl$ are presented in Scheme 56.[11,180,332–336]

The reaction starts with the oxidative addition of dialkoxyborane to the catalyst **15** producing the intermediate **16**. The structures of its analogs with PPr^i_3 ligands have been established.[337–339] The structure **17**, based on spectroscopic studies, has been proposed when the ligand is a bidenate phosphine.[335] The associative complexation of an olefin leads to **18**, while dissociative complexation, which has also been considered, may lead to **19**.[336,340–342] In the next step, the formation of **20** and **21** by the olefin insertion into the Rh–H bond is followed by reductive elimination affording the α- and/or β-addition products. α-Addition is favored for vinylarenes, whereas monosubstituted 1-alkenes give the β-addition products. Styrene reacts with deuterated CatBH in the presence of $Rh(PPh_3)_3$ Cl in THF, and the α-addition product is obtained with high regioselectivity, 99:1. Deuterium is cleanly placed in the terminal position and is not incorporated into the recovered olefin.[22] It indicates that the insertion of styrene into the Rh–H bond is irreversible and determines the regioselectivity. In contrast, the reaction with 1-decene under the same conditions, affording the β-addition product, proceeds with deuterium scrambling in the 1- and 2-positions, and unreacted 1-decene also contains deuterium at the double bond. The result has been accounted for by assuming reversibility of the insertion



Scheme 55



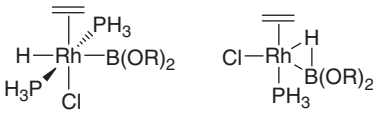
Scheme 56

step, with irreversible reductive elimination being the regioselectivity-determining step. Consequently, the reaction mechanism depends on the olefin structure. It also depends on the borane reagent and catalyst, as observed in the hydroboration of styrene with PinBH, catalyzed by $[Rh(cod)_2]BF_4$/1,4-diphenylphosphinobutane (dppb), proceeding with deuterium scrambling.[343]

Alkene insertion into Rh–B bond is also possible, particulary with more hindered alkenes, and may lead either to the same α- and β-addition products or to 1-alkenylboronates and 1-alkylboronates by the dehydrogenative borylation–reduction, which are side reactions.[344–347]

Theoretical studies predict associative and dissociative pathways.[348–351] For example, DFT calculations on the model reactions of ethylene with HBR_2 (R=OH; 2R=OCH=CHO), catalyzed by $Rh(PH_3)_3Cl$, indicate energetically similar barriers for olefin

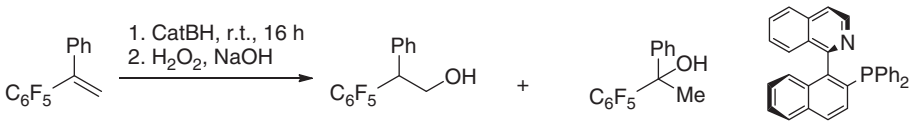
insertion into the Rh–H and Rh–B bonds of the intermediate **22** (Figure 10) and also for the reductive elimination of the insertion products.[350] However, calculations of pathways from the intermediate **23** (Figure 10) indicate a much lower insertion barrier into the Rh–H bond as compared to the Rh–B bond, and reversed barriers in the reductive eliminations of the insertion products, which may be the regioselectivity-determining step.



22 **23**

Figure 10 Calculated intermediates on the model reaction of ethylene with $HB(OR)_2$, catalyzed by $Rh(PH_3)_3Cl$.

The regioselectivity of the Rh-catalyzed hydroboration of vinylarenes with dialkoxyboranes favoring the α-addition product has been rationalized considering stabilization of benzylrhodium complexes by η^3-interactions with the aromatic π-system.[337,341,352] Later, the π-stacking interactions between the alkene and the aryl ligand, depending on steric and electronic effects, have been shown to influence the regio- and enantioselectivity of the reaction.[11,332,336] The Hammett plot of log (isomer ratio) versus σ for *Z*-stilbenes *p*-substituted in one phenyl ring hydroborated with PinBH/$[Rh(cod)_2]BF_4$ dppb features a minimum at $\sigma = 0$, indicating mechanistic differences exerted by the electron-withdrawing and electron-donating substituents. However, the boron atom is placed in the α-position of the substituted ring regardless of the substituent type, achieving the greatest selectivity for the most electron-withdrawing CF_3, and the most electron-donating NMe_2, used in the study.[343] In contrast, the reaction of substituted *Z*-stilbenes with CatBH/QUINAPRh$^+$OTf$^-$ affords preferentially the products substituted in the α-position to the more electron-deficient aromatic ring.[353] The regioselectivity of the same reactions catalyzed with DppbRh$^+$OTf$^-$ is lower but the trend is similar. The results indicate the influence of electronic effects on the regioselectivity. However, it also depends on the reagent and catalyst as follows from the above-mentioned study[343] and shown in equation 17.[353]



QUINAPRh$^+$, 60%	4	:	96, 31% *ee*	(*R*)-QUINAP
DppbRh$^+$	70	:	30	

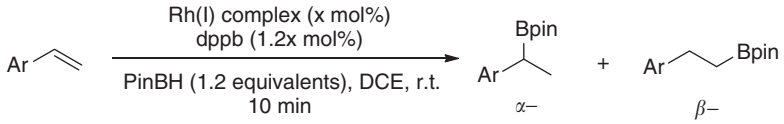
(17)

The enantioselectivity of the above described hydroboration of stilbenes catalyzed by QUINAPRh$^+$ has been accounted for in terms of the π-stacking interactions between the substrates and the catalyst ligands.

Noteworthy is the reaction sensitivity to the catalyst oxidation, as observed in the hydroboration of styrene with CatBH in the presence of $Rh(PPh_3)_3Cl$.[22] The reactivity and regioselectivity of the catalyst is affected by oxidation of its phosphine ligand with oxygen in the reaction medium or with peroxides present in the alkene. When excess PPh_3 is added to the oxidized catalyst, the regioselectivity is the same as under oxygen-free conditions.

A dramatic effect of Lewis acids on the Rh-catalyzed hydroboration of olefins has been described.[354] For example, the addition of 2% $(C_6F_5)_3B$ to the reaction of vinylarenes and aliphatic olefins with PinBH in the presence of $[Rh(cod)(dppb)]BF_4 \cdot THF$ results in the accelerated rate and much higher yield and regioselectivity. *Cis*-cyclooctene and (*E*)-2-methyl-2-pentene, unreactive in DCE without the additive, react in its presence in 90% and 94% yield, respectively. Its role as a mediator in the oxidative addition has been proposed (Scheme 57).

A counterion-accelerated catalytic hydroboration with PinBH has also been observed[355] (equation 18).

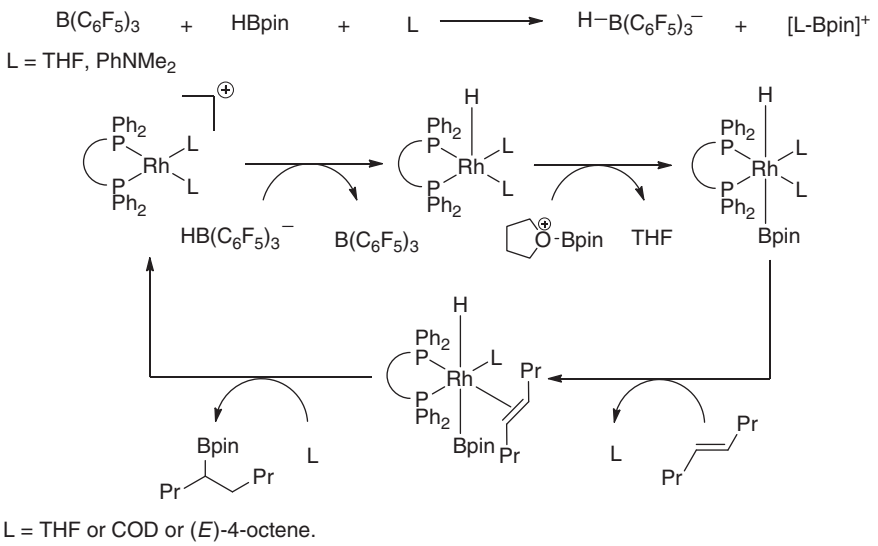


(18)

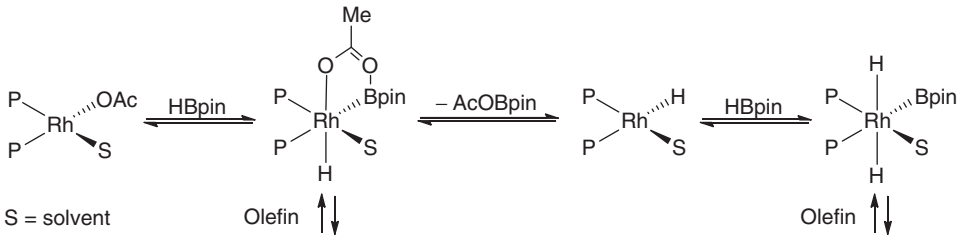
Ar = Ph; *m*-, *p*-BrC_6H_4; *p*-Me, Ph, Cl, MeO-C_6H_4; 2-naphthyl, 6-MeO-2-naphthyl.
catalyst = 5 mol% $[RhCl(cod)]_2$, $[Rh(cod)_2]BF_4$; Rh(acac)(cod); $[Rh(OMe)(cod)]_2$ - traces of product
1.2 mol% $[Rh(OAc)(cod)]_2$, 88–98% yield, α–/β–98:2.

The reaction should be completed rapidly, before the Rh–H generation leading to the dehydrogenative borylation and reduction. Two possible alternate intermediates coordinating an olefin in the next step have been proposed (Scheme 58).

Other coordinating counterions, for example, pivalate or benzoate, give similar results.



Scheme 57



Scheme 58

8.24.1.6.2.2 Boron reagents

CatBH, PinBH, and bis(pinacolato)diboron, B_2pin_2, are the most often used reagents in catalytic hydroborations, and other boranes shown in Figure 11 have occasionally been employed. The Cu-catalyzed monoboration of carbon–carbon double bonds with B_2pin_2, via the Cu–B bond addition–protonation, furnishes the product equivalent to hydroboration.

CatBH has been the most commonly used reagent in catalytic hydroboration. It is more reactive than PinBH and enables catalytic reactions at low temperatures. The already mentioned disproportionation, dehydrogenative borylation, and hydrogenation are the possible side reactions with the less reactive or certain functionalized alkenes.[344–347] Vinylarenes, 1-alkenes, 1,1-disubstituted alkenes, and unhindered disubstituted internal alkenes react rapidly. Selective reactions with dienes or even unprotected enones are possible.[356]

Sensitivity to moisture of the catecholboronates hydroboration products practically prevents their chromatography and limits the scope of further transformations.

PinBH is more convenient to handle, the hydroboration products are stable to moisture and chromatography, and its selectivity is often complementary to CatBH. Consequently, applications of this reagent are increasing.[354]

In contrast to CatBH, PinBH hydroborates various olefins, including internal disubstituted alkenes, in the presence of rhodium and zirconium catalysts producing preferentially the linear boronate, also from internal alkenes[357,358] (Scheme 59).

The sterically demanding Bpin group migrates to the least-hindered terminal position. Hydroboration–isomerization of internal olefins under mild conditions to the terminal organoboranes, which can be transformed into valuable products, has a potential for practical applications.[354,359] In the later reports, the hydroboration–isomerization of *E*-4-octene could not be achieved in the presence of oxygen-free $Rh(PPh_3)_3Cl$; however, it proceeds with the oxidized catalyst.[360] Styrene gives the linear pinacolboronate as the major product in the presence of $Rh(PPh_3)_3Cl$,[357] and even pentafluorostyrene and perfluoroalkylethylene, undergoing the uncatalyzed Markovnikov hydroboration, furnish the linear products preferentially.[361] However, the branched product is formed from styrene, substituted styrenes, and 2-vinylnaphthalene in the reaction with PinBH, catalyzed by $[Rh(OAc)(cod)]_2$, and $[Rh(cod)_2]BF_4$/diphosphines.[355,362,363]

Reversal of the enantioselectivity between CatBH and PinBH under the same reaction conditions has been observed (Scheme 60).[362]

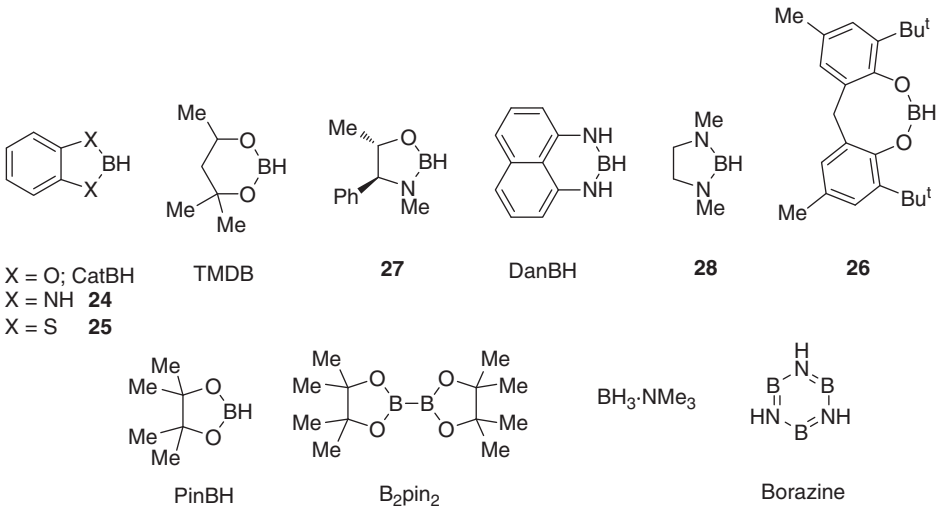
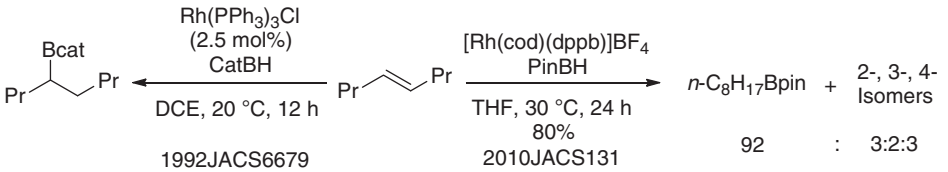
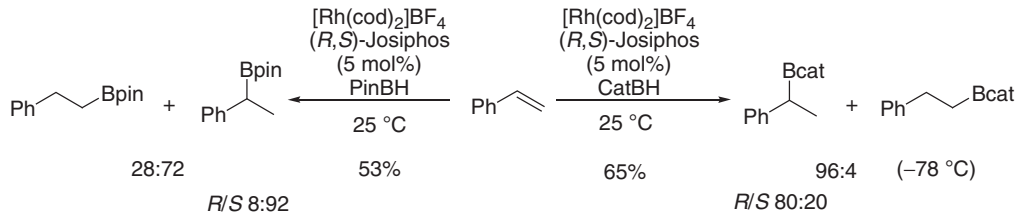


Figure 11 Boron reagents used for catalytic hydroboration.



Scheme 59



Scheme 60

The reactivity of CatBH and its nitrogen and sulfur analogs, **24** and **25** (Figure 11), in the uncatalyzed hydroboration of 1- and 4-octene decreases in the order: O > S > N.[364] In the reaction catalyzed with $Rh(PPh_3)_3Cl$, disproportionation of CatBH is the side reaction, whereas its sulfur analog disproportionates only in ~2%.

The nitrogen analog reacts with 1-octene without disproportionation and does not react with 4-octene. 4,4,6-Trimethyl-1,3,2-diaoxaborinane (TMDB) is slightly more reactive than PinBH, it hydroborates alkenes and alkynes, and the boronic esters produced are air and chromatography stable. In the Rh-catalyzed hydroboration of 4-octene the linear product is formed. The Zr-catalyzed reaction of TMDB with propargyl bromide furnishes the addition product whereas PinBH does not react.[365] The enantioselectivity of asymmetric hydroboration of *β,γ*-unsaturated Weinreb amides with TMDB is the highest (92–97% *ee*) among 11 other cyclic dioxaboranes, including CatBH and PinBH.[366] Dioxaborocine **26** hydroborates 1-alkenes in the presence of $[Cp^*IrCl_2]_2$, but not $Rh(PPh_3)_3Cl$, providing the terminal boronate.[367] Norobornene also undergoes hydroboration, but limonene does not react, indicating high sensitivity of the reagent to the alkene structure. The reaction with *p*-methoxystyrene follows the dehydrogenative borylation pathway. The chiral pseudoephedrine-derived oxazaborolidine **27** has been used in the hydroboration of *p*-methoxystyrene, catalyzed by an achiral rhodium catalyst, affording the product of 76% *ee*.[368] The iridium-catalyzed hydroboration of alkynes with 1,8-naphthalenediaminatoborane, DanBH (Figure 11), makes possible a direct introduction of the masked boryl group into an organic molecule. The boron-masked strategy finds applications in the iterative organic synthesis.[30,31,369,370]

Diazaborole **28** has been used successfully in the samarium-catalyzed hydroboration–cyclization of 1,5-hexadienes, where other boranes failed.[371] Recently, the hydroboration of *tert*-butylethylene with $BH_3 \cdot NMe_3/[Rh(PBu^tBu^i_2)]^+$ producing 3,3-dimethylbutylborane has been reported.[372]

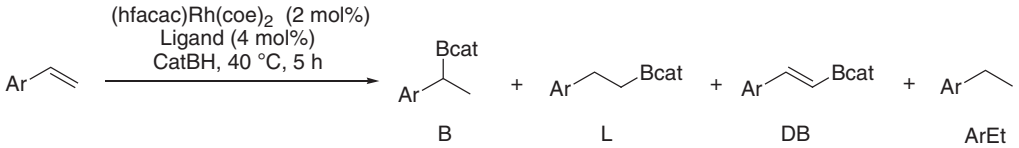
Borazine finds application in the Rh-catalyzed hydroboration of olefins and acetylenes leading to mono-, di-, and trialkylborazines, and dialkylvinylborazines.[373]

Bis(pinacolato)diboron is widely used in the catalytic monoboration and diboration of carbon–carbon multiple bonds.[374] It is commercially available, and its preparation has been described.[375]

8.24.1.6.2.3 Reaction media and catalyst recycling

Catalytic hydroboration is usually carried out in DCM, DCE, THF, benzene, and toluene, and at low temperatures in DME or DME/THF. Catalysts bearing fluorinated ligands exhibit high affinity for fluorous media, making possible the reaction under biphasic or monophasic conditions. On workup, the catalyst remains in the fluorous layer and can be recycled. Thus, $Rh(PPh_3)_3Cl$, soluble only slightly in $CF_3C_6H_5$, has been transformed into $ClRh(PCH_2CH_2C_6F_{13})_3$ **29**, soluble in $CF_3C_6H_5$ and $CF_3C_6F_{11}$. Hydroboration of various aliphatic olefins with CatBH at 40 °C in a biphasic system toluene/CF3C6F11/**29** affords the *anti*-Markovnikov product in 77–90% yield.[376] The regioselectivity of the reaction with styrene and *p*-methoxystyrene is low, α/β 55:45 and 39:61, respectively. The catalyst has been recycled five times, TON 2411.[377] The reaction of *p*-methoxystyrene with CatBH in supercritical carbon dioxide ($scCO_2$), catalyzed by rhodium complexes with fluorinated phosphines, shows higher regioselectivity than with triphenylphosphine and is influenced by solvents[378] (**Table 10**).

Table 10 Hydroboration of *p*-methoxystyrene with CatBH catalyzed by Rh complexes with fluorinated phosphines



Ligand	*Solvent*	*Conversion (%)*	*B*	*L*	*DB*	*ArEt*
No ligand	$scCO_2$	89	14	14	31	41
PPh_3	$scCO_2$	92	71	13	13	3
$P(R_F)_3$	$scCO_2$	94	82		17	1
Cy_2PR_F	THF	100	32	34	17	17
	$CF_3C_6F_{11}$	91	25	41	17	17
	$scCO_2$	100	100			

Ar = $MeOC_6H_4$; coe = cyclooctene; $scCO_2$ 2800 psig; $R_F = CH_2CH_2C_6F_{13}$.

The reaction carried out in THF or $CF_3C_6F_{11}$ in the presence of $P(R_F)_3$ or Cy_2PR_F gives a mixture of the four products, whereas the α-substituted product is cleanly formed in $scCO_2/Cy_2P(R_F)$. Hydroboration of 2-vinylnaphthalene with PinBH catalyzed by [Rh(diphenylphosphinoethane (dppe))(cod)]BF_4 in the ionic liquid $[Bu_4N]BF_4/scCO_2$ is less selective, α/β 70:30.[363]

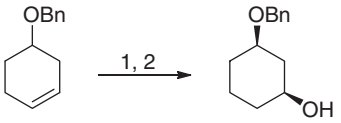
An alternative way of recycling the catalyst is to immobilize it on a solid support. A polymer-supported rhodium catalyst has been prepared by the copolymerization of ethylene glycol dimethyl acrylate and the *p*-isopropenylphenyl analog of [(nbd)Rh(dppe)]BF_4 2% in the presence of dimethylformamide (DMF) used as a porogen.[363] The polymer catalyst, 3 mol%, has been recycled three times in the hydroboration of styrene in THF, achieving 100% conversion and α/β 92:8. However, the combined crude materials from the three runs contain 4–5% of the Rh initially present in the polymeric catalyst.

In another approach, natural bentonites have been used as support of the asymmetric rhodium complex. The highest activities and enantioselectivities in the hydroboration of vinylarenes, competitive with the homogenous counterpart, have been obtained in the presence of (*S*)-QUINAP/Rh^+X^-, immobilized in predried MK-10 when X = BF_4, PF_6, and SO_3CF_3. The catalyst can be recycled and its important feature is the activity remaining even when manipulated in air between the runs.[379,380]

The hydroboration of simple vinylarenes with CatBH catalyzed by rhodium complexes bound to the SiO_2-immobilized CH_2CHPPh_2 group (Si-DPP) affords preferentially the branched product.[381] In the presence of $Rh(acac)(cod)_2$ and Si-DPP (two equivalents), *p*-methoxy and *p*-fluorostyrene are transformed into the branched products with 100% regioselectivity. Styrene and 2-vinylnaphthalene react with the same excellent selectivity. The immobilized catalyst can be recycled with no significant loss of activity or selectivity. However, the reaction lacks selectivity with more hindered vinylarenes or when PinBH is used instead of CatBH.

8.24.1.6.2.4 Iridium catalysts

Iridium catalysts often lead to hydroboration products or selectivity complementary to rhodium catalysts. In the early studies on diastereoselective hydroboration of homoallylic amides, Crabtree's catalyst, [382] [Ir(cod)PCy_3(py)]PF_6, showed higher activity than rhodium catalysts.[22] Later, high selectivity was achieved in the Ir-catalyzed hydroboration of 3-cyclohexenyl benzyl ether (equation 19).[383] The crucial role of the indenyl or cyclopentenyl ligands is attributed to their strong coordination with the metal and propensity for ring slippage to a lower coordination (η^5 to η^3).[383,384]



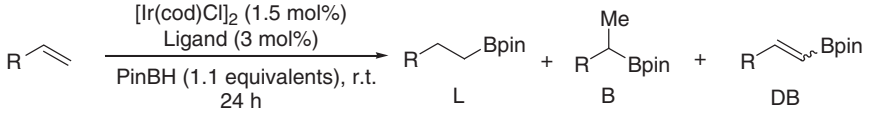
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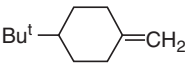
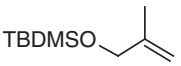
98% selectivity

1. [Ir(cod)Ind(CF_3)$_2$] (10 mol%), CatBH; 2. H_2O_2, NaOH.

Neutral iridium(I)–phosphine complexes, [Ir(cod)Cl]$_2$/2dppe or 2dppm, 2dppb, and 2dppp, are excellent catalysts for the hydroboration of terminal and internal alkenes, including vinylarenes, with PinBH.[385] The catalysts, prepared *in situ* from an air-stable iridium complex, avoid the air-sensitivity inconvenience encountered with Rh(PPh_3)$_3$Cl. The reaction carried out at room temperature provides the terminal boronate with more than 99% selectivity (Table 11).[385]

Table 11 The Ir-catalyzed hydroboration of 1-alkenes and vinylarenes with PinBH



R	*Ligand/solvent or catalyst/solvent*	*Yield (%)*	*L:B*	*R or olefin*	*Ligand/solvent*	*Yield (%)*	*L:B*
Ph	dppb/THF	99[a]	>99:1	*n*-Hexyl	dppm/DCM	89[b]	99:1
2-Naphthol	dppe/DCM	91[b]	99:1	$MeCOCH_2CH_2$	dppm/DCM	68[b]	99:1
p-ClC_6H_4	dppb/THF	99[a]	>99:1	$BrCH_2CH_2$	dppm/DCM	77[b]	99:1
p-$MeOC_6H_4$	dppb/THF	98[a]	>99:1	$PhOCH_2$	dppm/DCM	89[b]	99:1
4-Pyridyl	dppm/DCM	21[b]	99:1	$NCCH_2$	dppm/DCM	15[b]	99:1
C_6F_5	dppe/DCM	82[b]	100L		dppm/DCM	97[b]	99:1
C_6F_5	Rh(PPh_3)$_3$Cl/THF	70[c,d]	71:29		dppm/DCM	73[b]	99:1

[a]2004JACS9200.
[b]2004TET1065.
[c]1999OL1399.
[d]15% of DB product was also obtained.
Abbreviation: TBDMSO (also abbreviated as TBSO), *tert*-butyldimethylsilyl oxo.

High regioselectivity of the addition to vinylarenes is achieved regardless of the electronic effects of substituents. 5-Hexenyl-2-one reacts selectively at the C=C bond, and low yields obtained with the nitrile and vinylpyridine indicate the catalyst deactivation.

Other complexes, such as [Cp*IrCl]$_2$,[386] Ir(η^6-catBcat)dppb,[387] zwitterionic K2-P,N Ir(I) complexes,[388] Cp_2TiMe_2,[389,390] Cp*SmCH(TMS)$_2$,[11,371,391] and complexes with other lanthanides,[392] $RuCl_2(PPh_3)_4$,[393] $RuH_2(H_2)_2(PCy_3)_2$,[394] RuH(μH)$_2$B-pin(σHBpin),[394] and CpNi(PPh_3)Cl, [357–358] also afford terminal products for styrene or other vinylarenes. Reversed selectivity is obtained with Rh(PPh_3)$_3$Cl, [RhCl(cod)]$_2$/4PPh_3,[342] Rh(η^3-methylallyl)$_4$ (dppb),[341] and [Rh(cod)$_2$]BF_4/dppb.[352]

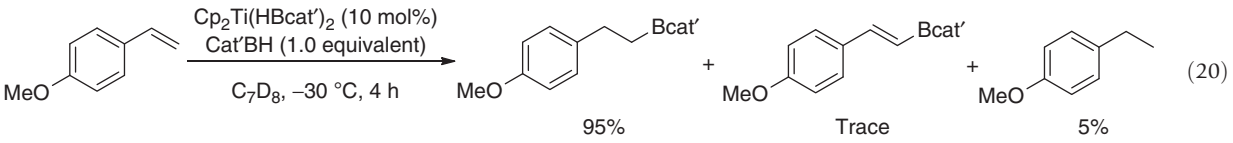
Hydroboration of internal alkenes with PinBH in the presence of [Ir(cod)Cl]$_2$/2dppm under the same conditions as for 1-alkenes (Table 11) proceeds with isomerization and results in the formation of 1-alkylboronates, for example, (*E*)- and (*Z*)-4-octene are cleanly transformed into pinacol 1-octylboronate in 78% yield.[385] Norbornene and cyclohexene react readily, whereas 2-methyl-2-butene is practically unreactive (5% yield) and reacts sluggishly in the absence of the phosphine ligand (36% yield). Internal alkenes undergo hydroboration–isomerization with PinBH also in the presence of [Rh(cod)(dppb)]BF_4 in THF, and the reaction is accelerated by $(C_6F_5)_3B$ in DCE.[354] Interestingly, the trisubstituted double bond of 2-methyl-2-pentene reacts readily and pinacol 1-(2-methylpentyl)boronate is obtained with 99:1 selectivity in 84% yield in spite of another terminal position available.

In a practically oriented Ir-catalyzed hydroboration–isomerization with pinacoborane at room temperature, methyl oleate has been transformed into the saturated methyl ester bearing the terminal boronate group, 45% yield, methyl stearate, 47% yield, and small amounts of other products.[395]

8.24.1.6.2.5 Titanium catalysts

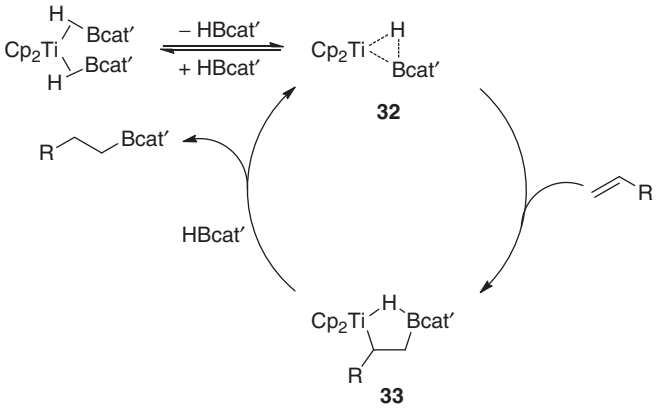
Initially, $Cp_2Ti(CO)_2$ and Cp_2TiMe_2,[389] **30**, and later $Cp_2Ti(HBcat')_2$, **31**, complexes were used for the hydroboration of alkenes with 4-tert-butylcatecholborane (Cat'BH).[390] The reaction with vinylarenes provides the *anti*-Markovnikov product with high selectivity, exclusively with styrene and indene, and predominantly with alkyl-substituted olefins. Hydroboration in the presence of **31** is complete in 10 min at 25 °C, whereas the rate is slower with **30,** 10 h at 25 °C.

Side products are formed only in small amounts (equation 20).



(20)

Mechanistic studies have revealed a different mechanism when compared with the Rh(I)-catalyzed reaction.[390] Thus, Cat′BH is not only the hydroborating agent, but also the ligand in the resting state of the catalyst (Scheme 61). Initial dissociation of coordinated Cat′BH generates the monoborane intermediate, **32**, which reacts with an olefin to give the five-membered intermediate **33**. A less-hindered α-position of the R group to the Cp_2Ti group determinates the regioselectivity of the reaction. In the last step, the addition product is formed by the reductive elimination.



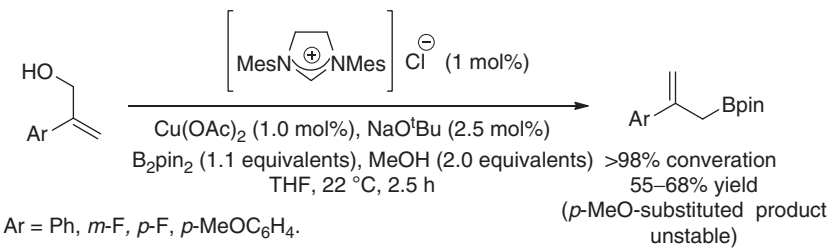
Scheme 61

Pathways leading to the addition product and side products, based on DFT calculations, have been proposed.[396]

8.24.1.6.2.6 Copper catalysts

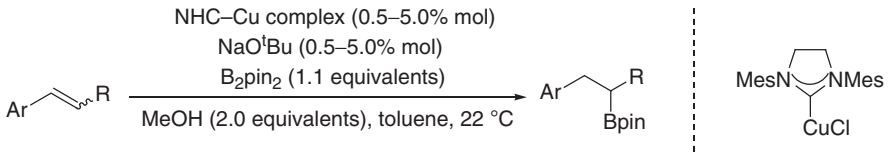
An important expansion of the hydroboration scope and its synthetic potential provides the recently reported *N*-heterocyclic carbene (NHC)–Cu-catalyzed reaction of vinylarenes and alkynes with bis(pinacolato)diboron.[331] The reaction proceeds via the B–Cu bond addition across the carbon–carbon multiple bonds, followed by protonolysis of the Cu–C bond with alcohols, for example, methanol. The overall product is equal to the hydroboration product. Olefins that do not bear an aryl group do not react, whereas the corresponding alkynes react.[397] The hydroboration of representative *β*-substituted vinylarenes with B_2pin_2 catalyzed by the NHC–Cu complex is shown in Table 12.[331]

(*E*)-*β*-Methylstyrene in the presence of deuterated methanol affords the *anti*-boronate, >98% *dr*, selectively deuterated in the benzylic position. The Mes-substituted NHC–Cu catalyst is more sensitive than the cyclohexyl analog or the P-based variants, what has been interpreted assuming a more strongly *σ*-donating aryl-substituted NHC–Cu. The *σ*-donation is important since the olefin acts as a *π*-Lewis acid in such transformations.[398] The copper-containing organo-boronate intermediates open new synthetic possibilities.[399,400] For example, the addition of the Cu–B bond to 2-aryl allylic alcohol gives the Cu-substituted terminal organoboronate, which eliminates the Cu-alkoxide faster than the rate of Cu–C protonation, producing the rearranged 2-aryl allylic boronate[401] (equation 21).



(21)

Table 12 The (NHC)-Cu-catalyzed hydroboration of vinylarenes with B_2pin_2/MeOH



Arylalkene or derivative	*Solvent*	*Catalyst (mol%)*	*Time*	*Yield (%)*
(*E*)-β-Methylstyrene	Toluene	0.5	10 min	>98
(*Z*)-β-Methylstyrene		5.0	10 min	41
(*E*)-*p*-MeOC$_6$H$_4$CH=CHMe		3.0	10 min	95
p-CF$_3$C$_6$H$_4$CH=CHMe (*E*/*Z*=62:38)		1.0	5 h	91
Indene		1.0	24 h	92
X = CH$_2$		0.5	10 min	97
X = O	THF	1.0	3 h	98
Ph, OCO$_2$Me	THF	5.0	20 min	76
Ph, OH[a]	Toluene	2.0	20 min	80

[a]No MeOH.

8.24.1.6.3 Dienes

1,2-Monohydroboration of conjugated dienes with CatBH is catalyzed by Ni(II)dppe in THF and its regioselectivity is shown in Figure 12.[402] Rhodium-catalyzed hydroboration of 1-phenyl-1,3-butadiene with CatBH in the presence of PPh_3 or dppf gives the dihydroboration products *anti*/*syn* 3:1, 67% *ee* when (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP) is the ligand. In the presence of dppe, 4-phenyl-3-butenyl boronate is the main product.[403]

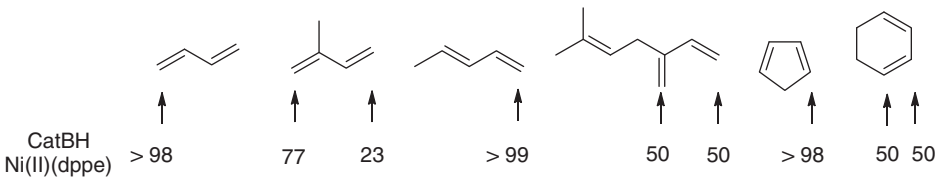
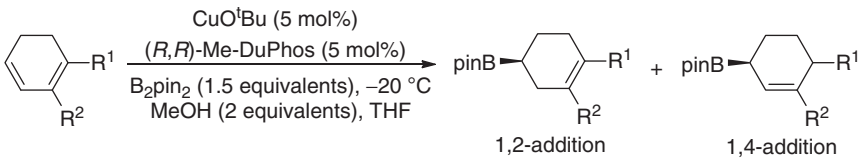


Figure 12 Regioselectivity of the hydroboration of conjugated dienes with CatBH catalyzed by Ni(II)(dppe).

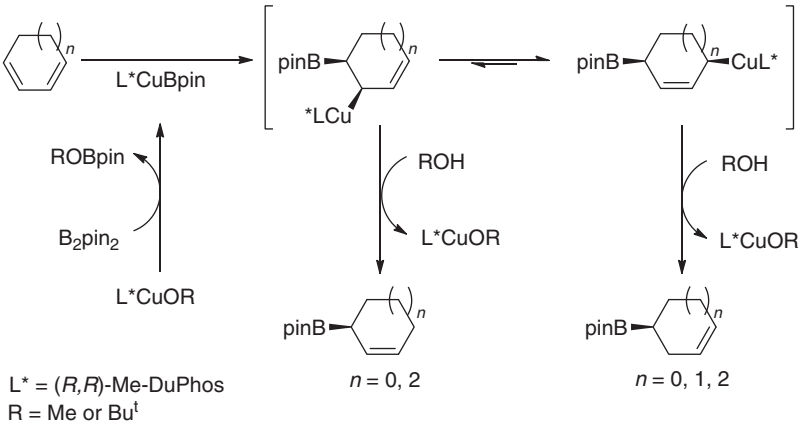
Homoallylic 1,2-addition products are also formed in asymmetric Cu-catalyzed monoboration of 1,3-dienes with bis(pinacolato)diboron.[404] The reaction of 1,3-cyclohexadiene carried out in the presence of phosphines, such as Me-DuPhos, QuinoxP, BINAP, and Segphos, is highly regioselective, and with (*R*,*R*)-Me-DuPhos at −20 °C in THF the homoallylic addition product, 94% *ee*, has been obtained. Substituted 1,3-cyclohexadienes react similarly (Table 13), whereas α-terpinene is unreactive.[404]

Table 13 Cu-catalyzed hydroboration of 1,3-cyclohexadienes with B_2pin_2/MeOH



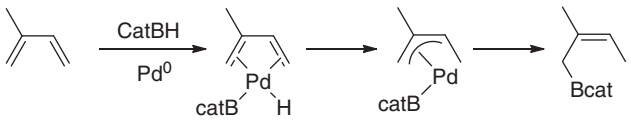
R^1	*R*^{2}	*Time (h)*	*1,2-/1,4- ratio*	*Yield (%)*	ee *(%)*
Me	H	17	>20:1	90	95
n-Bu	H	17	>20:1	97	95
Ph	H	25	94:6	95	95
H	*n*-Bu	22.5	>20:1	91	93
H	TMSO	16	>20:1	99	88

Isoprene and 2-methyl-2–4-undecadiene react at the less-substituted double bond with the selectivity > 20:1 and 91:9, 42% *ee*, respectively. The reaction course with 1,3-pentadiene and 1,3-heptadiene is temperature dependent. At room temperature, the homoallylic products are formed, whereas at low temperature the 1,4-addition products are obtained. The proposed possible reaction mechanism is shown in Scheme 62.[404]



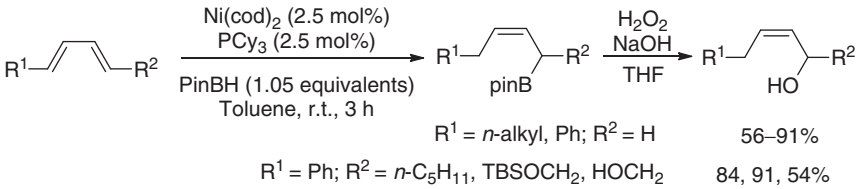
Scheme 62

The 1,4-addition of CatBH to 1,3-butadiene, isoprene, myrcene, 2,3-dimethyl-1,3-butadiene, and 1,3-cyclohexadiene, catalyzed by $Pd(PPh_3)_4$ or $Rh_4(CO)_{12}$, gives the corresponding (*Z*)-allylic boronates in 77–89%. The proposed mechanism is shown in equation 22.[405]



(22)

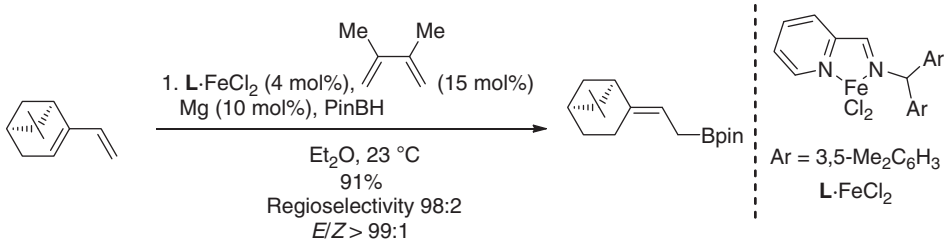
Regio- and stereoselective Ni-catalyzed 1,4-hydroboration of terminal and internal aliphatic 1,3-dienes, and functionalized derivatives with PinBH, provides (*Z*)-allylic boronates[406] (Scheme 63). Derivatives functionalized in the homoallylic position, (phthal)N, EtO_2C, OH, BnO, TBDPSO, and 2- or 3- or 4-methyl-substituted terminal dienes, also react as shown in Scheme 63.



Scheme 63

As part of the steady progress of ecologically benign iron-catalyzed reactions, the 1,4-hydroboration of terminal aliphatic 1,3-dienes and 1,3-cyclohexadiene with PinBH affording (*E*)-γ-disubstituted allylic boronates has been developed.[407] The catalyst is generated by the reaction of high-purity (99.998%) iron chloride complexed with the iminopyridine ligand.

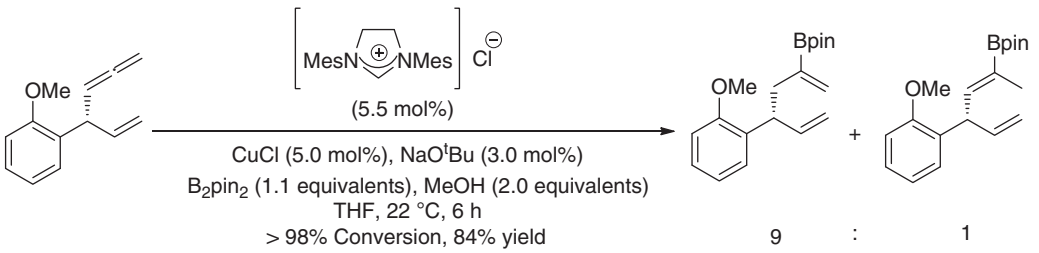
Isoprene is cleanly transformed into prenylboronate with 9:1 regioselectivity, and myrcene gives geranylboronate 93:7, *E*/*Z* > 99:1, in 68% yield. The regioselectivity of the reaction with myrcene has been inverted by changing the ligand's substituent. Several other terminal 1,3-dienes and derivatives react with high regio- and stereoselectivity, and the reaction with (+)-nopadiene is shown in equation 23.[407]



(23)

2,3-Dimethyl-1,3-butadiene is added to stabilize low-valent iron generated by the reduction of the iron(II) chloride–ligand complex.

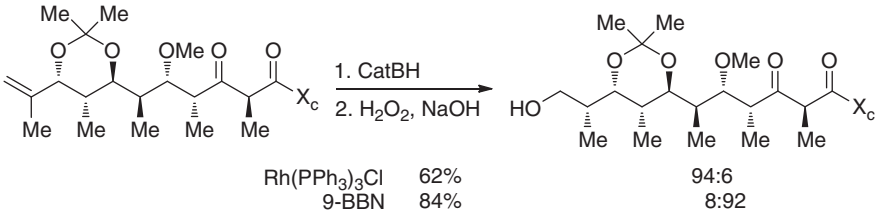
Chemo- and regioselective hydroboration of a terminal allene in the presence of a terminal alkene with B_2pin_2, catalyzed by the Cu–NHC complex, proceeds with preferential boron addition to the central carbon atom of the allenyl group (equation 24).[408] The mixture of products has been oxidized to the corresponding methyl ketone used for the asymmetric synthesis of α-cuperenone.



(24)

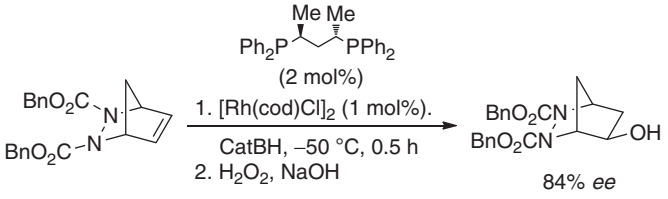
8.24.1.6.4 Diastereoselective and asymmetric hydroboration

The reagent- and substrate-controlled uncatalyzed hydroboration is further expanded by the catalytic substrate-controlled and catalyst-controlled reactions. Highly diastereoselective hydroborations of acyclic and cyclic allylic and homoallylic alcohols and amides, in the presence of Rh(I) and Ir(I) catalysts, preferentially affording the isomer complementary to the uncatalyzed reaction, have been achieved,[24,265,409] for example, equation 25,[410] and the third example in Scheme 55.



(25)

More recently, studies have concentrated on the catalytic asymmetric hydroboration of vinylarenes with CatBH, providing preferentially the Markovnikov products, complementary to the uncatalyzed reaction. Initially, rhodium(I) complexes with chiral phosphine ligands such as BINAP, DIOP, and ChiraPhos have been used.[352,411–413] The highest enantioselectivity, 96% *ee*, has been achieved for the reaction of styrene with CatBH in the presence of $Rh(PPh_3)_3Cl$/(*R*)-BINAP at −78 °C, and *p*-chloro- and *p*-methoxystyrene react with a slightly lower selectivity[352] (Figure 13, Table 14). 2,3,3-Trimethyl-1-butene reacts in the presence of [Rh(cod)Cl] · 2DIOP at −5 °C to give, after oxidation of the organoborane, 2,3,3-trimethy l-1-butanol, 69% *ee*, a remarkable result for the 1,1-disubstituted alkene.[411] Desymmetrization of the Diels–Alder adduct has been achieved with the Rh(I)/BDPP catalyst at low temperature (equation 26).[414]



(26)

Among the chiral diphosphines developed later, *trans*-1,2-bis(dicyclohexylphosphino)cyclohexane (*R*,*R*)-**34**[415] and Josiphos[416] (Figure 13) achieve 92% *ee* in the rhodium-catalyzed hydroboration of styrene with CatBH at −35 and −70 °C, respectively, whereas at room temperature their selectivity is much lower, similarly to the above-mentioned diphosphine ligands.

Change of the hydroborating agent may be helpful, as shown for the reactions of styrene, *p*-substituted styrenes, and 2-vinylnaphthalene, with PinBH in the presence of 5% $[Rh(cod)_2]BF_4$/(*R*,*S*)-Josiphos at room temperature producing the corresponding branched pinacolboronates with 95:5–72:28 regioselectivity and 88–76% *ee*.[362] The reaction with 6-methoxy-2-vinylnaphthalene has been used in the synthesis of naproxen, 88% *ee*. Desymmetrization of methylcyclopropene carboxylic acid ester by the hydroboration with PinBH in the presence of Rh(I)/(*R*)-BINAP at room temperature, assisted by the *cis*-directing ester group, is highly selective (equation 27).[417]

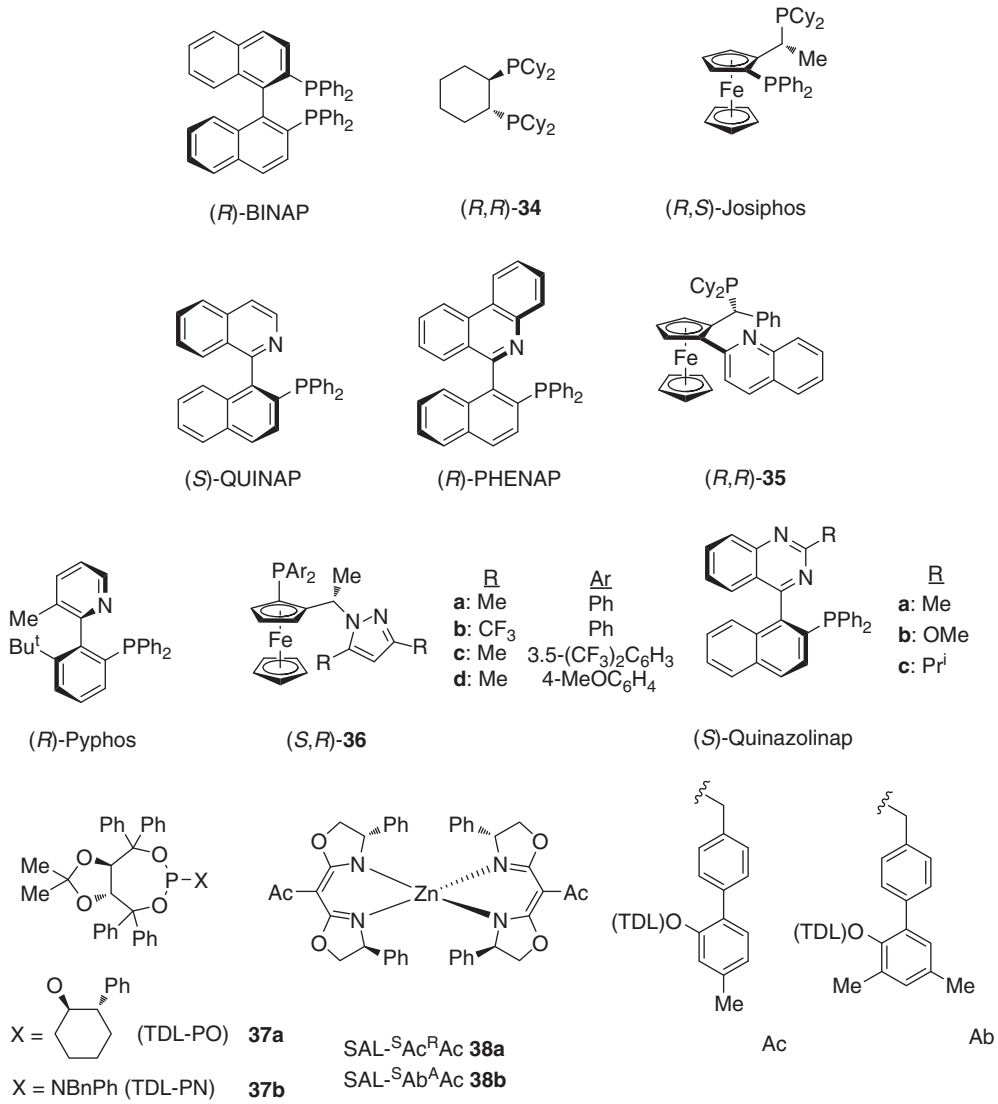
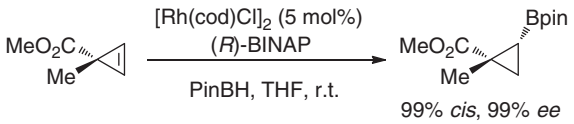


Figure 13 Chiral ligands used in catalytic hydroboration. TDL (also abbreviated as TADDOL), α,α,α′,α′,-tetraaryl-1,3-dioxolan-4,5-dimethanol.



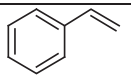
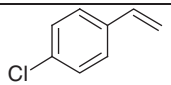
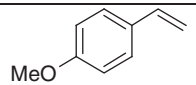
(27)

In a search for the ligand enabling a highly selective catalytic hydroboration of unhindered and moderately hindered vinylarenes with CatBH at room temperature a series of chiral P,N ligands has been developed beginning with QUINAP[418] (Figure 13). Cationic rhodium complexes are effective at room temperature and achieve high enantioselectivity in the hydroboration of styrene, substituted styrenes (Table 14), and 1,2-substituted double bonds (Table 15). The isoquinoline part of the ligand is less hindered than the diphenylphosphinonaphthalene group of BINAP, enabling a better π-stacking interaction with β-substituted vinylarenes, influencing the enantioselectivity of the reaction. The ligand achieves 94% *ee* in the reaction with the electron-rich *p*-methoxystyrene, and the selectivity is lower for *p*-chlorostyrene (Table 14). Stilbenes, indenes, and dihydronaphthalenes undergo hydroboration with high regio- and enantioselectivity (Table 15).

Modification of the diphenylphosphino group by substitution with the difurylphosphino group results in an increased selectivity of the reaction with electron-poor vinylarenes.

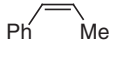
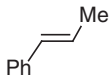
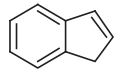
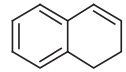
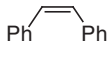
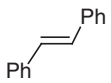
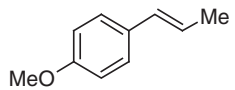
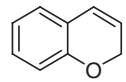
The PHENAP ligand (Figure 13) is a close analog of QUINAP and achieves comparable selectivity.[419] The ferrocenyl ligand **35** can be modified by substitution of the 2-quinolinyl group and also the phenyl group.[420] Its analogs with 2-pyridyl, 2-pyrimidyl, *o*-tolyl, and 3,5-xylyl groups have been prepared and tested in the rhodium-catalyzed hydroboration of styrene with CatBH at −45 °C. The ligand **35** gives 64:36 regioselectivity and the highest enantioselectivity, 92% *ee*.

Table 14 Rh-catalyzed asymmetric hydroboration of styrene and derivatives

Ligand/HB(OR)$_2$	*Solvent*	*Temperature (°C)*										*References*
			Yield (%)	*α/β*	*%ee*	*Yield (%)*	*α/β*	*%ee*	*Yield (%)*	*α/β*	*%ee*	
(*R*)-**BINAP**	DME	−78	91	>99:1	96*R*	98	>99:1	91		>99:1	89	1991TL601
CatBH	DME	25	90	99:1	58*R*							
PinBH	DCE	25	30	56:44	40*S*	90	72:28	80	69	88:17	76	2004JACS9200
(*R,R*)-**34**/CatBH	DME	−35	85	99:1	92*S*	84	99:1	85	69	99:1	93	2001Angew1235
(*S*)-**QUINAP**	THF	25							90	99:1	98[a]	2004CEJ6456
CatBH	THF	r.t.	71	99:1	91*S*	78	94:6	82	82	96:4	94[b]	1999CEJ1320
CatBH	DCE	25	69	97:3	88*S*							2004JACS9200
PinBH	DCE	25	30	65:35	82*S*	90	72:28	80	69	83:17	76	
(*S*)-**Quinazolinap**												2010T:A1458
a, CatBH	THF	20	100[c]	81:12	90*S*				99[c]	88:12	95	
b, CatBH	THF	20	97[c]	89:11	90*S*	75[c]	92:8	80	91[c]	82:18	94	
(*R*)-**Pyphos**												2002JOC2769
CatBH	THF	0	72	99:1	90*R*	72	>98:2	79	70	>98:2	99	
		r.t.	72	99:1	70*R*							
(*R,S*)-**Josiphos**	DME	−78		65[d]	92*R*							1994JACS4062
CatBH	DCE	−70	65	99:1	92*R*							2004JACS9200
CatBH	DCE	25			60*R*							
PinBH	DCE	25	87	72:28	84*S*							
(*S,R*)-**36**												1995Angew931
a, CatBH	THF	20	91	66:34	95*R*							
b, CatBH	THF	20	78	61:39	33*R*							
c, CatBH	THF	20	68	60:40	98*R*							
d, CatBH	THF	20	28	61:39	90*R*							
TDL-PO (**37a**), -PN (**37b**)												2006OL3097
37a, PinBH	DME	r.t.	96	78[d]	95	94	77[d]	91	96	71[d]	93	
37b, PinBH	DME	r.t.	96	82[d]	96	95	77[d]	94	96	67[d]	94	
SAL-												
38a, PinBH	THF	r.t.			94							2008Angew894
38b, PinBH	THF	r.t.						96				2012CC263
DC[e], PinBH	THF	r.t.								98[d]	96	2012CC263

[a](*R*)-QUINAP, $BnMe_3NCl$ additive.
[b](*R*)-QUINAP.
[c]Conversion.
[d]% α-.
[e]*See* equation 29.

Table 15 Rhodium-catalyzed hydroboration of 1,2-disubstituted olefins

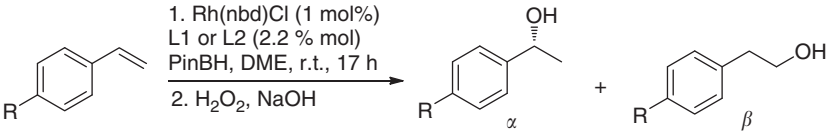
Ligand/HB(OR)$_2$	*Solvent*	*Temperature (°C)*													*References*
			Yield (%)	*α/β*	ee *(%)*	*Yield (%)*	*α/β*	ee *(%)*	*Yield (%)*	*α/β*	ee *(%)*	*Yield (%)*	*α/β*	%ee	
(*R*)-**BINAP**															[a]
CatBH	THF	25	58	99:1	18	65	>99:1	42	65	93:7	13				
(*R*)-**QUINAP**															[b]
CatBH	PhMe	r.t.	80	99:1	93*R*	80	99:1	95	80	99:1	78	78	99:1	96	
(*S*)-**Quinazolinap**															[c]
a, CatBH	THF	0	100[d]	99:1	97	100[d]	99:1	79.5	60[d]	99:1	88				
a, CatBH	THF	20							100[d]	99:1	99.5	90[d]	99:1	93	
b, CatBH	THF	20	12[d]	75:25	94	89[d]	84:16	94	60[d]	99:1	80	76[d]	>99:1	91	
															
(*S*)-**Quinazolinap**															[c]
a, CatBH	THF	20				50[d]		87	100[d,e]	99:1	97				
b, CatBH	THF	20	23[d]		97	34[d]		92	52[d,e]	79:21	94				
c, CatBH	THF	20	84[d]		99										
(*R*)-**QUINAP**															[b]
CatBH	PhMe	r.t.	86		91*R*			85*R*	84	99:1	97	82	96:4	90	

[a] 1995TL601.
[b] 1999CEJ1320.
[c] 2010 T:A1458.
[d] Conversion.
[e] 0 °C.

Another N,P-ligand, Pyphos (Figure 13), gives the Markovnikov products from styrene, *p*-methyl, and *p*-methoxystyrene with 99:1–98:2 regioselectivity and ≥90% *ee*, whereas the enantioselectivity of the reaction with *p*-chlorostyrene is lower, 79% *ee*[421] (Table 14). Variation of the R and Ar_2P substituents of the pyrazolyl and the ferrocenyl groups of **36** (Figure 13) indicates the influence of their electronic effects on the enantioselectivity of the rhodium-catalyzed hydroboration of styrene. The results obtained for **36a–d**, shown in Table 14, are illustrative.[422] The highest selectivity, 98% *ee*, is achieved for **36c** with the electron-rich pyrazol ring, a good σ-donor (R=Me), and the electron-poor phosphino group, a good π-acceptor (Ar=3,5-$(CF_3)_2C_6H_3$), whereas for **36b** ($R=CF_3$, Ar=Ph) the reversed electronic effects result in low selectivity, 33% *ee*.

A series of Quinazolinap ligands (Figure 13) modified by variation of the R substituent have been prepared in an effort to improve the efficiency and substrate scope of their rhodium complexes.[423] Very high enantioselectivity is achieved in the reaction with styrene, *p*-substituted and β-substituted styrenes, stilbenes, and dihydronaphthalene, up to 99.5% *ee* obtained from (*E*)-β-methylstyrene and indene, as shown in Tables 14 and 15 for the best Quinazolinap **a–c** ligands.

The TADDOL-derived monodenate *trans*-2-phenylcyclohexylphosphite and *N*-benzyl-*N*-phenylphosphoramidite ligands **37a** and **37b** (Figure 13) achieve moderate regio- and high enantioselectivity in the rhodium-catalyzed hydroboration of styrene and derivatives bearing electron-withdrawing and electron-donating *para*-substituents[424] (Table 14 and equation 28).

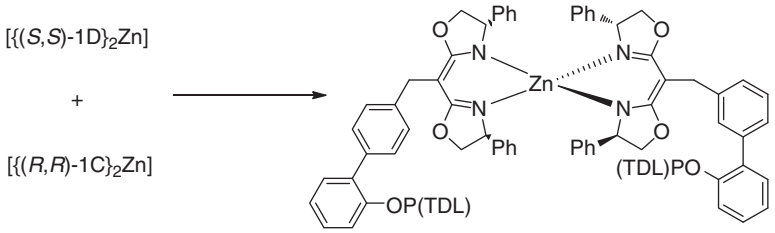


(28)

R = H, Me, MeO, Cl, F, CF_3; L1 **37a** 94–96% α 62–79%; 90–95% *ee*
L2 **37b** 92–96% α 62–80%; 90–95% *ee*

Both ligands, **37a** and **37b**, lead to products of the same configuration obtained with similar selectivity, attributed to their similar spatial requirements.

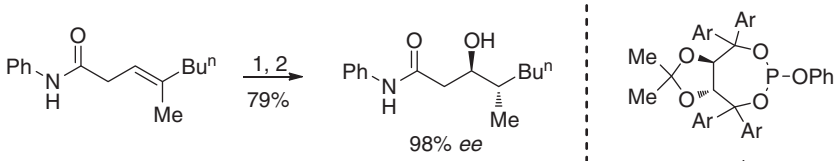
In a further development, a library of supramolecular TADDOL-derived tetrahedral bisoxazoline self-assembling ligands (SAL) has been screened in rhodium-catalyzed hydroboration of representative *m*- and *o*-substituted styrenes (Me, OMe, Cl, F, and CF_3) with PinBH in DME at room temperature.[425,426] Fine tuning of the supramolecular ligand scaffolds by varying the *o*-, *m*-, and *p*-substitution of the biphenyl tether enables achieve high regio, 95–98%, and enantioselectivity, 94–97% *ee* (Table 14). The assembly of the heterodimer (*SS*,*RR*)-SAL DC (D=1,4-Ar^1, 1,2-Ar^2 substituted biphenyl tether; C=1,3-Ar^1, 1,2-Ar^2) is shown in equation 29.[426]



(*SS*,*RR*)-SAL DC

(29)

The TADDOL-derived phosphites and phosphoamidites are also effective rhodium ligands for the catalyzed asymmetric hydroboration at β,γ-unsaturated amides affording the β-addition products with up to 98% *ee*.[427–429] Trisubstituted double bonds react, and either Felkin or *anti*-Felkin acetate–aldol products can be obtained with high selectivity (equation 30).[428]

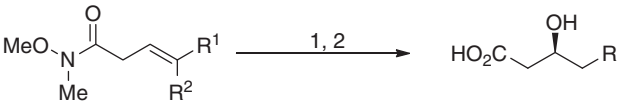


(30)

1. $Rh(nbd)_2BF_4$ (0.5 mol%), Ligand (1.1 mol%), PinBH (2 equivalents), THF, 40 °C,
2. H_2O_2, NaOH.

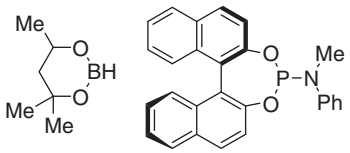
Rhodium complexes with BINOL-derived phosphoamidites are used for more sterically congested double bonds.

A striking influence of dialkoxyboranes on the catalytic efficiency and level of enantioselectivity has been observed in the hydroboration of Weinreb amides.[366] Screening the reaction across CatBH, PinBH, and 10 other cyclic dialkoxyboranes, the highest selectivity was obtained with TMDB (equation 31).



(*E*): R^1 = Bu^n, CH_2Bn, Et; R^2 = H 73–77% R = Bu^n, CH_2CH_2Ph, Et; 92–97% *ee*

(*Z*): R^1 = H; R^2 = Et 72% 97% *ee*



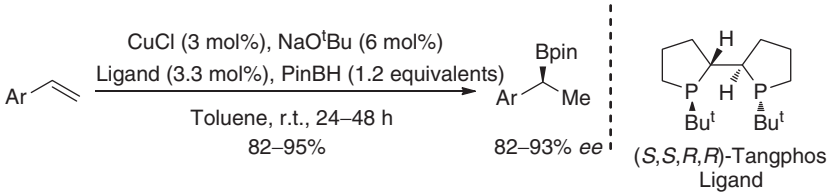
TMDB L

(31)

1. [Rh(I)/2L]BF_4 (1 mol%), TMDB (2 equivalents), THF, 40 °C; 2. H_2O_2, NaOH (aqueous).

Selectivities achieved with PinBH and CatBH are lower, 50–83% *ee* and 10–20% *ee*, respectively. Nevertheless, PinBH is the preferred reagent with other amides. No difference in enantioselectivity is observed in the reaction of the *E*-isomer (R^1 = Et, R^2 = H) with (*R*)- or (*S*)-TMDB.

Asymmetric hydroboration of 1,1-disubstituted vinylarenes has been catalyzed by iridium complexes, achieving 92% *ee* with [IrOMe(cod)]2/phosphinooxazoline (phox) ligands in the reaction of α-methylstyrene with PinBH. The ring-substituted derivatives react with 76–80% *ee* for 4-Cl, 4-Br, 3-Br, 4-I, 4-CF_3, and 44–55% *ee* for 4-Me, 4-F, and 3-Me substituents.[430] The Cu-catalyzed asymmetric hydroboration of substituted styrenes with PinBH in the presence of the Tangphos ligand is highly selective, up to 95% *ee* for (*E*)-β-methyl styrene and 92% *ee* for styrene (equation 32).[431]



(32)

Ar = Ph, *p*-F, *m*-Cl, *p*-Cl, *p*-Me, *o*-MeO, *p*-$MeOC_6H_4$.

Vinylnaphthalenes react faster, 12 and 5 h, but with lower enantioselectivity, 60% and 51% *ee*. A two-step mechanism, based on the experimental data and DFT calculations, has been proposed.[431,432] The rate-limiting first step is the addition of LCuH to styrene, and in the second step the LCu–C intermediate reacts with PinBH to give the reaction product.

Highly enantioselective hydroboration of simple 1,1-disubstituted alkenes has been a long-standing problem in the catalyzed and uncatalyzed reaction. Only recently, products in up to 92–93% *ee* have been obtained by the above-mentioned Ir-catalyzed hydroboration of α-methylstyrenes.[430] It was recently reported that the NHC–Cu-catalyzed hydroboration of 1,1-disubstituted vinylarenes, including exocyclic double bonds,[401] is highly selective regardless of the substitution (**Table 16**).

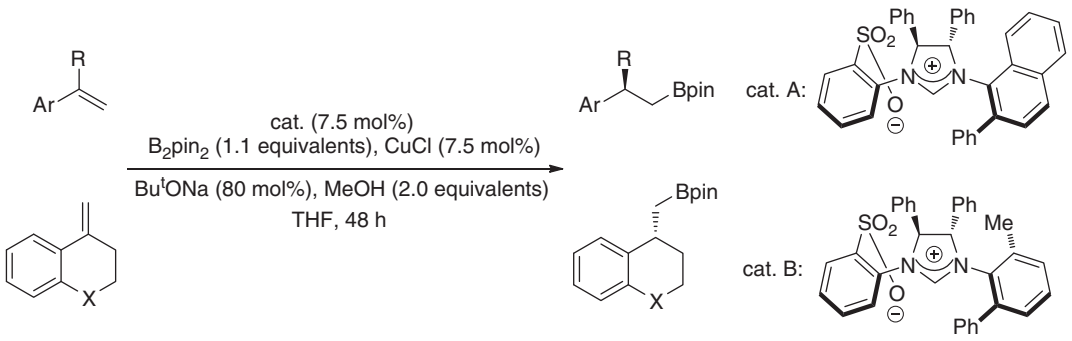
The regioselectivity of the reactions shown in **Table 16** is >98%. The 1-naphthyl-substituted olefin is less reactive and the conversion and yield are lower than the 2-naphthyl isomer, 84% conv., 62% yield, 84% *ee*, and the CF_3-substituted olefins react with lower selectivity. A two-step mechanism of the NHC–Cu-catalyzed hydroboration of 1-arylalkenes has been proposed[401] (**Scheme 64**).

The Cu-catalyzed asymmetric β-boration of α,β-unsaturated esters and nitriles with B_2pin_2 is markedly accelerated with methanol,[433] and DFT calculations indicate protonolysis of the Cu–C bond of the β-borylated organocopper intermediate.[398,434,435] Consequently, the overall reaction is the addition of boron and hydrogen atoms to the double bond of the substrates.

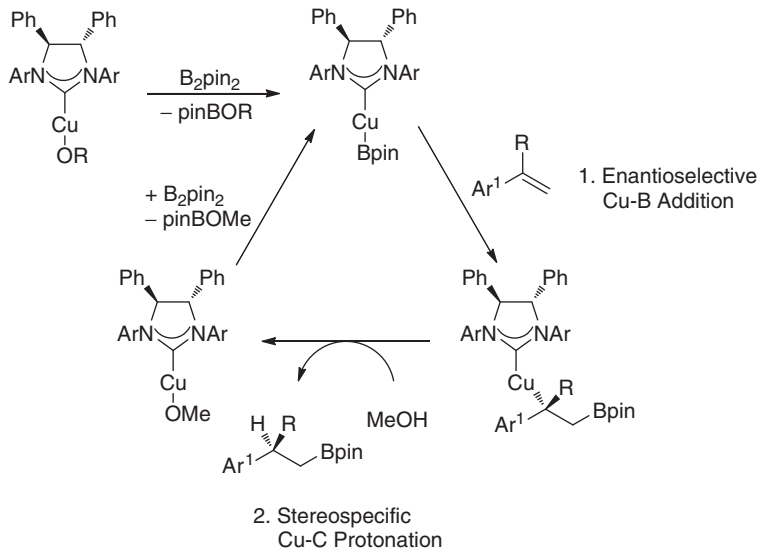
High enantioselectivity has been achieved with the (*R*,*S*)-Josiphos ligand (**Figure 13**) as shown in **Table 17**.[433] No effect of the ester moiety on the enantioselectivity of the reaction with methyl and *tert*-butyl cinnamate was observed.

The QUINAP and Quinazolinap ligands used for the reaction with (*E*)-MeCH=$CHCO_2R$ (R=Me, Et, Bu^i, and Bu^t) give the β-boration products of the 51–79% *ee*.[436] High enantioselectivity (82–96% *ee*), similar to that presented in **Table 17**, has been obtained for 10 α,β-unsaturated esters in the reaction catalyzed by the six-membered annulated NHC–Cu complex, which can be prepared on a gram scale as presented in **Scheme 65** and shows 10 000 t at 0.01 mol% without significant decrease in enantioselectivity (**Scheme 65**).[437]

Table 16 The (NHC)-Cu-catalyzed hydroboration of 1,1-disubstituted vinylarenes with B_2pin_2/MeOH



Ar	*R*	*X*	*Catalyst*	*Temperature (°C)*	*Conversion (%)*	*Yield (%)*	ee *(%)*
Ph	Me		A	−50	96	95	87
1-Naphthyl					50	37	92
m-$CF_3C_6H_4$					63	52	61
m-$MeOC_6H_4$					>98	>98	83
p-$CF_3C_6H_4$					93	79	64
p-MeC_6H_4					80	80	74
2-Benzofuryl					>98	89	87
Ph	Et		B	−15	95	90	90
Ph	Pr^i				61	57	93
Ph	Bu^i				96	89	86
		CH_2	B	−15	>98	72	83
		O			>98	75	92
		S			>98	74	84

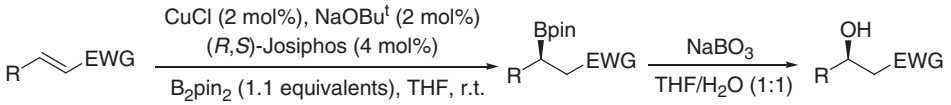


Scheme 64

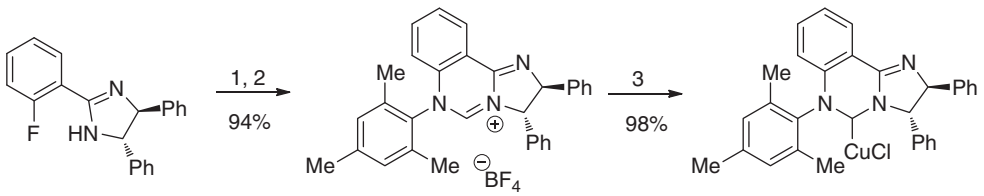
Copper(I) complexes of chiral five-membered NHC-ligands catalyze the asymmetric β-boration of α,β-unsaturated acyclic esters containing a trisubstituted double bond (Table 18).[438] High conversions indicate good reactivity of the trisubstituted double bonds. The *syn* products are slightly favored, and their *ee* values are much higher as compared to the *anti* products.

The NHC–Cu-catalyzed β-boration of α,β-unsaturated esters and thioesters containing β-disubstituted double bonds provides a convenient, highly enantioselective approach to boron-substituted quaternary carbons[439] (equation 33).

Table 17 The Cu-catalyzed β-boration of α,β-unsaturated esters and nitriles with B_2pin_2



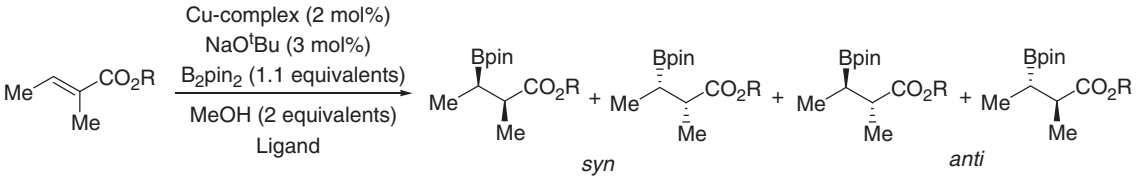
R	*Boronate yield (%)*	*Alcohol* ee *(%)*	*R*	*EWG*	*Boronate yield (%)*	*Alcohol* ee *(%)*
Me	94	90	2-MeC_6H_4	CO_2Et	87	88
Pr^i	92	91	3-$AcOC_6H_4$	CO_2Et	95	87
$PhCH_2CH_2$	97	89	2-Furyl	CN	93	82
Ph	93	90	4-MeC_6H_4	CN	94	90
4-ClC_6H_4	90	91	2-$EtOC_6H_4$	CN	90	92



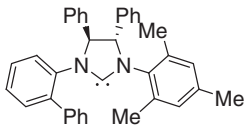
1. $LiNH_2$, 1,3,5-$Me_3C_6H_2NH_2$, THF, reflux, 16 h; 2. NH_4BF_4, $(EtO)_3CH$, 120 °C, 5 h;
3. CuCl, KO^{t}Bu, THF, DCM 0 °C to r.t., 18 h.

Scheme 65

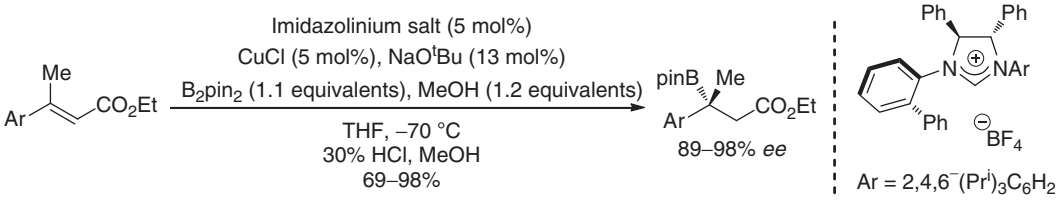
Table 18 The (NHC)–Cu-catalyzed β-boration of α,β-unsaturated esters containing the trisubstituted double bond



R	*Conversion (%)*	syn/anti	syn ee *(%)*	anti ee *(%)*
Me	99	60/40	54	5
Et	94	64/36	57	11
Pr^i	65	55/45	70	20
Bu^i	93	70/30	74	5



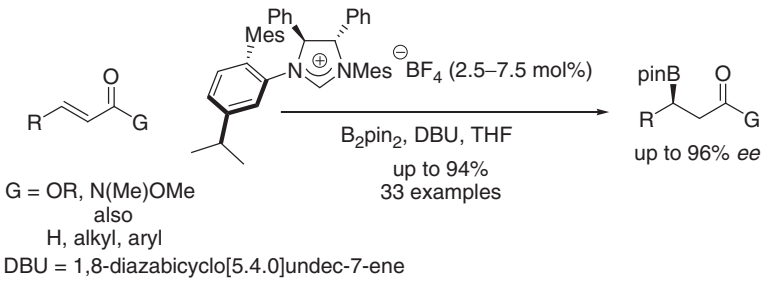
Ligand



Ar = Ph, 2-Naphthyl, C_6H_4X (X=*o*-Br, *m*-Br, *p*-Br, *p*-CF_3, *o*-MeO). (33)

Among the esters tested, only *o*-tolyl-substituted ester reacts with lower conversion, 38%, and lower selectivity, 6% *ee*. Thioesters react with higher selectivity and the boronate products can be functionalized by Ag-mediated or Pd-catalyzed reactions.

Finally, the metal-free enantioselective *β*-boration of *α,β*-unsaturated esters, Weinreb amides, aldehydes, and ketones, promoted by chiral NHC carbenes, has been developed[440] (equation 34). This is the first general metal-free protocol for the synthesis of various *β*-boryl carbonyl compounds, including aldehydes and ketones. The reactivity of substrates and the yields of the reaction products are higher as compared to the corresponding Cu-catalyzed reactions. Chemoselective *β*-boration in the presence of an alkyne and allene functional group is possible. Mechanistic details of the transformations are not yet available.



(34)

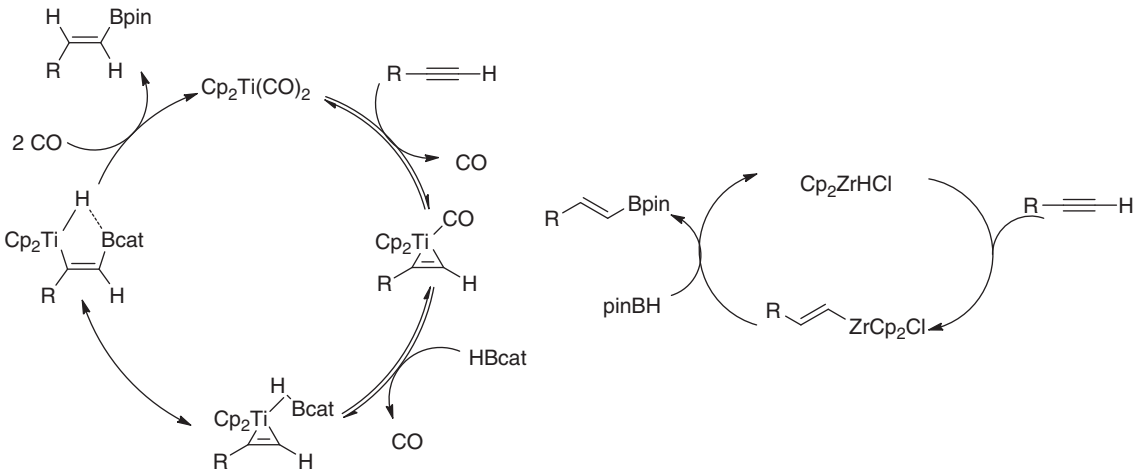
8.24.1.6.5 Alkynes and derivatives

The catalytic hydroboration of alkynes has been reviewed.[441] Initial studies on the hydroboration of phenylacetylene with CatBH in the presence of $Rh(PPh_3)_3Cl$ revealed the formation of a mixture of products.[342] Later, it was discovered that terminal alkynes RC≡CH (R=Ph, Pr^i, *c*-C_5H_9, $ClCH_2CH_2CH_2$, $MeOCH_2$, and $TMSCH_2$) undergo a clean, 99:1, *anti*-Markovnikov *cis*-monohydroboration with PinBH in the presence of $Rh(CO)(PPh_3)_2Cl$ and $CpNi(PPh_3)Cl$ at room temperature, furnishing *trans*-1-alkenylboronates in 98–99% yields.[358] Hydroboration of the same alkynes, catalyzed by Cp_2ZrHCl, also proceeds with high regioselectivity, 94–99%, providing the same *trans*-1-alkenylboronates in 82–95% yield.[292] Similarly, the dicarbonyltitanocene-catalyzed hydroboration of *n*-butyl- and *o*-tolylacetylene, conducted simply by mixing the alkyne with one equivalent of CatBH and 4 mol% of the catalyst, affords the *anti*-Markovnikov addition products with >99% regioselectivity, in 96–97% yield.[389]

Trans-1-alkenylboronates are also the major products obtained by hydroboration of aliphatic terminal alkynes and derivatives with TMDB/Cp_2ZrHCl,[365] and a range of substituted arylacetylenes and aliphatic-1-alkynes with DanBH/$[IrCl(cod)]_2$/$(o\text{-}Ph_2PC_6H_4)_2O$, or dppm in DCM.[31] The later reaction with phenylacetylene affords (*E*)-*β*-borylstyrene in 89% yield along with its (*Z*)-isomer and the regioisomer, 90:5:3. The DanB masking group has been used for further iterative reactions leading to oligo(phenylene-vinylene)s.

The high selectivity of $Rh(CO)(PPh_3)_2Cl$, as compared to $Rh(PPh_3)_3Cl$, in the hydroboration of alkynes may reflect a mechanistic difference, involving the preferential insertion into the less-hindered Rh–B bond with rhodium bearing the small (CO) and two bulky PPh_3 ligands.[441]

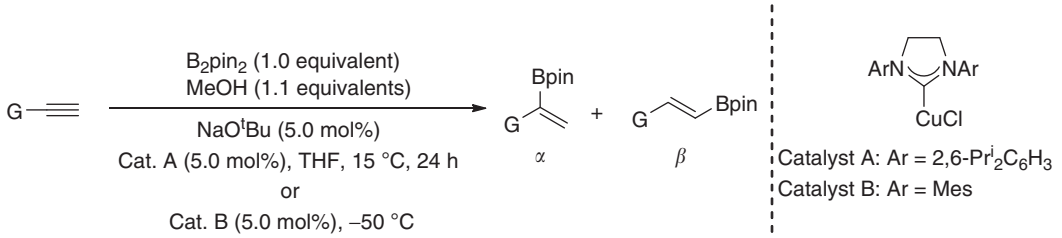
The reaction catalyzed by $Cp_2Ti(CO)_2$ proceeds via the five-membered intermediate determining the regioselectivity of the addition[390] (Scheme 69). Hydroboration catalyzed by Cp_2ZrHCl involves hydrozirconation in the first step followed by the transmetalation with PinBH[442] (Scheme 66).



Scheme 66

The NHC–Cu-catalyzed hydroboration of terminal alkynes and functionalized derivatives with bis(pinacolato)diboron/MeOH provides flexible and selective access to either α- or β-substituted vinylboranes, depending on the structural and electronic features of the catalyst and alkynes.[397] Thus, the reaction with arylacetylenes and propargylic *N*- and *O*-derivatives selectively affords the α-substituted vinylboranes (Table 19).

Table 19 (NHC)-Cu-catalyzed α-selective hydroboration of terminal alkynes and derivatives with B_2pin_2/MeOH

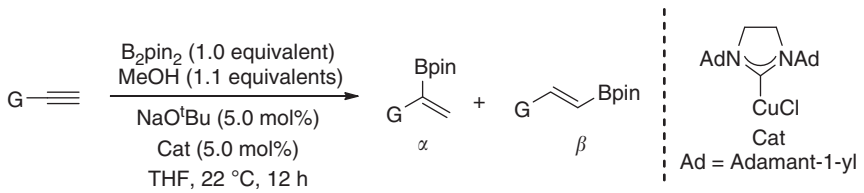


G	*Catalyst A*		*α:β*	*Yield α (%)*	*G*	*Catalyst B*			*α:β*	*Yield α (%)*
	Conversion (%)					*Solvent*	*Time (h)*	*Conversion (%)*		
Ph	94		88:12	78	$BocHNCH_2$	THF	9	>98	>98:2	93
o-FC_6F_4	98		94:6	87	$TsHNCH_2$	THF	24	92	>95:5	73
o-$MeOC_6F_4$	78		41:59	nd	$HOCH_2$	THF	21	96	93:7	82
o-MeC_6F_4	76		70:30	51	$BnOCH_2$	THF	3	93	84:16	76
m-FC_6F_4	>98		94:6	78	$TBSOCH_2$	THF	24	>95	85:15	78
m-$CF_3C_6F_4$	64		89:11	52		Toluene	24		>98	95
m-$MeOC_6F_4$	86		79:21	67		Toluene	24		>98	88
p-FC_6F_4	53		87:13	45						
p-$MeO_2CC_6F_4$	69		92:8	61						
p-$MeOC_6F_4$	58		62:38	33						

The catalyst A is more sterically discriminating than the mesityl analog B, which is more active and performs better at low temperature. The α-selectivity for other RC_6H_4 groups is as follows: 91% (*o*-Cl, *o*-Br, *p*-Br, *p*-NO_2), 94% (*p*-CF_3). Arylacetylenes containing electron-withdrawing substituents react with higher selectivity than electron-donating *o*-, *m*-, and *p*-methoxyphenylacetylenes.

In contrast to aryl-substituted NHC–Cu complexes, the alkyl-substituted complexes catalyze β-selective hydroboration of aryl and alkylacetylenes and also *N*- or *O*-propargylic derivatives. The reaction in the presence of diadamantyl NHC–Cu complexes is shown in Table 20.

Table 20 The (NHC)–Cu-catalyzed β-selective hydroboration of aryl- and alkylacetylenes with B_2pin_2/MeOH



G	*Conversion (%)*	*α:β*	*Yield β (%)*	*G*	*Conversion (%)*	*α:β*	*Yield β (%)*
Ph	89	2:98	91	*c*-$C_5H_9CH_2$	83	11:89	65
o-FC_6H_4	>98	7:93	80	$Cl(CH_2)_2CH_2$	85	18:82	63
o-$CF_3C_6H_4$	90	5:95	71	$MeO_2C(CH_2)_2CH_2$	85	19:81	64
o-MeC_6H_4	90	3:97	75	$HOCH_2$	82	13:87	65
o-$MeOC_6H_4$	95	<2:>98	88	$BuᵗOCH_2$	>98	12:88	80
m-$CF_3C_6H_4$	82	<2:98	78	$PhthNCH_2$	84	27:73	56
p-$CF_3C_6H_4$	82	<2:98	80	$TsHNCH_2$	82	13:87	70

As follows from the results presented in Table 20 arylacetylenes react in the presence of the alkyl-substituted NHC–Cu catalyst with high β-selectivity regardless of the electronic effects of aryl groups, whereas the regioselectivity of the reaction with

alkylacetylenes, propargylic alcohol, ether, and amine derivatives is slightly lower. Alkylacetylenes also react with β-selectivity in the presence of the aryl-substituted Mes_2NHC–Cu catalyst. The indifference of alkylacetylenes to the nature of the NHC–Cu complex has been attributed to the lack of an electron-withdrawing group proximal to the triple bond. The unusual α- or β-selectivity of the Cu–B addition to terminal alkynes has been accounted for assuming the alkyne coordination to the NHC–Cu–Bpin complex as the rate- and product-determining step. The HOMO–LUMO alkyne–catalyst interactions, and plausible reaction pathways influenced by electronic and steric effects of substrates and catalysts, have been proposed to explain the flexible site selectivity.[397]

The intermediate NHC–Cu-substituted vinylboronates, undergoing protonolysis with methanol in the next step, have synthetic potential of their own and may be trapped by other electrophiles. The terminal triple bond is more reactive than olefins and their derivatives in the NHC–Cu-catalyzed hydroboration, as demonstrated for *tert*-butyl propargyl ether, which cleanly undergoes monohydroboration in the presence of styrene, α- and β-methylstyrenes, and (*E*)-(penten-1-yl)boronate.[397]

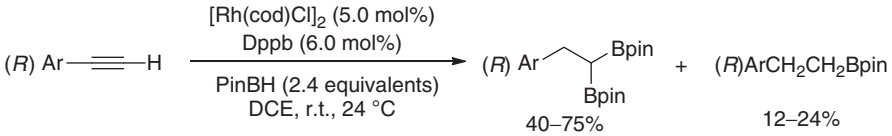
The unconventional *trans*-hydroboration of terminal alkynes with CatBH or PinBH, catalyzed by $[Rh(cod)Cl]_2/4PPr^i_3$ or $4PCy_3$ in the presence of triethylamine, produces (*Z*)-1-alkenylboronates[443] (**Table 21**).

Triethylamine is necessary for the regioselectivity and its absence results in the formation of the *E*-isomer as the major product. In the presence of $[Ir(cod)Cl]_2$ the reaction with 1-octyne is less selective, whereas trimethylsilylacetylene reacts with high *Z*-selectivity, 98%. Internal alkynes do not undergo *trans*-hydroboration under these conditions. The reversed stereochemistry of the reaction as compared to the uncatalyzed and other catalyzed borane additions, and the deuterium migration from the terminal position of 1-deuterio-1-octyne to the 2-position of the reaction product, has been accounted for assuming a catalytic cycle involving the vinylidene intermediate (**Scheme 67**).

Recent DFT calculations indicate vinylidene insertion into the Rh–H bond, as the regioselectivity-determining step, followed by the reductive elimination of the C–B bond.[444] The unconventional *trans*-hydroboration of $TBSOCH_2C{\equiv}CH$ affords the corresponding (*Z*)-boronate used for the asymmetric synthesis of homoallylic (*Z*)-hydroxyalkenyl esters.[445]

Surprisingly, under the same conditions as in **Table 21**, but with a $PinBH/Et_3N$ ratio of 3:5, di- and triethynylbenzene and other diethynyl-substituted di-, tri-, and tetracyclic aromatic hydrocarbons give *E*- or *E*/*Z*- or *Z*-vinylboronates depending on the substrate.[446] Mixtures of *E*/*Z* and branched isomers containing the *E*-isomer as the major product have also been obtained by the hydroboration of *n*-hexyne, phenylacetylene, and its 4-substituted derivatives (MeO, NO_2, and CH) with PinBH catalyzed by various Rh–NHC complexes in the presence of triethylamine.[447]

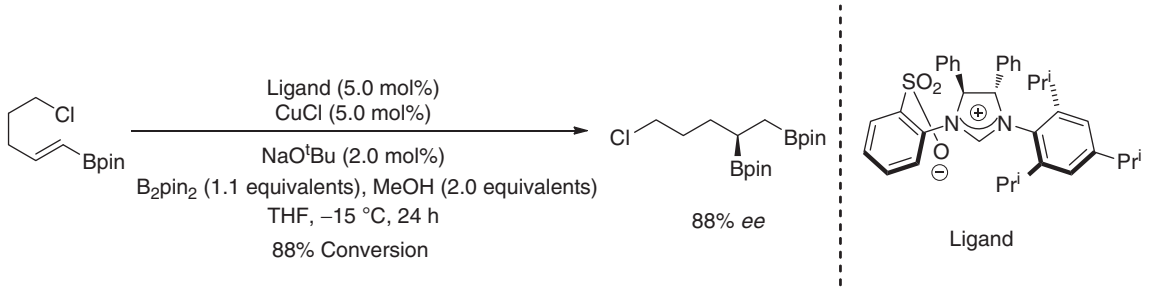
A one-step Rh-catalyzed hydroboration of terminal alkynes with PinBH provides the geminal diboronates (equation 35).[448]



(35)

Ar = Ph, 1-naphthyl, *o*-,*m*-, *p*-tolyl, XC_6H_4 (X=*o*-, *m*-, *p*-OMe, *p*-Br, *p*-Ph).
R = $Ph(CH_2)_2CH_2$, Ph(TBSO)CH, Bu^t(26% yield).

Vicinal boronates can be obtained with >98% regioselectivity and enantioselectivity up to 95% *ee* by the reaction of vinylboronates with B_2pin_2 in the presence of the NHC–Cu complex shown in equation 36.[449] The synthesis of vicinal boronates can be carried out directly from an alkyne using two equivalents of B_2pin_2.



(36)

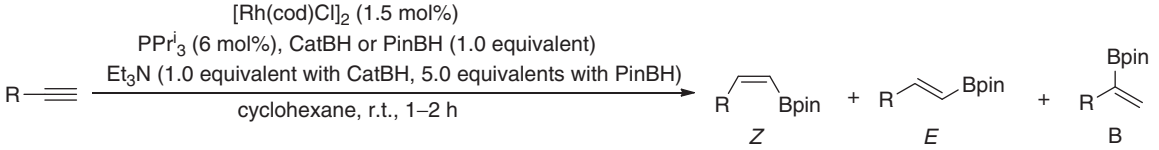
8.24.1.6.6 Enynes

Rhodium-, palladium-, and nickel-catalyzed 1,4-hydroboration of 1,3-enynes with a terminal triple bond gives 1,3-dienylboranes.[450–452] Representative examples are shown in **Figure 14**.

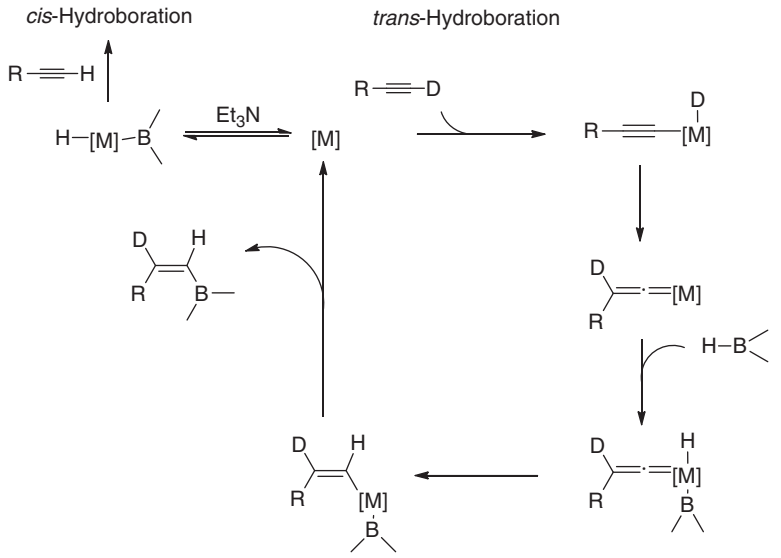
Although the palladium-catalyzed hydroboration of 1-substituted vinylacetylenes proceeds by the 1,2-addition, 2-substituted vinylacetylenes also react by the 1,4-addition to give the corresponding allenylboronates, as the main product (**Table 22**).[451]

The Cu-catalyzed monoboration of 1,3-enynes bearing an internal triple bond affords 1,3-dienylboronates and 3-alkynylboronates.[453] Unhindered terminal monosubstituted double bonds are more reactive and 3-alkynylboronates are formed in

Table 21 Rh-catalyzed *trans*-hydroboration of alkynes in the presence of triethylamine



R	>B–H	*Yield (%)*	Z:E:B			*R*	>B–H	*Yield (%)*	Z:E:B		
n-Octyl	CatBH	79	99	1		$TBDMSO(CH_2)_3$	CatBH	72	98	2	
	PinBH	81	91	7	2	$TBDMSOCH_2$	CatBH	71	>99	<1	
Bu^t	CatBH	62	89	11		Me(TBDMSO)CH	CatBH	70	98	2	
	PinBH	69	95	5			PinBH	59	89	10	1
Ph	CatBH	60	99	1		Me_3Si	CatBH	70	98	2	
	PinBH	67	97	2	1		PinBH	59	97	3	



Scheme 67

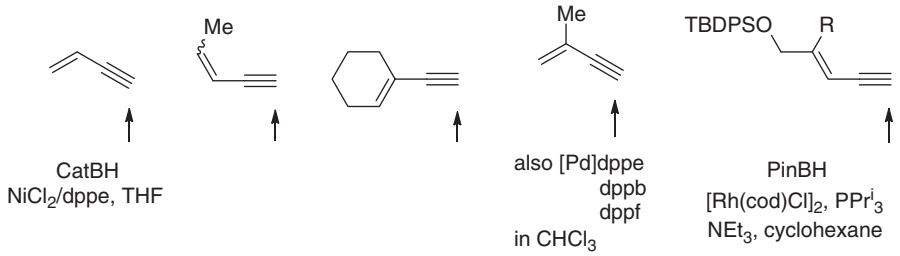
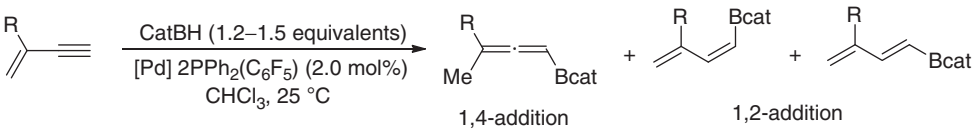


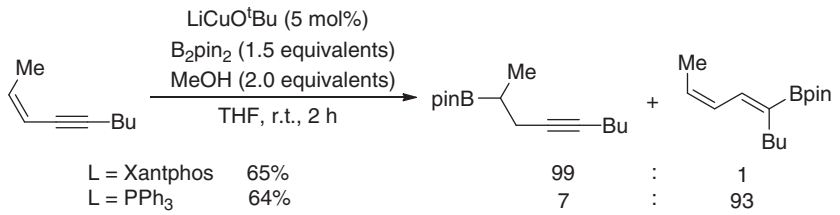
Figure 14 Regioselectivity of the catalytic hydroboration of conjugated enynes.

Table 22 The Pd-catalyzed hydroboration of α-substituted vinylacetylenes with CatBH



R	*Yield (%)*	*1,4-*	*1,2-*	
Me	73	83	17	
n-C_5H_{11}	74	88	12	
Bu^t	89	83	4	13

the presence of all ligands used in the study. Moderately hindered disubstituted double bonds react to give either 1,3-dienylboronates or 3-alkynylboronates, depending on the ligand (equation 37).



(37)

Hindered tri- and tetrasubstituted double bonds are not reactive and the addition to the triple bond affords 1,3-dienylboronate, except in the reaction with $Me_2C{=}CH{-}C{\equiv}CPh$, placing boron in the β-position to the phenyl group, opposite to CatBH/Ni(II)dppe, which places boron in the α-position.[452]

The regioselectivity of the reaction has been accounted for in terms of the interaction between HOMO of the borylcopper intermediate and LUMO of the interacting bond, according to the reported mechanistic studies.[398,434,435]

The unconventional *trans*-hydroboration of (*E*)-$TBDMSOCH_2CH{=}CH{-}C{\equiv}CH$ has been applied to the asymmetric synthesis of (+)-fostriecin.[454]

8.24.2 Hydroalumination of C=C and C≡C Bonds

8.24.2.1 Introduction

The hydroalumination of alkenes and alkynes has been reviewed.[455–460] The reaction has been studied since the 1950s. It shares certain common features with hydroboration, such as *anti*-Markovnikov *cis*-addition and further oxidation of the products to alcohols. However, its scope is more limited due to competitive carboalumination, dissociation, and displacement. The uncatalyzed hydroalumination of olefins requires elevated temperatures, and the reactivity decreases in the following order: $CH_2{=}CH_2 > RCH{=}CH_2 > RRC{=}CH_2 > RCH{=}CHR$. Alkynes react more readily, and the monoaddition products have a growing synthetic potential. Hydroalumination catalyzed by transition metal salts and complexes proceeds under mild conditions.

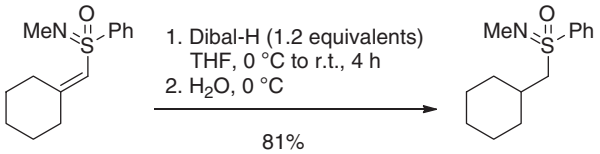
Over the past 20 years considerable progress has been achieved in the development of regio- and stereoselective hydroalumination, mechanistic and structural studies, and further transformations of the addition products. Thus, the catalyzed and uncatalyzed reduction of alkynols with lithium aluminum hydride provides *E*- or *Z*-alkenols, respectively. New sterically highly encumbered dialkyl aluminum hydrides have been introduced. Diastereoselective additions and the first enantioselective desymmetrizations demonstrate new synthetic possibilities in this direction. The palladium-catalyzed transfer hydroalumination and the zirconium-catalyzed addition of Dibal-H expand the already known procedures. A new protocol was reported for enantioselective synthesis of methyl-substituted alkanols and derivatives through tandem hydroalumination-zirconium-catalyzed alkylation, and further studies resulted in the development of the zirconium-catalyzed asymmetric carboalumination of alkenes (the ZACA process[461]).

The recently developed synthesis of 1,1-substituted alkyl- and arylvinylalanes, and stereochemically pure 1,2- and trisubstituted vinylalanes, makes possible the catalytic asymmetric allylic alkylation of unactivated alkenes.

Transformations of vinylalanes provide convenient access to vinylepoxides, vinyltellurides, functionalized allyl alcohols, and γ-lactones. The continuing extensive studies on the hydroalumination of alkynes result in a new insight into the course of the known reactions, and the synthesis of a number of new structures, such as carboalanes, cage molecules, persistent carbocations, and frustrated ion pairs.

8.24.2.2 Alkenes and Derivatives

The uncatalyzed hydroalumination of alkenes has been studied for more than 50 years, and the results are described in monographs and reviews.[455–460] The reagents most often used, $LiAlH_4$, Bu^i_2AlH (Dibal-H), and Bu^i_3Al (TIBA), react at elevated temperatures. Although the reaction scope is limited, the clean addition of Dibal-H to terminal alkenes finds synthetic applications, for example, in the synthesis of a C15 vitamin E side chain[462] and 3-alkoxypropyl(dialkyl)alanes.[463] Olefins bearing an activating group may react at lower temperatures. For example, exocyclic alkenylsulfoximines react with Dibal-H at 0 °C (equation 38).[464] The reaction proceeds diastereoselectively with 2-substituted derivatives and has been applied to the asymmetric cascade hydroalumination–cyclization–reduction leading to an aggrecanase inhibitor mimic.[464]

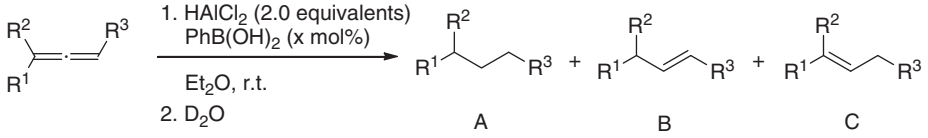


(38)

Hydroalumination of alkenes can be catalyzed by organoboranes and several transition metal complexes. Among them, the best results have been obtained with Ni, Ti, Zr, and Pd compounds. Thus, the reaction of olefins with $HAlCl_2$ catalyzed by phenylboronic acid or triethylborane (5 mol%) proceeds at room temperature with high *anti*-Markovnikov selectivity for terminal alkenes, 4-vinylcyclohexene, 3-trimethylsilylpropene, and 10-undecenol.[465] More substituted double bonds, for example, cyclohexene and β- and α-pinene, require an increased amount of triethylborane (10–20 mol%), and the addition to both pinenes is stereoselective, proceeding from the less-hindered side of the double bond. The same reagent in the presence of phenylboronic

acid, but not triethylborane, reacts selectively with mono- and disubstituted allenes, placing the aluminum at the central allene carbon atom[466] (Table 23).

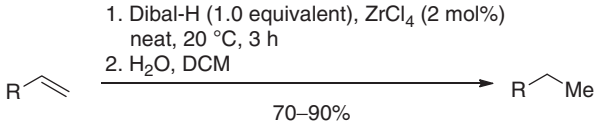
Table 23 Hydroalumination of substituted allenes with $HAlCl_2$ catalyzed by phenylboronic acid



R^1	R^2	R^3	X (mol%)	Time (h)	Conversion (%)	A	Yield (%)	C
Hex^n	H	H	5	6	75	6	92	2
$(CH_2)_5$		H	5	15	87	6	93	1
Hex^n	H	$SiMe_3$	20	24	53		99	1
$(CH_2)_5$		Et	20	6	71	45	38	17

The trialkyl allene reacts unselectively with deuterated reagents affording *n*-butylcyclohexane as the major product, containing geminal and vicinal deuterium atoms incorporated into the butyl group.

Zirconium complexes are highly active catalysts, as shown by the reactions of terminal and cyclic olefins with Dibal-H/$ZrCl_4$ (equation 39).[467]

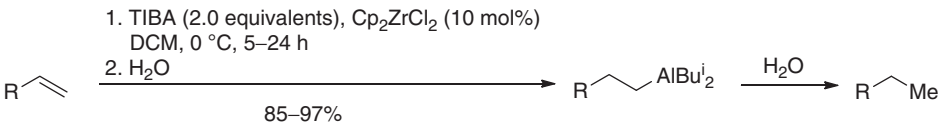


(39)

R = Bu^n, *n*-C_5H_{11}, *n*-$C_{10}H_{21}$, cyclohex-3-en-1-yl.

Cyclohexene and 2-ethyl-1-hexene react at 60 °C in 12 h to give the reduction products in 60% yield, and 40% of unreacted olefin remains. Even C_{60} fullerene reacts with Dibal-H/$ZrCl_4$ in toluene at 20 °C affording a mixture of hydro- and carboalumination products in 90% yield.[460]

The hydrogen transfer hydroalumination of olefins with Bu^i_3Al/Cp_2ZrCl_2 proceeds under mild conditions leading to *anti*-Markovnikov products[468] (Scheme 68).



R = Hex^n, $Br(CH_2)_3$, $HO(CH_2)_3$, $HO(CH_2)_9$, cyclohex-3-en-1-yl, $PhSCH_2$ (36 h).

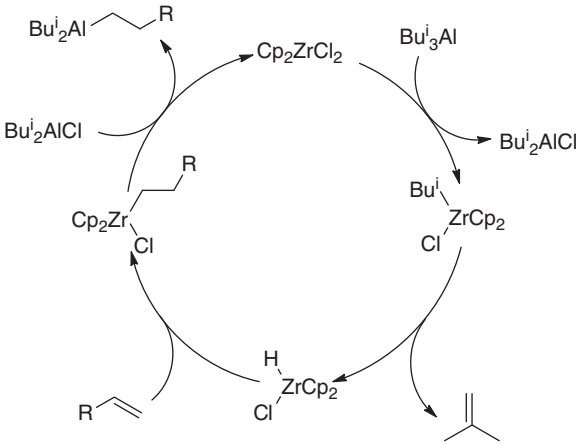
Scheme 68

(*Z*)-3-Decene and cyclohexene require longer reaction times (72–78 h) to give the products in 73% yield. An advantage of the method is its regio- and chemoselectivity, making possible the reaction with functionalized 1-alkenes. For example, allyl phenyl sulfide reacts with 97:3 regioselectivity and benzenethiol is the minor side product, 12% yield, as compared to the significant C–S bond cleavage (53%) when $LiAlH_4/TiCl_4$ is the reagent.[469]

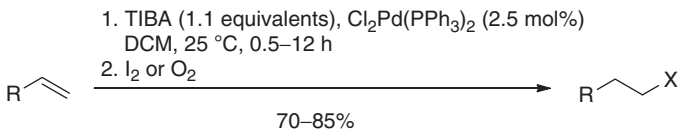
The high reactivity of the catalytic system is attributed to the intermediate formation of zirconium hydrides, which react with the olefins, followed by transmetalation in the last step[468] (Scheme 69).

Experimental studies and recent DFT and *ab initio* calculations on the mechanism of the olefin hydroalumination by Bu^i_2AlX in the presence of Cp_2ZrCl_2 indicate, in addition to the alkyl-Zr intermediate shown in Scheme 69, alkyl-Zr–Al intermediates in an expanded catalytic cycle.[470–472]

The hydrogen transfer hydroalumination of terminal olefins, dienes, and derivatives with TIBA is also catalyzed by $Cl_2Pd(PPh_3)_2$, $LiPdCl_4$, $KPtCl_4$, and chlorine-containing Ni, Co, and Rh complexes with triphenylphosphine. The cleanest products have been obtained with Pd and Pt catalysts[473] (equation 40).



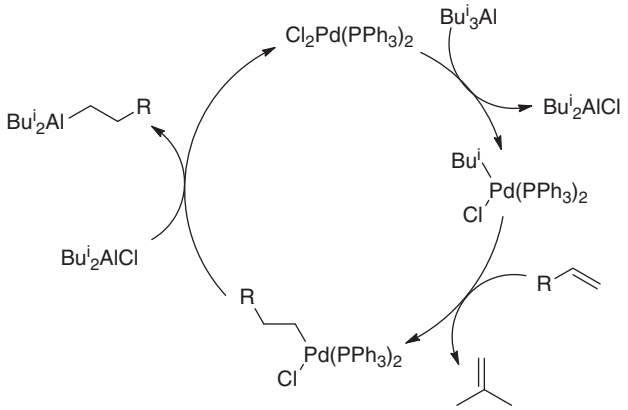
Scheme 69



(40)

R = Oct^n, Chx, Bn, Cl(CH$_2$)$_9$, Br(CH$_2$)$_9$, cyclohex-3-en-1-yl, (*Z*)-BuCH=C(SiMe$_3$)CH$_2$, S(CH$_2$)$_3$ (2.3 equivalents TIBA).

1,5-Hexadiene undergoes the hydrometalation–cyclic carbometalation to give cyclopentyl-carbinylalane. Longer α,ω-dienes react by the addition to the first double bond, and the reaction with the second double bond is affected by the alkylaluminum group, leading to the addition, isomerization, and reduction products. The catalytic cycle is shown in **Scheme 70**.[473]

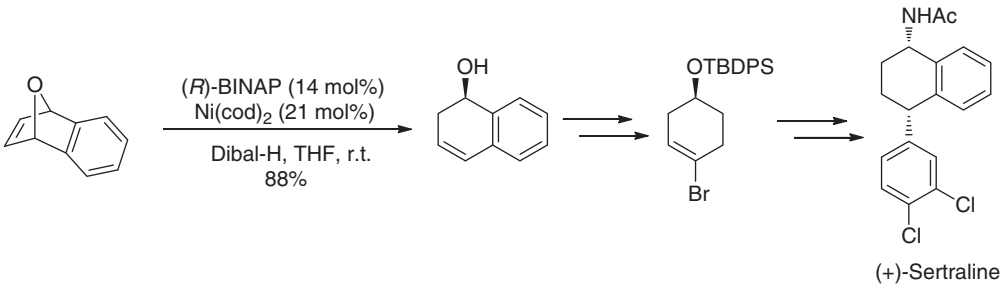


Scheme 70

The long-known Ni-catalyzed hydroalumination of alkenes[474] has been further studied to clarify its mechanism[475] and to find an enantioselective variant of the reaction. Resolution of racemic alkenes carried out with TIBA/Ni/chiral amines resulted in a very low enantiomeric excess.[476] Later, the hydroalumination of 1,1-disubstituted alkenes with the same reagent reached 27% *ee* for 2,3,3-trimethyl-1-butene.[477] Much more successful has been the desymmetrization of oxabicyclo[*n*.2.1] alkenes ($n=2$, 3), including the bridgehead-substituted hydroxy and alkoxy derivatives, carried out with Dibal-H/Ni(cod)$_2$/(*R*)-BINAP,[478–480] which has been reviewed.[481] The reaction proceeds by the Ni–H bond addition to the double bond, followed by highly selective Ni–O elimination leading to homoallylic alcohols. An asymmetric synthesis of (+)-sertraline starts with this approach[479] (**Scheme 71**).

The rate of Dibal-H addition has a dramatic effect on the enantioselectivity of the reaction with [2.2.1] substrates, whereas with [3.2.1] substrates it reacts at 60 °C with higher selectivity than at room temperature.

The lack of asymmetric induction in the reaction of α-methylstyrene with Dibal-H in the presence of chiral Zr complexes with neomenthylindenyl ligands has been attributed to the formation of structurally different intermediate Zr hydride complexes.[482]



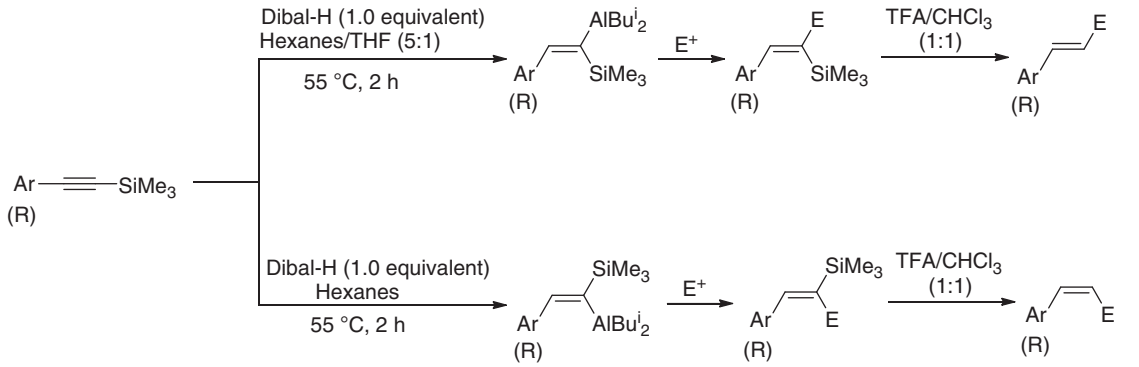
Scheme 71

8.24.2.3 Alkynes

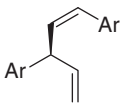
8.24.2.3.1 Terminal alkynes

The monohydroalumination of alkyl-substituted acetylenes with Dibal-H at 50–60 °C is a well-established reaction producing *E*-vinylalanes in excellent yields.[483–485] The products are important synthetic intermediates used in the substitution and catalytic cross-coupling reactions.[486] The more acidic aryl-substituted acetylenes suffer from the competitive alkyne deprotonation affording alkynylalanes when moderately bulky dialkylaluminum hydrides are used.[487,488] This inconvenience can be circumvented by employing the more bulky reagent, $HAl[CH(SiMe_3)_2]_2$.[487]

Alternatively, stereochemically pure trisubstituted α-silylvinyl aluminums, generated by the hydroalumination of silyl-substituted alkyl- and arylacetylenes, are masked *E*- and *Z*-vinylaluminums convenient for the synthetic transformations, followed by proto-desilylation[489] (Scheme 72).



Ar = Ph, X-C_6H_4 (X = *o*-Me, *o*-MeO, *o*-NO_2, *m*-Br, *p*-Cl, *p*-NO_2, *p*-TsO, *p*-Me).
R = Chx, $(CH_2)_2C_6H_5$.



(–)-Nyasol
Ar = *p*-HOC_6H_4

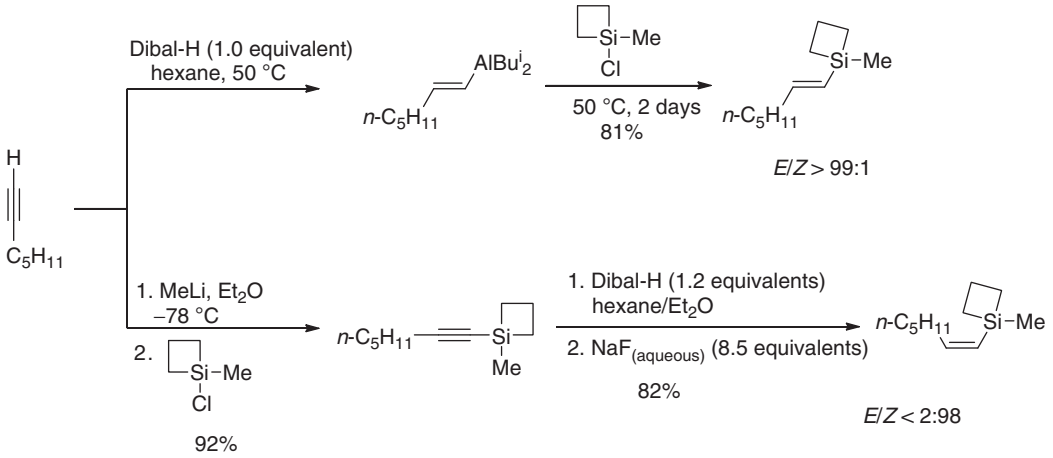
Scheme 72

The *cis*-hydroalumination products are stabilized by THF complexation, whereas in the noncomplexing hexanes they undergo isomerization to the more stable *E*-isomers via the proposed pathways.[488–490] The one-pot procedure presented in Scheme 72 has been used for the enantioselective synthesis of (–)-nyasol.[489]

A similar approach to *E*- and *Z*-alkenylsilacyclobutanes via *E*- and *Z*-alkenylalanes, generated in complexing or noncomplexing solvents, respectively, affords the products with high selectivity (Scheme 73).[491]

In a related procedure, phenylethynylsilacyclobutane has been cleanly transformed into the corresponding *Z*-vinylalane by hydroalumination with Dibal-H.[492] The reaction product of 1-pentyne with Dibal-H has been used for the Cu-catalyzed asymmetric conjugate addition to 3-methylcyclohexanone.[493]

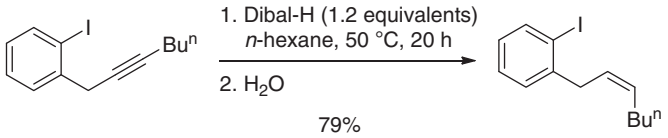
The $AlH_3 \cdot NMe_3$ adduct is a useful reagent providing access to cluster carboalanes of rhombic dodecahedron structure, by the dihydroboration of acidic terminal alkynes RC≡CH (R=Ph, CH_2SiMe_3), and further thermal transformations.[494] Ferrocenylacetylene has been transformed into a nanosized carboalane, which is a model for the fixation of an organometallic fragment onto a carbide structure.[495] Hydroalumination with $AlH_3 \cdot NMe_3$ has been reviewed.[496]



Scheme 73

8.24.2.3.2 Internal alkynes and derivatives

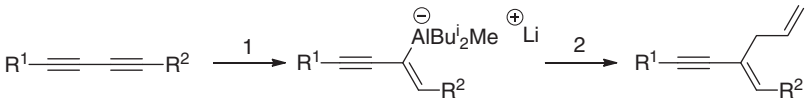
The *cis*-hydroalumination of disubstituted alkynes is a well-established chemo selective reaction, used in contemporary organic synthesis (equation 41).[497]



(41)

The *trans*-addition products can be obtained by the reaction with lithium trialkylaluminum hydrides, carried out at elevated temperatures with simple alkynes, and at ambient temperatures with various derivatives.[484,498]

The monohydroalumination of 1,3-diynes with lithium trialkylaluminum hydrides is a highly chemo-, regio-, and stereoselective addition placing aluminum at the internal position of the conjugated system. The nonsilyl bearing triple bond of the trimethylsilyl-substituted diyne reacts selectively[499] (**Scheme 74**).

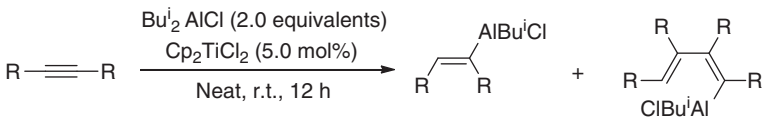


1. Li[Bu$^i_2$MeAlH] (1.2 equivalents), $(MeOCH_2CH_2)_2O$, 25 °C, 8 h; 2. Allyl bromide, 25 °C, 2 h.

Scheme 74

Catalytic hydroaluminations proceed under mild conditions, and several procedures, developed in the past, have been reviewed.[500] The recently introduced reagent for the hydroalumination of olefins, Bu^i_2AlCl/Cp_2TiCl_2,[501] also reacts stereoselectively with alkynes.

Conjugated dienes formed by carboalumination are the side products[502] (equation 42).

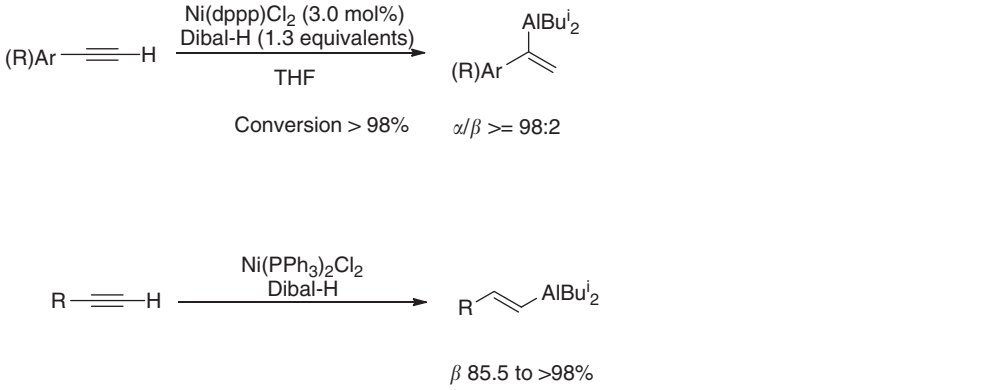


(42)

4-Decyne reacts unselectively producing regioisomers in a 1:1 ratio. However, the reaction of phenylpropyne followed by the cross-coupling with allyl chloride affords 4,5-methyl(phenyl)-substituted 1,4-dienes in a ~9:1 ratio indicating the regioselective addition.[502] The hydrogen transfer hydroalumination of 3-hexyne with Bu^i_3Al/Cp_2ZrCl_2 is accompanied by isomerization and

affords the *cis*-addition product (38%) and (*E*)-MeCH=C(Pr)AlBu$^i_2$ (35%).[503] The reaction with 5-decyne proceeds similarly. 1-Decyne gives the monohydroalumination and geminal dihydroalumination products in a 1:1 ratio, and the reaction of 5-decyne with (*n*-Pr)$_3$Al/Cp$_2$ZrCl$_2$ involves simultaneous hydroalumination and C–H activation.[504]

Highly selective Ni-catalyzed hydroalumination of terminal alkynes with Dibal-H provides simple and convenient access either to α- or β-vinylalanes depending on the catalyst.[505] Thus, the α-selective hydroalumination is catalyzed by Ni complexes bearing a bidentate phosphine ligand, and Ni(dppp)Cl$_2$ provides the product with the highest selectivity among the tested complexes. The β-selectivity is favored in the reaction of alkyl-substituted acetylenes, catalyzed by Ni complexes, with monodentate phosphines[505] (Scheme 75).

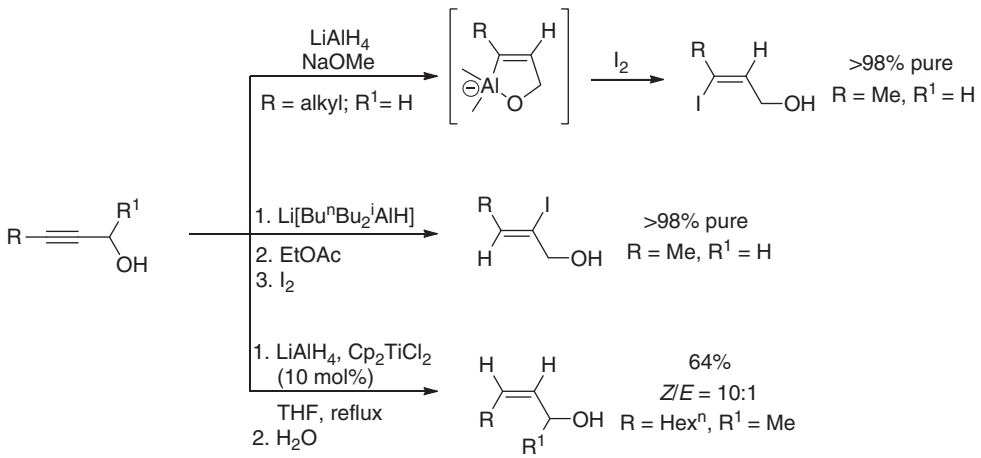


Ar = Ph, X-C$_6$H$_4$ (X = *o*-, *p*-MeO, *o*-Me, *m*-CF$_3$ 95:5), 4 °C, 12 h;
3-Py, 3-thienyl, X-C$_6$H$_4$(X = *m*-MeO, *p*-F, *o*-Cl, *o*-Br, *p*-CF$_3$ 93:3), 22 °C, 2 h.
R = Hex^n, *c*-Hex, *c*-PentCH$_2$, cyclohex-1-yl, X-CH$_2$CH$_2$CH$_2$ (X = Cl, OH, OTBS), 22 °C, 2 h 96.5–98-3.5–2.

Scheme 75

Both alkyl- and arylacetylenes undergo >98% conversion into α-vinylaluminums at room temperature or below. High selectivity is achieved regardless of the electronic effects of substituents. Only *m*- and *p*-CF$_3$-substituted phenylacetylenes react with a slightly lower selectivity. Alkynylaluminum side products are formed in small amounts of <2%, and only ~5% for 1-ethynylcyclohexene. α-Vinylaluminums can be readily transformed into α-vinylboronates and α-vinyl halides and have been used for the Cu-catalyzed enantioselective alkylation. Hydroalumination of the same alkyl-substituted acetylenes in the presence of Ni(PPh$_3$)$_2$Cl$_2$ proceeds under mild conditions with β-selectivity, 85.5% to >98%, to give the *E*-vinylaluminum products.[505]

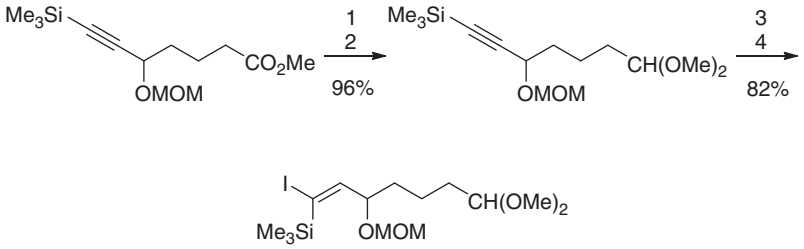
The reduction of alkynols with LiAlH$_4$ at elevated temperatures is a long-known reaction leading to *E*-alkenols.[506,507] When Li[Bu^{n}Bu$^i_2$AlH] is used, the regioselectivity of addition is reversed (Scheme 76).[508] The reaction with LiAlH$_4$ in the presence of Cp$_2$TiCl$_2$ proceeds with reversed stereoselectivity producing 2-alkenols (Scheme 76)[509] and has been used in the synthesis of (*R*)-nostrenol.[510] Functional groups such as acetal and ether are tolerated, and 4-octyne is also reduced to *Z*-4-octene.



Scheme 76

1-Chloroalkynes,[511] 3-trimethylsilylpropargyl alcohol,[512] and propargylic amines, including 1-(trifluoromethyl) propargylamines,[513] also undergo *trans*-hydroalumination with $LiAlH_4$ in THF at reflux or at $-30\,^{\circ}C$ to $0\,^{\circ}C$ (1-chloroalkynes). 3-[4-(2-Furyl)phenyl]-2-propyn-1-ol reacts with Red-Al at $-30\,^{\circ}C$ in 15 min,[514] and other alkynols are also readily reduced with the reagent.[515–517]

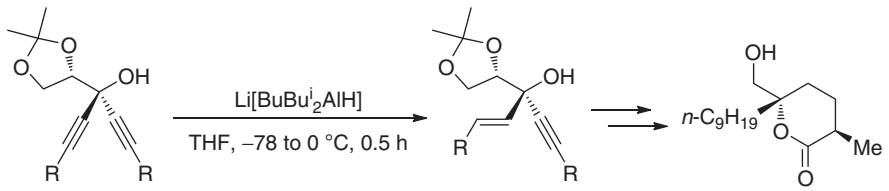
A highly chemo- and stereoselective sequential reduction of a methyl ester, followed by the reduction of protected alkynol, has been achieved with Dibal-H (Scheme 77).[518]



1. Dibal-H, DCM, –78 °C; 2. MeOH, *p*-TsOH, $(MeO)_3CH$; 3. Dibal-H, Et_2O, 50 °C, 24–48 h; 4. NIS, Py.

Scheme 77

A group-selective hydroalumination of tertiary bis-alkynyl alcohols bearing an adjacent stereogenic center with $Li[R_3AlH]$ or $LiAlH_4$ proceeds with high selectivity (Scheme 78).[519,520] The group selectivity is reversed (R=*n*-Bu) when the reduction is carried out with $LiAlH_4$. The product shown in Scheme 78 (R=H) has been used for the synthesis of (–)-malyngolide.[519]



R = H 79% >99% *ds*

R = Bu^n 94% >99% *ds*

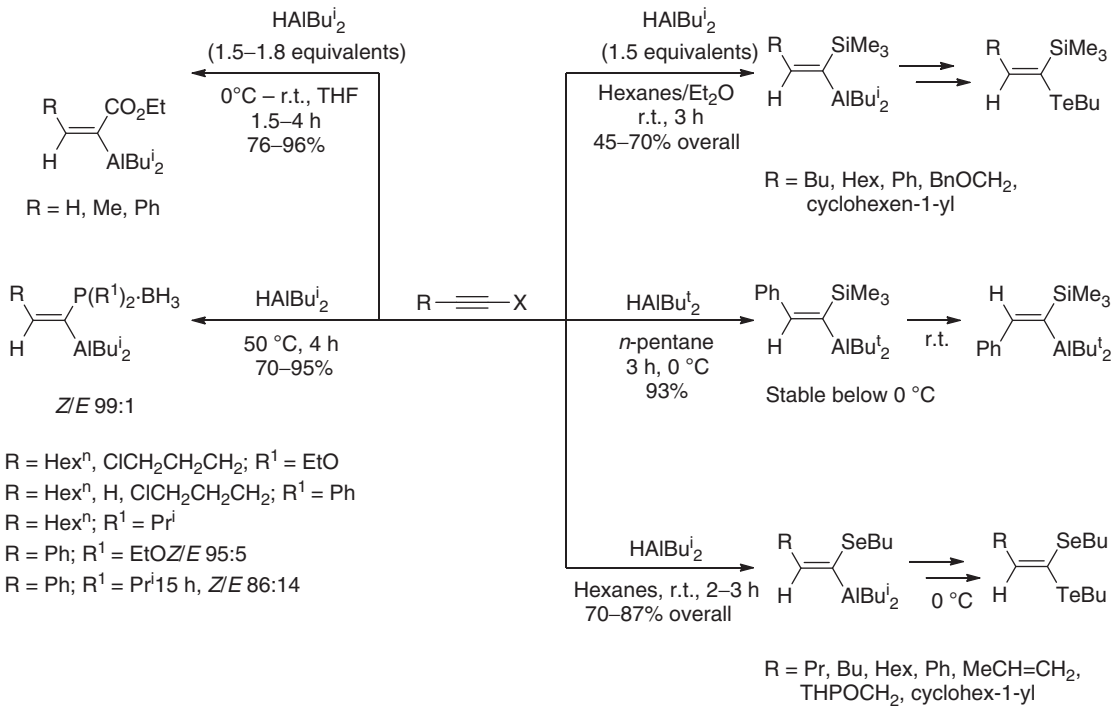
Scheme 78

A modified protocol for the *cis*-hydroalumination of α,β-acetylenic esters with Dibal-H in 4-methylmorpholino-*N*-oxide, instead of hexamethylphosphorictriamide, affords the corresponding vinylaluminum products (Scheme 79), which have been used for the synthesis of functionalized allylic alcohols, vinyl epoxides, and α-alkylidene-β-hydroxy-γ-lactones.[521] Alkynylphosphine–borane complexes react with Dibal-H to give *Z*-alkenylphosphine–borane complexes with high selectivity[522] (Scheme 79). Alkynylsilanes and alkynylselenides are readily transformed into the corresponding (*E*)-telluro(silylo) and (*E*)-tellulo(seleno)ketene acetals via α-aluminate vinyl intermediates[523,524] (Scheme 79). The isomers of opposite stereochemistry (*Z*)-telluro(seleno)ketene acetals have been obtained via the α-aluminate intermediates produced by the reaction with Li[*n*-$BuBu^i_2AlH$].[490] The intermediates generated at room temperature are stable in hexanes/Et_2O, whereas in the absence of ethers, silylated *Z*-vinylalanes isomerize to *E*-vinylalanes at room temperature[490,525] (Scheme 79). Silylated 1,3-enynes undergo cyclodimerization promoted by Dibal-H.[526]

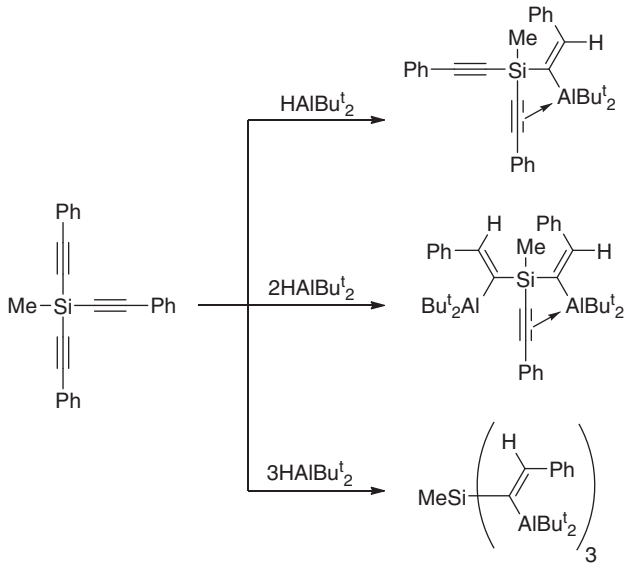
Extensive studies on the hydroalumination of mono-, di-, and trialkynylsilanes and germanes with highly sterically demanding $HAl[CH(SiMe_3)_2]_2$ and other dialkylaluminum hydrides reveal a range of structures formed from the initial *cis*-hydroalumination products, which often immediately isomerize to the *trans*-addition products.[527] The reaction of trialkynylsilane with $HAlBu^t_2$ is illustrative[528] (Scheme 80).

The hydroalumination of dialkynylsilane and dialkynylgermane with $HAlBu^t_2$ provides the isomerized *trans*-addition products complexing anions[529,530] (Scheme 81).

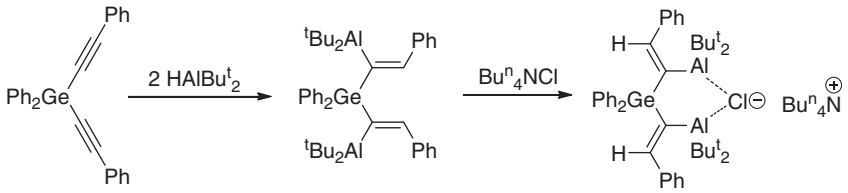
The *cis*-monoaddition product obtained with $HAl[CH(SiMe_3)_2]_2$ is stable and the hindered aluminum atom does not interact with the triple bond as observed with the less bulky aluminum groups. The reaction of tetraphenylethynylgermane with two equivalents of $HAl[CH(SiMe_3)_2]_2$ provides the *cis*-addition product, which on heating undergoes transformation into the spiro-structure[531] (Scheme 82).



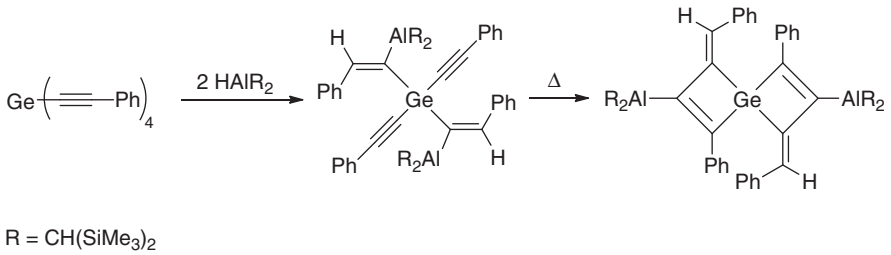
Scheme 79



Scheme 80

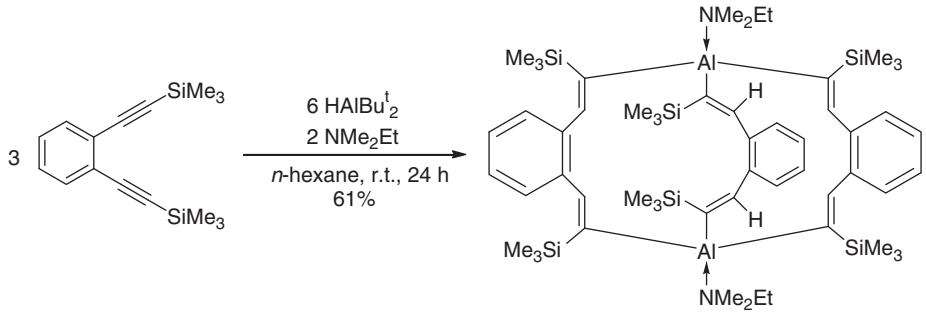


Scheme 81



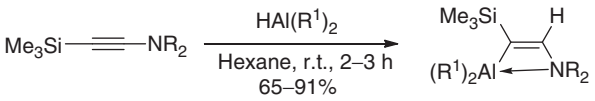
Scheme 82

Treatment of 1,2-bis(trimethylsilylethynyl)benzene with $HAlBu^t_2$ in the 3:6 ratio affords a molecular capsule (equation 43).[532]

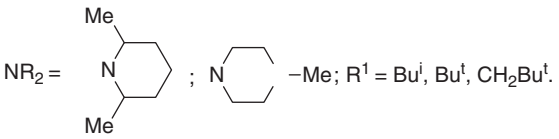


(43)

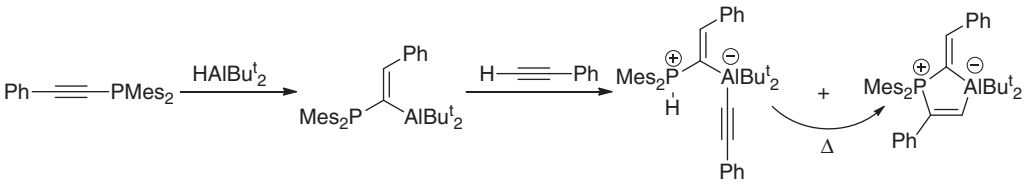
Weakly bound Al–N Lewis pairs are generated by the hydroalumination of ynamines (equation 44).[533]



(44)



The C–H bond activation of phenylacetylene by the pair, and the insertion of one C=N bond of dicyclohexylcarbodiimide into its Al–C (vinyl) bond, has been observed. The Al–C–P Lewis pairs are obtained by the hydroalumination of alkynylphosphines[534] (Scheme 83).



Scheme 83

The pair shown in Scheme 83 is unreactive toward dihydrogen, and reacts with phenylacetylene producing a cyclic pair. The reactivity of both pairs can be influenced by structural modifications.

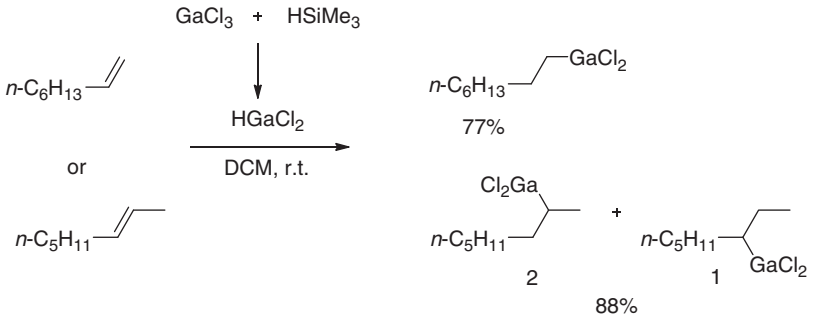
8.24.3 Hydrogallation of C=C and C≡C Bonds

8.24.3.1 Introduction

The hydrogallation of alkynes has been reviewed.[527] In comparison to the uncatalyzed hydroalumination, the reaction with alkenes and alkynes proceeds under milder conditions and the addition products can be easily isolated. The availability of dialkylgallium hydrides and dichlorogallium hydride makes possible the progress of further studies.

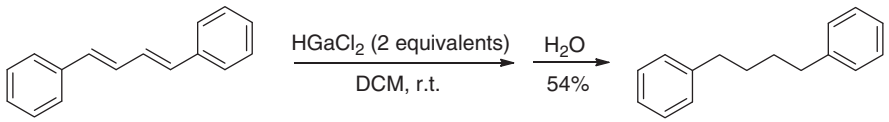
8.24.3.2 Alkenes and Derivatives

The hydrogallation of alkenes is poorly represented in the literature. In 1993, the reaction of 1-octene with dichlorogallium hydride, generated from gallium(III) trichloride and trimethylsilane, was reported to give 1-octylgallium dichloride in 77% yield[535] (Scheme 84). The addition proceeds with high regioselectivity and no other regioisomers have been detected. Under the same reaction conditions, 2-octene produces the 2:1 mixture of regioisomers. In contrast, a mixture of products has been obtained from (*E*)-stilbene.



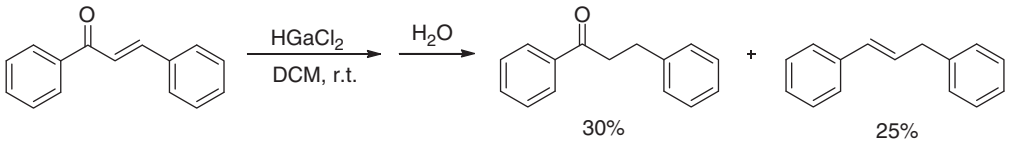
Scheme 84

1,4-Diphenyl-1,3-butadiene reacts readily with two equivalents of $HGaCl_2$ and the product is hydrolyzed to 1,4-diphenylbutane in 54% yield[535] (Scheme 85).



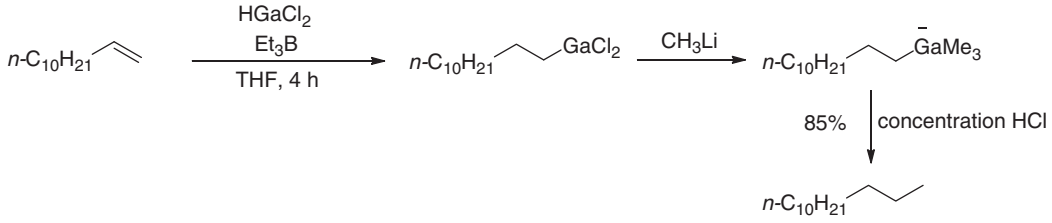
Scheme 85

The hydrogallation of chalcone followed by hydrolysis gives a mixture of the 1,4-hydrogallation–hydrolysis product and 1,3-diphenylpropene[535] (Scheme 86).



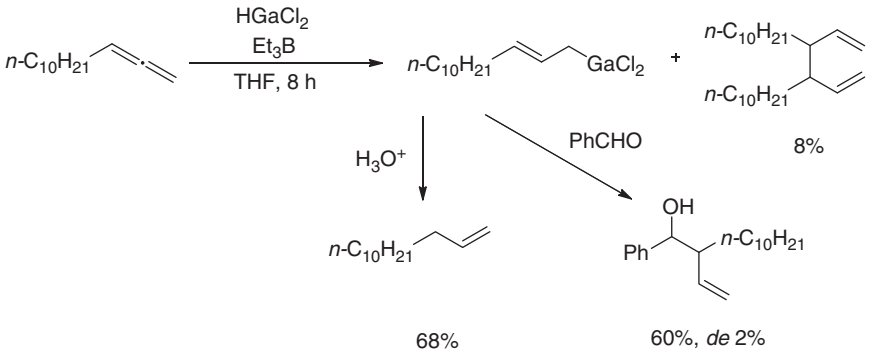
Scheme 86

The radical addition of $HGaCl_2$, prepared from $GaCl_3$/Red-Al, to 1-dodecene proceeds with two equivalents of the hydride and a catalytic amount of triethylborane.[536] The subsequent reaction with methyllithium, followed by hydrolysis with concentrated hydrochloric acid, provides dodecane in 85% yield (Scheme 87).



Scheme 87

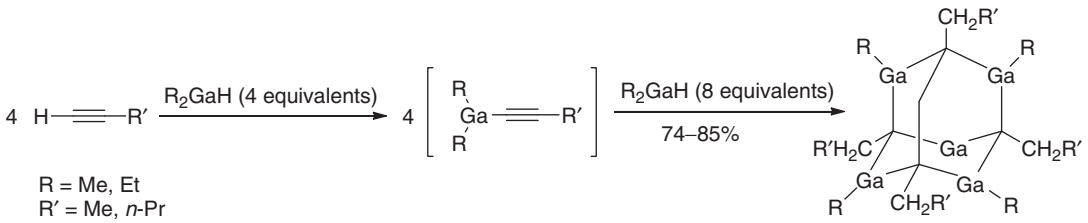
Hydrogallation of allenes under the same reaction conditions gives the allylic gallium products, indicating the addition of gallium radical to the terminal carbon atom. The products react with electrophiles providing alkenes and alcohols[536] (Scheme 88).



Scheme 88

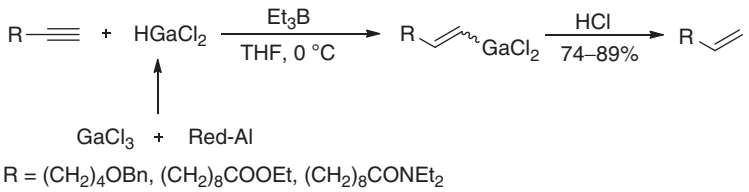
8.24.3.3 Terminal Alkynes

Dialkylgallium hydrides react with terminal alkynes to give gallium alkynides. In the presence of an excess of the hydride, they are directly transformed into heteroadamantane-type trialkylgallium compounds (Scheme 89).[537]



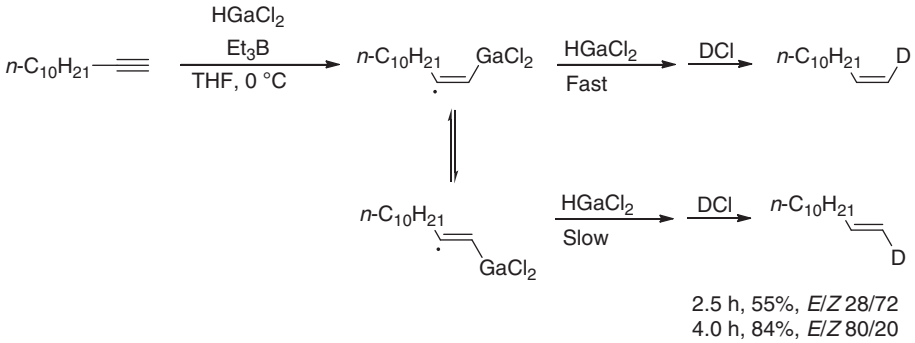
Scheme 89

With $HGaCl_2$ in the presence of triethylborane, the radical initiator, alkenylgallium dichlorides are obtained from terminal alkynes.[536] The formation of gallium alkynides is suppressed by the dichlorogallium radical, which adds to the triple bond. Protonolysis of vinylgallium dichlorides with hydrochloric acid produces the corresponding alkenes in good yields (Scheme 90).



Scheme 90

The reaction of 1-dodecyne with dichlorogallium hydride and quenching with DCl produces 1-deuterio-1-dodecene with the *E*/*Z* selectivity strongly depending on the reaction time.[536] The initially formed (*Z*)-alkenylgallium isomerizes to its (*E*)-isomer, via the gallium radical addition–elimination sequence (Scheme 91).

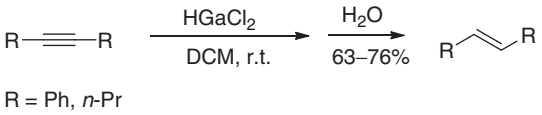


Scheme 91

The cross-coupling reaction of 3-iodoanisole with alkenylgallium provides the coupling product with low yield and selectivity.[536]

8.24.3.4 Internal Alkynes and Derivatives

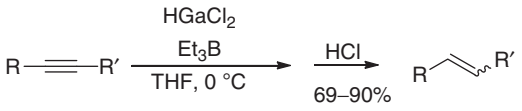
Hydrogallation of diphenylacetylene with $HGaCl_2$ in DCM followed by hydrolysis cleanly produces (*E*)-stilbene in 76% yield[535] (Scheme 92). 4-Octyne, under similar conditions, gives 4-(*E*)-octene in 63% yield.



R = Ph, *n*-Pr

Scheme 92

Triethylborane-mediated hydrogallation of internal alkynes proceeds smoothly, although the products are mixtures of *E*/*Z* isomers (Scheme 93).

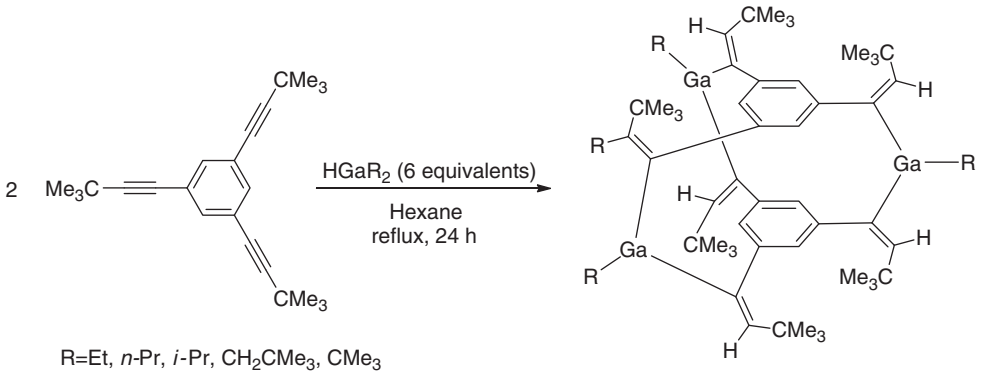


R = *n*-C_5H_{11}, CH_2OMe, CH_2OH
R′ = *n*-C_5H_{11}, *n*-C_6H_{13}

E/*Z*
59/41–92/8

Scheme 93

The formation of trialkylgallium compounds is observed in all reactions of trialkynylbenzenes with various dialkylgallium hydrides.[538,539] The [3,3,3]cyclophane-type molecules are formed, and in the first step, the gallium atom exclusively attacks the carbon atoms bonded to the benzene ring (Scheme 94), and the *syn*-addition is observed. The second step involves the intermolecular release of the corresponding trialkylgallanes and the formation of cages.



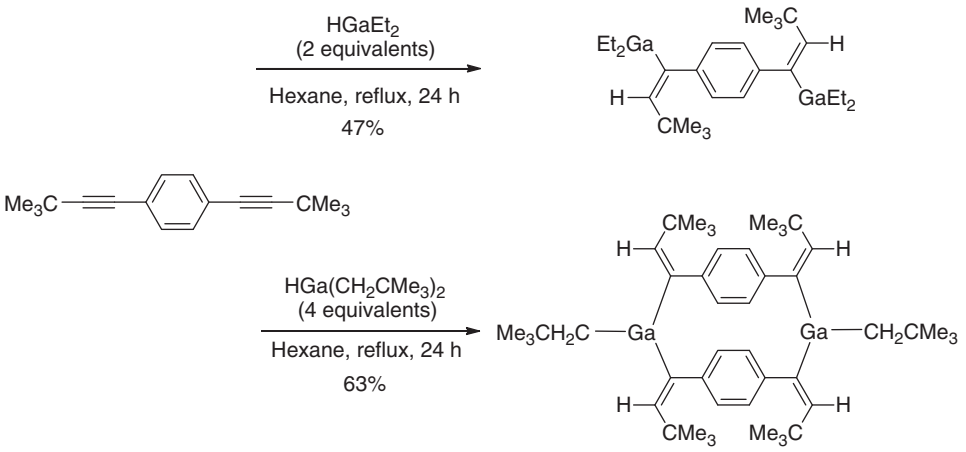
R=Et, *n*-Pr, *i*-Pr, CH_2CMe_3, CMe_3

Scheme 94

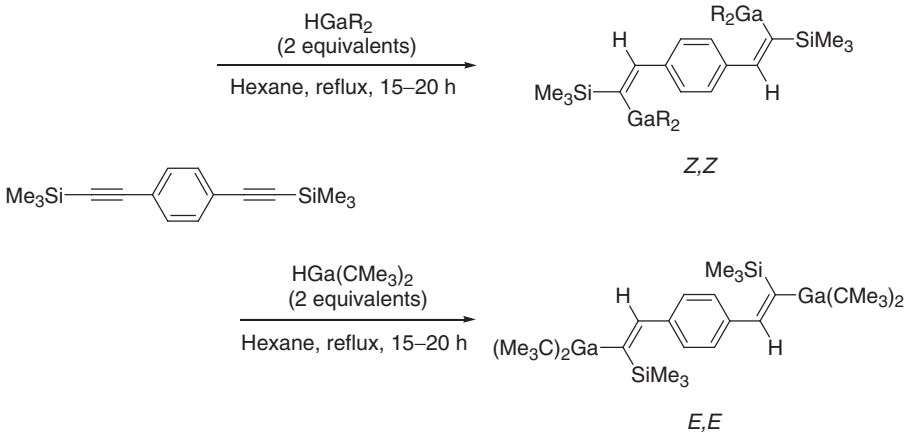
The *cis*-arrangement of gallium and hydrogen is also observed in the hydrogallation of 1,4-di(*tert*-butylethynyl)benzene.[540] The reaction with diethylgallium hydride provides the addition product in 47% yield, and further reaction with dineopentylgallium hydride affords [3,3]cyclophane (Scheme 95).

The hydrogallation of 1,4-bis(trimethylsilylethynyl)benzene and 1,3,5-tris(trimethylsilylethynyl) benzene with dialkylgallium hydrides affords the corresponding addition products with the intact GaR_2 groups and two or three alkenyl substituents.[490,541] In all products, the gallium atoms attack the carbon atoms bearing the trimethylsilyl groups (Scheme 96).

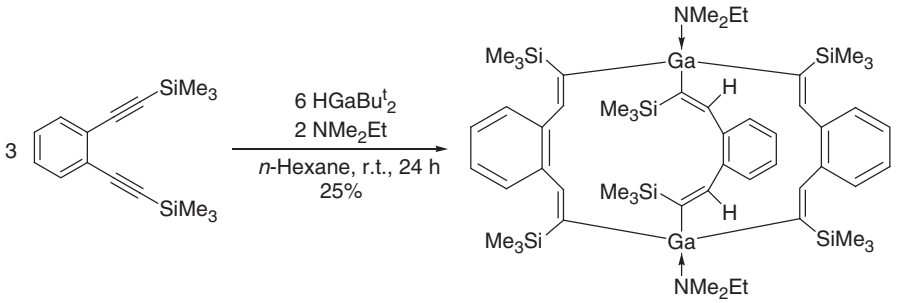
Treatment of 1,2-bis(trimethylsilylethynyl)benzene with $HGaBu^t_2$ in a 3:6 ratio affords a molecular capsule (Scheme 97).[532]



Scheme 95



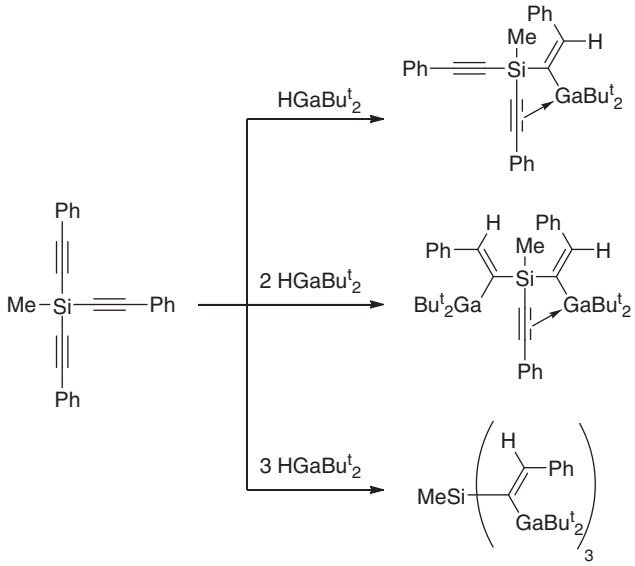
Scheme 96



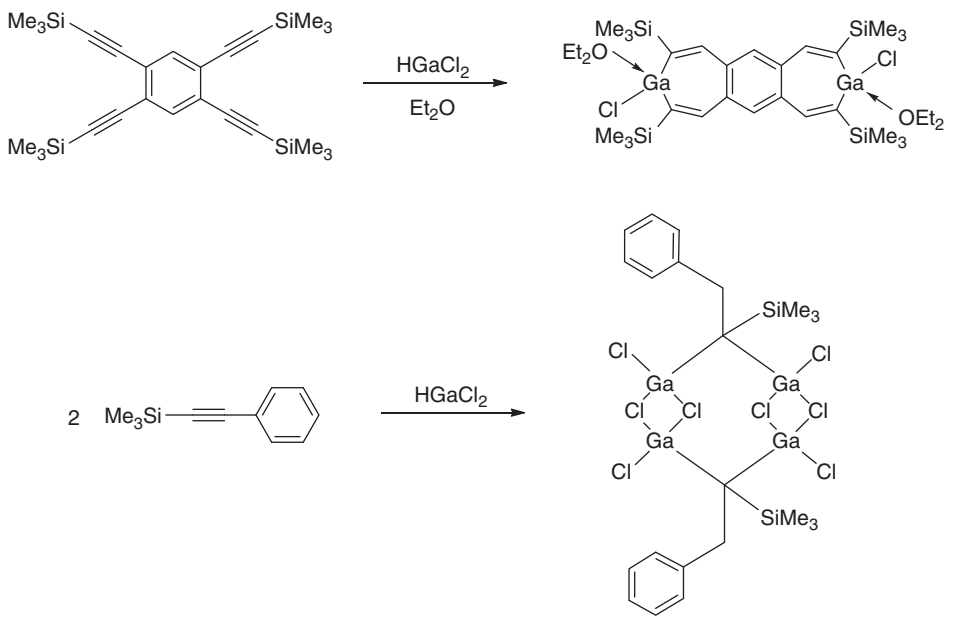
Scheme 97

Extensive studies on hydrogallation of trialkynylsilanes with highly sterically demanding $HGa[CH(SiMe_3)_2]_2$ and other dialkylgallium hydrides reveal a range of structures formed from the initial *cis*-hydrogallation products, which often immediately isomerize to the *trans* products (Scheme 98).[528]

The hydrogallation of silylated alkynes with $HGaCl_2$ provides access to chelating Lewis acids, potential polyacceptors (Scheme 99).[542,543]



Scheme 98



Scheme 99

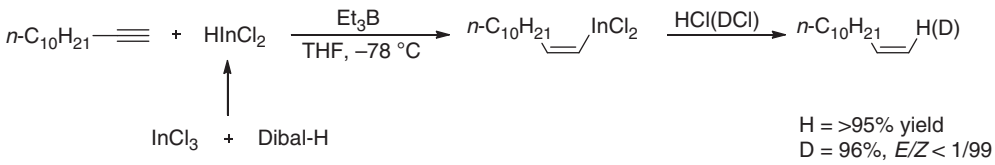
8.24.4 Hydroindation of C=C and C≡C Bonds

8.24.4.1 Introduction

Organoindium reagents tolerate a wide range of functional groups and can be used under mild reaction conditions.[544] They are readily available, relatively inert to air and water, thermally stable, and can be handled without special precautions. The hydroindation of alkynes is still not widely explored. It has been initiated by the convenient generation of dichloroindium hydride, $HInCl_2$, which is used in a number of reduction procedures.[545–550] The addition of indium hydrides to multiple carbon–carbon bonds was first reported in 2002.[547]

8.24.4.2 Alkynes and Enynes

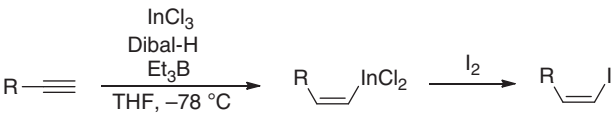
Triethylborane-induced hydroindation of alkynes with dichloroindium hydride, generated by a combination of indium trichloride and diisobutylaluminum hydride (Dibal-H), provides (*Z*)-alkenylindium dichlorides that can be converted into alkenes, (*Z*)-iodoalkenes, and (*Z*)-*β*-substituted styrenes with good yields and selectivity.[536,547] Triethylborane is a radical initiator and makes possible quantitative yields at 1-dodecene (Scheme 100). Quenching the organoindium species with DCl selectively gives (*Z*)-1-deuterio-1-dodecene.



Scheme 100

A range of alkynes undergo the hydroindation reaction followed by iodolysis, or by the palladium-catalyzed cross-coupling reaction with aryl iodides. These one-pot reactions provide access to a variety of (*Z*)-iodoalkenes (Table 24) and (*Z*)-*β*-substituted styrenes (Table 25). Functional groups, such as hydroxyl, ester, ether, and nitro, are tolerated (Table 1).

Table 24 Hydroindation of alkynes followed by iodolysis



R	*% Yield*	E/Z
$PhCH_2O(CH_2)_3$	79	1/99
$PhCH_2O(CH_2)_3$[a]	91	2/98
$C_2H_5O_2C(CH_2)_6$	99	<1/99
$HO(CH_2)_4$	78	<1/99
$HOCH_2$	57	<1/99
n-$C_4H_9CO(CH_2)_6$	73	<1/99
$HO_2C(CH_2)_6$	98	3/97
$CH_2=CH(CH_2)_8$	74	1/99
Ph	99	7/93

[a]The reaction performed at –40 °C.

Enynes also undergo hydroindation, followed by 5-*exo*-*trig* cyclization leading to the methylenecyclopentane skeleton by a radical process[536] (Scheme 101). The vinyl radical formed in the first step adds to the double bond.

The same procedure has been used in the alkenylation reaction of α-iodoesters via a radical process. After extensive modifications, the two reactions have been successfully combined by using dimethyl sulfoxide (DMSO) as a cosolvent. A stereoselective alkenylation reaction is achieved in this one-pot reaction (Scheme 102).[551]

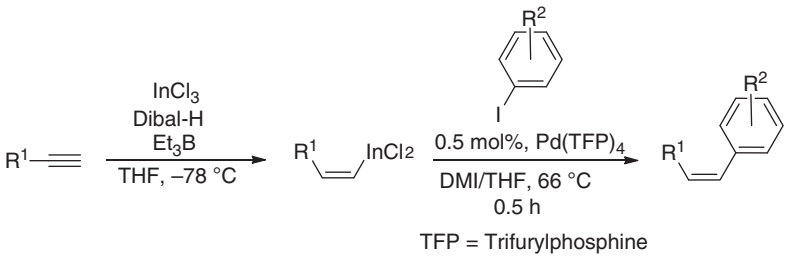
The reaction of indium trichloride with triethylsilane, generating dichloroindium hydride, is an alternative procedure to $InCl_3$/Dibal-H and $InCl_3/Bu_3SnH$ reactions.[552] The procedure has been used in the hydroindation–reduction of terminal and internal alkynes (Table 26). In the case of disubstituted alkynes, *E*-isomers are obtained preferentially. The mild conditions make possible the reduction of triple bond without affecting the ester group (Table 26).

The hydroindation of allylpropargylmalonate and *N*-tosyl allylpropargylamine with $InCl_3/Et_3SiH$ in the presence of triethylborane gives *exo*-methylene compounds (Scheme 103). The amount of the reduction product increases when $NaBH_4$ is used instead of triethylsilane for the generation of dichloroindium hydride.

The indium trichloride/sodium borohydride system has been successfully applied in the hydroindation and subsequent hydrolysis of arylalkynylphosphonates producing (*E*)-2-arylvinylphosphonates.[553] Acetonitrile is the preferred solvent in which the products are obtained in good yields and with high *E*-selectivity (Scheme 104).

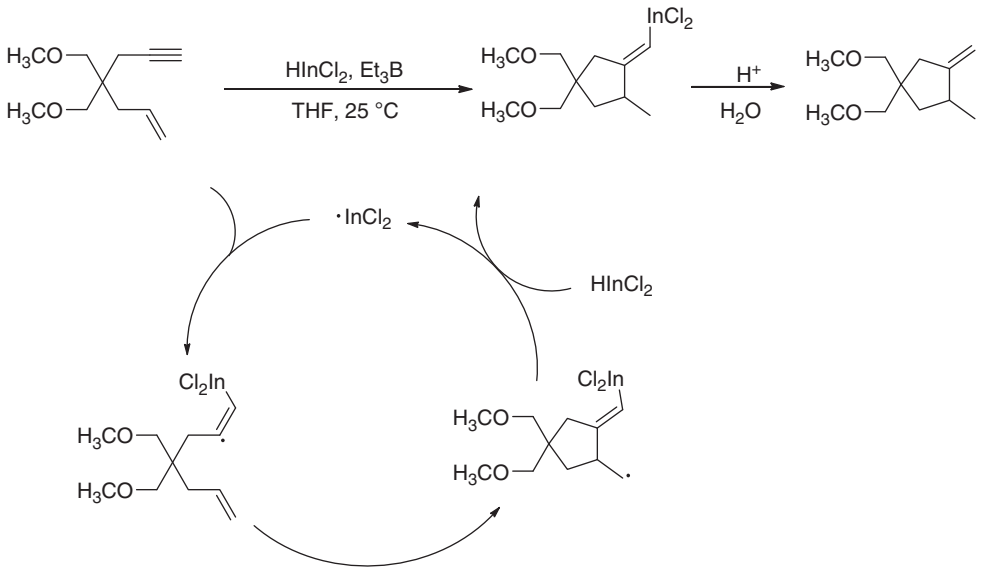
Under the above reaction conditions, the hydroindation and the cross-coupling reaction with aryl halides can be performed.[554] The alkenylindium intermediates obtained from terminal aryl alkynes couple with aryl iodides or bromides, giving the products with good yields and high regio- and stereoselectivity (Scheme 105).

Table 25 One-pot hydroindation cross-coupling reaction of alkynes



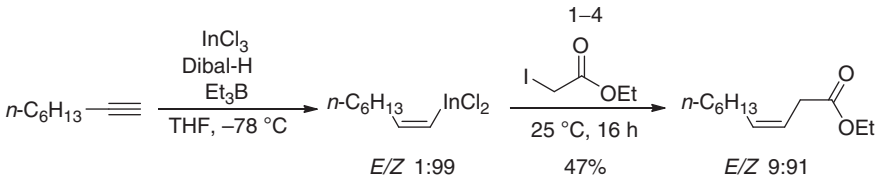
R^1	R^2	% Yield	E/Z
n-C_6H_{13}	H	94	5/95
n-C_6H_{13}	2-NO_2	98	5/95
n-C_6H_{13}	4-NO_2	99	5/95
n-C_6H_{13}	2-CO_2-n-C_4H_9	91	5/95
n-C_6H_{13}	3-OCH_3	89	5/95[a]
n-C_6H_{13}	2-Iodopyridine	75	3/97[a]
n-C_6H_{13}	4-CH_3	68	4/96
n-C_6H_{13}	3-OH	46	1/99
$C_2H_5O_2C(CH_2)_6$	H	92	3/97
$C_2H_5O_2C(CH_2)_6$	4-NO_2	99	5/95
$TBSO(CH_2)_3$	H	70	2/98
$TBSO(CH_2)_3$	4-NO_2	90	5/95
$HO(CH_2)_4$	4-NO_2	99	2/98
$HO(CH_2)_4$	3-OCH_3	99	3/97[a]
$HO(CH_2)_4$	3-OH	36	3/97[a]
$PhCH_2O(CH_2)_3$	3-OCH_3	91	20/80[b]
$PhCH_2OCH_2$	3-OCH_3	78	11/89[b]

[a]The reaction was performed at −40 °C.
[b]The reaction was performed at 0 °C.



Scheme 101

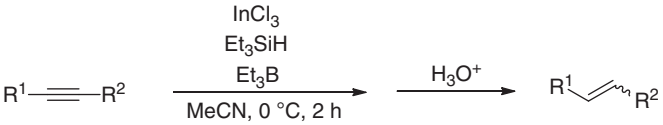
By changing the solvent from acetonitrile to THF, alkynylsilanes are reduced with satisfactory selectivity and yield (Table 27). Arylalkynylsilanes are converted into vinylsilanes with very good selectivity in contrast to aliphatic alkynylsilanes, which give a mixture of *E*/*Z* alkenes and alkyltrimethylsilanes (Table 27).



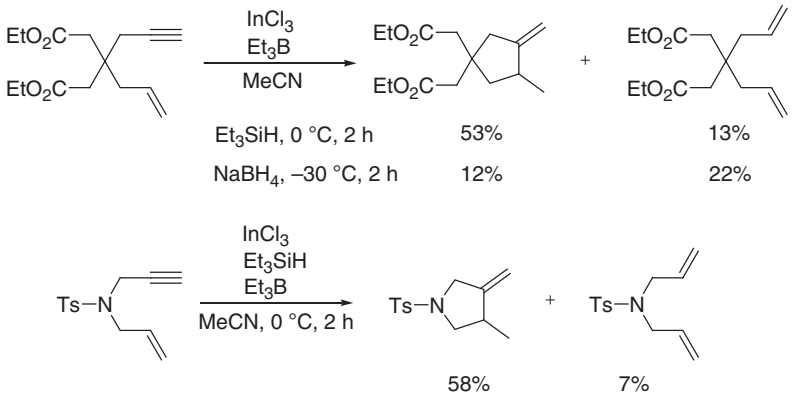
1. Removal of THF; 2. Et_2O; 3. DMSO; 4. 0.50 equivalent Et_3B

Scheme 102

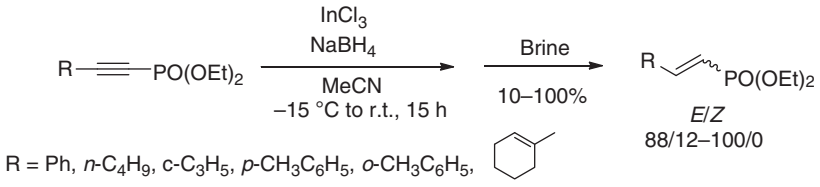
Table 26 Reduction of alkynes with $InCl_3/Et_3SiH$



R^1	R^2	% Yield	E/Z
Ph	H	90	–
n-$C_{10}H_{21}$	H	59	–
$PhOCH_2$	H	70	–
Ph	Ph	77	86/14
Ph	CO_2Et	68	96/4

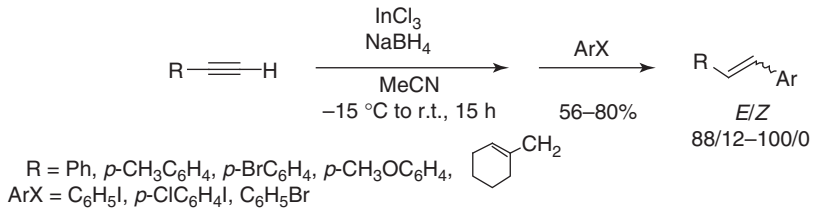


Scheme 103



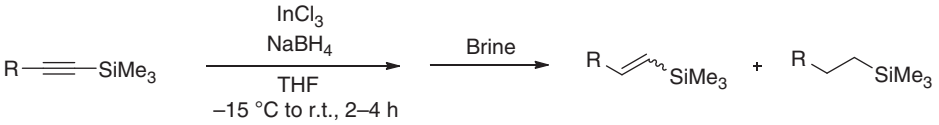
Scheme 104

The $InCl_3$–$NaBH_4$–MeCN system is also used in the hydroindation of aryl terminal alkynes affording vinylindiums that can undergo a highly regio- and stereoselective cross-coupling reaction with diaryliodonium salts (Scheme 106).[555] The reaction is a complementary method to previously reported procedures involving aryl iodides and a palladium catalyst for the cross-coupling reaction that selectively gives (*Z*)-alkenes.[536,547]

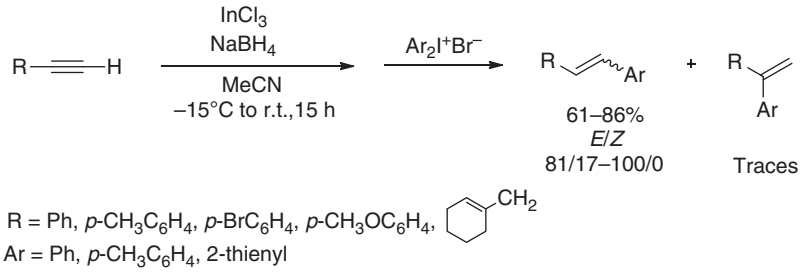


Scheme 105

Table 27 Reduction of alkynylsilanes with $InCl_3/NaBH_4$

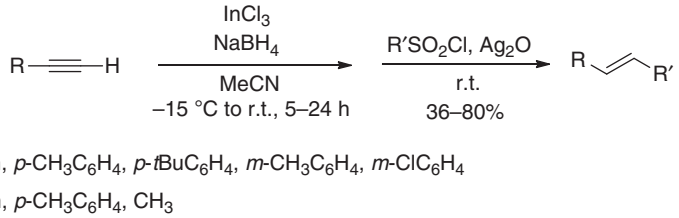


R	*% Yield*	*E/Z/alkane*
Ph	92	90/5/5
p-$CH_3C_6H_4$	70	70/5/25
p-FC_6H_4	88	88/5/7
p-BrC_6H_4	94	95/2/3
p-ClC_6H_4	93	90/4/6
n-C_4H_9	Mixture	3/1/4
n-C_5H_{11}	Mixture	3/1/3



Scheme 106

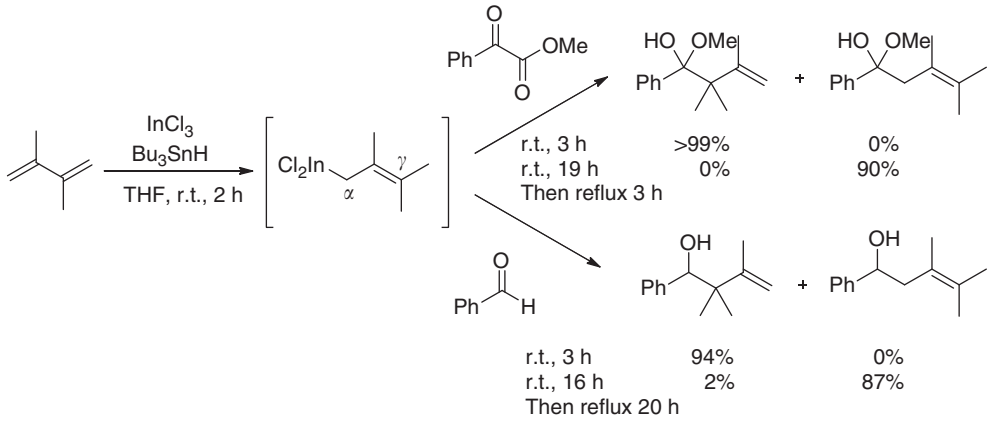
Vinylindiums generated from terminal alkynes and $InCl_3$–$NaBH_4$ in acetonitrile react with sulfonyl chlorides providing vinyl sulfones.[556] The nucleophilic substitution reaction is performed in the presence of Ag_2O promoting the chloride substitution. Aryl alkynes give satisfactory yields and excellent *E*-selectivity, whereas the aliphatic terminal alkynes do not react (Scheme 107).



Scheme 107

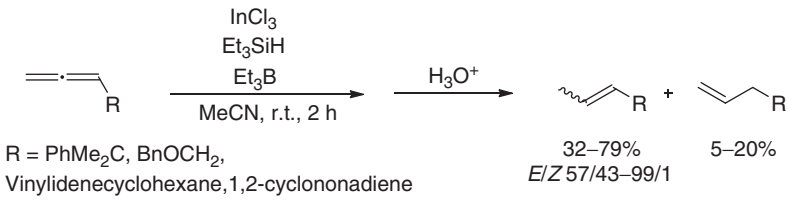
8.24.4.3 Dienes and Allenes

1,3-Dienes are another group of compounds undergoing the hydroindation reaction. The addition of dichloroindium hydride generates an allylic indium that reacts with aldehydes, ketones, diketones, ketoesters, and imines in a one-pot allylation.[557,558] Thus, dichloroindium hydride, generated from $InCl_3/Bu_3SnH$, undergoes the 1,4-radical addition to 2,3-dimethyl-1,3-butadiene, isoprene, and 1,3-butadiene to furnish substituted allylic indiums. The selectivity of the subsequent allylation reaction strongly depends on the reaction conditions. If the reaction is performed at room temperature, the γ-allylation products are formed predominantly. When the reaction is carried out at room temperature and then at reflux, the α-addition product is obtained as the major product (Scheme 108). In this reaction system, the retroreaction is easily promoted by heating to achieve the transformation of the γ-adduct into thermodynamically stable α-adduct.

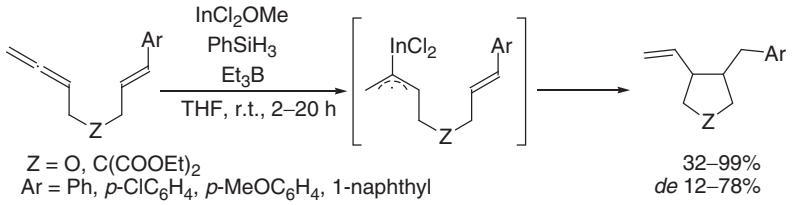


Scheme 108

Hydroindation of allenes provides the vinylic indium species which can be hydrolyzed to alkenes in good yields (Scheme 109).[559] The hydroindation is highly regioselective, placing indium at the central carbon atom of the allene, as confirmed by quenching the reaction mixture with iodine. The cyclization of 1,2,7-trienes (allenenes) by $HInCl_2$ proceeds with high regioselectivity to afford a variety of cyclic compounds (Scheme 110). Very slow generation of dichloroindium hydride from $InCl_2OMe/PhSiH_3$ is crucial for good yields. This system has an advantage over $InCl_3$–Et_3SiH because a strong Lewis acid is not formed during the generation of $HInCl_2$.



Scheme 109



Scheme 110

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8.25 Hydrometallation Group 4 (Si, Sn, Ge, and Pb)

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Glossary

Hydrogermylation The addition of H–Ge, i.e., a hydrogen and a germanium-containing group across a multiple bond, such as an alkyne, alkene, or carbonyl group.

Hydroplumbation The addition of H–Pb, i.e., a hydrogen and a lead-containing group across a multiple bond, such as an alkyne or alkene.

Hydrosilylation The addition of H–Si, i.e., a hydrogen and a silicon-containing group across a multiple bond, such as an alkyne, alkene, or carbonyl group.

Hydrostannylation The addition of H–Sn, i.e., a hydrogen and a tin-containing group across a multiple bond, such as an alkyne, alkene, or carbonyl group.

 doi:10.1016/B978-0-08-097742-3.00827-2

8.25.1 Introduction

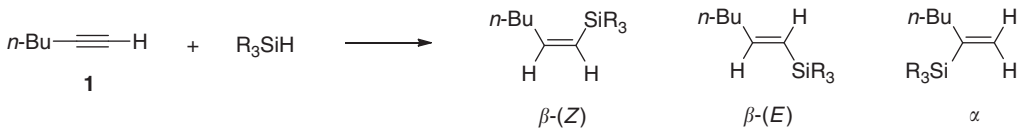
This chapter will discuss the addition reactions of the hydrides of the Group IV elements to carbon–carbon double and triple bonds. Although there is no corresponding chapter in the first edition of Comprehensive Organic Synthesis, the material presented here will follow on from Chapters 3.9 and 3.12 and the reader is referred back to these.

8.25.2 Hydrosilylation

8.25.2.1 Introduction

The addition of hydrosilanes to alkenes and alkynes is called hydrosilylation, a reaction that was discovered when a mixture of L-octene and trichlorosilane was heated in the presence of diacetyl peroxide. This reaction is particularly useful for the synthesis of organosilicon compounds. Since then, a variety of catalysts and conditions have been reported. The characteristic features and applications of the reactions are discussed in this chapter. A review of the synthesis of silicon-containing compounds via Lewis acid-catalyzed reactions has been published.[1] Reactions of organosilanes and organogermanes have developed as popular alternatives to the Stille and Suzuki reactions for Pd-catalyzed cross-coupling reactions. Their use has been reviewed.[2] Si-C coupling reaction of hydrosilanes with activated organic compounds have also been reviewed.[3]

Before discussing hydrosilylation or the related reactions covered in this chapter, it is worth mentioning the nomenclature associated with the adducts obtained; this is illustrated in the example below the hydrosilylation of 1-hexyne **1**, where it is possible to obtain three isomeric products: β-(*E*), β-(*Z*), and α (Scheme 1). The selectivity of the hydrosilylation/stannylation reactions is briefed as follows.



Scheme 1

8.25.2.1.1 Hydrosilanes available

Many hydrosilanes are now commercially available from all the leading suppliers and are too numerous to list here.

8.25.2.1.2 Theoretical and mechanistic aspects

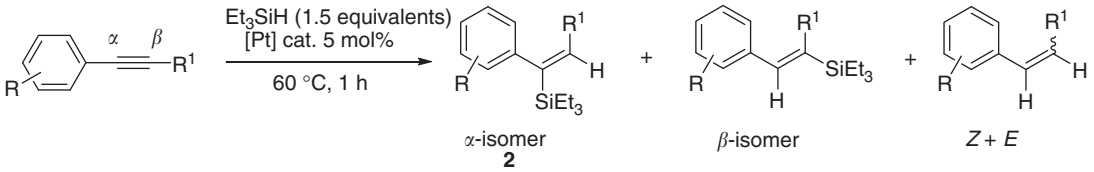
A detailed review of the reactivity of the metal–silicon bond in organometallic chemistry has been published.[4] Carbene complexes of the type M=E (E=Si or Ge) have been reported with hydrogen atoms on both the metal center and the E atom. These readily undergo hydrosilylation and hydrogermylation reactions, as well as reaction with nitriles, ketones, and heterocumulenes.[5]

Lewis has studied the relative rates of platinum-catalyzed hydrosilylation of terminal olefins versus internal alkynes in competitive reactions. $(EtO)_3SiH$ added almost exclusively (97%) to PhC=CPh rather than styrene. With equimolar amounts of 2-decyne and 1-hexene, it gave a 78:22 ratio of alkyne products to alkene products. Its reaction with equimolar amounts of styrene and 1-phenyl-1-propyne gave a 78:22 ratio of alkyne products to alkene ones. The silane, $Me_3SiOSiMe_2H$ reacted with equimolar amounts of 2-decyne and 1-hexene to give a 90:10 ratio of alkyne products to alkene products. All of the products had *E* stereochemistry about the C=C double bond.[6]

The mechanisms and kinetics of the hydrosilylation of phenylacetylene by iridium complexes including [Ir(COD)(η^2-^{i}Pr$_2$PCH$_2$CH$_2$OMe)][BF_4] have studied.[7] Alkyne hydrosilylation has been examined in detail for the catalysts [IrH(H_2O)(bq)L_2]SbF_6 (L=PPh_3, bq=7,8-benzoquinolinato) and $RhCl(PPh_3)_3$. In addition to the expected products, two unusual products are reported, namely the dehydrogenative silation product RC=CSiR_3, formed by β-elimination from a vinylmetal intermediate, and secondly allylsilane products of vinylsilane isomerization. The iridium catalyst is advantageous in that it does not give fast vinylsilane isomerization cf $RhCl(PPh_3)_3$, thus allowing formation and isolation of the thermodynamically less stable *cis* rather than the more stable *trans*-vinylsilane isomer RCH=CH(SiR_3').[8]

The photoactivated hydrosilylation of alkynes has been reported, involving irradiation at λ=350 nm and a platinum(II) bis (acetylacetonato) catalyst.[9] Ozawa has studied the crossover in selectivity (*E*/*Z*) with substrate and terminal alkynes for ruthenium-catalyzed hydrosilylation.[10]

A detailed investigation of the platinum-catalyzed hydrosilylation of internal arylalkynes has demonstrated that the position of substituents on the aromatic ring can influence regioselectivity (Scheme 2).[11] On addition of triethylsilane to the triple bond, an *ortho*-substituent in arylalkylalkynes and diarylalkynes always gave the α-isomer **2** regardless of the electronic nature (π-electron withdrawing or σ-electron donating) of the substituent. Both H_2PtCl_6 and, for the first time, PtO_2 were efficient catalysts for the hydrosilylation reaction.



R = CO_2Et, R^1 = n-C_5H_{11}
[Pt] cat. = H_2PtCl_6, Pt $(PPh_3)_4$, Pt/C, PtO_2

Scheme 2

There is evidence for the intermediacy of colloids in hydrosilylation reactions involving Karstedt's catalyst (Pt[(vinyl) $Me_2SiOSiMe_2$(vinyl)]).[12]

The hydrosilylation of deuterated acetylene with triethoxysilane[13] is important because the hydrosilylation may be directed to be either *cis* or *trans*, by the use of an appropriate metal catalyst, thus permitting selective D labeling. The hydrosilylation of non-1-ene with phenylsilane in the presence of yttrium and lutetium bisguanidinate hydride complexes[14] is first order in olefin and zero order in phenylsilane, indicating that the insertion of non-1-ene into the Ln–H bond is the rate-determining stage of the process. The current mechanism of asymmetric induction in catalytic hydrogenation, hydrosilylation, and cross-coupling reactions on metal complexes has been reviewed.[15]

8.25.2.2 Hydrosilylation of Carbon–Carbon Triple Bonds

A number of excellent reviews have appeared covering both alkyne hydrosilylation reactions[16,17] and methods for preparing vinylsilanes from alkynes. A comprehensive review of iron-catalyzed hydrosilylation reactions has been published.[18] Anderson has published a comprehensive review on the synthesis of vinylsilanes, including many examples involving hydrosilylation reactions of alkynes.[19] Trost has reviewed the addition of metalloid hydrides to alkynes, with particular emphasis on boron, silicon and tin.[20] Yi has published a short review/summary of his own group's work on regio- and stereoselective hydrosilylation and oxidative silylation of alkenes and alkynes.[21] Treatment of terminal alkynes with $HSiEt_3$ in the presence of $(PCy_3)_2(CO)RuHCl$ gave the *cis*-alkenes, whereas dehydrosilylation of α-olefins under the same conditions gave the *trans*-vinylsilane. A review has been published on the preparation and applications of heterogenous catalysts for hydrosilylation reactions[22] and solid-phase hydrosilylation reactions with the participation of modified silica surfaces have been reviewed.[23]

There have been many reports of novel catalysts being developed for the hydrosilylation of alkynes; some are described in detail in this section, whereas others will simply be listed here. For example, using $AlCl_3$/hydropolysilanes[24] including for the cyclization of 1,6-heptadiyne; ethyl aluminum dichloride and diethyl aluminum chloride are efficient Lewis acids for the regioselective hydrosilylation of propiolate esters with tris(trimethylsilyl)silane giving β-silicon substituted Z-alkenes;[25] lithium aluminum hydride for dehydrogenative coupling reactions;[26] *N*-heterocyclic carbene complexes of zero-valent platinum divinyltetramethyldisiloxane (for alkynes, alkenes, ketones, and α,β-unsaturated ketones) giving in the former cases high selectivity for the 1-functionalized product;[27] iron(0) dinitrogen (^{iPr}PDI)Fe$(N_2)_2$ and silane complexes;[28] rhodium(I) complexes with hemilabile *N*-heterocyclic carbenes gave predominantly β-(*Z*)-vinylsilanes with 1-hexyne and β-(*E*) and α-bis(silyl)alkenes with trimethylsilylacetylene;[29] silver and platinum complexes of *N*,*C*-chelating oxazole-carbene ligands;[30] using [$Cp^*Ru(MeCN)_3$] PF_6;[31–35] diphosphinidenecyclobutene ruthenium complexes $[RuCl(\mu\text{-}Cl)(CO)(DPCB\text{-}OMe)]_2$ and $[RuH(\mu\text{-}Cl)(CO)(DPCB\text{-}OMe)]_2$[36] for both Ru–C and H–Si metathesis and hydrosilylation of terminal alkynes; one example of solvated gold atoms being used to catalyze the hydrosilylation of 1-hexyne, giving primarily β-(*E*) products;[37,38] organoyttrium complexes such as $Cp^*_2YCH_3$·THF.[39] Although the majority of transition metal-catalyzed hydrometalations and carbometalations proceed in a *cis* manner, the Lewis acid promoted reactions tend to proceed in a *trans* manner, as reported by Yamamoto: hydrosilylation, hydrostannylation, carbosilylation, and carbostannylation or unactivated alkynes with organosilanes or organostannanes all gave the *trans*-vinylsilyl or vinylstannyl compounds.[40]

A detailed study of the catalytic hydrosilylation of acetylenes mediated by phosphine complexes of cobalt(I), rhodium(I), and iridium(I) has been reported by Field and has demonstrated that complexes including $[Co(PPh_3)_3Cl]$, $[Co(PPh_3)_2(CO)_2Cl]$, $[Co(PMe_3)_3Cl]$, $[Co(PMe_3)_2(CO)_2Cl]$, [Rh(dppe)(CO)Cl], $[Rh(PPh_2Me)_2(CO)Cl]$, [Ir(dppe)(CO)Br], and $[Ir(PPh_2Me)_2(CO)Cl]$ all catalyze the hydrosilylation of a number of alkynes including 1-hexyne, phenylacetylene, and 1-phenyl-1-propyne with triethylsilane.[41] Iridium complexes including $[Ir(COD)(\eta^2\text{-}^iPr_2PCH_2CH_2OMe)][BF_4]$ have also been studied for the hydrosilylation of phenylacetylene.[7] Rhodium(III) and iridium(III) complexes of Tröger's base (TB) have been prepared by reaction of TB with MCl_3 (M = Rh or Ir) and the rhodium complex found to be a highly regio- and stereoselective catalyst for the hydrosilylation of alkynes.[42]

Eisen has started to report the use of organoactinide metal complexes in dimerization and hydrosilylation reactions of terminal alkynes.[43–45] The cationic actinide complex $[(Et_2N)_3U][BPh_4]$ was reported as an active catalyst precursor for the dimerization of terminal alkynes. Furthermore, in the presence of $PhSiH_3$, the complex promoted the hydrosilylation of terminal alkynes, albeit producing a myriad of products depending on the nature of the alkene, the solvent, and reaction temperature.[45] An intermediate

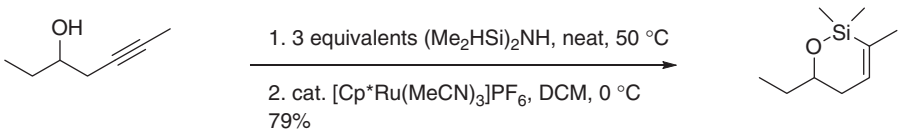
uranium-hydride complex is proposed. The same authors reported $Cp^*_2AnMe_2$ (An = Th or U) also as efficient hydrosilylation catalysts for terminal alkynes.[44] Organothorium complexes have also been reported and studied in hydrosilylation reactions.[43]

8.25.2.2.1 Hydrosilylation of ethyne

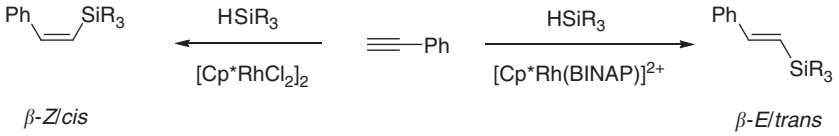
The vapor-phase hydrosilylation of acetylene with trichlorosilane or trimethoxysilane using a tetraammineplatinum(II) chloride catalyst in polyethylene glycol medium supported on silica gel has been reported.[46] The insertion of ethyne into the Ru–Si bond of coordinatively unsaturated ruthenium silyl complexes has been reported by Roper, including the crystal structures of several adducts.[47] Reaction of $Mes_2Si(F)H$ with ethyne in the presence of H_2PtCl_6 gives dimesitylvinylfluorosilane $Mes_2Si(F)CH=CH_2$, which on reaction with *tert*-butyllithium gives a highly stable silene, dimesitylneopentylsilene, $Mes_2Si=CHCH_2{}^tBu$.[48]

8.25.2.2.2 Hydrosilylation of monosubstituted alkynes

Trost has widely studied and applied the ruthenium-catalyzed hydrosilylation of alkynes. The cationic complex $[Cp^*Ru(MeCN)_3]PF_6$ catalyzed the hydrosilylation of numerous alkynes:[31,34] terminal alkynes afforded the α-vinylsilane product via *trans*-addition; the same complex also gave *trans*-addition with internal alkynes. Propargylic alcohols and α,β-alkynyl carbonyl compounds gave regioselective vinylsilane formation. An order of reactivity for the silanes was reported as $SiEt_3 \approx SiMe_2Cl > SiMe_2OR \approx Si(OR)_3 > SiMe_2Bn \approx SiMe_2Ph$. The authors have performed a theoretical study, using density functional calculations – the B3LYP method with 6–31 G* basis set (for C, H, N, and O atoms) and Lanl2dz basis set and ECP for Si and Ru atoms – to understand the *anti*-addition stereochemistry and Markovnikov regiochemistry of the hydrosilylation of terminal alkynes and the *endo*-dig product of intramolecular hydrosilylation of homopropargylic alcohols, all catalyzed by the same $[Cp^*Ru(MeCN)_3]PF_6$ catalyst.[49] Markovnikov alkyne hydrosilylation is catalyzed by the same ruthenium complexes.[31] The same group have also utilized the vinylsilanes produced in the reaction as a masked form of α-hydroxyketones. Thus internal alkynes bearing either propargylic, homopropargylic, or bishomopropargylic hydroxyl groups undergo regioselective hydrosilylation catalyzed by $[Cp^*Ru(MeCN)_3]PF_6$ to give vinylsilanes which may subsequently be oxidized to a ketone.[35] This masking approach has also been used in 'synthetic stitching with silicon': geminal alkylation-hydroxylation of alkynyl carbonyl compounds to give β-carbonyl-substituted tertiary alcohols.[33] The catalyst produced regioselective alkyne hydrosilylation by a *trans*-addition process, followed by one-pot C–C bond formation by Si→C migration and subsequent silane oxidation. The same catalyst was used by Trost in a late-stage Ru-catalyzed hydrosilylation as part of a formal synthesis of aspergillide B.[50] Finally, Trost has also investigated the use of the same catalyst in the intramolecular *endo*-dig hydrosilylation of alkynes (**Scheme 3**).[32] Cox has shown that Grubbs' first generation Ru metathesis catalyst efficiently catalyzes the hydrosilylation of terminal alkynes.[51] The product selectivity depended on both reaction concentration and the silane employed: use of Et_3SiH with 1-hexyne gave predominantly the β-(*Z*)-stereoisomer, whereas the bulkier 3,3-dimethylbut-1-yne have the β-(*E*)-product and propargyl alcohol gave the α-stereoisomer (cf $(EtO)_3SiH$, which gave in all cases the α-stereoisomer as the major product). Two complementary Rh catalysts have been reported for the hydrosilylation of phenylacetylene.[52] In the hydrosilylation reaction of triethylsilane, triethoxysilane, or triphenylsilane with phenylacetylene, $[Cp^*RhCl_2]_2$ was found to give predominantly *anti*-addition to the β-*Z*-isomer, whereas $[Cp^*Rh(BINAP)](SbF_6)_2$ added in the *syn* manner to form the β-*E*-isomer. An inorganic-organic hybrid mesoporous material incorporating organoruthenium complexes within its organosilica framework (HMM-phRuCpPF_6) has been reported as a unique heterogenous catalyst for hydrosilylation, and in the case of 1-hexyne produced α-vinylsilane at elevated temperatures.[53] With the exception of the cationic $[Cp^*Ru(MeCN)_3]PF_6$ catalyst and also $Cp^*RuH(PPh_3)$, which both afford selectively α-vinylsilanes, there is only a handful of other examples of methods for the preparation of the Markovnikov product with Ru catalysis. Cossy has developed several ruthenium-alkylidene complexes for just this outcome.[54] Oro has reported *trans*-additions of silanes to 1-alkynes by ruthenium complexes and investigated the role of *in situ* formed polynuclear aggregates.[55] Faller has reported various Cp*Rh complexes, including $[Cp^*RhCl_2]_2$ and $[Cp^*Rh(BINAP)](SbF_6)_2$ as effective catalysts for the hydrosilylation of phenylacetylene with triethylsilane, triethoxysilane, and triphenylsilane.[52] The former was selective for the β-(*Z*)-isomer, whereas the latter gave the β-(*E*) isomer (**Scheme 4**).



Scheme 3



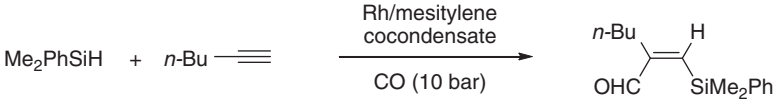
Scheme 4

The $RhCl(PPh_3)_3$-catalyzed hydrosilylation of phenylacetylene and styrene with phenylsilanes (Ph_2SiH_2 and $PhSiH_3$) has been reported by Osakada and proceeds in THF in high yields, giving primarily $PhSiH_2(CH{=}CHPh)$ from phenylacetylene and $Ph_2SiH(CH_2CH_2Ph)$ (from styrene).[56] A $(Rh(COD)Cl)_2$ catalyst has given high stereoselectivity in the hydrosilylation of alk-1-ynes giving either the *E*- or the *Z*-vinylsilane depending on the conditions. Using the catalyst in ethanol or DMF as a solvent gave *Z*-selective reactions, whereas the same catalyst with additional PPh_3 and using acetonitrile as a solvent gave *E*-selective reactions.[57] A follow-up paper from the same group demonstrated that *E*-vinylsilanes could be obtained with high selectivity using $Rh(COD)_2BF_4$/$2PPh_3$-catalyzed hydrosilylation of 1-alkynes and alkenes with triethylsilane.[58]

Oshima has developed a rhodium-catalyzed hydrosilylation of alkynes in an aqueous micellar system, combining $[RhCl(nbd)]_2$ and sodium dodecylsulfate (SDS). Although the rhodium chloride dimer is insoluble in water, in combination with SDS formed a homogenous solution. Addition of dppp favored (*E*)-selective hydrosilylation while adding NaI gave predominantly the (*Z*)-product.[59]

A number of reports have started to emerge involving rhodium complexes with *N*-heterocyclic carbenes. For example, Jimenez has reported a series of alkylammonium-imidazolium chloride salts as precursors for a library of rhodium(I) complexes with hemilabile character by varying the substituent on the heterocyclic ring and the length of the linker with the dimethylamino moiety. The rhodium complexes were good hydrosilylation catalysts for terminal alkynes using $HSiMe_2Ph$. Excellent selectivities were found in the β-(*Z*)-vinylsilane with 1-hexyne and β-(*E*) and α-bis(silyl)alkene isomers with trimethylsilylacetylene.[29] Rhodium complexes of $PC^{NHC}P$ have been prepared from the silver transfer reagent $[Ag_3(PC^{NHC}P)_2Cl]Cl_2$ and $[Rh(COD)Cl]_2$; these novel complexes catalyzed the hydrosilylation of alkynes and showed excellent selectivity for (*E*)-alkenylsilanes.[60] Mazzoni has also repeated an in-depth study of *N*-heterocyclic carbene-amide rhodium(I) complexes.[61] Their catalysts led only to the formation of the β-(*E*)-vinylsilane and α-bis(silyl)alkene isomers. Rhodium(III) complexes with monoanionic C,C,C-tridentate dicarbene ligands activate Si–H bonds and also further catalyze the hydrolysis of hydrosilanes to form silanols and siloxanes; in the presence of alkenes rapid hydrosilylation occurred, whereas carbonyl groups were unaffected.[62] Fluorinated *N*-heterocyclic carbene rhodium(I) complexes have been used in the hydrosilylation of propargylic alcohols.[63]

Although strictly not hydrosilylation, a number of related and relevant silylformylation reactions of alkynes have been reported. Ojima has published a detailed investigation of the $Rh_2Co_2(CO)_{12}$-catalyzed silylformylation of terminal alkynes.[64,65] Solvated rhodium atoms – prepared by metal vapor synthesis technique – have been shown to promote the silylformylation reaction of terminal alkynes with excellent chemoselectivity (for silylformylation rather than hydrosilylation) and giving exclusively *Z*-silylalkenals (Scheme 5).[66] The tetracationic complex $[Rh_2(MeCN)_2(Naft)_4](BF_4)_4$ (where Naft = μ–1,8-naphthyridine) is an efficient catalyst for the silylformylation of internal and functionalized alkynes.[67] Matsuda has reported an efficient silylformylation of alkynes (internal and terminal) catalyzed by $Rh_4(CO)_{12}$[68] and has also published detailed mechanistic studies on the rhodium-catalyzed silylformylation reaction of alkynes.[69]



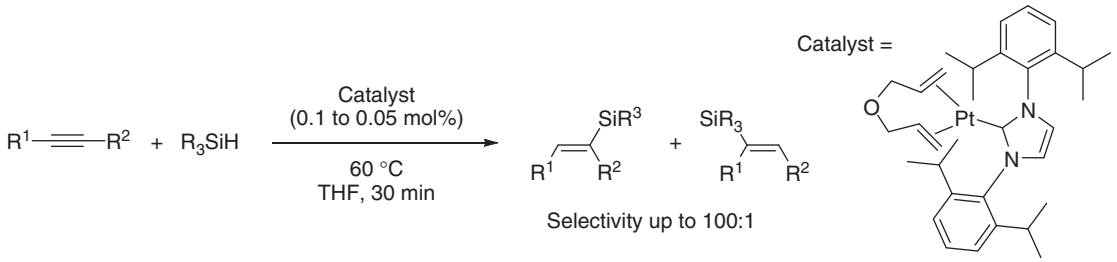
Scheme 5

Many platinum catalysts have been developed for hydrosilylation reactions of alkynes, including: platinum on titania;[70] platinum complexes synthesized with polydentate *N*-heterocyclic carbenes for hydrosilylation phenylacetylene and *p*-tolylacetylene;[71] a tetraammineplatinum(II) chloride catalyst in polyethylene glycol medium supported on silica gel for vapor-phase hydrosilylation of acetylene with trichlorosilane or trimethoxysilane;[46] $PtCl_2$/XPhos for the hydrosilylation of propargylic alcohols;[72] a platinum/mesitylene solution (i.e., solvated Pt atoms) for the stereo- and regioselective functionalization of propargylic alcohols via intramolecular hydrosilylation;[73] platina-β-diketones as catalysts for the hydrosilylation of alkenes and alkynes;[74] platinum on titania;[70] the Karstedt catalyst;[75] Pt(II) mono- and biscarbene complexes formed by reaction of imidazolium; and benzimidazolium halides with $PtBr_2$ and/or PtI_2.[76] Unusually, the α-addition products are greatly favored (rather than the *trans*-β-addition) in the chloroplatinic acid-catalyzed hydrosilylation of terminal acetylenes catalyzed by $(\eta^5\text{-}C_5H_5)Fe(CO)_2SiPh_2H$ when the reaction is performed in the presence of CO.[77] Platinum on carbon has been shown to be a cheap and efficient catalyst for the hydrosilylation of alkynes under mild conditions. High-resolution electron microscopy showed that colloidal Pt is formed during the reaction. Excellent yields were obtained, with chlorosilanes usually producing one vinylsilane, whereas alkoxysilanes and alkylsilanes usually yielded a mixture of two or more isomeric vinylsilanes.[78] Bulky phosphabarrelene ligands act as very efficient ligands in the Pt(0)-catalyzed hydrosilylation of terminal alkynes, using $[(COD)PtCl_2]$ as the Pt source and give excellent β(E) selectivity.[79]

Markó has reported a highly β-(*E*)-selective hydrosilylation of both terminal and internal alkynes catalyzed by a novel (IPr)Pt(AE) diene complex X (IPr = bis(2,6-diisopropylphenyl)imidazo-2-ylidene; AE = allyl ether) (Scheme 6).[80] They have also reported the same reaction catalyzed by *N*-heterocyclic carbene platinum(0) complexes, including [Pt(*N*,*N*′-dicyclohexylimidazol-2-ylidene)(η^2-dimethylacetylenedicarboxylate)$_2$].[81]

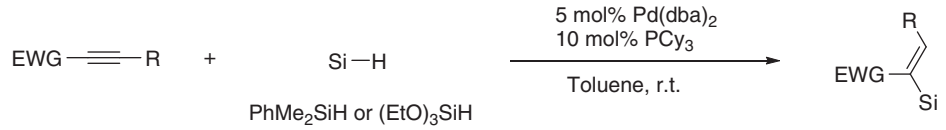
A more unusual example is the photoactivated hydrosilylation of alkynes, involving irradiation at $\lambda = 350$ nm and a platinum(II) bis(acetylacetonato) catalyst.[9]

Park has demonstrated that palladium nitrate catalyzes the *anti*-hydrosilylation reaction of terminal alkynes to give predominantly the thermodynamically less stable *cis* isomers, together with low quantities of dialkynylated silanes.[82] The palladium-catalyzed



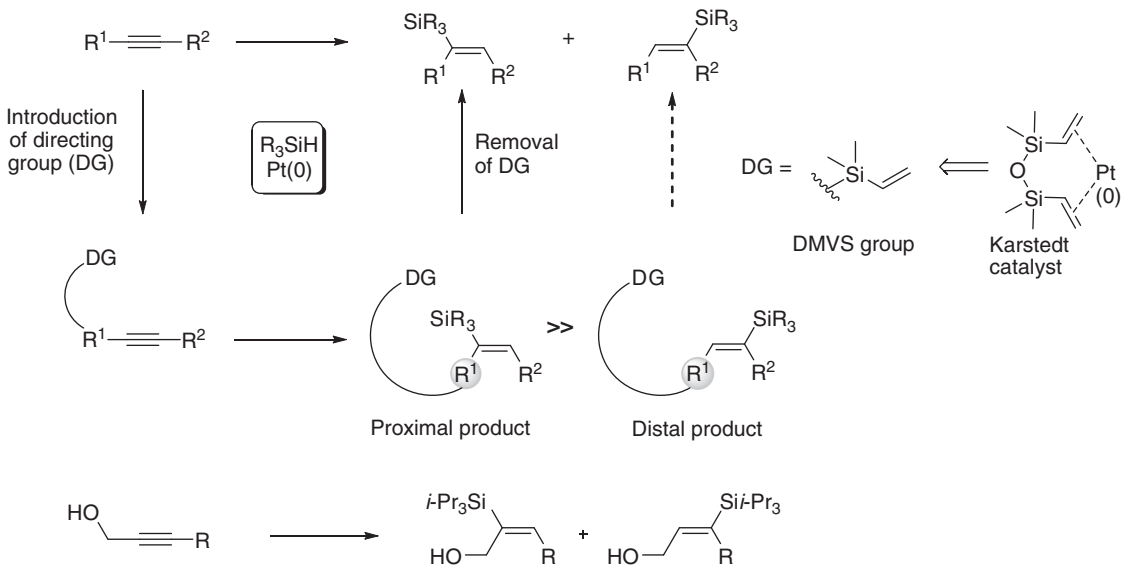
Scheme 6

regio- and stereoselective hydrosilylation of electron-deficient alkynes has been described by Hosoya.[83] A variety of silyl groups were introduced to the alkynes bearing a single electron-withdrawing group using $Pd(dba)_2/PCy_3$ (Scheme 7). The product α-silylalkenes were utilized in both Hiyama couplings (with retention of configuration) and stereoinverting iododesilylation/Suzuki–Miyaura coupling reactions. The electron-rich Pd(0) complex $Pd_2(dba)_3$ $CHCl_3$-tricyclohexylphosphine catalyzes a highly efficient hydrosilylation of alkynes at room temperature with Ph_3SiH or Ph_2MeSiH in the absence of a solvent. The regioselectivity was higher than that with the corresponding conventional Pt(0)-catalyzed hydrosilylation.[84] Palladium(0) complexes obtained *in situ* from $½[(\eta^3\text{-}C_3H_5)PdCl]_2$ and $P(OAr)_3$ catalyze the hydrosilation of 1-alkynes with $HSiCl_3$ at room temperature giving 1,3-dienylsilane derivatives in which alkyne dimerization accompanies hydrosilation. The head-to-tail adduct, R–CH=CH–C(R)=$CHSiCl_3$ predominates over other regioisomers.[85] Tomooka has employed a dimethylvinylsilyl (DMVS) directing group – a substructure of the Karstedt catalyst – in the Pt(0)-catalyzed hydrosilylation of unsymmetrical alkynes to afford a single silylalkene regioisomer from proparglyic and homopropargylic alcohols.[86] The reaction pathway was studied by density functional theory (DFT). The *E*-silylalkenes produced are utilized in the synthesis of multisubstituted alkenes and oxy-functionalized compounds. The principle of Tomooka's approach is presented in Scheme 8.



EWG = EtO(CO), MeO(CO), Me(CO), Ph(CO), CHO, $Me_2N(CO)$, *p*-Tol(SO_2)
R = Me, Ph, TMS, OTBS, alkyl, $(CH_2)_3C(CH)$
Time = 0.5–16 h
Yield range: 42–99%

Scheme 7



Scheme 8

Mixed metals complexes have also been employed in alkyne hydrosilylation reactions, including cobalt-rhodium $Co_2Rh_2(CO)_{12}$ and $Co_3Rh(CO)_{12}$ (both giving *cis*-1-triethylsilyl-1-hexene as the major product from the hydrosilylation of 1-hexyne with triethylsilane);[87] a homologous series of catalysts of general formula $MPt_2(CO)_5(PPh_3)_2(PhC_2Ph)$ where M = Fe, Ru, or Os has been investigated mechanistically for its ability to catalyze the hydrosilylation of diphenylacetylene with triethylsilane.[88]

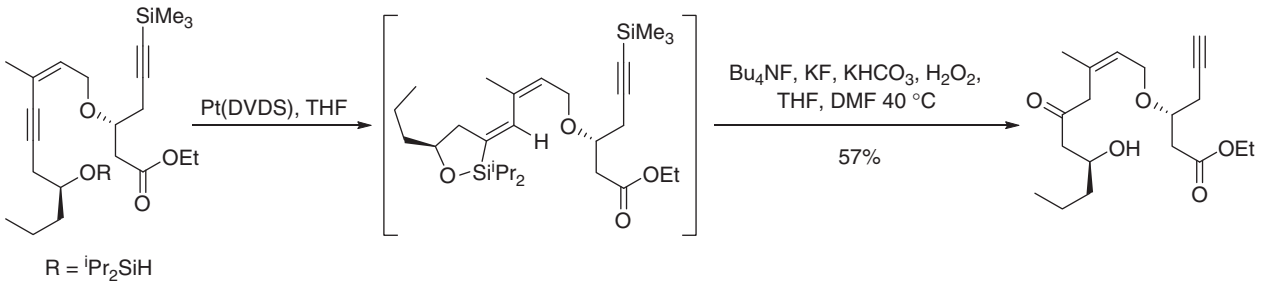
The preparation and reactions of pentafluorophenyldimethylvinylsilanes have been developed, providing a convenient and robust method for the diversity-orientated synthesis of *E*-, *Z*-, and *α*-disubstituted alkenes, all starting from terminal alkynes. The pentafluorophenyldimethylvinylsilanes were shown to be an attractive alternative to existing masked silanols[89] and have been utilized in cross-coupling reactions.[90]

Ab initio Car–Parrinello simulations have been employed to help determine the mechanism of grafting of phenylacetylene on the crystalline, hydrogenated surfaces of silicon catalyzed by the Lewis acid aluminum trichloride.[91]

A unique white-light promoted hydrosilylation reaction of alkenes and terminal alkynes has been studied in detail, using photoluminescent nanocrystalline (porous) silicon.[92] It is claimed to be one of the safest methods for hydrosilylation. Features of the reaction included no significant loss of the photoemissive qualities of the material and its quenching both by charge-transfer and energy-transfer complexes (but not by radical spin traps).

8.25.2.2.3 Hydrosilylation of disubstituted alkynes

The overall transformation of alkyne hydration has been achieved by Floreancig by combining intramolecular alkyne silylation using Pt(DVDS) (DVDS = divinyl dimethyldisoloxane) and Tamao oxidation (Scheme 9).[93]



Scheme 9

The stereoselective synthesis of *α*-silylenones has been achieved through $PtCl_2$ catalysis.[94] *α*-Hydroxypropargylsilanes react, via alkyne activation, to give *Z*-silylenones through a highly selective silicon-migration process, whereas the complementary *E*-silylenones were obtained via regioselective hydrosilylation of the appropriate ynone precursor.[94] The hydrosilylation of internal alkynes has also been studied under the same catalytic conditions, with the regioselectivity being governed primarily by electronic effects (Scheme 10).[94,95]

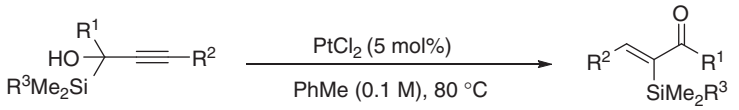
Molander has reported that the organoyttrium complex $Cp^*_2YCH_3.THF$ is an effective precatalyst for the hydrosilylation of internal alkynes.[39] Symmetrical alkynes gave the single *cis*-addition hydrosilylation product, whereas nonsymmetrical alkynes gave the silane-addition product to the least hindered carbon of the alkyne. The reaction tolerated a wide range of functional groups elsewhere in the alkyne (halides, amines, protected alcohols, and olefins). The same group has subsequently shown that the catalyst may be employed for the selective sequential cyclization/silylation of 1,6- and 1,7-enynes (Scheme 11).[96,97] Nitrogen-containing enynes have been cyclized to azabicycles using the same catalyst or the lutetium equivalent in high yields and good-to-excellent diastereoselectivity.[98] Roesky has reported bis(phosphinimino)methanide rare earth (Y, La, Sm, Ho, Lu) amides catalyze hydrosilylation and sequential hydroamination/hydrosilylation reactions of both alkenes and alkynes.[99]

A highly efficient and broad substrate alkyne hydrosilylation reaction has been reported involving Ni(0) complexes of *N*-heterocyclic carbenes.[100] The variable regioselectivity of the process depended on the structure of the alkyne, silane, and *N*-heterocyclic carbene ligand. Berding has also developed nickel(II) dihalide complexes with small monodentate *N*-heterocyclic carbene ligands as catalysts for hydrosilylation reactions of internal alkynes; the nickel(0) active species being generated from the complex using diethylzinc.[101] Silicon (II) hydride-stabilized $Ni(CO)_3$ has also been reported as efficient for the hydrosilylation of diaryl alkynes (Scheme 12).[102]

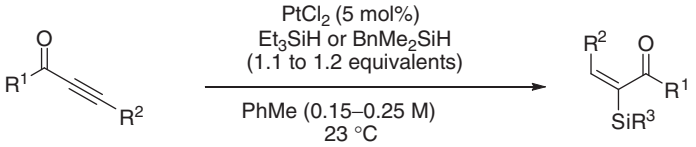
An efficient end-capping method for the preparation of [2]rotaxanes, using acetylene–dicobalt hexacarbonyl complexation has been reported, along with their subsequent transformation into a series of vinylsilanes through hydrosilylation.[103]

8.25.2.2.4 Applications of alkyne hydrosilylation

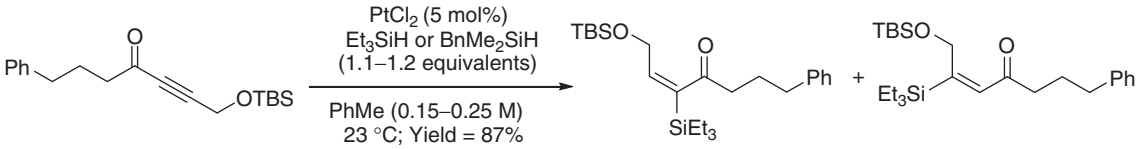
Furstner has reported a highly chemo and stereoselective two-step reduction of cycloalkynes to (*E*)-cycloalkenes via *trans*-selective hydrosilylation followed by a AgF-mediated desilylation (Scheme 13).[104]



R^1 = CH_2CH_2Ph, *n*-Hept, *t*-Bu, homoallyl, $CH_2CH_2CH_2OTBS$, $CH_2CH_2CH_2OAc$, $CH_2CH_2CH_2CO_2NHPh$
R^2 = *n*-Bu, Ph, CH_2OTBS, CH_2OPMB, CH_2OTHP
R^3 = Me, Ph
Yield = 76 to 99%
Z:E = 10:1 to > 19:1



R^1 = CH_2CH_2Ph, *t*-Bu, $CH_2CH_2CH_2OTBS$
R^2 = *n*-Bu
R^3 = Et, Me_2Bn
Yield = 65–99%; *Z:E* = >19:1



α-isomer : β-isomer 2:1

Scheme 10

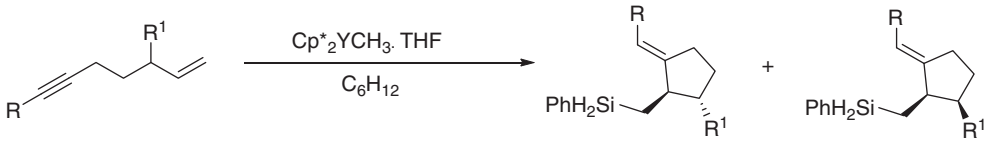
Various (hex-5-ynyl)silanes have been prepared and undergo intramolecular hydrosilylation to give the corresponding 2-methylidene-1-silcyclohexane (Scheme 14).[105] Welker has reported the synthesis of enynyloxy dimethyl and diisopropylsilanes and their conversion into siloxacyclopentenes containing a 1,3-diene moiety via intramolecular hydrosilylation reactions of the alkyne. The products underwent facile Diels–Alder reaction (Scheme 15).[106]

The formal addition of an aryl-H or alkenyl-H bond across a terminal alkyne has been achieved by the combination of platinum-catalyzed hydrosilylation followed by palladium-catalyzed cross-coupling. The catalytic system of *t*-Bu_3P-Pt(DVDS) in combination with tetramethyldisiloxane gave the highest yields and best regio- and stereoselectivity (Scheme 16).[107]

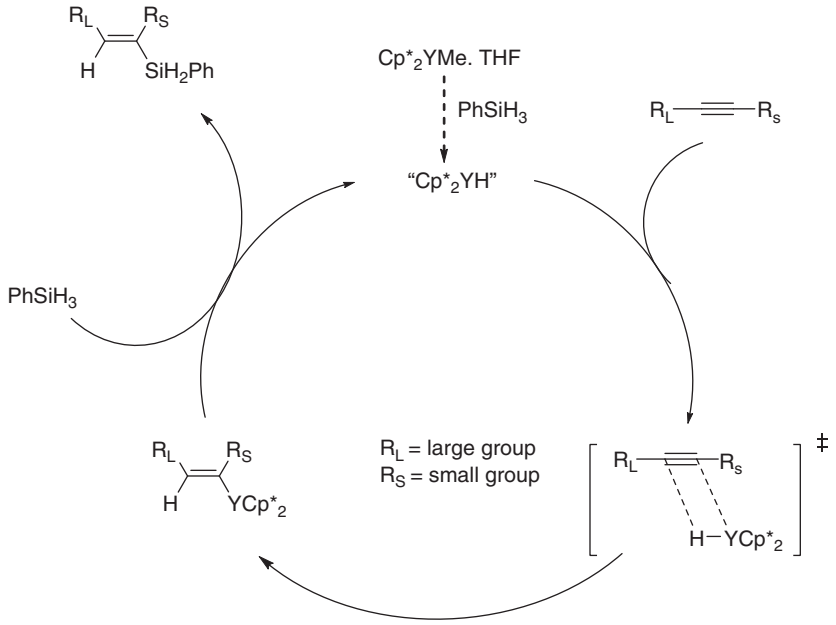
A hydrosilylative cross-coupling reaction of alkynes with several alkenes is catalyzed by cationic palladium complexes without or with an added triphenylphosphine ligand and using $HSiCl_3$.[108] Functionalized 1,6-diynes undergo facile cyclization/hydrosilylation catalyzed by cationic platinum complexes containing bidentate nitrogen ligands (Scheme 17).[109] The palladium complex, $[(\eta^3\text{-}C_3H_5)Pd(cod)]^+[PF_6]^-$, catalyzes the hydrosilylation of 1-dodecene-6,11-diyne and 1-tridecene-6,11-diyne, and their 9-oxo congeners, with $HSiCl_3$ to form regioisomeric cyclization products.[110]

The use of rhodium(I) iodide complexes in the hydrosilylation of terminal alkynes at differential temperatures affords (*Z*)-silanes (room temperature) or (*E*)-silanes (60 °C). The stereodivergent hydrosilylations have been applied to the polyaddition of bifunctional alkynes and silanes to generate silicon-containing polymers – poly(aryleneethylenesilylenes)s.[111] $RhI(PPh_3)_3$ has also been used as a polymerization catalyst to effect the hydrosilylation polymerization of D-(−)-*p*-hydroxyphenylglycine-derived diethynyl monomers with dihydrosilanes to give novel optically active poly(silylenevinylenephenyleneethynylene)s.[112] Rh(I) catalysts have also been immobilized on polyamide supports, but are still able to catalyze the hydrosilylation of alkenes, dienes, and alkynes.[113] The physical characteristics of the immobilized Rh(I) catalyst were studied by WAXS, SAXS, DSC, the nitrogen BET adsorption method, ISEC and pycnometry: catalyst activity was decreased with increasing polymer crystallinity. The presence of 2,5- and 2,6-pyridines in the polymer also affected the *cis/trans* selectivity of the hydrosilylation. Alkyne polymers obtained by radical polymerization of conjugated enynes ($CH_2{=}CH{-}C{\equiv}C{-}R$ where R = Ph or nBu) have been modified by various process, including radical addition of thiol fragments, hydrosilylation, and reduction by hydroalumination to give polymers bearing alkenyl sulfide, alkenylsilane, and alkene moieties.[114]

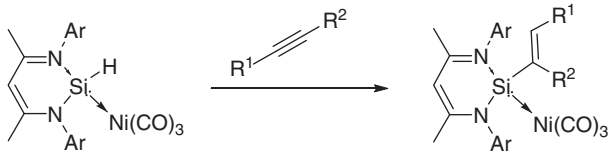
Bis(dichlorosilyl)methane **3** undergoes a double hydrosilylation and a dehydrogenative double silylation on reaction with alkynes such as acetylene and activated phenyl-substituted acetylenes in the presence of Speier's catalyst to give 1,1,3,3-tetrachloro-1,3-disilacyclopentanes and 1,1,3,3-tetrachloro-1,3-disilacyclopen-4-enes (Scheme 18).[115]



R = cyclohexyl; R^1 = OTBDMS, OTIPS, OTr, isoindoline, Me, Et, CH_2OMe, $CH_2OTBDMS$;
Yield = 64–93%; *E:Z* = >50:1 to 6.5:1
R = $TBDMSOCHCH_3$; R^1 = OTr; Yield = 77%
R = $(CH_3)_2CO_2(CH_2)_2CH$; R^1 = OTr; Yield = 88%; *E:Z* = 35:1

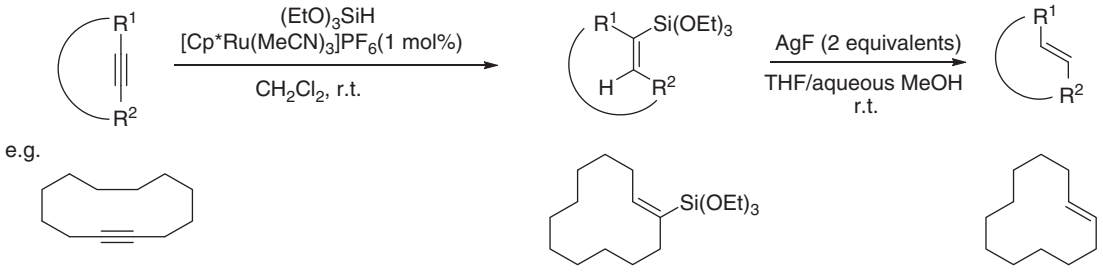


Scheme 11

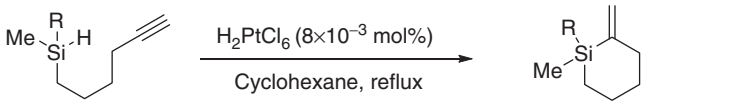


Ar = 2, 6-*i*-$Pr_2C_6H_3$
R^1 and R^2 = Ph or *p*-Tol

Scheme 12

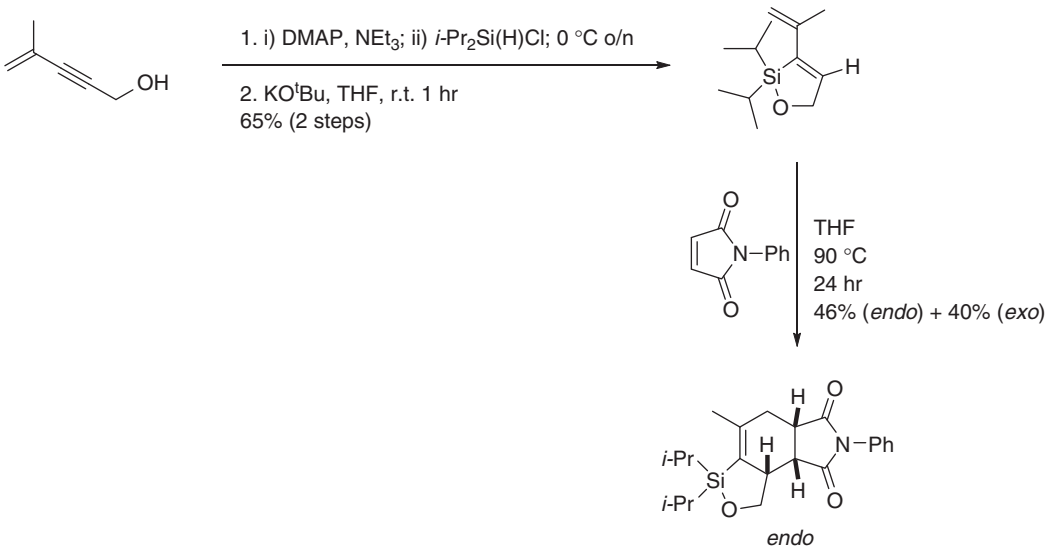


Scheme 13



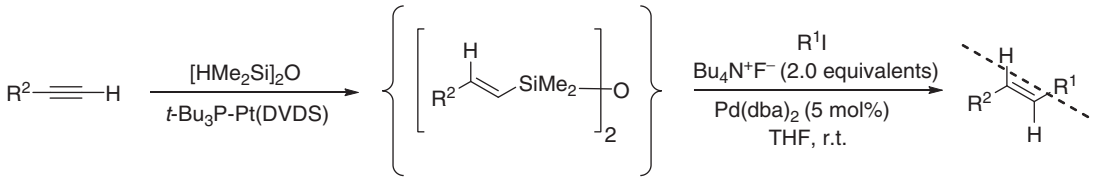
R = alkyl, Ph, allyl 18–66%

Scheme 14



endo

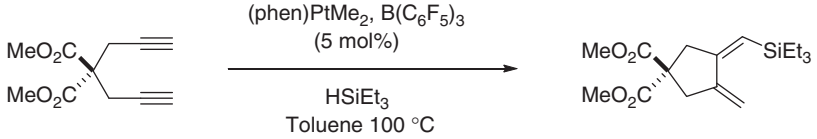
Scheme 15



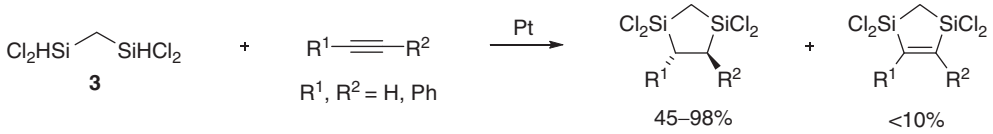
R^1= 1-naphthyl, 4-$(CH_3CO)C_6H_4$, 4-$(CH_3O)C_6H_4$, 3-$(NO_2)C_6H_4$, 3-$(CH_3)C_6H_4$, 2-$(CH_3OCO)C_6H_4$, 2-$(CH_3O)C_6H_4$, (*E*)-ICH=CHC_5H_{11}, (*E*)-BrCH=CHC_6H_5; R^2 = *n*-C_5H_{11}; Yield = 67 to 94%; *E*:*Z* = 91.4:8.6 to 99.4:0.6

R^1 = 4-$(CH_3CO)C_6H_4$ or 4-$(CH_3O)C_6H_4$; R^2 = C_6H_5, $HO(CH_2)_3$, $C_6H_5C(OH)(CH_3)$, CH_2 = $CHCH_2O(CH_2)_3$; Yield = 72 to 89%; Ratio: > 99%

Scheme 16



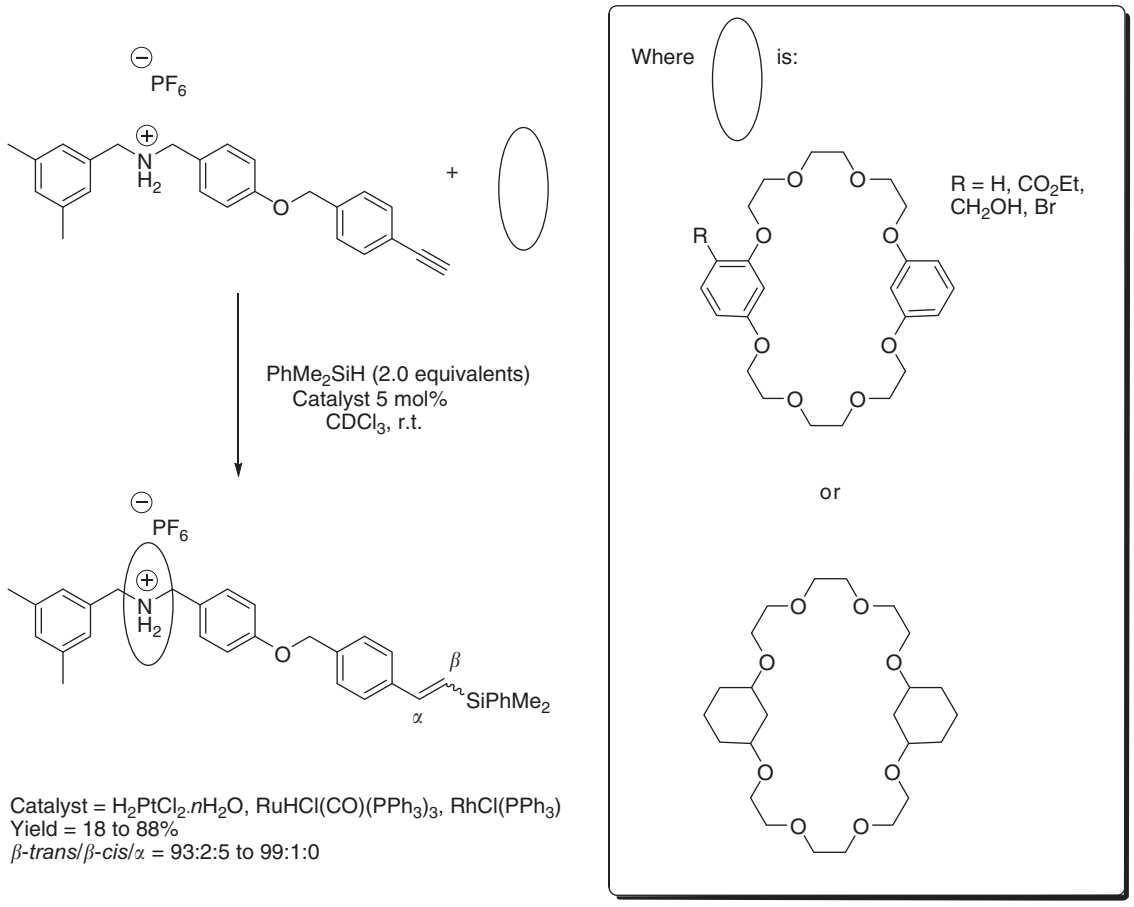
Scheme 17



Scheme 18

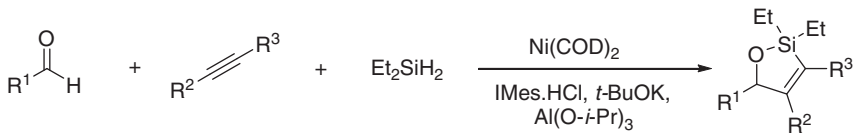
The stereocontrolled synthesis of poly(phenylenevinelene)s (PPVs) with (*E*)- and (*Z*)-vinyl units has been achieved using ruthenium-catalyzed hydrosilylation of *p*-diethynylbeneze; $RuHCl(CO)(PPh_3)_3$ was found to give the (*E,E*) product with $HSiMe_2Ar$ and *p*-diethynylbenzene, whereas $RuCl_2(CO)(P^iPr_3)_2$ afforded the (*Z,Z*) product.[116]

$RuHCl(CO)(PPh_3)_3$ and $RhCl(CO)(PPh_3)_3$ complexes both catalyze the hydrosilylation reaction of a terminal alkyne moiety in several pseudorotaxanes at ambient temperature.[117] This has proven to be a powerful end-capping method for pseudorotaxanes having an alkyne at the axle terminal, and the reaction proceeded in high yields and excellent regio- and stereoselectivities (Scheme 19).



Scheme 19

Dialkylsilanes have been used as silylene synthetic equivalents in a Ni(0)-catalyzed multicomponent oxidative cyclocondensation cyclization with an aldehyde and an alkyne to form silacycles (Scheme 20).[118]

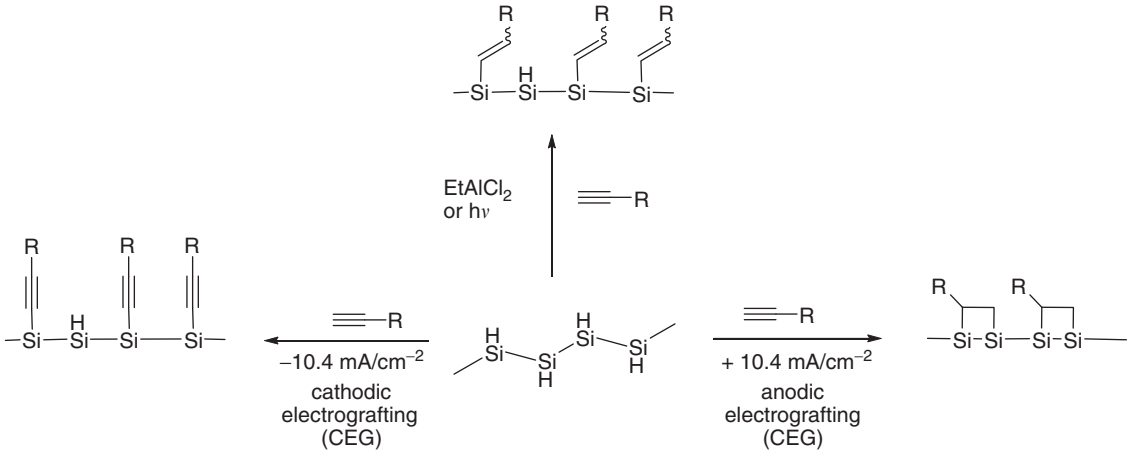


R^1 = Ph, Cy, *n*-Pr, *n*-pentCH(OTBS)
R^2 = Me, Et, H
R^3 = Ph, Et, *n*-pent, *n*-hex, $CH(Me)CH_2$
Yield = 53 to 85%, regioselectivity 62:38 to 98:2

Scheme 20

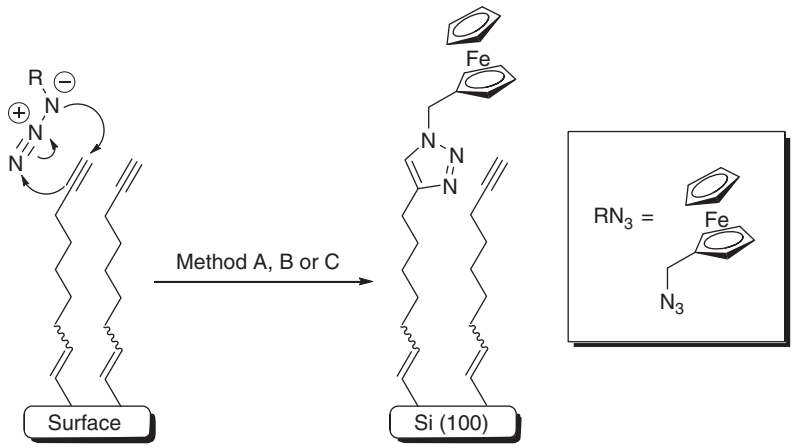
Roesky has reported bis(phosphinimino)methanide rare earth (Y, La, Sm, Ho, Lu) amides catalyze hydrosilylation and sequential hydroamination/hydrosilylation reactions of both alkenes and alkynes.[99]

Hydrosilylation reactions have been widely used to secure a variety of molecules on to silicon surfaces, to investigate certain properties or reactions at the other end of a carbon chain, once attached to the surface. For example, the relative reactivity of alkynes and alkenes on silicon(100) surfaces has been assessed, by preparing monolayers of each via hydrosilylation.[119] X-ray photoelectron spectroscopy (XPS) and electrochemical studies showed that the alkynes were more reactive than the alkenes, in the ratio *c*. 1.7–2.0:1 at 120 °C, although the ratio was lowered as the temperature decreased. Another study has shown that functionalization of the surface of porous silicon with organic monolayers can have important effects on the electrochemiluminescence (ECL) characteristics (**Scheme 21**).[120] Surfaces could be terminated with alkyne, alkene, and alkyl functionalities through cathodic electrografting, Lewis acid-mediated hydrosilylation, and anodic electrografting.



Scheme 21

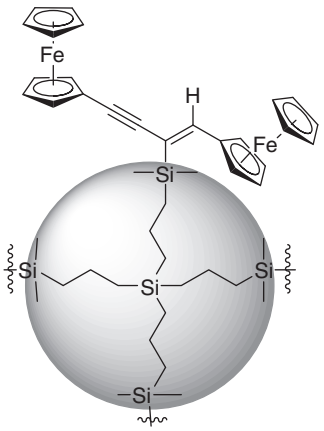
Despite the densest monolayers preventing good electrical contact between electrolyte and the nanocrystallites, the surface was protected from degradation, leading to extended lifetimes but low light emission. The nanopatterning of alkynes on hydrogen-terminated silicon surfaces has been reported by scanning probe-induced cathodic electrografting.[121] The copper-catalyzed azide-alkyne 'click' cycloaddition reaction has been utilized on many occasions to functionalize monolayers on Si(100) surfaces[122] (which themselves were prepared via hydrosilylation). For example, a 'click' reaction was utilized to covalently confine substituted ferrocene derivatives on passivated silicon(100) surfaces (**Scheme 22**).[123] The electronic communication between the ferrocene



Method A:
i) 10mM RN_3, 1 mol% CuI-$P(OEt)_3$, dry PhMe, reflux, 12 h
ii) 0.05% EDTA, r.t., 24 h
Method B:
i) 10mM RN_3,1 mol% CuI, dry PhMe, reflux, 12 h
ii) 0.05% EDTA, r.t., 24 h
Method C:
i) 10mM RN_3, 1 mol% $CuSO_4 \cdot 5H_2O$, Na ascorbate, H_2O/*i*-PrOH 1:2, r.t., 24 h
ii) 0.05% EDTA, r.t., 24 h

Scheme 22

center and semiconductor surface was examined by cyclic voltammetry and found to be in agreement with that expected for a redox interface. The same group has reported the synthesis of functionalized oligoethylene glycol molecules, with an azido group at one end and an ionizable group at the other, and their attachment on to alkyne-terminated silicon(100) surfaces using click chemistry. The surfaces were characterized using XPS and water contact angle goniometry. The surfaces were found to possess antifouling properties.[124] A similar approach allowed the differential functionalization of the internal and external surfaces of mesoporous materials, for biosensing applications,[125] and in the preparation of 'clickable' monolayers grown from α,ω-alkenynes, with the alkyne-terminus protected with a trimethylgermanyl (TMG) group. After degermylation, the alkynes readily underwent click reactions with various azides to tag various biological molecules (e.g., mannose, biotin) on to the surface. The mannose-tagged material was used to capture living targets (*E. coli*) on to the surface. The regio- and stereoselective hydrosilylation reactions of ferrocenylalkyne-dicobalthexacarbonyl complexes with either $HSiEt_3$ or dendrimer $Si[CH_2CH_2CH_2Si(CH_3)_2H]_4$ have been reported by Delgado and Alonso and generated a range of ferrocenylvinylsilanes and ferrocenylvinyl-functionalized carbosilane dendrimers which were studied by cyclic voltammetry (**Scheme 23**).[126] Porphyrins – such as nickel(II) β-azido-*meso*-tetraphenylporphyrin – have been anchored on to a Si(100) surface at the β-pyrrolic position and utilizing a linker with two terminal alkynes by the sequence: (1) hydrosilylation of a C≡C bond of the linker by surface Si–H groups and (2) 1,3-Huisgen cycloaddition between the alkyne-terminated silicon surface and the azidoporphyrin derivative.[127,128]



Scheme 23

8.25.2.3 Hydrosilylation of Carbon–Carbon Double Bonds

A number of excellent reviews have appeared covering alkene hydrosilylation reactions.[16,17] Marciniec has published a detailed review on all aspects of transition metal-catalyzed alkene silylation, covering topics including silylation of alkenes by hydrosilanes, silylation of alkenes by vinylsilanes, silylative couplings and competitive silylation of alkenes with vinylsilanes and hydrosilanes.[129] Full mechanistic discussions are included through the review. Anderson has published a comprehensive review on the synthesis of vinylsilanes, including many examples involving hydrosilylation reactions.[19] The same group has also reported the one-step preparation of functionalized *E*-vinylsilanes from aldehydes via a chromium(III)-mediated olefination, employing dihalomethylsilane reagents.[130] A review of the challenges in late transition metal-catalyzed olefin hydrosilylation reactions, from an industrial perspective, has been published,[131] which has a detailed review of iron-catalyzed hydrosilylation reactions.[18]

A number of platinum-based catalysts have been developed for the hydrosilylation of alkenes, including platina-β-diketones;[74] expanded ring *N*-heterocyclic carbene complexes of zero-valent platinum divinyltetramethyldisiloxane;[27] platinum supported on styrene-divinylbenzene copolymer for the hydrosilylation of terminal *n*-alkenes and allyl chloride;[132] several carboxylated polyethylene glycols have been used as promoters for the platinum-catalyzed hydrosilylation of alkenes, giving the β-adduct as the major product and with polyethylene glycol maleic acid monoester being particularly studied;[133] polymeric monolith supported Pt-nanoparticles have been used as ligand-free catalysts for terminal olefin hydrosilylation under both batch and continuous flow conditions.[134]

A new concept for chirality transfer from an optically active ligand of the catalyst to prochiral olefins has been discussed by Brunner for the asymmetric hydrogenation of alkenes, and extended to the development of new catalysts for enantioselective hydrosilylation of alkenes.[135] Rather than focussing on the metal, Gibson has published a structure-activity survey of monophosphane ligands for the asymmetric palladium-catalyzed hydrosilylation reaction of alkenes, in an attempt to assess the role of secondary interactions on catalyst activity and selectivity.[136]

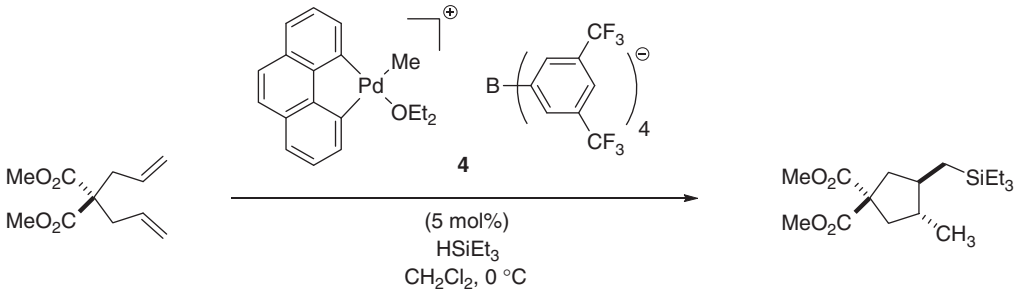
In an attempt to move away from precious metal catalysts, Chirik has published extensively on the use of iron catalysts for hydrosilylation reactions,[137,28,138–142] in particular the iron-catalyzed selective *anti*-Markovnikov addition of sterically hindered tertiary silanes to alkenes under mild conditions.[141]

A rare metal-free *N*-heterocyclic carbene catalyst has been reported for the hydrosilylation of styryl and propargylic alcohols with dihydrosilanes.[143]

8.25.2.3.1 Hydrosilylation of monosubstituted alkenes

Yi has published a short review/summary of his own group's work on region- and stereoselective hydrosilylation and oxidative silylation of alkenes and alkynes.[21] Treatment of terminal alkynes with $HSiEt_3$ in the presence of $(PCy_3)_2(CO)RuHCl$ gave the *cis*-alkenes, whereas dehydrosilylation of α-olefins under the same conditions gave the *trans*-vinylsilane. The $RhCl(PPh_3)_3$-catalyzed hydrosilylation of styrene and phenylacetylene with phenylsilanes (Ph_2SiH_2 and $PhSiH_3$) has been reported by Osakada and proceeds in THF in high yields, giving primarily $Ph_2SiH(CH_2CH_2Ph)$ (from styrene) and $PhSiH_2(CH{=}CHPh)$ from phenylacetylene.[56] The reactivity of the Rh(I) complex $Rh(CF_3COO)(NHC)(COD)$ (where NHC = 1,3-bis(2,4,6-trimethylphenyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene) in the hydrosilylation of 1-alkenes, alkynes, and α,β-unsaturated compounds has been thoroughly investigated, with TONs up to 1000 reached.[144] A poly(styrene-codivinylbenzene) supported version of the catalyst is also reported.

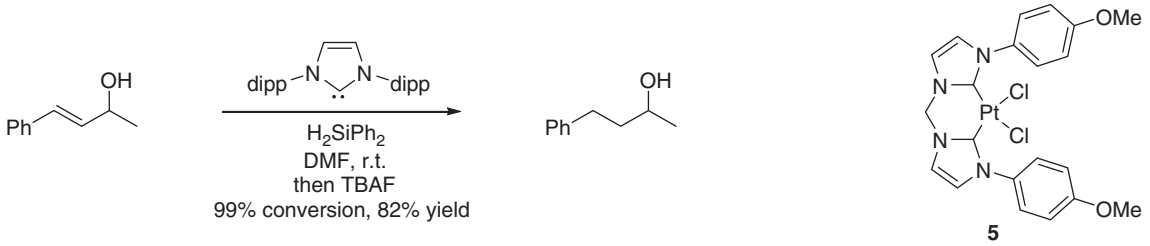
Widenhoefer has reported the cyclization/hydrosilylation of 1,6- and 1,7-dienes catalyzed by cationic palladium complexes. For example, the reaction of dimethyl diallylmalonate with triethylsilane with the catalyst **4** gave the *trans*-silylated cyclopentane in 93% after 5 min (**Scheme 24**).[145–151] This has been developed into an asymmetric version using optically active palladium bisoxazoline and pyridine-oxazoline complexes.[147]



Scheme 24

The commercial catalyst $[Ir(OMe)(COD)]_2$ and 4,4-di-*tert*-2,2-bipyridine catalyze the *Z*-selective dehydrative silylation of terminal alkenes (but not 1,2-disubstituted alkenes) with triethylsilane or benzyldimethylsilane in THF at 40 °C.[152]

A rare metal-free *N*-heterocyclic carbene catalyst has been reported for the hydrosilylation of styryl and propargylic alcohols with dihydrosilanes.[143] In conjunction with TBAF, this gave a highly efficient method for the reduction of alkenes (**Scheme 25**). Li has also reported the use of rhodium *N*-heterocyclic carbene complexes for the hydrosilylation of alkenes in an ionic liquid medium $BMimPF_6$.[153] Strassner has investigated the use of platinum(II)-bis-(*N*-heterocyclic carbene) complexes in hydrosilylation reactions of alkenes and found that they favor the β-product.[154] Pleasingly, the catalyst **5** did not decompose during the reaction to platinum black, offering an important advantage over the Karstedt catalyst.



Scheme 25

A silica-supported chitosan-platinum complex has been prepared and characterized by ICP-AES, FT-IR, and XPS, and found to show high catalytic activity in the hydrosilylation of allyl glycidyl ether with triethoxysilane.[155] The hydrosilylation of *n*-alkenes and allyl chloride over platinum supported on styrene-divinylbenzene copolymer has been reported.[132]

A range of alkyllanthanum biphenolate complexes have been prepared and screened as catalysts. One, $[La\{(R)\text{-Biphen}\}]_2$ and its THF adduct $[La\{(R)\text{-Biphen}\}\{CH(SiMe_3)_2\}(THF)_3]$ exhibited good catalytic activity and diastereoselectivity in the hydrosilylation of styrene, 1-hexene, and norbornene.[156]

8.25.2.3.2 Hydrosilylation of disubstituted alkenes

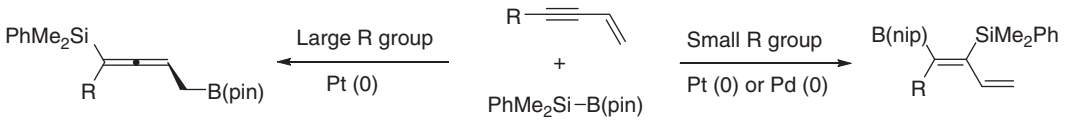
Roesky has reported bis(phosphinimino)methanide rare earth (Y, La, Sm, Ho, Lu) amides catalyze hydrosilylation and sequential hydroamination/hydrosilylation reactions of both alkenes and alkynes.[99] A rare catalyst-free thermal hydrosilylation of

cycloalkenes has been reported, employing trichlorosilane with cyclopentene, cyclohexene, cycloheptene, or cyclooctene to give cycloalkyltrichlorosilanes.[157]

8.25.2.4 Hydrosilylation of Conjugated and Related Systems

Le Gendre has prepared an open-bent titanocene complex [$Me_2C(C_5H_4)_2TiMe_2$] which was demonstrated to be efficient for the hydrosilylation of a variety of substrates such as disubstituted dienes, including 2,3-dimethylbutadiene, activated alkenes, and acetylenes.[158]

The silaboration of 1,3-enynes catalyzed by group 10 metal complexes affords 1,3-dienes with vinylborane and vinylsilane functions, or 1,2-dienes with allylborane and vinylsilane functions, the exact nature of the product formed being determined by the size of the alkyne substituent (Scheme 26).[159]



Scheme 26

$Rh(acac)(CO)_2$ efficiently catalyzes the hydrosilylative carbocyclization of various allenynes and trialkoxysilanes under an atmosphere of CO to give cyclic hydrosilylated products. Silylrhodation of the internal olefin of the allene proceeded exclusively, followed by carbometalation to the alkyne to give the cyclic 1,4-diene.[160] The reactivity of the Rh(I) complex $Rh(CF_3COO)$(NHC)(COD) (where NHC = 1,3-bis(2,4,6-trimethylphenyl)-3,4,5,6-tetrahydropyrimidin-2-ylidene) in the hydrosilylation of 1-alkenes, alkynes, and α,β-unsaturated compounds has been reported.[144] A poly(styrene-codivinylbenzene) supported version of the catalyst is also reported.

A series of monometallic and bimetallic catalysts, based on noncalcined and calcined platinum on titania, have been utilized in the hydrosilylation of 1,3-diynes. Symmetric diaryl- and dialkyl-substituted 1,3-diynes were successfully employed and in all cases, the reactions were highly regio- and stereoselective, affording monosilyl enynes and disilyl dienes with exclusively (*E*)-stereochemistry and the silicon attached to the internal carbon of the conjugated system.[161]

8.25.2.5 Synthetic Transformations and Applications

8.25.2.5.1 Applications of hydrosilylation reactions

The triethylborane-initiated radical hydrosilylation reactions of phenyldimethylsilane and trichlorosilane with various alkenes proceed efficiently; on subsequent oxidation, the alcohol products show the net result of *anti*-Markovnikov hydrations of the original alkene.[162]

There have been a number of examples of the anchoring of molecules to Si surfaces via alkene hydrosilylation. For example, the hydrosilylation of styrene on water-saturated Si(001)-2×1 surface at room temperature has been reported by Bournel and Pietzsch.[163] Lee has investigated the initiation mechanisms for surface hydrosilylation with 1-alkenes at 200 °C initiated by visible light or more slowly at room temperature in the dark.[164] Hydrosilylation has also be utilized to tag α,ω-alkenynes on to a Si(111) surface, via alkene hydrosilylation, and with the alkyne-terminus protected with a TMG group. After degermylation, the alkynes readily underwent click reactions with various azides to tag various biological molecules (e.g., mannose, biotin) on to the surface.[165] The mannose-tagged material was used to capture living targets (*E. coli*) on to the surface. The same 'click' approach has been used to immobilize antimicrobial peptides to surfaces.[166] Zuilhof has utilized the reactions of silyl radical cations with nucleophiles to mimic the reactivity at silicon surfaces.[167] They demonstrated that a delocalized Si radical cation (a surface localized hole) can initiate the hydrosilylation chain reaction at the Si surface.

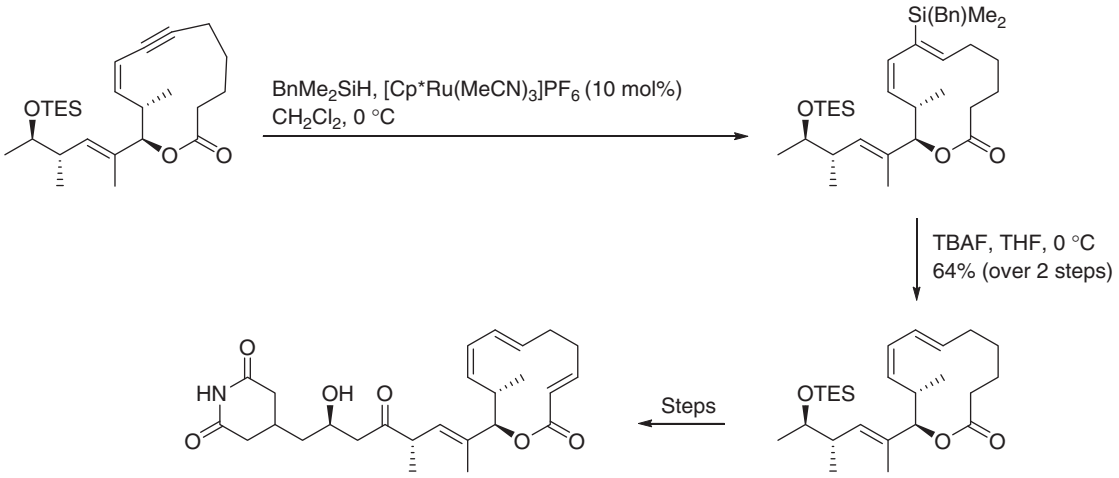
There have been a number of studies concerning the reaction of silicon nanoparticles. Terminal alkenes of varying chain length has been added to silicon nanoparticles between 2.5–30 nm in diameter by photoassisted hydrosilylation reactions in the aerosol phase.[168] It was found that smaller particles functionalized with shorter chains at the interior (β) alkenyl carbon atom, whereas particles >10 nm in diameter attached via the exterior (α) alkenyl carbon atom irrespective of chain length. A similar study has been conducted into the influence of nanocrystal size on the reactivity of silicon nanocrystals (Si-NCs) near-UV photochemical hydrosilylation with 1-dodecene and phenylacetylene.[169]

The *in situ* gas-phase hydrosilylation of plasma-synthesized silicon nanocrystals using 1-alkenes and 1-alkynes has been reported.[170] The method has considerable potential in the surface passivation of semiconductor nanocrystals, for use in novel optoelectronic devices, solar cells, and chemical sensors.

8.25.2.5.2 Applications of hydrosilylation reactions in total synthesis

Numerous total syntheses have been reported which include a hydrosilylation reaction at some stage during a multistep sequence. Furstner has described a concise, practical, and stereoselective route to macrocyclic (*E*)-alkenes via ring closing alkyne metathesis,

trans-selective hydrosilylation of the resulting cycloalkyne catalyzed by $[Cp^*Ru(MeCN)_3]PF_6$ and finally protodesilylation of the resulting vinylsilane with AgF in THF/MeOH.[171] Furstner employed a similar strategy, namely ring-closing alkyne metathesis followed immediately by *trans*-hydrosilylation of the resultant alkyne and protodesilylation as the key steps in the synthesis of the potent translation and cell migration inhibitor lactimidomycin (**Scheme 27**).[172] The same group employed similar strategies in the total synthesis of the macrolide tulearin C[173] and myxovirescin A_1.[174] Cossy has developed a one-pot hydrosilylation-ring closing metathesis-protodesilylation strategy for the synthesis of ω-alkenyl α,β-unsaturated lactones.[175] Floreancig achieved an overall alkyne hydration reaction in the synthesis of the Carribean sponge cytotoxin neopeltolide by combining an intramolecular hydrosilylation reaction, using a Pt(DVDS) catalyst (DVDS = divinyl dimethyldisoloxane) to form a siloxane, followed by a Tamao oxidation.[93]



Scheme 27

The ruthenium-catalyzed alkyne hydrosilylation reaction developed by Trost[35,34] was utilized by Feringa in the asymmetric total synthesis of the virulence factor of *Mycobacterium tuberculosis*, known as phthiocerol dimycocerosate A or PDIM A.[176] A suite of silylation reactions were employed by Denmark in the total syntheses of isodomoic Acids G and H.[177]

Rh(I) catalysts immobilized on polyamide supports are still able to catalyze the hydrosilylation of alkenes, dienes, and alkynes.[113] The presence of 2,5- and 2,6-pyridines in the polymer also influenced the *cis*/*trans* selectivity of the hydrosilylation.

8.25.3 Hydrostannylation

8.25.3.1 Introduction

Lautens has published an excellent and comprehensive review of metal-catalyzed hydrostannations up to 2000.[178] This gives an excellent introduction to the synthesis of organostannanes, presents mechanistic considerations, and comprehensively reviews the literature on hydrostannation reactions of alkynes, alkenes, allenes, and conjugated systems.

8.25.3.1.1 Hydrostannanes available

A few hydrostannanes are now commercially available, and include nBu_3SnH, Ph_2SnH_2, and the fluorous stannane $[CF_3(CF_2)_4CF_2]_3SnH$.

8.25.3.2 Hydrostannylation of Carbon–Carbon Triple Bonds

8.25.3.2.1 Hydrostannylation of ethyne

Reaction of $(Me_2Sn)_2CuCNLi_2$ with ethyne gives a bis(trimethylstannylvinyl)cuprate reagent which readily undergoes 1,4-conjugate addition with cyclic α,β-unsaturated ketones.[179]

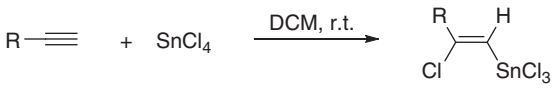
8.25.3.2.2 Hydrostannylation of monosubstituted alkynes

Tributyltin hydride has been generated *in situ* from tributylchlorostannane and triethylsilane in the presence of catalytic amounts of a Lewis acid ($ZrCl_4$ or $B(C_6F_5)_3$) and utilized for the hydrostannation of carbon–carbon multiple bonds, including (internal and terminal) alkynes, alkenes, and allenes.[180]

Although hydrostannylation reactions, followed either directly or after isolation/purification by a Stille coupling, are well known, they have always suffered the drawback of requiring stoichiometric amounts of tin. Maleczka has reported a one-pot tandem palladium-catalyzed hydrostannylation/Stille coupling for the stereoselective generation of vinyltins and their subsequent coupling that is for the first time catalytic in tin. Using Me_3SnCl as the tin source, it was possible to recycle the tin halide Stille byproducts back to the tin hydride using the mild hydride donor polymeththylhydrosiloxane (PMHS).[181]

The regioselective palladium-catalyzed hydrostannylation of terminal arylalkynes has been achieved using Bu_3SnH and $PdCl_2(PPh_3)_2$, in the presence of an *ortho*-substituent on the aromatic ring to direct the regioselectivity of the Sn–H bond addition. Irrespective of the nature of the substituent, the α-branched vinylstannane was always obtained. The products were utilized in Stille cross-couplings to give 1,1-diraylethylenes.[182]

The addition reaction of tin tetrachloride to PhC≡CH, ^{t}BuC≡CH, ^{n}BuC≡CH, or $HOCH_2C{\equiv}CH$ in dichloromethane has been reported to give the stannylated products with exclusively α-regioselectivity, with the steric bulk of the substituent being attributed with this outcome (Scheme 28).[183] Reaction of norbornene or norbornadiene under the same conditions gave the *exo* stannylation product.[183] In contrast, nickel, cobalt, or molybdenum-catalyzed hydrostannylation reactions, using tributyltin chloride, polymethylhydrosiloxane, potassium fluoride, and 18-crown-6 (as an *in situ* method of preparing the tin hydride) generally gave a mixture of α- and β-stannylated products, except when using $MoBI_3$, which gave the proximal vinyltins as the major product.[184]



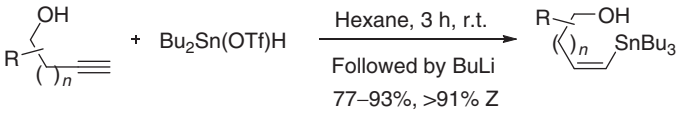
Scheme 28

The hydrotelluration of alkynes occurs in a highly selective antimanner to give *cis*-vinyltellurides that do not undergo isomerization. The under-utilized lithium/tellurium exchange reaction has been employed by Williams as part of a two-step highly efficient method for the synthesis of *cis*-vinyltrimethylstannanes and *cis*-vinylpinacolboronates; this comprised hydrotelluration followed by lithium/tellurium exchange and quenching with either trimethyltin chloride or 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.[185] The same authors have prepared *cis*-vinylstannanes from alkynes bearing oxygen-containing substituents elsewhere in the molecule, also using the Li/Te exchange pathway; this is something that is impossible using $ZrCl_4$, which is incompatible with oxygenated substrates.[186]

Roesky has published extensively on the reactions of tin(II) hydride species with unsaturated molecules, including alkynes.[187,188] Stable β-diketiminate tin(II) hydride LSnH (L=HC(CMeNAr)$_2$, Ar=2,6-i$Pr_2C_6H_3$) reacts with activated terminal alkynes to give the tin(II)-substituted terminal alkene (and not dihydrogen elimination).[188] It also reacted with disubstituted alkynes $RO_2C{\equiv}CCO_2R$ to form the stannylene-substituted internal alkene. LSnH also reacted with ketones to give tin(II) alkoxides.

The radical addition of trineophyltin hydride to ethynylcyclohexene gives exclusively (*Z*,*E*)-1-(2-trineophylstannylvinyl) cyclohexene, a conjugated dienylstannane, which could, in one pot, undergo Diels–Alder reaction with activated dienophiles, with the stannyl group in the resultant allylic position.[189] Cai has reported the one-pot synthesis of 2-ethoxycarbonyl-substituted 1,3-dienes and 1,3-enynes by the palladium catalyzed hydrostannylation of alkynyl esters, followed by a Stille coupling with alkenyl or alkynyl halides.[190]

$Bu_2Sn(OTf)H$ has been found to be an excellent reagent for the regio- and stereoselective hydrostannylation of propargylic alcohols (and longer chain alkynols) to give (*Z*)-stannylated allyl alcohols.[191] The tin reagent was prepared *in situ* from Bu_2SnH_2 and TfOH. Coordination of the hydroxyl group to the Lewis acidic tin center was found to be crucial for the observed high regio- and stereoselectivity (Scheme 29).



Scheme 29

Kazmaier has reported distannylations and silastannylations of allenes generated *in situ* from propargylic ethers.[192] Only Bu_3SnH and $Pd(PPh_3)_4$ were required to convert propargylic ethers and esters directly into distannylated alkenes, the reaction postulated to occur via a stannylated allyl alcohol derivate, which subsequently underwent elimination and dimetallation. The two processes could be decoupled by utilizing a molybdenum catalyst in the hydrostannylation step. This permitted the selective reaction of the stannylated intermediate with other dimetallic compounds, for example to introduce silicon. Kwon has studied the palladium-catalyzed hydrostannylation of ethyl ethynyl ether, using 0.001 equivalent of $Pd(PPh_3)_4$ and 1 equivalent of tributyltin hydride.[193] The hydrostannylation occurred in 95% yield, as a 1:0.69 β:α mixture. However, only the β-regioisomer underwent subsequent Stille coupling reactions, providing a facile method for the separation of the two products.

Although the majority of transition metal-catalyzed hydrometalations and carbometalations proceed in a *cis* manner, the Lewis acid promoted reactions tend to proceed in a *trans* manner, as reported by Yamamoto: hydrosilylation, hydrostannylation, carbosilylation, and carbostannylation or unactivated alkynes with organosilanes or organostannanes all gave the *trans*-vinylsilyl or vinylstannyl compounds.[40]

8.25.3.2.3 Hydrostannylation of disubstituted alkynes

The palladium-catalyzed hydrostannylation of substituted propargyl alcohols with the bulky trineophyltin hydride reagent has been reported by Podesta, giving exclusively the products of *syn*-addition but in variable ratios of *syn*-α and *syn*-β products.[194] The hydrostannylation of carbonyl-activated alkynes proceeds in good yields when catalyzed by CuCl in the presence of KOtBu, triphenylphosphine, and tributylstannane. The reaction generates copper hydride *in situ*, adding to the alkyne before transmetallation. Addition of the tin always occurred at the alkyne carbon attached to the adjacent C=O.[195] Tanner has reported that (E)-β-trialkylstannyl-α,β-unsaturated ketones can also be prepared from secondary propargylic alcohols via a two-step sequence of Pd (0)-catalyzed hydrostannylation followed by tetrapropylammonium perruthenate oxidation. This was used in an approach toward the marine natural product Zoanthamine.[196]

The palladium-catalyzed hydrostannylation of α-heteroalkynes and alkynyl esters has been performed in the ionic liquid 1-butyl-3-methyl-imidazolium hexafluorophosphate. The reaction tolerated both S- (sulfides and sulfones) and Se-substituents on the alkyne.[197] 1,4-Dienyl selenides have been stereoselectively prepared by the palladium-catalyzed hydrostannylation of acetylenic selenides, followed directly by Stille coupling with allylic bromides.[198]

Roesky has reported that stable β-diketiminate tin(II) hydride LSnH (L=HC(CMeNAr)$_2$, Ar=2,6-iPr$_2$C$_6$H$_3$) reacts with disubstituted alkynes RO$_2$C≡CCO$_2$R to form the stannylene-substituted internal alkene.[188]

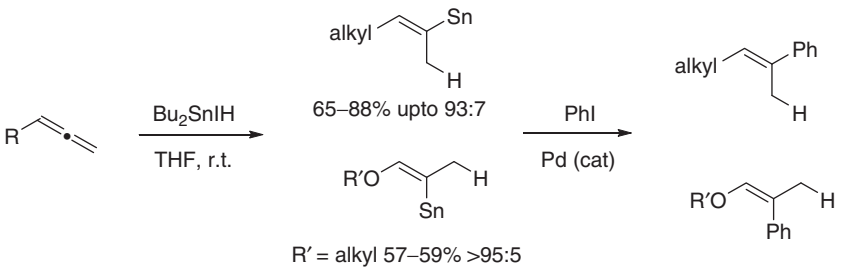
Moses has reported the first regioselective hydrostannation (using tributyl- or triphenyltin hydride) of an aryne, generated *in situ* from o-trimethylsilylphenyl triflates or anthranilic acid, without the use of additives or catalysts.[199]

8.25.3.3 Hydrostannylation of Carbon–Carbon Double Bonds

8.25.3.3.1 Hydrostannylation of monosubstituted alkenes

Tributyltin hydride has been generated *in situ* from tributylchlorostannane and triethylsilane in the presence of catalytic amounts of a Lewis acid ($ZrCl_4$ or $B(C_6F_5)_3$) and utilized for the hydrostannation of carbon–carbon multiple bonds, including (internal and terminal) alkynes, alkenes, and allenes.[180] This is reported to be the first example of a Lewis acid-catalyzed hydrostannation of an alkene.

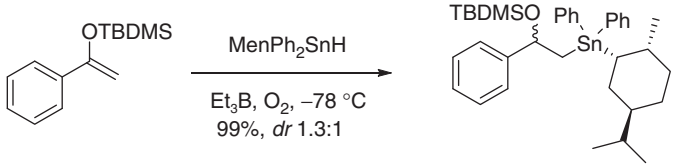
The regio- and stereoselective hydrostannylation of monosubstituted allenes has been performed using di-*n*-butyliodotin hydride, to give α,β-disubstituted vinyltins (Scheme 30).[200] Without isolation, these products could subsequently be employed in palladium-catalyzed cross-couplings with aromatic halides to give multisubstituted alkenes in a one-pot overall procedure. The regioselectivity of the initial hydrostannylation was highly dependent on the nature of the allene substituent.



Scheme 30

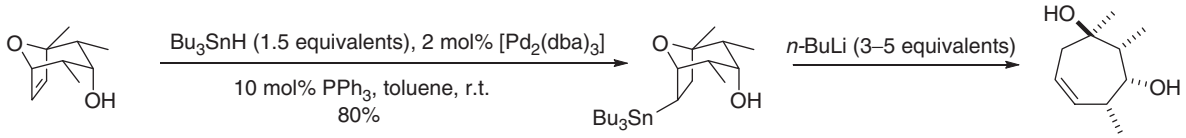
8.25.3.3.2 Hydrostannylation of disubstituted alkenes

The free radical hydrostannylation of unactivated alkenes using chiral trialkylstannanes has been reported by Schiesser (Scheme 31).[201]



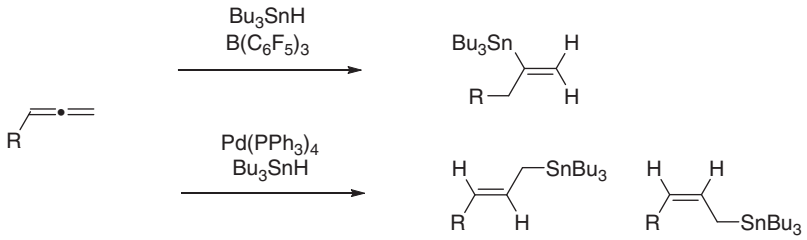
Scheme 31

Lautens has reported a palladium-catalyzed hydrostannylation of unsymmetrical oxabicyclic alkenes (oxabicyclo-heptenes and -octenes).[202] The products of the Pd-catalyzed hydrostannylation underwent elimination to the cyclohexenol (Scheme 32).



Scheme 32

Yamamoto has described differing outcomes for the hydrostannation of allenes depending on the reaction conditions employed: the use of tributyltin hydride with a Lewis acid $B(C_6F_5)_3$ produced vinylstannanes regioselectively, whereas tributylstannyl- and triphenylstannyl hydrides in the presence of $Pd(PPh_3)_4$ gave allylstannanes regioselectively (Scheme 33).[203]



Scheme 33

8.25.3.3.3 Synthetic transformations and applications

One acyclic, two heterocyclic, and two bicyclic alkenyl stannanes were prepared by de Meijere, including one by $[RhClCOD]_2$ catalyzed hydrostannylation of (*tert*-butyldimethylsilyl)acetylene with tri-*n*-butyltin hydride and the products used in the synthesis of 1,3,5-hexatrienes, which were subsequently utilized in studying thermally induced 6π-electrocyclizations.[204]

The stereoselective synthesis of (Z)-α-arylsulfanyl-α,β-unsaturated ketones via a Stille coupling reaction has been reported, starting from arylsulfanylvinylstannanes, acyl halides, and a Pd(PPh3)4/CuI catalyst.[205]

Quintard has performed a study on the synthesis, characterization, and reactions of supported vinyltins and allyltins grafted on to an insoluble cross-linked polystyrene matrix.[206] The starting materials were prepared by alkyne hydrostannylation (or other methods, such as transmetallation or S_N2' substitution of β-stannylacrolein by cyanocopper reagents). The grafted organotin reagents were analyzed by HRMAS NMR, which permitted unambiguous assignment of their isomeric distribution and also identification of side products. The supported reagents demonstrated similar reactivity and stereoselectivity to their tributyltin analogs when involved in Stille cross-coupling reactions or addition reactions to aldehydes, but without any tin contamination of the products.

8.25.3.4 Applications of Hydrostannylation Reactions in Total Synthesis

The hydrostannylation of alkynes has played a key role in the total syntheses of many molecules, including the C1-C9 and C10-C21 segments of the lycoperdinosides (Bu_3SnH, $Pd(Ph_3P)_2Cl_2$, THF, r.t.);[207] in two different approaches to combretastatin A4 and related compounds;[208,209] in a protecting group free synthesis of (+)-Crocacin C, including an enzymatic enantioselective desymmetrization of a *meso*-diol and a one-pot alkyne hydrostannylation, subsequent Stille coupling ($PdCl_2(PPh_3)_2$ (5 mol%), Bu_3SnH, THF, 0 °C; and followed by substituted vinyl iodide, 100 °C, microwave irradiation, 15 min).[210]

8.25.4 Hydrogermylation

8.25.4.1 Introduction

In this section, the addition reactions of hydrogermanes to alkenes and alkynes and their synthetic transformations and applications are considered. There have been a number of syntheses of hydrogermanes from a variety of precursors and the methods reported in the previous edition are still relevant.[211]

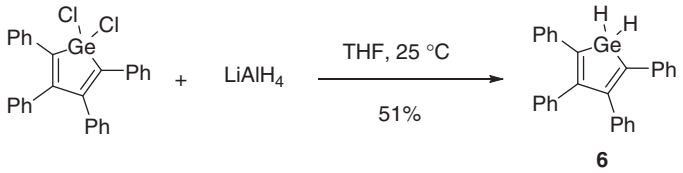
Organosilanes and organogermanes have developed as popular alternatives to the Stille and Suzuki reactions for Pd-catalyzed cross-coupling reactions; their use has been reviewed.[2]

8.25.4.1.1 Available germanes

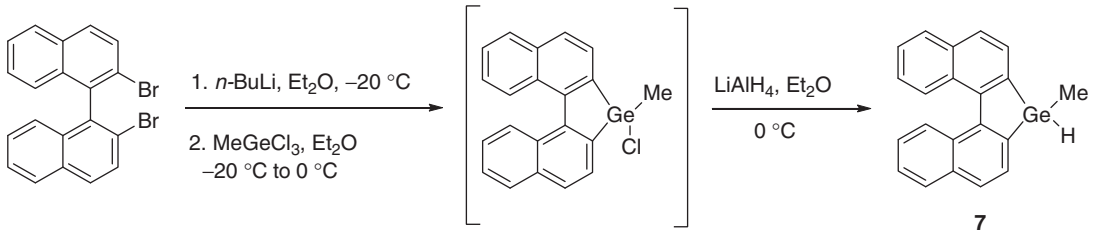
A few germanes are now commercially available and include GeH_4, Et_3GeH, $(TMS)_3GeH$, nBu_3GeH, $nHex_3GeH$, and Ph_3GeH.

8.25.4.1.2 Synthesis of organohydrogermanes

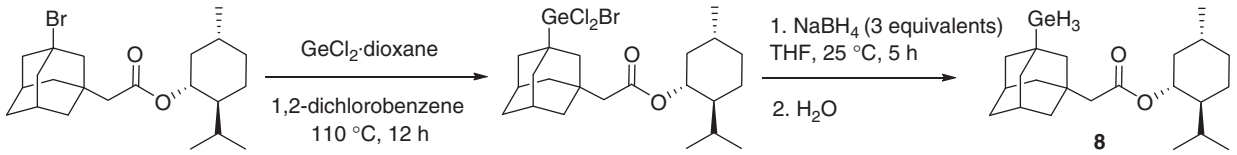
A common route for the preparation of organohydrogermanes is by the direct reduction of organogermanium halides using the reducing agents $LiAlH_4$ or $NaBH_4$.[212] The preparation of the germole **6** (Scheme 34) and the optically active species **7** and **8** (Schemes 35 and 36) are some examples.



Scheme 34

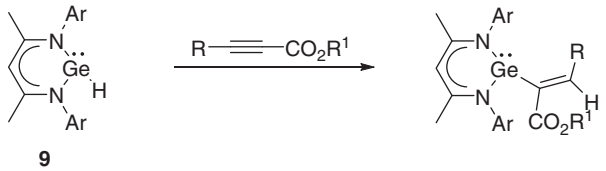


Scheme 35



Scheme 36

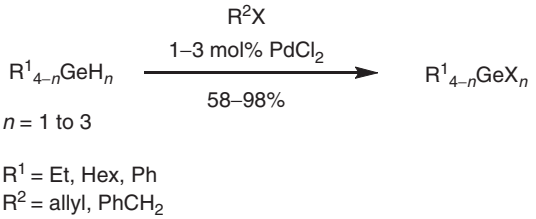
Dimethylgermylene Me_2Ge inserts rapidly and easily into the O–H, S–H and N–H bonds of water/deuterium oxide, alcohols, carboxylic acids, oximes, and phthalimide to yield substituted organogermanium hydrides Me_2Ge-H. $PhSMe_2GeH$ was found to bring about spontaneous hydrogermylation of alkenes. Further complexes were found to add to alkenes and alkynes.[213] The synthesis of the germanium(II) hydride **9** has been reported. This reacts with alkynes at room temperature to form germanium(II)-substituted alkenes (Scheme 37). The catalyst was also capable of reaction with carbon dioxide and elemental sulfur.[214,215] Another structurally similar *N*-heterocyclic germanium(II) hydride, namely [(^{Me}MesNacnacn)GeH], has been prepared from the *β*-diketiminato germanium(II) chloride complex [(^{Me}MesNacnacn)GeCl], and undergoes reversible hydrogermylation with a phosphaalkyne P≡C^{t}Bu.[216]



Scheme 37

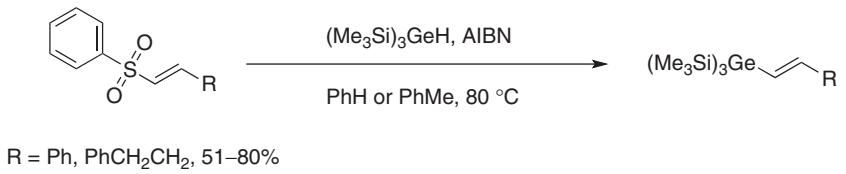
The hydrogen donation or transferability of a range of substituted germanium hydrides toward primary alkyl radicals has been investigated by kinetic studies and reviewed.[217]

The procedures reported in *Comprehensive Organometallic Chemistry I and II* for the halogenation of Ge–H bonds are still extensively utilized. Recently, their preparation by the reaction of hydrosilanes with alkyl or allyl halides catalyzed by $PdCl_2$ or $NiCl_2$ (Scheme 38) was reported.[218]

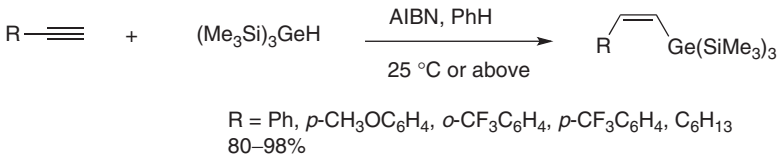


Scheme 38

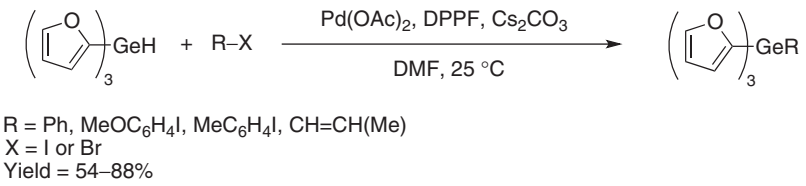
Two methods have been reported for the alkylation of the Ge–H bond, based around radical and palladium-catalyzed methodologies. First, radical-promoted desulfonylation of vinyl sulfones for the alkylation of organohydrogermanes are still relevant (Scheme 39).[219,220] The bulky germanium hydride tris(trimethylsilyl)germane has been used to react with alkynes to give selectively (*Z*)-alkenes (Scheme 40).[219,220] The products from both schemes have been utilized in Pd-catalyzed couplings.[219] Second, alkylation of the Ge–H bond may be achieved by the palladium catalyzed coupling with aryl iodides (Scheme 41).



Scheme 39



Scheme 40



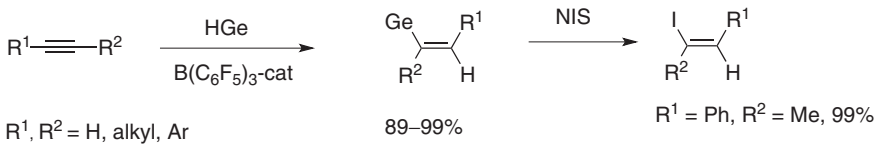
Scheme 41

Carbene complexes of the type M=E (E=Si or Ge) have been reported with hydrogen atoms on both the metal center and the E atom. These have been shown to undergo hydrosilylation and hydrogermylation reactions readily, as well as reaction with nitriles, ketones, and heterocumulenes.[5]

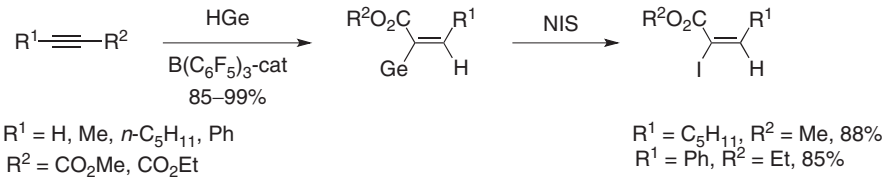
8.25.4.2 Hydrogermylation of Carbon–Carbon Triple Bonds

Examples of Lewis acid-catalyzed hydrogermylation of alkynes have been reported by Schwier and Gevorgyan[221] cf. the related hydrostannation of allenes discussed previously.[203] This mild method displays relatively higher functional group tolerance, compared with hydrometalation reactions promoted by Lewis acids which are only compatible with a narrow range of functional groups, for example, bulky TBS- or TIPS-protected alcohols. The method has been found to undergo selectively *trans*-addition when simple alkynes were employed (Scheme 42) and *cis*-addition when propiolates were used as starting materials (Scheme 43).

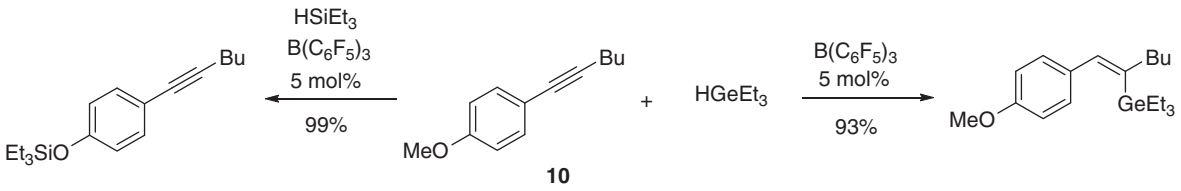
Under these conditions, treatment of the alkyne **10** with triethylsilane gave the quantitative product of O–Me cleavage and no hydrosilylation products were observed (Scheme 44). In contrast, it was found that by changing the silicon to germanium, the reaction proceeded with complete hydrogermylation, conserving the methoxy moiety in the processs.[221]



Scheme 42



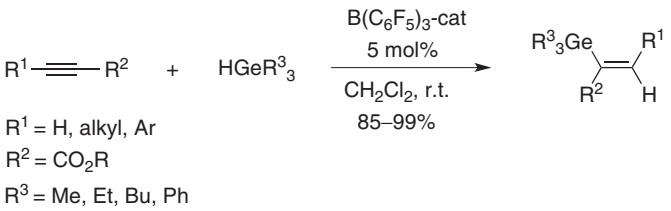
Scheme 43



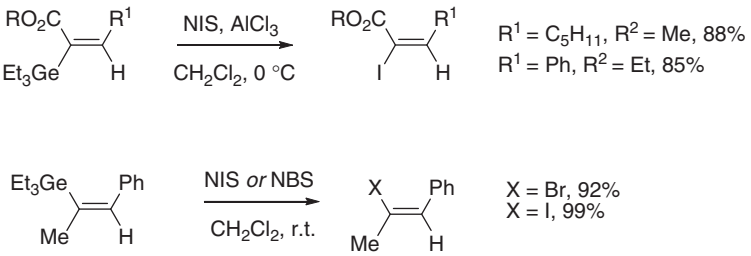
Scheme 44

Using a range of hydrogermanes, the formation of various (*Z*)-vinylgermanes, have been reported, including bifunctional vinylgermanes, in all cases with complete regio- and stereoselectivity in excellent yields (Scheme 45).[221]

Vinylgermanes are important intermediates and their utility for the transformation into vinyl halides have also been demonstrated in the same publication (Scheme 46).[221]

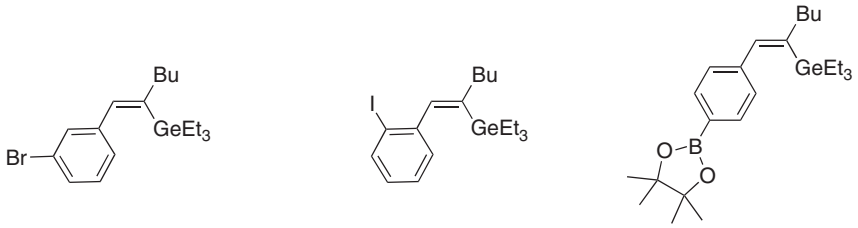


Scheme 45



Scheme 46

These bifunctional vinylgermanes containing both electrophilic and nucleophilic components can be used in cross-coupling reactions, either at the aryl halide handle or in a Suzuki reaction before halogermylation to attain the vinyl halide moiety (Scheme 47).[221]

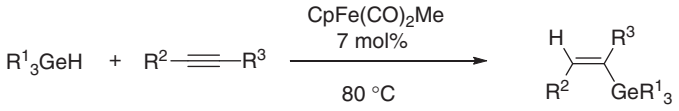


Scheme 47

Triethylborane induces the intramolecular hydrogermylation of homoallylic and homopropargylic alcohols. It was found that the platinum-catalyzed hydrogermylation of 3-hexenoxydipropylgermane gave the five-membered ring product 5-propyl-1-germa-2-oxacyclopentane as a main product, but the triethylborane-induced radical cyclization gave the six-membered ring product 6-ethyl-1-germa-2-oxacyclohexane selectively.[222] The hydrosilylation and hydrogermylation of alkyl esters of propiolic acids gave mixtures of alkyl esters of 2-triethylsilyl(germyl)- and (*E*)-3-triethylsilyl(germyl)acrylic acids. Alkyl esters of organosilicon(germanium) *β*-amino (hydrazino)propionic acids were obtained by amination of the alkyl esters of 2-triethylsilyl(germyl)acrylic acids.[223]

$PhSMe_2GeH$, prepared by the insertion of Me_2Ge into the PhS–H bond, was found to bring about spontaneous hydrogermylation of alkenes.[213]

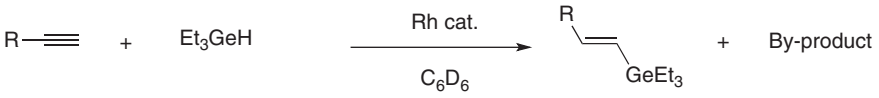
The catalytic *trans*-selective hydrogermylation of both terminal and internal alkynes has been reported by Nakazawa, employing $CpFe(CO)_2(Me)$ and a bis(germyl)hydridoirom(IV) complex as a catalyst precursor (Scheme 48).[224] The crystalline structures of the proposed catalytic intermediates are reported.



R^1 = Et, Ph, *n*-Bu,
R^2 = Ph, 4-F-C_6H_4, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-NH_2-C_6H_4, Hex, *c*-Hex, Pr, CO_2Me
R^3 = H, Me, Ph, Pr, CO_2Me
Time = 6 – 18 h
Yield = 43 to >99%

Scheme 48

The reaction of alkynols or alkynes with Et_3GeH catalyzed by rhodium complexes affords the corresponding alkenes in quantitative yields (Scheme 49).[225,226] Some of the reaction intermediates have been isolated in reasonable yields and the mechanism has been proposed (Scheme 50).[226]



R = CO_2Me, Ph

Scheme 49

Alkenyl complexes can also be prepared by the reaction of similar rhodium species with alkynes.[225] Various hydrogermylation catalysts using other transition metal complexes, including a 1:1 mixture of palladium phenanthroline complex (Phen)Pd(Me)Cl and $NaBAr_4$ (Ar = 3,5-$C_6H_3(CF_3)_2$) have also been reported.[227]

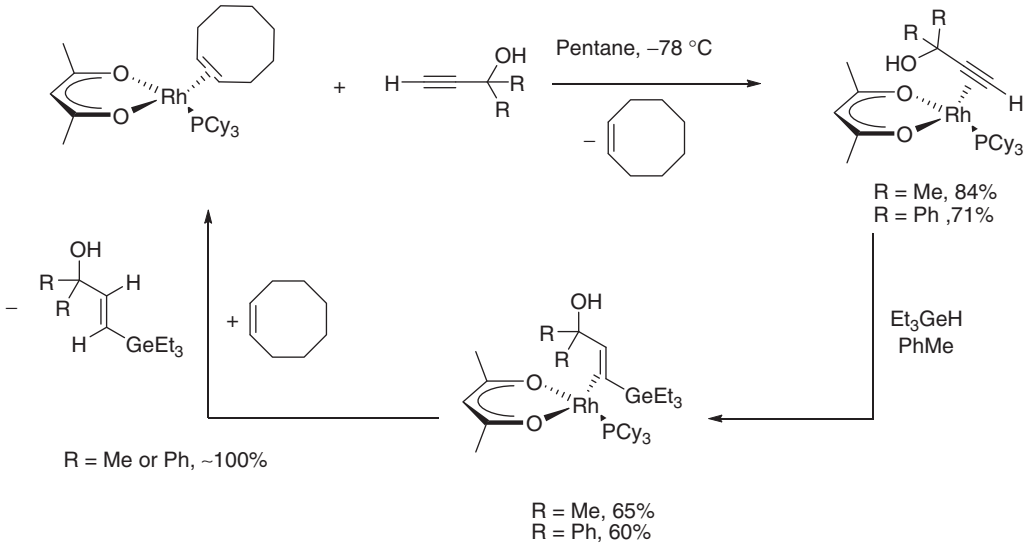
Duchene has reported a highly regio- and stereoselective Lewis acid-free synthesis of vinylgermanes via the hydrogermylation of alkynes. Using ultrasound or microwave heating, hydrogermylation occurred without a transition metal catalyst or AIBN initiator; the (*Z*)-alkenylgermane was the major product.[228]

A tandem hydrogermyl-carbonylation functionalization of alkynes in the presence of CO has also been achieved (Scheme 51).[229]

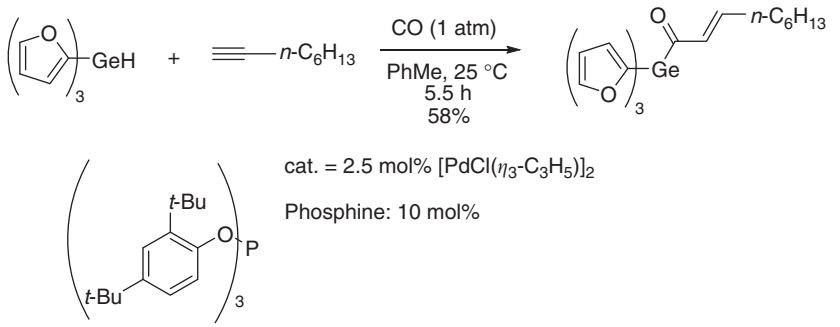
The hydrogermylation polymerization of diphenylgermane with aliphatic and aromatic diynes proceeded smoothly in the presence of Pd–PCy_3 to give new germylene–divinylene polymers in high yields.[230]

8.25.4.3 Hydrogermylation of Carbon–Carbon Double Bonds

Dibutylchlorogermane (Bu_2GeClH) is another hydrogermylating agent used on alkenes that has appeared in recent literature. Following the preparation of this agent from germanium tetrachloride, high yields of a range of alkyl germanes were isolated



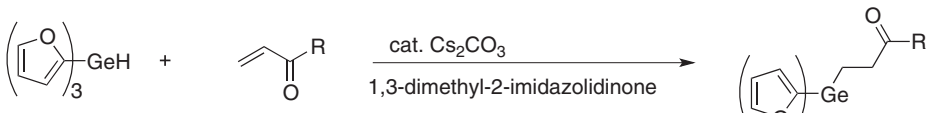
Scheme 50



Scheme 51

under homolytic conditions in an Et_3B-dry air atmosphere at room temperature.[231] Curran has reported two members of a new class of dithiogermanium hydride that have been prepared in both racemic and enantiopure forms. Reaction of 2,2′-dithiobinap and 3,3′-bis-trimethylsilyl-2,2′-dithiobinap with $^tBuGeCl_3$ followed by reduction gave the corresponding germanium hydrides. These were utilized in the hydrogermylation of methyl methacrylate, with the latter giving the best selectivity.[232]

It has been found that alkenes, dienes, alkynes, and carbonyl compounds will all undergo hydrogermylation using tri(2-furyl) germane.[229,233,234] The hydrogermylation process proceeds selectively on the soft center for α,β-unsaturated carbonyl derivatives (Scheme 52). A mini-review of the use of tri(2-furyl)germane, triphenylgermane and their derivatives in synthesis has been published and the reader is directed to this for comprehensive discussion and results.[235]

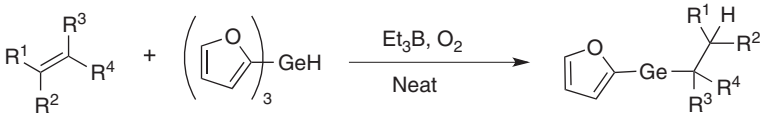


$R = CH_3$, 84%; R = chex, 83%; R = OBun, 95%; $R = NH_2$, 87%

Scheme 52

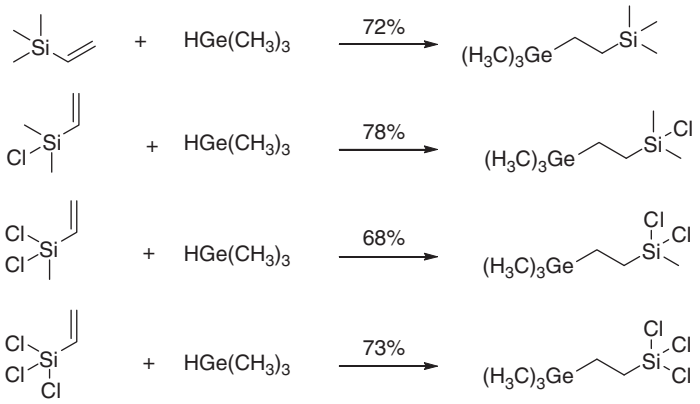
Nakamura has reported the use of triethylborane-promoted hydrogermylation of alkynes and terminal as well as internal alkenes employing tri-2-furylgermane (Scheme 53).[236]

The nucleophilic mechanism of hydrogermylation utilizing trichlorogermane has been suggested by Lakhtin in the preparation of silyl-substituted ethylenes (Scheme 54).[237]



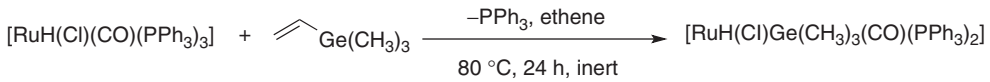
R^1 = *n*-C_3H_7, *n*-C_5H_{11}, Et, Me, C_6H_9Me, H
R^2 = H, Me, Et
R^3 = H, *n*-C_5H_{11}, Me
R^4 = H, Me, *n*-C_3H_7, CH_2OR, $(CH_2)_2COMe$, $(CH_2)_2CH(Me)CH_2CHO$, $CH_2OCH_2CHCH_2$
Yields = 70–100%

Scheme 53



Scheme 54

Functional vinylgermanes have the important synthetic utility as organometallic reagents. Their preparation via germylation of nonisomerising olefins using vinyl-trisubstituted germanes in a novel ruthenium-catalyzed coupling reaction has been reported (Scheme 55).[238] This new catalytic method evades their alternative synthesis by olefin cross-metathesis, which has been found to be limited to vinylsilanes and vinylboronates only.



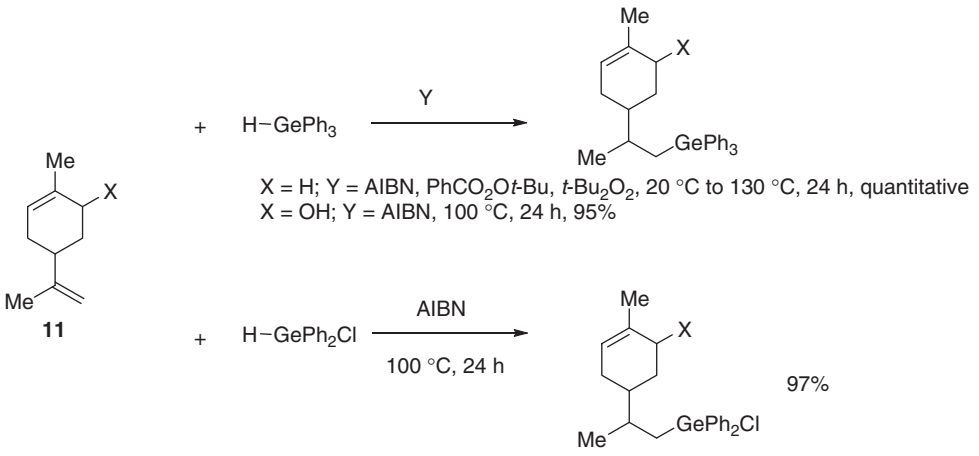
Scheme 55

The radical addition of Ph_3GeH to the ethylenic starting material **11** afforded the near quantitative yields the hydrogermylation products as shown (Scheme 56). The hydrogermylation of the same starting material (**11**) with Ph_2ClGeH was also effective, giving the product in 97% yield (Scheme 56). Ph_2ClGeH has been found to be more reactive than Ph_3GeH, as the Ge radical formed has greater molecular electronegativity and molecular hardnesse owing to the presence of the halogen on the starting material.[239]

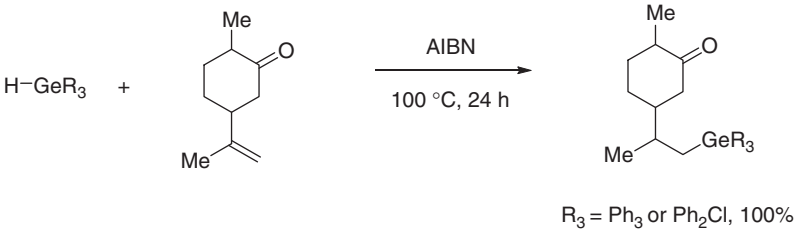
Regioselectivity appears to be influenced by the availability of the HOMO electrons on the exocyclic double bond. Based on DFT calculations, it was found that the structure of the intermediate radical also has an impact on its addition to the substrate and subsequent abstraction of hydrogen. Hydrogermylation of the C=C double bond was also observed when the conditions were applied to nonconjugated systems, with near quantitative yields (Scheme 57).

8.25.4.4 Synthetic Transformations and Applications

The reaction of triethylgermane with alkynes in the presence of a ruthenium catalyst, $[Cp^*Ru(MeCN)_3]PF_6$, occurs in a *trans* manner. The *trans*-hydrogermylation of 1,3-diynes with dihydrogermanes such as Ph_2GeH_2, affords 2,5-disubstituted germoles and in a double addition process was applied to the synthesis of 2,2′-bigermole (Scheme 58).[240] Catalytic copolymerization has been employed to introduce germanium into extended polymeric systems. Examples include the incorporation of the germylene $Ge[N(SiMe_3)_2]_2$ into acetylene monomers using rhodium catalysis (Scheme 59) and copolymerization with different sized cyclic ketones have also been reported (Scheme 59). These novel functional germanium polymers bearing a germanium enolate

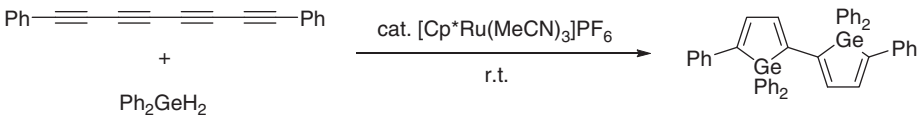


Scheme 56



Scheme 57

structure in the main chain have been prepared for the first time. These unusual germanium enolate units make the polymers structurally interesting particularly in the context of material science.[241]



Scheme 58

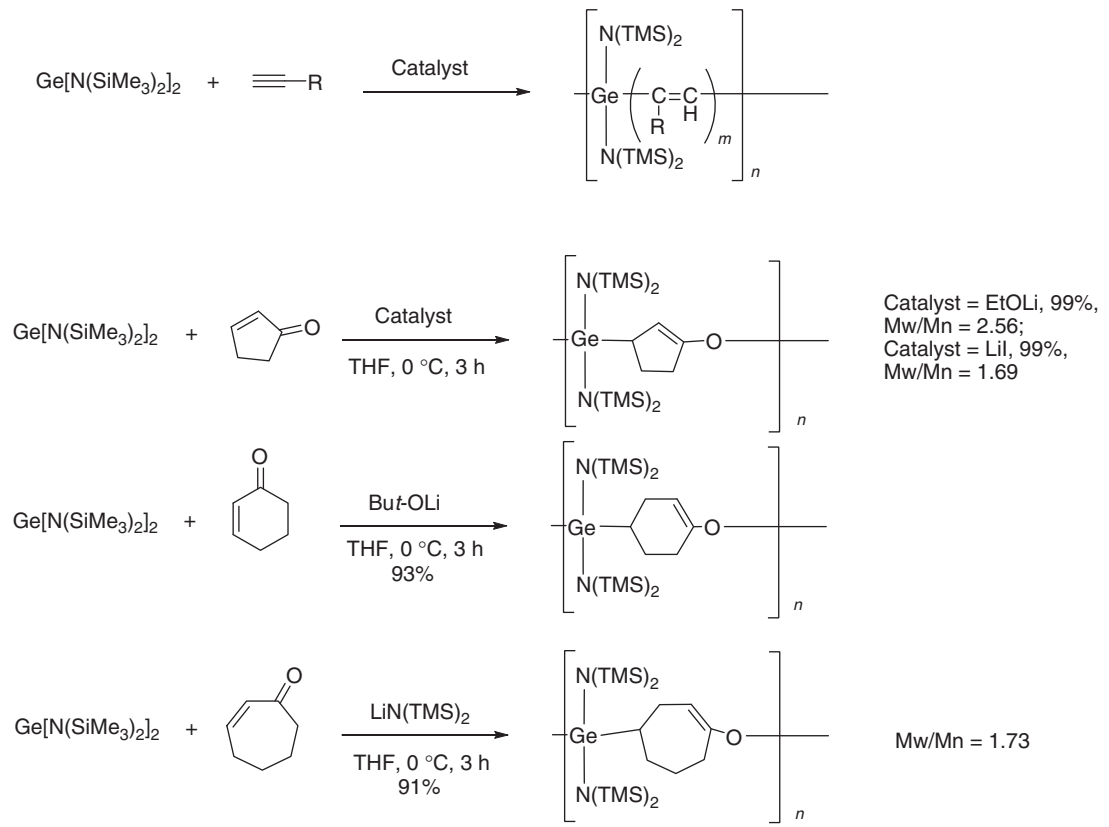
The products of hydrogermylation have a number of multidisciplinary applications. In the field of electronics, germanium nanowires can be incorporated into field effect transistors (FETs). Following their *in situ* preparation, alkylation provides a coating that is resistant to oxidation (Scheme 60).[242]

Karpenko and Kolesnikov have investigated the synthesis and biological activity of germylated steroid analogs for their potential antitumor and antiviral properties. Hydrogermylation was carried out on the conjugated steroid 16-en-20-ones by the addition of trichlorogermane to the double bond in position 16 (Scheme 61).[243] The isomeric ratio was influenced by reaction temperature, with increasing the temperature favoring the formation of isomer b.

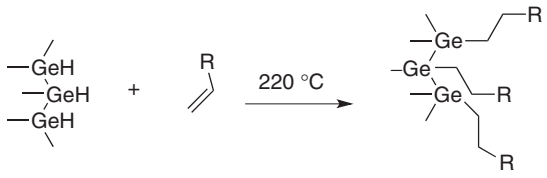
The synthesis and diastereomeric resolution of 2,6-diethyl-4,8-dimethyl-1,5-dioxo-*s*-hydrindacene has been described and the properties of this compound discussed with respect to radical, anionic, and cationic germylation reactions; in particular it acts as an efficient spin trap in the radical hydrogermylation of alkenes.[244]

Substituted vinylgermanes and divinylgermanes have been prepared by the reaction of olefin and dienes catalyzed by [RuHCl(CO)(PCy_3)$_2$] that is, germylative coupling and also by dehydrogenative germylation with hydrogermanes.[245] The reaction of styrene with nBu_3GeH employing ruthenium and rhodium complexes (of which $Ru_3(CO)_{12}$ was the most efficient) gave the corresponding vinylgermanes (α, β-(*Z*)- and β-(*E*)-) as the dehydrogenative germylation products.[246]

The Lewis acid-mediated hydrogermylation of alkenes and alkynes on hydride-terminated Ge(100) surfaces has been described by Buriak.[247] The resultant monolayers were characterized by IR spectroscopy, stability studies, and contact angle measurements. The surface oxidation and chemical passivation of single-crystal Ge nanowires has been studied by Korgel, using wires of diameter 7–25 nm. The behavior was found to be quite different from monolithic atomically single-crystal substrates. Among many reactions studied, thermally initiated hydrogermylation reactions with alkenes produced chemically stable covalently bonded monolayer coatings and this enabled ohmic electrical contacts to be made to the nanowires.[248] The preparation and

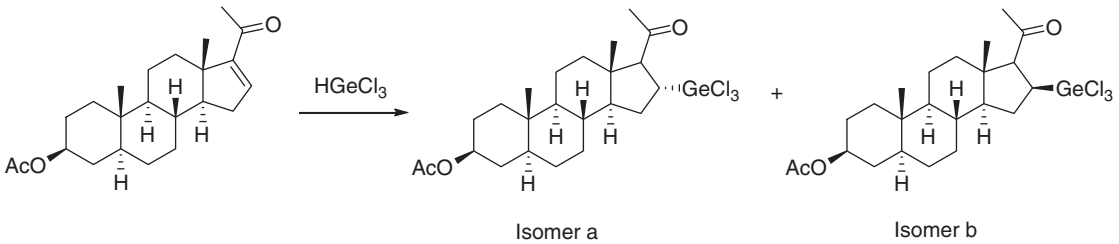


Scheme 59



Thermal hydrogermylation

Scheme 60



Scheme 61

functionalization of porous germanium (PG) has been achieved using a novel bipolar electrochemical etching technique, and scanning electron microscopy has shown the formation of a porous layer a few microns thick and which is Ge–H terminated, as determined by FTIR spectroscopy. Although the material is resistant to thermal oxidation, it does undergo hydrogermylation reactions with alkenes and alkynes.[249]

8.25.5 Hydroplumbation

8.25.5.1 Introduction

In this section, the addition reactions of hydroplumbates to alkenes and alkynes and their synthetic transformations and applications are considered. The reader is referred to Finet's chapter for a general review on well-defined organolead reagents.[250] The authors are aware that there are only limited recent examples of hydroplumbation and therefore related examples will also be presented. The synthesis and chemistry of tin and lead compounds was reviewed in 1992.[251]

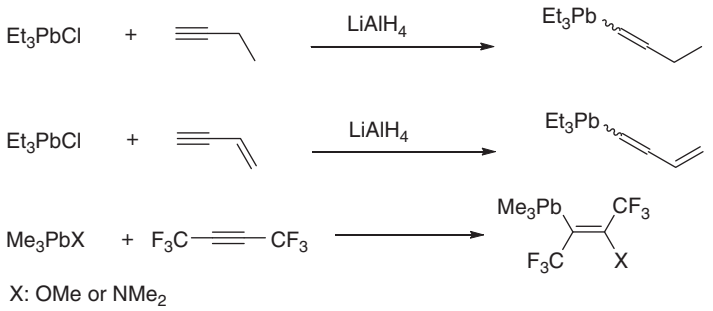
8.25.5.1.1 Available plumbanes

A few plumbanes are now commercially available, and include tricyclohexylplumbane c-hex$_3$PbH, tris(4-methylphenyl)plumbane, tris(1-naphthyl)plumbane, tris(2-methylphenyl)plumbane, tris(2-ethoxyphenyl)plumbane, tris(4-ethoxyphenyl)plumbane, and trimesitylplumbane.

8.25.5.2 Hydroplumbation of Carbon–Carbon Triple Bonds

The synthesis of butadienyl- and butenyl-plumbanes and stannanes by hydroplumbylation and hydrostannylation of vinylacetylene and 1-butyne has been reported.[252]

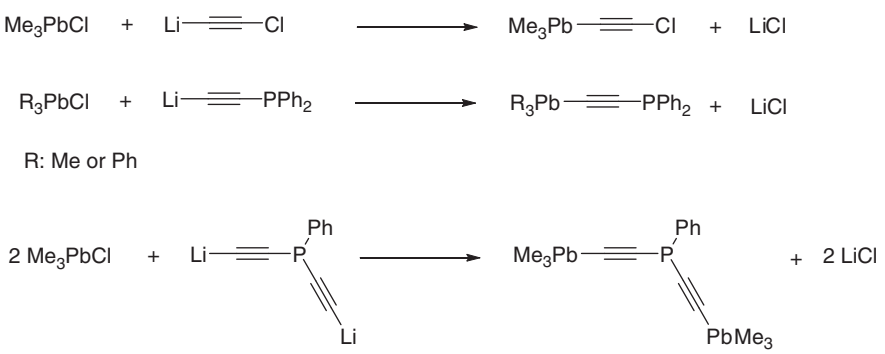
The majority of the examples of hydroplumbylation, alkoxyplumbylation, and amino-plumbylation of alkynes (Scheme 62) date back in the literature to periods outside the scope of this chapter.[252–254]



Scheme 62

The conjugate addition of Et_3PbM (M = Na, Li) to HC≡CSR (R = methyl or ethyl) has been found to be both stereoselective and regioselective to give *cis*-$Et_3PbCH{=}CHSR$. The reaction also proceeded with HC≡COEt to give $CH_2{=}C(OEt)PbEt_3$.[255]

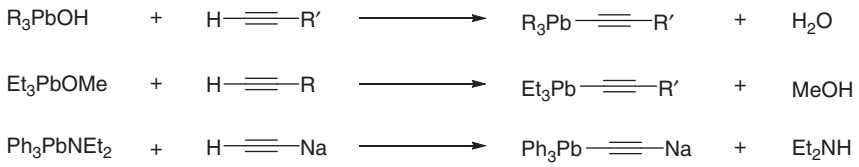
A few related reactions will now also be mentioned. Metathesis reactions coupling an alkynyllithium, an alkynylsodium or a Grignard reagent with the corresponding organolead chloride have been employed to give triorgano(alkynyl)lead and diorganobis (alkynyl)lead compounds (Scheme 63).[256–259]



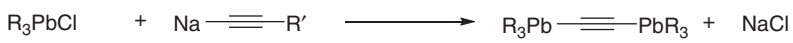
Scheme 63

The protonolysis of triorgano(alkynyl)lead alkoxides, hydroxides, and amines can also afford triorgano(alkynyl)lead derivatives (Scheme 64).[260,261] Bis(metallo)-substituted alkynes may also be prepared using this method (Scheme 65).

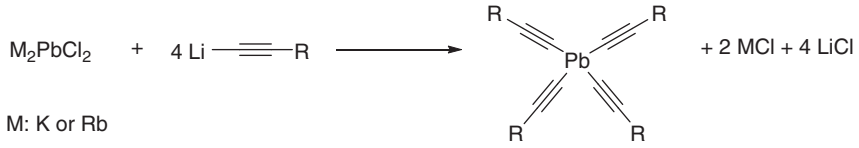
Metathesis between alkali metal hexachloroplumbate (IV) salts and alkynyllithium reagents successfully afforded tetrakis (alkynyl)lead compounds (Scheme 66).[262]



Scheme 64

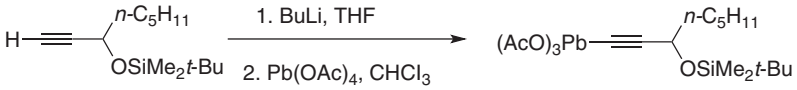


Scheme 65



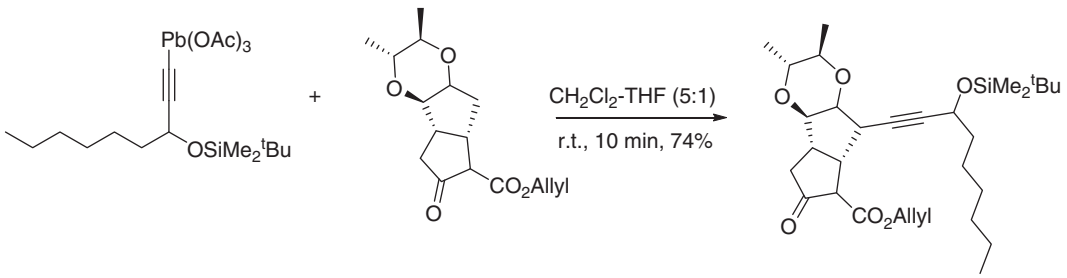
Scheme 66

Traditional transmetallation involving tin-lead exchange or mercury-lead exchange have both been used to generate alkynyllead triacetates.[263,264] However, these approaches involve the isolation of unstable alkynylmetal derivatives and *in situ* transmetallation methods employing lithium or zinc have since been developed. Lithium acetylide in THF can be added to lead tetracetate in CH_2Cl_2 at low temperatures to generate the alkynylmetal reagent *in situ* (Scheme 67). The addition of benzyl β-ketoesters to this reaction mixture yields the corresponding benzyl α-alkynyl-β-ketoesters.[265]



Scheme 67

The use of the optically active (*S*)-alkynyllead triacetate is an example of the alkynylation of enolates, prepared by lithium-lead tetracetate metal–metal exchange (Scheme 68).[266]

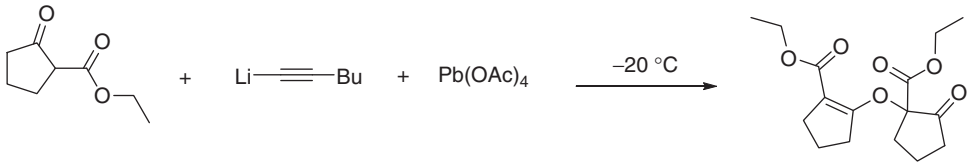


Scheme 68

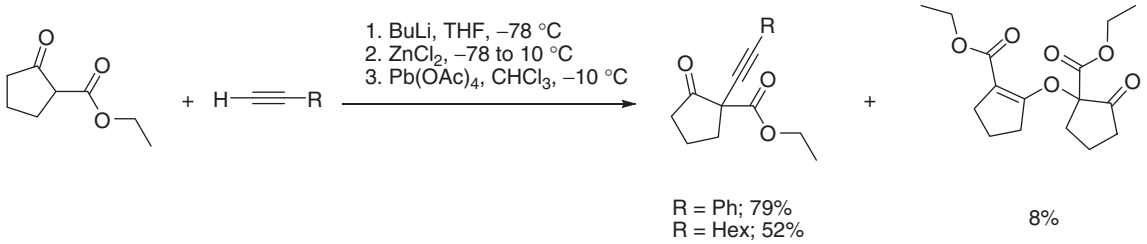
It was observed that the alcohol functional group of the β-ketoester is essential to the success of the alkynylation reactions shown, similar to what has been observed for the alkenylation reactions,[267] with good yields obtained when methyl or benzyl esters are used.[268] However, when the alkynyllead reagent prepared by Li-Pb exchange failed to react with ethyl 2-oxocyclopentanecarboxylate to give the desired alkynylated product and a dimer was isolated instead. (Scheme 69). The addition of $ZnCl_2$ in the generation of a zinc-lead reagent discourages the oxidation of the lead tetraacetate and as a result the dimer has been isolated only as a minor product (Scheme 70).

The zinc-lead metal–metal exchange has been utilized in the alkynylation of a range of soft nucleophiles and several examples are shown in Schemes 71 and 72.[268]

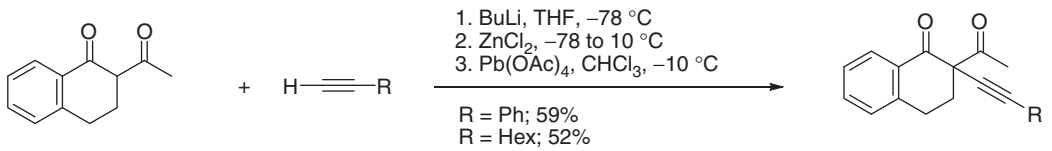
Interestingly, in the final example involving mesitol as a starting material, no alkynylated product was isolated and no dimer resulting from the tin-lead exchange was observed (Scheme 72). Instead, 2-acetoxydienone (**12**) was afforded along with a new

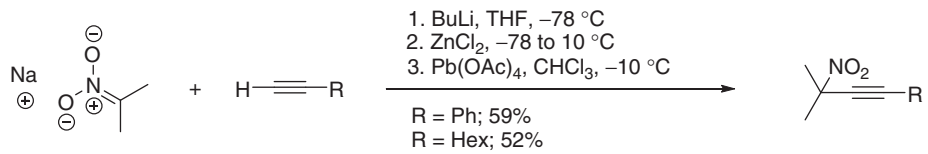


Scheme 69

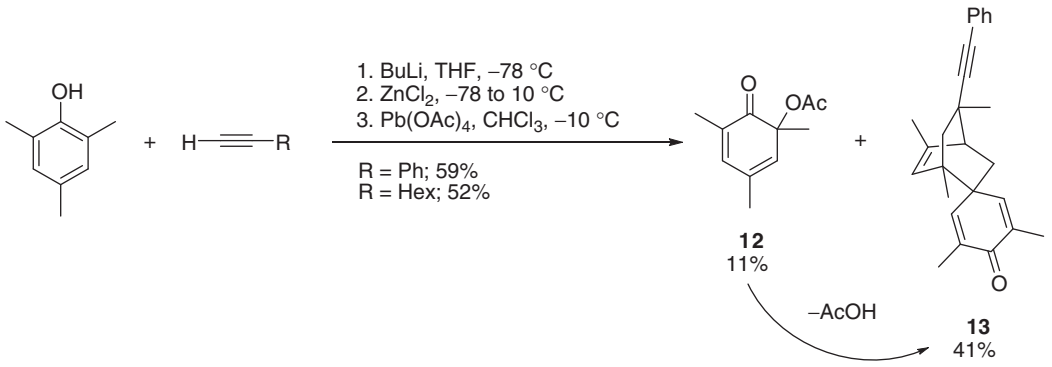


Scheme 70





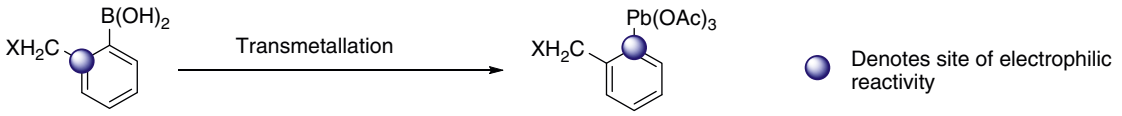
Scheme 71



Scheme 72

dimer **13**, which could be derived from a Diels–Alder reaction between 6-phenylethynyldienone with the aforementioned acetoxylation byproduct (**12**).

Fedorov et al. reported back in 2005 the use of functionalized organolead arylation reagents in the reductive coupling of benzopyran derivatives. Aryllead triacetates were prepared from a boron-lead transmetallation, thereby inverting the reactivities at the electrophilic centere (Scheme 73).[269] These 2-(halomethyl)aryl functionalized organolead reagents were established as efficient tools for the cascade synthesis of benzopyran derivatives in a series of one-pot reactions.



Scheme 73

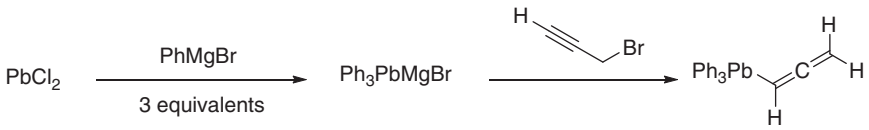
Both vinylmercury and vinylstannane compounds, which may be generated by hydrostannylation reactions or other methods, undergo rapid metal–metal exchange with lead tetraacetate to generate vinyl-lead triacetates; these proved to be unstable, undergoing thermodynamically favorable reductive elimination of lead(II) acetate to give an alkyne or an enol acetate, depending on the original alkene-substitution pattern.[270]

8.25.5.3 Hydroplumbation of Carbon–Carbon Double Bonds

There are no new examples to be considered.

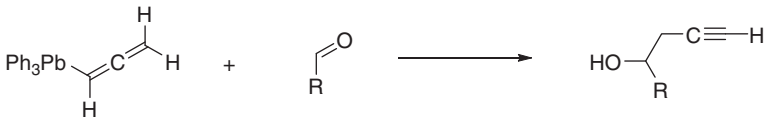
8.25.5.4 Synthetic Transformations and Applications

Triphenyl(allenyl)lead is a good example of an organolead compound having an important synthetic application in organic chemistry. This reagent is prepared from reacting triphenylplumbylmagnesium bromide with the commercially available propargyl bromide (Scheme 74).



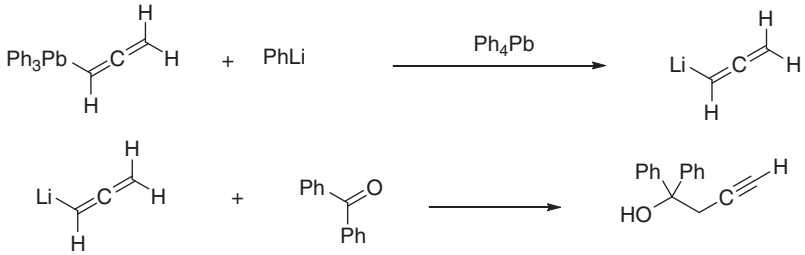
Scheme 74

This is then utilized as a versatile propargylating reagent when subsequently exposed to selected aldehydes under Lewis acidic conditions to yield the corresponding homopropargylic alcohols (Scheme 75).



Scheme 75

It is noted that in order for benzophenone to react under the aforementioned conditions, an extra step of transmetallation between triphenyl(allenyl)lead and phenyllithium was required to generate the reactive organolithium compound (Scheme 76). Treating this with benzophenone gave the desired homopropargylic alcohol 1,1-diphenyl-3-butyn-1-ol in 69% yield (Scheme 76).



Scheme 76

Kang has published extensively on the palladium-catalyzed coupling reactions of organolead compounds with olefins,[271] alkynes,[272] organostannanes,[273] organoboranes,[274] and aryl- and alkenyliodonium salts.[275]

Plumboles have recently been prepared by the reaction of 1,4-dilithio-1,2,3,4-tetraphenyl-1,3-butadiene with dichlorodiphenylplumbane to give hexaphenylplumbole and spirobiplumbole; these were the first examples to be characterized as fluorescent organolead compounds.[276]

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8.26 Reduction of Saturated Alkyl Halides to Alkanes

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Glossary

Dissolving metal reduction The use of a (usually elemental) metal to donate electrons for the purpose of reduction.

Heterogeneous metal A metal that is in the solid phase, rather than in solution.

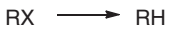
Homogeneous metal A metal or metal complex that is in solution with the reactants.

Hydrogenolysis Breaking a C–X sigma bond so that X is replaced by hydrogen.

Photoredox A redox reaction that is mediated by photochemistry.

8.26.1 Introduction and Scope of the Review

Hydrogenolysis is a fundamental transformation in chemistry. It involves the breaking of a sigma bond so that a functional group is replaced by a hydrogen. In this chapter, reactions where a halogen (I, Br, Cl, or F) is replaced by hydrogen are considered. When reactions of this type are viewed as a single transformation outside the context of synthesis, this may seem like a regressive step. The process effectively removes a valuable functional group from a molecule, limiting the number of reactive handles that may be transformed in later steps – but there are times when such reactions are a critical component of the organic chemist's toolbox. Reactions such as the iodo-lactonization and other halo-functionalization reactions[1] are proven synthetic strategies that add considerable complexity to a molecule, and the residual halide group may no longer be desired after such transformations are achieved. Such methods are also a key component in deoxygenation procedures, where a hydroxyl group is first substituted by a halide, then reduced. Dehalogenation reactions that remove toxic materials from the environment (e.g., the dehalogenation of polychlorinated biphenyls, pesticides, chlorinated solvents, chlorofluorocarbons, or freons and dioxins) may also be extremely important.[2]



R = alkyl group, X = F, Cl, Br, and I

There are a considerable number of reducing agents and reagent systems that are suitable for dehalogenative hydrogenolysis. The choice of a particular set of conditions will be based on these conditions' compatibility with other functionalities present in the molecule, and the convenience of the method in terms of availability, expense, ease of application, as well as environmental impact.

In this chapter, methods for the reduction of alkyl halides to alkanes are surveyed. An excellent review on the hydrogenolysis of organic halides was published by Pinder in 1980;[3] many of the methods available then remain relevant to present day organic synthesis.

The methods are assessed by the type of reagent that is being used to carry out the transformation, with the emphasis being placed on reliable methods that are chemoselective and generally applicable. References to reviews are provided to facilitate an in-depth view of particular reaction types and their uses.

8.26.2 General Observations

The ease of reductive dehalogenation of organic halides is generally proportional to the strength of the carbon–halogen bond. Within the same structural environment, in terms of ease of removal, I > Br > Cl. Fluorine is a special case and is much more difficult to remove. There is strong contemporary interest in defluorination reactions, and promising methods for such procedures are beginning to appear,[4,5] which may eventually lead to the development of more generally useful methods.

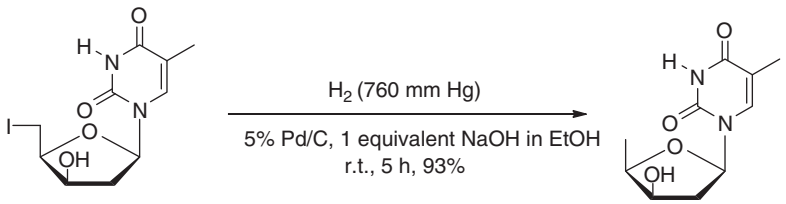
The reactivity of primary, secondary, and tertiary halides will be dependent on the mode of action of the reagents used to perform the reaction. Reactions that occur via carbocations (S_N1-like) and radical intermediates will generally be easier to implement if the halogen is on a tertiary or secondary carbon center. Reactions that proceed through a displacement of the halogen by a nucleophile (S_N2-like) will be faster in the case of a primary halide. Steric considerations may also be important depending on the mechanism of hydrogenolysis.

8.26.3 Catalytic Hydrogenolysis with Metals

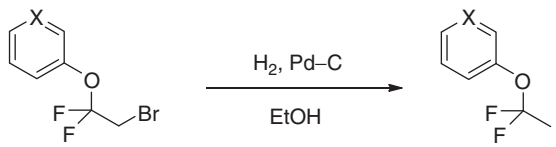
8.26.3.1 Heterogeneous Metals

A convenient way to remove halogens under mild conditions is to use a metal catalyst and a source of hydrogen. Pd is preferred as metal: Raney nickel is deactivated by the halide ion released, so superstoichiometric 'catalyst' is required.[6] Examples of this method in synthesis are typically reported using the inexpensive catalyst Pd/C,[3] whereas Pd on alumina may be preferred for the hydrodechlorination of CFCs.[7] A recent review discussing different supported transition metal catalysts for hydrodechlorination reactions is available.[2b] These reactions are generally done in the presence of a base to neutralize any haloacids formed during the course of the reaction, as both halogen and hydrogen ions may deactivate the catalyst. Hydroxide anions are often used, but acetates, ammonia, and amines can be used for base-sensitive compounds.

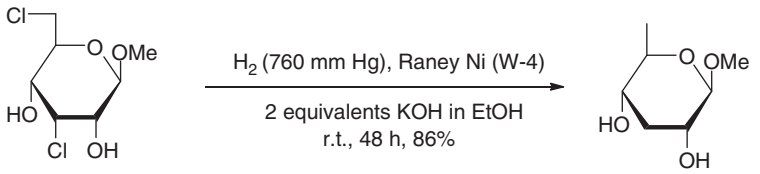
The rate of catalytic hydrogenolysis will depend on the halogen involved and the structure of the molecule. Alkyl halides are generally less easy to hydrogenolyze than aryl, vinyl, benzyl, and allyl halides. Tertiary and secondary halides will be dehalogenated faster than primary halides. For rates of carbon–chlorine hydrogenolysis over a Pd/C catalyst, the following trend was reported: $PdCH_2Cl > PhCl > ClCH_2CO_2H >$ decyl chloride.[7] Benzylic halogens and other activated variants can thus readily be reduced at room temperature under 1 atm of molecular hydrogen.[8] Iodides will generally react faster than bromides and chlorides. Fluorides are not suitable for these procedures. Iodides can be cleaved under Pd/C, MeOH, NaOAc, and H_2 (1 atm) conditions selectively. Scheme 1 illustrates cleavage of a primary iodide;[9] Scheme 2, an example showing excellent selectivity for hydrogenolysis of an alkyl bromide over activated fluorines;[10] Scheme 3, double dechlorination with Raney nickel;[11] and Scheme 4, removal of activated bromines in the presence of sensitive functional groups.[8] An example of the influence of base effecting a competing process when the iodide is eliminated is shown in Scheme 5.[12]



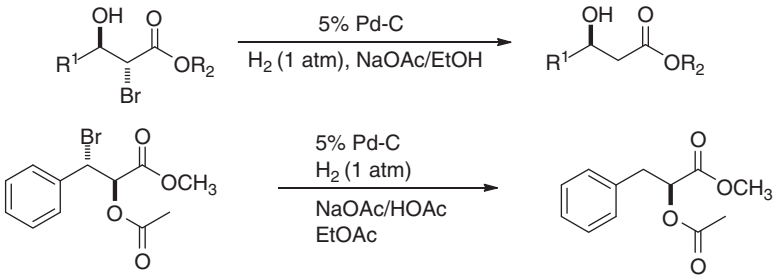
Scheme 1



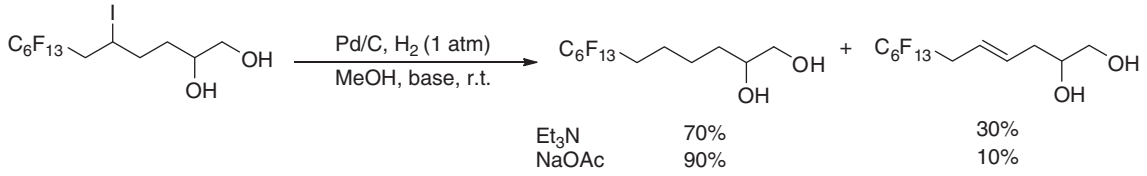
Scheme 2



Scheme 3

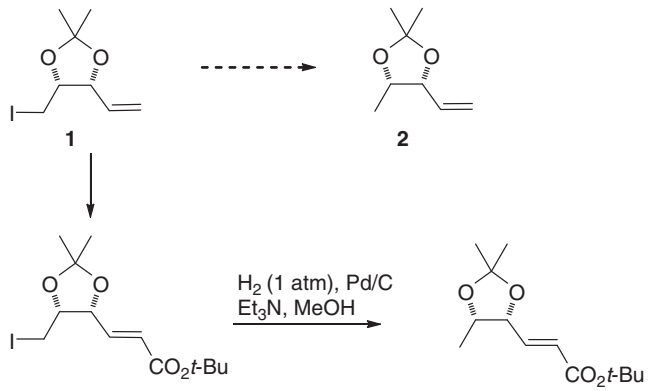


Scheme 4



Scheme 5

The presence of other functional groups can have a profound outcome on the success of these reactions. For example, extensive attempts to reduce iodide **1** to **2** were unsuccessful, but conversion of the olefin to an α,β-unsaturated system by cross-metathesis allowed the iodide to be chemoselectively reduced in the presence of several functional groups by treatment with palladium on charcoal (Scheme 6).[13]

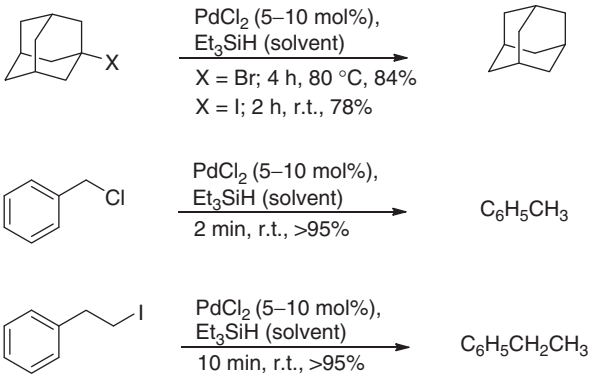


Scheme 6

8.26.3.2 Homogeneous Metals

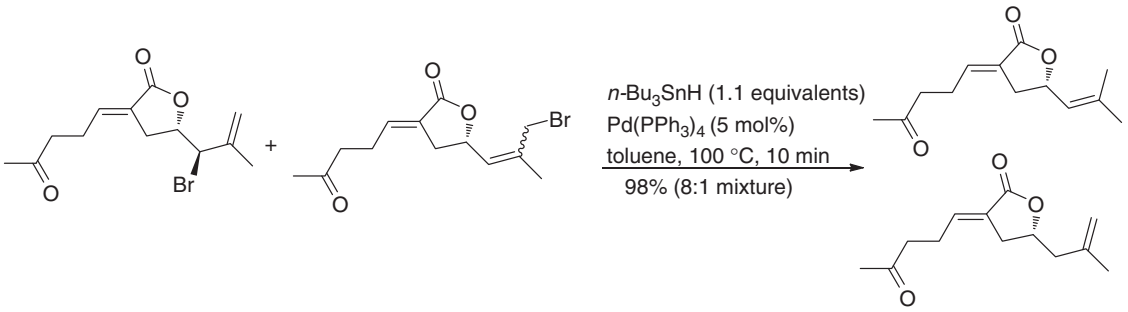
In principle, homogeneous metals could be used much more often in reductive halogenation procedures. In practice, the plethora of other suitable hydrogenolysis conditions probably makes it unnecessary, but the variety of Pd sources, bases, and ligands that are potentially available would provide an extensive opportunity to optimize reaction conditions. There are additional opportunities in using alternative hydrogen sources to H_2, such as formate salts.[14]

Useful procedures have been developed using the combination of $PdCl_2$ and triethylsilane,[15] which will reduce a wide variety of organic halides effectively and rapidly (Scheme 7).



Scheme 7

Allylic and propargylic halides readily undergo palladium-catalyzed hydrogenolysis; even less reactive allyl fluorides can be activated for attack by a hydrogen source.[16] A variety of hydrogen sources can be used to this end.[17] In Scheme 8, a mixture of isomeric bromides was reduced using catalytic homogeneous palladium and stoichiometric tributyltin hydride. Silica gel doped with K_2CO_3 was used to remove tin residues from the mixture.[18]

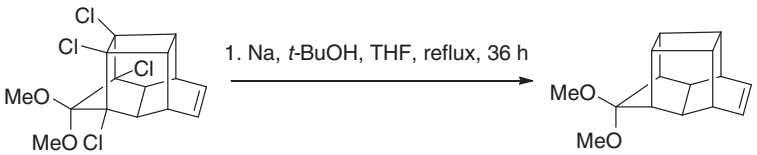


Scheme 8

8.26.4 Dissolving Metals

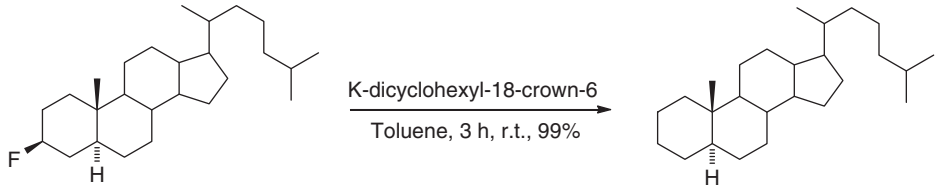
8.26.4.1 Elemental Metals

Alkyl halides may be reduced using reducing metals such as Li, Na, K, Mg, Zn, Fe, etc. The metal-mediated reductive hydrodehalogenation of organic halides has been extensively reviewed by Yus.[7] These are highly reactive conditions and may not be tolerant of some functional groups. In general, Li or Na in an alcohol will reduce saturated halides. Halogens at bridgehead positions are more effectively reduced using these conditions and some functional groups can survive such procedures (Scheme 9).

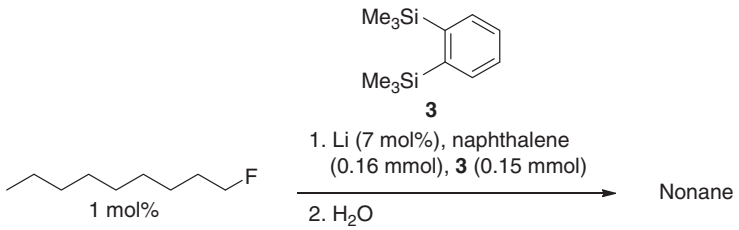


Scheme 9

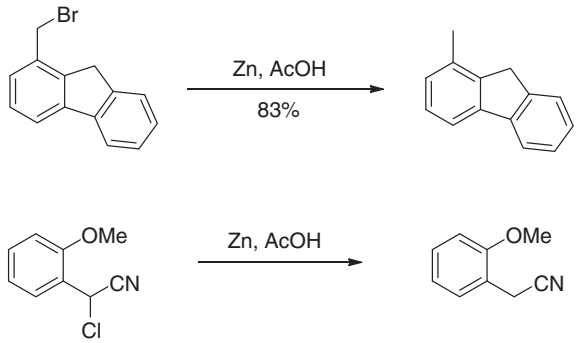
Alkyl fluorides may be reduced using conditions with strong reducing ability. Potassium-crown ether, for example, can reduce unactivated alkyl fluorides at room temperature.[19] An alternative method is to use reducing metal conditions in combination with an organosilicon catalyst, such as **3**, which activates the fluorine toward displacement (Schemes 10–12).[20–22]



Scheme 10



Scheme 11

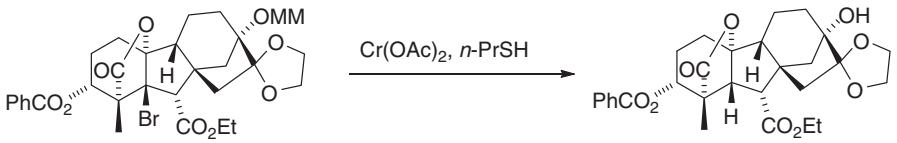


Scheme 12

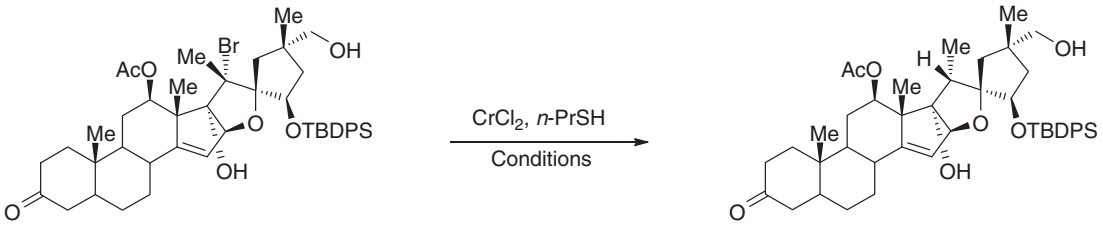
Zinc dust in acetic acid is an effective and mild method for the cleavage of allylic and benzylic halides at room temperature.[21,22]

8.26.4.2 Cr(II) Complexes

Hindered halogens may undergo radical reduction using chromium reagents.[23] The procedure is compatible with an extensive array of functional groups. Retention or inversion of configuration can be observed, and this will depend on the substrate. Generally, thiols are used as a hydrogen source. In the case of the gibberellic acid synthesis shown in Scheme 13, retention of configuration was observed,[24] whereas in the case shown in Scheme 14, the ratio of α- to β-isomers recovered could be adjusted by careful choice of reaction conditions.[25]



Scheme 13



Equivalents of *n*-PrSH	Solvent, temperature	Time (h)	Yield (%)/ratio
100	DMSO, 25 °C	0.5	87% (α/β = 3.6:1)
200	DMF, –15 °C	2.5	84% (α/β = 9:1)
200	DMF, –40 °C	6	80% (α/β = 6:1)

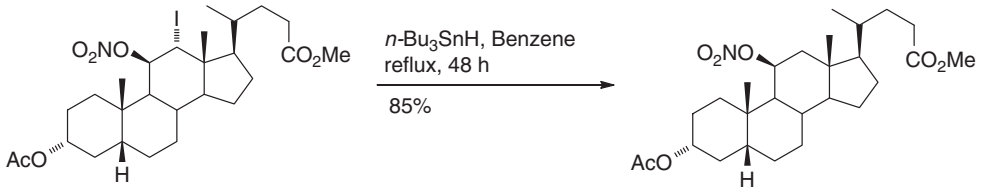
Scheme 14

8.26.5 Nucleophilic Reactions with Metal Hydrides

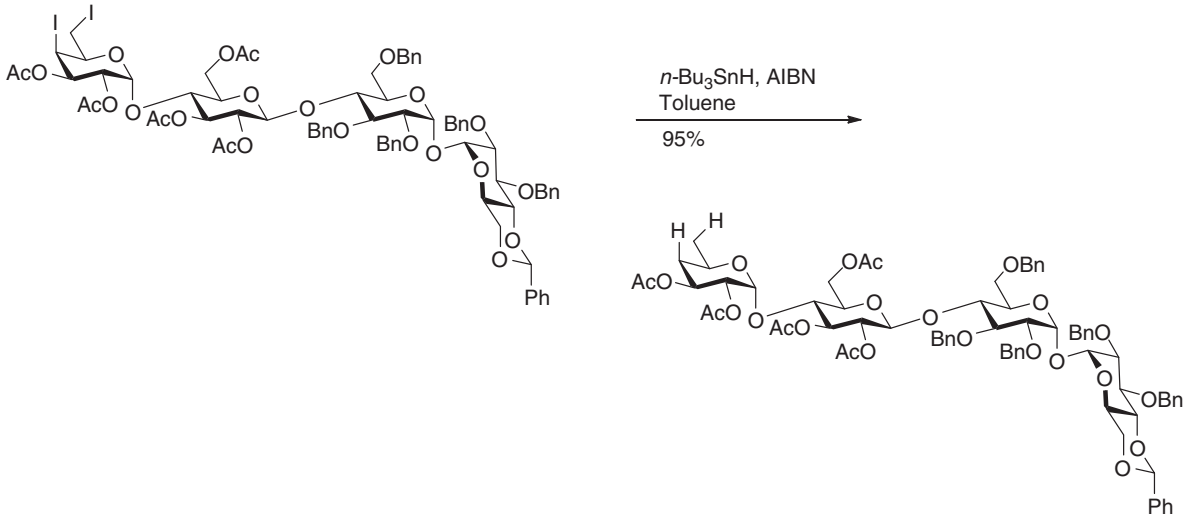
8.26.5.1 Tin Hydrides

Tin hydrides – particularly tributyltin hydride and triphenyltin hydride – are extremely effective for replacing halogens with hydrogen. The high chemoselectivity of these methods has made them a standard reaction choice in the context of complex molecule synthesis. This area has been discussed in an excellent review by Neumann.[26] These reactions occur by radical chain reactions and sensitive functional groups are tolerated. To initiate the radical process, heating in the presence of a free radical source is typically used, but variations include initiation by ultraviolet irradiation or Et_3B in the presence of oxygen. The reactions are easiest for iodides and tertiary substrates. A potential side reaction involves cyclization of the intermediate alkyl radical onto unsaturated groups to form rings.

As shown in Schemes 15[27] and 16,[28] potentially sensitive functional groups are tolerated.



Scheme 15

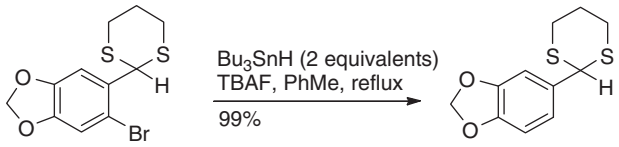


Scheme 16

There are drawbacks associated with methods using stannanes. These include the high toxicity of the organic tin compounds and the difficulty in purifying the product from the residual tin byproducts. Significant efforts have been made to find substitutes for tin hydrides in radical reactions and several useful variations are known. Studer has prepared an excellent review on this subject.[29] The tin reagent itself can be derivatized to be removed more easily – for example, by aqueous extraction.[30]

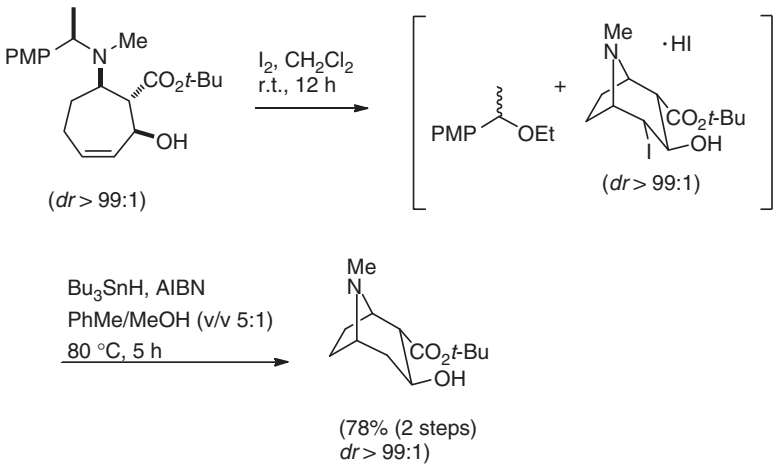
The use of column chromatography with silica gel doped with salts has emerged as an effective method of removing tin residues. The effectiveness of various additives on the chromatographic removal of residual tin was recently evaluated by the groups of Harrowven and Curran;[31] certain fluoride, acetate, and carbonate salts were found to be particularly effective at reducing residues to less than 100 ppm with potassium carbonate and potassium fluoride being particularly effective (Table 1).[31]

Table 1 Various additives and their effectiveness at removal of tin residues from the reduced product via chromatography



Additives	*Levels of tin impurity observed*
Potassium fluoride	28 ppm
Potassium chloride	2–5 mol%
Potassium carbonate	13 ppm
Sodium fluoride	>10 mol%
Sodium carbonate	>10 mol%
Sodium acetate	76 ppm
Calcium fluoride	>10 mol%

This method has been used in a synthesis of (+)-pseudococaine, where iodine-mediated cyclization is followed by radical dehalogenation and chromatography on silica gel containing 10% KF (Scheme 17).[32]

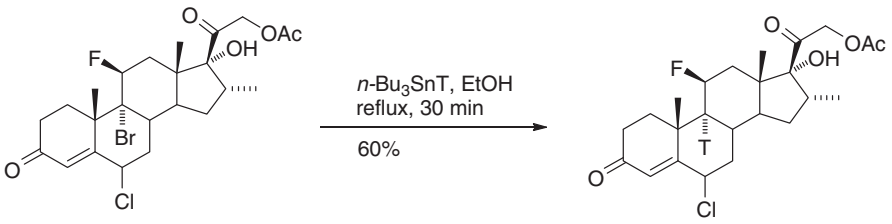


Scheme 17

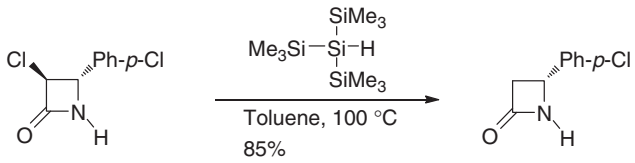
Isotopically labeled stannanes may be prepared and used to introduce deuterium and even tritium labels to compounds.[33] *n*-Bu_3SnT is a potentially versatile tritiation reagent.[34] The example also illustrates excellent selectivity in reactivity between a tertiary Br, an activated Cl, and a secondary F, as well as other functional groups (Scheme 18).

8.26.5.2 Silanes

Tris(trimethylsilyl)silanes are good hydrogen donors and are capable of sustaining radical chain reactions in much the same way as stannanes.[35] For an excellent review, *see* Chatgilialoglu's assessment.[36] Other silanes tend to have stronger H–Si bonds which impede cleavage and effective radical chain generation under mild conditions.[37] Using tris-silylsilanes in the presence of a radical initiator (such as azobisisobutyronitrile (AIBN)) at 80 °C effectively and selectively reduces a variety of halides.[36] For example, see Scheme 19.[38]

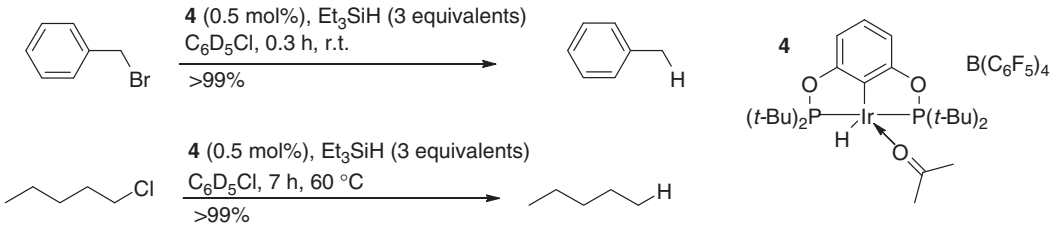


Scheme 18



Scheme 19

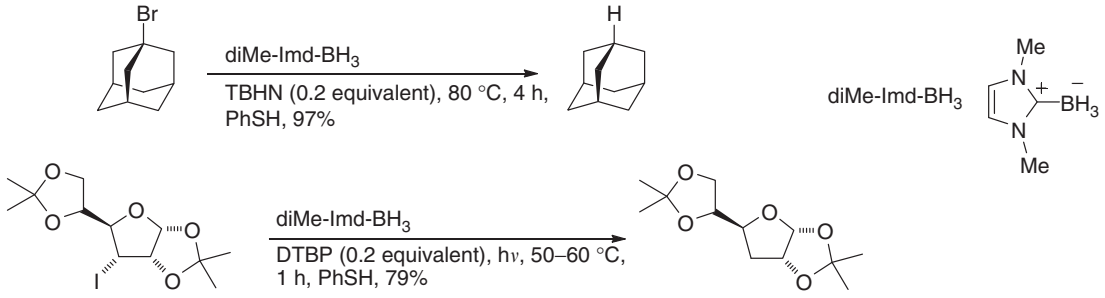
Iridium-catalyzed reduction of alkyl halides by triethylsilane appears to be highly effective, even for reduction of alkyl fluorides (Scheme 20).[39,40] A $PdCl_2$-catalyzed example[15] is shown in Section 8.26.3.2 (Scheme 7).[41]



Scheme 20

8.26.5.3 *N*-Heterocyclic Carbene (NHC)–Boranes

A catalytic amount of an NHC–borane complex has been demonstrated to reduce halides efficiently[42]: thiols are used as the stoichiometric hydrogen source for hydrogenolysis reactions. Radical initiators such as AIBN, Et_3B, and air, di-*tert*-butyl hyponitrite, or the combination of peroxides, light, and heat can be used to initiate these reactions. This method has significant synthetic potential, and a few applications are highlighted in Scheme 21.



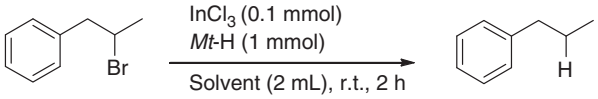
Scheme 21

8.26.5.4 *In situ*-Generated Indium Species

Dihalogen-indium hydrides, generated *in situ* by the transmetallation of indium(III) trihalides and metal hydrides, are increasingly being used as a method to replace tin hydride reagents. Typically sodium borohydride is often used as the hydride source,[43] but many

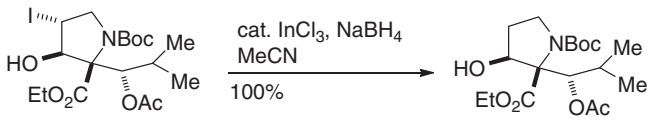
other combinations are possible (Table 2), including Et_3SiH, which may be less likely to cause side reactions due to adventitious borane formation during the course of the reaction.[44] Hydrosilanes can be used in combination with indium salts to reduce bromo- and iodoalkenes at 70 °C in tetrahydrofuran (THF), or near room temperature in the presence of Et_3B and air (Table 2).[45]

Table 2 *In situ* generation of indium hydrides[44]



Mt–H	*Solvent*	*Yield (%)*
Bu_3SnH	THF	82
$NaBH_4$	MeCN	78
Et_3SiH	MeCN	32
Et_3SiH	CH_2Cl_2	83

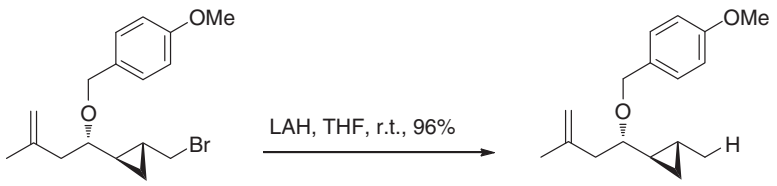
In situ-generated indium hydride appears comparable to tin hydrides in terms of tolerance to functional groups (as seen in the Scheme 22),[41] and avoids the need for extensive purification to remove tin residues.



Scheme 22

8.26.6 Nucleophilic Reductions with Complex Metal Hydrides

A number of hydride reducing agents and systems are capable of highly successful hydrogenolysis reactions with alkyl halides. These reagents have been evaluated and compared in detail by H. C. Brown. $LiEt_3BH$ exhibits the highest hydride transfer ability and is 10 000 times more active than $LiAlH_4$.[46,47] $LiEt_3BH$ or 'superhydride' can be purchased as a solution. Lithium aluminum hydride itself is highly effective for reducing alkyl halides when it is used as a clear solution in THF, so that the reagent is dissolved rather than a slurry.[48] These reactions exhibit typical characteristics of S_N2 substitution reactions, and exhibit little, if any, radical character.[49] Allyl and benzyl bromides are reduced instantaneously, and *n*-alkyl iodides and bromides are reduced rapidly and quantitatively in 15–30 min at room temperature; *n*-alkyl chlorides and secondary bromides and iodides require refluxing THF.[48] These conditions are useful for reduction in the presence of other functional groups that would be sensitive to palladium-mediated or radical procedures (Scheme 23).[50]

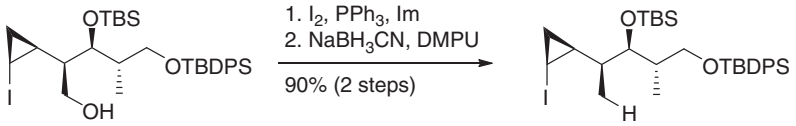


Scheme 23

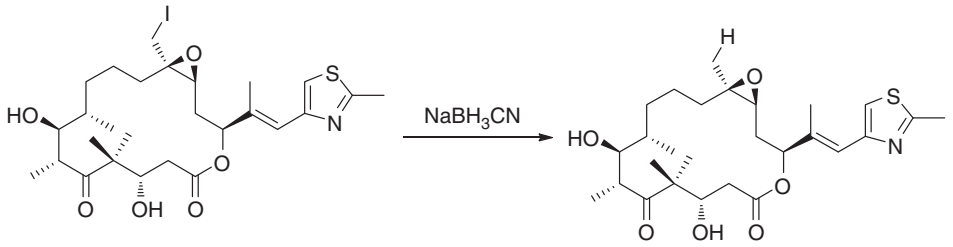
$Li(MeO)_3AlH$, $Li(t\text{-}Bu)_3AlH$, $NaBH_4$, and $LiBH_4$ all react with primary alkyl iodides and bromides at a moderate rate and are essentially inactive toward alkyl chlorides. The body of work by H. C. Brown has also identified which reducing agents are ineffective at reducing halogens, so that these reagents can be used for the chemoselective reduction of other functional groups in the presence of halides. Sodium borohydride, for instance, can tolerate the presence of esters and carboxylic acid groups.[47]

The use of cyanoborohydride reagents, particularly in the (highly toxic) solvent hexamethylphosphoramide (HMPA), is reported to be an exceptionally chemoselective reducing agent for halogens.[51] A particularly impressive example involving the selective removal of one of two iodides is shown in Scheme 24. This procedure was used in a synthetic route to discodermolide.[52]

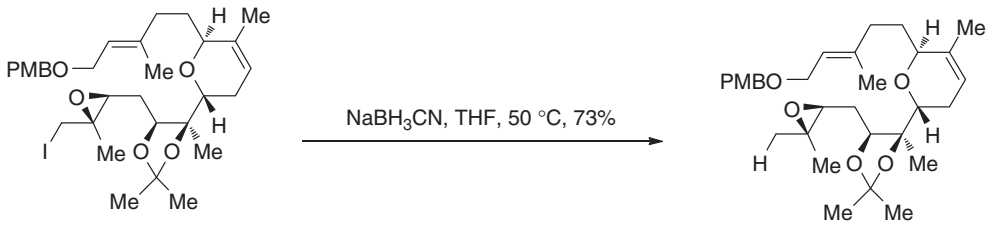
A similarly impressive example, used in the final step of the epothilone B synthesis,[53] is shown in Scheme 25, where it served as a deoxygenation procedure; numerous other conditions examined were incompatible with the array of functional groups present. As illustrated in Scheme 26, it may be possible to use solvents other than HMPA, as THF is used in this case.[54]



Scheme 24



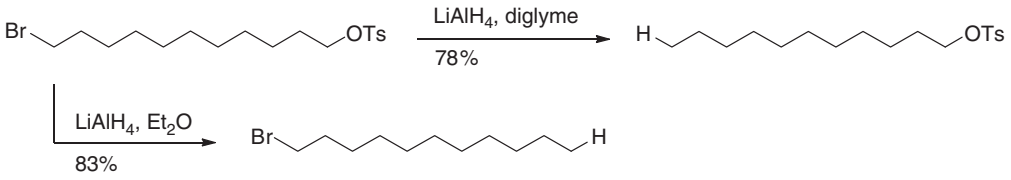
Scheme 25



Scheme 26

Zinc-modified cyanoborohydride in ethyl ether reduces tertiary, allylic, and benzyl halides, but is inert toward other halides.[55]

The solvent plays a key role in determining the functional group selectivity in metal hydride reductions – for example, $LiAlH_4$ in ether selectively reduces alkyl tosylates in the presence of alkyl bromides and iodides, whereas when diglyme is the solvent, the reactivity pattern is reversed (Scheme 27).[56]

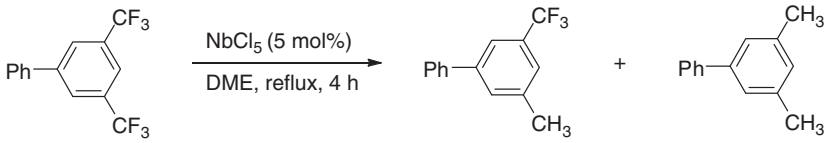


Scheme 27

Catalytic amounts of metal halides can significantly increase the reducing ability of complex metal hydrides. The $LiAlH_4$–$NiCl_2$ system is sufficiently reactive to reduce primary, secondary, and cyclic halides (I, Br, and Cl) at room temperature.[57] The addition of Lewis acids (such as aluminum chloride or cerium chloride) imparts powerful reducing ability, and also enables the reduction of primary alkyl fluorides.[58] As seen below (Scheme 28)[60], trifluorotoluene derivatives can be reduced to toluenes using the rather aggressive reagent combinations of $LiAlH_4$ and $NbCl_5$,[59] or superhydride in combination with nickel catalysts.

Copper hydride species, generated from copper salts and other metal hydrides[61] or organolithiums and copper hydride,[62] are also effective at reducing halogens and can proceed with retention of configuration.

Iron hydride species, generated *in situ* from $NaBH_4$ and catalytic $FeCl_2$, have recently been shown to effectively dehalogenate saturated alkenes through a radical mechanism.[63]



$LiAlH_4$ (10 equivalents)	0%	78%
$LiAlH_4$ (3 equivalents)	77%	4%

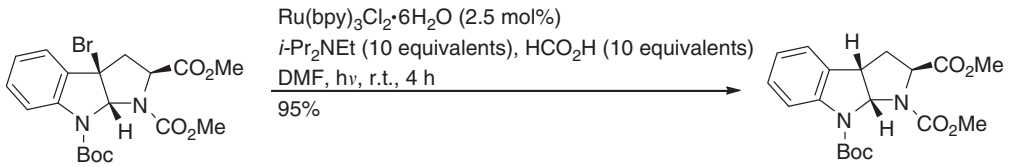
Scheme 28

8.26.7 Samarium Diiodide

A mixture of samarium diiodide, HMPA, and THF will reduce alkyl halides very effectively, much more so than unactivated SmI_2 complexes.[64] These complexes initiate radical reactions via halide reduction, but further reduction of the radical to the anion is competitive with this process.[65] Although competitive processes (e.g., cyclization or reduction of carbonyl moieties) are possible, SmI_2 in the presence of HMPA effectively reduces iodides and bromides to the corresponding alkanes at room temperature, whereas chlorides may require heating and fluorides are inert.

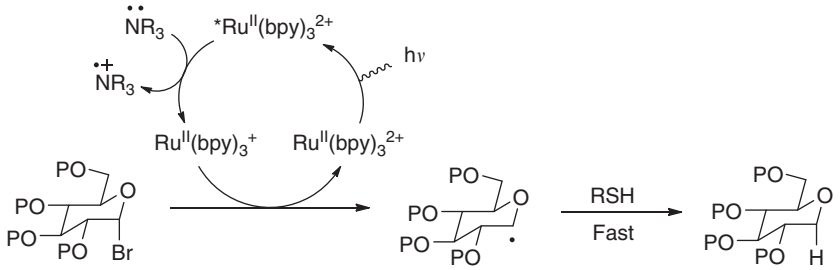
8.26.8 Photoredox Reactions

Electron-transfer photoredox catalysts has tremendous potential in reductive halogenation reactions (Scheme 29).[66] Application of photoredox catalysis inflow has been demonstrated by Jamison and Stephenson.[67] Flow reactions of this type demonstrate high efficiency in terms of material throughput and very high rates of substrate conversion are possible.[67]



Scheme 29

The dehalogenative photoredox cycle is dependent on several variables including the hydrophobicity of the catalyst and the presence of cosolvents. Mechanistic studies by Gagne show that even quite difficult transformations with high synthetic relevance can be achieved with careful consideration of conditions (Scheme 30).[68]



Scheme 30

It seems likely that in the near future additional useful reactions for reductive halogenation will appear based on expansion of photoredox and/or flow processes.

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8.27 Reduction of Saturated Alcohols and Amines to Alkanes

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Glossary

Barton McCombie deoxygenation A radical reaction, first devised by Barton and McCombie, which formally replaces a C–O bond by a C–H bond.

Ionic deamination A heterolytic reaction which formally replaces a C–N bond by a C–H bond.

Ionic deoxygenation A heterolytic reaction which formally replaces a C–O bond by a C–H bond.

Lithium deamination A deamination reaction, formally replacing a C–N bond by a C–H bond, promoted by lithium metal.

Molybdenum-based redactor A chemical-reducing agent based on molybdenum metal.

NHC borane Lewis acid base complex between an *N* Heterocyclic Carbene (NHC) and a borane derivative.

Phosphine borane Lewis acid base complex between a phosphane and a borane derivative.

Phosphine oxide Compound of the general formula $R_3P=O$, with in general R = Ph.

Photocatalytic reduction A reductive process catalyzed by a light-activated catalyst.

Samarium deamination A deamination reaction, formally replacing a C–N bond by a C–H bond, promoted by samarium diiodide.

Samarium reduction A reductive process promoted by samarium diiodide.

Tin hydride Compound of the general formula R_3SnH, with in general R = *n*-Bu.

8.27.1 Introduction

Over the past two decades, the reduction of alcohols and amines to alkanes has continued to motivate intense research developments. The principal reason for this is the fact that alcohol or amine functional groups are pivotal to the construction of elaborated molecules and in some cases need to be introduced only in a temporary fashion. An application of this type of method is the finely tuned modification of complex natural products or molecules with relevant properties by removal of the alcohol or amine function. Among the methods for reducing alcohols, homolytic reactions still hold the lion's share, and in particular those featuring Barton–McCombie-derived processes. Emphasis has been put on the development of more environmentally benign processes: catalytic pathways and tin-free mediators, for example. Metal-mediated radical processes, which have also witnessed some valuable developments, are presented. Heterolytic deoxygenation processes make use of very different types of reagents, and feature versatile catalytic processes. For deaminations, a series of reductive processes relying on the use of metal-promoted or metal-catalyzed processes, as well as astucious ionic reactions have been devised.

8.27.2 Reductive Deoxygenation of Alcohols and Their Derivatives

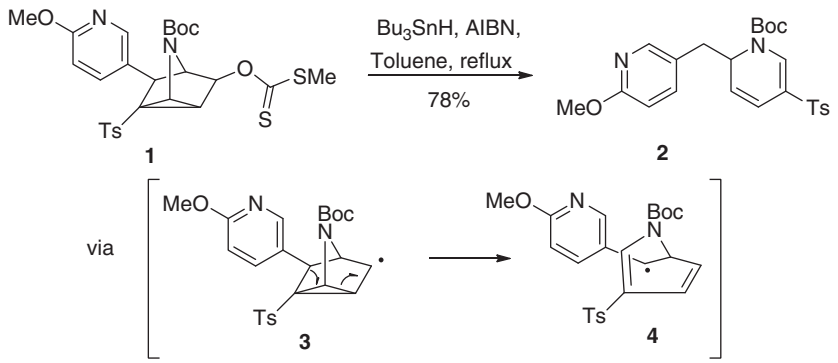
8.27.2.1 Deoxygenation by Radical Processes

8.27.2.1.1 Applications of the traditional Barton–McCombie reaction

Radical deoxygenation of alcohols is a well-established process. Seminal work was covered in the previous edition of Comprehensive Organic Synthesis[1] and have established the Barton–McCombie reaction and related protocols as the most versatile methods to accomplish this type of transformations.

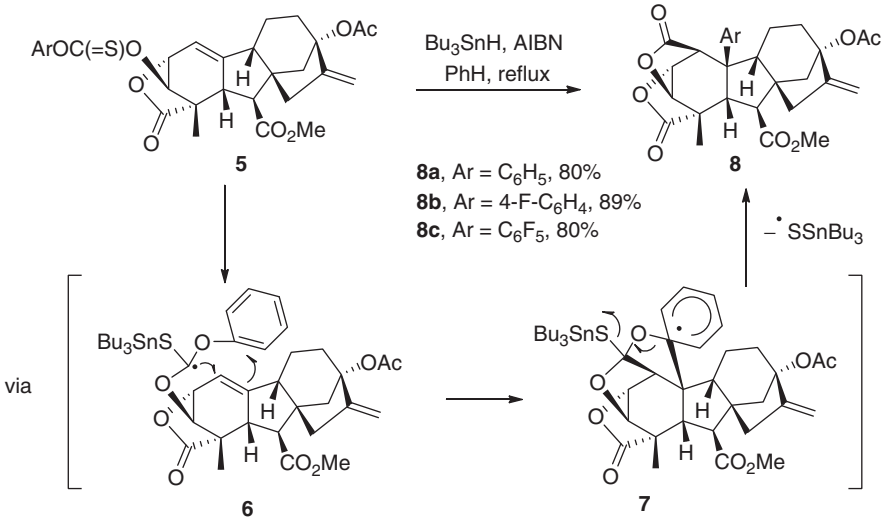
Since then, this reaction has truly entered mainstream chemistry and has been for instance regularly employed in total synthesis studies of various targets such as capnellene,[2] pleuromutilin,[3] siphonarienal,[4] callipeltoside C,[5] anominine,[6] wiedemannic acid,[7] lanosterol,[8] serricornin,[9] and marcfortine B.[10]

The reaction was also exploited in the preparation of molecules with relevant bioactive profiles. Matsuda thus reported the synthesis of 2′,3′-dideoxy-2′-*C*-methyl- and 2′-*C*-ethynyl-*β*-D-*threo*-pentafuranosyl pyrimidines and adenine as potential antiviral and antitumor agents,[11] as well as of 2′-*C*-alkynyl-2′-deoxy-1-*β*-D-arabinofuranosylpyrimidines.[12] In this chapter, we will not deal with aborted Barton–McCombie type of reactions that do not lead to deoxygenation,[13] but we will cover works in which the generated radical intermediate may undergo some intramolecular rearrangements before being reduced and may lead to interesting products. Thus, Hodgson and coworkers, during the development of novel analgesics related to epibatidine, have reported a homoallylic rearrangement driven by the stabilization of a nitrogen atom leading to 2-azabicyclo[2.2.1]hept-5-enes.[14] Introducing an aryl group at position **7** as in **1** induced a different reaction pathway, featuring the intermediate formation of a benzylic radical **4**, and allowed access to dihydropyridines such as **2** (Scheme 1).[15]



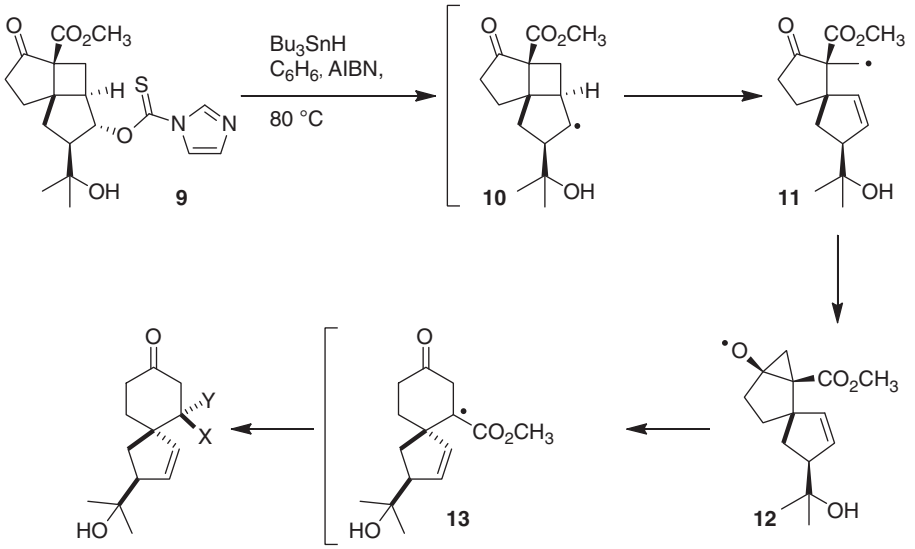
Scheme 1

Although investigating new routes to Gibberellins, Sherburn[16] reported, instead of the expected deoxygenation products, an efficient *C*-arylation from aryl 3-*O*-thionocarbonates **5** on treatment with Bu_3SnH and AIBN yielding products **8**. This intriguing rearrangement involving a homoallylic secondary alcohol inspired the intramolecular carboxyarylation approach to podophyllotoxin that was later developed by the same group (Scheme 2).[17]



Scheme 2

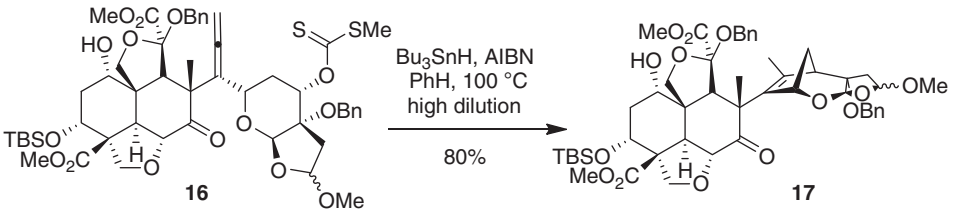
The use of radical rearrangement and fragmentation allows the construction of complex systems in remarkable ways. Crimmins and coworkers during the total synthesis of lubinol, introduced a quaternary spirocenter through a multi-step sequence (Scheme 3).[18] The preliminary deoxygenation step is followed by a radical cyclobutane opening. The resulting methyl radical **11** then undergoes a Dowd–Beckwith ring expansion step[19] involving the carbonyl function of the cyclopentanone. The final product is obtained in 92% yield and consists of two diastereomers **14** and **15**.



Scheme 3

Versatile applications have been developed consisting of tandem deoxygenation–cyclization reactions. One such application was proposed by Nicolaou in the total synthesis of platencin.[20] Two possible modes of evolution of a homoallyl radical resulting from a deoxygenation step are possible depending on the nature of a neighboring OH protecting group. The side 5-*exo*-trig product is major with a pivalate group, whereas a 2-(trimethylsilyl)ethoxymethyl group yields the desired [2.2.2] bicyclic product, originating from a homoallyl rearrangement.

In the total synthesis of azadirachtin, Ley used an allene moiety (substrate **16**) as a radical acceptor in a 5-*exo* process that allowed the assembly of the polycyclic framework **17** (Scheme 4).[21]

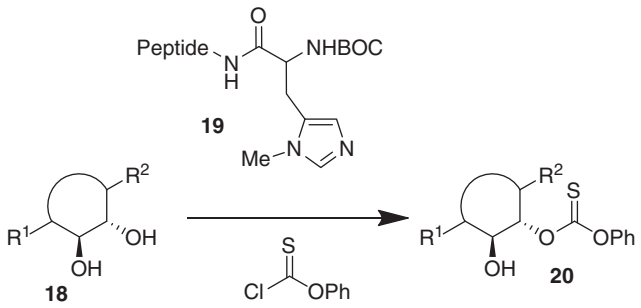


Scheme 4

The regioselective deoxygenation of polyols has been investigated by the Miller group. They have demonstrated that the selective thiocarbonylation of one hydroxyl group from a polyol structure was possible by the use of short peptide derivatives of histidine **19**, as in the transformation of **18** to **20** (Scheme 5).[22]

8.27.2.1.2 Methodological developments in the Barton–McCombie reaction

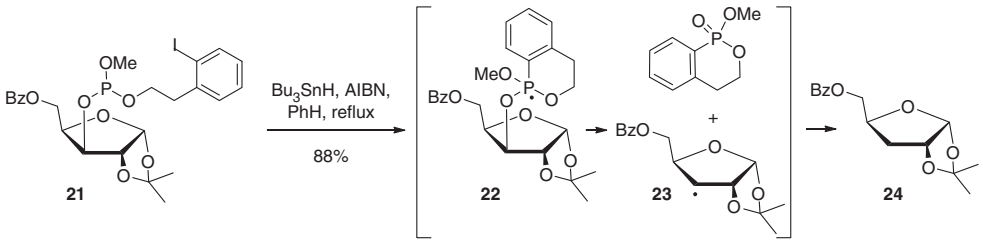
This section focuses on optimizations of the Barton–McCombie reaction, introducing new substrates amenable to this transformation, new hydrogen-donors or new sets of reagents.



Scheme 5

8.27.2.1.2.1 New substrates

In 2004, Koreeda introduced phosphites as new derivatives for radical deoxygenation. The intramolecular addition of an aryl radical derived from **21** generates an intermediate phosphoranyl radical **22**. This fragments to give the deoxygenated product **24** after reduction of the radical **23** (Scheme 6). The method works best with hindered – especially tertiary – alcohols, and the phosphonate byproduct is easily removed from the desired compound. These two features ensure that this method is an attractive alternative to the Barton–McCombie deoxygenation of alcohols.[23]



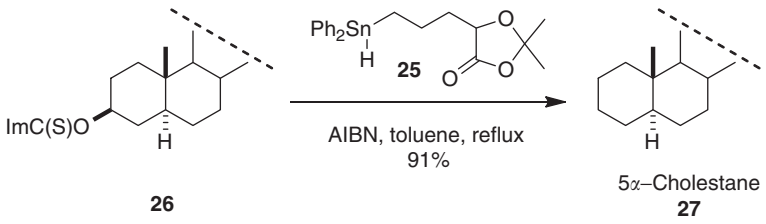
Scheme 6

8.27.2.1.2.2 New mediators

The Barton–McCombie deoxygenation initially made use of tin hydrides as mediators, but the latter are no longer desirable as reagents because of their toxicity and the residues that contaminate final products. Different groups have proposed solutions to this problem.

8.27.2.1.2.2.1 Modified tin hydride mediator

The group of Clive developed and used a tin hydride reagent that, after a reaction activated by AIBN or Et_3B/air, can be easily removed by flash chromatography. This tin hydride mediator **25** (Scheme 7) was designed in order to facilitate the removal of tin-containing byproducts, using a mild hydrolysis (LiOH–water–tetrahydrofuran (THF) or TsOH–water–THF), which converts them into base-soluble (aqueous $NaHCO_3$) materials, and then flash chromatography (Scheme 7).[24]

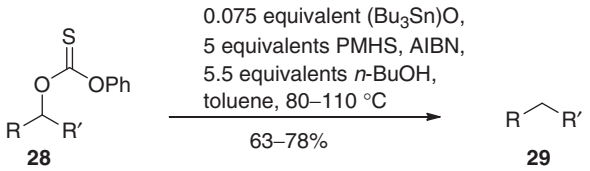


Scheme 7

8.27.2.1.2.2.2 Diminishing the quantity of tin reagents

In 1997, Fu was the first to report a Bu_3SnH-catalyzed Barton–McCombie deoxygenation of alcohol thionocarbonate derivatives **28**, relying on the use of 0.075 equivalent of $(Bu_3Sn)O$ as the catalyst and polymethylhydrosiloxane $(TMSO–(SiHMeO)_n–TMS$ or PMHS) as the stoichiometric reductant (Scheme 8).[25] Yields similar to the stoichiometric reaction were obtained. $(Bu_3Sn)_2O$ and Bu_3SnH can be used interchangeably, $(Bu_3Sn)_2O$ having the advantage of being cheaper and more stable. The addition of *n*-BuOH

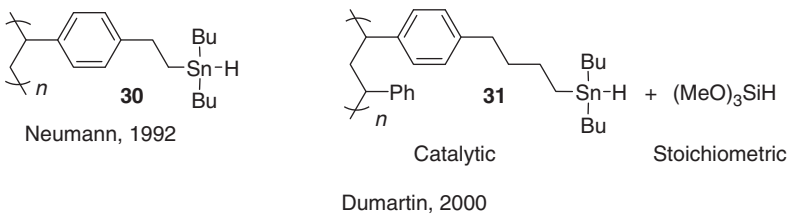
proved to be critical to the turnover of the reaction by helping the formation of Bu_3SnH from $(Bu_3Sn)_2O$ and by regenerating Bu_3SnH from Bu_3SnOPh.



Scheme 8

An alternative way to diminish the quantity of tin residues was devised by Neumann who developed the polystyrene-supported di-*n*-butyltin hydride reagent **30** which gives good yields of reduction products contaminated with a few ppm of tin (as determined by atomic absorption analysis).[26] Another advantage of the polymeric mediator is that it can be recycled by treating the spent polymers containing tin–sulfur adducts.

A more ambitious approach has been followed by Dumartin who looked at the possibility of using only a catalytic amount (0.1 equivalent) of polymer-supported tin hydride **31** in the presence of trimethoxysilane as a stoichiometric reducing agent.[27] Secondary phenoxythionocarbonates were deoxygenated in yields comparable to the traditional tin hydride method. It was shown that the best silanes to achieve the reduction of phenoxytributyltin were trimethoxysilane and PMHS (Scheme 9).



Scheme 9

8.27.2.1.2.2.3 Silanes

Silanes have been used as substitutes for tin hydride derivatives by several groups. Nishiyama devised the radical reduction of alcohols via their thionocarbamate derivatives formed *in situ* by the addition of isothiocyanates using triethylsilane,[28] triphenylsilane and tris(trimethylsilyl)silane as mediators[29] and the use of peroxides as initiators. Contemporary to these findings, Jaszberenyi et al. showed that phenylsilane, triphenylsilane, and triethylsilane could be used in the presence of benzoyl peroxide for the radical deoxygenation of primary, secondary, and vic-diols leading to the corresponding hydrocarbon and alkene derivatives.[30] In this study, they also established, using the model 1,2;5,6-di-*O*-isopropylidene-alpha-D-glucofuranose 4-fluorophenyl thionocarbonate **30a**, the following order of reactivity of the silanes: $Bu_3SnH > (Me_3Si)_3SiH > PhSiH_3 \approx PH_2SiH_2 \approx Ph_3SiH > Et_3SiH$. Complementary results were provided with diphenylsilane and it was shown that AIBN and Et_3B could be used as initiators.[31] Using also diphenylsilane, Jang developed the reduction of trifluoroacetate derivatives of various alcohols.[32] This method proved especially versatile when dealing with tertiary alcohols.[33]

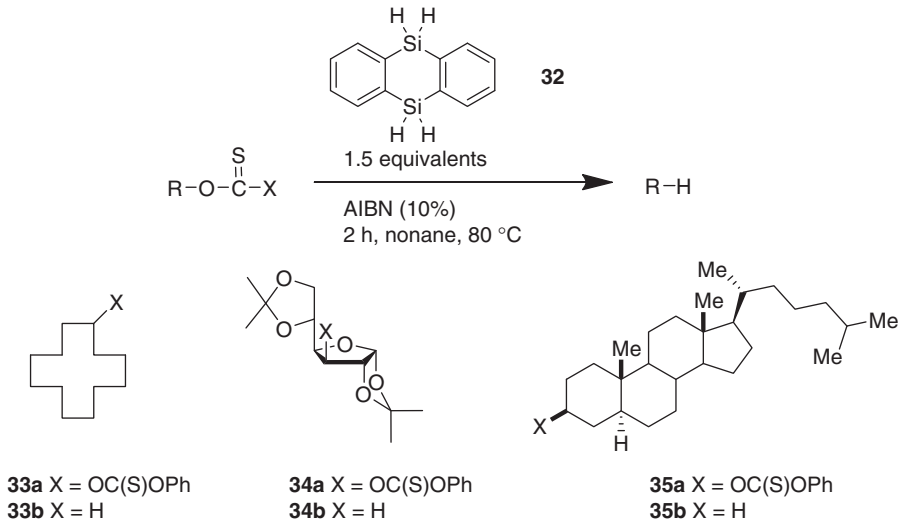
Following the initial work by Nishiyama on 5,10-dihydrosilanthrenes,[34] Chatgilialoglu studied in detail the reduction of secondary alcohols by the unsubstituted 5,10-dihydrosilanthrene **32**, giving good yields of products (Table 1).[35] Reactions were run at 0.2 M concentration in nonane (Scheme 10).

Table 1 Reduction of some organic derivatives by silane **32**

Substrate	*Product*	*Yield (%)*
33a	**33b**	99[a]
34a	**34b**	91[a]
35a	**35b**	85[b]

[a]GC yield.
[b]Isolated yields.

In 2000, B.P. Roberts reported the deoxygenation of methoxymethyl (MOM) ethers in the presence of peroxide and a thiol catalyst.[36]



33a X = OC(S)OPh
33b X = H

34a X = OC(S)OPh
34b X = H

35a X = OC(S)OPh
35b X = H

Scheme 10

8.27.2.1.2.2.4 Phosphine oxides and related

Di-*n*-butylphosphine oxide has been used by Jang and Barton for the radical deoxygenation of *S*-methyl dithiocarbonate derivatives (Table 2). The advantages of the process reside in the applicability of various radical initiators (*t*BuOO*t*Bu, AIBN, 1,1′-azobis(cyclohexanecarbonitrile (ABCN)), the nonrequirement for a large amount (1.5 equivalents) of hydrogen donor in most cases and of reaction conditions which need not strictly exclude moisture (Scheme 11).[37]

Table 2 Deoxygenation of *S*-methyl dithiocarbonate derivatives with di-*n*-butylphosphine oxide in refluxing dioxane

Substrate	*$^{n}Bu_2P(O)H$ (equivalents)*	*Initiator[c] (equivalents)*	*Time (h)*	*Product*	*Yield (%)*
36a	1.5	ABCN (0.75)	24	**36b**	92[a]
37a	1.5	^{t}BuOO^{t}Bu (0.5)	16	**37b**	85
38a	1.5	ABCN (0.25)	8	**38b**	90[a]
39a	1.5	^{t}BuOO^{t}Bu (0.5)	16	**35b**	97
40a	3.0	AIBN (0.75)	24	**34b**	93
41a[b]	5.0	AIBN (1.0)	32	**41b**	80

[a]Measured by GC.
[b]In refluxing xylenes.
[c]ABCN = 1,1′-azobis(cyclohexanecarbonitrile).

Other phosphorus derivatives can be used. In the context of industrial synthesis, Graham et al.[38] from the Abbott Laboratories developed a large-scale (15 kg) deoxygenation procedure of erythromycin derivatives using sodium hypophosphite in alcoholic solvents and a phase transfer agent.

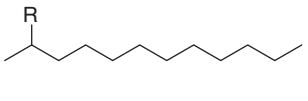
8.27.2.1.2.2.5 Lewis acid and base complexes

Water or boranes are not good hydrogen donors, the O–H and B–H bond dissociation energies (BDE) being too high (>100 kcal mol^{-1}). However, when complexed to a Lewis base or to a Lewis acid, lowering of the BDE occurs[39] and the resulting complexes become competent hydrogen donors, through O–H and B–H bond homolysis.

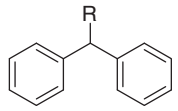
In this context, an interesting alternative to stannanes has been shown by Wood and coworkers[40] to consist in the use of water–trialkylborane complexes. These systems could manage the deoxygenation of xanthate esters. The deoxygenated products were obtained in good yields with trimethylborane and triethylborane (Scheme 12). Oxygen-triggered initiation generates a primary alkyl radical (methyl or ethyl) that adds to the xanthate moiety (Scheme 13). After fragmentation, the released secondary radical **45** is reduced by the water complexed to the borane. After H-donation, a primary radical is formed which propagates the radical chain.

8.27.2.1.2.2.6 Phosphine–boranes

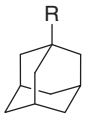
Barton studied the deoxygenation of the xanthate derivative 1,2:5,6-di-*O*-isopropyliden-α-D-glucofuranose **36a** with various phosphine–boranes in the presence of AIBN as the initiator (Scheme 14). Phosphine–boranes were found to be good and



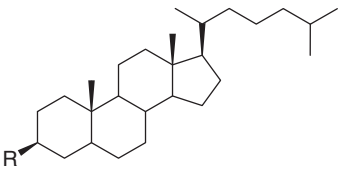
36a : R = O(C=S)SMe
36b : R = H



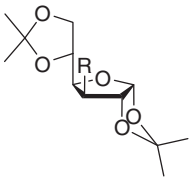
37a : R = O(C=S)SMe
37b : R = H



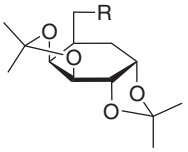
38a : R = O(C=S)SMe
38b : R = H



39a : R = O(C=S)SMe
35b : R = H

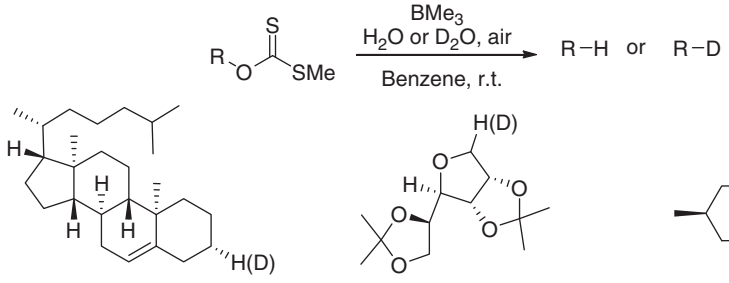


40a : R = O(C=S)SMe
34b : R = H



41a : R = O(C=S)SMe
41b : R = H

Scheme 11

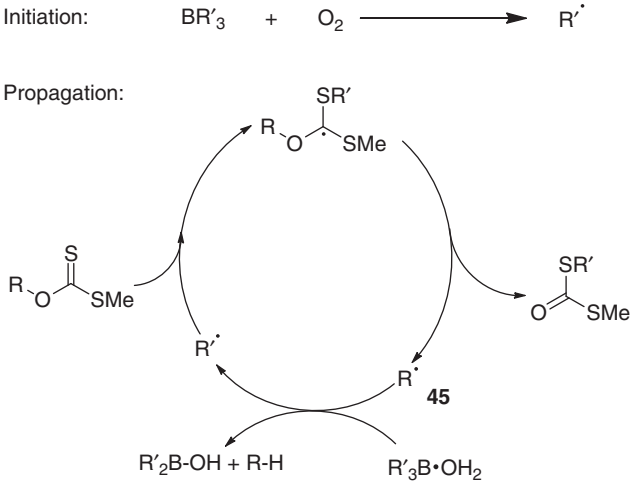


42-H 71%
42-D 67%

43-H 91%
43-D 68%

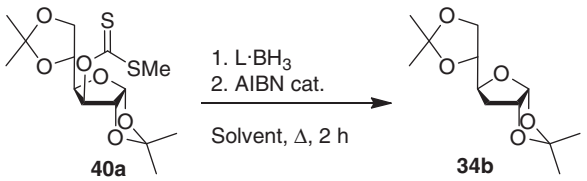
44-H 77%
44-D 72%

Scheme 12



Scheme 13

selective reagents for the deoxygenation of alcohol and diol xanthates.[41] The phosphorus derivatives (R,P) ligated to the borane exhibited reactivity as hydrogen-donors in the following order: $(iPrO)_3P < (MeO)_3P < (Et_2N)_3P < (Me_3SiO)_3P = Ph_3P < nBu_3P$ (Table 3).



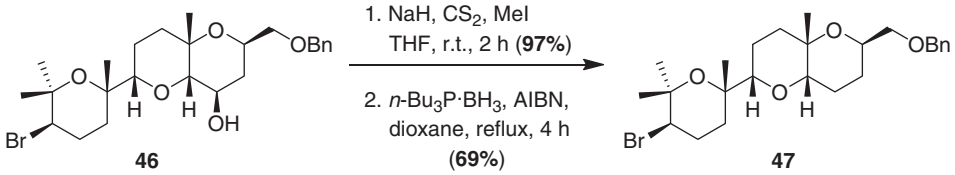
Scheme 14

Table 3 Deoxygenation of 1,2:5,6-di-*O*-isopropyliden-α-D-glucofuranose 40a with various phosphine–boranes in the presence of AIBN

Entry	*$R_3P \cdot BH_3$*	*Equivalents*	*AIBN equivalent*	*Solvent*	*34b (%)*[a]	*40a (rec.) (%)*[a]
1	$(i\text{PrO})_3P \cdot BH_3$	5	0.4	Benzene	23	61
2	$(MeO)_3P \cdot BH_3$	5	0.4	Benzene	31	51
3	$(Et_2N)_3P \cdot BH_3$	5	0.4	Benzene	44	37
4	$Ph_3P \cdot BH_3$	5	0.4	Dioxane	90	n.d.
5	$(Me_3SiO)_3P \cdot BH_3$	5	0.4	Dioxane	85	n.d.
6	$n\text{Bu}_3P \cdot BH_3$	5	0.3	Benzene	80[b]	n.d.
7	$n\text{Bu}_3P \cdot BH_3$	5	0.2	Dioxane	89	n.d.

[a]^{1}H NMR yield.
[b]Starting from 1 mmol of xanthate in 6 ml of dioxane, isolated yield after chromatography.
Note: rec., recovered starting material.

These deoxygenation conditions tolerate halide substituents. Little and coworkers showed that during the synthesis of an intermediate en route to thyrsiferol, a hindered hydroxyl group can be easily removed using the borane-tri-*n*-butylphosphine complex and AIBN as initiator in 69% yield, as illustrated by the generation of **47** from **46** (Scheme 15).[42,43]



Scheme 15

8.27.2.1.2.2.7 NHC–boranes

Recently, it was found that the complexation of borane by *N*-heterocyclic carbenes (NHC–boranes) results in a lower BDE of the B–H bond due to π-conjugation than that of amine and phosphine–boranes (Scheme 16). It was initially calculated that the BDE of some NHC–boranes lies between 74 and 80 kcal mol^{-1}, which is in the range of the BDE of tin hydrides (Bu_3Sn–H: 79 kcal mol^{-1}).[44] These values were then reevaluated after kinetic studies so that for iPr-BH_3 **49**, the calculated value 80 kcal mol^{-1} was revised to 88 kcal mol^{-1}.[45]



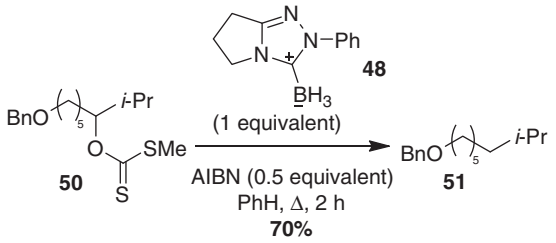
Calculated B–H: 79 kcal mol^{-1}

Calculated B–H: 80 kcal mol^{-1}
Estimated B–H: 88 kcal mol^{-1}

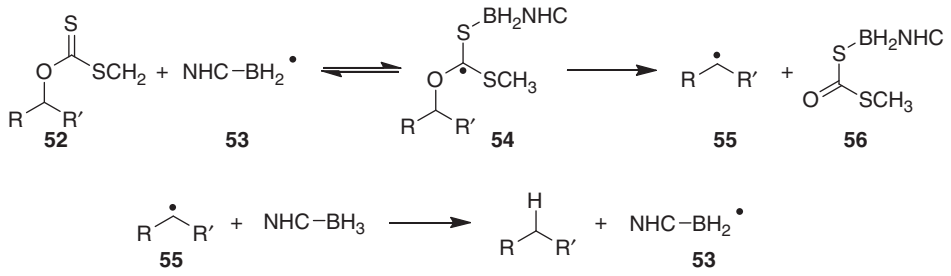
Scheme 16

A series of NHC–boranes are able to reduce xanthates with AIBN or Et_3B/O_2 as initiator with good yields (Scheme 17).

The radical character of these reactions was established thanks to a series of probes. The postulated radical mechanism involves a NHC-boryl radical (NHC-$BH_2^{\bullet}$) **53** that was well characterized by EPR (Scheme 18).[45,46]

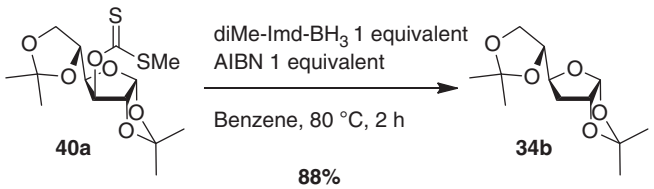


Scheme 17



Scheme 18

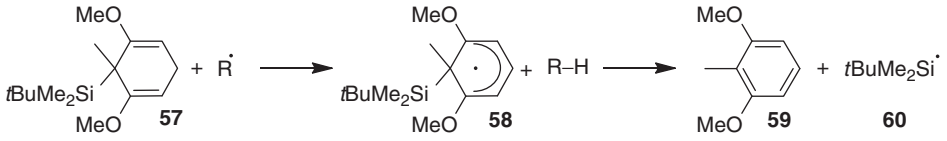
The most recent studies on the NHC–boranes have shown that the best NHC–borane for deoxygenation reactions is the 1,3-dimethylimidazol-2-ylideneborane (diMe-Imd-BH_3) (Scheme 19). This reagent is stable, easy to handle and has a low molecular weight and the best rate constant ($8 \times 10^4\ M^{-1}\ s^{-1}$) for hydrogen-atom transfer.[46] It gives also the best results for deoxygenation initiated by AIBN.[47]



Scheme 19

8.27.2.1.2.2.8 Silylated cyclohexadiene studies

Based on the previous literature in the use of silanes as radical mediators and cyclohexadienes as hydrogen donors, Studer and coworkers introduced silylated 1,4-cyclohexadienes such as **57** as new radical reducing agents based on a rearomatization step which generates the propagating radical **60** (Scheme 20).

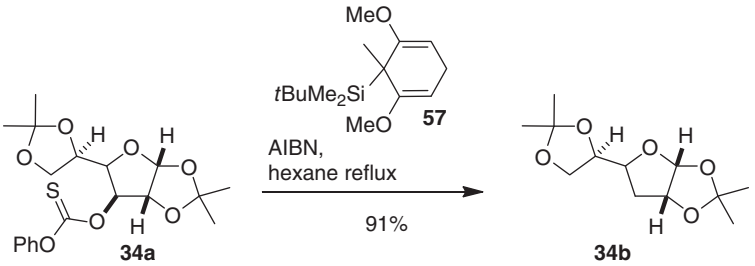


Scheme 20

Silylated cyclohexadienes were used as tin hydride substitutes for the conduction of various radical reductions and they were also applied successfully to deoxygenation reactions (Scheme 21). Using these reagents with AIBN as a radical initiator, some thionoesters and xanthates were reduced with very good yields as in the reduction of **34a** into **34b**.[48]

8.27.2.1.3 Metal-promoted processes

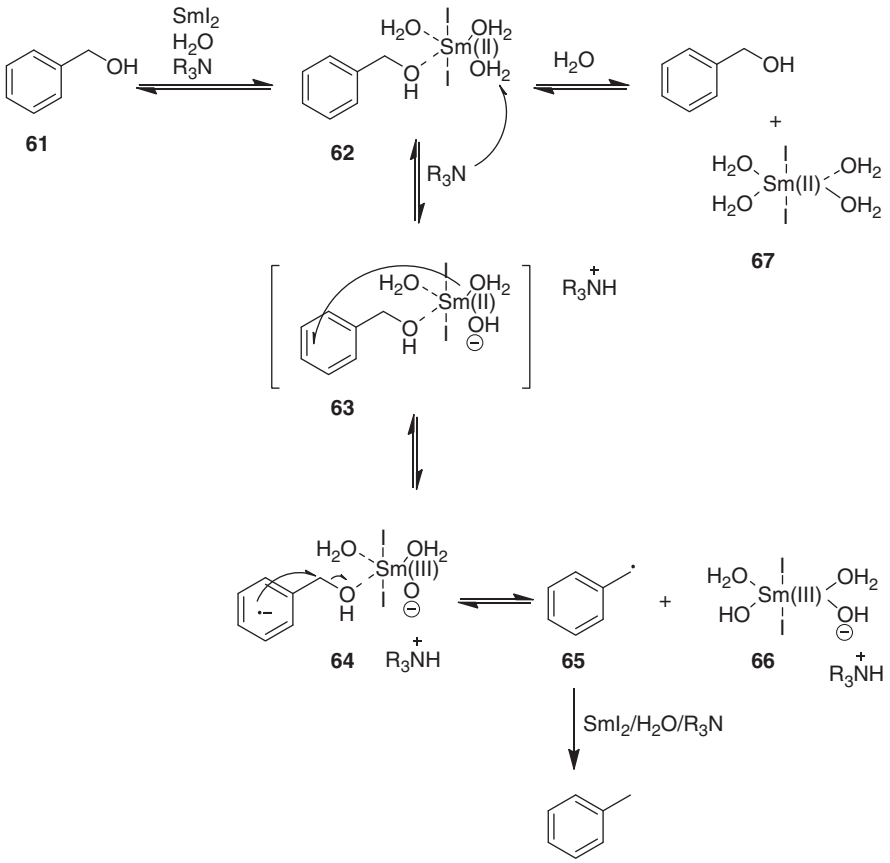
A convenient method for the reduction of hydroxyl groups has been reported by Liu and coworkers. They were able to reduce in good yields primary and secondary hydroxyl groups, previously converted into tetramethylphosphorodiamidates (TMPDA), using



Scheme 21

lithium naphthalenide in THF. They also noted the compatibility of the reduction conditions with diverse functional groups, such as a ketal, a silyl ether, an anisole moiety, and a carbon–carbon double bond.[49] Interestingly also, an enol could be converted to the corresponding alkene.

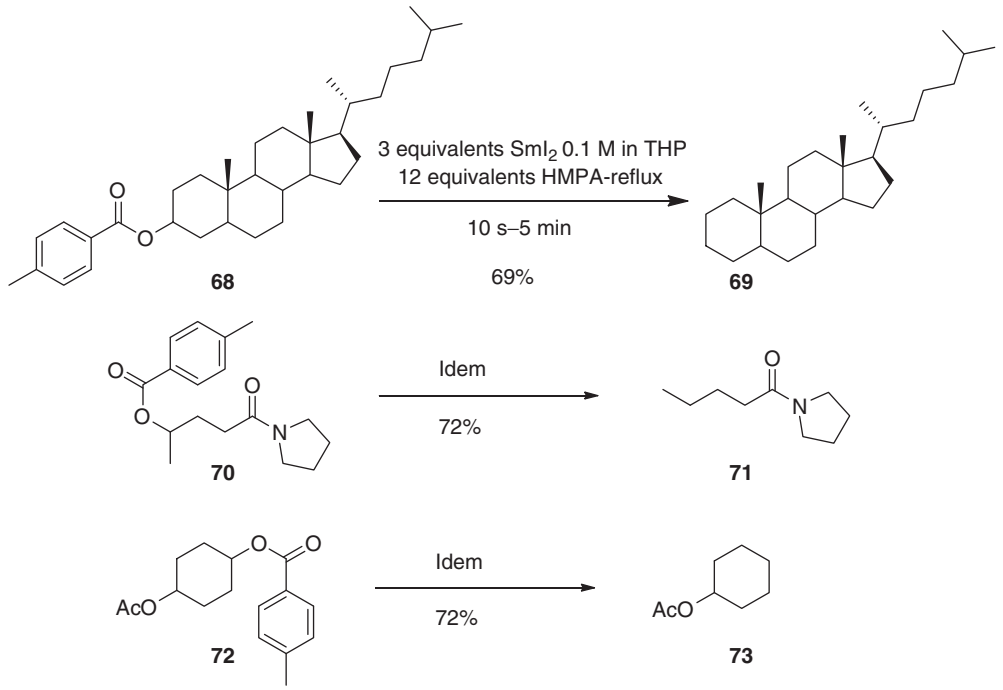
In order to extend the deoxygenation reactions, the chemistry of samarium was also investigated. An interesting report by Beau and coworkers showed that an acetate group at the anomeric position of some sugar derivatives can be reduced by samarium diodide, the resulting organosamarium species could be engaged in coupling reaction with ketones.[50] Hilmersson developed a SmI_2/H_2O/amine system, which promotes the efficient deoxygenation of a variety of benzyl alcohols. Interestingly, benzylamines, thiols, and esters can also be reduced. The proposed mechanism relies on the preliminary formation of an alcohol–samarium complex **62**, which after deprotonation of a coordinated water molecule yields a much more powerful reducing agent **63**.[51] Innersphere electron transfer to the aromatic ring yields a radical anion **64** that then fragments and liberates a benzyl radical **66** that further undergoes hydrogen capture (Scheme 22).



Scheme 22

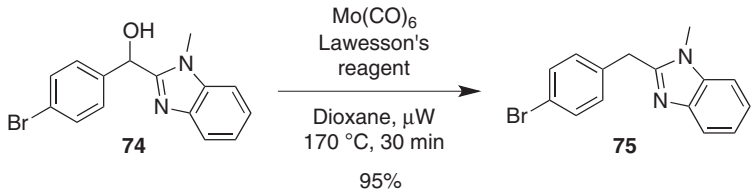
Another intriguing deoxygenation reaction based on the use of samarium(II) was reported by Markó and coworkers, who showed that a secondary or tertiary toluate group can be efficiently removed in good yields in THP using SmI_2 as monoelectronic reducing agent (Scheme 23). An interesting example of chemoselectivity was given the transformation of **70** and **72** into **71** and

73, respectively. They were able to accomplish C–C bond formation reaction through cyclization processes as well as allylation reactions with ketones through organosamarium species.[52]



Scheme 23

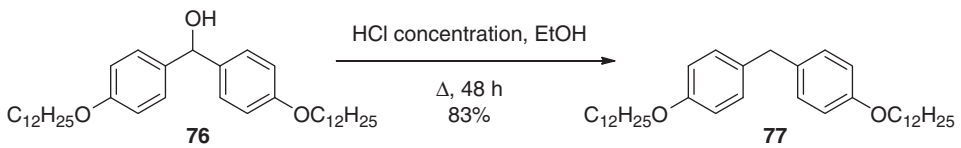
The group of Alterman developed a high-yielding one-pot deoxygenation reaction of heterocyclic halo-benzyl alcohols such as 74 catalyzed by $Mo(CO)_6$ and in the presence of Lawesson's reagent under microwave heating (Scheme 24).[53]



Scheme 24

8.27.2.2 Deoxygenation by Ionic Processes

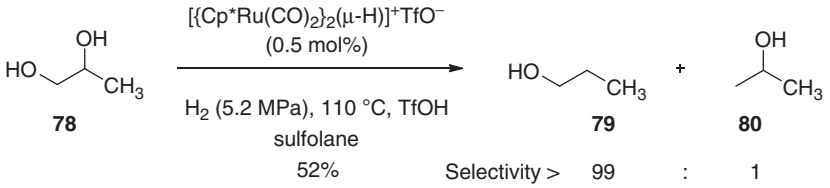
The deoxygenation of diarylmethanol derivatives under mild conditions in the presence of catalytic amount of hydrochloric acid and ethanol has been reported (Scheme 25).[54] In 48 h, compound **76** was deoxygenated to **77** in 83% yield. This reaction proved to be highly selective for this type of substrate, whereas no reduction was observed with primary and secondary alcohols bearing only one phenyl group. Compatibility with aryl ethers and phenols was demonstrated. Such conditions allowed the concomitant deprotection of acid-sensitive silyl ethers and gave birth to tandem processes. This transformation can be seen as complementary to the Barton–McCombie deoxygenation, but avoids the use of toxic or expensive reagents. The reduction of benzhydrols to



Scheme 25

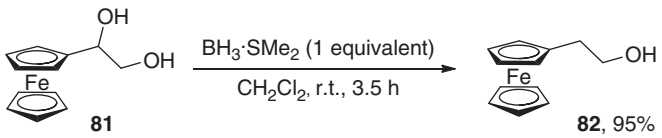
diarylmethylene derivatives has been also reported with a hypophosphorous acid/iodine system in acetic acid,[55] in which the active reducing agent is hydrogen iodide.

Organometallic catalysts can also be used in deoxygenation reaction. Directed toward the development of industrial processes, the selective reduction of 1,2-propandiol **78** has been studied with [{Cp∗Ru(CO)$_2$}$_2$(μ-H)]OTf as precatalyst (**Scheme 26**).[56] The reaction was conducted under hydrogen atmosphere (P_{H2} = 5.2 MPa) and triflic acid with sulfolane as solvent. A low precatalyst loading of 0.5 mol% was sufficient to obtain *n*-propanol **79** selectively in 52% yield with only traces of i-propanol **80**. The proposed mechanism involved dehydration of 1,2-propandiol leading to the formation of propanal and acetone and hence the observed selectivity. When [{Cp∗Ru(CO)$_2$}$_2$(μ-H)]OTf was treated with hydrogen under acidic conditions, a ruthenium monohydride complex was obtained which catalyzed the hydrogenation of carbonyl compounds. Thus, the major product propanal was reduced to *n*-propanol and the catalyst was reactivated by hydrogen. This transformation has also been applied to 1-phenyl-1,2-ethanediol and glycerol.



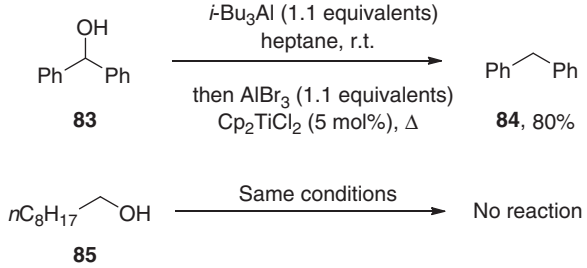
Scheme 26

Hydride donors have successfully been applied to the deoxygenation of activated alcohols. Among different reagents, the simple borane–dimethyl sulfide complex (BMS) allowed the selective reduction of α-ferrocenyl alcohols (**Scheme 27**).[57] 1,2-Dihydroxyethylferrocene **81** reacted with 1 equivalent of BMS in dichloromethane to afford the monodeoxygenation compound **82** in 95% yield. The total selectivity in favor of the α-hydroxy group is certainly due to the high stabilization effect of α-carbocation by the ferrocene moiety. This method appears competitive with conditions involving metallic Lewis acids such as $TiCl_4/Et_3SiH$[58] or $ZnCl_2/Zn(BH_4)_2$.[59]



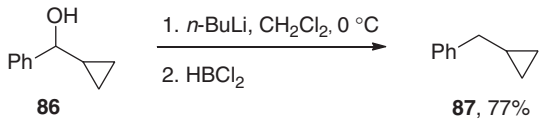
Scheme 27

The combination of trialkylaluminum reagent and a strong Lewis acid, $AlBr_3$, has been used for the deoxygenation of alcohols and ketones (**Scheme 28**).[60] This transformation was accelerated by a catalytic amount of titanocene dichloride, also playing the role of Lewis acid. Benzhydrol **83** has been converted to diphenylmethane **84** by this two-step procedure in refluxing heptane with stoichiometric amounts of aluminum reagents in 80% yield. Primary aliphatic alcohols and phenols were not reactive under these conditions. Thus, the deoxygenation mechanism appeared to be driven by the formation and the stability of the carbenium ion derived from the corresponding alcohol.



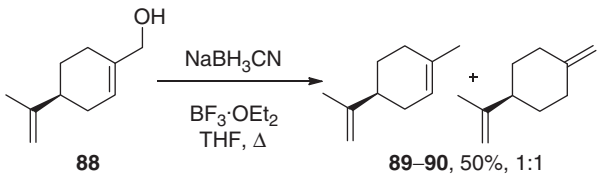
Scheme 28

Benzylic alcohols have been reduced in a two-step deoxygenation process with a boron hydride as the active species (**Scheme 29**).[61] The compound **86** was deprotonated by *n*-butyllithium to generate the corresponding lithium alkoxide that reacted with dichloroborane. A boron alkoxide intermediate was formed followed by a concerted hydride transfer from boron to carbon. The compound **87** was obtained in 77% yield, indicating that the reaction did not involve a carbenium ion intermediate.



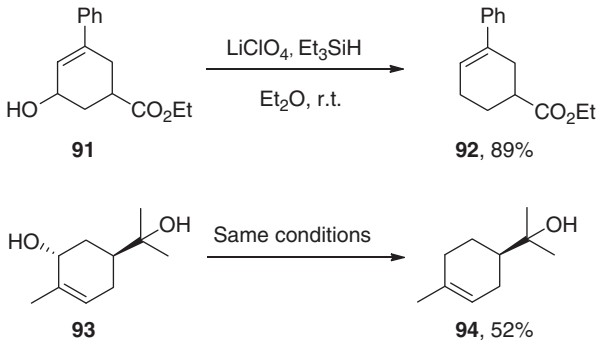
Scheme 29

A selective method for the deoxygenation of allylic alcohols has been developed by using a hydride source in the presence of a Lewis acid.[62] Perillyl alcohol **88** was treated with excess of sodium cyanoborohydride and boron trifluoride etherate in refluxing THF (Scheme 30). A mixture of limonene **89** and **90** (1:1) was obtained in 50% yield. This was indicative of the formation of allylic carbenium ion that reacted with sodium cyanoborohydride as hydride source. This transformation was also applied to the chemoselective reductive deoxygenation of α,β-unsaturated ketones.



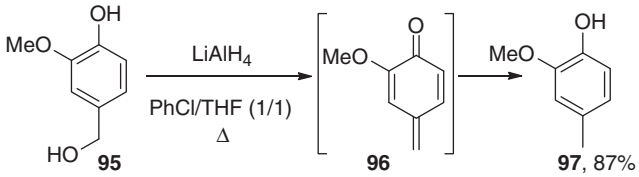
Scheme 30

The deoxygenation of allylic alcohols has also been investigated in the presence of lithium perchlorate with silane as hydride source (Scheme 31).[63] Allylic alcohol **91** was treated with excess of $LiClO_4$ and triethylsilane at room temperature. The deoxygenated compound **92** was obtained in 89% yield. These experimental conditions were compatible with sensitive organic functions like esters, ketals, or olefins. Primary allylic alcohols were not deoxygenated by this method. Interesting selectivity was observed when **93**, containing a tertiary aliphatic alcohol, was used in this reaction. Only the allylic alcohol was deoxygenated and **94** was obtained in 52% yield. Triisopropylsilane and *tert*-butyldimethylsilane were tested in place of triethylsilane. These two sterically hindered hydride donors slowed the reaction considerably, leading to inefficient reaction.



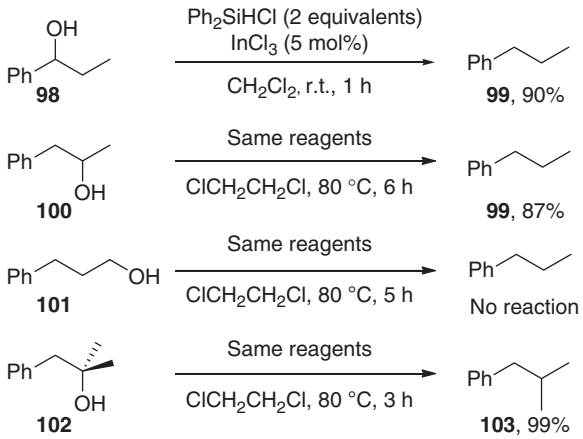
Scheme 31

Lithium aluminum hydride was able to promote the reductive deoxygenation of hydroxybenzyl alcohol through the formation of benzoquinone methide (Scheme 32).[64] The compound **95** was transformed to phenol **97** in 87% yield. First, LAH acted as a base to deprotonate the phenol function to get the lithium phenoxide and the AlH_3 thus formed reacted with the benzylic hydroxyl group. The resulting aluminum alkoxide gave benzoquinone methide **96** through an elimination reaction. In this process, **96** was also intercepted by 2,3-dimethylbutadiene to afford the related spiroketone by a Diels–Alder reaction. Phenol **97** was obtained by hydride addition to **96**.



Scheme 32

Benzylic and aliphatic alcohols were efficiently deoxygenated by chlorosilane derivatives with indium(III) chloride as catalyst.[65–67] In dichloromethane or dichloroethane, 2 equivalents of chlorodiphenylsilane and 5 mol% of $InCl_3$ allowed the reduction of secondary benzylic and homobenzylic alcohol **98** and **100** (Scheme 33). The corresponding phenylpropane **99** was obtained in 90% and 87%, respectively. No reaction was observed with **101** under the same conditions, whereas the tertiary alcohol **102** was quantitatively reduced. This transformation showed functional group tolerance toward esters, aliphatic and aromatic halides, and nitro groups. The choice of the solvent was crucial: no conversion was observed in THF or acetonitrile, and hexane and benzene led to low yield. Triethylsilane and chlorodimethylsilane were tested and did not allow deoxygenation. The mechanism of this reaction involves initial formation of diphenylsilyl ether. Indium(III) chloride activates the oxygen atom and promotes intramolecular hydride transfer from silicon to carbon. The low affinity of indium for oxygen allowed recovery of the active catalyst.

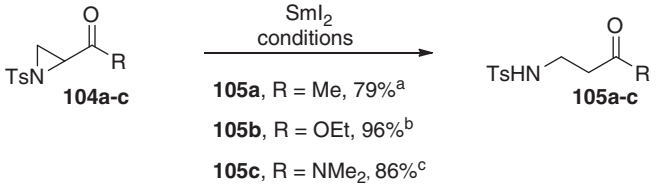


Scheme 33

8.27.3 Reductive Deamination of Amines and Their Derivatives

8.27.3.1 Reduction Involving Radical Pathways

Radical chemistry has been used as a powerful tool for the reduction of carbon–nitrogen bonds. By homolytic cleavage, it is possible to generate the corresponding carbon-centered radical, which can be reduced by hydrogen or single electron transfer to afford an alkane. Samarium(II) iodide has proved to be an efficient electron reducing agent able to reduce functional groups such as esters, ketones, aldehydes, sulfones, halides, etc., selectively. Following such reactions, 2-acylaziridines **104a–c**, in the presence of SmI_2 and a proton source, yield β-amino carbonyl derivatives **105a–c** (Scheme 34).[68] One electron is transferred to the carbonyl function to give a ketyl radical intermediate that undergoes a β-fragmentation of the aziridine ring. Enolate and aminyl radicals are formed and are, respectively, protonated by methanol (or *N*,*N*-dimethylethanolamine) and reduced by a second equivalent of Sm(II) to the corresponding nitrogen-centered anion that is also protonated by methanol. This reaction has been applied to ketones, esters, and amides with generally good-to-excellent yields. A variety of nitrogen protecting groups, such as Ac, RCO_2, Tr, or Fmoc, are tolerated. Without a proton source, the intermediate enolate may even be trapped by electrophiles to create carbon–carbon bonds.

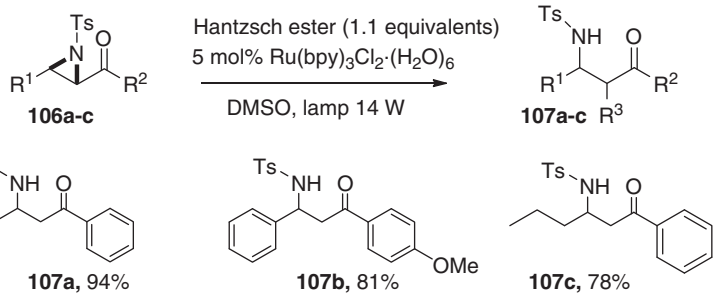


Conditions: [a]SmI_2 (2.05 equivalents), MeOH, THF, 0 °C. [b]SmI_2 (2.5 equivalents), DMEA (5 equivalents), THF, 0 °C. [c]Same conditions than [b]at –25 °C.

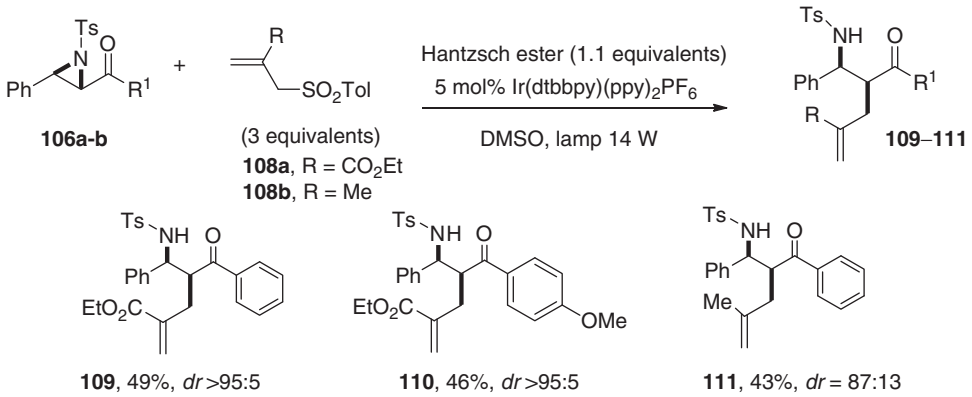
Scheme 34

Photocatalysis using Ru(II) and Ir(III) catalysts has been used to promote the homolytic ring opening of aziridines **106a–c**, giving good yields of amine products **107a–c** (Scheme 35).[69] Gratifyingly, the intermediate radical can be trapped by allylsulfone

derivatives **108a–b** to provide fair yields of allylated adducts **109–111** with very high to complete diastereoselectivities (Scheme 36).

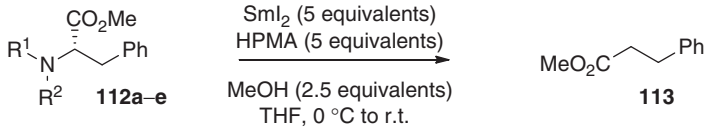


Scheme 35

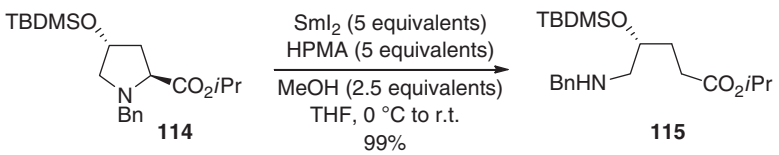


Scheme 36

The deamination of amino acid derivatives by a related SmI_2 single electron transfer reduction of α-amino carbonyl compounds has been reported (Scheme 37).[70] This reaction has been applied to phenylalanine methyl ester derivatives **112a–e** with different substitution patterns at the nitrogen atom. In order to improve the reductive power of samarium(II) iodide, HMPA has been added. This procedure allowed the ring opening of proline derivatives **114** but also of 2-acetylpiperidine and ethyl pipecolinate. A reductive deprotection of the phthalimide group occurs under these mild reaction conditions.

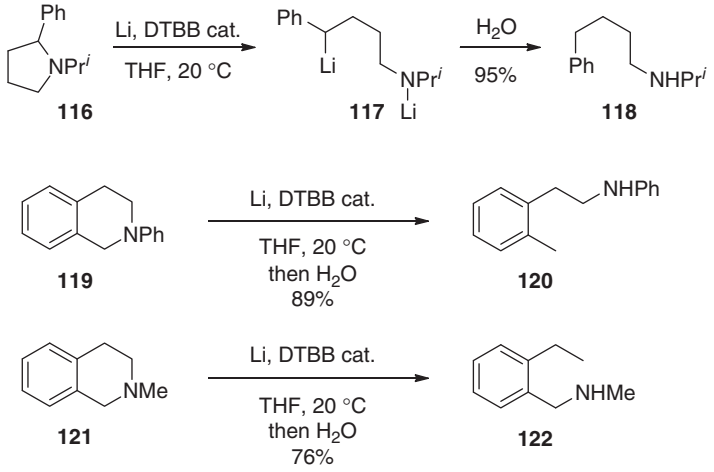


96	R^1	R^2	Time	Yield
a	H	H	30 min	73%
b	H	Me	30 min	71%
c	Me	Me	<5 min	90%
d	H	Bn	4 h	93%
e	H	Ac	15 min	99%



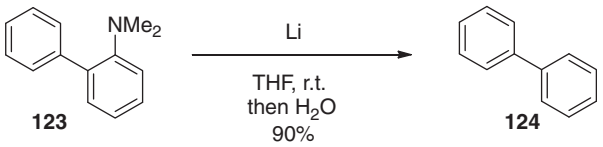
Scheme 37

The reductive ring opening of saturated heterocycles by C–N bond cleavage received attention, whereas such substrates have limited reactivity. Thus, powerful reducing reagents have to be used, such as Li(0). This method has been applied to the reductive opening of aziridines[71,72] and azetidines[73] using lithium metal and a catalytic amount of naphthalene or 4,4′-di-*tert*-butylbiphenyl (DTBB) as electron transfer carriers. The same process was extended to the reduction of five- and six-membered nitrogen-containing rings (Scheme 38).[74] Under such conditions, *N*-isopropyl-2-phenylpyrrolidine **116** is reduced in the corresponding dilithiated dianion **117** to afford the linear amine **118** in 95% yield. This dianion may be trapped by other electrophiles such as alkyl halides or aldehydes. *N*-phenyl- and *N*-methyltetrahydroisoquinoline (**119** and **121**, respectively) have been submitted to this DTBB-catalyzed lithiation and two different regioisomers were obtained. In the case of **119**, *β*-scission occurred to generate the more stable radical whereas the reduction of **121** went through a benzylic metallation followed by a *β*-elimination. In both cases, ring-opened compounds **120** and **122** were obtained in good yields.



Scheme 38

Aryl-nitrogen bonds have also been reduced by lithium through a single electron transfer process (Scheme 39).[75] Phenyl-substituted dimethylaniline **123** was treated with Li in THF at room temperature. Homolytic cleavage of the C–N bond occurred to generate the corresponding aryl radical that was reduced to afford the aryl lithium derivative and thus biphenyl **124**. Sodium proved to be inefficient in this process whereas potassium gave complex mixtures.

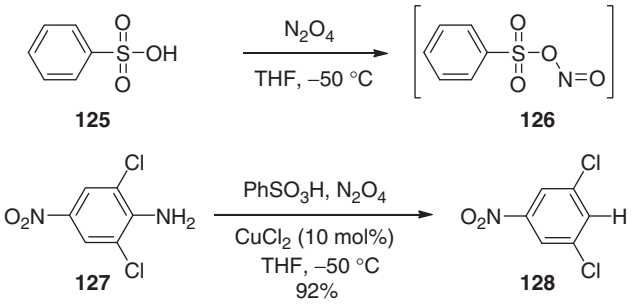


Scheme 39

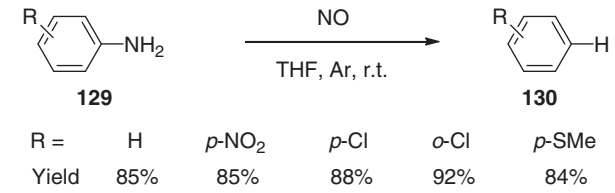
Usual procedures for the deamination of aromatic amines pass through a diazotization step followed by decomposition in the presence of an H-donor.[76] Depending on the decomposition mode and the final product, this type of process is known as Sandmeyer,[77] Pschorr,[78] Gomberg-Bachmann,[79] or Meerwein[80] reaction. In these transformations, the intermediate diazonium salt is usually formed by alkyl or sodium nitrite in acidic medium. Arenesulfonyl nitrites proved to be also efficient reagents for the activation of primary aromatic amines (Scheme 40).[81] Benzenesulfonic acid **125** reacted with dinitrogen tetraoxide in THF at − 50 °C to form unstable benzenesulfonyl nitrite **126**. In the presence of copper(II) chloride followed by the addition of 2,6-dichloro-4-nitroaniline **127**, the reduced product **128** was quickly formed in 92% yield. In this process, the hydrogen atom originated from the THF by H-abstraction of the intermediate aryl radical.

Nitric oxide has also been used in the reductive deamination of aromatic amines (Scheme 41).[82] Aniline derivatives **129** reacted in the presence of 20 equivalents of NO to form the corresponding diazonium salts. It has been postulated that NO acts as an electron-donor to reduce the diazonium moiety and generate the aryl radical.

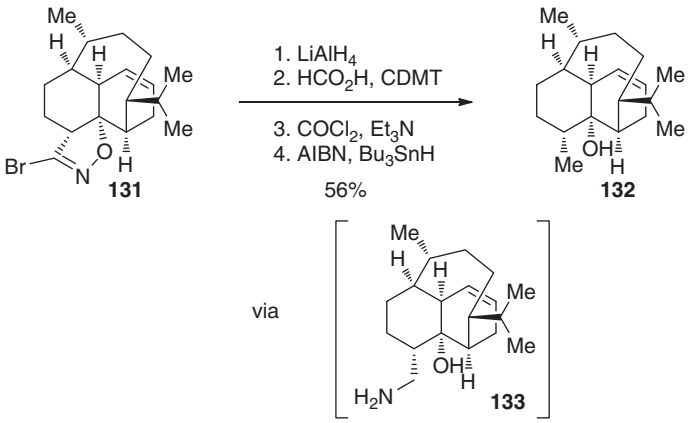
Free radical deamination through isonitrile derivatives was first illustrated by Saegusa et al.[83] and further developed by Barton et al.[84] An amine group is converted into a formamide that is dehydrated to the corresponding isonitrile. In the presence of an H-donor and a radical initiator, homolytic cleavage of the C–N bond occurs to afford a carbon-centered radical, which is reduced by H-transfer and maintains the chain reaction. This transformation has been used in the total synthesis of vinigrol (Scheme 42).[85] The Saegusa deamination sequence has been applied to the free amine **133** obtained by the reduction of the bromoisoxazole derivative **131**. The corresponding alkane **132** was formed in 56% yield after this four-step sequence.



Scheme 40



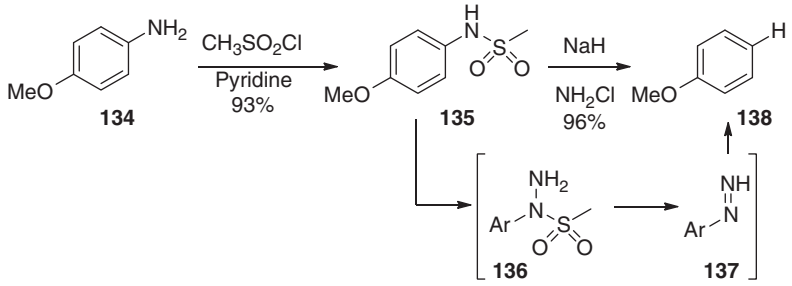
Scheme 41



Scheme 42

8.27.3.2 Reduction Involving Ionic Pathways

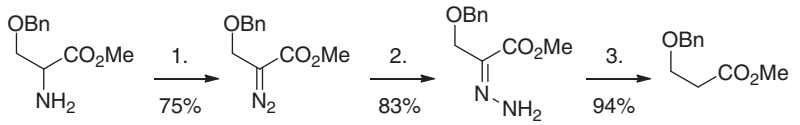
The reduction of C–N bonds can also be achieved through ionic pathways. The reductive deamination of aromatic amines has been carried out in order to obtain the corresponding phenyl derivatives (Scheme 43).[86] Arylamine **134** reacted with



Scheme 43

methanesulfonyl chloride to afford the methanesulfonamide **135**. After isolation, **135** was treated with sodium hydride followed by chloramines. The intermediate sulfonyl hydrazine **136** was obtained and decomposed at room temperature to afford diazene **137**. A subsequent nitrogen extrusion allowed the formation of the corresponding reduced compound **138** in good-to-excellent yield. This transformation has been previously reported with sodium hydroxide as base and led to lower yield.[87] When 2 equivalents of chloramines were used, the corresponding halodeamination products were obtained in moderate yield.

A three-step sequence has been reported for the reductive deamination of α-aminoesters (Scheme 44).[88] Compound **139** was transformed into the corresponding α-diazoester derivative **140** with isoamyl nitrite and acetic acid. Sodium borohydride allowed the reduction of **140** to the hydrazonoester **141**. The final reductive deamination was achieved through a Wolff–Kishner-like process by heating **141** in the presence of DBU to obtain **142** in 94% yield.

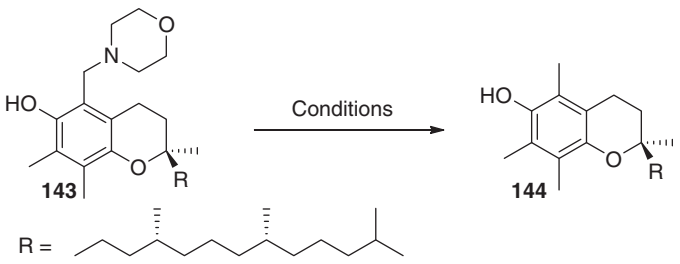


139 **140** **141** **142**

1. Isoamyl nitrite, AcOH, $CHCl_3$ reflux. 2. $NaBH_4$, THF, r.t. 3. DBU, $CHCl_3$, reflux.

Scheme 44

A wide range of reagents has been used for the transformation of δ-tocopherol into α-tocopherol **144**.[89] A set of experimental conditions has been reported involving first the acylation of phenoxy group followed by quaternization of the amino group in order to transform it into a better leaving group, assisting attack of the reducing agent (Scheme 45). Based on this strategy, the best yield of 88% was obtained by activation with diphosgene and reduction with lithium aluminum hydride. An easier procedure has been reported based on a one-step reduction involving different sources of hydrides. Sodium borohydride proved to be more efficient in refluxing iso-butanol (90% yield) than in refluxing *N*,*N*-dimethylformamide (DMF), which led to partial decomposition of **143**. The use of $NaBH_3CN$ instead of $NaBH_4$ allowed **144** to be obtained in 95% yield. This can be explained by the higher stability of $NaBH_3CN$ in protic conditions. To increase the stability of the reducing agent, basic conditions were used. Sodium borohydride in the presence of sodium hydroxide led to quantitative formation of **144**.



Conditions	Yield of **144**
1. Ac_2O. 2. HCl. 3. $SnCl_2$	47%
1. Ac_2O. 2. MeI/Ag^+. 3. $NaBH_3CN$	71%
1. Diphosgene/Hünig's base. 2. $LiAlH_4$	88%
$NaBH_4$, DMF, Δ	50%
$NaBH_4$, *i*BuOH, Δ	90%
$NaBH_3CN$, *i*BuOH, Δ	95%
$NaBH_4$/OH–, *i*BuOH, Δ	100%

Scheme 45

8.27.4 Conclusion

In conclusion, it appears that there has been over the past two decades a constant need for reactions that reduce saturated alcohols and amines to alkanes. These reactions have been used in the context of total synthesis or for the preparation of molecules with

relevant properties. Radical processes relying on the implementation of an adequate function amenable to homolytic reactivity constitute the most important group of used processes.

Although some versatile examples of radical or transition metal catalytic processes have already been devised, it is obvious that the effort has to be put in this direction in the coming years, photocatalysis being an attractive option.

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8.28 Reduction of Sulfur–Carbon Bonds and of Other Heteroatoms Bonded to Tetrahedral Carbon

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This chapter is a revision of the previous edition chapter by P. Caubère and P. Coutrot, Vol. 8, pp 835–870, © 1991, Elsevier Ltd.

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8.28.1 Reduction of Sulfur–Carbon Bonds

8.28.1.1 Introduction

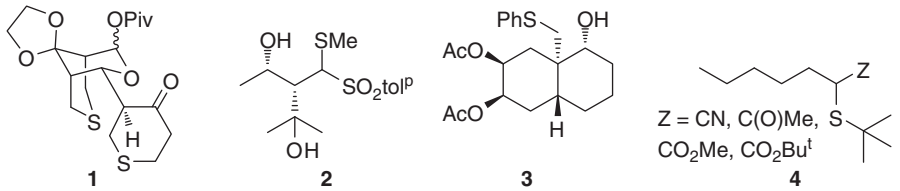
Sulfur-containing functional groups (such as thiols, sulfides, sulfoxides, and sulfones) (*see* Chapters 6.04 and 7.28) provide organic chemists with an impressive array of reactivity and can function as a variety of different synthons. These powerful synthetic tools are augmented by the facile reductive cleavage of sulfur from the final product. Such desulfurization is formally a hydrogenolysis and can be effected by an assortment of reagents and conditions. Each reagent has its preferred scenarios and chemo- and regioselectivities, as well as drawbacks. As such, there is no universal reagent for desulfurization; however, many reagents exhibit the desired characteristics of low cost and straightforward handling. In the following sections you will see that there is a mixture of overlap and complementarity in different approaches to reductive cleavage of sulfur–carbon bonds.

8.28.1.2 Raney Nickel and Nickel(0) Complexes

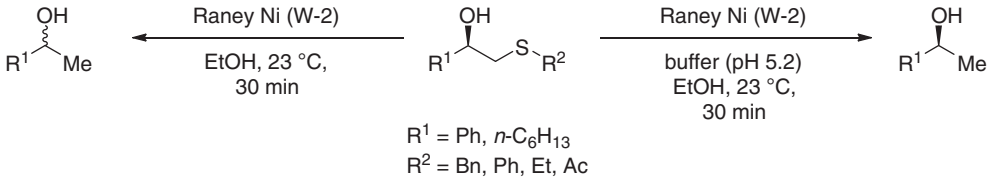
One of the oldest and broadest approaches to desulfurization is the use of Raney nickel.[1–3] There are several different grades of Raney Ni, termed W-1 to W-8, and each is prepared from nickel aluminum alloy with slightly varied reaction conditions. W-2 is the most commonly used variant.[4] The properties (reactivity, stability, etc.) vary from one grade to another and in general, the reactivity of all grades decreases over time. Without specific information on the type of Raney Ni used, it may be difficult to fully reproduce reported results. In some literature Raney Ni is abbreviated Ra-Ni or Ni(H). Raney Ni is a fine, extremely porous powder

and thus has a very high surface area; it also contains large quantities of hydrogen adsorbed to its surface, a property that is underscored by the Ni(H) depiction. Slow loss of this hydrogen is partly responsible for lowered reactivity of older samples of Raney Ni. Though Raney Ni is often termed a catalyst, it is always used in very significant excess (weight ratio of Raney Ni to substrate is typically ca. 1:1 to 10:1). Moreover, in desulfurization reactions, the mechanism may vary depending on the sulfur functional group and structure of the substrate and it is generally accepted that the sulfur atom will ultimately form a nickel–sulfur bond, making Raney Ni a stoichiometric reagent in reductive desulfurization processes.[2c] Despite this, Raney Ni is a popular choice for the cleavage of C–S bonds. It is most commonly used to reductively cleave aromatic and aliphatic sulfides,[1b,5] dithioacetals,[6] and sulfoxides.[1b,7] Examples of the excision of thiols,[8] thiolesters,[9] disulfides,[1b,10] and thioacetals[11] are also known. Sulfones[1b,12] and sulfonates[11c,d] require more forcing reaction conditions[13] or extended reaction times; sulfonamides are highly resistant to Raney Ni.[2a,6d] This allows for chemoselective cleavage of other sulfur functional groups in the presence of sulfones, sulfonates, and sulfonamides.

Below are some representative examples of sulfides cleaved by Raney Ni. Tetrahydrothiopyran **1** is noteworthy because Raney Ni desulfurization also resulted in partial reduction of the ketone. This was easily remedied by treating the mixture with 2-iodoxybenzoic acid (IBX).[14] The sulfide of compound **2** was chemoselectively reduced, leaving the sulfone intact.[15] Compound **3** demonstrated the tolerance of esters and alcohols to Raney Ni.[5b] The tolerance of cyanides, ketones, and esters has also been demonstrated by compounds such as **4**.[16]

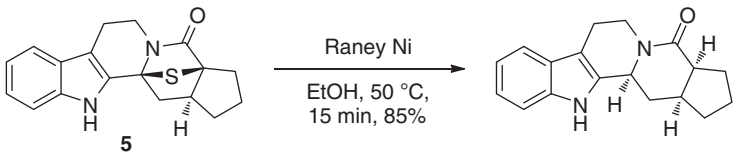


For all its breadth as a desulfurization reagent, Raney Ni has several significant drawbacks. These include its preparation, deactivation on standing and difficulty in accurate measurement of the amount of reagent used because Raney Ni is pyrophoric unless it is wet. Raney Ni also suffers from limited tolerance of several functional groups, including reduction of alkenes, nitro, and carbonyl groups. In addition, Raney Ni is also known to oxidize alcohols (EtOH is a common solvent in Raney Ni reactions), which thus act as a source of hydrogen, though this is not necessarily a problem. However, if Raney Ni is used in nonalcoholic solvents the oxidation of alcohols in the substrate should not be ruled out.[17] Even in alcoholic solvents, Raney Ni has been known to cause epimerization of secondary alcohols, presumably via an oxidation/reduction pathway (**Scheme 1**).[18] However, the authors found experimental conditions to ameliorate this issue. The reduction of ketones with Raney Ni is also known.[14,19]



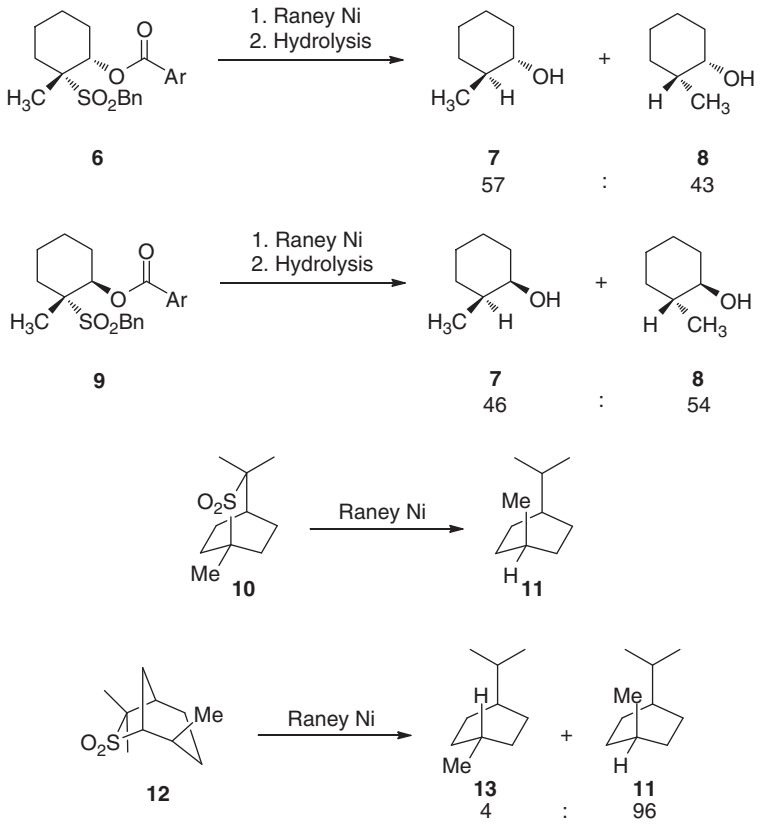
Scheme 1

The hydrogenolysis of carbon–sulfur bonds by Raney Ni is not stereospecific and in most cases is not stereoselective, as the reduction is believed to proceed via radical intermediates, and racemization/epimerization is observed at the site of bond cleavage in chiral substrates. Nevertheless, examples of diastereoselective reduction are known. For example, hydrogenolysis of sulfide **5** results in inversion at both sites of C–S bond fragmentation (equation 1).[5a] Such results are not general and diastereoselectivity is highly substrate dependent.



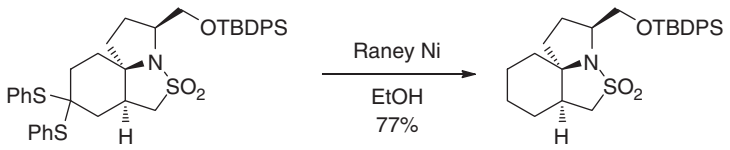
(1)

Reductive cleavage of sulfones has been shown to proceed without complete racemization; however, the degree of inversion and retention is variable.[2c,13a,20] For example, sulfone **6** shows 43% inversion but its isomer **9** shows 54% inversion (**Scheme 2**).[20b] Bicyclic sulfone **10** proceeds via inversion to afford *p*-menthane **11** as the only observed isomer. The same mechanistic pathway for isomeric sulfone **12** should lead to *trans*-*p*-menthane **13**; however, again, **11** is the major product.[13a] Thus, the mechanism of sulfone desulfurization is variable and substrate dependent.

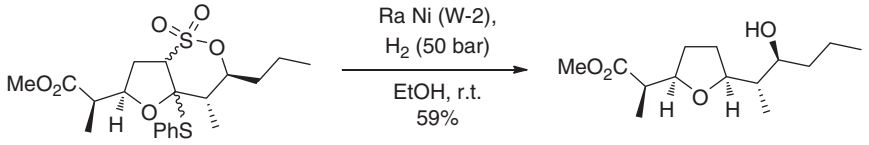


Scheme 2

Raney Ni allows for the chemoselective desulfurization of sulfides and sulfoxides in the presence of sulfones due to the lower reactivity of sulfones (e.g., **2**).[15] Sulfonamides are also readily tolerated (equation 2).[6d] Sulfonates can be reduced under forcing conditions, such as high pressures of H_2. Equation 3 demonstrates the concomitant reduction of a thioacetal and a sulfonate.[11c,d] Sulfur functional groups adjacent to electron-withdrawing groups (EWGs), such as carbonyls and nitriles, are more readily cleaved and therefore milder reagents may be used for these substrates (vide infra). Carbon–halide bonds are not tolerated.[21]

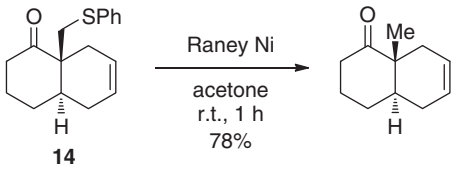


(2)

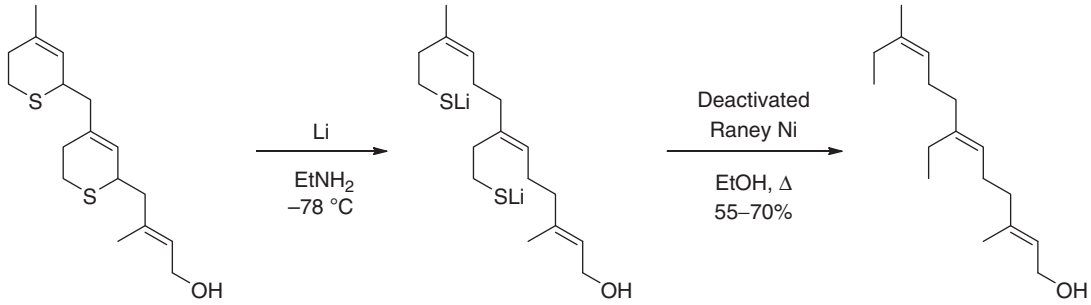


(3)

Electron-poor and electron-neutral alkenes are generally only tolerated when the Raney Ni has been deactivated (typically by acetone).[5b] For example, sulfide **14** was reduced in 78% yield in the presence of a disubstituted *cis*-alkene (equation 4). More substituted alkenes afforded even higher yields. Electron-rich alkenes are more tolerant.[14] Vinyl sulfides can be desulfurized with[22] or without[23] concomitant alkene reduction, depending on reaction conditions. Interestingly, Raney Ni desulfurization of dihydrothiapyrans was unsatisfactory but the allylic C–S bond was readily regioselectively cleaved with Li in $EtNH_2$ (vide infra) and subsequent reductive cleavage of lithium thiolate proceeded smoothly (**Scheme 3**).[24]

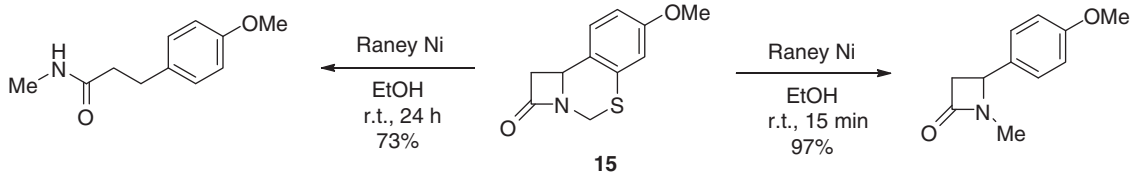


(4)

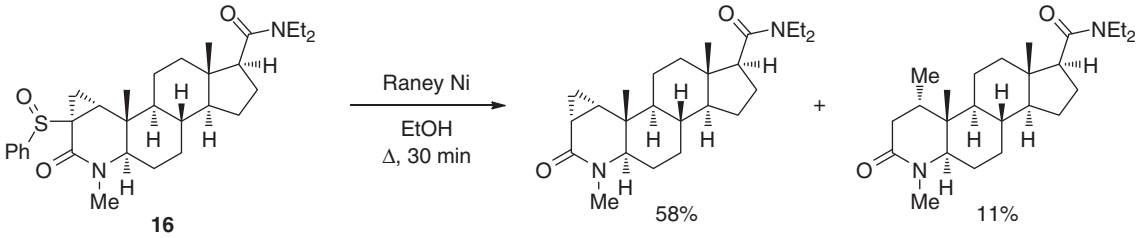


Scheme 3

It is also worth noting that strained ring systems, such as β-lactams and cyclopropanes, are not completely compatible with Raney Ni. Scheme 4 shows that extended reaction time led to opening of β-lactam **15**,[5c] whereas shorter reaction time afforded virtually no lactam cleavage. Azasteroidal cyclopropane **16** (equation 5) is an example of cyclopropane fragmentation to yield a methyl group.[7h]

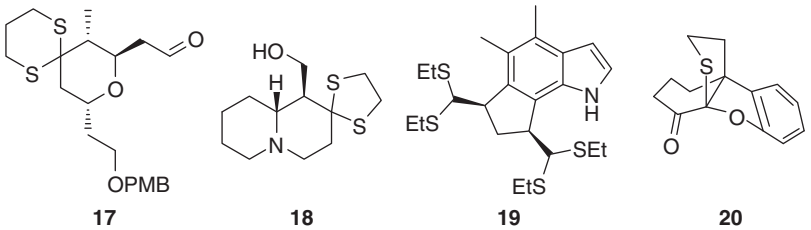


Scheme 4

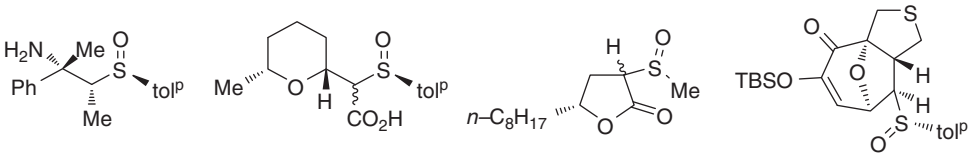


(5)

Reduction of dithioacetals and thioacetals is also common in organic synthesis. The former is frequently employed as a method of reducing ketones and aldehydes to alkanes. In addition to equations 2 and 3, compounds **17**–**20**[6b,11c,25,11d] serve as illustrative examples.

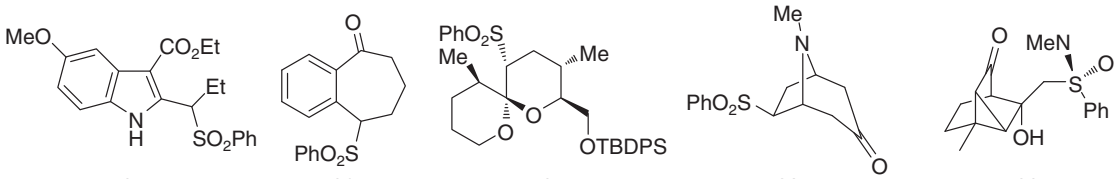


Sulfoxides also readily undergo C–S bond cleavage with Raney Ni. Sulfoxides **21**–**23**[7a,c,f] demonstrate the tolerance of a variety of functional groups. Notably, compound **24** demonstrates concomitant sulfide excision.[7g]



21 **22** **23** **24**

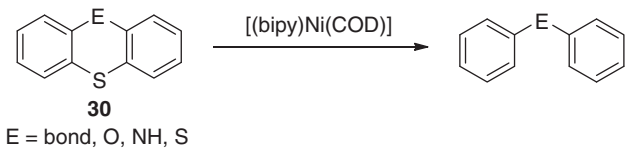
Sulfones are more challenging to remove with Raney Ni; therefore other reagents, such as Mg in MeOH, are typically preferred (vide infra). However, examples of sulfone reduction with Raney Ni (e.g., **25**–**28**)[12b,c,d,f] are known. Sulfoximines (e.g., **29**)[26] are an analog of sulfones and are also known to be excised by Raney Ni.[7g,26,27] Thiocarbonyls, such as thioesters and thioamides, can also be reduced by Raney Ni.[28]



25 **26** **27** **28** **29**

The above discussion clearly demonstrates that Raney Ni is an exceptionally useful reagent for the desulfurization of a wide array of organic functional groups. However, its utility is hampered by the requisite large excess of reagent, the array and inconsistency of reactivity of various Raney Ni sources, and its pyrophoric behavior on drying.

Desulfurization with Raney Ni is performed under heterogeneous conditions. It has been surmised that a soluble nickel(0) reagent could be more efficient and may offer new insight into the mechanism of Raney Ni reduction. A common reagent for this task has been [(bipy)Ni(COD)]. These reductions have been largely limited to trigonal planar systems, such as **30**[29] (equation 6), and are thus beyond the scope of this review.



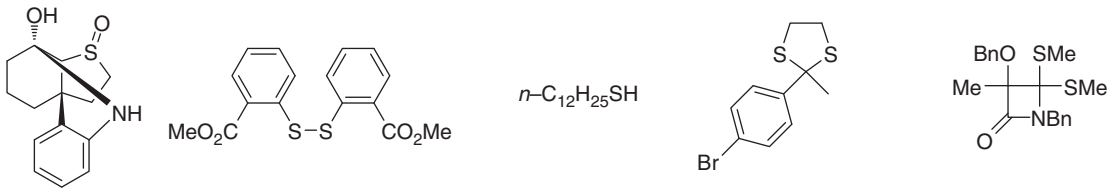
30
E = bond, O, NH, S

(6)

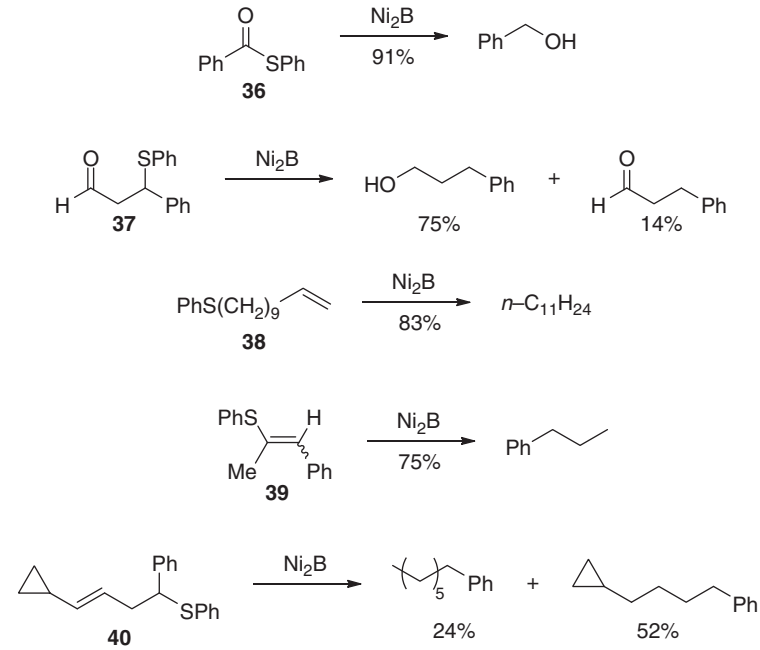
8.28.1.3 Hydrides or Organometallics Combined with Transition Metal Salts or their Complexes

The undesirable properties of Raney Ni (pyrophoric, loss of activity over time, lack of precise measurement of Ni used, etc.) prompted researchers to evaluate other low-valent Ni sources as candidates for reduction of C–S bonds. In 1963, Truce and Roberts reported the use of Ni boride as a reagent for the desulfurization of dithioacetals,[30] though they did not explicitly describe it as Ni boride. Ni boride is typically prepared *in situ* using readily handled and measured reagents – Ni(II) salts (usually $NiCl_2 \cdot 6H_2O$) and $NaBH_4$ – thus completely mitigating the objectionable attributes of Raney Ni. Ni boride is a black reagent typically described by with the formula Ni_2B; however, this convenient description is inadequate and belies the complexity of the reagent. The formula $(Ni_2B)_2H_3$ has been suggested; but this also does not account for solvent and salts trapped in the reagent.[31,32] Ni boride appears to be a finely divided metal and has some properties similar to a metal despite the fact that is indeed not. The reaction of Ni(II) salts with $NaBH_4$ in an alcoholic solvent also results in significant and rapid evolution of hydrogen gas (hence the more complex molecular formula) and this is the putative hydrogen atom source, rather than $NaBH_4$. Several other metal borides, such as Co boride, have been prepared and are known to act as desulfurizing agents;[33] however, Ni boride is generally more effective and remains the most popular.

Ni boride is less reactive than Raney Ni – it will desulfurize thiols, sulfides, disulfides, thioacetals, dithioacetals, sulfoxides but it does not generally reduce sulfones.[33] Molecules **31**–**35**[11,33–35] are examples of various sulfur-containing compounds that have been successfully desulfurized with Ni boride, which will also reduce thioamides[28] to the analogous amine and thioesters (e.g., **36**, Scheme 5) to the corresponding alcohol. Chemoselective desulfurization can be achieved in the presence of esters, chlorides, and aromatic rings. Iodides, nitro groups, aldehydes (e.g., **37**), and nitriles are concomitantly reduced. Alkenes (e.g., **38** and **39**) and ketones are also typically simultaneously reduced in C–S bond cleavage. Bromides and cyclopropanes (such as **40**) have variable chemoselectivity with respect to desulfurization by Ni boride.[33]



31 **32** **33** **34** **35**



36 **37** **38** **39** **40**

Scheme 5

Ni boride is typically used in significant excess: a common stoichiometry is a 1:7:21 molar ratio of substrate to Ni(II) salt to $NaBH_4$.[33] Care must be taken to add the $NaBH_4$ in small portions to the mixture of substrate and Ni(II) salt due to the vigorous hydrogen evolution. Despite these minor drawbacks, Ni boride is a simple and cost-effective method of desulfurization.

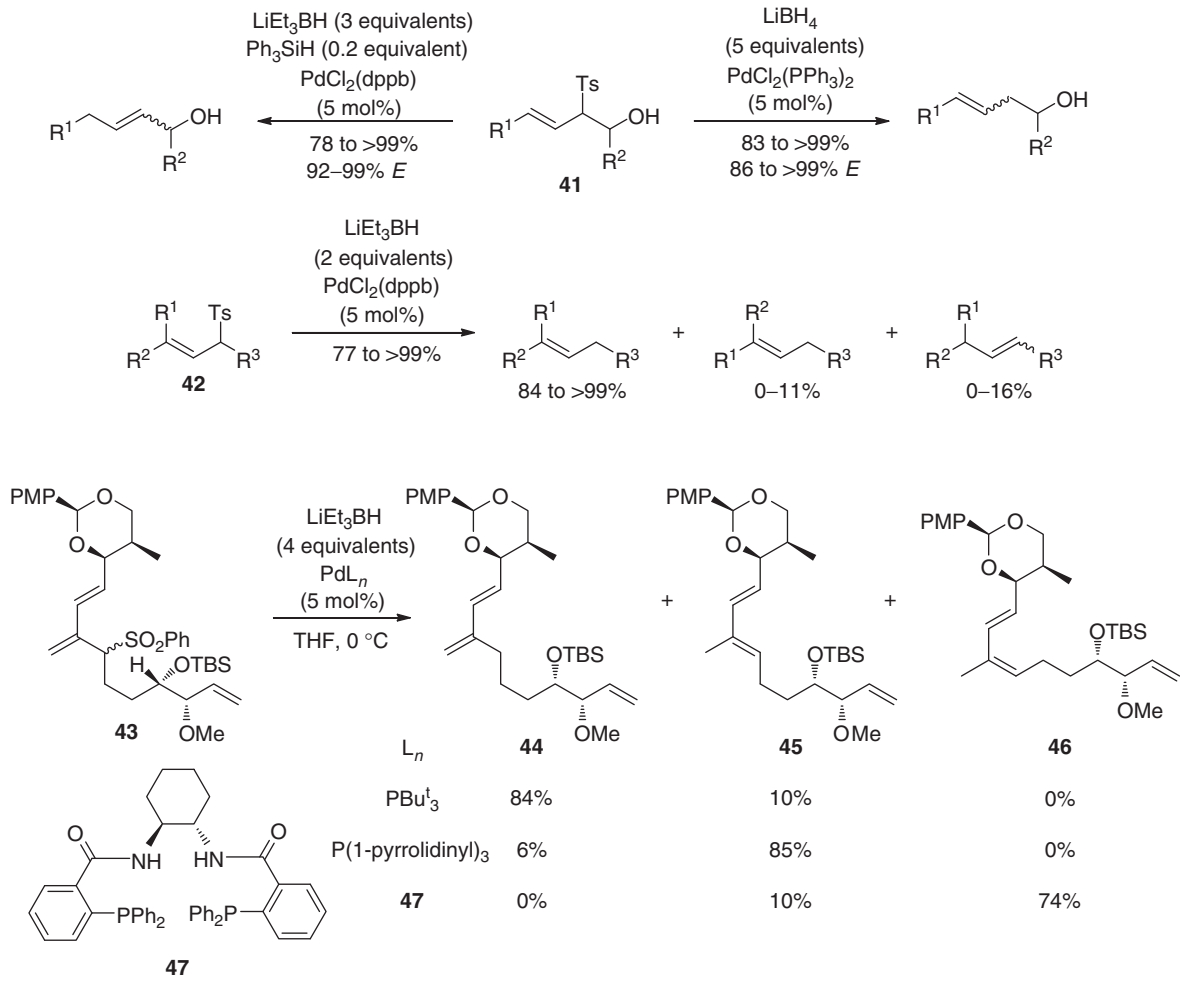
Mechanistically, Ni boride is distinct from Raney Ni, as Ni boride affords retention of stereochemistry, presumably via Ni insertion into the C–S bond followed by reductive elimination.[33] However, at least one example of epimerization is known.[36]

Although $NaBH_4$ has been used with other metals, notably Co to yield Co boride,[33] none of these are as popular as Ni boride. An interesting variation on desulfurization with boron hydrides and transition metals is the palladium-catalyzed desulfonylation of allylic sulfones.[37] Hydroxy sulfones **41** form a chelate with the borohydride ($LiBH_4$ proved to be a superior reagent, **Scheme 6**), leading to the observed regioselectivity. Switching to $LiEt_3BH$ resulted in a reversal in regioselectivity. Allylic sulfones **42** afforded hydride addition primarily at the less substituted position. This approach was used in the synthesis of polyprenols.[38] It has also been shown that in the more complex dienyl sulfone **43**, the phosphine ligand can alter the reduction regioselectivity.[39] Palladium-catalyzed reduction of allylic thiophenyl ethers with $LiEt_3BH$ has also been reported.[40]

Low-valent Fe and Co complexes for the reduction of thiols and thioketones have been reported but these methods have not been widely adopted.[41]

Lithium aluminum hydride (LAH) has been used alone[42] and in conjunction with Ni and Cu complexes to induce reductive desulfurization – a combination $CuCl_2$ and LAH has been shown to reductively cleave sulfides without reducing alkenes; $CuCl_2$, $ZnCl_2$, and LAH effectively cleaved a dithioacetal.[43] Cp_2NiCl_2 reacts with LAH in tetrahydrofuran (THF) to provide Cp_2NiAlH_2Li•THF, a homogeneous reagent that will desulfurize thiols, sulfides, sulfoxides, and sulfones, usually in moderate yield.[44] $NiBr_2$•DME, PPh_3, and LAH combine to make an effective desulfurization agent, capable of reducing thiols, sulfides, dithioacetals, sulfoxides, and sulfones.[45] Despite their advantages (such as easy handling, *in situ* preparation, etc.) over Raney Ni and other reagents, none of these reagents has received a thorough exploitation in organic synthesis.

Metal complex reducing agents (MCRAs) are a curious class of reagents and nickel complex reducing agent (NiCRA) has distinguished itself as a useful desulfurization agent. NiCRAs are prepared by combining NaH, a sodium alkoxide, and $Ni(OAc)_2$ – none of which is typically employed as a standalone reductant.[46] The related NiCRAL reagents are prepared by including



Scheme 6

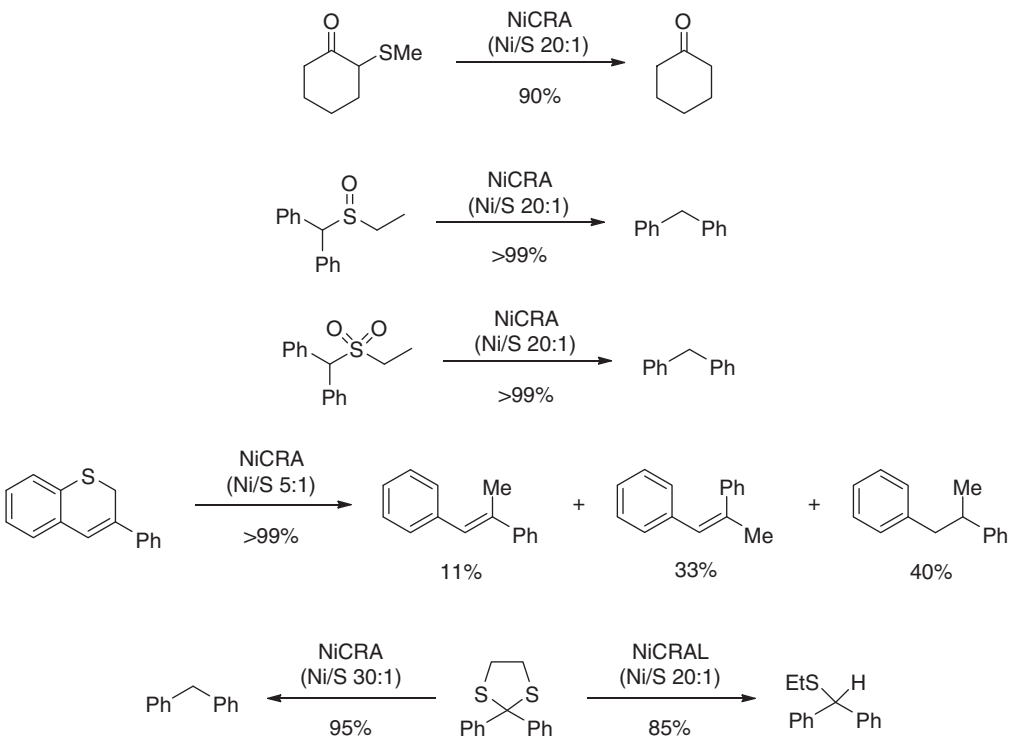
bipyridine in the reaction mixture. Both NiCRAs and NiCRALs are easily prepared and handled and are highly active desulfurizing agents, with reactivity comparable to Raney Ni and greater than Ni boride: thiols, sulfides, disulfides, sulfoxides, and sulfones are cleaved, whereas ketones and esters are readily tolerated. Vinyl sulfides, sulfoxides, and sulfones are reduced to the corresponding alkene; however, mixtures of *E* and *Z* alkenes are typical. Allylic sulfides afforded nearly equimolar amounts of alkene and alkane (Scheme 7). It is also noteworthy that NiCRAs and NiCRALs are typically used in very significant excess, with Ni to S molar ratios typically in the range of 20–30 to 1.

Intriguingly, dithioacetal reduction with NiCRAs afforded complete reduction to the alkane, whereas NiCRALs yielded semireduction to the corresponding sulfide (Scheme 7).[46b,c] As noted above, these reagents are often used in significant excess, with a Ni/S ratio of 20–30 to 1. Lower Ni/S ratios lead to substrate dimerization to afford alkenes.[47] More recent work has shown that replacing the sodium alkoxide with a 3° amino alkoxide affords NiCRAs with dramatically increased reactivity.[46d] Despite their apparent utility and ease of handling, NiCRAs and NiCRALs have not been widely embraced by the synthetic community.

8.28.1.4 Metal Amalgams

Given the highly thiophilic nature of mercury, it is not surprising that alloys of mercury, known as amalgams, are commonly used to reduce sulfur–carbon bonds. The most common amalgams are those of sodium and aluminum, but zinc amalgam has also been used.

Sodium amalgam is used primarily for desulfurization of alkyl aryl sulfones, but it has been shown to reduce alkyl aryl sulfides and sulfoxides as well.[48–50] Although a number of undesirable side reactions can occur, the use of excess 6% Na(Hg) buffered with Na_2HPO_4 or $B(OH)_3$[51] in MeOH has been shown to be particularly reliable and these have become the standard conditions for use with sodium amalgam (though the sodium percentage is often slightly varied).[52] These conditions also permit the chemoselective reduction of sulfones in the presence of sulfides[53] and are tolerant of ethers,[54,55] silyl ethers,[56] acetals,[50,57–59] alkenes,[56,60–63] alkynes,[59,63] ketones,[62] esters,[64] amides,[56,59] lactones,[50,61] cyclopropanes,[57,65,66] and sulfinamides.[67] Vinyl



Scheme 7

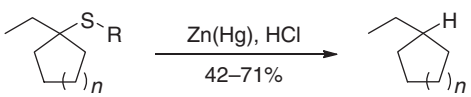
sulfones undergo *E*/*Z*-isomerization, with the product heavily favoring the *E* alkene.[68] Several examples are shown in Scheme 8. The first example demonstrates a chemoselective C–S bond cleavage in the presence of a C–P bond,[69] whereas the last two examples illustrate that epimerization will occur at the reaction site and product mixtures should be expected in the absence of significant stereoinducing constraints.

The use of sodium amalgam suffers from several drawbacks. The most noteworthy is that several equivalents of reagent are typically required (though not nearly as large an excess as Ni_2B). Given the environmental and toxicological risks associated with mercury, this is not without significant consequence. In addition, it has been reported that the reduction of conjugated dienyl vinyl sulfones affords concomitant reduction of the sulfonylated alkene.[70] However, perhaps the most notable issue with Na(Hg) is the β-elimination of vicinal leaving groups to afford alkenes.[65] In truth, this is not a drawback but is actually the Julia (-Lythgoe) olefination,[71] a popular, broad scope method for the formation of *E*-alkenes (*see* Chapter 1.15).

Aluminum amalgam is noticeably different from Na(Hg) – it is a less reactive desulfurization agent[72] and it is typically prepared by dipping aluminum foil in an aqueous solution of $HgCl_2$, and thus contains far less mercury.[73] Virtually all examples Al(Hg)-promoted desulfurization of sulfides,[74] sulfoxides,[73b,75,76] sulfones,[73b,75] and sulfonamides[75] involve a sulfur atom that is α to a carbonyl or other EWG, such as a sulfone[70] (1,1-bis(sulfones) are reduced to sulfones)[77] or cyanide.[72] This electronic requirement stands in stark contrast to desulfurizations using Na(Hg). This allows for chemoselective reduction of selected sulfur–carbon bonds (Scheme 9).[50] Though cases of C–S bond cleavage in the absence of such an EWG are known,[78,79] so is the reduction of sulfoxides to sulfides.[80] If a vicinal OH group is present, sulfoximines can be cleaved without the presence of an EWG to afford an alkene.[81]

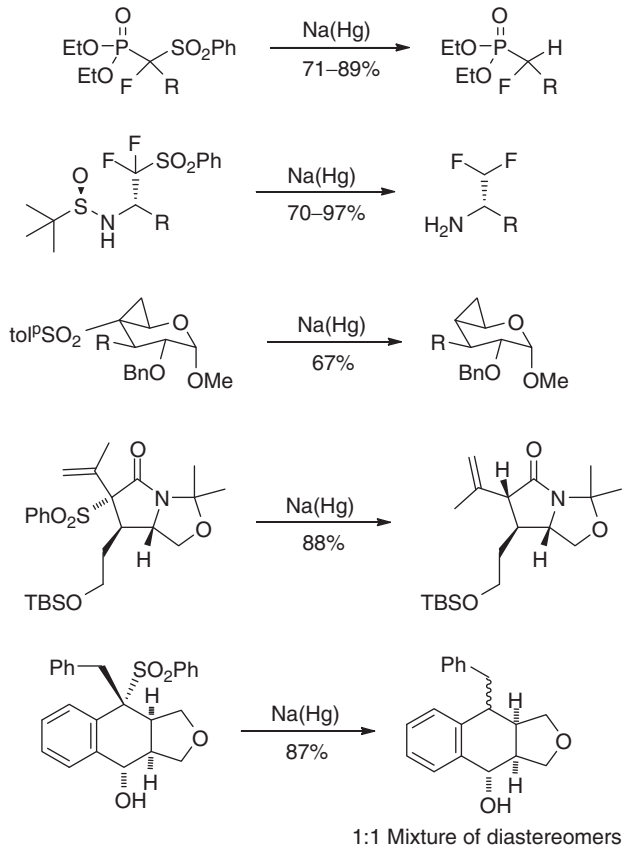
Al(Hg) will also reduce carbon–halogen bonds in preference to sulfur–carbon bonds, depending on position of the EWG.[21b] However, alkenes are not reduced[82] and vinyl sulfones can be reduced stereospecifically.[79,83] There are some drawbacks to Al(Hg): epimerization at the reaction site can be observed,[74] as can concomitant reduction of nitro groups and occasionally, ketones.[84] As with Na(Hg), Al(Hg)-mediated reduction of conjugated dienyl vinyl sulfones affords concomitant reduction of the sulfonylated alkene.[70] Scheme 10 illustrates several examples of reductions with Al(Hg).[74,85,86]

Though Na(Hg) and Al(Hg) are by far the most commonly employed amalgams in desulfurization, Mg(Hg) has seen some use in the reduction of sulfones.[87] In addition, Zn(Hg) has been reported to reduce sulfides in moderate yield (equation 7).[88]

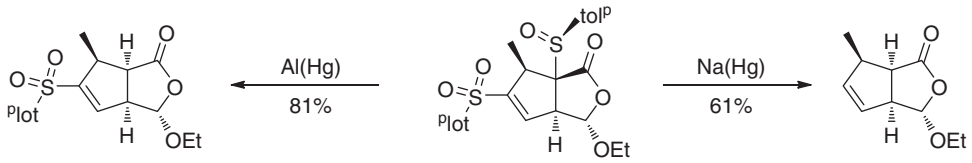


R = Et, Ph
n = 1–3

(7)



Scheme 8



Scheme 9

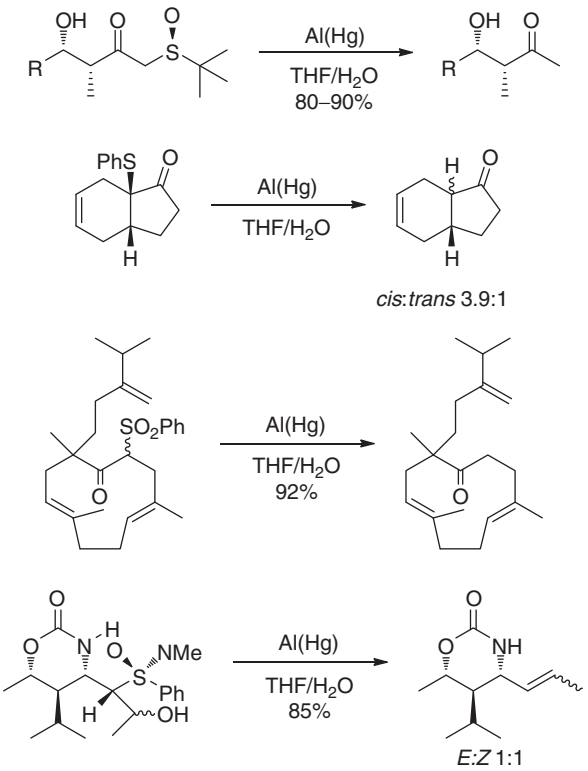
8.28.1.5 Metals and Single-Electron Transfer (SET) Reagents

Electropositive metals such as Li, Na, Mg, Zn, and Ca have been used to reduce sulfur–carbon bonds. Alkali metals, especially Li, are the most widely employed and can cleave sulfides, sulfoxides, sulfones, dithioacetals, etc.

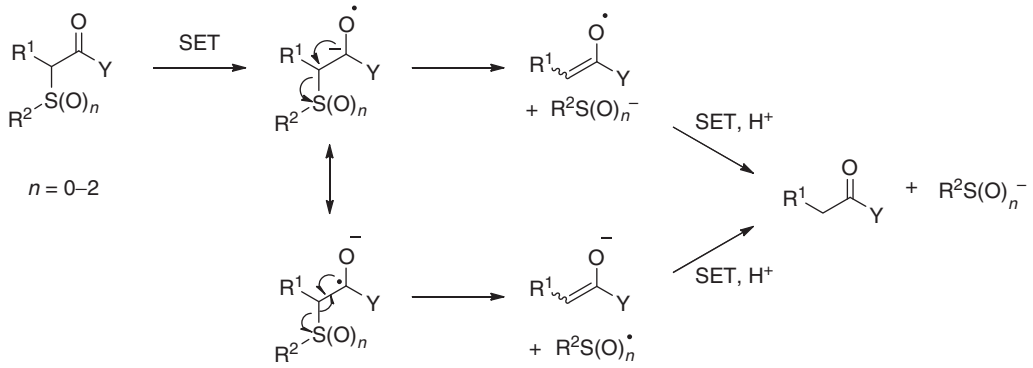
It is important to note that the mechanism of these reductions involves two SET steps and that an excess of reducing agent is typically required. Therefore, diligence should be taken to employ the least reactive metal required if other groups prone to SET are present in the substrate. If the sulfur atom is bonded to the carbon α to a carbonyl this allows for SET to the carbonyl and facilitates C–S bond fragmentation (Scheme 11). Similar processes can occur if the sulfur atom is bound to an aromatic ring (e.g., aryl sulfides and sulfones) or is in an allylic or benzylic position.

Cleavage of C–S bonds by SET reagents can also lead to elimination if a reasonable leaving group is located on the vicinal carbon (Scheme 12). This is the crux of the Julia (-Lythgoe) olefination (*see* Chapter 1.15).

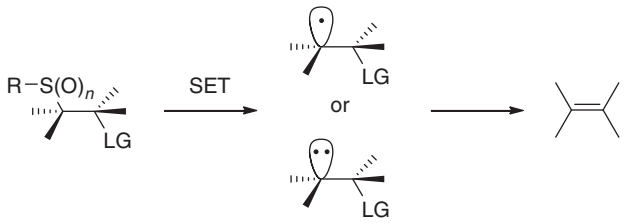
Li, Na, and K have been used in hydrocarbons, ethers, HMPA, and DMA to reduce simple sulfides[89] but by far the most popular technique for C–S bond fragmentation with alkali metals uses amines such as NH_3 or $EtNH_2$ as solvent. Regardless of the choice of conditions, the alkyl C–S bond is preferentially reduced over the aryl C–S bond.[89] This allows for cleavage of aryl alkyl sulfides[90] and sulfones,[91] including aryl allylic sulfides[92] and sulfones.[93] Alkene migration or isomerization is not observed. Dithioacetals[94] and sulfonamides (with both C–S and N–S bond reduction) are also reduced.[95] Several examples are shown in Scheme 13. It is important to note that alkali metals have a high enough reduction potential that an adjacent carbonyl is not required for C–S



Scheme 10

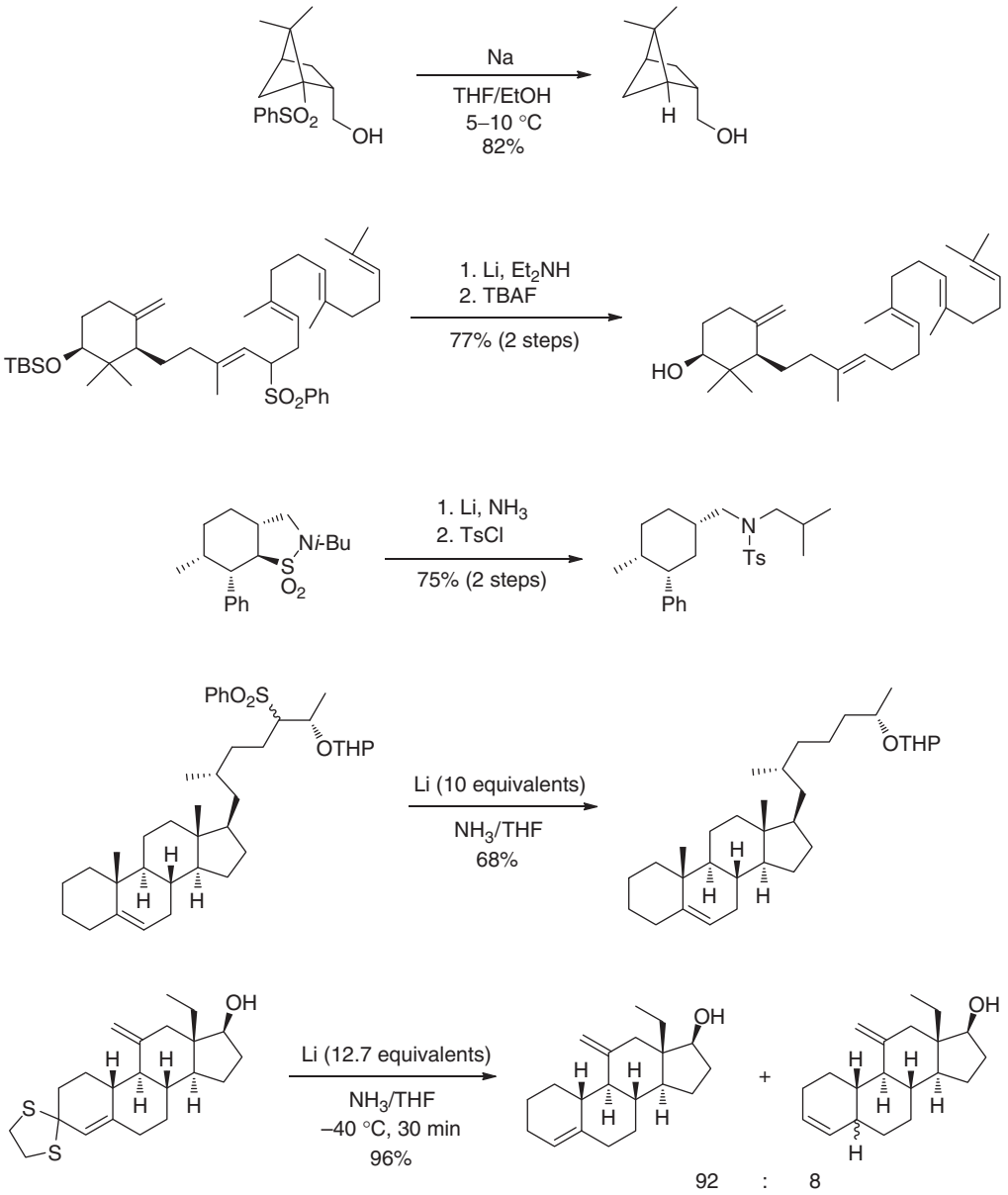


Scheme 11

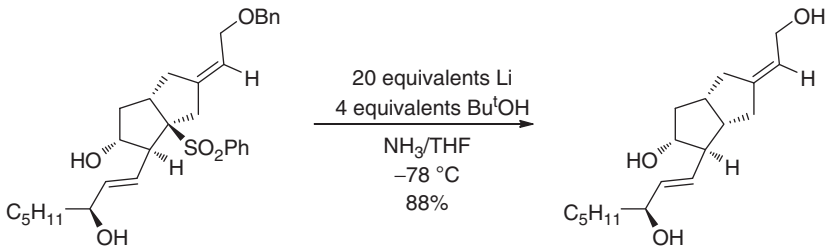


Scheme 12

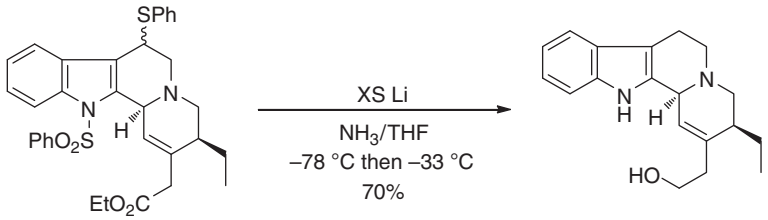
bond reduction. However, this high reduction potential also leads to concomitant cleavage of benzylic ethers under these conditions (equation 8).[91a,93d] This is not necessarily a drawback, as it can be used to simultaneously desulfurize and deprotect alcohol groups. Sulfonamide reductions are common and ester reductions are not unknown but typically require higher temperatures (equation 9).[90b] Enones typically undergo concurrent conjugate reduction (equation 10).[96] Halides are not compatible.



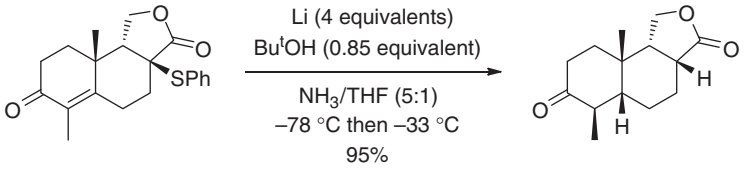
Scheme 13



(8)

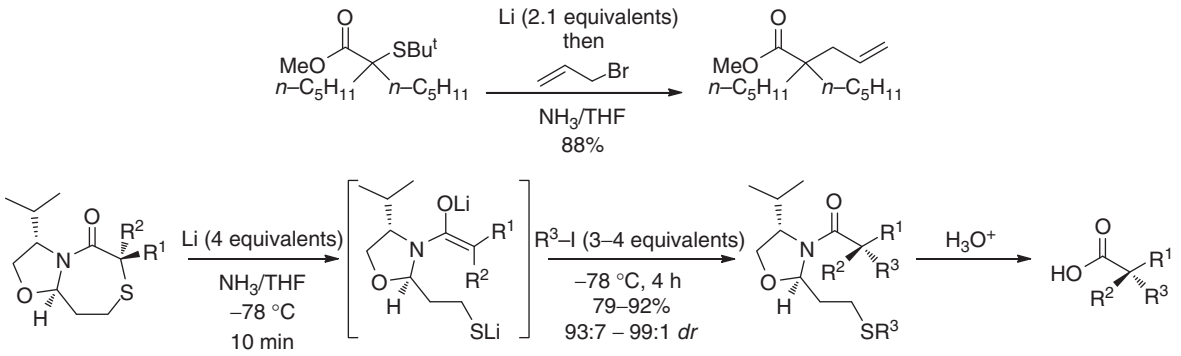


(9)



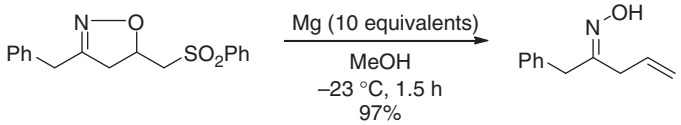
(10)

Although in virtually all cases C–S bond reduction results in a protonated product, in some methodologies this does not have to been the case. Li in liquid NH_3 has been used to reductively generate enolates (*see* Chapter 2.06), which can then be alkylated (*see* Chapter 3.01).[16] Stereoselective variations on this process have been used for the asymmetric synthesis of quaternary carbons (Scheme 14).[97]



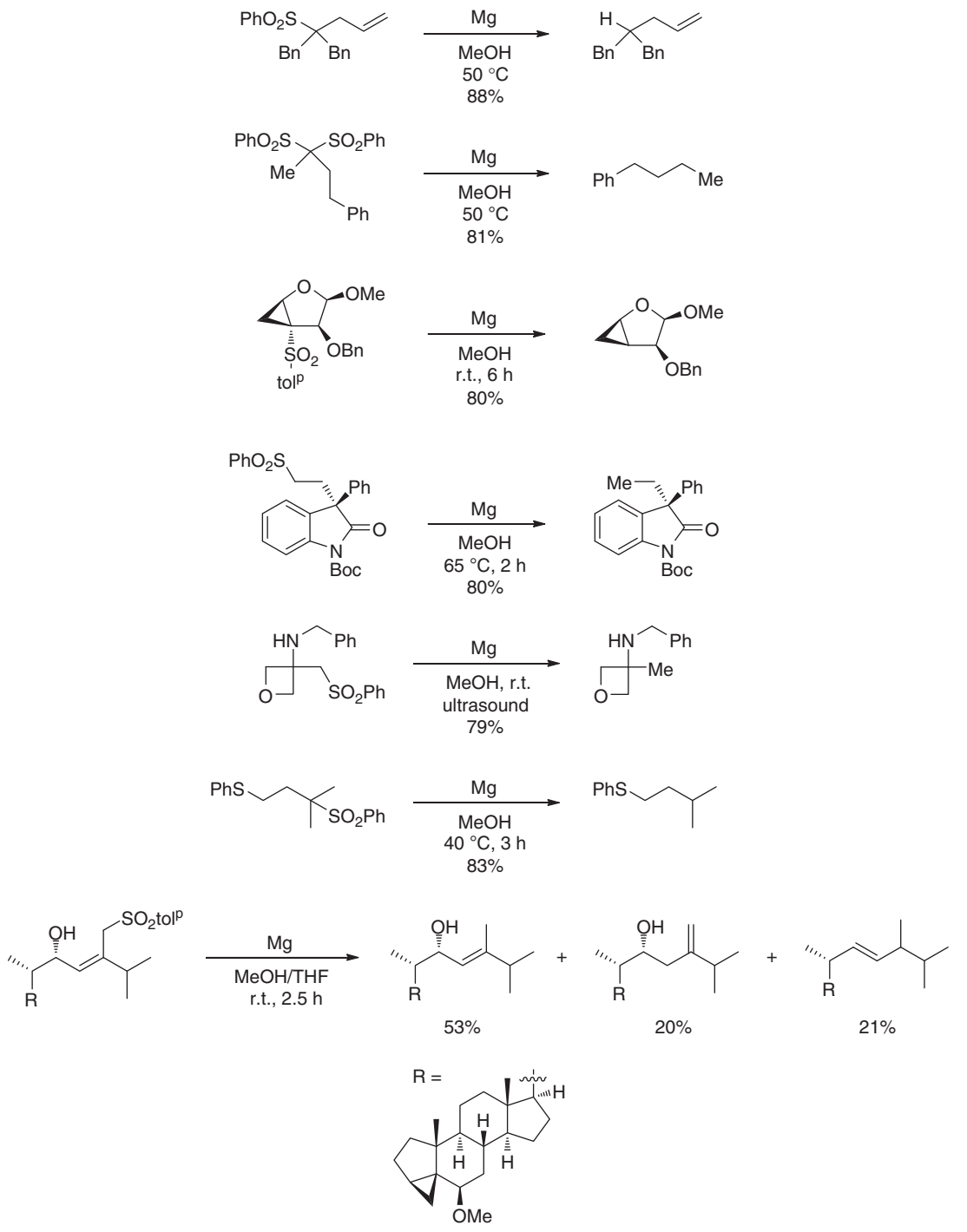
Scheme 14

Amongst the alkali earth metals magnesium is the only one that sees significant employment in desulfurization. Mg does not have as high a reduction potential as alkali metals; nevertheless, Mg in MeOH is a popular, mild, and highly chemoselective method to cleave alkyl aryl sulfones (Scheme 15).[3,42b,98] 1,1-Bis(sulfones) afford complete reduction[98b] but yields are not universally high.[87e] Most functional groups (including other sulfur functional groups) except sulfonamides[99] and halides tolerate these conditions, though allylic aryl sulfones can suffer from partial alkene migration.[100] There is also one report of reduction of a γ-thioaryl α,β-unsaturated ester.[101] Vicinal leaving groups can also be subject to elimination (equation 11).[102] Mg also reduces sulfonium salts to sulfides.[103] The use of Mg with a catalytic amount of $NiBr_2$ for the cleavage of sulfones has also been reported.[104] Ca has seen far less use than Mg in C–S bond reduction but has been used in liquid NH_3 to reduce mono- and dithioacetals[105] and α-ethoxylcarbonyl sulfones.[106]



(11)

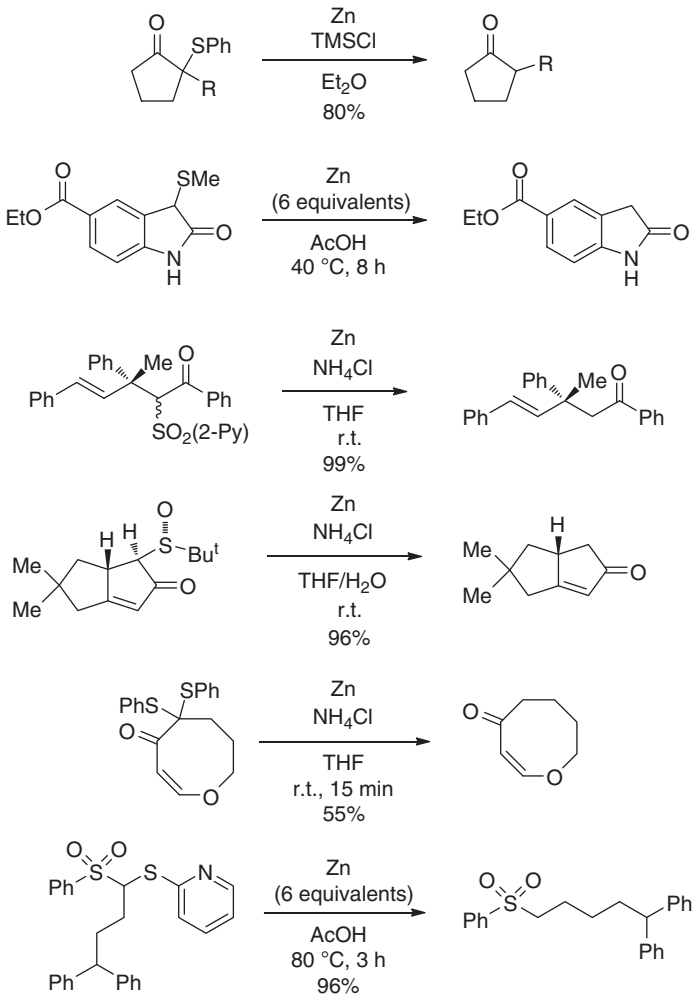
Zinc has a reduction potential even lower than Mg – its C–S bond cleavage capacity is limited to α-thioalkyl and α-thioaryl carbonyls. A mild Lewis or Brønsted acid such as AcOH, NH_4Cl, or TMSCl is also requisite (Scheme 16). Sulfides[107] are reduced more slowly than sulfoxides[107b,108] and examples of reduction of sulfones,[109] and α-thiophenyl aliphatic esters are rare.[107b,108e] Lactones, esters, amides, α,β-unsaturated ketones, and isolated alkenes are all tolerated. N–O bonds are cleaved and can lead to some spectacular cascades (equation 12).[110]


PhO2S
Bn
Bn
Mg
MeOH
50 °C
88%
H
Bn
Bn
PhO2S
SO2Ph
Me
Ph
Mg
MeOH
50 °C
81%
Ph
Me
O
OMe
OBn
SO2
tolp
Mg
MeOH
r.t., 6 h
80%
O
OMe
OBn
PhO2S
Ph
O
N
Boc
Mg
MeOH
65 °C, 2 h
80%
Me
Ph
O
N
Boc
HN
Ph
O
SO2Ph
Mg
MeOH, r.t.
ultrasound
79%
HN
Ph
Me
O
PhS
SO2Ph
Mg
MeOH
40 °C, 3 h
83%
PhS
OH
SO2tolp
R
Mg
MeOH/THF
r.t., 2.5 h
OH
R
53%
+
OH
R
20%
+
R
21%
R =
H
H
H
H
OMe

Scheme 15

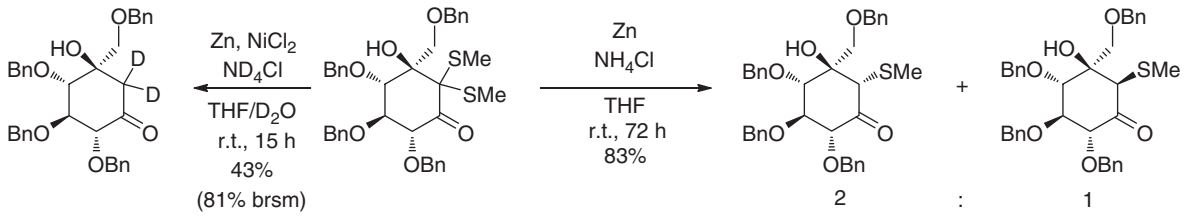

O
SO2Ph
*
N
SO2Ph
O
TIPSO
Zn
(50 equivalents)
Aqueous NH4Cl
76%
TIPSO
O
*
N
HO

(12)

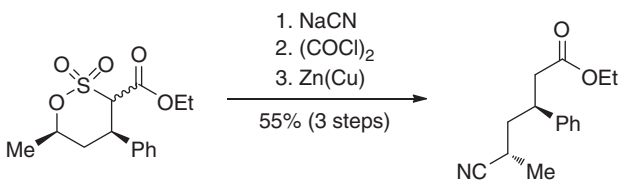


Scheme 16

Though examples of successful dithioacetal reductions with Zn are known,[107g] there are also examples of semireduction (Scheme 17). However, by combining Zn with excess $NiCl_2$, complete reduction was achieved. In related chemistry, the use of excess $TiCl_4$ and Zn results in reduction of α-keto sulfones.[111] Zn(Cu) was used to reduce an α-chlorosulfonyl ester (equation 13).[112]

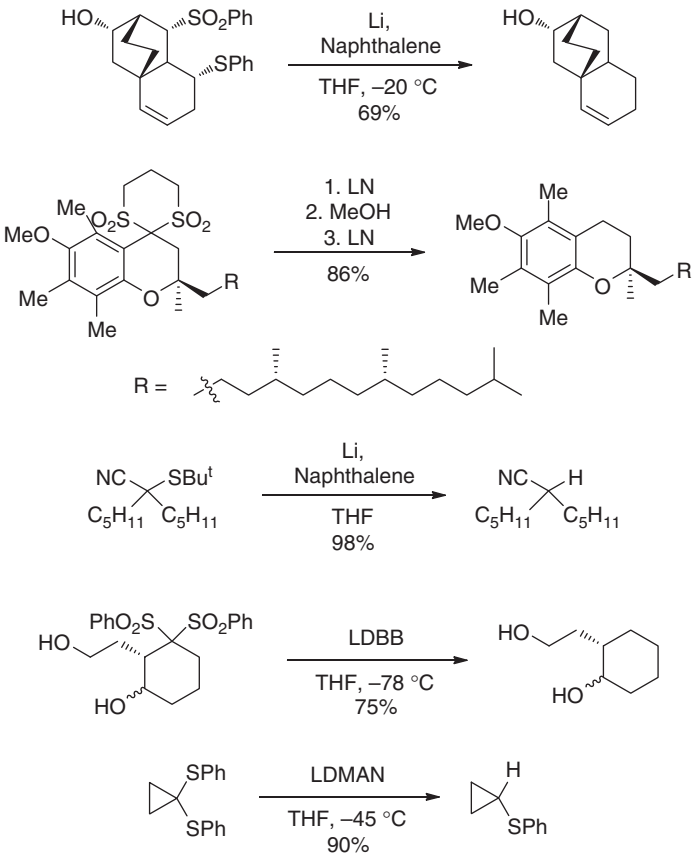


Scheme 17



(13)

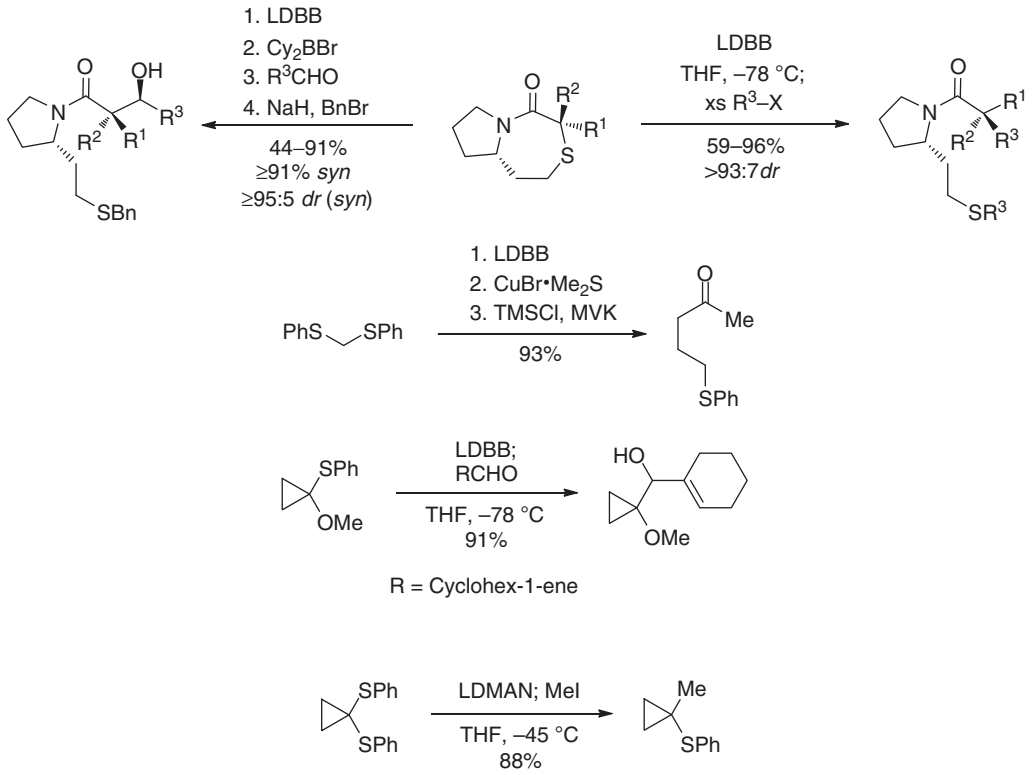
It is clear that many metals and metal alloys are effective desulfurization agents. However, they all present at least one of the following difficulties: low reactivity (e.g., sulfur must be α to an EWG), heterogeneous reaction conditions, operationally challenging solvents (e.g., NH_3 or $EtNH_2$), or toxic metals (e.g., amalgams). One class of reagents that does not fall into any of these categories are the radical anions derived from combining lithium or sodium and an aromatic system such as naphthalene, 4,4′-di-*tert*-butylbiphenyl, or 1-dimethylaminonapthalene, in an ethereal solvent, typically THF. This combination results in an electron transfer from the metal to the aromatic system to generate a radical anion of the aromatic system, which then transfers an electron to the substrate. These highly colored radical anions, dubbed lithium naphthalenide (LN), lithium 4,4′-di-*tert*-butylbiphenylide (LDBB), and lithium 1-*N*,*N*-dimethylaminonaphthalenide (LDMAN), are soluble in THF and have a reasonable lifetime of up to a few days if stored below room temperature.[113] These reagents sometimes can be used titrometrically due to their colored nature and the rapid kinetics afforded by their homogeneous character.[114,115] Alternatively, they may be generated and consumed *in situ* by using stoichiometric quantities of the metal and a catalytic amount of the aromatic system (**Scheme 18**).



Scheme 18

LDBB, LN, and LDMAN have all been used to reductively cleave aryl alkyl sulfides, dithioacetals (which undergo monoreduction), sulfones, and 1,1-bis(sulfones). This generates the corresponding alkyllithium species (*see* Chapter 1.01), which can be protonated[16,116] (**Scheme 19**) or utilized in a variety of C–C bond-forming reactions (**Scheme 19**), including alkylation,[16,114a,b,117] silylation,[118,119] 1,2-addition to carbonyls[114c,115,118] and imines,[114d] as well as 1,4-addition,[117] addition to disulfides,[117] and 5-*exo*-trig cyclizations of unactivated alkenes.[116] It is important to note that the bond fragmentation always favors cleavage of the alkyl C–S bond. With these three reagents there is no requirement for an adjacent EWG and sulfides and sulfones bonds will be cleaved anywhere in the substrate. However, sulfur groups α to an EWG are more readily reduced than comparable groups in other positions and controlling stoichiometry leads to regioselective C–S bond cleavage.[120] In the case of dialkyl sulfur systems with an EWG on one side, the C–S bond fragmentation occurs on the side of the EWG.[16,114]

Of these three reducing reagents, LDBB has the highest reduction potential,[113b,121] whereas LDMAN has the convenience of being removed in an acidic extraction.[118] These reagents are also capable of reductive lithiation of halides[121] and cleavage of benzylic ether[122] and benzyloxymethyl ether protecting groups.[123] As with all SET reagents, epimerization will occur if the site of C–S bond cleavage is a stereocenter.



Scheme 19

Potassium graphite is a solid-state SET reagent but has similar electron transfer properties similar to LDBB, LN, and LDMAN.[124] It has been shown to desulfurize alkene sulfones without alkene migration; however, some *E*/*Z* isomerization was observed.[125]

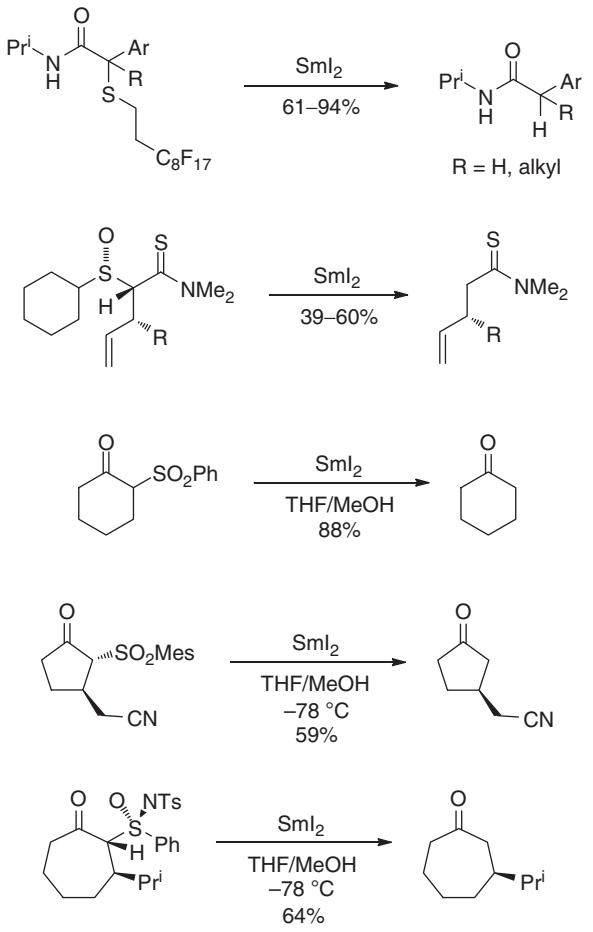
Like LN, LDBB, and LDMAN, SmI_2[126] is one electron transfer reagent that is soluble in THF. However, it differs from these reagents in that it is commercially available as a solid or solution in THF and has a reasonable shelf life. If desired, it can be prepared from samarium metal.[127] This has led to a substantial increase in its popularity as a desulfurizing agent. It has been shown to reduce C–S bonds in aryl sulfides,[128,129] sulfoxides,[128,130] sulfones,[128,131–133] and sulfoximines[134] α to carbonyls (Scheme 20). 1,1-Bis(sulfones) undergo monoreduction.[135] In addition, the reductive cleavage of sulfones does not require the presence of an EWG.[131,132] The reduction of sulfonium ions has also been reported,[136] as has the use of SmI_2 in Julia-Lythgoe olefinations (*see* Chapter 1.15).[137] SmI_2 is tolerant of most functional groups, including enones,[138] cyanides,[133b] and isolated alkenes,[133d] though there have been reports of partial ketone reduction,[139] α-keto cyclopropanes undergoing ring opening,[140] and elimination of halides.[141]

8.28.1.6 Tin and Silicon Hydrides

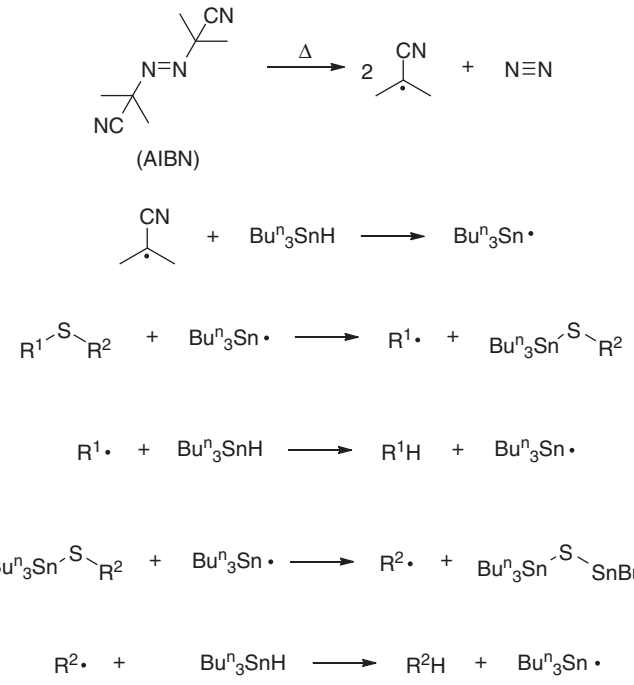
Tin hydrides, most commonly Bu_3SnH (tri-*n*-butyltin hydride (TBTH)) or Ph_3SnH (triphenyltin hydride (TPTH)), are typically used in hot toluene or benzene in the presence of a catalytic amount of a radical initiator such as AIBN or Et_3B. As is typical with this combination of reagents, the reaction proceeds via a radical mechanism (Scheme 21).[142] Relative to other substrates for radical reactions, the C–S bond is not very reactive. Substantive reviews of tin hydride chemistry have covered desulfurization,[143] as have other reviews.[144]

This type of C–S bond reduction is performed on sulfides[145] and thiols[146] and works best when the radical generated ($R^1\cdot$ and/or $R^2\cdot$) is resonance stabilized. Carbonyls are typically the best stabilizing group, followed by benzylic and allylic systems.[142] Sulfides that afford unstabilized alkyl radicals are typically less reactive.[142,147] The thioalkyltin intermediate is more reactive than the starting sulfide and as a result regioselective desulfurization of nonsymmetrical sulfides is not possible. Allylic sulfides may react via an S_H or S_H' pathway, leading to reduced or stannylated products. Reductive stannylation of allylic or propargylic sulfur compounds is a well-known reaction.[148]

In addition to the reduction of sulfides (and by analogy, thiols) shown in Scheme 21, thiocarbonates,[149] dithiocarbonates,[150] dithiocarbamates,[151] thiocyanates,[152] and β-keto sulfones[110b,153,154] are also cleaved by tin hydrides and AIBN. Dithioacetals can undergo mono-[155] or bis-reduction.[156] Recent examples demonstrate reduction of an allylic sulfone over an allylic dithioacetal[157] and a vinyl sulfone over an allylic one.[158] TBTH/AIBN reductions are tolerant of nitriles,[152] esters,[145g,146] ketones,[154a,b]

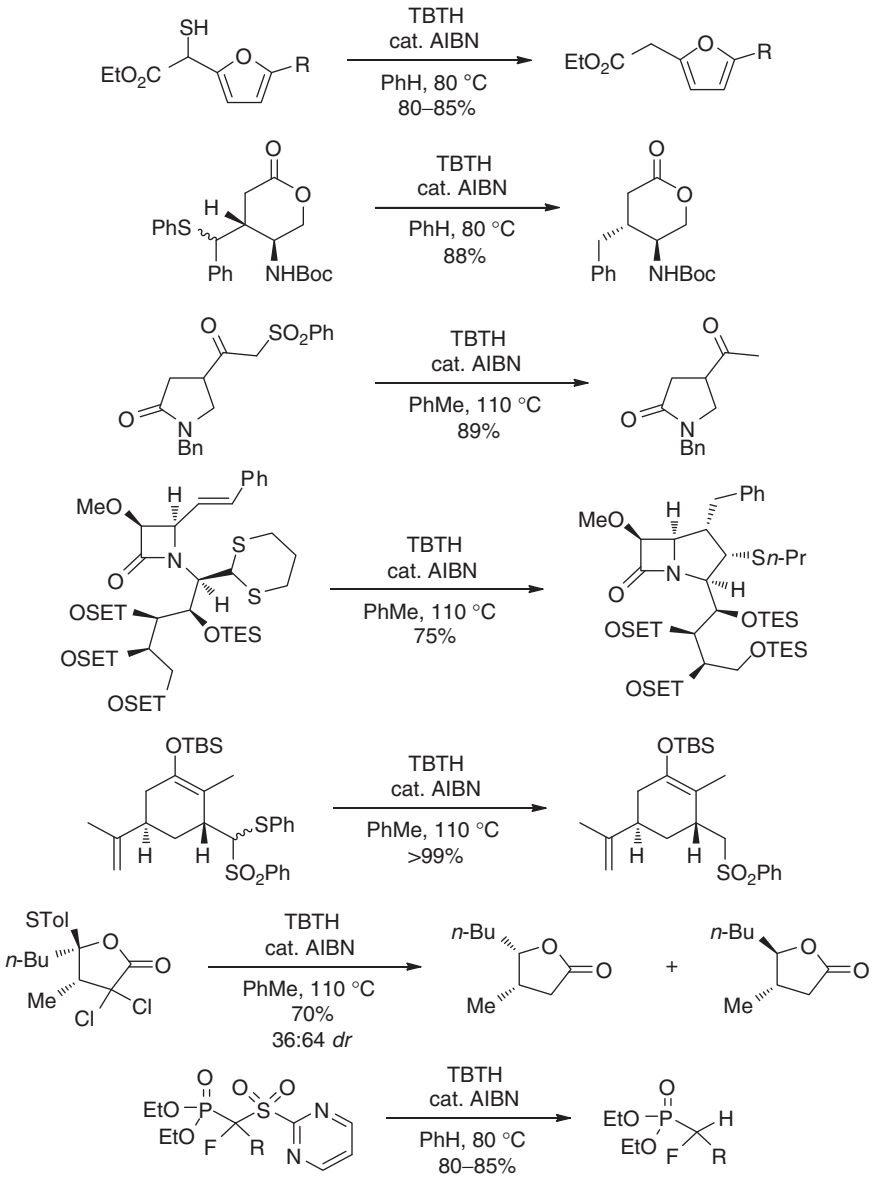


Scheme 20



Scheme 21

ethers,[147f,154a] acetals,[147f,154a] lactones,[145h] amides,[153] carbamates,[145h] imides,[145b] β-lactams,[145e] and nitro groups.[145a] Isolated alkenes[110b,145b] are generally tolerated, although radical cyclizations may occur to form five- and six-membered rings via radical cascades.[155] The stereochemistry at the reaction site is not conserved due to epimerization of the radical intermediate. Yields are moderate to excellent and β-eliminations may occur in vicinally substituted compounds. Care should be taken when working with organotin materials due to their toxicity. In addition, the removal of reaction byproducts is known to be challenging. As a result, protocols have been developed to overcome this,[159] including techniques employ catalytic amounts of tin.[160] Scheme 22 illustrates some examples of C–S bond cleavage with TBTH/AIBN. Note that the final entry offers a chemoselective C–S bond reduction in the presence of the C–P bond;[160] however, similar conditions with the corresponding phenyl sulfone result in fragmentation of the C–P bond (equation 36).[69]



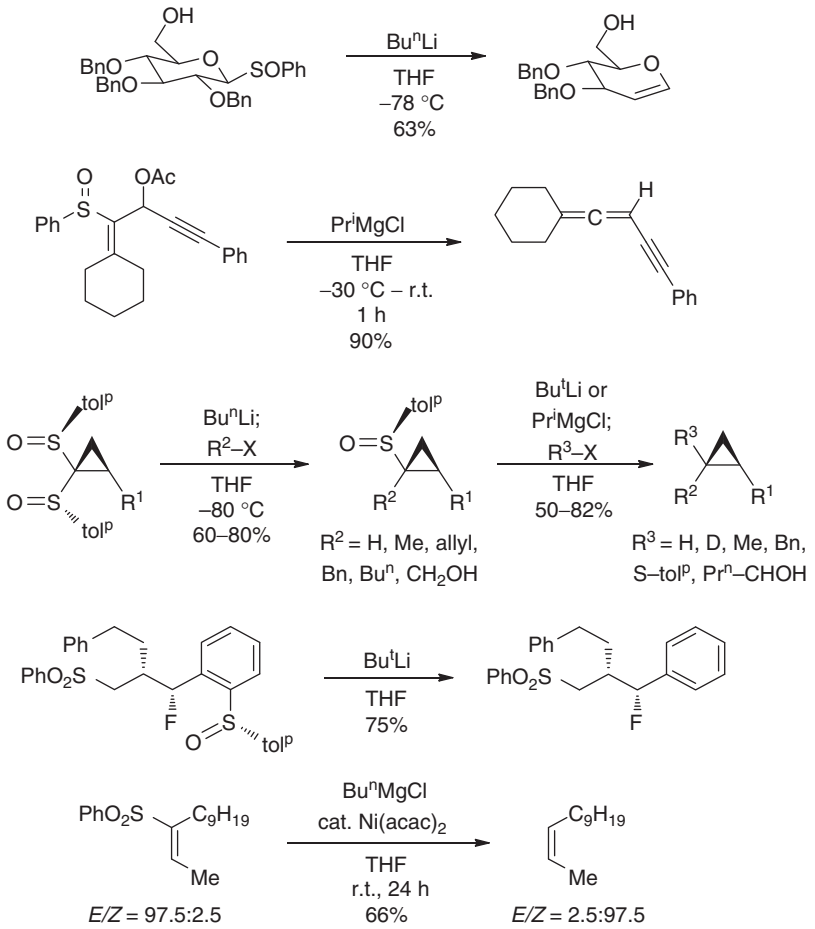
Scheme 22

Another method of avoiding toxicity and purification issues surrounding tin hydride reagents is to employ a silicon hydride such as tris(trimethylsilyl)silane (TTMSS). To date this reagent has not demonstrated the same versatility as TBTH but it has been used in the reduction of xanthates,[161] α-thia carbonyl compounds,[162] dithiolanes, oxathiolanes, and thiazolidines.[163]

8.28.1.7 Grignard, Organolithium, and Other Organometallic Reagents

Highly nucleophilic metal species, such as Grignard and organolithium reagents are capable of performing sulfoxide exchange[164,165] through nucleophilic attack at sulfur (with inversion of sulfur stereochemistry) to afford a new sulfoxide and a different organometal species, which is then protonated or alkylated. The regioselectivity of C–S bond cleavage is typically sterically driven, though this is not always the case. The intermediate organometal species must be more stable than the starting nucleophile. The nucleophile is used in excess, as the new sulfoxide may be deprotonated *in situ* by the highly basic nucleophile. Elimination will occur if a vicinal leaving group, such as an alkoxide, acetal, carboxylate, or sulfonate is present.[166]

Similar examples of nucleophilic attack on sulfones are also known, but generally include a transition metal catalyst.[167] There is a report of a nonmetal-catalyzed exchange but this may be an elimination–addition sequence.[145d] In the presence of both a sulfone and sulfoxide, the sulfoxide is more labile.[165c] Several examples of nucleophilic addition are depicted in **Scheme 23**.



Scheme 23

The reduction of the C–S bond of arenesulfonates can be achieved with Grignard reagents in the presence of a nickel catalyst.[168]

Dithioacetals derived from diaryl ketones are attacked at sulfur by Bu^nLi, leading to the corresponding sulfide.[169] Similarly, Bu^n_3SnLi desulfurizes dithioacetals, α-thioaryl cyanides, and α,α-bis(trimethylsilyl)alkyl sulfides.[170]

Lithium dimethylcuprate has been used in the desulfurization of species that afford highly stabilized conjugate bases, such as enolates.[171]

8.28.1.8 Miscellaneous Desulfurizations

Sodium dithionite has been shown to reduce vinylic sulfones to alkenes via an addition/elimination mechanism. This method is stereospecific and results in retention of alkene geometry.[172] Sodium dithionite has also been used as the reducing agent in viologen-mediated reduction of α-nitro sulfones.[173]

In the case of alkyl aryl sulfides, desulfurization may be induced via S_N2 reactions with a variety of nucleophiles, including RS^-,[89b] RSe^-,[89b] RO^-,[89b] and occasionally $R^1R^2N^-$.[174] 1,2-Eliminations of thioaryl groups can also occur.[89b] Nucleophilic attack of RS^- on the sulfur atom of α-thia carbonyl compounds can be a very mild reduction.[175]

Metal carbonyls have also seen some use in desulfurization. Thiols and thiophene have been reduced by $Mo(CO)_6$.[176] Although $Mo(CO)_6$ affords mixtures of reduced products and dimers are formed in dithioacetal reduction,[177] $W(CO)_6$ affords only dimeric products.[178] Alkyl phenyl sulfides have been cleaved by $Os_3(CO)_{12}$,[179] whereas $Fe_3(CO)_{12}$[180] and $Co_2(CO)_8$[181] also reduce thiols.

Electrochemical reduction of C–S bonds has been reported,[182] as have enzymatic[183] and microbial processes.[184] β-Keto-sulfones can be reduced photochemically in the presence of ascorbic acid as a reductant.[185]

8.28.2 Reduction of Selenium–Carbon Bonds

8.28.2.1 Introduction

Organoselenium compounds behave very similarly to their organosulfur analogs; however, selenium–carbon bonds are typically weaker.[186] The only selenium functionality to see broad application in organic synthesis is the selenide, analogous to the sulfide. Selenols are very prone to aerobic oxidation to the corresponding diselenide and thus are typically only generated and used *in situ*. Selenides can be installed via an electrophilic source of RSe^+, radical addition of RSe• or nucleophilic attack by RSe^-. Oxidation to the corresponding selenoxide is facile (*see* Chapter 7.28), and this results in rapid elimination at or below room temperature to afford an alkene (*see* Chapter 6.18). This is arguably the most common role of organoselenium chemistry in organic synthesis.

In the realm of reduction, the homology of organoselenium and organosulfur reactivity has led, not surprisingly, to most methods of reductive cleavage of selenium–carbon bonds paralleling those of sulfur–carbon bond reduction. However, there are some important differences, the most noteworthy being that selenium is more prone to nucleophilic attack.

8.28.2.2 Raney Nickel

Raney nickel is a highly effective C–Se bond reductant but still retains all the drawbacks cited in Section 8.28.1.2.[2b] In selenide reduction, Raney Ni is typically used in EtOH or an ethereal solvent, though the conditions required to effect reduction are typically milder than those for sulfides and are tolerant of alkyl and aryl ethers,[187,188] acetals,[189,190] alcohols,[189,191] ketones,[187,190b] esters,[191–193] lactones,[191] sulfoxides,[165b] sulfinamides,[165b] and sulfonamides.[187,194] Alkenes can also survive in some instances.[189,190] However, forcing conditions can result in alkene and carbonyl reduction.[195] Several examples are presented in Scheme 24.

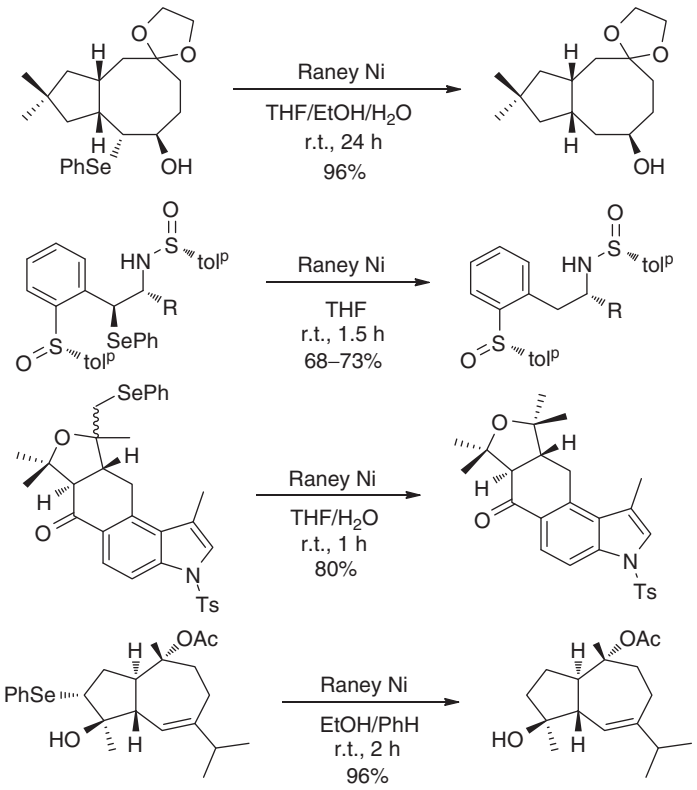
The drawbacks of Raney Ni use in C–Se bond cleavage are handling a hazardous and pyrophoric reagent (especially on larger scales), the lack of chemoselectivity with respect to other reducible functionalities such as unsaturation, allylic and benzylic C–O bonds, dithioacetals, and sulfides. In addition, information on the grade of Raney Ni used is required to reliably reproduce literature results, as yields for a particular reaction can vary considerably depending on the grade employed. Lactones, for example, can be sensitive to residual basic impurities present in the reagent.[196] Mechanistic work has shown that the reduction can proceed, or partially so, via an alkene formed by formal elimination of RSeH.[197] If the Se is bonded to a chiral center, the reduction proceeds to epimerize that stereocenter. Moreover, if the carbon atom adjacent to carbon of the C–Se bond is a stereocenter, this center may also be epimerized. It is significant that some of these disadvantages, such as poor chemoselectivity, can be used productively: Raney Ni and H_2 (under pressure) have been used to perform concomitant deselenation, alkene reduction, and benzyl ether cleavage.[188a]

8.28.2.3 Metal Borides

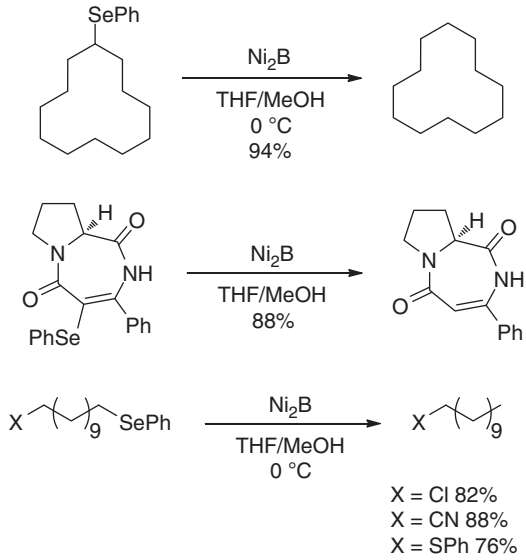
As with desulfurization, nickel boride is an effective deselenization reagent; other metal borides have not seen significant use. A judicious and thorough exploration of Ni_2B-promoted deselenization[198] led to several important conclusions: (1) the optimal solvent mixture is THF–MeOH at 0 °C, (2) both $NaBH_4$ and the Ni(II) salt (usually $NiCl_2$•6 H_2O) must be used in excess relative to the selenide and 3–3.5 mol of $NaBH_4$ is needed to completely reduce a mole of Ni(II) salt, (3) the reaction is most efficient when $NaBH_4$ is added to the other reaction components, thus generating Ni_2B *in situ*, (4) the hydrogen incorporated into the reagent originates from both the MeOH and $NaBH_4$. No hydrogen incorporation from THF was observed and this ruled out a radical mechanism, and (5) alkyl and vinyl selenides, as well as diselenoacetals can be reduced in good to very good yields. Several examples are shown in Scheme 25.

This protocol tolerates alkyl chlorides,[198a,199] (but not iodides)[198a] nitriles,[198a] esters,[200] amides,[201] sulfonamides, sulfides, and sulfones (an interesting and synthetically useful property for deselenations) but not sulfinate esters.[198] Moderately hindered alkenes were unreactive but unhindered olefins are reduced.[198c,202] Ketones are tolerated unless quite unhindered.[198c] β-Selenoketones can afford β-elimination and complications arise if the selenide is vicinal to a good leaving group.[198c]

Allylic selenides were reduced by $LiHBEt_3$ in the presence of a catalytic amount of $Pd(PPh_3)_4$ but the alkenes suffered from migration and *E*/*Z* isomerization.[40]



Scheme 24

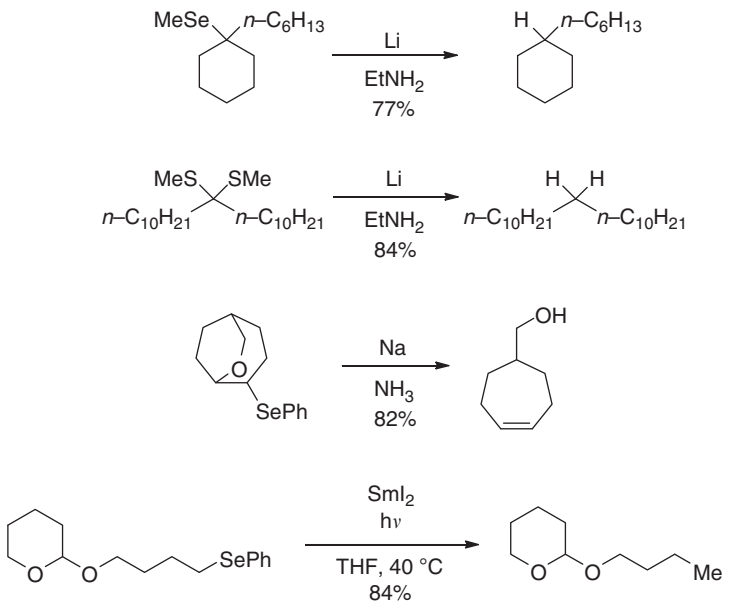


Scheme 25

8.28.2.4 Alkali Metals

Cleavage of C–Se bonds with alkali metals is not nearly as popular as C–S bond reduction. Nevertheless, several manuscripts describe this approach and focus on two systems: Li in $EtNH_2$[186b,203] and Na in liquid NH_3.[188b,196,204] Na has also been used in HMPA or DMA in rare cases.[89b] As is typical, vicinal leaving groups such as carboxy and alkoxy groups are eliminated to afford alkenes and this has been exploited synthetically.[186b,196] As the C–Se bond is weaker than the C–S bond, it is more readily cleaved;

however, few selective deselenations have been performed with alkali metals. In most other respects this chemistry is very similar to alkali metal-promoted desulfurization. Scheme 26 provides representative examples.



Scheme 26

To date there have been a few reports of SmI_2 used under photochemical conditions to fragment C–Se bonds.[205] The examples reported thus far have shown good yields and tolerance of aromatic rings, esters, acetals; however, halides, sulfides, and sulfonates are also reduced under these conditions and the precise chemoselectivity has not yet been elaborated. The use of YbI_2 was also reported but the lone example was low yielding.[205a]

8.28.2.5 Tin Hydrides

Tin hydride-mediated radical reduction is a common technique for reduction of C–Se bonds in selenides and diselenoacetals.[143c,144a,186a,c,206] As with desulfurization (Section 8.28.1.6), the tin hydrides of choice are TBTH and TPTH in conjunction with a radical initiator such as AIBN or Et_3B/O_2 and the reaction is conducted at reflux in PhMe or PhH. TPTH is typically the more suitable reagent and freshly distilled TPTH affords decreased reaction times. Interestingly, deselenations can be performed with TPTH in refluxing PhMe without AIBN,[197,207] thus affording even greater chemoselectivity as most other groups susceptible to TPTH reduction, including sulfur functional groups, require the presence of AIBN. Deselenation with TPTH/TBTH is tolerant of isolated alkenes,[188,197,208–211] alcohols[212] (including allylic alcohols), ethers[211] (including vicinal[213] and benzylic[214] ethers), acetals,[215] sulfides,[188b] dithioacetals,[216] ketones,[211,217,218] esters,[212,213,215,218,219] lactones,[213,220] amines,[221,222] amides,[215,217,219,223] β-lactams,[210] carbamates,[207,224] and quite surprisingly, peroxides.[220] Stereochemistry at the carbon adjacent to the selenium-bearing position is not typically affected during reduction[218,222] but slight erosion has been observed.[225] If the Se atom is bonded directly to a stereocenter epimerization is observed.[210] Several examples are provided in Scheme 27. As with other tin-mediated chemistry, the tin byproducts can be challenging to remove and functionalized tin reagents have been prepared to ameliorate this issue.[226]

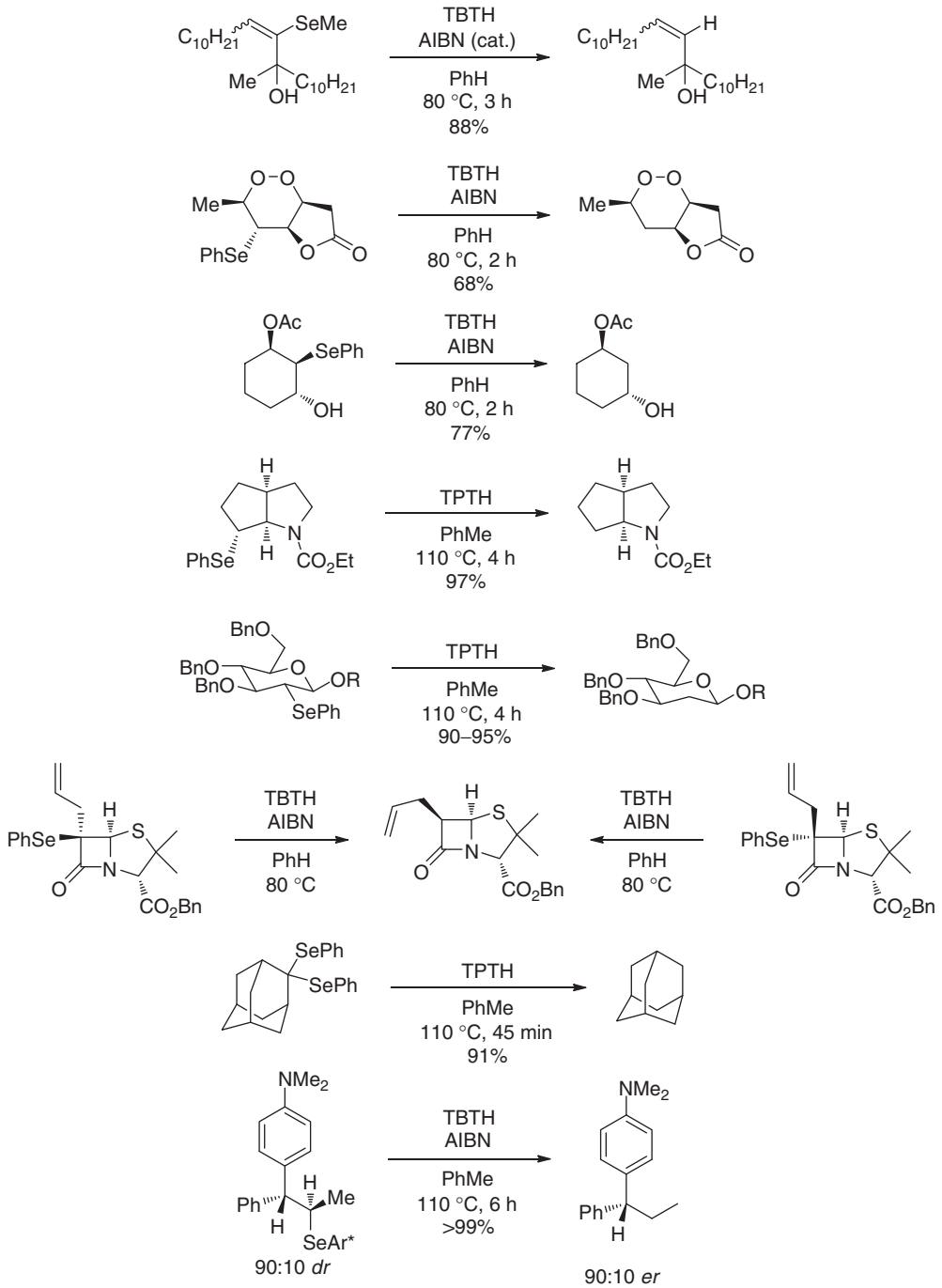
It is also important to note that the radical intermediates in these deselenations can undergo cyclization reactions, typically to form five-[227,228] or six-membered rings,[229] before hydride quenching. Acyl selenides, though technically beyond the scope of this review, bear mention because of their utility in acyl radical cyclizations.[230] Several examples are provided in Scheme 28.

Rearrangements may also occur,[143c,227,231] particularly if a cyclopropylcarbinyl radical is generated.[227] In addition, allyl triphenyltin and allyl tributyltin have been used to quench the radical intermediate with an allyl fragment,[217,232] rather than a hydrogen atom. Scheme 29 depicts examples of these reactions.

8.28.2.6 Miscellaneous Deselenations

The majority of remaining deselenations in the literature focus on attack at Se by highly nucleophilic species. Selenium is much more prone to nucleophilic attack than sulfur and as such, this presents a potentially chemoselective technique for deselenation. The most common nucleophiles are Bu^nLi[89b,186a,c,233] and PhSeLi.[89b,186b,234]

Deselenation in this manner may be carried out on benzylic,[235] allylic,[235c] α-silyl,[236] or aryl alkyl selenides,[237,238] as well as 1,1-diselenides (diselenoacetals),[235a,237,239,240] 1,1,1-triselenides,[239] and 1,1,1,1-tetraselenides.[239] Notably, the insensitivity of

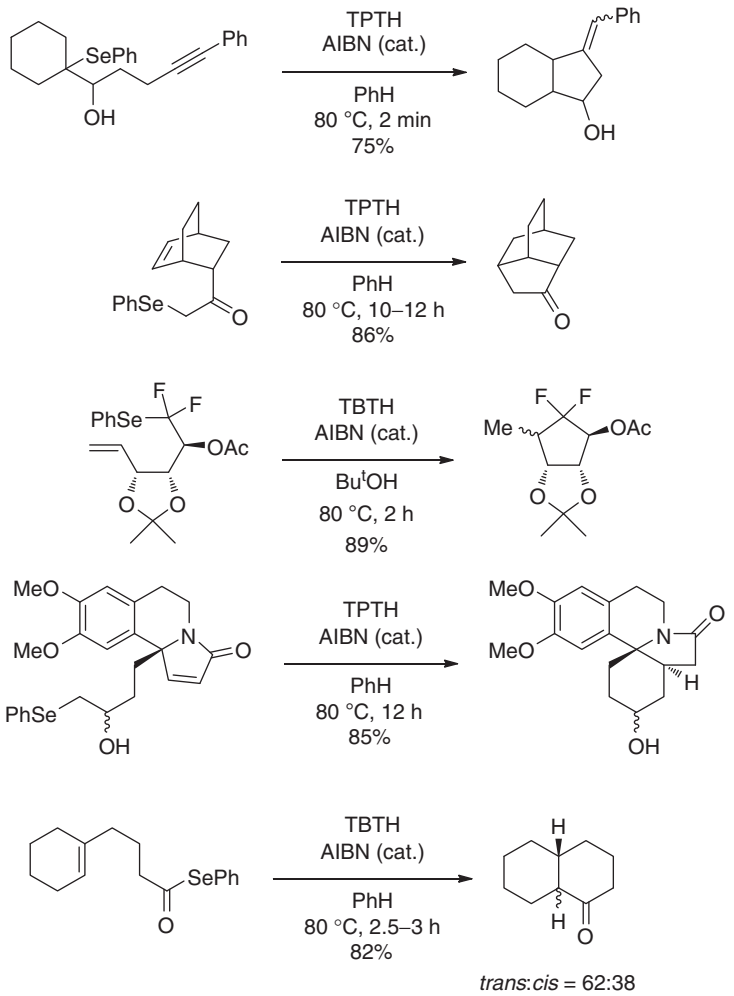


Scheme 27

sulfur toward nucleophilic attack allows selective deselenation of thioselenoacetals.[241] The reaction is typically performed in ethereal solvents such as THF at low temperature. In addition, this approach generates organometallic species *in situ*, which may then be protonated,[238,240a] alkylated,[235a,b,e,238–241] or undergo cyclization;[235a,b,c,d] however, this methodology does suffer from the tendency of organolithiums to react with a variety of functional groups. **Scheme 30** provides several examples.

Ketones are tolerated by the milder PhSeLi, which can be used for the formation of ketone enolates-[242] a species far less basic than the alkyllithiums accessed via Bu^nLi.

The cleavage of aryl alkyl selenides under photochemical conditions using 1,5-dimethoxynaphthalene as a reductant has been reported.[243] Selenonium salts have also been reduced with Grignard reagents and Mg metal.[103,244]



Scheme 28

8.28.3 Reduction of Tin–Carbon Bonds

8.28.3.1 Introduction

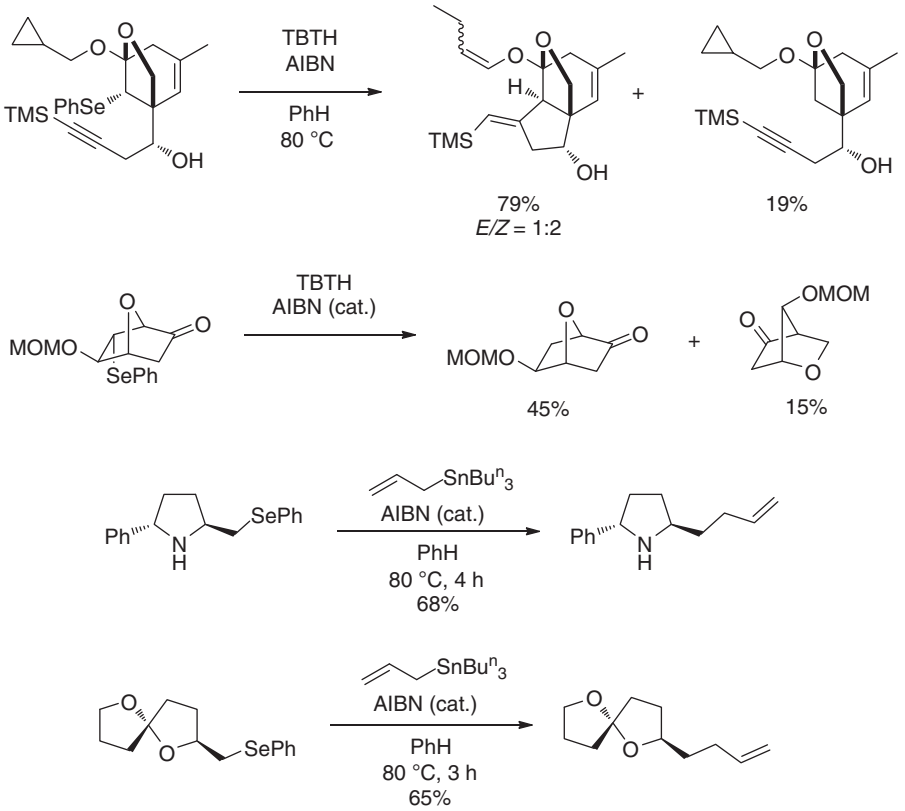
The reduction of tetrahedral tin–carbon bonds is not as common as its planar and linear cousins. In particular, the major use of tin reagents in organic chemistry is in the Stille cross-coupling. This palladium-catalyzed reaction cross-couples an sp^2- (i.e., aryl or vinyl) or *sp*-hydrized (i.e., alkynyl) halide or pseudohalide with most commonly, an sp^2- or *sp*-hybridized trialkylstannane. The sp^2 or *sp* C–Sn bond is preferentially cross-coupled, thus underscoring the lower reactivity of sp^3 C–Sn bonds. Nevertheless, there are two primary ways that tetrahedral C–Sn bonds are cleaved – protonolysis and Sn–Li transmetallation.

8.28.3.2 Protonolysis

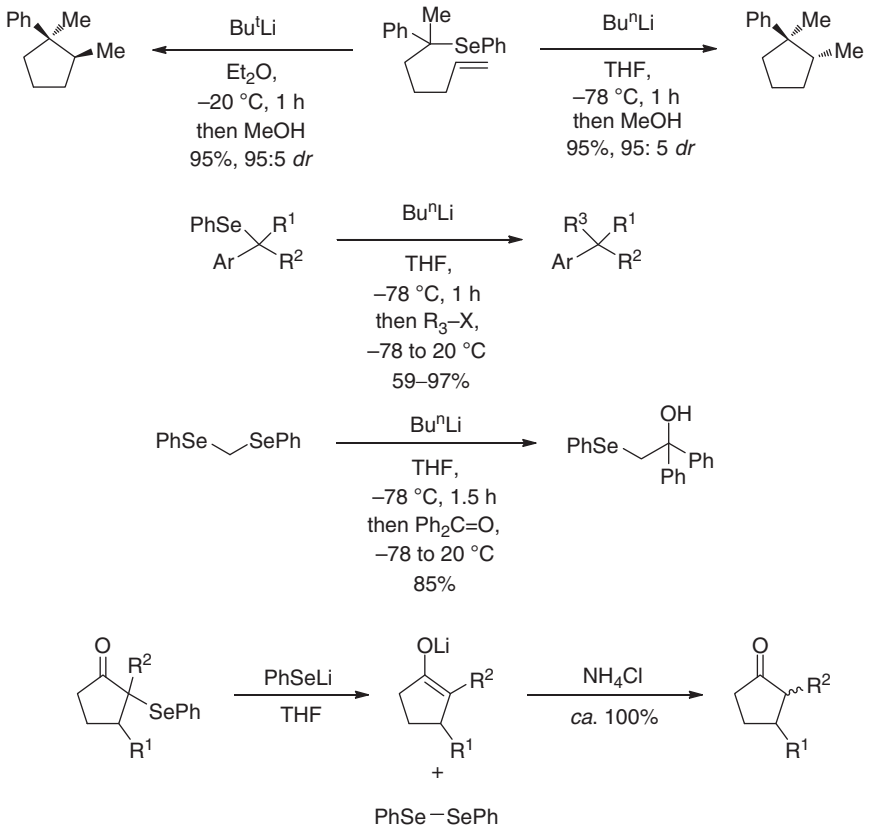
As noted above, the sp^3 C–Sn bond is less reactive than its linear and planar counterparts. As a result, few examples of protonolysis of tetrahedral C–Sn bonds have appeared in the literature. Nevertheless, enough work has been done to conclude that the process occurs with retention of stereochemistry.[245] In addition, once a single group has been cleaved from a tetraalkyltin species, each successive protonolysis becomes more difficult.[246] Though protodestannylation at sp^2 and *sp* carbon atoms is formally beyond the scope of this review, this process has been widely used in organic synthesis, as the presence of the trialkyltin substituent can influence regiochemistry in other reactions. Examples of protonolysis at sp^3 carbons are provided in Scheme 31.

8.28.3.3 Tin–Lithium Transmetallation

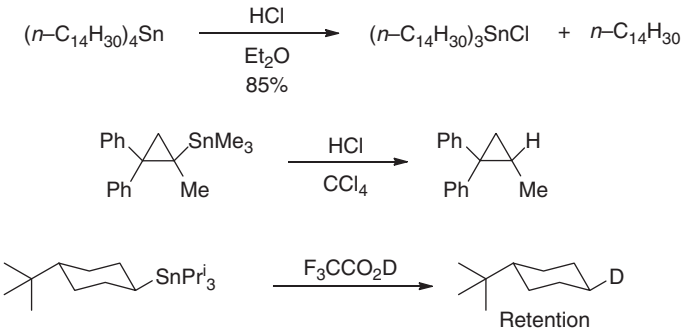
Although sp- (*see* Chapter 3.09) and sp^2-hydrized carbons are popular substrates for palladium-catalyzed cross-coupling, also known as the Stille reaction, tetrahedral carbons see little use in this area because of potential β-hydride elimination and



Scheme 29



Scheme 30



Scheme 31

challenges in the chemoselectivity of which organic group is transferred off the tin atom. The most common method of sp^3 C–Sn bond cleavage is tin–lithium transmetallation.[247] This process proceeds via a reversible addition of the organolithium reagent to the tin atom, affording a pentacoordinate tin anion.[248] In fact, this addition to tin is rapid enough to tolerate the presence of ketones.[249] When one R group is more electronegative than the others (i.e., RLi is more stable/less basic), that group selectively undergoes elimination to afford an organolithium and the reaction becomes preparatively useful. Virtually all tin–lithium exchange reactions occur with net retention of stereochemical configuration if the site of C–Sn bond cleavage is a stereocenter.[250] However, only those organolithiums with a heteroatom in close proximity tend to be configurationally stable.[251] Benzylic organolithiums are prone to rapid configurational inversion.[252] Once the organolithium has been generated *in situ* it may be protonated, used as a nucleophile, or involved in rearrangements[253] or further transmetallation, usually to copper(I).[254]

Tetrahedral carbons that are commonly involved in Sn–Li transmetallation include cyclopropyl,[255] allylic,[249,254,256] benzylic,[252,257] α-alkoxy,[247h,251,258] α-amino,[247h,259] and pendant alkoxide and amide systems,[260] including homoenolates (*see* Chapter 2.15).[261] Scheme 32 provides instructive examples. Although Sn–Li exchange works quite well, the corresponding Sn–Mg exchange using Grignard reagents has afforded limited results.[262]

8.28.4 Reduction of Mercury–Carbon Bonds

8.28.4.1 Introduction

Mercury–hydrogen reactions of organomercurials with an overall reduction at the carbon center are an important transformation in organic synthesis and have been extensively reviewed.[263] Generally, this reduction is accompanied by several transformations in sequence including the solvomercuration reaction (addition of HgX_2 over an unsaturated carbon–carbon π-bond), displacement of the resulting organomercurial with a more potent nucleophile (as in oxy- and aminomercuration reactions) or with an excess of a weaker anion (chloride, bromide) to generate an organomercurial. This is followed by a reduction or oxidation of the resulting C–Hg bond.

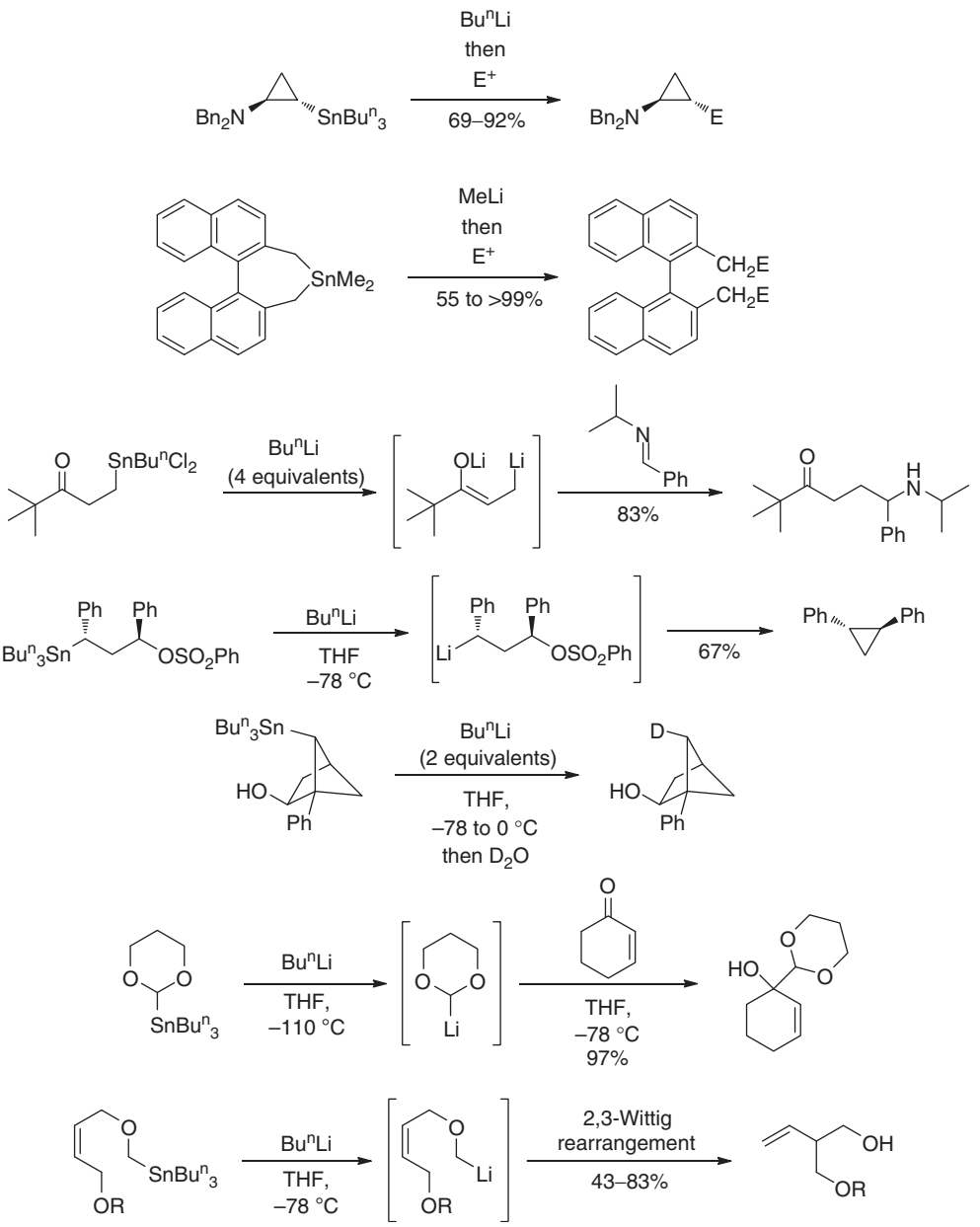
Synthetically useful processes involving organomercurials include oxidative demercuration and reductive demercuration. Reductive demercuration is further divided into protonolysis (protodemercuration), metal hydride-mediated reductive demercuration, and miscellaneous methods. Halodemercuration is formally an oxidation and hence is not covered here in any depth.

The field of reductive demercuration has not had many major breakthroughs in the past two decades but still remains a relevant and noteworthy part of organomercurial chemistry. The most significant improvement in this field has been the development of a variety of Hg(II)-catalyzed transformations.[264] This review will cover major developments in Hg(II)-catalyzed transformations, classic reductive demercuration protocols, and applications to natural product synthesis in addition to fundamental concepts covered in the previous edition.

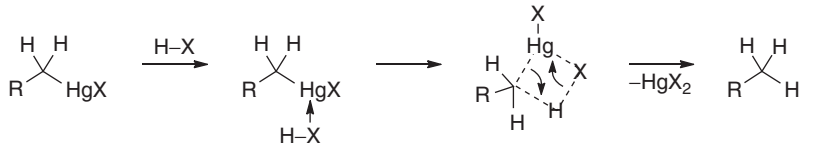
8.28.4.2 Protonolysis

The protic cleavage of carbon–metal σ-bonds ranks amongst the simplest electrophilic substitution reaction processes while displaying a wide variety of reactivity, methodology, and other chemical aspects with each hybridization of the carbon atom – sp^3 carbon–Hg, sp^2 carbon–Hg and, sp carbon–Hg bonds.

Most mechanistic studies of organomercurials have focused on the protic or halogen cleavage of sp^3 carbon–mercury σ-bonds. Protodemercuration by HCl in organic solvents proceeds through a cyclic four-membered transition state through a simultaneous nucleophilic attack on the Hg atom and electrophilic attack on the C atom (Scheme 33). Reaction rate is inversely proportional to water content.[265] However, the ease of use, reliability, and broad synthetic utility of metal hydride demercurations (see Section 8.28.3.2) has by far replaced protonolysis of organomercurials as the most popular method for reduction to the C–H bond.



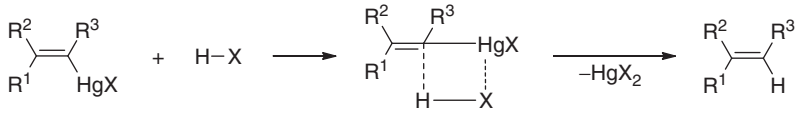
Scheme 32



Scheme 33

Proto- and halodemercuration via electrophilic substitution of unactivated vinylic organomercurials (accessible via solvomercuration of alkynes)[266] does not appear to proceed through a cationic intermediate since deterioration of geometric configuration would be observed. However, nucleophilic participation indicates that vinylic organomercurials undergo reaction through a cyclic four-membered transition state without π-complexation of molecular halogens (**Scheme 34**).

Protonolysis of sp^2-hybridized C–Hg σ-bonds has been long used in the industrial synthesis of acetaldehyde from acetylene. An efficient hydration of terminal alkynes has recently been reported (**Scheme 35**).[267] Alternatively, terminal alkenes will undergo



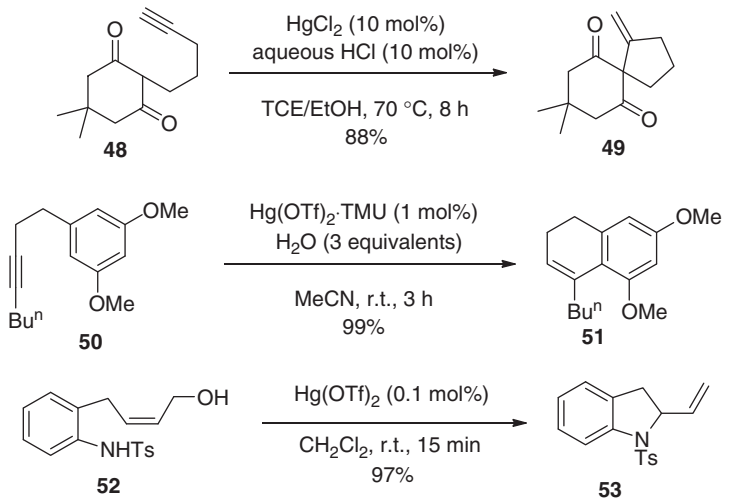
Scheme 34



Scheme 35

a mercuric-catalyzed oxymercuration–oxidation–demercuration in the presence of Jones reagent to afford methyl ketones in high yields.[268] This important discovery was observed when aminomercuration of alkynes using stoichiometric quantities of Hg(II) salts afforded indoles following protodemercuration.[269] As a result, these methods have become extremely efficient with only catalytic amounts of Hg(II) salts necessary to facilitate reaction.

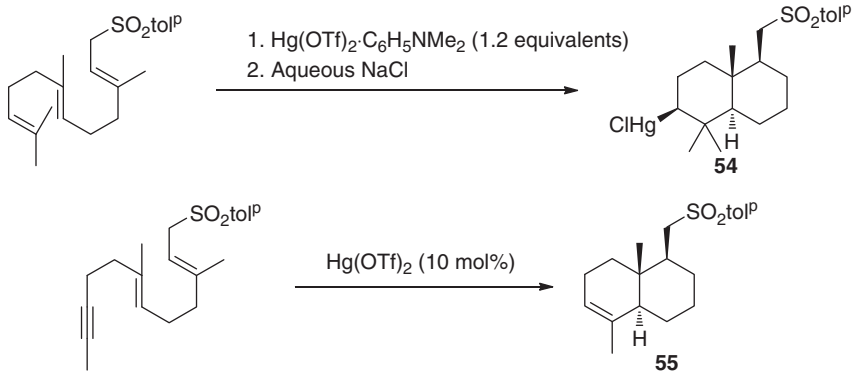
In the past, mercuric-catalyzed mercuration-demercurations that include a protonolysis of sp^2 C-Hg σ-bonds as a key feature have been studied but were limited to heteroatom–carbon bond formation.[270] Conia developed one of the first examples of carbon–carbon bond formation protocols for the transformation of acetylenic carbonyls such as **48** to cyclized carbonyl **49** (Scheme 36).[271] Recent developments include mild carbon–carbon bond forming systems with cation stabilizing groups[272] and protic acid-activated leaving groups[273] adjacent to the carbon bearing the mercury atom. Nishizawa and coworkers have developed a 6-*endo*-dig cyclization of alkynyl aryl **50** to dihydronaphthalene **51**. In this case, catalytic cyclization afforded a trisubstituted olefin and was enabled by adding 3 equivalents of *N*,*N*,*N*′,*N*′-tetramethylurea (TMU) relative to $Hg(OTf)_2$, generating a highly active catalyst selective for the formation of endocyclic olefins.[272,274] The same research group has developed an intramolecular allylic alkylation affording 5-*exo* cyclized indoline **53**. Intermolecular proton transfers allow activation of allylic alcohol **52**, forming water as the sole byproduct. Although $Hg(OTf)_2$ is hygroscopic, the formation of water had no observed effect on its catalytic activity.



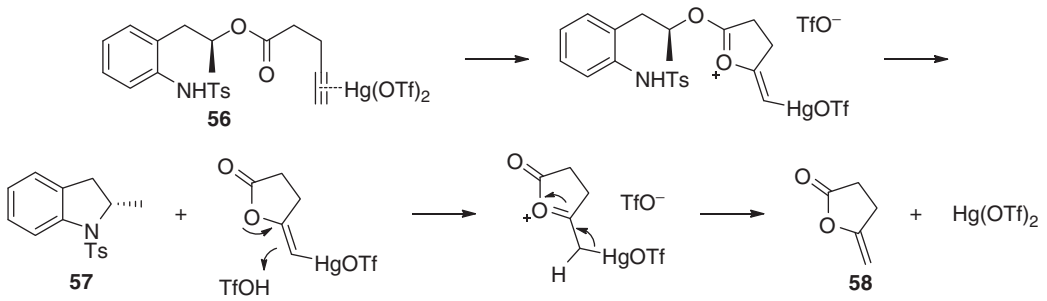
Scheme 36

The susceptibility of inorganic Hg(II) salts to alkynes and the development into a catalytic process has improved methodology for biomimetic tandem cyclization of polyeneynes.[275] Initially, polyenes were cyclized with stoichiometric quantities of Hg(II) to afford systems such as bicyclic mercurial **54**, requiring further isolation and synthetic manipulation (Scheme 37).[276] Simple replacement of an olefin with an internal alkyne effected double cyclization, whereas protodemercuration of the *in situ* generated vinylmercury species produced bicycle **55**.

The 5-*exo* cycloisomerization of ω-alkynoic acids to yield γ-methylene-γ-lactones[277] was applied to the design of a novel mercuric-catalyzed activation of a leaving group as an alternative to the Mitsunobu reaction. Typical substrates were 4-pentynoates such as tosylaniline **56** (Scheme 38).[278] Indoline **57** was rapidly obtained with high enantiomeric ratio corresponding to an S_N2 inversion, along with lactone **58**.



Scheme 37



Scheme 38

Many other methods and applications are known for which an overall removal of sp^3-hybridized organomercury compounds. Most of these synthetically useful species exist as reaction intermediates with adjacent EWG. This includes Ferrier carbocyclizations, which generate an intermediate α-mercuroenolate from a cyclic vinyl ether as a masked enolate equivalent. This is followed by an intramolecular aldol reaction affording highly substituted cyclohexanones with high stereoselectivity.[279]

Meanwhile, deuterium-labeling studies of mercury-promoted Schmidt reactions (*see* Chapter 6.15) have shown that demercuration of the α-mercuro imine species occurs on addition of water.[280] Subsequent metal hydride reduction of the intermediate imine generates the corresponding amine. Other applications protodemercuration of organomercurial reaction intermediates include arylene cyclization,[281] spiroketalizations,[282] and hydrolysis of enol ethers.[283] Panek and coworkers have also used a Wittig olefination/hydrolysis sequence as a two-step process for aldehyde homologation in the total synthesis of (+)-leucascandrolide A (*see* Chapter 1.15).[284]

Tandem hemiamination/vinylogous semipinacol rearrangements (*see* Chapter 3.14) affording 1,4-dihydroquinolines proceed via regeneration of the mercuric catalyst from an α-mercuroimine species. Thorough screening of Lewis acids has shown Hg(II) to be superior since most other metals used were incapable of initiating rearrangement.[285]

Mercuric-catalyzed intramolecular allylic alkylations proceeding through sp^3 C–Hg intermediates have also been extensively studied and are proposed to eliminate an equivalent of water along with regeneration of the catalyst. Internal nucleophiles known to undergo these cyclizations include sulfonamides,[273] sulfamates,[286] electron-rich aryls,[287] and acyltosylhydrazines.[288]

As the previous discussion demonstrates, the last quarter century of organomercury chemistry has seen a transition from stoichiometric to catalytic processes. Given toxicological concerns surrounding mercury compounds, this is quite logical and is a welcome development, as these processes are quite synthetically useful.

8.28.4.3 Metal Hydride Demercuration

The use of metal hydrides is by far the most common reagent for the reduction of organomercurials. Commonly used metal hydrides include *n*-Bu_3SnH, Ph_3SnH, $NaBH_4$, $LiBH_4$, and $LiAlH_4$ but Et_2AlH, and $HCuP(n\text{-}Bu_3)$ have also been used.[289]

Reduction of organomercurials with $LiAlH_4$ has been proposed to undergo an electron transfer mechanism from $LiAlH_4$ with eventual termination via hydrogen abstraction of an alkyl radical with aluminum hydride (**Scheme 39**).[290] Previous efforts toward mechanism elucidation favor formation of an organoaluminum intermediate. However, formation of dimeric and

diorganomercurials as side products has disproven this theory.[291] $LiAlH_4$ has been used as a facile method for reduction of organomercury compounds generated through mercury-promoted cyclopropane fragmentation.[292] However, the high reactivity of $LiAlH_4$ along with formation of significant quantities of byproducts has made this reagent an unpopular choice for organomercurial reduction.

$$R\bullet + AlH_4^- \longrightarrow RH + AlH_3^-\bullet$$

$$AlH_3^-\bullet + RHgX \longrightarrow AlH_3 + R\bullet + Hg + X^-$$

Scheme 39

The use of borohydrides for demercuration of organomercurials was first used by Henbest and Nicholls,[293] although use of borohydrides in aqueous solutions was first reported by Robson and Wright[294] and Traylor and Baker.[295] A free radical mechanism is generally accepted for the reduction of organomercurials with sodium borohydride (Scheme 40), though studies toward mechanism elucidation did not appear until almost a decade later.[287] The source of hydrogen in the reduction of alkylmercuric halides by aqueous sodium borohydride was $NaBH_4$ as determined by Bordwell and Douglass using deuterium-labeling experiments.[296]

$$RHgX \xrightarrow{NaBH_4} RHgH + NaBH_3X$$

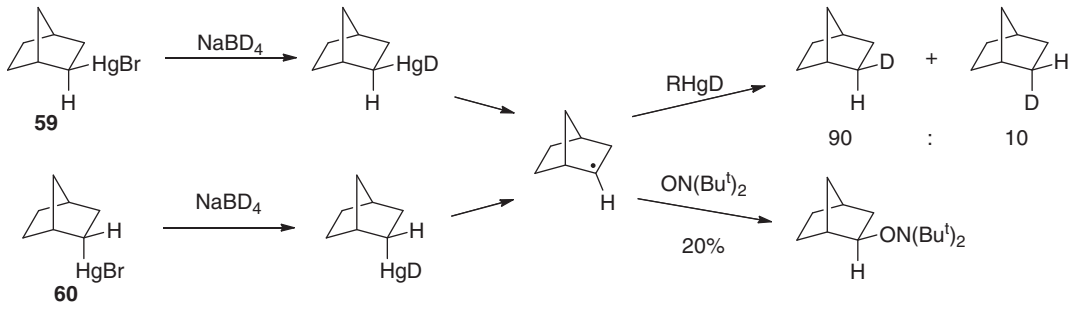
$$R\bullet + RHgH \longrightarrow RH + RHg\bullet$$

$$RHg\bullet \longrightarrow R\bullet + Hg$$

Scheme 40

The reduction of RHgX with $NaBH_4$ in D_2O and with $NaBD_4$ in H_2O showed primarily R–H under the former conditions and R–D under the latter conditions. Also determined in these studies was the pH dependency on aqueous sodium borohydride reduction. Optimal conditions observed were 0.5 M NaOH in water, at pH 7 in absolute ethanol or in 1 M NaOEt in ethanol. Reductive deoxymercuration, as well as the formation of other side products was observed in water at pH 4, 1:1 ethanol-ether or 1 M in pyridine in ethanol.[296]

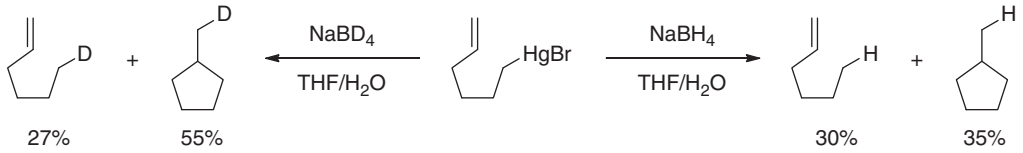
Extensive mechanistic experiments proved elucidation to be challenging in the determining the distinction between (1) an ionic or radical mechanism and (2) radical-cage and radical chain processes. In these efforts, Whitesides subjected *exo*- and *endo*-norbornyl mercuric bromides **59** and **60** to deuterium-labeling studies (Scheme 41). These efforts showed that reduction proceeds with the following characteristics: (1) loss of stereochemistry; (2) the ratio of *exo*- to *endo*-d_1-norbornanes is independent of ratio of *exo*- and *endo*- starting materials; and (3) stereochemistry of reduction is independent of reaction progress concluding that reduction proceeds via free radical intermediates.[289]



Scheme 41

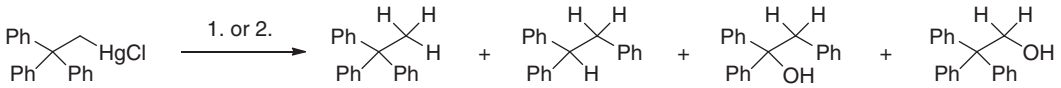
Key observations were made by Quirk, who subjected 5-hexenylmercuric bromide to $NaBH_4$ and observed significant amount of rearrangement product methylcyclopentane (Scheme 42).[297] The formation of methylcyclopentane is consistent with the formation of a radical rather than a carbocation intermediate since the 5-hexenyl cation is known to cyclize to the cyclohexyl cation, whereas the cyclohexyl radical is known to rearrange to the methylcyclopentyl radical.[298]

Meanwhile, the same reduction in the presence of molecular oxygen gives hex-5-en-1-ol as the major product. These results are consistent with the relative rates of hydrogen abstraction, radical-alkene cyclization, and oxygen-radical trapping ($k_{(O2\ trapping)}$ »



Scheme 42

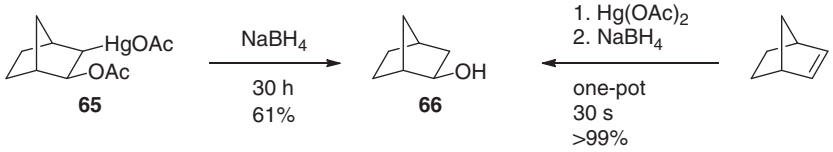
$k_{(\text{cyclization})} \gg k_{(\text{H abstraction})}$). Reductions with $NaBH_4$ afford higher proportions of rearrangement products suggesting that the lifetime of hexenyl radicals has increased due to deuterium isotope effects. The reaction of hex-5-enylmercuric chloride with sodium borohydride in MeOH/NaOH proceeds via hydrogen abstraction by the hexenyl radical from RHgH and not $NaBH_4$. They observed a ratio of 1-hexene/methylcyclopentane that is independent of the concentration of BH_4^- suggesting that an $S_{RN}1$ chain mechanism is at play here but through an alkylmercuric hydride RHgH. In similar experiments on the reduction of 1,1,1-triphenylethylmercuricbromide, Quirk showed that when the reaction flask was open to the atmosphere under the Brown reduction conditions,[299] a 6% yield of 1,1,1-triphenylethane **61** was obtained along with quantitative amounts of elemental mercury and 70% of rearrangement product 1,1,2-triphenylethanol **62**.[297a] Rigorous exclusion of oxygen led to a mixture of 8% 1,1,1-triphenylethane **61**, 92% 1,1,2-triphenylethane **62**, and 99% elemental mercury (Scheme 43). It is significant that under these conditions that if molecular oxygen is added to the flask after degassing cycles, the reaction products are 1,1,1-triphenylethane **61** (13%), 1,1,2-triphenylethane **62** (3%), 1,1,2-triphenylethanol **63** (58%), and 2,2,2-triphenylethanol **64** (19%).[297]



	61	**62**	**63**	**64**
1. $NaBH_4$, degassed DMF	8	92	0	0
2. $NaBH_4$, O_2, DMF	13	3	58	19

Scheme 43

Brown investigated improvements for Markovnikov and anti-Markovnikov hydrations of olefins.[299] From the work of Hofmann and Sand,[300] oxymercurations of simple olefins proceed with Markivnikov regioselectivity and have side reactions that include polymerization, formation of dialkylmercurials, oxidation and substitution products. In these studies, Brown observed that (1) solvomercuration–demercuration can be performed as a one-pot procedure and (2) longer reaction times for solvomercuration–demercuration of alkenes were unnecessary, and in many cases resulted in formation of the unwanted side-products previously mentioned. Traylor and Baker[295] had shown that solvomercuration product of norbornene, norbornylmercuric acetate **65**, was obtained in 61% yield after 30 h, whereas Brown obtained *exo*-norborneol **66** from norbornene using his one-pot solvomercuration–demercuration procedure in quantitative yield in 30 s (Scheme 44). As organomercury compounds are highly toxic, this one-pot protocol was a substantial and very welcome advance.



Scheme 44

Phase transfer catalysts (PTCs) have been employed when neutral or basic $NaBH_4$ cannot be used or higher reactivity is required.[301] It was found that using excess $BnNEt_3Cl$ as a phase transfer catalyst with $NaBH_4/NaOH/CH_2Cl_2$ significantly suppressed rearrangement side-products (Figure 1). Although the examples used demonstrated the benefits of PTC reductive demercuration, it was also found that in all cases demercuration was rapid, the yields were high, independent of the anionic ligand on Hg (chloride or acetate) or the organomercury(II) salt. The ratio of diastereomers in stereoselective intramolecular solvomercuration reactions were unaffected by reduction whereas in other conditions (e.g., bicycle **69**) this is not the case. Contrary to previous work,[302] formation of hydrochroman **71** and pyrrolidine **72** (from rearrangement of **69** and **70**, respectively) were drastically reduced (**71**) or eliminated (**72**) under phase transfer conditions. Barluenga and coworkers have found that these heterogeneous conditions provide a superior method for the reductive alkylation *β*-alkoxyl-*β*-hydroxylmercurials with electron-deficient and electron-rich olefins.[303] Seebach has found that $NaBH_4$ reduction of organomercurials in a biphasic CH_2Cl_2/H_2O significantly minimized the undesired elimination side reaction.[304]

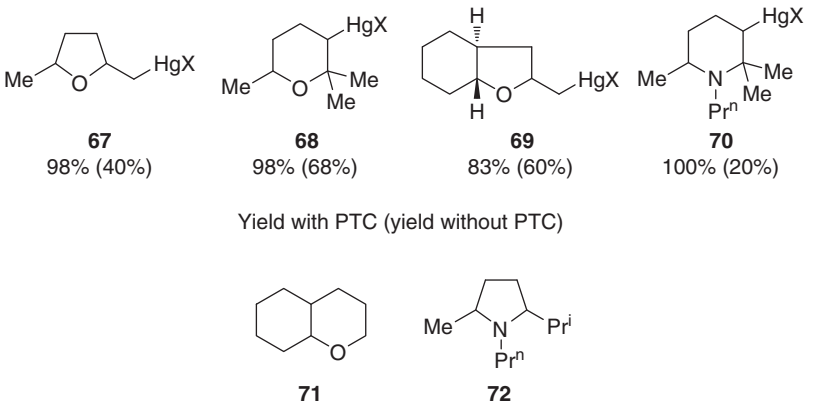


Figure 1 Examples of organomercurials reduced in the presence of PTC (**67**–**70**) and potential rearrangement products that were largely avoided (**71**–**72**).

On repetition of Lattes' PTC conditions, Kang and coworkers found that reductive demercuration was accompanied by varying amounts of oxidative demercuration and rearrangement products, along with significant recovery of starting materials.[305] As an alternative, they employed stoichiometric quantities of Et_3B in conjunction with $NaBH_4$ under mild conditions (Figure 2). This method has been successfully utilized in oxymercurations from alkenyl alcohols where amounts of oxidative demercuration products (**73** and **74**) and loss of stereoselectivity (**74**) have been observed under PTC conditions. It also shows promise as a viable mercurilactonization reduction method to access γ- and δ-lactones such as **75**–**77**, as significant amounts of hydrolysis and reduction were observed under basic PTC conditions.

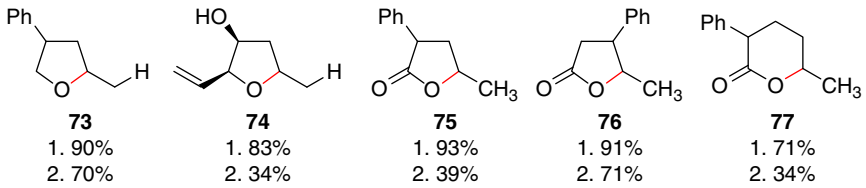
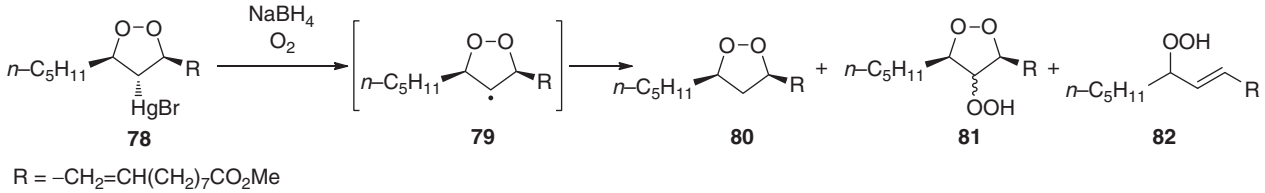


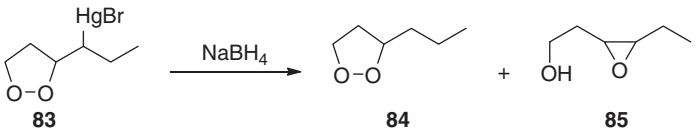
Figure 2 Comparison reductive demercuration in the presence of Et_3B vs. PTC and base.

Reductive demercuration has been used in the mechanism elucidation of allylic hydroperoxide rearrangements. This challenge was overcome by preparation of peroxymercurial **78** via intramolecular peroxymercuration (Scheme 45).[306] Many unsuccessful attempts have been made to trap the suspected radical rearrangement intermediate (**79**). Metal hydride reduction of the corresponding organomercurial **78** formed peroxide **80**, along with peroxides **81** and **82**, leading to the conclusion that a radical mechanism is unlikely for the rearrangement of allylic peroxy radicals.



Scheme 45

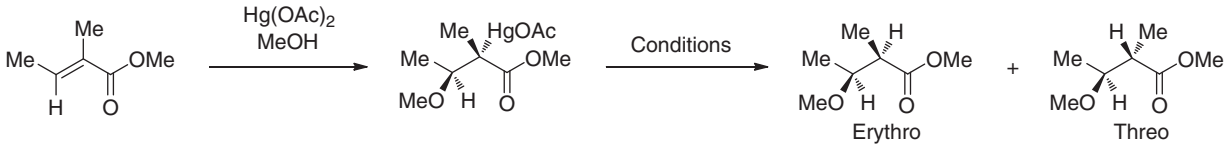
It is known that certain allylic peroxides undergo competitive radical cyclization under reductive conditions (Scheme 46).[307] $NaBH_4$ reduction of **83** forms cyclic peroxide **84** and epoxy alcohol **85** as a mixture of stereoisomers via S_Hi mechanism. This is a striking contrast to **78**, where the endocyclic radical intermediate **79** did not rearrange.



83 **84** **85**

Scheme 46

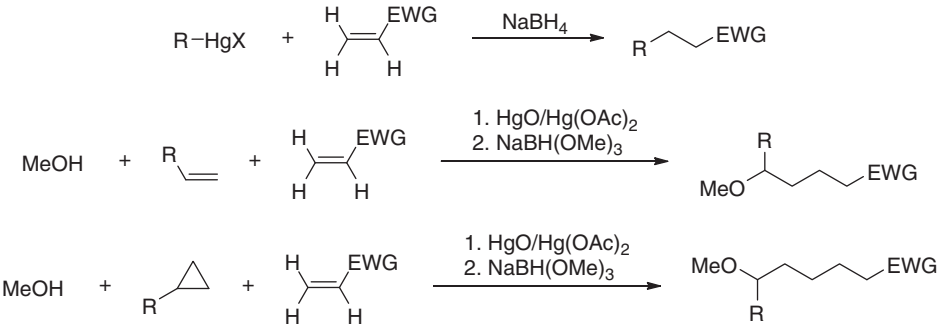
Gouzoules and Whitney investigated diasteroselective protodemercuration and found a correlation between diastereoselectivity and demercuration mechanism.[308] Erythro selectivity was encountered with use of a thiol-based demercuration reagent such as 1,3-propanedithiol, whereas threo selectivity was found with hydride demercurations (Scheme 47). An excess of hydride in alcoholic solvents was found to be optimal, whereas the corresponding aprotic demercuration with triethylamine and dichloromethane resulted in remarkable threo selectivity. Deuterium-labeling experiments showed that formation of the erythro isomer in metal hydride demercurations occurs via an ionic mechanism, whereas formation of the threo isomer operates under a radical mechanism where hydrogen abstraction from EtOH [*H*-CH(CH_3)OH] occurs. Bartlett has used this methodology in the synthesis of the Prelog–Djerassi lactone,[309] as well as demercuration after a stereoselective (1,2-stereoinduction) mercurilactonization en route to serricornin.[310]



$HS(CH_2)_3SH$, EtOH (99%)	95	:	5
$NaBH_4$, EtOH (85%)	20	:	80
Et_3N, CH_2Cl_2 (84%)	12	:	88

Scheme 47

Radical intermediates generated from metal hydride reduction have been trapped with both electron-rich and electron-poor olefins. This constitutes a formal Michael addition with radical nucleophiles and has been well studied by Giese and others (Scheme 48).[302,311–313] In addition, products of solvomercuration reactions from olefins and cyclopropanes can be trapped by electron-poor olefins.



Scheme 48

Solvomercuration–metal hydride demercuration is highly applicable in natural product synthesis and is mainly used as a method to form ethers via intramolecular oxymercuration (Figure 3). It can be quite functional group tolerant and will allow access to complex and highly substituted structures as demonstrated in Danishefsky's gelsemine (**86**),[314] Font's (+)-lineatin (**87**),[315] Sorensen's citrinadin B core (**88**),[316] Nicolaou's platencin (**89**)[317] syntheses, and Nolen's α-C-glucosyl amino acids (e.g., **90**),[318] as well as in mercuric-mediate cyclopropane fragmentation from cyclopropyl carbinols.[319]

These recent applications of demercuration reactions utilized a number of concepts previously discussed. Sorensen utilized Kang's mild borane radical initiator methodology to reduce pentacycle **88** after an intramolecular indole mercuration. Nolen applied the Kang protocol in a diastereoselective oxymercuration in the construction of α-*C*-glucosides. Gratifyingly, α- and β-diastereomers were easily separable by chromatography, rending this approach highly applicable. Meanwhile, Nicolaou achieved facile separation after reductive conjugate addition using **89** as a mixture of diastereomeric tertiary alcohols. A noteworthy solvomercuration-mediated rearrangement was discovered in Mori's synthesis of (+)-anatoxin A.[320] They performed a chemoselective hydroxy-mercuration–demercuration as an alternative to a Wacker oxidation but encountered an unexpected reversal of optical activity as a result of the rearrangement.

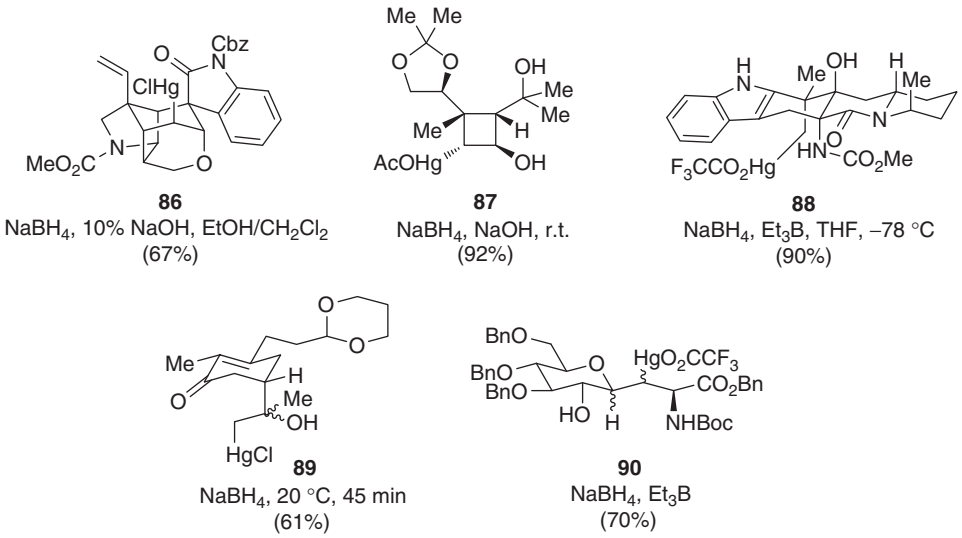


Figure 3 Selected examples of reductive demercuration with $NaBH_4$ in natural product synthesis.

Various tin hydrides are used as an alternative to borohydride reductions of organomercurials. They are often used as a mild method where other metal hydrides afford products of overreduction. There have been a few examples of demercuration with tin hydrides exhibit functional group tolerance and without skeletal rearrangement in organomercurials such as the advanced intermediate **91** in Cossy's zincophorin synthesis,[321] THF **92** in Perlmutter's remote stereocontrol approach with allylic silyloxy groups,[322] and enantioselective etherification to **93** (Figure 4).[323] Interestingly, construction of Corey's advanced intermediate **94** proved successful in good yields with $Bu^n_2SnH_2$ but was unreactive with the typically used Bu^n_3SnH reagent.[324]

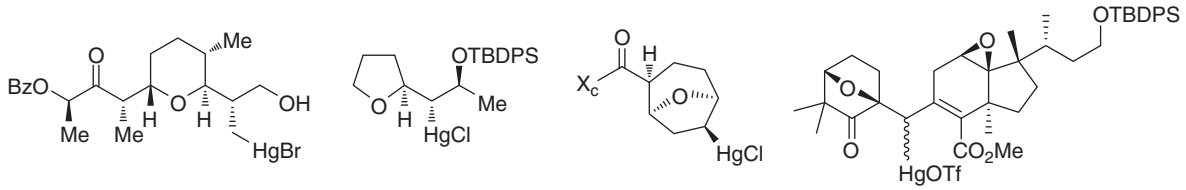
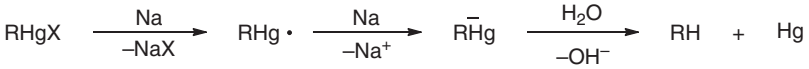


Figure 4 Selected examples of reductive demercuration with tin hydrides in natural product synthesis.

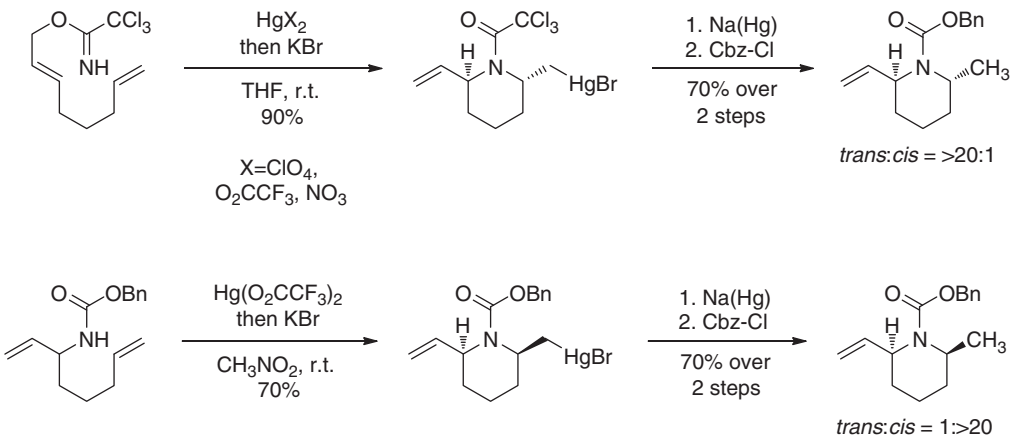
8.28.4.4 Miscellaneous Methods

Due to scientific breakthroughs over the past 20 years research efforts have focused less on solvomercuration reactions in general, whereas the development and usage of nonmetal hydride reductions of organomercurials has become almost obsolete. Other common approaches to reductive demercuration that have been used in the past include sulfur-based reagents,[312,325] metals,[326,327] hydrazine,[328] alcohols,[329] amines,[330,331] tin oxides,[332] thermal decomposition,[333] hydrogenolysis reagents,[334] and electrochemical methods.[335] Regardless of their popularity, their mechanistic course of action has been studied for a number of these reagents.

Evidence shows that reductive demercuration of alkylmercuric salts using sodium amalgam does not proceed through a free radical pathway similar to metal hydride reduction (Scheme 49).[336] Na(Hg) reduction of hex-5-enyl-1-mercuric bromide in a mixture of THF and D_2O produces only 1-hexene with no traces of methylpentane. Recently, Han has used Na(Hg) to concomitantly reduce an organomercurial and cleave a trichloroacetamide group in the preparation of 2,6-piperidines via stereocontrolled tandem Overman rearrangement-amidomercuration reactions (*see* Chapter 5.20; Scheme 50).[337]

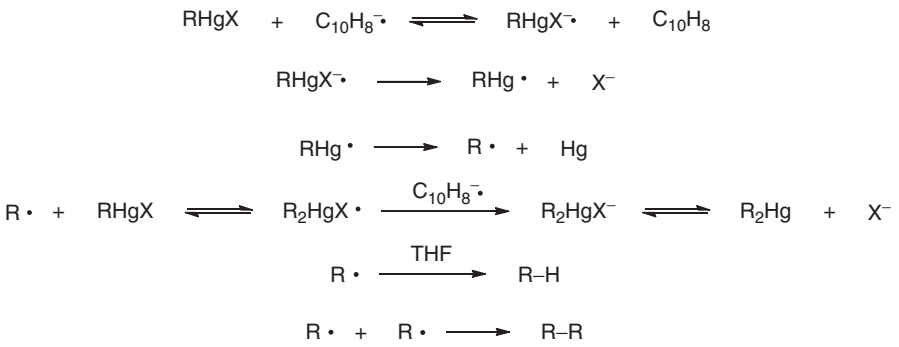


Scheme 49



Scheme 50

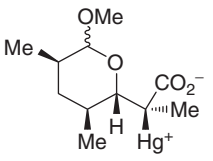
The naphthalene radical anion as reducing agent has been known for decades and its mechanism has been proposed to undergo an electron transfer process unlike other reducing agents for the reduction of organomercurials (Scheme 51).[338] The possibility of anion generation during the course of the mechanism for alkyls and aryls has been ruled out.[339] However, use of excess naphthalene radical anion will generate these anions. Thiols such as 1,3-propanedithiol are known to promote reductive demercuration through an ionic mechanism producing an oligomeric thiolate complex of mercury.[340]



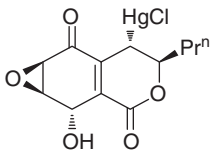
Scheme 51

Less common reduction methods, including N_2H_4, $Na_2S_2O_3$ and Na_2SnO_3, were studied for their partial reduction of alkylmercuric salts to dialkylmercurials. These methods have been shown to proceed by a free radical intermediate, S_E2, and rearrangement via free radical intermediates with an overall retention of stereochemistry.[328,332] Efforts to develop a synthetically useful catalytic reduction of organomercurials with noble metals proved unfruitful.[334] Reaction with metal complexes of type L_2RhCl and PhHgOAc affords a bimetallic complex via oxidative addition. In the presence of H_2, the bimetallic complex decomposes to PhH, Hg(0), and AcOH with regeneration of the rhodium catalyst in reasonable yield but its substrate scope is quite limited; and therefore, further development of these reagents has been avoided because of the lack of synthetic utility.

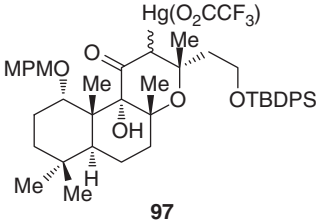
An excess of zinc powder in AcOH was used to assist a protodemercuration of carboxymercurial **95** en route to the first asymmetric total synthesis of epi-*ent*-EI-1941–2.[327] Hydrogen sulfide was used to access an *erythro*-*β*-methoxycarboxylic acid **96** in Bartlett's stereoselective synthesis of the Prelog–Djerassi lactone.[309] Hashimoto and coworkers have used LiI and Et_3N as a reductive work-up after an intramolecular oxymercuration to tricyclic compund **97** en route to *rac*-6,7-dideoxyforskolin.[341]



95

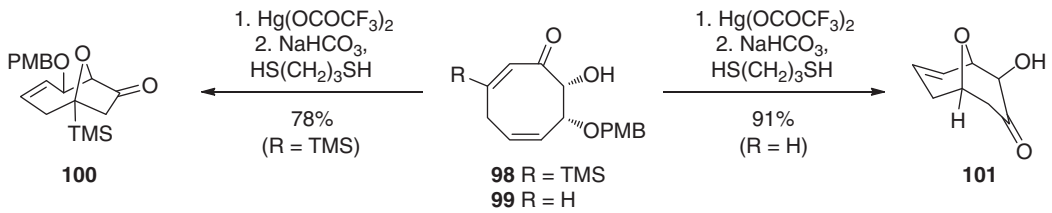


96



97

Paquette showed that silylated octadiene **98** was necessary to promote regioselective intramolecular oxymercuration to yield **100**. Nonsilylated octadiene **99** saw participation and deprotection of the OPMB functionality to afford **101** (Scheme 52).[342] Here 1,3-propanedithiol was used under basic conditions to affect demercuration in good yield.



Scheme 52

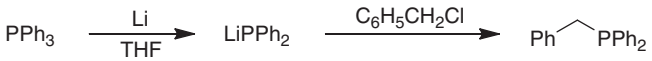
8.28.5 Reduction of Phosphorus–Carbon Bonds

Various methods exist and have been developed for the reduction of phosphorus–carbon bonds, depending on the oxidation state of phosphorus (*see* Chapter 8.15). Unlike other heteroatom–carbon bond cleavages, which are usually carried out with the object of preparing reduced carbon compounds, the cleavage of P–C bonds is achieved with the aim of preparing new phosphorus compounds.

8.28.5.1 Reduction of Tervalent Organophosphorus Compounds

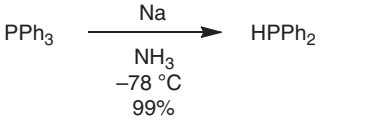
The cleavage of C–P^{III} bonds can be achieved by using alkali metals, transition metal complexes, organometallics, and by photolysis.

The reductive cleavage of a C–P^{III} bond by an alkali metal (Li/THF or NH_3, Na or K/dioxane, NH_3 or diglyme) is limited to a tertiary phosphine with at least one aromatic group, in which the LUMO accepts an electron from the metal. The reductive cleavage leads to the formation of the corresponding phosphide anion, which can be alkylated with electrophiles to give substituted tertiary phosphines or protonated to afford secondary phosphines on treatment with water or an alcohol (Scheme 53).[343]

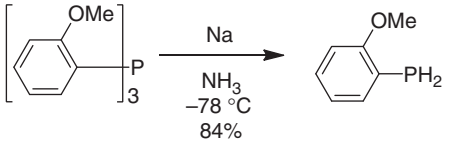


Scheme 53

Meijboom and coworkers have studied extensively the reductive cleavage of functionalized triphenylphosphines, mixed functionalized triarylphosphines, and arylalkylphosphines with Na/NH_3 or Li/THF to prepare secondary phosphines (equations 14–17).[344] For instance, a quantitative yield of diphenylphosphine is obtained from the reduction of triphenylphosphine with Na/NH_3 and hydrolytic work-up (equation 14). Secondary phosphines with halogen substituents or with several aromatic rings with strong electron-donating groups, such as 4-SMe, 4-NMe_2, 4-CH_2OR, and 4-OMe, cannot be prepared by reductive cleavage of the corresponding tertiary phosphine as these functional groups are either cleaved from a phenyl group before C–P^{III} bond reduction or are reduced further to primary phosphines (equation 15). Also, the cleavage of tris(1-naphthyl)phosphine proceeds very rapidly to give the primary phosphide as the main reduced product.

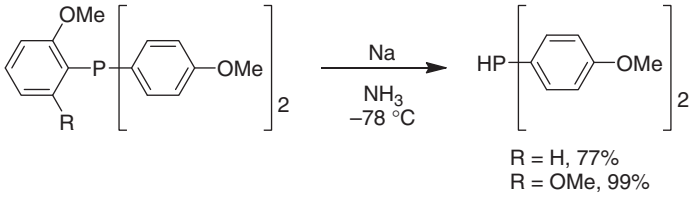


(14)



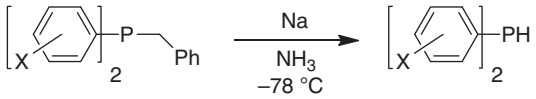
(15)

Further studies on the facile reductive cleavage of functionalized phenyl phosphines led to the selective cleavage of an *ortho*-substituted (Me, NMe_2, and OMe) phenyl group to prepare mixed secondary phosphines (equations 16 and 17).[345,346]



R = H, 77%
R = OMe, 99%

(16)



X = 2-OCH_3, 89%
X = 2,4-$(OCH_3)_2$, 89%

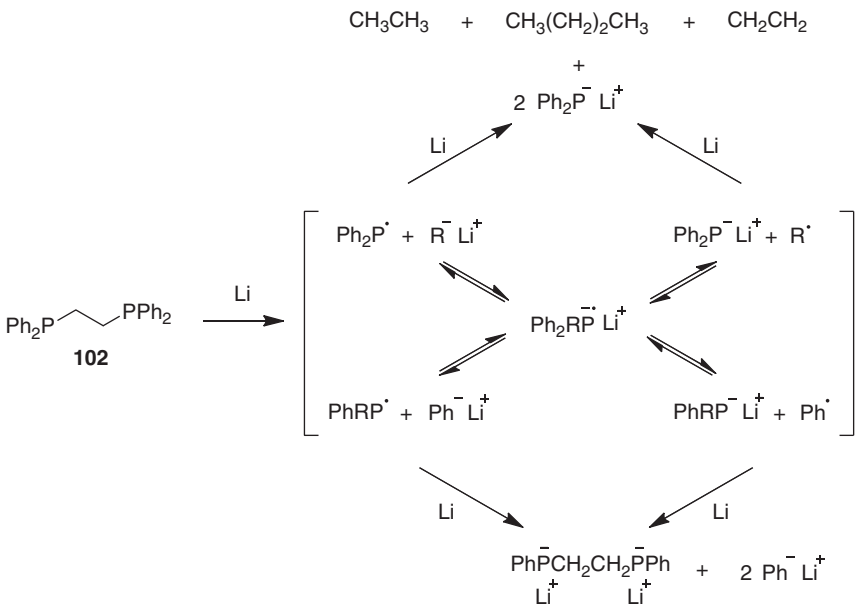
(17)

Alkyl groups may be cleaved when the corresponding radical form is stabilized, as in the case of Bu^t, $PhCH_2$, and allyl. Benzyl and allyl groups are cleaved before 2-methoxy and 2,6-dimethoxyphenyl groups, allowing the selective formation of di-2-methoxyphenylphosphine and bis-2,6-dimethoxyphenylphosphine (equation 17).[346] Based on the collection of various functionalized tertiary phosphines, the preference of cleavage of groups from phosphorus with Na/NH_3 is:

$$PhCH_2 \gg 2,6-(MeO)_2C_6H_3 > 2-MeOC_6H_4 > Ph \approx 2-MeC_6H_4$$
$$Bu^t \gg Ph$$

The mechanism of C–P bond cleavage appears to be very similar to the two-step reductive cleavage of an Ar–X bond.[342] The transfer of an electron from an alkali metal to its LUMO leads to a radical anion, and then Ar–X bond is cleaved to form a radical and an anion.

The reductive cleavage of diphosphines of the general formula $Ph_2P(CH_2)_nPPh_2$ (**102**) with an alkali metal has shown that the regioselectivity between C_{aryl}–P and C_{alkyl}–P bond cleavage depends on the value of n.[347] For $n=3$–5, P–C_{aryl} bond cleavage is predominant, but for $n=1$, P–C_{alkyl} bond cleavage is favored. In the reaction with lithium when $n=2$, a mixture of products from P–C_{aryl} and P–C_{alkyl} bond cleavage is obtained. Wild and coworkers have investigated the mechanism and conditions influencing the C_{aryl}–P and C_{alkyl}–P bond cleavage in the reaction of 1,2-bis(diphenylphosphino)ethane with lithium in THF (**Scheme 54**).[348] The mechanism involves a rapid equilibrium between the anions and radicals produced from C_{alkyl}–P and C_{aryl}–P cleavage, followed by their reaction with lithium and stabilization as lithium salts. The temperature dependence of the cleavage indicates that the equilibrium is thermodynamic in nature.

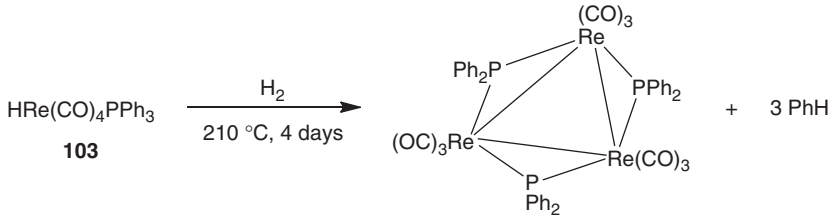


Scheme 54

As organophosphorus compounds are the most used ligand class in organometallic chemistry, there have been a large number of studies about the reactions between the C–P^{III} bond and transition metals.[349–351] A few examples have been reported for the

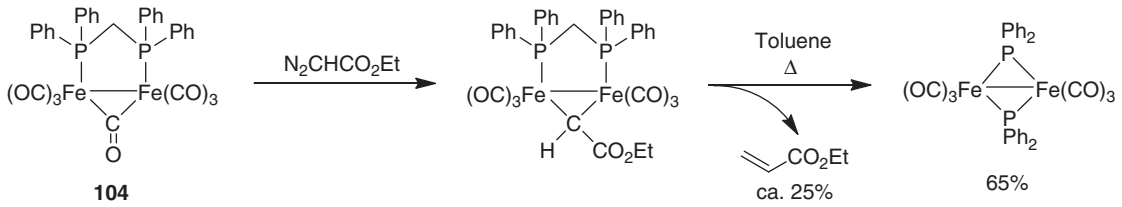
reductive cleavage of C–P^{III} bonds, successfully releasing the substituent from phosphorus. As many other examples have resulted in the migration of substituents on phosphorus onto the metal atom or being lost through the formation of phosphido bridged dinuclear metal complexes, the transition metal-mediated C–P bond cleavage reaction does not provide a strong synthetic utility.

Nishiguchi and coworkers observed in 1980 that reductive cleavage of C–P bonds occurs when $[RuH_2(PPh_3)_4]$, $[RuCl_2(PPh_3)_3]$, $[RhH(PPh_3)_4]$, and $[RhCl(PPh_3)_3]$ are heated at 140 °C in pyrrolidine. These experiments found that the triphenylphosphine ligands were hydrogenolyzed almost completely to benzene.[352] Likewise, Haupt et al. have observed a cleavage of phenyl groups by hydrogenolysis of a triphenylphosphine ligand from rhenium hydride **103** to form a diphenylphosphido bridged trinuclear rhenium cluster (equation 18).[353]



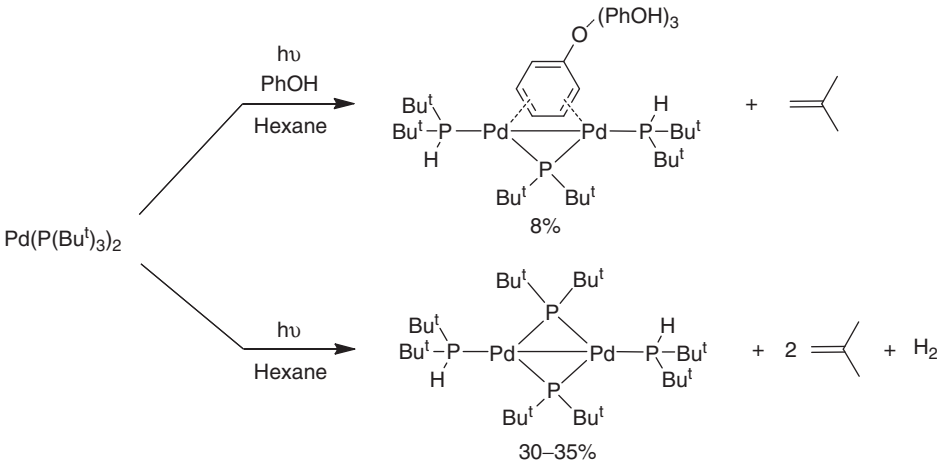
(18)

The ease of C–P bond cleavage using transition metals has been generalized based on the hybridization of carbon as $P–C_{sp} > P–C_{sp2} > P–C_{sp3}$. Examples of $P–C_{sp3}$ bond reduction are rare, but the treatment of the complex $[Fe_2(CO)_6(\mu\text{-}CO)(\mu\text{-}Ph_2PCH_2PPh_2)]$ **104** with ethyl diazoacetate under UV irradiation promotes ligand exchange to form dinuclear complex. On heating, the complex undergoes double P–C bond cleavage and C–C bond formation, resulting in ethyl acrylate and a complex with a diphenylphosphido bridge (**Scheme 55**).[354]

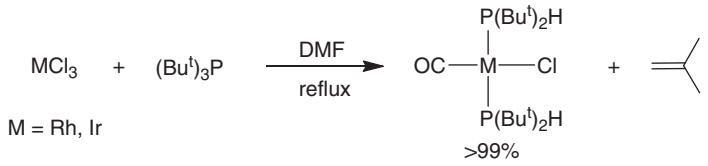


Scheme 55

Phosphorus-bound *tert*–butyl groups are particularly susceptible to cleavage with some transition metals. The reaction of $P(Bu^t)_3$ with rhodium or iridium trichloride in dimethylformamide (DMF) leads to the cleavage of the tertiary butyl group from the phosphorus giving methylpropene and formation of a complex in the +1 oxidation state (equation 19).[355] Also the photochemical treatment of $Pd[P(Bu^t)_3]_2$ with an excess of phenol in *n*-hexane gives a modest yield of a dinuclear complex with a phosphido bridge and a bridging π-bonded phenoxide, and methylpropene (**Scheme 56**).[356]

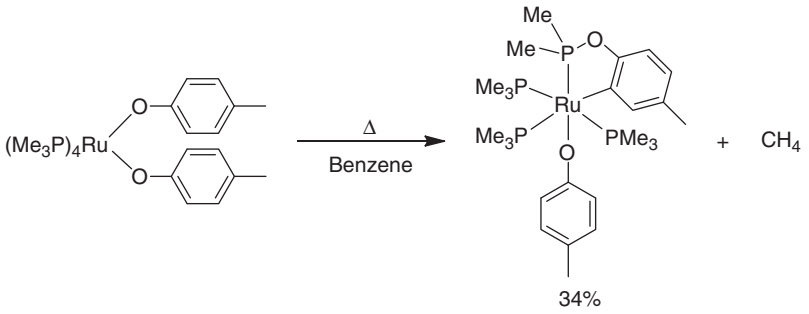


Scheme 56



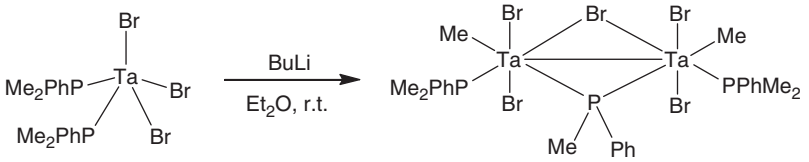
(19)

Bergman and coworkers have reported an unusual reaction, which involves the migration of a *p*-methylphenolate ligand from ruthenium to phosphorus and subsequent *ortho*-metalation of the benzene ring, resulting in the release of methane (equation 20).[357]



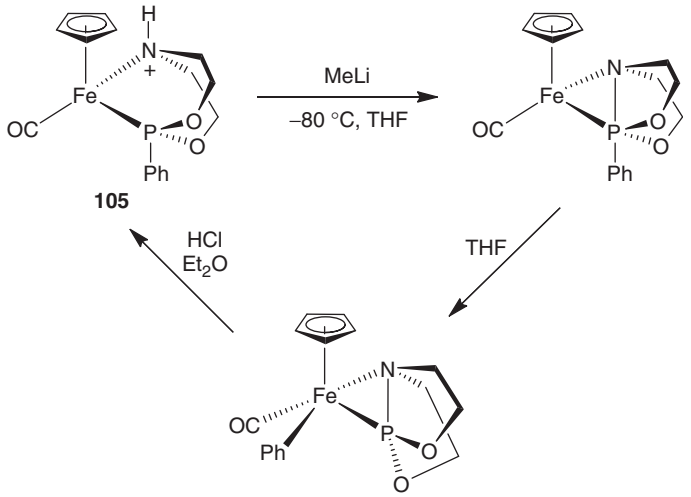
(20)

Migration of substituents on phosphorus to a metal atom via C–P bond cleavage has also been reported. When tribromobis(dimethylphenylphosphine)tantalum is treated with Bu^{n}Li at room temperature, a methyl, rather than phenyl group, transfers from phosphorus to tantalum with the formation of a phosphide bridge (equation 21).[358] A very similar migration of a methyl group is observed from dimolybdenum tetraacetate[359] and dinuclear cyclopentadineyl nickel tungsten carbonyl hydride[360] in the presence of trimethyphosphine, resulting in the bridging dimethylphosphido group. Additionally, 1,1-bis(diphenylphosphino)methane frequently undergoes P–C$_{alkyl}$, rather than P–C$_{aryl}$, bond cleavage with various transition metals, such as Mo,[361] W,[362] Fe,[363] and Co.[364]



(21)

Macgregor has surveyed reactions of transition metal–phosphine complexes that result in P–C bond cleavage and the replacement of a substituent on phosphorus by some other group, X.[351] This group, X, can be another C-, N-, or O-based moiety or fluoride; thus, these processes result in a net P–C/X exchange reaction. An example of P–C/N exchange was reported by Vierling and Riess. They found that deprotonation of the P,N-chelating phosphine in the complex **105** leads to the formation of a bicyclic phosphine and migration of a phenyl group onto iron (**Scheme 57**).[365]

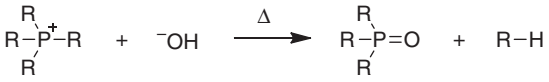


Scheme 57

8.28.5.2 Reduction of Tetravalent Organophosphorus Compounds

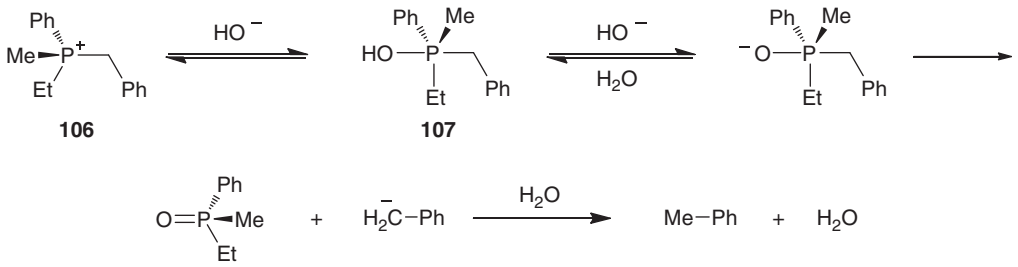
There are limited methods developed for reductive cleavage of C–P^{IV} bonds. The main methods are alkaline hydrolysis and LAH reduction of phosphonium salts. Electrochemical reductions can also be applied to C–P^{IV} bond cleavage.

The most documented method is the alkaline cleavage of quaternary phosphonium salts with hydroxide ion, in which phosphine oxide is produced by displacement of hydrocarbon (equation 22).



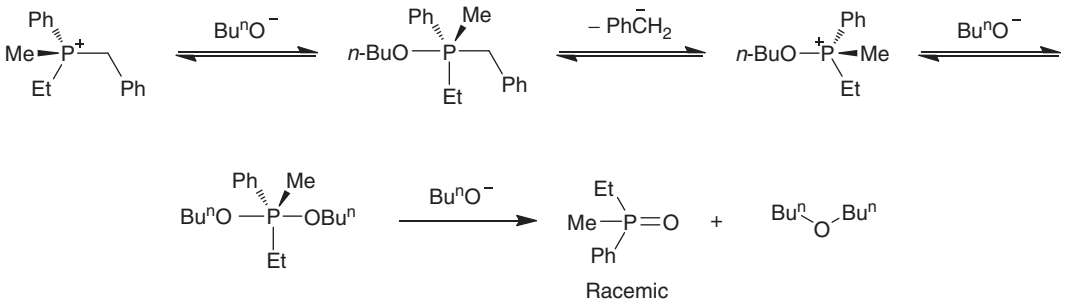
(22)

The mechanism and kinetics of this reaction have been carefully studied and well described.[366,367] The kinetics of the reaction between the phosphonium salt and hydroxide ion has been shown to be of the third order, with a first-order dependence on phosphonium ion concentration and second-order dependence on the concentration of hydroxide ions.[366] Inversion of configuration at phosphorus is observed during the reaction. An optically active, noncyclic quaternary methylethylphenylbenzylphosphonium salt **106**, in which the phosphorus atom is the sole center of asymmetry, undergoes stereospecific decomposition with sodium hydroxide to produce toluene and optically active methylethylphenylphosphine oxide **107**. Accounting for these observations, the mechanism is proposed as **Scheme 58**.[367]



Scheme 58

When an optically active phosphonium salt undergoes decomposition by alcoholic sodium alkoxide (R′O-) to toluene, phosphine oxide and the ether (R′OR′), the resultant phosphine oxide is racemic, suggesting that at some stage a 5-coordinated intermediate is formed (**Scheme 59**).[368]

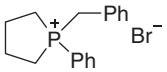
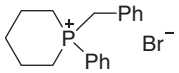
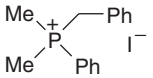


Scheme 59

The order of ease of displacement of a hydrocarbon group from a phosphonium salt is dependent on their relative electronegativity. In other words, the group leaving phosphorus generally produces is the most stable carbanion. Thus, carboxymethyl, enolate anions, benzyl, and allyl are preferentially cleaved before aryl and alkyl groups, and among aromatic groups the order is: 4-nitro- > 4-chloro- > 4-carboxylethyl-phenyl > 4-biphenyl > α- or β-naphthyl > phenyl > 4-amino- > 4-methyl- > 4-methoxy- > 4-hydroxy-phenyl.[366,367,369]

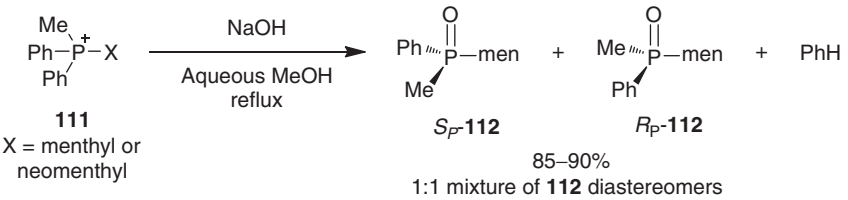
For cyclic phosphonium salts, ring size is an important factor in the reaction rate and stereospecificity.[370] It has been found that the enhanced reaction rate was observed as the ring sizes became smaller (**Table 1**). A benzyl group in the five-membered cyclic phosphonium salt **108** is cleaved faster than a benzyl group in a six-membered cyclic derivative **109** or in the acyclic compound **110**.

Table 1 Rates of debenzylation of phosphonium salts

Phosphonium ion	k_3 *at 25 °C* ($l^2\ m^{-2}\ s^{-2}$)
 **108**	0.171
 **109**	1.59×10^{-3}
 **110**	3.29×10^{-4}

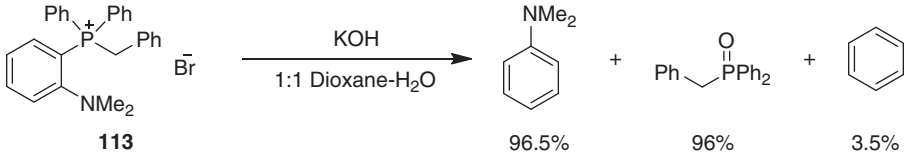
Source: Adapted from Gallucci, J. C.; Holmes, R. R. *J. Am. Chem. Soc.* **1980**, *102*, 4379–4386, with permission from American Chemical Society.

Depending both on the nature of the substituents on phosphorus and on the reaction conditions, the alkali hydroxide-induced decompositions of chiral phosphonium salts have been found to occur with retention, inversion, or racemization of the configuration. Menthyl- and neomenthylmethyldiphenylphosphine **111** were treated with boiling aqueous methanolic sodium hydroxide to give a 1:1 mixture of *R* and *S* phosphorus epimers of menthylmethylphenylphosphine oxide **112** (equation 23).[371]

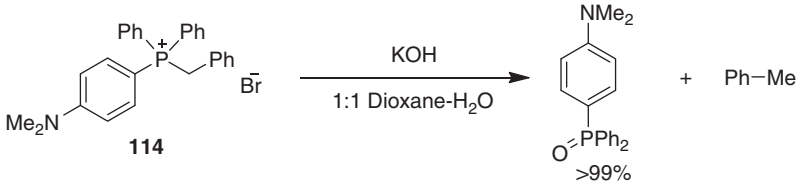


(23)

Different rate and the regioselectivity of the alkaline cleavage of quaternary phosphonium salts are observed when an *o*- or *p*-methoxy- or *o*- or *p*-dimethylamino-phenyl group is present in the molecule. For example, phosphonium bromide **113** undergoes an alkaline cleavage to give *N*,*N*-dimethylaniline predominantly, instead of toluene or benzene (equation 24). However, phosphonium bromide **114** gives only toluene from a cleavage of the benzylic C–P bond (equation 25).[372] The hydrolysis reaction of phosphonium bromide **113** is 1.1×10^3 times more rapid at 37.7 °C than the hydrolysis of phosphonium bromide **114**.

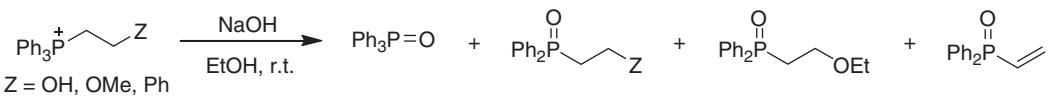


(24)



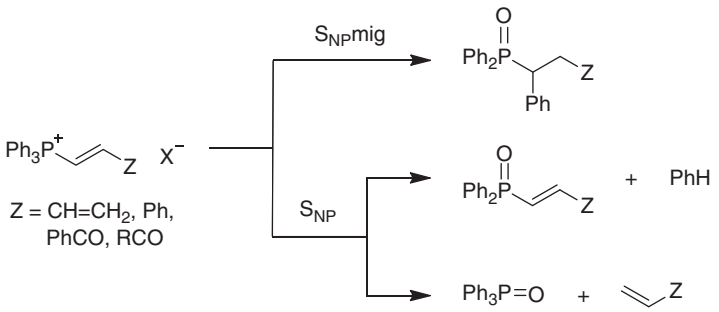
(25)

In some cases of alkaline hydrolysis, phosphonium salts with inductively electron-withdrawing substituents at the β-position have been found to undergo anomalous fragmentations such as elimination reactions, inversion in cleavage selectivity or participation of the reaction solvent (equation 26).[373] In the case of γ-functional phosphonium salts, the alkaline hydrolysis leads only to the predicted compounds corresponding to the usual selective cleavage of one phenyl group.



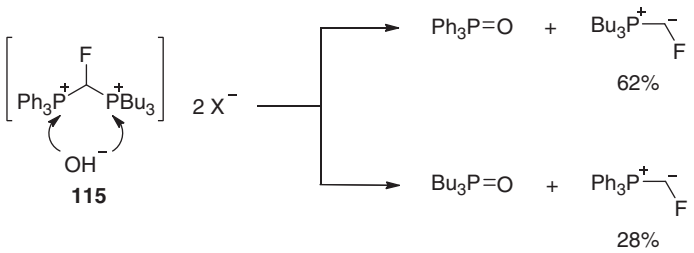
(26)

Certain vinylphosphonium salts substituted by an EWG react with aqueous bases to give phosphine oxides resulting from an anionotropic migration of a phenyl group from phosphorus to the α-carbon (S_{NP}mig) (Scheme 60).[374]



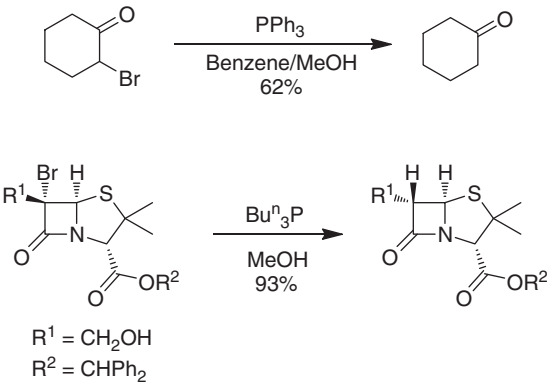
Scheme 60

The regioselectivity of C–P bond cleavage in the base hydrolysis of the unsymmetrical fluoromethylene bisphosphonium salt **115** can be accounted for by the susceptibility of the phosphonium center to nulceophilic attack by hydroxide ion. It is not believed that the relative stability of the newly formed fluoromethylene ylide is a factor in deciding the regioselectivity (Scheme 61).[375]



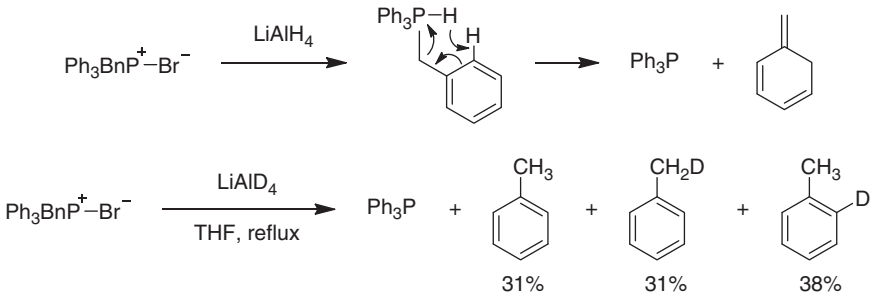
Scheme 61

The usefulness of alkaline hydrolysis of phosphonium salts can be further extended to dehalogenation, as phosphonium salts are easily prepared from simple phosphines and alkyl halides (Scheme 62).[376,377] However, the value of this method is generally confined to substrates where the conjugate base is of moderate pK_b (e.g., α-halo carbonyl compounds→enolates). Note that stereocenters epimerize under these conditions.

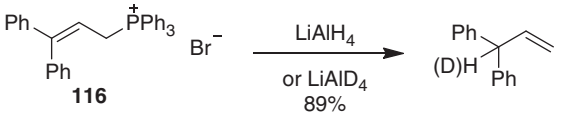


Scheme 62

LAH is the second method that is used to cleave C–P^{IV} bonds. The mechanism of attack at phosphorus by hydride is similar to the attack of hydroxide ions; however, the decomposition of the 5-coordinate intermediate proceeds not only via elimination, like hydrolysis, but also with S_N2 type substitution (Scheme 63).[378] The reduction of allylic phosphonium salt **116** with LAH is reported to undergo exclusive allylic inversion, supporting an S_N2' pathway (equation 27).[379] The preferential removal of benzyl groups is still preserved with LAH in the presence of allylic groups, whereas the reduction of $Me_nPh_{4-n}PX$ ($n=1$ or 2) with LAH has resulted in the mixture phosphines by the cleavage of either methyl or phenyl groups.[380,381]

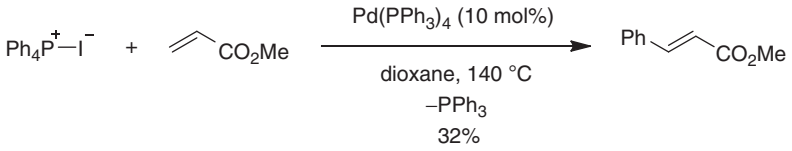


Scheme 63



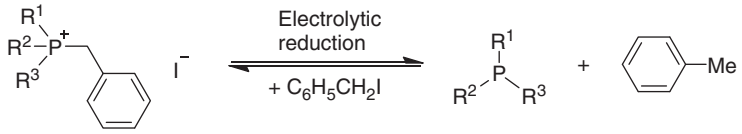
(27)

Metals, such as Na or alkali metal amalgams, can promote C–P^{IV} bond cleavage.[382] In the latter case, reductive cleavage of achiral and optically active quaternary phosphonium salts have been accomplished in high yield with retention of configuration.[383] It has been reported by Yamamoto and coworkers that treatment of phosphonium salts with palladium complexes resulted in C–P^{IV} bond cleavage (equation 28).[384]



(28)

Reductive cleavage of C–P^{IV} bond in phosphonium ions may also be accomplished via electrolysis. Benzyl groups are especially easily cleaved, and with electrolytic reduction, it has been found that the cleavage of benzyl group occurs with retention of configuration at phosphorus. Thus, Horner et al.[385] have prepared several optically active phosphines by electrolytic reduction of the corresponding benzylphosphonium salts (equation 29).

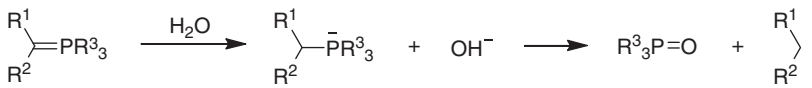


(29)

8.28.5.3 Reduction of Pentavalent Organophosphorus Compounds

The reductive cleavage of C–P^{V} bonds is generally performed on pentavalent organophosphorus compounds with coordination number four, such as phosphorous ylides, phosphine oxides, and phosphonates. Various methods and reagents exist to reduce a C–P^{V} bond to a C–H bond, including alkaline hydrolysis, metal hydrides and metal naphthalenides, radical processes, thermolysis and photolysis.

Phosphonium ylides generally are susceptible to hydrolytic cleavage. Protonation of ylides affords a phosphonium hydroxide, which can further react with hydroxide ion to afford a hydrocarbon and a phosphine oxide (**Scheme 64**). The susceptibility to hydrolysis varies with the reactivity of the ylide, with some ylides so reactive that they need to be prepared and handled in the complete absence of moisture, whereas others resist hydrolysis under severe conditions.[386] In general, the stability of an ylide toward hydrolysis parallels its basicity, with the most basic being the most susceptible to hydrolysis. Though most commonly an

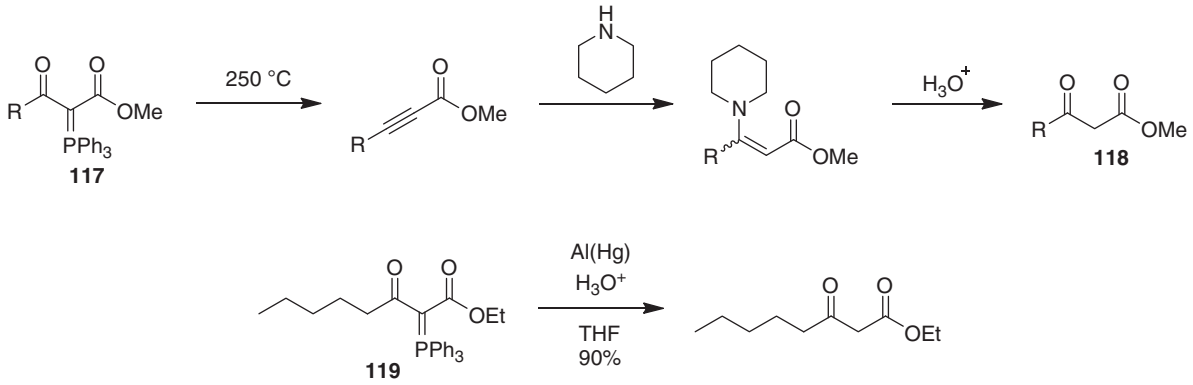


Scheme 64

undesired reaction, hydrolysis can be a useful C–P bond cleavage reaction under controlled conditions. There is a consistent pattern to the hydrolytic cleavage of the C–P bond in ylides, with the phosphorus leaving group generally being that which can produce the most stable carbanion.[387]

Bestmann has reported a thermal decomposition of (acylalkylidene)phosphorane **117** and the procedure for its conversion to *β*-keto ester **118** (Scheme 65).[388] The direct reductive removal of triphenylphosphine from ylide **119** is achieved with excess Al(Hg) in wet THF, with periodic addition of acid.[389]

There have been a few reports of the reduction of phosphonium ylides to tertiary phosphines and alkanes using LAH. The mechanism must be different from that of phosphonium salts because even in the presence of benzyl groups, most reductions of triphenylphosphonium ylides (e.g., benzylidene- and isopropylidenetriphenylphosphorane) result in cleavage of a phenyl-phosphorus bond and the formation of benzene and a tertiary phosphine (equation 30).[390]



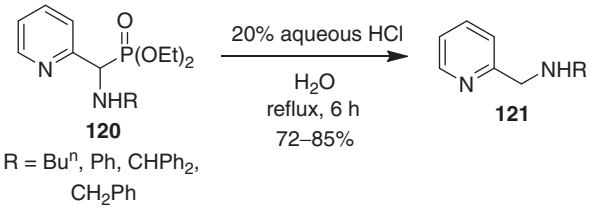
Scheme 65



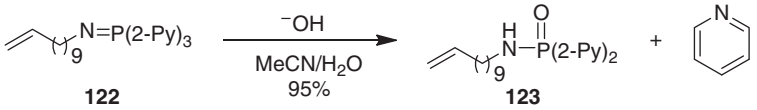
(30)

Hydrolysis of alkyl substituted phosphine oxides is generally difficult. Heating with solid sodium or potassium hydroxide is required in order to break the C–P bond as the cleavage usually occurs at the P–O bond in preference to the P–C bond. There have been exceptions reported with aromatic phosphine oxides containing *p*- and *o*-nitrobenzyl groups and other stabilized groups like trichloromethane.[391] Perfluorinated phosphine oxides can also be hydrolyzed to the phosphinic and phosphonic acids.[392]

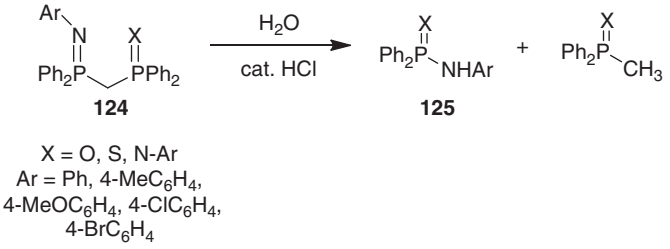
Phosphonates have shown a facile C–P^V bond cleavage under acidic and basic conditions depending on the substituents. Phosphonate compounds with electron-donating groups, such as pyridine aminophosphonate **120**, are hydrolyzed in acidic condition to amine **121** via the cleavage of C–P^V bond (equation 31).[393,394] A simple imino tris(2-pyridyl)phosphorane (**122**), is readily hydrolyzed under basic conditions to form *N*-substituted phosphinoyl amides **123** and pyridine (equation 32).[395] *N*-Aryl-*P,P*-diphenyl-*P*-(diphenylphosphinoyl)methyl-λ^5-phosphazene **124** undergoes smooth acid-catalyzed hydrolysis with C–P^V bond cleavage yielding *N*-aryl-*P,P*-diphenylphosphinamides **125** and diphenylmethylphosphane oxide (equation 33).[396]



(31)

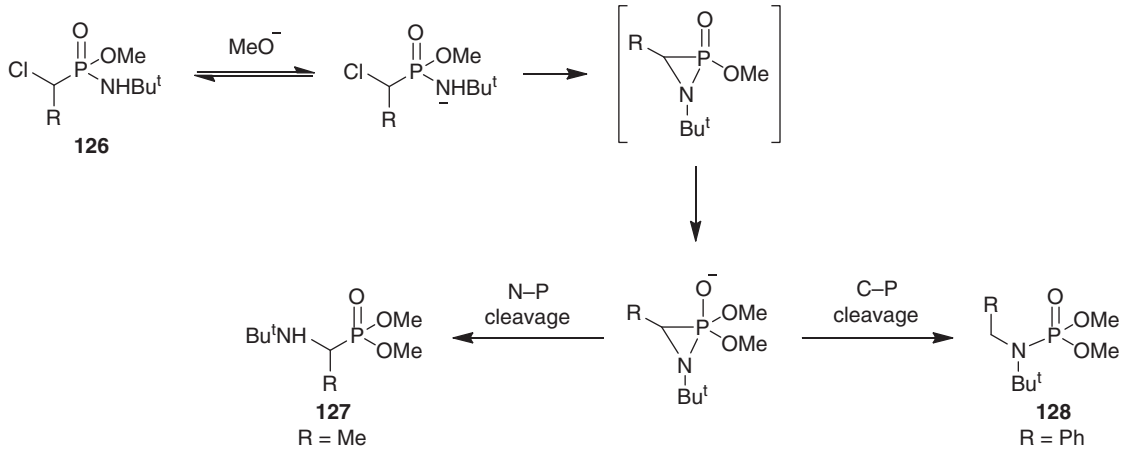


(32)

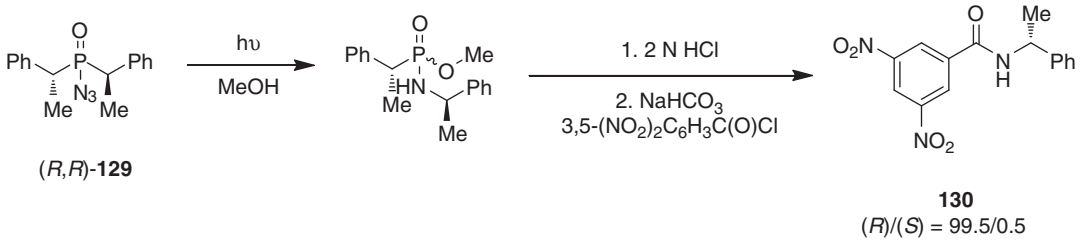


(33)

Under certain conditions, rearrangements can result in reductive C–P^V bond cleavage. *N*-*t*-butyl-α-chlorophosphonoamidate **126** undergoes methoxide-induced rearrangement to give product **127** and **128** via either N–P or C–P bond cleavage (Scheme 66).[397] Denmark and Dorow[398] have reported the photolytic Curtius rearrangement of phosphinic azides (*R*,*R*)-**129** and (*S*,*S*)-**129** to phosphonamidates, subsequent hydrolysis and acylation to give amide **130** with 99% net retention of configuration, in which the stereogenic carbon unit migrated to the nitrogen atom (*see* Chapter 6.15; Scheme 67).

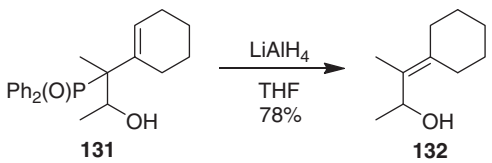


Scheme 66



Scheme 67

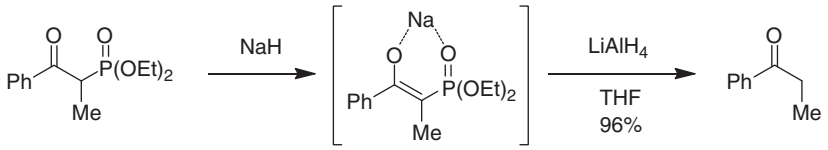
LAH is a strong reducing reagent, which can effect dephosphonylation of functionalized phosphine oxides and phosphonates with C–P^V bond cleavage. Allylphosphine oxides **131** lose the Ph_2PO group on the reduction with LAH to give allyl alcohol **132** via an S_N2' type reaction (equation 34).[399]



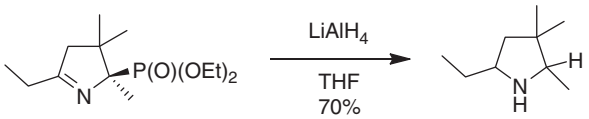
(34)

Dephosphonylation with LAH is effective for β-keto or enamino phosphonates. The reduction is actually performed on the enolate form of β-keto phosphonates, and it has been suggested that the cleavage of C–P bond is not caused by direct attack of

hydride on the α-carbon attached to phosphous but appears to result from direct attack on the phosphorus atom (Scheme 68).[400] Similarly, pyrrolidines have been obtained by the reduction of 2,4-dialkyl-5-phosphonyl pyrrolines with LAH (equation 35).[401]

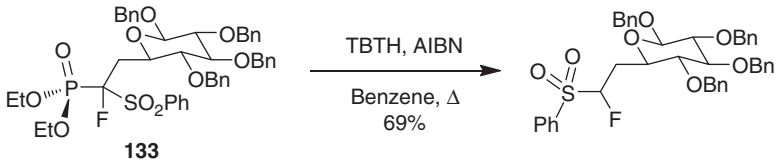


Scheme 68



(35)

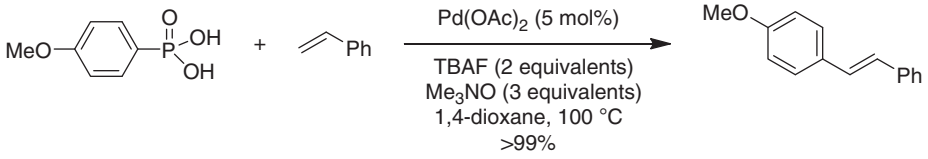
Radical processes to cleave C–P^V bonds have been reported. Okamoto and coworkers demonstrated the photo-dephosphonylation of *p*-nitrobenzylphosphonic acid to give *p*-nitrotoluene.[402] Frost and coworkers used lead tetraacetate and TBTH to break the C–P bond of alkylphosphonic acids and *p*-methoxybenzylphosphonates.[403] Most recently, Berkowitz and coworkers achieved dephosphonylation of **133** under free radical conditions using TBTH and AIBN, thereby providing a novel route to α-fluoroalkyl sulfones (equation 36); however, treatment of **133** with Na(Hg) inverted the reduction chemoselectivity and led to C–S bond reduction.[69] Interestingly, Wnuk and coworkers demonstrated that switching from the phenyl sulfone to the 2-pyrimidinyl sulfone led to C–S cleavage on exposure to TBTH and AIBN.[160] It is noteworthy that phosphonates lacking the fluorine at the α-carbon are reported to be inert toward the radical conditions with TBTH and AIBN for both benzene- or methanesulfonyl groups.[404]



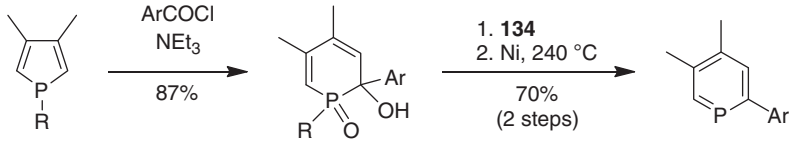
133

(36)

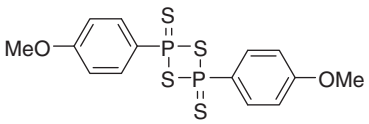
For transition metal induced C–P^V bond cleavage, Oshima and his coworkers have reported a Pd-catalyzed oxidative Heck-type cross-coupling reaction which makes use of arylphosphinic acids as an aryl group source (equation 37).[405] Also, nickel has been used for the cleavage of the phosphorus–phenyl bond in the conversion of 1-phenyl-3,4-dimethylphosphole to 2-(2′pyridyl)phosphorin (Scheme 69).[406]



(37)

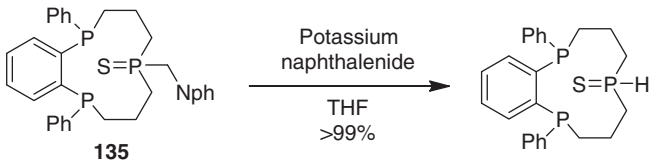


134:



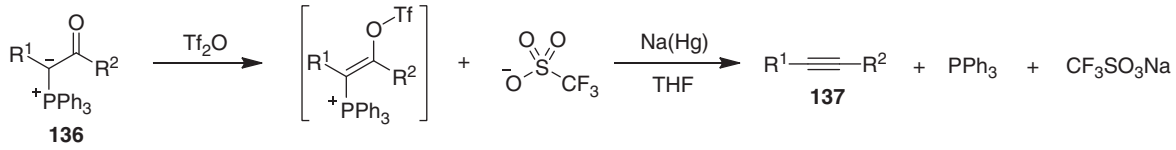
Scheme 69

The first macrocycle containing a secondary phosphine was synthesized by the use of the 1-naphthylmethyl moiety as a P–H protecting group. The napththylmethyl protecting group is cleaved from phosphine sulfide **135** using potassium naphthalenide (equation 38).[407]



(38)

Thermolysis can also be used to cleave C–P^V bonds, particularly in the preparation of dialkylalkynes from β-keto ylides. Thermolysis of β-keto ylide **136** leads to pure acetylene **137** at 300 °C only when R^1 and R^2 are aryl groups or when R^2 is an alkoxy group.[408] Bestmann et al. have developed a methodology demonstrating the decomposition of β-keto ylides with aryl or aliphatic substituents to alkynes. β-Keto ylide **136** is converted to an enol triflate ester and then reduced with Na(Hg) in THF at elevated temperature to give the alkyne **137** along with triphenylphosphine and sodium triflate (**Scheme 70**).[409]



Scheme 70

References

1. (a) Bougault, J.; Cattelain, E.; Chabrier, P. *Bull. Soc. Chim. France* **1940**, *7*, 780. (b) Mozingo, R.; Wolf, D. E.; Harris, S. A.; Folkers, K. *J. Am. Chem. Soc.* **1943**, *65*, 1013.
2. (a) Pettit, G. R.; van Tamelen, E. E. *Org. React.* **1962**, *12*, 356. (b) Hauptmann, H.; Walter, W. F. *Chem. Rev.* **1962**, *62*, 347. (c) Bonner, W. A.; Grimm, R. A. *Org. Sulfur Compd.* **1966**, *2*, 35.
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8.29 Reduction of Epoxides

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This chapter is a revision of the previous edition chapter by S. Murai, T. Murai, and S. Kato, Vol. 8, pp 871–893, © 1991, Elsevier Ltd.

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 doi:10.1016/B978-0-08-097742-3.00831-4

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Glossary

Ate-complex A salt resulting from the reaction of a Lewis acid with a base whereby the central atom increases its valence.

Brassinosteroids A class of steroid hormones ubiquitously found in plants but first purified from Brassica. Brassinosteroids contribute to growth, reproductive development, and vascular differentiation.

Episelenide Organic compounds analogous to epoxides (or episulphides) in which a selenium atom replaces the oxygen (or the sulfur).

Pheromone Compound produced by an animal, usually an insect, which influences the development or the behavior of others of the same species.

Single electron transfer A reaction mechanism characterized by the transfer of a single electron between the species occurring on the reaction coordinate of the reaction steps.

Single-walled nanotubes They are an allotrope of sp2-hybridized carbon. The structure consist in a cylindrical tube formed by six-membered carbon rings. The cylindrical tubes can have one or both ends capped with a hemisphere of the buckyball or fullerene structure.

8.29.1 Introduction

Epoxides are very useful intermediates in organic synthesis. Not only do they commonly feature in natural products and biologically important substances, but they also undergo countless transformations: ring-opening reactions leading to diols, aminoalcohols, diamines, reduction to alcohols, deoxygenation to alkenes, bioconversions in microorganisms, electrochemical transformations to ketones, and many others.

The reductive ring opening of epoxides is a fundamental process that can be performed also in the context of C–C bond-forming reactions, as when the oxirane reacts with trialkylaluminum, organocoppers, Grignard reagents, and the likes of. The formal reduction of epoxides occurs also with α-metalated epoxides, such as in the reductive alkylation process or in domino reactions when oxirane metalation is followed by alkylation with electrophiles and further nucleophilic addition to the oxiranyl ring. In spite of the extensive work that involves this kind of reduction and the great importance of this ring-opening methodology in synthesis, this peculiar aspect of the chemistry of epoxides will not be touched in this chapter, since it results in the generation of new carbon skeletons.

This chapter focuses on epoxide reduction that leads to the synthesis of alcohols and alkenes with no changes or further elaboration of the carbon skeleton of the starting epoxide, grouping the reductions into two types: (1) reduction to alcohols and (2) deoxygenation to alkenes or to saturated compounds.

8.29.2 Reduction of Epoxides to Alcohols

The reductive ring opening of epoxides, especially in enantiopure form, to the corresponding alcohols is a powerful tool in synthetic organic chemistry.[1] Reductive cleavage of oxiranes can be performed in the presence of various dissolving metals, metal hydrides (*see* Chapter 8.01),[2] or hydrogen, although milder reagents have also been developed to enhance the chemical yields.[3] Hydrogenation in various heterogeneous catalytic systems, based on Ni, Pd, Ti, and Pt, can be used. The chemo- and regioselectivity of such reactions depends on the choice of catalyst (*see* Chapter 8.04).[4]

The reductive ring opening of epoxides will be described on the basis of the reducing agent, with particular emphasis addressed to the chemo-, stereo-, and regioselectivity, focusing on methods that are regio- and stereoselective and that are compatible with other functional groups and that have been used in the preparation of target molecules.

8.29.2.1 Hydrogenolysis of Epoxides with Metal Catalyst

Hydrogenolysis of epoxides to alcohols generally involves ring opening at the less substituted carbon atom.

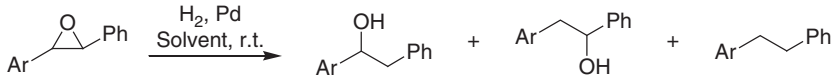
8.29.2.1.1 Palladium

Although catalytic hydrogenation over Pd/C is typically a simple and clean reduction procedure,[5] it is not often used for the reduction of epoxides,[6] often because of the undesired isomerization of the epoxides to ketones as byproducts.

$Pd/BaSO_4$ is a useful reducing agent for epoxides even in the presence of sensitive functional groups and has been used in the synthesis of natural products.[7]

Diarylepoxides have been reduced with hydrogen in the presence of Pd/C in the appropriate solvent (CH_3OH or EtOAC/AcOH (1%)), affording only one of the two possible regioisomers in good-to-excellent yields (Table 1).[8]

Table 1 Catalytic hydrogenation of *trans* nonsymmetrical 2,3-disubstituted oxiranes

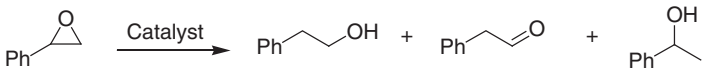


1 **2** **3** **4**

Ar	*Solvent*	*Time (h)*	*2%*	*3%*	*4%*
2-Pyridyl	CH_3OH	2	90	–	–
4-Pyridyl	CH_3OH	2	90	–	–
2-$CH_3OC_6H_4$	EtOAc/1% AcOH	12	72	28	–
4-$CH_3OC_6H_4$	EtOAc/1% AcOH	7	87	13	–
2-$CF_3C_6H_4$	EtOAc/1% AcOH	2	70	–	–
2-$CF_3C_6H_4$	CH_3OH	3	60	–	40
4-$CF_3C_6H_4$	EtOAc/1% AcOH	2	60	–	40
4-$CF_3C_6H_4$	CH_3OH	3	50	–	50
4-FC_6H_4	CH_3OH	3	70	–	–

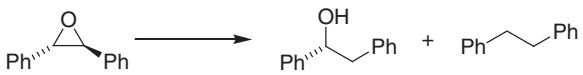
The regioselectivity seems to be independent of the electronic properties of the substituents. In fact, for all oxiranes bearing either an electron-withdrawing group (EWG) or an electron-releasing group on the aryl ring, regioisomer **2** was obtained as the major product.[9] The reaction was interesting particularly for the preparation of *ortho*-substituted alcohols of potential use as ligands in asymmetric synthesis.

Styrene oxide reduction over Pd catalysts was performed on different supports activated carbon, alumina, and magnesia using a continuous flow reactor. The acid–base nature of the support played an important role in the regioselectivity of the reaction. An acid support, such as alumina or activated carbon, favored the formation of phenyl acetaldehyde and 1-phenylethanol (1-PEA). However, when a basic support such as MgO was used, the main product was 2-phenylethanol (2-PEA) (*see* Chapter 9.03),[10] which is useful in the formulation of cosmetics, in the preparation of detergents, as flavoring agents in foods and beverages, and in the preparation of its esters, which are also used as fragrance compounds (equation 1).[11]



(1)

Aryl epoxides can also be efficiently reduced using Pd(0) EnCat™ 30NP under conventional catalytic hydrogenation conditions (atmospheric pressure of H_2) with good selectivity and conversion.[12] *trans*-Stilbene oxide was chosen as a model for the hydrogenolysis of aromatic epoxides. The effect of different heterogeneous palladium catalysts and their propensity to overreduce the benzylic alcohol generated after hydrogenolysis of the epoxide was investigated. The use of Pd(0) EnCat™ 30NP in EtOH or ammonium formate gave the benzylic alcohol in high yields, unlike reductions using Pd/C that resulted in deoxygenation products (equation 2).[13]

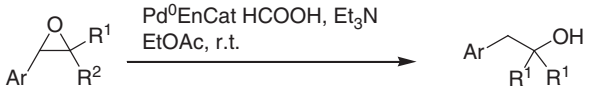


(2)

Palladium supported on hydrotalcite [$Mg_6Al_2CO_3(OH)_{16}$] (Pd/HT) has been successfully applied to the hydrogenation of styrene oxide to give 2-PEA with high yields and selectivity, without deoxygenated product formation.[14] Pd nanoparticles

microencapsulated in polyurea have been reported to be very efficient in the reductive ring opening of different benzyl and alkyl epoxides (Table 2).[15]

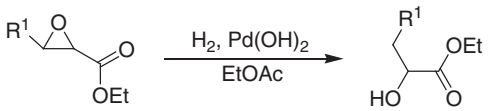
Table 2 [Pd(0) EnCat] – catalyzed hydrogenolysis of arylepoxides



Ar	*R*^{1}	*R*^{2}	*Time (h)*	*Yield (%)*
Ph	H	H	4	84
4-C_6H_4	H	H	24	82
Ph	Me	H	3	90
Ph	Ph	H	5	99
Ph	H	Ph	5	93
Ph	CH_2OH	H	5	95
Ph	CH_2OH	Me	3	93
Ph	COOEt	H	13	92
Ph	CH_3CO	H	6	87

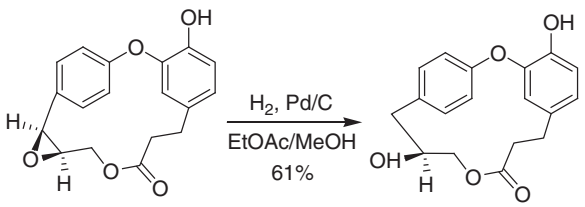
A magnetically separable Pd catalyst, synthesized simply through a sol–gel process incorporating Pd nanoparticles and superparamagnetic iron oxide nanoparticles in an AlO(OH) matrix,[16] showed better activity and selectivity than all the commercial Pd catalysts for hydrogenolysis under mild conditions. The less hindered C–O bonds were cleaved in the reactions of a wide range of terminal oxiranes, including those bearing esters and hydroxyl groups, which do not perturb the regioselectivity. The hydrogenolysis of an internal oxirane, cyclohexene oxide, was also successful, giving cyclohexanol in 93% yield.

Racemic aryllactic esters have also been prepared in moderate-to-excellent yields (28–99%) by hydrogenation with $Pd(OH)_2$ performed in EtOAc to achieve the regioselective reduction of the benzylic C–O bond. The use of methanol led to the addition of solvent to the oxirane ring (equation 3).[17]



(3)

The configuration (3*R*,4*S*)-(+)-Combrestatin D-1 was clarified through its reductive transformation into the corresponding secondary alcohol in the presence of H_2/Pd/C by hydride addition to the benzylic carbon atom (equation 4).[18]

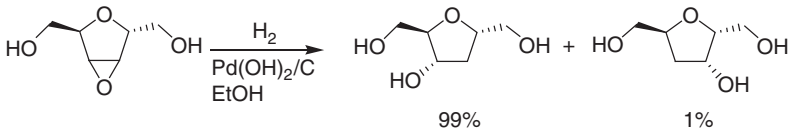


(+)-Combrestatin D-1

(4)

Different hydrogen sources, such as $HCOONH_4$,[19] and catalysts, such as the ethylenediamine Pd/C complex, have been used to improve selectivity and prevent further hydrogenolysis of the alcoholic C–O bond. Nevertheless, solvolysis with methanol remains a problem, particularly in the case of benzylic epoxides.

The hydrogenolysis of epoxides was studied in the stereoselective synthesis of carbohydrates by reacting 2,5:3,4-dianhydro-D-altritol in the presence of Pearlman's catalyst in absolute ethanol,[20] yielding the corresponding [(2*R*,3*S*,5*S*)-3-hydroxytetrahydrofuran-2,5-diyl]dimethanol in 92% yield (99:1 regioselectivity, equation 5). Hydrogenolysis with D_2 suggests that the reaction proceeds stereoselectively with inversion at C_3 via *anti* insertion of H_2.

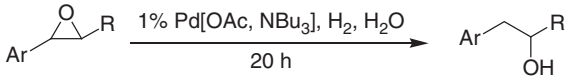


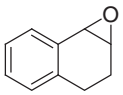
(5)

A new Pd(II) azo complex anchored to macroporous polystyrene was synthesized and characterized and the catalytic activity of PS-[(AzNap)Pd(OAc)]$_2$ was studied in the hydrogenation reaction of styrene oxide,[21] which took place with excellent yields and selectivity. 2-PEA was the major product with a small amount of phenylacetaldehyde and 1-PEA (depending on temperature and solvent) as side products. *N*,*N*-Dimethylformamide (DMF) was the best solvent for this catalytic hydrogenation under atmospheric pressure, with a decrease of the selectivity for 2-PEA with an increase in temperature more than 60 °C. These supported catalysts are prepared easily and require phosphine-free conditions, showing high thermal stability and applicability.

Hydrogenolysis of various benzylic epoxides in water using recyclable Pd nanoparticles as a catalyst was used for the regioselective synthesis of primary alcohols (Table 3). The particles were obtained from *n*-Bu_4NBr, *n*-Bu_3N, and $Pd(OAc)_2$.[22] Ester functionalities tolerated the experimental conditions, and water was found as the best solvent, although stilbene oxide required MeCN as cosolvent to react in high yields. Epoxyalkanes could not be efficiently reduced in water alone; *n*-Bu_4NBr was needed as an additive, which also increased the recyclability of the catalyst.

Table 3 Hydrogenolysis of benzylic epoxides in water



Ar	*R*	*Yield (%)*
Ph	CH_3	81
Ph	$CO_2CH_2CH_3$	80
Ph	Ph	92
4-ClC_6H_4	H	51
3-ClC_6H_4	H	82
		74

8.29.2.1.2 Platinum

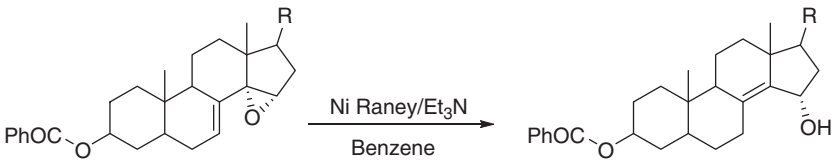
Platinum catalysts (i.e., Adam's catalyst) have been used in the reductive ring opening of epoxides to the corresponding alcohols.[23]

2-PEA can be obtained by styrene oxide reduction over Pt catalysts.[24] The reduction was performed on different supports: activated carbon, alumina, and magnesia, with the aim of exploring the role of the support on the regioselectivity of the ring opening. Basic supports led to the formation of the less substituted alcohol (2-PEA), with high conversion (85%), whereas the use of more acidic supports such as alumina led to the formation of the more substituted alcohol (1-PEA) and phenylacetaldehyde. 2-PEA can be obtained in high yield and selectivity, with the safety, low cost, and simplicity required for industrial-scale applications.

Pt supported on hydrotalcite ($Mg_6Al_2CO_3(OH)_{16}$), has been successfully applied to the hydrogenation of styrene oxide to give 2-PEA in high yields and selectivity, with no deoxygenated product formation.[14]

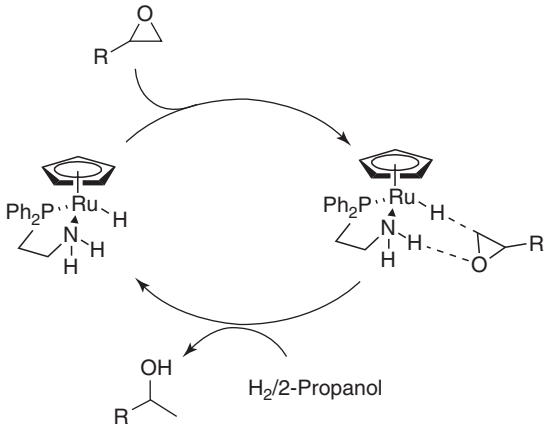
8.29.2.1.3 Raney nickel

Hydrogenolysis of epoxides with Raney Ni can be used for the preparation of alcohols: Generally, the ring opening occurs at the more substituted carbon atom, affording the less substituted regioisomer of the alcohol.[11] The reduction of the oxirane ring proceeds smoothly in the presence of a base, and high regioselectivity can be also obtained in the presence of Ni/Et_3N, as reported in the reduction of epoxy-cholestene, where the resulting hydroxyl function had the same configuration of the starting epoxide, probably due to a SN2′ hydride attach.[25]



8.29.2.1.4 Ruthenium

An [η-$C_5(CH_3)_5$]Ru complex bearing a 2-(diphenylphosphino)ethylamine ligand was highly efficient for the chemoselective hydrogenolysis of epoxides. Terminal epoxides are hydrogenolyzed to give secondary alcohols with high regioselectivity using this ternary catalyst system in 2-propanol under mild conditions.[26] The reaction outcome depends on the ligand structure and the reaction conditions. A P–N chelating ligand bearing NH functionality is crucial for efficient hydrogenolysis of the epoxide, since replacement of the primary amino group with a diphenylphosphino group completely suppresses the reaction. Hence, it is conceivable that the hydride and proton of the Ru-complex are transferred to the epoxides simultaneously via a six-membered transition state, in which steric repulsion in the epoxide becomes minimal, to produce secondary alcohols with the regeneration of the catalyst (Scheme 1).



Scheme 1

8.29.2.2 Oxirane Ring Opening by Metal Hydrides

8.29.2.2.1 Aluminum hydrides

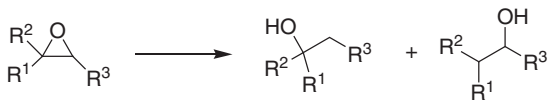
8.29.2.2.1.1 $LiAlH_4$

$LiAlH_4$ is commonly used in epoxide reductive ring opening.[27] In general, the reduction of the epoxide ring with lithium aluminum hydride (LAH) proceeds by S_N2 nucleophilic substitution with hydride transfer and takes place at the less substituted carbon atom to give the more substituted alcohol.

The mechanism of LAH addition was investigated in some cases,[28] by using $LiAlD_4$, and demonstrating *anti* hydride addition to the epoxide carbon atom.

The reduction of some mono-, di-, and trisubstituted alkyl and aryl epoxides with LAH is summarized in Tables 4 and 5.[29–33] In some cases, different results have been observed. For example, different mechanisms can occur in the presence of different reducing species ($LiAlH_4$ alone or AlH_3),[34] as reported in studies of regioselectivity in the ring opening of substituted cyclohexene oxides.[35]

Table 4 Reduction of alkyl- and vinyl-epoxides with $LiAlH_4$

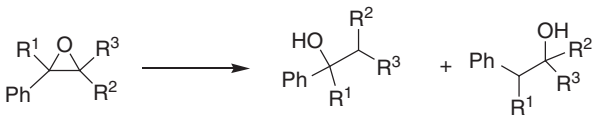


5 **6** **7**

No.	*R^1*	*R^2*	*R^3*	*Yield (%)*	*Ratio 6:7*
i	Me	H	H	60	100:0
ii	$PhCH_2$	H	H	84	100:0
iii	Me	Me	H	26	95:5
iv	CH_2=CH	Me	H	48	100:0
v	Me	Me	Me	25	100:0
vi	Me	Me	Bu^t	21	0:100

The reduction of B-norcholestane epoxide **11** with LAH gives the 3,5-diol **12** in 90% yield trough hydride attack at the less substituted C(6) position of epoxide.[36,37]

Table 5 Reduction of arylepoxides with $LiAlH_4$



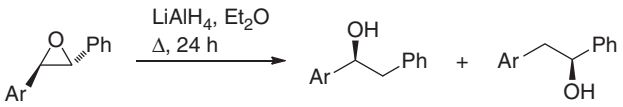
8 **9** **10**

No	R^1	R^2	R^3	*Yield (%)*	*Ratio 9:10*
i	H	H	H	82	95:5
ii	Ph	H	H	97	96:4
iii	H	H	Me	90	10:90

Intramolecular chelation plays an important role in the reductive ring-opening reaction by $LiAlH_4$ of 1,2-epoxides bearing polar functionalities: different regioselectivities have been observed in the presence of metal ions or by the formation of 'unchelated' intermediates, as demonstrated by performing the reaction in the presence of crown ether reagents.[38]

In the reductive ring opening of unsymmetrically substituted *trans*-diaryl epoxides with $LiAlH_4$, good regioselectivity was observed in the reaction of anthryl–phenyl and naphthyl–phenyl-substituted *trans*-epoxides, with the alcohols **13** being isolated in high enantiomeric purity. Conversely, the benzylic alcohol **14** was isolated as the main product in the phenanthryl–phenyl-substituted epoxide reduction (Table 6).[39]

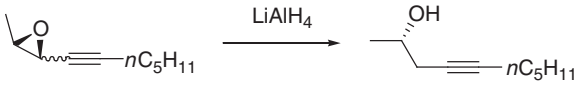
Table 6 Enantiopure alcohols obtained by ring opening of arylepoxides



trans (*R*,*R*) **13** (*S*) **14** (*S*)

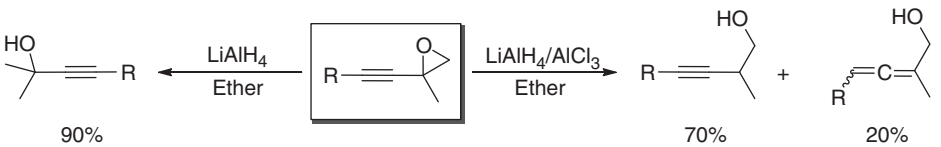
Ar	*Ratio* ***13***(S):***14***(S)
9-Anthryl	0:100
9-Phenanthryl	64:36
1-Naphthyl	33:67

Several optically active insect pheromones can be easily prepared by reduction of a mixture of *trans*- and *cis*-epoxides in high yield and with excellent regioselectivity.[40] By this approach, homopropargylic alcohols can be prepared in high yields by reduction of alkynyl epoxides with $LiAlH_4$ (equation 6).



(6)

Propargylic alcohols can be isolated in high yield and regioselectivity by reaction of α-acetylenic epoxides with $LiAlH_4$, whereas the use of $LiAlH_4/AlCl_3$ reversed the product distribution, as already reported for other systems (equation 7).[41]

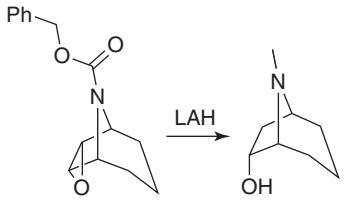


90% 70% 20%

(7)

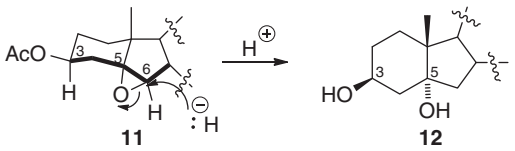
$LiAlH_4/AlCl_3$ reduces 3,3-diarylcyclopentene oxides to 2,2-diarylcyclopentanols.[42]

$LiAlH_4$ reduced the *endo*-epoxide derivatives of tropanes, which are more reactive than the corresponding *exo*-epoxides. The *endo*-hydroxytropane was obtained in 70% yield.[43]



(8)

$LiAlH_4$ was used in the key step of the total synthesis of (2*S*,3*S*,7*S*)-3,7-dimethylpentadecan-2-yl acetate (and propionate), the active enantiomers of the pheromones of pine sawflies. The synthesis was accomplished and a plausible mechanism is depicted in Scheme 2.[44]



Scheme 2

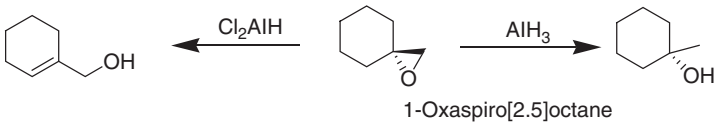
The regioselective reductive epoxide opening reaction at the terminal carbon is the key step of this one-pot, chemo-, regio-, and stereoselective transformation, allowing the establishment of all the three chiral centers of the target (2*S*,3*S*,7*S*)-3,7-dimethyl-2-pentadecanol.

$LiAlH_4$ can be used also complexed with amines, such as *N*-methylpyrrolidine (LAHNMP), for the regioselective reduction of aliphatic and aromatic epoxides, without the use of inert atmosphere.[45]

The reduction of optically pure trifluoromethyloxirane with $LiAlH_4$ allows the preparation of trifluoromethyl alkanol in enantiopure form.[46]

8.29.2.2.1.2 AlH_3

By using a tetrahydrofuran (THF) solution of aluminum hydride–triethylamine complex (AHTEA),[34] a reductive reagent stable at room temperature for at least 1 month, aliphatic epoxides can be rapidly reduced giving exclusively the product of hydride addition to the less hindered carbon. Lower regioselectivity was observed for aromatic epoxides, with styrene oxide giving a 77:23 ratio of 1-PEA:2-PEA. The same behavior was also observed in the reduction of 1-oxaspiro[2.5]octane,[47] with AlH_3 to 1-methylcyclohexanol as the sole regioisomer. In contrast, the use of Cl_2AlH afforded the unsaturated alcohol in 38% yield (equation 9).



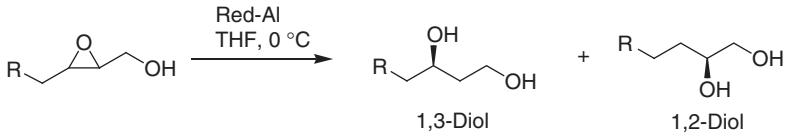
(9)

8.29.2.2.1.3 Sodium–aluminum hydrides

By using sodium–aluminum hydride (SAH) in THF solution,[48] aliphatic epoxides can be reduced regioselectively by hydride addition to the less hindered epoxide carbon. A slower reaction was observed than in LAH reductions, because of a role of the cation in the ring opening. Good regioselectivity was observed in the reduction of epoxides with aromatic substituents: the two PEAs are formed in a 97:3 ratio on reduction of styrene oxide.

8.29.2.2.1.4 Red-Al

The stereoselective ring opening of epoxy alcohols in the presence of Red-Al [$NaAlH_2(OCH_2CH_2OCH_3)_2$] affords 1,3-diols in high yields and enantioselectivities (equation 10).[49] Reductive ring opening of epoxy alcohol should provide two regioisomeric diols, in a ratio depending on the stereochemistry and the R group of the starting epoxide, and also the used reducing agent. When the R group contains an alkyl chain, 1,2-diol and the 1,3-diol can be obtained in near equal amount in the reduction with Red-Al (or even by using $LiAlH_4$), whereas if R contained one ethereal functional group in the position α or β to the epoxide, the 1,3-diol yielded almost exclusive product when Red-Al was used. The hydroxyl group is essential for reactivity: the ethereal analogs do not react under these conditions.[50] This reagent could also be used in the presence of unsaturated functional groups.[51]



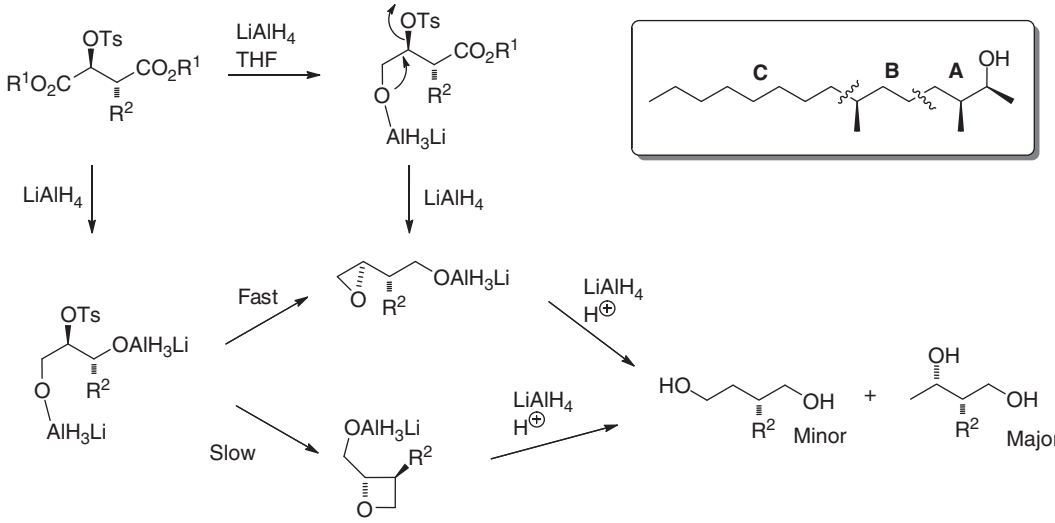
(10)

Red-Al was efficiently employed for the regioselective cleavage of epoxy intermediates into the synthesis of C_{22}–C_{34} subunit of the immunosuppressant FK-506.[52]

8.29.2.2.1.5 DIBAL-H

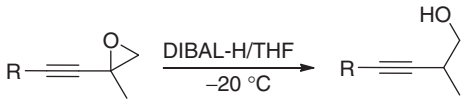
The use of diisobutylaluminium hydride (DIBAL-H) as reducing agent for epoxy alcohols yielded the 1,2-diol as the main product. Because of the Lewis acid properties of DIBAL-H, the reduction by DIBAL-H seems to involve the initial complexation of the reducing agent with the oxygen of hydroxy group, in which the aluminum serves as a Lewis acid to facilitate intramolecular hydride transfer.

The use of neutral hydride sources as DIBAL-H was investigated in the reduction of epoxy tosylates, in different reaction conditions.[53] With an excess of DIBAL-H/CH_2Cl_2, epoxy tosylates lead to the fully reduced methyl carbinols in high yields, whereas no reaction was observed with only 1 equivalent (**Scheme 3**). Conversely, with 2 equivalents of DIBAL-H at lower temperature (−40 °C) in CH_2Cl_2 or ether solvent, high yields of hydroxy tosylates have been isolated, either from *cis*- or *trans*-epoxides, either with alkyl or aryl monosubstituted derivatives.[54]



Scheme 3

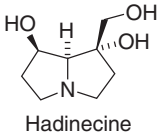
Homopropargylic alcohols can be obtained and isolated in gram scale by reaction of α-acetylenic epoxides with 1.2 equivalents of DIBAL-H in THF, with high regioselectivity unlike other reductive agents (equation 11).[40]



(11)

The regiochemistry of reduction of alkyl terminal epoxides depends on the experimental conditions: the secondary alcohol was obtained as the main product with *i*-Bu_2AlH in the presence of a Lewis base such as R_3N, $AlR_2(OR)$, and R_2O, whereas silyl-substituted epoxides show reversed behavior with *i*-Bu_2AlH, since different species and reduction mechanisms are involved.

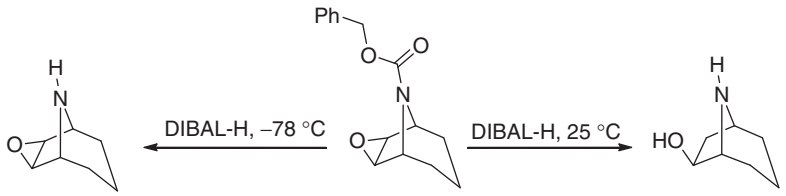
An example of the stereoselective epoxide ring opening with *i*-Bu_2AlH was reported for the enantioselective synthesis of hadinecine (equation 12), through the reduction of an epoxy intermediate.[55]



(12)

DIBAL-H was used efficiently in the stereoselective ring opening of allylic epoxides in the synthesis of (+)-combrestatin D-2, through the hydride transfer at the benzylic position of the functionalized styrene oxide intermediate.[56]

DIBAL-H reduced selectively the *exo*-epoxide ring of tropane derivatives, which are less reactive with respect to the corresponding *endo*-epoxides, in the total synthesis of scopine derivatives. When the reaction was performed at 25 °C the *exo*-hydroxytropane was obtained, whereas under milder conditions at − 78 °C the deprotection of the benzyloxycarbonyl group was achieved by reacting the epoxide with the same reductive agent (equation 13).[42]



(13)

Al-acetoxydiisobutylalane (DIBAOAc) and *Al*-trifluoroacetoxydiisobutylalane ($DIBAO_2CCF_3$) constitute a new class of reducing reagents showing unique and excellent selectivity in the reduction of epoxides.[57] A variety of alkyl- or/and phenyl-monosubstituted epoxides were easily converted to the corresponding primary alcohols as the sole ring-opening products. The less substituted alcohol was obtained also from the reduction of α,α- and α,β-disubstituted epoxides. The fluorinated derivative $DIBAO_3SCF_3$ is more reactive than $DIBAO_3SCH_3$.[58] $DIBAO_3SCF_3$ appears to be extremely mild and absolutely inert toward other organic functional groups such as carboxylic acids, esters, acid chlorides, amides, nitriles, and sulfur compounds.

8.29.2.2.2 Boron hydrides

The reductive epoxide ring-opening reaction can be effected by borohydrides that often require milder reaction conditions and tolerate the presence of carbamoyl, carbonyl, nitro, and cyano groups that are reduced by $LiAlH_4$.[59] Borohydrides usually are used in the presence of Lewis acids, capable of activating the epoxide toward hydride attack. However, diborane $(BH_3)_2$ reduces epoxides giving a mixture of products. Borane alone is not the first choice in the reduction of alkenyl-epoxides, due to the competitive hydroboration of double bonds. However, in the reduction of spirocycloalkane oxides such as 1-oxaspiro[2.5]octane, BH_3 was found to react affording the corresponding cyclohexenylmethanol as the sole regioisomer.[47]

$NaBH_4$/diborane reacts selectively in the epoxide ring opening, sparing ketals, and tosyl functionalities, eventually present in the substrate structure.[60]

8.29.2.2.2.1 Boron alkoxides

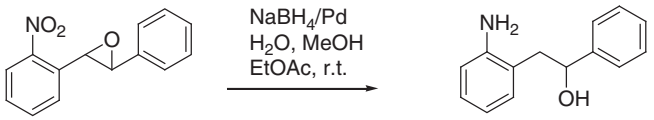
Boron alkoxides, such as boron triisopropoxide, react with epoxides to produce the ring-opened reduction products. The mechanism probably involves the formation of a coordination complex via a cyclic transition state,[61] where the β-hydrogen of the boron atom attacks preferentially the phenyl-bearing carbon atom of the epoxy ring. No reaction occurs with aliphatic epoxides, whereas aromatic epoxides undergo reduction in refluxing THF. Various functional groups are tolerated, except aldehydes and ketones under the recommended reaction conditions. The reagent usually attacks the carbon site where the phenyl group is attached, except for the case of β-methylstyrene. The reaction of *trans*-β-methylstyrene yielded 1-phenyl-1-propanol with 100% selectivity. Among the solvents examined, DMF was the best for conversion and yield, whereas THF showed the highest selectivity.

8.29.2.2.2.2 $NaBH_4$

α,β-Unsaturated epoxides undergo conjugate reduction with diborane to give allylic alcohols selectively, whereas reverse selectivity has been described with diborane/BF_3, $NaBH_4$/diborane, borohydride/trichlorotrispyridine-Rh, $NaCNBH_3/BF_3$.[62]

$NaBH_3CN–BF_3 \cdot Et_2O$ was efficiently used to promote the ring opening of the oxirane ring in 82% yield in the key step of the synthesis of the *trans*-hydrindane systems in vitamin D synthesis.

$NaBH_4$ reduces palladium salts to Pd^0, that in turn catalyzes the slow release of hydrogen from the borohydride. $NaBH_4$/Pd has been used in the reduction of *trans*-2-(aryl)-3-phenyloxirane to the corresponding aminoalcohols,[63] as a complementary method with respect to $[Cp_2TiCl]/H_2O$ system (equation 14).

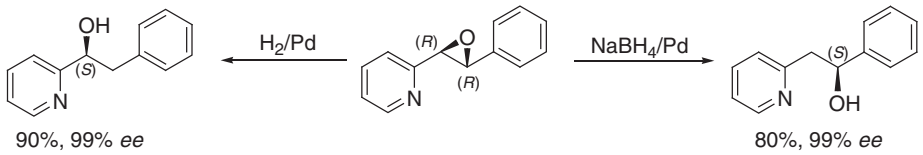


(14)

However, the catalytic system exhibited high sensitivity to different reaction parameters, such as the borohydride/substrate and Pd/substrate ratios: different Pd/substrate ratios influenced only the reaction times, whereas different $NaBH_4$/substrate ratios influenced the regioselectivity of the reaction. Low conversion and high regioselectivity are observed with a lower $NaBH_4$/substrate ratio, because the reaction conditions are closer to catalytic hydrogenation. Conversely, higher borohydride/substrate ratios favor reductive ring opening over side reactions and give opposite regioselectivity, because a more 'hydridic' reducing reagent is working, with properties different to those of H_2 in catalytic hydrogenation reactions.

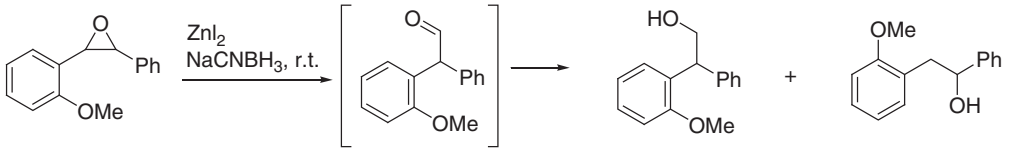
In general, the regioselectivity was highly affected also by the aryl substituents: *ortho*- and *para*-substituted substrates gave the same type of regioisomer in similar chemical yield, whereas very strong EWGs on the aryl group (2-CF_3 and 4-CF_3), afforded the hydrogen ring opening by attacking the *β*-carbon with respect to the EWG-substituted aryl ring. Conversely, an electron-donating group (EDG) on the aryl promotes the *α*-ring opening, affording the corresponding 1-phenyl-2-arylethanols in good yields.

Application of these procedures to enantiopure epoxides resulted in no loss of optical purity in the products (equation 15).



(15)

$NaBH_4/ZrCl_4$[64] and $Zn(BH_4)_2/SiO_2$[65] systems have been reported to work efficiently and $NaCNBH_3$ in the presence of ZnI_2 was found to effect regioselective ring opening of benzylic epoxides (equation 16).[66]

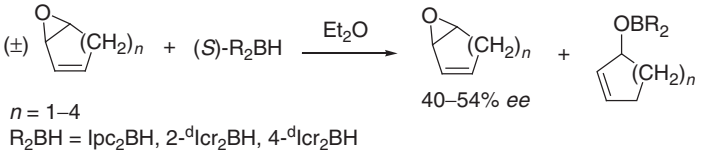


(16)

Sodium borohydride under solid–solution biphasic conditions ($NaBH_4$)/moist alumina in hexane in the presence of a catalytic amount of palladium(II) chloride ($PdCl_2$)[67] is an efficient system for the regioselective reduction of aliphatic and aromatic epoxides; in both cases the less substituted alcohols were isolated. Aliphatic were less reactive than aromatic epoxides, although chlorine and nitro groups on the aryl ring were further reduced, giving a lower yield of the desired products. Under these experimental mild conditions small amounts of deoxygenation products were found. The reaction takes place on the alumina surface, since no conversion was observed without the solid support, which can be filtered and reused by simple filtration after the reaction.

8.29.2.2.2.3 Dialkylboranes

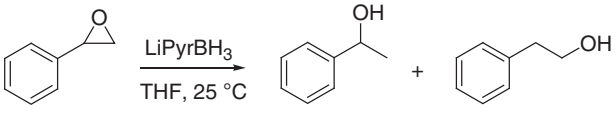
The use of optically active dialkylboranes allows kinetic resolution of epoxide racemic mixtures. The synthesis of enantiomerically enriched 2-vinyloxirane and monoepoxides of 1,3-cycloalkadienes was accomplished by kinetic resolution of racemates with Ipc_2BH, 2-$^{d}Icr_2BH$, and 4-$^{d}Icr_2BH$ of high enantiomeric purity.[68] Allylic alcohols were obtained by reduction of dialkylborinates, on treatment with ethanolamine or standard alkaline hydrogen peroxide. For all the examined epoxides, the di-2-isocaranylborane gave the higher *ee*% (equation 17).



(17)

8.29.2.2.2.4 Aminoborohydrides

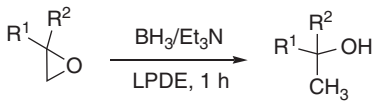
Aminoborohydrides, easily obtained by treatment of primary or secondary amines with $LiBH_4$,[69] are powerful, selective, and stable reducing agents for the reduction of epoxides such as styrene oxide or cyclohexene oxide in high isolated yields (equation 18).[70]



(18)

Lithium perchlorate-diethylether (LPDE) catalyzes ring opening of epoxides in the presence of a borane–Et_3N complex, causing a regioselective clean and fast conversion into the secondary alcohol in very good yields (Table 7).[71]

Table 7 Reduction of terminal epoxides with BH_3/Et_3N/LPDE



No	*R^1*	*R^2*	*Alcohol (%)*
i	$PhOCH_2-$	H	90
ii	CH_3-	CH_3	85
iii	$CH_2{=}CH_2CH_2OCH_2-$	H	76
iv	$(CH_3)_2CHOCH_2-$	H	77

8.29.2.2.2.5 Lithium triethylborohydride

$LiBHEt_3$ was efficiently used as modified metal hydride; it reduces tri-, tetrasubstituted and cyclic epoxides, and carbohydrate epoxides.[72] Only tertiary alcohols are obtained in the case of trisubstituted epoxides.

8.29.2.2.3 Lithium hydride

LiH is a stable metal hydride that needs to be activated by a nucleophile and/or a base to induce the hydrogen evolution. With *t*-BuOH/Ni-acetate in THF, LiH affords the reducing reagent Li-NiCRA, that was used *in situ* for the efficient regioselective reduction of styrene oxide into 2-PEA in high yields (92%), together with *t*-BuOLi and Ni^0.[73]

8.29.2.2.4 Gallium and indium hydrides

Some gallium hydride complexes, for example, $[GaH_3\{P(C_6H_{11})_3\}]$, have been applied to the reduction of carbonyl containing functionalities.[74]

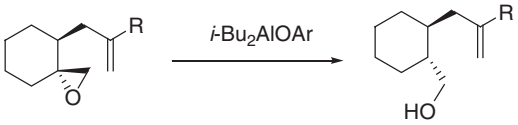
Indium hydride reagents have been also studied and characterized, although most of them are difficult to handle, being thermally unstable and air-sensitive. Different regiochemistry has been reported in these reductions, because of the different electronegativity of indium relative to aluminum and gallium. In the reduction of styrene oxide it was observed that tricyclohexylphosphine gallane reduces the epoxide to the secondary alcohol with $>99\%$ selectivity, whereas formation of 1- and 2-PEAs in roughly equivalent yield was reported by performing the reaction in the presence of the indium-reducing complex.[75]

8.29.2.3 Organoaluminum Reagents

The use of neutral hydride sources like *i*-Bu_3Al has been investigated in the reduction of alkyl terminal epoxides.[51] The regiochemistry depends on the experimental conditions giving exclusive primary alcohols by using *i*-Bu_3Al and a donor solvent such as THF.

Primary alcohols were obtained from aryl terminal epoxides using *i*-Bu_3Al with and without a donor solvent. Silyl-substituted epoxides showed a reversal of behavior, because different species and reduction mechanisms are involved in the reaction with *i*-Bu_3Al.

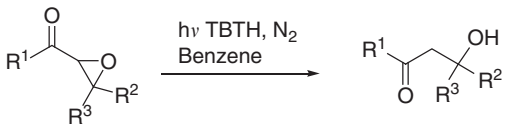
Dialkyl-alkoxyalanes are useful for the reduction of functionalized epoxides bearing groups sensitive to reduction: for example, methylenecycloalkane oxides are reduced by four substituted *i*-Bu_2AlOAr, giving the less substituted alcohols with good selectivity (equation 19).[47]



(19)

8.29.2.4 Tin Hydride Reduction

α,β-Epoxy ketones can be selectively reduced with Bu_3SnH (tributyltin hydride (TBTH)) to the corresponding aldols.[76] The photoreaction is particularly useful for aroyl epoxides, and the generation of a catalytic amount of $Bu_3Sn^{\bullet}$ is enough to initiate the reaction, allowing the use of this reaction for the reductive ring opening of substrates that undergo other photochemical reactions (equation 20). Epoxy esters and epoxyalcohols react with TBTH at the carbonyl group; the epoxides lacking this functional group can be reduced in the presence of azobisisobutyronitrile, under thermal conditions. Selective photoreduction of epoxy ketones to hydroxy ketones can be performed with TBTH.



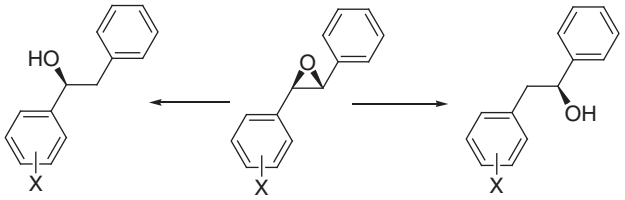
(20)

Bu_3SnH together with Mg or Li iodides has been used in the chemoselective preparation of 2-alkanols from tosyloxy-2,3-epoxyalkanes; the reduction proceeds through the formation of diiodohydrin intermediates. This reaction was found useful in the synthesis of aliphatic alcohols and natural pheromones.[77]

8.29.2.5 Titanium Reagents

Cp_2TiCl_2 reacts with epoxides by C–O homolysis, with a regiochemistry depending on the relative stability of radicals formed in the ring-opening step. The radical species so formed are scavenged by a second Ti radical to generate intermediates that need a proton source to afford the reduction products. The H sources are typically 1,4-cyclohexadiene (1,4-CHD), *t*-BuSH, and so on. The lack of similar H^+ donor gives the oxido-titanium organometallic intermediates that undergo elimination to olefins. Ti-ligands control the regio- and stereochemical outcome of the reaction. Titanocene(III) chloride has been claimed to be one of the best reagents for reductive epoxide ring opening with opposite regiochemistry with respect to S_N2-type metal-hydride-mediated reductions.[78] In fact, in the case of alkyl epoxides, high regioselectivity leading to the less substituted alcohol has been reported. [79]

The regioselective reductive ring opening of nonsymmetrical substituted 2,3-diaryloxiranes has been chosen as a reaction model with the aim of finding a general and efficient method of the regioselective ring opening of epoxides (equation 21). The reduction products of this reaction (diarylethanols) are interesting because they can be envisaged as chiral auxiliaries or ligands in asymmetric synthesis, due to the presence of a coordinating heteroatom on the aryl ring.[80]

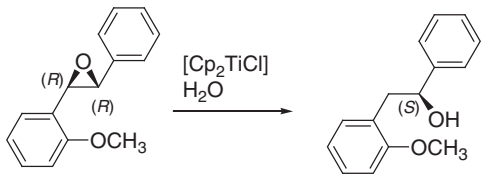


X = N, O, S

(21)

Arylphenylepoxides have been reduced with $[Cp_2TiCl]/H_2O$, with good regiolectivity, which depends on the electronic properties of the aryl groups: in the presence of an EDG, the 2-aryl-1-PEA is the major product, whereas the regioisomer 1-aryl-2-PEA is preferred in the presence of an EWG.

Application of this method to the reduction of enantiopure epoxides resulted in no loss of optical purity in the corresponding products (equation 22).

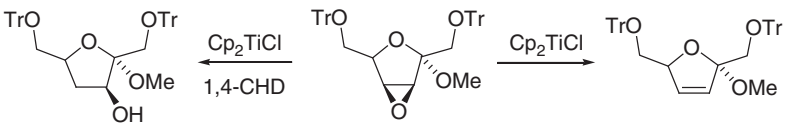


(*R*,*R*) 99% *ee* (*S*) 72%, 99% *ee*

(22)

Alcohols can be prepared from epoxides by ring opening with titanium(III) complex (Cp_2TiCl) in the presence of 1,4-CHD, a common hydrogen atom donor.[81]

These mild reaction conditions yield less substituted alcohols (6–95%): deoxygenation side reaction generally occurs with monosubstituted epoxide. However, interesting chiral synthons can be prepared such as the reductive ring-opening products of methyl furanoside, that yield the corresponding olefinic product or the 4-deoxy derivative, depending on the reaction conditions (equation 23).



(23)

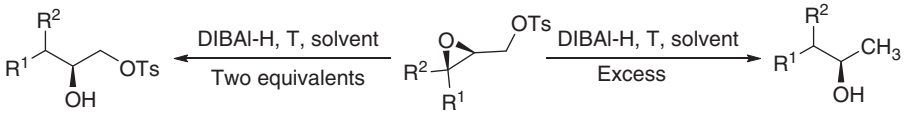
Addition of *trans*- or *cis*-5-decene oxide to (Cp_2TiCl) afforded an identical mixture 73:27 of *cis*- and *trans*-5-decene,[82] probably via a carbanion-like intermediate.

Another limitation of this transformation is the toxic, expensive, and foul-smelling nature of the hydrogen atom donor used, such as 1,4-CHD, Bu_3SnH, or *tert*-butyl thiol.

More recently, a significant improvement was made. Water has been used as source of hydrogen atoms;[83] probably, the reaction proceeds through the *in situ* generation of (aqua) titanocene(III) complex as the real hydrogen atom donor.

By this procedure, mono-, di-, and trisubstituted epoxides are always reduced to the less substituted alcohols: the only limitation seems to be the susceptibility of the phenyl-substituted epoxides to cationic ring opening. Only antiMarkovnikov

regiochemistry was observed, thus this synthetic methodology can be considered a successful alternative to the hydroboration/oxidation reaction. Moreover, β-deuterated alcohols have been obtained by this efficient methodology, by using D_2O as a deuterium atom source (72% yield and 76% deuterium incorporation). It is noteworthy that the reduction reaction can also be carried out with the use of only substoichiometric amounts of the titanocene(III) complex, thus opening the way for possible industrial applications. In this case, a titanocene(III) regenerating agent is required (Scheme 4).[84]



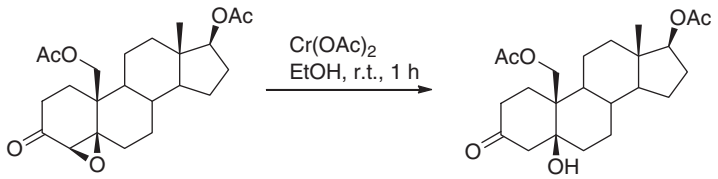
Scheme 4

8.29.2.6 Low-Valent Metal Ions

Low-valent metal ions such as Cr(II), V(II), Sm(II), and so on could be used for the reduction of epoxides under mild reaction conditions. $CrCl_2$ and $Cr(OAc)_2$ salts combined with $[Cr(en)_2]^{2+}$ complex were used to reach the required reactivity and selectivity.[85]

8.29.2.6.1 Chromium(II) reagents

Low-valent chromium(II), such as chromium(II) acetate, was used in the reduction of a steroid epoxy ketone to the corresponding hydroxy ketone (equation 24).[82]



(24)

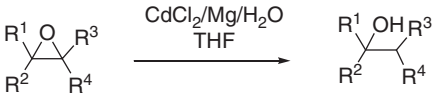
The reductive ring opening of stilbene oxide failed even when an excess of $Cr(OAc)_2$ was applied. Modification of the coordination sphere of Cr(II) ion by adding ethylenediaminetetraacetate ligand makes the reductive ring opening possible. The formation of 1,2-diphenyl-ethan-1-ol was obtained by varying the reactivity of Cr(II) ion by generating $[Cr(edta)]^{2-}$ complex in aqueous, neutral medium.[86]

8.29.2.6.2 Samarium(II) reagents

SmI_2 reduces selectively epoxy esters and epoxy ketones to the corresponding alcohols even in the presence of cyano, carbonyl, and alkoxy-functional groups (Table 8),[87] as in the reduction of spiro-epoxides to the corresponding hydroxy intermediates in the synthesis of mitomycin analogs.[88]

8.29.2.6.3 Cadmium(II) reagents

Combining Mg with $CdCl_2$ in a protic solvent gives rise to a useful reducing agent for the regioselective synthesis of tertiary alcohols (equation 25). The system cadmium chloride/magnesium/THF/water efficiently reduces aliphatic epoxides to the corresponding alcohols.[89]

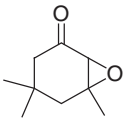
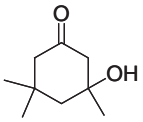
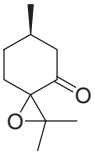
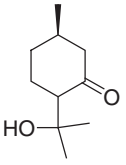
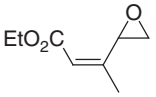
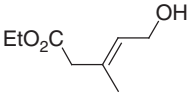
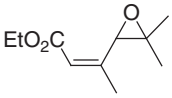
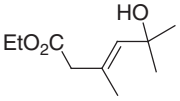
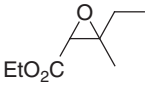
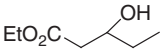
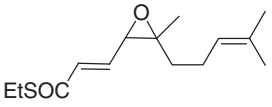
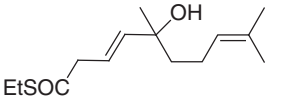
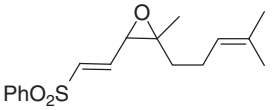
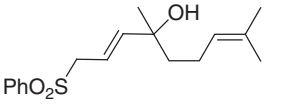
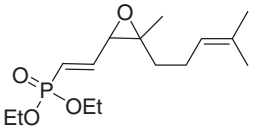
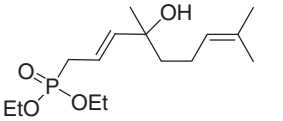


(25)

8.29.2.6.4 Scandium(III) reagents

A chiral scandium–bipyridine complex catalyzes the highly enantioselective addition of phenylselenol to aromatic meso-epoxides and furnishes 1,2-seleno alcohols in good yields and up to 94% *ee*. In addition, a sequential, one-pot epoxide opening–reduction protocol has been developed for the direct synthesis of 1,2-diaryl carbinols (Table 9).[90] Aliphatic meso-epoxides are not suitable substrates for this method of reduction because of the low enantioselectivity. The carbinol deselenization begins with the partial hydrogen abstraction at the benzylic carbinol center under the radical conditions, leading to partial racemization. Notably, this one-pot sequence constitutes an elegant alternative to the currently difficult enantioselective hydride addition to meso-epoxides.[91]

Table 8 Reduction of epoxy ketones, esters, and vinyl epoxides with SmI_2

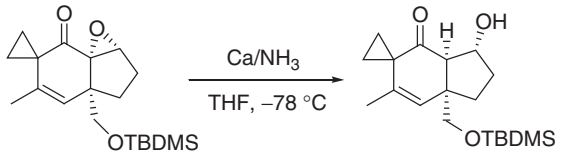
Epoxide	*Yield (%)*	*Product*
	82	
	79	
	77	
	72	
	68	
	80	
	82	
	84	

8.29.2.7 Dissolving Metals

Dissolving metals such as sodium[92] and lithium[93] in ammonia or other amines have been used in the past for the oxirane ring opening, achieving selectivity in the presence of functional groups like carbonyls, acetyl, and so on that do not tolerate metal hydride reductive conditions. Iron, aluminum, calcium, and zinc have been also used in the large-scale synthesis of alcohols.

8.29.2.7.1 Calcium

Calcium in liquid ammonia has been used in the ring opening of epoxides, even in the presence of varied functional groups in the molecule.[94] This reducing mixture (Ca/NH_3) was applied to the total synthesis of ptaquilosin, the aglycon of ptaquiloside. In the key step, the reductive ring opening of epoxy intermediate gives the β-hydroxy ketone in 90% yield (equation 26).[95]

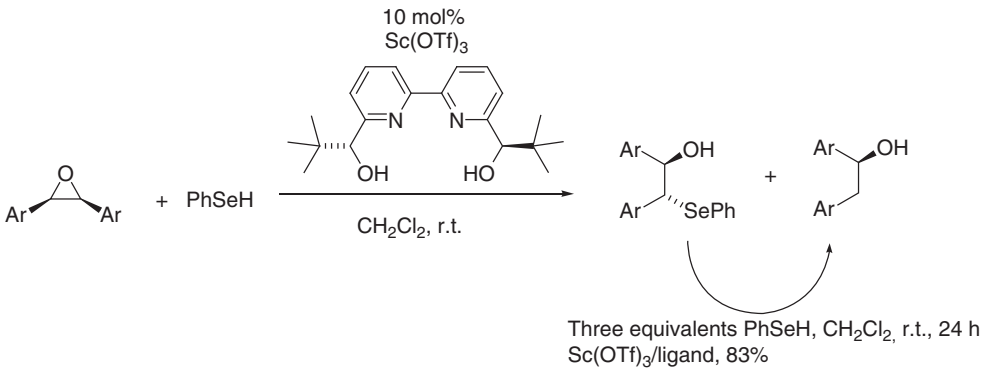


(26)

8.29.2.7.2 Zinc

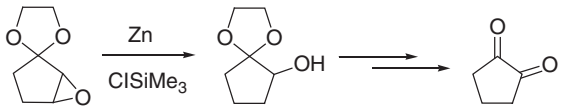
High regioselectivity was observed in the ring-opening reaction of epoxides when carried out in the presence of zinc metal/$ClSiMe_3$, as in the reduction of 2,3-epoxy acetals,[96] which is the key step in the synthesis of 1,2 diones (equation 27).[97]

Table 9 Scandium–bipyridine-catalyzed selenol addition to aromatic meso-epoxides



Ar	Ar(OH)CH(Ar)SePh *Yield* (% ee)	Ar(OH)CH(Ar)H *Yield* (% ee)
Ph	7 (94)	63 (90)
4-F–C_6H_4	6 (n.d.)	60 (75)
4-Cl–C_6H_4	10 (89)	64 (87)
4-Br–C_6H_4	12 (92)	64 (92)
3-Me	<5 (94)	64 (92)

Reaction with reagent-grade solvent under daylight, 2 equivalents PhSeH added at the start of the reaction followed by another 2 equivalents after 24 h.
Abbreviation: n.d., not determined.

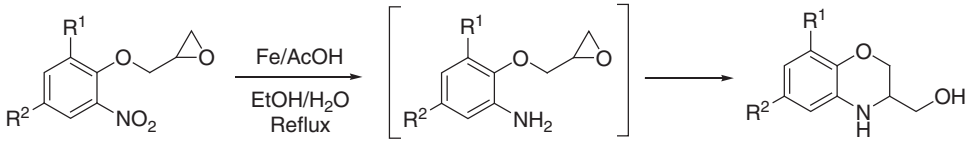


(27)

Dialkylzinc hydride 'ate-complexes,' generated *in situ* from dialkylzinc and metal hydride (LiH or NaH and Me_2Zn) reduce monosubstituted epoxides, showing reactivity different from metals. NaH–Me_2Zn 'ate' complex reacts with styrene oxide to give 1-phenethyl alcohol in 92% yield with high regioselectivity.[98]

8.29.2.7.3 Iron

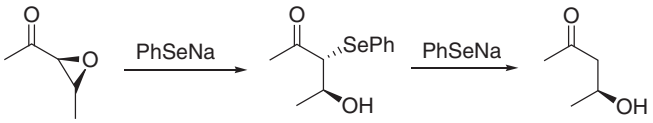
The reduction of oxirane can be performed in the presence of iron. The ring-opening reaction promoted by iron has been recently applied to the one-pot regioselective synthesis of 2,3-dihydro-3-hydroxymethyl-1,4-benzoxazines, isolated in good yields and as single regioisomers (equation 28).[99]



(28)

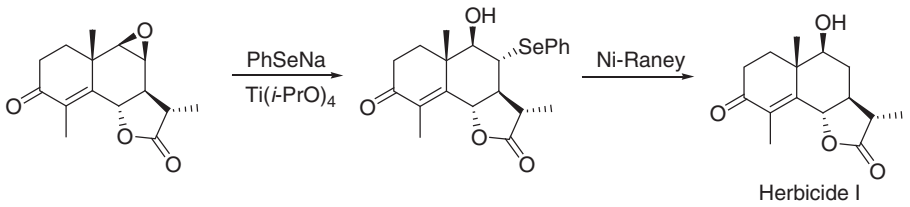
8.29.2.8 Phenylselenolate

α,β-Epoxy ketones can be catalytically reduced by benzeneselenolate to afford β-hydroxy ketones in good yields and in a stereospecific way. As for the mechanism, the epoxy ring is attacked by the selenolate at the carbon α to the CO group, generating an α-selenyl-β-hydroxyketone intermediate that reacts with a second benzene selenolate to give the corresponding β-hydroxy ketone (aldol). The catalytic reaction proceeds through the generation of the benzeneselenolate *in situ* in continuous, favored by the presence of *N*-acetylcysteine sodium salt that reacts with the diselenide in aqueous medium under mild reaction conditions (equation 29).[100]



(29)

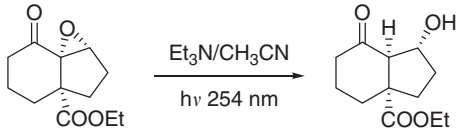
Sodium benezeneselenolate was also efficiently used in the synthesis of herbicide I from artemisin (equation 30), in a synthetic plan involving, as the key step, the formation of a hydroxyselenide in high yields from the corresponding epoxide, followed by final reduction to the corresponding alcohol with Ni-Raney.[101]



(30)

8.29.2.9 Reductive Opening of Epoxides by Photoreductions

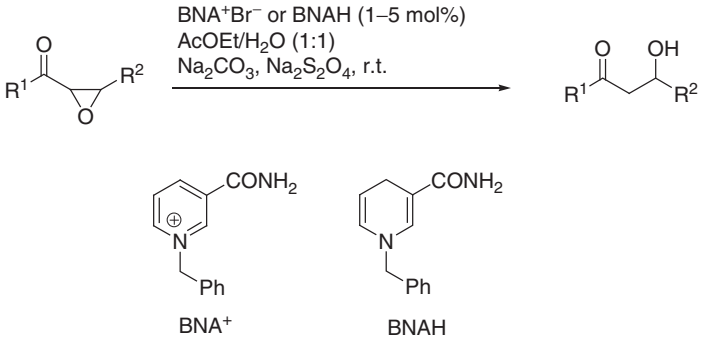
The reductive opening of the epoxide ring has also been performed photochemically. At 254 nm the following epoxy ketone, in the presence of triethylamine, is reduced to a β-hydroxy ketone (aldol), even in the presence of other functional groups.[102] The reaction conditions are mild, and were used in the formal synthesis of racemic and optically active ptaquilosin, the aglycon of the antitumor agent ptaquiloside (equation 31).[103]



(31)

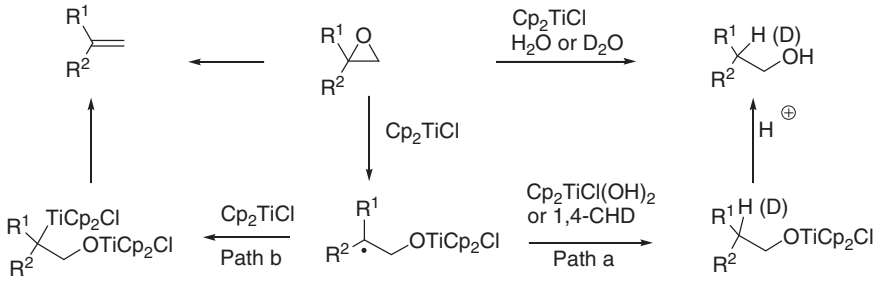
8.29.2.10 Reduction of α,β-Epoxy Ketones with NADH Model Compound

An efficient catalytic version for hydrogenation of α,β-epoxy ketones to form β-hydroxy ketones has been developed as the first example of catalytic hydrogenation mediated by 1-benzyl-1,4-dihydronicotinamide (BNAH), a common model of the NAD^+/nicotinamide adenine dinucleotide (NADH) coenzyme (equation 32).[104]



(32)

A catalytic amount of BNA^+Br^- or BNAH mediates the hydrogenation of α,β-epoxy ketones to form β-hydroxy ketones in excellent yields. A mixed organic/water solvent is necessary for the reaction because of the presence of both neutral aromatic and ionic species. A radical regioselective ring-opening mechanism was proposed, since the rate was accelerated by irradiation, and because the presence of O_2 (a radical trap) suppresses the reaction (**Scheme 5**). Complete conversion and high yields (90–94%) were obtained in all cases in which R^1 was an aromatic ring, whereas lower yields were obtained when R^1 was a methyl group.

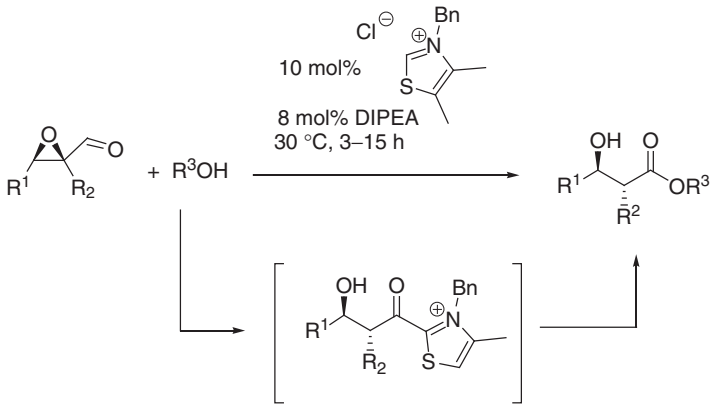


Scheme 5

8.29.2.11 Reduction of α,β-Epoxy Aldehydes with Thiazolium Chloride

β-Hydroxy esters, synthetically valuable building blocks for the construction of natural products and pharmaceuticals, have been prepared from α,β-epoxy aldehydes in high yields (79–89%) by using a waste-free catalytic method (Table 10). The key step resides in the generation of an acyl thiazolium species that reacts diasteroselectively with the substrate in good yields, with the formation of the antihydroxy ester as the major product. The epoxy group acts as a reducible functionality for the catalyst-induced intramolecular redox reaction, but reactions quenched at 50% in the presence of CD_3OD reveal no deuterium incorporation in the recovered epoxyaldehyde, thus suggesting either a concerted process or a rate-determining deprotonation step.[105]

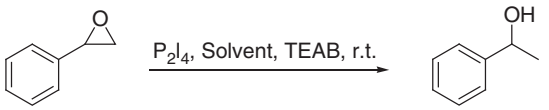
Table 10 Synthesis of β-hydroxy esters from epoxyaldehydes



R^1	R^2	R^3	Yield (%)	dr
Ph	Me	Bn	89	>10:1
Ph	Me	Pr^i	79	>10:1
Ph	H	Et	84	
Cyclohexyl	Me	Et	82	7:1

8.29.2.12 Phosphorus Reagents

Epoxides are converted regioselectively to the more substituted alcohols under safe reaction conditions at room temperature by using catalytic amount of diphosphorus tetraiodide (P_2I_4) as a reducing agent in combination with tetraethylammonium bromide (TEAB) (equation 33).[106]



(33)

There is no reaction in the absence of TEAB or with different alkylammonium salts. Traces of moisture are required, since the use of dry solvents was not effective: dichloromethane was the most suitable solvent for the conversion with diphosphorus tetraiodide (P_2I_4). Different aromatic and cycloaliphatic epoxides were converted into the corresponding alcohols in good yields

and in the presence of a variety of functional groups. Stereoselective reductive cleavage of epoxides to the corresponding optically active alcohols proceeds with retention of configuration.

8.29.3 Deoxygenation of Epoxides

Deoxygenation of epoxides to alkenes is an important process, particularly in the synthesis of complex molecules (*see* Chapter 6.18.[107] A number of reagents for this transformation have been developed. Deoxygenations of epoxides can be conducted using various metallic reductants,[108] silanes,[109] or phosphines,[110] under varied reaction conditions that require the use of a homogeneous or heterogeneous medium. The development of highly efficient and environmentally benign catalysts to be used in the deoxygenation of epoxides is still a challenging issue.

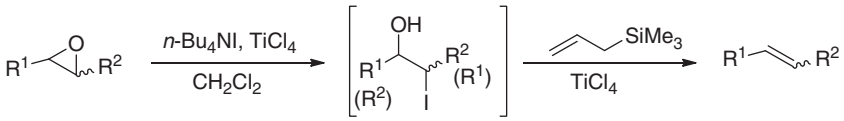
In this section, various kinds of reagents capable of one-step deoxygenation of epoxides to alkenes will be described. Deoxygenation to give a saturated carbon–carbon bond will not be included, because the process is synthetically less important.

8.29.3.1 Silicon Reagents

The deoxygenation reaction of epoxides in the presence of silyl anion metals such as trimethylsilylpotassium (TMSK)[111] and $PhMe_2SiLi$,[112] proceeds with inversion of geometry. Although the exact mechanism of the reaction with TMSK is not known, backside attack of TMSK on the *cis* (and *trans*)-epoxides generates the threo- (and erythro) *β*-alkoxysilanes. *Syn* elimination provides the olefin with inverted stereochemistry. A similar reaction mechanism has been invoked in the case of $PhMe_2SiLi$.

The stereospecific conversion of epoxides into alkenes on treatment with tetrabutylammonium iodide and allyltrimethylsilane in the presence of titanium tetrachloride proceeds with retention of geometry.[113] The overall retention of configuration can be explained by assuming a S_N2 opening of epoxide by iodide, followed by the antielimination of the iodo–hydrin intermediate (Table 11).

Table 11 One-pot conversion of epoxides into alkenes



R^1	R^2	*Epoxide* cis/trans	*Yield (%)*	*Alkene Z/E*
n-C_5H_{11}	n-C_5H_{11}	<1/99	78	<1/99
n-C_5H_{11}	n-C_5H_{11}	92/8	62	89/11
n-C_5H_{11}	$(CH_2)_3OCOCH_3$	87/13	63	85/15
n-C_5H_{11}	$(CH_2)_8OH$	93/7	83	92/8
H	n-$C_{10}H_{21}$	–	36	–

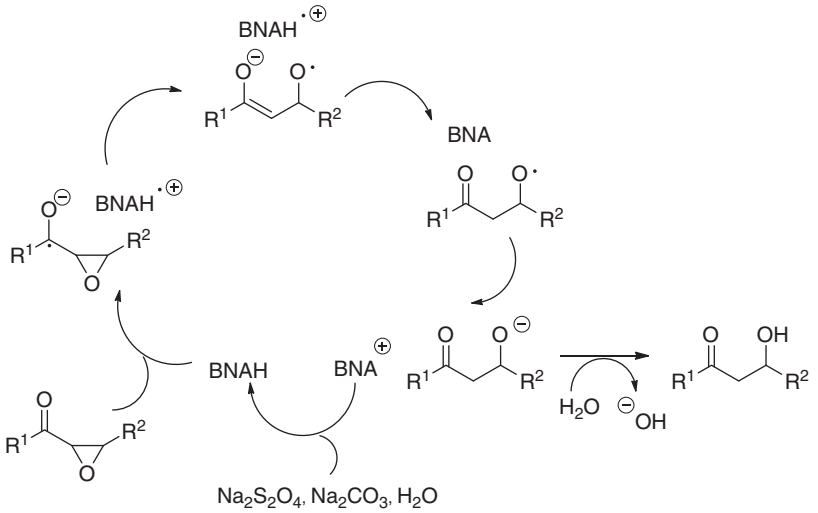
8.29.3.2 Phosphorus Reagents

It is well known that Ph_3P reacts with epoxides inducing the deoxygenation with inversion of the stereochemistry, through the *anti* addition to the oxirane, followed by the *syn* elimination of Ph_3PO from a betaine intermediate.[114] Ph_2PLi efficiently induces deoxygenation, with product ratios depending on the steric properties of the epoxide.[115] Diphosphorus tetraiodide, Ph_3PI, and Ph_3PI_2 react with retention of configuration, through two antistereospecific steps, in mild reaction conditions that tolerate well the presence of other functional groups.[116] Diphosphorus tetraiodide and phosphorus triiodide were found to react with vinylcyclopropane epoxides in nonpolar solvents to produce vinylcyclopropanes cleanly, with complete stereocontrol and high overall yields.[117] Iodine/Ph_3P[118] was also used in the reductive deoxygenation of natural pentacyclic triterpenoids, affording the double bond between C_2 and C_3 of the A ring (Scheme 6).

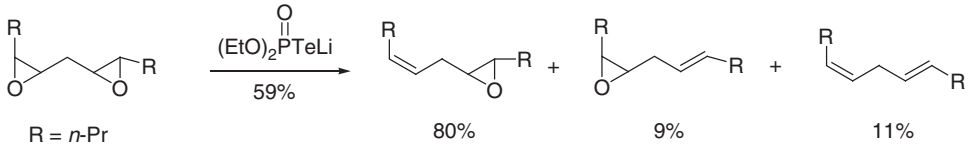
8.29.3.3 Tellurium and Selenium Reagents

8.29.3.3.1 Tellurium reagents

Epoxides are deoxygenated to olefins by alkali metal *O*,*O*-diethyl phosphorotelluronate below room temperature under acidic conditions. Terminal epoxides are converted to alkenes very quickly, and acyclic *cis*-epoxides are reduced more easily than *trans*-epoxides, whereas among cyclic derivatives cyclohexane oxides react faster than cyclopentane oxides (equation 34).[119]

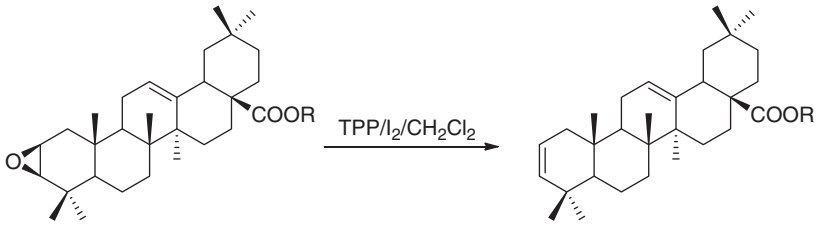


Scheme 6



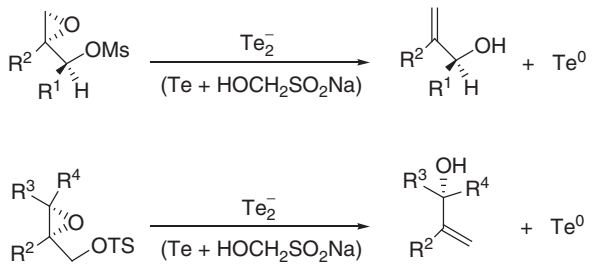
(34)

An initial nucleophilic stage is consistent with the enhanced reactivity of terminal epoxides over other types, and the greater facility of deoxygenating *Z* epoxides, as compared with the *E* isomers. Formation of a cyclic intermediate accounts for the slowness of reaction involving cyclopentane oxides because for this compounds such an intermediate is geometrically unfavorable (Scheme 7).



Scheme 7

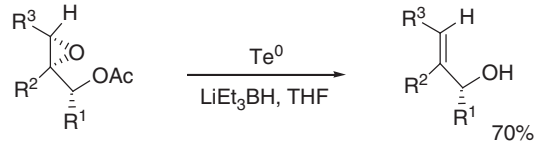
Tellurium was used in the reduction of glycidyl derivatives as telluride, Te^{2-}, obtained by reduction of elemental Te by $HOCH_2SO_2Na$, $LiEt_3BH$, or $NaBH_4$. The reaction of Te^{2-} occurs at C-3 of unsubstituted glycidyl tosylates or mesylates, whereas reduction at C-1 was observed in the case of substituted oxiranes.[120] Elemental Te precipitated during the course of the reaction and could be recovered and reused (equation 35).



(35)

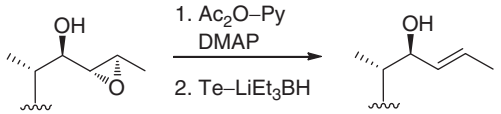
Changing the leaving group to a relatively poor one, such as acetate, favors C-3 attack with $LiEt_3BH$ the reaction proceeds smoothly and in high yields: allylic alcohols are formed from monosubstituted and disubstituted substrates, with deacetylation of acetate group and chirality preservation at C_1 (Table 12).[121]

Table 12 Deoxygenation of epoxides with $Te^0/LiEt_3BH$



R^1	R^2	R^3
Ph	H	H
H	Me	H
H	H	*n*-Pr
n-Bu	Me	H
C_6H_{11}	H	Me

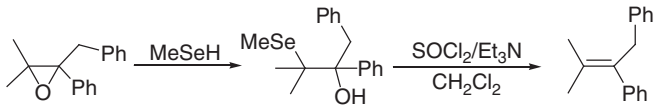
In the synthesis of brassinosteroids, the deoxygenation reaction with tellurium and lithium triethylborohydride have been reported for the synthesis of an allylic alcohol intermediate, obtained in 75% yield through the conversion to the corresponding epoxy acetate (equation 36).[122]



(36)

8.29.3.3.2 Selenium reagents

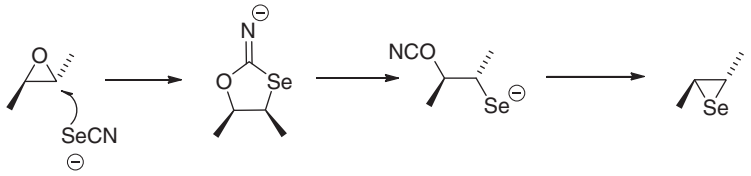
Substituted oxiranes were deoxygenated by reaction with MeSeH followed by further treatment of the hydroxy selenide intermediates with thionyl chloride/triethylamine for the final conversion into the corresponding tri- or tetrasubstituted alkenes (equation 37).[123]



(37)

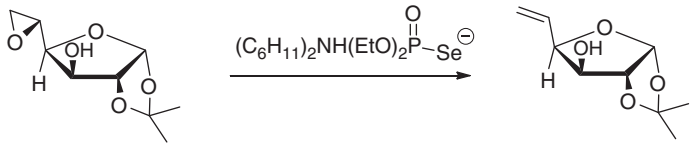
Ph_3PSe, KSeCN, and 3-methyl-2-selenoxobenzothiazole[124] are commonly used in the one-step deoxygenation of oxiranes. An alkaline medium is necessary in the reaction with Ph_3PSe, and the geometry of the product is always retained,[125] since the reactions proceed via an episelenide intermediate, followed by selenium extrusion.

Stereospecific conversion of epoxides into olefins was also carried out under slightly alkaline conditions by KSeCN. Epoxy groups in straight-chain compounds undergo two '*anti*' reaction steps: $SeCN^-$ nucleophilic addition and the '*anti*' selenide attack to the cyclic intermediate that affords the episelenide intermediate. Epoxy derivatives of cyclic compounds show a remarkable variation in reactivity (equation 38).[126]



(38)

O,O-Dialkyl phosphoroselenoate was used in the deoxygenation of carbohydrate epoxy derivatives (equation 39).[127]



(39)

Thionocarbonates,[128] episulfides,[129] and episelenides[130] have been used to convert epoxides to olefins.

8.29.3.4 Transition Metal Reagents

Transition metals such as Ti, Zr, Mo, Nb, V, Sm, W, Au, and Ag have been widely used to deoxygenate epoxides to alkenes, through the formation of radicals or metallaoxetane intermediates. Chromous salts[131] such as $CrCl_2$[132] convert epoxides to olefins in one step, but yields are usually low or moderate and stereochemistry is largely or completely lost.

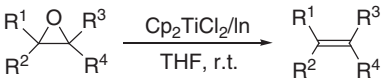
8.29.3.4.1 Titanium reagents

Low-valent titanium combines high reducing ability with a pronounced oxophilicity. A mixture of titanium powder and chlorosilane has been used for the deoxygenation of epoxides. (*E*)-Stilbene was obtained in high yields starting from *trans*- or *cis*-stilbene oxides, probably because a nonsynchronous cleavage of the C–O bonds, since (*Z*)/(*E*)-stilbene isomerization does not occur under the same reaction conditions.[133]

Titanocene dichloride, employed in combination with magnesium as a reductant, can efficiently convert trisubstituted epoxides to alkenes: *trans*-epoxides are deoxygenated to the corresponding *trans*-alkenes with high stereoselectivity, whereas *cis*-alkenes formed from *cis*-epoxides with little lower selectivity. Carbonyls, acetals, ethers, and alkenes are well tolerated under these reaction conditions.[134]

Cp_2TiCl_2/Mg was efficiently applied also to the deoxygenation of unprotected epothilone A to give epothilone C in 80% yield as a single geometrical isomer.[135]

The reactions of Cp_2TiCl_2/In (2:1) system[136] with various epoxides have been investigated: it was found that epoxides can be rapidly deoxygenated in less than 10 min to give the corresponding olefins in good-to-excellent yields in THF. Under these mild conditions carbonyl functions, ether, ester, vinyl, and bromo groups are well tolerated. α,β-Epoxy ketones and aromatic epoxides gave an excellent yield of deoxygenated products, and stereochemistry was preserved in the deoxygenation of (*E*)-stilbene oxides. The low-valent titanium(III) complex was readily generated by the *in situ* reduction of bis(cyclopentadienyl)titanium(IV) dichloride with powdered indium for 30 min at reflux; epoxides could not be deoxygenated by Cp_2TiCl_2 or indium alone (equation 40).

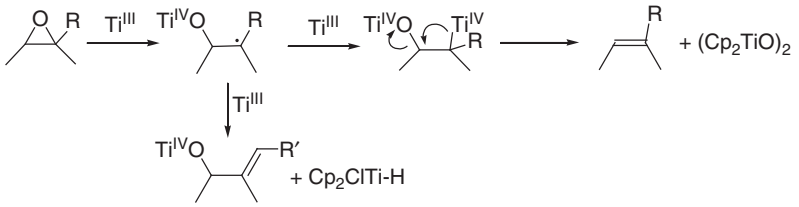


(40)

Cp_2TiCl reacts with epoxides by C–O homolysis, with a regiochemistry depending on the relative stability of radicals formed in the ring-opening step. In the absence of radical acceptors or proton sources, the radical species so formed are scavenged by a second Ti radical, thus giving an oxido-titanium organometallic intermediate that undergoes elimination to olefins.[77]

Titanocene(III)/water mixtures have also been used[137] in the deoxygenation of monosubstituted epoxides under mild reaction conditions.

In general, monosubstituted epoxides always lead to deoxygenated compounds, whereas more complex behavior has been found in the deoxygenation of disubstituted epoxides. Trisubstituted epoxides, under anhydrous conditions, give allylic alcohols through the elimination of a hydrogen atom instead of deoxygenation, due to the incipient sterically hindered tertiary radical (equation 41).[138]

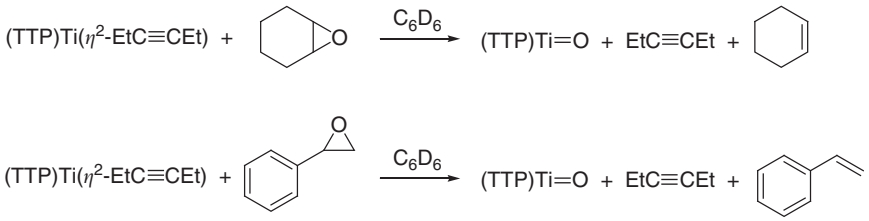


(41)

Styrene oxide gave only a 6% yield of the corresponding deoxygenated product, due to the formation of a very stable benzylic radical, which may go on to generate dimerization products[139]; this constitutes the main limitation of this deoxygenation method. The reaction of a series of 2,3-epoxy alcohols and the corresponding formates, acetates, and benzoates promoted by Cp_2TiCl has been studied.[140] Ti(II) porphyrin complex has been also employed for the deoxygenation of epoxides and sulfoxides.[141]

A mild and efficient method for the deoxygenation of α,β-epoxyketones to enones with Cp_2TiCl_2 and Zn has been reported to occur in high yields, but with loss of stereochemical control in the products.[142]

Ti(II) tetratolylporphyrinato (TTP) complexes function as good oxygen atom acceptors in electron-transfer reactions. Oxygen atom transfer occurs when the Ti(II) porphyrins are treated with a variety of epoxides, resulting in two-electron redox products: (TTP)Ti$=$O, alkene, and EtC$\equiv$CEt or THF. The reaction of (TTP)Ti(η^2-EtC$\equiv$CEt) with styrene oxide was quantitative after 9 h at ambient temperature, yielding styrene and (TTP)-Ti$=$O. In contrast, the reaction between (TTP)Ti(η^2-EtC$\equiv$CEt) and cyclohexene oxide required higher temperature and was incomplete even after 6 days (equation 42).

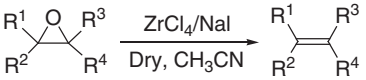


(42)

With an electron-withdrawing phenyl group, styrene oxide is more susceptible to reduction than is cyclohexene oxide, in which the α-carbon substituents are methylenes.

8.29.3.4.2 Zirconium reagents

Deoxygenation of a variety of epoxides in short reaction times was found by using safe and inexpensive $ZrCl_4$/NaI in anhydrous CH_3CN. The method was efficient and highly chemoselective and proceeded with retention of relative stereochemistry of the epoxides.[143] Epoxides, carrying alkyl, aryl, ether, carbonyl, ester, and hydroxy groups α or β to the oxirane ring, can be converted in excellent yields (equation 43).



(43)

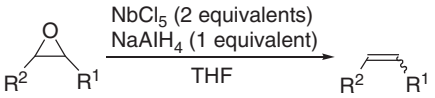
8.29.3.4.3 Vanadium reagents

Among transition metals, vanadium(II)–THF complex was used to deoxygenate epoxides to alkenes. The reductant $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ was obtained by mixing $VCl_3(THF)_3$ and Zn: the *cis*-configuration of starting epoxides was not retained, although this method is compatible with esters, ethers, enoates, acetals, enones, and enoate functional groups, and it was applied also to the synthesis of carbohydrate derivatives.[144] Oxirane deoxygenation was reported also with low-valent β-diketonate V(II) complexes, with the stereoselectivity depending on the substituent present on oxirane ring.[145]

8.29.3.4.4 Niobium reagents

Low-valent Nb complexes have been used in the deoxygenation of epoxides. However, high temperatures and 2 equivalents of niobium reagent must be used: the corresponding olefins formed with low stereoselectivity (**Table 13**).[146]

Table 13 Deoxygenation of epoxides using $NbCl_5/NaAlH_4$



Substrate	*Temperature (°C)*	*Time (h)*	*Yield (%)*	E/Z
E-Cyclododecene oxide	80	1	53	87/13
Z-Cyclododecene oxide	80	1	50	71/29
E-Stilbene oxide	25	1	75	*E* only
E-Dodecene oxide	80	15	50	–

A mild and operationally simple deoxygenation of epoxides has been developed by using a substoichiometric amount of low-valent niobium complexes generated *in situ* from commercially available $NbCl_5$ and zinc dust.[147] The deoxygenation proceeds through a single electron transfer (SET) from zinc metal to the niobium–substrate complex, due to the highly oxophilic nature of the niobium species. The presence of adjacent radical stabilizing groups is beneficial to epoxide substrates. By studying the deoxygenation reaction of styrene oxide with Nb in the presence of various metals, it was concluded that the best reactivity is achieved working in the presence of indium and zinc metals, whereas no deoxygenation was observed with Zn in the absence of $NbCl_5$. Substoichiometric amounts of Nb can be used with respect to Zn, but longer reaction times are needed; the solvent has also an important effect on the deoxygenation, since low yields and rates were observed in the presence of noncoordinating solvents. The use of methanol gave good conversion accompanied by the MeOH ring-opening adduct. The best results were obtained when mixture of THF and noncoordinating solvent were used in equal amounts. Generally, the deoxygenation of alkyl

epoxides was significantly slower than that of aryl epoxides, because of the preferential radical formation at the carbon adjacent to phenyl group. Deoxygenation of trisubstituted alkyl epoxides takes place with low yields. Different reduction products have been observed in the presence of hydroxy functionalities and unsaturated ketones, whereas good yields were obtained with epoxy esters and amides. *cis*-Stilbene oxide was deoxygenated with a higher rate and yield than the *trans*-isomer, although it gives rise only to *trans*-stilbene product.

8.29.3.4.5 Thallium reagents

$(t\mathrm{Bu_3SiO})_3\mathrm{Ta}$ reacts with various functional groups; among these, epoxides have been cleanly deoxygenated to give the corresponding olefin and $(t\mathrm{Bu_3SiO})_3\mathrm{Ta{=}O}$: probably a concerted process[148] occurs in the reaction, on the basis of the stereospecific (>95%) O-atom removal from *cis*- and *trans*-decene oxide and since no intermediates were detected, even at −78 °C.[149]

8.29.3.4.6 Molybdenum reagents

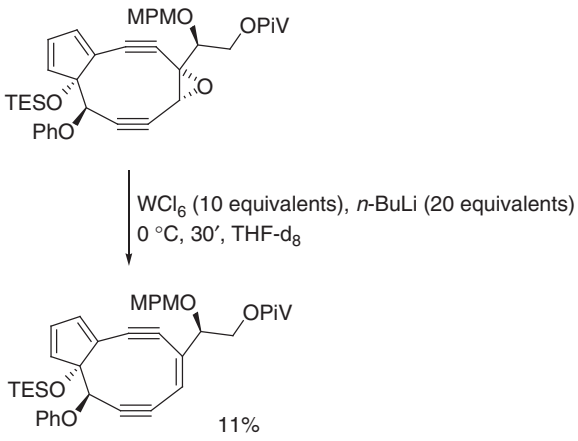
Oxirane deoxygenation with molybdenum (VI) *oxo* complex $\mathrm{MoO(S_2CNEt_2)_2}$ was found to proceed with retention of configuration (*cis*-2-butene oxide is converted to *cis*-2-butene in 83% yield).[150] Stereoselectivity depends on the substituent present on oxirane ring when low-valent β-diketonate Mo-complexes are used.

Among metal carbonyls, the deoxygenation of α,β-epoxy ketones and α,β-epoxy esters can be performed in the presence of $\mathrm{Mo(CO)_6}$ in benzene or toluene under mild conditions: the presence of functional groups such as ketones, esters, and olefins is tolerated. The reaction displays *E* stereoselectivity, since mixtures of *trans*- and *cis*-ethyl α,β-epoxy-β-phenylpropionate give only *trans*-ethyl cinnamate after reaction with $\mathrm{Mo(CO)_6}$.[151]

8.29.3.4.7 Tungsten reagents

$\mathrm{WCl_6}$/*n*-BuLi[152] was efficiently used in a one-step method to deoxygenate di- or trisubstituted epoxides to olefins in high yield and with high retention of stereochemistry, also in the presence of other functional groups such as ethers and esters. Cyclododecene (*trans*/*cis*: 92/8) was obtained from *trans*-cyclododecene oxide by using low-valent tungsten ($\mathrm{WCl_6}$/*n*-BuLi): the W/epoxide ratio is important for the yield of the alkene. The best condition was found using a ratio of 2:1, whereas lower amount of W caused an incomplete reaction, and ratios greater than 3:1 did not improve the yield of the alkene, that in some cases actually diminished.[153]

The Sharpless reagent was recently used to perform the epoxide deoxygenation in the preparation of bicyclo[7.3.0]dodecatrienediyne core of C-1027 (an important antitumoral chromophore)[154] and in the study of formation of Oleandiene intermediate, in the reductive deoxygenation of natural pentacyclic triterpenoids, affording the C_2–C_3 double bond in the A ring, although in very low yield (8%).[155] Stereospecific deoxygenation using the kinetic Sharpless conditions with $\mathrm{WCl_6}$/*n*-BuLi was observed also in the key step of *trans*-olefin formation in the total synthesis of (–)-Kendomycin,[156] and in the stereoselective synthesis of epothilone D in 78% yield from epothilone B.[144] Sharpless conditions were also useful in the synthesis of (+)-Orientalol F (equation 44).[157]



(44)

The deoxygenation of epoxides using tungsten(II) complexes such as $\mathrm{WCl_2(PMePh_2)_4}$ and $\mathrm{WCl_2(CH_2{=}CH_2)_2(PMePh_2)}$ takes place with predominant retention of configuration, the more substituted oxiranes being less reactive than the monosubstituted ones. In the case of styrene oxide derivatives, the reactivity increased with conjugating or EDGs. The mechanism was not well clarified: the observed stereoselectivity and electronic effects seem to be in accordance with a deoxygenation proceeding via a concerted oxygen abstraction and not through an oxametallacyclobutane intermediate.[138]

8.29.3.4.8 Rhenium reagents

High-valent rhenium plays a fundamental role in processes dealing with O-atom transfer. Some organometallic *oxo*-rhenium complexes have been reported to catalyze the deoxygenation of epoxides to alkenes via *oxo*-transfer to phosphines.[158]

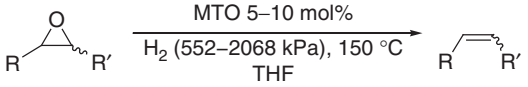
In situ reduction of Cp^*ReO_3 by PPh_3 to form $(Cp^*ReO)_2(\mu\text{-}O)_2$ allows catalytic deoxygenation of epoxides. The catalyst deactivation was studied,[159] since it causes removal of rhenium from the catalytic cycle and loss of activity. Catalytic turnover seems to be dependent on the epoxide electronic properties: the optimum turnover was seen in the case of electron-withdrawing substituted systems.

Catalytic deoxygenation of epoxides was performed by using Re complexes with triphenylphosphine.[160] Triphenylphosphine is known to effect epoxide deoxygenation, however, the uncatalyzed reaction requires higher temperatures and proceeds with inversion of configuration.

Polypyrazolylborates have long been known to act as 'cyclopentadienyl equivalents,' although their steric properties are substantially different from those of Cp-ligands. Transfer of oxygen atoms from epoxides to triphenylphosphine is efficiently catalyzed by hydrido-*tris*-(3,5-dimethylpyrazolyl)borate ReO_3 (Tp'ReO_3) (**Table 14**).[161] Reaction of 1–5 mol% Tp'ReO_3 with epoxide and PPh_3 (1:1 stoichiometry) in benzene leads to high yields of alkene. Ethereal solvents and acetonitrile are also good solvents for the reaction. The epoxide electronic and structural features have a significant impact on the oxygen atom transfer. *cis*-Epoxides react faster than *trans*-epoxides. The reaction is highly stereospecific, giving retention of configuration: the rhenium-catalyzed reaction preserves the stereochemistry of the epoxide in the formation of the C═C bond.[162]

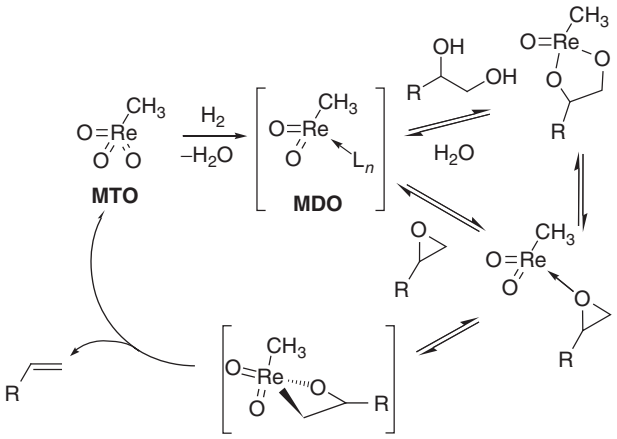
Some functional groups are not tolerated under these reaction conditions: free alcohols impede catalysis because of the formation of unreactive bis-alkoxyrhenium compounds. Also primary amines are precluded, and protection strategies are necessary to circumvent these limitations. Low rates of reaction have been observed in the presence of several functional groups (ketone, ester, and nitrile) that are conceivable competitors for binding to the metal. *trans*-Disubstitution slows the reaction considerably, whereas the deoxygenation of α,β-epoxy-ketone is much faster than other reactants that do not afford conjugated products, since the formation of electron-deficient C═C bonds is in general favored.

Methyltrioxorhenium (MTO) catalyzes the conversion of epoxides and vicinal diols to olefins with hydrogen (H_2) as the reductant, producing only water as reaction byproduct. MTO has the advantage of being water soluble (equation 45).[163]



(45)

With MTO 1-hexene oxide was reduced at 552 kPa in elongated reaction time, but in quantitative conversion to 1-hexene (95%). Styrene oxide was deoxygenated to styrene with very good selectivity and 80% yield; *cis*- and *trans*-stilbene oxide afforded moderate yields of both alkene isomers, signaling a mechanism that involves isomerization of the epoxide: early in the reaction, some styrenediol is formed, and MTO is known to catalyze the ring opening of epoxide to diol. Conceivably, the mechanism proceeds with alkene extrusion from a coordinated epoxide via a metallaoxetane intermediate (equation 46).

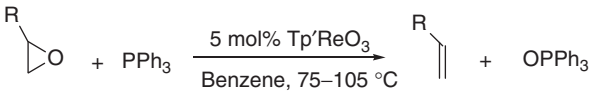


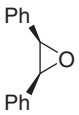
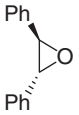
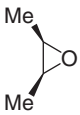
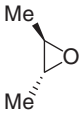
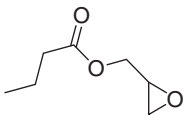
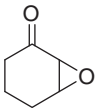
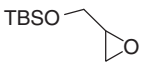
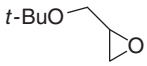
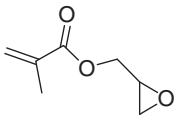
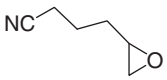
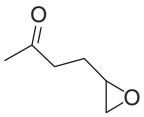
(46)

The deoxygenation of epoxides with MTO has been observed also in the absence of hydrogen, in the MTO-catalyzed oxygen transfer to *trans*-cyclooctene in the presence of H_2O_2, and without PPh_3 as oxygen acceptor. The authors suggested the formation of a monoperoxo intermediate as deoxygenating species under the reaction conditions that catalyzed the conversion of the *trans*-epoxide to the cyclooctenes.[164]

$MeReO_3$ (MTO)/H_2O_2 and PPh_3 as oxygen acceptors were used for the deoxygenation of sidewall functionalization of single-walled carbon nanotubes (SWNTs), and for the quantification of the epoxide content in O-SWNTs. This reaction can be useful as a further purification method of SWNTs. The presence of oxygen functional groups (including epoxides) added to the SWNTs during 'purification' may possibly affect the overall electronic structure of a SWNT. The knowledge of the starting PPh_3 and

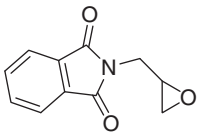
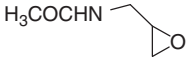
Table 14 Catalytic deoxygenation of epoxides with $Tp'ReO_3$



Epoxide	*% Conversion, 75 °C, 100 h*	*% Conversion, 105 °C, Time (h)*
	>95	
	14	>95 (48)
	82	>95 (48)
	55	>95 (48)
	16	>95 (1104)
	–	– (1317)
	26	>95 (288)
	Trace	39 (1317)
	39	87 (288)
	>95 (25 h)	
	39	>95 (144)
	38	>95 (144)
	30	>95 (288)
	18	>95 (1317)
	–	>95 (1317)

(*Continued*)

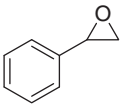
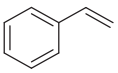
Table 14 Continued

Epoxide	*% Conversion, 75 °C, 100 h*	*% Conversion, 105 °C, Time (h)*
	28	85 (294)
	Trace	

O-SWNT reagents allows the quantitative measure of epoxide content, since the amount of $O{=}PPh_3$ formed is the same as the amount of epoxide removed.[165]

Sulfite was not widely used, although it is an efficient reductant, economical, noncarbon-based mineral resource, and moreover is recyclable and thermodynamically comparable to H_2 and CO as a reductant/oxygen acceptor.[166] The epoxide deoxygenation to alkenes was studied by comparing different sulfite/$MReO_x$ pairs such as Na_2SO_3 and $MeReO_3$, $NaReO_4$, and NH_4ReO_4 (Table 15).

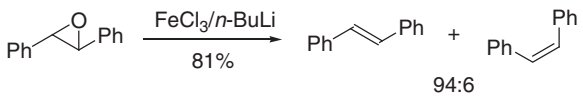
Table 15 Epoxide deoxygenation with Na_2SO_3 and Re catalysts

Substrate	*Catalyst*	*Time (h)*	*Conversion (%)*	*Yield (%)*	*Major product*
	$MeReO_3$	30	75	40	
	NH_4ReO_3	48	40	20	
	$NaReO_3$	24	0	0	
	$MeReO_3$	20	95	30	
	NH_4ReO_3	3	100	15	
	$NaReO_3$	96	0	0	

Since epoxide was not appreciably converted in the presence of $NaReO_4$, epoxide deoxygenation seems to depend on catalyst's acidity, which may promote the epoxide conversion through *O*-electrophilic attack.

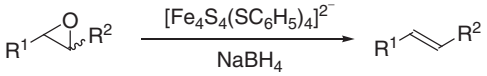
8.29.3.4.9 Iron reagents

Among direct methods developed for converting epoxides into alkenes, $FeCl_3$/butyllithium has been used with a low-valent metal species produced *in situ*,[167] but yields are usually low or moderate and stereochemistry is sometimes lost (equation 47).



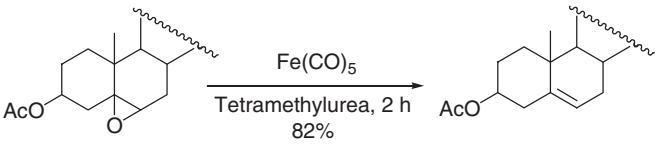
(47)

Fe complex with $NaBH_4$ has been reported to cause deoxygenation reaction of oxirane compounds to olefins.[168] The dianion complex $[Fe_4S_4(SC_6H_5)_4]^{2-}$ in the presence of $NaBH_4$ generates the reduced form $[Fe_4S_4(SR)_4]^{3-}$, that was suggested as an active reductant. These homogeneous catalytic systems suffer from tedious work-up procedures, air- and moisture-sensitive reaction conditions, low atom efficiency and low catalytic activities (equation 48).



(48)

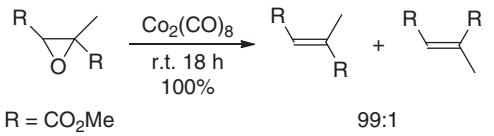
Although deoxygenation of epoxides using sodium (cyclopentadienyl)dicarbonylferrate[169] works well with inversion of stereochemistry, the use of iron pentacarbonyl $Fe(CO)_5$[170] shows low stereoselectivity but was found to tolerate the presence of other functional groups such as carbonyls (equation 49).



(49)

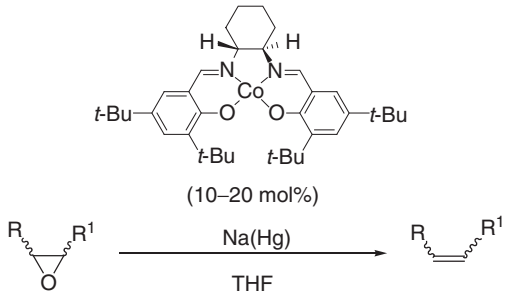
8.29.3.4.10 Cobalt reagents

Dicobaltoctacarbonyl $Co_2(CO)_8$ was efficiently used in the selective reduction of epoxides, affording the deoxygenation products even in the presence of other functional groups, such as ester derivatives (equation 50).[171]



(50)

Epoxide deoxygenation can be mediated by *N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II), in the presence of Na(Hg) in THF, or by *N*,*N*′-bis(salicylidene)-ethylenediaminocobalt(II) [$Co(Salen)_2$] in DMF. The simpler *N*,*N*′-bis(salicylidene)-ethylenediaminocobalt(II) [$Co(Salen)_2$] failed to catalyze deoxygenation in THF but reacts in DMF. The catalyst is essential for the reaction in the presence of Na(Hg) in THF (with five to ten catalytic turnovers) whereas no reaction was observed with other reductant [Al(Hg) or $NaBH_4$]. In these homogeneous catalytic systems, taking place with lower yields, longer reaction times are often required as well as air- and moisture-sensitive reaction conditions (equation 51).[172]



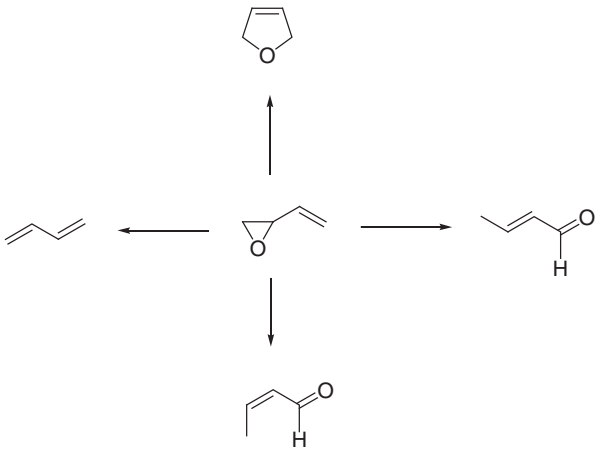
(51)

8.29.3.4.11 Copper reagents

The hydrogenolysis of vinyloxirane and ethyloxirane were studied on a $Cu–SiO_2$ catalyst at 373 K, at various hydrogen pressures and in the presence of deuterium. This study was of particular interest for the preparative chemistry and applications, since two functional groups are present in the same molecule.[173]

The deoxygenation was observed first in the transformation of ethyloxirane by copper catalyst, which takes place even in the absence of hydrogen. The deoxygenation leads to the formation of 1-butene, which is not further reduced to butane, due to the low reductive ability of the Cu catalyst. However, after longer reaction times butanal formation was detected, due to a competitive isomerization. In the course of the measurements in the presence of deuterium, no D was found in unreacted ethyloxirane, nor in 1-butene, indicating that deoxygenation proceeds without the cleavage of the C–H bonds.

Vinyloxirane is transformed, even in the absence of hydrogen, in *trans*-2-butenal, 2,5-dihydrofuran, and 1,3-butadiene, as a consequence of the removal of oxygen, isomerization, and oxirane ring enlargement that take place on the reduced catalyst. Olefins are formed on Cu(0), whereas isomerization occurs on copper–copper oxide interfaces, as demonstrated in the low hydrogen pressure range (equation 52).

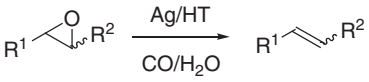


(52)

1,3-Butadiene was the main product in the presence of hydrogen since Cu(0) surface sites are continuously generated by the hydrogen; it is not converted further to butene and butane, and in the course of the measurements in deuterium, unreacted vinyloxirane and 1,3-butadiene were found to contain no deuterium.

8.29.3.4.12 Silver reagents

Silver nanoparticles (Ag NPs) are used not only for the industrial production of ethylene oxide from ethylene in the gas phase,[174] but have also been used in the deoxygenation of epoxides to alkenes, by using a green catalytic methodology, in the presence of alcohols, CO/H_2O or H_2 as reducing reagents.[53] The best results were found when Ag NPs are supported on hydrotalcite ($Mg_6Al_2CO_3(OH)_{16}$). Excellent selectivity for alkenes have been observed, and CO_2 is the sole byproduct, which can be easily removed from the reaction medium (equation 53).



(53)

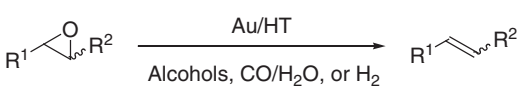
Epoxides bearing diverse other functional groups (ester, ketone, amide, and cyano) were chemoselectively deoxygenated into the desired alkenes, without further hydrogenation even after long reaction times. Benzylic and aliphatic epoxides did not react at all, whereas high reactivity of Ag/HT was found toward the aromatic oxiranes, since differently substituted styrene oxides were completely converted into the desired alkenes; Ag/HT was also applicable to a preparative-scale deoxygenation reaction.

8.29.3.4.13 Gold reagents

Gold nanoparticles (Au NPs) have been very recently described as a powerful catalyst in oxirane deoxygenation, using cheap and easily accessible reductant. Au NPs supported on titania (Au/TiO_2) revealed some interesting synthetic advantages: high activity under very mild conditions, high selectivity and functional group tolerance, safe and easy-to-handle catalysts and reducing reagents, and a simple workup procedure, namely, catalyst/product separation by filtration.[175]

Au/TiO_2 VS (very small nanoparticles) promotes the deoxygenation of styrene epoxide by using a green catalytic methodology under a mild CO atmosphere (203 kPa) at room temperature, affording styrene in 99% yield without any byproducts such as ethylbenzene and 1- or 2-PEA. The reaction with Au/TiO_2 VS successfully promoted the deoxygenation reaction even at low temperature (5 °C) and does not occur in the absence of the catalyst, or in the presence of just TiO_2. Aromatic, alicyclic, and aliphatic epoxides were deoxygenated in high yields (**Table 16**). Halogen-substituted styrene epoxide was cleanly reduced to the corresponding chlorostyrene without any dehalogenation, whereas carbonyl and hydroxy groups also remained unaffected.

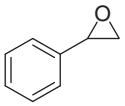
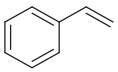
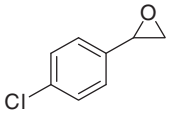
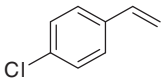
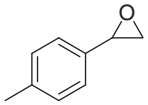
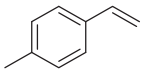
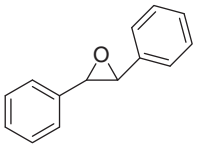
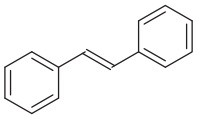
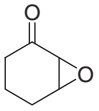
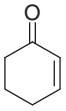
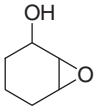
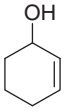
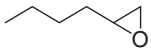
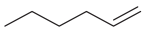
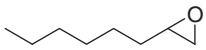
Au NPs supported on hydrotalcite ($Mg_6Al_2CO_3(OH)_{16}$) have also been used in the deoxygenation of epoxides to alkenes in the presence of alcohols, CO/H_2O or H_2 as the reducing reagent (equation 54).[176]



(54)

In these studies,[177] it was found that a basic support is necessary to achieve high catalytic activity for the deoxygenation of epoxides with Au NPs. Deoxygenation of *trans*-stylbene oxide was deeply studied, and a wide range of epoxides were deoxygenated to the corresponding alkenes with more than 99% selectivities: epoxides with ether and hydroxy groups, aromatic, and aliphatic epoxides, and epoxyketones were successfully deoxygenated (**Tables 17** and **18**). The deoxygenation of epoxides using Au/HT was also applicable to a preparative-scale reaction. The C═C bonds of the products were not hydrogenated at all in the presence of

Table 16 Deoxygenation of epoxides with CO/H_2O – Au/TiO_2

Substrate	*Conditions*	*Product*	*Time (h)*	*Conversion (%)*
	Substrate (1 mmol), 0.5 mol% Au/TiO_2 VS, CO(1103 kPa), 25 °C H_2O (2.8 mmol)		0.7	99
	Substrate (1 mmol), 0.5 mol% Au/TiO_2 VS, CO(1103 kPa), 25 °C H_2O (2.8 mmol)		2	96
	Substrate (1 mmol), 0.5 mol% Au/TiO_2 VS, CO(1103 kPa), 25 °C H_2O (2.8 mmol)		2	97
	Substrate (1 mmol), 0.5 mol% Au/TiO_2 VS, CO(1103 kPa), 25 °C H_2O (2.8 mmol)		2	97
	Substrate (0.3 mmol), 3.3% mol Au/TiO_2 VS, CO(1103 kPa), 25 °C H_2O (2.8 mmol)		5	99
	Substrate (0.3 mmol), 3.3% mol Au/TiO_2 VS, CO(1103 kPa), 25 °C H_2O (2.8 mmol)		5	97
	Substrate (0.3 mmol), 3.3% mol Au/TiO_2 VS, CO(1103 kPa), 25 °C H_2O (2.8 mmol)		4	96
	Substrate (0.3 mmol), 3.3% mol Au/TiO_2 VS, CO(1103 kPa), 25 °C H_2O (2.8 mmol)		10	99
	Substrate (0.3 mmol), 3.3% mol Au/TiO_2 VS, CO(1103 kPa), 25 °C H_2O (2.8 mmol)		10	98

particle size <3 nm.[178] After the reaction, the solid Au/HT catalyst is easily separated and reused without loss of activity or selectivity.

8.29.3.4.14 Indium reagents

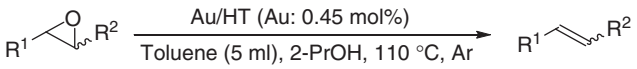
The deoxygenation of epoxides to alkenes using indium metal and indium(I) chloride or ammonium chloride in alcohol has been developed in a novel, mild, and eco-friendly protocol.[179] The deoxygenation reaction of *trans*-stilbene oxide was studied using In/InCl in different solvents: among these nonanhydrous *tert*-butyl alcohol was the most effective, since some epoxides could be sensitive to the alcohol nucleophilic attack on the oxirane ring, as in the case of ethanol. The importance of minute quantities of water for the deoxygenation was proved. A SET process was proposed. Epoxides without the activating group adjacent to the oxirane ring did not undergo deoxygenation. In fact, the deoxygenation reaction typically requires a good radical-stabilizing group adjacent to the oxirane ring, such as carbonyl moieties.

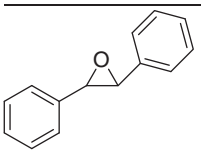
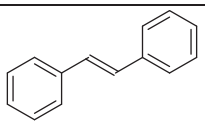
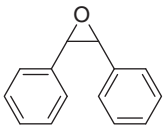
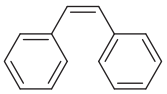
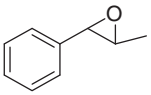
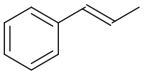
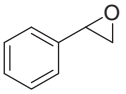
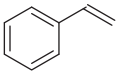
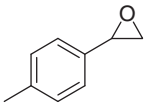
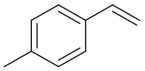
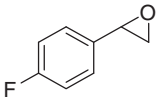
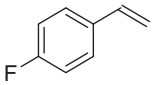
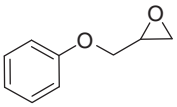
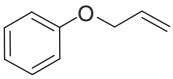
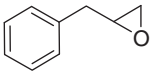
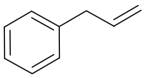
8.29.3.4.15 Samarium reagents

Among low-valent metals used for the deoxygenation of epoxides, SmI_2 requires prolonged reaction time at room temperature, with general high stereoselectivity, in the conversion of *cis*-epoxides into *cis*-alkenes.[180] SmI_2 reacts via a SET mechanism, with the formation of β-alkoxyalkyl radical intermediates,[115] and has been used for the catalytic reduction of various oxiranes to give the corresponding olefins.[181] An easy reduction process in the presence of D_2O was performed with samarium diiodide, giving an efficient method for synthesizing 2,3-dideuterioesters.[182] The oxirane ring of the starting epoxyesters can be di-, tri-, or tetra-substituted, and R^1, R^2, R^3, and R^4 can be varied widely (**Table 19**).

R^1 can be aliphatic (linear, branched, or cyclic), unsaturated, or aromatic; R^3 could also be changed by using different α-haloesters to prepare the starting epoxyesters, and the reaction was unaffected by the presence of bulky groups R^4 on the carbonyl

Table 17 Deoxygenation of various aromatic epoxides using Au/HT



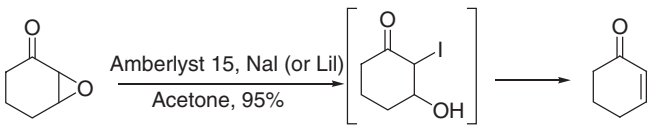
Substrate	*Product*	*Time (h)*	*Yield (%)*
		4	99
		4	97 (*E*/*Z*=2/3)
		4	98
		6	98
		6	92
		6	91
		6	90
		24	89

ester. The synthesis of nondeuterated saturated esters can be also carried out starting from the same epoxyesters by treatment with H_2O instead of D_2O and no important differences were observed.

Styrene oxide was deoxygenated with 10 mol% SmI_2 with Zn–Hg amalgam affording the deoxygenation. The reaction proceeds efficiently with 90% yield by gas chromatography analysis, and 67% isolated yield on a 1 mmol scale.[183] SmI_2 was used for the *E*-selective deoxygenation of epoxy esters in high yields, and was found also to react with vinylcyclopropane epoxides in *t*-BuOH to produce vinylcyclopropanes with complete stereocontrol, whereas some stereoisomerization has been found for aryl derivatives.

8.29.3.5 Metal Halide Reagents

α,β-Epoxy ketones give α-halo-α,β-enones when reacted with NaBr or LiBr/Amberlyst 15 (equation 55).[184] NaI or LiI can be used for the epoxy ketone deoxygenation in the presence of Amberlyst to give the corresponding conjugated olefin in high yields: *cis*-epoxides isomerized during the elimination step to give *trans*-olefins. This easy and high-yielding transformation was applied also to the reduction of phenyl-substituted epoxides to *trans*-olefins in a diastereoselective process.[185]



(55)

Table 18 Deoxygenation of various aliphatic epoxides using Au/HT

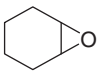
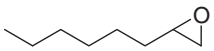
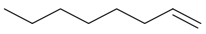
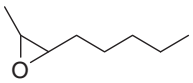
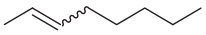
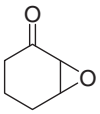
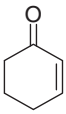
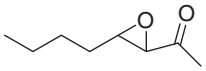
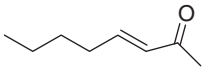
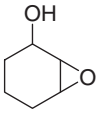
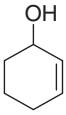
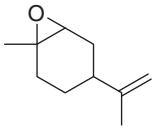
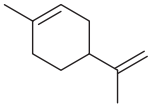
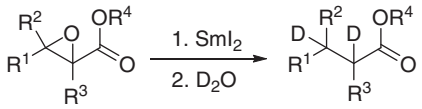
Substrate	*Product*	*Time (h)*	*Yields (%)*
		24	87
		4	97
		12	77 (*E*/*Z*=1/1)
		24	85
		24	94
		6	91
		24	68

Table 19 Deoxygenation of epoxides into alkenes with SmI_2



R^1	R^2	R^3	R^4	*Yield (%)*
4-(MeO)C_6H_4	H	H	Me	81
MeCH(C_6H_5)	H	H	Me	49
n-Bu	H	Ph	*i*-Pr	61
C_7H_{15}	H	Me	Et	70
Cy	H	Me	Et	81
C_6H_5	H	Bu	Et	64
4-(MeO)C_6H_4	H	Me	Et	68
MeCH(C_6H_4)	H	C_6H_{12}	Et	62
$(CH_3)_2C{=}CH(CH_2)_2CH(Me)CH_2$	H	Me	Et	67
C_6H_5	Me	Me	Et	85
C_6H_5	Et	Me	Et	71

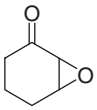
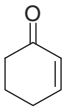
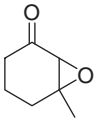
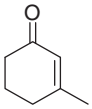
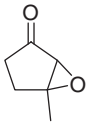
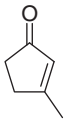
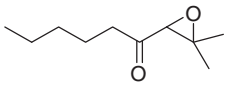
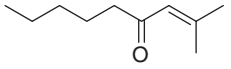
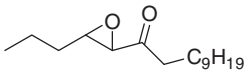
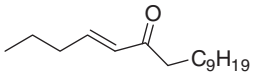
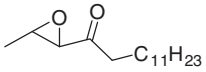
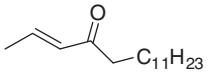
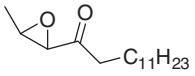
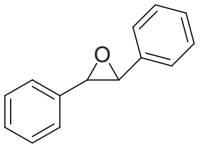
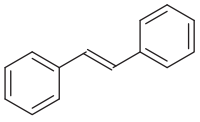
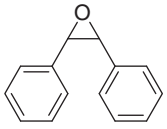
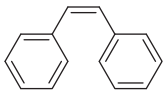
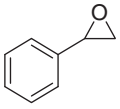
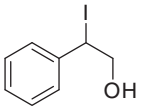
Epoxides carrying phenyl groups in the α-position gave an excellent yield of deoxygenated product, and the reaction worked well with carbonyl-substituted epoxides, both β-substituted and unsubstituted (Table 20).

The mechanism could be described as a regioselective nucleophilic attack of the halide to the oxirane ring at C-2, with a formation of an intermediate iodohydrin, followed by the elimination of HOI in a nonconcerted process.

The method was applied to the selective C-25 hydroxy-functionalization of 3-keto-D4-cholestan-3-one, a key intermediate for the synthesis of C-25 hydroxy vitamin D_3.[185]

Substituted vinyl oxiranes were easily prepared and studied with reference to the influence of electronic effects and steric hindrance on the oxirane ring deoxygenation.

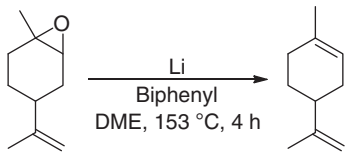
Table 20 Deoxygenation of epoxides using metal halides

Entry	*Substrate*	*Halide*	*Time (h)*	*Product*	*Yield (%)*
1		LiI	3		95
2		NaI	3		98
3		LiI	3		93
4		NaI	3		96
5		LiI	3		94
6		NaI	3		98
7		LiI	3		92
8		NaI	3		97
9		LiI	6		94
10		NaI	6		98
11		LiI	6		95
12		NaI	6		98
13		LiI	6		95
14		NaI	6		97
15		NaI	6		92
16		LiI	3		93
17		NaI	3		95
18		LiI	8		93
19		NaI	8		92
20		LiI	3		85

The driving force of the elimination seems to be the formation of the conjugated system. Under the same reaction conditions, the reactivity of vinyl epoxides, where a C=C double bond instead of C=O was present, was studied with LiI/Amb. 15 observing high-yield deoxygenation.[186]

8.29.3.6 Lithium

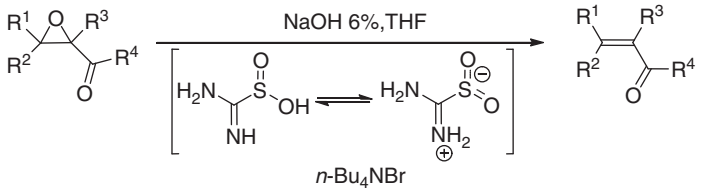
Lithium has been used for the oxirane deoxygenation,[187] in the high-yield conversion of limonene oxide to the corresponding alkene, performed in the presence of lithium/biphenyl in DME (equation 56).[188]



(56)

8.29.3.7 Thiourea Dioxide

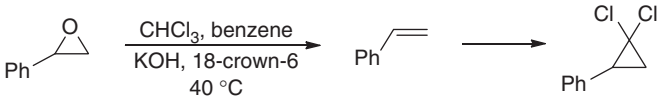
An efficient deoxygenation of α,β-epoxy ketones to enones was performed with aminoiminomethanesulfinic acid and thiourea dioxide (TDO), easily obtained from thiourea and H_2O_2, in THF/alkaline medium and using tetra-*n*-butyl ammonium bromide as the phase-transfer catalyst.[189] Mesityl oxide and the epoxides of isophorone, (–)-carvone, (+)-6-methyl-carvone, (+)-6-ethylcarvone, and (–)-myrtenal have been reduced easily in high yields by this methodology (equation 57).



(57)

8.29.3.8 Dichlorocarbenes

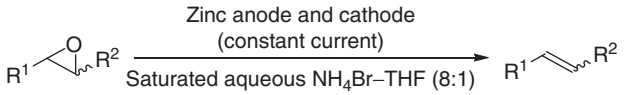
Although the deoxygenation of epoxides is a facile and clean reaction, often it proceeds with low yields, because of the further reactivity of the obtained alkene.[190] The deoxygenation of styrene oxide with dichlorocarbene was studied.[191] The reaction is stereospecific, retaining the *cis* or *trans* stereochemistry of the original epoxide. Solid KOH with some water and a crown ether reduces the side reaction of basic hydrolysis of the oxirane (equation 58).



(58)

8.29.3.9 Electrochemical Deoxygenation

Electrochemical-supported deoxygenation of epoxides into alkenes[192] have been studied in the presence of organized zinc nanostructures, which mediated eliminative deoxygenation reaction in aqueous solution of NH_4Br and THF (8:1) mixture, under electrochemical conditions. It was observed that ammonium salts were more efficient than neutral KNO_3. Both aromatic and aliphatic epoxides can be deoxygenated by this methodology, although long-chain aliphatic epoxides are less reactive than aromatic epoxides. Ether and ester functional groups are compatible with the reductant, conversely ketones were deoxygenated in very low yields. *Z*–*E* isomerization occurs during the deoxygenation process of *cis*-stilbene oxide, affording a 95:5 mixture of *trans*/*cis*-stilbene. Deposition of Zn(0) on the cathode in multidimensional nanostructures is important for the efficiency of the conversion. The deoxygenation of epoxides by using commercial Zn powder in saturated aqueous NH_4Br/THF (8:1) under nonelectrochemcial conditions yields only a 43% of alkene, whereas the use of other metals instead of Zn as electrodes gives much lower yields (equation 59).



(59)

R^1 = Aryl, alkyl
R^2 = Aryl, alkyl, H

Up to 96% yield

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8.30 Reduction of Alkenyl Halides to Alkenes, and of Aryl Halides and Related Compounds to Arenes

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Glossary

Hydrodehalogenation The process of replacing a carbon–halogen bond with a carbon–hydrogen bond.
Hydrogenation The process of using molecular hydrogen, usually in the presence of a catalyst, to reduce or saturate organic compounds.
Hydrogenolysis The process of using molecular hydrogen, usually in the presence of a catalyst, to replace carbon–carbon and carbon–heteroatom bonds with carbon–hydrogen bonds.
Metal halogen exchange The process of converting a carbon–halogen bond to a carbon–metal bond (metal = Li, Mg, Zn, Cu, etc.).
Pseudohalide An inorganic functional group (azide, thiocyanate, cyanide, etc.) that resembles a halide in its charge and reactivity.

8.30.1 Reduction of the sp^2 Carbon–Halogen Bonds

8.30.1.1 General

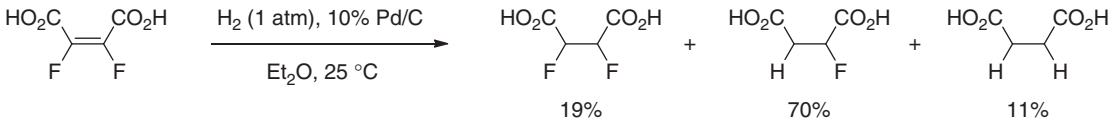
It is well established that the ease of reducing $C(sp^3)$–X bonds typically follows the general order I > Br > Cl > F, which corresponds to the bond dissociation energies of the indicated bonds.[1] Therefore, it is not surprising that this trend is the same for $C(sp^2)$–X bonds. For example, the C–X bond strengths of fluoroethylene, chloroethylene, and bromoethylene are 123.3, 91.2, and 80.8 kcal mol^{-1}, respectively.[1] In addition, the bond strengths of Ph–F, Ph–Cl, Ph–Br, and Ph–I are 127.2, 97.1, 84, and 67 kcal mol^{-1}, respectively.[1]

The hydrogenolysis and the reductive hydrodehalogenation of alkenyl $C(sp^2)$–X bonds has proven challenging as compared to $C(sp^3)$–X bonds due to the stronger bond strengths as well as the tendency for the resulting alkene to be further reduced to the alkane. In addition, even though the $C(sp^2)$–X bonds of aryl halides are stronger than the $C(sp^2)$–X bonds of alkenyl halides, more research effort has been invested in developing dehalogenation reactions for aryl halides due to the environmental threat posed by polyhaloarenes, such as PCBs (polychlorinated biphenyls).[2] However, many of the prevalent methods developed to reduce alkyl halides are applicable to both aryl and alkenyl halides (and pseudohalides).

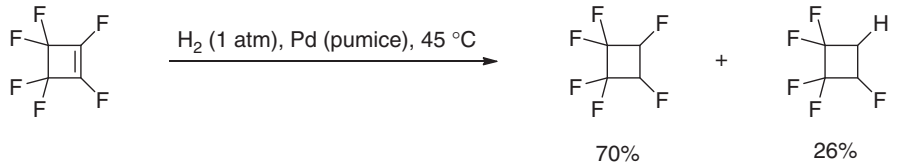
Although the reduction of halogenated compounds appears to be an impractical transformation, there are several advantages of being able to replace a halogen with a hydrogen atom. For example, aryl halides can act as both protecting groups and directing groups, which can then be removed after serving their intended purpose.[3] More importantly, the different reductive hydrodehalogenation protocols have been applied on many occasions to probe the mechanism of reactions involving radical, cationic, or anionic species.[4] In addition, these methods are potentially convenient means of synthesizing molecules with selective incorporation of deuterium for structure elucidation and mechanistic studies.[5]

8.30.1.2 Hydrogenolysis of Alkenyl and Aryl Fluorides

There are very few reports of the hydrogenolysis of alkenyl and aryl fluorides resulting from the difficulty associated with the reduction of C–F bonds, as well as the limited methods to fluorinate aromatic rings[6] and synthesize alkenyl fluorides.[7] Traditional methods to reduce alkenyl fluorides with hydrogen gas and a heterogeneous metal catalyst typically result in overreduction to the alkane as is illustrated with *cis*-2,3-difluorobutenedioic acid (equation 1)[8] and 1,2,3,3,4,4-hexafluorocyclobutene (equation 2).[9]

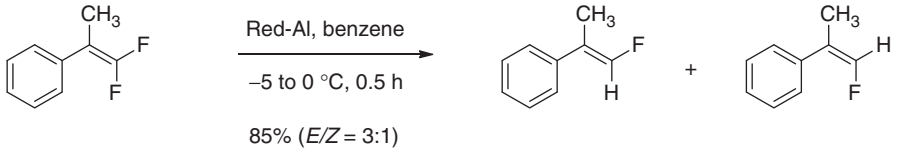


(1)

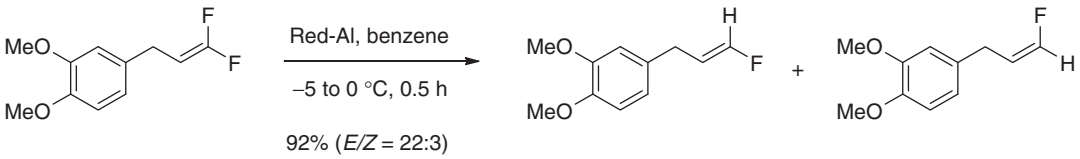


(2)

$LiAlH_4$,[10] $NaBH_4$,[11] and Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride)[12] have been shown to provide chemoselective reduction of alkenyl fluorides to alkenes. In particular, Red-Al was found to be useful for the monodefluorination of *gem*-difluoroalkenes such as (1,1-difluoroprop-1-en-2-yl)benzene (equation 3)[12a] and 1,2-dimethoxy-4-(3,3-difluoro-2-propenyl)benzene (equation 4).[12b]

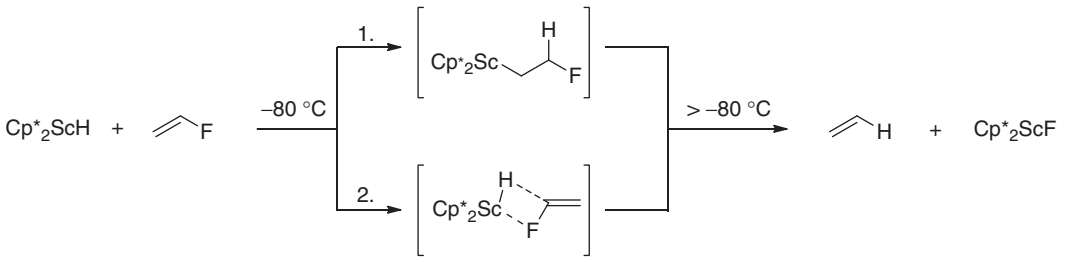


(3)

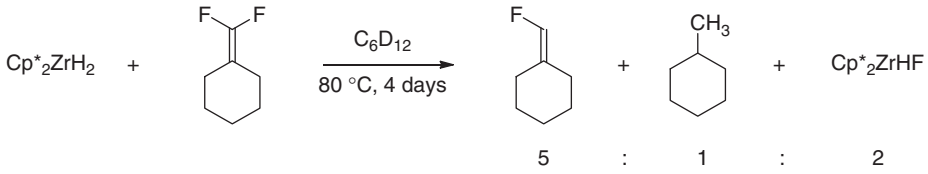


(4)

In 1987, Burger reported the use of Cp^*_2ScH to effect the reduction of fluoroethene.[13] The mechanism of the reaction is postulated to involve either (1) an olefin insertion by Cp^*_2ScH onto fluoroethene and subsequent β-fluoride elimination to generate Cp^*_2ScF and ethene or (2) a σ-bond metathesis reaction (equation 5). Studies with similar complexes such as $Cp^*_2ZrH_2$ (equation 6),[14] $(PPh_3)_3RhCl$,[15] and Cp^*2HfH_2[16] indicate that the former mechanism is more likely.

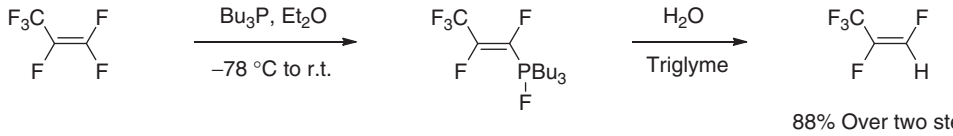


(5)

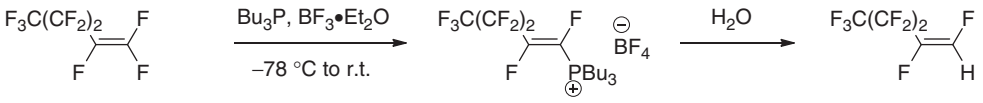


(6)

One of the most interesting examples of a hydrodefluorination of a alkenyl fluoride is reported by Burton with the use of PBu_3.[17] When perfluoroalk-1-enes are treated with PBu_3, *trans*-perfluoroalk-1-enyl(tributyl)fluorophosphoranes (equation 7)[17a,17d] or *trans*-perfluoroalk-1-enyl(tributyl)phosphonium salts (equation 8)[17b,17c] are generated and hydrolyzed with water to give *trans*-1*H*-perfluoroalk-1-ene in high yield, which is, notably, the less thermodynamically stable isomer.[17c]

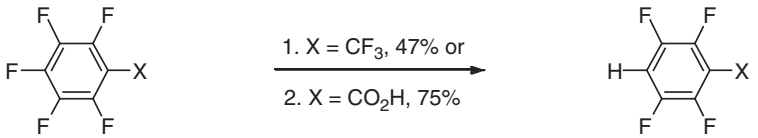


88% Over two steps (7)



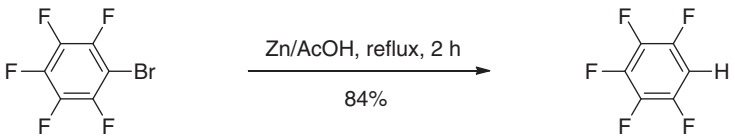
72% Over two steps (8)

The ease of aryl fluoride reduction is highly dependent on the substitution and the type of aromatic ring. The past literature contains many examples of defluorination attempts of perfluor- and polyfluorinated aromatic rings. Octafluorotoluene undergoes monodefluorination *para* to the trifluoromethyl group when treated with lithium aluminum hydride.[18] The electrochemical reduction of pentafluorobenzoic acid at a fixed potential of 1.20 V versus SCE also led to exclusive monodefluorination *para* to the carboxyl group (equation 9).[19]

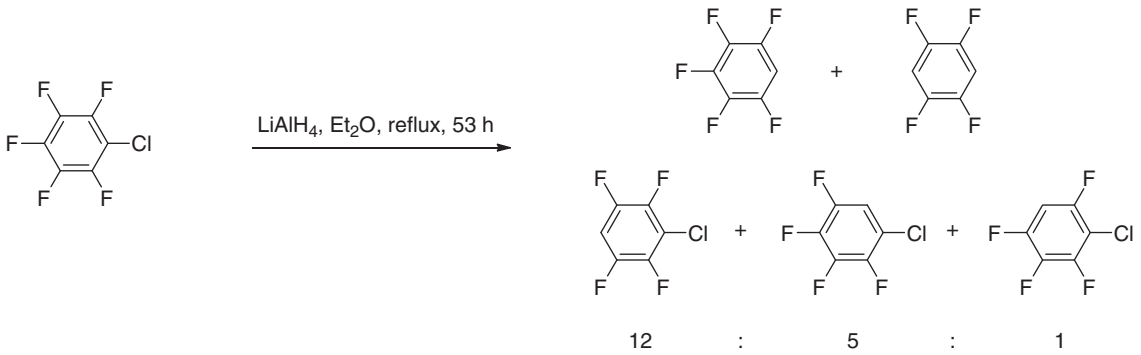


1. $LiAlH_4$, Et_2O, reflux, 85 h; 2. Electrolysis, 20% H_2SO_4, –1.2 V, Hg cathode (9)

When bromopentafluorobenzene is treated with zinc, these mild reducing conditions result only in debromination (equation 10).[20] In contrast, when chloropentafluorobenzene is treated with lithium aluminum hydride, a mixture of compounds is produced which include monodechlorination and/or monodefluorination (equation 11).[21]

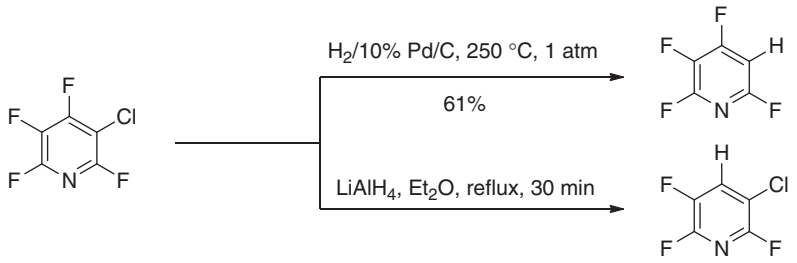


(10)



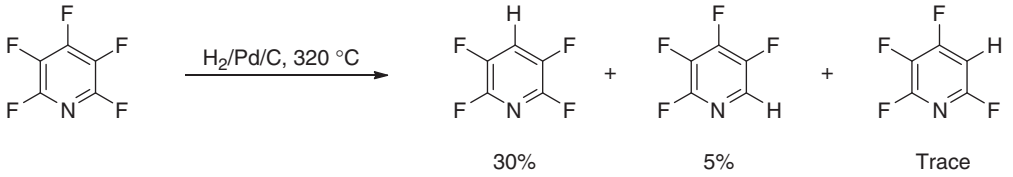
(11)

3-Chlorofluoropyridines exhibit interesting reactivity under dehalogenation conditions. Standard catalytic hydrogenation conditions result in exclusive dechlorination,[22] whereas the use of lithium aluminum hydride results in exclusive defluorination at the C4 position (equation 12).[23]



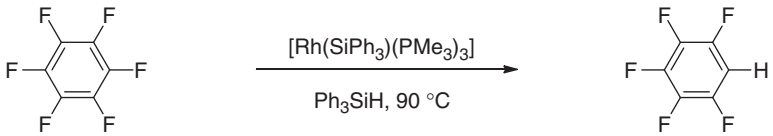
(12)

This reactivity is due to the lower electron density of the C2 and C4 positions of chlorofluoropyridines and is further illustrated by the catalytic hydrogenation of pentafluoropyridine in which the two major products are those from C2 and C4 monodefluorination (equation 13).[22]



(13)

Although the use of transition metals to activate C–F bonds has been known since the 1970s,[24] the development of a homogeneous transition metal complex to effect defluorination was not reported until 1994 by Milstein.[25] In this report, Milstein introduced Rh(I) silyl complexes as efficient catalysts for the monodefluorination (equation 14) and didefluorination of hexafluorobenzene. Additional reports of the use of homogeneous transition metal complexes to defluorinate polyfluoroaromatic rings followed shortly.[26]

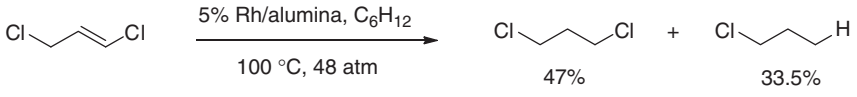


(14)

Defluorination methods for monofluorinated aromatic rings are scarce even though these C–F bonds are typically weaker than the C–F bond of polyfluorinated aromatics.[27] Several reports of defluorination are scattered in the literature, but a more concentrated effort to develop generalized aromatic defluorination methods has emerged in the 2000s.[28]

8.30.1.3 Hydrogenolysis of Alkenyl and Aryl Chlorides

Many of the issues associated with the overreduction of alkenyl fluorides also exist for alkenyl chlorides when catalytic hydrogenolysis is utilized. One example that illustrates this point is the treatment of *trans*-1,3-dichloropropene with catalytic hydrogenation conditions using Rh as the catalyst (equation 15).[29] However, there is a larger variety of available protocols for the dehalogenation of alkenyl chlorides than alkenyl fluorides.

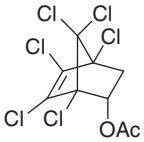
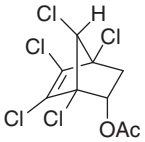
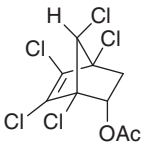
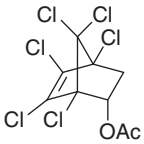
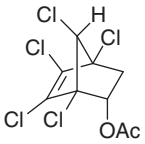
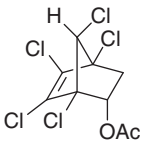
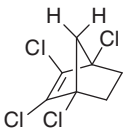
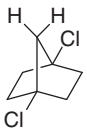
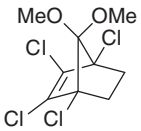
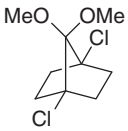
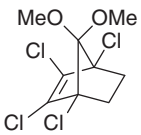
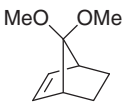
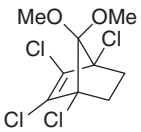
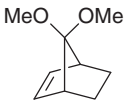
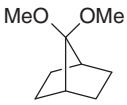
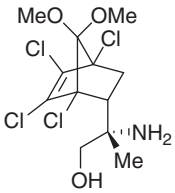
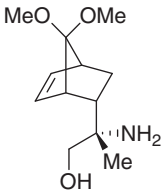
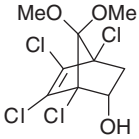
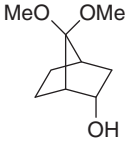


(15)

Highly chlorinated norbornylenes have become the model substrate with which to illustrate the chemoselective nature of dechlorination protocols because of the varying bond strengths of the alkenyl, bridgehead, and bridge C–Cl bonds (**Table 1**). The use of zinc in acetic acid or chromium(II) acetate only results in the monodechlorination of the bridge chlorides.[30] The use of stronger reducing conditions comprising hydrogen gas and Raney nickel in a solution of potassium hydroxide and absolute methanol gave dechlorination of the alkenyl chlorides as well as reduction of the alkene without affecting the bridgehead chlorides.[30a] The same transformation can be carried out with hydrogen gas, 5% palladium-charcoal and an excess of triethylamine in ethanol.[31] However, the use of alkali metals such as lithium and sodium results in full dechlorination with the alkene maintained to varying degrees.[32] The use of Birch conditions can allow for either solely complete dechlorination or complete dechlorination along with hydrogenation of the alkene.[33] Finally, the use of tributyltin hydride selectively dechlorinates all of the alkyl chlorides but does not affect the alkenyl chlorides.[34]

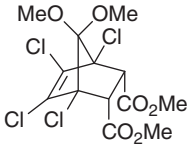
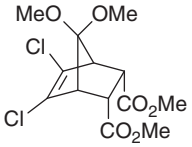
More general methods for the reduction of alkenyl chlorides include the use of $LiAlH_4$,[35] Li/DTBB (4,4′-di-*tert*-butylbiphenyl),[36] and zero valent metals.[37] The treatment of **1** with $LiAlH_4$ to give **2** illustrates the difficulty of developing chemoselective reductions of alkenyl chlorides in the presence of other functional groups, such as esters and alkenyl selenides (equation 16).[35b]

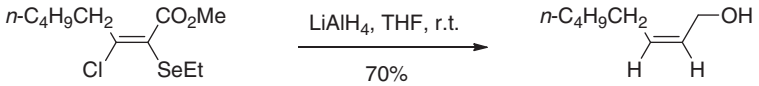
Table 1 Dechlorination of highly chlorinated norbornylenes

Substrate	*Reaction conditions*	*Product*	*Yield (%)*	*References*
	Zn, AcOH, reflux, 4.5 h		70	30a
			9	
	$Cr(OAc)_2$, AcOH, reflux, 16 h		78	30b
			18	
	H_2/Raney Ni, KOH, r.t.		82	30a
	H_2/5% Pd/C, EtOH, Et_3N		93	31
	Na, *t*-BuOH, THF, reflux, 8 h		62.8	32
	Li, *t*-BuOH, THF, reflux		42	32
			22	
	Li, liquid NH_3, EtOH, Et_2O, –78 °C		85	33a
	Na, liquid NH_3, EtOH		72	33b

(*Continued*)

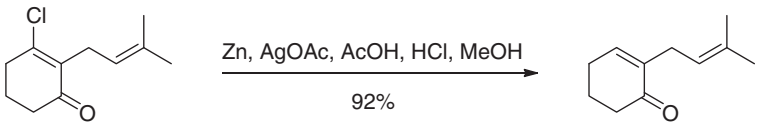
Table 1 Continued

Substrate	*Reaction conditions*	*Product*	*Yield (%)*	*References*
	Bu_3SnH, AIBN, PhH, reflux, 8 h		97	34



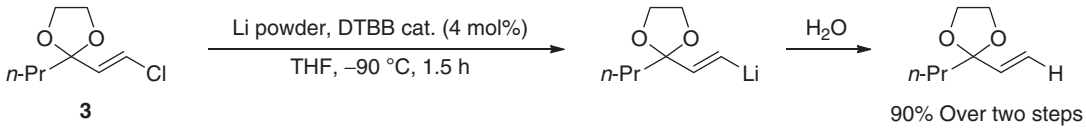
1 **2** (16)

In contrast to the nonselective reduction shown above utilizing $LiAlH_4$, Coltart applied the use of zinc metal in a very selective reduction of a alkenyl chloride intermediate toward the synthesis of (+)-clusianone (equation 17).[37c]



(17)

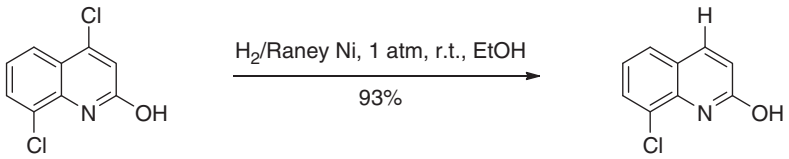
The two-step reduction protocol of **3**, which involves the *in situ* generation of a alkenyl lithium species, followed by quenching with water, has been developed into an efficient method for the synthesis of *trans*-selective α,β-unsaturated ketones (equation 18).[36]



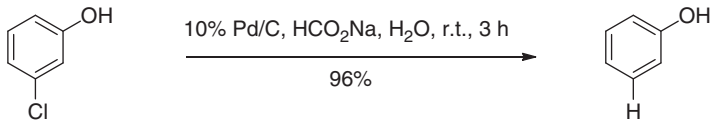
3 90% Over two steps (18)

Traditional methods for the dechlorination of aromatic compounds typically involve one of the following methods: a hydrogen source (usually hydrogen gas) and a heterogeneous catalyst, a complex metal hydride, a homogeneous transition metal catalyst, or a zero valent metal.[2] Most research efforts toward aromatic dechlorination have been focused on improving the traditional methods with the ultimate goal of developing a dechlorination protocol capable of being adapted to the removal of organochlorine pollutants in the environment.[38]

The use of hydrogen gas has been a mainstay of dechlorinating aryl chlorides since the 1940s as illustrated by the monodechlorination of 4,7-dichlorocarbostyril (equation 19),[39] but the use of hydrogen gas has largely been phased out by the use of other hydrogen sources, such as hydrosilanes, alcohols, and formic acid and its salts (equation 20).[40]

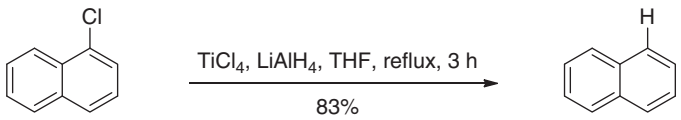


(19)

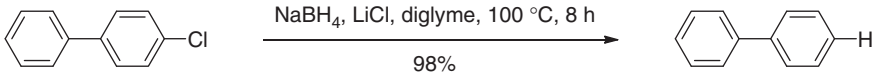


(20)

Although not as commonplace as hydrogen gas, the use of complex metal hydrides as a hydrogen atom source has been reported on several occasions.[41] The use of $LiAlH_4$ in conjunction with $TiCl_4$ resulted in the high-yielding dechlorination of 1-chloronaphthalene (equation 21), whereas the use of $LiAlH_4$ alone led to low yields of naphthalene.[41a] The use of $NaBH_4$, a milder complex metal hydride, in the presence of LiCl can also be utilized for the dechlorination of aryl chlorides, although the reaction conditions require higher temperatures (equation 22).[41b]

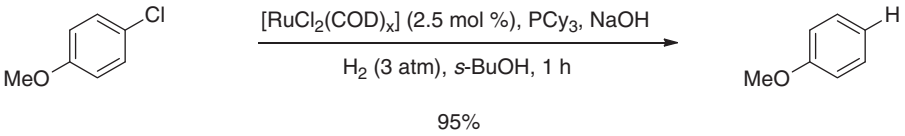


(21)



(22)

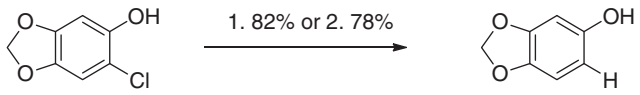
Homogeneous transition metal catalysts containing palladium,[40b,42] nickel,[43] rhodium,[44] ruthenium (equation 23),[45] titanium,[46] and zirconium[47] have come to prominence due to the higher chemoselectivity observed when compared with catalytic hydrogenolysis with heterogeneous catalysts.



(23)

The use of zero valent metals to dechlorinate aromatic chlorides is not typically reported as a generalized method, but several individual reports using sodium,[48] potassium–sodium alloy,[49] and iron[50] are known.

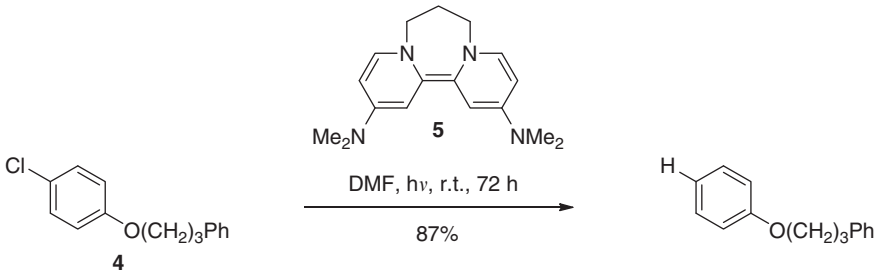
Several nontraditional examples of aromatic dechlorination have appeared in the literature and are worth mentioning. The first example is the use of tosylhydrazine to selectively reduce an activated aryl chloride in the presence of an aryl bromide.[51] The second example is the use of UV light and isopropanol,[52] Et_3SiH,[53] or H_3PO_2[52] to dechlorinate through homolysis of the C–Cl bond and H-atom abstraction from one of the hydrogen atom donors listed above by the phenyl radical. In equation 24, two of these methods are shown, resulting in comparable yields when either isopropanol or H_3PO_2 is employed.



1. hν, H_3PO_2, 15 h; 2. hν, *i*-PrOH, 15 h

(24)

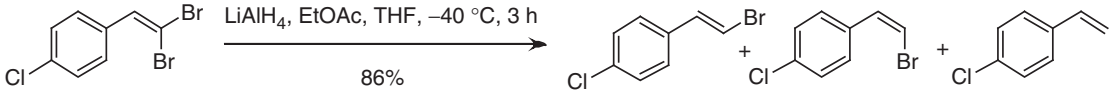
The successful reduction of aryl chloride **4** was reported with the use of a neutral organic electron donor **5** and near UV light irradiation (equation 25).[54] These metal-free and mild reaction conditions truly illustrate the progress that has been made in the study of hydrodehalogenation.



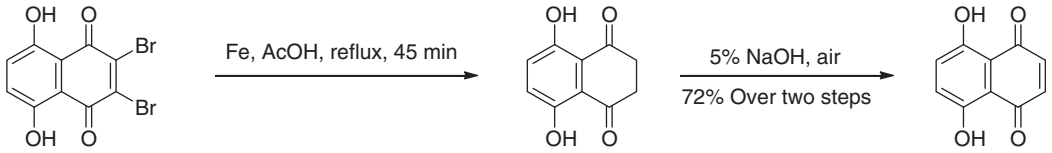
(25)

8.30.1.4 Hydrogenolysis of Alkenyl and Aryl Bromides

Many of the same techniques used to reduce alkenyl chlorides can also be applied to alkenyl bromides, although the reaction conditions are typically milder due to the weaker dissociation energy of the C–Br bond as opposed to the C–Cl bond. For example, $LiAlH_4$ has been shown to produce alkenyl bromides from *gem*-dibromoalkenes with high diastereoselectivity toward the *E* isomer (equation 26).[55] Iron powder has been utilized to synthesize naphthazarins from polyhalogenated naphthazarins prepared from the Friedel–Crafts cycloacylation of hydroquinones with dichloro- or dibromomaleic anhydrides (equation 27).[56]

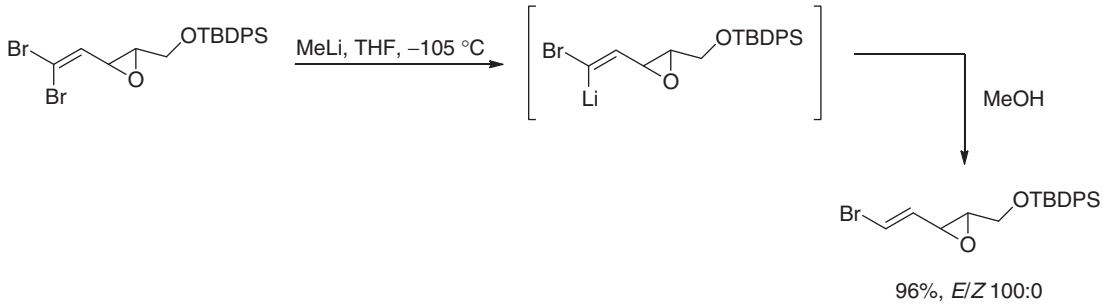


(26)

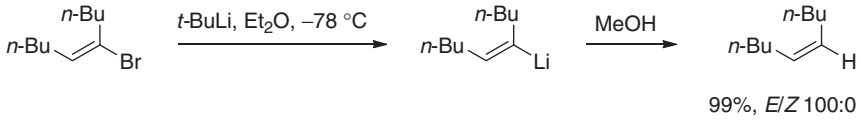


(27)

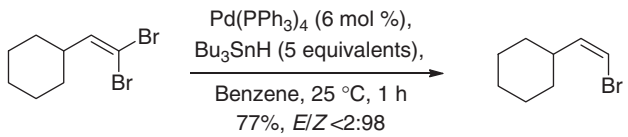
Additionally, the weaker C–Br bond makes certain reduction protocols better suited for alkenyl bromides than alkenyl chlorides. Metal halogen exchange followed by protic quenching has been used to reduce alkenyl bromides, whereas alkenyl chlorides are largely inert to exchange (equations 28 and 29).[57] A combination of transition metal catalysts and hydrogen atom sources, such as palladium and tributyltin hydride, have been used to effect debromination with high *Z* selectivity, initiated by an oxidative addition of alkenyl bromides and completing with a *syn*-elimination of hydridopalladium (equation 30).[58]



(28)

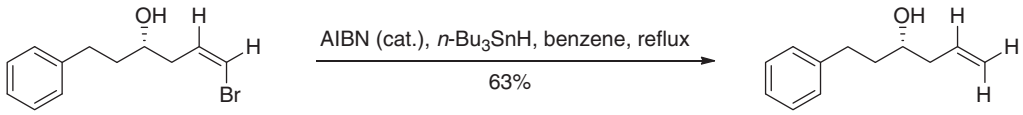


(29)



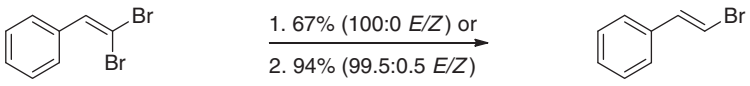
(30)

Radical reductions using SmI_2[59] and AIBN/Bu_3SnH (equation 31)[60] have also been reported for alkenyl bromides but are unknown for alkenyl chlorides.



(31)

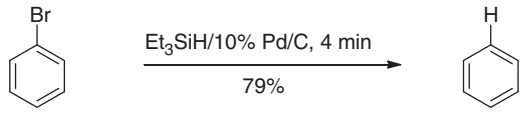
The monoreduction of *gem*-dibromoalkenes has been of particular interest to organic chemists because they are simple to synthesize[61] and because alkenyl bromides themselves are useful synthetic precursors of alkenyl anions and for transition metal-catalyzed coupling reactions. The most well-known monoreduction protocol for *gem*-dibromoalkenes was introduced by Hirao in 1981 using diethylphosphite and triethylamine.[62] Slight modifications to the procedure have been reported using different bases and solvents. However, a key advancement of the Hirao reduction was developed by Tokuda in which the reaction is performed quickly and efficiently in a microwave reactor (equation 32).[63]



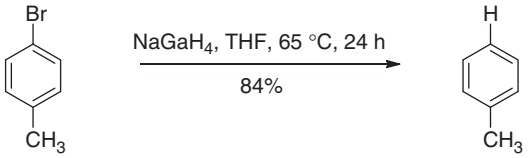
(32)

1. $(MeO)_2POH$, Et_3N, DMF, 70 °C, 16 h; 2. $(EtO)_2POH$, NaOEt, EtOH, MW, 1 min

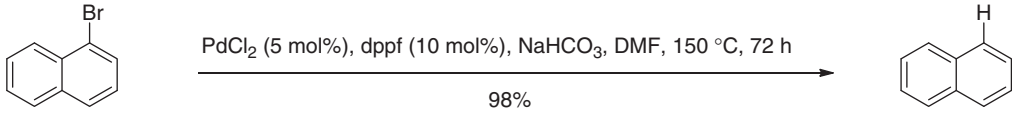
The reduction methods of aryl bromides closely mimic those of aryl chlorides with numerous examples of debromination methods[2] utilizing one of the following protocols: a hydrogen source (usually hydrogen gas) and a heterogeneous catalyst (equation 33),[53] a complex metal hydride (equation 34),[64] a homogeneous transition metal catalyst (equation 35),[65] or a zero valent metal (equation 36).[66]



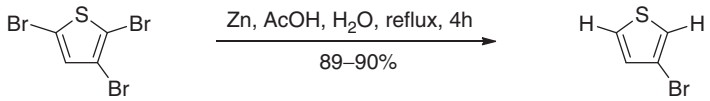
(33)



(34)

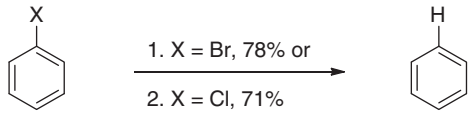


(35)



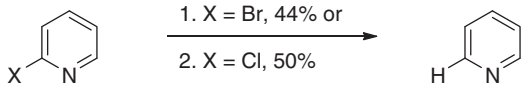
(36)

As a matter of fact, many methods that have been developed for aromatic debromination also initiate aromatic dechlorination. This drawback is not confined to any particular type of reduction method, as a heterogeneous palladium catalyst (equation 37)[67] and a homogeneous zirconium catalyst are both reported to have the same limitation (equation 38).[46] Also, neutral organic electron donor **6** was reported to be an efficient reductant of aryl iodides to aryl anions and shows reactivity with aryl bromides and aryl chlorides as well (equation 39).[68]



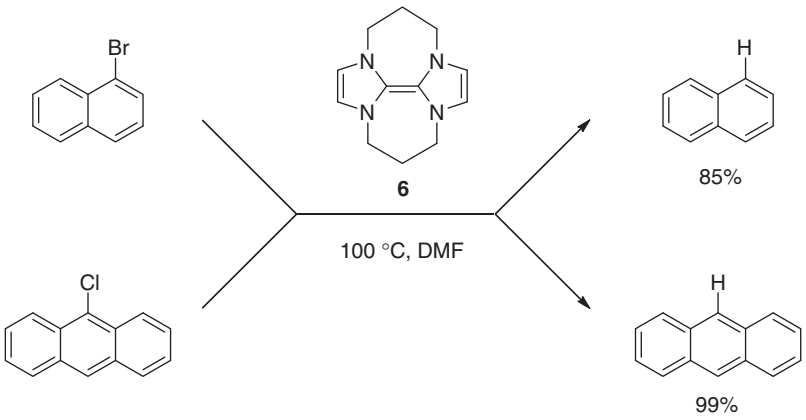
(37)

1. PdMCM-41, HCO_2NH_4, MeOH, 83 °C, 3.5 h; 2. PdMCM-41, HCO_2NH_4, MeOH, 83 °C, 3.0 h



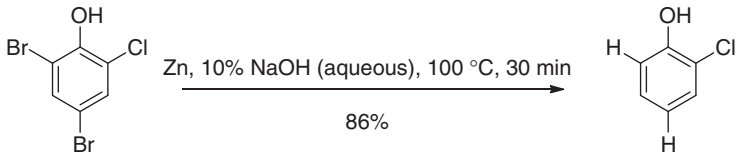
(38)

1. and 2. Cp_2ZrCl_2, Red-Al, toluene, 25 °C, 36 h



(39)

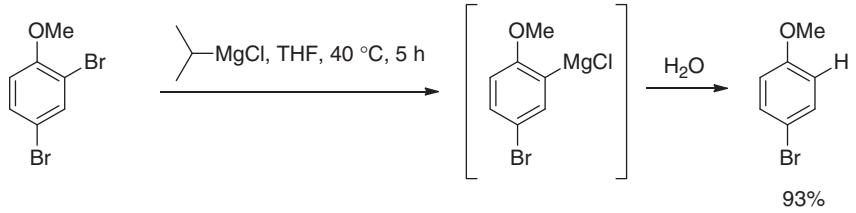
However, selective methods for aromatic debromination in the presence of aromatic chlorides do exist. A series of polyhalophenols are treated with zinc in a basic solution to give sole debromination (equation 40), whereas treatment of zinc in an acidic solution gave no reaction.[69]



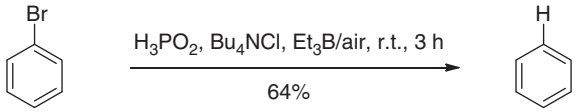
(40)

4-Bromochlorobenzene can be exclusively reduced to chlorobenzene when treated with a homogenous palladium catalyst and poly(methylhydrosiloxane) as a hydrogen donor.[70] In addition, Lipshutz reports that the use of low-valent nickel complexes at room temperature will result in the selective reduction of 2′-bromoacetophenone without reduction of 2′-chloroacetophenone, although increasing the temperature allows for dechlorination to occur.[43a]

Presumably, some chemoselectivity for the reduction of aryl bromides over aryl chlorides is offered by methods employing metal halogen exchange (equation 41)[71] and radical halide abstraction (equation 42),[72] as these methods are well documented for aryl bromides but, for the most part, are unreported for aryl chlorides.

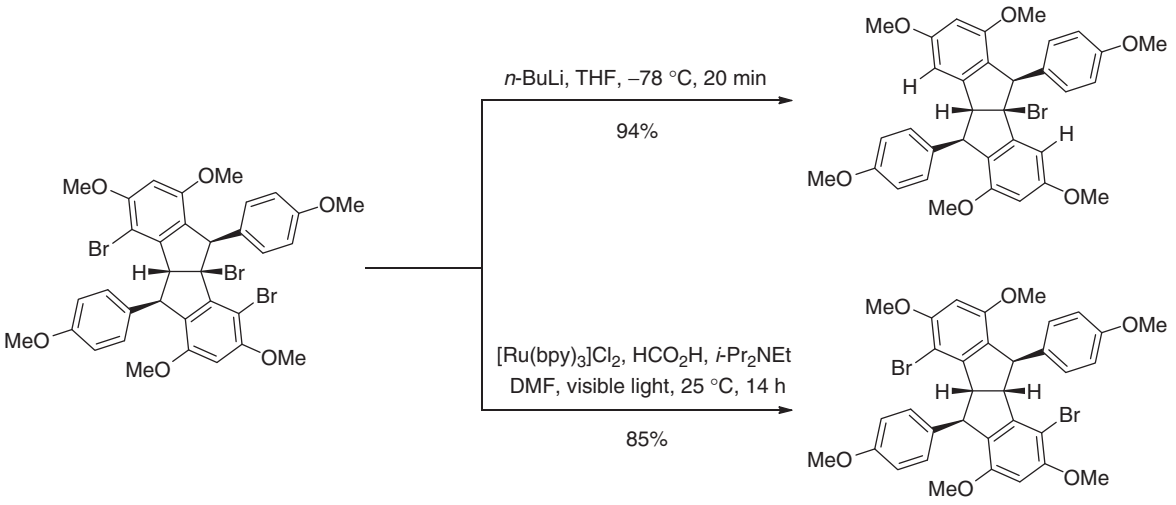


(41)



(42)

An interesting example of aromatic debromination in the presence of alkyl halides is reported by Snyder in the synthesis of carasiphenol C. In this case, *n*-BuLi undergoes lithium-bromide exchange with the aromatic bromides, whereas the alkyl bromide is unaffected (equation 43).[73] The opposite selectivity is observed when the same compound is treated with the photocatalyst $[Ru(bpy)_3]Cl_2$ under reductive dehalogenation conditions (equation 43).[74] For more details on the topic of the reduction of alkyl halides to alkanes, *see* Chapter 8.26.



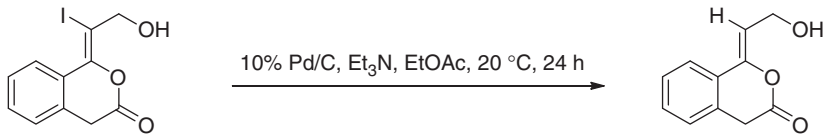
(43)

8.30.1.5 Hydrogenolysis of Alkenyl and Aryl Iodides

There are surprisingly few accounts of alkenyl iodide reductions to alkenes, but this is more a result of the usefulness of alkenyl iodides as precursors rather than a reflection of their ease of hydrodehalogenation. In fact, many of the methods available for the

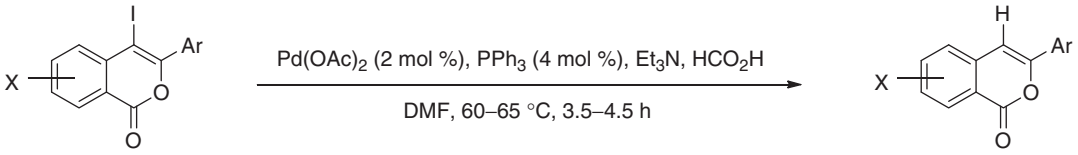
reduction of alkenyl chlorides and alkenyl bromides to alkenes can be applied directly to the reduction of alkenyl iodides to alkenes as well.

Heterogeneous catalysts, such as palladium on carbon, are utilized under mild conditions to effect hydrodehalogenation without further reduction of the alkene (equation 44).[75]



(44)

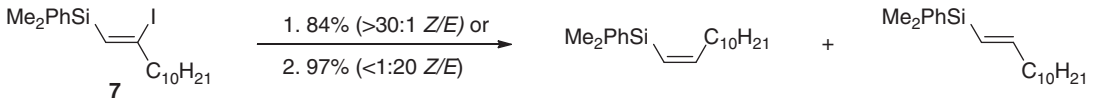
Homogeneous transition metal catalysts, such as $Pd(OAc)_2$, have been applied quite successfully to the reduction of alkenyl iodides, including 3-aryl-4-iodoisocoumarins (equation 45).[76]



(45)

X = 8-MeO, Ar = 3,4-$(MeO)_2C_6H_3$	93%
X = 8-MeO, Ar = C_6H_5	90%
X = 6-MeO, Ar = 4-$MeOC_6H_4$	93%
X = 6, 8-$(MeO)_2$, Ar = 3,4-$(MeO)_2C_6H_3$	98%

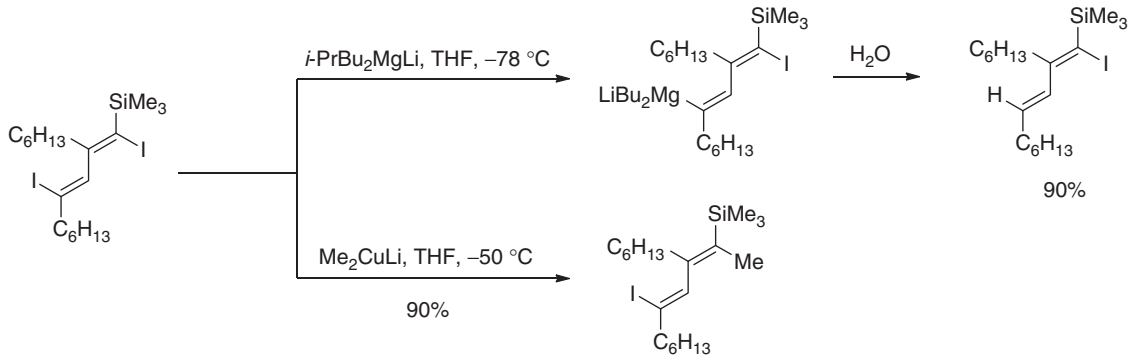
The reduction of alkenyl iodides via radical abstraction of the iodine atom is not surprising, because alkenyl bromides are also susceptible to these same conditions. The deiodination of β-iodosilylalkene **7** can produce drastic changes in the diastereoselectivity based on the hydrogen atom source. Presumably, the selectivity is caused by the differing rates of hydrogen atom abstraction from tris(trimethylsilyl)silane (TTMSS) and tributyltin hydride by the alkenyl radical in comparison to the rate of alkenyl radical isomerization (equation 46).[77]



(46)

1. TTMSS, Et_3B, benzene, r.t.; 2. *n*-Bu_3SnH, Et_3B, benzene, r.t.

One of the most popular methods for the deiodination of alkenyl iodides is through metal halogen exchange because the rate of exchange is known to be very fast. In the example shown below, a compound containing two alkenyl iodides can undergo site selective exchange depending on whether magnesium or copper is present (equation 47).[78]

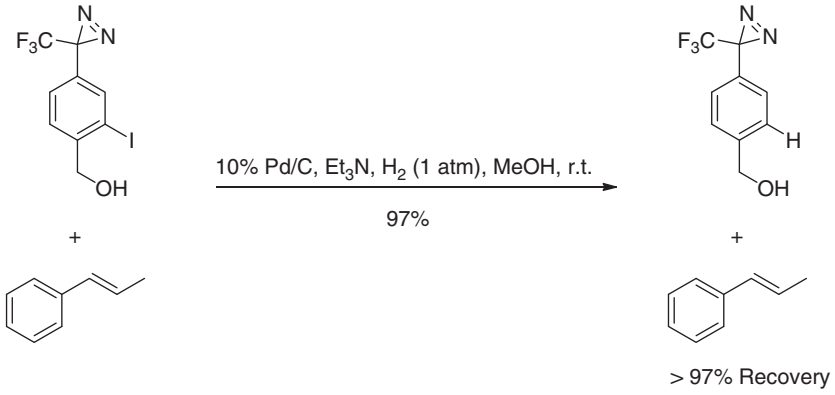


(47)

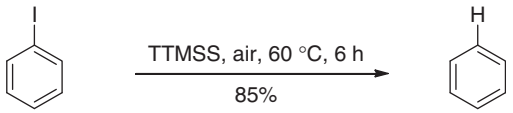
Similar to alkenyl iodides, aryl iodides are important precursors in organic chemistry. Aryl iodides are generally more reactive than aryl bromides and aryl chlorides, which explains why they are used more frequently to form aryl anions, aryl radicals, and carbon–carbon and carbon–heteroatom bonds in transition metal-catalyzed processes, such as Heck-, Stille-, Suzuki-, and Ullmann-type coupling reactions.

A myriad of methods exist for the reduction of aryl iodide bonds including hydrogen or hydrogen atom sources over a heterogeneous catalyst,[79] radical iodine atom abstraction,[80] radical reductive cleavage,[81] metal halogen exchange,[82] transition metal catalysis,[83] and complex metal hydrides.[46,84] These general methods have been presented for aryl chlorides or aryl bromides and have been extensively discussed in the review literature.[2] A survey of selective and/or modern aromatic deiodination protocols will be presented below.

Rousseau reported in 2000 that the use of hydrogen gas and palladium on carbon could be used for selective reductions of aromatic iodides in the presence of functional groups known to be more susceptible to reduction.[79] Rousseau demonstrated that although an individual functional group may reduce at a faster rate with hydrogen gas in the presence of palladium than an aryl iodide, when the two functional groups are both present on the same molecule or on different molecules, the aryl iodide will react selectively because of the high affinity of the iodide for the heterogeneous palladium catalyst (equation 48). A highly efficient, metal- and solvent-free reduction of iodobenzene was reported requiring only the inclusion of TTMSS (tris(trimethylsilyl)silane) and air (equation 49).[85] Water could be added as a solvent without any loss of efficiency.

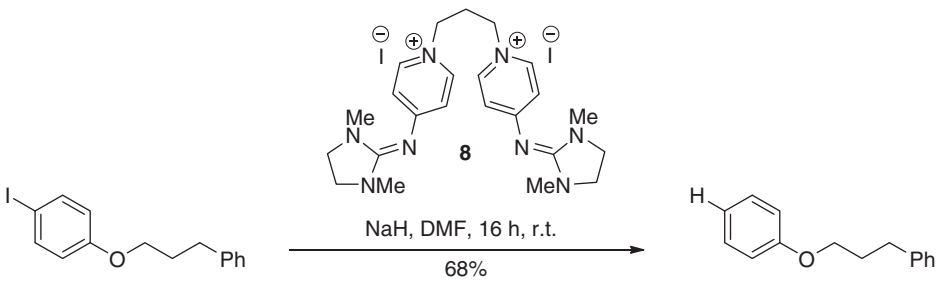


(48)

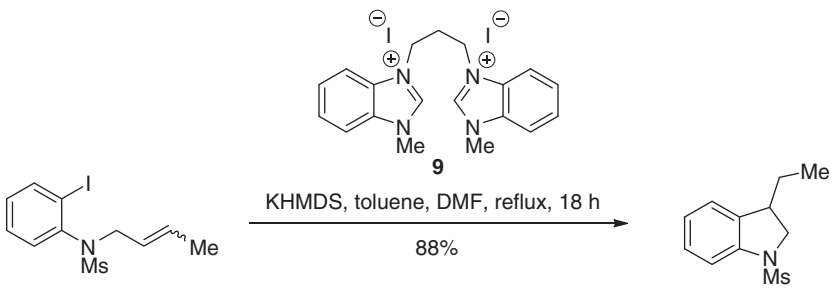


(49)

Neutral organic electron donor **8** has been shown to be successful at performing radical reductive cleavage of C–I bonds of aromatic iodides (equation 50),[81b] whereas organic electron donor **9** has been used to promote reductive cyclization of aryl iodides containing tethered alkenes and alkynes (equation 51).[86]



(50)

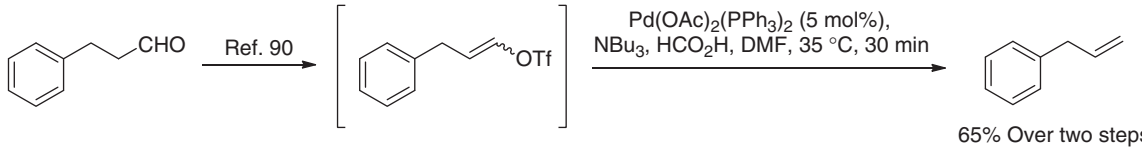


(51)

8.30.2 Reduction of sp^2 Carbon–Oxygen Bonds

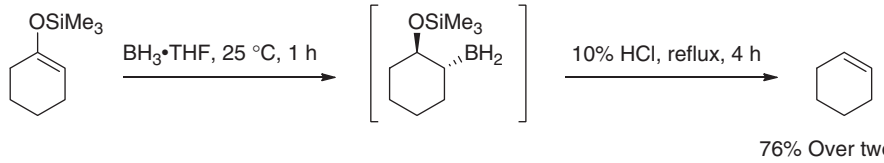
8.30.2.1 Hydrogenolysis of Enols

Several well-known methods are used to perform deoxygenation of alkyl alcohols, such as the Barton–McCombie deoxygenation[87] and the Markó–Lam deoxygenation,[88] (for more details on the topic of the reduction of saturated alcohols, *see* Chapter 8.27) but the reduction of enol derivatives, like enol triflates and silyl enol ethers, is less precedented. The reduction of alkenyl triflates derived from ketones has been known for decades, and has been generalized well enough to be implemented in total syntheses.[89] For more details on the topic of the reduction of ketones to alkenes, *see* Chapter 8.31. Surprisingly, the reduction of alkenyl triflates derived from aldehydes was not reported until 2007 by Poisson (equation 52).[90]



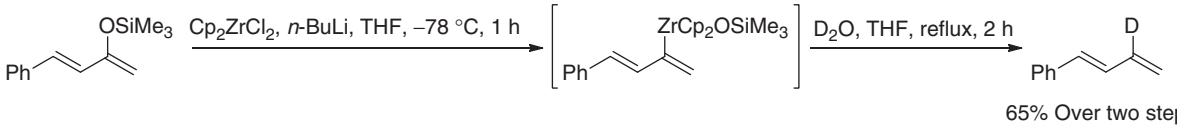
(52)

The reduction of silyl enol ethers to alkenes is rare, but some examples of such methods have been reported. Cyclic trimethylsilyl enol ethers undergo hydroboration followed by an acid-catalyzed elimination to generate alkenes (equation 53).[91] Unfortunately, the method cannot be generalized to acyclic systems because the β-trimethylsiloxy organoborane is too unstable and spontaneously generates the alkene, which then undergoes a second hydroboration.

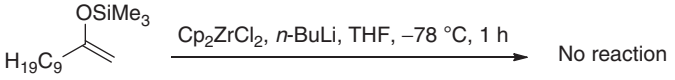


(53)

Acyclic silyl enol ethers can be converted to alkenes utilizing D_2O or water and zirconocene dichloride (Cp_2ZrCl_2), in which the zirconium undergoes oxidative addition into the C–O bond (equation 54).[92] This same technique has been used previously on alkenyl tosylates, fluorides, chlorides, bromides, and phenyl vinyl ether.[93] However, this method is also limited to activated silyl enol ethers and has been shown ineffective for unactivated acyclic silyl enol ethers (equation 55).



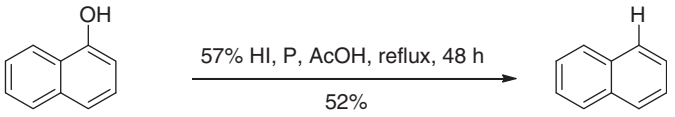
(54)



(55)

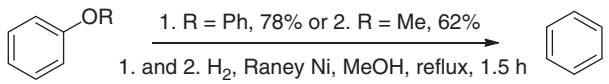
8.30.2.2 Hydrogenolysis of Phenols and Their Derivatives

The reduction of phenol and phenol derivatives has been studied much more extensively than enol derivatives. Phenols can undergo direct reduction via hydrogenolysis or indirect reduction by activation of the C–O bond. Direct reduction of phenols normally occurs under very harsh conditions.[94] For example, the direct reduction of naphthalene-1-ol can be achieved by refluxing a solution composed of hydroiodic acid, acetic acid, and red phosphorus (equation 56).

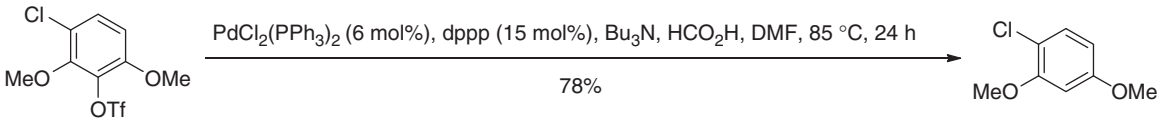


(56)

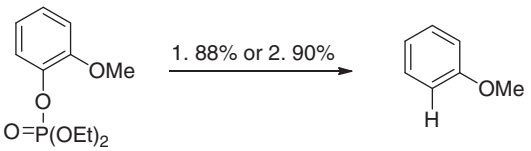
Phenols can be activated toward deoxygenation as ethers, esters, arylisoureas, sulfonates (mesylates, tosylates, and triflates), aryloxytetrazoles, and phosphate esters.[95] These phenol derivatives can undergo reduction through one of three types of reactions: heterogeneous catalytic hydrogenation (equation 57),[96] homogeneous palladium-catalyzed reduction (equation 58),[97] or zero valent metal reduction (equation 59).[98]



(57)



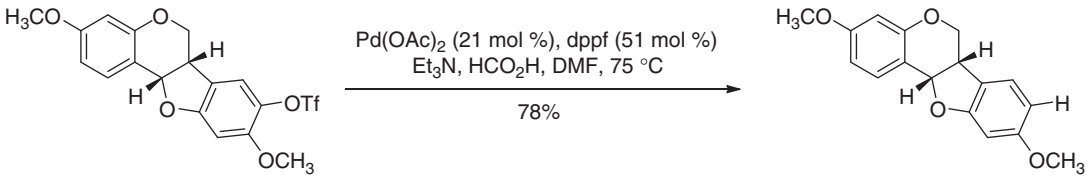
(58)



(59)

1. Li, NH_3 (liquid); 2. Na, NH_3 (liquid)

Many syntheses have employed the deoxygenation of phenol derivatives[99] as a means to remove oxygen-containing directing groups, such as the chemoselective palladium-catalyzed removal of a triflate group by Engler to finalize the synthesis, the isoflavonoid phytoalexin (±)-homopterocarpin (equation 60).[99c]



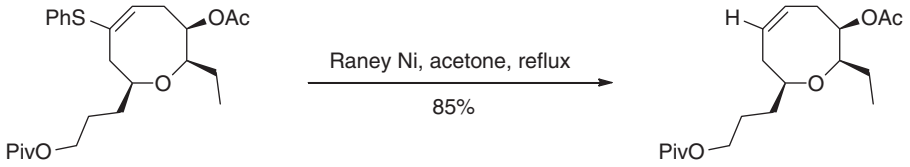
(60)

(±)-Homopterocarpin

8.30.3 Reduction of sp^2 Carbon–Sulfur Bonds

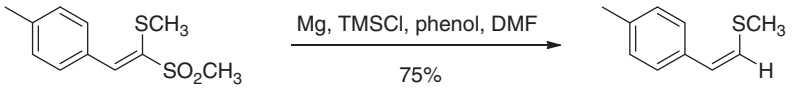
The reduction of alkenyl sulfides, sulfoxides, and sulfones has traditionally been difficult to perform without overreduction of the alkene to the alkane.[41a] However, reports of the chemoselective reduction of alkenyl sulfides, sulfoxides, and, most notably, sulfones are scattered in the literature and have become more prominent since the 1970s.[100]

Alkenyl sulfides are typically desulfurized with complex metal hydrides,[41a] zero valent metals (Li or Na),[101] Raney nickel,[102] NiCRA,[103] or homogeneous transition metal complexes containing zirconium.[104] In the synthesis of (+)-laurencin, Overman utilizes Raney nickel to desulfurize a key intermediate formed by a Prins cyclization (equation 61).[105]



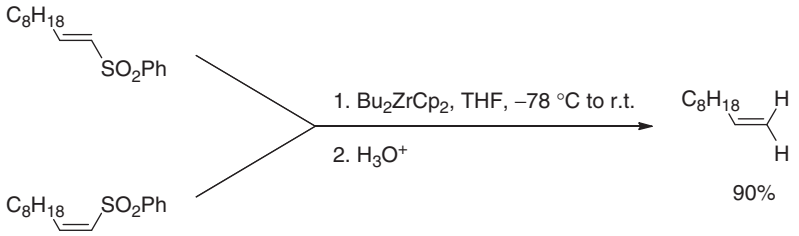
(61)

Alkenyl sulfoxides are also reported to undergo desulfurization with zero valent metals,[106] as well as homogeneous transition metal complexes containing zirconium.[107] In addition, alkenyl sulfoxides can undergo lithium exchange to form alkenyl anions.[108] Magnesium metal can be used to effect a selective desulfurization, converting β-aryl-α-(methylthio)alkenyl-*p*-tolyl-sulfones into (*E*)-α-aryl-β-(methylthio)ethylenes (equation 62).[106]



(62)

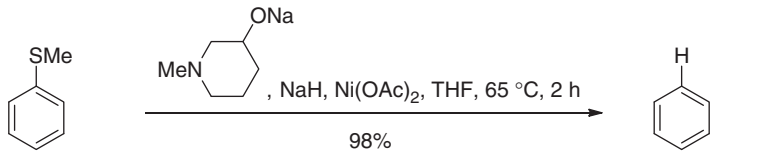
As compared with alkenyl sulfides and alkenyl sulfoxides, alkenyl sulfones have the most methods reported for undergoing desulfurization due to the weaker C–S bond. The Negishi reagent (Bu_2ZrCp_2) has been reported to convert alkenyl sulfides, sulfoxides, and sulfones to zirconocene derivatives capable of reacting with a variety of electrophiles (equation 63).[107]



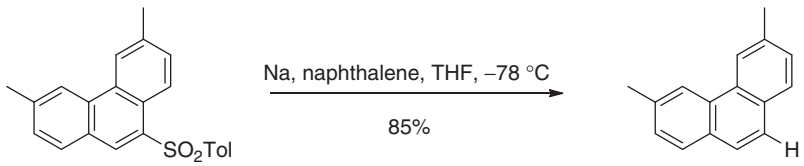
(63)

In addition to the desulfurization methods mentioned for alkenyl sulfides and sulfoxides, alkenyl sulfones can be desulfurized with aluminum amalgam,[109] sodium dithionite,[110] and SmI_2.[111]

Aryl sulfides, sulfoxides, and sulfones can be reduced with many of the same methods mentioned for alkenyl sulfides, sulfoxides, and sulfones. However, much of the past and current literature has been focused on the use of nickel-based catalysts (equation 64),[112] complex metal hydride reagents,[113] metal exchange,[114] and zero valent metals (equation 65).[115]



(64)

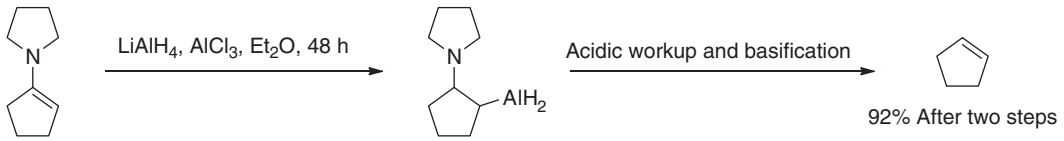


(65)

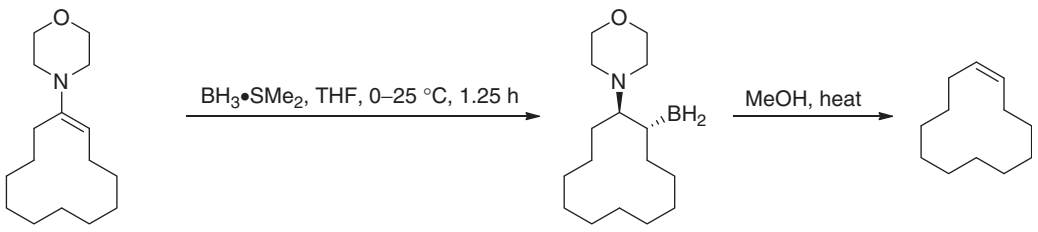
8.30.4 Reduction of sp^2 Carbon–Nitrogen Bonds

8.30.4.1 Hydrogenolysis of Enamines

Most reductions involving enamines produce saturated amines via hydrogenation of the π-bond.[116] However, several methods are available to effect the deamination of enamines to alkenes. These methods typically involve regioselective hydroalumination (equation 66)[117] or hydroboration (equation 67)[118] of the π-bond followed by 1,2 elimination.



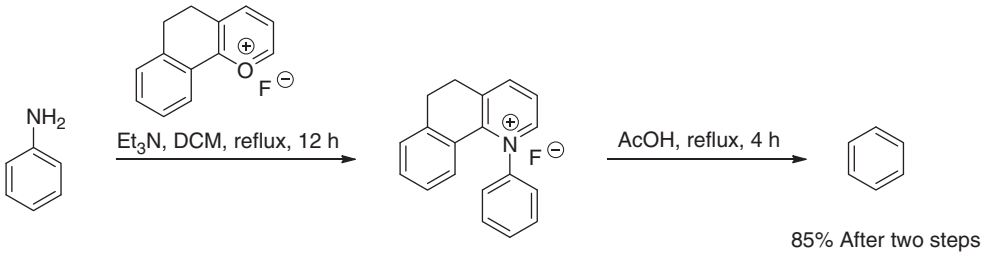
(66)



(67)

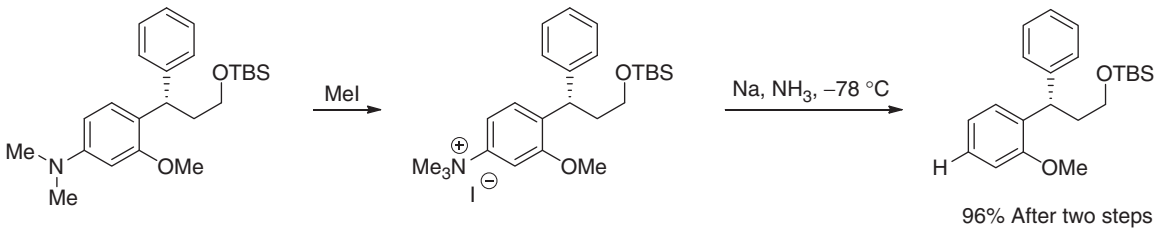
8.30.4.2 Hydrogenolysis of Aromatic Amines

The deamination of primary aromatic amines typically involves the conversion of the primary aromatic amine to a diazonium salt followed by reduction (*vide infra*). However, the direct deamination of a naphthalen-1-amine has been observed with the use of solid lithium aluminum hydride at 350°C.[119] A more reliable reduction method was developed by Katritzky, in which a primary aromatic amine and a pyrilium salt were converted to a pyridinium fluoride, which subsequently underwent C–N bond cleavage and protonation (equation 68).[120]



(68)

Quaternary aromatic amines have been shown to undergo deamination via electrolysis[121] and photolysis.[122] However, a reliable deamination method of quaternary aromatic amines, derived in one-pot from tertiary aromatic amines, was developed by MacMillan (equation 69).[123]

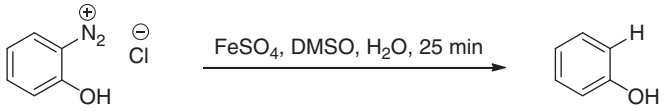


(69)

8.30.4.3 Hydrogenolysis of Arenediazonium Salts

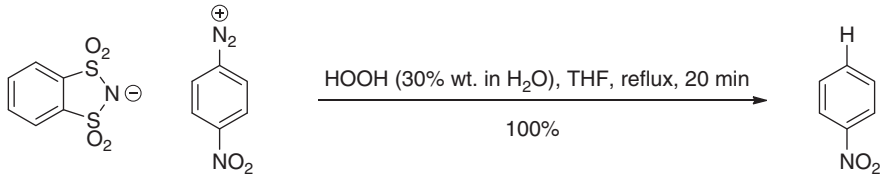
As mentioned above, the conversion of an aniline derivative to an arenediazonium salt (diazotization) followed by reduction is the preferred two-step protocol for the deamination of primary aromatic amines. Most arenediazonium salts are unstable at room temperature and are typically used directly after formation,[124] however some salts are stable at room temperature such as hexafluorophosphates,[125] bis(trifluoromethanesulfonyl)amidates,[126] tosylates,[127] and tetrafluoroborates.[128] Beyond simple reductions, arenediazonium salts are well-established substrates in organic synthesis for named reactions including the Sandmeyer, Gatterman, Schiemann, Meerwein, Pschorr, Gomberg–Bachmann, Japp–Klingemann, Heck, and Suzuki reactions.

Reductive dediazotization can either occur via an ionic pathway, a radical pathway or a combination of both (radical-polar crossover). When the ionic mechanism is operational, aryl cations are generated and reduced by a hydride source.[129] When the radical mechanism is operational, aryl radicals are generated and undergo hydrogen atom abstraction from a reagent or solvent.[130] The iron(II) sulfate-mediated dediazotization of the arenediazonium salt shown below follows a radical mechanism to generate a phenyl radical, which is believed to abstract a hydrogen atom from both DMSO and water activated by iron (equation 70).[130a]

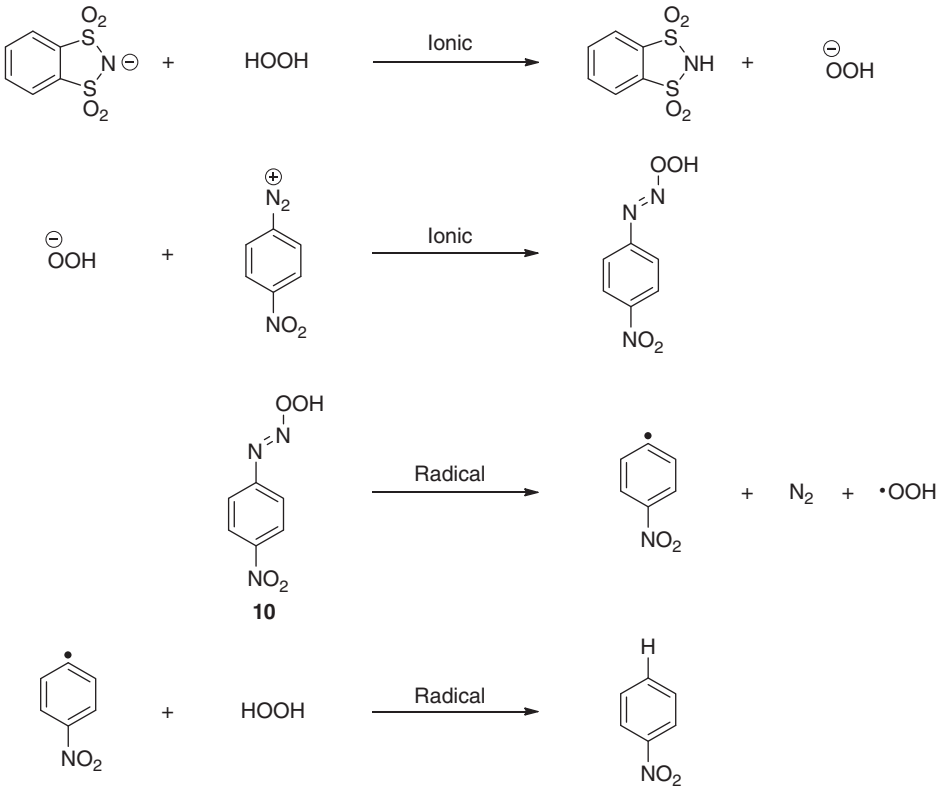


(70)

An example of reaction conditions that proceed through a radical-polar crossover is the hydrodediazotization of arenediazonium *o*-benzenedisulfonimides with hydrogen peroxide (equation 71).[131] The proposed mechanism of the reaction is initiated by an ionic pathway, but the highly reactive intermediate **10** undergoes radical disproportionation with heat to generate the phenyl radical (equation 72).

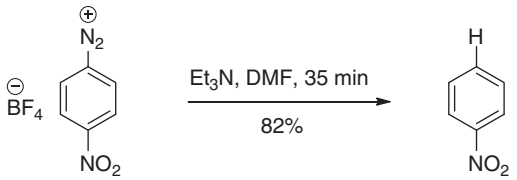


(71)



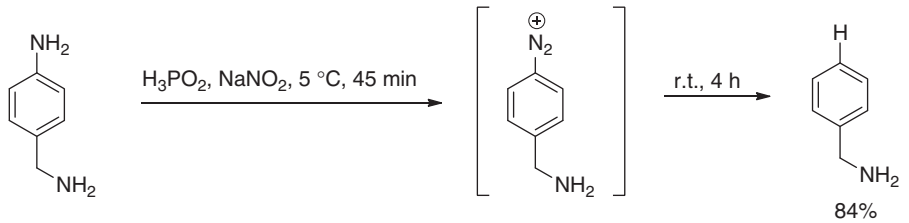
(72)

An interesting reductive dediazotization is observed when DMF/Et_3N is mixed with an arenediazonium salt containing electron-withdrawing groups.[128a] Mechanistic studies reveal that the formamide hydrogen atom of DMF is the sole hydrogen source (equation 73).



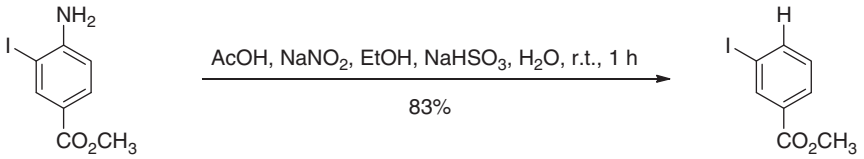
(73)

Hypophosphorous acid has continued to remain one of the most utilized reagents for the reduction of arenediazonium salts owing to its chemoselectivity.[132] In addition, hypophosphorous acid can be utilized to perform a one-pot deamination of primary aromatic amines by acting as an acid in the diazotization step and the hydrogen atom donor in the reduction step (equation 74).[133]

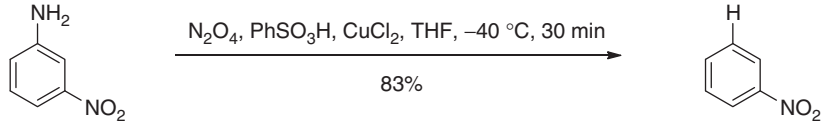


(74)

Acetic acid and sodium bisulfite (equation 75),[134] as well as dinitrogen tetraoxide (equation 76),[135] can also be utilized for one-pot deamination of primary aromatic amines.



(75)



(76)

References

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8.31 Reduction of Ketones to Alkenes

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Glossary

Bamford–Stevens reaction A reduction reaction where a sulfonylhydrazone derivative of an aldehyde or ketone is reacted with a base or metallic sodium to give alkenes via the intermediacy of a carbene (aprotic Bamford–Stevens) or a cation (protic Bamford–Stevens reaction).

Protodesilylation Reaction of a C–Si bond to give a C–H bond.

Shapiro reaction A reduction reaction where a sulfonylhydrazone derivative of an aldehyde or ketone is reacted with two equivalents of a strong base (normally alkyl lithiums) to give an alkene via the intermediacy of a vinyl anion.

Wharton reaction A reaction where a hydrazone derivative of an α,β-epoxy carbonyl compound undergoes an elimination of N_2 and H_2O to give an allylic alcohol with a 1,3-transposition of oxygen.

Wolff–Kishner reaction A reduction reaction where an aldehyde or ketone is reacted with hydrazine and a base at high temperature to give an alkane.

8.31.1 Introduction

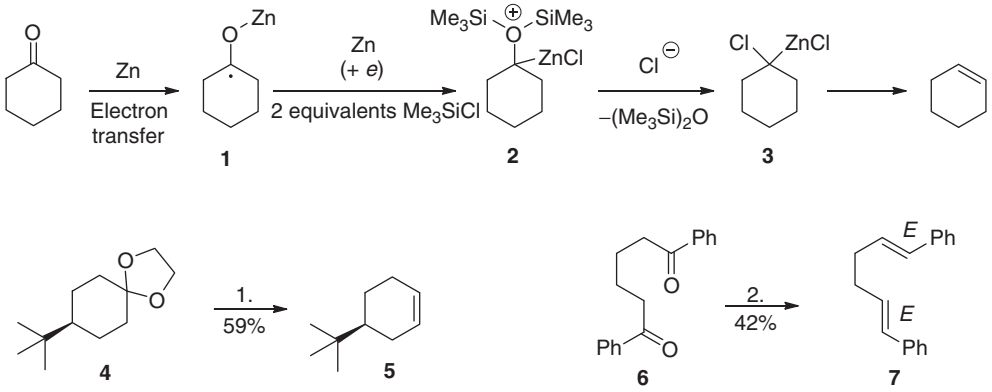
The carbonyl and alkene functionalities are arguably the most important functional groups in organic chemistry. Aldehydes and ketones can be transformed into alkenes with the addition of further carbon atoms by different processes (e.g., Wittig, Horner–Wadsworth–Emmons, Peterson, and McMurry reactions). For more details on this topic within the reference work (*see* Chapter 1.15). The direct interconversion of ketones to alkenes by reduction without a change in the carbon framework is a much rarer transformation. Direct methods are scarcely used, most commonly, the reduction of ketones to alkenes is accomplished in a two- or three-stage process. Thus, reduction of ketones to alcohols followed by elimination of water (or derivatization of the alcohol to a better leaving group followed by elimination) is employed. However, because both reduction reactions of ketones and elimination reactions of alcohols and their derivatives are covered in great depth elsewhere within 'Comprehensive Organic Synthesis' only a brief mention of this approach will be given (*see* Chapters 8.01, 8.04, and 6.18).

The past 20 years have seen an increase in the reduction of vinyl-heteroatom derivatives (e.g., vinyl triflates and silanes) to give alkenes themselves produced from ketones. Reduction of vinyl triflates to alkenes is normally catalyzed by transition metals with palladium derivatives being the catalysts of choice. In addition, the improvement in the synthesis of vinyl silanes from ketones means that protodesilylation of vinyl silanes is also a powerful method to deliver alkenes from ketones in a two-step protocol. Other common approaches include the reductive elimination of hydrazone derivatives, namely the Bamford–Stevens and Shapiro reactions.

8.31.2 Direct Methods

There are few reports of direct conversion of ketones into alkenes. These normally require high temperatures 205–550 °C and consequently are not useful laboratory procedures.[1,2] Mitsui Chemicals have a patent[3] to reduce ketones to alkenes by reacting with hydrogen in the presence of a silver-containing catalyst at 300 °C and at least one other catalyst selected from a Group 6 metal oxide, zeolite, alumina, and a heteropoly acid salt. One particular focus of their invention was to take the acetone side product of the cumene process for the production of phenol and recycle it to give propylene, one of the reactants in the original process. The procedure has therefore been developed to work on an industrial scale with high yields and selectivity for the desired product. A related continuous process suitable for industrial application involves the high temperature reduction of ketones via hydrogen transfer from secondary aliphatic alcohols by an amorphous zirconium hydroxide catalyst followed by dehydration.[4] All these 'direct methods' are in reality 'two-step' processes involving reduction to the alcohol followed by elimination.

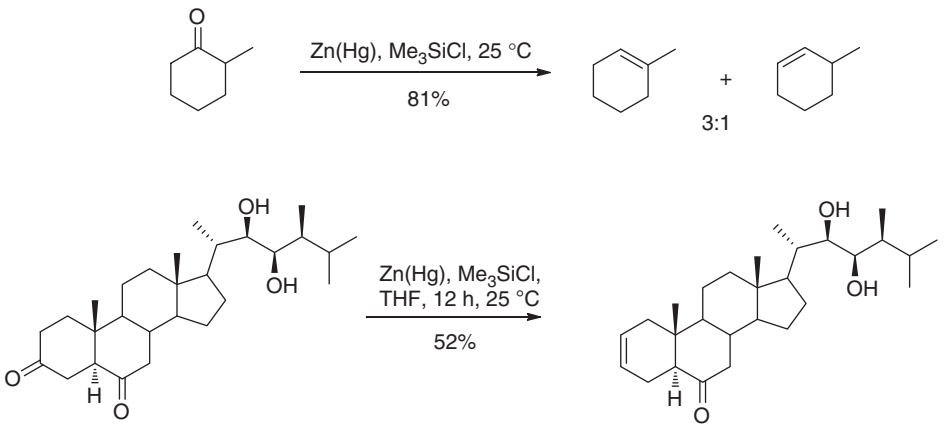
The most versatile direct approach suitable for laboratory transformations exploits organozinc carbenoid chemistry.[5,6] Reaction of ketones with trimethylsilyl chloride and zinc is thought to proceed via initial generation of the ketyl radical **1**, followed by ylid generation **2** and organozinc carbenoid **3** formation followed by insertion of the carbenoid into the adjacent C–H bond (Scheme 1). Two equivalents of the silicon electrophile are required.[7] Consequently, Motherwell introduced the use of 1,2-bis(chlorodimethylsilyl)ethane as a replacement for trimethylsilyl chloride to act as a bis electrophile which would permit intramolecular delivery of the second equivalent of silicon.[8]



1. 10 equivalents Zn(Hg), 4 equivalents Me_3SiCl, Et_2O, reflux, 16 h;
2. 10 equivalents Zn(Hg), 2 equivalents $Me_2ClSiCH_2CH_2SiClMe_2$, THF, 1 h

Scheme 1

The zinc carbenoid can be generated either from ketones directly **6** or from ketals **4** (Scheme 1). It should be noted that preferential (*E*)-alkene geometry is formed for acyclic ketones **6**→**7** and that the more substituted alkenes are favored, although regioselectivity is not high (Scheme 2).[6] The reaction is applicable to a range of substrates[9] and has been used in the synthesis of brassinolides. In this example, the A-ring ketone (C-3) of steroid **8** is regio- and chemoselectively reduced to give the ketosteroid **9**



Scheme 2

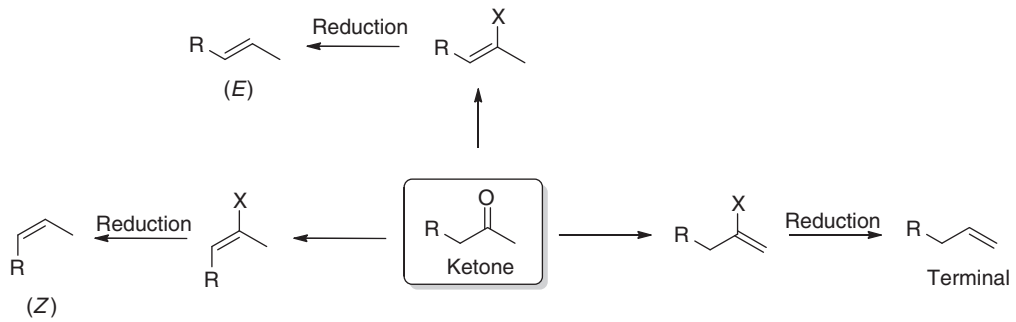
in 52% yield.[10] The chemoselectivity is thought to arise on steric grounds alone (the C-3 carbonyl being less sterically hindered). In fact it was possible to reduce selectively a C-3 carbonyl in the presence of C-6, C-7, C-12, C-17, and C-20 *oxo*-steroids.[9]

The Zn/Me_3SiCl approach for reduction of ketones to alkenes has not been extensively adopted, and instead longer (two- or three-step) transformations are normally utilized. This is probably due to two reasons: First, large amounts of reagents are required (typically 10 equivalents of Zn(Hg) and 2–4 equivalents of silicon electrophile), and second, the intermediacy of the ketyl radical **1** (Scheme 1) can often lead to pinacol products (dimerizations) which lower the synthetic utility of this approach.[6]

8.31.3 Reduction of Vinyl-Heteroatom Derivatives

8.31.3.1 Vinyl Esters and Ethers

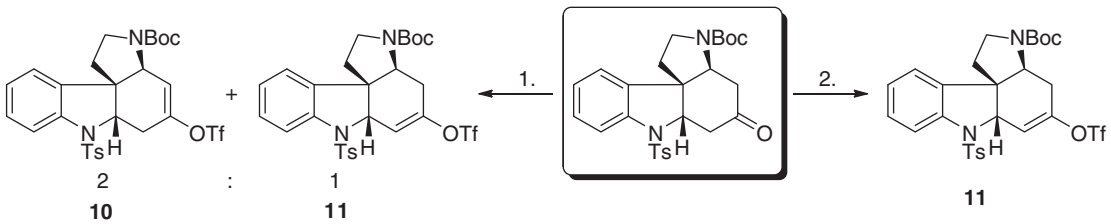
The ability to trap out either the kinetic or thermodynamic enolate of a ketone with a variety of alkylating or acylating agents is a powerful tool for making regio- and stereoselective vinyl-heteroatom derivatives. Reduction of these derivatives then leads to alkenes (Scheme 3). This approach is increasing in importance as a way of introducing an alkene bond with stereo- and regiocontrol. Over the years, the heteroatom group of choice has changed. In the 30-year period (1960–90) the reduction of vinyl phosphates was popular, whereas over the past 20 years the use of vinyl triflates has gained favor. This is presumably due to the versatility of vinyl triflates in other processes, such as coupling procedures with other organic fragments using palladium catalysis. However, the extra stability of vinyl phosphates, phosphonates, and phosphonites compared with vinyl triflates often makes them easier to handle and as a consequence they should not be overlooked when planning synthetic procedures. In fact, for this reason vinylic phosphorus compounds are starting to find favor in palladium coupling and metathesis reactions.



Scheme 3

8.31.3.2 Vinyl Triflates

These can be prepared from ketones in a variety of ways, to give either the kinetic or thermodynamic vinyl triflates (Scheme 3, $X = OSO_2CF_3$). They are normally prepared by the trapping of enolates with triflating agents[11] or by treatment of the ketones directly with triflic anhydride[12,13] and nonnucleophilic bases. The formation of regio- and stereocontrolled vinyl triflates requires the generation of regio- and stereocontrolled enolates, as trapping of these enolates with triflating agents proceeds with retention of stereochemistry.[14] Methods include the use of 2,6-di-*t*-butyl-4-methylpyridine[15] or pyridine/triflic anhydride,[16] sodium bicarbonate/triflic anhydride,[17] and the use of *N*-phenyltriflimide with various bases including lithium diisopropyl amide (LDA) (kinetic),[18] $i\text{-}Pr_2NMgBr$ (thermodynamic),[19] $KN(TMS)_2$,[20] and $NaN(TMS)_2$.[21] The Comins reagent [3-Cl-PyrN(Tf)$_2$][22] is increasingly being used to prepare vinyl triflates.[23,24] Mori has shown that changing the reaction temperature during the synthesis of the enol triflate can allow control over which regioisomer is obtained.[25] At $-78\ ^\circ C$ the kinetic isomer **10** was the major product but by increasing the temperature to $-35\ ^\circ C$ the thermodynamic product **11** was the only product obtained (Scheme 4).

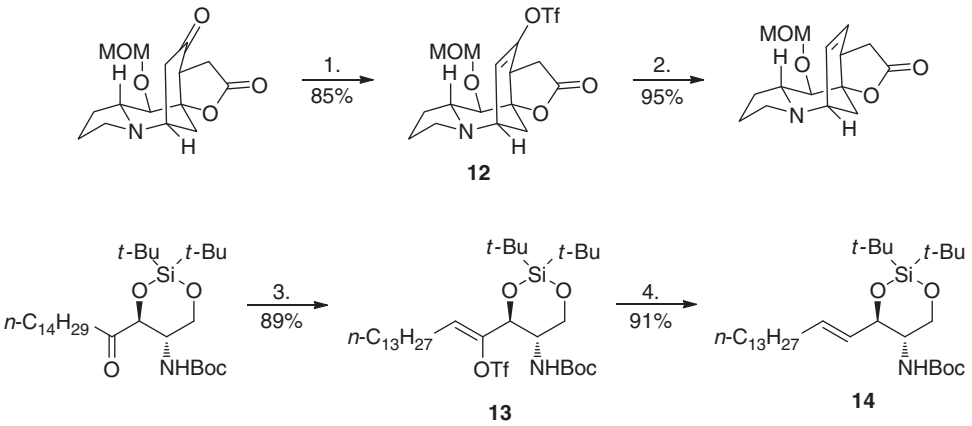


1. $PhNTf_2$, KHMDS, THF, –78 °C; 2. $PhNTf_2$, KHMDS, THF, –35 °C

Scheme 4

Once prepared, reduction can be achieved using palladium catalysis and various hydrogen sources. Cacchi's original conditions using trialkylammonium formate–palladium in DMF [HCO_2H, *n*-Bu_3N, $Pd(OAc)_2(PPh_3)_2$][26] have been applied to the synthesis of a wide range of different compounds including alkaloids,[25,27] terpenoids,[28,29] steroids,[30–32] sphingosine,[20,33] and carbocycles. The conditions are tolerant of a range of functional groups including ketones, esters, ethers, and alcohols. Dimethylformamide remains the solvent of choice although other solvents such as dioxane,[34] ethanol,[35] tetrahydrofuran,[36] toluene,[37] dimethylsulfoxide,[38] and ethyl acetate[39] have been used successfully. Nitrogen bases are used in the majority of cases, Et_3N, Bu_3N and *i*-Pr_2NEt[38] are the most common, but there are also reports of successful reductions with 2,6-lutidine[36] and K_2CO_3.[40] The use of DCO_2D as the reducing agent[41] can provide an attractive way of introducing a deuterium into an alkene. A range of palladium systems have been employed[42] including $Pd(acac)_2/Bu_3P$,[36] $PdCl_2(PPh_3)_2$,$Pd(PPh_3)_4$,[43] $Pd(PPh_3)_4$/dppf,[44] $Pd(OAc)_2/P(OMe)_3$,[45] Pd/C,[46] and $PdCl_2$(dppf) [dppf = 1,1′-bis(diphenylphosphino)ferrocene].[47] Similarly a range of reducing agents have been employed including HCO_2NH_4,[45] Et_3SiH,[48] H_2,[49] *n*-Bu_3SnH,[19,36,50] and $Me_2NH \cdot BH_3$.[40] Cacchi provides a good review of work in this area up to 2011 with a comprehensive list of the different conditions employed.[42]

In recent years, the reduction of ketones to alkenes via the intermediacy of vinyl triflates has proven the most versatile of all of the vinyl-heteroatom reduction strategies, particularly in application to natural product synthesis. Reduction of an enol triflate **12** was one of the final steps in the first reported total synthesis of (–)-secu'amamine,[27] a member of the *Securinega* alkaloid family, a group of compounds with a wide range of biological activites.[51] A key step of the synthesis of D-*erythro*-sphingosine, a component of glycosphingolipids and ceramides involved a reduction of an acyclic vinyl triflate **13** to the corresponding alkene **14** with control of alkene stereochemistry (**Scheme 5**).



1. KHMDS, $PhNTf_2$, THF; 2. $Pd(OAc)_2$, PPh_3, HCO_2H, *i*-Pr_2NEt, DMF; 3. KHMDS, THF/toluene, $PhN(Tf)_2$, –68 °C to –20 °C, 3 h; 4. HCO_2H, Et_3N, cat. $Pd(OAc)_2$, $(PPh_3)_2$, DMF, 60 °C, 4 h

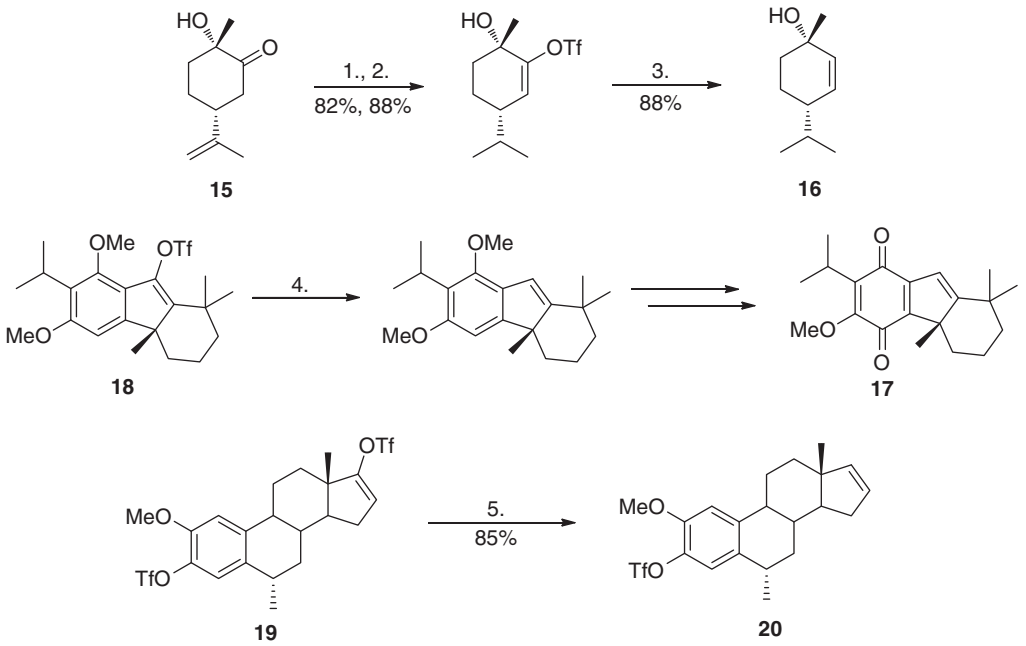
Scheme 5

A similar strategy has been employed as a key step in the diastereoselective and enantiopure route from limonene glycol **15** to the (1*S*, 4*S*) isomer of 4-isopropyl-1-methyl-2-cyclohexen-1-ol **16**, an aggregation pheromone of the ambrosia beetle *Platypus quercivorus* (**Scheme 6**).[46] The sensitive tertiary alcohol functionality of **15** survived during the transformations. A number of taiwaniaquinoids **17**, a family of unusual diterpenes isolated from East Asian conifers with interesting biological activities have been synthesized via an enol triflate **18** as a key intermediate.[27] In this case the extent of the steric hindrance of the enol triflate **18** called for a smaller ligand (trimethylphosphite) for palladium to be used instead of the normal bulkier triphenyl phosphine (**Scheme 6**). Selective reduction of a vinyl triflate in the presence of an aryl triflate **19**→**20** has been carried out using $Pd(dppf)Cl_2$ – in CH_2Cl_2 (**Scheme 6**).[32]

The counterintuitive reduction of a ketone to an alkene followed by hydration back to the alcohol has recently been used by Ghosh in the reduction of a ketone **21** via the enol triflate in the synthesis of the bottom tetrahydropyran ring of the antitumor macrolide **23**, (–)-lasonolide A (**Scheme 7**).[21] Direct reduction of the ketone to the desired alcohol proved troublesome with poor diastereoselectivity, hence their devised strategy of conversion to the enol triflate, reduction to the alkene **22**, diastereoselective epoxidation, and diisobutyl aluminium hydride (DIBAL-H) reduction of the epoxide to give the desired alcohol as a single isomer in excellent yield.

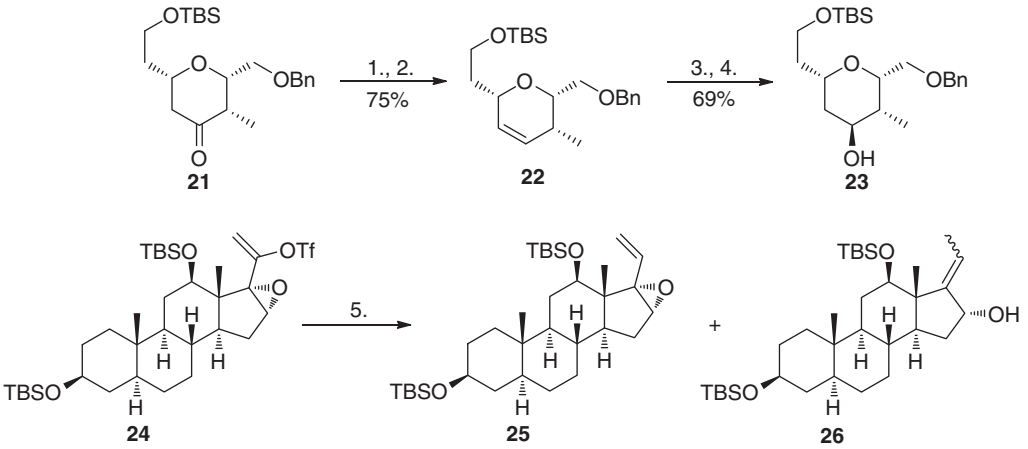
Tributyltin hydride has also been used as a reducing agent coupled with tetrakis(triphenylphosphine)palladium(0) in the presence or absence of lithium chloride.[19,50] Yamamoto et al. have successfully used these conditions for the reduction of steroidal α,β-epoxy vinyl triflates **24**, although they also obtained the allenic alcohol **26** as the side product in a 4:1 ratio in favor of the alkene **25** (**Scheme 7**).[24]

Careful choice of the reducing agent (i.e., Bu_3SnH vs. HCOOH) is often crucial for a successful transformation. Matsuo's study on the stereocontrolled formal synthesis of (±)-platenismycinin, using a palladium-catalyzed reduction of a vinyl triflate as a key step, gave a good yield only when formic acid was used as the hydrogen source, with tributyltin hydride providing the alkene in poor yields.[52]



1. KHMDS, THF, –78 °C, then $PhNTf_2$, –78 °C to r.t.; 2. PtO_2, H_2, MeOH; 3. $Pd(OAc)_2$, PPh_3, HCO_2H, *i*-Pr_2NEt, DMF, 70 °C; 4. $Pd(OAc)_2$, $P(OMe)_3$, HCO_2NH_4, Bu_3N; 5. $Pd(dppf)Cl_2$, HCO_2H, Et_3N

Scheme 6

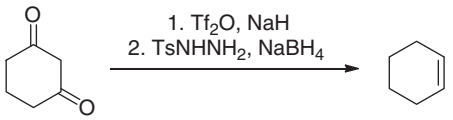


1. NaHMDS, THF, –78 °C, 1 h, then $PhNTf_2$, 30 min, warm to 23 °C, overnight; 2. $Pd(OAc)_2$, PPh_3, HCO_2H, *i*-Pr_2NEt, DMF, 65 °C, 1 h; 3. DMDO, MeCN, –15 °C, 20 min, warm to 23 °C, 4 h; 4. DIBAL-H, THF, –15 °C to 23 °C, 2 h; 5. $Pd(OAc)_2$, PPh_3, LiCl, Bu_3SnH, THF

Scheme 7

Metals other than palladium have been used to reduce vinyl triflates. Although less common, it has proved possible to use $NiCl_2 \cdot 2H_2O$ or $CuCl_2 \cdot 2H_2O$[53] with an excess of lithium powder and a catalytic amount (5 mol%) of 4,4′-di-*t*-butylbiphenyl (DTBB) in THF at room temperature. The $CuCl_2$ system successfully reduced both alkyl and conjugated enol triflates. The reactions were clean with over-reduction rarely observed, even when an excess of the reducing system was used or with long reaction times. The $CuCl_2$ system can also be used to make deuterium-labeled alkenes through the use of the deuterated copper salt, $CuCl_2 \cdot 2D_2O$.[53]

In a related reaction, a 1,3-dicarbonyl functionality has been transformed into the vinyl triflate with excess triflic anhydride and sodium hydride and then after treatment with tosylhydrazone and sodium borohydride reduced to cyclohexene. This transformation is a hybrid of the reduction of a vinyl-heteroatom bond and the Bamford–Stevens reaction.[54]

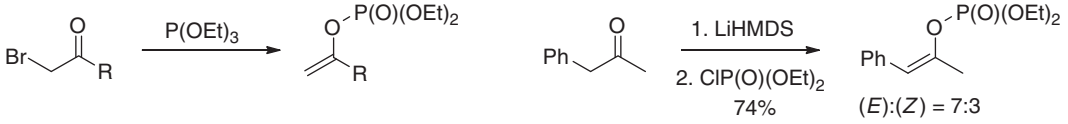


(1)

8.31.3.3 Vinyl Phosphates

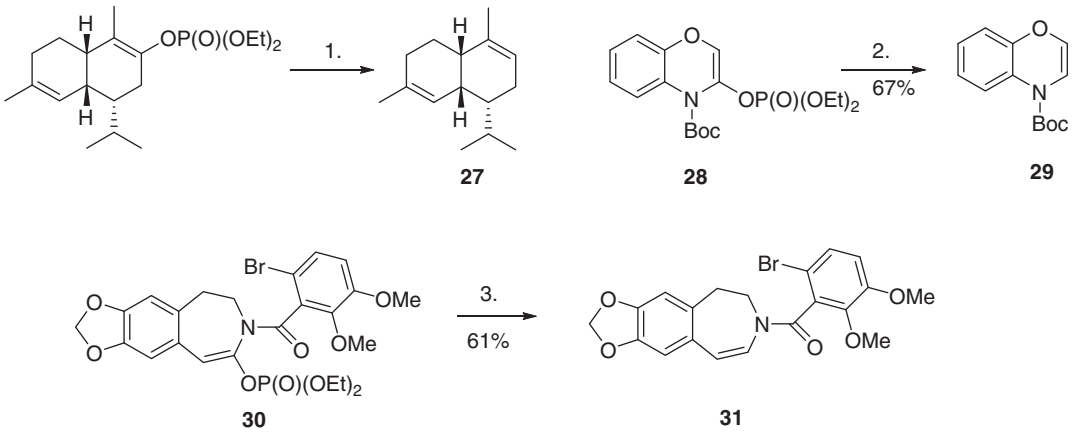
Although the reduction of vinyl triflates is perhaps the most exploited protocol to make alkenes from ketones (presumably due to their high reactivity) the use of vinyl phosphates and other P-activated enol derivatives are gaining favor.[55] This is likely due to their extra stability compared with vinyl triflates, the cheaper cost of their production and the more benign byproducts produced during their preparation.[56]

Vinyl phosphates can be prepared by a range of methods.[57,58] They were first prepared by Arbuzov in 1905 from α-haloketones and trialkylphosphites (Scheme 8).[59] However, the disadvantage with this approach is that there is poor regio- and stereocontrol. A better-controlled procedure starts from a preformed enolate followed by acylation with the appropriate phosphorous electrophile.[60] As with vinyl triflates the stereochemistry arises from that of the enolate (*see* Chapter 2.06). Recently, solid-supported vinyl phosphonates have been prepared.[61] Diphenyl phosphate analogs are generally more stable and easier to handle than dialkyl phosphates with phosphonates being even more stable.[62] Originally, enolates were accessed from ketones and α,β-unsaturated ketones by the addition of lithium in ammonia,[63] but greater regio- and stereocontrol can be accomplished using LDA, lithium hexamethyldisilazide (LiHMDS), or potassium hexamethyldisilazide (KHMDS), with or without added tetramethylethylenediamine (TMEDA) or hexamethylphosphorous triamide (HMPA).[64–66]



Scheme 8

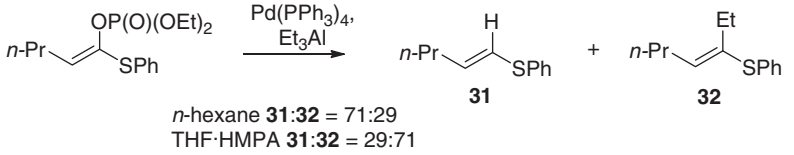
Reduction of vinyl phosphonates to alkenes can be accomplished by either Li or Na in liquid NH_3,[67] Li/$EtNH_2$ in *t*-BuOH,[68] or titanium metal in THF.[69] Although these seem relatively harsh conditions, the protocol has been used successfully as key steps in the preparation of a range of natural products, including (±)-α-amorphene **27**[70] and (±)-β-himachalene (Scheme 9).[71] More recently, milder conditions employing transfer hydrogenation in the presence of palladium catalysts have been employed to remove the phosphorus group from **28** (Scheme 9).[72] Both formic acid and dimethylphenyl silane[73] have been used as sources of hydrogen, with the latter being mild enough not to cause reduction of an aryl bromide **30** (Scheme 9).



1. Li, Liquid NH_3,THF; 2. HCOOH, Et_3N, $Pd(OAc)_2$, PPh_3, DMF, heat; 3. Me_2PhSiH, $Pd(PPh_3)_4$, DMF, 80 °C

Scheme 9

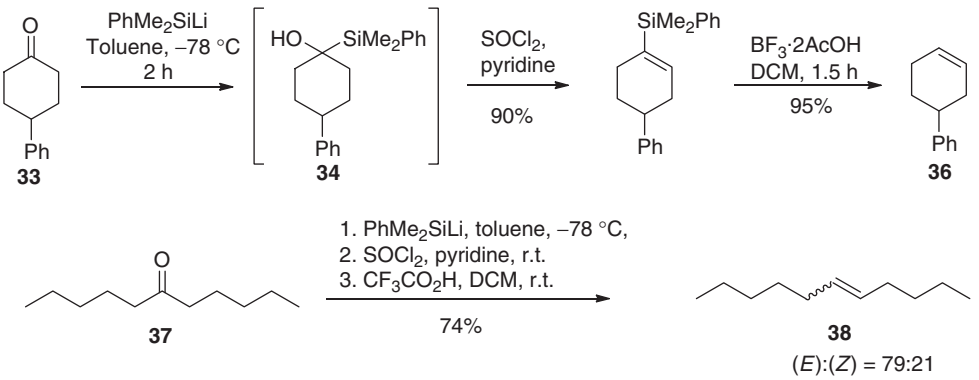
Reduction also occurs with a combination of triethylaluminium and tetrakis(triphenylphosphine)palladium, although competing ethylation can also occur with the ratio of products **31**:**32** being dependent on the solvent (Scheme 10).[74] The stereoselectivity of reduction is also influenced by solvent as well as temperature.[75] The example shown in Scheme 10 is a reduction of an enol phosphate, not from a ketone but from a thioester.



Scheme 10

8.31.3.4 Vinylsilanes

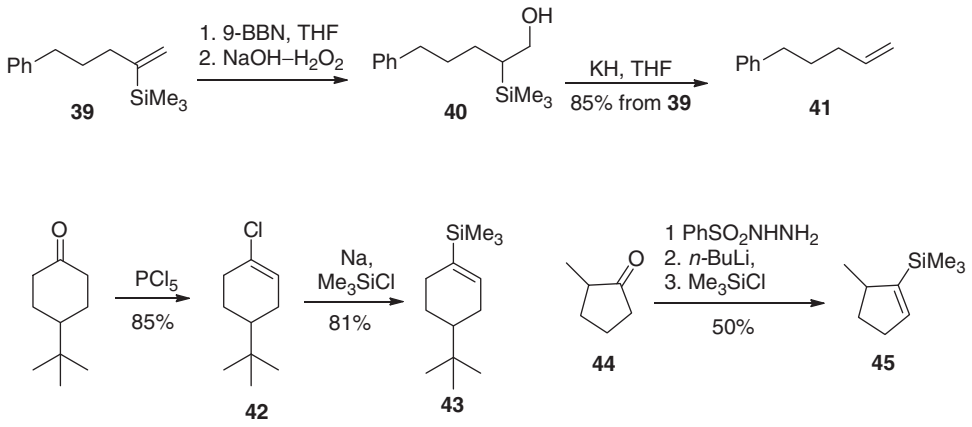
Vinylsilanes are versatile intermediates that can be protodesilylated with retention of configuration to give alkenes.[76] Although most vinylsilanes are prepared by hydrosilylation of alkynes (*see* Chapters 1.02, 8.25, and 4.05), they can also be prepared directly from ketones by the addition of phenyldimethylsilyllithium followed by elimination of the intermediate α-hydroxysilane **34** (Scheme 11).[77] Fleming has shown that simple cyclic **33** and acyclic ketones **37** can be transformed into vinyl silanes by the addition of phenyldimethylsilyllithium at −78 °C in toluene followed by the addition of thionyl chloride and pyridine at room temperature.[78] Protodesilylation under mildly acidic conditions using either $BF_3 \cdot 2AcOH$ in dichloromethane or trifluoroacetic acid in dichloromethane then liberated the corresponding alkenes **36** and **38**. For the acyclic ketone **38** (Scheme 11), a 79:21 mixture of *E*/*Z* vinylsilanes was produced that led to the same alkene selectivity.[78] It was not possible to prepare styrene from acetophenone using this approach. Protodesilylation using acids is well established (e.g., HI[79,80] and p-TsOH[81]) and proceeds with retention of alkene geometry, however the approach is not suitable for acid sensitive substrates or C-2 substituted vinylsilanes of terminal alkenes. Consequently, many other conditions have been investigated, the more common of which include tetrabutylammonium fluoride (TBAF) at 80 °C in DMF[82] or THF-MeCN,[83,84] anhydrous KF in DMSO,[80] tris(dimethylamino)sulfoniumdifluorotrimethylsilicate (TASF) in MeCN,[85] and AgF in THF/MeOH.[86]



Scheme 11

Alternative strategies for protodesilylation of C-2 substituted trimethylsilyl vinyl silanes of terminal alkenes have been reported. This class of vinylsilane under conventional acidic protodesilylation conditions often provides poor yields of alkenes, presumably due to the necessary formation of the relatively unstable primary carbocation intermediate.[87] Even protodesilylation under basic conditions (e.g., TBAF) for some substrates of this class is not high yielding. A two-step hydroboration–Peterson elimination protocol has been developed to circumvent these disadvantages. This involves regioselective hydroboration of the vinyl silane **39** with 9-BBN followed by basic peroxide work up to give the β-hydroxysilane **40** followed by a classic Peterson elimination (KH in anhydrous THF) to furnish the terminal alkene **41** (Scheme 12). Alternatively, high yields of protodesilylation of phenyldimethylsilyl analogs could be accomplished in a one pot procedure using *t*-BuOK, 18-crown-6, and TBAF. In this approach, the initial vinyl silane is transformed to a silanol which then undergoes protodesilylation.[88]

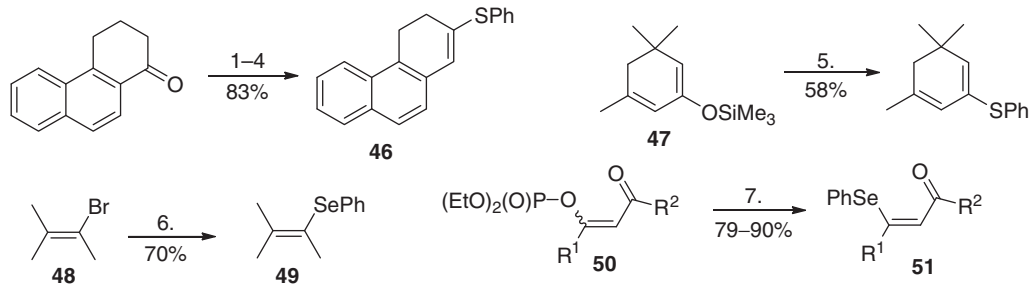
Vinylsilanes can be prepared from ketones in a two-step procedure via vinyl chlorides.[89] Hence, reaction of the ketone with PCl_5 initially gives the vinyl chloride **42** which after treatment with sodium metal and trimethylsilyl chloride provides the desired vinylsilane **43** (Scheme 12). However, as the direct reduction of vinyl chlorides leads to alkene products directly this is not necessarily an efficient process for the formation of alkenes from ketones (*see* Chapter 8.30). It is also possible to prepare vinylsilanes from ketones **44** via the intermediacy of arenesulfonylhydrazones. In this case, reaction with butyllithium provides the vinyl anion which can be trapped with trimethylsilyl chloride to give the corresponding vinylsilane **45** which can then undergo protodesilylation. However, as before this introduces unnecessary extra steps as trapping out of the vinyl anion with a proton source provides the desired alkene (via the Shapiro reaction) without the requirement of the intermediacy of vinylsilanes.[90]



Scheme 12

8.31.3.5 Vinyl Sulfides, Sulfones, and Selenides

Reduction of the sp^2 C–S and C–Se bond of vinyl sulfides, sulfones and selenides gives rise to alkenes (*see* Chapter 8.28).[91] Traditionally the main methods for the formation of vinyl sulfides or selenides from ketones involved multistep transformations. For example, regioselective introduction of an α-phenylthiol group via the kinetic or thermodynamic enolate, followed by reduction of the ketone to the alcohol, and elimination furnishes the desired vinyl sulfide **46** (Scheme 13).[92] This approach introduces the sulfide or selenide group α to the starting ketone. It is also possible to introduce the sulfide directly at the carbon of the carbonyl via the addition of thiols in the presence of Montmorillonite KSF clay in refluxing toluene. The regioselectivity of this process for unsymmetrical ketones was modest with only a 4.2:1 ratio of the thermodynamic to kinetic product being formed in the reaction of 2-methylcyclohexanone.[93] This approach can also be used for the formation of vinyl sulfoxides if the initial sulfide is oxidized (e.g., by H_2O_2/Na_2WO_4).[94] Better regiocontrol is observed if preformed silyl enol ethers **47** are reacted with phenylthiotrimethylsilane with an equimolar amount of $BF_3 \cdot Et_2O$ in chloroform (Scheme 13).[95] Vinyl selenides can be prepared directly from vinyl bromides, phosphates, or triflates.[96] The $Pd(PPh_3)_4$-catalyzed reaction of [bis(phenylseleno)-iodo-indium (III)], prepared from diphenyldiselenide and indium(I) iodide, with (*E*)-vinyl bromides was 100% stereoselective, but reaction of (*Z*)-vinyl bromides gave mixtures of products.[97] Chang and Bao have developed a CuI, L-proline, Zn catalyst system for the formation of vinyl selenide **49** from vinyl bromide **48**. Both (*E*)- and (*Z*)-vinyl bromides react with near retention of configuration (Scheme 13). Immobilizing the catalyst system in ionic liquids allowed for recycling of the catalyst system up to four times.[98,99] Vinyl phosphates **50** derived from 1,3-dicarbonyl compounds give (*Z*)-vinylselenides at −78 °C, even starting from a mixture of vinyl phosphate isomers (Scheme 13).[100]

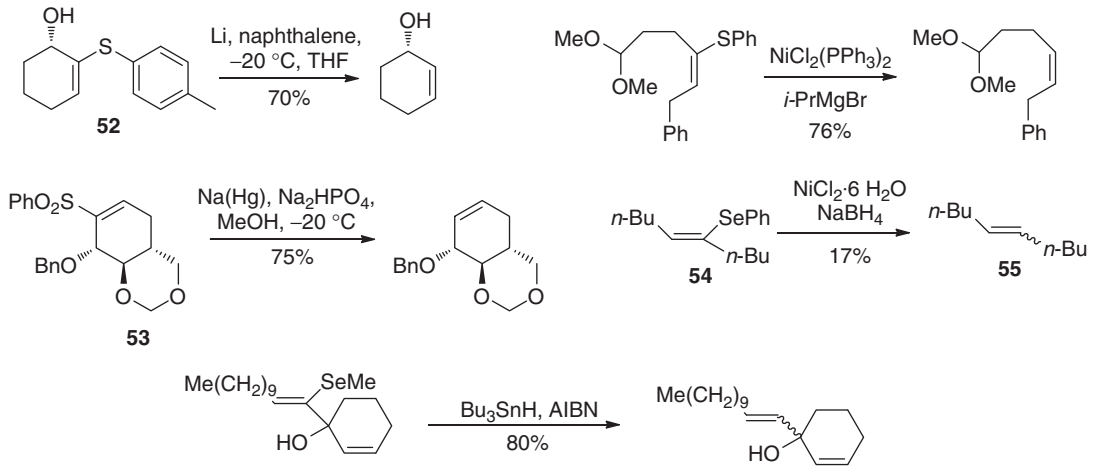


1. LDA, THF, –78 °C; 2. PhSSPh, HMPA, 0 °C; 3. $NaBH_4$, MeOH; 4. TsOH, C_6H_6, reflux; 5. $PhSSiMe_3$, $BF_3.Et_2O$; 6. CuI, L-proline, Zn, PhSeSePh, $[Bmim]BF_4$, 110 °C, 24 h; 7. PhSeLi, THF, –78 °C

Scheme 13

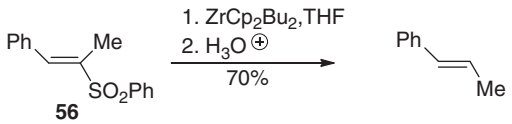
Reductive cleavage of the C–S bond has been achieved with 'NiH' using secondary Grignard reagents in combination with $NiCl_2(PPh_3)_2$,[101] as well as with other low-valent transition metals including $Pd(PPh_3)_4/LiEt_3BH$[102], $TiCl_4/LiAlH_4$,[102] and Rayney nickel (Scheme 14).[103] Reduction of enantiopure alcohol **52** was not possible with the conventional approaches above, instead reduction of the alkene occurred. The problem was solved by using Li-naphthalenide at −20 °C in THF (Scheme 14).[104] The 'NiH' procedures can also be used to reduce sulfones. Sensitive vinyl sulfone **53** has been reduced using Na(Hg) under strictly anhydrous conditions with buffered MeOH as solvent (Na_2HPO_4).[105] Vinyl selenides are easier to reduce than the corresponding

sulfides and as a consequence the procedures above often are not appropriate. For example, vinyl selenide **54** was reduced to **55** with $NiCl \cdot 6\ H_2O$ and $NaBH_4$ in only 17% yield and was not stereospecific.[106] Instead, the reduction method of choice is to use Bu_3SnH[107] or other radical reducing conditions (**Scheme 14**).[108]



Scheme 14

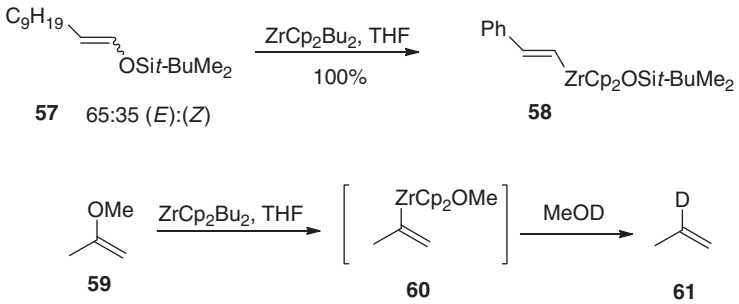
Vinyl sulfides and sulfones can be transformed into vinylzirconium derivatives by reaction with Cp_2ZrBu_2 in THF.[109] These vinylzirconium derivatives can then be hydrolyzed with acid or MeOD to introduce a proton or deuteron, respectively. A single (*E*)-isomer was obtained from vinyl sulfone **56**.



(2)

8.31.3.6 Enol Acetates, Ethers, and Silyl Enol Ethers

Although the synthesis of enol acetates, ethers, and silyl ethers from ketones is well established, these are only occasionally employed in the ketone to alkene reductive transformation. This is unfortunate as all three functional groups can be prepared from ketones with good regio- and stereoselectivity (*see* Chapter 2.06). The most promising procedures involve reaction of 'ziconocene' (prepared from Cp_2ZrCl_2 and 2 equivalents of BuLi) with all three functional groups giving vinylzirconium compounds under mild conditions. Protodezirconation then leads to alkenes with retention of configuration with respect to the C–Zr bond.[109] The size of the ether group controls the rate of the reaction. A 65:35 ratio of silylenol ethers of **57** furnished the vinylzirconium species **58** exclusively as the (*E*)-isomer (**Scheme 15**). Reaction of enol ether **59**, derived from acetophenone yielded vinylzirconium intermediate **60** which after reaction with MeOD furnished the dueterated alkene **61** (**Scheme 15**).[109]

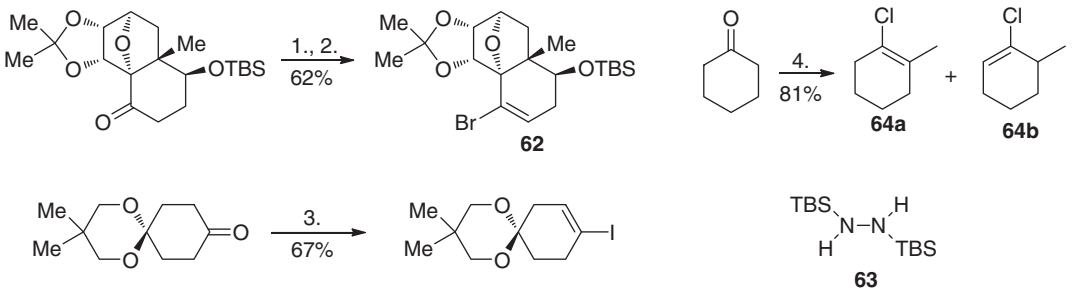


Scheme 15

Vinyl acetates[110] have been reduced with $Fe(CO)_5$ in refluxing dibutyl ether, although the yields are low[111] and only a few cases of enol ether reduction to alkenes have been reported, again at relatively high temperatures.[112] Silylenol ethers can be reduced by initial hydroboration followed by acid-catalyzed elimination of the trimethylsiloxy and borane groups.[113]

8.31.3.7 Vinyl Halides

Vinyl chlorides, bromides, and iodides can be prepared directly from ketones and reduced via a metallation–protonation strategy,[114] or via a radical reduction[114] (*see* Chapter 8.30). Traditional methods for transforming ketones into vinyl halides can be divided into two classes. The first involves the reaction of the ketones with hydrazine, followed by the addition of the halogen in the presence of a base. This approach has been used in the synthesis of **62** an intermediate in the total synthesis of nakiterpiosin.[115] This is a variant of the Wolff–Kishner reduction, and was originally championed by Barton for the transformation of steroidal ketones into vinyl iodide derivatives.[116] The synthesis of hydrazones can be problematic due to their instability and for less encumbered substrates yields of vinyl iodides were low. Consequently, Myers developed a new approach using *N*-*t*-1,2-bis(*tert*-butyldimethylsilyl)hydrazine **63** as a reagent to form *N*-*tert*-butyldimethylsilylhydrazones from ketones catalyzed by 0.1 mol% $Sc(OTf)_3$. This allows stable hydrazones to be prepared under mildly acidic conditions (Scheme 16). Reaction of the hydrazones, prepared *in situ* with 1,1,3,3-tetramethylguanidine (TMG) and iodine provides vinyl iodides in high yields. A more hindered base, 2-*t*-butyl-1,1,3,3-tetramethylguanidine (BTMG), was necessary to produce vinyl bromides.[117] The second major method for the transformation of ketones into vinyl halides involves reaction of ketones with phosphorus halides such as PCl_5,[89] catechol phosphorus tribromide or thionyl chloride.[118] A milder procedure using chlorotriphenoxyphosphonium chloride or bromide has been developed by Prati.[119] The chemistry tolerates a number of functional groups but is not significantly regioselective, the vinyl chloride **64** being formed as a 55:45 ratio of thermodynamic **64a** to kinetic **64b** products. Vinyl halides can also be prepared directly from vinyl triflates using $Pd_2(dba)_3$ and KBr or KCl,[120] or from vinyl phosphates using PPh_3 and the halogen X_2 (Scheme 16).[121]

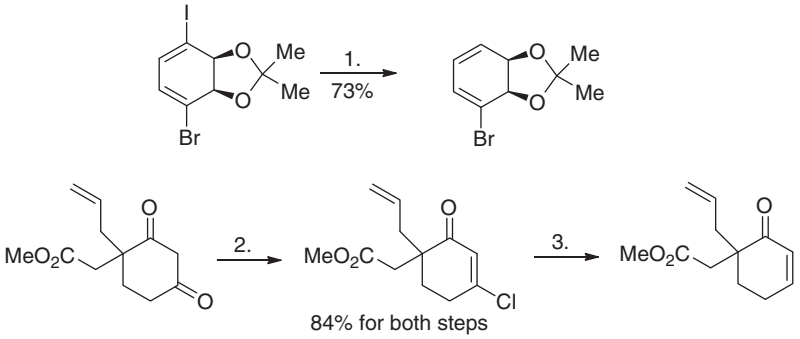


1. NH_2NH_2, Molecular seives, MeOH; 2. Br_2, *t*-BuOK, Et_2O; 3. **63**, cat. $Sc(OTf)_3$, I_2, TMG, THF, 0 °C; 4. $(PhO)_3P$, Cl_2, Et_3N

Scheme 16

Reduction of vinyl halides via metallation–protonation is the most common method for direct replacement of the halogen with a proton or deuteron, and there is an excellent review on this topic.[114] Typically metallation is carried out with alkyllithiums. Nicolaou used this approach in his synthesis of the echinopines A and B.[122] An alternative approach is to reduce the C–halogen bond under reductive radical conditions. A number of radical reducing agents can be employed with the most common being based on trialkylstannanes or silanes.[123] Vinyl halides can be reduced electrochemically and yields are often higher than for tributyltin hydride-mediated reactions (Scheme 17). It should be noted that it is possible to reduce chemoselectively the weaker of two carbon–halogen bonds.[124]

Monoreduction of 1,3-diketones can be accomplished by reaction with oxalyl chloride followed by reduction with a Zn–Ag couple (Scheme 17).[125]

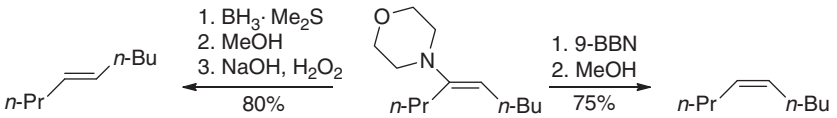


1. –2.2 V, 1M Bu_4NOH; 2. $(COCl)_2$, $CHCl_3$, reflux; 3. Zn–Ag, MeOH, r.t.

Scheme 17

8.31.3.8 Enamines

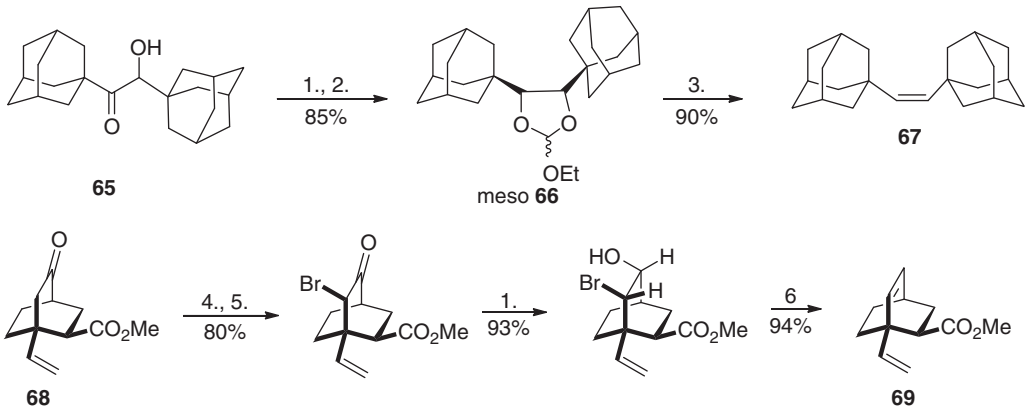
Enamines can be readily prepared from ketones, however their reduction to alkenes is less straight forward. The most commonly employed procedure involves hydroboration followed by elimination of the boron and amine entities.[126] Brown developed a mild procedure using hydroboration with 9-BBN followed by methanolysis. Both cyclic and acyclic enamines can be reduced and either pure (*Z*)- or (*E*)-alkenes can be obtained from the same enamine by varying the nature of the reductant (Scheme 18).[127]



Scheme 18

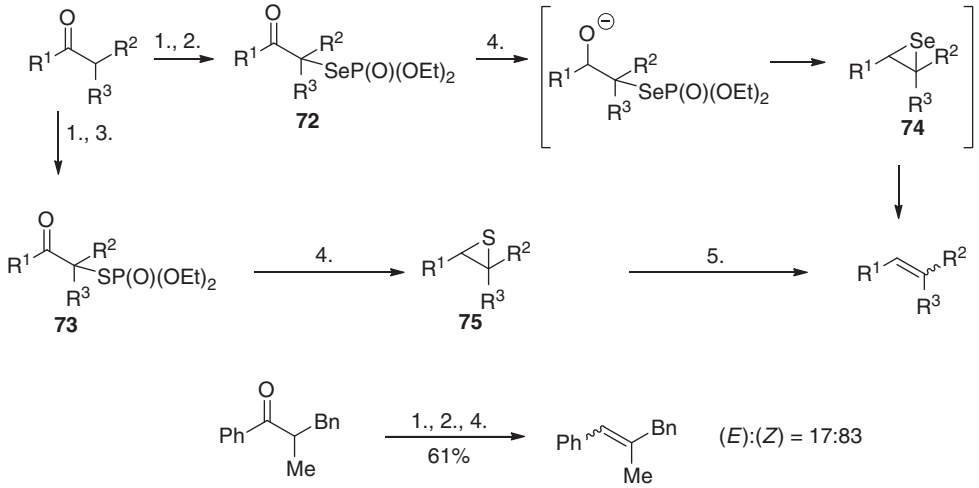
8.31.4 Reductive Elimination of α-Substituted Ketones

The regioselective introduction of an α-oxygen, α-sulfur, α-halo, or α-amino substituent to a ketone scaffold followed by reduction of the ketone and 1,2-elimination is a common approach to the preparation of alkenes from ketones (*see* Chapter 7.07). Hydride reduction of α-hydroxyketones provides vicinal diols that can be deoxygenated by application of the Crank–Eastwood elimination sequence **65**→**66**→**67** (Scheme 19).[128] Cyclic sulfates, prepared by reaction of diols with thionyl chloride can be converted to alkenes with Na naphthalide, although this often gives rise to mixtures of (*E*)- and (*Z*)-isomers.[129] Isomeric mixtures are often produced in the Bu_3SnH-mediated reduction of 1,2-bisxanthates, although channeling to give the thermodynamic alkene product is possible in some cases.[130] The same xanthate approach can be used to reductively eliminate β-hydroxysulfides and sulfones, β-hydroxyhalides, and β-hydroxyethers.[108] It is not always necessary to functionalize the alcohol as a xanthate before reaction as elimination of HOX is also possible with zinc. Paquette has used this approach to produce bicyclic alkene **69** from the ketone **68** (Scheme 19).[131]



Scheme 19

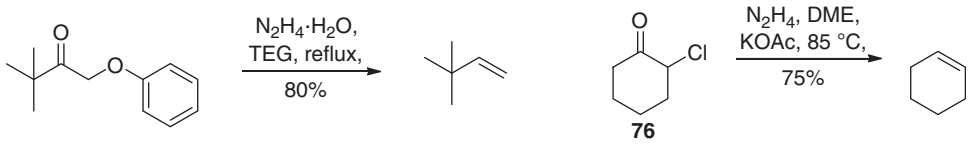
The stereoselective synthesis of trisubstituted alkenes from ketones via *S*-(β-oxoalkyl)thiophosphates and their selenium analogs has been described[132] and also applied to unsaturated ketones to give dienes.[133] The overall procedure can be carried out in one pot. The process involves regioselective formation of the silylenol ether and reaction with either the selenium salt $(EtO)_3P^+SeClSO_2Cl^-$ **70** or sulfenyl chloride $(EtO)_2P(O)SCl$ **71** to give seleno **72** and thiophosphates **73**, respectively. Kinetically controlled reduction of the ketone with $NaBH_4$ occurs with Felkin–Anh control. For acyclic selenophosphate systems migration of the phosphorus group from selenium to oxygen followed by episelenide **74** formation occurs with inversion at carbon. Spontaneous selenium elimination from the episelenide **74** then gives rise to (*Z*)-alkenes predominantly. With the sulfur analogs the intermediate episulfides **75** can be isolated and desulfurization initiated by reaction with triethyl phosphite (Scheme 20).[133] The desulfurization was shown to occur with retention of configuration from the episulfide. Episulfide intermediates can also be obtained by $NaBH_4$ reduction of α-ketosulfides of benzothiazole.[134] Control of alkene geometry by variation of the reducing agent is possible for α-ketosulfones of benzothiazole.[135] Hence, reaction with $LiBH_4$ in MeOH furnishes (*E*)-alkenes predominantly, whereas reaction with $NaBH_4$ and $ZnCl_2$ gave rise to the (*Z*)-alkenes as the major products.[136]



1. Me_3SiCl, Et_3N, NaI, –60 °C; 2. **70**, –78 °C to 0 °C; 3. **71** –78 °C to 0 °C; 4. $NaBH_4$, MeOH; 5. $(EtO)_3P$

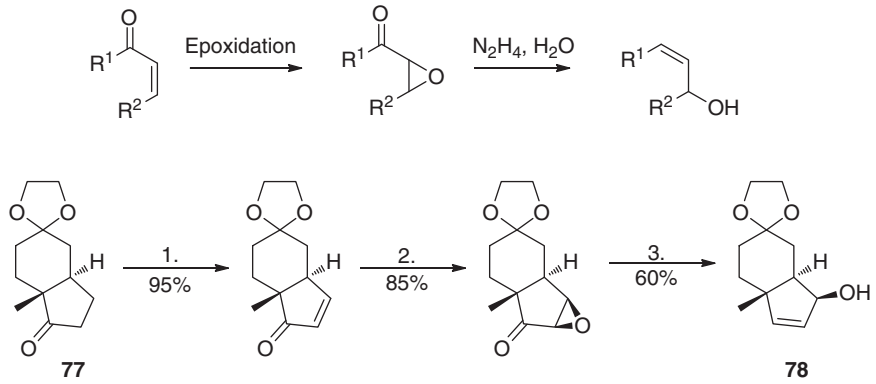
Scheme 20

Perhaps one of the earliest methods for elimination of α-substituted ketones is the Kishner eliminative reduction.[137] A number of α-substituents including amino groups, aryl ethers, and thioethers undergo reductive elimination in varying yields along with the standard Wolf–Kishner reduction product.[138,139] α-Halo ketone **76** underwent efficient Kishner reductive elimination with 2–3 equivalents of hydrazine at 85 °C in the presence of potassium acetate as a buffer (Scheme 21).[140] Reductive elimination of α-halocholestanones also proceeds in moderate-to-good yields; however, other types of α-haloketones often give poor yields (Scheme 21).



Scheme 21

The most common variation of the Kishner reductive elimination is the Wharton rearrangement in which an α,β-epoxy ketone undergoes reductive elimination to give an allylic alcohol on treatment with hydrazine (Scheme 22).[141] The α,β-epoxy ketone can be formed direct from an enone and hence the reaction represents a two-step procedure from enones to allylic alcohols, with a 1,3-transposition of oxygen and a migration of a carbon–carbon double bond.



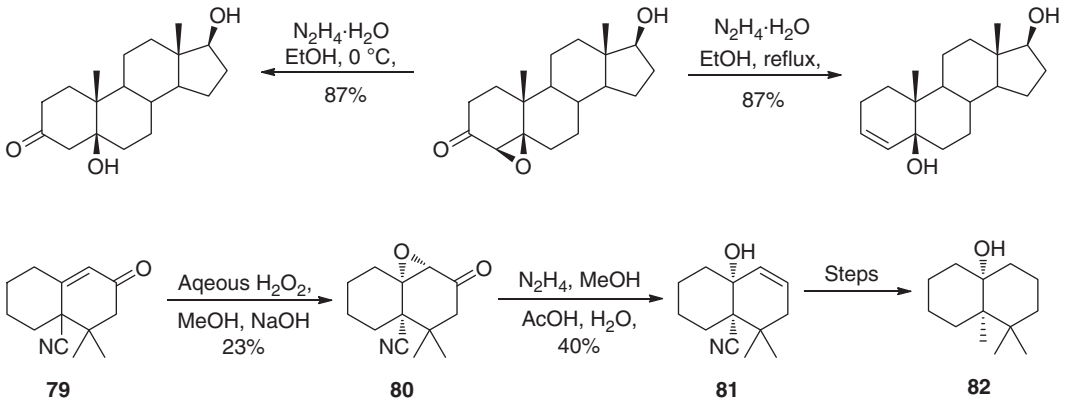
1. LDA, TMSCl, Et_3N, then $Pd(OAc)_2$, CH_2Cl_2–MeCN, 35–40 °C; 2. TBHP, DBU, CH_2Cl_2, r.t., 30 h, 85%; 3. $N_2H_4·H_2O$, TMSCl, DMF, r.t., 5 min

Scheme 22

The reaction has been used extensively to give allylic alcohols from cyclic ketones in the synthesis of a plethora of natural products, particularly on five- and six-membered rings; (+)-lepadin B,[142] bicycle[3.3.0]octane core of geodinA,[143] lairdinol A,[144] azaspiranic alkaloids.[145]

It is often necessary to screen a range of different solvents, temperatures, and proton sources to optimize the reaction. When the standard Wharton conditions were used only poor yields of **78** were obtained (<40%), however, 60% yield could be obtained using $N_2H_4 \cdot H_2O$ in dry DMF in the presence of TMSCl at room temperature (Scheme 22).[146] With these new conditions, a one-pot reaction was possible with a 30–40% yield of the allylic alcohol **78** over three steps from the acetal **77**.

Short reaction times (10 min) are often needed in order to prevent over-reduction.[147] Salvador has carried out a study into the reductive cleavage of α,β-epoxy ketones to both allylic alcohols and β-hydroxyketones by hydrazine hydrate in ethanol.[148] They found that the reaction temperature was the key in determining the products of the reaction; reactions carried out at 0 °C or lower gave exclusively the β-hydroxyketone, whereas reactions carried out at reflux gave the allylic alcohol expected under Wharton conditions. Reactions carried out at room temperature or 50 °C resulted in mixtures of the two products (Scheme 23).



Scheme 23

The Wharton rearrangement can be paired with a stereocontrolled epoxidation in order to introduce a chiral center into a molecule. Kraft et al. have used this methodology in the synthesis of compounds structurally related to (–)-patchoulol,[149] an important base note ingredient in around a third of all fine fragrances. Their target compound (4aR^*, 8aR^*)-1,1,8a-trimethyldecahydronaphthalen-4a-ol **82** required *syn*-selective introduction of the oxygen functionality which was achieved via a Weitz–Scheffer epoxidation[150] to give the α,β-epoxy ketone **80** ready for Wharton rearrangement. Wharton rearrangement of the α,β-epoxy ketone gave the desired allylic alcohol **81** in 40% yield, retaining the *cis* stereochemistry of the bridgehead (Scheme 23).

The Wharton rearrangement has also been employed in the synthesis of 5-6-7-fused tricyclic analogs of dictyoxetane,[151] a diterpene isolated from *Dictyota dichomota*.[152] An inseparable mixture of the two regioisomers **83** and **84** was treated with *t*-butyl hydroperoxide to give a mixture of *exo*-epoxides **85** and **86**, which again were inseparable. These were subjected to Wharton rearrangement giving two regioisomers **87** and **88** which were now separable by chromatography (Scheme 24).

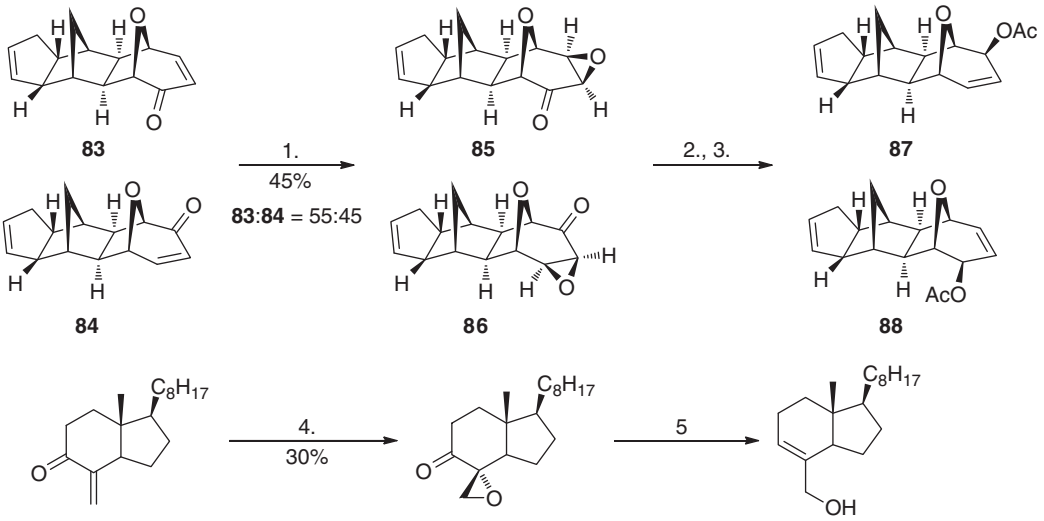
There are also examples of the conversion of exocyclic α,β-epoxy ketones into the corresponding exocyclic hydroxyl methylene products (Scheme 24)[153] as well as the conversion of exocyclic ketones into their ethylindene derivatives.[154] In such reactions there is little stereoselectivity in the production of (*E*)- or (*Z*)-alkenes.

The transformation has also been applied to acyclic enones, which can show good stereoselectivity. In the total synthesis of (+)-cyclindricine C reported by Hsung,[155,156] treatment of α,β-epoxy ketone **89** with hydrazine in the presence of 0.5 equivalent of AcOH led exclusively to the *trans*-allylic alcohol **90** in 66% yield. The *cis*-allyl alcohol **91** was observed in one instance when 10 equivalents of AcOH were used but it was unclear whether this was as a result of the amount of AcOH used or the stereochemistry of the epoxide (Scheme 25).

In a reaction related to the Wharton rearrangement 2-ketoaziridines **92**, formed from enones by treatment with NH_2OMe, underwent hydrazinolysis to give allyl amines **93** (Scheme 25).[157] The reaction proceeds well in ethylene glycol with KOH as the base and in *t*-BuOH with NaOMe as the base, both at 100 °C. 3,5-Disubstituted pyrazoles are produced as byproducts but the selectivity for the allyl amine is moderate-to-high. The scope of the reaction has been investigated and shown to include both unsubstituted aziridines and sterically hindered aziridines. It was also shown that reaction of one enantiomer of the aziridine affords the corresponding homochiral allylamine, indicating that the reaction is stereospecific.

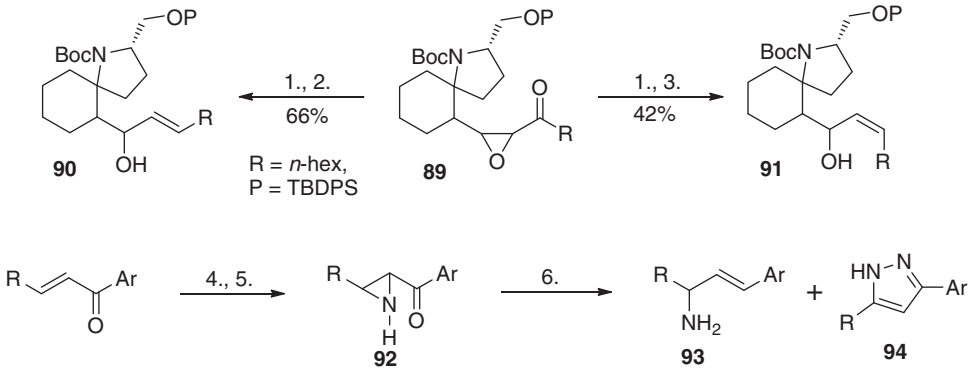
8.31.5 Reductive Elimination of Hydrazone Derivatives

The reductive elimination of hydrazone derivatives provides another route from ketones to alkenes and can be split into three main classes of reactions; the protic Bamford–Stevens reaction, the aprotic Bamford–Stevens reaction, and the Shapiro



1. *t*-BuOOH, Na_2CO_3, MeOH, H_2O; 2. $NH_2NH_2{\cdot}H_2O$, MeOH, AcOH; 3. Ac_2O, Et_3N; 4. H_2O_2, NaOH, MeOH; 5. N_2H_4, MeOH, 0 °C

Scheme 24



1. $N_2H_4{\cdot}H_2O$, MeOH, –10 °C; 2. 10.0 equivalents AcOH; 3. 0.5 equivalent AcOH; 4. NH_2OMe, EtOH, 70 °C; 5. NaOMe, DMF, r.t.; 6. $N_2H_4{\cdot}H_2O$, KOH, ethylene glycol, 100 °C

Scheme 25

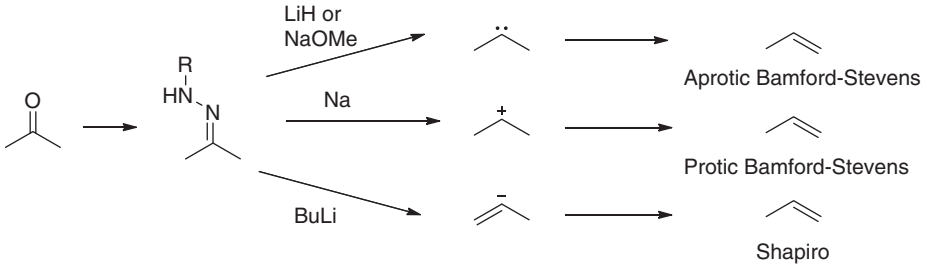
reaction, which all proceed via different intermediates leading to different alkene products with different selectivities (Scheme 26). The early work in this area up until 1990 is covered well in three comprehensive reviews.[158–160] The reactions most commonly employ tosylhydrazones[161,162] or 2,4,6-triisopropylbenzenesulfonylhydrazones (trisylhydrazones),[163–165] however, more recently *N*-2-phenylaziridinyl hydrazones[166–168] have been used successfully.

8.31.5.1 Synthesis of Hydrazones

Sulfonylhydrazones are readily prepared in quantitative yields by reacting equimolar amounts of the ketone with the corresponding hydrazine in solvents such as methanol, ethanol or diethyl ether along with an acid catalyst, commonly concentrated HCl or *p*-toluenesulfonic acid (*see* Chapter 1.17). Common hydrazone derivatives are those of toluenesulfonylhydrazine (Ts) and triisopropylbenzenesulfonylhydrazine (Tris). In recent years dehydrating agents such as $MgSO_4$[162] or molecular sieves[169] have been added to the reaction. Phenylaziridinyl hydrazones are prepared in a similar manner via a condensation reaction between the ketone and 1-amino-2-phenylaziridine.[167]

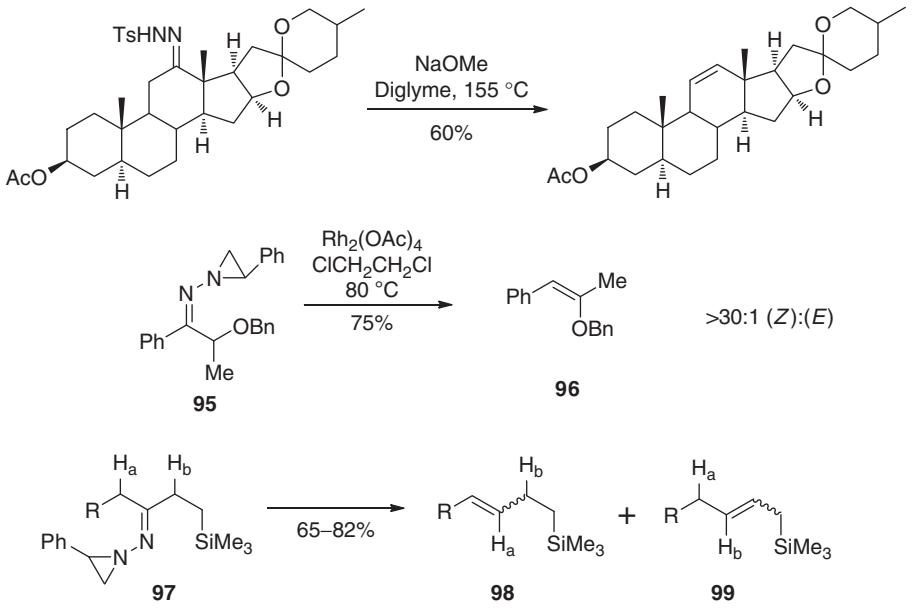
8.31.5.2 The Bamford–Stevens Reaction

The aprotic Bamford–Stevens reaction, most commonly carried out in diethylene glycol dimethyl ether, proceeds via carbene intermediates to give alkenes in good yields, and has found particular use in the synthesis of multicyclic, strained hydrocarbons.



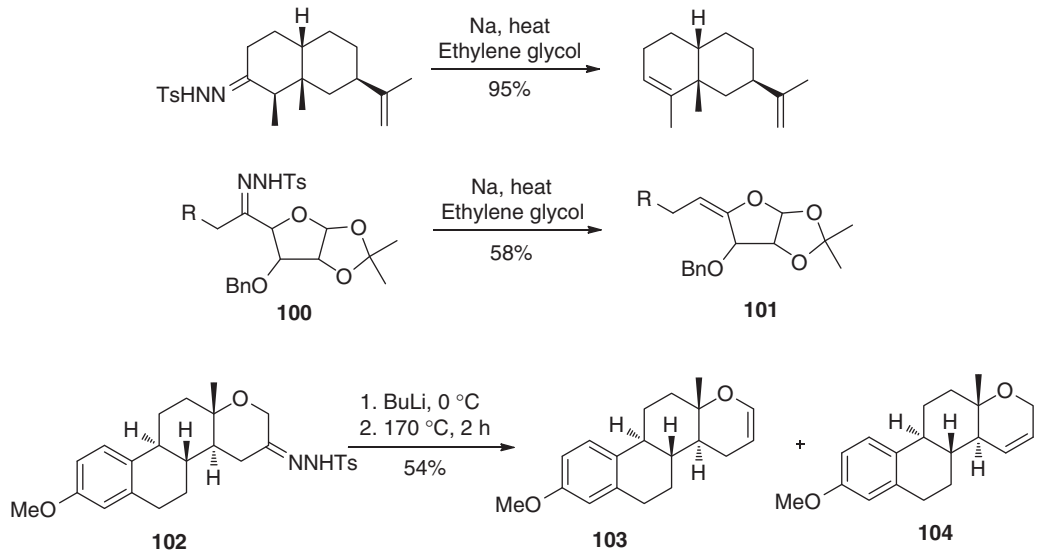
Scheme 26

Only relatively weak bases need to be employed to deprotonate the NH proton of sulfonylhydrazones and initiate decomposition, but high temperatures are normally required (Scheme 27). Decomposition normally requires heating and lead directly to the alkene. In some reactions other products such as the β-insertion product and skeletal rearrangement products are observed. Whereas five- and six-membered rings give predominantly the alkene product,[170] medium-sized rings tend to result in bicyclic products via transannular carbene insertion.[171] In general the more highly substituted alkene is the favored product, but the selectivity is often low, with high selectivity only observed in a few cases. Recently, $Rh_2(OAc)_4$ has been used as a catalyst to decompose *N*-aziridinyl imine **95** to give (*Z*)-selective alkene **96** via a rhodium–carbenoid intermediate (Scheme 27).[166] It was postulated that in the presence of the rhodium catalyst dediazotization leads to a rhodium–carbenoid intermediate resulting in a more selective carbenoid type reaction as opposed to the highly reactive carbene intermediate. 1,2-Hydride migration then occurs to give the enol ether in a high yield and with high levels of stereoselectivity favoring the (Z)-alkene **96**. Sarkar also found that the presence of $Rh_2(OAc)_4$ (2 mol%) led to little or no byproducts in the Bamford–Stevens reaction of β-trimethylsilyl *N*-aziridinylimines **97** while investigating the directive effect of silicon on the product.[168] In the absence of the rhodium catalyst the silyl group directed the formation of allylsilanes **99** (70–92%) over homoallylsilanes **98** (8–30%) with a selectivity for the *E* isomer [~80:20 (*E*):(*Z*)]. With the catalyst, not only was the overall reaction yield increased, but it was highly regioselective giving almost exclusive production of allylsilanes **99** (98%) but with a reversal in the (*E*):(*Z*) stereoselectivity [~14:86 (*E*):(*Z*)] (Scheme 27). This reversal of stereoselectivity was explained by orientational constraints for hydrogen migration in the transient metal–carbene intermediate.



Scheme 27

The protic reaction, normally carried out in ethylene glycol, proceeds via carbocations and can lead to a number of carbocation-derived products,[172,173] often as a complex mixture, hence reducing its synthetic value. The base in these reactions is commonly prepared by dissolving metallic sodium in the solvent before the addition of the hydrazone, or NaOMe can be used instead (Scheme 28). In reactions where the alkene product does dominate, the regioselectivity is generally poor, and only a few cases of high regioselectivity have been reported. There are reported cases where the more substituted alkene is produced with high selectivity[174] (Scheme 28), and conversely where the less substituted alkene is favored[175] and as such predicting the regiochemistry in these reactions is often problematic.



Scheme 28

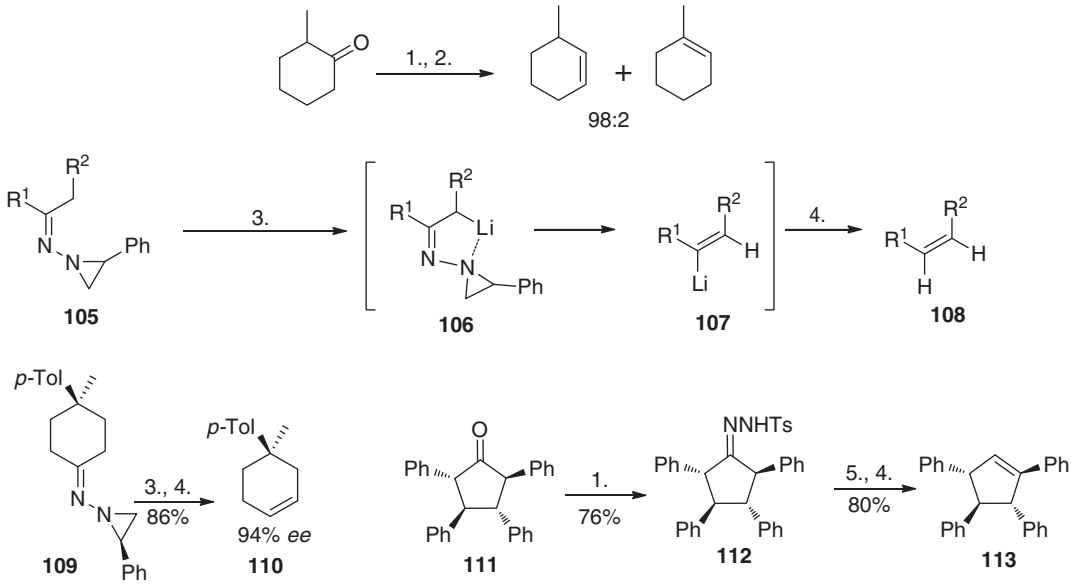
In recent years there has been a limited amount of interest in the Bamford–Stevens reaction with more work focusing on the Shapiro reaction. Chandrasekhar has studied the Bamford–Stevens reaction of α-oxy tosylhydrazones **100** derived from carbohydrate sources.[176] The hydrazone of 5-ulofuranose **100** was shown to furnish the more substituted alkene **101** with no trace of the less substituted regioisomer (Scheme 28). Other studies have investigated the directing effect of substituents during the 1,2-shift after carbene generation in the aprotic Bamford–Stevens reaction. Alkoxy groups direct alkene formation toward themselves so that reaction of **102** furnishes the two regioisomers **103**:**104** in a 21:1 ratio, respectively (Scheme 28). The same researchers discovered that adjacent equatorial methyl groups promote 1,2-shifts more efficiently than axial methyl groups.[177–179]

8.31.5.3 Shapiro

The Shapiro reaction utilizes the reaction of hydrazones with 2 equivalents of a strong base, typically an organolithium to prepare the alkene via an elimination and provides an intermediate vinyl lithium intermediate.[160] Protonation, deuteration, or tritiation of this intermediate is then possible delivering the alkene.[180] Initially the NH proton is removed followed by the α-hydrazone proton. The regiochemistry of alkenes derived from unsymmetrical ketones is highly predictable generally favoring the less substituted alkene by ratios of 50:1 or more (Scheme 29). This is likely due to two reasons, first, the least hindered α-position is the most likely to be deprotonated under kinetic conditions (**105**) and second, internal chelation of the organolithium with the nitrogen will stabilize the intermediate (**106**), both factors will normally be working together (Scheme 29). Little regiochemical control is observed if both α-positions are equally substituted[181–183] and α,β-unsaturated systems can lead to a number of different products due to multideprotonation sites being available. This does not preclude regiocontrol in such systems and there are examples of high selectivity in the literature.[184]

Shapiro's conditions reported in 1975 required the use of excess base (≥3 equivalents) rather than the 2 equivalents required by the mechanism. This was shown to be due to additional deprotonation of the protons *ortho* to the SO_2 of the tosyl group and the use of a trisylhydrazone with no *ortho* protons allowed for the reaction to proceed with just 2 equivalents of base.[163] Yamamoto has since developed a catalytic variation of the Shapiro reaction using ketone phenylarizidinylhydrazones **105** with a catalytic amount of lithium amides (Scheme 29).[167] The reaction offers excellent regio- and stereoselectivity with *cis:trans* ratios of at least 96:4. This high level of selectivity for the *cis* product can be explained by the internal chelation structure **106**; this is an example where both the kinetic deprotonation and the preferential (*E*)-geometry of the hydrazone favor chelation. Both LDA and lithium 2,2,6,6-tetramethylpiperidide (LiTMP) were shown to be good catalysts, however, $LiNEt_3$ and $LiN(SiMe_3)_2$ gave less satisfactory results. The amount of base could be lowered to 0.05 equivalent without effecting the yield or selectivities. It was also shown that the reaction could be applied to the synthesis of optically active alkenes, synthesizing both (*R*)- and (*S*)-3-methyl-3-*p*-tolyl-cyclohexene **110** from **109** with high *ee* (>92%). The *R*-enantiomer was then used in a formal synthesis of (+)-α-cuparenone (Scheme 29).[167]

The Shapiro reaction is generally not successful with substrates with only tertiary α-carbon atoms as formation of the dianionic intermediate is problematic and substitution at the imino carbon atom competes with elimination. Shapiro has reported optimized conditions for the synthesis of trisubstituted alkenes using 2.5 equivalents of LDA as a base in TMEDA as the solvent, giving moderate yields in some cases, with only trace amounts of the desired alkene in others.[184] Siemeling has reported a high-yielding Shapiro reaction on a substrate **111** with only tertiary α-carbon atoms[185] using 2 equivalents of LDA to give the trisubstituted

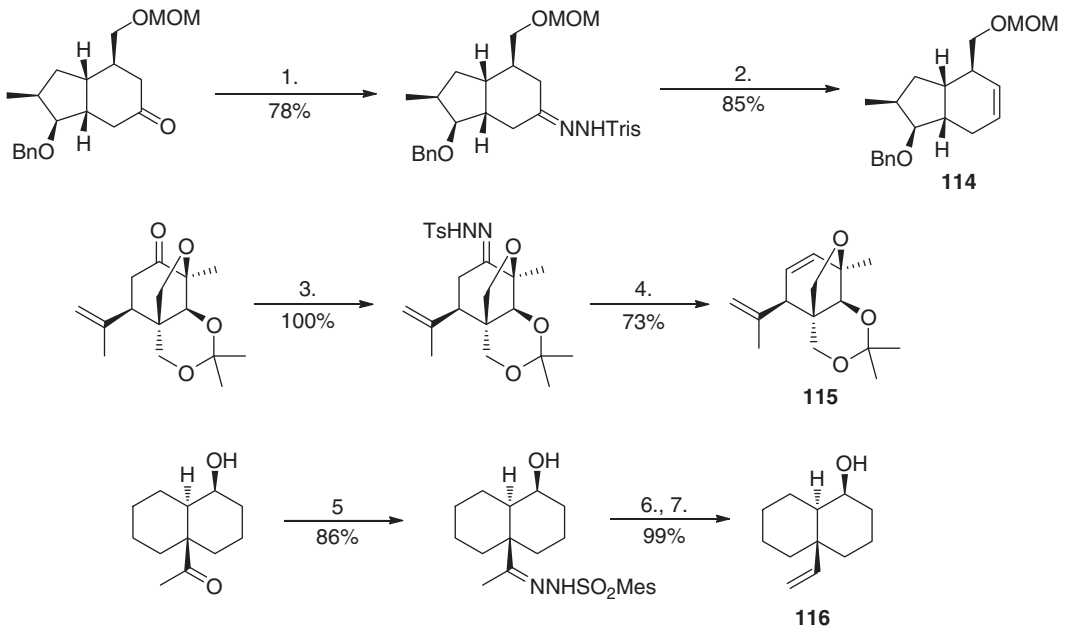


1. $TsNHNH_2$, EtOH; 2. MeLi, Et_2O; 3. 10 mol% LDA, Et_2O; 4. H_2O; 5. 2 equivalents LDA, THF

Scheme 29

alkene **113** in 80% yield (Scheme 29). It is thought this reaction proceeds with readily due to the high acidity of the benzylic α-hydrogen atoms allowing for easy formation of the dianion.

The Shapiro reaction has been used in the synthesis of a number of different natural products.[186] Gössinger et al. reported the synthesis of the hydrindene subunit **114** of both cochleamycins and macquarimicins with good regioselectivity and in good yield[164,165] (Scheme 30). The methodology was also employed by Shing in studies into the functionalization of the C-ring in both quassimarin and simalikalactone D.[162] Exposure of the ketone to tosylhydrazine in the presence of a toluenesulfonic acid afforded the hydrazone which, when treated with *tert*-butyllithium in THF gave the desired alkene **115** in 73% yield (Scheme 30).



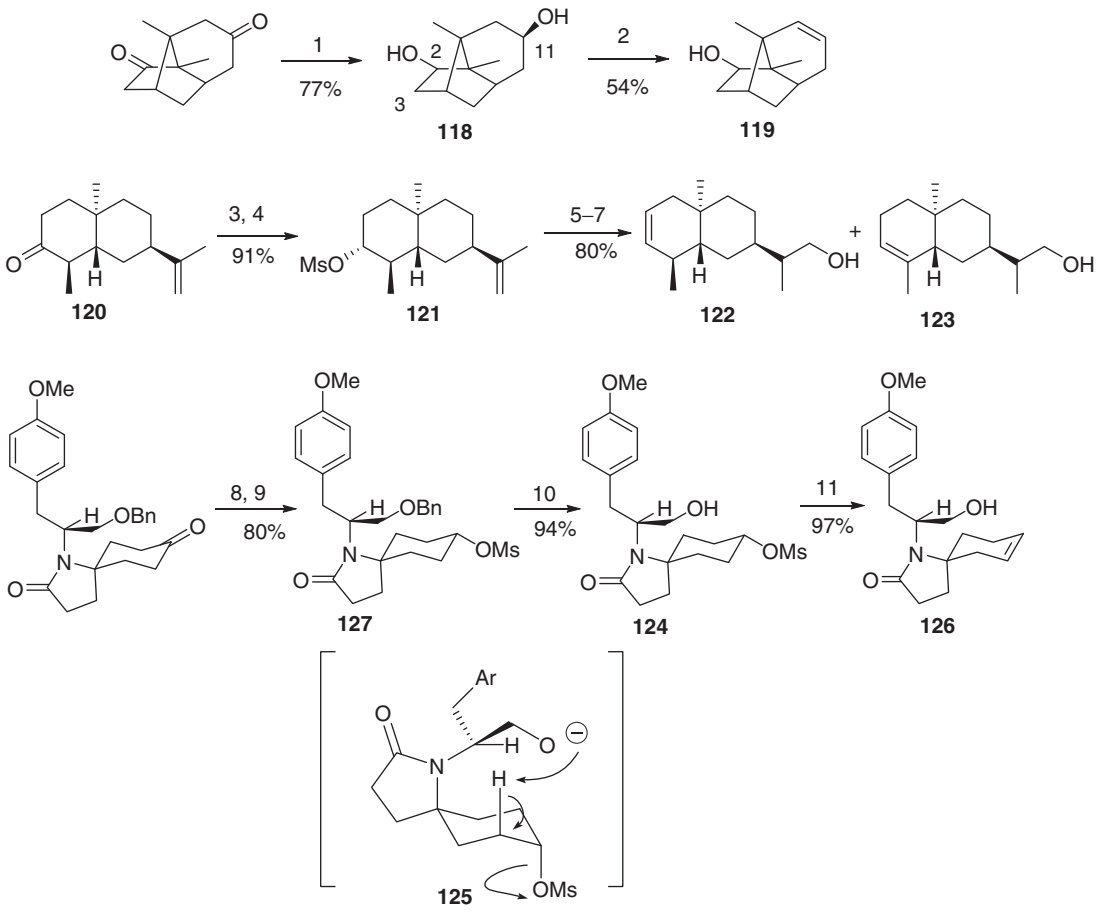
1. H_2NNHSO_2Tris, ether, r.t.; 2. 2 equivalents BuLi, THF, –78 °C; 3. *p*-$TsNHNH_2$, *p*-TsOH (cat.), $MgSO_4$, THF, r.t.; 4. *t*-BuLi, THF, 0 °C to r.t.; 5. H_2NNHSO_2Mes, EtOH, *p*-TsOH, 4 Å MS, reflux, 3 h; 6. *n*-BuLi, –78 °C to r.t., Et_2O, 1.5 h; 7. NH_4Cl

Scheme 30

Uosis-Martin et al. have prepared the endocyclic alkene **116** by treating a mesitylenesulfonohydrazone with 3 equivalents of butyllithium (Scheme 30).[169]

8.31.6 Reduction and Dehydration

As stated in the introduction, one of the most general transformations is the reduction of ketones to alcohols followed by elimination of water (or derivatization of the alcohol, e.g., to a mesylate, to a make better leaving group followed by elimination). However, because both reduction reactions of ketones and elimination reactions of alcohols and their derivatives are covered in great depth (*see* Chapters 8.01, 8.04, and 6.18), the authors only briefly mention them here. Regiochemistry in the elimination of alcohols can often be poor unless a conjugating substituent is present to direct the elimination. Acid-catalyzed elimination of the alcohol is often carried out with sulfonic acids. Wijnberg used this approach to chemoselectively eliminate the C-11 hydroxyl group in **118** in the presence of the C-2 alcohol group to give alkene **119** regioselectively (Scheme 31).[187] The explanation given for the chemoselectivity was that the *exo* nature of the C-2 alcohol precluded an anti-elimination with either of the C-3 hydrogen atoms. Basic elimination is normally carried out on alcohol derivatives such as mesylates. Mesylate **121** was prepared from ketone **120** by standard chemistry and eliminated to give **122** by LiBr and $LiCO_3$ at 150 °C, under these conditions the primary alcohol was untouched but minor amounts of the other regioisomeric alkene **123** was produced (**122**:**123** = 10:1)[188] (Scheme 31). Sorensen and Seike used a regioselective elimination as a key step in their synthesis of FR901483. In this case, reaction of mesylate **124** with 5 equivalents of *t*-BuOK in *t*-BuOH at 80 °C furnished only one alkene regioisomer **126**. The regioselectivity was postulated to arise due to elimination occurring through the intermediate **125** where the internal alkoxide initiates elimination by



1. L-selectride; 2. *p*-TsOH, C_6H_6 reflux; 3. Li, NH_3, *t*-BuOH, THF, –78 °C; 4. MsCl, pyridine; 5. B_2H_6·THF; 6. NaOH, Pd/c, H_2, H_2O_2; 7. LiBr, $LiCO_3$, DMF, 150 °C; 8. $NaBH_4$, MeOH, 0 °C; 9. MsCl, *i*-Pr_2NEt, DCM, 0 °C; 10. Pd/c, H_2, EtOAc; 11. *t*-BuOK, *t*-BuOK, 80 °C.

Scheme 31

attack of the axial proton shown. Evidence for this mechanism was that reaction of the benzyl derivative **127** under the same conditions gave no eliminated products (Scheme 31).[189]

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8.32 Hydrogenolysis of Allyl and Benzyl Halides and Related Compounds

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This chapter is a revision of the previous edition chapter by Ian D. Entwistle, William W. Wood, Vol. 8, pp 955–981, © 1991, Elsevier Ltd.

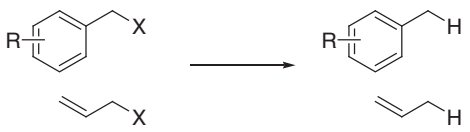
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Glossary

Allyl Propenyl substituent, $CH_2{=}CHCH_2R$.
Allylic Describes a carbon atom adjacent to one or more alkenes.
Benzyl Phenylmethyl substituent, $C_6H_5CH_2R$, abbreviated as Bn.
Benzylic Describes a carbon atom adjacent to one or more phenyl rings.
Dissolving metal reduction Use of a (usually elemental) metal to donate electrons for the purpose of reduction.
DMB/DMP 3,4-Dimethoxybenzyl/3,4-dimethoxyphenyl.
Heterogeneous metal A metal that is in the solid phase, rather than in solution.
Homogeneous metal A metal or metal complex that is in solution with the reactants.
Hydrogenolysis Breaking a C–X σ-bond so that X is replaced by hydrogen.
Phenylbenzyl ether 4-Phenylbenzyl ether, 4-(C_6H_5)-$C_6H_4CH_2OR$.
PMB/PMP 4-Methoxybenzyl/4-methoxyphenyl.
Trityl Triphenylmethyl substituent, $(C_6H_5)_3CR$, abbreviated as Tr.

8.32.1 Introduction and Scope of the Review

Hydrogenolysis is a fundamental transformation in chemistry. It involves the breaking of a σ-bond so that a functional group is replaced by a hydrogen atom. This chapter describes reactions involving cleavage of allylic- and benzylic-heteroatom bonds where the heteroatom is replaced by a hydrogen atom. The reduction of C–X bonds is generally much easier at allylic and benzylic positions than on saturated alkyl chains. The hydrogenolysis of benzyl and allyl halides (X=F, Cl, Br, I) can usually be achieved by the same methods described in Chapter 8.26 but they tend to proceed much more readily here. This chapter will, therefore, focus on the cases where X=O, N, and S, and the reactions are facilitated by benzyl or allyl groups. These hydrogenolysis reactions are common transformations in organic synthesis (Scheme 1), perhaps most frequently seen in protecting group chemistry, as benzyl and allyl derivatives are useful protecting groups for alcohols, amines, and thiols. The utility of this chemistry is not limited to deprotections, however, and applications are often seen as a key part of synthetic strategies in complex molecule construction.



Scheme 1

The aim of this chapter is to give an overview of widely used approaches with an emphasis on generality and selectivity, rather than to give a comprehensive account. For further details, references to relevant reviews[1–3] and books[4,5] are provided.

 doi:10.1016/B978-0-08-097742-3.00834-X

8.32.1.1 General Observations

The ease of the overall hydrogenolysis reaction is generally dictated by the strength of the carbon–heteroatom bond. However, the intermediates generated during bond cleavage may be reactive (i.e., cationic, organometallic, radical, etc.) and undergo competitive pathways reducing the yield of the desired C–X to C–H transformation. There are a large number of options available, from fine-tuning reaction conditions to using an alternative class of reagents, that would proceed by an entirely different mechanism. As will be seen below, remarkable levels of selectivity can be obtained through judicious choice of reaction conditions.

The C–X cleavage event itself is highly sensitive to the identity of the heteroatom, the substitution pattern of, and substituents on, the allylic alkene or aromatic ring, as well as other groups adjacent to the heteroatom. In molecules containing multiple benzyl or allyl groups, the order of cleavage – and hence selectivity – varies with the reagents employed. Very generally, it may be noted that cleavage mediated by transition metals tend to occur more readily if the C–X bond is unhindered by large groups. Cleavage reactions that occur by cationic, or cation-like, intermediates occur more readily when the resultant cation is stabilized, for example, by electron-donating substituents (e.g., PMB) or additional phenyl rings (e.g., trityl).

8.32.1.2 Debenzylation

8.32.1.2.1 General comments

Benzyl groups are typically stable to mild aqueous acids/bases, metal hydrides, and mild oxidants. The most common methods for their cleavage can be classified as hydrogenolysis, single-electron reduction, oxidation, and acidolysis, although other methods including photolysis are known.[4,5]

8.32.1.2.2 Catalytic hydrogenolysis with heterogeneous metals and hydrogen

Hydrogenolysis with molecular hydrogen over Pd/C is one of the mildest and most straightforward methods of cleaving benzyl ethers, and is very widely employed in deprotection steps. Isolation of the desired product from the catalyst and toluene byproduct is often as simple as degassing and filtration. For example, Ley and coworkers reported the one-step removal of 16 benzyl ethers from an oligosaccharide in excellent (>90%) yield,[6] with isolation by filtration only (Scheme 2).

Although these procedures are quite general and tolerate many functional groups, they can be limited by issues of chemoselectivity, regioselectivity, and overreduction, particularly when reducible groups such as alkenes, nitriles, and halides are present. These problems can be overcome through variation of the catalyst, solvent, or temperature, or through the use of alternative sources of hydrogen. In many cases, selectivity and efficiency can be achieved through careful choice of solvent and additives. Modification of the catalyst species or the use of additives can increase selectivity; for example, using Ti-loaded hexagonal mesoporous silica (Ti-HMS) as an additive allows selective removal of benzyl ethers in the presence of other ethers such as *t*-butyldimethylsilyl (TBS), tetrahydropyranyl (THP), and acetals.[7] Conversely, additives such as Na_2CO_3 and 2,2′-bipyridine inhibit hydrogenolysis of benzyl esters, allowing their retention during the reduction of other functional groups such as alkenes. The rate of hydrogenolysis is strongly solvent-dependent, and tetrahydrofuran (THF), ethanol, and ethyl acetate are widely used.

Modification of the benzyl ring or addition of extra rings allows discrimination between multiple benzyl ethers. The common methoxybenzyl variants (PMB, DMB, etc.) are readily removed under catalytic hydrogenation conditions. 4-Phenylbenzyl ethers are more easily cleaved by hydrogenolysis than benzyl ethers (Scheme 3).[8] Hydrogenation over Raney nickel has been used to cleave benzyl ethers in the presence of other reduction-sensitive groups. The example in Scheme 4 shows selective hydrogenolysis in the presence of secondary PMB ethers and chlorides.[9]

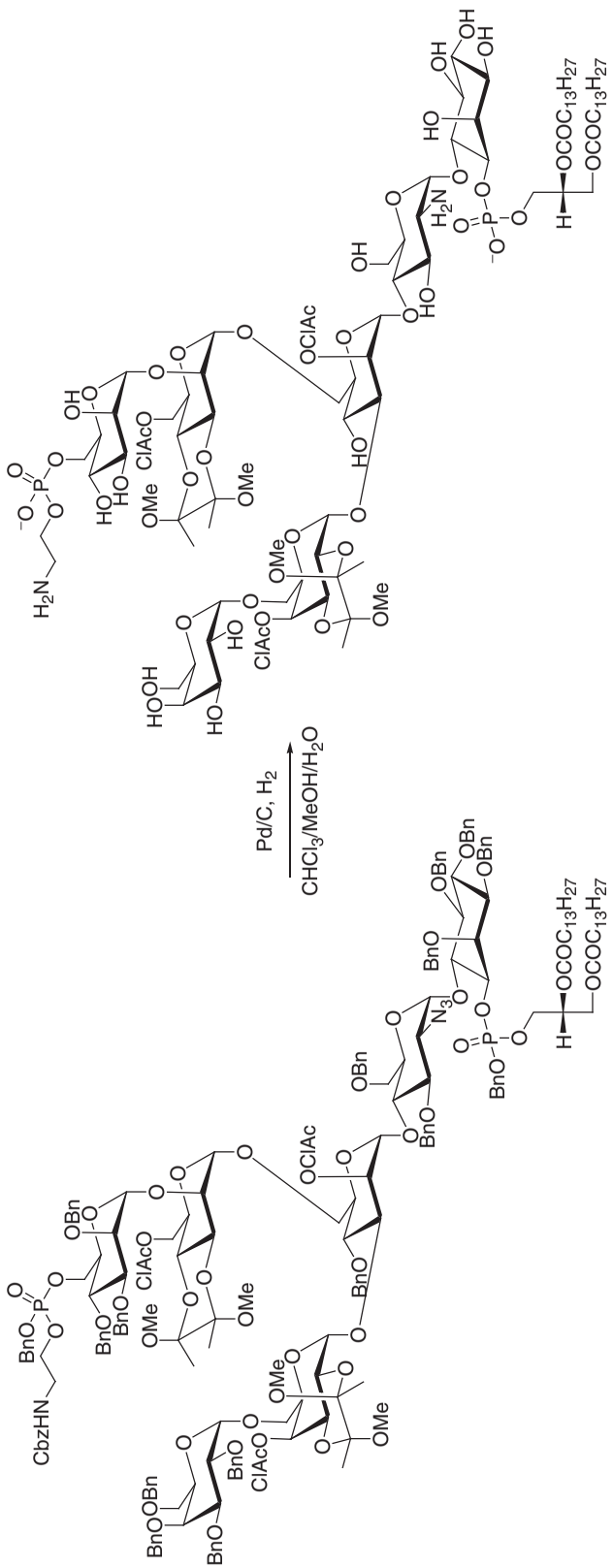
Benzylamines are typically less susceptible to catalytic hydrogenolysis than benzyl ethers, and generally require higher catalyst loadings, temperatures, and pressures. Again, structural variations have a large influence on stability; methoxybenzylamines are generally inert to catalytic hydrogenolysis, whereas diphenylmethylamines are more easily cleaved than benzylamines. Acidic conditions are also known to facilitate the hydrogenolysis of benzylamines. Transfer hydrogenolysis is often more effective than catalytic hydrogenolysis, and is the method of choice for the cleavage of benzylamines.[5] For example, the dibenzylamine product of an aza-Diels–Alder reaction can be singly or doubly cleaved (Scheme 5), where catalytic hydrogenation first cleaves the *endo*-cyclic benzylamine, followed by the methylbenzylamine.[10]

Benzylidene acetals are readily hydrogenolyzed under catalytic hydrogenation conditions (Scheme 6).[11]

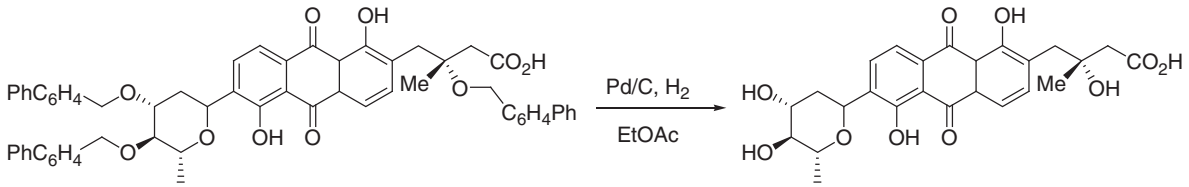
8.32.1.2.3 Catalytic hydrogenolysis with heterogeneous metals and transfer hydrogenation

Transfer hydrogenolysis can be an attractive alternative to using molecular hydrogen for a number of reasons. In some cases it may be desirable to bypass the specific techniques and hazards associated with the use of hydrogen gas; better selectivity and functional group tolerance have been observed in many cases; and there may be less opportunity for catalyst poisoning, which could potentially be a problem when using Pd/C–H_2.[5] A wide variety of catalysts (both homogeneous and heterogeneous) and hydrogen donors are available; typical conditions involve the use of palladium in refluxing methanol or ethanol, and a hydrogen donor such as cyclohexene, formic acid, or isopropanol. The use of transfer methods has been reviewed by Johnstone et al.[2]

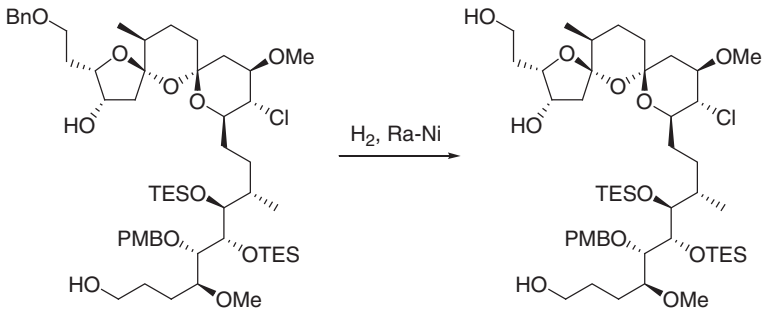
Transfer methods are compatible with a variety of functional groups, such as benzylidene acetals, esters, methoxymethyl ethers, silyl ethers, and THP ethers. The appropriate choice of conditions and modifications to the benzyl ring allows fine discrimination



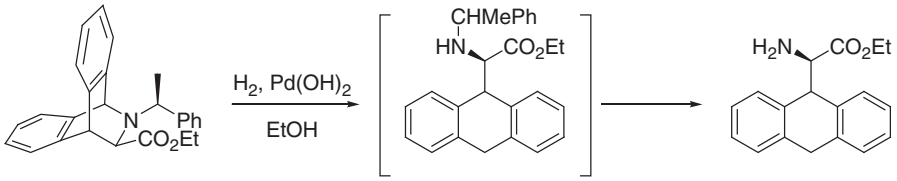
Scheme 2



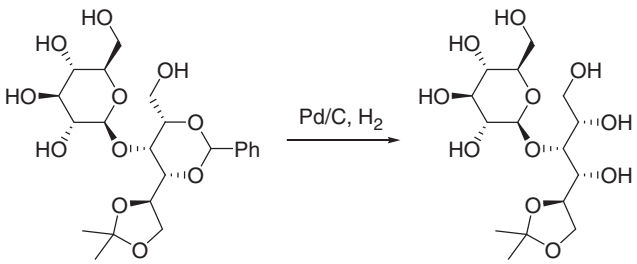
Scheme 3



Scheme 4



Scheme 5



Scheme 6

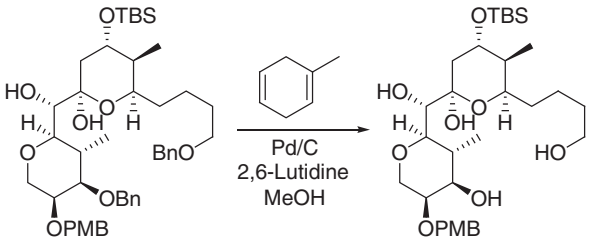
between very similar alcohols and protecting groups. For example, Smith et al. selectively cleaved two benzyl ethers in the presence of a very similar PMB ether through the use of 2,6-lutidine and 1-methyl-1,4-cyclohexadiene (Scheme 7).[12] Analogous selectivity was obtained in the synthesis of (–)-calyculin A by Tanimoto et al. using formic acid as a hydrogen source (Scheme 8).[13]

Benzylamines can be removed selectively without affecting benzyl esters with an appropriate hydrogen source, for example, 10% Pd/C with 1,4-cyclohexadiene (Scheme 9).[14]

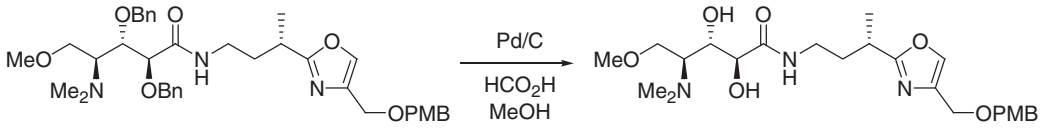
Benzylidene acetals are easily cleaved by transfer hydrogenolysis. The use of ammonium formate as a hydrogen donor has allowed the selective removal of the acetal of a 1,2-diol in the presence of the acetal of a 1,3-diol (Scheme 10).[15] Similarly, *N*,*O*-benzylidene acetals have been removed by transfer hydrogenolysis.

8.32.1.2.4 Dissolving metal reduction

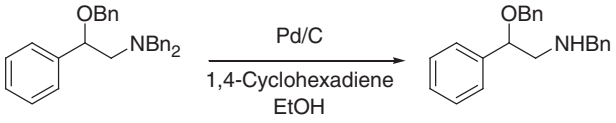
A variety of metals and metal complexes can be used to reductively cleave benzyl ethers. Most commonly, Na or Li is used at low temperature in liquid ammonia or an alcohol. In many cases these methods are simple, clean, and high-yielding; although functional group tolerance is generally poor, impressive exceptions do exist. For example, Paulsen et al. cleaved three benzyl



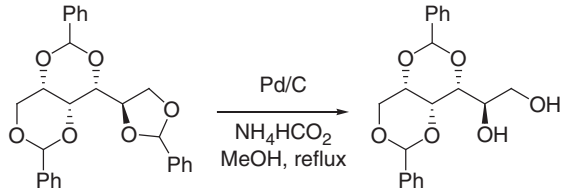
Scheme 7



Scheme 8

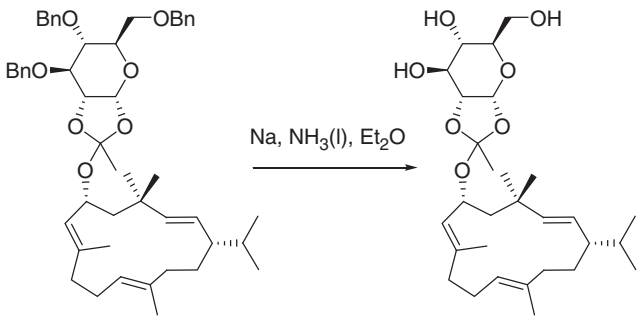


Scheme 9



Scheme 10

groups (in the presence of two alkenes and an allylic ether) in a glucose derivative (Scheme 11), isolating the product in quantitative yield.[16]

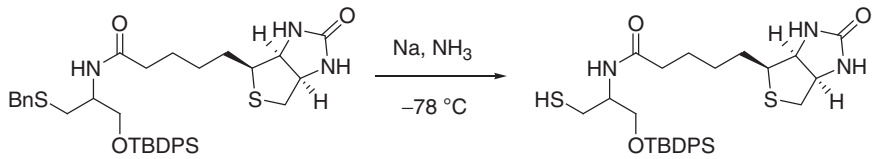


Scheme 11

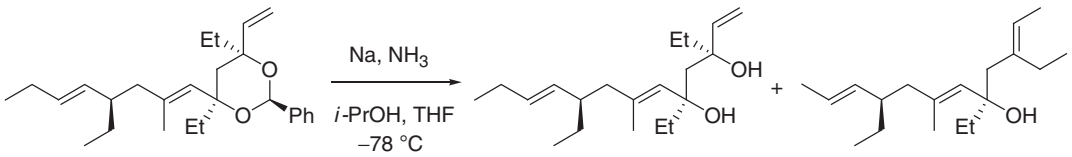
The use of Ca in liquid NH_3 is a milder alternative, and this method is tolerant of alkynes, cyclopropanes, phenyl rings, and furans. Lithium naphthalenide is another alternative and is compatible with alkenes, phenyl rings, and a variety of ethers including silyl, methoxymethyl ether (MOM), and THP.

Dissolving metal reduction is the most common method of cleaving benzyl thioethers; for example, the Birch reduction has been used to this end in a biotin-derived system by Brodersen et al. (Scheme 12).[17]

Benzylidene acetals are readily cleaved by Birch reduction. Additives can be used to improve selectivity and functional group tolerance; for example, during the cleavage shown in Scheme 13,[18] competitive elimination of one of the allylic alcohols was



Scheme 12

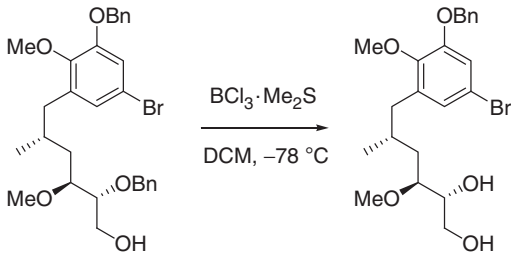


Scheme 13

initially observed, but addition of *i*-PrOH/THF as a proton source was found to inhibit this side-reaction, allowing isolation of the desired diol in 65% yield.

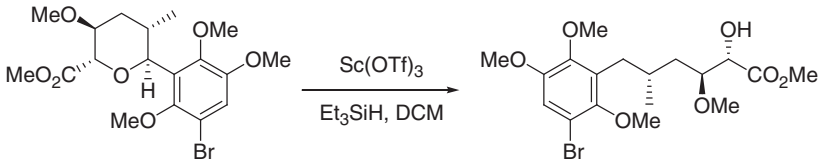
8.32.1.2.5 Lewis acids

A wide variety of Lewis acids can be used to cleave benzyl ethers, and excellent functional group tolerance can be obtained by careful choice of reagents. Typical reagents include TMS-I, $FeCl_3$, trihaloboranes, and $SnCl_4$, but many others can also be used. Scavengers are often added to trap cationic byproducts and prevent side-reactions.[1] Cleavage is typically faster when the benzyl cation produced during cleavage is stabilized, for example, by electron-donating ring substituents or by additional phenyl groups. In their synthesis of reblastatin,[19] Wrona et al. used BCl_3 to selectively cleave a secondary benzyl ether adjacent to a primary alcohol, without affecting phenolic methyl and benzyl ethers, or an aryl bromide (Scheme 14).



Scheme 14

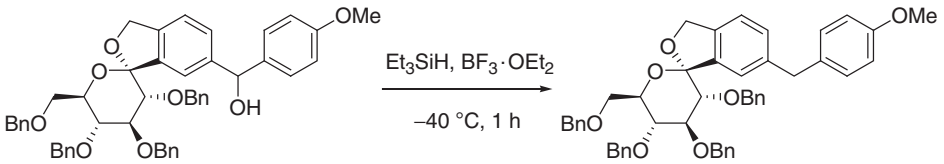
The use of $Sc(OTf)_3$ allows the mild opening of cyclic benzyl ethers (Scheme 15).[20] Here, the benzyl cation produced during the ring opening is trapped with Et_3SiH, a nucleophilic source of hydrogen. The authors demonstrated that by substituting Et_3SiH for other nucleophiles, opening of pyranosides and incorporation of synthetically useful groups can be combined into one step.



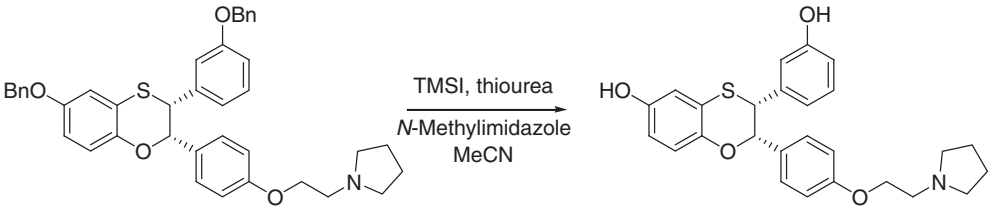
Scheme 15

Ethers with cation-stabilizing substituents (additional rings, electron-donating ring substituents, etc.) tend to cleave more readily, and the use of a scavenger to trap reactive cations produced during cleavage may be desirable. For example, an alcohol activated by two benzyl groups (Scheme 16) has been reduced in the presence of several benzyl ethers and a sensitive benzylidene acetal moiety using Et_3SiH and $BF_3 \cdot OEt_2$ at low temperature.[21] In contrast, however, Song et al. (Scheme 17)[22] have demonstrated that using trimethylsilyl iodide unhindered phenolic benzyl ethers can be cleaved leaving phenolic alkyoxybenzyl ether and benzyl thioether unchanged.

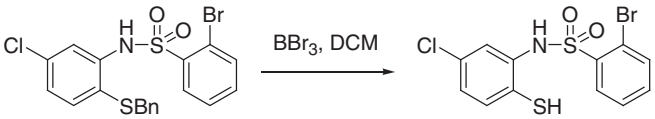
Benzylamines are typically stable to Lewis acids, although tribromoborane has been used (Scheme 18).[23] Similarly, cleavage of benzyl thioethers with Lewis acids is not typical, but the use of $AlCl_3$[24] and BBr_3[25] among others has been reported.



Scheme 16

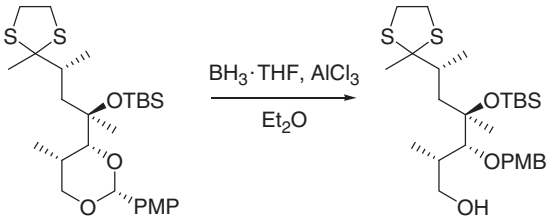


Scheme 17



Scheme 18

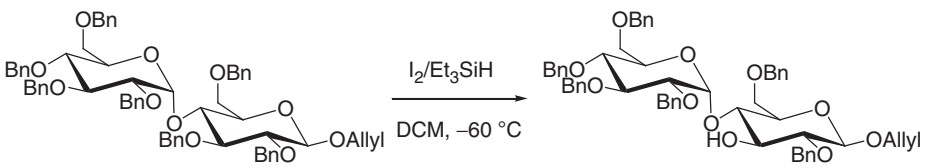
Benzylidene acetals are readily cleaved by trihaloboranes, $FeCl_3$, and other Lewis acids.[26] Partial cleavage to a benzyl ether and hydroxyl group can be achieved through careful choice of conditions. For example, the use of borane and aluminum trichloride allowed the partial cleavage of a *p*-methoxybenzylidene acetal in the presence of a protected tertiary alcohol and thioacetal during the synthesis of erythromycin B (Scheme 19).[27]



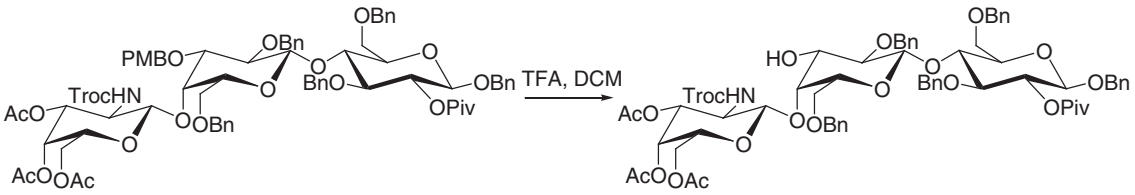
Scheme 19

8.32.1.2.6 Protic acids

Protic acids can be used to cleave unsubstituted benzyl ethers, but they generally require harsh conditions. The generation of acids *in situ* may circumvent some problems associated with strongly acidic conditions. The combination of I_2 and Et_3SiH has been used to generate anhydrous HI *in situ* and mono deprotect heavily benzylated mono- and disaccharides with impressive selectivity (Scheme 20).[28] Under these conditions, only the most hindered benzyl ether is cleaved, without adversely affecting glycosidic bonds, methyl or allyl ethers, or isopropylidene acetals. Modified benzyl ethers, such as PMB, are much more labile under acidic conditions; 0.5% TFA in DCM at room temperature (r.t.) is sufficient in many cases.[4] In the example shown in Scheme 21, excess TFA in DCM removed a single PMB ether from a multiply benzylated trisaccharide in 98% yield.[29]

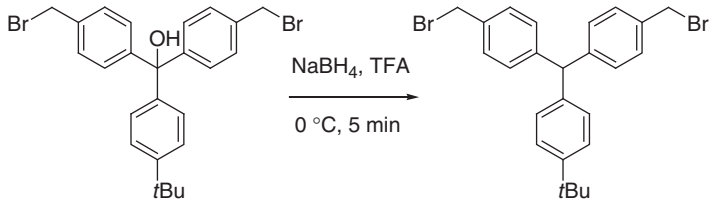


Scheme 20

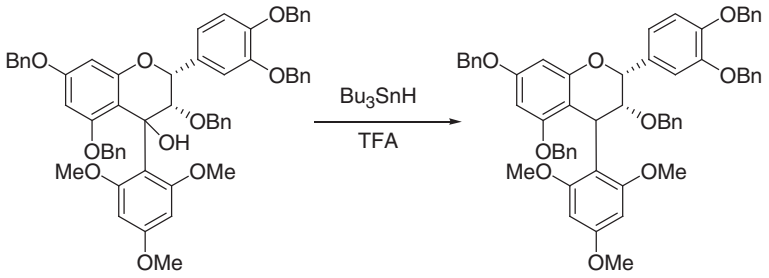


Scheme 21

Although benzyl ethers are typically stable to metal hydrides, hydride sources can be used to quench benzyl cations generated under acidic conditions. For example (Scheme 22), a triphenylmethyl alcohol was reduced by the $NaBH_4$–TFA combination. Remarkably, two benzyl bromides were unaffected by this procedure when the reaction time was kept very short.[30] Similarly, Bu_3SnH–TFA was found to be a more selective alternative to Et_3SiH–TFA when cleaving the doubly benzylic alcohol in Scheme 23, which features several phenolic benzyl ethers.[31] The authors found that when using Et_3SiH, significant competitive dehydroxylation by elimination of H_2O to form the styrene was observed.

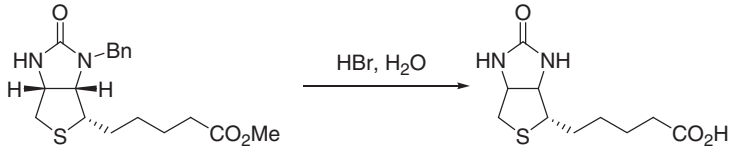


Scheme 22



Scheme 23

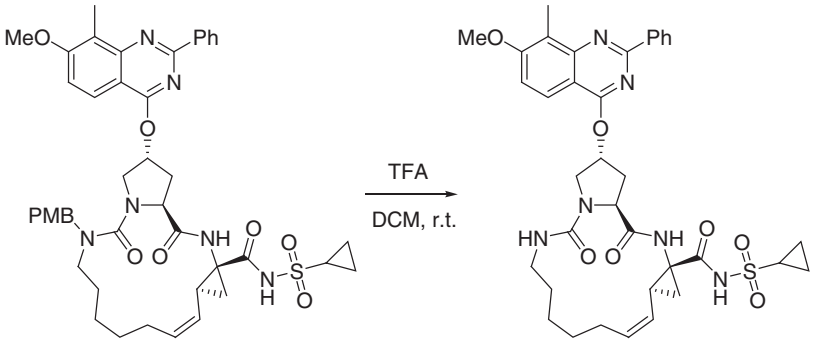
N-Benzylamides are cleaved more readily than benzylamines, which are not typically cleaved by protic acids, although examples are known. Rombouts et al. report the microwave-assisted cleavage of benzylamides with triflic acid in toluene at 150 °C.[33] *N*-Benzyl ureas can also be cleaved, for example, aqueous HBr was used in the synthesis of biotin (Scheme 24).[32] Electron-rich variations, such as PMB, DMB, and trityl, are more labile, and can often be removed by TFA at r.t. (Schemes 25 and 26).[34,35]



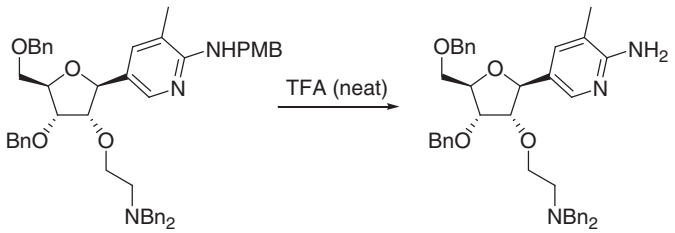
Scheme 24

Benzyl thioethers are more stable to acid than ethers; they have been cleaved by HF at r.t., typically with a scavenger such as triisopropylsilane (TIPS) to trap cationic byproducts (Scheme 27).[36] Modifications such as PMB thioethers can be cleaved under these conditions, or using refluxing TFA. The addition of Hg(II) salts may allow milder conditions to be used (Scheme 28).[37] Trityl thioethers are cleaved with neat TFA; the most common scavenger for the trityl cation is triethylsilane (Scheme 29).[38]

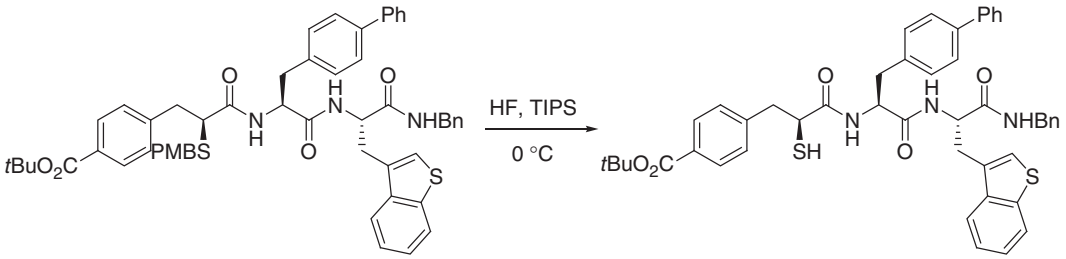
Benzylidene acetals can be cleaved by acid hydrolysis, and again PMP acetals are rather more labile. Relatively harsh conditions may be required to fully cleave the acetal, typically prolonged heating in acetic acid for unmodified benzylidene acetals. Under milder conditions, partial cleavage to the benzyl ether is common and other benzyl ethers can be preserved (Scheme 30).[39]



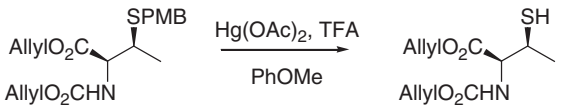
Scheme 25



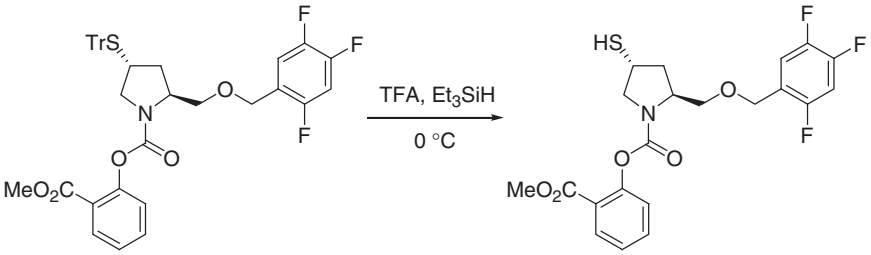
Scheme 26



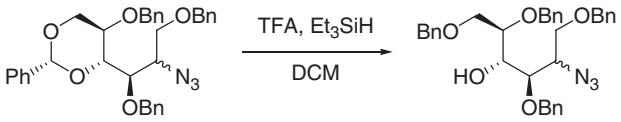
Scheme 27



Scheme 28

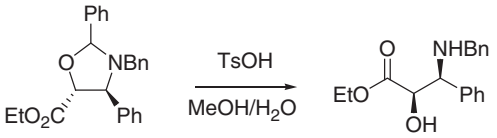


Scheme 29



Scheme 30

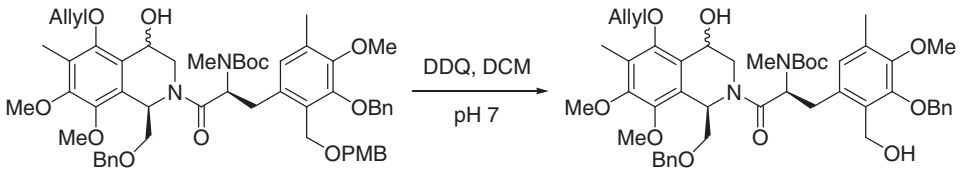
Regioselectivity varies with substrate and conditions. *N,O*-Benzylidene acetals are quite labile under acidic conditions; strong protic acids have been used to remove a benzylidene acetal in the presence of a benzylamine (Scheme 31).[40] Hydrochloric acid is commonly used for this transformation.



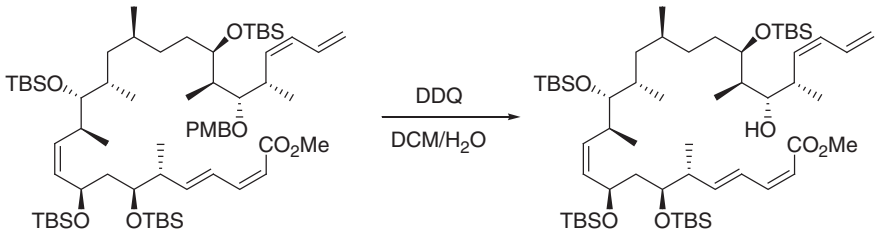
Scheme 31

8.32.1.2.7 Oxidation

Oxidation is a standard method for the cleavage of PMB ethers, which are selectively removed by stoichiometric aqueous DDQ (Scheme 32).[41] DDQ is compatible with many protecting and functional groups, including esters, acetals, epoxides, boronate, and a number of ethers. Conjugated dienes and trienes are generally not compatible with DDQ, although examples are known (Scheme 33).[42] A disadvantage of this method is that the byproduct of DDQ oxidation can be difficult to remove, but other stoichiometric oxidants are available.[1]

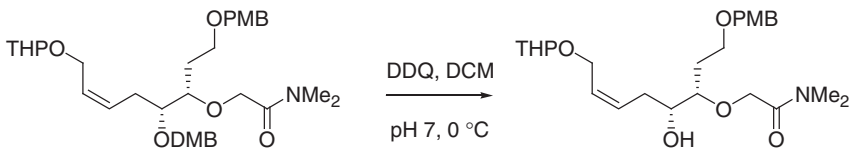


Scheme 32



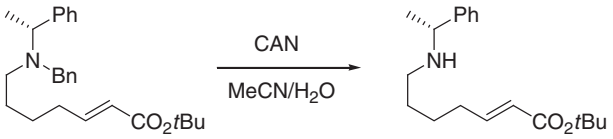
Scheme 33

Unsubstituted benzyl ethers can be difficult to cleave oxidatively, and may require harsh conditions or long reaction times. Many methods have been reported without any single method becoming generally taken up by the synthetic community. As the cleavage of PMB ethers is much faster than that of benzyl ethers or benzylamides, some selectivity can be achieved. The number and position of methoxy substituents on the benzyl ring affect the rate of cleavage, allowing for selectivity; cleavage of multiply-substituted rings typically occurs first (Scheme 34).[43]

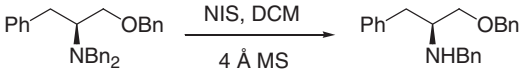


Scheme 34

A number of methods are available for the oxidative cleavage of benzylamines. The use of CAN in aqueous MeCN allows selectivity between different primary and secondary benzylamines (Scheme 35).[44,45] Cleavage of dibenzylamines in multiply-protected substrates with NIS was shown to be sensitive to the equivalents of NIS used, as well as the addition of Lewis acids, water, bases, and reaction time. Single or double debenzylation could be realized, and protected hydroxyl groups were unaffected.[46] This example illustrates the scope for optimization with oxidative methods (Scheme 36).

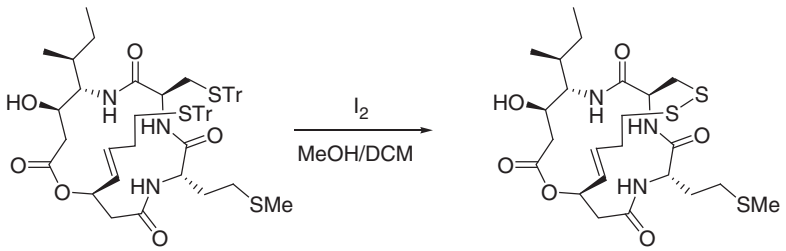


Scheme 35



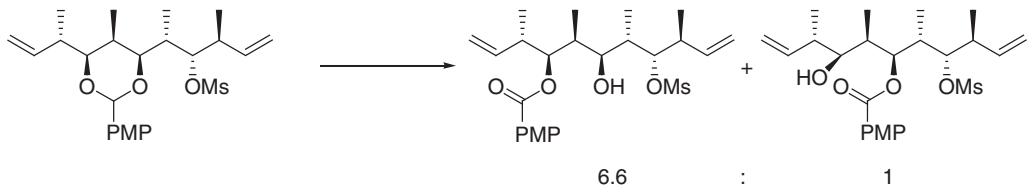
Scheme 36

Trityl thioethers may be cleaved and oxidized by iodine/MeOH to give the disulfide, which can be subsequently reduced to the free thiol if necessary. This method has been used in the synthesis of a number of closely related macrocyclic natural products, exemplified here by burkholdac B (Scheme 37).[47]



Scheme 37

Oxidative cleavage of benzylidene acetals typically gives a free hydroxyl and a benzoate ester. Regioselectivity is variable, and often a mixture of regioisomers is obtained. For example, in the synthesis of a section of irumamycin,[48] a PMP acetal was partially cleaved to give the benzoate ester in the presence of two terminal alkenes (Scheme 38).

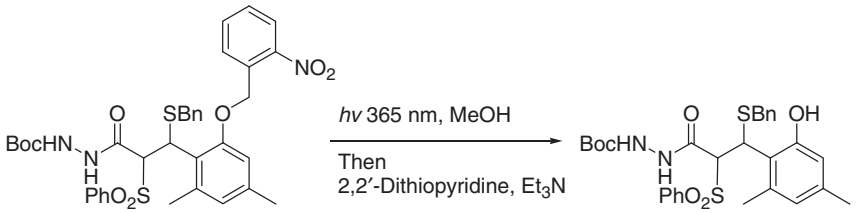


Scheme 38

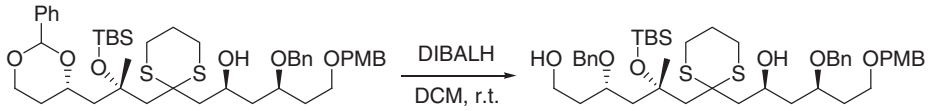
8.32.1.2.8 Others – photolysis, metal hydrides

The most notable alternative to the methods listed above involves photolysis of *o*- and *p*-nitrobenzyl groups. This offers clean, selective cleavage in sensitive or highly functionalized molecules (Scheme 39).[49]

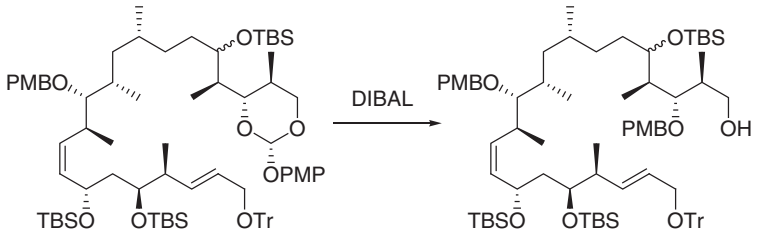
Benzylidene acetals can be partially cleaved by hydrides such as DIBAL. Selectivity is influenced by steric and electronic effects, as well as the nature of the reducing agent. Typical conditions use DIBAL in DCM at r.t.or lower; using these conditions, Terauchi and Nakata selectively cleaved one benzylic C–O bond in the presence of benzylic, PMB, and TBS ethers, as well as a dithiane (Scheme 40).[50] The regioselectivity observed here is consistent with DIBAL coordination to the least-hindered oxygen atom, before hydride delivery. These methods are compatible with benzyl ethers, including PMB and trityl (Scheme 41).[51]



Scheme 39



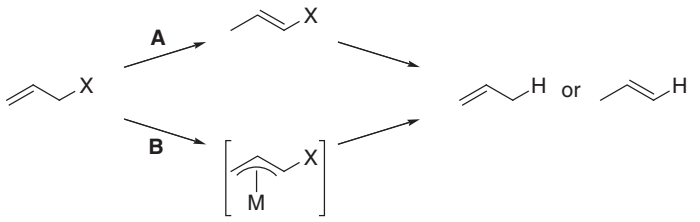
Scheme 40



Scheme 41

8.32.1.3 Deallylation

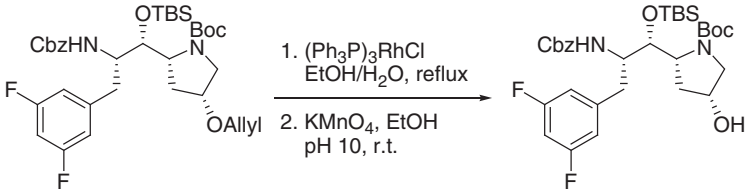
Methods for cleaving C–X bonds where the heteroatom is located at an allylic position (i.e., $H_2C{=}CH{-}CH_2{-}X$) can be divided into indirect and direct approaches. Indirect methods typically involve either oxidation to an ester followed by hydrolysis, or isomerization of the double bond to form an enol ether followed by hydrolytic or oxidative cleavage (Scheme 42A). Direct methods usually use Pd(0) or Ni(0) to form an activated π-complex, which then undergoes further reaction with a nucleophile. In many cases this nucleophile is a hydride source (Scheme 42B). Alternatively, mechanistically distinct oxidative and reductive methods can also be used to effect direct cleavage.



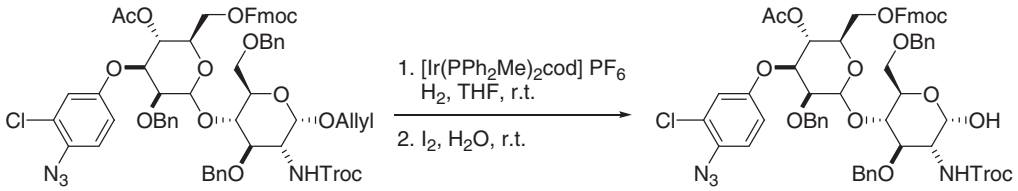
Scheme 42

8.32.1.3.1 Indirect methods

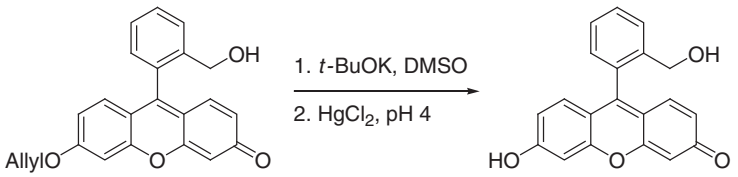
Allyl ethers and amines can be rearranged to the enol ether or enamine, respectively, by the use of a base (typically *t*-BuOK/DMSO) or a transition metal complex such as Wilkinson's catalyst (Scheme 43).[52] These methods are often used in benzyl-protected saccharides, but are rarely applied to highly functionalized compounds. Rearrangement protocols may be limited in various ways; for example, Wilkinson's catalyst may require the addition of BuLi to prevent competing reduction of the alkene.[53] The use of iridium-based catalysts in conjunction with hydrogen allows rearrangement at r.t., avoiding many of these issues (Scheme 44).[54] Allylamines rearrange at similar rates to allyl ethers, but hindrance around secondary amines may prevent the formation of the enamine.[3] Following rearrangement, a variety of hydrolytic and oxidative methods for cleavage are available. In acid-sensitive substrates the use of Hg(II) salts provides a gentler and often faster alternative (Scheme 45).[55] Oxidative methods employing systems such as H_2O_2/SeO_2 (cat) or NMO/OsO_4 (cat) are common alternatives to acidolysis.



Scheme 43



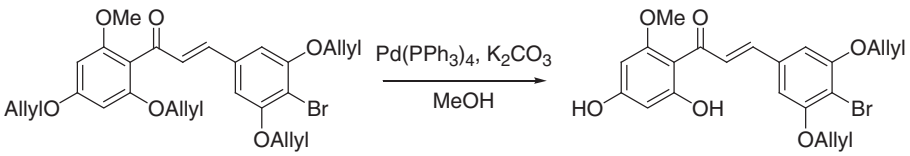
Scheme 44



Scheme 45

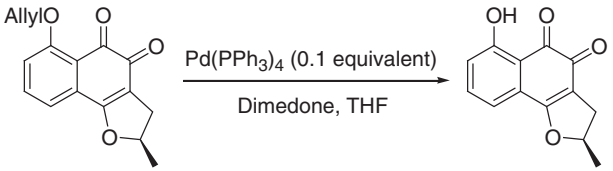
8.32.1.3.2 Transition metal-catalyzed cleavage

Catalytic Pd(0) or Ni(0) complexes activate allyl ethers and amines, and *N*- and *O*-Alloc groups, to attack by a nucleophile, cleaving the heteroatom–carbon bond in the process. The methods typically require the resulting oxygen anion to be stabilized, hence phenols and carboxyl groups are the 'leaving groups' most often used in these procedures; however, at reflux, alkyl allyl ethers are also cleaved.[56] A representative example uses $Pd(Ph_3P)_4$ (0.01 equivalent) and K_2CO_3 (3 equivalents) in MeOH to selectively cleave two of four aryl allyl ethers[57] (Scheme 46) in the starting material. Here, anions produced in the deallylation are stabilized by the carbonyl located at the *ortho*- or *para*-positions. Pd is more popular than Ni for a number of reasons, such as toxicity and air sensitivity.[58] The choice of catalyst and additive allows selectivity between different allyl groups. Tsukamoto et al.[59] report excellent discrimination between several allyl ether derivatives, including methallyl and prenyl, simply using Pd and varying the solvent, temperature, and ligands.

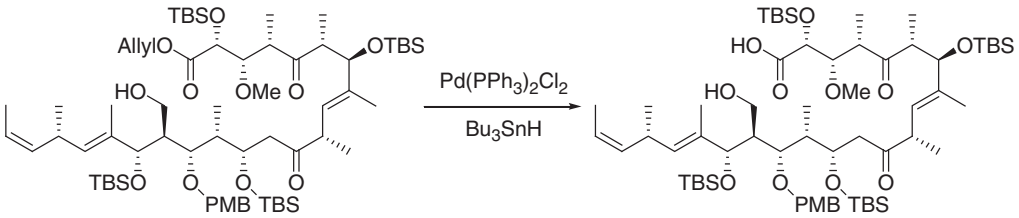


Scheme 46

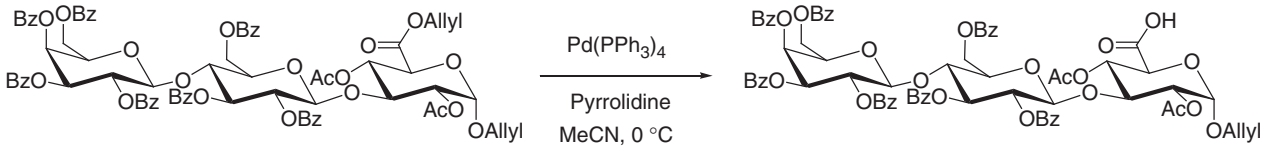
Pd-mediated deallylation procedures can be particularly mild. Organic nucleophiles, such as dimedone and other 1,3-dicarbonyls, can be used to cleave the palladium-allyl species produced in these reactions and regenerate the Pd catalyst.[60] For example, in the synthesis of (+)-nocardione A, the natural product was found to be sensitive to various deprotection conditions: racemization was observed when removing the analogous methyl ether (Scheme 47), and hydrogenolysis of the corresponding benzyl ether gave poor yields, presumably due to competitive reduction of the *o*-quinone. The use of Pd(0) allowed deallylation in minutes at r.t.. These methods are compatible with a variety of other ether-protecting groups, including benzylic, silyl, and THP ethers.[1] For example, in the synthesis of (+)-tedanolide,[61] an allylic ester was cleaved in the presence of a PMB ether and TBS-protected allylic alcohols (Scheme 48). Leyden et al.[62] report the use of morpholine and $Pd(PPh_3)_4$ to achieve the selective cleavage of an allyl ester in the presence of an allyl ether (Scheme 49). Similarly, Goess and coworkers[63] used $Pd(PPh_3)_4$ and sodium 2-ethylhexanoate to remove a phenol allyl ether in the presence of a complex tertiary allyl ether (Scheme 50).



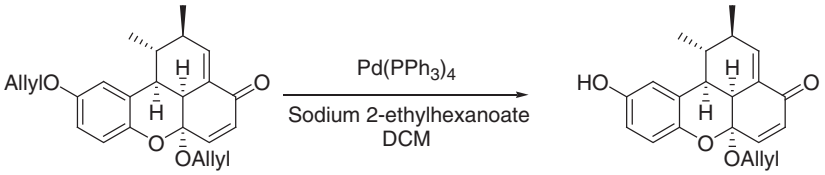
Scheme 47



Scheme 48



Scheme 49

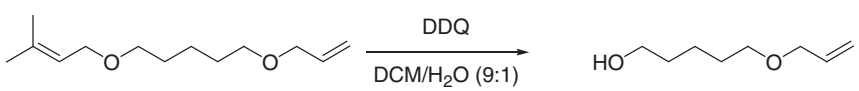


Scheme 50

8.32.1.3.3 Oxidative and reductive cleavage

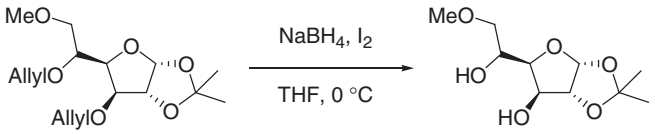
Many miscellaneous methods for the cleavage of allyl ethers have been reported, often using oxidants such as peroxides, or reductants such as dissolving metals. These methods have been discussed quite comprehensively in reviews by Wuts and Greene[4] and Weissman and Zewge,[1] but a small selection are presented here for illustration nonetheless.

A variety of oxidizing agents can be used to directly cleave allyl esters, often by oxidation to the ester followed by hydrolysis in one-pot. Tetrabutylammonium peroxydisulfate and I_2 were shown to remove primary, secondary, and tertiary allyl ethers,[64] whereas DDQ in wet DCM cleaves primary ethers only. The latter reagent is selective for substituted allyl ethers; it will remove prenyl ethers selectively before allyl ethers (Scheme 51).[65] Similarly, I_2/DCM in the presence of molecular sieves is sufficient to cleave secondary prenyl ethers.[66]



Scheme 51

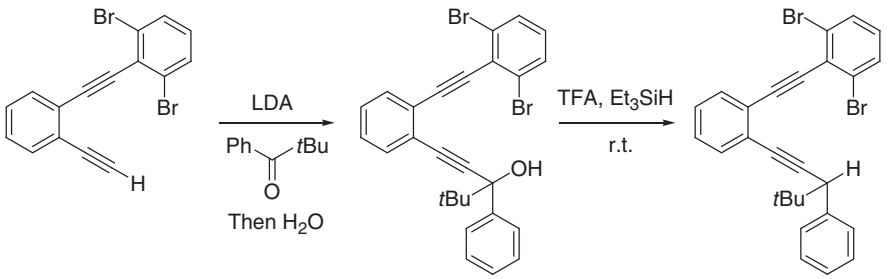
Reductive methods can provide useful selectivity. An excess SmI_2 was shown to selectively cleave nonanomeric allyl ethers in the presence of anomeric allyl ethers.[67] The combination of $NaBH_4$ and Lewis acids (such as BF_3 or I_2) will selectively cleave allyl ethers in the presence of benzyl and other ethers (Scheme 52).[68]



Scheme 52

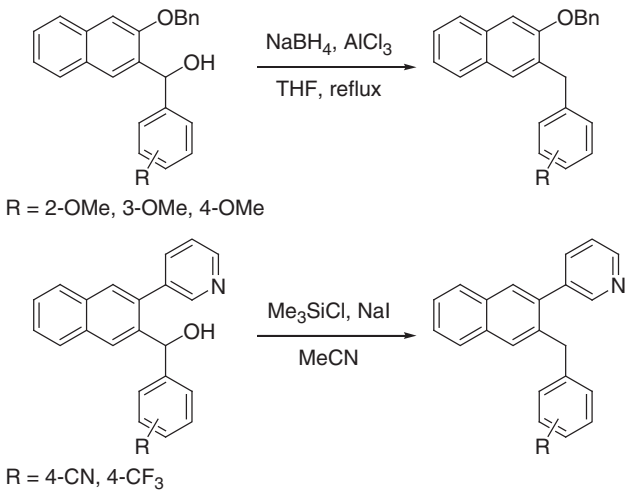
8.32.1.4 Strategic Use in Complex Molecule Synthesis

The focus is on when these methods have been used to accomplish strategic transformations rather than removal of protecting groups. In the synthesis of polycyclic aromatic compounds, Kim et al.[69] introduced a phenyl ring by nucleophilic addition, in order to set up a radical cyclization. Before cyclization, the vestigial alcohol was easily cleaved in 5 min by TFA and Et_3SiH without adversely affecting aryl bromides or conjugated alkynes (Scheme 53).



Scheme 53

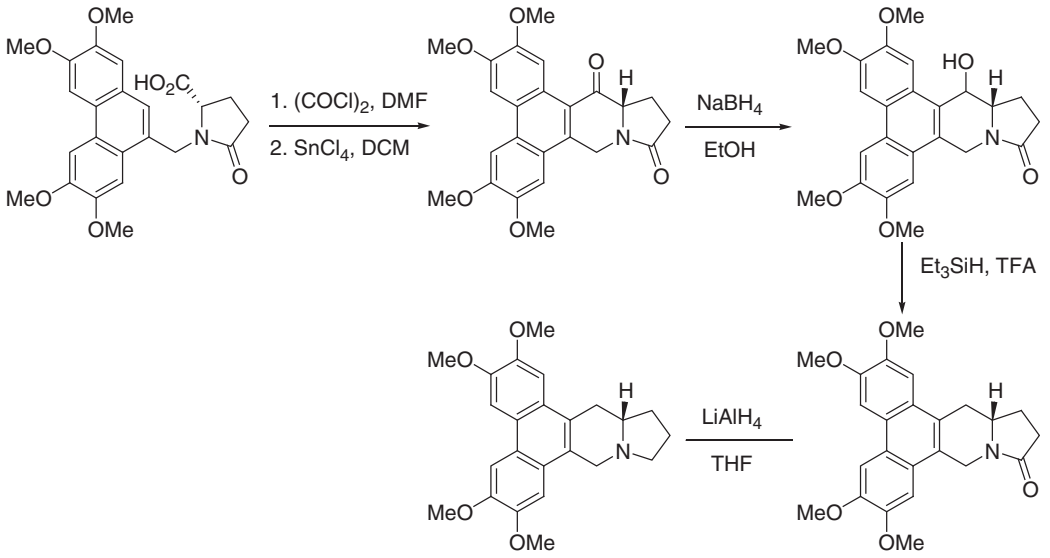
The use of $NaBH_4$ with $AlCl_3$ allowed the selective reduction of a benzyl alcohol in the presence of a benzyl ether during the synthesis of aldosterone synthase inhibitors.[70] The product of the addition of an aryl Grignard to an aldehyde was dehydroxylated before further elaboration by Pd-catalyzed aryl coupling. These conditions were unsuccessful when applied to pyridyl analogs, which were instead dehydroxylated with Me_3SiI generated *in situ* (Scheme 54).



Scheme 54

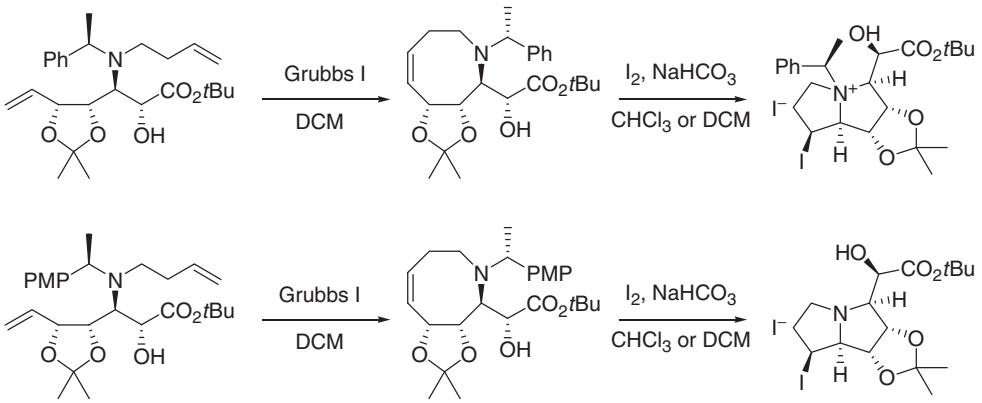
In the synthesis of (*S*)-(+)-tylophorine,[71] a ring is installed by ketone formation from an alkene and acid. The ketone is subsequently reduced to the benzyl alcohol, which is cleaved by Et_3SiH in TFA without affecting a neighboring allylic amide. The amide is then reduced to the amine by $LiAlH_4$ to give the natural product (Scheme 55).

Davies and coworkers[72] have developed diastereoselective halogen-mediated C–N bond-forming cyclizations. In these reactions residual benzylamine groups, previously used to control the absolute stereochemistry of the molecules, may be cleaved if they are properly substituted. In the following example, an α-methylbenzylamine is installed by conjugate addition and an 8-membered ring is formed by olefin metathesis. Reaction with iodine under basic conditions effects cyclization and simultaneous cleavage of the benzylamine by an S_N1-type mechanism. When the α-methylbenzyl ring was unsubstituted, the quaternary



Scheme 55

ammonium product was stable and difficult to cleave. Use of α-methyl-*p*-methoxybenzylamine allowed the reaction to proceed as intended (Scheme 56).



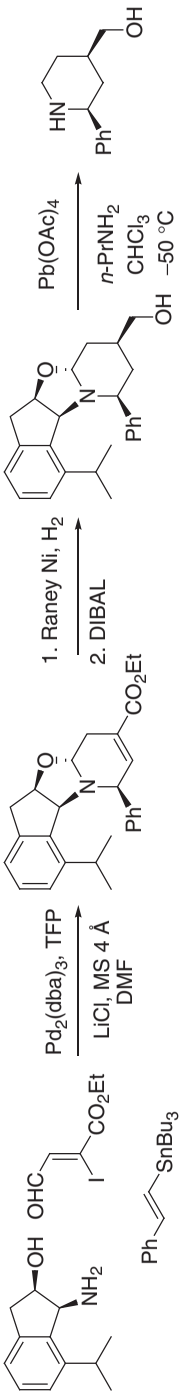
Scheme 56

The oxidative cleavage of benzylamines was used to remove a chiral auxiliary used for the stereoselective synthesis of piperidines.[73] A trisubstituted piperidine precursor bound to a chiral amino alcohol is synthesized in a one-pot reaction from three components, and the auxiliary cleaved by lead(IV) acetate (Scheme 57).

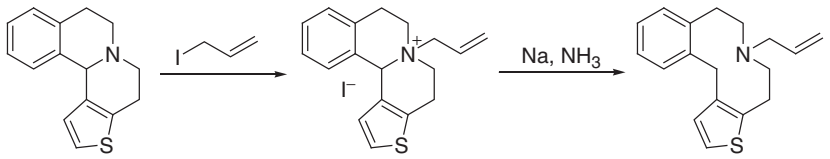
Maryanoff and Almond, Jr.[74] used the cleavage of a bicyclic quaternary benzylammonium salt to generate 9-membered rings. This transformation has been applied by Hoefgen et al.[75] to the synthesis of azecine derivatives and related compounds, exemplified here by a benzothienoazecine containing a 10-membered ring. Following quaternization of the amine, no purification beyond filtration is required before Birch reduction. The newly generated allylamine is neither cleaved nor reduced during cleavage of the benzylamine (Scheme 58).

The ability to differentiate between allyl- and PMB-protected phenols was central to the function of the chemically driven molecular motor described by Feringa.[76] Orthogonal cleavage of allyl and PMB ethers drove the rotation of a phenyl rotor in one direction relative to a naphthyl stator between two of the four rotational stages of the motor's operation. Cleavage of the PMB ether was carried out using $Ce(OTf)_3$, and was accompanied by spontaneous lactone formation. A second unidirectional rotational event was driven by selective cleavage of an allyl group with $Pd(PPh_3)_4$ and formic acid. Under these conditions the phenol from deallylation was stable, and the lactone was formed by addition of DCC (Scheme 59).

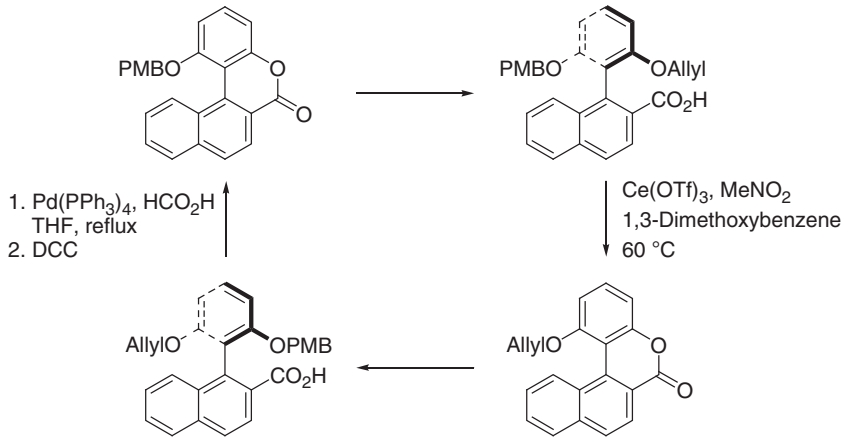
Hunter and O'Doherty[77] used the Sharpless asymmetric dihydroxylation followed by reduction of an allylic alcohol as key steps toward a synthetic precursor of leucascandrolide A. Pd-catalyzed cleavage of benzyl and ethyl carbonate derivatives, used to activate the alcohol for reduction, gave poor yields and some doubly-dehydroxylated byproduct, but the use of a cyclic carbonate as an activating group allowed selective cleavage of the allylic alcohol (Scheme 60).


OH
NH2
OHC
I
CO2Et
Ph
SnBu3
Pd2(dba)3, TFP
LiCl, MS 4 Å
DMF
O
N
Ph
CO2Et
1. Raney Ni, H2
2. DIBAL
OH
Pb(OAc)4
n-PrNH2
CHCl3
–50 °C
HN

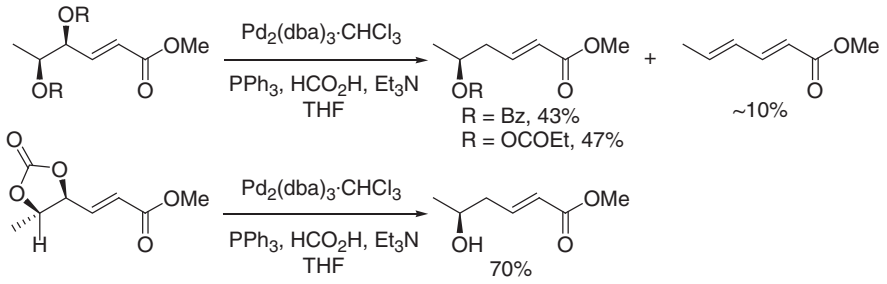
Scheme 57



Scheme 58

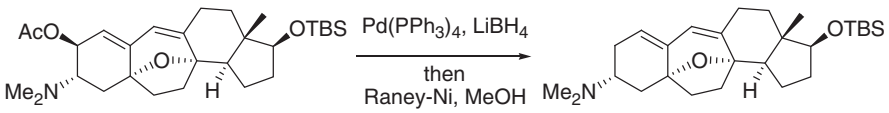


Scheme 59



Scheme 60

Myers and coworkers[78] used $Pd(PPh_3)_4$ and excess $LiBH_4$ in the synthesis of cortistatin K to selectively cleave an allylic acetate in the presence of a complex allyl ether. The product was isolated as a borane complex which was then cleaved with Raney nickel, to give the desired product in 90% overall yield (Scheme 61).

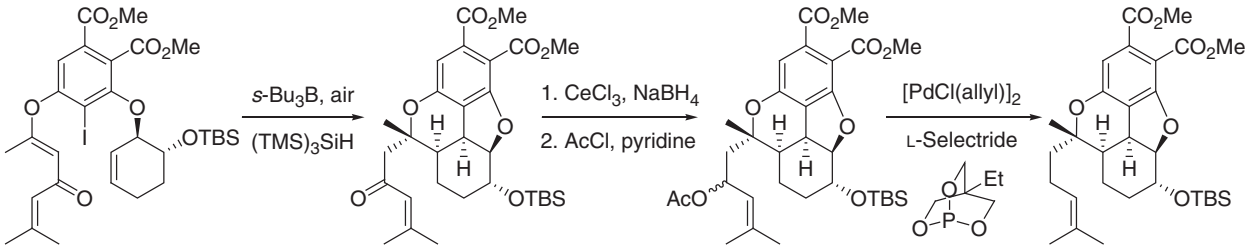


Scheme 61

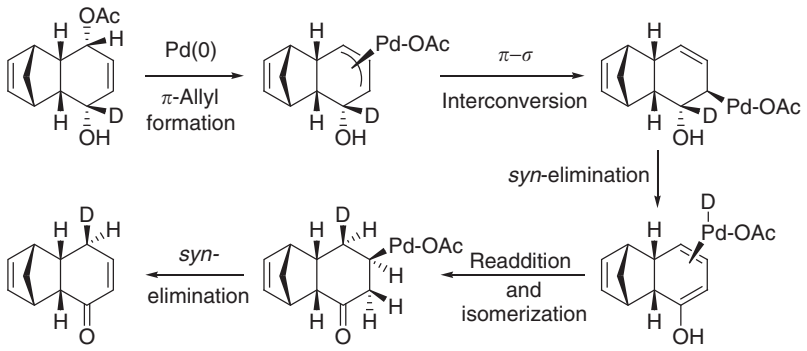
The gentle cleavage of allyl acetates by Pd(0) was a crucial part in the synthesis of bisabosqual A.[79] Radical cyclization onto an alkene activated by a carbonyl group was followed by removal of the residual carbonyl group of an enone. Luche reduction, acetylation, and regioselective palladium-mediated hydrogenolysis provided the desired trisubstituted alkene (Scheme 62).

Takano, Ogasawara, and coworkers[80] have described an unusual variation of the cleavage of allylic alcohols, in which cyclic ene-diols undergo a stereospecific intramolecular 1,4-hydrogen shift to give the corresponding cyclohexenone (Scheme 63). This has been applied to the synthesis of several natural products. For example, Yoshida and Ogasawara used the resultant cyclohexenone to control the stereochemistry of three carbon atoms in a concise synthesis of (–)-shikimic acid (Scheme 64).[81]

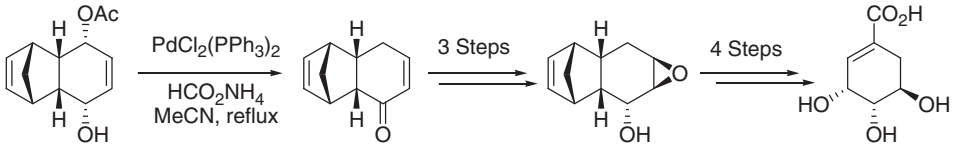
The simple reduction of allylic thioethers with Raney nickel enabled a key Diels–Alder reaction in the synthesis of (–)-acanthoic acid.[82] A diene bearing a thiophenyl substituent reacts with an α,β-unsaturated aldehyde to complete the core of



Scheme 62

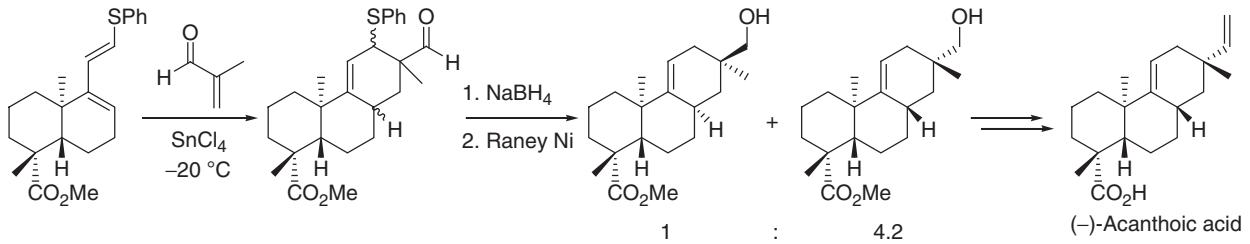


Scheme 63



Scheme 64

acanthoic acid with moderate diastereoselectivity (4.2:1). Reduction of the aldehyde and cleavage of the allyl thioether allowed isolation of the correct diastereoisomer (Scheme 65).



Scheme 65

This chapter has described an array of complementary methods that are generally useful for the selective cleavage of benzyl- and allyl-heteroatom bonds. The chapter has focused on O, N and S heteroatoms, but these methods may also be useful for other heteroatoms located at allylic and benzylic positions.

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