INTRODUCTION TO VOLUME 7: OXIDATION

Oxidation reactions are key transformations in organic synthesis. This volume covers various aspects of oxidation reactions and reagents in organic syntheses.

Since the first Comprehensive Organic Synthesis edition of this topic by Steven V. Ley in 1991, a number of new selective oxidations have been described in the chemical literature and this volume summarizes the advances in this important field since 1990. The details of material covered are described below.

The oxidation of inactivated C–H bonds has experienced huge developments and the dehydrogenation of inactivated positions will be treated in detail in the first chapter. The two major approaches, namely the generation of radical intermediates and the selective activation of inactivated C–H bonds by metal-complexes, will be presented. Dehydroaromatisation reactions are also shown to be of great synthetic value for the synthesis of complex aromatic and heterocyclic compounds. Furthermore, the use of transition metal nitrene transfer and insertion reactions will be described. All aspects of these important reactions including mechanistic studies and the characterization of reaction intermediates will be reported as well as applications in alkene aziridination, C–H amidation or amination, and sulfimidation reactions. The activation of C–H bonds using transition metal-catalyzed carbene transfer reactions have been greatly improved in recent years and numerous applications have been found including asymmetric C–H functionalizations. Oxidations involving microbial methods allow a high selectivity, economy, and excellent safety for large scale oxidations. Recent developments such as oxidative deamination or oxidative decarbonylations will also be described. Allylic C–H activations leading to oxidations, amination, and alkylation methods are described in detail. A chapter emphasizes especially chemoselective, regioselective, and stereoselective applications and shows the potential of this method for constructing natural products. The conversion of carbonyl groups to α,β-unsaturated carbonyl compounds by a dehydrogenation is also an important topic. A comparative study of all methods is made emphasizing the most practical and relevant reactions. The α-oxygenation of carbonyl derivatives can be accomplished by a range of oxidation reagents. Especially high enantioselectivities are reached by using organo-catalytic methods. The oxidation of enolates and enolates will be covered in detail and several metal-free methods using oxaziridines, nitrosoarenes, or hypervalent iodine reagents have been used with great success. C–H activation at the α-position to nitrogen atoms are leading to useful molecules and a range of methods allowing such oxidations are presented both from the preparative point of view and mechanistically. Also, the oxidation adjacent to ethers has been dramatically extended beyond autoxidation reactions. Thus, ethers can be converted to various functionalities using various oxidants. Recent advances of chromium-mediated and -catalyzed oxidations of alcohols are described in this volume as well as oxidations of activated allylic and benzylic alcohols to carbonyl compounds using DMSO and palladium-catalysts for the aerobic oxidation. Main-group metal oxidations of aryl C–H bonds have recently been extended to polyfunctional substrates and directed aryl C–H oxidations using transition metal complexes become a very powerful tool. A range of aryl C–H oxidations are now possible, allowing the synthesis of C–X, C–N, and C–C bonds. The synthetic scope of such oxidations is constantly increasing. Alternatively, nondirected aryl C–H oxidations with or without metals are also described. Quinones are an important class of organic molecules and a range of oxidations are available for preparing *para*- and *ortho*-quinones. The oxidative difunctionalization of alkenes have revolutionized organic synthesis and the asymmetric dihydroxylation, amino-hydroxylation, and 1,2-diamination have become major methods for the enantioselective construction of oxygenated and aminated organic molecules. Considerable extension of the scope and practicability of the Wacker-oxidation has occurred in the past 20 years. It will be shown in the corresponding chapter that the course of Wacker-oxidations critically depends on the chosen reaction conditions. Mechanistic aspects of new Wacker-reactions exploiting Pd(II)/Pd(IV) intermediates will be presented. A related reaction: the oxidative Heck-reaction will also be discussed in a separate chapter. The oxidation of alkenes with the formation of carbon–nitrogen bonds leading to substituted amines and nitrogen heterocycles has also been strongly improved by the use of tailored transition metal complexes as well as organocatalysts. Metals like palladium, copper, and rhodium as well as the growing use of iodine(III) oxidants have shaped the vast research field of such addition reactions. Electrophilic sulfur and selenium reagents have been used extensively to stereoselectively functionalize unsaturated organic molecules. In particular, the convenient entry to optically pure sulfur and selenium reagents has led to very useful applications in asymmetric synthesis. Methods for performing halogenations of alkenes have been considerably improved over the past 20 years. Besides dihalogenations and hydrofluorinations, methods allowing oxy-, amino-, and carbohalogenations in a stereoselective manner will also be described. The stereoselective oxidation of carbon–boron bonds has been considerably improved and belongs now to the most reliable methods for stereoselectively forming new carbon–heteroatom bonds. The selective oxidation of carbon–metal bonds can proceed via various mechanisms which will be discussed. Again, the fine tuning of the metal center and the attached ligands allows achieving unprecedented selectivities. The oxidation of organic halides to carbonyl compounds has proven to be a unique method for preparing some heterocyclic aldehydes and 1,2-diketones. The Beckmann rearrangement and fragmentation have been improved by using organo-catalytic reactions or new inorganic catalysts including supported reagents. Also the glycol cleavage of vicinal diols has been greatly improved by the choice of new lead, manganese, and tin metallic reagents and by using periodinanes and related compounds. The Hunsdieker reaction allows the formation of organic halides starting from carboxylic acids. Alternative trappings of the intermediate radicals have been reported in recent years allowing extending considerably the scope of this reaction. The oxidation of sulfur, selenium, and tellurium leads to selective reagents for various applications in organic synthesis. The preparation of these oxidized sulfur,

selenium, and tellurium reagents can be achieved with high selectivity. Asymmetric oxidations can also be achieved to prepare enantio-enriched sulfoxides and selenoxides. Finally, the use of hypervalent organic iodides has allowed many new oxidation reactions due to the exceptional chemoselectivity of hypervalent iodine reagents. The use of chiral hypervalent iodine reagents has been applied in asymmetric synthesis. Besides hypervalent (II)- and (V)-reagents, hypervalent bromine compounds have also found applications.

In summary, tremendous progress has been observed for many oxidation reactions, which extended enormously their reaction scope. The discovery of new more selective oxidation reagents and catalysts has further expanded the scope of oxidation reactions and has led to several new oxidation methods. I hope that this volume dedicated to oxidation will be useful for the readers and will give a good selectively comprehensive overview of this very active field of organic synthesis.

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7.01 Oxidation by Dehydrogenation

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Glossary

Aromaticity Strong stabilization in a conjugated cycle. Unsaturated bonds, lone pairs, and an empty orbital can participate in the delocalization.

Functional group Specific group within the molecule that is able to control reactions.

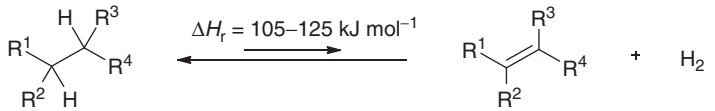
Regioselectivity The selectivity of a reagent to one of the many possible positions of a molecule. A regioselective reaction favors one constitutional isomer over other possible products.

Steroid A type of compounds with a core consisting of three cyclohexanes (A, B, and C rings) and one cyclopentane (D ring) annealed to each other.

Terpene A diverse class of natural products formally derived from isoprene units (isopentenyl pyrophosphate IPP and dimethylallyl pyrophosphate DMAPP).

7.01.1 Introduction

As equation 1 illustrates, dehydrogenation is understood as the oxidative transformation of a saturated compound to an olefin (or other unsaturated units) under the formal release of hydrogen, a reaction that constitutes a thermodynamic equilibrium and features a high reaction enthalpy (105–125 kJ mol^{-1}).[1]



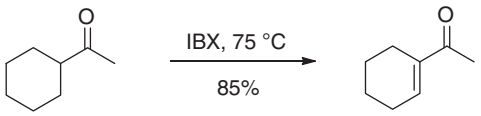
(1)

In the chemical industry, dehydrogenation processes are of an ever-increasing importance, especially in the case of propylene production. As the second largest commodity in the petrochemical industry (behind ethylene), the ever-growing demand for propylene can no longer be satisfied by the obtainment as a byproduct of cracking processes. As a result, a variety of commercial technologies such as Oleflex (UOP), Catofin (Lummus), Steam-Active Reforming (STAR, Krupp Uhde), Propane Dehydrogenation Technology (PDH, Linde-BASF-Statoil), and Fluidized-Bed Dehydrogenation (FBD, Snamprogetti-Yarsintez) is employed in the dehydrogenation of propane for the on-purpose production of propylene.[1–3]

In general, for a dehydrogenation reaction to proceed with a reasonable conversion, the thermodynamic limitations and high enthalpy must be overcome. In industrial processes, for instance, this is typically achieved by using high temperatures and comparatively low pressure, while applying catalytic systems suitable for such conditions. However, as the complexity of the starting material increases, so does the challenge of controlling the chemoselectivity of the reaction, since more and more possible sites for dehydrogenation become available. Furthermore, as the reaction progresses, the introduction of unsaturated positions may increase the reactivity of sites in their vicinity compared with the starting material, thus lowering the selectivity and leading to unwanted overoxidation. The presence of functional groups complicates matters even further, since they not only have to be tolerated by the reaction conditions, but may also create the situation that positions adjacent to the functional groups are activated toward dehydrogenation, making it more difficult to selectively target an unactivated position.

When considering means of dehydrogenation, a differentiation between activated and unactivated positions is required. Dehydrogenation methods that target activated C–H bonds are far more common in contemporary synthesis, an important example being the formation of α,β-desaturation adjacent to carbonyl or imine functional groups. Reactions such as the dehydrogenation of ketone **1** with 2-iodoxobenzoic acid (IBX), as illustrated in equation 2, proceed selectively and with high yields.[4]

However, in the absence of the carbonyl group, the dehydrogenation will not occur. Furthermore, such carbonyl and imine functional groups create the opportunity to halogenate, sulfenylate, or selenylate in the α-position, thus introducing groups that can subsequently be eliminated to form the double bond. Positions adjacent to double bonds or aromatic systems can also be considered as activated.



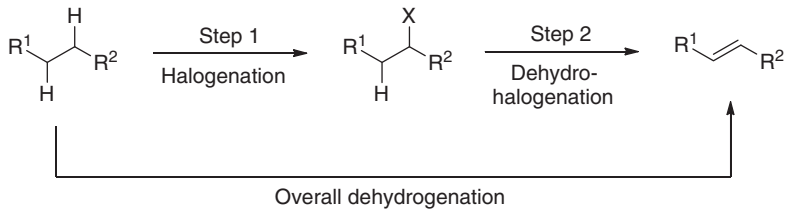
1 (2)

The dehydrogenation of C–H bonds that are not in the immediate proximity of such activating functional groups poses a considerable challenge. Other pathways have to be found that can deal with the high reaction enthalpy as well as the presence of functional groups and usually high abundance of similarly unactivated positions in a substrate, both of which impede a selective dehydrogenation. In this chapter, we present an overview over the different strategies that have been employed to overcome these difficulties. For the most part, the attempt has been made to cover the respective fields of research in a comprehensive way. However, due to a high randomness or a vast abundance of applications (notably halogenation–dehydrohalogenation reactions and aromatization methods, respectively), certain areas are discussed using only a limited selection of examples.

7.01.2 Dehydrogenation by Halogenation–Dehydrohalogenation Sequences

7.01.2.1 Substrate Specificity

Dehydrogenation can be achieved in a two-step process by first oxidatively introducing a halogen at the targeted position of the substrate, and subsequently performing an elimination step to generate the double bond (Scheme 1). Although such halogenation–dehydrohalogenation sequences are a broadly used tool for the dehydrogenation of activated C–H bonds, the application of this method with external reagents on unactivated positions is only feasible in random, specific cases. A major issue here is the regioselectivity of the halogenation step, which usually has to be realized through radical pathways in order to achieve the abstraction of an unactivated hydrogen (modern metal-catalysis offers a powerful alternative to circumvent the use of radicals, as will be discussed later in Section 7.01.4). In addition, the dehydrohalogenation step may suffer from regioselectivity issues as well, depending on the availability of adjacent C–H bonds that can undergo elimination.

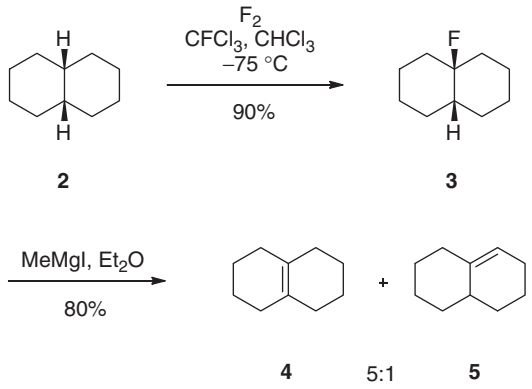


Scheme 1

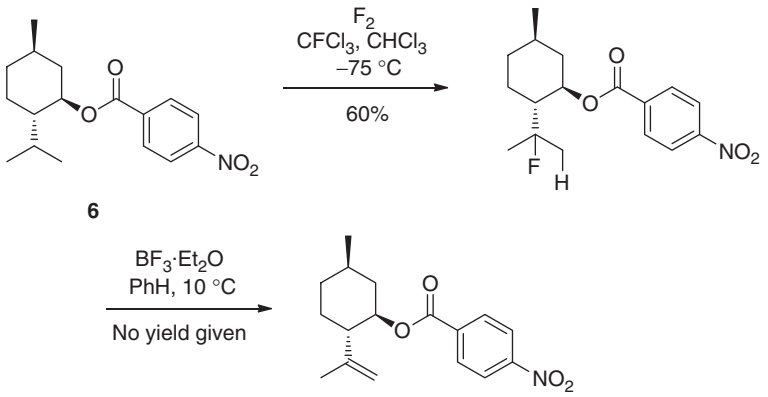
Due to the limitations of this method and its high specificity in the present context, only a small selection of applications is discussed herein, all of them are efforts to find a method that can be used on a broader scope of substrates. One example for such an attempt is shown in Scheme 2, which depicts the fluorination and dehydrofluorination of *cis*-decalin **2**.[5] Here, elemental fluorine is used as fluorinating agent, which gives the selectively fluorinated decalin **3** in high yield. Elimination under basic conditions results in a mixture of dehydrofluorination products **4** and **5**, with the higher substituted olefin being favored. These reactions also proceed in a similar fashion with *trans*-decalin, albeit with lower selectivity in the elimination step.

The selective fluorination and subsequent elimination of the menthol derivative **6** has also been successfully demonstrated (Scheme 3). A proposed explanation for the selectivity is based on a polarizing effect of chloroform on fluorine, which results in an electrophilic fluorine species. Additionally, the *p*-nitrobenzoate moiety influences the distribution of electron density in the menthol skeleton in such a way that a selective fluorination takes place.

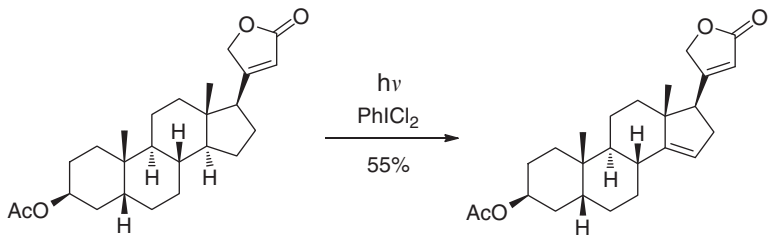
Substituent effects have also been shown to enable the site selective halogenation of steroids, in which case the use of iodobenzene dichloride as radical chlorination reagent has been particularly successful.[6–9] A striking example of use for this concept is the Δ14-selective dehydrogenation step depicted in equation 3, which is part of a formal total synthesis of digitoxigenin.[10] In contrast to previous findings, the olefin is formed directly in this instance, without the need of an additional dehydrogenation step. Also of note is the fact that the butenolide moiety is tolerated by this reaction.



Scheme 2



Scheme 3



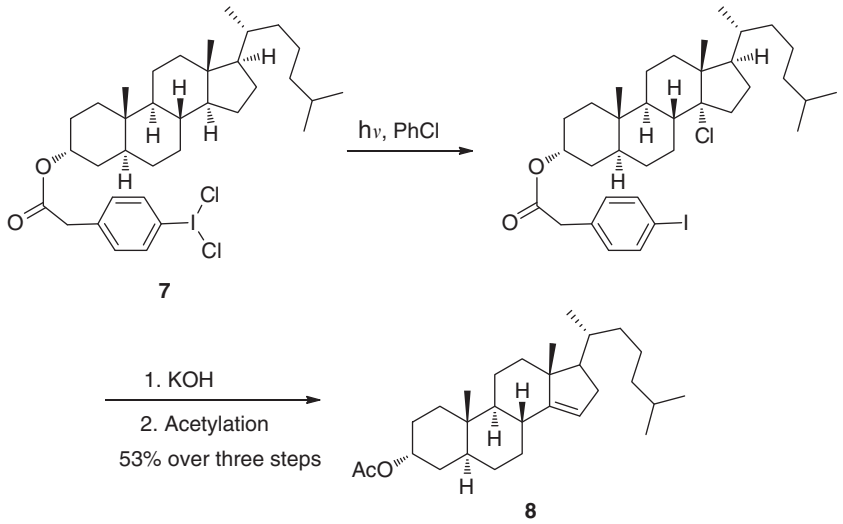
(3)

7.01.2.2 Remote Oxidation

A major concept in the oxidation of unactivated C–H bonds is the employment of temporary, internal directing groups that, by their proximity to the targeted position, force a degree of regioselectivity that would not be feasible otherwise. This strategy, in combination with the use of highly reactive radicals, has found important application in the selective oxidation of steroid frameworks, which also includes chlorination and dehydrochlorination sequences.[7,9] Steroids are well suited for this kind of approach due to their rigidity, but one also has to make sure that the degrees of freedom of the attached directing group are highly limited, since far distances between the attachment and the point of functionalization have to be bridged.

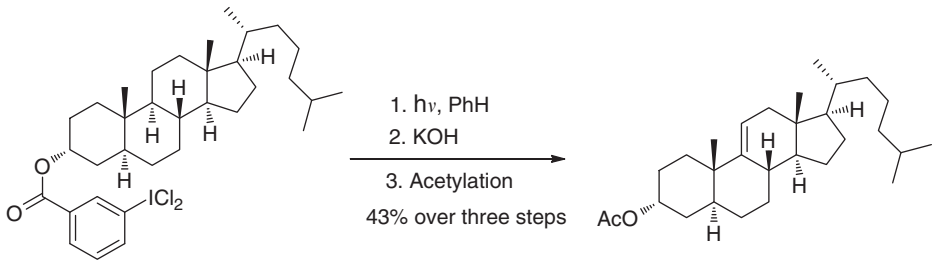
The example in Scheme 4 shows the Δ14-selective dehydrogenation of 3α-cholestanol.[7] The directing functional group, a rigid aryl iodide dichloride, which at the same time serves as internal reagent, is attached to the cholestanol by formation of the *p*-iodophenylacetic ester and subsequent treatment with chlorine to obtain the dichloride **7**. Irradiation of this intermediate prompts a selective chlorination by forming a radical species at the iodine chloride that is positioned in such a way that the hydrogen at C-14 is selectively abstracted. After the ensuing radical chain reaction gives the chloride, subsequent dehydrogenation, saponification, and acetylation yield Δ14-cholestenyl acetate **8**. Control reactions indicate that any other olefinic side products arise from a residual percentage of intermolecular interactions, and that the observed selectivity can indeed be ascribed to the

intramolecular reaction. It has been shown that this approach cannot be applied to the corresponding 3β-isomer, since the resulting equatorial position of the directing group complicates an attack from the β-side, which, in the case of cholestanol, is in addition sterically hindered by the methyl groups at the quaternary carbons. However, the 3α-isomer is easily accessible from the 3β-isomer.[11]



Scheme 4

The regioselectivity of the reaction can be influenced by modifying the iodoaryl ester attached to the cholestanol, as equation 4 demonstrates.[7] Here, changing to an *m*-iodobenzoate moiety as directing group and applying the same sequence of steps as above results in a selective dehydrogenation at the $\Delta 9(11)$ position.

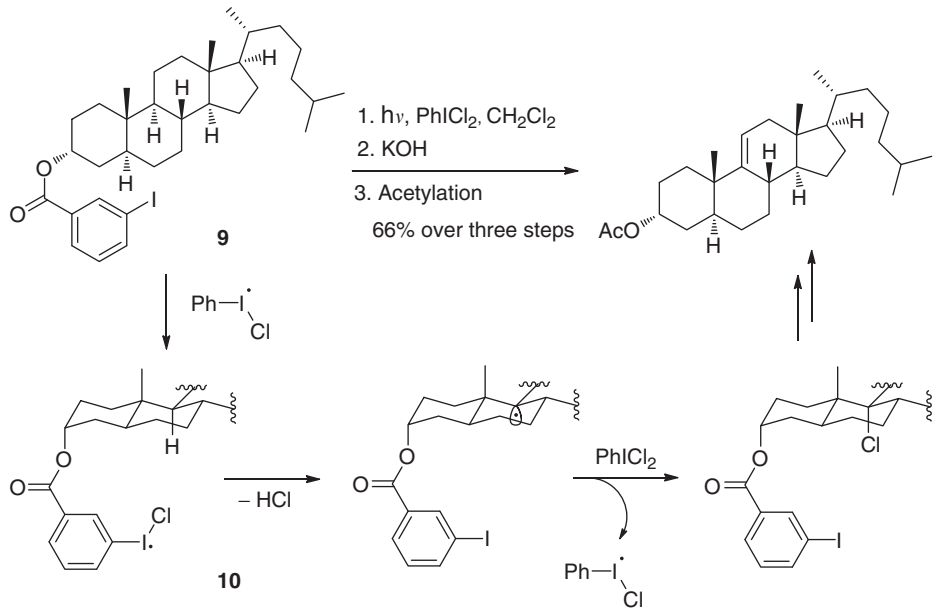


(4)

A further development of this chlorination method involves the use of iodobenzene dichloride as an external chlorine transfer reagent in combination with an aryl iodide attached to the steroid.[12–14] On irradiation, a radical relay mechanism is proposed to proceed under formation of the hydrogen-abstracting species **10** from the iodoaryl ester **9** (Scheme 5). Alternatively, it has been shown that instead of iodobenzene dichloride and irradiation, the reaction can also be performed with sulfuryl chloride in the presence of benzoyl peroxide under reflux conditions. A major advantage of this approach, compared with the reactions shown in Scheme 4 and equation 4, is the fact that it is no longer necessary to subject the whole steroidal framework to a treatment with chlorine in order to form the internal aryl iodide dichloride, which improves the tolerance toward functional groups within the steroid considerably. A selection of applications is given in Table 1.

In quite similar fashion, the strategy of remote functionalization could also be used for the preparation of an intermediary olefin in the synthesis of eudesmantetraol, a eudesmane terpene (Scheme 6).[18] The original purpose of the method used for the bromination–dehydrobromination sequence shown in Scheme 5 is the formation of 1,3-diols, which occurs similarly to a Hofmann–Löffler–Freytag reaction via the selective, radical bromination to alkyl bromide **12** by photolysis of *N*-bromocarbamate **11** (involving a 1,6-hydrogen transfer).[19] In this instance, however, instead of converting alkyl bromide **12** to the corresponding triol, it was subjected to an elimination reaction by treatment with 2,2,6,6-tetramethylpiperidine (TMP) to furnish olefin **13**, which was further converted as crude material.

Aside from the halogenation–dehydrohalogenation sequences discussed in Section 7.01.2 it should be noted that, in general, all methods that effect the functionalization of unactivated C–H bonds potentially open up the possibility to desaturate unactivated positions, provided that the introduced functional group is suited to undergo an elimination reaction.



Scheme 5

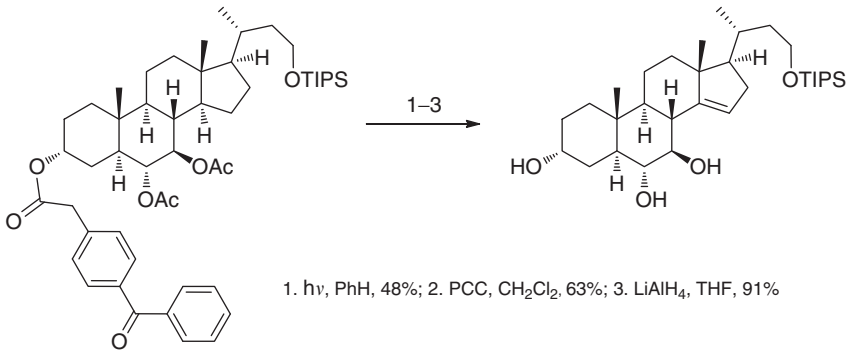
7.01.3 Direct Dehydrogenation by Internal Hydrogen Abstraction

Although Section 7.01.2 certainly demonstrates that the dehydrogenation of unactivated C–H bonds can be very elegantly managed by halogenation–dehydrohalogenation pathways, methods involving a direct hydrogen abstraction and thus providing the desired olefin in one single step would be even more convenient (Scheme 7).

Analogously to the halogenation of unactivated positions, the strategies discussed in this section also make use of highly reactive radical species to achieve cleavage of the targeted C–H bond. In this regard, studies on the remote oxidation of steroids have once again produced important results.[20,21] Applying the same principle as with the site-selective chlorination from Section 7.01.2.2, a reactive moiety is covalently attached to the substrate via esterification with a hydroxy group present in the structure. In this case, as the example of 3α-cholestanol in Scheme 8 shows, the reactive attachment consists of a suitably rigid benzophenone unit, with the nature of the linkage chosen in such a way that an ideal proximity to the targeted position in the steroid framework is achieved.

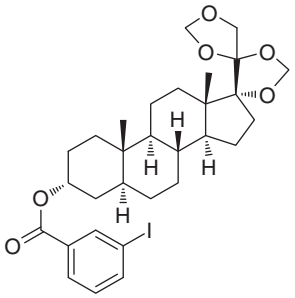
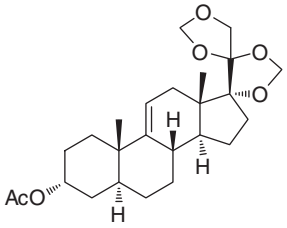
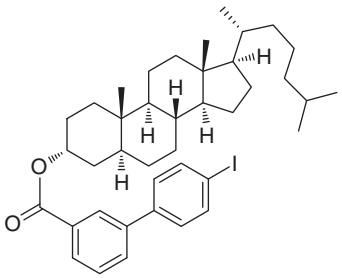
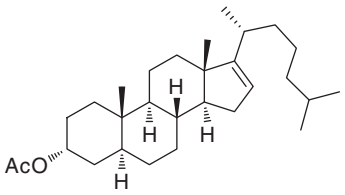
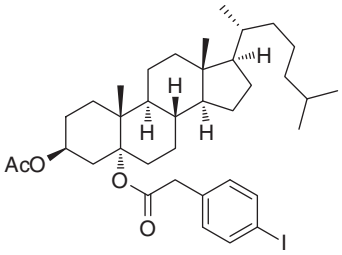
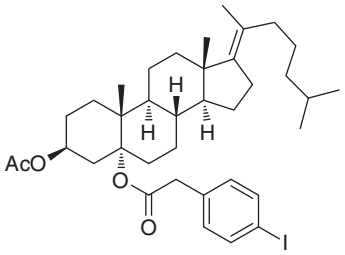
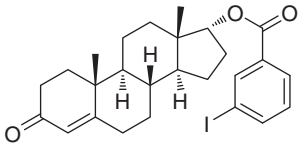
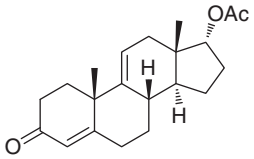
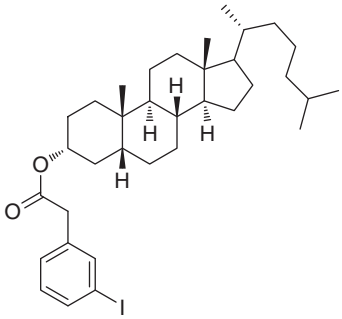
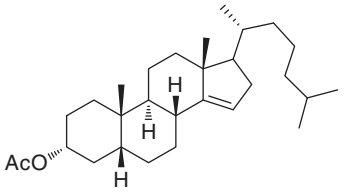
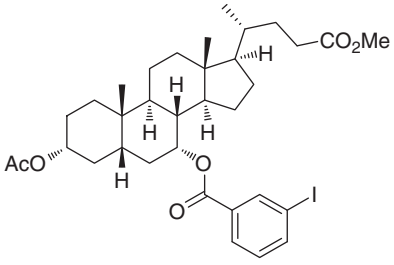
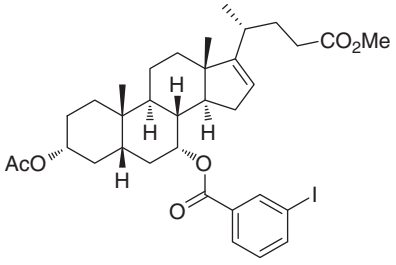
Selective dehydrogenation of the cholestanol to the Δ14-olefin is prompted by irradiation, on which the benzophenone unit is excited to its triplet state and the hydrogen at C-14 is abstracted by the carbonyl oxygen. The resulting radical intermediate collapses under formation of the double bond. Analogous to the directed chlorination of steroids discussed in Section 7.01.2.2, subsequent removal of the attachment can once again be accomplished by simple saponification of the ester. Control experiments confirm that, with benzophenone attached to the steroid, an improved selectivity is achieved compared with the intermolecular reaction with benzophenone, and that competing reactions with the solvent can be successfully suppressed. Also in accordance with the directed chlorination is the fact that the 3β-isomer cannot be functionalized in that fashion.

Although this method works well with the benzophenone-4-acetic ester for the introduction of a Δ-14 double bond, targeting other positions with other esters does not proceed as selectively.[21,22] As a result, when it comes to dehydrogenation, this kind of remote oxidation has not found as broad applications as the corresponding chlorination–dehydrochlorination method, which has also been shown to produce the desired olefins in superior yields. Nevertheless, the directed dehydrogenation with an attached benzophenone-4-acetic ester has been successfully employed in a series of syntheses of xestobergsterols and analogs, as exemplified by the oxidation step in equation 5.[23–25] Here, pyridinium chlorochromate (PCC) is used to oxidize the benzhydryl alcohol that is formed after the photolysis in order to facilitate purification. Liberation of the triol is achieved reductively with lithium aluminum hydride.

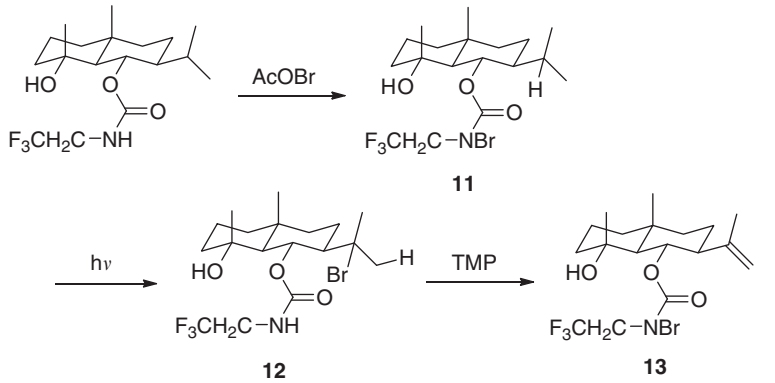


1. hν, PhH, 48%; 2. PCC, CH_2Cl_2, 63%; 3. $LiAlH_4$, THF, 91% (5)

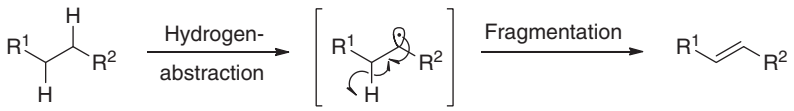
Table 1 Chlorination-dehydrochlorination reactions of steroids using remote oxidation

Entry	*Substrate*	*Product*	*Yield (%)*	*Reference*
1			75 (over 3 steps)	15
2			66 (over 3 steps)	9
3			64[a] (over 2 steps)	16
4			77 (over 3 steps)	9
5[b]			45 (over 3 steps)	8
6[b]			65 (over 2 steps)	17

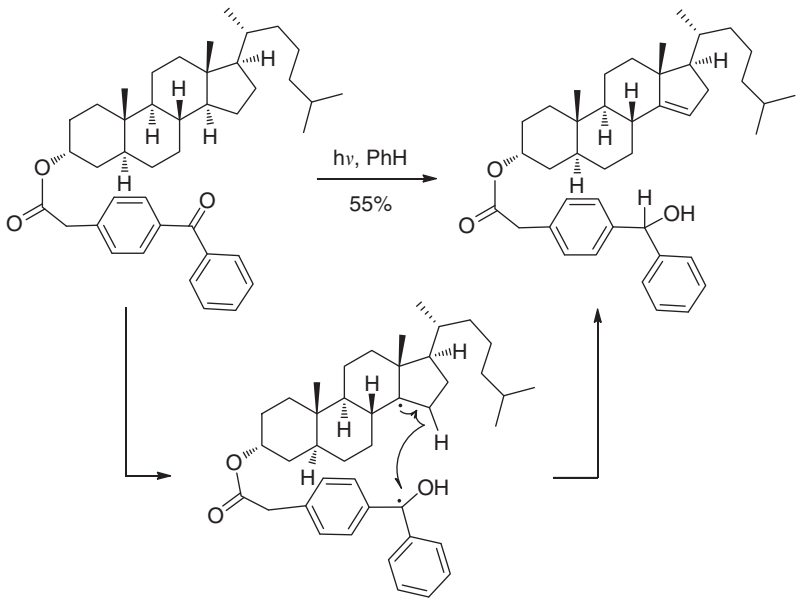
[a]4:1 Mixture of depicted product and Δ16 olefin, DBU used for dehydrochlorination.
[b]Substrates with A/B *cis* fusion.



Scheme 6



Scheme 7

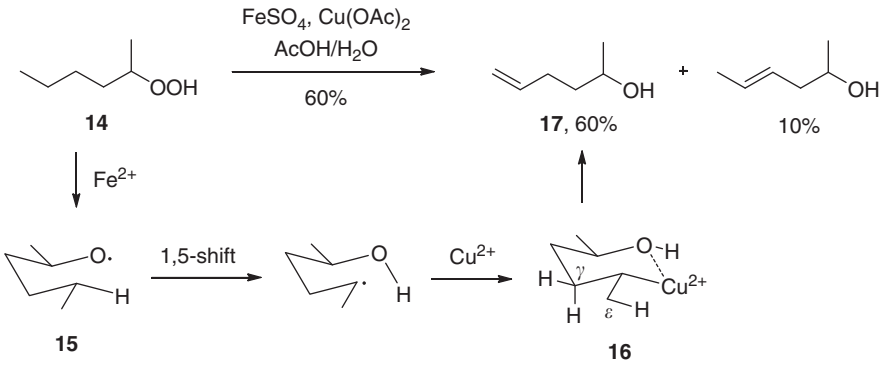


Scheme 8

The principle of remote functionalization also finds application in the dehydrogenation of alkyl hydroperoxides by conversion with iron(II) sulfate and copper(II) acetate to obtain olefinic alcohols.[26–28] In this case, modification of the substrate with some kind of temporary directing group is not necessary, since the mechanism at work here is based on the internal abstraction of an unactivated hydrogen by an alkoxy radical generated from the peroxide, with site selectivity being solely controlled by the proximity of the hydrogen and the conformation of the substrate.

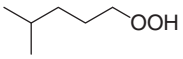
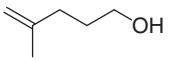
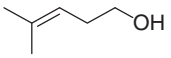
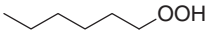
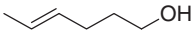
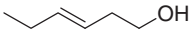
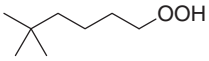
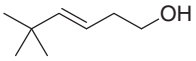
As Scheme 9 illustrates by the example of 2-hydroperoxyhexane **14**, iron(II) prompts the formation of the alkoxy radical **15**, which results in an iron species that does not further interact with the alkoxy radical due to its stable electron configuration. Thus, the abstraction of one hydrogen at the δ-carbon via a 1,5-hydrogen-shift can proceed, which generates a carbon radical that might be trapped by copper(II) acetate. The fact that the terminal δ,ε-unsaturated olefin **17** is the main product of the reaction (with the γ,δ-olefin being observed in 10% yield) points to the formation of a six-membered intermediate **16**, which then undergoes *syn*-elimination. With this in mind, it can be rationalized that one of the ε-carbon–hydrogen bonds finds itself in a more eclipsed position to the carbon–copper bond than any of the γ-carbon–hydrogen bonds, resulting in the preferred elimination to the

δ,ε-double bond and copper hydride. This is supported by further examples, some of which are listed in Table 2. Observed side products in all cases are, to varying extent, the corresponding saturated alcohol and carbonyl compounds.



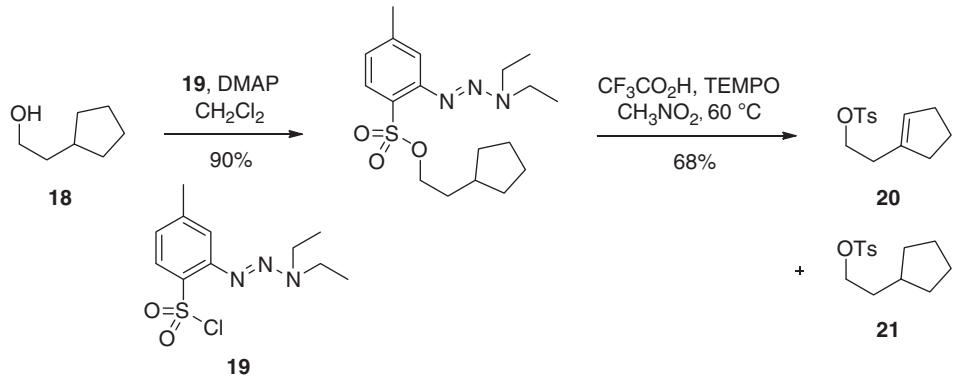
Scheme 9

Table 2 Synthesis of olefinic alcohols by remote oxidation

Entry	*Substrate*	*Products*	*Yield (%)*	*References*
1			76	28
			8	
2			56[a]	27
			17	
3			39	28

[a]Mixture of *cis*- and *trans*-isomers.

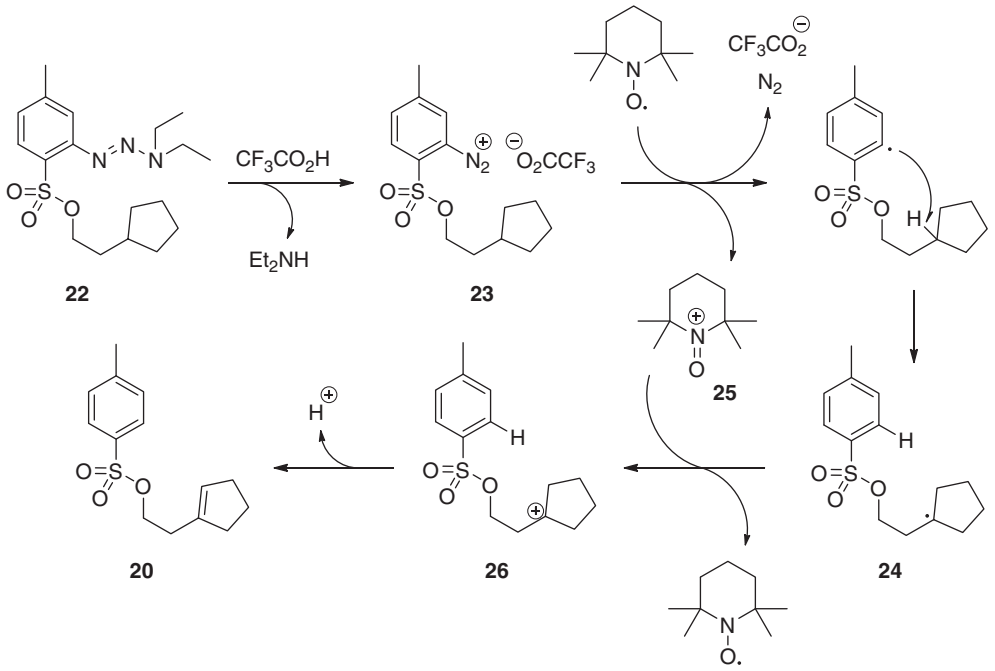
Although undeniably elegant in their conception and impressive in their performance, one drawback that all strategies developed for the dehydrogenation of unactivated C–H bonds share is their specificity to a certain kind of substrate. A striking attempt at a method that may be applicable to a broader scope of structures is shown in Scheme 10.[29] This reaction also follows the principle of attaching a directing group to a substrate and subsequently generating a highly reactive, radical intermediate that can perform an internal, site selective hydrogen abstraction. Here, the directing group is a triazenyl-*p*-toluolsulfonyl moiety that is easily installed at the hydroxy group of the 2-cyclopentylethanol **18** by conversion with the corresponding triazenyl-*p*-toluolsulfonyl chloride **19** and 4-dimethylaminopyridine (DMAP). Subsequent treatment with trifluoroacetic acid and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) yields 2-(cyclopent-1-en-1-yl)ethyl tosylate **20** in a 10:1 mixture with saturated tosylate **21**, a byproduct obviously formed by reduction of olefin **20**. When triflic acid is used instead of trifluoroacetic acid, the reduction to the



Scheme 10

saturated byproduct is suppressed altogether, and the reaction proceeds rapidly even at room temperature, albeit in slightly diminished yield. Of important note is the fact that, in the course of the reaction, the triazenyl-*p*-toluolsulfonyl directing group is transformed into a tosylate, which may serve as a useful functional group for further modification.

Scheme 11 depicts a proposed mechanism for this dehydrogenation reaction. As illustrated, the acid's role is simply the liberation of an aryl diazonium species in the form of carboxylate salt **22**. Aryl radical **23** is generated from the diazonium salt in a commonly known way by electron transfer from TEMPO under release of nitrogen. Hydrogen abstraction occurs by way of an unusual 1,7-hydrogen shift, which leads to the formation of a tosylate moiety and an aliphatic radical in intermediate **24**. The oxopiperidinium species **25**, generated in the reduction step before, can now accept an electron and oxidize intermediate **24** to carbocation **26**, under regeneration of TEMPO. Subsequent loss of a proton prompts the formation of olefin **20**. This mechanism would lead to the assumption that TEMPO could mediate the reaction in a catalytic manner, and experiments indeed confirm a certain degree of catalytic activity. However, with TEMPO only present in catalytic amounts, the reaction does not proceed efficiently under the given conditions.



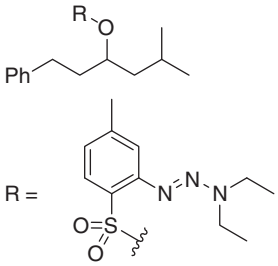
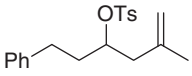
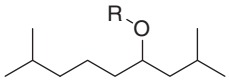
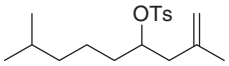
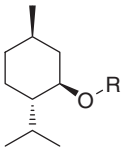
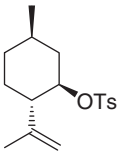
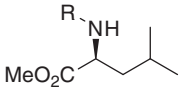
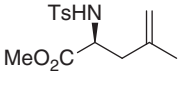
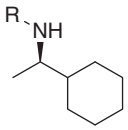
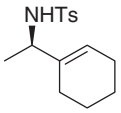
Scheme 11

Table 3 shows a selection of additional examples for this dehydrogenation reaction. The secondary alcohols in entries 1 and 2 demonstrate that, as can be expected considering the radical pathway of the reaction, hydrogen abstraction is favored at a tertiary carbon, ideally at γ-position to the directing group. The method proves to be especially effective in the case of menthol (entry 3), which features a more rigid structure. Furthermore, it has been shown that amines can be converted in an analogous fashion to olefinic tosyl amines, in which case both homoallylic and allylic products are observed (entries 4 and 5, respectively). In contrast, alcohols lead exclusively to the isolation of homoallylic tosylates. This fact, combined with oftentimes moderate yields, may point to the possibility that allylic tosylates are formed as well along with their homoallylic isomers, but are not stable under the reaction conditions. In addition, it should be noted that saturated side products such as tosylate **21** (Scheme 10) are only observed with certain substrates.

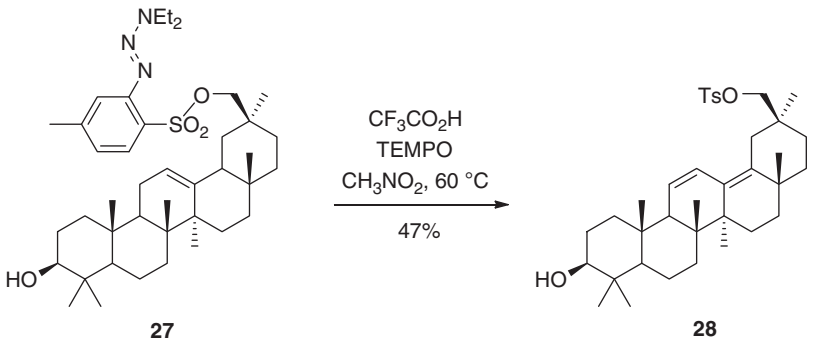
Selectivity and functional group tolerance of this strategy have also been put to test with more complex structures such as the reduced derivative **27** of glycyrrhetinic acid (equation 6). The dehydrogenation, controlled by the directing group selectively attached to the primary alcohol, gives diene **28** in moderate yield (with small amounts of reduction byproduct). Since an allylic hydrogen is abstracted by a 1,8-shift in this particular instance, the reaction proceeds via a stabilized, allylic radical intermediate, and one could argue that the somewhat activated nature of the targeted site helps influence the selectivity of the dehydrogenation.

A remarkable tolerance toward functional groups is evident in the application of this method to the dehydrogenation of polypeptide **29** (equation 7), in which case the directing group is bonded to the terminal amino moiety of a leucine unit. Here, selective oxidation occurs at the leucine side chain whereas the various reactive sites and chiral centers remain intact in the resulting tosyl amine **30**, which is formed in acceptable yield.

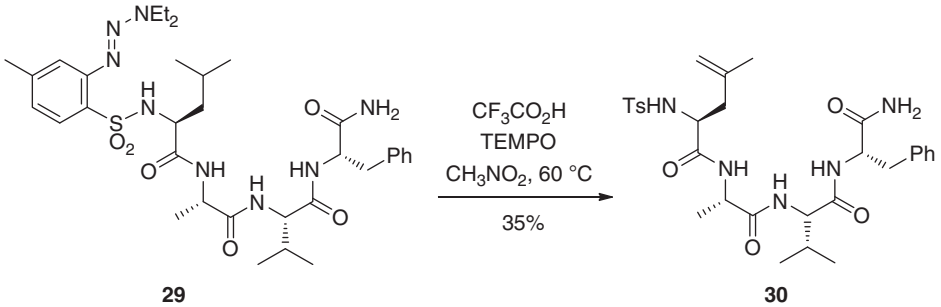
Table 3 Directed dehydrogenation of alcohols and amines

Entry	*Substrate*	*Product*	*Yield (%)*	*References*
1[a]			36	29
2[a]			41	29
3[a]			92	29
4[a]			47	29
5[b]			50	29

[a]Conditions: CH_3CO_2H, TEMPO, CH_3NO_2, 60 °C.
[b]Conditions: TfOH, TEMPO, CH_3NO_2, r.t.



27 **28** (6)



29 **30** (7)

7.01.4 Transition-Metal-Mediated C–H Activation Methods

All of the methods discussed in Sections 7.01.2 and 7.01.3 make use of radical intermediates to accomplish the dissociation of unactivated C–H bonds and thus induce reactivity. Another major concept that has emerged as a very important tool in organic synthesis is the activation of C–H bonds by transition metals.[30–32] This activation usually involves an insertion of the metal into a C–H bond (which proceeds via different mechanisms depending on the various parameters of the reaction system) and ultimately relies on the reactivity of the resulting organometallic species. Rather unsurprisingly, this concept has also found application in dehydrogenation reactions.

7.01.4.1 Dehydrogenation of Aliphatics

As far as the dehydrogenation of unactivated C–H bonds is concerned, the one area that has seen by far the most extensive research is the desaturation of simple alkanes. The development of an efficient access to important olefinic commodities from cheap and readily available alkanes is of immense value to industrial processes, and to realize this by means of direct desaturation would obviously be most convenient.

Although heterogeneous catalysts are successfully employed in the industrial dehydrogenation of lower alkanes, their need for high temperatures and issues of selectivity prevent an effective dehydrogenation of higher alkanes. Instead, the C–H activation by homogeneous transition metal catalysts stands at the forefront of these investigations. What lead to a rapid initiation of this field of research were early discoveries that certain bisphosphine complexes of iridium and rhenium in the presence of an olefin as hydrogen acceptor can stoichiometrically dehydrogenate cyclopentane and cyclooctane under formation of cyclopentadienyl and 1,5-cyclooctadiene complexes.[33–36] Similar complexes were soon found to be catalytically active in the dehydrogenation of cyclooctane to cyclooctene (Table 4, entries 1 and 2, respectively).[37,38] The presence of an olefin as hydrogen acceptor is mandatory for the reaction to proceed at moderate temperatures, since the transfer of hydrogen in an accompanying hydrogenation process makes the reaction thermodynamically more favorable. 3,3-Dimethylbutene (*tert*-butylethene, TBE) has proved to be an effective acceptor, since the absence of an allylic hydrogen prevents unwanted dehydrogenation. Additionally, in comparison, ethylene and styrene derivatives have been shown to inhibit dehydrogenation of the substrate, most likely due to an overly strong binding to the metal in the former case, and the formation of arene complexes in the latter.[34]

Table 4 Systems for the catalytic dehydrogenation in equation 8

Entry	*Catalyst*	*Conditions*	*TON*[a]/t	*References*
1	$ReH_7[P(p\text{-}FC_6H_4)_3]_2$	TBE, 80 °C	9/10 min	37
2	$\{IrH_2(Me_2CO)_2[P(p\text{-}FC_6H_4)_3]_2\}SbF_6$	TBE, base[b], 140 °C	8/140 h	38
3	$IrH_5(PPr^i_3)_2$	TBE, 150 °C	70/5 d	39
4	$IrH_2(CF_3CO_2)[P(p\text{-}FC_6H_4)_3]_2$	TBE, 150 °C	16/2 d	40
5	$IrH_2(CF_3CO_2)[P(C_6H_{11})_3]_2$	TBE, hν, r.t.	21.41/h[c]	40
6		hν, r.t.	8/7 d	41
7		150 °C	1.41/h[c]	42
8	$RhCl[P(p\text{-toloyl})_3]_3$	150 °C	13/48 h	43
9	$RhCl(CO)(PMe_3)_2$	hν, r.t.	300/h[c]	44
10		norbornene, H_2, 100 °C	950/15 min	45
11	$RhCl(PMe_3)_2(PPr^i_3)$	norbornene, H_2, 50 °C	640/18 h	46
12	$[RhCl(AsPh_3)_2]_2$	ethylene, H_2, 60 °C	1385/4 h	47

[a]Turnover number.
[b]1,8-Bis(dimethylamino)naphthalene.
[c]Initial rate.

The dehydrogenation of cyclooctane to cyclooctene (equation 8) has been established as a benchmark reaction in the development of catalytic systems for this process. Table 4 showcases the evolution of such systems and the progress in their catalytic activity as observed for the cyclooctane dehydrogenation. Apart from the initially discovered, thermal transfer-dehydrogenation process (entries 1–4), in which case the released hydrogen is formally consumed in the hydrogenation of an acceptor olefin, it has also been shown that certain catalysts allow the dehydrogenation to proceed under photochemical instead of thermal conditions, as well as, in both cases, in the absence of a hydrogen acceptor.



(8)

The iridium trifluoroacetate complex $IrH_2(CF_3CO_2)[P(C_6H_{11})_3]_2$ has been shown to be catalytically active at room temperature under irradiation with UV light, both in the presence and absence of a hydrogen acceptor (entries 5 and 6, respectively), although the turnover number is still significantly higher in the former case.[40,41] Furthermore, the same system is able to effect catalytic dehydrogenation in the absence of a hydrogen acceptor under solely thermal conditions (entry 7), which has also been found for the monomeric Wilkinson-type complex of entry 8.[42,43] For this to proceed efficiently, reflux conditions are essential in order to remove the evolved molecular hydrogen from the reaction system.[42,43] In the case of the Wilkinson-type catalyst, the catalytic system shows a slight preference for hydrogen transfer in the presence of an acceptor olefin when compared with the evolution of molecular hydrogen, although the rates are quite similar.[48] Of interest in this regard is the observation that alkylphosphine analogs of the employed catalyst exhibit a considerably slower rate for the reductive elimination of molecular hydrogen in comparison to the hydrogen transfer process, which seems to be owed to a stabilizing effect that the alkylphosphine ligands, with their good electron-donating properties, have on an intermediary dihydride complex.

Compared with all of these systems described above (**Table 4,** entries 1–8), a major leap in catalytic activity has been achieved with the introduction of rhodium carbonyl bisphosphine complexes in this field (entries 9 and 10). Under irradiation at room temperature, in the absence of a hydrogen acceptor, high initial rates are observed in the dehydrogenation of cyclooctane, with maximal turnover numbers of up to 5000.[44] The driving force behind this remarkably efficient process is the photoinduced cleavage of the carbon monoxide–rhodium bond, and mechanistic investigations suggest that this liberation step is actually included within the catalytic cycle, in contrast to first forming an active catalytic species which then enters the cycle. The activity of this system has been found to be even higher when adapted to a thermal transfer-dehydrogenation (entry 10), with norbornene used as hydrogen acceptor and, remarkably, under a high pressure atmosphere of hydrogen.[45] These conditions result in a largely excessive hydrogenation of the acceptor olefin, which facilitates the liberation of carbon monoxide to form the active catalytic species for the dehydrogenation step. In the case of the conversion of cyclooctane, staggering turnover numbers of 950 in just 15 min are observed. It has also been shown that the reaction is no longer limited by the lifetime of the catalyst, but rather by the availability of acceptor olefin.

As can be seen in entry 11, the use of analogous, mixed trisphosphine rhodium complexes lead to still further improvement of this system, enabling high rates at lower temperatures and lower hydrogen pressure, which can be attributed to the more facile loss of a sterically demanding phosphine ligand (in this case triisopropylphosphine) compared with carbon monoxide.[46] High turnover numbers under similar conditions have also been demonstrated for Rhodium arsine complexes (entry 12), which exhibit a decreased ratio of hydrogenation of the acceptor olefin to dehydrogenation of the substrate compared with the phosphine analogs, and are surprisingly efficient with ethylene employed as hydrogen acceptor.[47]

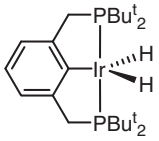
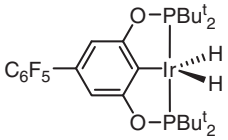
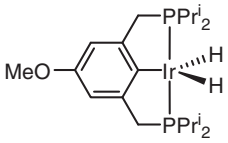
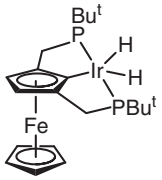
The use of tridentate aryl bisphosphine pincer complexes of iridium marks another crucial development in the dehydrogenation of unactivated aliphatics. In contrast to the iridium systems presented in **Table 4**, which are plagued by catalyst decomposition and thus deactivation, especially under thermal conditions,[40,41] pincer complexes such as those shown in **Table 5** exhibit a vastly improved thermal stability, and can be used as efficient thermal dehydrogenation catalysts at temperatures of up to 200 °C, with and without a hydrogen acceptor, although lower rates are observed in the latter case (entries 1 and 2 in **Table 5** show the respective performances of these systems in the dehydrogenation of cyclooctane).[49,50] Experiments indicate that these systems are solely limited by the reaction equilibrium, with catalyst stability not being a factor anymore. Consequently, the reaction is inhibited by high concentrations of the dehydrogenation product, and in the case of an acceptor-less reaction, hydrogen has to be removed in a constant gas flow to ensure a continuous conversion. In transfer-dehydrogenation processes, the catalytic activity has been shown to be additionally limited by high concentrations of acceptor olefin.[49,54]

The transfer-dehydrogenation system of entry 3, with an electron-deficient, *p*-substituted bisphosphinite pincer complex, is particularly effective, reaching turnover frequencies of up to 2.4 s^{-1}.[51,55] In this instance, it is also possible to generate the catalytically active species *in situ* by treatment of the corresponding, air-stable chloro-precatalyst (PCP)IrClH ('PCP' being the bisphosphinite ligand) with sodium *tert*-butoxide. A similar activity can be observed for the system shown in entry 4, which, together with analogs, has also been successfully employed in the acceptor-less dehydrogenation of cyclodecane to cyclodecene (in which case mixtures of *cis*- and *trans*-isomers are obtained).[52,56] Of interest is the obvious disparity in the electronic properties of the pincer ligands used in the entries 3 and 4, which seems to be at odds with the observed similarity in catalytic activity. It has been argued that the π-donating abilities of the methoxy-substituted aryl moiety in the phosphine ligand and the σ-withdrawal of electron density from the phosphorus in the case of the phosphinite ligand have similarly positive effects on the capability of the respective complex to active C–H bond.[52] Further proof that the factors influencing the activity of such pincer-ligated iridium systems are highly complex is given by the fact that the ferrocenyl-derivative in entry 5 (and to a lesser extent its ruthenocenyl-analog) produces even higher turnover numbers than all the other catalysts.[53] These results suggest that the angles of the ligands surrounding the metal center, and consequently its accessibility, play an important role as well.

Although all of the systems above decompose at temperatures greater than 200 °C, an even higher thermal stability has been shown for anthracene-1,8-diphosphine complexes of iridium. These have been successfully employed in the catalytic dehydrogenation of cyclodecane at temperatures of up to 250 °C.[57] However, these complexes exhibit inferior turnover numbers in the dehydrogenation of cyclooctane compared with the benzylic pincer complexes listed in **Table 5**.

The dehydrogenation of *n*-alkanes has also been demonstrated to be feasible with the catalytic systems discussed in this section, although usually mixtures of isomers are obtained due to isomerization.[41,45,47,52] However, it has been established that these catalysts preferably activate primary hydrogens over secondary hydrogens, whereas the activation of tertiary hydrogens is hardly observed. For the iridium pentahydride system of entry 3 (**Table 4**) it has been shown that 1-hexene is the kinetic product

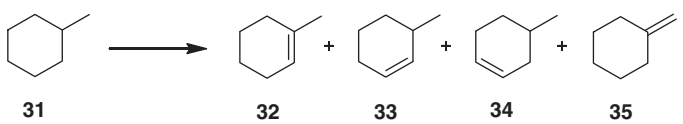
Table 5 Iridium pincer complexes in the catalytic dehydrogenation of cyclooctane

Entry	*Catalyst*	*Conditions*	*TON*[a]/t	*References*
1		TBE, 200 °C	12/min[b]	49
2		200 °C	11/h[b] 104/44 h 190/120 h	50
3		TBE, 200 °C	2.39/s[b] 2056/40 h[c]	51
4		TBE, 200 °C	542/8 min	52
5		TBE, 180 °C	3300/8 h	53

[a]Turnover number.
[b]Initial rate.
[c]Combined TON for cyclooctene and 1,3-cyclooctadiene (formed in a 77:23 ratio).

of *n*-hexane dehydrogenation at 45 °C, before rapid isomerization occurs to *cis*- and *trans*-2-hexene.[58] Although this reaction proceeds with negligible catalytic activity, rhodium carbonyl bisphosphine complexes as shown in entry 9 (Table 4) have been proven to be highly efficient in the photochemical dehydrogenation of *n*-heptane to 1- and 2-heptene, with observed turnover frequencies as high as 795 h^{-1}.[59] The pincer-ligated iridium complex of entry 1 (Table 5) also exhibits a kinetic selectivity toward the terminal oelfin in the transfer-dehydrogenation of *n*-octane.[60,54] However, the ultimate yield of 1-octene is limited by isomerization simultaneously catalyzed by the iridium complex in a competing secondary cycle. In this regard, the use of 1-decene as a hydrogen acceptor instead of TBE or norbornene leads to an improvement in selectivity. It can be rationalized that, in the case of the sterically demanding hydrogen acceptors TBE and norbornene, the catalyst favors the insertion of dehydrogenation product 1-octene over the hydrogen acceptor, and thus the isomerization cycle over the hydrogenation–dehydrogenation pathway. When the sterically less demanding 1-decene is employed as the hydrogen acceptor, this situation is changed in favor of the hydrogenation–dehydrogenation cycle.

A varying degree of intramolecular selectivity, depending on the catalytic system that is used, can be observed in the dehydrogenation of substituted cyclohexanes, which usually yields a mixture of isomers. Transfer-dehydrogenation of methylcyclohexane **31** (equation 9) under the conditions of entry 1 (Table 4) favors olefin **34** over isomer **33** (65% to 29% in the overall distribution of isomers), whereas only small amounts of methylene isomer **35** are observed.[37] Since the thermodynamically most stable isomer, 1-methylcyclohexane **32**, is only found in traces, it can be assumed that the formed olefinic products do not isomerizes under the reaction conditions. Experiments with alkylphosphine analogs of the used catalyst indicate that steric influence of the ligands is responsible for the observed preference to dehydrogenate at the sterically least hindered position. Turnover numbers for this particular system, however, are low. The rhodium system of entry 9 (Table 4) exhibits a similar selectivity in this reaction under photochemical conditions, albeit with vastly improved turnover numbers. Here, strictly kinetic reaction control seems to be in effect as well, with no signs of isomerization.[44] Analogous experiments with isopropylcyclohexane show results consistent with these findings.[44,46]



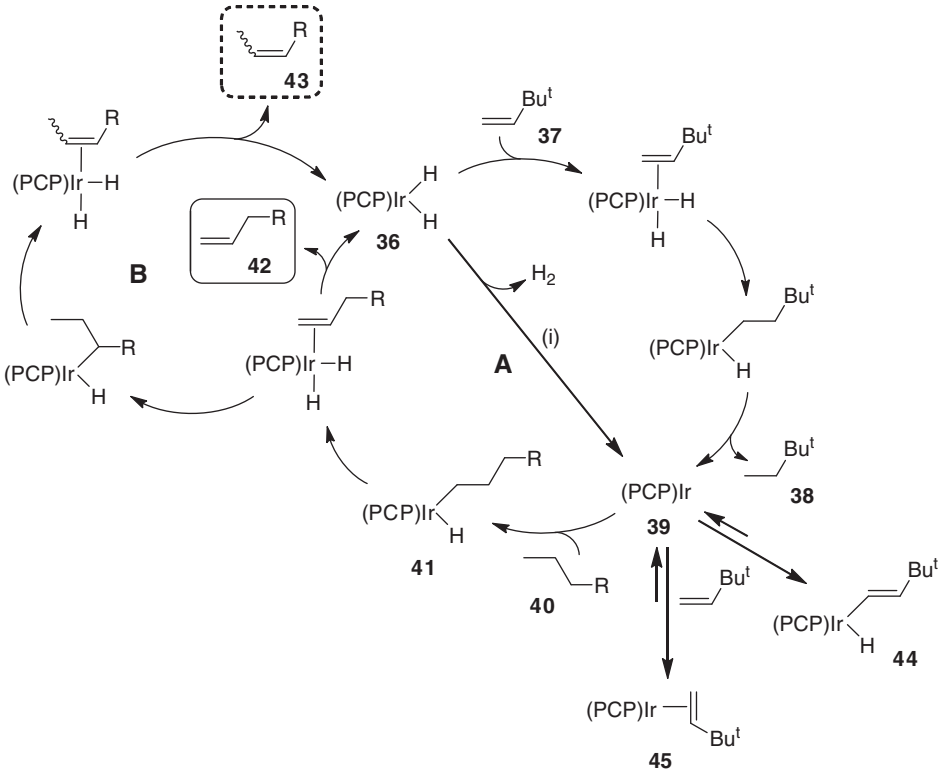
(9)

The iridium pentahydride system in entry 3 (Table 4), while giving similarly low turnover numbers, exhibits a quite different selectivity in the reaction shown in equation 9.[58] Although all possible isomers are observed, the major kinetic product at 100 °C is methylene isomer **35** (71% in initial distribution), but then isomerization occurs. After running the reaction for 65 h at 150 °C, 1-cyclohexene **32** is found to be the major product. This is in agreement with observations for such systems that the stronger C–H bond of primary hydrogen is preferably activated. Photochemical dehydrogenation with the iridium trifluoroacetate complex shown in entry 5 (Table 4) gives similar results, whereas the analogous system of entry 4 under thermal conditions yields the thermodynamically favored 1-methylcyclohexene, most likely formed primarily by isomerization.[40,41] Similar to the photochemical rhodium system, the pincer-ligated iridium complex in entry 1 (Table 5) gives 3-methylcyclohexene **34** as initial major kinetic product in moderate turnover numbers, but subsequent isomerization is observed to the thermodynamic product **32**, accompanied by, notably, further dehydrogenation to toluene.[54]

Regarding the metal-catalyzed dehydrogenation processes discussed in this section, mechanistic considerations have always embraced the concept of C–H activation by oxidative addition of the alkane to the metal, and subsequent β-hydride elimination to generate the olefin, whereas the involvement of radicals, carbocations, or colloidal metal have generally been discarded.[34,36,37] This is supported by independent findings that iridium(III) can activate aliphatic C–H bonds under mild conditions.[61,62]

Scheme 12 summarizes the major mechanisms that are at work in the dehydrogenation process catalyzed by the iridium pincer complexes of Table 5.[54,60,63,64] The dehydrogenation of the aliphatic substrate follows cycle A, the core of which can be generally applied to all catalytic systems discussed in this section (with modifications necessary in the case of the photochemical reaction with rhodium carbonyl complexes, see entry 9, Table 4). Cycle A includes the two different pathways for either transfer- or acceptor-less dehydrogenation. In the former case, a hydrogen acceptor **37** is hydrogenated by migratory insertion and subsequent reductive elimination resulting in the corresponding alkane **38** and the active metal species **39**.[54] In the absence of an acceptor olefin, species **39** is directly generated from dihydride **36** under liberation of molecular hydrogen (path i). Intermediate **39** can then perform the C–H activation step by oxidative addition of the aliphatic substrate **40**, which is followed by β-hydride elimination from the alkyl complex **41** and release of olefin **42** under regeneration of the catalyst **36**.

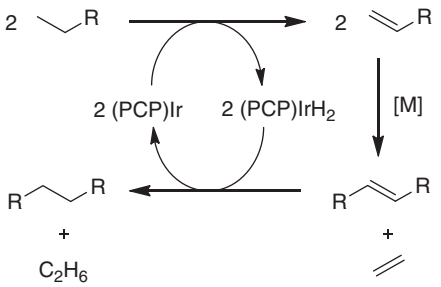
Since iridium catalysts have been shown to catalyze the isomerization of *n*-alkenes or substituted cyclohexenes, a competing pathway must be in action.[54,60] This pathway is described by the extension B of the catalytic cycle in Scheme 12, which proceeds by reinsertion of the newly formed olefin at a branching position. After β-hydride elimination, isomer **43** is released and the catalyst regenerated.



Scheme 12

Furthermore, the observation for the pincer-ligated iridium systems, particularly the phosphine complexes, that high concentrations of acceptor olefin inhibit the reaction rate can be explained by the formation of the intermediary, thermodynamically stable vinyl–metal species **44**, from which the olefin must be eliminated before the addition of the alkane **40** can occur.[63,64] In the case of bisphosphinite complexes (entry 3, Table 5), this insertion of an acceptor olefin such as TBE is not observed.[64] Instead, due to the electron deficiency of the ligand, species **39** is not as prone to oxidation, and TBE is only coordinated in a π-complex **45**. As a result, this particular system is less limited by high concentrations of acceptor olefin.

The value of this type of dehydrogenation process is strikingly evident in the application of iridium pincer complexes as a means to activate alkanes via dehydrogenation toward metathesis in a remarkable tandem process.[65,66] As illustrated in Scheme 13, the dehydrogenation step furnishes terminal alkenes (which undergo isomerization to some extent), followed by olefin metathesis catalyzed by [M] (in which case homogeneous molybdenum or tungsten catalysts, as well as heterogeneous, alumina-supported rhodium oxide, have been employed). The metathesis products then enter the dehydrogenation–hydrogenation cycle of the iridium catalyst and are thus reduced to linear alkanes. This process usually yields a mixture of lower and higher alkanes, their distribution depending on the catalyst combination. It has also been demonstrated that this concept can be applied to cyclic alkanes as well, in which case ring-opening metathesis results in ring expansion and polymerization to higher alkanes.[67] Furthermore, an entirely heterogeneous system has been introduced for this process, making use of alumina-supported, pincer-ligated iridium catalysts.[68,69]

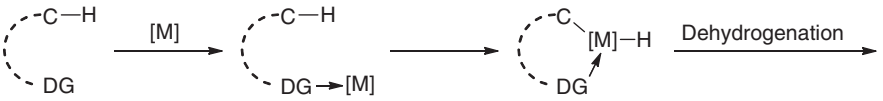


Scheme 13

7.01.4.2 Dehydrogenation by Use of Directing Units

When applying methods involving C–H activation by metals to more complex organic compounds, increasing issues of reactivity and selectivity inevitably arise. Oftentimes, harsh reaction conditions are necessary to achieve the desired C–H activation, resulting in poor tolerance toward most functional groups. Also, given the abundance of C–H bonds in most organic compounds, activating one specific bond selectively poses a considerable challenge. Naturally, in the case of targeting unactivated C–H bonds, this task becomes even more difficult, since the known preference of C–H activating metals toward already activated C–H bonds (notably aryl C–H bonds) has to be overcome.[30,31]

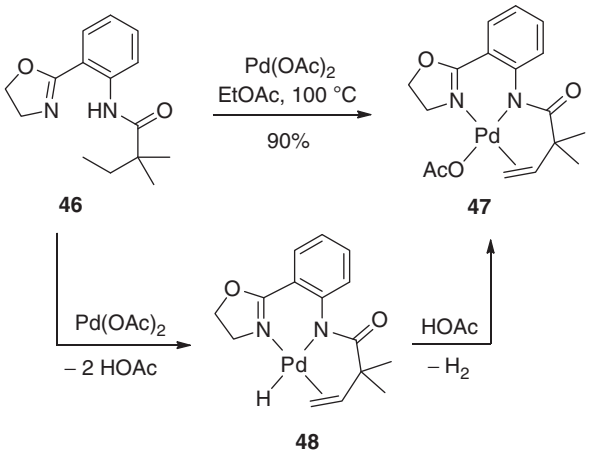
Having to deal with these issues is certainly one major factor that makes the development of general methods applicable to a wide substrate scope so difficult. As a result, most of the time unique strategies have to be found to solve specific problems, which holds just as true for dehydrogenation reactions. Similar to the remote oxidation methods discussed in Section 7.01.2.2, the concept of introducing suitable directing groups to achieve selectivity can also be applied to metal-mediated C–H activation, the basic principle of which is outlined in Scheme 14.



DG, directing group

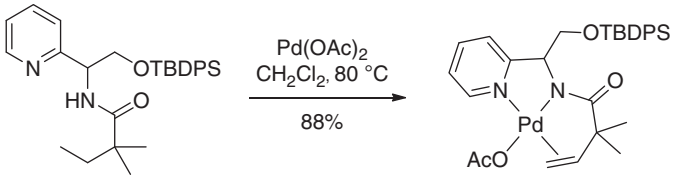
Scheme 14

A realization of this principle is evident in the reaction depicted in Scheme 15. Here, it has been shown that connecting 2,2-dimethylbutyric acid to a ligating auxiliary via amide bond formation can direct palladium-mediated C–H activation and thus enable selective dehydrogenation of substrate **46** to palladium complex **47** in high yield.[70] It is expected that this proceeds via initial coordination of the metal and subsequent oxidative addition and β-hydride elimination to generate the intermediary hydride complex **48**, which is obviously protonated by previously liberated acetic acid under formation of molecular hydrogen and complex **47**.



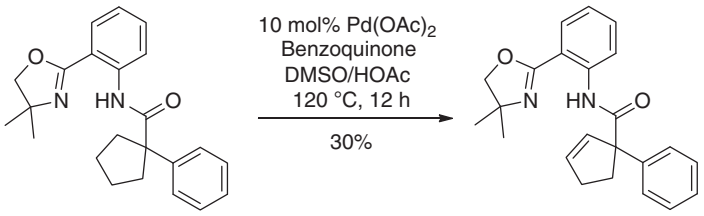
Scheme 15

The steric and electronic properties of the employed ligand have a strong influence on the yield of this reaction, as well as on the required reaction conditions. Equation 10 demonstrates that the dehydrogenation of this system can be similarly successful in a different solvent and at a lower temperature when using a different, pyridyl-substituted auxiliary.

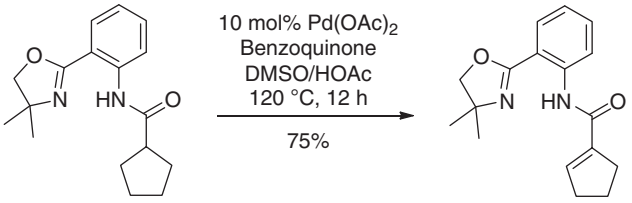


(10)

Of interest is the finding that the dehydrogenation reaction shown in equation 11 can proceed with catalytic amounts of palladium acetate in the presence of benzoquinone as stoichiometric oxidant, albeit in a low yield. Another example for this catalytic reaction is given in equation 12, for which a considerably higher yield is observed. However, in this instance, dehydrogenation takes place at an activated position adjacent to the amide moiety, which is likely to influence the reaction positively. Open-chain analogs such as substrate **46** (Scheme 15) do not react in this manner.

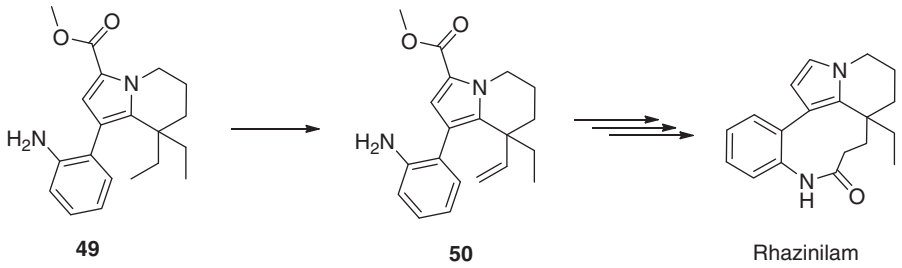


(11)



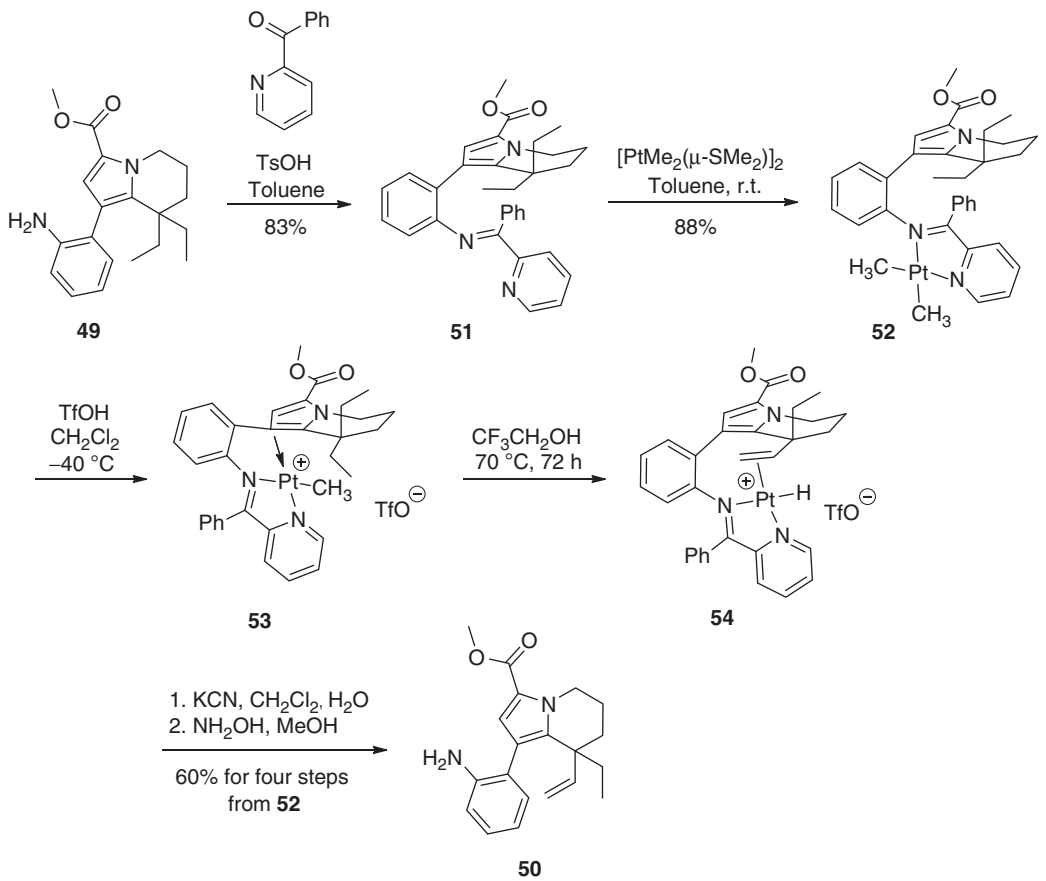
(12)

Scheme 16 shows the key step in a total synthesis of the antitumor agent rhazinilam, which consists of the selective dehydrogenation of an unactivated ethyl group in structure **49**.[71] The newly introduced double bond of intermediate **50** creates opportunity for further transformations at a position in the structure that has not exhibited any obvious reactivity before. In order to ensure a selective dehydrogenation and at the same time a tolerance toward the multiple functional groups present in compound **49**, a ligand is temporarily attached to the structure with the goal to coordinate an active metal and direct it toward the targeted C–H bond.



Scheme 16

Here, this is done by making use of the amino functional group to form imine **51**, followed by the preparation of platinum(II) complex **52** (Scheme 17). To create a cationic species with a free coordination site, treatment of complex **52** with triflic acid gives complex **53** under liberation of methane, with triflate acting as a noncoordinating anion. It has been shown that the sterically demanding phenyl group of the ligating attachment is necessary to minimize η^1-complexation of the pyrrole moiety to the platinum in this species. Subsequent thermolysis leads to the desired C–H activation in one of the two geminal ethyl groups under loss of another methane molecule, with β-hydride elimination yielding alkene complex **54**. Two additional steps are required to remove the metal and hydrolyze the imine linkage of the ligating group, before the terminal olefin **50** is liberated.

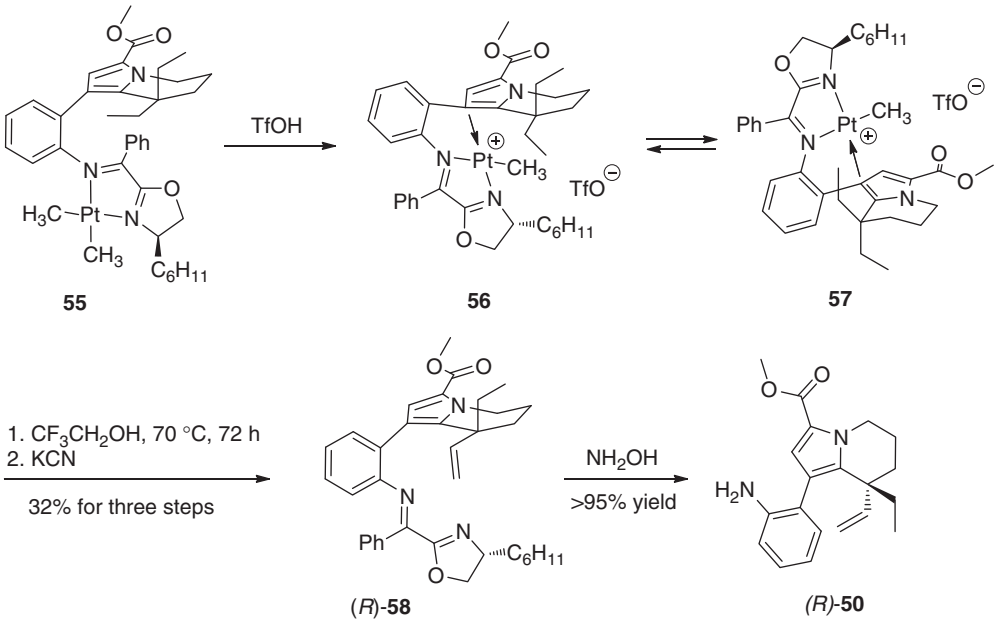


Scheme 17

This reaction sequence is a prime example of how effective such a strategy can be if specifically tailored for the problem and structure at hand, achieving impressive selectivity while leaving a variety of functional groups intact, actually making a convenience out of the aryl amino group and its proximity to the targeted reaction site. Consequently, it is hardly sensible to consider this approach from a general methodological viewpoint. Although the dehydrogenation process involves multiple steps and

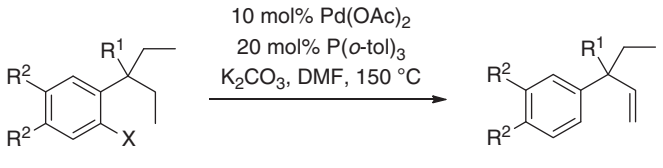
stoichiometric amounts of platinum, in the context of natural product synthesis, introducing functional groups in this manner, with exclusively high-yielding steps, opens pathways that may shorten a synthesis considerably and thus render this strategy rather efficient in ways that cannot be reached by different approaches.

The dehydrogenation step in Scheme 16 has also been realized in a stereoselective fashion as part of an asymmetric total synthesis of (–)-rhazinilam.[72] Here, platinum(II) complex **55** is prepared, which in this instance features a chiral auxiliary coordinated to the metal (Scheme 18). Analogous to the racemic route depicted in Scheme 17, complex **55** is treated with triflic acid to form the cationic species, in which case the two isomers **56** and **57** are obtained. Subjecting this mixture of isomers to the dehydrogenation reaction and subsequent removal of the metal gives imine **58** as a mixture of diastereoisomers. The desired imine (*R*)-**58** is the major isomer and can be separated by preparative HPLC. Conversion of this sole diasteroisomer analogous to Scheme 17 liberates the optically pure olefin (*R*)-**50**. A difference in the ratio of isomers **56** and **57** compared with enantiomers (*R*)-**50**/(*S*)-**50** suggests that isomerization takes place between complexes **56** and **57** under decomplexation of the pyrrole moiety and rotation around the biaryl C–C axis.



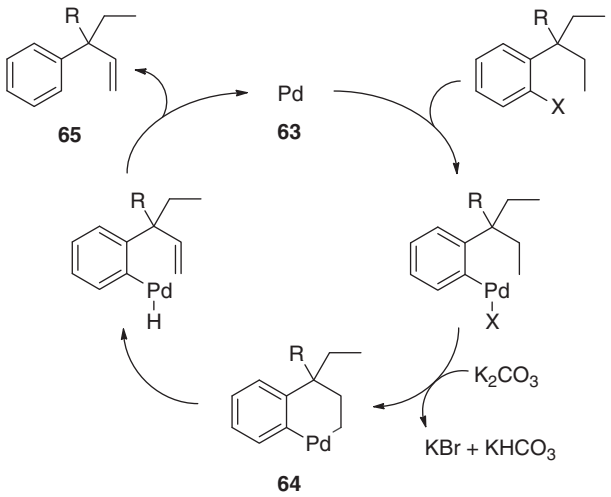
Scheme 18

Similarly, the selective dehydrogenation at an unactivated position in one of two geminal ethyl groups in structure **59** (equation 13) can be effected via metal-mediated C–H activation, albeit following a different, catalytic approach.[73] In this case, the halogen 'X' in *ortho*-position to the targeted moiety is utilized as a directing group of sorts, since it controls the proximity of the palladium to the unactivated C–H bond after the oxidative addition of the metal. However, the halogen functional group is sacrificed in the course of the C–H activation, which is necessary for the reaction to proceed catalytically (see catalytic cycle as shown in Scheme 19). A selection of substrates is listed in Table 6.



(13)

Converting substrate **60** with two geminal propyl groups analogously reveals that the thermodynamically more stable product is preferably formed, since an excess of the internal olefin **61** compared with the terminal olefin **62** is observed in the product mixture (equation 14). Noteworthy is the fact that substrates with one methyl group at the quaternary alkyl carbon favor the formation of benzocyclobutanes over the dehydrogenation.

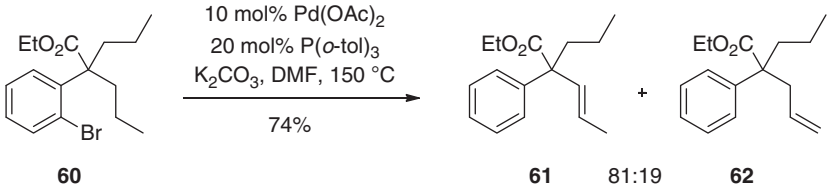


Scheme 19

Table 6 Examples for the dehydrogenation in equation 13[73]

Entry	*R^1*	*R^2*	*X*	*Yield (%)*
1	CH_2OTIPS[a]	H	I	82
2	CH_2OTIPS[a]	H	Br	83
3	CO_2Et	H	Br	83
4	CN	H	Br	65
5	CO_2Et	OMe	Br	93

[a]TIPS = triisopropylsilyl.



60 **61** 81:19 **62** (14)

Scheme 19 shows the proposed catalytic cycle for this dehydrogenation. The catalytically active palladium(0) species **63**, which is generated *in situ* by reduction of the $Pd(OAc)_2$ precatalyst, inserts into the aryl–halogen bond in an oxidative addition. This is followed by the C–H activation step, in which the activated position is deprotonated by the base under formation of alkyl complex **64**. Subsequently, *β*-hydride elimination generates the double bond, before reductive elimination liberates the dehydrogenation product **65** under regeneration of palladium(0) species **63**.

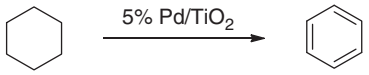
Evidently, the examples discussed in Section 7.01.4 are quite specific. The considerable attention attracted by the field of metal-induced C–H activation, however, promises a rapid progress in the development of more generally applicable methods.

7.01.5 Dehydroaromatization

The induction of aromaticity into organic compounds by dehydrogenation is a procedure widely used in organic synthesis, with a variety of methods available to this end. In this section, no attempt has been made to be comprehensive on this topic. Instead, a personal selection of reactions is given with the intent to keep this section in accordance with the concept of oxidizing unactivated C–H bonds.

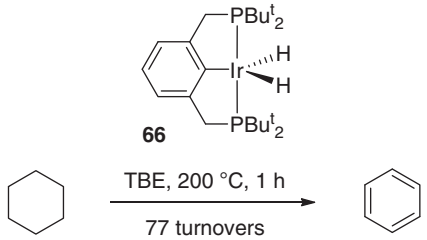
The dehydrogenation of cycloalkanes to arenes is an important process in the industrial production of aromatic commodities, and new catalytic systems that can mediate this kind of reaction with improved efficiency are constantly sought. Heterogeneous systems for oxidative dehydrogenation involving a variety of transition metals have received a lot of attention in this regard.[74,75] As an example, equation 15 shows the dehydrogenation of cyclohexane to benzene with a palladium–titanium oxide catalyst.[76] At 200 °C, a conversion of 28.1% with a selectivity to benzene of 98.3% is observed. Increasing the temperature to 400 °C leads to a

considerably higher conversion, although the selectivity drops to 51.9%. These incongruous relations of the catalyst to the reaction temperature illustrated one of the major issues of such heterogeneous dehydrogenation systems.



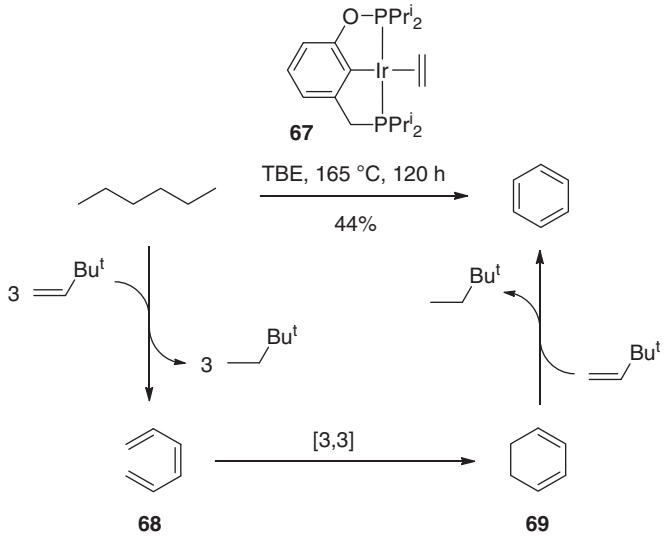
(15)

Thus, it is of particular interest that major advancements have also been made with homogeneous iridium dehydrogenation catalysts (see Section 7.01.4.1) that promise high efficiency and selectivity under mild conditions. Initial reports of benzene formation in the reaction of cyclohexane with stoichiometric amounts of iridium complex established that elevated temperatures are necessary to liberate the arene from intermediary complexes, which prevents the reaction from proceeding catalytically due to the limited thermal stability of the employed catalysts.[38,77] The enhanced stability at elevated temperatures of pincer-ligated iridium catalysts, such as complex **66**, remedies this limitation, and catalytic turnover numbers in the transfer-dehydrogenation of cycloalkanes to arenes, as exemplified by the formation of benzene in equation 16, can be accomplished.[54]



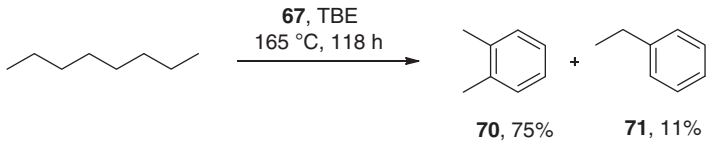
(16)

Following a report that the dehydrogenation of *n*-hexane to *n*-hexenes with a similar iridium system leads to the formation of small amounts of benzene as a side-product, a transfer-hydrogenation system has been developed that, in a combination with iridium catalyst **67** and 3,3-dimethylbutene (TBE), affords benzene from *n*-hexane in high yield after 120 h (Scheme 20).[52,78] The assumed pathway of this reaction proceeds via initial dehydrogenation and isomerization to triene **68**, which then undergoes [3,3]-sigmatropic rearrangement to cyclic diene **69**. Another dehydrogenation step effects the aromatization to benzene.

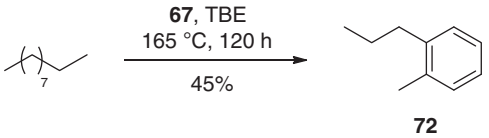


Scheme 20

Application of the same system to *n*-octane (equation 17) gives aromatic products in even higher yields, and in addition shows a striking selectivity toward *o*-xylene **70**, which is formed as the major product in a roughly 7:1 ratio with the only side product, ethylbenzene **71**. The analogous dehydroaromatization of *n*-decane (equation 18) yields *o*-propyltoluene **72**, also with good selectivity, together with minor amounts of several side products.

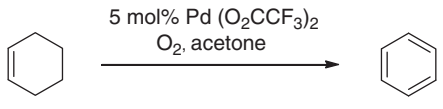


(17)

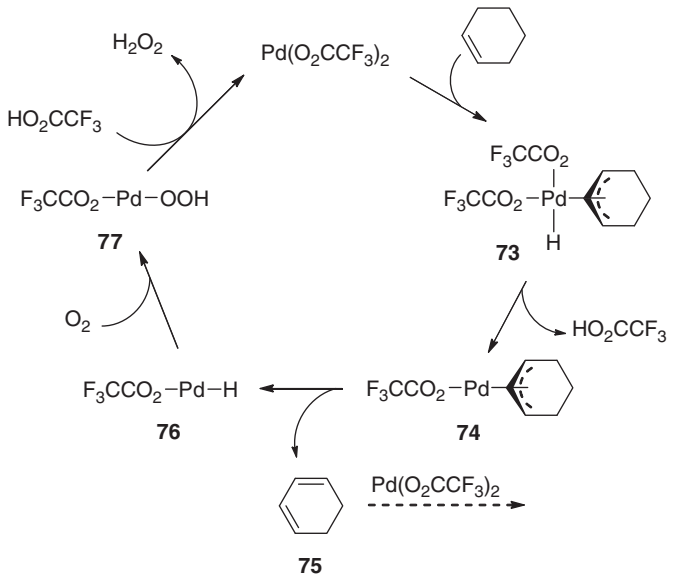


(18)

In terms of transition-metal catalysis, C–H activation by palladium has also been successfully applied to the dehydrogenative formation of benzene and derivatives.[79,80] Of particular note are reactions that use molecular oxygen as a formal hydrogen acceptor that prompts the regeneration of the catalyst and thus maintains a homogeneous reaction (similar reactions in the absence of oxygen have been found to be catalyzed by heterogeneous palladium species).[81–83] Equation 19 shows the palladium-catalyzed oxidation of cyclohexene, which after 24 h at room temperature affords benzene in 25% yield with a selectivity of 100%. However, as it is evident in this example, for this kind of palladium-catalyzed dehydrogenation to work, at least one double bond must already be present in the targeted cycle of the starting material.



(19)



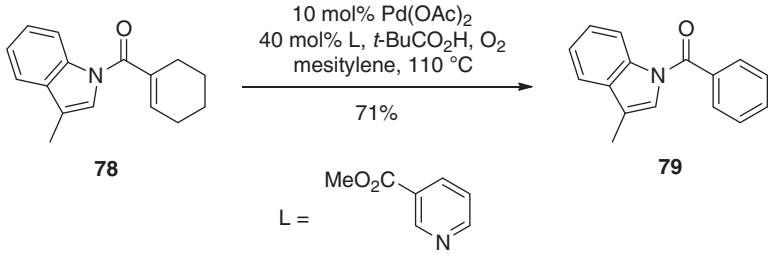
Scheme 21

The reason behind this requirement becomes obvious when considering the mechanism for this dehydrogenation. As illustrated in Scheme 21, oxidative addition of the catalyst adjacent to the preexisting double bond has to occur in order to form the π-allylic complex **73**. Reductive elimination leads to palladium(II) species **74** which is then capable to generate diene **75** by β-hydride elimination. Insertion of oxygen into the hydride complex **76** prevents decomposition of this intermediate to metallic palladium, instead forming the peroxy complex **77**, which is subsequently protonated by trifluoroacetic acid under liberation of hydrogen peroxide and regeneration of the catalyst.

Since hydrogen peroxide is not detected after the reaction, it can be assumed that it is either somehow involved in the reaction mechanism, or simply decomposed under the reaction conditions. Eventually, benzene is formed as diene **75** reenters the catalytic

cycle and is further dehydrogenated, which has been shown to proceed much faster compared with the initial oxidation of the cyclohexene.

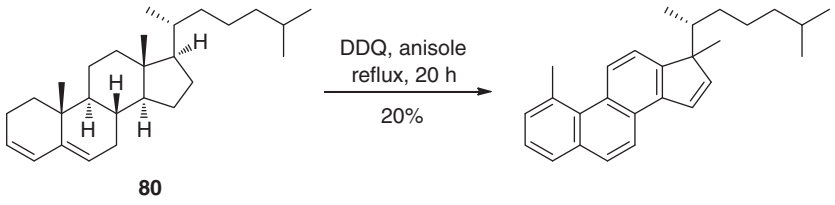
In similar fashion, indole amides such as substrate **78** can be oxidized to the corresponding benzoyl product **79** (equation 20), in which case the dehydrogenation is obviously favored over the initially expected C–C bond formation between the C-2 of the indole moiety and the olefin.[83] Experiments suggest that the C–H bond at the C-2 of the indole is somehow involved in the dehydrogenation and may have some sort of directing effect toward the formation of a π-allylic palladium complex.



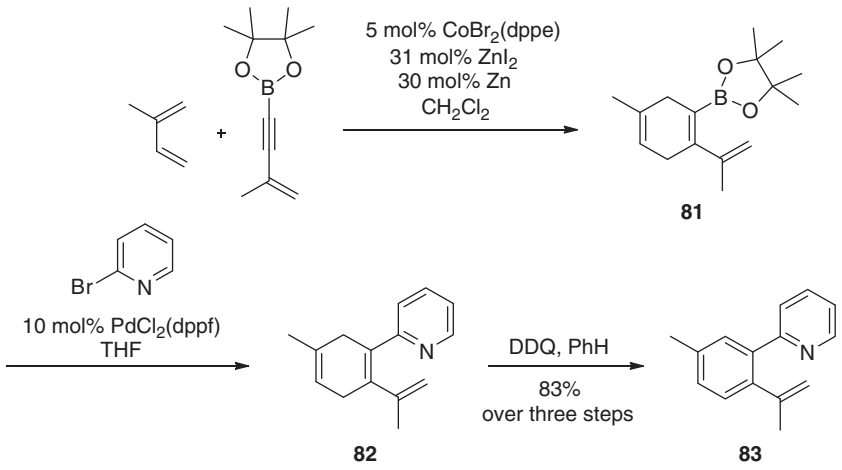
(20)

Despite the increasing value of transition-metal catalysis in dehydrogenation processes, one class of oxidant that has been far more commonly utilized as a means to generate aromaticity in organic compounds are quinones. Especially 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been established as a strong oxidant applicable in a broad variety of reactions, including the dehydrogenation of C–H bonds.[84–91] In fact, DDQ has become such a regularly used reagent that the following examples have been randomly selected for the purpose of illustration, with further examples given in the references above.

One early finding of note is the aromatization of cholestadiene **80** (equation 21), which goes along with a Wagner–Meerwein-type migration of both methyl groups that are attached to the core of the steroid, whereas the rest of the carbon framework remains intact.[92] Although the desaturated product is obtained in low yield, and harsh reaction conditions have to be applied, the effectiveness of DDQ as a dehydrogenating agent is very much in evidence.



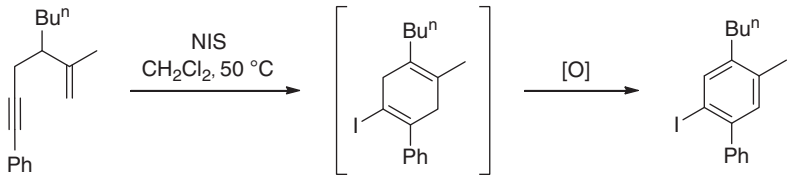
(21)



Scheme 22

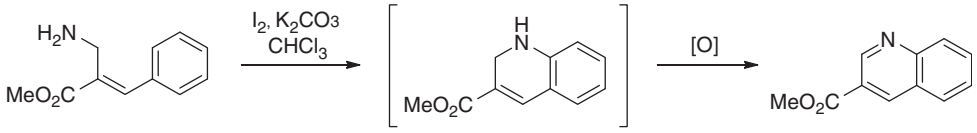
In terms of further synthetic applications, aromatization with DDQ is, for instance, often applied subsequently to a Diels–Alder reaction in order to obtain complex arenes.[93–104] **Scheme 22** shows an example for such a sequence, which makes use of a cobalt-catalyzed Diels–Alder reaction to furnish the boron-substituted cyclohexadiene **81**.[105] The boron moiety enables further conversion of this intermediate in a Suzuki cross-coupling reaction, here with 2-bromopyridine, to give the coupling product **82**. Finally, treatment with DDQ prompts the dehydrogenation under formation of biaryl **83**. This reaction sequence can be conducted as a one-pot synthesis in excellent yields.

The formation of arenes and heteroarenes has also been observed in carbo- and heterocyclization reactions induced by various electrophiles.[106] In these cases, an electrophilic cyclization step is followed by further oxidation under the reaction conditions of a still partly saturated intermediate to a thermodynamically favored aromatic compound. This aromatization may be owed either to the presence of air during the reaction or to the oxidative properties of the used iodine reagent in the cases of iodocyclization. Scheme 23 shows an example for the electrophilic cyclization of 1,5-enynes to highly substituted benzene derivatives with *N*-iodosuccinimide, which is likely to proceed via the diene **84**.[107] When conducting this reaction under an inert atmosphere, diene **84** can be isolated as the major product. Similarly, even though the hetero-cyclization of Scheme 24 to quinoline **87** proceeds through a different pathway, it can be expected that the initially formed dihydroquinoline **86** is further oxidized under the reaction conditions.[106] In an analogous fashion, albeit in the absence of any iodine reagent, the selenyl-mediated cyclization of alkynyl–aniline **86** to quinoline **88** (Scheme 25) is likely to involve the oxidation of an intermediary dihydroquinoline **87** by air.[108–110] Since besides the above examples electrophilic carbo- and heterocyclizations are powerful tools to rapidly access cyclic structures of value, their number is steadily growing.[111–112] It is easy to predict that this trend will also lead to an increasing number of electrophilic cyclizations that contain a dehydrogenative aromatization step (either triggered by air or the electrophile).[113–114]



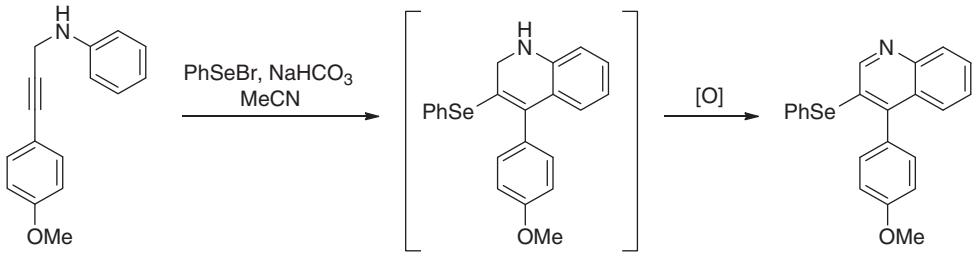
84 **85**, 92%

Scheme 23



86 **87**, 84%

Scheme 24



88 **89** **90**, 74%

Scheme 25

7.01.6 Summary

The considerable challenge of realizing dehydrogenation at saturated, unactivated positions in simple as well as complex organic compounds requires rather unique methods that can overcome the thermodynamic limitations whereas at the same time ensuring a chemoselective progress of the reaction. Two major concepts are employed to create reactivity at unactivated positions: the generation of radical intermediates and the activation of C–H bonds by metals. In both cases, the use of free, external reagents or catalysts always entails problems in terms of selectivity, and can only yield satisfactory results in either very specific or rather simple structures. The strategy of making use of directing groups that are temporarily attached to a substrate and can thus guide an internal, radical hydrogen abstraction, or metal-mediated C–H activation, has found intriguing application in the context of both of these concepts. In addition, dehydroaromatization reactions are of immense importance for the formation of aromatic carbo- and heterocycles, in which case a broad variety of synthetic tools are available.

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7.02 Oxidation by Metals (Nitrene)

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Glossary

Axial chirality Chirality defined by an axis that is rigid to rotation. A set of substituents is held by this axis in a spatial arrangement that is not superimposable onto its mirror image.

Aziridination A [2 + 1] cycloaddition reaction of alkene and nitrene to form an *N*-containing three-membered ring system.

Electrospray ionization mass spectrometry (ESI-MS) Electrospray ionization (ESI) is the softest ionization technique for mass spectrometry. ESI helps in preventing fragmentation of sample molecules.

Formal synthesis Can be considered as a partial work of total synthesis. A formal synthesis involves the preparation of a known precursor for a desired complex organic molecule.

Total synthesis A complete synthesis of a desired complex organic molecule, which is usually a natural product or pharmaceuticals, from simple starting materials without the use of biological processes.

7.02.1 Introduction

Nitrene transfer reaction is analogous to carbene and oxo transfer reactions and involves formation of a new covalent X–N bond, where X is mainly C atom for most of the metal-catalyzed nitrene transfer and insertion reactions. This class of reactions can also be viewed as oxidation due to the higher electronegativity of nitrogen atom than carbon atom. Compared with carbene and oxo transfer reactions, nitrene transfer reactions catalyzed by transition metal complexes have a relatively short history with only sparse reports before 1980s.

Nitrene could exist in two possible forms, the triplet nitrene and singlet nitrene (Figure 1). These two forms of nitrene display different reactivities accounting for their different reaction pathways. It is widely accepted that singlet nitrene undergoes concerted transfer and insertion reactions, whereas triplet nitrene favors reactions with stepwise mechanism. Although free nitrenes can be generated by thermal or photochemical conditions, they are too reactive and hence their reactions are mostly nonselective. The use of transition metal ion to efficiently stabilize the free nitrene intermediate is a strategy to improve both the yield and selectivity of the product arising from nitrene transfer/insertion reactions.

 doi:10.1016/B978-0-08-097742-3.00703-5

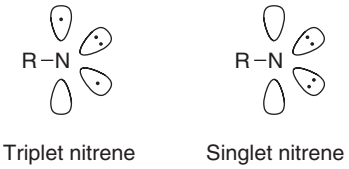
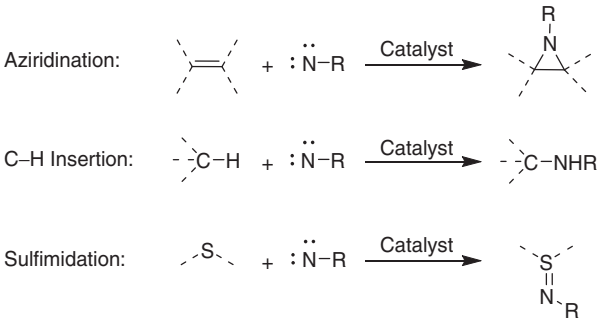


Figure 1 Singlet and triplet nitrenes.

In this chapter, the focus is on the transition metal-catalyzed nitrene transfer and insertion reactions reported since the year 2000. A brief description of earlier studies is provided in the beginning. Mechanistic studies including the preparation and characterization of the reaction intermediates and the identification of short-lived reactive species are discussed. The recent important findings in transition metal-catalyzed alkene aziridination, C–H amidation/amination, and sulfimidation reactions are highlighted in this review (Scheme 1). The authors would like to express their sincere apologies for the missing attention to any important literature reports.



Scheme 1

7.02.2 Nitrene Sources

Decomposition/conversion of a nitrene precursor to nitrene is an important step in the reaction mechanism of metal-catalyzed nitrene transfer and insertion reactions. Until now, there are five common nitrene sources used for nitrene transfer/insertion reactions (Scheme 2). In the following, the syntheses of these nitrene sources are described. The advantages and difficulties encountered in using these nitrene sources are also briefly discussed.

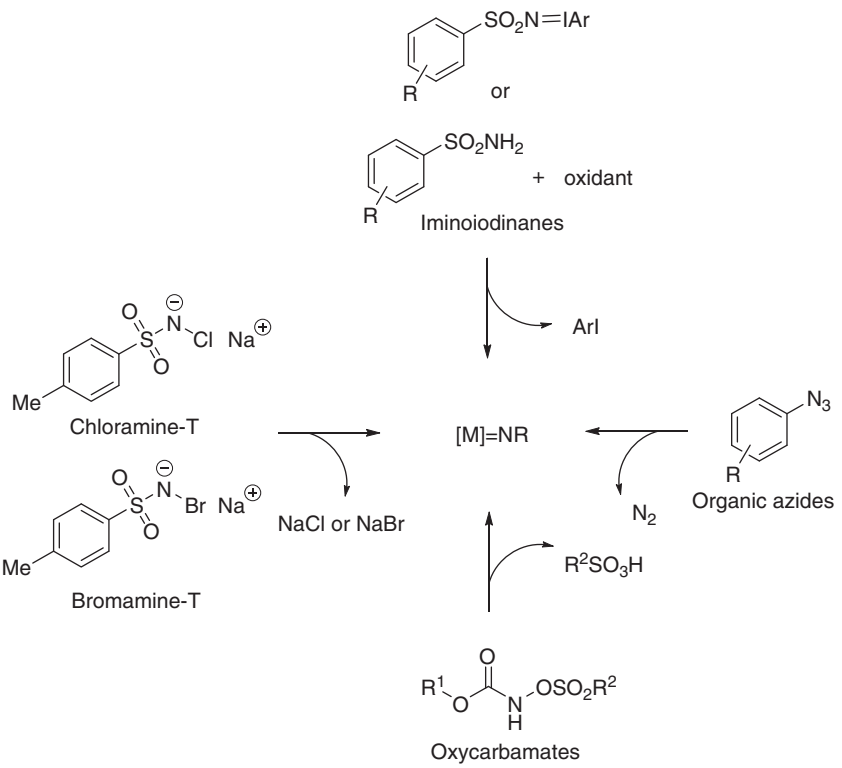
7.02.2.1 Iminoiodinanes

Iminoiodinanes[1] were reported in 1975 and have been frequently used as nitrene source in metal-catalyzed nitrene transfer/insertion reactions (*see* Chapter 7.29). This class of hypervalent iodine(III) compounds ArI=NR (R=arylsulfonyl) are white to pale yellow solids and are synthesized by the reaction between (diacetoxyiodo)arene $ArI(OAc)_2$ and sulfonamides by the presence of KOH in MeOH at low temperature (Scheme 3).[2]

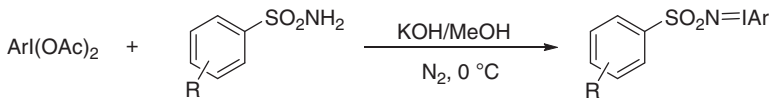
Iminoiodinanes are stable under open atmosphere and can be stored in refrigerator for months, despite its light-sensitivity. Compared with other nitrene sources, the decomposition of iminoiodinanes in the presence of transition metal catalysts requires only mild conditions. However, the formation of iodoarene as by-product lowers the atom economy of using iminoiodinanes as nitrene source. The low solubility/insolubility of this class of compounds in common solvents also requires the usage of a large excess of iminoiodinane reagent in the reaction.

7.02.2.2 *In Situ* Oxidation of Amines and Amides

To bypass the presynthesis of solid iminoiodinanes, Che and coworkers reported the generation of nitrene species from *in situ* oxidation of amines or amides.[3] By replacing PhI=NTs (**1**) with $TsNH_2/PhI(OAc)_2$ in the nitrene C–H insertion catalyzed by the manganese porphyrin complex [Mn(F_{20}-TPP)Cl] (**2**), comparable substrate conversions and yields were obtained under similar reaction conditions (Scheme 4). This '$RNH_2 + PhI(OAc)_2$' protocol was also applicable to other sulfonamides (R=Ns, SO_2Me) and trifluoroacetamide.



Scheme 2 Generation of metal–nitrene reaction intermediate from the common nitrene sources.



Scheme 3

The importance of this *in situ* generation of nitrene species by oxidation of amines and amides is twofold: (1) the scope of nitrene species can be extended to include those which are unstable in the form of *N*-aryliminoaryliodinanes ArI═NR; and (2) a new gateway for the development of intramolecular nitrene transfer and insertion reactions is opened (Scheme 5).

7.02.2.3 Chloramine-T and Bromamine-T

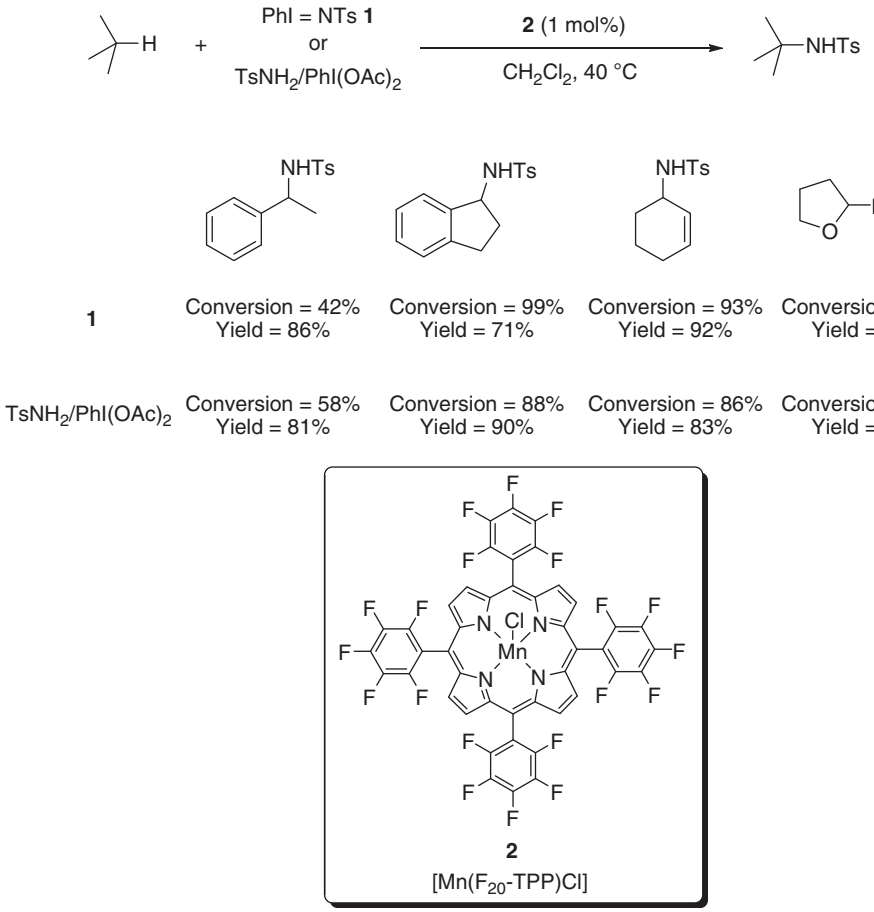
Chloramine-T (**3**) and bromamine-T (**4**) are two most widely used examples of *N*-halogeno-*N*-metallo reagents as a nitrene source.[4] Their structures are depicted in Figure 2. Compound **3** is commercially available in the form of a trihydrate and is a stable white to pale yellow solid, whereas **4** needs to be freshly prepared by the procedure reported by Roberts (Scheme 6).[5]

Both **3** and **4** should be dried over P_2O_5 under vacuum before use. Dehydration of **3** by strong heating is not recommended as explosion has been reported.[6]

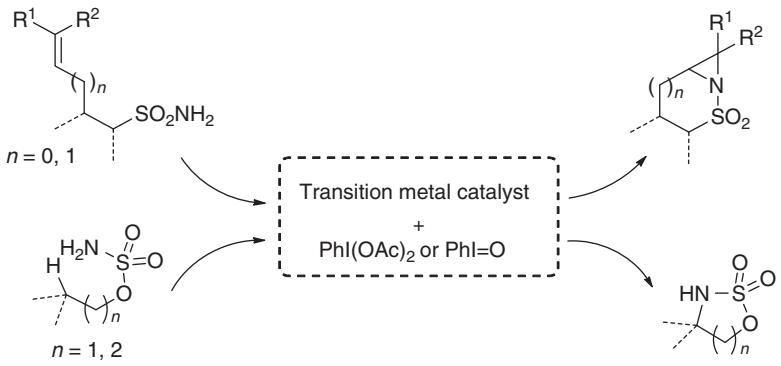
Compounds **3** and **4** are environmental friendly nitrene source as the by-product generated from their decomposition is NaCl and NaBr, respectively. However, the nitrenes that could be generated from *N*-halogeno-*N*-metallo reagents are limited to aryl-sulfonyl nitrenes.

7.02.2.4 Organic Azides

In recent years, there has been a surge of interests in using organic azides, usually aryl or acyl azides, as the nitrene sources for C–N bond-forming reactions.[7] Hundreds of organic azides and polymer-bound azides are stable enough to be commercially available and their preparations in laboratory are relatively simple.[7b,8] Aryl azides can be easily prepared by diazotization of anilines followed by treatment with sodium azide (Scheme 7), whereas acyl azides can be synthesized from the corresponding acyl chlorides or acyl anhydrides (Scheme 8). Other protocols, including classical nucleophilic substitution reactions of aliphatic or aromatic halides, Mitsunobu reaction of alcohols, and addition reactions of alkenes have also been developed for the preparation of organic azides.[8]



Scheme 4



Scheme 5

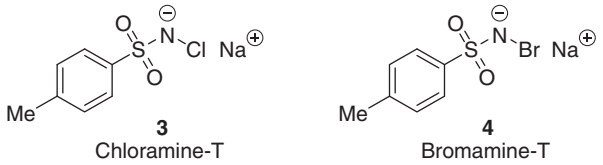
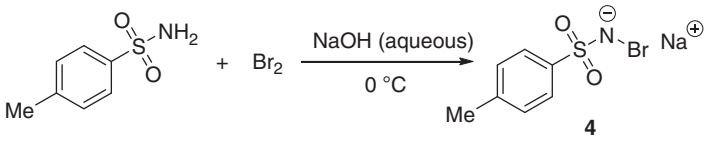
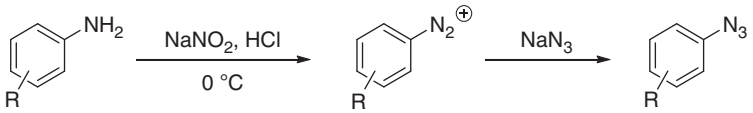


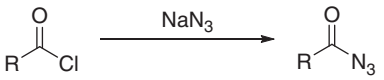
Figure 2 Structures of chloramine-T (**3**) and bromamine-T (**4**).



Scheme 6



Scheme 7

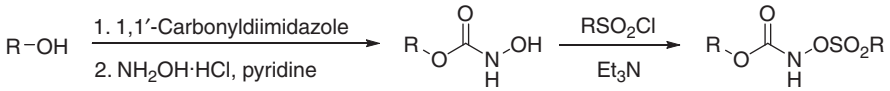


Scheme 8

Organic azides are environmentally benign nitrene sources with the high atom economy as the only by-product after decomposition is nitrogen gas. But the release of nitrogen gas gives rise to safety concern in using this class of compounds. Although aryl azides are stabilized by π-conjugation and hence are relatively safer, the possibility of having violent decomposition in the presence of strong heat, heavy metal, or acids cannot be excluded. It is highly recommended to consider organic azides as potential explosives and they should be handled with great care.

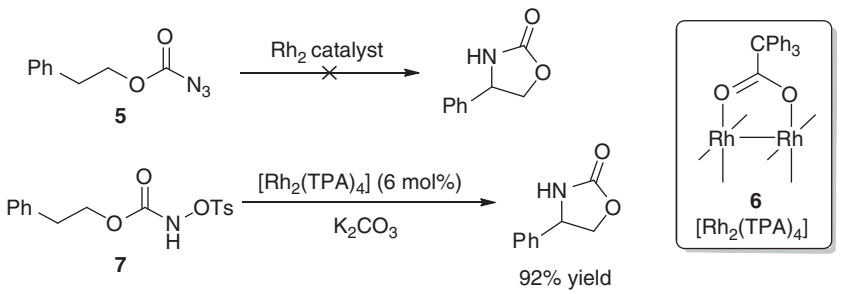
7.02.2.5 Oxycarbamates

Oxycarbamates are prepared by the coupling of alcohols with hydroxyamine hydrochloride to form *N*-hydroxycarbamates, followed by sulfonylation with sulfonyl chloride in the presence of triethylamine (Scheme 9).[9]



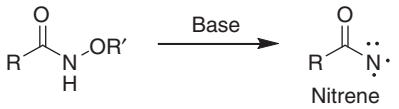
Scheme 9

In 2005, Lebel and coworkers reported the use of oxycarbamates as nitrene source analogous to organic azides.[9] An example of oxycarbamates is azide **5** (Scheme 10), which was reported to be stable in the presence of the rhodium catalyst **6**. Presumably, the stability comes from coordination of the terminal nitrogen atom of the azide moiety to the rhodium complex. The latter hinders the decomposition of the azide moiety. By changing the leaving N_2 group with sulfonate group, the formation of nitrene from oxycarbamate **7** becomes more facile (Scheme 10).



Scheme 10

Treatment of oxycarbamates **7** and its derivatives with base could produce the corresponding nitrenes via deprotonation and α-elimination (Scheme 11). However, the use of oxycarbamates as a source of nitrenes suffers from the disadvantage arising from the steps required for their preparation, and the formation of RSO_2OH as a by-product would significantly lower the atom economy. The free RCON nitrenes are highly reactive, usually leading to nonselective reactions with low yields.



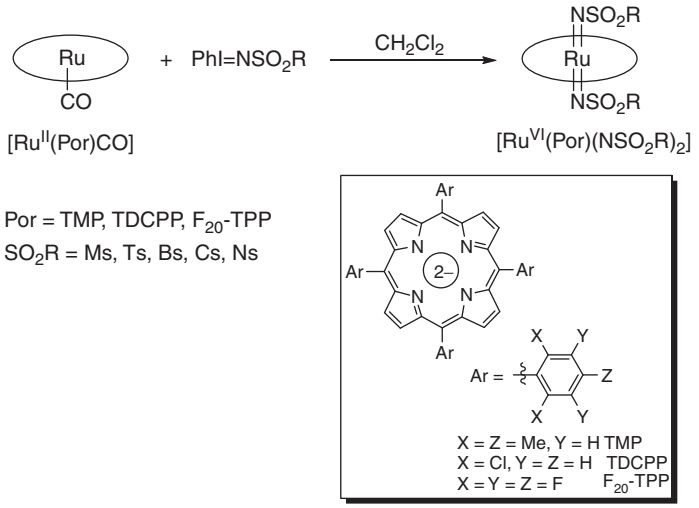
Scheme 11

7.02.3 Reactive Metal Nitrene–Imido Intermediates

In order to have a better insight into the mechanism of transition metal-catalyzed nitrene transfer reactions, efforts have been made to develop the synthesis of reactive metal nitrene/imide complexes that are generally believed to be the reaction intermediates responsible for C–N bond-forming reactions after the report of alkene aziridination by the putative '$Mn{=}NC(O)CF_3$' intermediate by Groves and Takahashi.[10] In the 1990s, transition metal nitrene/imide complexes, including those of molybdenum,[11] tungsten,[12] ruthenium,[13,14] and osmium[15] were reported. Some of these complexes are able to transfer and/or catalyze the transfer of nitrene moiety to organic compounds.

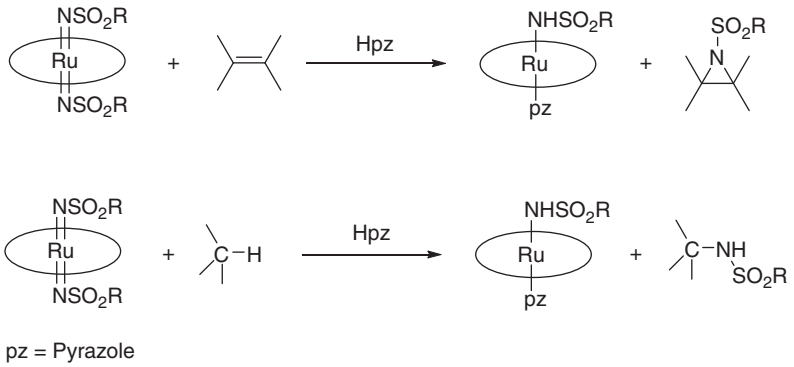
In this section, the synthesis, spectroscopic characterization, and X-ray crystal structures of several representative metal nitrene/imide complexes are described. Among them, some of these complexes are present as reactive intermediates and are able to transfer/catalyze the transfer of nitrene moiety to organic compounds. Studies of these metal nitrene/imide reactive intermediates with electrospray ionization mass spectrometry (ESI-MS) are discussed briefly, but the computational studies and mechanistic pathways of their reactions are not mentioned in this section.

Che and coworkers reported the synthesis of a series of bis(arylsulfonylimido)ruthenium(VI) porphyrins by treatment of the corresponding [Ru(Por)CO] with iminoiodananes (Scheme 12).[14d,16] The high oxidation state VI of these complexes is revealed by various spectroscopic methods, including the oxidation state markers at approximately 1020 cm^{-1} showing a ruthenium(VI) oxidation state and the diamagnetism of these complexes suggesting a d^2 metal–imido system.[14a,16] The cyclic voltammograms of $[Ru(Por)(NSO_2Ar)_2]$ show two reversible or quasi-reversible reduction couples and one reversible oxidation couple, attributing to porphyrin-centered reductions and porphyrin-centered oxidation, respectively.[16] These complexes can perform stoichiometric aziridination of alkenes and C–H amination of alkanes in the presence of pyrazole (Scheme 13). The X-ray crystal structure of one of these bis(arylsulfonylimido)ruthenium(VI) complexes has been determined.



Scheme 12

Smieja and coworkers reported the synthesis of the bis(arylimido)ruthenium(VI) porphyrin complex $[Ru(TTP)(NC_6H_4NO_2)_2]$ from [Ru(TTP)CO] (**8**) and *p*-nitrophenyl azide. $[Ru(TTP)(NC_6H_4NO_2)_2]$ could transfer its arylimido group to alkenes to form the corresponding aziridines.[17] The X-ray crystal structures of the more stable osmium analogs $[Os(TTP)(NC_6H_4NO_2)_2]$[15a] and $[Os(4\text{-}Cl\text{-}TPP)(NC_6H_4NO_2)_2]$ (**9**)[17] (Figure 3) have been determined. These two bis(arylimido)osmium porphyrin complexes were



Scheme 13

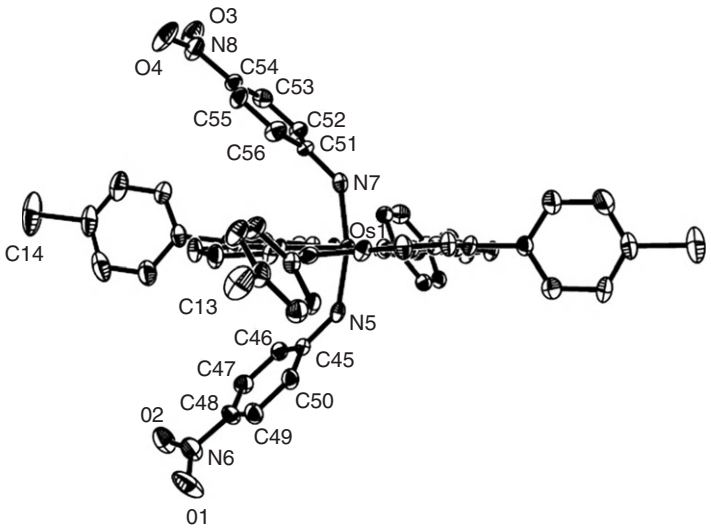


Figure 3 X-ray crystal structure of bis(imido)osmium porphyrin complex **9**. Adapted from Smieja, J. A.; Shirzad, K.; Roy, M.; Kittilstved, K.; Twamley, B. *Inorg. Chim. Acta* **2002**, *335*, 141–146.

obtained by the reactions of $[Os(Por)]_2$ with 4-nitrophenyl azide (Scheme 14). The X-ray crystal structures reveal that the Os–N(imido) distances fall between 1.81 and 1.82 Å with the two arylimido ligands in a nearly eclipsed conformation. This is different from the *anti*-conformation of bis(tosylimido)osmium(VI) porphyrin complex reported by Che and coworkers.[15b] In contrast to their ruthenium analogs, the bis(arylimido)osmium complexes are inactive toward nitrene transfer to C=C bonds.

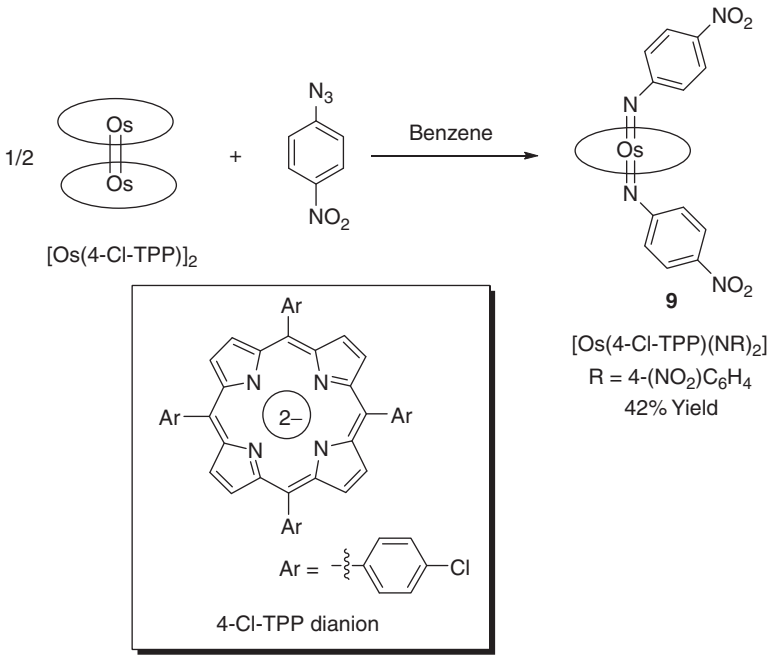
In 2009, Gallo and coworkers reported the synthesis of $[Ru(TPP)(NAr)_2]$ (Ar=3,5-$(CF_3)_2$-C_6H_3) (**10**) from the reaction between [Ru(TPP)(CO)] (**11**) and organic azide (Scheme 15).[18,19] The X-ray crystal structure of **10** shows that the two imido ligands adopt a nearly eclipsed conformation as shown in Figure 4, which is similar to the osmium analog **9**. The relatively short Ru–N distances (1.808(4) and 1.806(4) Å) support the arylimido formulation. The Ru–N–C angles of 139.8(3) and 143.7(4)° indicate that the lone pairs on the nitrogen atoms are more exposed.

Complex **10** is able to insert one of the imido groups to allylic or benzylic C–H bond, implying that this complex could be a reactive intermediate for direct amination of activated C–H bonds with organic azide catalyzed by ruthenium(II) porphyrins.[18,19]

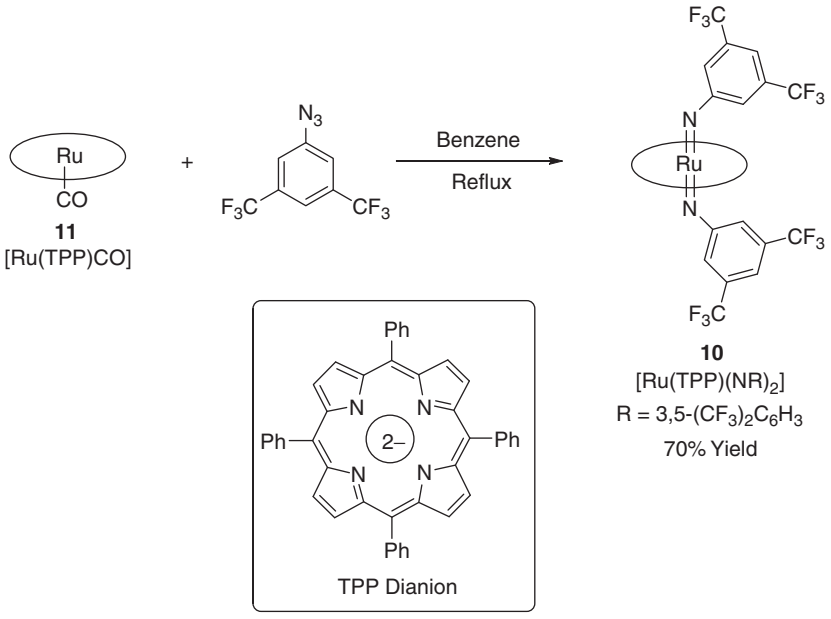
Compared with the imido complexes of osmium and ruthenium, reports on the isolation and characterization of nitrene/imide complexes of first row transition metals are sparse,[20] presumably this is hampered by their high reactivity.

In 2001, Mindiola and Hillhouse reported the synthesis of nickel–imido complex $[(dtbpe)Ni\{N(2,6\text{-}iPr_2C_6H_3)\}]$ (**12**) (dtbpe=1,2-bis(di-*tert*-butylphosphino)ethane) from $[(dtbpe)NiCl_2]$ (Scheme 16).[21] The imido ligand is generated by deprotonation of the corresponding amide species. The X-ray crystal structure of **12** shows a short Ni–N(nitrene) distance of 1.702(2) Å (Figure 5) revealing a double bond. The imido ligand is bent at the nitrogen atom with ∠Ni–N–C=162.8(2)°. This bond angle is less acute than expected, and is attributed to the steric effect between the aryl substituent of the imido and *tert*-butyl groups of the phosphine ligands.

Complex **12** was found to undergo stoichiometric nitrene transfer to ethylene to give aziridine, in a later report by Waterman and Hillhouse (Scheme 17).[22]



Scheme 14



Scheme 15

Recently, Betley and coworkers reported the synthesis of iron(III)–imido radical intermediate **13** by reacting bis(pyrrole)iron(II) complex with organic azide (Scheme 18).[23] The X-ray crystal structure of this intermediate shows a relatively long Fe–N bond (1.768(2) Å; Figure 6), revealing a significant reduction in Fe–N multiple bonding character. This iron(III)–imido complex could undergo stoichiometric aziridination of styrene and benzylic C–H insertion with toluene (Scheme 18).

To gain evidence for the involvement of reactive transition metal nitrene/imido reaction intermediates which are not stable enough to be isolated and studied by X-ray crystallography, mechanistic studies by means of high-resolution ESI-MS have been adopted. Several reactive iron nitrene/imido reaction intermediates have been detected by ESI-MS.

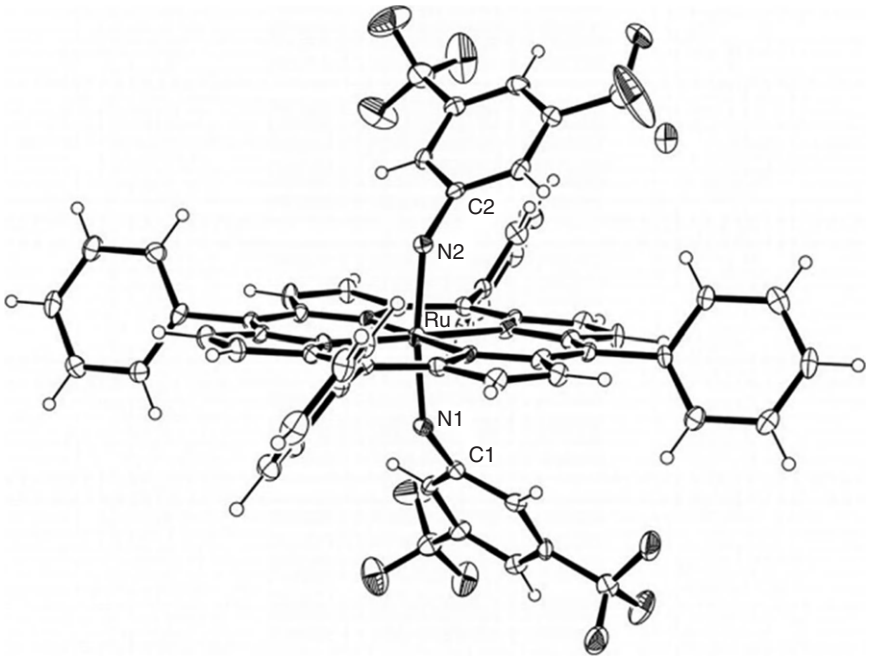
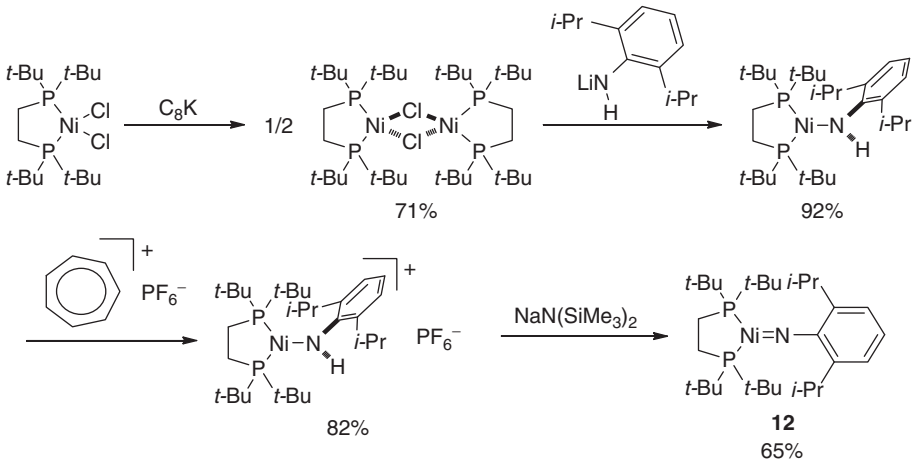


Figure 4 X-ray crystal structure of bis(imido)ruthenium porphyrin complex **10**. Adapted from Intrieri, D.; Caselli, A.; Ragaini, F.; *et al. Eur. J. Inorg. Chem.* **2012**, 569–580, with permission from Wiley.



Scheme 16

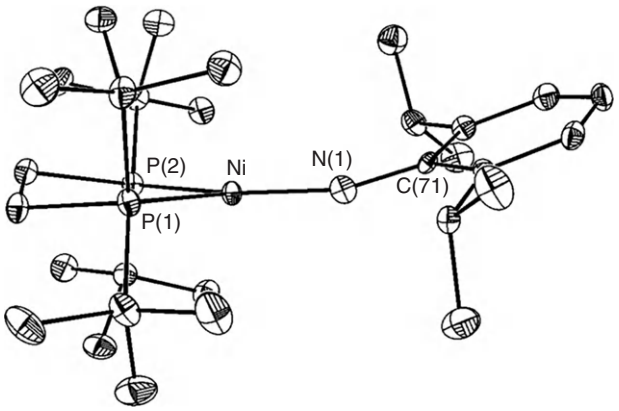
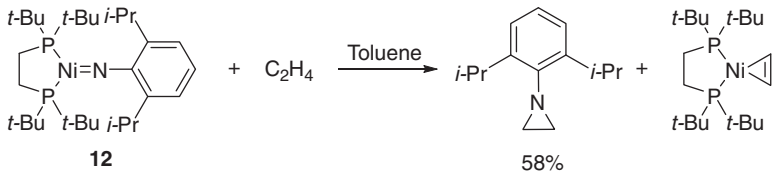
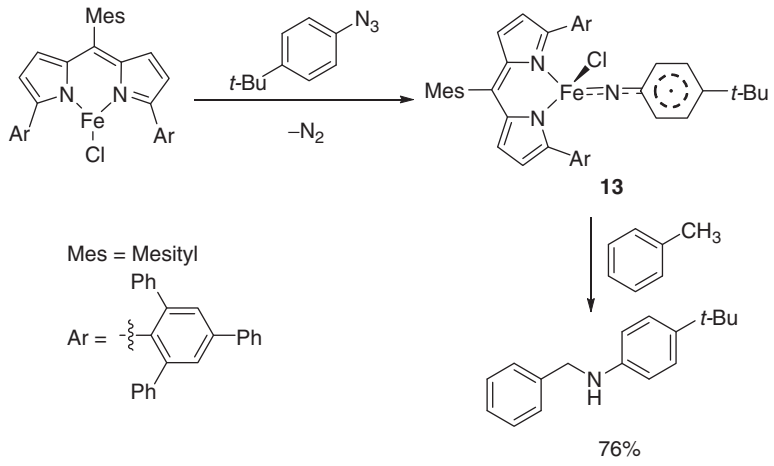


Figure 5 X-ray crystal structure of nickel–imido complex **12**. Adapted from Mindiola, D. J.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2001**, *123*, 4623–4624, with permission from American Chemical Society.



Scheme 17



Scheme 18

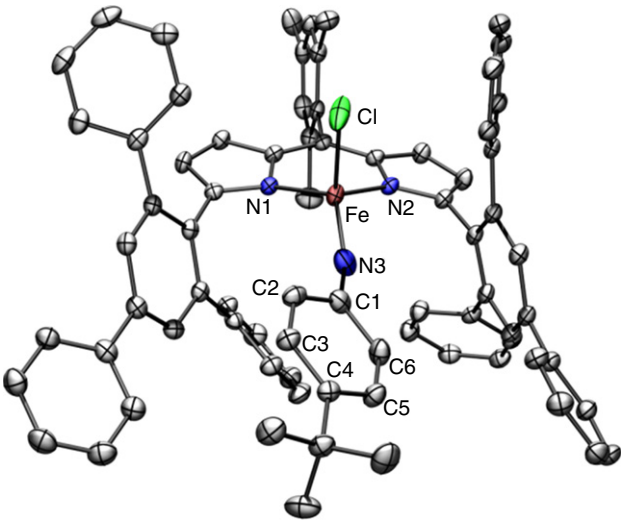


Figure 6 X-ray crystal structure of iron(III)–imido complex **13**. Adapted from King, E. R.; Hennessy, E. T.; Betley, T. A. *J. Am. Chem. Soc.* **2011**, *133*, 4917–4923, with permission from American Chemical Society.

Che and coworkers reported the detection of $[Fe(Cl_3terpy)_2NTs]^{2+}$ (Cl_3terpy=4,4′,4″-trichloro-2,2′:6′,2″-terpyridine) intermediate by analysis of the reaction mixture of $[Fe(Cl_3terpy)_2](ClO_4)_2$ and PhI=NTs (**1**) with high-resolution ESI-MS.[24] The cluster peak at *m*/*z* 448.4501 with peak separation of 0.5 Da was attributed to the $[Fe(Cl_3terpy)NTs]^{2+}$ formulation (calcd. *m*/*z* for $[C_{37}H_{23}N_7Cl_6FeSO_2]^{2+}$ =448.4545).

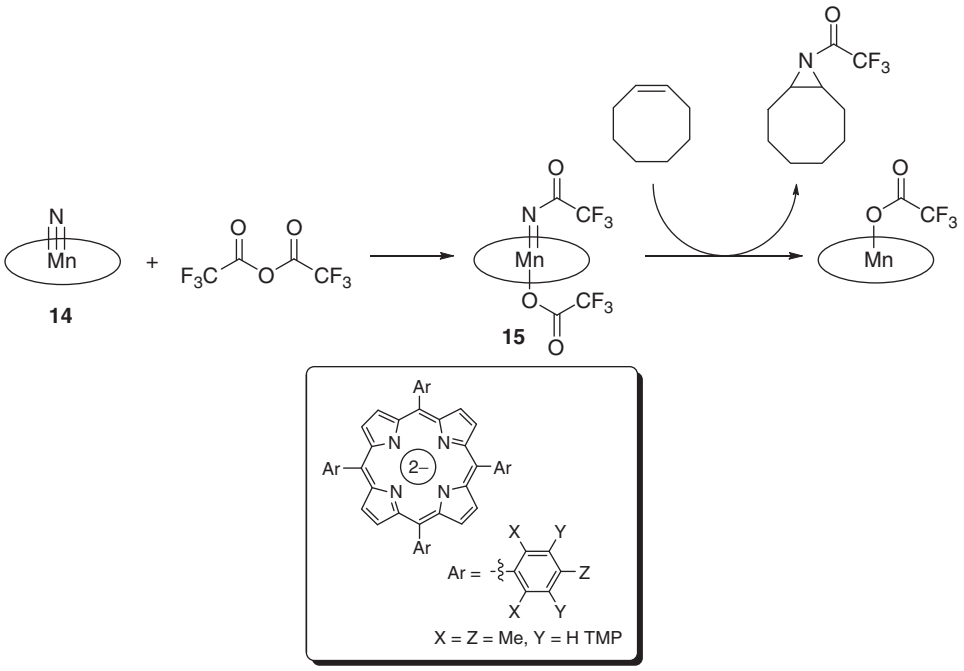
The same method has been applied to support the involvement of reactive iron–imido intermediate in iron-catalyzed nitrene insertion to aldehyde C–H bonds. By ESI-MS analysis of a reaction mixture of **1**, $FeCl_2$ and terpyridine, a cluster peak at *m*/*z* 345.4 with peak separation of 0.5 units attributed to $[Fe(tpy)_2(NTs)]^{2+}$ (calcd. *m*/*z* for $[C_{37}H_{29}N_7O_2SFe]^{2+}$ =346.5) was detected.[25]

7.02.4 Reactions

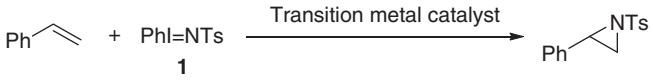
7.02.4.1 Aziridination of C=C Bonds

7.02.4.1.1 Intermolecular aziridination

Aziridination,[26] being analogous to epoxidation and cyclopropanation, is widely used in the synthesis of pharmaceuticals as aziridine is a versatile synthon used in synthetic organic chemistry.[27] The first aziridination of alkenes was reported by Kwart and Khan in 1967.[28] In their work, aziridination of cyclohexene by sulfonyl azide was catalyzed by copper metal powder, and a nitrene transfer mechanism was proposed. In 1982, Groves and Takahashi reported the reaction between nitridomanganese(V) porphyrin complex [Mn^{V}(TMP)(N)] (**14**) and trifluoroacetic anhydride; a manganese(V) imido complex **15** was proposed to be formed *in situ*, which stoichiometrically transfers its imido group to alkenes to give aziridines (Scheme 19).[10] Some other metal–nitride complexes have also been reported to undergo the same reaction in the presence of trifluoroacetic anhydride.[29,30] Mansuy and coworkers developed the catalytic alkene aziridination using iron(III) or manganese(III) porphyrin catalysts in 1984.[31] By employing PhI=NTs (**1**) as nitrene source, aziridination of styrenes and stilbenes were achieved in moderate to good yields. Since then, this protocol 'M(III) + PhINTs' has become the model reaction for studying the catalytic activity of new transition metal catalysts toward intermolecular alkene aziridination (Scheme 20).



Scheme 19

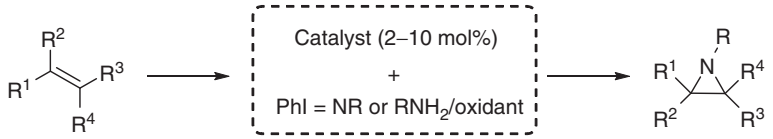


Scheme 20

Before the year 2000, numerous transition metal complexes, including that of copper,[32] ruthenium,[33] rhodium,[34] and iron,[35] have been found to be catalytically active toward intermolecular aziridination of styrenes by iminoiodanes. After the independent reports by Che and coworkers[3] and Du Bois and coworkers[36] on the generation of metallonitrene species by *in situ* oxidation of amides or amines, the scope of nitrene sources used in C–N bond-forming reactions has been expanded tremendously. Some of the important catalytic systems for intermolecular aziridination reactions are summarized in Table 1. The structures of the catalysts or ligands are depicted in Figure 7.

Copper(I) and copper(II) catalysts, either in the form of simple salts or supported by ligands,[48] were found to be catalytically active toward aziridination of styrenes with hypervalent iminoiodinanes. However, the analogous aziridination of aliphatic alkenes or α,β-unsaturated systems were found to proceed in relatively poor yields using the same copper catalysts. Vedernikov and Caulton reported the use of C_3-ligand [2.1.1]-(2,6)-pyridinophane for copper-catalyzed aziridination of aliphatic alkenes with PhI=NTs (**1**) (entry 6, Table 1),[41] and various aliphatic alkenes and α,β-unsaturated esters were found to react in good to excellent yields (Scheme 21).

Table 1 Transition metal-catalyzed intermolecular aziridination by using PhI=NR or *in situ* PhI=NR as nitrene source



Entry	*Catalyst*	*Nitrene source*	*Yield (%)*	*References*
1	$[Cu(CH_3CN)_4](ClO_4)$ (**16**)	$SesNH_2$/PhI=O	40–76	37
2	CuCl/Tp*Na	PhI=NTs (**1**)	18–88	38
3	$CuCl_2$/Dp*Na	**1**	17–89	38
4	$[Rh_2(tfacam)_4]$ (**17**)	$H_2NSO_3CH_2CCl_3$ (**18**)/$PhI(OAc)_2$	57–95	39
5	$[Cu(acac)_2]$ on polystyrene	**1**	35–95	40
6	$[Cu(C_3\text{-L})]BAr_4$	**1**	5–98	41
7	$[Ag_2(t\text{Bu}_3\text{tpy})_2(NO_3)](NO_3)$ (**19**)	**1**	66–91	42
8	[Tp*Cu]	**1**	30–>95	43
9	$[Cu(pyridine)_2Cl_2]$	**1**	31–97	44
10	$[Au(t\text{Bu}_3\text{tpy})]OTf$ (**20**)	$NsNH_2/PhI(OAc)_2$	25–95	45
11	[IPrCu(DBM)] (**21**)	**18**/PhI=O	43–88	46
12	CuI	RNH_2/PhI=O	40–99	47

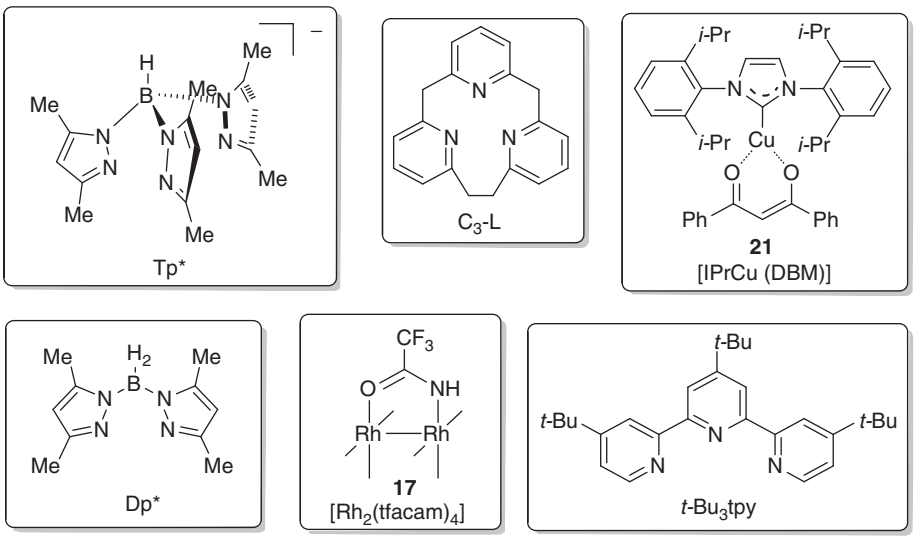
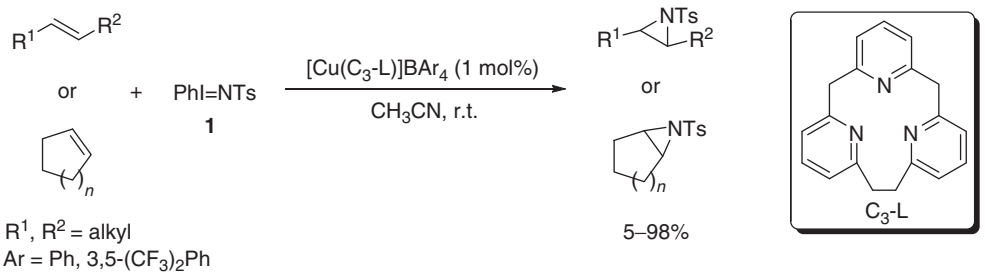
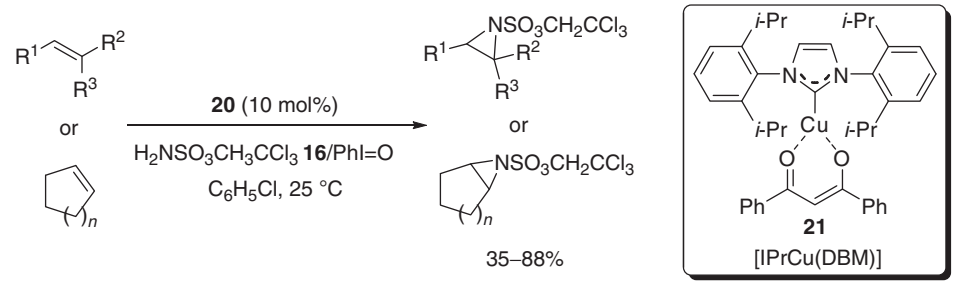


Figure 7 Structures of transition metal catalysts and auxiliary ligands used for metal-catalyzed intermolecular aziridination reactions.



Scheme 21

Recently, there has been a surge of interest in using *N*-heterocyclic (NHC) ligands to develop robust metal catalysts. Complex [IPrCu(DBM)] (**21**) (entry 11, Table 1) was found to be a robust catalyst for aziridination of aliphatic alkenes in good yields through *in situ* oxidation of sulfonamides (Scheme 22).[46]



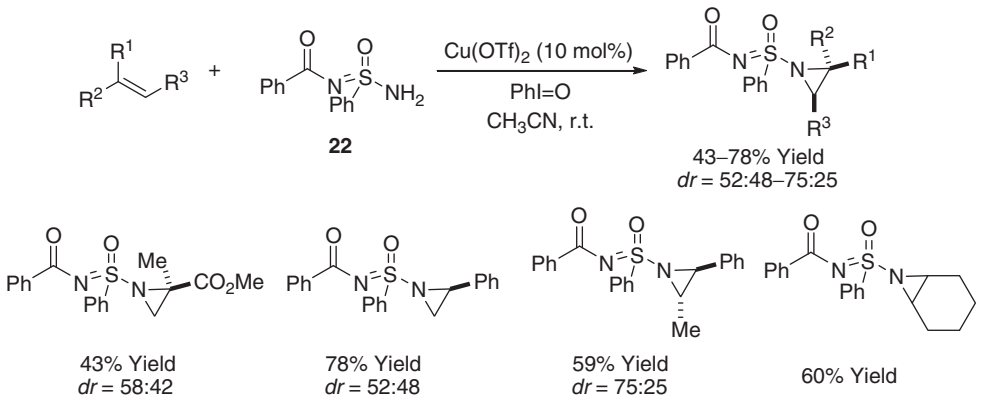
Scheme 22

This copper catalyst and its derivatives could be immobilized on solid supports such as polymers to facilitate the catalyst recycling after reaction. $[Cu(acac)_2]$ supported on polystyrene could be recycled for five times without significant loss of catalytic activities (entry 5, Table 1).[40]

Although copper complexes are well-known catalysts for alkene aziridination, there are only a few reports on the uses of silver and gold complexes to catalyze similar reactions. Cui and He reported the first disilver(I) complex $[Ag_2(t\text{Bu}_3\text{tpy})_2(NO_3)](NO_3)$ (**19**)-catalyzed intermolecular alkene aziridination with PhI=NTs (**1**) (entry 7, Table 1).[42] The dinuclear structure of **19** is crucial for its catalytic activity. Later study revealed that mononuclear gold complex $[Au(t\text{Bu}_3\text{tpy})]OTf$ (**20**) bearing the same ligand is also catalytically active toward intermolecular aziridination of alkenes with *in situ* oxidation of sulfonamides by $PhI(OAc)_2$ (entry 10, Table 1).[45]

The use of dirhodium(II,II) catalysts for intermolecular alkene azidination is not as common as C–H insertions and intramolecular aziridinations. Guthikonda and Du Bois reported the use of $[Rh_2(tfacam)_4]$ (**17**) as catalyst for aziridination of styrene compounds and aliphatic alkenes (entry 4, Table 1).[39] Higher yields were obtained for styrene compounds (65–95%) than for aliphatic alkene substrates (57–82%). The one-pot aziridination/nucleophilic ring-opening reaction was reported to give the ring-open products in excellent yields (80–95%).

To improve the diastereoselectivity of intermolecular alkene aziridination, Fensterbank, Lacôte, Malacria and coworkers reported the use of a chiral sulfonimidamide **22** to generate chiral nitrene in the presence of PhI=O as oxidant.[49] As depicted in Scheme 23, the chiral sulfonimidamide underwent intermolecular aziridination of alkenes in the presence of 10 mol% of $Cu(OTf)_2$ to give aziridines in moderate yields and diastereoselectivity (Scheme 23). Dauban and coworkers extended the concept of this chiral sulfonimidamide.[50] In the presence of 10 mol% of CuOTf, chirality induction could be achieved with chiral sulfonimidamide **23**, particularly when electron-deficient alkenes are used as substrates (Scheme 24).

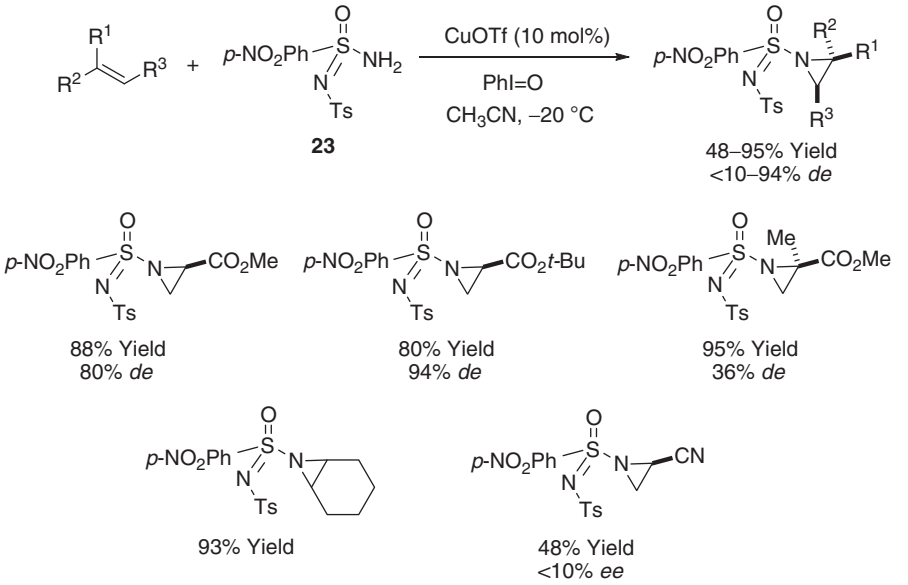


Scheme 23

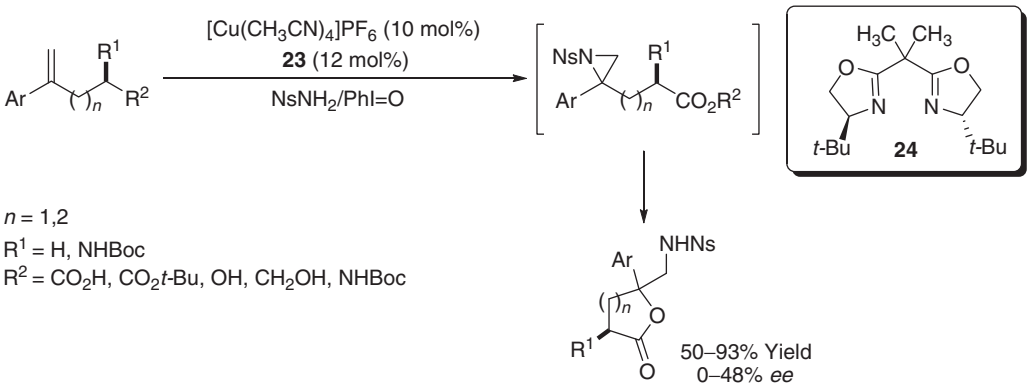
Dodd and coworkers reported the one-pot copper(I)-catalyzed intermolecular aziridination of alkenes by PhI=NNs followed by intramolecular nucleophilic aziridine ring-opening to give *gem*-disubstituted lactones in 50–93% yields (Scheme 25). Although a chiral bis(oxazoline) (**24**) ligand was used in this reaction, poor enantioselectivity was observed.[51]

Other than iminoiodinanes, intermolecular aziridination of alkenes can be achieved using chloramine-T (**3**), bromamine-T (**4**), organic azides, or oxycarbamates as nitrene source. Simkhovich and Gross reported the use of iron(IV) corroles as catalysts for aziridination of styrene compounds using **3** as nitrene source.[52] Although these catalysts showed a tendency to favor aziridination over oxidation (up to 11.4:1), the yields of aziridination were only moderate (32–60%).

Chanda et al. reported that transition metal-catalyzed aziridination of alkenes with bromamine-T (**4**) could be accelerated under ultrasound irradiation or microwave-assisted conditions.[53] Copper(II) halides were found to be superior over other transition metal catalysts. Reaction time could be shortened to 20 min when the reaction was performed under ultrasound

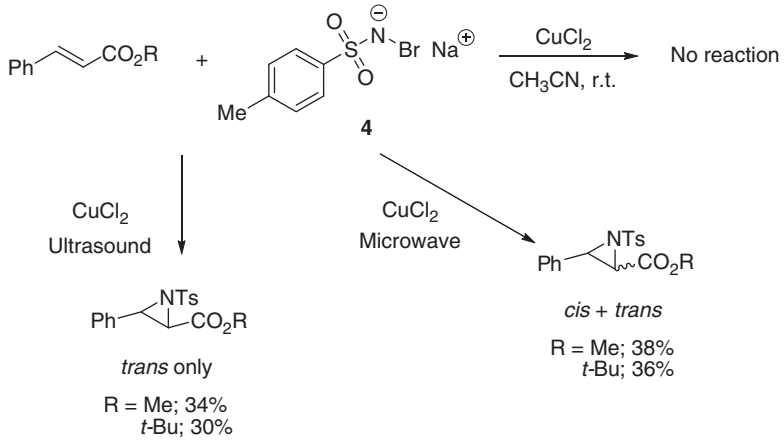


Scheme 24



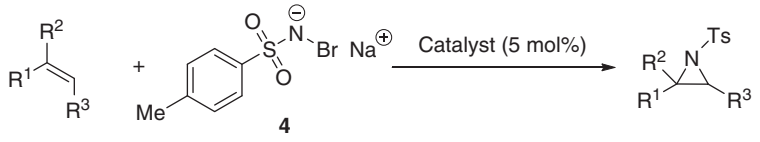
Scheme 25

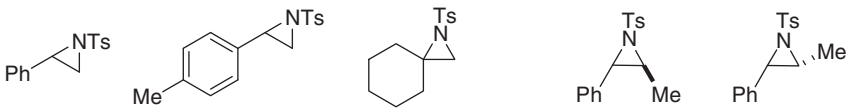
irradiation, and further shortened to 12 min under microwave-assisted condition. α,β-Unsaturated esters which were inactive toward aziridination under thermal conditions, underwent copper(II)-catalyzed aziridination reaction with 4 under ultrasound irradiation or microwave-assisted conditions (Scheme 26).



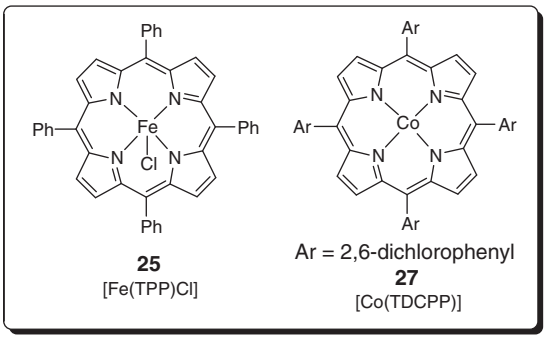
Scheme 26

Zhang and coworkers reported the use of **4** as a nitrene source for aziridination of a wide range of alkenes, including α,β-unsaturated esters, catalyzed by the iron(III) porphyrin complexes [Fe(TPP)Cl] (**25**) and [Fe(F_{20}-TPP)Cl] (**26**).[54] Complex [Co(TDCPP)] (**27**) was an effective catalyst for aziridination of a wide range of alkenes with **4**, leading to aziridines in high yields and good stereoselectivity (Scheme 27).[55]



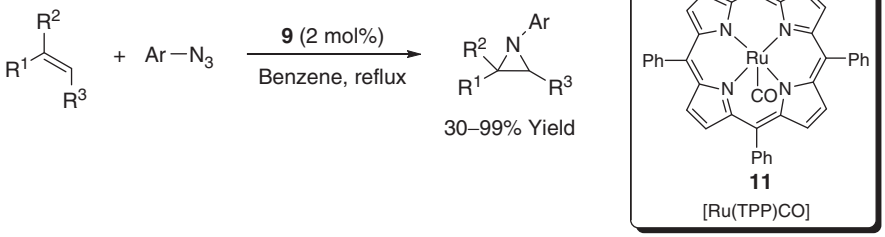


[Fe(TPP)Cl] **25**	77%	75%	50%	*cis*:*trans*	54% 56:44	75% 18:72
[Co(TDCPP)] **27**	83%	76%	67%	*cis*:*trans*	94% 9:91	87% 8:92



Scheme 27

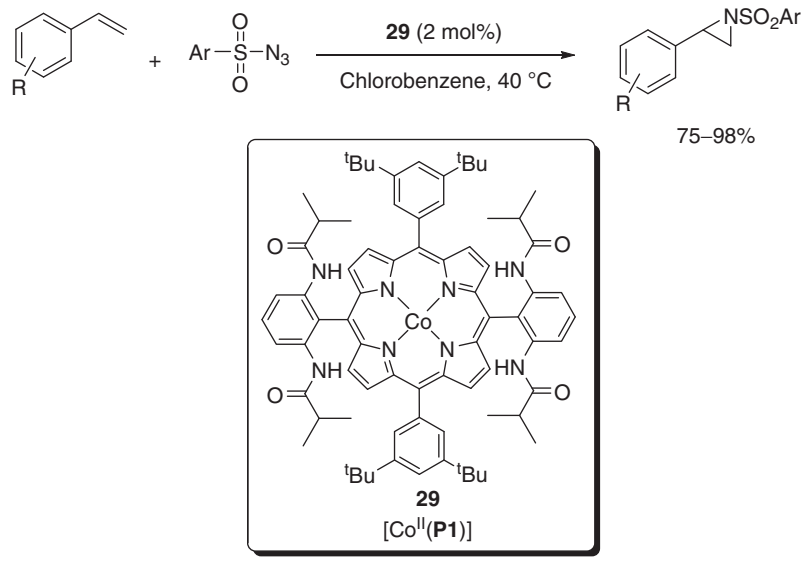
Gallo and coworkers utilized [Ru(TPP)CO] (**11**) as catalyst for the aziridination of styrenes with organic azides in excellent yields (Scheme 28).[56] Complex **11** showed a high product turnover number of 2300.



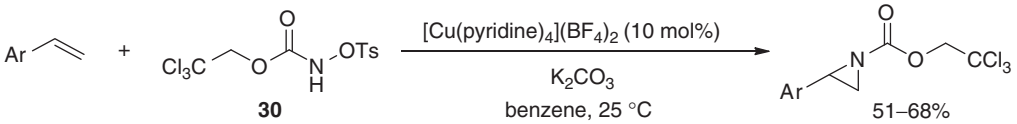
Scheme 28

However, these complexes were found to be inactive toward decomposition of organic azides. Zhang and coworkers developed the aziridination of styrenes using [Co(TPP)] (**28**) as catalyst.[57] These authors also designed new C_2-symmetric porphyrin ligand **P1**.[58] The amide functional group was introduced to the porphyrin ligand, aiming to stabilize the metallonitrene intermediate through hydrogen-bonding interactions. The complex [Co(**P1**)] (**29**) was prepared and found to catalyze intermolecular aziridination of styrene compounds with sulfonyl azides (Scheme 29).

Lebel and coworkers used the oxycarbamate **30** for intermolecular aziridination of styrenes.[59] In the presence of K_2CO_3 as base and 10 mol% of [Cu(pyridine)$_4$](BF_4)$_2$, the desired aziridines were obtained in good yields (Scheme 30).



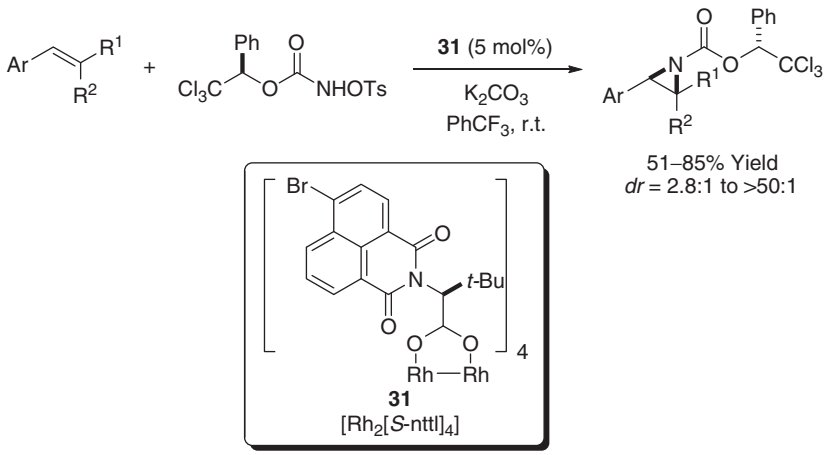
Scheme 29



Scheme 30

With the use of chiral oxycarbamate and the chiral dirhodium(II,II) catalyst **31**, diastereoselective aziridination of styrene compounds proceeded smoothly to give the desired aziridines in good yields and excellent diastereoselectivities (Scheme 31).[60]

In 1993, Evans and coworkers reported the first enantioselective intermolecular aziridination of alkenes using bis(oxazoline)–copper(I) complexes as catalysts.[61] Since then, chiral transition metal catalysts bearing bis(oxazoline),[62] diimine,[63] D_4-Halterman porphyrin **32**,[64] and Schiff base ligands[65] have been developed and used in enantioselective aziridination of alkenes. The structures of the chiral ligands used in these asymmetric reactions are depicted in Figure 8.



Scheme 31

Scott and coworkers reported copper(I) and copper(II) complexes containing C_2-symmetric diimine ligands.[66] These complexes were found to catalyze asymmetric aziridination of styrene derivative **33** to form the corresponding aziridine in up to 99% enantiomeric excess (*ee*) (Scheme 32).

After the work by Evans on the copper-catalyzed enantioselective intermolecular alkene aziridination with bis(oxazoline) ligand **24**,[61] there have been extensive studies on the modification of this class of bi-dentate diimine ligands for improving the

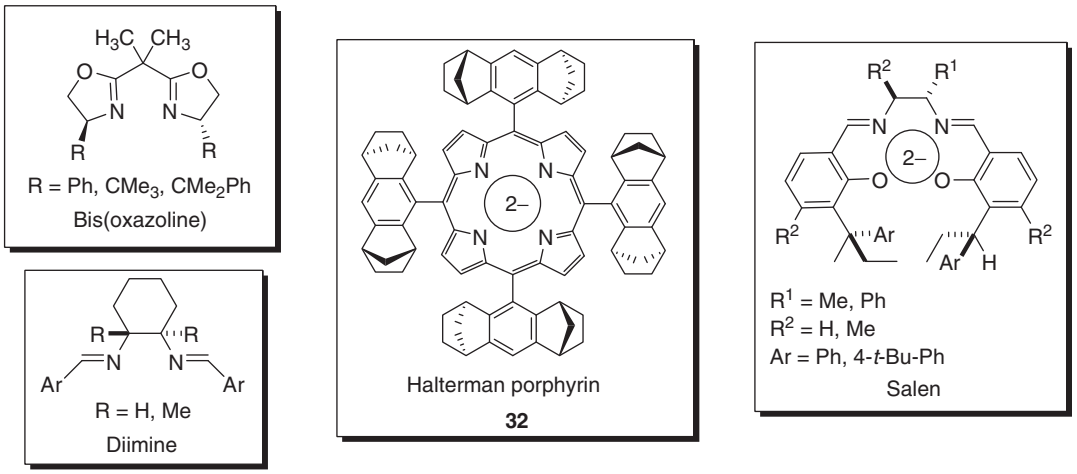
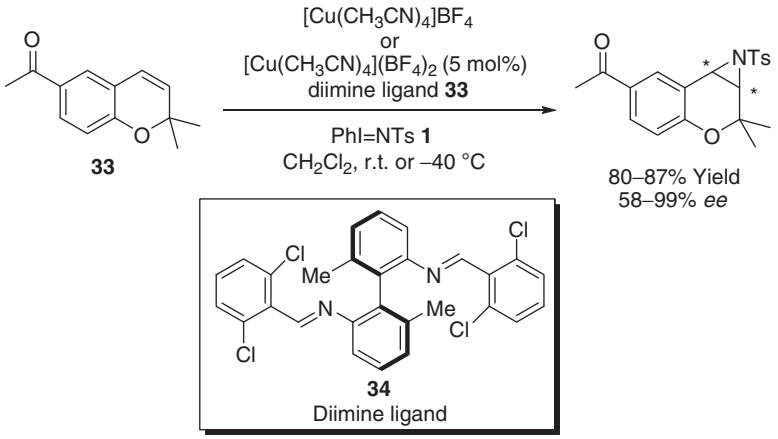
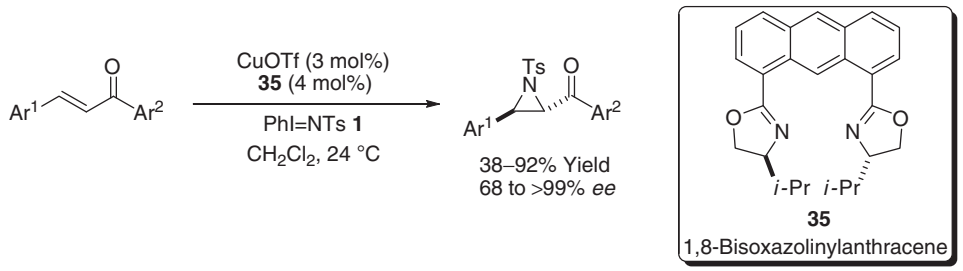


Figure 8 Structures of chiral ligands used for enantioselective aziridination reactions.



Scheme 32

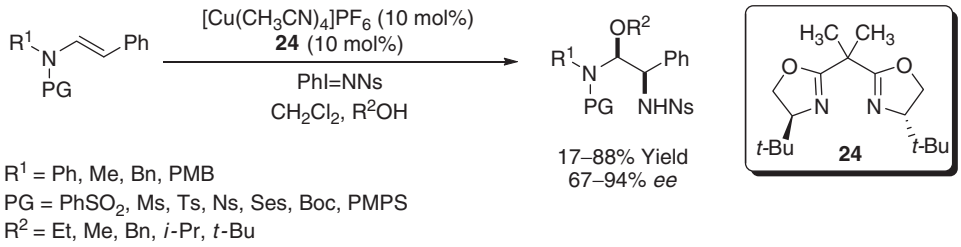
enantio-differentiation. Xu and coworkers developed 1,8-bisoxazolinylanthracene ligand **35** used in copper-catalyzed aziridination of α,β-unsaturated ketones (Scheme 33),[67] and excellent enantioselectivities (68 to >99% *ee*) were obtained.



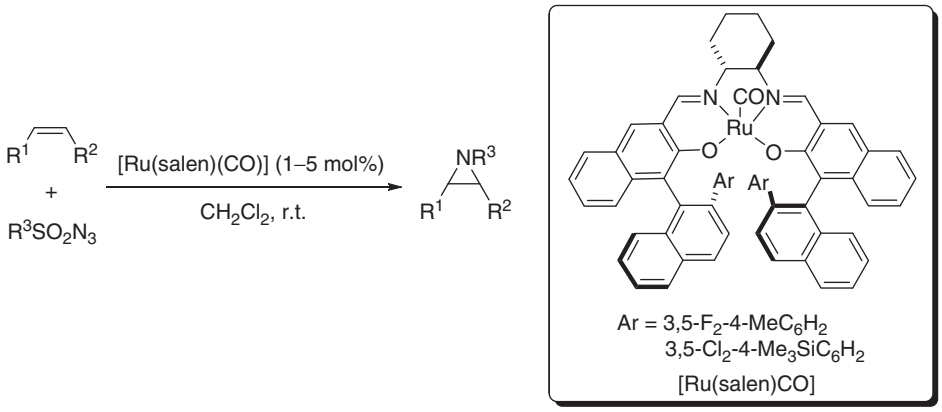
Scheme 33

The copper-catalyzed intermolecular aziridination of C=C bonds can be coupled with a nucleophilic aziridine ring-opening reaction. Dodd and coworkers reported the copper(I)-catalyzed enantioselective aziridination of alkenes in the presence of bis(oxazolidine) ligands, followed by nucleophilic attack by alcohols.[68] Enantioselective alkoxyamination products were obtained in moderate to good yields with excellent enantioselectivities (Scheme 34).

Katsuki and coworkers designed the chiral ruthenium(II)–salen complexes for enantioselective aziridination of alkenes with sulfonyl azides (Scheme 35).[69] As depicted in Scheme 35, the bulky naphthalene substituents constitute the chiral pocket that restricts the approach of alkene substrates to the ruthenium–imido intermediate, leading to the formation of aziridines with



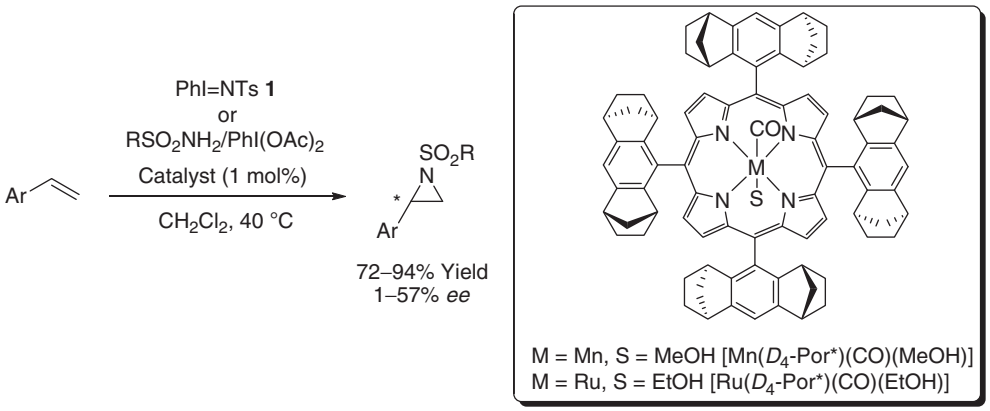
Scheme 34



Scheme 35

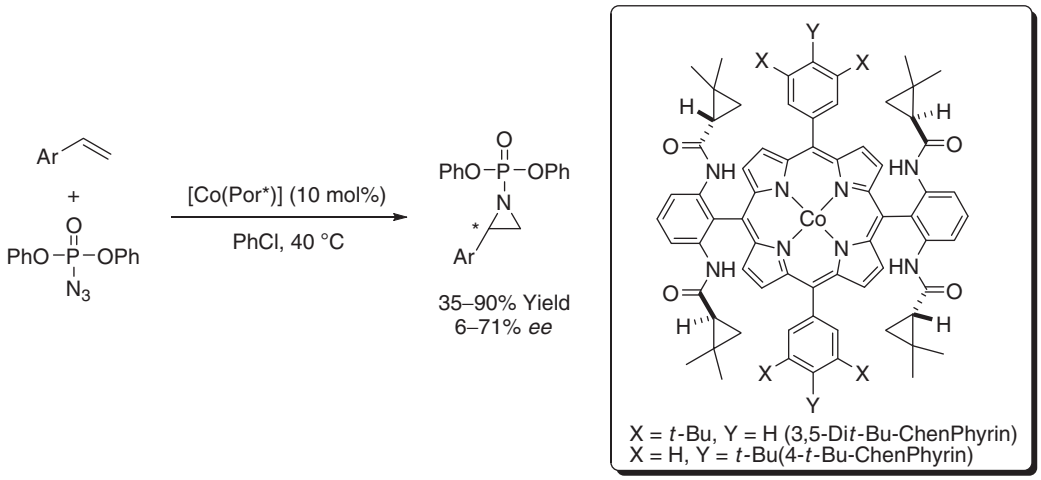
excellent enantioselectivity (up to 99% *ee*). It is noted that the less reactive α,β-unsaturated esters and amides were also found to react to give products with excellent enantioselectivities and in moderate to good yields. The ruthenium–salen complexes developed by Katsuki showed high product turnovers of up to 990 for terminal alkenes.

Che and coworkers reported catalytic aziridination of styrene compounds with PhI=NTs (**1**) or $ArSO_2NH_2$/PhI$(OAc)_2$ using chiral [Ru(D_4-Por*)CO] as catalyst (**Scheme 36**).[70] The corresponding aziridines were obtained in good yields and moderate enantioselectivities. The reactive [Ru(D_4-Por*)$(NTs)_2$] complex was prepared by the reaction of [Ru(D_4-Por*)CO] with PhI=NTs (**1**) and could undergo stoichiometric alkene aziridination.

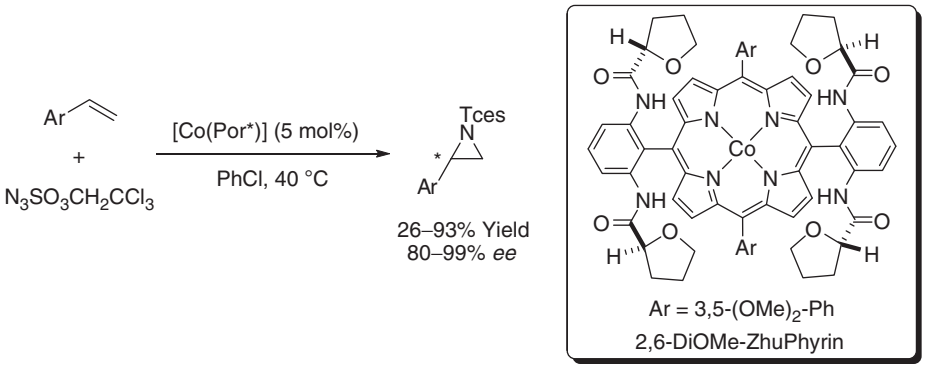


Scheme 36

After their works on cobalt porphyrins-catalyzed intermolecular alkene aziridination with organic azides, Zhang and coworkers reported modification of their porphyrin ligand by installing chiral amide functional groups at the *ortho*-positions of the *meso*-phenyl rings for enantioselective aziridination of styrene compounds with diphenylphosphoryl azide (**Scheme 37**)[71] or trichloroethoxysulfonyl azide (**Scheme 38**).[72] The corresponding aziridines were obtained in good yields and with moderate to excellent enantioselectivities.



Scheme 37

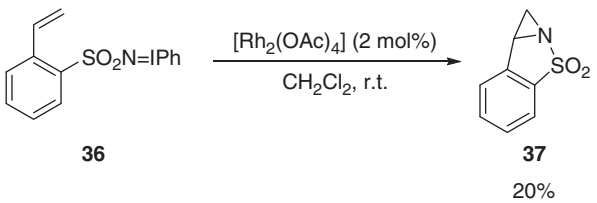


Scheme 38

7.02.4.1.2 Intramolecular aziridination

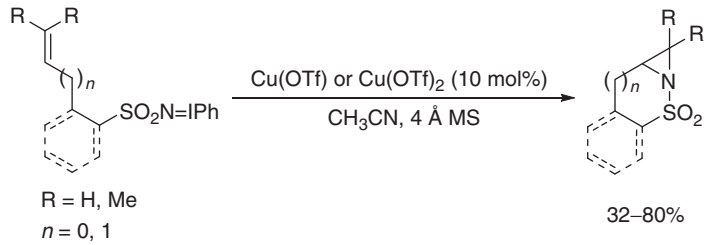
After the report by Che and coworkers on *in situ* generation of nitrene precursors by oxidation of amines or amides,[3] intramolecular aziridination of C=C bonds has become a strategy for the generation of bicyclo[3.1.0] or [4.1.0] sultam ring compounds. Through nucleophilic aziridine ring-opening, amine or amide moiety can be incorporated to organic compounds. In the following sections, the transition metal-catalyzed intramolecular aziridination of alkenes, alkynes, and allenes are discussed. With the use of chiral transition metal catalysts, asymmetric aziridination of C=C bonds can be realized in high yields and enantioselectivity.

In 1998, Müller and coworkers reported the first intramolecular aziridination of alkenes.[34b] In the presence of $[Rh_2(OAc)_4]$, presynthesized iminoiodinane **36** bearing an alkene functional group was converted into bicycle[3.1.0] sultam **37** in only 20% isolated yield (Scheme 39). The low yield might be due to the isolation problem of **36**.



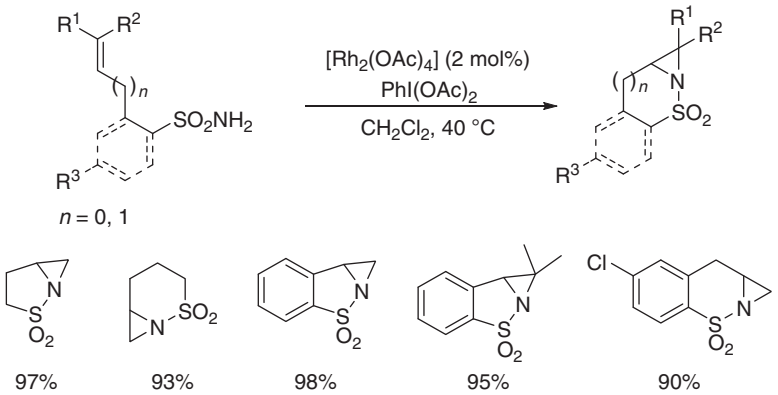
Scheme 39

Dauban and Dodd examined the reaction using similar substrates and with 10 mol% of copper(I) or copper(II) triflate as catalyst.[73] The yields were increased to 32–80% (Scheme 40). However, these copper catalysts were not active toward substrate **36**.



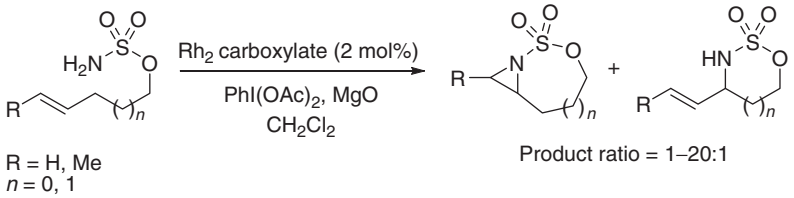
Scheme 40

Che and coworkers modified Müller's reaction by *in situ* generation of the nitrene precursors through oxidation of sulfonamide with $PhI(OAc)_2$ (Scheme 41).[74] The isolated yield of the desired bicyclo[3.1.0] sultam was improved to 83%. This intramolecular aziridination reaction is particularly efficient for bicyclic sultams having five- and six-membered rings ($n=0$, 1). The same reaction could be catalyzed by $[Cu(CH_3CN)_4]PF_6$,[37] $[Rh_2(NHCOCF_3)_4]$ (**38**),[75] $[Rh_2(oct)_4]$,[75] $[Ru(F_{20}\text{-TPP})(CO)]$ (**39**),[76] or the 'AgOTf–tBu$_3$tpy' system.[77]



Scheme 41

In a later study by Du Bois and coworkers, intramolecular allylic C–H nitrene insertion was detected besides intramolecular alkene aziridination.[78] Depending on the auxiliary ligand, a mixture of products in ratios of 1:1 to 20:1 and with aziridination products being the major ones were observed (Scheme 42).



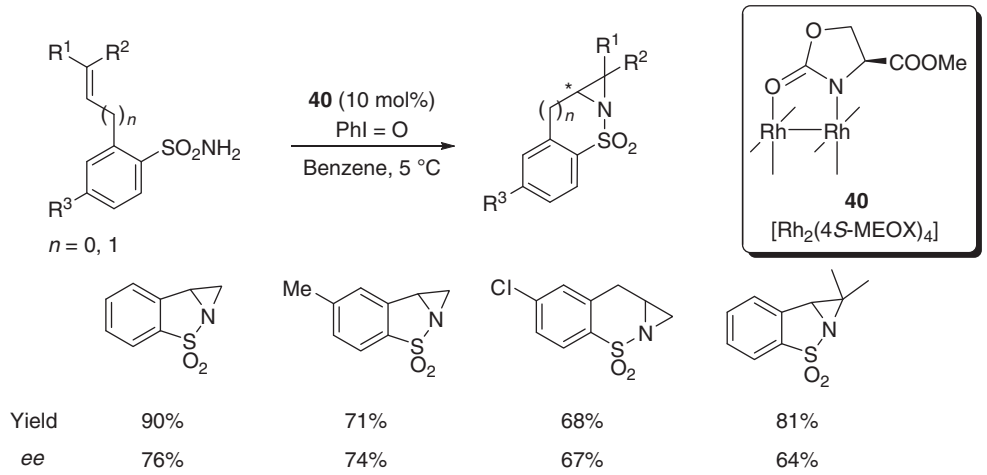
Scheme 42

With the use of dirhodium(II,II) catalyst **40** supported by the chiral bridging ligands derived from oxazolidinones, Che and coworkers reported enantioselective intramolecular alkene aziridination with *ee* values up to 76% (Scheme 43).[79]

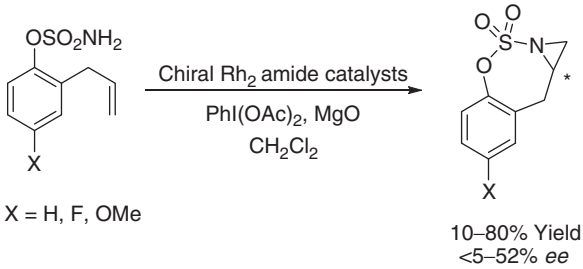
As depicted in Scheme 44, the dirhodium(II,II)-catalyzed asymmetric intramolecular aziridination has also been extended to 2-allylphenyl sulfamates, giving fused 7,3-bicyclic compounds in moderate yields and enantioselectivities.[80]

Besides alkenes, alkynes could also similarly react with metal–nitrene intermediates. Blakey and coworkers reported intramolecular nitrene insertion of alkynes catalyzed by $[Rh_2(esp)_2]$ (**41**), followed by reduction to form seven-membered ring compounds.[81] A mechanism was proposed to involve *in situ* generation of metal–nitrene intermediate, followed by aziridination of alkyne with subsequent ring opening to form the short-lived vinyl cation intermediate **42**. After a series of rearrangement reactions, *N*-sulfonyl imine intermediate **43** was reduced by $NaBH_4$ to give the desired seven-membered sulfamate esters (Scheme 45).

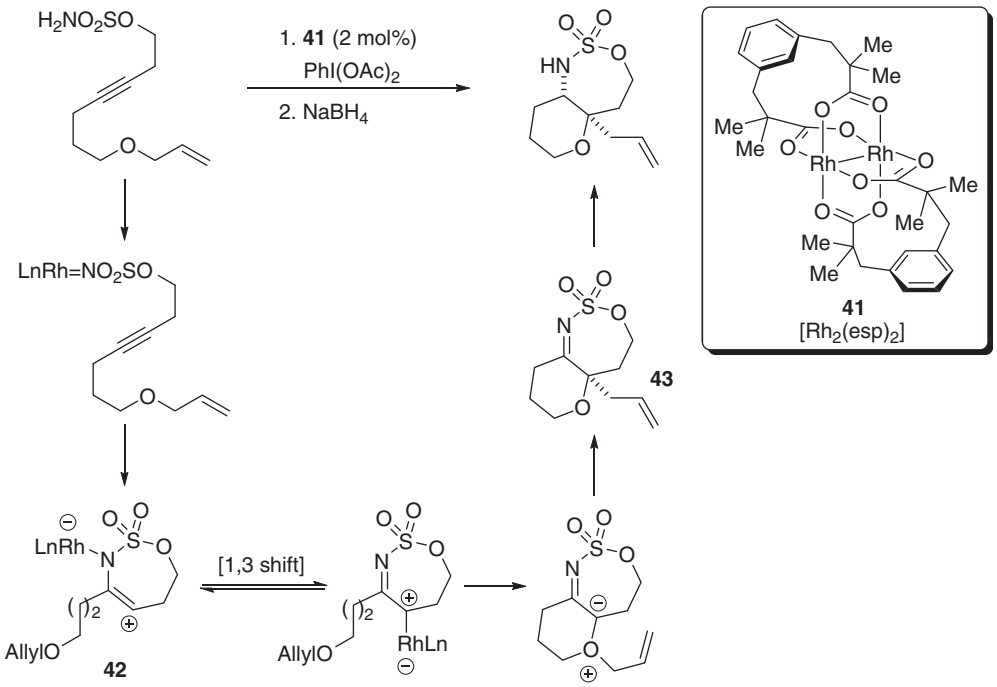
In 2009, Stoll and Blakey reported stereoselective intramolecular reaction of nitrene with allenes followed by nucleophilic addition of Grignard reagents to form compounds having a fused [7,3]-aminocyclopropane structure as depicted in Scheme 46.[82]



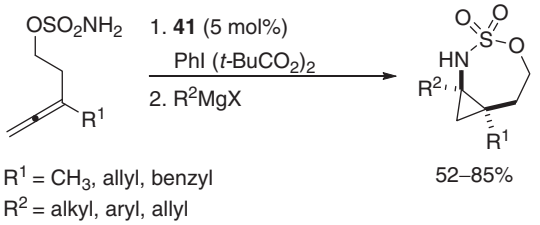
Scheme 43



Scheme 44

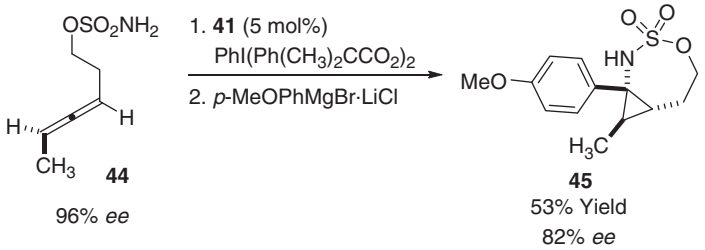


Scheme 45



Scheme 46

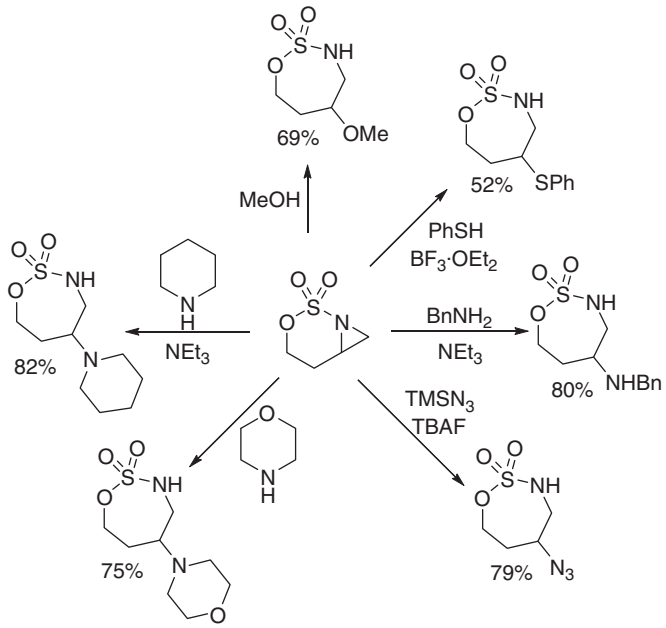
When the axially chiral allene **44** (96% *ee*) was used as substrate, chiral aminocyclopropane **45** was obtained in 82% *ee* as a single diastereomer (Scheme 47).



Scheme 47

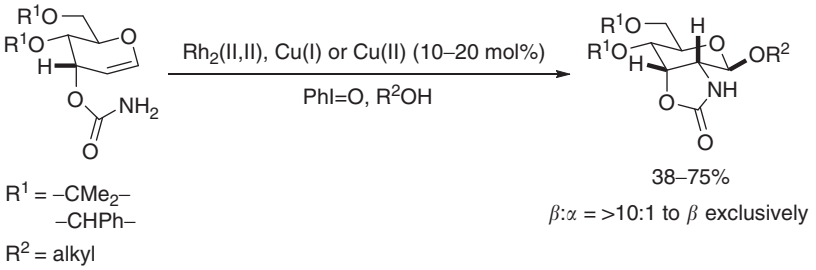
Nucleophilic aziridine ring-opening of fused bicyclic sultams could be used to install amide or amine functional groups. This strategy can be considered as an alternative to achieve C–H amidation or amination.

Dauban and coworkers reported the copper(I)-catalyzed intramolecular aziridination of sulfamate esters giving fused 6,3-bicyclic sultams in 53–94% yields.[73,83] Subsequent regioselective intermolecular nucleophilic attack on the aziridine ring-opening of sultams gave the seven-membered sulfamate esters as depicted in Scheme 48.



Scheme 48

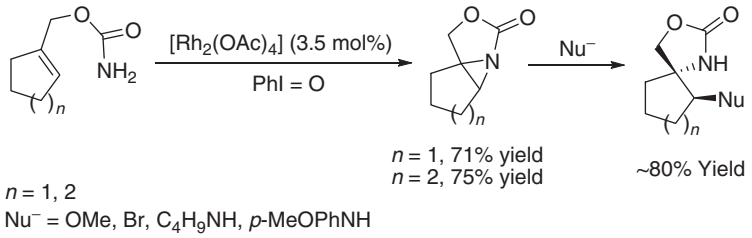
Other than sulfonamides, oxidation of carbamates can also be used to produce nitrene precursors. In 2002, Rojas and coworkers reported a one-pot *β*-stereoselective glycosylation of glycal enol ether (Scheme 49).[84] The metal–nitrene species was generated by *in situ* oxidation of carbamate with $PhI(OAc)_2$ followed by intramolecular aziridination of C–C bond with



Scheme 49

$[Rh_2(OAc)_4]$, $[Cu(CH_3CN)_4]PF_6$, or $[Cu(acac)_2]$ as catalyst. Subsequent nucleophilic attack at the backside of aziridine moiety by alcohol, either through metal-catalyzed activation of aziridine or under metal-free condition, led to highly stereoselective glycosylation.

Nearly at the same time, Padwa and Stengel reported intramolecular aziridination of cyclic alkenes by *in situ* oxidation of carbamates with dirhodium(II,II) acetate as catalyst, and this was followed by nucleophilic aziridine ring-opening to give cyclized products in the *trans* configuration as depicted in Scheme 50.[85] It is worth noting that although the reaction depicted in Scheme 50 worked well and appeared to be similar to that depicted in Scheme 49, a different reaction mechanism involving a metal-free zwitterionic intermediate was proposed to account for the *cis*-configuration of the products obtained.



Scheme 50

A similar study with substrates bearing an allene functional group had also been reported. Schomaker and coworkers reported the dirhodium(II,II) complexe-catalyzed intramolecular aziridination of allene with the metal–nitrene generated *in situ* by oxidation of carbamate moiety.[86] Bicyclic methylene aziridines were obtained preferentially as *E*-isomers in moderate yields and with minor formation of products from nucleophilic aziridine ring-opening reaction and C–H insertion at the α-position to the allene moiety. The bicyclic methylene aziridine was found to undergo Lewis acid-catalyzed aziridine ring-opening (Scheme 51). In some cases, subsequent [3,3]-sigmatropic rearrangement might occur to form products containing an *endo*-cyclic alkene functional group.

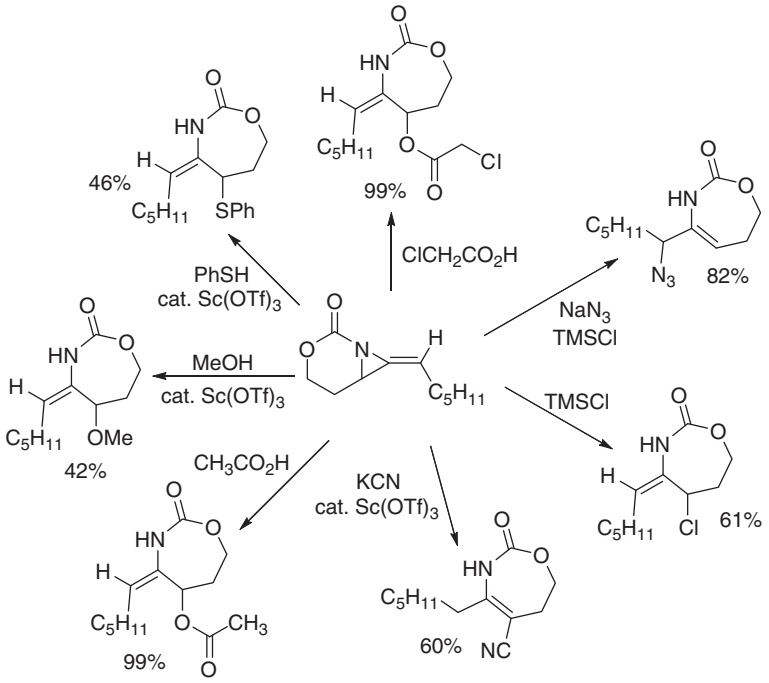
Since the discovery of *N*-tosyloxycarbamates by Lebel in 2005,[9] this class of compounds have been used as nitrene source for intramolecular aziridination of alkenes. In the course of their study on complex **6**-catalyzed intramolecular nitrene C–H insertion, Lebel and coworkers found that Nopol-derived *N*-tosyloxycarbamate **46** containing electron-rich alkene moiety underwent both C–H insertion and C=C aziridination to form **47** having a fused tricyclic structure as a single diastereomer (Scheme 52).[87] Although this reaction worked well with *N*-tosyloxycarbamate substrates bearing alkyl substituents, 7 equivalents of K_2CO_3 were used to ensure a reaction bias toward aziridination. In their later work, Lebel and coworkers used $[Cu(pyridine)_4](OTf)_2$ as catalyst for similar reactions. The catalyst loading was lowered to 2 mol% and the use of K_2CO_3 was reduced to 5 equivalents (Scheme 53).[59]

In 2007, Fleming and coworkers reported a related copper(I)-catalyzed intramolecular aziridination of *N*-tosyloxycarbamates.[88] They extended their study to reactions including regio- and stereoselective nucleophilic aziridine ring-opening reactions as previously described by Dauban and Dodd.[73,83]

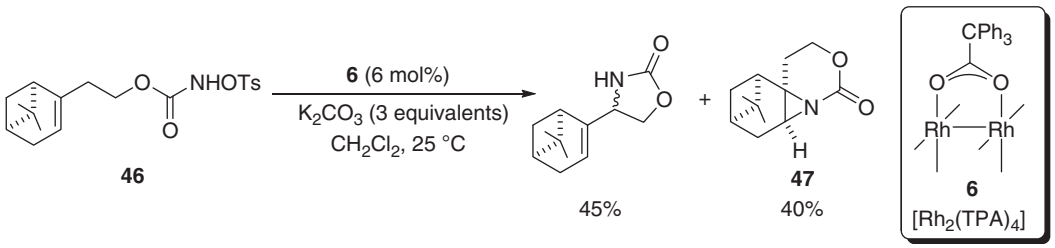
N-Tosyloxycarbamate also undergoes aziridination with allenes to form bicyclic methylene aziridines,[89] which can be considered as an alternative method for *in situ* oxidation of carbamates. In the presence of Brønsted acid, aziridine ring-opening occurs to give aminoallyl cation which could undergo intramolecular [4 + 3] cycloaddition with the furan moiety present in the substrate molecule (Scheme 54).

7.02.4.2 C–H Insertion

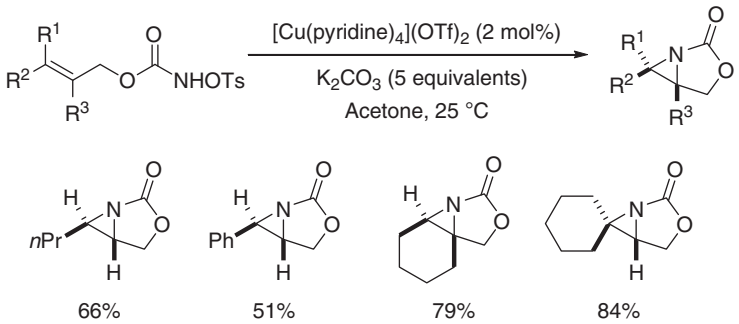
Nitrene insertion to C–H bond is an appealing method for C–N bond formation since it obviates traditional functional group transformation thereby streamlining the synthesis of amine compounds. In early works, organic azides were usually used as



Scheme 51



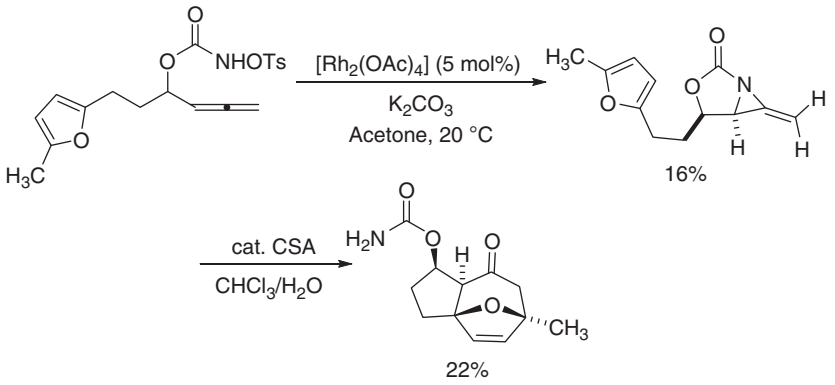
Scheme 52



Scheme 53

nitrene source for C–H amination. Decomposition of organic azides under thermal or photochemical conditions generates free nitrenes, which often lead to products with poor yields and selectivity. In 1982, Breslow and coworkers reported the first metalloporphyrin-catalyzed intermolecular C–H amination of hydrocarbons with PhI=NTs (**1**) as nitrene source.[90] Following this work, Müller demonstrated that dirhodium carboxylates are effective catalysts for nitrene insertion to allylic C–H bond of alkenes.[34a]

In 1999, Che and coworkers reported the synthesis and characterization of a series of bis(tosylimido)ruthenium(VI) porphyrins by treating [Ru^{II}(Por)(CO)] with PhI=NTs (**1**). These complexes can undergo stoichiometric C–H insertion with



Scheme 54

hydrocarbons. Subsequent mechanistic studies revealed the [Ru(Por)(CO)]-mediated C–H amination to involve rate-determining formation of a carboradical intermediate generated via hydrogen atom abstraction by the putative [Ru(Por)(CO)(NTs)] intermediate.[33,91]

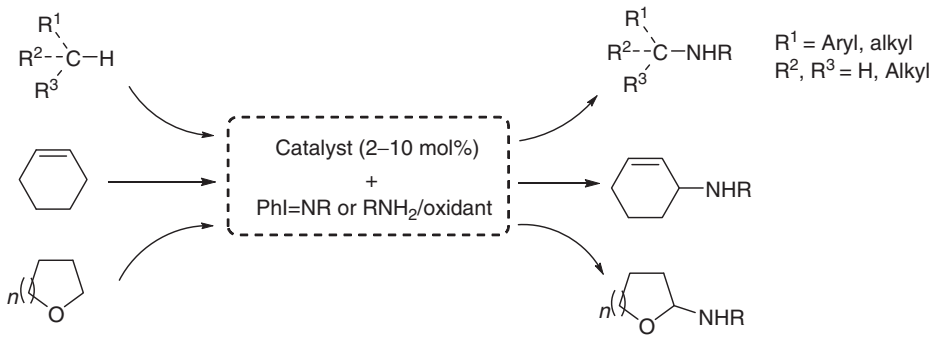
Another significant advance is the development of protocols for *in situ* generation of iminoiodinanes by Che and coworkers.[3] Such protocols circumvent the problems encountered in the isolation of labile iminoiodinanes (especially for carbamate and amide derivatives), thereby expanding the scope of substrates.

7.02.4.2.1 Intermolecular C–H insertion

7.02.4.2.1.1 sp^3 C–H Bond insertion

In 1982, Breslow and coworkers reported the first use of PhI=NTs (**1**) as nitrene source in transition metal-catalyzed C–H amination in which case cyclohexane was aminated by **1** in less than 10% yield with [Fe(TTP)Cl] (**48**) or [Mn(TTP)Cl] (**49**) as catalyst.[90] Although this reaction is not synthetically useful because of its low yield, this work indeed paved the way for the use of iminoiodanes as nitrene source in nitrene transfer/insertion reactions. Since then, **1** and its derivatives have been widely used in diverse nitrene transfer reactions including C=C aziridination, C–H insertion, and sulfur imination. Some of the important catalytic systems for nitrene insertion into sp^3 C–H bonds are summarized in **Table 2**. The structures of the catalysts or ligands used for these reactions are depicted in **Figure 9**.

Table 2 Transition metal-catalyzed nitrene insertion into sp^3 C–H bonds by using PhI=NR or *in situ* PhI=NR as nitrene source



Entry	*Catalyst*	*Nitrene source*	*Temperature (°C)*	*Conversion (%)*	*Yield (%)*	*References*
1	[Ru(F_{20}-TPP)(CO)] (**39**)	PhI=NTs (**1**) or H_2NR/PhI$(OAc)_2$	40	32–99	28–90	3
2	[Mn(F_{20}-TPP)Cl] (**2**)	**1** or H_2NR/PhI$(OAc)_2$	40	42–99	60–92	3
3	[Ru^{III}(Me_3tacn)$(CF_3CO_2)_3 \cdot H_2O$]	**1** or H_2NR/PhI$(OAc)_2$	25	38–79	80–93	94
4	*cis*-[Ru^{II}(6,6′-Cl_2bpy)$_2Cl_2$]	**1** or H_2NR/PhI$(OAc)_2$	25	40–70	81–92	94
5	Iron phthalocyanine	**1**	25	>99	72–85	95
6	Tp^{Br3}Cu(NCMe)	**1**	25	>99	50–95	96,97
7	$Tp^{*,Br}$Ag	**1**	80	>99	65–90	98
8	[$Rh_2(esp)_2$] (**41**)	$TcesNH_2$/PhI$(O_2{}^tBu)_2$	23	>99	50–74	99
9	[Co(acacen)]	**1**	75	>99	40–70	100
10	$Cu(OTf)_2$	H_2NTs/PhI$(OAc)_2$	40	64–99	30–87	101
11	[$Ag_2(OTf)_2(bp)_2$]	PhI=NNs	50	>99	25–71	102

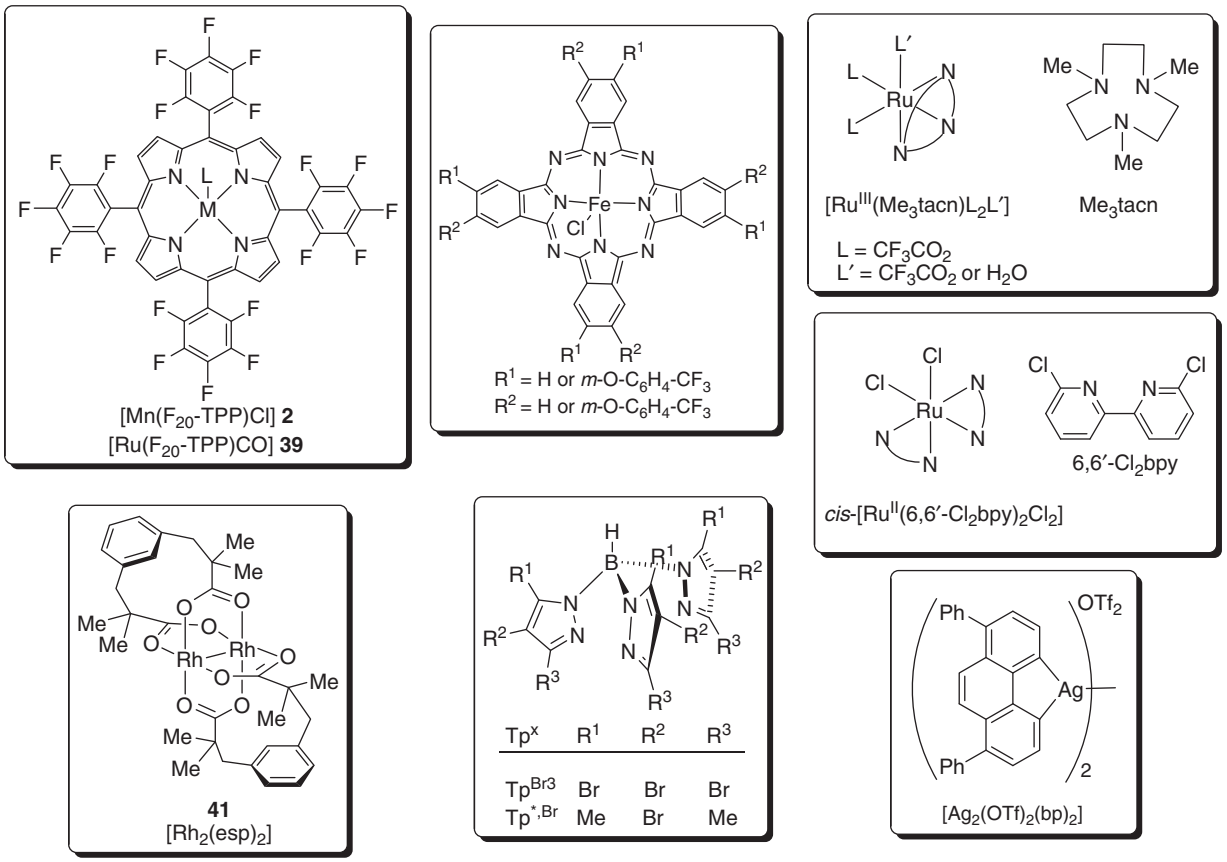


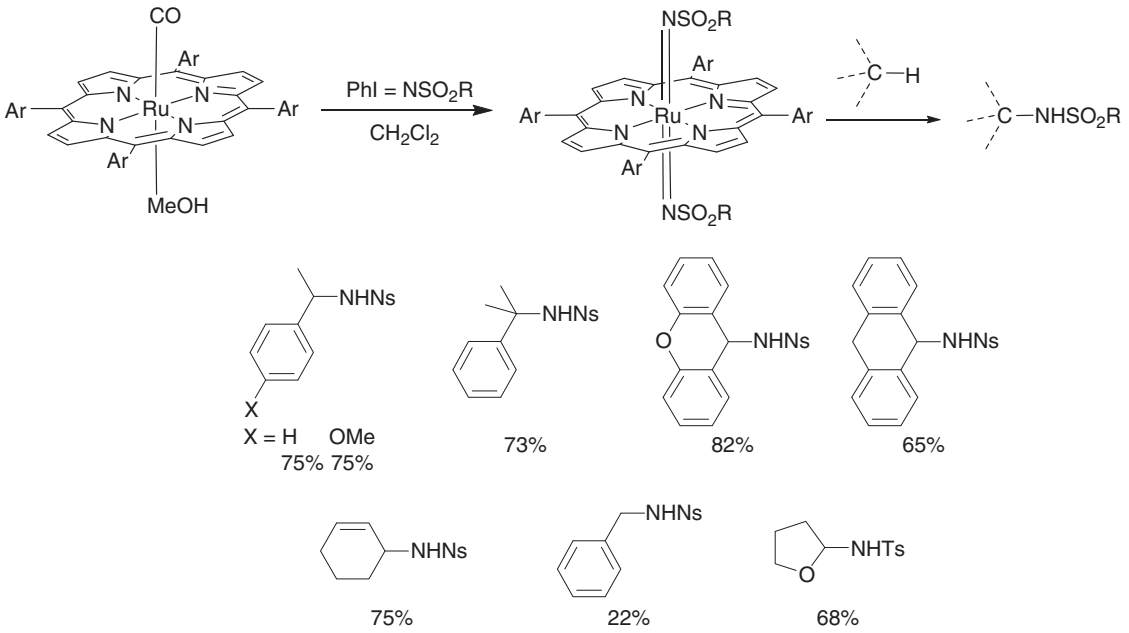
Figure 9 Structures of catalysts or ligands for intermolecular nitrene C–H insertion.

In 2000, Che and coworkers reported the use of metalloporphyrins to catalyze amination of saturated C–H bonds with PhI=NTs (**1**).[3] [Mn(F_{20}-TPP)Cl] (**2**) and [Ru(F_{20}-TPP)(CO)] (**39**) were effective catalysts for the amination of benzylic and allylic ethereal C–H bonds giving corresponding products in up to 92% yields and with up to 99% substrate conversion (Table 2, entry 1). Complex **2** displayed a higher activity than **39** toward nitrene C–H insertion. In the amination of indane, **2** gave a high TON of 2600. In this work, Che and coworkers first reported *in situ* generation of iminoiodanes PhI=NR from the 'PhI$(OAc)_2 + H_2NR$' protocol; such a protocol has been shown to be effective for amination of saturated C–H bonds giving products with comparable yields to those obtained with isolated **1**. The 'PhI$(OAc)_2 + H_2NR$' protocol offers two advantages: (1) simplified amination procedure and (2) broad scope of nitrene precursors. PEG-supported ruthenium porphyrins have been prepared and found to catalyze similar amination reactions giving corresponding products with yields in up to 90% and with up to 94% substrate conversion.[92]

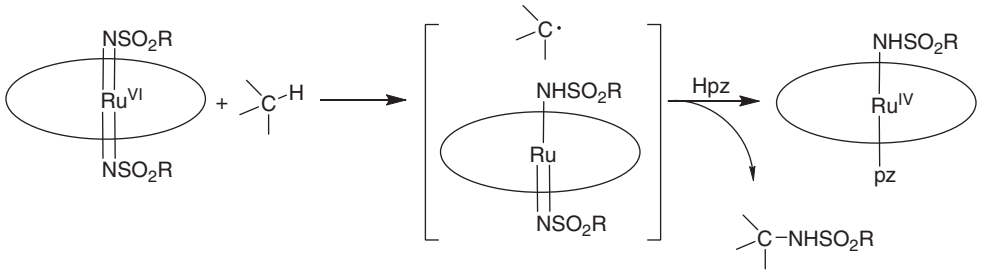
By reacting ruthenium(II) porphyrins with PhI=SO_2R, Che and coworkers prepared a series of bis(tosylimido)ruthenium(VI) porphyrins [Ru^{VI}(Por)$(NSO_2R)_2$] (Por=TPP, TMP, 2,6-Cl_2TPP, SO_2R=Ms, Ts, Bs, Cs, Ns).[16] These complexes underwent C–H amination of benzylic, allylic, and α C–H bonds of THF to give corresponding amination products in 22–80% yields (Scheme 55). Subsequent studies revealed that the second-order rate constants of these reactions correlate with C–H bond dissociation energies, providing support for an H-atom abstraction mechanism (Scheme 56).

Decomposition of bis(tosylimido)ruthenium(VI) porphyrins in solutions or oxidation of bis(ammine)ruthenium(II) porphyrins with NBS afforded ruthenium (VI)–nitrido porphyrins [Ru^{VI}(Por)(N)(OH)]. These Ru≡N complexes underwent C–H amination with indane in the presence of trifluoroacetic anhydride (TFAA) to give the amide product in 52–63% yields (Scheme 57). The reaction presumably involves an [Ru=NC(O)CF_3] intermediate which is formed through the reaction of Ru≡N with TFAA; the reactive [Ru=NC(O)CF_3] intermediate undergoes C–H insertion with indane.[93]

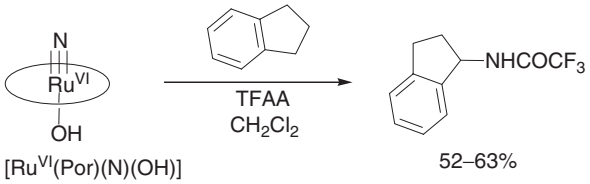
The ruthenium complexes [Ru(Me_3tacn)$(CF_3CO_2)_3 \cdot H_2O$] and *cis*-[Ru(6,6′-Cl_2bpy)$_2Cl_2$], reported by Che and coworkers (Figure 9) are active catalysts for C–H amination of hydrocarbons.[94] With PhI=NTs (**1**) or *in situ* formed iminoiodanes as nitrene source, amination of cycloalkanes and allylic and benzylic C–H bonds gave corresponding products in 81–92% yields based on 38–61% substrate conversions (Table 2, entries 3 and 4). Competitive amination of *para*-substituted ethylbenzenes (ρTE ≈ 0.63) and the kinetic isotope effect for the amination of cyclohexene/cyclohexene *d*10 (k_H/k_D=6.5) altogether revealed a mechanism that involves hydrogen atom abstraction by a reactive [Ru=NTs] species to form a carboradical intermediate.



Scheme 55



Scheme 56



Scheme 57

A report by Zhou showed that iron phthalocyanine is an efficient catalyst for intermolecular amination of saturated C–H bonds.[95] With 1.5 equivalents of PhI=NTs (**1**), amination of benzylic, 3°, and allylic C–H bonds were achieved in 72–85% yields (Table 2, entry 5).

After the success of using $Tp^{Br3}Cu(NCMe)$ to catalyze carbene C–H insertion,[96] Pérez and coworkers examined the activity of $Tp^{Br3}Cu(NCMe)$ and its silver analog $Tp^{*,Br}Ag$ (Figure 9) toward intermolecular nitrene C–H insertion (Table 2, entries 6–7). With PhI=NTs as nitrene source, $Tp^{Br3}Cu(NCMe)$-catalyzed/mediated the C–H amination of benzylic hydrocarbons, cyclic ethers, and cyclohexane efficiently at room temperature to give products with yields up to 95%. When toluene was used, amination of 1° C–H bond was achieved in 95% yield.[97] The silver analog $Tp^{*,Br}Ag$ also displayed high catalytic activity toward amination of aliphatic C–H bonds converting linear and branched alkanes into corresponding amines in 65–90% yields. The involvement of radical species in the Ag-catalyzed amination was proposed based on the following observations: (1) inhibition of the reaction in the presence of radical inhibitor 2,6-di-*tert*-butylhydroxytoluene, (2) 3° C–H bond is the most reactive, and (3) formation of chlorinated compounds when CCl_4 was used as solvent.[98]

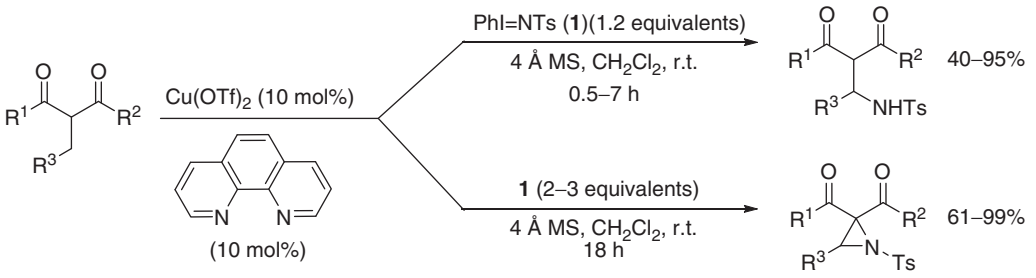
Compared with $[Rh_2(OAc)_4]$, the complex $[Rh_2(esp)_2]$ (**41**) developed by Du Bois is a more active catalyst for intermolecular nitrene C–H insertion (Table 2, entry 8).[99] With $Cl_3CCH_2OSO_2NH_2$ (**18**) as nitrogen source and $PhI(O_2t\text{-}Bu)_2$ as oxidant, selective amination of benzylic and 3° C–H bonds in 50–74% yields and in the presence of **41** have been reported. The 3° C–H bond amination reactions were stereospecific with retention of the configuration of chiral starting materials. Mechanistic study revealed that these dirhodium(II,II)-catalyzed intermolecular amination reactions proceed via concerted C–H insertion of a singlet nitrene intermediate.

Cenini and coworkers showed that Co(acacen) (acacen = 2,11-dihydroxy-4,9-dimethyl-5,8-diaza-2,4,8,10-dodecatetraene dianion) is an effective catalyst for the allylic amination of alkenes with PhI=NTs as nitrene precursor (Table 2, entry 9).[100] Under the Co(acacen)-catalyzed conditions, allylic amines were obtained in 40–70% isolated yields.

With $TsNH_2/PhI(OAc)_2$ as nitrene source, $Cu(OTf)_2$ was reported by Yu to be effective for the amination of α C–H bonds of cyclic ethers affording amidation products in 30–86% yields (Table 2, entry 10).[101] The tosylamidated products can undergo facile reductive ring-opening to give α,ω-amino alcohols in high yields.

He and coworkers reported a dinuclear silver(I) complex $[Ag_2(OTf)_2(bp)_2]$ (bp = bathophenanthroline) (Figure 9), which catalyzed amination of benzylic C–H bonds and cycloalkanes with PhI=NNs in up to 71% yield (Table 2, entry 11).[102] The dinuclear Ag(I) core was crucial since mononuclear silver complexes with 2- or 9-substitutued phenanthroline ligand showed no activity toward nitrene C–H insertion. Because two silver(I) ions are involved in the catalysis, the direct nitrene insertion to C–H bond of alkanes is most likely, in contrast to the radical pathway proposed for the mononuclear silver complex $Tp^{*,Br}$Ag-catalyzed nitrene C–H insertion.

2-Alkyl-substituted 1,3-dicarbonyl compounds were reported by Chan and coworkers to undergo β C–H insertion in 40–95% yields when 1.2 equivalents PhI=NTs (**1**) was used as nitrene source and 'Cu(OTf)$_2$/1,10-phenanthroline' was used as catalyst (Scheme 58).[103] Interestingly, when the amount of **1** was increased from 1.2 to 2–3 equivalents, the same catalyst led to aziridination products in 61–99% yields. The divergence of product selectivity caused by slight modification of the reaction conditions could be rationalized by the reaction mechanism depicted in Scheme 59. The coordination of the Cu(I) catalyst to 2-alkyl-substituted 1,3-dicarbonyl compounds gives the copper–enolate species **I** which could undergo allylic C–H bond amination with **1** to give intermediate **II**. Demetalation of **II** gives β C–H insertion product. When 2–3 equivalents of **1** were used, **II** could further react with **1** to give aziridine **III**. Ring-opening of **III** affords the diamine **VI**, which undergoes cyclization with elimination of $TsNH_2$ to give aziridination product.

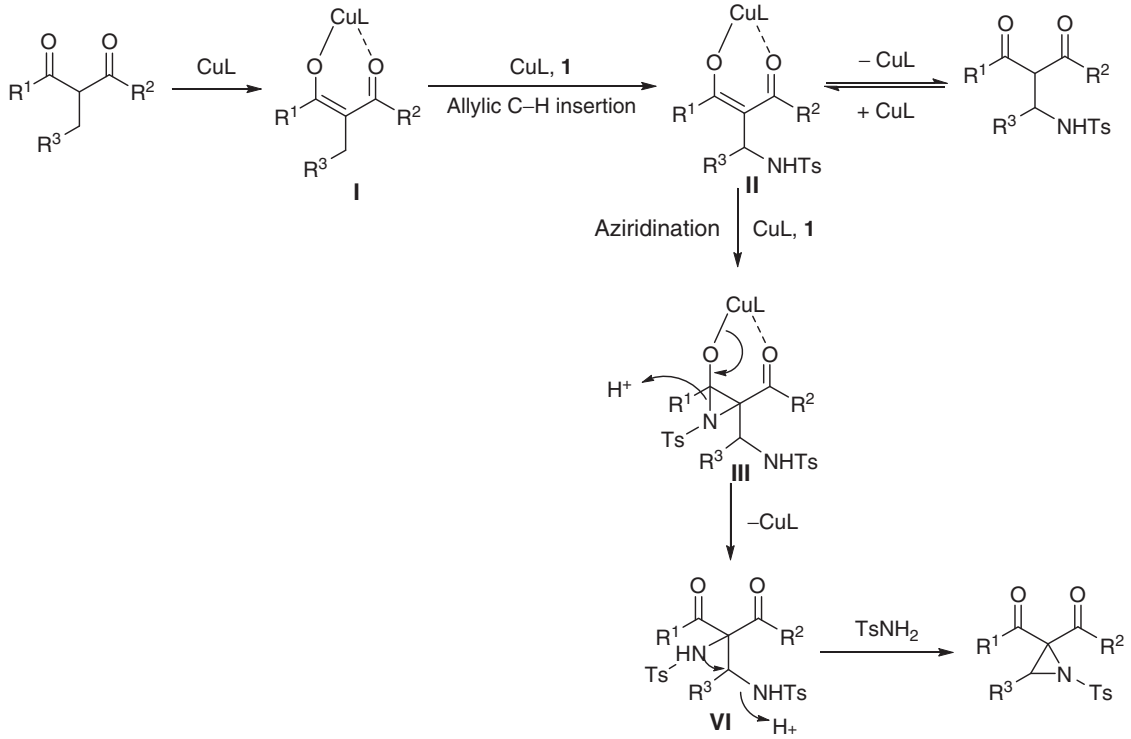


Scheme 58

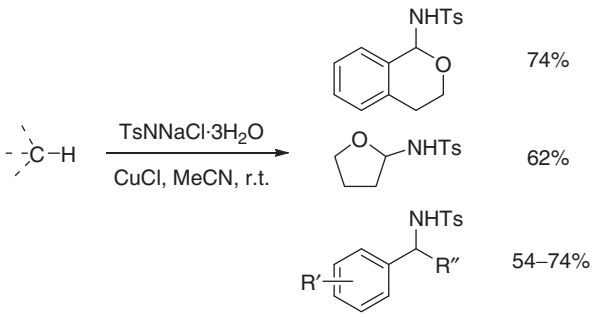
One of the earliest uses of *N*-haloamides as nitrene source was reported by Breslow and Sloan. These authors found that refluxing a mixture of dichloramine-T and Zn dust in dry cyclohexane could give nitrene C–H insertion product *N*-cyclohexyltosylamides.[104] In 1998, Taylor and coworkers reported the first Cu-catalyzed C–H amination of hydrocarbons with chloramine-T (**3**). With $(CuOTf)_2 \cdot C_6H_6$/*N*-(2-pyridinylmethylene)-1-pentanamine as catalyst, cyclohexene and tetralin were aminated in 22 and 46% yields, respectively.[105] Later on, these authors extended this process to other benzylic substrates and ethers.[106] With CuCl as catalyst, amination of α C–H bond of cyclic ethers and benzylic C–H bonds with **3** gave the corresponding products in 62–74% and 54–74% yields, respectively (Scheme 60). Anhydrous **3** was found to be more efficient than its hydrated counterparts in the $[Cu(CH_3CN)_4]PF_6$-catalyzed amination of benzylic C–H bonds giving benzylic sulfonamides in 55–77% yields (Scheme 61). The higher efficiency of anhydrous **3** can be attributed to the inhibition of hydrolysis of nitrene intermediate to form $TsNH_2$.[107]

Bromamine-T (**4**) was reported as a superior nitrene source than its analog chloramine-T (**3**) by Bedekar in 1998.[108] His preliminary study focused on the aziridination reactions of alkenes with **4**. In his following study, the amination of benzylic C–H bonds with **4** was also achieved in 33–70% yield with $[Rh_2(OAc)_4]$ as catalyst under ultrasound irradiation (Scheme 62).[53] Similar reactions have also been reported by Zhang's group with [Co(TDCPP)] as catalyst and resultant benzylic C–H amination products were obtained in 14–73% yields.[109]

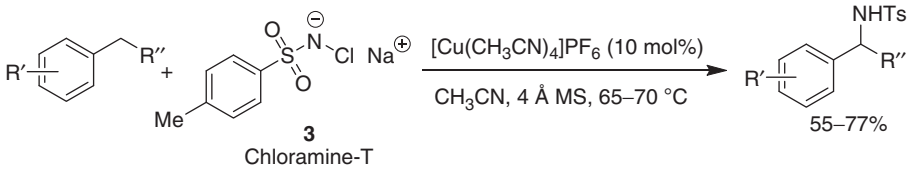
With carboxamides, and sulfonamides as nitrogen source and NBS as oxidant, CuBr-catalyzed benzylic C–H amination in 39–79% product yields (Scheme 63).[110] *N*-Haloamide is presumably formed *in situ* by the reaction of amide with NBS and acts as a real nitrene precursor in the reaction. An interesting feature of this work is that the nitrenes derived from carboxamides, which are known to undergo facile Curtis rearrangement, could undergo benzylic C–H insertion in moderate yields. With NCS as oxidant, the α C–H amination reactions of *N*,*N*-dimethylaniline and carboxamides were achieved in 40–61% yields.



Scheme 59

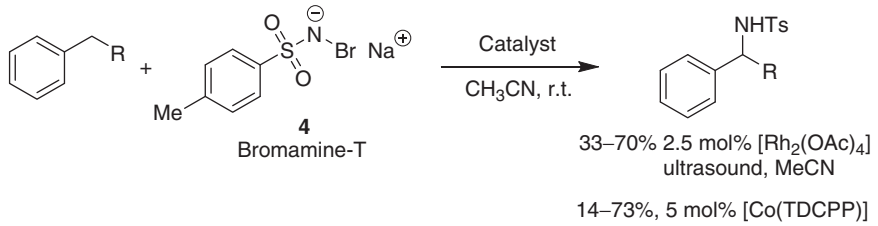


Scheme 60

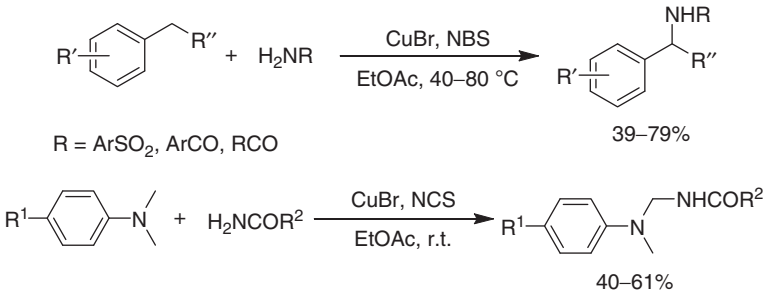


Scheme 61

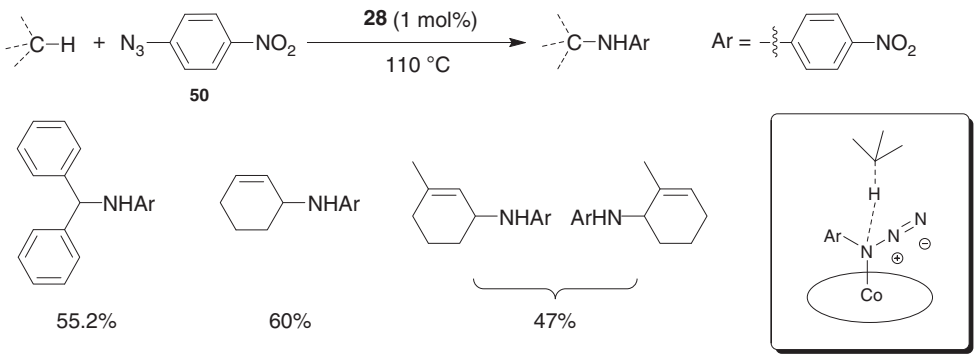
p-Nitrophenyl azide (**50**) is an effective nitrene source commonly used in cobalt porphyrin-catalyzed amination reactions. With [Co(TPP)] (**28**) as catalyst, benzylic and allylic C–H bonds were aminated in up to 60% yields (Scheme 64).[111] Kinetic and spectroscopic studies revealed that a cobalt–nitrene/imido complex is not the reactive intermediate of these amination reactions. The cobalt porphyrin-catalyzed amination probably involves a reversible coordination of aryl azide to **28** to generate a cobalt–azide adduct that reacts with benzylic and allylic C–H bonds. The cobalt–azide adduct can also undergo elimination of dinitrogen to form a cobalt–nitrene complex, the latter was proposed to be responsible for the formation of the by-products diaryldiazene and *p*-nitroaniline.



Scheme 62



Scheme 63

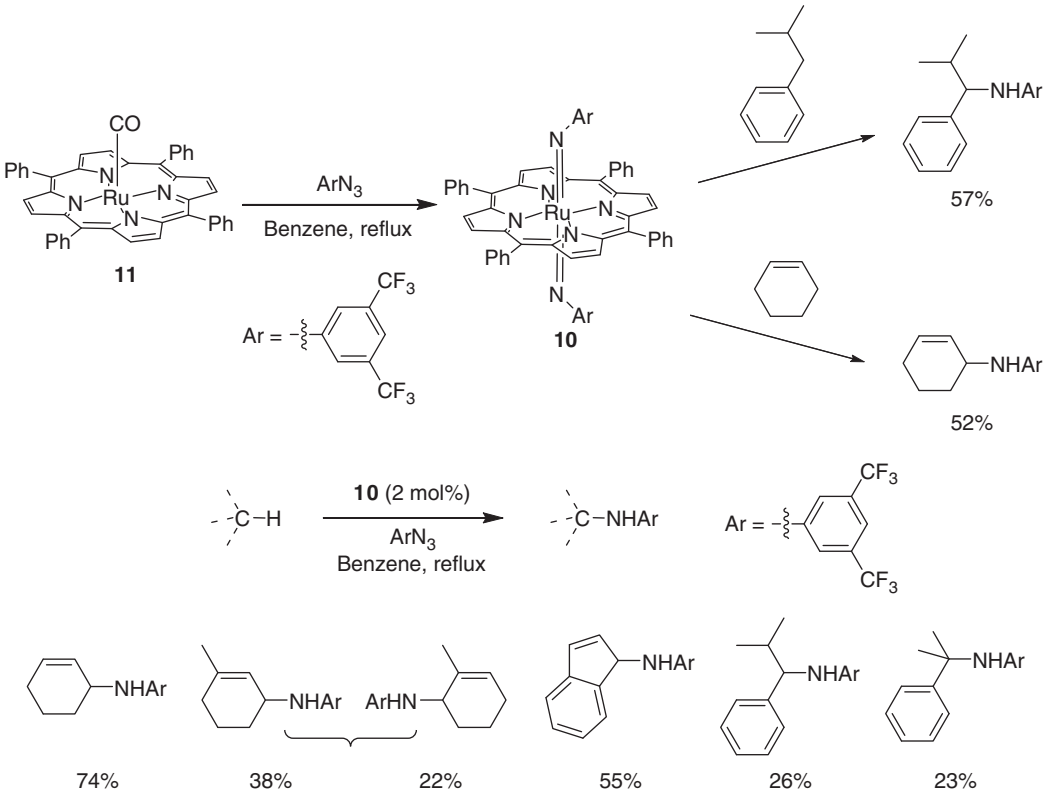


Scheme 64

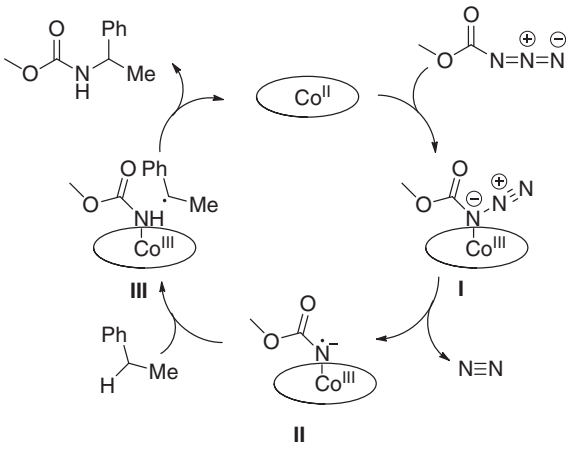
In 2009, Gallo and coworkers reported the synthesis of an (arylimido)ruthenium(VI) complex [Ru(TPP)$(NAr)_2$] (Ar = 3,5-$(CF_3)_2C_6H_3$) (**10**) in 70% yield by the stoichiometric reaction of ArN_3 with [Ru(TPP)(CO)] (**11**) (Scheme 65).[18] This complex was found to undergo stoichiometric reaction with *iso*-butylbenzene and cyclohexene to give corresponding benzylic and allylic C–H amination products in 57% and 52% yields, respectively (Scheme 65); it could also catalyze the C–H amination of benzylic and allylic C–H bonds of hydrocarbons with the aryl azide with product yields up to 74%.

A DFT computational study on the mechanism of cobalt(II) porphyrin-catalyzed C–H amination of hydrocarbons with organic azides was reported by Zhang and coworkers in 2011.[112] The calculations revealed a stepwise radical mechanism as depicted in Scheme 66. The catalytic cycle starts with coordination of the α-nitrogen atom of azide to cobalt porphyrin to give the azide complex **I** which subsequently undergoes elimination of N_2 to give intermediate **II**. Based on the calculations, this intermediate was formulated to have 'nitrene radical ligand.' It undergoes H-atom abstraction of benzylic CH_2 unit of ethylbenzene to give a catalyst–radical pair **III** comprising of benzylic radical PhCH•CH_3 and the cobalt(III) amide complex [(Por)Co^{III}–NHC(O)OMe]. Subsequent radical rebound of intermediate **III** gives the amination product. Isotropic solution electron paramagnetic resonance study also revealed the presence of cobalt(III)–nitrene radical intermediate on reacting cobalt(II) porphyrin with organic azide.

Although arylsulfonyl azides (TsN_3 and NsN_3) have been reported by the groups of Katsuki and coworkers[113] and Zhang and coworkers[58] to be effective nitrene sources for alkene aziridination, studies on their applications in metal-catalyzed C–H amination are comparatively sparse. In 2010, Che and coworkers reported that [Fe(F_{20}-TPP)Cl] (**26**)-catalyzed allylic C–H amination of α-methylstyrenes with arylsulfonyl azides and 4-nitrophenyl azide to give corresponding products in 68–83% yields (Scheme 67).[114] However, when hydrocarbons having benzylic C–H bonds and saturated cyclic hydrocarbons were used as substrates, the sulfonyl azides remained unchanged in the presence of catalyst **26**. In contrast, 4-nitrophenyl azide (**50**) led to



Scheme 65

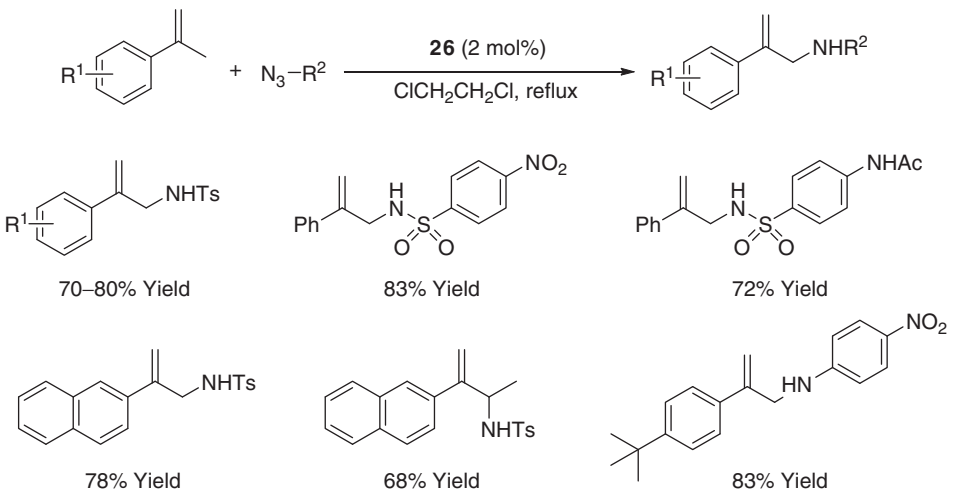


Scheme 66

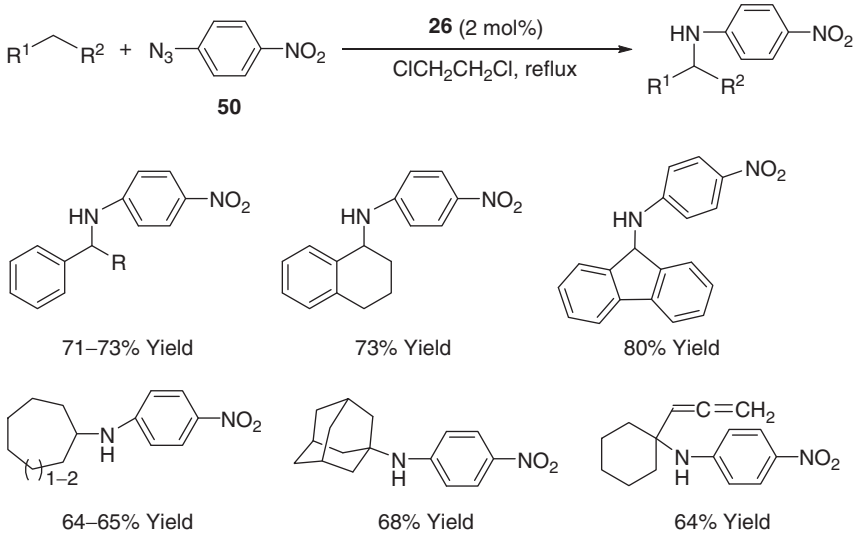
amination of benzylic and sp^3 C–H bonds with yields up to 80% (Scheme 68). The **26**-catalyzed amination of both adamantane and 1-cyclohexylallene were regioselective with only the products derived from nitrene insertion to 3° C–H bond(s) detected.

Compared with arylsulfonyl azides, phosphoryl azide, or carbamate azide, 2,2,2-trichloroethoxycarbonyl azide (**51**) was much more reactive in cobalt porphyrin-catalyzed benzylic C–H amination. With [Co(TTP)] (**52**) as catalyst, various alkylbenzenes were aminated by **52** in up to 92% yield (Scheme 69). The complexes of iron, copper, and nickel supported by porphyrins are less active than cobalt porphyrin.[115]

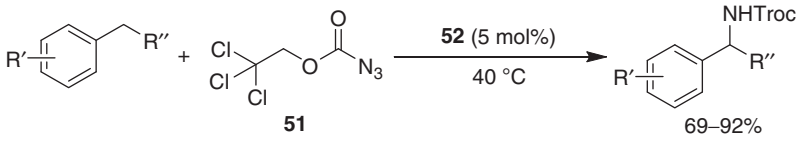
In 2005, Lebel and coworkers reported that dirhodium(II,II) carboxylates can efficiently and selectively catalyze intramolecular nitrene C–H insertion of *N*-tosyloxycarbamates.[9] Subsequently, these authors developed the intermolecular version of this catalysis.[116] In the presence of potassium carbonate and a catalytic amount of $[Rh_2(TPA)_4]$ (**6**), amination of benzylic, 2°, 3°, and 1° C–H bonds with oxycarbamate **30** were observed in good to high yields (Scheme 70). 2,2,2-Trichloroethyl and *N*-tosyl



Scheme 67



Scheme 68

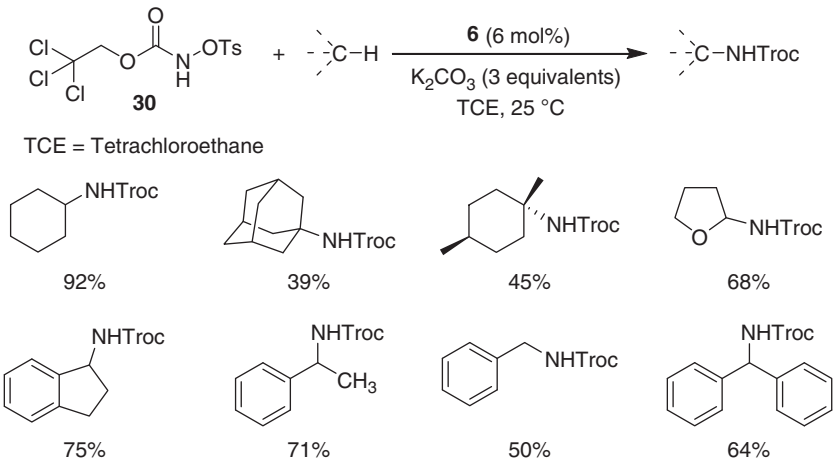


Scheme 69

substituents of the nitrene precursor were found to be crucial for achieving the reaction since other substituents led to low substrate conversions and low yields.

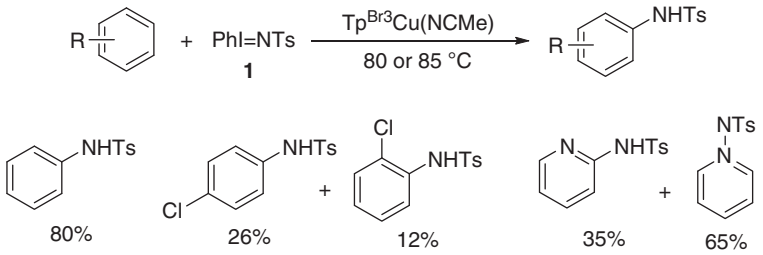
7.02.4.2.1.2 Nitrene insertion to sp^2 C–H bonds

Compared with the numerous works on nitrene insertion to sp^3 C–H bonds, successful examples of metal-catalyzed nitrene insertion to sp^2 C–H bond are comparatively sparse. In 2003, Pérez and coworkers reported examples of aromatic C–H amination with PhI=NTs (**1**) catalyzed by copper(I)–homoscorpionate complexes $Tp^{Br3}Cu(NCMe)$.[97] When benzene was used as substrate, the sp^2 C–H amination product was achieved in 80% yield. However, the use of chlorobenzene led to the formation of a mixture of two regioisomers (*ortho* and *para*) in 38% overall yield. The use of pyridine as a substrate led to the formation of zwitterionic



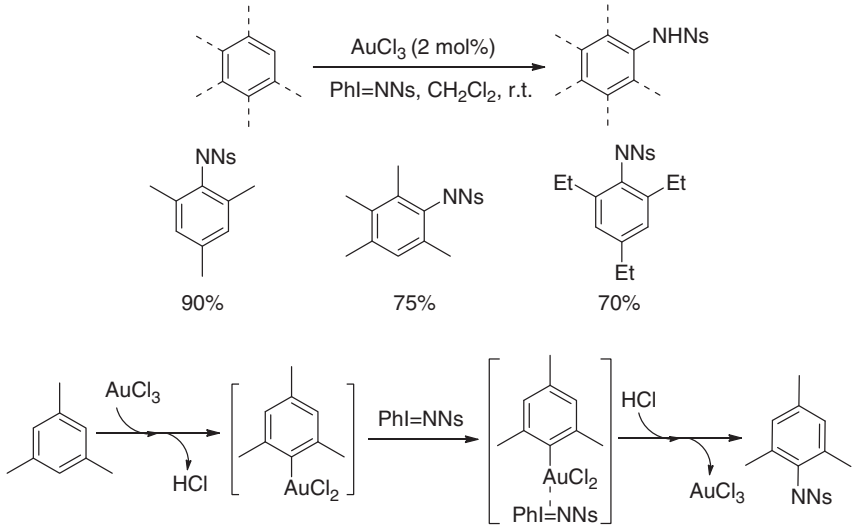
Scheme 70

compound $C_6H_5{}^+N{-}N^-Ts$ as the major product, and the nitrene insertion into the *ortho* C–H bond was a minor pathway. The overall yield was 35% (Scheme 71).



Scheme 71

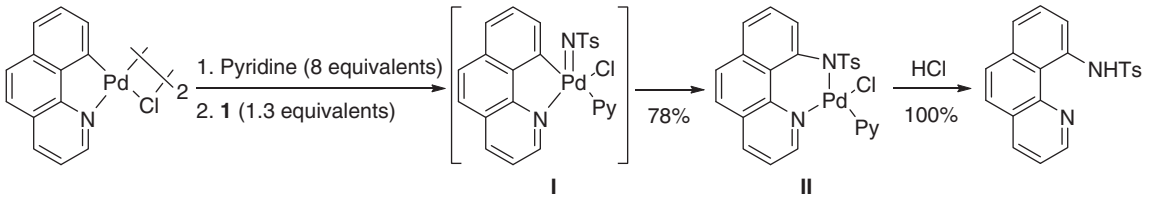
With PhI═NNs as nitrene source, $AuCl_3$ was reported to catalyze aromatic C–H amination of polyalkyl-substituted benzenes at room temperature in 60–90% yields (Scheme 72).[117] Less substituted benzenes and benzene itself were poor substrates giving the amination products in less than 5% yield. This $AuCl_3$-catalyzed C–H amination exhibited high chemoselectivity toward aromatic C–H bonds over 1° and 2° benzylic C–H bonds. The reaction of a mixture of mesitylene and mesitylene-d_{12} with PhI═NNs and $AuCl_3$ gave a k_H/k_D value of 1:1, suggesting that the step of C–H functionalization might not be rate-determining.



Scheme 72

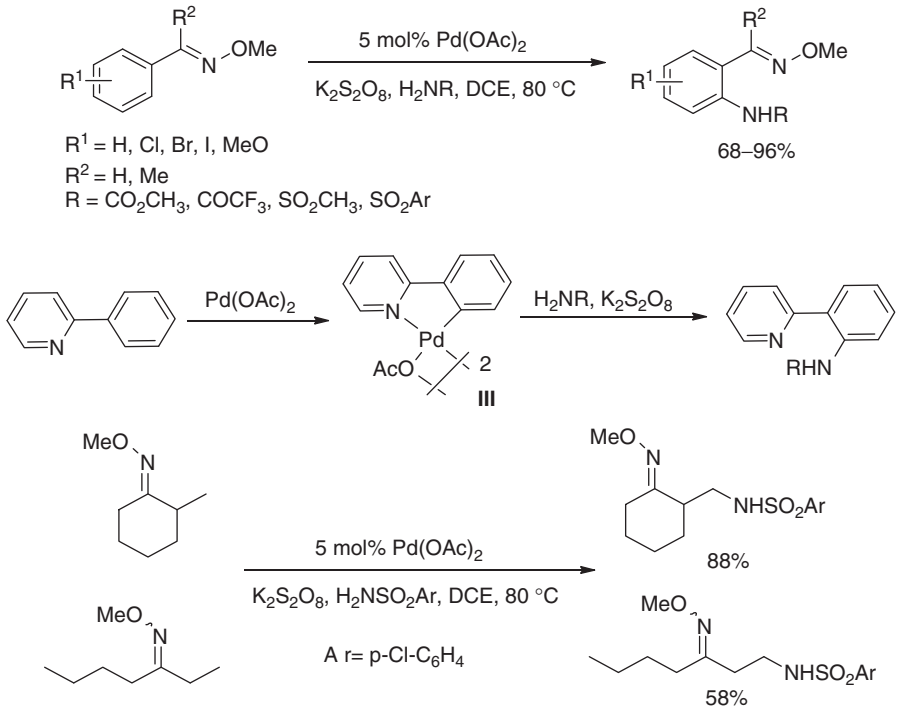
He and coworkers proposed a mechanism that involves aromatic C–H insertion by $AuCl_3$ to give arylgold(III) species, which subsequently reacts with PhI=NTs (**1**) to give the amination product.

By using the strategy of chelation-directed/assisted transition-metal-mediated C–H activation, Sanford and coworkers developed a stoichiometric palladium complex-mediated aromatic C–H bond amination via a palladacyclic intermediates (Scheme 73).[118] The reaction is proposed to proceed via a stepwise mechanism involving initial formation of Pd^{IV}–imido intermediate **I** by reacting palladacycle with PhI=NTs (**1**) and subsequent collapse of this intermediate to give a palladium amide complex **II**. Protonolysis of **II** with HCl gives the final C–H amination product.



Scheme 73

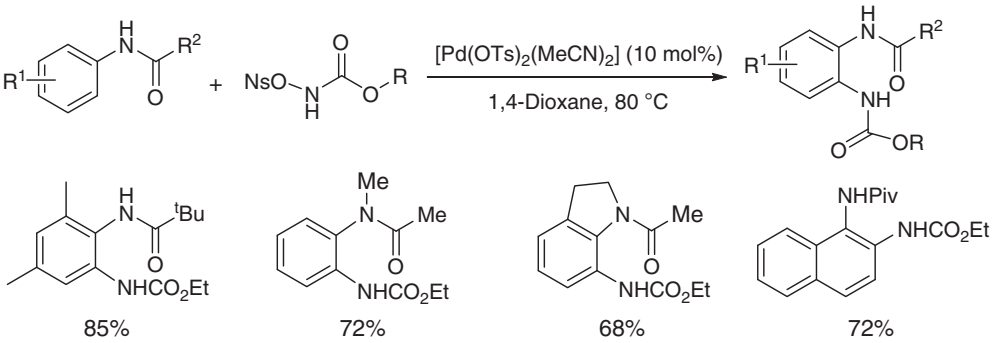
By using $K_2S_2O_8$ as oxidant and sulfonamides, carbamates, or carboxamides as nitrogen source, Yu and Che developed a catalytic aromatic C–H bond amination mediated by $Pd(OAc)_2$ (Scheme 74).[119] A range of 2-arylpyridines, *O*-methyl oximes derived from benzaldehyde, and acetophenone were found to undergo *ortho* C–H amination. The amination reaction is proposed to proceed via initial chelation-directed cyclopalladation to form **III**, and this is followed by nitrene insertion to the Pd–C bond. This protocol is also applicable to amination of sp^3 C–H bonds of aliphatic *O*-methyl oximes.



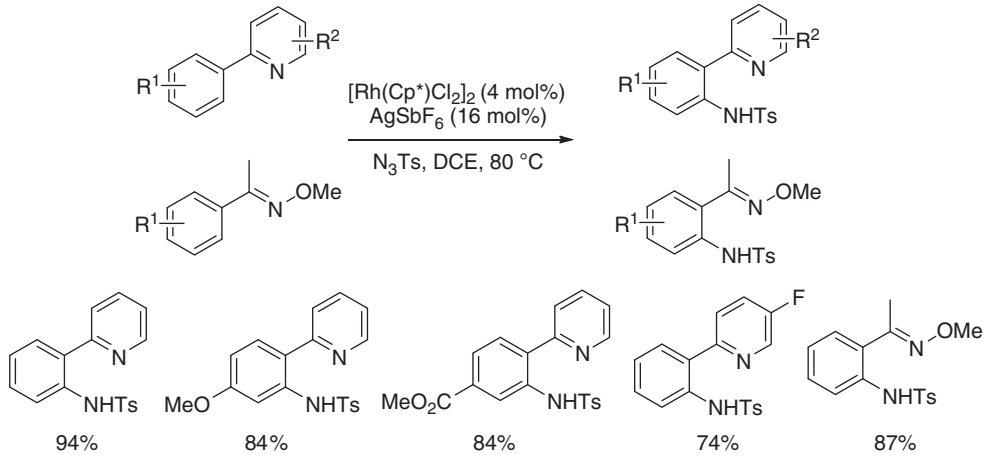
Scheme 74

With a similar strategy, Yu and coworkers developed a palladium-catalyzed intermolecular *ortho* C–H amination of anilides that could be used for the synthesis of 2-aminoanilines (Scheme 75).[120] In this reaction, *N*-nosyloxycarbamate was used as nitrene source and $[Pd(OTs)_2(MeCN)_2]$ was found to be more effective than $Pd(OAc)_2$ for the reaction.

Sulfonyl azides have been used as a nitrene source in $[Rh(Cp^*)Cl_2]_2$-catalyzed *ortho* C − H amination of 2-arylpyridines and *O*-methyl oximes derived from benzaldehyde and acetophenone, resulting in high yields and with excellent functional group tolerance (Scheme 76).[121] The reaction mechanism is similar to that proposed for the palladium catalysis via chelation-assisted C–H bond activation.

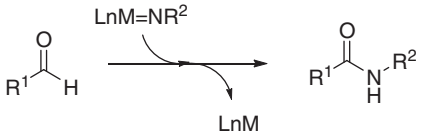


Scheme 75



Scheme 76

Transition metal-catalyzed nitrene insertion to the formylic C–H bond of aldehydes provides a straightforward synthetic route to amides (Scheme 77). In contrast to the conventional preparation of amides by coupling of activated carboxylic acid compounds with amines,[122] the direct nitrene insertion to formylic C–H bond of aldehydes has the advantage of avoiding the handling of labile activated acid intermediates.

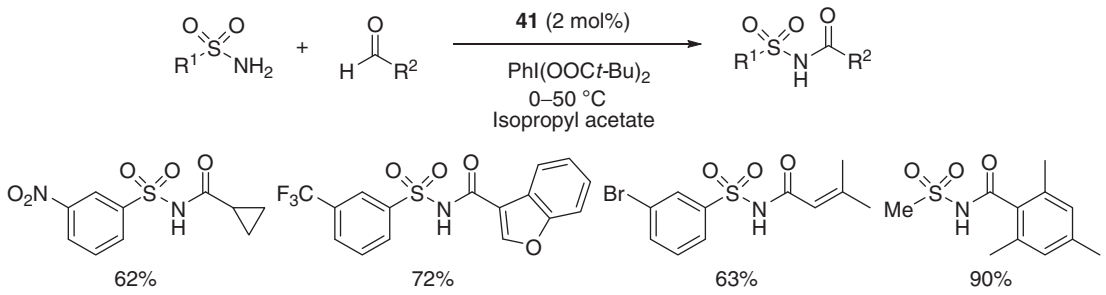


Scheme 77

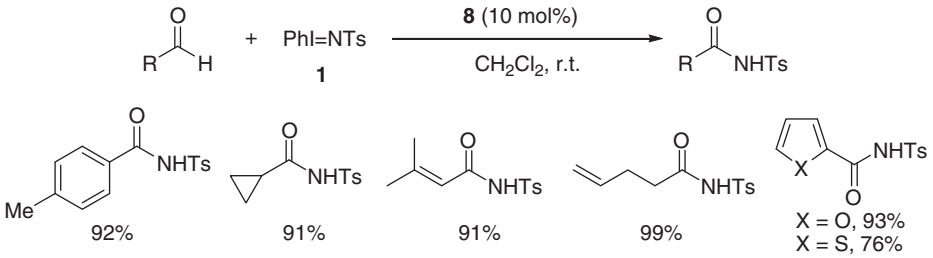
In 2007, Chan and coworkers reported the first intermolecular nitrene insertion to aldehydes catalyzed by $[Rh_2(esp)_2]$ (**41**). Various aromatic and aliphatic aldehydes were converted by '$RSO_2NH_2 + PhI(O_2tBu)_2$' to *N*-sulfonylcarboxamides in 62–98% yields (Scheme 78).[123] The reaction is highly chemoselective, favoring formylic C–H insertion over aziridination of C=C bond and aryl/benzylic C–H insertion. Competitive rate experiment of amidation of benzaldehyde and *p*-anisaldehyde revealed a slightly higher rate for *p*-anisaldehyde (1.5:1), suggesting that the nitrene insertion should proceed in a concerted asynchronous manner where positive charge is accumulated on the carbonyl in the transition state.

In 2008, Chan and coworkers found that ruthenium(II) porphyrin complex [Ru(TTP)(CO)] (**8**) can efficiently catalyze nitrene insertion to formylic C–H bond of aldehydes with PhI=NTs (**1**) to give *N*-acylsulfonamides in high yields (Scheme 79).[124] The reactive intermediate for this reaction is proposed to be bis(imidosulfonyl)ruthenium(VI) porphyrin complex generated from the reaction between **53** and **1** (Scheme 80) based on the reference of previous reports.[16,33]

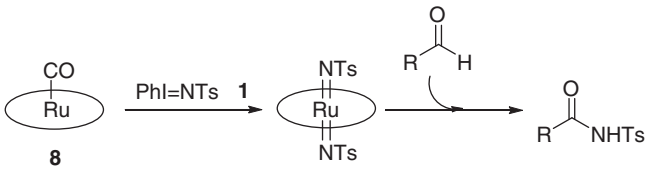
Following the report by Lebel and coworkers on alkene aziridination catalyzed by pyridyl–copper(II) complex,[59] Taylor and coworkers demonstrated the amidation of aldehydes catalyzed by copper pyridine complex generated *in situ* from copper(I) halide and pyridine using either PhI=NTs (**1**) or chloramine-T trihydrate (**3**) as the nitrene source (Scheme 81).[125] Compared



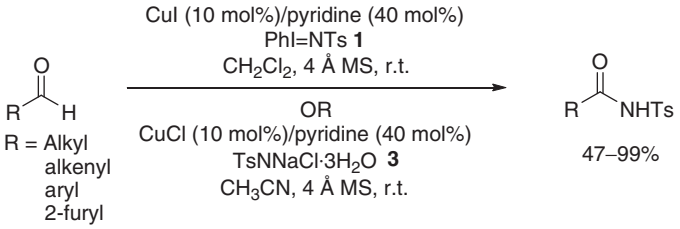
Scheme 78



Scheme 79



Scheme 80

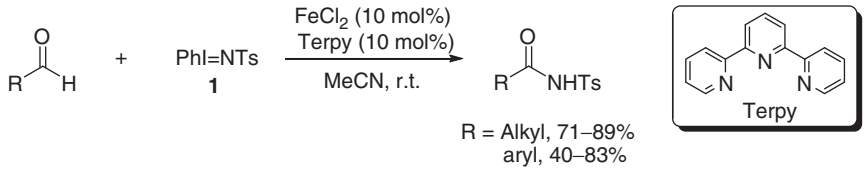


Scheme 81

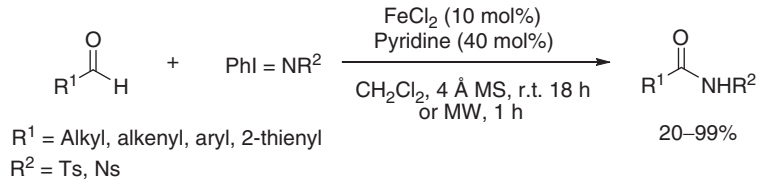
with ruthenium(II) porphyrin catalysts, this copper catalytic system is inexpensive with simplified procedure in removal of metal catalysts. Analysis on kinetic isotope effect revealed a k_H/k_D value of 3.8, suggesting the involvement of the insertion of a copper–nitrenoid species into formylic C–H bond of aldehyde as the rate-determining step in the reaction mechanism.

Iron(II) complex generated *in situ* by the reaction of $FeCl_2$ with 2,2′:6′,2″-terpyridine (terpy) was found to be effective catalyst for the amidation of aldehydes with PhI=NTs (**1**) (Scheme 82).[25] This catalytic system is more reactive for aliphatic aldehydes compared with aromatic ones, giving the corresponding amides in higher yields. ESI-MS analysis of the reaction mixture of '$FeCl_2$ + terpy + **1**' revealed a cluster peak attributed to $[Fe^{IV}(terpy)_2(NTs)]^{2+}$, indicating the possible involvement of Fe^{IV}=NTs species in the reaction mechanism.

A similar catalytic system using '$FeCl_2$ + pyridine' for amidation of aldehydes was reported by Chan and coworkers (Scheme 83).[126] This protocol afforded comparable yields to that obtained by ruthenium(II) porphyrin and CuI/pyridine systems. On microwave irradiation, the reaction time can be shortened from 18 h to 1 h with slightly improved yields. A proposed mechanism involving rate-determining insertion of iron–nitrene/imido group to aldehyde C–H bond is via an H-atom abstraction/radical rebound pathway based on a k_H/k_D value of 4.4 from the study of the kinetic isotope effect. This value is



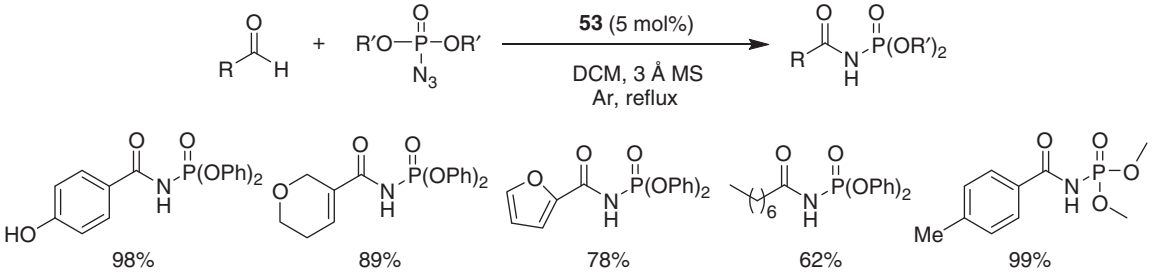
Scheme 82



Scheme 83

comparable to k_H/k_D values reported for the analogous nitrene/imido insertion into the dibenzyl ether in the presence of CuCl as catalyst[106] and [Ru(TMP)(NNs)$_2$]-mediated amidation of ethyl benzene,[16] where a radical process was proposed.

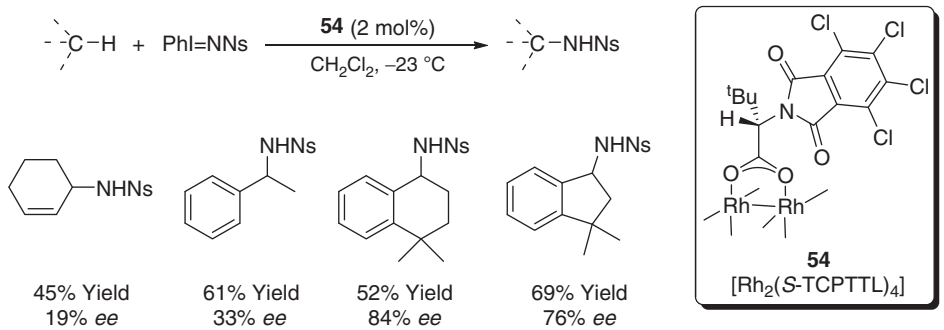
When phosphoryl azide was used as nitrene source, the nitrene insertion to aldehyde C–H bond would lead to *N*-acylphosphoramidates, which are present in a number of bioactive natural products. Che and coworkers found dichlororuthenium(IV) porphyrin complex [Ru^{IV}(TTP)Cl$_2$] (**53**) are superior than its Ru(II) analogs, dirhodium carboxylate and Cu(I) salt effecting the phosphoramidation in the yield up to 99% and with high chemoselectivity and excellent functional group tolerability (Scheme 84).[127]



Scheme 84

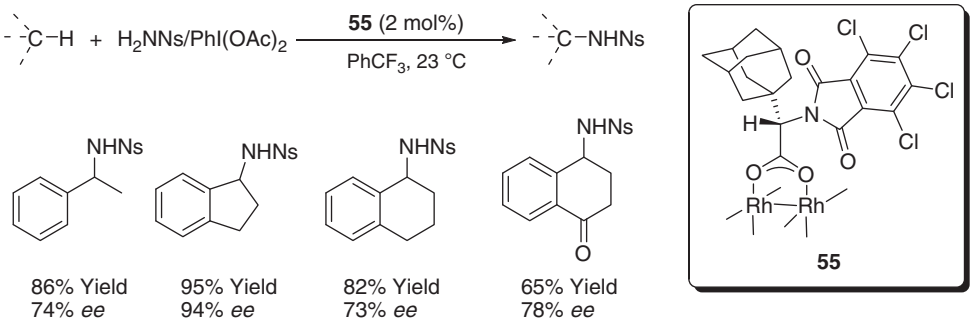
7.02.4.2.1.3 Asymmetric intermolecular C–H insertion

Compared with the extensive literature on enantioselective carbene C–H insertions, examples of asymmetric nitrene C–H insertion are comparatively sparse. In 1997, Müller and coworkers reported the first enantioselective intermolecular nitrene C–H insertion with *ee* values up to 33% using PhI=NNs as nitrene source and a chiral dirhodium(II) phosphate as catalyst.[128] Following this work, Hashimoto and coworkers reported enantioselective amination of benzylic and allylic C–H bonds catalyzed by a chiral dirhodium carboxylate (Scheme 85).[129] The dirhodium(II,II) complex [Rh$_2$(*S*-TCPTTL)$_4$] (**54**) bearing chlorinated ligand was found to be more effective than its parental counterpart [Rh$_2$(*S*-PTTL)$_4$] resulting in *ee* values up to 84%.



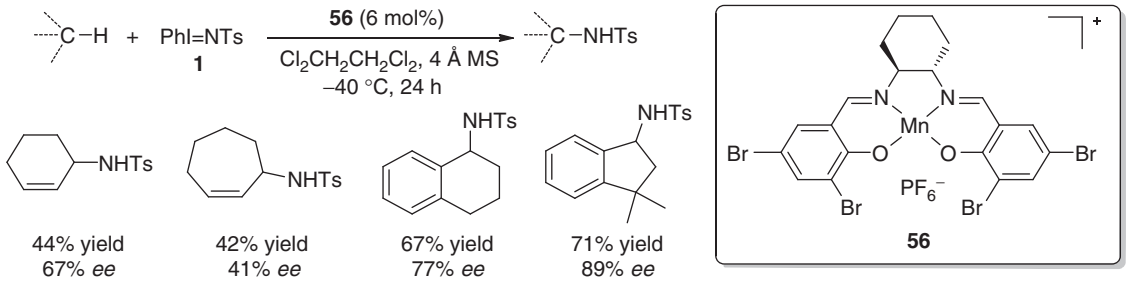
Scheme 85

Subsequently, Davies and coworkers developed a chiral dirhodium(II,II) carboxylate **55** bearing an adamantyl substituent for asymmetric nitrene C–H insertion (Scheme 86).[130] With $H_2NNs/PhI(OAc)_2$ as nitrene source, benzylic C–H amination was achieved in up to 95% yield and 94% enantioselectivity.



Scheme 86

In 2001, Katsuki and coworkers reported an enantioselective C–H amination of hydrocarbons catalyzed by a chiral manganese salen complex **56** (Scheme 87).[131] With PhI=NTs (**1**) as a nitrene source, allylic and benzylic C–H bonds were aminated with *ee* values in up to 89%. The cationic $[Mn(salen)]^+$ catalyst (H_2salen = *N*,*N*′-bis(3,5-dibromosalicylidene)-1,2-cyclohexanediamine) has been found to be more effective than its neutral counterpart in terms of enantioselectivity and yield.



Scheme 87

Ruthenium and manganese catalysts supported by the Halterman porphyrin ligand exhibited moderate enantioselectivity in catalytic benzylic C–H amination with PhI=NTs (**1**) or $H_2NSO_2R/PhI(OAc)_2$ as nitrene source (Scheme 88). The *ee* values of the amination products were determined to be 46–56% (Scheme 88).[70]

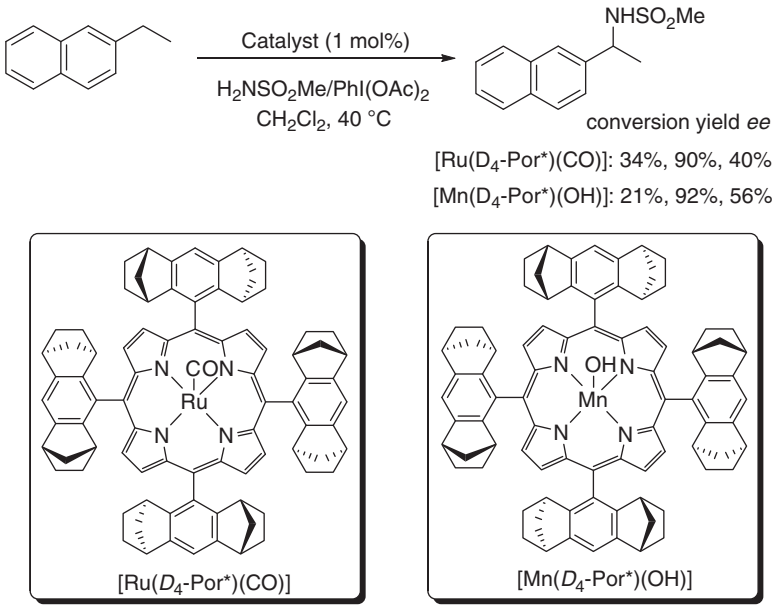
To achieve C–H amination in high yield and enantioselectivity, hydrocarbons are often used in excess. In 2006, Dauban and coworkers reported an efficient diastereoselective intermolecular C–H amination under stoichiometric conditions and using an enantiomeric pure nitrene precursor (*S*)-*N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide and a chiral dirhodium carboxylate $[Rh_2(S\text{-NTA})_4]$ (**57**) derived from alanine as catalyst (Scheme 89).[132] The reaction could occur even at −35 °C. Various benzylic and allylic C–H bonds were aminated in yields up to 91% and diastereoselectivity up to 99%. The strongly matched effect between sulfonimidamide and rhodium complex **57** was crucial to the high yield and excellent diastereoselectivity of the products obtained. Such a cooperative effect has also been found applicable to asymmetric benzylic C–H amination involving kinetic resolution of the racemic sulfonimidamides. Under conditions of kinetic resolution, benzylic C–H amination were achieved in 56–80% yields (based on benzylic substrates) and with excellent diastereoselectivities (88–99%) and enantioselectivities (97–99%). A subsequent study revealed that the '(*S*)-*N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide + **57**' protocol can also be extended to complex substrate such as terpenes giving the products in 68–91% yields and 90–96% *de* values.[133]

Using optically active hydrocarbons as substrates, a diastereoselective C–H amination catalyzed by achiral catalyst was reported by Bach (Scheme 90).[134] Aryl-alkanes bearing a stereogenic center at the *β*-position reacted with $H_2NTces/PhI(OAc)_2$ and $[Rh_2(esp)_2]$ (**41**) in a diastereoselective manner giving C–H amination products in 80/20–95/5 *dr* values. No racemization of a stereogenic center in the *β*-position was observed.

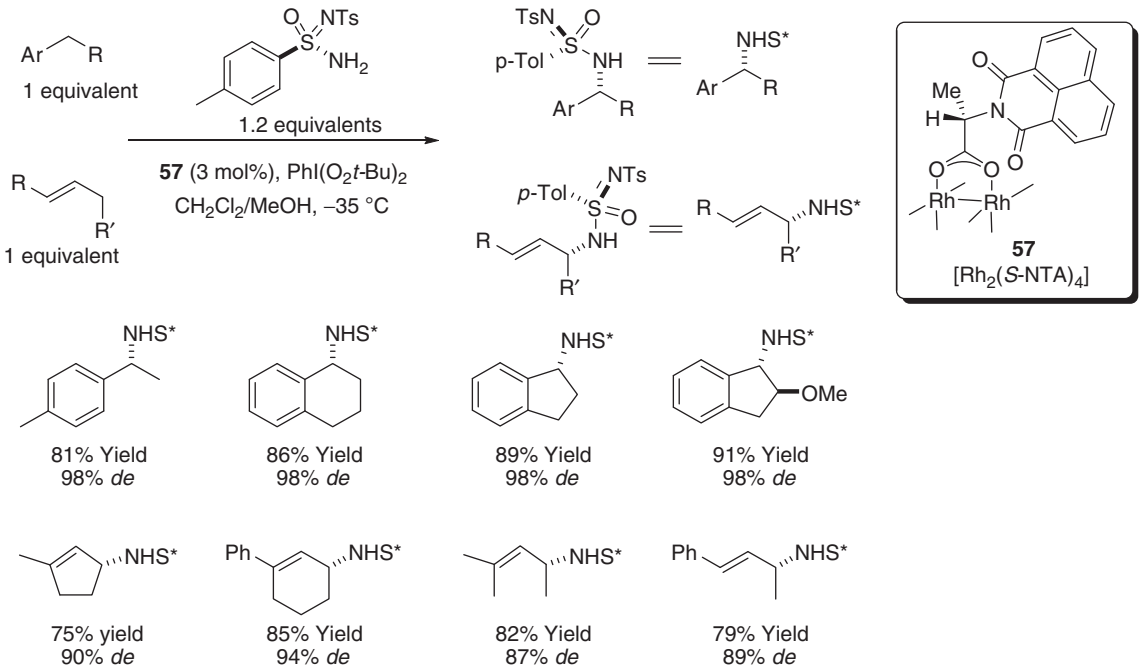
7.02.4.2.2 Intramolecular C–H insertion

7.02.4.2.2.1 Carbamates and sulfamate esters

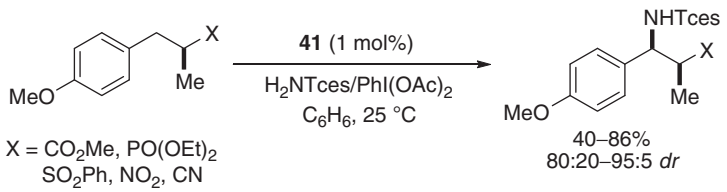
Compared with its intermolecular analogs, transition metal-catalyzed intramolecular nitrene C–H insertion reactions usually display high efficacious and selectivity and have been used in total synthesis of a number of complex natural products. In 2001, Du Bois reported a dirhodium(II,II)-catalyzed intramolecular C–H amination of carbamates to form five-membered oxazolidinones (Scheme 91), the latter can be readily hydrolyzed to give 1,2 amino alcohols.[135] With $[Rh_2(TPA)_4]$ (**6**) as catalyst and



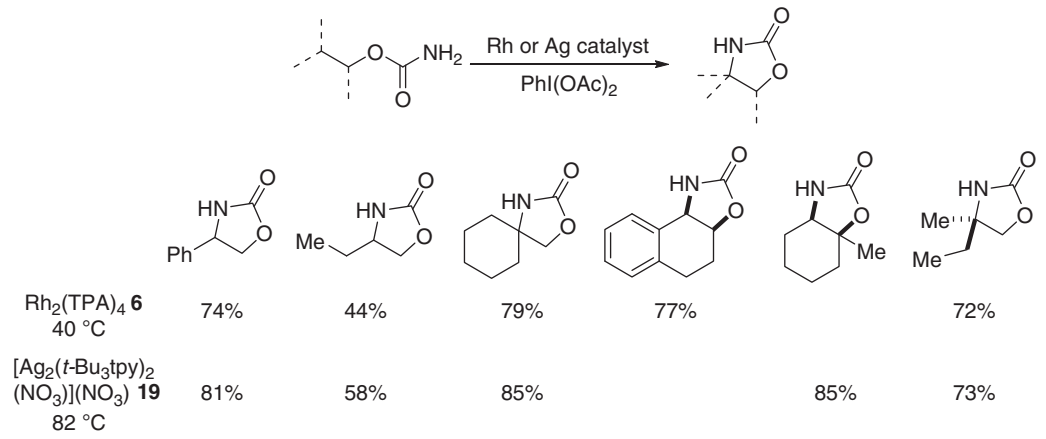
Scheme 88



Scheme 89



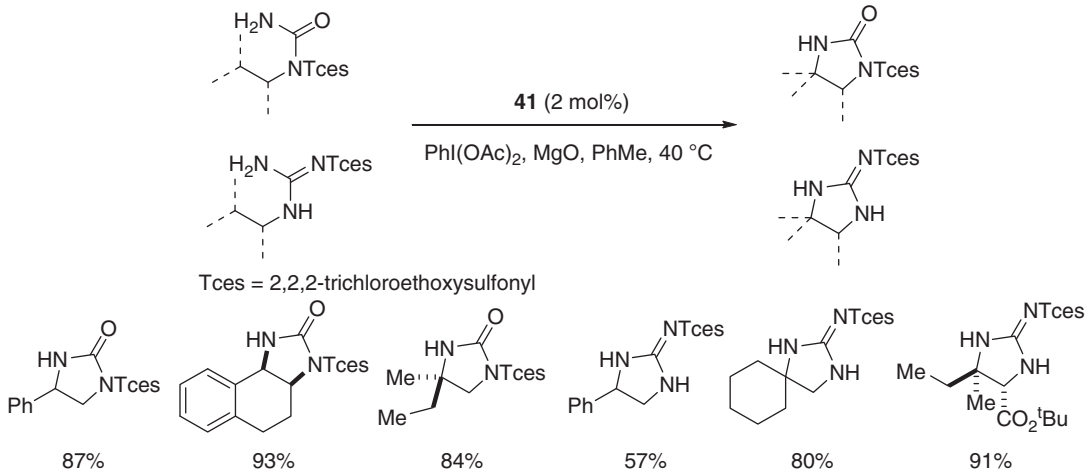
Scheme 90



Scheme 91

$PhI(OAc)_2$ as oxidant, both 2° and 3° C–H bonds of carbamates can be aminated in excellent diastereoselectivity and stereospecificity. The observed stereospecific C–H amination of chiral carbamates has been rationalized by concerted C–H insertion of a singlet nitrene intermediate. A disilver(I) complex $[Ag_2(t\text{Bu}_3\text{tpy})_2(NO_3)](NO_3)$ (**19**) generated *in situ* from $AgNO_3$ and *t*-Bu_3tpy was also found effective for the oxidative cyclization with similar diastereoselectivity and stereospecificity, albeit a higher temperature (82 °C) was required.[136]

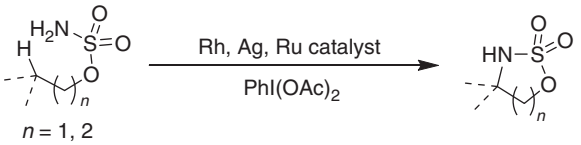
Subsequently, Du Bois extended the Rh_2(II,II)-catalyzed intramolecular C–H amination of carbamates to the synthesis of imidazolidin-2-ones and 2-aminoimidazolines, both of which are prevalent in natural compounds and pharmaceuticals, by using *N*-trichloroethoxysulfonyl-protected urea and guanidine as nitrogen source (Scheme 92).[137] The electron-withdrawing 2,2,2-trichloroethoxysulfonyl (Tces) substituent of the urea and guanidine is crucial for the reactions to have high yields. Other substituents such as tosyl and carbonyl groups were found to cause complication of the reaction. $[Rh_2(esp)_2]$ (**41**) proved to be an effective catalyst for the intramolecular C–H amination giving cyclic urea and guanidine compounds in 31–93% yields.

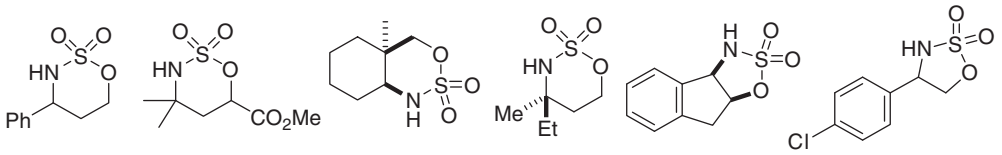


Scheme 92

Different from carbamates which preferentially give oxazolidinones with five-membered ring via intramolecular amination of β C–H bond, sulfamate esters have a strong tendency to form six-membered ring products through γ C–H insertion. This selectivity is ascribed to the elongated S–O and S–N bonds and the obtuse angle of N–S–O in sulfamate. When γ C–H bond is not available in sulfamate, formation of the five-membered ring compounds oxathiazinanes via β C–H insertion becomes possible. $[Rh_2(OAc)_4]$,[36,78] disilver(I) complex $[Ag_2(t\text{Bu}_3\text{tpy})_2(NO_3)](NO_3)$ (**19**)[136] and ruthenium porphyrin $[Ru^{II}(F_{20}\text{-TPP})(CO)]$ (**39**)[76] have been shown to be effective catalysts for intramolecular C–H amination of sulfamate esters. With $PhI(OAc)_2$ as oxidant, nitrene insertion to benzylic, 2° and 3° C–H bonds take place in diastereoselective and stereospecific manner (Scheme 93).

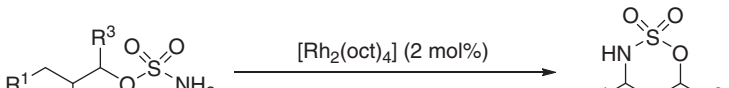
A systematic study on diastereoselective C–H amination of chiral sulfamate esters was reported by Du Bois. With $[Rh_2(oct)_4]$ as catalyst, various substituted chiral sulfamate esters underwent intramolecular C–H amination with high diastereoselectivities (Scheme 94).[138] A chiral transition state, in which the equatorial C–H insertion is favored over axial C–H insertion, was proposed to account for the high diastereoselectivity and product conformation.

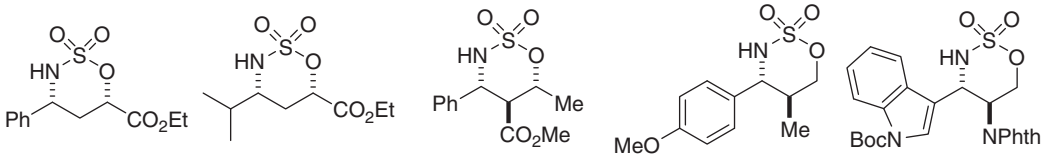




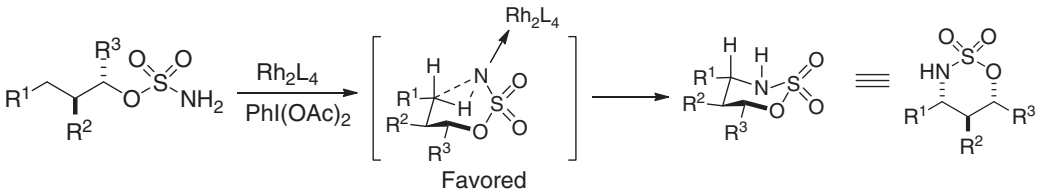
$[Rh_2(OAc)_4]$	84%	86%	85%	91%	60%	
19	87%			90%	65%	
39	77%	76%	88%	72%	61%	69%

Scheme 93





91%, *dr* = 15:1 | 55%, *dr* = 8:1 | 87%, Single isomer | 85%, *dr* = 20:1 | 85%, *dr* = 12:1



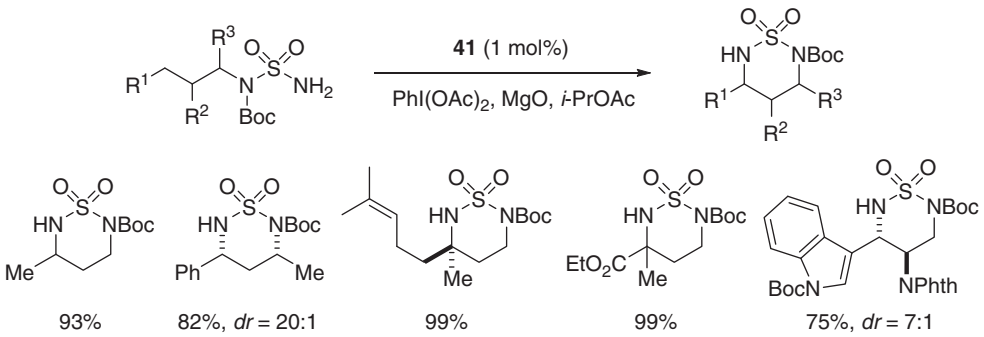
Scheme 94

Similar to sulfamate esters, sulfamides were found to undergo intramolecular C–H amination to afford six-membered ring heterocyclic products. In the presence of $PhI(OAc)_2$ and 1 mol% $[Rh_2(esp)_2]$ (**41**), amination of 3°, benzylic, and unactivated 2° C–H bonds of sulfamides took place with high efficiency and excellent chemoselectivity, diastereoselectivity, and stereospecificity (Scheme 95).[139]

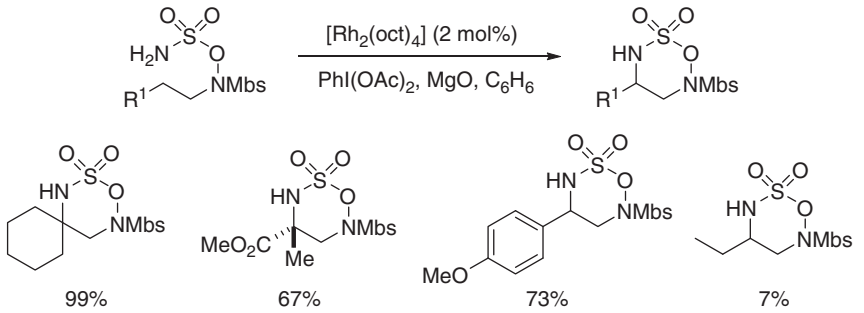
1,2-Diamine is a valuable building block in organic synthesis. By using intramolecular C–H amination of *N*-alkylhydroxylamines derived sulfamates, Du Bois developed an efficient synthesis of [1,2,3,6]-oxathiadiazinane-2,2-dioxide heterocycles, the latter can be readily converted to protected 1,2-diamines under reductive conditions (Scheme 96).[140] Tertiary and benzylic C–H bonds were reactive with the reactions in 67–99% product yields, whereas the unactivated 2° C–H bonds were less reactive giving corresponding products in low yields.

Dirhodium(II,II) carboxylate-catalyzed intramolecular amination of ethereal α C–H bond of sulfamate esters give oxathiazinane N,O-acetals, the latter can serve as iminium ion equivalent to react with various nucleophiles including alkynylzincs, allylsilanes, and silyl enol ethers leading to more complex oxathiazinanes (Scheme 97).[141] The two steps sequence is high-yielding and highly diastereoselective.

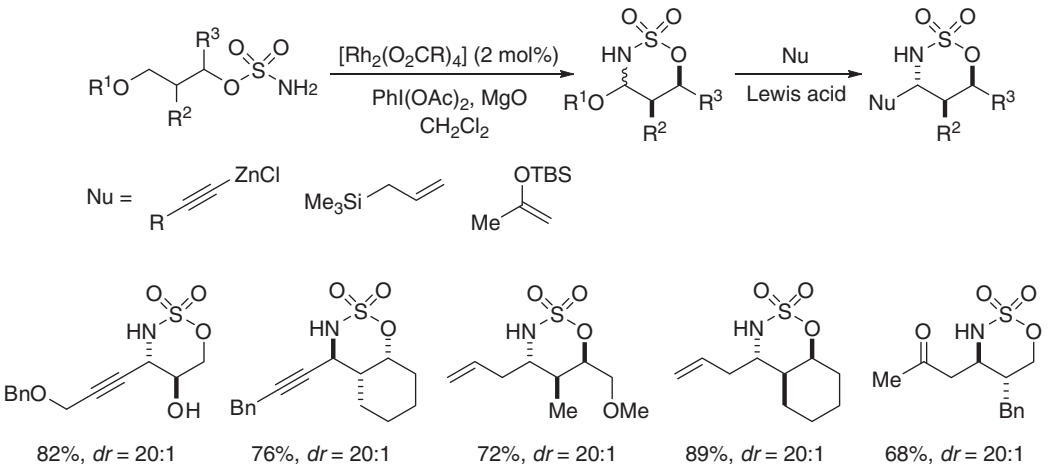
After the work by Che[3,76,94] and Blakey[142] revealing that ruthenium(II) complexes of porphyrin and pybox ligands are effective catalysts for C–H amination reactions, Du Bois developed a mixed-valent paddlewheel ruthenium complex tetrakis(2-oxypyridinato)diruthenium(II,III) chloride, $[Ru_2(hp)_4Cl]$, which can efficiently and selectively catalyze intramolecular allylic C–H amination with bis(homoallylic) sulfamate esters.[143] The preference to allylic C–H amination is in contrast to the



Scheme 95



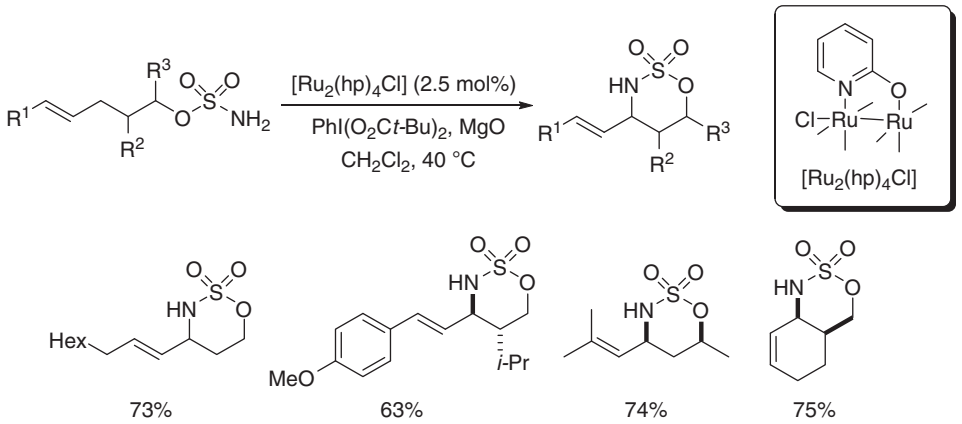
Scheme 96



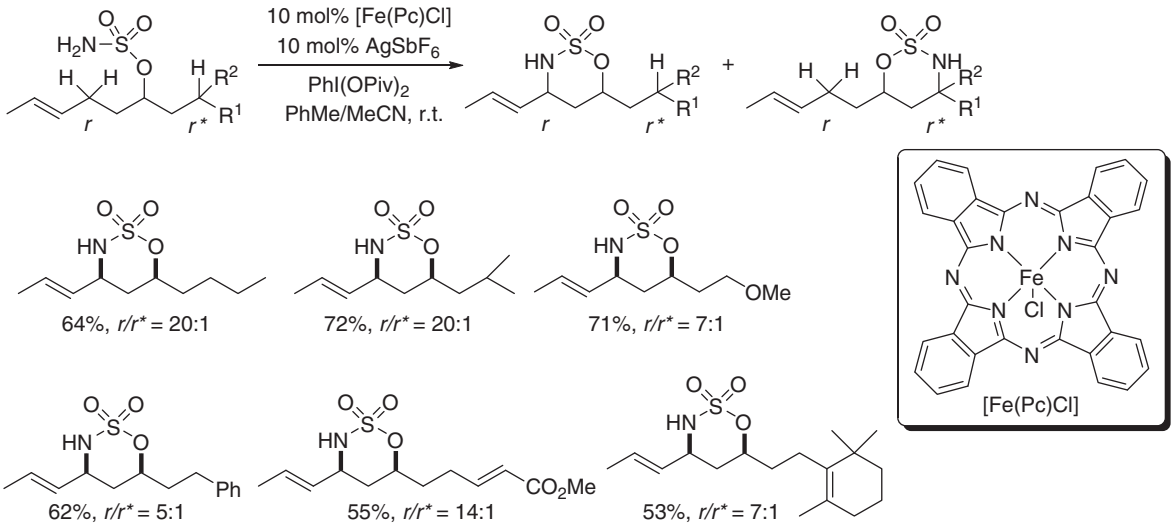
Scheme 97

reactions catalyzed by dirhodium(II,II) carboxylates which favor aziridination over C–H amination (Scheme 98). Computational and experimental studies revealed that the $[Ru_2(hp)_4Cl]$-catalyzed C–H amination proceeds via stepwise radical pathway similar to that proposed by Che for the analogs ruthenium porphyrin-catalyzed reactions.

A study by White and coworkers revealed that [Fe(Pc)Cl]/$AgSbF_6$ (Pc = phthalocyaninato) is a highly chemo- and regioselective catalyst favoring allylic C–H amination over aziridination and 3° and 2° aliphatic, ethereal, or benzylic C–H bond amination of sulfamate esters (Scheme 99).[144] For polyolefinic substrates, allylic C–H amination selectively takes place at the most electron-rich, least sterically hindered site. The iron-catalyzed C–H amination is proposed to proceed via a hydrogen atom abstraction/radical recombination stepwise mechanism.



Scheme 98



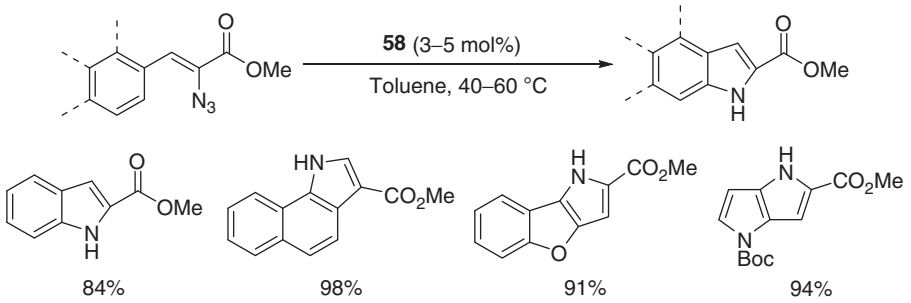
Scheme 99

7.02.4.2.2.2 Organic azides

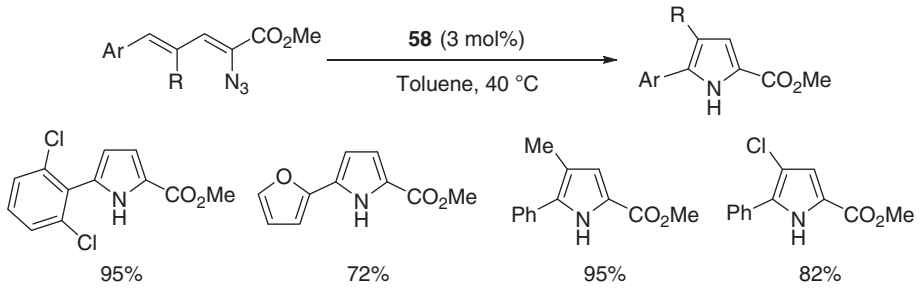
Under thermal (~ 200 °C) and photochemical conditions, aryl azides and vinyl azides would loss N_2 to generate arylnitrene and vinylnitrene both of which are capable of inserting into proximal aromatic and vinylic sp^2 C–H bonds to form indoles. However, handling potentially explosive azides under such harsh reaction conditions could be dangerous. In 2007, Driver and coworkers was the first to show that dirhodium carboxylates are effective catalysts to decompose vinyl azides under mild conditions.[145] At 40–60 °C, a variety of 1-azido-2-arylvinylazides were converted to corresponding indoles and pyrroles in 71–98% yields in the presence of catalytic amount of dirhodium(II) perfluorobutyrate $[Rh_2(O_2CC_3F_7)_4]$ (**58**); a metal-associated vinyl nitrene intermediate was proposed as depicted in Scheme 100. Electron-deficient dirhodium catalyst **58** was found to be more reactive than $[Rh_2(OAc)_4]$ for the similar reactions.

Complex **58** has also been used in the synthesis of a range of 2,5-disubstituted and 2,4,5-trisubstituted pyrroles from dienyl azides in good to high yields (Scheme 101).[146] Besides **58**, copper(II) triflate and zinc iodide proved to be competent catalysts to readily catalyze/mediate pyrrole formation at room temperature.

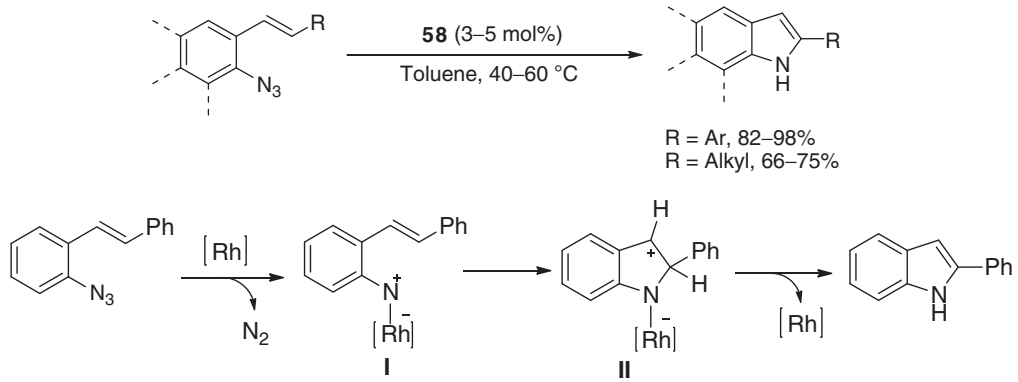
Subsequently, Driver extended the protocol to *ortho*-vinyl aryl azides. With complex **58** as catalyst, *ortho*-vinyl aryl azides undergo intramolecular amination of vinylic sp^2 C–H bond to give indoles in 61–98% yields (Scheme 102).[147] Functionalization of the vinylic C–H bond is proposed to proceed in a stepwise fashion with C–N bond formation preceding C–H bond cleavage through intermediate **II** rather than direct concerted insertion of nitrene to vinylic C–H bond (Scheme 102).[148] This stepwise mechanism is supported by a control reaction of *β*,*β*-diphenyl-substituted stryryl azide the latter resulted in the formation of 2,3-diphenyl indole via 2,3-phenyl shift (Scheme 103). This 2,3-phenyl shift implicates the intermediacy of cation **III**. When biaryl azides were used as substrates, the synthesis of carbarzoles could be achieved in high yields via *ortho*-amination of aromatic C–H bond (Scheme 104).



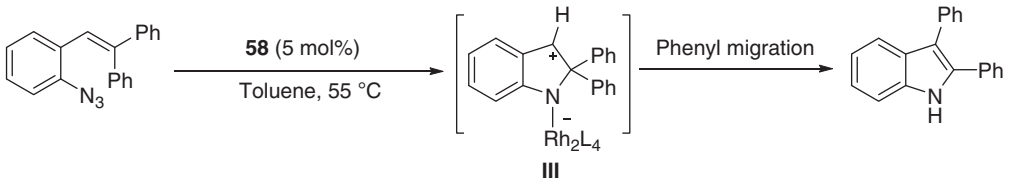
Scheme 100



Scheme 101

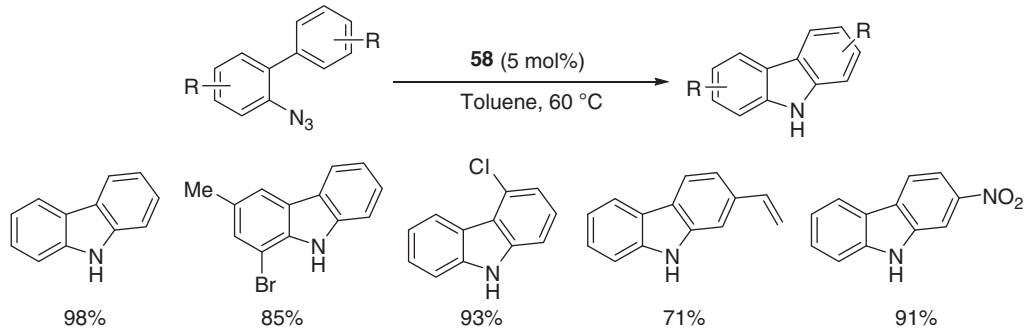


Scheme 102

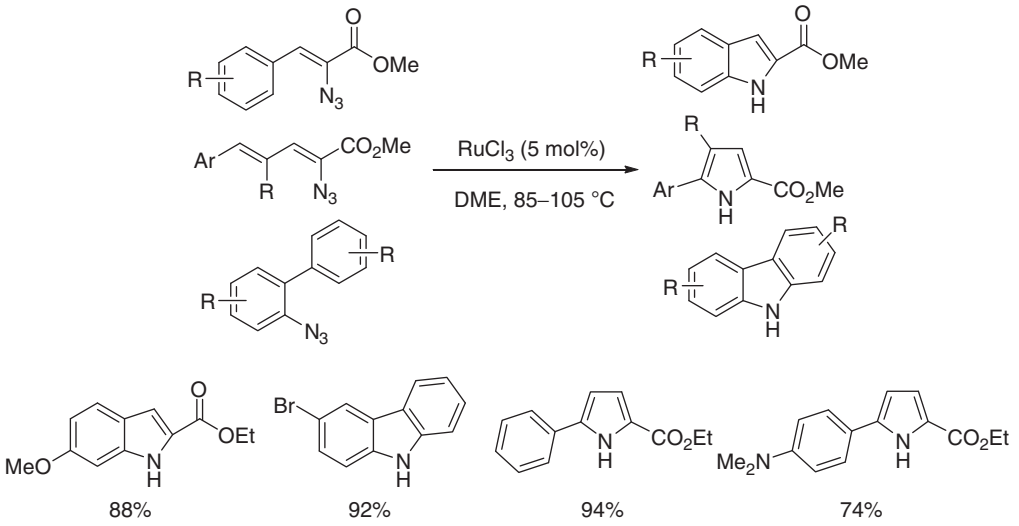


Scheme 103

$RuCl_3$ has also been found to be effective catalyst for intramolecular C–H amination of *ortho*-aryl phenyl azides, 1-azido-2-arylvinyl azides, and 1-azido-1,3-butadienes giving carbazoles (91–96% yields), indoles (35–88%), and pyrroles (74–94%), respectively (Scheme 105).[149] Compared with dirhodium(II,II) carboxylate and its derivatives, $RuCl_3$ is less active requiring a higher temperature to effect the reaction. Computational and experimental studies revealed that the $RuCl_3$-catalyzed reaction proceeds via a two-step process involving electrocyclization, which is similar to mechanism of related reactions catalyzed by Rh_2(II,II) proposed by Driver and coworkers.[148]

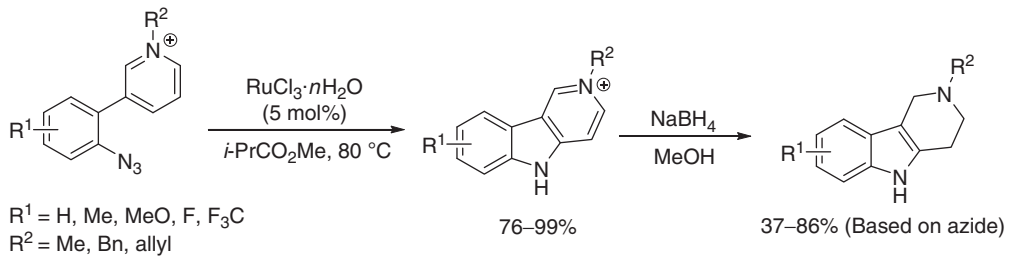


Scheme 104



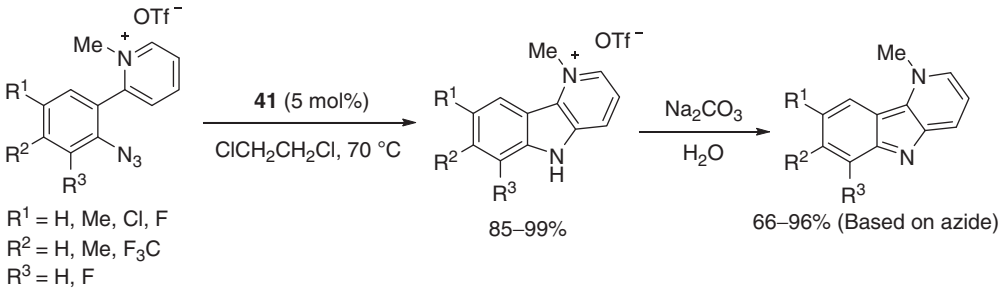
Scheme 105

Carbolines and tetrahydrocarbolines are structural motifs commonly found in bioactive natural products and pharmaceuticals. 3-Pyridyl-substituted aryl azides can be converted by $RuCl_3 \cdot nH_2O$ to γ-carbolinium ions in good to high yields via intramolecular C–H amination; the γ-carbolinium ions are readily reduced by $NaBH_4$ to γ-tetrahydrocarboline (Scheme 106).[150] This Ru-catalyzed reaction is regioselective as γ-tetrahydrocarbolines are the only products detected. However, complex **58** $[Rh_2(O_2CC_3F_7)_4]$ is a less selective catalyst than $RuCl_3 \cdot nH_2O$ giving a mixture of two regioiosmers in a ratio of 75:25.

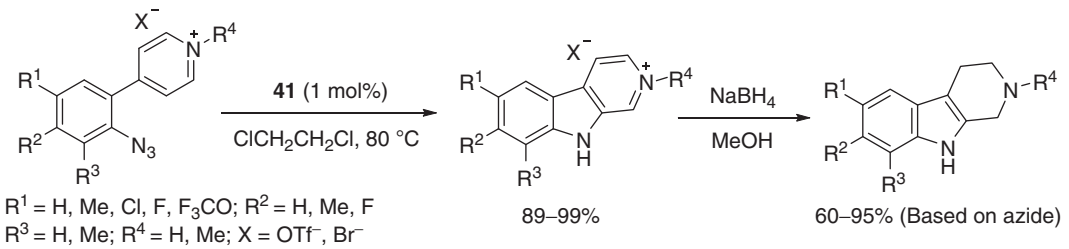


Scheme 106

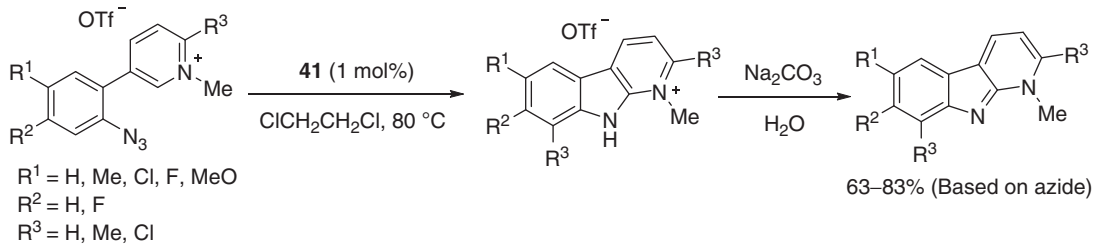
Although $RuCl_3 \cdot nH_2O$ can selectively catalyze/mediate the conversion of 3-pyridyl-substituted aryl azides to γ-carbolinium ions, extension of this catalysis to the synthesis of other carboline isomers was not successful. Driver and coworkers reported that $[Rh_2(esp)_2]$ (**41**) is an effective catalyst for the conversion of 2-pyridyl, 3-pyridyl, and 4-pyridyl-substituted aryl azides to corresponding δ-, β-, or α-carbolinium ions in good to high yields, respectively. Deprotonation of the carbolinium ions using aqueous Na_2CO_3 gave corresponding carbolines (Schemes 107–109).[151] It is noteworthy that 3-pyridyl-substituted aryl azides, which could be transformed to γ-carbolinium ions under the conditions of $RuCl_3 \cdot nH_2O$ catalysis, were found to convert to



Scheme 107

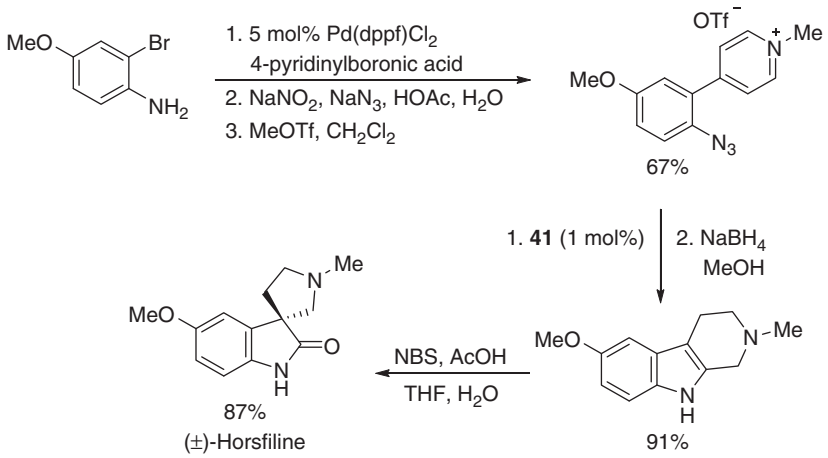


Scheme 108



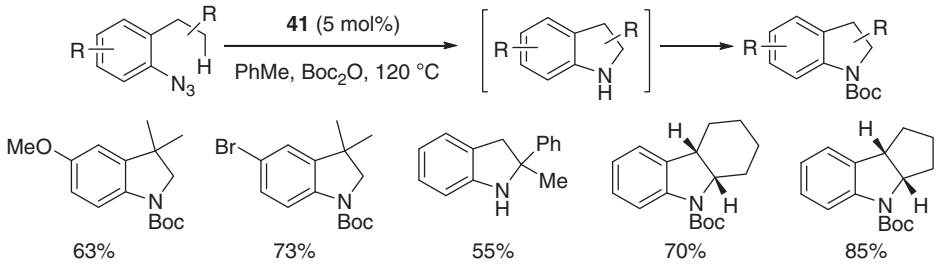
Scheme 109

α-carbolinium ions exclusively when **41** was used as catalyst. The synthetic utility of the $[Rh_2(esp)_2]$ (**41**) catalysis has been illustrated in a concise total synthesis of (±)-horsfiline in a 53% yield via six steps using the commercially available 2-bromo-4-methoxyaniline as starting material (Scheme 110).



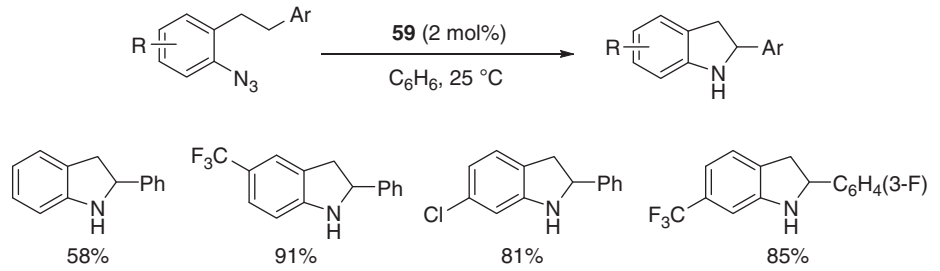
Scheme 110

Besides aromatic C–H insertion, aryl nitrenes can also undergo insertion to saturated C–H bonds in the presence of transition metal catalysts. With **41** as catalyst, intramolecular C–H amination of *ortho*-alkyl-substituted aryl azides afforded indolines in good to high yields (Scheme 111).[152] Aryl azides containing electron-rich and electron-deficient substituents could be used as nitrene sources for the generation of reactive metal–nitrene intermediates for subsequent intramolecular C–H amination reactions. In contrast, the intermolecular C–H amination of organic azides typically requires the nitrene to have an electron-withdrawing group. The yields of indolines from *ortho*-alkyl-substituted aryl azides could be improved by *in situ* protection of the nitrogen atom of indolines with Boc; this protection prevents indolines from oxidative decomposition. Single *cis*-isomers were obtained from substrates bearing *ortho*-cyclopentyl or cyclohexyl groups, this diastereoselectivity can be accounted for by preferential reaction of reactive rhodium-nitrene intermediate with the *syn*-C – H bond of cyclopentyl or cyclohexyl groups.



Scheme 111

Complex [(cod)Ir(OMe)]$_2$ (**59**) was found to catalyze intramolecular benzylic C–H amination of *ortho*-homobenzyl-substituted aryl azides at 25 °C in up to 93% yields (Scheme 112).[153] Although **59** displayed substantially higher catalytic activity than [$Rh_2(O_2CC_3H_7)_4$] (**58**) which failed to catalyze the reaction even at 100 °C, no C–H amination of *ortho*-alkyl-substituted aryl azides was observed under similar conditions of the iridium catalysis.

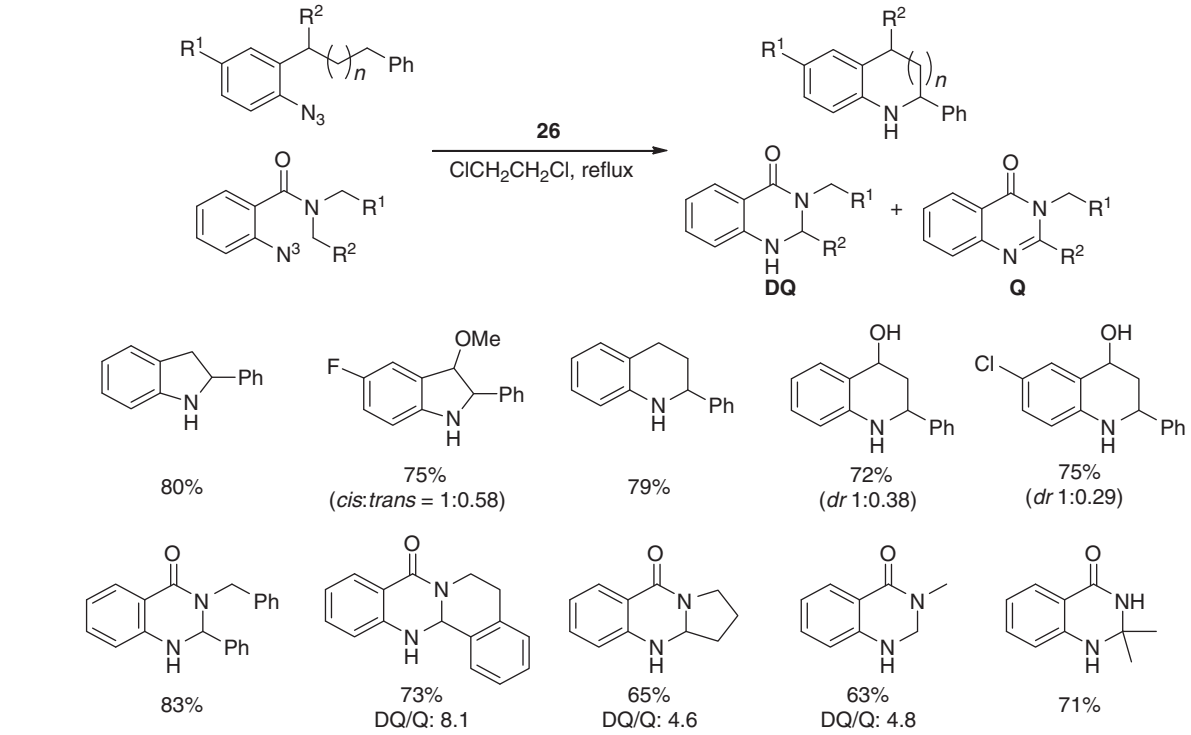


Scheme 112

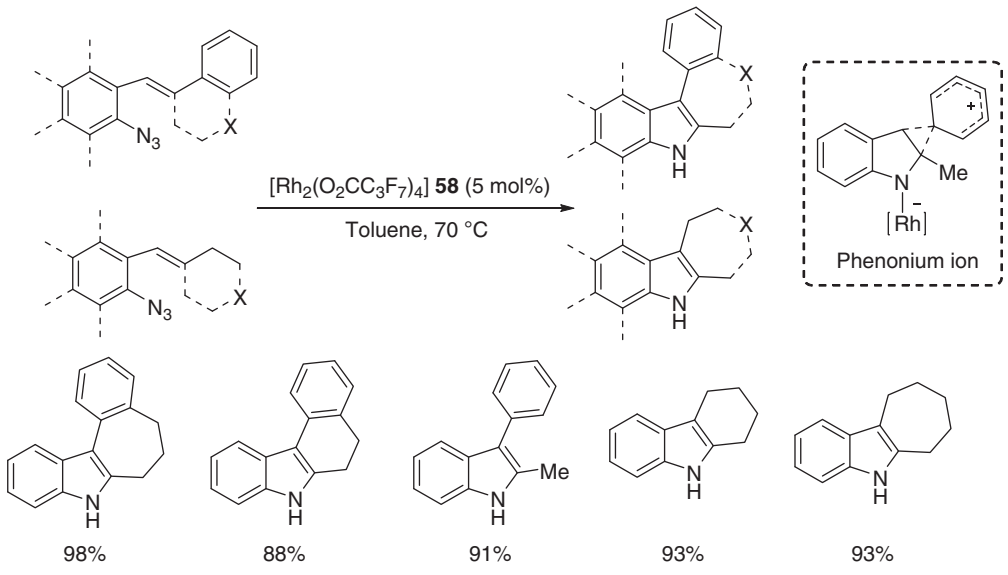
A study by Che and coworkers revealed that [Fe(F_{20}-TPP)Cl] (**26**) is an efficient catalyst for intramolecular amination of saturated C–H bonds of aryl azides leading to the formation of various alkaloids in good yields.[154] The amination of benzylic C–H bond of *ortho*-azido-alkylbenzenes gave indolines and tetrahydroquinolines in 72–81% yields with moderate diastereoselectivities (*dr* = 2–4:1) (Scheme 113). Intramolecular amination of the 2°, 3°, benzylic C–H bonds of *ortho*-azidobenzamide compounds gave dihydroquinazolinones (**DQ**) as the major products (Scheme 113). Formation of quinazolinones (**Q**) was observed along with the dihydroquinazolinones (DQ/Q = 3.7–8.1:1). In the absence of such C–H bonds, amination of 1° C–H bond was found in 63% yield.

When *β*,*β*-disubstituted stryryl azides without *β*-vinylic hydrogen atom(s) were used as substrates, 2,3-disubstituted indoles were obtained via a migratory process (Scheme 114).[155] [$Rh_2(esp)_2$] (**41**) was found to be an effective catalyst for converting a range of *β*,*β*-disubstituted stryryl azides to 2,3-disubstituted indoles in 78–98% yields. Aryl groups were found to migrate more readily than the alkyl groups. This selectivity can be accounted for by the formation of a phenonium ion intermediate. A subsequent extensive study on the effect of substituent on the selectivity revealed the relative order of migratory aptitude is alkyl < aryl < amide < H < sulfonyl < ketone < nitro. Utilizing preferential migration of electron-withdrawing groups over hydrogen, the selective synthesis of 3-substituted indoles from *β*-substituted styryl azides were achieved good to high yields (Scheme 115).[156]

In the presence of a stoichiometric amount of CuI, thermal and photochemical decomposition of 3-(2-azidobenzylidene)-lactams yield a range of fused indoles in 55–88% yields (Scheme 116). In line with the order of migratory aptitude observed in Rh catalysis, only the 1,2-migration of the carbonyl group was observed in the reaction. The reaction is proposed to involve cyclization via reaction of Cu-nitrene with double bond and subsequent 1,2 shift of carbonyl group, similar to mechanism proposed by Driver.[156]



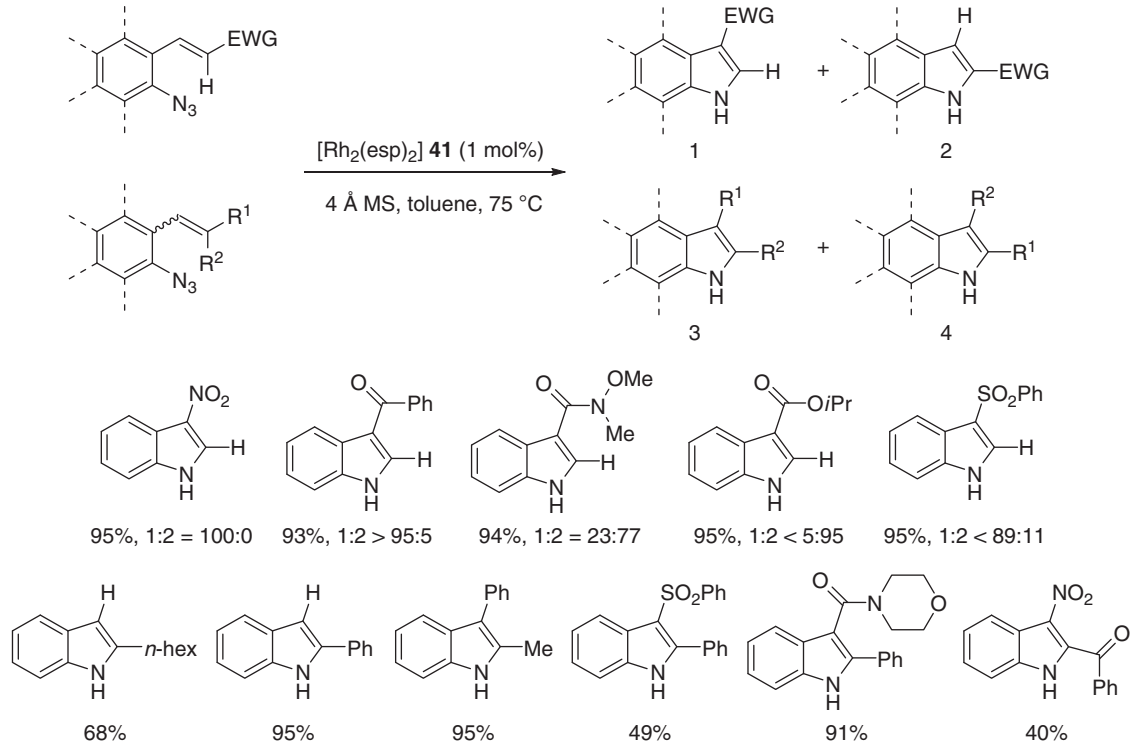
Scheme 113



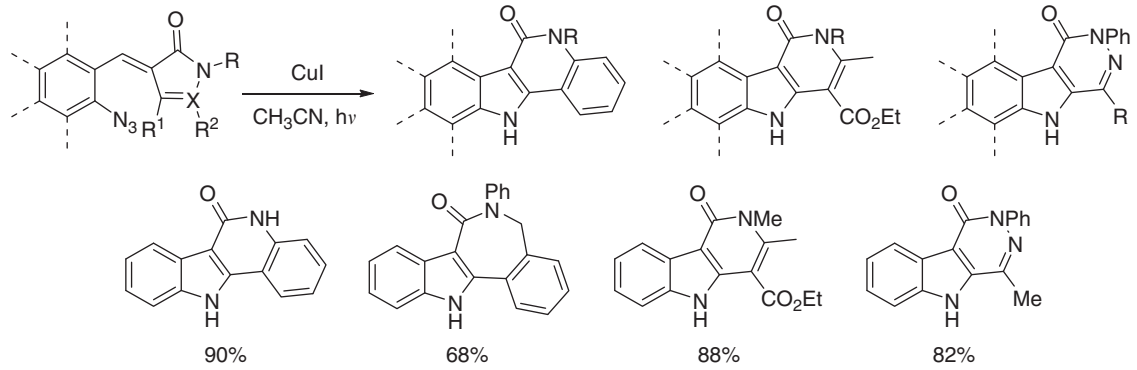
Scheme 114

Zhang and coworkers reported, in 2007, a cobalt porphyrin-catalyzed intramolecular amination of arylsulfonyl azides (Scheme 117).[157] The benzylic C–H amination were achieved in 87–99% yields with [Co(TPP)] (**28**) as catalyst. The reactivity of C–H bond for the amination is in the order 3° > 2° > 1°. In the absence of 2° and 3° C–H bonds, the 1° C–H amination occurred in 91–96% yields.

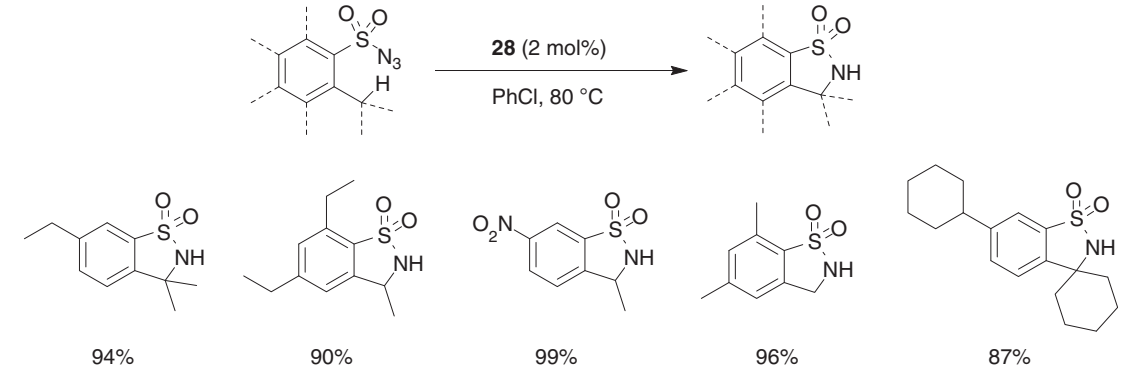
Subsequently, Zhang reported a cobalt porphyrin-catalyzed intramolecular amination of phosphoryl azides.[158] Although **28** was found to be an ineffective catalyst for the reaction, [Co(**P1**)] (**29**), in which the D_{2h}-symmetric porphyrin has amide functionalities at the *ortho*-positions of two *meso*-phenyl groups, effectively catalyzed benzylic or allylic C–H bonds amination of phosphoryl azides in up to 99% yield (Scheme 118). For the substrates lacking benzylic, allylic, secondary, and tertiary C–H



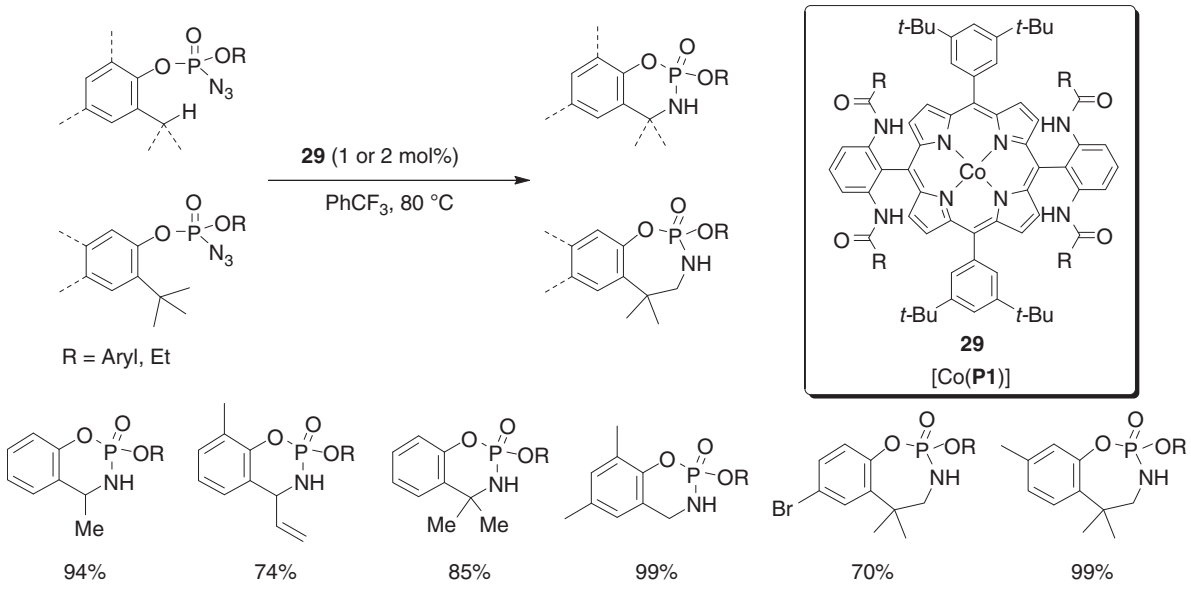
Scheme 115



Scheme 116



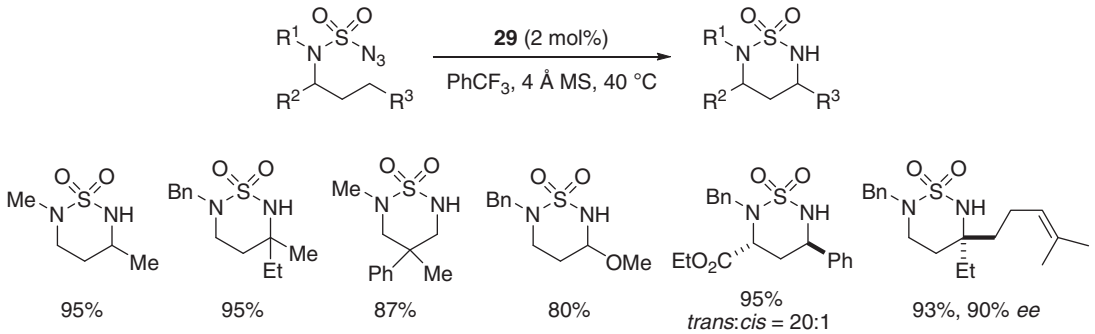
Scheme 117



Scheme 118

bonds, the amination of primary C–H bonds in 70–99% yields was observed. The high catalytic activity of **29** can be ascribed to a potential hydrogen-bonding interaction between the P═O and N–H groups in the supposed nitrene intermediate.

Complex **29** is also an effective catalyst for intramolecular C–H amination of sulfamoyl azides to furnish six-membered cyclic sulfamides in high yields and in excellent regioselectivity, high diastereoselectivity, and stereospecificity under mild reaction conditions (Scheme 119).[159] In addition to 2°, tertiary and benzylic C–H bond, even the unactivated strong 1° C–H bonds could be aminated with this cobalt catalyst in high yields. Zhang ascribed the high activity of **29** to the involvement of a radical Co–nitrene intermediate, which was supported by DFT calculations and cyclopropane clock experiment.



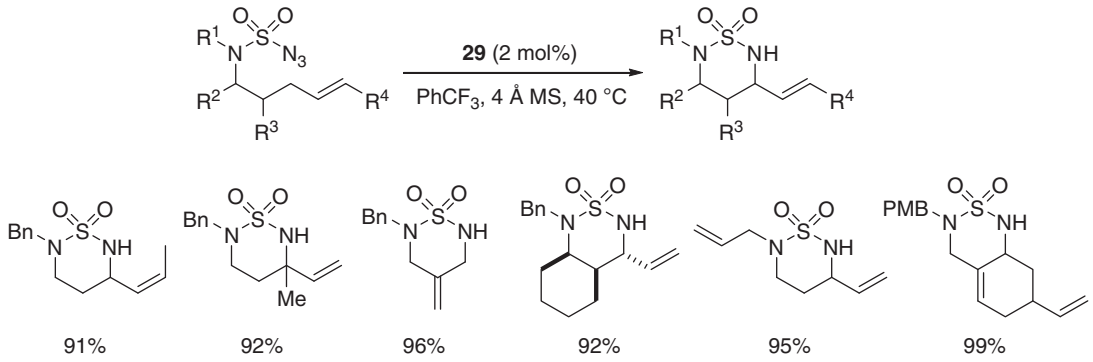
Scheme 119

The issue of chemoselectivity in intramolecular allylic C–H amination versus competitive C═C aziridination is often encountered in rhodium catalysis. Zhang addressed this issue by using cobalt porphyrin as catalyst. With **29** as catalyst, both *N*-allylic and *N*-bishomoallylic sulfamoyl azides undergo intramolecular amination of various types of allylic C–H bonds, including the 1°, 2°, and 3° C–H bonds in excellent chemoselectivity without aziridination being observed (Scheme 120).[160] The involvement of a radical Co–nitrene intermediate, low dissociation energy of allylic C–H bonds, and the stability of allylic radical altogether account for the high chemoselectivity. The findings of radical probe studies and kinetic isotope effect are supportive of the involvement of H-atom abstraction in the stepwise radical mechanism.

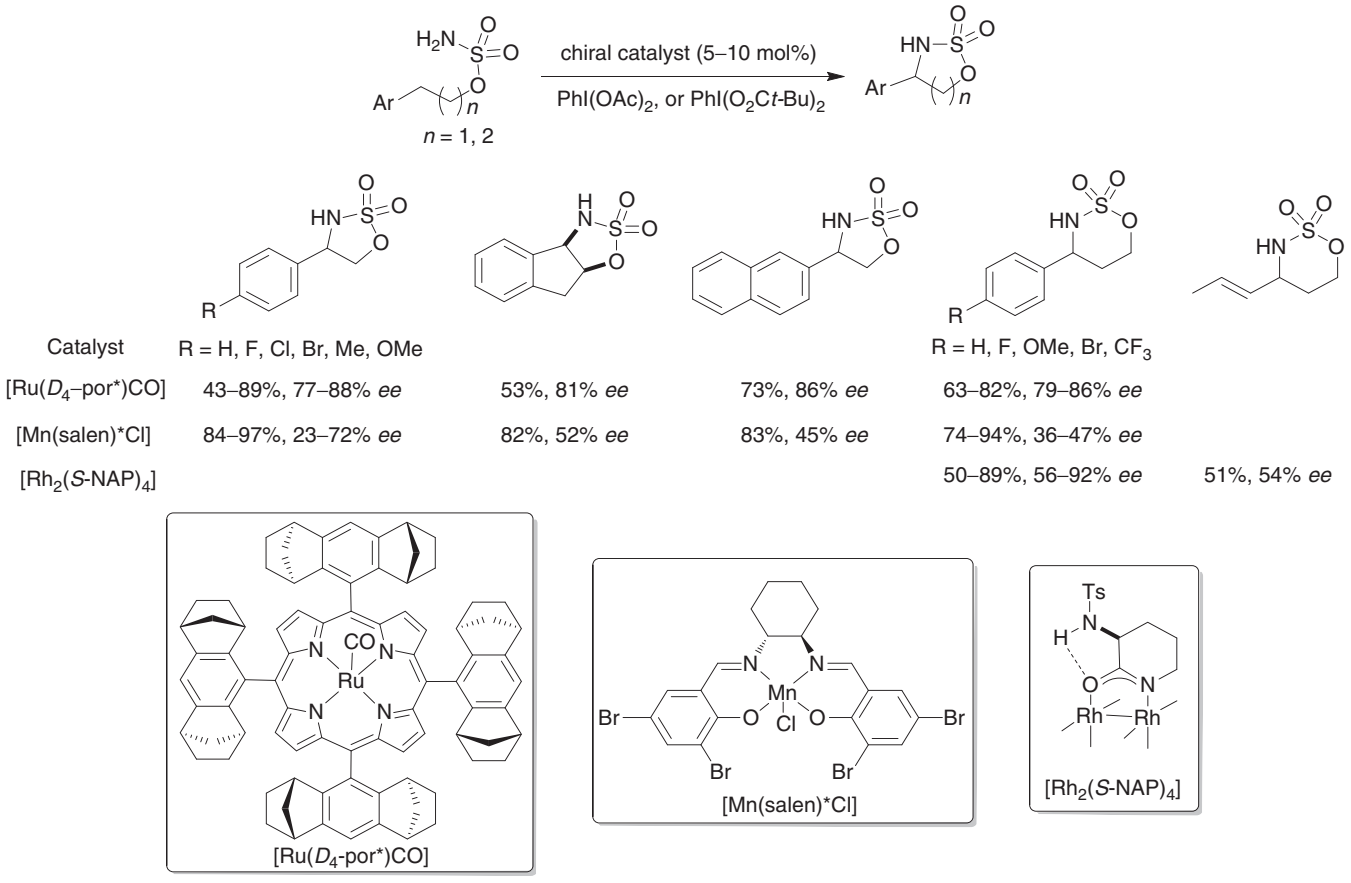
7.02.4.2.2.3 Asymmetric intramolecular C–H insertion

One of the earliest examples of enantioselective intramolecular amination of saturated C–H bonds was reported by Che and coworkers. The chiral ruthenium porphyrin [Ru(D_4-Por*)(CO)] was shown to catalyze enantioselective amination of benzylic C–H bond of sulfamate esters in up to 88% *ee* (Scheme 121)[76,161] which is higher than those *ee* values (up to 56%) found for the intermolecular C–H amination catalyzed by [Ru(D_4-Por*)(CO)] or [Mn(D_4-Por*)(OH)].[70] When the chiral manganese(III) Schiff base complex **2** was used as catalyst *ee* values up to 79% were obtained (Scheme 121).

The protocol of 'chiral ruthenium(II) pybox catalyst + Ag(OTf)' was effective in catalyzing asymmetric intramolecular amination of benzylic and allylic C–H bonds of sulfamate esters giving corresponding heterocyclic compounds in up to 90% *ee*.[142]



Scheme 120



Scheme 121

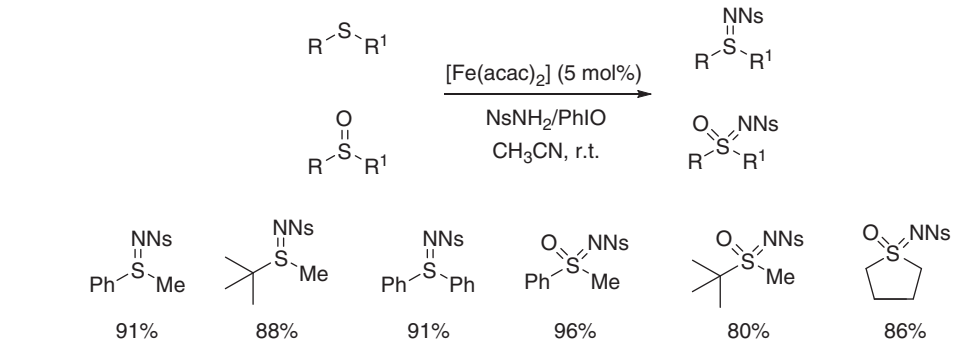
Removal of coordinated bromide by Ag(OTf) generates the cationic ruthenium complex which is an active and selective catalyst as depicted in Scheme 121.

Using dirhodium(II,II) carboxamides [Rh_2(*S*-NAP)$_4$] as catalyst, Du Bois and coworkers[162] developed a highly enantioselective intramolecular amination of sulfamate esters giving corresponding products in up to 89% yields and enantioselectivity up to 99%. The high activity and enantioselectivity of the [Rh_2(*S*-NAP)$_4$] catalyst is ascribed to the intramolecular hydrogen-bonding interactions rendering the rhodium atoms of the [Rh_2(*S*-NAP)$_4$] catalyst more resistant to oxidation (Scheme 121).

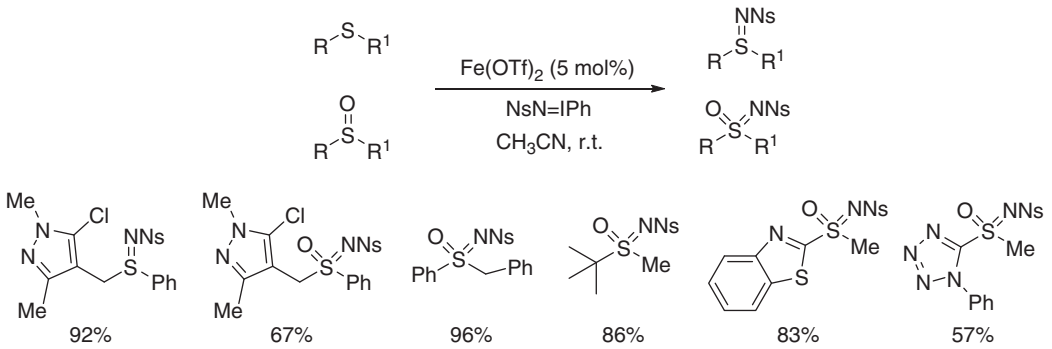
7.02.4.2.3 Sulfimidation

Oxidative imination of sulfides and sulfoxides via transition metal-catalyzed nitrogen group transfer reaction is an efficient and straightforward strategy that can be used for the synthesis of sulfoximides and sulfimides both of which are useful auxiliaries or

building blocks in organic synthesis.[163] In 2006, Bolm and coworkers reported a [Fe(acac)$_2$]-catalyzed imination of sulfides and sulfoxide with NsNH$_2$/PhI=O as nitrene source (Scheme 122).[164] Various sulfoximides and sulfimides could be obtained in high yields under mild conditions. The oxidant PhI(OAc)$_2$ was found less efficient than PhI=O. Subsequently, Bolm reported that Fe(OTf)$_2$ is a more efficient catalyst for sulfur imination especially for some sluggish substrates bearing benzyl, bulky alkyl, and/or heteroaryl substituents. These substrates were iminated by PhI=NNs in the presence of Fe(OTf)$_2$ in good to high yields (Scheme 123).[165] The iron-catalyzed sulfur imination was found to be stereospecific with retention of configuration at the sulfur atom when chiral sulfoxides were used.

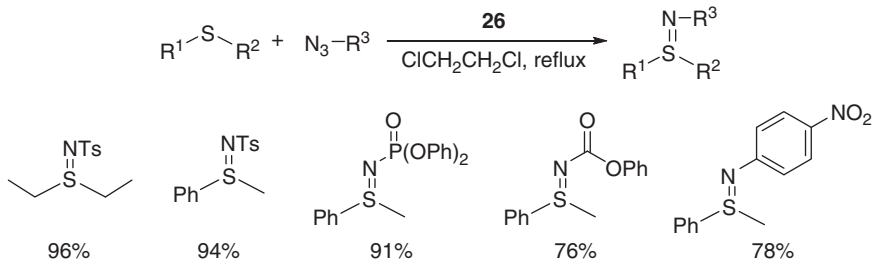


Scheme 122



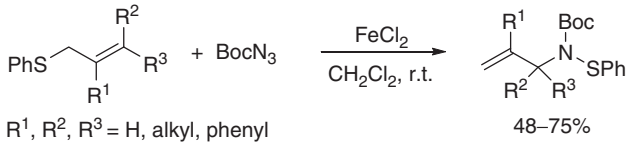
Scheme 123

With TsN$_3$ as the nitrene source, [Fe(F$_{20}$-TPP)Cl] (**26**) is an effective catalyst to catalyze imination of sulfides in high yields (90–96%) (Scheme 124).[114] Other organic azides such as *p*-nitrobenzenesulfonyl azide, diphenyl phosphoryl azide, phenyl carboxyl azide, and 4-nitrophenyl azide were also applicable affording the corresponding sulfimidation products in 76–95% yields.

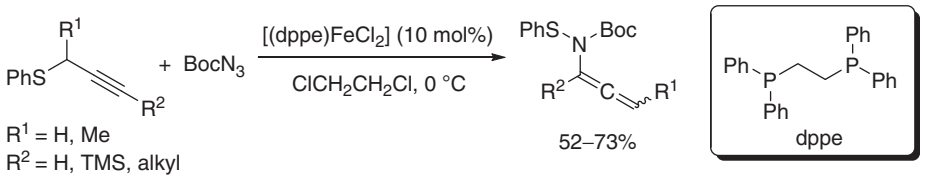


Scheme 124

When allyl sulfides were used as substrates, tandem imination/[2,3]-sigmatropic rearrangement to afford *N*-allyl sulfenamides as products were observed. Bach found that treatment of allyl phenyl sulfides with BocN$_3$ and a catalytic amount of FeCl$_2$ gave *N*-Boc-protected *N*-allyl sulfenamides in moderate to good yields (Scheme 125).[166] When propargyl sulfides and [(dppe)FeCl$_2$] catalyst were used, *N*-allenyl sulfonamides were obtained in 52–73% yields (Scheme 126).[167]

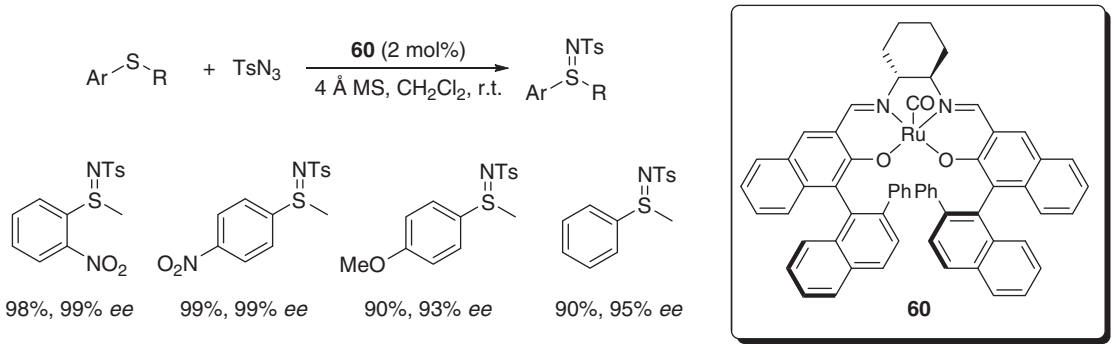


Scheme 125

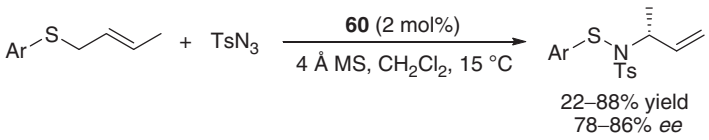


Scheme 126

With chiral metal catalysts, asymmetric sulfimination can be achieved. The ruthenium Schiff base complex **60** developed by Katsuki proved to be an effective catalyst for enantioselective imination of aryl sulfides with TsN_3 giving sulfoxides in high yields and with excellent enantioselectivities (Scheme 127).[113a] When allyl aryl sulfides were used, asymmetric imination/[2,3]-sigmatropic rearrangement took place to give corresponding allylic amines in 78–86% *ee* (Scheme 128). The electronic effect of substituent on phenyl ring showed a slight effect on the *ee* value.[168]



Scheme 127

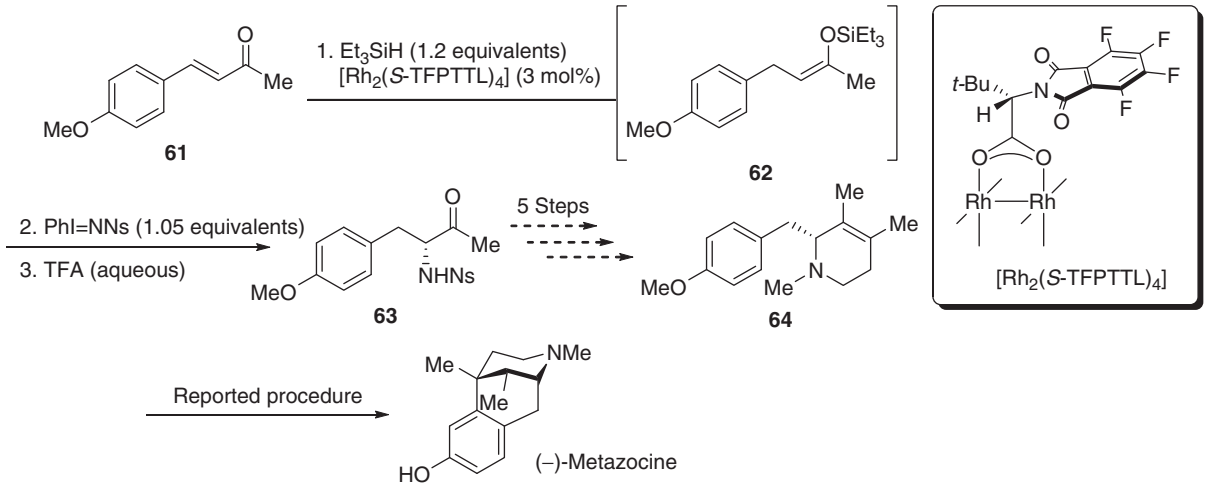


Scheme 128

7.02.4.3 Applications in Total Synthesis

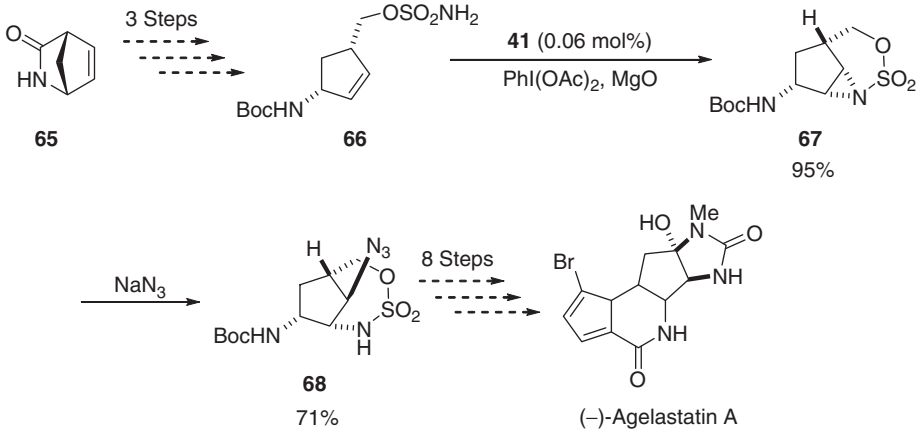
With the advancement of metal-catalyzed nitrene transfer/insertion reactions, many of these reactions have been applied to the total/formal synthesis of natural products or pharmaceuticals.[169] The following are examples of total synthesis with transition metal-catalyzed nitrene transfer reaction as a key step in the synthesis.

Hashimoto and coworkers reported the application of enantioselective intermolecular aziridination of silyl enol ethers catalyzed by chiral $[Rh_2(S\text{-TFPTTL})_4]$ followed by ring opening of the aziridine intermediate to the formal synthesis of benzomorphan analgesic (–)-Metazocine.[170] By a one-pot generation of silyl enol ether **61** from α,β-enone **62** followed by enantioselective intermolecular amination using PhI=NNs as nitrene source and in the presence of 3 mol% of $[Rh_2(S\text{-TFPTTL})_4]$, α-aminoketone **63** was obtained in 66% yield with > 99% *ee* (Scheme 129). Compound **63** was transformed to tetrahydropyridine **64** in five steps. (–)-Metazocine was synthesized from **64** according to the procedure reported by Meyers and coworkers.[171]



Scheme 129

Wehn and Du Bois applied intramolecular aziridination of alkenes catalyzed by dirhodium(II,II) carboxylates followed by nucleophilic ring opening of aziridines by azide to the total synthesis of (–)-agelastatin A (Scheme 130), a bromopyrrole-based natural product isolated from coral sea marine sponge showing high cytotoxicity against several human cancer cell lines.[172] Starting from a commercially available optically enriched lactam **65**, sulfamate ester **66** bearing an alkene moiety was prepared in a three-step reaction. Compound **66** underwent stereoselective intramolecular aziridination in the presence of $[Rh_2(esp)_2]$ (**41**) to give aziridine **67** as a single diastereomer and with less than 1% of competitive C–H insertion product. The aziridine ring opening of **67** with sodium azide gave the bridging [1,2,3]-oxathiazepane-2,2-dioxide **68** in a highly regioselective manner. Compound **68** was converted to (–)-agelastatin A in eight steps.

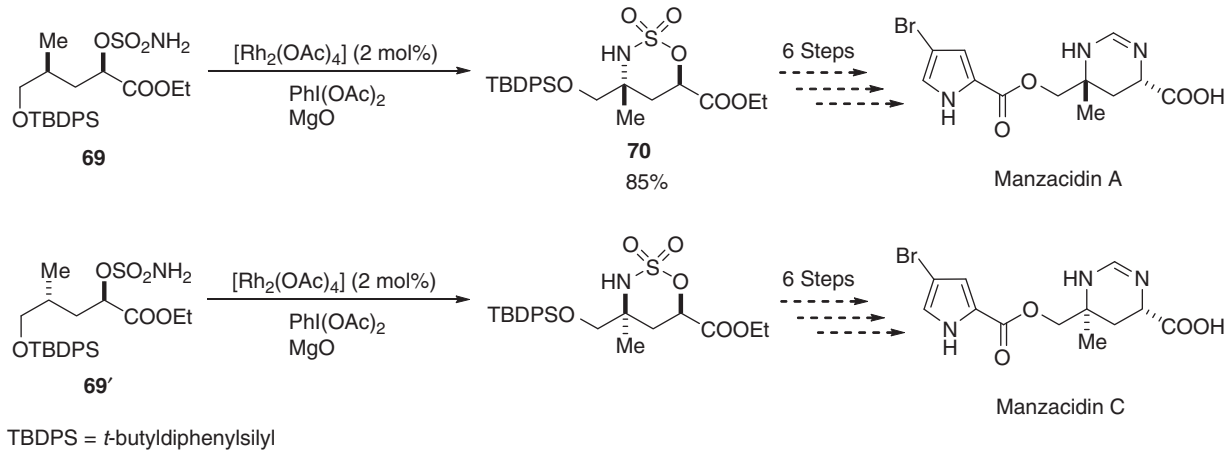


Scheme 130

The stereospecific intramolecular nitrene C–H insertion developed by Du Bois and coworkers using dirhodium(II,II) carboxylates as catalyst and $PhI(OAc)_2$ as terminal oxidant has opened a new gateway to stereoselective synthesis of oxathiazinanes.[141a] Several total syntheses of natural products have involved this protocol. The followings are some of the selected examples of these synthetic routes.

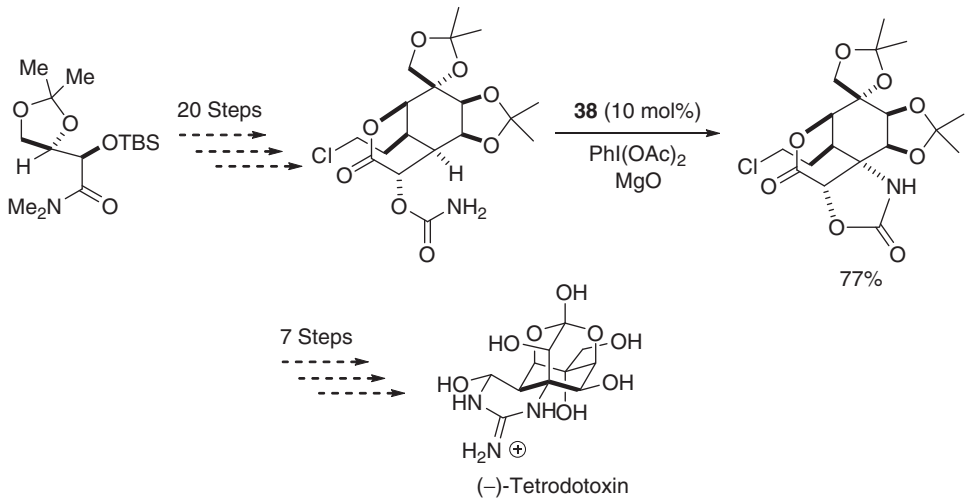
In 2002, Wehn and Du Bois reported the synthesis of manzacidin A and C via dirhodium(II,II) carboxylate-catalyzed intramolecular nitrene C–H insertion of sulfamate ester with $PhI(OAc)_2$ as terminal oxidant (Scheme 131).[173] Manzacidin A and C, which are two examples of bromopyrrole alkaloids, are isolated from an Okinawan sponge *Hymeniacidon* sp.[174] showing pharmacological activities such as α-adrenoreceptor blockers, serotonin antogonists, and actomyosin ATPase activators. Using sulfamate ester **69** as the starting material, $Rh_2(OAc)_4$-catalyzed intramolecular C–H amination of **69** stereospecifically to give oxathiazinane **70** as a single diastereomer in 85% yield. Oxathiazinane **70** was converted to manzacidin A in further six steps. Manzacidin C was synthesized using the same strategy, despite starting with the diastereomer of sulfamate ester **69′**.

Following the success in the total synthesis of manzacidin A and C, Du Bois and coworkers extended this oxathiazinane synthetic route to the syntheses of other natural products. Guanidium poisons (–)-tetrodoxin, (+)-saxitoxin, and (+)-gonyautoxin 3 were synthesized by Du Bois and coworkers using intramolecular nitrene C–H insertion as a key step.



Scheme 131

In 2003, Hinman and Du Bois reported the total synthesis of (–)-tetrodoxin,[175] a guanidinium poison isolated from the puffer fish family showing excellent potency as selective blocker of voltage-gated Na^+ ion channels.[176] In the synthesis of (–)-tetrodoxin, the regioselective intramolecular amidation of C–H bond was achieved in 77% yield with the correct stereochemistry using $[Rh_2(NHCOCF_3)_4]$ (**38**) as catalyst and $PhI(OAc)_2$ as terminal oxidant (Scheme 132).

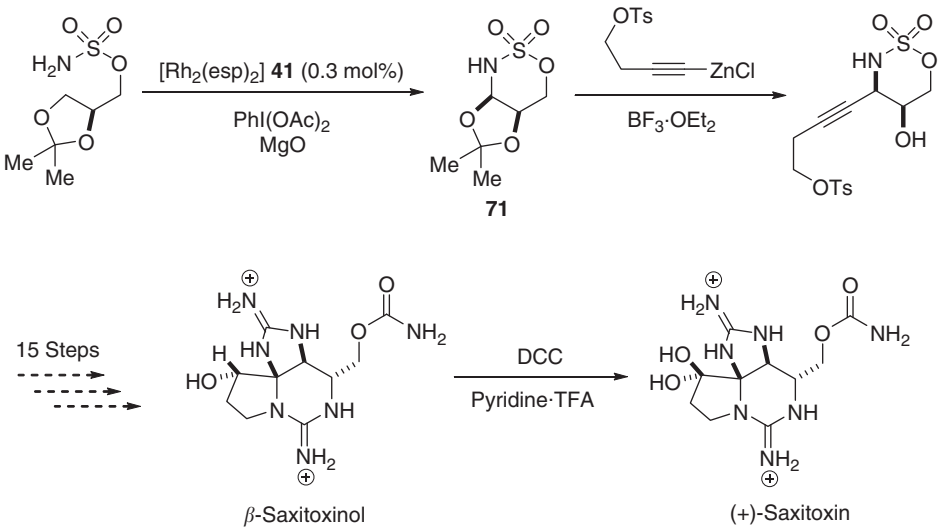


Scheme 132

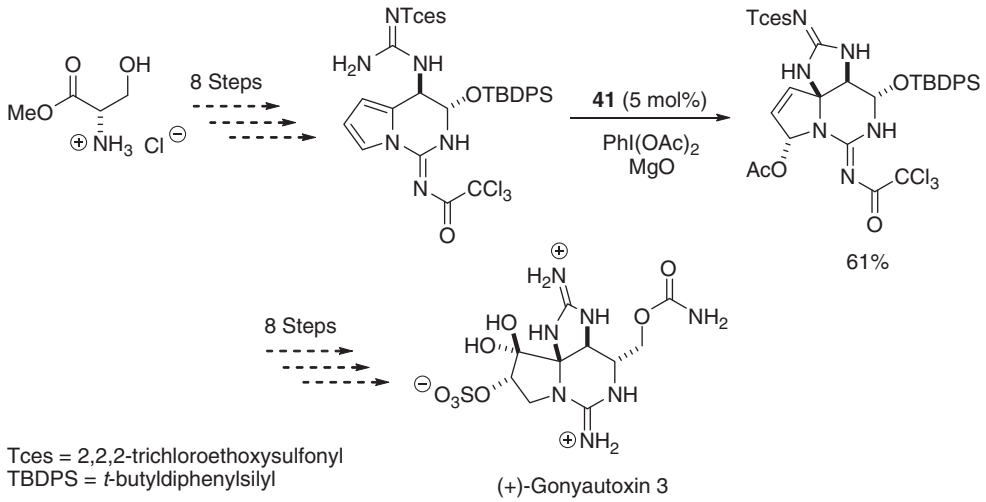
Four years later, Du Bois and coworkers reported the total synthesis of bis-guanidinium paralytic shellfish poison (+)-saxitoxin via the oxathiazinane synthetic route.[177,178] Through the same strategy as that for the synthesis of manzacidin A and C, oxathiazinane N,O-acetal **71** was prepared and used as the starting material for the synthesis of (+)-saxitoxin in 17 steps (Scheme 133).

In 2008, Mulcahy and Du Bois reported the synthesis of (+)-gonyautoxin 3, which is another example of paralytic shellfish poisons containing a bis-guanidinium structure.[179] Instead of intramolecular nitrene insertion to the C–H bond for oxathiazinane as in the synthesis of (+)-saxitoxin, the total synthesis of (+)-gonyautoxin 3 involved intramolecular nitrene insertion to the sp^2 C–H bond of aromatic pyrrole moiety leading to the generation of the guanidinium moiety in 61% yield (Scheme 134).

Ichikawa and coworkers utilized the same protocol of intramolecular nitrene C–H insertion for the synthesis of cyclic guanidine amino acid L-*epi*-capreomycidine (L-*epi*-Cap), which is part of the structure of muraymycin D2 (Figure 10). Muraymycin D2 exhibits excellent antimicrobial activity against Gram-positive bacteria.[180] Sulfamate ester **72** was prepared from D-tyrosine in six steps. The $[Rh_2(esp)_2]$ (**41**)-catalyzed intramolecular nitrene C–H insertion using $PhI(OAc)_2$ as terminal oxidant gave oxathiazinane **73** as a single product in 92% yield (Scheme 135). Compound **73** was transformed into protected L-*epi*-Cap **74**, which is one part of the truncated muraymycin analog **75**, in 10 steps. L-*epi*-Cap **74**, together with the other three components, was assembled to give the truncated muraymycin analog **75** in four steps (Scheme 136).



Scheme 133



Scheme 134

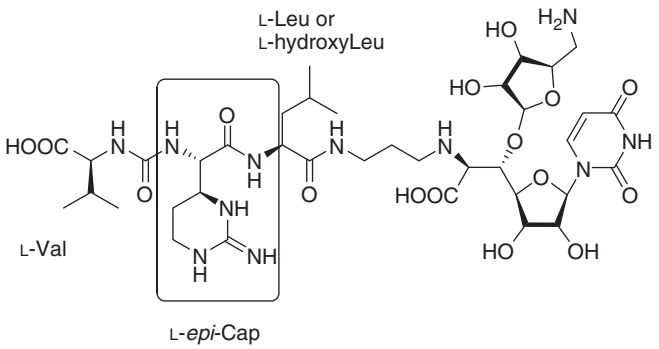
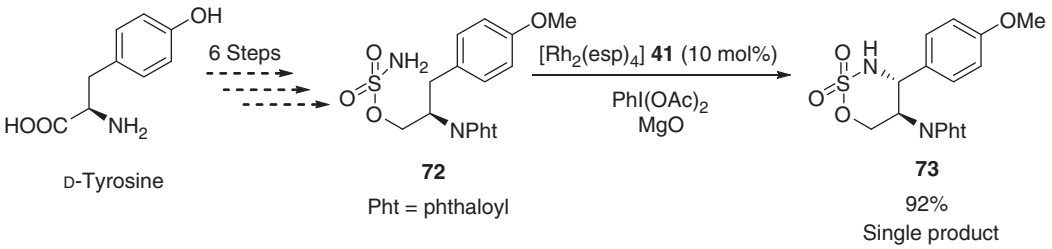
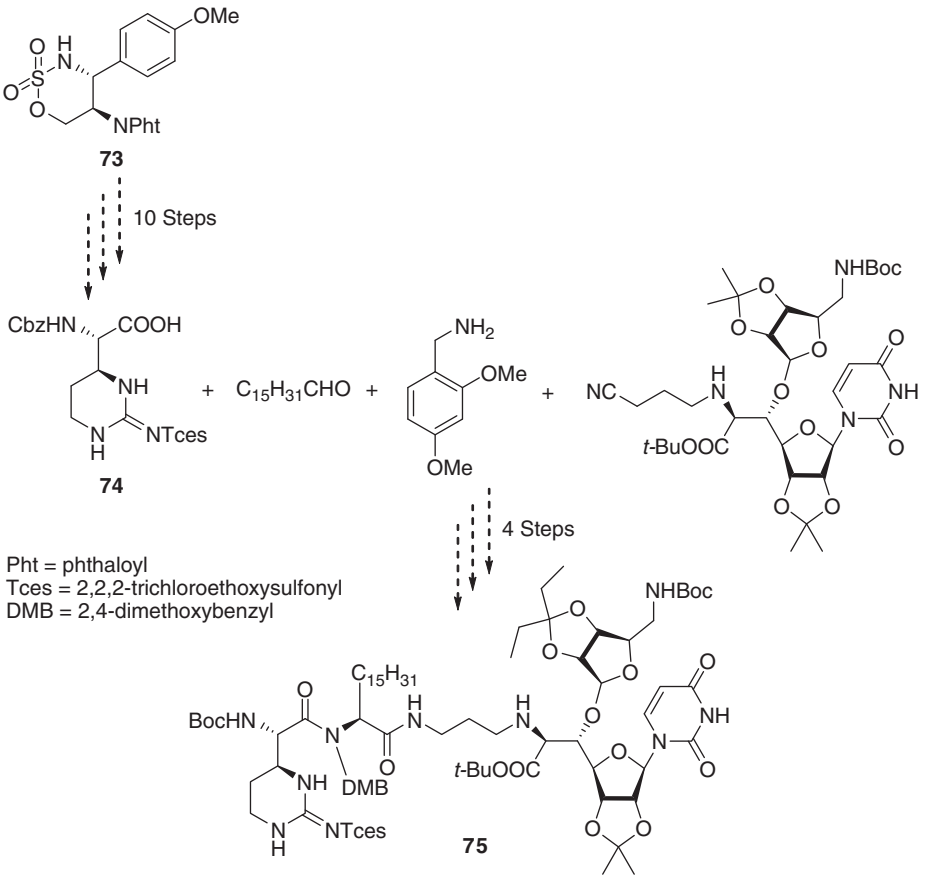


Figure 10 Structure of muraymycin D2.



Scheme 135



Scheme 136

7.02.5 Conclusion

In conclusion, transition metal-catalyzed nitrene transfer/insertion reactions are powerful strategies for installing amide or amine moiety to organic molecules. These catalytic reactions including C═C aziridination, C–H insertion, and sulfimidation, can be easily achieved in high yields and in good selectivity with the appropriate design of transition metal catalyst and choice of nitrene source. With the appropriate chiral auxiliary ligands, highly enantioselective transition metal-catalyzed nitrene transfer reactions could be achieved. To probe the mechanisms of metal-catalyzed nitrene transfer/insertion reactions, various reactive metal nitrene/imido complexes have been prepared and characterized. Some of these complexes are able to directly react with the C–H or C═C bonds of organic compounds leading to the formation of C–N bonds.

It is envisaged that the development of metal-catalyzed nitrene transfer/insertion reactions will be in the following directions: (1) development of new chiral transition metal catalysts for asymmetric nitrene transfer and insertion reactions, especially for highly regio- and enantioselective nitrene C–H insertion to hydrocarbons; (2) expanding the applications of these reactions to the total/formal synthesis of natural products and molecules with biological activities; and (3) mechanistic studies by means of the synthesis and X-ray characterization of reactive metal nitrene/imido intermediates, detection and characterization of reaction intermediates by ESI-MS and/or spectroscopic means, and DFT calculations.

7.02.6 Acknowledgments

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7.03 Asymmetric C–H Functionalization by Transition Metal-Catalyzed Carbene Transfer Reactions

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Glossary

Asymmetric induction Asymmetric induction describes the preferential formation of one enantiomer or diastereoisomer over the other in a chemical reaction as a result of the influence of a chiral feature present in the catalyst, substrate, reagent, or environment.

Carbene The electrically neutral species H_2C, and its derivatives, in which the carbon is covalently bonded to two univalent groups of any kind or to a divalent group. It bears two nonbonding electrons, which may be spin-paired (singlet state) or spin-nonpaired (triplet state).

Chiral ligand A specially adapted ligand based on an enantiopure organic compound. It coordinates with a metal center to form a chiral catalyst, which is used for asymmetric synthesis. The catalyst transfers its chirality to the resulting product of chemical reaction that it catalyzes.

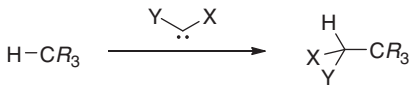
Diazo compound A type of organic compound that has two linked-nitrogen atoms (azo) as a terminal functional group.

Stereoselectivity The preferential formation in a chemical reaction of one stereoisomer over the other. When the stereoisomers are enantiomers, the phenomenon is called enantioselectivity; when they are diastereoisomers, it is called diastereoselectivity.

Transition metal carbene complex An organometallic compound featuring a divalent carbon-based organic ligand. The complex has the carbon in a trigonal planar geometry and at least formally contains an M═C double bond.

7.03.1 Introduction

More than half a century ago, it was discovered that methylene, the simplest free carbene, undergoes an insertion reaction into C–H bonds of organic molecules.[1] This process causes the cleavage of the unactivated C–H bond, followed by the formation of a new C–C bond (Scheme 1). In principle, it provides a potentially general approach for direct functionalization of unactivated C–H bonds, which are ubiquitous in organic molecules. In view of the ever-present nature of C–H bonds in organic molecules, this approach would be synthetically meaningful only if the transformation could be controlled to take place selectively on specified C–H bonds. With free methylene, the distribution of products resulting from C–H insertion was found to be generally very close to statistical ratio, indicating the indiscriminate nature of this type of transformation. Little improvement in selectivity

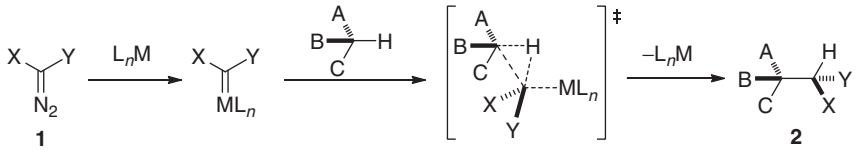


Scheme 1 Free carbene insertion into C–H bonds.

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was observed by tuning the structures of the free carbenes.[2] In general, free carbene-based C–H insertion processes have not been developed as widely applicable synthetic strategies.

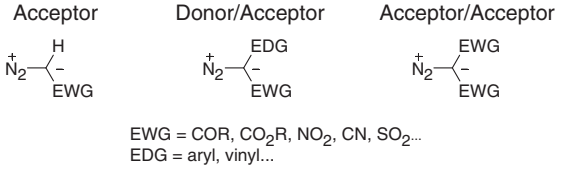
Revolutionary developments have been made by the incorporation of transition metals in carbene C–H functionalization chemistry. Diazo reagents (**1**) are usually used as the carbene precursors that can be decomposed by transition metal compounds to form the corresponding metal carbene complexes. As described in the most accepted mechanism (**Scheme 2**), these metal carbene intermediates still retain highly electrophilic carbon centers, which enable them to undergo insertion reactions into C–H bonds. Formation of the product **2** is accompanied by the regeneration of the metal complex, resulting in a catalytic process for these insertion reactions.[3,4]



Scheme 2 Mechanism of transition metal-catalyzed C–H insertion.

Although almost all transition metals are known to form carbene complexes, only few, including Rh,[3–12] Cu,[8,13] Ir,[14,15] Fe,[16–18] Ag,[19–25] Au,[25–27] Ru[28–36] complexes, have been reported to catalyze carbene transfer reactions that functionalize C–H bonds. With the development of these Lewis acidic metal catalysts during the past two decades, high levels of control in chemo- and regioselectivity have been achieved. The design of the supporting ligands, in particular chiral ligands, has attracted increasing attention as it enables the stereocontrol of this type of transformation.[6,37] Tremendous efforts have been devoted to diastereo- and enantioselective carbene transfer reactions to functionalize C–H bonds, leading to the development of a number of effective catalytic systems. Although the majority of the chiral catalysts are dirhodium(II)-based complexes, Cu-, Ir-, and Fe-based chiral catalysts have also been reported.[8,14–16] Catalytic functionalization of C–H bonds based on transition metal-mediated carbene transfer has already become one of the most general and direct methods for enantioselective formation of new C–C bonds from C–H bonds.

The reactivity and selectivity of metal-catalyzed C–H functionalization via carbene transfer can be highly influenced by the electronic properties of the diazo reagents. Three types of relatively stable diazo reagents have been largely explored, acceptor-substituted, donor/acceptor-substituted, and acceptor/acceptor-substituted diazo reagents, the names of which are originated from the electronic nature of their two α-substituents (**Scheme 3**).[10] Acceptor- and donor/acceptor-substituted diazo reagents, which generally possess a considerable degree of electron richness on the α-carbon, usually have high reactivity toward Lewis acidic metal catalysts. Acceptor/acceptor-substituted diazo reagents, which bear two electron-withdrawing groups at the α-carbon, typically show lower levels of reactivity in forming the metal carbene intermediates. The subsequent insertion step of the intermediates is also greatly influenced by their α-substituents. While many catalysts were shown to mediate highly effective C–H insertion reactions via acceptor- and donor/acceptor-substituted metal carbenes, acceptor/acceptor-substituted metal carbenes, once formed, are generally too reactive to control selectivity toward C–H insertion as a result of their highly increased electrophilicity.



Scheme 3 Commonly used diazo reagents.

To date, asymmetric C–H functionalization via carbene transfer has been demonstrated with a number of transition metal-based catalytic systems, in both intermolecular and intramolecular fashions. This review chapter is structured to describe the different types of chiral metal catalysts that have been developed for stereoselective carbene transfer reactions. Emphasis will be placed on the issue of stereoselectivity, especially enantioselectivity. Within each type of metal-catalyzed system, catalytic reactions are organized based on intramolecular and intermolecular processes. The structure and electronic properties of the diazo reagents, which play a critical role in the control of stereoselectivity, will be classified and discussed for each type of reaction. The chapter ends with a discussion about the remaining challenges associated with transition metal-catalyzed carbene C–H functionalization and future research directions.

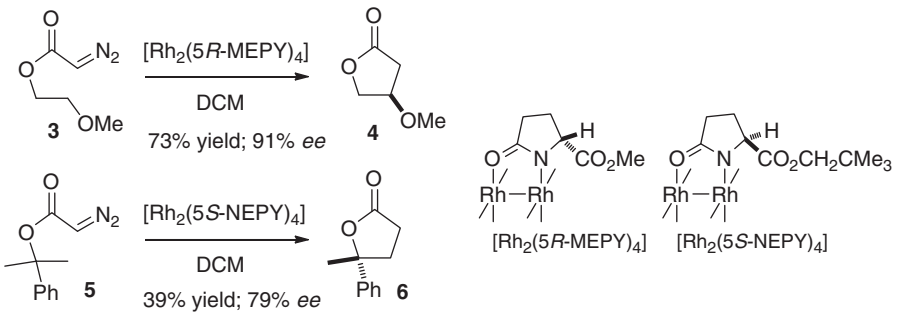
7.03.2 Rhodium(II)-Catalyzed Asymmetric Carbene C–H Insertion

The majority of asymmetric carbene C–H functionalization reactions via carbene transfer have been catalyzed by dirhodium(II)-based catalysts (Scheme 2). With a single bonded Rh–Rh dinuclear unit as the core, a variety of chiral ligands have been developed for constructing paddlewheel complexes as the catalysts. Dirhodium(II) complexes of chiral carboxamidates and carboxylates are some of the most versatile and selective catalysts for tuning the reactivity, regioselectivity, and stereoselectivity of the C–H insertion processes.[3,4,6,8,38] Common side reactions such as carbene dimerization can be largely minimized through slow addition of the diazo reagents and/or use of excess C–H substrates. So far, chiral dirhodium(II)-based catalysts have been widely used to explore intra- and intermolecular insertion reactions with different types of diazo reagents and have thus resulted in a number of effective catalytic systems.

7.03.2.1 Intramolecular Insertion

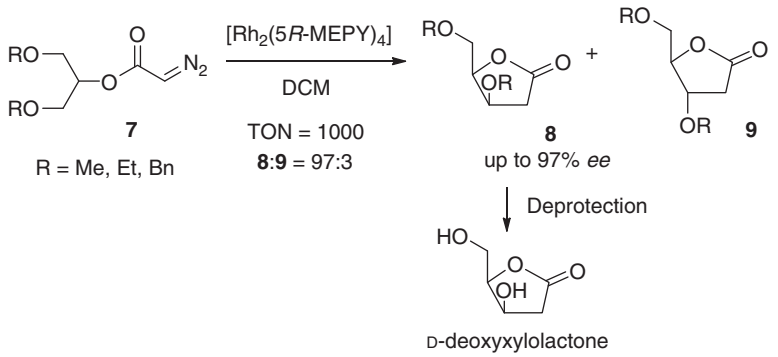
7.03.2.1.1 Reactions with acceptor-substituted diazo reagents

Intramolecular C–H insertion with acceptor-substituted diazo reagents was first reported and has been subsequently developed by Doyle and coworkers into a process with high enantiocontrol. In 1991, they developed an enantioselective lactone synthesis via Rh_2-catalyzed intramolecular C–H insertion (Scheme 4).[38–40] Alkyl diazoacetate **3** was converted to lactone **4** with 91% *ee* when pyrrolidinone-based chiral catalyst [Rh_2(5*R*-MEPY)$_4$] (0.5–1 mol%) was employed. High asymmetric induction could be achieved for similar C–H insertion reactions by using varied alkoxy groups as the neighboring functionality next to C–H bonds. However, benzylic C–H bonds could only be intramolecularly inserted in moderate yields and enantiomeric excesses (*ee*). The catalytic system features unusual reactivity toward primary C–H bonds, which is normally disfavored. For example, [Rh_2(5*S*-NEPY)$_4$] could catalyze carbene insertion reaction of primary C–H bonds in **5** to afford lactone **6** in 39% yield with 79% *ee*.[39] Attempts to use polymer-bound Rh_2 complex as a recoverable catalyst for conversion of **3** to lactone **4** resulted in moderate yield and enantioselectivity.[41]



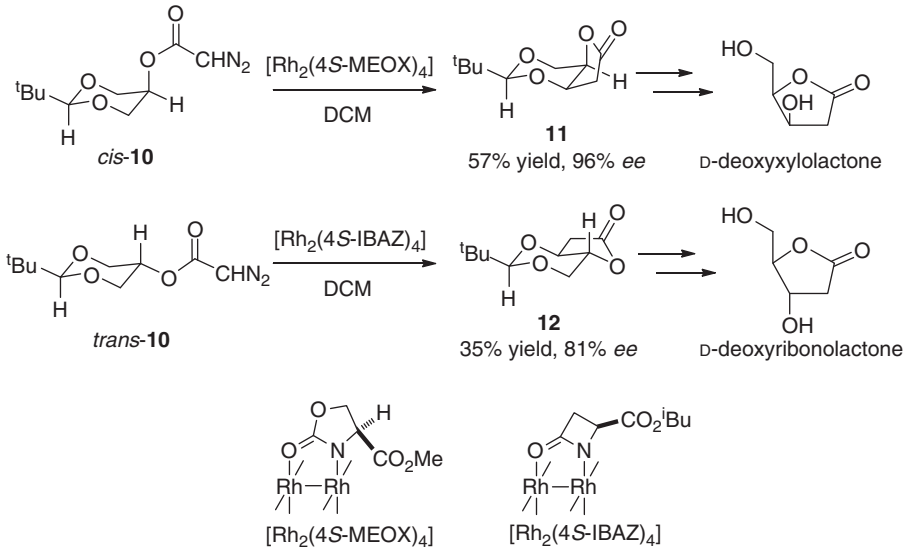
Scheme 4 Asymmetric lactone synthesis via Rh_2-catalyzed intramolecular C–H insertion. DCM, dichloromethane.

With 1,3-dialkoxy-2-propyl diazoacetates (**7**), Doyle et al. reported [Rh_2(5*R*-MEPY)$_4$]-catalyzed C–H insertion, affording alkyl-protected 2-deoxyxylolactones (**8**) as the major diastereomer with up to 97% *ee* (Scheme 5).[42] The catalyst exhibited satisfactory activity as well as good stability, which led to a turnover number (TON) of 1000. The formation of the other diastereomer 2-deoxyribonolactone derivative **9** was almost completely inhibited in this process. The high stereoselectivity of the catalytic process in combination with straightforward subsequent deprotection makes this an effective method to asymmetrically synthesize D-deoxyxylolactone.



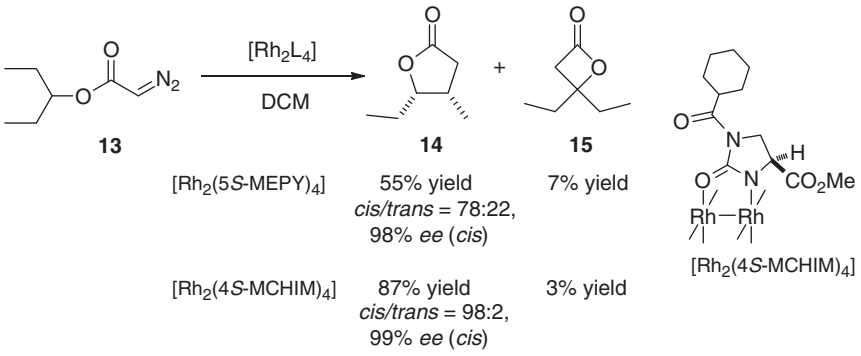
Scheme 5 Asymmetric synthesis of D-deoxyxylolactone.

The incorporation of additional diastereocontrol with the use of suitable diazo reagents led to selective access to both D-deoxyxylolactone and D-deoxyribonolactone, respectively (Scheme 6).[43] Two diastereomers of diazo reagent **10** with the *tert*-butyl acetal protecting unit were shown to undergo intramolecular C–H insertion with high levels of diastereocontrol. With the bulky *tert*-butyl groups always occupying the equatorial position, *cis*-**10** has an axial diazoacetate unit whereas *trans*-**10** has an equatorial diazoacetate. Both diastereomers were observed to favor insertion reactions into the equatorial C–H bonds only. As a result, *cis*-**10** was selectively converted to lactone **11** with 96% *ee*, which was transformed to 2-deoxyxylolactone. Accordingly, *trans*-**10** was converted to lactone **12** with 81% *ee*, affording D-deoxyribonolactone as the target molecule. Although the stereoselectivities were excellent, the yields were moderate due to competitive carbene dimerization of the diazo reagents.



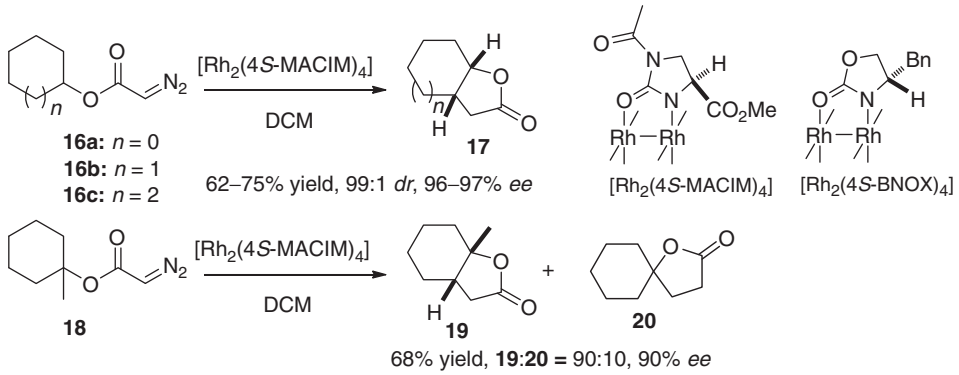
Scheme 6 Diastereocontrolled asymmetric synthesis of D-deoxyxylolactone and D-deoxyribonolactone.

Similar to the bisalkoxy diazo reagents **7**, *cis*-selective C–H insertion of the dialkyl diazo reagent **13** could also be catalyzed by $[Rh_2(5S\text{-MEPY})_4]$ with 98% *ee*, albeit in moderate yield and diastereocontrol. Further improvements in yield, diastereomeric ratio, and regioselectivity were achieved through catalyst design. The use of dirhodium(II) tetrakis[methyl L-(cyclohexylacetyl)-imidazolidin-2-one-4(*S*)-carboxylate], $[Rh_2(4S\text{-MCHIM})_4]$, gave exclusive *cis*-**14** in 87% yield with complete enantiocontrol. The formation of *β*-lactone **15** was further minimized through the use of $[Rh_2(4S\text{-MCHIM})_4]$ (Scheme 7).[44]



Scheme 7 $[Rh_2(4S\text{-MCHIM})_4]$-catalyzed *cis*-selective intramolecular C–H insertion.

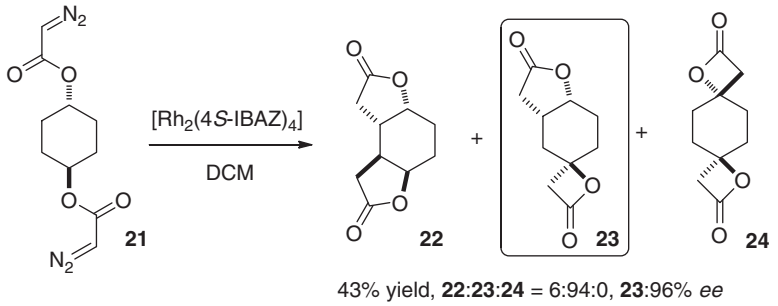
Dirhodium(II) carboxamidates have proven to be generally effective for asymmetric intramolecular carbene C–H insertion reactions of diazoacetates, forming chiral lactone products in high enantioselectivity.[45] Among different types of C–H bonds, insertions to cycloalkyl C–H bonds allowed for the formation of bicyclic compounds. Doyle and coworkers carried out systematic studies on this type of transformation.[46,47] In 1994, they showed that $[Rh_2(4S\text{-MACIM})_4]$ could catalyze asymmetric C–H insertion reactions of cyclohexyl, cycloheptyl, and cyclooctyl diazoacetates (**16**) (Scheme 8).[46] Fused bicyclic lactones **17** could be synthesized as exclusive *cis*-diastereomers. In addition to the excellent enantiocontrol, $[Rh_2(4S\text{-MACIM})_4]$ was able to provide much higher yields of the desired products than sterically less hindered $[Rh_2(OAc)_4]$, which only gave 29–46% yields under identical conditions. Moreover, $[Rh_2(4S\text{-MACIM})_4]$ seems to provide a steric influence that forces the formation of **17b** to be



Scheme 8 Asymmetric insertion reactions into cycloalkyl C–H bonds.

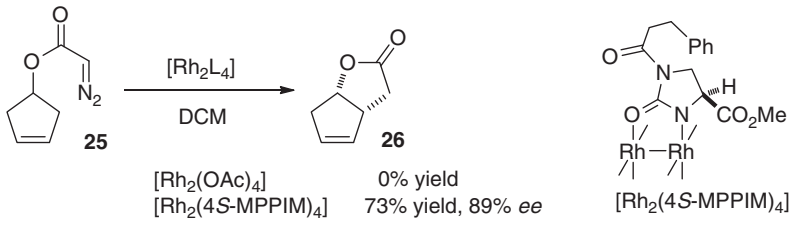
cis-selective because $[Rh_2(OAc)_4]$ was shown to be slightly *trans*-selective when used as the catalyst.[48] By using chiral catalyst $[Rh_2(4S\text{-BNOX})_4]$, Müller and coworkers demonstrated that *trans*-**17b** could be synthesized asymmetrically with 67:33 *trans*/*cis* ratio and 60% *ee*, although the reaction only gave a low yield of 30%.[48] Under the catalysis of $[Rh_2(4S\text{-MACIM})_4]$, cyclohexyl diazo reagent **18** bearing additional methyl group was shown to favor the insertion into cyclic secondary C–H bonds over methyl primary C–H bonds. *cis*-fused bicyclic lactone **19** was produced as the major product with 90% *ee* with only minor formation of spiro bicyclic lactone **20** (Scheme 8).[45]

While γ-lactone formation was shown to be favored from cyclohexyl diazoacetate (**16b**), two sequential intramolecular C–H insertions of *trans*-bisdiazoacetate **21** by chiral dirhodium(II) carboxamidate catalysts dominantly produced a β-lactone moiety after formation of the first γ-lactone unit (Scheme 9).[49] With less sterically hindered catalyst $[Rh_2(4S\text{-IBAZ})_4]$, **23** was found to be the major product of the three, with 96% *ee*. The β-lactone formation may be related to a configuration mismatch between the chiral catalyst and the enantioenriched mono-cyclized chiral intermediate, which is known to result in the strained β-lactone formation.[50,51]



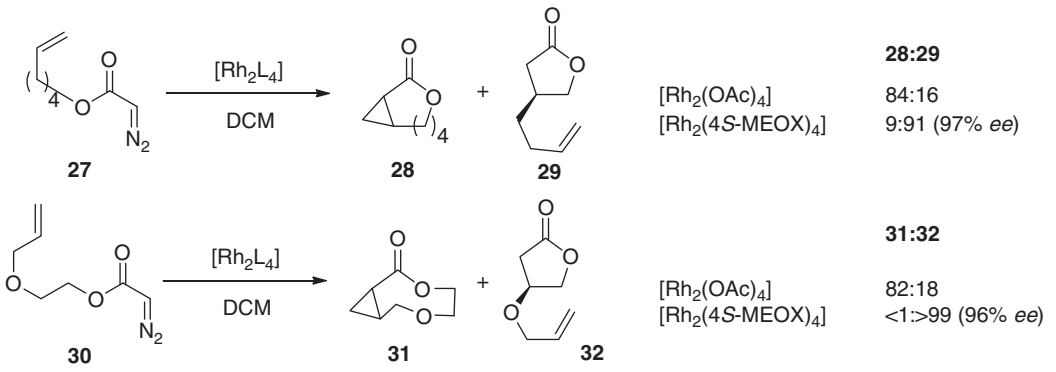
Scheme 9 Intramolecular C–H insertion with β-lactone formation.

Fischer-type dirhodium carbene intermediates potentially undergo facile cyclopropanation reactions with electron-rich olefins,[11,52–54] thus making the C–H insertion more challenging in the presence of double bonds. Although dirhodium(II) acetate failed to produce any product from the cyclopentene-containing diazoacetate **25**, Doyle and coworkers showed that $[Rh_2(4S\text{-MPPIM})_4]$ was capable of asymmetric intramolecular allylic C–H insertion of **25** without intramolecular cyclopropanation. With exclusive regiocontrol, *cis*-fused γ-lactone **26** was afforded in 73% yield and 89% *ee* (Scheme 10).[55]



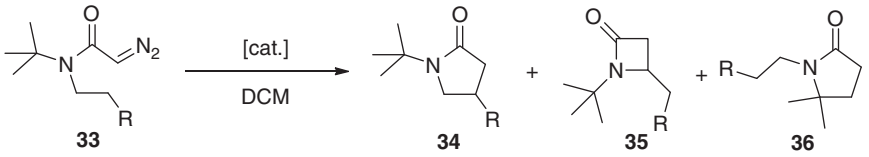
Scheme 10 Intramolecular insertion into allylic C–H bonds.

High control of both chemoselectivity and enantioselectivity was also reported by Doyle and coworkers for intramolecular C–H insertion of diazoacetates containing acyclic alkene units. They showed that $[Rh_2(4S\text{-MEOX})_4]$ could selectively catalyze intramolecular insertion of the C–H bonds in diazoacetates **27** and **30** without significant complication from intramolecular cyclopropanation of the C=C bonds, forming lactone **29** and **32**, respectively, in excellent enantioselectivities (Scheme 11).[56] Interestingly, when $[Rh_2(OAc)_4]$ was used as the catalyst, intramolecular cyclopropanation of the C=C bonds prevailed, affording the bicyclic lactones **28** and **31**, respectively, as the major products.



Scheme 11 Intramolecular C–H insertion of terminal vinyl-containing diazoacetates.

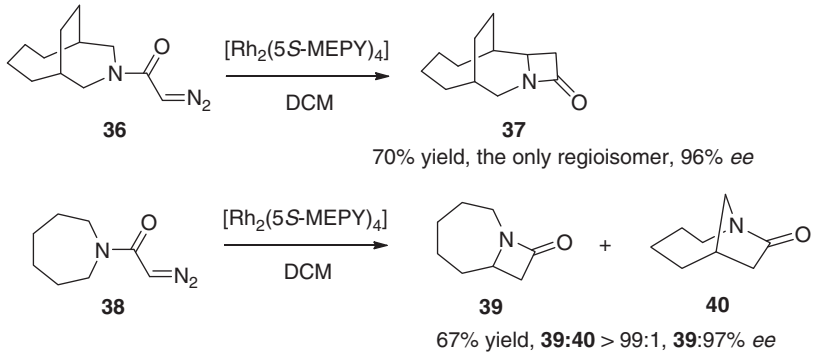
Compared to diazoacetates, diazoacetamides can exhibit more insertion patterns when they have two different *N*,*N*-substituents as the insertion candidates. Using different chiral dirhodium(II) catalysts, Doyle and coworkers systematically studied the regio- and enantioselectivity of intramolecular C–H insertion of diazoacetamides and illustrated the detailed relationship between catalyst type, substrate structure, and product distribution (Scheme 12).[40,57,58] With disubstituted diazoacetamides **33** as the substrates, formation of the five-membered ring structure from insertion of the secondary C–H bonds was observed as the predominant or exclusive reaction when the substituent R is electron donating, such as ethyl and ethoxy groups. Using $[Rh_2(4S\text{-MEOX})_4]$ as the catalyst, the reaction provided good asymmetric induction for both the substrates to produce enantioenriched γ-lactams **34** in excellent yields. When R in **33** is electron-withdrawing substituent such as ester group, it was found that carbene insertion into the electron-deficient C–H bonds adjacent to R substituent was almost completely inhibited. Instead, different regioselectivity could be achieved depending on the nature of the catalyst. With $[Rh_2(5S\text{-MEPY})_4]$ as the catalyst, regioselective insertion into the more challenging primary C–H bonds was observed, forming dimethyl-substituted γ-lactam **36** in a high yield with moderate enantioselectivity. Switching the catalyst to $[Rh_2(4S\text{-BNOX})_4]$ led to regioselective insertion into the relatively more electron-rich secondary C–H bonds, affording the highly strained β-lactam **35** in high yield but poor enantioselectivity, even though γ-lactam formation is conformationally preferred. The poor reactivity toward electron-deficient C–H bonds could be explained by the insertion mechanism, where the rhodium carbene intermediate favors electron-rich C–H bonds due to its electrophilic nature. These transformations clearly indicate that, through structural and/or electronic tuning of the catalysts and substrates, carbene C–H insertions can be regioselectively controlled to functionalize different C–H bonds. This flexible reaction profile enables the formation of different types of ring structures from the same type of starting compounds.



$R = C_2H_5$	cat. = $Rh_2(4S\text{-MEOX})_4$ 82% yield	91 71% *ee*	:	9	:	0
$R = OC_2H_5$	cat. = $Rh_2(4S\text{-MEOX})_4$ 97% yield	100 78% *ee*	:	0	:	0
$R = CO_2C_2H_5$	cat. = $Rh_2(5S\text{-MEPY})_4$ 64% yield	2	:	9	:	89 44% *ee*
$R = CO_2C_2H_5$	cat. = $Rh_2(4S\text{-BNOX})_4$ 64% yield	12	:	88 20% *ee*	:	<1

Scheme 12 Lactam formation via intramolecular C–H insertion of diazoacetamides.

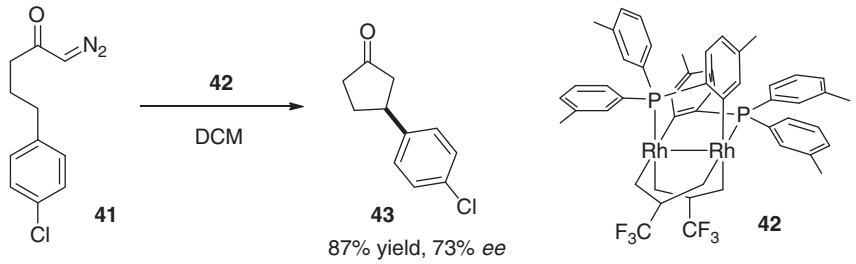
Additional strategies have been demonstrated for the synthesis of chiral β-lactams from diazoacetamides. Since the conformational flexibility of acyclic *N*-alkyldiazoacetamides usually provides favorable access to β-C–H bonds for insertion to form γ-lactam structures, Doyle and coworkers explored diazoacetamides with cyclic amine units, expecting the β-C–H bonds in the ring structures to be restricted from approaching the carbene center. This hypothesis led to the discovery of a highly favored β-lactam formation by [Rh_2(5*S*-MEPY)$_4$] (Scheme 13). 3-Diazoacetyl-3-azabicyclo[3.2.2]nonane (**36**) was shown to form fused β-lactam **37** as the only regioisomer with 96% *ee*. Similarly, azepane-containing diazoacetamide **38** was transformed to β-lactam 1-azabicyclo[5.2.0]nonan-9-one (**39**) exclusively in excellent enantioselectivity. In both cases, no γ-lactam formation was observed. Reactions of diazoacetamide homologs with larger cyclic amine units, such as eight-membered azocane, however, only provided moderate regioselectivity between formation of β- and γ-lactams, most likely due to increased flexibility of the larger ring systems making β-C–H insertion accessible.[59]



Scheme 13 Asymmetric synthesis of β-lactam from cyclic *N*-alkyldiazoacetamides.

In addition to the synthesis of D-deoxyxylolactone from 1,3-dialkoxy-2-propyl diazoacetates **7** (Scheme 5), a similar approach for D-deoxyxylolactams from corresponding diazoacetamides was established as an application of this catalytic intramolecular insertion system.[60]

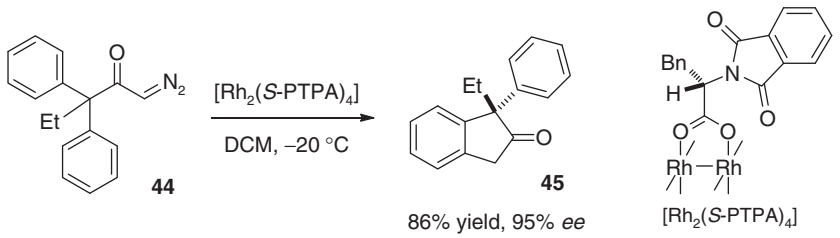
Among several common types of α-diazocarbonyls, diazoketones have been less known as substrates for asymmetric intramolecular C–H insertions.[61,62] One of the most stereoselective examples so far is the intramolecular insertion of 5-(4-chlorophenyl)-1-diazopentan-2-one (**41**) (Scheme 14).[63] Dirhodium(II) complex **42** was employed as the optimal chiral catalyst, giving cyclopentanone **43** in high yield and 73% *ee*. Catalyst **42** represents the first effective chiral dirhodium(II) catalyst that does not contain any chiral ligand. However, the stereoselectivity for this system was generally modest. For example, when the chlorine atom was replaced by other substituents, the *ee* dropped off to a moderate level.



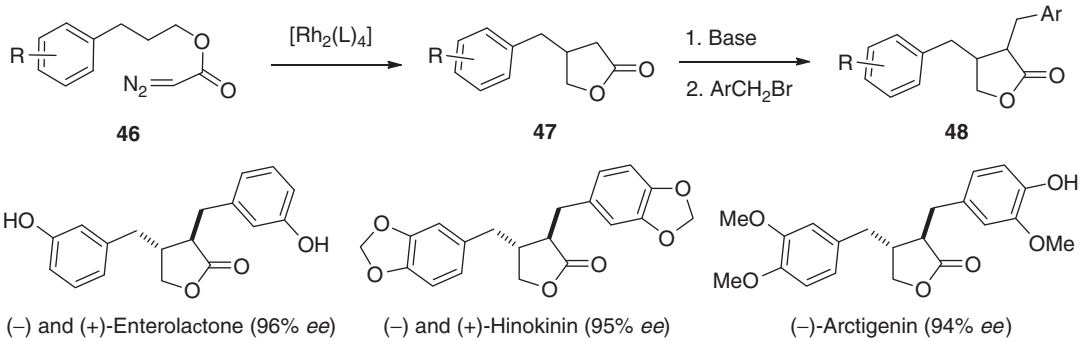
Scheme 14 Asymmetric intramolecular C–H insertions with α-diazoketone.

Metal carbenes have also been known to insert into electron-rich aromatic C–H bonds.[16,64–69] Although carbene insertion into aromatic C–H bonds does not directly form stereocenters, asymmetric versions of this type of transformation have been achieved through desymmetrization strategy. Hashimoto and coworkers used α-diazoketone **44** to explore asymmetric intramolecular insertion into C–H bonds of benzene rings. Dirhodium carboxylate complex [Rh_2(*S*-PTPA)$_4$] was able to differentiate between the two enantiotopic benzene rings in a high degree, affording 1-ethyl-1-phenyl-2-indanone (**45**) with a chiral quaternary carbon center in 86% yield with 95% *ee* (Scheme 15).[70]

Asymmetric intramolecular C–H insertion reactions with acceptor-substituted diazo reagents, α-diazocarbonyls in particular, have been largely developed with the use of dirhodium(II) catalysts, especially Doyle's dirhodium(II) carboxamidates. This well-established method has been widely applied for the synthesis of various useful targets, such as natural products and biologically relevant molecules. In 1996, Doyle and coworkers reported a versatile total synthesis of natural lignan lactones **48** based on their asymmetric intramolecular C–H insertion systems (Scheme 16).[71] Chiral lactone cores with installation of the first chiral center were obtained from asymmetric intramolecular C–H insertion of diazoacetates **46**, which could be synthesized from primary



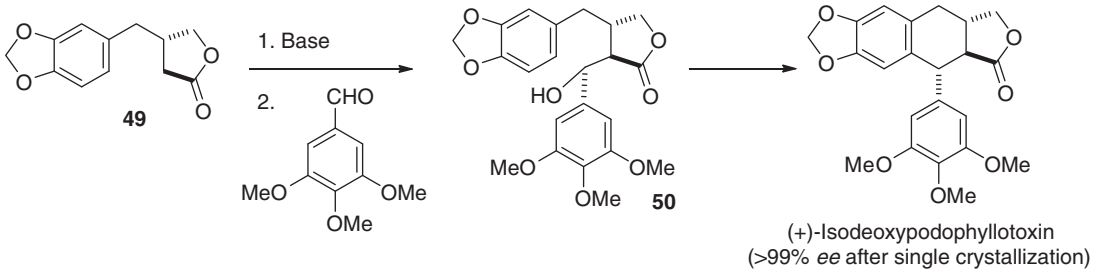
Scheme 15 Asymmetric intramolecular C–H insertions into aromatic C–H bonds.



Scheme 16 Natural product syntheses based on asymmetric chiral lactone formation.

alcohols. The acidic α-C–H bond of lactone **47** was deprotonated and then underwent a diastereocontrolled nucleophilic substitution reaction, forming the second chiral carbon center. With this general pathway, (–) and (+)-enterolactone, (–) and (+)-hinokinin, and (–)-arctigenin were asymmetrically synthesized in 19–27% overall yields with 94–96% *ee*.

Formation of lactones with bicyclic ring structures was also reported with high enantiocontrol. Starting with the enantioenriched lactone core **49**, (+)-isodeoxypodophyllotoxin was prepared as the sole enantiomer through addition to an aldehyde, followed by dehydrative cyclization (Scheme 17).[71]

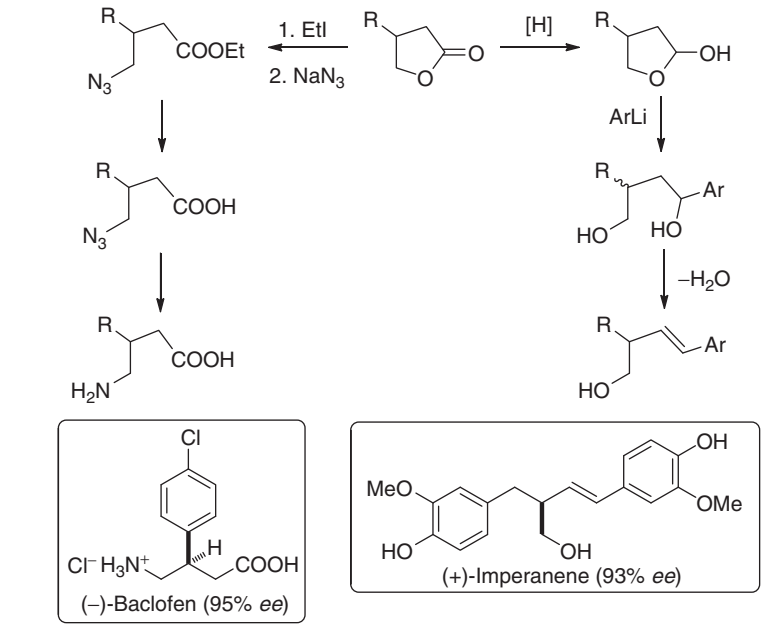


Scheme 17 Asymmetric total synthesis of (+)-isodeoxypodophyllotoxin.

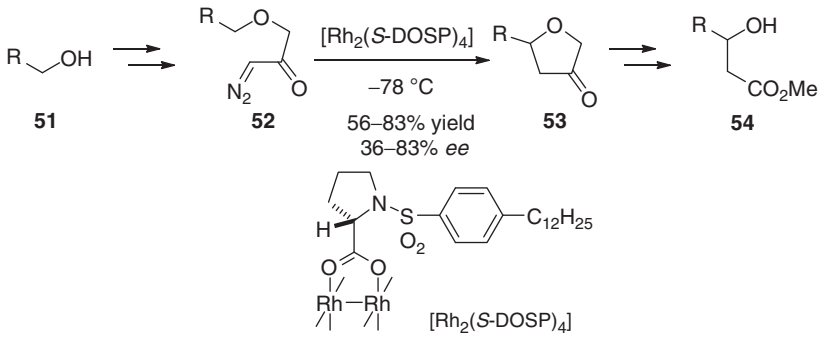
Transformation of lactone structures resulting from asymmetric C–H insertion has been used to construct chiral moieties beyond cyclic structures. For example, asymmetric synthesis of optically pure (–)-baclofen[72] and (+)-imperanene[73] was achieved by Doyle and coworkers through subsequent transformations of the chiral lactone core (Scheme 18).

Intramolecular C–H insertion with α-diazoketones by chiral dirhodium(II) catalysts has also been utilized for synthetic applications, although with much less success due to limited asymmetric induction of the catalytic systems for this type of substrate. From primary alcohol **51**, a general synthesis of chiral secondary alcohol **54** has been designed and performed asymmetrically (Scheme 19).[74] The key step for introducing the chiral center is an intramolecular C–H insertion reaction with α-diazoketones **52**, which could be derived from widely available primary alcohols (**51**). Dirhodium(II) carboxylate [Rh_2(*S*-DOSP)$_4$] was found to be the optimal chiral catalyst for the insertion reaction, obtaining the desired product **53** in moderate yields with modest-to-good enantiocontrol. During the same period of time, few other catalytic systems were reported for intramolecular C–H insertion with α-diazoketones and with considerably less enantiocontrol.[75,76] Instead, [Rh_2(OAc)$_4$]-catalyzed enantiospecific synthesis from optically pure starting materials was shown to be effective for the synthesis of several natural products in their enantiopure form, e.g., (–)-4-thiocyanatoneopupukeanane[77] and 2-thiocyanatoneopupukeanane.[78]

While all the asymmetric insertion systems summarized above were based on the formation of stereogenic carbon centers, a compound with planar chirality was synthesized by Merlic and coworkers in its optically pure form from asymmetric



Scheme 18 Natural product syntheses through transformations of chiral lactones.



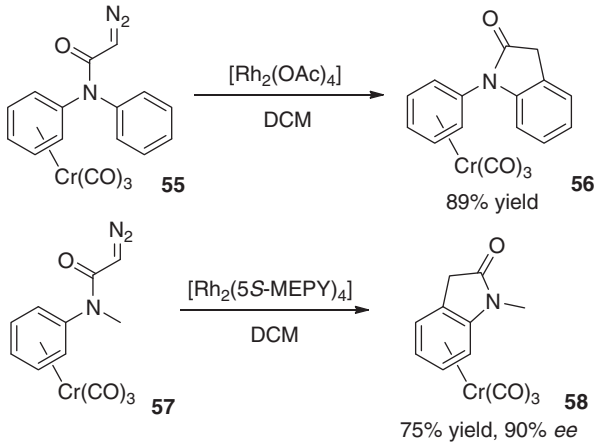
Scheme 19 Synthesis of chiral secondary alcohols from primary alcohols.

intramolecular C–H insertion (Scheme 20).[79] A highly selective formation of **56** from diazo reagent **55** indicates that complexation by chromium carbonyls could deactivate the arene from C(sp^2)–H insertion when compared with noncomplex ones. However, it was also shown that complexation by chromium carbonyls did not totally inhibit an arene from C(sp^2)–H insertion. By using monophenyldiazoacetamide **57**, which contains only chromium-complexed arene, as the substrate, the use of Doyle's [Rh_2(5*S*-MEPY)$_4$] catalyst could catalyze C(sp^2)–H insertion to furnish product **58** in 75% yield, with 90% *ee*.

7.03.2.1.2 Reactions with donor/acceptor-substituted diazo reagents

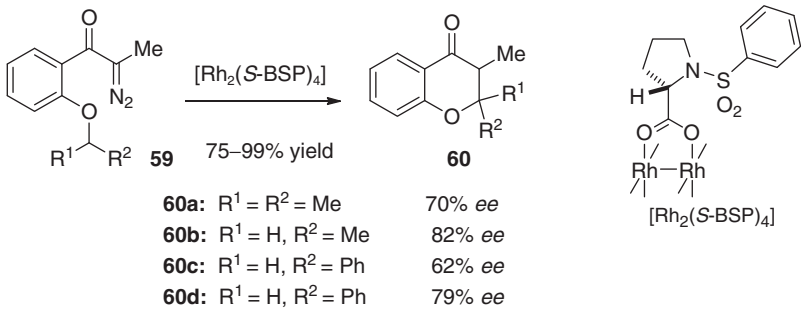
Compared to acceptor-substituted diazo reagents, donor/acceptor-substituted diazo reagents bear one additional electron-donating α-group, such as commonly used aryl and vinyl groups. In addition to aryl- and vinyldiazoacetates, alkyldiazoacetates, which contain electron-donating α-alkyl groups, constitute a special class of diazo reagents that may be generally considered as donor/acceptor-substituted diazo reagents as well. A number of literature reports indicated that aryl- and vinyldiazoacetates possess sufficient reactivity toward Lewis acidic dirhodium(II) catalysts to form corresponding metal carbene species that can proceed the subsequent C–H insertion reactions with well-regulated reactivity and selectivity by the donor substituents.[4,9,10,80] Intramolecular C–H insertion of this type of carbene precursor has proven to be effective and stereoselective.[4,10,81] Due to the presence of two different α-substituents, insertion reactions with donor/acceptor-substituted diazo reagents typically generate two new contiguous stereogenic carbon centers. In addition to enantiocontrol, this type of catalytic transformation poses the challenge of diastereocontrol.

α-Alkyldiazoacetates are often challenging substrates for metal-catalyzed carbene transfers because the corresponding metal carbene intermediates have a high tendency to undergo intramolecular β-hydride elimination.[82,83] In 1992, McKervey and



Scheme 20 Construction of planar chirality via asymmetric intramolecular C–H insertion.

coworkers demonstrated that dirhodium(II) prolinate catalyst [Rh_2(*S*-BSP)$_4$] could successfully catalyze asymmetric intramolecular C–H insertion reaction of α-methyldiazoketone **59** with effective suppression of *β*-hydride elimination. The desired insertion products chroman-4-one derivatives **60** were formed with a good level of enantiocontrol (62–82% *ee*). For products **60b–d,** their *cis*-isomers were afforded as the exclusive diastereomer (Scheme 21).[84]

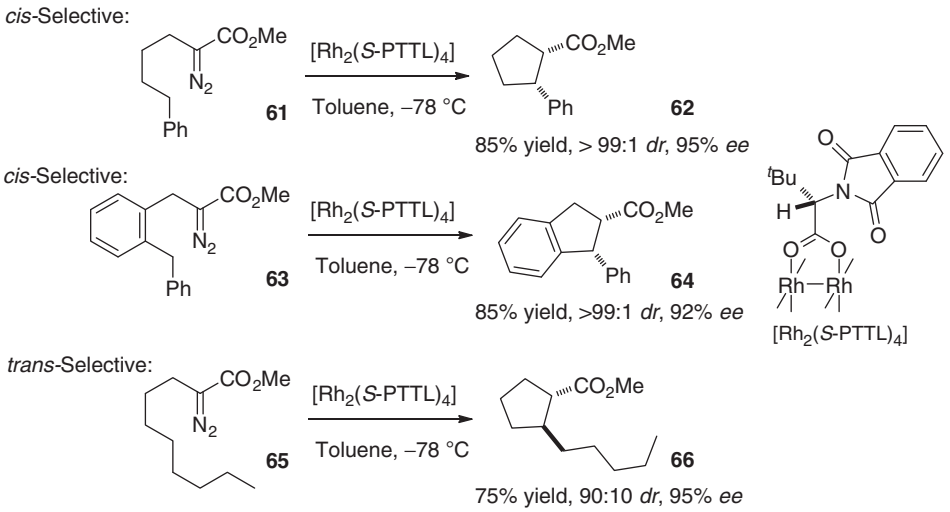


Scheme 21 Asymmetric intramolecular C–H insertion reactions of α-alkyldiazoketones.

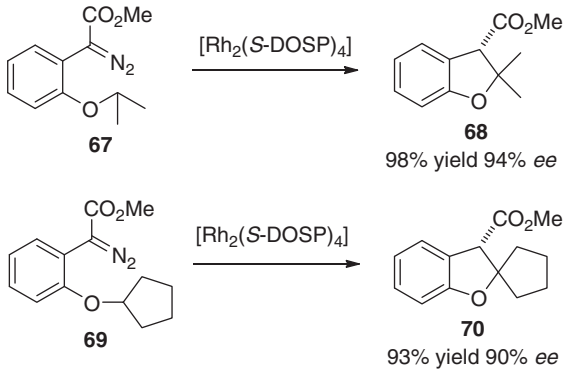
Different from the reactions of diazos **59** that bear primary α-methyl group, insertion reaction with C–H bonds of α-alkyldiazoacetates with longer alkyl chains would result in the formation of all-carbon cyclic structures. Hashimoto and coworkers reported a highly stereoselective synthesis of chiral cyclopentanes via intramolecular C–H insertion of α-alkyldiazoacetates. [Rh_2(*S*-PTTL)$_4$] was the catalyst of choice for this type of selective insertion reaction.[85] Insertions into the benzylic C–H bonds of diazos **61** and **63** afforded exclusively *cis*-2-phenylcyclopentanecarboxylate **62** and *cis*-1-phenyl-indane-2-carboxylate **64**, respectively, both with excellent enantiocontrol. Although without detailed explanation, a very interesting reversal of the diastereoselection was observed for the insertion into the adjacent nonbenzylic C–H bonds of the aliphatic chain. Using the same catalyst under the identical reaction conditions, methyl 2-diazodecanoate (**65**) was shown to form *trans*-cyclopentane **66** as predominant diastereomer with 95% *ee* (Scheme 22).

The asymmetric intramolecular C–H insertion process has been successfully applied for enantioselective synthesis of 2,3-dihydrobenzofuran derivatives. Stereoselective intramolecular insertion into ethereal C–H bonds is the key to this type of transformation. Davies and coworkers reported the first asymmetric insertion into tertiary C–H bonds by using [Rh_2(*S*-DOSP)$_4$] as catalyst (Scheme 23).[86] Donor/acceptor-substituted diazo reagents **67** and **69** with *iso*-propyl and cyclopentyl ether units, respectively, were effectively transformed into corresponding trisubstituted dihydrobenzofurans **68** and **70** with high enantiocontrol. However, intramolecular C–H insertion of the diazo analog with the cyclohexyl ether unit only gave the insertion product in 12% yield, although with 80% *ee*, due to competitive carbene dimerization side reactions.[86]

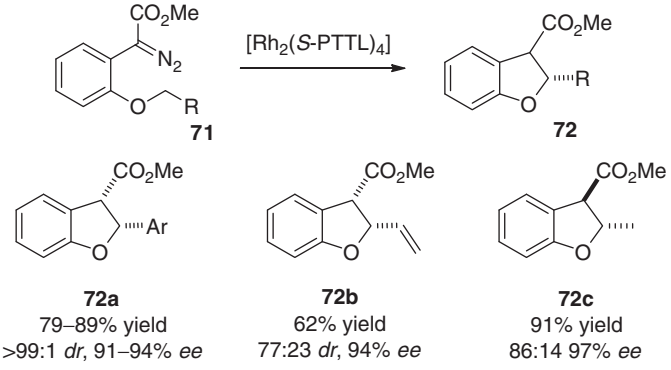
While applying the same catalytic system shown in Scheme 23 for the insertion into secondary C–H bonds only resulted in a moderate level of enantioselectivity,[86] Hashimoto and coworkers were able to use [Rh_2(*S*-PTTL)$_4$] to catalyze asymmetric insertion reactions into various secondary C–H bonds (Scheme 24).[87] Hashimoto's system was generally *cis*-selective. All examples of insertion into benzylic C–H bonds resulted in complete formation of *cis*-2-aryl-2,3-dihydrobenzofuran **72a** with 91–94% *ee*. Allylic C–H insertion was shown to give both moderate yield and diastereoselectivity, affording the major diastereomer **72b** with 94% *ee*. Interestingly, the diastereoselectivity of the insertion process by the same catalytic system was switched to be *trans*-selective for diazo **71** with R=Me, forming 2,3-dihydrobenzofuran **72c** in high yield with *trans*/*cis* ratio of 86:14 and 97% *ee* for the *trans*-isomer.



Scheme 22 Asymmetric intramolecular C–H insertion of α-alkyldiazoacetates.

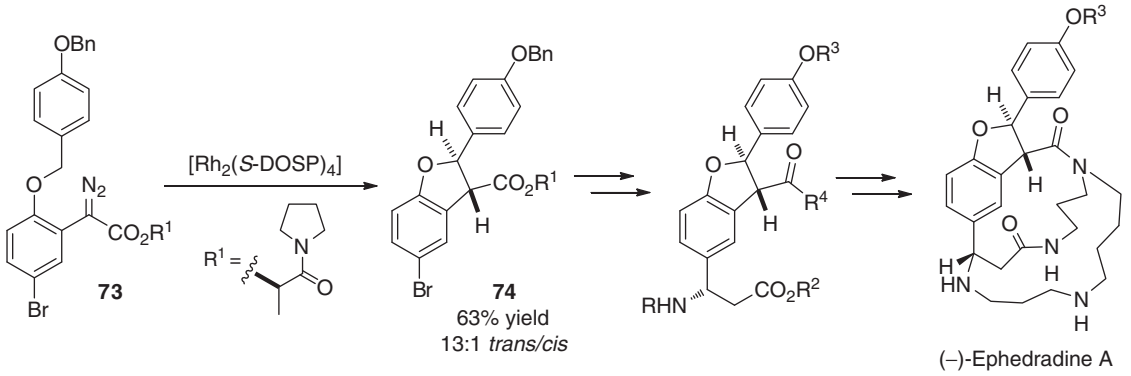


Scheme 23 Asymmetric intramolecular C–H insertion into tertiary C–H bonds of aryldiazoacetates.



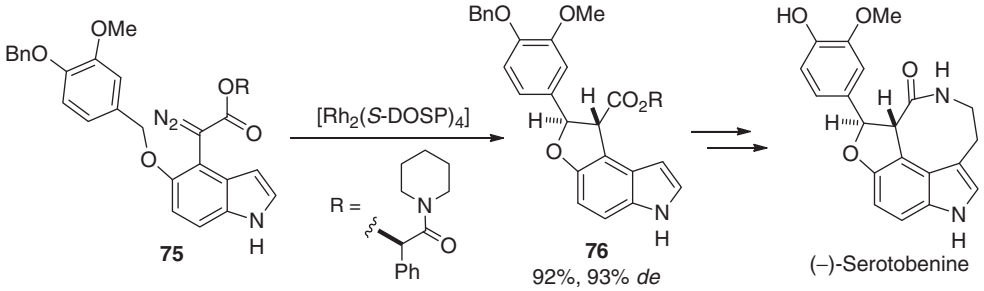
Scheme 24 Asymmetric intramolecular C–H insertion into secondary C–H bonds of aryldiazoacetates.

Dirhodium(II)-catalyzed intramolecular C–H insertion with donor/acceptor-substituted diazo reagents has been successfully applied for total synthesis, particularly through the stereoselective formation of 2,3-dihydrobenzofuran units. Although the above catalytic systems are generally *cis*-selective, many natural products contain 2,3-dihydrobenzofuran units with *trans*-substituents. To address this issue, Fukuyama and coworkers developed a [Rh_2(*S*-DOSP)$_4$]-catalyzed intramolecular insertion with exceptionally high *trans*-selectivity through effective use of chiral auxiliary. Aryldiazoacetate **73** bearing the R^1 chiral auxiliary was transformed into dihydrobenzofuran **74** with a *trans*/*cis* ratio of 13:1, which served as a key chiral building block in their total synthesis of (–)-ephedradine A (Scheme 25).[88,89]



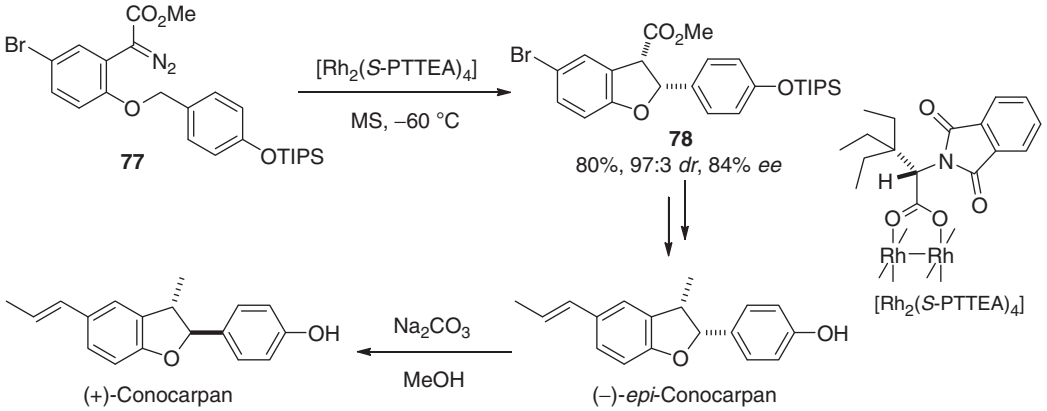
Scheme 25 Total synthesis of (–)-ephedradine A.

A similar strategy was successfully applied for indole-bearing diazo reagent **75**, affording dihydrobenzofuran derivative **76** in a *trans*-configuration. The combination of $[Rh_2(S\text{-DOSP})_4]$ and the chiral auxiliary promoted this high-yielding insertion reaction with high *trans*-diastereoselectivity (93% *de*). Subsequently, (–)-serotobenine was synthesized from **76** through several facile transformations, including deprotection of the chiral auxiliary and construction of the cyclic amide moiety (**Scheme 26**).[90]



Scheme 26 Total synthesis of (–)-serotobenine.

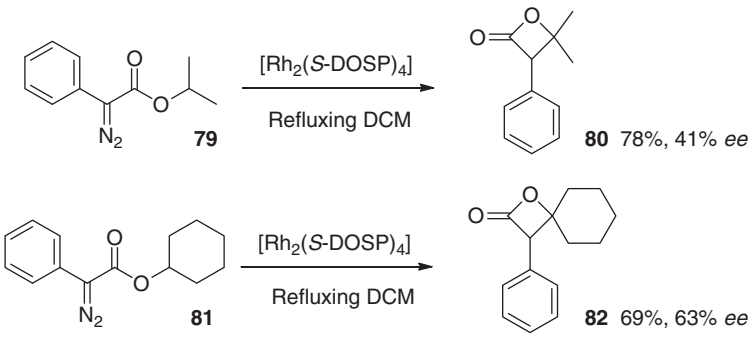
In the absence of the chiral auxiliary, formation of 2,3-dihydrobenzofurans has been shown to be *cis*-selective, as exemplified with the transformation of diazo substrate **77**–**78**. Notably, a facile epimerization process was employed to convert the resulting *cis*-dihydrobenzofuran into its *trans*-epimer. This led to the synthesis of both neolignan natural products (–)-epi-conocarpan and (+)-conocarpan, which contains dihydrobenzofurans in *cis*- and *trans*-configuration, respectively (**Scheme 27**).[91] This effective epimerization strategy was used earlier by Davies and coworkers to convert catalytically generated *cis*-**74** derivative without chiral auxiliary to *trans*-74 isomer, providing a more direct route for asymmetric total synthesis of (–)-ephedradine A.[92]



Scheme 27 Epimerization of 2,3-dihydrobenzofuran in total synthesis.

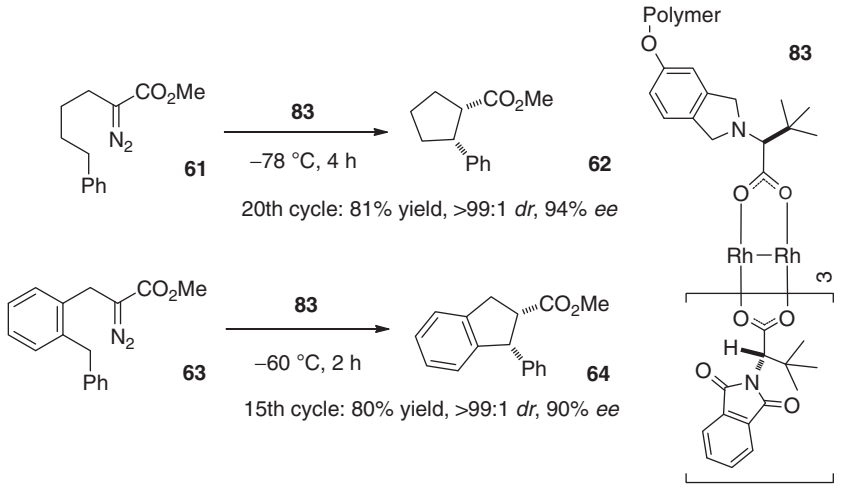
In contrast to the well-established syntheses of five-membered rings via dirhodium(II)-catalyzed intramolecular C–H insertion with donor/acceptor-substituted diazo reagents, asymmetric processes for products with other ring sizes have been less reported.

In 2001, Doyle and coworkers reported a synthesis of four-membered β-lactone with high regioselectivity (generally >50:1) (Scheme 28).[93] With isopropyl phenyldiazoacetate (**79**), insertion into the tertiary C–H bond was much favored over the primary C–H bonds, although the primary C–H bonds should be statistically favored and tertiary C–H insertion leads to highly strained four-membered ring structure. While $[Rh_2(OAc)_4]$ was able to give β-lactone **80** in 84% yield, chiral catalyst $[Rh_2(S\text{-DOSP})_4]$ was shown to produce **80** in 78% yield with 41% *ee*. Cyclohexyl phenyldiazoacetate (**81**) also underwent a selective β-lactone formation, producing **82** in 69% yield with 62% *ee*. Apart from the five-membered ring systems and this four-membered ring system, reports on asymmetric formation of other ring sizes with donor/acceptor-substituted diazo reagents are still rare.



Scheme 28 Synthesis of β-lactone via asymmetric intramolecular C–H insertion of phenyldiazoacetates.

Recently, it has been discovered that polymer-supported Rh_2 catalysts catalyze intramolecular C–H insertion reactions. With chiral-supporting ligands, this type of heterogeneous catalyst can be stereoselective and recyclable. In 2010, polymer-supported catalyst **83** was reported by Hashimoto and coworkers to be effective for intramolecular C–H insertion of different types of alkyldiazoacetates (**61** and **63**), producing chiral cyclopentane derivatives (**62** and **64**) with high yields and stereoselectivity similar to those in homogeneous catalysis,[85] even after 15–20 cycles of recovery and reuse of the catalyst (Scheme 29).[94] The impressive reactivity and selectivity will likely encourage further development of recyclable catalysts for more broad applications in catalytic carbene insertion chemistry.



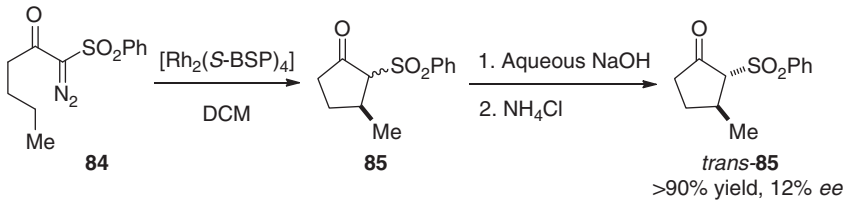
Scheme 29 Intramolecular C–H insertion by polymer-supported recyclable Rh_2 catalyst.

7.03.2.1.3 Reactions with acceptor/acceptor-substituted diazo reagents

While many dirhodium(II) catalysts have been shown to be highly effective with acceptor- and donor/acceptor-substituted diazo reagents in intramolecular C–H insertion chemistry, acceptor/acceptor-substituted diazo reagents, which bear two electron-withdrawing groups at the α-carbon, have also been extensively studied. A number of racemic carbocyclic and heterocyclic compounds were effectively synthesized by using $[Rh_2(OAc)_4]$ as the catalyst[3,11,12,34,95–106] and applied for target synthesis.[107–111] Nevertheless, asymmetric intramolecular C–H insertion with acceptor/acceptor-substituted diazo reagents still remains challenging despite extensive efforts. The ineffectiveness of this process is closely related to the electronic nature of the

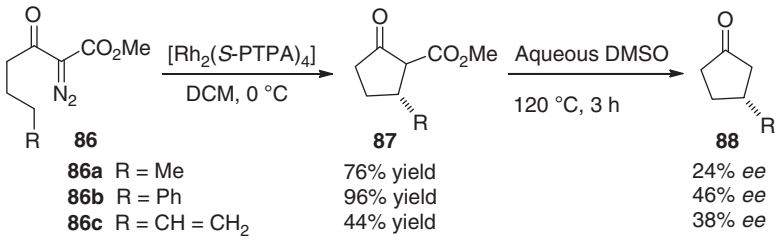
acceptor/acceptor-type diazo compounds and the Lewis acidity of dirhodium(II)-based catalysts. Due to the presence of two electron-withdrawing groups, acceptor/acceptor-type diazo reagents have generally lower reactivity toward Lewis acidic metal catalysts. In contrast to more electron-rich acceptor- and donor/acceptor-substituted diazo reagents, this type of electron-deficient diazo reagent is usually decomposed by dirhodium(II) catalysts at a much slower rate. Even though they can be decomposed under more demanding conditions, the resulting acceptor/acceptor-type metallocarbenes, although usually reactive enough, are intrinsically too electrophilic to undergo a subsequent insertion reaction with high control of stereoselectivity. Although racemic versions of intramolecular C–H insertions with acceptor/acceptor-substituted diazo reagents are known, the difficulty with control of stereoselectivity of these highly electrophilic metallocarbenes has impeded the development of general catalytic systems for effective asymmetric C–H insertion processes.

In 1990, McKervey and coworkers reported the intramolecular C–H insertion with α-diazo-β-ketosulfones **84**, a sulfone-containing acceptor/acceptor-substituted diazo reagent (Scheme 30). By using [Rh_2(*S*-BSP)$_4$] as the catalyst, asymmetric induction was shown for the first time to be possible for this type of transformation, albeit with only 12% *ee* observed. Although the catalytic reaction produced cyclopentanone **85** as a mixture of both diastereomers, *cis*-**85** was able to undergo base-mediated epimerization to form *trans*-**85**.[112]



Scheme 30 Intramolecular C–H insertion with acceptor/acceptor-substituted diazo reagent.

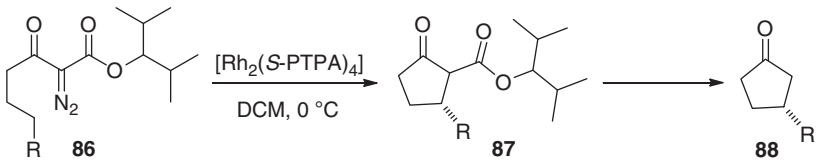
As one of the most common acceptor/acceptor-type diazo reagents, α-diazo-β-ketoesters have been extensively studied for catalytic intramolecular C–H insertion. In 1990, Ikegami and coworkers demonstrated an asymmetric process for insertion into various C–H bonds with this type of diazo reagent.[113] Smooth insertion into alkyl groups in diazo **86a** was demonstrated with the use of [Rh_2(*S*-PTPA)$_4$] as the catalyst, forming 2,3-disubstituted cyclopentanone **87a** in 76% yield. Without addressing the issue of diastereoselectivity, **87a** was converted to 3-substituted cyclopentanone **88a** through demethoxycarbonylation. The *ee* of the final product **88a** was determined to be 24%. In addition, less electron-rich benzylic and allylic C–H bonds (**86b** and **86c**) were also found to be suitable for this catalytic system, but again with limited asymmetric induction. Whereas benzylic C–H insertion (**87b**) was shown to be high yielding (96%), insertion into allylic C–H (**87c**) only resulted in a moderate yield (44%) (Scheme 31).



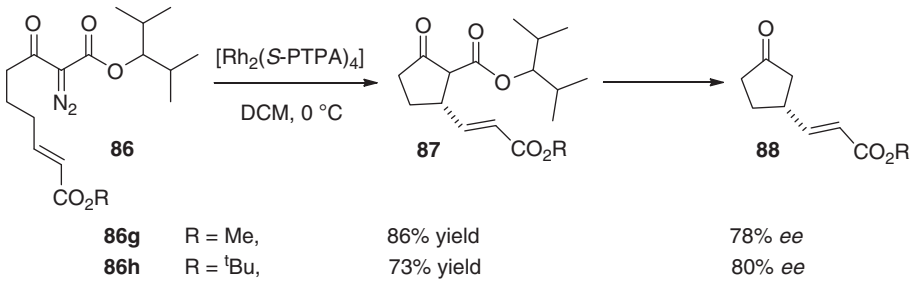
Scheme 31 Asymmetric intramolecular C–H insertion with α-diazo-β-ketoesters. DMSO, dimethyl sulfoxide.

Further efforts were made by Ikegami and coworkers toward improving asymmetric induction by tuning the structure of diazo substrates **86**. With [Rh_2(*S*-PTPA)$_4$] as the optimal catalyst, increase in *ee* was observed for substrates with sterically more hindered ester groups, among which the use of 2,4-dimethylpentan-3-yl group appeared to be the most effective (**86d–f**). Diazo reagents **86d–f** underwent insertion reactions with increase in *ee* by 8–30% over the corresponding methyl esters (**86a–c**) (Scheme 32).[114]

More dramatic substituent effects were observed for allylic C–H insertion reactions as demonstrated with α-diazo-β-ketoester **86g** and **86h** (Scheme 33). Comparing the terminal olefin-based allylic C–H bonds in diazo **86f** (Scheme 31), the insertion reactions into allylic C–H bonds in **86g** and **86h**, which were derived from internal (*E*)-olefins bearing ester groups, proceeded with 78% *ee* (**88g**) and 80% *ee* (**88h**), respectively.[115] It was proposed that the decreased electron density of the allylic C–H bonds as a result of the electron-deficient ester group would reduce the rate of C–H insertion and thus improve the stereoselectivity. Although steric effects could not be ruled out, this explanation is thought to be rational as it is consistent with the experimental observation and the electrophilic insertion mechanism. However, a similar substituent effect was not observed when electron-withdrawing groups were introduced for benzylic C–H bonds.



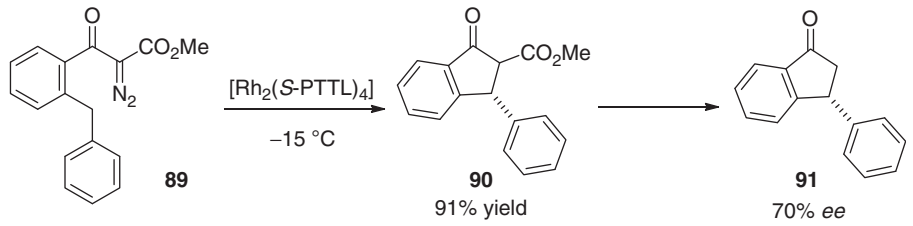
Scheme 32 Asymmetric C–H insertion with sterically hindered α-diazo-β-ketoesters.



Scheme 33 Electronic effect in the insertion of α-diazo-β-ketoesters.

In addition to improving asymmetric induction through fine-tuning structures of chiral catalysts, other strategies have also been explored to obtain cyclic β-ketoesters with high optical purity. Diazo reagents containing enantiomerically pure chiral auxiliaries were used either to undergo diastereocontrolled insertion to enhance chiral induction by achiral catalyst $[Rh_2(OAc)_4]$,[116–120] or in combination with the use of chiral Rh_2 catalysts.[114,121,122] In spite of these efforts, catalytic systems that are general and effective for intramolecular C–H insertion of α-diazo-β-ketoesters remain to be developed.[3]

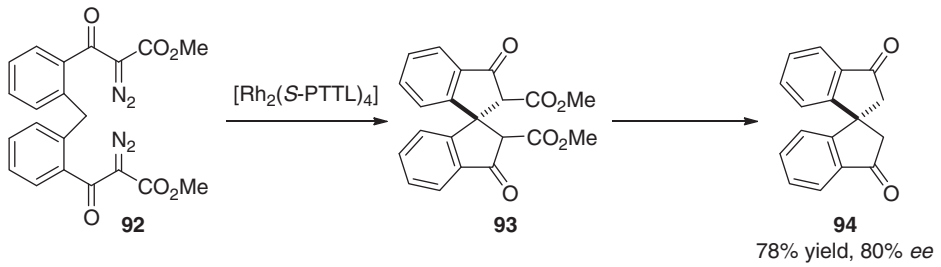
3-Arylindan-1-ones, which serve as important intermediates in the synthesis of several pharmaceuticals, have been shown to be asymmetrically accessible from α-diazo-β-arylketoester **89** by Hashimoto and coworkers (Scheme 34).[123] The intramolecular insertion into the methylene between two aryl groups turned out to be generally effective, giving the desired product in more than 90% yields by chiral Rh_2 catalysts. $[Rh_2(S\text{-PTTL})_4]$ was found to be the optimal catalyst for the transformation to give β-ketoester **90** in 91% yield. Subsequent demethoxycarbonylation led to the formation of 3-phenyl-indan-1-one (**91**) with 70% *ee*.



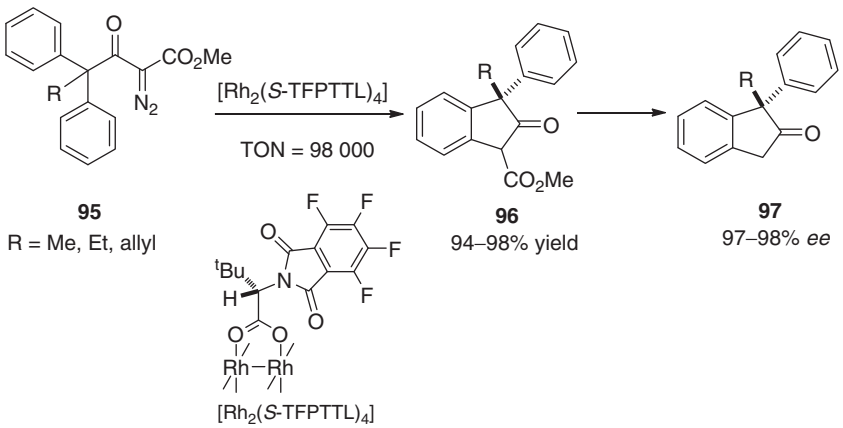
Scheme 34 Intramolecular insertion into methylene between two aryl groups.

An interesting double intramolecular C–H insertion process was reported by Hashimoto and coworkers with the use of dimethyl 2,2′-methylenebis(α-diazo-β-oxobenzenepropanoate) (**92**). The chiral spiro compound **93** with C_2-symmetry was produced after two sequential insertions into the methylene unit, leading to generation of the quaternary carbon center. 1,1′spirobi[indan-3,3′-dione] (**94**) was readily obtained from the insertion product **93** in an overall yield of 78% and with 80% *ee* (Scheme 35).[124] The first insertion into one of the methylene C–H bonds in bisdiazo **92** was believed to construct the chiral methine unit asymmetrically. In accordance with the concerted insertion mechanism, the second insertion into the initially formed methine should be a highly stereospecific process with retention of the configuration.

Enantioselective acceptor/acceptor-type carbene insertion into electron-rich aromatic C–H bonds has also been reported. Dirhodium(II)-based catalysts were shown to be suitable for desymmetrization of diazo reagents **95** via insertion into the aromatic sp^2 C–H bonds (Scheme 36).[70,125] While Hashimoto's earlier report demonstrated that $[Rh_2(S\text{-PTPA})_4]$ could catalyze the formation of 1-methyl-1-phenyl-2-indanone (**96**) (R=Me) with 74% *ee* after removal of the ester group,[70] his modified catalyst $[Rh_2(S\text{-TFPTTL})_4]$ with tetrafluoroaryl unit enabled a high-yielding insertion reaction with exceptionally high enantiocontrol (97–98% *ee*).[125] The catalyst was effective and highly stable; a TON of 98 000 was achieved by using 0.001 mol% catalyst



Scheme 35 Asymmetric double intramolecular C–H insertion.



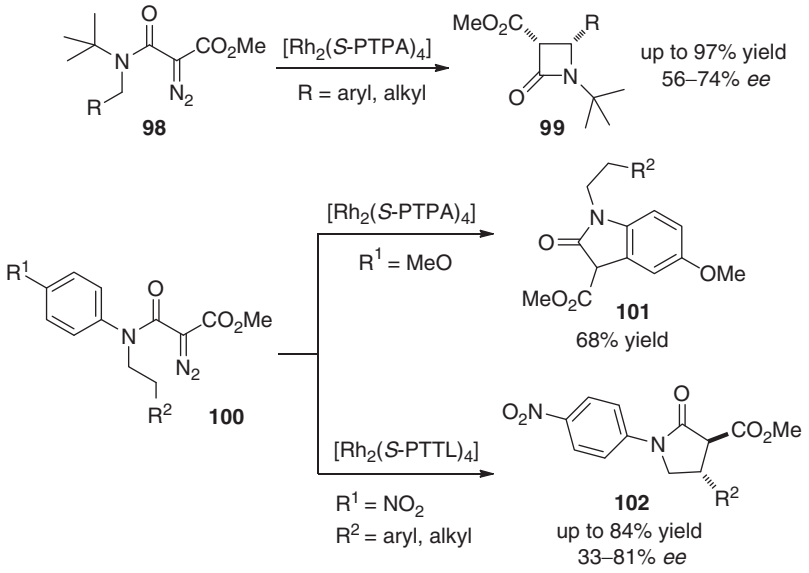
Scheme 36 Desymmetric intramolecular insertion reactions into aromatic sp^2 C–H bonds.

loading. This desymmetrization based on aromatic C(sp^2)–H insertion of α-ketodiazoacetates, together with the diazoketone-based system in Scheme 15, provides a fundamentally important approach to access quaternary chiral centers, which is challenging to achieve through direct insertion of tertiary C–H bonds.

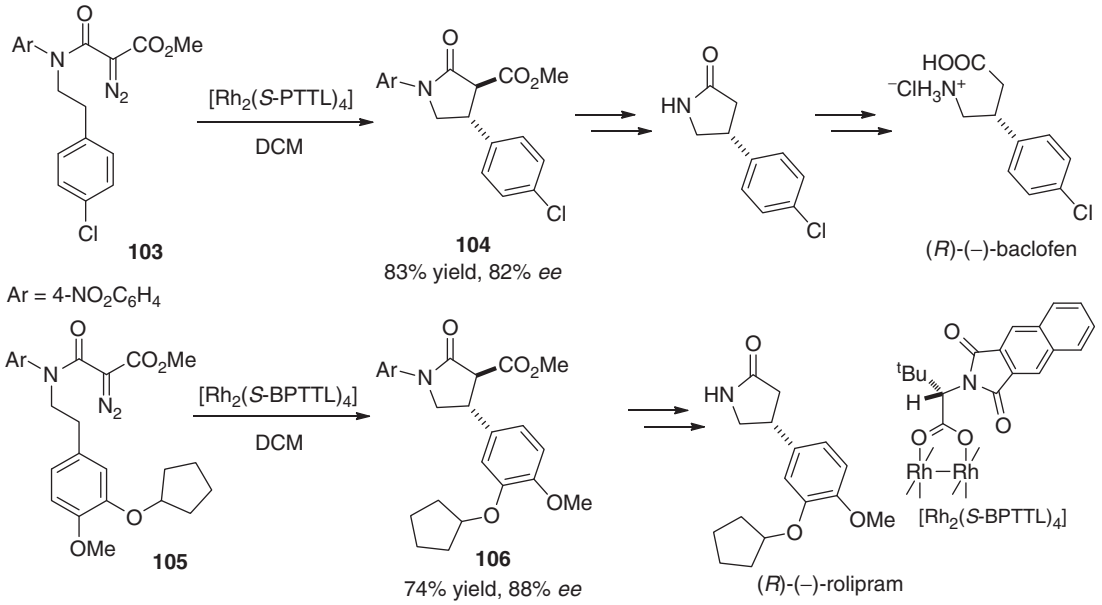
The involvement of amide moieties in the acceptor/acceptor-substituted diazo reagents leads to a more diversified reaction profile. Different ring structures could be formed through substituent control and catalyst design. For example, due to the presence of the *N*-^{t}butyl group, diazoacetamides **98** were completely cyclized by [Rh_2(*S*-PTPA)$_4$] to form β-lactams **99**, even when formation of a five-membered ring was possible (R = *n*-propyl). Apart from the complete regioselectivity, this transformation was exclusively *cis*-selective, producing β-lactams **99** with 56–74% *ee*.[126] While the nitrogen atom generally activates the adjacent C–H bonds, the effect of *N*-substitution was also shown to be crucial to the regioselectivity. *N*-Aryl groups, instead of *N*-*tert*-butyl groups, could function as a site-control element for the insertion of diazo reagents **100**.[127] The electron-donating MeO group highly activates the phenyl group, making the electrophilic insertion into the *N*-aryl C(sp^2)–H bonds more favorable than the *N*-alkyl C(sp^3)–H bonds.[128] Accordingly, the C(sp^2)–H insertion product oxoindoline **101** was isolated as the predominant product. In contrast, the electron-withdrawing NO_2^- group deactivates the aryl group, making the electrophilic insertion into the *N*-aryl C(sp^2)–H bonds less favorable than that into the *N*-alkyl C(sp^3)–H bonds. Although only moderate enantiocontrol was observed with the optimal catalyst [Rh_2(*S*-PTTL)$_4$], the C(sp^3)–H insertion product γ-lactam **102** was exclusively formed as *trans*-isomer, without formation of either oxoindoline or β-lactam (Scheme 37).[128]

Although lactam formation from acceptor/acceptor-type diazoacetamides by Rh_2 catalysts is generally known to be modestly enantioselective, it was successfully employed with a good level of enantiocontrol for several specific target syntheses, such as the syntheses of pharmaceutically important molecules (*R*)-(–)-baclofen[128] and (*R*)-(–)-rolipram[129] by Hashimoto and coworkers. Both syntheses are based on a key step of Rh_2-catalyzed intramolecular asymmetric C–H insertion of diazoacetamides. Substitution of the amide moiety with 4-nitrophenyl group in diazoacetamides **103** and **105** resulted in highly selective formation of *trans*-γ-lactam key intermediates **104** (82% *ee* by [Rh_2(*S*-PTTL)$_4$]) and **106** (88% *ee* by [Rh_2(*S*-BPTTL)$_4$]), respectively (Scheme 38).

In addition to γ-lactam-based applications, formation of β-lactam by intramolecular C–H insertion has also been employed as a key step for construction of target molecules, as demonstrated by Hashimoto and coworkers for the synthesis of trinem antibiotics.[130,131] Using [Rh_2(*S*-PTPA)$_4$] as the catalyst, intramolecular C–H insertion of acetyldiazoacetamide **107** proceeded smoothly to give β-lactam **108** in high yield, but with no asymmetric induction at all (Scheme 39). Although it is a difficult concept to understand, experimental results revealed that the enantioselectivity for the β-lactam formation could rise from racemic to ≥90% *ee* by simply replacing the acetyl-containing diazo reagent **107** with a sterically similar methoxycarbonyl-containing diazo reagent **109**. Another remarkable feature of this fused β-lactam synthesis is its exclusive *trans*-selectivity, which is



Scheme 37 Intramolecular insertion of acceptor/acceptor-substituted diazoacetamides.

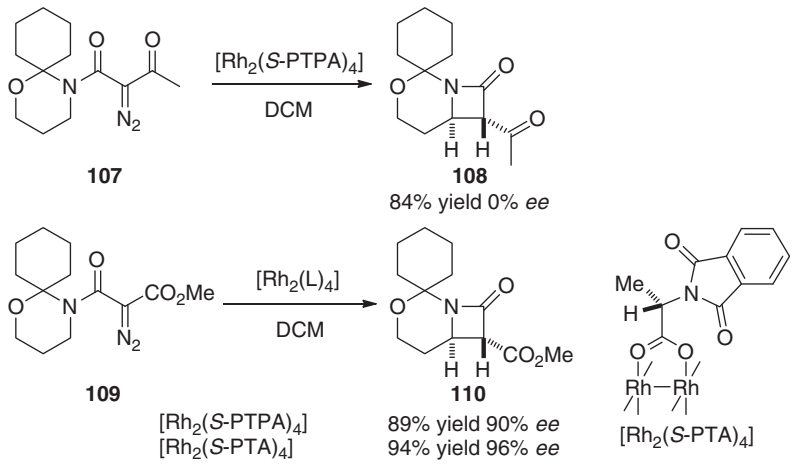


Scheme 38 Total synthesis of (*R*)-(–)-baclofen and (*R*)-(–)-rolipram.

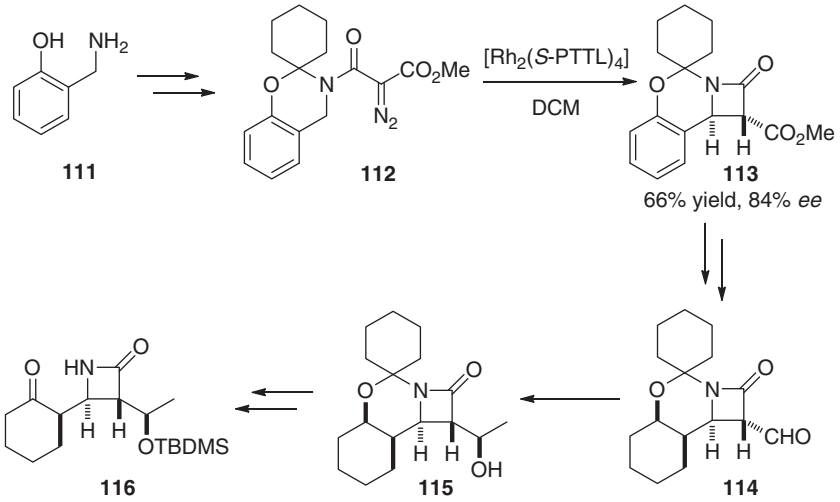
opposite to the *cis*-selectivity observed for the formation of β-lactam **99** from structurally flexible diazo reagent **98** (Scheme 37). Using the optimal catalyst [Rh_2(*S*-PTA)$_4$], the fused β-lactam **110** could be obtained from diazo reagent **109** in 94% yield and 96% *ee*, which serves as a key chiral intermediate for the chemical synthesis of carbapenem antibiotics (Scheme 39).[130]

By employing asymmetric formation of chiral β-lactam core, Hashimoto and coworkers were able to construct more complex target molecules with multiple chiral centers. Starting from 2-(aminomethyl)phenol (**111**), acceptor/acceptor-type diazo **112** was synthesized in 3 steps in 66% overall yield. Intramolecular C–H insertion reaction of **112** by [Rh_2(*S*-PTTL)$_4$] furnished *trans*-**113** as the sole diastereomer with 84% *ee*. The resulting β-lactam **113** was recrystallized to afford optically pure (+)-enantiomer. Subsequently, sequential reduction of the phenyl and ester groups produced β-lactam alcohol **115** bearing five consecutive stereogenic carbon centers. Compound **115** was then converted to β-lactam-containing cyclohexanone (+)-**116**, which served as a key intermediate for the synthesis of sanfetrinem and its derivatives (Scheme 40).[131]

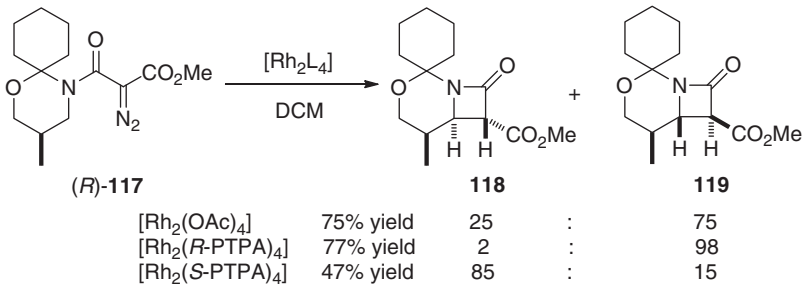
An alternative strategy to synthesize β-lactam derivatives with multiple chiral centers is based on the use of chiral, nonracemic precursors, such as diazoacetamide (*R*)-**117** (Scheme 41).[132] This insertion process is controlled jointly by the catalyst and substrate. Compared to the [Rh_2(OAc)$_4$]-based system, Hashimoto and coworkers reported that the combination of



Scheme 39 Fused β-lactam formation via asymmetric intramolecular insertion.



Scheme 40 Synthetic applications of chiral β-lactam compounds.



Scheme 41 Substrate-controlled synthesis of β-lactam with multiple chiral centers.

$[Rh_2(R\text{-PTPA})_4]$ and (*R*)-**117** could constitute a matching pair for achieving good reactivity and enhancing diastereoselectivity. As a result, β-lactam isomers **118** and **119** were obtained in an exceptionally high ratio of 2:98. With the opposing configuration, $[Rh_2(S\text{-PTPA})_4]$ was shown to be mismatched with (*R*)-**117**, resulting in the decrease in yield for the β-lactam formation. Interestingly, the diastereoselection of the insertion was dramatically reversed, affording β-lactam **118** as the major isomer. This diastereocontrolled strategy has been applied for the synthesis of natural product, including (–)-eburnamonine[133] and (–)-astrogorgiadiol.[134]

The dirhodium(II)-based catalytic system has been employed for intramolecular C–H insertion of other acceptor/acceptor-type diazo reagents such as α-diazo-α-phosphorylacetamides, producing phosphoryl lactams with different ring sizes. Efforts have been made to enable asymmetric versions of this process, including development of suitable chiral Rh_2 catalysts[135,136] and the use of chiral ionic liquids as media.[137] However, these attempts only resulted in low levels of enantiocontrol (up to 40% *ee*).

In general, intramolecular C–H insertion has been extensively studied with different types of diazo reagents. A number of enantiomerically enriched cyclic structures, such as lactones, lactams, and all-carbon cyclic compounds, have been synthesized via dirhodium(II)-based catalytic systems. Effective chiral catalysts, including dirhodium(II) carboxamidates and dirhodium(II) carboxylates, have been developed for highly stereoselective insertion reactions of acceptor- and donor/acceptor-substituted diazo reagents. By contrast, highly selective systems for acceptor/acceptor-substituted diazo reagents are still limited and warrant further development. The high electrophilicity of the resulting acceptor/acceptor-type metal carbene is believed to be mainly responsible for the challenge associated with stereoselective control for insertion reactions of this type of diazo reagent. In addition to designing new generation chiral ligands to improve the Rh_2-based catalytic system toward reactions of acceptor/acceptor-substituted diazo reagents, exploration of different metal ions for catalyst development could open new opportunities for regulation of the stereochemistry of the acceptor/acceptor-type carbene species.

7.03.2.2 Intermolecular Insertion

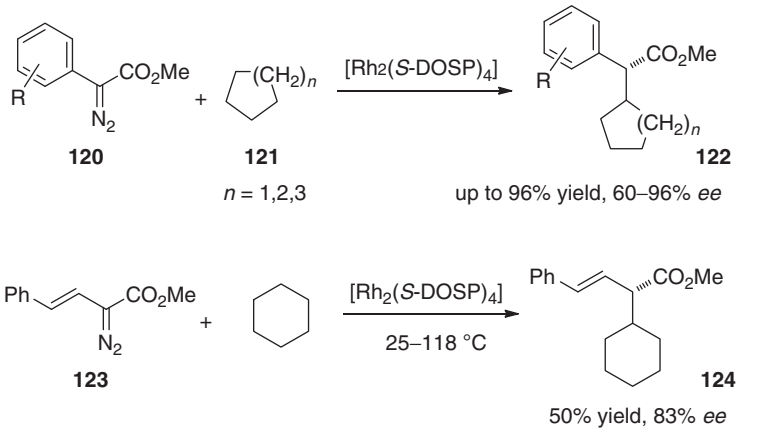
Intermolecular carbene insertion into C–H bonds catalyzed by transition metals has been known for decades.[3,4,10,138–140] Early reports on copper- and rhodium-based catalysts indicated that they were not able to promote this type of reaction in a highly selective manner. High levels of chemoselectivity were shown to be challenging in many cases, largely due to the competitive carbene dimerization reaction. Without the advantages associated with intramolecularity, intermolecular processes often suffered from low regioselectivity. These selectivity issues chronically limited the synthetic applications of intermolecular carbene C–H insertion reactions. Since the 1990s, Davies and coworkers have developed stereoselective intermolecular C–H insertion chemistry by using aryl- and vinyldiazocarbonyl compounds, two important types of donor/acceptor-substituted diazo reagents, as carbene sources.[4,7,9,10,141,142] These diazo reagents were shown to be effectively decomposed by dirhodium(II) carboxylates and to undergo insertion reactions into various C–H bonds. With [Rh_2(*S*-DOSP)$_4$] and several other chiral dirhodium(II) carboxylates as catalysts, intermolecular C–H insertion reactions could be well-regulated to achieve high levels of regio- and stereoselectivity. Recently, Fox and coworkers demonstrated that alkyldiazoacetates, another type of donor/acceptor-substituted diazo reagent with known challenges for metal-catalyzed carbene transfers, were also able to function as suitable carbene sources for selective intermolecular C–H insertion reactions through the employment of proper catalysts.[143,144] Although typically more challenging than intramolecular systems, intermolecular carbene C–H insertion processes enjoy flexibility with the use of various combinations of C–H substrates and diazo reagents, allowing formation of products with more diversified structures.

7.03.2.2.1 Reactions with aryl- and vinyldiazocarbonyl compounds

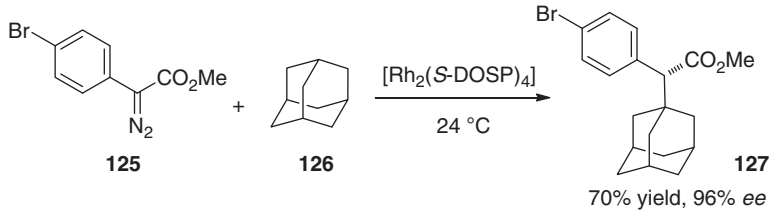
During the past two decades, aryl- and vinyldiazocarbonyl compounds have been systematically studied by Davies and coworkers as effective carbene sources for Rh_2-catalyzed C–H insertion reactions.[3,4,7,10,81] The resulting donor/acceptor-type metal carbene intermediates were shown to asymmetrically insert into different types of C–H bonds, including C–H bonds in alkanes, benzylic C–H bonds, allylic C–H bonds, and C–H bonds adjacent to heteroatoms. The combination of Rh_2-based catalysts and donor/acceptor-substituted diazo reagents has led to the development of a number of highly stereoselective insertion systems. Since several comprehensive reviews by Davies on these insertion systems have already appeared,[4,7,9,10,80,81,141,142,145–147] this section mainly introduces some representative examples of dirhodium(II)-based catalytic systems for asymmetric intermolecular C–H insertion with aryl- and vinyldiazocarbonyl compounds. In addition, select applications for target synthesis are also summarized to illustrate the great synthetic potential of these catalytic systems.

Enantioselective intermolecular C–H insertion of aryl- and vinyldiazoacetates was first demonstrated by Davies and coworkers in 1997.[148] Using cycloalkanes **121** as solvent, phenyldiazoacetate derivatives **120** underwent effective catalytic insertion reactions into the C–H bonds in the alkanes (Scheme 42). The use of chiral catalyst [Rh_2(*S*-DOSP)$_4$] resulted in highly enantioselective formation of 2-cycloalkyl-2-arylacetates **122**. While the reactions produced insertion products only in moderate yields at room temperature, large increases in yield (up to 96%) were achieved when the reactions were carried out in refluxing cycloalkanes. A later study indicated that a high temperature was not necessary for achieving high yields if degassed cycloalkanes were used. For example, at 10 °C, aryldiazoacetates **120** were smoothly converted to the corresponding products with generally more than 90% *ee*.[149] The substituents on α-aryl group of the diazo reagents were found to influence both reactivity and enantioselectivity of the insertion process. In general, electron-withdrawing groups (such as Cl^-) gave better yields and enantioselectivity for the reaction than electron-donating groups (such as MeO^-). In addition to aryldiazoacetates, vinyldiazoacetate **123** was also demonstrated for the first time to undergo intermolecular C–H insertion reaction with cycloalkanes such as cyclohexane, furnishing the insertion product **124** with high enantioselectivity (83% *ee*), although in a moderate yield.

The insertion into the tertiary C–H bond with aryldiazoacetates was also possible as successfully demonstrated for the reaction of adamantane (**126**).[149] Using [Rh_2(*S*-DOSP)$_4$] as the catalyst, reaction of adamantane (**126**) with methyl 4-bromophenyldiazoacetate (**125**) produced the insertion product **127** in 70% yield with 96% *ee* (Scheme 43). In addition to cycloalkanes, C–H bonds of simple acyclic alkanes could also be generally functionalized with aryldiazoacetates by similar catalytic systems. Among



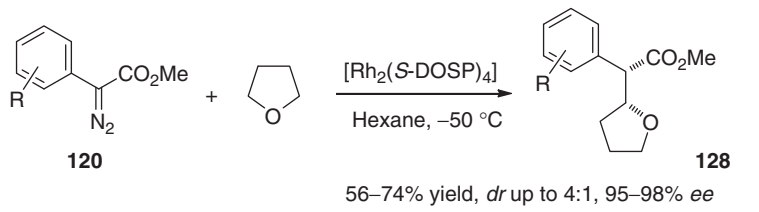
Scheme 42 Enantioselective intermolecular C–H insertion into simple alkanes with aryl- and vinyldiazoacetates.



Scheme 43 Enantioselective intermolecular C–H insertion into adamantane with aryldiazoacetates.

different types of C–H bonds in alkanes, the catalytic carbene insertion usually favors the tertiary C–H bonds, which are relatively more electron rich, although sterically more hindered.[149]

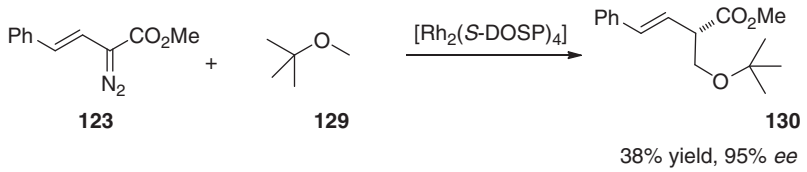
Oxygen and nitrogen atoms can usually direct the electrophilic carbene insertion into their α-C–H bonds as they are able to electronically stabilize the transition state during the catalysis.[150,151] Insertion reactions into C–H bonds that are adjacent to oxygen and nitrogen atoms have been successfully demonstrated by Rh_2-based catalysts, building new stereogenic centers at the α-position to the heteroatoms. [Rh_2(*S*-DOSP)$_4$] has been shown to be a generally effective chiral catalyst for this type of insertion process. In 2000, Davies and coworkers showed that [Rh_2(*S*-DOSP)$_4$] could catalyze stereoselective C–H insertion reaction of tetrahydrofuran (THF) with aryldiazoacetates **120** (Scheme 44).[149] The catalytic insertion reaction occurred selectively into the α-C–H bonds of the oxygen atom, providing compound **128** in moderate-to-good yields. While diastereoselectivity was sometimes moderate, conducting the reaction at low temperature (− 50 °C) allowed for the production of all major diastereomers **128** with excellent enantiocontrol. Due to the high reactivity with THF, the reaction could be effectively performed with only 2 equivalents of the substrate.



Scheme 44 Enantioselective intermolecular C–H insertion into THF with aryldiazoacetates.

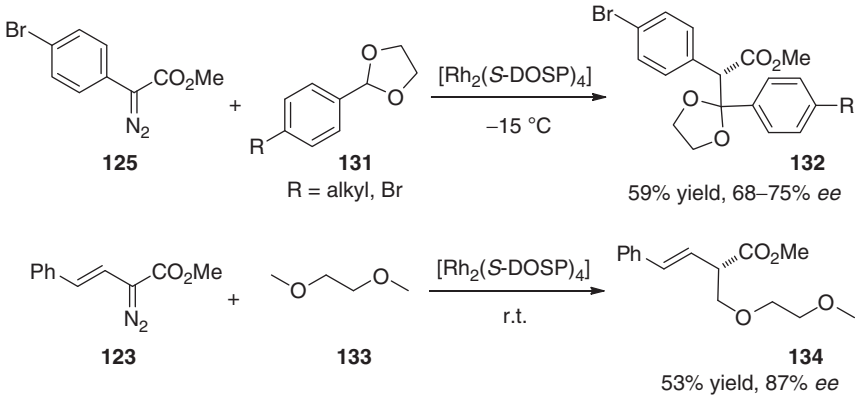
Acyclic ethers are also suitable substrates for intermolecular asymmetric C–H insertion by [Rh_2(*S*-DOSP)$_4$]. For example, Davies and coworkers showed that methyl *tert*-butyl ether (**129**) could be selectively functionalized at the methyl group, although low yields were usually observed (Scheme 45).[150] Styryldiazoacetate **123** was found to be a more suitable reagent than aryldiazoacetates for the C–H insertion reaction by [Rh_2(*S*-DOSP)$_4$], affording the corresponding insertion product **130** with excellent enantioselectivity (95% *ee*).

For substrates containing more than one oxygen atom, these heteroatoms often have different effects on the reactivity and regioselectivity of C–H insertion. Taking cyclic acetal **131** as an example, the tertiary C–H bond α to both oxygen atoms was preferred for intermolecular carbene insertion with aryldiazoacetate **125** by [Rh_2(*S*-DOSP)$_4$] (Scheme 46).[152] Another interesting



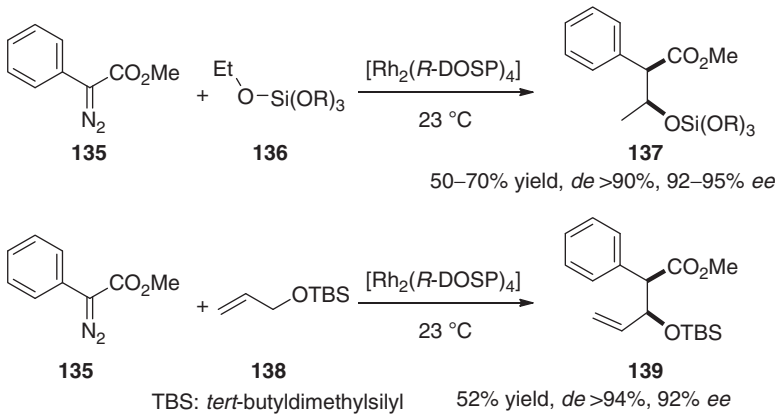
Scheme 45 Asymmetric intermolecular C–H insertion into ether with vinyldiazoacetates.

regioselectivity was observed for C–H insertion reaction of 1,2-dimethoxyethane (**133**) with styryldiazoacetate **123**, which was again found to be a more suitable carbene source than aryldiazoacetates (Scheme 46).[150] Using $[Rh_2(S\text{-DOSP})_4]$ as the catalyst, the product **134**, which resulted from carbene insertion into one of the primary C–H bonds, was isolated in 53% yield with 87% *ee*. Although an α-alkoxy group usually activates the C–H bond, this result indicates that a β-alkoxy group seems to have a stronger deactivating effect, causing the unusual insertion into the primary C–H bond.



Scheme 46 Asymmetric intermolecular C–H insertion into polyethers.

Intermolecular asymmetric insertion with donor/acceptor-substituted diazo reagents has also been extended to employ alkoxysilanes (**136**) as the C–H substrate (Scheme 47).[153,154] With aryldiazoacetate **135** as the carbene source, the insertion reactions of **136** afforded products **137** in moderate yields but with high stereocontrol. Allyl ethers are potentially challenging substrates for C–H insertion because of competitive cyclopropanation of the alkene units. Davies and coworkers reported that the

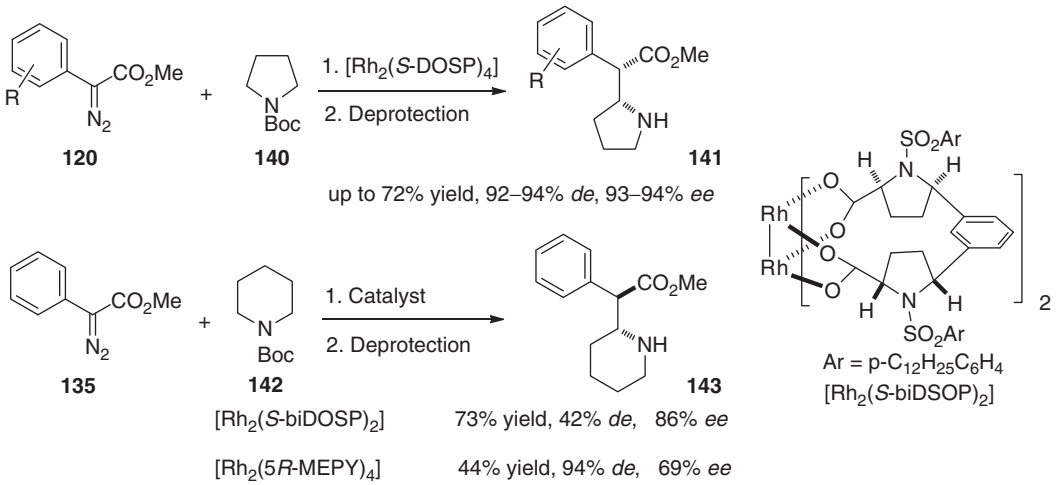


Scheme 47 Synthesis of *syn*-aldol products via asymmetric intermolecular C–H insertion.

$[Rh_2(S\text{-DOSP})_4]$-based catalytic system could undergo highly selective allylic C–H insertion of allyl ether **138** with aryldiazoacetate **135** to produce compound **139** in a moderate yield while minimizing the formation of competitive cyclopropanation product to only 19% yield. Through deprotection of the silyl group, this strategy provides an alternative method for the synthesis of *syn*-aldol products (Scheme 47).[155]

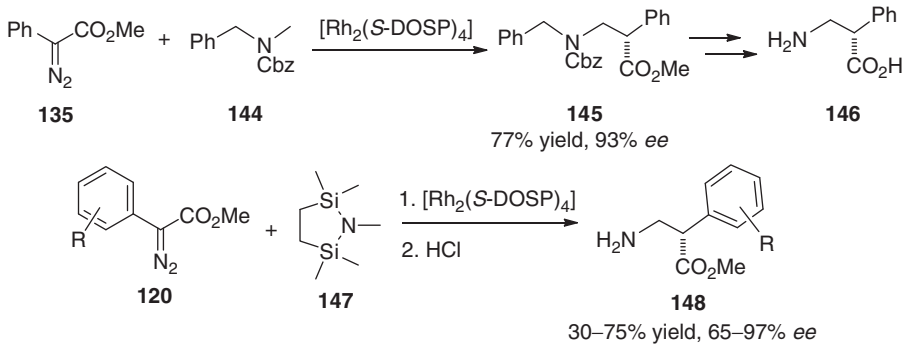
Asymmetric intermolecular carbene insertion into C–H bonds that are adjacent to nitrogen atoms with donor/acceptor-substituted diazo reagents has been fruitfully developed as well. Early examples were reported for insertion reactions of cyclic

substrates, such as cyclic amine derivatives. In 1999, Davies and coworkers reported that asymmetric insertion into the α-C–H bond of Boc-protected pyrrolidine (**140**) with aryldiazoacetates **120** by [Rh_2(*S*-DOSP)$_2$] could produce chiral β-aminoacetates **141** with excellent diastereoselectivity and enantioselectivity in up to 72% overall yields after Boc deprotection (Scheme 48).[156] With the modified catalyst [Rh_2(*S*-biDOSP)$_2$], Boc-protected piperidine (**142**) was enantioselectively transformed to threo-methylphenidate (**143**) with (2*R*, 2′*R*) configuration by carbene C–H insertion. At the same time, Winkler and coworkers independently reported similar synthesis of the same target molecule by using Doyle's [Rh_2(5*R*-MEPY)$_2$] catalyst.[157] Although the yield and enantioselectivity of Davies' synthesis were higher, Winkler's synthesis gave **143** with better diastereoselectivity (Scheme 48). Subsequent systematic studies by Davies and coworkers led to the development of highly selective insertion reactions of pyrrolidine derivatives with different substitution patterns.[158,159]



Scheme 48 Asymmetric intermolecular carbene C–H insertion into nitrogen-containing heterocycles.

Asymmetric insertion into C–H bonds that are adjacent to nitrogen atoms with diazoacetates provides a potentially effective approach to synthesize chiral β-aminoacetates and β-amino acids.[160–163] Davies and coworkers have reported two alternative strategies for this approach, which are based on the use of methylamines with different protecting groups such as **144** and **147** (Scheme 49).[160,161] The resulting chiral β-amino acid derivatives served as key synthons for target syntheses such as the total synthesis of venlafaxine.[161]

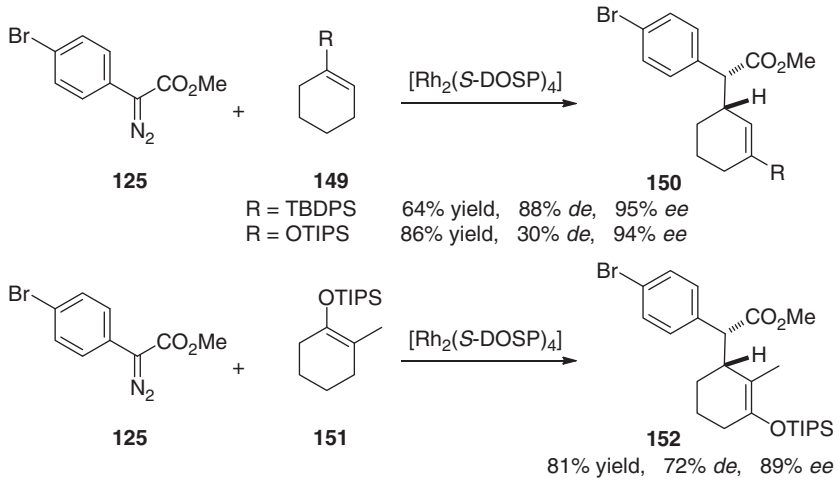


Scheme 49 Asymmetric synthesis of chiral β-amino acid derivatives.

Intermolecular carbene insertion reactions into C–H bonds adjacent to a vinyl group, one of the most common functional groups in organic compounds, have been extensively studied. The major challenge for allylic C–H insertion is the competitive C=C bond addition reactions, namely, cyclopropanation. Electrophilic metal carbene intermediates are usually more reactive toward electron-rich C=C double bonds. While copper-based catalysts were known to favor C=C cyclopropanation over allylic C–H insertion,[164] dirhodium(II)-based catalysts have been shown to promote insertions into allylic C–H bonds in certain types of substrates.

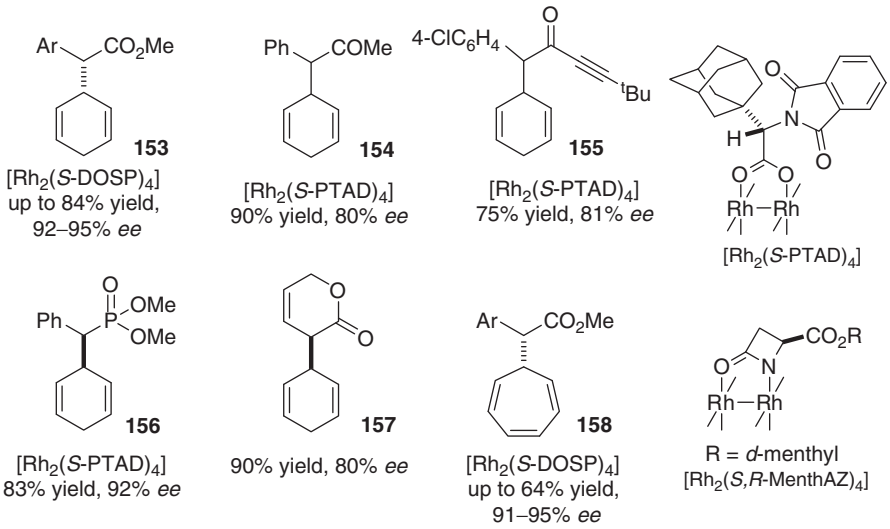
Most examples of allylic C–H insertion with aryldiazoacetates were demonstrated with cyclic olefins with multiple substituents. For nonsubstituted cyclohexene, allylic C–H insertion with aryldiazoacetates was found to be low yielding due to the competitive cyclopropanation and to have poor diastereoselectivity, albeit with a reach of up to 93% *ee*.[164,165] However,

tetrasubstituted alkenes were shown to favor insertion reactions, as demonstrated for reaction of 1-substituted (**149**) and 1,2-substituted cyclohexenes (**151**) with aryldiazoacetate **125**, which provided insertion products **150** and **152**, respectively, in much improved yields with high enantioselectivity (**Scheme 50**).[165,166]



Scheme 50 Asymmetric intermolecular carbene insertion into allylic C–H bonds of substituted cyclohexenes. TBDPS, *tert*-butyldiphenylsilyl ether.

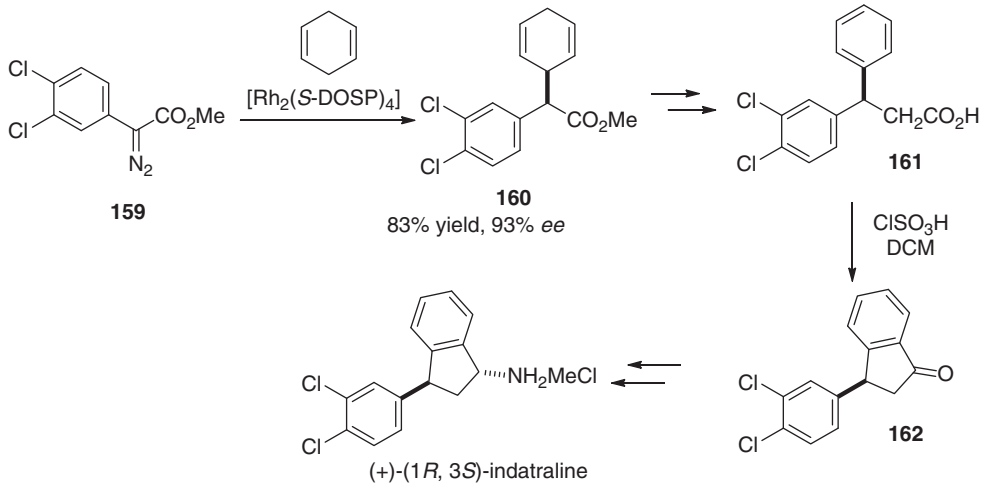
1,4-Cyclohexadiene has been demonstrated to be an exceptionally suitable substrate for Rh_2-catalyzed asymmetric allylic C–H insertion with a wide variety of donor/acceptor-substituted diazo reagents (**Scheme 51**). Davies and coworkers reported several enantioselective insertion systems for allylic C–H insertion of 1,4-cyclohexadiene, including with aryldiazoacetates to produce **153** by $[Rh_2(S\text{-DOSP})_4]$,[167] with aryldiazoketones to produce **154** and **155** by $[Rh_2(S\text{-PTAD})_4]$,[168] and with aryldiazophosphonates to produce **156** by $[Rh_2(S\text{-PTAD})_4]$.[92] Doyle and coworkers reported a $[Rh_2(S,R\text{-MenthAZ})_4]$-catalyzed asymmetric system for insertion reaction of 1,4-cyclohexadiene with cyclic *Z*-vinyldiazoacetates, affording **157** in 90% yield with 80% *ee*.[169] It was shown that dirhodium(II) carboxamidate catalysts played an essential role in achieving high chemoselectivity toward formation of the insertion product **157**, as the same reactions catalyzed by dirhodium(II) carboxylates such as $[[Rh_2(OAc)_4]$ and $Rh_2(S\text{-DOSP})_4]$ resulted in cyclopropane formation as the major product. In addition to 1,4-cyclohexadiene, cycloheptatriene was also shown by Davies and coworkers to be a suitable substrate for asymmetric allylic C–H insertion with aryldiazoacetates by $[Rh_2(S\text{-DOSP})_4]$.[170]



Scheme 51 Asymmetric intermolecular carbene insertion into bisallylic C–H bonds.

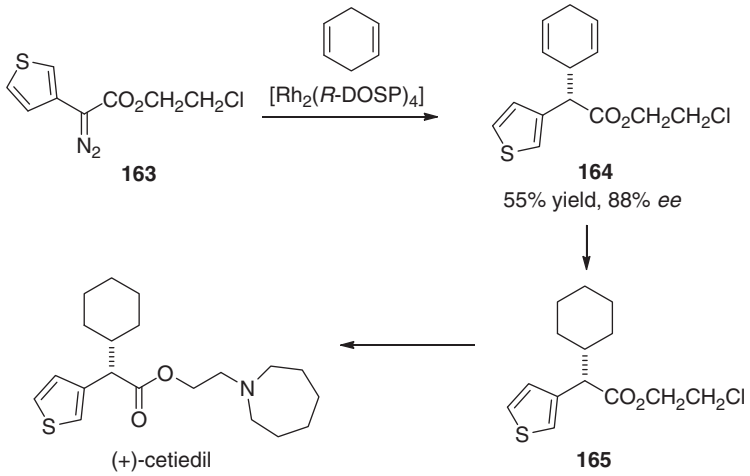
Catalytic asymmetric insertion into bisallytic C–H bonds of 1,4-cyclohexadiene with aryldiazoacetates has been successfully applied for synthesis of several target molecules. For example, $[Rh_2(S\text{-DOSP})_4]$-catalyzed formation of optically pure **160** from

asymmetric insertion reaction of 1,4-cyclohexadiene with diazo reagent **159** was the key step for the 11-step synthesis of (+)-(1*R*, 3*S*)-indatraline by Davies and coworkers (Scheme 52).[171]



Scheme 52 Asymmetric synthesis of (+)-(1*R*, 3*S*)-indatraline.

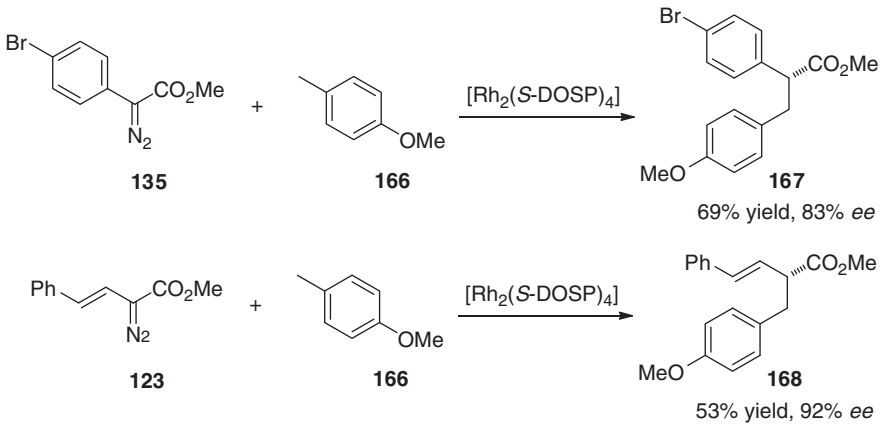
Heteroaryldiazoacetates such as thiophene-based donor/acceptor-substituted diazo reagent were shown to be tolerable in dirhodium(II)-catalyzed carbene insertion reactions. With 2-chloroethyl 2-diazo-2-(thiophen-3-yl)acetate (**163**) as the carbene source, [Rh_2(*R*-DOSP)$_4$]-catalyzed asymmetric allylic carbene insertion of 1,4-cyclohexadiene produced **164** in moderate yield and with 88% *ee*. Enantioenriched **164** was used as an intermediate for the asymmetric synthesis of K^+ channel blocker (+)-cetiedil through a facile reduction and amination sequence (Scheme 53).[172]



Scheme 53 Asymmetric synthesis of (+)-cetiedil.

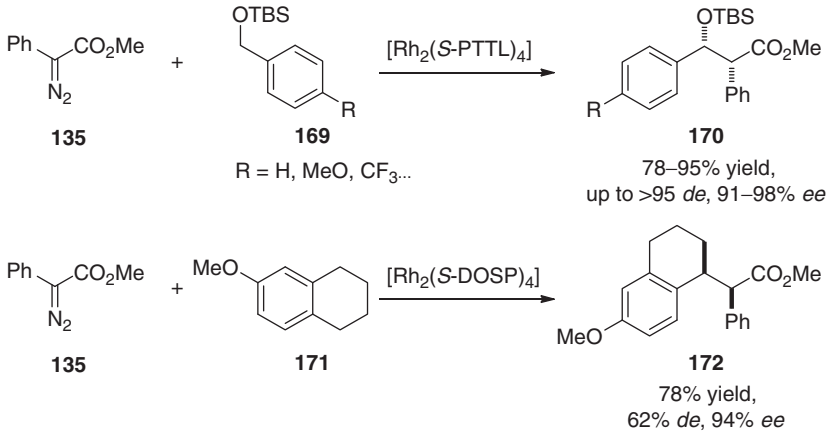
Chemo- and enantioselective insertion into acyclic allylic C–H bonds with aryldiazoacetates has been relatively less reported.[173] Allylic C–H insertion reactions with styryldiazoacetates were found by Davies and coworkers to produce unexpected products through a combined insertion/Cope rearrangement pathway. This catalytic process usually features a high level of stereocontrol as a result of its concerted mechanism. Since several recent reviews by Davies have given a comprehensive treatment of this type of transformation,[4,7,141] no detail is provided here.

Intermolecular carbene insertion into primary C–H bonds at a benzylic position has been shown to be possible with Rh_2^- based catalytic systems. Using Davies catalyst [Rh_2(*S*-DOSP)$_4$], reactions of *p*-methoxytoluene (**166**) with both aryldiazoacetate **135** and styryldiazoacetate **123** gave the corresponding insertion products **167** and **168** in moderate yields with good enantiocontrol (Scheme 54).[174] Methyl styryldiazoacetate (**123**) generally led to more enantioselective insertions than aryldiazoacetates, albeit in a slightly lower yield.



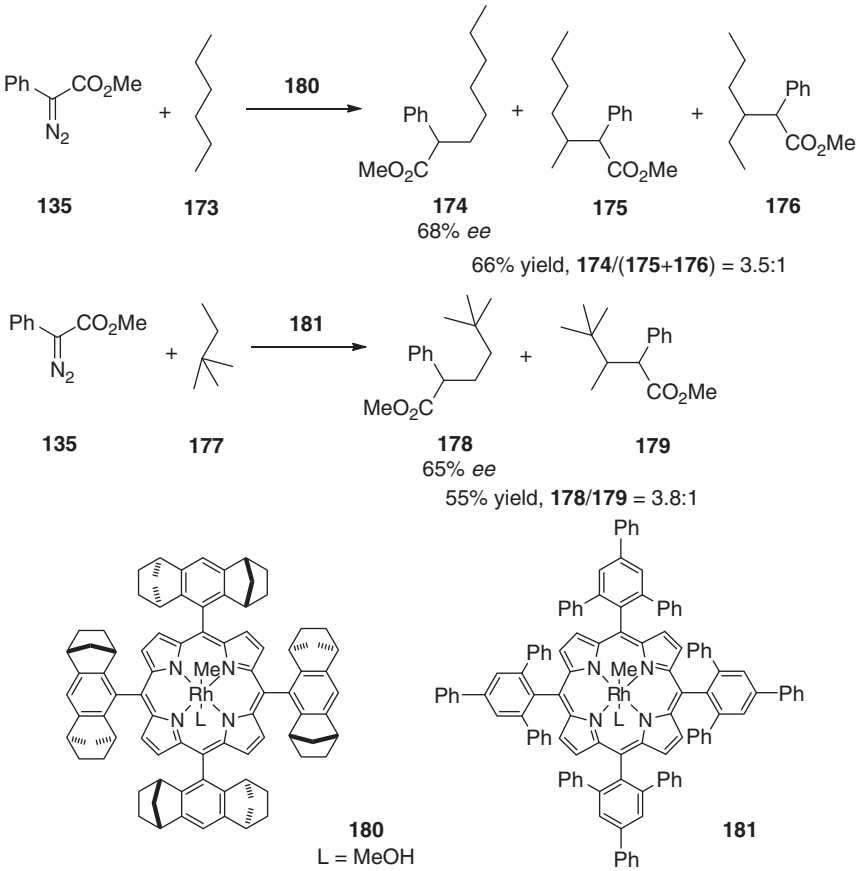
Scheme 54 Asymmetric intermolecular carbene insertion into benzylic primary C–H bonds with donor/acceptor-substituted diazo reagents.

Asymmetric induction for carbene insertion into secondary benzylic C–H bonds could be influenced by the adjacent groups. Davies and coworkers reported that benzyl silyl ethers **169** are suitable substrates for intermolecular insertion reactions by Rh_2-based catalysts. [Rh_2(*S*-PTTL)$_4$] was shown to be the optimal catalyst for promoting the reactions of **169** derivatives, regardless of the electronic properties of the aryl substituents, affording the desired insertion products in up to 95% yield with excellent levels of diastereo- and enantiocontrol.[175] While insertion reaction of ethylbenzene was moderately selective, 6-methoxy-1,2,3,4-tetrahydronaphthalene (**171**) could undergo selective insertion into the more electron-rich benzylic C–H bond in the *para* position of the MeO directing group, forming the corresponding insertion product **172** with high *ee* but moderate diastereoselectivity (Scheme 55).[176] Intermolecular carbene insertion into benzylic tertiary C–H bonds has also been observed but with poor-to-moderate asymmetric induction.[177]



Scheme 55 Asymmetric intermolecular carbene insertion into benzylic secondary C–H bonds with methyl phenyldiazoacetate.

Rh_2-catalyzed electrophilic carbene insertion reactions are generally more favorable toward electron-rich C–H bonds. Accordingly, their reactivity typically follows in the order $3^\circ > 2^\circ \gg 1^\circ$.[3,4] An exception to this reactivity order of carbene C–H insertion was demonstrated by Che and coworkers using mono rhodium complexes of porphyrins as the catalysts. They reported that Rh(III)–Me complex of the sterically hindered porphyrin **180** was capable of catalyzing asymmetric carbene insertion reactions of simple alkanes with a particular preference for primary C–H bonds over secondary C–H bonds (Scheme 56).[178] For example, the catalytic reaction of hexane (**173**) with methyl phenyldiazoacetate (**135**) by catalyst **180** gave a mixture of products that correspond to insertion of both primary and secondary C–H bonds. With a ratio of 3.5:1 for primary to secondary C–H insertion products, compound **174** was obtained as the major product with 68% *ee*. Differentiation of different primary C–H bonds for the catalytic insertion process was also possible as shown with the reaction of 2,2-dimethylbutane (**177**) with phenyldiazoacetate (**135**) by catalyst **180**. Although similar preference for primary C–H insertion over secondary C–H insertion was recorded, only the primary C–H bond next to the secondary carbon was observed to involve insertion reaction, giving the corresponding product **178** in 65% *ee*; no reaction was detected for the nine primary C–H bonds next to the tertiary carbon. These results indicated that steric effect could become a dominant factor to enable unusual primary C–H insertions, which are typically less favored from an electronic point of view. The Rh(III)–Me complex of the nonchiral porphyrin **181** with more steric hindrance



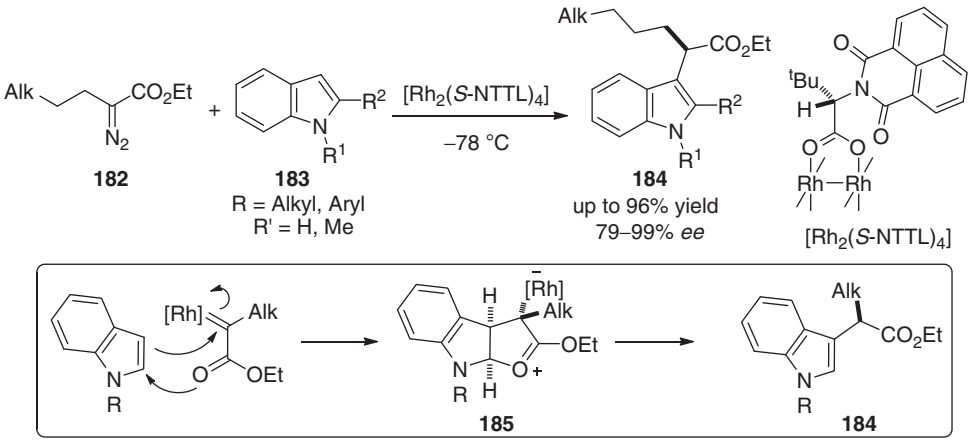
Scheme 56 Asymmetric intermolecular insertion into alkanes by mono-Rh complexes of porphyrins.

was shown to have enhanced selectivity toward insertion of primary C–H bonds of alkane **177**, resulting in a ratio of up to 11.4:1 for primary to secondary C–H insertion products.

Dirhodium(II)-based chiral catalysts have been demonstrated to be generally effective for intermolecular asymmetric carbene C–H insertion reactions with donor/acceptor-substituted diazo reagents. Among them, Davies' $[Rh_2(S\text{-DOSP})_4]$ appeared to be the most versatile catalyst for this type of stereoselective transformation. Compared to metal carbene species generated from other classes of diazo reagents, the rhodium carbene intermediates bearing both donor and acceptor groups have been shown to possess suitable electrophilicity to be reactive toward various C–H bonds while allowing for high control of stereoselectivities. Further studies by Davies and coworkers indicated that heterogeneous catalysts based on immobilization of $[Rh_2(S\text{-DOSP})_4]$ could perform asymmetric carbene C–H insertion reactions as effective as its homogenous systems. It was shown that immobilized rhodium catalysts could be reused several times without losing activity and selectivity.[179]

7.03.2.2.2 Reactions with alkyldiazoacetates

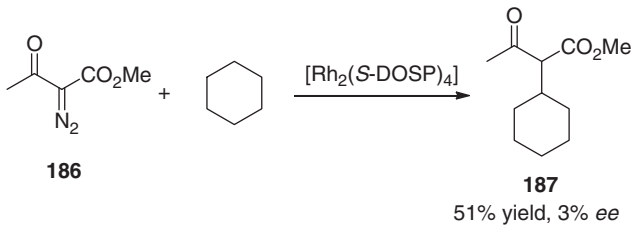
Although alkyldiazoacetates are known to be challenging carbene sources for metal-catalyzed carbene transfer processes due to competitive β-hydride elimination reaction,[83] they have been recently applied for asymmetric intermolecular C–H functionalization. Fox and coworkers demonstrated that the combined use of low reaction temperature and bulky ligand environment could effectively minimize the β-hydride elimination of the resulting metal carbenes formed with alkyldiazoacetates. This discovery has led to the recent development of alkyldiazoacetate-based catalytic systems for cyclization reactions.[180,181] By using the same strategy, they have recently developed a new catalytic system for asymmetric intermolecular C–H functionalization of indoles with alkyldiazoacetates **182** (Scheme 57).[143,144] Using $[Rh_2(S\text{-NTTL})_4]$ as the optimal catalyst, at $-78\ ^\circ C$, *N*-aryl and *N*-alkyl indoles **183** could undergo enantioselective C–H alkylation at the C-3 position with alkyldiazoacetates **182**, providing the desired products **184** in good yields and high enantioselectivity without significant formation of the side products by β-hydride elimination. Although a possible cyclopropanation/rearrangement pathway has been experimentally excluded, DFT calculation supported an ylide formation/proton-transfer pathway for the $[Rh_2(S\text{-NTTL})_4]$-catalyzed process. The proposed ylide **185** is believed to serve as a key intermediate in the catalytic pathway,[143] which is fundamentally different from the concerted insertion mechanism (Scheme 2). With the exception of those indole derivatives, it is noted that asymmetric functionalization of other types of $C(sp^2)$–H bonds, such as those in benzene and its derivative, has not been established with the use of alkyldiazoacetates as the carbene source.



Scheme 57 Asymmetric intermolecular C–H functionalization of indoles with alkyldiazoacetates.

7.03.2.2.3 Reactions with other types of diazo reagents

Dirhodium(II)-based catalysts have been known to catalyze intermolecular C–H carbene insertion reactions with other types of diazo reagents. However, few systems have been shown to have a considerable level of enantioselectivity. Although acceptor-substituted diazo reagents, in particular α-diazocarbonyl compounds, have been successfully utilized for stereoselective C–H insertion reactions in an intramolecular manner, intermolecular versions of these catalytic processes were found to proceed with poor selectivity. Without intramolecularity, the existing Rh_2-based systems seem to be ineffective in controlling stereoselectivity and in many cases even chemo- and regioselectivity for carbene C–H insertion processes.[3,4,10,140,164,182,183] Acceptor/acceptor-substituted diazo reagents could be decomposed by dirhodium(II) catalysts, although under forced conditions in many cases, to form corresponding metal carbene species. Although these highly electrophilic metal carbene intermediates could undergo subsequent insertion reactions with different C–H bonds, such as cycloalkyl and allylic C–H bonds, these intermolecular C–H insertion processes have not been demonstrated with high capability of controlling stereoselectivity.[148,164] For example, the reaction of cyclohexane with methyl 2-diazo-3-oxobutanoate (**186**) by [Rh_2(*S*-DOSP)$_4$], which is an effective catalyst for asymmetric carbene C–H insertion with donor/acceptor-substituted diazo reagents, resulted in the formation of the desired insertion product **187** with only 3% *ee* (Scheme 58).



Scheme 58 Intermolecular carbene insertion into cyclohexane with acceptor/acceptor-substituted diazo reagent.

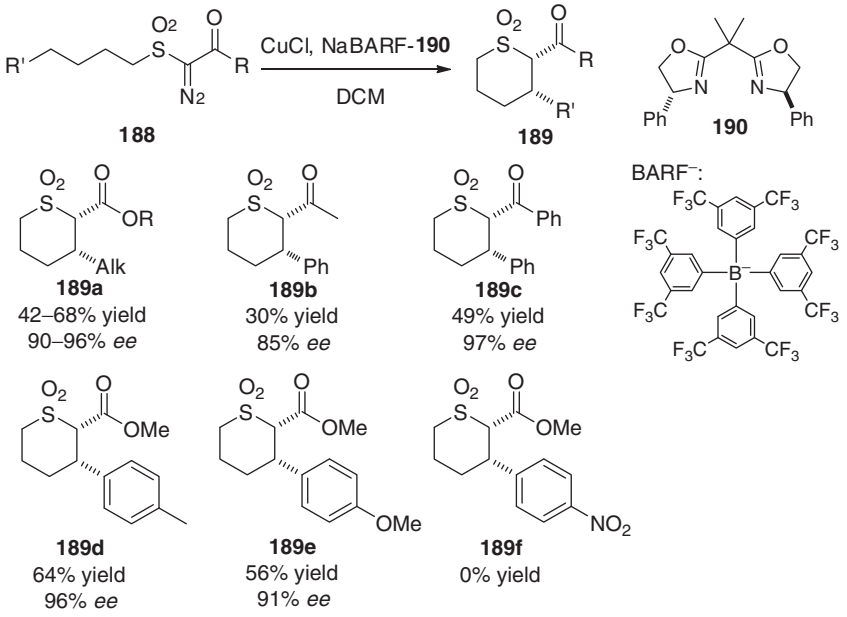
Recently, α-halogenated diazo reagents, including α-chlorodiazoacetates and α-bromodiazoacetates, have been reported to undergo dirhodium(II)-catalyzed intermolecular C–H insertion reactions, providing a direct approach to install halogen functional groups from C–H bonds.[184–186] It was shown that both catalyst and substrate structures could influence the reactivity and diastereoselectivity of these transformations.

7.03.3 Copper(I)-Catalyzed Asymmetric Carbene C–H Insertion

Decomposition of the diazo functional group by copper oxides for subsequent intramolecular C–H insertion reaction was first discovered in 1958.[187] Since then, a number of copper-based catalytic C–H insertion systems have been developed, including both intermolecular[69,138,139,188–192] and intramolecular[25,193–195] variants. Copper complexes, either with or without supporting organic ligands, were the major type of catalysts for studying carbene C–H insertion until the wide use of dirhodium(II) compounds as catalysts. Attempts to achieve asymmetric induction have been made with the employment of chiral ligands, such as the members of the C_2–symmetric chiral bis(oxazoline) ligand family. Instead of using preformed metal ligand complexes, copper-based catalytic systems usually operated in an in situ procedure with direct additions of both copper salts and organic

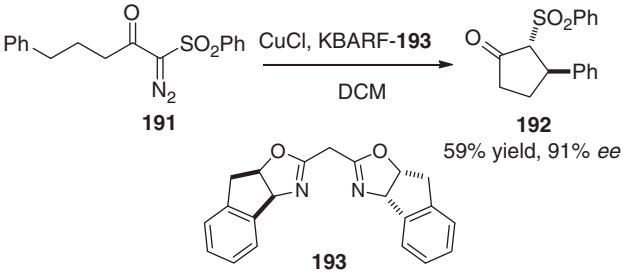
ligands into reaction mixture. Early studies with Cu-based catalysts generally achieved only a poor-to-moderate level of diastereocontrol and enantiocontrol in both intermolecular[157,196–198] and intramolecular[197–201] carbene C–H insertion reactions.

In general, copper-catalyzed asymmetric carbene C–H insertion has not been well developed in comparison with dirhodium-based catalytic systems. Some recent reports on asymmetric intramolecular C–H insertion reactions with the use of α-diazosulfonyl compounds, however, stimulated renewed interest in the copper-based catalytic system. In 2010, Maguire and coworkers reported that the combination of CuCl precursor and chiral bis(oxazoline) ligand **190** could effectively catalyze enantioselective intramolecular C–H insertion reactions of α-diazosulfones **188** with high control of both diastereoselectivity and enantioselectivity (Scheme 59).[202] The catalytic system was shown to be suitable for both α-sulfonyl-α-diazoacetates and α-ketodiazosulfones, and to favor six-membered ring formation to produce *cis*-thiopyran derivatives **189** as the only insertion products, with up to 97% *ee*. Although the insertion process was effective for electron-rich aliphatic and benzylic C–H bonds (**188a–e**), electron-deficient benzylic C–H bonds, such as those containing a nitro group (**188f**), appeared to be completely unreactive for this catalytic system. Although not addressed in the report, this dramatic electronic effect might be closely related to the high electrophilicity of the copper carbene intermediates, which prefer electron-rich C–H bonds but are ineffective for electron-poor C–H bonds. The highly electrophilic nature of the corresponding copper carbene species, which might lead to less controllable reactivity, is likely to also be responsible for the moderate yields of catalytic reactions.



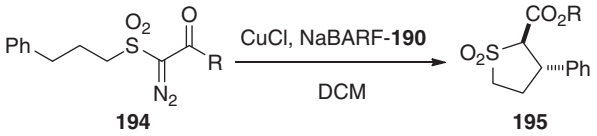
Scheme 59 Cu(I)-catalyzed asymmetric intramolecular C–H insertion of α-diazosulfones.

Detailed studies by Maguire and coworkers revealed that the presence of noncoordinating counteranions is another key factor for reaching high enantiocontrol. Among different noncoordinating counteranions, $BARF^-$ was shown to promote the insertion process with much higher asymmetric induction.[203,204] When formation of a six-membered ring structure is impossible, the Cu-based system could also catalyze the formation of five-membered ring structures as demonstrated with the intramolecular asymmetric C–H carbene insertion reaction of α-ketodiazosulfone **191.** Using the combination of CuCl and bis(oxazoline) ligand **193** in the presence of potassium tetrakis(pentafluorophenyl)borate (KBARF), the catalytic cyclization reaction resulted in the formation of *trans*-cyclopentanone derivative **192** in 59% yield with 91% *ee* (Scheme 60).[204]



Scheme 60 Cu(I)-catalyzed asymmetric intramolecular C–H carbene insertion for cyclopentanone formation.

The observed *trans*-selectivity seemed to be quite general in Maguire's Cu(I)-based systems for formation of five-membered rings. Further examples include intramolecular asymmetric C–H carbene insertion reactions of α-ketodiazosulfones **194**. Under the same catalytic conditions, sulfolanes **195** were isolated as exclusively *trans*-diastereomer, although with moderate yields and low enantioselectivity (Scheme 61).[202]



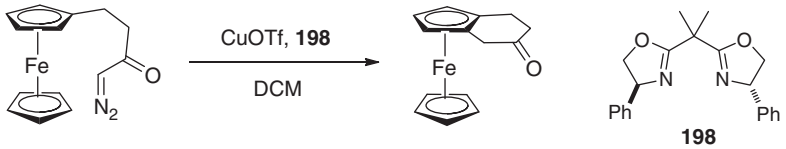
194 **195**

R = OMe 57% yield, 60% *ee*

R = Me 40% yield, 40% *ee*

Scheme 61 Cu(I)-catalyzed asymmetric intramolecular sulfolane formation.

Enantioenriched planar chirality could be generated via asymmetric intramolecular C–H carbene insertion by the Cu(I)-based catalytic system (Scheme 62).[205] Schmalz and coworkers demonstrated that treatment of ferrocene-containing diazoketone **196** with a combination of CuOTf and chiral ligand **198** let to formation of corresponding copper carbene species that could undergo subsequent insertion reaction into electron-rich Cp–H bonds. The resulting planar-chiral ferrocene complex **197** was isolated in 72% yield with 78% *ee*.



196 **197** **198**

72% yield, 78% *ee*

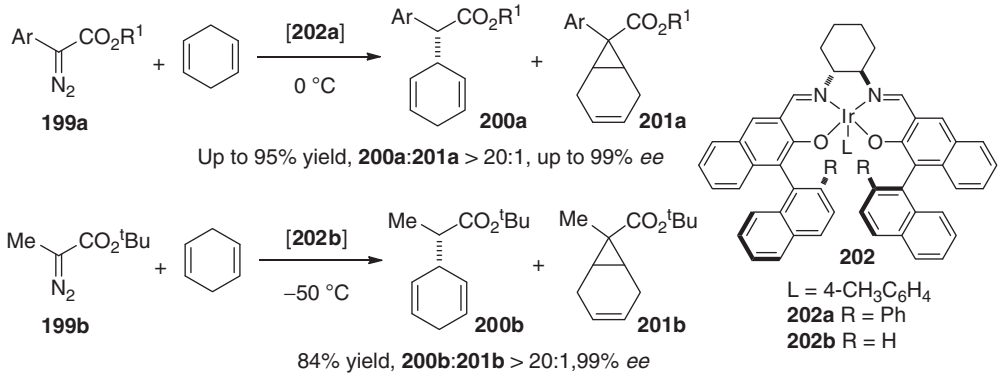
Scheme 62 Generation of planar chirality via catalytic asymmetric intramolecular C–H carbene insertion.

7.03.4 Iridium(III)-Catalyzed Asymmetric Carbene C–H Insertion

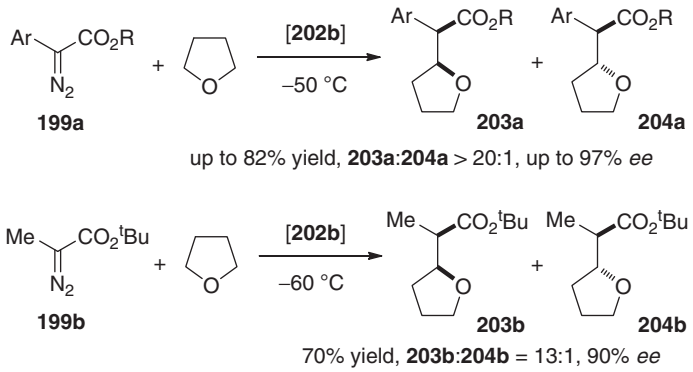
In addition to the above studies on catalytic carbene C–H insertion with rhodium- and copper-based catalysts, other metal complexes, including silver,[19–25,192,206] gold,[25–27] and ruthenium,[28–36,207–211] have also been known to catalyze this type of transformation. Many of these catalytic systems were nonasymmetric and only addressed the issue of regioselectivity and diastereoselectivity. However, asymmetric versions of the catalytic systems based on these metal ions remain to be developed. Recently, chiral iridium(III) complexes were shown by Katsuki and coworkers to catalyze asymmetric intermolecular C–H insertion reactions with excellent enantioselectivity. They demonstrated that iridium(III) complexes of chiral salen ligands **202** bearing an aryl group at the apical position could catalyze allylic C–H insertion reaction of 1,4-cyclohexadiene with α-aryl-α-diazoacetates (**199a**) as the carbene source (Scheme 63).[15] Under neat conditions of 1,4-cyclohexadiene, the catalytic reaction resulted in effective formation of the alkylation products **200a** in up to 95% yield and 99% *ee*, with minimum generation of cyclopropanation byproducts **201a**. Under modified conditions, *t*-butyl α-diazopropionate (**199b**) could also function as a suitable carbene source for Ir(III)-catalyzed carbene insertion reaction of 1,4-cyclohexadiene without significant side reactions from competitive *β*-hydride elimination as well as olefin cyclopropanation. The corresponding insertion product **200b** was produced in high yield with perfect enantiomeric control.

In addition to allylic C–H insertions, asymmetric insertion reactions into tetrahydrofuran (THF) have also been demonstrated successfully with the same catalytic system (Scheme 64). Both α-aryl- and α-alkyldiazoacetates (**199a** and **199b**) underwent insertion reactions at C2-methylene of THF. Tetrahydrofuran-2-yl acetates (**203**) were obtained as the major isomer with high diastereoselectivity and up to 97% *ee*.

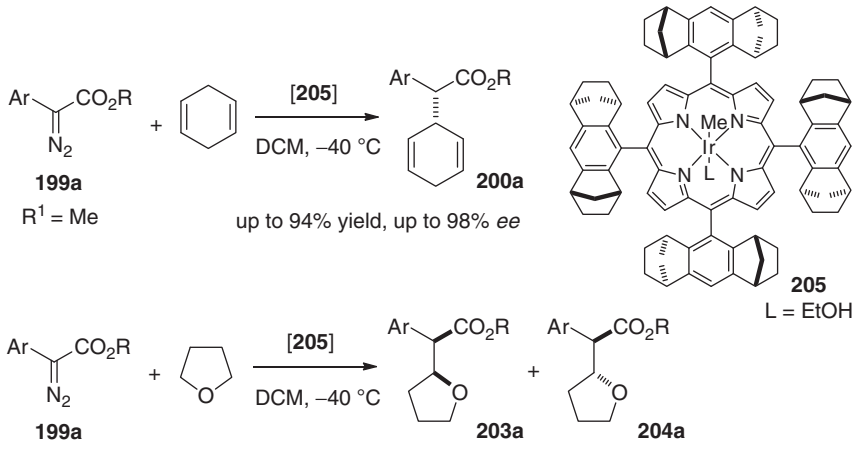
In 2012, Che and coworkers reported that iridium(III) methyl complex of chiral porphyrin **205** is an effective catalyst for asymmetric intermolecular C–H carbene insertion reactions of 1,4-cyclohexadiene and THF with α-aryl-α-diazoacetates (**199a**) as carbene precursor (Scheme 65).[14] The choice of methyl group as the axial ligand was shown to be important for the high activity of the catalyst, while the rigid D_4-symmetric chiral porphyrin environment ensured the high stereoselectivity of the insertion processes. In contrast to Katsuki's system, insertion reaction of THF by iridium porphyrin catalyst **205** gave diastereomer **204a** as the major alkylation product. By using diazo reagent **199a** with varied aryl groups, a series of tetrahydrofuran-2-yl acetates (**204a**) were synthesized in up to 96% yield with up to 97% *ee*.



Scheme 63 Ir(III)-catalyzed asymmetric C–H carbene insertion into 1,4-cyclohexadiene.



Scheme 64 Ir(III)-catalyzed asymmetric C–H carbene insertion into THF.

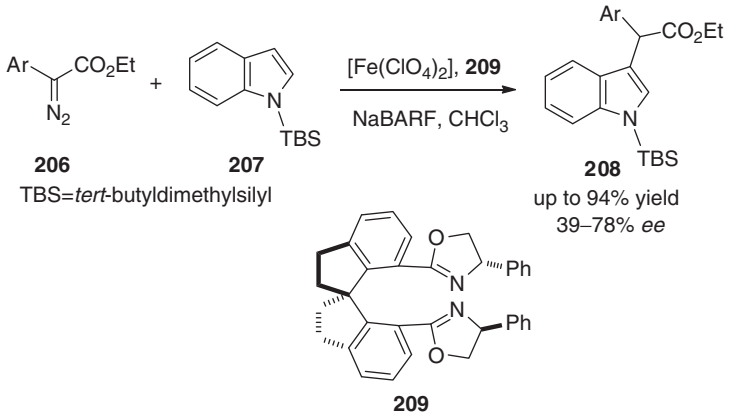


Scheme 65 Ir(III) porphyrin-catalyzed asymmetric C–H carbene insertion with aryldiazoacetates.

7.03.5 Iron(II)-Catalyzed Asymmetric Carbene C–H Insertion

As the second most abundant metal element in the earth's crust, iron, in its complexed forms, has been known to effectively form metal carbene species, some of which have even been shown to be relatively stable.[18] Iron carbene species have also been demonstrated with the capability of inserting into C–H bonds.[212,213] Collectively, these studies suggest that iron complexes are

capable of catalyzing C–H carbene insertion reaction. Woo and coworkers reported that Fe(III)-porphyrin complexes were able to catalyze intermolecular carbene insertion reactions into sp^3 C–H bonds, including the secondary C–H in alkanes and primary C–H in toluene.[17] With [Fe(TPP)Cl] as the catalyst, these transformations generally required high temperature (above 80 °C) and suffered from low selectivity in many cases. In addition to modest regioselectivity, carbene dimerization of diazo reagents was another challenge for the iron-catalyzed insertion process. Recently, Fe(II) complexes of bidentate nitrogen ligands were shown by Zhou and coworkers with capability to functionalize indole at C-3 position.[16] The combination of $Fe(ClO_4)_2$ and spiro chiral ligand **209** could effectively catalyze asymmetric C–H carbene insertion reaction of *N*-protected indole **207** with α-aryldiazoacetates (**206**), enabling high-yielding synthesis of functionalized 3-alkylated indoles **208** with moderate-to-good enantiomeric excesses (**Scheme 66**). This iron(II)-catalyzed system is believed to proceed with an electrophilic addition/proton-transfer pathway, in a similar way to the Rh_2-catalyzed indole alkylation process.[143]



Scheme 66 Fe(II)-catalyzed asymmetric C–H carbene insertion of indole with α-aryldiazoacetates.

Iron-catalyzed asymmetric carbene insertion is largely an underdeveloped area and has not been extended to other types of C–H bonds, such as sp^3 C–H bonds. Intramolecular versions of asymmetric C–H carbene insertion processes by Fe-based catalysts remain unknown. Among other challenges, carbene dimerization of diazo reagents was shown to be the dominating side reaction in Fe-catalyzed systems. In view of the many advantages associated with iron, including its low cost, wide availability, and low toxicity, further development of iron-based C–H carbene insertion systems would be highly desirable.

7.03.6 Summary

Direct functionalization of C–H bonds with control of reactivity and selectivity is one of the central topics in modern organic chemistry. Development of new asymmetric catalytic systems that enable the functionalization of C–H bonds enantioselectively is highly attractive to stereoselective organic synthesis as it would provide a powerful approach to construct optically active molecules directly from ubiquitous C–H bonds. Such asymmetric transformations are highly challenging as the catalytic systems are required to possess sufficient reactivity to activate the otherwise inert C–H bonds while being controllable in order to reach desired selectivities including chemo-, regio-, and stereoselectivity. During the past two decades, the C–H insertion process based on transition metal-catalyzed carbene transfer with diazo reagents has been developed as one of the most general approaches for enantioselective construction of C–C bonds directly from C–H bonds. Dirhodium(II) complexes of chiral carboxamidates and carboxylates, which have been mainly developed by Doyle, Davies, and Hashimoto, have emerged as the most active catalysts for asymmetric C–H carbene insertion reactions.[6,37,214,215] Doyle's dirhodium(II) complexes of chiral carboxamidates, including pyrrolidinones, oxazolidinones, azetidinones, and imidazolinones, constitute a toolbox of highly effective catalysts for asymmetric intramolecular C–H carbene insertion reactions with various α-diazocarbonyls.[3,6] Under the catalysis of these dirhodium(II) carboxamidates, a number of α-diazoesters and α-diazoketones have been shown to undergo selective intramolecular C–H insertion reactions, forming enantiomerically enriched lactones and lactams with varied ring sizes. Dirhodium(II) carboxylates, especially Davies' [Rh_2(S-DOSP)$_4$], have proven to be the most effective and selective catalysts for both intermolecular and asymmetric intramolecular C–H carbene insertion reactions with α-aryl- and α-vinyldiazoacetates.[4,7,10,143] Asymmetric intramolecular C–H insertion reactions of these diazo compounds have been further advanced with the introduction of new dirhodium(II) catalysts derived from phthalimide-based chiral carboxylates by Hashimoto. These phthalimide-based catalysts are exceptionally suitable for enantioselective synthesis of cyclopentane derivatives from α-alkyldiazoacetates.[85,94] Also with α-alkyldiazoacetates, highly enantioselective intermolecular alkylation reactions of aromatic C–H bonds have been demonstrated.[143]

In comparison with the extensive studies on dirhodium(II)-based catalytic systems, catalysts based on other metal complexes have been much less explored for asymmetric C–H carbene insertion reactions. However, several reports have already shown that other metal catalysts could be effective for specific substrate types. Using suitable chiral ligands and accompanied by non-coordinating counteranions, the copper(I)-based catalytic system has been developed for catalyzing intramolecular C–H carbene insertion with excellent asymmetric induction.[202] Recent reports indicated that iridium(III)-based catalytic systems may have great potential for asymmetric intermolecular C–H carbene insertion.[14,15] In principle, with the introduction of suitable new chiral ligands, metal complexes based on Cu, Ir, Fe, and other metal ions could also be developed into effective catalysts for asymmetric C–H carbene insertion reactions. With expected complementary catalytic profiles, these new catalytic systems, together with the existing dirhodium(II) catalytic systems, may allow the remaining challenges in the field to be addressed. Several of these challenges are listed below.

As the most versatile carbene sources, the two adjacent groups of diazo compounds can significantly influence the reactivity and selectivity of metal-catalyzed carbene C–H insertion reactions. While current catalytic systems are effective for α-diazocarbonyls, asymmetric C–H insertion with other acceptor-substituted diazo reagents, including diazosulfones, has not been developed. Furthermore, catalytic carbene C–H insertion with acceptor-substituted diazo reagents, including α-diazocarbonyls, is largely limited to intramolecular reactions. Stereoselective intermolecular C–H carbene insertion with acceptor-substituted diazo reagents remains an underdeveloped area.[10] Although tremendous efforts have been made, acceptor/acceptor-substituted diazo reagents continue to pose major challenges as carbene precursors for asymmetric C–H insertion. These challenges are likely a result of mismatch of electronic properties between this class of diazo compounds and existing metal catalysts. With the presence of two electron-withdrawing groups, acceptor/acceptor-substituted diazo reagents have intrinsically low reactivity toward Lewis acidic metal catalysts for the generation of metal carbene intermediates. Even when generated (typically under forcing conditions), the corresponding metal carbene intermediates bearing two electron-withdrawing α-substituents have very high electrophilicity and are often too reactive for the subsequent C–H insertion step to be stereoselectively controlled. In addition to modifications of existing catalytic systems, the challenges offer a great opportunity for developing different types of new catalysts that would be effective for asymmetric C–H insertion reactions, in both an inter- and intramolecular fashion, with acceptor/acceptor-substituted diazo reagents.

In terms of C–H substrates, existing catalytic systems have been shown to be effective for catalyzing carbene insertion into a variety of C–H bonds, including aryl C–H bonds, benzylic and allylic C–H bonds, C–H bonds that are adjacent to heteroatoms, and simple alkyl C–H bonds.[3,9,10] All these C–H substrates that have been demonstrated for carbene insertion can be considered to belong to the common family of electron-rich C–H bonds. It has been shown that catalytic reactivity of C–H carbene insertion is usually inhibited or significantly decreased by the presence of neighboring electron-withdrawing groups, even when they are not directly adjacent to the C–H bonds.[202] The decreased reactivity toward electron-deficient C–H bonds observed for existing catalytic systems is consistent with the electrophilic nature of their key metal carbene intermediates, which could be related to electrophilic Fischer-type carbenes. To develop catalytic systems that are effective for carbene insertion reactions into electron-poor C–H bonds, including those that are adjacent to esters, amides, ketones, nitriles, and other electron-withdrawing functional groups, it seems evident that new strategies based on mechanisms that are fundamentally different from the well-established electrophilic insertion are needed.

Like any other catalytic process, catalyst development will be the key for further advancement of catalytic C–H carbene insertion chemistry. For the most common Rh_2-based system, judicious modification of suitable chiral ligands has proven to be very fruitful for regulating the reactivity and selectivity of asymmetric C–H insertion processes. In addition to seeking more effective ligands, new catalysts based on different metal ions should also continue to be actively pursued.[20,26–32,207] With different electronic configurations, the use of varied metal ions may lead to the discovery of new catalytic systems with dissimilar reactivity profiles, allowing some of the long-standing challenges in the field to be addressed. Together with existing catalytic systems, they will further advance the potential of the asymmetric carbene insertion process for stereoselective C–H functionalization.

Acknowledgments

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7.04 Oxidation by Microbial Methods

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Glossary

Biocatalyst General designation of an enzyme in any form ranging from whole cells via crude cell extracts and enzyme preparations of increasing purities to highly purified enzymes.

Cofactor Molecules which are required by the biocatalyst to perform its catalytic function and which need to be recycled for preparative work. The cofactor type can vary from simple ions over substrate-like free coenzymes to prosthetic groups tightly bound to the enzymes, which during the oxidation are being reduced and need to be reoxidized to the oxidized state by a cofactor regeneration system.

Deracemization Complete conversion of a racemic mixture to one of its enantiomers.

Desymmetrization Complete conversion of a symmetric molecule to a new nonsymmetrical product.

EC Enzyme Commission.

EC number The Enzyme Commission number consists of four numbers separated by dots starting with the main class followed by subclasses, whereby each class classifies the enzymes according to the type of reaction catalyzed.

ee Enantiomeric excess.

7.04.1 Introduction

The study of the microbial oxidizing capacity in vinegar manufacturing, which Louis Pasteur described in 1862 as serving as a means of transport of oxygen from the air on various organic substances and designated as '*Mycoderma aceti*,' has started the understanding of the oxidation of alcohol to acetic acid in vinegar production.[1] The discovery of microbial oxidation of glucose to

gluconic acid and not to lactic acid, as first mentioned, also by '*Mycoderma aceti*,'[2] underlines the importance of analytical methods for product identification. The discovery of the sorbitol oxidation to sorbose by a microorganism simply designated as 'bactérie de sorbose' by Gabriel Bertrand[3] stimulated much scientific interest in selective sugar oxidation reactions. The investigations on the selective oxidation of acyclic polyhydric alcohols by *Acetobacter xylinum* and *Acetobacter suboxydans* have been condensed into the Bertrand–Hudson rules (**Figure 1**).[4,5] Microbial oxidations have from the beginning been not only of fundamental scientific interest, but also had the understanding and problem solving of practical industrial production processes as the starting point for innovative synthetic methods (**Figure 2**).

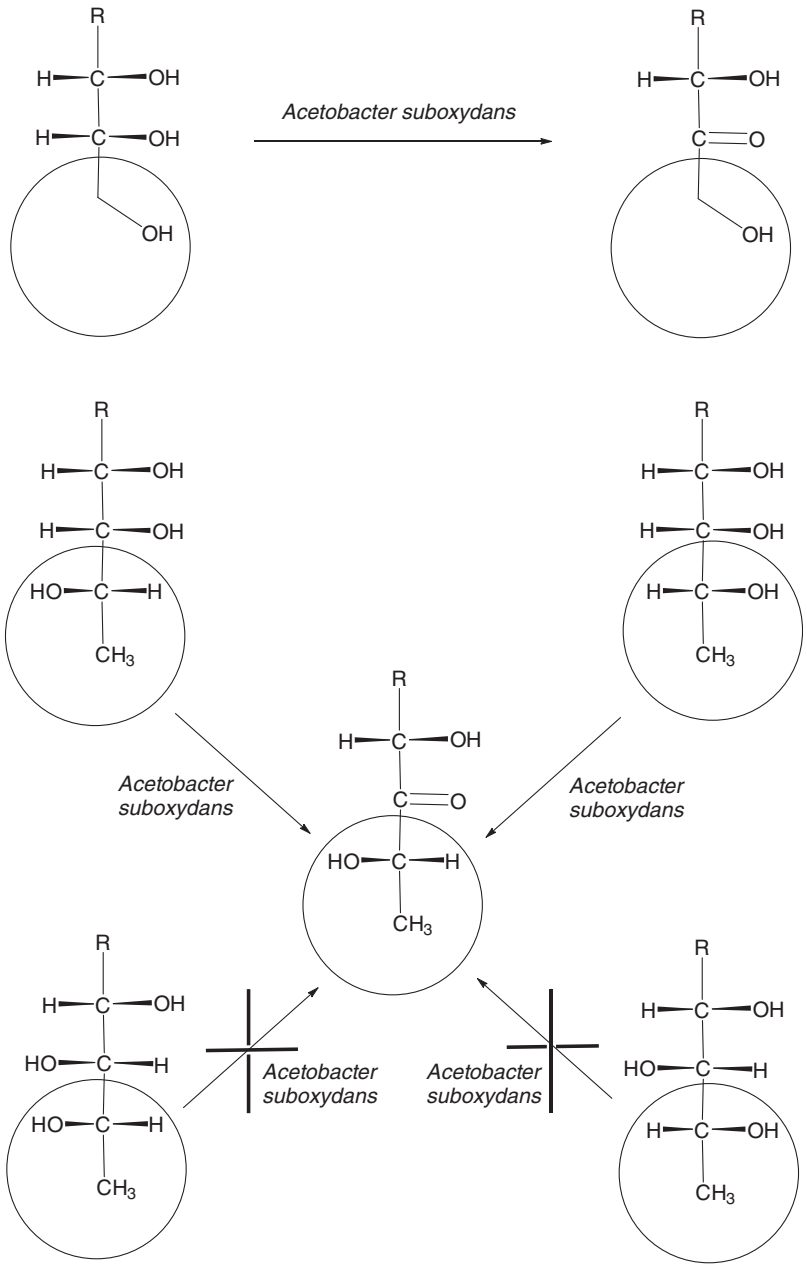


Figure 1 Bertrand–Hudson rules.

Oxidations by microbial methods have been developed very early for key steps in the industrial production of vitamin C,[6,7] for pharmaceutically important steroids[8–11] and for a series of applications in organic synthesis.[12,13] The increasing use of biocatalysts in oxidation reactions[14–18] and the inherent chirality of the enzymes enable a wide variety of biocatalytic asymmetric oxidations.[19] The chemoselective oxidation of one specific single hydroxy group among various other hydroxy groups and/or other oxidizable functional groups continues to be of great practical value. The industrial use of D-sorbitol dehydrogenase in the oxidation of

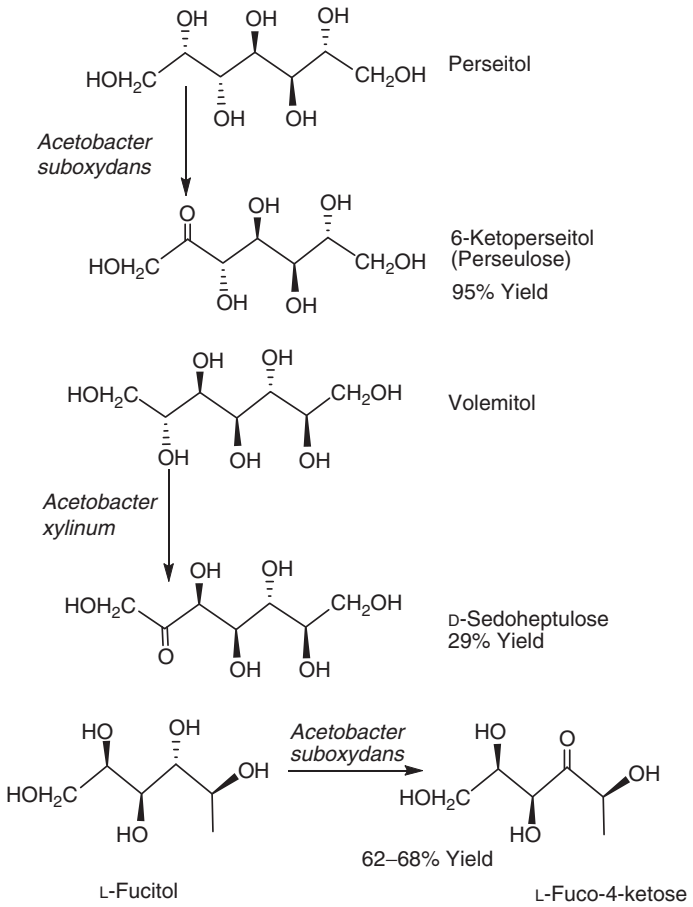


Figure 2 Historical oxidations by microbial methods.

D-sorbitol to L-sorbose in vitamin C synthesis[6,7] or the oxidation of *N*-protected 1-amino-1-deoxy-D-sorbitol to the key intermediate in miglitol synthesis[20] are classical demonstrations of the great utility of polyol dehydrogenases. The key success factor for the application of these selective single-step microbial oxidations is to bypass a number of chemical protection–deprotection steps, which would be required in conventional nonselective oxidations. A variety of biooxidations of the steroid backbone and side-chain including hydroxylation, Baeyer–Villiger oxidation, dehydrogenation, and side chain cleavage can be performed with high regio- and stereoselectivity and are of practical industrial importance.[21] The important biooxidations of primary and secondary alcohols to the corresponding aldehydes, ketones, or carboxylic acids are of great practical importance and utilize mild oxidants and reaction conditions.[22] The microbial oxidation of *meso*-diols with secondary hydroxyl functions to (*S*)-α-hydroxy aldehydes is an interesting direct route to chiral hydroxyaldehydes.[23] A wide variety of prochiral and *meso*-diols including sterically demanding bicyclic *meso*-diols can be converted to the corresponding chiral lactones with excellent enantiomeric purity by selective desymmetrization in a two-step one-pot method.[24] Desymmetrization through enantioselective microbial oxidation (**Figure 3**) has been effectively achieved in a series of other reaction classes ranging from the asymmetric oxidation of *meso*- and prochiral diols to enantiopure hydroxy ketones and hydroxycarboxylic acids, oxidation of sulfides to enantiopure sulfoxides, monohydroxylation of methylene groups in prochiral alkanes to enantiopure secondary alcohols, *cis*- and *trans*-dihydroxylation of carbon–carbon double bonds to optically active vicinal diols to Baeyer–Villiger oxidation of *meso* and prochiral ketones.[25]

Large-scale industrial oxidations of organic compounds with oxidants in flammable solvents pose not only safety, health, and environmental challenges,[26] but often suffer from insufficient selectivity. The development of selective oxidation reactions meeting these challenges is therefore of prime importance for providing new direct routes to target compounds and at the same time improving the safety, health, and environment issues in manufacturing. With the increasing availability of off-the-shelf biocatalysts, biocatalytic oxidations using mild oxidants represent a practical choice for scalable and selective oxidations for the synthetic chemist.[27] The use of oxygen as oxidant is common to a variety of microbial biocatalysts, whether as whole cells, cell-free extracts, or isolated enzymes. Water as the end product of the reduced oxidant of molecular oxygen is harmless, but intermediate oxidation states such as superoxide anions or hydrogen peroxide as reactive oxygen species can generate oxidative damage and stress to the microbial cells. Therefore, the concentrations of superoxide and hydrogen peroxide have to be kept very low in order to preserve biocatalytic activity and cellular integrity. Biocatalysts are key to the oxidation by microbial methods and progress has been connected to the development of the class of oxidoreductase catalysts. The application of oxidases toward selected amino acids has

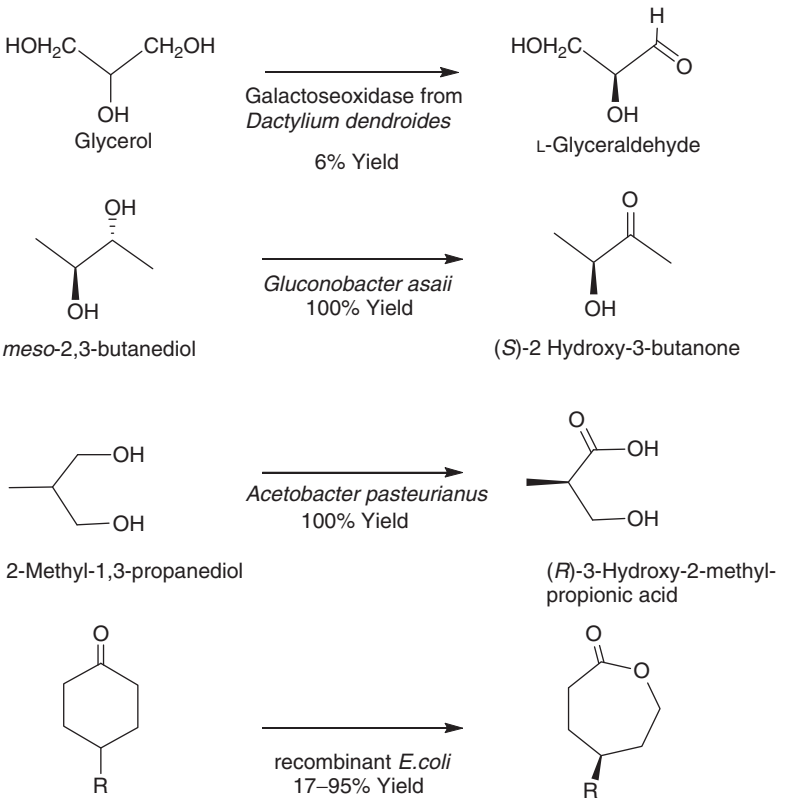


Figure 3 Desymmetrizations through enantioselective microbial oxidations.

been useful for the resolution of nonnatural racemic amino acids. Monooxygenases are versatile biocatalysts for a range of asymmetric oxidations such as epoxidations, Baeyer–Villiger oxidations, sulfur and nitrogen oxidations. Classical Baeyer–Villiger oxidations often give rise to nonspecific side reactions, overoxidation, rearrangements and disadvantages in chemo- and enantioselectivities. Biocatalytic asymmetric Baeyer–Villiger oxidations show excellent selectivity over a broad substrate range and the Baeyer–Villiger monooxygenases have been prepared on a large scale. Microbial dioxygenases have opened new synthetic routes by dearomatizing *cis*-dihydroxylations, a characteristic of microbial dihydroxylations, of aromatic starting compounds. Its successful application in a large variety of regioselective asymmetric dihydroxylations has secured this type of microbial oxidation a prominent place among the synthetic methods of organic chemistry.

Crucial roles in microbial oxidation reactions are played obviously by microorganisms, which are responsible for producing, interconverting and decomposing molecules in our biosphere and oxidation control is an important component of biosynthetic logic.[28] The functional characterization of the involved reactions and the corresponding microbial biocatalysts has therefore attracted great interest from the science of synthesis. Valuable resources for microbial oxidation biocatalysts can be found in microbial-type culture collections, microbial genetic stock centers and databases on microbial genomes. Biooxidations can be classified according to different categories such as the classes and types of microorganisms or the classes and types of enzymes. In this chapter, however, the microbial oxidation reactions and the microbial biocatalysts are described from the perspective of organic synthesis according to the corresponding reaction types and bond formation reactions that are catalyzed. The chapter on oxidation by microbial methods in the first edition of Comprehensive Organic Synthesis focused on substrate classes such as steroids and nonsteroids such as hydrocarbons, isoprenoids, and alkaloids.[29]

7.04.2 General Methodological Aspects

The huge diversity of oxidation biocatalysts from both natural as well as recombinant microbial cells as well as practical handbooks and detailed procedures have brought the microbial oxidation toolboxes closer to the organic chemistry laboratory. One prerequisite for straightforward applications of microbial oxidations in organic synthesis (Figure 4) is the access and availability of microbial biocatalysts. It is therefore important to have long-term, technically viable and high-quality conservation of living and pure microbial cultures as part of a global bioeconomy infrastructure in order to have rapid access and information in a simple and standardized way. The World Federation of Culture Collections includes more than 625 culture collections in 71 countries (status: December 2012). The aim of its Global Catalog of Microorganisms is to facilitate information exchange on the microbial

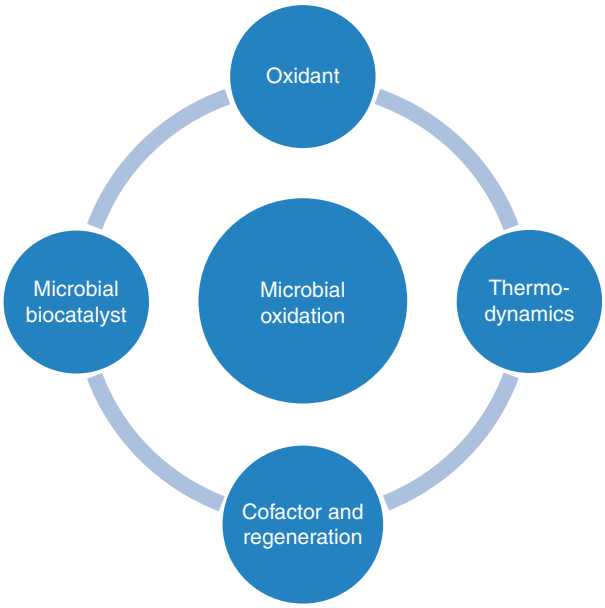


Figure 4 Key determinants of microbial oxidations.

resources between culture collections and the scientific and technological users (see website: http://www.wfcc.info) and currently lists 233 789 strains from 36 culture collections in 19 countries. The microorganisms from these collections have to be grown in the adequate growth medium in order to obtain the desired biomass, which can then be either used as whole cells or further processed to obtain cell extracts or purified microbial biocatalysts. An increasing number of microbial biocatalysts for oxidation reactions have also become commercially available as off-the-shelf catalysts for immediate utilization in organic synthesis.

7.04.2.1 Oxidants

As stoichiometric amounts of oxidants are required in any types of oxidations, the corresponding reduced forms will also be formed in stoichiometric amounts, ending up as waste and byproducts, which need to be separated from the product. In addition, some oxidants have to be handled with special care because of their highly toxic nature and because of their high-energy content in conjunction with the use of flammable organic solvents. Organoiodine(V) reagents such as 2-iodoxybenzoic acid or Dess–Martin periodinane have found numerous applications as versatile and environmentally benign oxidants in organic synthesis.[30] As oxidants such as nitric and sulfuric acid, oleum, chromium trioxide, manganese dioxide, potassium permangananate, or periodate need first to be produced using oxygen, the cheapest oxidant is simply molecular oxygen. Although organic peroxides, peroxyacids, and hydrogen peroxide are often used as oxidants, its high energy, incompatible, and nonselective nature restrict their broad use. There are additional benefits in using oxygen instead of some high-energy oxidants which are routinely used in standard oxidation reactions. It has also safety, health, and environmental advantages. Although oxidations with molecular oxygen are less selective than with other oxidants, biocatalysts can offset this by minimizing unwanted side reactions. A variety of redox-active cofactors and metals are widely used as oxidants in biooxidations.

7.04.2.2 Catalyst Classes for Oxidations

Oxidation biocatalysts can be classified according to their form (homogeneous or heterogeneous biocatalyst), structure, mechanism or type of reaction, which is catalyzed. The EC system, which classifies biocatalysts according to the type of reaction catalyzed, lists six classes of enzymes, of which only one class is relevant for microbial oxidations.[31] The EC class 1 of the oxidoreductases classifies these enzymes according to the functional group acting as electron donor and then after the type of electron acceptor.

7.04.2.3 Microbial Biocatalysts – Whole-Cell versus Isolated Biocatalysts

The use of stable isolated biocatalysts which can directly be used for a particular oxidation reaction is attractive for reactions where whole cells would have limitations, for example, the presence of other enzymatic functions leading to side products or limitations for inbound substrate transport or outbound product transport. Whole-cell biocatalysts, however, are preferably used when

substrates and product structures are insensitive toward other enzymatic functions or when cofactor recycling systems of whole cells are required.

7.04.2.4 Cofactors and their Regeneration

In the course of many oxidations substrate-like free coenzymes or prosthetic groups tightly bound to the enzymes are being reduced and need to be reoxidized to the oxidized state by a cofactor regeneration system. Efficient methods to regenerate the cofactor in microbial oxidation reactions are important for the implementation of these processes on an industrial scale.[32]

7.04.2.5 Thermodynamics

As the compound that gets oxidized gives up electrons, the oxidant takes up these electrons, whereby the oxidant becomes more reduced. As the microbial biocatalyst will only accelerate the rate at which thermodynamic equilibrium will be reached, it is for synthetic purposes highly relevant to know the thermodynamics of a reaction system and tools to change the thermodynamic equilibrium in order to drive the reaction to completion (Figure 5).

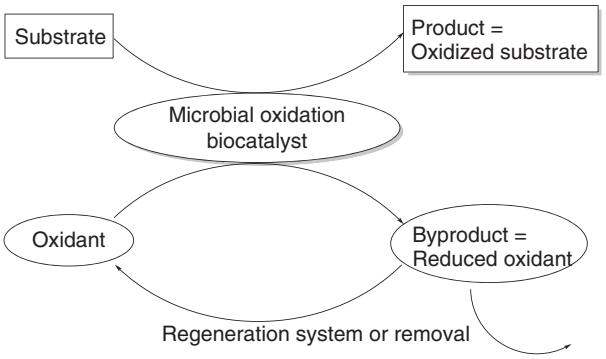


Figure 5 Redox system for microbial oxidations.

7.04.2.6 Solvents

The replacement of flammable organic solvents by water is a great step for improved process safety, but requires new solutions for more hydrophobic and only poorly soluble substrates and products. The use of oxidoreductases in organic solvents provides interesting opportunities for the oxidation of poorly water-soluble substrate.[33] Water-miscible and polar organic solvents can enhance the solubility of substrates, which can lead to increased reaction rates, regio- and enantioselectivity but they may inactivate enzymes. Ionic liquids, even when having the same polarity as polar organic solvents, do not inactivate enzymes and can be used as solvents for nonaqueous reactions and to dissolve polar substrates.[34]

7.04.2.7 One-Step versus Multistep Oxidation

One-step microbial oxidation reactions can be coupled together in order to achieve higher degrees of oxidation, as for example, in the three-step oxidations in the plant hormone gibberellin pathway[35] by cytochrome P450 monooxygenases. The formal transformation of a methyl functional group to a carboxylic acid can be achieved in a three-step microbial oxidation reaction via the intermediate primary alcohol and aldehyde (Figure 6). Impressive improvements have been achieved in the three-step oxidation of amorpha-4,11-diene to artemisinic acid using in the first step CYP71AV1/CYB5/CPR1-catalyzed hydroxylation of amorphadiene to artemisinic alcohol, then alcohol dehydrogenase-catalyzed oxidation of the primary alcohol to the artemisinic aldehyde in the second step, and finally the aldehyde dehydrogenase-catalyzed oxidation to artemisinic acid.[36,37]

7.04.2.8 Safety, Health, and Environmental Aspects

The safety, health, and environmental aspects of oxidations have obtained increased attention in organic synthesis and have a great influence on the choice of oxidation method.[38] As oxidants such as organic peroxides, peroxide-containing materials including hydrogen peroxide in conjunction with toxic catalysts and flammable solvents require special safety, health and environment precautions, the reengineering of such oxidations by the use of molecular oxygen as oxidant, environment-friendly microbial oxidation biocatalysts, and nonflammable aqueous solvents provides important safety, health, and environmental benefits (Figure 7).[12–22]

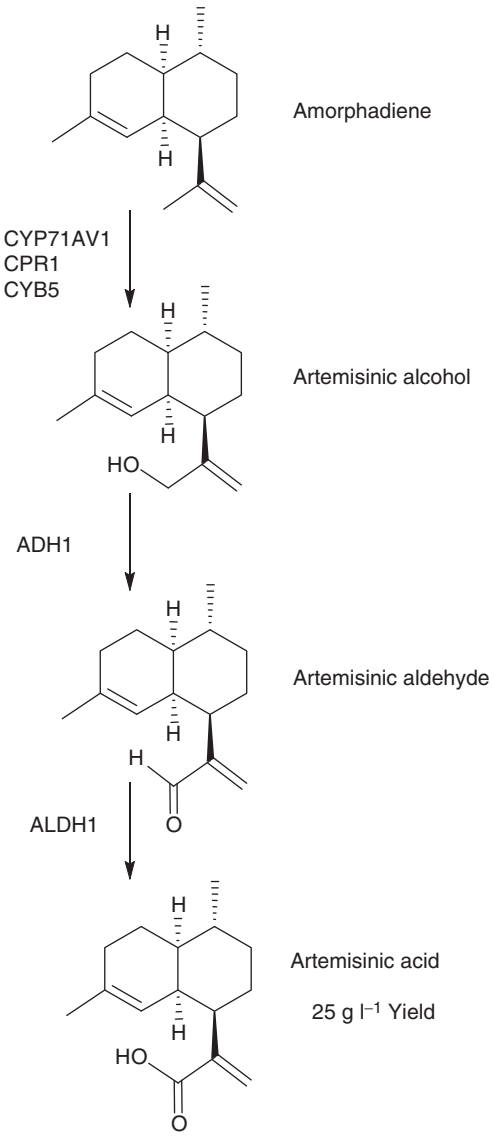


Figure 6 Microbial multistep oxidations.

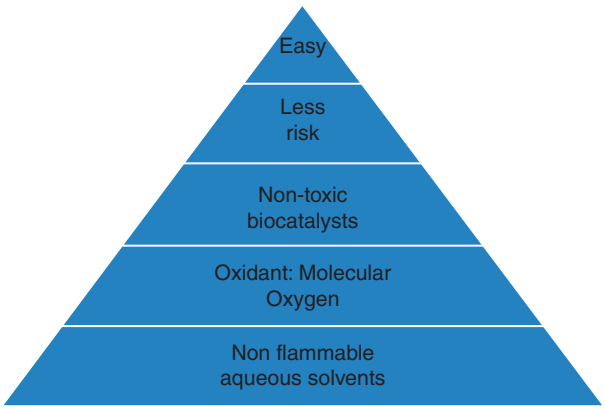


Figure 7 Safety, health, and environmental benefits of microbial oxidations.

7.04.3 Formation of R–C Bonds

The regio- and stereoselective formation of new carbon–carbon bonds by biocatalytic oxidative coupling reactions of phenolic compounds is of much interest, because no toxic reagents are required and with microbial oxidoreductases, oxygen can be used as one of the cheapest and greenest oxidants. Fungal laccases, despite not being very selective, have enabled a variety of interesting oxidative coupling reactions (Figure 8) using air as oxidant such as the biocatalytic oxidative dimerization of salicylic acid esters[39] and of substituted vanilliden derivatives[40] by laccase from *Trametes versicolor* and *Agaricus bisporus*, the highly regioselective reaction between catechols and heterocyclic 1,3-dicarbonyls to benzofuropyridinones, benzofuroquinolinones, and thiocoumestans with 55–98% yield[41]; the biocatalytic 3-arylation of *N*-BOC-protected 3-substitued oxindoles with catechols by laccase from *Pleurotus ostreatus*[42]; and the synthesis of anhydrovinblastine from the oxidative coupling of vindoline with catharanthine.[43] The oxidative trimerization of sesamol has been achieved with laccase from *Trametes versicolor* in 56% yield.[44] The berberine bridge enzyme, which catalyzes the intramolecular oxidative carbon–carbon bond formation between the *N*-methyl group and the phenolic ring of (*S*)-reticuline to (*S*)-scoulerine,[45] has been used for the kinetic resolution of racemic mixtures in the synthesis of novel (*R*)-benzylisoquinolines and (*S*)-berbine derivatives with very high enantioselectivity.[46] A range of oxidative coupling reactions using amino acid oxidase and chromopyrrolic synthase for tryptophane condensations and P450 oxygenases for aryl–aryl couplings have been the key for the combinatorial synthesis of indolocarbazole alkaloids such as rebeccamycin, staurosporin, and their derivatives.[47]

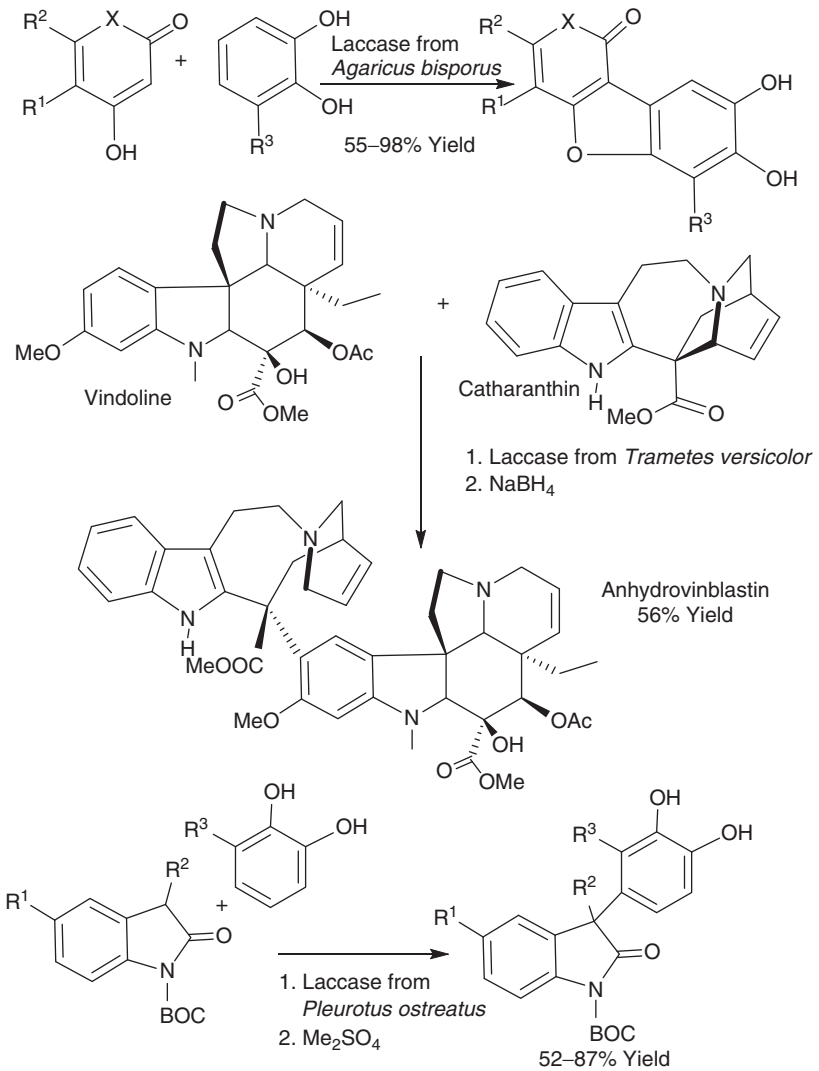


Figure 8 Laccase-catalyzed oxidative coupling reactions.

7.04.4 Formation of R–O Bonds

The formation of new R–O bonds can be achieved either by oxidative coupling of phenolic substrates or by oxidations of C–H or C–O bonds by oxidoreductases. The oxidative cyclization of 2′,3,4,4′,6′-pentahydroxy-chalcone into aureusidin is catalyzed by a

crude peroxidase extract from onion.[48] Both new C–O and C–C bonds are formed in the oxidative dimerization–cyclization of methyl *p*-coumarate, methyl caffeate, and methyl ferulate catalyzed by a crude peroxidase extract from onion.[49]

Chemoselective oxidation methods that lead to one single oxyfunctionalized product instead of more or less complex product mixtures have been one of the key synthetic research areas in organic synthesis for more than 100 years. A variety of microbial oxidation methods have become standard technologies in organic synthesis due to their excellent chemo-, regio-, and enantioselectivities.

7.04.4.1 Oxidation of C–H Bonds – Monohydroxylation Methods

Biocatalytic hydroxylations of carbon–hydrogen bonds progress at a rapid pace and surpass chemical oxidation methods by far with respect to performance and selectivity[50] and have in addition safety, health, and environmental advantages such as mild reaction conditions and oxidants such as molecular oxygen (Figure 9). Bottlenecks such as low space–time yields, biocatalyst

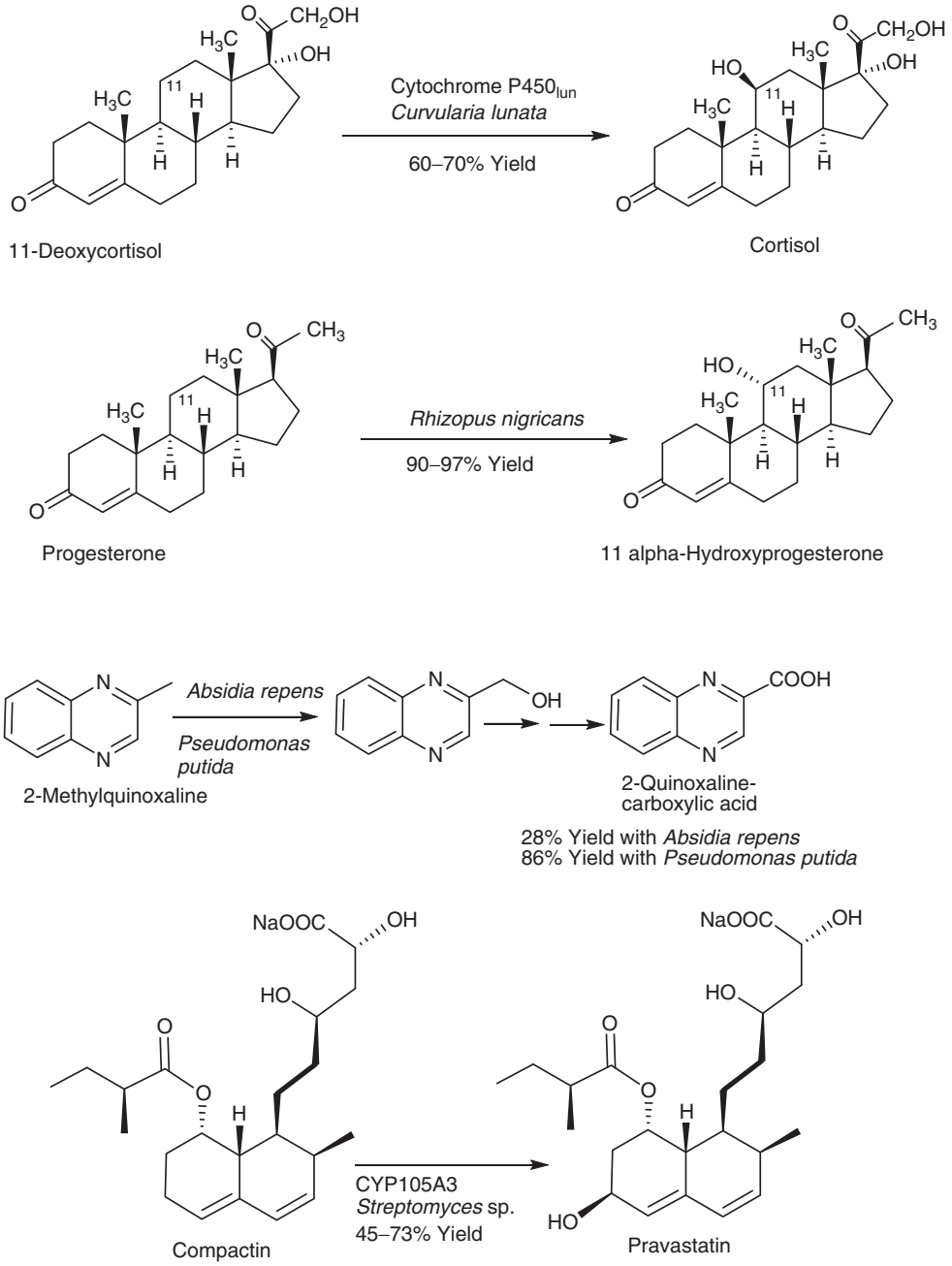


Figure 9 Monohydroxylations.

activities and stabilities, and substrate tolerance need to be overcome for industrial-scale applications.[51,52] Successful industrial applications of cytochrome P450-catalyzed microbial hydroxylations have been established in the hydroxylation of steroids,[10,11,53] the 6β-hydroxylation of compactin to pravastatin catalyzed by CYP105A3 from *Streptomyces carbophilus*,[54] the 1α- and 25-hydroxylation of vitamin D_3 to 1α-, 25-dihydroxyvitamin D_3 catalyzed by CYP107 from *Pseudonocardia autotrophica*, and CYP105A1 from *Streptomyces griseolus*.[55] Although monohydroxylations have been performed with isolated enzymes, the majority of applications have been done with whole-cell biocatalysts due to the nature of the cytochrome P450 enzymes and the cofactor regeneration systems.[56–58] A large range of microbial hydroxylations of aliphatic and aromatic hydrocarbons, terpenes, steroids, alkaloids, and antibiotics are not only of fundamental interest but are also of practical interest to the flavor, fragrance, and pharmaceutical industries, because the hydroxylation of nonactivated carbon centers has only very few counterparts in classical organic chemistry (*see* Chapters 7.12, 7.13 and 7.14).[10–14]

The versatility of CYP105A1 from *Streptomyces griseolus* toward other substrates has been shown by the conversion of resin acids such as abietic acid and dehydroabietic acid to 15-hydroxyabietic acid and 15-hydroxydehydroabietic acid.[59] Highly regio- and enantioselective hydroxylation for the allylic 3-position of cyclohexene-1-carboxylic acid methyl ester has been achieved by directed evolution of wild-type P450-BM3 and mutants with >95% R-selectivity or >95% S-selectivity, whereas regioselectivity was maximized to >93% by reducing other oxidation products.[60] The great potential of microbial hydroxylation for the stereoselective preparation of authentic human metabolites has been demonstrated by the *endo*- and *exo*-hydroxylation of an A2a receptor antagonist and its *N*-desmethyl metabolite.[61]

R-6-hydroxybuspirone, the authentic human metabolite of buspirone, was obtained with 99.5% *ee* in a hydroxylation reaction from buspirone catalyzed by an engineered cytochrome P450 BM-3 variant.[62]

7.04.4.2 Oxidation of Alcohols

Microbial oxidations of alcohols are among the oldest biotransformations (**Figure 10**) and impressive progress has been achieved over the past decades.[15,22–24,27] Biocatalytic oxidations with dehydrogenases or oxidases can be performed under mild reaction conditions with high selectivity.[19]

Microbial oxidations of primary alcohols to aldehydes or of secondary alcohols to ketones by alcohol dehydrogenases often show inhibition by the aldehyde or ketone products. Continuous product removal can resolve this issue, for example, by subsequent lactol formation and lactol oxidation to the lactone in the case of *meso*-diols such as the 1,4-diols or 1,5-diols, where the alcohol dehydrogenase also oxidizes the lactols which are formed in an equilibrium reaction from the corresponding hydroxyaldehydes. Horse liver alcohol dehydrogenase has been used in the stereospecific oxidation of only one of the two enantiotopic hydroxy groups in acyclic, monocyclic, and oxabicyclic *meso*-diols. Enantiomerically pure chiral y-lactones of the oxabicyclic series, which are not easily available by any other route, have been prepared in a one-pot oxidation with >98% *ee* from both *meso-exo*- and *endo*-oxabicyclo-[2.2.1]heptanediols using horse liver alcohol dehydrogenase,[63] which has been expressed also in recombinant microorganisms. Horse liver alcohol dehydrogenase (HLADH) has been one of the most used dehydrogenase in organic synthesis and as the preparation extracted from liver tissue consists of a mixture of isoenzymes and suffers from raw material supply, the transition from the animal-derived enzyme to single isoform HLADH provides new perspectives for this classical biocatalyst.[64]

The polyoldehydrogenases, catalyzing the oxidation of a large variety of hexitols to the corresponding ketohexoses, are an integral part of the Izumoring concept for the bioproduction of all hexose sugars.[65] Recombinant *Escherichia coli* cells containing xylitol-4-dehydrogenase have enabled direct transformations of xylitol to L-xylulose in high substrate concentrations, D-iditol to L-sorbose, D-threitol to erythrulose, D-talitol to D-tagatose, and D-arabitol to D-ribulose.[66]

For the microbial oxidation of ribitol to L-ribulose a maximal production rate of 15.7 g l^{-1} h^{-1} could be reached and the level of aeration proved to be one of the most critical factors.[67] A variety of polyoldehydrogenases such as the D-arabitol 2-dehydrogenase, mannitol 1-dehydrogenase, and xylitol 4-dehydrogenase have been used for the production of rare sugars.[68]

The selective oxidation of a primary alcohol to the aldehyde requires chemoselective reagents/catalysts and careful reaction control in order to avoid carboxylic acid formation due to overoxidation as demonstrated by the highly chemoselective oxidation of benzyl alcohol derivatives to the corresponding benzaldehydes by *Janibacter terrae*,[69] whereby the formation of the corresponding carboxylic acids was avoided by employing acetaldehyde as the hydrogen acceptor.

The oxidation of alcohols by oxidases is also of much interest, because (a) only the oxidative direction is catalyzed, (b) nature utilizes a large range of flavoprotein oxidases,[70] and (c) molecular oxygen is directly used as an electron acceptor and is in general reduced to hydrogen peroxide, which can be removed by catalase. A practical biocatalytic oxidation of glycolic acid to glyoxylic acid with >98% selectivity at 100% conversion has been achieved by a glycolate oxidase/catalase system.[71]

The highly enantioselective oxidation of racemic 2-hydroxy acids to their 2-ketoacids catalyzed by glycolate oxidase has been used as a convenient method for preparing (*R*)-2-hydroxy acids.[72,73] 5-Keto-D-fructose has been prepared by regioselective oxidation of L-sorbose using pyranose 2-oxidase (P2Ox) and the quantitative oxidation of 180 g l^{-1} L-sorbose to 5-keto-D-fructose could be achieved within 4 h.[74] The enantioselective oxidation of alcohols is particularly interesting and a variety of microbial alcohol oxidases such as aliphatic short- and long-chain alcohol oxidases,[75] aromatic alcohol oxidases, alditol oxidases, lactate oxidases, glycolate oxidases, and galactose oxidases[76] have been used, with the M3–5 variant of galactose oxidase having a broad range of practical applications.[77]

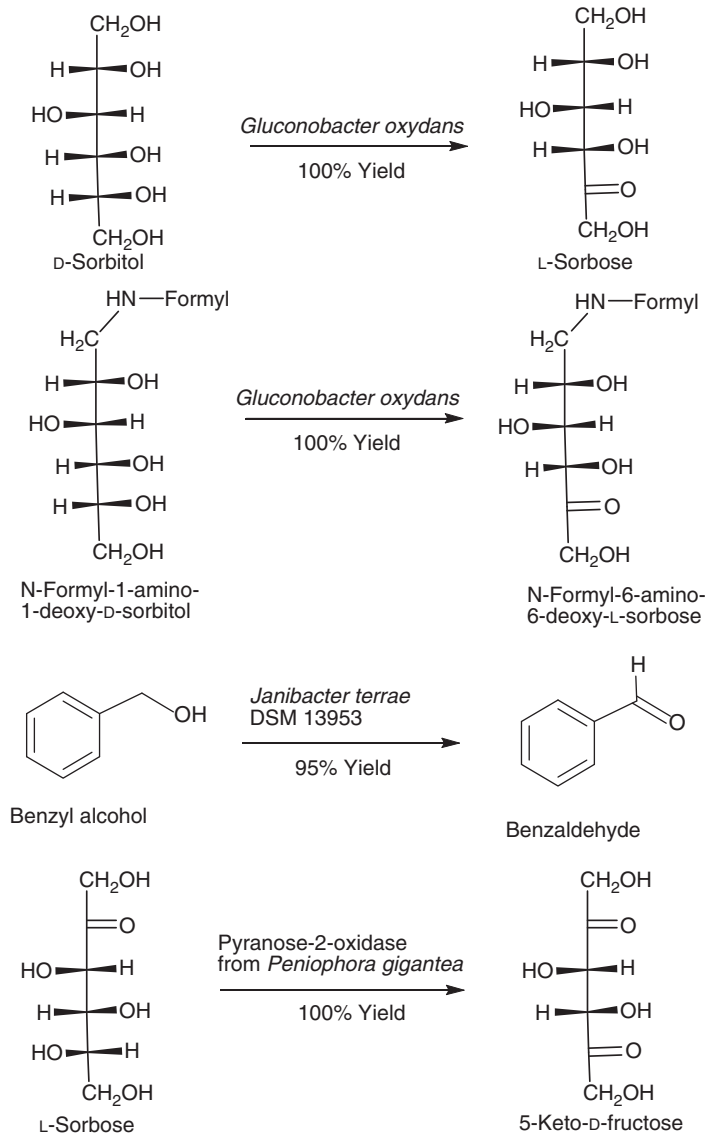


Figure 10 Alcohol oxidations.

The selective catalytic oxidation of alcohols to carboxylic acids is an important industrial reaction.[78] Microbial oxidations of primary alcohol groups directly to carboxy groups provide rapid access to chiral building blocks and have been found by classical microbiological screening, for example, in the catalytic asymmetric oxidation of prochiral 2-methyl-1,3-propandiol with *Acetobacter pasteurianus* to the captopril building block (*R*)-3-hydroxy-2-methyl propionic acid, which was obtained with 97% *ee* and 100% molar conversion within 2 h.[79]

7.04.4.3 Oxidation of Aldehydes

Although chemical oxidation procedures of aldehydes to carboxylic acids utilizing bleach, transition-metal oxidants, or oxone are highly efficient and straightforward, selective microbial aldehyde oxidations are still of interest (Figure 11). The highly selective oxidation of aldehydes to carboxylic acids has been demonstrated in the oxidative dynamic kinetic resolution of profens catalyzed by alcoholdehydrogenase in the presence of a suitable cofactor regeneration system.[80] 3-Hydroxypropionaldehyde and various aliphatic C_2–C_5 aldehydes are efficiently converted to their C_2–C_5 carboxylic acids by the NAD^--dependent aldehyde dehydrogenase PuuC from *Klebsiella pneumoniae*, cloned and expressed in *E. coli*.[81] Various aromatic aldehydes such as 1- and 2-naphthaldehydes, cinnamaldehyde, vanillin, syringaldehyde, and benzaldehydes have been converted to their corresponding

carboxylic acids by the *Sphingomonas* aldehyde dehydrogenase PhnN, which was overexpressed in *E. coli*.[82] The aldehyde functional group in glyoxal, but not in glyoxylic acid, has been oxidized by a *Pseudomonas* aldehyde oxidase expressed in *E. coli*.[83]

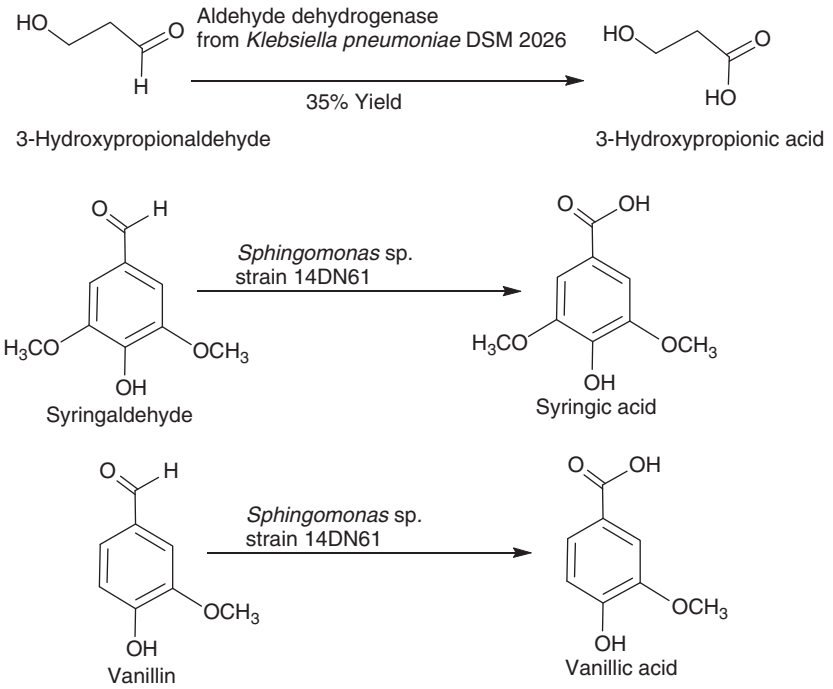


Figure 11 Aldehyde oxidations.

7.04.4.4 Oxidation of Phenols

Microbial oxidations of phenolic compounds catalyzed by laccases, polyphenol oxidases, and laccase-mediator systems[84–87] have found a variety of applications (Figure 12) in addition to the formation of new carbon–carbon bonds.[39–44] The highly efficient and sustainable synthesis of annulated benzofuranes has been achieved using phenol and various cyclic 1,3-dicarbonyls in a domino reaction catalyzed by a crude *Agaricus bisporus* extract containing tyrosinase and laccase.[88] Two enantiomeric lignans can be formed during laccase-catalyzed phenol coupling of (*E*)-coniferyl alcohol depending on the dirigent protein. When the dirigent protein AtDIR6 is present, the (–)-pinoresol is formed with 78% *ee*. Preferential formation of the (+)-pinoresol is observed in the presence of the dirigent protein FiDIR1, whereas only racemic product is formed in the absence of dirigent proteins.[89] Benzofuro[2,3c] pyrazolin-5-ones have been prepared by laccase-catalyzed oxidation of catechols in the presence of pyrazolin-5-ones.[90] Fungal laccases from *Trametes* spec. and *Myceliophthora thermophila* have been discovered to catalyze the formation of new carbon–nitrogen bonds in the nuclear amination of *p*-hydroquinones with primary aromatic amines,[91] which will be discussed in Section 7.04.7.

Low-molecular weight phenols are key natural substrates of fungal, plant, and insect laccases and are oxidized into phenoxyl radicals which then can either undergo oxidative coupling of natural phenols or can be cross-coupled to large-molecular weight compounds.[92] Kotanin is formed in a regio- and steroselective oxidative phenol coupling reaction from 7-demethylsiderin.[93] New regio- and stereoselective intermolecular oxidative phenol couplings have been discovered in *Penicillium viride*.[94]

7.04.4.5 Oxidation of C=C Bonds

A variety of selective microbial oxidation reactions of the C=C double bond such as asymmetric epoxidations, asymmetric dihydroxylations,[95] peroxidation, and cleavage reactions have enabled access to new chiral building blocks and new synthetic routes.

7.04.4.5.1 Epoxidation reactions

The excellent enantioselectivity of biocatalysts in the epoxidation of terminal olefins to give optically pure (R)-(+)-epoxides was discovered in 1978[96] and the regioselective oxidation of C=C double bonds in an asymmetric way is a competence of biocatalytic systems (Figure 13).[97] Mutants of cytochrome P450 monooxygenase BM-3 from *Bacillus megaterium* have been shown to catalyze the epoxidation of geranylacetone with 97% *ee* to the 9,10-epoxygeranylacetone, whereas geraniol was epoxidized to the

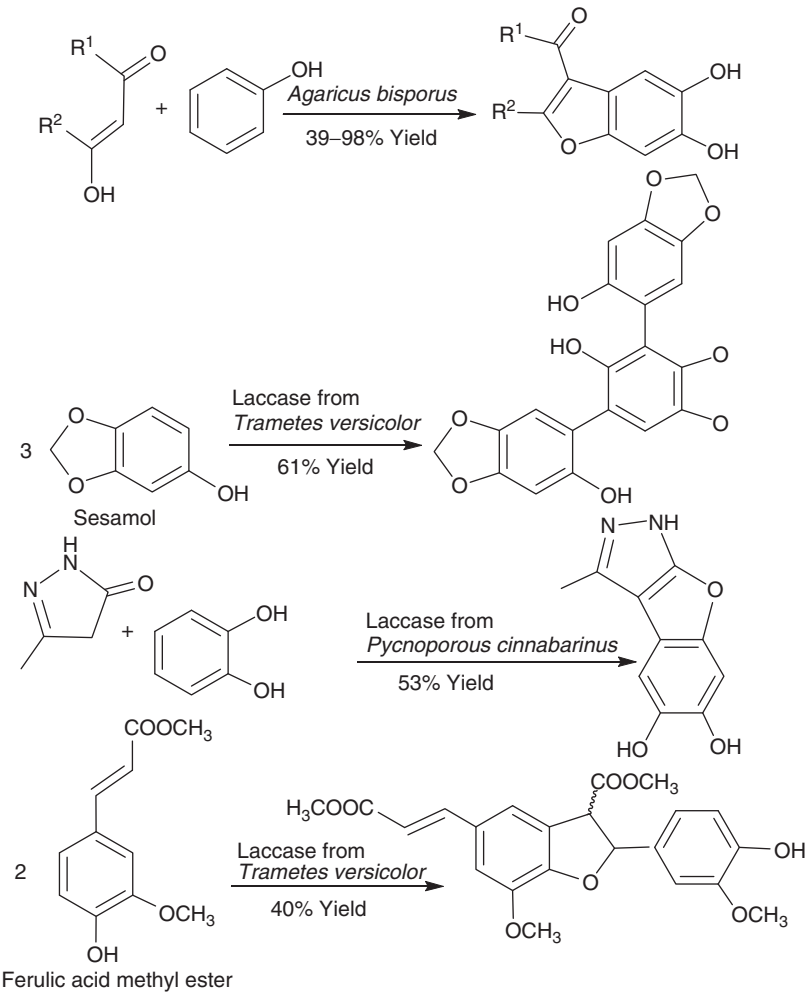


Figure 12 Phenol oxidations.

6,7-epoxide with 90% *ee* and 90% regioselectivity.[98] The first example of a catalytic enantioselective epoxidation by cyclohexanone monooxygenase was shown with a fosfomycin-related model compound.[99] The efficient asymmetric epoxidation of styrene to (*S*)-styrene oxide by recombinant styrene monooxygenase has been achieved by increasing biocatalyst concentrations and reducing the exposure time of the biocatalyst to the product.[100]

7.04.4.5.2 Dihydroxylation reactions

Catalytic asymmetric *cis*-dihydroxylation of aromatic compounds was pioneered by Gibson and coworkers[101–104] in their investigations on the degradation pathways of aromatic compounds. Mutant bacterial strains containing dioxygenases but lacking the corresponding diol dehydrogenase activity[102] enabled the synthesis of a remarkable range of *cis*-dihydrodiols with excellent stereoselectivity by asymmetric dihydroxylation of aromatic compounds (*see* Chapter 7.16).[103–106] Highly interesting synthons can thereby be obtained from aromatic compounds in a safe, environment-friendly, and resource-efficient way (Figure 14), because both of the atoms of molecular oxygen are introduced into an organic substrate.[107–110] Dioxygenases for biocatalytic dihydroxylations (see Figure 7) have been made available by biodiversity,[111] recombinant protein expression of dioxygenase genes in *E. coli*,[112–114] and by directed evolution.[115] Dioxygenases have also been used in asymmetric dihydroxylation of a series of conjugated monoalkenes and polyenes with *cis*-1,2-diols from arenes, cyclic alkenes, and dienes generally having >98% *ee*, whereas 1,2-diols from acyclic alkenes had a lower *ee*.[116] The diol metabolites were obtained from monosubstituted, gem-disubstituted, *cis*-disubstituted, and trisubstituted alkene substrates, using whole cells of *Pseudomonas putida* strains containing toluene and naphthalene dioxygenases, whereby the preference was 1,2-dihydroxylation for conjugated alkene or arene groups, and monohydroxylation at benzylic or allylic centers.[116] Recombinant toluene dioxygenase and chlorobenzene dioxygenase whole-cell biocatalysts can perform *cis*-vicinal dihydroxylation of aromatic nitriles to nitriledihydrodiols,[117,118] the isolated yield of which can be improved by *in-situ* product recovery and which can also be hydrolyzed by nitrilase to the corresponding carboxylic acids.[119] More than 300 *cis*-vicinal diol-metabolites have now been prepared with dioxygenases[120] from aromatic substrates, a selection of which is

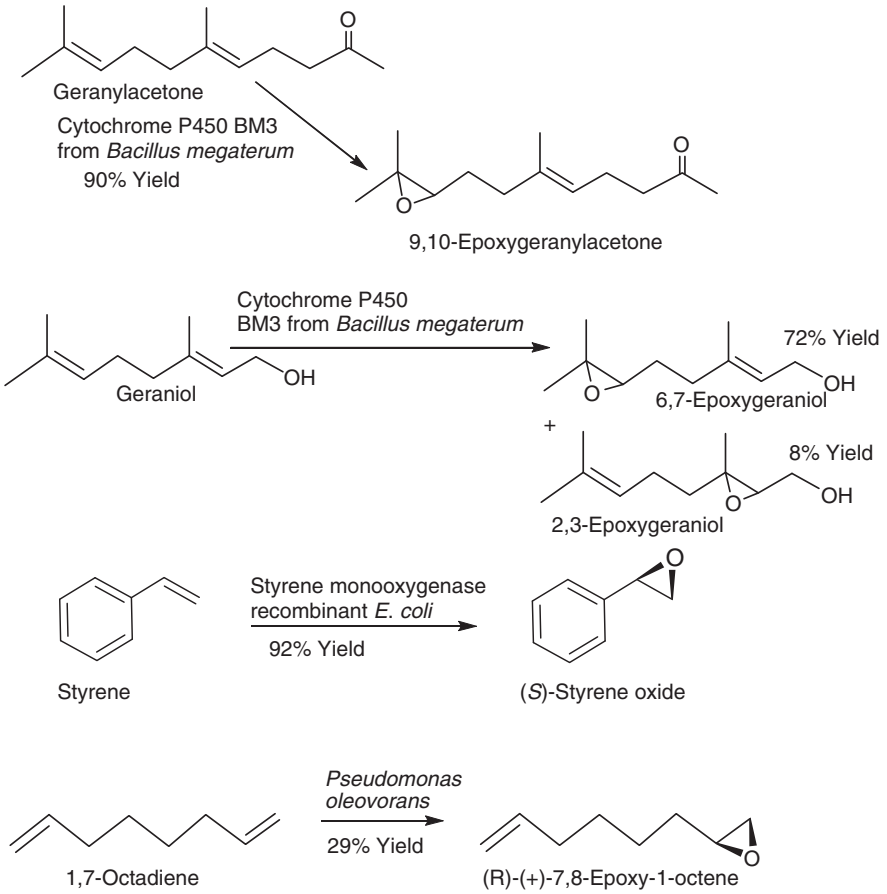


Figure 13 Epoxidation of C=C bonds.

shown in Figure 8. Recombinant *E. coli* cells expressing toluene dioxygenase have enabled access to para-functionalized cyclohexadiene-*cis*-diols.[121] In contrast to the most common asymmetric dihydroxylation in the *ortho*, *meta*-position with respect to the aromatic substituent in the substrate, the asymmetric dihydroxylation in the *ipso*, *ortho*-position by *R. eutrophus* B9 gives direct access to the synthetically useful *ipso*, *ortho*-diol of benzoic acid.[122] Recent evidence for the synthesis of tetraoxygenated chiral metabolites[123] by the action of toluene dioxygenase and biphenyl dioxygenase shows that *cis*-dihydrodiols and acetonide derivatives can itself be substrates for these enzymes.

Both *N*-substituted enantiomers (+)-(3*R*,4*R*)-3,4-dihydroxypiperidine and (−)-(3*S*,4*S*)-3,4-dihydroxypiperidine have been prepared with high enantiomeric purity and high yield from the corresponding *N*-substituted 1,2,5,6-tetrahydropyridines by an overall *trans*-dihydroxylation with *Sphingomonas* sp. HXN-200 containing a monooxygenase and an epoxide hydrolase.[124]

Intermolecular dioxygenases incorporate the two oxygen atoms into two molecules. The prokaryotic deacetoxycephalosporin synthase is an α-ketoglutarate- and Fe(II)-dependent oxygenase, which catalyzes the oxidative ring expansion of penicillins.[125] Selective microbial oxidations of L-proline and L-pipecolic acid have been achieved with recombinant *E. coli* cells containing α-ketoglutarate- and Fe(II)-dependent proline hydroxylases.[126,127] Recombinant *E. coli* strains expressing bacterial dioxygenases have been found to catalyze the hydroxylation of other free amino acids such as leucine, isoleucine, and threonine producing 4-hydroxyleucine, 4-hydroxyisoleucine, and 4-hydroxythreonine, respectively.[128]

7.04.4.5.3 Peroxidation reactions

Secondary hydroperoxides and their alcohols have been obtained in excellent *ee* by kinetic resolution of the racemates using horseradish peroxidase and *Coprinus* peroxidase.[129,130] Eight regiospecific 5-, 8-, 9-, 10-, 11-, 12-, 13-, and 15-lipoxygenases catalyze position-specific dioxygenation of polyunsaturated fatty acids, forming position-specific hydroperoxy fatty acids, which are further metabolized into signaling compounds.[131,132] The insertion of oxygen into arachidonic acid catalyzed by cyclooxygenases yields interesting cyclic endoperoxides and prostaglandins.[133]

7.04.4.5.4 Cleavage reactions

Biocatalytic oxygen incorporation into substrates from molecular oxygen and not from the oxygen of the water molecule has been discovered by Osamu Hayaishi in oxygenase-catalyzed reactions of tryptophan metabolism, thereby confirming the old Lavoisier

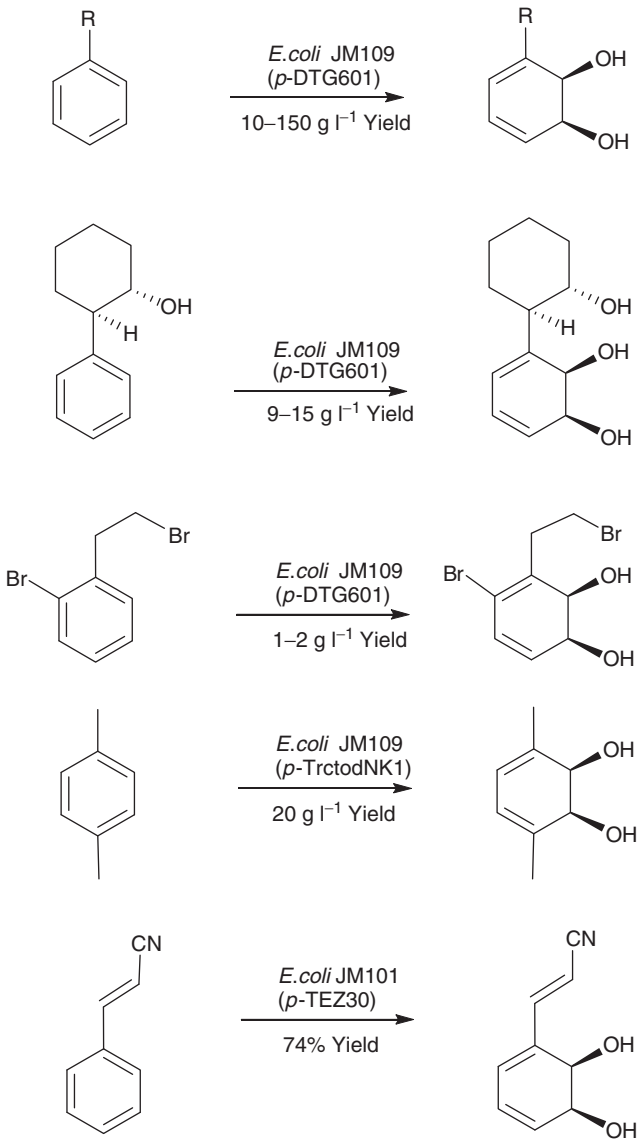


Figure 14 Dihydroxylation.

concept of biological oxidation.[134] The biocatalytic single-step cleavage of arylalkenes is a useful synthetic tool and an equivalent to reductive ozonization.[135] Biocatalytic oxidative cleavage of certain alkenes has been obtained with high chemo- and regioselectivity under mild reaction conditions (**Figure 15**), thereby providing an interesting alternative to chemical methods of double-bond cleavage with selectivity, yield, and safety challenges and suffering from the use of toxic reagents or special equipment such as ozonolysis.[136,137] A cell-free enzyme preparation from *Trametes hirsuta* has been successfully used for the regioselective cleavage of aromatic dialkenes with excellent conversions and chemoselectivities up to >99%.[138] The alkene-cleavage activity in *Trametes hirsuta* could be improved by the addition of the fungicide *t*-anethole and up to >99% conversion was obtained in the microbial oxidation of the carbon–carbon double bond adjacent to an aromatic ring for various aromatic substrates.[139] Cleavage enzymes from *Novosphingobium aromaticivorans* cleaved the interphenyl double bond of stilbenes having an oxygen functional group at the 4′-carbon atom to the corresponding aldehydes.[140] The preparation of retinal can be achieved from various carotenoids by the action of beta-carotene-15,15′-oxygenase and the cleavage of the 15–15′-double bond in beta-carotene and from beta-apo-8′-carotenal by the action of apocarotenoid-15,15′-oxygenase.[141]

7.04.4.6 Oxidation of C–C Bonds

The microbial oxidation of carbon–carbon bonds provides highly selective synthetic tools for desaturation, Baeyer–Villiger oxidation, and other oxidative cleavage reactions (*see* Chapter 7.26).

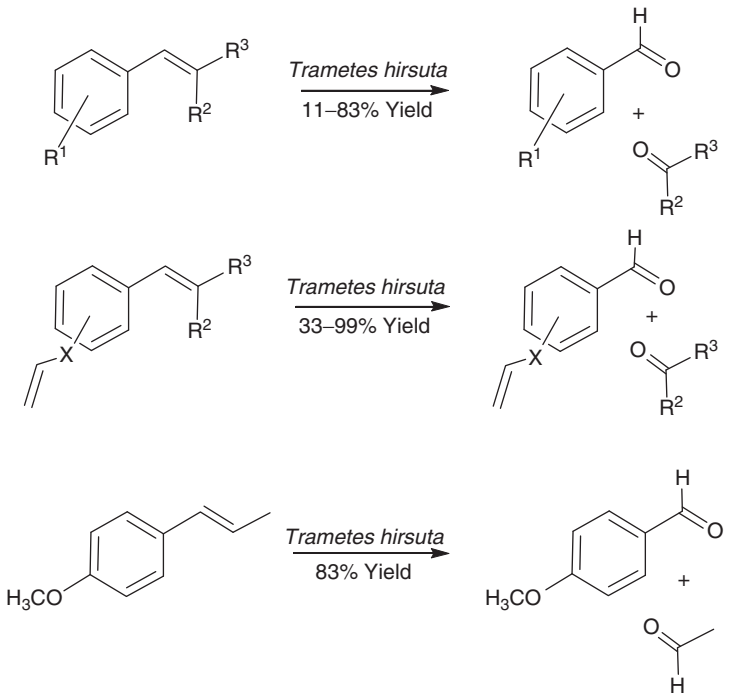


Figure 15 Oxidative C=C bond cleavage reactions.

7.04.4.6.1 Baeyer–Villiger oxidation reactions

Microbial Baeyer–Villiger oxidations utilize molecular oxygen as oxidant and have been shown to transform a large range of ketone substrates into esters or cyclic ketones into lactones with a high regio- and enantiospecificity (Figure 16), not reached by the use of inorganic, organometallic or organocatalysts.[142–145] The crystal structure of cyclohexanone monoxygenase from *Rhodococcus* sp. with cyclohexanone shows the ketone substrate in an ideal position for the formation of the Criegee intermediate while providing space and flexibility for the binding of a wide range of substrates.[146] With the NADP cofactor being recycled and water as byproduct, microbial Baeyer–Villiger oxidations are also attractive from the safety, health, and environmental perspectives for large-scale industrial applications.[147,148] The process engineering and scale up of the asymmetric microbial Baeyer–Villiger oxidation of racemic bicyclo [3.2.0]hept-2-en-6-one to the kilogram scale yielded both regioisomeric lactones [(−)-(1*S*,5*R*)-2 and (−)-(1*R*,5*S*)-3] in nearly enantiopure form (*ee* > 98%) and good yield.[149–152] Efficient *in-situ* substrate feeding and product removal using an adsorber resin enables microbial Baeyer–Villiger oxidations at high substrate concentrations.[153–155] Enantioselective Baeyer–Villiger monooxygenases for substrates that are not accepted by the wild-type enzyme have been discovered by directed evolution, for example, catalyzing with high enantioselectivity the oxidative kinetic resolution of 2-substituted cyclohexanone derivatives or the desymmetrization of 4-substituted cyclohexanones.[156,157] Racemic bicyclic diketones such as the Wieland–Miescher and the Hajos–Parrish diketones have been oxidized with high regio- and enantioselectivity to their corresponding lactones by cyclohexanone monooxygenase from *Acinetobacter calcoaceticus*.[158] The exploration of the substrate range of recombinant cyclopentadecanone monooxygenase from *Pseudomonas* sp. showed that not only flexible cyclopentadecanone rings but also structurally more demanding steroids are accepted and the regioselective Baeyer–Villiger oxidation of 3-keto- and 17-ketosteroids gave the corresponding lactones in yields up to 42%.[159]

7.04.4.6.2 Cleavage reactions

Recombinant hydroxyethylphosphonate dioxygenase from *E. coli*, a nonheme iron(II)-dependent dioxygenase, converts 2-hydroxyethylphosphonate to hydroxymethylphosphonate (Figure 17) and formate without requiring additional cofactors.[160,161] Methylphosphonate synthase is a nonheme iron-dependent oxygenase that converts 2-hydroxyethylphosphonate to methylphosphonate.[162] The carbon–phosphorus bond of 2-aminoethylphosphonic is cleaved to inorganic phosphate and glycine by the α-ketoglutarate/Fe(II)-dependent dioxygenase PhnY and PhnZ, a Fe(II)-dependent PhnZ.[163] The aromatic ring dioxygenase StnB1/B2 system has been found to catalyze a regiospecific N–C8′ bond cleavage of the indole ring of the lavendamycin methyl ester.[164]

7.04.4.7 Oxidation of C–N Bonds

The catalytic oxidation of the carbon–nitrogen bond in primary and secondary amines and amino acids by a variety of amino acid oxidases and monoamine oxidases coupled with hydrogen peroxide removal by catalase is well established (Figure 18) and has led to many practical resolutions and deracemizations.[76,165–169] The availability of racemic unnatural amino acids as well as D- and L-specific amino acid oxidases has made amino acid oxidase-catalyzed resolutions a preferred synthetic method.

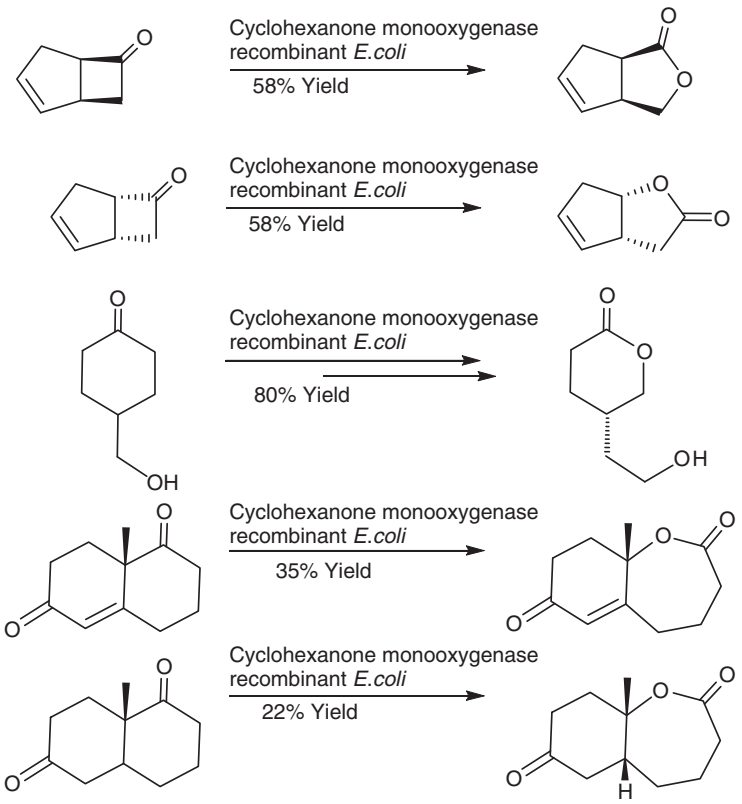


Figure 16 Baeyer–Villiger oxidation.

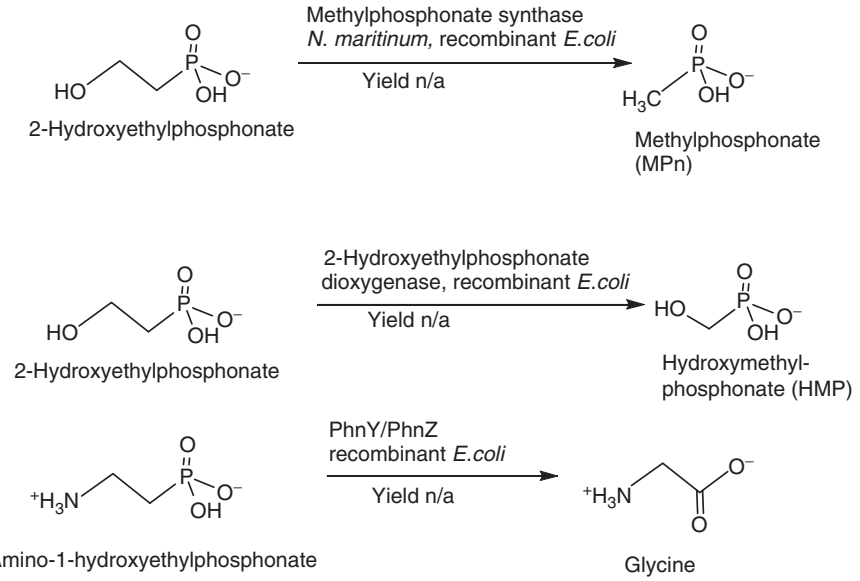


Figure 17 Oxidative C–C bond cleavage reactions.

(*R*)-Amino acid oxidase from *Trigonopsis variabilis* has been used in the preparation of (*S*)-2-amino-3-(6-*o*-tolylpyridin-3-yl)propanoic acid from its racemate by deracemization.[170] The catalytic oxidation of the carbon–nitrogen bond in amino acids by amino acid dehydrogenases avoids hydrogen peroxide side product formation. Leucine dehydrogenase catalyzes the oxidation L-*tert*-leucine thereby making it possible to prepare D-*tert*-leucine with an *ee* of >99% by a biocatalytic oxidative resolution of the racemic mixture of DL-*tert*-leucine.[171] Microbial amine oxidases have been used for resolutions, deracemizations, and desymmetrizations in the preparation of chiral amines for pharmaceutical and agrochemical applications. (*R*)-*O*-methyl-*N*-hydroxycyclohexylethylamine has been prepared with 99% *ee* by resolution of the racemate, using monoamine oxidase N from

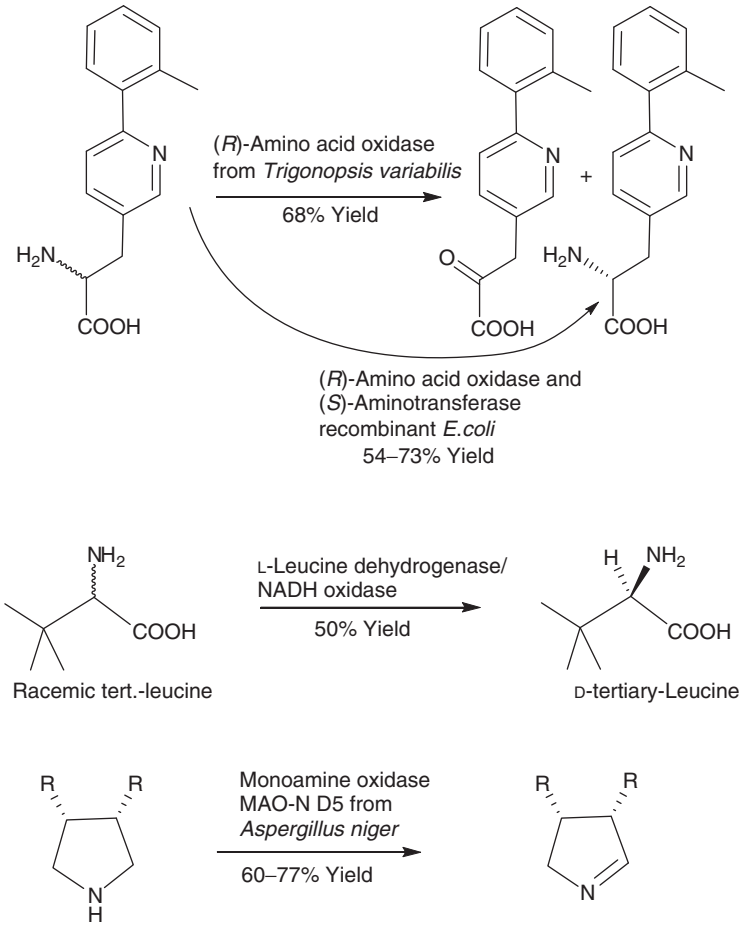


Figure 18 C–N bond oxidations.

Aspergillus niger, yielding the oxime exclusively in the (*E*)-configuration.[172] The oxidation of 3,4-substituted *meso*-pyrrolidines is catalyzed by monoamine oxidase from *Aspergillus niger* (MAO-N D5) catalyzed also the asymmetric oxidation of 3,4-substituted *meso*-pyrrolidines to the corresponding Δ1-pyrrolines, which can be used synthesizing L-proline analogs and enantiopure α-amino nitriles.[173] The bicyclic [3.1.0]-proline intermediate in the hepatitis C drug boceprevir has been prepared by an amine oxidase-catalyzed desymmetrization of a prochiral amine substrate.[174]

7.04.5 Formation of R–X Bonds (X = F, Cl, Br, I)

Microbial halogenation follows in general an oxidative strategy and catalytic machinery by converting the nucleophilic chloride, bromide, and iodide anions to oxidized states reacting as electrophiles or radical species in the formation of the new R–X bond.[175,176] Fluorinase from *Streptomyces cattleya* has been shown to utilize directly the nucleophilic fluoride and chloride anion.[177,178] Polymer-immobilized fluorinase has been used for the synthesis of 5′-fluoro-5′-deoxy-adenosine from *S*-adenosyl-L-methionine and fluoride anion in phosphate buffer with up to 68% fluorination efficiency.[179] Production of the fluoroanalog of the anticancer agent salinosporamide A has been achieved by replacing the chlorinase gene salL in the marine bacterium *Salinispora tropica* with the fluorinase gene flA from Streptomyces cattleya.[180] The control of regioselectivity in tryptophan halogenation catalyzed by tryptophan-7-halogenase PrnA is also synthetically interesting.[181]

7.04.6 Formation of R–S Bonds

Oxidative carbon–sulfur coupling has been achieved in the laccase-catalyzed mono- and dithiolation of 1,4-napththoquinones to form 1,4-nathoquinone sulfides and 1,4-napthoquinone dimers.[182] Phophoserine can be directly sulfhydrylated with sulfide to cysteine by *O*-phosphoserine sulfhydrylase from *Aeropyrum pernix*, which is homologous to *O*-acetylserine sulfhydrylase and cystathionine beta-synthase in bacteria.[183,184] A new carbon–sulfur bond is formed in the enantioselective ComA-catalyzed Michael addition of sulfite to phosphoenolpyruvate, giving (*R*)-phosphosulfolactate.[185]

7.04.7 Formation of R–N Bonds

The laccase-catalyzed synthesis of aminoquinones by oxidative amination of *p*-hydroquinones with primary aromatic amines in the presence of oxygen formed new carbon–nitrogen bonds (Figure 19) and gave the corresponding monoaminated or diaminated quinones, but no hydroquinonoids side products were formed.[91,186] Seven novel β-lactam antibiotics have been synthesized with yields of 30–60% by laccase-catalyzed amination of 2,5-dihydroxyphenylacetic acids, whereby *para*-substituted 2,5-dihydroxyaromatic acid substructures were better reaction partners than *ortho*-substituted substrates.[187] 5-Alkylamino- and 2,5-bis (alkylamino)-1,4-benzoquinones have been synthesized by coupling of 2-methoxy-3-methyl-hydroquinone with primary amines such as *n*-octylamine, geranylamine, and cyclooctylamine using laccases from *Myceliophthora thermophila* and *Pycnoporus cinnabarinus*, whereby the carbon–nitrogen coupling reaction led to monoaminated products at the benzoquinone C-5 position when using equimolar reactant concentrations.[188] The tyrosinase-catalyzed oxidative intramolcular cyclization reaction of *N*,*N*-dimethyltyramine to the anachelin chromophore has been a key step in the first biomimetic total synthesis of the iron chelator anachelin H and the enzyme tyrosinase has been found to be activated by the product.[189]

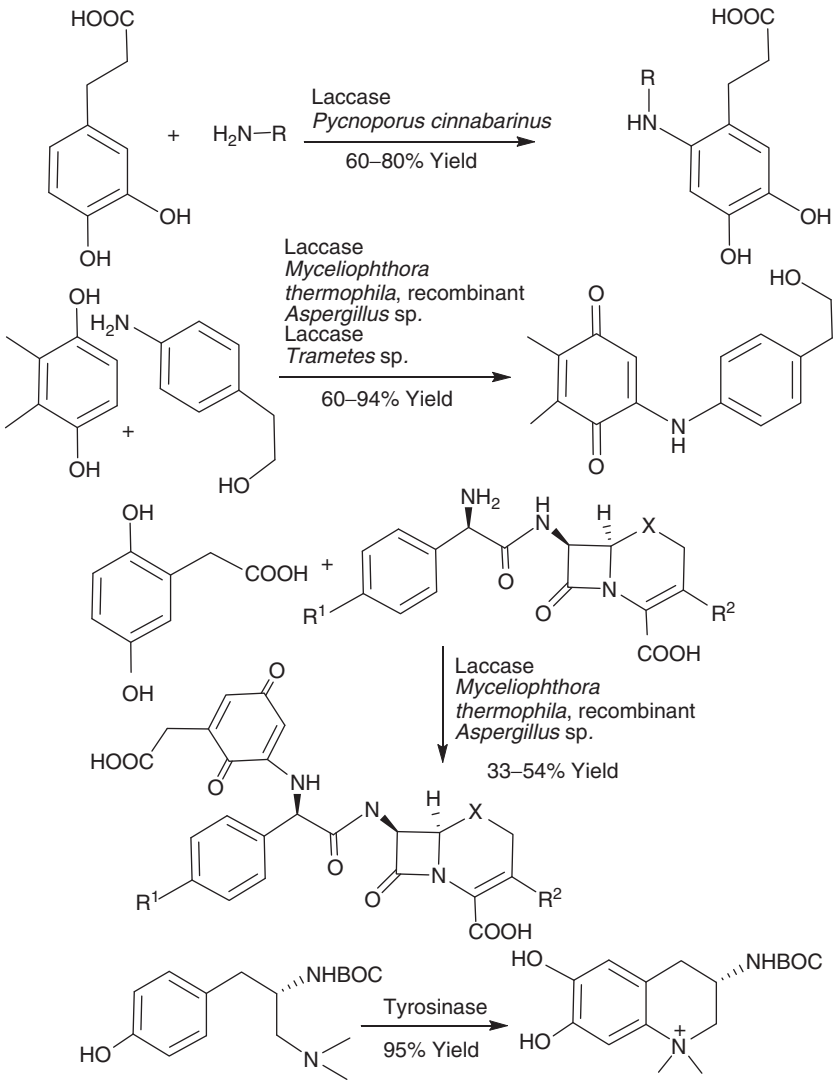


Figure 19 Oxidative aminations.

7.04.8 Formation of S–O Bonds

The microbial oxidation of sulfides to sulfoxides without overoxidation to the sulfones has been achieved by using isolated enzymes or whole cells (Figure 20) for the synthesis of a variety of chiral alkyl aryl sulfoxides, 1,3-dithioacetal-1-oxides, dialkyl sulfoxides, and thiosulfinates in high *ee* (*see* Chapter 7.28).[190–192] The proton pump inhibitor, rabeprazole has been obtained as

pure (*S*)-enantiomer with >99% *ee* and 92% conversion without the sulfone side product by microbial oxidation of the corresponding sulfide 2-[4-(3-methoxypropoxy)-3-methylpyridin-2-yl] methyl-thiobenzimidazole with *Cunninghamella echinulata* MK40.[193] Microbial sulfoxidation of omeprazole sulfide to the enantiopure (*S*)-sulfoxide esomeprazole has been achieved with 77% conversion, 100% *ee*, and no overoxidation to the sulfone by *Lysinibacillus* sp. B71.[194]

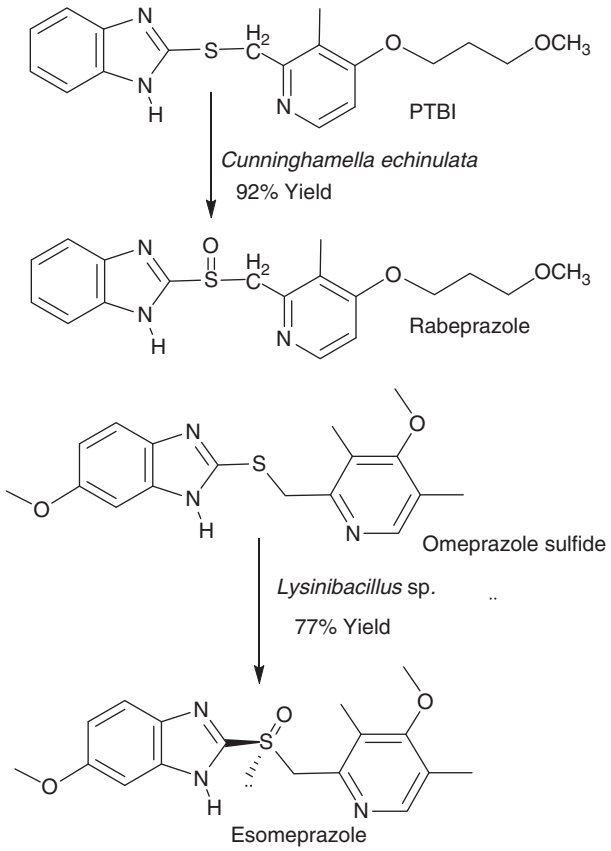


Figure 20 Microbial sulfoxidations.

7.04.9 Emerging Microbial Oxidation Reactions

The biocatalytic oxidative formation of new carbon–carbon bonds such as oxidative cyclization and oxidative ring expansion, oxidative deamination, or oxidative decarboxylation in natural product biosynthesis is also of synthetic interest. The oxidative formation of an intramolecular carbon–carbon bond in (*S*)-reticuline catalyzed by the berberine bridge enzyme, a reticuline oxidase, is a complex oxidation reaction,[45] which has been applied to the synthesis of a range of benzylisoquinoline compounds[195–197] and the resolution of racemic 1-substituted tetrahydroisoquinolines.[198]

Isopenicillin N synthase (IPNS) catalyzes the two iron-dioxygen-mediated oxidative ring closure of the tripeptide δ-(L-α-aminoadipoyl)-L-cysteinyl-D-valine (ACV) to isopenicillin N, the precursor to all penicillins and cephalosporins.[199] The four-electron oxidation of ACV by IPNS is unusual, requiring no 2-oxoglutarate cofactor. In contrast, clavaminate synthase (CAS) is a remarkable Fe(II)- and 2-oxoglutarate-dependent oxygenase, which catalyzes the construction of the bicyclic clavam ring system of clavaminic acid from a monocyclic β-lactam. CAS thereby catalyzes the three quite different oxidation reactions of hydroxylation, oxidative cyclization to dihydroclavaminic acid, and the final desaturation reaction to clavaminic acid.[200] Enantioselective epoxidation followed by regioselective epoxide opening reaction are the key processes in the construction of the polyether skeleton. Lsd18-catalyzed stepwise enantioselective epoxidation of prelasalocid to the bis-epoxide followed by Lsd19-catalyzed regioselective epoxide opening reaction are the key reactions in the construction of the lasalocid skeleton.[201] Selected examples of other biocatalytic asymmetric oxidations are shown in **Figure 10**. In the area of the polyether ionophore monensin a recently proposed mechanism of oxidative cyclization of a linear polyketide intermediate by four enzymes, the products of *monBI*, *monBII*, *monCI*, and *monCII*, has been supported experimentally by the analysis of a biosynthetic gene cluster[202] and the accumulation of an *E*,*E*,*E*-triene, when oxidative cyclization was blocked.[203] Oxidative ring expansion by an additional carbon atom is performed by expandases different from the Baeyer–Villiger monooxygenases capable of introducing oxygen into cyclic ketones.

The Fe(II)- and 2-oxoglutarate-dependent oxygenase deacetoxycephalosporin C synthase[204] catalyzes the unusual oxidative ring expansion of penicillin N to deacetyoxycephalosporin C.

7.04.10 Summary and Outlook

The number and type of synthetically useful microbial oxidations has been expanded and many new reaction platforms have become available. Nevertheless, the search for new microbial catalysts and their application in oxidations in organic synthesis continues to be important[205] and has the potential to provide key contributions to chemo-, regio-, and enantioselectivity, and also to safety, health and environmental aspects of oxidation reactions. The integration of microbial oxidations with synthetic methods such as kinetic resolution, kinetic asymmetric transformation, dynamic kinetic resolution, deracemization, desymmetrization, asymmetric synthesis with or without diastereo control, and multistep asymmetric biocatalysis has a lot of potential for improving atom economy, step economy, and redox economy in synthetic routes.[206] Careful studies of metabolic pathways, enzyme discovery, and development as well as interfacing the chemical and enzymatic reaction steps in a synthetic scheme are thereby the key for advancing microbial oxidations.[207] The new methods of selection and optimization bring also tremendous opportunities to tailor the biocatalyst to the desired reaction conditions, degrees of conversion, selectivity, substrate or product inhibition in order to develop viable large-scale industrial oxidations.[208] New synthetic tools for selective partial oxidation of inexpensive non-functionalized raw materials can provide more direct synthetic routes to chiral compounds.[209] With the continuing trends to process improvements, cost reductions, increasing quality, safety, health, and environmental requirements for synthetic methods in research, development, and production, there is a bright future for biocatalytic oxidations as a sustainable manufacturing technology in industry and research institutions.[210]

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7.05 Oxidation Adjacent to C=C Bonds

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Glossary

Aminopalladation A reaction where palladium and an amine species add across a double or triple bond to form new carbon-palladium and carbon-nitrogen bonds. The metal does not undergo a redox change.

Homolytic C–H cleavage Bond breaking in which the bonding electron pair is split evenly between the products. Homolytic cleavage typically produces radicals.

β-hydride elimination A reaction in which a metal-carbon bond undergoes elimination to form a metal-hydride and olefin. The metal must have a *cis* open coordination site to facilitate elimination of a hydrogen beta to the metal-carbon bond. The metal does not undergo redox change.

π-allyl A complex between a metal and an allylic carbon species where the metal binds to all three carbon centers simultaneously through delocalized bonds. The allyl group takes up two coordination sites on the metal and has a negative one charge.

7.05.1 Introduction

Allylic oxidation is an important transformation that has traditionally been used to construct valuable allylic alcohols and α,β-unsaturated carbonyls from simple olefins. Many of the classic methods (i.e., selenium dioxide and stoichiometric chromium(VI)) are still widely used in synthesis and were extensively reviewed in the first volume.[1] In the past 15 years, there has been explosive growth in the development of transition-metal-catalyzed allylic C–H oxidation (as well as aromatic and aliphatic C–H oxidation).[2] There are many examples where fine tuning of the metal and ligand can lead to highly chemo-, regio-, and stereoselective oxidation. The wide reactivity of transition metals has also allowed for novel allylic C–H amination[3] and allylic C–H alkylation reactions[4] (Figure 1).

The present review will briefly cover the well-known selenium dioxide and copper/perester-based approaches to allylic alcohols and esters. Newer, metal-catalyzed oxidations to form α,β-unsaturated enones will also be described. The main focus of the review will cover palladium-catalyzed allylic oxidation, amination, and alkylation methods. Allylic amination via ene type pathways and metal nitrenoids will also be discussed.

Most allylic oxidation/amination/alkylation methods occur by one of three general mechanisms: (1) radical- or metal-promoted homolytic C–H cleavage (Figure 2, top), (2) metal-promoted heterolytic C–H cleavage (Figure 2, middle), and

(3) ene-type pathways (Figure 2, bottom). The mechanism of each method will be discussed as it can have a profound influence on oxidation selectivity and functional group tolerance.

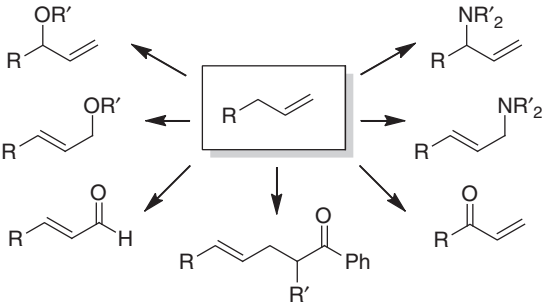


Figure 1 Diverse products generated from allylic C–H oxidation.

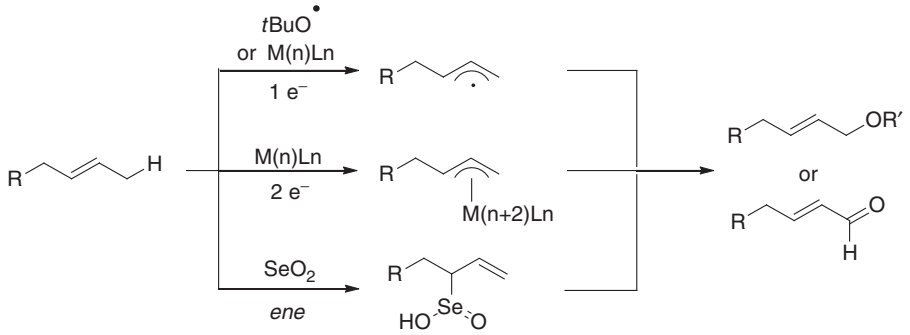


Figure 2 General mechanistic pathways for allylic oxidation.

One of the main challenges within allylic oxidation is controlling the regioselectivity of C–H cleavage and C–O bond formation. The regioselectivity of C–H cleavage is not well controlled for simple internal olefins as there is low steric or electronic bias. Many synthetic examples involving complex olefins demonstrate highly regioselective C–H cleavage. Alternatively, many recent oxidation methods have utilized α-olefins which avoid this problem. The regioselectivity of C–O bond formation is controlled by subtle steric and electronic effects within both the molecule and catalyst, particularly when the mechanism proceeds through a π-allyl-metal intermediate. Fortunately, many times the regioisomers can be separated by column chromatography. Stereoselectivity and site-selectivity of oxidation are also important considerations. Almost all reactions will favor the formation of the thermodynamically more stable (*E*)-olefin for acyclic molecules, however it is still important to generate the product in very high stereoselectivity as the olefin isomers are often inseparable by column chromatography. Most bulky transition metals and electrophilic oxidizing agents promote oxidation at the less-sterically hindered double bond when more than one olefin is present.

7.05.1.1 Allylic Oxidation Reactions Which Produce Allylic Alcohols or Esters

7.05.1.1.1 Selenium dioxide-based reagents

Allylic oxidation using selenium dioxide is an extremely important synthetic method that has been widely used in complex molecule synthesis. As numerous reviews have extensively covered this reaction, the transformation will only be discussed briefly here.[1,5] The reaction was initially developed using stoichiometric selenium dioxide and Sharpless later introduced catalytic conditions using *tert*-butyl hydrogen peroxide (TBHP) as a terminal oxidant.[6] The major reaction pathway proceeds by an ene reaction to generate allylseleninic acid **2** followed by [2,3]-sigmatropic rearrangement to form selenite ester **3** (Figure 3).[7] Selenite ester **3** is decomposed to allylic alcohol **4** by hydrolysis. The pericyclic transition states of the reaction mechanism lead to regio- and stereoselective (*E*)-allylic alcohol formation from trisubstituted olefins, however there are some instances where reduced selectivity has been observed. Reduced olefin selectivity has been rationalized by addition of $HSeO_2+$ across the double bond instead of the ene pathway.[8] However, recent elegant mechanistic studies by Singleton show that this would be a minor pathway if at all operative.[9] Alternatively, Woggon suggested that the ene step does not always proceed with high regioselectivity for the less hindered olefin face.[10] It is important to note that selenium dioxide conditions sometimes lead to α,β-enones selectively or mixtures of alcohols and α,β-enones via overoxidation of the allylic alcohol by selenium dioxide (equation 1).[1,11]

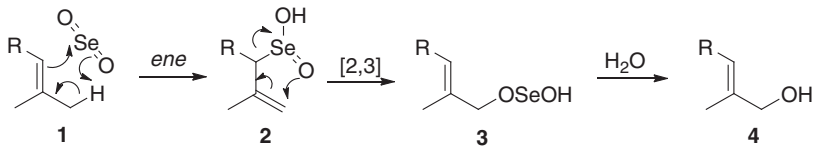
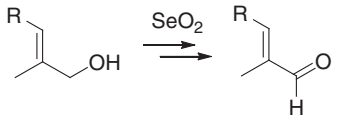
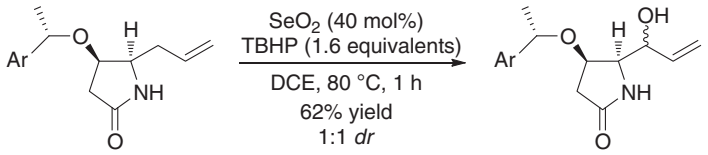


Figure 3 Mechanism of selenium dioxide promoted allylic oxidation.

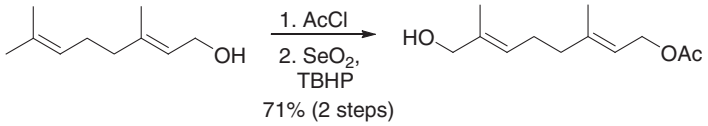


(1)

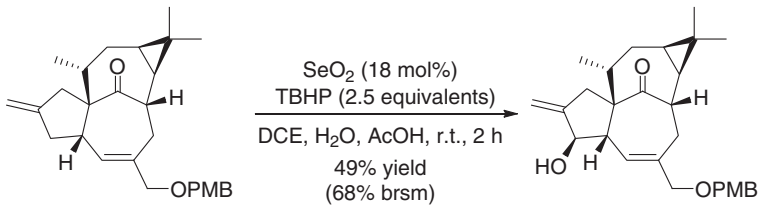
The reaction has been extensively used in synthesis because of its selectivity,[12] scope, and functional group tolerance. For simple α-olefins, the reaction proceeds with high regioselectivity but is not diastereoselective (equation 2).[13] High regio-, stereo-, and site-selectivity were observed during the oxidation of a trisubstituted olefin of geranyl acetate (equation 3). Oxidation occurs at the least sterically hindered primary C–H bond on the olefin distal to the bulky, inductively withdrawing acetate.[14] Some of the most impressive examples of selectivity are observed for more complex molecules. In the synthesis of an intermediate toward Ingenol, the ene reaction proceeded from the less hindered secondary site of the 1,1-disubstituted olefin followed by [2,3]-sigmatropic rearrangement from the convex face (equation 4).[15]



(2)



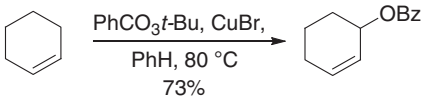
(3)



(4)

7.05.1.1.2 Copper/perester-based catalysts

Copper-catalyzed allylic oxidation using stoichiometric peresters (the Kharasch–Sosnovsky reaction) is a well-known way to perform allylic C–H oxidation. Although it is a powerful method, its use in synthesis has been limited because of the need for superstoichiometric amounts of olefin (2.5–10 equivalents). This classic oxidation method has been previously reviewed,[16] therefore the present review will only cover the basic reaction scope and mechanism along with recent advances. In 1958, Kharasch and Sosnovsky reported that catalytic copper(I) bromide along with *tert*-butyl perbenzoate or *tert*-butyl peracetate promoted the oxidation of cyclohexene and α-olefins (equation 5).[17] The choice of oxidant dictated whether an allylic benzoate or acetate product was formed. Since the initial discovery, numerous copper salts [CuBr, CuCl, and Cu(carboxylate)$_2$] and oxidants ($PhCO_3t$-Bu, $MeCO_3t$-Bu, *t*-BuOOH)[18] have been used to perform the chemistry.



(5)

The exact reaction mechanism is quite complex and may be dependent on substrate, catalyst, and oxidant. The proposed mechanism using simple copper salts is shown in **Figure 4**. Copper(I) promotes homolysis of the perester to generate copper(II) carboxylate and *tert*-butoxy radical, followed by allylic hydrogen abstraction to form an allylic radical species and *tert*-butanol.[19] For more complex systems using ligated copper, the olefin is believed to bind to copper before allylic hydrogen abstraction.[20] The exact nature of C–O bond formation has also been debated though Beckwith and Zavitsas' classic mechanism[19a] is now commonly accepted. It is proposed that η^1–Cu(III)-allylcarboxylate species **5** and **7** are formed and undergo reductive elimination via a 7-membered pericyclic transition state to form **6** and **8**, respectively.[21] Recent studies on reductive elimination have shown the η^1–Cu(III)-allylcarboxylate species can interconvert via the intermediacy of a η^3–Cu(III)-allylcarboxylate,[22] though η^1–Cu(III)-allylcarboxylate species are the preferred lower energy state.[23] This mechanism correctly predicts the high branched regioselectivity for oxidation of (*E*)-2-butene as intermediate **5** should be the lower energy η^1–Cu(III)-allylcarboxylate species because of steric bulk at the metal.

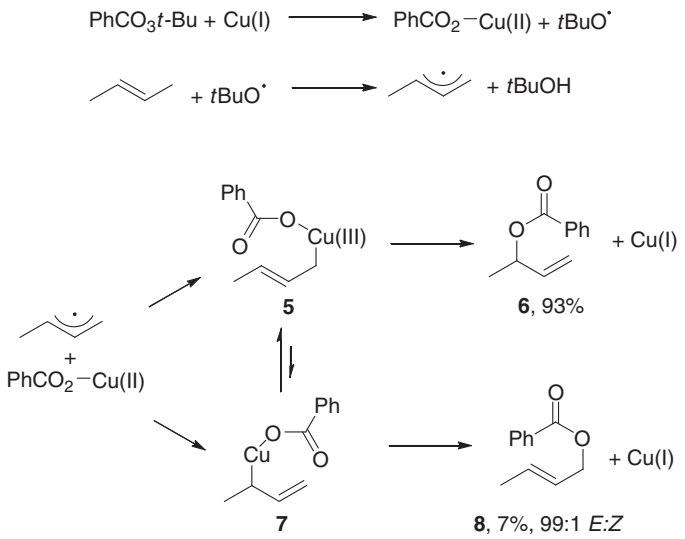
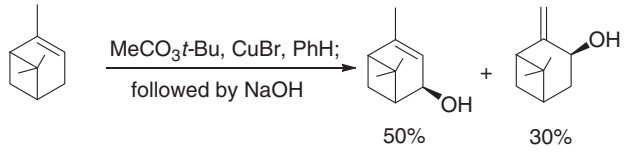
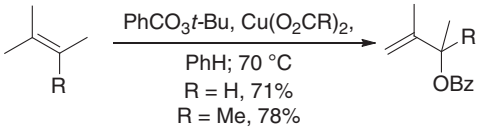


Figure 4 Proposed mechanism of copper/peroxyester oxidation.

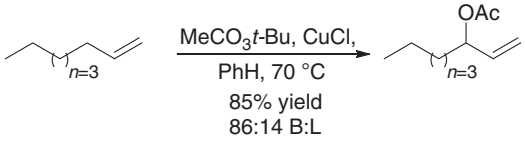
The reaction shows broad scope for various types of olefins. Simple cyclic olefins like cyclohexene and cyclopentene undergo straightforward C–H oxidation.[24] It is difficult to predict the product distribution of more complex cyclic substrates where multiple sites for catalytic C–H abstraction exist (equation 6).[25] Acyclic olefins are also viable substrates. Tetra- and tri-substituted olefins regioselectively form the C–O bond at the most substituted carbon substituent (equation 7).[26] Oxidation of α-olefins also favors the more substituted branched allylic ester products in approximately 6:1 regioselectivity (equation 8).[27]



(6)



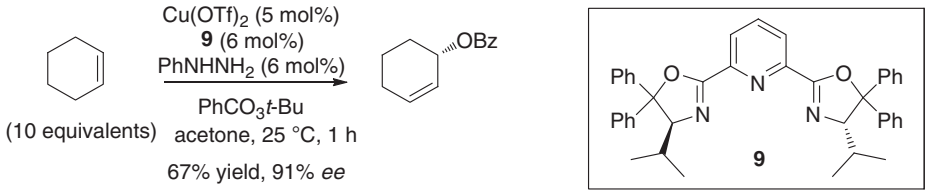
(7)



(8)

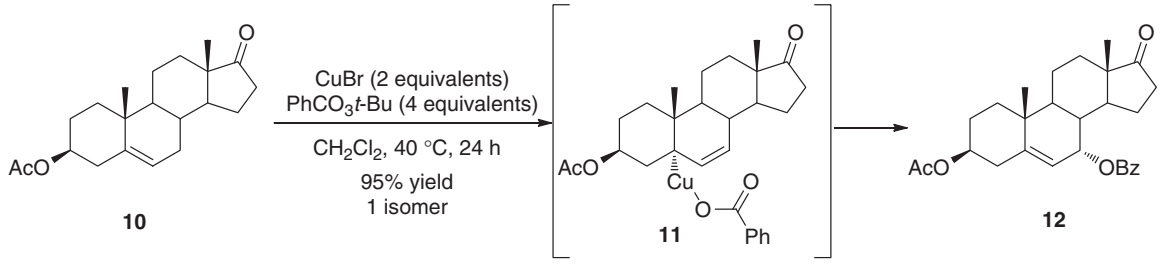
Many researchers have studied enantioselective Kharasch oxidation. One initial breakthrough using a bisoxazoline ligand showed very high enantioselectivity (99% *ee*) but extremely sluggish conversion (41% yield after 8 days).[28] The reaction rate has

been dramatically increased with the use of bis(oxazolinyl)pyridine ligand **9** and phenyl hydrazine additive while only modestly reducing enantioselectivity (equation 9).[29] Note that common enantioselective variants all require a large excess of substrate and give complex mixtures and low enantioselectivity for more substituted cyclic or acyclic olefins.[30]

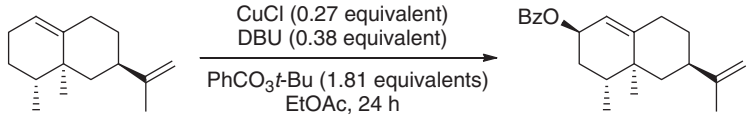


(9)

There have been some recent examples of oxidation using limiting substrate. A notable case is the highly diastereoselective allylic benzoylation of cholesterol derivatives (equation 10).[31] The authors rationalize that high diastereoselectivity is because of the rigid structure promoting the selective formation of a 5α-copper(III) intermediate **11** that undergoes reductive elimination to allylic benzoate **12**. As an alternative to relying on substrate conformation for high selectivity and reactivity, researchers have also begun to use multivariate optimization methods to optimize reaction conditions (equation 11).[32] Impressive examples of regio, stereo, and site-selectivity can be obtained using just one equivalent of starting material, however each substrate requires a new round of multivariate optimization. During the study the authors found that amine bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or pyrrolidine accelerated reaction rates, which suggests that the common additive phenyl hydrazine may serve a greater role than just reducing copper(II) to copper(I).[33] Phenyl hydrazine in this system showed only modest success.



(10)



(11)

7.05.1.1.3 Palladium reagents

7.05.1.1.3.1 Stoichiometric palladium reagents

It has long been known that stoichiometric palladium salts in AcOH can promote allylic acetoxylation for internal olefins, although the initial report was not further explored as a synthetic method.[34] Allylic oxidation of α-olefins or functionalization using different nucleophiles has been a more challenging problem and was first developed using a step wise, palladium-promoted allylic C–H oxidation with stoichiometric amounts of metal (**Figure 5**). In the first step, a highly electrophilic palladium species supported by acetone as a σ/π-donating ligand affects allylic C–H cleavage in the absence of a nucleophile.[35] After C–H cleavage and isolation of the more stable π-allylpalladiumCl species **13**, regioselective functionalization is performed in the presence of a nucleophile and a π-acidic ligand. Importantly, the two-step, stoichiometric method allows for functionalization using oxygen,[36] carbon,[37] and nitrogen[38] nucleophiles.

Recent advances have now allowed for palladium-catalyzed allylic C–H oxidation, amination, and alkylation and will be described throughout this review. There are three keys to the development of the catalytic system: (1) development of one or a set of ligands that can support both electrophilic C–H cleavage and nucleophilic π-allyl functionalization, (2) use of weakly basic nucleophiles that do not interfere with C–H cleavage and that can be deprotonated *in situ* under mild conditions, and (3) inclusion of an oxidant to regenerate palladium(II).

7.05.1.1.3.2 Palladium-catalyzed oxidation of internal olefins

McMurry and Åkermark independently developed catalytic, allylic oxidation conditions for internal olefins. McMurry studied the allylic oxidation of geranylacetone **14**, a molecule containing numerous allylic C–H bonds (**Figure 6**).[39] He found that the choice of ligand and quinone oxidant had a very strong effect on product conversion and regioselectivity. The combination of *o*-methoxyacetophenone ligand (**19**) and benzoquinone (BQ) oxidant (**15**) provided the highest overall yield (85%) and modest

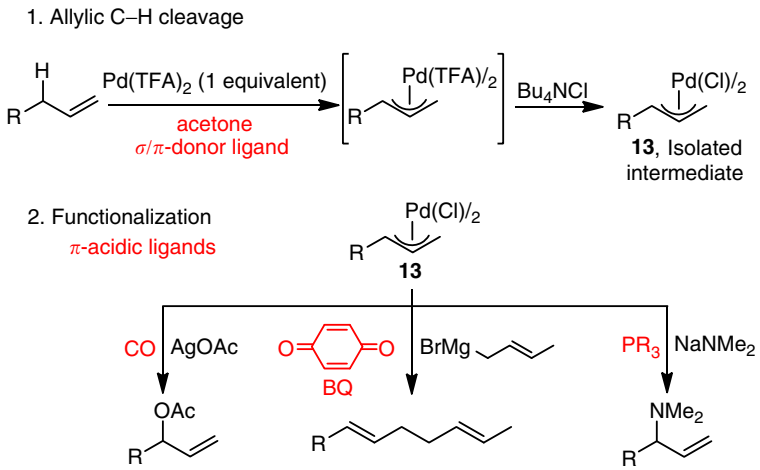
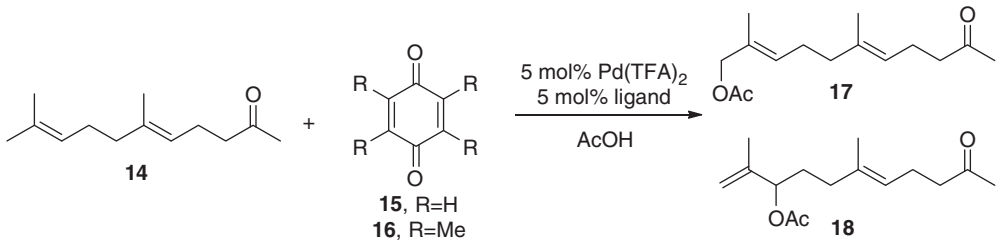


Figure 5 Stepwise, stoichiometric allylic C–H oxidation systems.

2:1 regioselectivity for **17**, whereas diethyl malonate ligand (**20**) and duroquinone (**16**) provided very high 24:1 regioselectivity for the opposite regioisomer **18**, albeit in just 32% yield. Both sets of conditions showed high site selectivity for the distal olefin.



Oxidant	Ligand	Temperature	Time	Regioselectivity (**17**:**18**)	Yield (%)
15	**19**	20	48 h	1.9:1	85
16	**20**	90	48 h	1:24	32

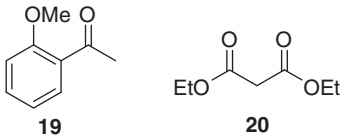
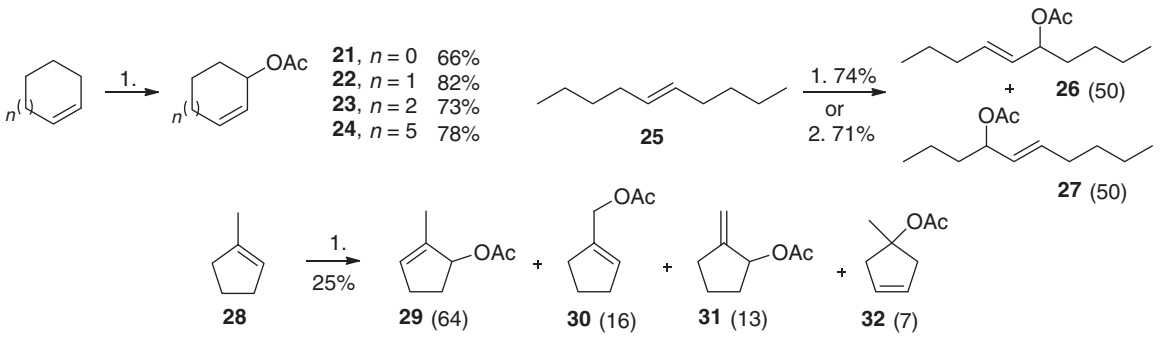


Figure 6 Allylic oxidation of geranylacetone **14**.

Åkermark studied the oxidation of cycloolefins and found that 5 mol% $Pd(OAc)_2$ in AcOH using an oxidant system provided good conversion (Figure 7).[40] The best terminal oxidant for cyclohexene oxidation was a mixture of BQ/MnO_2. He found that various cyclic olefins could be reacted in good yield to generate allylic acetates **21–24**. Acyclic olefins such as *trans*-5-decene **25** also worked, however a 1:1 mixture of regioisomers (**26** and **27**) was formed. More substituted cyclopentene and cyclohexene derivatives such as 1-methylcyclopentene **28** typically provided a complex mixture of products. Åkermark has further developed his reaction conditions to use catalytic BQ and hydrogen peroxide as the terminal oxidant.[41]

Bäckvall studied the mechanism of $Pd(OAc)_2$/BQ-catalyzed oxidation of cyclohexene by using the deuterated substrate 1,2-dideuteriocyclexene **33** (Figure 8).[42] The study differentiated between two potential mechanisms: (1) π-allyl and (2) acetoxypalladation. The π-allyl mechanism would proceed through allylic C–H cleavage to generate π-allylpalladium intermediate **34** followed by C–O reductive elimination to generate **35** and **36**. Alternatively, the acetoxpalladation pathway would occur by migratory insertion of the palladium acetate across the olefin to generate palladium alkyl intermediate **37** followed by *syn* β-hydride elimination to produce **38**. When the deuterated substrate was subjected to several sets of Pd-promoted stoichiometric and catalytic reaction conditions, **35** and **36** were observed consistent with the π-allyl mechanism. Although this elegant experiment has shed significant light on the acetoxylation of cyclohexene, it is hard to generalize the findings. In particular, Åkermark has shown that allylic oxidation of more complex substrates such as **28** likely proceeds through both acetoxypalladation and π-allyl mechanisms.

It is important to note that the $Pd(OAc)_2$/AcOH catalyzed allylic oxidation systems described have included a quinone species such as BQ. Benzoquinone is known to serve as a re-oxidant of palladium in the presence of carboxylic acid, thus generating $Pd(OAc)_2$ and dihydroquinone (DHQ) (equation 12).[43] BQ has also been shown to serve as a π-acid to promote inner-sphere C–O bond functionalization from an intermediate such as **39** (Figure 8).[44]



1. 5 mol% $Pd(OAc)_2$, 20 mol% benzoquinone, 1.1–2 equivalents MnO_2, AcOH, 40–60 °C
2. 5 mol% $Pd(OAc)_2$,10 mol% benzoquinone, 1.1 equivalents TBHP, AcOH, 70 °C

Figure 7 $Pd(OAc)_2$/benzoquinone (BQ)-catalyzed allylic oxidation of internal alkenes.

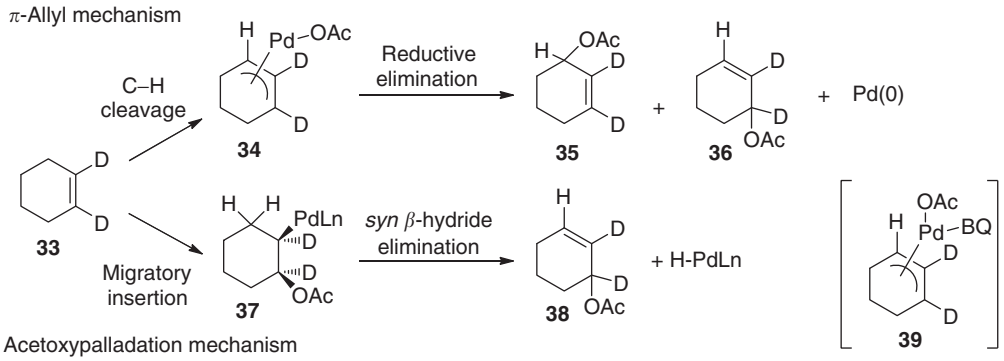
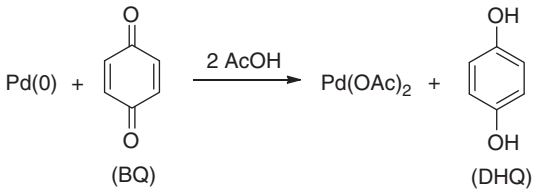


Figure 8 Mechanistic study of 1,2-dideuteriocyclohexene **33** oxidation.



(12)

7.05.1.1.3.3 Palladium-catalyzed oxidation of α-olefins: linear selectivity

Contrary to internal olefins, α-olefin **40** forms the products of Wacker oxidation (vinyl acetate **41**[34] and methyl ketone **42**[45]) under $Pd(OAc)_2$/AcOH-promoted allylic oxidation conditions (Figure 9, olefin oxidation). In 1966, Winstein observed that a mixture of dimethylsulfoxide (DMSO)/AcOH led to selective formation of linear allylic acetate product in one stoichiometric example but did not comment on this interesting reversal in selectivity.[34]

White and Chen were intrigued by Winstein's result and discovered that adding DMSO as a solvent to the $Pd(OAc)_2$/BQ/AcOH catalyst system diverts the reactivity of α-olefins toward the formation of linear (*E*)-allylic acetate **43** (Figure 9, C–H oxidation).[46] The products are formed with high regio- and stereoselectivities and in preparatively useful yields (50–68%). The catalytic reaction conditions are general across a wide range of substrates and exhibit excellent tolerance for molecules containing acidic protons (**44**), acid labile acetals (**45**), and free phenols (**46**). Allylic oxidation of homoallylic substrates provides products with very high stereo- and regioselectivity (**47**). Deacetylation of the allylic acetates leads to useful linear (*E*)-allylic alcohols in high yield.

Although the mechanism of this transformation has not been studied in detail, the authors hypothesize that the mechanism proceeds through acetate-promoted allylic C–H cleavage to form a π-allylpalladium intermediate followed by functionalization with acetate (Figure 10). Anti-Markvonikov oxy-palladation followed by regioselective β-hydride elimination cannot be ruled out, though this type of mechanism is unprecedented. The exact role of DMSO is unclear, however it is known that DMSO can bind to palladium and promote the formation of a cationic, highly electrophilic palladium species[47] which may be capable of allylic C–H cleavage. The authors rationalize the high regioselectivity by hypothesizing that π-acidic DMSO promotes outer-sphere acetate

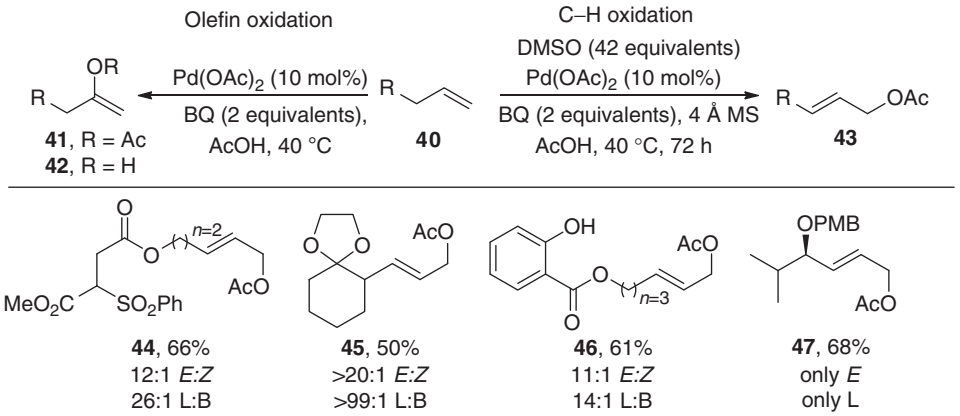


Figure 9 $Pd(OAc)_2$/DMSO/BQ/AcOH system for the synthesis of linear (*E*)-allylic acetates.

functionalization at the least sterically hindered position of a cationic π-allylpalladium$(DMSO)_2$ intermediate such as **49**.[48] Contrary to the acetoxylation of internal olefins, there are many instances where a π-acid besides BQ promotes C–O bond formation.

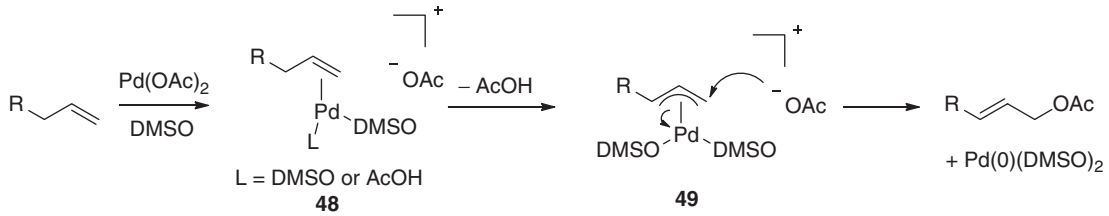


Figure 10 Potential mechanism for $Pd(OAc)_2$/DMSO/BQ allylic oxidation.

White has further developed the linear allylic oxidation method to allow for the use of a wide variety of carboxylic acids (Figure 11).[49] The addition of catalytic *N,N*-diisopropylethylamine (DIPEA) was found to allow for efficient coupling with just 1.5–3.0 equivalents of acid, presumably by generating a higher concentration of carboxylate anion which is necessary to promote allylic C–H cleavage and π-allylpalladium functionalization. The new fragment coupling method generates the products in 50–75% yield and with >10:1 *E:Z* selectivity. Aryl (**50**), vinylic (**51**), and complex α-amino acids (**52**) have been shown to undergo the reaction. The new reaction conditions were also found to promote allylic C–H acetoxylation using just 3 equivalents of AcOH which expands the scope of the reaction to include highly acid-sensitive functionality such as a PMP acetal (**53**).

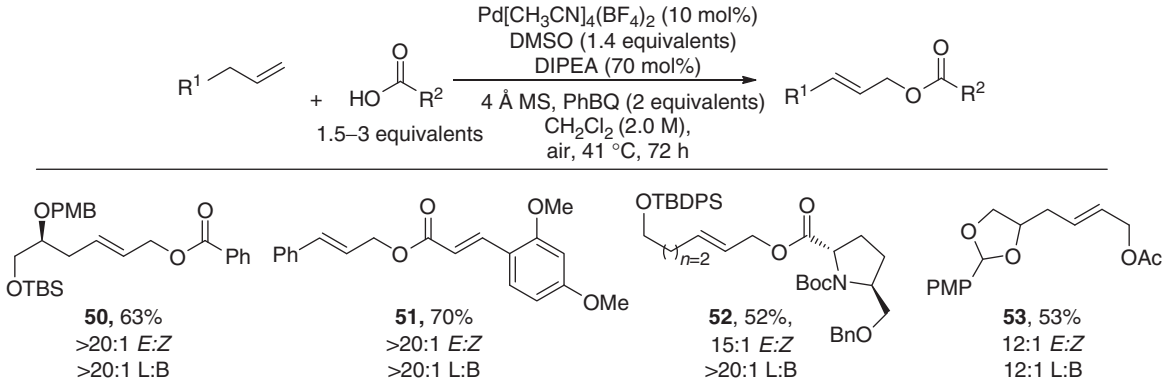


Figure 11 $Pd(OAc)_2$/DMSO system for general allylic C–H esterification.

The development of the $Pd(OAc)_2$/sulfoxide/BQ-promoted allylic C–H oxidation systems inspired other researchers to explore similar reactivity of α-olefins. Kaneda and coworkers developed a $PdCl_2$/DMAc/NaOAc/O_2-catalyzed allylic C–H oxidation reaction to form linear allylic acetates (Figure 12).[50] The products were formed in moderate to excellent yield (50–90%) with highly variable stereoselectivity (1:1 to >99:1 *E:Z*) and with good to excellent regioselectivity (7:1 to 45:1). Acetals (**45**), esters (**54**), and nitriles (**55**) are all tolerated and show good stereoselectivity. The reaction shows very low stereoselectivity for long alkyl

chains (**56–57**). The use of dimethylacetamide (DMAc) as solvent was critical to the reaction's success. DMAc promotes the formation of allylic acetate products rather than vinyl acetates and allows for Pd(0) reoxidation using molecular oxygen. Alternatively, in some instances AcOH solvent can be used for allylic C–H oxidation of α-olefins when simple bases such as NaOAc or LiOH are included.[51]

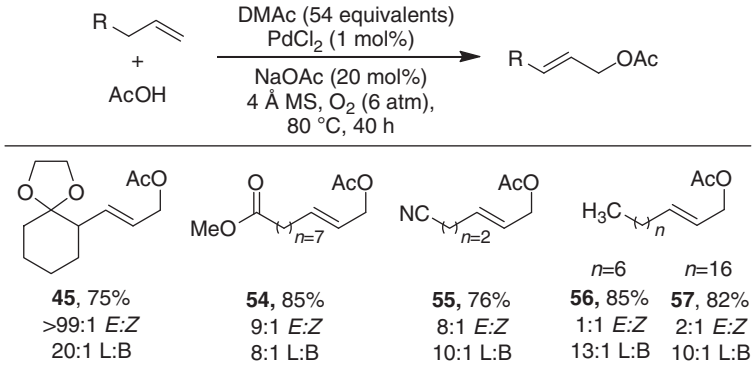


Figure 12 $PdCl_2$/DMAc system for the synthesis of linear (*E*)-allylic acetates.

Other researchers have developed linear allylic acetoxylation conditions using more complex ligands than DMSO or DMAc (Figure 13). Stambuli and coworkers have found that 2-tolyloxylethyl phenyl sulfide **58** promotes allylic C–H oxidation in AcOH.[52] The reactions proceed in just 12–20 h and provide the desired linear allylic acetate in 42–68% yield. Notably, the products were typically formed with >20:1 *E:Z* stereoselectivity and approximately 20:1 L:B (linear:branched) regioselectivity. The reaction shows good functional group compatibility for acetals (**59**), esters (**61**), and aryl fluorides (**63**). The authors also demonstrate that stoichiometric BQ can be replaced with catalytic amounts of $Cu(OAc)_2$ and DHQ under 1 atm of O_2. The origin for linear regioselectivity is intriguing as similar ligands have led to branched regioselectivity in other systems (Figure 17).

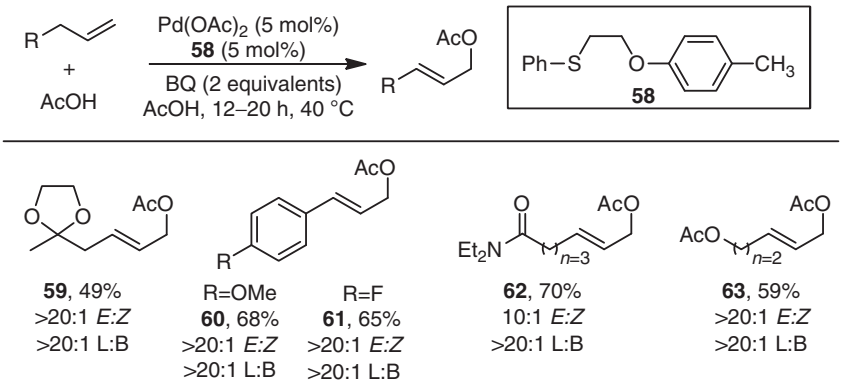


Figure 13 $Pd(OAc)_2$/thioether-catalyzed system for the synthesis of linear of (*E*)-allylic acetates.

Bercaw has found that 2,2′-bipyrimidine can serve as a ligand for allylic oxidation. Although the reaction is only synthetically useful for allyl benzene substrates because of olefin isomerization in the product, the authors provide the first detailed mechanistic study for a reaction that generates linear (*E*)-allylic acetate products from α-olefins (Figure 14).[53] Reductive elimination to Pd-olefin complex **65** is promoted by cationic Pd-allyl species **64**. The authors also show that formation of the allylic acetate is reversible under the reaction conditions and that BQ association to the catalyst promotes dissociation of the allylic acetate product and formation of **66**.

Finally, Stahl has found that a different bidentate amine ligand, 4,5-diazafluorenone (**68**), can promote catalytic, allylic C–H oxidation (Figure 15).[54] Although Bercaw's system required the use of 2 equivalents benzoquinone, Stahl's system allows for oxygen as the sole oxidant. The allylic oxidation conditions provide the desired product in moderate to excellent yield (52–84%) with moderate to high olefin stereoselectivity (6:1 to 36:1) and high regioselectivity (generally >20:1). The reaction appears to provide good functional group tolerance as well for acetals (**59**), amides (**69**), and silyl ethers (**70**). Similar to 2,2′-biyprimidine, Stahl found that 4,5-diazafluorenone promotes reversible reductive elimination in the absence of oxygen or benzoquinone. Although the Bercaw system needed benzoquinone, both oxygen and BQ can bind to the 5-diazaflurorenone-Pd(0)-olefin complex and promote dissociation of the product.

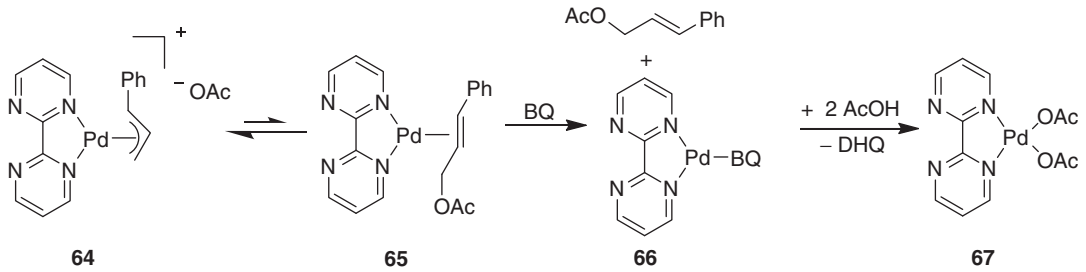


Figure 14 Mechanism of $Pd(OAc)_2$/2,2′bipyridimine catalyzed allylic oxidation.

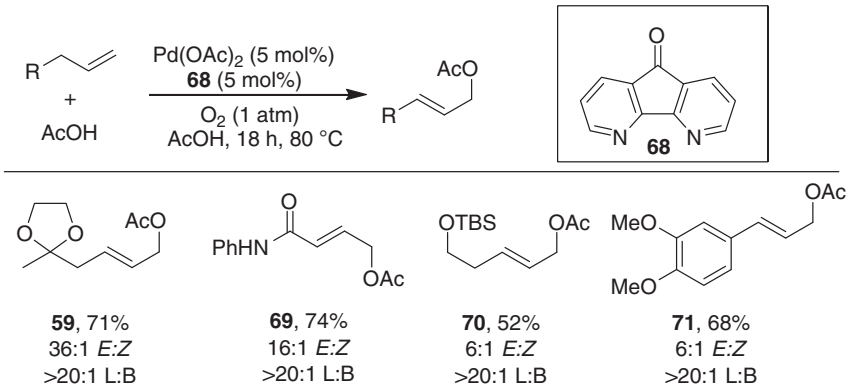


Figure 15 $Pd(OAc)_2$/**68** system for the synthesis of linear (*E*)-allylic acetates.

The linear (*E*)-allylic oxygenates are useful intermediate in organic synthesis. Late-stage oxidation of a complex substrate containing an olefin provides a new approach to the synthesis of linear (*E*)-allylic oxygenates and showcases the reaction's functional group compatibility (Figure 16).[55] This approach has been used to synthesize allylic acetate **74**, an intermediate toward miyakolide C_6–C_{13} fragment **75**. White has also utilized a C–H oxidation approach toward the synthesis of differentially protected L-galactose (**78**) and developed a general route to useful chiral (*E*)-2-buten-1,4-diols such as **77**.[56]

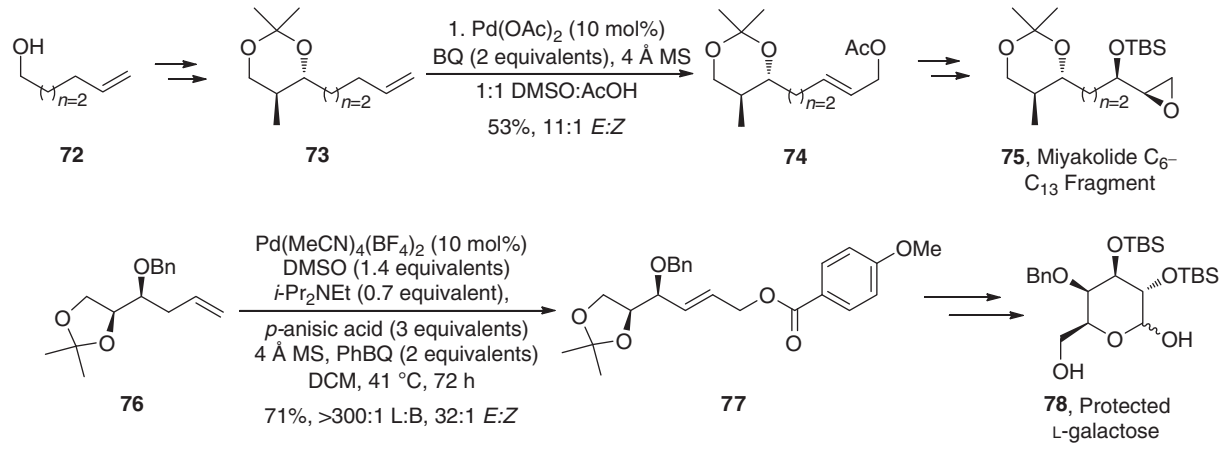


Figure 16 Linear allylic acetoxylation used in complex molecule synthesis.

7.05.1.1.3.4 Palladium-catalyzed oxidation of α-olefins: branched selectivity

While exploring the possible use of sulfoxides other than DMSO as ligands for the Pd(II)-catalyzed allylic C–H acetoxylation, White discovered that $Pd(OAc)_2$/bis-sulfoxide complex **79**/BQ led to the highly regioselective formation of branched allylic carboxylates, which is a complete reversal of the linear selectivity seen in the $Pd(OAc)_2$/DMSO/BQ system (Figure 17).[57] As little

as 1.5 equivalents of the acid are required in the branched system, making this coupling process amenable for alkyl (**80**) and aryl acids (**81–82**). The mild conditions were tolerant of a wide range of functional groups such as silyl ethers and phenols (**81** and **82**). The allylic oxidation is also selective for terminal olefins such as in **84**.

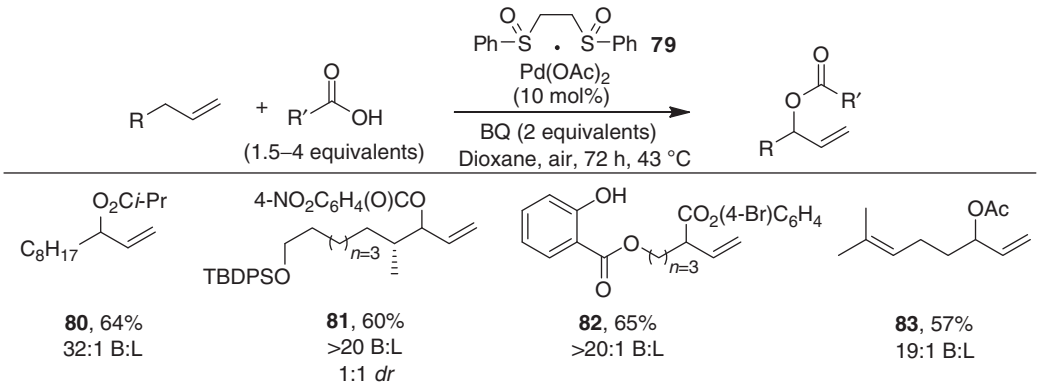


Figure 17 $Pd(OAc)_2$/bis-sulfoxide **79**/BQ system for the synthesis of branched allylic carboxylates.

The unique mechanism for this reaction has been given the name serial ligand catalysis, where the sulfoxide and BQ interact sequentially with the palladium to independently promote separate steps of the catalytic cycle (Figure 18). In the catalytic cycle, **79** promotes allylic C–H cleavage to generate π-allyl intermediate **85**. Ligand exchange between bis-sulfoxide and BQ then occurs. According to the trans effect, **86** forms as the π-acidic BQ should align opposite to the internal carbon of the $\pi-$allylpalladium intermediate as this position can better stabilize a partial positive charge.[44,58] Inner sphere reductive elimination from **86** then regioselectively forms the branched product. Finally, the Pd(0)-BQ undergoes oxidation and ligand exchange to regenerate **79**.

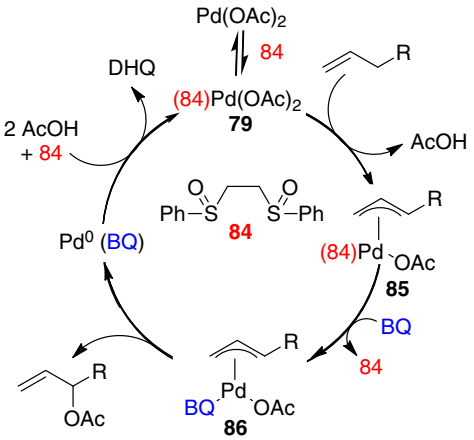


Figure 18 Serial ligand catalysis mechanism for branched allylic C–H oxidation.

White and coworkers have developed a catalytic, enantioselective branched-selective oxidation reaction.[59] They found that the two rapidly interconverting π-allylpalladium species could undergo asymmetric functionalization in the presence of BQ and catalytic Cr(salen)F (Figure 19). The chiral, oxophilic Cr(salen)F is believed to serve as a one point binder of benzoquinone,[60] increasing the π-acidity of the quinone species and accelerating the C–O bond forming step while leading to enantioenriched products. The reaction conditions were found to induce the highest levels of enantioselectivity to date for an allylic C–H oxidation of α-olefins (45–63% *ee*) and were used to generate a variety of stereochemically enriched acetate products. When the asymmetric C–H oxidation method was paired with enzymatic resolution, highly enantiomerically enriched products could be accessed (**88**) (Scheme 1).

The allylic oxidation methodology has been extended toward the synthesis of macrolides. The method affords 14–19 membered macrolactones in 52–63% yield (Figure 20).[61] The reaction is run at 10–20 mM without the need for high dilution techniques or precautions to exclude moisture or air. Macrolactonization occurs with excellent branched regioselectivity and functional group tolerance with a wide variety of aryl, alkyl, and vinylic acids. Notably, the cyclization can be used to construct challenging structural motifs such as (*Z*)-α,β-unsaturated macrolides (**89**)[62] and ortho-substituted salicylic macrolides (**90–91**).[63] Complex, macrocyclic bisindolylmaleimide **92** and cyclic depsipeptide **93** can also be synthesized. Mechanistic studies suggest why high dilutions are not necessary as the product is believed to form from a templated[64] π-allylpalladium complex such as **94** that undergoes BQ-promoted inner sphere functionalization to generate the product.

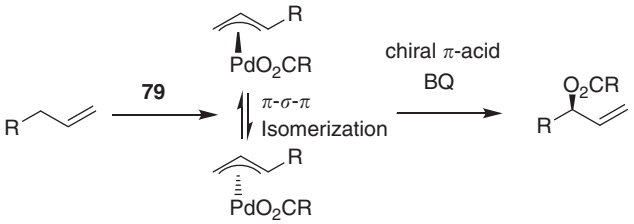
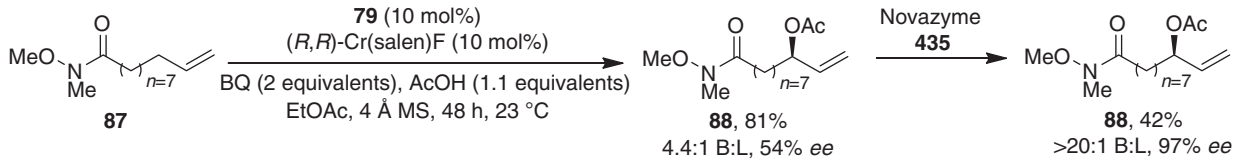


Figure 19 Approach to asymmetric allylic C–H esterification.



Scheme 1 Asymmetric oxidation/resolution to generate enantioenriched branched allylic acetates.

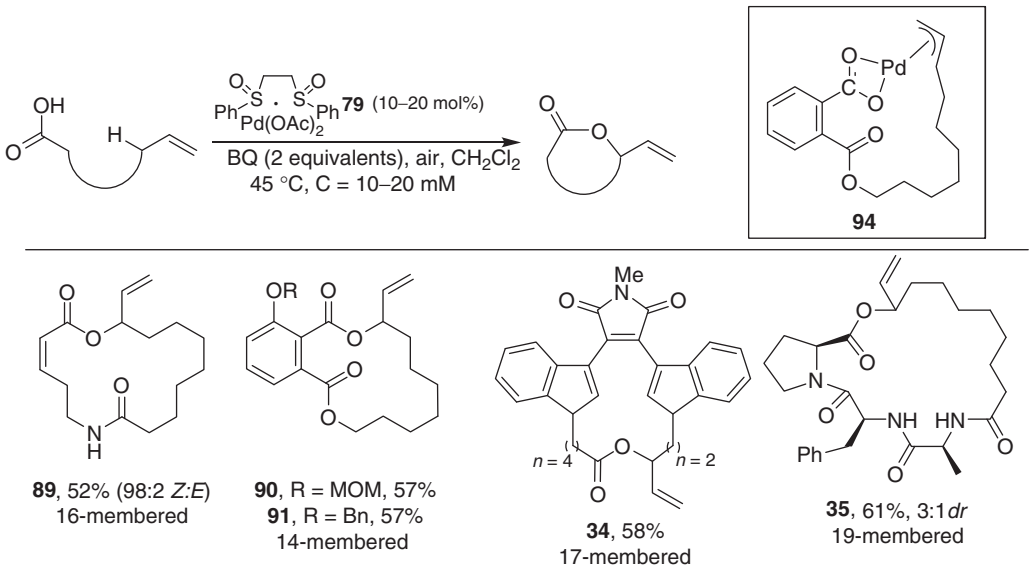
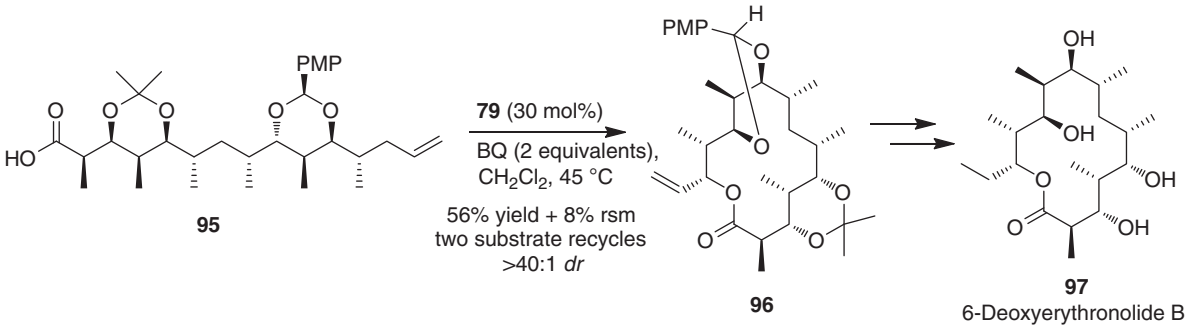


Figure 20 $Pd(OAc)_2$/bis-sulfoxide **79**/BQ-catalyzed system for macrolactonization.

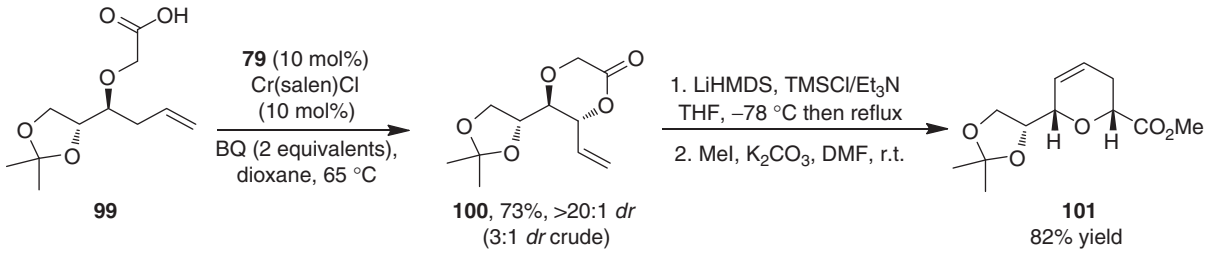
A highly regio-, stereo-, and diastereoselective C–H oxidative macrocyclization reaction to produce macrolactone **96** was the key transformation in the synthesis of 6-deoxyerythronolide B (**97**) (Scheme 2).[65] This is an exceptional example of a highly diastereoselective C–O bond formation for a flexible, acyclic substrate (**95**). The authors postulated that the formation of a chelated π-allylpalladium carboxylate intermediate created a transition structure with product-like transannular character. In cases where the two epimeric products have very different energies, such as the two products here which were calculated to have a 3 kcal mol^{-1} energy difference, high diastereoselectivity can be achieved from a chelated intermediate. Notably, the route enabled by C–H macrolactonization proceeded in 22 steps with 7.8% overall yield, which is the most efficient route to 6-deoxyerythronolide B to date.

Oxidative cyclization of simple alkenoic acids to synthesize 5 and 6-membered lactones has also been demonstrated using Pd/DMSO[66,67] and $Pd(OAc)_2$/bis-sulfoxide **79**.[68] Simple systems have shown very modest diastereoselectivity; however, a recent example has achieved enantioselective oxidation as high as 82% *ee*.[69] The cyclization has shown its greatest utility for more complex substrates. The addition of Cr(salen)Cl to the allylic oxidation conditions promotes the formation of *anti*-1,4-dioxan-2-ones (Scheme 3).[70] As in the enantioselective allylic C–H oxidation, Cr(salen)Cl additive is thought to promote more facile C–O bond formation through formation of an activated quinone moiety. The general reaction conditions are selective for oxidation at only the terminal olefin when other 1,2-disubstituted, tri-, or tetrasubstituted olefins are present. Although the products are still formed in low to moderate (2:1 to 9:1) diastereoselectivity, they can be purified as a single isomer.



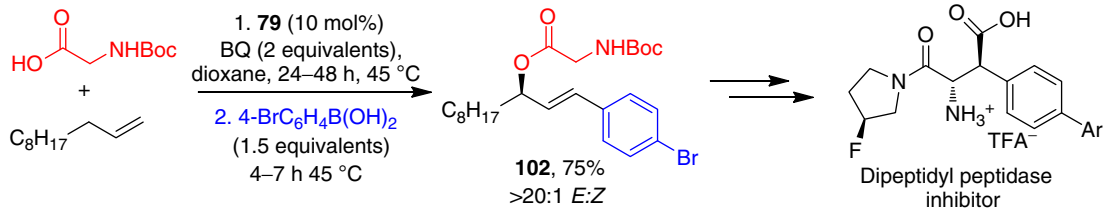
Scheme 2 C–H macrolactonization approach to 6-deoxyerythronolide.

The *anti*-1,4-dioxan-2-one can be further functionalized to prepare *syn*-1,2-diols and *syn*-pyran (**101**) synthetic intermediates for natural product synthesis.



Scheme 3 Intramolecular C–H esterification to *anti*-1,4-dioxan-2-ones.

Finally, White has been able to demonstrate a three component, one-pot coupling reaction with an $\alpha-$olefin, a carboxylic acid, and a boronic acid reagent to generate (*E*)-aryl allylic esters (Scheme 4).[71] The highly electrophilic catalyst is able to promote allylic C–H oxidation followed by Heck arylation (boronic acid transmetallation then migratory insertion/β-hydride elimination). The (*E*)-aryl allylic ester products are isolated in good yield (52–77%) as single regio- and olefin isomers. The methodology has been used to rapidly transform 1-undecene to **102**, an intermediate toward the synthesis of a dipeptidyl peptidase inhibitor.[72]



Scheme 4 Three component coupling to (*E*)-aryl allylic esters.

7.05.1.1.3.5 Palladium-catalyzed approaches via Pd(II)/Pd(IV)

Allylic acetoxylation reactions using benzoquinone, manganese dioxide, copper salts, or air as the terminal oxidant are believed to occur through a Pd(0)/Pd(II) cycle. Szabó[73] and Stambuli[74] have recently disclosed catalytic, allylic C–H oxidation conditions using stronger oxidants that are believed to occur through a Pd(II)/Pd(IV) cycle.[75] Activators such as BQ are not needed to promote functionalization because of the high reactivity of the π-allylpalladium(IV) complex. The timing of the oxidation to Pd(IV) in the catalytic cycle may be dependent on substrate, catalyst, and oxidant (Figure 21).

Cyclohexene derivatives and β,γ-unsaturated ester, ketone, nitrile, and sulfone derivatives undergo C–H oxidation in the presence of iodonium salts as oxidants. $Pd(OAc)_2$ or Pd pincer complex **103** can be used to catalyze the transformation (Figure 22). The choice of iodonium salt [$PhI(OAc)_2$ or $PhI(OBz)_2$] can lead to either acetylated (**104–106**) or benzoylated products (**107–108**). Similarly, Szabó has also demonstrated that a different oxidant, sodium perborate, in the presence of acetic or pivalic anhydride can perform allylic oxidation on β,γ-unsaturated compounds.[76]

Allylic trifluoromethylation using $PhI(TFA)_2$ can occur at temperatures as low 0 °C for cyclohexene derivatives, which allows for regio- and diastereoselective functionalization (equation 13). The authors propose that the Pd(II) species is first oxidized to a Pd(IV) intermediate, which then undergoes allylic C–H cleavage at the axial proton to generate **109**. Inner-sphere reductive elimination from π-allylpalladium(IV) intermediate forms the carbon-carboxylate bond *trans*- to the ester moiety.

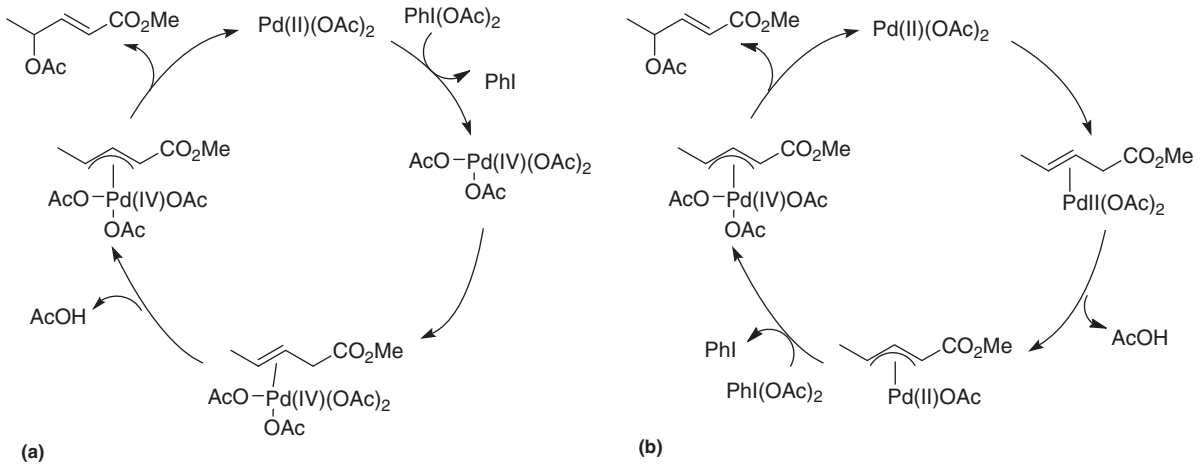


Figure 21 Allylic oxidation by Pd(II)/Pd(IV). (a) allylic cleavage by Pd(IV). (b) Allylic cleavage by Pd(II).

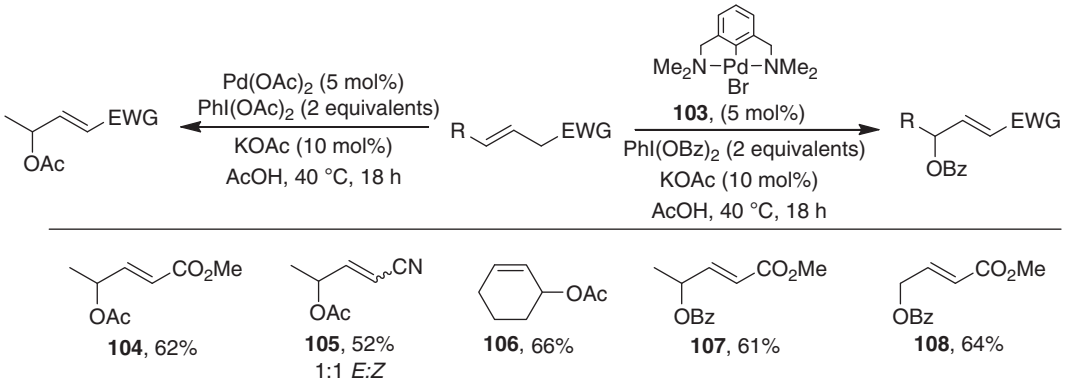
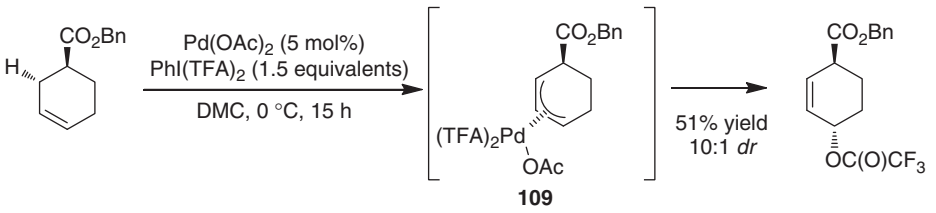


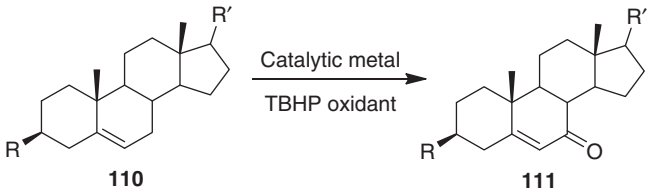
Figure 22 Allylic acetoxylation or benzoylation with Pd(II)/iodonium salts.



(13)

7.05.1.2 Allylic Oxidation Reactions Which Produce α,β-Unsaturated Carbonyl Compounds

Stoichiometric chromium (VI) reagents have classically been used to promote enone formation from olefins and have previously been reviewed.[1,77] Although chromium-promoted allylic oxidation is an important reaction and has been widely used, alternatives have been sought to avoid the use of toxic, stoichiometric metal. Recent efforts have focused on the use of metal-catalyzed conditions using TBHP as oxidant. Δ^5-steroids (**110**) are arguably the most studied set of substrates for enone oxidation as the Δ^5-en-7-one products (**111**) are interesting chemotherapeutic agents and have been shown to inhibit sterol biosynthesis (equation 14).[78] A wide array of metal-catalyzed conditions using TBHP have been demonstrated for the above-mentioned transformation (CrO_3,[79] $RuCl_3$,[80] Bi salts,[81] Cu salts,[82] Co species,[83] $Mn(OAc)_3$,[84] dirhodium caprolactamate,[85] Cu(II)-2-quinoxalinol salen[86]). In addition, there are some metal-free examples (sodium chlorite,[87] phenyliodiodiacetate[88]). This review will focus on allylic oxidation methods that have proven general across a wider set of substrates than the Δ^5-steroids (i.e., Perlman's catalyst,[89] dirhodium caprolactamate,[90] manganese triacetate,[84] and copper(II)-2-quinoxalinol salen).[91]



110 111 (14)

The general mechanism for the metal-catalyzed allylic oxidation methods is shown in Figure 23.[92,93] The metal-catalyzes *tert*-butylperoxy radical formation, and the *tert*-butylperoxy radical promotes selective allylic C–H abstraction. Allylic radical **112** can then combine with a second *tert*-butylperoxy radical to form *tert*-butylperoxy ether **113** or with dioxygen to form allylic hydroperoxide radical **114**. Both species can undergo further reaction to form the desired α,β-unsaturated enone (**115**), though in some cases **113** or **116** are isolated. *tert*-Butylperoxy ether **113** can decompose to α,β-unsaturated enone under basic[94] or radical disproportionation conditions.[93,95] The exact mechanism of enone formation from allylic hydroperoxide **114** is not as well understood. In addition, there is debate on whether a free or metal-bound *tert*-butylperoxy radical species promotes the C–H abstraction and/or radical recombination steps and this may be metal dependent.

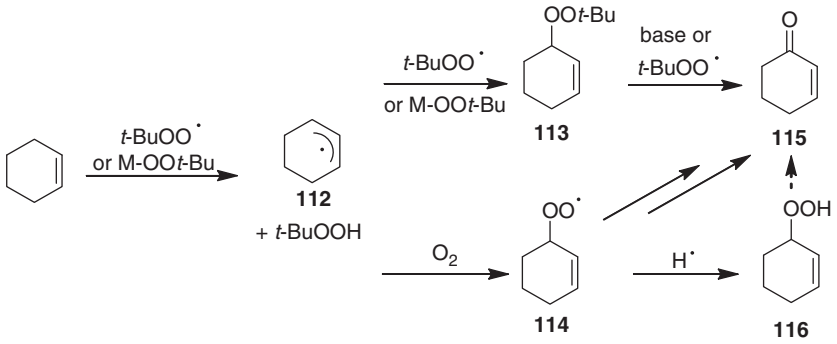
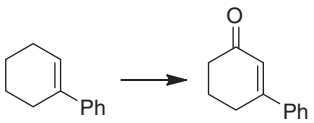


Figure 23 Mechanism of metal/*tert*-butyl hydrogen peroxide-(TBHP) catalyzed allylic oxidation.

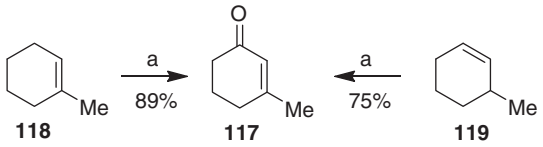
The oxidation of 1-phenylhexene is a benchmark reaction between each system (Table 1). Corey was the first to demonstrate palladium-catalyzed allylic oxidation to α,β-enones, first using Pd/C (Table 1, Entry 1) then $Pd(OH)_2/C$ (Perlman's catalyst).[92] Shortly thereafter, other researchers demonstrated oxidation using rhodium, manganese, or copper-based systems (Entries 2–4). Although the yields are fairly similar for all 4 systems (70–88%), the reaction times are significantly shorter for the rhodium and copper-catalyzed systems (Entries 2 and 4), and the copper-catalyzed system requires the least amount of oxidant (Entry 4).

Table 1 Allylic oxidation of 1-phenylcyclohexene



Entry	*Catalyst*	*Conditions*	*Time (h)*	*Yield (%)*	*References*
1	10 wt.% Pd/C (2.5 mol%)	K_2CO_3 (0.25 equivalent), *tert*-butyl hydrogen peroxide (TBHP) (5 equivalents), dichloromethane (DCM)	12	75	92
2	$Rh_2(cap)_4$ (0.1 mol%)	K_2CO_3 (0.5 equivalent), TBHP (10 equivalents), 1,2-dichloroethene (DCE)	1	77	90
3	$Mn(OAc)_3$ (10 mol%)	3 Å MS, TBHP (4 equivalents), EtOAc, r.t.	48	70	84
4	Cu(2-quinoxaliniol) Salen (2.5 mol%)	TBHP (3 equivalents), CH_3CN, 70 °C	1	88	91

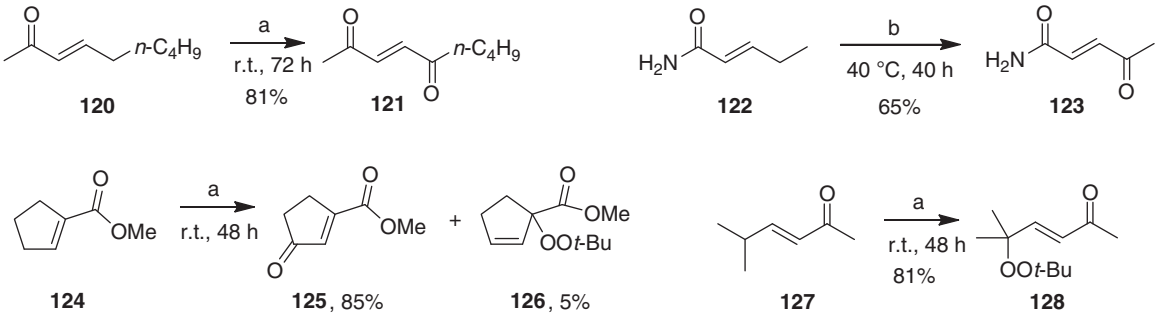
For simple substrates the allylic C–H abstraction exhibits high regioselectivity for the allylic C–H bond with the lowest bond dissociation energy ($3^\circ > 2^\circ > 1^\circ$).[96] The regioselectivity for C–O bond formation favors the formation of the more thermodynamically stable olefin product. The high level of selectivity is highlighted by the fact that both 1-methyl cyclohexene (**118**) and 3-methyl cyclohexene (**119**) provide the same product (**117**) (Scheme 5).[90]



a. $Rh_2(cap)_4$ (0.1 mol%), K_2CO_3 (0.5 equivalent), TBHP (10 equivalents) DCE, 0.3–1 h

Scheme 5 Selectivity for metal/TBHP-catalyzed oxidation.

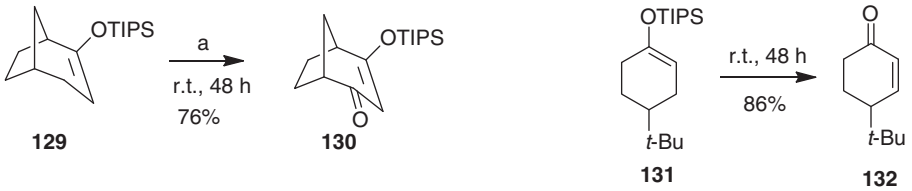
The oxidation of α,β-enones to 1,4-enediones has also been demonstrated (**Figure 24**).[89,93] Acyclic substrates can be oxidized under palladium and rhodium-catalyzed conditions (**120** and **122**). A notable example is the synthesis of **121**, a natural product found in the fire bee *Trigona tataira*.[97] For cyclic substrates small amounts of *tert*-butylperoxy ethers can sometimes be observed (**126**). In some cases *tert*-butylperoxy ethers can even be isolated in high yield when there is only one γ-hydrogen (**128**).[89]



a. $Pd(OH)_2/C$ (5 mol%), TBHP (5 equivalents), K_2CO_3 (0.5 equivalent), CH_2Cl_2
b. $Rh_2(cap)_4$ (1 mol%), T-HYDRO (8 equivalents), DCE

Figure 24 Oxidation of α,β-unsaturated carbonyl compounds.

Finally, Corey has shown that silyl enol ethers can undergo oxidation to form β-keto silyl enol ethers (**Figure 25**).[98] The use of cesium carbonate under oxygen-free conditions promotes the formation of *tert*-butylperoxy ether decomposition to the β-keto silyl enol ether (**130**). Similar reactions using the weaker base sodium hydrogen phosphate under molecular oxygen give the α,β-enone product (**132**).



a. $Pd(OH)_2/C$ (5 mol%), TBHP (5 equivalents), Cs_2CO_2 (1 equivalent), CH_2Cl_2
b. $Pd(OH)_2/C$ (5 mol%), TBHP (5 equivalents), Na_2HPO_4 (1 equivalent), CH_2Cl_2, air

Figure 25 Oxidation of silyl enol ethers.

The metal-catalyzed enone oxidation has been quickly adopted for use in the late stages of total synthesis because of its selectivity and functional group tolerance (**Figure 26**). Even ethereal functionality has been tolerated under the radical-based conditions in the synthesis of **134**, an intermediate used to construct (–)-samaderine Y.[99] The scope of the oxidation reaction has also been extended through complex molecule synthesis. For example, the manganese-catalyzed conditions have been used to synthesize complex α,β-unsaturated amide **136** toward the synthesis of the tetrapetalone A core.[100] Vinyl ethers can also undergo selective oxidation under the conditions developed for silyl enol ethers, as demonstrated in the synthesis of **138**, an intermediate in the synthesis of Nemorosone.[101]

Alternative oxidation methods have recently been developed that rely on hypervalent iodine ($PhI(OAc)_2$[88] or $PhI(TFA)_2$[102]) to mildly generate the active *tert*-butyl hydroperoxide radical[103] and promote allylic oxidation. The conditions using $PhI(OAc)_2$ have been applied to the oxidation of Δ^5-steroids and terpenes (equation 15).

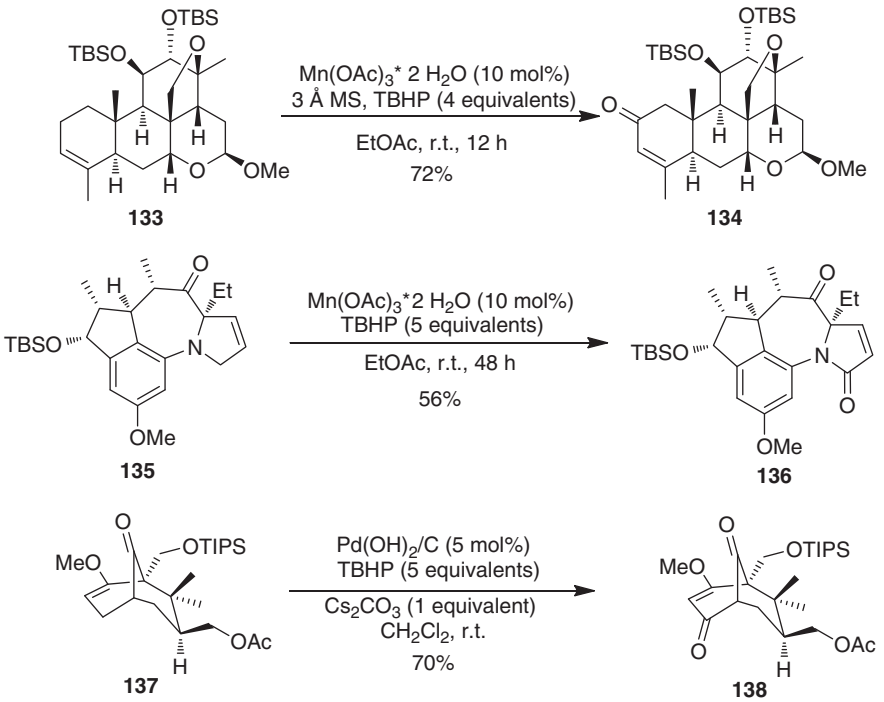
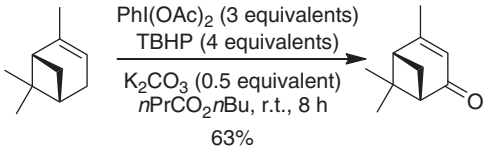
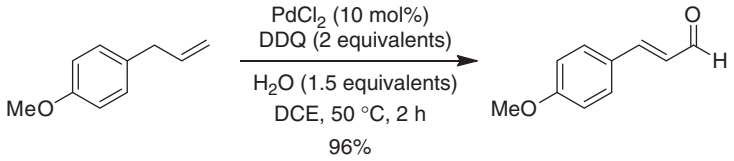


Figure 26 Metal/TBHP-catalyzed allylic oxidation in synthesis.



(15)

Recently palladium[104] and iron[105]-catalyzed oxidation methods have been reported that do not rely on TBHP. The methods promote oxidation of allyl arenes to alkenyl aldehydes (equation 16). The mechanism is believed to occur via a metal-allyl intermediate which undergoes attack by water to reversibly generate branched and linear allylic alcohols. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) then selectively promotes oxidation of the linear allylic alcohol to the alkenyl aldehyde. Note that the iron-catalyzed conditions were shown to promote lower levels of stereoselectivity for olefin geometry (as low as 3:1 *E:Z* in some cases).



(16)

7.05.1.3 Allylic Oxidation Reactions Which Produce Allylic Amines

7.05.1.3.1 Ene-type approaches

There are numerous examples of allylic amination using S/Se-imido reagents analogous to allylic oxidation using selenium dioxide. The reaction proceeds through an initial thermal ene reaction immediately followed by [2,3]-sigmatropic rearrangement (Figure 27). These methods, pioneered by Sharpless,[106] Kresze,[107] and Katz,[108] have been extensively reviewed.[109]

Recently, Tambar has disclosed a novel two-step, enantioselective variant of this reaction (Figure 28).[110] He found that reacting benzenesulfonyl sulfurdiimide with a terminal olefin can generate stable ene adduct **139** at 4 °C, which can be purified by simple filtration. This intermediate then undergoes enantioselective, palladium-catalyzed [2,3]-rearrangement. The branched allylic amine products were formed with >90% *ee* and in good to excellent yield (61–93%). Common functional groups such as phthalimides (**142**), aldehydes (**143**), nitriles (**144**), and alkyl chlorides (**145**) were all tolerated. Two limitations for the method are use of excess olefin (3–5 equivalents) and very slow [2,3]-rearrangement (2–7 days). The authors demonstrate the utility of the method by synthesizing the antiepileptic drug Vigabatrin **148** in just 3 steps (Scheme 6). The nitrogen–sulfur bond is easily cleaved under basic conditions and the *N*-benzenesulfonyl group of **147** is removed under mildly reductive conditions.

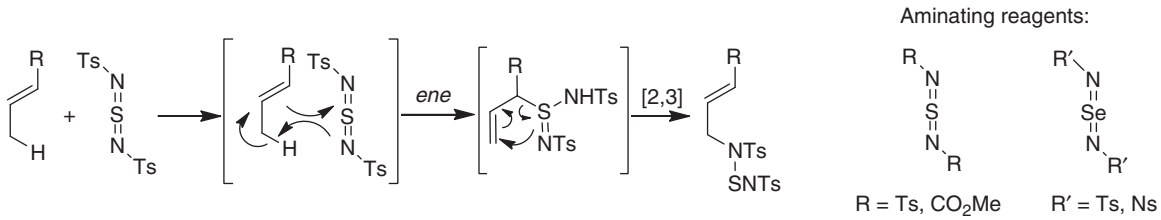


Figure 27 Allylic amination from S/Se-imido reagents.

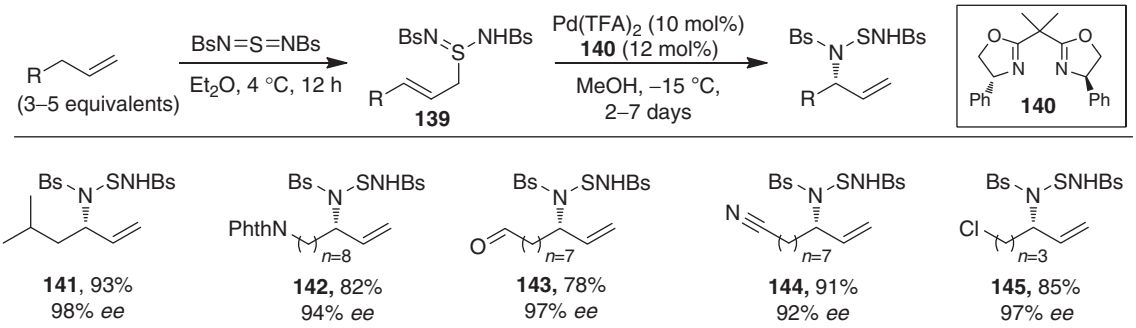
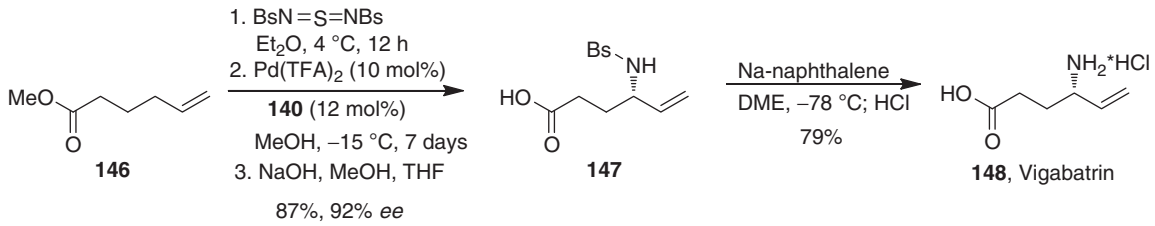


Figure 28 Two-step, enantioselective allylic amination.



Scheme 6 Synthesis of Vigabatrin using enantioselective allylic amination.

Alternatively, ene-type chemistry with aza (X═NR) and nitroso (X═O) compounds has been developed which is an allylic amination method with olefin transposition (Figure 29(a)). Although the majority of these methods have been reviewed through 2003,[109,111] this review will focus on recent examples utilizing aryl and acyl nitroso species.

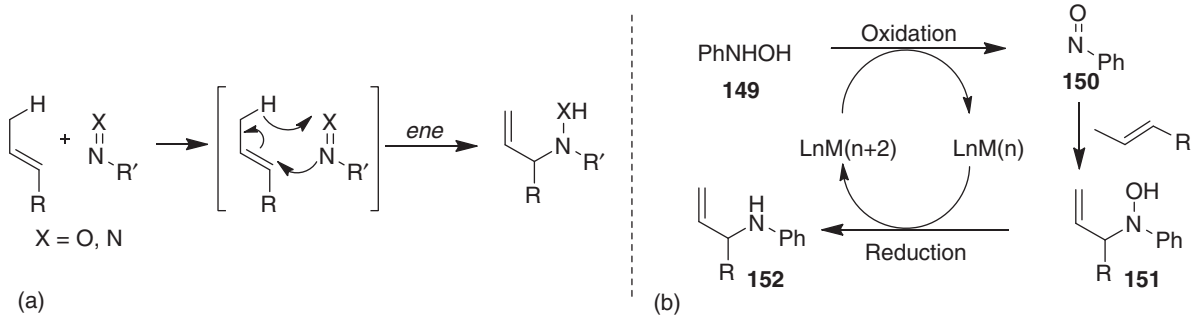
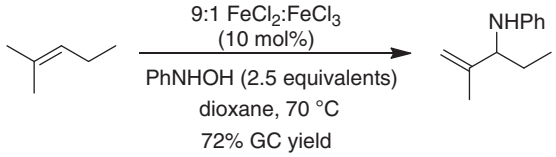


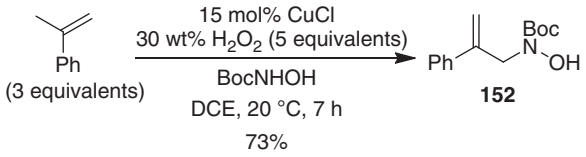
Figure 29 (a) Allylic amination using aza and nitroso compounds. (b) Metal-catalyzed allylic amination with hydroxylamine.

Building upon stoichiometric work by Sharpless,[112] Nicholas followed by Jørgensen and Lau developed metal-catalyzed allylic amination conditions starting from aryl hydroxylamine rather than nitrosobenzene. The proposed mechanism of allylic amination using aryl hydroxylamine is shown (Figure 29(b)). In some cases the metal serves solely as a redox shuttle to generate nitrosobenzene **150** from hydroxylamine **149** and reduce the allylic hydroxylamine product **151** to allylic amine **152** (Mo dioxo[113] or Fe-phthalocyanine[114]). Alternatively, some metals perform the redox shuttle and are also thought to bind both the olefin and nitrosobenzene to promote C–N bond formation ($FeCl_2/FeCl_3$,[115] $Cu[(CH_3CN)_4]PF_6$,[116] and $CuCl/CuCl_2$[117]).

Consistent with an ene-type mechanism, more substituted olefins are the best substrates and the C–H bond breakage is regioselective for the least hindered C–H bond (equation 17). The main drawbacks of the aryl hydroxylamine amination are the widely varying yields and use of large excess of the olefin (many times >5 equivalents). Nicholas has also demonstrated a CuCl-catalyzed intermolecular allylic amination using Boc-protected hydroxylamine (equation 18).[118] The reaction requires hydrogen peroxide as a stoichiometric oxidant for the metal as the Boc-protected hydroxylamine product **152** remains intact. The reaction conditions show similar limitations to the aryl hydroxylamine amination method.



(17)



(18)

Building upon the intermolecular example by Nicholas and a very early example by Kirby,[119] there are several synthetically useful acylnitroso ene reactions that have recently been developed. Read de Alaniz[120] and Malkov[121] independently demonstrated metal-catalyzed intramolecular acylnitroso ene cyclization beginning with hydroxamic acids (**153**) as stable precursors (Figure 30). The products formed are *N*-hydroxy analogs of oxazolidinones and oxazinanones. A key for both researchers was to find a mild oxidant that would avoid decomposition of the intermediate nitroso species (**154**) and hydroxylamine product (**155**). Read de Alaniz developed a system using 5 mol% CuCl catalyst, 1.25 mol% pyridine additive, and air as the terminal oxidant. Malkvov used 4 mol% $FeCl_3$ and 1.2–3.0 equivalents hydrogen peroxide in IPA.

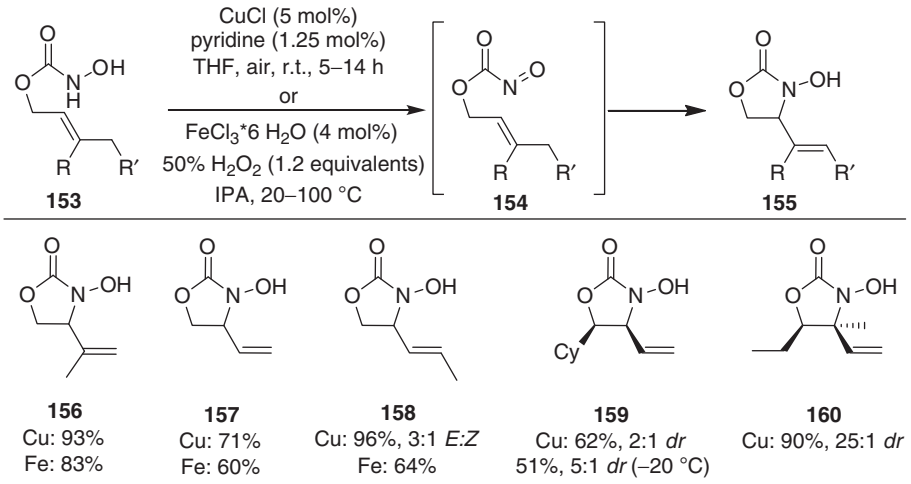
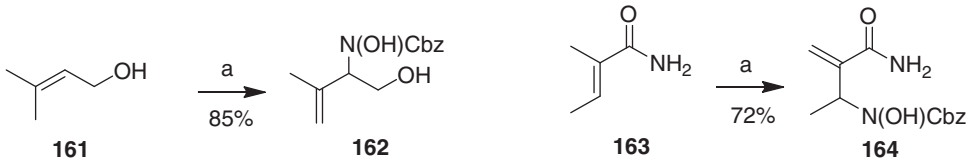


Figure 30 Metal-catalyzed hydroxamic acid cyclization.

The scope of cyclization for *N*-hydroxyoxazolidinones appears to be fairly broad. As is the case with the intermolecular ene reactions, trisubstituted olefins (**156**) are excellent substrates and provide better yields than the analogous 1,2-(*E*)-disubstituted olefins (**158**). Note that the copper system shows modest 3:1 stereoselectivity for a 1,2-(*E*)-disubstituted olefin product, whereas the iron-catalyzed system did not comment on the olefin geometry. Both systems do not work with 1,2-(*Z*)-disubstituted olefins. Aside from simple cyclizations, Malkov demonstrated more complex examples. The 5-membered cyclization has very modest 2:1 diastereoselectivity favoring the 1,2-*syn*-diastereomer, even when the steric bulk of the substituent is varied from a simple methyl group to a cyclohexane group (**159**). Lowering the temperature to −20 °C did result in 51% product yield with 5:1 *syn*-diastereoselectivity. The stereoselectivity was significantly higher (25:1) when a more complex tertiary C–N bond was formed (**160**).

The extremely mild Cu-catalyzed conditions have allowed for the development of an intermolecular amination method using Cbz-protected hydroxylamine (Figure 31). Importantly, the method uses just 1.2 equivalents of olefin and demonstrates good regioselectivity and functional group tolerance. One limitation of the method is that 1,2-(*E*)-disubstituted and α-olefins generate

products with modest 3:1 olefin stereoselectivity. Tri- and tetra-substituted olefins are the best substrates for the transformation, as in the allylic oxidation of allylic alcohol **161**. Tiglic amide **163** also shows efficient C–H oxidation.



a. CuCl (5 mol%), pyridine (1.25 mol%), Cbz-NHOH (1 equivalent), THF, air, r.t., 8–48 h

Figure 31 Metal-catalyzed intermolecular amination using Cbz-protected hydroxylamine.

There has been much less progress for the development of synthetically useful aza-ene aminations. Jørgensen has demonstrated the first example of Lewis-acid catalyzed amination[122] using bis(2,2,2-trichloroethyl)azodicarboxylate (BTCEAD, **166**) as the nitrogen source (Figure 32).[123] The chemistry works for trisubstituted (**165**) and α-olefins (**169**), although 2 equivalents of olefin are required. The hydrazine product can be cleaved to the deprotected amine using zinc powder.

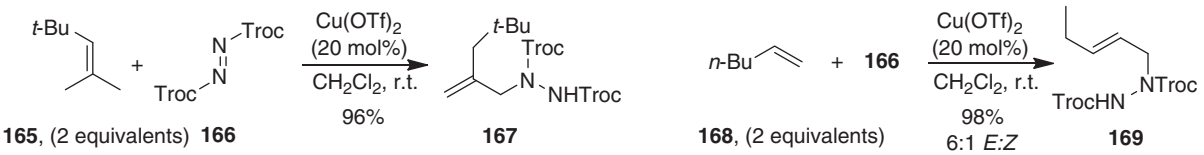


Figure 32 Copper-catalyzed allylic amination using BTCEAD (**166**).

7.05.1.3.2 Palladium-catalyzed amination

Palladium has typically been shown to promote addition of amine nucleophiles to olefins (aminopalladation) (Figure 33). This type of reactivity has formed the basis of many useful transformations such as oxidative amination (aminopalladation followed by β-hydride elimination), aminoacetoxylation, aminohalogenation, and diamination.[124] Although oxidative amination can form allylic amine products,[125] this particular topic will be reviewed in a different Chapter 4.10. Until recently, palladium-promoted allylic C–H amination has been challenging to achieve as aminopalladation has been the predominant pathway (Figure 33). Two-step, stoichiometric systems have avoided aminopalladation by performing C–H cleavage in the absence of a nitrogen nucleophile (Figure 5).[126]

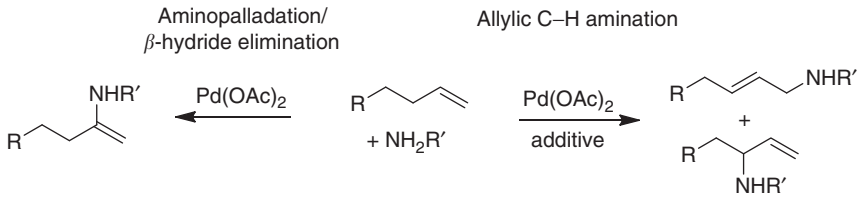
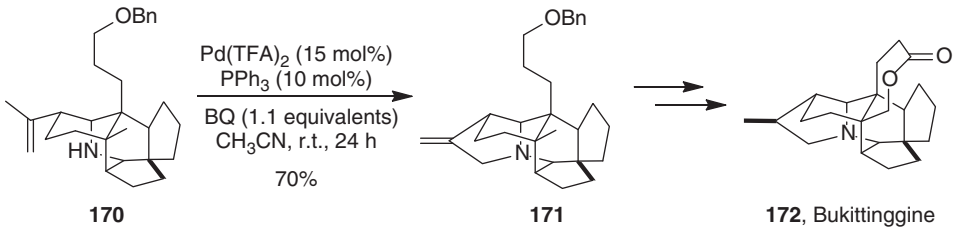


Figure 33 Oxidation of olefins by aminopalladation versus allylic C–H amination.

In the 1990s and early 2000s, several isolated examples of intramolecular catalytic, allylic C–H amination were identified. Heathcock used a $Pd(TFA)_2/PPh_3$/BQ catalyzed cyclization to form exocyclic olefin **171**, an intermediate toward the synthesis of Bukittinggine **172** (Scheme 7).[127] He reasoned that the mechanism involved a π-allyl intermediate and that the sterically hindered secondary aliphatic amine could not bind to palladium and inhibit allylic C–H cleavage. Larock[128] and Broggini[129] independently demonstrated cyclizations of weakly basic aryl tosylamides to form 5- and 6-membered rings using catalytic $Pd(OAc)_2$ in DMSO solvent.

In 2007 the first general example of catalytic, intramolecular allylic C–H amination was discovered. Building upon the previous $Pd(OAc)_2$/bis-sulfoxide **79**-catalyzed allylic acetoxylation, White developed a diastereoselective, catalytic allylic C–H amination of homoallylic *N*-tosyl carbamates to synthesize vinyl *anti*-oxazolidinones (Figure 35).[130] The proposed catalytic cycle is shown in Figure 34. Importantly, the weakly basic *N*-tosyl carbamate nucleophile does not interfere with the electrophilic C–H cleavage step to form **173**. In addition, the nucleophile was acidic enough to be deprotonated by the acetate counter ion of $Pd(OAc)_2$ to promote intramolecular C–N bond formation (**174**). The acetate counter ion/base is catalytically regenerated upon palladium reoxidation with phenylbenzoquinone.



Scheme 7 Allylic C–H amination toward the synthesis of Bukittinggine.

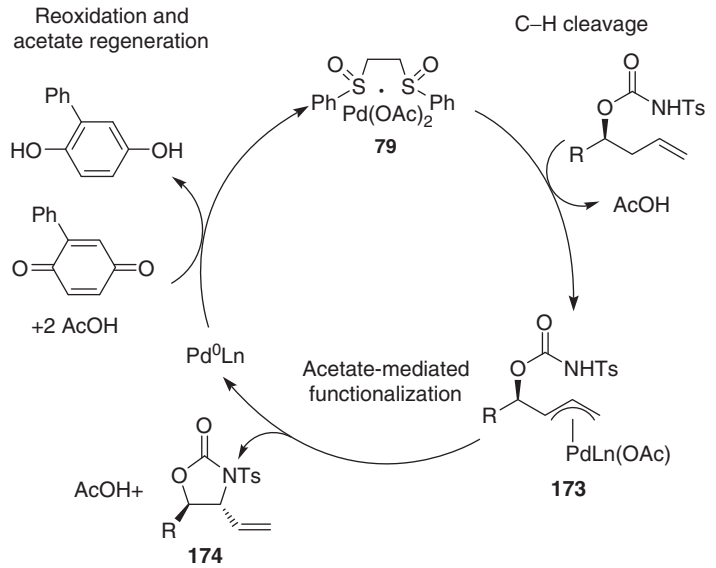


Figure 34 Proposed mechanism for Pd/sulfoxide-catalyzed allylic amination.

As is the case with the allylic acetoxylation, the intramolecular allylic amination reaction exhibits good scope and functional group tolerance (Figure 35). For substrates bearing one stereogenic center, good yields and diastereoselectivities are achieved when there is one branching element adjacent to the *N*-tosyl carbamate (**175**), whereas unbranched substrates provide good yields but low levels of diastereoselectivity (**176**). The reaction reliably generates the *anti*-oxazolidinone products when there are multiple stereogenic centers (**177–179**). Note that diastereomerically pure products can be obtained after standard column chromatography.

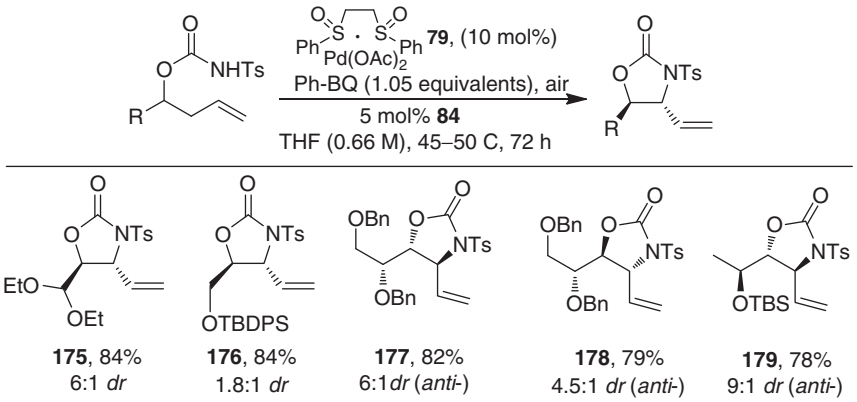


Figure 35 $Pd(OAc)_2$/bis-sulfoxide **79**/PhBQ-catalyzed intramolecular allylic amination.

The five-membered cyclization was extended to the synthesis of 6-membered oxazinanones (Figure 36).[131] The reaction requires the use of *N*-nosyl carbamate nucleophiles, presumably to generate a higher concentration of deprotonated nucleophile. The *N*-nosyl oxazinanones are formed in moderate to good yield (58–83%) and generally with moderate *syn*-diastereoselectivity

(most examples are 4:1 to 6:1 *dr*). This Pd-catalyzed method demonstrates orthogonal reactivity to nitrene-based aminations as allylic C–H amination occurs over benzylic (**180**) and ethereal C–H amination (**181–182**). The cyclization provides predictable stereocontrol for the *syn*-1,3-product when the substrate contains multiple stereogenic centers (**181–182**). *N*-Nosyl carbamates can also be used in the cyclization to oxazolidinones (**184**) and require one-third of the reaction time compared to *N*-tosyl carbamates (**183**).

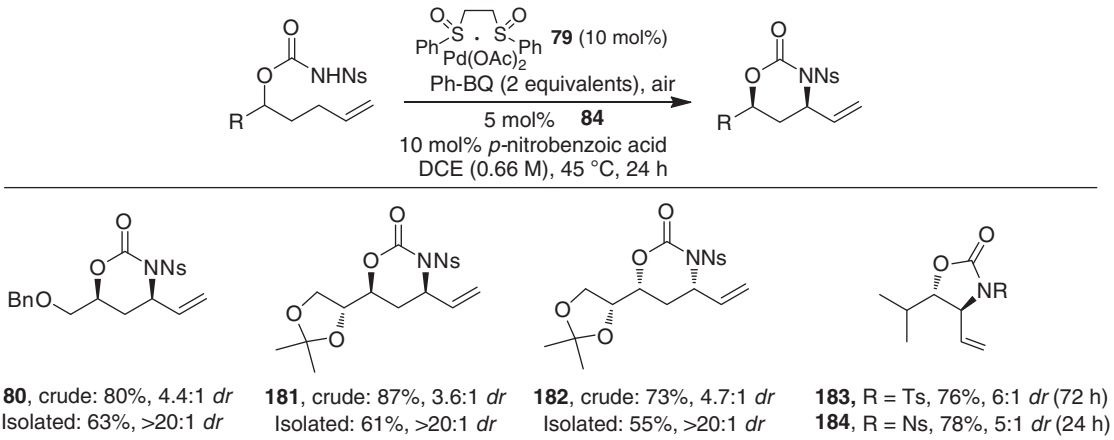
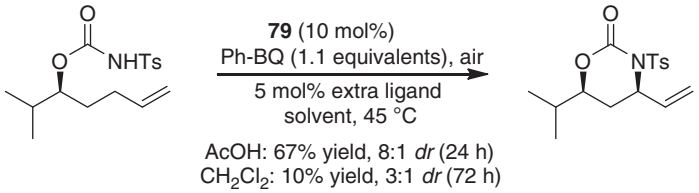


Figure 36 $Pd(OAc)_2$/bis-sulfoxide **79**/PhBQ-catalyzed intramolecular allylic amination for *syn* oxazinanones.

Alternatively, Poli has found that intramolecular C–H amination of *N*-tosylcarbamates can be accelerated using AcOH as the solvent system when compared to CH_2Cl_2 (equation 19).[132] The method has been demonstrated for formation of both 5- and 6-membered rings and provides the products in modest to good diastereoselectivity (1.5:1 to 9:1) and moderate yield (typically 54–69%). The authors note that AcOH could be accelerating multiple steps within the catalytic cycle (i.e., BQ-promoted Pd(0) reoxidation or reductive elimination from a cationic π-allylpalladium intermediate).[133]



(19)

White was also able to develop intermolecular C–H amination to furnish linear (*E*)-allylic amines (**Figure 37**).[134] The intramolecular amination conditions were not effective at activating the π-allylpalladium for intermolecular C–N bond formation. Two different additives were found to address this issue and render a catalytic, intermolecular amination: (1) Cr(III)salenCl and (2) catalytic Brønsted base (iPr_2NEt). Cr(III)salenCl interacts with BQ and accelerates C–N bond formation, and this additive has also been shown to accelerate intramolecular C–H amination.[135] Catalytic iPr_2NEt is thought to increase the concentration of deprotonated nucleophile.

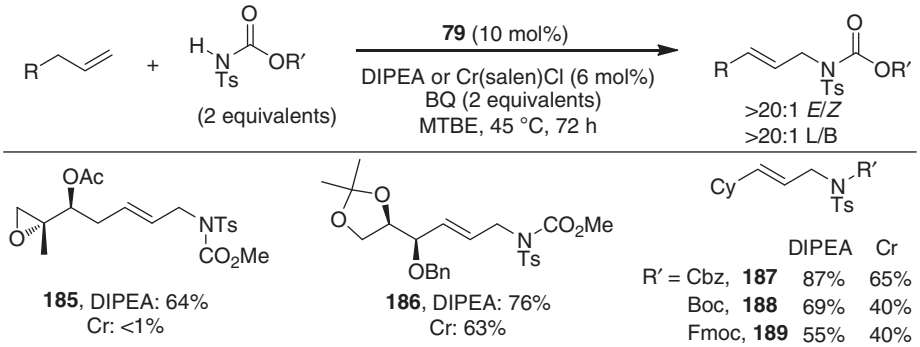


Figure 37 $Pd(OAc)_2$/bis-sulfoxide **79**/BQ intermolecular C–H amination.

Both the catalytic Cr and catalytic base systems exhibit excellent selectivity (>20:1 L:B; >13:1 *E*:*Z*) for the linear allylic amine product. Typically the catalytic base conditions provide higher yields than the originally developed catalytic chromium conditions, especially for substrates containing terminal epoxides (**185**). Highly sensitive, densely functionalized products can be rapidly constructed from readily available olefin building blocks (**186**). Nucleophiles protected with Cbz, Boc, and Fmoc were all suitable for the amination conditions optimized for the methyl carbamate nucleophile (**187–189**).

In 2008, Liu and coworkers developed a $Pd(OAc)_2$/DMAc/O_2/MA (maleic anhydride)-catalyzed system for the intermolecular formation of linear allylic amines.[136] Although the reaction represented an early example of intermolecular allylic C–H amination, it required the use of 3 equivalents of olefin and the product included variable amounts of nonallylic olefin isomers (53–87% overall yield). Liu has since disclosed new conditions that lower catalyst loading, minimize olefin isomers, and use the α-olefin as the limiting reagent (**Figure 38**).[137] The authors found that the combination of Bu_4NOAc base and $PhI(OPiv)_2$ oxidant promoted efficient conversion, while eliminating starting material isomerization and minimizing product isomerization. Under the new reaction conditions 20 mol% naphthoquinone (NQ) additive proved to be the best π-acid, however the yield was only 15% lower in the absence of any π-acid. The reaction is completed in only 5–8 h versus the 48 h or more that other intermolecular amination systems require and uses just 5 mol% catalyst. The reaction conditions generate the linear amine in moderate to excellent yield (60–95%) and with no reported branched or *Z* isomers. The nucleophile can be varied at both the nitrogen and ester positions (**190–192**) and the reaction shows good functional group tolerance for molecules containing imides (**193**), and aryl iodides (**194**).

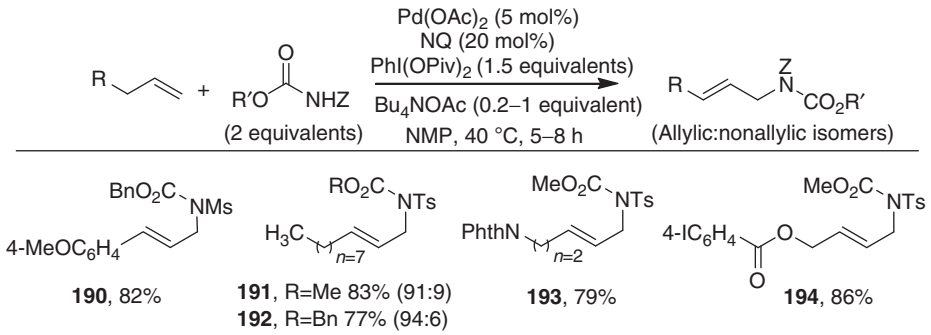


Figure 38 $Pd(OAc)_2$/NQ/$PhI(OPiv)_2$ systems for intermolecular linear C–H amination.

The authors performed detailed mechanistic studies of both sets of reaction conditions (with and without NQ). In the absence of NQ, the turnover-limiting step is olefin coordination to Pd(II) (**Figure 39(a)**). They hypothesize that reductive elimination in the absence of NQ likely proceeds through a Pd(IV) intermediate (**195**). The presence of NQ promotes fast and reversible coordination between the olefin and palladium (**Figure 39(b)**). The authors propose that the π-acidic nature of NQ increases the electron deficiency of the palladium which facilitates α-olefin coordination. Under this reaction manifold the allylic C–H cleavage or C–N functionalization is rate-limiting, depending on the exact nucleophile type and concentration. The role of $PhI(OPiv)_2$ is less clear when π-acidic NQ is present as the functionalization could proceed through a Pd(IV) (**195**) or Pd(II) intermediate (**196**).

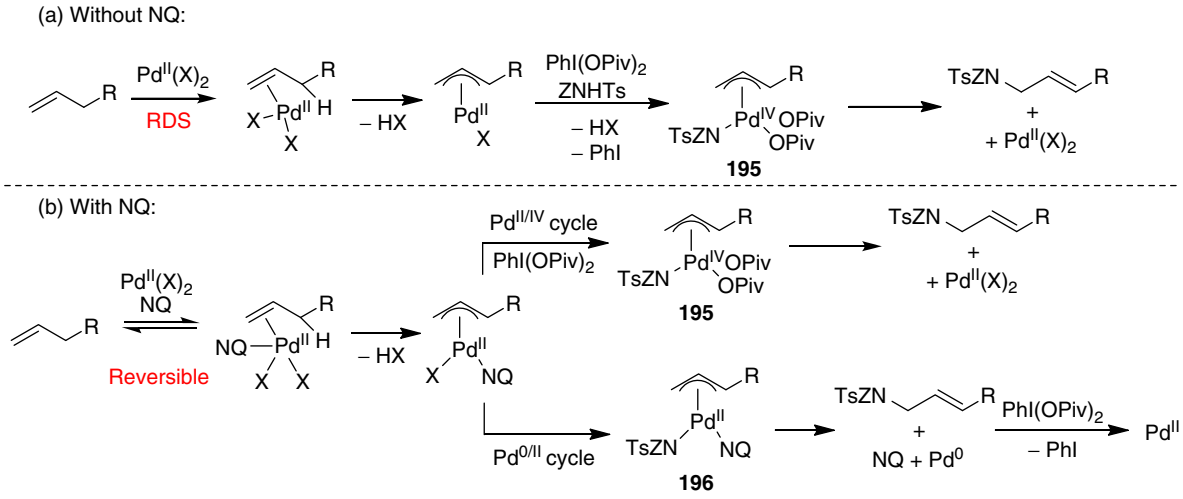
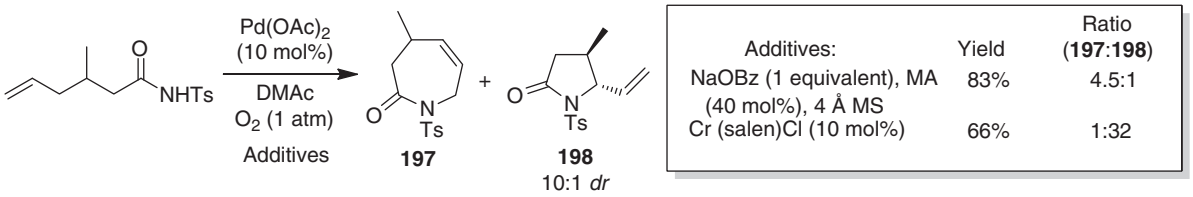


Figure 39 Mechanism for $Pd(OAc)_2$/$PhI(OPiv)_2$ amination system (a) without NQ and (b) with NQ.

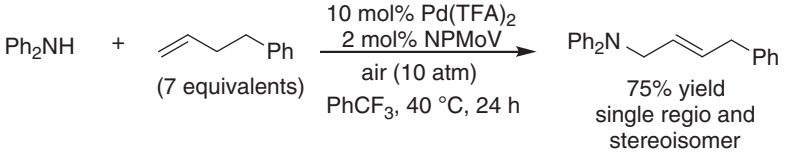
Liu extended his system for the intramolecular allylic amination of *N*-tosylamides (Figure 40).[138] He found that he could control the regioselectivity of product formation for α-olefin substrates depending on the choice of additive. Brønsted base such as sodium benzoate promoted the 7-membered ring, whereas Cr(salen)Cl promotes the formation of the 5-membered ring.



Additives:	Yield	Ratio (**197**:**198**)
NaOBz (1 equivalent), MA (40 mol%), 4 Å MS	83%	4.5:1
Cr (salen)Cl (10 mol%)	66%	1:32

Figure 40 Regioselective intramolecular C–H amination.

Recently, alternative Pd-catalyzed intermolecular C–H amination conditions have been developed using different nitrogen nucleophiles, Pd sources, or oxidants. Obora and Ishii recently demonstrated an aerobic oxidative system involving the coupling of diarylamines and α-olefins (equation 20).[139] The linear (*E*)-allylamine product is formed in modest to good yield (44–75%) with high regio- and stereoselectivity. Molybdovanadophosphate is believed to promote a $Pd^{0/II}$ cycle. It is important to note that the reaction requires a large excess of olefin (7 equivalents).



(20)

Li and Zhang have demonstrated allylic amination using *N*-fluorobenzenesulfonimide (NFSI) as both the oxidant and nitrogen source (Figure 41). Water was found to be an important additive for the reaction, and the authors hypothesize that a Pd(II) hydroxo complex facilitates allylic C–H cleavage. Allylbenzene derivatives (**199–200**) and other homoallylic-substituted substrates (**201**) work best in the reaction; other substrates have been shown to form nonallylic isomers (**202**). The reaction displays good functional group tolerance for nitrile, silyl, and imide functionality (**199–201**) and the reaction times are generally <24 h. The system has also been extended to room temperature allylic C–H amination of allylbenzenes with *N*-tosylcarbamates in water using selectfluor as oxidant.

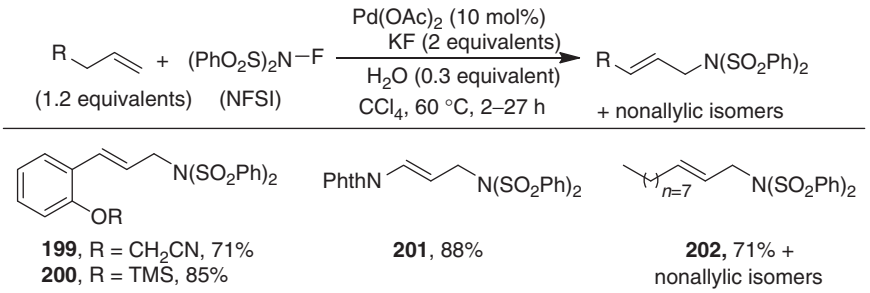


Figure 41 $Pd(OAc)_2$/NFSI system for intermolecular linear C–H amination.

The products of C–H amination are useful intermediates in synthesis (Figure 42). The vinyl *anti*-oxazolidinone products **183** can be transformed to *syn*-1,2-amino alcohols such as (+)-(*2R, 3S*)-3-hydroxyleucine **204**, an unnatural β-hydroxy-α-amino acid present in the antitumor agent lactacystin.[140] Vinyl *syn*-oxazinanones (**205**) are synthons for the synthesis of *syn*-1,3-amino alcohols as shown in the synthesis of (+)-allosedridine **208**, a member of the sedum alkaloids showing promising memory enhancing effects.[141] Late-stage, intermolecular C–H amination can be used to efficiently install isotopic labels. Reaction of **209** with labeled nitrogen nucleophile generated the free amine (+)-**210** with 99.7% isotopic enrichment after subsequent deprotection. White has also demonstrated that sequential intramolecular allylic C–H amination/Heck arylation can be used for the synthesis of unnatural amino acids.[142]

7.05.1.3.3 Metal-nitrenoid catalyzed amination

There have been numerous elegant examples of aliphatic and benzylic C–H amination via metal nitrenoids, especially with rhodium catalysts.[143] The mechanism of reactions using common rhodium carboxylate catalysts such as $Rh_2(OAc)_4$ and $Rh_2(esp)_2$ proceed through a concerted, asynchronous nitrene pathway that favors amination at electron-rich C–H bonds such as

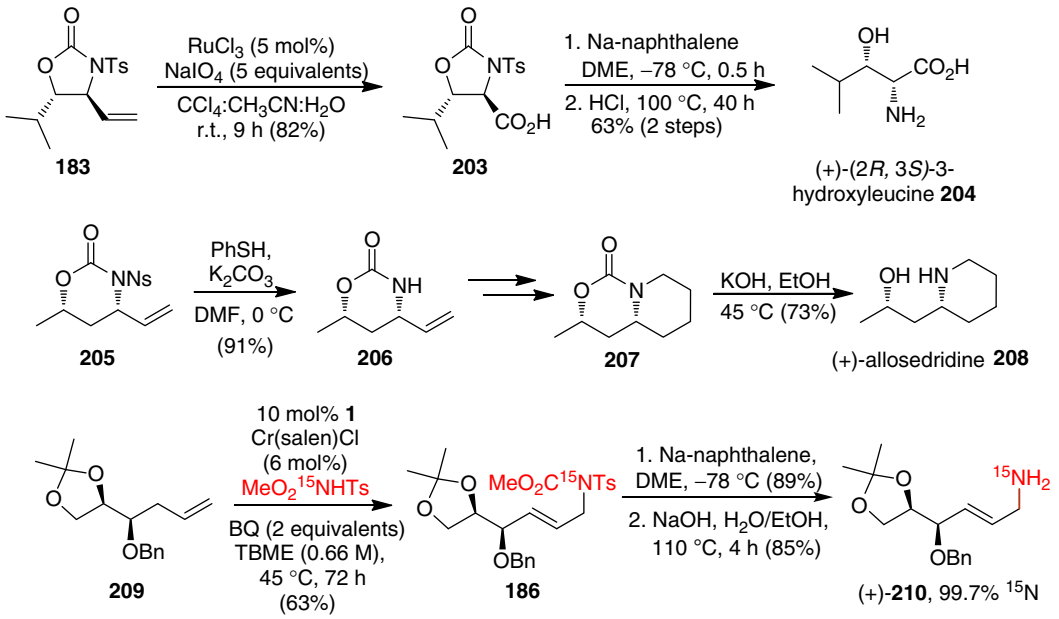


Figure 42 Synthetic applications of allylic C–H amination.

tertiary sites.[144] These same catalysts typically show low selectivity for C–H insertion (I) over competing olefin aziridination (A) (Figure 43(a)).[145,146]

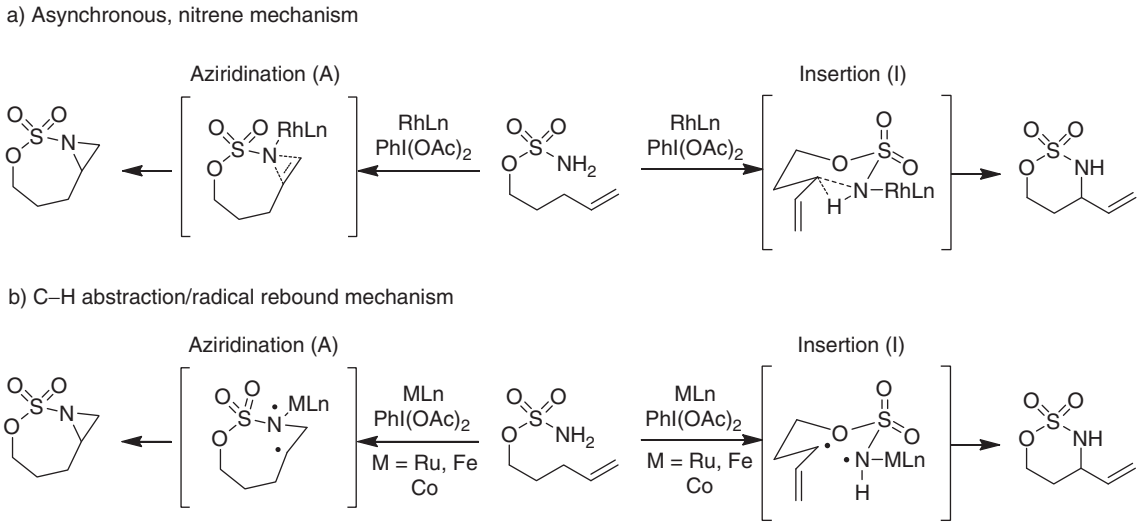
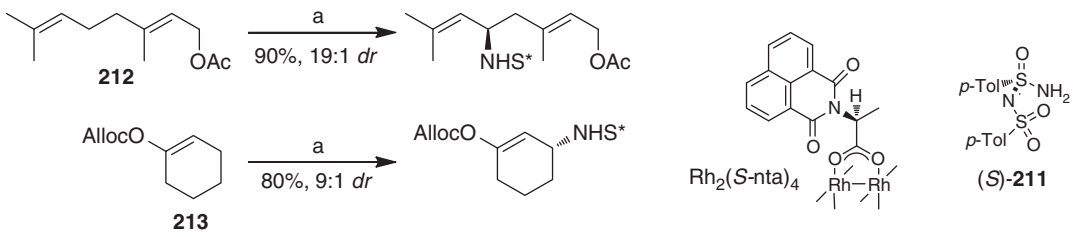


Figure 43 Mechanistic pathways for allylic insertion (I) versus alkene aziridination (A).

More complex carboxamidate and carboxylate dirhodium catalysts have shown enhanced selectivity for allylic amination. For example, carboxamidate catalyst Rh_2(*S*-nap)$_4$ promotes enantioselective, intramolecular allylic C–H amination in up to 84% *ee*.[147] In addition, carboxylate catalysts Rh_2(*S*-nta)$_4$[148] and Rh_2[(*S*)-Br-nttl)$_4$[149] selectively form allylic amines with moderate to good diastereoselectivity (60–90%), though the reactions also require the use of a chiral, stoichiometric amine such as **211**. The reaction using Rh_2(*S*-nta)$_4$ shows very high regio-, diastereo-, and site-selectivity for geranyl substrate **212** (Figure 44). Unlike selenium dioxide, oxidation occurs at the secondary C–H bond. Enol ethers such as **213** undergo selective amination with moderate to high diastereoselectivity (4:1 to >20:1). The exact mechanism of amination using the more complex dirhodium catalysts has not been studied.

Ruthenium catalysts have also been shown to promote allylic amination.[150] Recently, Du Bois has developed a diruthenium catalyst that shows markedly better selectivity for allylic C–H insertion than simple dirhodium catalysts.[151] The catalyst promotes the cyclization of a wide range of sulfamate esters to generate oxathiazinanes (Figure 45). Oxathiazinanes are synthetically useful intermediates that can lead to 1,3-amino alcohols and other products.[152] The selectivity for allylic C–H insertion over



a. Rh_2(*S*-nta)$_4$ (3 mol%), (*S*)-**211** (1.2 equivalents), PhI(Piv)$_2$ (1.4 equivalents), $(Cl_2CH)_2$:MeOH(3:1), –35 °C

Figure 44 Intermolecular allylic amination using chiral dirhodium catalyst and chiral amine nucleophile.

aziridination (I:A) is typically >8:1 (except for α-olefin **214** which gives 2:1) and the reaction is tolerant of synthetically useful groups such as triisopropylsilyl-protected alkynes, indoles, and methoxybenzenes. Disubstituted, trisubstituted, cyclic, and styrenyl olefins are all excellent substrates (**215–218**). Du Bois performed detailed computational and experimental studies which suggest that the diruthenium oxidation occurs through a hydrogen-atom abstraction/radical recombination pathway rather than the concerted, asynchronous nitrene pathway (Figure 43(b)). The radical mechanism is consistent with the fact that allylic (and benzylic) C–H bonds are more reactive than tertiary C–H bonds.

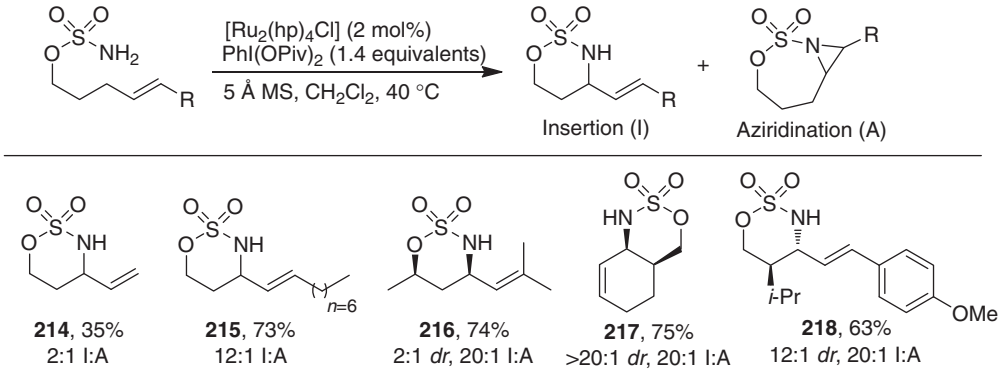


Figure 45 Ru-nitrenoid catalyzed allylic C–H insertion.

Inspired by the work of Du Bois, other researchers have explored allylic amination using alternative, nitrenoid-based catalysts with first-row metals. White has recently disclosed that sulfamate esters can also undergo allylic C–H amination using an iron phthalocyanine catalyst (Figure 46).[153] The iron catalyst shows several important reactivity advantages over the ruthenium and rhodium catalysts. All types of olefin classes (α-olefin, disubstituted, trisubstituted, cyclic, and styrenyl) show >12:1 selectivity for allylic amination over aziridination using iron (**216**, **219–221**), whereas the dirhodium and diruthenium systems promote competitive aziridination of α-olefins (**214**). Furthermore, the iron catalyst shows very high chemoselectivity for allylic amination over secondary and tertiary aliphatic amination (>20:1 allylic), as well as good selectivity over benzylic (5:1) and ethereal positions (7:1, equation 21). The chemoselectivity with iron phthalocyanine is higher than what is observed in the rhodium or ruthenium-catalyzed conditions. Experimental evidence suggests that the mechanism of allylic amination also proceeds through a hydrogen-atom abstraction/radical recombination pathway.

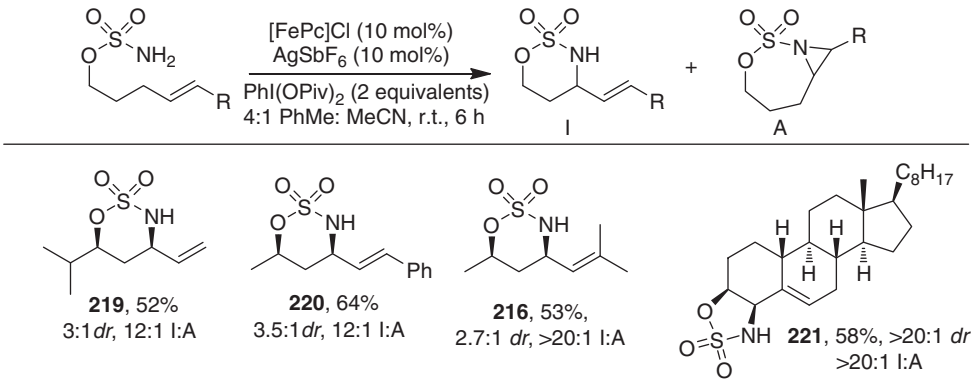
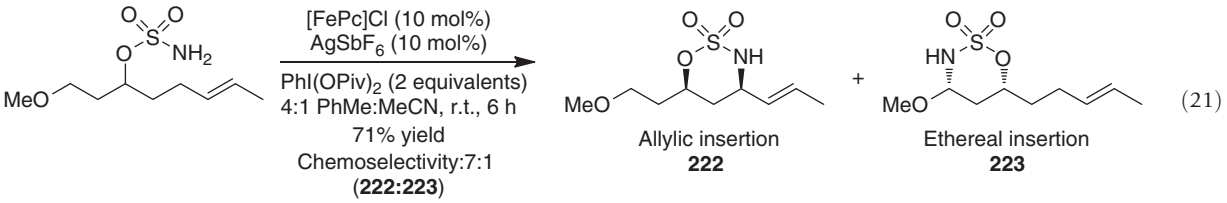


Figure 46 Fe-nitrenoid catalyzed allylic insertion.



(21)

Zhang has demonstrated the intramolecular insertion of sulfonyl azides using a cobalt porphyrin as a catalyst (Figure 47).[154] Notably, these reactions show excellent yields (>90%) and very high selectivity of insertion versus aziridination for both α-olefins (99:1) and (*E*)-1,2-disubstituted olefins (30:1) (**224–225**). The selectivity observed for cobalt is higher than the selectivity observed for iron (12:1 α-olefin and disubstituted) and ruthenium (2:1 α-olefin; 12:1 disubstituted). The cobalt catalyst cyclizes a (*Z*)-1,2-disubstituted olefin that leads to just 5% (*E*)-olefin product (**226**). The catalyst shows efficient cyclization of α,β-substituted esters which were sluggish substrates for the iron-catalyst (**227**). The authors demonstrate selective allylic amination over a secondary aliphatic site (**228**) but show no other competitive reactivity studies with more activated benzylic or ethereal sites.

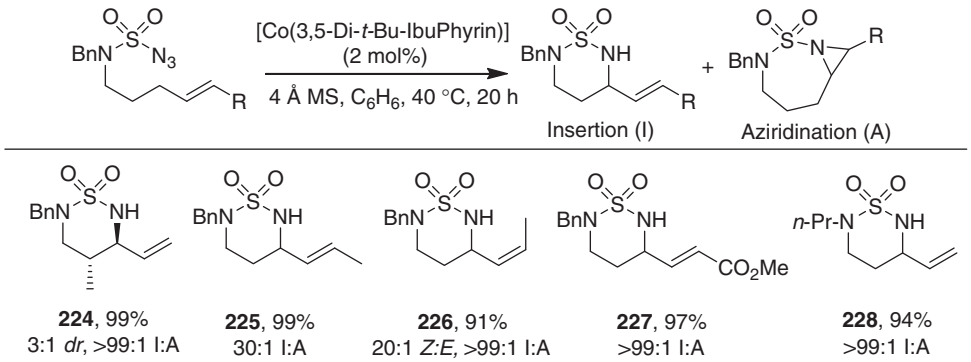
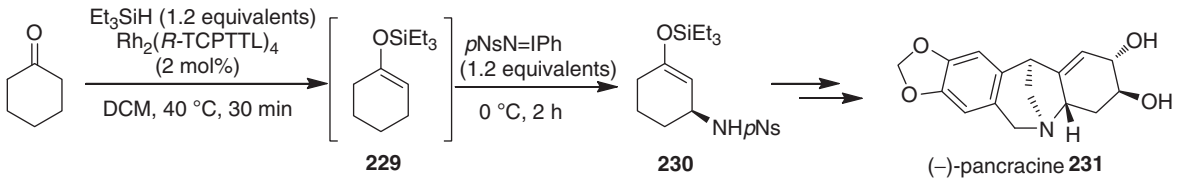


Figure 47 Co-nitrenoid catalyzed allylic insertion.

Allylic amination via metal nitrenoids is a fairly new field and the methodology has not been extensively used within synthesis. Hashimoto has demonstrated the Rh_2(*R*-TCPTTL)$_4$-catalyzed enantioselective allylic amination of silyl enol ether **229** to generate **230** in 72% *ee*, which was a key intermediate in the formal total synthesis of (–)-pancracine **231** (Scheme 8).[155] The method was only demonstrated for cyclohexanone-based silyl enol ethers as (*Z*)-substituted silyl enol ethers have been shown to undergo α-amination.[156]



Scheme 8 Allylic amination of silyl enol ether **229** toward the synthesis of (–)-pancracine.

7.05.1.3.4 Miscellaneous amination methods

A recent metal-free allylic amination has been developed by Muñiz using a hypervalent iodine source (Figure 48). The authors demonstrate that the iodine does not promote a radical pathway as has been previously described for allylic oxidation of diarylmethylene cycloalkanes.[157] Instead, the iodine species is believed to bind to the olefin to form iodonium intermediate **232**. For less substituted olefins, the iodonium is regioselectively attacked by the nitrogen nucleophile at the less hindered position to form **233**, followed by elimination of the iodine species to generate **234** by a formal allylic C–H amination mechanism. More substituted olefins may undergo an alternative mechanism. Similar formal C–H amination and C–H oxidation reactions have been developed using disulfide[158] and *N*-propylthiosuccinimide[159] as oxidant/olefin activators, however the scope for these reactions was quite narrow.

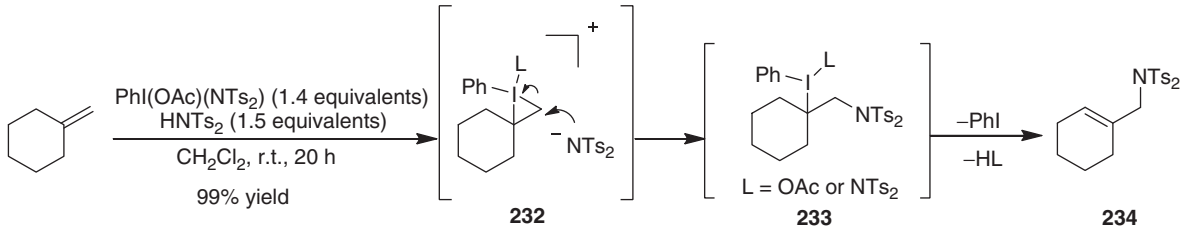


Figure 48 Hypervalent iodine-promoted formal allylic C–H amination.

7.05.1.4 Allylic Oxidation Reactions Which Produce Allylic C–C bonds

7.05.1.4.1 Copper and oxidant-promoted alkylation

There are relatively few examples of catalytic, allylic C–C bond oxidation compared to allylic C–O and C–N oxidation. One of the main reactivity challenges is preventing carbon nucleophile oxidation under the reaction conditions, which was initially circumvented by using stoichiometric palladium to promote sequential allylic C–H cleavage/functionalization (Figure 5). In 2006, Li was able to demonstrate the first example of intermolecular catalytic, allylic C–H alkylation of cyclic olefins using 1,3-dicarbonyl nucleophiles (Figure 49).[160] He found that the reaction requires both catalytic copper (CuI, $CuBr_2$, or CuCl) and catalytic $CoCl_2$ using TBHP as the oxidant. The reaction works best for cyclohexene derivatives (**235**, **239–240**); however 5-, 7-, and 8-membered rings also work in lower yield (**236–238**). Various 1,3-dicarbonyl nucleophiles can also be used. One limitation is that the olefin is required in large excess (5 equivalents). Although the authors do not speculate on the exact role of copper and cobalt, they postulate that homolytic allylic cleavage leads to a π-allyl metal intermediate which facilitates C–C reductive elimination.

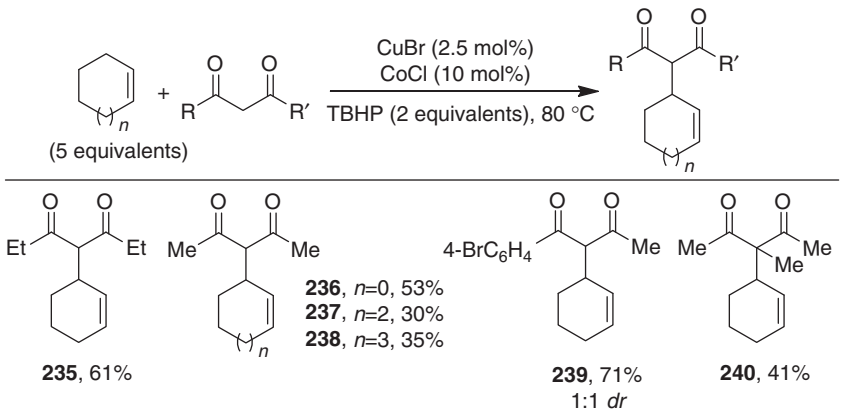
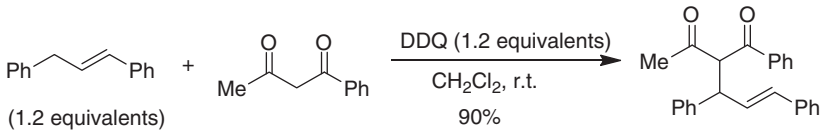
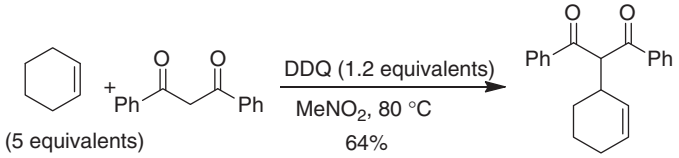


Figure 49 Cu/Co/TBHP system for cycloalkene C–H alkylation.

After Li's seminal work, other researchers continued to look for alternative reaction conditions to achieve allylic alkylation of internal olefins. Both Bao and later Venkateswarlu demonstrated allylic alkylation under metal-free conditions using DDQ. Bao was able to perform allylic C–C bond formation of 1,3-dicarbonyls using a slight excess of the chalcone substrate (equation 22).[161] Venkateswarlu performed oxidative coupling of 1,3-dicarbonyl compounds with 5 equivalents excess cyclohexene or cyclopentene (equation 23).[162] The olefin scope is limited to activated olefins as DDQ must promote one-electron oxidation to generate an intermediate allylic radical species.



(22)



(23)

7.05.1.4.2 Palladium-catalyzed alkylation

Recently, substantial progress has been made for allylic alkylation of α-olefins with Pd(II)/bis-sulfoxide catalysts that allow for the use of olefin as limiting reagent. White has shown $Pd(OAc)_2$/bis-phenylsulfoxide complex **79**-catalyzed C–H functionalization with methyl nitroacetate to form aromatic and heteroaromatic linear (*E*)-α-nitro-arylpentenoates (Figure 50).[163] Although this reaction has many similarities to the original Pd/sulfoxide-catalyzed allylic acetoxylation and amination systems, the BQ π-acid cannot be used here as it undergoes conjugate addition with the carbon nucleophile. The key discovery was that DMSO could promote C–C bond formation of the π-allylpalladium intermediate, therefore benzoquinone's role of oxidant could be replaced by a sterically hindered quinone. A highly acidic carbon pronucleophile was also required so that the catalytic acetate base from $Pd(OAc)_2$ can be used to deprotonate it. Complex allylbenzene derivatives can undergo allylic C–H alkylation in modest to good regioselectivity (3:1 to 15:1) and with modest to good yield (42–70% isolated yield, single isomer after chromatography). The authors also demonstrate that the nitro group can be selectively reduced to generate α-amino esters.

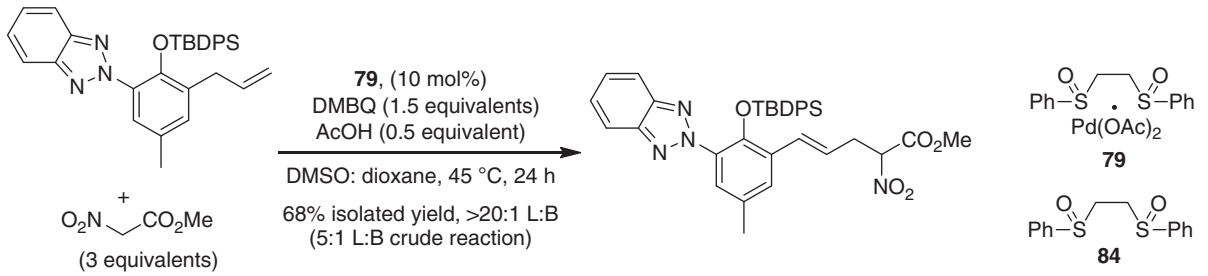


Figure 50 $Pd(OAc)_2$/phenyl bis-sulfoxide (**79**)-catalyzed C–H alkylation of allyl benzenes.

Shortly after the initial publication from White, Shi and coworkers disclosed that 10 mol% $Pd(OAc)_2$/bis-benzylsulfoxide complex **242** promotes intermolecular allylic C–H alkylation using 1,3-dicarbonyl nucleophiles such as benzoylacetone **241** (Figure 51).[164] It is interesting to note that the 1,3-dicarbonyl nucleophiles do not appear to undergo conjugate addition with benzoquinone, which was an issue with methyl nitroacetate nucleophile in the White system. Allylbenzene derivatives are coupled with very high linear regioselectivities (>20:1) compared to the White system and the reaction requires just a slight excess of the carbon nucleophile (1.2 equivalents).

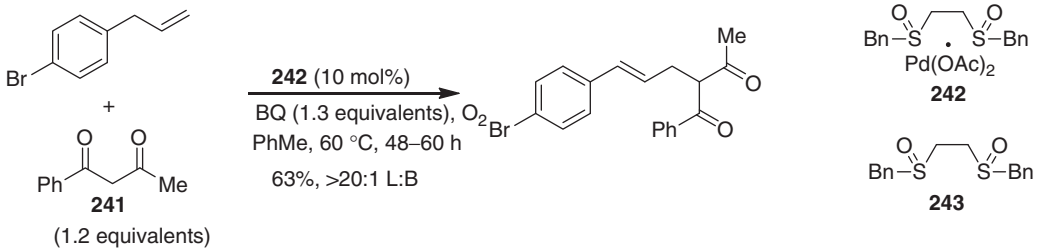


Figure 51 $Pd(OAc)_2$/benzyl bis-sulfoxide (**242**)-catalyzed C–H alkylation of allyl benzenes.

Although both the White and Shi systems work for intermolecular coupling of allylbenzene derivatives, neither system demonstrated efficient intermolecular coupling of unactivated α-olefins. Careful mechanistic studies by White suggested that DMSO outcompeted phenyl bis-sulfoxide ligand **84** for binding to palladium which led to low conversion and/or stalling with aliphatic α-olefins. Similarly, benzoylacetone **241** outcompeted the benzyl bis-sulfoxide ligand **243** used in Shi's system and led to similar results. Although $Pd(OAc)_2$/DMSO or $Pd(OAc)_2$/benzoylacetone could promote allylic C–H cleavage of allylbenzenes, it was not electrophilic enough to promote C–H cleavage of unactivated aliphatic α-olefins. When White switched from the phenyl bis(sulfoxide) ligand **84** to more σ-donating alkyl bis(sulfoxide) ligands like **243**, DMSO no longer inhibited allylic oxidation of aliphatic α-olefins.[165] White's new reaction conditions, incorporating $Pd(OAc)_2$/bis-benzylsulfoxide catalyst **242** and 4 equivalents of benzoyl nitromethane nucleophile, are general for both unactivated (**244–245**) and activated α-olefins such as allylbenzenes (**246**) and a β,γ-unsaturated amide (**247**) (Figure 52). The new reaction conditions provide better linear regioselectivity (11:1 to >20:1) than the original system while still demonstrating efficient coupling of complex olefins.

Shi has also demonstrated intramolecular cyclization to form branched 5- and 6-membered rings. It appears that the 1,3-dicarbonyl nucleophile does not inhibit aliphatic allylic C–H cleavage for the intramolecular system as both aromatic and aliphatic allylic olefins were shown to cyclize. In some cases the cyclization can proceed with very high diastereoselectivity (equation 24).

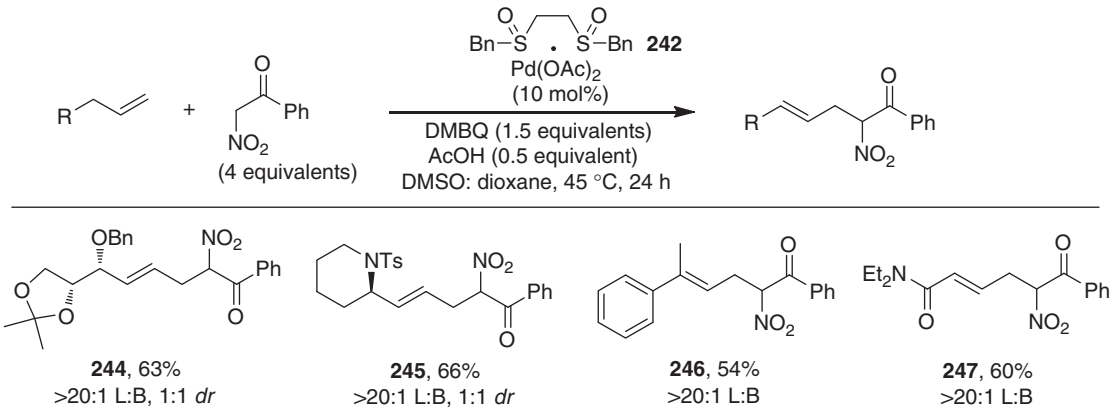
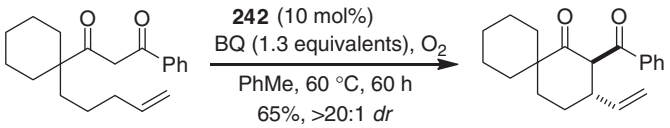


Figure 52 $Pd(OAc)_2$/benzyl bis-sulfoxide (**242**)-catalyzed C–H alkylation of α-olefins.



(24)

7.05.2 Conclusion

There is a wide array of allylic oxidation methods at the disposal of the synthetic organic chemist. Although selenium dioxide and chromium(VI) reactions remain popular, the metal-catalyzed allylic oxidation methods are fairly new and their total impact on the field of synthesis remains to be seen. However, there are already impressive oxidation examples using palladium/sulfoxide and catalytic metal/TBHP in complex molecule settings. Mechanistic study of known methods should continue to lead to new insights for developing more predictable and selective oxidation reactions.

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7.06 Oxidation Adjacent to C=X Bonds by Dehydrogenation

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Glossary

***β*-hydride elimination** Net transfer of a hydride equivalent ($H^+ + 2e^-$) from the beta position to another group resulting in the introduction of another site of unsaturation in the molecule (typically an alkene).

Dehydrosilylation Net removal of $R_3Si–H$ from an organic compound introducing another site of unsaturation in the molecule. For example, dehydrosilyation of silyl enol ethers results in the formation of enones.

Oxidative addition A reaction of a substrate with a transition metal or other element that increases both the coordination number and oxidation state of the element.

Sulfenylation Net transfer of a 'RS^+' group to a nucleophile. For example, the reaction of an enolate with the PhSSPh is a sulfenylation reaction that affords an organic sulfide.

Sulfinylation Net transfer of a '$RS(O)^+$' group to a nucleophile. For example, the reaction of an enolate with the PhS(O)Cl is a sulfinylation reaction that affords a sulfoxide product.

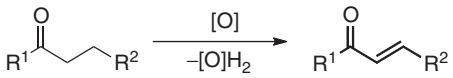
Transmetallation Transfer of a nucleophile from one metal (or metalloid) to another.

7.06.1 Introduction

α,β-Unsaturated carbonyl compounds are versatile intermediates in the synthesis of pharmaceuticals and biologically active compounds.[1] Many of the synthetic methods to access such structures rely on condensation reactions that construct the C=C bonds from simpler molecular fragments. An oxidative strategy that introduces unsaturation into a preestablished molecular skeleton provides an appealing alternative method to access α,β-unsaturated carbonyl compounds (equation 1).[2] For decades, the field of α,β-dehydrogenation of carbonyl compounds was dominated by stoichiometric methods, including sequential halogenation/dehydrohalogenation, elimination reactions employing sulfur, and selenium reagents, and more recently developed hypervalent iodine-mediated direct dehydrogenation. Transition metal catalyzed dehydrogenation reactions, employing environmentally benign oxidants, have begun to emerge as appealing alternatives. This chapter provides a summary and overview of historical methods, including halogenation/dehydrohalogenation, and the use of sulfur/selenium reagents and quinone-based oxidants. The majority of the chapter, however, will focus on progress during the past two decades, including the development of

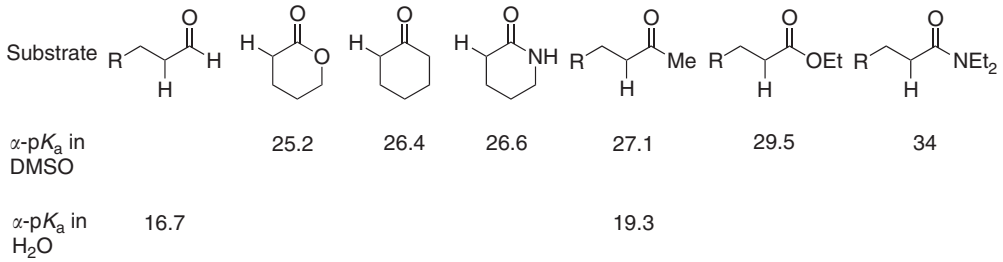
 doi:10.1016/B978-0-08-097742-3.00707-2

hypervalent iodine and transition-metal mediated and catalyzed reactions. Comparison of various reagents is presented, together with the inclusion of selected synthetic examples.



(1)

Different dehydrogenation methods proceed by different mechanisms, but the pK_a of the α-C–H of the carbonyl substrate often correlates with substrate reactivity and selectivity. The pK_a values of a series of carbonyl compounds are summarized in Scheme 1.[3] Aldehydes have the most acidic α-C–H bond and are often the most reactive substrate among carbonyl compounds. Carboxylic esters and amides have the least acidic α-C–H bonds, and they often exhibit the lowest reactivity.



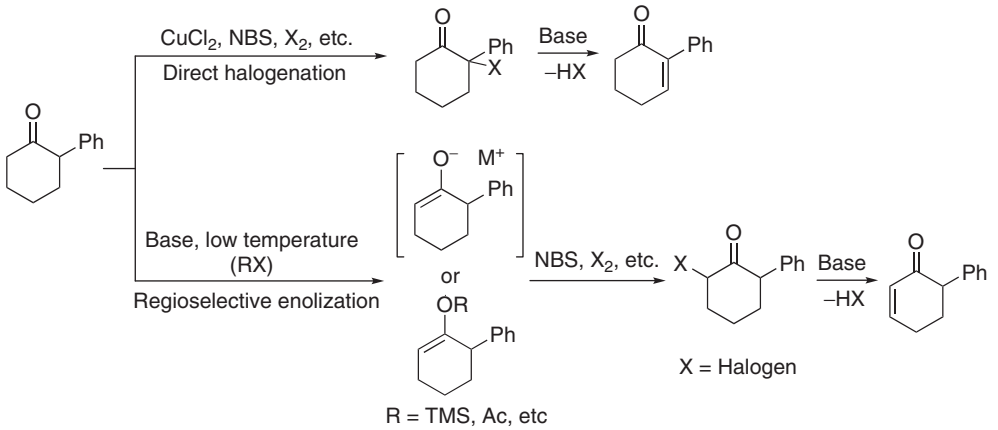
Scheme 1

The selectivity of various dehydrogenation methods is discussed in this chapter. Chemoselectivity is associated with the relative reaction rate between α,β-dehydrogenation adjacent to a carbonyl group and oxidation of other functional groups, such as alcohols and benzylic C–H bonds. Different carbonyl compounds, when present in the same molecule, can undergo competing dehydrogenation as well. In cases where the resulting α,β-unsaturated carbonyl compound is susceptible to further reaction, the selectivity between mono-dehydrogenation and multiple dehydrogenation steps is also of interest. For example, dehydrogenation of a cyclohexanone could afford the corresponding cyclohexenone or phenol. In addition, dehydrogenation of an unsymmetrical ketone could lead to two regioisomers. Dehydrogenation reactions that selectively afford one regioisomer relative to the other are especially valuable. Furthermore, the newly formed C═C bond following dehydrogenation raises the possibility of forming (*E*) and (*Z*) stereoisomers when substituents are attached. Mechanistic aspects and stereoelectronic effect of reagents are discussed within the context of various selectivity issues.

7.06.2 Summary and Progress of Historical Methods

7.06.2.1 Halogenation-Dehydrohalogenation Reactions

Stepwise α-halogenation-dehydrohalogenation reactions represent classic protocols for preparing α,β-unsaturated carbonyl compounds (Scheme 2).[2] The initial α-halogenation typically proceeds by one of two pathways: direct halogenation of the carbonyl compound or sequential stoichiometric-enolate formation followed by quenching with halogenation reagents.



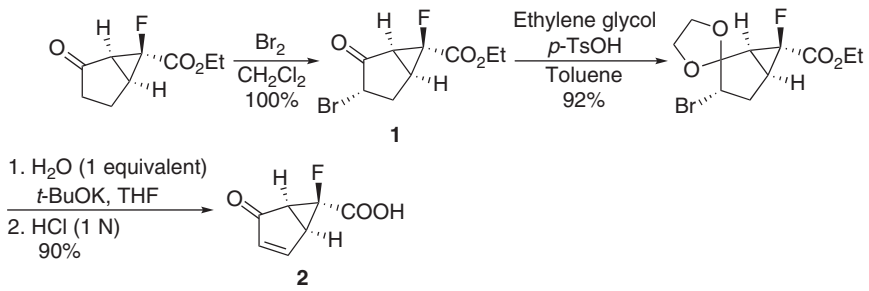
Scheme 2

Widespread synthetic interest in these reactions has led to development of various halogenation reagents, including *N*-bromosuccinamide (NBS),[4,5] Br_2,[6] and $CuBr_2$,[7,8] among which NBS is the most compatible with sensitive functional groups. For example, $CuBr_2$ and Br_2 can lead to undesired halogenation of aromatic rings.[9] α-Halogenation of an unsymmetrical ketone can afford different regioisomers. Direct α-halogenation via *in situ* enolization often proceeds by competing mechanisms, including acid/base-catalyzed enolization[10] and radical pathways.[11] In general, direct α-halogenation requires high temperature or exposure to light, and exhibits poor control of regioselectivity.[12] In some cases, regioselectivity can be improved by controlling the mechanism of *in situ* enolization, such as addition of a radical initiator to favor the radical pathway.[11]

The alternative pathway, stoichiometric-enolate formation followed by quenching with a halogenation reagent, often provides good control of the regioselectivity under mild conditions (Scheme 2).[13] This pathway benefits from the wide variety of conditions for regioselective enolate formation and the facile halogenation of enolates.[14] Pregeneration of stable enolate derivatives, such as silyl enol ethers[15,16] or enol acetates,[17,18] has also been used in halogenation reactions. Relative to direct α-halogenation, the stoichiometric-enolate methods allow good chemoselectivity in the presence of functional groups that are susceptible to halogenation.

The second step, elimination from the α-halocarbonyl intermediates, is typically promoted by a base to afford the corresponding α,β-unsaturated carbonyl compounds. The mechanism of elimination (E*1*, E*1*cB, or E*2*) and the rate depend significantly on the leaving group, the base, the substituents, and the solvent.[19] These factors also influence the (*E*)/(*Z*) stereochemistry of the newly formed C═C bond with acyclic substrates. A large variety of organic and inorganic bases have proven to be effective with different substrates. Common organic bases include 1,5-diazabicyclononene (DBN), 1,8-diazabicycloundec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), and Et_3N. These sterically hindered bases are useful when substitution is a possible side-reaction. Conversely, strong inorganic bases, such as alkali metal hydroxides, alkoxides, and amides, induce elimination under milder conditions.

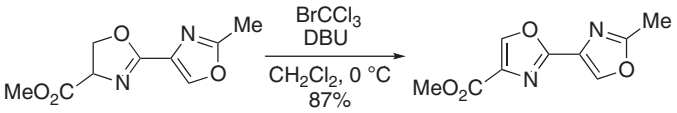
The basic conditions sometimes determine the substrate scope of the halogenation–dehydrohalogenation method, as many functional groups are sensitive to strong bases. However, this limitation can be overcome by performing a stepwise halogenation-functional group protection-elimination sequence. For example, the α-brominated bicyclic cyclopentanone **1** decomposes when exposed to DBU or *t*-BuOK (Scheme 3).[20] This substrate decomposition is avoided by converting the carbonyl into an acetal with ethylene glycol before elimination. The resulting bicyclic cyclopentenone derivative **2** is an important synthetic intermediate to the mGluR 2 receptor agonist.[20] Direct dehydrogenation by another commonly used reagent, 2-iodoxybenzoic acid (IBX), suffers from low yield because of substrate decomposition (cf. Section 7.06.3.1).[20] The same sequential halogenation-protection-elimination strategy is also employed in a synthesis of derivatives to glaziovine.[21]



Scheme 3

Numerous well-developed enolization methods for aldehydes, ketones,[13] esters,[22,23] and lactones[24,25] provide the basis for a broad substrate scope for the halogenation–dehydrohalogenation reaction. Amides have the highest pK_a and are the most difficult to halogenate. Ghosez and coworkers reported successful halogenation–dehydrogenation of amides in a one-pot protocol without requiring strong base. The method employs phosgene, in combination with Et_3N and pyridine *N*-oxide, and is proposed to go through a keteniminium ion intermediate.[26]

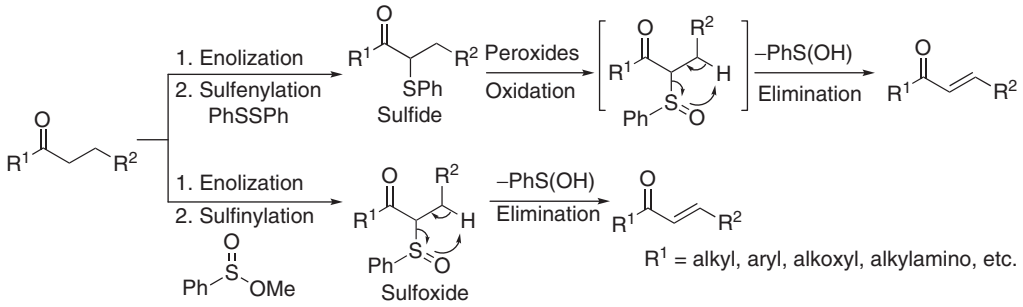
The scope of halogenation–dehydrohalogenation reaction has been expanded by the development of $BrCCl_3$ in combination of DBU for preparing heterocycles (equation 2).[27] In particular, $BrCCl_3$ is capable of converting 4-carboxyoxazoline and thiazoline derivatives into the corresponding oxazoles and thiazoles under mild conditions. The method exhibits good functional group tolerance toward esters and acetals.[27] Other dehydrogenation reagents, including NiO_2, NBS, and PhSeCl, were unsuccessful with these substrates. This $BrCCl_3$/DBU-mediated dehydrogenation has found applications in the syntheses of tiazofurin[28] and a thiazole analog to pyochelin.[29] Moreover, 4-carboxyoxazole derivatives can be prepared via one-pot cyclocondensation of β-hydroxy amides followed by $BrCCl_3$/DBU-mediated dehydrogenation.[30] In addition, the sequential α-bromination/elimination reaction led to construction of an indole ring from the pyrrolocyclohexenone purcursor, employing $CuBr_2$ as the bromination reagent in the synthesis of exiguamines A and B.[31] $CuBr_2$ has also been used to dehydrogenate thiolactones.[32] In addition to serving as an α-bromination reagent, $CuBr_2$ can mediate dehydrogenation reactions via single-electron transfer (SET) pathways involving radical intermediates (cf. Section 7.06.4.2).



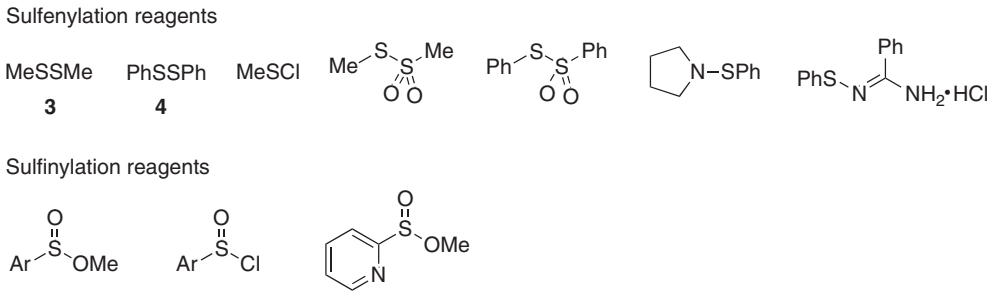
(2)

7.06.2.2 Organosulfur Reagents

In the 1970s, Trost and several others developed and studied a series of organosulfur reagents for dehydrogenation of carbonyl compounds. The most common protocol consists of stepwise α-sulfenylation followed by oxidation and elimination (Scheme 4).[33,34] The initial enolization step determines the chemo- and regioselectivity of the overall reaction. The α-sulfide intermediates are often formed by reaction of enolates or enol ethers with one of various sulfenylation reagents (Scheme 5).[35] Dimethyl disulfide **3**[36] and diphenyl disulfide **4**[37] are readily available, stable during storage, and relatively inexpensive. Therefore, these reagents have been among the most commonly used.[33] Subsequent oxidation to the corresponding sulfoxide intermediates can be achieved with a number of oxidants, including peroxides, periodates, ozone, and iodosobenzene.[33]



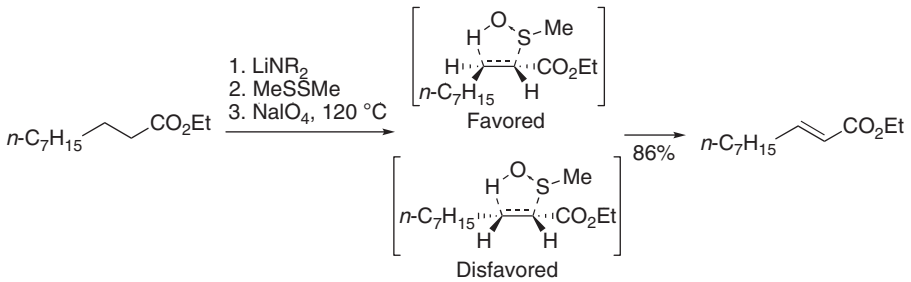
Scheme 4



Scheme 5

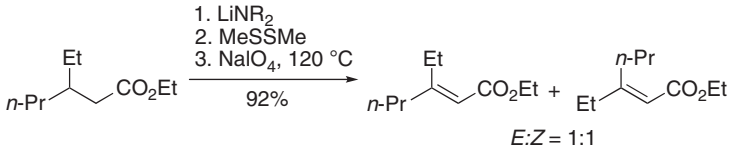
Alternatively, the reaction of a carbonyl compound with one of the sulfinylation reagents forms the sulfoxide intermediate in one step (Scheme 4).[38–40] This process avoids the use of oxidants during the reaction, and some of the sulfinylation reagents exhibit superior reactivity with specific substrates, such as medium-sized rings.[40]

The subsequent elimination of the sulfoxide intermediates proceeds via a stereospecific 5-membered concerted transition-state (Scheme 6).[41] Usually, elevated temperature is required for the elimination. The *syn* configuration for elimination dictates the (*E*)/(*Z*) stereochemistry of the new formed C═C bond.[33] For example, dehydrogenation of ethyl decanoate exclusively affords ethyl



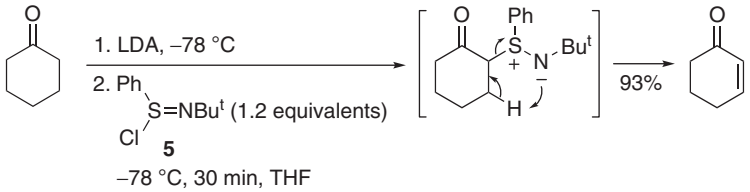
Scheme 6

dec-(*E*)-2-enoate (Scheme 6). The (*Z*) product is disfavored because of the steric interaction between the ester and the *n*-heptyl group in the 5-membered transition-state. In contrast, dehydrogenation of methyl 3-ethylhexanoate under the same conditions affords a 1:1 mixture of (*E*) and (*Z*) product (equation 3). The substrate scope of the α-sulfenylation-oxidation-elimination reactions includes a large variety of carbonyl compounds, including ketones, aldehydes, lactones, lactams, esters, and amides.[34] Relative to organoselenium reagents (cf. Section 7.06.2.3), organosulfur reagents require higher temperature to achieve the elimination of sulfoxide intermediates; however, their lower cost and toxicity give them an advantage over selenium reagents.

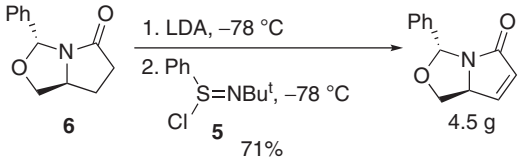


(3)

Recently, a new organosulfur reagent, N-*tert*-butyl phenylsulfinimidoyl chloride **5**, has emerged as an alternative to other sulfoxide-based reagents. On reacting with enolates, **5** forms a strongly nucleophilic sulfimide intermediate that undergoes facile *syn*-elimination under mild conditions (Scheme 7).[42] The two-step process is carried out in one pot without purification of the intermediate. Furthermore, **5** is easily accessible via condensation of *S*-aryl thioacetates with N,N-dichloro-*tert*-butylamine.[43] A noteworthy application of **5** involves dehydrogenation of bicyclic lactam **6**, which is a key intermediate to (2*S*,3*S*)-N-methyl-5-hydroxyisoleucinea (equation 4).[44] Good yield of the unsaturated lactam is achieved on a 4.5 g scale. In comparison, PhSeBr-mediated dehydrogenation (cf. Section 7.06.2.3) provides good yield of the unsaturated lactam, but this method is limited to small scale because of the cost and toxicity of PhSeBr.[45] Other oxidants and dehydrogenation methods, including IBX (cf. Section 7.06.3.1) and Saegusa oxidation (cf. Section 7.06.4.1.3), fail to furnish any desired product.

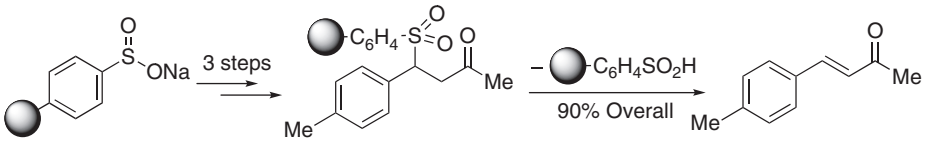


Scheme 7



(4)

Polymer-bound sodium benzenesulfinate has been used in a solid-phase organic synthesis (SPOS) of β-(*p*-tolyl)butenone (Scheme 8).[46,47] Analogous to other SPOS processes, the work-up procedure of this dehydrogenation reaction involves simple filtration, and the sulfur reagent can be recovered. Nevertheless, because of the intrinsic difficulty of the elimination of the sulfinyl intermediates, this method has been thus far limited to β-arylbutenones.

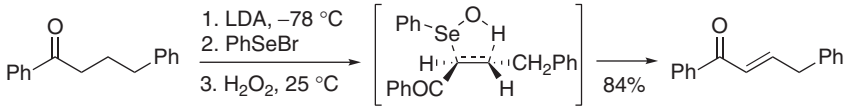


Scheme 8

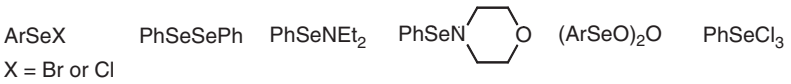
7.06.2.3 Organoselenium Reagents

Organoselenium-mediated dehydrogenation reactions proceed by pathways similar to those of organosulfur reagents (Scheme 9).[48] Various Se-based reagents react with preformed enolates or silyl enol ethers to afford the selenide or selenoxide

intermediates (Scheme 10). Subsequent *syn*-elimination furnishes the enone product in good yield.[49–51] The 5-membered transition-state for the elimination step typically favors the (*E*) conformation to minimize steric interactions and results in (*E*)-olefins (Scheme 9). The enhanced basicity of the selenoxide relative to a sulfoxide allows for more facile elimination.[52] Generally, room temperature conditions are sufficient for the elimination to occur. As a result, organoselenium reagents have found more widespread application than organosulfur reagents.[53] The groups of Reich[54–56] and Sharpless[50,57] played a key role in establishing the utility of these methods. Comprehensive book chapters[58,59] and two books[60,61] provide thorough summaries and analyses of the reactivity and selectivity of various organoselenium reagents.

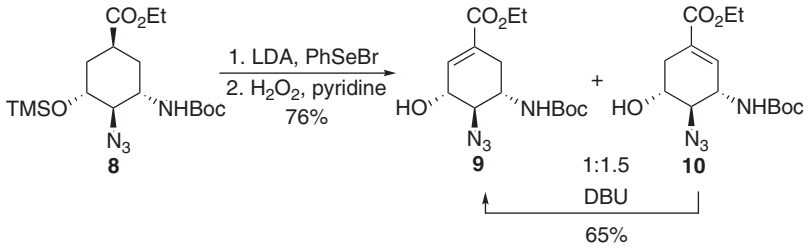


Scheme 9



Scheme 10

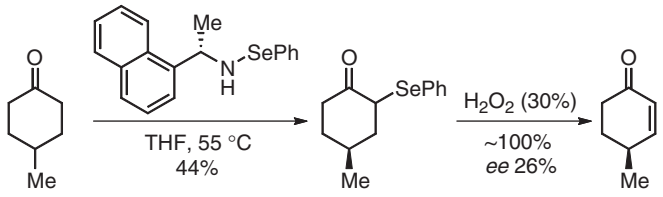
The mild conditions employed in organoselenium-mediated dehydrogenation enable good functional group tolerance. Conventionally reactive groups, such as azides, esters, hydroxyl groups, and carbamates, are compatible with the method (equation 5).[62] For example, when treated with IBX (cf. Section 7.06.3.1), ester **8** is transformed into a complex mixture. In contrast, PhSeBr-mediated dehydrogenation furnishes a mixture of two regioisomers of the unsaturated ester, **9** and **10**, in a 1:1.5 ratio in good yield. The majority of the undesired isomer **10** can be converted into the desired one in the presence of a base to give a 65% overall yield of **9**. The resulting unsaturated ester **9** is a precursor to oseltamivir phosphate.[62]



(5)

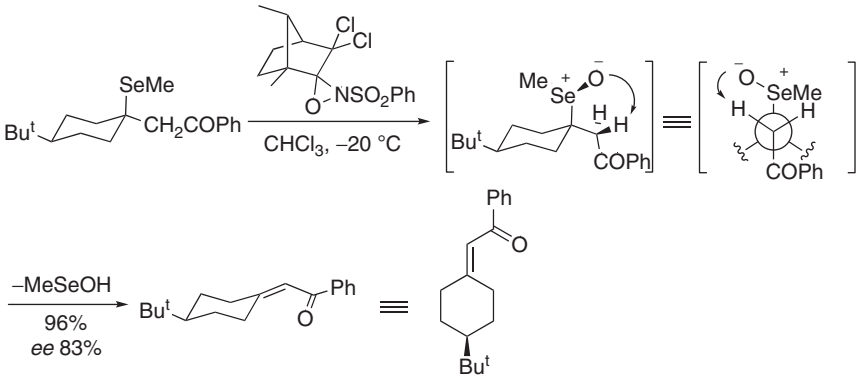
The development of solid-supported selenium reagents has been the focus of recent attention.[63] Several nucleophilic[64] and electrophilic[65] polymer-tethered selenide reagents have accomplished dehydrogenation of cyclohexanones in yields comparable to those with analogous unbound reagents. These solid-supported selenium reagents minimize undesirable odors and are easier to handle.[65] Thus far, however, these reagents have not been demonstrated with diverse substrates.

A chiral selenamide has been used to desymmetrize a C_s-symmetric 4-substituted cycohexanone by forming a chiral 4-substituted cyclohexen-1-one (Scheme 11).[66] Formation of the α-selenide intermediate is diastereoselective and is proposed to determine the *ee* of the final cyclohexenone product.



Scheme 11

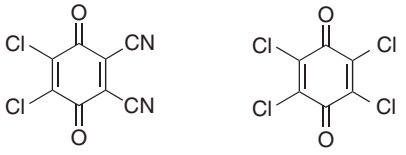
Another enantioselective dehydrogenation was achieved by a chiral-oxidant-induced oxidative elimination of the α-selenide (Scheme 12).[67] The chiral Davis oxidant, *N*-phenylsulfonyloxaziridine, is readily available from camphor, and oxidation of the *cis*-4-*tert*-butylcyclohexyl selenide[68] furnishes a chiral selenoxide intermediate in 83% *ee*. Stereospecific elimination from the chiral selenoxide leads to the corresponding chiral 4-*tert*-butylcyclohexylidenemethyl ketone with retention of *ee*. The demonstrated substrate scope of this reaction is restricted to *cis*-4-substituted cyclohexyl selenides.



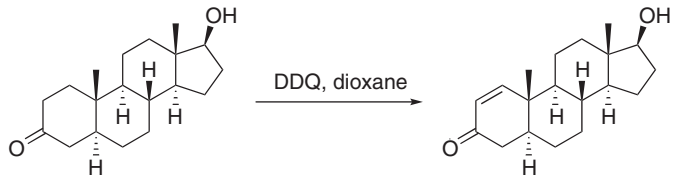
Scheme 12

7.06.2.4 Dichlorodicyanoquinone (DDQ)

Among various quinone derivatives,[69] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) **11** displays high reactivity for α,β-dehydrogenation adjacent to C═X bonds.[70,71] Another common quinone, chloranil **12**, is often used for further oxidation of enones to dienones.[72] Mechanistic investigations of DDQ-mediated dehydrogenation of 1,4-dihydronaphthalene implicate slow hydride transfer from the substrate to quinone as the initial step, followed by fast deprotonation.[73] Acids often accelerate the reaction by protonating the quinone and facilitating the rate-limiting hydride transfer.[73]



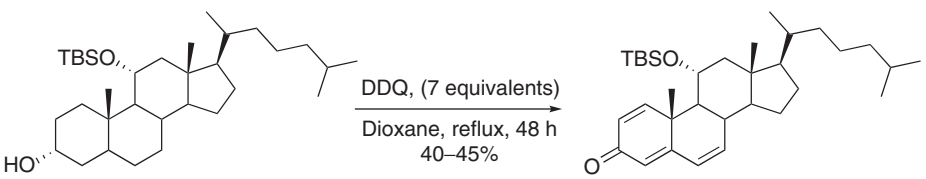
DDQ-mediated dehydrogenation is particularly successful for the preparation of unsaturated 3-ketosteroid derivatives, which frequently exhibit important biological activity. The regioselectivity is dependent on the stereochemistry of the substrate.[70] In general, dehydrogenation of 5α-3-keto steroids furnishes Δ^1-products (equation 6),[74] whereas 5β-3-keto steroids afford Δ^4-3-keto products (equation 7).[75] Increasing the stoichiometry of DDQ can lead to a higher degree of oxidation. As shown in equation 8, use of seven equivalent of DDQ enables 8-electron oxidation of a cholesterol derivative into the corresponding trienone.[76] This transformation has been used to convert a commercially available dihydro-cholesterol into stoloniferone derivatives that have antitumor activity.[76]



5α-Androstan-17α-ol-3-one — 5α-Androst-1-ene-17β-ol-3-one (6)

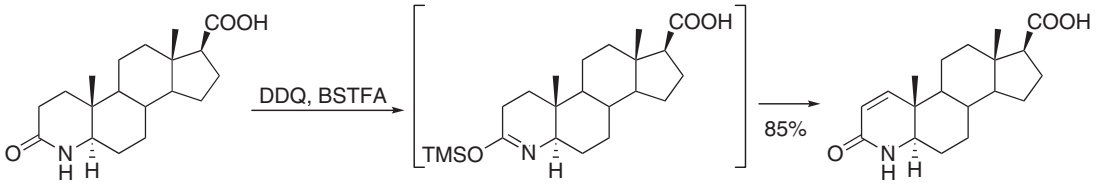


5β-Androstan-17β-ol-3-one — Androst-4-ene-17β-ol-3-one (7)



(8)

The strong oxidizing ability of DDQ provides the basis for dehydrogenative synthesis of heterocycles[77,78] and unsaturated lactones,[79] which are challenging reactions with other oxidants. For example, dehydrogenation of a 4-aza-3-ketosteroid is achieved with the assistance of bis(trimethylsilyl)trifluoroacetamide (BSTFA). The reaction is proposed to proceed via a silyl ketene aminal intermediate (Scheme 13).[80]



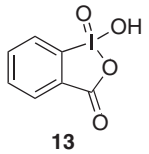
Scheme 13

For dehydrogenation of simple ketones, the strong oxidation potential of DDQ limits their utility to substrates that are not susceptible to overoxidation.[81] However, selective mono-dehydrogenation can be achieved under mild conditions with preformed silyl enol ethers.[82]

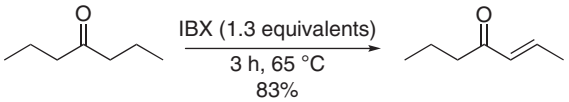
7.06.3 Hypervalent Iodine Reagents

7.06.3.1 Direct Dehydrogenation

The hypervalent iodine reagent IBX **13** was first prepared in 1893,[83] and during the last century, IBX has been widely used as an oxidant in alcohol oxidation reactions.[84,85] Use of IBX was not developed for α,β-dehydrogenation of carbonyl compounds, however, until 2000 by Nicolaou et al. (equation 9).[86] IBX and several related derivatives exhibit broad substrate scope and versatile functional group tolerance for α,β-dehydrogenation of ketones and aldehydes. In addition, IBX is relatively air-stable and easy to handle. As a result, IBX has been employed as a dehydrogenation reagent in numerous target-directed syntheses.[87,88] Representative applications include the synthesis of platensimycin,[89,90] platencin,[91] and pallavicinolide A.[92]

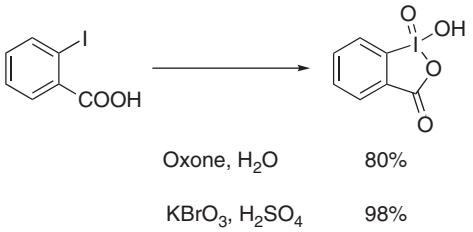


13



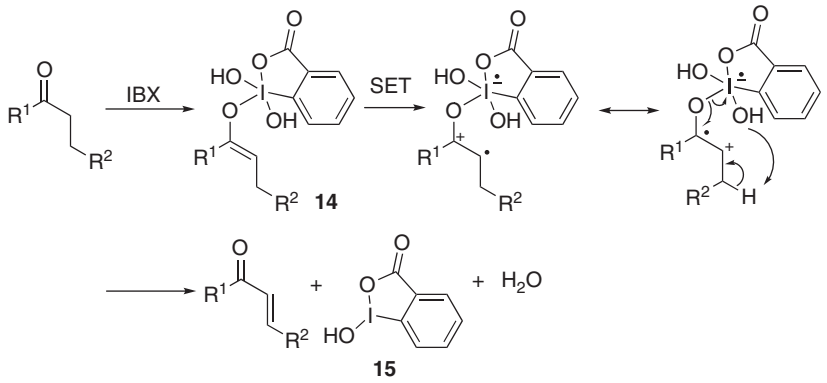
(9)

IBX is readily prepared via the oxidation of 2-iodobenzoic acid by either oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$)[93] or potassium bromate (Scheme 14).[94] Both methods proceed with high yield after a short reaction time. IBX was considered explosive on impact or at temperatures >200 °C;[95] however, later investigation discovered that residual bromine derived from the preparation procedure with $KBrO_3$ is the source of the explosion hazard, rather than IBX.[96] The IBX sample obtained by oxone oxidation is highly pure ($>95\%$), and shows no significant degradation after storage at 25 °C in the dark for 6 months.[97] Although bromine is absent from these samples, heating above 200 °C is still not recommended.[98]



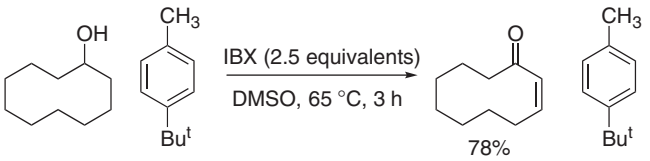
Scheme 14

Mechanistic studies suggest that IBX-mediated dehydrogenation of ketones proceeds via a SET mechanism (Scheme 15).[97,99] The ketone substrate is proposed to form an enolate adduct with IBX (**14**) and SET from the enolate fragment to the hypervalent iodine center generates a radical cation, which is stabilized by the α-oxygen. Deprotonation of the β-H by the hydroxyl group of IBX and concerted homolytic cleavage of the O–I bond furnish the enone and 1-hydroxy-3H-1,2-benziodaoxol-3-one (IBA) **15** as the by-product. The standard conditions employ 1.5 equivalents of IBX per C–C bond to be oxidized.[86,97] An excess of IBX is detrimental, as the side-product IBA, formed by reaction of IBX with the dimethylsulfoxide (DMSO) solvent retards the reaction rate.[97]



Scheme 15

IBX can mediate a number of oxidation reactions in addition to α,β-dehydrogenation (e.g., alcohol oxidation and benzylic oxygenation).[97] Study of the chemoselectivity of IBX, among α,β-dehydrogenation, alcohol oxidation, and benzylic oxidation, reveals that alcohol oxidation is often faster than α,β-dehydrogenation of carbonyl compounds, whereas oxidation of benzylic C–H bonds is slower than α,β-dehydrogenation. This reactivity sequence is consistent with the proposed SET mechanism (Scheme 15). Alcohols are the most nucleophilic and electron-rich, thereby facilitating formation of the IBX-substrate adduct (cf. **14**) and subsequent SET. Conversely, benzylic methylene groups are expected to have negligible interaction with IBX, and thus exhibit lower reactivity than ketones.[97] An intermolecular competition experiment, shown in equation 10, illustrates these chemoselectivity patterns. Cyclodecanol undergoes a two-step oxidation to afford cyclodecenone in the presence of an equimolar amount of 4-*tert*-butyltoluene, within which the benzylic C–H bonds remain intact.[97] In comparison, 4-*tert*-butyltoluene undergoes oxidation to afford 4-*tert*-butylbenzaldehyde in 95% yield at 80 °C with 3 equivalents of IBX.[97] A variety of other functional groups, including silyl ethers, halides, heterocycles,[97] and carbamates,[100] tolerate the IBX oxidation conditions.



(10)

The scope of IBX-mediated dehydrogenation is dependent on the nucleophilicity and the ease of electron transfer from the substrate. While aldehydes exhibit the highest reactivity under the standard conditions, ketones, including cyclic, and acyclic examples, undergo smooth dehydrogenation.[97] Carbonyl compounds with less acidic α-C–H, such as lactones, lactams, esters, and amides, however, are challenging substrates for IBX. Intramolecular competition experiments showed excellent chemoselectivity among different carbonyl groups (Table 1). Dehydrogenation of an aldehyde is favored relative to a ketone (entry 1).[97] In the presence of an amide group, the primary alcohol fragment of the protected amino acid in entry 2 undergoes selective oxidation to an aldehyde followed by α,β-dehydrogenation of the aldehyde. The dehydrogenation product of 1-octen-7-one contains allylic C–H bonds that are susceptible to further oxidation; however, in the presence of 2 equivalents of IBX, overoxidation into the octatrienone is not observed (entry 3).[97] In contrast, 5α-androst-3,17-dione undergoes sequential dehydrogenation to afford the corresponding dienone in the presence of excess IBX. Selective mono-oxidation to the enone can be achieved with 1.5 equivalents of DMSO with shorter reaction time (entry 4).[97] These observations are consistent with the proposed mechanism, in which formation of a substrate-IBX adduct **14** is required. Such an adduct between 1,5-octadien-7-one and IBX does not enable the required conformation for dehydrogenation of the γ,δ-position, whereas that of 5α-androst-1-ene-3,17-dione is subject to further SET and deprotonation. The cyclopentanone fragment in 5α-androstane-3,17-dione exhibits low reactivity and remains intact. In addition, the mono-dehydrogenation affords 5α-androst-1-ene-3,17-dione, which exhibits the same regioselectivity as DDQ-mediated dehydrogenation of steroids (cf. Section 7.06.2.4).[75]

Oxidation of an unsymmetrical ketone can lead to two different regioisomers. IBX-mediated dehydrogenation of simple cyclic ketones lacks a mechanism to control such regioselectivity. Dehydrogenation of 3-methylcyclohexanone generates 3-methylcyclohexenone and 5-methylcyclohexenone in a 1:2 ratio (Table 2, entry 1), consistent with the statistic ratio of the available hydrogen

Table 1 Chemoselectivity of 2-iodoxybenzoic acid (IBX)–mediated dehydrogenation reactions[97]

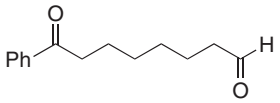
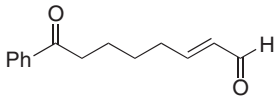
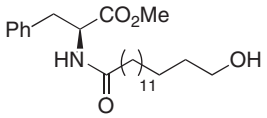
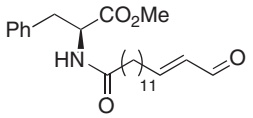
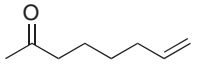
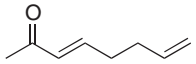
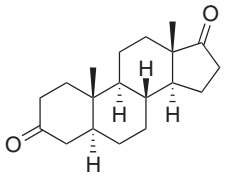
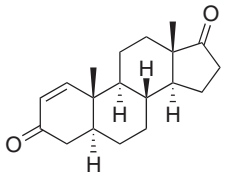
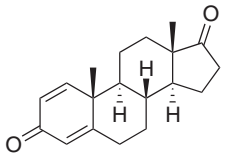
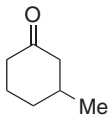
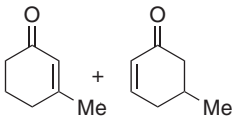
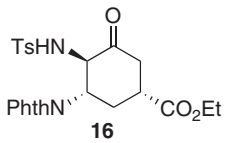
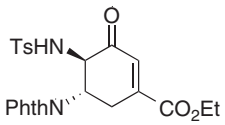
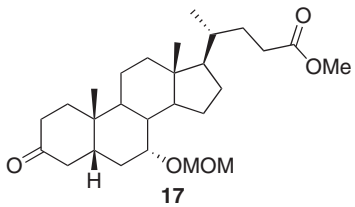
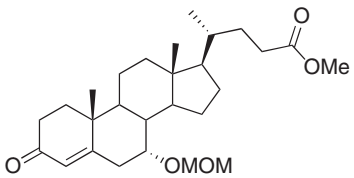
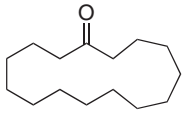
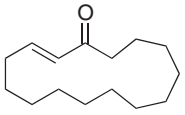
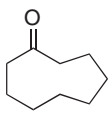
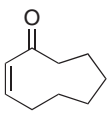
Entry	*Substrate*	*Conditions*	*Product*	*Yield (%)*
1		15 h/70 °C IBX (1.3 equivalents)		79
2		12 h/65 °C IBX (2.5 equivalents)		86
3		12 h/70 °C IBX (2.0 equivalents)		71
4		24 h/70 °C IBX (1.5 equivalents)		84
		48 h/85 °C IBX (4.0 equivalents)		72

Table 2 Regio and stereoselectivity of 2-iodoxybenzoic acid (IBX)-mediated dehydrogenation of cyclic ketones

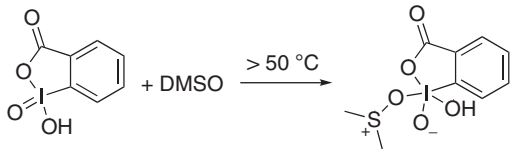
Entry	*Substrate*	*Conditions*	*Enone*	*Yield (%)*	*References*
1		10 h/65 °C IBX (2.0 equivalents)	 1:2	76	97
2	 **16**	120 °C IBX (1.5 equivalents)		>95	101
3	 **17**	25 °C IBX (2 equivalents) trifluoroacetic acid (TFAH) (30 mol%)		87	104
4		24 h/65 °C IBX (2.0 equivalents)		83	97
5		9 h/85 °C IBX (1.8 equivalents)		83	97

for oxidation.[97] Nevertheless, good regioselectivity can be achieved under the influence of various functional groups. Dehydrogenation of 2,3,5-substituted cyclohexanone 16 favors formation of the desired 3,5,6-substituted cyclohexenone derivative in high yield (entry 2).[101] This compound is a synthetic intermediate to Tamiflu.[101] Analogous selectivity for dehydrogenation of the unsubstituted α-C–H is observed in the oxidation of a 2,3,4,5-substituted cyclohexanone fragment in the synthesis of (–)-galbulimima alkaloid 13.[102] The preference for dehydrogenation of unsubstituted α-position is presumably associated with the difficulty of generating substrate-IBX adduct 14 on the α-substituted side because of steric hindrance (cf. **Scheme 15**).[103] Exceptions are observed with steroids, the regioselectivity of which is determined by the stereochemistry of the substrate.[75] For example, dehydrogenation of a 5β-chenodeoxylcholanate derivative 17 forms the more substituted C═C double bond (**Table 2**, entry 3).[104]

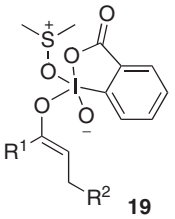
Formation of a C═C bond on dehydrogenation can result in *cis*- and *trans*-stereoisomers. The *cis*/*trans*-stereochemistry is determined by the deprotonation step of the radical cation intermediate (cf. **Scheme 15**). Acyclic carbonyl compounds usually form the *trans*-product (equation 9) because of 1,3-allylic strain.[97] An analogous effect is observed in dehydrogenation of large cyclic ketones, wherein the *trans*-product is favored (**Table 2**, entry 4). Medium rings, however, favor the *cis*-product because of the influence of ring strain (entry 5).

Addition of a catalytic quantity of acid (0.3 equivalent) tends to accelerate IBX-mediated dehydrogenation, whereas a full equivalent of acid inhibits the reaction.[97] The beneficial effect of catalytic acid may arise from the accelerated enolization of the carbonyl group. Alternatively, the conjugate base of the added acid may act as a ligand to activate IBX by coordinating to iodine. Addition of catalytic acid allows milder reaction conditions that improve the functional group tolerance. For example, the methoxymethyl (MOM) protecting group of the chenodeoxylcholanate derivative 17 in **Table 2**, entry 3 decomposes at 85 °C in the presence of IBX. Addition of trifluoroacetic acid (TFAH) or *p*-toluenesulfonic acid (*p*-TsOH) reduces the reaction temperature to 25 °C, and the MOM- group survives.[104]

DMSO is often an essential solvent to dissolve IBX, whereas fluorobenzene or THF are used as cosolvents to enhance the solubility of hydrophobic substrates.[97] These cosolvents exhibit a deterious effect on the reaction rates, however. DMSO is not only a polar solvent, but it is also capable of stabilizing the radical cation generated from the SET step (cf. **Scheme 15**).[105] Moreover, increased temperature triggers formation of an adduct **18** between DMSO and IBX, as revealed by ^{1}H NMR spectroscopic data (equation 11).[106] The adduct **18** is proposed to be a more reactive oxidant. When **18** reacts with a ketone, the resulting intermediate **19** is believed to be stabilized by DMSO coordination and serves as a better electron acceptor.[106]

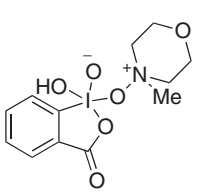


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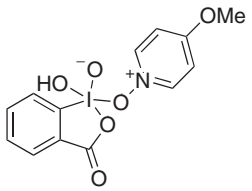


19

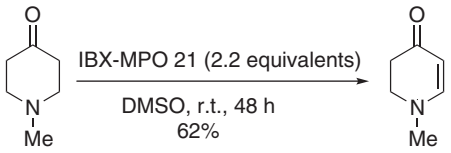
As a result of the beneficial effect of DMSO, a number of ligands have been examined and found to increase the dehydrogenation rate.[106] In particular, complexes between IBX and *N*-methylmorpholine-*N*-oxide (NMO) **20** and 4-methoxypyridine-*N*-oxide (MPO) **21** lead to the fastest reaction rates. MPO hydrate is commercially available and less hygroscopic than NMO. Therefore, MPO represents a user-friendly reagent to promote IBX-mediated dehydrogenation. Comparable yields with various ketone substrates are obtained with **21** at ambient temperature relative to the unligated-IBX at elevated temperature. Dehydrogenation of *N*-methyl 4-piperidone is unsuccessful with unligated-IBX, but is accomplished smoothly by **21** at room temperature (equation 12).



20

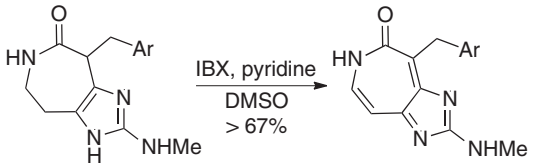


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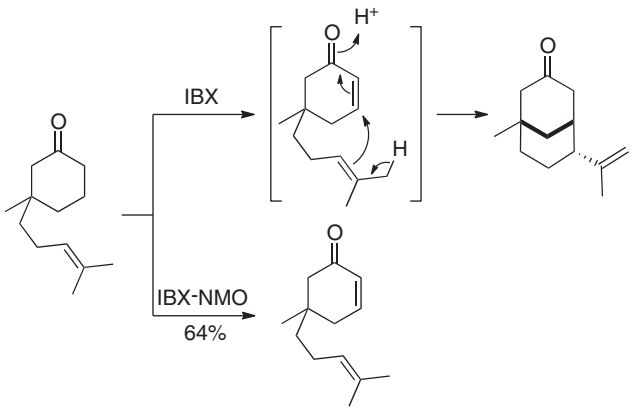
(12)

Although IBX is generally unreactive with amides, an exception is observed with a caprolactam derivative in the presence of pyridine (equation 13).[107] Sequential dehydrogenation leads to the corresponding conjugated lactam, ceratamine B.



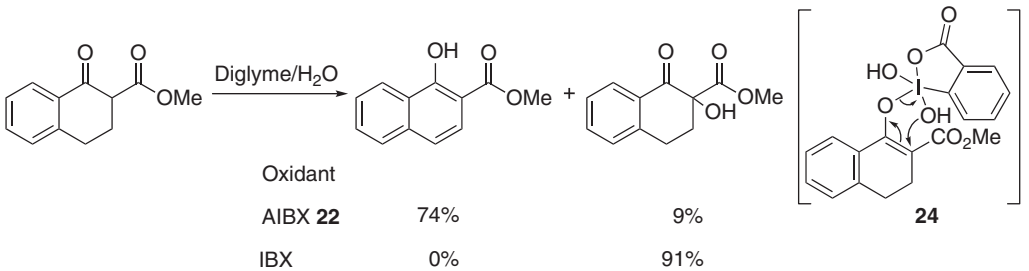
(13)

Williams and coworkers determined the pK_a of IBX to be 2.18 in water and 6.4 in DMSO, and it is typically anionic under the reaction conditions.[108] In contrast, IBX-NMO **20** is less acidic. This feature has important implications in dehydrogenation of acid sensitive substrates. For example, in the preparation of a cyclohexenone derivative as a synthetic precursor to Vibsanin E, the use of IBX leads to tandem acid-catalyzed ene reaction of the cyclohexenone product to afford a bridged bicyclic product (Scheme 16).[108] Conversely, the use of IBX-NMO **20** affords the desired cyclohexenone with no observation of the ene product.[109]

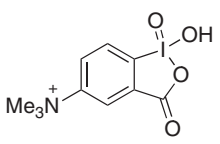


Scheme 16

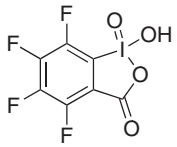
An ionic *para*-trimethylamino-substituted IBX (AIBX) **22** has been prepared that enables efficient dehydrogenation of methyl 1-hydroxy-2-naphthoate in a diglyme and water mixture (Scheme 17).[110] In contrast, IBX leads to the α-hydroxyl product, which was proposed to arise from hydroxyl migration from the iodine to the α-C in intermediate **24**. AIBX is less prone to undergo this pathway, because the positively charged trimethylamino group *para*- to the iodine increases its electron-deficiency and hence promotes the SET pathway. The use of water as a solvent reduces any explosion hazard associated with IBX and organic solvents. Another electron-deficient IBX derivative, tetrafluoro-substituted IBX **23**, is soluble in general organic solvents such as CH_3CN and THF, and displays higher reactivity for alcohol oxidation compared to IBX.[111] Although α,β-dehydrogenation of indanone by **23** was shown to be unsuccessful in a water/CH_3CN mixture, its reactivity for α,β-dehydrogenation of a general ketone substrate has not yet been investigated.



Scheme 17

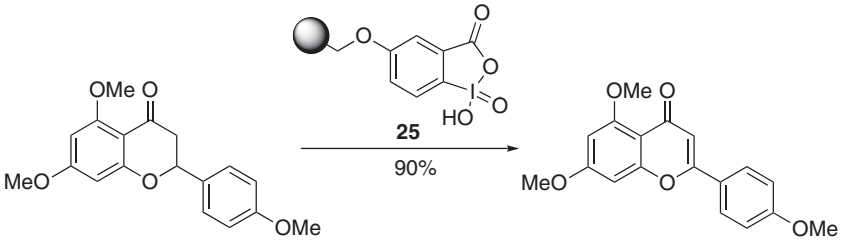


22



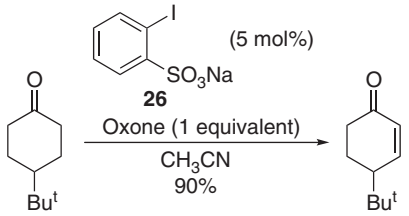
23

These modified IBX variants have addressed some of the limitations of IBX. However, these reagents require multistep synthetic routes starting from expensive reagents, which limit their applications in large-scale processes. Efforts to develop practical and scalable IBX-based reagents have focused on three approaches: (1) attaching IBX to a solid support to facilitate recycling; (2) developing an inexpensive stoichiometric oxidant to regenerate catalytic IBX; and (3) replacing IBX with other inexpensive hypervalent iodine reagents. Rademann and coworkers reported a polystyrene-supported IBX **25**, prepared by esterification of a hydroxyl-substituted IBX precursor with chloromethylpolystyrene.[112] The resulting resin exhibits comparable reactivity (90% yield) for dehydrogenation of methylated naringenin relative to unbound IBX (88% yield) (equation 14).[113] Dehydrogenation reactions mediated by solid-supported IBX also benefit from simple purification procedures. After filtration, the resulting polystyrene-IBA can be collected and regenerated by treating with a solution of tetrabutylammonium oxone and methanesulfonic acid.[112]

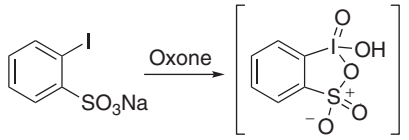


(14)

Catalytic sodium 2-iodobenzenesulfonate **26** in combination with stoichiometric oxone was recently developed for alcohol oxidation and dehydrogenation of cyclic ketones (equation 15).[114] The reaction can be carried out in various organic solvents, including CH_3NO_2, CH_3CN, and EtOAc. Oxone is insoluble in these solvents, and the reaction can be purified by simple filtration. During the reaction, sodium 2-iodobenzenesulfonate **26** is proposed to serve as the precatalyst that forms an IBX analog, 2-iodoxybenzensulfonic acid **27**, on oxidation by oxone (equation 16). Formation of 2-iodoxybenzensulfonic acid **27** is confirmed by ^{1}H NMR spectroscopy, but **27** is too unstable to isolate.[114]



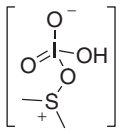
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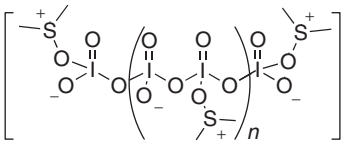
(16)

26 **27**

HIO_3 and its anhydride I_2O_5 represent inexpensive alternatives to IBX.[115] They dissolve in DMSO and generate hypervalent iodine compounds **28** and **29**, respectively, analogous to the IBX-DMSO adduct **14** (cf. **Scheme 15**).[115] Although the substrate scope for **28** and **29** is similar to IBX, they exhibit a superior reactivity with five-membered cyclic ketones, including cyclopentanone, and indanone (**Table 3**, entries 1–2). The conversion of cyclopentanone into cyclopentenone is of particular interest to pharmaceutical companies. Indenone derivatives are synthetic intermediates to a number of natural products,[116] and dehydrogenation of indanone is problematic with previous methods, including bromination-dehydrobromination[21] and use of selenium reagents.[117] When both 5- and 6-membered cyclic ketones are present, **28** is selective for the 6-membered cyclic ketone (entry 3). This selectivity is analogous to IBX.[97] Although IBX lacks selectivity between alcohol oxidation and α,β-dehydrogenation, **28** displays a remarkable chemoselectivity, favoring α,β-dehydrogenation in the presence of an alcohol (entry 4). Nicolaou and coworkers attribute this selectivity to the less basic oxide ligand on HIO_3 relative to the one on IBX.

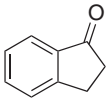
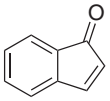
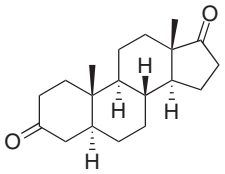
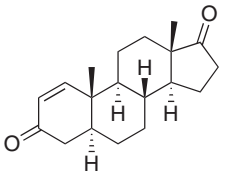
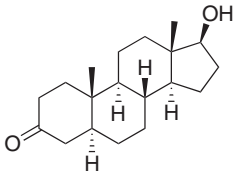
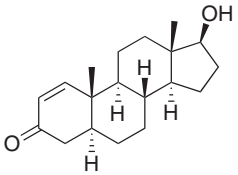


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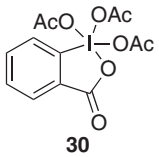
29

Table 3 HIO_3-mediated α,β-dehydrogenation of cyclic ketones[115]

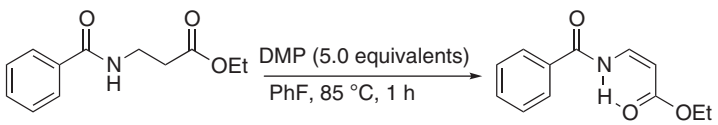
Entry	*Substrate*	*Conditions*	*Product*	*Yield (%)*
1		6 h/45 °C HIO_3 (1.7 equivalents)		74
2		6 h/50 °C HIO_3 (1.7 equivalents)		78
3		6 h/50 °C HIO_3 (1.4 equivalents)		90
4		12 h/50 °C HIO_3 (1.5 equivalents)		92

Note: Reaction conditions: reactions were performed in DMSO with cyclohexenone as the cosolvent, in a sealed tube with light excluded from the vessel.

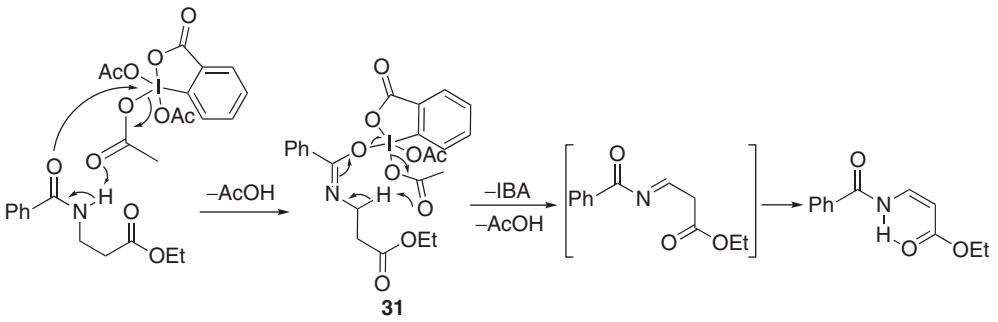
While IBX-mediated dehydrogenation is ineffective for amides and esters. Dehydrogenation of *N*-β-carbonyl amides to the corresponding *cis*-*N*-acyl vinylogous carbamates is achieved with Dess–Martin periodinane (DMP) **30** (equation 17).[118] In contrast to the SET mechanism with IBX-mediated dehydrogenation, DMP-mediated dehydrogenation of *N*-β-carbonyl amides is proposed to proceed via a two-electron transfer pathway (**Scheme 18**). Nucleophilic attack of the amide on the iodine atom of DMP and subsequent deprotonation of the *N*-H by the acetate affords a carboximidate intermediate **31**. The acetate of DMP can deprotonate the α-C–H of the amide of **31** and induce a two-electron transfer to afford the *N*-acyl imine.[118] Fast tautomerization provides the *N*-acyl vinylogous carbamate. The *cis*-geometry of the product is favored because of hydrogen bonding between the carbonyl of the ester and the *N*-H. This reaction, however, is highly restricted to this specific substrate class.



30



(17)

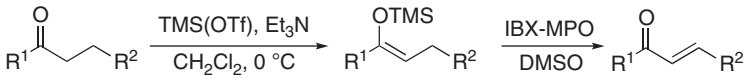


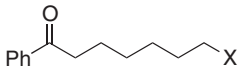
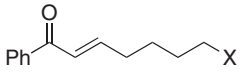
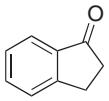
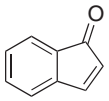
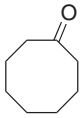
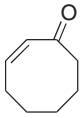
Scheme 18

7.06.3.2 Dehydrosilylation of Silyl Enol Ethers and Esters

Dehydrosilylation of silyl enol ethers and silyl ketene acetals represents a common strategy (cf. Section 7.06.4.1.3) for preparing double bonds adjacent to C═X groups because of their increased reactivity relative to the corresponding carbonyl compounds. Most silyl enol ethers and silyl ketene acetals convert into the carbonyl compounds under the acidic conditions of IBX-mediated reactions; however, treatment of these substrates with the less acidic IBX-MPO **21** conditions lead to efficient dehydrosilylation to the corresponding enones (Table 4).[119] A one-pot process of silylation of a ketone followed by dehydrosilylation by IBX-MPO **21** is possible at room temprature.[119] The mild conditions result in excellent tolerance of functional groups, including methoxy, sulfinyl, and iodo substituents (Table 4, entries 1–3). Although indenone decomposes in the presence of acidic IBX,[21] IBX-MPO **21** performs dehydrosilylation of trimethylsilyloxyindene to afford indenone in excellent yield (entry 4).[119] This method is also effective for mono-dehydrogenation of cyclooctanone to cyclooctenone (entry 5). By comparison, IBX generates cyclooctadienone as the major product.

Table 4 2-Iodoxybenzoic acid(IBX)-MPO mediated dehydrogenation of silyl enol ethers[119]



Entry	*Substrate*	*Conditions*	*Product*	*Yield (%)*
1	 X = OMe	40 h/r.t. IBX-MPO (1.5 equivalents)		96
2	X = OSO_2Me			92
3	X = I			88
4		40 h/r.t. IBX-MPO (1.3 equivalents)		94
5		30 h/r.t. IBX-MPO (1.1 equivalents)		96

The high reactivity of silyl enol ethers allows dehydrogenation of substrates that are challenging with other methods. Direct oxidation of a pyridine fused bicyclic ketone by IBX or IBX-MPO **21** furnishes trace enone product, and organoselenium-mediated elimination affords the product in modest yield (Scheme 19).[120] Converting the ketone to the corresponding silyl enol ether increases its reactivity. $Pd(OAc)_2$-mediated dehydrosilylation proved to be unsuccessful, possibly because of the inhibitory effect of pyridine on the catalyst by coordination to Pd^{II}. In contrast, IBX-MPO **21** provides the desired enone product in good yield. Other recent applications of IBX-MPO **21** mediated dehydrosilylation include the syntheses of platencin,[121,122] platensimycin,[123] and cortistatins A and J.[124]

Sequential silylation-dehydrosilylation is facilitated by numerous methods developed for preparing silyl enol ethers from carbonyl compounds.[125] Common bases for silylation include triethylamine, lithium diisopropylamine (LDA), and lithium bis(trimethylsilylamine) (LiHMDS). TMSCl and TMS(OTf) are the most common trimethylsilylation reagents.[126] The regioselectivity of the silylation of an unsymmetrically substituted ketone (and of the final product) can be controlled by the choice of



1. LHMDS, PhSeCl; 2. $NaIO_4$	44%
IBX, DMSO, 70 °C	Trace
IBX-MPO r.t.	Trace
1. LHMDS, TMSCl; 2. $Pd(OAc)_2$	Trace
1. LHMDS, PhSeCl; 2. IBX-MPO r.t.	80%

Scheme 19

base and reaction conditions.[13] Alternatively, silyl enol ethers can be obtained from within a synthetic sequence, such as a Diels–Alder reaction of Danishefsky's diene[127] or conjugate addition of organometallic reagents (Grignard reagents, cuprates, and organoaluminum reagents) to enones followed by trapping with TMSCl.[106,128]

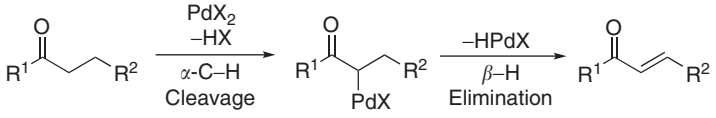
Different silyl groups of the enol ethers have considerable effect on the dehydrosilylation reactivity. TMS- and TES (triethylsilyl)-enol ethers are the most commonly used substrates and afford the desired cyclohexenone as the major product. More stable enol ethers, such as *tert*-butyldimethylsilyl (TBS) enol ethers and vinyl acetates, are inert under the reaction conditions.[106] Methyl and allyl enol ethers, in contrast, undergo hydrolysis as the major pathway. In general, dehydrogenation and dehydrosilylation reactions with hypervalent iodine reagents are not successful for the preparation of α,β-unsaturated esters and amides. These substrates enolize less readily than ketones under direct dehydrogenation conditions, and the corresponding silyl ketene acetals and aminals are more susceptible to hydrolysis.

7.06.4 Transition Metals Reagents and Catalysts

7.06.4.1 Palladium(II)

7.06.4.1.1 Direct dehydrogenation

Pd^{II}-promoted dehydrogenation of C–C bonds adjacent to C═O bonds has been the subject of investigation since the early 1970s.[129] Such reactions are believed to be initiated by 'C–H activation' α to the carbonyl group,[130] forming a Pd-enolate intermediate **32** (Scheme 20),[131,132] which can undergo subsequent β-hydride elimination to afford a C═C double bond.[133,134] This pathway is analogous to the formation of α-sulfoxide/selenoxide intermediates from the reaction of organosulfur/selenium reagents to carbonyl compounds (cf. Section 7.06.2.2). These processes have low transition-state energies because of the formation of organometallic intermediates and the facility of the intramolecular elimination steps. As a result, the reaction conditions are often mild and display good functional group tolerance. Historical studies of stoichiometric Pd^{II}-mediated dehydrogenation reactions provide important insights into the reaction mechanism and a foundation for the contemporary development of catalytic methods that use alternative stoichiometric oxidants.



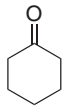
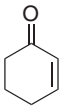
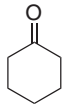
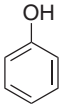
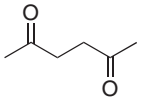
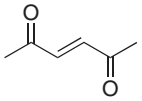
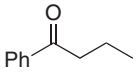
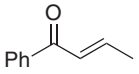
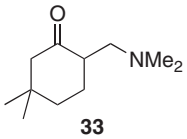
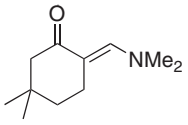
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Scheme 20

Pd^{II}-mediated dehydrogenations of ketones were first developed in the 1970s.[135,136] Early examples focused on cyclic ketones and substrates that can lead to stable conjugated products on dehydrogenation. Several simple Pd^{II} salts were identified as effective reagents. Bierling and coworkers reported the use of $PdCl_2$ as a stoichiometric reagent for dehydrogenation of cyclohexanone to afford cyclohexenone in Bu^tOH (Table 5, entry 1).[135,136] Changing the solvent from Bu^tOH to water results in overoxidation of cyclohexanone to phenol (entry 2). Aromatization of 3,5-dimethylcyclohexenone to the corresponding phenol occurs with the $PdCl_2/Bu^tOH$ conditions.[137]

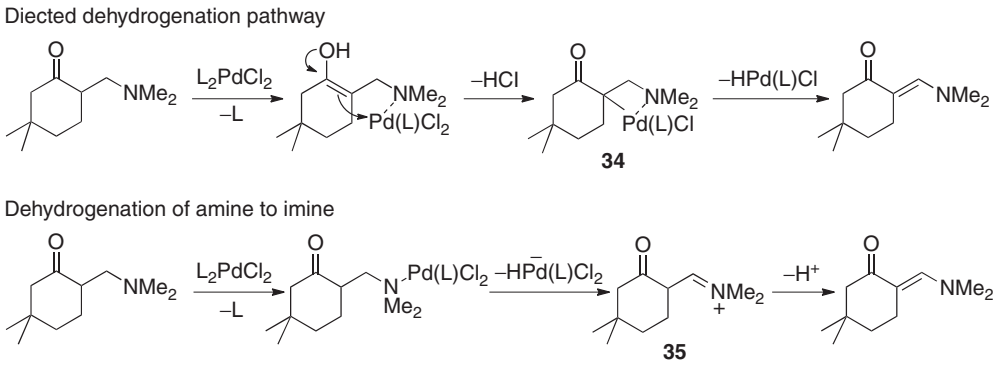
Another Pd complex, $PdCl_2(PhCN)_2$, exhibits good reactivity in the dehydrogenation of 2,5-hexanedione (Table 5, entry 3).[138] Addition of metal salts, such as Ag(OTf) or $Sn(OTf)_2$, to the $PdCl_2(PhCN)_2$ system leads to improved yields with a number of aldehydes and acyclic ketones (entry 4).[139] The beneficial effect of metal additives is proposed to arise from their ability to form

Table 5 α,β-Dehydrogenation of carbonyl compounds with stoichiometric Pd^{II}

Entry	Ketone	Equivalents to Pd^{II}	Product	Conditions	Yield (%)[a]	References
1		50		$PdCl_2$ Solvent: Bu^tOH	82	136
2		17		$PdCl_2$ Solvent: H_2O	95	136
3		3		$PdCl_2(PhCN)_2$ Solvent: Bu^tOH 80 °C, 3 h	90	138
4		1		$PdCl_2(PhCN)_2$ Ag(OTf) or $Sn(OTf)_2$	78	139
5	 **33**	1		$PdCl_2(PhCN)_2$ Et_3N (2 equivalents) Solvent: CH_3CN	95	140

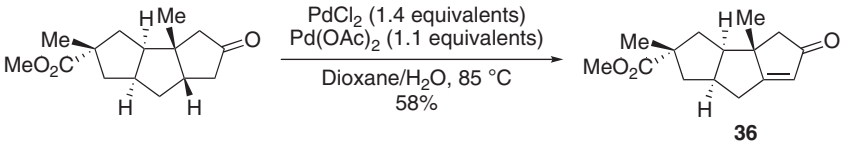
[a]Yields are relative to Pd^{II}.

metal enolates with carbonyl compounds, followed by transmetallation to Pd^{II}. Dehydrogenation of a β-amino ketone 33 with $PdCl_2(PhCN)_2$ selectively generates the β-amino enone product (entry 5).[140] The authors attribute this regioselectivity to amine-directed formation of a Pd-enolate intermediate 34 (Scheme 21). Alternatively, Pd^{II} could first oxidize the amine to an iminium intermediate 35, followed by tautomerization to generate the β-amino enone product. The use of ligand-modified Pd^{II} complexes, including $(Ph_3P)_2PdCl_2$, $Pd(acac)_2$ (acac=acetylacetonate),[141] and $(i\text{-}Bu_2S)_2Pd_3(OAc)_6$,[133] are effective in oxidizing cyclohexanone derivatives.

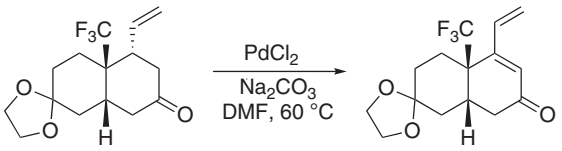


Scheme 21

The use of stoichiometric Pd^{II} complexes as the oxidant for dehydrogenation reactions has found applications in several natural product syntheses on laboratory scale, often with substrates that are challenging with other dehydrogenation methods.[142] For example, a cyclopentenone compound **36** is prepared as a key intermediate in the preparation of (±)-hirsutic acid C in 58% yield by using a combination of stoichiometric $PdCl_2$ and $Pd(OAc)_2$ (equation 18).[143,144] In comparison, selenium-based reagents (cf. Section 7.06.2.3) and Saegusa oxidation (cf. Section 7.06.4.1.3) lead to unsatisfactory overall yields.[143] Many Pd^{II}-mediated dehydrogenation conditions are mild, allowing reactions to take place at room temperature. This feature is beneficial for substrates that are sensitive to harsh oxidation conditions.[145] For dehydrogenation of unsymmetrical cyclic ketones, regioselectivity is possible. Dehydrogenation of a trifluoromethylated bicyclic compound **37** favors formation of the conjugated cyclohexenone product **38** (equation 19).[146] The origin of this regioselectivity is unclear, but the alkene substituent may coordinate to Pd^{II} and direct the enolate formation.

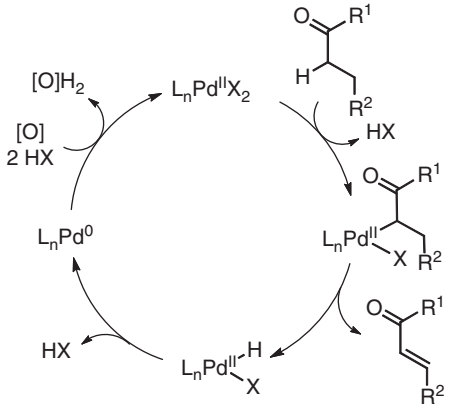


36 (18)



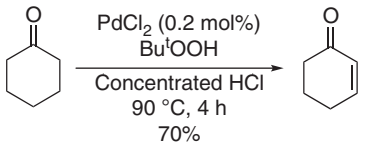
37 38 (19)

Catalytic reactions that employ catalytic Pd^{II} in combination with a stoichiometric oxidant have been achieved by using a Pd^{II}/Pd^{0} catalytic cycle, as illustrated in Scheme 22. The dehydrogenation of ketones by Pd^{II} is consistent with the Pd^{II}-mediated reactions described above (Scheme 20). Pd^{II} reacts with a ketone to form a Pd^{II}-enolate intermediate and subsequent β-hydride elimination affords the corresponding enone. The Pd^{II}-hydride formed in this step can be oxidized by an external oxidant to regenerate the Pd^{II} catalyst. A wide variety of oxidants have been shown to be capable of oxidizing Pd^{0} to Pd^{II}, including Cu^{II} salts, peroxides, phosphates, 1,4-benzoquinone, and O_2. Reactions described below focus on applying these oxidants to Pd-catalyzed dehydrogenation of C═X compounds.

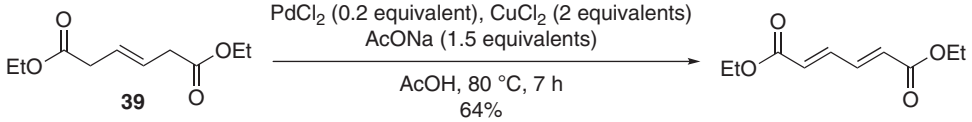


Scheme 22

In addition to $PdCl_2$ being used as a stoichiometric oxidant,[135] $PdCl_2$ has been used as a catalyst in combination with Bu^tOOH (equation 20)[147] or $CuCl_2$ (equation 21) as the oxidant.[148] These methods have been used for dehydrogenation of unsubstituted cyclohexanone and diethyl-3-hexenedioate **39**, respectively. In the latter example, a (π-allyl) palladium intermediate is proposed, formed from deprotonation of the substrate by sodium acetate.[148]



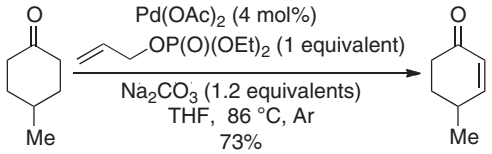
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39 (21)

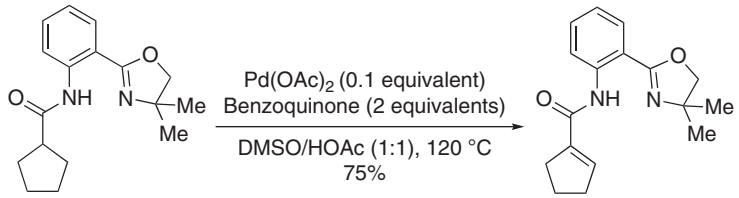
Oxidative addition of allyl esters to Pd^{0} generates (π-allyl)Pd^{II} complexes, which provides the basis for using allyl esters as oxidants for Pd-catalyzed dehydrogenation reactions. Shvo and coworkers report $Pd(OAc)_2$-catalyzed dehydrogenation with diethyl allyl phosphate as the oxidant (equation 22).[149] This method exhibits an improved substrate scope relative to previous methods with Cu^{II} and peroxides. Aldehydes and cyclic ketones undergo dehydrogenation in modest to good yields. The oxidant,

diethyl allyl phosphate, is readily accessible from condensation of the commercially available diethyl chlorophosphate and allyl alcohol.[150]



(22)

The substrate scope of Pd-catalyzed dehydrogenation reactions is highly affected by the acidity of the α-C–H bond. The high α-C–H pK_a values of esters and amides result in poor reactivity under the majority of dehydrogenation conditions. Yu and coworkers employed a tethered oxazoline substituent as the directing group to facilitate $Pd(OAc)_2$-catalyzed dehydrogenation of amide **40** (equation 23).[151] The reaction utilizes 1,4-benzoquinone to regenerate the Pd catalyst. The scope of this reactivity was not explored.



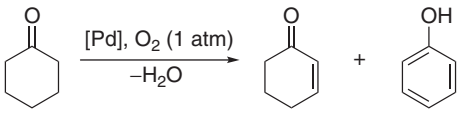
40

(23)

Molecular oxygen is effective as an oxidant in a number of Pd^{II}-mediated oxidation reactions.[152–154] On laboratory scale, 1 atm O_2 can be achieved by using O_2 balloons. In higher pressure and large-scale processes, safety issues associated with mixing O_2 and flammable organic components can be addressed by utilizing dilute O_2 in N_2 (typically, 5–8% O_2).[155]

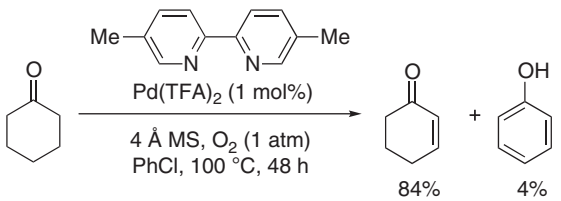
Early efforts of aerobic Pd-catalyzed dehydrogenation reactions focused on simple unsubstituted cyclohexanone with 1 atm O_2.[129] Although cyclohexenone is obtained as the major product, concomitant formation of the side-product phenol is observed under various conditions (**Table 6**). Cocatalysts are often necessary to facilitate the reoxidation of Pd^0 by O_2. Examples include $Cu(acac)_2$, 1,4-benzoquinone and Ag(OTf); however, <30% yields are generally obtained (entries 1–2).[141,156] $Pd(TFA)_2$ is superior to other Pd^{II} sources and the use of unligated $Pd(TFA)_2$ affords cyclohexenone in 51% yield with 13% phenol as a by-product (entry 3).[157] Addition of phosphine ligands fails to improve the yield (entry 4).[158] It is reasonable to anticipate that the phosphine ligands undergo oxidation under aerobic conditions to generate phosphine oxides.

Table 6 Historical examples of Pd-catalyzed aerobic dehydrogenation of cyclohexanone



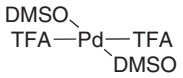
Entry	*Catalyst*	*Cyclohexenone (%)*	*Phenol (%)*	*References*
1	0.2% $Pd(acac)_2$, 20% $Cu(acac)_2$ or 1,4-benzoquinone	19	11	141
2	2% $PdCl(NO_2)(MeCN)_2$, 2% Ag(OTf)	27	1	156
3	2% $Pd(TFA)_2$, r.t., 5 days	51	13	157
4	5% $Pd(TFA)_2$, P(*p*-Tol)$_3$	6	0	158

Improvement of the yield for dehydrogenation of cyclohexanone was reported by Tsuji and coworkers in 2007 using a 5,5′-Me_2bpy-ligated $Pd(TFA)_2$ catalyst (1 mol%, equation 24).[159] Reactions with substituted cyclohexanones, such as 2-*tert*-butylcyclohexanone and 3,5-dimethylcyclohexanone, however, lead to the corresponding cyclohexenones in only 19% and 9% yields, respectively.[159] Dehydrogenation of an acyclic ketone, 4-phenyl-2-butanone, also results in low yield (<20%).



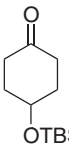
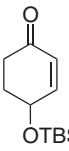
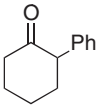
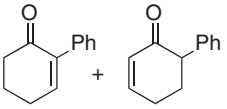
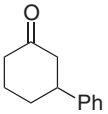
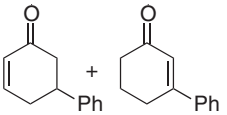
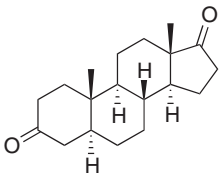
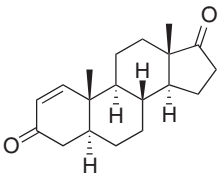
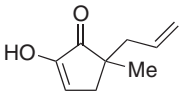
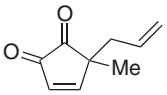
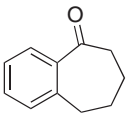
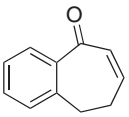
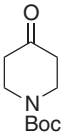
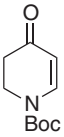
(24)

Diao and Stahl recently reported a $Pd(DMSO)_2(TFA)_2$ catalyst **41** for dehydrogenation of cyclic ketones.[160] The Pd^{II} catalyst has two DMSO ligands, and NMR spectroscopic studies show that one is coordinated via the *S* atom and the other coordinated via the *S* or *O* atom of DMSO.[161] A variety of cyclic ketones undergo aerobic dehydrogenation in the presence of **41** (Table 7). Different solvents, including AcOH, EtOAc, toluene, and DMSO, are used depending on the substrate. Dehydrogenation of 2- and 3-substituted cyclohexanones can lead to two different enone products, and the reactions of 2- and 3-phenylcyclohexanone proceed with modest (~ 3:1) regioselectivity (entries 2 and 3). High regioselectivity is achieved with the 5α-androstane-3,17-dione, affording the less substituted alkene in excellent yield. The cyclopentanone fragment in this steroid is unreactive under the reaction conditions (entry 4). The same selectivity with this steroid substrate has been observed in DDQ and IBX-mediated dehydrogenation.[97] Five- and seven-membered rings also undergo dehydrogenation (entries 5 and 6), and the aerobic conditions are effective with heterocycles, including chromanone and *N*-methyl- and *N*-Boc-piperidone derivatives (e.g., entry 7).



41

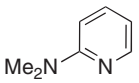
Table 7 $Pd(DMSO)_2(TFA)_2$-catalyzed aerobic dehydrogenation of cyclic ketones[160]

Entry	*Substrate*	*Solvent*	*Enone*	*Yield (%)*[a]
1		AcOH		76
2		EtOAc	 3.0 : 1.0	84
3		EtOAc	 2.7 : 1.0	86
4		AcOH		93
5		EtOAc		90[b]
6		Toluene		81
7		DMSO		72

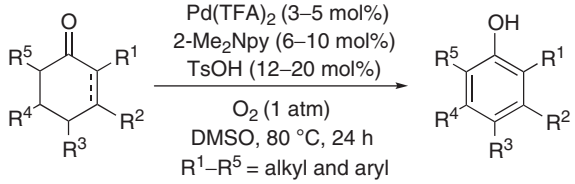
[a]Reactions conditions: $Pd(TFA)_2$ (5 mol%), DMSO (10 mol%), O_2 (1 atm).
[b]$Pd(TFA)_2$ (10 mol%), DMSO (30 mol%), O_2 (1 atm).

A different catalyst system, consisting of $Pd(TFA)_2$/2-*N*,*N*-dimethylpyridine (2-Me_2Npy) **42**/*p*-TsOH promotes dehydrogenation of cyclohexanones to phenol derivatives (equation 25).[162] A number of alkyl and aryl-substituted cyclohexanones and

cyclohexenones undergo aromatization under these conditions in the presence of various functional groups.[162] The abundant methods for preparing substituted cyclohexanone and cyclohexenone derivatives, including conjugate addition, annulation, and substitution reactions, suggest this reaction class could be a useful route to substituted phenol derivatives.

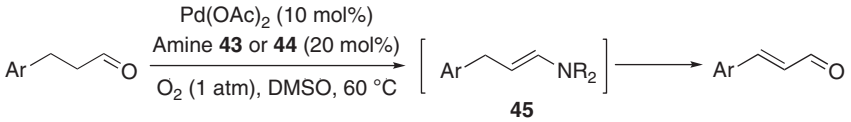


42



(25)

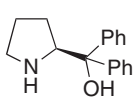
The first example of Pd-catalyzed direct dehydrogenation of aldehydes was reported with $Pd(OAc)_2$ and amine additives **43** or **44** as cocatalysts (Scheme 23).[163,164] Hydrocinnamaldehyde derivatives have more acidic α-C–H bonds relative to ketones and other carbonyl compounds, and they form the conjugated cinnamaldehyde product in modest yield on dehydrogenation (Scheme 23). The amine additives are proposed to activate hydrocinnamaldehyde by forming an enamine intermediate **45**. β-Arylbutanones, such as benzylacetone, have a similar structure, but these ketone substrates do not react under the same conditions.[163]



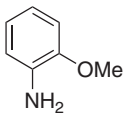
45

Yield = 41–72%

Scheme 23

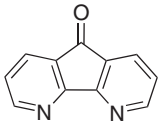


43



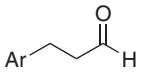
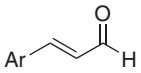
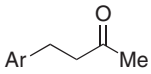
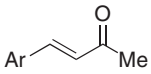
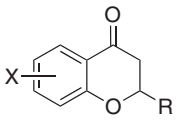
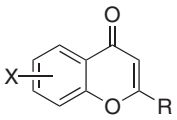
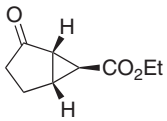
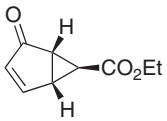
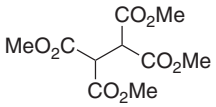
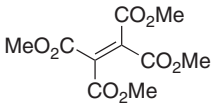
44

A $Pd(OAc)_2$/4,5-diazafluorenone (**46**) catalyst promotes aerobic dehydrogenation of hydrocinnamaldehyde derivatives with improved yield (Table 8, entries 1 and 2).[165,166] The cinnamaldehyde product undergoes slow oxidative decomposition under the conditions, evident from formation of benzaldehyde as a by-product.[166] This catalyst system is also successful for dehydrogenation of β-arylbutanone derivatives at elevated temperatures to form the corresponding β-arylbutenones (entry 3).[166] The more-forcing conditions for dehydrogenation of ketones relative to aldehydes are consistent with the less acidic α-C–H of ketones. Although the ligand **46** is proposed to stabilize the Pd catalyst,[166] unligated $Pd(OAc)_2$ in combination with K_2CO_3 in DMF also leads to dehydrogenation of β-arylbutanones in high yields (entry 4).[165] The diazafluorenone catalyst system promotes dehydrogenation of chromanone and flavanone derivatives to the corresponding chromones and flavones, which have important biological activities (entry 5).[166] A bicyclic cyclopentanone derivative is a key precursor to an anatagonist of the metabotropic glutamate receptor (mGluR),[167] and this substrate undergoes dehydrogenation under higher pressure O_2 (entry 6).[166] These conditions have limited success with carbonyl compounds with less acidic α-C–H bonds, such as esters and amides.[165,166] Only the very active ethanetetracarboxylate **47** undergoes dehydrogenation with the $Pd(OAc)_2/K_2CO_3$ catalyst (entry 7).[165] Dehydrogenation of acyclic ketones lacking an aryl group in the β-position are susceptible to further dehydrogenation at the γ,δ-position and result in a mixture of enone and dienone products.[166]



46

Table 8 Pd-catalyzed direct dehydrogenation of ketones

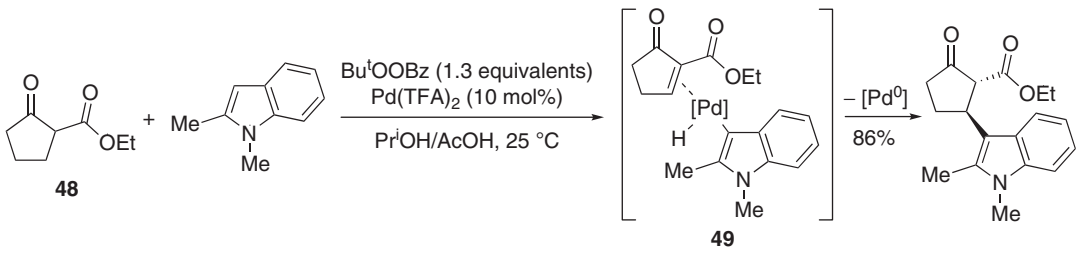
Entry	Substrate	Enone	Conditions[a]	Yield (%)	References
1			A	Ar = Ph, 91	166
2			B	66–88	165
3			A	83–87	166
4			C	53–95	165
5			A	X = OH, Br, Cl R = H or Ar 81–96%	166
6			A	79[b]	166
7	 **47**		C	99[c]	165

[a]Conditions: A: $Pd(TFA)_2$ (5 mol%), **46** (5 mol%), DMSO, 80–100 °C, 1 atm O_2; B: $Pd(OAc)_2$ (6 mol%), **46** (9 mol%), K_2CO_3 (10 mol%), DMF, 30 °C, air; C: $Pd(OAc)_2$ (6 mol%), K_2CO_3 (10 mol%), DMF, 110 °C, air or 1 atm O_2.
[b]7.2 atm O_2 (9% in N_2).
[c]60 °C.

These examples of Pd-catalyzed direct dehydrogenation demonstrate the possibility of using O_2 as the oxidant, and they reveal the challenges and opportunities in this field. Substrates that are susceptible to further dehydrogenation at the γ,δ-position often result in a mixture of products with various degree of oxidation. Catalysts that can perform selective oxidation to afford one product relative to others would be particularly valuable. Substrates with less acidic α-C–H bonds, including esters and amides, are unreactive with current Pd catalysts. In addition, decomposition of the Pd catalyst is observed in many reactions with insufficient gas-liquid mixing at low O_2 pressure.

7.06.4.1.2 Tandem dehydrogenation-enone functionalization

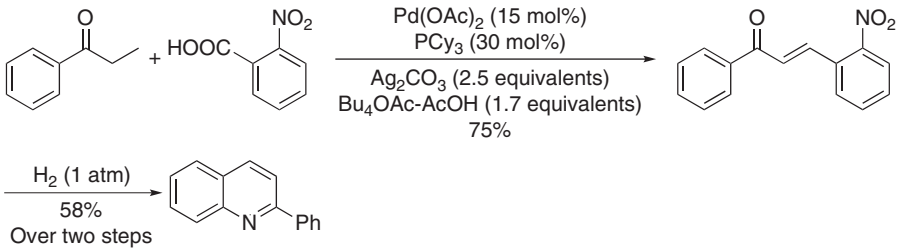
Pd-catalyzed α,β-dehydrogenation reactions have been used in several tandem reactions that involve dehydrogenation and enone functionalization in one pot. These reactions are inspired by the known transmetallation and reductive elimination reactions of Pd^{II} organometallic intermediates. Pihko and coworkers reported oxidative coupling of β-keto-ester **48** with indole at the β'-position to produce β'-aryl-β-keto ester, in the presence of catalytic $Pd(TFA)_2$ and *tert*-butyl perbenzoate (Bu^tOOBz) as the oxidant (Scheme 24).[168] The reaction is proposed to proceed via an indolyl-Pd^{II} intermediate with a coordinated α,β-unsaturated β-keto-ester (**49**). Insertion of the alkene into the indolyl-Pd bond followed by C–H reductive elimination from Pd^{II} could generate the product and Pd^0. The olefin insertion step accounts for the *anti* selective stereochemistry of the product. $Pd(OAc)_2$ also catalyzes oxidative coupling of β-keto ester **48** with electron-rich arenes under aerobic conditions.[169]



Scheme 24

Tricyclohexylphosphine-ligated $Pd(OAc)_2$ catalyzes decarboxylation of 2-nitrobenzoic acid followed by dehydrogenative coupling with propiophenone. A second dehydrogenation step then furnishes a β-aryl enone product (Scheme 25).[170] *In situ*

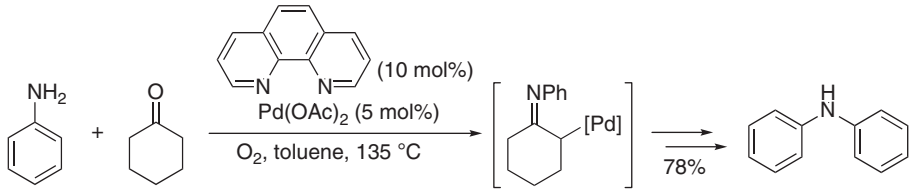
reductive cyclization of the product under an H_2 atmosphere affords 2-aryl quinoline, in which the Pd from the previous step is reduced to Pd^0 and serves as a hydrogenation catalyst.[170] Propiophenone also undergoes dehydrogenative coupling with heterocycles, such as thiophenes, furans, and indoles, under similar conditions.[171]



Scheme 25

Chromanones undergo Pd-catalyzed sequential dehydrogenation/arylation at the β-position in the presence of a Cu^{II} cocatalyst and Ag^{I} as the oxidant.[172] The same conditions also lead to dehydrogenation of 1-methyl-2,3-dihydroquinolin-4(1H)-ones, and these products can undergo subsequent Pd-catalyzed oxidative Heck reaction with *tert*-butyl acrylate via C–H activation of the α-position of quinolinone.[172]

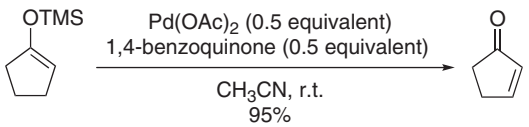
Inspired by Pd-catalyzed aerobic dehydrogenation of cyclohexanone derivatives to phenols (cf. equation 25),[162] several groups have reported dehydrogenative synthesis of substituted arylamine[173–175] and aryl ether[176] derivatives via tandem condensation-dehydrogenation reactions of amines or alcohols with cyclohexanones or cyclohexenones. For example, Ph_2MeP-ligated Pd^{II} catalyzes aerobic dehydrogenative coupling of piperidine with cyclohexenones to afford a series of aryl amines.[173] Sequential condensation–dehydrogenation of aniline to cyclohexanones is also achieved with a 1,10-phenanthroline-ligated $Pd(OAc)_2$ catalyst (Scheme 26).[173] The authors propose that α-palladation occurs after condensation of the amine/aniline with cyclohexenone/cyclohexanone (Scheme 26).[173] A similar Cu-catalyzed method has been developed for oxidative condensation of alcohols to cyclohexenones followed by dehydrogenation to furnish aromatic ethers.[177]



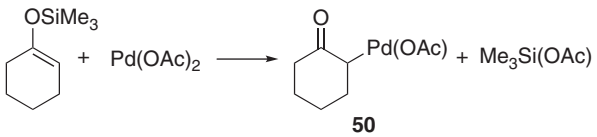
Scheme 26

7.06.4.1.3 Dehydrosilylation of silyl enol ethers

Silyl enol ethers are readily accessible from the corresponding carbonyl compounds and are more reactive than the parent aldehydes and ketones.[125] Saegusa and coworkers reported the first dehydrosilylation of trimethylsilyloxyalkene derivatives to generate α,β-unsaturated enones, using substoichiometric $Pd(OAc)_2$ (0.5 equivalent) in combination with 1,4-benzoquinone as a cooxidant (equation 26).[178] Cleavage of the trimethylsilyl group is expected to be mediated by $Pd(OAc)_2$, forming a Pd-enolate intermediate **50** (equation 27), analogous to the intermediate formed from Pd-mediated direct dehydrogenation of ketones (cf. Schemes 20 and 22). Subsequent β-H elimination from **50** affords the corresponding enone product and Pd–H. Alkyl enol ethers are synthetic equivalents to silyl enol ethers, but have received less attention for preparing α,β-unsaturated carbonyl compounds because of the limited scope. $Pd(OAc)_2$-catalyzed conversion of alkyl enol ethers to enals has been reported.[179]



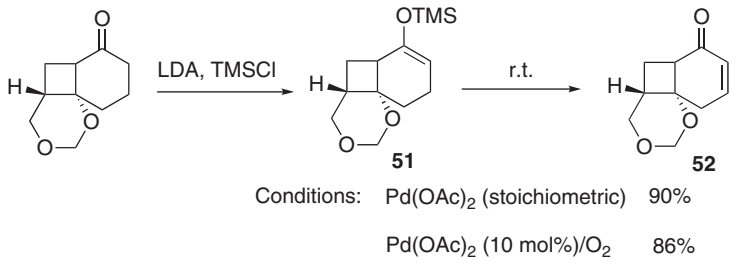
(26)



50

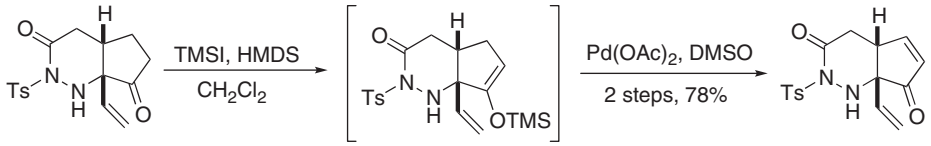
(27)

In the process of preparing a tricyclic enone **52** for the synthesis of taxane, Larock and Kraus developed a method for aerobic dehydrosilylation using a catalytic quantity of $Pd(OAc)_2$ (Scheme 27).[180] Catalytic $Pd(OAc)_2$ in DMSO under 1 atm O_2 leads to dehydrosilylation of trimethylsiloxycyclohexene derivative **51** to afford **52** in a yield comparable to that obtained with stoichiometric $Pd(OAc)_2$.[181] The DMSO solvent is expected to serve as a ligand and stabilize the Pd catalyst under aerobic conditions.[182,183] Oxone has also been used under aerobic conditions to facilitate catalyst regeneration in dehydrosilylation reactions.[184] The intrinsically higher reactivity of silyl enol ethers with Pd^{II} enables good conversion of substrates that are challenging under direct dehydrogenation conditions (cf. Section 7.06.4.1.1), such as highly substituted cyclic ketones[185] and indenone.[186] In addition, the mild conditions are beneficial for compounds with sensitive functional groups. These features result in extensive utility of Saegusa dehydrosilylation in natural product and pharmaceutical syntheses.[101]



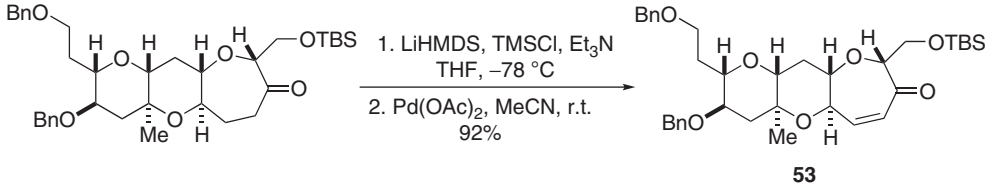
Scheme 27

A large number of methods are available for preparing silyl enol ethers, thereby enhancing the utility of Saegusa-type dehydrosilylation reactions.[125] Both kinetic[187] and thermodynamic[188] silyl enol ethers are readily available by varying the conditions. Although TMSCl and TMSOTf are the common trimethylsilylation reagents, particular substrates often require optimization of the conditions for making silyl enol ethers. For example, a bicyclic cyclopentenone intermediate is a precursor to palau'amine and has been synthesized by dehydrosilylation with stoichiometric $Pd(OAc)_2$ in DMSO in 78% yield (Scheme 28).[189] Silylation of the cyclopentanone fragment requires use of TMSI in combination with bis(trimethylsilyl)amine (HMDS), whereas conventional silylation reagents such as TMSCl and TMSOTf fail to afford the desired trimethylsilyloxycyclopentenone. Meanwhile, other dehydrogenation protocols, including halogenation–dehydrohalogenation, selenium reagents and IBX, proved to be unsuccessful with this substrate.[189]



Scheme 28

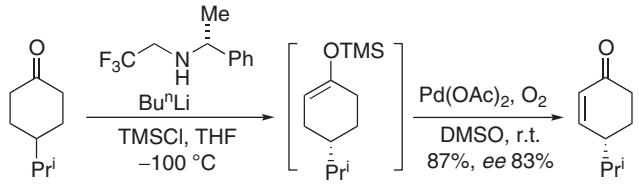
Most sequential trimethylsilylation–dehydrosilylation reactions require isolation and purification of the silyl enol ether intermediate. In some cases, however, only solvent removal after the silylation step is necessary and the resulting mixture can be directly subjected to Pd^{II}-mediated dehydrosilylation. For instance, dehydrogenative synthesis of the 3-oxepinone derivative **53**, as an intermediate for (–)-gambierol, proved to be unsuccessful with selenium reagents and IBX (equation 28).[190] One-pot silyl enol ether formation followed by $Pd(OAc)_2$-mediated dehydrosilylation affords 3-oxepinone **53** in good yield. Analogous Saegusa procedures have also been used in the synthesis of enone intermediates to palau'amine and (+)-aspidospermidine.[191]



(28)

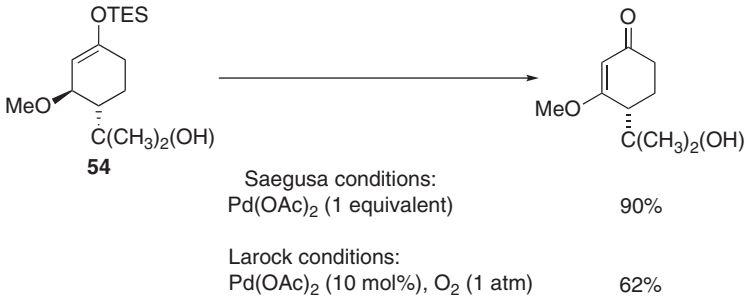
In addition to control of regioselectivity, sequential silyl enol ether formation-dehydrosilylation provides a means to control product stereochemistry. Chiral bases have been developed for enantioselective deprotonation of 4-substituted cyclohexanones to generate the corresponding chiral silyl enol ethers (Scheme 29).[192–194] The subsequent dehydrosilylation step retains the stereochemical configuration.[195] This strategy has found applications in the enantioselective synthesis of a fragment of Labiatin[196]

and a fumagillin analog, as a potential MetAP-2 reversible inhibitor.[197] Despite great potential in synthesis, this strategy is limited by the lack of chiral bases leading to highly enantioselective deprotonation under practical conditions. The best reported *ee* obtained with chiral bases requires temperatures as low as − 100 °C.

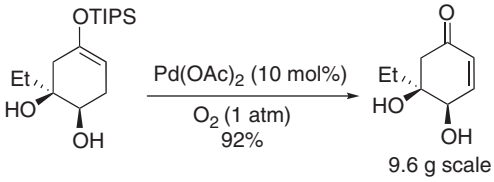


Scheme 29

The identity of the silyl group has a significant influence on the substrate reactivity. In dehydrosilylation of a triethylsilyloxycyclohexene derivative **54**, Saegusa conditions with stoichiometric $Pd(OAc)_2$ afford the corresponding cyclohexenone in good yield, whereas catalytic conditions result in modest yield (**Scheme 30**).[127] This product is a precursor to the natural product (–)-platyphyllide. In the total synthesis of (–)-lomaiviticin aglycon, the aerobic catalytic conditions are successful, producing the desired cyclohexenone intermediate on a 9.6 g scale via dehydrosilylation of a triisopropylsilyloxy cyclohexene precursor (equation 29).[198] Although $Pd(OAc)_2$ is known to be capable of oxidizing alcohols to ketones, the secondary alcohol substituent in the substrate just noted does not interfere with or undergo reaction under the dehydrosilylation conditions.

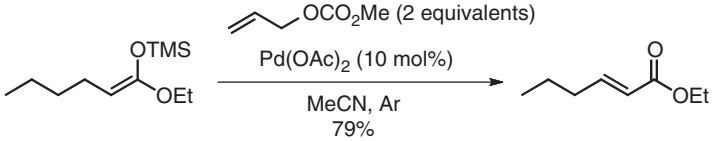


Scheme 30



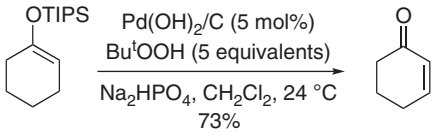
(29)

The Saegusa/Larock dehydrosilylation conditions are versatile for a variety of trimethylsilyloxyalkenes derived from cyclic and acyclic ketones and aldehydes, but attempts to oxidize silyl ketene acetals typically result in low yields because of the hydrolysis of the substrate to the corresponding esters.[180] Tsuji and coworkers achieved catalytic dehydrosilylation of silyl ketene acetals with $Pd(OAc)_2$ under Ar, using allyl methyl carbonate as the stoichiometric oxidant (equation 30).[199] Several unsaturated esters and lactones have been prepared via this reaction.[200]



(30)

A heterogenous catalyst, $Pd(OH)_2/C$, has been reported by Corey and coworkers for dehydrosilylation of triisopropylsilyloxy cyclic alkene derivatives, using *t*-BuOOH as the oxidant (equation 31).[201] Analogous to the Saegusa and Larock conditions, $Pd(OH)_2/C$-catalyzed dehydrosilylation proceeds at room temperature. The substrate scope includes silyl enol ethers derived from 5- and 6-membered cyclic ketones.



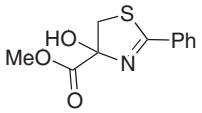
(31)

7.06.4.2 Other Transition Metals

7.06.4.2.1 Direct dehydrogenation

A number of transition metals other than Pd, including Cu, Ni, and Mn, promote dehydrogenation reactions as well. These reactions probably involve different mechanisms and, therefore, exhibit different substrate scope. Pd-catalyzed dehydrogenation of heterocycles can suffer from oxidative degradation of the product and/or catalyst poisoning by strong coordination of heteroatoms to the electrophilic Pd^{II} center. Interactions between heterocycles and other heteroatom-containing functional groups and first-row metals tend to be more labile. Barrish and coworkers demonstrated that in the presence of 2 equivalents of $Cu^{II}Br_2$ and DBU, 4-carboxyoxazoline undergoes dehydrogenation to afford 4-carboxyoxazole (Table 9, entry 1).[202] These conditions have been used to prepare a synthetic precursor to calyculin C.[203] Meyers and coworkers reported a similar dehydrogenation reaction with 4-carboxyoxazoline derivatives, using stoichiometric Cu^{I} salts in combination with *tert*-butyl perbenzoate as the oxidant (entry 2).[204,205] A catalytic method for the oxidation of dihydrocoumarin and other oxazoline and thiazoline derivatives has been achieved by Shi and coworkers with the Cu^{I} loading reduced to 10% in the presence of *N*,*N*-di-*tert*-butyldiaziridinone as the oxidant (entry 3).[206] Aerobic oxidation of 4-carboxythiazolines to the corresponding thiazoles is achieved with $Cu(OAc)_2$[207] and a diimine-ligated dicationic Cu^{II} catalyst (entries 4 and 5).[208] The former catalyst is also effective in dehydrogenating 4-carboxyoxazolines,[207] whereas oxidation of 4-carboxyoxazoline with the latter catalyst leads to dramatically decreased yields.[208] Stoichiometric nickel peroxide promotes dehydrogenation of 4-carboxyoxazolines and flavanone in moderate yields (entries 6 and 7).[209] In addition, manganese dioxide is another inorganic oxidant capable of dehydrogenating 4-carboxyoxazolines[210] (entry 8) and thiazolines.[211]

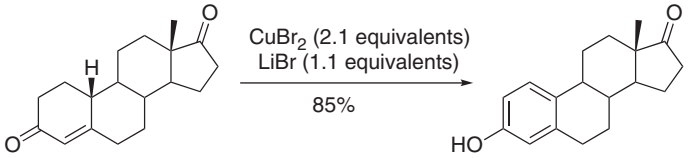
Despite limited mechanistic characterization, the dehydrogenation reactions presented above are expected to proceed via radical or other single-electron mechanisms. For example, Scheme 31 illustrates a mechanism for $Cu^{I}Br$-catalyzed dehydrogenation of a 4-carboxyoxazoline proposed by Meyers and coworkers.[204] The reaction is initiated by oxidation of Cu^{I} to Cu^{II} by *tert*-butyl perbenzoate with concomitant formation of *tert*-butoxyl radical **55** (Kharasch–Sosnovsky reaction).[212] The *tert*-butoxyl radical **55** abstracts a hydrogen atom from the oxazoline to form a radical intermediate **56**, which is stabilized by the adjacent carboxylate and the imine groups. Further oxidation of **56** by the Cu^{II} species affords an acyloxyoxazoline, followed by fast elimination to afford the corresponding oxazole. The diimine Cu catalyst system does not involve long-lived radical intermediates (Table 9, entry 5), as revealed by the lack of inhibitory effect of added radical inhibitors.[208] An α-hydroxyl intermediate **57** is observed, in which the oxygen atom originates from O_2, as supported by isotope labeling studies.



57

In the absence of a transition metal, K_2CO_3 can promote similar aerobic oxidation of 4-carboxythiazoline derivatives to the corresponding thiazoles (Scheme 32).[213] The 4-peroxide **58** and 4-hydroxide **59** intermediates were observed during the reaction; the latter was also isolated and characterized. Intermediate **58** presumably arises from reaction of an ester enolate with O_2. A different base, DBU, promotes similar reactivity with 4-carboxythiazolines.[208] Other herocycles, such as oxazolines react with considerably lower yields.

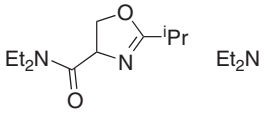
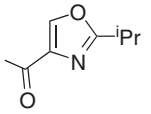
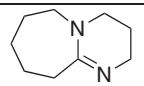
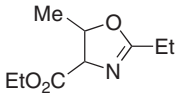
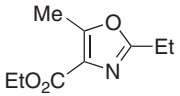
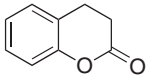
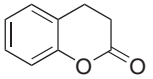
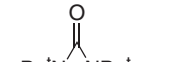
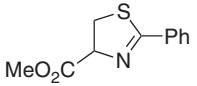
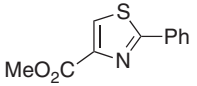
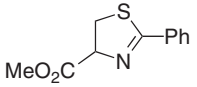
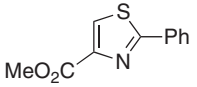
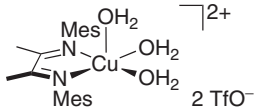
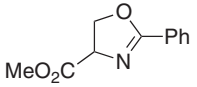
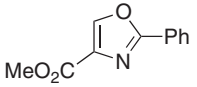
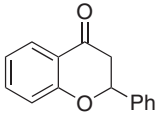
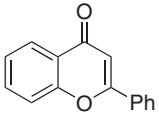
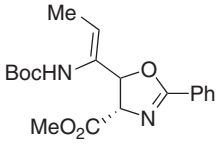
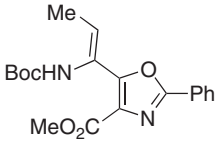
Cu^{II} salts have been used to convert cyclohexenone derivatives into phenols. Stoichiometric $CuBr_2$ oxidizes the cyclohexenone fragment of estr-4-ene-3,17-dione to the corresponding phenol (equation 32),[214] leaving the cyclopentanone fragment intact. In the synthesis of moluccanic acid ester, $CuBr_2$ dehydrogenates the cyclohexenone moiety to the corresponding phenol.[215]

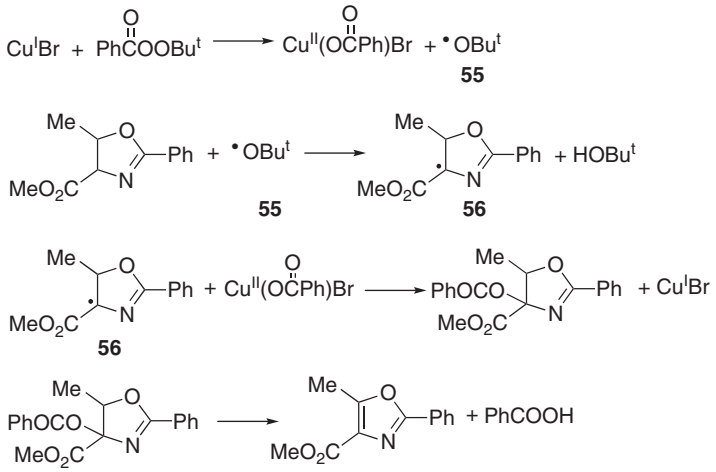


(32)

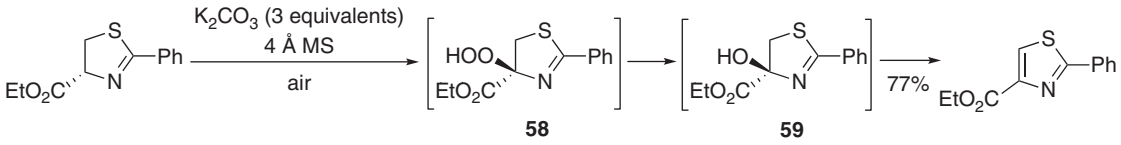
Cu and Ni are capable of catalyzing tandem coupling-dehydrogenation reactions similar to the Pd-catalyzed reactions described above (Section 7.06.4.1.2). For example, $Cu(OTf)_2$-catalyzed condensation of alcohols to cyclohexenones followed by

Table 9 Cu, Ni, and Mn-promoted dehydrogenation of heterocycles

Entry	*Substrate*	*Product*	*Catalyst/additive*	*Oxidant*	*Yield (%)*	*References*
1			 DBU (2 equivalents)	$Cu^{II}Br_2$(2 equivalents)	65	202
2			$Cu^{I}Br$(1.1 equivalents)	 (1.5 equivalents)	63	204
3			$(PPh_3)CuCl$(10 mol%)	 (2 equivalents)	60	206
4			$Cu(OAc)_2$ (10 mol%)	O_2(1 atm)	92	207
5			 DBU (10%)	air	88	208
6				$Ni^{II}O_2$(1.5 equivalents)	69	209
7				$Ni^{II}O_2$(1.6 equivalents)	71	209
8				$Mn^{IV}O_2$	42	210

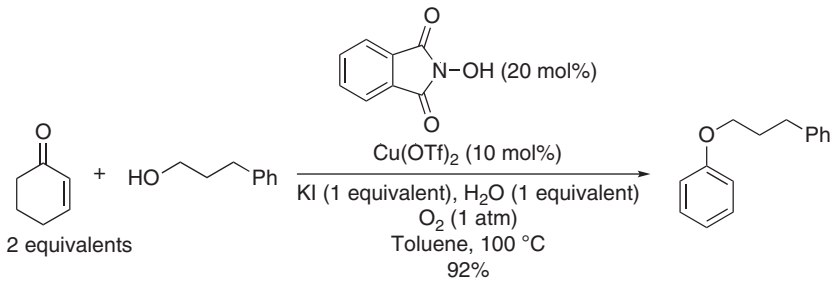


Scheme 31

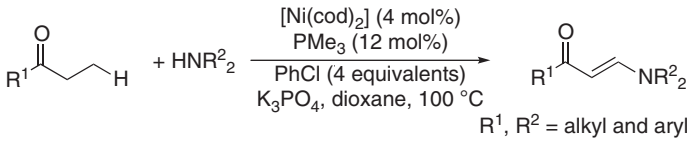


Scheme 32

aerobic dehydrogenation generates aromatic ethers in one step (equation 33).[177] *N*-Hydroxyphthalimide is used as a cocatalyst. It generates phthalimido-*N*-oxyl (PINO) radical *in situ*, which mediates hydrogen-atom abstraction from the substrate. Trimethylphosphine-ligated Ni^0 catalyzes dehydrogenative coupling of propiophenone and secondary amine via a Ni^0/Ni^{II} catalytic cycle with chlorobenzene as the oxidant (equation 34).[216]

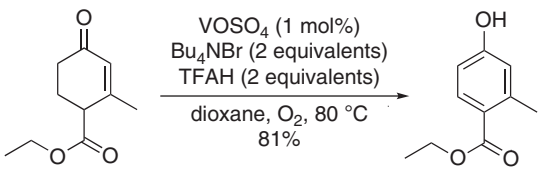


(33)



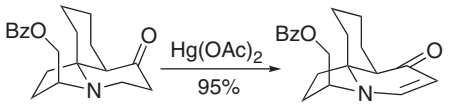
(34)

A vanadium catalyst, $VOSO_4$, mediates aerobic dehydrogenation of 3-methyl-4-ethylcarboxycyclohexenone to the corresponding phenol (equation 35).[217] Electron-rich substrates, such as 3,5-dimethylcyclohexenone, however, undergoes aryl bromination in addition to dehydrogenation, to afford 2,4,6-tribromo-3,5-dimethylphenol.



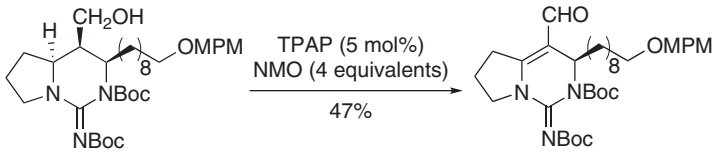
(35)

Stoichiometric metal-based oxidants have been used to achieve α,β-dehydrogenation of challenging substrates. Padwa and coworkers reported the use of $Hg(OAc)_2$ to oxidize an azadecalin ring into the corresponding 2*H*-piperidonyl enone in the total synthesis of (±)-cylindricine C (equation 36).[218] A variety of the aforementioned oxidative methods and reagents, including α-halogenation/elimination, $PhSeCl/H_2O_2$, IBX, and Saegusa dehydrosilylation, failed to produce any useful quantity of the cyclohexenone product.[219]



(36)

Tetrapropylammonium perruthenate (TPAP) is commonly used to oxidize alcohols to aldehydes and ketones.[220] Catalytic TPAP was used in combination with 4-methylmorpholine *N*-oxide (NMO) to mediate the synthesis of (+)-batzellatin A in a one-pot oxidation of the guanidine derived primary alcohol **60** to the corresponding β-amino enal in modest yield (equation 37).[221] The reaction is regioselective; only the desired enal isomer is produced.

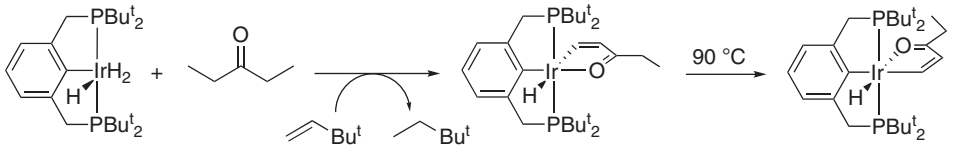


60

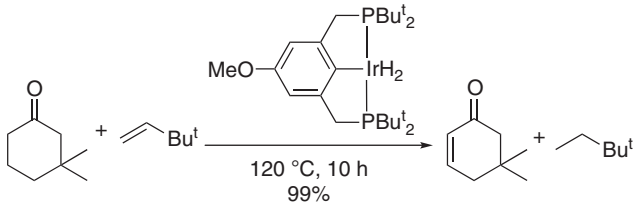
(37)

7.06.4.2.2 Transfer dehydrogenation

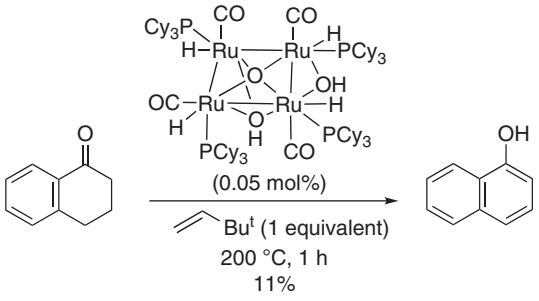
Transfer dehydrogenation reactions with an inexpensive alkene as a hydrogen acceptor have been used to convert saturated ketones into the corresponding α,β-unsaturated ketones. The substrate scope of these reactions is currently quite limited, because aromatic and heteroatom functional groups often poison the catalyst.[222] **Scheme 33** illustrates one of the pathways of forming an inactive cyclometallated complex after dehydrogenation of 3-pentanone by a 'PCP pincer'-Ir catalyst.[223] An exception is observed with 3,3-dimethylcyclohexanone, where cyclometallation is prohibited by the substitutents, and 5,5-dimethylcyclohexenone is obtained in good yield (equation 38). A tetra-nuclear ruthenium cluster mediates dehydrogenation of α-tetralone into 1-naphthol in low yield (equation 39).[224]



Scheme 33



(38)

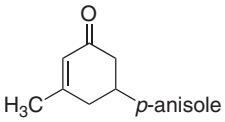
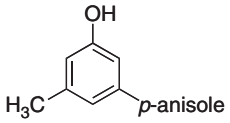
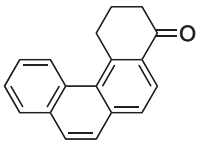
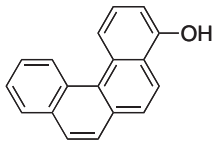
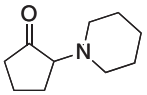
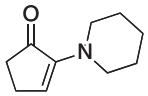
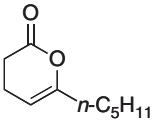
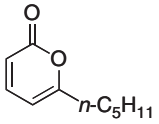


(39)

7.06.4.3 Heterogeneous Catalysts

Heterogenous catalysts for dehydrogenation typically require harsh conditions and constant removal of H_2 to drive the reaction forward. The conversion of cyclohexanone derivatives into the corresponding phenols benefits from the thermodynamic driving force of aromatization, and reactions of this type have been the primary focus of heterogenous catalytic dehydrogenation. Several examples of Pd/C-catalyzed dehydrogenation reactions have been developed (Table 10). Aromatization of cyclohexenones and benzo-fuzed cyclohexanones takes place at high temperatures in the presence of catalytic Pd/C (entries 1 and 2).[225,226] In addition, mono-dehydrogenation is achieved with α-piperidylcyclopentanone (entry 3);[227] and a γ,δ-unsaturated lactone derivative undergoes dehydrogenation to afford a pyranone derivative (entry 4).[228]

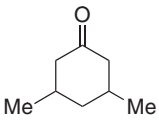
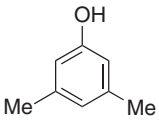
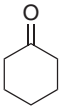
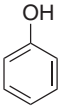
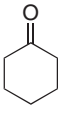
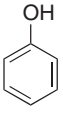
Table 10 Pd/C-catalyzed dehydrogenation of ketones and lactones

Entry	Substrate	Product	Conditions[a]	Yield (%)	References
1			Ph_2O, reflux	84	225
2			*p*-Cymene 230–300 °C	71	226
3			350–370 °C	85	227
4			*p*-Cymene reflux	60[b]	228

[a]Reactions carried out with 5% Pd/C.
[b]Reaction carried out with 10% Pd/C.

A few Ni- and Re-based heterogenous catalysts mediate dehydrogenative aromatization of cyclohexanone derivatives (Table 11). These reactions have been carried out in continuous-flow reactors with a carrier gas, such as N_2 and air, in order to remove H_2 continuously during the reaction.[229–231] Only simple cyclohexanone substrates have been demonstrated with these catalysts (Table 11, entries 1–3).

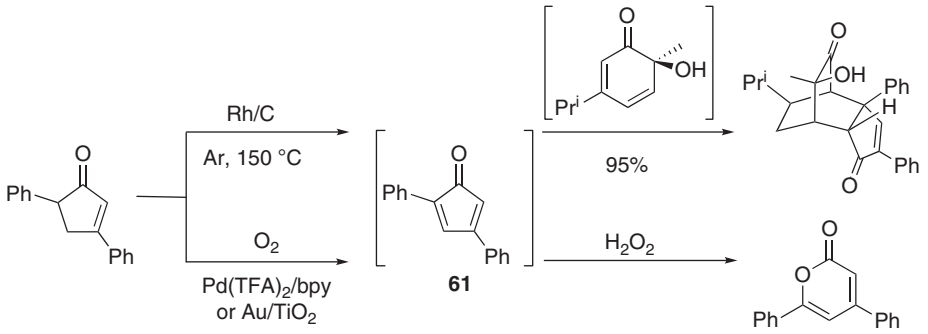
Table 11 Heterogeneous dehydrogenation of simple cyclohexanones[a]

Entry	Substrate	Catalyst	Major product	Yield (%)	References
1		Ni^0 catalyst		36	229
2		Sn–Ni–SiO_2		60	230
3		$Cs_4[Re_6S_8]SS_{2/2}(S_2)_{3/2}$		82	231

[a]Reaction conditions: temperature = 320–400 °C.

Porco and coworkers have reported a Rh/C-catalyzed dehydrogenation of a cyclopentenone derivative as a synthetic intermediate to chamaecypanone C (Scheme 34).[232] The cyclopentadienone intermediate **61** is antiaromatic and difficult to isolate.

In situ trapping of **61** by a diene affords the desired product in excellent yield. Aerobic dehydrogenation conditions furnish **61**, but H_2O_2 generated as a by-product *in situ* reacts with **61** to afford the pyrone as a Baeyer–Villiger oxidation product.

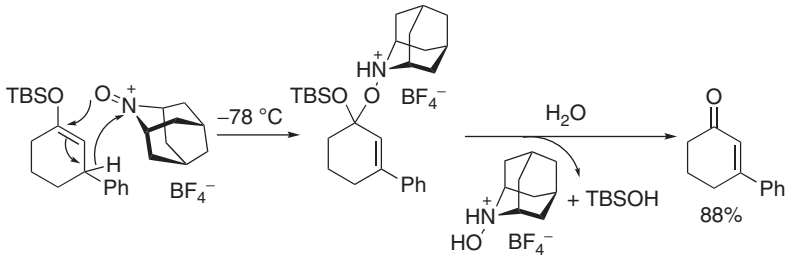


Scheme 34

7.06.5 Miscellaneous Methods

7.06.5.1 Oxoammonium Salts

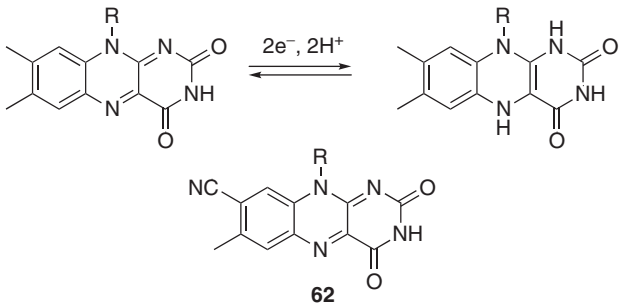
The conversion of TBS-protected silyl enol ether into α,β-unsaturated ketones has been achieved with the oxoammonium reagent AZADO$^+$BF$_4^-$. This reaction is proposed to proceed by an ene-like hydride transfer process followed by hydrolysis (Scheme 35).[233] A number of cyclic silyl enol ethers have been demonstrated to undergo dehydrosilylation under these conditions, and the low reaction temperature enables functional group tolerance. The resulting AZADOH by-product can be recovered by recrystallization, and AZADO$^+$BF$_4^-$ can be regenerated with HBF_4 and NaOCl.



Scheme 35

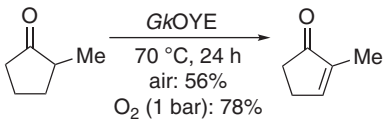
7.06.5.2 Old Yellow Enzymes

Old yellow enzyme (OYE) is a mixture of homo and heterodimeric proteins arising from yeast genes. Each monomer binds to a molecule of flavin mononucleotide that is capable of conducting $2e^-/2H^+$ redox processes (equation 40). Although early studies established that OYE can lead to aromatization of cyclohexanone derivatives and preparation of unsaturated steroids,[234] a recent report by Massey and coworkers demonstrates the dehydrogenative reactivity of a modified OYE **62** with simple carbonyl compounds.[235] The oxidation potential of OYE is increased by introducing a nitrile group at the flavin 8-position, and a number of substrates including aldehydes acyclic ketones and cyclopentanone derivatives, undergo facile aerobic dehydrogenation.[235]



(40)

An OYE derived from a *Geobacillus kaustophilus* microbe (*Gk*OYE) also achieves catalytic dehydrogenation of carbonyl compounds under aerobic conditions.[236] Oxidation of racemic 2-methylcyclopentanone is regiospecific to afford 2-methylcyclopenten-1-one in the presence of *Gk*OYE (equation 41). Such regioselectivity is distinct from all other chemical methods, which usually favor the less substituted side. The two enantiomers of the substrate undergo dehydrogenation with a similar rate (k_1:k_2=1.2).



(41)

7.06.6 Summary and Outlook

This chapter highlights a number of different methods available for dehydrogenation adjacent to carbonyl groups. By taking advantage of selective enolate formation methods and facile *syn*-elimination of β-hydrogen atoms, sulfur, and selenium reagents exhibit good regioselectivity and broad substrate scope. In particular, otherwise unreactive substrates, including esters and amides, can often undergo dehydrogenation with these methods. The drawbacks of these reagents, however, include the relatively high cost, toxicity and unpleasant odor, and the requirement of a multistep procedure. The use of hypervalent iodine reagents, such as IBX, has grown significantly, and they exhibit broad utility in α,β-dehydrogenation reactions. In comparison to other reagents, IBX is relatively safe and inexpensive, and it is capable of performing different levels of oxidation in a single step, often with good selectivity. Regioselective dehydrogenation of unsymmetrical substrates represents a challenge for IBX and related reagents that proceed via direct dehydrogenation pathways. The regioselectivity issue can be addressed by stepwise silyl enol ether formation followed by dehydrosilylation.

Catalytic dehydrogenation methods, especially those compatible with the use of O_2 or other desirable oxidants, remain an important goal for modern organic synthesis. In this context, important advances have been made in the development of new Pd-catalyzed aerobic dehydrogenation methods. Nevertheless, there is still need for the development of more robust catalysts with expanded substrate scope. Such achievements, together with improved control of chemo- and regioselectivity, will benefit from a more sophisticate understanding of the reaction mechanisms.

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7.07 α-Oxygenation of Carbonyl Compounds

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7.07.1 Introduction

α-Oxygenated carbonyl compounds are important building blocks in the synthesis of heterocycles, diols, amino alcohols, and epoxides, and are furthermore valuable templates in asymmetric C–C bond formation.[1] The α-hydroxycarbonyl group is also present in many types of natural products, including polyketides, terpenoids, and alkaloids. The asymmetric synthesis of α-oxygenated carbonyl compounds is of major interest in the pharmaceutical industry, as many antibiotics and other biologically active compounds contain α-hydroxycarbonyl fragments (**Figure 1**).

α-Hydroxyketones are also called acyloins or α-ketols, and are classically synthesized by acyloin/benzoin condensations or oxidations. Substrates already containing a carbonyl group can be α-oxygenated using a variety of strategies. Early methods employed stoichiometric amounts of toxic metals, whereas recent discoveries have focused on metal-catalyzed or even metal-free reactions. Many reviews and chapters have been devoted to this topic, either focusing on the synthesis of the entire α-hydroxycarbonyl fragment from various starting materials,[2] or on strategies for α-oxidation of carbonyl compounds.[3]

This latter is the topic of this chapter, which is divided into four sections based on the type of oxidant used in the α-oxygenation reaction. Each section gives a background with early discoveries, followed by a more detailed description of recent methods and illustrative applications in the synthesis of complex molecules. The reader is referred to the reviews and books cited in each section for comprehensive coverage of the literature.

Section 7.07.2 describes the use of metal oxides (M–O oxidants) in reactions with enolates and enol ethers. The stoichiometric use of metal oxides is only briefly mentioned, as they are rarely applied nowadays, and the focus of the section lies in catalytic asymmetric reactions.

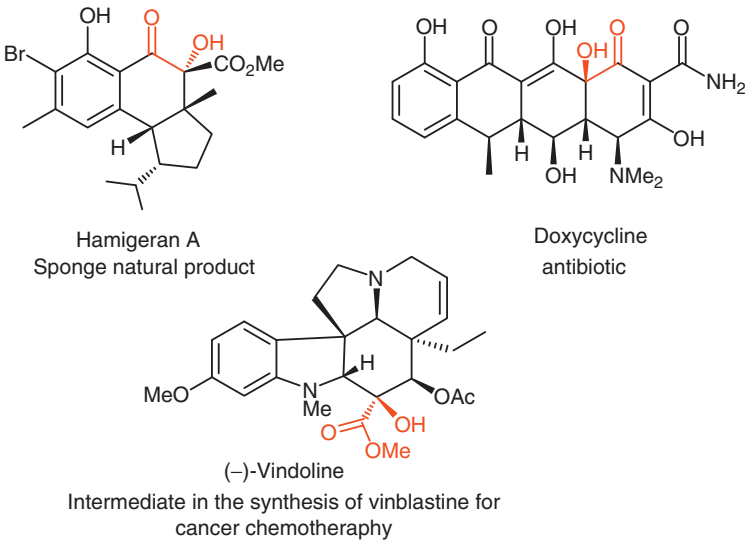


Figure 1 α-Oxygenated natural products and biologically active compounds.

Section 7.07.3 discusses oxidations with molecular oxygen, peroxides, and peracids (O–O oxidants), which are classical oxidation reagents. The section focuses on the enantioselective reactions recently achieved with organocatalysis.

Section 7.07.4 focuses on transformations with N–O oxidants, oxaziridines, nitrosoarenes, and TEMPO. The combination of nitrosoarenes with organocatalysis is currently the best method for enantioselective α-oxygenations.

Section 7.07.5 deals with hypervalent iodine oxidants (I–O oxidants), which have been recognized as efficient and green alternatives to many metal-mediated reactions. The area of asymmetric α-oxygenations is currently under development, and high enantioselectivities have only been achieved in intramolecular reactions and epoxidations.

Scheme 1 summarizes the most important reactions presented in this chapter based on starting material and reaction type, as a complement to the section division that is based on oxidant type.

α-Oxygenations that result in loss of the carbonyl group in the final product are outside the scope of this chapter, except for some tandem transformations. Likewise, reactions that deliver α-oxygenated carbonyl compounds from starting materials not containing the carbonyl functional group are not covered, except for preformed enolate equivalents like silyl enol ethers.

7.07.2 Metal Oxides in α-Oxygenations (M–O)

Metal salts have traditionally been used as stoichiometric reagents in α-oxygenation of carbonyl compounds. Lead tetraacetate, mercury diacetate, thallium triacetate, and other stoichiometric metal salts were employed, but the toxicity and expense of these reagents prevent their use in modern organic synthesis. The reader is referred to previous reviews for details on these transformations,[4] which are briefly summarized here. More environmentally benign, catalytic α-oxygenations have later been realized, and these are discussed in more detail.

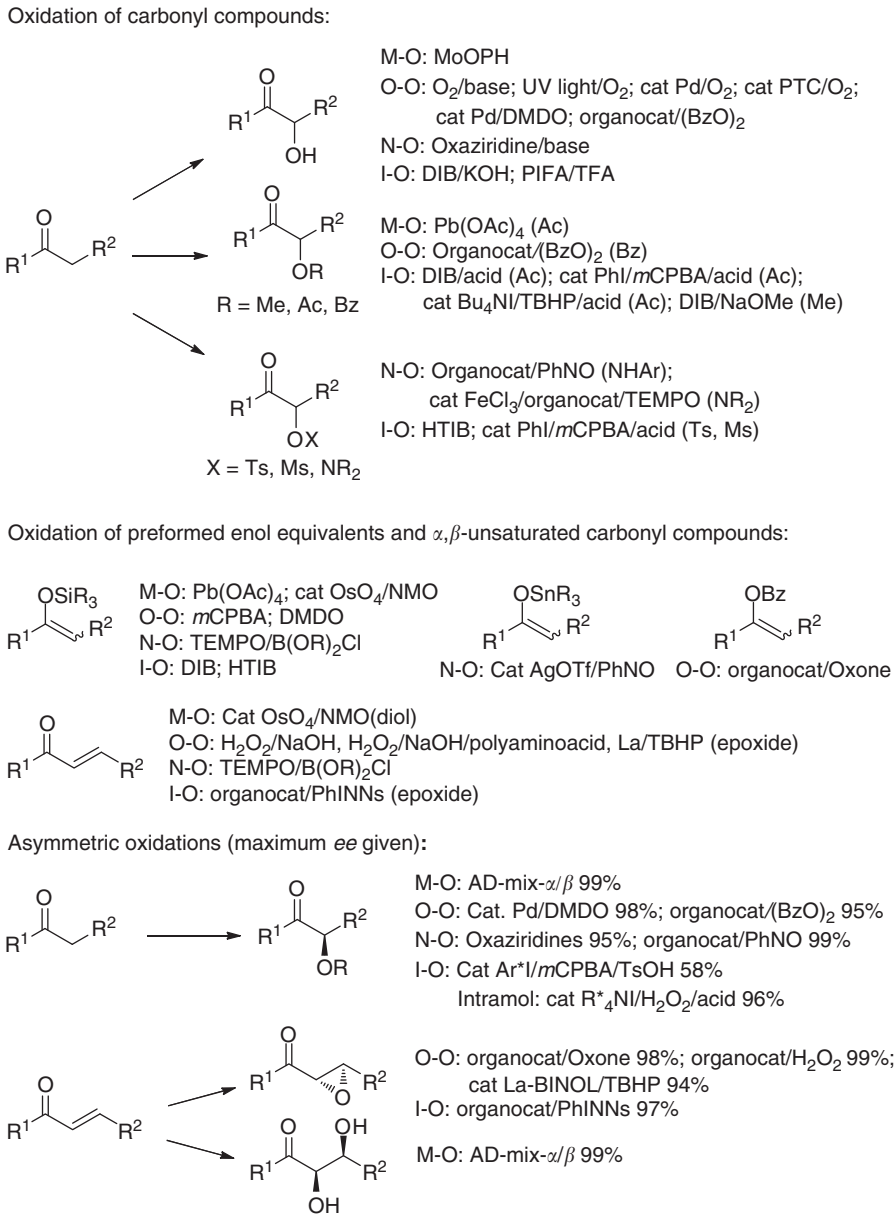
7.07.2.1 Acetoxylations

Acetoxylation of aldehydes and ketones using metal salts is one of the oldest and most well-known α-oxygenation methods. The most widely used oxidant for such reactions is lead tetraacetate, which is used in stoichiometric amount together with enolizable carbonyl compounds, usually in refluxing benzene or acetic acid (Scheme 2).[4] The acetoxylations are generally achieved in moderate yields, due to byproduct formation such as multiple acetoxylations or rearrangement reactions.

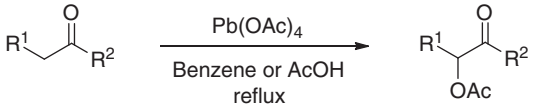
The mechanism has been proposed to be either radical or ionic, both pathways taking place via an enol intermediate. The addition of a Lewis acid enhanced the reaction rate by facilitating the enol formation, and rapid ketone acetoxylation was observed in the presence of boron trifluoride etherate. The Lewis acid-catalyzed procedure is unsuitable for aryl ketones, due to aryl migration to yield ester products.

The reaction is regioselective for the least hindered side of a ketone, but opposite selectivity has also been observed and reliable predictions cannot be made. Diastereoselective α-acetoxylations can be obtained in systems with large differences between the enol faces. Despite the harsh conditions and the toxic nature of the stoichiometrically used metal reagent, this method is useful in synthesis, as shown in the recent total synthesis of taiwaniaquinones A and F (Scheme 3).[5]

Silyl enol ethers react with lead tetrabenzoate followed by triethylammonium fluoride to give α-oxygenated products under milder conditions with higher yields. Alternatively, enamines can be treated with lead tetraacetate to give the same products, both strategies avoiding regioselectivity problems.[4]



Scheme 1 α-Oxygenation of carbonyl compounds at a glance.

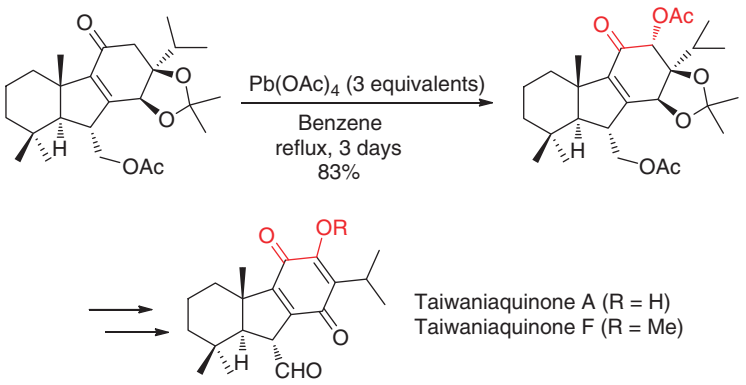


Scheme 2 Acetoxylation with lead tetraacetate.

Carbonyl compounds can also be α-acetoxylated using mercury diacetate or thallium triacetate in similar yields and scope. Thallium triacetate was reacted with enamines to form α-acetoxy ketones after hydrolysis. Morpholine enamine derivatives of both linear and cyclic aliphatic ketones were good substrates and moderate yields were obtained.[4]

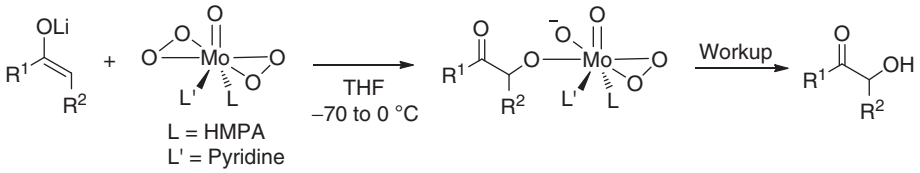
7.07.2.2 Hydroxylation of Enolates and Enol Ethers

Vedejs reported the hydroxylation of enolates with a molybdenum peroxy complex in the 1970s.[6] The transformation was achieved with $MoO_5 \cdot$ pyridine $\cdot$ hexamethylphosphoramide (HMPA), abbreviated as MoOPH or Vedejs reagent. The lithium



Scheme 3 Recent total synthesis using a lead tetraacetate acetoxylation.

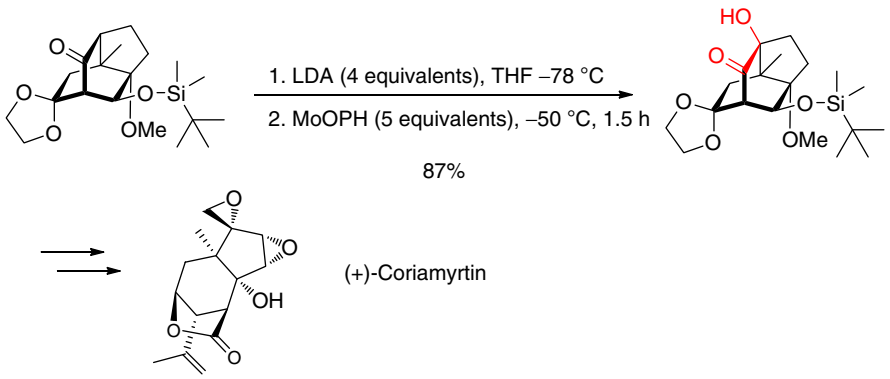
enolate attacked the peroxide oxygen of MoOPH to form a Mo(VI) ester, which was hydrolyzed to the corresponding α-hydroxy carbonyl compound (Scheme 4).[6]



Scheme 4 α-Hydroxylation of enolates with MoOPH.

The regioselectivity was controlled by selective formation of the kinetic, less hindered, enolate with lithium diisopropylamide (LDA) at low temperature. A slight excess of MoOPH is generally used, but high-yielding reactions have been reported with less than stoichiometric amounts of molybdenum, indicating that both peroxide moieties are involved in the reaction. Ketones, esters, and lactones were suitable substrates for this reaction.[4]

Enolate hydroxylation with MoOPH proceeded easily with a bridgehead enolate, as demonstrated in the total synthesis of coriamyrtin (Scheme 5).[7] Because the conformation of the cyclohexanone ring was locked in the boat form, formation of the bridgehead enolate was favored and the regioselectivity was complete.



Scheme 5 Enolate hydroxylation with MoOPH in the synthesis of Coriamyrtin.

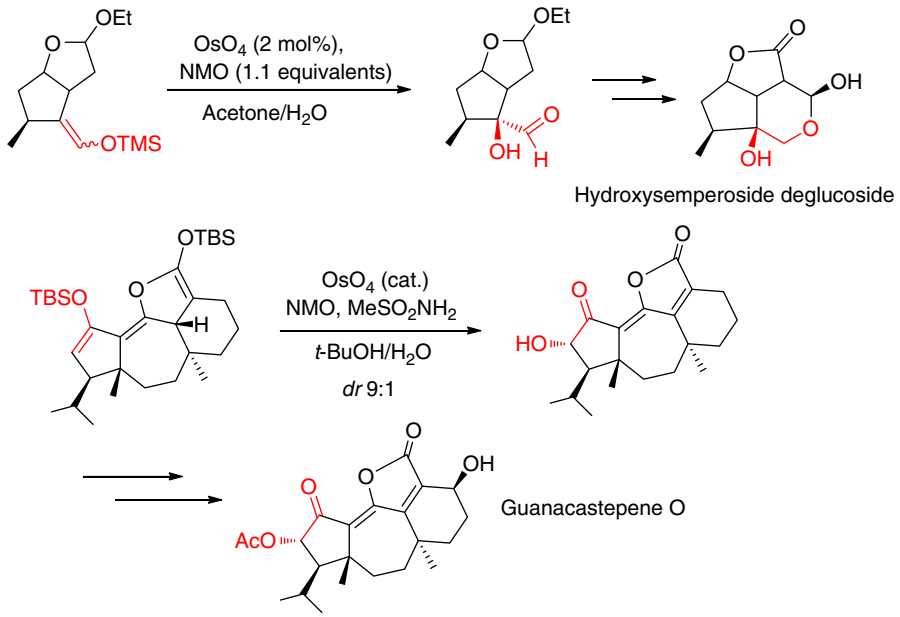
Due to the toxicity of HMPA, alternative reagents were later developed. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) was used instead of HMPA in the reagent $MoO_5 \cdot$ pyridine $\cdot$ DMPU (MoOPD), and similar reactivity was observed with this safer choice of reagent.[8]

7.07.2.2.1 Dihydroxylation of enol ethers

Silyl enol ethers can be dihydroxylated with osmium tetroxide to provide α-hydroxy carbonyl compounds after hydrolysis.[4] Osmium tetroxide is a well-known dihydroxylation agent of alkenes and, although osmium tetroxide can be used in

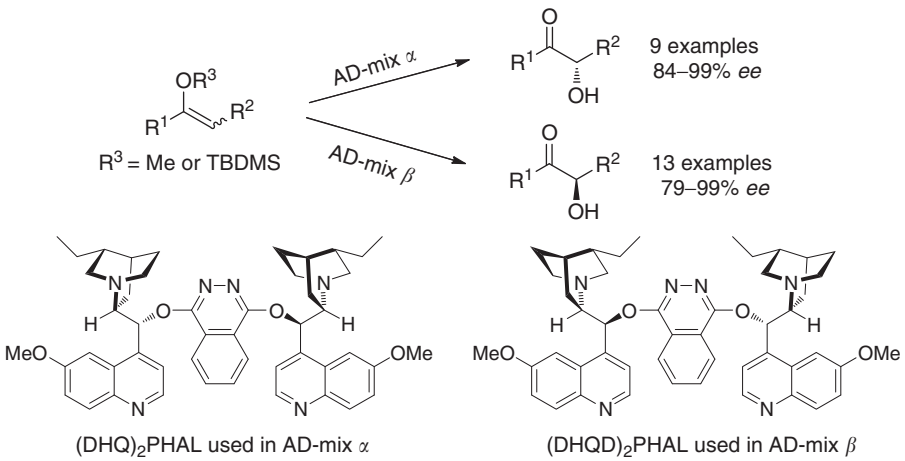
stoichiometric amounts, the highly toxic nature of the reagent has made catalytic versions of the oxidation necessary.[9] Among several reported secondary oxidants, the Upjohn dihydroxylation is a quite general and high-yielding reaction where *N*-methylmorpholine *N*-oxide (NMO) is applied as the stoichiometric oxidant.[10]

This osmium tetroxide/NMO dihydroxylation of silyl enol ethers takes place with high diastereoselectivity and has been used in several total syntheses, including tirandamycin A,[11] hydroxysemperoside deglucoside,[12] and guanacastepene O[13] (**Scheme 6**).



Scheme 6 Dihydroxylation with OsO_4/NMO in total synthesis.

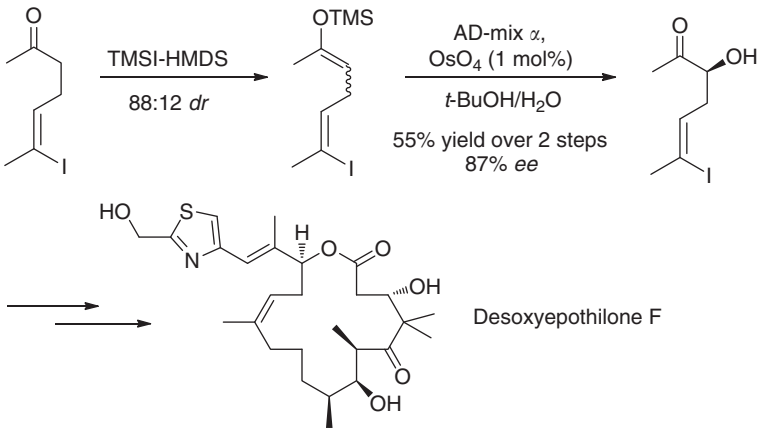
An enantioselective version of this reaction was developed by Sharpless and coworkers in 1992, as an extension of the previous asymmetric dihydroxylation of simple alkenes (**Scheme 7**).[14] Importantly, the asymmetric induction was completely controlled by the reagent, and *E*/*Z*-mixtures of the enol ethers could be used. High yields and enantioselectivities were obtained for a range of substrates with both types of chiral ligands.



Scheme 7 Enantioselective formation of α-hydroxy ketones via dihydroxylation.

The well-known, commercially available AD-mixes contain all the necessary reagents for the reaction; $K_2OsO_2(OH)_4$ as osmium tetroxide source, $K_3Fe(CN)_6$ as secondary oxidant, K_2CO_3, and chiral ligands. The chiral ligands are phthalazines (PHAL) coupled to dihydroquinine (DHQ) for AD-mix-α or dihydroquinide (DHQD) for AD-mix β.[14]

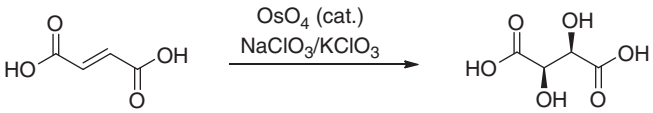
The dihydroxylation has been widely used in total synthesis of complex natural products, including the synthesis of desoxyepothilone F (**Scheme 8**).[15]



Scheme 8 AD-mix α as reagent in total synthesis.

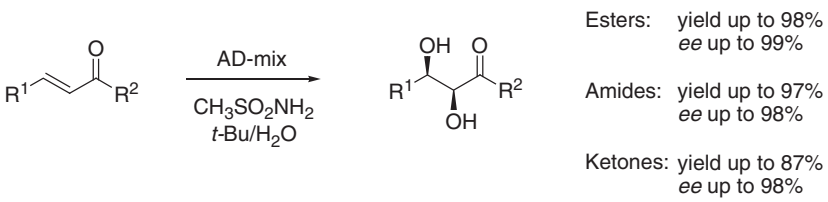
7.07.2.3 Dihydroxylation of α,β-Unsaturated Carbonyl Compounds

The dihydroxylation of α,β-unsaturated carbonyl compounds has been known since the beginning of the twentieth century. Hofmann used OsO_4 to oxidize maleic acid and fumaric acid into different isomers of tartaric acid, and found that the expensive and toxic osmium tetroxide could be used in catalytic amounts if reoxidized *in situ* using potassium or sodium chlorate as stoichiometric oxidant (Scheme 9).[16] Nowadays, the most common stoichiometric oxidant for catalytic OsO_4-catalyzed dihydroxylations is NMO, as described in Section 7.07.2.2.1.



Scheme 9 Early example of a catalytic dihydroxylation with osmium tetroxide.

Sharpless asymmetric dihydroxylation is applicable also for α,β-unsaturated carbonyl compounds (Scheme 10).[17] Esters and *N*,*N*-disubstituted amides are suitable substrates for this reaction and give excellent yields and enantioselectivities. Ketones were found to epimerize easily under standard reaction conditions, but this was overcome by using a basic buffer.



Scheme 10 Asymmetric dihydroxylation of α,β-unsaturated carbonyl compounds.

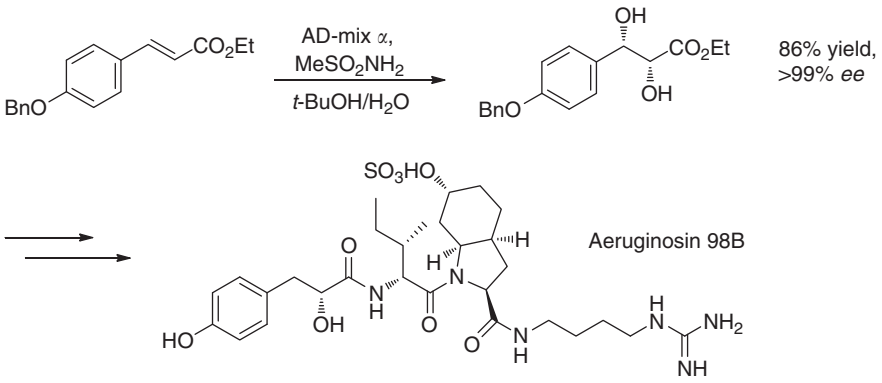
The method has been applied in total synthesis, for example, in the synthesis of Aeruginosin 98B (Scheme 11).[18]

Since osmium tetroxide is expensive and very toxic, alternatives to this catalyst system have been sought,[19] and dihydroxylation of α,β-unsaturated carbonyl compounds can also be performed with permanganate ions or ruthenium tetroxide.[20] Permanganate has a high oxidation potential and its use can easily lead to overoxidations or other side reactions. It also has to be used in stoichiometric amounts and is thus less suitable.

Ruthenium tetroxide can be formed *in situ* from $RuCl_3 \cdot (H_2O)_3$ and $NaIO_4$ and catalyzes the *syn*-dihydroxylation of α,β-unsaturated esters and cyclic enones within minutes in good yields.[21] The amount of ruthenium could be decreased to 0.5 mol% by adding a strong Brønsted acid to the mixture.[22] Some auxiliary-based asymmetric dihydroxylations using ruthenium exist, but analogs of the osmium tetroxide-catalyzed asymmetric dihydroxylations using chiral ligands have yet to be developed.

7.07.3 Molecular Oxygen and Peroxides in α-Oxygenations (O–O)

The cheapest and most readily accessible oxidant is oxygen in air. It is nontoxic, environmentally benign and atom-efficient, and can thus be considered the ideal green oxidant. Unfortunately, reactions with molecular oxygen often require high pressures and

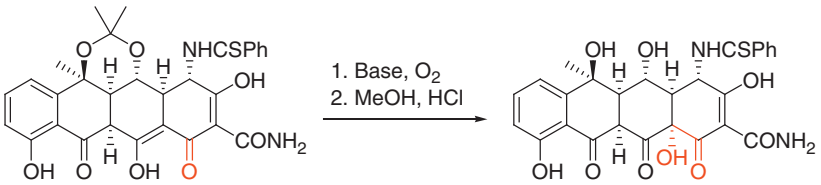


Scheme 11 Natural product synthesized using AD-mix α in a key step.

elevated temperatures, which limits its use in organic synthesis. Hydrogen peroxide is another highly atom-efficient and green oxidant, as water is formed as the only byproduct in the reaction. Organic peroxides, such as dimethyldioxirane (DMDO), *tert*-butyl hydroperoxide (TBHP), and *m*-chloroperbenzoic acid (*m*CPBA) are useful alternatives when direct reactions with oxygen or hydrogen peroxide fail.

7.07.3.1 Oxygen as Oxidant

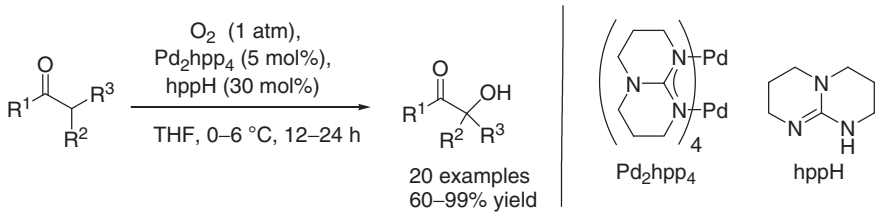
Simple exposure to air can lead to oxidation reactions, and a few cases of α-hydroxylation reactions have been reported.[3a] In some early examples, highly enolizable structures underwent hydroxylation by just bubbling air or oxygen through the reaction mixture in basic media. The formed α-hydroperoxide was hydrolyzed by acid or reduced by zinc dust or phosphites. This method has also been used for diastereoselective α-hydroxylations in some early total syntheses of tetracyclines (Scheme 12).[23]



Scheme 12 α-Hydroxylation in the synthesis of Terramycin.

For less enolizable compounds, the equilibrium was shifted to the reactive enol form by addition of reagents such as metal fluorides. In the majority of cases, the benefits of oxygen as a green oxidant were annihilated by the use of stoichiometric amounts of additives.[3a]

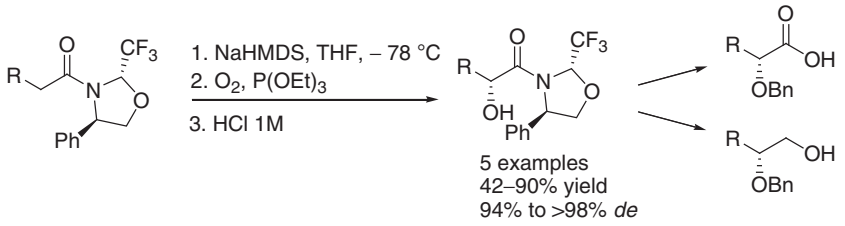
The reaction between oxygen and carbonyl functions can be facilitated by various catalysts, which also enables the use of chiral ligands to obtain enantioselective hydroxylations. Transition metal catalysts, such as $Mn(OAc)_2$, $CoCl_2$, and $CeCl_3$, have broadened the hydroxylation scope, and β-dicarbonyl compounds could smoothly be hydroxylated using 1 atm of O_2.[3a,24] The use of dinuclear palladium(II) complex Pd_2hpp_4 was recently reported to efficiently hydroxylate ketones (Scheme 13).[25] Enantioselective α-oxygenations using molecular oxygen and transition metals unfortunately remain unknown.



Scheme 13 Dinuclear palladium-catalyzed α-hydrogenation of ketones.

The first catalytic asymmetric approach was published in 1988 using chiral phase transfer catalysts, and up to 79% enantiomeric excess was obtained in the α-hydroxylation of cyclic ketones.[26] It was later shown that this method was also successful in the hydroxylation of oxindoles.[27] The need for phosphites to reduce the intermediate was overcome by employing pentanidium as a chiral phase transfer catalyst.[28]

A recent diastereoselective α-hydrogenation with molecular oxygen employed chiral auxiliary-based amides to form enolates with sodium hexamethyldisilazane (NaHMDS) (Scheme 14). Using a trifluoromethylated oxazolidine, diastereomerically pure products could be obtained in good yields. The intermediate peroxide was reduced *in situ* by treatment with triethyl phosphite, and the chiral auxiliary was removed by $LiAlH_4$ without loss of enantiopurity. However, isolation of the resulting α-hydroxy aldehyde was troublesome and a sequence of benzyl protection/ $LiAlH_4$ cleavage followed by oxidation to the corresponding carboxylic acid or reduction to the alcohol to was necessary to obtain pure oxygenated compounds.[29]



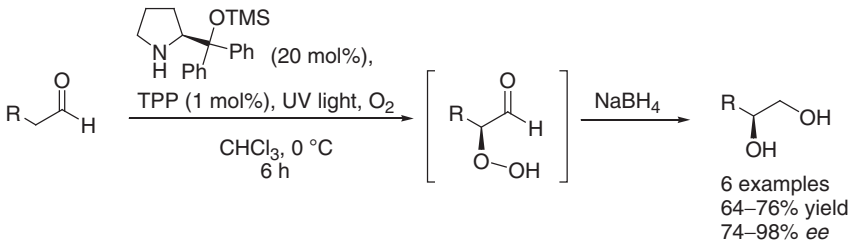
Scheme 14 Auxiliary-based diastereoselective α-hydroxylation.

α-Hydroxylation of fatty acids with molecular oxygen is a natural process for many higher plants, such as peas and cucumbers, and it is possible to hydroxylate similar long chain carboxylic acids with the same natural enzymes.[30] Some examples give excellent enantioselectivity, although the scope of the reaction remains rather narrow and the yields were sometimes poor due to byproduct formation.[31] An engineered microbial cytochrome P450 was reported to catalyze the α-hydroxylation of benzylic esters with good selectivities.[32]

7.07.3.1.1 Use of singlet oxygen

Singlet oxygen is more reactive than triplet oxygen, and can be formed by the use of a UV light source to electronically excite electrons from the triplet oxygen ground state. Singlet oxygen can also be chemically formed and used *in situ*. Indeed, photooxygenation of certain enol ethers and enol esters was possible, but low yields were obtained due to byproduct formation.[33]

Hydroxylation of aldehydes with singlet oxygen was reported using a proline-derivative as catalyst. The reactive singlet oxygen was generated using UV light, tetraphenylporphyrin (TPP) and oxygen or air. Several aliphatic aldehydes were obtained in good yields and enantiomeric excesses up to 66% of the α-hydroperoxide products, which were isolated as diols.[34] The enantioselectivity was further improved by changing the catalyst (Scheme 15).[35]



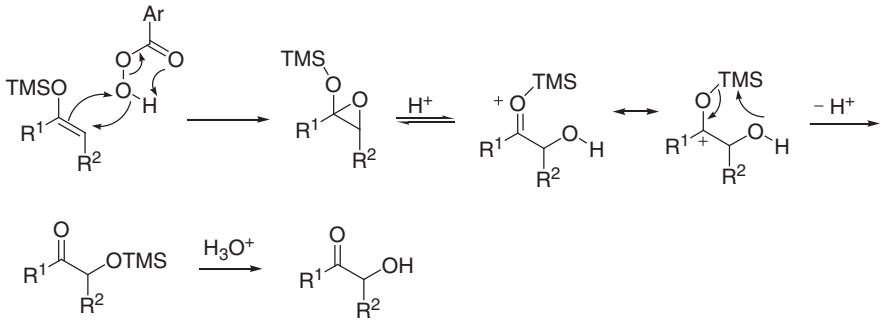
Scheme 15 Organocatalyzed oxidation with singlet oxygen.

7.07.3.2 Peroxides as Oxidant

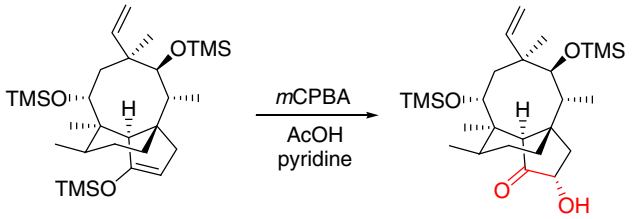
The oxidation of silyl enol ethers with *m*CPBA or DMDO to yield α-hydroxy ketones was discovered in 1974 by Rubottom et al., and is commonly known as the Rubottom oxidation.[36] Both aromatic and aliphatic silyl enol ethers can undergo this transformation smoothly. The reaction begins by epoxidation of the double bond, followed by formation of a stabilized carbocation. A subsequent 1,4-silyl migration gives an α-silyloxy ketone that is hydrolyzed to the corresponding α-hydroxy ketone (Scheme 16).[37]

The Rubottom oxidation has been applied in the total synthesis of a variety of complex molecules such as Danishefsky's total synthesis of Baccatin III and Taxol.[38] A more recent report examined the diastereoselective hydroxylation of pleuromutilin into 2*S*-hydroxymutilin (Scheme 17).[39]

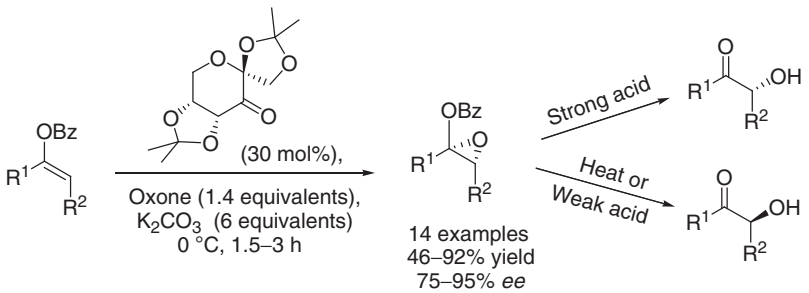
Shi has developed an organocatalytic asymmetric epoxidation based on a fructose-derived ketone as catalyst, which forms a chiral dioxirane as active oxidant on reaction with the stoichiometric oxidant Oxone®.[40] This epoxidation system was applied to the highly enantioselective epoxidation of enol ethers and enol esters, which were subsequently rearranged to the corresponding α-hydroxylated carbonyl compounds (Scheme 18).[41] Remarkably, the rearrangement occurred with retention using strong Lewis



Scheme 16 Mechanism of the Rubottom oxidation.



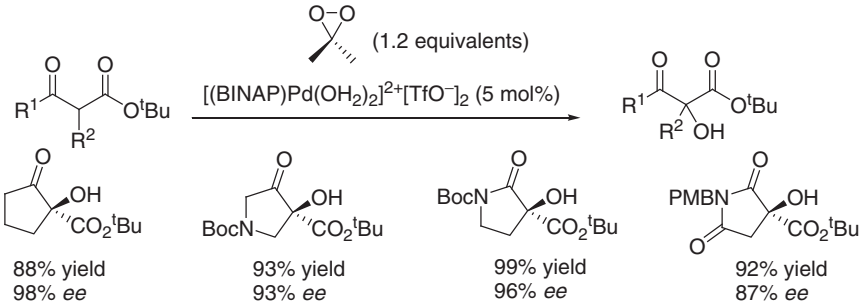
Scheme 17 Recent example of a Rubottom oxidation in complex molecules.



Scheme 18 Recent example of a Rubottom oxidation in complex molecules.

acids, although weaker Lewis acids afforded the α-hydroxy ester with inversion of configuration. Thermal rearrangements also resulted in inversed configuration.[41b]

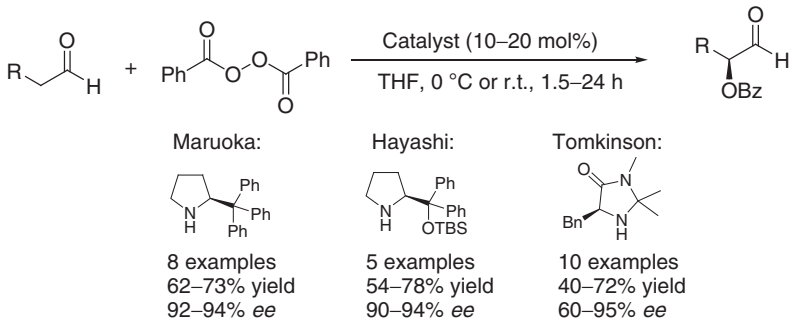
The hydroxylation of β-ketoesters can be achieved with DMDO and a dicationic Pd(II)-BINAP catalyst system (Scheme 19). Cyclic β-ketoesters gave excellent yields in short reaction times and enantiomeric excesses of up to 98%. The scope could be extended to nitrogen containing heterocycles as well, although lower selectivities were obtained with acyclic β-ketoesters.[42]



Scheme 19 Pd-catalyzed enantioselective hydroxylation of cyclic β-ketoesters.

Organic hydroperoxides can be employed in metal-free oxidations of β-ketoesters with cinchona-alkaloid derivatives as organocatalysts. Up to 80% enantiomeric excess could be obtained using cumyl hydroperoxide as oxidant and DHQ as catalyst, but the scope of the reaction was rather limited.[43]

The organocatalytic, asymmetric oxidation of aldehydes with benzoyl peroxide to yield α-benzoyl aldehydes was simultaneously reported by three different research groups in 2009 (Scheme 20).[44] Bulky proline derivatives or imidazolidinones were used in combination with unhindered aldehydes to give good yields and excellent enantiomeric excesses of the α-oxygenated products. The reaction is very useful synthetically, although sterically demanding aldehydes are unsuitable substrates.

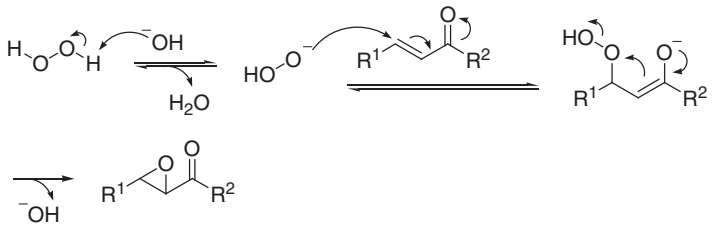


Scheme 20 Organocatalyzed benzoyloxylation of aldehydes.

A more general method was recently disclosed using primary amines as catalysts. With this system, cyclic ketones and 1-indanones could be benzoyloxylated with good to excellent enantioselectivities.[45] The method could also be extended to the use of α-branched aldehydes, but lower selectivities were observed.[46]

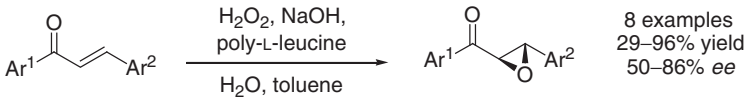
7.07.3.3 Epoxidation of α,β-Unsaturated Carbonyl Compounds

The epoxidation of α,β-unsaturated carbonyl compounds, with subsequent ring opening to yield α-hydroxy carbonyl compounds, is a very useful transformation. Electrophilic epoxidation reagents such as *m*CPBA, Sharpless or Jacobsen asymmetric epoxidation systems are unsuitable for electron-deficient carbonyl compounds.[3g,47] Nucleophilic oxidants, such as hydrogen peroxide under basic conditions, are better suited for epoxidation of enones. This kind of epoxidation is called the Weitz–Scheffer epoxidation, and proceeds via an enolate intermediate (Scheme 21).[48]



Scheme 21 Mechanism of the Weitz–Scheffer epoxidation.

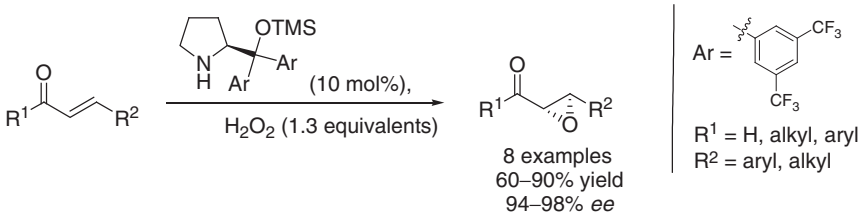
Asymmetric induction can be achieved by the use of cinchona alkaloid-derived phase transfer catalysts, but enantioselectivities were often modest and heavily substrate dependent.[49] Chiral peroxides can be employed to epoxidize chalcones in moderate enantioselectivities.[50] The Juliá–Colonna epoxidation is a classical asymmetric epoxidation that employs a triphasic reaction system (Scheme 22).[51] A basic aqueous phase contains hydrogen peroxide, the second phase is a non-miscible organic solvent, and the final phase consists of polyamino acid derivatives that are used as catalysts. High enantioselectivities can be obtained for a narrow range of substrates, consisting mainly of chalcones.[3g]



Scheme 22 Standard Juliá–Colonna epoxidation reaction.

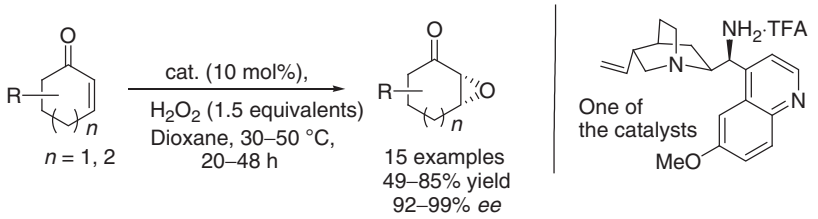
7.07.3.3.1 Organocatalytic methods

In an extension of the Juliá–Colonna epoxidation, the use of proline-derived chiral amines expanded the scope of the reaction so that α,β-unsaturated aldehydes were suitable substrates as well. The epoxides were formed in good yields and in excellent enantioselectivities with hydrogen peroxide (Scheme 23).[52] TBPH was a better oxidant for the epoxidation of enones with a similar catalyst.[53]



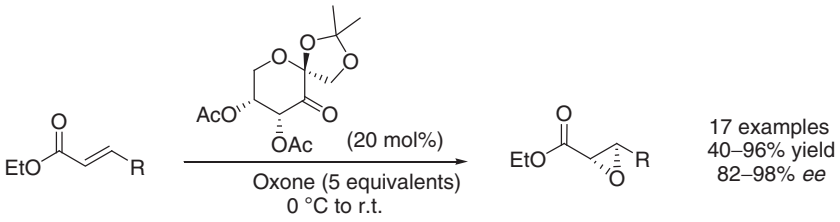
Scheme 23 Organocatalytic epoxidation of α,β-unsaturated carbonyls.

The challenging cyclic enones were successfully epoxidized in the presence of various primary chiral amine salts, often with a bulky chiral 1,1′-Bi-2-naphthol (BINOL)-derived phosphoric acid counterion. Excellent enantiomeric excesses were obtained for many different cyclic enones, although several amine catalysts were needed (Scheme 24).[54] For cyclopentenones, a quinidine derived primary amine salt system with Mosher's acid as counterion gave the best results.[55]



Scheme 24 Organocatalytic epoxidation of cyclic enones.

The Shi epoxidation was briefly described in Section 7.07.3.2, and is based on the *in situ* formation of a chiral dioxirane from a fructose-derived ketone and Oxone®. This dioxirane is electrophilic and the epoxidation takes place in a concerted way.[40] The reaction was first developed for electron-rich alkenes, but small alterations in the catalyst broadened the substrate scope to include α,β-unsaturated esters as well (Scheme 25).[56] Up to 98% enantiomeric excess was obtained with this method.

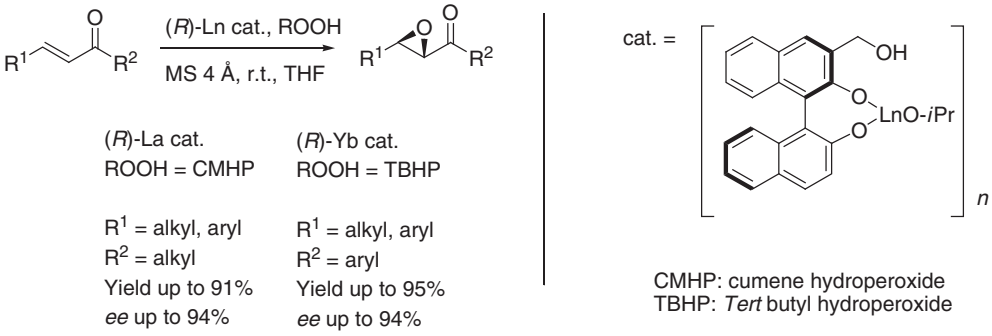


Scheme 25 Shi epoxidation using a chiral ketone as catalyst.

7.07.3.3.2 Lanthanide catalysis

Complexes of lanthanides with BINOL are efficient and general catalysts in the epoxidation of electron-deficient olefins. It was found that the lanthanum complex La-BINOL-catalyzed the reaction of TBHP and chalcones, although the related ytterbium complex Yb-BINOL was more suitable for aliphatic enones. High yields and enantioselectivities were obtained for a wide variety of substrates (Scheme 26).[57]

The catalytic activity was increased and a lower amount of catalyst was needed on adding $Ph_3As{=}O$. With this La–BINOL–$Ph_3As{=}O$ complex, also α,β-unsaturated esters, amides, and carboxylic acid imidazolides easily underwent the epoxidation reaction with high enantioselectivities.[58]



Scheme 26 Lanthanide catalysts in epoxidation.

7.07.4 Oxidants Containing a Nitrogen–Oxygen Bond (N–O)

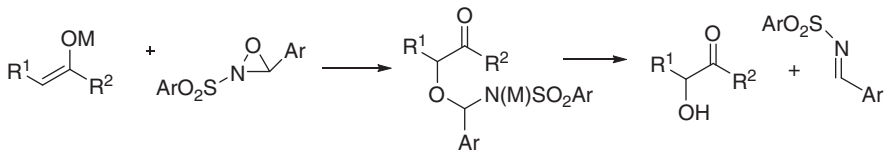
An efficient way to generate α-hydroxylated carbonyl compounds is by treatment of an enolate (equivalent) with an electrophilic oxygen source. Peroxides and peracids, which contain a weak O–O bond, were discussed in Section 7.07.3, and this section is devoted to oxidants containing an N–O bond.

Oxaziridines are commonly employed electrophilic oxidants, as the relatively weak N–O bond in a strained ring causes high reactivity. Oxaziridines generally act as amination reagents, but a bulky or a strongly electronegative substituent on the nitrogen makes them chemoselective oxygen-transfer reagents. Examples of these reagents are *N*-sulfonyloxaziridines,[3c] *N*-phosphinoyloxaziridines, oxaziridinium salts,[59] and polyfluorinated oxaziridines.[60] *N*-sulfonyloxaziridines, also called Davis reagents, are the most common reagents in α-hydroxylation reactions and will be discussed in Section 7.07.4.1.

The focus in N–O based oxidation reagents has recently been shifted toward the use of nitrosobenzene, which can act either as amination or oxygenation reagent depending on the conditions. These reactions are described in Section 7.07.4.2, followed by the oxidations with 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO) in Section 7.07.4.3.

7.07.4.1 Oxidations with *N*-Sulfonyloxaziridines

The hydroxylation of enolates by *N*-sulfonyloxaziridines was discovered by Davis et al. in 1984.[61] The reaction begins by an S_N2 attack by the enolate on the oxaziridine oxygen to form a hemiaminal, which fragments into a sulfonylimine and the hydroxylated carbonyl compound (Scheme 27). The final product is obtained after aqueous workup.[3c] The use of polymer-supported Davis reagent gives a cleaner reaction and facile recycling of the resulting sulfonylimine.[62]



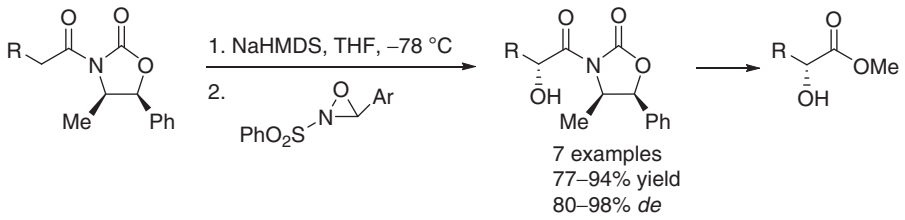
Scheme 27 Hydroxylation of enolates using *N*-sulfonyloxaziridines.

7.07.4.1.1 Diastereoselective oxidations

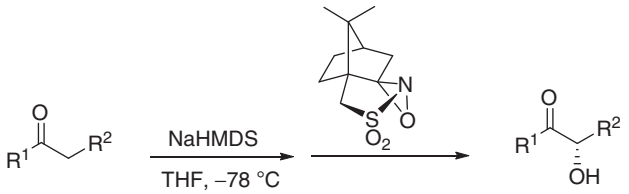
Besides some scattered examples of substrate-induced asymmetric hydroxylations on very bulky compounds, several auxiliary-based stereoselective hydroxylations have been developed. For example, the group of Evans reported a method using chiral auxiliaries based on oxazolidinones (Scheme 28).[63] Stereoselective formation of the *Z*(*O*)-enolate with NaHMDS at low temperature followed by addition of the oxaziridine resulted in good yields and high diastereoselectivities of the α-hydroxylated products. The chiral auxiliary was cleaved with magnesium methoxide to yield the corresponding methyl ester without racemization.

7.07.4.1.2 Enantioselective oxidations

A few years later, the group of Davis reported the use of an oxaziridine derived from camphor sulfonic acid as the first chiral *N*-sulfonyloxaziridine to give asymmetric induction (Scheme 29).[64] Good yields and enantiomeric excesses up to 95% were obtained. More substituted enolates gave lower selectivities due to the formation of *E*/*Z* enolate mixtures. The reaction resulted in reversed enantioselectivity with sterically demanding substrates, for example, *tert*-butyl-substituted ketones. Both enantiomers of the *N*-sulfonyloxaziridine are easily obtainable and give opposite selectivity, making both enantiomers of the product accessible.



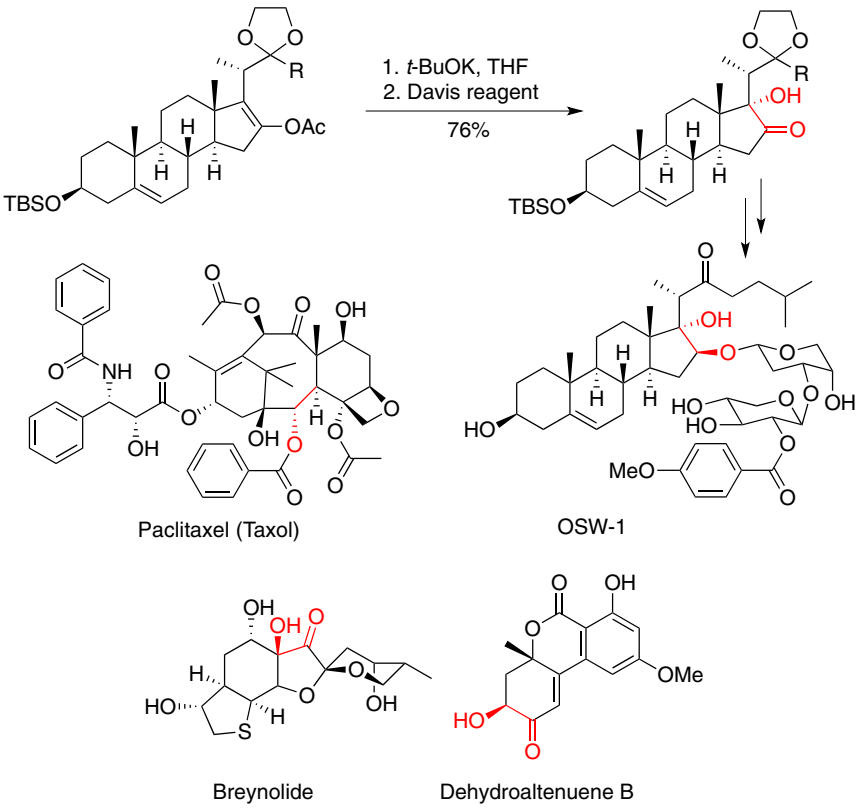
Scheme 28 Asymmetric hydroxylation using a chiral auxiliary.



R^1	R^2	Yield	*ee*
Ph	Ph	84%	95%
Ph	Me	73%	62%
Me	Ph	70%	40%
t-Bu	Me	71%	89%

Scheme 29 Asymmetric hydroxylation of enolates using a chiral oxaziridine.

This mild method has been frequently used in the total synthesis of complex natural products, as exemplified in Scheme 30. It was applied in the first total synthesis of Paclitaxel (Taxol®) by Holton,[65] and other important examples include the anticancer compound OSW-1[66] and the hypocholesterolemic Breynolide.[67] In a more recent example, Davis reagent was used in the final step of the first total synthesis of dehydroaltenuene B.[68]



Scheme 30 Natural products synthesized using Davis reagent.

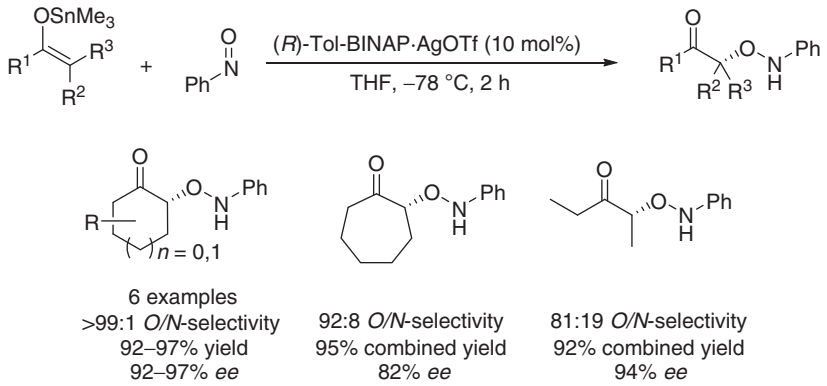
To avoid stoichiometric amounts of chiral reagents, *N*-sulfonyloxaziridines can be combined with transition metal catalysts with chiral ligands. This was demonstrated in the α-hydroxylation of β-ketoesters, giving enantiomeric excesses up to 94% using titanium catalysis.[69] The selectivity was, however, highly substrate-dependent and rather low for many substrates. Proline-derived organocatalysts could also be used, but only moderate selectivities were achieved.[70]

7.07.4.2 Aminoxylation Reactions with Nitrosobenzene

Nitrosoarenes can behave like carbonyls toward nucleophiles, due to the polarization of the nitrogen–oxygen bond, and can react either at the nitrogen or at the oxygen of the nitroso functional group. Although the *N*-nitroso aldol reaction has been described reasonably well,[71] use of the electrophilic oxygen in an *O*-nitroso aldol reaction was largely unexplored until recently. The formed α-aminoxy carbonyl can be transformed into an α-hydroxy carbonyl compound by cleavage of the nitrogen–oxygen bond. Although conditions should be carefully chosen to avoid concurrent reactivity at nitrogen, this method has rapidly emerged to one of the most important α-hydroxylation strategies. The reaction has been thoroughly covered in several previous reviews and chapters.[3h–j,72]

7.07.4.2.1 Aminoxylation of tin enolates

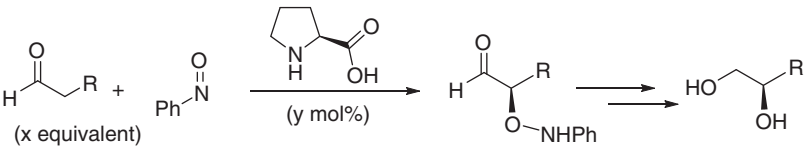
In 2002, Momiyama and Yamamoto first disclosed an unexpected *O*-selective trimethylsilyl triflate-catalyzed nucleophilic addition of preformed silyl enol ethers to nitrosobenzene to yield the corresponding aminoxy ketones.[73] This reaction was not very general, but served as a starting point for the first enantioselective Lewis acid-catalyzed *O*-selective nitroso aldol reaction, which was reported by the same group.[74] Excellent *O*-chemoselectivity and up to 97% *ee* were obtained using a complex of AgOTf and (*R*)-Tol-BINAP as catalytic system in the reaction between nitrosobenzene and a preformed cyclic tin enolate (**Scheme 31**). Acyclic enolates were considerably less chemoselective, and silyl enol ethers did not afford the product at all. The formed aminoxy ketones could easily be transformed with copper sulfate into the corresponding α-hydroxy ketones without loss of enantiomeric purity.



Scheme 31 Enantioselective α-aminoxylation of tin enolates.

7.07.4.2.2 Proline-catalyzed direct aminoxylation

Independently, the groups of Zhong, MacMillan, and Hayashi reported the first direct catalytic asymmetric α-aminoxylation of aldehydes using proline as organocatalyst.[75] The previous need for preformed tin enolates was overcome by *in situ* formation of chiral enamines, which subsequently reacted with nitrosoarenes to yield the α-aminoxylated products. The three research groups reported nearly identical methods, which only varied in solvent, reaction time, and reagent amounts (**Scheme 32**).

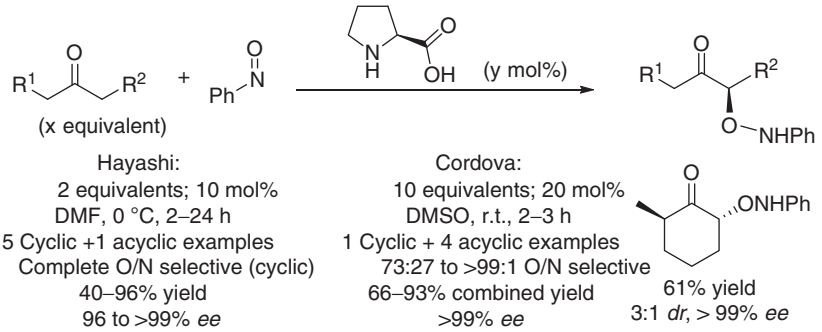


Scheme 32 Enantioselective α-aminoxylation of aldehydes.

The reaction could be performed in DMSO at room temperature, or in less polar solvents at lower temperature to avoid byproducts. With longer reaction times, the amount of catalyst could be decreased to 5 mol%. The α-aminoxy aldehydes were reduced *in situ* to the corresponding α-aminoxy alcohols for easier isolation and characterization. The N–O bond could easily be

cleaved by hydrogenation to afford the corresponding diol without loss of enantiomeric excess. The reaction was very general, as both aliphatic and aromatic aldehydes underwent the reaction smoothly with excellent enantiomeric excesses. Substrates that incorporated olefinic or indolic functionalities were also well tolerated under these mild conditions.

The scope of this reaction was later extended to the use of ketones, which are more challenging substrates (Scheme 33).[76] Since the ketones were enolizable on both sides, slow addition of nitrosobenzene to an excess of the ketone (2–10 equivalents) was necessary in order to avoid a second aminoxylation reaction. DMSO or DMF were used as solvent, and dry conditions were unnecessary. Cyclic ketones gave excellent yields and chemoselectivity, whereas acyclic ketones showed lower *O*-selectivity. The enantioselectivity was excellent for all reported substrates. Racemic 2-metylcyclohexanone gave complete *O*-selectivity with a 3:1 diastereomeric ratio (*trans*/*cis*) in >99% enantiomeric excess of the major diastereomer.

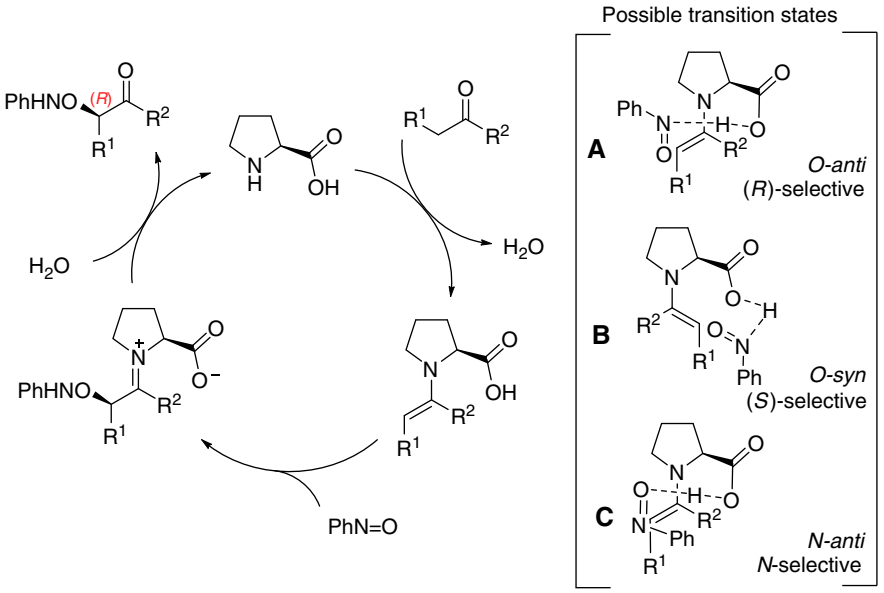


Scheme 33 α-Aminoxylation of ketones.

Hydroxylated proline derivatives work equally well as catalysts, and proline-derived *N*-sulfonylcarboxamides were successfully employed in the aminoxylation of ketones. A pyrrolidine sulfonamide-based organocatalyst gave a wider solvent scope.[72] The use of 4-siloxyproline as alternative to proline was interesting, since it showed a better solubility in organic solvents while maintaining the selectivity. The catalyst loading could be reduced and the obtained results were more reproducible.[77] Proline derivatives also catalyzed the α-aminoxylation reaction in room temperature ionic liquids[78] and as polymer-supported catalysts,[79] which improved the regeneration of the catalyst and the isolation of the product.

Yamamoto reported the use of a proline-related tetrazole, which was a superior catalyst in terms of both *O*-selectivity and yield.[80] The enantioselectivity was excellent for both aldehydes and ketones. The increased catalytic activity was demonstrated by a competition experiment using a mixture of L-proline-based tetrazole and D-proline in the reaction. The catalysts should both give full selectivities but to opposite enantiomers; (*R*) and (*S*), respectively. The (*R*)/(*S*)-ratio was 66:34, showing the dominance of the tetrazole catalyst over D-proline.

In the generally accepted mechanism of direct proline-catalyzed aminoxylation, the proline attacks the carbonyl compound to form an enamine, which reacts with nitrosobenzene to afford the aminoxylated product after hydrolysis (Scheme 34).[72]



Scheme 34 Mechanism of the proline-catalyzed α-aminoxylation.

Quantum mechanical computational studies revealed the possible origins of the observed chemo- and enantioselectivity of this reaction using L-proline.[81] Of the three possible proposed transition states, the (*R*)-*O*-*anti*-TS **A** was calculated to be lowest in energy. In this TS, the enamine attacks the oxygen of nitrosobenzene from the *Si* face to form the (*R*)-aminoxylated product. The *pseudo* six-membered transition state is stabilized by hydrogen bonding between the nitrogen of nitrosobenzene and the carboxylic acid hydrogen in proline. The higher basicity of the nitrogen atom leads to a preferred hydrogen bonding to the nitrogen instead of the oxygen atom, which finally leads to a more electrophilic oxygen and *O*-selectivity.[81]

A study of the reaction kinetics, however, revealed that the mechanism might be more complex.[82] During the course of the reaction, the rate is enhanced and the enantiomeric excess is improved, which points to the formation of a more active catalyst during the reaction. An intermediate bearing two enamine units was suggested. The addition of a bifunctional urea was found to enhance the rate of the reaction, possibly through the formation of an oxazolidine intermediate. In this case, the reaction was not autocatalytic, suggesting yet another mechanism.[83]

7.07.4.2.3 Aminoxylations with other catalysts

Axially chiral catalysts can be employed instead of proline-based catalysts in the α-aminoxylation. Both an axially chiral amino acid and a related binaphthyl-based amino sulfonamide have been reported to catalyze the reaction (**Figure 2**).[84] The latter catalyst could compete with proline-based catalysts regarding yields and enantioselectivities, and the catalyst loading could be as low as 0.2 mol%.

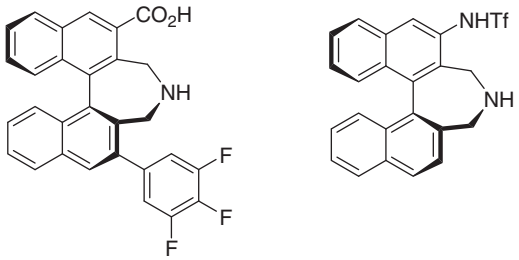
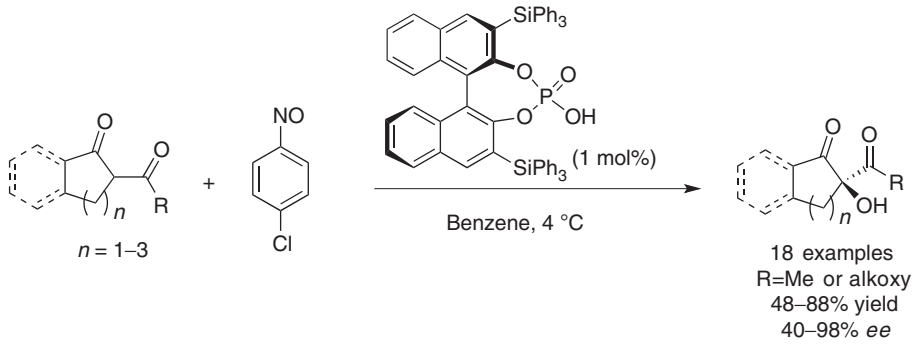


Figure 2 Axially chiral catalysts for α-aminoxylations of carbonyl compounds.

Zhong reported that BINOL-derived phosphoric acids catalyzed the α-hydroxylation of β-dicarbonyl compounds, making this protocol complementary to the proline-catalyzed procedures (**Scheme 35**).[85] Spontaneous N–O bond heterolysis occurred and the product was isolated as the α-hydroxy compound. Cyclic β-diketones and β-ketoesters gave high selectivities also with sterically hindered ester moieties.



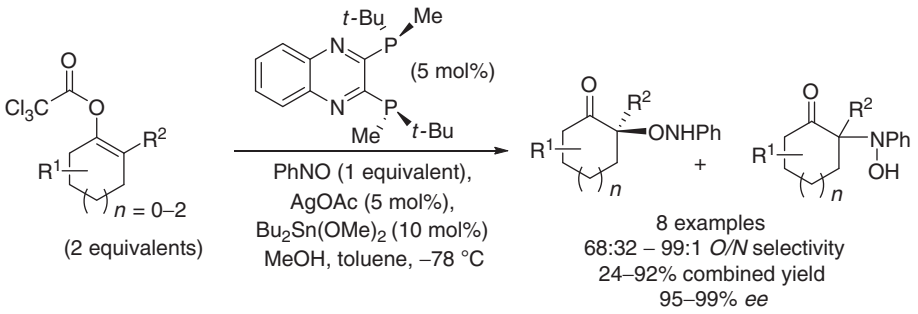
Scheme 35 Brønsted acid-catalyzed α-hydroxylation of β-dicarbonyl compounds.

A recent Brønsted acid-catalyzed method used the easily accessible α,α-diphenylprolinol trimethylsilyl ether as catalyst together with *p*-nitrobenzoic acid.[86] Very high selectivities were obtained using a wide range of aldehydes. Although the catalyst is a proline-derivative, the selectivity was entirely determined by steric factors.

A chiral phosphine/AgOAc complex was utilized as catalyst with $Bu_2Sn(OMe)_2$ as a cocatalyst in the addition of cyclic alkenyl acetates to nitrosobenzene. The formed α-aminoxy ketones were isolated in good yield and with excellent enantioselectivities, albeit with varying *O*/*N*-selectivities (**Scheme 36**).[87] Acyclic substrates were α-aminoxylated in modest yields and *O*/*N*-selectivities.

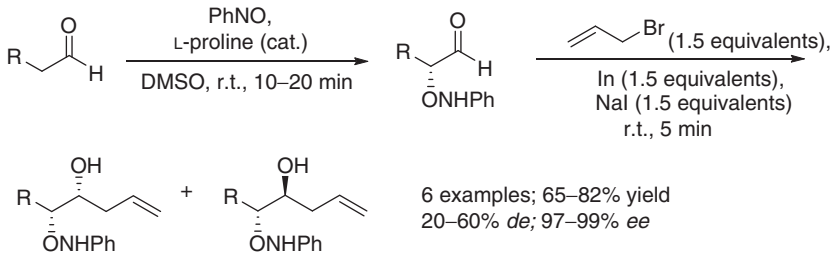
7.07.4.2.4 Tandem processes and applications

The α-aminoxylation has been coupled with other reactions in various tandem processes. The most common reaction is a reduction to the corresponding alcohols, as aminoxy aldehydes are generally too unstable to allow isolation.[3h–j,72] Zhong



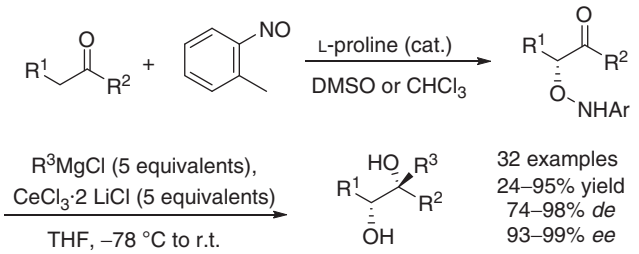
Scheme 36 Aminoxylation reaction with chiral phosphine/silver complex.

reported a subsequent allylation reaction of the formed aminoxy aldehydes to deliver aminoxy alcohols in a diastereo- and enantioselective fashion (Scheme 37).[88]



Scheme 37 Aminoxylation followed by allylation reaction.

syn-1,2-Diols can be obtained by reacting the aminoxy aldehydes with excess amounts of Grignard reagents. Yamamoto and coworkers found that the presence of $CeCl_3 \cdot 2LiCl$ was crucial to obtain high diastereo- and enantioselectivity. The Grignard addition in the presence of additives also caused clean cleavage of the O–N bond. A wide variety of both aldehydes and Grignard reagents were suitable in this sequential reaction, whereas the ketone scope was limited to cyclohexanones (Scheme 38).[89]



Scheme 38 Sequential α-aminoxylation and Grignard addition.

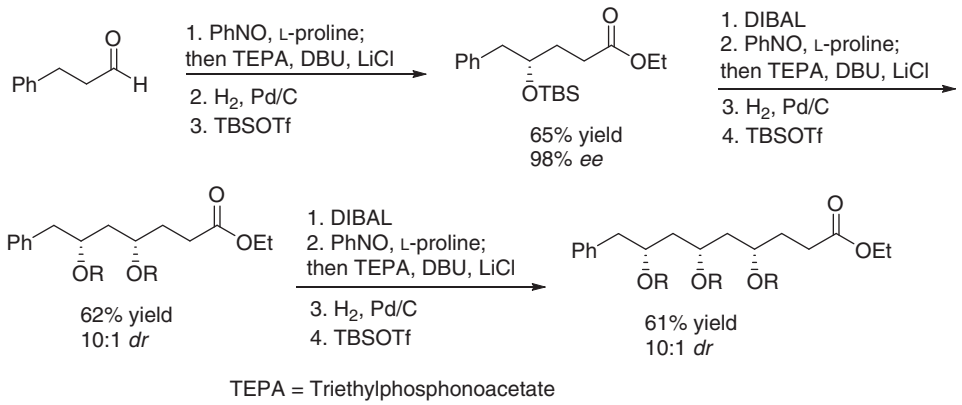
The aminoxy aldehydes can be transformed to γ-hydroxy-α,β-unsaturated ketones by an *in situ* Horner–Wadsworth–Emmons (HWE) olefination.[90] This strategy can be extended to a series of aminoxylation/HWE olefination/reduction sequences to synthesize 1,3-polyols in a highly diastereo- and enantioselective way (Scheme 39). The use of D-proline instead of L-proline resulted in opposite selectivity, making both *anti* and *syn* products accessible each iteration.[91]

A subsequent intramolecular Michael addition can occur if the aldehyde contains a nitro-substituted double bond, giving access to substituted tetrahydro-1,2-oxazines (Scheme 40).[92]

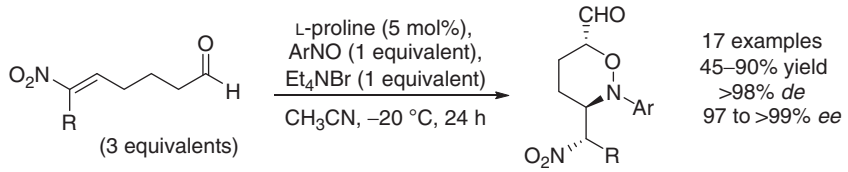
Aminoxylation reactions are also widely used as the enantioselective step early in synthetic routes to natural products and biologically important molecules.[93] Examples include the anticancer drug (+)-Cytotrienin A,[94] a formal synthesis of the antimicrobial agent Fumagillin[95] and the complex natural products Brasoside and Littoralisone (Figure 3).[96]

7.07.4.3 Aminoxylations with TEMPO

Aminoxylations can be accomplished using TEMPO instead of nitrosobenzene.[97] With this reagent more robust aminoxy carbonyl compounds are generated. An early example of an aminoxylation of metal ester enolates was described in 1998.[98] Ester enolates were formed by treatment with LDA, and stoichiometric amounts of ferrocenium ions were used as single electron transfer (SET)



Scheme 39 Iterative aminoxylation/HWE olefination/reduction.



Scheme 40 Tandem aminoxylation-intramolecular Michael addition reaction.

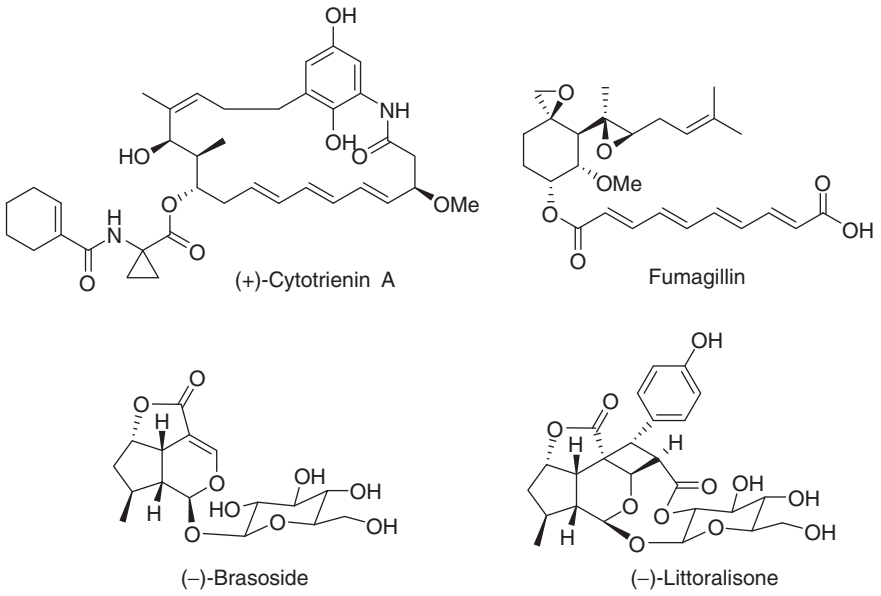
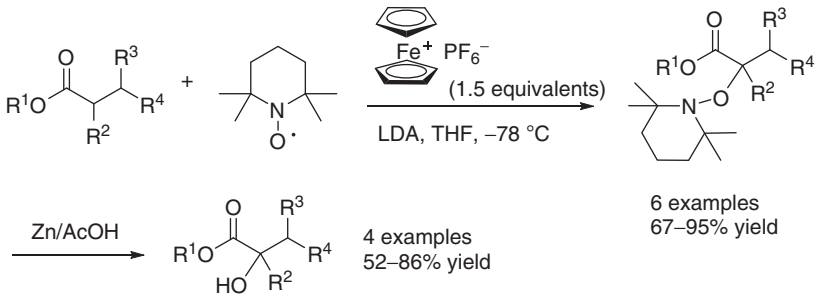


Figure 3 Complex molecules synthesized with an α-aminoxylation as key step.

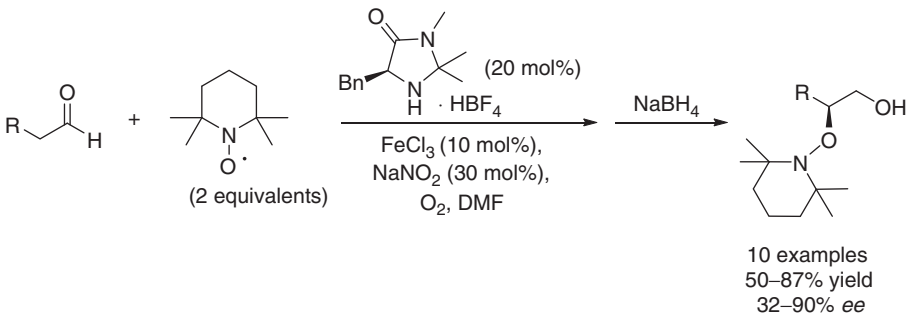
oxidant. The resulting radical was further oxidized with TEMPO to the α-aminoxy product. The N–O bond was cleaved with Zn/AcOH to yield α-hydroxy esters in moderate to good yields (Scheme 41).[98] The formation of ester dimers as byproducts supports the proposed radical mechanism.

Sibi and Hasegawa reported the first enantioselective α-aminoxylation of aldehydes using a chiral imidazolidinone, TEMPO, and $FeCl_3$ (Scheme 42).[99] Aldehydes containing aromatic moieties gave high enantioselectivities, whereas simple aliphatic aldehydes were unselective. The final N–O bond could be cleaved using Zn/AcOH without loss of enantioselectivity.

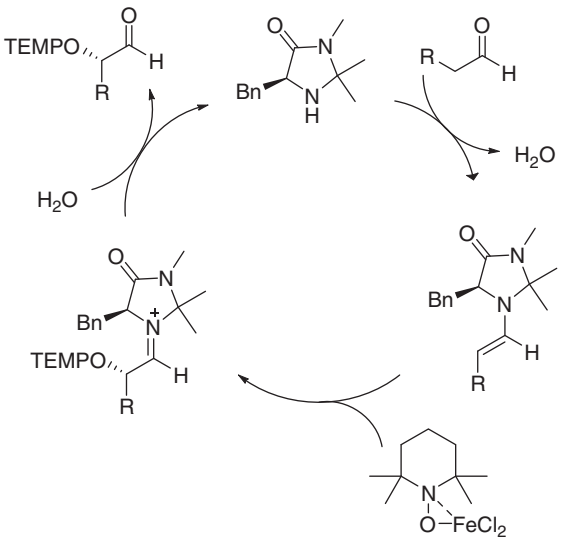
The first suggested mechanism involved a radical cation intermediate and the $FeCl_3$ was thought to be a SET reagent. $FeCl_3$ could be used in catalytic amount when molecular oxygen and sodium nitrite were added.[100] Following detailed mechanistic studies by MacMillan, an alternative catalytic cycle was proposed (Scheme 43).[101] In this mechanism, the iron(III) chloride was



Scheme 41 α-Hydroxylation of ester enolates by TEMPO and ferrocenium ions.



Scheme 42 The use of TEMPO in asymmetric α-aminoxylation reactions.



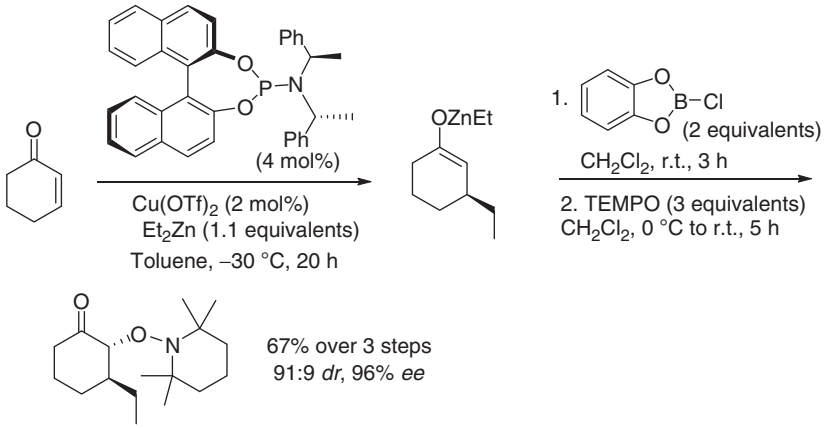
Scheme 43 Revised mechanism of enamine addition to TEMPO · Fe complex.

bound in a complex with TEMPO, which underwent an ordinary enamine addition. The oxidant appeared to be TEMPO itself and $NaNO_2$ and O_2 were not required.

Catalytic amounts of copper(II) chloride gave a similar complex with TEMPO, and broadened the scope to several functionalized aliphatic aldehydes with enantiomeric excesses up to 95%.[102] This method was extended to the use of resin-bound peptides instead of chiral imidazolidinones, used $FeCl_2 \cdot 4H_2O$ as second catalyst and took place in aqueous media.[103] The procedure became even greener with air as oxidant and the enzyme laccase as cocatalyst instead of $FeCl_2$.[104]

Maruoka reported an interesting metal-free reaction, where TEMPO was oxidized with benzoyl peroxide. The *in situ*-generated oxoammonium salt was used in an aminoxylation reaction of aldehydes in the presence of a binaphthyl-based chiral amine catalyst. Excellent enantioselectivities were obtained for a variety of aliphatic aldehydes.[105]

Recently, the α-aminoxylation of enones and silyl enol ethers using TEMPO and chlorocatecholborane was described.[106] A radical mechanism was initially proposed, but further mechanistic studies pointed at a more complex mechanism, including a reactive oxoammonium salt where two equivalents of TEMPO were needed.[107] A wide range of ketones and enones could be α-aminoxylated, and good *trans*-diastereoselectivity was observed in cyclic substrates with a methyl substituent. The combination of an asymmetric 1,4-addition and a subsequent α-aminoxylation gave high diastereo- and enantioselectivity (Scheme 44).



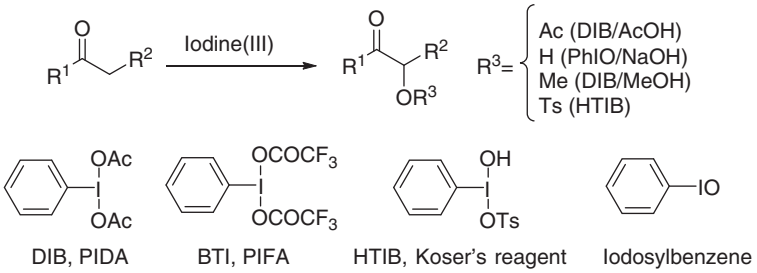
Scheme 44 Asymmetric tandem conjugate addition/aminoxylation.

7.07.5 Hypervalent Iodine in α-Oxygenations (I–O)

Hypervalent iodine reagents are stable and selective reagents for a wide range of transformations.[108] They are green alternatives to reagents based on heavy metals, such as Cr, Pb, Hg, and Tl, and to expensive organometallic catalysts for a range of oxidations (*see* Chapter 7.29). The use of hypervalent iodine reagents in α-oxygenation has become widespread in recent years. The reactions are generally performed with stoichiometric amounts of hypervalent iodine reagent, creating stoichiometric amounts of iodobenzene waste.

To a certain extent, this can be circumvented using polymer-bound or otherwise recyclable reagents, but recent progress also includes many promising catalytic α-oxygenations with hypervalent iodine compounds.[109] Asymmetric reactions with hypervalent iodine reagents have been difficult to achieve, and the first highly enantioselective reactions have only recently been reported.[109a,110]

The α-functionalization of carbonyl compounds with hypervalent iodine reagents was last reviewed in 2009,[3e,111] and α-oxidations utilized in the synthesis of natural products were covered in 2011.[112] α-Oxygenation of carbonyl compounds is mainly performed with iodine(III) reagents, including (diacetoxyiodo)benzene (DIB, PIDA), [bis(trifluoroacetoxy)]iodobenzene (BTI, PIFA), [hydroxy(tosyloxy)iodo]benzene (HTIB, Koser's reagent), and iodosylbenzene (Scheme 45). The reactions are insensitive to air and moisture, and the iodobenzene byproduct can easily be removed in the purification. Iodine(V) reagents, mainly 2-iodoxybenzoic acid (IBX) and Dess–Martin periodinane (DMP), are rarely employed.[113]

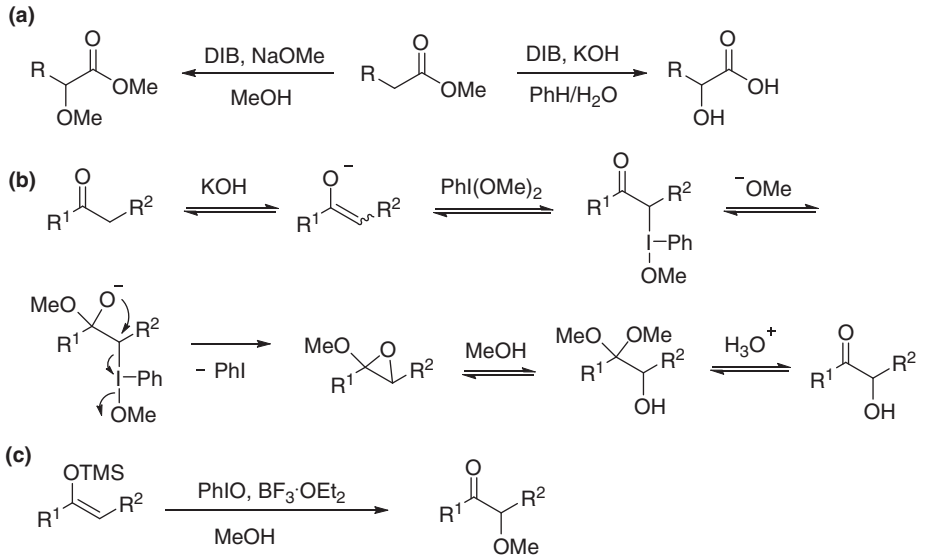


Scheme 45 Common hypervalent iodine reagents for α-oxygenation.

Acyloxylations, hydroxylations, and methoxylations are described in Section 7.07.5.1, followed by sulfonyloxylations in Section 7.07.5.2. Section 7.07.5.3 is devoted to intramolecular α-oxygenations and Section 7.07.5.4 describes epoxidations of α,β-unsaturated carbonyl compounds.

7.07.5.1 Acyloxylation, Hydroxylation, and Methoxylation

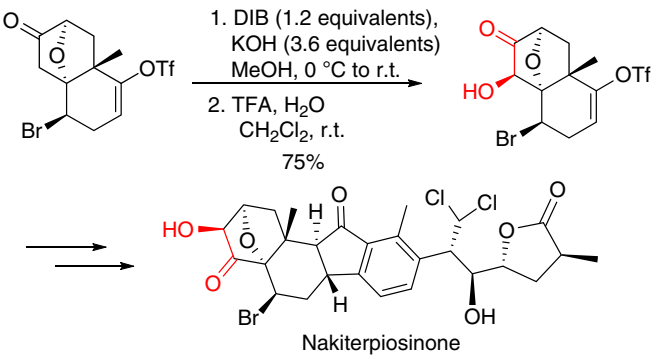
The α-acetoxylation of ketones and β-diketones with DIB under acidic conditions was reported in 1978,[114] as the first α-oxygenation with hypervalent iodine reagents. Moriarty subsequently developed the α-hydroxylation of carbonyl compounds with iodosylbenzene or DIB under basic conditions,[115] and the corresponding methoxylation was achieved by performing the reaction in methanol (**Scheme 46(a)**).[116] The active reagent is (dimethoxyiodo)benzene, which is formed *in situ* from DIB and MeOH. A general mechanism is given in **Scheme 46(b)**, and involves formation of the common T-shaped iodine(III) intermediate, followed by cyclization to the epoxide. This is further transformed to the corresponding α-hydroxy dimethyl acetal, followed by acidic hydrolysis to the α-hydroxylated product.[111b]



Scheme 46 α-Methoxylation and α-hydroxylation under basic conditions.

The transformation can be achieved using PIFA and trifluoroacetic acid,[117] or with the iodine(V) reagent IBX.[113b,118] Trimethylsilyl enol ethers can be α-methoxylated with PhIO activated by BF_3 in methanol (**Scheme 46(c)**).[119] Tandem DIB-mediated acetoxylation and cyclization of *ortho*-acyl phenols and *ortho*-acyl anilines were recently reported, resulting in α-acetoxy benzofuranones and 3-oxyindols, respectively.[120]

Stereoselective α-hydroxylations have been reported in several syntheses of natural products, demonstrating the mild and selective features of these reagents.[112] In the synthesis of Nakiterpiosinone the hydroxyl group was introduced under basic conditions, followed by treatment with trifluoroacetic acid to remove the dimethyl acetal (**Scheme 47**).[121]

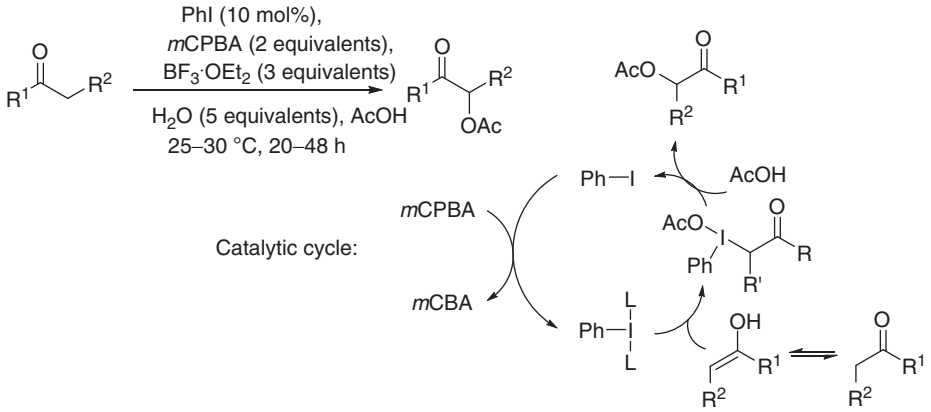


Scheme 47 α-Hydroxylation in the synthesis of complex molecules.

Polymer-supported hypervalent iodine reagents can be used to simplify the purification, and to recover and reoxidize the stoichiometric amount of iodoarene formed in the reaction.[109] Poly[4-(diacetoxyiodo)styrene] has been successfully employed instead of DIB in α-hydroxylations of ketones under both basic and acidic conditions.[122]

The first reactions performed with a catalytic amount of hypervalent iodine reagent were published independently by the groups of Ochiai[123] and Kita[124] in 2005. This opened a new field of applications, and catalytic systems for many other

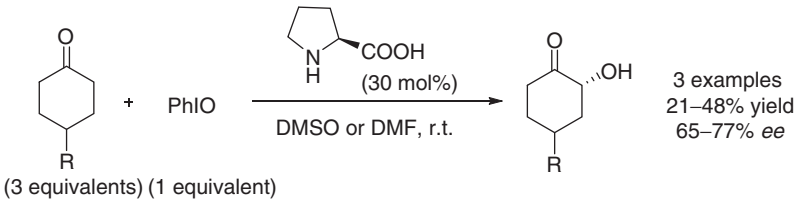
transformations have since appeared.[109] Ochiai et al. reported an α-acetoxylation employing stoichiometric amounts of *m*CPBA and $BF_3 \cdot OEt_2$ together with a catalytic amount of iodobenzene, generating the iodine(III) species *in situ* (Scheme 48).[123] Peracetic acid, generated *in situ* from hydrogen peroxide in acetic anhydride, has also been employed in catalytic α-acetoxylation in the presence of $BF_3 \cdot OEt_2$.[125]



Scheme 48 The first catalytic hypervalent iodine reaction.

Oxone® can be used as the stoichiometric oxidant in α-hydroxylations catalytic in iodoarene, albeit with higher reaction temperature and longer time.[126] Ishihara has recently developed a catalytic α-acyloxylation using TBHP, which is described in Section 7.07.5.3.[127]

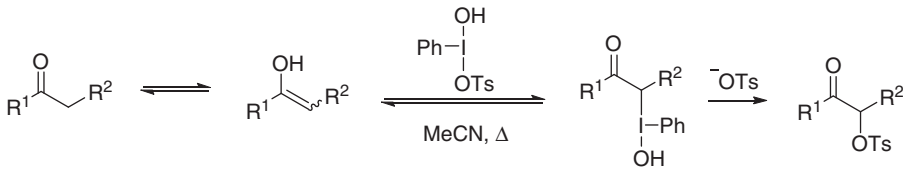
Asymmetric α-oxygenation with hypervalent iodine reagents remains a difficult area, and few reports have enantioselectivities exceeding 50%. One exception is the (*S*)- proline-catalyzed oxidation of cyclohexanones with iodosylbenzene to give α-hydroxylated products with up to 77% *ee* (Scheme 49).[128]



Scheme 49 Asymmetric α-hydroxylation of cyclohexanones.

7.07.5.2 Sulfonyloxylation

The most common α-oxidation with hypervalent iodine reagents is the incorporation of an α-tosyloxy group, which enables facile transformation into other functionalities by subsequent nucleophilic displacement. The reaction is generally performed with HTIB in refluxing acetonitrile, without need for acid or base addition, and was first reported in 1982 (Scheme 50).[129] HTIB is often called Koser's reagent, as it has been utilized in many reactions by Koser's group.[130]



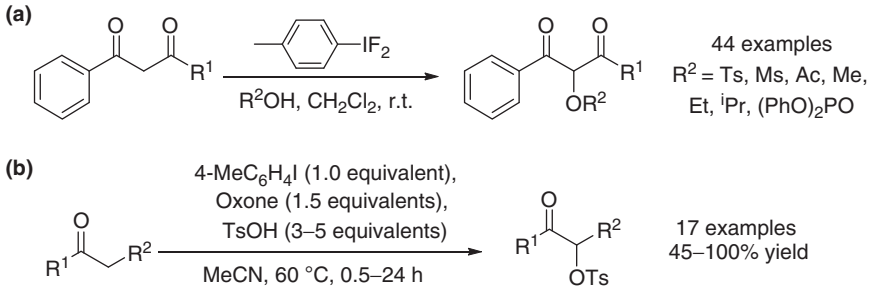
Scheme 50 α-Tosyloxylation of ketones with HTIB.

Substituted versions of HTIB ([hydroxy(tosyloxy)iodo]arenes) have been screened, and introduction of trifluoromethyl substituents *meta* to the iodine increased the α-tosyloxylation yields.[131] Other α-sulfonyloxylations of ketones can be achieved by exchanging the tosyloxy group in HTIB with mesyloxy ([hydroxy(mesyloxy)iodo]benzene (HMIB)),[132] (+)-10-camphorsulfonyloxy,[133] or 2,4-dinitrobenzenesulfonyloxy groups.[130,134]

Trimethylsilyl enol ethers can be α-oxygenated with either HTIB or HMIB. This approach gives control of regioselectivity, as well as better yields with some substrates.[135]

7.07.5.2.1 In situ *formation of the HTIB reagent*

[Hydroxy(tosyloxy)iodo]arenes can be formed *in situ* by treating various iodine(III) precursors, such as DIB or iodosylbenzene, with *p*-toluenesulfonic acid (TsOH).[130,136] 4-Iodotoluene difluoride is an efficient α-oxygenation reagent in the presence of oxygen-containing nucleophiles like TsOH, MsOH, AcOH, diphenyl phosphate, MeOH, EtOH, and ^{i}PrOH (Scheme 51(a)).[137] The active oxygenation reagent is believed to form *in situ*, and the reaction conditions are much milder than the standard ones. Cyclic hypervalent iodine reagents, called iodoxolones, can also be utilized in the preparation of α-tosyloxyketones, and fluorinated versions of the reagent increased the conversion.[138] Iodine(V) reagents are rarely employed, but Dess–Martin periodinane (DMP) can be used in the presence of TsOH or MsOH.[139]

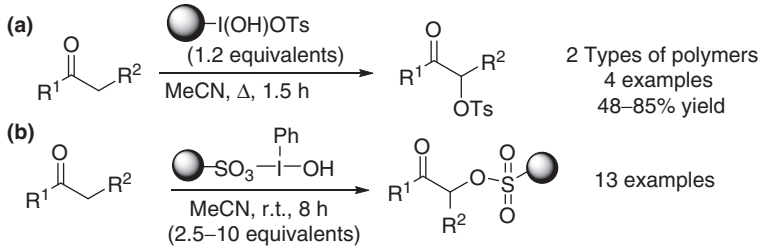


Scheme 51 α-Oxygenation with *in situ* formation of the reagent.

In situ formation of HTIB from iodine(I) has recently been reported, thereby avoiding the need for preformed hypervalent iodine reagents. The α-tosyloxylation of ketones was instead performed with stoichiometric amounts of 4-iodotoluene and Oxone® in the presence of excess TsOH (Scheme 51(b)).[140]

7.07.5.2.2 *Recyclable HTIB reagents*

Stoichiometric amounts of iodoarene waste are formed in oxidations with iodine(III) reagents. The use of polymer-bound or otherwise recyclable reagents minimizes the waste, as the iodoarene can be easily reoxidized to iodine(III) again. Togo has investigated poly[4-hydroxy(tosyloxy)iodo]styrenes in the synthesis of α-tosyloxyketones, and found them to be superior reagents for some substrates (Scheme 52(a)).[141] Another polymer-bound variant of HTIB was formed by treating a polystyrenesulfonic acid resin with DIB, which gave resin-bound α-sulfonyloxy ketones that were used in further transformations (Scheme 52(b)).[142]



Scheme 52 Oxidations with polymer-bound HTIBs.

Figure 4 displays some recyclable HTIB-derivatives that have been employed in α-tosyloxylation.[143] The resulting iodoarenes from the adamantane and tetraphenylmethane derivatives were recovered almost quantitatively after the reactions, making these reagents good alternatives to polymer-bound reagents. Biphenyl and terphenyl-based HTIB reagents showed similar reactivity to the monomeric reagents, but could be easily recovered.[144]

7.07.5.2.3 *Catalytic and asymmetric α-tosyloxylations*

Following Ochiai's breakthrough with the first catalytic hypervalent iodine reaction (see Section 7.07.5.1), several similar transformations with *m*CPBA have been reported. The corresponding iodobenzene-catalyzed α-tosyloxylation is depicted in Scheme 53.[145]

Asymmetric α-tosyloxylation of ketones has been investigated for many years by Wirth et al., and several types of chiral HTIB-derivatives have been screened for asymmetric induction.[146] Intramolecular coordination of various oxygen-based functional groups at the stereocenter has been most successful, but the obtained enantioselectivities have been modest (Scheme 54(a)).

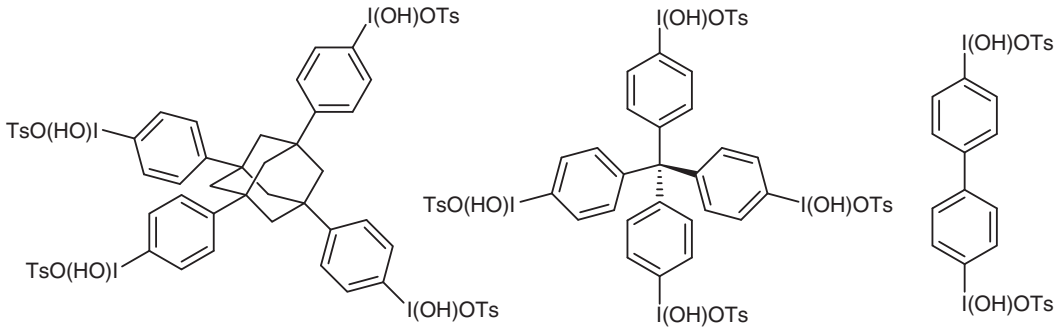
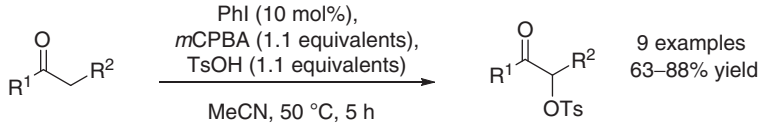
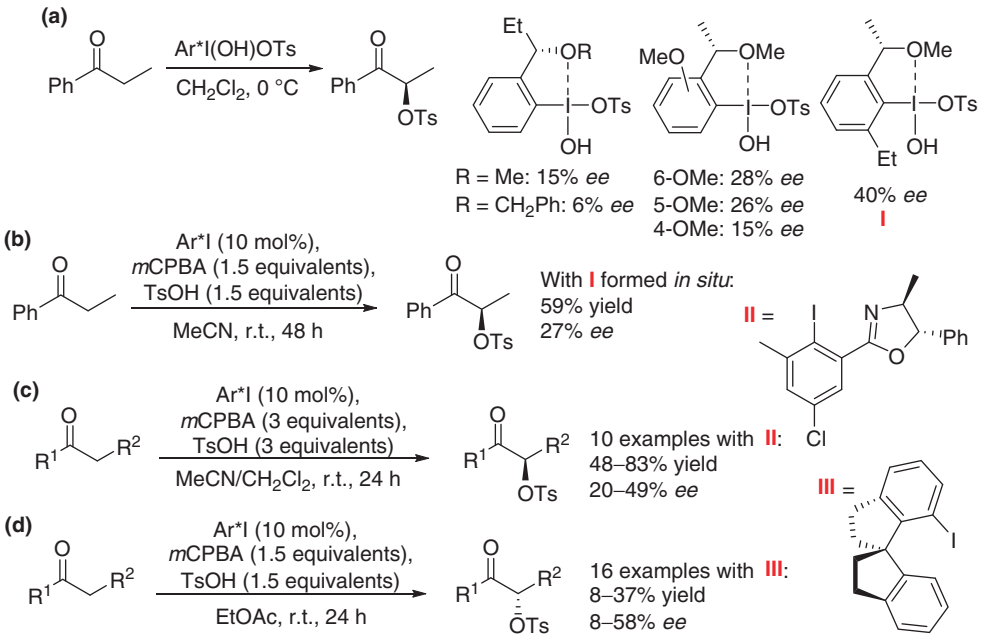


Figure 4 Recyclable HTIB reagents.



Scheme 53 PhI-catalyzed α-tosyloxylation.



Scheme 54 Asymmetric α-tosyloxylation.

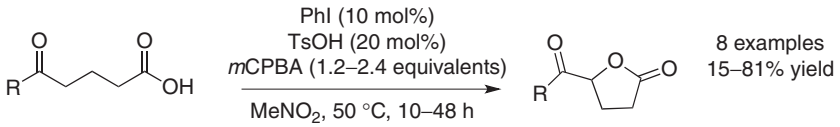
The first catalytic asymmetric α-tosyloxylation was reported in 2007, using the established *m*CPBA system with a catalytic amount of enantiopure iodoarene (Scheme 54(b)).[147] The asymmetric induction was increased to 39% *ee* by introduction of a sterically hindered ester moiety at the stereocenter.[148]

Chiral iodoaryl oxazolines could also be used in the catalytic asymmetric α-tosyloxylation with moderate enantiomeric excess (Scheme 54(c)).[149] Introduction of an *ortho*-methyl group in the hypervalent iodine reagent increased the yield substantially, and a hypervalent twist was described as a key feature to enhance the catalytic activity in this reaction.

The highest selectivity to date is 58% *ee,* which was obtained in low yields using a derivative of Kita's chiral spirobiindane catalyst[150] (Scheme 54(d)).[151] The search for hypervalent iodine reagents that give higher enantioselectivities continues, and has greater chances of success with catalytic reaction conditions. These have enabled the use of previously unobtainable chiral HTIB reagents, which are not stable enough to allow isolation.

7.07.5.3 Intramolecular α-Oxygenations

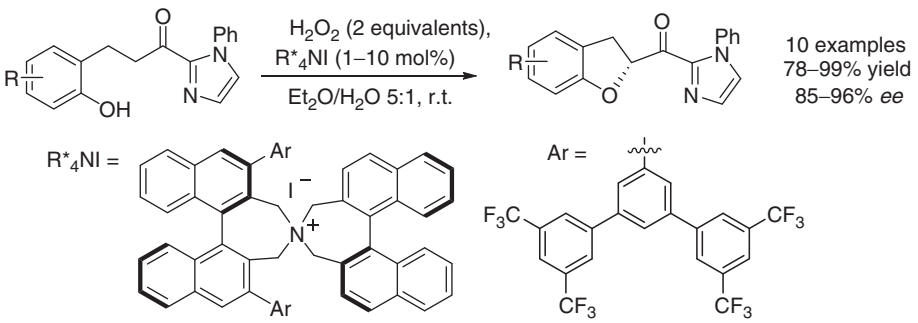
α-Tosyloxylated carbonyl compounds can easily be transformed into other α-oxygenated products, either by intramolecular cyclizations or by addition of an external nucleophile.[152] Moriarty reported the synthesis of keto-γ-lactones from 5-ketoacids in 1990,[153] and the reaction sequence is often utilized in the synthesis of oxygen-containing heterocycles.[154] A catalytic version of this reaction was recently achieved with Ochiai's established *m*CPBA protocol (Scheme 55).[155] Moderate yields were obtained due to byproducts from Baeyer–Villiger oxidation. Two catalytic lactonizations using chiral iodoarenes under similar conditions have been reported with up to 51% *ee*.[148b,156]



Scheme 55 PhI-catalyzed synthesis of lactones.

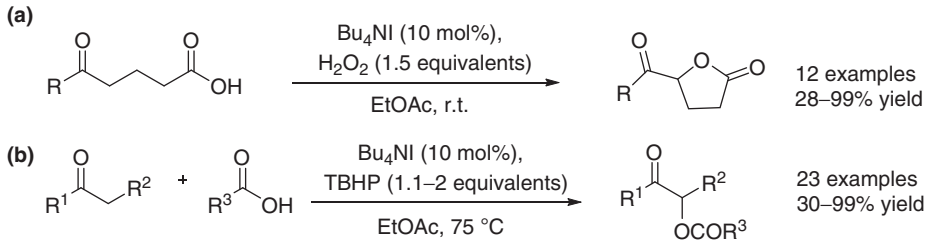
Intramolecular α-oxygenations can also be achieved with other iodine(III) reagents. In the rhodium-catalyzed synthesis of furanones from β-ketoesters, DIB was utilized to form an intermediate iodonium ylide, which cyclized to the corresponding 2-substituted heterocycle.[157] Iodosylbenzene mediates the transformation of tricarbonyl compounds into fused dihydrofurans via a [1,5]-oxidative cyclization.[158]

In 2010, Ishihara reported a highly enantioselective oxidative cycloetherification using hydrogen peroxide as the stoichiometric oxidant and a chiral quaternary ammonium iodide catalyst as the source of asymmetric induction (Scheme 56).[159] The products were obtained in excellent yields and enantioselectivities, and the active oxidant was proposed to be hypoiodite (IO^-) or iodite (IO_2^-).[109a]



Scheme 56 Asymmetric cycloetherification with hydrogen peroxide.

This oxidation system was subsequently applied to the synthesis of lactones, thus avoiding the *m*CPBA-related problem with Baeyer–Villiger byproducts (Scheme 57(a)). Furthermore, intermolecular couplings of both ketones and aldehydes with carboxylic acids were realized by using TBHP instead of hydrogen peroxide (Scheme 57(b)).[127]

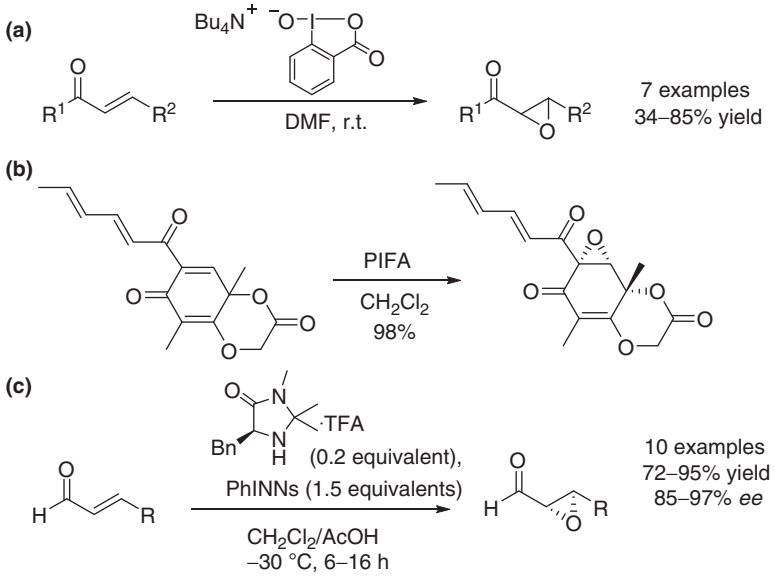


Scheme 57 Lactonization and α-acyloxylation with peroxides.

7.07.5.4 Epoxidation of α,β-Unsaturated Carbonyl Compounds

Hypervalent iodine compounds can be used in oxidation of the alkene moiety in α,β-unsaturated carbonyl compounds, despite their electrophilic character. Ochiai et al. described the first hypervalent iodine compound that could epoxidize enones in 2000.

The tetrabutylammonium oxido-λ^3-iodane reagent contains an oxyanion that attacks the electron-deficient alkene, followed by ring-closure to the epoxide and reductive elimination of the iodoarene (Scheme 58(a)).[160]



Scheme 58 Epoxidation of enones; Ns = (4-nitrophenyl)sulfonyl.

PIFA was employed in a chemo- and stereoselective epoxidation in the total synthesis of epoxysorbicillinol, demonstrating the mild and selective features of many hypervalent iodine-mediated transformations (Scheme 58(b)).[161] Epoxidation of enones can also be achieved by sequential addition of IBX − I_2 and 10% NaOH, and proceeds by initial iodohydroxylation followed by cyclization.[162]

An enantioselective epoxidation of α,β-unsaturated aldehydes was achieved by combining [(nosylimino)iodo]benzene (PhINNs) with a chiral imidazolidinone catalyst (Scheme 58(c)).[163] The hypervalent iodine reagent PhINNs is broadly applied in metal-catalyzed aziridination reactions,[3e] although its use in epoxidation is less common. The reaction proceeds by enamine formation, followed by epoxidation with PhIO, which is slowly formed from PhINNs under the reaction conditions.

7.07.6 Conclusion

In this chapter, the most important methods for α-oxygenations of carbonyl compounds have been covered, ranging from classical procedures using excess of toxic reagents to mild asymmetric catalytic methods. Apart from α-hydroxylations, also α-sulfonyloxylations, α-acetyloxylations, and epoxidations and dihydroxylations of α,β-unsaturated carbonyl compounds have been described.

The classical α-acetyloxylation is carried out using stoichiometric amounts of $Pb(OAc)_4$ or related metal oxides. This reaction is still sometimes applied in total synthesis, but harsh conditions are needed, in combination with very toxic and environmentally harmful reagents. Moreover, regioselectivity cannot easily be predicted and yields are generally moderate. A modern alternative is the α-acetyloxylation by hypervalent iodine reagents under mild and metal-free conditions.

α-Hydroxylations can be done from ketone or ester enolates using MoOPH. High regioselectivities can be obtained but usually an excess of molybdenum complex has to be used. Alternatively, metal-based hydroxylation of enol ethers can be performed using the catalytic oxidation system OsO_4/NMO. This reaction is particularly useful for α,β-unsaturated carbonyl compounds, which can be enantioselectively dihydroxylated using the commercially available AD-mixes.

Molecular oxygen is the cheapest and most environmentally benign oxidant, but despite some isolated examples of direct α-oxygenation of highly enolizable ketones, unactivated oxygen is generally unsuitable for such oxidations. α-Hydroxylations with molecular oxygen can be facilitated by transition metal catalysis, but this field is underdeveloped and enantioselective reactions remain unknown.

Organic peroxides are good alternatives to molecular oxygen, and silyl enol ethers can be hydroxylated with peroxides in the Rubottom reaction. However, the most valuable use of peroxides is in epoxidation reactions of α,β-unsaturated carbonyl compounds. High enantiomeric excesses can be obtained using lanthanide catalysis or several different organocatalysts.

N-Sulfonyloxaziridines can α-hydroxylate enolates, and asymmetric oxidations can be obtained using chiral modifications of the *N*-sulfonyloxaziridines. The major drawback with this method is the need for stoichiometric amounts of the chiral reagent, as catalytic methods are still lacking.

Other kinds of α-oxygenations give products containing O–heteroatom bonds, such as the *O–N* products obtained with nitrosobenzene. Highly enantioselective α-oxygenations of aldehydes and ketones are achieved with proline-catalyzed aminoxylations using this oxidant. An excess of carbonyl substrate is often needed and in some cases the nitrogen–oxygen bond of nitrosobenzene is hard to cleave in the final product, but the mild conditions and high selectivities have already led to many applications of this method.

Hypervalent iodine reagents are efficient oxidants not only for mild and metal-free α-acetoxylations but also for hydroxylations and methoxylations depending on the reaction conditions. Tosyloxylations can easily be performed with Koser's reagent. The reactive iodine(III) species can be formed *in situ* or used in catalytic amounts. Despite the many recent improvements in the field, highly enantioselective catalytic reactions are still restricted to intramolecular oxygenations.

Many different methods are known in the α-oxygenations of carbonyl compounds, but there is still room for improvement and the quest for the ideal, high-yielding, general, enantioselective and environmentally benign α-oxygenation of carbonyl compounds is still continuing.

For related chapters in this Comprehensive, you can refer to – Chapters 1.16, 2.06, and 7.16.

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7.08 Oxidation Adjacent to Nitrogen

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Glossary

Acoustic emulsification A technique has been developed to study the phenomenon where oil is dispersed as a fine suspension into water at the frequency of 20 kHz.

Atom efficiency An important concept of green chemistry which describes overall conversion efficiency of any chemical processes in terms of all atoms involved. It can also be defined as the ratio between the molecular weight of the desired product and that of all reactants.

Cytochrome P-450 A superfamily of closely related enzymes widely spread over all kingdoms of life and exhibit extraordinary diversity in their involvement in oxidation of organic substances.

Electroauxiliary Functional groups used in electrochemical organic synthesis to control the reactivity of substrates and reaction pathways, which are quite effective for driving otherwise difficult reactions to obtain the desired product in a more selective way.

Electron spin resonance (ESR) A technique used for studying chemical substances with unpaired electrons, especially for the study of radicals formed in chemical reactions.

Single-electron transfer (SET) An electron moves from one chemical species (e.g., a molecule) to another one, where the oxidation state of both reaction components change. In chemical reactions, it usually refers to the process where an electron transfers from nucleophile to the substrate to produce a radical intermediate.

7.08.1 Introduction

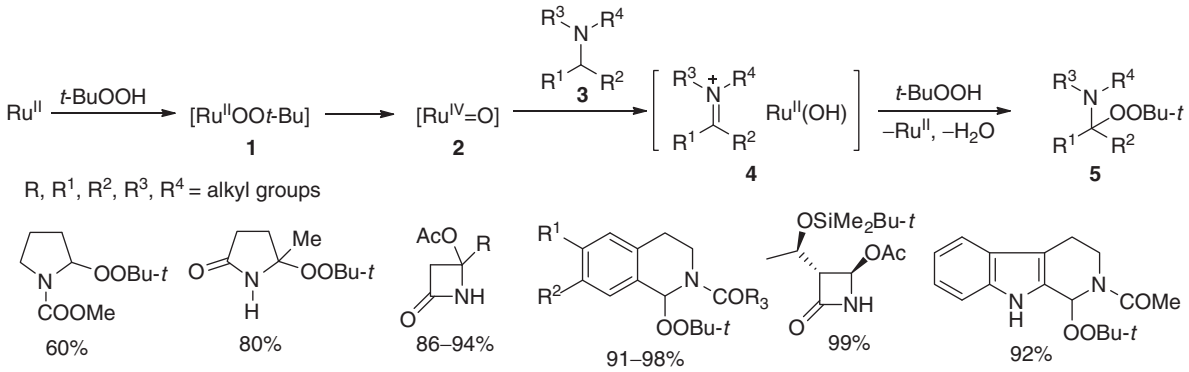
C–H bonds, although ubiquitous in organic molecules, are not traditionally regarded as functional groups due to their low reactivity and selectivity. The high dissociation energy of C–H bonds (generally 90–130 kcal mol^{-1}) makes them inert under a variety of reaction conditions. Furthermore, a slight difference in reactivity among different C–H bonds in a molecule makes it difficult to control selectivity and therefore prevents an extensive application of C–H bond functionalization in organic synthesis. However, the strength of C–H bonds is greatly influenced by substituents. For example, Csp^3–H bonds adjacent to heteroatoms typically show higher activities than their isolated alkyl counterparts, either through coordination with transition metals or via radical processes. Over the past few decades, tremendous efforts have been devoted to the oxidative functionalization of C–H bonds adjacent to a nitrogen atom as well as relevant mechanistic studies. These reactions can be mainly classified into four categories depending on various strategies used to generate the reactive iminium species: transition-metal-catalyzed approaches under thermal conditions, metal-free chemical approaches, electrochemical methods and photoredox pathways using visible light irradiations. All these methods of oxidative functionalization of C–H bonds adjacent to a nitrogen atom are discussed in this chapter.

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7.08.2 Transition-Metal-Catalyzed Oxidation

7.08.2.1 Oxygenation Reactions

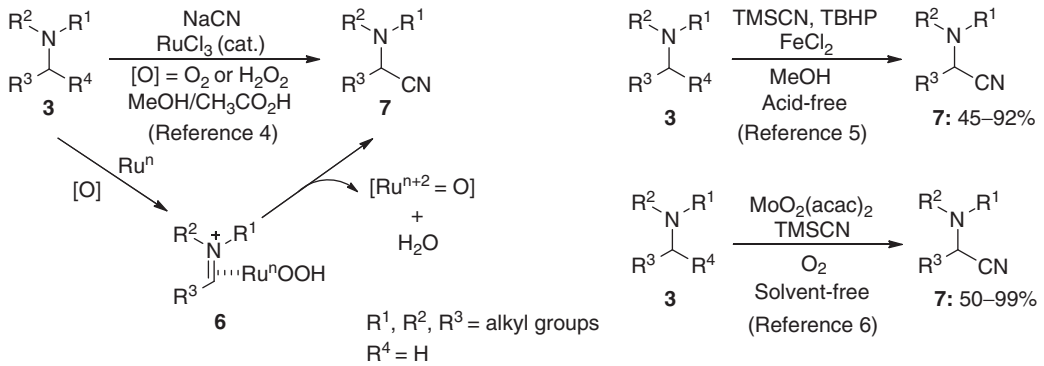
α-Alkoxy tertiary amines are an important series of heteroatomic compounds because their unique *N,O*-hemiacetal structures can allow further elaborations. Although α-oxidation of tertiary amines is a common biological process, only until 1988 Murahashi and coworkers disclosed one of the earliest examples of chemical functionalization of this class of compounds by directly introducing a *tert*-butoxy substituent at the α-position of tertiary amines **3** in the presence of ruthenium complex **2** under oxidative conditions.[1] Since the oxidative reaction led to the formation of α-(*tert*-butoxy)alkylamines **5**, which is quite similar to the reaction of cytochrome P-450, the authors proposed a cytochrome P-450 type mechanism based on both kinetic studies and isotope effects. Later on, the scope of oxygenation of tertiary amines has been expanded to the *tert*-butoxylation of other cyclic amides as well as the acetoxylation of β-lactams (Scheme 1).[2]



Scheme 1 Oxygenation of tertiary amines. Reproduced from Murahashi, S. I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490–1501, and Murahashi, S.; Naota, T.; Kuwabara, T.; *et al. J. Am. Chem. Soc.* **1990**, *112*, 7820–7822.

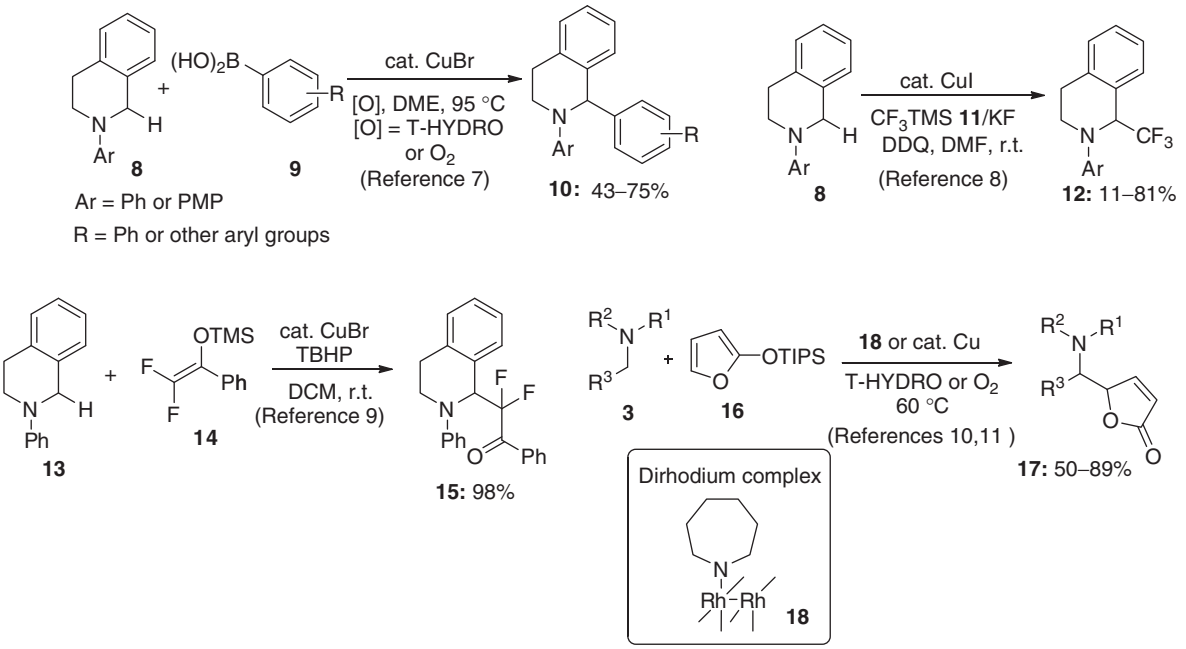
7.08.2.2 C–C Bond Formation from Carbon Nucleophiles

In 2003, Murahashi et al. reported an aerobic oxidative cyanation, where tertiary amines **3** were converted into their corresponding α-aminonitriles **7** using sodium cyanide and molecular oxygen in the presence of a catalytic amount of $RuCl_3 \cdot nH_2O$.[3] Further studies showed that the ruthenium-catalyzed oxidative cyanation of tertiary amines can also proceed by using hydrogen peroxide as the external oxidant.[4] In the next several years, oxidative cyanation of amines have also been successfully carried out by means of other transition metals such as iron[5] and molybdenum (Scheme 2).[6]



Scheme 2 Oxidative cyanation of tertiary amines. Reproduced from Murahashi, S. I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490–1501; Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, *45*, 5024–5026, and Alagiri, K.; Prabhu, K. R. *Org. Biomol. Chem.* **2012**, *10*, 835–842.

During the next few years, a vast array of carbon nucleophiles have been examined carefully by using copper salts as transition metal catalysts under the optimized thermal conditions (Scheme 3). Arylboronic acids **9**[7] and the Rupper–Prakash reagent **11**[8] have been proved to be effective nucleophiles to form new C–C bonds adjacent to nitrogen atoms in *N*-aryltetrahydroisoquinolines. Subsequently, Qing et al. explored the use of difluoroenol silyl ether **14** as a nucleophile, allowing the formation

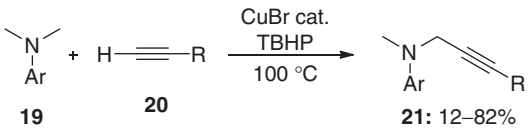


Scheme 3 Broad examination of carbon nucleophiles. Reproduced from Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661–3663; Mitsudera, H.; Li, C.-J. *Tetrahedron Lett.* **2011**, *52*, 1898–1900; Chu, L.; Zhang, X.; Qing, F.-L. *Org. Lett.* **2009**, *11*, 2197–2200; Shen, Y.; Tan, Z.; Chen, D.; *et al. Tetrahedron* **2009**, *65*, 158–163, and Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649.

of α,β-amino-α,α-difluoroketones **15**.[9] Additionally, Guo et al. have reported the use of siloxyfuran **16** as an excellent carbon nucleophile,[10] albeit the first example of siloxyfurans was established by Doyle and coworkers using dirhodium complex **18** as a metal catalyst in a pseudo-Mannich oxidative coupling dating back to 2006.[11]

7.08.2.3 C–C Bond Formation from Two C–H Bonds

While searching for a new efficient method for C–C bond formation from two different C–H bonds, Li proposed a new concept named cross-dehydrogenative coupling (CDC) in 2003. The initial work demonstrated the formation of desired C–C bonds in propargylic amines **21** between alkynyl Csp–H bonds and Csp^3–H bonds of nitrogen in amines **19**, in the presence of copper salts and an oxidant *tert*-butyl hydroperoxide (TBHP) under thermal conditions (Scheme 4).[12]

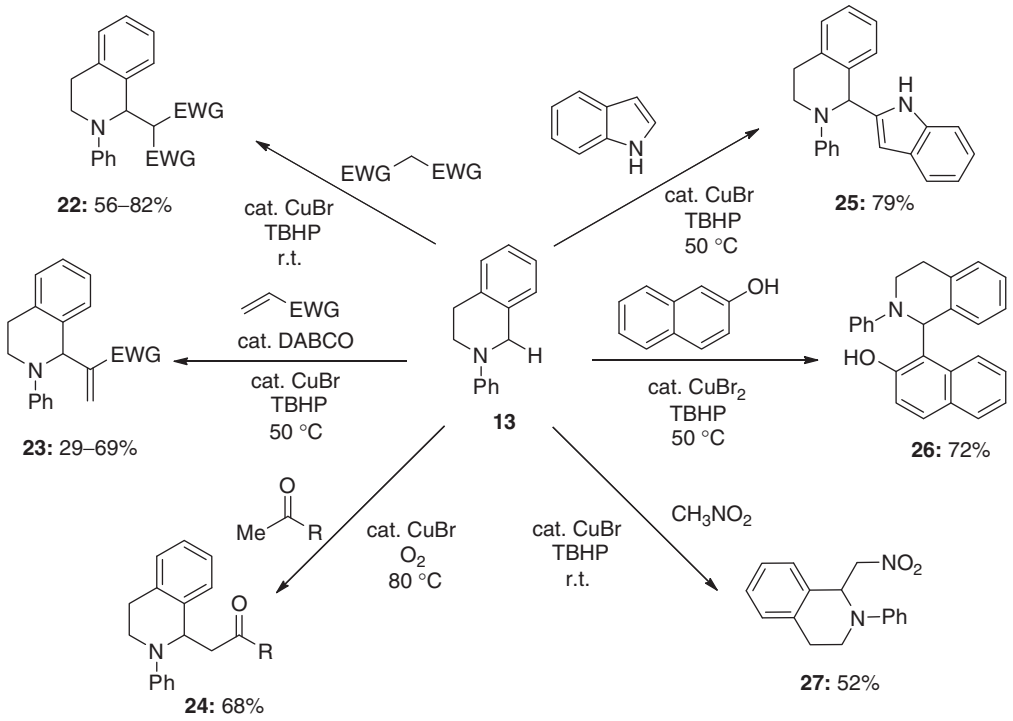


Ar = Ph, 4-MeC_6H_4, 2-MeC_6H_4, 4-BrC_6H_4
R = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 2-MeC_6H_4, 4-BrC_6H_4, 4-PhC_6H_4, 2-Py

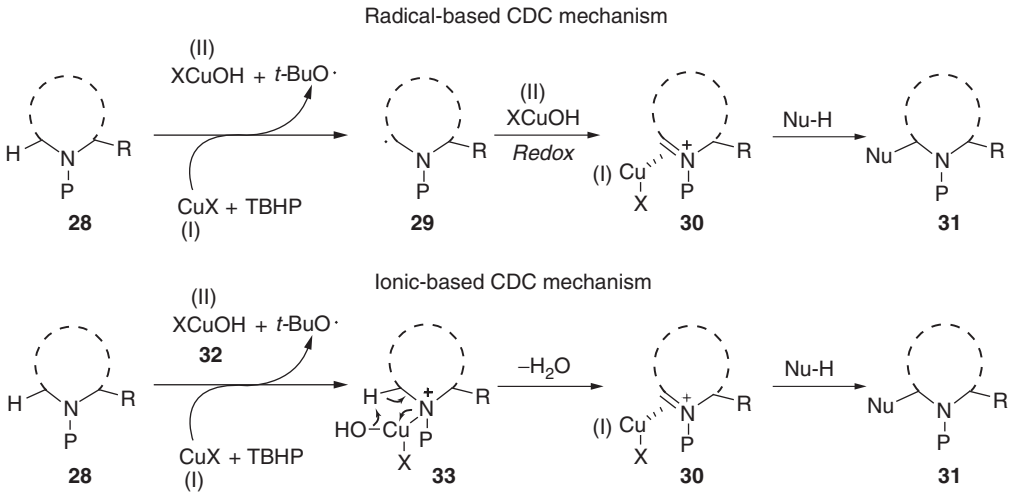
Scheme 4 A (Csp^3–Csp) CDC reaction: alkynylation of tertiary amines. Reproduced from Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811.

Subsequent efforts on CDC reactions were made to expand the scope of pronucleophiles. Screening various pronucleophiles such as nitromethanes,[13] malonates,[14] indoles,[15] naphthols,[16] methyl ketones[17] and Morita–Baylis–Hilman (MBH) adducts[16] under optimized conditions, Li and others have developed a vast array of CDC reactions derived from two C–H bonds (Scheme 5). Although CDC reactions are mainly catalyzed by copper salts, there are also elegant examples using other transition metals such as iron[18] and vanadium.[19]

Based on the previous literature, the mechanism of generation of iminium species in the CDC reaction could proceed via either a radical or an ionic process (Scheme 6). In the former, a *tert*-butoxyl-mediated H-abstraction from an α-carbon adjacent to a nitrogen atom, followed by a single-electron transfer (SET) process, gives rise to iminium complex **30**. In the latter, the high Lewis-acidic oxy-copper species **32**, formed via the oxidation of copper salts by TBHP, coordinates with the nitrogen atom to generate the



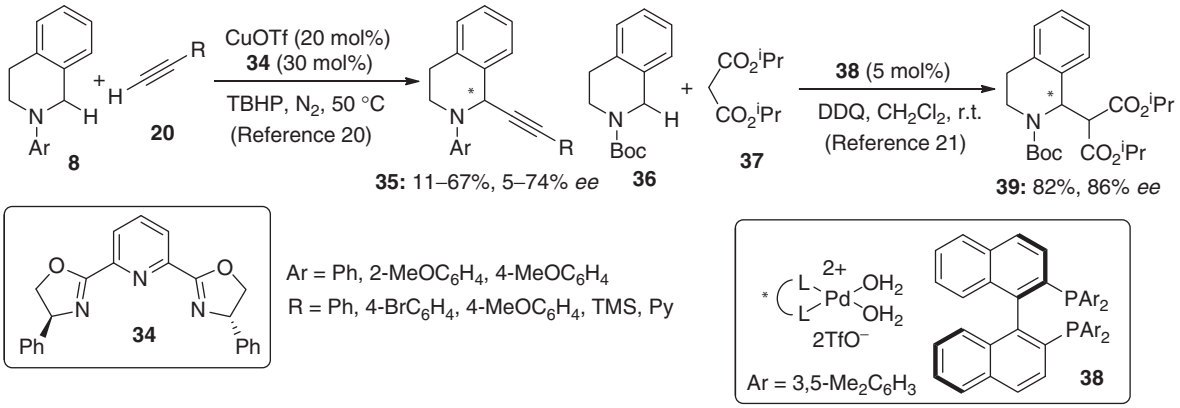
Scheme 5 Extension of the scope of pronucleophiles in CDC reaction. Reproduced from Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673; Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, *2005*, 3173–3176; Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968–6969, and Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928–8933.



Scheme 6 Two possible pathways to the iminium intermediate in CDC reaction.

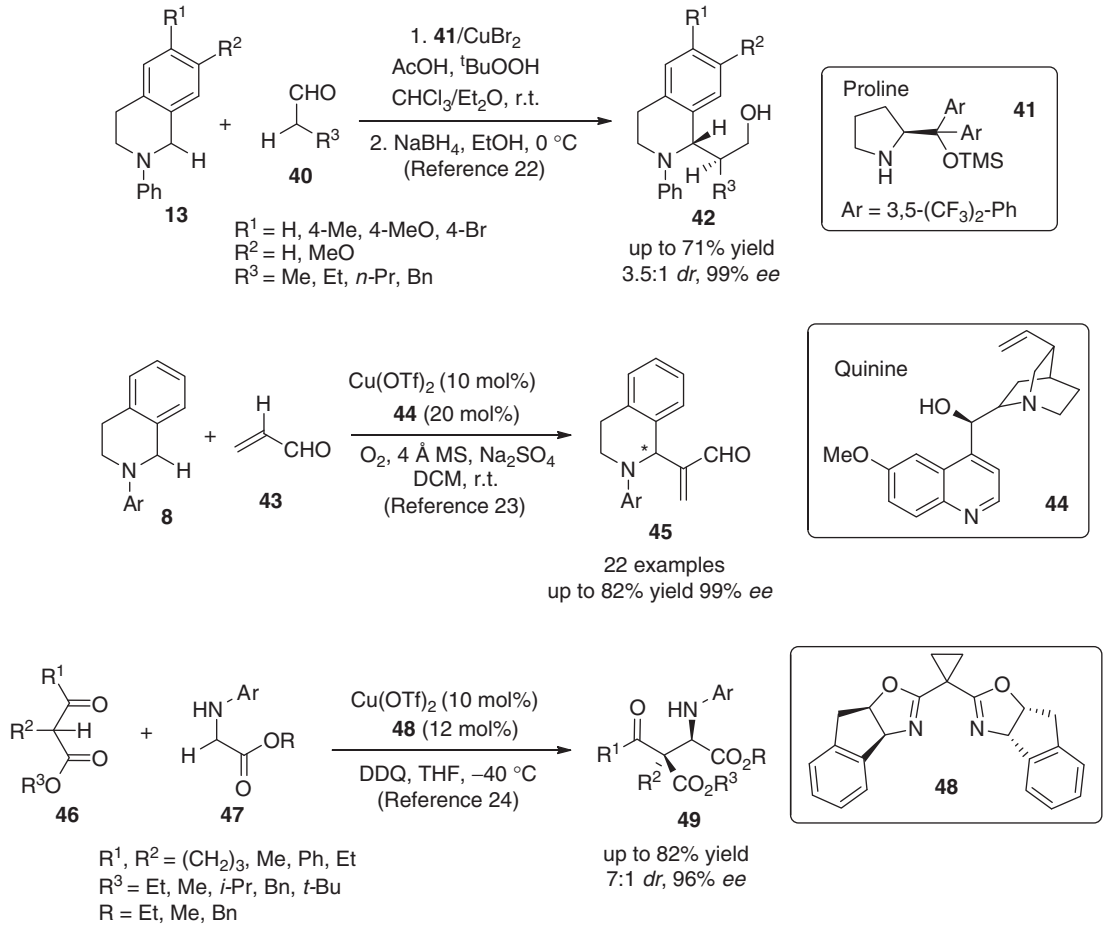
complex **33**. A subsequent release of water in **33** gives rise to the same reactive species **30**. In both cases, CDC reactions can be completed by addition of nucleophiles to iminium species and simultaneous regeneration of Cu(I) species.

Of paramount importance to broadening the scope of pronucleophiles in CDC reactions is the enantioselective formation of C–C bonds next to nitrogen atoms in tertiary amines. The first asymmetric CDC reaction between prochiral benzylic methylenes in tertiary amines **8** and Csp–H bonds in terminal alkynes **20** was achieved using CuOTf and the chiral pyridinyl bisoxazoline auxiliary **34**.[20] Though the overall enantioselectivity is moderate (*ee* 5–74%), this work is significantly important as it leads to the potential application of CDC reactions in asymmetric synthesis of tetrahydroisoquinoline alkaloids. Sodeoka and coworkers designed an asymmetric approach to construct tetrahydroisoquinoline skeleton **39** by using the chiral palladium complex **38** along with an external oxidant 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[21] The advantages of this strategy over the previous one are its synthetically useful *ee* value as well as an easily removable *N*-Boc protecting group in substrate **36** (Scheme 7).



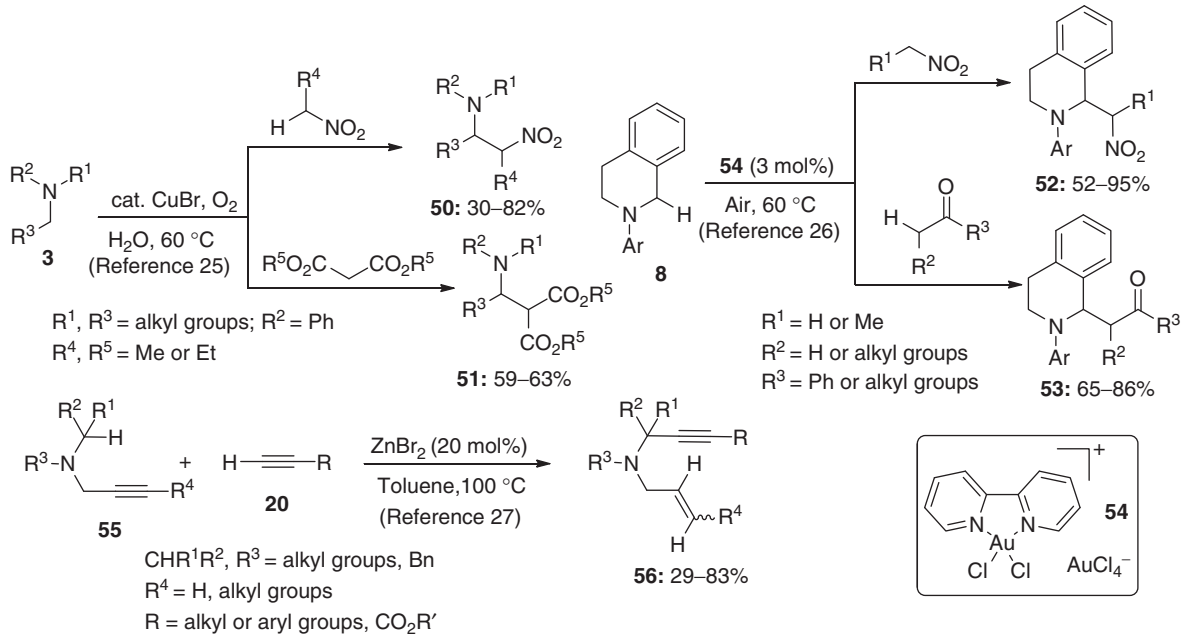
Scheme 7 Asymmetric C–C bond formation in CDC reaction. Reproduced from Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997–4999, and Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010–14011.

Chi and coworkers reported a successful application of a dual catalyst system by combining copper salts with proline derivatives **41**.[22] This combination allowed a highly enantioselective oxidative coupling between tertiary amines **13** and aldehydes **40**. Similarly, Wang and coworkers described a novel metal/organocatalyst-catalyzed oxidative olefination of tertiary amines **8** in the presence of molecular oxygen.[23] Most examples in this work showed excellent enantioselectivities (69–99% *ee*), where the bifunctional cinchona alkaloid **44**, instead of proline derivatives, was used as a Lewis acid organocatalyst. Apart from commonly used tertiary amines, Wang and coworkers have also discovered a versatile asymmetric approach for the construction of optically active amino acid skeletons **49** (Scheme 8).[24]



Scheme 8 Application of dual catalytic enantioselective approaches in CDC reaction. Reproduced from Zhang, J.; Tiwari, B.; Xing, C.; Chen, X.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2012**, *51*, 3649–3652; Zhang, G.; Ma, Y.; Wang, S.; Zhang, Y.; Wang, R. *J. Am. Chem. Soc.* **2012**, *134*, 12334–12337, and Zhang, G.; Zhang, Y.; Wang, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 10429–10432.

Equally important are some outstanding examples of C–H bond oxidative functionalization catalyzed by transition metals through much greener pathways (Scheme 9). For example, Basle and Li have demonstrated that water can be used as an alternative solvent, and molecular oxygen can be used as an alternative oxidant in CDC reactions.[25] Very recently, Zhu and coworkers disclosed another green protocol with the use of air as a sole oxidant in the presence of gold complex **54**, where both nitroalkanes and unmodified ketones were acted as pronucleophiles.[26] Sugiishi and Nakamura have explored the use of zinc dibromide in the oxidative coupling between propargylic amines **55** and terminal alkynes **20**, leading to the formation of iminium intermediates by means of 1,5-hydride shift.[27] The beauty of this work lies in the fact that the zinc(II)-catalyzed redox CDC reaction proceeds without an external oxidant, following the principle of sustainable and green chemistry.



Scheme 9 Greener approaches in CDC reaction. Reproduced from Basle, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047–1050; Xie, J.; Li, H.; Zhou, J.; Cheng, Y.; Zhu, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 1252–1255, and Sugiishi, T.; Nakamura, H. *J. Am. Chem. Soc.* **2012**, *134*, 2504–2507.

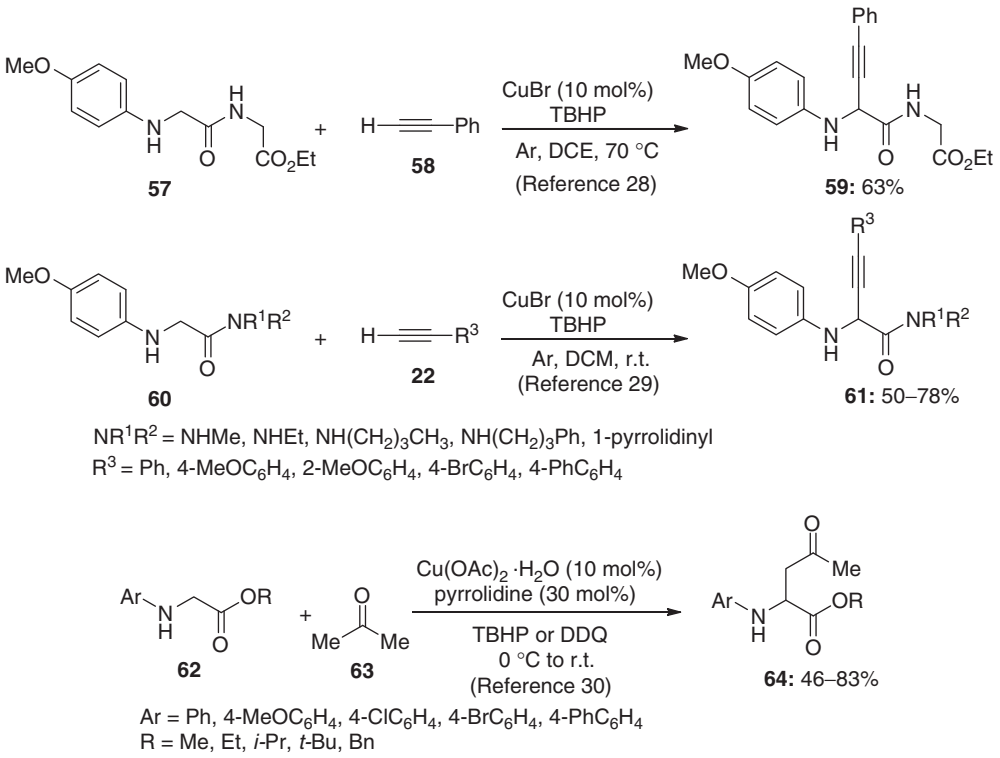
In searching for general methods to synthesize nonnatural α-amino acids and natural amino acids through site-specific modifications, Zhao and Li have studied direct α-functionalization of natural peptides via CDC reactions. In 2008, they pioneered a novel method for the functionalization of α-amino acid derivative **57** via its oxidative coupling with terminal alkyne **58**.[28] Subsequently, they developed a complementary method involving the site-specific modification of peptides and glycine derivatives **60** by adapting the CDC strategy.[29] Such a strategy offers an attractive opportunity to rapidly construct various amino acid- and peptide-based skeletons. Recently, the synthesis of amino acid derivatives has been carefully investigated by cooperative interplay of transition metals and aminocatalysts. Xie and Huang have disclosed a mild protocol to synthesize *N*-aryl amino acid derivatives **64** by combining copper salts with pyrrolidine in the presence of TBHP or DDQ under air.[30] Based on radical inhibition experiments, they tentatively proposed a SET mechanism as a pathway to generate iminium intermediates (Scheme 10).

Further demonstration of the utility of the CDC reaction comes from its recent combination with electrochemical oxidation, a widely studied area for the generation of carbocation intermediates. To access the reactive iminium species **65**, an electrochemical method (the 'cation pool' named by Yoshida will be discussed in detail in section 7.08.4) was introduced by Li and coworkers.[31] In this regard, the CDC reaction between *N*-phenyl tetrahydroisoquinoline **13** and either nitromethane or diethylphosphite was carried out in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([BMiM][BF_4]) in the presence of NEt_3. Another practical example of CDC reactions derives from the application of magnetically recoverable iron nanoparticles. Easy separation and reuse of magnetic Fe_3O_4 nanoparticles allowed a facile Csp^3–Csp^3 bond formation in the presence of molecular oxygen (Scheme 11).[32]

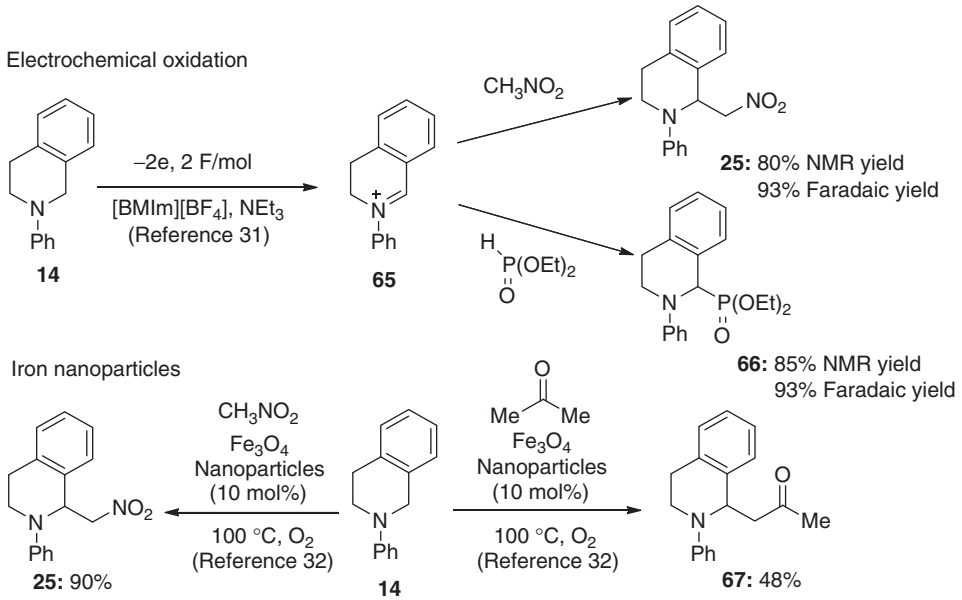
Very recently, Klussmann and coworkers have performed a series of elegant mechanistic studies on a Cu-catalyzed aerobic oxidative coupling with *N*-phenyl tetrahydroisoquinoline **13**, in which the structure of iminium dichlorocuprate **69** was characterized by X-ray crystallography for the first time (Scheme 12).[33] Their studies lead to a better understanding of the oxidative functionalization of Csp^3–H bonds adjacent to nitrogen atoms in tertiary amines.

7.08.2.4 C–Y (Heteroatom) Bond Formation

Although there have been less intensive studies toward oxidative C–Y bond formation (Y refers to heteroatom), except oxygenations previously mentioned in Section 7.08.2.1, examples recently reported show some promising prospects in this field. The

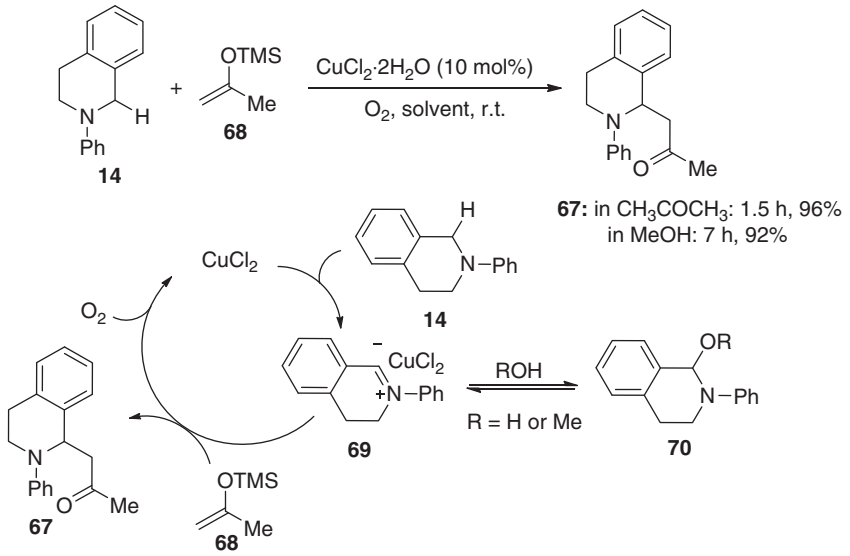


Scheme 10 Synthesis of amino acid derivatives in CDC reaction. Reproduced from Zhao, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 7075–7078; Zhao, L.; Baslé, O.; Li, C.-J. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4106–4111, and Xie, J.; Huang, Z.-Z. *Angew. Chem. Int. Ed.* **2010**, *49*, 10181–10185.

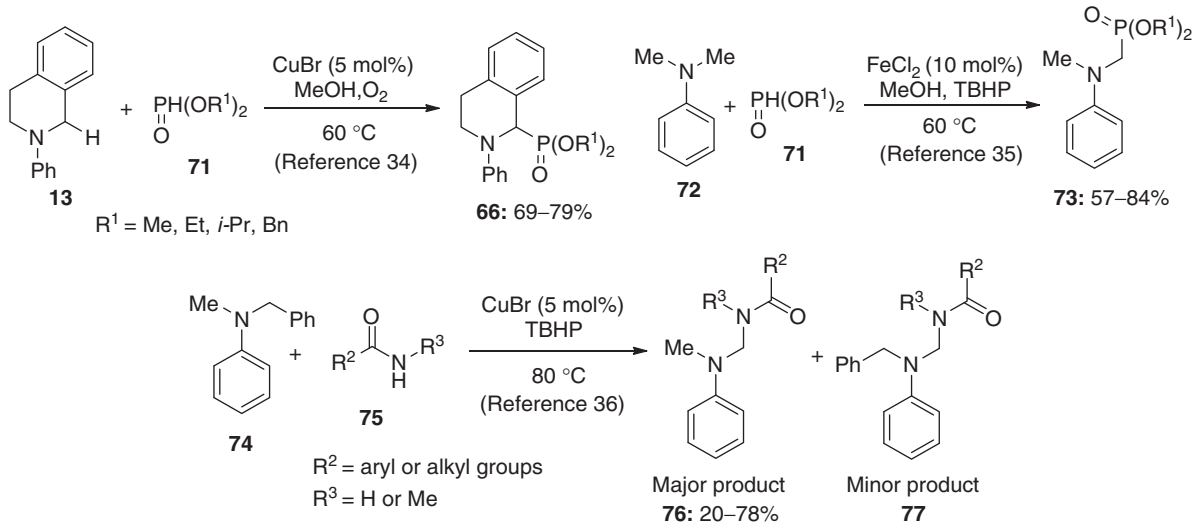


Scheme 11 Combination of CDC reaction with electrochemistry and nanoparticles. Reproduced from Baslé, O.; Borduas, N.; Dubois, P.; *et al. Chem. Eur. J.* **2010**, *16*, 8162–8166, and Zeng, T.; Song, G.; Moores, A.; Li, C.-J. *Synlett* **2010**, 2002–2008.

most frequently used nucleophiles to form C–P bond are dialkyl phosphonates **71**. Li and Ofial have discovered a method to construct C–P bonds adjacent to nitrogen atoms in tertiary amines catalyzed by either copper[34] or iron[35] salts with slightly different loadings. In terms of C–N bond formation, Zhao and coworkers have described an amidation of unactivated Csp^3–H bonds adjacent to nitrogen atoms in tertiary amines.[36] Interestingly, when *N*-methyl-*N*-benzylaniline **74** was treated with various amides **75**, the major product was found to be the dephenylation product **76** instead of the desired CDC product **77** (Scheme 13).



Scheme 12 Mechanistic studies on CDC reaction. Reproduced from Boess, E.; Sureshkumar, D.; Sud, A.; *et al. J. Am. Chem. Soc.* **2011**, *133*, 8106–8109.

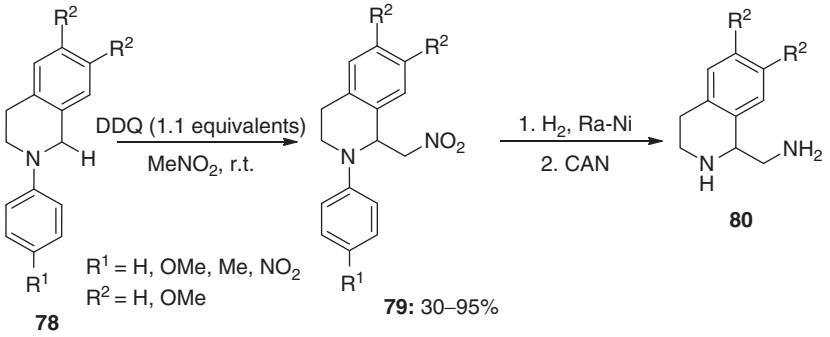


Scheme 13 C–P and C–N bond formation via transition-metal-catalyzed oxidation. Reproduced from Basle, O.; Li, C.-J. *Chem. Commun.* **2009**, *45*, 4124–4126; Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, *45*, 6023–6025, and Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2007**, *9*, 3813–3816.

7.08.3 Metal-Free Oxidation

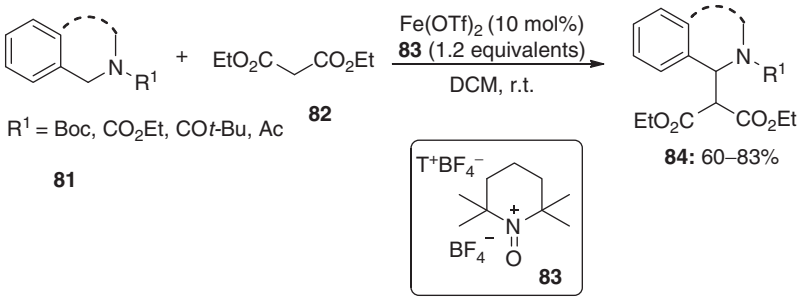
7.08.3.1 C–C Bond Formation from Two C–H Bonds

Despite the fact that a significant achievement has been made in the area of transition-metal-catalyzed oxidative functionalization adjacent to nitrogen atoms in tertiary amines, the strategy of metal-free oxidation receives little attention. In the Section 7.08.2, it was known that DDQ can be employed as a hydrogen acceptor in the transition-metal-catalyzed oxidative functionalization of tertiary amines. Alternatively, a stoichiometric amount of DDQ, instead of a combination of external oxidants and transition metals, can be directly used to effect oxidative C–H bond activation. Inspired by Li's work on the DDQ-mediated CDC reaction between benzyl ethers and ketones,[37] Tsang and Todd have reported another similar reaction between tetrahydroisoquinolines **78** and nitromethane, followed by a reduction of **79** to synthesize vicinal diamines **80**.[38] A screen of both electron-poor and electron-rich *N*-aryl tetrahydroisoquinolines suggested the compatibility of a broad range of substituents under mild metal-free conditions (Scheme 14).



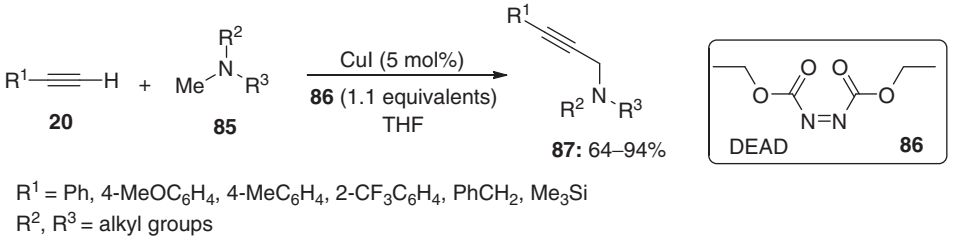
Scheme 14 DDQ-mediated metal-free CDC reaction. Reproduced from Tsang, A. S. K.; Todd, M. H. *Tetrahedron Lett.* **2009**, *50*, 1199–1202.

Analogously, oxoammonium TEMPO salts have been found to act as effective oxidants to trigger the formation of iminium species. A recent protocol established by Richter and Mancheño showed the oxidative ability of the oxoammonium TEMPO salt **83**, in which C–C bond formations took place between Csp^3–H bonds adjacent to nitrogen atoms in tertiary amines **81** and Csp^3–H bonds in malonates **82** (Scheme 15).[39] Aside from a stoichiometric amount of oxidant, a catalytic amount of $Fe(OTf)_2$ was required as a Lewis acid to ensure the activation of malonates. However, their preliminary mechanisitic investigation showed that the iron salt is not involved in the oxidation of amines.



Scheme 15 TEMPO-mediated CDC reaction. Reproduced from Richter, H.; Mancheño, O. G. *Eur. J. Org. Chem.* **2010**, *2010*, 4460–4467.

Inspired by the previous methodologies developed for the synthesis of propargylic amines in Li[12] and Zhao[36] group respectively, Li and Xu explored a dehydrogenation pathway of unactivated aliphatic tertiary amines **85** in the presence of diethyl azodicarboxylate **86** (DEAD) and their subsequent reactions with terminal alkynes **20** (Scheme 16).[40] Surprisingly, this DEAD-mediated regioselective alkynylation occurred exclusively at the methyl group of tertiary amines, whereas both α-hydrogen atoms located at the other two substituents remained intact. Meanwhile, a catalytic amount of copper iodide was necessary to facilitate the nucleophilic attack from terminal alkynes.

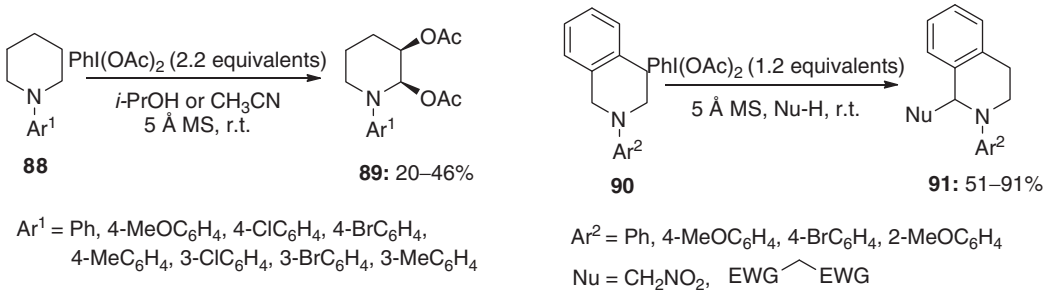


Scheme 16 DEAD-mediated CDC reaction. Reproduced from Xu, X.; Li, X. *Org. Lett.* **2009**, *11*, 1027–1029.

7.08.3.2 C–Y (Heteroatom) Bond Formation

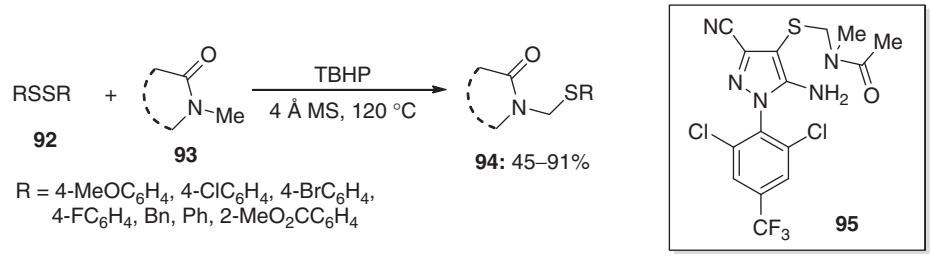
Although most methods for the oxidative functionalization of tertiary amines aim at C–C bond construction, several strategies with regard to C–O, C–S and C–N bond formation have emerged in the literature as powerful tools to elaborate *N*-containing molecular structures. By using a stoichiometric amount of diacetoxyiodobenzene (DIB) as an oxidant, Liang et al. have developed

a selective α-functionalization method for various tertiary amines to form C–O bonds adjacent to their nitrogen atoms under metal-free conditions (Scheme 17).[41] The importance of this work lies in two aspects: on one hand, various *cis*-2,3-diacetoxylated *N*-arylpiperidines **89** have been successfully synthesized when 2.2 equivalents of DIB is employed, demonstrating the efficiency of this method for dioxygenation of less reactive Csp^3–H bonds in piperidines **88**; on the other hand, moderate to high yields can be obtained from the reactions of tetrahydroisoquinolines **90** with a host of pronucleophiles such as nitroalkanes, dialkyl malonates and α-amino nitriles under mild conditions. Accordingly, oxidative C–C bond formation can be readily accessible by adapting this strategy with a decreased amount of DIB (1.2 equivalents).



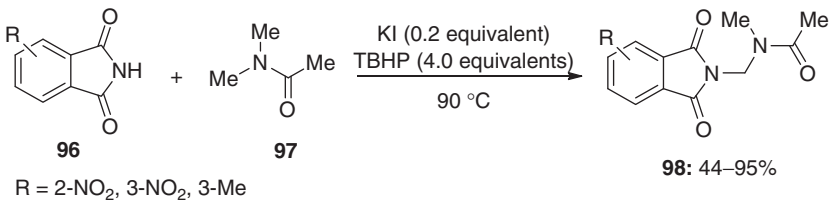
Scheme 17 DIB-mediated metal-free C–O and C–C bond formation. Reproduced from Shu, X.-Z.; Xia, X.-F.; Yang, Y.-F.; *et al. J. Org. Chem.* **2009**, *74*, 7464–7469.

The formation of C–S bond via C–H bond oxidative activation remains largely unexplored. Very recently, Li et al. have explored a direct oxidative thiolation of Csp^3–H bonds adjacent to nitrogen atoms in various amides **93**, where a stoichiometric amount of TBHP served as an oxidant and molecular sieves acted as an additive (Scheme 18).[42] It is noteworthy that some promising applications in the field of pharmaceuticals and materials have been disclosed by applying this facile method to synthesizing bioactive compounds such as the fipronil analog **95**. Although the genuine mechanism was unknown at the moment, the fact that the reaction cannot occur in the presence of radical inhibitors suggested a possible involvement of a radical process in the overall oxidative thiolation reaction.



Scheme 18 TBHP-mediated metal-free C–S bond formation. Reproduced from Tang, R.-Y.; Xie, Y.-X.; Xie, Y.-L.; Xiang, J.-N.; Li, J.-H. *Chem. Commun.* **2011**, *47*, 12867–12869.

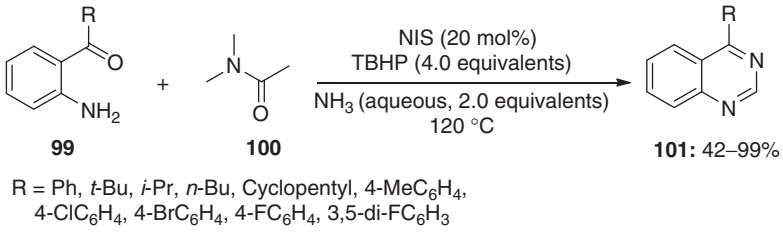
Compared with the traditional C–N bond formation relying on functional group interconversions, direct cleavage of C–H bonds and subsequent coupling with amine or amide nucleophiles to form new C–N bonds appear to be a more attractive pathway for the synthesis of important *N*-containing drugs and natural products. Meng and coworkers have investigated the possibility of an oxidative amidation of Csp^3–H bond adjacent to an amide nitrogen atom, using KI–TBHP as a metal-free catalyst system (Scheme 19).[43] A new C–N bond was successfully formed via the oxidative coupling between various phthalimides **96** and



Scheme 19 KI-mediated metal-free C–N bond formation. Reproduced from Lao, Z.-Q.; Zhong, W.-H.; Lou, Q.-H.; Li, Z.-J.; Meng, X.-B. *Org. Biomol. Chem.* **2012**, *10*, 7869–7871.

unreactive aliphatic amide **97**. However, one obvious disadvantage is the excessive loading of TBHP (4 equivalents), especially on large-scale reactions.

Wang and coworkers have reported a iodine-catalyzed intermolecular oxidative amination to form a new C–N bond adjacent to a nitrogen atom of *N*-alkylamide **100**, which was characterized by a domino process including four sequential reactions (Scheme 20).[44] Quinazolines **101** with different substituents were obtained as corresponding products in moderate to excellent yields. In addition, several control experiments were carried out to test the importance of four reagents used and the possible mechanism involved in this reaction. Ammonia turned out to be necessary as an external nitrogen source to promote an annulation step. A radical pathway was proposed based on a radical trapping experiment.



Scheme 20 NIS-mediated domino C–N bond formation. Reproduced from Yan, Y.; Zhang, Y.; Feng, C.; Zha, Z.; Wang, Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 8077–8081.

7.08.4 Electrochemical Oxidation

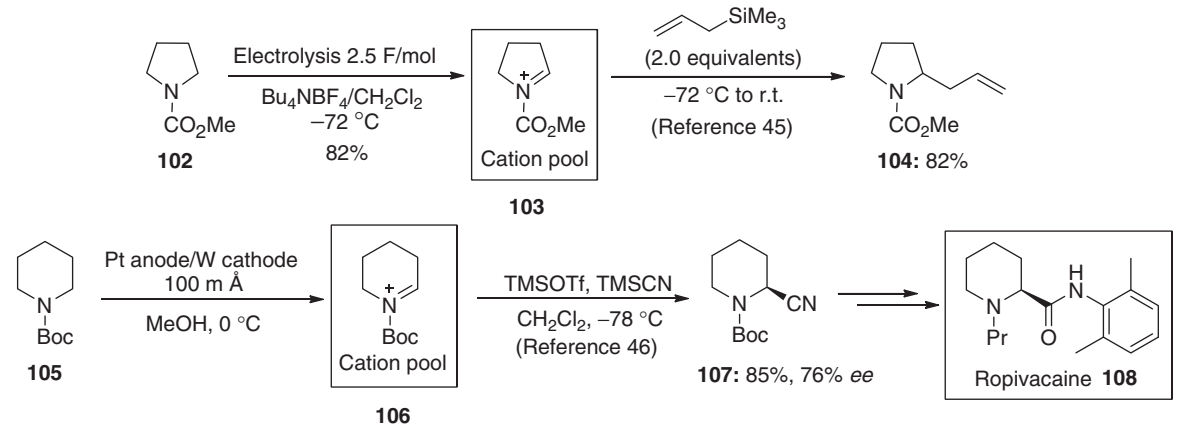
7.08.4.1 Direct C–H Bond Oxidation

Although extensive work has been carried out by means of traditional chemical methods in the field of oxidative C–H bond activation adjacent to nitrogen atoms in tertiary amines, relatively less attention has been drawn to the electrochemical pathway. This is mainly due to the fact that several unique challenges exist in electrochemical syntheses such as difficult control over the electron transfer, the poor chemoselectivity among substrates and the low atom efficiency in chemical transformations. In this regard, a large number of strategies have been developed and advanced in the literature to address those issues, providing new opportunities for the electroorganic synthesis to accomplish the oxidative α-functionalization of *N*-containing compounds. Some representative examples will be discussed in this section.

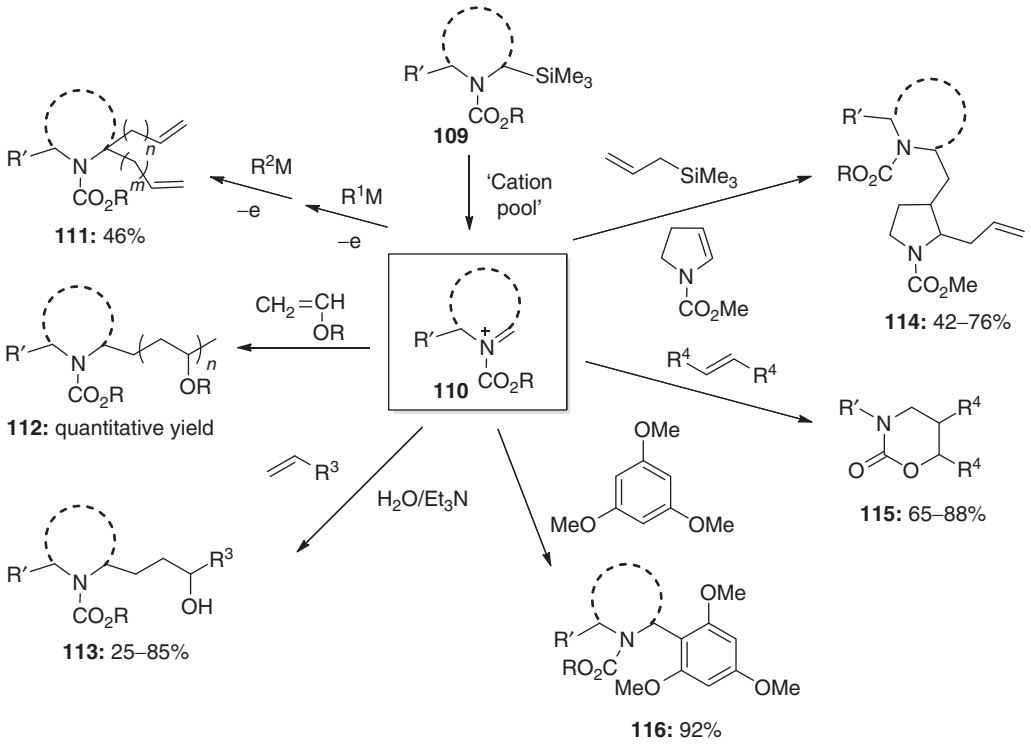
One of the most important progresses within the context of electrochemical oxidation of tertiary amines is the invention of the 'cation-pool' method by Yoshida and coworkers in 1999. In their pioneering work, *N*-methoxycarbonylpyrrolidinium **103** was formed at −72 °C by anodic oxidation of the corresponding carbamate **102** in Bu_4NBF_4/CH_2Cl_2, followed by a nucleophilc attack of allylsilane, leading to the formation of α-allyl substituted *N*-methoxycarbonylpyrrolidine **104.**[45] Compared with the traditional electrochemical reactions generally carried out at or near room temperature, this protocol allows electrolysis to be conducted at very low temperatures (−70 to −78 °C). Therefore, some unstable reactive species such as iminium ions can be generated for the ultimate α-functionalization of cyclic tertiary amines by nucleophilic attacks. Moreover, the stepwise procedure, featured first by the generation of a cation pool via low-temperature electrolysis and second by the nucleophilic attack under nonoxidative conditions, solves the problems associated with the *in situ* reactions of iminium ions with nucleophiles. Another example related to the application of direct C–H bond oxidation of carbamates by employing the 'cation pool' is Santos's protocol, where the diastereoselective syntheses of the anesthetic Ropivacaine **108** and its analogs were accomplished.[46] The key step in this work was the addition of cyanide to *N*-acyliminium 'cation pool' **106** obtained from the anodic oxidation (Scheme 21).

7.08.4.2 Electroauxiliary-Assisted Oxidation

To increase the selectivity and reproducibility of the oxidation, an electroauxiliary (EA) was introduced to tune the electron-transfer-driven process for the 'cation pool' method. In general, the involvement of EAs enables the adjustment of either oxidation or reduction potentials of substrates, and hence facilitates only one reaction pathway rather than many other possibilities. The use of silyl groups has been proved to be effective in enhancing both the reactivity and selectivity of oxidation of *N*-containing compounds. By applying them in the oxidative α-functionalization of tertiary amines **109**, the scope of carbon nucleophiles has been significantly expanded in the following years (Scheme 22). For example, a construction of spiro ring structures with two allylsilanes in a sequential manner,[47] polymerization using microsystems with vinyl ether,[48] carbohydroxylation of alkenes and alkynes,[49] a three-component coupling with enamine derivatives and allylsilanes,[50] a Friedel-Crafts-type alkylation with aromatic compounds,[51] and a [4+2] cycloaddition with alkenes and alkynes have all been developed.[52] In all cases, either a cyclic or an acyclic *N*-acyliminium ion pool **110** was generated at a low temperature, facilitating its subsequent capture by various nucleophiles to afford different final products.



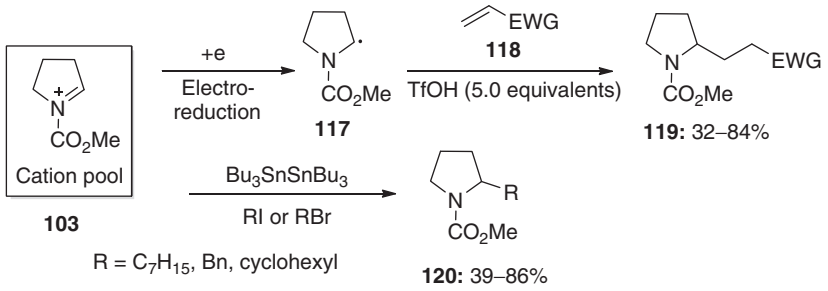
Scheme 21 Generation of 'cation pool' and its applications. Reproduced from Yoshida, J.; Suga, S.; Suzuki, S.; *et al. J. Am. Chem. Soc.* **1999**, *121*, 9546–9549, and Shankaraiah, N.; Pilli, R. A.; Santos, L. S. *Tetrahedron Lett.* **2008**, *49*, 5098–5100.



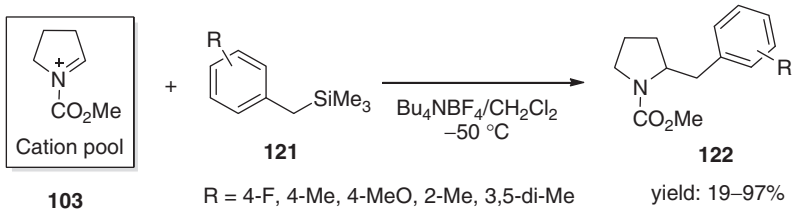
Scheme 22 EA-assisted 'cation pool': broaden the scope of nucleophiles.

The versatility of *N*-acyliminium ion has also been demonstrated by reduction of the 'cation pool' involving radical processes. Yoshida et al. have reported a radical mediated C–C bond formation at α-position of carbamates based on the reduction of the 'cation pool' of *N*-acyliminium ion **103** (Scheme 23).[53] In this work, once the *N*-acyliminium ion **103** was produced by electrolysis, further electrochemical reduction would allow the formation of the corresponding α-amino radical intermediate **117**. Consequently, various electron-deficient olefins **118** were served as radical acceptors to capture that reactive radical species.

Similarly, Yoshida et al. have investigated a possible reverse process of radical cation fragmentation by employing radical addition to *N*-acyliminium ion **103** (Scheme 23).[54] Interestingly, their research disclosed a new possibility for the generation of a radical cation as well as the subsequent C–C bond formation via a crossover radical coupling between organohalides and amides. Another particularly interesting result was obtained from Yoshida's recent studies on the reaction of *N*-acyliminium ion **103** with benzylsilanes **121**, where the cleavage of C–Si bond was demonstrated to proceed through a SET mechanism (Scheme 24).[55]



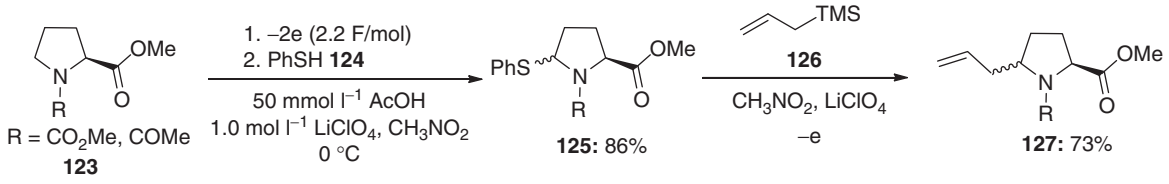
Scheme 23 Reduction of 'cation pool' via radical processes. Reproduced from Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30–31, and Maruyama, T.; Suga, S.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2005**, *127*, 7324–7325.



Scheme 24 Cleavage of C–Si bond via a reductive radical process in 'cation pool.' Reproduced from Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 1902–1903.

7.08.4.3 Modification of Hardware

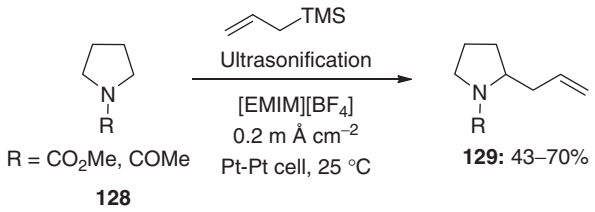
In recent years, many efforts have been made to modify the electrolytic medium and other hardware concerning the 'cation pool' method, with the aim of maximizing the efficiency and utility while encountering more practical problems in the electrochemical synthesis. Some representative examples are listed below. By using a lithium perchlorate/nitromethane solution instead of other anodic electrolytic medium, Chiba et al. have described a practical method that enabled the generation of *N*-acyliminium ions in an undivided cell at 0 °C, where subsequent nucleophilic attacks of either thiophenol **124** or allyltrimethylsilane **126** to the imminium species obtained from **123** gave the corresponding proline derivatives **125** or **127** (Scheme 25).[56]



Scheme 25 Modification of anodic electrolytic medium in 'cation pool.' Reproduced from Kim, S.; Hayashi, K.; Kitano, Y.; Tada, M.; Chiba, K. *Org. Lett.* **2002**, *4*, 3735–3737.

Recently, Atobe and coworkers have established a one-step electrosynthetic system using acoustic emulsification in order to overcome the laborious multi-step drawback of reactions run under the previous conditions.[57] In this work, an ionic liquid (1-ethyl-3-methylimidazolium tetrafluoroborate, [EMIM][BF_4]) was selected as an ideal electrolytic media (Scheme 26). Interestingly, with such a new technique in hand, a phase separation caused by acoustic dispersion can prevent the simultaneous oxidation of allyl nucleophilic species with low oxidation potential at the anode, giving rise to the efficient chemoselective generation of the corresponding α-allyl substituted *N*-methoxycarbonylpyrrolidines **129**.

On the basis of the original 'cation pool' approach, Yoshida et al. have integrated continuous flow systems with the aim of advancing the capability of catalytic processes. Early in 2001, they successfully developed a new approach with the modification of reactors in the 'cation pool' by using microflow systems.[58] Outstandingly, different iminium intermediates were generated in separate micro reactors and sequentially reacted with various nucleophiles to afford the corresponding α-substituted *N*-methoxycarbonyl pyrrolidines by simple flow-switching. This parallel method demonstrates the compatibility of the electrochemical



Scheme 26 One-step acoustic emulsification in 'cation pool.' Reproduced from Asami, R.; Fuchigami, T.; Atobe, M. *Chem. Commun.* **2008**, *44*, 244–246.

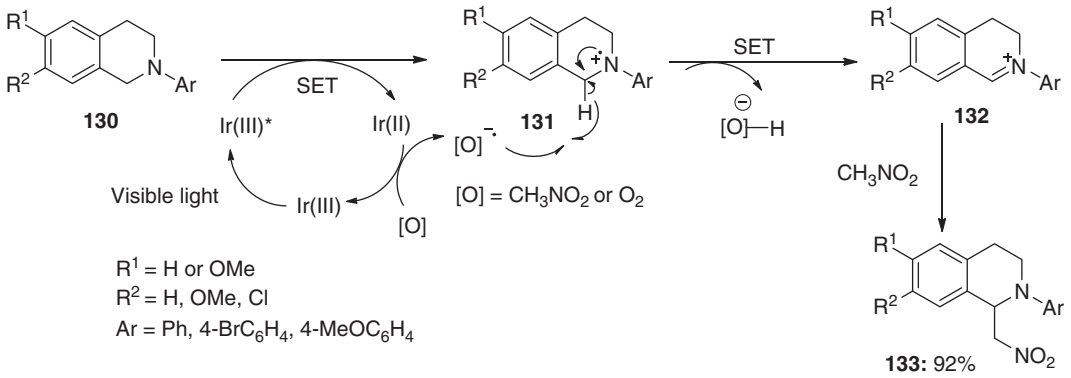
synthesis in the microflow system and therefore may pave a new way for chemistry using the carbocation adjacent to a nitrogen atom. Very recently, Yoshida et al. have proposed another advanced terminology called 'space integration' to clarify the confusion in the field of flow chemistry combined with the 'cation pool' method.[59] By doing so, a 'cation flow' rather than a 'cation pool' was created by the electrochemical oxidation in a microreactor. The *N*-acyl-pyrrolidinium intermediates generated under these conditions could thus be further functionalized by adding different nucleophilic components in different places, suggesting a controlled sequential pathway for the corresponding synthetic targets.

7.08.5 Visible Light Induced Photoredox Catalytic Oxidation

7.08.5.1 Inorganic Metal Complexes Catalyzed C–C Bond Formation

Over the past three years, one particularly amazing and appealing tactic for oxidative α-functionalization of tertiary amines involves the use of visible light sources and a photocatalyst. Overall, this new technique for oxidation of amines is based on the interplay between the photoredox cycle invoked by a photocatalyst under visible light irradiation and various tertiary amines.

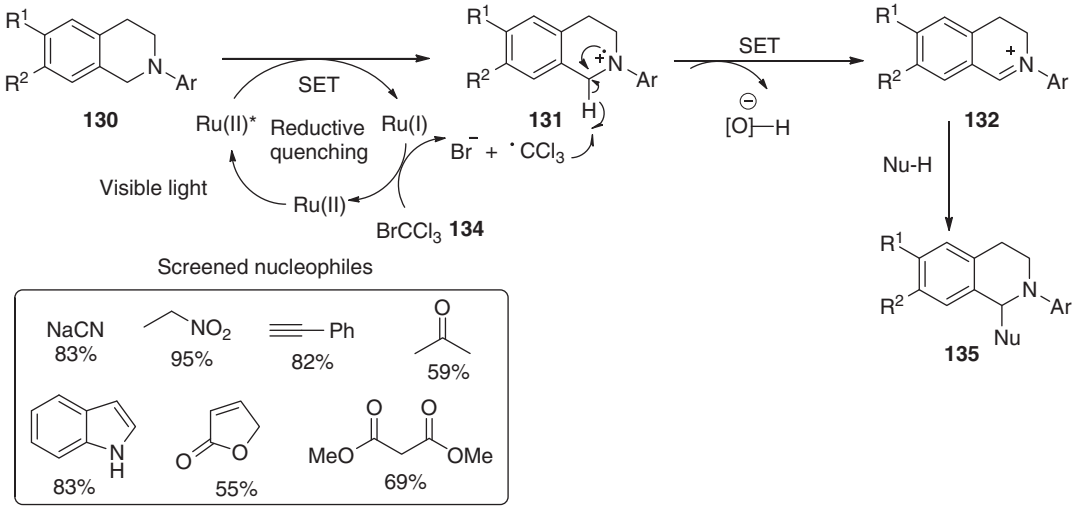
Only until recently, the work of Stephenson et al. has demonstrated the successful application of photochemical reactions to achieve oxidative C–H bond functionalization adjacent to a nitrogen atom. In 2010, Stephenson and coworkers disclosed the first mild protocol to generate iminium ions **132** catalyzed by an iridium(III) complex under visible light irradiation, where the aza-Henry reaction was carried out smoothly by subjecting the reactive iminium species to nitromethane (Scheme 27).[60] Although the problem of limited substrates exists and the mechanism insights are insufficient at the current stage, this pioneering work provides an alternative way to form key iminium intermediates via photoredox catalysis.



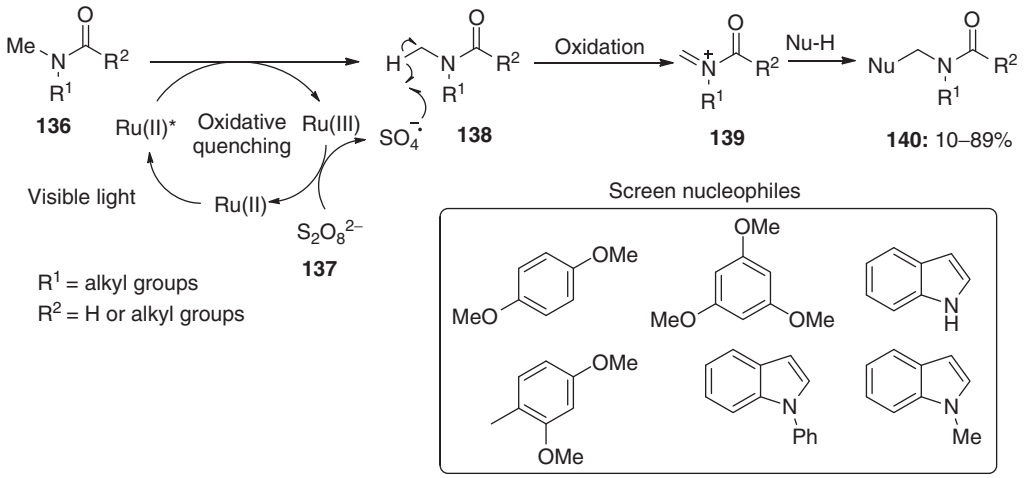
Scheme 27 Visible light induced aza-Henry reactions. Reproduced from Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465.

Stephenson and coworkers have reported a complementary versatile approach featuring the replacement of iridium(III) with ruthenium(II) complex, as well as the modification of an oxidant by using bromotrichloromethane **134** (Scheme 28).[61] Remarkably, various reactions such as the Strecker reaction, Cu-alkynylation, the Mannich reaction, the Friedel-Crafts reaction, the Sakurai reaction and the aza-Henry reaction were all able to proceed under optimized conditions, demonstrating the compatibility of a broad range of nucleophiles.

More recently, Stephenson and coworkers have reported a visible light-driven oxidative Friedel-Crafts aminoalkylation by using persulfate **137** as a terminal oxidant (Scheme 29).[62] An oxidative quenching cycle (Ru(II) to Ru(III)) was involved in this oxidative reaction instead of the reductive counterpart (Ru(II) to Ru(I)) applied in the previous example. Additionally, higher yields and better selectivities were observed in most cases under photoredox conditions than that under thermal conditions.



Scheme 28 A complementary approach using $BrCCl_3$ as an oxidant. Reproduced from Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2011**, *14*, 94–97.

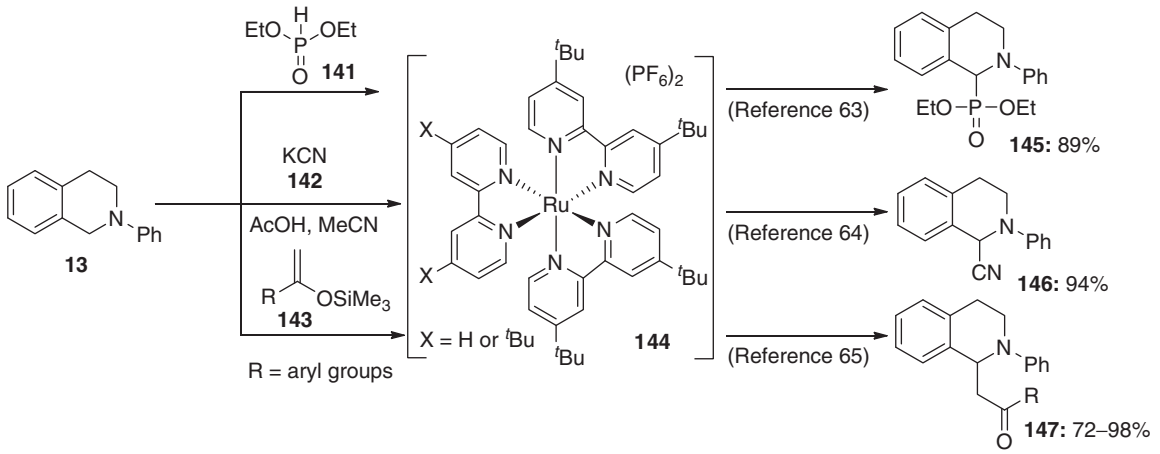


Scheme 29 Visible light driven oxidative Friedel-Crafts aminoalkylation. Reproduced from Dai, C.; Meschini, F.; Narayanam, J. M. R.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 4425–4431.

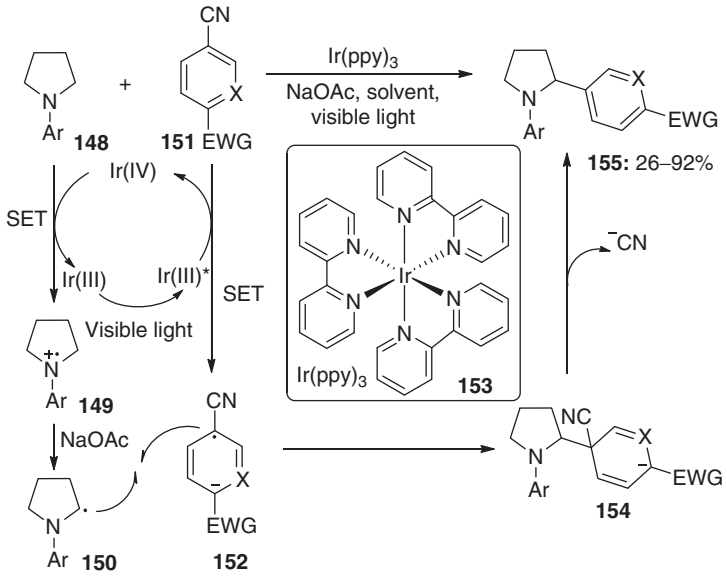
Subsequent efforts were focused on the reaction scope of photoredox oxidative functionalizations (Scheme 30). α-Aminophosphonates and α-aminonitriles are important compounds due to their diverse and useful bioactivities. In 2011, Rueping et al. established an oxidative phosphonylation pathway in the presence of ruthenium photocatalysts **144** under visible light irradiation, providing a ready access to the valuable α-aminophosphonate **145**.[63] Subsequently, they reported an aerobic photocatalytic oxidative cyanation of amines **13** with a low photocatalyst loading in the presence of KCN.[64] Mannich-type reactions have also been established with a photocatalytic system consisting of ruthenium complex **144**, blue LEDS and methanol.[65] In this work, Xia et al. successfully employed silyl enol ethers **143**, instead of unmodified ketones, to capture iminium ions generated *in situ* under oxidative conditions.

As a prominent structural class, α-arylamines are widely found among medicinal agents. By taking advantage of the concept of 'accelerated serendipity,' MacMillan et al. have discovered a photoredox pathway to achieve oxidative amine C–H arylation (Scheme 31).[66] During the proposed photoredox catalytic cycle, the key intermediate, amine radical cation **149**, was generated via a SET mechanism and further converted into the α-amino radical **150** by using NaOAc as a deprotonating agent.

With the development of visible light photoredox catalysis, both intermolecular and intramolecular cyclizations have been achieved by means of oxidative activation of C–H bonds adjacent to a nitrogen atom (Scheme 32). Recently, starting from amine **156**, Xiao and coworkers have established a photocatalytic strategy to construct *N*-containing heterocycles **161**, which featured a tandem oxidation/[3+2] cycloaddition/oxidative aromatization sequence.[67] Similarly, Rueping et al. attempted to convert tertiary



Scheme 30 Extension of the reaction scope of photoredox oxidative functionalization. Reproduced from Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 8679–8681; Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011**, *47*, 12709–12711, and Zhao, G.; Yang, C.; Guo, L.; *et al. Chem. Commun.* **2012**, *48*, 2337–2339.

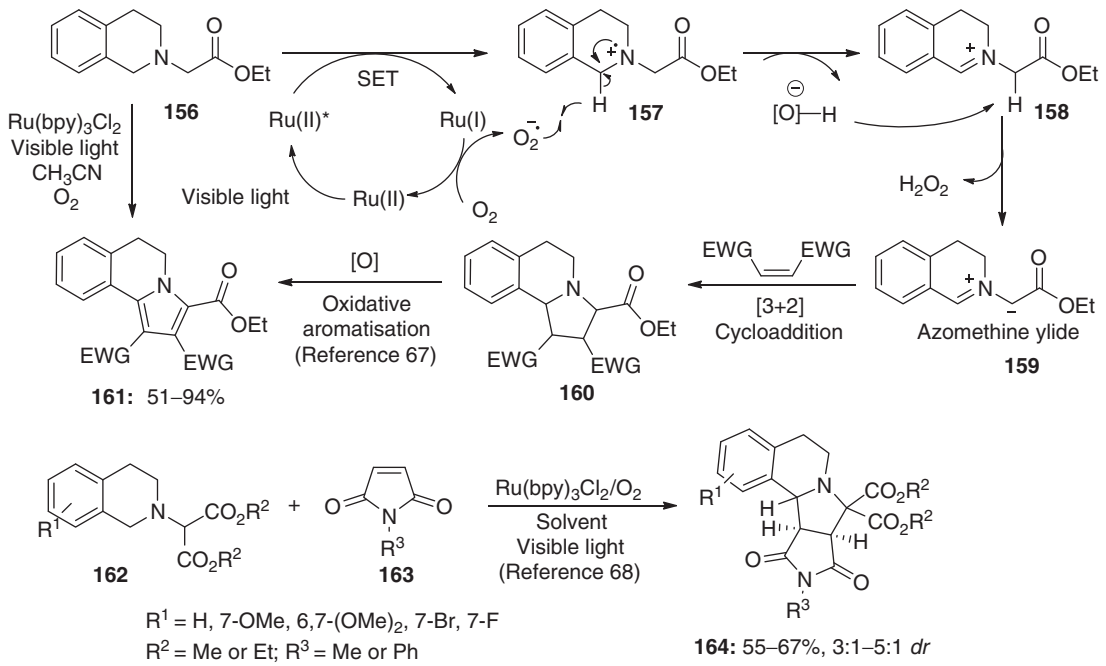


Scheme 31 Visible light induced α-arylation of amines. Reproduced from McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114–1117.

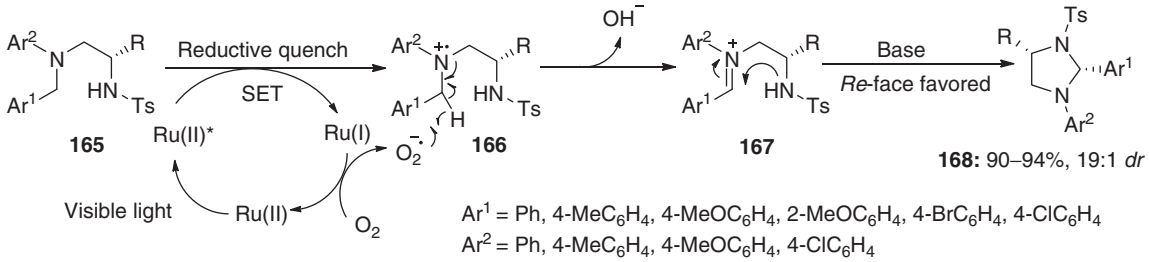
amines **162** to azomehtine ylides using photocatalysts under visible light, where the highly functionalized *N*-heterocycles **164** were formed from cycloaddition of azomethine ylides with maleimide derivatives.[68]

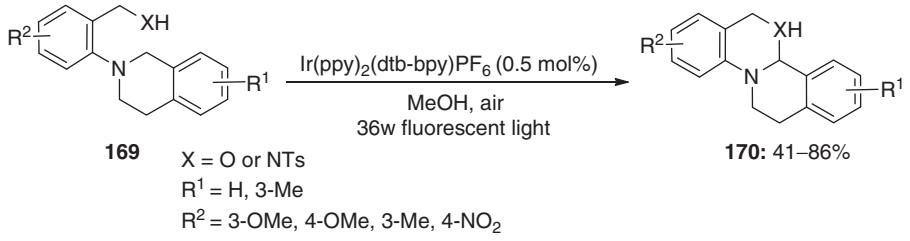
Apart from intermolecular examples, visible light-assisted intramolecular cyclization of tertiary amine derivatives has also been exploited (Scheme 33). In 2011, Xiao and coworkers treated enantiomerically pure diamines **165**, derived from L-amino acid, with visible light irradiation in the presence of ruthenium complex, allowing the construction of tetrahydroimidazole scaffolds **168** through oxidative cyclization.[69] The excellent diastereoselectivities observed in this work can be attributed to a preferential attack of NH group to iminium intermediates **167**. Xiao and coworkers have developed a simple and efficient procedure to construct both isoquino oxazine and isoquino pyrimidine frameworks **170** by using photoredox catalysis, which provides a rapid access to furnish bioactive fused heterocycles.[70]

Further demonstration of the utility of photoredox oxidative functionalization comes from its recent combination with organocatalysts (Scheme 34). For instance, Rueping et al. recently accomplished direct Mannich reactions between benzylic amines **130** and ketones **171** through an interplay of photoredox and organocatalytic cycles.[71] DiRocco and Rovis stepped further into this dual-catalysis area by establishing a novel asymmetric α-acylation of tertiary amines.[72] Under co-catalytic



Scheme 32 Visible light induced [3+2] dipolar cycloaddition of azomethine ylides. Reproduced from Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 7171–7175, and Rueping, M.; Leonori, D.; Poisson, T. *Chem. Commun.* **2011**, *47*, 9615–9617.



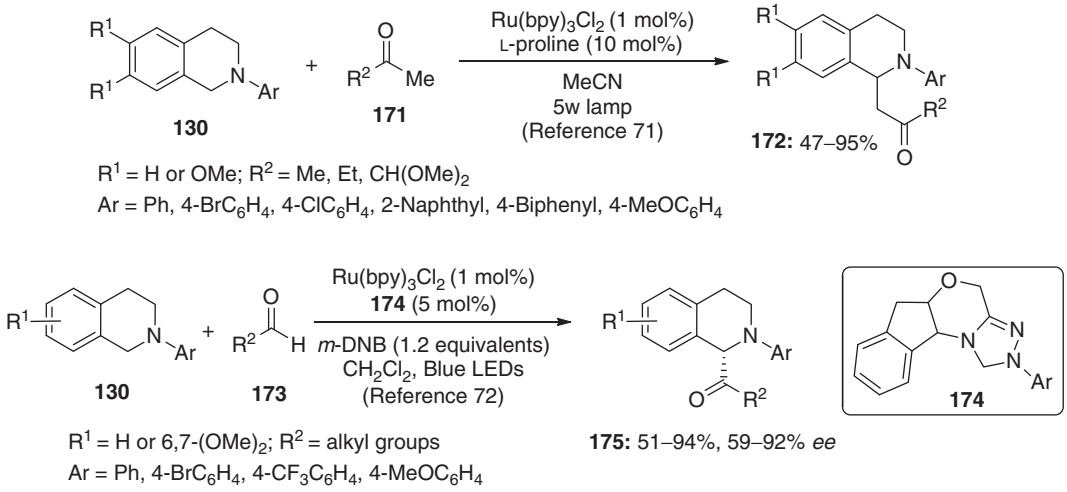


Scheme 33 Visible light intramolecular oxidative functionalization of tertiary amines. Reproduced from Xuan, J.; Cheng, Y.; An, J.; *et al. Chem. Commun.* **2011**, *47*, 8337–8339, and Xuan, J.; Feng, Z.-J.; Duan, S.-W.; Xiao, W.-J. *RSC Adv.* **2012**, *2*, 4065–4068.

cycles created by the chiral NHC (*N*-heterocyclic carbene) catalyst **174** and a ruthenium photocatalyst, a direct oxidative functionalization of C–H bonds adjacent to nitrogen atoms with aldehydes **173** was achieved in a highly enantioselective manner. Another interesting example of a dual catalyst system involves the combination of photocatalysts and metal catalysts.[73]

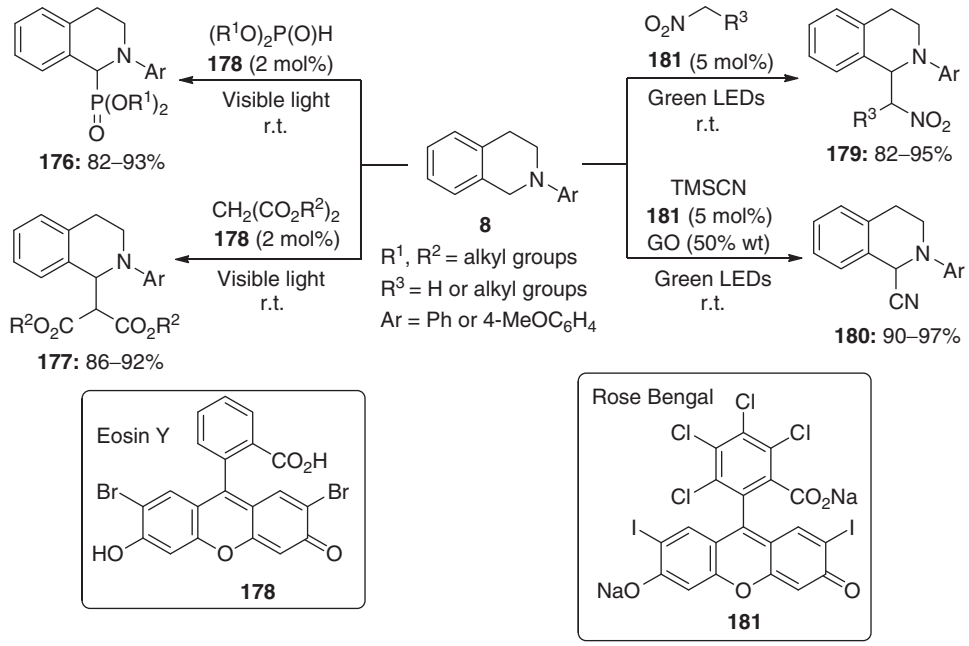
7.08.5.2 C–C Bond Formation Catalyzed by Organic Dyes

Metal-free organic dyes can trigger the photoredox catalytic cycle as well, probably because many conjugated double or triple bonds in these dyes can store energy by means of quantum vibration. Searching for an environmentally friendly strategy of oxidative C–H functionalization based on photoredox catalysis, Tan et al. recently reported the use of Rose Bengal (**181**),



Scheme 34 A dual catalytic system: organocatalysts and photocatalysts. Reproduced from Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360–2362, and DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094–8097.

an organic dye, to promote the aza-Henry reaction under visible light radiation between benzylic amines **8** and nitroalkanes (Scheme 35).[74] Apart from nitroalkanes, both cyclic and acyclic ketones also acted as nucleophiles when using L-proline as an additive. Subsequently, a complementary protocol involving a combination of graphene oxide (GO) and Rose Bengal was developed by the same group, where the scope of nucleophiles was extended to TMSCN and $TMSCF_3$.[75]

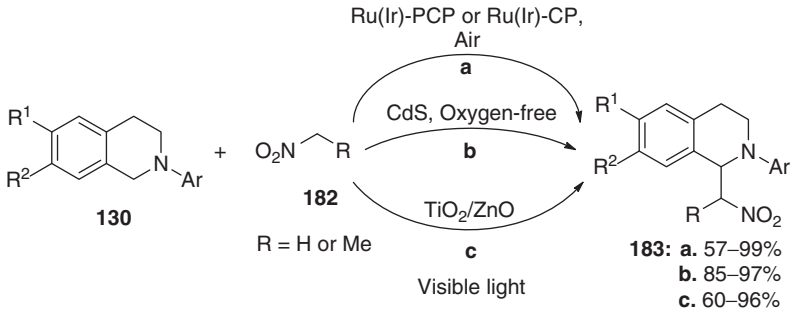


Scheme 35 Application of organic dyes photocatalysis in oxidative functionalization of amines. Reproduced from Pan, Y.; Kee, C. W.; Chen, L.; Tan, C.-H. *Green Chem.* **2011**, *13*, 2682–2685.

Another representative example of the application of organic dyes in oxidative functionalization of tertiary amines has been reported by Hari and König (Scheme 35).[76] In this reaction, Eosin Y (**178**) was selected as an alternative organic dye to perform an initial SET process in the photoredox cycle. Consequently, the scope of the pronucleophiles was extended to dialkyl malonates, malononitriles, and dialkyl phosphonates. Very recently, a series of examples have been carried out by Wu and coworkers, using TBA-Eosin Y and molecular oxygen as a photocatalysis system.[77] Mechanistic study demonstrated the generation of a superoxide radical anion for the first time under the visible light irradiation, which resulted in acceleration of the reaction. The proposed mechanism supported by electron spin resonance (ESR) can provide an opportunity for further improvement of atom efficiency.

7.08.5.3 Heterogeneous Catalysis and Flow Method

The advantages of heterogeneous catalysts over the homogeneous catalysts, such as easy separation and efficient recycling, make it attractive to apply them in the context of photoredox oxidative C–H functionalization. In 2011, Lin et al. designed two kinds of porous metal complexes, UiO-67 metal-organic-frameworks[78] and cross-linked polymers,[79] as heterogeneous photocatalysts to promote the subsequent aza-Henry reactions of benzylic amines **130** in nitroalkanes **182** (Scheme 36). In both cases, the heterogeneous catalysts can be readily reused three or four times without a decrease in catalytic activity in the presence of air.



Scheme 36 Application of heterogeneous catalysts in photoredox catalysis. Reproduced from Wang, C.; Xie, Z.; deKrafft, K. E.; Lin, W. *J. Am. Chem. Soc.* **2011**, *133*, 13445–13454; Xie, Z.; Wang, C.; deKrafft, K. E.; Lin, W. *J. Am. Chem. Soc.* **2011**, *133*, 2056–2059; Mitkina, T.; Stanglmair, C.; Setzer, W.; *et al. Org. Biomol. Chem.* **2012**, *10*, 3556–3561, and Rueping, M.; Zoller, J.; Fabry, D. C.; *et al. Chem. Eur. J.* **2012**, *18*, 3478–3481.

Simultaneously, the utilization of CdS,[80] a readily available semiconductor, and TiO_2/ZnO[81] as heterogeneous photocatalysts turned out to be effective to facilitate the photoredox-catalyzed aza-Henry reaction under an oxygen-free atmosphere (Scheme 36). However, radical intermediates of benzylic amines **130** were believed to be involved in the former example.

Directed toward greater efficiency and a more predictable scale-up, flow reactors, instead of traditional batch reactors, have been recently exploited to initiate the photoredox transformation. Stephenson and coworkers have established a facile photochemical flow system to carry out a series of oxidative cross-dehydrogenative coupling reactions, allowing for the remarkable acceleration of substrate conversion compared to those observed in typical batch reactors.[82] Similar results were obtained by Neumann and Zeitler when they applied microflow conditions in visible light photoredox processes.[83] In particular, the aza-Henry reaction of some unreactive amine substrates proceeded more smoothly in microflow systems than under batch conditions.

7.08.6 Conclusion

The ongoing interests in direct oxidative functionalization of C–H bonds adjacent to a nitrogen atom have led to the rapid development of innovative chemical technologies that are highly efficient and sustainable in this particular area. Specifically, four general strategies aiming at generating the reactive iminium species have been developed and advanced rapidly over the past two decades, facilitating further enormous elaboration next to a nitrogen atom. Based on above-mentioned methods, there will be more concise and flexible ways to construct more complex *N*-containing compounds. In the meantime, there will be ample opportunities for discovering more versatile catalysts, useful transformations and practical utilizations in the field of oxidation adjacent to a nitrogen atom in tertiary amines.

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7.09 Oxidation of C–H Bond Adjacent to Oxygen of Ethers

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Glossary

Autoxidation It is the spontaneous oxidation of a compound under oxygen, especially air atmosphere even in the absence of any catalyst. For example, ethers are subject to oxidize under air to form hydroperoxides and dialkyl peroxides.

Baeyer–Villiger reaction It is the oxidation accompanied by oxidative cleavage of a carbon–carbon bond adjacent to carbonyl group of ketones, leading to esters from aliphatic ketones and lactones from cyclic ketones. The Baeyer–Villiger reaction is initiated by nucleophilic attack of oxidant to carbonyl group followed by insertion of an oxygen atom to generate esters.

Dess–Martin oxidation It is a hypervalent iodine compound, which offers selective and very mild oxidation of alcohols and ethers. The Dess–Martin periodinane is commercially available, but it is reported to be heat- and shock-sensitive, and exothermally decomposes when heated at temperatures greater than 130 °C.

Jones reagent It is an oxidizing agent prepared from a solution of chromium(VI) oxide and sulfuric acid in water.

Oxidative coupling It is a carbon–carbon bond forming reaction through dehydrogenation process of two molecular components. The reaction is usually catalyzed by a transition metal compound under dioxygen as the oxidant.

7.09.1 Introduction

Ethers are known to be subject to autoxidation under molecular oxygen and much research on this topic has been carried out.[1] For example, diethyl ether is autoxidized by molecular oxygen to accumulate the production of acetaldehyde and hydrogen peroxide.[2] It has been shown that oxygen initially attacks a carbon atom adjacent to the ether oxygen to form a hydroperoxide (*see* Chapter 7.10).[1–2]

However, the ether moiety that possesses a C–H bond adjacent to oxygen is oxidized by various oxidants, including metallic oxidants such as chromium-based reagents (Jones reagent and pyridinium chlorochromate (PCC), RuO_2) as well as cerium(IV) ammonium nitrate (CAN), peroxide, *m*-chloroperbenzoic acid (MCPBA), dioxirane, Dess–Martin periodinate, iodosylbenzene, heteropolyacid, ozone, molecular oxygen, etc., to convert the ether into aldehydes, carboxylic acids, ketones, and esters.

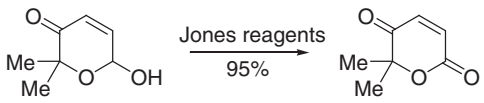
The recent development of transition metal-catalyzed oxidative coupling via C–H bond functionalization of ethers is also documented in this chapter. In addition, a unique approach of ether oxidation in total synthesis and in asymmetric synthesis is documented.

 doi:10.1016/B978-0-08-097742-3.00710-2

7.09.2 Oxidation Using Metal-Based Oxidants

7.09.2.1 Chromium(VI) in Sulfuric Acid in Water (Jones Reagent)

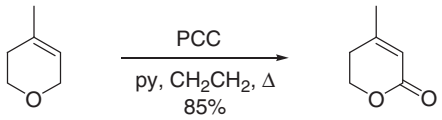
Chromic acid combined with sulfuric acid in water, which is referred to as the Jones reagent, has been widely used as a convenient oxidizing reagent of ethers.[3] Oxidation of 6-hydroxy-2-(4-methoxyphenyl)-2-methyl-2*H*-pyran-3(6*H*)-ones with the Jones reagent affords diones (equation 1), which are intermediates in the synthesis of substituted pyrrolidinones and oxaspiro derivatives.[4,5]



(1)

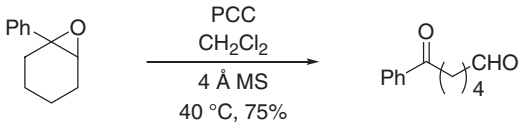
7.09.2.2 PCC

PCC is a good oxidant in allylic oxidation of activated methylene compounds. For example, 3,6-dihydro-4-methyl-2*H*-pyran is oxidized by PCC to the corresponding lactones in good yield (equation 2).[6,7]

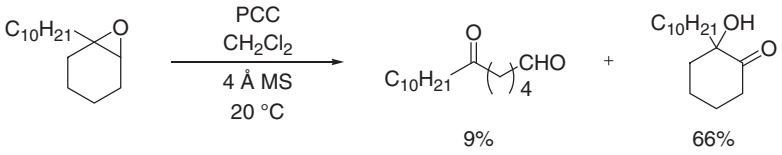


(2)

Phenyloxiranes are cleaved by the reaction with PCC in the presence of 4 Å molecular sieves to lead to carbonyl compounds (75%) (equation 3).[8] Under similar reaction conditions, alkyl-substituted oxiranes are converted into α-hydroxy ketones as a major product (equation 4).

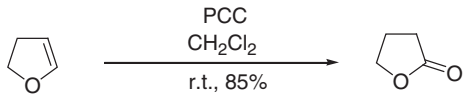


(3)



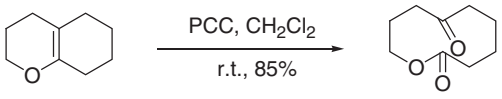
(4)

PCC can behave as a good oxidizing agent for oxidation of C═C double bond activated by oxygen atom. Thus, PCC oxidizes dihydrofuran to the corresponding lactone in 85% yield (equation 5).[9] The oxidation reaction involves a 1,2-hydride shift from the α-carbon to the *β*-carbon of the ether.



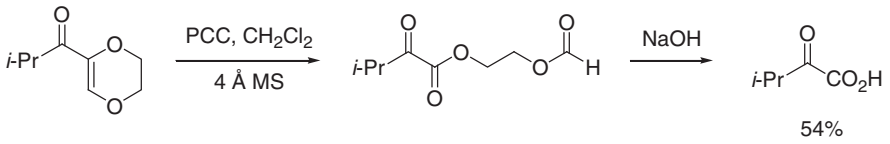
(5)

Alternatively, in the case of α,α′-disubstituted enol ethers having no hydrogens such as 3,4,5,6,7,8-hexahydro-2*H*-1-benzopyran, oxidative cleavage of the C═C double bond takes place, giving keto lactones in good yield (equation 6).[10]



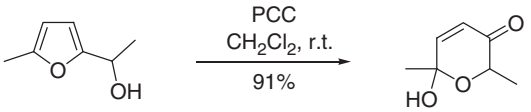
(6)

Selective oxidation of 1,4-dioxene derivatives can be achieved by PCC. Thus, the reaction of 2-alkynoyl-1,4-cyclodioxene with PCC followed by treatment with NaOH provides an α-keto acid (54%) (equation 7).[11]



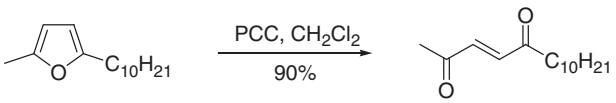
(7)

PCC has been employed toward the oxidation of furan derivatives.[12] Thus, 5-methyl-2-furylcarbinol undergoes oxidative ring enlargement to form hexenulose (equation 8).[13]



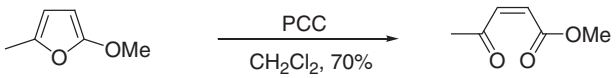
(8)

By the use of PCC, 2,5-dialkylfurans are easily oxidized to *trans*-α,β-unsaturated 1,4-dicarbonyl compounds through oxidative ring fission. The reaction is accompanied by isomerisation of the double bond to form the *trans*-product exclusively (equation 9).[14]



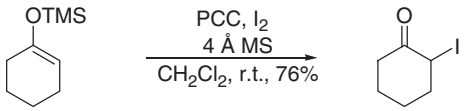
(9)

PCC shows high reactivity toward nucleophilic furans such as 2-alkylthiofurans, which are rapidly converted into methyl (*Z*)-4-oxo-2-pentenoate by the action of the reagent in dichloromethane.[15] Here, rapid *cis*/*trans* isomerization is based on the acidic character of PCC, and the *cis*-isomer is obtained exclusively (equation 10).[15]

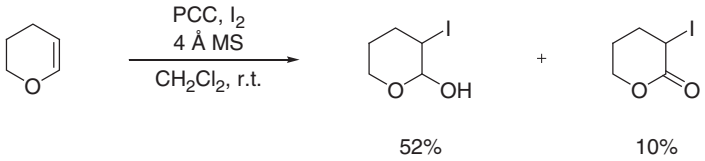


(10)

Both cyclic and linear silyl enol ethers can be easily converted into α-iodocarbonyl compounds by using PCC in the presence of iodine in dichloromethane (equation 11). The reaction of dihydropyran is reported to form the α-iodolactone in 52% yield (equation 12).[16]



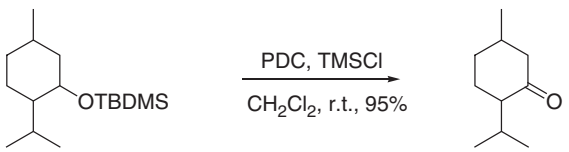
(11)



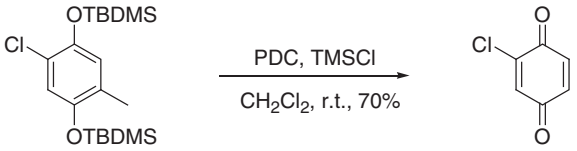
(12)

7.09.2.3 Pyridinium Dichromate

Pyridinium dichromate (PDC) combined with chlorotrimethylsilane (TMSCl) serves as a selective deprotection–oxidation reagent of silyl ethers and silyl enol ethers.[17] For example, *tert*-butyldimethylsilyl ethers are subject to the deprotection–oxidation reaction, affording the corresponding ketones in high yields (equation 13). The combination of PDC and TMSCl is employed as an effective oxidant for the preparation of quinines from hydroquinone silyl ethers (equation 14).[17]

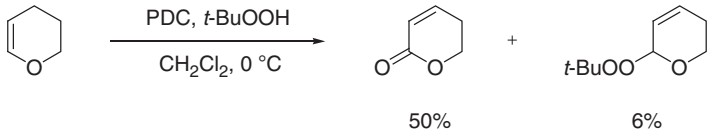


(13)



(14)

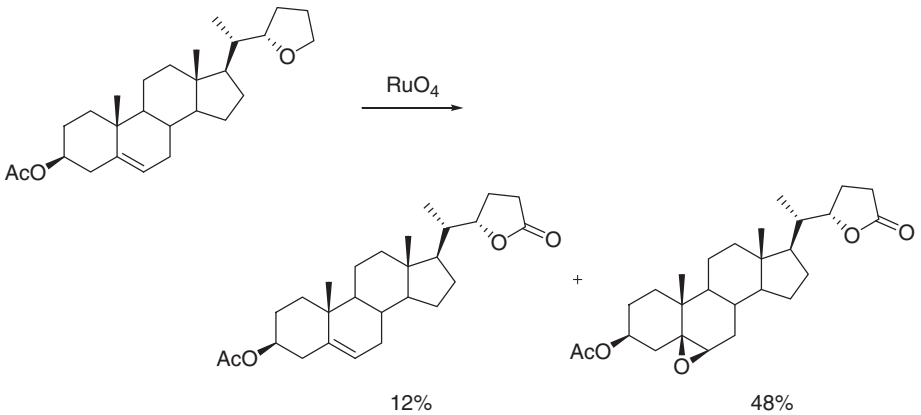
The PDC/*t*-BuOOH system is used for the conversion of dihydropyran into 5,6-dihydro-2*H*-pyran-2-ones together with the formation of a small amount of *tert*-butylperoxy derivative as a byproduct (equation 15).[18]



(15)

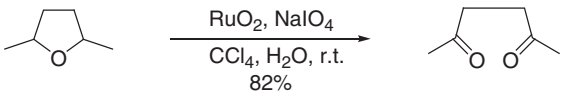
7.09.2.4 Ruthenium-Based Oxidants

RuO_4 acts as an effective simultaneous oxidant of both the C–H bond of an ether moiety to generate a lactone and the C=C bond to create an epoxide. Thus, the oxidation of a pregnenolone derivative involving both a cyclic ether and a C=C double bond affords an epoxy lactone as a major product (equation 16).[19,20]



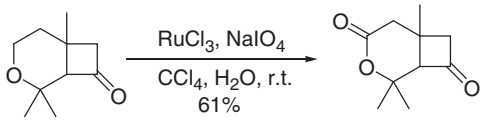
(16)

The oxidation of 2,5-dimethylfuran with RuO_2 and $NaIO_4$ leads to a carbon–oxygen bond cleaved product, 2,5-hexanedione (equation 17).[21]

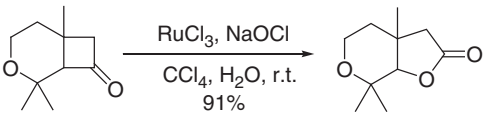


(17)

In general, carbonyl groups are inert under the oxidation conditions created by Ru (equation 18), but a Baeyer–Villiger reaction can be induced in preference to an oxidation of the ether moiety when sodium hypochlorite is employed as a cooxidant (equations 18 and 19).[22]

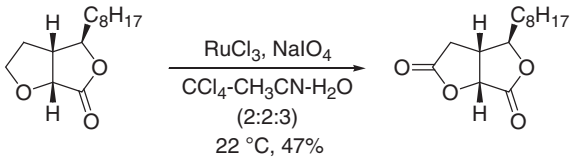


(18)



(19)

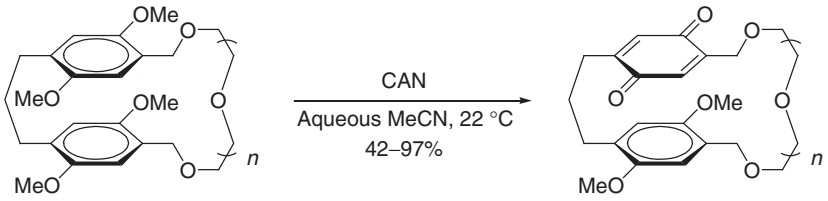
The oxidation using $RuCl_3$–$NaIO_4$ system is successfully extended to the lactonization of a bicyclic ether/lactone to a bicyclic lactone[23] which is an intermediate for the synthesis of drugs displaying antibacterial activity (equation 20).[24]



(20)

7.09.2.5 CAN

CAN has been used for the oxidation of ethers. Thus, catechol methyl ethers are readily oxidized to quinines by CAN.[25] Partial demethylation is induced to convert these materials into intramolecular quinhydrones (equation 21),[26] which are intermediates of daunomycinones.[27]

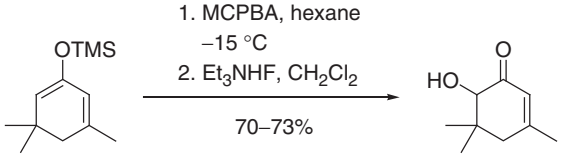


(21)

7.09.3 Oxidation Using Peroxides

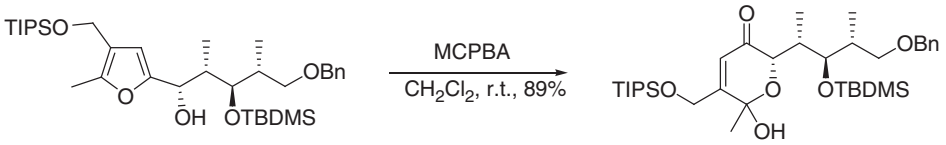
7.09.3.1 MCPBA

MCPBA has been widely used for ether oxidation, especially oxidation of enol silyl ethers and furans. For example, α-hydroxy enones have been prepared in two steps from α,β-unsaturated ketones, namely, the enol silyl ether derived from an enone is allowed to react with MCPBA followed by the treatment with triethylammonium fluoride to give an α-hydroxy enone (equation 22).[28]



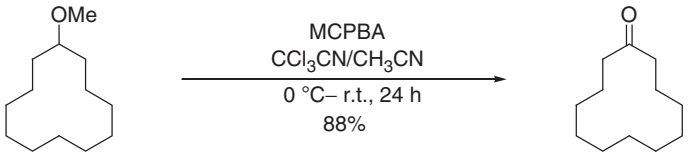
(22)

The MCPBA oxidation can also be used for the transformation of furfuryl alcohols to pyranones (equation 23).[29]



(23)

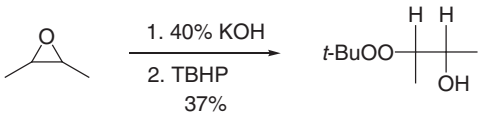
In the MCPBA-mediated ether oxidation of cyclododecyl methyl ether, the addition of CCl_3CN is reported to be efficient, affording cyclododecyl ketone in good yield (equation 24).[30]



(24)

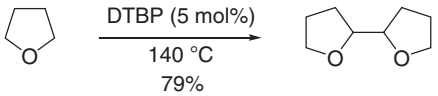
7.09.3.2 *tert*-Butyl Hydroperoxide (TBHP) and 1,1-Di-*tert*-Butyl Peroxide (DTBP)

When epoxides are allowed to react with *t*-BuOOH, TBHP under basic conditions (KOH), β-hydroxy dialkyl peroxides are formed although the yield is low (equation 25).[31]



(25)

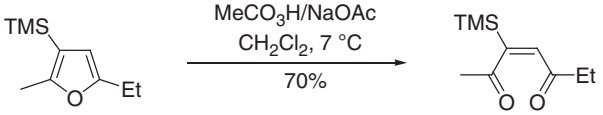
DTBP serves as an efficient reagent for dehydrodimerization. Thus, the treatment of tetrahydrofuran in the presence of a catalytic amount of DTBP afforded the corresponding dimerization product in high yield. The dimerization is thought to occur via coupling of the α-carbon radical formed as a transient intermediate (equation 26).[32]



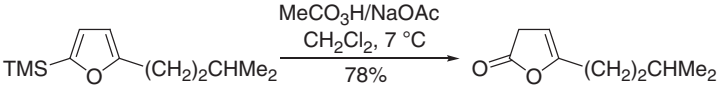
(26)

7.09.3.3 Peracetic Acid

2,5-Disubstituted furans are oxidatively cleaved by peracids, affording diketones (equation 27).[33] 2-Trimethylsilyl furans give rise to butenolides by the oxidation with peracetic acid and NaOAc in methylene chloride (equation 28).[34]



(27)

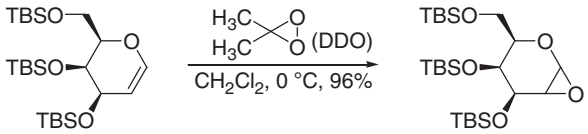


(28)

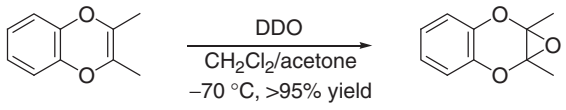
7.09.3.4 Dimethyldioxirane

Dimethyldioxirane (DDO) is a very effective oxidant for epoxidation of C=C bonds adjacent to ether oxygens, and the reaction is usually carried out under neutral, nonnucleophilic conditions. The oxidation with DDO occurs with high selectivity under low temperature to give the corresponding epoxides in high yields, and DDO leaves acetone after the reaction.

Therefore, many examples have been demonstrated on the selective epoxidation of C=C double bonds such as enol ethers and silyl enol ethers (equation 29).[35,36] Epoxidation of alkenes having two ether parts has also been made by using DDO in CH_2Cl_2/acetone to give the corresponding epoxides (equation 30).[37]



(29)



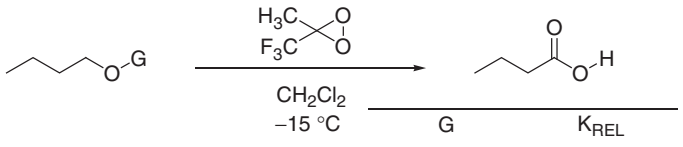
(30)

The reactivity of alkyl ethers with methyl-(trifluoromethyl)dioxirane is compared with that of silyl ethers. As shown in Scheme 1, the reaction proceeds faster when a trimethylsilyl group was introduced adjacent to the oxygen atom.[38]

7.09.4 Oxidation Using Iodine-Based Oxidants

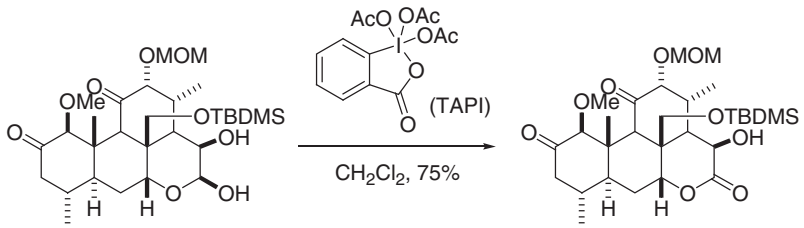
7.09.4.1 Dess–Martin Periodinane

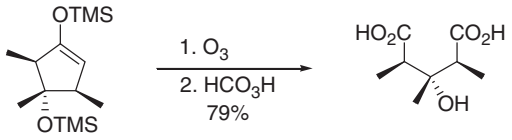
The Dess–Martin periodinane 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (TAPI) is used as the reagent for the selective oxidation of 2,3-dihydropyran derivatives to the corresponding γ-lactones, which are synthetic intermediates of the synthesis of glaucarubolone and holacanthone, displaying potent antileukemic activity (equation 31).[39]



G	K_{REL}
$(CH_3)_3Si$	25.5
$(CH_3)_3C$	19.3

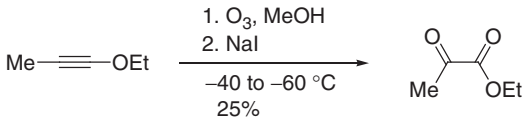
Scheme 1


AcO OAc
OAc
I
O
O
(TAPI)
CH2Cl2, 75%
OMOM
OMe
OTBDMS
OH
OH
H
H
O
O
O



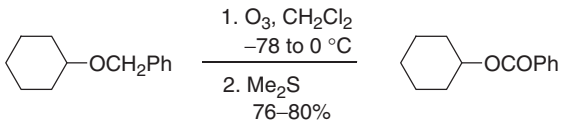
(36)

However, alkynyl ethers can be made to react with O_3 followed by the reductive workup with NaI, leading to α-keto esters (equation 37).[48]



(37)

The reaction of benzyl ethers with O_3 affords the corresponding benzoate esters in high yields (equation 38).[49]



(38)

7.09.6 Metal–Salt/Heteropolyacid-Catalyzed Dimethyl Ether Oxidation with Molecular Oxygen

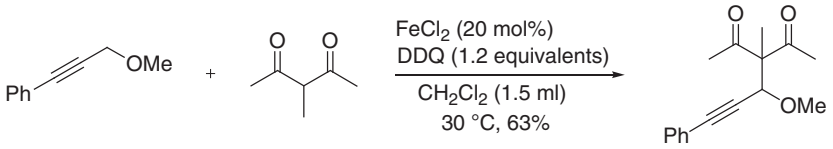
Dimethyl ether (DME) has been under consideration for use as an alternative fuel and an additive in diesel engines. Therefore, intense research has been performed in the oxidation of DME. DME oxidation is an important process and produces formaldehyde, methanol, methyl formate, etc. The oxidation is usually carried out under the influence of a MoO_x catalyst supported on Al_2O_3, ZrO_2, and SnO_2. Peroxy radicals such as $CH_3OCH_2OO^{\bullet}$ and $CH_3OCH_2O^{\bullet}$ are suggested as transient intermediates.[50]

However, Iglesia and coworkers reported the one-step selective synthesis of dimethoxymethane (DMM; $CH_3OCH_2OCH_3$) (56.8% selectivity) by the oxidation of DME with O_2 at 513 K on a heteropolyacid such as $H_5PV_2Mo_{10}O_{40}$.[51] In a recent publication, the detailed kinetics and a mechanistic study of the aerobic oxidation of DME have been proposed.[52]

7.09.7 Metal-Catalyzed Oxidative Functionalization of C–H Bond Adjacent to Oxygen

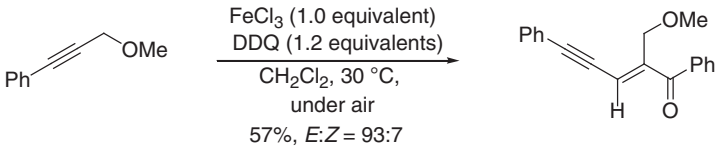
A tremendous effort from both academic and industrial laboratories has been made for the transition metal-catalyzed functionalization of C–H bonds directed to atom- and step-economical synthesis. The advantages of this strategy are high efficiency, low cost, and minimal environment impact.[53]

Direct oxidative coupling of sp^3 C–H adjacent to oxygen atom in propargyl ethers such as (3-methoxyprop-1-ynyl)benzene with 3-methylpentene-2,4-dione is achieved by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of a catalytic amount of $FeCl_2$ combined under air (equation 39).[54] The reaction can be carried out with a variety of 1,3-diketones, leading to β-dicarbonyl ethers in moderate yields.



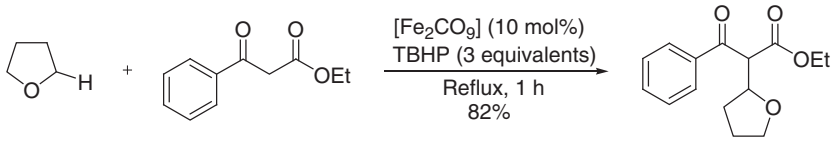
(39)

However, an ynenone is obtained from phenylpropargyl methyl ether by using $FeCl_3$ and DDQ oxidants under air (equation 40).[54]



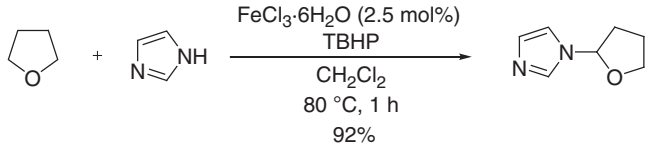
(40)

An iron-catalyzed C–C bond forming reaction of C–H bonds adjacent to the oxygen atom of ethers with activated methylene compounds is illustrated. The reaction of THF with ethyl benzoylacetate in the presence of an iron catalyst and TBHP as an oxidant affords the desired oxidative coupling product (82% yield) (equation 41).[55]



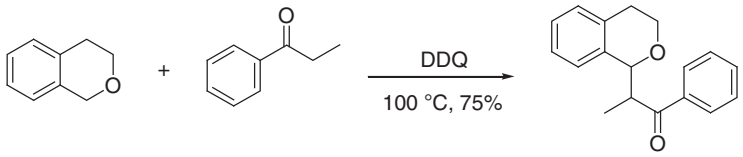
(41)

Furthermore, the $FeCl_3 \cdot 6H_2O$/TBHP system is efficient for the *N*-alkylation of azoles with cyclic ethers via the activation of the C–H bond adjacent to the oxygen atom (equation 42).[56]



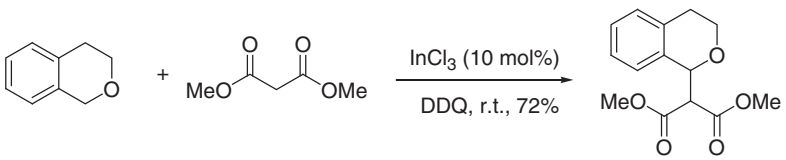
(42)

Li and coworkers reported the DDQ-mediated oxidative coupling between simple ketones and benzyl ethers such as isochroman (equation 43).[57]



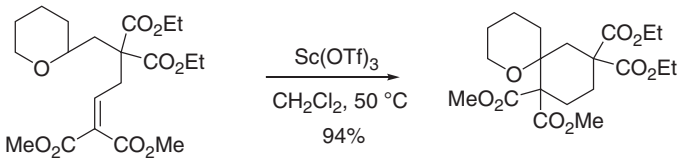
(43)

Efficient oxidative C–H bond functionalization of ethers with active methylene compounds was achieved by using $InCl_3$ catalyst combined with DDQ (equation 44).[58]



(44)

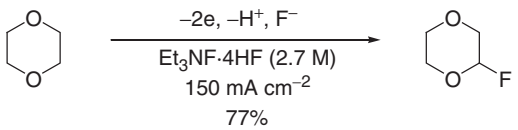
Sames and coworkers succeeded in the $Sc(OTf)_3$-catalyzed intramolecular cyclization of α,β-unsaturated malonate, wherein the sp^3 C–H bond adjacent to the oxygen atom of tetrahydropyran moiety couples with the activated malonate carbon (equation 45).[59]



(45)

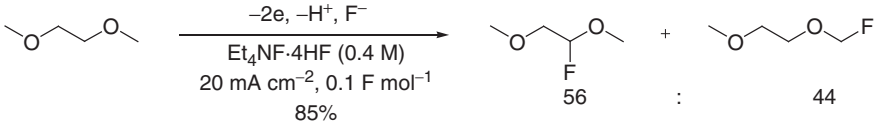
7.09.8 Electrochemical Oxidation

By electrochemical anodic fluorination of ethers, a fluorine atom is successfully introduced into an α-carbon atom of cyclic ethers. For example, the anodic fluorination of 1,4-dioxane in the presence of $Et_3NF \cdot 4HF$ was carried out at platinum electrodes with a current of 150 mA cm^{-2} without solvent, and 2-fluoro-1,3-dioxane was obtained (equation 46).[60]



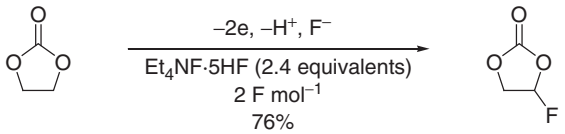
(46)

In the case of 1,2-dimethoxyethane under the conditions of anodic fluorination, a fluorinated product mixture was generated (equation 47).[61]



(47)

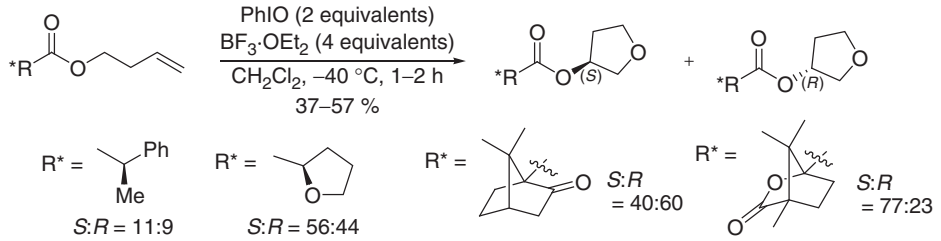
Similar anodic fluorination of ethylene carbonate gives rise to the corresponding monofluorinated products in 76% yield (equation 48).[60]



(48)

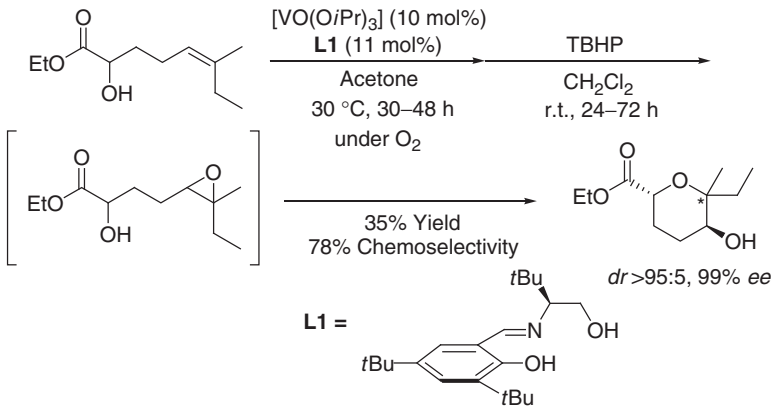
7.09.9 Ether Oxidation in Asymmetric Synthesis

Chiral substituted tetrahydrofurans are important motifs in many biologically active compounds.[62] Therefore, asymmetric cycloetherfication of a series of chiral but-3-enyl carboxylates was examined using iodosylbenzene combined with $BF_3 \cdot OEt_2$ (Scheme 2).[63] A favorable choice of a chiral auxiliary in the acyloxy group of the substrates was crucial to improve the enantioselectivity in the cycloetherification. The reaction using (1*S*)-camphanate as a chiral auxiliary preferentially gave (*S*)-3-acyloxytetrahydrofuran.



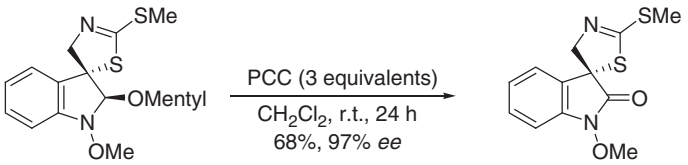
Scheme 2

When racemic unsaturated α-hydroxyester is allowed to react in the presence of $[VO(OiPr)_3]$ catalyst, chiral hydroxydimethylbutylsalicylaldimine ligand (**L1**), and TBHP in acetone under O_2, tandem resolution/oxidative cyclization takes place to afford 2,5-*trans*-tetrahydropyran derivatives (Scheme 3).[64] The reaction proceeds with highly chemo-, regio-, and stereoselectivities.

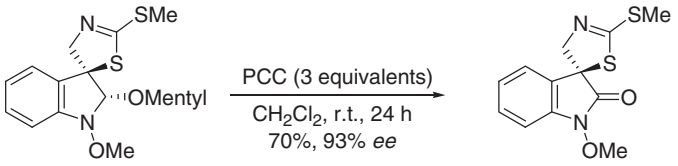


Scheme 3

The stereoselective synthesis of indole phytoalexins such as (+)- and (–)-1-methoxyspirobrassinin was examined by means of PCC oxidation of (+)- and (–)-1-methoxy spirobrassinol menthyl ether to obtain the desired enantiomers of 1-methoxyspirobrassinin with high *ee* values (equations 49 and 50).[65]

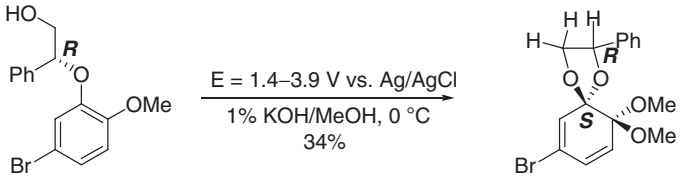


(49)



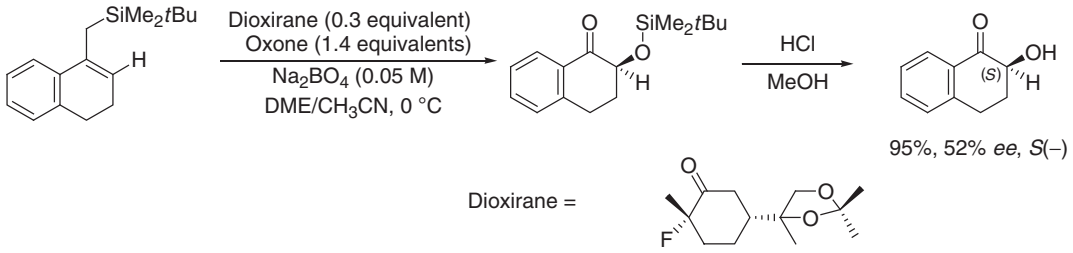
(50)

Asymmetric anodic oxidation of chiral *β*-(5-bromo-2-methoxyphenoxy)phenylethanol results in chiral orthoquinone monoketal (equation 51).[66] This reaction proceeds via spirocyclization followed by anodic oxidative dearomatization.



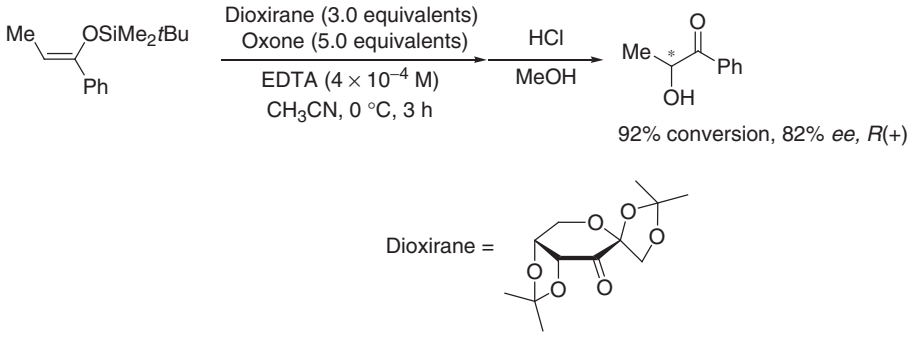
(51)

Asymmetric oxidation of *tert*-butyldimethylsilyl enol ether using a chiral dioxirane-generated *in situ* from chiral dioxirane and oxone provides a silyl-proteced hydroxyl ketone, which is then hydrolyzed with 5% HClaq/MeOH to form hydroxyl ketones in high yield (equation 52).[67]

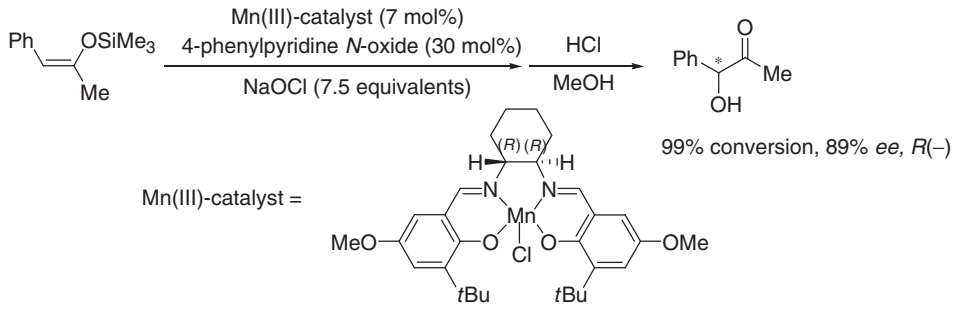


(52)

Adam et al. reported the highly enantioselective synthesis of α-hydroxy ketones by dioxirane[68] or (salen) manganese(III)/4-phenylpyridine *N*-oxide/NaOCl system (equation 54)[69] oxidation of silyl enol ethers derived from fructose and oxone (equation 53).



(53)



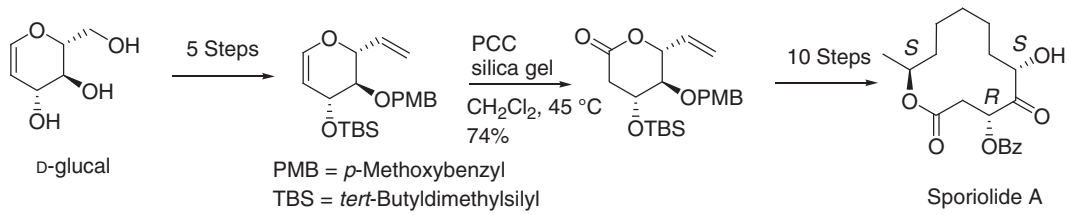
(54)

7.09.10 Application of Ether Oxidation in Total Synthesis

The oxidation of C–H bonds adjacent to oxygen of ethers provides an important step to access various natural products via total synthesis.

For example, sporiolide A is a natural cytotoxic macrolide of marine-derived fungal metabolites containing 12-membered lactone rings.[70]

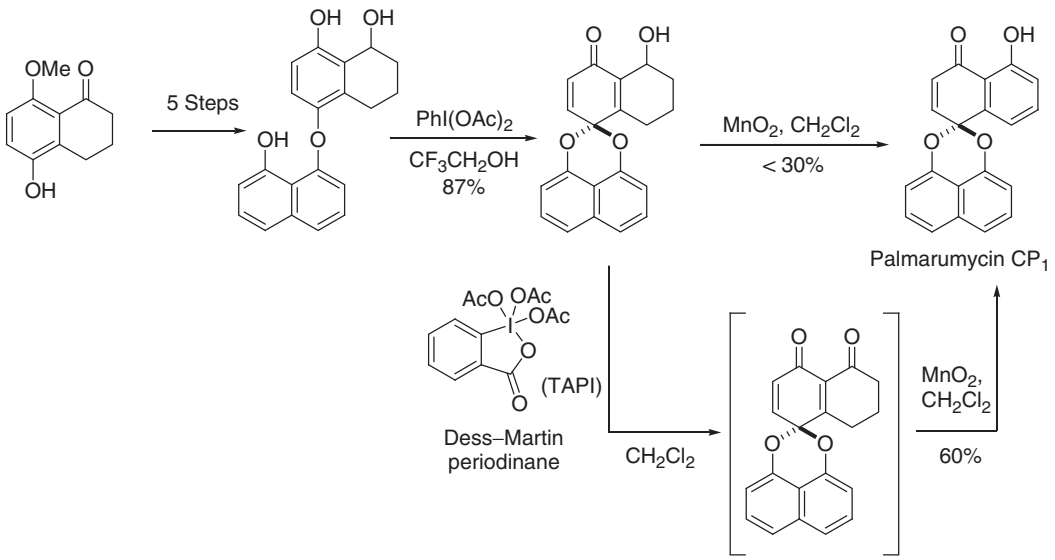
The total synthesis of the natural cytotoxic agent, sporiolide A, is made from D-glucal in 16 steps with 6.1% overall yield (Scheme 4). In this reaction, PCC-promoted oxidation of cyclic enol ether to lactone is involved as a key step.[71]



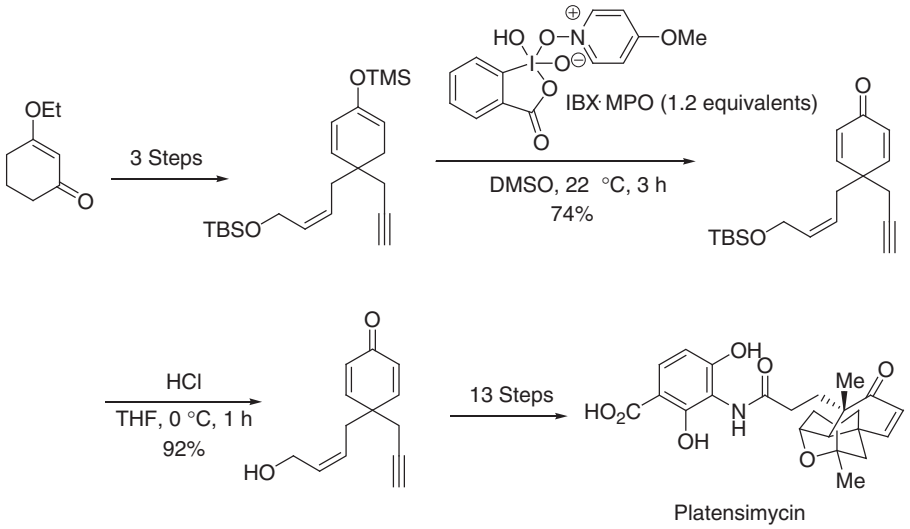
Scheme 4

Palmarumycins are naphthalenediol spiroketals showing high antifungal activity.[72]

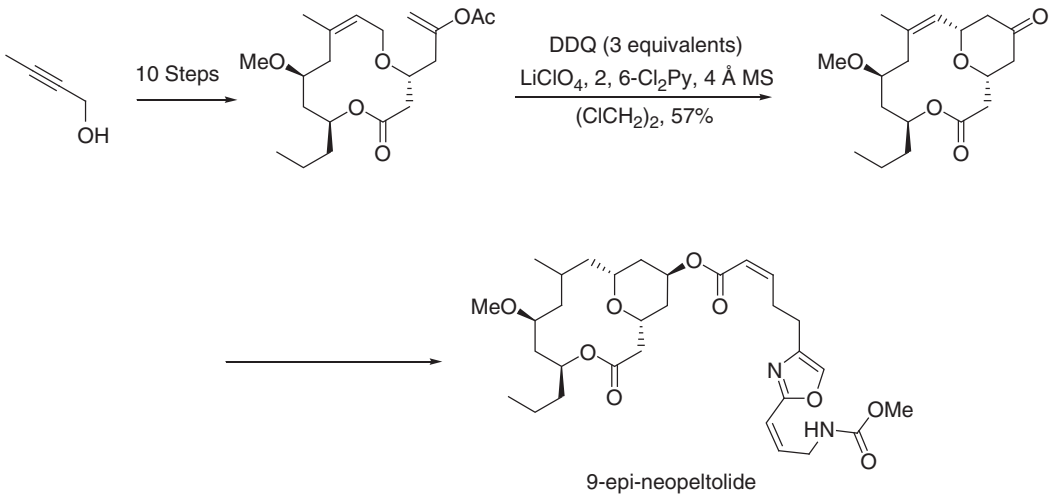
Oxidative cyclization of bis-hydroxynaphhtyl ethers derived from 5-hydroxy-8-methoxy-1-tetralone by using $PhI(OAc)_2$ in trifluoroethanol affords naphthalenediol spiroketal, followed by MnO_2 or Dess–Martin periodinane/MnO_2 oxidation to lead to palmarumycin (Scheme 5).[73]



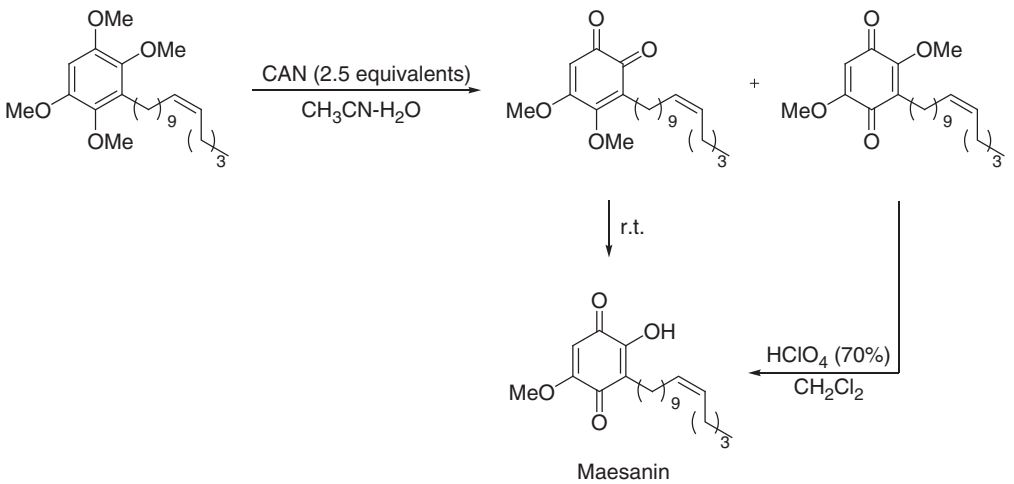
Scheme 5



Scheme 6



Scheme 7



Scheme 8

The oxidation of silyl enol ethers is also employed in the total synthesis of platensimycin, which is an antibiotic with promising antibacterial properties against drug-resistant bacteria.[74] Here, the oxidation of trimethylsilyl enol ether with IBX (*o*-iodoxybenzoic acid)/MPO (4-methoxypyridine-*N*-oxide) to dienone is involved as a key step in the total synthesis (**Scheme 6**).[75]

As shown in **Scheme 7**, the oxidative cyclization of macrocyclic vinyl acetate with DDQ/$LiClO_4$ led to bicyclic tetrahydropyran, which is a key intermediate to access 9-epi-neopeltolide, which exhibits potent cytotoxic and antifungal activity.[76]

Oxidation of 1,2,4,5-tetramethoxybenzene with CAN provokes the formation of quinone (**Scheme 8**).[77] The oxidation furnishes a variety of 2-hydroxy-5-methyl-1,4-benzoquinolines (Maesanin and analogies) displaying antimicrobial activity.[78]

7.09.11 Conclusion

Through the oxidation of C–H bonds adjacent to the oxygen of ethers with various oxidants, easily accessible cyclic and acyclic ethers can be easily converted into synthetically useful carbonylated compounds such as lactones, esters and carboxylic acids. This method is currently widely applied in asymmetric synthesis as well as being the key step in the total synthesis of important natural products.

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7.10 Oxidation Adjacent to Oxygen of Alcohols by Chromium Reagents

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Glossary

π-Allyl and σ-allyl bonds Two typical bonding modes of allylic moieties that bind to an atom either with all three carbon centers (π-allyl) in a η^3-mode or with only one terminal carbon centers (σ-allyl) in a η^1-mode.

Collins and Sarrett reagents Chromium trioxide bispyridine complex $CrO_3 \cdot (Py)_2$ (CAS no. 26412-88-4) (similar to Sarrett reagent). Major difference is that the Collins reagent is filtered whereas the Sarrett is used in pyridine. It is used to selectively oxidize primary alcohols to aldehydes and can tolerate many other functional groups within the molecule.

***N*-Heterocyclic Carbene (NHC)** NHC, cyclic carbenes stabilized by the adjacent nitrogens prepared from imidazole derivatives, being used as strong electron-donating ligands to metals to form stable complexes.

***β*-Hydrogen elimination** The reverse reaction of the addition of a metal–hydrogen bond to an unsaturated bond.

Jones reagent $[CrO_3 + H_2SO_4 + H_2O]$ Primary alcohols are converted to acids; secondary alcohols to ketones; alkenes and alkynes are resistant. Related reagents: the Conforth reagent, pyridine/chromic acid; Fieser's reagent, acetic acid/chromic acid.

Oxidative addition A general type of reaction between transition metals and substrates in which both the oxidation state and coordination number of the metal increase.

Oxidative transposition A rearrangement reaction in which the carbon skeleton of a molecule is rearranged to give a structural isomer of the original molecule in an oxidative manner.

Phase transfer catalyst It is a compound soluble in both aqueous and organic phase. Used in special form of heterogeneous catalysis (intransfer catalysis) that facilitates the migration of a reactant from one phase into another phase where reaction occurs.

Pincer ligand A type of ligand that chelate to an atom, usually a transition metal, by three coplanar coordinating sites forming stable complexes with constrained geometries.

Pyridinium chlorochromate (PCC) PCC, Corey reagent (yellow-orange solid; (CAS no. 26299-14-9) $C_5H_6ClCrNO_3$ (M_w 215.57) mp 205 °C). Stable versatile oxidizing agent for many functional groups; can oxidize activated C–H bonds: C–C bonds; and C–B bonds; can halogenate enolsilyl ethers.

Pyridinium dichromate (PDC) PDC (bright orange solid; (CAS no. 20039-37-6) $C_{10}H_{12}Cr_2N_2O_7$ (M_w 376.24) mp 152–153 °C). Mild and selective oxidizing agent for primary and secondary alcohols; can oxidize unsaturated tertiary alcohols; silyl ethers; the C–B bonds; and oximes.

Reductive elimination The reverse reaction of oxidative addition that often constitutes the final step of catalytic cycles to create a new bond.

Single electron transfer (SET) It is a transfer of an electron from a metal or a molecule to a substrate to form radical species.

Transmetalation Reactions to exchange ligands between two organometallic complexes.

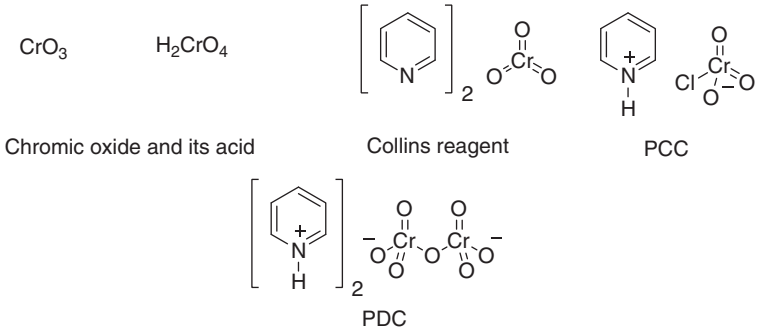
Turnover frequency It is a turnover number per unit time.

Turnover number It is a mole of product/a mole of catalyst.

7.10.1 Introduction

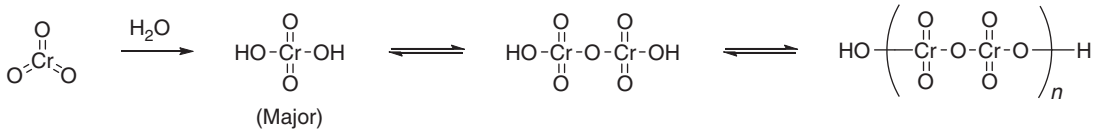
Chromium ([Ar] $3d^5\ 4s^1$) belongs to group six of the transition metal block elements of the periodic table. Out of a number of possible oxidation states that the metal can adopt (-2 to $+6$), the $+6$ oxidation state has attracted the interest of organic chemists due to the stability, ability to oxidize a number of functional groups, abundance and ease of handling. For example, the oxidizing ability of dichromate ($E°_{red} = +1.3$) is between that of molecular oxygen and chlorine.[1] Though chromium(VI) reagents are strong oxidizing agents, the reactivity and selectivity can be fine-tuned using additives that can control the rate of the reaction. Ley and Madin have covered the key aspects of the oxidation of alcohols with chromium(VI) reagents and highlighted the ease of handling of these reagents in the first edition of this book.[2] A number of excellent review articles are available on these oxidizing agents. The present chapter will cover the developments in the field of oxidation adjacent to oxygen of alcohols by chromium reagents with new examples.[2–8]

Most common oxidizing agents used in target-oriented synthesis are chromic oxides, halochromates, chromate esters, and dichromates.



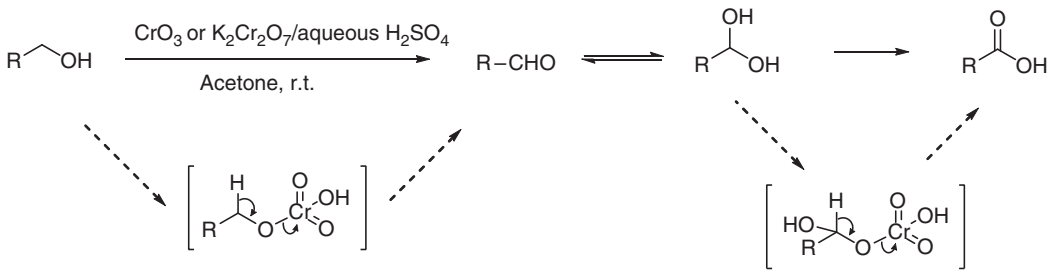
7.10.2 Chromium(VI) in Acid Media

Oxidation with CrO_3 in aqueous acids is one of the oldest and most common methods for converting alcohols to aldehydes or carboxylic acids.[9,10] The oxidation is mediated by chromic acid that is formed *in situ* with other polyanhydride species when dissolved in water. Most of the chromium(VI) salts are strong oxidizing agents at low pH.[11] At low pH, the rate of oxidation by Cr(VI) salts is very high and the reaction is slightly exothermic. Hence, selective oxidation of alcohols to their corresponding aldehydes is challenging under these conditions. In the presence of aqueous acids, the formed aldehyde can get hydrated facilitating further oxidation to their corresponding carboxylic acid.[12,13] The reactivity of Cr(VI) salts in aqueous H_2SO_4 and acid (catalytic amount) in DMF/DMSO has been discussed in the first edition.[2]



7.10.2.1 In Aqueous Sulfuric Acid/Acetone (Jones Oxidation)

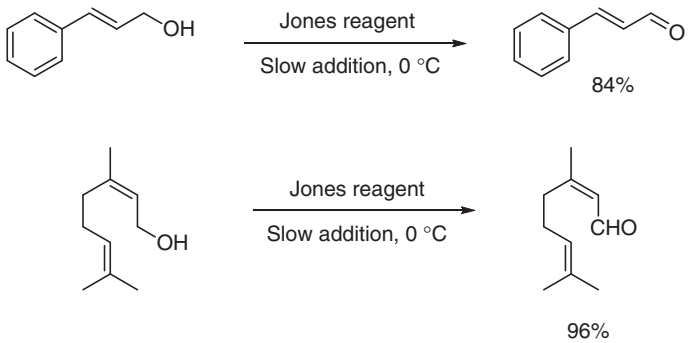
Jones oxidation is a common protocol for the synthesis of carboxylic acids from primary alcohols in the presence of a wide variety of functional groups. The basis of Jones oxidation is similar to that of Cr(VI) salts in aqueous sulfuric acid where the reactive species is chromic acid. The reaction proceeds through C–H bond activation of the chromate ester intermediate. Typically, the reaction is carried out by titrating chromic acid against the substrate dissolved in acetone. Acetone not only helps in the dissolution of the substrate but also prevents epimerization by acid-catalyzed enolization of the α-center in the ketones during oxidation of the secondary alcohols.[14,15] The resulting carboxylic acids often react with the starting alcohols to give the corresponding ester as a side product in considerable amounts. To avoid this side reaction, an inverse addition protocol was reported, wherein the alcohol is added dropwise to Jones reagent.[16]



Jones reagent is tolerant to unsaturation and oxidation of a number of substrates has been demonstrated with alcohols containing double (C═C) and triple bonds (C≡C). Even in the case of highly conjugated, unsaturated alcohols, the oxidation was found to proceed efficiently (entries 1–3, Table 1).[17,18] Jones oxidation has been successfully employed for the synthesis of amino acids from the corresponding amino alcohols in high enantiomeric purity, without racemization of the α-center of the amino acid (product) (entries 5–9, Table 1).[19–25] Use of acid-labile protecting group for alcohols facilitates simultaneous deprotection followed by oxidation to the desired acids. Similarly a range of secondary alcohols has been efficiently oxidized to their respective ketones under similar conditions. The silyl protection and the acyclic ketal protections were found to be less tolerant with Jones oxidation conditions, whereas the cyclic ketal protecting groups were found to be capable of withstanding the acidic conditions. The reagent has been employed successfully on carbohydrate skeleton quite frequently.[22,26–32]

Under these conditions, the conversion of alcohols to aldehydes is quite challenging, as it always leads to overoxidation. In a few cases, the aldehydes obtained from a different route have been converted to the carboxylic acids using this protocol.[33–34] Hemiacetals, lactols and α-amino alcohols have also been shown to undergo oxidation to their corresponding esters/lactones and amides efficiently (entries 18–20, Table 1).[35–37]

Though the isolation of product at the aldehyde stage is a challenge, Harding et al. achieved selective oxidation of allylic alcohols to their corresponding α,β-unsaturated aldehydes, by slow addition of Jones reagent to the substrate. Common substrates like cinnamyl alcohol, geraniol, and nerol have been converted to their respective aldehydes in good yields.[38]



Recently, a silica gel-supported Jones reagent was developed and studied. Under these conditions due to the absence of water, the formed aldehyde does not get hydrated and oxidized further. The sticky chromium(III) salts are adsorbed on to the silica surface and do not leach out to the solution. This method serves to be an efficient method for the synthesis of aldehydes in good yields.[39,40]

7.10.3 Chromium(VI) with Heterocyclic Bases

The ability of chromium(VI) oxides to oxidize the substrate largely depends on the pH of the reaction medium. At lower pH, they behave as strong oxidizing agents (see Section 7.10.2). On complexation with organic heterocyclic bases, the reagents become mild oxidizing agents, thereby exhibiting good selectivity toward oxidation of alcohols to aldehydes. These are the reagent of choice when aldehydes are desired from alcohols. The reaction of organic bases with chromium salts is exothermic and generally carried out at low temperature.

7.10.3.1 Sarett/Collins Oxidation

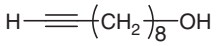
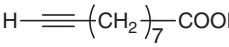
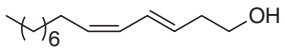
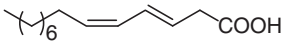
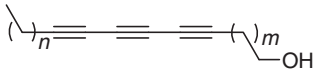
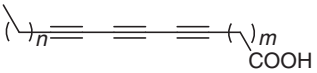
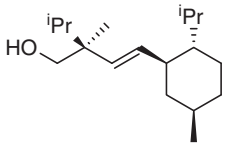
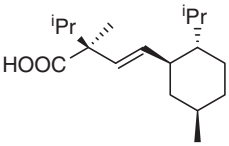
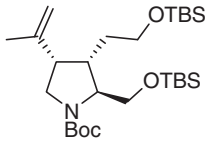
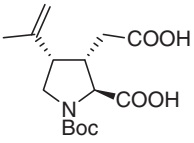
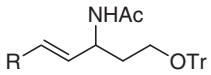
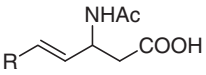
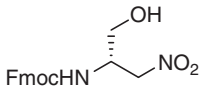
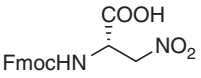
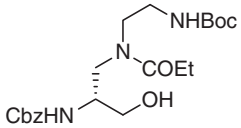
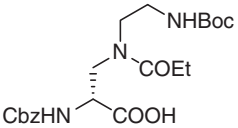
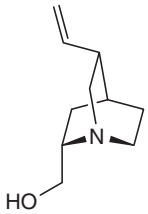
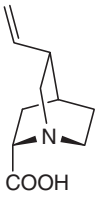
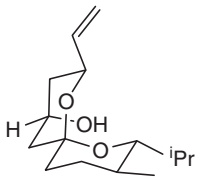
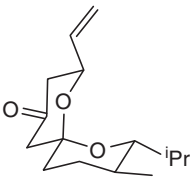
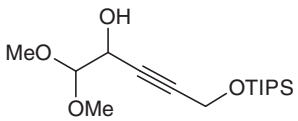
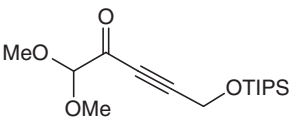
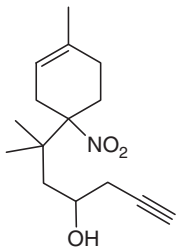
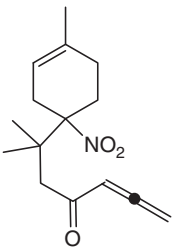
The use of Sarett[41] and Collins reagents[42,43] followed by a few other modifications has been well-documented in the first edition of this book.[2] The work of Sarett and coworkers led to the development of various heterocycle-based chromium oxidants.[41] The reagent is an efficient oxidizing agent for secondary alcohols to ketones. Though the reagent is very hygroscopic, generating the reagent *in situ* has become a routine, practical protocol.

The reaction is generally carried out at 0 °C or r.t. typically from 30 min to 5 h of the reaction time. The use of a solid adsorbent like Celite® or silica helps in easy isolation of the product from the sticky chromium by-product after the reaction.[44] The reaction conditions are mild to acid-sensitive protecting groups like trityl, TBS, and TES groups (entries 1, 6, 7, and 11, Table 2).[45–53]

Primary alcohols protected as its TMS-ether were found to be intolerant under Collins oxidation conditions. Fuji's report on the total synthesis of indole alkaloid (–)-eburnamonine highlights the efficiency of Collins reagent in the final stages of their synthesis (entry 9, Table 2).[50] The reagent has been demonstrated to oxidize alcohols chemoselectively in the presence of other oxidizable heteroatoms like sulfur.[54] Generally, epimerization of chiral center at the β-position is not observed during oxidation.[55–57]

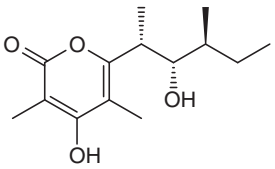
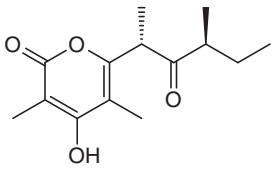
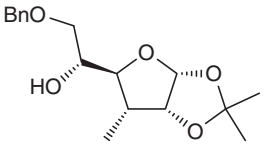
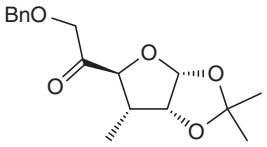
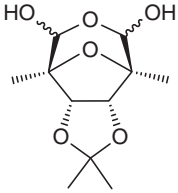
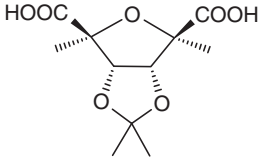
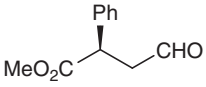
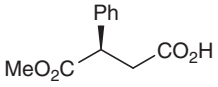
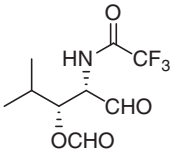
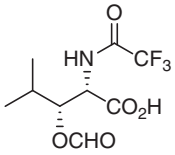
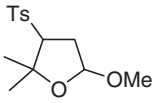
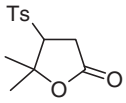
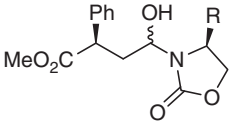
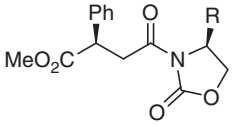
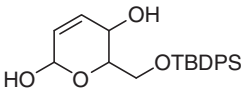
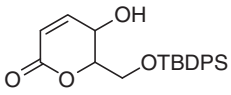
The rearrangement of tertiary allylic alcohols to epoxyketones has been discussed earlier. McIntosh utilized this rearrangement for the synthesis of massileunicellin C.[58]

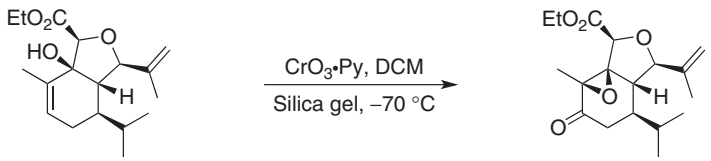
Table 1 Oxidation of primary and secondary alcohols using Jones oxidation

Entry	*Substrate*	*Product*	*Yield (%)*	*References*
1			92	18
2			95	18
3			58–60	17
4			85	24
5			76	21
6			94	25
7			66	19
8			64	20
9			60	23
10			80	28
11			88	29
12			77	30

(*Continued*)

Table 1 Continued

Entry	*Substrate*	*Product*	*Yield (%)*	*References*
13			63	31
14			76	32
15			100	27
16			50	33
17			60	34
18			96	35
19			56	36
20			92	37

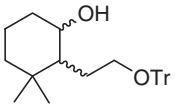
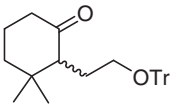
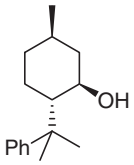
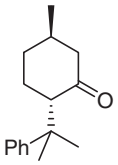
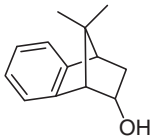
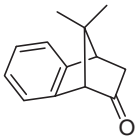
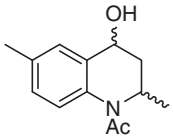
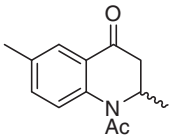
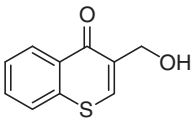
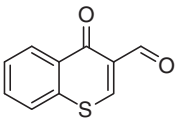
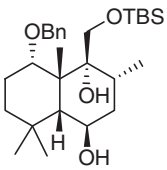
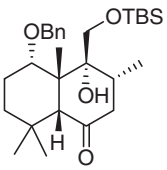
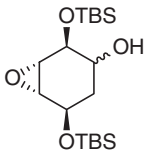
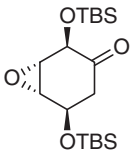
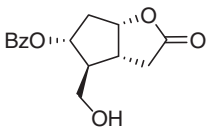
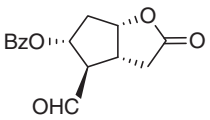
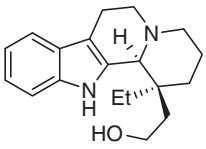
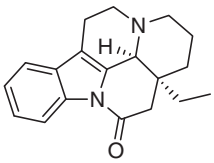
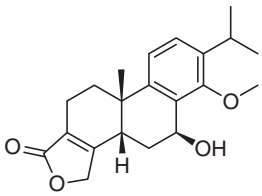
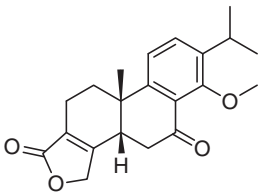


7.10.3.2 Pyridinium Chlorochromate (PCC)

Pyridinium chlorochromate (also known as Corey–Suggs reagent) is prepared in the laboratory as a yellow-orange crystalline solid, by dropwise addition of pyridine to CrO_3 dissolved in aqueous HCl in ice-cold conditions.[59,60] To avoid acidic impurities when used with acid-sensitive substrates, pyridine is added in slight excess during the preparation of the reagent. Other modified procedures are also available in the literature with easy handling of toxic chromium compounds.[61,62]

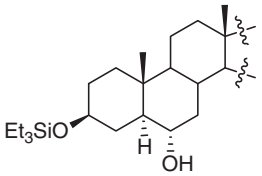
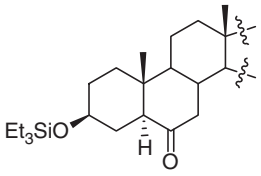
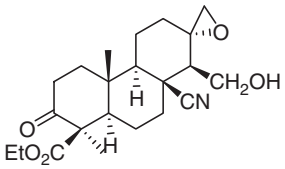
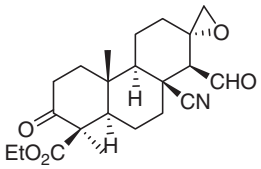
PCC is not as moisture sensitive as the Sarett reagent, but it is moderately soluble in chlorinated solvents like dichloromethane, which is the general choice of solvent for the oxidation reaction. Kinetic isotope data reveal that the rate-determining step is the activation of C–H bond after the formation of the chromate ester.

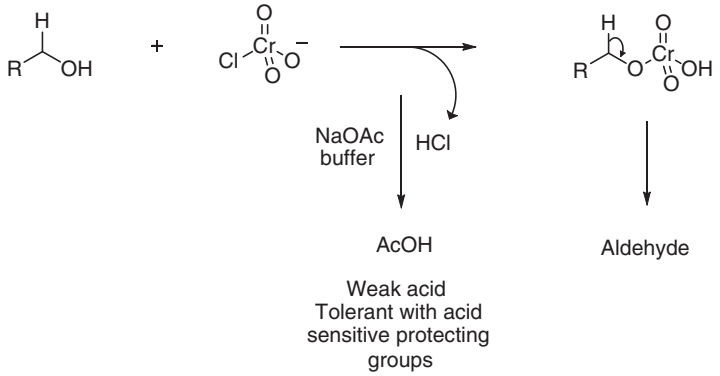
Table 2 Oxidation of primary and secondary alcohols using Sarett/Collins reagent

Entry	*Substrate*	*Product*	*Yield (%)*	*References*
1			81	53
2			96	55
3			80	57
4			68	46
5			65	54
6			97	52
7			90	45
8			93	56
9			74	50
10			89	49

(*Continued*)

Table 2 Continued

Entry	*Substrate*	*Product*	*Yield (%)*	*References*
11			66	48
12			60	47



Use of buffering agents like sodium acetate and other mild bases improves the selectivity in oxidation and tolerance to acid-sensitive protecting group like silyl and THP ethers.[63] However, the addition of excess base decreases the rate of the reaction. On the contrary, addition of activators like acetic acid and PTSA accelerates the reaction, and a slight improvement in yield is also observed.[61,64–66]

The reaction of primary alcohols proceeds smoothly with 1.2–1.5 equivalents of PCC in CH_2Cl_2 for 1 h at room temperature (entries 1–6, **Table 3**).[61,67–74] Additives like silica gel, molecular sieves, and Celite help in the isolation of the product from the chromium precipitate after the reaction.[70,75] The rate-determining step for the oxidation is the cleavage of the C–H bond of the intermediate chromate ester. In general, secondary alcohols react slowly to give the desired ketone as the sole product and the reaction time is approximately 1.5–3 h at r.t. (entries 8–17, **Table 3**).[63,76–86]

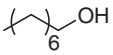
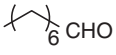
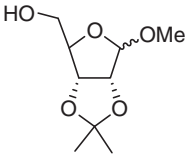
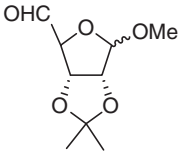
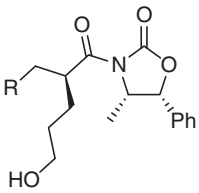
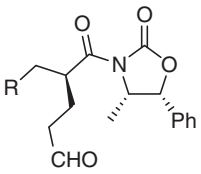
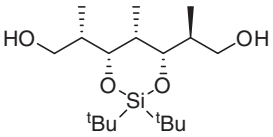
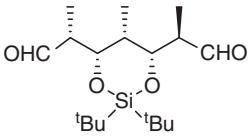
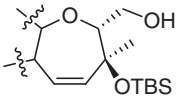
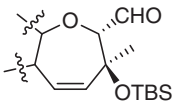
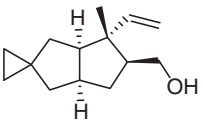
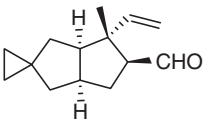
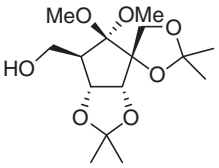
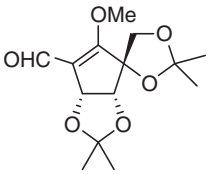
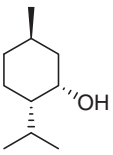
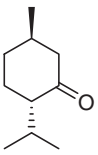
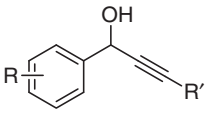
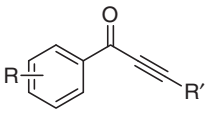
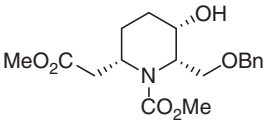
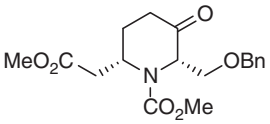
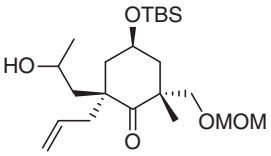
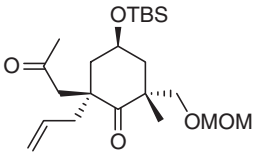
The reaction conditions were found to be tolerant to moderately acid-sensitive functional groups like cyclic ketals. Addition of basic salts to buffer to the medium enables the reaction condition to be tolerant to acid-labile functional groups. The reagent is handy and reliable to convert multiple hydroxyl groups to the corresponding carbonyl compounds in a single step without disturbing the adjacent chiral centers in complex molecular skeletons. Analogous to Collins oxidation, PCC also oxidizes hemiacetals/lactols to the corresponding ester/lactones almost quantitatively (entries 18–21, **Table 3**).[82,87–89]

The reagent is also capable of oxidizing C–H and C–C bonds adjacent to oxygen as in the case of cyclic allyl ethers to the corresponding α,β-unsaturated lactones (entries 22 and 23, **Table 3**)[90,91] and the furanose system to a lactone with 3 equivalents of the reagent (entry 24, **Table 3**).[67]

7.10.3.3 Chromium Oxide-3,5-Dimethylpyrazole

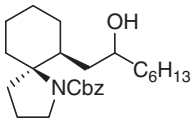
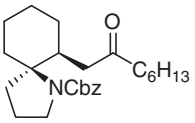
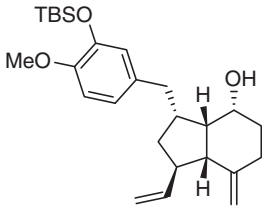
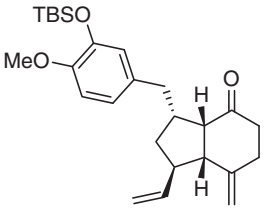
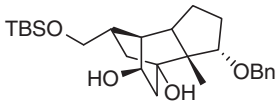
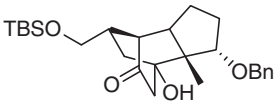
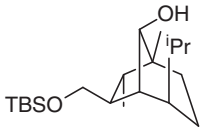
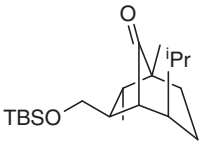
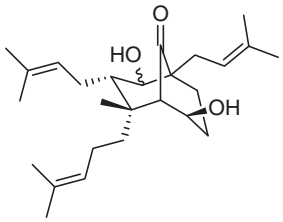
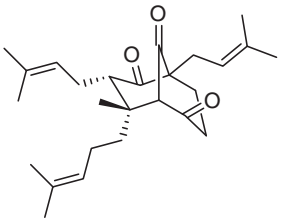
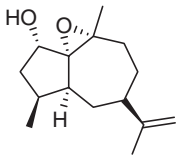
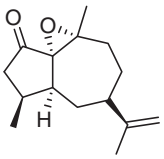
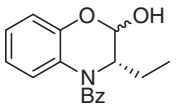
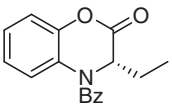
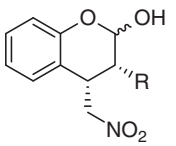
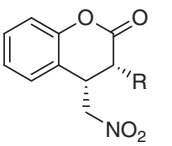
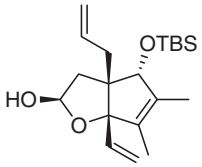
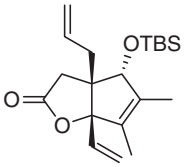
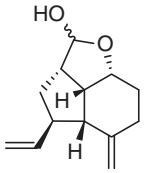
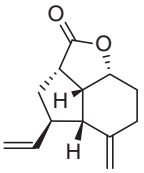
Dimethylpyrazole forms a complex with chromium oxide and is generally generated *in situ* by adding both the heterocyclic base and CrO_3 sequentially. The reagent possesses high solubility in dichloromethane. Earlier, the reagent has been extensively used for the oxidation of alcohols to aldehydes and ketones. Recently, the reagent has been widely used in a number of oxidation reactions of allylic C–H bonds to α,β-unsaturated ketones in moderate yields.[92–97]

Table 3 Oxidation of alcohols using PCC

Entry	*Substrate*	*Product*	*Yield (%)*	*References*
1			92	61
2			87	74
3			83	69
4			85	72
5			92	72, 73
6			95	68
7			73	79
8			85	70
9			93	84
10			96	85
11			83	80

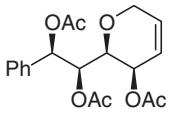
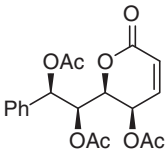
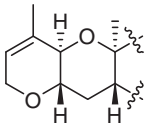
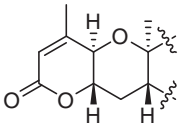
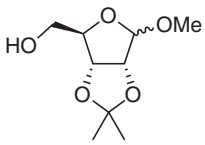
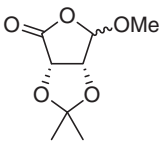
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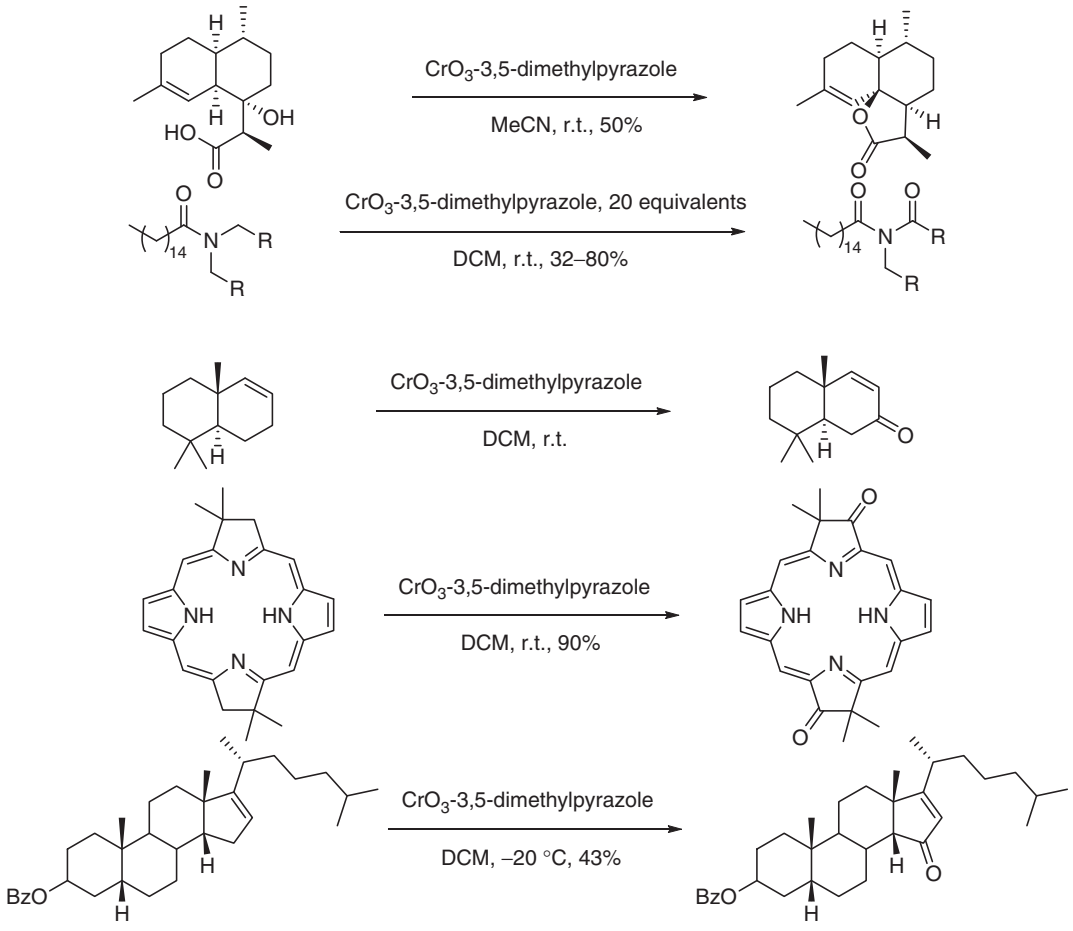
Table 3 Continued

Entry	*Substrate*	*Product*	*Yield (%)*	*References*
12			91	83
13			88	86
14			85	77
15			79	78
16			82	81
17			80	76
18			85	87
19			93	89
20			92	88
21			78	82

(*Continued*)

Table 3 Continued

Entry	*Substrate*	*Product*	*Yield (%)*	*References*
22			79	91
23			85	90
24			63	74



7.10.3.4 Pyridinium Dichromate

Pyridinium dichromate is an orange crystalline solid prepared by dropwise addition of pyridine to a concentrated aqueous solution of CrO_3 at ice-cold temperature.[98–101] Like PCC, PDC is a mild, easy to handle reagent used extensively for the oxidation of secondary alcohols to ketones.[102–112] In the case of primary alcohols, PDC can lead to overoxidization giving carboxylic acids apart from the corresponding aldehyde.[104,113]

The rate-determining step for the oxidation is the activation of the C–H bond in chromate esters and the rate of the reaction follows similar trend as in the case of PCC.

Addition of activators like acetic acid and salts of strong organic acids (PPTS, pyridinium, TFA) and molecular sieves accelerates the reaction. In the case of oxidation of carbohydrate substrates, the addition of acetic anhydride helps in the oxidation.[64–66,114,115]

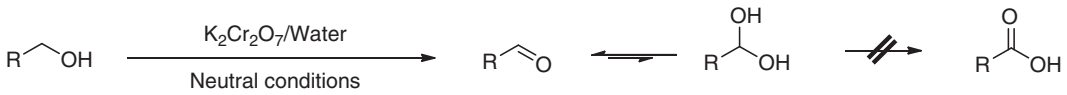
Chlorinated solvents are in general the solvent of choice as in the case of PCC. The reagent is highly soluble in polar solvents like DMF, DMSO, and water. A few new examples of oxidation with PDC are summarized in Table 4.

7.10.4 Chromium(VI) Under Neutral Conditions

Oxidation with chromium(VI) salts under neutral conditions is generally mild and does not result in overoxidation products. However, the reaction condition is so mild that the substrate scope is limited to benzylic and allylic alcohols. Aliphatic alcohols always result in poor yields of the corresponding aldehydes.[116,117] Hence, the scope of chromium(VI) oxidation under neutral conditions is very limited in multistep, target-oriented synthesis.

7.10.4.1 With Water as Solvent

Under neutral conditions, using aqueous sodium dichromate for the oxidation of alcohols was found to be effective in stopping the overoxidation of the intermediate aldehydes to their corresponding carboxylic acids. Though the overoxidation of the aldehydes occurs through the hydration under acidic conditions, the hydration is not favorable under neutral conditions (See Section 7.10.2). This avoids the problem of removing the aldehyde intermediates from the reaction mixture before they undergo overoxidation. The reagent is effective for the oxidation of benzylic and allylic alcohols, but in the case of aliphatic alcohols, the reaction was found to be sluggish.



7.10.4.2 With Phase Transfer Catalysts in Organic Solvents (Biphasic Conditions)

Chromium(VI) salts have moderate solubility in polar solvents. When the reaction is carried out in DMSO or DMF as solvent and benzene–water biphasic media under neutral conditions with chromium(VI) oxide for the oxidation of primary alcohols, good selectivity was observed. The reaction is efficient in the case of benzylic and allylic alcohols, but in general, the isolation of the oxidized products from the high-boiling solvents is tedious. A report by Brown on the oxidation of secondary alcohols in biphasic medium to the corresponding ketones has been highlighted in the first edition.[118,119]

Adogen 464 (methyltrialkyl(C_{8-10})ammoniumchloride) is one of the most efficient phase transfer catalysts for dichromate salts under neutral conditions. Using Adogen, the oxidation of benzylic and allylic alcohols with dichromates yields the desired aldehydes efficiently without overoxidation.[120–122]

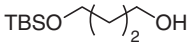
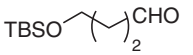
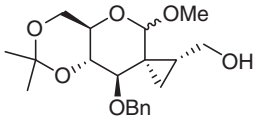
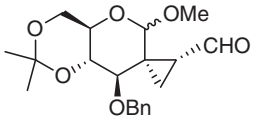
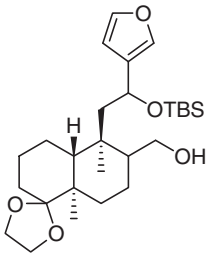
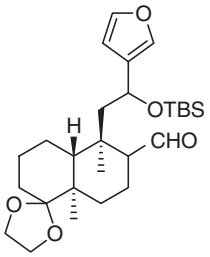
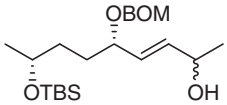
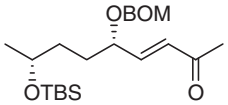
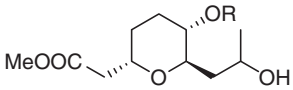
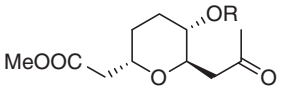
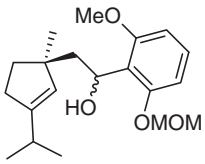
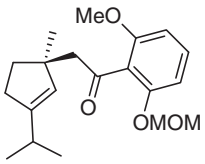
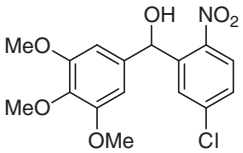
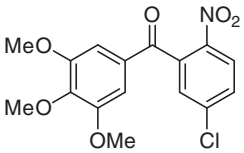
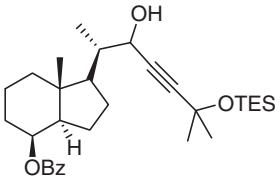
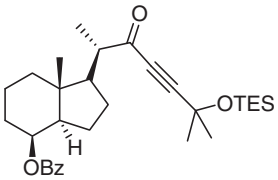
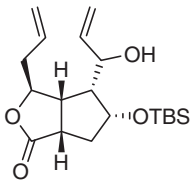
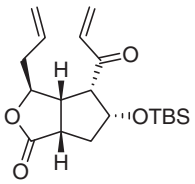
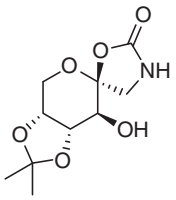
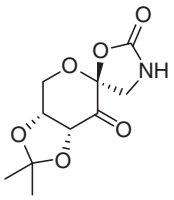
7.10.4.3 Solvent-Free Conditions

A number of solvent-free conditions for the oxidation of alcohols have been developed in recent years.[123–126] Generally, solid chromate is vigorously stirred with the desired substrate for 3–5 h to give the corresponding aldehyde in good yields (Table 5). The reaction appears to proceed efficiently with aliphatic alcohols as well, probably because the reaction system is not diluted by the use of solvents. Other solid supported chromates on wet Al_2O_3, zeolites have also been explored in detail.[127]

7.10.5 With Chromium(VI) in Catalytic Amounts Under Acidic Conditions

Oxidation with chromium(VI) salts in catalytic amounts under acidic conditions is a very attractive protocol. Using chromium salts in catalytic amounts, the protocol can be considered more environmentally benign, and the tedious work-up procedure of handling a sticky chromium by-product or removing of high-boiling solvents by distillation can be avoided. It has been shown that with periodic acid as both cooxidant and protic source, the oxidation of benzylic alcohols can be controlled and the aldehydes have been isolated successfully as the only products in excellent yields.[128,129] The reaction is typically carried out at $-78\ ^{\circ}C$. Simultaneous deprotection and oxidation of TBS protected alcohols has also been demonstrated. Analogous to Jones oxidation (see Section 7.10.2.1), direct oxidation to acids was reported later under similar conditions, but at $0\ ^{\circ}C$.[129] Under these conditions, the chiral center adjacent to the reaction site is undisturbed (Table 6).

Table 4 Oxidation of alcohols with PDC

Entry	*Substrate*	*Product*	*Yield (%)*	*References*
1			77	102
2			62	113
3			89	104
4			86	107
5			91	107
6			80	106
7			65	112
8			69	109
9			85	105
10			60	103

(*Continued*)

Table 4 Continued

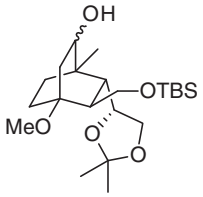
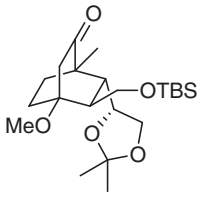
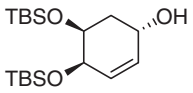
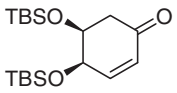
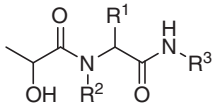
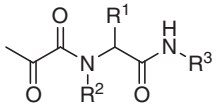
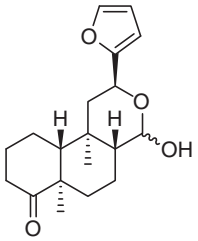
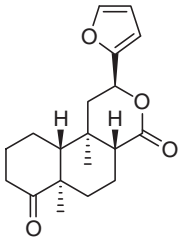
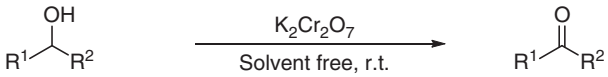
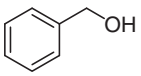
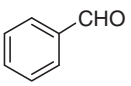
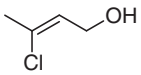
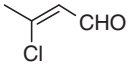
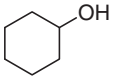
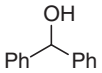
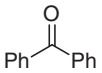
Entry	*Substrate*	*Product*	*Yield (%)*	*References*
11			90	108
12			78	110
13			50–60	111
14			>95	104

Table 5 Oxidation under solvent-free conditions with $K_2Cr_2O_7$



Entry	*Substrate*	*Product*	*Yield (%)*	*References*
1			80	123
2			88	123
3			75	123
4			80	123
5			95	123

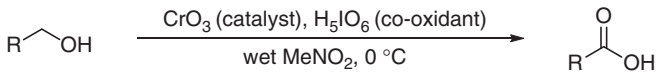
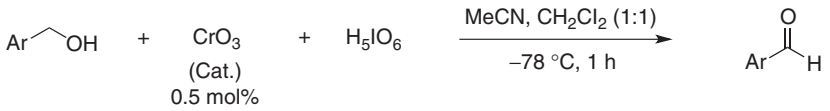
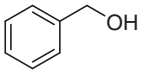
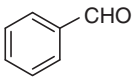
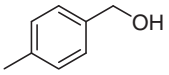
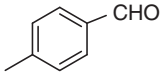
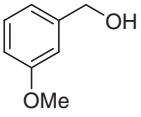
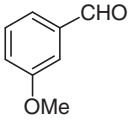
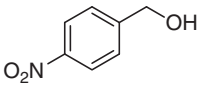
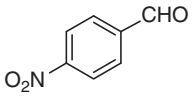
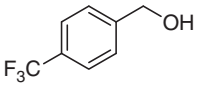
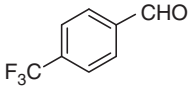
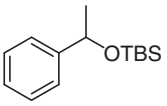
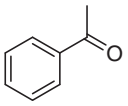


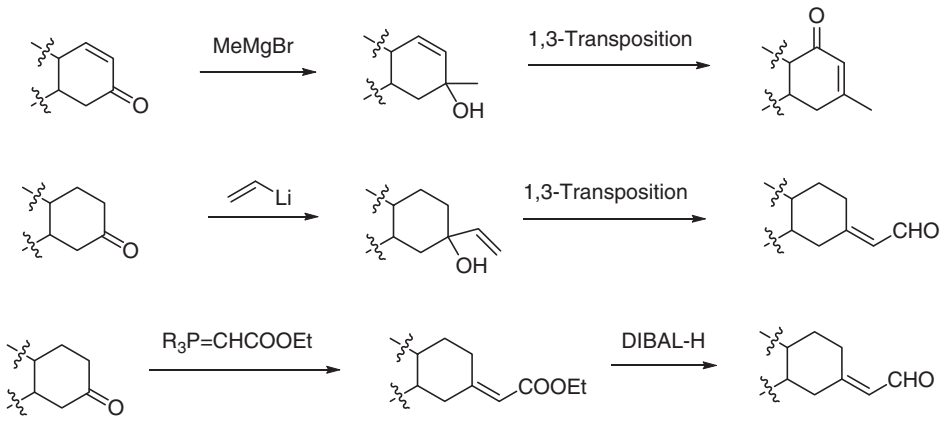
Table 6 Oxidation with chromium trioxide in catalytic amount under acidic conditions



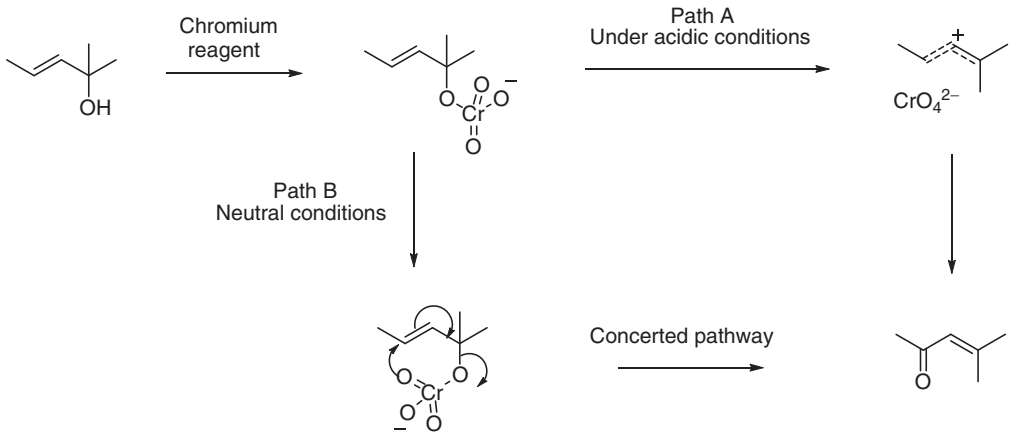
Entry	*Substrate*	*Product*	*Yield (%)*	*References*
1			86	128
2			88	128
3			90	128
4			78	128
5			55	128
6			95	128

7.10.6 Oxidative Transposition of Tertiary Allylic Alcohols

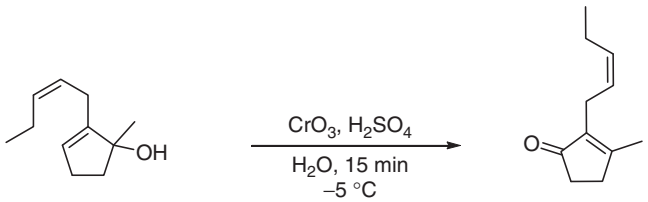
Oxidative transposition of tertiary allylic alcohols is one of the key transformations used in the total synthesis of complex natural product skeletons.[130] The tertiary allylic alcohols are easily prepared by nucleophilic addition of vinyl magnesium halides or vinyl lithium onto ketones. The transposition reaction leads to an α,β-unsaturated aldehyde, without any change in the carbon skeleton. This two-step transformation is equivalent to the Wittig reaction with stabilized ylides followed by reduction to aldehydes. Numerous oxidizing agents are capable of carrying out this transformation, out of which chromium reagents are first in the list of choices to carry out this transposition reaction effectively.[130]



The mechanism of transposition can follow either a stepwise pathway (path A) or a concerted pathway (path B) depending on the nature of the reagent used. With acidic reagents like Jones reagent and PCC, the reaction follows a stepwise mechanism, whereas with PDC, the reaction follows a concerted pathway.[130]

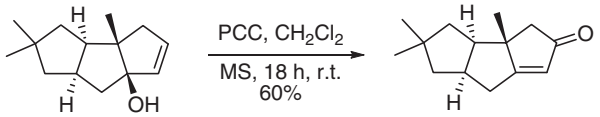


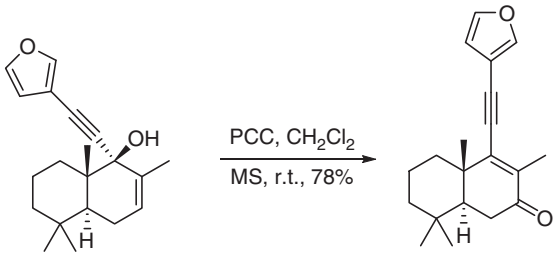
Jones reagent has been used for 1,3-transposition reaction in substrates without any acid-sensitive functional groups.[131–133] Büchi and coworkers demonstrated the 1,3-transposition in the synthesis of jasmone using Jones reagent.[134,135]

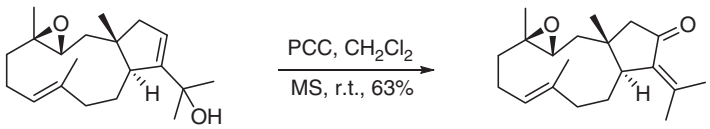


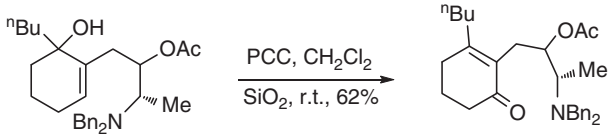
Jasmone

The most commonly used reagent for the 1,3-transposition reaction is PCC as it is milder than Jones oxidation conditions and high yielding. The transposition reaction comes in handy at the final stages of a total synthesis with PCC. A few important examples are highlighted below. Even under these conditions some acid-sensitive groups are affected.[136–140]

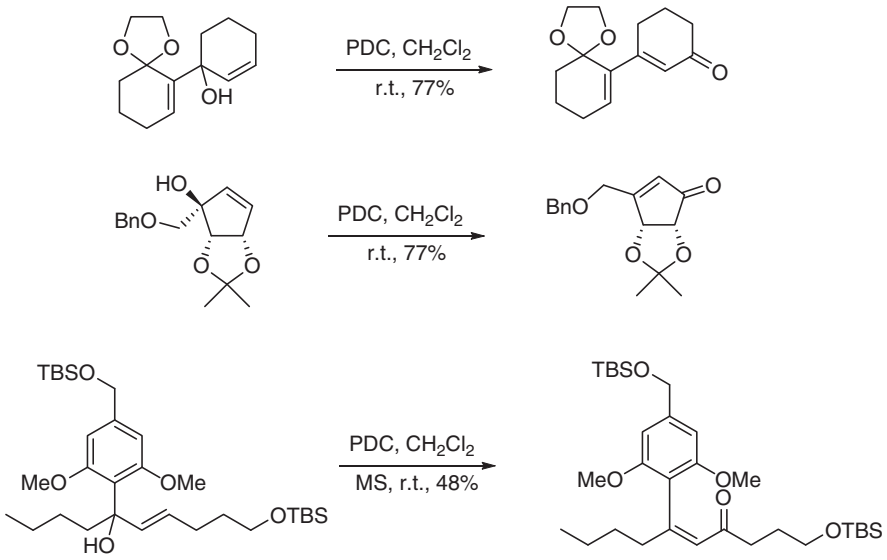








PDC is the best choice for the transposition reaction in the presence of acid-sensitive groups. The reaction is slightly sluggish when compared with PCC. The reaction is expected to go through a concerted pathway under these conditions.[141,142]



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7.11 Oxidation Adjacent to Oxygen of Alcohols Catalyzed by Palladium/Dimethyl Sulfoxide

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Glossary

1,10-Phenanthroline It is a ligand used for coordination to a transition metal.
Ambidentate character This term is used for a molecule having two different ways to coordinate to palladium.
Beta-H elimination It corresponds to the elimination of a palladium hydride.
Dibenzylidene acetone It is a ligand used for coordination to a transition metal.
Disproportionation It corresponds to the transformation of hydrogen peroxide into water and oxygen.
Hexafluoroacetylacetonate It is a ligand used for coordination to a transition metal.
Molecular sieves These are species trapping water.
Peroxo ligand It is a O–O or O–OR group coordinated to a transition metal dium.
Second coordination sphere It corresponds to the area where species can belong to a transition metal complex via their binding to ligands of this transition metal.
Turnover number It corresponds to the number of catalytic cycles mediated by a catalyst.

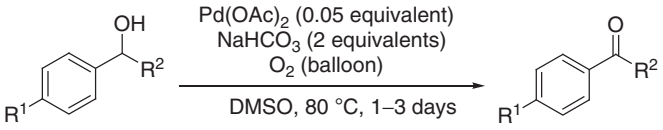
7.11.1 Introduction

In 1991, Bäckvall and coworkers disclosed the improvement of the aerobic $Pd(OAc)_2$/quinone-catalyzed 1,4-diacetoxylation of l,3-cyclohexadiene, with a sulfoxide as cocatalyst.[1] Subsequently, Larock and Hightower observed that, in the presence of dimethyl sulfoxide (DMSO), oxygen alone is efficient in reoxidizing palladium (Pd).[2] Thus, the $Pd(OAc)_2$/DMSO/O_2 catalytic system has been utilized for oxidative cyclizations,[2–5] the conversion of enol silanes into α,β-unsaturated carbonyl compounds[6] and the 1,4-oxidation of l,3-cyclohexadiene,[7] before its use for the oxidation of alcohols by Larock and Peterson reported in 1998.[8]

7.11.2 The $Pd(OAc)_2$/DMSO Catalyst

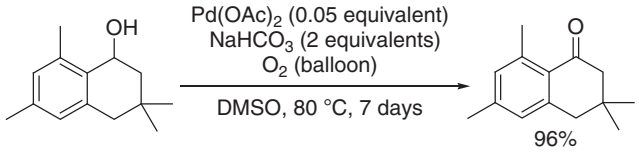
7.11.2.1 The Oxidation Potential

With 0.05 equivalent of $Pd(OAc)_2$ and 2 equivalents of $NaHCO_3$, the heating at 80 °C of oxygenated solutions of secondary benzylic alcohols in DMSO (alcohol concentration 1 mol l^{-1}) slowly provides the corresponding ketones (equations 1 and 2).[8] The reaction rate is still lower in the absence of the base. Nevertheless, base-free conditions have been adopted for the oxidation of primary benzylic alcohols (equation 3) to preclude the generation of side-products, which is promoted by the base. A limitation of the procedure is the plausible Pd-catalyzed decarbonylation of the resulting aldehyde,[9] as exemplified with *p*-nitrobenzyl alcohol as the substrate (equation 4).[8]

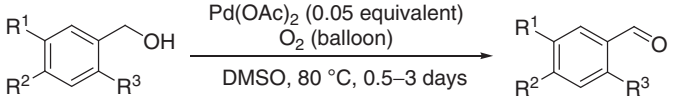


(1)

R^1 = H, R^2 = Me, 1 day: 91%; R^1 = H, R^2 = Ph, 1 day: 95%
R^1 = H, R^2 = COPh, 1 day: 83%; R^1 = R^2 = Me, 1 day: 81%
R^1 = NO_2, R^2 = Me, 3 days: 57%

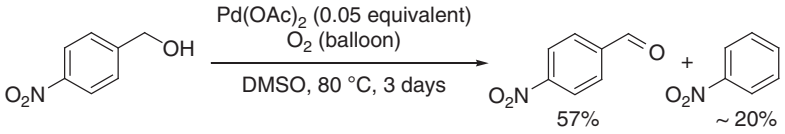


(2)



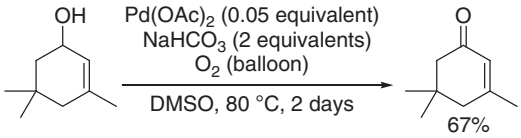
(3)

$R^1 = R^2 = R^3 = H$, 2 days: 90%; $R^1 = R^3 = H$, $R^2 = Me$, 1 day: 92%
$R^1 = R^3 = H$, $R^2 = COMe$, 3 days: 59%; $R^1 = Cl$, $R^2 = R^3 = H$, 3 days: 48%
$R^1 = OH$, $R^2 = R^3 = H$, 3 days: 66%; $R^2 = H$, $R^1 = R^3 = OMe$, 0.5 day: 95%

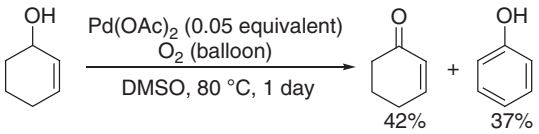


(4)

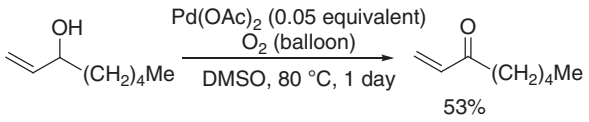
The aerobic $Pd(OAc)_2$/DMSO-catalyzed oxidation of allylic alcohols also occurs, but the selectivity can be more sensitive to the dilution; this latter was sometimes increased to 0.2 mol l^{-1}. Isophorone was isolated in 67% yield from 3,5,5-trimethylcyclohex-2-enol in the presence of $NaHCO_3$ (equation 5), whereas base-free conditions were used for the oxidation of other secondary allylic alcohols (equations 6 and 7) and also primary allylic alcohols (equations 8 and 9). The formation of phenol from 2-cyclohexen-1-ol (equation 6) is mediated by Pd[10]; this dehydrogenation reaction increased with $NaHCO_3$ as additive.



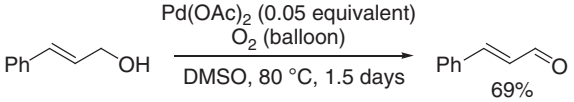
(5)



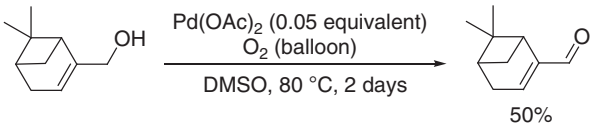
(6)



(7)



(8)

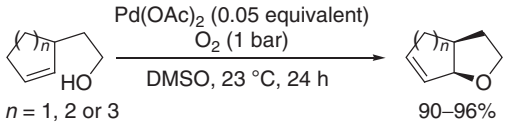


(9)

The above reactions were run on 1 mmol scale. A few of them have also been carried out using 10–100 mmol of the alcohol, providing the expected carbonyl compounds with slightly decreased yields.

In 2003, Grushin and coworkers reported that the Larock–Peterson system has a low activity for the oxidation of 5-(hydroxymethyl)furfural, the conversion being lesser than 10%.[11] More recently, Stahl's team discovered the stabilization of the Larock–Peterson system with the addition of 3 Å molecular sieves (MS), allowing with 0.005 equivalent of $Pd(OAc)_2$ to increase, from 62 to 194, the turnover number (TON) of the oxidation of 1-phenylethanol.[12]

The Larock–Peterson report does not mention experiments using saturated alcohols. To the best of the author's knowledge, the oxidation of such substrates with the Larock–Peterson method has never been published. It seems, however, of interest to mention the use of $Pd(OAc)_2/DMSO/O_2$ system for the efficient intramolecular cyclization of cycloalkenes bearing a hydroxylated side chain (equation 10), which shows that the Wacker-type reaction is preferred to the oxidation of the primary alcohol.[3,4]



(10)

7.11.2.2 Comparison with Previous Systems

Catalytic alcohol oxidations using oxygen as the sole reoxidant of Pd were known before 1998. In 1967, Lloyd reported the oxidation of undiluted 1-butanol to a mixture of butyraldehyde, 1,1-dibutoxybutane, and butyl butyrate with catalytic amounts of $PdCl_2$ at 100 °C under 3 bar of O_2 (TON ≈ 5).[13] The oxidation of ethanol, 1-hexanol, and 3-hexanol to acetic acid, hexyl hexanoate, and 3-hexanone, respectively, with $Pd(OAc)_2$ or $PdSO_4$ in oxygenated acidic media was documented by Brown et al. in 1969.[14] In 1977, Schwartz and Blackburn disclosed the first efficient Pd-catalyzed aerobic oxidation procedure of alcohols (TON up to 100); they used 0.01 equivalent of $PdCl_2$ and 0.5 equivalent of NaOAc at 38 °C in ethylene carbonate under 1 bar of O_2 for the oxidation of secondary saturated alcohols into the corresponding ketones, and benzyl alcohol into benzaldehyde, that of an allylic alcohol failing.[15]

In 1981–82, some catalysis under oxygen has been reported for the transformation of isopropanol into acetone with $PdCl_2$ in aqueous solutions,[16] and undiluted 1-propanol into a mixture of propanal, propyl propionate, and propyl trifluoroacetate with $Pd(F_6acac)_2$.[17] Subsequently, $PdCl_2$ (0.05 equivalent) with Adogen 464 (0.1 equivalent) and $NaHCO_3$ (2 equivalents) has been used in refluxing hexane under an air atmosphere for the oxidation of 1-indanol; under these conditions, the conversion reached 63% in 18 h, leading to 1-indanone with 81% selectivity.[18]

An interesting method, disclosed by Echavarren's team in 1994, consisting of 0.1 equivalent of soluble Pd^0 catalysts and 0.1 equivalent of NH_4PF_6 in refluxing toluene under an air atmosphere, oxidizes primary and secondary allylic alcohols in yields up to 90%.[19]

Pd-supported catalysts and clusters have also been used for the cooxidant-free aerobic oxidation of alcohols. Most of the corresponding experiments reported before 1998 led to mixtures[20] and, consequently, have a low interest for the organic chemist. Kaneda et al. have, however, disclosed the efficient synthesis of aldehydes from primary allylic alcohols, using $Pd_4(phen)_2(CO)(OAc)_4$ or $Pd_{561}(phen)_{60}(OAc)_{180}$ at 50–80 °C under 1 bar of O_2 (TON up to 30).[21]

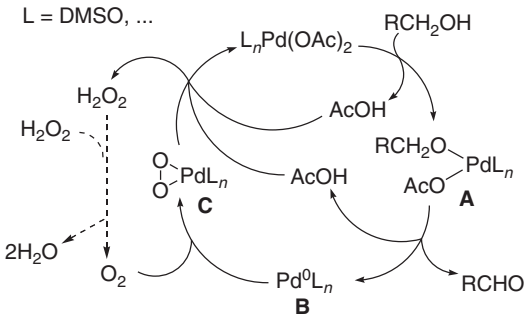
Given the above summary of the literature, the Larock–Peterson procedure was a breakthrough in the Pd-catalyzed aerobic oxidation of alcohols.

7.11.2.3 The Mechanism(s)

As noted by Peterson and Larock, the base is not required, but 2 equivalents of a mineral base such as $NaHCO_3$, $KHCO_3$, Na_2CO_3, or K_2CO_3 generally improves the rate. These authors have also observed that variations of the experimental conditions such as reducing the reaction temperature, the amount of solvent or base, or switching to (1) NaOAc, KOAc, LiOAc, or NEt_3 as the base, (2) either MeCN or a 9:1 mixture of $DMSO/H_2O$ as the solvent, or (3) $PdCl_2$, $Pd(O_2CCF_3)_2$, or $Pd(dba)_2$ as the catalyst, were detrimental to the efficiency. Despite these observations, Peterson and Larock did not provide details on the mechanism; they only suggested a palladium alcoholate as intermediate, β-H elimination from which leading to the carbonyl product and a palladium hydride species. Subsequent reductive elimination from this latter would produce Pd^0, the reaction of which with oxygen regenerates an active catalyst.[8] They do not comment on the structure of the catalyst, although the crystal structure of the isolated complex obtained from $Pd(OAc)_2$ and DMSO was previously reported as being the dimer $[Pd(OAc)_2]_2(DMSO)_2$, which has an S-bound DMSO on each Pd.[22]

The first mechanistic studies on the $Pd(OAc)_2/DMSO/O_2$ procedure were published in 2002 by Stahl's team, who demonstrated the nonparticipation of DMSO in the oxidation step of 2,5-dimethoxybenzyl alcohol and the consumption of 1 equivalent of O_2 for the production of 2 equivalents of 2,5-dimethoxybenzaldehyde.[23] The authors suspected that 'oxidation of palladium(0) by dioxygen constitutes the turnover-limiting step.'[23,24] The proposed mechanism, depicted in oversimplified **Scheme 1**, involves the formation of $L_nPd(0)$ and its reaction with O_2 to give the peroxopalladium complex L_nPdO_2, this oxidation being possibly

promoted by coordinated DMSO. Protonolysis of the peroxo ligand would afford H_2O_2 and the active Pd(II) catalyst. Pd-mediated disproportionation of H_2O_2 would give H_2O and O_2.



Scheme 1

A few years later, Privalov and Zierkiewicz reported a theoretical study mainly devoted to the interactions between DMSO and Pd, in the absence or presence of 2,5-dimethoxybenzyl alcohol.[25] Dissolution of $Pd(OAc)_2$ in DMSO would lead to the coordination of two DMSO to Pd; two other DMSO molecules can be in the second coordination sphere, interacting via H-bonds with the carbonyl group of each acetate. The interaction of the alcohol with the complex would occur in the second coordination sphere via H-bonding with a carbonyl group. This would mediate the deprotonation of the hydroxyl group, giving the palladium alcoholate and AcOH. The optimal structure of the Pd–H complex immediately obtained after the β-H elimination is with two O-bound DMSO molecules. Note that, given its ambidentate character, the mode of coordination of DMSO, i.e., S- or O-bound, to Pd is highly sensitive to the environment and thus, can be altered from one intermediate to the other. The authors studied the plausible structures of the Pd(0) complex which would be obtained after the departure of AcOH from the Pd–H intermediate. The S-bound coordination mode of DMSO would be preferable, leading possibly to $Pd(DMSO)_4$ with up to four other DMSO molecules in the second coordination sphere, each interacting with the O atom of a bound DMSO. Other Pd(0)/DMSO complexes, including Pd dimers, are plausible, as well as equilibration between O- and S-complexation of DMSO to accommodate Pd(0)–O_2 bonding, leading to $PdO_2(DMSO)_n$ ($n=2$–4). This latter would react with two AcOH to liberate H_2O_2, and to restore the original catalyst.

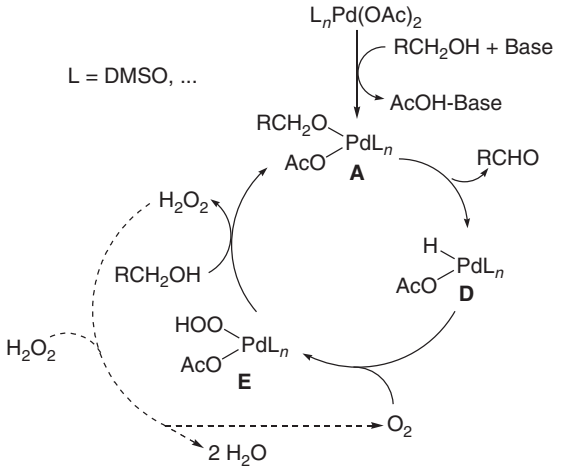
In 2006, Stahl and Steinhoff reported additional kinetic studies that provide new insights into the catalytic mechanism, in particular the role of mass-transfer effects which are, at least in part, due to the low solubility of O_2 in DMSO.[26] These new studies carried out with 2,5-dimethoxybenzyl alcohol and 1-phenylethanol as substrates led the authors to modify their previous proposal on the rate-limiting step. Indeed, this is due to the alcohol oxidation rather than to the Pd(0) oxidation when an adequate supply of O_2 is available in the solution. Thus, at elevated catalyst loading, the turnover frequency has a rate limited by the dissolution of O_2 in DMSO. The slow transfer of O_2 into the solution can contribute to catalyst decomposition, leading to inactive Pd black. Consequently, the TON is also related to the O_2 availability. The rate-determining step due to the alcohol part of the reaction cycle agrees with the theoretical studies of Privalov and Zierkiewicz.[25]

Although the inhibition of the oxidation of 1-phenylethanol by water is maintained in the presence of activated MS 3 Å, this additive, as noted above, has a beneficial effect on the TON. According to Stahl's team, its impact on the catalyst stability 'seems to arise from the ability of MS 3 Å to provide a heterogeneous surface that hinders bulk aggregation of Pd metal'.[12] Additionally, the authors demonstrated that MS 3 Å retards the rate of the Pd-promoted disproportionation of H_2O_2. This agrees with the gas-uptake course of the aerobic oxidation of 1-phenylethanol using the $Pd(OAc)_2$/DMSO/O_2/MS 3 Å system: more than 0.5 equivalent of O_2 was consumed in the first hour, and an O_2/acetophenone stoichiometry of 0.5 was then observed, whereas the stoichiometry of 0.5 was throughout the reaction with the $Pd(OAc)_2$/DMSO/O_2 system.

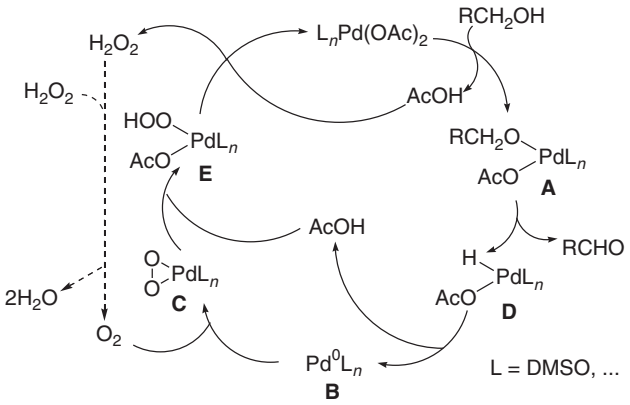
The above mechanistic studies concern oxidations carried out under base-free conditions. Some oxidations reported by Larock and Peterson, however, occurred in the presence of 2 equivalents of base (equations 1, 2, and 5), the base probably promoting the formation of the palladium alkoxide.[27] Under these experimental conditions, AcOH liberated in the course of the reaction (Scheme 1) is captured by the base, except if AcOH remains in the first or second coordination sphere of Pd. Since the catalyst regeneration depicted in Scheme 1 requires AcOH, a different catalytic cycle could operate under basic conditions. This led us, in 2003, to suggest a mechanism (Scheme 2) involving hydroperoxypalladium intermediate **E** produced from the insertion of O_2 into the Pd–H bond of **D**.[20] This **D QUOTE E** reaction could occur through different pathways.[28] The reaction of **E** with the alcohol would lead to H_2O_2 and palladium alcoholate **A**.

The number of papers published on the β-H elimination and the protonolysis of peroxopalladacycles urges the author to draw Scheme 3, which is more detailed than Scheme 1, and shows that both above plausible mechanisms involve intermediates **A**, **D**, and **E**. Note that, in the presence of AcOH, $L_nPd(OAc)_2$ could be regenerated without the intermediates **B** and **C**, the plausible insertion of O_2 into the Pd–H bond of **D** leading to **E** (see Scheme 2); Stahl's team suspects that this pathway is disfavored with the labile neutral-donor ligand DMSO.[29] However, DMSO is the solvent under Larock–Peterson conditions; consequently, this solvent/ligand role of DMSO could lead to an environment precluding the decoordination of the DMSO ligand(s).

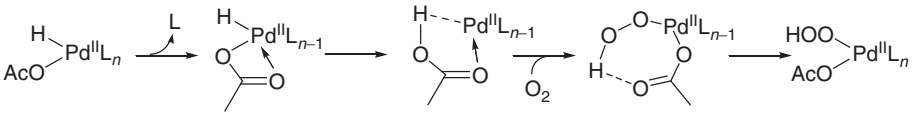
The formation of AcOPdOOH from AcOPdH and O_2 has been the subject of computational studies, some being in favor of the insertion of O_2 into the Pd–H bond (as in Scheme 2)[30,31] with, possibly, assistance by the coordinated acetate (Scheme 4),[32,3] whereas others prefer the reductive elimination of AcOH, the oxidation of the resulting Pd(0) species involving a peroxopalladacycle and its subsequent protonolysis (as in Scheme 3).[28,32–34]



Scheme 2



Scheme 3



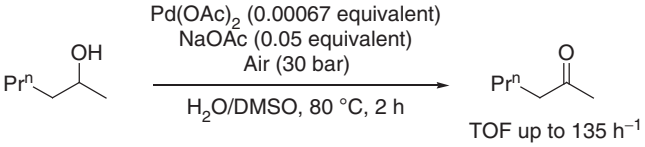
Scheme 4

In fact, the mechanism of the regeneration, with O_2, of the active catalyst from Pd–H species remains a matter of debate[35]; it probably depends highly on the experimental conditions, and on the different species that have the possibility to coordinate to Pd directly or to be in its second coordination sphere.[29,36]

To summarize, the whole mechanism of the Larock–Peterson oxidation method of alcohols remains uncertain. Even the traditional β-hydride elimination mechanism, which yields HPdOAc and R_2CO from $R_2CHOPdOAc$ can be questioned.[37] Moreover, (1) active DMSO-stabilized Pd clusters with plausible PdO structure could be formed under the reaction conditions,[38] (2) a peroxopalladacycle could directly oxidize an alcohol, possibly giving a PdO complex,[39] and (3) the aerobic oxidation of primary allylic alcohols mediated by palladium oxide has been reported.[40,41] Thus, more than one mechanistic cycle could be involved.

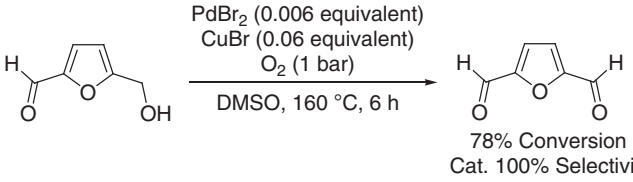
7.11.3 Other Pd/DMSO Catalysts

Sheldon's team, studying the (neocuproine)$Pd(OAc)_2$-catalyzed aerobic oxidation of alcohols has, for comparison, tested the use of $Pd(OAc)_2$ to catalyze the oxidation of 2-hexanol under conditions that strongly differ from those of Larock–Peterson's procedure, the reaction being performed in water/DMSO under 30 bar of air (equation 11).[42]



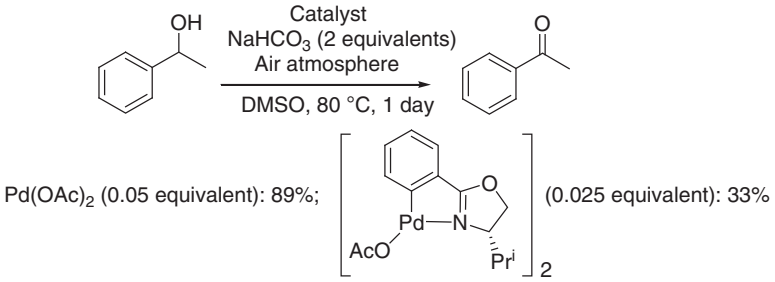
(11)

Although the Larock–Peterson system had a low activity for the oxidation of 5-(hydroxymethyl)furfural, Grushin et al. greatly increased the efficiency of this reaction with a mixture of $PdBr_2$ and CuBr as the catalyst at 160 °C (equation 12).[11]



(12)

With the palladacycle shown in equation 13 instead of $Pd(OAc)_2$, Moberg and Hallman observed a lower efficiency of the oxidation of 1-phenylethanol under experimental conditions similar to those of Larock and Peterson; this also exemplified the determinant role of the ligand on the catalytic activity.[43]



(13)

Neumann and Barats reported that the oxidation of primary aliphatic alcohols using $PdCl_2(DMSO)_2$ as the catalyst in benzotrifluoride under 2 bar O_2 at 110 °C was ineffective.[44]

The interstitial spaces of palladogels prepared by Xu et al. from the dissolution of $Pd(OAc)_2$ and multidentate ligands in hot DMSO are filled with DMSO.[45] These coordination polymers catalyze the oxidation of benzyl alcohol to benzaldehyde by air (1 bar) at 90 °C, the best TON being twice that of $Pd(OAc)_2$ under similar conditions.[46]

7.11.4 Conclusions

Although the Larock–Peterson paper was a breakthrough in the Pd-catalyzed oxidation of alcohols with oxygen gas as the sole reoxidant of the Pd, their procedure has been, apparently, seldom used. Nevertheless, this chapter, in pointing out the determinant role of the ligands to both the stabilization of the intermediates and the regeneration of an active catalyst, has resulted in an intensive research on ligands compatible with oxidation conditions. Thus, new catalytic procedures using, in particular, nitrogen ligands that are efficient for the aerobic oxidation of a variety of alcohols in various solvents have been discovered.[47,48]

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7.12 Directed Aryl C–H Oxidations with Main Group Metals

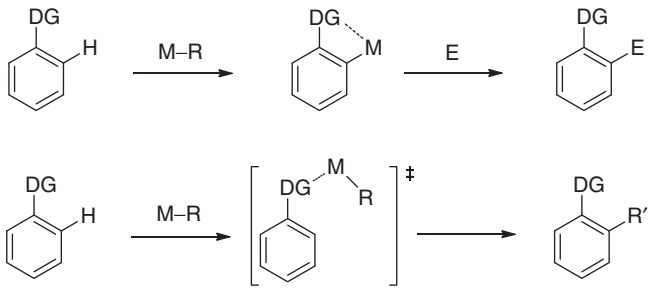
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7.12.1 Introduction

With the requirement of green and sustainable chemistry, the development of efficient, convenient, selective and environmentally benign synthetic methods is highly desirable in organic chemistry. The direct transformation of C–H bonds, which are ubiquitous in organic compounds, to desired functionalities could be a powerful and ideal strategy for organic synthesis. This approach not only offers direct efficient synthesis procedure but also contributes to changing the way chemists think. The past five decades have witnessed great progress in the development of C–H bonds functionalization. The synthesis of polysubstituted aromatic compounds is one of the most important and classic problems of synthesis organic chemistry. Various approaches had been developed. Among which, the selective activation of aryl C–H bond represented the most efficient pathway. A growing number of papers and many good reviews about aryl C–H bond functionalization reactions have been reported lately.[1] In most aryl C–H bond functionalization processes, a directing group was always necessary to coordinate with a metal center to approach a C–H bond and finally realize the desired activation. Research in this field has mainly focused on the C–H functionalization mediated by transition metal complexes. In a sense, less attention has been paid to the role of the main group metal complexes. Actually, main group metal complexes contributed much to C–H activation either in the history or recent development.[2] For example, organometallic compounds of main group metals such as Mg, Al, In, Tl, Si, Sn, and Pb always worked as important partners to afford C–H functionalization products in the transition metal complex mediated C–H bond functionalization reactions. Some main group metal Lewis acid can efficiently catalyze Friedel–Crafts reactions to afford direct aryl C–H functionalization products, which had been well developed and reviewed.[3] As the oxidation of aryl C–H bonds, transition metal complexes have displayed unique reactivity and good applications.[4] In this chapter, the authors focus on directed aryl C–H oxidation mediated by main group metal complexes. Generally, two pathways are practical for main group metal complexes to functionalize aryl C–H bonds: (1) metalation and subsequent functionalization and (2) direct functionalization (**Scheme 1**).[1f] However, most directed aryl C–H oxidation with main group metals take the first one: directed C–H metalation and subsequent oxidation.



Scheme 1 Metalation-functionalization and direct functionalization.

Treating aromatic compounds with strongly basic organometallic reagents, the heteroatom functionality easily undergoes coordination with metal center to lead to deprotonative metalation of a C–H bond at a neighboring position. That is so called directed *ortho* metalation (DoM) process. In principle, it is a permutation exchange between a C–M bond with a C–H bond of lower basicity to generate a more stable C–M bond. Once DoM takes place, newly formed C–M bond could undergo various substitution and addition reactions to afford aryl C–H functionalization products. While treating with oxidants, the newly formed C–M bond would undergo oxidation reactions to afford directed aryl C–H oxidation products. So far the DoM reaction has been

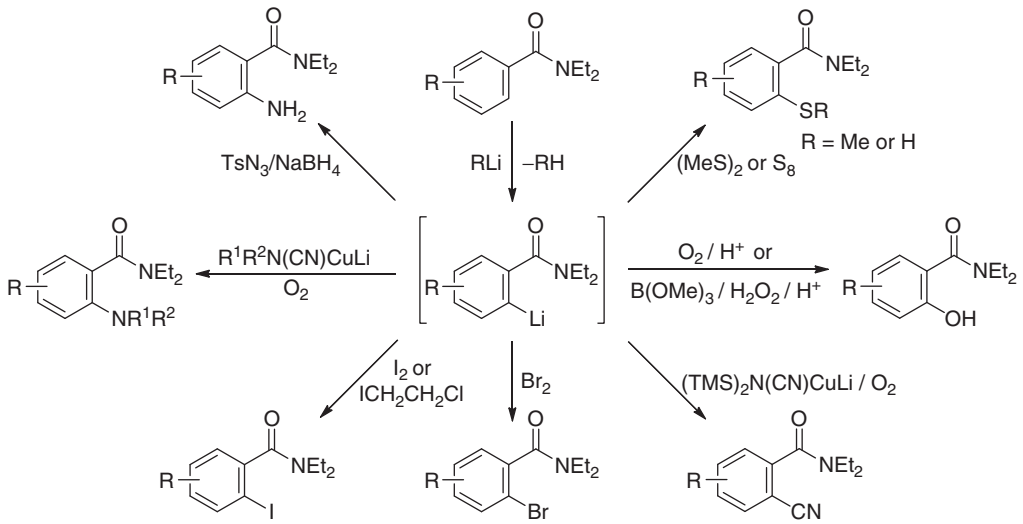
 doi:10.1016/B978-0-08-097742-3.00714-X

widely used as a powerful and efficient method for regioselective functionalization of aromatic compounds. Considering the general reactivity of organometallic compounds to electrophiles such as halides and carbonyl groups, the DoM of aryl C–H bond with different main group organometallic reagents and subsequent oxidation reactions will be mainly discussed here.

7.12.2 Directed Metalation–Oxidation of Aryl C–H Bond with Lithium Reagents

In 1939 and 1940, Gilman and Wittig independently discovered the *ortho* deprotonation of anisole with *n*-BuLi, which initiated a new conceptual framework in synthetic aromatic chemistry.[5] Further works primarily by Gilman, Wittig and Hauser and later by many contributions from other groups, expanded greatly the scope of directed metalation groups (DMGs). In the 1970s, the industrial use of alkyllithiums led to their commercial availability and allowed the metalation technique to be practiced widely from laboratory to industrial scale. Their easy preparation, commercial availability and good solubility in ethers and frequently in alkanes have made alkyllithium reagents and lithium amides the most convenient and practical tools for synthetic chemists. Further development in this field afforded some derivative reagents such as tetramethylethylenediamine (TMEDA)-activated alkyllithium reagents[6] and *tert*-butoxide-complexed alkyllithium reagents[7] (LIC-KOR superbase) show alternative and enormous reactivity toward deprotonative metalation.

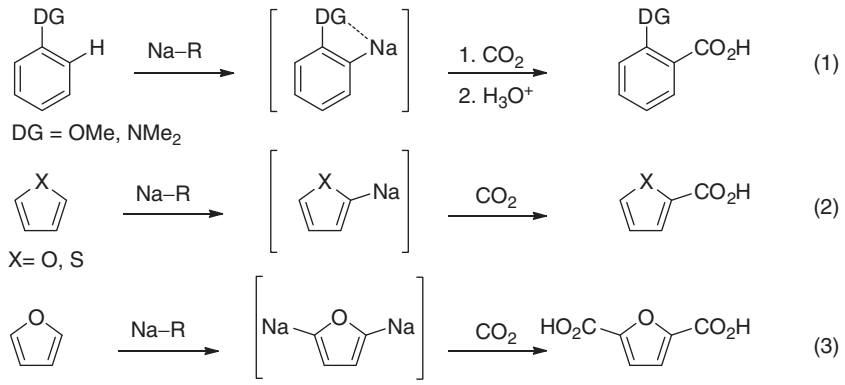
When treated with those lithium reagents, the aromatic compounds with directing groups could easily undergo directed *ortho* deprotonative lithiation to afford aryllithium intermediates, which could undergo not only substitution and addition reactions with various electrophiles to afford new C–C bonds but also oxidation reactions to afford new C–O, C–N and C–X bonds. With the example of *N,N*-diethylbenzamides, the *ortho* lithiation intermediates form after reaction with alkyllithium reagents at low temperature. These aryllithium intermediates could undergo various oxidation reactions to afford new C–O,[8,9] C–S,[10] C–N[9b,11] and C–X bonds (Scheme 2).[9b,10a,12,13] The past decades have witnessed the great evolution of DoM with organolithium reagents. Many excellent comprehensive reviews covering various aspects of this transformation have become available.[14]



Scheme 2 Directed *ortho* lithiation and subsequent oxidations of *N,N*-diethylbenzamides.

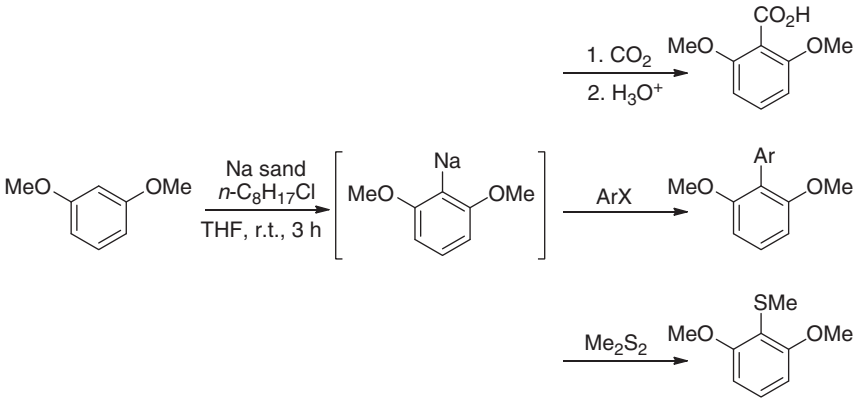
7.12.3 Directed Metalation–Oxidation of Aryl C–H Bond with Sodium Reagents

As early as 1908, sodium metal was reported to undergo deprotonative metalation with benzene in the presence of diethylmercury to afford phenylsodium.[15] Compared with alkyllithium reagents, alkylsodium reagents show similar and even stronger reactivity in the deprotonative metalation reactions.[16] For example, anisole and dimethylaniline react with alkylsodium reagents to form *ortho* metalation products (Scheme 3, equation 1).[17] Furan and thiophene were also metalated to give 2-furylsodium and 2-thienylsodium, respectively (Scheme 3, equation 2).[18] Frequently, alkylsodium reagents deprotonate another organosodium compound to afford dimetalated product (Scheme 3, equation 3).[18c] Organosodium compounds could even deprotonate benzene without any DMGs,[15] whereas similar reactions are not feasible for organolithium compounds without special activation. Despite the excellent reactivity of alkylsodium compounds, their troublesome synthesis and poor stability, especially in ethereal solvents,[19] greatly limited their application in organic synthesis. Compared with alkyllithium reagents, alkylsodium reagents are considered to be less valuable organometallic reagents and have received less development in organic synthesis.



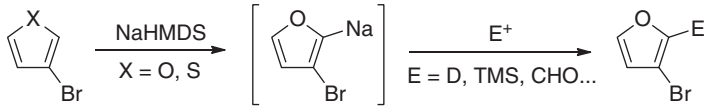
Scheme 3 DoM with alkyl sodium compounds.

In 2002, Wagner, Mioskowski and their coworkers developed a straightforward and efficient one-pot *ortho*-metalation procedure relying on the *in situ* generation of sodiated organic bases from 1-chlorooctane and metallic sodium in the presence of aromatic substrates (Scheme 4).[20] In this process, the preparation, handling and storage of the alkylsodium compounds was avoided. The *in situ* generated alkylsodium reagents preferred to undergo *ortho* metalation of the aromatic substrate rather than the usual coupling and solvolysis side reactions. So the DoM of 1,3-dimethoxybenzene (1,3-DMB) and further carboxylation, arylation, and oxidation with dimethyl disulfide took place efficiently under mild conditions.[21] These metalations with organosodium reagents generated *in situ* from 1-chlorooctane and sodium represented new prospects for the metalation of aromatic ethers and heterocycles in academic laboratories and in industry.



Scheme 4 Directed *ortho* sodiation and subsequent functionalizations of 1,3-DMB.

Recently, sodium hexamethyldisilazide (NaHMDS) was successfully applied in the directed metalation of 3-bromofuran to afford regioselective functionalization reactions (equation 4).[22] Owing to lower reactivity and bulky steric hindrance of sodium hexamethyldisilazide, the Ar–Br bond was well tolerated, and excellent regioselective DoM was achieved under mild conditions.



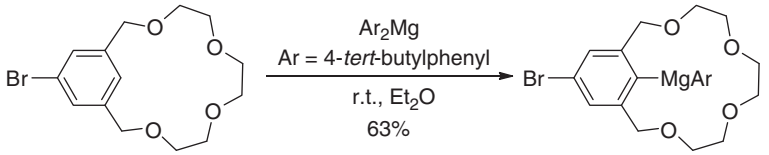
(4)

7.12.4 Directed Metalation–Oxidation of Aryl C–H Bond with Magnesium Reagents

Grignard reagents, organomagnesium halides named after the 1912 Nobelist Victor Grignard, have become the most important tools of all the organometallic compounds in academic laboratories and industry after their discovery in 1900. The deprotonative metalation with Grignard reagents was of value only for quite strong carbon acids ($pK_a \leq 25$) such as alkynes and cyclopentadienes. Grignard reagents are also effective with some polyhalogenated compounds, undergoing deprotonative metalation.

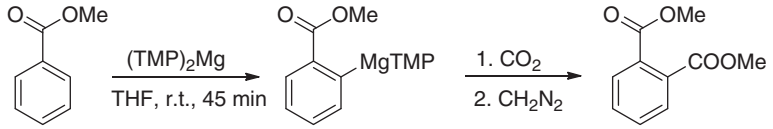
However, other reactions such as the versatile *ortho* metalation of substituted arenes by organolithium compounds have proven to be poor with organomagnesium compounds.

With the activation by crown ethers, deprotonation of 5-bromo-1,3-xylylene-([15]crown-4) was observed by using bis(4-*tert*-butylphenyl)magnesium in diethyl ether at room temperature (equation 5).[23] Even though the deprotonative metalation is available by a combination of macrocyclic coordinating agents and diorganomagnesium compounds (R_2Mg) or Grignard reagents, the high cost and limited substrate scope greatly lowered their further synthetic development.



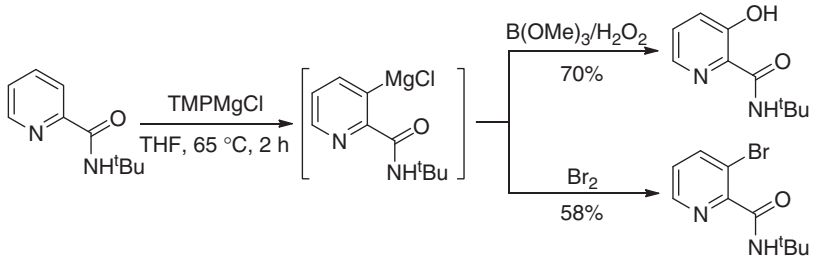
(5)

However, in 1989, Eaton et al. reported a selective magnesiation reaction of an alkyl benzoate by using magnesium bis(2,2,6,6-tetramethylpiperidide), $(TMP)_2Mg$, as a proton abstractor.[24] In analogy to lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP), $(TMP)_2Mg$ is probably less powerful but has the advantage of being stable even in boiling tetrahydrofuran (THF). Of particular note, the directed *ortho*-magnesiation reactions could be accomplished in the presence of esters. For example, the reaction of methyl benzoate with excess $(TMP)_2Mg$ in THF at room temperature afforded dimethyl phthalate in 81% isolated yield after metalation for 45 min, quenching with carbon dioxide, acidification, and esterification (equation 6).

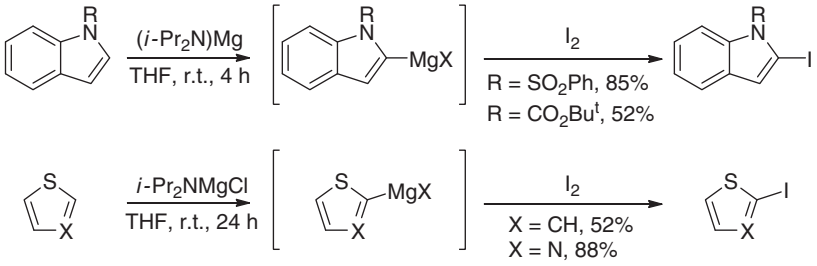


(6)

In 1995, Mulzer and coworkers demonstrated that chloromagnesium 2,2,6,6-tetramethylpiperidide (TMPMgCl) could also efficiently realize the directed metalation of pyridine carboxamides and carbamates (**Scheme 5**).[25] Kondo et al. later further extended this method to the directed magnesiation and iodization of heterocycles such as indoles, thiophene carboxylates, and thiazoles (**Scheme 6**).[26]



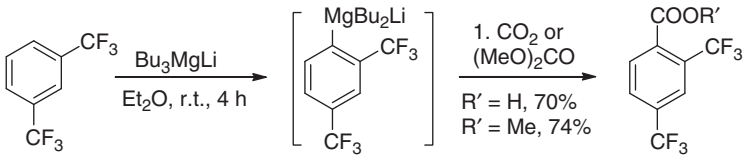
Scheme 5 Directed metalation–oxidation of pyridine carboxamide.



Scheme 6 Directed metalation–iodination of heterocycles.

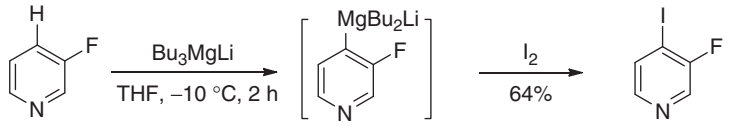
Lithium magnesiates, ate derivatives generated by mixing organolithium compounds and organomagnesium compounds in a certain ratio,[27] also proved to be useful as deprotonating agents.[28] In 1992, Castaldi and Borsotti claimed the directed metalation of activated substrates such as (trifluoromethyl)benzene derivatives with lithium magnesiates.[29] For example, the reaction between 1,3-bis(trifluoromethyl)benzene and lithium tributylmagnesiate in diethyl ether at room temperature resulted in the regioselective

deprotonation at the 4-position (equation 7). Lithium magnesiates here showed higher temperature tolerance and better efficiency in the deprotonation reactions compared to lithium-based-reagents reported later.[30]

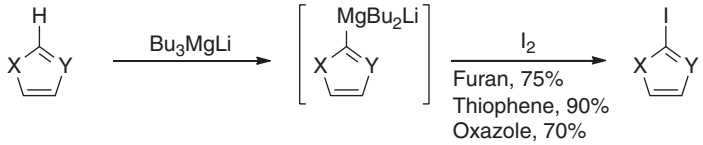


(7)

Treatment of pyridine in diethyl ether with solutions prepared by mixing diethylmagnesium and ethyllithium afforded a mixture of 4- and 2-ethylpyridines via nucleophilic aromatic substitution reactions (S_NAr).[31] While using more acidic substrates such as fluoro- and chloropyridines, the deprotonation turned out to be possible with lithium magnesiates.[32] For example, 3-fluoropyridine underwent deprotonation with lithium tributylmagnesiate at −10 °C for 2 h, and various 4-substituted pyridine derivatives were obtained after treatment with electrophiles. In the reaction with iodine, the pyridylmagnesiate intermediate afforded the iodination product in 64% yield (equation 8). Compared to the corresponding lithiopyridine, which decomposes easily between −60 °C and −20 °C, the generated pyridylmagnesiate intermediate did not decompose even at −10 °C. The good stability of the pyridylmagnesiate intermediate made it possible to participate in a palladium-catalyzed cross-coupling reaction with 2-bromopyridine to give a bipyridyl derivative. Similar reactions of thiophenes, furans, and oxazoles were also achieved with lithium magnesiates to afford DoM and further functionalization products (equation 9).[33]



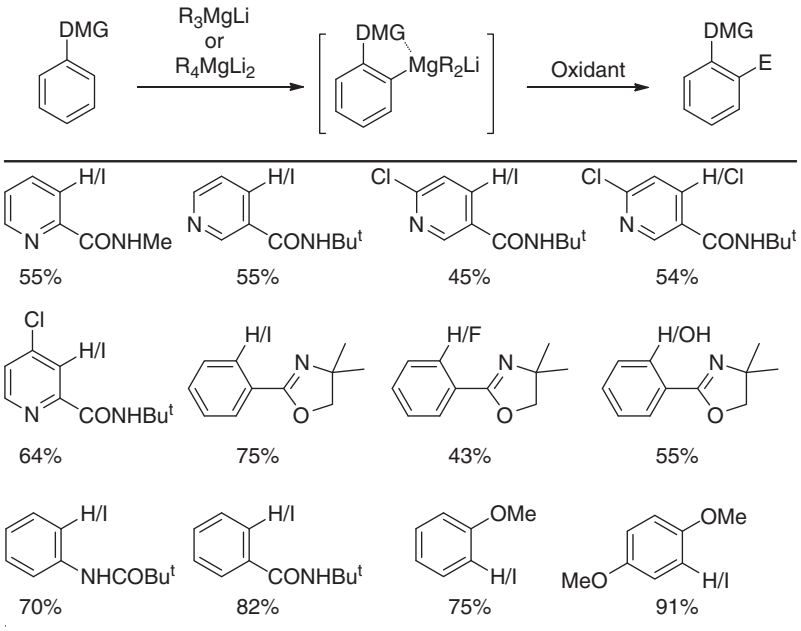
(8)



(9)

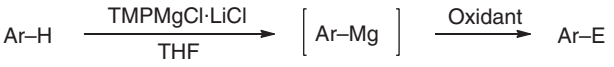
Recent developments have greatly broadened the substrate scope to pyridine carboxamides and various arenes such as (oxazolinyl)benzene, benzamides, aniline, and anisole (**Table 1**).[34]

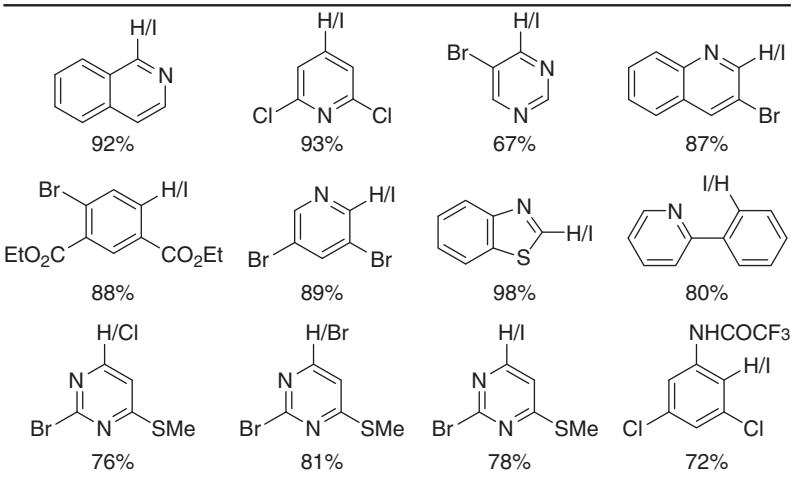
Table 1 Directed metalation with lithium magnesiates and further oxidation



Knochel and coworkers recently found that the addition of lithium chloride to alkylmagnesium chlorides can significantly enhance the reactivity of Grignard reagents in the bromine–magnesium exchange reactions.[35] The combination of lithium chloride with (TMP)MgCl affords a mixed amide (TMP)MgCl·LiCl, which has proven to be an excellent deprotonative metalation reagent under mild condition. Owing to the great contribution from Knochel group, the substrate scope now has covered various aromatic compounds and heteroaromatic compounds such as substituted arenes, pyridines, furans, and thiophenes.[36] Typical aromatic C–H bond deprotonation and subsequent oxidation are summarized in Table 2. Those deprotonative metalation reactions were successfully performed in THF at room or even lower temperature to afford aromatic magnesium intermediates, which could be trapped with oxidants to give the functionalized aromatic compounds in good yields. The excellent functional group tolerance of (TMP)MgCl·LiCl makes the deprotonative metalations take place smoothly in the presence of heterocycles, esters, amides, and C–X bonds, which makes this method an important development in the synthesis of functional aromatic compounds.

Table 2 Directed metalation with TMPMgCl·LiCl and further oxidation





7.12.5 Directed Metalation–Oxidation of Aryl C–H Bond with Aluminum Reagents

Organoaluminum compounds have been widely used as Lewis acids,[37] polymer synthesis catalysts,[38] and important synthetic building blocks[39] both in industrial and academic settings. Yamamoto and coworkers originally reported the use of $Et_2Al(TMP)$ as a new type of base for the regiospecific deprotonation of epoxides and Fischer indole synthesis.[40] However, tricoordinated aluminum reagents including $Et_2Al(TMP)$ have proven to be ineffective for the DoM of functionalized benzene derivatives.

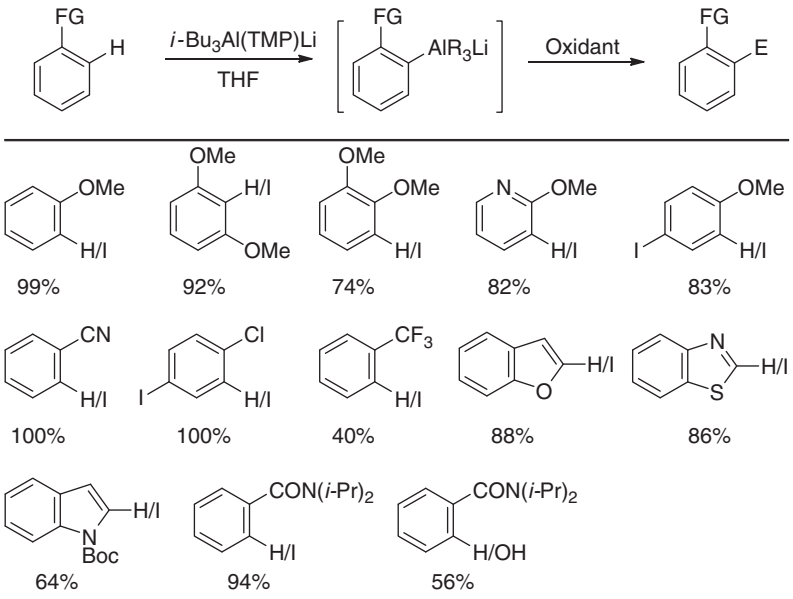
In 2004, Uchiyama et al. developed triisobutyl(tetramethylpiperidino)aluminate (i-$Bu_3Al(TMP)Li$) from triisobutylaluminum and LTMP as an efficient deprotonative metalation reagent for substituted arenes (Table 3).[41] This lithium aluminate base displayed high chemoselectivity and good tolerance toward various functional groups such as methoxy, ester and cyano groups. The deprotonative alumination occurred smoothly without the side reaction of nucleophilic addition to carbonyl and cyano groups. Notably, aryl iodides could be deprotonated in the directed metalation with i-$Bu_3Al(TMP)Li$, avoiding halogen-metal exchange reactions, a common process with other metal bases such as alkyllithium reagents, Grignard reagents and even ate compounds.

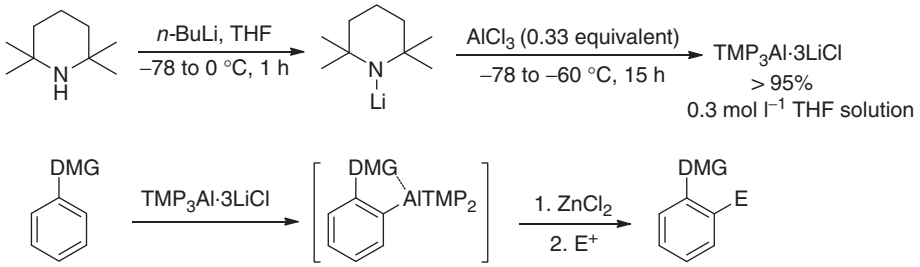
Inspired by recent structural investigations,[42] Knochel and coworkers recently reported new neutral aluminum trisamide bases made from lithium amide and $AlCl_3$ that undergo highly regioselective metalation reactions. In the presence of sterically hindered amide and lithium chloride, these bases displayed excellent reactivity and good solubility.[43] With those aluminum trisamide bases as deprotonation reagents, various aromatic and heteroaromatic compounds achieved selective metalation with good tolerance of a number of functional groups including esters, cyano groups, and halogen atoms. TMP–aluminum bases slowly decompose in THF at 25 °C (Scheme 7). Interestingly in the presence of an oxygen-containing substrate, deprotonative metalation takes place smoothly, and no decomposition could be observed. That is possibly owing to the strong Lewis acidic character of aluminum.

7.12.6 Directed Metalation–Oxidation of Aryl C–H Bond with Thallium (Tl) Reagents

Tl and its derivatives are quite useful reagents and have been systematically exploited and applied to organic synthesis during the past 60 years.[44] In particular, Tl(III) species exhibit some unique properties. The strong oxidizing strength of Tl(III) has been used

Table 3 Directed metalation with *i*-$Bu_3Al(TMP)Li$ and further oxidation

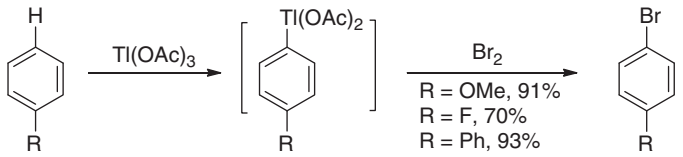




Scheme 7 Synthesis and application of neutral aluminum trisamide.

for many oxidative organic transformations where the easy transitions between the two oxidation levels are generally involved. The strongly electrophilic nature of the Tl(III) species facilitates aromatic substitution reactions.

Thallium(III) acetate (TTA) was found to be a super catalyst for the controlled bromination of a wide range of aromatic substrates. In contrast to the majority of electrophilic aromatic bromination procedures, this process led to the formation of a single, pure monobromo isomer, and only *para* bromination of monosubstituted benzenes was observed.[45] These results hinted at the existence of a highly ordered aromatic substrate–bromine–TTA complex oriented by the steric bulk of the substituent (equation 10).

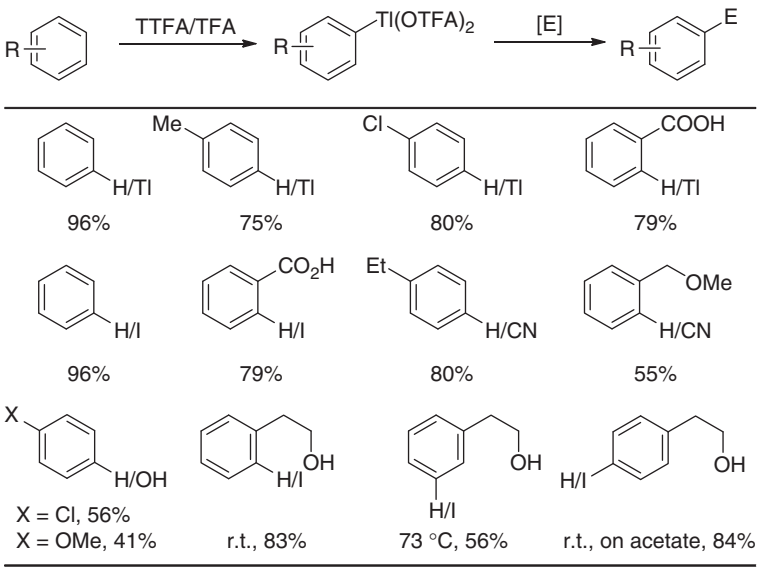


(10)

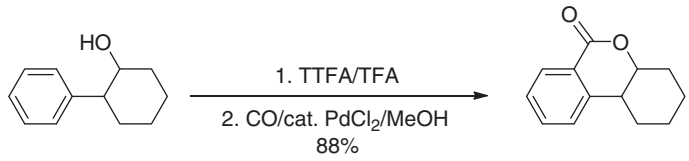
The first successful thallation of an aromatic substrate was achieved in 1943 by Gilman and Abbott. Bis(4-dibenzofuryl) thallium chloride was obtained in 9% yield by treatment of dibenzofuran with thallium(III) chloride at 165 °C.[46] Thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA) constitutes a more powerful reaction mixture than thallium(III) chloride and TTA for the direct thallation of organic compounds.[47] Owing to the bulkiness of Tl(III) species and the strong affinity of Tl for the oxygen atom of the substituent, quite high regioselectivity has been achieved in the direct thallation of aromatic compounds, especially in the presence of a directing group. Following aromatic thallation, various transformations of the arylthallium species afford substitution of the Tl moiety by a variety of groups such as halogens, pseudohalogens, NO_x, $B(OR)_2$, OH, SH, D, aryl, vinyl, alkynyl, CO, etc. (Table 4). For the oxidation capacity of Ti(III) compounds, no further oxidant is necessary for the further iodination and cyanation reactions. Treating the arylthallium species with KI or KCN, the corresponding products formed

smoothly. The addition of lead tetraacetate to the thallated aromatic compound in TFA, followed by addition of triphenylphosphine and then hydrolytic work-up, introduces a hydroxyl group into the aromatic ring. For the freely reversible thallation, the orientation of substitution can be controlled by either kinetic factors or thermodynamic factors, which could be useful in synthetic chemistry.

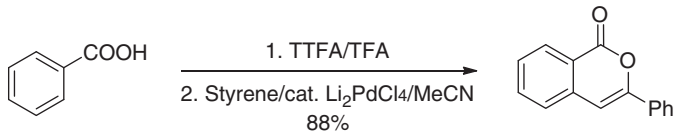
Table 4 Aromatic C–H thallation and further transformation



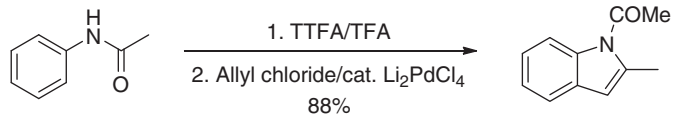
There is no necessity to isolate the arylthallium(III) compounds, which can be generated *in situ* to undergo the subsequent reactions. The arylthallium(III) intermediate is also available for Pd-catalyzed cross-coupling reactions, which makes this method quite useful in organic synthesis (equations 11–14).[48]



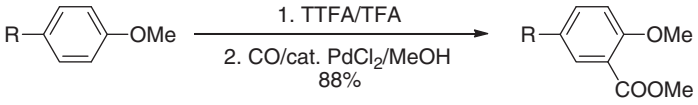
(11)



(12)



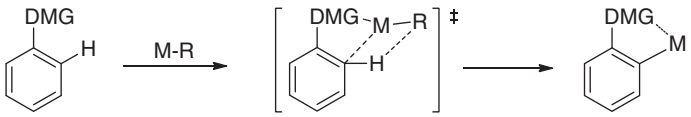
(13)



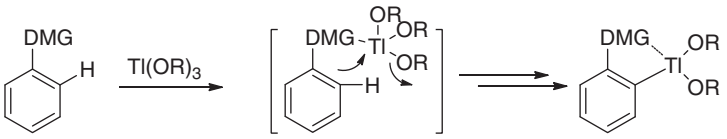
(14)

The direct thallation of arenes is highly complementary to the deprotonative metalation mentioned above. The deprotonative metalation with organo Li, Na, Mg, or Al compounds always requires low temperatures. The direct thallation of arenes, which are activated toward electrophilic substitution, is generally complete within a few minutes at room temperature. The thallation of mildly deactivated substrates such as the halobenzenes requires longer reaction times at room temperature or short heating, whereas deactivated substrates such as benzoic acid require heating under reflux for several hours. The different conditions for aromatic metalation arise from the different mechanistic pathways taken by different activating reagents and is dictated by the

nature of the reagents involved. The deprotonative metalation with strongly basic organometallic reagents is essentially a base-acid reaction between the strong basic alkyl anion and the acidic aromatic C–H bonds. The acidity of the aromatic C–H bonds arise from the electronics of the aromatic ring and is enhanced by a dynamic acidity owing to intramolecular coordination of the electron-deficient metal center by a directing group. The deprotonative metalation undergoes a process similar to that of σ-bond metathesis (equation 15). The direct thallation of arenes with TTFA takes place more easily with electron-rich aromatic compounds. This means that there is an interaction between the aromatic ring and the metal center, and probably the process is similar to aromatic electrophilic substitution reactions (equation 16).



(15)



(16)

Tl compounds are all very toxic, and thus very careful attention must be paid to their treatment and handling and also to waste disposal. This serious drawback has greatly limited the use of Tl salts in organic synthesis. Ideally, the catalytic use of Tl salts could be developed.

7.12.7 Summary and Outlook

As a summary, this chapter focuses on the directed aryl C–H bond oxidation reactions mediated by main group metal complexes. The reaction between an aromatic compound and a strongly basic organometallic reagent always starts with coordination of the directing group with the metal center. The strongly basic anion promotes the deprotonation to afford a metalation intermediate, which can react with various electrophiles to afford the C–H functionalization product. There are also some other possibilities that the coordination intermediate can undergo, including further interaction between ligands of the metal center to afford a metalation intermediate or direct C–H functionalization product.

The abundance and low price of most main group metals have made main group metal complexes very important tools in organic chemistry. However, there are several drawbacks in their use in aryl C–H bond functionalization. Various organometallic complexes have been used in directed deprotonative metalation of an aryl C–H bond to realize its functionalization, but few of them can achieve aryl C–H activation catalytically. Although some complexes can be used to achieve direct aryl C–H bond functionlization of phenols and anilines catalytically, the efficiency was still very low and the substrate scope was very limited.[49,50]

Considering the importance of the directed aryl C–H bond transformation, especially the aryl C–H oxidation, and the availability of main group organometallic compounds, many chemists began to think of achieving C–H bond activation with main group metal chemistry. It is expected that better catalytic efficiency and broad substrate scope will be achieved in the main group metal complex mediated C–H bond functionalization reactions.

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7.13 Directed Aryl C–H Oxidations with Transition Metals

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7.13.1 Introduction

Aryl C–H functionalization is one of the most important topics in synthetic organic chemistry.[1] Transition metal-directed aryl C–H oxidations provide a powerful tool to synthesize various aromatic oxygenated compounds, which exist in natural products, antioxidants, and drug-relevant and bioactive compounds. With the assistance of transition-metal catalysts, aromatic C–H bonds undergo site-selective transformation under appropriate reaction conditions.[2] In a wide range of aryl C–H oxidation, the transformation of aryl C–H bonds to C–X (halo, nitrogen) and C–C bonds under oxidation conditions is also called oxidation, or oxidative coupling,[3] due to the oxidation of aryl C–H bonds involved in the catalytic cycle in the presence of an oxidant.[4] Thus, the synthetic methods based on both aromatic C–H bond oxygenation/halogenation and aromatic C–H bond transformation through oxidative coupling have been described (Scheme 1).

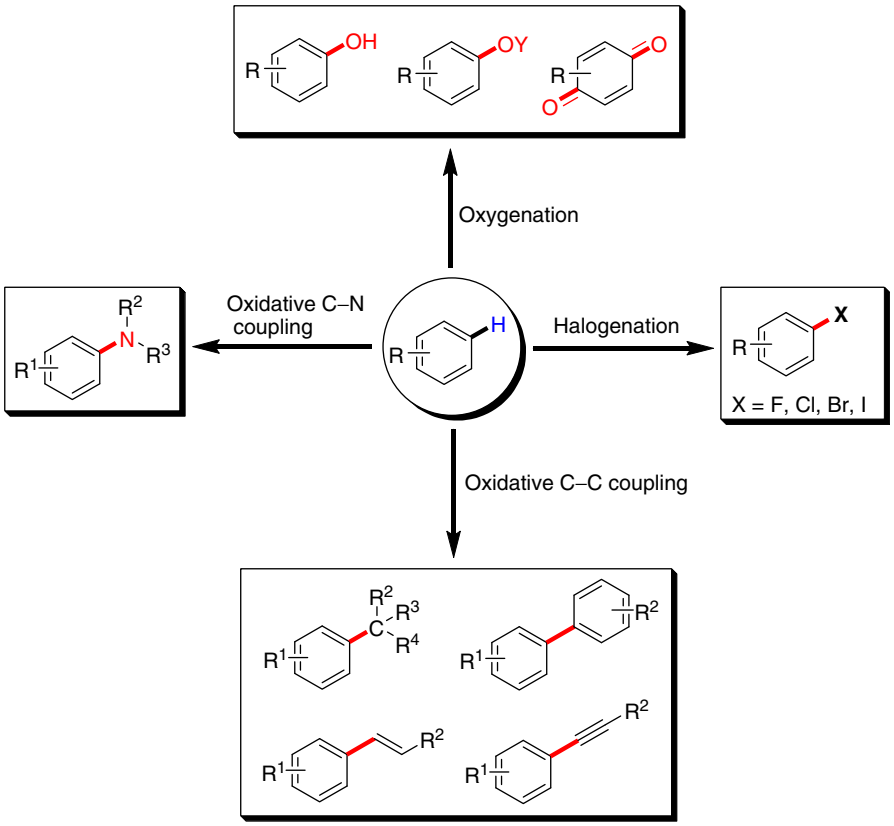
7.13.2 Phenol Synthesis

7.13.2.1 Hydroxylated Arenes with Nitrogen-Containing Groups

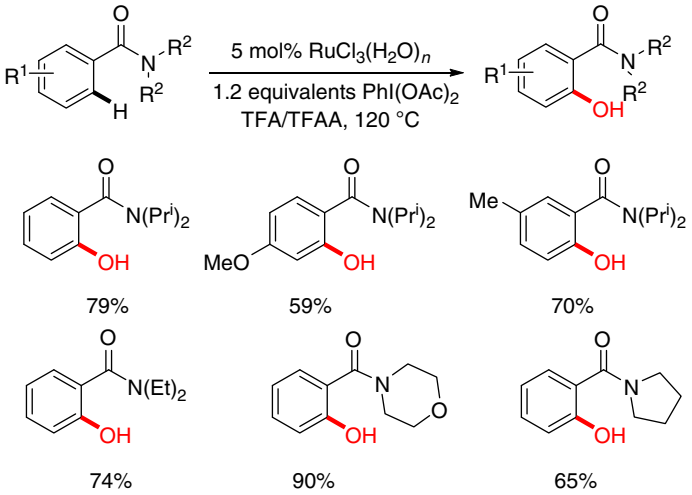
Arenes with nitrogen-containing groups (e.g., pyridine, amide, oxime ether, etc.) are the proper starting materials to prepare aromatic *ortho* C–H hydroxylated compounds with the assistance of transition-metal catalysts (Ru, Pd, etc.). Ru catalysts are one of the more efficient and economical catalysts used for such transformation.[5]

Benzamides underwent *ortho*-hydroxylation with inexpensive $RuCl_3(H_2O)_n$ as the catalyst and $PhI(OAc)_2$ as the oxidant.[6] Various hydroxylated benzamides can be easily prepared with this method (Scheme 2). The use of more complex $[Ru(O_2CMes)_2(p\text{-cymene})]$ catalyst (1 mol%) can efficiently increase the yields and substrate scope.

Treatment of aryl Weinreb amides with $[RuCl_2(p\text{-cymene})]$ and $PhI(OAc)_2$ at mild reaction temperatures provide the oxygenated aryl Weinreb amides (Scheme 3), which are easy to reduce to valuable *ortho*-hydroxylated aldehydes.[7]



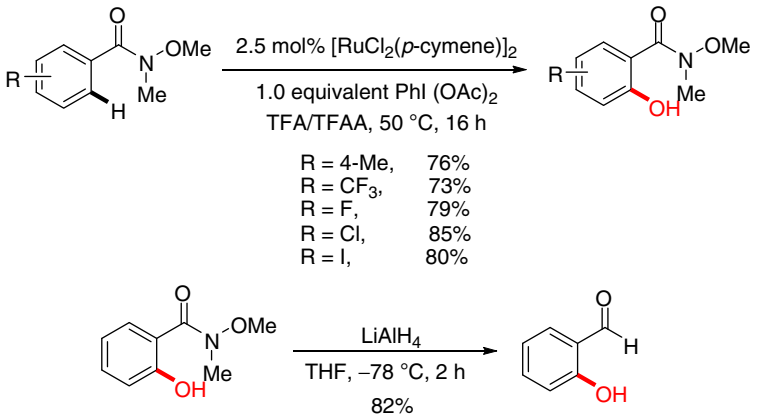
Scheme 1



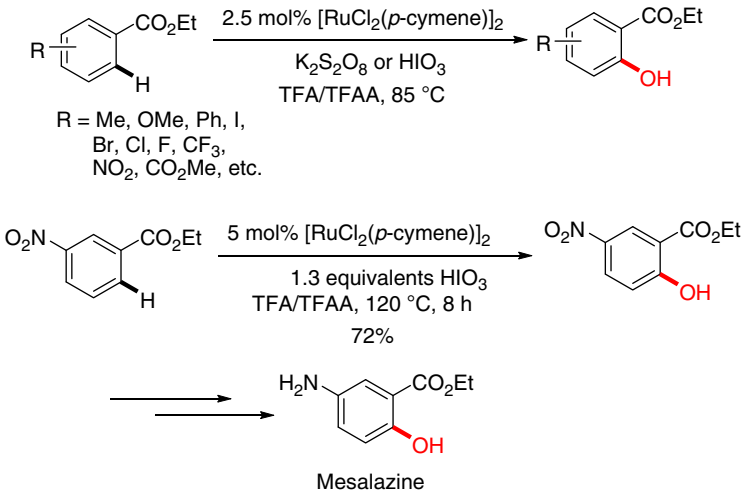
Scheme 2

7.13.2.2 Hydroxylated Arenes with an Ester Group

An ester group is commonly considered a weak directing group in transition metal-catalyzed aromatic C–H functionalization. Using [$RuCl_2$(*p*-cymene)] as the catalyst and $K_2S_2O_8$ (or HIO_3) as the oxidant, easily accessible ethyl benzoates undergo hydroxylation with good functional group tolerance (Scheme 4).[8] Moreover, ethyl 3-nitrobenzoate can be readily converted to the corresponding hydroxylated product, which can be further transformed into mesalazine, an anti-inflammatory drug, via a sequential hydrolysis and reduction.



Scheme 3



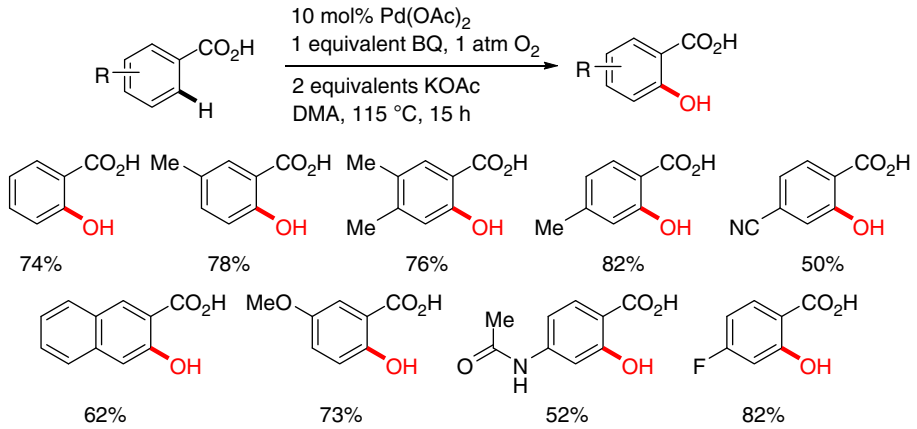
Scheme 4

7.13.2.3 Hydroxylated Arenes with Carboxylic Acid

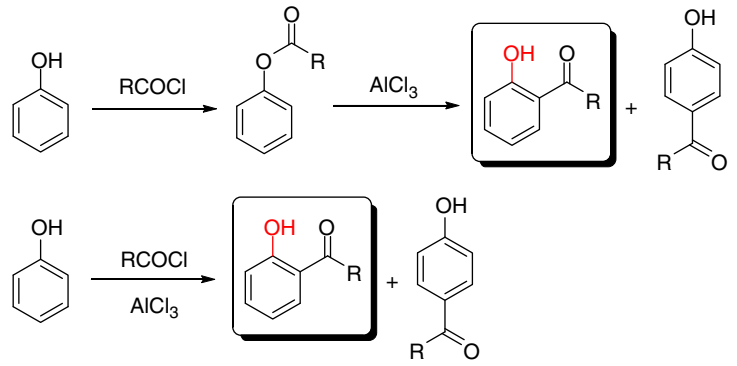
Benzoic acid is used to make a large number of chemicals. In transition metal-catalyzed *ortho* C–H activation, the carboxylic acid group is considered one of weak coordinating groups. Yu developed an efficient Pd-catalyzed *ortho*-hydroxylation of benzoic acids to synthesize hydroxylated benzoic acids (Scheme 5).[9] Using $Pd(OAc)_2$ as the catalyst and benzoquinone (BQ) as the oxidant, various benzoic acids underwent *ortho*-hydroxylation under 1 atm of oxygen atmosphere. Various functional groups, such as halides, acetyl, and cyanide, can be well tolerated under these reaction conditions. Weak basic conditions are required to confirm the reaction efficiency.

7.13.2.4 Hydroxylated Arenes with Ketones

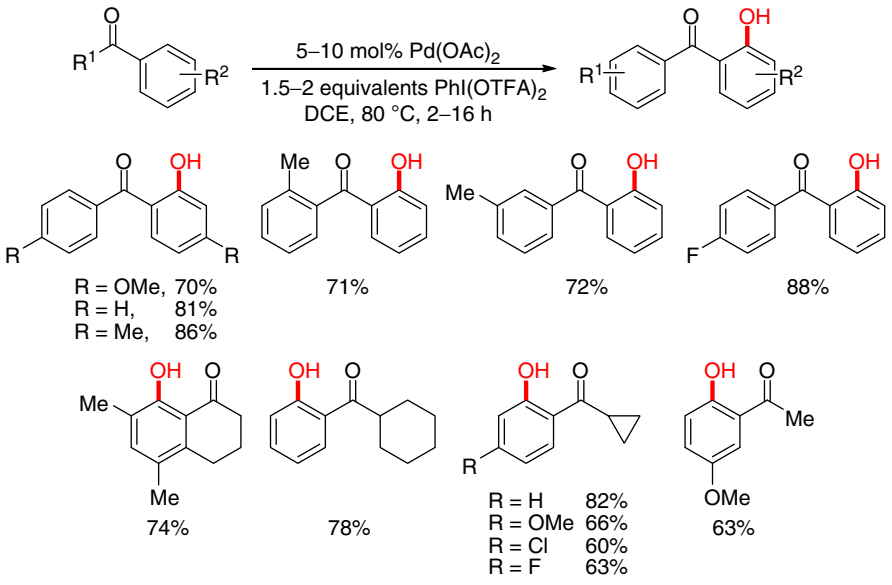
Phenols bearing an acyl group are an important subunit in a number of drug-relevant and bioactive compounds. A classical method for the synthesis of an ortho-acylphenol is the Fries rearrangement of phenyl esters, which suffers from a regioselective drawback. Friedel–Crafts acylation of phenols is another route to obtain acyl phenols, for which it is often hard to isolate the *ortho*-substituted product from the isomeric mixture (Scheme 6). Using $Pd(OAc)_2$ as the catalyst and $PhI(OTFA)_2$ as the oxidant, *ortho*-oxygenated benzophenone derivatives can be efficiently synthesized (Scheme 7).[10] Symmetrical diaryl ketones undergo oxygenation in good yields with high regioselectivity. Unsymmetrical diaryl ketones also allow regioselective hydroxylation of the unsubstituted phenyl ring. Aryl alkyl ketones can be used in such Pd-catalyzed *ortho*-oxygenation reactions with good to excellent yields as well.



Scheme 5

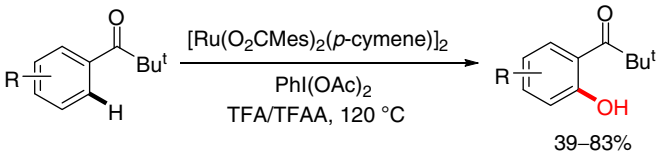


Scheme 6



Scheme 7

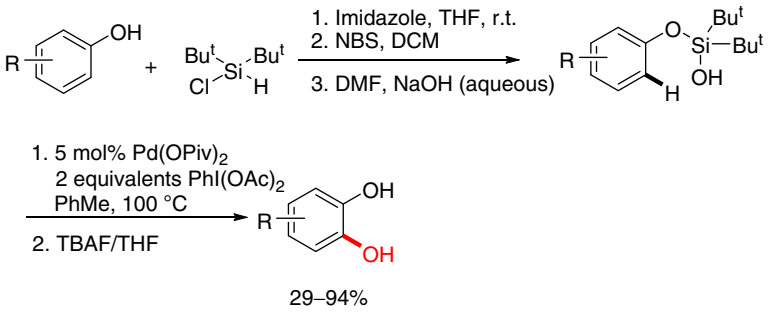
An alternative method is the Ru-catalyzed *ortho*-oxygenation, which converts aryl ketones to the corresponding hydroxylated products in good yields using $PhI(OAc)_2$ as the oxidant and $[RuCl_3(H_2O)_n]$ or $[Ru(O_2CMes)_2(p\text{-cymene})]$ as the catalyst, with limited functional group tolerance (Scheme 8).[11]



Scheme 8

7.13.2.5 Catechols

Catechols are widely found in natural products and bioactive compounds. Simple phenols are the main starting materials to produce catechols. Due to some drawbacks in industrial procedures, transition metal-catalyzed *ortho*-oxygenation became one of the most facile methods to construct catechols. Simple phenols are first converted to the corresponding phenoxy silyl ether through a facile one-pot reaction with di-*tert*-butylchlorosilane, then Pd-catalyzed *ortho*-oxygenation generates the intermediate product, followed by desilylation with tetrabutylammonium fluoride (TBAF) to release the desired catechol (Scheme 9).[12]

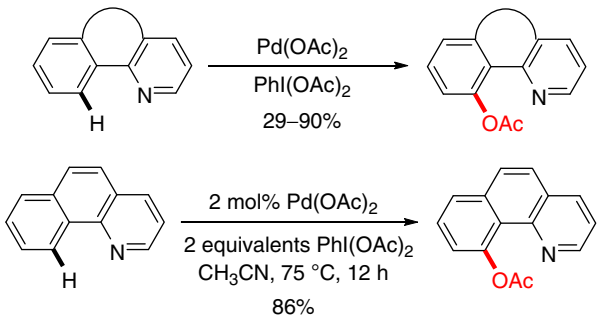


Scheme 9

7.13.3 Phenol Derivative Syntheses

7.13.3.1 Phenol Derivatives Bearing Nitrogen-Containing Groups

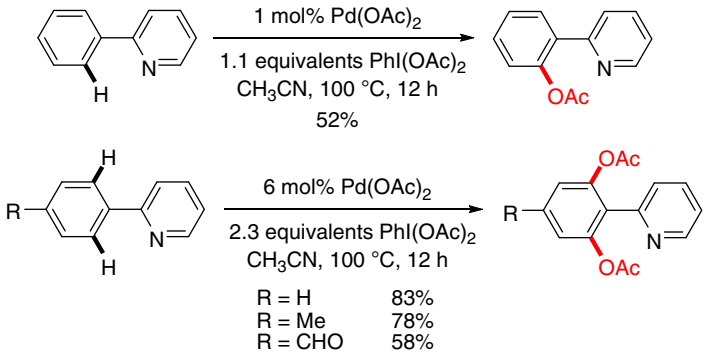
Using $Pd(OAc)_2$ as catalyst in conjunction with $PhI(OAc)_2$ as a stoichiometric oxidant, Pd-catalyzed aromatic C–H bond oxygenation of arenes with nitrogen-containing groups afforded highly selective oxygenated products in good to excellent yields. A variety of pyridine derivatives served as excellent directing groups, and the reactions produced *ortho*-acetoxylated products in good yields. Arenes with other nitrogen-containing coordinating groups, including imines, oxime ethers, azobenzene derivatives, and nitrogen heterocycles, are also effective substrates under such reaction conditions (Scheme 10). For example, benzo[*h*]quinoline can be transformed to *ortho*-acetoxylated products in good yield under $Pd(OAc)_2/PhI(OAc)_2$ conditions.[13]



Scheme 10

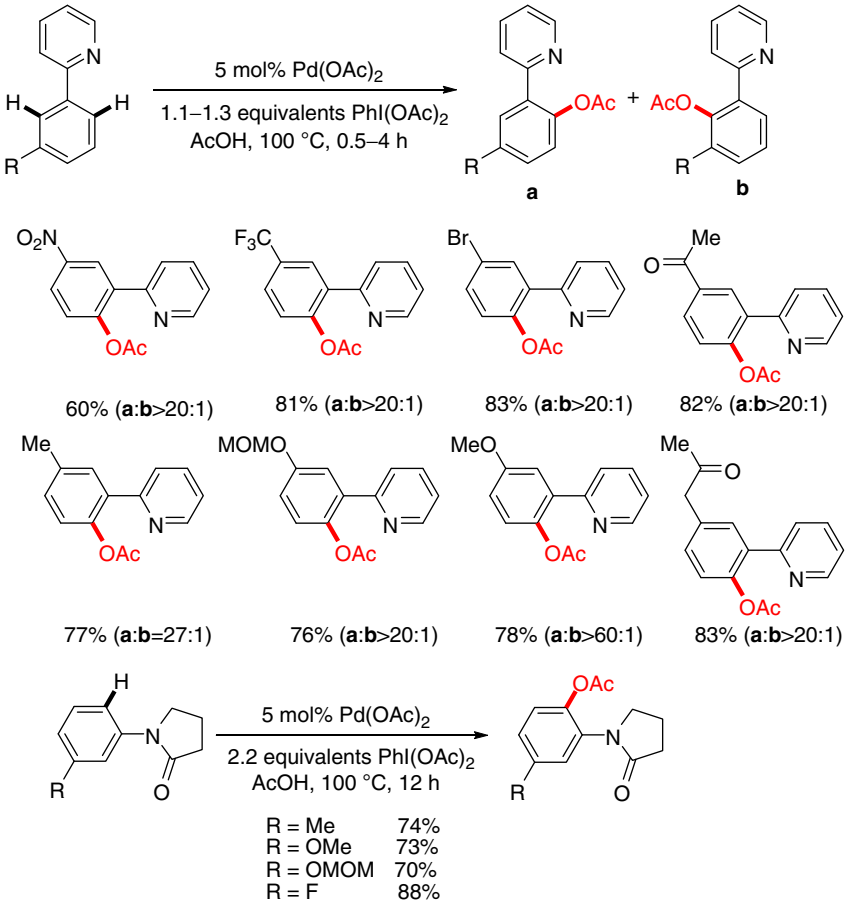
Considering the two activated aromatic C–H bonds in the *ortho* position in some substrates, the amounts of oxidant used have to be carefully controlled to achieve good chemoselectivity. 2-Phenylpyridine underwent highly selective mono-oxidization to

afford *ortho*-acetoxylated product by the addition of 1.1 equivalents of $PhI(OAc)_2$ relative to the substrate (Scheme 11). When 2.3 equivalents of $PhI(OAc)_2$ were used, dioxidized products were obtained in good to high yields.[13]



Scheme 11

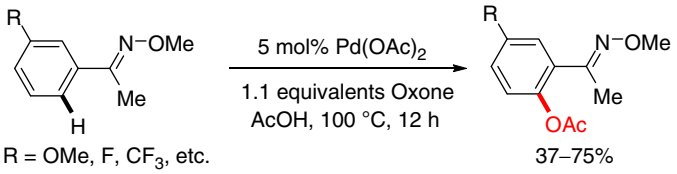
The $Pd(OAc)_2/PhI(OAc)_2$ system can be extended to prepare other, more complex substrates bearing nitrogen-containing groups. When the substituted arenes bear two *ortho* C–H bonds, high selectivity for oxygenation reactions can be achieved preferentially on the less sterically hindered *ortho* C–H bond. Furthermore, various acetoxylated aryl pyrrolidinones can be synthesized from the corresponding aryl pyrrolidinones in good yields with Sanford's conditions (Scheme 12).[14]



Scheme 12

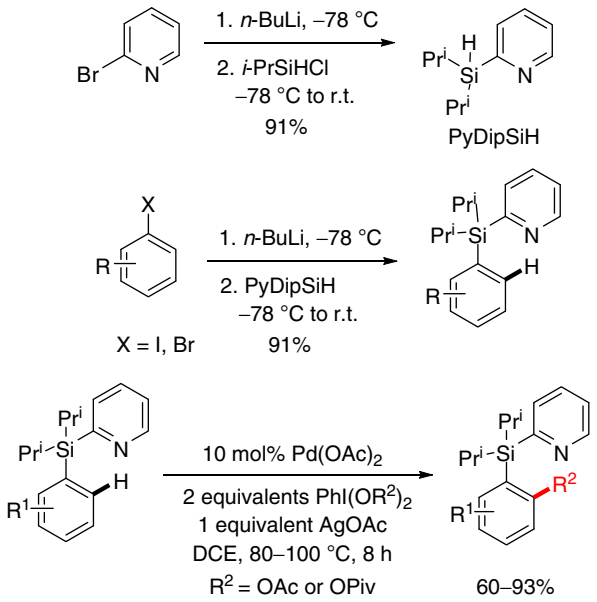
Peroxide oxidants are attractive alternatives to costly iodine-based reagents (e.g., $PhI(OAc)_2$and $PhI(OTFA)_2$) for Pd-catalyzed aromatic *ortho* C–H oxygenation. By using inorganic peroxides (e.g., Oxone and $K_2S_2O_8$) as the oxidant and AcOH as the solvent,

substrates containing a variety of nitrogen-containing directing groups including oxime ethers, amides, and isoxazolines can be transformed into the corresponding aryl esters in good yields (Scheme 13).[15]



Scheme 13

Si-tethered directing groups are attractive alternatives for C–H acyloxylation of arenes.[16] The synthesis of arylsilanes containing the 2-pyridyldiisopropylsilyl (PyDipSi) directing group is straightforward, and high yields of substrates containing a Si-tethered directing group can be obtained after several steps (Scheme 14). PyDipSi-containing arenes were transformed to the corresponding mono-acyloxylated products by Pd-catalyzed acyloxylation using $PhI(OAc)_2$ as the oxidant and AgOAc as the additive. When only the oxidant $PhI(OAc)_2$ was replaced with $PhI(OPiv)_2$, *ortho*-acyloxylation produced a pivaloxy group containing products in good to excellent yields under the same reaction conditions. A variety of functional groups, including OMe, F, Br, and CO_2Et, were perfectly tolerated under such reaction conditions. Furthermore, the PyDipSi group of products can be further transformed into other important moieties, such as an iodide, boronate, aryl unit, and catechols (Scheme 15).



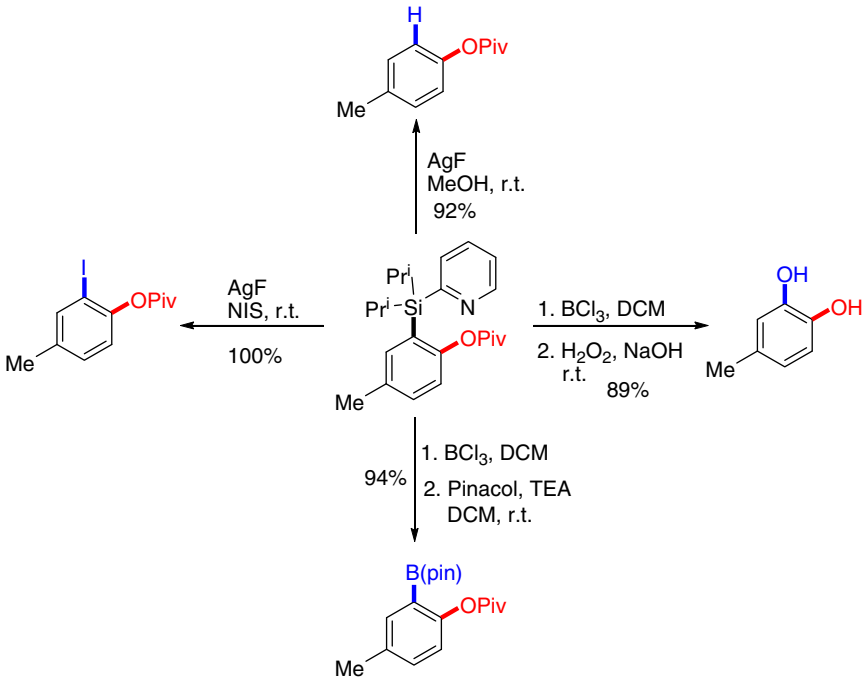
Scheme 14

When the PyDipSi group in the arenes is changed to a 2-pyrimidyldiisopropylsilyl (PyrDipSi) group, a double oxygenation reaction can take place in good to excellent yields with $Pd(OAc)_2$ as the catalyst and $PhI(OPiv)_2$ as the oxidant.[17] Using this method, various functional groups, such as methoxy, carbomethoxy, amide, and acetyl, are all tolerated (Scheme 16). Notably, to control the amount of oxidant used in the reactions, nonsymmetrical bisfunctionalization of PyrDipSi arenes via a sequential C–H acetoxylation/pivaloxylation reaction can be efficiently carried out in good yields. *ortho*-Substituted PyrDipSiAr groups can be tolerated under such reaction conditions, and mono-pivaloxylation can be achieved as well.

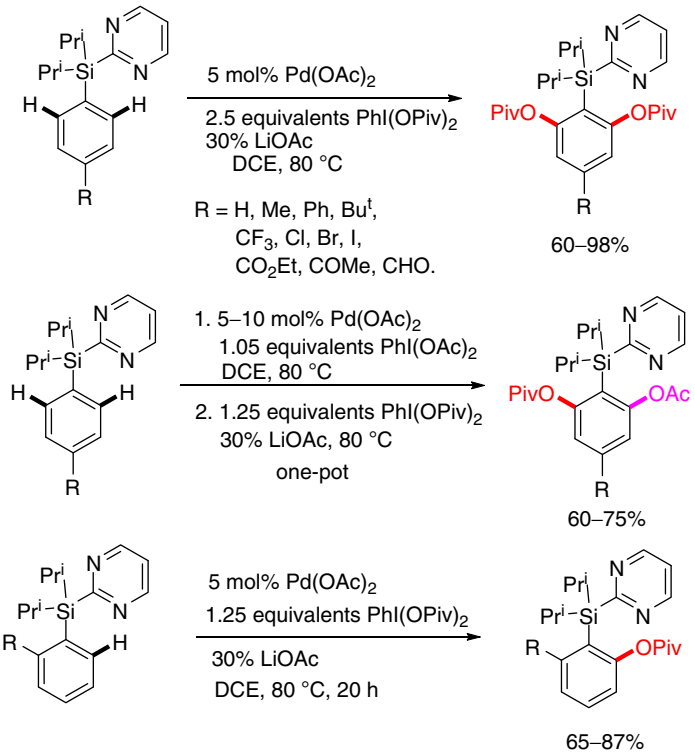
Using noble Rh-catalyst, *ortho*-benzoxylation of the aromatic C–H bond with carboxylic acids takes place smoothly with high selectivity (Scheme 17).[18] This procedure provides the benzoyloxylated products in good yields, in which methoxy, carboxyl, formyl, and nitro groups can be well tolerated. Importantly, no external oxidant is required for this transformation.

7.13.3.2 Phenol Derivatives Bearing a Carboxylic Acid

The carboxylic acid group is considered a weak directing group for metal-catalyzed aromatic C–H functionalization. Shi developed a novel method in which benzofuranones can be prepared by direct lactonization of 2-arylacetic acids through Pd-catalyzed C–H

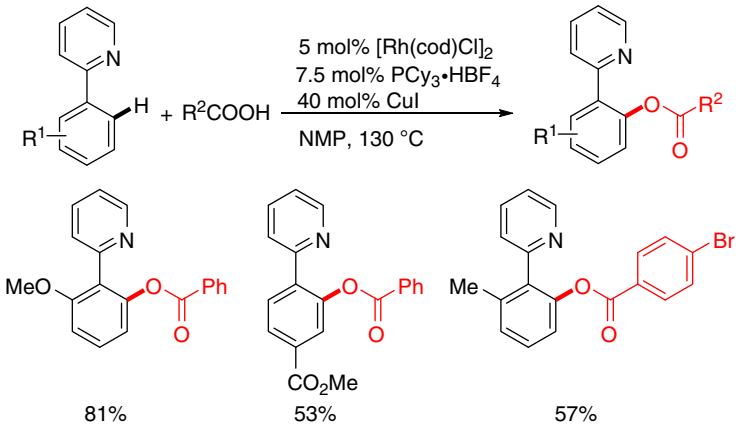


Scheme 15

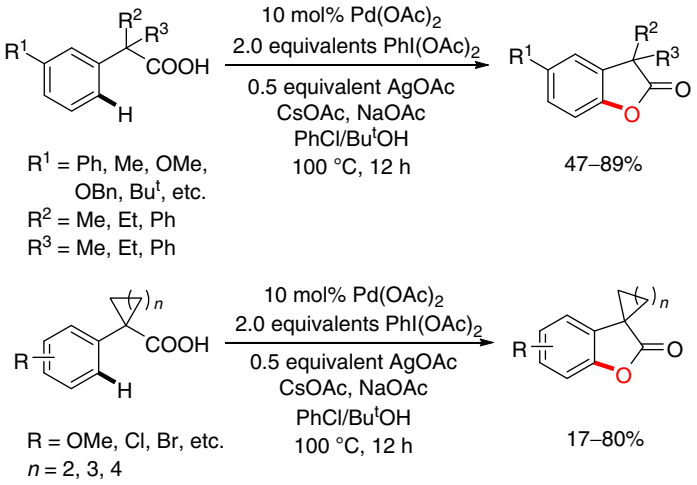


Scheme 16

oxygenation.[19] Using $Pd(OAc)_2$ as the catalyst and $PhI(OAc)_2$ as the oxidant, direct lactonization took place in good to excellent yields, and different functional groups, such as methoxy, bromide, chloride, and OBn, were all tolerated under such conditions (Scheme 18).



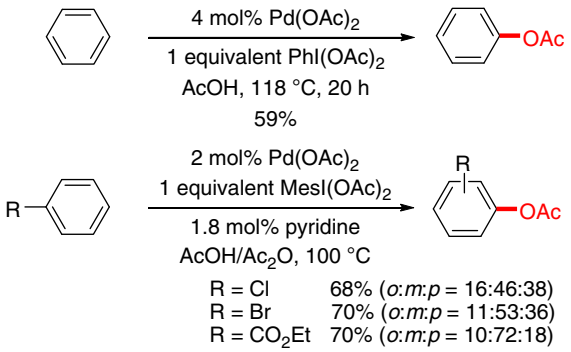
Scheme 17



Scheme 18

7.13.3.3 Simple Phenols

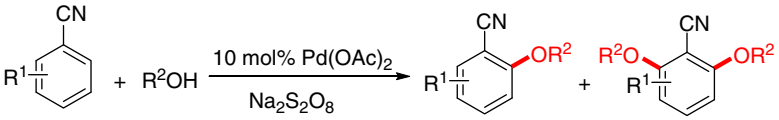
Phenol, naphthol, and other simple phenols are considered to be among the most basic chemical building blocks, and they can be produced by simple and cheap chemical processes. However, the direct aromatic C–H oxygenation of unactivated aromatic C–H bonds by metal catalysts is still a big challenge for chemists. Using $Pd(OAc)_2/PhI(OAc)_2$ conditions, simple benzene underwent C–H oxygenation to produce phenyl acetate in 59% yield at 120 °C (Scheme 19).[20] Other substituted arene substrates can be acetoxylated in good yields with $MesI(OAc)_2$ as the oxidant, although three isomers are obtained in the final products.[21]



Scheme 19

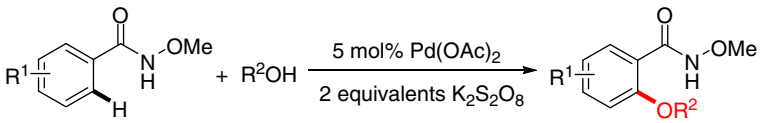
7.13.4 Alkoxylated Derivative Syntheses

The cyano group is an important precursor for a multitude of transformations into various functional groups such as carboxylic acids, amides, amines, aldehydes, and ketones. Using cyano as a directing group, the aromatic C–H bond can be functionalized efficiently to generate *ortho*-alkoxylated aryl nitrile derivatives in moderate yields with $Pd(OAc)_2$ as the catalyst and $Na_2S_2O_8$ as the oxidant.[22] This method is compatible with aryl nitriles containing either electron-withdrawing or electron-donating groups (Scheme 20).



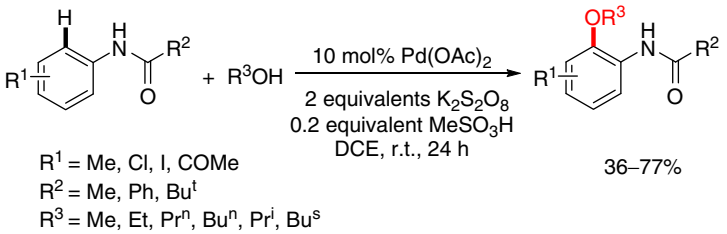
Scheme 20

Aryl alkyl ethers are important motifs found in many natural products and pharmaceuticals. *ortho*-Alkoxylation of *N*-methoxybenzamides is realized to afford aryl alkyl ethers in good to excellent yields with $Pd(OAc)_2$ as the catalyst and $K_2S_2O_8$ as the oxidant.[23] This method is compatible with either electron-withdrawing or electron-donating groups in the substrates. Commonly used alcohols, such as MeOH, EtOH, and *i*-PrOH, are efficient substrates (Scheme 21).



Scheme 21

Anilides are also suitable substrates for Pd-catalyzed *ortho*-alkoxylation with both primary and secondary alcohols.[24] This alkoxylation is promoted by a catalytic amount of methanesulfonic acid at room temperature (r.t.) and affords aryl alkyl ethers in good yields (Scheme 22).

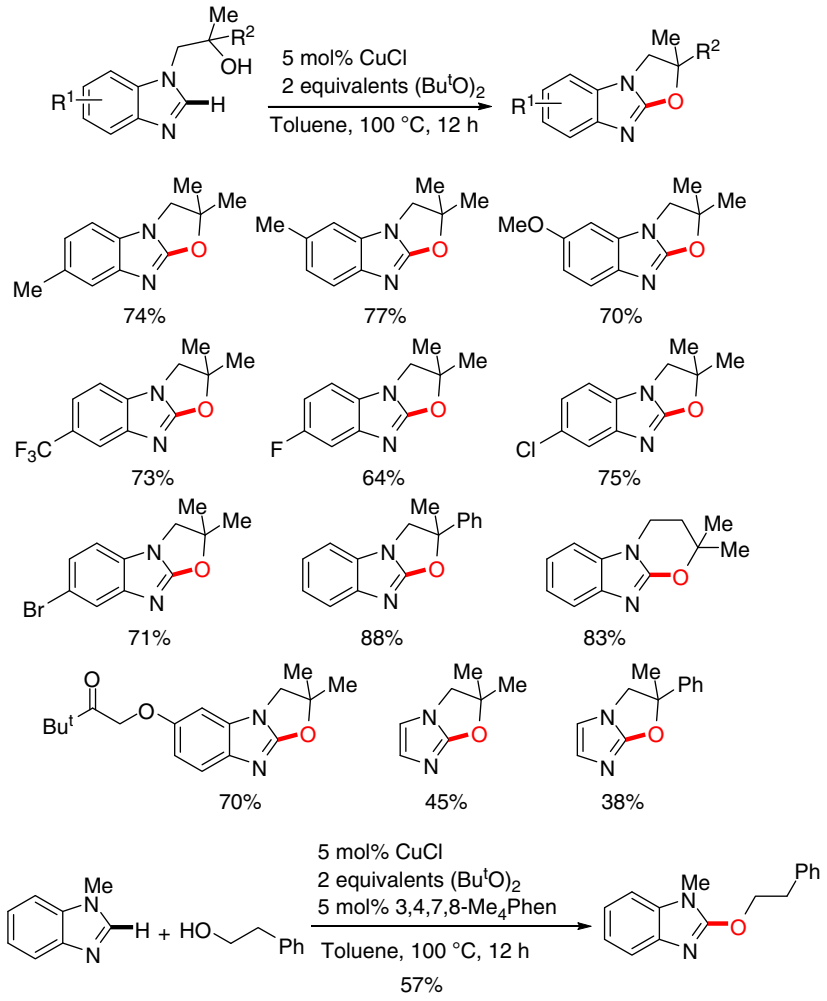


Scheme 22

More active azoles undergo intra- and intermolecular alkoxylation of aromatic C–H bonds using cheap CuCl as the catalyst and $(Bu^tO)_2$ as the oxidant under base-free conditions (Scheme 23).[25] Various substituents, including electron-donating and electron-withdrawing groups, as well as ester and amide functional groups, are tolerated, and good yields are achieved. Intermolecular alkoxylation of azoles offers the alkoxylated products in moderate yields using 3,4,7,8-tetramethylphenanthroline (3,4,7,8-Me_4phen) as a ligand.

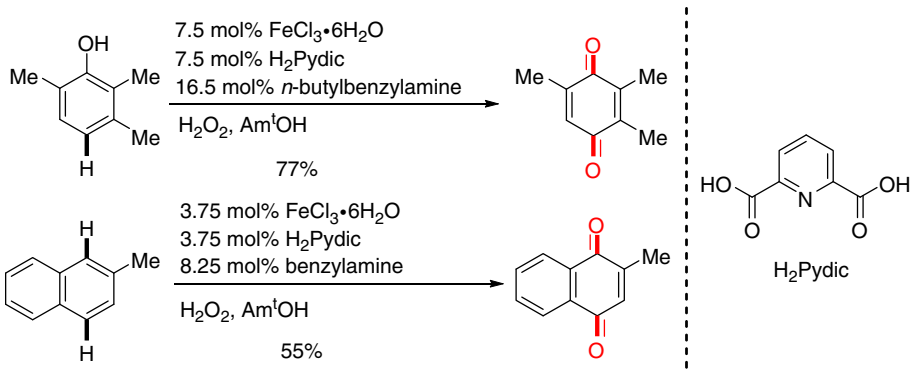
7.13.5 Quinone Synthesis

Phenols and some arenes can undergo selective oxidation of the aromatic C–H bonds with cheap and green metal (Fe and Co) salts as the catalyst.[26] For example, a three-component catalyst system consisting of $FeCl_3$, pyridine-2,6-dicarboxylic acid (H_2Pydic), and different benzylamines was used for the oxidation of 2,3,6-trimethylphenol (TMP) with nontoxic hydrogen



Scheme 23

peroxide (H_2O_2). Under similar conditions, the oxidations of TMP and 2-methylnaphthalene took place in 77% and 55% isolated yields, respectively (Scheme 24).



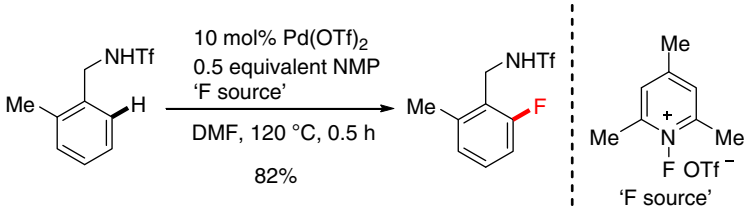
Scheme 24

7.13.6 Aryl Halides

Aromatic halides play a crucial role in synthetic chemistry toward various aromatic compounds, which are essential in organic synthesis as starting materials and synthetic building blocks for materials science, pharmaceuticals, and bioactive compounds.[27]

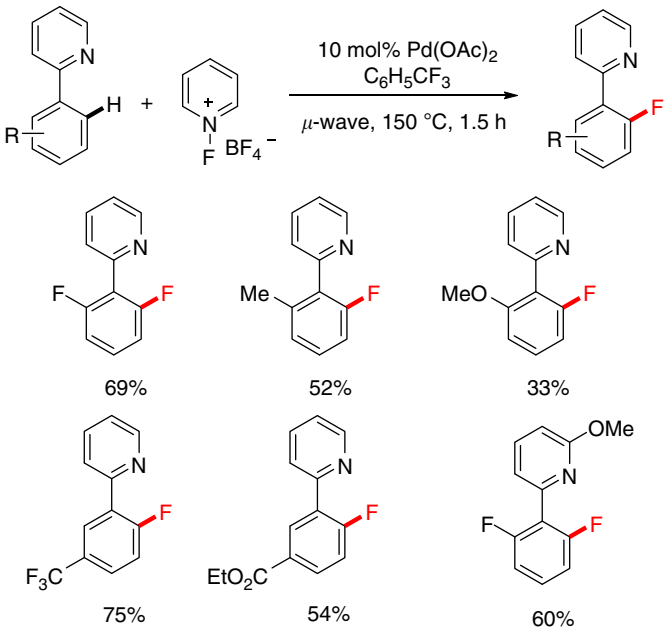
7.13.6.1 Fluorination of Aromatics

Direct C–H fluorination by metal catalysis is rare in limited substrates. Benzylamine-based substrates are able to undergo catalytic C–H fluorination in the presence of a Pd catalyst. *N*-fluoro-2,4,6-trimethylpyridinium triflate is used as a fluorination reagent along with *N*-methylpyrrolidinone as a key promoter for the fluorination of triflamide-protected benzylamines (Scheme 25).[28]



Scheme 25

Using *N*-fluoropyridinium tetrafluoroborate as the fluorination reagent and $Pd(OAc)_2$ as the catalyst, 2-arylpyridines are able to undergo *ortho*-fluorination to produce a variety of functionalized aryl fluoride-containing products in moderate to good yields (Scheme 26).[29]



Scheme 26

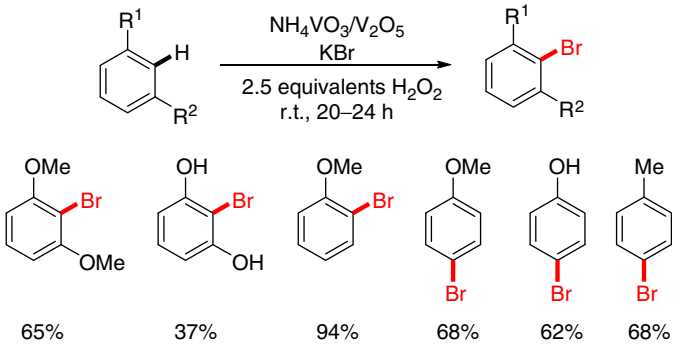
7.13.6.2 Bromination of Aromatics

Vanadium catalysts have been widely employed in aromatic oxidative bromination with H_2O_2, among which the two main catalysts are NH_4VO_3 and V_2O_5.[30] Using such vanadium catalysts, the oxidative bromination of electron-rich arenes is performed with 30% aqueous H_2O_2 as the oxidant and KBr as the halo source under mild reaction conditions (Scheme 27).

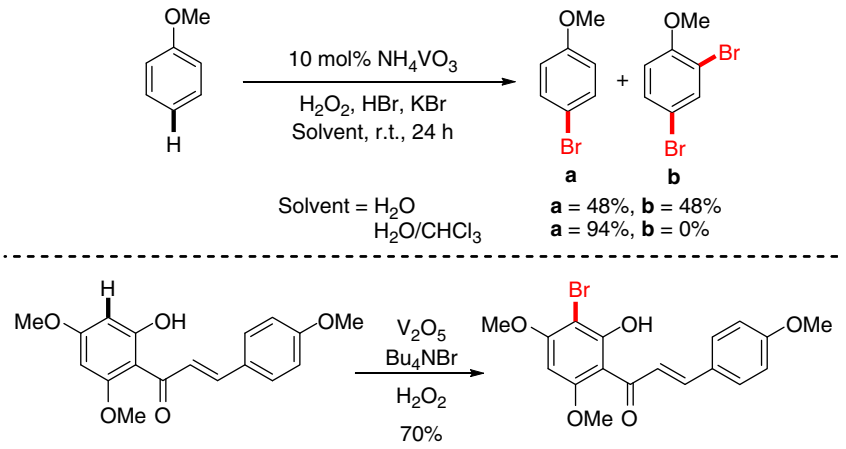
Using NH_4VO_3 as the catalyst and HBr as halo source, anisole can be brominated at r.t. in excellent yield to provide 4-bromoanisole as a single halogenated product when H_2O and $CHCl_3$ are used as cosolvents. When the solvent is changed to water, 48% dibrominated product was isolated under the same reaction conditions (Scheme 28). When V_2O_5 is used as the catalyst with tetrabutylammonium bromide (TBAB) as a bromide source, a more complex phenol can be brominated with excellent selectivity, providing a single halogenated product.

Molybdenum(VI) complexes represent another class of useful catalysts for oxidative bromination of arenes.[31] Using AcOH as a reaction medium and H_2O_2 as the oxidant, ammonium molybdate can catalyze the oxidative bromination of phenols, anilines, and their derivatives in high yields at the *p*-position (Scheme 29).

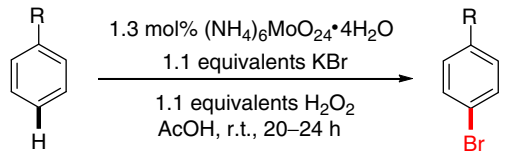
Using $CeCl_3$ as the catalyst and NaBr as the halide source, 1,3-dimethoxybenzene can be brominated at r.t. in excellent yield and gives 1-bromo-2,4-dimethoxybenzene as a single brominated product when H_2O is used as solvent (Scheme 30).[32]



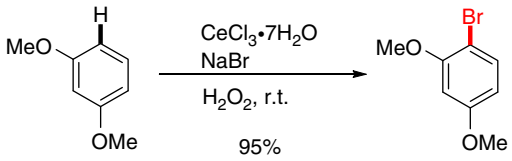
Scheme 27



Scheme 28

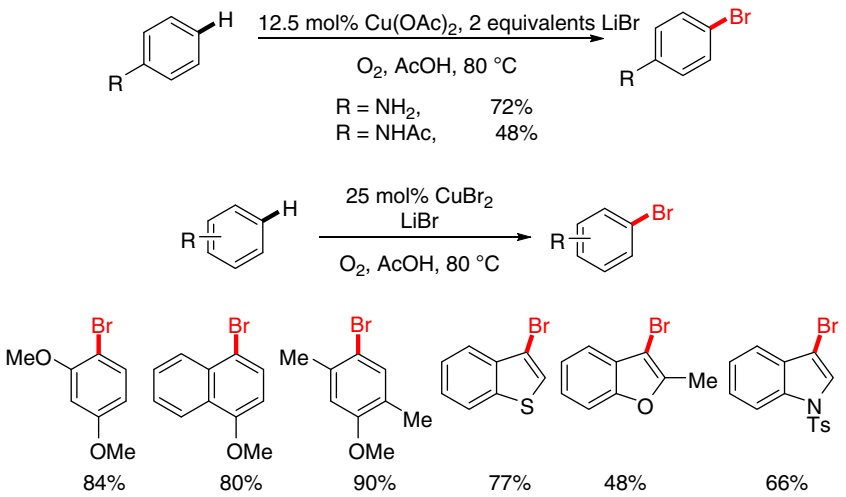


Scheme 29



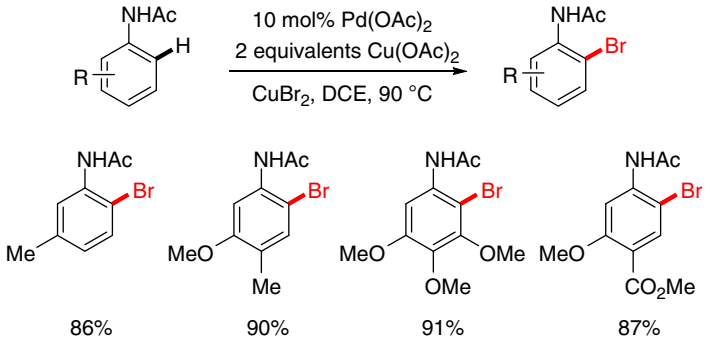
Scheme 30

Cheap copper salts are the most studied metal catalysts for aerobic oxidative halogenation. The oxidative bromination of electron-rich arenes is performed with LiBr and a catalytic amount of $Cu(OAc)_2$ at 80 °C under an oxygen atmosphere (Scheme 31).[33] Using a catalytic amount of $CuBr_2$ as the catalyst, the oxidative bromination of electron-rich arenes and heteroarene can be performed in good to excellent yields at 80 °C under an oxygen atmosphere.[34] Benzo[*b*]thiophene, 2-methylbenzofuran, and 1-tosyl-1H-indole all produce the corresponding brominated products at the *meta* position.



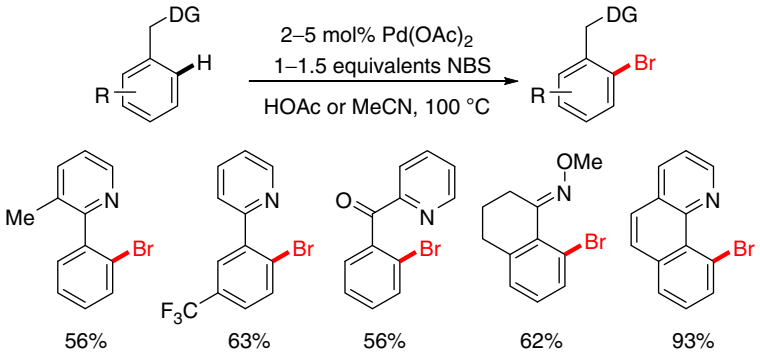
Scheme 31

Acetanilides can be converted to *ortho*-haloacetanilides by using a cocatalysis of $Pd(OAc)_2$ and $Cu(OAc)_2$ with $CuBr_2$ as the halogen source. A variety of functional groups can be tolerated. The brominations proceed in high yields under mild reaction temperature (Scheme 32).[35]



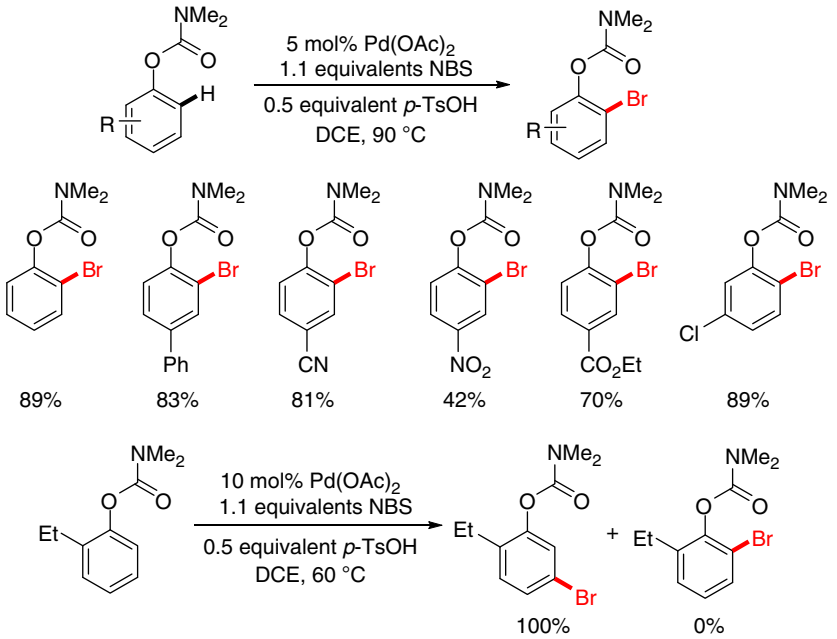
Scheme 32

Directed bromination of arenes with *N*-bromosuccinimide (NBS) can be extended to a variety of substrates bearing nitrogen-containing groups in good yields (Scheme 33).[36] Using MeCN as solvent, benzo[*h*]quinoline can be also brominated in excellent yields under similar reaction conditions.



Scheme 33

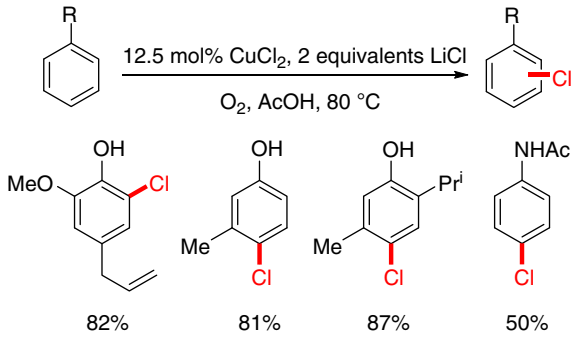
Using NBS as the oxidant and $Pd(OAc)_2$ as the catalyst, aryl carbamates are able to undergo selective *ortho* C–H bromination to produce the corresponding *ortho*-brominated carbamates in good to excellent yields (Scheme 34).[37] More electron-rich carbamates can lead to 100% *meta*-brominated carbamates when the reaction is performed at 60 °C.



Scheme 34

7.13.6.3 Chlorination of Aromatics

Copper salts are the most studied metal catalysts for oxidative halogenation.[38] Cheap $CuCl_2$ is able to catalyze the chlorination of various phenols and anilines. The reaction of 3-methylphenol with 2 equivalents of LiCl in the presence of O_2 and 12.5 mol% $CuCl_2$ in AcOH resulted in 82% yield of 4-chloro-3-methylphenol (Scheme 35).



Scheme 35

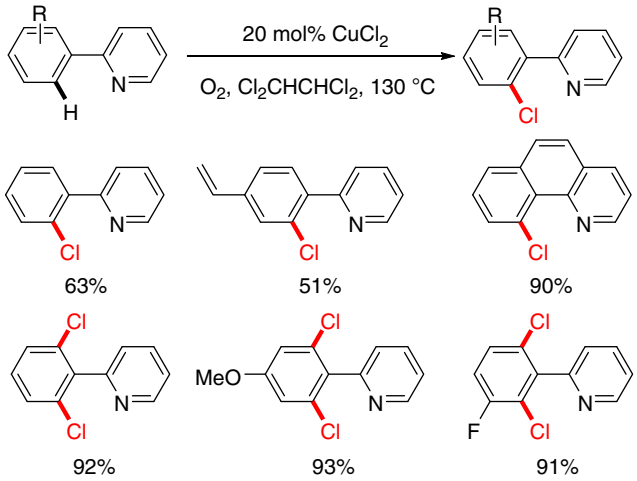
Cu-catalyzed halogenation can be extended to nitrogen-containing substrates using O_2 as the oxidant (Scheme 36).[39] *ortho*-Selectivity was observed with a wide range of 2-arylpyridines. In these cases, the solvent provided the source of the halogen atoms.

Ortho C–H chlorination of azobenzene is the first example utilizing a Pd catalyst in aromatic C–H functionalization in the presence of Cl_2 as the oxidant (Scheme 37).

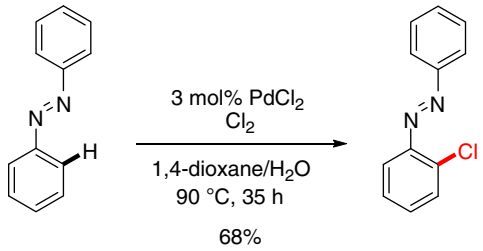
Acetanilides are a class of suitable substrates to produce *ortho*-chloroacetanilides catalyzed by $Pd(OAc)_2/Cu(OAc)_2$ with $CuCl_2$ as the chlorination source (Scheme 38).

Mono-chlorinated arylpyrimidines can be prepared with high selectivity and good functional group tolerance by using cheap calcium halides as halogenating reagents and copper trifluoroacetate as the oxidant in the presence of air and $Pd(OAc)_2$ catalyst (Scheme 39).[40]

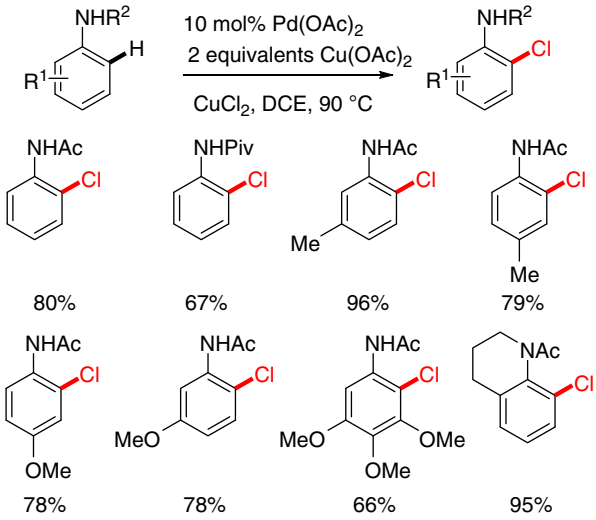
Sanford's method using Pd-catalyzed chelate-directed chlorination of arenes with *N*-chlorosuccinimide (NCS) could be extended to a variety of substrates (Scheme 40). In substrates containing two *ortho* C–H bonds, only modest yields of the mono-halogenated products were obtained, due to competitive formation of the corresponding di-*ortho*-halogenated compounds. These di-*ortho*-halogenated products can be isolated cleanly and in good yields by the use of excess oxidant (2.5 equivalents NCS). Using MeCN as the solvent, benzo[*h*]quinoline can be chlorinated in excellent yields under similar reaction conditions.



Scheme 36



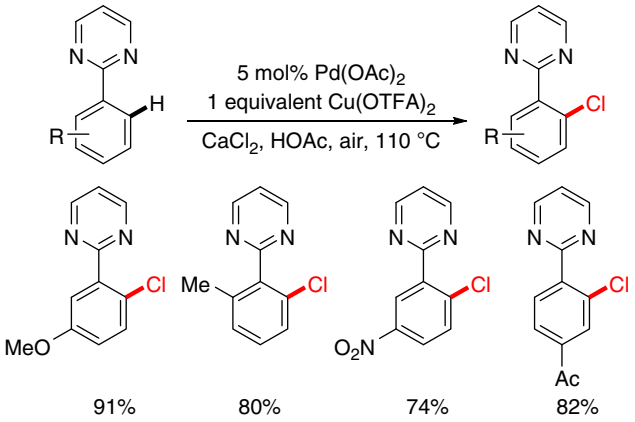
Scheme 37



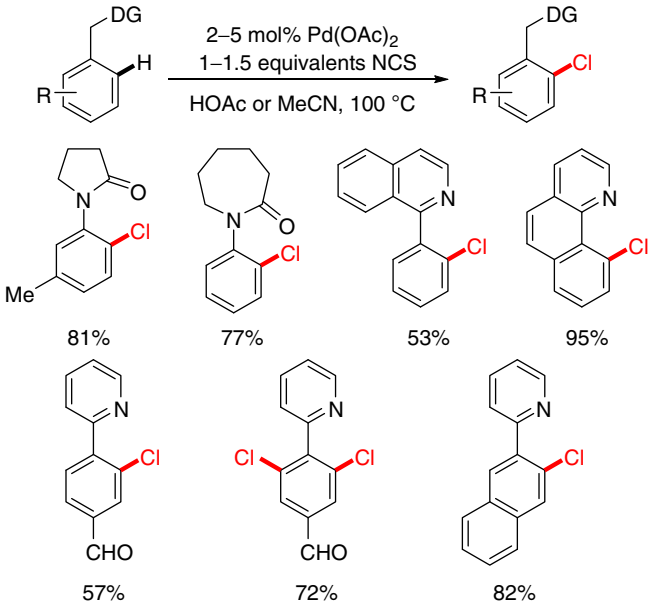
Scheme 38

7.13.6.4 Iodination of Aromatics

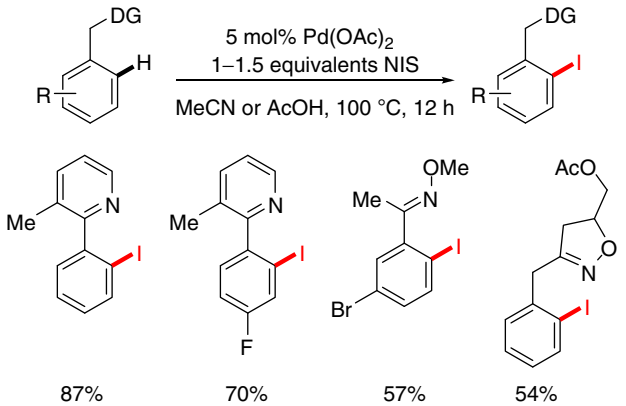
Pd-catalyzed regioselective iodination of arene C–H bonds using *N*-iodosuccinimide (NIS) as the oxidant proceeds in modest to good yields when the substrates have nitrogen-containing directing groups (Scheme 41). In general, similar yields were obtained in MeCN and AcOH solvents.



Scheme 39

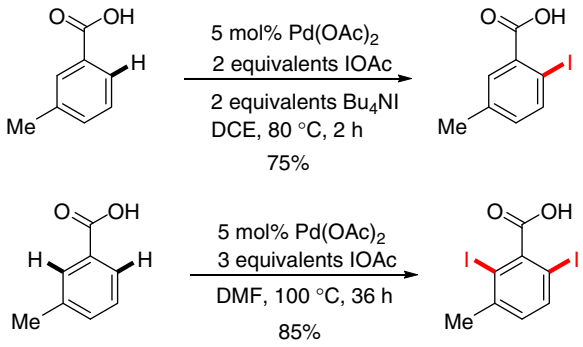


Scheme 40



Scheme 41

Using more active IOAc as the oxidant combined with $Pd(OAc)_2$ catalyst, arenes with an embedded carboxylic acid group are able to be iodinated in good yields. By increasing the amount of oxidant (3 equivalents IOAc) and prolonging the reaction time, substrates with two available *ortho* C–H bonds underwent diiodination in high yields (Scheme 42).[41]

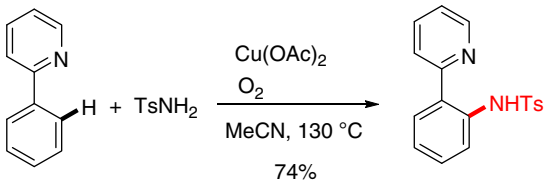


Scheme 42

7.13.7 Oxidative C–N Coupling

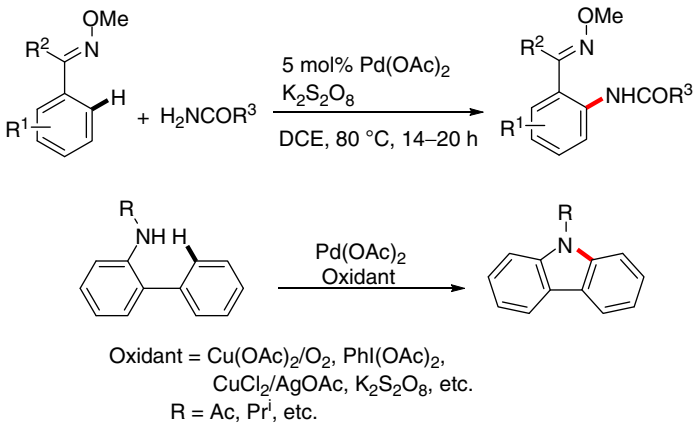
The aromatic C–N bond is one of the most common structures found in organic compounds. The most efficient methods to synthesize such motifs are the well-known Cu-catalyzed C–N coupling and Pd-catalyzed Buchwald–Hartwig C–N coupling, which utilize the coupling between aryl halides and amines. Considering the atom economy in chemical processes, direct aromatic C–H bond functionalization to produce various C–N bonds is highly desirable.

Aryl compounds bearing a pyridine group react easily with nitrogen nucleophiles in the presence of transition-metal catalysts. In the presence of cheap $Cu(OAc)_2$ and O_2, 2-phenylpyridine reacts with sulfonamides to generate the oxidative C–N coupling product at the *ortho* position (Scheme 43).[42]



Scheme 43

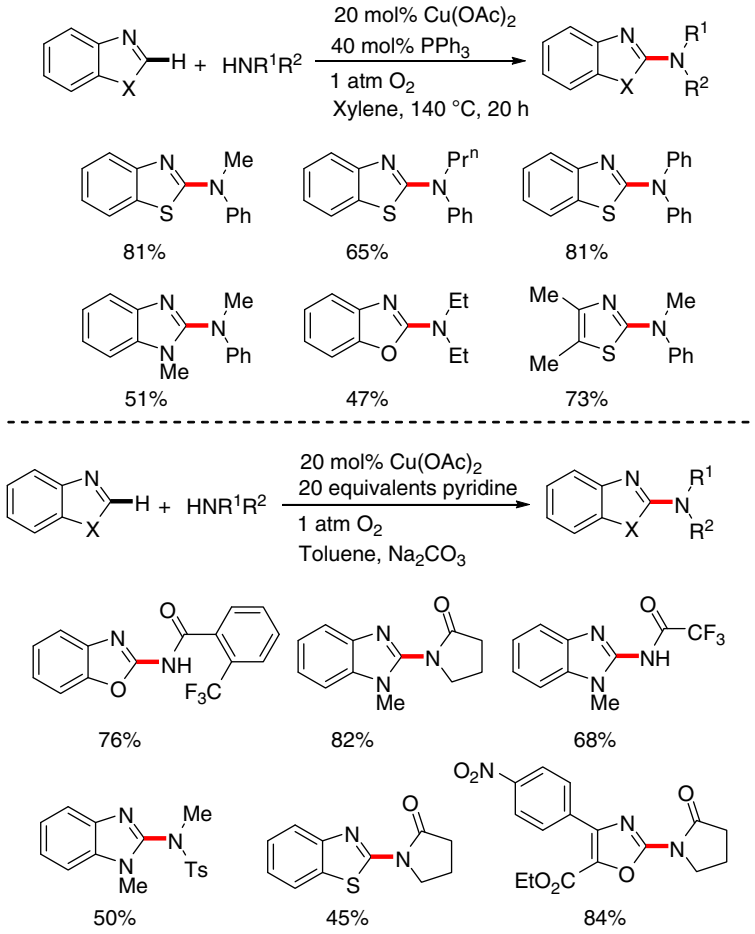
Using potassium persulfate as the oxidant, $Pd(OAc)_2$-catalyzed oxidative amidation reactions of aromatic C–H bonds with primary amides have been realized (Scheme 44).[43] The substrates containing a pendent oxime or pyridine group can be amidated



Scheme 44

with excellent chemo- and regioselectivities in excellent yields. The extension of oxidative intermolecular C–N coupling to intramolecular reactions can be achieved with Pd catalysis to synthesize cyclic compounds in the presence of an oxidant (e.g., $Cu(OAc)_2$ and $PhI(OAc)_2$).[44]

Using cheap $Cu(OAc)_2$ as the catalyst and PPh_3 as the ligand allows the direct amination of benzothiazole with *N*-methylaniline and provides the oxidative C–N coupling product in 81% yield under mild reaction conditions (Scheme 45).[45] Amination of azoles can take place at the 2-position with several amines in the presence of 1 atm O_2 under base-free conditions. Using $Cu(OAc)_2$ as the catalyst and pyridine as the additive, direct amidation of heterocyclic compounds takes place at the 2-position with several amides under 1 atm of O_2.[46]



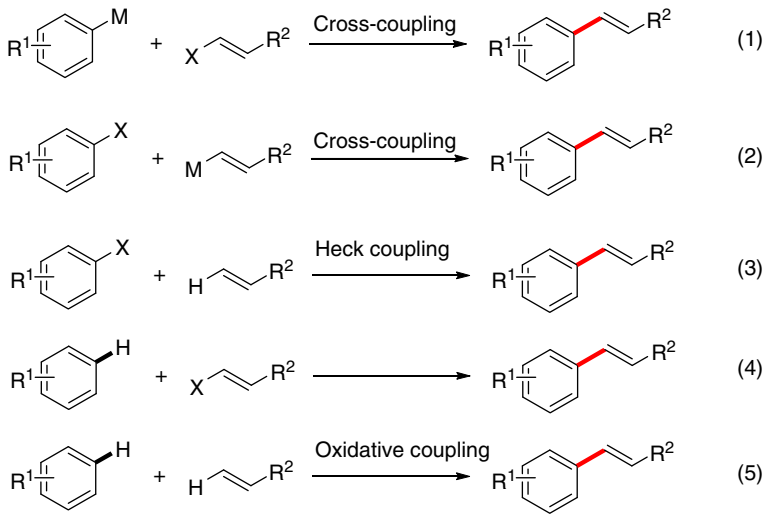
Scheme 45

7.13.8 Oxidative C–C Coupling

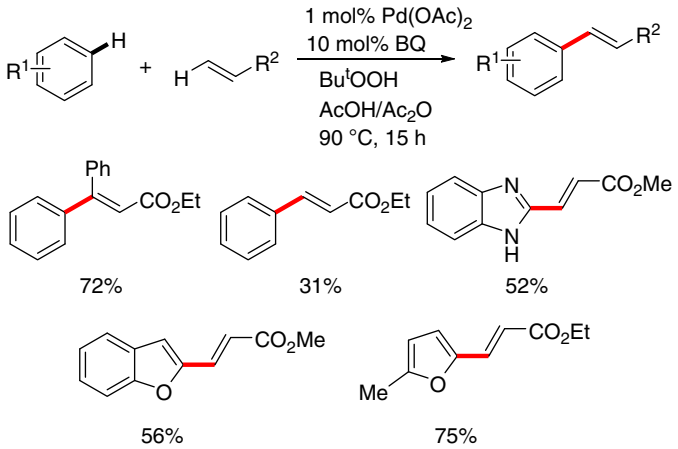
7.13.8.1 Arene–Alkene Coupling

The arene–alkene structures are among the most important structures widely existing in natural products, materials, and polymers. One of the most facile synthetic approaches to such structures involves cross-coupling reactions utilizing arylmetal reagents reacting with alkenyl halides or aryl halides reacting with alkenyl metal reagents in the presence of transition-metal catalyst (Scheme 46, equations 1 and 2). Heck coupling utilizing aryl halides and various alkenes as the coupling partners has become a classical method for the construction of arene–alkene motifs (equation 3). Due to the preactivation of the arene, the cross-coupling and Heck coupling are replaced by oxidative coupling, which directly utilize arenes and alkenes as the starting materials to finish this important task (equation 5).

An efficient oxidative cross-coupling of arenes with olefins can be performed in the presence of 1 mol% $Pd(OAc)_2$ and 10 mol% BQ as the catalyst and *tert*-butyl hydroperoxide as the oxidant. The catalytic system was especially active for the coupling of heteroarenes. such as furans and indoles, with electron-poor olefins with high regio- and stereoselectivity, predominantly giving *trans*-olefins in good yields (Scheme 47).

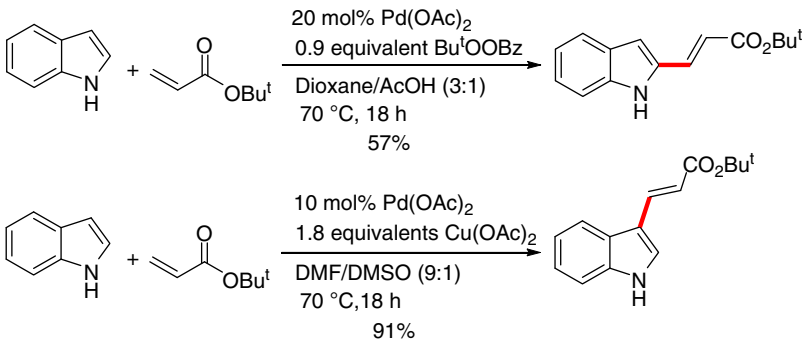


Scheme 46



Scheme 47

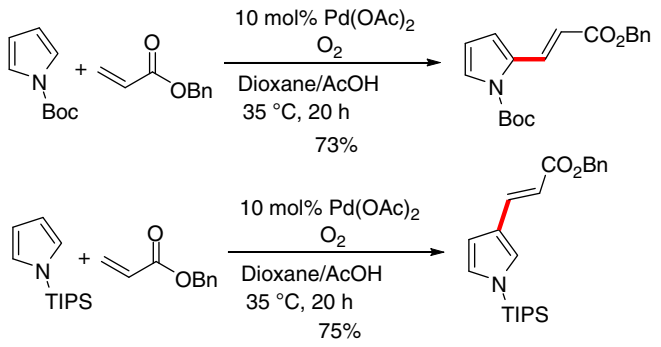
Using 10 mol% $Pd(OAc)_2$ as the catalyst, indole can be oxidatively coupled with *n*-butyl acrylate at the C3-position when the reaction is carried out in polar solvents such as dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF). However, using the nonpolar solvent dioxane together with AcOH as a cosolvent, alkenylation proceeds selectively at the C2-position (Scheme 48).



Scheme 48

N-substituent-controlled oxidative alkenylation of pyrroles proceeds under aerobic conditions. Electron-withdrawing *N*-protecting groups, such as *N*-Boc and *N*-Ts, reduce the reactivity of pyrrole and yields C2-alkenylation products in good yields,

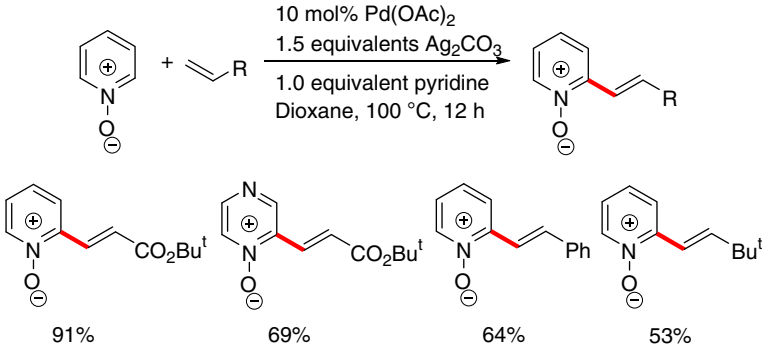
whereas the sterically hindered *N*-triisopropylsilyl (*N*-TIPS) group affords C3-alkenylation products with high selectivity under the same reaction conditions (Scheme 49).



Scheme 49

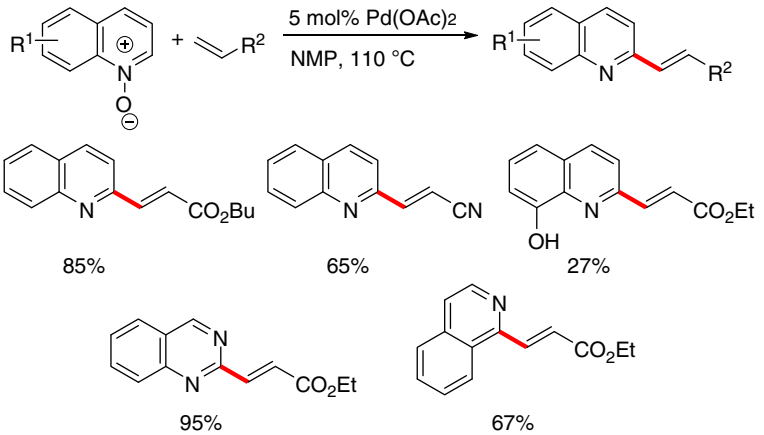
Electron-deficient heteroarenes, such as pyridine *N*-oxides, can be used as suitable substrates in oxidative coupling with alkenes. These transformations are performed selectively at the 2-position of pyridine *N*-oxides in the presence of $Pd(OAc)_2$ as the catalyst and Ag_2CO_3 as the oxidant. Unlike most other C–H activation processes, this reaction proceeds under basic conditions with 1 equivalent of pyridine as the additive.

Both electron-deficient and aliphatic alkenes react well in moderate to high yields. *N*-oxides of pyrazine and pyridazine were also found to be good substrates. This approach represents an attractive synthesis of 2-functionalized pyridines (Scheme 50).



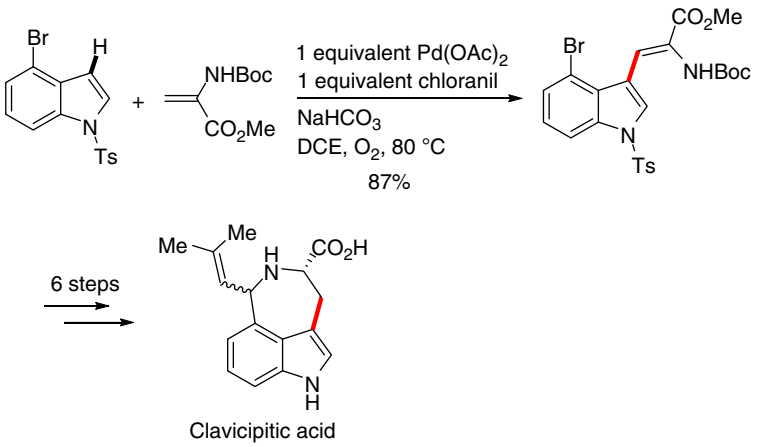
Scheme 50

Using $Pd(OAc)_2$ as the catalyst, quinoline *N*-oxides undergo an olefination in the absence of external oxidants to afford 2-alkenylquinolines in good yields (Scheme 51).



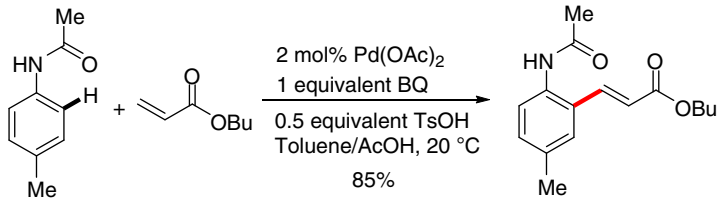
Scheme 51

Electron-rich heteroaromatic compounds undergo intermolecular oxidative Heck couplings and allow the synthesis of more complex compounds, for example, the total synthesis of (±)-clavicipitic acid via a Pd-mediated C3-oxidative alkenylation of an indole derivative (Scheme 52).



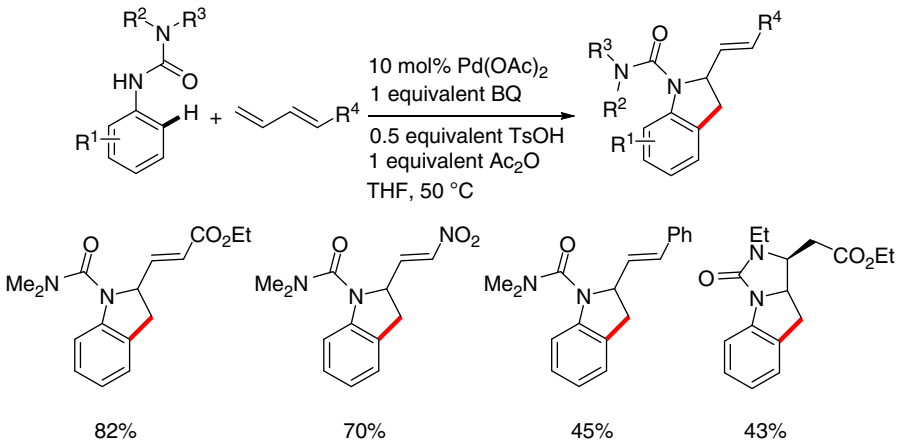
Scheme 52

An acetamido group is still very popular in this oxidative coupling reaction. This type of substrate cross-coupled with electron-deficient alkenes under mild conditions. Only the *ortho*-substituted product was observed, indicating the importance of the directing effect of the amido group. With $Pd(OAc)_2$ as the catalyst and BQ as the oxidant, the transformation proceeded smoothly in the presence of a TsOH additive even at r.t. (Scheme 53).



Scheme 53

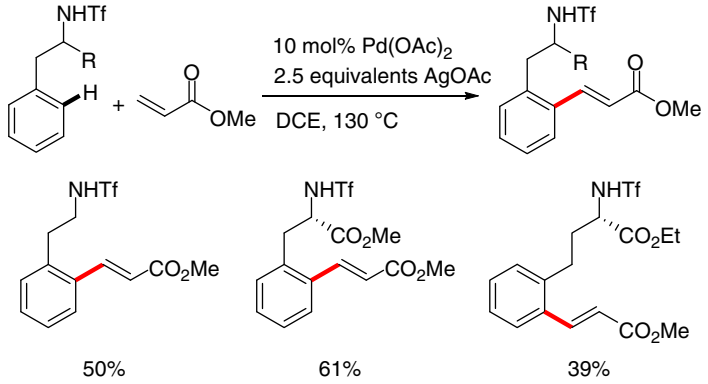
Intermolecular oxidative coupling between phenylureas and dienes affords indolines by *ortho*-alkenylation followed by cyclization (Scheme 54). Although oxidative conditions are used for this transformation, overoxidation to the corresponding indoles is not observed. Ac_2O is added to keep the conditions anhydrous. $Pd(OTs)_2$ is proposed to be the active catalyst for this



Scheme 54

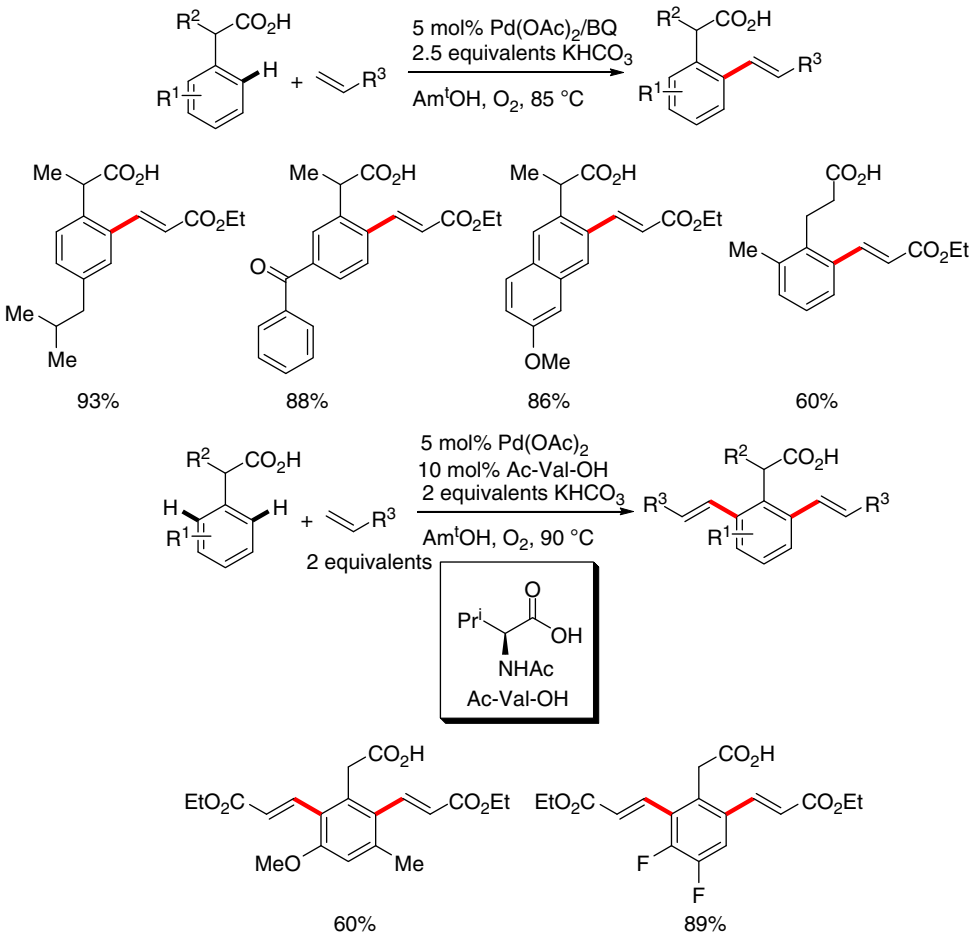
cyclization. In the case where either R^2 or R^3 = H, a second cyclization affords a tricyclic product as a single diastereomer. In this reaction, one C–C bond and two C–N bonds are formed.

Oxidative alkenylation of substituted phenyl rings with triflamido and carboxyl groups can be realized by a Pd catalyst. Highly regioselective alkenylation of protected 2-phenylethylamines at the *ortho* position were realized in the presence of a triflamido directing group with $Pd(OAc)_2$ as catalyst (Scheme 55).



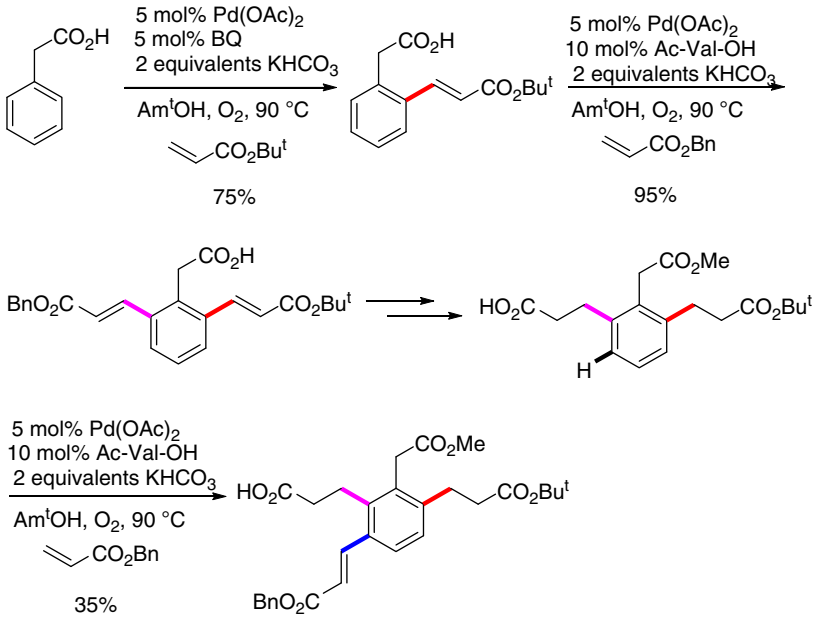
Scheme 55

When phenylacetic acids were subjected to oxidative couplings with olefins, the reaction also proceeded smoothly and regioselectively in the presence of a Pd catalyst and BQ ligand. Several drug substrates including ketoprofen, ibuprofen, and naproxen were found to be compatible with this protocol and afforded the *ortho*-olefination products in high yields (Scheme 56).



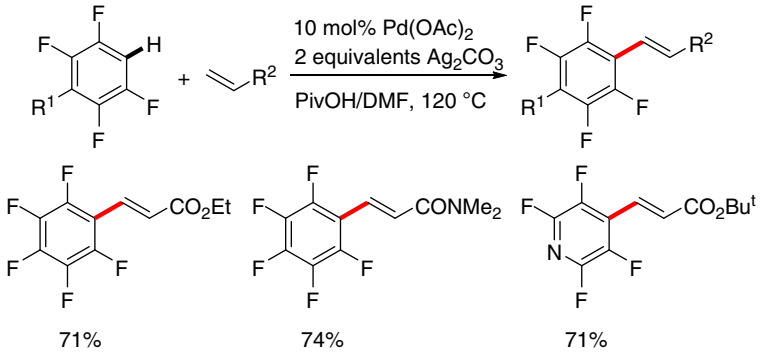
Scheme 56

Introducing amino acid ligands can enhance the smooth efficiency of *ortho*- and bis-alkenylation of phenylacetic and benzylacetic acids in the presence of Pd catalyst. In a three-step sequence, Pd catalysis provides phenylacetic acids with different *ortho*-alkene substituents (Scheme 57).[47]



Scheme 57

Electron-poor arenes, such as perfluorinated arenes, can undergo alkenylation in good yields using $Pd(OAc)_2$ as the catalyst and Ag_2CO_3 as both a base and an oxidant (Scheme 58).



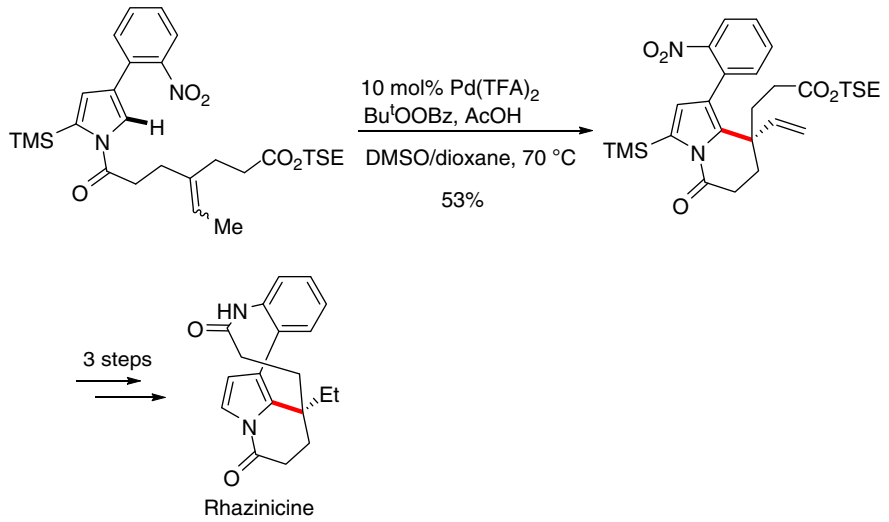
Scheme 58

Intramolecular oxidative alkenylations can be applied to total synthesis. The synthesis of (±)-rhazinicine using a Pd-catalyzed intramolecular oxidative coupling as the key step has been reported (Scheme 59).

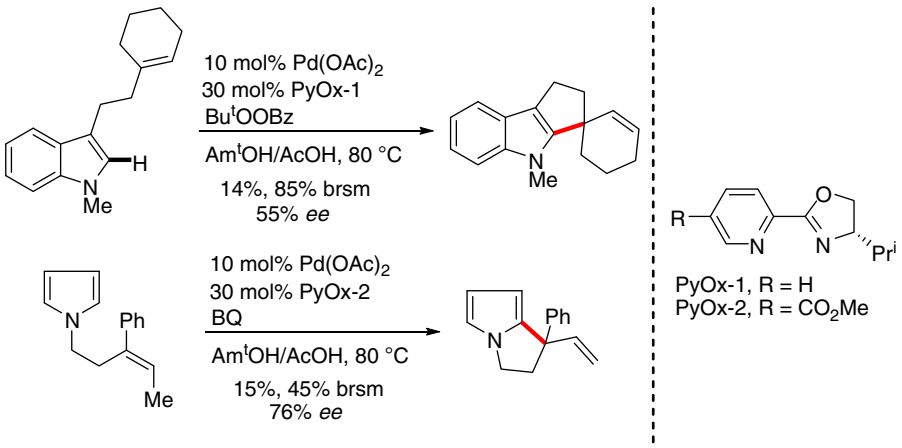
Enantioselective oxidative cyclizations have been achieved by Oestreich and coworkers. Indoles and pyrrole undergo 5-*exo*-trig cyclizations in the presence of Pd, PyOx-X (a chiral pyridine-oxazoline ligand), and an oxidant (e.g., Bu^tOOBz and BQ) with moderate enantiomeric excesses (Scheme 60).

7.13.8.2 Arene–Arene Coupling

Biaryl compounds are one of the most important structures in chemical science. Classical cross-coupling reactions offer a facile method to generate aryl–aryl bonds using aryl halides and arylmetal reagents as the starting material, which will produce large amounts of metal salts as side products. Directly utilizing various aryl C–H bonds as the starting material to synthesize a variety of biaryl compounds is more desirable.[48] In fact, there are two ways to construct aryl–aryl bonds: one is to react an aryl C–H bond

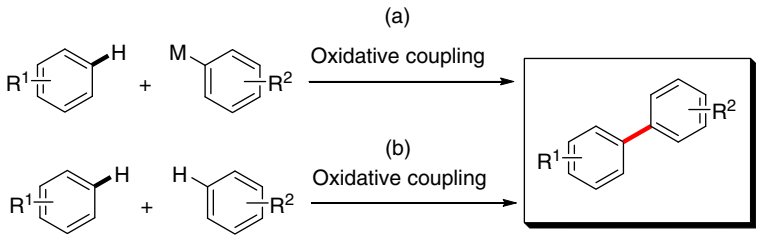


Scheme 59



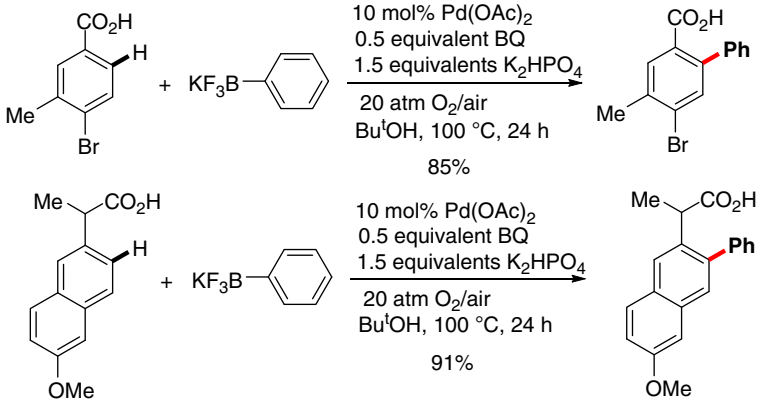
Scheme 60

with another arylmetal reagent in the presence of catalyst and oxidant (Scheme 61, path a) and the other is to directly utilize two aryl C–H bonds to homocouple or cross-couple to construct this motif in the presence of catalyst and oxidant (path b). Though utilizing arylmetal reagents is not as green as possible, high chemoselectivity can be achieved in most cases. Thus, the oxidative coupling between aryl C–H bonds and arylmetal reagents (e.g., Mg, Zn, B, Si, etc.) is very useful for the synthetic community.



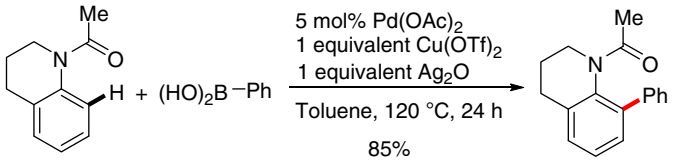
Scheme 61

Using organoboron reagents (aryltrifluoroborates) as the coupling partner, several benzoic acids react at the *ortho* position using 20 atm of air or O_2 (Scheme 62). This new protocol can produce the corresponding coupling products in good to high yields. It is also effective for arylacetic acids.



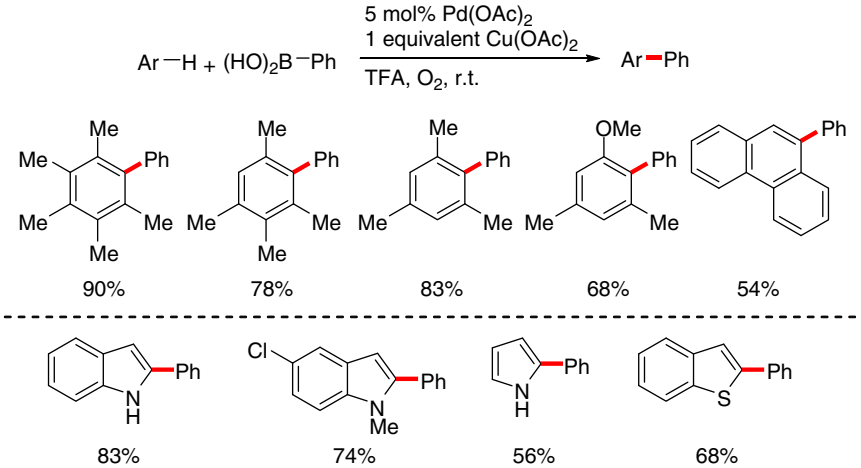
Scheme 62

Using the acetamido moiety as a directing group on the arene substrates, $Pd(OAc)_2$ combined with $Cu(OTf)_2$ as an oxidant and Ag_2O as the additive affords the desired cross-coupled product in good yields (Scheme 63).



Scheme 63

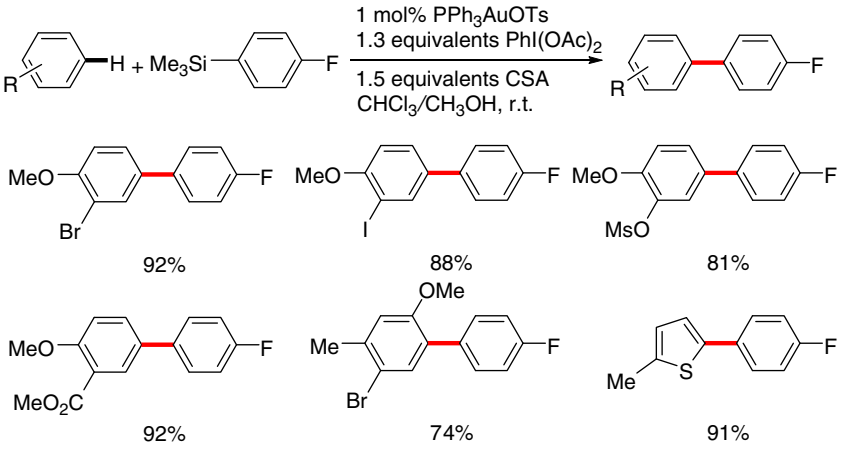
Using 5 mol% of $Pd(OAc)_2$ and 1 equivalent of $Cu(OAc)_2$ as a cooxidant under an O_2 atmosphere, simple arenes react with arylboronic acids to afford corresponding coupling compounds (Scheme 64). In general, electron-rich arenes bearing methyl substituents showed good reactivity, and electron-rich and methoxy-substituted polyarenes were also favorable for this transformation. In the presence of a stoichiometric amount of iron and manganese salts, arylboronic acids could also be coupled with aromatic compounds (benzene, thiophene) to afford biaryl compounds. Using such methods, oxidative coupling of heteroarenes with phenylboronic acid showed high regioselectivity for the 2-position of 2,3-benzothiophene, 2,3-benzofuran, and *N*-heterocycles such as pyrroles and indoles. Free N–H bonds were well tolerated under such mild reaction conditions.



Scheme 64

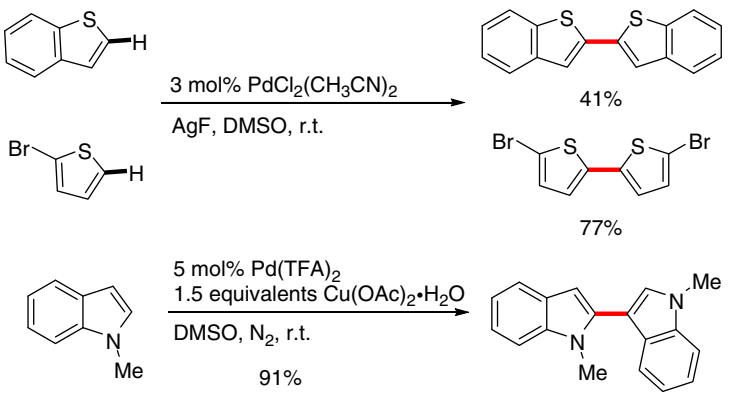
Besides the methods outlined above, other organometallic reagents are also used in organic synthesis. Recent gold-catalyzed direct arylation of unactivated arenes with arylsilanes represent a new approach with mild conditions and excellent site selectivity.[49] Using PPh_3AuOTs as the catalyst and $PhI(OAc)_2$ as the oxidant with camphorsulfonic acid (CSA) as the additive, a wide

range of arenes undergo site-selective arylation by arylsilanes (Ar-$SiMe_3$) to generate biaryls with a broad range of functional group tolerance (Scheme 65).



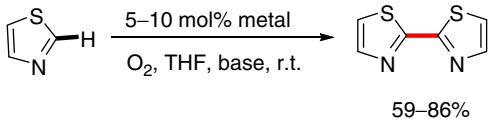
Scheme 65

With $PdCl_2(CH_3CN)_2$ as the catalyst and silver fluoride as the oxidant, the oxidative homocoupling of substituted thiophenes, benzothiophenes, and thiazoles can be successfully achieved in moderate to good yields (Scheme 66). Silver salt was essential for this reaction; other metal salts showed no efficiency in this transformation. Using $Pd(OTFA)_2$ as the catalyst and monohydrated $Cu(OAc)_2$ as the oxidant, the unsymmetrical homocoupling of *N*-methylindole produces a high yield of 2,3′-biindolyl at r.t.



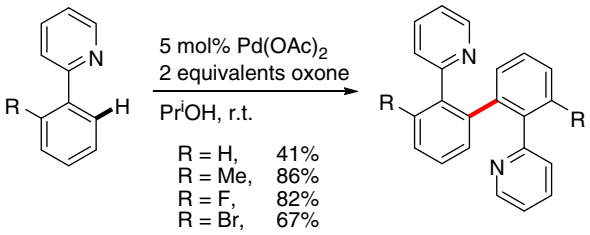
Scheme 66

Dimerization of azoles can be realized by using some cheap transition-metal salts as the catalyst under aerobic conditions. Under an atmosphere of oxygen, nickel, manganese, cobalt, and iron chlorides are all effective for this transformation under strongly basic conditions (Scheme 67).



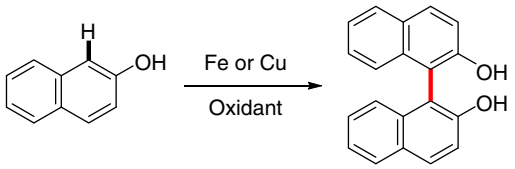
Scheme 67

2-Phenylpyridine and its derivatives can also dimerize regioselectively, directed by a pyridyl group in the presence of 5 mol% $Pd(OAc)_2$ catalyst and 2 equivalents of Oxone as the oxidant. The reactions proceed at r.t. and are compatible with various functional groups (Scheme 68).



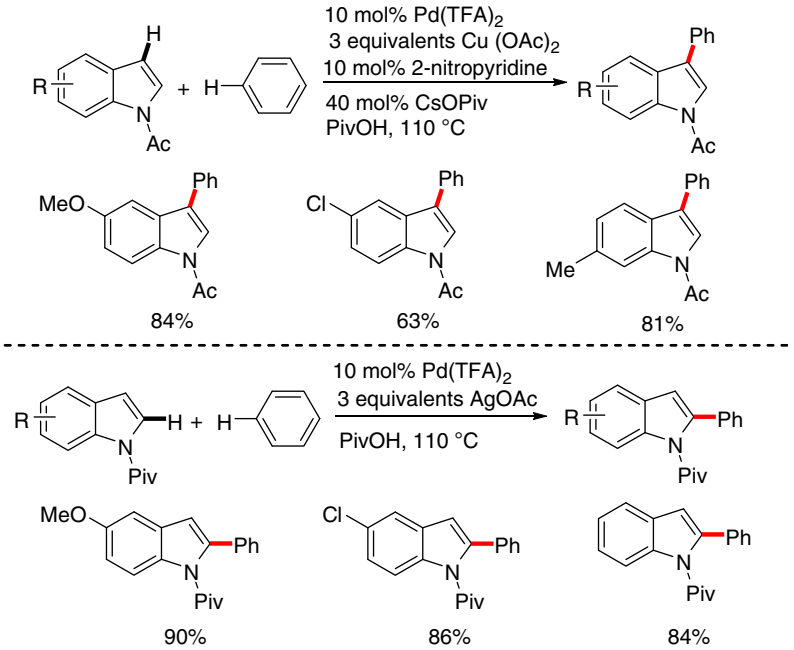
Scheme 68

Another useful homocoupling is the well-known oxidative dimerization of naphthols (Scheme 69). Many useful protocols have been developed for this purpose, especially for the enantioselective oxidative couplings of 2-naphthols. Transition metals such as copper and iron are efficient, and molecular oxygen is commonly used as an oxidant.



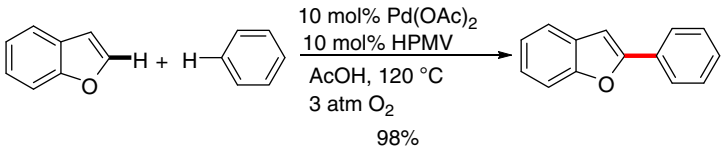
Scheme 69

Fagnou reported Pd-catalyzed oxidative cross-coupling between indoles and benzene (Scheme 70).[50] Using $Pd(TFA)_2$ as the catalyst and $Cu(OAc)_2$ as the oxidant, combined with a pyridine additive, these transformations proceeded smoothly in high selectivity and yields. The indole nitrogen substituent is important in this coupling. *N*-acetylindole gave the desired cross-coupling products. Interestingly, replacing $Cu(OAc)_2$ with AgOAc produced an inversion in regioselectivity favoring the C2-position. The removal of the pyridine additive and the change from *N*-acetyl to *N*-pivaloyl resulted in complete conversion and high selectivity.



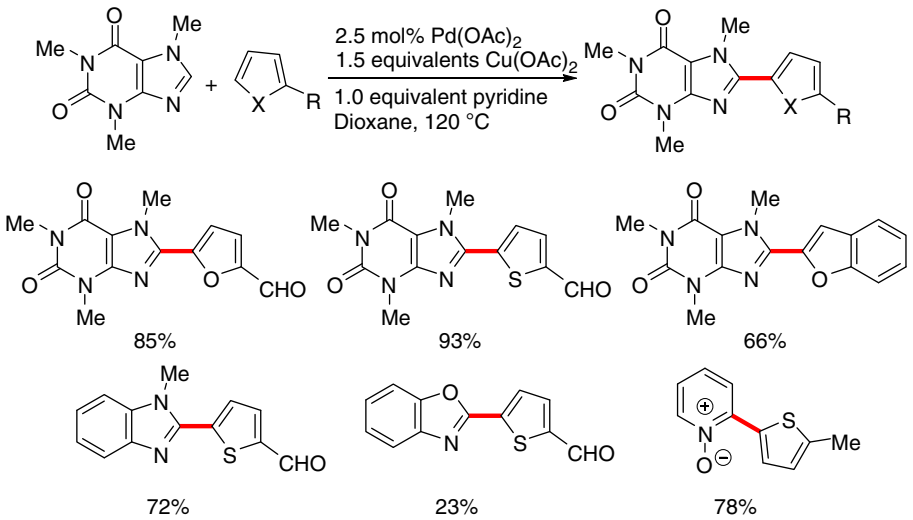
Scheme 70

In the presence of a catalytic amount of $Pd(OAc)_2$ and $H_4PMo_{11}VO_{40}$ (HPMV) together with O_2 as the terminal oxidant, oxidative coupling of benzene with benzofuran took place regioselectively at the 2-position of benzofuran in 98% yield (Scheme 71).



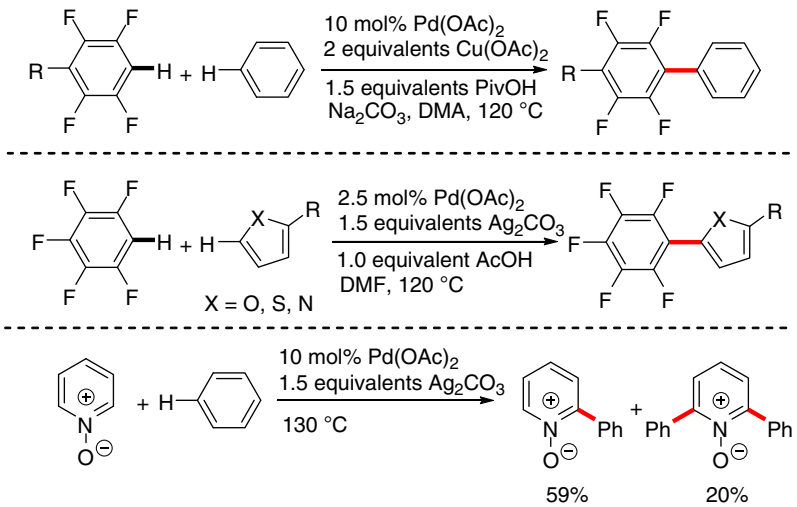
Scheme 71

Oxidative cross-couplings between two different heteroarenes have also been explored with Pd catalysis. A variety of thiophenes and furans were cross-coupled regioselectively at their 2-positions with several *N*-heteroaromatic substrates such as xanthines and azoles (Scheme 72).



Scheme 72

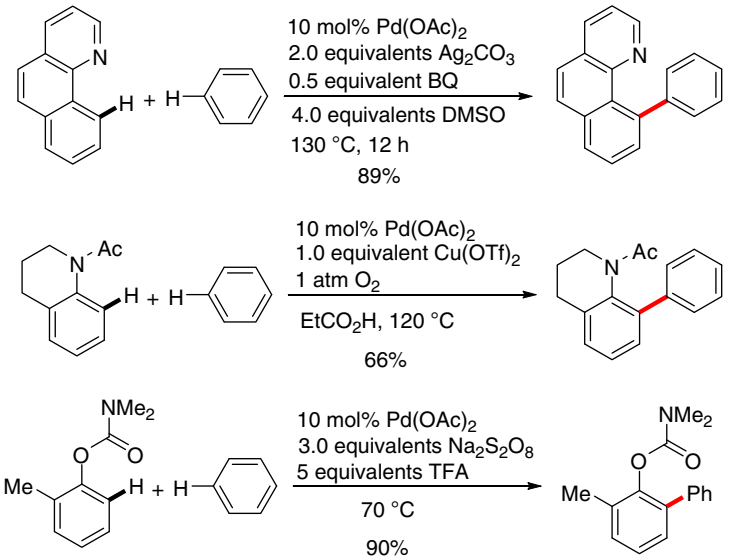
Using $Pd(OAc)_2$ as the catalyst and $Cu(OAc)_2$ or Ag_2CO_3 as the oxidant, perfluoroarenes undergo coupling reactions with benzene and heteroarenes such as thiophenes, furans, and indoles. The direct arylation of pyridine *N*-oxides with unactivated benzene can be also achieved under such reaction conditions (Scheme 73).



Scheme 73

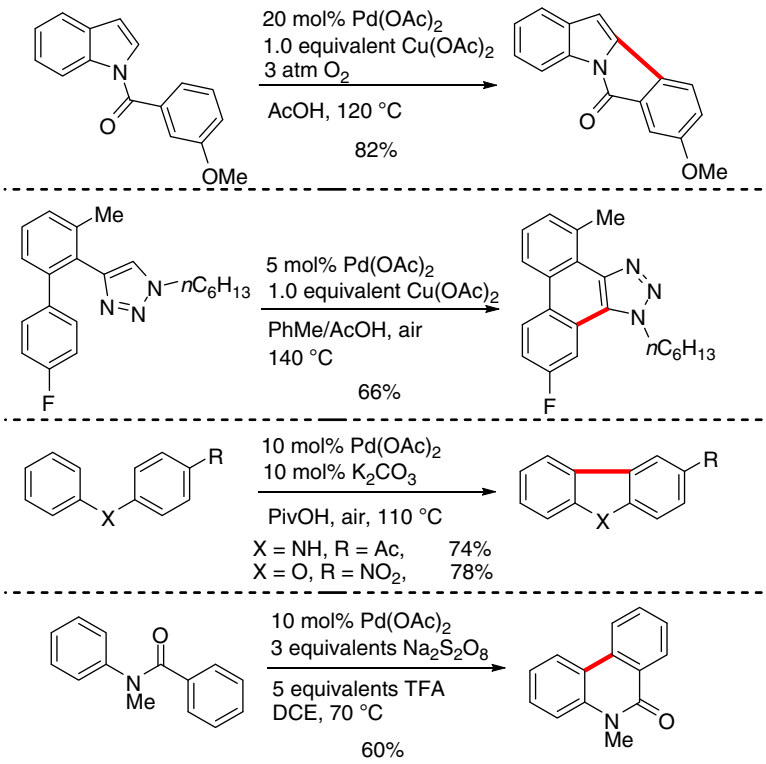
Sanford demonstrated a Pd-catalyzed, regioselective, oxidative cross-coupling of benzoquinoline with benzene. Due to the coordination of the nitrogen atom of benzoquinoline to the Pd catalyst, the coupling occurred selectively on the C10- position in a high yield. A combination of 0.5 equivalent of BQ together with 2 equivalents of Ag_2CO_3 was used and was found to be effective

for this transformation (Scheme 74). In the presence of $Cu(OTf)_2$ as the cooxidant and O_2 as the terminal oxidant, Pd can catalyze the direct arylation of arenes containing an acetamido substituent at the *ortho* position, controlled by the acetamido directing group. Using sodium persulfate as the oxidant, *O*-carbamate-directed *ortho*-arylation with simple arenes (e.g., benzene, xylene, etc.) takes place smoothly. Both trifluoroacetic acid (TFA) and sodium persulfate were critical for the transformation.



Scheme 74

Intramolecular oxidative coupling of aryl C–H bonds is more selective than the intermolecular version and can be applied to more attractive cyclizations. Using $Pd(OAc)_2$ as the catalyst, the oxidative cyclization can produce the desired products in moderate to good yields under oxidative conditions (Scheme 75). In most cases, O_2 or air as the oxidant is efficient for this transformation.

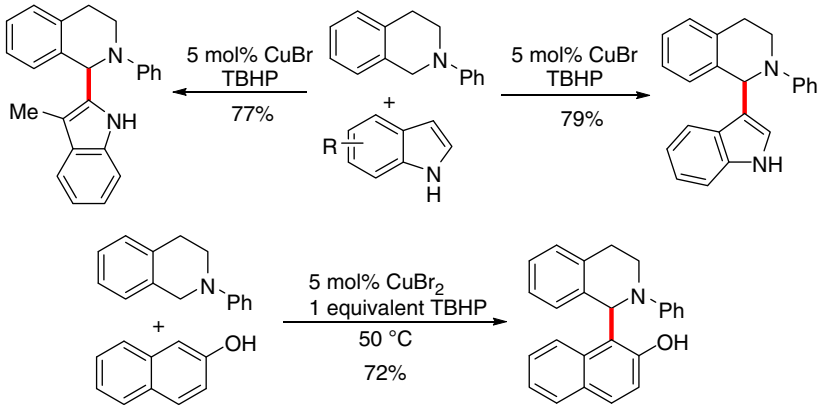


Scheme 75

7.13.8.3 Arene–Alkane Coupling

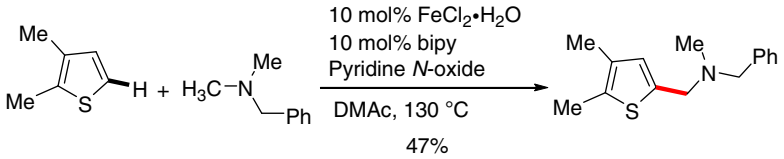
Traditional cross-coupling reactions represent a facile way to construct such motifs using arylmetal reagents coupling with alkyl halides or aryl halides with alkyl reagents. Due to the necessity for prefunctionalization, the synthesis of each coupling partner generates a large amount of metal salts, and thus direct use of arene coupling with an alkane is more desirable for synthetic chemists.

Using $CuBr_2$ as the catalyst and *tert*-butylhydroperoxide (TBHP) as the oxidant, indole was used as a substrate to couple with alkyl groups adjacent to tertiary amines (Scheme 76). The reaction took place selectively on the C3-position of indoles when both C2 and C3 were unsubstituted. When the C3-position of indole was substituted, the reaction proceeded smoothly at the C2-position. This method can be extended to the oxidative coupling of 2-naphthol with alkyl groups adjacent to tertiary amines with good yield.



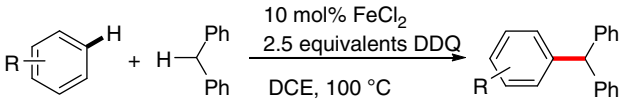
Scheme 76

Cheap iron catalysts are also effective for the oxidative coupling of indole with tertiary amines. Moreover, other heteroaromatic arenes such as thiophene and pyrroles are also suitable substrates under such conditions (Scheme 77).



Scheme 77

Using cheap $FeCl_2$ as the catalyst and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant, iron-catalyzed oxidative coupling of benzylic C–H bonds with electron-rich arenes offers the desired products in good to excellent yields (Scheme 78). Various electron-rich arenes and different diarylmethanes are suitable substrates, affording excellent regioselectivity in reactions of interest.

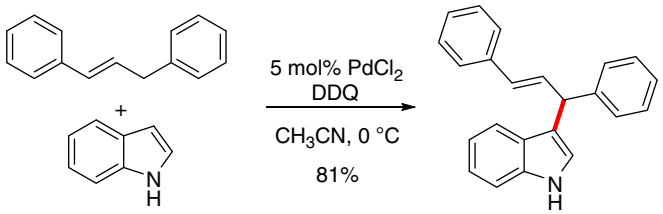


Scheme 78

Allylic sp3 C–H bonds that are not adjacent to nitrogen can react with indoles under oxidative conditions. $PdCl_2$ was found to be the most efficient catalyst, together with DDQ, which is a well-known oxidation reagent in organic synthesis, as the oxidant. The C3-position of indole is still the active site and participates in the reaction (Scheme 79).

7.13.8.4 Arene–Alkyne Coupling

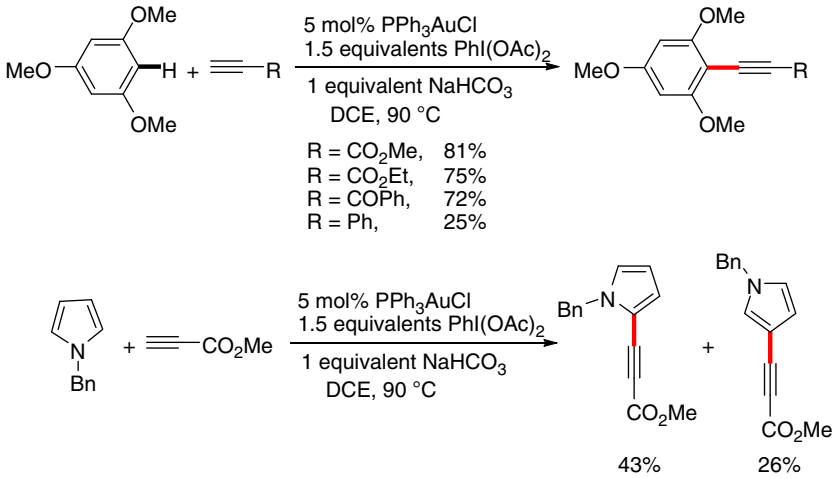
Traditionally, Pd-catalyzed Sonogashira couplings between aryl halides and alkynes are the most efficient method toward arene–alkyne structures. Normally, aryl halides are prepared by the halogenation of the corresponding arenes. In most cases, high-cost aryl iodides



Scheme 79

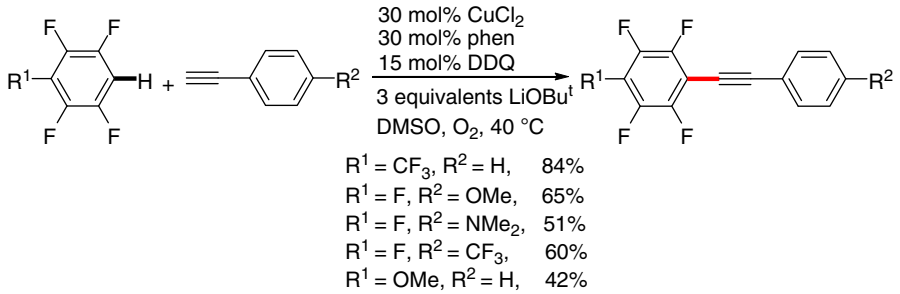
are needed to perform this transformation. The direct coupling of arenes with alkynes without the prehalogenation would be both a green and economical process.

Using Ph_3PAuCl as the catalyst and $PhI(OAc)_2$ as the oxidant, electron-rich arenes and electron-deficient alkynes are suitable partners for this oxidative cross-coupling in the presence of 1 equivalent of $NaHCO_3$ as the additive (Scheme 80). Phenylacetylene offered the coupled product in low yields due to the increased homocoupling of the alkyne. Electron-rich heteroaromatic rings, such as pyrrole, also reacted with electron-deficient alkynes without site selectivity.



Scheme 80

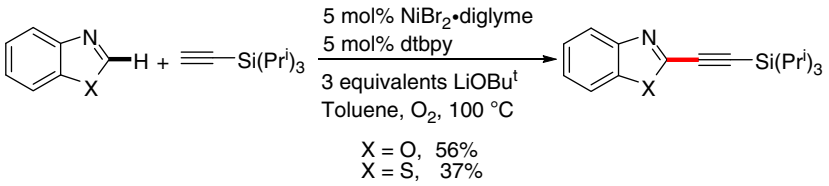
Considering the limitations and drawbacks of the noble gold catalysis, other simpler and cheaper reaction conditions were developed for such transformations. Using cheap $CuCl_2$ as the catalyst combined with 1,10-phenanthroline as the ligand, oxidative coupling between electron-deficient arenes and terminal alkynes take place in the presence of the strong base Bu^tOLi (Scheme 81). O_2 was used as a terminal oxidant with 15 mol% of DDQ as the cooxidant. Further, the more electron-deficient arenes afford better yields.



Scheme 81

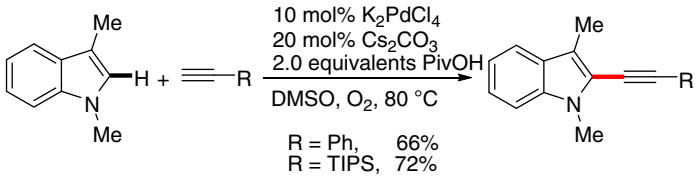
Nickel catalysts are another of the cheap metals applied in coupling reactions. Using $NiBr_2$ as the catalyst and dtbpy as the ligand, heteroarenes, such as benzoxazole, benzothiazole, and 5-aryloxazole, are all proper substrates to react with terminal alkynes in moderate yields. A strong base such as Bu^tOLi was required to deprotonate both heteroarenes and terminal alkynes.

O_2 was used as the sole oxidant without the use of a cooxidant. Moreover, the silyl group allows further transformation of the coupling products (Scheme 82).



Scheme 82

Using K_2PdCl_4 as the catalyst without an extra ligand, 3-substituted indoles can react with terminal alkynes in the presence of 1 atm O_2. The reaction system composed 0.2 equivalent Cs_2CO_3 and 2 equivalents pivalic acid in DMSO is required for this transformation. It should be noted that a slow addition of the substrates is also required to suppress the homocoupling of alkynes (Scheme 83).



Scheme 83

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7.14 Nondirected Aryl C–H Oxidations

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Glossary

EXAFS Extended X-ray absorption fine structure spectroscopy is an element-specific method where X-rays of narrow energy resolution impinge on a sample. Absorption is element specific and can be used to determine local coordination environments of metal centers in metalloproteins.

Mesoporous Describing porous material where the pore sizes typically range between 2 and 50 nm.

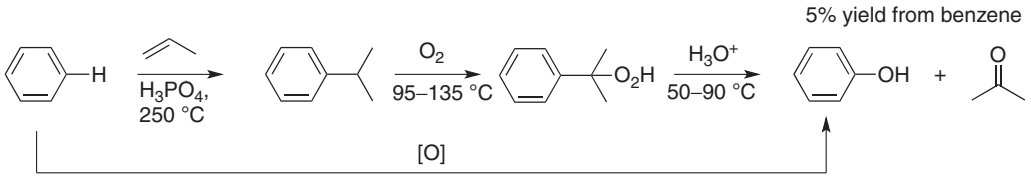
Photocatalytic A catalytic process that is initiated by a photon.

Rieske diooxygenases A family of Fe–S proteins that mediate oxygenation of organic substrates. The active site is typically a single Fe atom bound to two cysteine and two histidine amino acid residues.

Turnover number A measure of the average number of catalytic cycles that a catalyst participates in before it is deactivated.

Xenobiotic A material found in an organism that either normally does not exist in the organism, or is present at concentrations that are higher than normal.

Phenols are an important molecular class that serve as resin monomers, agrochemicals, flavors, metal binders, antioxidants, analgesics, etc. Due to their ubiquity, numerous phenol syntheses have been devised. Commodity scale production typically begins with an aromatic petroleum feedstock that is chemically transformed to produce the net oxidation of a C–H bond. In principle, the direct conversion of C–H to C–OH is the most atom economical route. Despite this fact, the largest volume chemical commodity in this class, phenol, is produced via an indirect process (Scheme 1) where benzene is first alkylated with propene to afford cumene, which is then oxidized to produce phenol. In this process, acetone is generated as a stoichiometric byproduct. The overall yield for the three-step synthesis from benzene is low, remarkably so, for an industrial process.



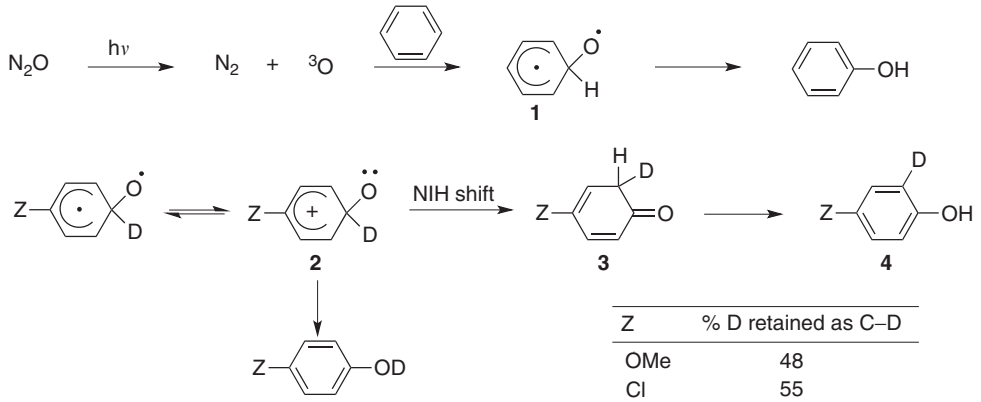
Scheme 1

While it is clear that direct routes involving formal insertion into the C–H bond would be more atom economical, catalysis of this reaction is yet to be economically viable. The fact that a circuitous route is used to produce a commodity chemical is a testament to the challenges that oxidation of aromatic C–H bonds pose. This chapter discusses nondirected oxidations of aromatic C–H bonds, many of which yield phenolic functionality. The discussion will begin with phenol syntheses from reactive oxygen species (ROS). This will be followed by photocatalytic phenol syntheses from benzenes. Next, enzymatic routes for functionalization will be described. The chapter will close with catalytic, nondirected functionalizations of aromatic C–H bonds.

7.14.1 Oxidations by ROS

Oxidation of aromatics can be accomplished by ROS such as ^3O, and $^{\bullet}OH$, and to a lesser extent O_2. Reactions with ^3O are believed to proceed through O–C bond formation with one of the ring carbons to generate a long-lived triplet biradical, C_6H_6O

(**1**, Scheme 2), where one spin resides on the O atom and the other delocalized over a pentadienyl framework. The biradical collapses to phenol in a reaction favored by 427 kJ mol^{-1}.[1] Isotopic labeling studies of 4-deuterated benzenes showed significant deuterium retention supporting the participation of an National Institutes of Health (NIH) shift, where tautomerization of zwitterions **2**, yield **3**, which can enolize to ring-deuterated phenols **4**, to the reaction pathway.[2]

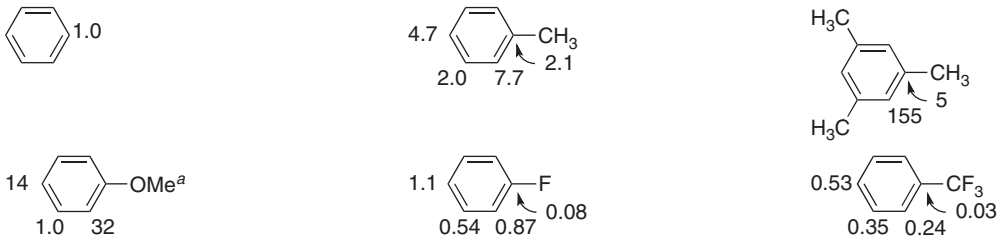


Z	% D retained as C–D
OMe	48
Cl	55

Scheme 2

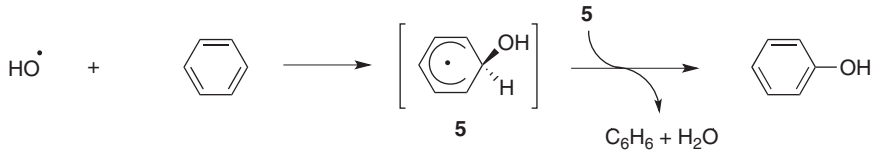
Substituted benzenes react primarily to afford regioisomeric phenols, although insertion into the C–C bonds of alkyl benzenes can compete. Table 1 shows relative rates of O atom insertion into C–H and C–C bonds of selected substituted benzenes.[3] The data are consistent with ^3O being an electrophilic species. For example, electron-rich species are more reactive than electron-poor ones and toluene favors oxygenation at the *o*- and *p*-positions. However, the selectivity does not rival those for nitrations, limiting the synthetic utility of this reaction.

Table 1 Relative rates for insertions of ^3O into C–H bonds of substituted benzenes to produce phenols at 30 °C[3]



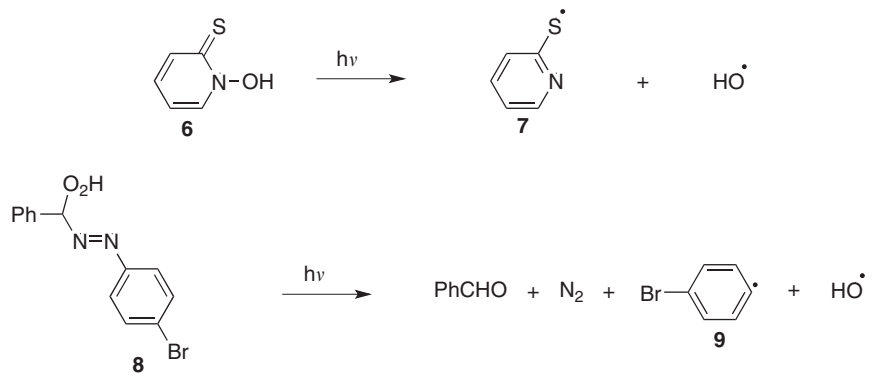
[a]The relative rate for methoxy cleavage was not determined.

Phenols can also be obtained through the reaction of hydroxyl radicals and arenes. In these reactions C–O bond formation yields pentadienyl intermediates that undergo intermolecular disproportionation to phenols in the absence of external oxidants (Scheme 3). There are many examples where phenol synthesis has been attributed to reactions of free hydroxyl radicals; however, variability in reaction outcomes depending on methods of generating •OH call some of these interpretations to question. Two systems that are believed to reliably generate •OH are shown in Scheme 4.



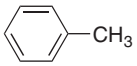
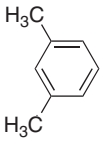
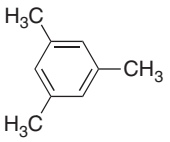
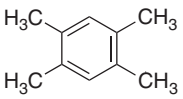
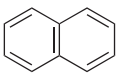
Scheme 3

The relative rates of arene reactions with hydroxyl radicals generated from **6** have been tabulated for a number of arenes by Hadad and Platz.[4] As shown in Table 2, the relative rates of reaction correlate with the ionization potential of the arene substrate with more electron-rich substrates exhibiting higher reactivity. Neither yields of phenol products nor regioselectivities of hydroxylation were reported in this study.

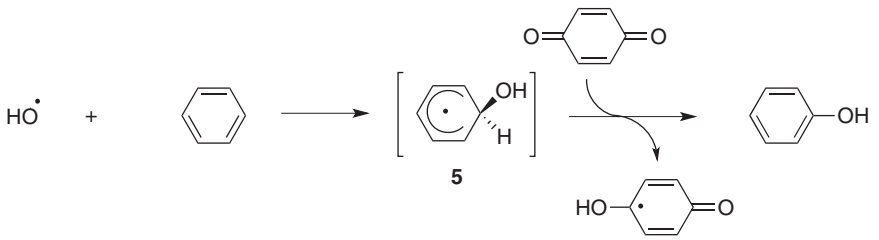


Scheme 4

Table 2 Relative rates for reactions of aromatic hydrocarbons with hydroxyl radicals generated from **6** in acetonitrile at 298 K[4]

Arene	k_{rel}	*IP (eV)*
	1.0	9.24
	3.3	8.83
	6.2	8.55
	11.5	8.40
	11.1	8.06
	13.9	8.14

Reaction yields and regioselectivities for reactions of a handful of substituted benzenes with HO• generated from **8** have been reported by Tezuka and coworkers.[5,6] Yields for these reactions are typically low, in part due to the fact that disproportionation of two equivalents of radical **5** yields only one equivalent of phenol. Adding an oxidant, such as *p*-benzoquinone, to intercept **5** as illustrated in Scheme 5, can increase yields.

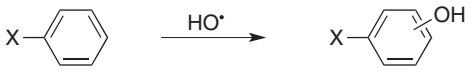


Scheme 5

Data for reactions of toluene, anisole, and nitrobenzene with hydroxyl radical are listed in Table 3. It is noteworthy that whereas addition of *p*-benzoquinone augments yields, the ratio of regioisomers is essentially unchanged by the addition of

quinone. This is consistent with hydroxyl radical addition, rather than H-atom abstraction, being product determining. For toluene, only traces of bibenzyl are generated, indicating that HO$^{\bullet}$ addition to the aromatic ring is kinetically favored over thermodynamically preferred abstraction of hydrogen from the benzylic C–H bond. From the data in Table 3, the regioselectivities favor *ortho*/*para* substitution for toluene and anisole and *meta* substitution for nitrobenzene. These regioselectivities are consistent with hydroxyl radical being electrophilic.[7] Unfortunately, the low yields and modest selectivities have limited the synthetic utility of this route to phenols from aromatic hydrocarbons.

Table 3 Regioselectivities and yields for phenol synthesis from substituted benzenes and HO·generated from **8**[5]



X p-*benzoquinone*	*CH_3*		*OCH_3*		*NO_2*	
	0 M	*0.05 M*	*0 M*	*0.05 M*	*0 M*	*0.05 M*
ortho	71	73	84	80	26	29
meta	9	11	0	2	48	46
para	21	16	16	18	26	25
Yield (%)	8	25	14	51	16	14

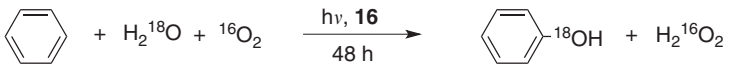
7.14.2 Photocatalytic Oxidations of Aromatic C–H Bonds

There are numerous reports of photocatalytic oxidations of aromatic hydrocarbons and applications which range from waste remediation to synthesis with organic and inorganic catalysts. The authors begin their discussion with the former catalyst class.

In 2004, Fukuzumi and coworkers have reported a reaction where 9-mesityl-10-methylacridinium ion (**10**, Mes–Acr^{+}) serves as a photocatalyst for the oxygenation of anthracene (Schemes 6 and 7).[8] Photoexcitation of **10** generates Mes$^{\bullet+}$–Acr$^{\bullet}$ (**10***), which in turn oxidizes anthracene to its radical cation, **11**, with concomitant formation of Mes–Acr$^{\bullet}$. Molecular oxygen then reacts with Mes–Acr$^{\bullet}$ to reform **10** with generation of $O_2^{\bullet-}$. Superoxide radical anion and **11** then combine to give an intermediate endoperoxide, **12**. For substrates with methyl group substituents, oxidation to aldehydes predominates.[9]

Compound **12** then undergoes rearrangement in a second photocatalytic process mediated by **10** (Scheme 7) to give compound **14**, by way of **13**. In a final photocatalytic process, compound **14** is oxidized to 9,10-anthracenedione, **15**. The net transformation requires four photons of visible light and is summarized in Scheme 7.

More recently, the Fukuzumi group has reported direct oxygenation of benzene to phenol using 3-cyano-1-methylquinolinium ion (QuCN^{+}, **16**) as the photocatalyst as shown in equation 1.[10] The reaction is 98% selective for phenol and proceeds with quantum yields ranging from 16% to 51%. On a preparative, gram-scale reaction a 41% yield of phenol was obtained after 48 h reaction time with a photocatalytic turnover number (TON) of 15. Analogous photocatalytic oxidation of chlorobenzene afforded *para*- and *ortho*-chlorophenol in 31% yield with a *para*:*ortho* ratio of 9:1.

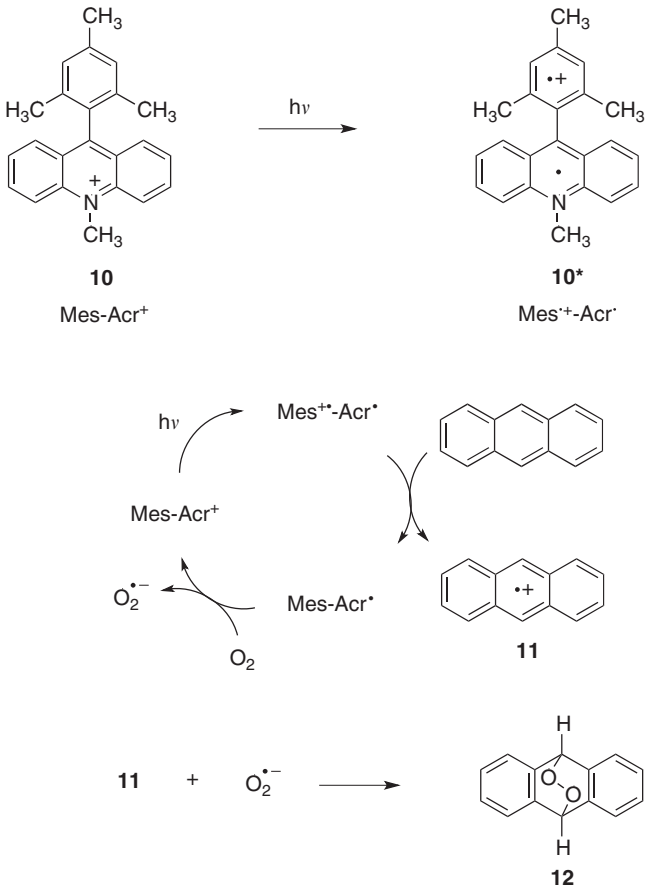


41% yield (1)

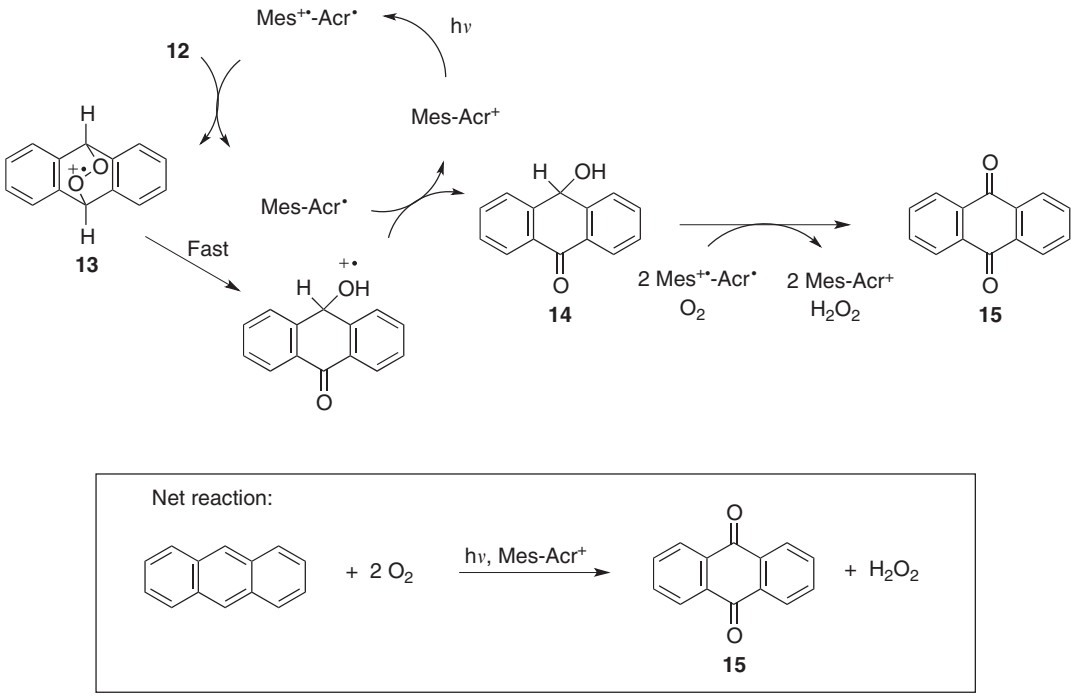
The singlet excited state of **16** is a potent oxidant (E_{red} vs. saturated calomel electrode (SCE) = 2.72 V) that is capable of oxidizing benzene (E_{ox} vs. SCE = −2.32 V). The proposed mechanism for the reaction in equation 1 is depicted in Scheme 8. In the mechanism, benzene reduces QuCN^{+*} to yield QuCN$^{\bullet}$ and benzene radical cation, which reacts with water to form radical **5**. QuCN$^{\bullet}$ reduces O_2 to $O_2^{\bullet-}$ regenerating **16**. Subsequently, $HO_2^{\bullet}$, from protonation of $O_2^{\bullet-}$, abstracts H from **5** to give phenol and H_2O_2.

If alcohols are substituted for H_2O, **16** mediates photocatalytic synthesis of alkylphenyl ethers from benzene.[11] Representative yields are given in Table 4. Other nucleophiles can trap the benzene radical cation. For example, photolysis of methoxybenzenes in the presence of **16** and Br^{-} afford the corresponding aryl bromides in good yields with high *para*-selectivity.[12]

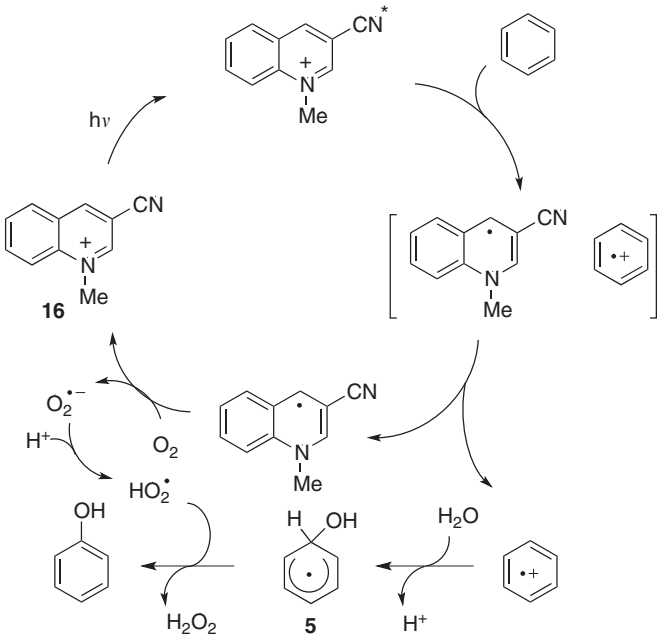
There is an extensive literature for photooxidation of organic compounds catalyzed by metal oxides such as TiO_2, and applications range from chemical synthesis to remediation of wastewater, where the main products of the reactions are carbon dioxide and water.[13] The outcome of these reactions can depend on the nature of the catalyst, the solvent, and presence or absence of O_2. A common feature of all these mechanisms is the absorption of an ultraviolet (UV) or visible photon by the catalyst, which is accompanied by promotion of an electron from the valence band to the conduction band of the metal oxide (Scheme 9). The hole in the conduction band that results can be sufficiently oxidizing to convert aromatic hydrocarbons to their radical cations. Under anaerobic conditions, subsequent attack of water and proton loss generates radical **5**, which can be disproportionate to phenol, aromatic hydrocarbon, and water. The protons that form are reduced by the electron in the conduction band to produce H_2.



Scheme 6

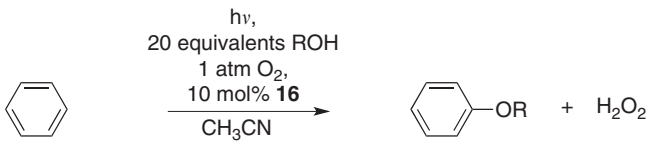


Scheme 7



Scheme 8

Table 4 Conversion and yields for photoalkoxylation of benzene by alcohols catalyzed by **16**[11]



ROH	*Time (h)*	*Conversion (C_6H_6), %*	*Yield (%)*
MeOH	4	63	26
EtOH	2	44	21
^{i}PrOH	2	16	12
^{t}BuOH	1	37	12

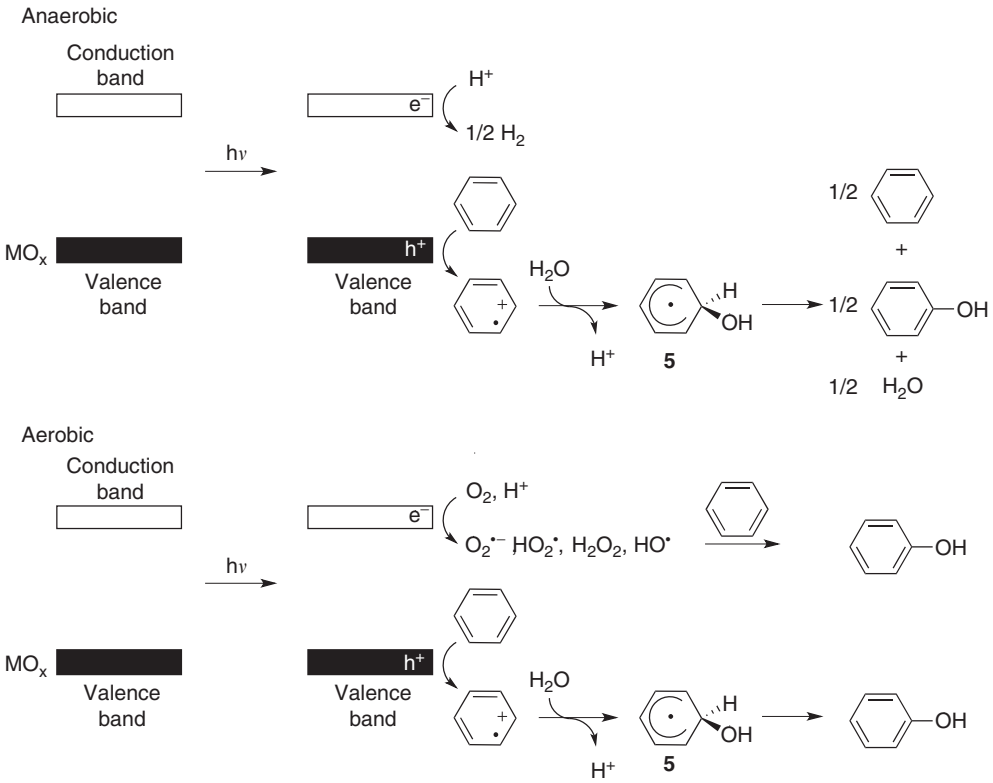
Under aerobic conditions, the electrons that are promoted to the conduction band reduce O_2 to $O_2^{\bullet-}$, which produces other ROS such as H_2O_2 and $HO^{\bullet}$. In particular, $HO^{\bullet}$ can react with arenes to give phenols. Thus, the source of the phenol O can be H_2O or O_2, depending on conditions.[14] For substituted benzenes where regioisomers can result, it is conceivable that regioselectivities of aerobic and anaerobic conditions could be different.

For aerobic, photocatalytic synthesis of phenols from substituted benzenes mediated by TiO_2, product distributions (**Table 5**) are consistent with an electrophilic substitution mechanism.[15] For toluene, benzylic oxidation dominates under aerobic conditions.[16] Isomer distributions for TiO_2 photocatalyzed oxidation of nitrobenzene in **Table 5** are similar to those obtained for additions of $HO^{\bullet}$ (**Table 3**). However, $HO^{\bullet}$ does not yield significant quantities of benzylic oxidation products in its reaction with toluene. Thus, TiO_2 does more than simply produce $HO^{\bullet}$.

To improve catalytic activity, metal oxides are sometimes doped with precious metals. Even so, photocatalytic oxidation of benzene mediated by Pt-doped TiO_2 generates significant quantities of CO_2 under aerobic conditions from overoxidation of the phenol that is produced.[17] Overoxidation can be minimized and selectivity improved by carrying out the photooxidation under aqueous anaerobic conditions.[18] Alternatively, it has been shown that overoxidation is avoided under aerobic conditions when the catalyst is Pt-doped WO_3.[17]

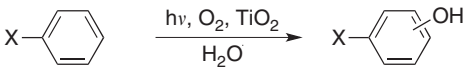
7.14.3 Enzymatic C–H Hydroxylation

Nature has evolved remarkable machinery for functionalizing C–H bonds and enzymatic C–H oxidation has been the subject of several reviews.[19–24] In this section, aromatic hydroxylation will be highlighted even though some of this reactivity falls under the



Scheme 9

Table 5 Regioselectivities for photocatalytic hydroxylation of substituted benzenes mediated by TiO_2[15]



X	*Conversion (%)*	*Phenol yield (%)*	o:m:p
OH	~70	~75	55:1:45
NH_2	~40	~50	50:0:50
$NHCOCH_3$	~50	~60	20:3:77
NO_2	~50	~20	29:34:37
CN	~60	~30	39:21:40

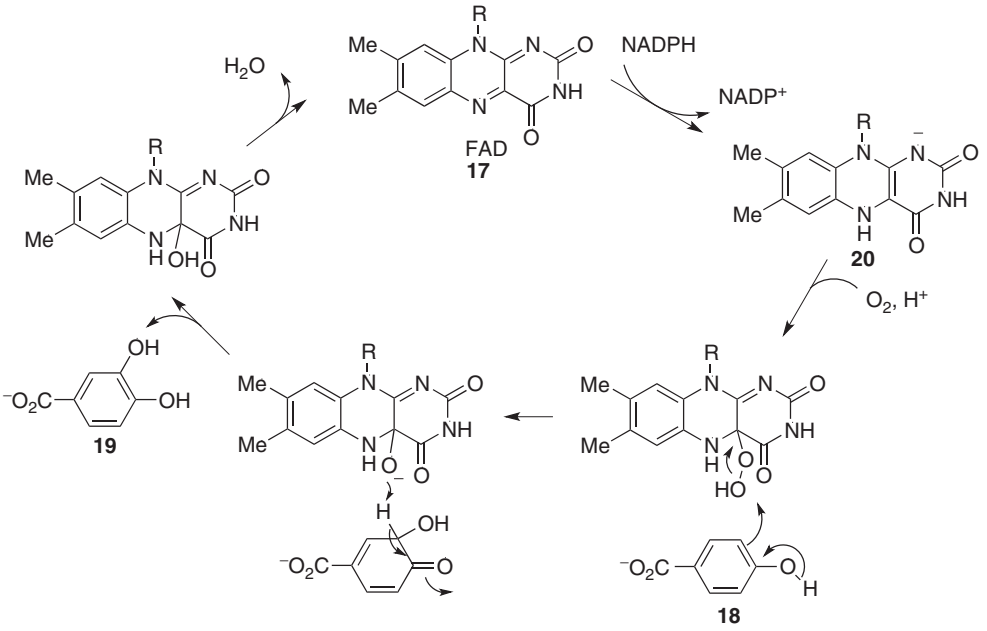
category of directed C–H oxidation. Specific cases where a directing group on the substrate coordination to the metal are not discussed.

The enzymes that mediate C–H oxidation are diverse. For example, flavoprotein monooxygenases operate organocatalytically to activate O_2 for oxidation of *p*-hydroxybenzoic acid and other substrates with electron donating groups. From the metalloenzyme literature a number of heme and nonheme iron proteins and a handful of copper metalloenzymes facilitate oxidations of aromatic C–H bonds.

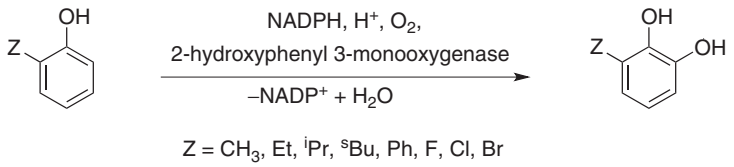
Flavin monooxygenases bind the cofactor flavin–adenine dinucleotide (FAD, **17**) within the protein active site. As a family they carry out a diverse array of biocatalytic oxidations.[25] The hydroxylase members of this family effect substrate specific hydroxylations in their role of metabolizing xenobiotics. The best studied of these hydroxylases is *para*-hydroxybenzoate hydroxylase (PHBH), whose mechanism for hydroxylation of *para*-hydroxybenzoate (**18**) to yield **19** is shown in Scheme 10.[26] PHBH is unusual in that both a reduction (**17** to **20**) and an oxidation (**18** to **19**) are carried out within the active site.

Related enzymes mediate hydroxylation of other substituted phenols, and a recombinant *E. coli* strain that expresses 2-hydroxyphenyl 3-monooxygenase has been engineered to convert 2-substituted phenols into 3-substituted catechols (Scheme 11). [27]

Although flavin monooxygenases require activated, electron-rich substrates for carrying out C–H oxidations, this restriction does not hold for most metalloenzymes, which can be divided into heme and nonheme subclasses. Cytochrome P450 enzymes

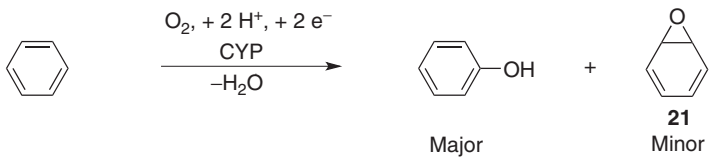


Scheme 10



Scheme 11

(CYPs) are the archetypal members of the heme enzymes. CYP is responsible for the biosynthesis of hormones and detoxification of xenobiotics by metabolizing them oxidatively. In this latter role, CYPs foster the oxidation of aromatic C–H bonds. As shown in equation 2, CYP oxidation of benzene gives phenol as the major product, although traces of benzene oxide have been identified in benzene oxidation by liver microsomes.[28]

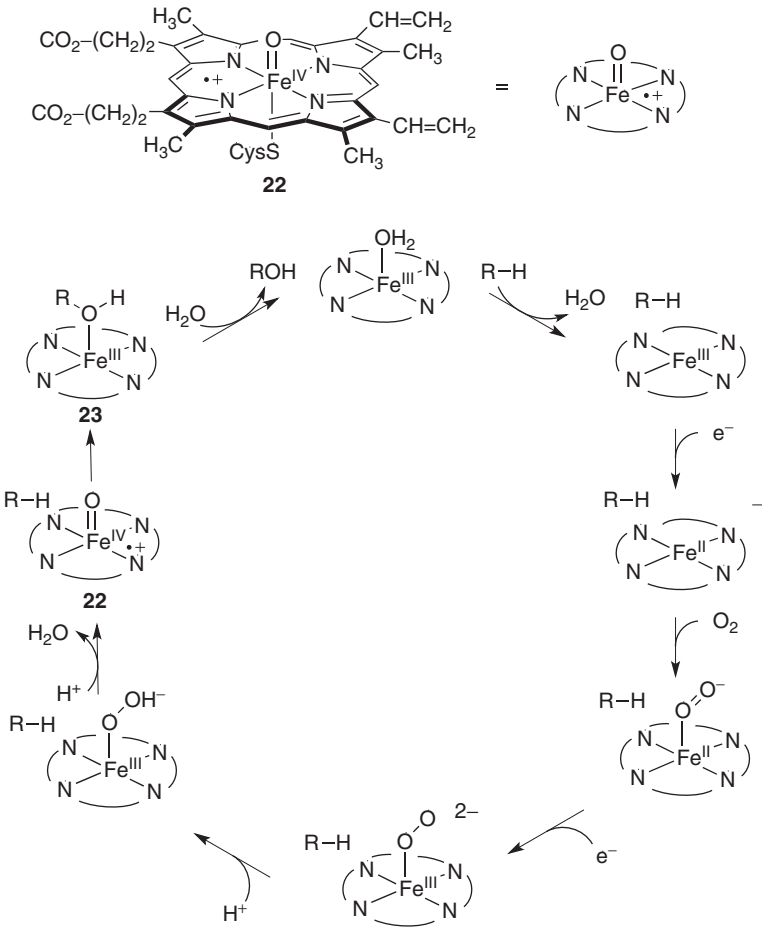


(2)

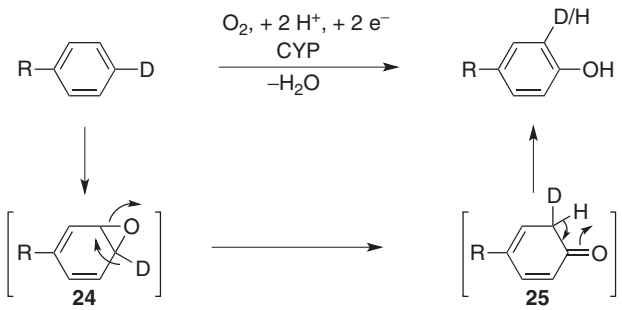
Theory and experiment strongly implicate compound **22** as the key oxidizing intermediate in CYP C–H functionalizations, whose general mechanism is shown in Scheme 12.

The mechanism by which **22** converts to **23** (i.e., the C–H oxidation step) has been the subject of considerable debate. Early observations that oxidation at deuterium labeled sites gave products where C–D bonds were retained led to the proposal that oxidation occurs via intermediate formation of benzene oxides (Schemes 13 and 14) that undergo a 1,2-hydrogen shift (commonly referred to as the NIH shift) to afford enones **25**, which tautomerize to the final product.

Subsequent kinetic studies of isotopically labeled chlorobenzenes revealed secondary kinetic hydrogen isotope effects that are inconsistent with the intermediacy of **24**.[29] More recently, the potential mechanisms of aromatic C–H oxidation have been probed computationally. These studies support the mechanisms in Scheme 14 as the lowest energy pathways. The first step can be viewed as a one- or two-electron reduction of the Fe oxo with formation of an O–C bond from an end-on approach of arene to yield **26a**,[30] or a side-on approach to give **26b**.[31,32] The aromatic π-system in these intermediates can be viewed as a superposition of pentadienyl radical and Meisenheimer intermediates, and the hybridization change from sp^2 to sp^3 at the *ipso* carbon is consistent with inverse hydrogen isotope effects for this position. Calculations indicate that the *ipso* proton in **26a** is then shuttled to the β-carbon via an *N*-protonated porphyrin intermediate **27** to yield the bound dienone **28**, which alternatively can arise from **26b**



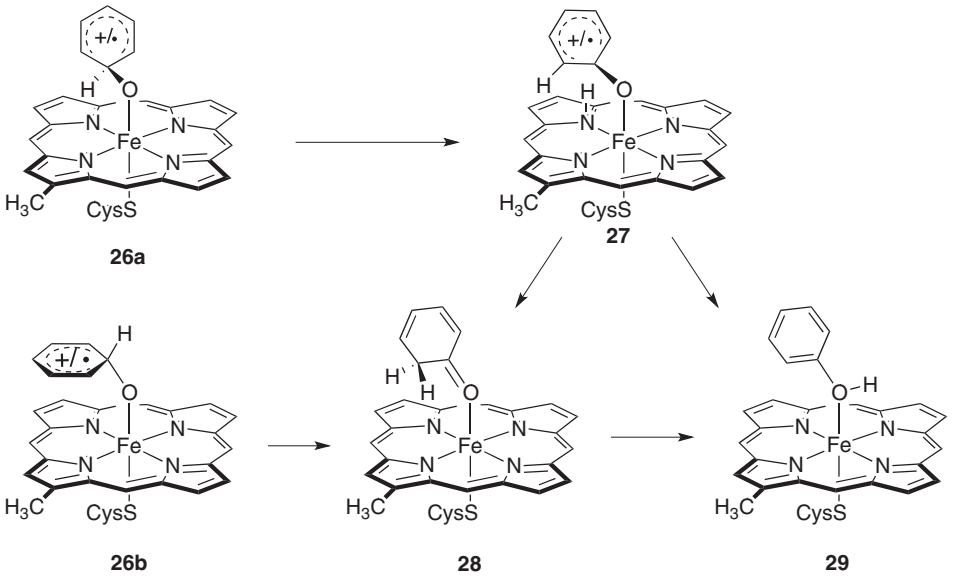
Scheme 12



Scheme 13

undergoing a 1,2-hydrogen shift. Tautomerization of **28** or a proton shift from **27** yields the bound phenol complex **29**. Either pathway may be operative, and it is significant that both account for isotope shifts that are experimentally observed without resorting to a benzene oxide intermediate, which was found to be higher in energy.[30]

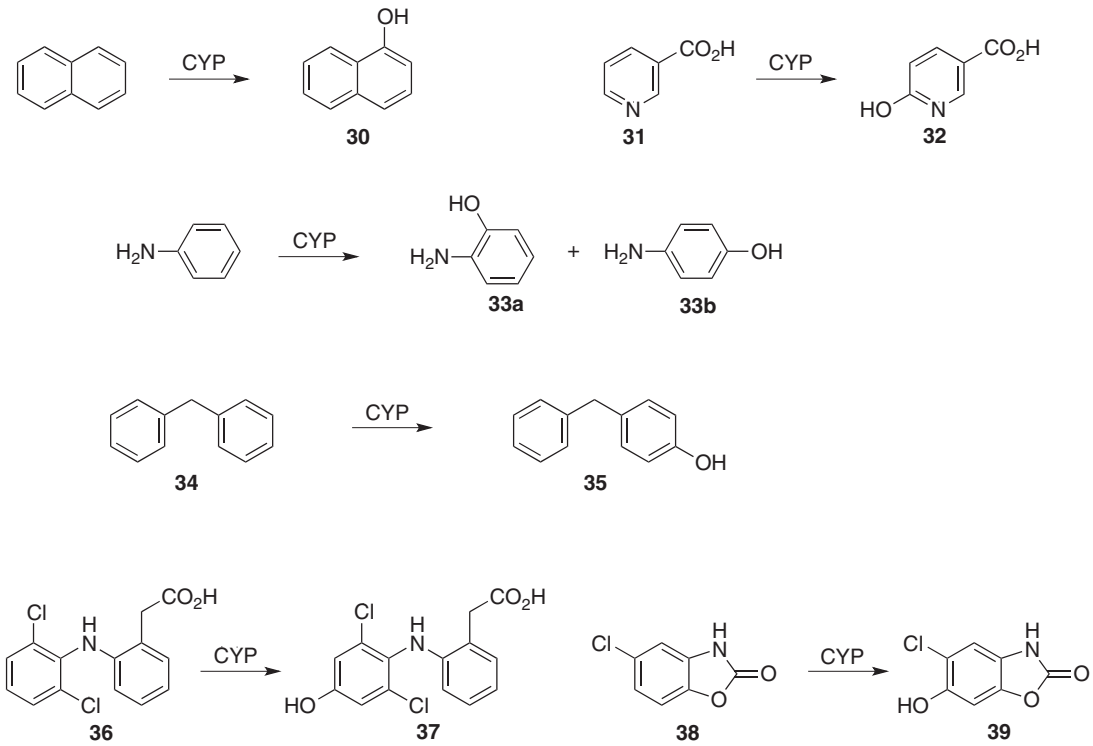
The experimentally determined regioselectivity for the hydroxylation of fluoroanilines have been correlated with frontier orbital densities at the carbon centers in the highest occupied molecular orbitals (HOMOs) of the neutral species and the singly occupied molecular orbitals of the radical cations. Similarly, the energies of the HOMOs of substituted anilines also correlate with rates of metabolism.[33] In both cases, the electronic effects are consistent with electrophilic aromatic substitutions. Interestingly, theory predicts that hydroxylation will be accelerated by electron withdrawing and electron donating groups, and a linear free



Scheme 14

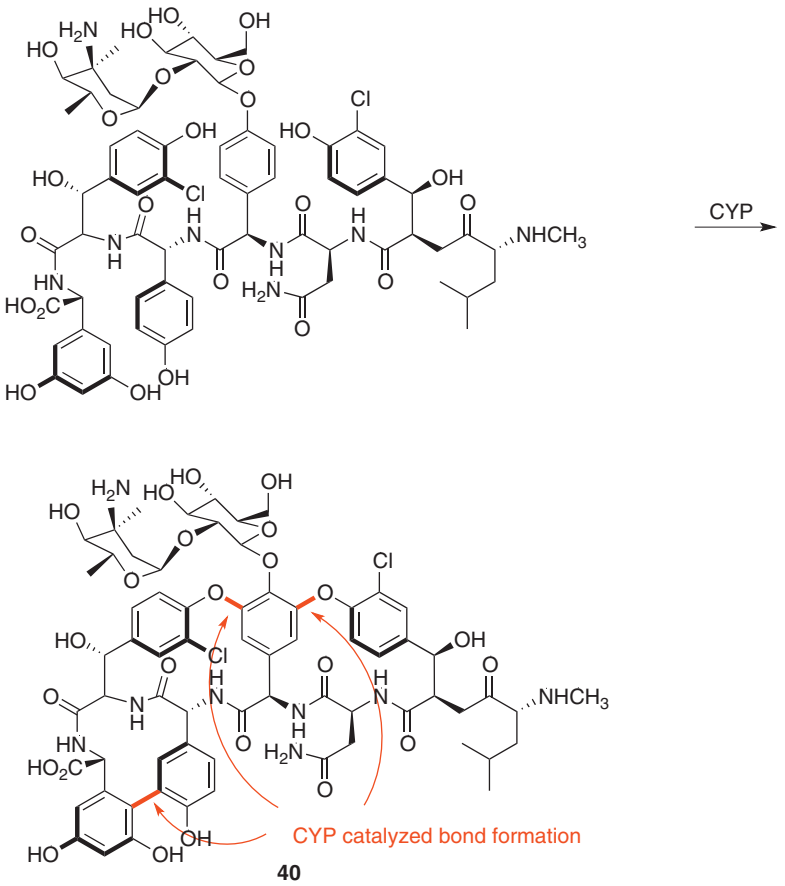
energy relationship was found when calculated activation energies were plotted versus $\sigma_{red} - 0.3\ \sigma^{+}$.[31,32] Although this has not been verified experiment in the real systems, a study of *meta*-chloroperoxybenzoic acid oxidations of substituted benzenes catalyzed by a Fe porphyrin model complex gave rate effects that support this prediction.[34]

There are numerous examples of aromatic hydroxylations catalyzed by CYPs and complete coverage is beyond the scope of this review. Instead, some representative examples are shown in **Scheme 15**. These include (1) hydroxylation of naphthalene, where selectivity between α-(**30**) and β-hydroxylation can be modulated by mutation,[35] (2) hydroxylation of nicotinic acid (**31**) to give **32** selectively,[36] (3) hydroxylation of aniline where *ortho*- and *para*-aminophenol ratios can by CYP dependent,[37] (4) selective hydroxylation of diphenylmethane (**34**) to **35**,[38] and (5) oxidation of the drugs diclofenac (**36**) and chlorzoxazone (**38**) for preparative scale synthesis of metabolites **37** and **39**.[39]



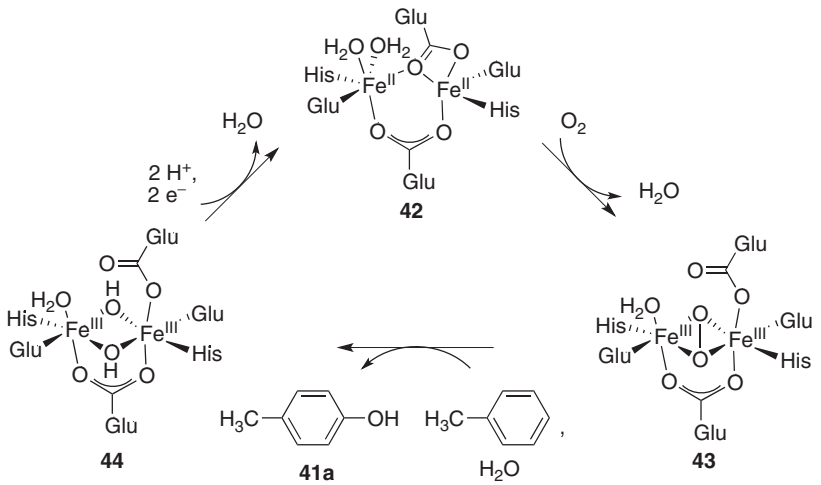
Scheme 15

CYPs can mediate other oxidative activations of C–H bonds such as oxidation C–O and C–C couplings. Both reactions are pivotal in the atroposelective biosynthesis of vancomycin in Scheme 16.[40] Thus, in addition to their better-known function as custodians of biological systems, CYPs have an important role in biosynthesis of complex natural products.



Scheme 16

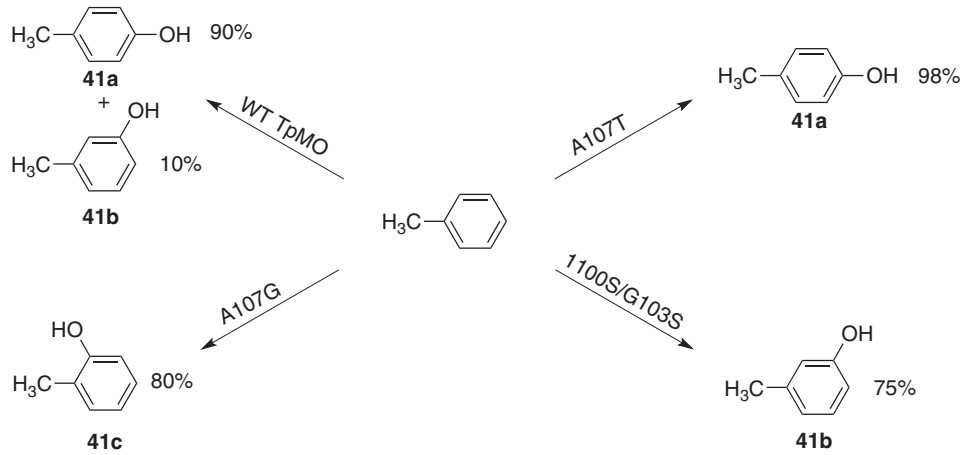
There are important examples of nonheme iron metalloenzymes that catalyze C–H oxidations. For instance, toluene monooxygenases (TMOs) facilitate hydroxylation of toluene with excellent regioselectivity for *para*-cresol (**41a**). The active site of the enzyme houses a diiron center and a simplified mechanism for the catalytic cycle is depicted in Scheme 17.[41] The reduced Fe^{II}–Fe^{II}



Scheme 17

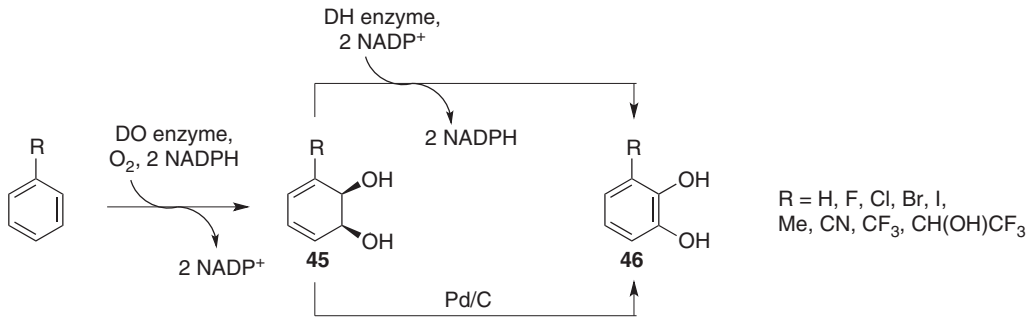
active site (**42**) reacts with O_2 to generate a bridging $Fe^{III}(O_2)Fe^{III}$ peroxo intermediate (**43**) that is believed to mediate hydroxylation of toluene producing **41a** and Fe^{III}–Fe^{III} dihydroxide **44** that is reduced to regenerate **42**.

Wild type enzyme toluene *para*-monooxygenase (WT TpMO) in *Ralstoni pickettii* catalyzes the hydroxylation of toluene to give 90% *para*-cresol and 10% *meta*-cresol. As illustrated in Scheme 18, the *para*-selectivity can be increased to 98% by site-directed mutagenesis (A107T).[42] By making other mutations, enzymes that selectively produce *meta*- (**41b**) and *ortho*-cresol (**41c**) at activities similar to those of the native enzyme have been expressed.



Scheme 18

There are indirect enzymatic routes to *cis*-dihydroxylated compounds, where an aromatic or heteroaromatic substrate is converted to a *cis*-diol **45** by a dioxygenase enzyme (DO). The resulting diol is then oxidized by a dehydrogenase (DH) to give the dihydroxylated product. Catechols **46** can be synthesized enzymatically using DO and DH enzymes or chemoenzymatically using a DO enzyme to produce diols followed by Pd/C dehydrogenation.[43] These pathways are shown in Scheme 19.



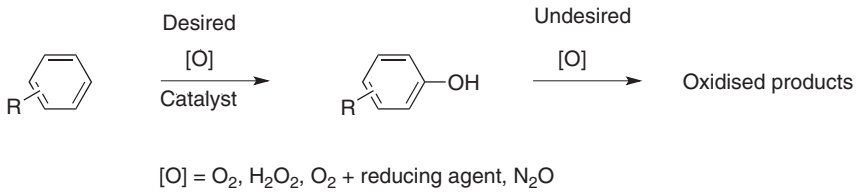
Scheme 19

Enzymatic oxidations of aromatic C–H bonds have tremendous potential for applications in synthesis. However, the number of cases where multigram quantities of products are produced in high yield are few. A recent review outlines some of the challenges that as yet limit applications of CYPs as biocatalysts and some of these pertain to the class of metal oxidases as a whole.[44]

7.14.4 Heterogeneous Catalysts for Arene Oxidation

Given phenol's importance as a commodity chemical and the inefficiencies of the direct synthesis in Scheme 1, the direct oxidative synthesis from benzene and oxygen has been considered one of the top 10 challenges for catalysis. Consequently, considerable effort has been invested in developing heterogeneous catalysts for this process and the subject has been reviewed.[45]

The generic catalytic reaction in Scheme 20 has been the focus of numerous studies with the most popular oxidants being O_2, O_2 combined with a reducing agent, H_2O_2, and N_2O. For practical synthesis on industrial scale, the reaction rates and selectivities must be high. The issue of selectivity is compounded by the fact that the phenol products are often more reactive than the aromatic



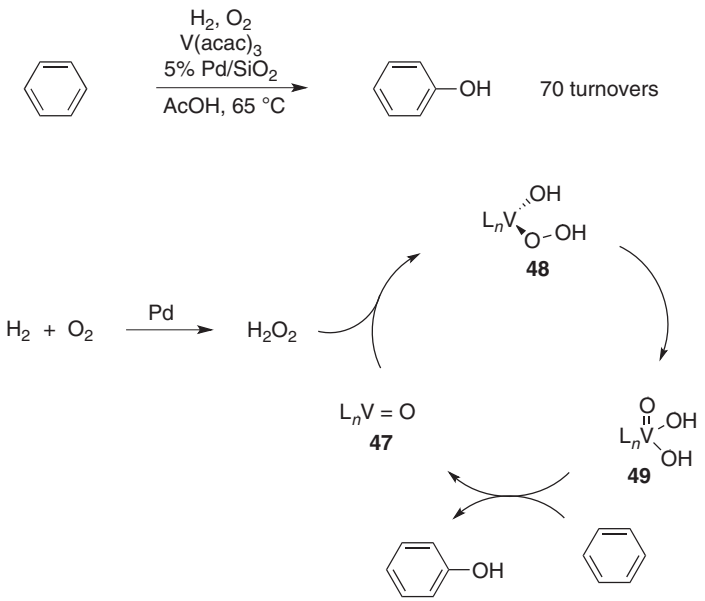
Scheme 20

feedstocks. Hence, overoxidation and other unwanted side reactions can be problematic. In addition, substituted benzenes add regioselectivity and chemoselectivity to the equation. To simplify the discussion, chemistry of benzene will be presented first, followed by reactivity of substituted arenes.

Early studies of direct reactions of metal oxide catalysts and benzene showed low conversions and poor selectivities. For example catalysts where Cu is supported on Zeolite Socony Mobil-5 (ZSM-5) produced phenol in 1.5% yield.[46] Later studies showed that phenol yield could be increased to 4% when mixtures of Ti and Cu were supported on ZSM-5; however, catalytic conversion peaked after 80 min.[47] Similar results have been obtained for V–Mo–O/SiO_2 catalysts.[48] These limited successes testify to the challenge that direct conversion of benzene and O_2 to phenol presents.

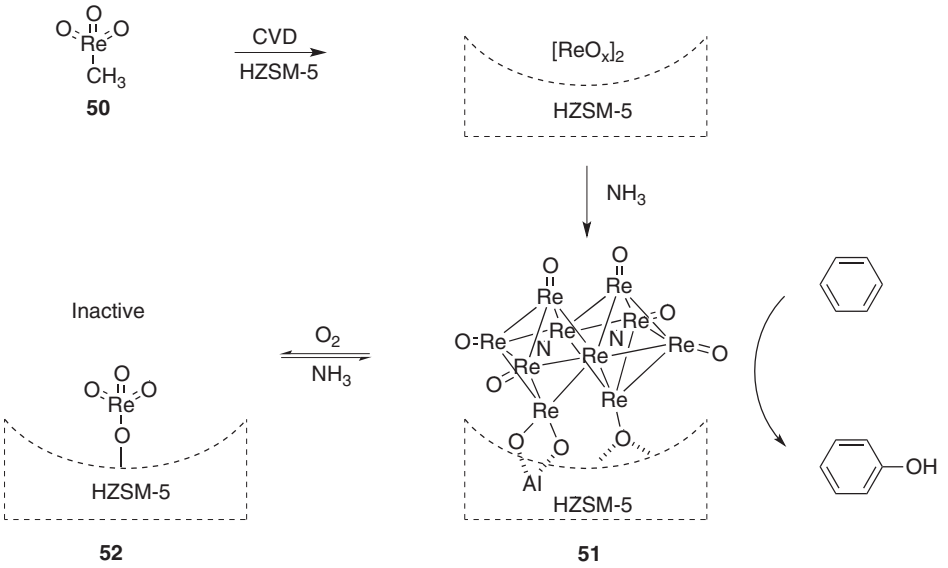
Nitrous oxide has been explored as an oxidant for conversions of arenes to phenols. It differs from O_2 in that it has a singlet ground state and produces N_2 as a byproduct of O atom transfer. Although it is a thermodynamically potent oxidant, it is kinetically inert. An early study shows the ZSM-5 type zeolites could catalyze benzene oxidation by N_2O with conversions of phenol as high as 27% with 98% selectivity of phenol were obtained.[49] There has been debate over whether the oxidation occurs at Al/Bronsted acidic sites or is mediated by Fe impurities present in commercial zeolites. A careful examination of Fe versus Al participation indicates that Fe is essential to catalytic activity.[50] Although experimental evidence for the mechanism is limited, a recent density functional theory study favors N_2O activation by Fe^{2+} sites with benzene oxidation occurring at $[FeO]2^+$ (formally Fe^{IV}) moieties that are generated.[51] In terms of selectivity and conversion, oxidations by N_2O are superior to those with O_2.

The performance of benzene hydroxylation by O_2 can be enhanced by addition of reducing agents such as H_2 or NH_3. A bimetallic system involving homogeneous V sources and Pd/Al_2O_3 has been shown to catalyze benzene hydroxylation under relatively mild conditions.[52] In the proposed mechanism (Scheme 21), Pd serves to catalyze the *in situ* generation of hydrogen peroxide. The H_2O_2 then reacts with a vanadium oxo species (**47**) to generate intermediate **48**, which in turn leads to a high-valent vanadium oxo (**49**) that oxidizes benzene to phenol. Although it is not known with certainty whether the V species are homogeneous or bound to the Al_2O_3 support, V is required as only traces of phenol are produced when V is absent. When 4-d_1-toluene is used as the substrate, the *para*-cresol that results retains 90% of the deuterium label. The fact that cyclopropane ring open products dominate for reactions of cyclopropylbenzene suggest that radical intermediates similar to **26a** (Scheme 14) may be involved.



Scheme 21

The synthesis of phenol from benzene in streams of O_2/NH_3 at 280 °C can be catalyzed by Re oxides supported on HZSM-5.[53] Selectivities for phenol as high as 88% have been obtained with no loss in catalytic activity after 6 h. The catalyst is prepared by chemical vapor deposition (CVD) of methyltrioxorhenium (**50**, Scheme 22) on HZSM-5. The initially formed supported Re oxide is catalytically inactive when NH_3 is absent. Treatment of the oxide with NH_3 gives a new material that is catalytically active in the absence of NH_3, although activity diminishes for C_6H_6/O_2 streams over time. Based on extended X-ray absorption fine structure spectroscopy (EXAFS) data and computational modeling, a Re_{10} oxo cluster with interstitial nitrogens (**51**) is proposed to be the active catalyst. If NH_3 is absent, these clusters disassemble during the course of oxidation to form mononuclear species **52**, which is inactive. In the presence of NH_3, the catalyst heals reforming **51**.



Scheme 22

Another intriguing heterogeneous system utilizes a Pd membrane to catalyze the oxidation of benzene to phenol using O_2 and H_2 as the oxidizing and reducing reagents.[54] In the reactor, represented in Scheme 23, the O_2 and H_2 gases are separated by the Pd membrane with benzene on the O_2 side and H_2 on the other side. It is believed that H_2 chemisorbs on the Pd and the H atoms diffuse through the membrane where chemisorbed oxygen atoms can react with them to generate water. The other option for the surface bound O atoms is to react with benzene to produce phenol. The individual steps have in Scheme 23 been computationally evaluated as being feasible.[55]

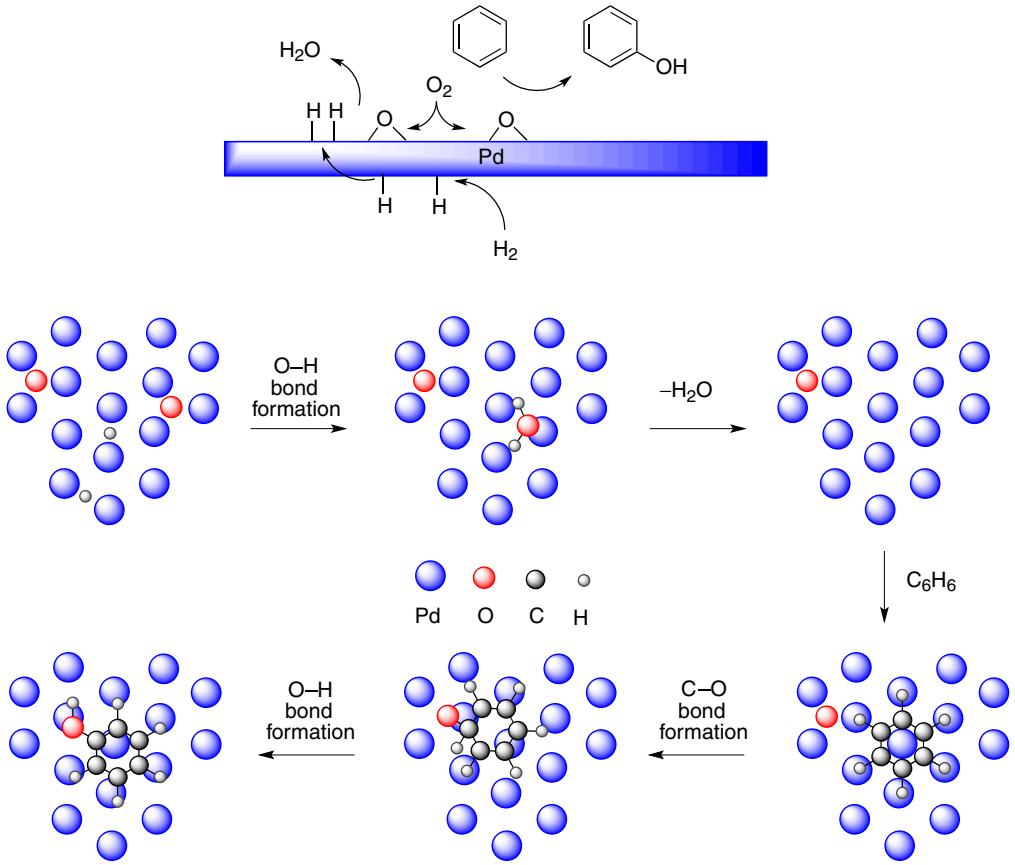
Most examples for direct synthesis of phenol with heterogeneous catalysts utilize H_2O_2 as the oxidant. Because this area has been reviewed, discussion here will be brief. Typical catalysts are V or Ti on solid supports ranging from zeolites to mesoporous silica[56] to carbon nitride.[57] A recent example of a V Schiff's base ligand complex grafted to periodic mesoporous organosilica is reported to give 100% selectivity for phenol at benzene conversions of 27%.[58] The catalyst can be recycled with minimal loss in activity. It is conceivable that commercially viable catalysts could emerge if the efficiency based on H_2O_2 (~9%) can be increased.

Given the number of hydroxylations of benzene there the literature of heterogeneous C–H oxidation of aromatic C–H bonds of substituted benzenes is remarkably barren. Oxidations of toluene by H_2O_2 catalyzed by Ti and V metallosilicate molecular sieves (TS-2 and VS-2, respectively) give the product distributions shown in Scheme 24.[59] In both cases the conversions are low. For the Ti catalyst (TS-2) ring hydroxylation dominates, yielding *ortho*- and *para*-cresol. The regioselectivity is consistent with an electrophilic peroxide attack on the aromatic ring. For the V catalyst, benzylic oxidation is significant, generating benzaldehyde as the major product. Benzylic oxidation is also the favored pathway for Ti, V, and Cr supported on Mobil composition of matter-41.[60]

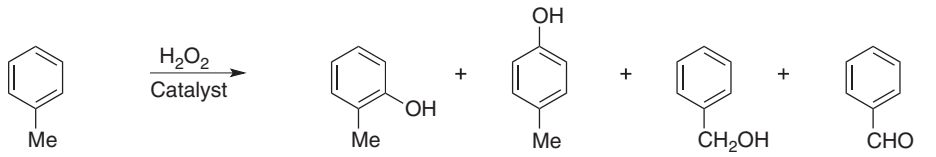
The oxidation of substituted benzenes with N_2O catalyzed by ZSM-5 has been examined at elevated temperatures and the results are given in Table 6.[61] Conversions range from low to moderate and selectivities for phenols exceed 50% for halobenzenes and benzonitrile. The mechanism is not known; however, the commercial zeolites used had an Fe/Al ratio of 0.02:1. The diminished reactivity of electron-deficient arenes would be consistent with catalysis by electron deficient, high-valent Fe oxo species.

7.14.5 Oxidation of Aromatic C–H Bonds by Homogeneous Catalysts

Aromatic C–H oxidation by homogenous catalysts has been studied extensively. One of the earliest compounds to oxidize aromatic C–H bonds is Fenton's reagent, which generally refers to an aqueous solution of an Fe salt and hydrogen peroxide. The



Scheme 23



Catalyst	% Conversion	% Products			
TS-2	13.2	36	59	–	–
VS-2	11.7	20	17	8	52

Scheme 24

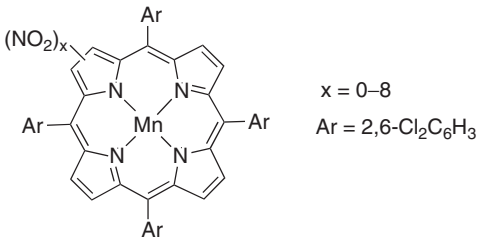
Table 6 Oxidation of substituted benzenes to phenols with N_2O catalyzed by ZSM-5[61]

Arene	*Temperature (°C)*	*Conversion (%)*	*Selectivity (%)*	*Isomer distribution (%)*		
				ortho	*meta*	*para*
Anisole	350	53	~1	~25	~25	~50
Aniline	500	13	29	65	2	33
Toluene	350	24	27	52	35	16
Chlorobenzene	350	23	58	28	72	–
Fluorobenzene	350	19	68	32	19	49
Nitrobenzene	350	5	0	–	–	–
Benzonitrile	350	12	76	64	26	11

mechanism(s) responsible for oxidations of C–H bonds by Fenton's reagent have been, and continue to be, the subject of considerable debate. A number of oxidizing species have been proposed, ranging from free hydroxyl radical to high-valent Fe=O intermediates.[62] It has been suggested that similar regioselectivities in the formation of substituted phenols from $HO^{\bullet}$ (Table 3) and oxidations with Fenton's reagent point to a common mechanism. However, there is considerable variance in reported regioselectivities for hydroxylations of substituted benzenes with Fenton's reagent. For example, the *ortho*-, *meta*-, and *para*-isomer distribution for cresols in an initial report was 71%, 5%, and 24%,[63] respectively, which is similar to the ratio produced from $HO^{\bullet}$ in Table 3. However, a report from the same group some years later gave the *ortho*-, *meta*-, and *para*-isomer distribution as 55.5%, 15%, and 29.5%.[64] Conversion to cresol in the first report was extremely low, calling the initial values, and the correlation to $HO^{\bullet}$ reactivity, to question. Depending on reaction conditions (pH, addition rates, presence of additives, etc.), yields vary to such an extent that the synthetic utility of Fenton's reagent for aromatic C–H oxidation is limited.

For inspiration in the design of catalysts for aromatic C–H oxidations, chemists have turned to nature.[65] For example, metalloporphyrin catalyst systems have been designed to mimic CYPs and applications have been made to catalytic expoxidations and C–H oxidations. Most of the C–H oxidation work has focused on sp^3-hybridized C–H bonds; however, examples of aromatic C–H oxidations have been reported. For example, Mn β-polynitroporphyrins complexes **53** catalyze hydroxylations of anisole, naphthalene, and ethylbenzene.[66] Yields and selectivities for these substrates are given in Table 7. The yields are based on H_2O_2 and it should be noted the aromatic substrate was held in excess. Yields increase with NO_2 substitution up to $x=4$ and then drop precipitously for $x=5$–8. Regioselectivities are consistent with oxidation by an electrophilic Mn–O intermediate with anisole favoring *para*-hydroxylation and naphthalene giving α-hydroxylation predominately. The ethylbenzene results show that benzylic C–H oxidation prevails, which is commonly found in metalloporphyrin catalyzed oxidations.

Table 7 Hydroxylation of aromatic compounds with H_2O_2 catalyzed by Mn β-polynitroporphyrins and ammonium mandelate[66]



53

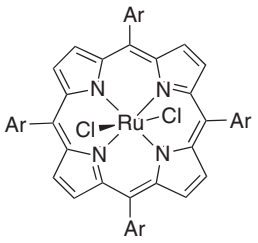
Number of catalyst NO_2 groups	*Anisole*			*Naphthalene*			*Ethylbenzene*			
	p-*OH*	o-*OH*	*Total yield (%)*	α-*OH*	β-*OH*	*Total yield (%)*	*PhCHOH–CH_3*	*PhCOCH_3*	p-*OH*+o-*OH*	*Aromatic selectivity (%)*
0	67	6	73	62	5	67	20	22	<2	<5
1	90	7	97	72	7	79	23	15	3	8
2	88	2	96	75	8	83	27	15	3	7
3	88	10	98	61	8	69	21	14	9	26
4	71	8	79	43	6	49	26	15	12	29
5	32	5	37	39	5	44	22	5	10	37
6	7	1	8	20	3	23	7	12	<2	–
7	5	<1	5	18	3	21	4	24	<2	–
8	<1	<1	<2	1	<1	1	1	5	<2	–

Reaction conditions: Mn–porphyrin:H_2O_2:cocatalyst ratio=1:50:20, [Mn–porphyrin]=2 mmol l^{-1} in CH_2Cl_2–CH_3CN (1:1), 2 h at 20 °C in the presence of substrate in excess; substrate/catalyst=3000, 1600, and 500 for anisole, ethylbenzene, and naphthalene, respectively. Yields (%) are based on H_2O_2.

Ru porphyrin complexes catalyze oxidations of a wide range of C–H bonds and sp^2-C–H oxidations have been reported. Precatalyst **54** mediates the oxidations of alkoxybenzenes and polycyclic aromatics with pyridine-*N*-oxide **55** to afford quinone products.[67] Representative examples populate Table 8. For alkoxybenzenes such as **60**, O–C_{alkyl} cleavage *en route* to quinone is common. It is noteworthy that benzylic C–H bonds in **62**, where oxidation of the unsubstituted aromatic ring is favored, survive in products **63a** and **63b**. The TONs for these reactions are higher than those found in Mn–porphyrin catalyzed oxidations.

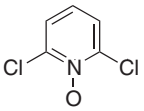
More recently, Ru and Fe catalysts where the metals are likely bound by pyridine-2,6-dicarboxylic acid (H_2pydic) and terpyridine (Ru) or benylamine (Fe) have been described.[68,69] These catalyze similar oxidations of arenes by hydrogen peroxide to quinones. Although catalysts loadings are higher than those in Table 8, the metal ligands are simple and much more readily available than the halogenated porphyrin in **54**. Even at relatively higher catalysts loadings in Scheme 24 the ability to catalyze the reaction with Fe as opposed to Ru may make the Fe-catalyzed process more economically viable. Perhaps more significantly, the

Table 8 Aromatic oxidations to quinones catalyzed by a Ru porphyrin complex[68]

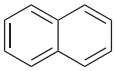
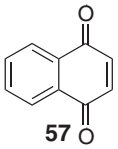
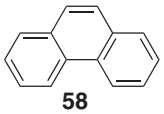
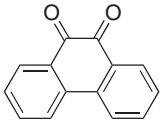
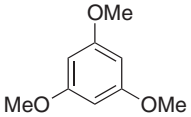
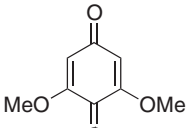
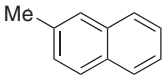
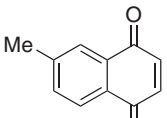
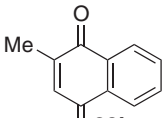


54

Ar = 2,6-$Cl_2C_6H_3$



55

Substrate	*Product*	*Time (h)*	*Conversion (%)*	*Yield (%)*	*TON*
 **56**	 **57**	12	40	99	400
 **58**	 **59**	12	58	99	570
 **60**	 **61**	6	99	99	980
 **62**	 **63a**  **63b**	12	80	87 **a**:**b** 6.7:1	800

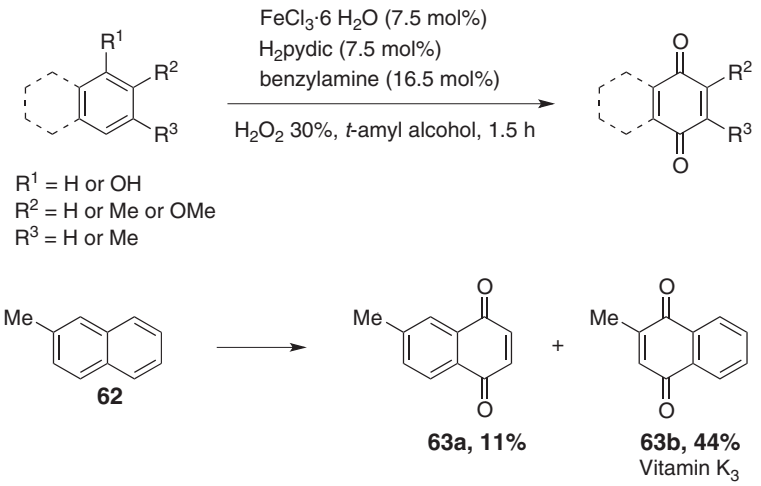
Reaction conditions: CH_2Cl_2, 40 °C. Yields based on converted substrate.

oxidation of **62** catalyzed by Fe favors oxidation of the more substituted ring to give **63b**, which is vitamin K_3, in contrast to the reaction catalyzed by **54**, which favors **63a** (Scheme 25).

Multidentate nitrogen-containing chelate ligands have been designed in attempts to mimic the chemistry of Rieske dioxygenases and diiron monooxygenases. Mononuclear Fe complexes ligated by **64–66** have been examined for catalytic hydroxylations of anisole and toluene, and yields of products are given in Table 9.[70] The best yields were obtained for (**64**)$Fe(ClO_4)_2$ which afforded hydroxyanisole and cresol products in 43% and 17%, respectively, corresponding to TONs of 8.6 and 3.4. Catalyst (**64**)$Fe(ClO_4)_2$ gave essentially equivalent amounts of *ortho*- and *para*-substituted isomers. Compared to many other catalytic systems, (**64**)$Fe(ClO_4)_2$ showed good selectivity for aromatic versus benzylic oxidation for toluene. The catalyst supported by pentadentate ligand **65** gave lower yields of oxidation products; however, higher selectivity for *ortho* hydroxylation of anisole was found. This indicates that regioselectivities can be modulated by varying ligands, which separates this chemistry from for hydroxylations with Fenton's reagent. Yields for aryl hydroxylation of toluene by (**65**)$FeCl(PF_6)$ dropped significantly and benzylic oxidation occurs preferentially with this ligand. For the tetradentate ligand **66**, the conversions were considerably lower. This has been confirmed in a recent study of (**66**)$Fe(NCCH_3)_2^{2+}$, which gave 1–2 turnovers in catalytic reactions.[71]

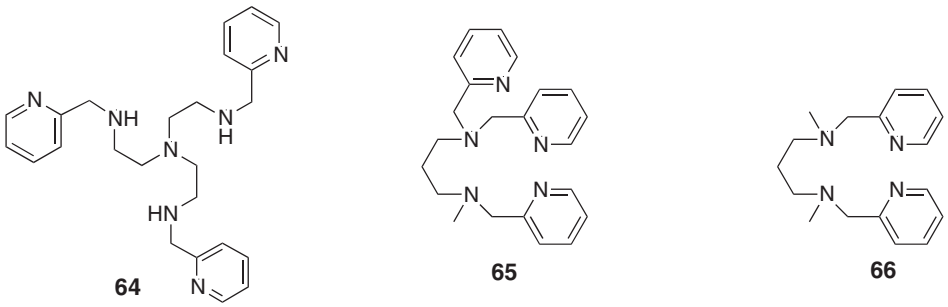
A copper-catalyzed 'oxygenase-type' oxidation of C–H bonds for electron-deficient arenes at room temperature using O_2 as the oxidant has recently been described.[72] Electron-deficient arenes smoothly underwent C–H oxidation in the presence of 5 mol% $CuCl_2$ and sodium *tert*-butoxide in dimethylformamide (DMF) to give the corresponding hydroxylated arenes in good yields (Scheme 26).

The proposed catalytic cycle is depicted in Scheme 27. Initially, $CuCl_2$ is reduced to CuCl by NaO*t*-Bu, which reacts with NaO^tBu to form the active copper species CuO*t*-Bu (**70**). The ArCuI intermediate **71** is generated by a formal metathesis of **70** with arene, and oxidation of **71** by oxygen generates bis(μ-oxo)dicopper^{III}–complex (**72**). Importantly, according to the report by Tolman and coworkers a bis(μ-oxo)dicopper core is efficient to hydroxylate an arene by intramolecular direct oxidative C–H bond



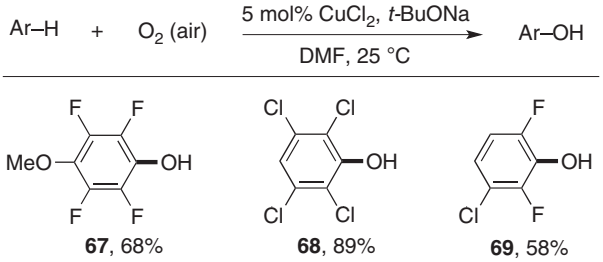
Scheme 25

Table 9 Hydroxylations of anisole and toluene with H_2O_2 catalyzed by Fe complexes of ligands **64–66**[70]



Catalyst	*Yield (%)*							
	Anisole			*Toluene*				
	o-*OH*	p-*OH*	*PhOH*	o-*OH*	m-*OH*	p-*OH*	*PhCH₂OH*	*PhCHO*
(**64**)$Fe(ClO_4)_2$	26	27	3	8	2	7	0.5	1
(**65**)$FeCl(PF_6)$	23	7	3	3	1.5	1.5	3	5
(**66**)$FeCl_2$	2	2	1	2.5	1	1.5	0.5	0.6

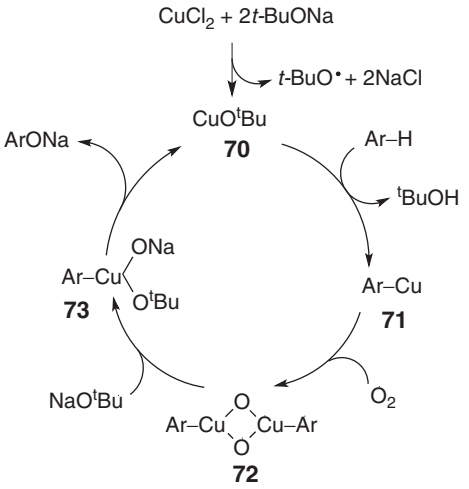
Reaction conditions: Catalyst:H_2O_2:substrate ratio = 1:20:3000, [Mn–porphyrin] = 2 mmol l^{-1} in CH_3CN/H_2O (9:1), 2 h at 20 °C. Yield (%) is based on H_2O_2.



Scheme 26

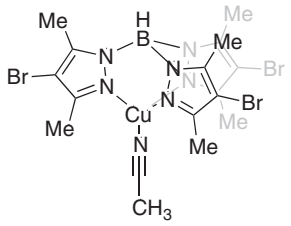
functionalization. Nucleophilic attack of NaO*t*-Bu at the Cu^{III} complex (**III**) break the $[Cu_2(\mu\text{-}O)_2]^{2+}$ core, giving intermediate (**73**), which undergoes reductive elimination to produce ArONa. Finally, the aqueous work-up provides ArOH from ArONa. In terms of substrate scope, this chemistry is limited to electron-deficient arenes.

Recently, researchers have stepped beyond the confines of biomimetic systems to devise promising catalysts for C–H oxidation. For example, Cu trispyrazolylborate complex **74** emerged from a panel of Cu trispyrazolylborate compounds as an effective

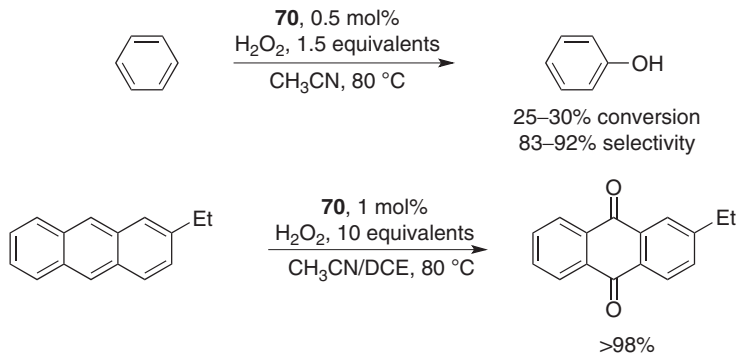


Scheme 27

catalyst for hydroxylation of benzene to phenol using H_2O_2 under nonacidic conditions (Scheme 28).[73] Selectivity can be compromised by overoxidation to benzoquinone; however, it was found that this side reaction could be suppressed by adding sulfolane to the reaction mixture. Significantly, benzylic C–H oxidation does not compete with arene C–H hydroxylation. Thus, 2-ethylanthracene can be oxidized to afford excellent yields of 2-ethyl-9,10-anthroquinone.



74



Scheme 28

Polyoxometalates (POMs) containing a broad range of transition metals have been utilized as catalysts for aromatic hydroxylation. As is the case with other metal catalysts, oxidations of substituted benzenes typically give mixtures of *ortho*-, *meta*-, and *para*-isomers and benzylic C–H bonds are prone to oxidation.[74] A new POM ($[\gamma\text{-}H_2PV_2W_{10}O_{40}]^{3-}$, **75**, Figure 1) has recently been described. It possesses two adjacent V atoms in the POM structure. Compound **75** has been shown to oxidize secondary C–H bonds in the presence of tertiary ones and primary C–H bonds in the presence of secondary bonds.[74] Compound **75** also catalyzes hydroxylations of substituted arenes with H_2O_2, exhibiting remarkable selectivity.[75]

Some representative hydroxylation examples are listed in Table 10. The reactions were carried out at 60 °C for 1 h. The conversions relative to arene are low, but the oxidations are reasonably efficient in their usage of H_2O_2. In general, oxidation at that *para* position is observed for monosubstituted benzenes. In OMe substituted cases, regioselectivity is electronically dictated,

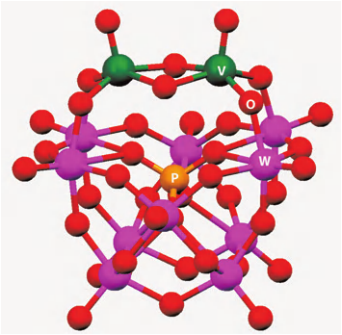
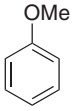
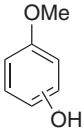
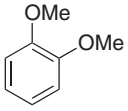
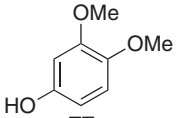
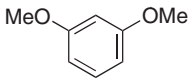
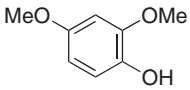
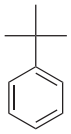
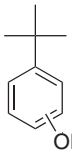
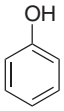
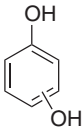
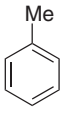
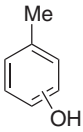


Figure 1 X-ray crystal structure of $[\gamma\text{-}H_2PV_2W_{10}O_{40}]^{3-}$, **75**. Colors of representative atoms are as follows: V, green; W, magenta; O, red; and P, orange. H atoms were not located and NEt_4 counterions are omitted for clarity.

best evidenced by conversion of **78** to **79**. Compound **75** is highly selective for aromatic hydroxylation with good selectivity for oxidation of phenol to catechols, as opposed to benzoquinones, and toluene to cresols with minimal benzylic oxidation.

Table 10 Hydroxylation of arenes with H_2O_2 catalyzed by **75**[75,76]

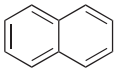
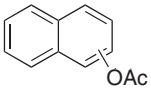
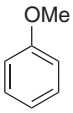
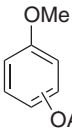
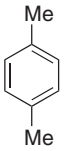
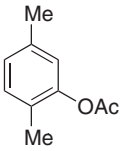
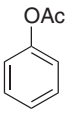
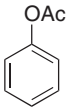
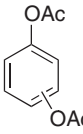
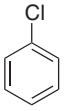
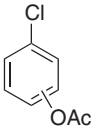
Substrate	*Yield (%, based on substrate)*	*Yield (%, based on H_2O_2)*	*Product*	*Selectivity (%)*
	2	85		>99 *o*/*m*/*p*=5:<1:95
 **76**	5	50	 **77**	>99
 **78**	8	80	 **79**	>99
	1	56		99*o*/*m*/*p*=<1:25:74
	2	86		85*o*/*m*/*p*=5:<1:95
	1	60		86*o*/*m*/*p*=7:16:77 ring/benzylic=98:2

Reaction conditions: $TBA_4[\gamma\text{-}HPW_{10}V_2O_{40}]$ (2.5 mmol), $HClO_4$ (2.5 mmol), substrate (5 mmol), $CH_3CN/^tBuOH$ (1:1, 2 ml), aqueous H_2O_2 (30%, 0.1 mmol), 333 K, 60 min, under Ar (1 atm).

7.14.6 Metal Catalyzed C–H Acetoxylation

In 1996, the acetoxylation of arenes was reported with $PhI(OAc)_2$ as the terminal oxidant.[76] The reactions were carried with 0.5 mol% loadings of $Pd(OAc)_2$ as the catalyst. Representative examples are shown in Table 11. Regioselectivities varied with substituent with *ortho* and *para* isomers being favored for benzenes with electron-donating substituents. Less electron-rich

Table 11 Pd-catalyzed acetoxylation of aromatic substrates[77]

Substrate	*Yield (% based on PhI(OAc)$_2$)*	*Product*	*Selectivity (%)*
	61		∈±:∈″ = 57:43
	40		*o*:*m*:*p* = 44:5:51
	43		1% *p*-methylbenzyl acetate 1.2% *p*-methybenzaldehyde
	39		0.8% biphenyl 2.8% X–C_6H_4OAc X = I, OAc
	15		*o*:*m*:*p* = 42:25:33
	14		*o*:*m*:*p* = 41:29:30

Reaction conditions: Arene 2 ml, AcOH 2 ml, $Pd(OAc)_2$ 22 μmol, $PhI(OAc)_2$ 4.47.

substrates gave significant quantities of *meta*-functionalized products. It was proposed that the mechanism utilized a Pd^{II}/Pd^{IV} cycle with the product being formed by reductive elimination from a $Pd^{IV}(Ar)(OAc)$ intermediate.

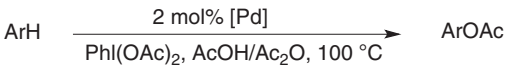
It has recently been shown that the activity of $Pd(OAc)_2$ catalysts can be improved by addition of pyridine.[77] This makes it possible to functionalize electron-deficient substrates that are recalcitrant in reactions catalyzed by $Pd(OAc)_2$ alone. Data for several monosubstituted benzenes are shown in **Table 12**. The optimum conversion was found when Pd:pyridine was approximately 1:1. For monosubstituted benzenes, reactions gave *ortho*-, *meta*-, and *para*-isomers. It was found that the terminal oxidant could affect both yields and isomer ratios. $MesI(OAc)_2$ gave improved yields for some substrates in **Table 12**. In acetoxylations of 1,2-dichlorobenzene, $MesI(OAc)_2$ showed a preference for acetoxylation at the less-hindered 4-position.

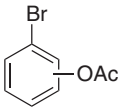
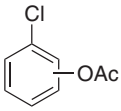
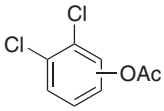
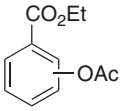
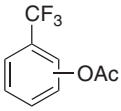
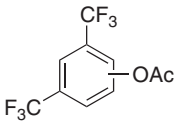
Gold catalysts have also been employed in acetoxylations. It has been shown that a variety of nonactivated hindered aromatic rings could be acetoxylated and acyloxylated in the presence of PPh_3AuCl catalyst and di(acetoxy)iodobenzene as the oxidant.[78] The reaction proceeds at 110 °C in an acid media, which allows the formation of both hindered acetoxylated and acyloxylated compounds. Thus, the developed method nicely complements the Pd-catalyzed arene acyloxylation reaction, which is not operational on hindered substrates. Inspired by this finding, the authors explored the substrate scope with respect to the both acetoxylation and acyloxylation reaction and the represented examples are shown in **Scheme 29**. Under the developed conditions a variety of methyl-substituted benzenes underwent acetoxylation giving good yields. Halogen-containing substrates are also well tolerated. Electron-deficient substrates showed lower reactivity and afforded mixtures of regioisomers. Electron-rich heteroaromatic systems such as 1,2-dimethylindol gave poor yield of the corresponding acetoxylated product. However, the acyloxylation reaction is general for substrates containing various carboxylic functionalities. The steric crowding of the carboxylic acid moiety does not seem to hamper the acyloxylation. The reaction conditions are also compatible with the bromo-substituted mesitylene.

7.14.7 Oxidative C–C Couplings Via C–H Activation

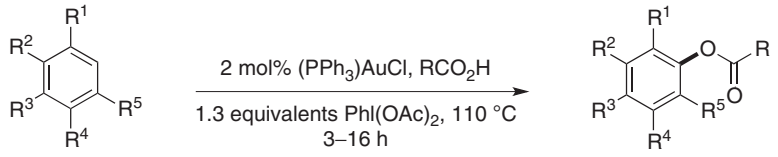
The construction of C–C bonds via C–H activation is an area of research that has received considerable attention.[79] Much of this chemistry utilizes directing groups to assist in the C–H activation step. By comparison there are relatively few examples where sp^2-C–H activation is accomplished without a directing group. An early example described the Ir-catalyzed cross-coupling of aryl C–H bonds of arenes with C–X bonds of aryl halides to form biaryl products (**Scheme 30**).[80] Most of the reactions involved benzene as

Table 12 Effects of pyridine on Pd-catalyzed acetoxylations[78]



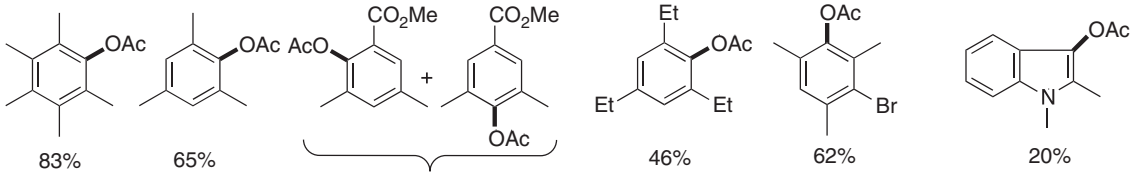
Entry	*Product*	*$Pd(OAc)_2$*	*Yield $Pd(OAc)_2$/pyridine (1:0.9)*	*$Pd(OAc)_2$/pyridine (1:2.1)*
1		8	70	5
2		–	70[a]	–
3		7	62	3
4		–	68[a]	–
5		8	59	4
6		–	64[a]	–
7		5	68	3
8		–	70[a]	–
9		5	47	3
10		–	61[a]	–
11		1	24	3
12		–	56[a,b]	–

[a] $MesI(OAc)_2$ was used as oxidant.
[b] 10 mol% Pd.

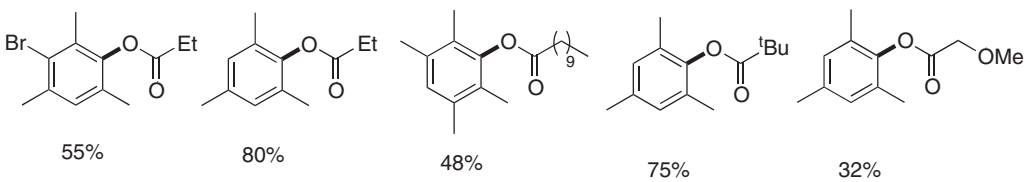


Represented examples:

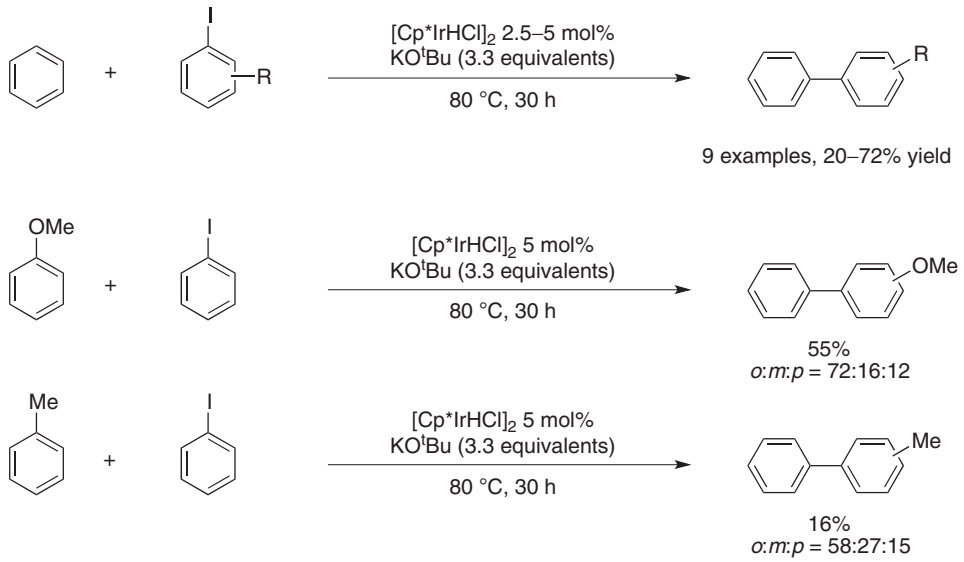
Acetoxylation



Acyloxylation



Scheme 29



Scheme 30

the C–H coupling partner, where regioselectivity is not an issue. Anisole and toluene both showed a preference for *ortho*-functionalization, with the selectivity being more pronounced for anisole. Other examples of this type of transformation have subsequently appeared, including examples where the C–H coupling partner is a heterocycle.

The Pd-catalyzed cross-coupling of fluorinated benzenes with aryl halides has been described, as shown in Scheme 31.[81] This chemistry is noteworthy as it conjoins two electron-deficient aromatic rings. With the exception of 1,2,3,4-tetrafluorobenzene, the reactivity of the fluorinated aromatic increases with F substitution. The mechanism in Scheme 31 was evaluated computationally. The energies of Pd^{IV} intermediates were deemed too high to be viable. Instead, sigma-bond metathesis pathways were proposed where activation of the C–H bond can be viewed as a deprotonation of the C–H bond, either by coordinated halogen or carbonate ligands.

Copper phenanthroline complexes can also catalyze C–H cross-couplings of C–H bonds in arenes and heterocycles with organic iodides and bromides in the presence of base.[82] Some representative examples are given in Scheme 32. The reactions are selective for functionalization of the most acidic C–H bond, even when that site is sterically hindered (viz. product **80**). Product **82** demonstrates that couplings of vinyl halides are viable. Products **83**–**86** extend the chemistry to the activation of heterocyclic C–H bonds and demonstrate compatibility of a relatively reactive C–Cl bond under the reaction conditions.

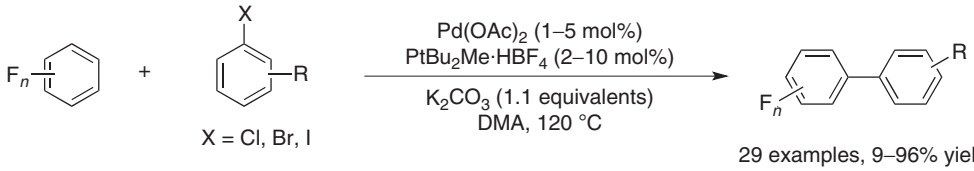
7.14.8 Formal C–H Oxidation

The conversion of C–H to C–O bonds can be accomplished by conversion of the C–H bond to some other functional group, which is then transformed to a C–O bond in a second step. For example, the Dow process for synthesis of phenol involves the reacting concentrated solutions of NaOH with chlorobenzene, which in turn is synthesized from benzene. Although this process has been used to prepare phenol on industrial scales, harsh conditions are required unless the arene is substantially electron deficient. Thus, extension of the Dow process to functionalized arenes is impractical.

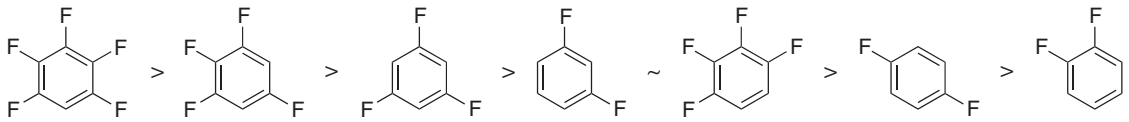
One process that transforms C–H bonds under mild conditions is catalytic C–H borylation, most commonly catalyzed by Ir complexes.[83] The reaction is sensitive to steric effects and gives regioselectivities that historically had been difficult to achieve in a single step transformation. The resulting arylboronate compounds can be transformed to a broad array of functional groups. Most relevant to the discussion at hand is oxidation of the arylboronate products of C–H activation to C–OH moieties. Using this two-step sequence, it is possible to transform C–H bonds in substituted benzenes to phenols in a 'one-pot' protocol.[84] The mild conditions of the C–H activation and oxidation make it possible to carry out this conversion in the presence of an array of functional groups. This chemistry made phenols that were previously unknown accessible, and for compounds that were known to the literature C–H borylation/oxidation was often the most efficient route. For example, prior to the one-pot borylation/oxidation method, the only synthesis for compound **87** involved ten steps beginning from 2,4,6-trinitrotoluene (Scheme 33).

7.14.9 Summary

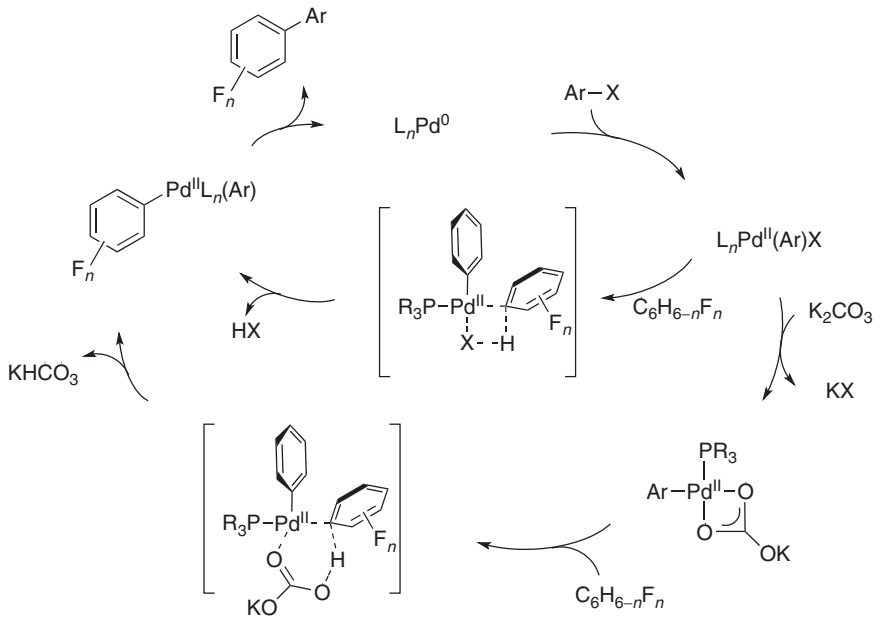
Although the scope of nondirected oxidations of sp^2-C–H bonds is still limited when compared to directed oxidations, there have been significant advances in the past 20 years. Nevertheless, significant challenges remain. For example, the Hock process



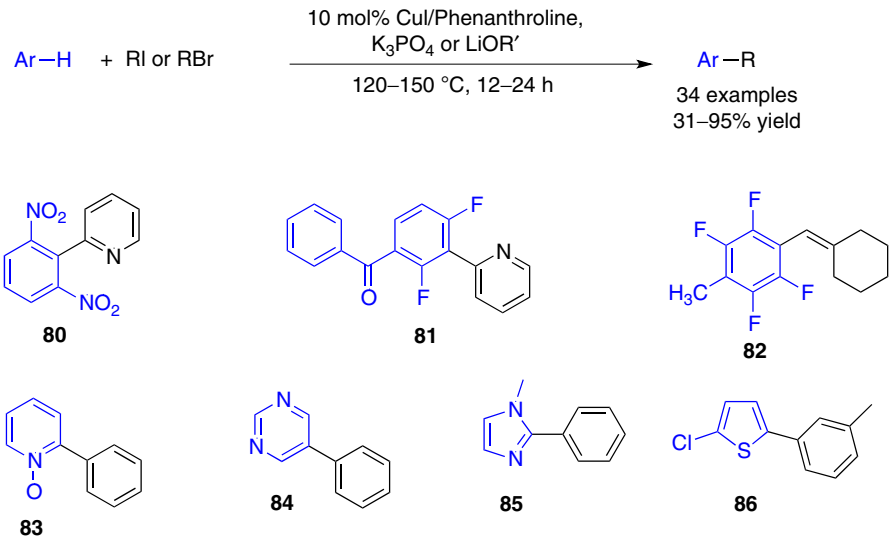
Relative reactivity



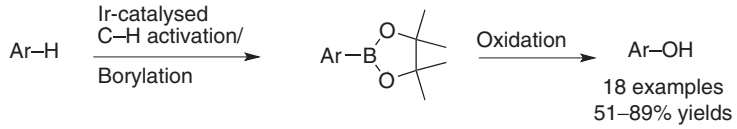
Proposed mechanism



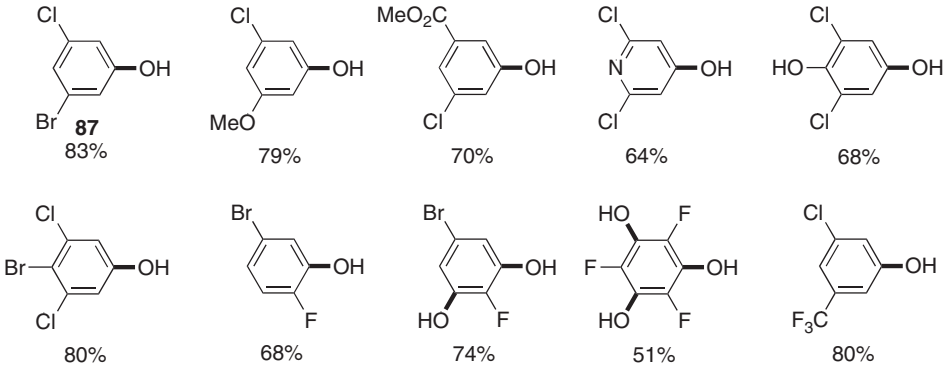
Scheme 31



Scheme 32



Conditions: 2 mol% (Ind)Ir(COD), 2 mol% dmpe, neat under N_2; then acetone, 1 equivalent B_2pin_2 (per boron)/HBpin; aqueous Oxone, 25–100 °C, 7 min.; isolated yields.



Scheme 33

continues to be the most commonly deployed route for phenol synthesis. Given recent progress, the prospects for developing an economical alternative appear to be bright. Likewise, the potential of enzymatic C–H oxidations has not been fully realized. The primary challenge is to engineer these systems to carry out oxidation on preparative scales that are useful to the synthetic chemist.

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7.15 Synthesis of *para*- and *ortho*-Quinones

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Glossary

Catechol An organic compound with the molecular formula $C_6H_4(OH)_2$ also known as 1,2-dihydroxybenzene. The *ortho*-isomer of the three benzene diols.

Hydroquinone An organic compound with the molecular formula $C_6H_4(OH)_2$ also known as 1,4-dihydroxybenzene. The *para*-isomer of the three benzene diols.

Oxidation The loss of electrons or loss of hydride by an atom, ion, or molecule.

***ortho*-Quinone** An organic compound with the molecular formula $C_6H_4O_2$ also known as 1,2-benzoquinone that is often derived from its aromatic counterpart 1,2-dihydroxybenzene, or catechol.

***para*-Quinone** An organic compound with the molecular formula $C_6H_4O_2$ also known as 1,4-benzoquinone that is often derived from its aromatic counterpart 1,4-dihydroxybenzene, or hydroquinone.

7.15.1 Introduction to Quinones

7.15.1.1 Molecular Description of Quinones

Quinones in their simplest form are classified as six-membered carbocyclic compounds containing two carbonyl residues, either separated by vinyl groups within a ring, *para*-quinones (**1**); or adjacent to one another, *ortho*-quinones (**2**) (Figure 1). This structure is embedded in a variety of more complicated heterocyclic and carbocyclic motifs with varying numbers of rings.

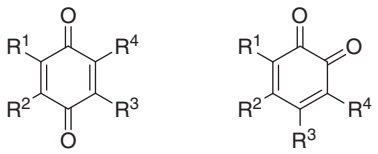


Figure 1 General classes of quinone substitution.

7.15.1.2 Applications of Quinones

Quinones serve in many capacities. They are used in manufacturing to dye fabrics (red violet),[1] in living organisms to transport energy and hydrogen atoms (Coenzyme Q_{10}),[2] to provide essential nutrients (Vitamin K),[3] to serve as cocatalysts (PQQ),[4] and in the pharmaceutical industry to eradicate cancer (doxorubicin),[5] HIV (streptonigrin, STN),[6] and bacteria (prekinamycin)[7] (Figure 2).

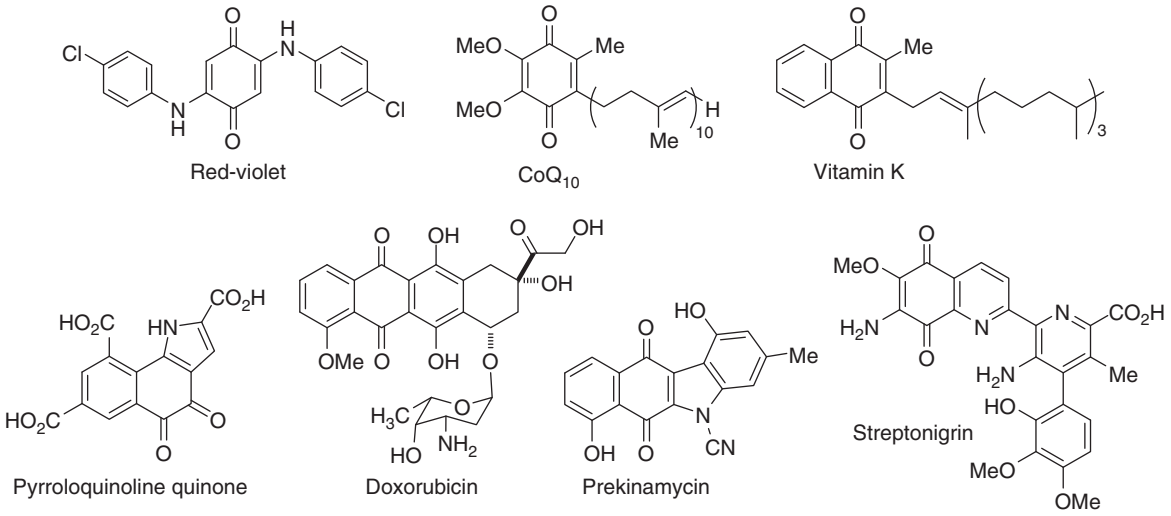


Figure 2 A variety of useful quinones and their applications.

7.15.1.3 Biosynthesis of Quinones

Quinone biosynthesis occurs by both the acetate–malonate pathway, as in the case of echinochrome A,[8] or by assembly of isoprenoids, as in the case of the diterpenoid royleanone (Figure 3).[9]

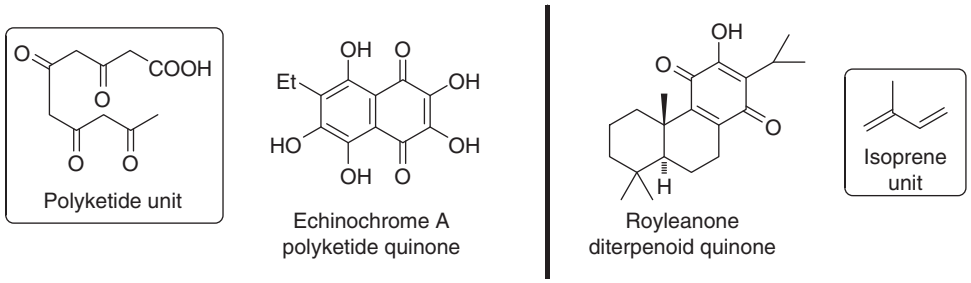


Figure 3 Two biosynthetic origins of quinones.

7.15.1.4 General Overview

From a synthetic perspective, the difficulty surrounding the preparation of a particular quinone (*ortho*- or *para*-) depends on the substitution pattern (R^1–R^4) of its hydroquinone precursor. Electron-rich systems are more easily oxidized than those that are electron-deficient. This chapter discusses many of the most common reagents that are known to effect the simple oxidation of hydroquinones, **3**, and catechols, **4** (Figure 4). However, the synthetic strategies for accessing the hydroquinone and catechol

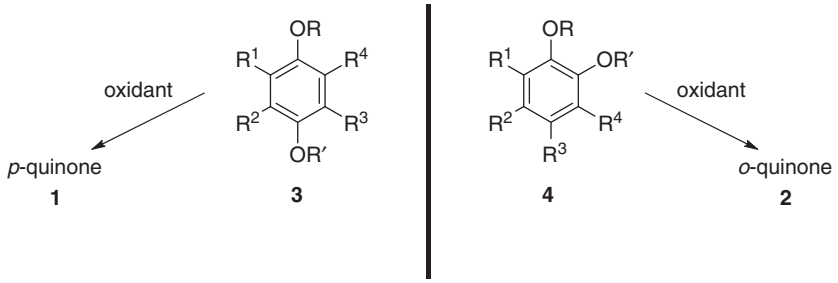


Figure 4 Oxidation of hydroquinones to *p*-quinones and *o*-quinones (1 ox.).

precursors themselves, as well as methods to construct these precursors from less oxidized substrates, are the principal focus. It is the selection from among these strategies which create these precursors and determines the efficiency of the overall synthetic plan. In the ensuing pages, the authors provide the practicing synthetic chemist with a robust toolbox that serves as a starting point of inspiration for the construction of either *para*- or *ortho*-quinones.[10]

7.15.2 *para*-Quinones; a Strategic Summary

para-Quinones can be accessed by a plethora of intertwined oxidative and C–C bond-forming strategies (Figure 5). For example, either an aryl ring or an enone can undergo three oxidations to produce a quinone. An anisole or phenol displaying a *para*-hydrogen or carbon substituent can undergo just two oxidations to arrive at the same entity. However, a hydroquinone and its protected or unprotected functional counterparts require just a single oxidation to reveal the underlying quinone core. Quinone ketals afford quinones on deprotection, whereas their quinol counterparts require rearrangement and subsequent oxidation. In addition, a variety of C–C bond-forming strategies have been shown to address naphthoquinones and larger systems. Some of these carbon–carbon bond-forming processes provide the quinone itself, while others provide access to a less oxidized substrate that can be further manipulated by an increasing number of oxidative processes.

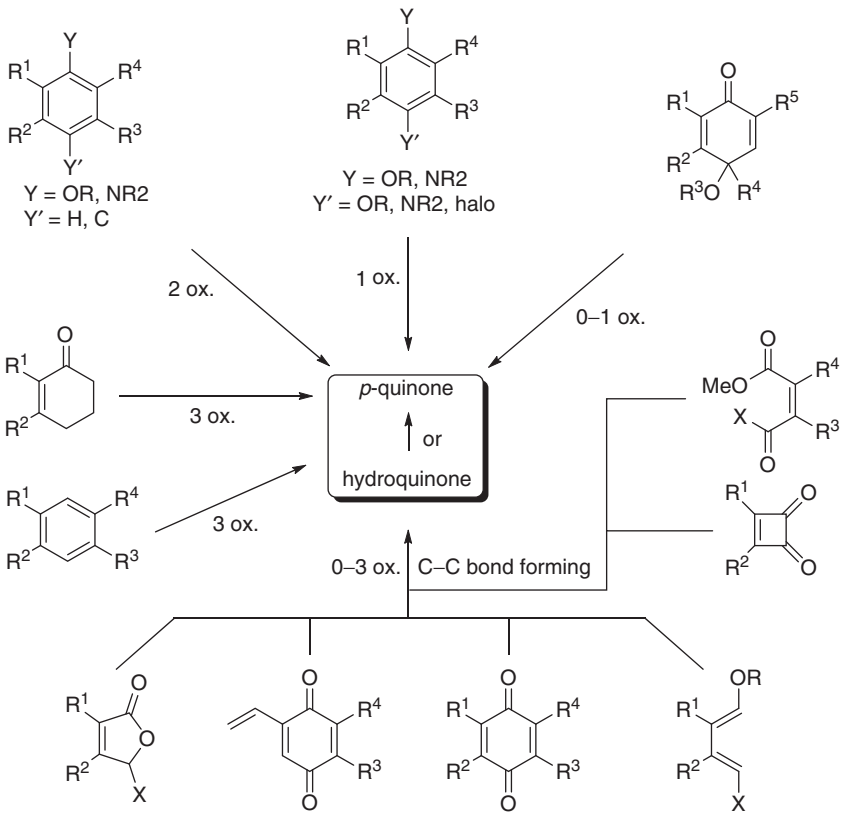
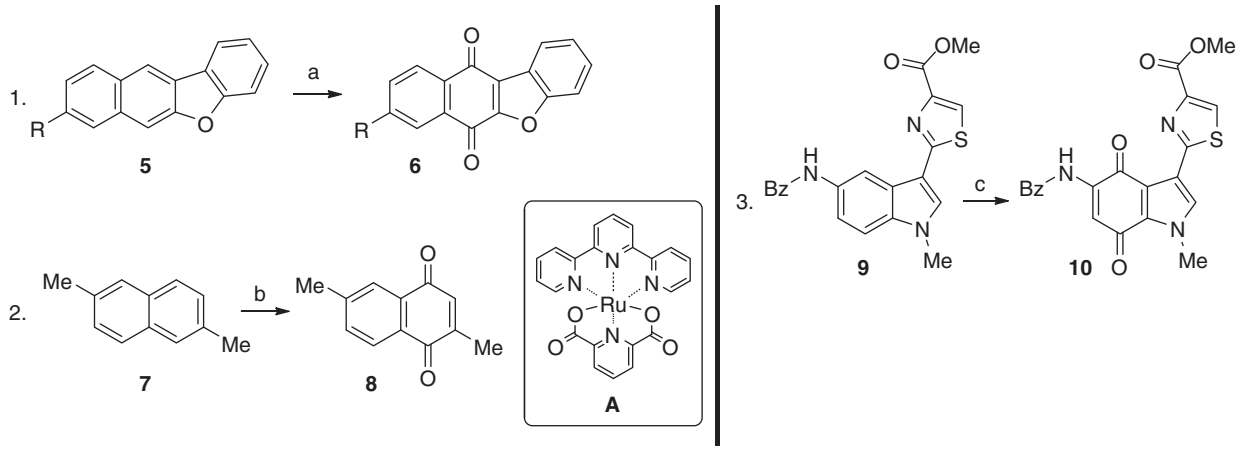


Figure 5 Methods to access *p*-quinones and hydroquinones from simpler precursors.

7.15.2.1 *p*-Oxidation of Benzene Derivatives (3 ox.)

The installation of two oxygen atoms directly onto an aryl system to form the corresponding quinone is indeed a very useful transformation. However, it requires very strong oxidative conditions and regioselectivity issues can arise. Such processes enable quinone preparation from very simple aromatic precursors; but these processes are by no means general.

Excess chromium trioxide in refluxing acetic acid has been shown to oxidize the electron-rich naphthalene-benzofuran **5** into the corresponding naphthoquinonefuran **6** with yields varying from 24% to 100% (1.-Scheme 1).[11] The regioselectivity reflects the relative orbital coefficients across the two ring systems for the installation of both new oxygen atoms. Researchers report that treatment of the *pseudo*-symmetric methylated naphthalene **7** with 1 mol% of the ruthenium catalyst **A** in the presence of hydrogen



a. CrO_3, AcOH, reflux, 24–100% yield; b. 1 mol% **A**, H_2O_2, MeOH, 40 °C, 90% yield; c. DMP, H_2O, CH_2Cl_2, 25 °C, 67% yield.

Scheme 1

peroxide afforded the corresponding naphthoquinone **8** in good yield (2.-Scheme 1).[12] Similar transformations on symmetrically, electronically, and sterically predisposed benzenes, anisoles, and phenols were also demonstrated. Dess-Martin periodinane (DMP) has been reported to oxidize anilides such as **9** into the corresponding *p*-quinone **10**.[13] The transformation is thought to proceed via an intermediate *o*-imidoquinone. However, it should be restated that these reactions are not general, but are specific to the cooperative structural attributes within the aryl cores themselves.

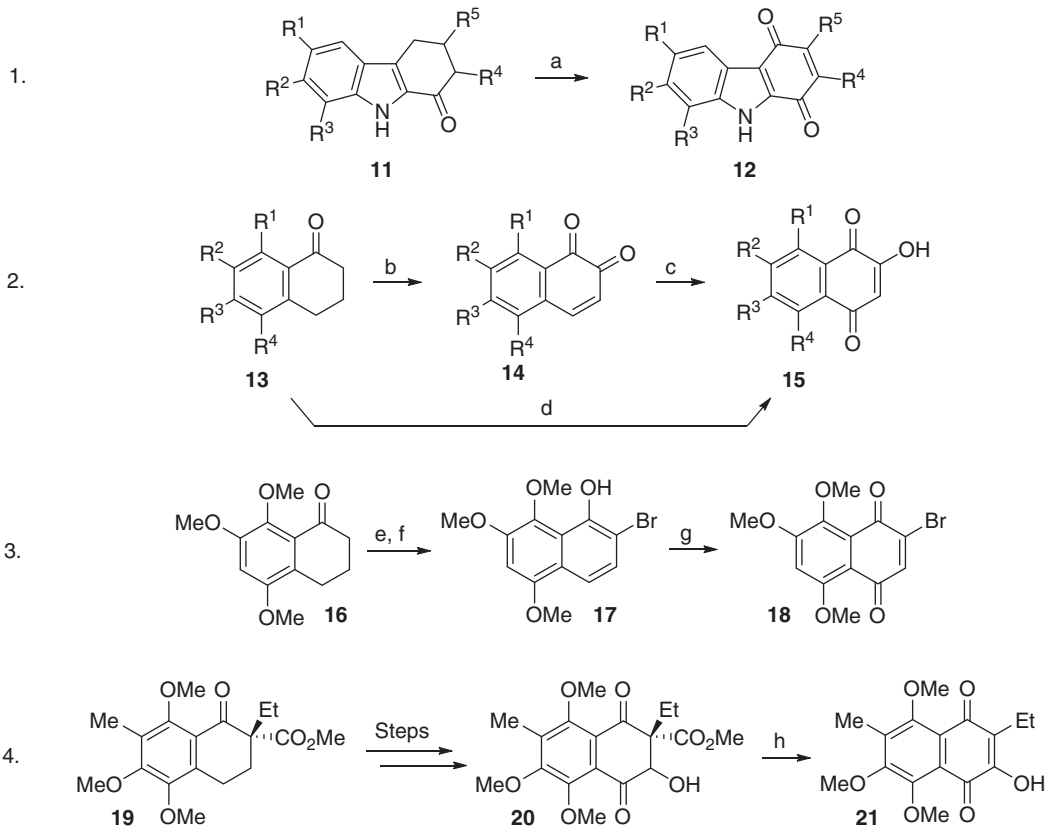
7.15.2.2 *p*-Oxidation of Enone Derivatives (3 ox.)

Another triple oxidation (3 ox.) strategy enables enone or tetralone precursors to be used. These intermediates are available from a number of cyclohexenone ring-forming strategies.

For example, the tetrahydrocarbazole derivative **11** undergoes oxidation using cerium ammonium nitrate dispersed on silica gel (CAN-SiO_2) resulting in the quinones **12** (1.-Scheme 2).[14] The reaction proceeds in yields ranging from 50–92% with various alkyl and hydrogen substituents at the R^4 and R^5 positions. However, again this three-oxidation process is not very general. The authors speculate that the nitrogen atom in **11** plays a critical role in the overall reaction success. Both selenium dioxide and molecular oxygen have separately been used to access *ortho*-hydroxy-*para*-naphthoquinones, such as **15**, from tetralones, such as **13** (2.-Scheme 2).[15] This transformation is speculated to proceed by a series of allylic oxidations to furnish the intermediate *o*-quinone **14**. This compound succumbs to reduction with sodium borohydride to produce the corresponding catechol (not shown), which undergoes a cycloaddition with molecular oxygen and further oxidation to afford **15**. However, this strategy proves difficult to carry out on a large scale, and the exchange of molecular oxygen for potassium superoxide offers few tangible benefits.[16] These tetralone strategies all parallel the original process that simply used molecular oxygen and potassium *tert*-butoxide,[17] but all of them still suffer from scalability issues and unpredictable substituent effects. A newer strategy that has proven more tolerant of substituents and electronic effects begins with bromination and elimination of the tetralone **16** to afford the corresponding bromonaphthol **17** (3.-Scheme 2).[18] Further *para*-oxidation of this material with cerium ammonium nitrate (CAN) and another oxidation of the initial hydroquinone affords the bromo-naphthoquinone **18**, an intermediate used in the total synthesis of (±)-γ-rubromycin. It should be noted that bromine serves as a useful functional group handle enabling access to hydroxy, alkyl, and hydrido derivatives of **18**. In a separate effort to reach alkyl derivatives, the ethyl substituted tetralone **19**, which was prepared by a Stobbe Condensation, was converted into the dione **20** by a three-step oxidation process employing $Pb(OAc)_4$, OsO_4, and 2-iodoxybenzoic acid (IBX) (4.-Scheme 2).[19] Saponification of the methyl ester, decarboxylation, and further air oxidation was found to afford the desired ethylated naphthoquinone **21**.

7.15.2.3 *p*-Oxidation of Phenols and Anisoles (*para*-H) (2 ox.)

Phenols and their protected (i.e., methoxy and siloxy) counterpart derivatives are fairly accessible synthetic materials and easily derived from aryl systems substituted with aldehydes, sulfates, chlorides, and alkyl residues. Phenols are also obtained by aromatization of the corresponding cyclohexanone and tetralone derivatives, which themselves are accessed by a cycloaddition or typical six-membered ring-forming strategies. These phenol intermediates can then be transformed into a *p*-quinone by several reagents that are selective for *para* installation of an oxygen atom and further oxidation.



a. CAN-SiO_2, r.t., 24 h, 50–92% yield; b. SeO_2, AcOH, 60 °C, 60–73% yield; c. KO_2, CH_2Cl_2, 20 °C, 98% yield or $NaBH_4$; O_2, KO*t*-BU, *t*-BuOH, 40% yield; d. KO*t*-BU, O_2, 16–72% yield; e. LHMDS, THF, –78 °C; NBS; f. DBU, –78 °C to r.t., (78% yield, 2 steps); g. CAN, MeCN/H_2O, 0 °C, 60% yield; h. 1M KOH, H_2O/THF (3:1), air, 1 h, 87% yield.

Scheme 2

7.15.2.3.1 Phenols

7.15.2.3.1.1 Fremy's salt

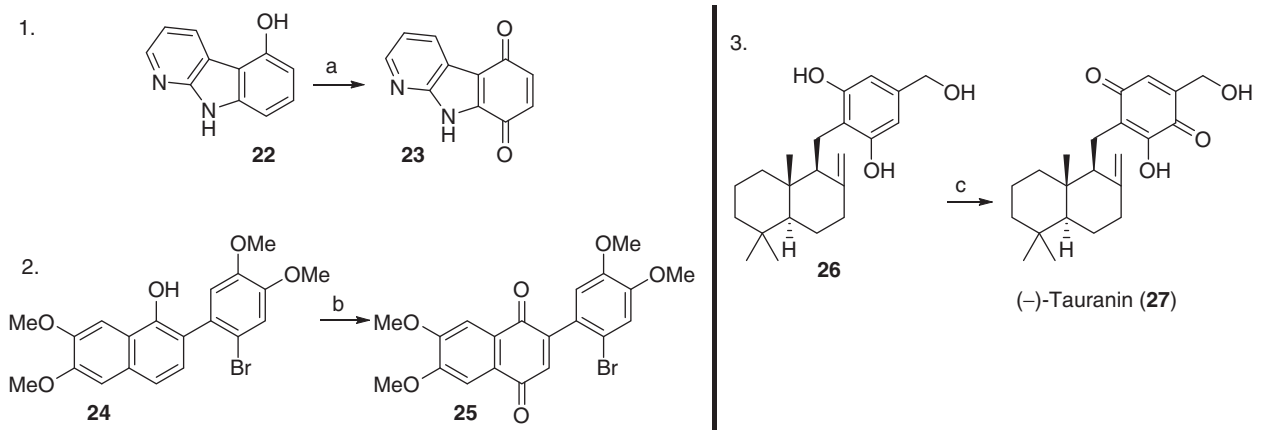
Fremy's salt displays a stable oxygen-free radical and possesses the formula $(KSO_3)_2NO$.[20] This reagent has been traditionally used to oxidize phenols into their corresponding *p*-quinones. *o*-Quinones are not accessible from this reagent, unless the *p*-position is blocked with a substituent other than an oxygen atom (see Section 7.15.3.2.2.2). The reagent is an orange powder, soluble in water, and most often used with a phosphate buffer in mixed polar solvent systems that include water. The transformation is thought to proceed by a free-radical mechanism, with the added oxygen atom coming from the reagent itself by intermolecular delivery.

Fremy's salt has been used in methanol to oxidize the indole **22** into the corresponding carboline quinone **23** in 57% yield (1.-Scheme 3);[21] whereas the corresponding implementation of silver carbonate and benzene selenic anhydride proved ineffective. The oxidation of the more electron-rich naphthol **24** into naphthoquinone **25** occurs under similar conditions with a better overall yield of 80% (2.-Scheme 3).[22] For the synthesis of tauranin (**27**), the unprotected symmetric resorcinol **26** was reported to afford the *ortho*-hydroxy-*para*-quinone on oxidation with Fremy's salt (3.-Scheme 3).[23] It should be noted that installation of an oxygen atom *para* to either phenolic substituent of **26** results in the same product because of the symmetry of the starting material.

7.15.2.3.1.2 Salcomine and other cobalt complexes

The salcomine complex, also known as a cobalt salen, has been used for mild oxidations of free phenols to afford their corresponding *p*-quinones when donating groups are present in the starting aryl system.[24] Salcomine is a brown or black–gray powder, stable to storage in air, soluble in variety of nonpolar organic solvents, and most often used in DMF at room temperature. This reagent is used in catalytic quantities provided that molecular oxygen is available as the stoichiometric oxidant.

The *meta*-amino phenol **28** was reported to undergo a double oxidation with salcomine in aerated DMF at room temperature to afford the tosyl amide substituted quinone **29** in a 94% yield in route toward mitomycin (1.-Scheme 4).[25] The mono-alkylated phenol **30** underwent oxidation with catalytic salcomine and oxygen in DMF at room temperature to afford (+)-avarone (**31**) in an 89% yield (2.-Scheme 4).[26] The chiral salen catalyst popularized by Jacobsen was used for the oxidation of **32** in a mixed



a. Fremy's salt, K_2HPO_4, MeOH, 57% yield; b. Fremy's salt, K_2HPO_4, acetone, 80% yield; c. Fremy's salt, K_2HPO_4, 63% yield.

Scheme 3 Fremy's salt oxidation of free phenols (2 ox.).

solvent system and proceeded in a 94% yield to afford CoQ_{10} (**33**) (3.-Scheme 4).[27] The authors mention that use of the original salcomine catalyst lowered the isolated yield to 84%. In another example, the naphthol **34** in aerated acetonitrile was reported to undergo oxidation with catalytic salcomine to smoothly afford the naphthoquinone **35** in an 84% yield (4.-Scheme 4).[28] The authors reported that attempts to use CAN to affect a similar outcome had failed in their hands. Subsequent demethylation with $AlCl_3$ resulted in an intervening tautomerization and afforded the more stable chloro-hydroquinone **36**. The binaphthol **37** was observed to oxidize in a moderate yield of 63% to the corresponding bis-*para*-naphthoquinone **38** under similar conditions (5.-Scheme 4).[29] This product served as an intermediate in the formation of the (*S*)-bisoranjidiol (**39**) bis-phenanthracene quinone with an oxygenated diene in a Diels–Alder C–C bond-forming strategy described later in this chapter (see Section 7.15.2.7.4).

7.15.2.3.1.3 Iodine(III) reagents

The hypervalent I(III) reagents most often reported to oxidize phenols, hydroquinones, and catechols into their corresponding quinones are iodosobenzene diacetate (PIDA) and bis(trifluoroacetoxyiodo)benzene (BTI, PIFA).[30] Both PIDA and PIFA are white solids, easily synthesized from iodosobenzene, (PhIO). Iodosobenzene is another useful I(III) reagent that is fairly insoluble in most solvents but displays an overlapping reactivity profile and performs similar oxidations. PIDA is thought to proceed through single-electron transfer mechanisms, whereas PIFA appears to involve more ionic mechanisms and renders improved yields. Both reagents are known to lead to *p*-quinones from phenols by an intermediary phenoxonium cation. In the presence of methanol, the corresponding *para*-quinone ketal forms, whereas reactions in water produce the *p*-quinone directly. It should be noted that different protic solvents change the nature of the reagents themselves. For example, use of PIDA or PIFA in the presence of water leads to significant amounts of PhIO, which in some instances may serve as the primary oxidant.

The cannabinoid quinone **41** was prepared by the PIFA oxidation of cannabinol (**40**) in a 60% yield (1.-Scheme 5).[31] This reaction likely involves a phenoxonium intermediate, which is intercepted at the *para* position by water to form the corresponding hydroquinone. Further *in situ* oxidation yielded its corresponding quinone, **40**. In addition, the bromo-naphthol **42** has been reported to oxidize under similar conditions to produce the bromo-naphthoquinone **43** (2.-Scheme 5).[32] Given the presence of water in both reactions, the active oxidant may be the I(III) reagent, PhIO.

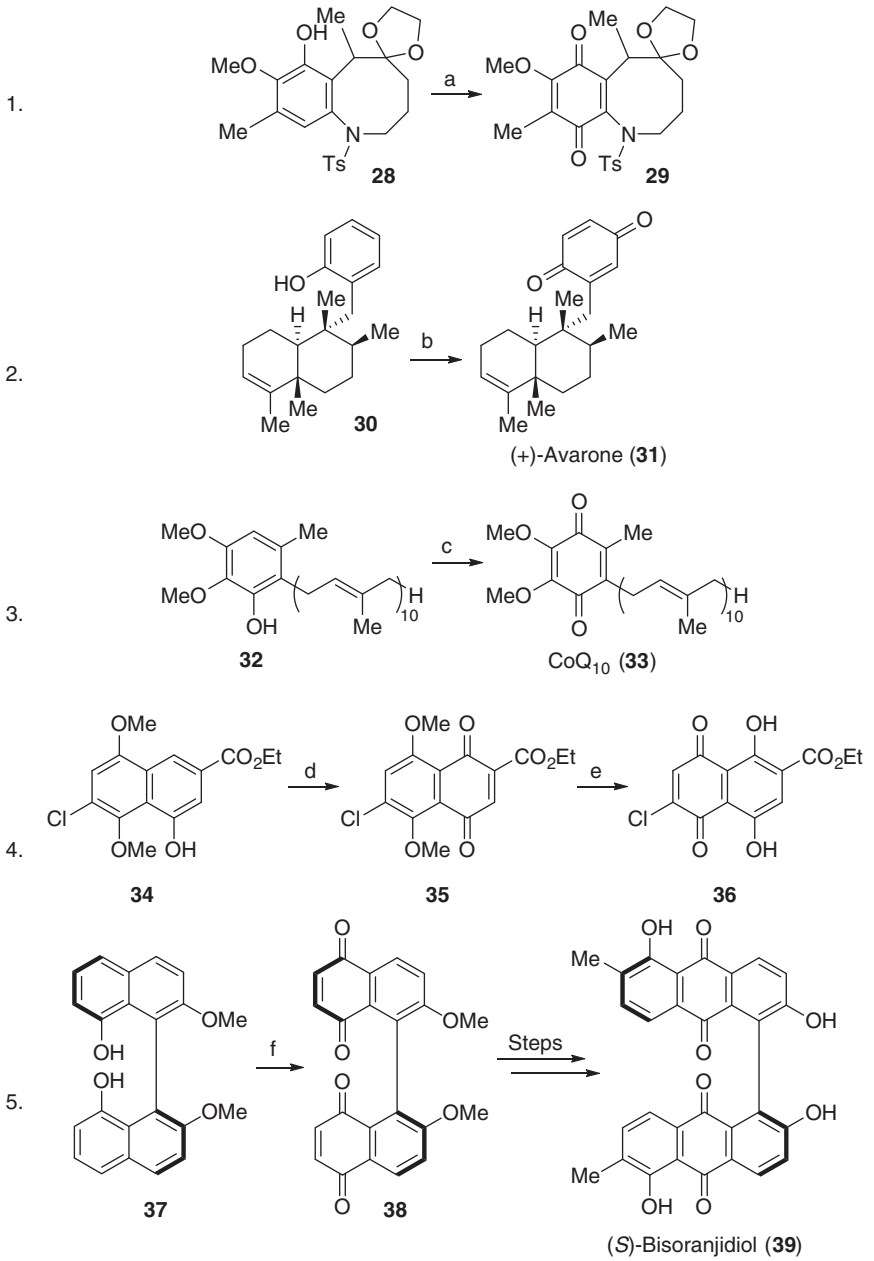
7.15.2.3.1.4 CAN

CAN is an orange solid with the chemical formula $(NH_4)_2Ce(NO_3)_6$.[33] Oxidations with CAN usually proceed through a single-electron transfer mechanism. Despite its strong oxidizing capabilities, the selectivity and functional group tolerance of this reagent is remarkable. It is very soluble in nitric acid and slightly soluble in polar solvents such as acetonitrile (MeCN) or dimethyl formamide (DMF). Most reactions are carried out in mixed solvent systems employing water; sometimes in the presence of a buffer or sodium carbonate. Reaction temperatures typically range from −10 °C to 25 °C, with at least a two-fold excess of CAN to give products in moderate-to-good yield. Although CAN is most often used in oxidative dealkylation processes (see Section 7.15.2.5.1.1), particularly for *para*-bis-methyl ethers, it also oxidizes electron-rich phenolic derivatives (Scheme 6).

The bromo-naphthol **17** was observed to undergo oxidation with CAN in a 1:1 mixture of acetonitrile and water at 0 °C to afford the bromo-*para*-naphthoquinone **44** in a 60% yield (1.-Scheme 6).[18] Similarly, the phenol **45** was reported to undergo oxidation under nearly identical conditions to afford the quinone **46** in a 60% yield (2.-Scheme 6).[34]

7.15.2.3.1.5 Molecular oxygen

Molecular oxygen can serve as a primary oxidant for quinone syntheses in both the presence and absence of light by hydride abstraction, cycloaddition, or electrophilic processes. Molecular oxygen has been reported to oxidize dimethoxy aryl systems with

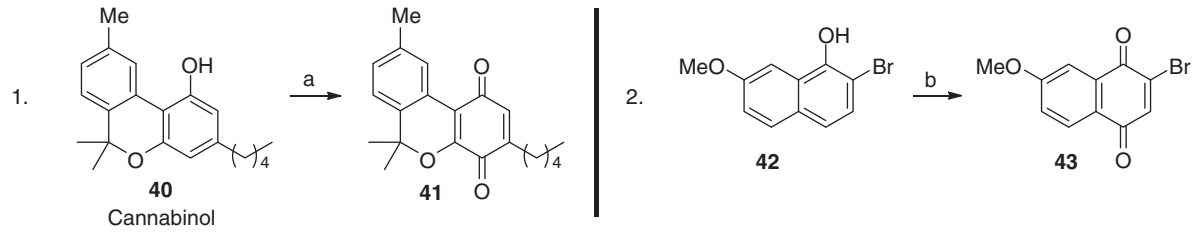


a. salcomine, O_2, DMF, r.t., 94% yield; b. salcomine, O_2, DMF, r.t., 89% yield; c. Co(chiral-salen) (cat.), DMF, toluene, O_2, r.t., 94% yield; d. salcomine (cat.), O_2, MeCN, r.t., 84% yield; e. $AlCl_3$, r.t., CH_2Cl_2, 83% yield; f. salcomine (18 mol%), O_2, DMF, 63% yield.

Scheme 4 Salcomine catalyst for phenol oxidation (2 ox.).

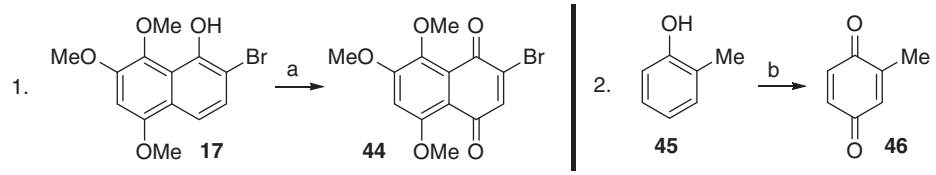
0–2 oxygen substituents. However, this 'green oxidant' is most often used to oxidize hydroquinones and catechols into their quinone counterparts (see Sections 7.15.2.5.2 and 7.15.3.6).[35] When oxidizing a phenol, it often proves difficult to stop at the hydroquinone intermediate, particularly for electron-rich systems.

In most instances this slow oxidative reaction is believed to follow an electrophilic pathway; whereby a phenoxide dienolate undergoes reaction on carbon at the *para* position with electrophilic oxygen. For example, aegyptinone B (**48**) was constructed in 87% yield from naphthol **47** by deprotection of the silyl residue with basic fluoride and exposure to molecular oxygen (1.-Scheme 7).[36] Similarly, the electron-rich anthracenol **49** was reported to produce the quinone danshexinkun A (**50**) in 91% yield (2.-Scheme 7).[37] The naphthol **51** has been reported to form the corresponding *p*-naphthoquinone **52** in low yields when exposed to potassium *tert*-butoxide and oxygen (3.-Scheme 7),[38] whereas the symmetrical resorcinol **53** was reported to afford the hydroxy-quinone **54** in addition to the dimerized product using potassium hydroxide and oxygen in a similar capacity (4.-Scheme 7).[39]



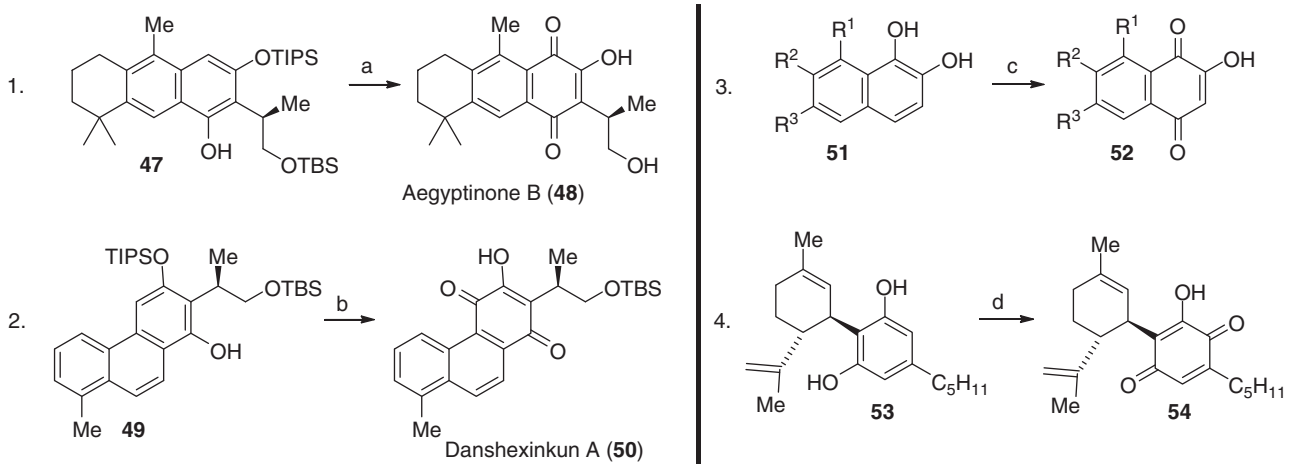
a. PIFA, MeCN/H_2O, r.t., 60% yield; b. PIFA, MeCN/H_2O, –5 °C, 58% yield.

Scheme 5 I(III) Oxidation of free phenols (2 ox.).



a. CAN, MeCN/H_2O, 0 °C, 60% yield; b. CAN, MeCN/H_2O, r.t., 60% yield.

Scheme 6 CAN-mediated oxidation of free phenols (2 ox.).



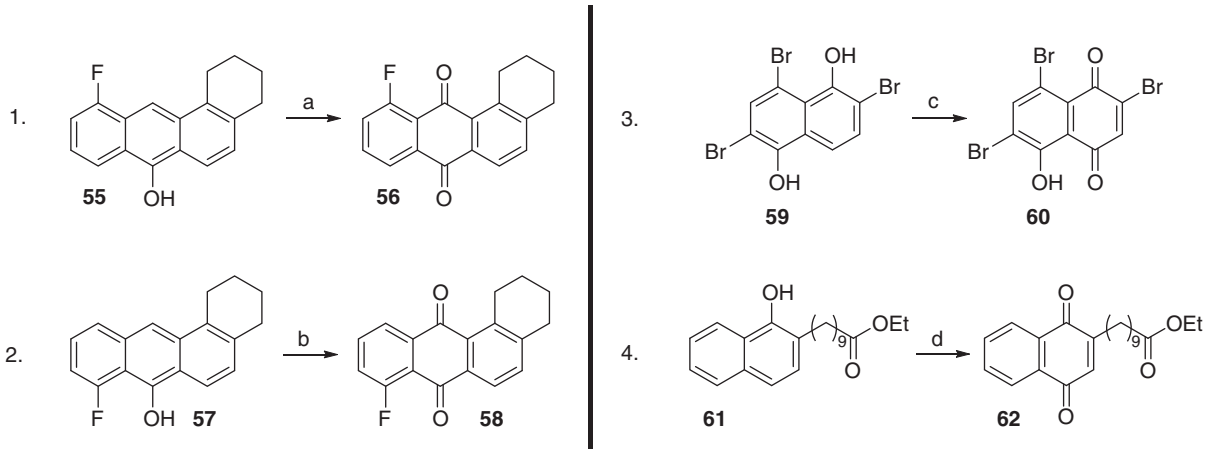
a. TBAF, THF, O_2, –78 °C to r.t., 87% yield; b. TBAF, THF; O_2, –78 °C to r.t., 91% yield; c. KO*t*-Bu, O_2, 8–15% yield; d. KOH, O_2, 5–25% yield.

Scheme 7 Molecular oxygen as an oxidant for free phenols (2 ox.).

7.15.2.3.1.6 Potassium dichromate or chromium trioxide

Examples of chromium(VI) being used to oxidize derivatives of phenols, anisoles, and hydroquinones into their corresponding quinones are scattered throughout literature. Both potassium dichromate ($K_2Cr_2O_7$) and chromium trioxide (CrO_3) are likely reformulated into hexavalent chromic acid (H_2CrO_4) with the acidic conditions that are used. This powerful albeit toxic oxidant is most often used in refluxing acetic acid; thus acid labile protecting groups such as -OAc, -OMOM, -OEVE, and -O-silyl residues are cleaved *in situ*, and this may precede the oxidation. Moreover, because these conditions are highly acidic, one might choose to precede this strategy with a Friedel–Crafts acylation to close a ring and form a phenol (see Section 7.15.2.7.1).

Among examples using Cr(VI), both the electron-poor anthracenol **55** and the electron-rich anthracenol **57** was reported to succumb to oxidation with potassium dichromate in refluxing acetic acid to afford the corresponding anthraquinones **56** or **58** in 30% and 71% yields (1., 2.-Scheme 8).[40] The lower yield of **56** was due to the formation of the 4-keto-anthraquinone. In a similar fashion, the tris-brominated dihydroxynaphthalene **59** affords the brominated naphthoquinone **60**, albeit in a low yield (3.-Scheme 8).[41] The naphthol **61** has also been transformed into its corresponding naphthoquinone **62** under similar conditions (4.-Scheme 8).[42]



a. $K_2Cr_2O_7$, HOAc, reflux, 30% yield; b. $K_2Cr_2O_7$, HOAc, reflux, 71% yield; c. CrO_3, acetic acid, 80 °C, no yield stated; d. CrO_3, AcOH, H_2O, 50 °C to 67 °C no yield stated.

Scheme 8 Chromium as a free phenol oxidant (2 ox.).

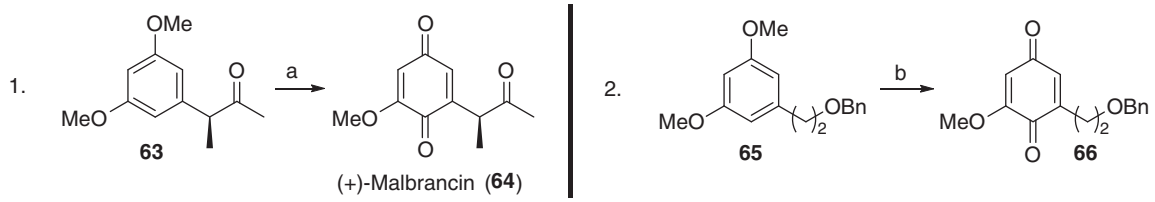
7.15.2.3.2 Anisoles

The *para*-oxidation of anisoles and related oxygen-protected ring systems can be an efficient synthetic strategy to form quinones, because this reaction precludes a separate cleavage of the phenolic protecting group. However, in most instances this transformation requires extremely powerful oxidants, such as Cr(VI) or I(V) reagents, which are sufficiently applied to some electron-rich aryl systems.

7.15.2.3.2.1 Chromium(VI)

The nature and utility of hexavalent Cr(VI) reagents have been described earlier (see Section 7.15.2.3.1.6). These powerful oxidants constitute a useful and irreplaceable reagent in the synthetic toolbox of organic chemists, particularly for the oxidation of symmetrical methoxy aromatic derivatives.

Oxidation of the *o*-methylated resorcinol derivative **63** with chromium trioxide in acetic acid at 0 °C produced the malbrancin quinone (**64**) in a 67% yield (1.-Scheme 9).[43] In a similar process, the *p*-quinone **66** was obtained in an 80% yield by oxidation of 1,3-dimethoxybenzene **65** with chromium trioxide (2.-Scheme 9).[44]



a. CrO_3, AcOH, H_2O 0 °C, 67% yield; b. CrO_3, AcOH, H_2O, 0 °C to r.t., 80% yield.

Scheme 9

7.15.2.4 *p*-Oxidation of Phenol and Anisole Derivatives (*para*-C) (2 ox.)

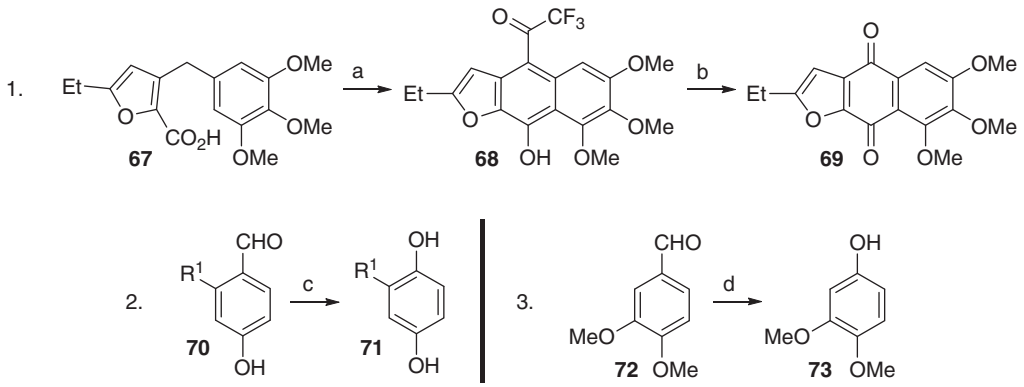
In many instances, it is desirable to oxidatively degrade a *para*-carbonyl substituted phenol or anisole derivative into a quinone by two oxidations. Three strategies can be used to accomplish this task: the Dakin, Baeyer–Villiger, and hydroperoxide rearrangements. In addition, degradation of amides to quinones by a Hofmann-like rearrangement has been carried out in a single step.

7.15.2.4.1 Dakin and Baeyer–Villiger reactions

Both the Dakin and Baeyer–Villiger methods degrade aryl ketone or aldehyde systems into the corresponding 'protected' phenol. The Dakin process usually employs hydrogen peroxide under basic conditions, whereas the Baeyer–Villiger uses per-acids under acidic conditions. Both reactions can be tuned to access either mono- or un-protected hydroquinones. In nearly all instances, a separate oxidative step is required to complete the conversion into the desired quinone system; a desirable option in some synthetic sequences.

One notable example among these strategies employs the degradation rearrangement in an unusual combination strategy (1.-Scheme 10).[45] Before the planned Dakin oxidation, the naphthazarin furan **68** was prepared by a Friedel–Crafts acylation of **67**

mediated by trifluoroacetic anhydride (TFAA). In this example, the use of TFAA caused both the ring closure and trifluoroacylation of the naphthazarin to afford the acylated naphthol–furan **68** in a 95% yield. Application of Dakin's conditions yielded the desired naphthoquinone furan **69** in a nearly quantitative yield. The second oxidation of the hydroquinone intermediate was attributed to the accessibility of molecular oxygen and the reactivity of the underlying electron-rich aryl system. The corresponding hydroquinone is usually isolable in less electron-rich systems. For example, benzaldehyde **70** was reported to undergo a similar Dakin reaction using sodium percarbonate to afford the corresponding hydroquinone **71** (2.-Scheme 10).[46] Depending on the R^1 substituent, yields ranged from 60% to 95%. Aromatic systems with donating groups (R^1 = OMe) afforded higher yields of product, whereas those with electron-poor substituents ($R^1 = NO_2$) resulted in lower yields. It is envisaged that these hydroquinones could be oxidized to their quinone counterparts using a variety of oxidants (see Section 7.15.2.8). The use of *m*-CPBA in methylene chloride at room temperature has been reported to convert the 3,4-dimethoxybenzaldehyde **72** into the corresponding phenol **73** in 96% yield by a Baeyer–Villiger reaction (3.-Scheme 10).[47] Further oxidation of this kind of mono-protected hydroquinones has been described earlier (see Section 7.15.2.5.2). Many other examples of this kind of Baeyer–Villiger reactions using slightly varied conditions and substrates are known.[48]



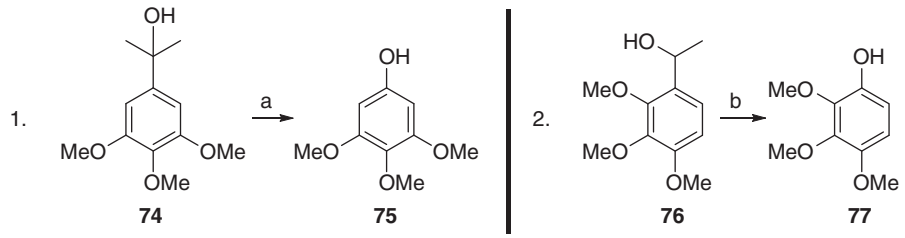
a. TFAA, CH_2Cl_2, 95% yield; b. H_2O_2, aqueous NaOH, 95% yield; c. Sodium percarbonate ($Na_2CO_3{\cdot}5H_2O_2$), THF/DMF/H_2O, 60–95% yield; d. *m*-CPBA, CH_2Cl_2; K_2CO_3, MeOH, 96% yield.

Scheme 10

7.15.2.4.2 Hydroperoxide rearrangement

The hydroperoxide rearrangement offers some advantages over the Dakin and Baeyer–Villiger rearrangements for conversion of electron-rich aromatic systems into their corresponding phenols, because electron-rich benzaldehydes and ketones are resistant to the initial reaction of their carbonyl with peracid and peroxide. However, on conversion to their secondary and tertiary alcohols, these adducts are readily transformed into their corresponding hydroperoxide under acidic conditions and then undergo further rearrangement to afford the desired phenol.

For example, the tertiary alcohol of the 3,4,5-trimethoxy aromatic compound **74** is easily derived from addition of methyllithium to the corresponding acetophenone or methyl ester. Compound **74** was reported to smoothly rearrange to the phenol **75** in 87% yield, when treated with a mixture of perboric acid and $BF_3{\cdot}Et_2O$ (1.-Scheme 11).[49] However, other combinations of acid and peroxide are known to work as well. The secondary alcohol **76** has also been reported to afford the corresponding phenol **77** in 95% yield when treated with *p*-toluenesulfonic acid and hydrogen peroxide at room temperature (2.-Scheme 11).[50] The straightforward oxidation of these kinds of mono-protected hydroquinones into their corresponding quinones is discussed later (see Section 7.15.2.5.2).

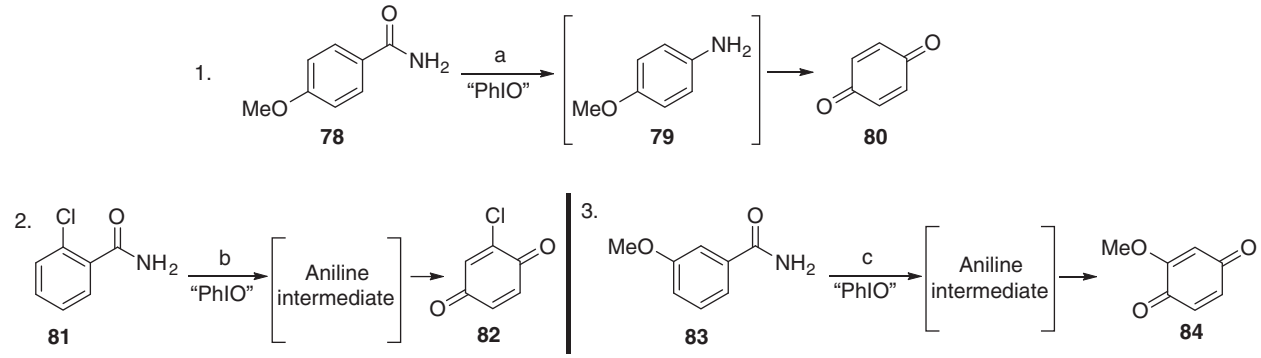


a. $NaBO_3{\cdot}4H_2O$, $BF_3{\cdot}OEt_2$, THF, r.t., 87% yield; b. 10 mol% *p*-TsOH, H_2O_2, THF, r.t., 95% yield.

Scheme 11

7.15.2.4.3 Hofmann rearrangement

In a related work, a Hofmann rearrangement of aryl systems substituted with primary amides has been carried out in the presence of a hypervalent iodide (I(III)) reagent so that the aniline intermediate undergoes further oxidation (Scheme 12).[51] Unlike the peracid and peroxide rearrangements mentioned above, this method proceeds directly to the corresponding *p*-quinone in instances with or without *para*-alkoxy substituents (2–3 ox.).



all reactions: PhI, oxone, MeCN/H_2O, r.t.; a. 94% yield; b. 95% yield; c. 97% yield.

Scheme 12

For example, the *para*-methoxy amide **78** was smoothly oxidized into the corresponding *p*-quinone **80** via the intermediacy of the corresponding aniline **79**, which undergoes further oxidation and hydrolysis (1.-Scheme 12). The active I(III) oxidant, PhI=O, is generated *in situ* from PhI and oxone in aqueous acetonitrile. In instances where the starting amide does not display a *para*-oxygen substituent, interception of the intermediate cation formed by oxidation of the aniline with water proceeds so that the quinone is still formed, as demonstrated by the conversion of the chloro and methoxy amides **81** and **83** to their respective quinones **82** and **84** (2., 3.-Scheme 12). Both electron-withdrawing and electron-donating groups appear to be well tolerated by this transformation.

7.15.2.5 *p*-Oxidation of Mono- and Bis-Protected Hydroquinones and Derivatives (1 ox.)

Although the deprotection and oxidation of bis-protected hydroquinone derivatives require fairly strong oxidants such as CAN and argentic oxide (AgO), the oxidations of mono-protected hydroquinones are known to proceed with a plethora of mild oxidants.

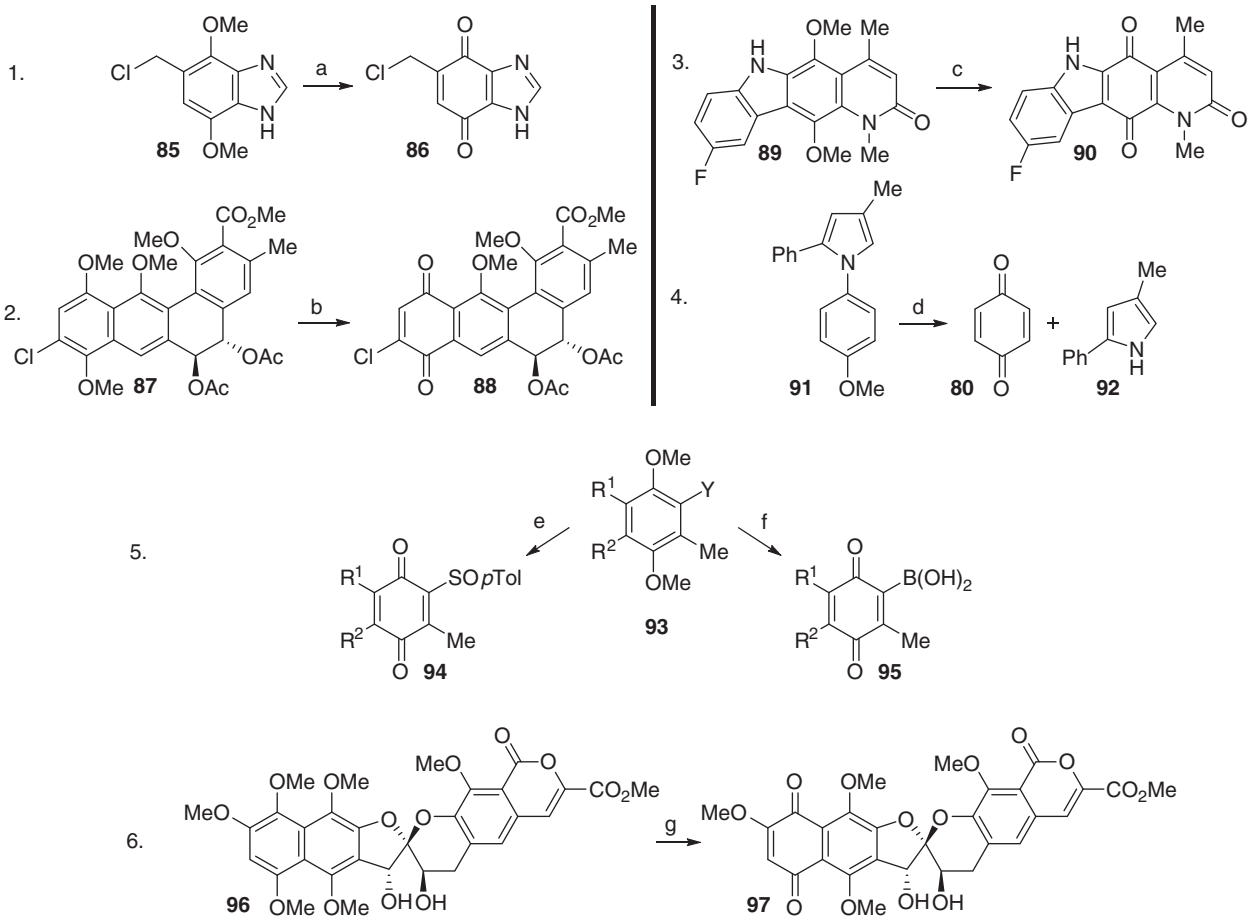
7.15.2.5.1 Hydroquinone derivatives requiring bis-deprotection

The oxidative deprotection of two protecting groups, commonly two methoxy residues, is often utilized because it enables the practitioner to carry two robust alkoxy-residues through a multistep synthetic sequence before revealing the underlying *p*-quinone. Within this realm of strategies CAN and AgO have proven particularly useful.

7.15.2.5.1.1 CAN

The venerable reagent, CAN, which has been discussed earlier in detail (see Sections 7.15.2.3.1.4 and 7.15.2.5.1.1), is probably best known for its use in affecting a concomitant bis-deprotection and oxidation of alkoxy-protected hydroquinone derivatives. It displays outstanding selectivity and tolerance among other functional groups as shown by the many examples presented (Scheme 13). Most examples involve the oxidation of a single ring within the compound to its corresponding *p*-quinone. However, oxidative demethylation with CAN has also occurred twice in different regions of the same structure, so long as the quinones are not in conjugation with one another.[52] Other oxidants such as AgO (see Section 7.15.2.5.1.2) and I(III) hypervalent iodides have proven useful in this capacity as well.[53] In addition, bis-protected systems can be subjected to demethylation with Lewis Acids (BX_3, HNO_3, HBr, etc.) and then be subjected to oxidation with one of many well-known milder oxidants.[54]

The chloro-benzimidazole **85** was reported to undergo oxidative demethylation in an acetonitrile and water with excess CAN to afford the corresponding quinone **86** in 80% yield (1.-Scheme 13).[55] The untouched chloro-methyl residue indicates these are fairly gentle conditions. The electron-rich naphthazarin **87** was observed to undergo oxidative-demethylation with CAN under similar conditions to afford the chloro-quinone **88** in a nearly quantitative yield (2.-Scheme 13).[56] The electron-poor quinoline **89** was found to undergo oxidative demethylation to afford its corresponding quinone **90** in a gratifying 38% yield (3.-Scheme 13).[57] Other surrogate heteroatoms can also participate in this transformation. For example, the *p*-methoxy pyrrazole **91** was observed to produce the quinone **80** and return the pyrrole **92** in a 70% yield (4.-Scheme 13).[58] A similar oxidation was carried out with CAN on an electron-rich *p*-methoxy aniline ring.[59] These CAN conditions can also be used in simple aryl systems carrying electron-withdrawing groups. For example, useful quinones displaying both sulfoxides **94** and boronic acids **95** have all been prepared in



all reactions: CAN, MeCN/H_2O; a. r.t., 80% yield; b. 0 °C, >99% yield; c. 0 °C, 38% yield; d. −10 °C, 76% yield; e. r.t., 71–89% yield; f. 0 °C, 65–99% yield; g. 0 °C, 77% yield.

Scheme 13 CAN oxidative demethylation.

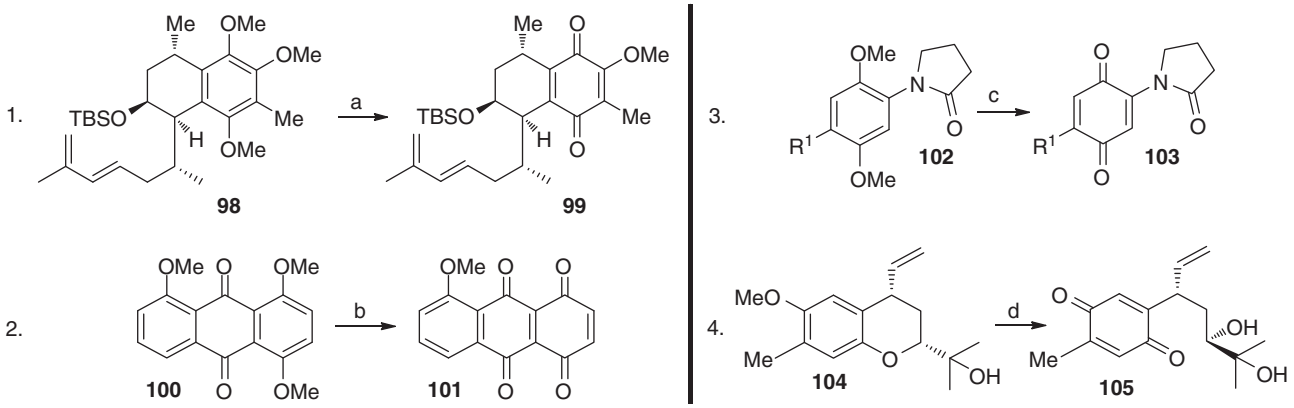
this manner from their respective bis-methoxy derivative **93** by treating with CAN (5.-Scheme 13).[60] Under CAN conditions the aryl rings of **96** were distinguished to afford the naphthoquinone **97** in a 77% yield (6.-Scheme 13).[61] However, although CAN is selective for the formation of *p*-quinones, it may lead to both *o*- and *p*-quinones depending on the quantity and placement of methoxy substituents on the aromatic ring as shown by problems in the syntheses of ilimaquinone,[62] hyatellaquinone,[63] and nakijiquinone.[64]

7.15.2.5.1.2 AgO

AgO is a powerful oxidant that is an equal mixture of Ag(I) and Ag(III) ($Ag_2O{\cdot}Ag_2O_3$). It is often erroneously believed to be Ag(II), as suggested by its compacted formula 'AgO.' This reagent should not be confused with silver(I) oxide (Ag_2O), a very mild oxidant that smoothly transforms hydroquinones and catechols into their corresponding *para*- and *ortho*-quinones (see Sections 7.15.2.8 and 7.15.3.6). AgO has been used in conjunction with nitric acid in dioxane at room temperature for oxidative demethylation.[65]

The naphthazarin intermediate **98** was reported to afford the quinone **99** in 27% yield along with numerous by-products, when treated with 5 equivalents of 'AgO' in 6M HNO_3 and dioxane at room temperature (1.-Scheme 14).[66] However, when the butadiene substituent within this molecule was masked as a cyclic sulfone, the yield of this oxidative demethylation increased to 79%. Although the authors make no mention, it can be speculated that the application of CAN with **98** likely results in a mixture of *para*- and *ortho*-quinones, which led to their examination of 'AgO'. The anthraquinone **100** was observed to undergo oxidative demethylation to its corresponding diquinone **101** in a 98% yield (2.-Scheme 14).[67] To the best of the chapter authors' knowledge, 'AgO' is the only oxidant documented to form diquinones, such as **101**. AgO oxidation of the trimethoxyaromatic lactam **102** (R=OMe) afforded the corresponding quinone **103** in a 39% yield (3.-Scheme 14).[68] When R=Br, the reaction was reported to proceed almost quantitatively. However, when R=H, the oxidation did not work, presumably because of the reactivity of the nitrogen atom's *para*-position. The oxidation of benzopyran **104** was observed to proceed to the quinone **105** in 62% yield when employing (AgO), whereas CAN led to the corresponding *mono*-demethylated product and a mixed quinone ketal by

participation of the tertiary alcohol (4.-Scheme 14, ketal and unprotected products not shown).[69] When (AgO) has been applied to aromatic systems containing four or more methoxy substituents, *ortho*-hydroxy-*para* quinones are formed as opposed to their *para*-hydroxy*ortho* quinone counterparts.[70]



a. AgO, 6 M HNO_3, dioxane, 25 °C, 27% yield; b. AgO, dil. HNO_3, acetone, 50 °C, 98% yield; c. AgO, 6 M HNO_3, dioxane, r.t., 39–99% yield; d. AgO, 6 M HNO_3, dioxane, r.t., 62% yield.

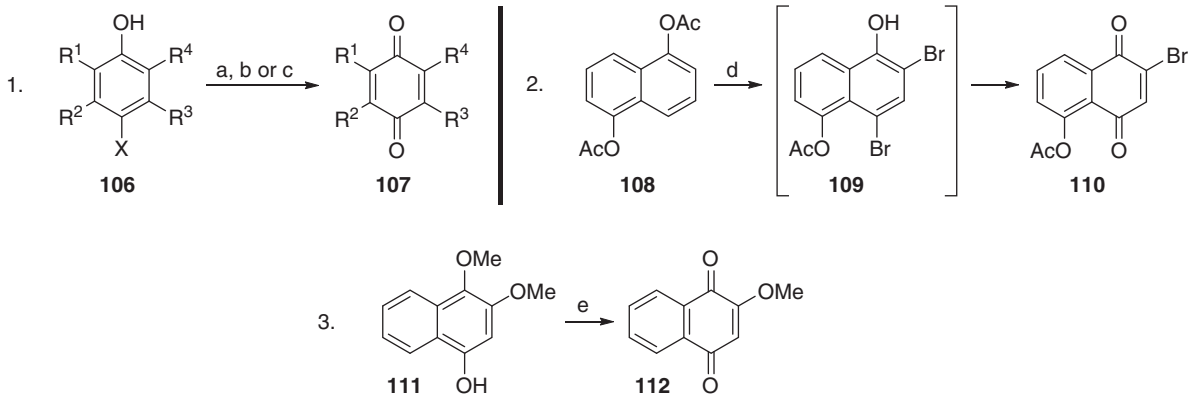
Scheme 14 AgO oxidative demethylation (Ag(I) and Ag(III)).

7.15.2.5.2 Oxidation of mono-protected hydroquinones and derivatives

Although nearly all of the oxidants that have been previously discussed (CAN, O_2, I(III) and I(V) reagents, CrO_3) are effective at this facile transformation, a plethora of very mild oxidants, such as Ag_2O, $FeCl_3$, and Me_2S-NCS, can prove just as useful for the oxidation of mono-protected hydroquinones.

7.15.2.5.2.1 p-Halo and p-alkoxy phenols

Oxidations of *para*-halo, amino, sulfoxy, and alkoxy phenols are rather facile to obtain *p*-quinones in a single step (Scheme 15). Thus, because it is often easier to introduce a *para*-halogen atom onto a phenol rather than an oxygen substituent, it can be a valuable strategy for building quinones.



a. CrO_3, AcOH, H_2O, 50 °C, 44% yield; b. $Ca(OCl)_2$, DMF, H_2O, 48% yield, X=Cl; c. CAN, MeCN, H_2O, r.t., 79–93% yield; d. NBS, AcOH/H_2O, 55 °C, 92% yield; e. CAN, MeCN/H_2O, 91% yield.

Scheme 15

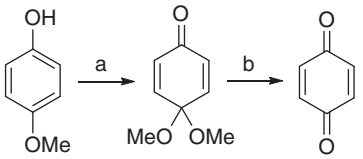
For example, chromium trioxide,[71] calcium hypochlorite,[72] and CAN[73] have all been used to transform various *p*-halo phenols **106** into their corresponding *p*-quinones **107** in moderate-to-good yields (1.-Scheme 15). Since phenols and their alkoxy derivatives are usually *para*-directors, it is possible to incorporate the halogenation into a two-step, double oxidation process to reach the quinone.[74] For example, the bis-acylated 1,5-naphthalenediol **108** was smoothly transformed to the bromo-naphthoquinone **110** in 99% yield on exposure to *N*-bromo-succinimide (>3 equivalents) and water (2.-Scheme 15).[75] The authors presume that

the first two equivalents of electrophilic bromine are incorporated onto the naphthoquinone to afford **109** or its bis-acetoxy counterpart, which succumbs to further oxidation with NBS resulting in a phenoxonium that is intercepted by water. This process has also been successfully used on several other naphthol derivatives not shown.[76] In addition to using the bromide as a surrogate for an oxygen substituent, *p*-quinones can also be realized from phenols bearing a *para*-sulfoxide that succumbs to a Pummerer rearrangement.[77] Additionally, the simple *p*-methoxy phenol, such as **111**, has been reported to undergo CAN oxidation and afford the α-methoxy naphthoquinone **112** in 91% yield (3.-Scheme 15).[78]

7.15.2.6 *p*-Quinone Ketals and *p*-Quinols (0–1 ox.)

p-Quinones can also be derived from deprotection of *p*-quinone ketals by hydrolysis of the ketal or by rearrangement and oxidation of *p*-quinols and their derivatives. The methods to synthesize and hydrolyze *p*-quinone ketals and to construct *p*-quinols have been extensively reviewed elsewhere, so the authors' discussions are confined to their deprotection and rearrangement.[79]

Mono-protected hydroquinones such as **113** are transformed into *para*-quinone ketals **114** by a number of oxidants deployed in methanol including DDQ; however, hypervalent I(III) reagents are most common (Scheme 16).[80] Hydrolysis of this quinone ketal substrate **114** is then accomplished by exposure to protic acid in the presence of water resulting in the formation of the quinone **80**. Though obscure, this protective stratagem can prove useful, should the reactivity of the quinone need to be temporarily masked.



a. Oxidation; b. Hydrolysis

Scheme 16

These, *p*-quinol precursors and their derivatives can be prepared in water or alcohol solvent by addition of an alkyl group to one of the carbonyls of a *p*-quinone, or by oxidation of a *p*-alkyl substituted phenol (Figure 6). In the presence of base a *p*-quinol can undergo a 1,2-sigmatropic shift. This transformation, which is known as an acyloin rearrangement or as subset of the dienone-phenol rearrangements, proceeds in both acidic and basic conditions to afford a *p*-hydroquinone or its mono-protected counterpart. The migratory aptitude of the R residue (1°, 2°, 3°) reverses under acidic or basic conditions (-methyl migration is facile under basic conditions, but difficult under acidic conditions). In both instances, further oxidation is required to access the *p*-quinone (see Section 7.15.2.8). More recently, the use of *tert*-butyl-peroxy ethers precludes the final oxidation step and accesses the *p*-quinone directly by rupturing the peroxide bond resulting in the release of a *tert*-butoxy radical to serve as the oxidant.

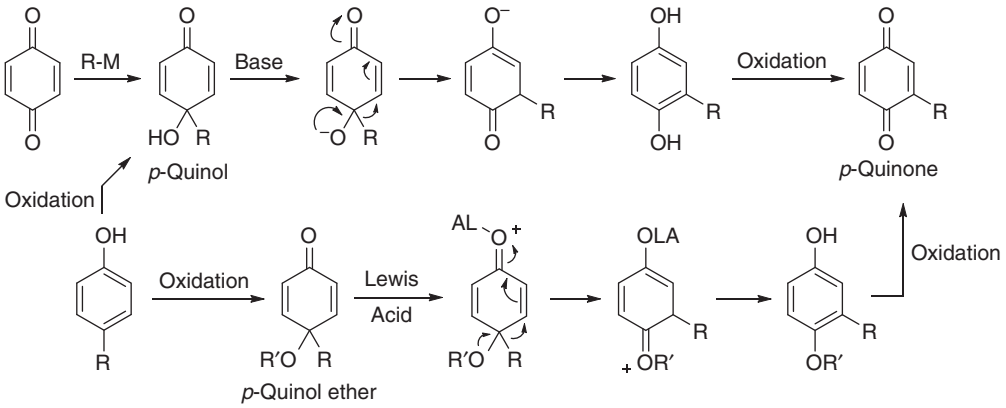
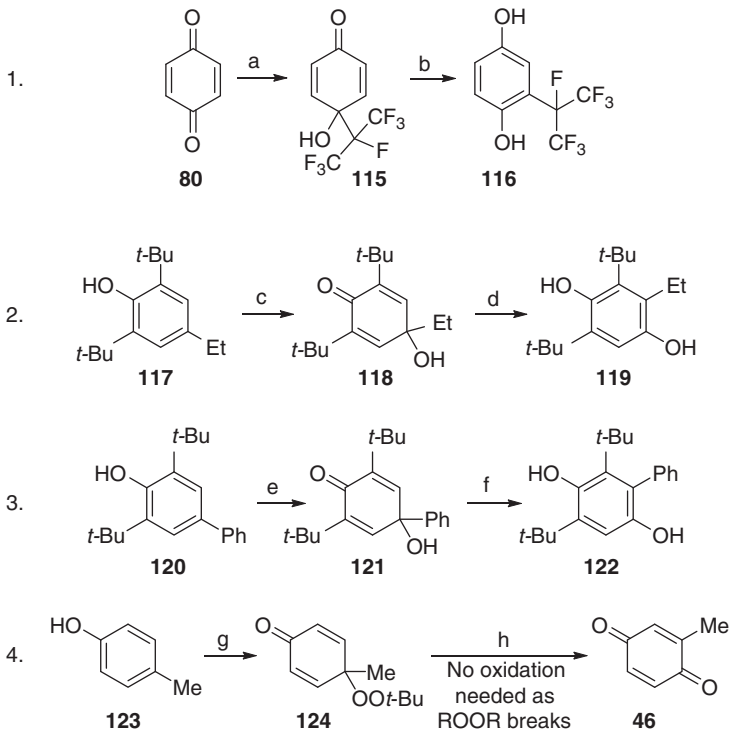


Figure 6 Base- and acid-promoted rearrangement of *p*-quinols and their derivatives.

The quinone **80** was shown to undergo addition of the per-fluorinated isopropyllithium species to afford a 22% yield of the *p*-quinol **115** and a 14% yield of the rearranged hydroquinone **116** (1.-Scheme 17).[81] Resubmission of the initial *p*-quinol product **115** to potassium *tert*-butoxide affords the hydroquinone **116** in a 76% yield. In a related example, the phenol **117** was converted to its *p*-quinol **118** by exposure to potassium hydroxide and oxygen (2.-Scheme 17).[82,83] Exposure of the *p*-quinol to potassium

tert-butoxide in DMF led to the hydroquinone **119**. In a related quinol example, the phenol **120** was oxidized to quinol **121** and then underwent rearrangement to form the phenyl-substituted hydroquinone **122** (3.-Scheme 17).[82] It is to presume that all these hydroquinone products can then be easily converted into their corresponding *p*-quinones by facile oxidation (see Section 7.15.2.8). More recently, *p*-alkylated phenols, such as **123**, have been found to undergo oxidation with ruthenium and *tert*-butyl hydrogen peroxide to afford their corresponding *p*-peroxy-quinols, similar to **124** (4.-Scheme 17).[84] Subsequent exposure of **124** to $BF_3 \bullet Et_2O$ in a mixture of toluene and hexafluoroisopropanol afforded the quinone **46** in 84% yield.



a. *i*-C_3F_7I, MeLi-LiBr, ether, –25 °C, 22% yield (**115**), 14% yield (**116**);
b. KO*t*-Bu, DMSO, 25 °C, 76% yield; c. O_2, KOH, EtOH, H_2O; DMS, >92% yield;
d. KO*t*-Bu, DMF, 25 °C, 100% yield; e. O_2, KOH, EtOH, H_2O, no yield given;
f. KO*t*-Bu, DMF, 25 °C, >99% yield; g. $RuCl_2(PPh_3)_3$ (1.5 mol%), *t*-BuOOH, benzene, r.t., 97% yield; h. $BF_3.Et_2O$, HFIP/toluene, 84% yield.

Scheme 17

A different outcome emerges from fused systems (Figure 7). In this instance, the initial rearrangement of the quinol results in an unstable spirocycle. The least sterically encumbered alkyl substituent, usually orientated axially, then undergoes a 1,2-shift. The resulting cation then loses a proton to restore aromaticity and produce the corresponding hydroquinone, which further oxidizes to the quinone. This strategy has been used to produce steroidal quinones from both *p*-quinols and their corresponding *p*-peroxy-quinol ethers (Scheme 18).[85]

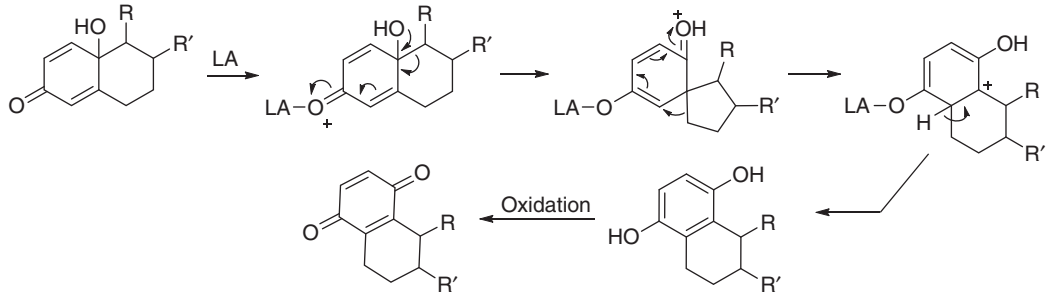
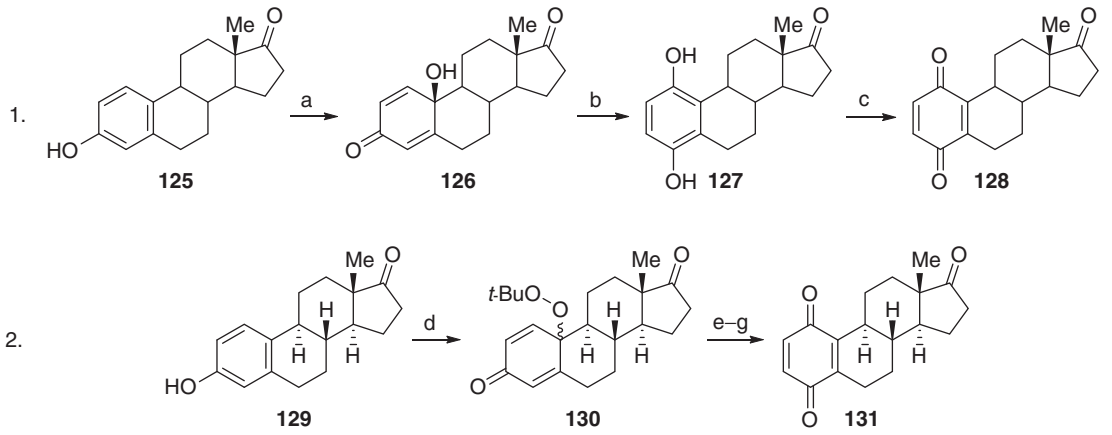


Figure 7 Lewis acid-promoted Dienone–Phenol rearrangement.



a. *m*-CPBA, $(BzO)_2$, CH_2Cl_2/acetone, hν, reflux, 57% yield; b. AcOH/HCl/H_2O, reflux; c. Ag_2O, THF, r.t., 99% yield (2 steps); d. $RuCl_2(PPh_3)_3$ (3 mol%), *t*-BuOOH, 89% yield (1:1 ratio); e. ZnI_2, Ac_2O/AcOH, r.t., 69% yield; f. HCl, MeOH, reflux; g. $FeCl_3$ (aqueous), 63% yield (2 steps).

Scheme 18

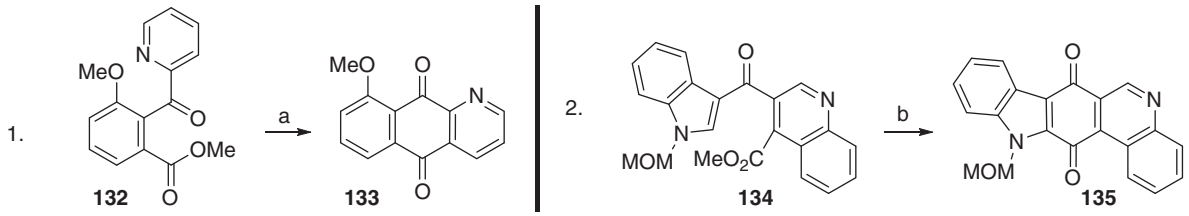
For example, photochemical irradiation of the phenol **125** in the presence of *m*-CPBA was shown to provide the quinol **126** in 54% yield (1.-Scheme 18).[86] Addition of acid was then found to produce the hydroquinone **127**, which produced the *p*-quinone **128** on oxidation with Ag_2O. The ruthenium-mediated oxidation of phenol **129** afforded the peroxy-ether **130** in 89% yield (2.-Scheme 18).[87] Further rearrangement, which was triggered by treatment of a Lewis acid, was found to afford the tetracyclic quinone **131** in 63% yield.

7.15.2.7 Carbon–Carbon Bond-Formation Strategies (≥0 ox.)

Quinones can also be accessed fairly easily by one of several six-membered ring-forming strategies involving a few transformations. The methods that follow stand out as particularly useful transformations: Friedel–Crafts acylation, 6π and bi-radical rearrangements of squaric acid adducts, application of maleoylmetal complexes or application of chromium carbenes with alkynes, Diels–Alder reactions of oxygenated dienes, and Hauser enolate chemistry of functionalized lactones.

7.15.2.7.1 Friedel–Crafts acylation and related processes

To access a *p*-quinone within an anthracene core, an intramolecular Friedel–Crafts acylation (see 1.-Scheme 10) can be performed with a benzophenone containing an *ortho*-positioned ester (Scheme 19). However, the construction of the desymmetrized benzophenone starting materials for these sequences can prove awkward.



a. LDA, HMPA, THF, –78 °C, 55% yield; b. TMEDA, LHMDS, THF, –78 °C, 54% yield.

Scheme 19

For example, the methyl benzoate **132** displaying an *ortho*-positioned acyl pyridine was reported to undergo lithiation with LDA on the pyridine ring and then cyclize onto the methyl ester to afford the quinone **133** in good yield (1.-Scheme 19).[88] In a related example, the MOM-protected pyrrole **134** undergoes a similar vinyl deprotonation and intramolecular cyclization with the neighboring methyl ester to form the *p*-quinone, **135** (2.-Scheme 19).[89]

7.15.2.7.2 6π Rearrangement of vinyl ketenes from vinylated hydroxycyclobutenones

Another general strategy for the synthesis of complex quinones begins by vinyl anion addition to derivatives of squaric acids or other cyclobutenediones.[90] On heating of the γ-hydroxy-cyclobutenone adduct, a vinyl ketene forms and then participates in a 6π rearrangement resulting in a hydroquinone that can be further oxidized (Figure 8).

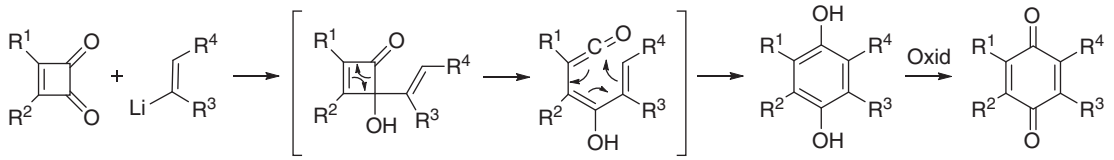
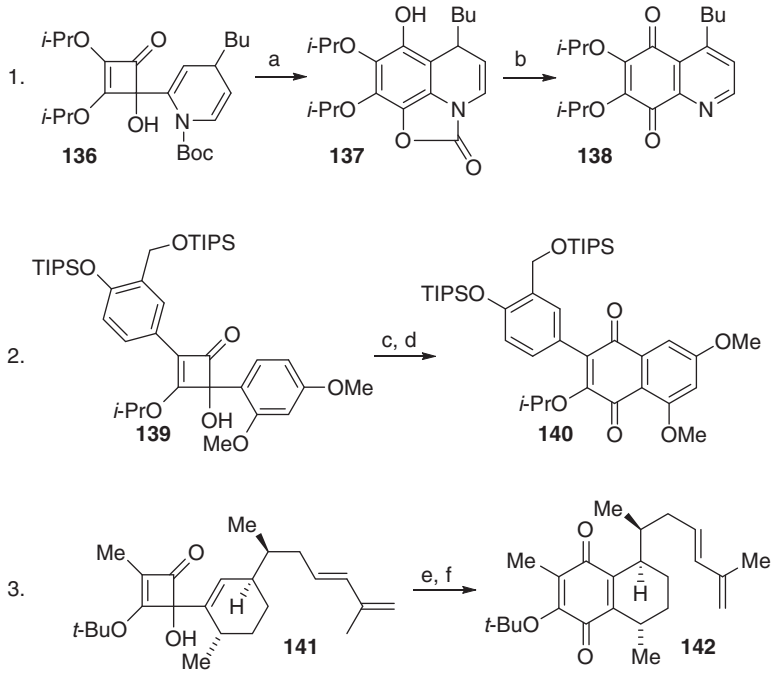


Figure 8 Rearrangement of cyclobutenediones by addition of vinyl anions.

If the intermediate hydroquinone is electron-rich, oxidation generally proceeds immediately with air; alternatively, other chemical oxidants can be used. However, the construction of dissimilarly functionalized squaric acid derivatives and cyclobutenones displaying dissimilar carbonyl reactivity can prove tedious. Despite these limitations, there are numerous examples and reviews of this transformation that was first popularized by Harold Moore.

For example, heating the dihydropyridine adduct **136** to 160 °C in an oxygen-free system furnished the 1,4-dihydroquinoline hydroquinone **137** in 65% yield (1.-Scheme 20).[91] Further oxidation of the hydroquinone was achieved by two equivalents of *o*-chloranil to produce the quinolinic quinone **138**. Heating of the nonsymmetrical cyclobutenone **139** and further oxidation of the intermediate hydroquinone with Ag_2O afforded the naphthoquinone **140** in 53% overall yield (2.-Scheme 20).[92] The quinone **142** was produced in a similar fashion in 80% overall yield, by simply heating the cyclobutenone **141** in tetrahydrofuran (THF) solvent followed by air oxidation (3.-Scheme 20).[93]



a. Heat, 65% yield; b. *o*-chloranil, AcOH, 93% yield; c. *p*-xylene, 138 °C; d. Ag_2O, K_2CO_3, 53% yield (2 steps); e. 110 °C, microwave, THF; f. Air oxidation, r.t., 80% yield (2 steps).

Scheme 20

Related alkynyl cyclobutenedione intermediates have been shown to rearrange through biradical species (Figure 9). Hydride abstraction from the solvent affords a hydroquinone that can be further oxidized to form the corresponding quinones. Alternatively, the carbon radical intermediate can be intercepted to form additional carbon–carbon bonds, thereby increasing the utility of this strategy.[94]

For example, the alkynyl cyclobutenone **143** undergoes rearrangement, hydride abstraction, and *in situ* air oxidation to afford the quinone **144** in 86% yield by simply heating in xylenes (1.-Scheme 21).[95] When both an alkynyl and an allyl ether fragment are annealed onto the *gamma* carbon of the cyclobutenone, the rearrangement initially produces a phenol biradical species **146** from **145**, and the vinyl radical then undergoes intramolecular addition to the allyl fragment to liberate another alkoxy radical that rearranges into the quinone **147** (2.-Scheme 21).[96] Heating of the alkynyl cyclobutenone **148**, which was outfitted with a benzhydrol-protected unsaturated amide at its distal propargylic carbon, was observed to undergo rearrangement and further intramolecular cyclization to form the six-membered lactam **149** (3.-Scheme 21).[97] Rearrangement of the cyclobutenone **150**,

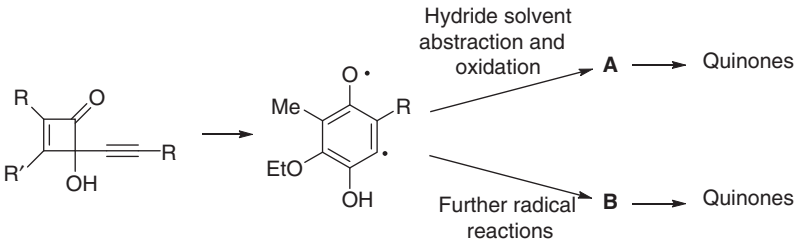
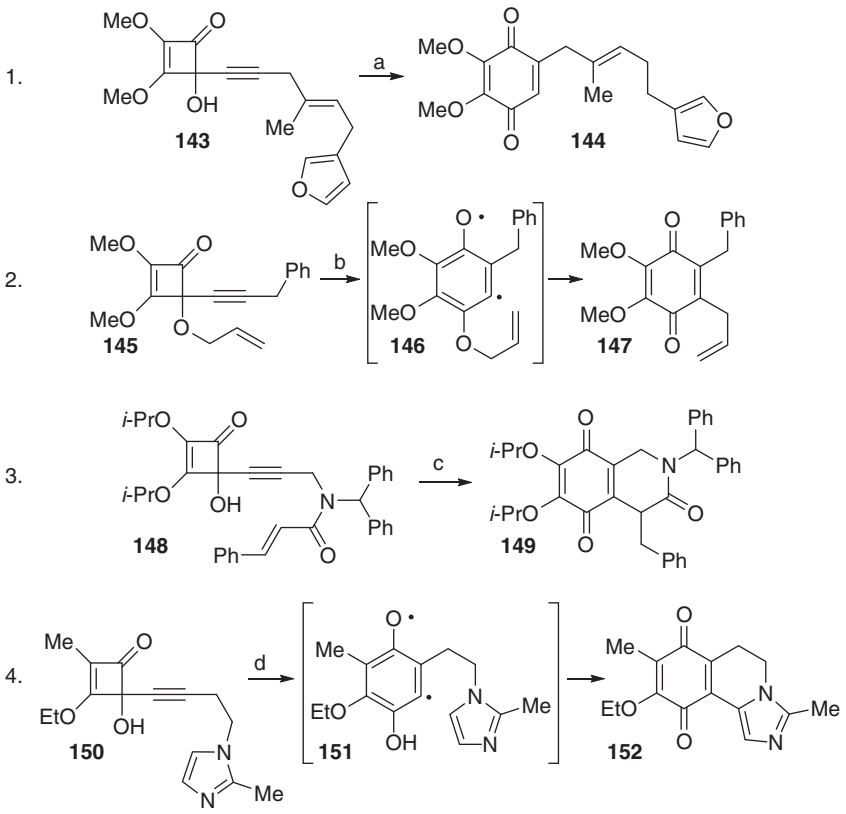


Figure 9 Alkynyl cyclobutenedione rearrangements.



a. *p*-xylene, 138 °C, 86% yield; b. *p*-xylene, 138 °C, 76% yield; c. xylenes, reflux, 67% yield; d. MeCN, reflux; O_2, r.t., 24% yield.

Scheme 21

which displays a homopropargylic imidazole ring, was found to proceed to the quinone **152** by the intermediacy of the biradical **151** (4.-Scheme 21).[98]

7.15.2.7.3 Transition metal species

There are smatterings of examples of maleoylmetal complexes undergoing reactions with acetylenes to afford quinones (a-Figure 10). These complexes arise from the reaction of Fe, Co, Mo, Mn, and Rh transition metal complexes with acetylenes, di-acid chlorides, di-halides, squarates, and various cyclobutenediones. However, in most of these examples, the regiochemical issues are not resolved and the strategy is relegated to symmetrical substrates. However, chromium hexacarbonyl has been used in conjunction with lithiated vinyl and aryl intermediates to assemble a carbenoid species, both of which lead to mono-protected hydroquinones on their regioselective reaction with acetylenes (b-Figure 10). Specific examples of these two processes follow.

7.15.2.7.3.1 Cobalt, rhodium, and iron maleoylmetal and phthaloylmetal complexes

A solid, which was speculated to be the maleoyl rhodium complex **153**, was observed to undergo addition with 3-hexyne **154** to afford the quinones **155** and **156** (1.-Scheme 22).[99] The phthaloyliron complex **157**, which was prepared from photolysis of a

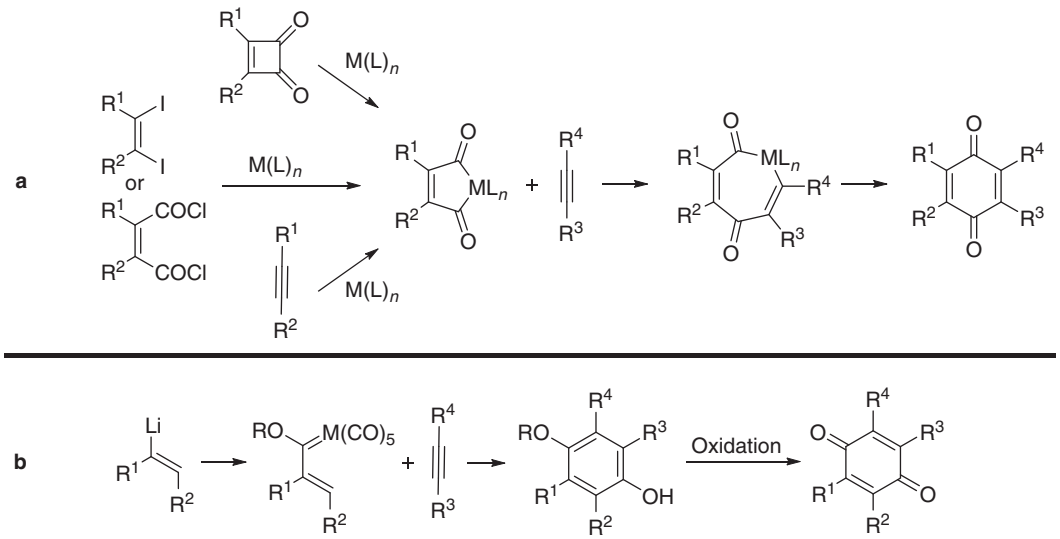


Figure 10 Metaleoylmetal complexes and their use in quinone formation.

mixture of $Fe(CO)_5$ with *o*-di-iodobenzene in acetone, has been shown to undergo reaction with various acetylenes including 2-butyne **158** (2.-Scheme 22).[100] On acidification in air the corresponding naphthoquinone **160** was produced in a 99% yield. The intermediate **159** was confirmed by isolation of its corresponding diacetate in reactions carried out in acetic anhydride. The phthaloylcobalt complex **161** showed reasonable regiocontrol in its intermolecular reaction with 1-butyne **162** mediated by Ag(I) to provide the naphthoquinone **163** (3.-Scheme 22).[100] Intramolecular regiochemical control was achieved from the cobalt species **164** in its reaction with the tethered acetylene (4.-Scheme 22).[100] The cobalt species **166** was also observed to exhibit some regiocontrol on reaction with a range of acetylenes containing electron-withdrawing and electron-donating substituents (5.-Scheme 22).[101]

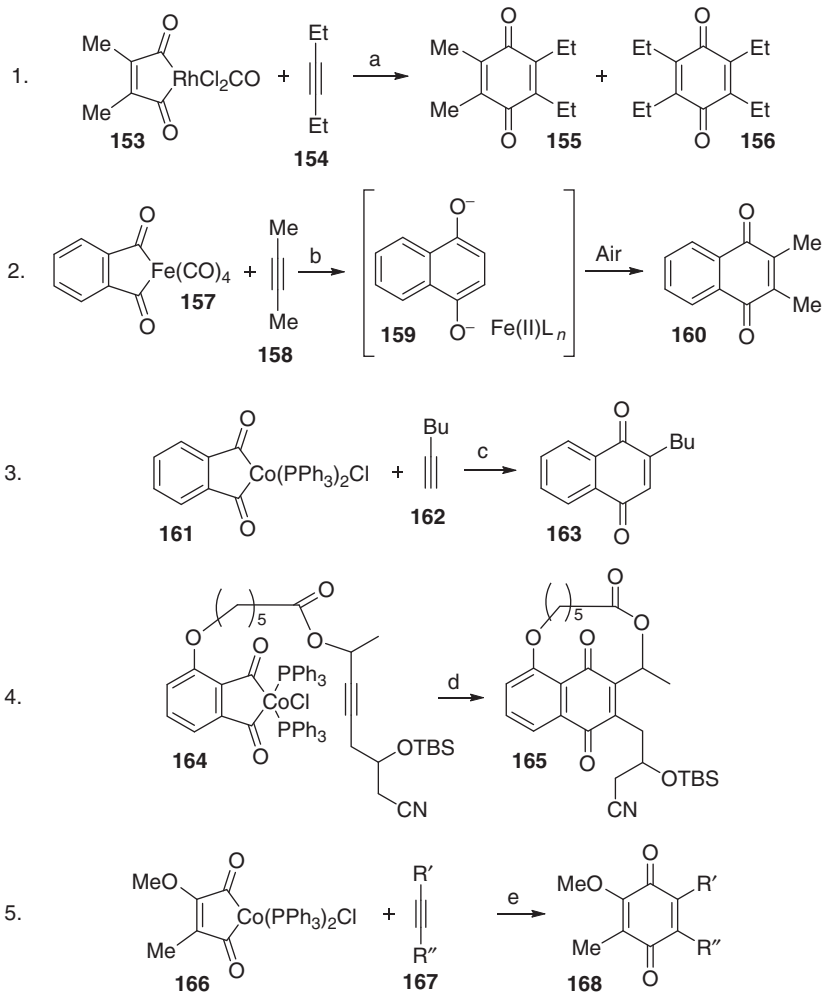
7.15.2.7.3.2 Chromium carbenes

The Wulff–Dötz reaction has often been used to construct quinones from pentacarbonyl chromium carbene intermediates and selected alkynes.[102,103] The regiochemistry is controllable; but the best results are usually observed with terminal alkynes.

In the synthesis of 12-*O*-methyl royleanone **173**, a Wulff-Dötz reaction was used to construct its *p*-quinone core (1.-Scheme 23).[9] The pentacarbonyl chromium complex was first prepared from the corresponding hydrazone **169** via the lithium intermediate **170**. Addition of chromium hexacarbonyl and triethoxytetrafluoroborate furnished the desired chromium carbene species **171**. Heating of the methoxyacetylene **172** with the chromium carbenoid **171** afforded a *p*-ethoxy-phenol intermediate that was subsequently oxidized with CAN to provide *p*-quinone **173** in 37% overall yield. For the total synthesis of (−)-arizonin C1 (**177**) the naphthalene core **176** was manufactured in 41% yield by submitting the chromium pentacarbonyl carbene **174** to the reaction with the siloxyacetylene **175** (2.-Scheme 23).[104] The resulting phenol product was protected as the corresponding methyl ether **176** and then further elaborated. Final deprotection and oxidation with CAN gave **177**. Chromium carbene complexes have also been used to form quinone boronic esters (4.-Scheme 23).[105] The indole **178** and alkyne **179** were observed to undergo reaction and afford the boronate ester derivative **180** in 64% yield. Although this chromium carbene reaction does not immediately access a quinone, it does access the mono-protected hydroquinone precursor in a short sequence, and methods to oxidize the mono-protected hydroquinone core are facile (see Section 7.15.3.3.1).

7.15.2.7.4 Diels–Alder strategies (≥0 ox.)

There are several Diels–Alder strategies that provide useful approaches for accessing quinones and their phenolic precursors.[106] Access to different dienes and dienophiles make these strategies flexible and useful for intricate systems, because a Diels–Alder reaction usually provides good regiocontrol. In general, a highly oxygenated diene is employed to accomplish the desired task. Dienes, such as the furan **181**, the Chan's bis-siloxy diene **182**,[107] and Brassard's diene (R=Me) **183**[108] all prove very useful for addressing monocyclic quinones. However, to reach the desired *p*-quinone systems with rudimentary dienophiles, a series of deprotections and oxidations are usually required after the deployment of these dienes, and combination with dienophiles carrying an additional easily eliminated group improve the efficiency of the overall strategy. In particular, α-halogenated enones **184** and **185** serve as pseudo-acetylenic dienophiles, along with various actual acetylenes, such as methyl propiolate **186** or benzyne **187**. For syntheses aimed at larger systems, such as *p*-naphthoquinones and *p*-anthraquinones, a Diels–Alder strategy can still be used by the individual combination of **184–187** with various respective oxygenated dimethide precursors, such as **188–190**. Vinyl quinones derivatives of **191** can also prove useful to address other *p*-quinone systems (Figure 11).



a. Benzene, 80 °C; b. MeCN, 100 °C, 99% yield; c. MeCN, $AgBF_4$, 65% yield; d. MeCN, $AgBF_4$, 47% yield; e. dichloroethane, r.t., 50–81% yield.

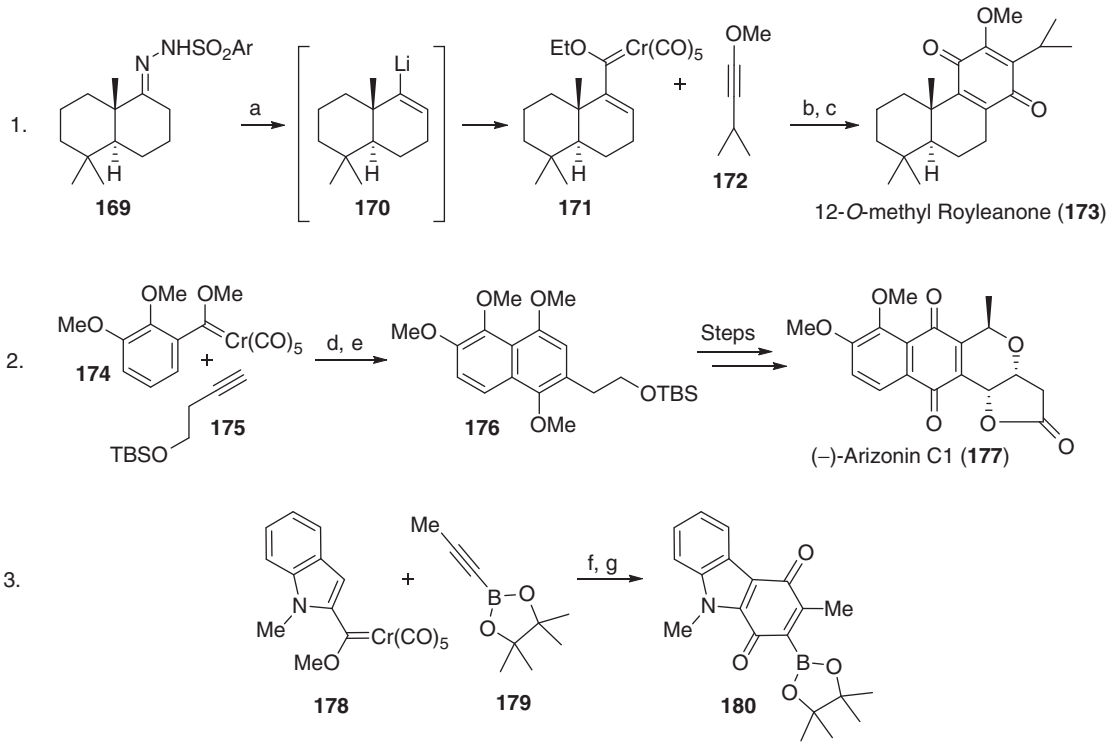
Scheme 22

7.15.2.7.4.1 Oxygentated butadienes and furan derivatives

Chan's bis-siloxy furan diene **192** serves as a bisketene synthon (1.-Scheme 24).[107] On reaction with acetylene **193** and hydrolytic workup, both the *p*-quinone **194** and the hydroquinone **198** products are formed in a 6:1 ratio. On refluxing diene **183** (R=TMS) with the α-brominated quinone **196** followed by the addition of silica gel, the naphthoquinone **197** was obtained in 73% yield (2.-Scheme 24).[73] The elimination of the methoxy group and the bromine atom from the intermediate adduct furnished the quinone **197** in the desired oxidation state. The related diene **198** was observed to undergo reaction with the quinone **199** to directly afford the anthraquinone **200** in low yield (3.-Scheme 24).[109] The diene **201** was found to undergo addition at 90 °C with the bis-chloroquinone **185** to afford the chlorinated naphthoquinone **202** (4.-Scheme 24).[110]

7.15.2.7.4.2 Aryl dimethides and isobenzofuran derivatives

The bis-oxygenated dimethide **204**, generated *in situ* by a thermal ring-opening of arylcyclobutene **203**, was observed to undergo cycloaddition with acetylene **193** to form the 1,4-oxygenated cyclohexadiene **205** (1.-Scheme 25).[111] Further addition of DDQ was reported to give the naphthoquinone **206** in 92% yield. In a related example, the isobenzofuran **207** was observed to undergo cycloaddition with a variety of benzynes **208** to furnish the corresponding bicycloadducts **209** (2.-Scheme 25).[112] Ring-opening with acid and further oxidation with PIDA provided the corresponding anthraquinone derivatives of **210**. The silylated isobenzofuran **212**, prepared by deprotonation of the lactone **211** in the presence of TMSCl, was found to undergo reaction with the cyclopentenedione **213** to afford the naphthazarin hydroquinone **214** in 62% yield (3.-Scheme 25).[113] Oxidative demethylation and tautomerization was induced at a later point so as to construct an analog of fredericamycin.



a. *n*-BuLi, –78 °C to –20 °C; $Cr(CO)_6$; Et_3OBF_4; b. THF, heat; c. CAN, HNO_3, 37% (3 steps); d. THF, 45 °C; e. MeI, K_2CO_3, acetone, 50 °C, 41% (2 steps); f. THF, 45 °C; g. CAN, HNO_3, r.t., 64% (2 steps).

Scheme 23

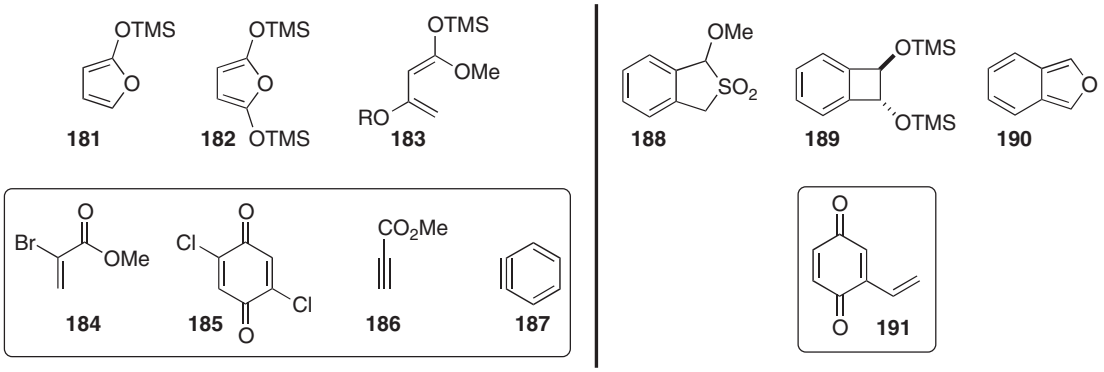


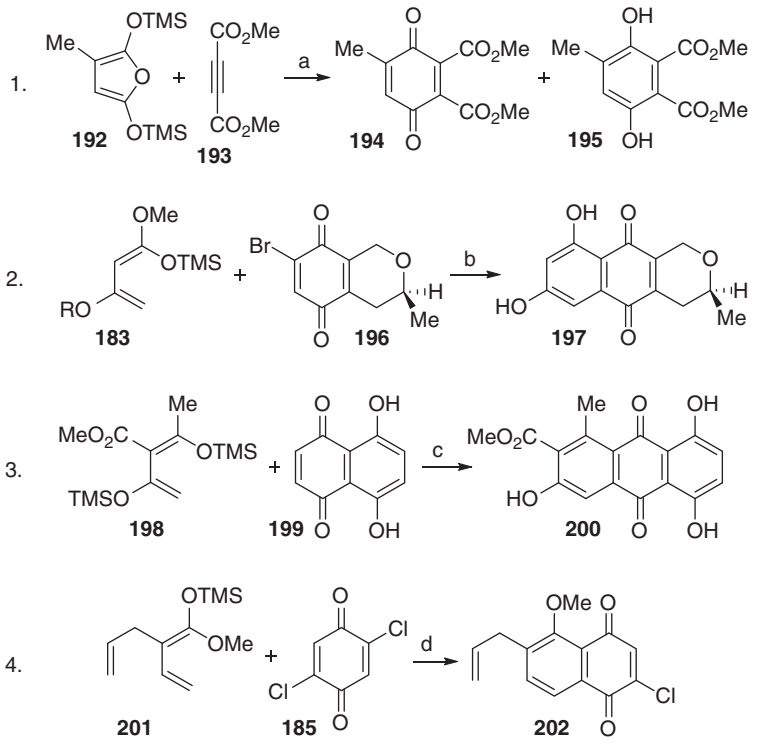
Figure 11 Useful dienes and dienophiles for Diels–Alder approaches.

7.15.2.7.4.3 Vinyl quinones

Some Diels–Alder approaches for complex *p*-quinones involve a vinyl *p*-quinone as the initial diene. Although the cycloaddition product is not a quinone, the adduct usually contains a group, or groups, that can be readily eliminated so as to furnish a hydroquinone core that can be further oxidized. For example, the vinyl quinone **215** was observed to undergo an intramolecular cycloaddition to furnish **216**, which rearranged to the hydroquinone **217** (1.-Scheme 26).[114] Further oxidation afforded (−)-pycnanthuquinone C (**218**). In another example, the vinyl quinone **219** undergoes an intramolecular cycloaddition to afford the cyclohexene-1,4-dione **220** (2.-Scheme 26).[115] Further 1,4-conjugate addition of water and elimination of the *β*-methoxy group from the resulting enol was found to produce the quinone **221**.

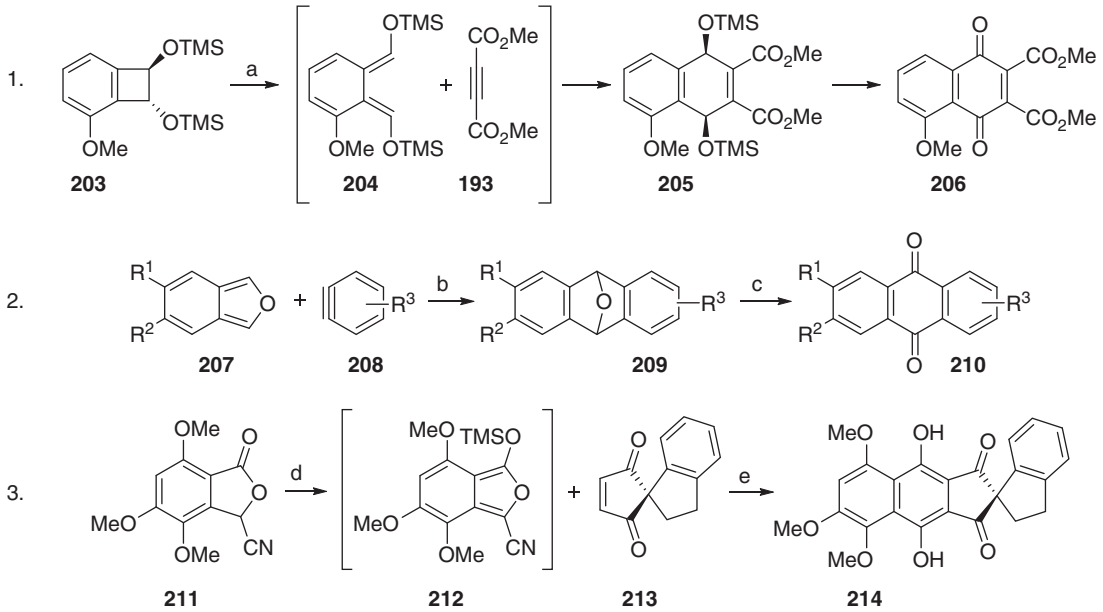
7.15.2.7.5 Hauser enolate chemistry

Hauser's enolate chemistry provides a strategy that is somewhat complementary to the foregoing Diels–Alder strategies.[116] Because the method employs an enolate for a sequential 1,4-conjugate addition and Dieckmann cyclization, it overpowers other directing



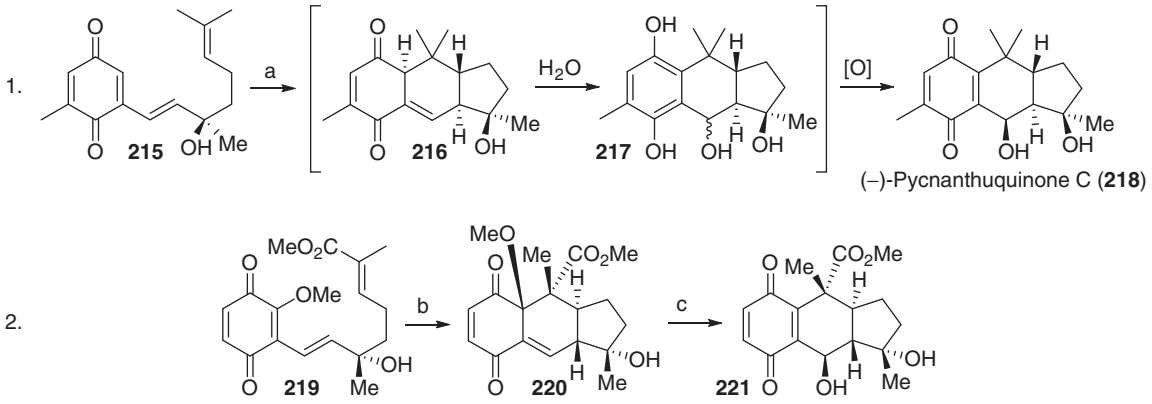
a. neat, r.t.; MeCN/H_2O, **194:195** (6:1), >95% yield; b. toluene, reflux; SiO_2, 73% yield; c. heat, toluene/H_2O/THF, air, 29% yield; d. benzene, 90 °C; 110–130 °C, 70% yield.

Scheme 24



a. 120 °C; DDQ, THF, 22 °C, 92% yield; b. $CHCl_3$ or CH_2Cl_2, r.t., 52–80% yield; c. PIDA, TfOH, CH_2Cl_2, r.t., 67–81% yield; d. *t*-BuLi, –78 °C, THF; TMSCl, –78 °C to 25 °C; e. –78 °C to 25 °C; SiO_2, 62% yield (2 steps).

Scheme 25

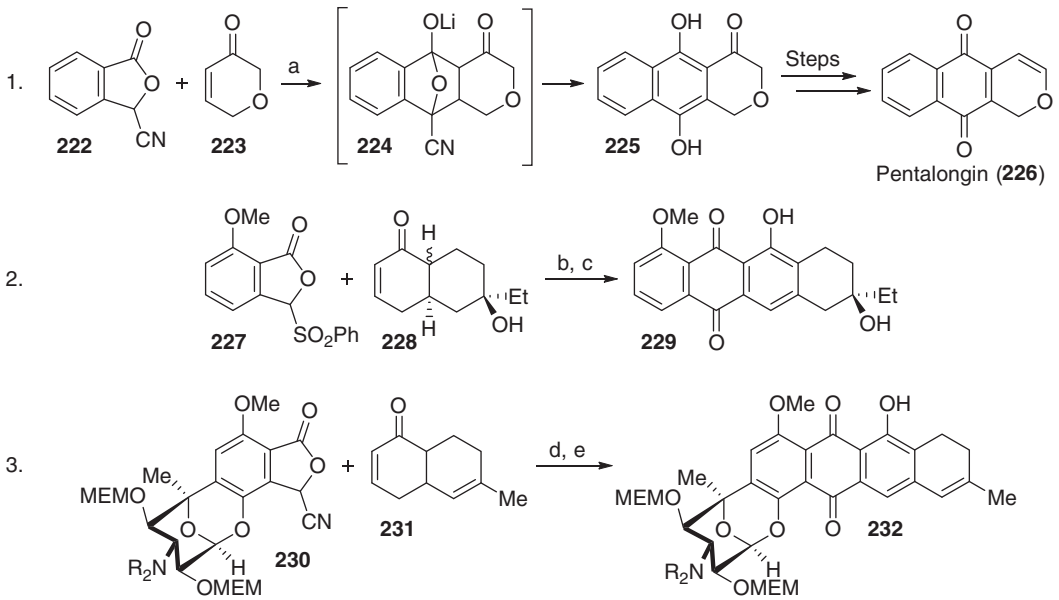


a. toluene/H_2O, 60 °C, 21% yield; b. toluene, 170 °C, 55% yield; c. toluene/H_2O, 80 °C, 70% yield.

Scheme 26

groups and provides good control of potential regiochemical outcomes. This reaction begins by deprotonation of a phthalide substituted in the 3-position with a leaving group, usually $-SO_2Ph$ or –CN. The most commonly used bases for deprotonation are lithium-derived, such as lithium *tert*-butoxide or lithium diisopropylamide (LDA). The reaction sequence proceeds through an oxo-bicyclic intermediate, which undergoes ring-opening and elimination of the leaving group –OS(O)Ph or –CN to form a cyclohexendione. Additional oxidation affords the corresponding *p*-quinone.

For example, the cyanophthalide **222** was deprotonated with lithium *tert*-butoxide and found to undergo addition with the 6*H*-pyran-3-one **223** to produce the dihydro-anthraquinone **225** via the intermediate bicyclic adduct **224** (1.-Scheme 27).[117] The hydroquinone was then converted into the anthraquinone **226** through additional steps concluding with a CAN oxidative demethylation. However, the methoxylated sulphonylphthalide **227**, which was deprotonated with lithium *tert*-butoxide, was observed to undergo addition with the cyclohexenone **228** and after *in situ* expected oxidation with molecular oxygen gave the anthraquinone **229** in 85% yield (2.-Scheme 27).[118] In addition, deprotonation of cyanophthalide **230**, in combination with the decalenone **231**, and oxidation with oxygen and salcomine was reported to afford the anthraquinone **232** in a 78% yield (3.-Scheme 27).[119]



a. LiO*t*-Bu, LiCl (cat.), THF, –78 °C, r.t., 16 h, 88% yield; b. LiO*t*-Bu, THF; c. O_2, DMF, 45 °C, 85% (2 steps); d. LDA, HMPA, THF, 65% yield; e. O_2, salcomine, DMF, 78% yield.

Scheme 27

7.15.2.8 Oxidation of Hydroquinones (1 ox.)

Hydroquinones and their derivatives are easily oxidized into their corresponding quinones using a variety of oxidants (Figure 12). Indeed, the reaction is often difficult to stop in the case of electron-rich substrates. Some of the most reliable oxidants include those reagents that have already been mentioned along with $FeCl_3$,[120] Ag(I),[121] MnO_2,[122] DDQ,[123] and DMDO.[124]

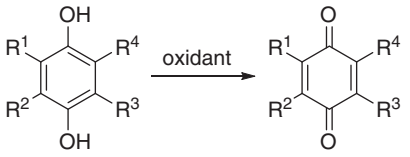


Figure 12 Oxidation of a hydroquinone to the corresponding *p*-quinone.

7.15.3 *ortho*-Quinones; a Strategic Summary

There are far fewer strategies for addressing *ortho*-quinones than there are for their *para*-quinone counterparts. This limitation is in part due to the polarity and instability of *o*-quinones resulting in their proclivity toward dimerization and other undesirable reactions. Moreover, *o*-quinones, which contain adjacent carbonyl residues, are dissonant compounds requiring an umpolung and are therefore not easily created by classical consonant carbon–carbon bond-formation strategies. Most efforts have chosen to target a precursor that requires at least two or three additional oxidations; one of which installs an additional *ortho* oxygen atom and accomplishes the umpolung. All of the strategies for *o*-quinones, of which the chapter authors are aware, are summarized (Figure 13). The section begins with those that are the most oxidatively removed from the *o*-quinone requiring three oxidations and count down to those requiring just a single oxidation. For example, cyclic enones and tetralones can be elaborated into *o*-quinones by three oxidations, one of which installs the additional oxygen atom adjacent to the existing carbonyl residue. Phenols and their equivalents that display an *ortho*-hydrogen or carbon substituent can be converted into *o*-quinones by just two oxidations; one of which first installs an additional oxygen substituent *ortho* to the phenol. Both of these phenol and enone precursors are accessible by a number of six-membered ring-forming reactions, most notably Diels–Alder chemistry. In addition, *o*-quinone ketals, which are formed by oxidation of *mono*-protected catechols in an alcoholic solvent, are well known to hydrolyze to their corresponding *o*-quinones. However, *o*-quinols, which are formed by *ortho* oxidation of *ortho*-carbon substituted phenols, can also be caused to rearrange and undergo further oxidation to provide *o*-quinones. Lastly, catechols like their hydroquinone counterparts are oxidized by a single oxidation. Specific examples of these strategies are presented in the ensuing sections.

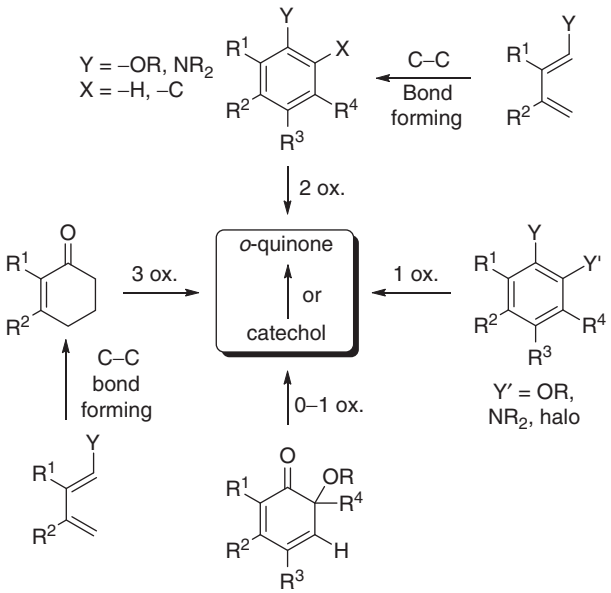
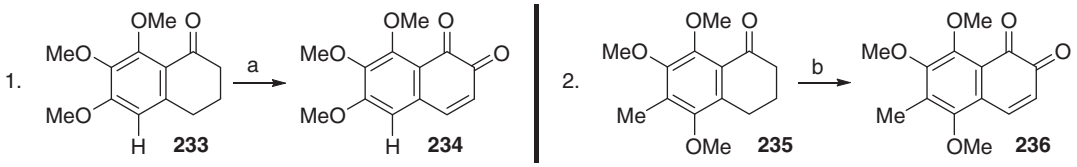


Figure 13 Methods to access *o*-quinones and their catechol precursors.

7.15.3.1 *o*-Oxidation of Enones and Tetralones (3 ox.)

7.15.3.1.1 Selenium reagents

Until fairly recently selenium dioxide had been the reagent of choice for transforming tetralones into their corresponding *o*-quinones. For example, the tetralone **233** was observed to smoothly convert into the *o*-naphthoquinone **234** on refluxing in acetic acid (1.-Scheme 28).[15] In a similar fashion the tetralone **235** was found to convert into the corresponding *o*-naphthoquinone **236** (2.-Scheme 28).[16] Although these selenium-mediated reactions tend to work well on a small scale, they often prove difficult to carry out with larger amounts of material due to selenide by-products.

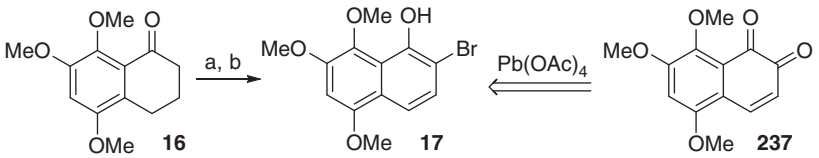


a. SeO_2, 60 °C, AcOH, 60% yield; b. SeO_2, 60 °C, AcOH, 73% yield.

Scheme 28

7.15.3.1.2 α-Bromination, aromatization, and further oxidation

The selenium method above has largely been supplanted by a milder three-step halogenation and aromatization protocol with tetralones, which is then followed by an additional IBX or lead tetraacetate oxidation of the corresponding *o*-halophenol (Scheme 29). For example, the tetralone **16** was observed to transform into the bromo-naphthol **17** after a double α-bromination using two equivalents of lithium hexamethyldisilazide (LHMDS) and NBS. Subsequent treatment of the intermediate dibromide with DBU was observed to cause bromide elimination and with further enolization to result in the 2-bromo-naphth-1-ol **17**. Lead tetraacetate (see Section 7.15.3.3.2.1) is known to subsequently convert these kinds of substrates into their corresponding *o*-quinones (Scheme 41), whereas oxidation with CAN leads to the corresponding *p*-naphthoquinone (3.-Scheme 2).[18]



a. LHMDS, THF, –78 °C; NBS; b. DBU, –78° C to r.t., 78% yield (2 steps).

Scheme 29

7.15.3.2 *o*-Oxidation of Phenols and Their Protected Counterparts (2 ox.)

7.15.3.2.1 o-Oxidation of anisoles (ortho-H)

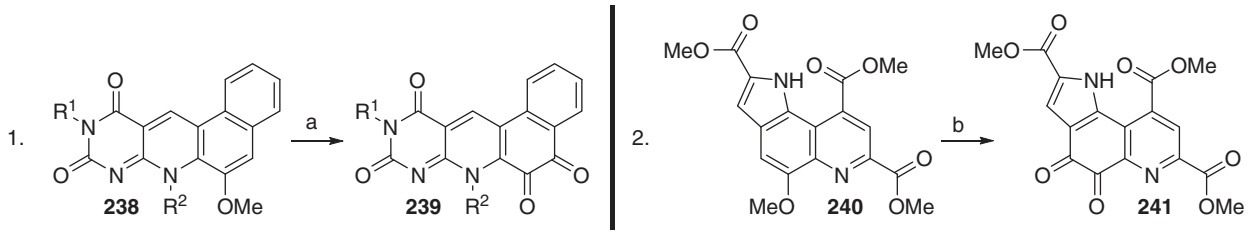
The oxidation of *protected* phenols, such as anisoles, into *o*-quinones is unknown because of the inherent polarization of *o*-quinones. Such a reaction is only plausible for anisole derivatives if the *para*-position is blocked; and the authors are aware of only a few isolated examples where Ce(IV) reagents effected this transformation.

7.15.3.2.1.1 CAN

A series of *ortho*-quinone deazaflavins were constructed that exemplify this uncommon approach. Analogs of the anisole **238** were reported to undergo reaction with CAN to give the *o*-quinones **239** in yields ranging from 9% to 65% (1.-Scheme 30).[125] The trismethyl ester *o*-quinone **241** was constructed in a similar fashion by a CAN-mediated oxidation of the anisole **240** (2.-Scheme 30).[126]

7.15.3.2.2 o-Oxidation of phenols and anilines (ortho-H)

There have been some scattered examples reporting intramolecular *ortho*-delivery of oxygen from phenols and anilines with either Pb(IV) reagents or benzene seleninic anhydride, as well as some transition metal hydroperoxides. Phenol oxidations using hypervalent I(III) reagents, Fremy's salt, CAN, and cobalt salcomine complexes favor *para* oxidation, unless the position is blocked with a substituent. However, several new and exciting developments have emerged with I(V) reagents, particularly the use of IBX at room temperature in polar solvents. Its mechanism of phenol oxidation is quite distinct from its thermal oxidation of alcohols, and of use in the formation of iminomethides.



a. CAN, HNO_3, 9–65% yield; b. CAN, MeCN/H_2O, 0 °C, 60% yield.

Scheme 30

7.15.3.2.2.1 IBX

IBX, an I(V) reagent, can perform two oxidations. The reagent is regioselective with electron-rich phenols, favoring oxidation of the least sterically encumbered and most electron-rich *ortho*-site. Mechanistic studies suggest that the reaction commences by formation of an I(V) phenol adduct with expulsion of water (**Figure 14**). This material undergoes an internal reaction delivering an oxygen atom from the I(V) reagent in an ortho fashion as it is reduced to an I(III) reagent. The resulting quinol intermediate undergoes further oxidation and provides the corresponding *o*-quinone, which can be reduced to its corresponding catechol to facilitate isolation.

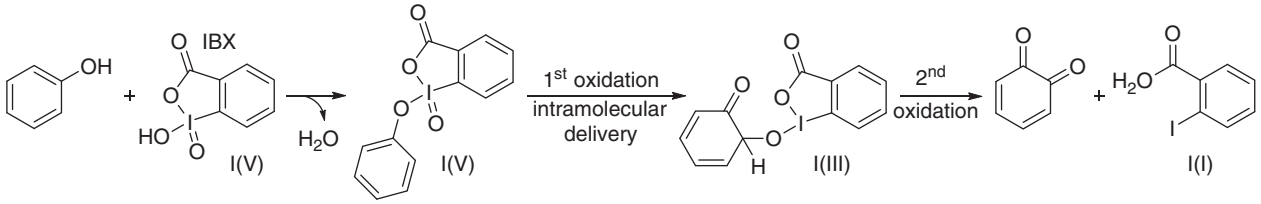
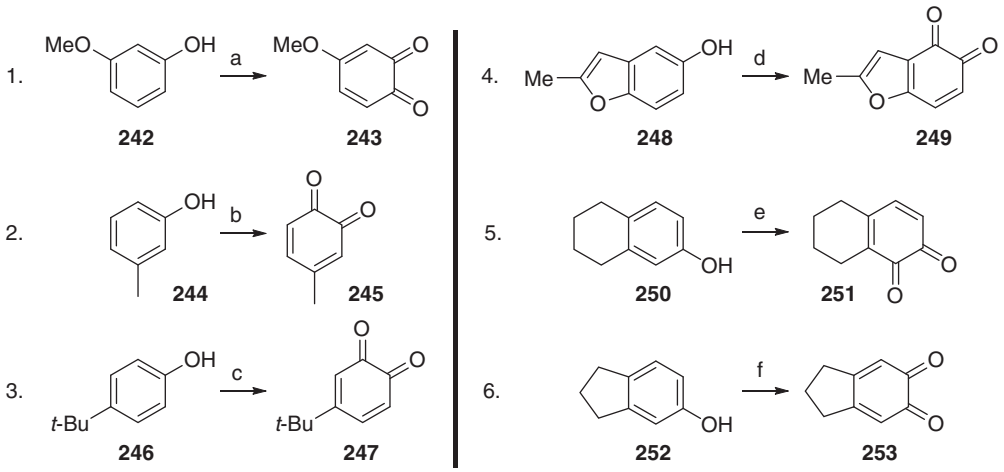


Figure 14 Mechanism of phenol oxidation with I(V) reagents.

Since the discovery of this transformation,[127] this new IBX oxidation method has found widespread applications.[128] A more stable variant of IBX has been reported, a mixture of IBX and benzoic acid, which is thought to be more thermally stable and is aptly named 'stabilized IBX' ((*S*)IBX).[129]

ortho-Selective phenolic oxidations with IBX have been demonstrated using a variety of nonsymmetrical electron-rich *meta*-substituted phenols. For example, the resorcinol **242** was reported to undergo regioselective oxidation in >99% yield to afford the *o*-quinone **243** (1.-**Scheme 31**).[127] The less electron-rich cresol derivative **244** was found to be less reactive, yet still proceeded to the *o*-quinone **246** in a 41% yield (2.-**Scheme 31**).[127] Electron-rich phenols substituted at the *para*-position were also found to



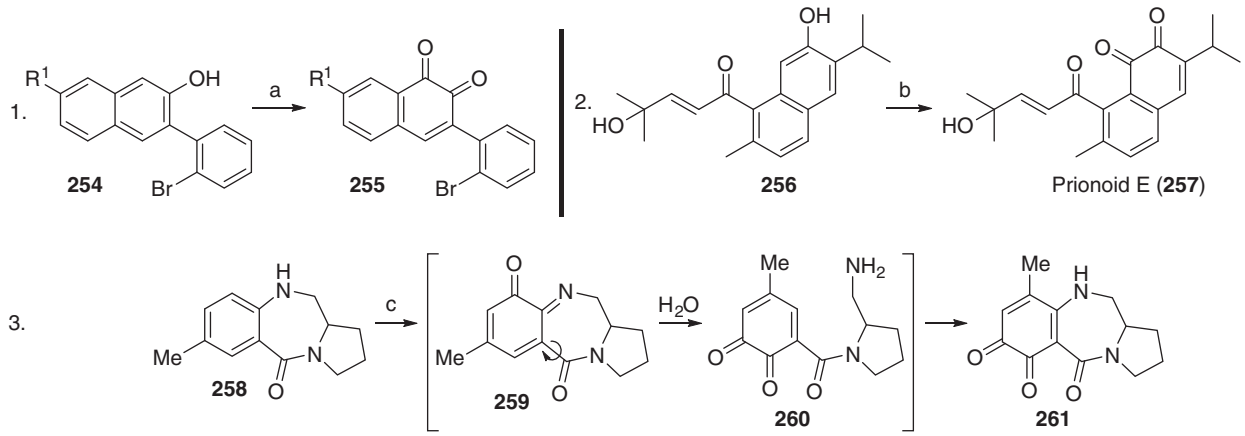
all reactions: IBX, 25 °C; a. $CDCl_3$, 99% yield; b. d_7-DMF, 41% yield; c. d_7-$CDCl_3$, 99% yield; d. DMF, >70% yield; e. d_7-DMF, 45% yield; f. d_7-DMF, 56% yield.

Scheme 31 I(V) reagents for oxidation of free phenols.

participate in this reaction as shown by the conversion of phenol **246** into *o*-quinone **247** (3.-Scheme 31).[127] Phenols appended with rings were reported to afford unusual selectivity effects. For example, oxidation of the phenolic benzofuran **248** with IBX was found to provide the *o*-quinone **249** (4.-Scheme 31).[130] However, phenols appended with five- and six-membered carbocycles were observed to favor different regiochemical outcomes, as shown by oxidation of **250** and **252** into their respective *o*-quinone products **251** and **253** (5., 6.-Scheme 31).[131] The regiochemical preference between *ortho* sites appears to be affected by both solvent polarity and substrate electronics.[132]

7.15.3.2.2.2 Fremy's salt

Fremy's salt, described earlier (see Section 7.15.2.3.1.1), is rarely used to afford *o*-quinones unless the *p*-position is blocked. For example, 2-naphthols derivatives **254** were observed to undergo oxidation with Fremy's salt and furnish the corresponding *o*-quinones **255** in yields ranging from 79% to 94% (1.-Scheme 32).[11] Oxidation of the 2-naphthol **256** with Fremy's salt was found to provide prionoid E (**257**) in a 52% yield (2.-Scheme 32).[133] In a rather unusual case, the *ortho*-quinone **261** was reported to emerge from the oxidation of the aniline **258** with Fremy's salt (3.-Scheme 32).[134] This transformation was speculated to proceed through the *o*-iminoquinone **259**, which further succumbed to hydrolysis to afford the *o*-quinone **260**, whereupon 1–4-conjugate addition of the amine and further oxidation provided the product.

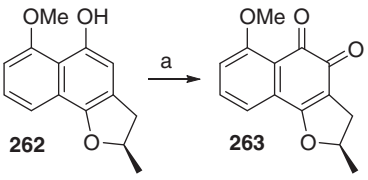


all reactions: Fremy's salt, 25 °C; a. K_2HPO_4, acetone, 79–94% yield; b. acetone, H_2O, 52% yield; c. MeCN/pH 7 buffer (1:1), 88% yield.

Scheme 32 Fremy's salt oxidation of free phenols.

7.15.3.2.2.3 Benzene seleninic anhydride

Though intuitive, examples professing the conversion of phenols into *o*-quinones with selenium reagents are rare. However, the reported oxidation of the 1-naphthol **262** with benzene seleninic anhydride (BSA) in THF at 50 °C resulting in the *o*-naphthoquinone **263** in a 71% yield (Scheme 33) clearly suggests a good potential for BSA.[135] The authors made note that their attempts to perform this transformation using Fremy's salt were unsuccessful and had caused the five-membered dihydrofuran ring to open resulting in the corresponding *p*-naphthoquinone.



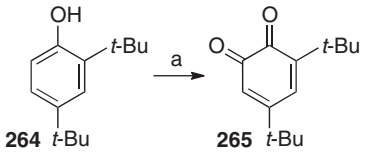
a. $(PhSeO)_2O$, THF, 50 °C, 71% yield.

Scheme 33 Benzene selenic anhydride oxidation of free phenols.

7.15.3.2.2.4 Dimethyldioxirane

Dimethyldioxirane (DMDO) is a powerful neutral oxidant that is most often associated with epoxidation of acid-sensitive systems. Nevertheless, it has been reported to transform a phenol into its corresponding *o*-quinone. For example, use of an excess of DMDO in

acetone was observed to transform the phenol **264** into the *o*-quinone **265** in a 53% yield (Scheme 34).[136] The authors also indicated that DMDO proved useful for the oxidation of catechols (*o*-dihydroquinones) into their corresponding *o*-quinones (see Section 7.15.3.6).

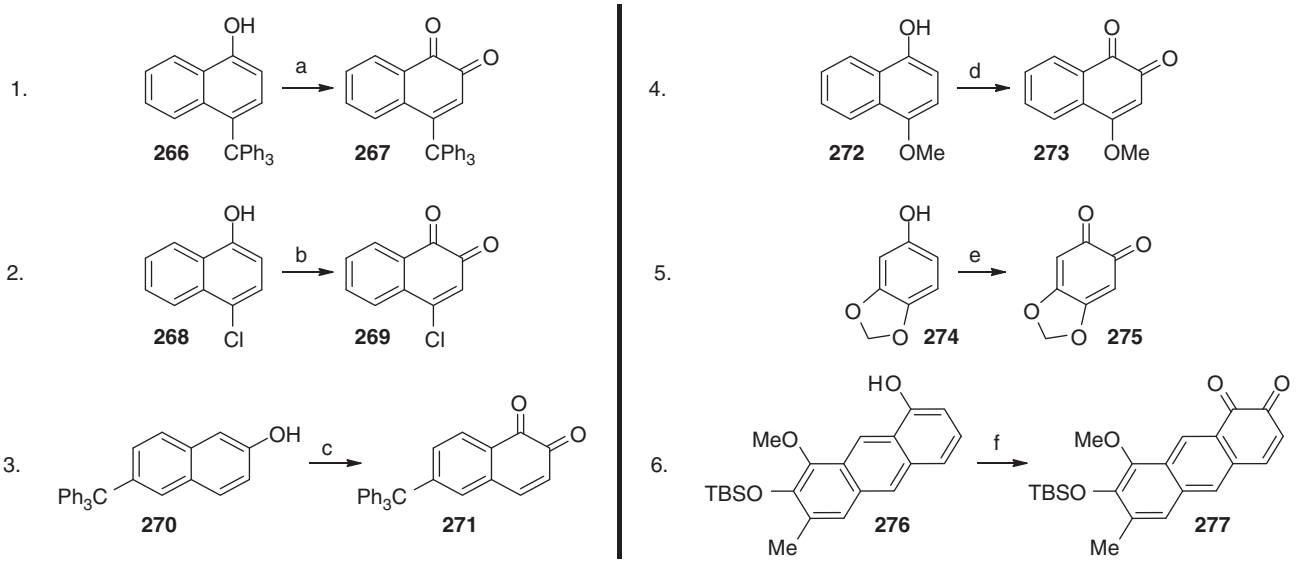


a. DMDO, acetone, 55% yield.

Scheme 34 DMDO oxidation of phenols.

7.15.3.2.2.5 Transition metal hydroperoxides

Transition metal hydroperoxides are most often used for epoxidation of allylic alcohols. However, these venerable species are beginning to find applications among phenols specifically for their conversion into *o*-quinones. For example, the *p*-substituted naphthol **266** was observed to undergo a titanium-mediated oxidation with *tert*-butyl hydrogen peroxide at low temperature to produce the *o*-naphthoquinone **267** in 85% yield (1.-Scheme 35).[137] Similar transformations were also reported for the naphthols **268** and **270**, which were converted into their corresponding naphthoquinones **269** and **271** (2., 3.-Scheme 35).[138] The naphthol **272** was found to convert to its corresponding *o*-naphthoquinone **273** in 89% yield using $Zr(acac)_4$ with *tert*-butyl hydrogen peroxide (4.-Scheme 35).[137] In addition, the conversion of the methylenedioxyphenol **274** into its *o*-quinone **275** has been found to proceed in a 90% yield with a molybdenum reagent (5.-Scheme 35).[139] These conditions also proved useful for the conversion of the anthracenol **276** into its corresponding *o*-anthraquinone **277** (6.-Scheme 35).[140] However, from inspection of these many examples it still appears that the *para*-site must remain blocked to prevent *p*-quinone formation.

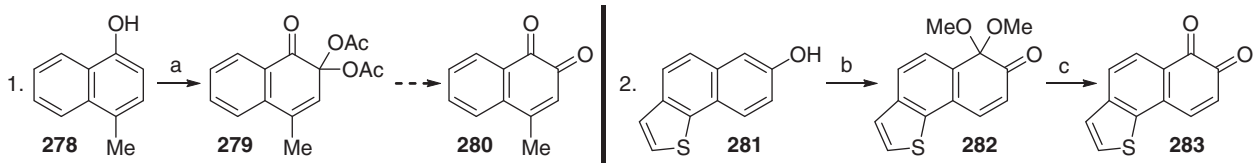


a. Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, –23 °C, 85% yield; b. Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, 3 Å MS, 85% yield; c. Ti(O*i*-Pr)4, TBHP, CH_2Cl_2, 3 Å MS, 66% yield; d. $Zr(acac)_4$, TBHP, CH2Cl2, –20 °C, 89% yield; e. $[Mo(O_2)_2O]$·py·HMPT, TBHP, CH_2Cl_2, 20 °C, 90% yield; f. $[Mo(O_2)_2O]$·py·HMPT, CH_2Cl_2, 22 °C, 24% yield.

Scheme 35 Transition metal hydroperoxides as phenol oxidants.

7.15.3.2.2.6 Pb(IV) and I(III)

Pb(IV) and I(III) reagents have both been used separately to convert phenols and naphthols into their corresponding *o*-quinone ketals, when the *para*-site is blocked. For example, the 1-naphthol **278** has been transformed into the ketal acetate **279** (1.-Scheme 36).[141] The chapter authors speculate that saponification would likely afford the previously prepared corresponding *o*-naphthoquinone **280**.[142] The 2-naphtholthiofuran **281** was reported to transform into the ketal **282** by application of PIDA in methanol, whereupon addition of acid furnished the *o*-quinone **283** (2.-Scheme 36).[143]



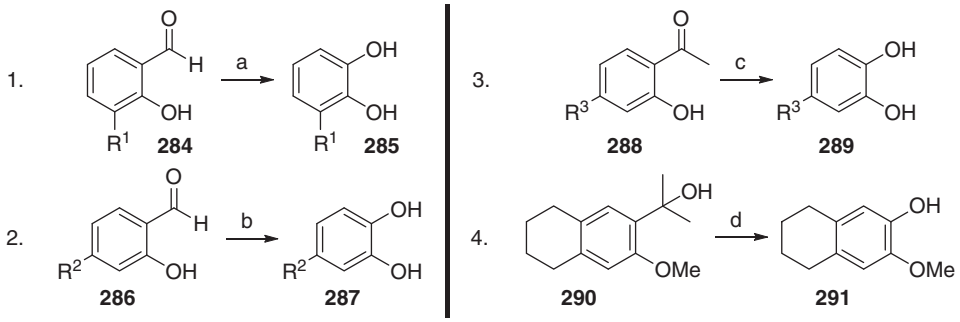
a. $Pb(OAc)_4$, benzene, 55% yield; b. PIDA, MeOH, r.t., 61% yield; c. HCl, AcOH, H_2O, r.t., 85% yield (2 steps).

Scheme 36 Pb(IV) and I(III) oxidation of free phenols.

7.15.3.2.3 Phenol and anisole derivatives (ortho-C)

7.15.3.2.3.1 Dakin and Baeyer–Villiger oxidations and the cumene hydroperoxide rearrangement

Dakin oxidations usually employ hydrogen peroxide, whereas Baeyer–Villiger oxidations use peroxyacids (see Section 7.15.2.4.1). One potential benefit of applying either of these two oxidation protocols with salicylaldehyde derivatives is that the phenolic oxygen atom, which is *ortho* to the carbonyl, can remain protected so that the subsequent oxidation to the *o*-quinone might be deferred. However, these oxidative reactions also prove successful with unprotected *o*-carbonylated phenols and stop sharply at the respective catechol. For example, the *meta*-substituted salicyladehydes **284** (R^1 = H or OMe) were found to undergo oxidation and rearrangement to the corresponding catechol products **285** with sodium percarbonate in mixed aqueous solvent systems in excellent yield (1.-Scheme 37).[46] The salicylaldehydes **286**, which displayed *para* substitution (R^2 = OMe, Cl, or NO_2), were found to afford their respective catechols **287** in a similar fashion (2.-Scheme 37). However, the acetophenones **288** (R^3 = H, OMe) were observed to undergo a related transformation resulting in catechols **289** (3.-Scheme 37). Both flavin derivatives and organoselenides are reported to catalyze these processes.[144,145] However, the Dakin and Bayer–Villiger reaction often run into trouble with extremely electron-rich aryl systems such as those containing two or more oxygen substituents, as these substituents thwart the initial combination of the peroxy species with the reacting carbonyl. In these instances, a surrogate to the reported cumene rearrangement of tertiary hydroperoxide offers a good alternative, and it can be easily accessed from similar acetophenones by addition of methyl Grignard. For example, the tertiary alcohol **290**, on treatment with *p*-toluenesulfonic acid and hydrogen peroxide, was observed to undergo rearrangement to the methoxy-phenol **291** in an 85% yield (4.-Scheme 37).[50]



a. sodium percarbonate, THF/DMF/H_2O; b. sodium percarbonate, THF/DMF/H_2O; c. sodium percaronate, THF/DMF/H_2O; d. *p*-TsOH (10 mol%), H_2O_2, THF, 22 °C, 85% yield.

Scheme 37

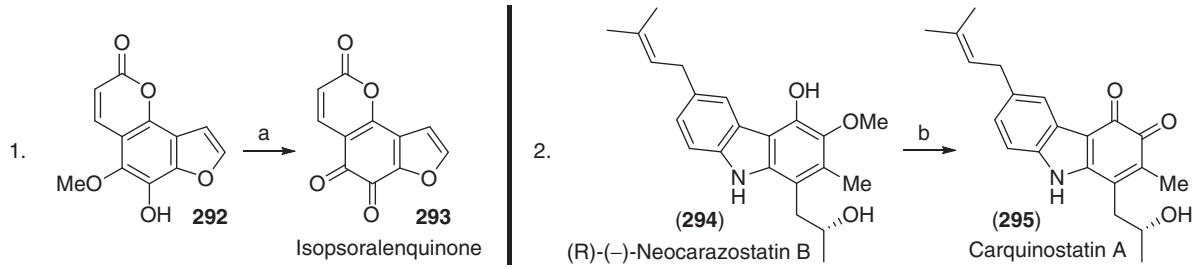
7.15.3.3 *o*-Oxidation of Mono- or Bis-Protected Catechols and Their Equivalents (1 ox.)

Oxidative demethylation of the *mono*- or *bis*-protected catechols or their functional equivalents could lead to *o*-quinones. However, the authors are unaware of any examples of *bis*-alkyl protected catechols being smoothly transformed into their corresponding *o*-quinones, despite the extensive precedent for conversion of bis-alkyl protected *p*-hydroquinones into their corresponding *p*-quinones with CAN (see Section 7.15.2.5.1.1).[146] However, there are a few examples of *mono*-protected catechols undergoing conversion into the *o*-quinone transformation using CAN, phenylselenic acid, or IBX.

7.15.3.3.1 Mono-protected catechol derivatives (ortho–OR)

7.15.3.3.1.1 CAN

Some of the most notable examples using CAN are displayed (Scheme 38). For example, mono-demethylation and oxidation of the catechol derivative **292** with CAN was reported to afford the *o*-quinone product **293** in 84% yield



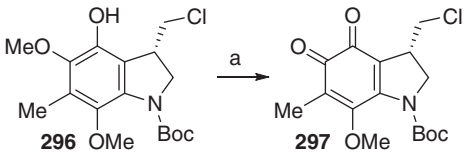
a. CAN, $MeCN/H_2O$, 84% yield; b. CAN, $MeCN/H_2O$, 0 °C, 92% yield.

Scheme 38 CAN-mediated oxidation of mono-protected catechols.

(1.-Scheme 38).[147] In addition, CAN was reported to transform neocarazostatin (**294**) into carquinostatin A (**295**) in a 92% yield (2.-Scheme 38).[148] In both these instances, the *para*-site is blocked by a substituent.

7.15.3.3.1.2 Selenium reagents

Benzene seleninic anhydride (BSA), easily prepared by mixing phenylselenic acid with acetic acid, has been used for the oxidative demethylation of *mono*-protected catechols as well (Scheme 39). For example, the *mono*-protected catechol **296** was observed to smoothly convert into the *o*-quinone **297** in 85% yield on addition of BSA (1.-Scheme 39).[149] These selenide conditions were found to be better than other oxidative conditions that were examined including reagents such as CAN, Fremy's salt, salcomine, and DDQ.

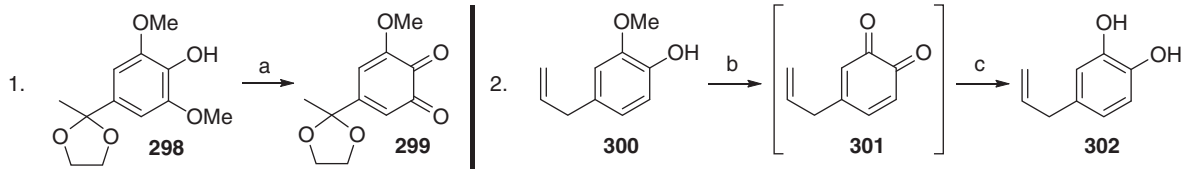


a. $PhSeO_2H$, Ac_2O, 85% yield.

Scheme 39 Selenium oxidation of mono-protected catechols.

7.15.3.3.1.3 Hypervalent I(V) reagents

IBX has been reported to undergo reaction with phenols at the neighboring *ortho*-site that is the most electron-rich. Thus, in the case of a *mono*-protected catechol, the reagent is directed to the adjacent alkoxy substituent to form an *o*-quinolic hemiketal intermediate, which can collapse to give the corresponding *o*-quinone (Scheme 40). For example, oxidation of the symmetric phenol **298** with IBX was observed to furnish the *o*-quinone **299** in 82% yield (1.-Scheme 40).[150] However, when the *mono*-protected catechol **300** was oxidized by stabilized IBX ((*S*)IBX), it was found to undergo deprotection and oxidation to the *o*-quinone **301**, which succumbed to reduction to afford the catechol **302** (2.-Scheme 40).[151]



a. IBX, DMSO, r.t., 82% yield; b. (*S*)IBX, THF, r.t.; c. aqueous $Na_2S_2O_4$ workup, 77% yield.

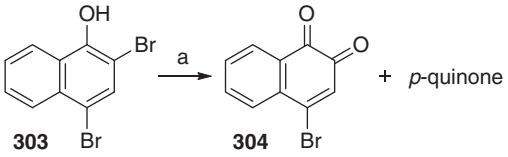
Scheme 40 I(V) oxidation of mono-protected catechols.

7.15.3.3.2 o-Halogenated phenols (ortho–X); masked mono-protected catechol equivalents

7.15.3.3.2.1 Lead reagents

Ortho-halogenated phenols are oxidatively equivalent to *mono*-protected catechols, and they have been reported to undergo reaction with Pb(IV) reagents to give *o*-quinones. The authors assume a similar reaction would occur with IBX in examples of

electron-rich systems, but as yet they have found no reports. The bis-brominated naphthol **303** was observed to undergo oxidation with $Pb(OAc)_4$ to afford the *o*-quinone **304** in 81% yield along with a 12% yield of the corresponding bromo-*para*-quinone (Scheme 41).[152] When analogous chlorinated substrates were examined, similar yields were obtained.

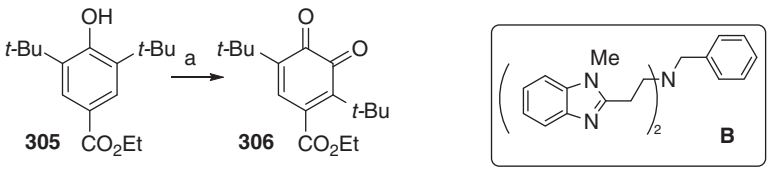


a. $Pb(OAc)_4$, benzene, 81% yield.

Scheme 41

7.15.3.4 *o*-Quinols (0–1 ox.)

o-Quinols, just as their *p*-quinol counterpart does (see Section 7.15.2.6), should undergo rearrangement to the corresponding catechol on treatment with acid or base, and further oxidize to the *o*-quinone. However, the authors could find, but a single example, a reaction mediated by copper and oxygen (Scheme 42). It is speculated that the reaction begins by coordination of the phenoxide with the copper so as to assist in intramolecular delivery of molecular oxygen to the *ortho*-position. In this example, the phenol **305** was observed to proceed to the *o*-quinone **306** with migration of the *tert*-butyl group in 40% yield.[153]



a. O_2, $[Cu(CH_3Me)_4]BF_4$, **B**, MeCN, r.t., 40% yield.

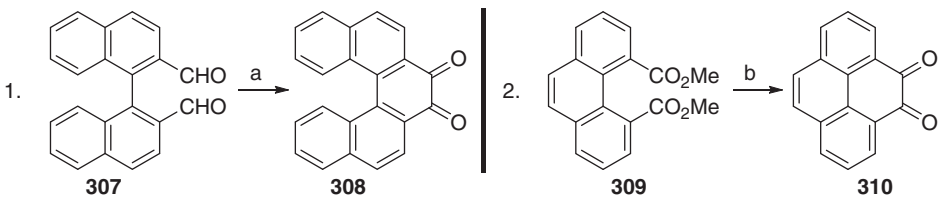
Scheme 42

7.15.3.5 Carbon–Carbon Bond-Forming Strategies (≥0 ox.)

Carbon–Carbon bond-forming strategies aimed at fully elaborating *o*-quinones are fairly rare, because of the need for a polarity reversal or umpolung reaction in the overall planned strategy. Besides a few scattered examples of benzoin condensations and pinacol couplings, or Diels–Alder and Michael Dieckmann strategies, most practitioners have chosen to target a tetralone or a phenol that is subsequently elaborated into the *o*-quinone. In this regard, the newly discovered IBX oxidation, which enables an umpolung *ortho* oxidation of a phenol, has proven exceedingly valuable (see Section 7.15.3.3.1.3).

7.15.3.5.1 Benzoin condensation and Pinacol coupling

Bis-aldehydes and bis-esters are known to couple with one another by a number of umpolung reactions. One of these is the benzoin condensation.[154] For example, the bis-aldehyde **307** was observed to afford the *o*-quinone **308** in a 73% yield, when the starting material was refluxed in DMF with sodium cyanide in the presence of air (1.-Scheme 43).[155] Similar transformations have



a. NaCN, DMF, reflux; H_2O, O_2, 73% yield; b. Na, THF, reflux, 95% yield.

Scheme 43

been reported using a two-step procedure that commences with a single electron-transfer reagent, such as sodium and samarium diiodide,[156] and is then followed by an additional oxidation reaction that tolerates diols without cleavage. Diesters such as the *bis*-methyl ester **309** have been found to afford the corresponding pyrenequinone **310** in 95% yield on reflux with sodium in the presence of oxygen (2.-Scheme 43).[157]

7.15.3.5.2 o-Quinones as dienophiles and Michael acceptors

Several net [4+2] carbon–carbon bond-forming strategies have been utilized to ultimately reach *o*-quinones. Among these, a variety of dienes can be imagined as providing viable phenolic precursors. These nucleophilic donors include Brassard's diene **183** (R=Me), the sulfoxide **311**, the sulfone **312**, the thiolactone **313**, the lactone **314** (or their corresponding sulfones) and lactone **222**, all of which are enolate precursors.[158] Some plausible electrophilic precursors include derivatives of the halogenated *o*-quinone **315** as well as the *o*-quinone ketals **316**. In both these cases, which lead to compounds resembling **317**, the desired *o*-quinone motif is already preexistent in these electrophilic coupling partners (Figure 15).

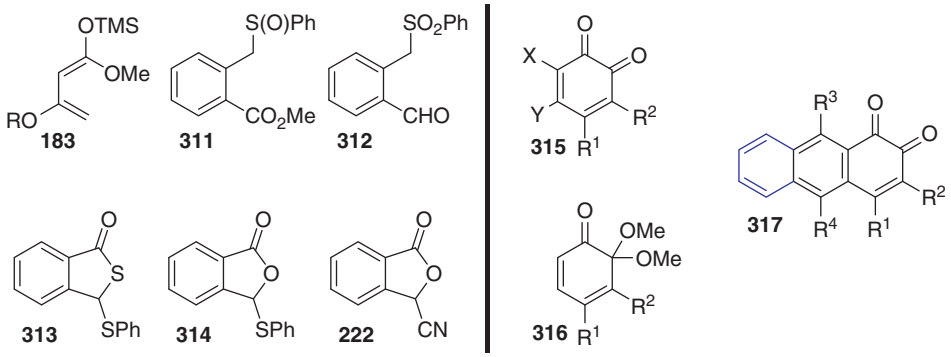
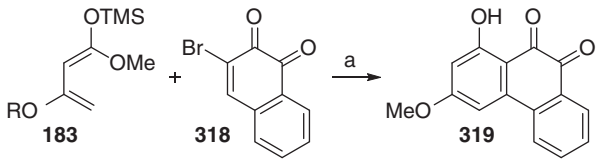


Figure 15 Useful diene precursors and *o*-quinones for phenol formation.

7.15.3.5.3 α-Halogenated o-quinones as dienophiles

Brassard's diene **183** (R=Me) was observed to undergo reaction with the *α*-brominated *o*-naphthoquinone **318** in THF at 0 °C to afford the corresponding *o*-quinone **319** in a 70% yield (Scheme 44).[159] Chloro analogs of **318** were also found to participate in this transformation. However, in cases where the dienophile displayed a *β*-halogen, the desired reaction failed to proceed and instead underwent a hetero Diels–Alder reaction with a carbonyl moiety of the *o*-quinone to afford an unexpected spirocyclic pyran ring system.

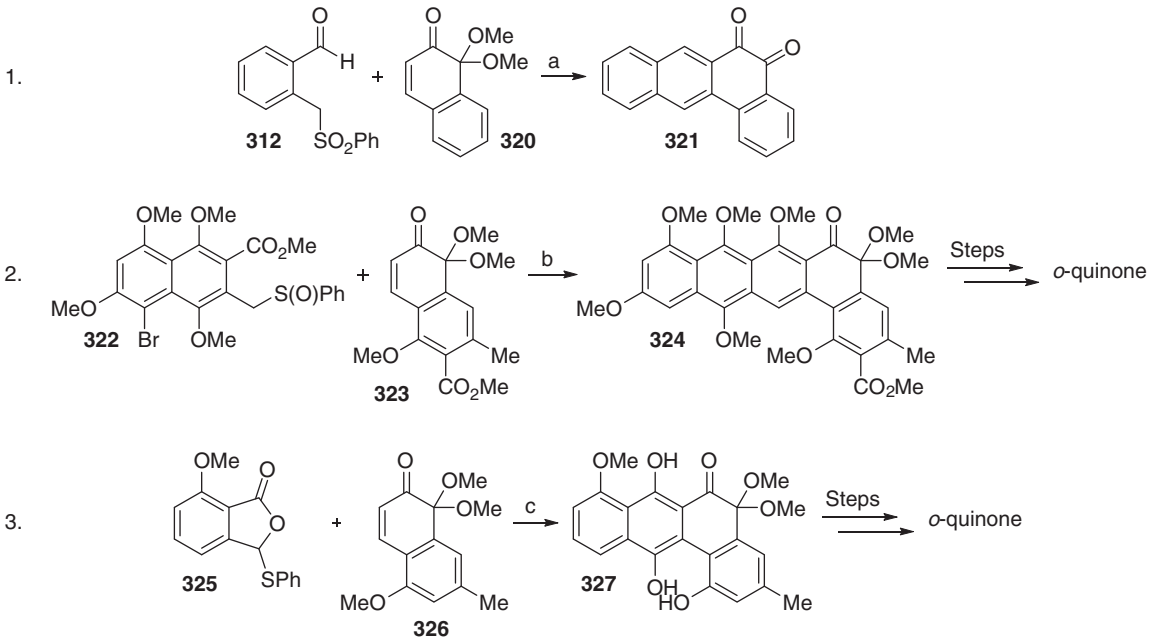


a. THF, 0 °C; O_2, r.t., 70% yield.

Scheme 44

7.15.3.5.4 o-Quinone ketals as Michael acceptors and Dieckmann donors

There are several examples of *o*-quinone ketals participating as electrophiles in Michael–Dieckmann reactions. The three examples shown indicate the overall scope of this process (Scheme 45). The enolate species that combine with each *o*-quinone ketal can be outfitted in such a manner so as to introduce adjoining aromatic rings containing 0–2 attendant oxygen substituents. For example, annulation of the naphthoquinone monoketal **320** with the sulfone-aldehyde **312** mediated by potassium *tert*-butoxide was reported to afford the *o*-quinone **321** displaying an unsubstituted naphthalene (1.-Scheme 45).[158] However, the deprotonated sulfoxide-ester **322** was observed to undergo a Michael–Dieckmann combination with the naphthoquinone monoketal **323** whereupon addition of dimethyl sulfate afforded the *mono*-methyl etherified product **324** in a 31% yield (2.-Scheme 45).[160] The enolate of phthalide sulfide **325** was reported to undergo reaction with the *o*-quinone ketal **326** to afford the benz[a]anthracene **327** displaying two free phenols in its *para*-naphthoquinone (3.-Scheme 45).[161]



a. LiO*t*-Bu, THF, –60 °C; Me_2SO_4, K_2CO_3, reflux, acetone; HCl, MeOH, 73% yield; b. LiO*t*-Bu, THF/DMSO; $(MeO)_2SO_2$, acetone, K_2CO_3, 31% (2 steps); c. LiO*t*-Bu, THF, –78 °C, 72% yield.

Scheme 45

7.15.3.6 Oxidation of Unprotected Catechols

Unprotected catechols are nearly as easily oxidized to *o*-quinones as their dihydroquinone counterparts oxidize to *p*-quinones. However, because *o*-quinones are less stable than their *p*-quinone, some care must be taken to ensure that the resulting nucleus does not undergo further reaction with itself or with side products emerging from the oxidant. In this regard, both Ag_2O[162] and *o*-chloranil[163] have proven very useful for mild oxidation of catechols to quinones.

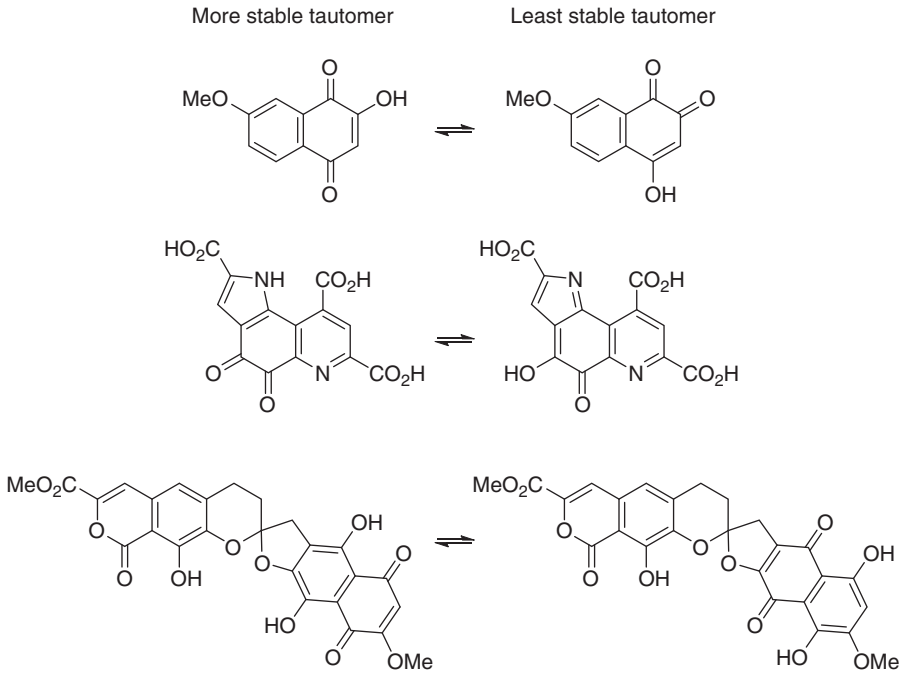
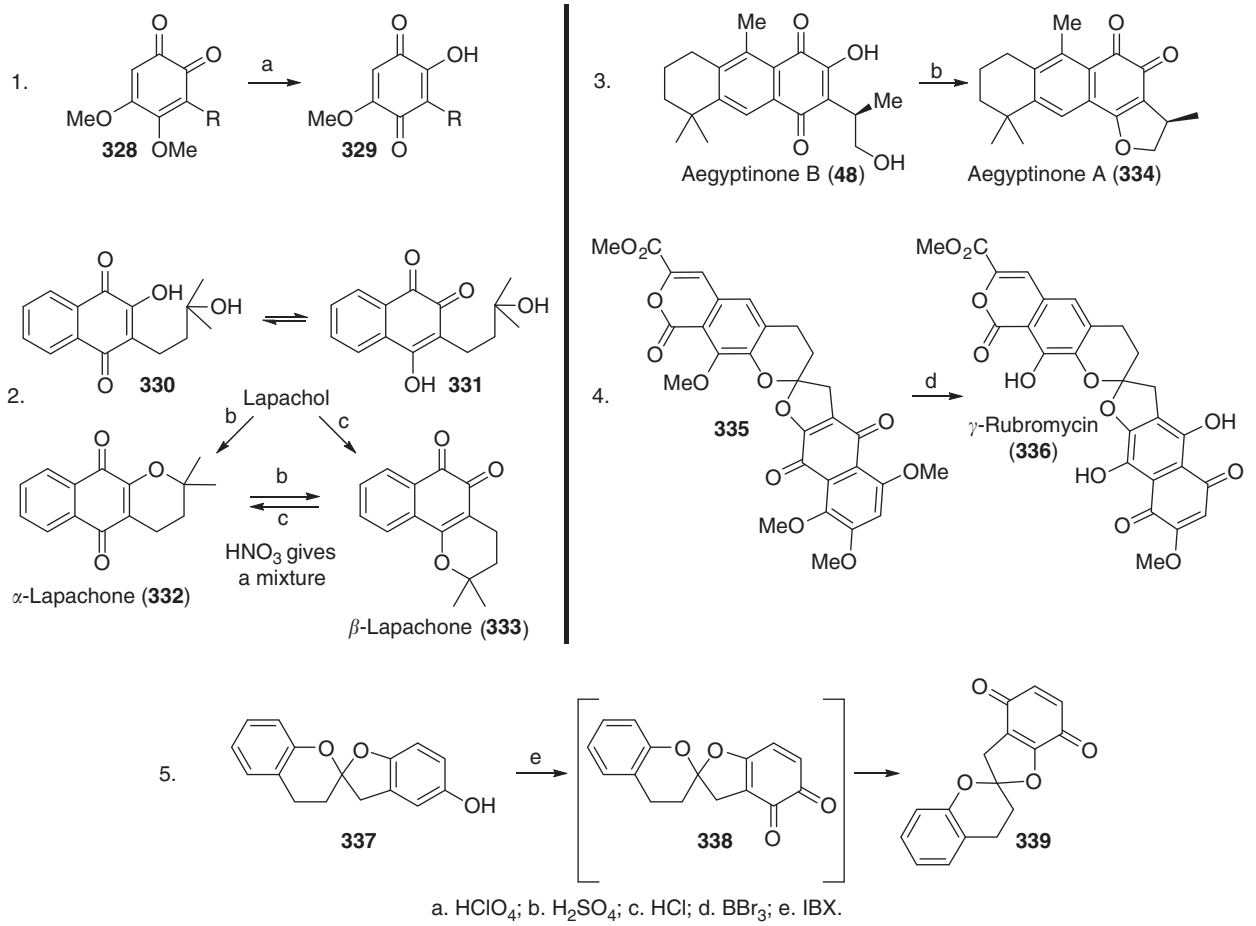


Figure 16 Some quinone tautomerizations.

7.15.4 Rearrangements and Tautomerizations between *o*- and *p*-Quinones

It should be noted that quinones that bear additional oxygen substituents have the ability to tautomerize between two or more counterparts and in some cases between *o*- and *p*-quinones. Factors that affect this tautomerization and favor one tautomer over another include: pH, product stability, hydrogen bonding, metal complexation, and aromatic stabilization (Figure 16). As it is possible to convert a less stable tautomer into a more stable tautomer, the construction of the least stable quinone can be thought of as a precursor to the more stable quinone.

A few examples of complications and exploitations of these rearrangements and isomerizations within the literature are shown (Scheme 46).



Scheme 46

For example, the *ortho*-quinone **328** was reported to afford the *p*-quinone **329** on exposure to perchloric acid via regioselective hydrolysis of the more hindered methyl ether (1.-Scheme 46).[164] Along similar veins, the hydroxy-napthoquinone lapachol (**330**), which exists in a tautomeric mixture with its corresponding *o*-quinone **331**, has been shown to selectively convert to *α*-lapachone (**332**) on treatment with hydrochloric acid (2.-Scheme 46).[165] However, treatment of the tautomeric mixture of quinones **330** and **331** with H_2SO_4 was observed to afford *β*-lapachone (**333**), whereas the use of nitric acid was reported to give mixtures of **332** and **333**. These separate conditions could also be used to cause the respective pyrans to interconvert among themselves. This knowledge was applied in the conversion of the aegyptinone B (**48**) into aegyptinone A (**334**) by selection and application of sulphuric acid (3.-Scheme 46).[36,37] Tris-demethylation was observed to cause the inner-ring naphthoquinone of **335** to transform into the outer-ring naphthoquinone found in *γ*-rubromycin (**336**) (4.-Scheme 46).[18] In another example, where a less stable *o*-quinone precedes a more stable *p*-quinone, the *ortho*-oxidation of the phenol **337** with IBX was shown to afford the *p*-napthoquinone **339** (5.-Scheme 46).[166] It is believed to be preceded by *o*-naphthoquinone **338**, which undergoes rearrangement via a zwitterion.

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7.16 Addition Reactions with Formation of Carbon-Heteroatom Bonds: (III) Asymmetric Methods of Dihydroxylation, Aminohydroxylation, and Diamination

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7.16.1 Introduction

Carbon-heteroatom bonds represent essential functional units in organic molecules. In principle, a broad arsenal of synthetic method is available for their selective construction. Among these reactions, a particular class of transformations is devoted to the construction of 1,2-difunctionalized entities. An attractive approach to this class of compounds consists of the oxidative vicinal difunctionalization of alkenes.[1] With the advent of the alkene metathesis reaction,[2] this approach has gained even more versatility as all different kinds of alkenes can now be accessed for their subsequent oxidative diversification.

In the following, selected processes for the 1,2-difunctionalization of alkenes are discussed.

Where possible, enantioselective methods are discussed with preference over achiral transformations unless the latter are considered important for special applications.

7.16.2 Osmium-Catalyzed Dihydroxylation of Alkenes: Vicinal Diol Synthesis

The osmium(VIII) catalyzed dihydroxylation of alkenes represents the classic transformation in the area of difunctionalization of alkenes.[3] It is based on extensive mechanistic insight generated by Criegee in the first half of the twentieth century. Among other observations, Criegee determined the selectivity of this reagent for double bond oxidation and the acceleration of the reaction in the presence of ligands such as pyridine.[4,5]

The most important improvements of the Criegee reaction were the discovery that suitable oxidants permit the reaction to be conducted with catalytic amounts of osmium. The most important contribution in the field was the introduction of *N*-methylmorpholine N-oxide (NMO) within the so-called Upjohn process.[6]

7.16.3 Sharpless Asymmetric Dihydroxylation of Alkenes (AD process)

Sharpless developed suitable chiral ligands for temporary coordination to the electrophilic osmium center in OsO_4 in order to render the dihydroxylation process enantioselective. This process has been termed as asymmetric dihydroxylation or AD process and it allows for the enantioselective preparation of chiral diols from alkenes.[7] Even though the origin of the AD dates back to the 1980s, it still represents the most powerful oxidative vicinal difunctionalization of alkenes known to date.[8–10] Over the course of its development, the reaction underwent several modifications of the reaction conditions. The generally best procedure is obtained with ligands that are derived from two cinchona alkaloid entities that are tethered to a phthalazine (PHAL) core (**Figure 1**). Ligands of this series are abbreviated $(DHQ)_2PHAL$ for the one containing dihydroquinine and $(DHQD)_2PHAL$ for the one containing dihydroquinidine as chiral units, respectively.

The two cinchona alkaloids dihydrochinine and dihydroquinidine are not enantiomers of each other, but diastereomers. However, they were found to lead to opposite selection of the two prochiral alkene faces in the stereoinduction step. Thus, they

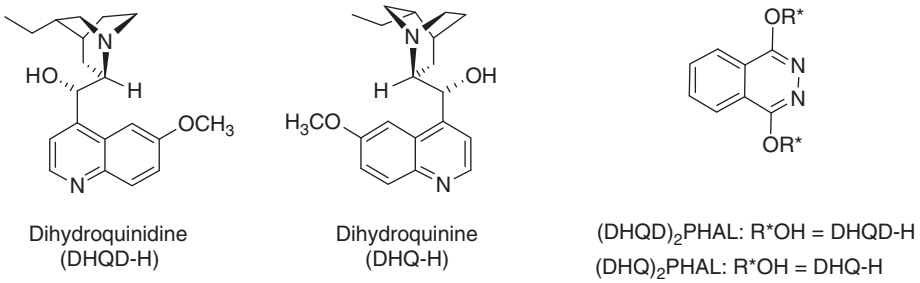


Figure 1 Standard cinchona alkaloid ligands.

lead to opposite absolute configurations, albeit the enantioselectivities obtained of dihydroxylations with each of them are comparable. Their behavior has been referred to as that of pseudo-enantiomers. Several models for face selectivity have been suggested in order to rationalize the enantioinduction in the AD process. The respective preferred face selectivity can usually be predicted following an empiric model devised by Sharpless. For a given depiction of the alkene, the osmium(VIII) oxide complex bearing the chiral ligand will attack from the top of the prochiral face for the dihydroquinidine ligand and from the bottom side for the dihydroquinine ligand (Figure 2).

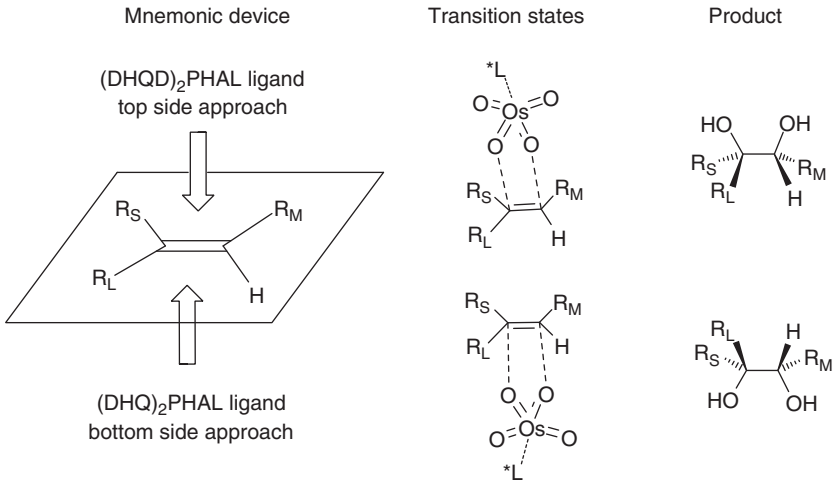


Figure 2 Rules for face selection in the AD reaction.

This attack is believed to proceed through a concerted pathway of a [3 + 2] cycloaddition mode as evidenced from mechanistic data and theoretical calculations.[11,12] An alternative stepwise mechanism was initially proposed by Sharpless.[13]

The oxidation of the alkene gives rise to an intermediary osmium(VI) glycolate, which undergoes ligand-assisted hydrolysis with the water medium to provide the free diol and regenerate an osmium(VI) catalyst precursor. Various reoxidants are known to regenerate the osmium(VIII) catalyst, and for the optimized AD process iron hexacyanoferrate has been identified as optimum oxidant.

7.16.4 Glossary: Asymmetric Ligand Acceleration[14]

In cases in which the presence of a chiral ligand results in formation of an equilibrium between the free metal and the corresponding metal–chiral ligand complex and in which both compounds can act as catalyst for the same process, there are different relative rates for the individual catalytic reactions. If the rate constant k_1 for product formation with the chirally ligated catalyst exceeds the one for the free metal (k_0), i.e. if $(k_1/k_0) > 1$, an asymmetric ligand acceleration is present.

It is important to note that the role of the ligand is twofold: it interacts with OsO_4 to form the active chiral catalyst in the alkene oxidation step and supports the hydrolysis of the intermediate osmium(VI) glycolate. In both cases a significant rate acceleration is obtained. This is particularly important in the initial step because osmium tetroxide itself is reactive toward alkenes giving rise to racemic material. Although the interaction between the ligand and OsO_4 is reversible and follows an equilibrium,

the ligated osmium tetroxide complex L^*-OsO_4 reacts at significantly higher rate than the achiral catalyst. For stilbene as a prominent substrate in the AD reaction, this rate increases because of ligand acceleration was estimated to be in the range of 500.

Ligand acceleration is also present in the hydrolysis step of the intermediate from oxidation. Here, a rapid hydrolysis is required in order to prevent competitive oxidation to an osmium(VIII) glycolate, which itself can serve as a catalyst in alkene oxidation. Since only the remote stereochemical information in the glycolate backbone is present, such a dihydroxylation proceeds usually with low diastereoselectivity and hence erases the overall enantiomeric excess. This catalytic process was called the second cycle of the AD and is usually effectively prevented through the high hydrolysis rate induced by the cinchona alkaloid ligand.

7.16.5 Glossary: First Cycle Catalysis

Reactions with osmium tetroxide proceed with the kinetically dominating osmium tetroxide–ligand complex as the active catalyst. This catalyst adds oxidatively to the alkene forming a monoglycolate osmium(VI) ester within an enantioselective reaction. Reoxidation of the osmium atom results in the corresponding monoglycolate osmium(VIII) ester. This one undergoes rapid product hydrolysis to regenerate the original osmium tetroxide (**Figure 3**). As long as this process is maintained within this catalytic cycle, high enantioselectivity in the AD is obtained.

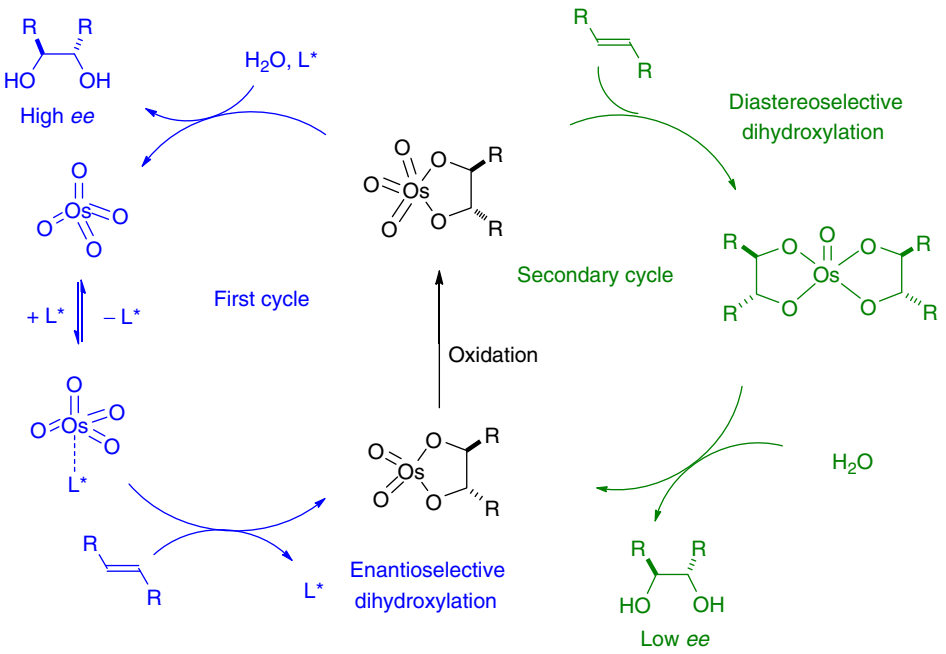


Figure 3 First and second cycle catalysis in the AD reaction.

7.16.6 Glossary: Second Cycle Catalysis

If hydrolysis of the monoglycolate osmium(VIII) ester is slow, the osmium(VIII) oxidizes another alkene directly from this catalyst state. This leads to formation of the corresponding bisglycolate osmium(VI) intermediate within a reaction of low diastereoselectivity. Hydrolysis leads to a diol product with undesired diminished *ee*.

Under the optimized conditions of the Sharpless AD process, a broad range of alkenes can be converted into the corresponding enantioenriched vicinal diols. In general, the PHAL ligand class represents the preferred ligands. As to the osmium source, use of osmium tetroxide should be prevented because of the high volatility of this compound. An appropriate catalyst precursor was identified in the form of nonvolatile salt potassium osmate [$K_2OsO_2(OH)_4$]. Together with potassium hexacyanoferrate $K_3Fe(CN)_6$ as terminal oxidant, the reaction requires base, which is usually added in the form of potassium carbonate within a solvent combination of water and *tert*-butanol. For some alkenes, the presence of methyl sulfonamide was found to have a beneficial effect on the overall rate, although the exact nature of this effect is not understood.

In some cases, and particularly for large-scale application, the required components can be preprepared leading to a blended reaction mixture for immediate use. The resulting mixtures are commonly referred to as AD-mix-α and AD-mix-β, referring to the preferential face selectivity of the containing ligand.[15]

Under these general conditions, terminal alkenes are efficiently converted into the corresponding diols (Figure 4). For example, a series of mono-substituted alkenes undergoes dihydroxylation to the corresponding diols using AD conditions. These reactions proceed with synthetically useful induction in up to 97% *ee*.

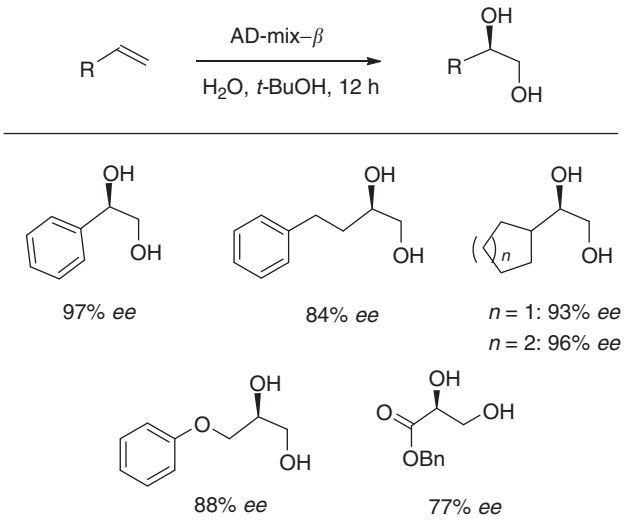


Figure 4 AD reaction: terminal mono-substituted alkenes.

Other types of alkenes represent even more preferred substrates. In general, geminally disubstituted, (*E*)-1,2-disubstituted and trisubstituted alkenes give the highest enantioselectivities in the AD reaction (Figure 5). For the former class of compounds a series of examples are known, in which α-alkyl styrenes represent particularly well-suited alkenes.

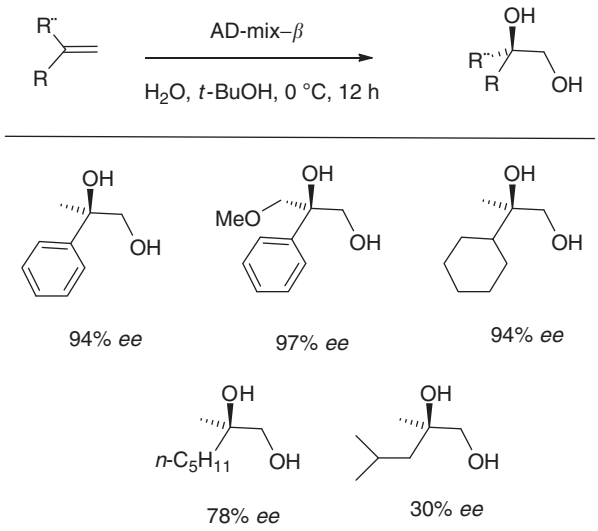


Figure 5 AD reaction: terminal disubstituted alkenes.

Among the examples of 1,2-disubstituted alkenes, (*E*)-stilbene leads to one of the most impressive examples resulting in almost perfect enantiomeric excess (Figure 6). Usually, oxidation of this class of substrates gives products with over 90% *ee*. It is also one of the cases in which addition of methyl sulfonamide shows a beneficial effect.

In contrast, (*Z*)-disubstituted alkenes are the least efficient substrates for the AD process. Although symmetrical substitution pattern provides achiral products, unsymmetric substitution meets with poor face selectivities and hence low *ee*s. A reasonable exception is found for the oxidation of chromene derivatives (Figure 7), which requires an indolinylcarbonyl derived ligand bearing a single cinchona alkaloid unit instead of the standard PHAL class.[16,17]

Trisubstituted alkenes usually again represent efficient substrates for the AD reaction. Again, addition of methyl sulfonamide is beneficial, and the reaction proceeds with high enantioselectivity (Figure 8).

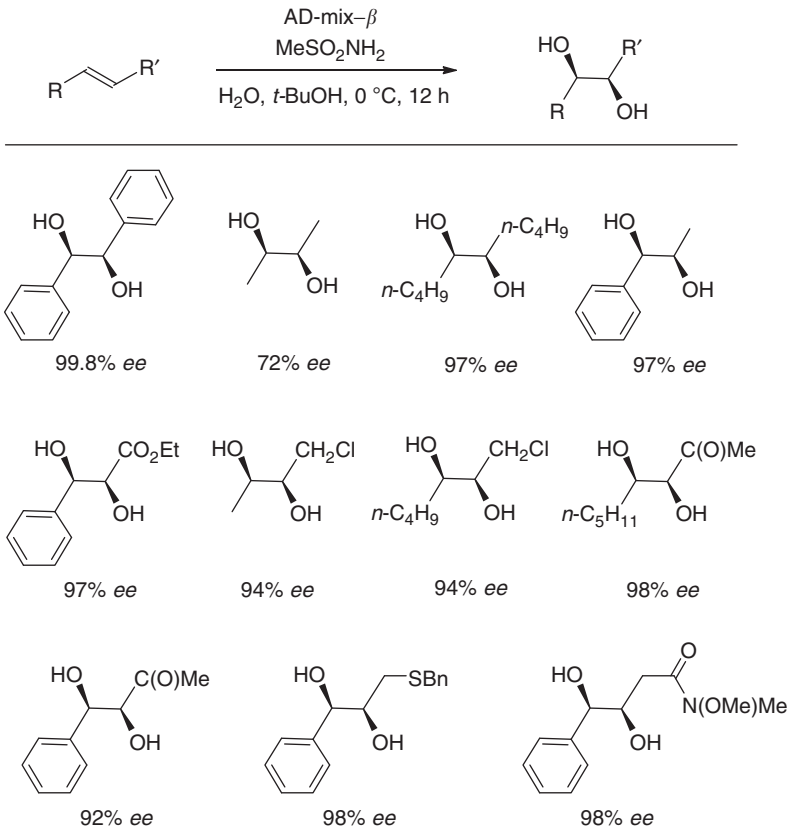


Figure 6 AD reaction: (*E*)-disubstituted alkenes.

The high fidelity of the AD process in face selectivity of trisubstituted alkenes allowed carrying out an unprecedented perhydroxylation of squalene (Figure 9).[18] High selectivities in such a process require the chiral catalyst to override any substrate control after the initial dihydroxylation. Under standard AD conditions, squalene is efficiently oxidized into the corresponding dodecanol, which forms as a single enantiomer in diastereoselective manner in 78% yield. On an average, the perhydroxylation event proceeds with at least 96% asymmetric induction and 96% yield per dihydroxylation step.

In addition to this remarkable perhydroxylation, single dihydroxylation events were described for nonconjugated dienes and trienes (Figure 10). As expected on the basis of the earlier examples, the AD reaction exercises preference for higher substituted alkenes.

In addition to these examples, conjugated dienes and trienes were investigated as well. Useful inductions were observed in these reactions, which all are selective in favor of 1,2-dihydroxylation products.

Tetrasubstituted alkenes represent challenging substrates that in some cases require the replacement of the standard PHAL ligand by a pyrimidine-derived ligand (Figure 11). Under such conditions, some face discrimination can be accomplished, although the *ee* values remain lower than in reactions with the former alkene classes.

As to another ligand modification, the introduction of a ligand displaying an anthraquinone (AQN) bridge enabled some improvement for a series of substrates (Figure 12).[19] For example, some 1,2-disubstituted alkenes underwent an improved dihydroxylation with this ligand. The most remarkable improvement was observed in the AD reaction of functionalized allylic compounds.

The robustness of the AD conditions led to an additional protocol by Muñiz for the direct synthesis of cyclic boronic esters from alkenes (Figure 13).[20] Under otherwise unchanged conditions, addition of arylboronic acids to the AD reaction directly provides the cyclic boronic ester with *ee* values that are comparable to the ones from the parent asymmetric dihydroxylation.

7.16.6.1 Second Cycle Catalysis

As mentioned in the discussion on ligand acceleration, catalysis in the secondary cycle of the osmium-catalyzed dihydroxylation represented an undesired pathway because of a significant loss in enantiomeric excess for these reactions. However, Sharpless observed that certain classes of alkenes, in particular carbamides and free carboxylates, led to almost complete oxidation within this cycle.[21] Apparently, such polar functional groups enhance the rate for product dissociation at the stage of a bisglycolate osmium ester intermediate. In a separate screening, Sharpless discovered an optimum pH range of 4–6 and identified citric acid as

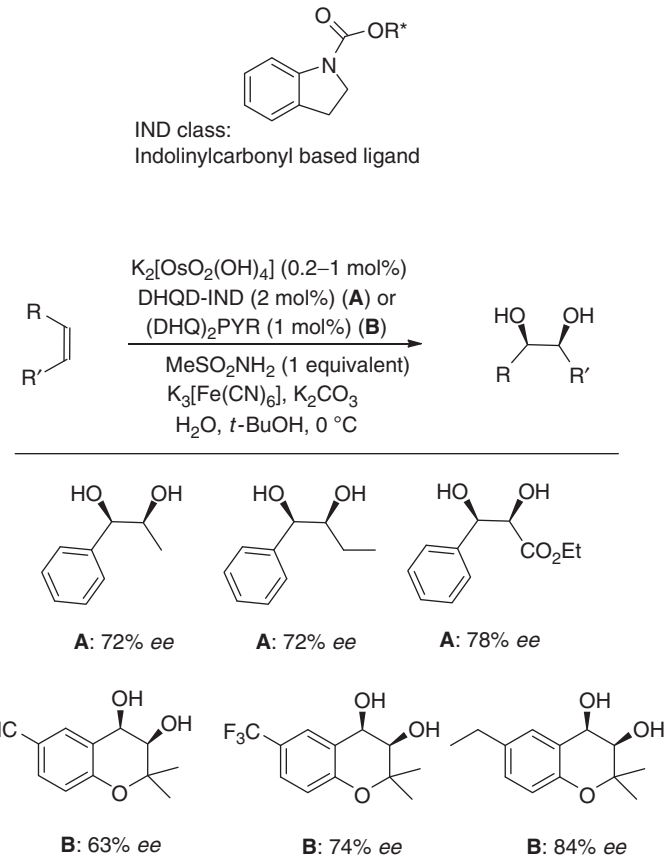


Figure 7 AD reaction: (*Z*)-disubstituted alkenes.

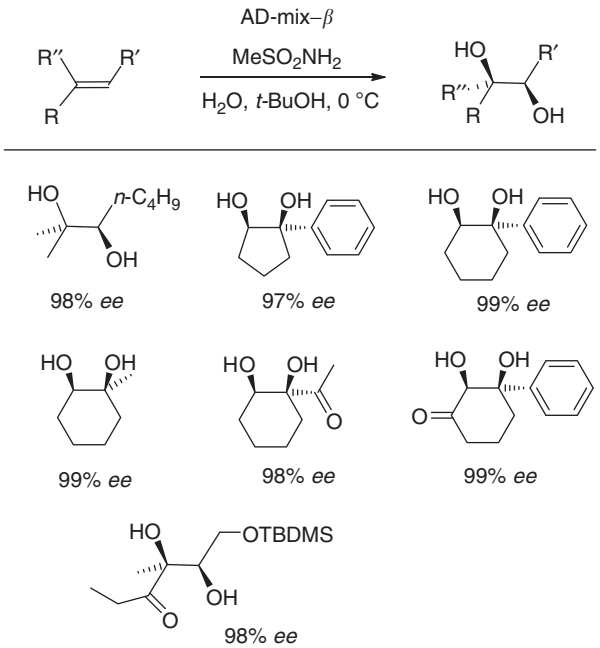


Figure 8 AD reaction: trisubstituted alkenes.

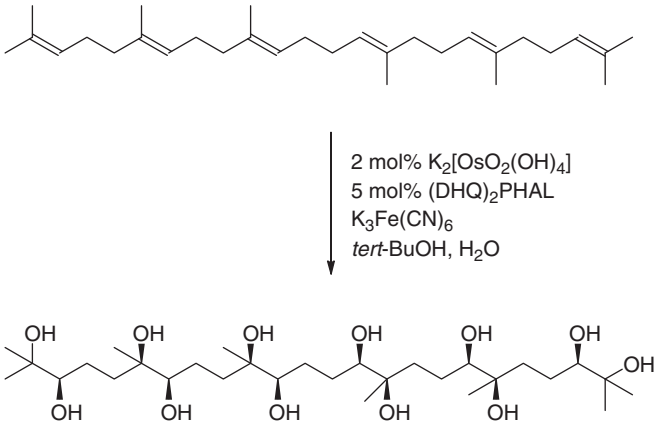
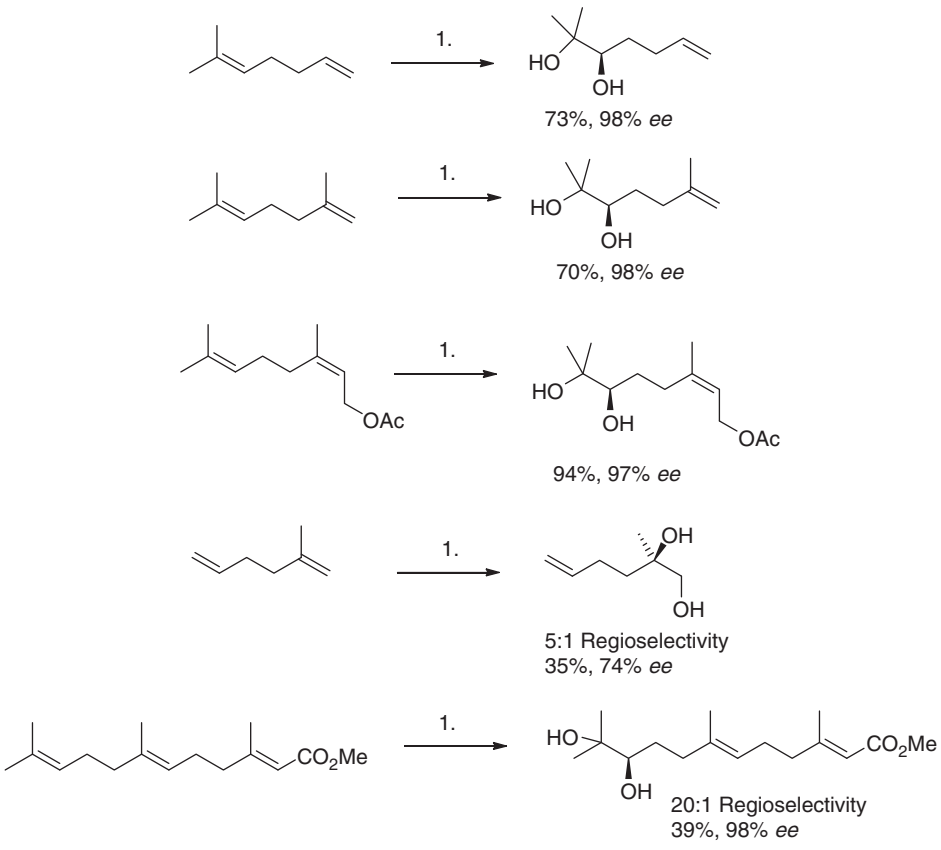


Figure 9 Perhydroxylation of squalene.



1. AD-mix-β or $K_2[OsO_2(OH)_4]$ (0.2–1 mol%), $(DHQD)_2PHAL$, $MeSO_2NH_2$ (1 equivalent), $K_3[Fe(CN)_6]$, K_2CO_3, H_2O, *t*-BuOH, 0 °C

Figure 10 AD reaction: nonconjugated dienes.

a privileged ligand for a rapid and productive dihydroxylation that is presumable based on an *in situ* formation of a stable chelated osmium catalyst derived from potassium osmate and NMO as oxidant on condensation with citric acid.[22]

Under these conditions, diols from the often problematic substrate class of acrylic acid derivatives can be generated under exceptionally simple reaction conditions (Figure 14).

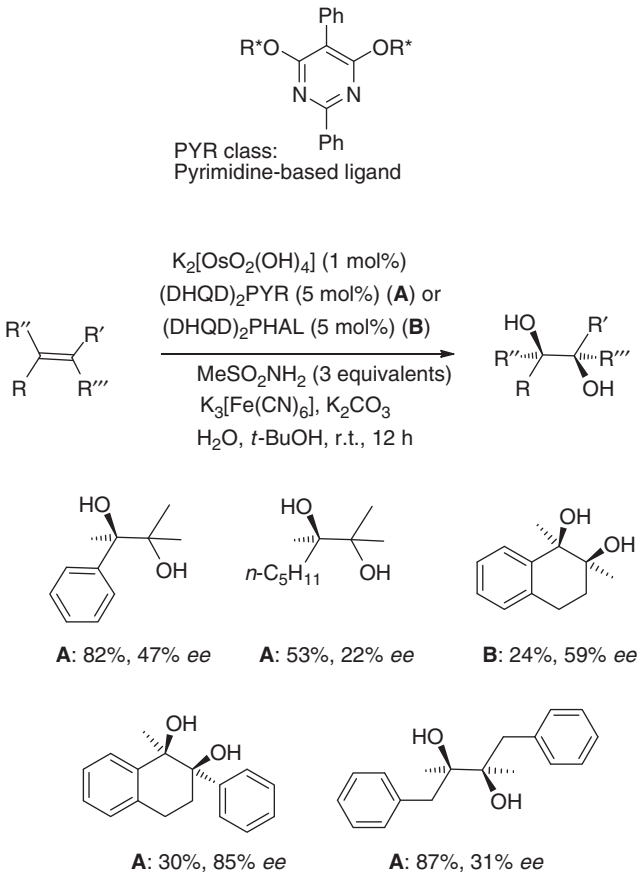


Figure 11 AD reaction: tetrasubstituted alkenes.

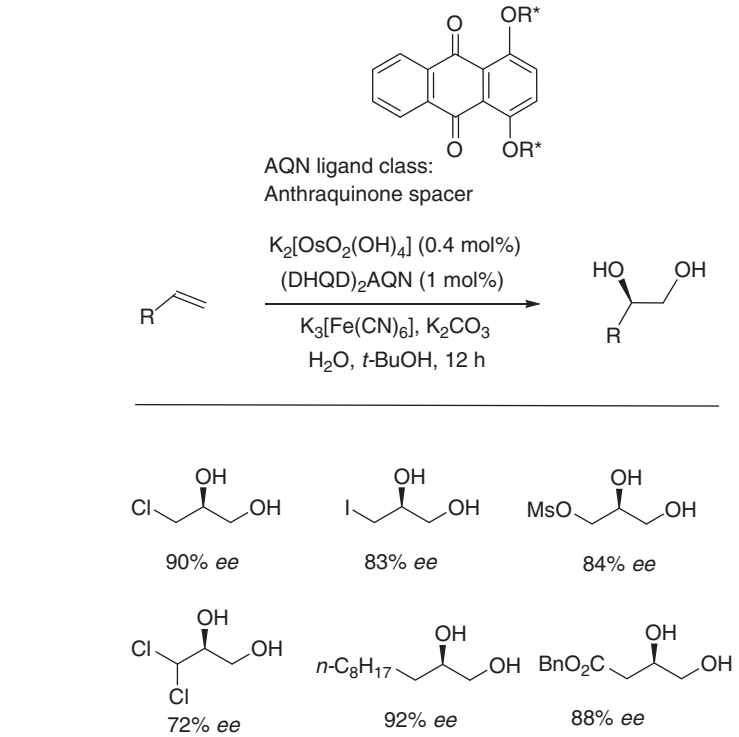


Figure 12 AD reaction: allylic substrates with the AQN ligand.

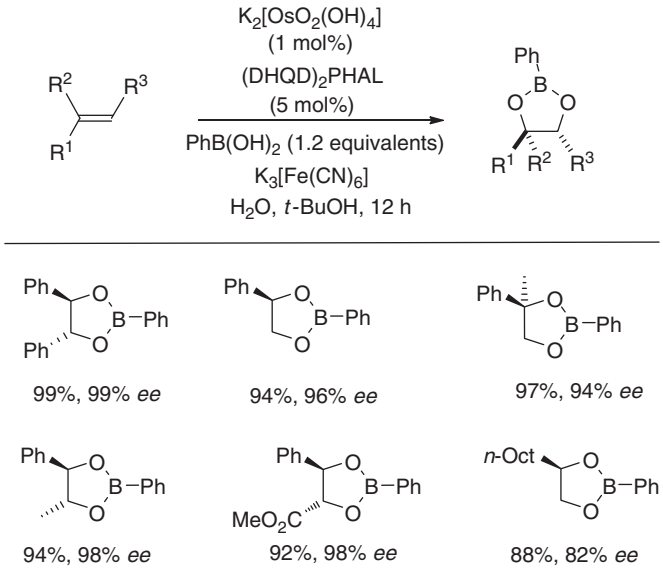


Figure 13 AD reaction: synthesis of boronic esters.

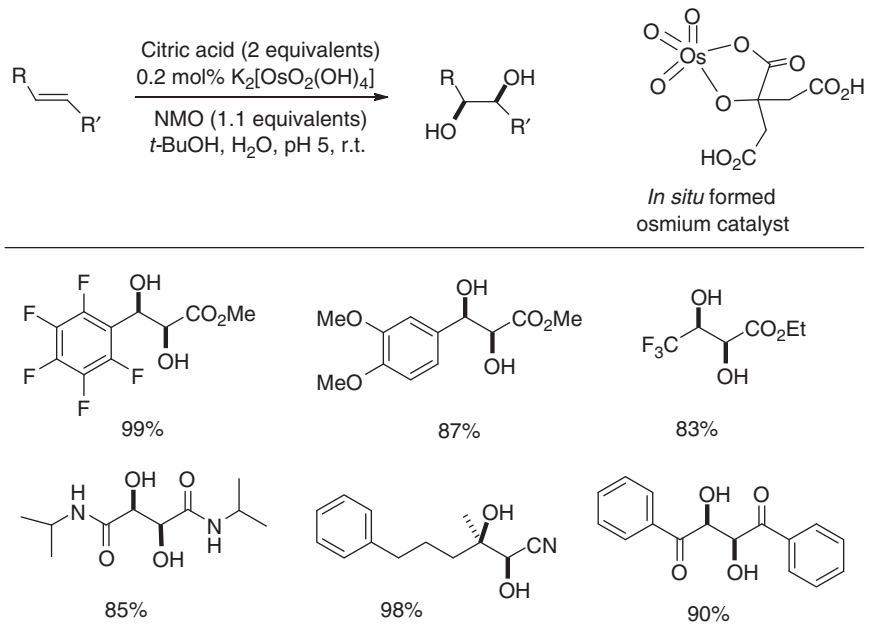


Figure 14 Dihydroxylation of alkenes: second cycle catalysis.

A preliminary attempt for an enantioselective process is based on the use of chiral amino alcohol ligands bearing free carboxylic acid groups. Hence, serine- and threonine-derived ligands were investigated for such processes and gave reasonable induction for some cinnamate substrates (Figure 15).[23] Obviously, the potential of this approach toward a new asymmetric dihydroxylation reaction remains largely unexplored.

7.16.7 Ruthenium-Catalyzed Dihydroxylation of Alkenes

Owing to the cost of osmium metal, ruthenium appears as a reasonable alternative. However, chemoselectivity problems because of overoxidation with concomitant C–C cleavage had been a long-standing problem. This could be overcome by the development

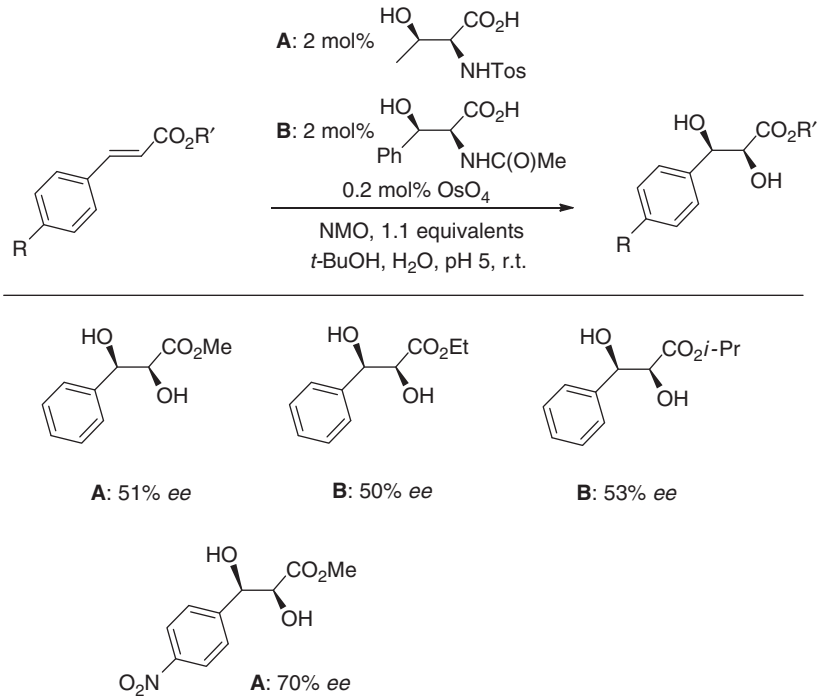


Figure 15 AD reaction: second cycle catalysis.

of suitable conditions, initially under stoichiometric conditions and later through realization of a so-called flash dihydroxylation using *in situ* formed ruthenium tetroxide with extremely fast reaction times (Figure 16).[24,25]

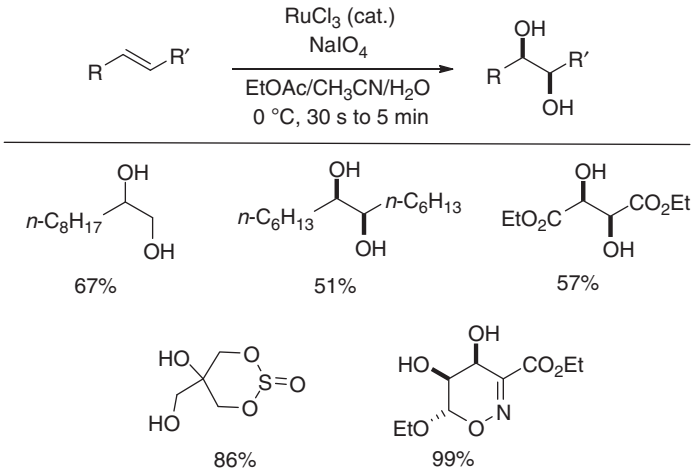


Figure 16 Ruthenium-catalyzed dihydroxylation.

An important accomplishment by Plietker has added additional improvements to arrive at more general conditions, while maintaining the rapid rate of dihydroxylation (Figure 17).[26–28] This particularly useful protocol arrived at from the observation that the presence of strong acid significantly benefits a rapid and productive diol formation. For some cases, an additional amount of cerium(III) chloride was found to be helpful. The reaction requires a rather low substrate concentration, still generates the diol products with remarkable selectivity. It is particularly noteworthy to observe excellent reactivity for alkenes bearing electron-withdrawing substituents such as chalcone, cinnamate, or fumarate, which tend to cause problems in some osmium-promoted dihydroxylation reactions. In the case of cyclohexenol, complete stereoselectivity in favor of the *anti*-product following the Kishi-selection rule was observed. In general, the ruthenium(VIII)-catalyzed dihydroxylation is now a mature reaction that can replace osmium(VIII) catalyses in most cases.

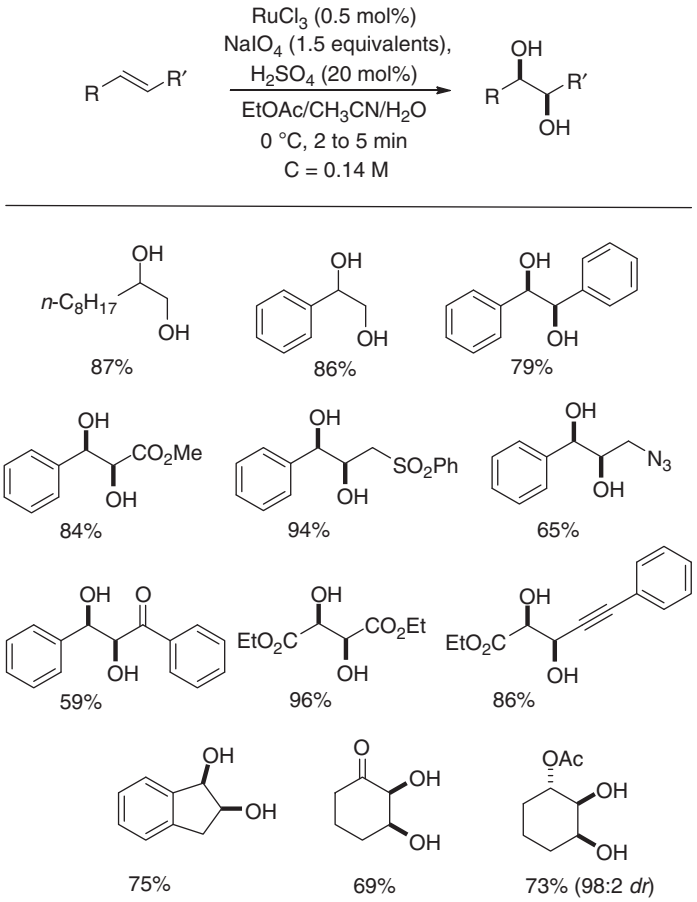


Figure 17 Improved ruthenium-catalyzed dihydroxylation.

7.16.8 Osmium-Catalyzed Aminohydroxylation of Alkenes: Vicinal Amino Alcohol Synthesis

In addition to the work on vicinal dihydroxylation, Sharpless developed a seminal second transformation that provides vicinal amino alcohols from alkenes.[9,29,30] This transformation originates from a stoichiometric reaction using isolated imidoosmium(VIII) reagents, which because of its high cost was of little synthetic use. The discovery that the combination of common osmium salts together in combination with commercially available chloramine-T as oxidant and nitrogen source led to suitable reactivity triggered the development of a catalytic reaction. Its development is closely related to the parent AD reaction and shows the inherent features of ligand acceleration as well as the asymmetric reaction course based on the use of cinchona alkaloid ligands. Again, water is added as part of the solvent combination and serves as a hydroxyl source. The overall working mode of the reaction is closely related to the parent AD reaction and has become known as the Sharpless asymmetric aminohydroxylation (AA). Despite its relation, this reaction is inherently more complicated as the parent AD process. For example, regioselectivity becomes an issue for unsymmetrically substituted alkenes. In addition, depending on the nitrogen source that is employed, dihydroxylation may become a competing pathway.

The reaction was initially developed using chloramine-T as nitrene precursor. In the presence of the standard ligands $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$, enantioselective aminohydroxylation takes place. In contrast to the AD process, the reaction works preferentially well for electron-deficient alkenes. As to an important advantage, it also generates chiral products from symmetrically substitute (*Z*)-alkenes such as (*Z*)-stilbene or cyclohexene, which are substrates that form *meso*-products in the AD process (Figure 18).

In addition to chloramine-T, the corresponding *N*-chloro-methylsulfonamide salt chloramine-M could be employed obtaining significantly better yields and enantioselectivities. It is important to note that because of the crystallinity of the *N*-protected amino alcohol products, greatly increased enantioselectivities can be obtained through single crystallization. The chloramine salt from *N*-chloro *tert*-butylsulfonamide was also used in racemic aminohydroxylation reactions.

The reaction was significantly improved on introduction of N-halogenated carbamate salts as nitrogen sources. The latter require an *in situ* formation of these nitrene precursors and are usually employed in threefold excess. It bears the advantage that the reactions proceed with better asymmetric induction and also can be fine-tuned regarding the individual carbamate source

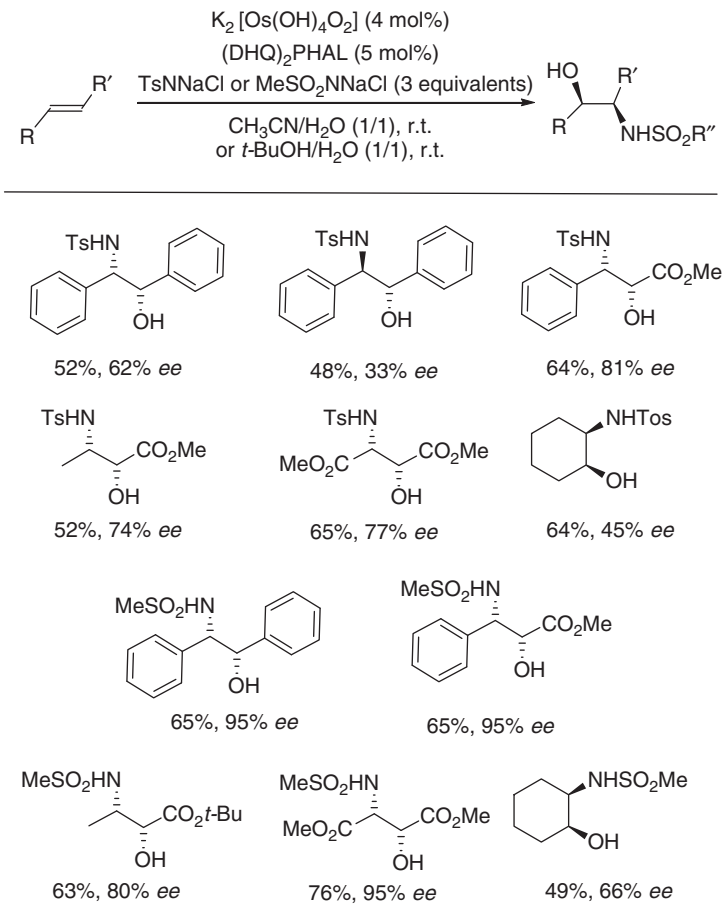


Figure 18 AA reaction: sulfamide variant.

depending on the required deprotection reaction at a later stage. As nitrene sources, benzyl carbamate, ethyl carbamate, trimethylsilylethylcarbamate, and *tert*-butyl carbamate were all employed in this AA variant (Figure 19).

Although regioselectivity does not constitute an issue in these examples, it may require solutions for other alkenes as substrates. For example, styrenes constitute a particularly problematic class of substrates yielding products mixtures in the range of 1:1–1:3 with respect to regioselectivity. This represents a significant limitation regarding a general synthetic application; however, Sharpless has devised conditions for a subsequent second homogenous oxidation using a ruthenium trichloride catalyst and sodium periodate. This oxidizes the mixture of regioisomeric amino alcohols to the corresponding α-amino acids and 2-amino ketones, respectively, which allow for an efficient separation. The isolation of the former products represents a versatile enantioselective access to the important class of aryl glycines. For example, Cbz-protected phenyl glycine is available in 93% *ee* from this sequence (Figure 20).[31]

A solution to the regioselectivity issue of the AA reaction was provided by Sharpless, who observed that a change in the ligand core could provide a reversal in regioselectivity.[32,33] When $(DHQD)_2AQN$ was employed as ligand, a reversed selectivity was observed in the aminohydroxylation of cinnamates yielding the α-amino ester products with regioselectivities in the range of 4:1 and excellent enantioselectivities (Figure 21). Although these are inherently lower values than the ones obtained from the PHAL ligand cores, it nevertheless adds to the versatility of the AA reaction.

Another improvement was achieved with the introduction of a third class of nitrogen source in the form of *N*-brominated amides (Figure 22). This is a versatile protocol that requires only a slight excess of nitrene precursor and hence avoids the sometimes tedious purification that arises from the use of excess nitrogen source as can be the case in the carbamate variant.

For the present case, *N*-bromo acetamide represents the most versatile nitrogen source, which is commercially available, but also readily accessible from bulk starting materials. Apart from acetamide, other carbamides can also be employed, although the enantioselectivities and regioselectivities can depend on the size of the amide substituent resulting in decreased values for larger amide groups. The superiority of the acetamide-based AA variant was demonstrated by its application in the synthesis of the Taxol side chain on a 120 g scale.[34]

The reaction can be extended to heterocyclic amines, which require preformation of their *N*-chloro salts, after which they can be employed under the usual conditions. Among various candidates, the chloramine salt of 2-amino-4,6-dimethyl-1,35-triazine showed best performance (Figure 23).

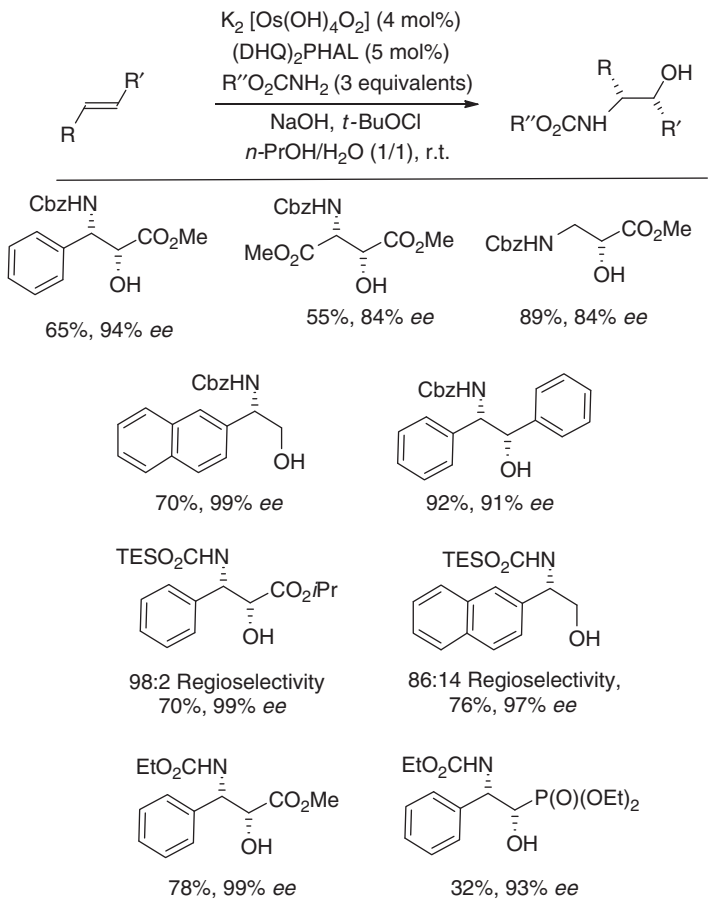


Figure 19 AA reaction: carbamate variant.

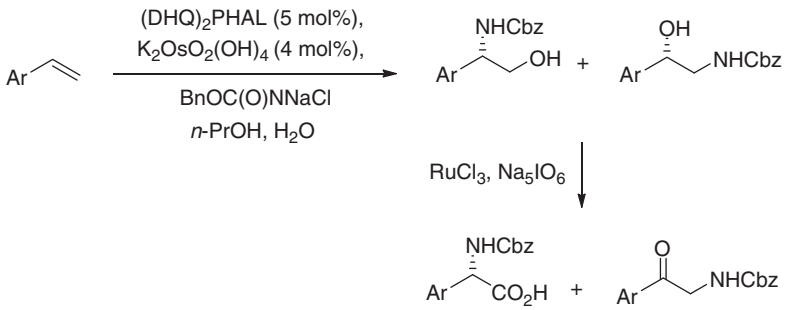


Figure 20 AA reaction: aryl glycine synthesis.

The AA reaction can also proceed within a second catalytic cycle, which is independent of the cinchona alkaloid ligands and hence provides racemic products. Despite significant efforts, an enantioselective approach to the corresponding products within an AA reaction has remained elusive. This refers to the classes of electron-deficient alkenes from Baylis–Hillman reactions, acrylamide derivatives and to substrates containing heterocyclic nitrogen sources (Figure 24). Still, for some cases of diastereoselective oxidations, useful induction was obtained.[35–38]

This observation of efficient aminohydroxylation within the second cycle led to the discovery of a very productive aminohydroxylation of acrylates.[39] This class of compounds only requires to be dissolved in an aqueous bicarbonate solution and treated with chloramine-T (Figure 25). Usually it is of general applicability for acrylic acids, which provide single regioisomers with terminal alkenes, but again suffer from limited regioselectivity in the case of substituted ones.

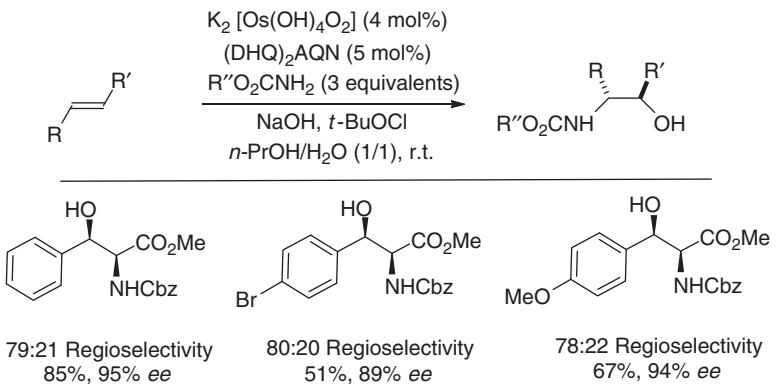


Figure 21 AA reaction: inversion of regioselectivity.

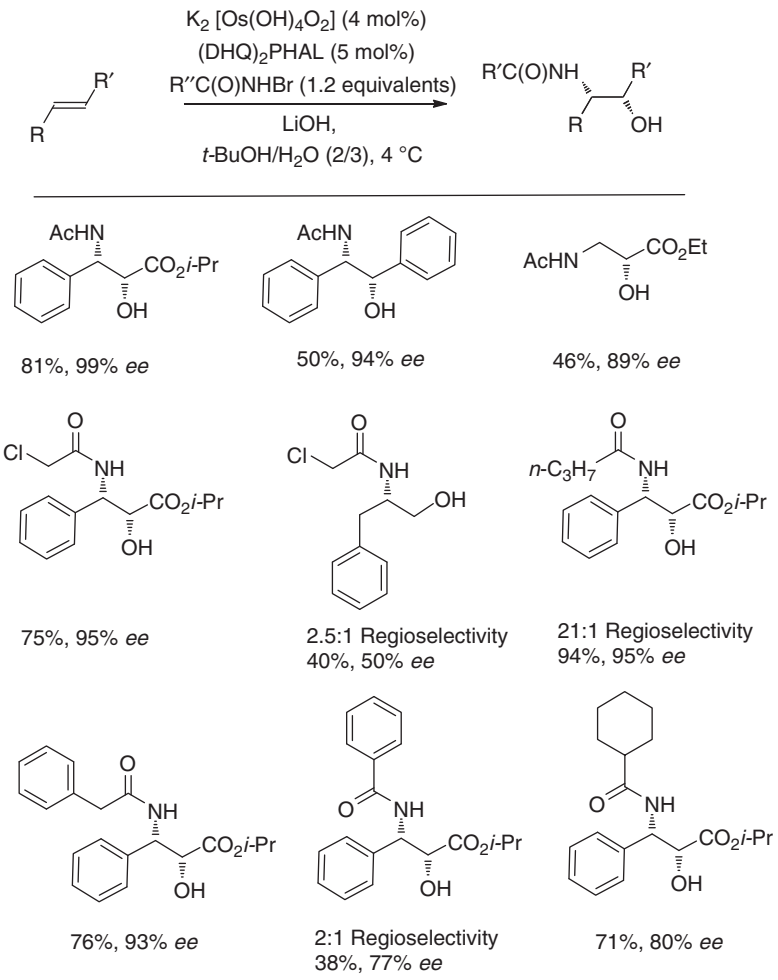


Figure 22 AA reaction: amide variant.

Finally, this chemistry was extended to the use of preformed ligands from enantiopure amino alcohols bearing free carboxylic acids. This approach to second cycle AA catalysis remains notably underdeveloped, although enantiomeric excesses remained below 60% (Figure 26).[23]

As to another feature of second cycle catalysis, Muñiz observed the direct formation of 2-amino ketones from alkenes in the absence of the standard cinchona alkaloid ligands. This reaction proceeded best with styrene and stilbenes. A series of different

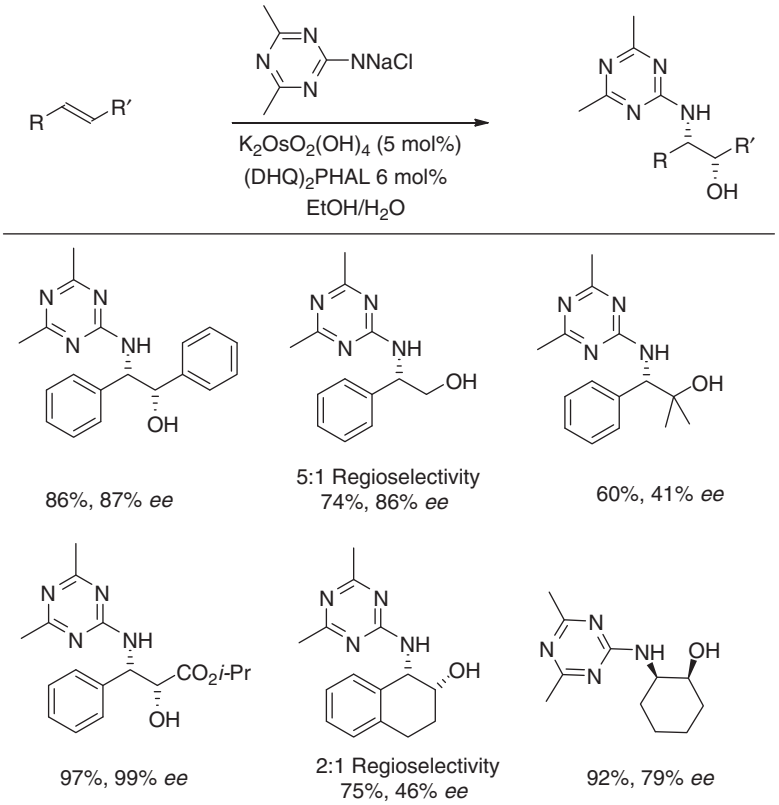


Figure 23 AA reaction: heterocycle variant.

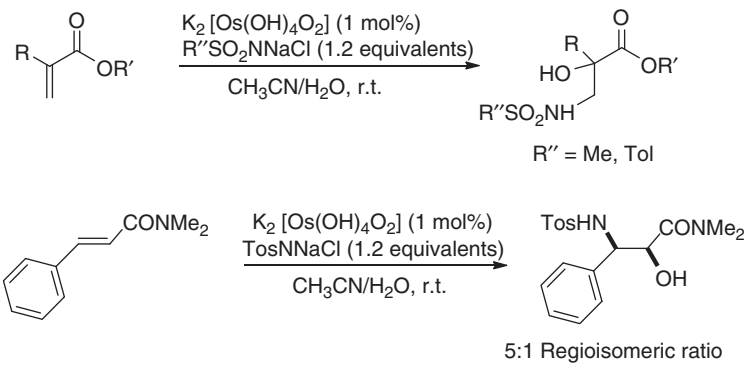


Figure 24 Aminohydroxylation reaction: second cycle catalysis.

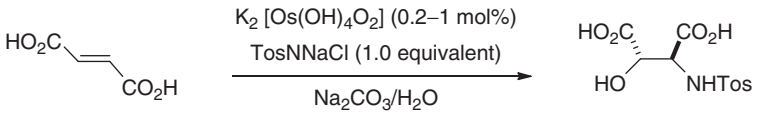


Figure 25 Aminohydroxylation reaction: second cycle catalysis of fumaric acid.

N-chloro sulfamide salts could be employed. The products are believed to be formed from oxidation of the intermediary osmaazaglycolate esters because of their diminished hydrolysis in the absence of the alkaloid ligands. The reaction suffers from regioselectivity problems in the initial step of aminohydroxylation and provides only racemic products, although in acceptable chemical yields (Figure 27).[40]

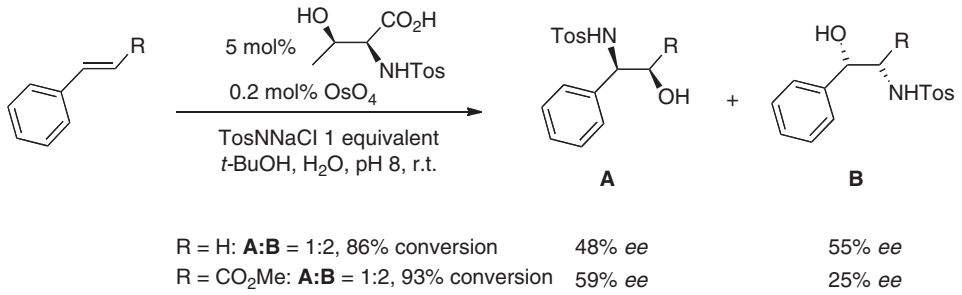


Figure 26 AA reaction: second cycle catalysis.

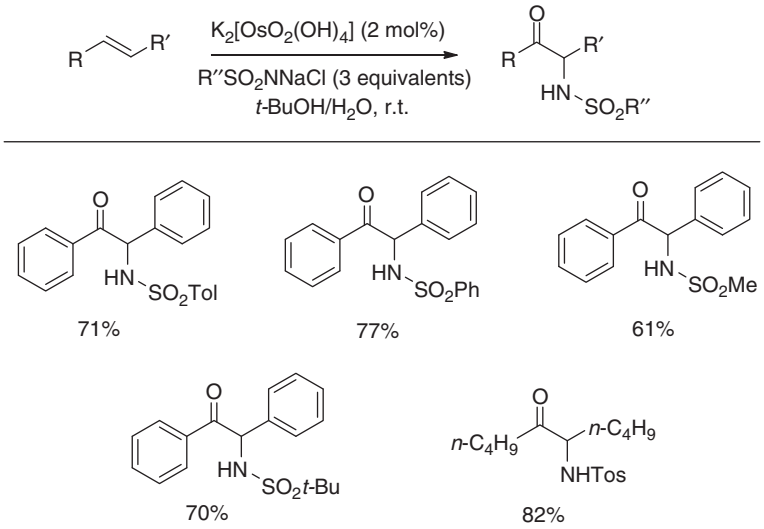


Figure 27 Ketamination of alkenes.

7.16.8.1 Intramolecular Aminohydroxylation

This chemistry was extensively developed by Donohoe. It is an exceedingly useful protocol to access a series of heteroatom triads. Unfortunately, this intramolecular aminohydroxylation proceeds without influence by the chiral cinchona alkaloid ligands and hence proceeds only in racemic form. However, several protocols have been developed that allow for high diastereoselectivities in these reactions. The topic has been reviewed authoritatively.[41]

7.16.8.2 Intermolecular Diamination

Attempts to transfer the conditions of the AD and AA processes to develop a corresponding diamination of alkenes did not materialize in a practical reaction. First, only bis- and trisimidoosmium(VIII) complexes with *N*-alkyl imido group could be generated and such complexes show a rather diminished electrophilicity at the osmium center. As a consequence, enantioselective reactions with the standard chiral cinchona alkaloid ligands did not result in any asymmetric induction. Although some diastereoselective and enantioselective reactions could be developed (Figure 28), these protocols suffer from the extended stability of the resulting osmaimidazolidine products, from which the free diamines could only be released on reaction with hydride reagents. Hence, these reactions are stoichiometric in osmium metal and do not represent a useful method.[42,43]

7.16.9 Hypervalent Iodine(III) Reagents

Hypervalent iodine(III) reagents represent metal-free alternatives in oxidation reactions. To date, this chemistry remains rather unexplored with respect to the development of enantioselective transformations. However, there are some recent accomplishments that suggest that hypervalent iodines[44,45] can serve as suitable reagents for enantioselective oxidation of alkenes.

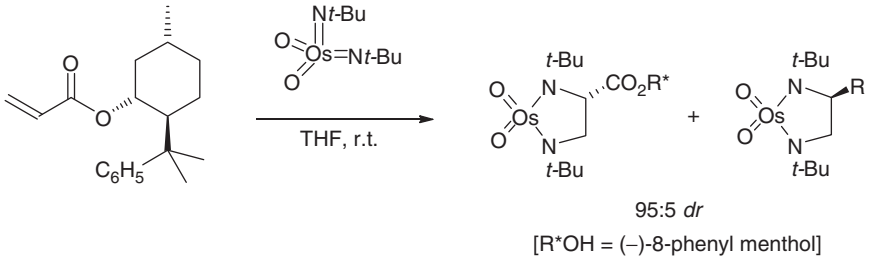


Figure 28 Bisimidoosmium-promoted asymmetric diamination of alkenes.

Within this context, Wirth initiated the application of hypervalent iodine(III) reagents for enantioselective oxidative 1,2-difunctionalization of alkenes (Figure 29).[46] This work is based on defined chiral iodine(III) reagents and was initially reported for the 1,2-bistosylation reaction of styrene. The corresponding reagents make use of a chiral 1-arylalkyl ether and a chelation of the ether moiety to the iodine center to provide a more rigid stereochemical environment at the iodine(III).[47] This approach allowed for the proof of principle that dioxygenation of styrenes can be achieved by acid-mediated oxidation of styrene with suitable chiral reagent. Within an extensive optimization, a series of different reagents **A** were prepared, the maximum enantiomeric excess that could be obtained amounted to 65% *ee*.[48]

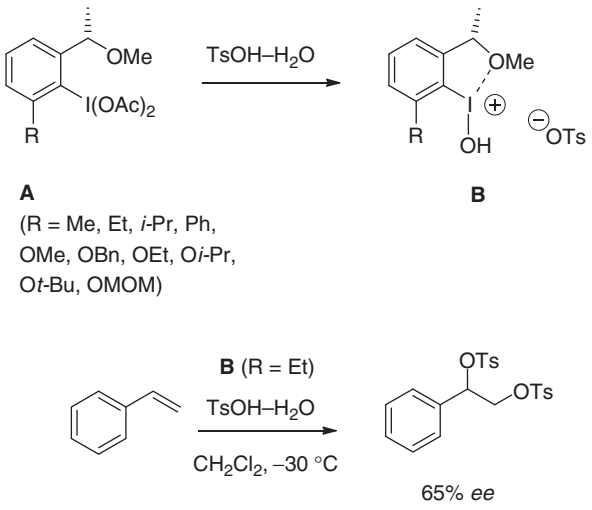


Figure 29 Iodine(III)-promoted enantioselective bistosylation of alkenes.

The area of dioxygenation of alkenes further benefitted from an improved protocol from Fujita, who employed chiral iodine reagents **A–C** with stereochemical information derived from lactic esters. This work employed acetic acid as the oxygen source and proceeds with excellent enantioselectivity. Depending on the reaction conditions, the transformation proceeds with *syn*-selectivity in a Woodward-type mechanism. Alternatively, high *anti*-selectivity can be accomplished following the Prévost mechanism (Figure 30).[49]

These inductions are suitable and can compete with the enantiomeric excesses obtained for the asymmetric dihydroxylation of styrene in the case of osmium catalysis in the AD process.

In the case of aminooxygenation reactions, no intermolecular reactivity has so far been developed. However, Wirth recently reported that an intramolecular reaction could indeed proceed with suitable induction, when the chiral iodine(III) reagent was pretreated with trimethylsilyl triflate followed by reaction at low temperature (Figure 31).[50]

Muñiz introduced the use of hypervalent iodine(III) reagents for an intermolecular enantioselective diamination of styrenes. These reactions usually employ an *in situ* formation of the active reagent ArI[N(SO_2R)$_2$]$_2$. For a standard diamination of styrene, several hypervalent iodine reagents promoted an enantioselective diamination.[51] For example, a spiro-reagent led to 32% *ee* with bistosylimide as nitrogen source, whereas the binaphthyl derivative afforded 14% for the same transformation and 32% for the reaction with bismesylimide.[52] Reagent **C** was identified as the most suitable one leading to 50% *ee* for bistosylimide and 66% *ee*

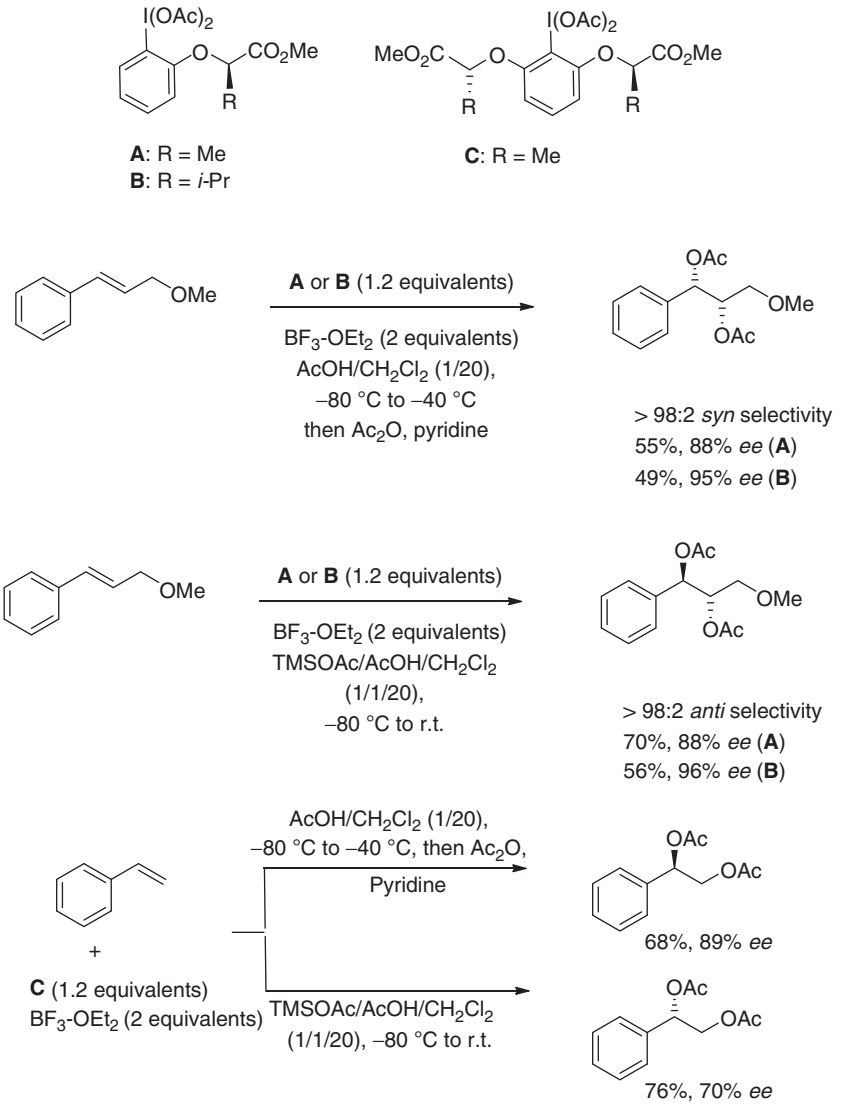


Figure 30 Iodine(III)-promoted enantioselective bisacetoxylation of alkenes.

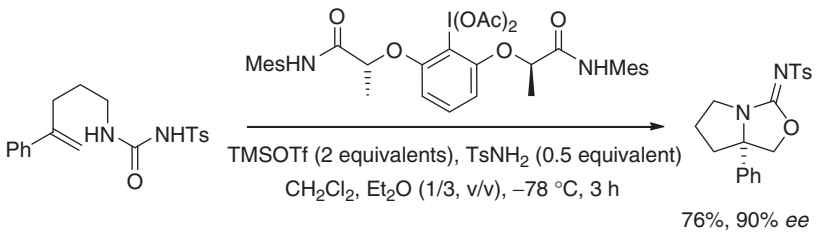


Figure 31 Iodine(III)-promoted intramolecular enantioselective aminohydroxylation of alkenes.

for bismesylimide (Figure 32). The latter value could be increased to 85% for a reaction at lower temperature, and the product was crystallized to enantiopurity within a single crystallization.

Under these reaction conditions, a series of styrene derivatives underwent an enantioselective diamination reaction under metal-free conditions (Figure 33).[51,53] A series of substituents and substitution pattern are tolerated and all compounds could be crystallized to enantiopurity within a single crystallization step.

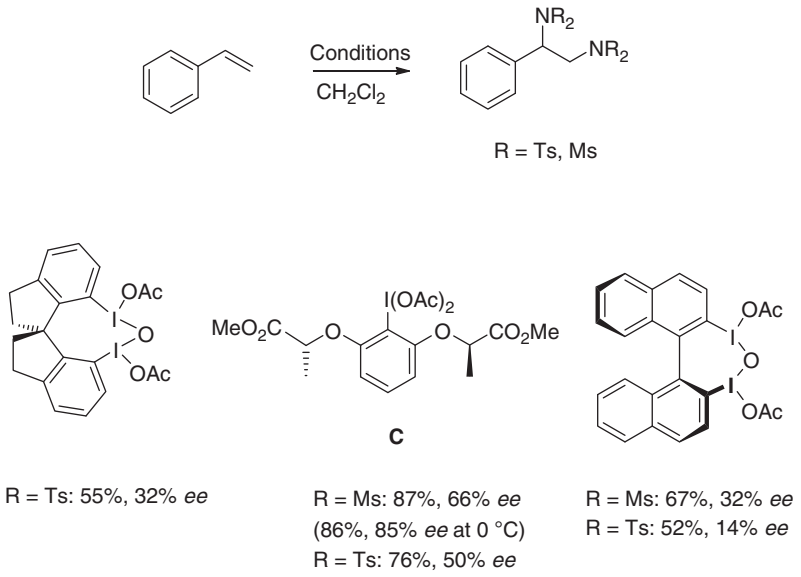


Figure 32 Iodine(III)-promoted enantioselective diamination of alkenes (1).

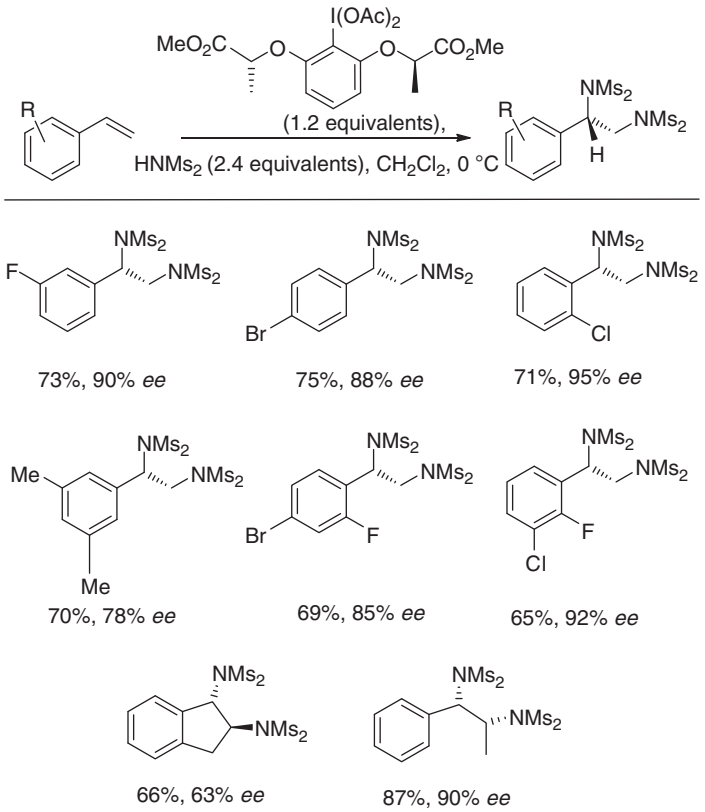


Figure 33 Iodine(III)-promoted enantioselective diamination of alkenes (2).

7.16.10 Conclusion

The area of oxidative difunctionalization has reached a mature stage. Although historically the AD process was the dominating reaction in the area, recent accomplishment have added useful protocols to this field. Hence, asymmetric aminoalkoxylation and

aminohydroxylation protocols are now available for some class of alkenes. The long quest for a corresponding protocol for a related direct diamination of alkenes is appearing now also.

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7.17 Addition Reactions with Formation of Carbon–Oxygen Bonds: (iv) The Wacker Oxidation and Related Reactions

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Glossary

Carbonylative A reaction that forms a carbonyl group by combination with carbon monoxide.

β–H elimination An elementary step in organometallic chemistry in which an alkyl group bonded to a metal center is converted into the corresponding metal hydride species and an alkene.

Migratory insertion An elementary step similar to Pd–H insertion in which two ligands on a metal complex combine to one component.

Oxypalladation An elementary step in organometallic chemistry in which an oxygen atom and a palladium atom are added across a carbon–carbon multiple bond to form a reactive intermediate.

Pd–H insertion It is a retro-reaction of the β-H elimination in which an alkene inserts into a palladium–hydride bond to form a palladium–alkyl species.

7.17.1 Introduction

The reaction of transition metal π-alkene or π-alkyne complexes with nucleophiles has contributed extensively to the growing use of organometallic complexes in organic synthesis (*see* Chapter 7.19). The transition metal most widely employed for the activation of carbon–carbon unsaturated bonds toward nucleophilic attack is palladium.[1a,b] A representative example is the oxidation of ethylene to acetaldehyde by oxygen in water in the presence of a tetrachloropalladate catalyst ($[PdCl_4]^{2-}$), which has been known for a long time as the Wacker process or the Hoechst–Wacker process (named after the chemical companies of the same name).[1c,d] This chemical reaction was the first organometallic and organopalladium reaction applied on an industrial scale. The overall reactions can be described as follows:

$$[PdCl_4]^{2-} + C_2H_4 + H_2O \rightarrow CH_3CHO + Pd(0) + 2\,HCl + 2\,Cl^- \quad (1)$$

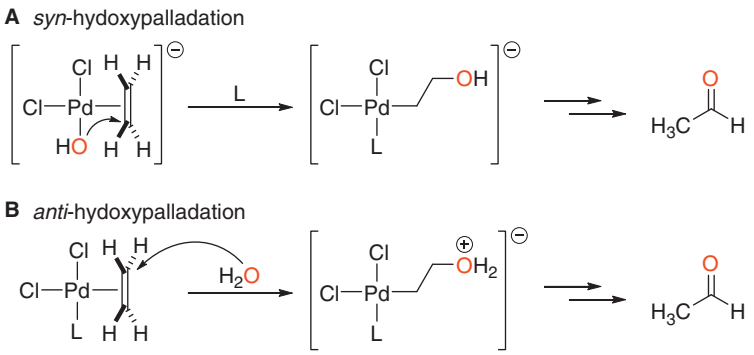
$$Pd(0) + 2\,CuCl_2 + 2\,Cl^- \rightarrow [PdCl_4]^{2-} + 2\,CuCl \quad (2)$$

$$2\,CuCl + 1/2\,O_2 + 2\,HCl \rightarrow 2\,CuCl_2 + H_2O \quad (3)$$

$$\text{Net:} \quad C_2H_4 + 1/2\,O_2 \rightarrow CH_3CHO \quad (4)$$

Note that all catalysts are regenerated and only the alkene and oxygen are consumed. Without $CuCl_2$ as an oxidizing agent, Pd(0) metal (resulting from reductive elimination of Pd(II) in the final step) would precipitate out and the reaction would come to a halt. Air, pure oxygen, or a number of other oxidizers can then oxidize the resultant CuCl back to $CuCl_2$, allowing the cycle to repeat.

The reaction mechanism for the industrial Wacker process has received significant attention for several decades.[2] A number of mechanistic studies based on the kinetics, stereochemistry, and theoretical calculation have been reported. Stereochemical analysis in the addition step of the oxygen nucleophile to the olefin (oxypalladation) is complicated because the product of the reaction, acetaldehyde, is achiral (Scheme 1). Nevertheless, Henry provided strong kinetic arguments supporting a *syn*-hydroxypalladation pathway. His argument was based on determination of the rate law for the reaction and careful kinetic analysis, which revealed that nucleophilic attack of external hydroxide on a Pd(II)-coordinated ethylene molecule would require a bimolecular reaction to proceed faster than diffusion. Subsequently, a number of groups designed studies to probe the stereochemistry of oxypalladation of alkenes. These studies employed modified reaction conditions (e.g., reactions carried out in the presence of carbon monoxide, high Cl^- concentration, and/or high $CuCl_2$ concentration) that lead to the formation of products amenable to stereochemical analysis. Most of these studies provided clear evidence for *anti*-hydroxypalladation of the alkene. During the same time period, studies of stoichiometric aminopalladation and carbopalladation reactions also were shown to proceed via *anti*-addition of an amine or carbon nucleophile to a coordinated alkene. The clarity and elegance of these experiments had a profound impact on the



Scheme 1

field, to the extent that early evidence for *syn*-hydroxypalladation of ethylene in the Wacker reaction seemed to be overlooked. The term 'Wacker-type reaction' was often used as a synonym for *anti*-nucleopalladation of an alkene. Later, work by Henry and coworkers, however, provided convincing evidence that the reaction conditions used in stereochemical studies by other groups caused a switch in the stereochemical outcome of the reaction. Evidence obtained from this work points out that the Wacker process is quite sensitive to and dependent on reaction conditions, specifically Cl^- and $CuCl_2$ concentrations. Experimental results support the conclusion that *syn*-hydroxypalladation leading to ethanal is the active mechanism of the Wacker process under industrial conditions (low concentrations of Cl^- and $CuCl_2$) and *anti*-hydroxypalladation leading to chlorohydrin is the active mechanism under conditions with high concentrations of Cl^- and $CuCl_2$. This conclusion that two mechanisms are in effect relies heavily on kinetic evidence ruling out proposed *anti*-hydroxypalladation pathways and the validity of stereochemical studies at low concentrations of Cl^- and $CuCl_2$ that some have found controversial. These conclusions have evolved over decades and provide a picture that is noticeably different or neglected in most mechanism discussions. A general observation emerges from stereochemical data. In reactions where a strongly coordinating ligand such as carbon monoxide exists *in situ*, nucleophilic attack should be *anti* because the second coordination site necessary for *syn* addition is not available. Such strongly coordinating ligands also stabilize oxypalladation adducts against decomposition to oxidation products because vacant coordination sites are not available for hydrogen transfers. Thus, the same factors that favor *anti*-addition also favor stable oxypalladation intermediates that may, in turn, undergo different reactions to form different products. Results from theoretical calculations have clarified the mechanism somewhat. All calculations on the originally proposed *syn*-hydroxypalladation mechanism rule out internal migration of OH^- as a possible mechanism. However, a novel *syn*-hydroxypalladation mechanism involving a water transfer simultaneously coupled to a deprotonation may be consistent with current interpretations of experimental and theoretical calculations; this mechanism warrants more investigation.

7.17.2 Formation of Carbonyl Group

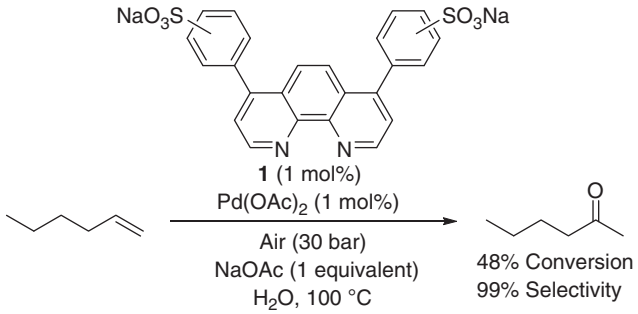
The oxidative functionalization of alkenes by means of Pd-catalyzed reactions is important for both large-scale industrial processes mentioned above and research scale synthetic organic chemistry.[3] Many of these reactions proceed according to the following general principle:

- An oxygen nucleophile attacks a carbon–carbon double bond activated by Pd(II) through the coordination: oxypalladation step.
- The intermediate alkylpalladium species undergoes β-H elimination, releasing the oxygenated organic product and H–Pd–X.
- The loss of HX from H–Pd–X results in the formation of Pd(0) species, which must be reoxidized to Pd(II) in order to start a new catalytic cycle.

Alkenes with three and more carbon atoms are oxidized regioselectively to ketones under Wacker conditions: the carbonyl group is formed at the carbon atom that would accept a nucleophile in a Markovnikov addition. Terminal alkenes thus form methyl ketones. This laboratory scale modification of the Wacker process, the so-called Wacker–Tsuji oxidation, is useful for the synthesis of various ketones.[4]

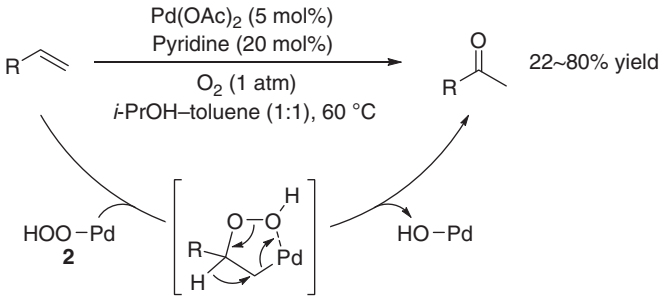
7.17.2.1 Ketone Formation

Sheldon and coworkers first developed the catalyst system consisting of $Pd(OAc)_2$ and a water-soluble bathophenanthroline ligand **1** for the oxidation of terminal alkenes into the corresponding methyl ketones in aqueous solution (equation 1).[5a] The reaction conditions avoid the use of cocatalysts and high chloride concentrations that cause the traditional Wacker conditions to be highly corrosive. No isomerization of the olefinic part and no palladium black formation were observed. The kinetic studies indicate saturation kinetics for the substrate up to 50% conversion, thereafter the reaction becomes a first-order reaction in the substrate. When the substrate/catalyst ratio was increased from 100 to 200, the reaction was zeroth order in the substrate up to 100 turnovers. The reuse of the catalyst could be done with the further addition of NaOAc. Without NaOAc, formation of palladium black was observed after the second and third cycles. Addition of NaOAc to the reaction mixture helps to prevent palladium metal deposition. Although this system alleviates the need for chloride, substrate solubility for higher alkenes remains a challenge.



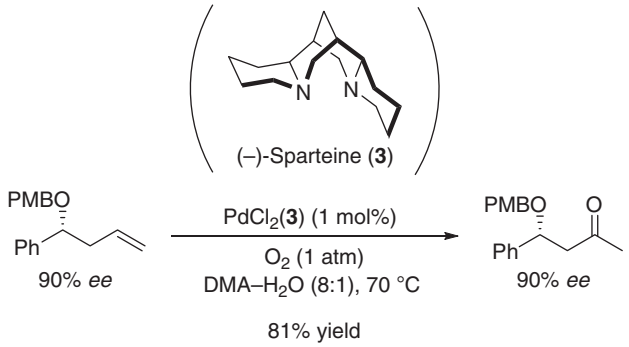
(1)

The $Pd(OAc)_2$/pyridine catalyst system is also successful for the conversion of terminal alkenes into methyl ketones.[5b] In this case, the reactions are conducted in a solvent mixture of toluene and *i*-PrOH under an O_2 atmosphere. As water is not present at the start of these reactions, the authors proposed an alternative mechanism in which a palladium hydroperoxide species **2** undergoes oxygen atom transfer to a coordinated alkene (Scheme 2).



Scheme 2

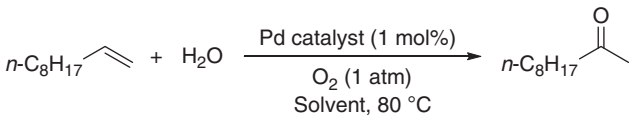
Sigman et al. discovered a direct O_2-coupled Wacker–Tsuji oxidation with use of balloon pressure of O_2 and low catalyst loading (equation 2).[5c] Use of (–)-sparteine (**3**) as a ligand on Pd prevents olefin isomerization and leads to the selective formation of methyl ketones from terminal olefins in good yields. The substrate scope and chemoselectivity of this system is highlighted by the functional group tolerance and ability to oxidize enantiomerically enriched substrates with no racemization.



(2)

Ancillary ligands are not always necessary for the promotion of the Wacker–Tsuji oxidation. Kaneda and coworkers reported that the combination of $PdCl_2$ and dimethylacetamide (DMA) allows highly effective oxygenation of terminal olefins under cocatalyst-free conditions (Table 1, entry 1).[5d] The use of *N*-methylpyrrolidone (NMP) and *N*,*N*-dimethylpropionamide (DMPA) in place of DMA gave moderate yields (entries 2 and 3), whereas *N*,*N*-dimethylformamide (DMF), ethanol, and acetonitrile were

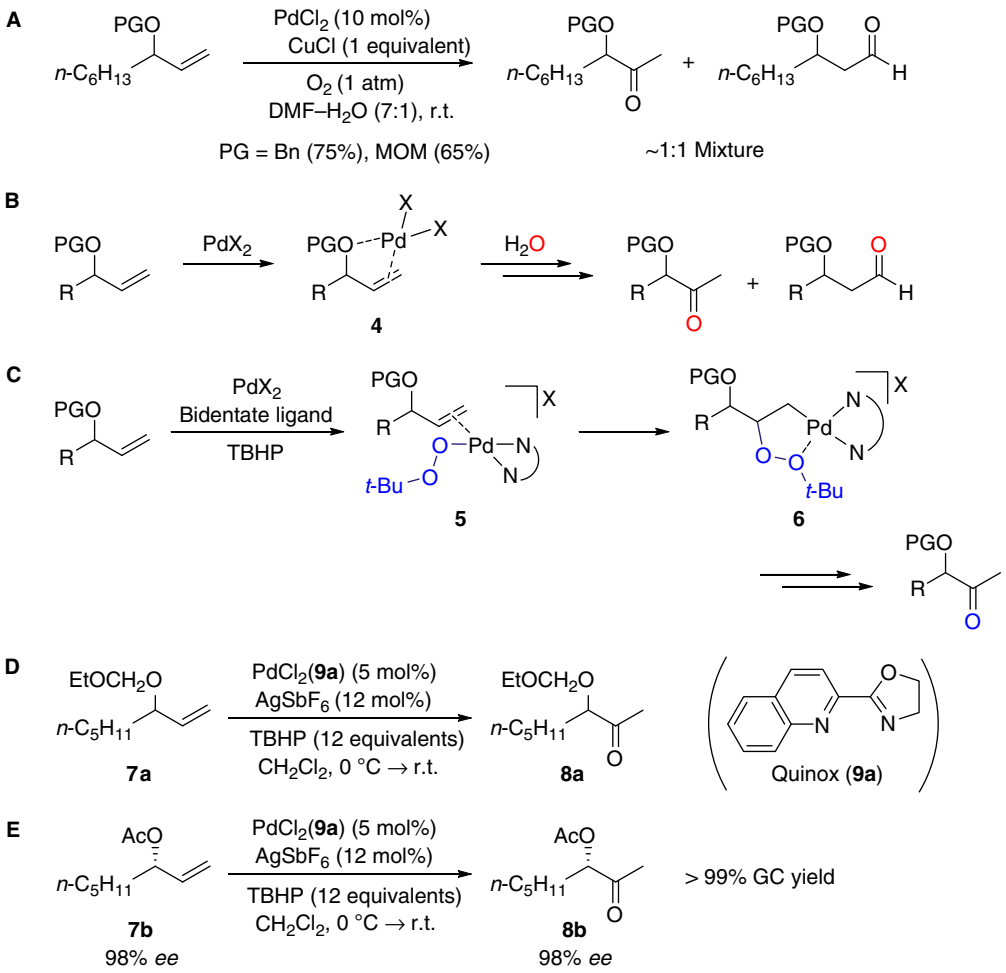
Table 1 Effects of solvent and Pd source in the Wacker oxidation of 1-decene



Entry	*Catalyst*	*Solvent*	*Isolated yield (%)*
1	$PdCl_2$	DMA	84
2	$PdCl_2$	NMP	74
3	$PdCl_2$	DMPA	33
4	$PdCl_2$	DMF	Trace
5	$PdCl_2$	EtOH	Trace
6	$PdCl_2$	MeCN	Trace
7	$Pd(OAc)_2$	DMA	Trace
8	$[Pd(NH_3)_4]Cl_2$	DMA	Trace

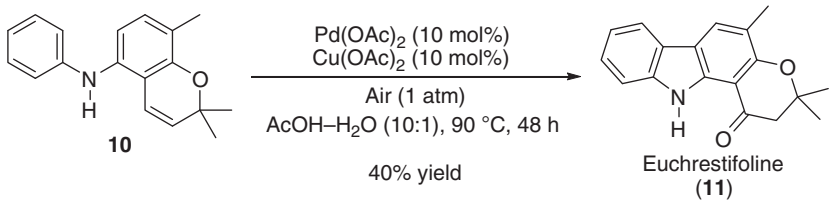
significantly less effective (entries 4–6). The choice of Pd source was found to influence catalytic efficiency: only $PdCl_2$ could function as a catalyst (entry 1 vs. entries 7 and 8). No palladium precipitation was observed during the reaction and the retention of monomeric Pd(II) species was confirmed after the reaction by Pd K-edge X-ray absorption fine structure (XAFS) spectroscopic analysis.

Although the high regioselectivity (the Markovnikov addition) is usually observed in the Wacker–Tsuji oxidation, a major limitation in the scope is for allylic alcohols and their protected variants. Previous reports of the Wacker–Tsuji oxidation on protected allylic alcohols found diminished selectivity for the desired methyl ketone. A noticeable example is from the results observed by Kang and coworkers, who obtained methyl ketone and aldehyde in an inseparable 1:1 mixture (Scheme 3A).[5e] This problematic nature of protected allylic alcohols in Wacker–Tsuji oxidations has been proposed to arise from coordination of the oxygen atom to the Lewis acidic palladium as in complex **4** (Scheme 3B). This can cause water to attack through multiple pathways, resulting in both the Markovnikov and *anti*-Markovnikov products. Sigman et al. hypothesized that the selectivity issue can be mitigated by ligand modulation in conjunction with a *tert*-butyl hydroperoxide (TBHP)-mediated Wacker–Tsuji oxidation, which is proposed to proceed via a pathway mechanistically distinct from the classical Wacker–Tsuji oxidation.[5f,g] Specifically, the use of a bidentate ligand, with TBHP, on palladium is thought to lead to a coordinatively saturated species similar to **5**, which can block the coordination of allylic oxygen atom. Consequently, insertion would be directed to the Markovnikov position yielding species **6**, which decomposes to yield the methyl ketone product (Scheme 3C). They indeed discovered a highly efficient Wacker–Tsuji oxidation system capable of converting protected allylic alcohol **7a** to the desired acyloin derivative **8a** using Quinox **9** and aqueous 70 wt% TBHP (T-Hydro) as the terminal oxidant (Scheme 3D). In this system, no loss of enantiopurity was observed for the oxidation of enantioenriched-protected allylic alcohol **7b** (Scheme 3E).



Scheme 3

Knölker and a coworker have applied the Wacker–Tsuji oxidation to a total synthesis of natural products.[5h] Heating of the diarylamine **10** with catalytic amounts of $Pd(OAc)_2$ and $Cu(OAc)_2$ in a mixture of AcOH and H_2O (10:1) in air at 90 °C for 48 h resulted in direct conversion to euchrestifoline **11** through the ketone formation followed by cyclization via double aromatic C–H bond activation (equation 3).

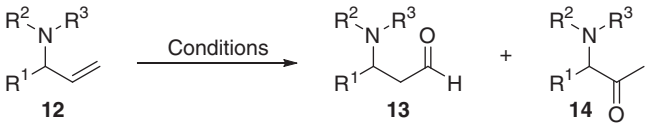


(3)

7.17.2.2 Aldehyde Formation

As described above, the Wacker–Tsuji oxidation follows Markonikov's rule and thus yields methyl ketones from the majority of terminal olefins. Hence, the Pd-catalyzed *anti*-Markovnikov Wacker–Tsuji oxidation of olefins remains a major challenge. In specific cases, aldehyde selectivity has been observed: these examples are restricted to the case where the olefin is functionalized with a directing group. For instance, Feringa and coworkers have demonstrated that the Wacker–Tsuji oxidation selectively produces aldehydes **13** from allylic amine derivatives **12** through the coordination of the nitrogen-protecting group to the Pd catalyst.[6a] They have found that an electronic nature of the nitrogen functional group can play a key role: allylic phthalimides furnish aldehydes selectively, whereas the *N*-tosyl- and *N*-nosyl-substituted substrates give full conversion to the ketones **14** (Table 2).

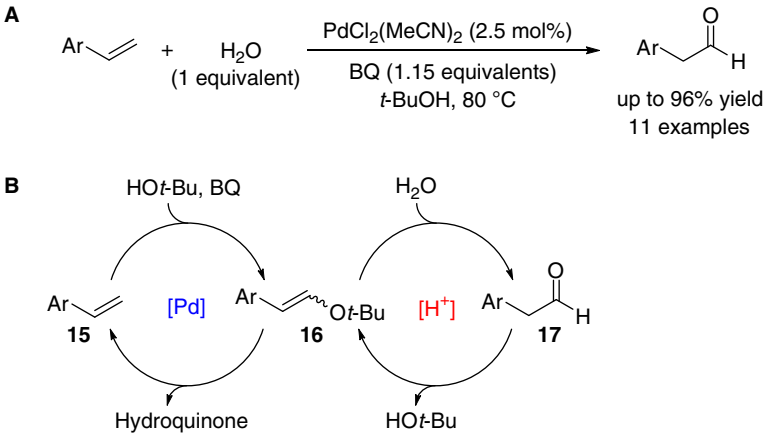
Table 2 Screening for protecting group and catalyst system[a]



Entry	*Substrate (R^1,R^2,R^3)*	*Conditions*	*Conversion (%)*	***13:14***[b]
1	**12a** (Ph, PMP, H)	A[c]	0	–
2	**12a**	B	0	–
3	**12b** (Ph, Cbz, H)	A[c]	100	60:40
4	**12b**	B	100	70:30
5	**12c** (Ph, Ts, H)	A[c]	100	45:55
6	**12c**	B	100	3:97
7	**12d** (Ph, Boc, H)	A[c]	10	35:65
8	**12e** (Me, Bz, H)	A[c]	12	77:23
9	**12e**	B	100	80:20
10	**12f** (Me, *o*-Ns, H)	B	100	4:96
11	**12g** (Me, phthalimide)	A[d]	100	96:4
12	**12g**	B	100	>99:1

[a]A: $Pd(MeCN)_2Cl(NO_2)$ (1–5 mol%), $CuCl_2$ (5–20 mol%), *tert*-BuOH, O_2; 16 h. B: $PdCl_2$(10 mol%), CuCl (1 equivalent), DMF/H_2O (7:1). O_2; 3 days.
[b]Determined by ^{1}H NMR.
[c]5 mol% Pd-cat, 20 mol% $CuCl_2$.
[d]1 mol% Pd-cat, 5 mol% $CuCl_2$.

The use of *t*-BuOH to deliver high aldehyde selectivity in the Wacker–Tsuji oxidation has been well established, albeit often in low yields.[6b] Grubbs and coworkers elaborated on a strategy for the *anti*-Markonikov Wacker–Tsuji oxidation of styrenes by combining $PdCl_2(MeCN)_2$, *p*-benzoquinone (BQ), and *t*-BuOH in the presence of stoichiometric amounts of water (Scheme 4A).[6c,d] They found that both high aldehyde selectivity and high yields could be obtained with styrene as the substrate (turnover frequency (TOF) of 37 h^{-1} with 98% aldehyde selectivity). Without BQ, no appreciable turnovers were observed. When the reaction is carried out in *i*-PrOH instead of *t*-BuOH, the selectivity fell to 74% and the TOF was nearly halved. A kinetic study for the oxidation of styrene indicated that the product yield started decreasing significantly on reaching a maximum, probably due to aldehyde self-condensation. Hence, all styrene oxidation reactions must be stopped once the product yield reaches its maximum to avoid product degradation. It was found from earlier mechanistic studies that, in the presence of *t*-BuOH, the olefin **15** would undergo Pd-catalyzed oxidation to generate a *tert*-butyl vinyl ether intermediate **16**. Owing to the bulkiness of *t*-BuOH, the linear vinyl ether is preferred, which constitutes the key factor for high *anti*-Markonikov selectivity. During the Wacker process, acid is generated and, in the presence of water, vinyl ether **16** is converted into aldehyde **17** via acid-catalyzed hydrolysis (Scheme 4B).



Scheme 4

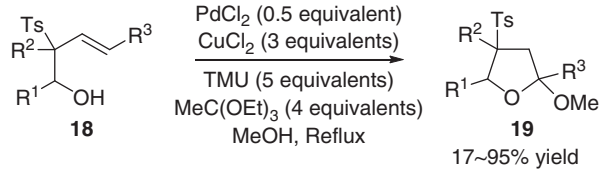
7.17.3 Acetalization

When the vinylic ether intermediate arising from the oxypalladation of an alkene undergoes a nucleophilic attack by an alcoholic function, acetals are formed. This is typically the case whenever oxypalladation is carried out with a diol, but alkenols can also yield acetals if a second alcohol is present in the reaction medium. Both intra- and intermolecular processes are conceivable.[7] Such chemistry strictly resembles the Wacker reaction, but more peculiar systems are formed in this protocol, particularly in intramolecular reactions potentially leading to ring-closed products.

7.17.3.1 Intramolecular Reactions

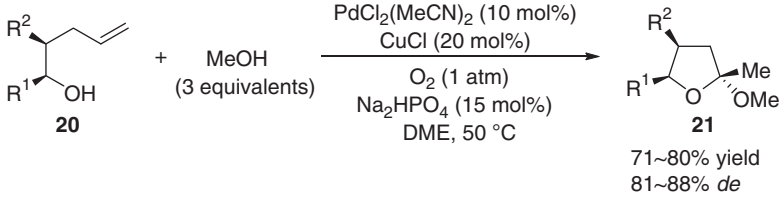
7.17.3.1.1 Alkene electrophiles

The Pd(II)-catalyzed intramolecular cyclization of 2-(*p*-toluenesulfonyl)-3-alkenols **18** in methanol served to prepare several 2-methoxytetrahydrofurans **19** (equation 4).[8a] A coordinating group in the allylic position was necessary to make oxidation selective. The best results were obtained when the cyclization was carried out using tetramethylurea (TMU) to quench the HCl produced, together with ethyl orthoacetate, anhydrous $CuCl_2$, and $PdCl_2$.

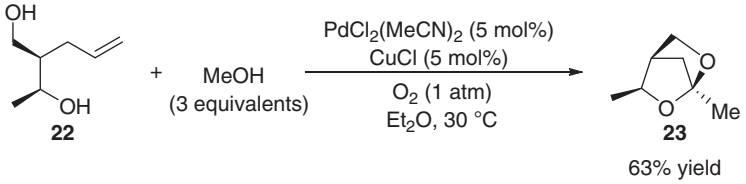


(4)

The diastereoselective cyclization of enantiomerically pure (2*S*,3*S*)-alkenols **20** in the presence of methanol with catalytic amounts of $PdCl_2(MeCN)_2$ and CuCl under O_2 afforded 2-methoxytetrahydrofurans **21** in 71–80% yields and 81–88% *de* (equation 5).[8b] The cyclization of (2*R*,3*S*)-2-allylbutane-1,3-diol **22** gave diastereoselectively the bridged compound **23** (equation 6).

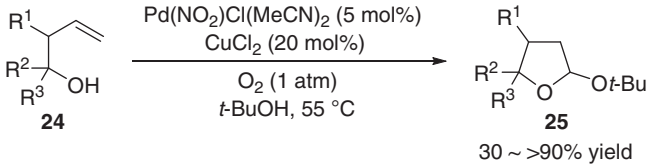


(5)



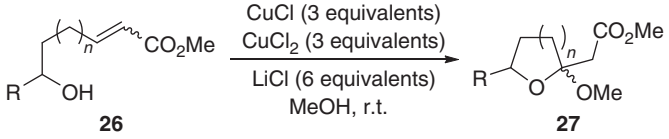
(6)

The oxidative cyclization of alkenols **24** to 2-*tert*-butoxytetrahydrofurans **25** by $Pd(NO_2)Cl(MeCN)_2$ in the presence of $CuCl_2/O_2$ in *t*-BuOH was described by Feringa and coworkers (equation 7).[8c] The reaction also proceeded in the absence of a substituent in the allylic position.



(7)

Sturgess and coworkers reported the conversion of hydroxysubstituted α,β-unsaturated esters **26** into tetrahydrofuran derivatives **27**, which behave as protected β-ketoesters (equation 8).[8d] The best results were obtained using a catalytic amount of $PdCl_2$ and a mixture of CuCl (3 equivalents) and $CuCl_2$ (3 equivalents) as reoxidant in the presence of LiCl and in methanol. It was found that either the use of less reoxidant or the omission of LiCl lowered the yield of **27**.

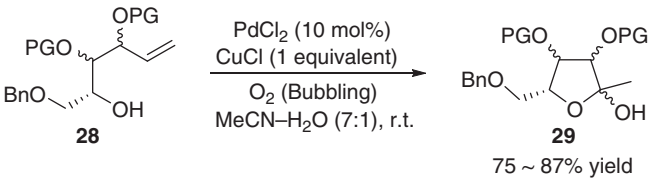


R	*n*	Yield (%)
H	2	87
H	1	62
Bn	2	61
n-C_7H_{15}	2	79
n-C_5H_{11}	1	87

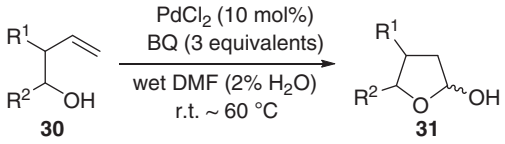
(8)

Under the action of Pd(II) salts, the Wacker-type oxidation of alkenols also furnish hemiacetals. Alkoxysubstituted alkenols **28** underwent cyclization to hemiacetals **29**, which can be converted into *C*-glycosides (equation 9).[8e] The optimized protocol, using $PdCl_2/CuCl/O_2$ in aqueous MeCN at room temperature, yielded five-membered heterocycles in good yields exclusively via 5-*exo*-mode cyclization.

Nokami and coworkers showed that γ-butyrolactols **31** could be obtained by the oxypalladation of 1-alken-4-ols **30** using $PdCl_2$/BQ in wet DMF at room temperature (equation 10).[8f] The unsaturated alcohol requires a substituent in the allylic position; γ-butyrolactols are formed in 43–87% yields along with smaller amounts of hydroxyketone side products.



(9)



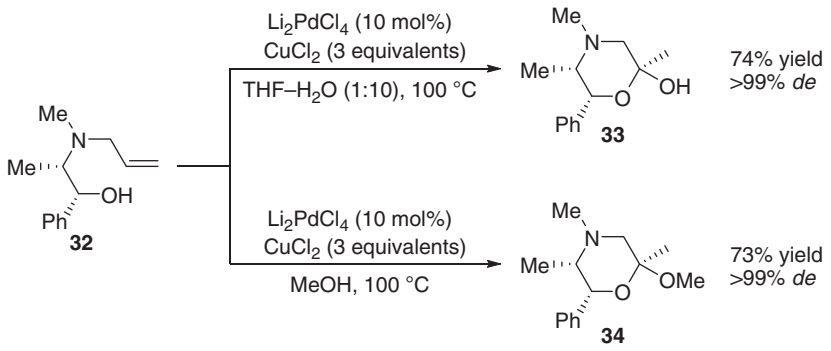
R^1	R^2	Yield (%)
Me	*n*-C_6H_{13}	43
$(CH_2)_7CO_2Me$	*n*-C_5H_{11}	74
$(CH_2)_7CO_2Me$	H	58
CO_2Me	*n*-C_6H_{13}	62
Ts	*n*-C_6H_{13}	82
OBn	CH_2OBz	81
OBn	CH_2OBn	87

(10)

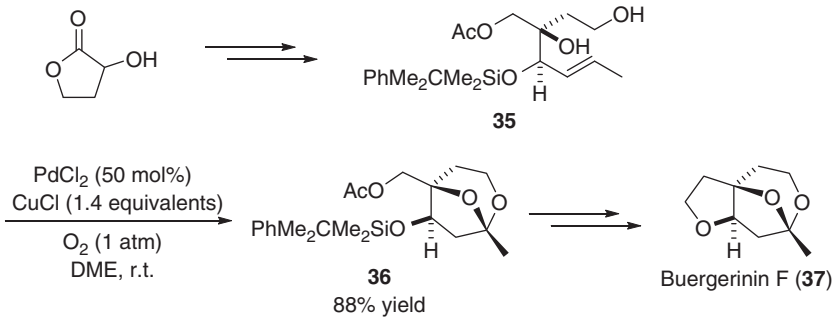
Optically active morpholine-type acetals **33** and **34** were obtained in high yields from enantiopure *N*-allyl amino alcohol **32** by making slight changes in the $Li_2PdCl_4/CuCl_2$ reagent system, as depicted in Scheme 5.[8g]

The intramolecular Wacker-type acetalization was utilized as one of the key steps in total synthesis of a natural product. (+)-Buergerinin F (**37**), a potentially antiphlogistic and febrifuge agent, was efficiently synthesized by way of the key bicyclic intermediate **36**, which was obtained in 88% yield through the intramolecular Wacker-type acetalization of an optically active alkenediol **35** (Scheme 6).[8h]

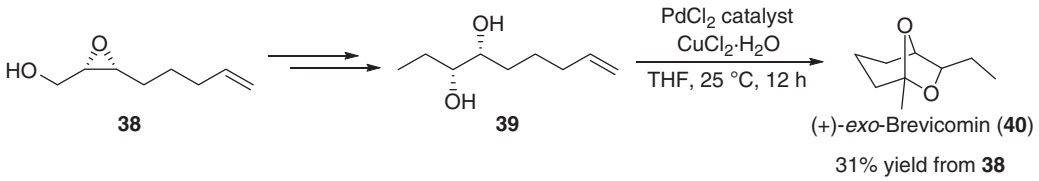
Unsaturated vicinal diols gave the corresponding cyclic bridged acetals by Pd(II)-catalyzed intramolecular acetalization. *threo*-3,4-Dihydroxy-8-nonene (**39**) derived from epoxy alcohol **38** was cyclized in the presence of $PdCl_2$ and $CuCl_2$ to give (+)-*exo*-brevicomin (**40**) in 31% overall yield from **38** (Scheme 7).[8i] Likewise, the same catalytic system was used in the synthesis of *endo*-brevicomin, frontalin, and rosaramicin.



Scheme 5



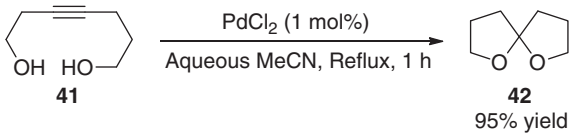
Scheme 6



Scheme 7

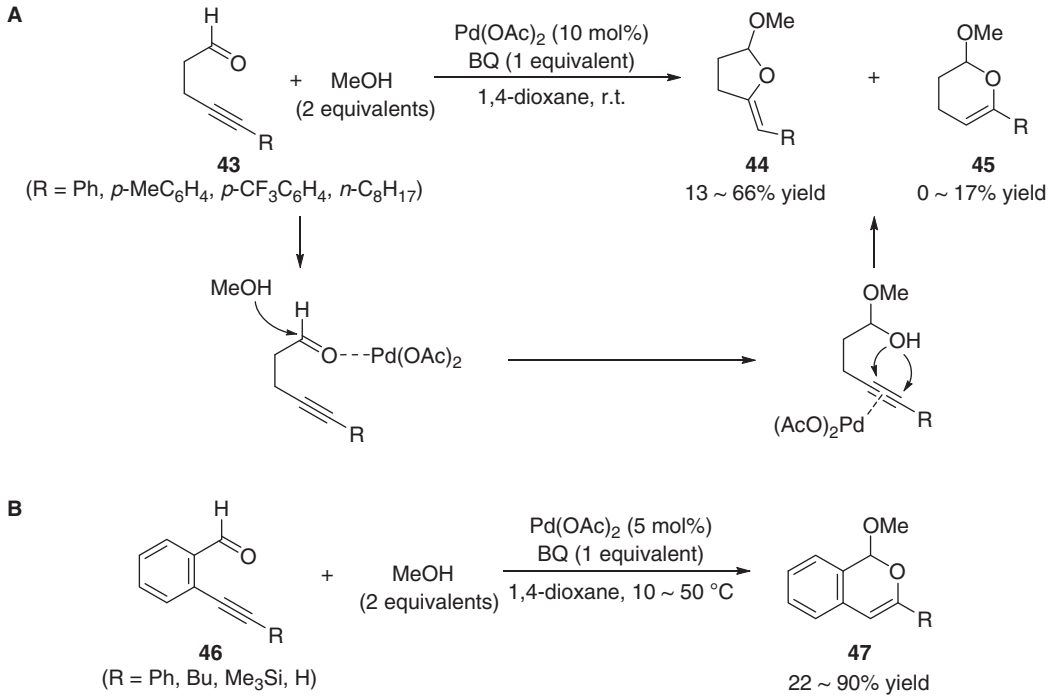
7.17.3.1.2 Alkyne electrophiles

The Pd(II)-catalyzed cyclization of alkynes having an oxygen nucleophile is also a powerful method for the construction of oxygen-containing heterocycles. The successive intramolecular addition of two hydroxy groups to the internal triple bond of alkynediol **41** was achieved with 1 mol % of $PdCl_2$ to give the spirocyclic acetal **42** in 95% yield (equation 11).[8j]



(11)

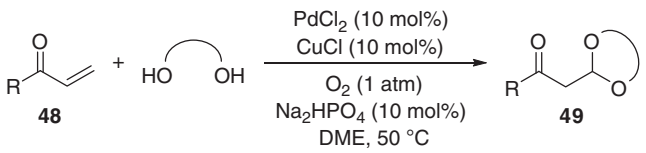
Acetylenes bearing aldehyde functional group have been found to produce cyclic alkenyl ethers (Scheme 8).[8k] The Pd(II) salt is employed as a Lewis acid to induce hemiacetal formation and also to affect cyclization of the alkyne onto the acetal. In this way, aldehydes **43** in the presence of 10 mol% $Pd(OAc)_2$ and benzoquinone afford the five-membered ring acetals **44**, together with a small amount of the six-membered ring products **45**. However, aryl acetylenic aldehydes **46** when treated with 5 mol % $Pd(OAc)_2$ in methanol exclusively produce the six-membered ring acetals **47**.

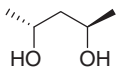
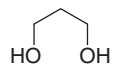
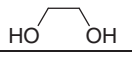


Scheme 8

7.17.3.2 Intermolecular Reactions

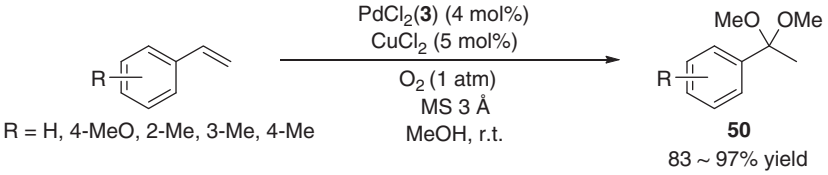
Terminal olefins **48** bearing electron-withdrawing substituents were regioselectively acetalized at the terminal carbon by diols in the presence of catalytic amount of $PdCl_2$ and CuCl in DME at 50 °C under an atmospheric pressure of O_2 to provide acetals **49** (equation 12).[9a] Na_2HPO_4 was used as an additive to prevent the formation of Michael-type adducts. The process was also employed with optically active diols. When (*R*,*R*)-2,4-pentanediol was used, homochiral cyclic acetals were obtained in good yields.



R	Diol	Yield (%)
Ph		75
Me		69
t-Bu		64
Ph		82
Ph		55

(12)

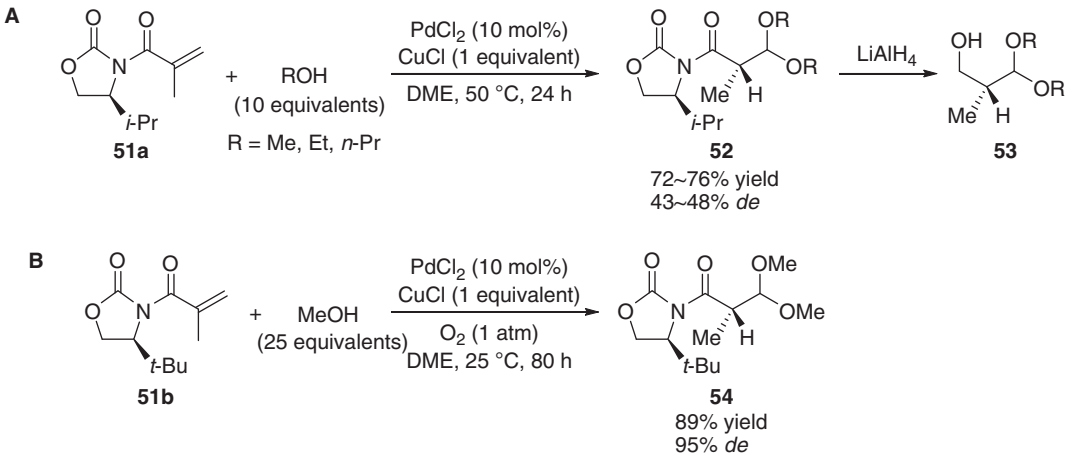
The treatment of styrenes with 4 mol% $PdCl_2$(**3**) (**3**: (–)-sparteine), 5 mol% $CuCl_2$, and MS 3 A in MeOH at room temperature under O_2 atmosphere afforded Markovnikov acetals **51** in high yields (equation 13).[9b]



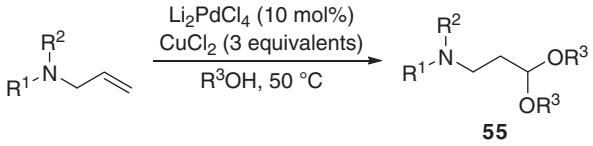
(13)

Diastereoselective acetalization of methacryloyl derivatives **51** having a 4-substituted oxazolidin-2-one unit as chiral auxiliary opened a route to the enantiomers of 3-hydroxy-2-methylpropanal acetals **53** via the precursor **52** (**Scheme 9**).[9c] The best stereochemical result (**54**, 95% *de*) was achieved with $PdCl_2$ as catalyst in the presence of CuCl and an oxygen atmosphere when substrate **51b**, in which *t*-Bu group was introduced on its oxazolidin-2-one ring, was subjected to the conditions.

With 10 mol% Li_2PdCl_4, 3 equivalents of $CuCl_2$, and alcoholic solvent, oxypalladation of allylamines took place at the external terminal carbon of the double bond to give the corresponding acetals **55** in good yields. The regioselectivity of the nucleophile attack is due to the directing influence of the heteroatom (equation 14).[9d]



Scheme 9

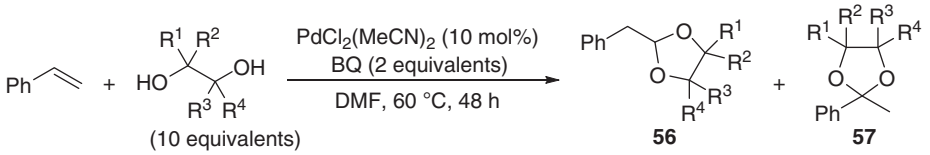


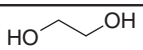
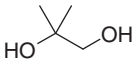
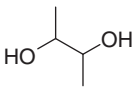
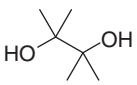
R^1	R^2	R^3	Yield (%)
Bn	Bn	Me	81
Bn	Bn	Et	81
Bn	PhMeCH	Me	82
Me	PhMeCH	Me	76
Et	Et	Et	85

(14)

A reliable, Pd-catalyzed method for synthesizing terminal acetals from vinylarenes, allyl aryl ethers, and 1,5-dienes has been established by Ura and coworkers. In this reaction, the nature of the substrates and the steric bulkiness of pinacol synergistically controlled the regioselectivity in an *anti*-Markovnikov manner (Table 3).[9e] When ethylene glycol, 2-methyl-1,2-propanediol, and 2,3-butanediol were employed, the formation ratios of the terminal acetals **56** and the internal acetals **57** were close to 1:1 (entries 1–3), along with the formation of a certain amount of acetophenone derived from styrene and a trace of contaminated water. It is noteworthy that the use of pinacol critically influenced the regioselectivity, giving **56** in preference to **57** in the ratio of >95:5 (entry 4). These results indicate that the steric bulkiness of the diol controls the regioselectivity to the terminal carbon in the nucleophilic attack of the diol on the coordinated styrene.

Table 3 Steric effect of 1,2-diols on the regioselectivity in Pd-catalyzed acetaliztion of styrene

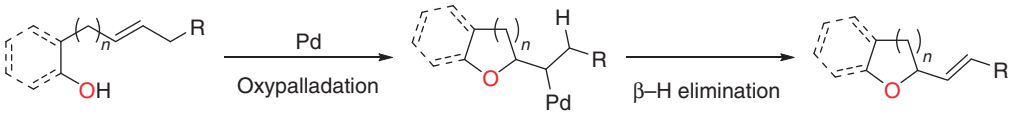


Entry	*Diol*	*Total yield (%)*[a]	***56*:*57***[b]
1		48	52:48
2		66	55:45
3		50	56:44
4		72[c]	>95:5

[a]NMR yield.
[b]Determined by ^{1}H NMR.
[c]GC yield.

7.17.4 Alkoxylation

Nucleophilic attack on a carbon–carbon unsaturated bond by the OH group of alcohols or phenols results in an alkoxylation reaction. Alcohols are an attractive class of nucleophiles for alkene functionalization; however, primary and secondary alcohols often undergo facile oxidation to the corresponding aldehyde or ketone derivatives in the presence of Pd(II) catalysts. The development of catalysts that promote effective alkoxypalladation of alkenes, therefore, requires high chemoselectivity. Alternatively, the problem of alcohol oxidation can be avoided by employing tertiary alcohols, for which formation of the carbonyl compounds is not possible. When the double bond bears an alkyl substituent, the oxypalladation intermediate may lead, through β-H elimination, to the formation of vinyl or allyl ether derivatives. The overall utilities of this type of reaction lies not only in the formation of new carbon–oxygen bonds resulting from the initial attack of a nucleophile at the π-alkene ligand on transition metal but also in the variety of reactions which the resulting carbon–metal bond can further be transformed to. Thus, the intermediate may undergo β-hydride elimination to generate a substituted alkene, insertion of carbon monoxide followed by trapping with an alcohol to give the ester addition product, or insertion of another alkene or alkyne to form a second carbon–metal σ-bonded complex. In many cases, reaction conditions requiring only catalytic amounts of palladium have been developed. The intramolecular version of these functionalizations is frequently called as a 'Wacker-type cyclization' (Scheme 10).[7]

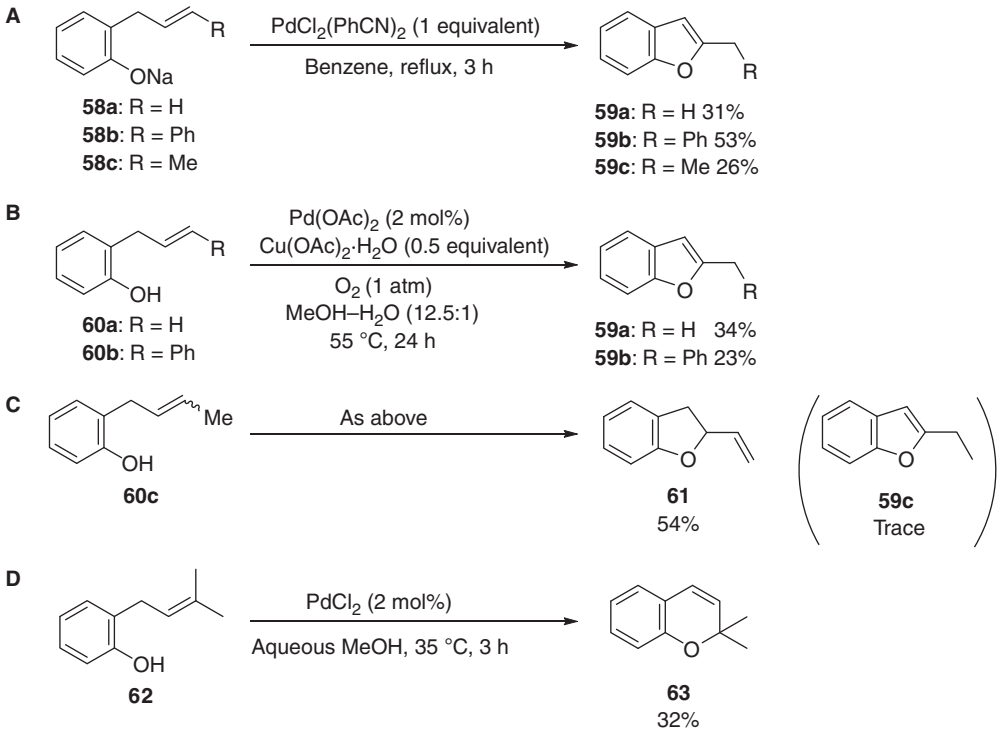


Scheme 10

7.17.4.1 Intramolecular Reactions Involving Alkene

7.17.4.1.1 Phenol nucleophiles

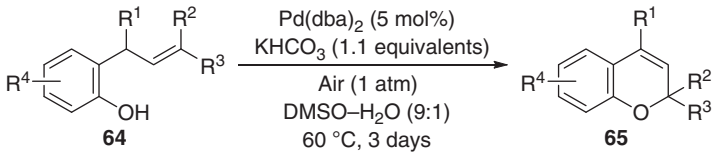
Alkenes bearing a phenol at an appropriate distance from the carbon–carbon double bond can readily undergo Pd(II)-catalyzed intramolecular cyclization to generate a wide variety of oxygen heterocycles under mild reaction conditions. The first report of the synthesis of a benzofuran by such a cyclization appeared in 1973, when the sodium salts of phenols **58** were cyclized to 2-substituted benzofurans **59** using stoichiometric amounts of $PdCl_2(PhCN)_2$ (Scheme 11A).[10a] Subsequently, the Hosokawa



Scheme 11

group studied the intramolecular oxypalladation of a variety of allylic phenols. 2-Allylic phenols undergo either 5-*exo-trig* or 6-*endo-trig* cyclizations depending on the catalyst system used. Phenols **60** bearing relatively simple allylic groups (R=H or Ph) reacted with catalytic amounts of $Pd(OAc)_2$ and substoichiometric amounts of $Cu(OAc)_2{\cdot}H_2O$ under an O_2 atmosphere to afford benzofuran products **59** in moderate yields (Scheme 11B).[10b] However, in the reaction of 2-(2′-butenyl)phenol (**60c**) under identical catalytic conditions, 2,3-dihydro-2-vinylbenzofuran (**61**) was obtained exclusively with a trace amount of 2-ethyl benzofuran (**59c**) as shown in Scheme 11C. Analogous reaction using $PdCl_2$ on 2-(3-methyl-2-butenyl)phenol (**62**) proceeded in a 6-*endo-trig* fashion to afford predominantly benzopyran (chromene) product **63** (Scheme 11D).[10c]

Larock and coworkers have reported that a catalytic amount of $Pd(dba)_2$ in the presence of O_2 and DMSO provides phenols **64** to benzopyrans **65** (equation 15).[10d] Optimal conditions for this cyclization utilize 1.1 equivalents of $KHCO_3$ in 9:1 DMSO/water at 60 °C in the air. The process is highly regioselective, accommodates a variety of substitution patterns in the aryl ring and allylic moiety, proceeds in good to excellent yields, and utilizes air as the sole reoxidant for Pd. However, better results were obtained using 1 atm of O_2 on larger scale reactions (10 mmol).

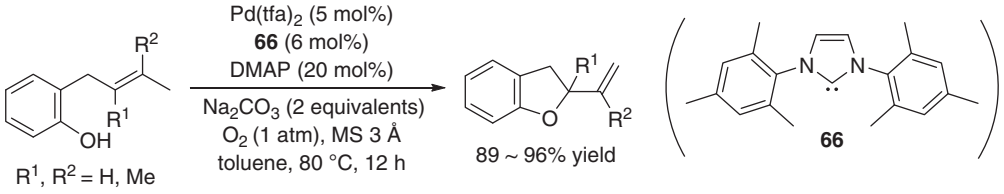


R^1	R^2	R^3	R^4	Yield (%)
H	H	H	H	80
Me	H	H	H	74
H	H	Me	H	80
H	Me	Me	H	72
H	H	Ph	H	65
Ph	H	H	H	59
H	H	H	2-Me	65
H	H	H	4-OMe	71
H	H	H	4-OAc	23[a]
H	Me	Me	4-CN	41[a]

[a]$Pd(OAc)_2$ was used.

(15)

An alternative intramolecular cyclization of 2-allylphenols was reported by Muñiz (equation 16).[10e] 2,3-Dihydrobenzofurans were obtained in high yields with Pd(II) catalyst derived from *in situ* complexation of *N*-heterocyclic carbene (NHC) **66** to Pd $(tfa)_2$. In this system, basic additives, DMAP and Na_2CO_3, were required to maintain the catalyst activity.



(16)

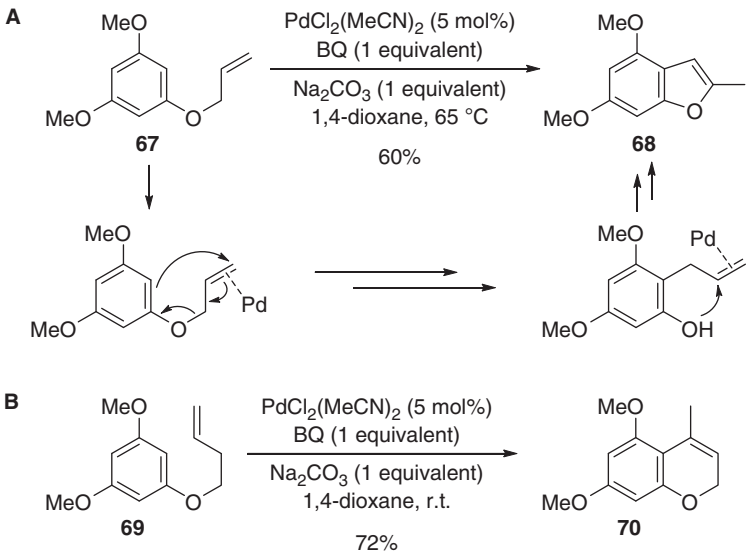
With $PdCl_2(MeCN)_2$ and BQ in 1,4-dioxane, aryl allyl ethers cyclized to benzofurans through the Claisen rearrangement and the Wacker-type cyclization. Thus, the Pd-assisted Claisen rearrangement of **67** occurred first to form an *ortho*-allylphenol derivative, which then underwent the Wacker-type cyclization to give **68** in 60% yield (Scheme 12A).[10f] When aryl homoallyl ether **69** was subjected to the similar conditions, substituted chromene **70** was produced selectively, probably through a direct oxidative coupling of the electron-rich arene to the alkene (Scheme 12B).

Wolfe's group has succeeded in the integration between the Pd(II)/Pd(0) Wacker chemistry and the Pd(0)/Pd(II) cross-coupling chemistry. They recently reported a new method for the construction of 2-substituted chroman derivatives **72** via a carboetherification reaction between alkenyl phenols **71** and aryl bromides or alkenyl bromides catalyzed by a $Pd_2(dba)_3$/*S*-phos system (Scheme 13).[10g] Although this transformation is not an oxidation reaction, the C–O bond forming step is facilitated through interaction of the alkene moiety with a Pd(II) species generated by the preceding oxidative addition of aryl bromides to Pd(0), which is quite similar to the Wacker-type reaction.

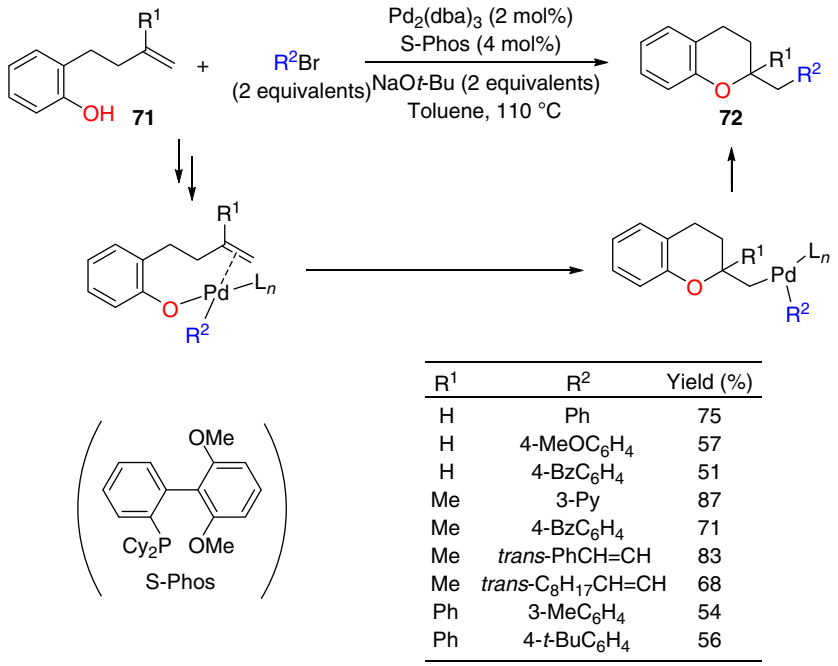
7.17.4.1.2 Alcohol nucleophiles

In 1976, Hosokawa et al. reported the Wacker-type cyclization of alkenyl alcohols. δ,ε-Unsaturated alcohols **73** were cyclized using a catalytic amount of $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$ and O_2 as a reoxidant in $MeOH/H_2O$ at room temperature (Scheme 14A).[11a] Under these reaction conditions, the 2-vinyltetrahydrofuran products **74** were obtained in only moderate yields as a mixture of diastereoisomers. The reaction of substrate **75** having two methyl groups in the ε-position proceeded in a 6-*endo-trig* mode to afford pyran product **76** (Scheme 14B). Hence, the substituents on the ε-position of δ,ε-unsaturated alcohols markedly affects the product composition.

The solvent control of the product distribution was also observed in the intramolecular alkoxypalladation of alkenols. The hydroxyalkene **77** was allowed to react with a stoichiometric amount of $Pd(OAc)_2$ in DMSO to produce tetrahydropyran



Scheme 12

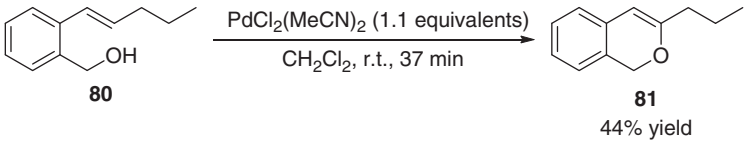


R^1	R^2	Yield (%)
H	Ph	75
H	4-$MeOC_6H_4$	57
H	4-BzC_6H_4	51
Me	3-Py	87
Me	4-BzC_6H_4	71
Me	*trans*-PhCH=CH	83
Me	*trans*-$C_8H_{17}CH$=CH	68
Ph	3-MeC_6H_4	54
Ph	4-*t*-BuC_6H_4	56

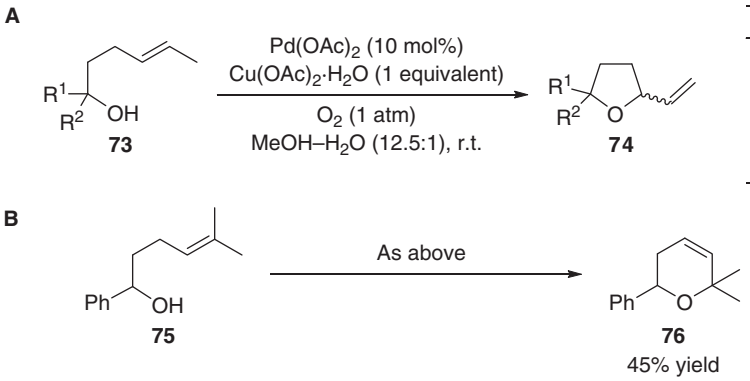
Scheme 13

78 selectively, whereas the reaction carried out in other solvents such as DMF, AcOH, MeCN, or THF gave **78** accompanied by the isomerized dihydropyran product **79** (Table 4).[11b]

The cyclization of *ortho*-alkenylbenzylic alcohols to the corresponding isochromenes has been described by Giles and co-workers.[11c] For example, the treatment of (*E*)-pent-1-enylbenzyl alcohol (**80**) with a stoichiometric amount of $PdCl_2(MeCN)_2$ in dry dichloromethane at room temperature afforded **81** in 44% yield (equation 17).



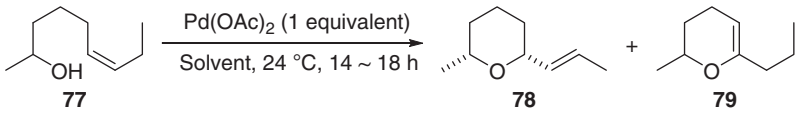
(17)



R^1	R^2	Yield (%)
Ph	H	40
Ph	Me	52
Ph	Et	36
Ph	Ph	15
Me	H	23

Scheme 14

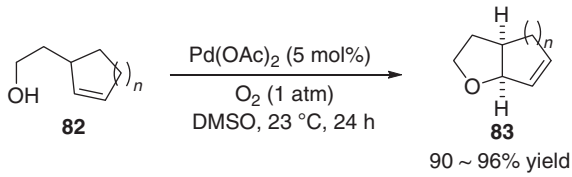
Table 4 Solvent effect on the product distribution



Entry	*Solvent*	*Conversion (%)*	***78*:*79*** [a]
1	DMSO	100	90:0
2	*t*-BuOH	95	75:7
3	Propylene carbonate	95	76:8
4	THF	85	53:12
5	DMF	97	43:46
6	AcOH	90	39:47
7	MeCN	60	12:36

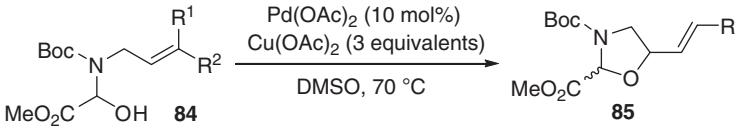
[a]Determined by GC analysis.

The Pd(II)-catalyzed intramolecular cyclization of cyclic alkenols using molecular oxygen as the reoxidant provides a useful route to bicyclic olefinic ethers. The most promising results were obtained when the alkenol **82** was allowed to react with 5 mol % of $Pd(OAc)_2$ in DMSO under an O_2 atmosphere at room temperature (equation 18).[11d] The addition of LiCl or K_2CO_3 was found to inhibit the reaction, and the use of DMSO/BQ as solvent/reoxidant was found to give the cyclized product **83** together with a larger amount of the olefin isomer.



(18)

Hiemstra showed that oxazolidines **85** were formed through oxypalladation and subsequent β-H elimination of the *N*-Boc-protected allylic amines **84** (equation 19).[11e] The 5-*exo* cyclization took place efficiently using 10 mol% of $Pd(OAc)_2$ and 3 equivalents of $Cu(OAc)_2$ oxidant to give **85** in good yields.

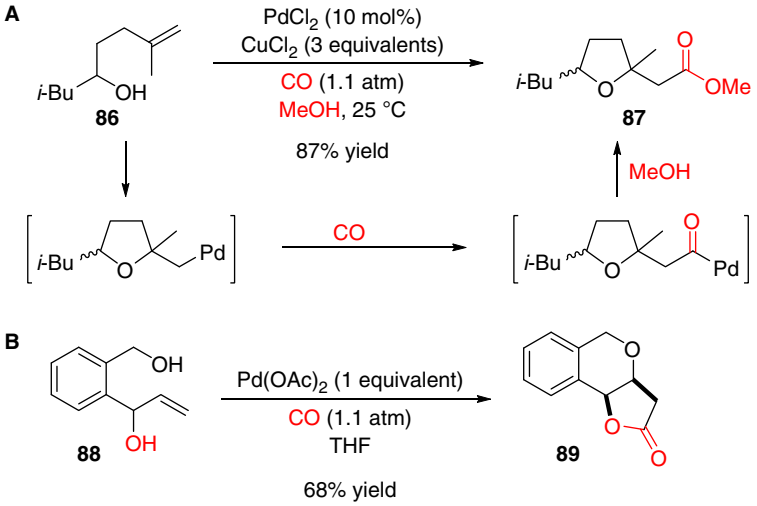


R^1	R^2	R	Yield (%)
Me	H	H	76
H	Me	H	64
n-Pr	H	Et	80
H	*n*-Pr	Et	56
Me	Me	no reaction	

(19)

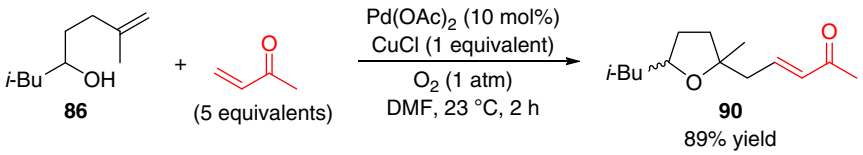
A sequential process consisting of the Wacker-type cyclization and alkoxycarbonylation, which can provide a very useful route to cyclic ethers bearing ester functional group in the side arm, has been established by Semmelhack and coworkers.[11f] When

alkenols possessing a 1,1-disubstituted terminal double bond are subjected to intramolecular oxypalladation, Pd–H elimination is impossible in the resulting alkylpalladium intermediate, which can be trapped by the insertion of carbon monoxide. Using catalytic amounts of $PdCl_2$ and 3 equivalents of $CuCl_2$ in MeOH solvent at room temperature under 1.1 atm of CO, alkenol **86** gave an inseparable 1:1 diastereomeric mixture of five-membered ring product **87** in high yield (Scheme 15A). The effect of the alkene geometry on the selectivity for pyran or furan formation was also studied. Intramolecular alkoxylation of the resulting acylpalladium intermediate was accomplished by using a stoichiometric amount of Pd salt. The reaction of olefinic diol **88** with 1 equivalent of $Pd(OAc)_2$ in THF under 1.1 atm of CO produced lactone-containing ether **89** (Scheme 15B). The reaction generally provided good yields with moderate stereoselectivity, and formation of the *cis*-lactone was favored over formation of the *trans*-lactone.



Scheme 15

The resulting alkylpalladium intermediate in the Wacker-type cyclization can also be trapped by an external olefin. Thus, the reaction of alkenol **86** with 10 mol % of $Pd(OAc)_2$ and $CuCl/O_2$ oxidant couple in the presence of an excess amount of methyl vinyl ketone formed furan **90** in high yield (equation 20).[11g] This Wacker/Heck domino process did not proceed efficiently when BQ or $CuCl_2/O_2$ were employed as the reoxidant instead of $CuCl/O_2$.

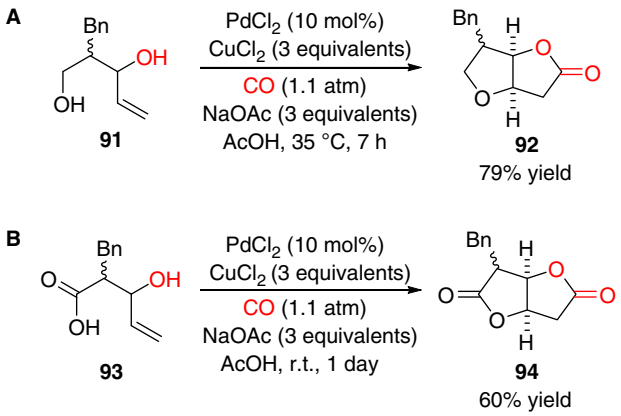


(20)

In a closely related investigation, Yoshida and Tamaru reported the use of 1,3-diols as a precursor to bicyclic lactones via oxypalladation/carbonylation catalyzed by Pd(II). For instance, the reaction of 2-benzylpent-4-ene-1,3-diol **91** was conducted in AcOH using $PdCl_2/CuCl_2$ as the catalyst system and NaOAc as the base under a CO atmosphere to produce *cis*-fused lactone **92** in 79% yield (Scheme 16A).[11h] In a similar manner, the double cyclization of 3-hydroxy-4-pentenoic acids provided bis-lactones. Thus, 2-benzyl-3-hydroxypent-4-enoic acid **93** afforded **94** under the same conditions in a moderate yield (Scheme 16B).[11i] Both the cyclizations proceeded under mild conditions (below 40 °C) with high stereoselectivity: this reaction exhibited high stereoselectivity with only *cis*-fused products being formed. The yields of the product were dependent on the substitution pattern of the substrate.

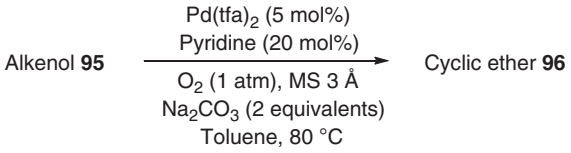
Stoltz and coworkers investigated the oxidative cyclization of primary alkenols **95**, which produced cyclic ethers **96** in moderate to excellent yields (Table 5).[11j] Starting from cyclic alkenols, the final bicyclic products may have a fused-ring or spiro skeleton depending on the structural relationship of the olefinic part and the hydroxyl group. In agreement with reports from Hayashi et al. on related systems, deuterium-labeling studies confirmed a *syn*-oxypalladation mechanism (*vide infra*).

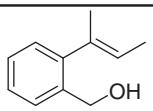
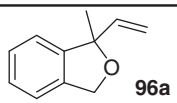
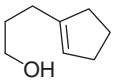
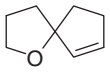
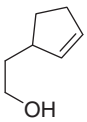
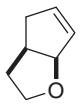
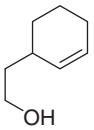
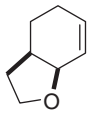
An intramolecular oxidative cyclization protocol, using the $Pd(OAc)_2/NaOAc/O_2$ system in DMSO, was developed for the efficient conversion of sugar-derived δ,ε-unsaturated alcohols **97** to *C*-vinyl furanosides **98** (equation 21).[11k]



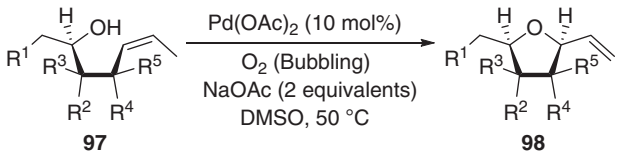
Scheme 16

Table 5 Intramolecular oxidative cycliztion of alkenols **95**



Entry	*Alkenol*	*Cyclic ether*	*Time (h)*	*Yield (%)*
1[a]	 **95a**	 **96a**	3	87
2	 **95b**	 **96b**	10	93[b]
3	 **95c**	 **96c**	7.5	69[c]
4	 **95d**	 **96d**	20	60[d]

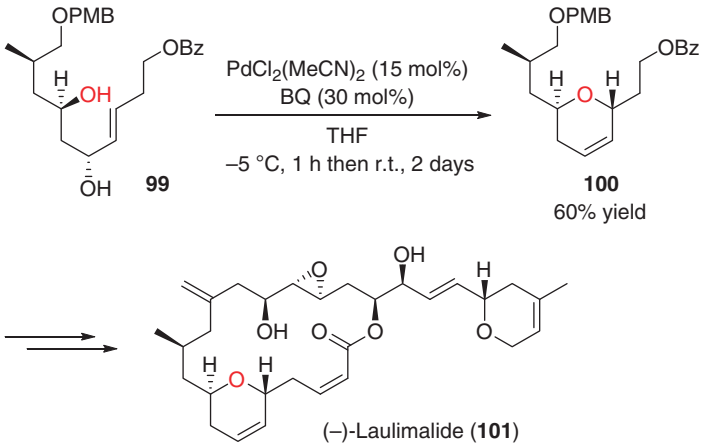
[a]The starting material was used as a mixture of *E* and *Z* olefins.
[b]Isolated with 7% of the aldehyde.
[c]Isolated with 7% of an olefin isomer.
[d]Isolated as a 5:2.3:1 mixture of **96d**/olefin isomer/aldehyde.



R^1	R^2	R^3	R^4	R^5	Yield (%)
BnO	H	BnO	BnO	H	83
H	H	MeO	BnO	H	79
BnO	BnO	H	H	BnO	75

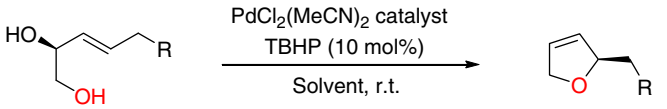
(21)

A similar strategy was applied to the stereospecific construction of the 3,6-dihydro[2*H*]pyran unit of (–)-laulimalide **101** (Scheme 17).[111] In the presence of 15 mol % $PdCl_2(MeCN)_2$ and 30 mol % BQ in THF, the enantiopure unsaturated diol **99** underwent ring formation in a 6-*endo-trig* fashion to give the desired *trans*-2,6-disubstituted pyran **100**. The cyclization of **99** occurred through a *syn* S_N2' process where the hydroxy group attacks the *re* face of the olefinic carbon atom to form the *trans*-(*R*)-dihydropyran ring.



Scheme 17

A Pd(II)-catalyzed dehydroxylative cyclization process yielding optically active 2,5-dihydrofurans **103** was also observed in the case of optically active substrates **102** (equation 22).[11m] This formal 5-*endo-trig* cyclization process, which was unfavorable according to the Baldwin rule, proceeded diastereoselectively.

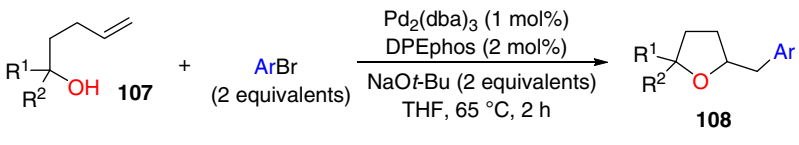


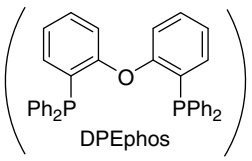
(22)

103a: R = OBn 66% (5 mol% Pd, AcOH)
103b: R = NHCbz 61% (10 mol% Pd, THF)

The cyclization of β'-hydroxy-α,β-unsaturated ketones **104** by the combined use of 10 mol % $PdCl_2$, O_2, CuCl, and Na_2HPO_4 was reported (Table 6). By this procedure, enantiopure enones, for example, **104e** were transformed into 2,3-dihydro-4H-pyran-4-one **105e** without loss of optical purity (entry 6).[11n] Under analogous conditions, dihydroxyenone **104f** cyclized to furan-3(2H) one pruduct **106** regioselectively (entry 7).[11o]

As another example of the Pd(0)-catalyzed carboetherification that constructed both C–C and C–O bonds in a single operation shown in Scheme 13, Wolfe and Rossi developed a related reaction of γ-hydroxy alkenes **107** and aryl bromides employing $Pd_2(dba)_3$ and DPEphos as the catalyst precursor (equation 23).[11p] From this synthetic strategy, a variety of substituted tetrahydrofurans **108** are obtained in good yields with high diastereoselectivity.



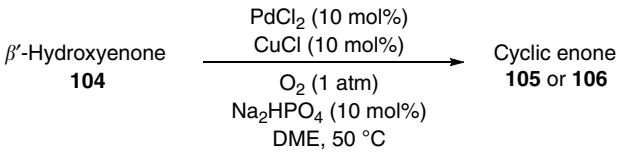


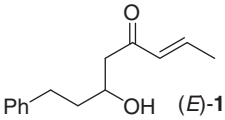
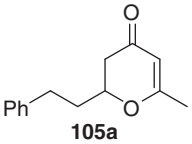
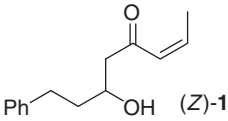
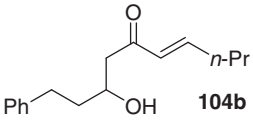
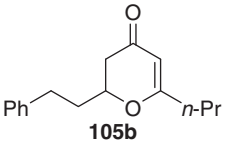
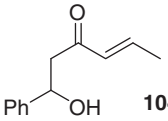
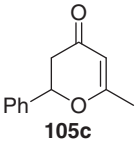
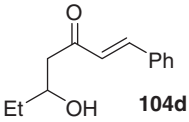
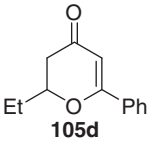
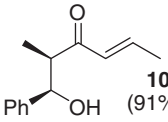
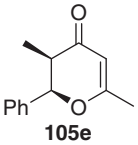
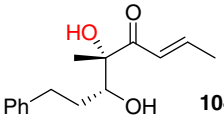
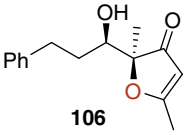
R^1	R^2	Ar	Yield (%)
H	H	4-PhC_6H_4	70
Me	Me	2-Naphthyl	80
Me	Me	1-Naphthyl	60
Ph	H	2-Naphthyl	60
Ph	H	4-$MeOC_6H_4$	62

(23)

Yorimitsu and Oshima have extended Wolfe's carboetherification to more rigid three-membered ring construction, which is a new synthetic strategy for the preparation of epoxides.[11q] Treatment of tertiary allyl alcohol **109a** with 1-bromonaphthalene in the presence of *t*-BuONa under palladium catalysis provided epoxide **110a** in 88% yield (Scheme 18A). Starting from enantiomerically enriched tertiary alcohol (*R*)-**109b**, the reaction proceeded diastereoselectively to give (*S,S*)-**110b** as a sole product without a loss of enantiomeric excess (Scheme 18B). In this reaction, both yield and diastereoselectivity became better as the substituents at the oxygenated carbon of the substrate became larger.

Table 6 Intramolecular oxidative cyclization of β′-hydroxyenones **104**

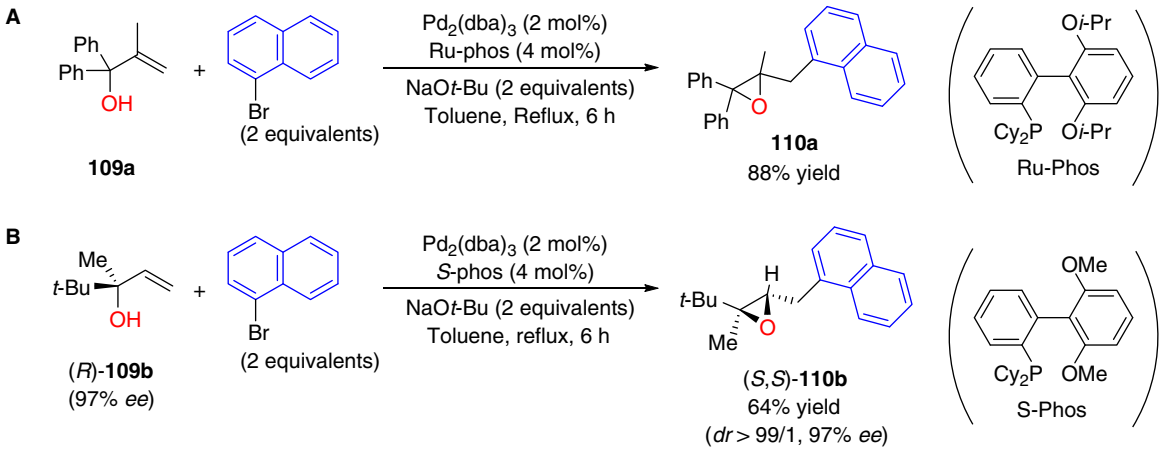


Entry	*β′-Hydroxyenones*	*Cyclic enone*	*Time (h)*	*Yield (%)*
1	 (*E*)-**104a**	 **105a**	4	79
2	 (*Z*)-**104a**		4	59
3	 **104b**	 **105b**	20	76
4	 **104c**	 **105c**	8	86
5	 **104d**	 **105d**	192	43
6	 **104e** (91% *ee*)	 **105e**	20	74 (89% *ee*)
7	 **104f**	 **106**	11	70

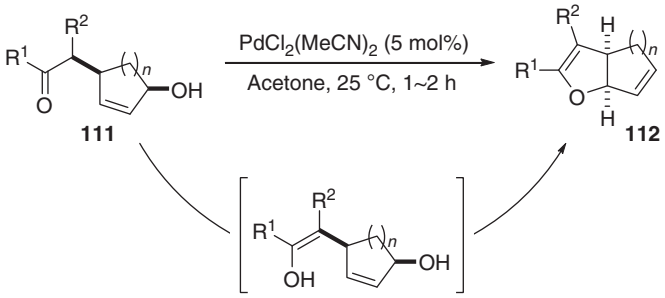
7.17.4.1.3 Enol nucleophiles

The oxidative alkoxylation is possible through the enolic form of a carbonyl substrate that behaves as an alkenol functional group. The bicyclic dihydrofurans **112** were obtained from *cis*-1,4-disubstituted cyclopentenones **111** in 71–98% yields using $PdCl_2(MeCN)_2$ as a catalyst (Scheme 19).[12a] The reaction is most efficient with a hydroxyl group as a leaving group. The corresponding acetate derivatives afforded the cyclization products in lower yields and required a longer reaction time. This process apparently involves cyclic oxypalladation followed by palladium hydroxide elimination.

The Pd(II)-promoted intramolecular cyclization of alkenes bearing an alcohol group at an appropriate distance from the carbon–carbon double bond is a versatile way to generate a wide variety of oxygen heterocycles under mild reaction conditions. Thus, 5-hydroxyuracil **113** is cyclized to pyrimidine-2,4-dione **114** in an 82% yield by refluxing with a stoichiometric amount of $PdCl_2(PhCN)_2$ in benzene in the presence of NaOMe for 3 h (equation 24).[12b]

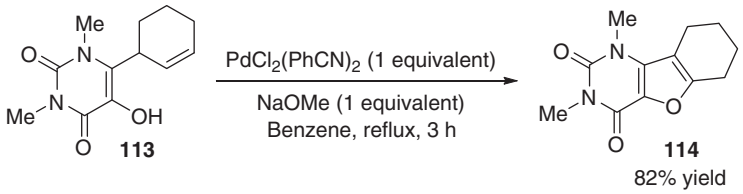


Scheme 18



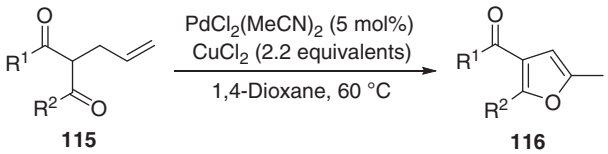
R^1	R^2	*n*	Yield (%)
Me	COMe	1	98
Me	CO_2Me	1	84
Ph	COPh	1	89
n-Bu	CO_2Me	1	81
CH_2CO_2Me	CO_2Me	1	92
Me	COMe	2	90
Me	CO_2Me	2	78
n-Bu	CO_2Me	2	71

Scheme 19



(24)

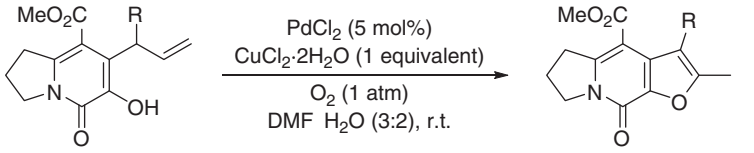
Treatment of α-alkenyl-β-diketones **115** with a catalytic amount of $PdCl_2(MeCN)_2$ and a stoichiometric amount of $CuCl_2$ in dioxane at 60 °C afforded 2,3,5-trisubstituted furans **116** in moderate to good yields (equation 25).[12c]



R^1	R^2	Yield (%)
Et	Et	68
Ph	Ph	72
Ph	Me	63
Ph	*n*-pentyl	62
Ph	$MeO(CH_2)_3$	61
4-$MeOC_6H_4$	Me	63
4-$CF_3C_6H_4$	Me	65
2-Furyl	Me	71
2-Thienyl	Me	63

(25)

An application of the classical Wacker-type oxidation conditions provided an efficient access to a furan ring assembled to an indolizinone core. Padwa found that when enol compounds **117** were treated with catalytic amounts of $PdCl_2$ and a stoichiometric $CuCl_2$ oxidant in aqueous DMF under an O_2 atmosphere, the polysubstituted furans **118** were formed in nearly quantitative yield (equation 26).[12d]



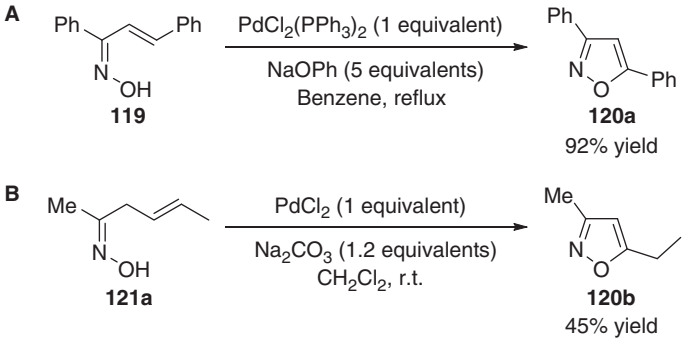
117

118a: R = H 97% yield
118b: R = Me 95% yield
118c: R = Ph 80% yield

(26)

7.17.4.1.4 Oxime nucleophiles

The Pd-promoted cyclization of the oxygen atom of an oxime onto a carbon–carbon double bond was first reported by Murahashi and coworkers. They observed the formation of isoxazole **120a** via 5-*endo-trig* cyclization of *α,β*-unsaturated ketoxime **119** using a stoichiometric amount of Pd and an excess amount of NaOPh (Scheme 20A).[13a] The same group also developed 5-*exo-trig* cyclization of *β,γ*-unsaturated ketoxime **121a** leading to isoxazole **120b**, in which a combination of $PdCl_2$ and Na_2CO_3 was employed in CH_2Cl_2 solvent (Scheme 20B).[13b]



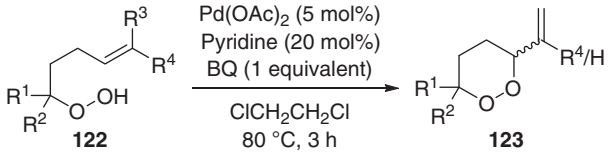
119 **120a** 92% yield

121a **120b** 45% yield

Scheme 20

7.17.4.1.5 Hydroperoxide nucleophiles

The discovery of peroxide-containing natural products as active agents against malaria and various cancers has led to an increased effort to synthesize these compounds and their derivatives. As a class, cyclic peroxides are the most common peroxide-containing motifs isolated. Woerpel and coworkers reported the Pd(II)-catalyzed cyclization of *δ,ε*-unsaturated tertiary hydroperoxides **122** to 1,2-dioxanes **123** resembling biologically active natural products, in which *syn*-oxypalladation was proposed (equation 27).[14]



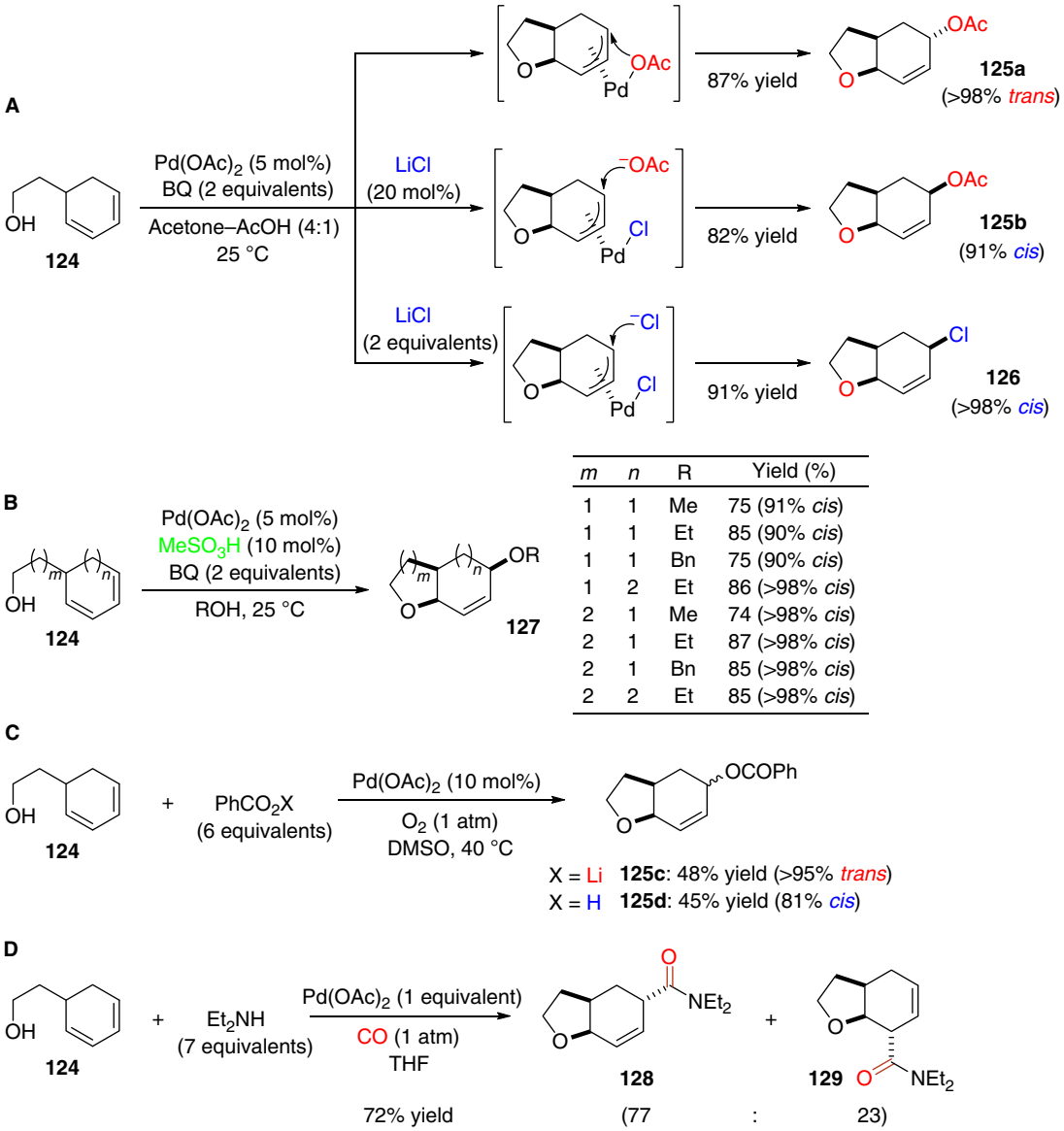
122 **123**

R^1	R^2	R^3	R^4	Yield (%)/*dr*
$PhCH_2CH_2$	Me	Me	Me	35/75:25
$PhCH_2CH_2$	MeO	H	Me	34/>97:3
4-MeC_6H_4	Me	Me	Me	30/75:25
Me	Me	Me	CO_2Et	31
Me	MeO	Me	CO_2Et	30/90:10

(27)

7.17.4.2 Intramolecular Reactions Involving Diene

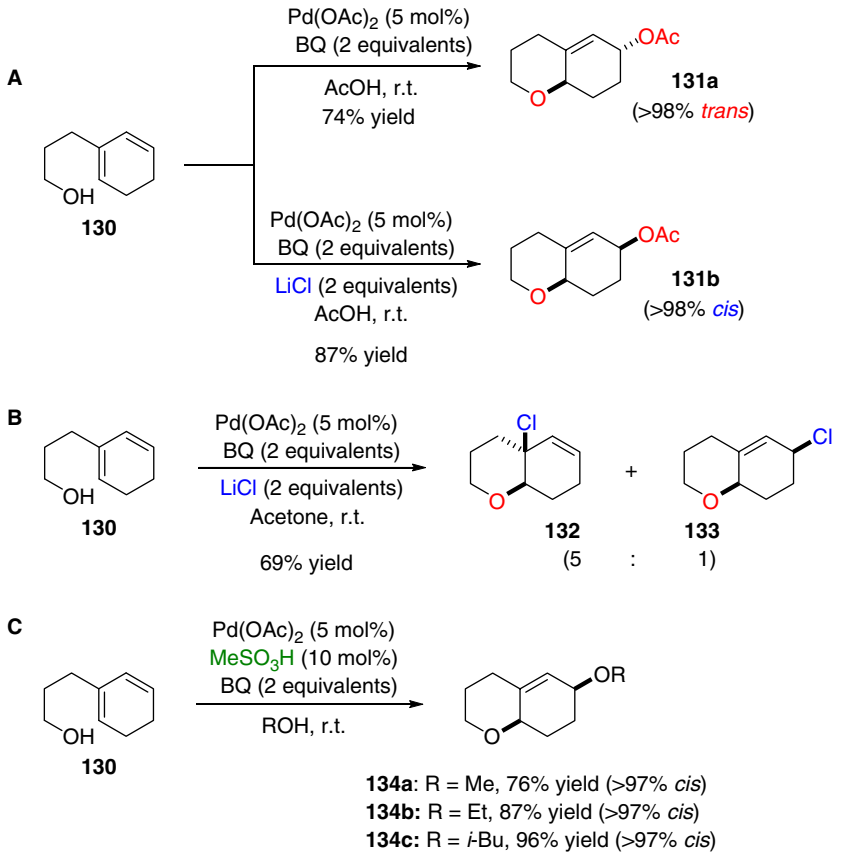
Bäckvall and coworkers have developed a Pd(II)-catalyzed stereocontrolled oxidative cyclization reaction of 1,3-cyclohexadienes bearing a hydroxyalkyl side chain, which affords a number of *cis*-fused hexahydrobenzofuran products in a highly diastereoselective manner. For example, the reaction of 5-(2-hydroxyethyl)-1,3-cyclohexadiene **124** in the presence of 5 mol % of $Pd(OAc)_2$ and 2 equivalents of BQ in a 4:1 mixture of acetone and AcOH produces acetoxy- or chlorosubstituted hexahydrobenzofurans **125** or **126** (Scheme 21A).[15a] These processes involve electrophilic addition of the alcohol functional group to the diene activated by Pd(II) to produce a *π*-allyl Pd intermediate, which subsequently undergoes substitution with an external nucleophile. The overall stereoselective outcome is determined by the existence of LiCl. In the absence of LiCl, *trans*-alkoxyacetoxylation product **125a** is formed, whereas its presence (20 mol %) furnishes *cis*-alkoxyacetoxylation product **125b** predominantly. In the presence of an excess amount of LiCl, chloride atom is incorporated instead of acetoxy group to give



Scheme 21

cis-alkoxychlorination product **126**. For this dual stereocontrol, it is considered that chloride blocks the coordination of acetate to Pd in the π-allyl Pd intermediate, thus suppressing the reductive elimination and concurrently promoting the backside nucleophilic attack. Such π-allyl Pd intermediates are able to be captured by an alcohol. The key to the success of this Pd-catalyzed dialkoxylation of 1,3-diene was the addition of a catalytic amount of a strong acid such as methanesulfonic acid ($MeSO_3H$), which increases the reactivity of the intermediate π-allyl Pd complex (Scheme 21B).[15a] The oxyacyloxylation of 1,3-diene **124** can also be done by using O_2 gas as the oxidant. The desired bicyclic products **125c** and **125d** are obtained by treatment of **124** with 10 mol % of $Pd(OAc)_2$ and an excess of $PhCO_2X$ in DMSO solvent under an O_2 atmosphere (Scheme 21C).[15b] Their *cis*/*trans* ratio depended on the RCO_2X species. Carboxylic acids generally favored a *cis* product, whereas their salts favored the *trans* isomers. The cyclization performed in the presence of CO and an amine using a stoichiometric amount of $Pd(OAc)_2$ affords 1,4-addition product **128** and 1,2-addition product **129** as a mixture (Scheme 21D).[15c] The choice of solvent and CO pressure significantly affects the regiochemistry at the aminocarbonylation step.

Cyclic dienes bearing the hydroxyalkyl substituent at the different position can be utilized as a starting material for the Wacker-type cyclization. One can prepare the corresponding six-membered ring acetoxy ethers **131** stereoselectively from 2-(3-hydroxypropyl)-1,3-cyclohexadiene **130** (Scheme 22A).[15d] The stereochemistry is once again determined by the presence or absence of LiCl in the reaction. Interestingly, no formation of allylic chlorides was observed even though 2 equivalents of LiCl was added to the reaction, which was different from the behavior of **124** shown in Scheme 21A. When the solvent was changed from AcOH to acetone, dienol **130** was allowed to react with chloride to produce the allylic chlorides **132** and **133** (Scheme 22B).[15d] Here, the

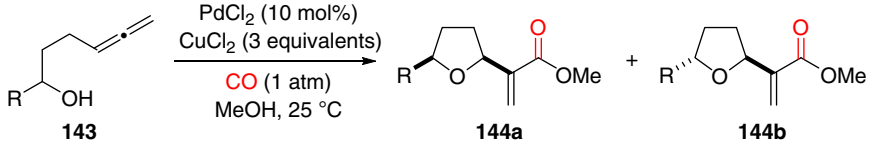


Scheme 22

regioselectivity at the nucleophilic attack by chloride on the π-allyl Pd intermediate was drastically changed: the 1,2-addition product **132** was favored over the 1,4-addition product **133**. Intramolecular 1,4-dialkoxylation of **130** was also described by Bäckvall's group. Compounds **134** were formed in high yields with excellent *cis* selectivity by treatment with catalytic amounts of $Pd(OAc)_2$ and $MeSO_3H$ in the appropriate alcohol (Scheme 22C).[15e]

In a similar fashion, oxyacyloxylation, oxyalkoxylation, and oxychlorination are possible for 1-(3-hydroxypropyl)-1,3-cyclohexadiene **135** to yield oxaspirocyclic compounds **136–138** with high regio- and stereoselectivity (Scheme 23A).[15e–g] This spirocyclization was applied to the total synthesis of theaspirone (**142**); however, catalytic approaches from substrate **139** to synthetic precursor **141** did not provide satisfactory results. Instead, the stoichiometric use of Pd(II) salt furnished two diastereomeric π-allyl Pd complexes (**140a** and **140b**), which were isolated and further converted to **142** (Scheme 23B).[15g]

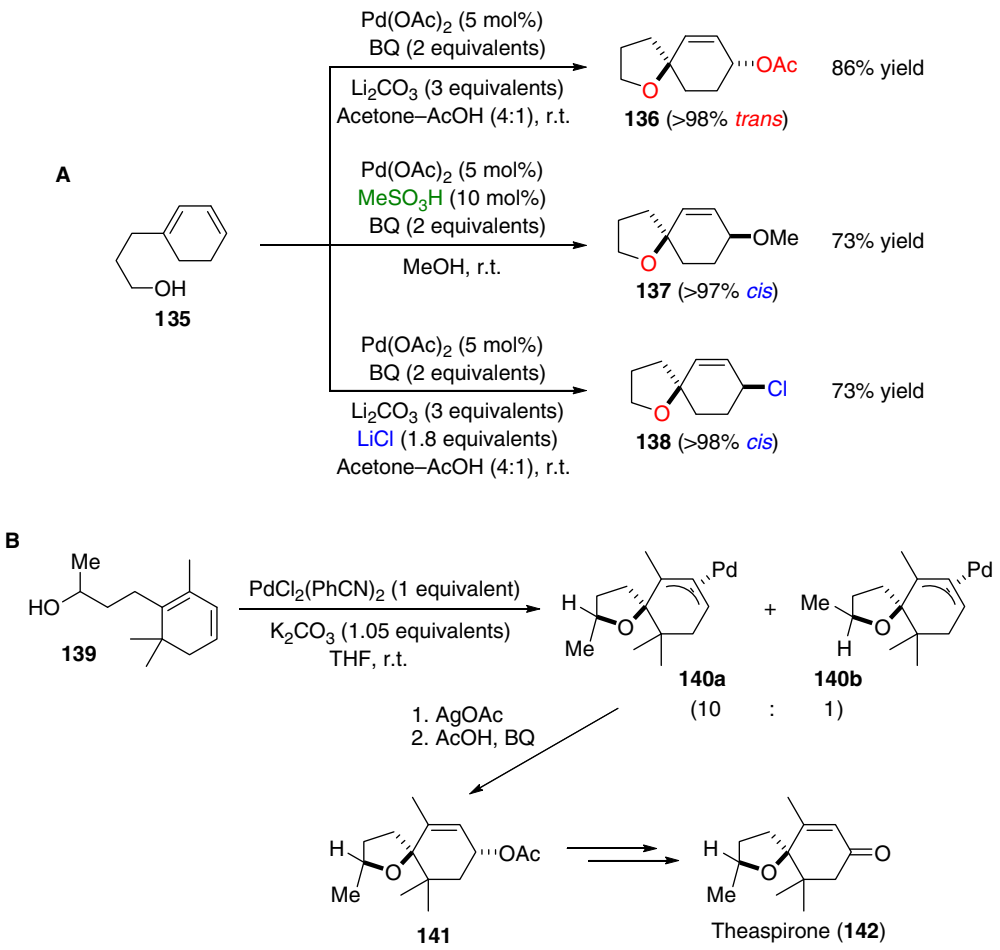
1,2-Dienes (allene) are also applicable to the Wacker alkoxylation. In 1987, Walkup and Park described the synthesis of tetrahydrofuran derivatives **144** by the Pd-catalyzed carbonylative cyclization of γ-hydroxyallenes **143** (equation 28).[15h] A mixture of *cis* and *trans* isomers was formed by a 5-*exo*-*trig* cyclization using $PdCl_2$ catalyst, $CuCl_2$ oxidant, and CO gas at room temperature. The corresponding TBS ethers could give **144** under identical conditions.



(28)

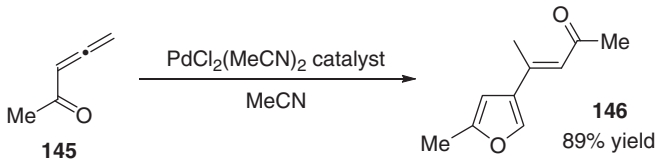
R	Yield(%)/*dr*
H	51/—
Me	72/50:50
$CH_2C(O)t$-Bu	92/50:50
$CH_2C(O)Me$	44/50:50

Hashmi et al. reported the formation of furan derivatives **146** as the major product by a sequence involving the Pd(II)-catalyzed cyclization/dimerization of allenic ketones **145** (equation 29).[15i] The yield is dependent on the solvent, and best results were



Scheme 23

obtained using acetonitrile. This reaction exhibits high selectivity for the allene moiety over other functional groups such as aryl halides, terminal alkynes, and enynes.



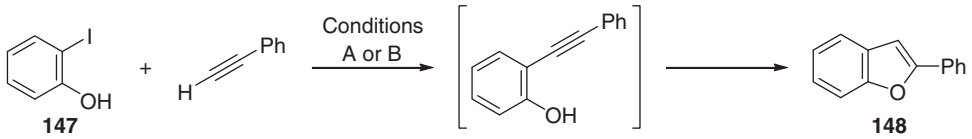
(29)

7.17.4.3 Intramolecular Reactions Involving Alkyne

7.17.4.3.1 Phenol nucleophiles

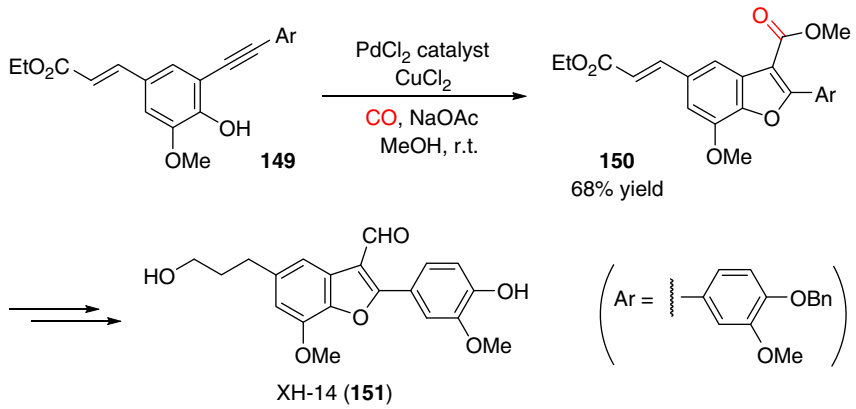
The cyclization of 2-(1-alkynyl)phenols available from aryl halides and terminal alkynes through the Sonogashira–Hagihara coupling provides a facile synthesis of benzofurans. Thus, Cacchi and coworkers found that the reaction of 2-iodophenol (**147**) and phenylacetylene using $Pd(OAc)_2(PPh_3)_2$/CuI catalytic system gave 2-phenylbenzofuran (**148**) in good yield (Scheme 24, conditions A).[16a] Various halogens and alkyl, aryl, and cyclic substrates were tolerated in this reaction. Later, a similar sequential process producing benzofurans was reported by Torii, in which $PdCl_2(PPh_3)_2$ complex was used as the catalyst (conditions B).[16b]

The Pd-catalyzed carbonylative cyclization of 2-(1-alkynyl)phenols in alcohol furnished a straightforward synthetic route to 3-benzofurancarboxylic acid esters (Scheme 25).[16c] For example, substrate **149** was treated with $PdCl_2/CuCl_2$ as the catalyst/reoxidant in the presence of NaOAc in MeOH under CO pressure to give cyclized product **150** in 68% yield. This chemistry has



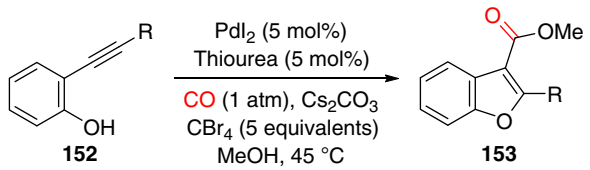
A: $Pd(OAc)_2(PPh_3)_2$ (2 mol%), CuI (4 mol%), piperidine (1 equivalent), DMF, 60 °C, 2 h; 80%
B: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), Et_3N, 90 °C, 10 h; 71%

Scheme 24



Scheme 25

been used to prepare a potential adenosine antagonist XH-14 (**151**). Another variant of this process has been reported by Yang and coworkers (equation 30).[16d] Thus, 2,3-disubstituted benzofurans **153** have been synthesized by the Pd(II)-catalyzed cyclization/carbonylation of 2-(1-alkynyl)phenols **152** using PdI_2/thiourea and CBr_4 as the catalyst system. This system affords good yields of benzofuran-3-carboxylates from both electron-rich and electron-deficient substrates. Benzo[*b*]furo[3,4-*d*]furan-1-ones **155** can also be obtained on reaction of 2-(1-alkynyl)phenols **154** bearing a hydroxyalkyl group with stoichiometric Pd complex in MeCN under a CO atmosphere (Table 7).[16e]

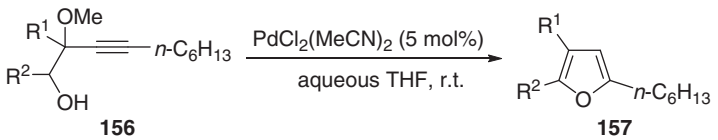


R	Yield (%)
Ph	80
4-MeC_6H_4	78
CH_2OMe	84

(30)

7.17.4.3.2 Alcohol nucleophiles

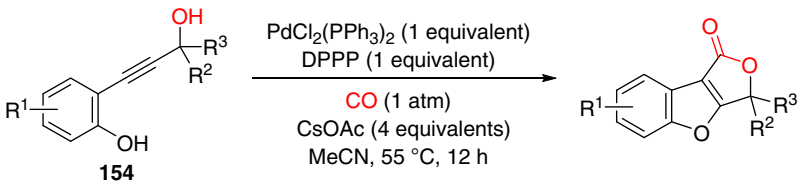
The Pd(II)-catalyzed cyclization of alkynols is a powerful method for the construction of various oxygen-containing heterocycles. For example, Utimoto first reported the Pd(II)-catalyzed cyclization of 2-methoxy-3-alkyn-1-ols **156** to furans **157** in good yields (equation 31).[8j]

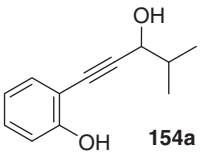
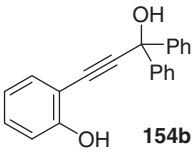
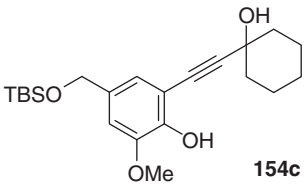
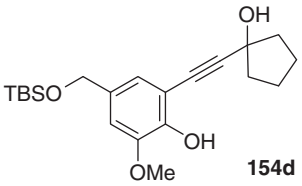
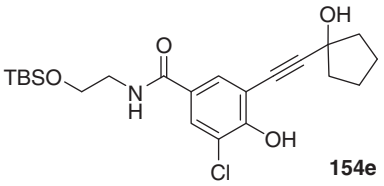
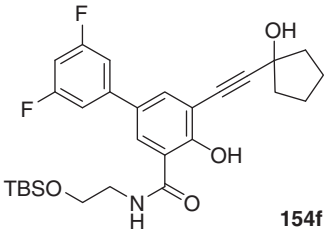


R^1	R^2	Yield (%)
Me	H	80
Me	Me	94
H	H	90

(31)

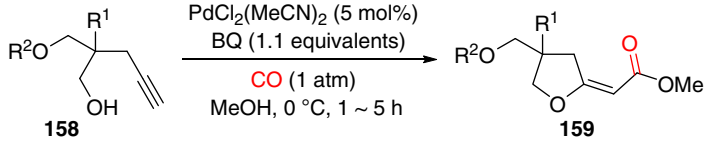
Table 7 Pd-promoted carbonylative annulations of 2-(1-alkynyl) phenols **154**



Entry	*Substrate*	*Product*	*Yield (%)*
1	 **154a**	**155a**	53
2	 **154b**	**155b**	52
3	 **154c**	**155c**	67
4[a]	 **154d**	**155d**	92
5	 **154e**	**155e**	83
6	 **154f**	**155f**	76

[a]Reaction time was 2 h.

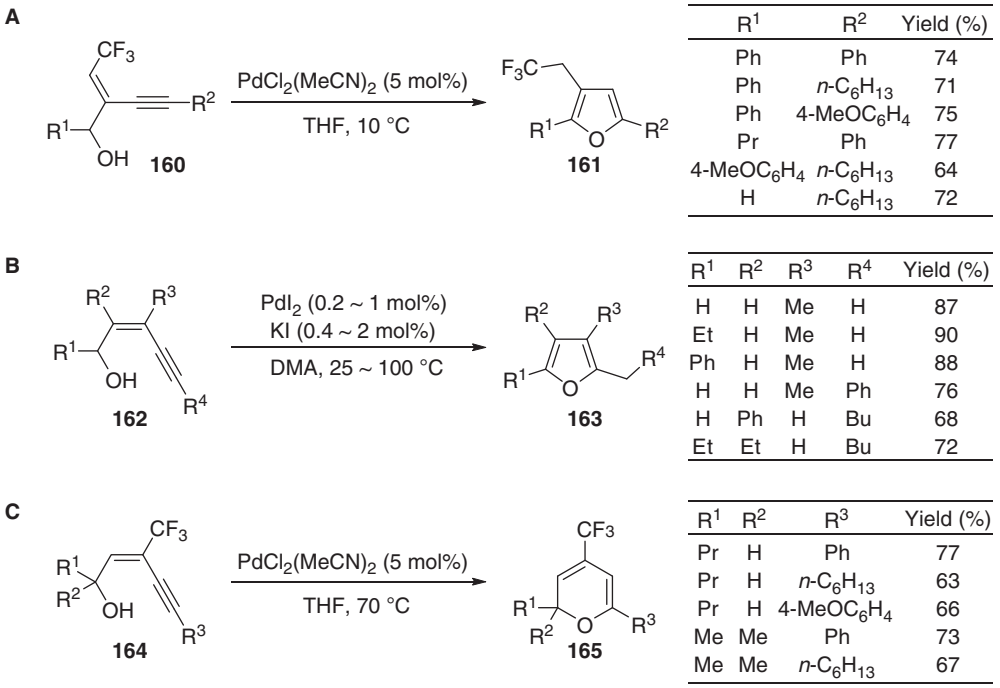
Kato and coworkers described the preparation of cyclic β-alkoxyacrylates **159** via the carbonylative Wacker-type cyclization of alkynols **158** (equation 32).[17a] The best results were obtained using the catalyst system $PdCl_2(MeCN)_2$/BQ in MeOH at 0 °C under a CO atmosphere.



R^1	R^2	Yield (%)
Bn	Ac	88
Bn	TBDMS	87
Bn	MOM	88
Bn	THP	69
Bn	H	79
Propargyl	Ac	87
Propargyl	TBDPS	91

(32)

Enynes bearing an alcohol unit have been examined for their utility as the substrate in the Pd(II)-catalyzed cyclization. Using various Pd reaction conditions, 3-(trifluoroethyl)furans **161**, a variety of substituted furans **163**, and 4-trifluoromethyl-*2H*-pyrans **165** have been obtained in good yields under mild reaction conditions from enynol substrates **160**, **162**, and **164**, respectively (Scheme 26).[17b–d] The Pd(II)-catalyzed cyclization of enynols was also conducted in the presence of CO. Enynols **166** bearing a terminal or internal triple bond were readily cyclized using a catalytic amount of PdI_2 and KI under CO pressure in MeOH to afford furan-2-acetic acid esters **167** in good yields (equation 33).[17e]

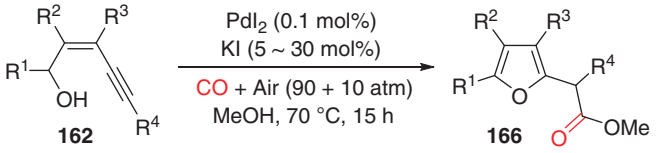


R^1	R^2	Yield (%)
Ph	Ph	74
Ph	n-C_6H_{13}	71
Ph	4-$MeOC_6H_4$	75
Pr	Ph	77
4-$MeOC_6H_4$	n-C_6H_{13}	64
H	n-C_6H_{13}	72

R^1	R^2	R^3	R^4	Yield (%)
H	H	Me	H	87
Et	H	Me	H	90
Ph	H	Me	H	88
H	H	Me	Ph	76
H	Ph	H	Bu	68
Et	Et	H	Bu	72

R^1	R^2	R^3	Yield (%)
Pr	H	Ph	77
Pr	H	n-C_6H_{13}	63
Pr	H	4-$MeOC_6H_4$	66
Me	Me	Ph	73
Me	Me	n-C_6H_{13}	67

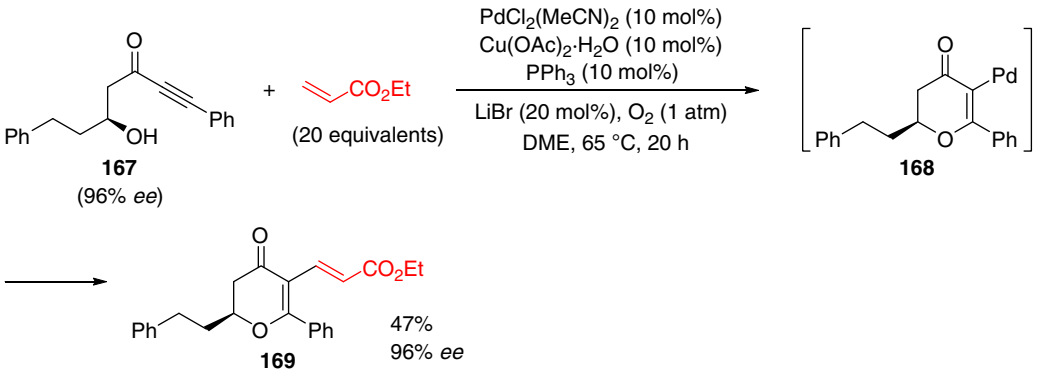
Scheme 26



R^1	R^2	R^3	R^4	Yield (%)
H	H	Me	H	73
H	H	Et	H	57
H	H	Ph	H	51
H	Et	H	Bu	68
H	Ph	H	Bu	75
H	Et	H	TMS(H)	70
Pr	H	H	TMS (H)	58

(33)

Gouverneur et al. reported a domino reaction consisting of the Wacker-type cyclization and subsequent Heck olefination.[17f] The reaction of hydroxyynone **167** with $PdCl_2(MeCN)_2/Cu(OAc)_2{\cdot}H_2O/PPh_3$ catalytic system in the presence of a large excess amount of ethyl acrylate furnishes highly functionalized dihydropyranone **169** bearing a conjugated diene moiety (Scheme 27).

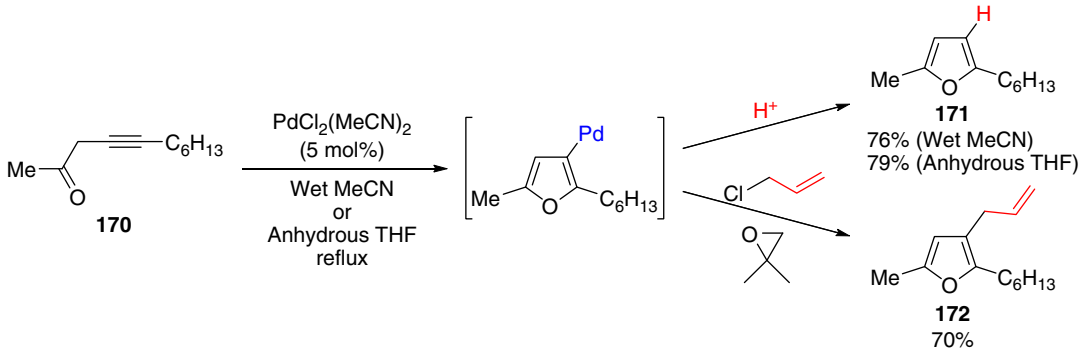


Scheme 27

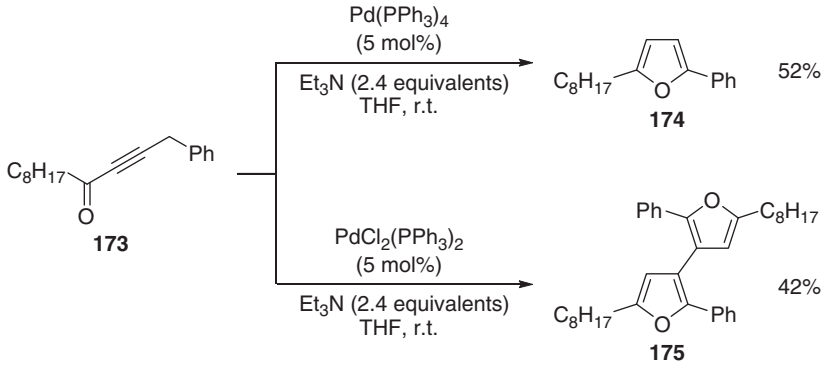
The reaction proceeds via intermediate **168**, which is formed by nucleophilic attack of the hydroxy group on the carbon–carbon triple bond. No loss of enantiopurity was observed in the reaction using optically active starting materials.

7.17.4.3.3 Enol nucleophiles

Alkynes containing a ketone group can be cyclized in the presence of a Pd(II) catalyst to a variety of furan products. For example, undec-4-yn-2-one **170** are cyclized to substituted furan **171** in good yields in the presence of a catalytic amount of $PdCl_2(MeCN)_2$ in MeCN containing a few percent of water or anhydrous THF (Scheme 28).[18a] This catalytic system was applicable to a domino reaction leading to 3-allylic furans **172** in the presence of 2,2-dimethyloxirane as a proton scavenger. The cyclization of alkynones using Pd(0) or Pd(II) catalysts in the presence of triethylamine forms either simple furans or bifurans: a treatment of 1-phenyldodec-2-yn-4-one **173** with $Pd(PPh_3)_4$ catalyst provides the 2,5-disubstituted furan **174**, whereas a catalytic amount of $PdCl_2(PPh_3)_2$ generates the dimer **175** (Scheme 29).[18b]



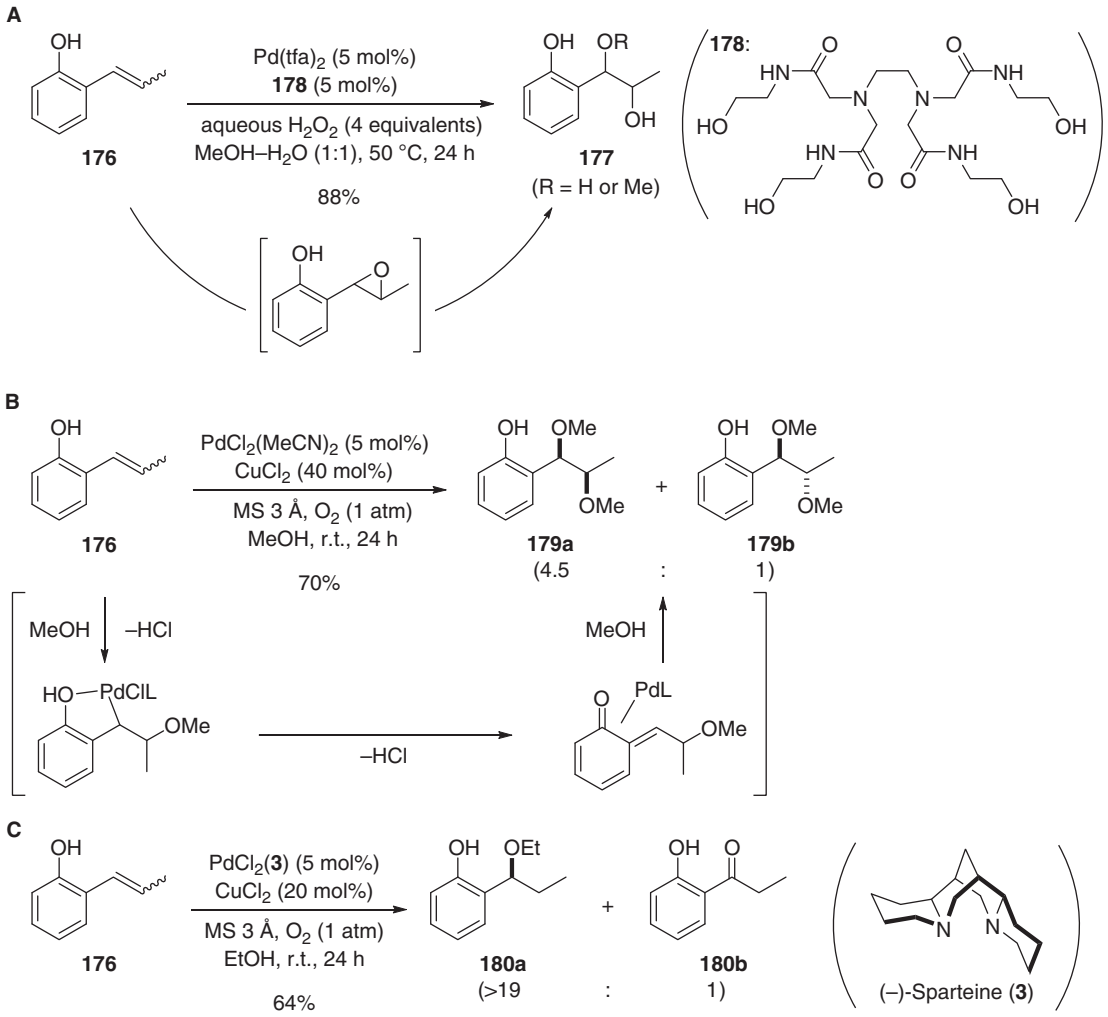
Scheme 28



Scheme 29

7.17.4.4 Intermolecular Reactions

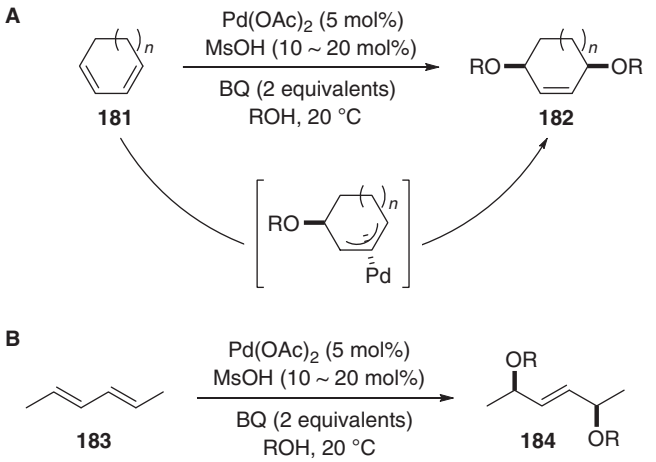
Intermolecular Pd(II)-catalyzed dialkoxylation of *ortho*-hydroxystyrenes was reported by Le Bras in 2005, and shortly thereafter by Schultz and Sigman in 2006. Although these two reports differ in reaction conditions and product, both of them result in the dioxygenation across an alkene. Le Bras proposes that this reaction occurs through initial Pd-catalyzed epoxidation of the propenyl moiety with H_2O_2, followed by attack at the benzylic position by either water or methanol (Scheme 30A).[19a] A procedure reported by Schultz and Sigman converted 2-(prop-1-enyl)phenol **176** into the diastereoisomeric products **179a** and **179b** with a *cis* to *trans* ratio of 4.5 to 1 (Scheme 30B).[19b] Because the presence of the phenol moiety was found to be essential for the dialkoxylation to occur, the observed outcome was attributed to nucleopalladation at the styrene β-carbon, after which a second equivalent of MeOH attacks a quinone methide species. The same authors disclosed a mild aerobic hydroalkoxylation of *ortho*-hydroxystyrenes, performed with 5 mol% $PdCl_2$(**3**) (3: (–)-sparteine), 20 mol% $CuCl_2$, and MS 3 Å at 35 °C under O_2 atmosphere in ethanol (Scheme 30C).[19c]



Scheme 30

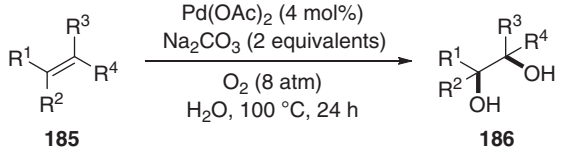
The reaction of 1,3-dienes **181** with 5 mol% $Pd(OAc)_2$ and excess BQ, carried out in an alcoholic solvent, afforded 1,4-dialkoxy-2-alkenes **182** (Scheme 31A).[19d] The reaction was highly regio- and stereoselective for both cyclic and acyclic systems. Internal acyclic dienes **183** gave 1,4-dialkoxylation products **184** with the (*E*)-double bond formation (Scheme 31B). A similar 1,4-acyloxy-alkoxylation reaction has also been reported by the same group.

Jiang and coworker developed an environmentally benign dihydroxylation of olefins **182**. This reaction proceeds in aqueous media with 5 mol% $Pd(OAc)_2$ catalyst and 8 atm of O_2 oxidant in the presence of Na_2CO_3 to give 1,2-diol products **183** (equation 34).[19e] A broad substrate scope has been demonstrated allowing monosubstituted aromatic and aliphatic terminal alkenes and 1,2- and 1,1-disubstituted olefins.



R	*n*	Yield (%)
Me	1	63
Et	1	72
Bn	1	53
Me	2	69
Et	2	82

Scheme 31



R^1	R^2	R^3	R^4	Yield (%)
Ph	H	H	H	83
4-BrC_6H_4	H	H	H	74
C_6H_{13}	H	H	H	71
Bn	H	H	H	82
$PhOCH_2$	H	H	H	79
Ph	H	H	Ph	76
Ph	H	Ph	H	75
Ph	Me	H	H	72

(34)

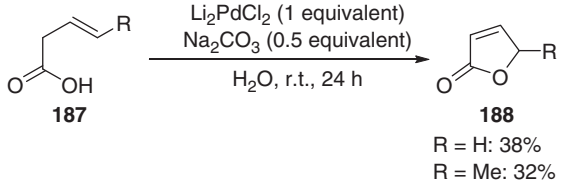
7.17.5 Acyloxylation

The use of carboxylic acids as nucleophiles on the carbon–carbon unsaturated bond results in acyloxylation (acetoxylation when acetic acid is used). Subsequent fast palladium hydride elimination at room temperature leads not to vinyl esters but typically to allylic esters or lactones. These products may arise via acyloxypalladation on the double (or triple) bond or a π-allyl Pd intermediate, depending on the reaction conditions and the substrate structure.[7]

7.17.5.1 Intramolecular Reactions Involving Alkene

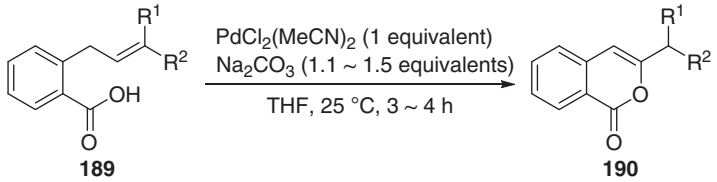
The cyclization of alkenoic acids using Pd is a very valuable synthetic method of unsaturated lactones. This transformation, employing stoichiometric or catalytic amounts of Pd, produces lactones via acyloxypalladation and subsequent Pd–H elimination.

An early study by Kasahara and coworkers demonstrated the potential utility of the Wacker-type cyclization, in which a stoichiometric amount of Li_2PdCl_4 was used with base.[20a] They accomplished the cyclization of 3-alkenoic acids **184** to butenolides **185**, albeit in low yields (equation 35). This reaction is interesting because it appears to proceed in a 5-*endo-trig* manner classified into an unfavorable process according to the Baldwin's rule.



(35)

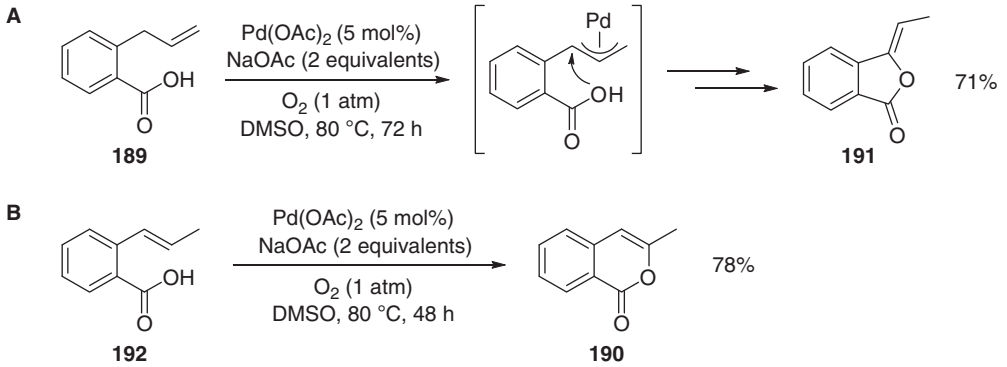
Hegedus and coworkers showed that isocoumarins **190** can be obtained from 2-allylbenzoic acids **189** using a Pd-promoted cyclization involving nucleophilic attack of a carboxylate group on an olefin activated by the Pd complex (equation 36).[20b] This process affords good yields using a stoichiometric amount of $PdCl_2(MeCN)_2$ and Na_2CO_3 in THF at room temperature. It proceeds by a 6-*exo-trig* pathway and subsequent double-bond isomerization.



R^1	R^2	Yield (%)
H	H	86
H	Me	86
Me	Me	96

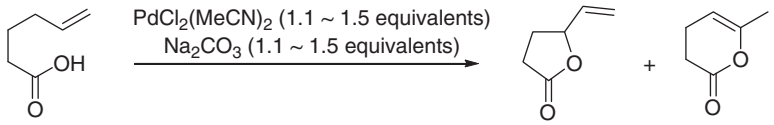
(36)

Larock et al. described similar Pd-catalyzed cyclizations using an experimentally simple, very mild, and versatile procedure employing only catalytic amounts of $Pd(OAc)_2$ and O_2/DMSO as the reoxidant.[20c] When this catalytic system was employed on 2-allylbenzoic acid (**189**), phthalide product **191** was obtained (Scheme 32A). This appears to be a particularly useful route to the naturally occurring 3-alkylidenephthalide ring system. Formation of the five-membered ring lactone suggested that perhaps the starting acid was first isomerized to 2-(1-propeny1)benzoic acid (**192**), which then affords the observed product. However, cyclization of **192** under the conditions afforded only 3-methylisocoumarin (**190**) (Scheme 32B). It appears that the phthalide product **191** arises by π-allyl Pd formation, intramolecular carboxylate displacement of palladium, and subsequent double-bond isomerization (*see* Chapter 7.05). Monocyclic, fused and bridged bicyclic, and spirocyclic lactones bearing five- or six-membered rings are formed readily by this process. They found that the relative reactivity of alkenoic acids follows the order disubstituted > trisubstituted > monosubstituted. There appears to be a fine balance between the effects produced by electron density and steric hindrance. In general, five-membered rings are more easily closed than 6-membered rings.



Scheme 32

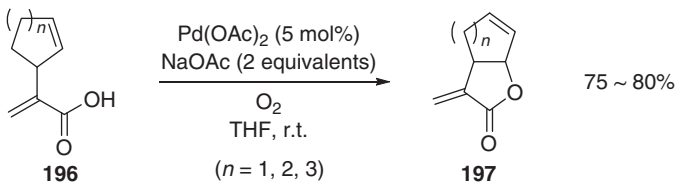
Annby and coworkers have shown that the acyclic unsaturated carboxylic acid **193** reacts in the presence of a stoichiometric amount of $PdCl_2(MeCN)_2$ and Na_2CO_3/DMSO to afford a 70:30 ratio of lactones **194** and **195** in a good yield (equation 37).[20d] The selectivity for formation of either the five- or six-membered unsaturated lactone is governed by the choice of solvent and base. Thus, MeCN and NaOAc give a very different ratio of lactones.



(DMSO/Na_2CO_3)	70	:	30
(MeCN/NaOAc)	10	:	90

(37)

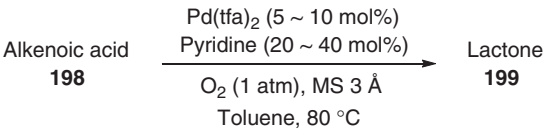
Exo-methylene-γ-butyrolactones **196** can be similarly synthesized from the corresponding 3-cycloalkenyl-3-butenoic acids **197** in good yields using only catalytic amounts of $Pd(OAc)_2$ with NaOAc as the base in THF in the presence of oxygen (equation 38).[20e]

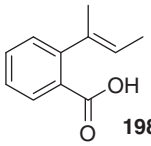
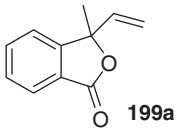
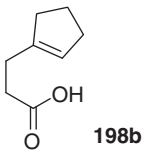
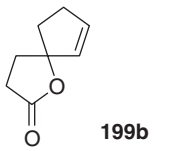
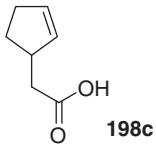
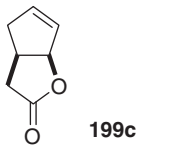
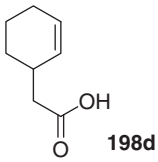
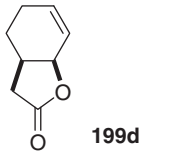


(38)

Stoltz and coworkers subjected a series of carboxylic acids **198** bearing an alkenyl moiety (Table 8).[11j,20f] They obtained spirocyclic and fused-ring lactones **199** in moderate to high yields. Only *cis* adduct was observed in the case of fused bicyclic lactones.

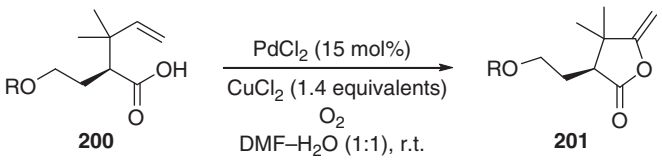
Table 8 Pd-catalyzed aerobic oxidative cyclization of carboxylic acids **198**



Entry	*Substrate*	*Product*	*Yield (%)*
1	 **198a**	 **199a**	90
2	 **198b**	 **199b**	62
3[a]	 **198c**	 **199c**	77
4[a]	 **198d**	 **199d**	86

[a] Na_2CO_3 (2 equivalents) was used as an additive.

An effective application of the Pd-catalyzed lactonization of alkenoic acids is the key step in the synthesis of precursors of the vitamin B_{12} C-ring. Enelactones **201** were prepared in three steps by carrying out the intramolecular cyclization of **200** with $PdCl_2$ and $CuCl_2$ under O_2 atmosphere (equation 39).[20g]

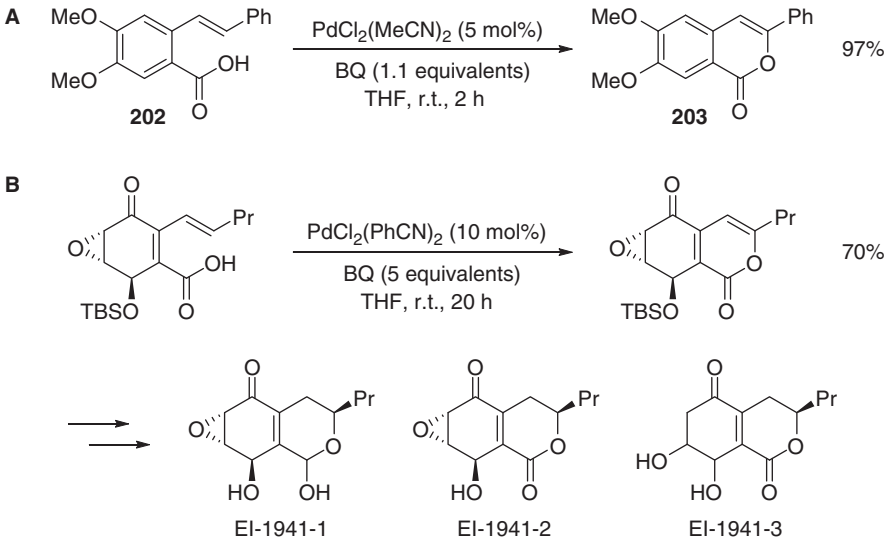


R	Yield (%)
H	60
Bn	84
TBDPS	52

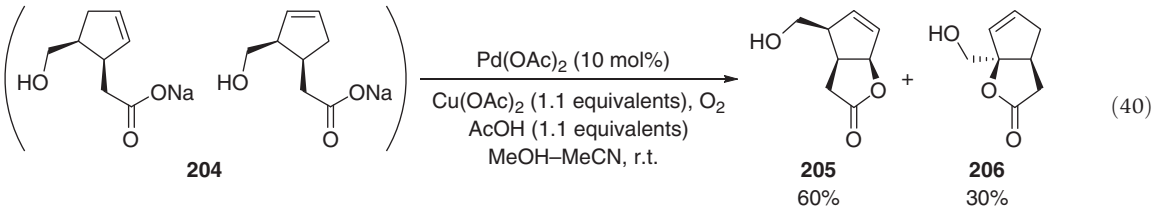
(39)

The intramolecular oxypalladation of *ortho*-alkenylbenzoic acid **202** took place in the presence of a catalytic amount of $PdCl_2(MeCN)_2$ with BQ in THF at room temperature to give isocumarin derivative **203** in high yield (Scheme 33A).[20h] This strategy was essential for building the δ-lactol or δ-lactone ring of the interleukin-1β inhibitors, EI-1941-1, -2, and -3, where 10 mol % of $PdCl_2(PhCN)_2$ was used as the catalyst (Scheme 33B).[20i]

The regioconvergent Pd(II)-catalyzed intramolecular cyclization of cyclopentenylacetic acid sodium salt **203** bearing a hydroxymethyl group afforded the versatile racemic lactone **204**, a building block for the synthesis of biologically active compounds such as iridoids and F_2-isoprostanes (equation 40).[20j] Under improved conditions (i.e., a combination of $Pd(OAc)_2$/Cu $(OAc)_2$ and 1.1 equivalents of AcOH as a proton source under a stream of O_2 in MeOH/MeCN as solvent), the reaction ran smoothly at room temperature to give **204** in 60% yield, along with isomeric lactone **205** in 30% yield. The authors provided some evidence for the intervention of two mechanisms involving an intramolecular 1,2-acyloxypalladation leading to **204** and the formation of π-allyl Pd complexes leading to **204** and **205**.

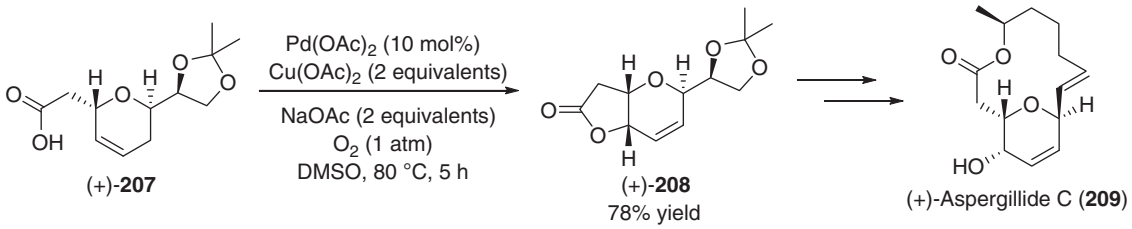


Scheme 33



(40)

Waters and his coworker achieved formal total synthesis of aspergillide C (**209**) in a simple and straightforward manner by applying the Wacker-type oxidative lactonization. Exposure of acid (+)-**207** to the Wacker conditions afforded lactone (+)-**208** in 78% yield (Scheme 34).[20k]

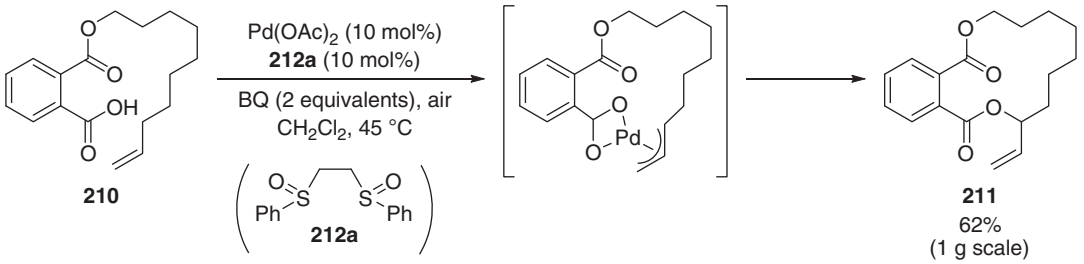


Scheme 34

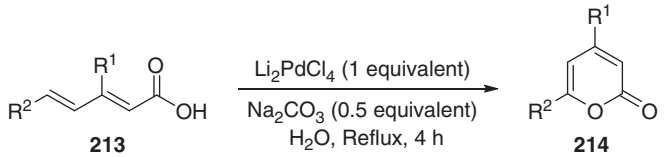
White and coworkers have developed Pd(II)-catalyzed macrolactonization of ω-alkenoic acids via C–H bond oxidation by utilizing bis-sulfoxide ligands **212**.[20l–o] This reaction can be performed at >10 mM without the use of high-dilution techniques to prepare 14- to 19-membered macrolides with high levels of regioselectivity and functional group tolerance. For example, treatment of *ortho*-(alkenyl)benzoic acid **210** with $Pd(OAc)_2$/**212a**/BQ catalytic system promoted macrolactonization to furnish 1 g of 14-membered macrocyclic benzolactone **211** in 62% isolated yield with outstanding regioselectivity (>20:1) shown in Scheme 35.[20l] Mechanistic studies support that the macrolactonization proceeds via a Pd-templated π-allyl carboxylate intermediate. This strategy has been successfully applied to total synthesis of natural products.[20m–o]

7.17.5.2 Intramolecular Reactions Involving Diene

The first report of the Pd(II)-promoted cyclization of 1,3-dienes came from Izumi and Kasahara in 1975.[21a] They reported that the intramolecular cyclization of alka-2,4-dienoic acids **213** with a stoichiometric amount of Li_2PdCl_4 in water affords exclusively six-membered ring pyrones **214** (equation 41).



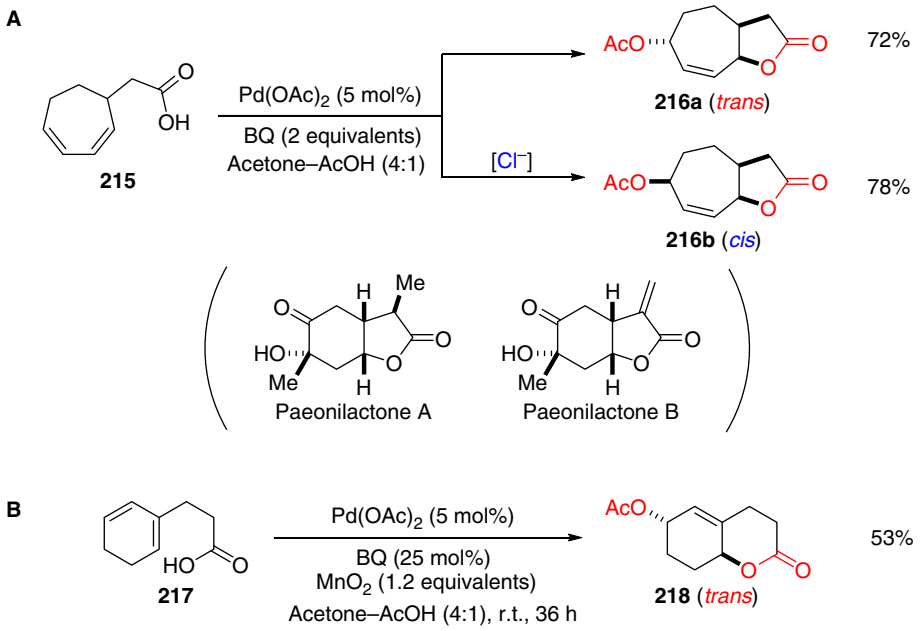
Scheme 35



R^1	R^2	Yield (%)
H	H	72
H	Me	75
H	Ph	68
Me	Me	65
Me	Ph	65
Ph	Ph	68

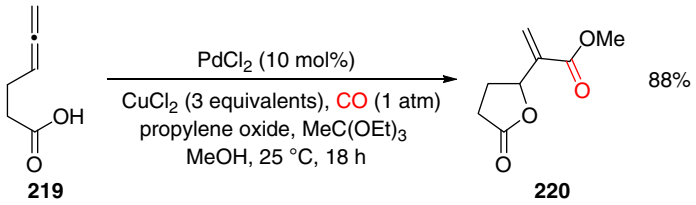
(41)

Catalytic versions of the 1,4-oxidative functionalizations of conjugated dienes bearing a carboxylic group have been developed by Bäckvall and coworkers. They demonstrated an intramolecular cyclization of cycloheptadienylacetic acid **215** to the corresponding acetoxylated *cis*-fused γ-lactone **216** (Scheme 36A).[21b] This reaction, which is highly regio- and stereoselective, takes place by successive intra- and intermolecular nucleophilic attacks. First, the carboxylate intramolecularly attacks the diene on Pd in *anti* fashion. This cyclization then generates a π-allyl Pd complex, which is attacked intermolecularly by acetic acid, leading to the observed stereochemistry. Manipulating the reaction conditions, to end up with either a *cis*- or *trans*-lactone, has elegantly controlled the intermolecular attack by acetic acid. This reaction has also been applied to the synthesis of natural products, i.e., paeonilactone A and B.[21c] In a more recent paper, the same research group reported the synthesis of acetoxylated δ-lactones **218** using an analogous protocol on 2-substituted 1,3-cycloalkadienes **217** bearing a carboxylic group in the side chain (Scheme 36B).[21d]



Scheme 36

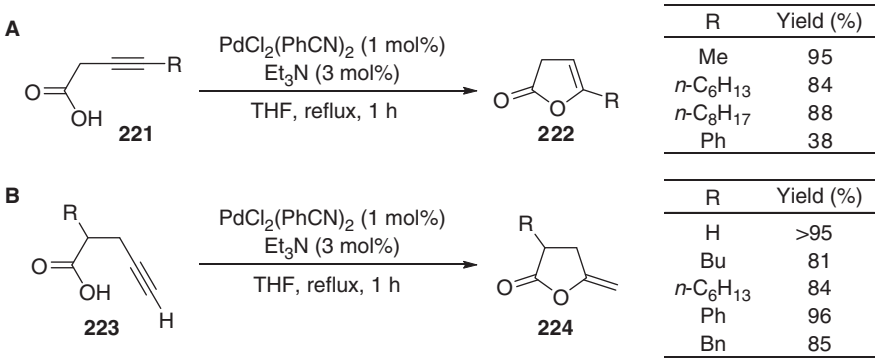
The intramolecular carbonylative oxypalladation of 4,5-hexadienoic acid **219** was reported by Walkup (equation 42).[21e] Furanone derivative **220** was formed in good yield. In this reaction, propylene oxide was used as an acid trap and triethyl orthoacetate as a water scavenger.



(42)

7.17.5.3 Intramolecular Reactions Involving Alkyne

The reaction of 3- and 4-alkynoic acids **221** and **223** with Pd(II) catalysts proceeds by intramolecular *endo* or *exo* addition of the carboxylic acid moiety to the carbon–carbon triple bond to afford unsaturated lactones **222** and **224**, respectively (Scheme 37).[22a]

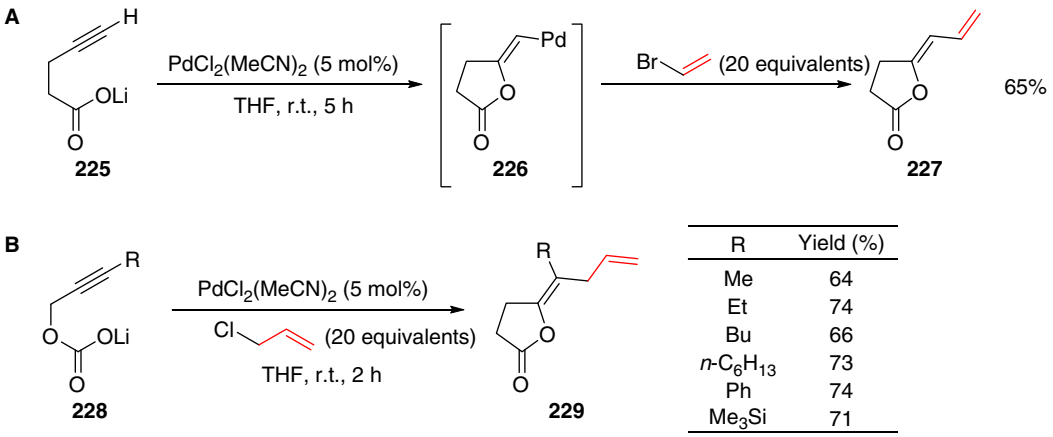


R	Yield (%)
Me	95
n-C_6H_{13}	84
n-C_8H_{17}	88
Ph	38

R	Yield (%)
H	>95
Bu	81
n-C_6H_{13}	84
Ph	96
Bn	85

Scheme 37

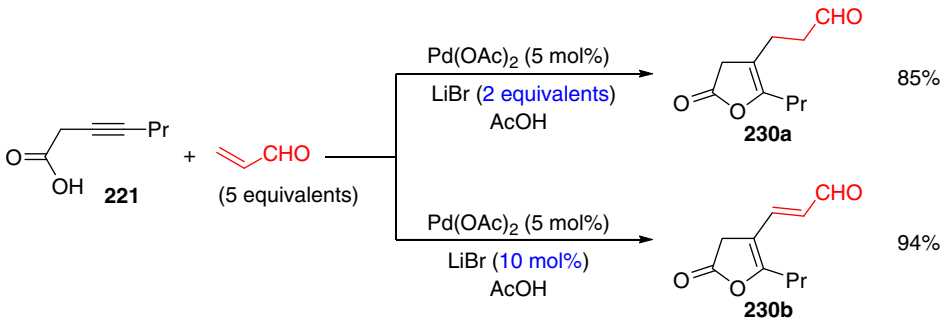
In a similar manner, the lithium alkynoates **225** react with $PdCl_2(MeCN)_2$ to afford alkenylpalladium intermediates **226**, which can react further with vinylic halides (or allyl halides) to produce the unsaturated 4-buten-4-olides **227** (Scheme 38A).[22b] The lithium 2-alkynyl carbonates **228** react in a similar manner with allyl chloride to afford the cyclic carbonates **229** in good yields (Scheme 38B).[22c]



R	Yield (%)
Me	64
Et	74
Bu	66
n-C_6H_{13}	73
Ph	74
Me_3Si	71

Scheme 38

The lactones **230** can be synthesized by the acyloxypalladation of 3-heptynoic acid (**221**) and subsequent trapping with acrolein (Scheme 39).[22d] When the reaction is conducted in the presence of an excess of LiBr, the saturated aldehyde **230a** is obtained. However, in the presence of only catalytic amounts of LiBr, the major product is the unsaturated aldehyde **230b**.

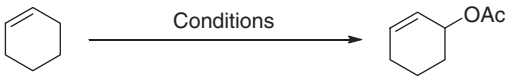


Scheme 39

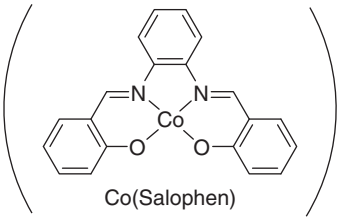
7.17.5.4 Intermolecular Reactions Involving Alkene

An oxidative allylic acetoxylation of olefins is achieved with Pd catalyst. Representative catalytic systems for the allylic acetoxylation of cyclohexene (**231**) to cyclohex-2-enyl acetate (**232**) are shown in Table 9. The $Pd(OAc)_2/BQ/MnO_2$ system is a synthetically useful tool for the allylic acetoxylation of olefins (entry 1).[23a] Employing an aerobic three-component catalytic system with Co(salophen) as oxygen-activating catalyst, cyclohexene is quantitatively oxidized to the desired product **232** (entry 2).[23b] A heteropolyacid[23c] or a copper salt[23d] can also be used as the oxygen-activating catalyst (entries 3 and 4). Other catalytic systems such as $Pd(OAc)_2/BQ/H_2O_2$,[23e] $Pd(OAc)_2/BQ/TBHP$,[23f] and $PdCl_2/AgOAc/TeO_2/TBHP$[23g] were reported for allylic acetoxylation of olefins (entries 5–7). Generally, substituents and ring size strongly influence the reaction outcome in the allylic acetoxylation.

Table 9 Pd-catalyzed oxidative allylic acetoxylation of cyclohexene

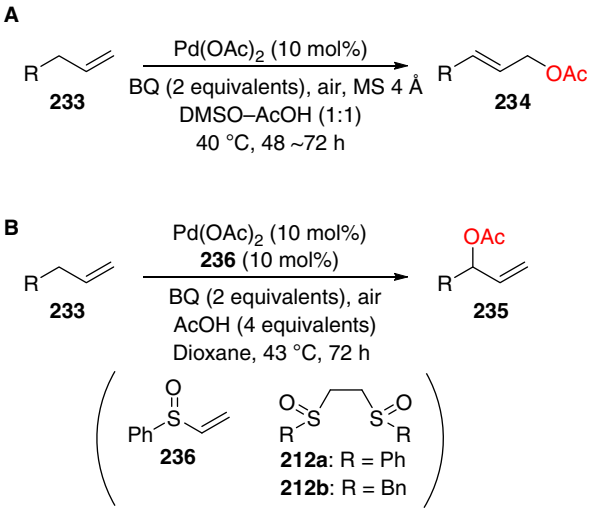


Entry	*Conditions*	*Yield (%)*
1	$Pd(OAc)_2$ (5 mol%), BQ (20 mol%), MnO_2 (1.2 equivalents) AcOH, 60 °C, 17 h	97
2	$Pd(OAc)_2$ (5 mol%), HQ (20 mol%), Co(salophen) (5 mol%) $LiOAc{\cdot}2H_2O$ (0.5 equivalent), AcOh, O_2 (1 atom), 60 °C	>95
3	$Pd(OAc)_2$ (5 mol%), HQ (20 mol%), molybdovanadophosphate AcOH, O_2 (1 atom), 60 °C, 4 h	>95
4	$Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (5 mol%), HQ (10 mol%) AcOH, O_2 (1 atom), 50 °C, 22 h	85
5	$Pd(OAc)_2$ (0.1 mol%), BQ (3 mol%), H_2O_2 (1.1 equivalents) AcOH, 50 °C	76
6	$Pd(OAc)_2$ (5 mol%), BQ (20 mol%), AcOH (2 equivalents) TBPH (1.1 equivalents), CH_2Cl_2, 40 °C, 24 h	67
7	$PdCl_2$ (5 mol%), AgOAc (10 mol%), TeO_2 (5 mol%) TBPH (0.5 equivalent), AcOH, 25 °C, 3 days	88 (based on TBHP)



White has reported a regioselective acetoxylation of terminal alkenes **233** using $Pd(OAc)_2$ as catalyst and BQ as reoxidant. Linear products **234** are predominant in the reaction without any ancillary ligands in DMSO solvent (Scheme 40A),[23h] whereas the addition of sulfoxide ligand **236** controls the regio- and chemoselectivity of the process to yield branched products **235** (Scheme 40B).[23i] Similar to **236**, bis-sulfoxide ligands, **212**, also provide **235** as the major product. The high functional group compatibility is demonstrated and variation in the steric and electronic properties of the carboxylic acid component is also well tolerated. Several useful transformations on the basis of this allylic oxidation have also been developed.[23j–l]

In a recent paper, Kaneda and coworkers described the regioselective acetoxylation of terminal alkenes to linear allylic acetates using molecular oxygen as oxidant in cocatalyst-free conditions (equation 45).[5d] Olefinic substrates bearing two substituents at the allylic position undergo Pd(II)-catalyzed acetoxylation at the terminal sp^2 carbon.[23m] Pd(II)-catalyzed allylic oxidation using different catalytic systems has been reported also on naturally occurring terpenes.[23n–q]

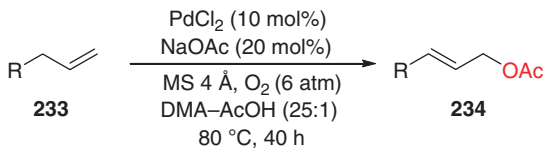


R	Yield (%)	L/B	*E*/*Z*
$TBDPSO(CH_2)_2$*	50	31:1	11:1
$BnO(CH_2)_2$*	57	31:1	11:1
$Et_2NC(O)(CH_2)_3$	62	12:1	12:1
$PhNHC(O)O(CH_2)_3$	64	12:1	12:1

*$Pd(tfa)_2$ was used.

R	Yield (%)	L/B
$TBDPSO(CH_2)_2$	72	1:16
$BnO(CH_2)_2$	59	1:18
$Et_2NC(O)(CH_2)_3$	56	1:18
$PhNHC(O)O(CH_2)_3$	64	1:26

Scheme 40



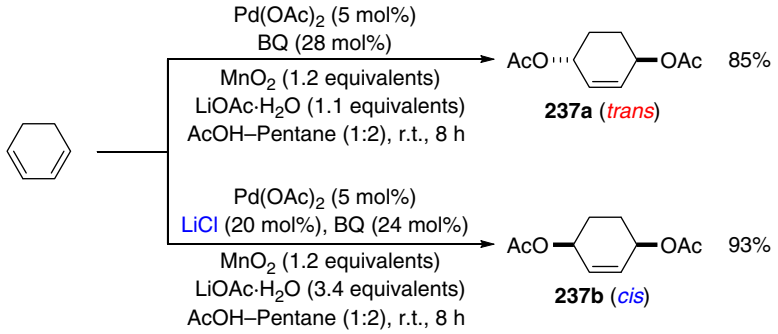
R	Yield (%)	B/L	*E*/*Z*
$n\text{-}C_7H_{15}$	85	13:1	1:1
$n\text{-}C_{17}H_{35}$	82	10:1	2:1
$MeO_2C(CH_2)_7$	85	8:1	9:1
$NC(CH_2)_2$	76	10:1	8:1

(43)

7.17.5.5 Intermolecular Reactions Involving Diene

Pd-catalyzed 1,4-oxidative functionalizations of conjugated dienes make up a group of synthetically useful regio- and stereoselective transformations in which a wide range of nucleophiles can be employed. The reaction proceeds smoothly at room temperature in conditions that are much milder than those required for the related allylic acetoxylation of monoalkenes discussed in the previous section.

A catalytic reaction of cyclohexa-1,3-diene that gives high yields of 1,4-diacetoxy-2-alkenes **237** was observed in acetic acid in the presence of LiOAc and BQ, where the difference was only in the use of catalytic amount of LiCl (Scheme 41).[24a] The reaction was highly regio- and stereoselective with both cyclic and acyclic dienes. The mechanism is quite similar to that of the corresponding 1,4-dialkoxylation shown in Scheme 21A, which involves an *anti*-acetoxypalladation of the conjugated diene followed by either *syn* or *anti* attack by acetate on the allyl group of the resulting π-allyl Pd intermediate. Several substituted cyclic 1,3-dienes have been studied to determine the scope of the reaction and the role of substituents on its stereoselectivity. With this method, 3,6-diacetoxy-4-cycloheptenol, an enantiopure intermediate for the synthesis of both enantiomers of the tropane alkaloids calystegines, was also prepared.[24b]

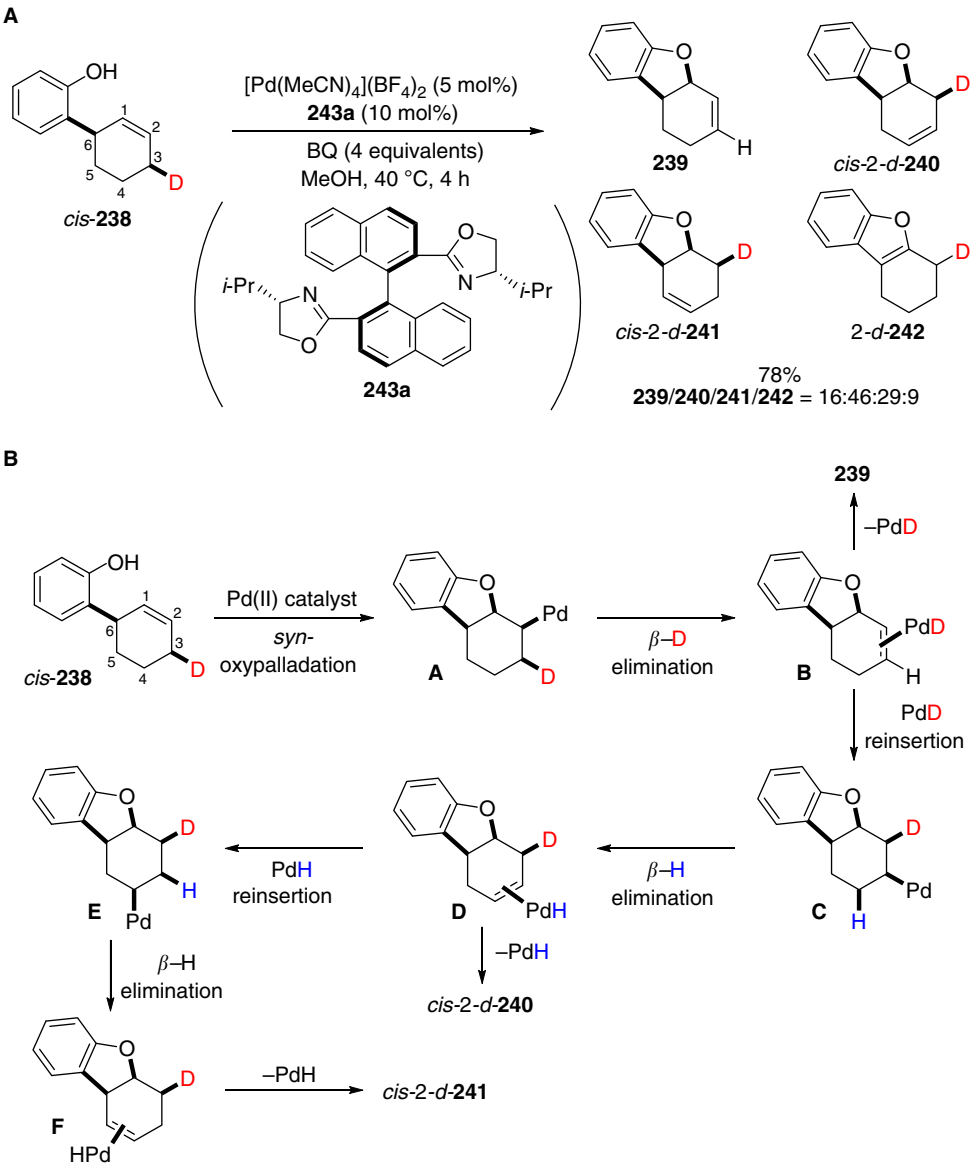


Scheme 41

7.17.6 Mechanistic Study

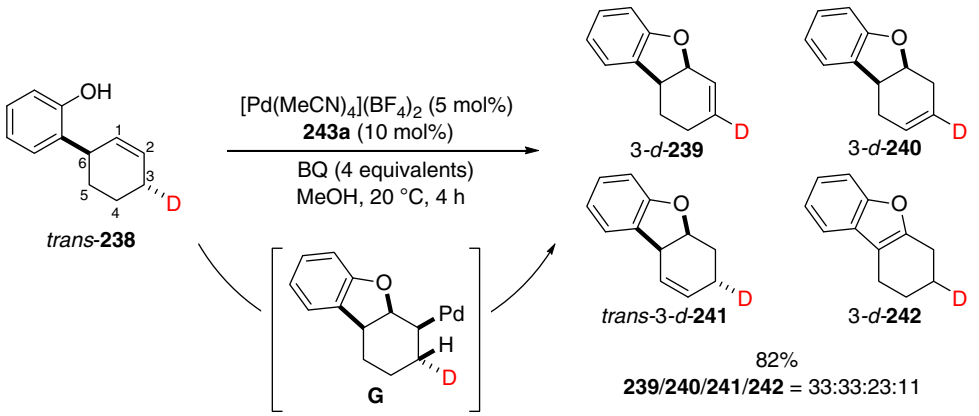
The Wacker-type reaction proceeds through a *β*-oxyethyl-Pd(II) intermediate that forms via the net addition of an oxygen nucleophile and Pd across the carbon–carbon double bond. This oxypalladation step has been the subject of extensive mechanistic research and controversy over the past decade. A major focus of this debate has centered on whether the reaction proceeds by a *syn*-oxypalladation pathway involving migration of a coordinated oxygen nucleophile to olefin or an *anti*-oxypalladation pathway involving nucleophilic attack of an exogenous oxygen nucleophile on the coordinated olefin.[25]

Intrigued by the high levels of stereocontrol demonstrated for the oxidative cyclization of *ortho*-allyl phenols as shown in Scheme 11C, Hayashi and coworkers employed a stereospecifically deuterated substrate to probe the mechanism of oxypalladation.[26] For example, phenol *cis*-**238** was subjected to $[Pd(MeCN)_4](BF_4)_2$, chiral ligand **243a**, and 4 equivalents of BQ in methanol. Analysis of the reaction mixture revealed four regioisomeric dihydrobenzofuran derivatives: **239**, *cis*-2-*d*-**240**, *cis*-2-*d*-**241**, and 2-*d*-**242** in a ratio of 16:46:29:9 (Scheme 42A). All of the products are consistent with a *syn*-oxypalladation pathway (Scheme 42B). Oxypalladation involving alkene insertion into the phenol oxygen–Pd bond (*syn*-oxypalladation) forms Pd–alkyl intermediate **A**. The *syn*-facial relationship of the Pd and deuterium leads to *β*-deuteride elimination, a step that has been shown to proceed in a *syn* fashion. The resulting Pd(D)(alkene) complex **B** furnishes dihydrobenzofuran **239** on alkene dissociation. The lack of a deuterium atom at C3 provides direct evidence for *syn*-oxypalladation. Alternatively, alkene **239** can reinsert into the



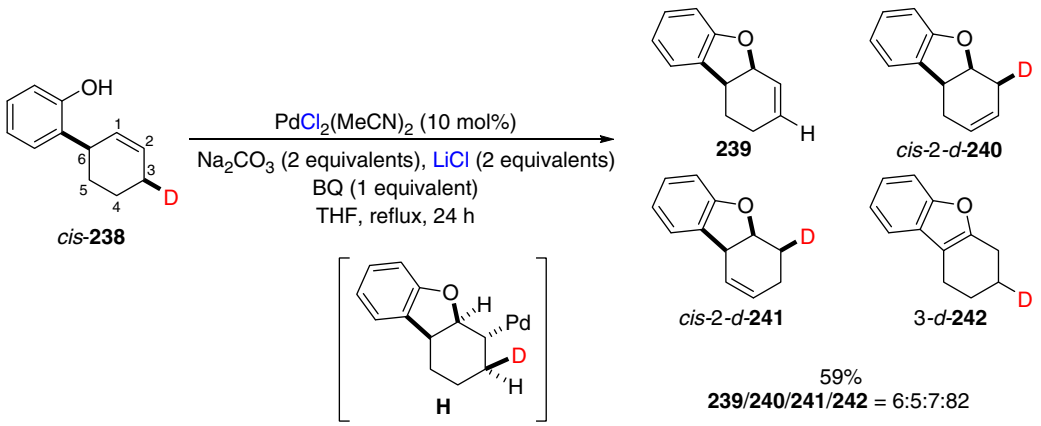
Scheme 42

Pd–deuteride to form Pd–alkyl intermediate **C**, which can undergo β-hydride elimination to give regioisomer *cis*-2-*d*-**240**. Analogously, alkene reinsertion of **D** and subsequent β-hydride elimination generates isomer *cis*-2-*d*-**241**. The lack of products containing a deuterium atom at C3 implies that an *anti*-oxypalladation pathway is not operable under these reaction conditions. The reaction of *trans*-**238** gave 3-*d*-**239**, 3-*d*-**240**, *trans*-3-*d*-**241**, and 3-*d*-**242** in a ratio of 33:33:23:11 (Scheme 43). The fact that the deuterium remained at the 3-position in all of the isomeric products also supports the *syn* stereochemistry of the oxypalladation step via alkylpalladium intermediate **G**.



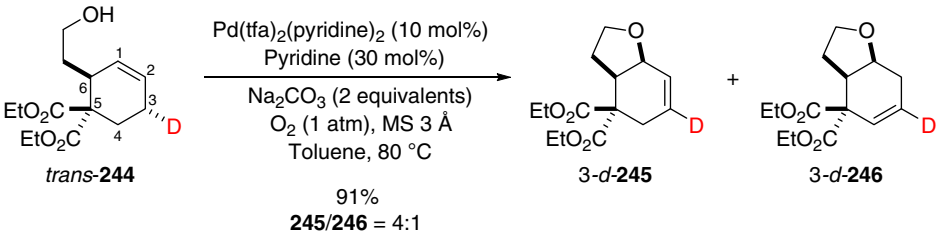
Scheme 43

As is observed in the Wacker reaction, the mechanism of phenol cyclization appears to change from *syn*- to *anti*-oxypalladation under high Cl^- concentration conditions (Scheme 44). Cyclization of *cis*-**238** with a $PdCl_2(MeCN)_2/Na_2CO_3$/LiCl/BQ catalyst system in THF (in the absence of chiral ligand **243a**) provided a mixture of **239**, *cis*-2-*d*-**240**, *cis*-2-*d*-**241**, and 3-*d*-**242** in a 6:5:7:82 ratio. Although the presence of small amounts of **239**, *cis*-2-*d*-**240**, and *cis*-2-*d*-**241** indicates that a *syn*-oxypalladation pathway is operable, formation of 3-*d*-**242** as the major product is consistent with *anti*-oxypalladation via intermediate **H** as the primary reaction pathway. These results clearly demonstrate that a single substrate can undergo both *syn*- and *anti*-oxypalladation under different reaction conditions. In light of this work and previous mechanistic studies of the Wacker reaction, it is tempting to suggest that a general correlation between Cl^- concentration and oxypalladation mechanism exists; however, the effect of Cl^- concentration on the oxypalladation mechanism is not consistent for all substrates/reaction conditions.



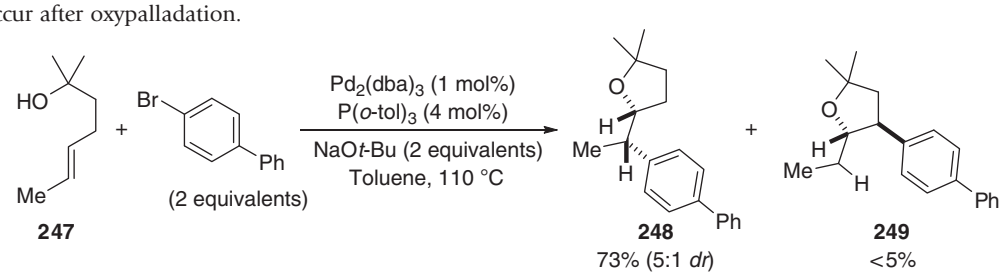
Scheme 44

Stoltz and coworkers observed *syn*-oxypalladation in the cyclization of the corresponding primary alcohol *trans*-**244**. Under identical conditions, *trans*-**244** underwent cyclization to provide 3-*d*-**245** along with alkene isomer 3-*d*-**246** in a 4:1 ratio and 91% overall yield (equation 44).[11j]



(44)

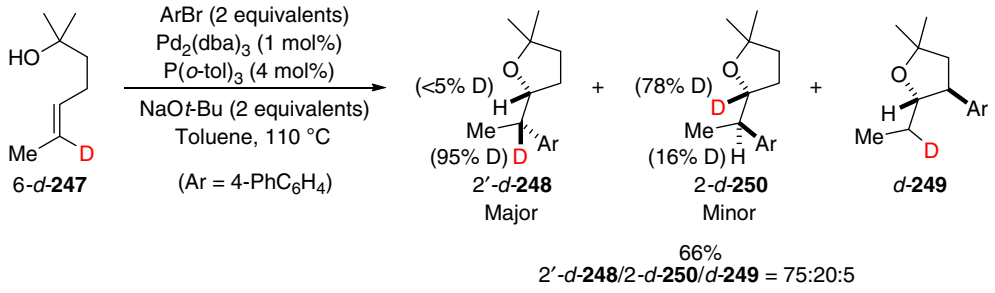
Further evidence for a *syn*-oxypalladation reaction mechanism during alcohol cyclization has been furnished by Wolfe and coworkers, who have developed a class of alkene difunctionalization reactions that are initiated by oxidative addition of aryl bromides by Pd(0) catalysts. Preliminary studies of the oxypalladation step focused on the stereochemical relationship of the nucleophilic oxygen atom and the aryl substituent. Tertiary alcohols bearing internal alkenes underwent alkoxyarylation to generate furans in which the aryl substituent and nucleophilic oxygen added to the alkene in a *syn* fashion (i.e., **248**), as was demonstrated by the reaction of *trans*-alkene **247** with 4-bromobiphenyl (equation 45).[11p] A trace amount of the regioisomeric product **249** was also observed. The authors proposed that the modest diastereoselectivity observed for the formation of **248** could be the result of competing *syn*- and *anti*-oxypalladation, or alternatively, the diastereomeric mixture could form by isomerization steps that occur after oxypalladation.



(45)

To distinguish between these two possibilities, deuterated tertiary alcohol *5-d*-**247** was subjected to the reaction conditions (Scheme 45A).[27a,b] The reaction yielded diastereomers *2-d*-**248** and *2′-d*-**250** in a 79:17 mixture and trace quantities of regioisomeric side product *d*-**249**. As illustrated in Scheme 45B, all products in the alkoxyarylation of *5-d*-**247** are proposed to arise from a *syn*-oxypalladation pathway. On formation of Pd–alkyl intermediate **B** through intermediate **A**, reductive elimination forms the major product *2-d*-**248**. Alternatively, σ-bond rotation, followed by β-deuteride elimination and alkene reinsertion, generates intermediate **D**, which accounts for the formation of deuterium-scrambled products. From **D**, a series of elementary steps lead to the minor diastereomer *2′-d*-**250**. Intermediate **D** also provides a mechanistic hypothesis for the formation of *d*-**249**. This deuterium scrambling study supports an exclusive *syn*-oxypalladation pathway, with the minor diastereomer *2′-d*-**250** arising from an isomerization pathway rather than from *anti*-oxypalladation.

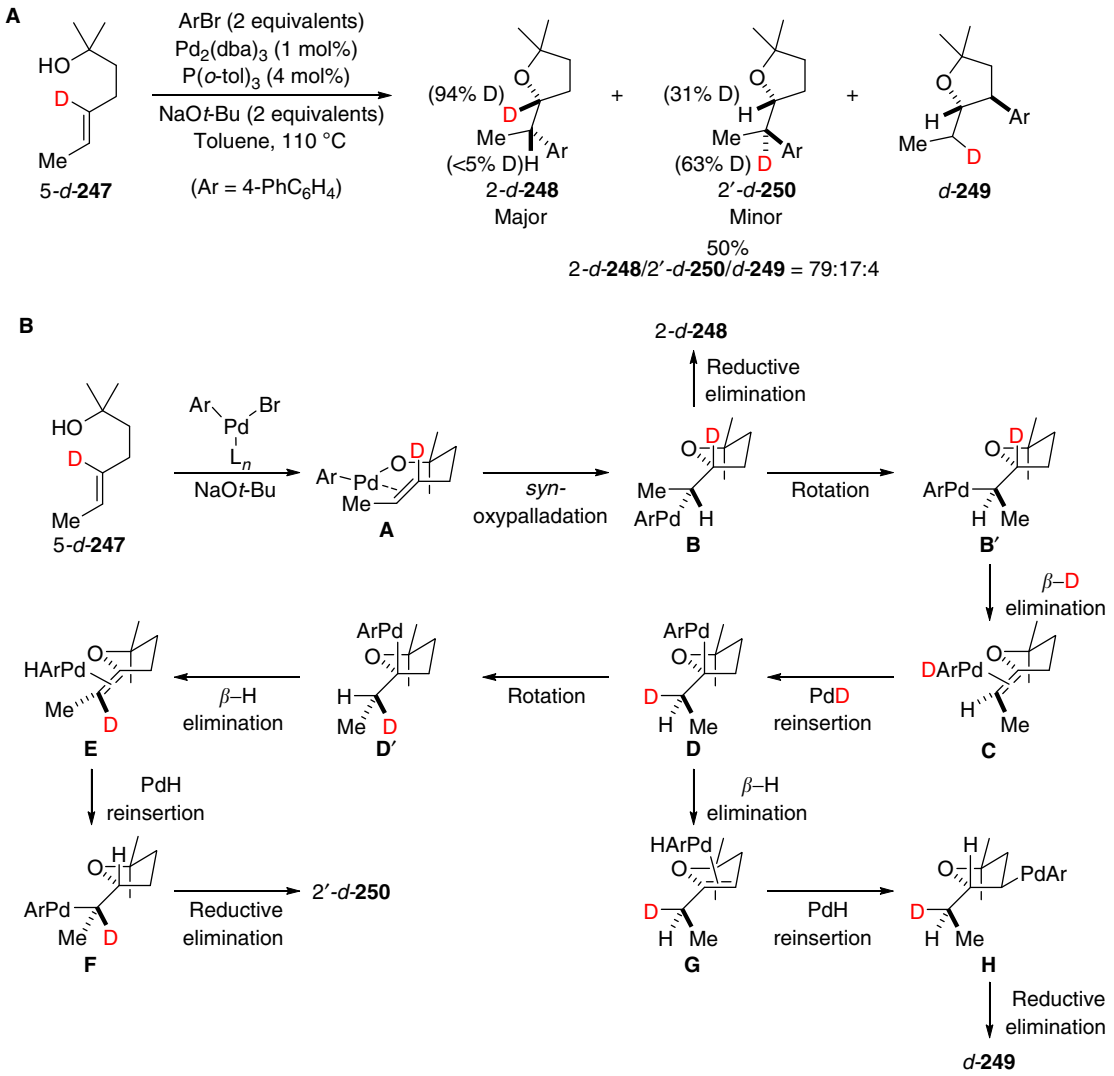
Alkene isomer *6-d*-**247** reacted in a similar fashion (equation 46). The major diastereomer *2′-d*-**248** appears to arise from *syn*-oxypalladation. The minor diastereomer *2-d*-**250** is formed with significant quantities of deuterium scrambling, an observation that cannot be readily explained by invoking an *anti*-oxypalladation reaction mechanism.



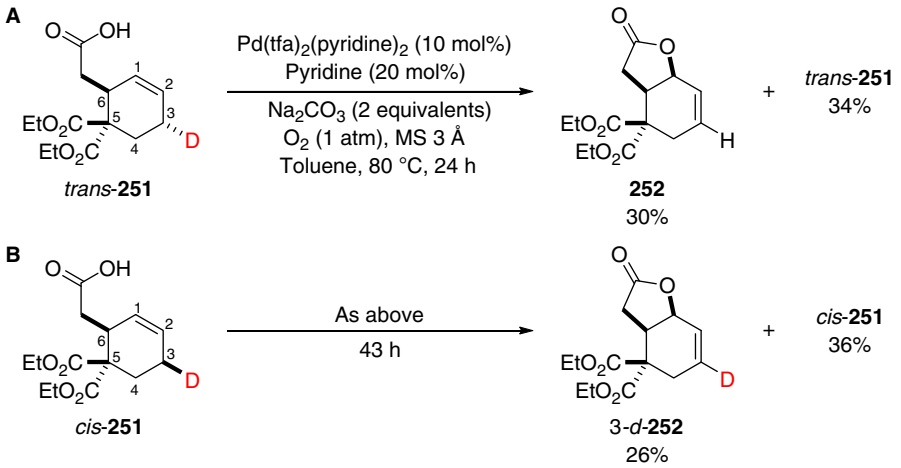
(46)

Stoltz and coworkers also explored the stereochemical course of an intramolecular alkoxyarylation reaction of unsaturated alcohols.[27c] For these transformations, the stereochemistry of oxypalladation was controlled by the identity of the phosphine ligand: reactions employing monodentate phosphines led to products arising from *syn*-oxypalladation, whereas the use of chelating ligands afforded products attributed to *anti*-oxypalladation.

The same authors probed the stereochemical pathway of a similar oxypalladation reaction using carboxylic acid substrates **251**.[11j] Subjecting *trans*-**251** and *cis*-**251** to the catalytic system provided **252** and *3-d*-**252** as the exclusive product, respectively (Scheme 46). A similar analysis as that described for alkoxylation shown in equation 44 indicates that the carboxylic acid cyclization occurs by an *anti*-oxypalladation pathway. Although the reasons for the change in product distribution between the primary alcohol and carboxylic acid substrates remain unclear, the authors suggest that geometrical constraints, pK_a differences, or the variation in nucleophilicity between an acid and an alcohol all influence the reaction mechanism.



Scheme 45



Scheme 46

The presentation above highlights the dramatic growth in mechanistic understanding of oxypalladation reactions in synthetically useful transformations. Many reactions that were once assumed to proceed by an *anti*-oxypalladation mechanism actually proceed by olefin insertion into the Pd–nucleophile bond. In fact, *syn*-oxypalladation appears to be the favored reaction pathway in the majority of the Wacker-type oxidations. Perhaps the most important lesson provided by the many studies over the past decade is that minor alterations in substrate, catalyst, or reaction conditions can change the stereochemical course of oxypalladation.

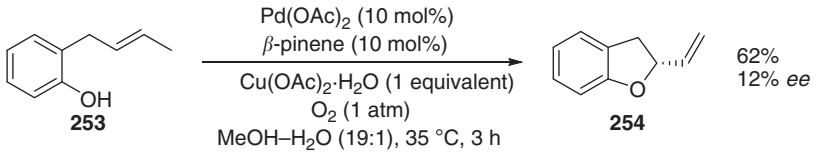
7.17.7 Enantioselective Reactions

Oxypalladation of an alkene often generates a new stereogenic center, and the synthetic utility of the catalytic reactions is enhanced significantly if the stereochemical course of C–O bond formation can be controlled. Enantioselective Pd(II)-catalyzed functionalization of alkenes has experienced considerably less success than many other classes of enantioselective transformations have, despite the extensive history of the Wacker process and related oxidation reactions.[25b,28] The former reactions face several challenges. Phosphine ligands, which have been highly successful in other enantioselective processes, are often incompatible with the oxidants used in these reactions (such as O_2) and their σ-donating ability can attenuate the electrophilicity and/or oxidizing ability of the Pd(II) salts. A mechanistic basis for the difficulty in achieving effective enantioselective catalysis is that oxypalladation reactions are capable of proceeding by two stereochemically different pathways: *syn*- or *anti*-nucleopalladation. Experimental results obtained over the past 40 years, especially in the past decade, demonstrate that the energy barriers associated with these different pathways can be very similar, in some cases similar enough that both pathways operate in parallel. This mechanistic scenario can increase the difficulty of achieving high levels of enantioinduction.

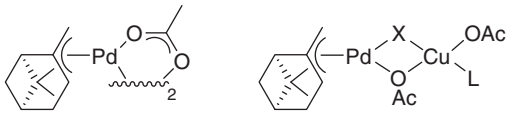
7.17.7.1 Intramolecular Reactions Involving Alkene

7.17.7.1.1 Phenol nucleophiles

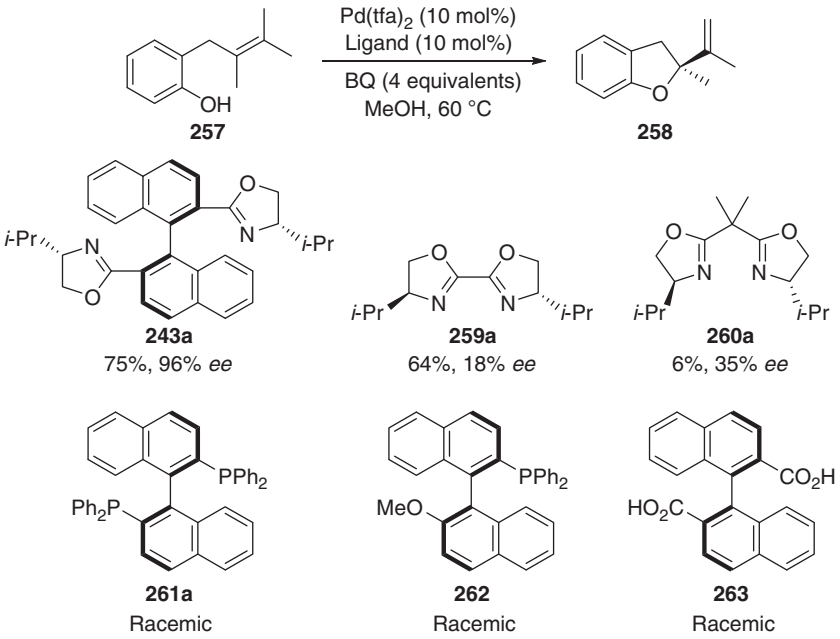
In 1978, Hosokawa, Murahashi, and coworkers reported the first example of an enantioselective Pd-catalyzed alkene functionalization.[29a] This pioneering work described the oxidative C–O bond-forming cyclization of *ortho*-allyl phenols and established phenol cyclization as a benchmark reaction for the identification of new enantioselective Pd(II) catalysts. In this report, a catalyst system consisting of the chiral alkene β-pinene, $Pd(OAc)_2$, and stoichiometric $Cu(OAc)_2{\cdot}H_2O$ provided low levels of asymmetric induction (12% *ee*) in the oxidative cyclization of **253** under an atmospheric pressure of O_2 in MeOH (equation 47). Similar enantioselectivity was obtained when a preformed π-allyl Pd-acetate dimer **255** was used as the precatalyst with catalytic quantities of $Cu(OAc)_2$ and O_2 as the stoichiometric oxidant. Mechanistic studies established that the reaction rate and enantioselectivity were strongly dependent on the concentration of Cu and provided strong evidence for a bimetallic Pd/Cu catalyst. Although the exact nature of the active catalyst could not be unambiguously established, the authors propose a bimetallic acetate-bridged complex consisting of a β-pinene-ligated Pd center **256**.[29b]



(47)

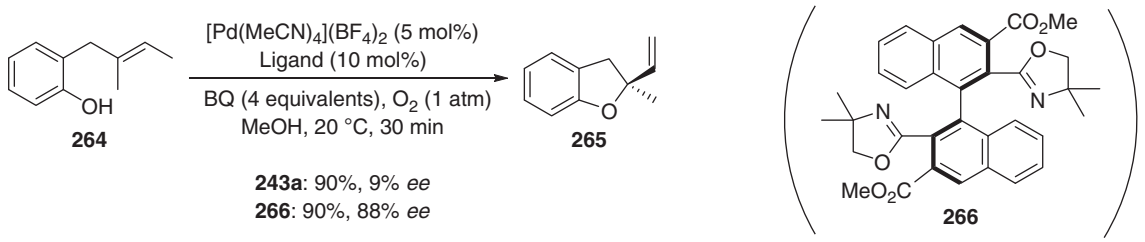


Following the initial work of Hosokawa and Murahashi, nearly 20 years passed before new reports of enantioselective Pd(II)-catalyzed alkene functionalization began to appear. In 1997, Uozumi, Kato, and Hayashi showed that a novel binaphthyl-derived bisoxazoline ligand (**243**, BOXAX) is a highly effective ligand for the enantioselective cyclization of *ortho*-allyl phenol (**Scheme 47**).[29c] The combination of $Pd(tfa)_2$, **243a**, and BQ in MeOH catalyzed the cyclization of tetrasubstituted alkene **257** in 96% *ee* and good yield. Bis(oxazoline) ligands **259** and **260** and other ligands, **261a–263**, derived from the binaphthyl framework provided poor stereocontrol and minimal reactivity. The quantity of the oxidant had a significant impact on the reaction efficiency; decreasing from 4 to 1 equivalent of BQ dramatically reduced the reaction yield (from 72% to 43%), although enantioselectivity was unaffected. Despite the limited substrate scope, this report demonstrated for the first time that excellent enantioselectivity and yields could be achieved for Pd(II)-catalyzed alkene functionalization. Reaction rates in the oxidative phenol cyclization were strongly dependent on the identity of the Pd source. Pd salts bearing less coordinating anionic ligands afforded improved catalysts. For example, $Pd(OAc)_2$ led to a decrease in reactivity and enantioselectivity to 54 and 96% *ee*, respectively, when compared with $Pd(tfa)_2$. Subsequent studies revealed that cationic Pd precursors generated more reactive catalysts and enabled reaction times to be decreased from 1 day to 1 h.[29d] With $[Pd(MeCN)_4](BF_4)_2$, the catalyst loading could be reduced from 10% to 2% without loss of yield or enantioselectivity. Although BOXAX ligand **243a** was highly effective for the enantioselective cyclization of phenol **257**,



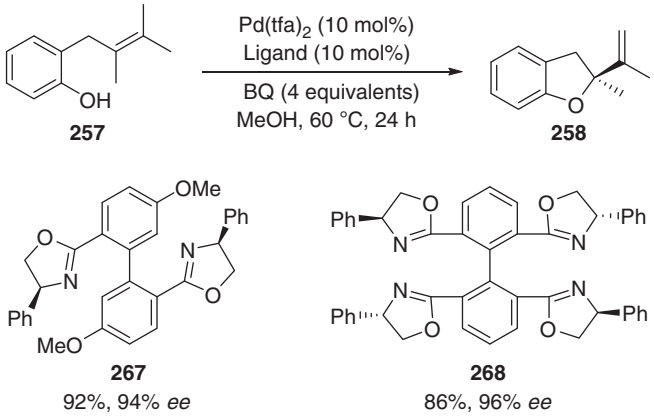
Scheme 47

the scope of successful reactions was limited to oxygen addition onto tetrasubstituted alkenes. For example, cyclization of trisubstituted alkene **264** occurred with only 9% *ee* (equation 48). This limitation was overcome through the use of ligands with achiral oxazoline moieties and steric bulk at the 3,3′-position of the binaphthyl ring. A catalyst generated from $[Pd(MeCN)_4](BF_4)_2$ and the 3,30-COOMe ligand, **266**, promoted the cyclization of **264** to give **265** in 90% yield with 88% *ee*.[29e]



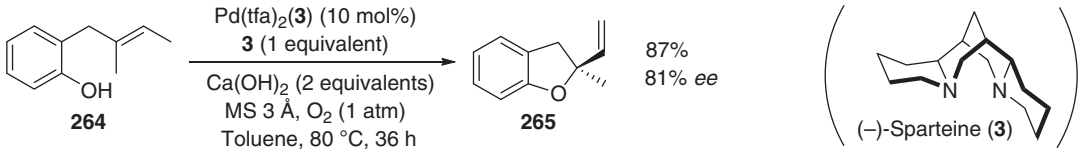
(48)

Zhang and coworkers have developed a unique class of chelation-induced axially chiral ligands that afford high levels of enantioselectivity for *ortho*-allyl phenol cyclization.[29f,g] In solution, these ligands exhibit free rotation around the biaryl bond, but on complexation to Pd(II), only one diastereomeric complex is formed. Use of bisoxazoline ligand **267** and tetraoxazoline ligand **268** under conditions previously optimized for the Pd–BOXAX catalysts enabled the cyclization of tetrasubstituted alkene **257** in >90% *ee* (equation 49). The tetraoxazoline ligand **268** also displays high utility in the asymmetric cyclization of trisubstituted alkene **264**. Identification of an appropriate Pd precursor was vital for the success of this reaction: the use of $Pd(tfa)_2$ and $Pd(OAc)_2$ was optimal, whereas $PdCl_2$, $PdCl_2(MeCN)_2$, and $[Pd(MeCN)_4](BF_4)_2$ resulted in decreased yields and stereoselectivity.



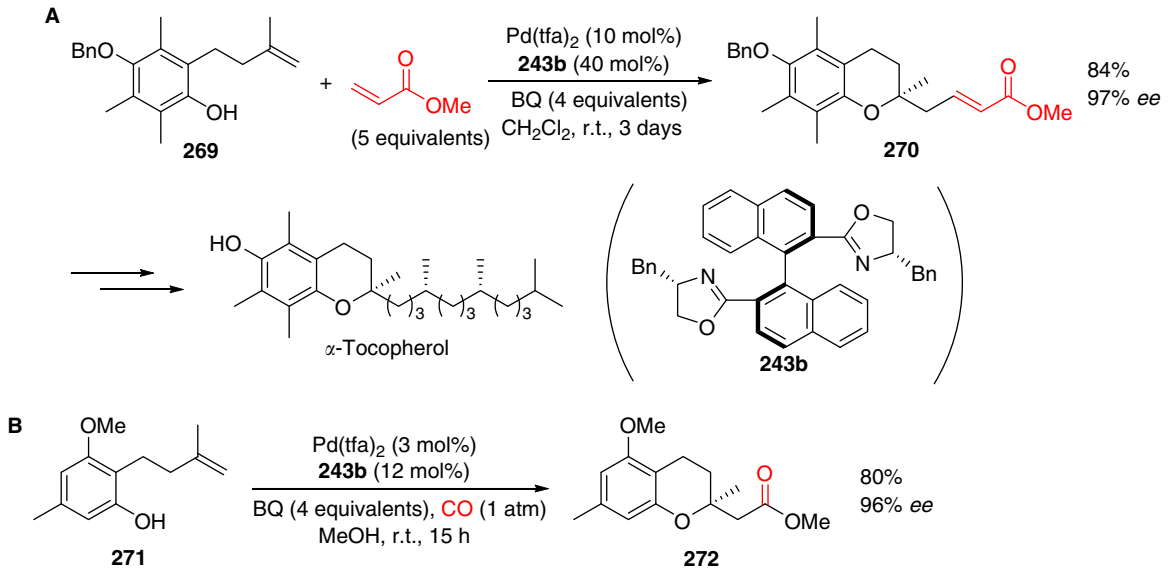
(49)

Stoltz and coworkers demonstrated the first example of a successful enantioselective aerobic Pd-catalyzed oxidative cyclization.[11j,20f] For the cyclization of phenol **264**, various Pd sources in conjunction with (–)-sparteine **3** were analyzed under 1 atm of molecular oxygen. The combination of a preformed $Pd(tfa)_2$(**3**) complex and excess **3** provided good yields and enantioselectivity. Chloride and bromide anionic ligands resulted in poor stereocontrol and $Pd(OAc)_2$ displayed low reactivity. The best results were obtained with MS 3 Å in the presence of 2 equivalents of $Ca(OH)_2$ (equation 50). Bisoxazolines, chiral bidentate amines, bisphosphines, and other common chiral ligands were ineffective for the oxidative cyclization of phenol **264** under aerobic conditions. The poor results obtained with these ligands highlight the difficulties associated with the discovery of catalysts for enantioselective aerobic alkene functionalization and the unique nature of (–)-sparteine as a chiral ligand.



(50)

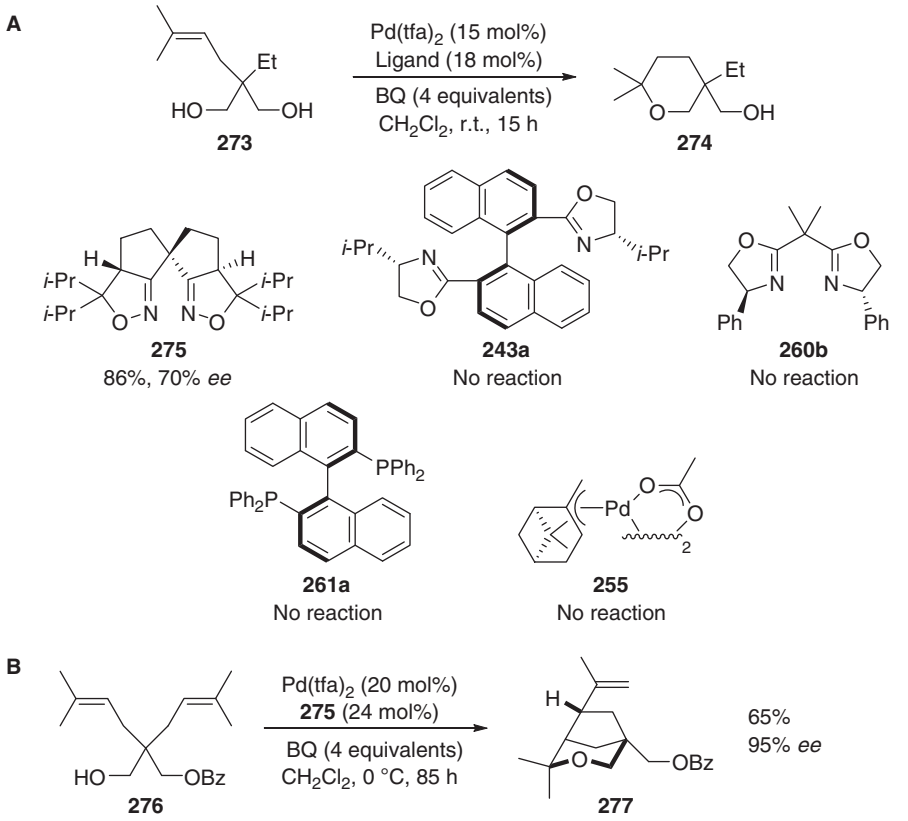
The Pd–alkyl intermediate generated by oxypalladation of *ortho*-allyl phenols can be efficiently trapped by methyl acrylate or CO. Tietze and coworkers designed phenol substrates that were unable to undergo β-hydride elimination and studied their cyclization in the presence of methyl acrylate. Using the $Pd(tfa)_2$/**243b**/BQ catalytic system, phenol **269** afforded dihydrobenzopyran **270** in 97% *ee* and 84% yield after 3 days (Scheme 48A).[29h] This transformation was applied to the asymmetric synthesis of α-tocopherol, a member of the vitamin E class of molecules. Similar phenol substrate was also cyclized in the presence of CO and MeOH, resulting in carbonylation of the Pd–alkyl intermediate (Scheme 48B).[20i] In agreement with the case for the alkoxy alkylation reaction, oxycarbonylation of phenol **271** provided the corresponding six-membered ring with excellent stereocontrol (>95% *ee*). These two transformations represent rare examples of enantioselective Pd(II)-catalyzed alkene functionalization that do not form five-membered rings.



Scheme 48

7.17.7.1.2 Alcohol nucleophiles

The use of oxygen nucleophiles other than phenol for an enantioselective Pd(II)-catalyzed alkene functionalization was first reported in 2001 by Sasai and coworkers.[30a] Enantioselective desymmetrization of primary diol **273** with $Pd(tfa)_2$ and SPRIX ligand **275** afforded cyclic ether product **274** in 70% *ee* (Scheme 49A). The reaction proceeds via an *endo* cyclization pathway to afford the six-membered heterocycle. This reaction did not proceed with BOXAX **243a**, bisoxazoline **260b**, BINAP **261**, or a preformed π-allyl Pd-acetate dimer **255**. The identity of the anionic ligand and solvent were both vital to the success of the reaction: $Pd(OAc)_2$, $[Pd(MeCN)_4](BF_4)_2$, $PdCl_2$, or $PdCl_2$/AgOTF instead of $Pd(tfa)_2$ resulted in lower yields. Low enantioselectivity, ranging from 27% to 39%, was observed if MeCN, MeOH, THF, or toluene was used instead of CH_2Cl_2. This demonstration marks an important departure from phenolic substrates, but high catalyst loading (15% $Pd(tfa)_2$ and 18% **275**) and modest stereoselectivity leave room for future improvement. Four equivalents of BQ were also required; a Cu-$(OAc)_2/O_2$ oxidant system

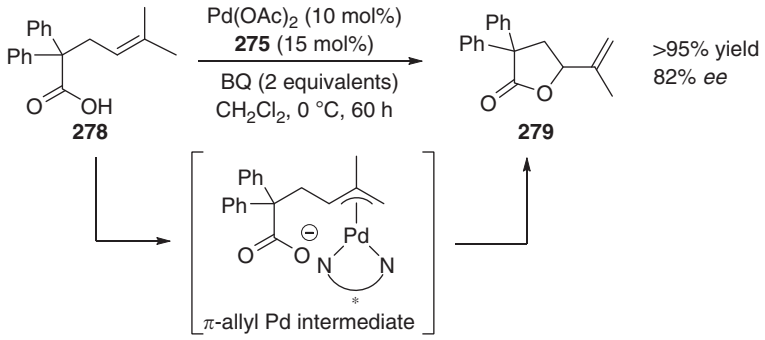


Scheme 49

provided a decrease in reactivity and enantioselectivity. Other spirocyclic chiral ligands related to SPRIX also proved to promote this reaction enantioselectively.[30b] The $Pd(tfa)_2$/SPRIX catalyst system was applied to an alkoxy alkylative desymmetrization reaction of **276** initiated by oxypalladation of an alkene, followed by trapping of the Pd–alkyl intermediate by a pendant alkene. This reaction gave high levels of enantioselectivity of up to 95% *ee*, although the high catalyst loading was necessary.

7.17.7.1.3 Carboxylic acid nucleophiles

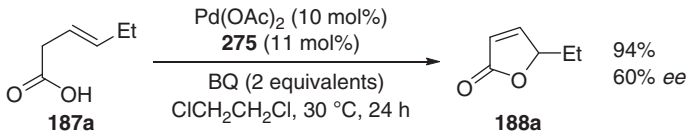
Sasai and coworkers successfully developed a Pd-catalyzed enantioselective synthesis of γ-alkenyl-γ-lactones **279** through an oxidative cyclization of 4-alkenoic acids **278** by utilizing SPRIX **275** (Scheme 50).[31a] Other chiral ligands were noticeably ineffective under identical conditions. A background reaction, without any chiral ligands added, was negligible even after 24 h, resulting in only a trace amount of **279**. From mechanistic studies including deuterium-labeling experiments, it is inferred that the present enantioselective cyclization proceeds through a π-allyl Pd species which is generated by the allylic C–H bond activation.



Scheme 50

The $Pd(OAc)_2$/SPRIX/BQ system can also catalyze the unfavorable 5-*endo*-*trig*-type cyclization of 3-alkenoic acid **187** requiring a stoichiometric use of the Pd salt for its promotion (see equation 35). The reaction of 3-hexenoic acid **187a** with SPRIX **275** led to

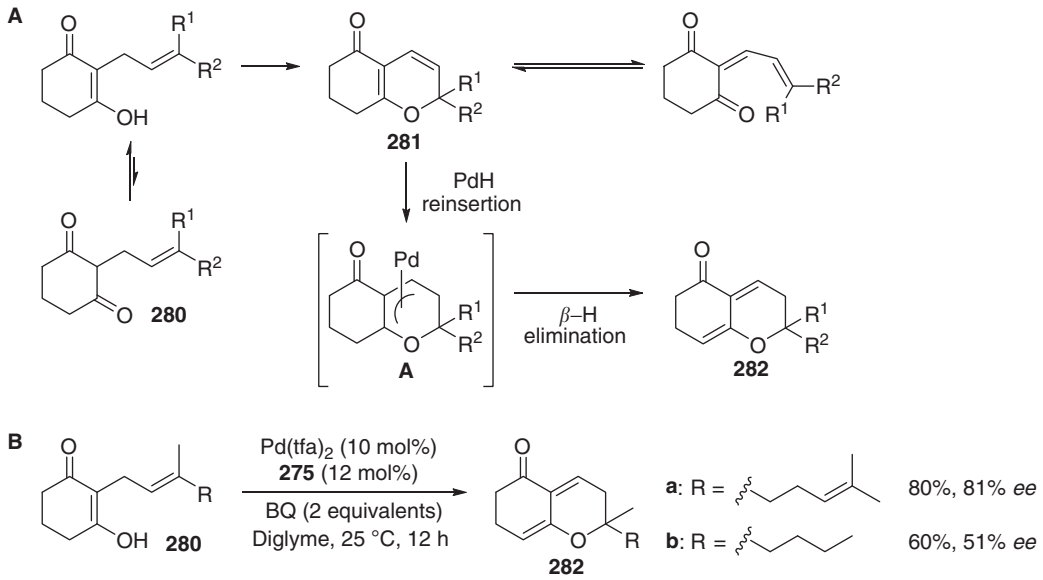
a quantitative formation of 5-ethylfuran-2(5*H*)-one **188a** with 60% *ee* (equation 51).[31b] No reaction was observed with other chiral ligands such as (–)-sparteine **3**, suggesting the unique property of SPRIX.



(51)

7.17.7.1.4 Enol nucleophiles

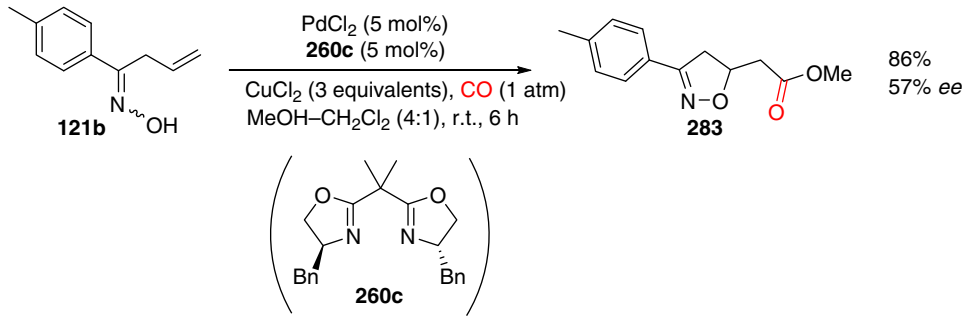
The use of *β*-dicarbonyl nucleophiles as the substrate in enantioselective cyclization was recently reported by Sasai and co-workers.[32a] Such nucleophiles, which can readily form an enol structure, cyclized in the presence of a $Pd(tfa)_2$/SPRIX **275** catalyst to furnish 6-*endo-trig*-products. In oxidative cyclization of **280**, it was suspected that initial products, 7,8-dihydro-2*H*-chromen-5(6H)-ones **281**, were obtained as a racemate due to an electrocyclic ring-opening/closing sequence (**Scheme 51A**).[32b] The authors conceived that isomerization of **281** to 6,7-dihydro-2*H*-chromen-5(3*H*)-ones **282** through a *π*-allyl Pd intermediate **A** would suppress such a problematic racemization. Indeed, the SPRIX ligand **275** appears to uniquely and successfully promote this reaction using 2-alkenylcyclohexane-1,3-dione substrates **280**. Interestingly, substrates containing a pendant alkene dramatically improved the reaction performance. For example, enol **280a** afforded the bicyclic product in 80% yield and 81% *ee*, whereas the corresponding Bu derivative **280b** cyclized in 60% yield and 51% *ee* (**Scheme 51B**).



Scheme 51

7.17.7.1.5 Oxime nucleophiles

Optically active Δ^2-isoxazoline **283** can be prepared by the Pd(II)-catalyzed carbonylative cyclization of *β*,*γ*-unsaturated oxime **121b**. The use of chiral bisoxazoline ligand **260c** has been shown to enhance the enantioselectivity and catalytic activity, whereas chiral phosphine ligands such as BINAP **261** do not promote this cyclization (equation 52).[33]



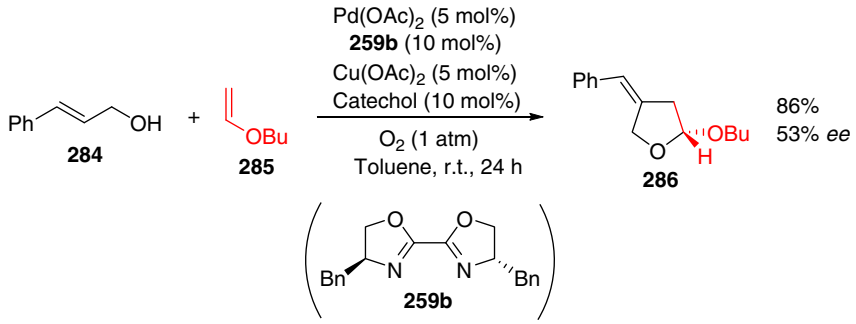
(52)

7.17.7.2 Intermolecular Reactions Involving Alkene

7.17.7.2.1 Alcohol nucleophiles

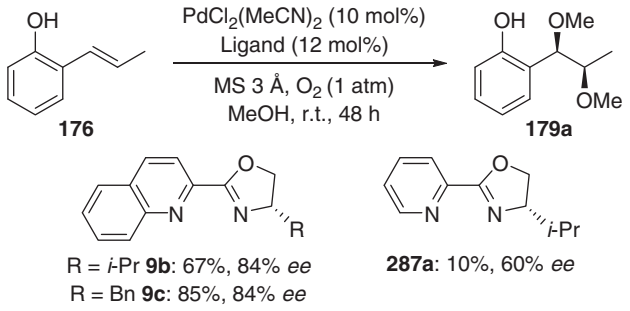
Very few examples of enantioselective intermolecular nucleopalladation reactions exist, and in all cases, carefully designed substrates that rapidly trap the Pd-alkyl intermediate are required.

Hosokawa and coworkers have developed an enantioselective coupling of allylic alcohols and vinyl ethers that proceeds via initial asymmetric oxypalladation, followed by intramolecular trapping of Pd–alkyl intermediate by a pendant alkene (equation 53).[34a] Treatment of cinnamyl alcohol (**284**) and butyl vinyl ether (**285**) with a combination of $Pd(OAc)_2$, bisoxazoline **259b**, $Cu(OAc)_2$, catechol, and molecular oxygen as the terminal oxidant resulted in a formation of benzylidenetetrahydrofuran **286** in 86% yield with 53% *ee*. Removing catechol from the reaction conditions decreased enantioselectivity, an observation attributed to competitive binding of the chiral ligand to copper in the absence of catechol. Furthermore, $Cu(OAc)_2$/catechol was required for catalytic efficiency, but their removal did not affect enantioselectivity. On the basis of these results, the authors proposed the binuclear catalyst consisting of a catechol-ligated copper center and bisoxazoline-ligated Pd.



(53)

Zhang and Sigman have recently developed an enantioselective aerobic oxidative difunctionalization of *ortho*-vinyl phenols **176** (*see* Chapter 7.16).[34b] Mechanistic studies support a reaction pathway involving oxypalladation followed by formation of an *ortho*-quinone methide intermediate shown in Scheme 30B.[34c] Various bidentate nitrogen ligands were screened in conjunction with $PdCl_2(MeCN)_2$ in MeOH using molecular oxygen as the stoichiometric oxidant. Although (−)-sparteine **3** and bisoxazoline ligands (**243**, **259**, and **260**) gave low yields and trace levels of stereoinduction, C_1-symmetrical quinoline oxazoline ligands **9b** and **9c** provided good reactivity and enantioselectivity (equation 54).[34d,e] The corresponding pyridine oxazoline **287a**–Pd complex exhibited poor catalytic activity.



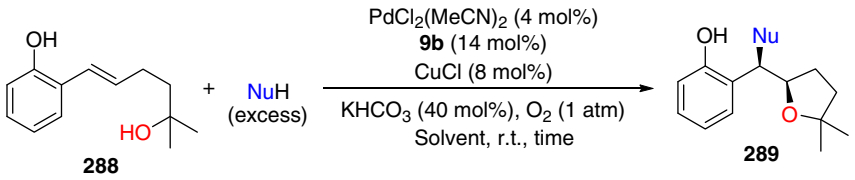
(54)

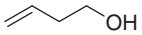
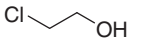
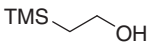
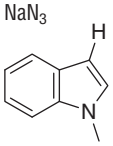
Alkene difunctionalization of *ortho*-vinyl phenols **288** can also be initiated by an intramolecular oxypalladation using quinoline oxazoline ligands **9b** to give products **289**. The proposed *ortho*-quinone methide intermediate can then be trapped by a wide variety of external nucleophiles including alcohols, water, sodium azide, indoles, and pyrroles (Table 10). These reactions proceed with excellent enantioselectivity and moderate to excellent diastereoselectivity. This method was applied to the synthesis of a small library of 3-substituted indoles whose biological activity against a luminal type breast cancer cell line was evaluated.

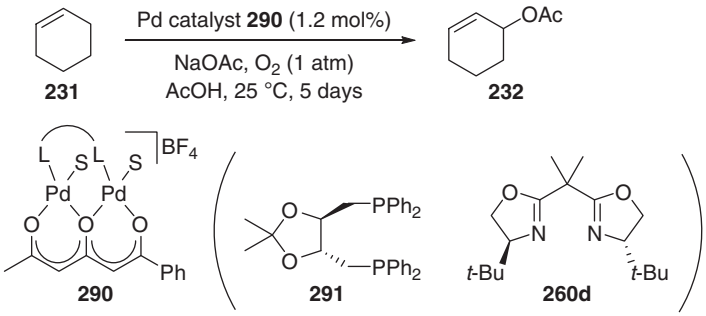
7.17.7.2.2 Carboxylic acid nucleophiles

Henry and coworkers have also shown that bimetallic Pd(II) complexes **290** containing a triketone ligand and a bridging phosphine **291** or **260d** ligand oxidize cyclic olefins such as cyclohexene (**231**) to give the corresponding allylic acetates such as **232** in high yields with moderate enantioselectivity (equation 55).[35a]

Table 10 Pd-catalyzed enantioselective difunctionalization of *o*-vinylphenols



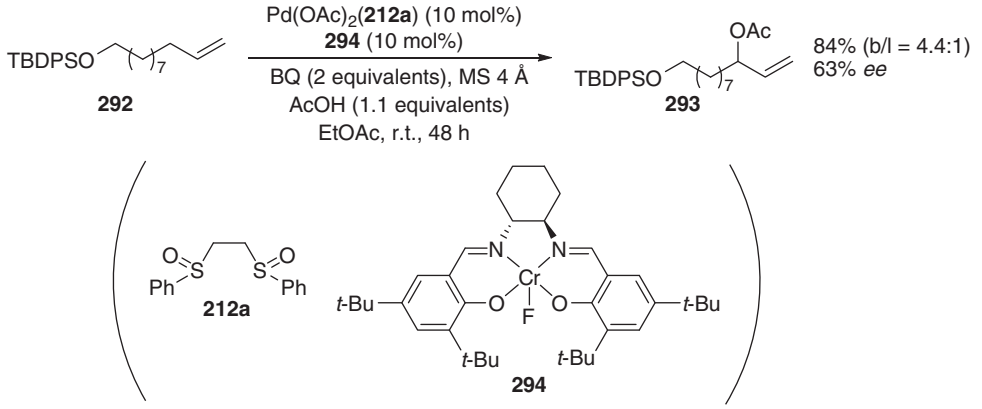
Entry	*NuH*	*Solvent*	*Time (h)*	*Yield (%)*	ee *(%)*
1	MeOH	Toluene-THF (1:1)	3	72 (10:1 *dr*)	96
2		Toluene	12	57 (4:1*dr*)	92
3		Toluene	12	60 (5:1 *dr*)	88
4		Toluene	16	64 (6:1 *dr*)	98
5	H_2O	*t*-AmylOH	24	63 (5:1 *dr*)	96
6	NaN_3	*t*-AmylOH	48	51 (1:4:1 *dr*)	84
7		Toluene-THF (4:1)	3	81 (>20:1 *dr*)	94
8		Toluene-THF (4:1)	4	53 (>20:1 *dr*)	85



(55)

290a (L⌒L = **291**): 95% (based on O_2 uptake), 52% *ee*
290b (L⌒L = **260d**): 90% (based on O_2 uptake), 55% *ee*

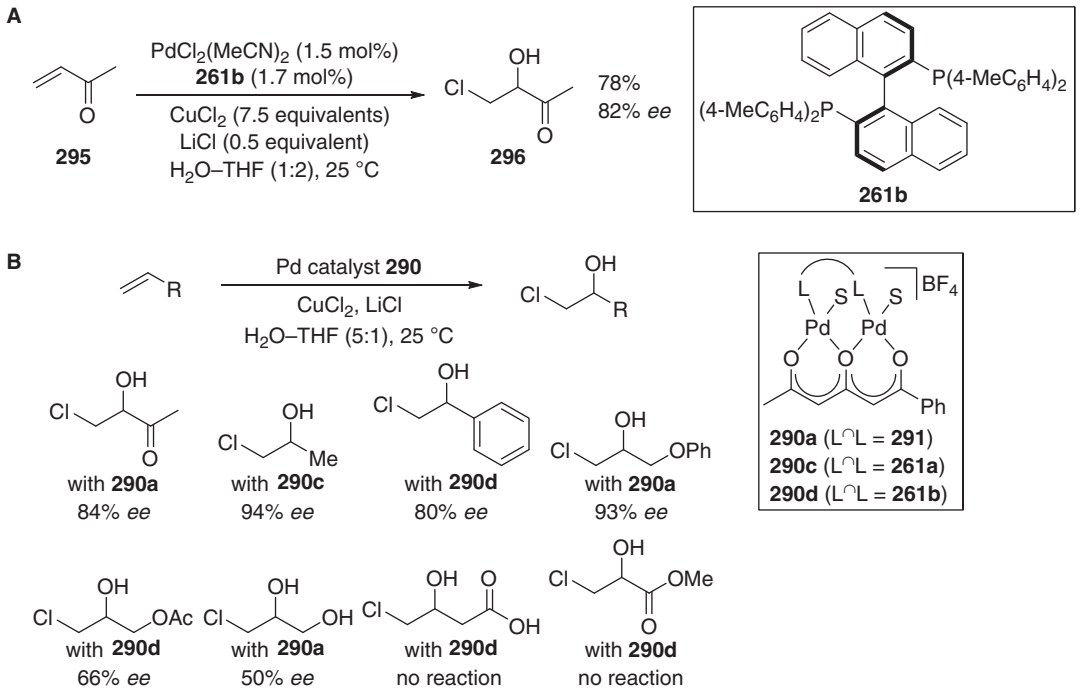
White and coworker applied their allylic C–H oxidation reaction utilizing bis-sulfoxide ligand **212a** (see section 7.17.5.4) to the enantioselective catalysis.[35b] In their approach, a chiral Lewis acid is used, which selectively interacts with an organopalladium intermediate to accelerate and induce asymmetry in the C–O bond-forming step. Significantly, by using this strategy, they obtained allyl acetate product **293** with 63% *ee* in the allylic C–H oxidation of terminal olefin **292** (equation 56). This system represents the first example of asymmetric induction from an organometallic intermediate that is affected by a chiral Lewis acid as well as a rare example of catalytic enantioselective C–H activation by palladium. They envisioned three mechanistic scenarios that were likely to effect the observed asymmetric induction during the C–O bond-forming step: **I**: coordination of [(salen)Cr^{III}F] **294** to BQ to promote and control the facial selectivity in the reductive elimination of acetate from a [(π-allyl)Pd(BQ)OAc] intermediate, **II**: delivery of an acetate group to a [(π-allyl)Pd(BQ)L] intermediate from [(salen)Cr^{III}OAc], or **III**: activation of a [(π-allyl)Pd(BQ)] intermediate by **294** with a concurrent delivery of acetate from [(salen)Cr^{III}OAc]. Mechanistic studies imply that although a dual activation mechanism (scenario **III**) cannot be ruled out, **294**·BQ-promoted functionalization (scenario **I**) is most likely to take place.



(56)

7.17.7.2.3 Water nucleophiles

Enantioselective alkene functionalization reactions that use water as the nucleophile represent an attractive route to enantioenriched alcohols. Extensive investigation of the Wacker reaction has revealed that the reaction can either provide traditional ketone products or undergo hydroxychlorination to generate chlorohydrin products, depending on the reaction conditions. Henry and coworkers evaluated the ability of chiral ligands to control the stereochemistry of this process. The use of chiral monodentate amines as chiral analogs to pyridine resulted in low enantioselectivity (~10% *ee*); however, phosphine ligands provided improved stereocontrol. For example, the reaction of methyl vinyl ketone (**295**) with a $PdCl_2(MeCN)_2$/tol-BINAP **261b** catalyst in an H_2O–THF (1:2) solvent system in the presence of $CuCl_2$ and LiCl yielded chlorohydrin product **296** in 82% *ee* and 78% yield (Scheme 52A).[36a] They also investigated the use of chiral bimetallic catalysts **290** having bisphosphine ligands DIOP **291**, BINAP **261a**, and tol-BINAP **261b** in the enantioselective chlorohydrin reaction. Unfunctionalized alkenes, methyl acrylate, allyl ethers, and styrenes reacted in the presence of bimetallic catalysts **290** with excellent stereocontrol, whereas alkenes with alcohols, carboxylic acids, and esters were not effective substrates (Scheme 52B).[36b]

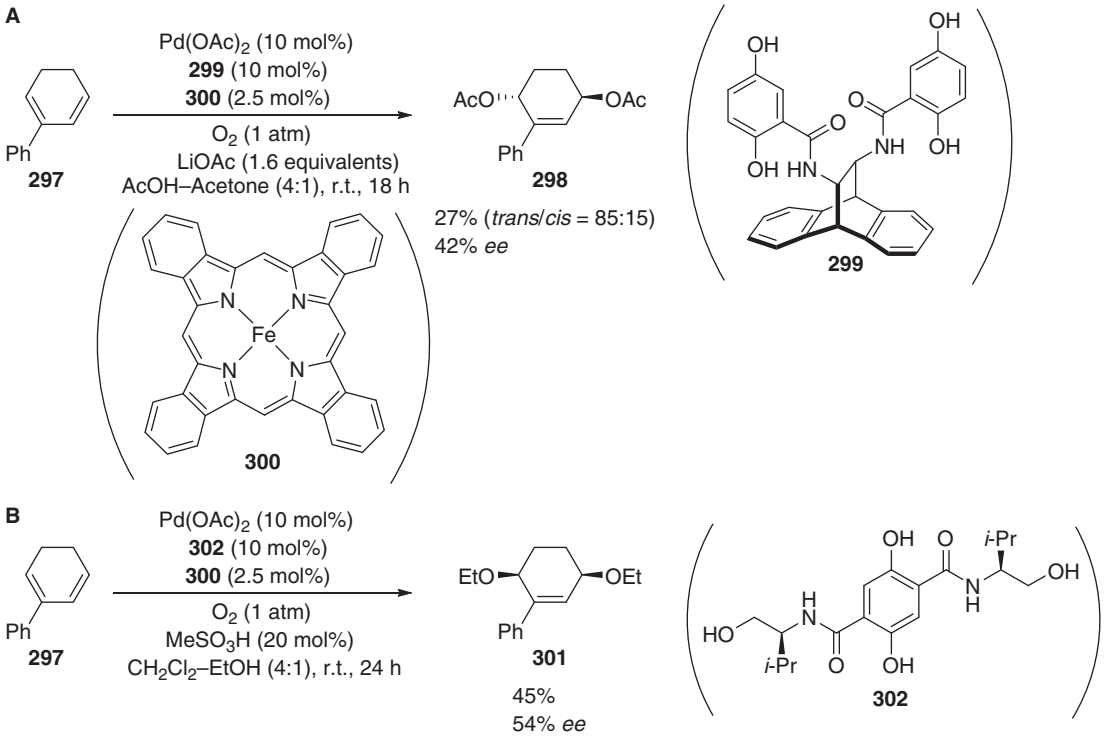


Scheme 52

7.17.7.3 Reactions Involving Diene

Bäckvall and coworkers performed the Pd(II)-catalyzed asymmetric 1,4-diacetoxylation of 1,3-dienes using a series of chiral ligands having a 9,10-dihydro-9,10-ethanoanthracene structure in the presence of Fe–phthalocyanine complex **300**. Application of

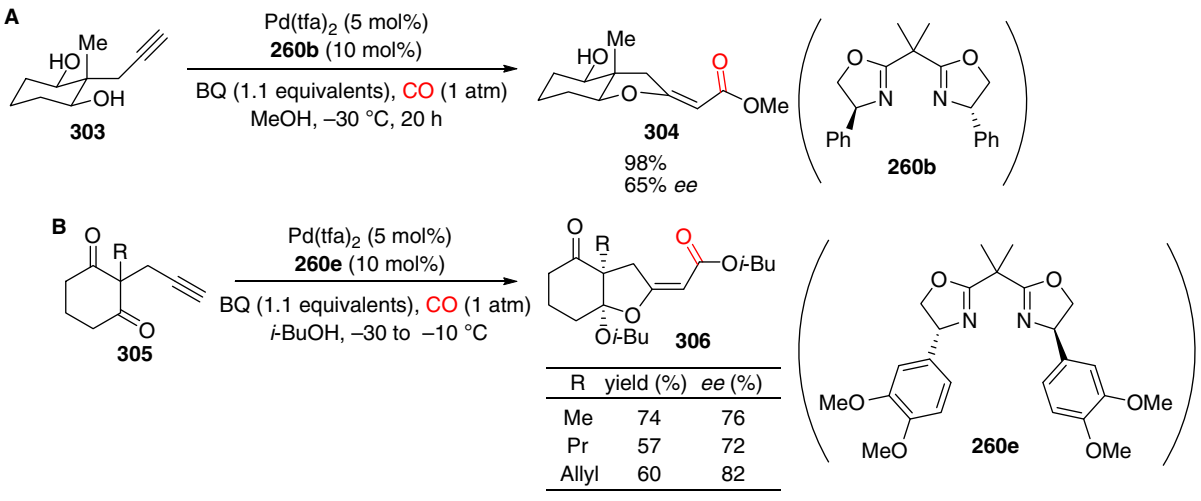
ligand **299** to 2-phenyl-1,3-cyclohexadiene **297** afforded the diacetoxylation product **298** with high regio- and diastereoselectivity and 42% *ee* (Scheme 53A).[37a] The authors also investigated the Pd(II)-catalyzed enantioselective 1,4-dialkoxylation of **297** using chiral C_2-symmetric 2,5-bisamide hydroquinone ligand **302** to furnish 2-phenyl-1,4-diethoxycyclohexene **301** with moderate yields and enantioselectivity (Scheme 53B).[37b]



Scheme 53

7.17.7.4 Reactions Involving Alkyne

An asymmetric variant of the oxidative cyclization–carbonylation reaction developed by Kato and coworkers (see equation 32) has been described by the same group. The desymmetrization reaction of cyclic alkynediol **303** with a Pd(II) catalyst and chiral bisoxazoline **260b** in methanol under a CO atmosphere affords bicyclic alkoxyacrylate **304** in good yield with moderate enantioselectivity (Scheme 54A).[38a] Other substrates and chiral ligands were also studied. Oxidative cyclization–carbonylation was



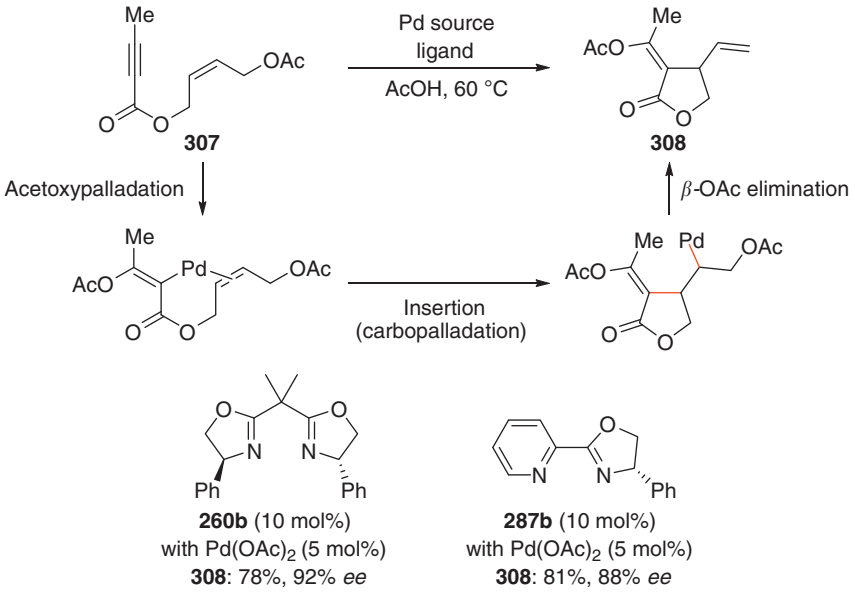
R	yield (%)	*ee* (%)
Me	74	76
Pr	57	72
Allyl	60	82

Scheme 54

successfully expanded to 2-alkyl-2-propargylcyclohexane-1,3-dione substrates **305**. The reaction of **305** with $Pd(tfa)_2$/**260e** catalyst afforded bicyclic-β-alkoxyacrylates **306** in moderate yields with high enantioselectivity (Scheme 54B).[38b] The bulkiness of the alcohols used in the reaction affected the enantioselectivity and yields of **306**, which suggests that the alcohol is incorporated into the substrate as a hemiacetal before cyclization.

7.17.7.5 Reactions Involving Enyne

Acetoxypalladation at an alkyne provides a convenient method for the formation of Pd–C bonds that are poised for carbopalladation of a pendant alkene. This approach has been applied to the synthesis of enantioenriched γ-lactones. The cyclization of enynes such as **307** is proposed to proceed through initial acetoxypalladation of the alkyne, subsequent intramolecular alkene insertion generating a new stereogenic center, and final β-acetoxy elimination to give γ-lactone **308** (Scheme 55). After screening chiral bidentate nitrogenous ligands in conjunction with $Pd(OAc)_2$, Zhang and Lu found that bisoxazoline **260b** and pyridine oxazoline **287b** provided high levels of enantioselectivity.[39]



Scheme 55

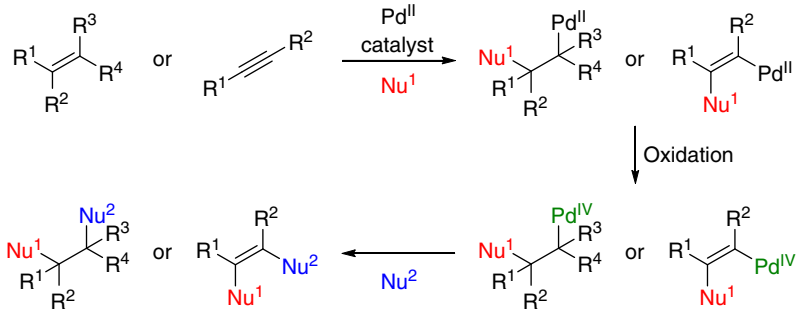
7.17.8 Reactions through Pd(IV) Intermediate

The Pd-catalyzed reactions, not only the Wacker-type reaction but also other reactions such as cross couplings, are extensively employed as a powerful tool for C–Y (Y = C, N, O, S, etc.) bond formations in organic synthesis. Such processes generally proceed through a Pd(0)/Pd(II) catalytic cycle, which rests on the smooth interconversion between Pd(0) and Pd(II) species. Recently, a catalytic reaction involving Pd(IV) intermediates that are generated *in situ* from a Pd(II) precursor by the action of a strong oxidant has been attracting widespread interest in synthetic chemistry (*see* Chapter 7.29).[40] The Pd(II)/Pd(IV) catalysis can realize unprecedented transformations complementary to the conventional Pd(0)/Pd(II) catalysis because of the unique reactivity of Pd (IV) complexes.

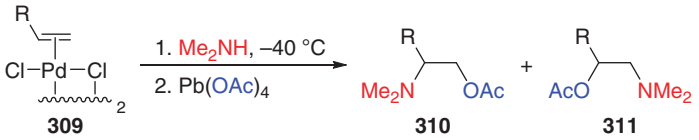
7.17.8.1 Oxidative Difunctionalization of Alkenes

Vicinal oxidative difunctionalizations of alkenes, such as Sharpless dihydroxylation and aminohydroxylation, are efficient and powerful transformations in organic synthesis. The comprehensive scope of the Pd-catalyzed reaction would provide great opportunity for difunctionalization of such unsaturated bonds. Generally, a Pd(II)/Pd(IV)-catalyzed difunctionalization of unsaturated bonds comprise two key steps: first, carbon–carbon multiple bonds coordinate to Pd(II) and accept the nucleophilic attack to form an alkyl/alkenyl Pd(II) intermediate with incorporation of the first functional group. After oxidation of Pd(II) to Pd (IV), the second functional group is installed by the elaboration of the resulting alkyl/alkenyl Pd(IV) species (Scheme 56).

An early study of Bäckvall demonstrated stoichiometric aminoacetoxylation using lead tetraacetate as stoichiometric oxidant.[41a] Olefin complexes **309** were reacted with Me_2NH at –40 °C followed by oxidation with $Pb(OAc)_4$ to give β-amino alcohol products **310** and **311** (equation 57). Reactions of *cis*- and *trans*-2-butene complexes were lower yielding but gave the respective *erythro*- and *threo*-3-dimethylamino-2-butanol with complete stereoselectivity. Although the author argued that a Pd(II) to Pb(IV) transmetalation is most likely involved, he also proposed an alternative Pd(IV) mechanism.



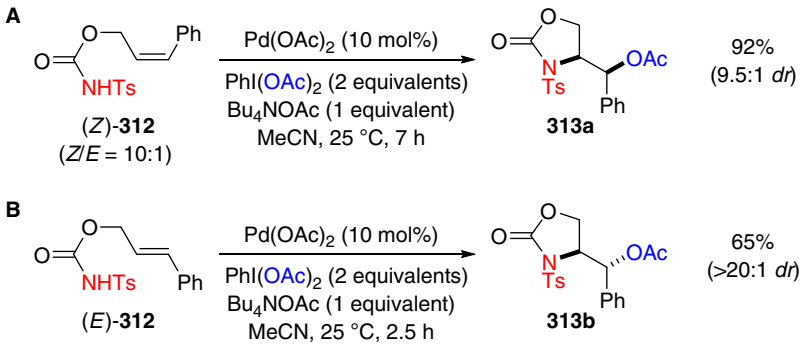
Scheme 56



R	310:311	Yield (%)
Et	7.3:1	84
Bu	4.9:1	77
n-C_8H_{17}	4.8:1	69

(57)

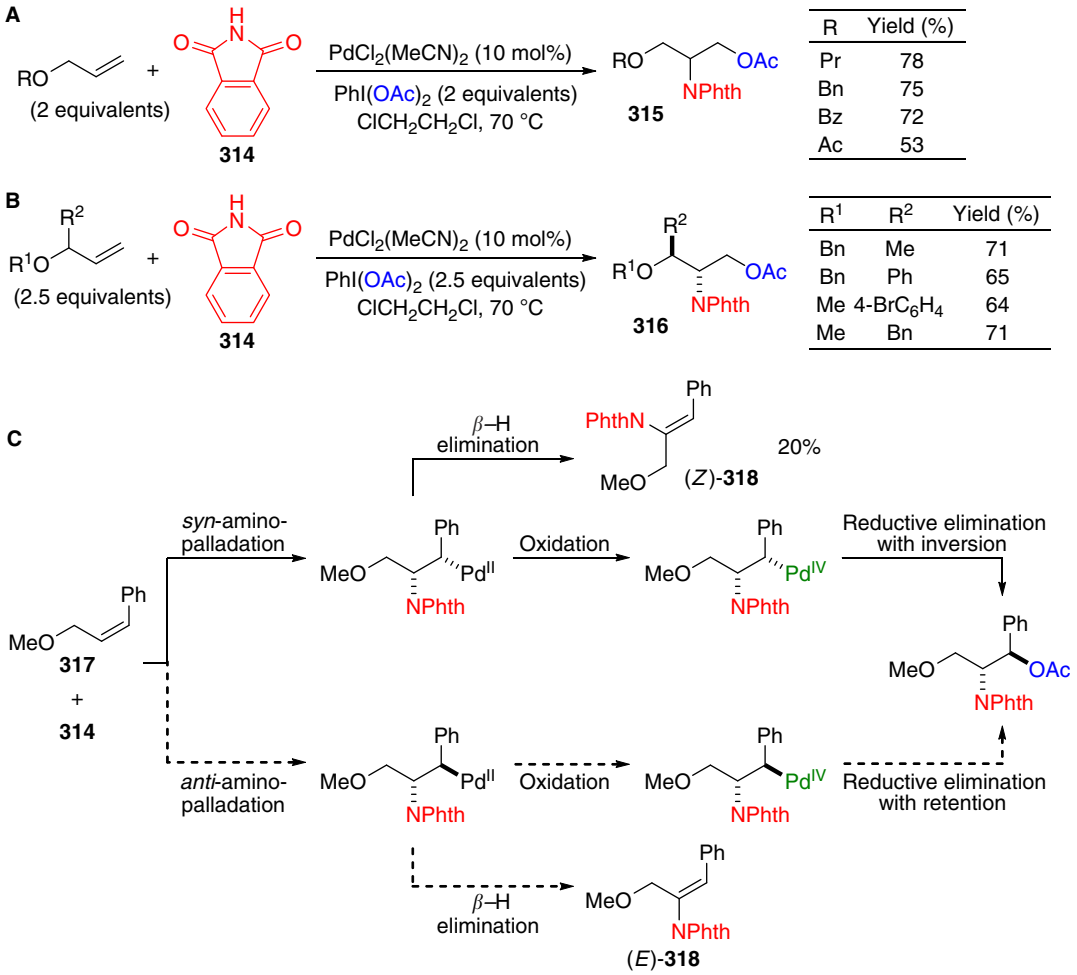
Sorensen and coworkers first developed the Pd(II)/Pd(IV)-catalyzed ring-forming aminoacetoxylation of unsaturated tosylamines and *N*-tosyl carbamates. $PhI(OAc)_2$, a common oxidant for the production of Pd(IV) species, was employed, thereby suggesting a potential Pd(II)/Pd(IV) catalytic cycle.[41b] To gain insight into the mechanism of the aminoacetoxylation process as well as to explore the diastereoselectivity of the reaction, they carried out the reaction using *N*-tosyl carbamates, (*Z*)-**312** and (*E*)-**312** (Scheme 57). On subjection of the predominantly *cis* carbamate (*Z*)-**312** to reaction conditions (10 mol % $Pd(OAc)_2$ and 1 equivalent of Bu_4NOAc in MeCN), an aminoacetoxylation afforded 4-acetoxyphenyl *N*-tosyl 2-oxazolidinone **313a** in 92% yield. This reaction proceeded with a high level of stereocontrol: from 10:1 *Z*:*E* mixture of (*Z*)-**312**, 9.5:1 *dr* was observed for **313a**. The reaction of *trans* carbamate (*E*)-**315** under identical conditions yielded **316b** in a highly diastereoselective fashion (>20:1 *dr*). From these experiments, it appears that the aminoacetoxylation process is a stereoselective *anti* alkene difunctionalization, and thus a useful alternative to related *syn*-selective, metal-catalyzed alkene aminohydroxylation processes. This reaction is proposed to proceed through a catalytic cycle involving *anti*-aminopalladation of the alkene, oxidation of the resulting alkyl–Pd(II) intermediate by $PhI(OAc)_2$ to an alkyl–Pd(IV) intermediate, and finally C–O bond-forming reductive elimination from the Pd(IV) center with retention of the configuration. However, another pathway involving *syn*-aminopalladation followed by reductive elimination to form a C–O bond with inversion of the configuration could not be excluded.



Scheme 57

Intermolecular aminoacetoxylation of alkenes with phthalimide (**314**) as nitrogen nucleophile was first achieved by Stahl and coworkers.[41c] This transformation proceeds highly regioselectively (Scheme 58A). Allyl ethers having an additional substituent in the allylic position give rise to only the *anti* diastereomer (Scheme 58B). Only two proposed mechanistic pathways could explain the stereochemical outcome of the products: (1) *anti*-aminopalladation and direct reductive elimination with retention of stereochemistry or (2) *syn*-aminopalladation and a C–O reductive elimination from Pd(IV) with inversion of stereochemistry via S_N2 displacement. To distinguish between these two pathways, (*Z*)-cinnamyl methyl ether (**317**) was subjected to the conditions which favor β-H elimination for the formed alkyl–Pd(II) intermediate. As the resulting (*Z*)-**318** provided evidence for *syn*-aminopalladation, the authors thus favored the latter mechanism (Scheme 58C).

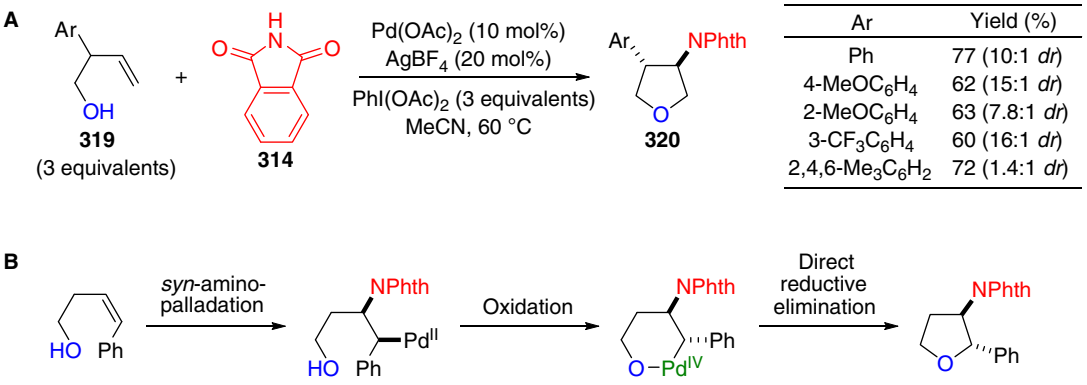
The same strategy was also employed by Sanford and coworkers for the diastereoselective construction of substituted tetrahydrofurans **320** through aminoalkoxylation of homoallyl alcohols **319** (Scheme 59A).[41d] Primary mechanistic investigation also implied a *syn*-aminopalladation process, which was again supported by performing the reaction under conditions that favor



R	Yield (%)
Pr	78
Bn	75
Bz	72
Ac	53

R^1	R^2	Yield (%)
Bn	Me	71
Bn	Ph	65
Me	4-BrC_6H_4	64
Me	Bn	71

Scheme 58



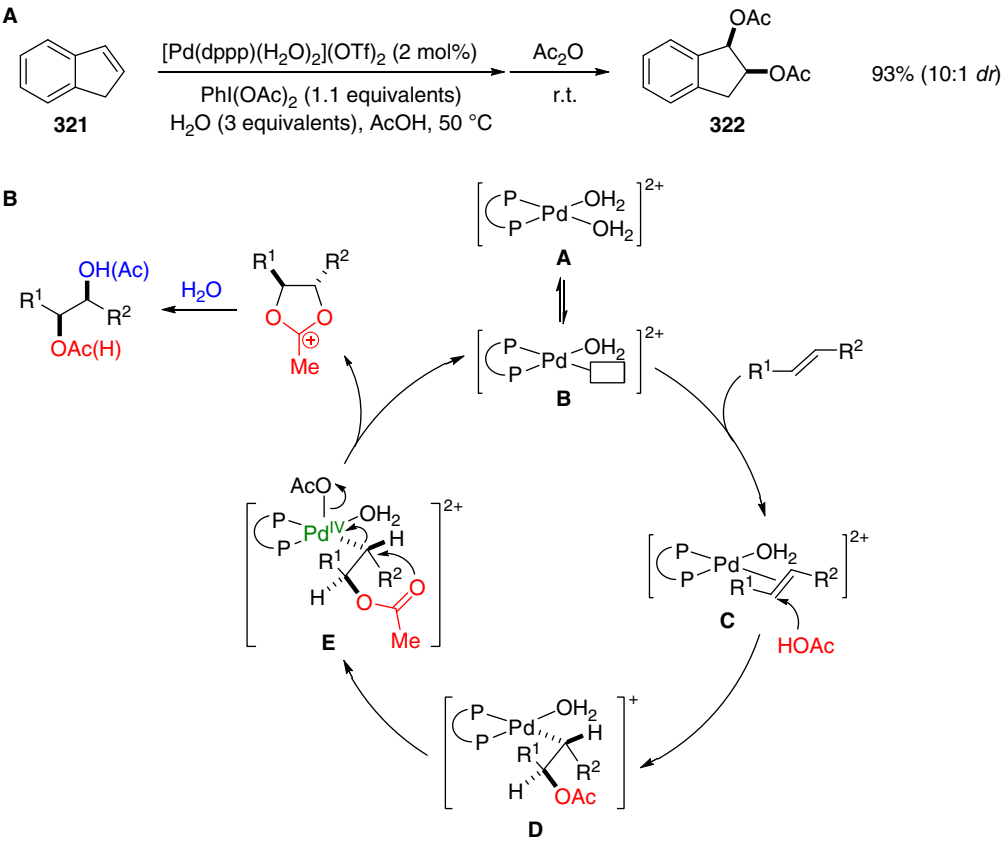
Ar	Yield (%)
Ph	77 (10:1 *dr*)
4-$MeOC_6H_4$	62 (15:1 *dr*)
2-$MeOC_6H_4$	63 (7.8:1 *dr*)
3-$CF_3C_6H_4$	60 (16:1 *dr*)
2,4,6-$Me_3C_6H_2$	72 (1.4:1 *dr*)

Scheme 59

β-hydride elimination. These experiments were similar to those carried out by Stahl and delivered identical results (Scheme 59B). Therefore, the C–O bond formation step would operate through a direct reductive elimination pathway in contrast to an S_N2-like attack of acetate in Stahl's studies shown in Scheme 58C. This difference may be attributed to either the intramolecularity of the ether-forming reductive elimination or the higher nucleophilicity of the alkoxide relative to acetate ligand.

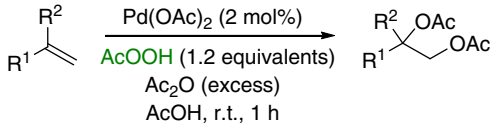
Dong and coworkers reported dioxygenation of olefins catalyzed by cationic palladium diphosphine complex [Pd(dppp)$(H_2O)_2$]$(OTf)_2$.[41e] For example, oxidation of the olefinic part of 1*H*-indene (**321**) took place in the presence of 2 mol % of [Pd(dppp)$(H_2O)_2$]$(OTf)_2$ and 1.1 equivalents of $PhI(OAc)_2$ to afford 93% of diacetoxylated product **322** after treatment of acetic

anhydride (Scheme 60A). This catalytic system was not limited to terminal olefins, and the presence of a directing group for the enhancement of reactivity is not necessary. On the basis of the isotopic labeling studies conducted in $H_2{}^{18}O$/anhydrous AcOH and the observation of *syn*-diastereoselectivity, the proposed mechanism was depicted in Scheme 60B. *anti*-Acetoxypalladation followed by the oxidation with hypervalent iodine reagent afforded the key Pd(IV) intermediate E, which was trapped by the dangling acetoxy group via an S_N2-like attack. Subsequent hydrolysis delivered the final *syn*-acetoxylation product.



Scheme 60

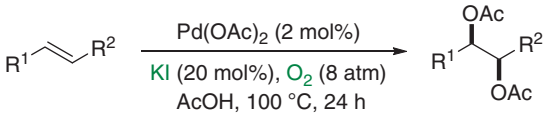
The use of $PhI(OAc)_2$ as a stoichiometric oxidant produces a large amount of by-product. Instead of such hypervalent iodine reagents, peracetic acid is also applicable as the oxidant in the Pd(II)/Pd(IV) catalysis. Jung and coworkers successfully developed a highly reactive Pd-catalyzed diacetoxylation for a broad range of alkenes, including conjugated and nonconjugated, at ambient temperature (equation 58).[41f]



R^1	R^2	Yield (%)
$NCCH_2$	H	93
Bn	H	86
$AcO(CH_2)_2$	Me	90
Ph	Me	88

(58)

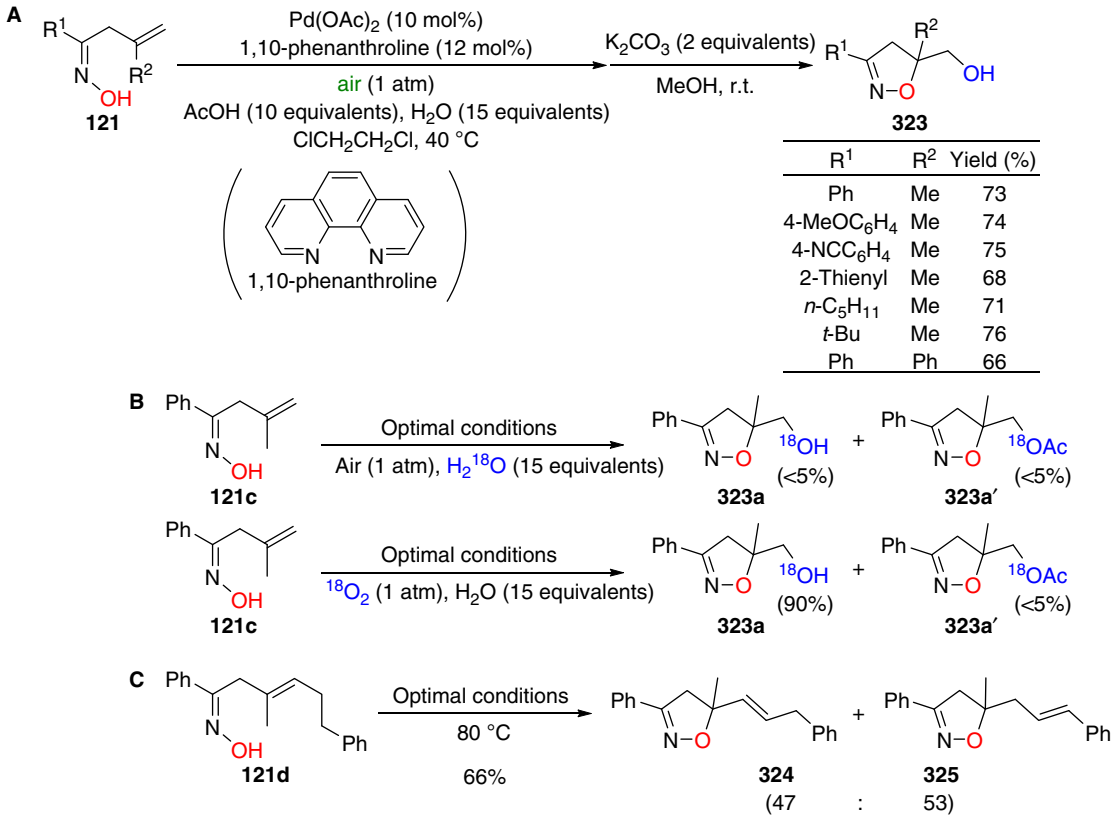
The group of Jiang developed a closely related highly stereoselective diacetoxylation of styrenes and other alkenes but without the need for hypervalent iodine reagents.[41g] The reaction appears to involve an unprecedented direct O_2-mediated Pd(II) to Pd(IV) oxidation in combination with a catalytic amount of KI as the additive (equation 59). Control experiments in the absence of O_2 were carried out with a stoichiometric $Pd(OAc)_2$ as the catalyst and with a stoichiometric amount of I_2 as the oxidant. In both the cases, the diacetate product was not detected. The former result indicates the low possibility of an alternative Pd(II)/Pd(0) cycle, whereas the latter implies that the oxidation of Pd(II) to Pd(IV) by I_2 can be excluded.



R^1	R^2	Yield (%)
4-FC_6H_4	H	91
4-ClC_6H_4	H	89
4-MeC_6H_4	H	83
Bn	H	84
$PhOCH_2$	H	81
n-C_6H_{13}	H	78
Ph	Ph	77 (98:2 *dr*)
Ph	CO_2Me	76 (97:3 *dr*)
Ph	CN	73 (98:2 *dr*)

(59)

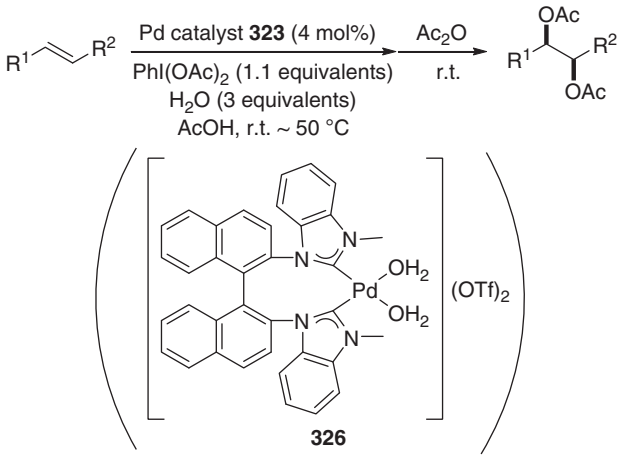
Loh and coworkers have recently developed a Pd(II)-catalyzed oxime-assisted intramolecular dioxygenation of alkenes **121** by using 1 atm of air as the sole oxidant (**Scheme 61A**).[41h] This method incorporated atmospheric O_2 into synthetically useful compounds efficiently under extremely mild conditions, which is promised to be environmentally benign, economical, and practical for the preparation of hydroxylated isoxazolines **323** (**Scheme 61B**). When substrate **121d** containing *β*-hydrogens after oxypalladation was subjected to the standard conditions, no dioxygenated product was observed, instead *β*-H elimination products **324** and **325** were formed (**Scheme 61C**). There was no reaction when the substrate was treated with stoichiometric Pd $(OAc)_2$ in the absence of air or O_2. Furthermore, when H_2O_2 was used as an oxidant, similar results with oxygen were observed. Based on these preliminary mechanistic studies, they assumed the involvement of Pd(II)/Pd(IV) redox system in this reaction.



R^1	R^2	Yield (%)
Ph	Me	73
4-$MeOC_6H_4$	Me	74
4-NCC_6H_4	Me	75
2-Thienyl	Me	68
n-C_5H_{11}	Me	71
t-Bu	Me	76
Ph	Ph	66

Scheme 61

The first application of bis(NHC)Pd catalysts to the dioxygenation of alkenes was reported by Shi and coworkers.[41i] Cationic diaquo complex **326** showed the highest catalytic activity to give 1,2-dioxygenation products with good *syn*-diastereoselectivity for 1,2-disubstituted alkenes (equation 60). Strong *σ*-donating properties of NHC ligands allow for the formation of strong NHC–metal bonds and prevent decomposition of these catalysts during the reaction. Consequently, the robust NHC ligands are attractive candidates for investigating the details of the Pd(II)/Pd(IV) catalytic cycle or facilitating the design of new catalysts for regio- and stereoselective Pd(II)/Pd(IV) catalyzes.

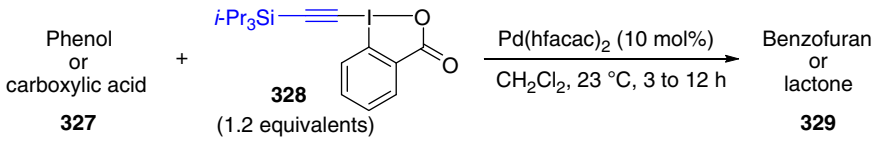


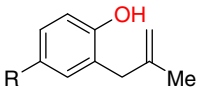
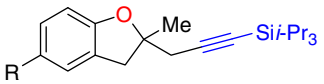
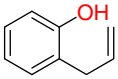
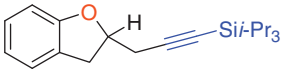
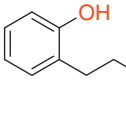
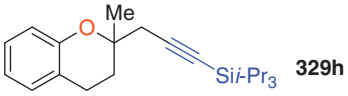
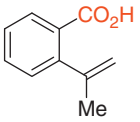
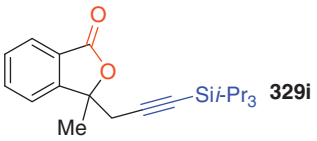
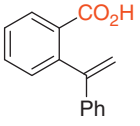
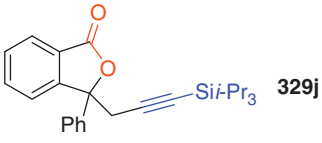
R^1	R^2	Yield (%)
Ph	Ph	79 (8:1 *dr*)
Ph	$BnOCH_2$	99 (4:1 *dr*)

(60)

The carbooxygenation triggered by the Wacker-type cyclization, which generates C–C and C–O bonds in a single transformation, has been accomplished by way of a Pd(IV) intermediate. Waser and coworkers established the first example of intramolecular oxyalkynylation of nonactivated alkenes utilizing $Pd(hfacac)_2$ (hfacac = hexafluoroacetylacetonato) as the catalyst and benziodoxolone-derived reagent **328**.[41j] Both phenols and aromatic or aliphatic acids **327** can be converted under mild conditions into alkynylated benzofuran and lactone derivatives **329**, respectively (Table 11). With phenols, good yields were obtained only

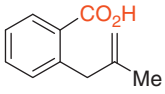
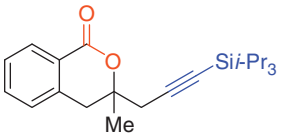
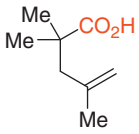
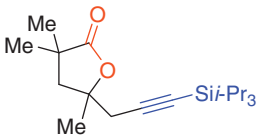
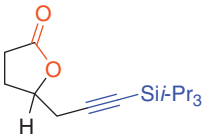
Table 11 Pd-catalyzed oxyalkynylation reaction of alkenes



Entry	*Substrate*	*Product*	*Yield (%)*
			
1	**327a**:R = H	**329a**	71
2	**327b**:R = Me	**329b**	34
3	**327c**:R = Br	**329c**	68
4	**327d**:R = CN	**329d**	76
5	**327e**:R = NO_2	**329e**	72
6	**327f**:R = Ac	**329f**	87
7	 **327g**	 **329g**	43
8	 **327h**	 **329h**	46
9	 **327i**	 **329i**	83
10	 **327j**	 **329j**	70

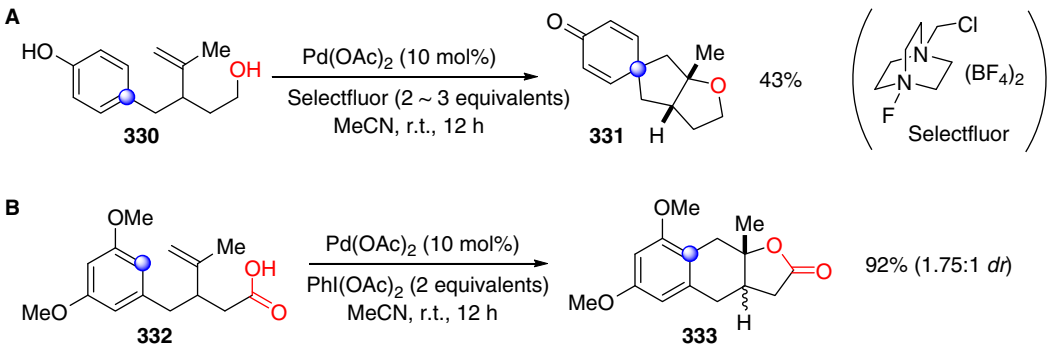
(*Continued*)

Table 11 Continued

Entry	Substrate	Product	Yield (%)
11	 **327k**	 **329k**	80
12	 **327l**	 **329l**	70
13	 **327l**	 **329l**	82

for substrates with a geminally disubstituted double bond, and electron-donating groups on the benzene ring were not tolerated. With acids, the scope was more general, and good yields were obtained, even for the monosubstituted double bond and in the case of aliphatic substrates.

Another C–C bond-forming olefin difunctionalization method employing a Pd(II)/Pd(IV) catalytic cycle was reported recently by Stephenson and coworkers.[41k] Their method provides rapid access to highly functionalized tricyclic compounds (Scheme 62). Phenolic substrate **330** furnishes spirocyclic cyclohexadienone **331** through the oxidative dearomatization, whereas electron-rich carboxylic acid substrate **332** affords fused aromatic product **333** via the C–H functionalization.



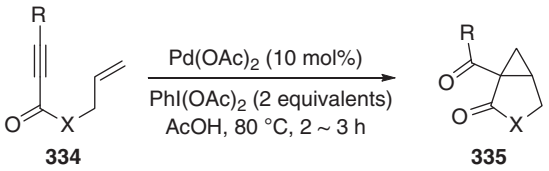
Scheme 62

7.17.8.2 Cyclization of Enynes

Tse's and Sanford's groups independently but simultaneously developed Pd-catalyzed cascade cyclization of 1,6-enynes **334** under oxidative conditions to afford cyclo propyl-fused butenolide products **335** (Scheme 63).[42a,b] These methods could be employed for the construction of lactones, lactams, tetrahydrofurans, and pyrrolidines. A proposed mechanism depicted in Scheme 64A rationalized the stereochemical outcome with a Pd(IV) intermediate. The vinylic C–Pd intermediate **A** was generated by *anti*-acetoxylpalladation of the alkyne and subsequent alkene insertion to close the five-membered ring. σ-Bond rotation of the resulting Pd(II) intermediate **B** followed by oxidation with $PhI(OAc)_2$ would afford the Pd(IV) intermediate **C**. From the outcome of experiments with (*E*)-**334a** and (*Z*)-**334a** (Scheme 64B), it is apparent that the key cyclopropane-forming step could proceed via S_N2-type attack by the electron-rich alkene moiety on the Pd(IV)-bound carbon to afford the bicyclo[3.1.0]hexane product **335** on further hydrolysis with inversion of configuration. As no β-hydride elimination product was detected, the closure of the cyclopropane ring is clearly rapid. Full investigations into the scope and mechanism of this transformation were reported later.[42c]

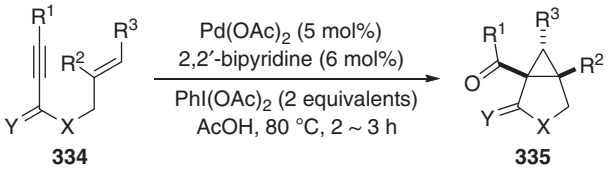
Sasai and coworkers showed that this oxidative cyclization proceeded with high levels of stereocontrol utilizing SPRIX **275** as a chiral ligand.[42d] Other chiral ligands such as (−)-sparteine **3**, BINAP **261a**, BOX **260d**, and BOXAX **243a** yielded racemic products. These observations imply the decomposition of the ligands under the oxidative conditions, leading to the rapid background

A (Tse's group)



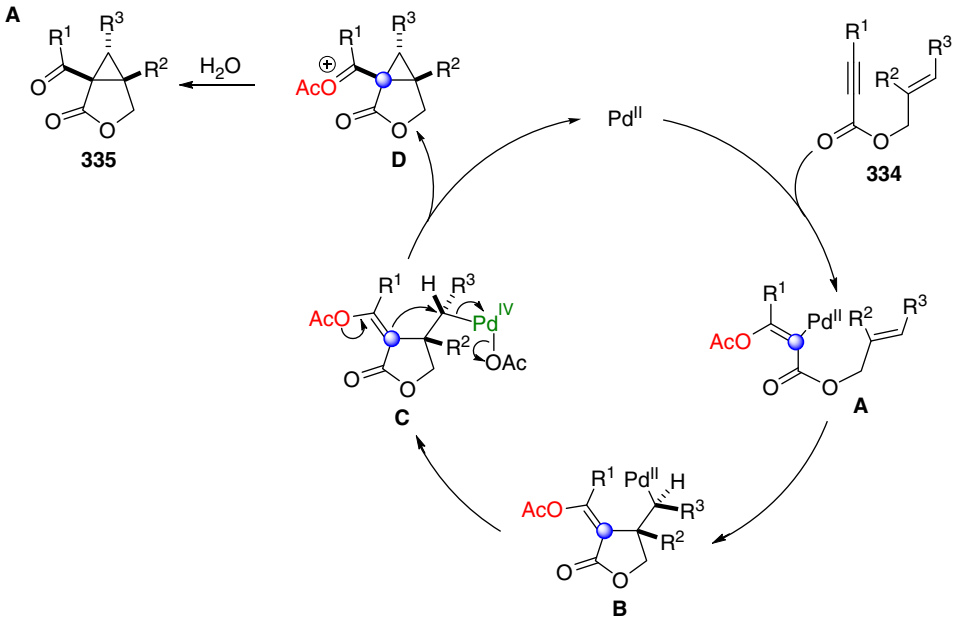
R	X	Yield (%)
Ph	O	63
Me	O	51
Bu	O	75
2-MeOC$_6$H$_4$	O	80
Ph	NTs	83
Bu	NTs	77

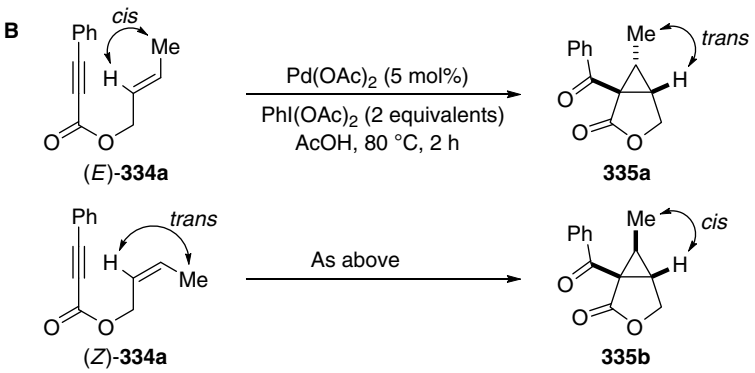
B (Sanford's group)



R^1	R^2	R^3	X	Y	Yield (%)
Ph	H	H	O	O	79
Me	H	H	O	O	55
Ph	Me	H	O	O	78
Me	Me	H	O	O	66
Ph	H	CO_2Et	O	O	79
Ph	H	H	O	H_2	48
Me	H	H	NTs	H_2	71
Ph	H	H	NMe	O	47

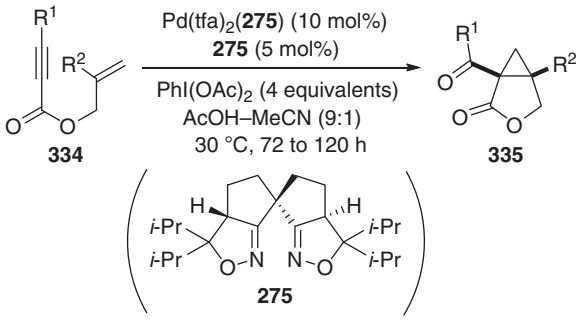
Scheme 63





Scheme 64

reaction described above. A variety of Pd sources generated active and stereoselective catalysts, but $Pd(tfa)_2$ led to the best combination of enantioselectivity and yield, and further optimization enabled product formation in >90% *ee* and excellent yields (equation 61). This study represents the first example of asymmetric catalysis proceeding through a Pd(IV) intermediate.



R^1	R^2	Yield (%)	*ee* (%)
Ph	Me	89	95
4-ClC_6H_4	Me	78	93
4-$MeOC_6H_4$	Me	89	80
2-Naphthyl	Me	92	91
Pr	Me	66	87
Ph	Et	78	91
Ph	$BnOCH_2$	81	94
Ph	H	62*	95*

*$PhI(tfa)_2$ was used instead of $PhI(OAc)_2$.

(61)

7.17.9 Conclusions

The Wacker-type reaction promoted by the Pd(II) catalyst constitutes an efficient strategy for functionalization of alkenes or alkynes with C–O bond formation and continue to offer new applications to synthesize a wide range of densely functionalized compounds. The intramolecular variant provides a highly valuable method for the synthesis of various heterocycles. Moreover, the organopalladium intermediate generated by oxypalladation can undergo further useful transformations including CO or alkene insertion. The good regio- and stereoselectivity, which are essential for practical organic syntheses, of the Pd(II)-catalyzed olefin functionalization must be underlined. These reactions proceed under relatively mild reaction conditions and tolerate a wide variety of functional groups, thus avoiding protecting group chemistry. One practical advantage of these reactions is the ease of handling Pd(II) complexes, which is usually stable and can be handled without rigorous exclusion of air and moisture.

The results described here demonstrate that the role of the catalytic species is critically important: profound alterations of the reaction course and product yields are observed by changing the catalyst. For example, the reactivity of palladium acetate and halides are quite different. Careful selection of reaction conditions in term of the catalyst and the solvent happens to be determinant. Additional key component of the Wacker-type reaction is the demand of an oxidizing agent. The majority of the Pd(II) oxidation catalysis still requires a terminal oxidant other than molecular oxygen: many of such reactions require the use of a large excess of undesirable oxidants such as benzoquinone. The use of an efficient oxidation system for the palladium is of great importance to favor a major impact on industry.

The mechanistic results challenge prevailing assumptions concerning the stereochemical course of the oxypalladation reaction. Examples of *syn*-oxypalladation not only exist, but they also appear to be more common than the widely established *anti*-oxypalladation pathway. Recent studies demonstrate that small changes of reaction conditions can alter the pathway of the oxypalladation step. Unfortunately, the factors that dictate the preferred pathway remain elusive. Further insights could be gained from additional studies probing systematic trends in the catalytic system, substrate structures, role of additives, solvent effects, and so forth.

Although the influence of chiral ligands on the preferred oxypalladation pathway remains to be established, a number of successful enantioselective Wacker-type reactions have expanded significantly over the past two decades. Nevertheless, significant challenges must be addressed to expand the synthetic utility of these reactions. Only a small number of reactions proceed with very high enantioselectivity, and the successful examples generally have been demonstrated for only a narrow substrate scope. In the near future, the discovery of new classes of chiral ligands can provoke potent enantioselective Wacker-type transformations, which are suitable for the chemical industry.

Chemistry exploiting the Pd(II)/Pd(IV) catalytic manifold has recently applied to the Wacker-type reaction, which often facilitate new transformations that are not easily available by the traditional Pd(0)/Pd(II) catalysis. Some drawbacks that limit the use of these novel Pd(IV) methods still remain (e.g., poor selectivity, low chemical yield, and/or an excess amount of expensive oxidants such as hypervalent iodine salts). Even so, promising synthetic protocols based on Pd(IV) intermediates will be developed due to the broad functional group compatibility in the rising Pd(II)/Pd(IV) catalysis. The opportunity to exploit enantioselective Pd(II)/Pd(IV) transformations is another intriguing possibility warranting further exploration.

Contrary to the Pd(0)/Pd(II) cross-coupling chemistry, where ppm-level Pd loadings are not exceptional, the Pd(II)/Pd(0) and Pd(II)/Pd(IV) Wacker-type catalyzes commonly require high catalyst loading (usually 5~10 mol %): This problem is probably caused by the small turnover numbers of the Pd catalyst, which makes the processes unsuitable for the industrial use due to the high cost. Therefore, turnover numbers and frequencies need to be improved in the next-generation process. The development of highly active catalysts and the oxidation system compatible with the use of molecular oxygen will have important implications for the practical application of the Wacker-type reaction. Such reactions in general minimize waste by-products, thus belonging to the

environmentally friendly chemical processes. Undoubtedly, the numerous advantages and vast potential associated with the Wacker chemistry as well as the related Pd(II)/Pd(IV) reactions will promote more and more research interest in this area.[43]

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7.18 Addition Reactions with Formation of Carbon–Carbon Bonds: (v) The Oxidative Heck Reaction

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Glossary

Bidentate ligand A ligand that binds via two atoms.

C–H functionalization A reaction involving a metal insertion into, and a formal substitution of, a C–H bond. Generally used in the context of Ar–H or alkyl–H bonds.

Heck-type reaction The substitution of a vinylic-H with an organyl moiety, catalyzed by a metal other than palladium, resulting in the formation of a substituted olefin product.

Oxidative Heck The palladium(II)-catalyzed substitution of a vinylic-H with an organyl reaction moiety. In the context of this chapter the reaction should terminate with a β-hydride or heteroatom elimination.

Transmetalation A kind of organometallic reaction that involves the transfer of ligands from one metal to another and is commonly used in catalysis, synthesis of main group complexes, and synthesis of transition-metal complexes. Electronegativities and access to empty orbitals on both metals are key factors for the outcome of the process.

7.18.1 Introduction

7.18.1.1 Palladium(II)-Catalyzed Coupling Reactions

Given that the first palladium-catalyzed C–C bond-forming reactions were palladium(II)-mediated processes (i.e., the seminal reports of Heck[1] and Moritani and Fujiwara[2]), it might seem strange that this reaction class has often been overshadowed by the

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significant advances in palladium(0)-catalyzed cross-couplings and Mizoroki–Heck reactions.[3,4] One of the many reasons behind this development is the fact that most of the palladium(II)-catalyzed coupling reactions require a stoichiometric reoxidant in order for the reaction to be catalytic. Mechanistically, the two pathways (palladium(0) and palladium(II) catalysis) differ in the way in which the transition-metal enters the catalytic cycle.[5] In palladium(II) catalysis the initial organopalladium species is formed through a nonredox mechanism, whereas in palladium(0) catalysis it is generated through an oxidative addition. Among the reactive organyl sources in palladium(II)-catalyzed vinylic substitution reactions, one will find various organometals and organometaloids, benzoic/cinnamic acids, aryl phosphonates, and aryl sulfinates, as well as arenes/heteroarenes/vinyls substituted or not substituted with catalyst-presenting moieties. Such palladium(II)-catalyzed Heck reactions have been named 'oxidative Heck reactions' in the literature and this terminology will be used throughout the chapter, although this classification might need to be expanded due to the discovery of nonpalladium-catalyzed 'oxidative' vinylic substitution reactions (Heck-type reactions).[6] Although the olefin scope for the intermolecular oxidative Heck method is not as well studied as for the corresponding Mizoroki–Heck reaction, the number of reported productive olefins is steadily increasing, and there are good reasons to believe that the range of useful olefinic coupling partners will be almost identical.[5,7] In the case of intramolecular Heck reactions, the dehydrogenative Heck method (Fujiwara–Moritani), employing arenes as arylpalladium precursors, is the most frequently used.[8]

The oxidative Heck reaction begins with the formation of the arylpalladium intermediate **B** according to different mechanisms for each starting materials class (**Figure 1**). In step 2, an olefin coordinates to the arylpalladium intermediate to form the cationic π-complex, C_π. Migratory insertion (step 3) generates the σ-complex C_σ, and internal rotation followed by *syn* β-hydride elimination (step 4) generates complex **D**. The arylated olefin dissociates (step 5) from the intermediate **D** to form the palladium-hydride species **E**. Finally, the starting palladium(II) catalyst **A** is regenerated from the palladium-hydride intermediate **E**, by oxidation (step 6).

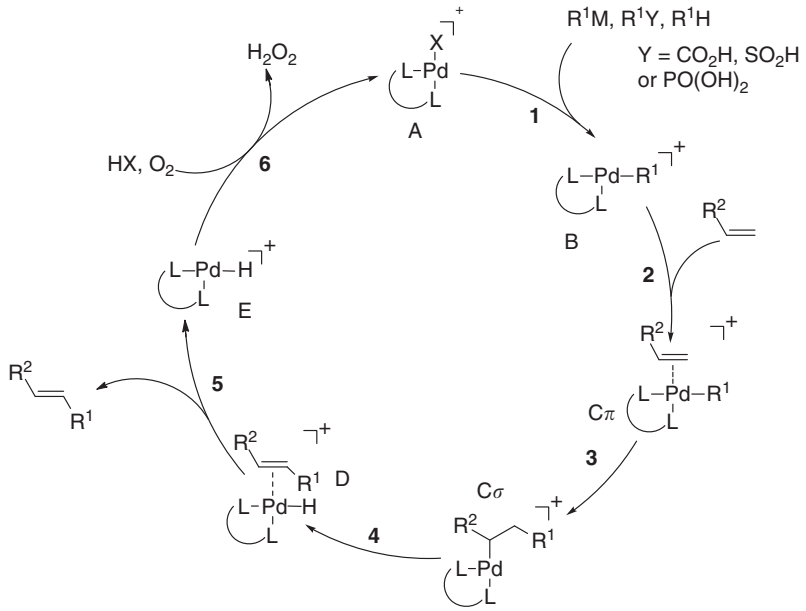


Figure 1 Generic catalytic cycle for the oxidative Heck reaction with different organopalladium precursors, a bidentate ligand L–L, a weak palladium(II)-coordinating anion X^-, and an electron-poor olefin.

Palladium(II)-catalyzed coupling reactions normally require a dedicated reoxidant to regenerate the active catalytic species and avoid the formation of nonproductive palladium black. Commonly used reoxidants are metal salts, such as copper[9] and silver salts,[10] MnO_2,[11] *p*-benzoquinone (*p*-BQ)[12] and other quinones,[13] 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),[14] desyl chloride,[15] and various peroxides.[14] The use of copper or silver salts is costly and *p*-BQ is toxic and relatively expensive, as is TEMPO and desyl chloride. In addition, all of these reoxidants produce stoichiometric amounts of waste, which may complicate purification procedures and have a negative environmental impact. Hydrogen peroxide, however, is inexpensive and produces water as byproduct, but it is a strong oxidant that is incompatible with many functionalities. The ultimate reoxidant, however, is molecular oxygen, preferably as ubiquitous air[16] (or even hypoxic air), as it is virtually cost-free and environmentally benign.[14] The use of oxygen as the terminal stoichiometric reoxidant in reactions employing cocatalysts, such as copper in the Wacker process, has been long known,[9] whereas the use of oxygen or air as the sole reoxidant is a relatively new strategy.[17]

During the past decade, the mechanistic understanding of oxygen-mediated palladium reoxidation has increased as a result of important contributions by the groups of Stahl,[18] Sigman,[19] Bäckvall,[14] Jutand,[20] Sävmarker,[21] and Goddard.[22] This improved understanding of reoxidation has led to improved reaction protocols, and two main reoxidation routes have been proposed: the

palladium(II)-hydride pathway and the palladium(0)-protonolysis pathway (Figure 2).[23–26] Mechanistic investigations have so far not been able to provide conclusive evidence for one pathway over the other, and it seems likely that both pathways may be possible, depending on the ligands, solvents, additives, and substrates used.

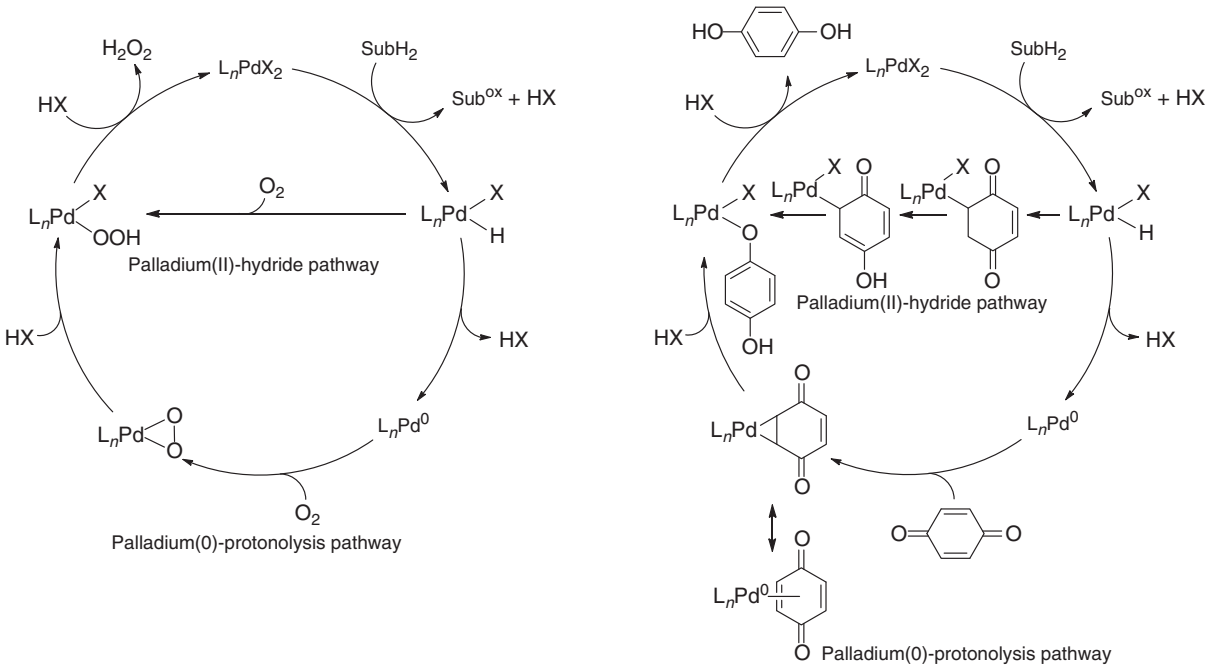


Figure 2 The two proposed pathways for the oxygen-mediated regeneration of Pd(II) and the related *p*-BQ mechanisms.

An alternative palladium(II)-preserving mechanism of importance for the oxidative Heck reaction is the *β*-elimination of heteroatom groups, such as OAc, OH, Br, and Cl, which generates the functionalized unsaturated product and a palladium(II) salt. This is in contrast to *β*-hydride elimination, which requires a reoxidant to regenerate the palladium(II) species. The *β*-elimination of heteroatom groups is generally faster than that of hydrogen and can provide an efficient route to catalytic reactions, without the addition of an external reoxidant.[27–29]

7.18.1.2 Substrates for Oxidative Heck Reactions

In palladium(II) catalysis an array of different substrates can be employed for C–C bond-forming coupling reactions. The organopalladium species can be generated by organyl transmetalation of a number of different organometal or metalloid compounds, for example, mercury, magnesium, lithium, zinc, thallium, tellurium, copper, tin, silicon, phosphorous, antimony, bismuth, arsenic, or boron. Arylmetal precursors are advantageous as they generally provide excellent regio- and chemoselectivity. Generally, methods using arylmetal precursors have a broader scope of efficient substrates than methods using C–H functionalization of arenes or decarboxylation of aryl carboxylic acids. Among the arylmetal precursors, arylboronic acids (and derivatives thereof) are the precursors of choice. They are attractive coupling partners, as they are widely commercially available, tolerate a broad variety of functional groups, and are easy to handle.[30] Furthermore, the byproducts formed in coupling reactions of arylboronic derivatives are usually nontoxic and water soluble, simplifying purification and making them attractive from an environmental point of view. Not surprisingly, the most common transmetalation substrates utilized in oxidative Heck reactions are organoboronic acids or boron derivatives.[5,7]

The mechanism behind the transmetalation between palladium and a boronic acid is not completely understood. Available information on base-assisted aryl-Pd transmetalation suggests two possible processes, one being the transmetalation between the boronic acid and an oxo-palladium(II) complex, and the other transmetalation of the preformed quaternized boron (Figure 3).[31] For many years it was believed that the R-B$(OH)_2$ substrate was inactive and required activation by a nucleophile to form the active boronate (R-B$(OH)_2$Nu). This issue was addressed by the introduction of the aryltrihydroxyborates as preactivated boronates.[32] In a recent study by Carrow and Hartwig, the first route was found to be dominant under the conditions studied, but both routes were energetically accessible and the strength of the base was found to play a role in the selection of pathway.[33]

Organotrifluoroborates have been known for quite some time,[34] but it was not until Vedejs et al.[35] reported a convenient method for their preparation that these compounds became widely available (Figure 4). The reaction occurs within minutes or hours, depending on the starting material, and the products are generally isolated by simple filtration. Organotrifluoroborates are

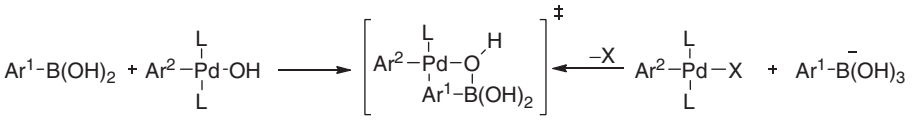


Figure 3 Simplified view of the suggested pathways for the transmetalation of arylboronic acids.

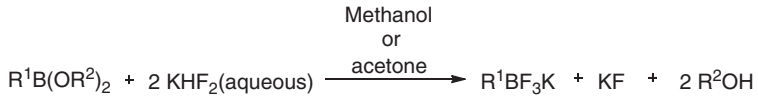


Figure 4 General method for the preparation of potassium organotrifluoroborates.

today widely commercially available as a result of their success in cross-coupling chemistry, mainly due to the pioneering work of Genet and coworkers[36,37] and the continued work by Molander and Canturk.[38] In addition to their superior shelf-life relative to boronic acids, organotrifluoroborates are capable of withstanding a variety of reaction conditions and provide the unique possibility to further functionalize the organic substructure.

Organoboronate esters are in many ways related to the trifluoroborates and have also emerged as particularly attractive alternative organoboron coupling partners. These boron reagents exhibit exceptional shelf-life, are easy to synthesize and isolate, and are compatible with many synthetic reagents. Organoboronate esters, such as *N*-methyliminodiacetic acids (MIDA) boronates, are generally activated by *in situ*, rate-controlled hydrolysis.[39]

Organo(tributyl)stannanes have been reported as useful coupling partners in the oxidative Heck reaction,[40] a finding that is in sharp contrast to the early work by Heck, who reported poor reactivity with these reactants.[1] However, organostannanes are toxic and produce environmentally harmful byproducts, which often complicate analysis and purification. Therefore, there has been significant effort directed toward the identification of alternative transmetalation substrates, such as organosilanes, which has led to the identification of arylsilanols as competent arylating agents in the oxidative Heck reaction.[41]

Different aromatic acids can also function as arylpalladium(II) precursors.[42] The possibility of using benzoic acids as arylpalladium(II) precursors merits special attention, as carboxylic acids are generally environmentally benign, more widely commercially available, and less expensive than their corresponding transmetalating agents, such as boronic acids. Monometallic palladium(II)-catalyzed decarboxylation is usually a highly endothermic process and therefore difficult to achieve,[43] but can be efficient for certain *ortho*-substituted benzoic acids, as was demonstrated by Myers and coworkers in an elegant and pioneering decarboxylative oxidative Heck reaction.[10,44] Stoichiometric amounts of expensive silver salts and high palladium loadings were required, thus limiting the usefulness of the reaction. Recently, a silver-free catalytic system employing *p*-BQ as the stoichiometric palladium reoxidant was reported, obviously lowering the cost of the reaction.[45]

Compared with the organic sources described so far, organophosphonates and aryl sulfinates (or aryl sulfinic acids) are by far the most anonymous. There are only a few substrates commercially available, but these classes of arylating/vinylating agents can be of increased importance in the future since they do not need activating groups in the *ortho*-position.[46,47]

Unfunctionalized arenes and heteroarenes are the ideal arylmetal source in cross-coupling chemistry and have consequently been extensively investigated, in a plethora of metal-catalyzed processes, over the past decade.[48] When compared to the other substrate types described above, they offer unparalleled advantages in terms of low cost, widespread availability, and stability. Moreover, the coupling of an olefin and an arene involves the direct coupling of two C–H bonds, with the formal loss of hydrogen gas, making it an exceptionally atom-efficient and step-economic strategy. In order to harness their enormous synthetic potential, two broad strategies have been developed to ensure the selective functionalization of a particular target C–H bond (**Figure 5**).

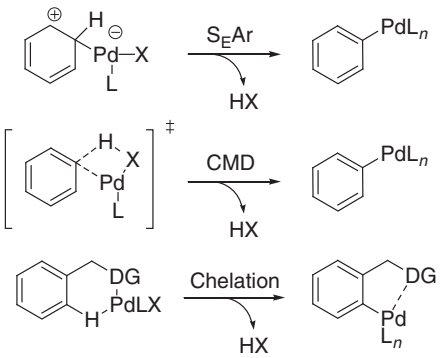


Figure 5 Generalized view of the most common mechanisms for C–H palladation.

First, site selectivity can be achieved by utilizing the inherent electronic bias present in an aromatic system. This strategy has been particularly successful for the selective functionalization of various heteroarenes. For electron-rich arenes metalation is believed to occur via an electrophilic C–H activation mechanism (S_EAr) and, in analogy to traditional electrophilic aromatic substitution, metalation takes place at the most nucleophilic carbon. Electron-poor arenes are thought to undergo metalation via the concerted metalation-deprotonation mechanism (CMD) and, in this case, site selectivity is governed by C–H acidity.[49,50] The second strategy involves using suitable directing groups, typically a Lewis basic atom or functional group, to afford selective *ortho*-metalation through chelation assistance. Although the use of directing groups has resulted in a wealth of *ortho*-selective C–H functionalization methods, in order to be truly useful, the directing group must either be present in the target molecule or easily removed. In the latter case, the additional cost and waste generated by the installation and removal of the directing group must be weighed against the benefits gained from the C–H functionalization.

7.18.2 Intermolecular Oxidative Heck Reactions

One of the major challenges in intermolecular Heck reactions, both in Mizoroki–Heck and oxidative Heck processes, is controlling the product regioselectivity.[51] In the reaction of a monosubstituted alkene, the organic group can be added either to the internal carbon, yielding an α-substituted product, or to the terminal carbon, giving *E*/*Z*-β-substituted products (Figure 6). Mechanistically, the π-complex formation and insertion steps dictate product regioselectivity, and these are, in turn, controlled largely by the electronic, steric, and coordinating properties of the olefin. In addition, the reaction outcome can also be influenced by the properties of arylpalladium species and the nature of the ligand. In general, high levels of regioselectivity can be readily obtained when using electronically biased olefins, whereas aliphatic olefins, which lack a significant electronic difference between the olefinic positions, are much more challenging substrates and often furnish product mixtures.[51]

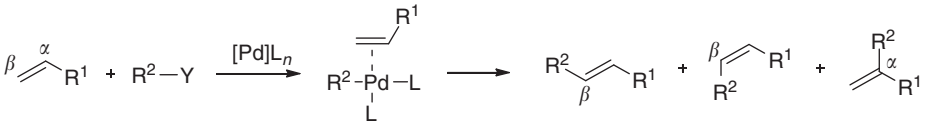


Figure 6 Possible regioisomeric outcomes in an intermolecular Heck reaction.

Electron-deficient alkenes are by far the most well studied class of substrates in the Heck reaction.[7,52–54] This is because they routinely afford very high levels of regioselectivity, as both steric and electronic factors favor arylation at the terminal position. The aryl group is added to the electron-poor β-carbon, while the metal inserts at the more electron-rich α-position (Figure 7). In contrast, electron-rich olefins experience counteracting influences from steric and electronic effects, resulting in the nonselective formation of linear (β) and branched (α) products. Electronic effects direct the aryl to the α-position, as the electrophilic palladium prefers to add to the electron-rich β-carbon, whereas steric factors direct the aryl to the less congested β-carbon. It is now well established that high levels of α-regioselectivity can be obtained by employing conditions that promote reaction via the cationic pathway (Figure 8).[51] Electronic effects are enhanced in the cationic pathway, leading to a greater selectivity for α-substituted products.[55–56] Typical cationic Mizoroki–Heck conditions involve the use of strongly coordinating bidentate ligands (e.g., 1,3-bis(diphenylphosphino)propane, dppp) and aryl sulfonates or aryl halides in the presence of a halide scavenger. More recently, the use of polar solvents and ionic liquid additives has been shown to alleviate the need to add external halide scavengers.[57,58] Additionally, chelation control has been efficiently used to attain selective β-arylation of electron-rich olefins, forcing the insertion of the metal to take place at the normally less favored α-position.[59] Importantly, the ligand-modulated oxidative Heck reaction proceeds via the cationic pathway and typically affords excellent α-regioselectivity.

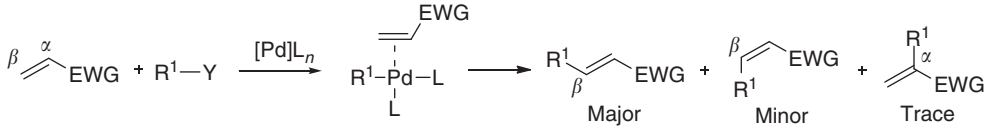


Figure 7 Typical reactivity of an electron-poor olefin in an intermolecular Heck reaction.

In addition to issues regarding terminal and internal selectivity, the Heck reaction of aliphatic alkenes is further complicated by the presence of multiple hydrogens available for β-hydride elimination. A simplified reaction scheme illustrating some of the possible products from the Heck arylation of an aliphatic alkene is given in Figure 9. As a result, there has been significant recent effort toward the development of selective and general protocols applicable to these substrates. There is now a range of methods

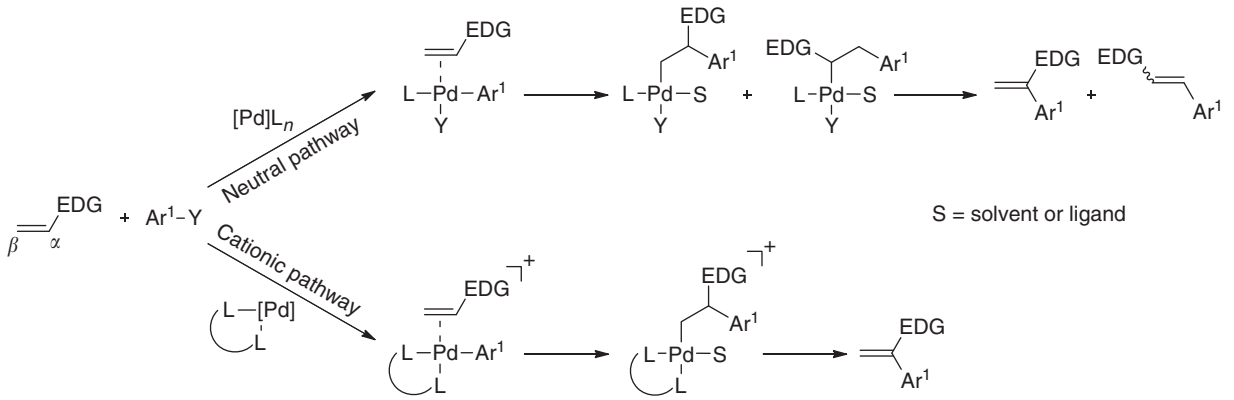


Figure 8 The neutral and cationic reaction pathways lead to different product outcomes in the Heck reaction of electron-rich olefins.

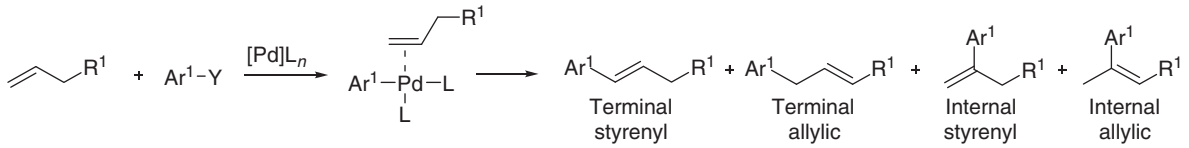


Figure 9 The possible reaction outcomes in the Heck arylation of an aliphatic olefin.

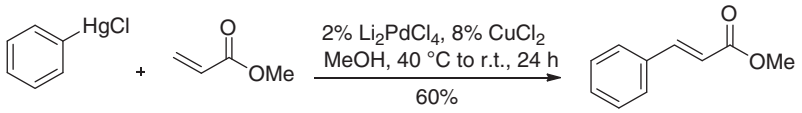
available that utilize either substrate control[60] or catalyst control[61,62] to selectively deliver internal or terminal, styrenyl or allylic Heck products.

7.18.2.1 With Electron-Poor Olefins Using Aryl–Z (Z=M, acid, H)

The first section of this chapter describes the intermolecular arylation of alkenes carrying one or more electron-withdrawing groups. These are the archetypical Heck reaction substrates, and the section is dominated by examples of regioselective terminal (β) functionalizations using a wide range of diverse arylating agents. Accordingly, this section is further organized into the following subsections based on the nature of the arylating agent: arylboron derivatives, arylstannanes, arylsilanols, aryl carboxylic acids, aryl sulfinic acids and derivatives, aryl phosphonic acids, and arenes.

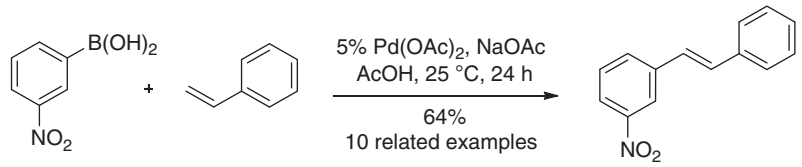
7.18.2.1.1 Arylboron derivatives

The first palladium-catalyzed arylation of an electron-poor olefin, utilizing an organometallic aryl source, was demonstrated by Heck in 1968.[1] In this seminal report, methyl acrylate was arylated with phenyl mercuric chloride using catalytic amounts of Li_2PdCl_4 and $CuCl_2/O_2$ as the palladium reoxidant (equation 1). Several years later Dieck and Heck reported the first example of an oxidative Heck reaction using a boronic acid as the coupling partner.[63] Although this reaction was stoichiometric in terms of palladium, it nonetheless represents an important milestone in the development of the oxidative Heck reaction.

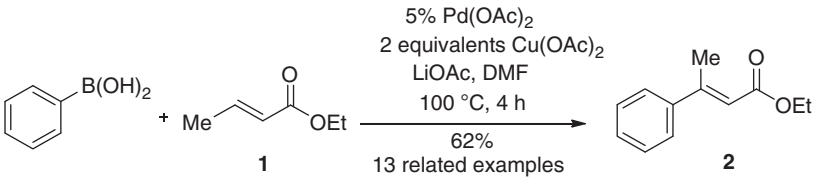


(1)

In the years following Heck's initial discoveries, the oxidative Heck reaction remained dormant as researchers focused their attention on developing the Pd(0)-catalyzed Mizoroki–Heck reaction. This all changed in 1994 when Cho and Uemura reported the first catalytic oxidative Heck reaction of arylboronic acids.[64] The reactions were performed in acetic acid at room temperature using $Pd(OAc)_2$ and NaOAc in the absence of an external reoxidant. Moderate-to-good isolated yields of the (*E*)-stilbene derivatives were obtained from styrenes (equation 2) and the reaction also performed well with acrylates; however, no isolated yields were reported with these substrates. In addition, these conditions performed poorly with disubstituted olefins, affording only complex mixtures of isomeric and mono and diarylated products. This reaction can also be performed using stoichiometric amounts of $Cu(OAc)_2$ as the palladium reoxidant.[65] Although this protocol requires the use of elevated temperatures, a range of electron-poor olefins was effectively arylated with a number of 4-substituted boronic acids. Furthermore, the disubstituted olefin **1** was selectively converted into the monoarylated product **2** under these conditions (equation 3). This protocol was later developed into the first example of a microwave-assisted oxidative Heck reaction.[66]



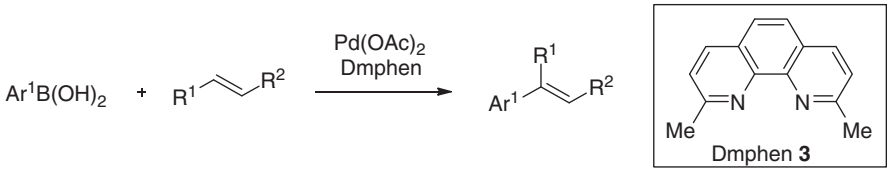
(2)

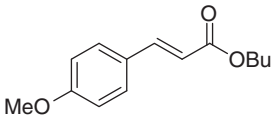
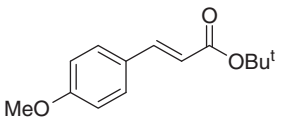
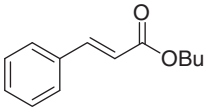
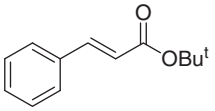
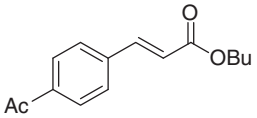


(3)

A significant breakthrough, in terms of waste minimization, was the discovery that oxygen[67] and air[68] could function as palladium reoxidants in the oxidative Heck reaction of arylboronic acids. Due to increased operational simplicity and safety considerations, as well as its lower cost (it is free), air is to be considered the ideal reoxidant for these transformations. Further development revealed that the reaction could be conducted in the absence of base[16,69] and that the addition of bidendate ligands, in particular dmphen (**3**), had a beneficial effect on the reaction outcome. Removal of the base was shown to reduce the formation of byproducts arising from the competing Pd(II)-catalyzed boronic acid homocoupling pathway. Ligand **3** is believed to suppress the formation of palladium black, allowing the use of lower catalytic loadings, and it may also facilitate palladium reoxidation. These discoveries culminated in the demonstration of three of the most general and useful protocols for the oxidative Heck arylation of electron-deficient olefins.[16,69] The most important aspects of these methods are summarized in **Table 1**.

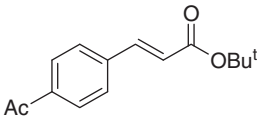
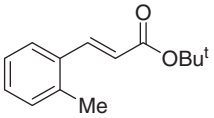
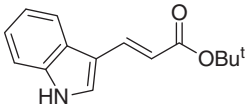
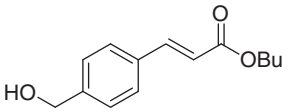
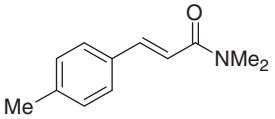
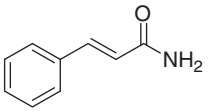
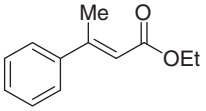
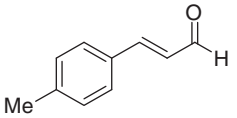
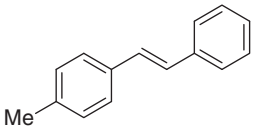
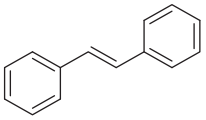
Table 1 Arylated olefins prepared via the base-free oxidative Heck reaction



Product	*Conditions*[a]	*Reoxidant*	*Yield (%)*	*References*
	A B	Air *p*-BQ	84 86	16
	C	O_2	61	69
	A B	Air *p*-BQ	93 89	16
	C	O_2	87	69
	A B	Air *p*-BQ	92[b] 90	16

(*Continued*)

Table 1 Continued

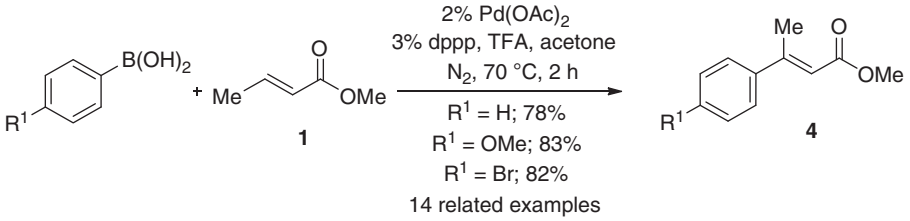
Product	*Conditions*[a]	*Reoxidant*	*Yield (%)*	*References*
	C	O_2	71	69
	C	O_2	84	69
	C	O_2	63	69
	A A	Air O_2	83 75[c]	16
	A B	Air *p*-BQ	71 75	16
	C	O_2	64	69
	C	O_2	82	69
	A B	Air *p*-BQ	82 37	16
	A B	Air *p*-BQ	75[d,e] 95[e]	16
	C	O_2	85	69

[a]Conditions A: boronic acid (2 equivalents), $Pd(OAc)_2$ (2 mol%), dmphen (2.4 mol%), MeCN, r.t., 24 h; conditions B: boronic acid (2 equivalents), $Pd(OAc)_2$ (2 mol%), dmphen (2.2 mol%), *p*-BQ (1 equivalent), MeCN, 100 °C, MW, 10 min; conditions C: olefin (3 equivalents), $Pd(OAc)_2$ (5 mol%), dmphen (5 mol%), DMF, r.t., 12 h.
[b]72 h.
[c]4:1 mixture of product and the corresponding aldehyde.
[d]48 h.
[e]α/β (20:80).

In general, all three methods presented in Table 1 demonstrate wide substrate scope and deliver the desired arylated olefins in good-to-excellent yields. The major difference between the three methods is the reoxidant (air, *p*-BQ, and O_2), and, if there are no additional considerations, method A should be regarded as the method of choice. In addition, the use of air as a reoxidant allows substrates that are sensitive toward oxidization to be used (benzyl alcohols and acrolein). Employing microwave (MW) heating (method B) results in a significant reduction in reaction times; however, this gain must be weighed against the need to add an external stoichiometric reoxidant (*p*-BQ). Methods A and B have both been successfully performed on a 50 mmol scale and method B has also been adapted into a flow chemistry process.[70] Furthermore, method A has recently been employed in the

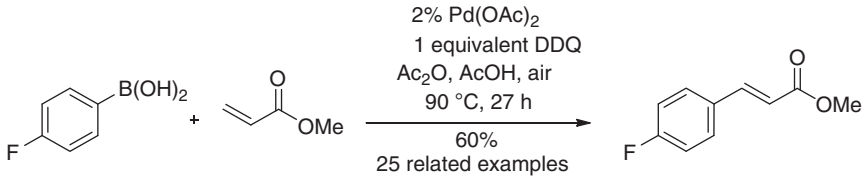
synthesis of *Mycobacterium tuberculosis* 1-deoxy-D-xylulose-5-phosphate reductoisomerase inhibitors.[71] Method C (O_2) demonstrates good compatibility with heterocyclic and 2-substituted boronic acids. This method also displays better regioselectivity for the arylation of styrene derivatives, although the use of the more electron-rich 4-tolylboronic acid in methods A and B may account for some of the observed selectivity difference. Finally, all three methods afford isomeric mixtures of terminally arylated products with 1,1-disubstituted alkenes.

An alternative procedure that does not require air, oxygen, or an external palladium reoxidant is also available.[72] The procedure employs $Pd(OAc)_2$, the bidendate ligand dppp, trifluoroacetic acid (TFA) as an additive, and acetone as the solvent. The scope of the reaction is wide, and excellent isolated yields were reported for the arylation of methyl acrylate with a range of electronically diverse boronic acids. In addition, the 1,2-disubstituted alkene **1** was also selectively transformed into various monoarylated products (**4**) in good yields (equation 4). Palladium reoxidation is believed to be facilitated by the acrylate substrate, which was shown to act as a hydrogen acceptor under the reported conditions. When compared to the methods in **Table 1**, this protocol requires the addition of 30 mol% TFA, which limits its application in the synthesis of acid-sensitive products. Furthermore, the reaction must be conducted under a nitrogen atmosphere, rendering it more operationally complex than those in **Table 1**.



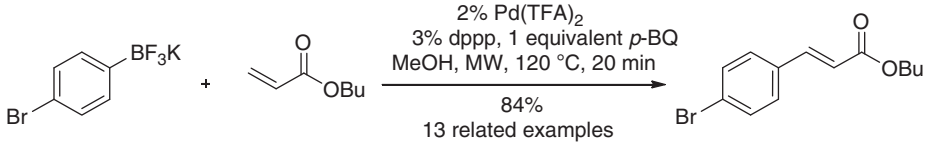
(4)

The arylation of electron-deficient olefins can also be conducted under nitrogen ligand- and base-free conditions.[73] Instead of the bidentate ligand, the procedure requires the addition of stoichiometric amounts of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and acetic anhydride and must be heated in AcOH for 27 h to achieve optimal results (equation 5). These factors limit the benefits derived from the ligand-free nature of the method and reduce the overall synthetic attractiveness of this procedure.



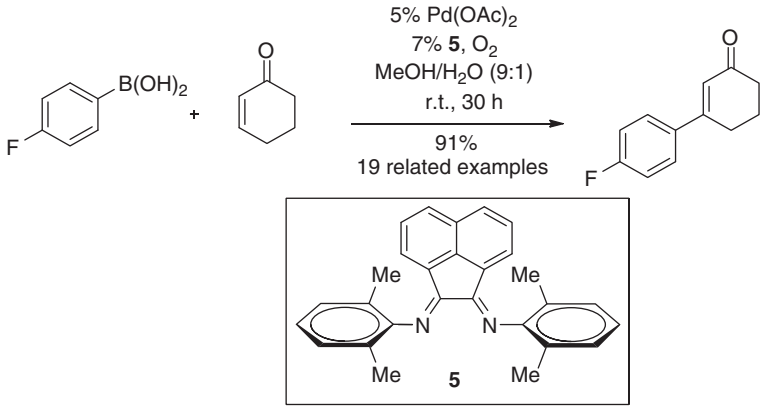
(5)

Aryltrifluoroborates and MIDA boronates are effective arylating agents in the oxidative Heck reaction of electron-poor olefins.[21] By using MW heating, in conjunction with $Pd(TFA)_2$, dppp, and *p*-BQ as the reoxidant, good-to-excellent yields of the terminally arylated (*E*)-olefin products were obtained after short reaction times (equation 6). This method provides a useful alternative to those employing boronic acids, especially when using substrates prone to undergo protodeboronation.



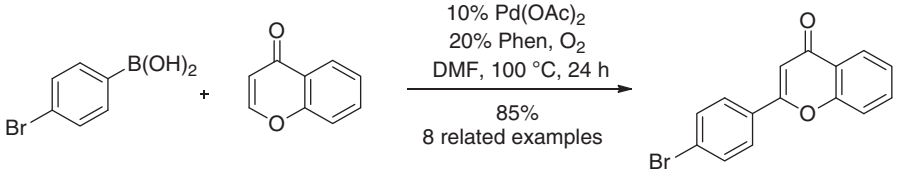
(6)

Cyclohex-2-en-1-one is a challenging substrate for the oxidative Heck reaction due to the competing formation of the saturated conjugate addition product. Complete selectivity for the Heck product can be achieved using a bis-imine ligand derived from acenaphthenequinone (**5**) together with $Pd(OAc)_2$ and O_2 as the reoxidant.[74] This protocol delivered good-to-excellent yields of the desired Heck products, with complete chemoselectivity, using a diverse set of arylboronic acids (equation 7). Furthermore, a number of enones including cinnamaldehyde and 2,3-dihydropyridin-4(1*H*)-one were also found to be suitable substrates for the transformation. One minor limitation of this method is that the ligand (**5**) is not commercially available; however, it can be readily prepared, in 90% yield over two steps, from acenaphthenequinone.

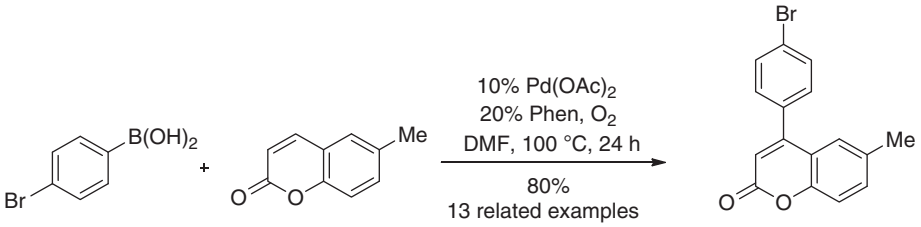


(7)

Flavones (2-aryl-4*H*-4-chromenones) and neoflavones (4-arylcoumarins) are commonly encountered structural elements in many biologically active compounds. These important heterocycles can be conveniently prepared via the oxidative Heck arylation of chromenones (equation 8) and coumarins (equation 9), respectively.[75,76] The optimized conditions are similar to method C in Table 1; however, 1,10-phenanthroline (phen) is the ligand of choice and heating for 24 h at 100 °C is required (equations 8 and 9). The reaction displays a wide substrate scope, and good-to-excellent yields were obtained with a variety of electronically diverse heterocycles and arylboronic acids. One limitation of this method is the need for relatively high catalyst and ligand loadings to be employed (10 mol% and 20 mol%, respectively).

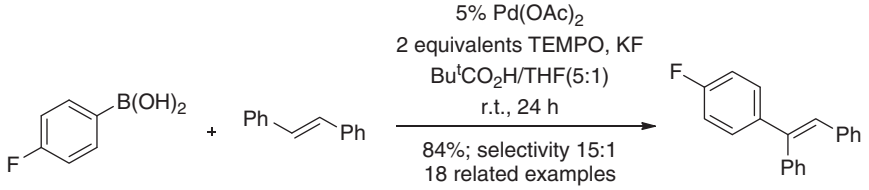


(8)



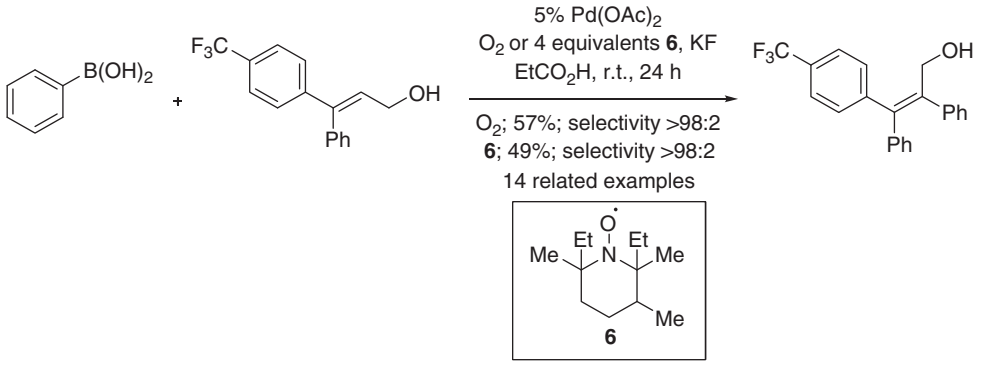
(9)

The synthesis of highly substituted olefins via a Heck arylation process is a challenging task. Increased steric crowding at the olefinic center retards the reaction rate and stereoselectivity problems arise due to the presence of multiple aryl substituents. The stereoselective synthesis of tri- and tetrasubstituted olefins can be accomplished using TEMPO or derivatives of TEMPO as the palladium reoxidant.[77] The arylation of (*E*)-stillbene with 3- and 4-substituted arylboronic acids affords good levels of stereoselectivity and excellent isolated yields (equation 10). Not surprisingly, the reaction is sensitive to steric effects and affords only modest yields with 2-substituted arylboronic acids. The stereoselectivity is dependent on the arylboronic acid, and higher selectivities were obtained when there was a significant electronic difference between the two aryl groups. The reaction of methyl cinnamate afforded moderate-to-excellent yields of the *β*-arylated product and the *E*/*Z* selectivity was again influenced by the nature of the arylboronic acid. The arylation of unsymmetrical stilbene derivatives was found to be very substrate specific and large differences in regio- and stereoselectivity were observed. Thus, it is unlikely that this method will find application as a general guideline for the preparation of olefins bearing three different aryl groups. Nonetheless, the high yields and mild reaction conditions make this an appealing method for the stereoselective synthesis of *β*,*β*-diaryl-acrylates and monoarylated styrene and stilbene derivatives.



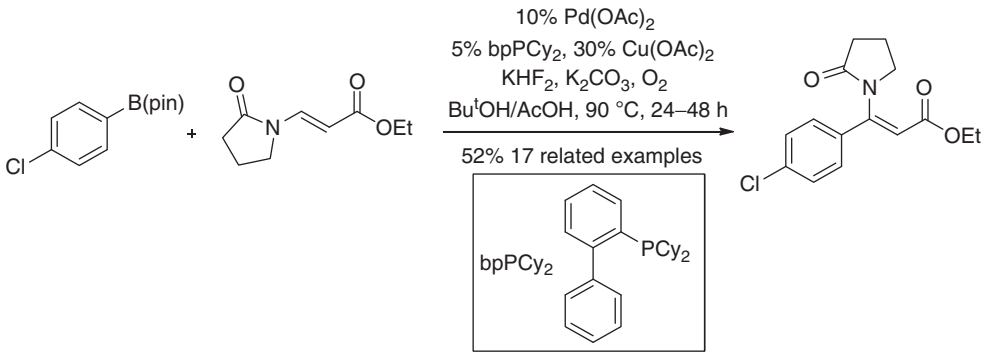
(10)

Tetrasubstituted olefins can be accessed via the stereoselective arylation of allyl alcohol derivatives derived from β,β-diarylacrylates.[77] Good yields and stereoselectivies were obtained for the coupling of these challenging substrates using 3- or 4-substituted arylboronic acids (equation 11). Interestingly, both O_2 and the TEMPO analog **6** can function as palladium reoxidants in this process, with O_2 affording slightly higher yields with electron-poor olefins and **6** performing better with electron-rich olefins. Finally, the methods presented in equations 10 and 11 were applied to the synthesis of the estrogen receptor antagonist (*Z*)-tamoxifen.



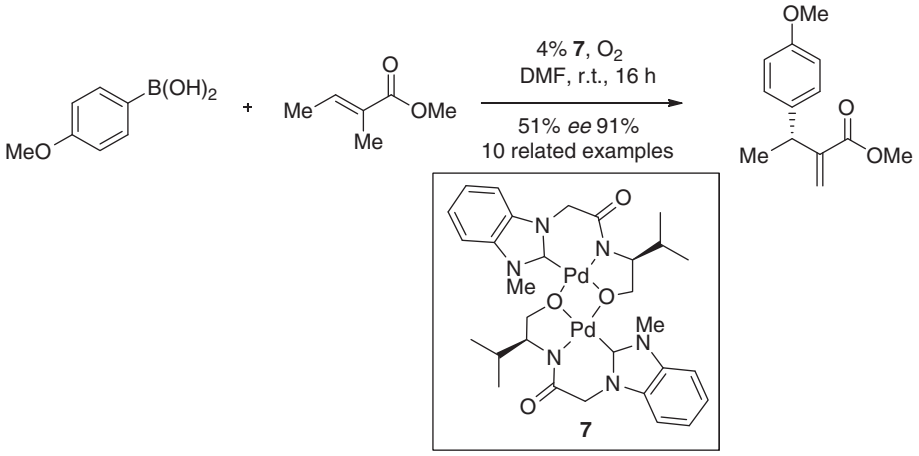
(11)

An oxidative Heck arylation strategy has been successfully utilized in the stereoselective synthesis of tri-substituted enamides.[78] The reaction performed well with electronically diverse 3- and 4-substituted arylboronic acids; however, no successful examples of 2-substituted arylboronic acids were reported (equation 12). A variety of different amides, including cyclic, acyclic, aromatic, secondary, and tertiary amides, were also well tolerated. Full regio- and stereoselectivity was observed using enamides bearing an electron-withdrawing group (ester or amide) and, as expected, regioselectivity decreases for substrates lacking an electron-withdrawing group.

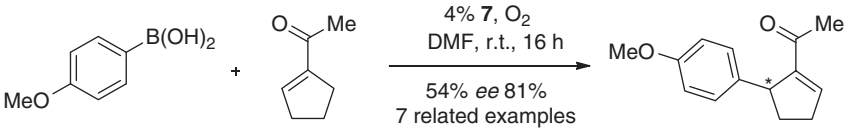


(12)

Asymmetric catalysis has become an indispensable tool in modern organic chemistry, especially in the synthesis of biologically active molecules. Surprisingly, there are only a limited number of reports concerning asymmetric oxidative Heck reactions. One of the most useful protocols, in terms of enantioselectivity, utilizes the chiral tridentate *N*-heterocyclic carbene palladacycle **7** to induce chirality (equation 13).[79] The use of **7** together with O_2 as the reoxidant afforded moderate yields and high enantioselectivies for the arylation of dialkyl-acrylates (equation 13) and 1-substituted cyclopentene derivatives (equation 14). Unfortunately, **7** is not commercially available, thus limiting the utility of this procedure.



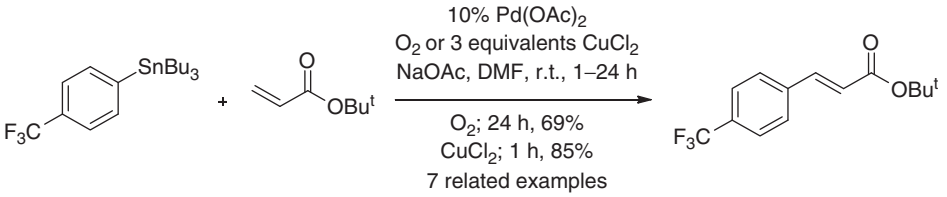
(13)



(14)

7.18.2.1.2 Arylstannanes

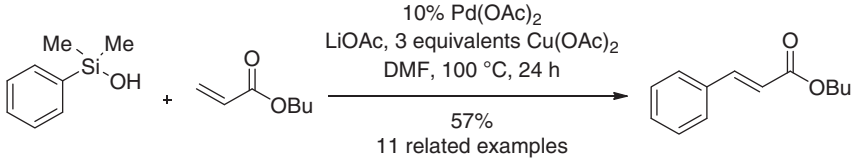
Arylstannanes have been reported as competent coupling partners in the oxidative Heck reaction.[80] The most useful conditions employ aryltributylstannanes, $Pd(OAc)_2$, NaOAc, and either O_2 or $CuCl_2$ as the reoxidant.[40] The O_2 protocol displayed wider substrate scope in terms of compatible olefins; however, $CuCl_2$ was the preferred reoxidant for the coupling of electron-poor and 2-substituted arylstannanes. Notably, the reaction takes place at room temperature and afforded good-to-excellent yields of *β*-arylated styrene and acrylate products (equation 15). Notwithstanding these factors, the inherent advantages of arylboronic derivatives (lower toxicity, lower cost, greener, widespread availability, and simplifed purification) render them much more attractive arylating agents than the corresponding arylstannanes.



(15)

7.18.2.1.3 Arylsilanols

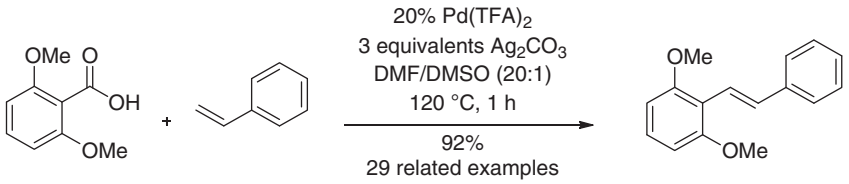
Arylsilanols can also be used as alternative aryl sources in oxidative Heck reactions.[41] Moderate yields of the standard *β*-arylated products were obtained using conditions similar to those in equation 3 (i.e., $Pd(OAc)_2$, LiOAc, and $Cu(OAc)_2$) with a number of electron-deficient olefins (equation 16). The reaction was also found to tolerate electronically diverse and 2-substituted arylsilanols, all of which afforded similar yields (*c.* 50%) to the parent substrate, dimethyl(phenyl)silanol. This reaction has also been shown to proceed under rhodium catalysis using the hydroxorhodium complex $[Rh(OH)(cod)]_2$.[81] Despite showing promise as an environmentally friendly aryl source, the widespread use of arylsilanols has undoubtedly been hampered by their limited commercial availability.



(16)

7.18.2.1.4 Aryl carboxylic acids

The development of decarboxylative coupling reactions bears a striking resemblance to that of the oxidative Heck reaction. The first metal-catalyzed decarboxylative cross-coupling was reported in 1966;[82] however, it took almost 40 years before chemists rediscovered the process and began to exploit its synthetic potential. In 2002, Meyers and coworkers reported the first modern palladium-catalyzed decarboxylative coupling, namely, the oxidative Heck arylation of electron-poor alkenes, using aryl carboxylic acids as the aryl source.[10] The optimal reaction conditions were found to be $Pd(TFA)_2$, Ag_2CO_3, and 5% DMSO/DMF, with each component proving critical to the reaction outcome. The electron-deficient catalyst is believed to facilitate coordination of palladium to the *ipso* carbon, allowing decarboxylation to occur; Ag_2CO_3 presumably functions both as a base and reoxidant; and DMSO acts as a palladium ligand and solvent, which, at high concentrations, impedes the reaction. The substrate scope in this reaction was limited to 2-substituted aryl or heteroaryl-2-carboxylic acids; however, a broad range of electron-deficient olefins, including various challenging 2-cycloalken-1-ones,[83] was found to be compatible (equation 17). This method has also been extended to the arylation of *p*-BQ with various electron-rich 2-substituted aryl carboxylic acids.[84] The attractiveness of this method is limited by the high catalyst loadings, the use of stoichiometric amounts of the expensive reoxidant Ag_2CO_3, and the need for 2-substituents on the aryl carboxylic acid. Indeed, this restriction to 2-substituted aryl carboxylic acids is a pervading issue in decarboxylative cross-coupling chemistry. Although various conditions have been developed to allow the use of 2-unsubstituted aryl carboxylic acids,[85] the majority of reported decarboxylative reactions feature 2-substituted carboxylic acids. On one hand, this can be seen as a limitation, restricting the scope of this method. On the other, this substrate preference can also be viewed as an advantage, as many traditional cross-coupling reactions perform best on sterically unencumbered substrates lacking 2-substituents.



(17)

Mechanistically, the decarboxylative Heck reaction proceeds via the initial formation of a palladium carboxylate species from a palladium(II) precursor through a carboxylate exchange process (Figure 10). Decarboxylation then takes place, generating the key arylpalladium intermediate and a molecule of carbon dioxide. Following formation of the arylpalladium species, the remaining catalytic steps resemble those in the traditional oxidative Heck reaction (i.e., migratory insertion, β-hydride elimination, and reoxidation).

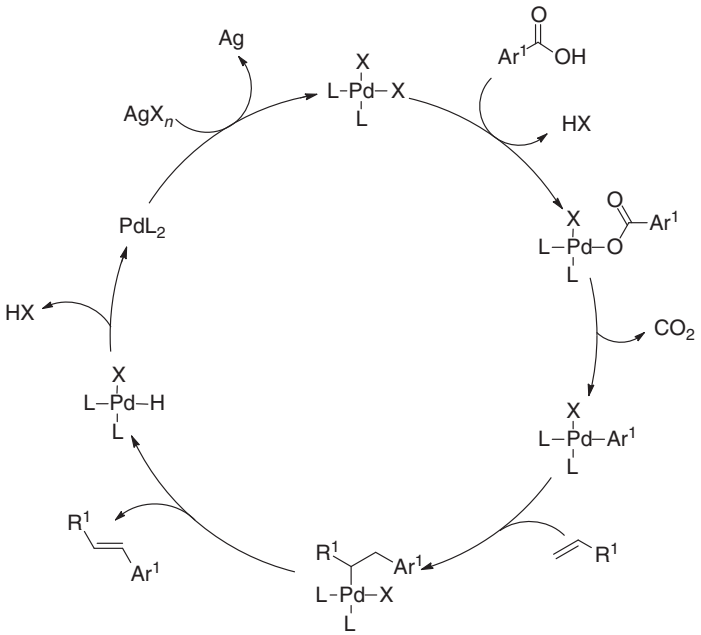
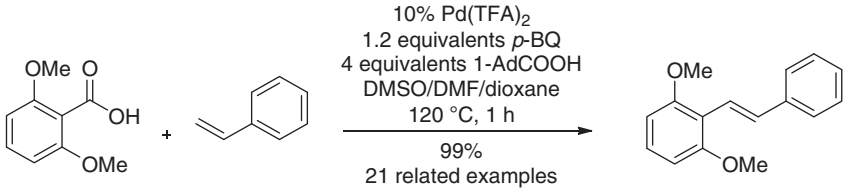


Figure 10 General mechanism of the decarboxylative Heck reaction.

The decarboxylative Heck reaction can also be performed using *p*-BQ instead of silver carbonate when 1-adamantane carboxylic acid (1-AdCOOH) is included as an additive.[45] Although this study was focused mainly on the arylation of aliphatic alkenes (see Section 7.18.2.2.2), there were a number of examples presented involving electron-deficient olefins (equation 18). This method provides a more inexpensive alternative to that shown in equation 17; however, the substrate scope is restricted to electron-rich aryl carboxylic acids bearing 2-substituents.



(18)

Electron-poor 2-nitrobenzoates can be effectively used as substrates for the decarboxylative Heck reaction using a bimetallic Cu/Pd catalyst system.[86] In contrast to the mechanism outlined in Figure 10, the decarboxylation step is believed to be mediated by CuF_2, which forms an arylcopper species that subsequently undergoes transmetalation to generate the key arylpalladium intermediate (Figure 11). This protocol was compatible with a variety of electron-deficient olefins including styrenes, acrylates, and acrylamide and delivered good yields of the standard (*E*)-configured linear products (equation 19). Unfortunately, the reaction was limited to 2-nitrobenzoates and only trace amounts of product were detected using other 2-substituted aryl carboxylates. Additional limitations of this method include its moisture sensitivity and the expensive nature of the nitrogen ligand and copper salt.

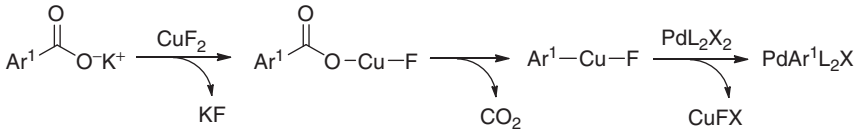
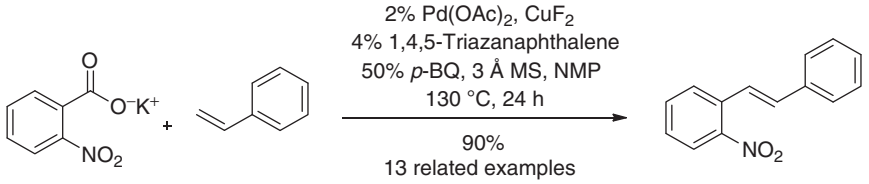
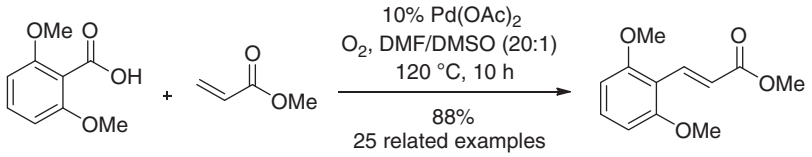


Figure 11 Formation of the key arylpalladium species via a Cu-mediated decarboxylation/transmetalation sequence.



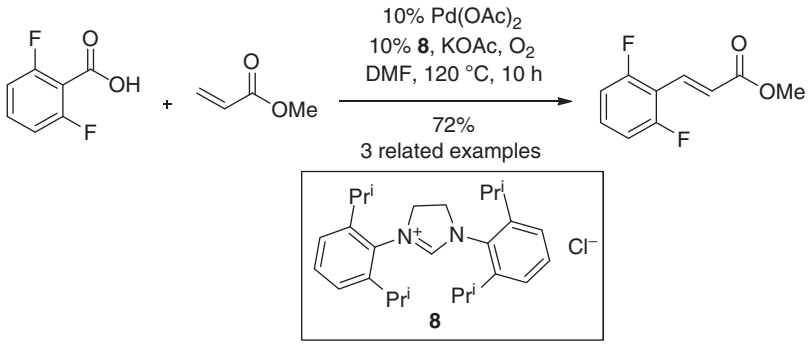
(19)

Oxygen has also been reported as an efficient palladium reoxidant in the decarboxylative Heck reaction.[87] The use of oxygen was found to eliminate the need to add Ag or Cu salts and to facilitate the olefination of both electron-rich and electron-poor aryl carboxylic acids. Electron-rich carboxylic acids were found to react effectively with an array of electron-deficient olefins in the presence of palladium acetate under 1 atm of oxygen (equation 20). The reaction was found to be more efficient when higher oxygen pressures (1.8–3.2 atm) were used, allowing the catalyst loading to be reduced and, in some cases, affording higher product yields.



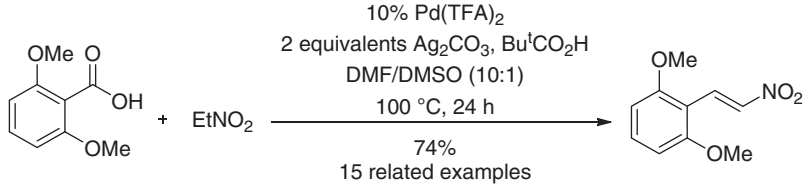
(20)

The *N*-heterocyclic carbene ligand 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidene (**8**) in combination with palladium acetate was found to catalyze the decarboxylative Heck reaction of electron-deficient aryl carboxylic acids with various acrylates (equation 21).[87] Although only four examples were reported and the isolated yields were moderate, this method still provides a valuable alternative to the Cu- and Ag-based protocols for the coupling of electron-poor 2-substituted aryl carboxylic acids.



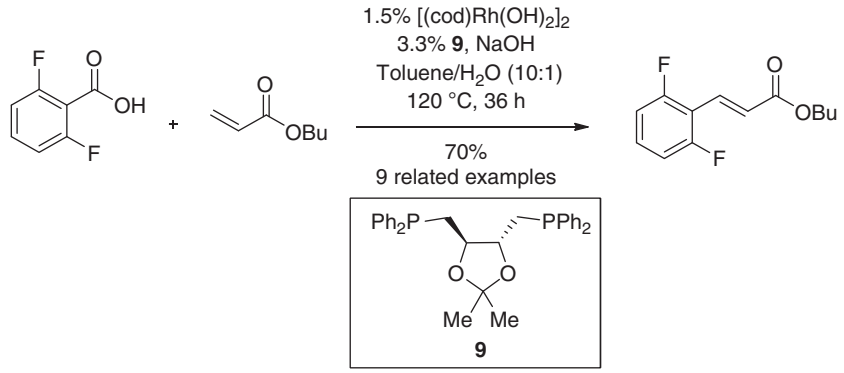
(21)

The formation of (*E*)-*β*-nitrostyrenes from aryl carboxylic acids and nitroethane using a bimetallic Pd/Ag system has been reported (equation 22).[88] Although the reaction mechanism was not investigated in detail, it is believed to occur via an initial *in situ* oxidation of nitroethane to nitroethylene, followed by a decarboxylative Heck coupling. Despite the uncertainty surrounding the mechanism, this protocol provides a straightforward entry to (*E*)-*β*-nitrostyrenes, a class of compounds that, at the time of writing this chapter, cannot be accessed via a traditional Mizoroki–Heck approach.



(22)

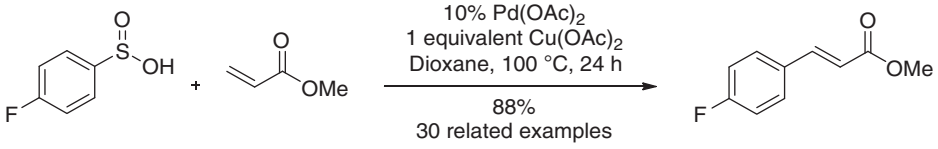
Finally, decarboxylative Heck-type reactions can also be performed under Rh(I) catalysis using a combination of [(cod)Rh(OH)$_2$]$_2$ and (*R*,*R*)-DIOP (**9**; equation 23).[89] Unfortunately, the scope of the reaction was limited to acrylate substrates, which, in combination with the expensive catalyst system, reduces the synthetic appeal of the procedure.



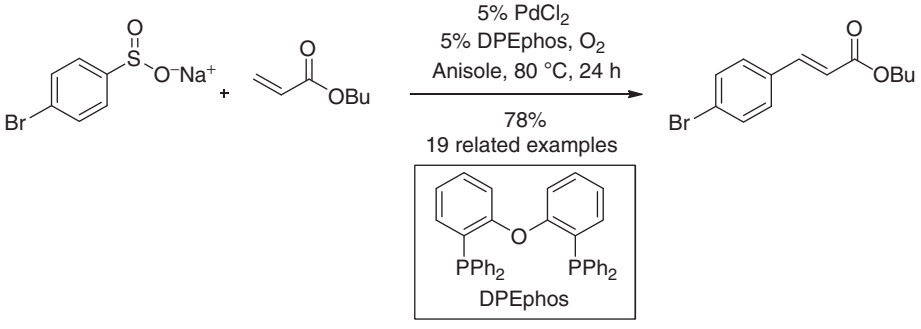
(23)

7.18.2.1.5 Aryl sulfinic acids, sulfinates, and sulfonyl hydrazides

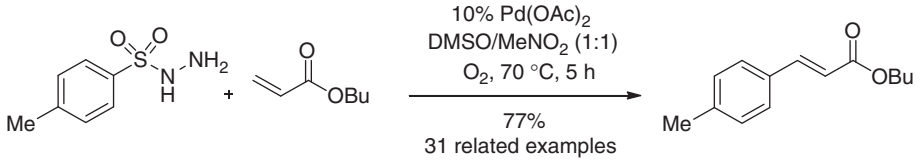
Cross-coupling reactions involving generation of the key arylpalladium intermediate via desulfitative processes have attracted considerable interest over the past few years. At present, three different substrate types, aryl sulfinic acids (equation 24),[90] aryl sulfinates (equation 25),[91] and aryl sulfonyl hydrazides (equation 26),[92] have been reported as efficient substrates for the desulfitative Heck reaction. All three protocols were applicable to a range of electronically diverse arylpalladium precursors and various styrene, acrylate, and acrylamide substrates, giving generally high yields of the standard *β*-arylated products. In contrast to the decarboxylative Heck reaction, the desulfitative methods demonstrated a wider substrate scope and were applicable to substrates lacking a 2-substituent. This has been attributed to the more facile extrusion of sulfur dioxide as compared to carbon dioxide. All three methods are, however, restricted by the lack of commercially available substrates and, in the case aryl sulfinic acids and sulfinates, their nontrivial synthesis and purification. In this respect, sulfonyl hydrazines are the preferred substrates due to their more convenient preparation.



(24)



(25)

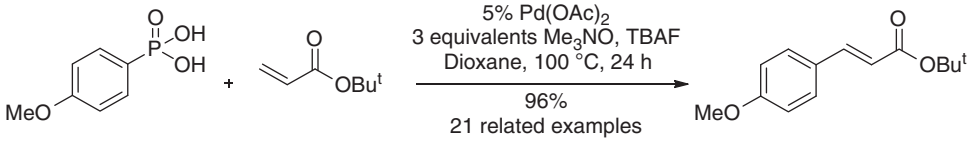


(26)

7.18.2.1.6 Aryl phosphonic acids

Aryl phosphonic acids undergo oxidative Heck-type reactions with styrenes, acrylates, and acrylamides to generate good yields of *β*-arylated products (equation 27).[47] The method employs palladium acetate as the catalyst and trimethylamine *N*-oxide as the

reoxidant, while tetrabutylammonium fluoride (TBAF) was found to be a crucial additive and presumably activates the C–P bond toward palladium insertion. As with the aryl sulfur derivatives described in Section 7.18.2.1.5, this method suffers from a lack of commercially available substrates and simple methods for their preparation.



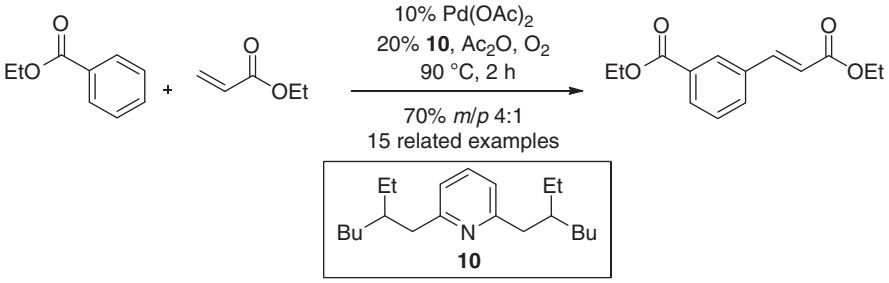
(27)

7.18.2.1.7 Arenes and heteroarenes

The first example of an oxidative coupling between an arene and an olefin (this reaction has been given many different names over the years but will be referred to here as the dehydrogenative Heck reaction) was reported by Fujiwara and Moritani in 1967.[2] Although the reaction required stoichiometric amounts of palladium and produced only modest yields of Heck-type products, it represents a landmark in the development of modern organometallic chemistry. This reaction type has been extensively developed over the past decade and there is now a plethora of methods available for the dehydrogenative olefination of various aromatic and heteroaromatic C–H bonds. Rather than presenting an exhaustive account of the literature, this section is intended to cover some of the more recent and synthetically useful advances in this area. For more comprehensive reviews on this topic the reader is directed to the recent reviews by Le Bras and Muzart,[93] Glorius and coworkers,[94] Yeung and Dong,[48] and Kozhushkov and Ackermann.[95] The material in this section is divided into two parts: substrates without directing groups and substrates with directing groups.

7.18.2.1.7.1 Substrates without directing groups

Simple arenes are challenging substrates for C–H functionalization chemistry due to their sluggish reactivity and, even if this problem can be overcome, they generally lead to the formation of isomeric product mixtures. Recently, progress has been made toward addressing these problems by utilizing the commercially available pyridine ligand **10** to enhance reactivity and control the reaction outcome. Ligand **10** in combination with $Pd(OAc)_2$, Ac_2O, and oxygen as the terminal reoxidant has been shown to afford good yields of the *β*-arylated products using various electron-deficient arenes and olefins (equation 28).[96] Good selectivity toward the *meta*-substituted products (typically *m*/*p*; 4/1) was achieved due to a combination of the sterically demanding ligand, which hindered *ortho*-substitution, and the inherent *meta*-directing properties of the electron-poor arenes.[97] In addition, ethyl acrylate was also effectively phenylated under these conditions. Finally, 3,5-dichloropyridine has also been identified as a suitable ligand for this reaction; however, lower selectivities were obtained due to competing formation of *ortho*-substituted products.[98]

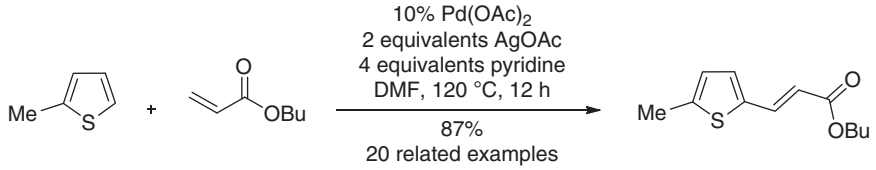


(28)

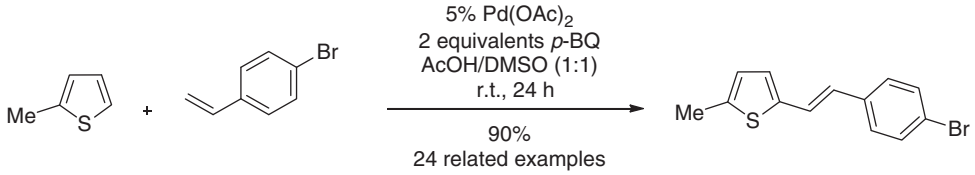
Pentafluorobenzene can undergo dehydrogenative olefination with a wide range of electron-deficient olefins using $Pd(OAc)_2$, Ag_2CO_3, and a mixed solvent system of DMSO in DMF.[99] Good yields and high (*E*)-selectivities were obtained for this substrate; however, the use of other perfluorinated benzene derivatives led to lower stereoselectivities and mixtures of mono- and di-alkenylated products.

In contrast to simple arenes, there are numerous examples of the successful use of electronically biased heterocycles as substrates in the dehydrogenative Heck reaction. These substrates generally exhibit higher reactivity due to their lower aromatic resonance energy, increased C–H acidity, and increased susceptibility to electrophilic attack. The remainder of this section describes the dehydrogenative Heck reaction of various heterocyclic systems.

Thiophenes and furans have been reported as suitable substrates for the dehydrogenative Heck reaction with acrylate derivatives (equation 29)[100] and styrenes (equation 30).[101] In both studies the majority of examples concerned the C5-olefination of 2-substituted furans and thiophenes. In cases where both the 2- and 5-positions were blocked, olefination occurred at 3-position, albeit with reduced efficiency. Mechanistically, both reactions are believed to commence with an electrophilic palladation (S_EAr), which is in accordance with the observed regioselectivity and preference for electron-donating substituents.

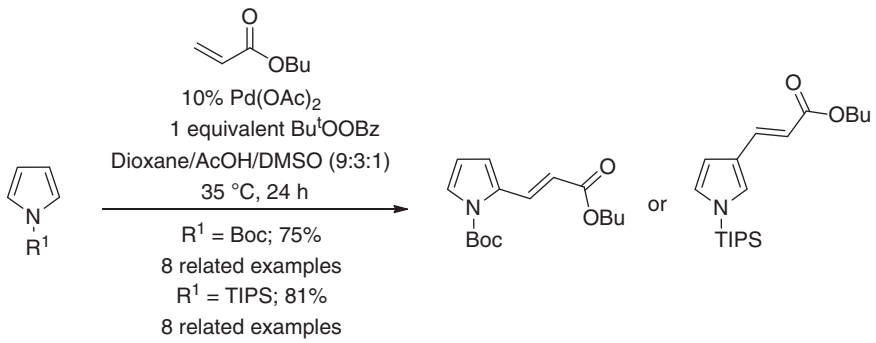


(29)



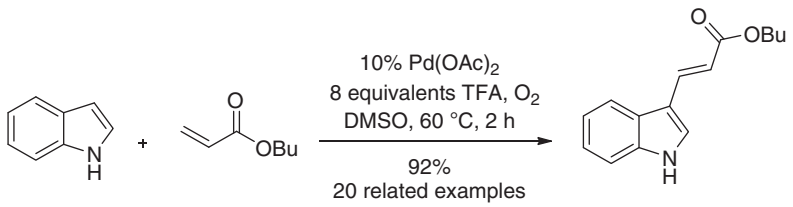
(30)

The regioselective dehydrogenative Heck reaction of pyrroles can be elegantly controlled through the judicious choice of the appropriate *N*-protecting group.[102] *N*-Boc pyrrole was found to undergo exclusive C2-olefination when treated with $Pd(OAc)_2$ and *t*-Butyl peroxybenzoate (Bu^tOOBz) in a dioxane/AcOH/DMSO solvent system with a variety of electron-deficient olefins (equation 31). In contrast, the reaction of *N*-TIPS pyrrole under identical conditions afforded only C3-alkenylated products (equation 31). The selectivity switch was attributed to the bulky TIPS group, which prevents C2 palladation and forces the metalation to take place at C3. Finally, the reaction could also be performed using either air or oxygen as the reoxidant; however, for less reactive olefins the Bu^tOOBz system was preferred.

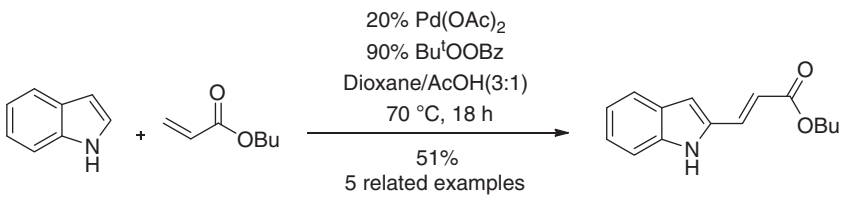


(31)

The regioselective C3-alkenylation of free NH indoles can be achieved using $Pd(OAc)_2$ as the catalyst, oxygen as the terminal reoxidant, DMSO as the solvent, and TFA as a key additive (equation 32).[103] The acidic conditions were found to enhance reactivity, and good-to-excellent yields of the C3-alkenylated products were obtained with a wide range of electron-deficient olefins and indole derivatives. This reaction can also be conducted under more neutral conditions using $Cu(OAc)_2$ as the stoichiometric oxidant.[104] In addition, the C2-functionalized indole products can be prepared in moderate yields and good selectivities when a weakly coordinating solvent system is used (dioxane:AcOH) in conjunction with Bu^tOOBz as the reoxidant (equation 33).[104] In this case, the high catalyst loadings detract from the overall attractiveness of the method.



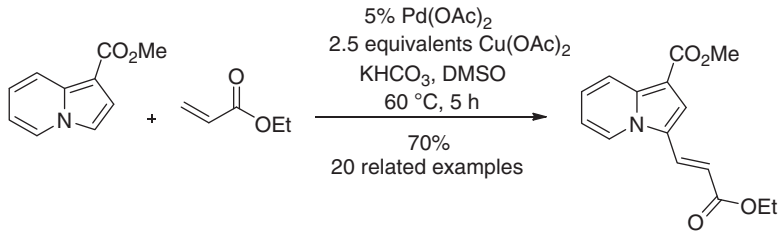
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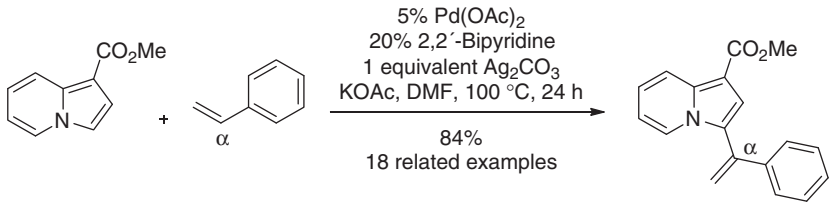
(33)

The regioselective C3-olefination of indolizines has been demonstrated using acrylates[105] and styrenes[106] as coupling partners. In the former reaction, the traditional *β*-arylated products were obtained in good yields using a variety of 1-substituted indolizines

(equation 34). In contrast, the coupling of styrenes and indolizines in the presence of $Pd(OAc)_2$ and 2,2′-bipyridine afforded the α-substituted products exclusively (equation 35). The reaction was compatible with a number of 1-substituted indolizines and styrenes; however, highly electron-deficient styrenes failed to react under the optimized conditions. This is a rare example of an α-selective Heck reaction of a styrene derivative, and, although the mechanism was not investigated in detail, the authors suggest that reaction occurs via the cationic pathway, leading to the observed selectivity (see Section 7.18.2). However, the complete α-selectivity observed in this reaction indicates that, in addition to electronic effects, other factors, possibly steric shielding or chelation effects, may also be operating.

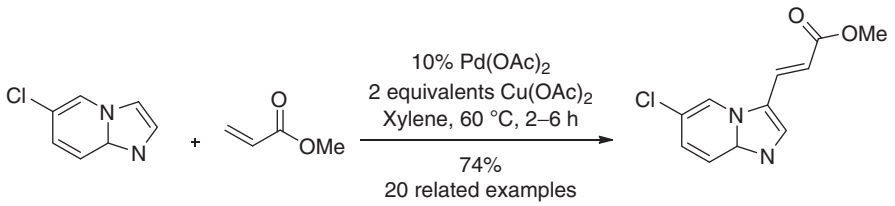


(34)



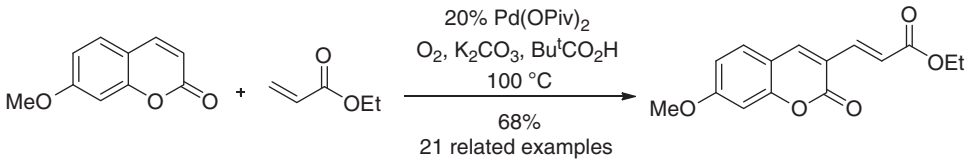
(35)

The C3-alkenylation of imidazolo[1,2-*a*]pyridines has been reported, under ligandless conditions, using $Pd(OAc)_2$ as the catalyst and $Cu(OAc)_2$ as the palladium reoxidant.[107] Good yields were achieved using various acrylates and vinyl ketones; however, acrylonitrile returned only low yields and a mixture of α- and *β*-arylated products was obtained with styrene (equation 36).



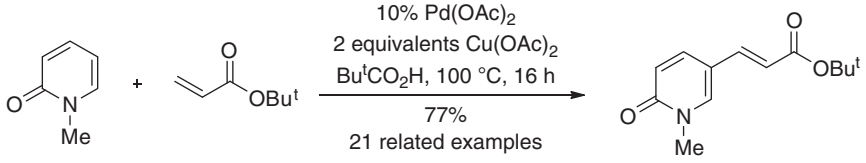
(36)

Chromones[108] and coumarins[109] undergo regioselective C3-alkenylation with electron-deficient olefins under palladium(II) catalysis. The former requires stoichiometric amounts of Ag_2CO_3 and $Cu(OAc)_2$ to achieve optimal results, thus limiting the benefits derived from the C–H functionalization. Although the latter protocol employs O_2 as the palladium reoxidant and K_2CO_3 as the base, the use of high loadings of the expensive catalyst $Pd(OPiv)_2$ reduces its synthetic attractiveness (equation 37).



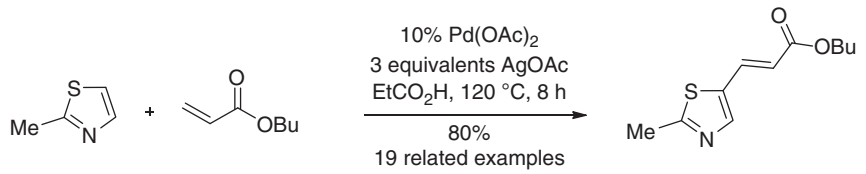
(37)

A palladium(II)-catalyzed method for the regioselective olefination of *N*-protected 2-pyridones has recently been reported.[110] Using $Pd(OAc)_2$ as the catalyst and $Cu(OAc)_2$ as the reoxidant a number of simple *N*-alkyl or *N*-aryl 2-pyridones underwent C5 functionalization with various acrylates and styrenes (equation 38). The introduction of C4- or C6-substituents effectively blocked the C5 position, allowing functionalization to take place at C3. In this case, the use of more expensive Ag salts instead of $Cu(OAc)_2$ was required to achieve full conversion.



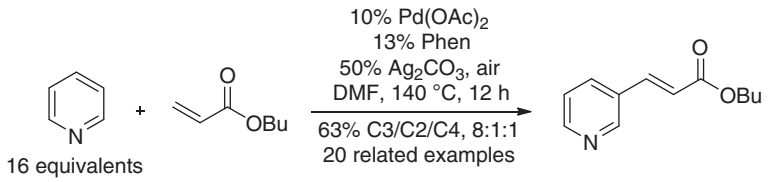
(38)

2-Substituted oxazoles and thiazoles have been utilized as suitable substrates for the dehydrogenative Heck reaction.[111] These heterocycles are selectively C5-alkenylated with acrylates and styrenes in the presence of $Pd(OAc)_2$ and AgOAc. The reaction tolerates a range of 2-substituents, including a free hydroxyl group, and even 2,4-disubstituted azoles were found to be compatible (equation 39). The C4-olefination of oxazoles has also been reported; however, the reaction was only exemplified using two different oxazoles.[112]



(39)

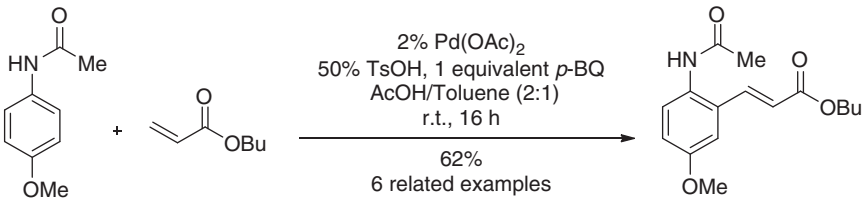
The C3 selective dehydrogenative olefination of pyridines has been described using $Pd(OAc)_2$ and phen as the catalytic system and Ag_2CO_3/air to regenerate Pd(II).[113] Good-to-excellent levels of regioselectivity (4.5/1–30/1) and useful yields (36–73%) were obtained with a range of pyridines bearing electron-withdrawing or electron-donating groups (equation 40). With respect to olefin compatibility, acrylates, acrylamides, and styrenes were all well tolerated. Unfortunately, the low reactivity of the pyridine C–H bond makes it necessary to employ a large excess (16-fold) of the pyridine substrate, thus limiting the synthetic appeal of the process.



(40)

7.18.2.1.7.2 Substrates with directing groups

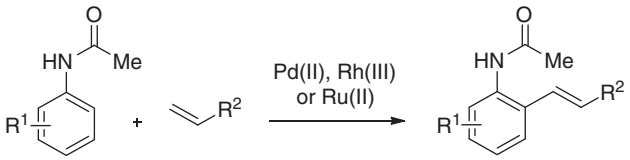
In 2002, de Fries and van Leeuwen reported their seminal discovery of a regioselective *ortho*-alkenylation reaction where a secondary amine group was used to facilitate the C–H functionalization process.[114] The authors demonstrated that various electron-rich acetanilides could be selectively alkenylated with butyl acrylate, in moderate-to-good yields, in the presence of $Pd(OAc)_2$ and *p*-TsOH using *p*-BQ as the reoxidant (equation 41). The addition of strong organic acids (*p*-TsOH or TFA) was found to be beneficial, indicating that efficient metalation requires a highly electrophilic Pd(II) center. This is in accordance with the results from competing experiments, where electron-rich arenes were found to react significantly faster than their electron-poor counterparts. Remarkably, the reaction proceeds at room temperature and employs only 2 mol% of the catalyst; however, the preparative scope is limited to electron-rich anilides. Similar reactions have also been carried out in water containing polyoxyethanyl α-tocopheryl sebacate (PTS) using the cationic palladium complex $[Pd(MeCN)_4](BF_4)_2$.[115] Although these reactions take place without an acid additive, they require the use of an expensive catalyst and are also limited to electron-rich anilides. More recently, a reaction system that promotes the olefination of a wider range of acetanilide substrates has been demonstrated.[116] The use of $Pd(OAc)_2$ with $K_2S_2O_8$ as the oxidant in a TFA/CH_2Cl_2 solvent system was found to afford moderate-to-good yields of the alkenylated products using electron-poor, electron-rich, and even 2-substituted acetanilides (method A, **Table 2**). Despite the impressive substrate scope, this reaction requires highly acidic conditions, a factor that will certainly limit its application in large-scale applications and in the synthesis of more complex target molecules.



(41)

The dehydrogenative Heck-type reaction of acetanilides has also been reported under Rh(III)[117] and Ru(II) catalysis.[118] A summary of the three different transition-metal-catalyzed protocols is presented in **Table 2**. Compared to the palladium-catalyzed

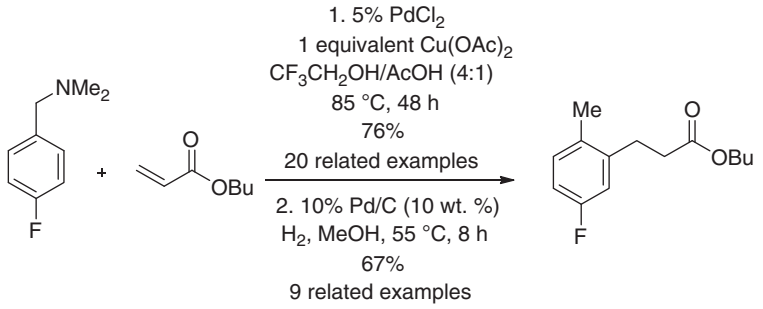
Table 2 The dehydrogenative alkenylation of acetanilides under Pd(II), Rh(III), or Ru(II) catalysis



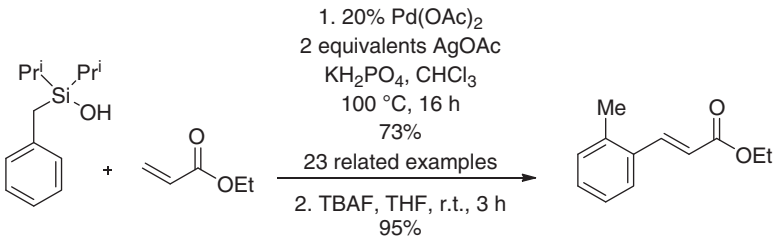
Conditions	*Substrate scope*	*No. of examples*	*Yield (%)*	*References*
Method A: 5% $Pd(OAc)_2$, 1 equivalent $K_2S_2O_8$, TFA/CH_2Cl_2 (4:1), r.t., 20–48 h	Acetanilides: e-poor, e-rich, 2-substituted Olefin: acrylates	31	37–88	116
Method B: 0.5% $[RhCp*Cl_2]_2$, 2% $AgSbF_6$, 2.1 equivalents $Cu(OAc)_2$, *t*-AmylOH, 120 °C, 16 h	Acetanilides: e^- poor, e^- rich, 2-substituted Olefin: acrylates, styrenes, ethylene	17	47–98	117
Method C: 5% $[RuCl_2(p\text{-cymene})]_2$, 10% KPF_6, 1 equivalent $Cu(OAc)_2$, H_2O, 120 °C, 20 h	Acetanilides: e^- poor, e^- rich Olefin: acrylates	13	52–74	118

method (method A), both the Rh (method B) and Ru (method C) protocols require elevated reaction temperatures, but importantly do not need a highly acidic reaction medium. Method B appears to be the most versatile as it was found to be compatible with a diverse range of acetanilide and olefin substrates. Although the catalytic system in method B is considerably more expensive than the other two, the low catalyst loadings mean that the cost per reaction is actually lower than in methods A and C. In addition, conditions similar to those in methods B and C have been found to promote the dehydrogenative olefination of a range of different aryl substrates including benzamides,[118,119] aromatic esters,[120,121] and carbamates.[122,123] Finally, the olefination of *N*-methoxybenzamides can be achieved under Ru(II)[124] or Ru(III) catalysis[125] in the absence of an external oxidant, as the N–O bond serves as a sacrificial internal oxidant generating *ortho*-olefinated primary benzamide products.

The *N*,*N*-dimethylamino (**Scheme 1**)[126] and diisopropylsilanol (**Scheme 2**)[127] moieties have been utilized as removable directing groups for the *ortho*-olefination of arene derivatives. In both cases a range of electronically diverse aryl substituents was tolerated and the reactions performed best using activated acrylates. In addition, the directing groups could be effectively removed, under mild conditions, to afford *ortho*-substituted toluene derivatives.

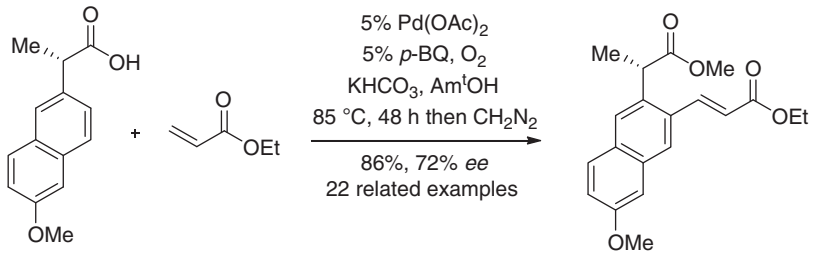


Scheme 1



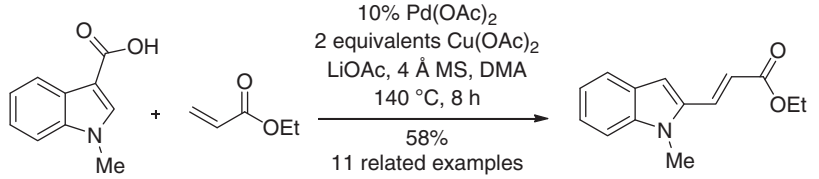
Scheme 2

The carboxylate group has been utilized to direct the *ortho*-alkenylation of phenylacetic acids with various acrylates, methyl vinyl ketone, and styrene.[128,129] Interestingly, the reactions were conducted under basic conditions and reoxidation was facilitated by catalytic quantities of *p*-BQ and 1 atm of oxygen. Moderate-to-excellent yields of the olefinated products were prepared from a broad array of diversely substituted phenylacetic acids (equation 42). Notably, the reaction was performed successfully on the nonsteroidal anti-inflammatory drugs ketoprofen, ibuprofen, and naproxen. In the latter case, an erosion in enantiomeric excess (*ee*) was observed when the reaction was conducted with an optically pure starting material (97% vs. 72%). Various *N*-protected amino acids were found to increase the efficiency of the reaction, extending the reaction scope to include benzylacetic acids and increase regioselectivity for substrates containing two reactive *ortho* C–H groups. Furthermore, these ligand-modulated conditions could also be applied to the di-olefination of phenylacetic acids[130] and the enantioselective olefination of diphenylacetic acids.[131]



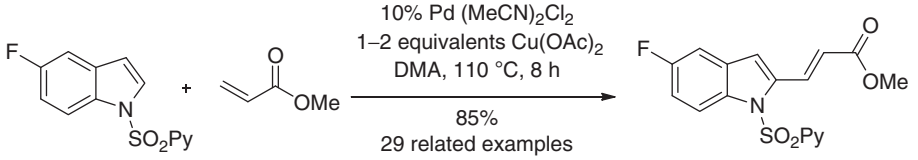
(42)

The carboxylate group has also been used as a traceless directing group to produce 2-alkenylated indoles.[132] In this study a small number of *N*-protected indole-3-carboxylic acids were coupled with various acrylates and styrene to generate moderate yields of the 2-fuctionalized indole products (equation 43). The reaction is believed to proceed via an *ortho*-palladation/reductive decarboxylation sequence. In addition, this method was extended to the C3-olefination of various heteroaryl-2-carboxylic acids and the C3-olefination of 1-methylindole-2-carboxylic acid.

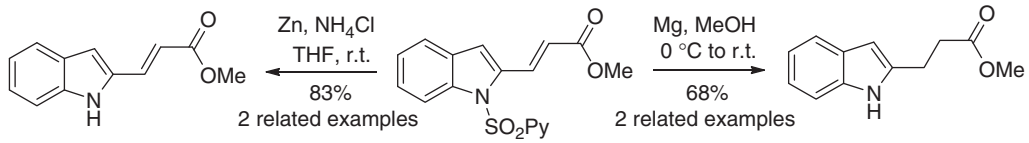


(43)

The regioselective C2-alkenylation of indoles and pyrroles has also been accomplished using the *N*-(2-pyridyl)sulfonyl group to directly facilitate *ortho*-palladation.[133] The reaction demonstrated a broad substrate scope and various electron-deficient olefins, including challenging 1,2-disubstituted alkenes, and various indole and pyrrole substituents were all effectively coupled (equation 44). Generally, isolated yields of approximately 70% were obtained and the reactions gave the C2-alkenylated isomer exclusively. Importantly, two sets of conditions were developed for the removal of the directing group, affording either the saturated or the unsaturated products (**Scheme 3**). In addition, this strategy has also been applied to the *ortho*-dehydrogenative Heck reaction of arenes.[134]



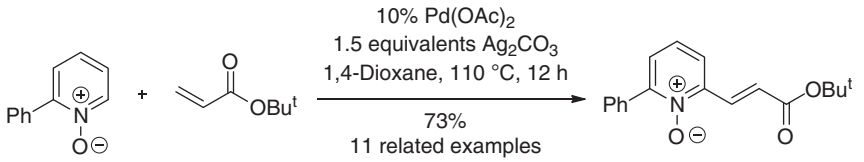
(44)



Scheme 3

The regioselective C2-alkenylation of pyridine *N*-oxides (equation 45)[135] and quinoline *N*-oxides (equation 46)[136] can be accomplished under palladium catalysis. In the former reaction, the optimal reaction conditions consisted of Ag_2CO_3 as the

external reoxidant and pyridine as an additive. In the latter reaction no external reoxidant was required, as the N–O bond served as a sacrificial internal reoxidant. In both cases the reactions performed well with a range of electron-deficient olefins; however, only a limited number of heterocyclic derivatives were evaluated.



(45)

(46)

Recently, the first *meta*-directed dehydrogenative olefination reaction was reported using an 'end on' interaction between a distal nitrile group and the palladium center.[137] The authors described two different linker classes (toluene and hydrocinnamic acid derivatives) that were designed to form energetically favorable 12- and 13-membered pretransition states with the target *meta* C–H (**11** and **12**, respectively; Figure 12). The use of these linkers enabled impressive levels of *meta*-selectivity (typically > 10:1) to be obtained and a broad substrate scope was observed. Remarkably, the toluene-derived linker even facilitated the arylation of di- and tri-substituted olefins and tetrasubstituted arenes could be prepared using both systems (equation 47). This high tolerance toward steric hindrance was attributed to the weak coordination between the nitrile and palladium, allowing it to be displaced by the incoming olefin before migratory insertion. The toluene linker could be efficiently removed via hydrogenolysis, to unmask *meta*-alkylated toluene derivatives. The hydrocinnamic acid linker could be removed under basic conditions and, importantly, could also be recovered after hydrolysis. This approach represents a valuable first step toward the development of general *meta*-selective C–H functionalization reactions; however, the large size and high cost associated with the linker will need to be addressed before the process becomes attractive for the synthesis of target molecules.

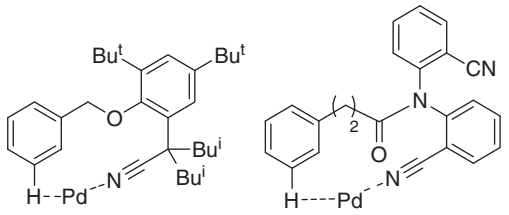
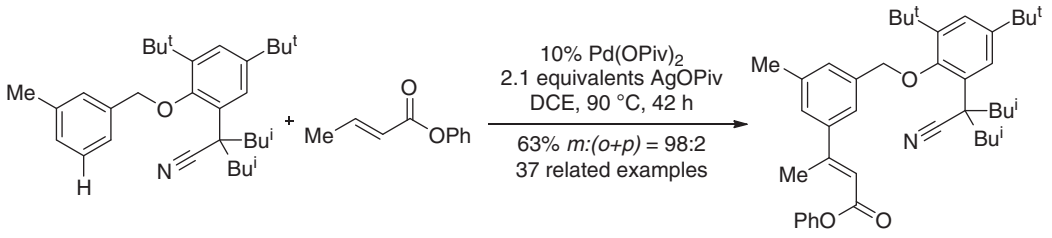


Figure 12 Toluene- (**11**) and hydrocinnamic acid (**12**)-derived templates for *meta*-selective C–H functionalization via an 'end on' interaction.



(47)

7.18.2.2 With Electron-Rich, Neutral, and Allylic Olefins Using Aryl–Z (Z = M, acid, H)

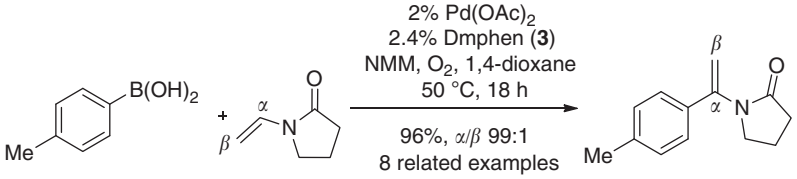
This section describes the intermolecular arylations of electron-rich, neutral, and allylic olefins. These are somewhat more complicated transformations than the arylation of electron-poor olefins, and the section is dominated by examples of arylations of electron-rich olefins and allylic esters.

The most frequently employed arylating agents in this section are arylboron derivatives, but a few examples using arenes and carboxylic acids will also be described. This section is organized into the following subsections: arylboron derivatives, aryl carboxylic acids, and arenes, based on the nature of the arylating agent.

7.18.2.2.1 Arylboron derivatives

7.18.2.2.1.1 Electron-rich olefins

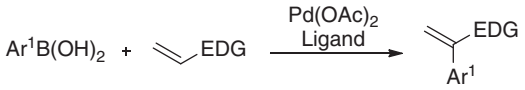
The oxidative Heck reaction using electron-rich olefins, such as vinyl ethers and enamides, can serve as an efficient route to obtain the corresponding acetophenone derivative of the arylating agent. In order for an oxidative Heck reaction to be synthetically useful the regioselectivity needs to be controlled (see Section 7.18.2.1). Efficient control over the regioselectivity with electron-rich olefins can be achieved using a suitable bidentate ligand. The first ligand-modulated oxidative Heck method using electron-rich olefins was developed by Larhed and coworkers (equation 48).[138] The method employed oxygen gas for environmentally benign reoxidation and it also enabled the use of the nitrogen bidentate ligand dmphen (**3**). The dmphen ligand binds strongly to copper and is therefore not suitable in reactions using copper as reoxidant. The dmphen ligand was used to promote palladium(II) regeneration and to control the regioselectivity, where internal arylation was strongly favored. This Heck method constitutes a facile and mild route to access functionalized enamides, and good yields of the internally (α) arylated enamides were obtained using electron-rich arylboronic acids, whereas electron-poor arylboronic acids provided moderate yields.

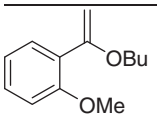
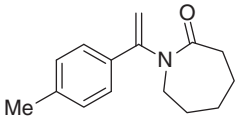
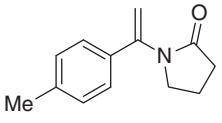
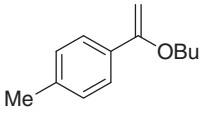
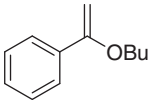


(48)

The use of oxygen gas as reoxidant, as reported by Larhed and coworkers[138] might be environmentally benign, but it requires the handling of pressurized gas cylinders, thereby reducing the convenience and safety of the procedure. By utilizing oxygen from the surrounding air, risks can be reduced and convenient open-vessel conditions can be employed. In a method developed by Enquist et al.,[68] oxygen from the air was efficiently used as the palladium reoxidant (**Table 3**, conditions B and C). As the oxygen content in air is relatively low ($\sim$21%), sufficient mass transport of oxygen into the reaction mixture may pose problems. In order to overcome this, reaction vessels possessing a large surface area (round-bottom flasks) and vigorous stirring were employed. The reactions could also be carried out at room temperature to further improve the safety and convenience of the process. Furthermore, performing reactions at ambient temperature can be beneficial for substrates with sensitive functionalities and would, in addition, save energy.

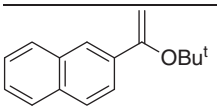
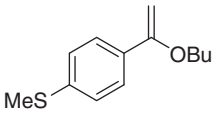
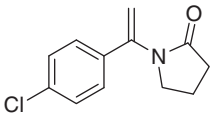
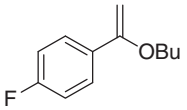
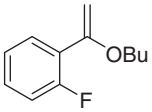
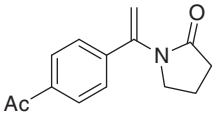
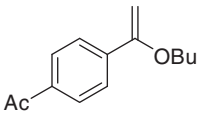
Table 3 Arylated electron-rich olefins prepared via the oxidative Heck reaction



Product	Conditions[a]	Reoxidant	Yield (%)	References
	A	–	74	72
	B	Air	57	68
	C	Air	67	68
	B	Air	71	68
	C	Air	68	68
	D	Air	70	16
	E	*p*-BQ	94	16
	A	–	92	72
	B	Air	35	68
	C	Air	91	68
	D	Air	91	16
	E	*p*-BQ	78	16
	A	–	89	72

(*Continued*)

Table 3 Continued

Product	Conditions[a]	Reoxidant	Yield (%)	References
	A	–	91	72
	F	*p*-BQ	85	70
	A	–	87	72
	F	*p*-BQ	43	70
	A	–	84	72
	A	–	61	72
	D	Air	15	16
	E	*p*-BQ	38	16
	A	–	75	72
	B	Air	35[b]	68
	C	Air	91[b]	68
	E	*p*-BQ	96	16
	G	*p*-BQ	66[b]	70

[a]Conditions A: arylboronic acid (1.0 mmol), olefin (2.0 mmol), $Pd(OAc)_2$ (0.02 mmol), dppp (0.03 mmol) and acetone (3 ml) at 70 °C for 15 h under N_2-atmosphere. Product isolated as the corresponding methyl ketone, after acidic hydrolysis (3 mol l^{-1} HCl). Conditions B: open vessel charged with arylboronic acid (2.0 mmol), olefin (1.0 mmol), *N*-methylmorpholine (2.0 mmol), $Pd(OAc)_2$ (0.02 mmol), dmphen (0.024 mmol), and MeCN (3 ml) under vigorous stirring at room temperature. Conditions C: open vessel charged with arylboronic acid (2.0 mmol), olefin (1.0 mmol), *N*-methylmorpholine (2.0 mmol), $Pd(OAc)_2$ (0.02 mmol), dmphen (0.024 mmol), and MeCN (3 ml) under vigorous stirring at 80 °C. Conditions D: open vessel charged with arylboronic acid (2.0 mmol), olefin (1.0 mmol), $Pd(OAc)_2$ (0.02 mmol), dmphen (0.024 mmol), and MeCN (3 ml) under vigorous stirring. Product isolated as the corresponding methyl ketone, after acidic hydrolysis (1 mol l^{-1} HCl). Conditions E: Pyrex glass vial charged with arylboronic acid (1.0 mmol), olefin (0.50 mmol), $Pd(OAc)_2$ (0.01 mmol), dmphen (0.012 mmol), *p*-benzoquinone (0.50 mmol), MeCN (2 ml), sealed under air and exposed to microwave irradiation for 10 min at 100 °C. Product isolated as the corresponding methyl ketone, after *in situ* hydrolysis. Conditions F: continuous flow conditions. Arylboronic acid (0.5 mmol, 0.25 mol l^{-1}), olefin (1 mmol, 0.5 mol l^{-1}), *p*-BQ (0.5 mmol, 0.25 mol l^{-1}), $Pd(OAc)_2$ (0.01 mmol, 0.005 m), dppp (0.011 mmol, 0.055 mol l^{-1}) in DMF, 130 °C, residence time 5 min. Product isolated as the corresponding methyl ketone, after subsequent hydrolysis with 1 mol l^{-1} HCl.

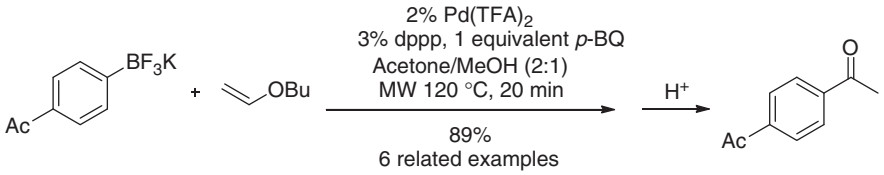
[b]Isolated as the corresponding methyl ketone after acidic *in situ* hydrolysis (glacial HOAc).

A modified method, using air as the palladium reoxidant and no dedicated base, was later reported by Lindh et al.[16] Under these base-free conditions, extensive hydrolysis of the arylated enamides and vinyl ether products occurred *in situ*, and the products were isolated as the corresponding acetophenones. In addition, the reactions could be performed at room temperature or with MW heating by introducing *p*-BQ as a stoichiometric reoxidant (Table 3, conditions D and E). The use of MW heating results in a significant reduction of reaction times, which must be weighed against the need to include a toxic stoichiometric reoxidant (*p*-BQ). Furthermore, this method is not suitable if the nonhydrolyzed product is desired (i.e., the arylated enamide or vinyl ether). The base-free method has also been successfully employed in continuous-flow chemistry,[70] where the electron-rich olefin *n*-butyl vinyl ether and a number of arylboronic acids were coupled. In the reaction, $Pd(OAc)_2$ and dppp served as a more thermostable catalytic system. As expected with the use of a bidentate ligand under cationic conditions, the reactions were highly regioselective in providing the internally (α) arylated products. The products were hydrolyzed before isolation as the corresponding acetophenones in moderate-to-good yields (Table 3, condition F).

In a recently developed method to perform base-free oxidative Heck reactions, acetone was used as solvent. No dedicated reoxidant was added and good yields were obtained for several arylations of vinyl ethers. The products were isolated as the corresponding acetophenones after treatment with 3 mol l^{-1} HCl at room temperature for 1 h. The reactions are carried out under a nitrogen atmosphere, which complicates the practical execution of the method (Table 3, condition A).[72]

The four methods described above can be regarded as the most useful for the arylation of electron-rich olefins using arylboronic acids. A summary of the reaction scope can be found in Table 3.

Very recently, an oxidative Heck arylation of *n*-butyl vinyl ether using aryltrifluoroborates as the arylpalladium precursor was reported by Sävmarker and coworkers.[21] Microwave irradiation was used to prepare the corresponding aryl methyl ketones, in useful yields, after hydrolysis with 1 M HCl (Scheme 4). The use of the bidentate phosphorus ligand dppp resulted in complete selectivity for the internally (α) arylated product.



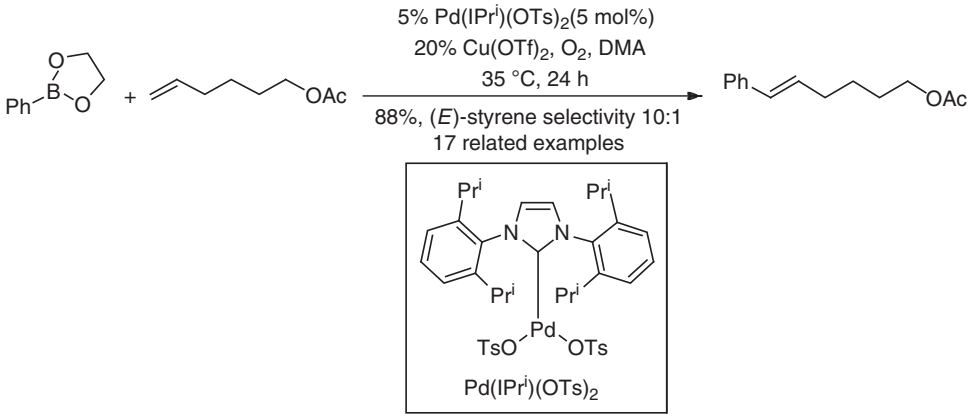
Scheme 4

A practical and efficient route to obtain styrene derivatives has been developed using a palladium(II)-catalyzed Heck-type reaction between arylboron derivatives and vinyl acetate (Table 4, conditions A and C). This reaction proceeded without the addition of a base or an external reoxidant, as β-acetate elimination regenerates the active palladium(II) species.[139] This reaction has also been performed under continuous-flow conditions (Table 4, condition B).[70] A mechanistic investigation using ESI-MS supports the mechanism is depicted in Figure 13. A possible drawback of this method is the concurrent minor protodeboronation of the arylboronic acids used, which might complicate isolation of the styrene products.

7.18.2.2.1.2 Neutral olefin

Neutral, electronically nonbiased olefins are challenging oxidative Heck substrates and can give rise to complex product mixtures (Figure 14). In the insertion step, the arylpalladium species can generate terminally or internally arylated olefins, which might be difficult to selectively control. Furthermore, following migratory insertion, the palladium can β-H eliminate in two ways, generating either a styrenyl product or an allylic product. To further increase the number of possible products, the double bond can reinsert into the palladium-hydride and the palladium can β-H eliminate with another accessible hydrogen to form another isomer, that is, double bond migration. Double bond migration can also occur in the starting olefin, which can give rise to regioisomers of olefins arylated in different positions. No general, highly selective method has been developed for oxidative Heck arylation of nonbiased, nonchelating aliphatic olefins. However, recent progress has been reported for relatively nonbiased and challenging olefins.

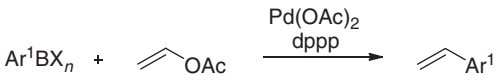
A general and selective oxidative Heck reaction for arylation of electronically nonbiased olefins lacking specific directing groups has been developed by Werner and Sigman.[140] The reoxidation system consisted of $Cu(OTf)_2$ (20 mol%) and oxygen gas. The reaction provided good yields under mild conditions without the need for an added base, and the selectivity was generally good (equation 49). A preliminary mechanistic investigation suggested that the high selectivity may be due to the catalyst's sensitivity to C–H bond strength in the selectivity determining β-hydride elimination step. A possible limitation of the method is the lack of commercially available catalytic complexes. The delicate synthesis of the carbene–palladium complex required glove box conditions and was performed in the absence of light.

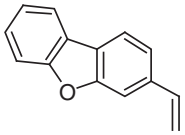
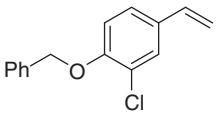
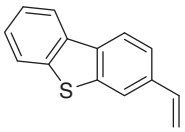
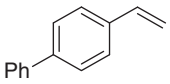
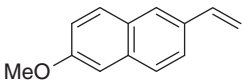
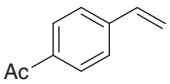
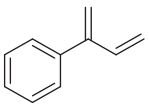
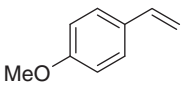
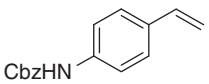
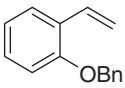


(49)

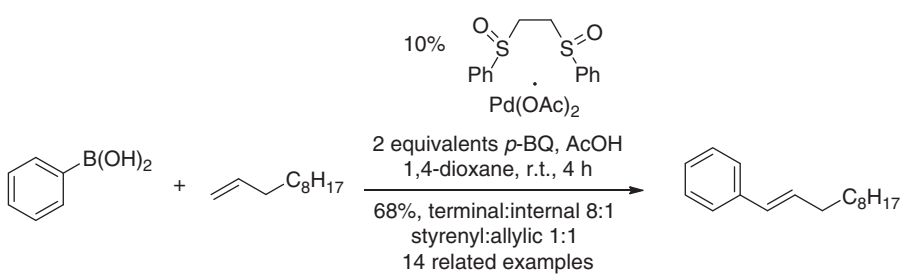
A palladium(II)/bis-sulfoxide catalytic system has been reported for the arylation of α-olefins to provide the corresponding styrenyl or allylic products.[60] Arylations of a range of nonresonance stabilized α-olefin substrates, for example, allylic esters, allylic ethers, *N*-Boc amines, and simple alkenes, were efficiently performed (equation 50). The reactions resulted in terminally arylated olefin products in good-to-moderate yields and regio- and *E*/*Z* stereoselectivities. The modest selectivities are, as expected, associated with the use of neutral, nonbiased olefins. The oxidative Heck reaction proceeded under mild conditions using *p*-BQ as reoxidant.

Table 4 Styrene formation from arylboron derivatives and vinyl acetate



Product	*Boron derivative*	*Conditions*[a]	*Yield (%)*	*References*
	$B(OH)_2$	A	74	139
	$B(OH)_2$	B	69	70
	$B(OH)_2$	A	71	139
	$B(OH)_2$	A	83	139
	$B(OH)_2$	A	77	139
	BF_3K	C	62	139
	$B(OH)_2$	A	71	139
	BF_3K	C	62	139
	$B(OH)_2$	B	71	70
	$B(OH)_2$	A	71	139
	$B(OH)_2$	C	46	139
	BF_3K	B	86	70
	$B(OH)_2$	A	64	139
	$B(OH)_2$	B	80	70
	$B(OH)_2$	B	63	70
	$B(OH)_2$	B	62	70

[a]Conditions A: A 5 ml Pyrex glass vial was charged with arylboronic acid (1.0 mmol), vinyl acetate (10.0 mmol), $Pd(OAc)_2$ (0.02 mmol), dppp (0.022 mmol), and DMF (2 ml). The vial was thereafter sealed under air and exposed to microwave heating for 30 min at 140 °C. Conditions B: continuous flow conditions. Arylboronic acid (1 mmol, 0.5 mol l^{-1}), vinyl acetate (10 mmol, 5 mol l^{-1}), $Pd(OAc)_2$ (0.02 mmol, 0.01 mol l^{-1}), dppp (0.022 mmol, 0.011 mol l^{-1}) in DMF, 150 °C, residence time 2 min. Conditions C: A 5 ml Pyrex glass vial was charged with aryltrifluoroborate (1.0 mmol), vinyl acetate (10.0 mmol), $Pd(OAc)_2$ (0.02 mmol), dppp (0.022 mmol), NaTFA (2 mmol), and DMF (2 ml). The vial was thereafter sealed under air and exposed to microwave heating for 30 min at 140 °C.



(50)

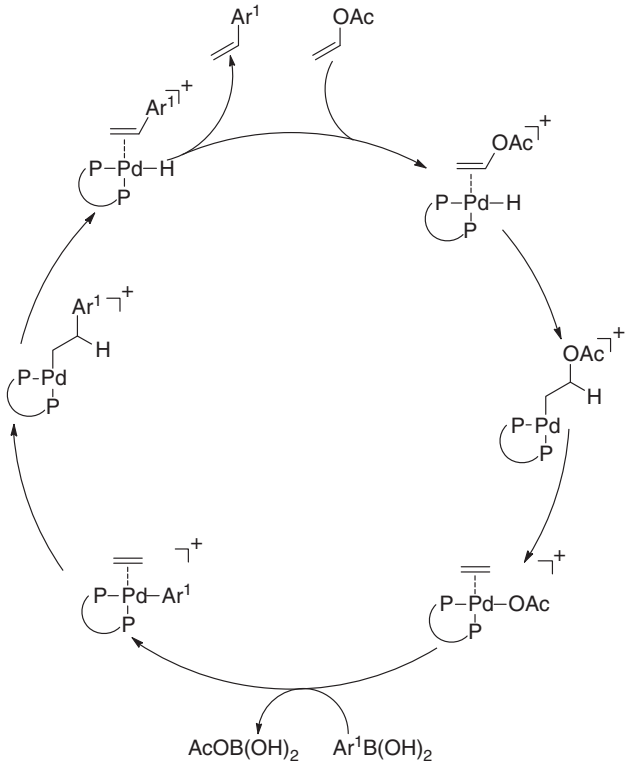


Figure 13 Proposed catalytic cycle for the formation of styrenes via arylation of vinyl acetate.

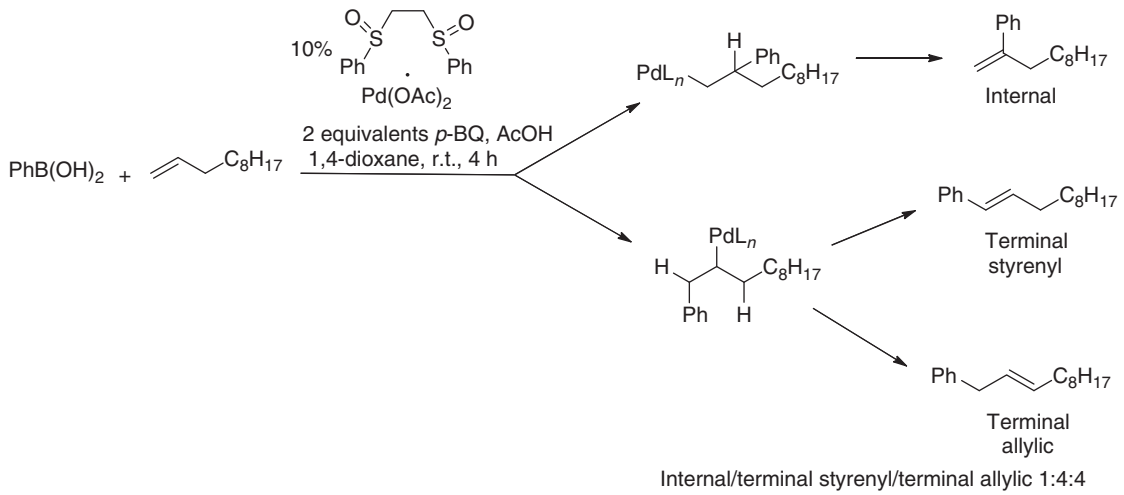


Figure 14 Possible reaction outcomes in the arylation of a nonbiased olefin. Reproduced from Delcamp J. H.; Brucks, A. P.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 11270–11271.

7.18.2.2.1.3 Allylic olefins

Allylic compounds have recently attracted considerable interest as they constitute interesting and challenging substrates for selective oxidative Heck couplings.[141] A good benchmark substrate class to illustrate the potential obstacles in oxidative Heck reactions with allylic substrates is the allylic esters. The monoarylation of allylic acetate can give four different products, as depicted in Figure 15. An allylic acetate double bond can insert into an arylpalladium species in two different ways: terminally or internally. This step is usually less problematic in terms of selectivity, as the carbonyl oxygen atom of the acetate group directs palladium to the internal position of the double bond. If an internal arylation takes place, only one product can form via β-H elimination (Figure 15, route a). However, if the aryl inserts in the terminal position, three different products can form. Palladium can β-H eliminate with either of the two accessible hydrogens (Figure 15, route b or c) to give the double bond at the β,γ-positions

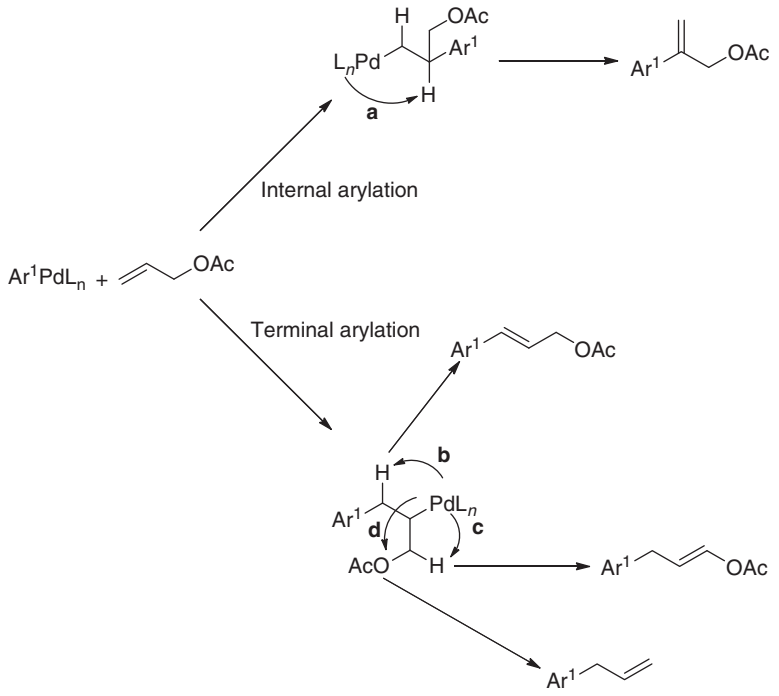
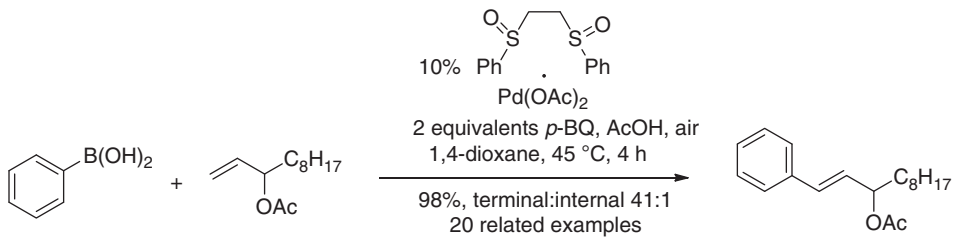


Figure 15 Possible reaction outcomes in the arylation of allyl acetate.

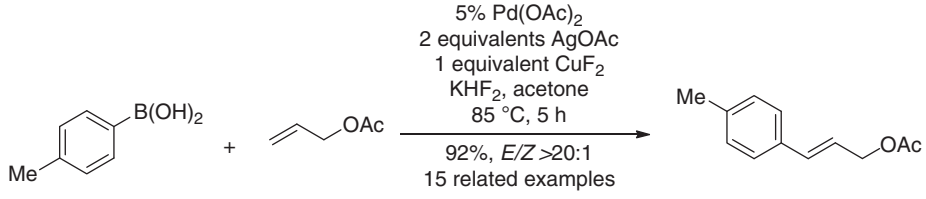
to the acetate (styrenyl ester product) or at the α,β-positions (allylic ester product). A third possibility also exists where palladium eliminates with the β-acetate to form an arylallene (Figure 15, route d). The β-acetate elimination is known to proceed in both *syn*- and *anti*- fashion, which might render it highly susceptible to β-elimination. Although the allylic esters are challenging substrates, useful methods to selectively obtain single products have been developed.[141]

A Pd(II)/bis-sulfoxide-catalyzed method for the selective terminal arylation of α-olefins to regioselectively provide (*E*)-arylated allylic esters through β-H elimination has been reported.[142] With this method, traces of internal arylation were observed using allylic esters having a terminal double bond (equation 51). The reaction was performed under mild conditions, using *p*-BQ as the reoxidant, and it was efficient for a range of different arylboronic acids and α-olefins.



(51)

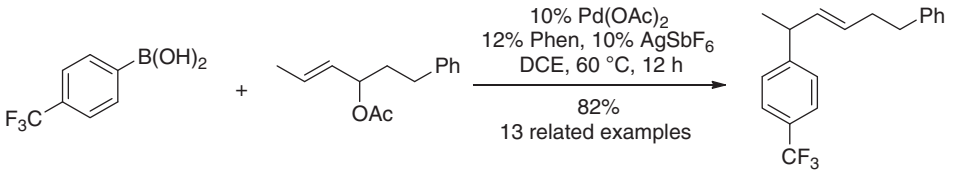
A ligand-free Pd(II)-catalyzed selective oxidative Heck reaction of arylboronic acids with allylic esters was recently reported.[143] With this method the β-H elimination was chemoselectively controlled, providing predominantly terminally arylated allylic esters (equation 52). The regio- and stereoselectivities are explained by the chelation between the coordinating oxygen atom of the acetate group and the palladium catalyst. A range of arylboronic acids and allylic esters was coupled in moderate-to-excellent yields. The usability of the method would benefit from lower loadings of copper and silver salts.



(52)

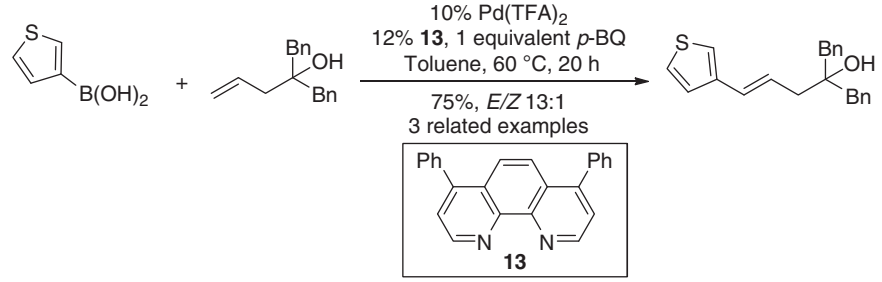
Palladium(II)-catalyzed couplings between allylic acetates and arylboronic acids in the presence of phen and $AgSbF_6$ provided the γ-arylallyl product with concomitant cleavage of the acetate group (equation 53).[144] The reaction was proposed to proceed via

a Heck-type mechanism, which is initiated by transmetalation of the arylboronic acid. The arylpalladium complex then forms a π-complex with allylic acetate followed by regioselective insertion of the double bond, which is assisted by the carbonyl oxygen of the acetate coordinating to the cationic palladium center to give a palladacycle. The catalytic cycle is completed by a *syn*-β-acetate elimination to stereoselectively provide the coupling product and regenerate the active Pd(II)-catalyst complex (equation 53). A broad range of both arylboronic acids and allylic esters was tolerated with this method. Interestingly, reactions of optically active allylic esters took place with excellent α-to-γ chirality transfer to provide the corresponding optically active arylated allyls with a stereogenic center at the benzylic position. The use of catalytic amounts of silver salt also merits attention.



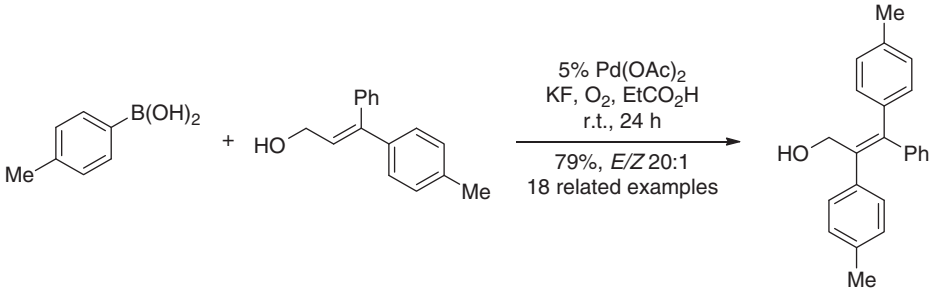
(53)

An oxidative Heck arylation of homoallylic alcohols to afford the styrenyl products in good yields and regioselectivities has been developed (equation 54).[145] The high regiocontrol was explained by the coordination between the catalyst and the hydroxy group. Furthermore, the Heck intermediate could be intercepted by an intramolecular palladium-catalyzed olefin oxyannulation, to provide a range of α-aryltetrahydrofurans.



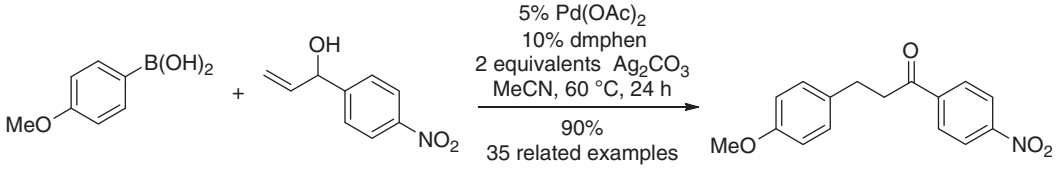
(54)

In a recently published method, triarylalkyl olefins were obtained by the arylation of diaryl allylic alcohols.[77] The reaction proceeded under mild conditions at room temperature using oxygen gas or TEMPO derivatives as reoxidants to provide tetra-substituted olefin products (equation 55). The reaction was not limited to bisarylated allylic alcohol, and also worked well for the corresponding bisarylated propene and butene derivatives. Finally, this stereoselective reaction was exemplified through the synthesis of *Z*-Tamoxifen.



(55)

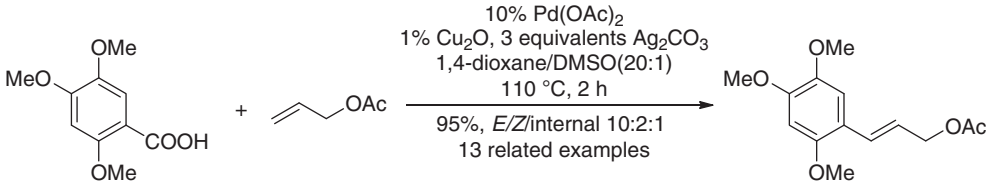
Using palladium(II)-catalysis, regioselective arylations of allylic alcohols provided functionalized β-aryl carbonyl derivatives in good-to-excellent yields (equation 56).[146] The use of the dmphen ligand (3) drastically improved the reaction yield. A wide range of arylboronic acids was tolerated and efficiently coupled under mild conditions. The use of excess silver salts might limit the usefulness of the method on a large scale.



(56)

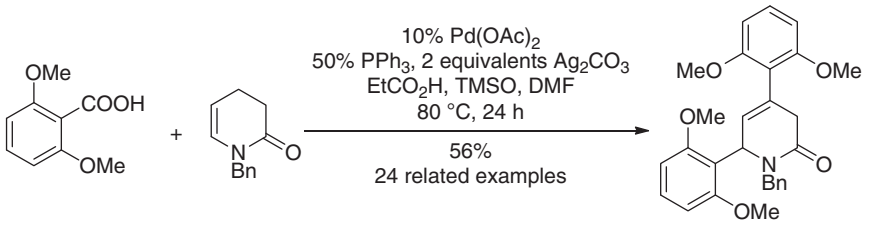
7.18.2.2.2 Aryl carboxylic acids

The concept of decarboxylation was utilized in the allylation of aryl carboxylic acids with allylic esters.[147] The catalytic system consisted of palladium(II) acetate and copper(I) oxide with an excess of silver as reoxidant (equation 57). The couplings were rapidly achieved at 110 °C in a mixture of 1,4-dioxane and DMSO to provide the terminally arylated allylic esters in moderate-to-excellent yields. The method is limited to the use of *ortho*-substituted aryl carboxylic acids.



(57)

In a recently published method, decarboxylative couplings of aryl carboxylic acids with cyclic enamides in the presence of palladium(II) acetate as catalyst provided the corresponding mono- or diarylated enamides.[148] The preference for mono- or diarylation was efficiently controlled by the choice of the enamide nitrogen protecting group. The reaction conditions were relatively mild, with a reaction temperature of 80 °C, and the products were obtained in moderate-to-good yields (equation 58). A limitation of the reaction lies in the requirement of *ortho*-substituents on the aryl carboxylic acid, which correlates well with the reactions described in Section 7.18.2.1.4.

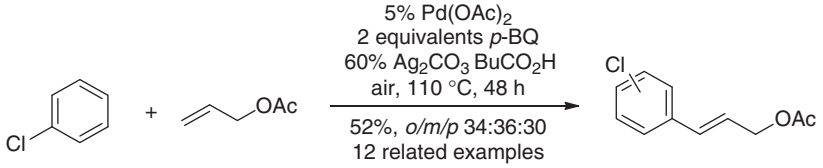


(58)

7.18.2.2.3 Arenes

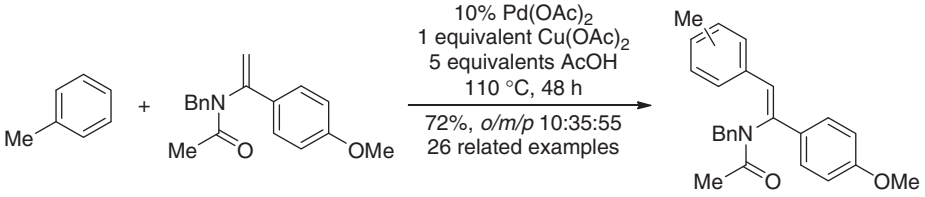
The use of arenes as arylating agents, via C–H functionalization, is beneficial for a number of reasons, and this is described in Section 7.18.2.1.2. However, the lack of easily accessible, reactive groups such as halides or boronic acids often causes severe difficulties in controlling the regioselectivity of the reactions. The use of arenes in intermolecular oxidative Heck reactions is more limited in terms of substrate scope and regioselectivity than comparable methods using transmetalating substrates. Despite the possible inherent limitations of C–H activation of arenes, the benefits of low cost and environmental aspects may well make up for the limitations.

In a selective dehydrogenative Heck reaction of allylic esters with simple arenes via C–H functionalization, palladium(II) acetate was used as catalyst.[149] Silver(I) was used as an oxidant and also assisted in controlling the regioselectivity and the position of the double bond. The use of silver(I) as the sole reoxidant was inefficient and *p*-BQ was included as a stoichiometric reoxidant. The solvent, pentanoic acid, had an essential role as a proton shuttle in the reaction. A number of unactivated arenes, including electron-poor arenes, were coupled with allylic acetate to provide the terminally arylated products via *β*-H elimination. The usefulness of the reaction is somewhat hampered by the low regioselectivity with certain arene substrates and by the requirement of a large excess of arene (100 equivalents) to obtain good yields. A trend in selectivity, consistent with electrophilic aromatic palladation, could be observed since benzenes substituted with an electron-withdrawing group were predominantly vinylated in the *meta*-position, whereas electron-donating groups directed the olefination mainly to the *ortho*- and *para*-positions.



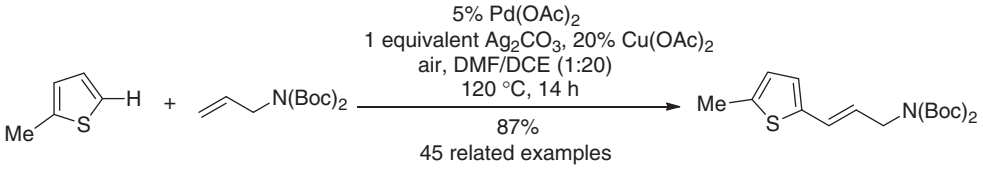
(59)

A palladium(II)-catalyzed direct arylation of enamides to generate substituted enamides with excellent (*Z*) selectivity was recently reported.[150] Copper(II) acetate was used as a stoichiometric reoxidant and acetic acid was an essential additive (equation 60). Enamides featuring *ortho*-substituents performed poorly due to steric reasons. A range of electronically different arenes could be coupled with complete (*Z*)-selectivity, although monosubstituted arenes produced regioisomeric mixtures. The use of a large excess of the arene might limit the reaction scope to simple arenes.



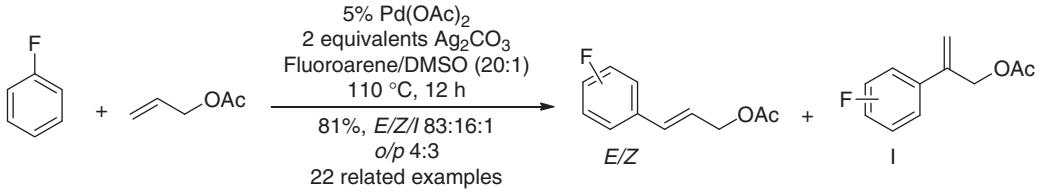
(60)

The direct palladium(II)-catalyzed arylation of allylamine derivatives with a range of furans and thiophenes has been developed.[151] A combination of silver(I) and copper(II) salts functioned as the palladium reoxidant in a mixture of DMF and 1,2-dichloroethane. Under these conditions *N*,*N*-diprotected allylamines underwent efficient terminal arylation with a number of different furans and thiophenes to provide the arylated (*E*)-allylamines in good yields and high regioselectivity (equation 61).



(61)

Recently, a palladium(II)-catalyzed protocol for the olefination of electron-poor perfluorated arenes was demonstrated.[152] The reaction proceeded selectively via *β*-H elimination, and several different olefination substrates and a number of arenes were successfully coupled in good-to-excellent yields (equation 62). Drawbacks of the method include the generation of regioisomers and the need for a large excess of the arene substrate.



(62)

7.18.2.3 Olefin Coupling of R^1–Z (R^1 = nonaryl, Z = M, H)

The interest in Heck couplings using organic moieties other than the usual arenes is increasing. Classically, a tricky problem associated with this ambition is the need to use proper halogenated substrates and/or organometallics as coupling partners with olefins. Substrate availability, reactivity, and side reactions such as premature *β*-elimination processes are often complicating factors. An alternative approach to the formation of the organopalladium species via oxidative addition is to use a transmetalation step with a Pd(II) catalyst. The possibility of using milder conditions is of special interest to suppress side reactions, as well as with regard to the opportunity to exploit simpler organopalladium precursors. In this context hydrogen-leaving groups, activated by breaking polarized C–H bonds, appears attractive due to their omnipresence. Furthermore, the atom economy achieved on direct C–H bond palladation, made possible via Pd(II) catalyst reoxidation systems, has spurred considerable development in this area.[93] As described in Sections 7.18.2.1.7.1 and 7.18.2.2.3, palladium-catalyzed C–H functionalization of arenes or electron-rich heterocyclic compounds has been well studied. Notably, several groups have reported direct C–C bond formation from unactivated sp^3 C–H bonds via palladium catalysis.[153,154] However, little attention has been devoted to the direct alkene–alkene coupling with an alkene as the coupling partner, activated via sp^2 C–H bond palladation. The dienes formed are evidently useful for further manipulations, but the difficulty of activating the essentially nonacidic alkenyl C–H bond has slowed the development of robust protocols. Detailed understanding of the actual mechanism by which the olefin coupling occurs via C–H activation would of course promote further development. Two alternative catalytic mechanisms, using electron-poor olefins, have been proposed (**Figure 16**).[155]

Using standard strategies such as Suzuki, Negishi, and Stille cross-coupling for the alkenylation of olefins via C–C cross-coupling reactions requires two leaving groups (M and X) to ensure a resulting single-product isomer (**Figure 17**). Attractive features are high yields and simple purification procedure but at the risk of poor atom economy and sometimes scarce substrate availability.

In comparison, Mizoroki–Heck alkenylation of electron-poor acrylate-type olefins provides a somewhat simpler synthetic approach and yields a single linear isomer (**Figure 18**). If electron-rich olefins are used, branched products may also be produced. The initial oxidative addition to Pd(0) requires the alkene to have an electronegative substituent X and a base to regenerate Pd(0) after the final *β*-hydride elimination according to the classic Mizoroki–Heck mechanism. As described in Sections 7.18.2.1 and 7.18.2.2, standard oxidative Heck protocols include alkaline, neutral, and acidic conditions to be used and hence allow a somewhat broader scope for pH-sensitive substrates.

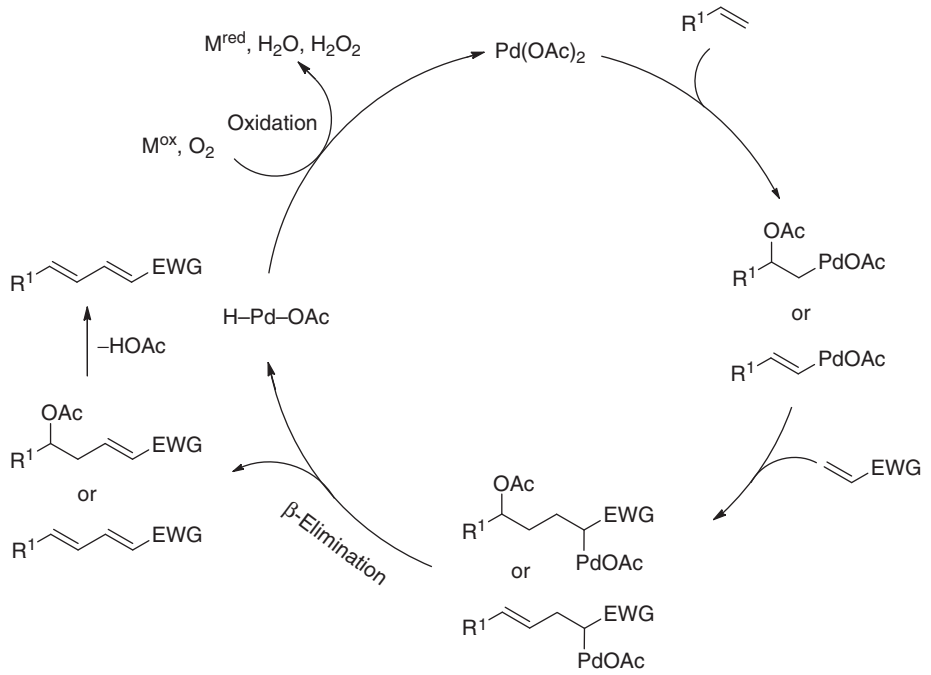


Figure 16 Schematic mechanism of two suggested Pd(II)-catalyzed oxidative Heck pathways using electron-poor olefins; direct C–H palladation and palladium acetate insertion.

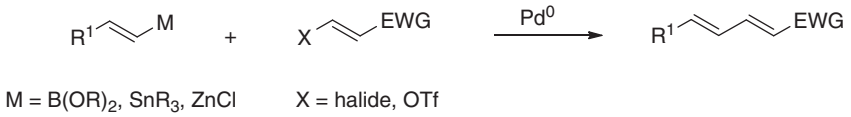


Figure 17 Pd(0)-catalyzed cross-couplings utilizing prefunctionalized olefins furnishing one single diene product isomer.

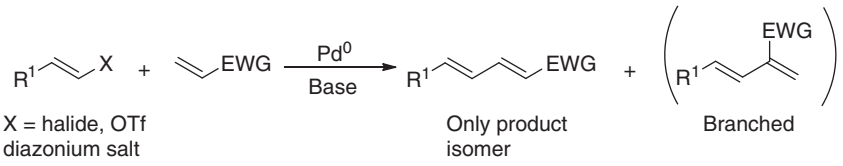


Figure 18 Standard Heck vinylation of electron-poor alkenes provides a stereo-defined product.

Currently, the corresponding oxidative Heck protocols found in the literature offer two possibilities: C–H bond activation and vinylation of alkenes via sp^2 C–M (Figure 19). The former offers more flexibility provided sufficient regiocontrol can be secured by proper selection of reaction conditions.

In general, there has been little study on the catalytic oxidative coupling reaction between different functionalized alkenes. As with the standard Mizoroki–Heck procedure, the oxidative method is most often applied to acrylate-type olefins due to the strong preference for selective linear product formation. The standard protocol for oxidative coupling of vinylic compounds with electron-poor olefins involves a Pd(II) source, typically $Pd(OAc)_2$, oxygen gas, and acetic acid as solvent or cosolvent. As cooxidant, copper(II) acetate or silver(I) acetate is commonly used in stoichiometric excess.

7.18.2.3.1 Oxidative Heck coupling of vinyl C–H with electron-poor olefins

Although dehydrogenative Heck systems provide very efficient and direct strategies for the synthesis of conjugated dienes, many of them suffer from a limited substrate scope as they often employ acidic reaction conditions that may be incompatible with electron-rich olefins bearing acid-sensitive functionalities. Early examples concerned functionalized alkenes, such as acrylates, which were shown to oxidatively homodimerize producing di-esters under palladium catalysis.[156,157] Some more recent and demonstrative examples of alkene–acrylate couplings using slight variations of the standard protocol are depicted in Table 5.

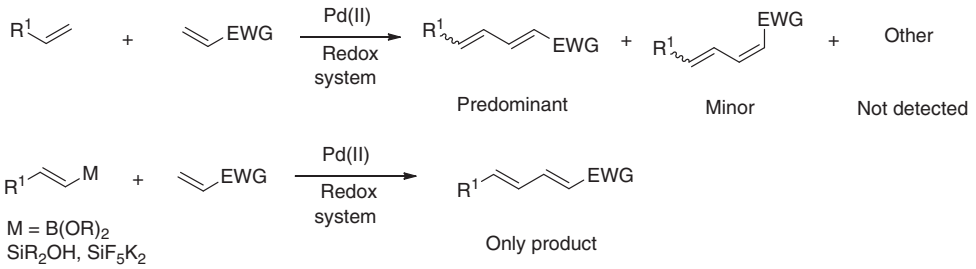
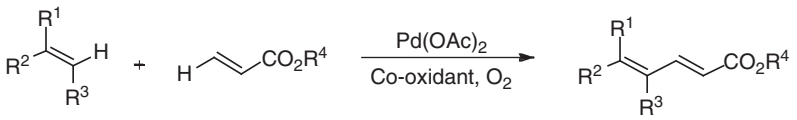
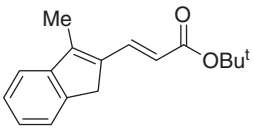
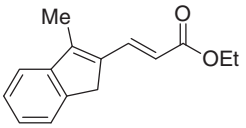
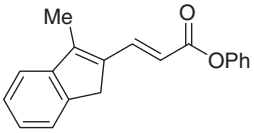
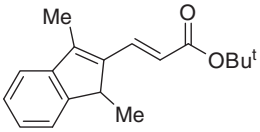
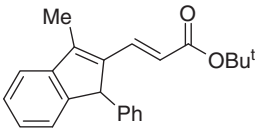
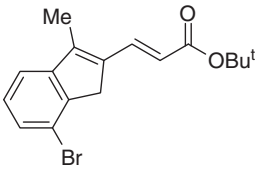
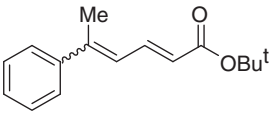
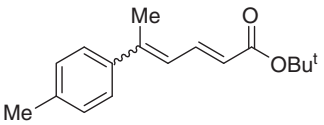


Figure 19 Stereoisomeric outcome of Pd(II)-catalyzed oxidative Heck vinylation via direct C–H palladation or via functionalized vinyl metals.

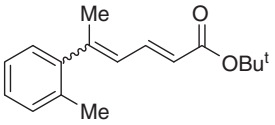
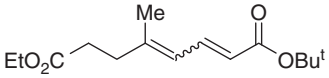
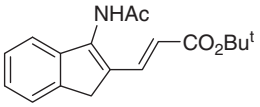
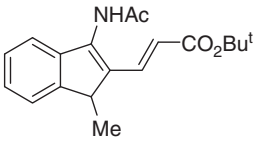
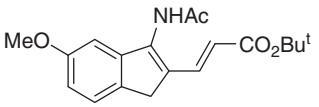
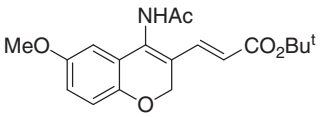
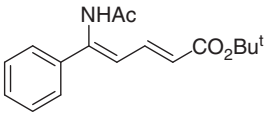
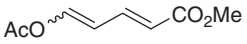
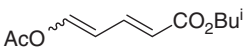
Table 5 Vinylated olefins prepared via oxidative Heck reaction using oxygen gas



Product	*Conditions*[a]	*Cooxidant*	*Yield (%) (Selectivity)*	*References*
	A	$Cu(OAc)_2$	70	159
	A	$Cu(OAc)_2$	93	159
	A	$Cu(OAc)_2$	92	159
	A	$Cu(OAc)_2$	49	159
	A	$Cu(OAc)_2$	40	159
	A	$Cu(OAc)_2$	52	159
	B	$Cu(OAc)_2$	71 (*E/Z* 87:13)	155
	B	$Cu(OAc)_2$	74 (*E/Z* 88:12)	155

(*Continued*)

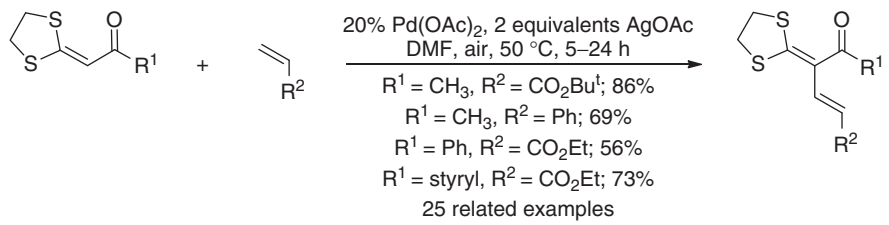
Table 5 Continued

Product	*Conditions*[a]	*Cooxidant*	*Yield (%) (Selectivity)*	*References*
	B	$Cu(OAc)_2$	52 (*E/Z* 62:38)	155
	B	$Cu(OAc)_2$	41 (*E/Z* 68:32)	155
	C[b]	–	80	158
	C[b]	–	67	158
	C[b]	–	79	158
	C[c]	–	76	158
	C[c]	–	67	158
	D	$H_4PMo_{11}VO_{40}$	45 (*E/Z* 56:44)	160
	D	$H_4PMo_{11}VO_{40}$	67 (*E/Z* 60:40)	160

[a]Conditions A: indene derivative (2 equivalents), acrylate (1 equivalent), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (1 equivalent), AcOH (0.5 ml), O_2 (1 atm), 60 °C, 48–96 h; conditions B: alkene derivative (2 equivalents), acrylate (1 equivalent), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1 equivalent), DMSO/AcOH (1:1, 0.4 ml), O_2 (1 atm), 60 °C, 24 h; conditions C: enamide derivative (2 equivalents), acrylate (1 equivalent), NaOAc (1 equivalent), $Pd(OAc)_2$ (10 mol%), O_2 (1 atm), 60 °C, 24 h; conditions D: vinyl acetate (5 equivalents), acrylate (1 equivalent), NaOAc (0.1 equivalent), $Pd(OAc)_2$ (10 mol%), $H_4PMo_{11}VO_{40}$ (0.02 equivalent), O_2 (1 atm), AcOH (5 ml), 90 °C, 5 h.
[b]AcOH.
[c]DMSO.

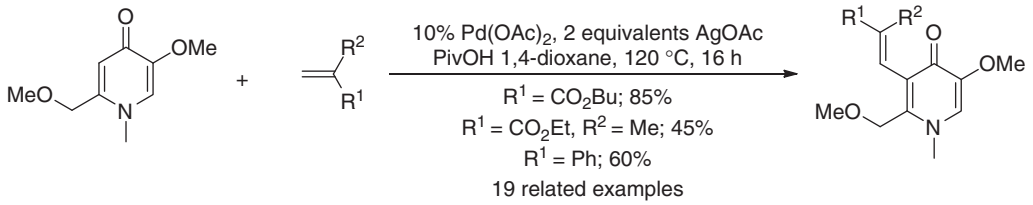
At modest temperatures (60–90 °C) both di- and tri-substituted vinyls can be prepared in moderate-to-high yields. Notably, condition C developed by the group of Loh requires no cooxidant, and coupling of acid-sensitive enamides was performed in both acidic and neutral media.[158] Perhaps even more remarkable is the performance of acid-sensitive vinyl acetate, delivering good yields employing vanadomolybdophosphoric acid as catalytic cooxidant, under elevated temperature (90 °C) in acetic acid (condition D).

Even uncommon tri-substituted vinyl substrates such as α-oxoketene dithioacetals have been shown to be useful in oxidative Heck couplings with olefins of different electronic character (equation 63).[161] Atmospheric air and two equivalents of silver acetate served as the reoxidation machinery. Electron-rich olefins such as allyl benzoate (56%) and vinyl acetate (35%) provided the hydrolyzed product while allyl alcohol (37%) oxidized to the aldehyde product under this neutral protocol.



(63)

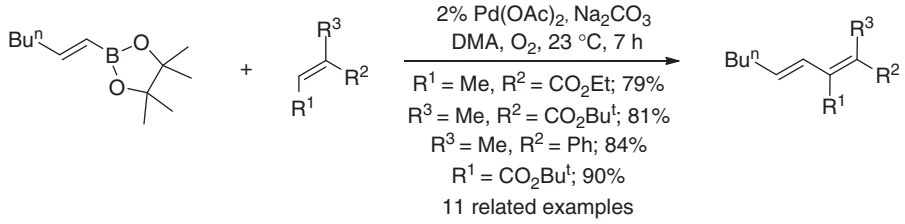
Heterocyclic vinyls such as the nonaromatic 2- and 4-pyridones have been a subject of interest and regioselective activation of the carbonyl α-hydrogen seems facile.[162,163] Using elevated temperature, a broad array of olefin substrates was successfully attached to the pyridine-4(1*H*)-one core (equation 64).[163] Slightly lower yields were encountered with sterically hindered α-methyl acrylates (R^2 = Me). Optimization of the reaction conditions revealed that basic additives were detrimental for the reaction and that addition of pivalic acid (PivOH) increased the coupling efficiency. The nonpolar solvent 1,4-dioxane was superior to the more common polar solvents DMF, DMA, CH_3CN, AcOH, and DMSO.



(64)

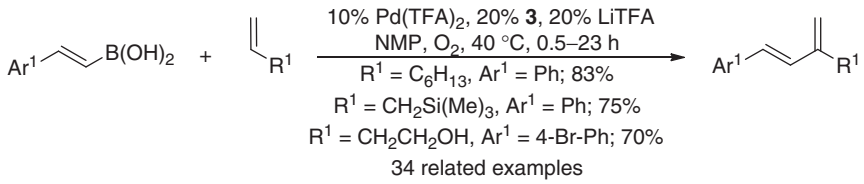
7.18.2.3.2 Coupling of vinyl C–M (M = B, Si) with olefins

As described in Sections 7.18.2.1.1 and 7.18.2.2.1, organoboron compounds are excellent substrates for oxidative Heck reactions. Vinyl boronic esters are reactive at room temperature under basic conditions with low catalyst loadings. A slow addition of the vinyl boronic ester is claimed to minimize vinyl homocoupling and afford a cleaner reaction (equation 65).[164] Noteworthy is that a difficult olefin substrate like cyclohex-2-en-1-one reacted smoothly under these basic conditions at ambient temperature, providing the Heck product in 76% yield.



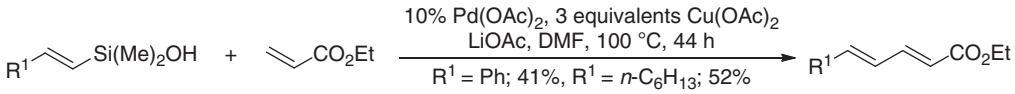
(65)

The well-known ability of the dmphen ligand **3** to influence the regioisomeric outcome of oxidative Heck reactions utilizing electron-rich olefins was recently demonstrated by the production of branched dienes (equation 66).[165] The neutral conditions and low temperature employed allowed a range of monosubstituted olefins to be coupled with high regioselectivities. Acid-sensitive vinyl amide was stable under the reaction environment whereas vinyl ethers hydrolyzed. A large excess of boronic acid relative to the olefin was used (7.5:1).



(66)

Organosilanes have not been as extensively used as the corresponding boron compounds in oxidative Heck couplings. The first example was published in 1982 by the group of Kumada where they showed for the first time that alkenylsilicates (K_2vinylSiF_5) could be coupled in low-to-moderate yields (20–53%) with electron-poor olefins using stoichiometric amounts of palladium.[166] A more recent example utilized alkenylsilanols as the transmetalation partner (equation 67), and reasonable yields could be achieved using electron-poor olefins after an extended reaction period.[167]

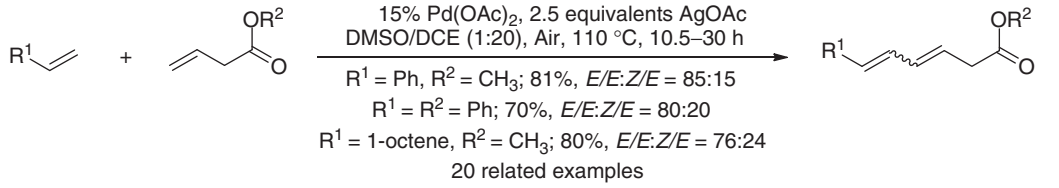


(67)

7.18.2.3.3 Coupling of vinyl C–H with electron-rich olefins

As mentioned in Section 7.18.2, Heck couplings with electron-rich olefins often suffer from poor regiocontrol unless a bidentate ligand is used (see equation 66). Nonetheless, acceptable selectivities can be obtained with certain olefins under optimized ligandless conditions. Allylic esters have been utilized in regiocontrolled oxidative Heck couplings of various olefins affording the linear products exclusively (equation 68).[168] In contrast to acrylate-type olefins, a mixture of geometrical (*E*/*Z*) isomers was

obtained, which may limit the usefulness of the method. Finally, a diverse array of alkenyl substrates was successfully coupled, including linear alkenes and various styrenes.



(68)

7.18.3 Intramolecular Oxidative Heck Reactions

The intramolecular oxidative Heck reaction follows the same historical evolution as for the intermolecular version, with the Pd(II)-mediated processes being the actual start of palladium-catalyzed intramolecular C–C bond chemistry. Similarly, it is the intramolecular palladium(0)-catalyzed Mizoroki–Heck reaction that is the most widespread method among the transition-metal-catalyzed annulations. Even so, the oxidative version is an important method for the formation of cyclic molecules, but unlike its intermolecular counterpart, this reaction class is almost exclusively based on C–H functionalization protocols, that is, intramolecular dehydrogenative Heck annulations (Fujiwara–Moritani annulations). This chapter is by no means a complete review of all reported examples, but rather an overview focusing on the latest advances in this field. In all reviewed cyclizations a double bond on a tethered moiety inserts into an aryl- or heteroarylpalladium bond and the process is terminated by a β-hydride elimination (Figure 20). Consequently, one-pot multistep tandem reactions, where the initially formed annulation product undergoes further transformations, are not covered. In addition, only the five- and six-membered ring will be covered. For a more comprehensive review on this topic the reader is directed to the recent review by Deng et al.,[8] or for the applicability of C–H annulations in total synthesis of complex natural products, the recent review by Chen and Youn.[169]

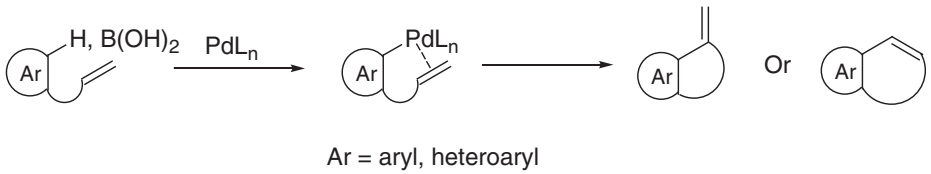


Figure 20 Schematic view of intramolecular oxidative Heck processes covered in this chapter.

Mechanistically, the intramolecular oxidative Heck involves the same steps as for the intermolecular version, starting with the formation of an arylpalladium species, followed by migratory insertion of an olefin and finally β-hydride elimination (Figure 21). In terms of the arylpalladium formation, the C–H functionalization method is by far the best studied. The logical explanation for this lies in the simplicity and atom economy of forming a C–C bond between a nonfunctionalized carbon atom of an aryl or heteroaryl moiety and an olefinic carbon, thereby circumventing the need for prefunctionalization of the arene substrate. In addition, recent progress in this field has provided effective catalytic protocols, using dioxygen, *tert*-butyl hydroperoxide, or *p*-BQ as stoichiometric oxidant to regenerate the catalytically active Pd(II) species. On the downside, these protocols suffer from having a substrate scope limited to electron-rich aryls or heteroaryls and usually require elevated reaction temperatures in order to activate the C–H bond.

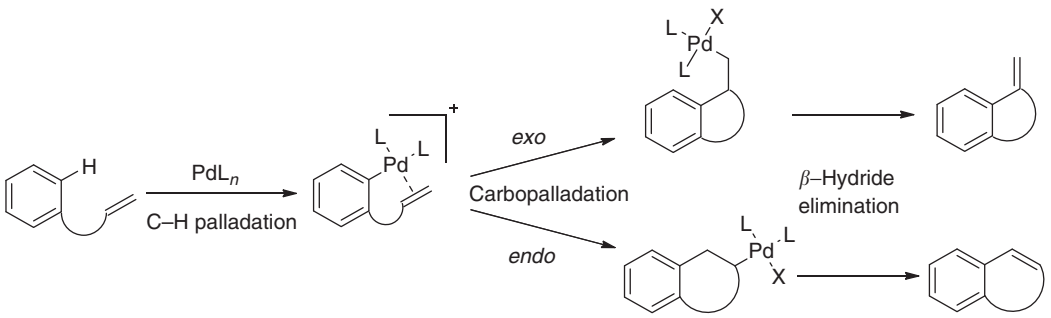


Figure 21 Cyclization pathway of the intramolecular Fujiwara–Moritani/dehydrogenative Heck reaction.

The next step in the mechanism is the migratory insertion or carbopalladation, which involves the *syn*-addition of an σ-aryl- or σ-heteroarylpalladium species to an alkene. One particularly important feature of this step is that it often results in the exclusive formation of a sole regioisomer, in most cases the *exo* cyclization product. This is rationalized by a preferred geometry preceding carbopalladation, where the squareplanar Pd(II)-complex favor the eclipsed over the twisted conformation (Figure 22).[170] Accessing an eclipsed conformation in an intermolecular reaction is not normally a problem, and regioselectivity is determined only by orientation and/or electronic considerations, as discussed in Section 7.18.2.1. In an intramolecular reaction, however, the alkene may be limited to only one eclipsed conformation due to the size and/or shape of the substrate and, in this case, only one of the possible regioisomers will be formed.

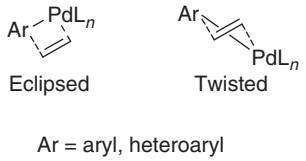


Figure 22 Schematic view of the eclipsed and twisted conformation of the Pd(II)-complex.

The final β-hydride elimination step adds to the complexity of this reaction class. In order for the elimination to occur, a vacant site on palladium is required and the eliminating hydride must be orientated *syn* to the metal. Elimination leads to a palladium-hydride (Pd-H) coordinated to the double bond of the newly formed product. As described above, the aryl-Pd carbopalladation of the olefin proceeds in a *syn* fashion and therefore rotation around the former double bond is necessary to place a hydrogen in a *syn* relationship with palladium. This rotation might be complicated in cyclic systems, leading to the formation of a new double bond in another direction, due to a more accessible β-hydrogen. In addition, this process is reversible, due to the facile reinsertion of the Pd-H species into double bond, which may result in a mixture of isomers (Figure 23).

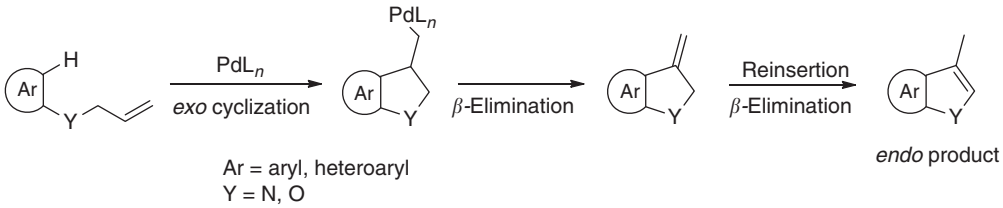


Figure 23 Isomerization of the double bond affording the thermodynamically more stable endocyclic position, due to Pd–H reinsertion.

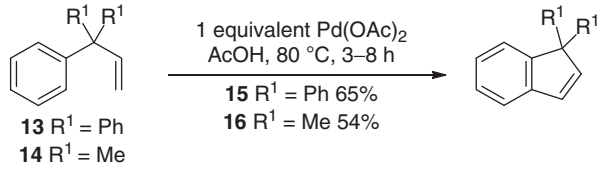
In the catalytic version of the oxidative Heck annulation, the Pd-H needs to be transformed into the catalytically active ligated palladium(II) species (see Section 7.18.1). This has proven to be rather complicated, and although there are effective catalytic protocols at hand today, many of the reactions presented in this chapter suffer from being stoichiometric in palladium or require an excess of an additional metal salt, typically silver or copper. Further development of more environmentally friendly processes that rely on oxidants such as oxygen or H_2O_2 are highly desirable for the continuation of this already convenient and atom-efficient method for the construction of five-, six-, seven-, and eight-membered rings.

7.18.3.1 Formation of Five-Membered Rings

The first section in this chapter describes the intramolecular annulation of nonfunctionalized arenes, that is, intramolecular dehydrogenative Heck or Fujiwara–Moritani reaction, for the formation of five-membered rings, which are the most frequent products in this reaction class. They are often formed through a 5-*exo-trig* cyclization pathway, unless the *exo*-carbopalladation would provide a four-membered cycle, in which case the 5-*endo-trig* process is preferred (Figure 21). This section is further organized into the following subsections: stoichiometric conditions and catalytic conditions.

7.18.3.1.1 Stoichiometric conditions

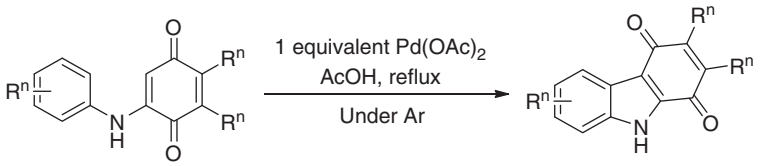
The first example of an intramolecular oxidative Heck reaction was the Fujiwara–Moritani annulation presented in equation 69.[171] In this pioneering work from 1970, two different arenes, **13** and **14**, were treated with a stoichiometric amount of $Pd(OAc)_2$ in acetic acid at 80 °C. Both substrates reacted via the 5-*endo-trig* pathway to form the annulated products **15** and **16** in acceptable yields. The mechanism discussed in Section 7.18.3 (Figure 21) was not considered at this time, but based on later examples of this type of reaction, it is most likely the operative mechanism.[3]

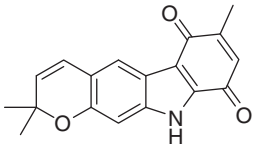
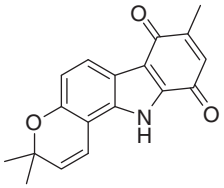
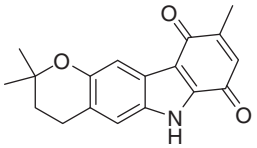
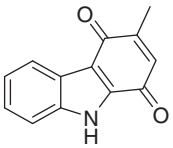
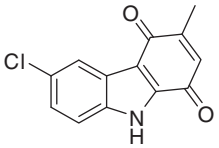
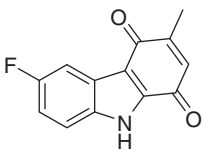


(69)

Since that groundbreaking first example of an intramolecular oxidative Heck reaction, relatively few stoichiometric applications have been described in the literature, with one notable exception seen for the formation of carbazole-1,4-quinones.[172,173] A selection of products reported through this method is summarized in Table 6. All methods used $Pd(OAc)_2$ in refluxing AcOH under an argon atmosphere to provide the 5-*endo-trig* products in good-to-moderate yields. Despite the addition of *p*-BQ, Bittner et al. were unable to accomplish a productive reaction using only catalytic amounts of palladium.[174]

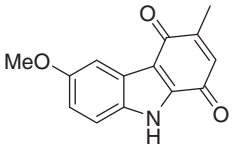
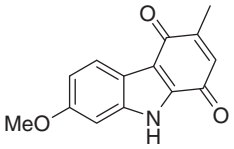
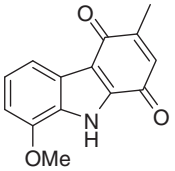
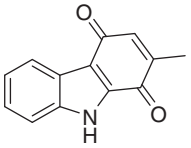
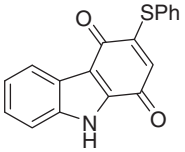
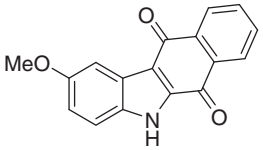
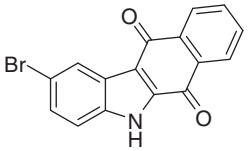
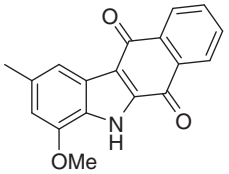
Table 6 Carbazole-1,4-quinones prepared via the stoichiometric intramolecular oxidative Heck reaction



Product	*Additive*	*Time*	*Yield (%)*	*References*
		4 min	78	172
		4 min	50	172
		4 min	50	173
		50 min	64	173
		50 min	46	173
		50 min	83	173

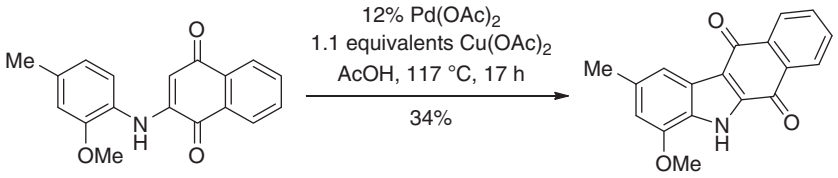
(*Continued*)

Table 6 Continued

Product	*Additive*	*Time*	*Yield (%)*	*References*
		50 min	52	173
		50 min	65	173
		50 min	55	173
		50 min	64	173
	*p*-BQ (1 equivalent)	2–5 h	66	174
	*p*-BQ (1 equivalent)	2–5 h	54	174
	*p*-BQ (1 equivalent)	2–5 h	40	174
		30 min	84	175

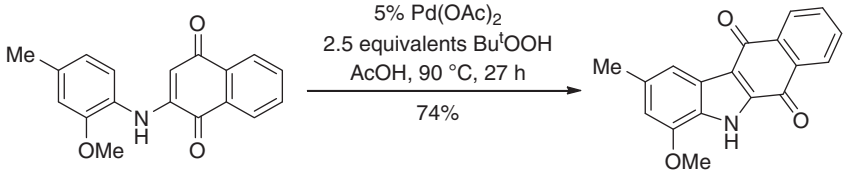
7.18.3.1.2 Catalytic conditions

In the mid-1990s, much effort was invested in making this reaction catalytic with respect to palladium, and even though *p*-BQ failed in this regard (Table 6), Knölker and O'Sullivan[176] within months managed to transform their previously published stoichiometric protocol (Table 6, bottom entry) into the first catalytic one. This was achieved by the addition of 1.1 equivalents of $Cu(OAc)_2$ as oxidant to the reaction mixture, furnishing a modest 34% yield of the desired product (equation 70). Although this was a modest improvement by today's standards, it was a very significant result at the time, as it demonstrated the possibility of an intramolecular oxidative Heck reaction using palladium in catalytic amounts.

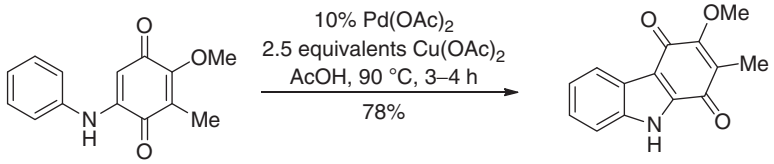


(70)

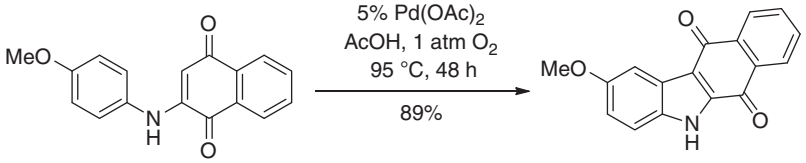
In addition to providing building blocks for the synthesis of various biologically active carbazole alkaloids,[177] these substrates became the playground for the development of the intramolecular oxidative Heck reaction. In 1995, Åkermark et al.[178] developed a system producing yields comparable to those achieved with the previously reported stoichiometric conditions (equation 71). In initial attempts a mixture of *tert*-butyl hydroperoxide and *p*-BQ was used, but the peroxide alone proved to be superior for the reoxidation in this protocol. A few years later, Knolker et al. were able to reach good yields by increasing the amount of $Cu(OAc)_2$ (equation 72),[179] but this work was followed up by Åkermark et al., introducing the environmentally benign molecular oxygen as the sole reoxidant (equation 73).[180]



(71)

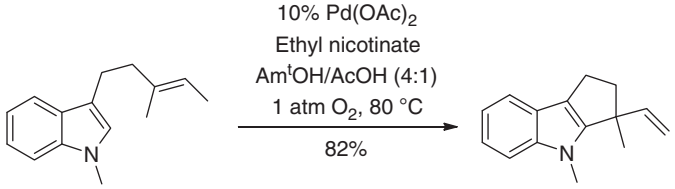


(72)



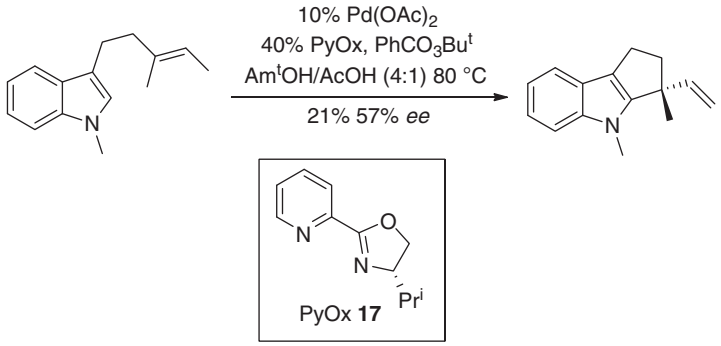
(73)

Indoles have also served as important substrates for the development of this method,[181–183] and the 5-*exo-trig* cyclization between C3 and C2, in particular, has been the subject of numerous palladium(II)-catalyzed oxidative couplings. Ferreira and Stoltz were successful in developing a catalytic ligand-modulated method for this annulation, using molecular oxygen at atmospheric pressure as sole oxidant (equation 74).[184] Interestingly, they were able to identify ethyl nicotinate as the ligand of choice by scanning various pyridines based on their pK_a. The more electron-rich pyridines were inefficient, and moving in the other direction proved detrimental for the reaction outcome. The *β*-hydride elimination was controlled by removing competing *β*-hydrogens, thus providing the terminal olefin. Additionally, moving the alkene tether to the indole nitrogen resulted in a 5-*exo-trig* cyclization to C2 under the same conditions in a good yield.

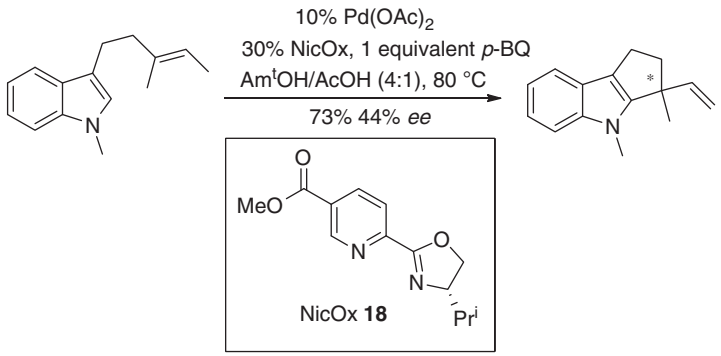


(74)

The scope of this work was later expanded by Oestreich and coworkers, who developed the first enantioselective dehydrogenative Heck annulation (equation 75).[185] Further studies indicated that the NicOx ligand was more effective regarding chemical yield, compared with the initially used PyOx ligand (equation 76).[186] The compromise between the choice of ligand, solvent, and oxidant, in order to reach high *ee* without impairing productivity, seemed to be a rather complex task for this reaction. At the time of writing, this is the best intramolecular enantioselective dehydrogenative Heck protocol at hand; however, it leaves obvious room for future development.

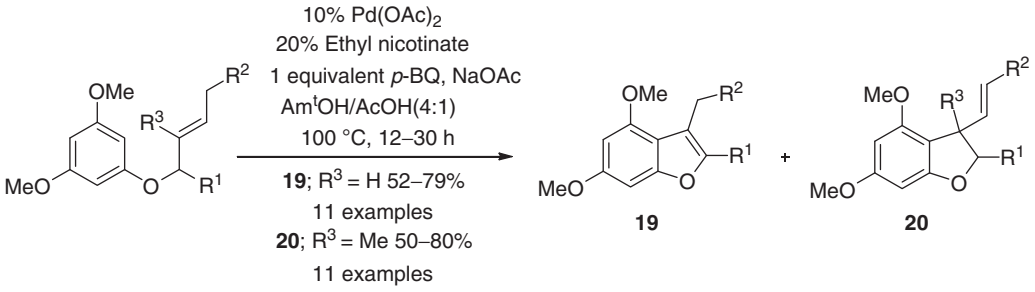


(75)



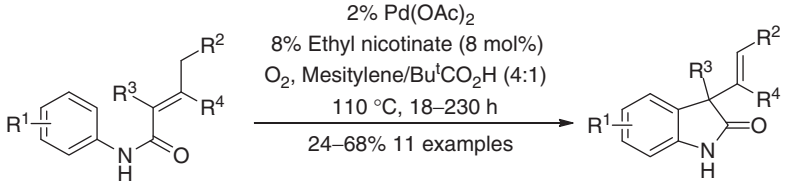
(76)

Building on the chemistry developed for the annulations of indoles, Stoltz and coworkers extended the scope of electron-rich aromatics, using allylphenols to produce benzofurans (equation 77).[187] This reaction serves as a typical example of the post-isomerization of the double bond (**19**) and how the product outcome could be controlled by removal of β-hydrogens (**20**). The substrate scope of this reaction is limited to electron-rich arenes; however, one could consider these substrates complementary to the corresponding Mizoroki–Heck reaction where halogenated electron-rich arenes may display low reactivity.



(77)

The analogous 5-*exo-trig* cyclization of *N*-aryl acrylamides was reported by Schiffner and Oestreich (equation 78).[188] As with previous examples, the scope was restricted to electron-rich aryls, but the palladium loading was reduced to an impressive 2%. Unsymmetrical amides were found to undergo regioselective cyclization, with a preference for substitution *para* to an electron-donating group. This suggests that the reaction likely involves an initial C–H palladation via an S_EAr mechanism.

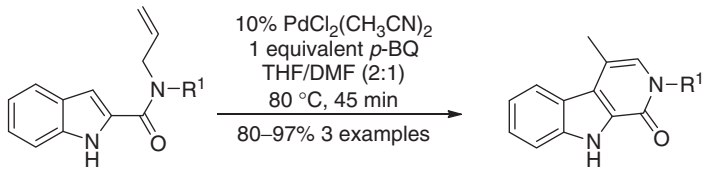


(78)

7.18.3.2 Formation of Six-Membered Rings

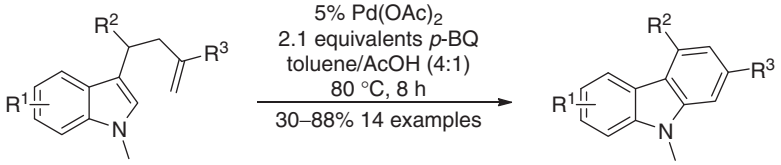
The formation of six-membered rings is not as commonly encountered as that of five-membered rings. Nonetheless, there are a number of useful methods, following both 6-*exo-trig* and 6-*endo-trig* cyclization pathways, available for their preparation. There are only a few stoichiometric examples reported in the literature, but these will not be discussed here.

The C–H functionalization of indoles in both the C2 and C3 positions has been sucessful for the formation of six-membered rings. One of the first examples to appear was the 6-*exo-trig* cyclization displayed in equation 79.[189] An allylic amide tether was, under neutral conditions, annulated in excellent isolated yields using *p*-BQ as a stoichiometric oxidant. An interesting feature of these conditions was the tolerance for the nonprotected indole nitrogen, which could undergo a competeting *N* annulation. Notably, the double bond in this *exo* product is isomerized to the thermodynamically favoured *endo* position.



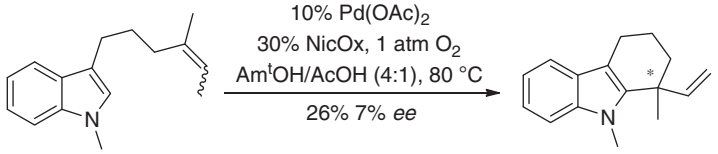
(79)

With an olefin tether on C3, the 6-*endo-trig* cyclization pathway provides carbazoles (equation 80).[190] In this study, *p*-BQ proved to be the superior oxidant using 2.1 equivalents in order to reach good yields of the aromatized product. The selectivity for the 6-*end*-trig cyclization was controlled by substituting the hydrogen in R^3, in order to eliminate the product forming *β*-elimination step, R^3 being the *β*-position, in the competing 5-*exo*-trig process, thereby providing a possible tool to direct the outcome of these reactions.



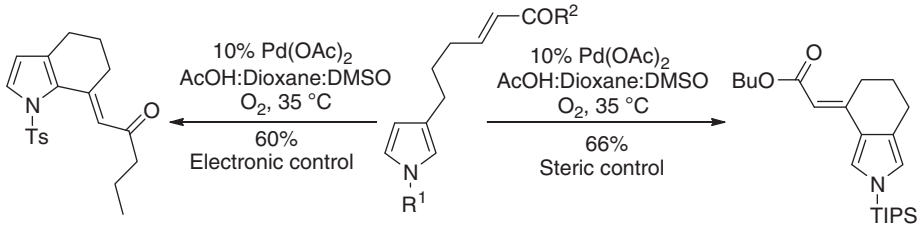
(80)

A much related substrate, initially explored by Ferreira and Stoltz,[184] was the subject for a recent asymmetric annulation investigation by Oestreich and coworkers (equation 81).[186] These annulations proved to be sluggish and unselective compared to the corresponding five-membered process discussed previously in Section 7.18.3.2 (equation 76).



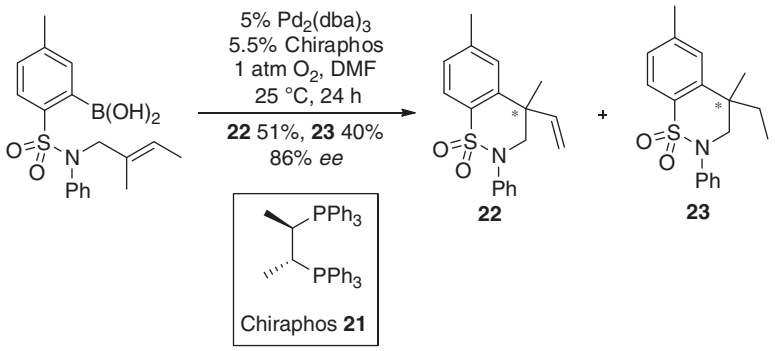
(81)

The oxidative method can also be applied on the related pyrrole substrate. With a tether on C3, Gaunt and coworkers presented an elegant control between C2 and C4, via the 6-*exo-trig* cyclization mode (equation 82).[102] These surprisingly mild C–H functionalization protocols have subsequently been applied in total synthesis regimes for complex natural products.[191,192]



(82)

Finally, in this class one will find a moderately successful example of an asymmetric intramolecular oxidative Heck reaction, using chiraphos (**21**) to induce chirality and a boronic acid for the generation of the arylpalladium species (equation 83).[193] Unfortunately, the substrate scope was rather limited and chemoselectivity poor, with mixtures of nonsaturated (**22**) and saturated (**23**) products being obtained. However, good enantioselectivity was achieved under these conditions, and as methods for the preparation of various arylboron derivatives are continuously improving, this might become an interesting field in the future.



(83)

7.18.4 Conclusion

Now more than 40 years old, the palladium(II)-catalyzed oxidative Heck reaction has been developed extensively and is already supplementing the palladium(0)-catalyzed Mizoroki–Heck reaction in many applications. However, and more importantly, the reactions are complementing each other, opening up new powerful opportunities for selective organic synthesis. Furthermore, it is now possible to perform regio- and stereoselective oxidative Heck reactions with electron-deficient and electron-rich, neutral and allylic olefins using a number of different organopalladium precursors. Numerous intermolecular and intramolecular examples are known. The experimental procedures offer several advantages, such as operational simplicity, absence of halide ions, short reaction times, and good yields. The authors foresee that an increased number of new oxidative Heck reactions will be introduced and that the method will continue to grow in importance.

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7.19 Addition Reactions with Formation of Carbon–Nitrogen Bonds

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Glossary

Aminohalogenation It is also known as haloamination. It refers to a chemical transformation of a C═C double bond into a vicinal haloamine.

Carboamination Describes the formation of both a new C(1)–N and C(2)–C(3) bond starting from a C(1)–C(2) double bond. When the new carbon component {C(3)} is an aryl, alkenyl, or alkyl group, aminoarylation, aminoalkenylation, or aminoalkylation are also used, respectively.

Diamination A chemical transformation of a C═C double bond into a 1,2-diamine unless otherwise stated.

Iodine(III) oxidants Hypervalent iodine species such as iodosylbenzene (PhI═O), iodosylbenzene diacetate ($PhI(OAc)_2$), or iminoiodinanes (PhINR). The term hypervalent indicates that the central iodine atom bears more electrons than an octet within the valence shell.

Metallanitrene A neutral monovalent nitrogen species stabilized by complexation with a metal (copper, rhodium, ruthenium, manganese, etc.). Also known as a metal imido complex.

Nucleometallation Refers to the addition of a nucleophile and an electrophilic metal species (palladium and copper) onto a C═C bond.

Oxyamination A chemical transformation of a C═C bond into a 1,2-amino alcohol regardless of the order of formation of the C–N and C–O bonds.

Tethered reaction A process allowing the intramolecular delivery of, at least, one functional group onto a C═C bond.

7.19.1 Introduction

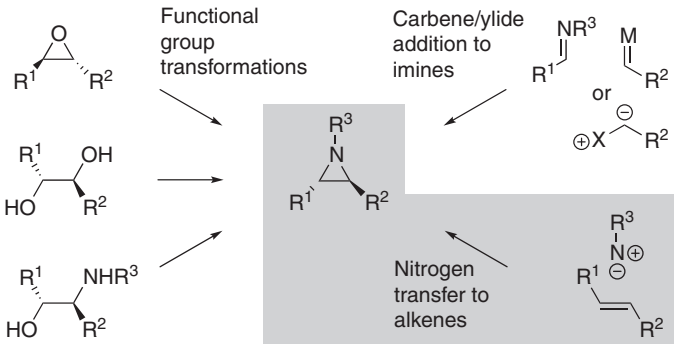
Alkenes are privileged platforms for the polyfunctionalization of molecules in a single pot. It therefore comes as no surprise that, given the ubiquity of amines and amides in organic and medicinal chemistry, addition reactions to alkenes have been widely applied to the formation of nitrogen-containing compounds with the production of 1,2-difunctionalized products. This chapter, which provides an update of the chapter previously written by Kemp,[1] deals with these oxidative processes that allow the formation of aziridines or the simultaneous addition of N + X groups onto C═C bonds. Thus, reactions of aziridination, oxyamination, diamination, aminohalogenation, and carboamination will be successively covered. By contrast, olefin hydroamination, aza-Wacker processes, and cycloadditions are excluded from the scope of this chapter.

Each section of the chapter starts with a general overview of the covered topic including the corresponding reviews published in the past 20 years. The main synthetic methods reported since the early 1990s will then be discussed with an emphasis on their application in organic synthesis.

7.19.2 Alkene Aziridination

7.19.2.1 Introduction

A brief survey of the literature published since 1990 demonstrates clearly that the chemistry of aziridines has exploded in the past two decades. Formally considered as 'under used as synthetic intermediates,'[1] the aziridines have received considerable attention since then as testified by the number of recently published reviews[2–11] and book chapters[12–16] devoted to their synthetic chemistry. Needless to say, the ability of the smallest saturated nitrogen heterocycle to undergo either efficient regioselective ring-opening with a wide range of nucleophiles[7–11] or ring-expansion reactions[17] makes them unique synthons for the preparation of value-added nitrogen-containing molecules. This paramount synthetic importance has caused a surge of interest in devising straightforward procedures for their preparation (**Scheme 1**). Whereas most of the former preparative protocols rely on functional group manipulations starting from epoxides, diols, and amino alcohols,[3] modern aziridination methods reported in the past 20 years involve either the addition of carbenes or ylides to imines[18,19] or nitrogen transfer to alkenes. Great attention has been paid to the latter, particularly with the development of catalytic nitrene transfers that has led to the publication of various synthetically useful transformations.[20–23] These catalytic methods are summarized below and classified according to the nature of the nitrogenous reagents (*see* Chapter 7.02).



Scheme 1

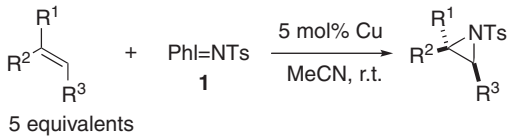
7.19.2.2 Metal-catalyzed Alkene Aziridination with Iodine(III) Oxidants

The most significant achievements in catalytic alkene aziridination, undoubtedly, have been made with the use of iminoiodinanes as summarized in several reviews.[20,22–28] These hypervalent iodine(III) reagents, of general formula PhI=NR, are the aza-analogs of the powerful oxo-donor iodosylbenzene PhI=O. They were first prepared by the reaction of a sulfonamide with $PhI(OAc)_2$ under basic conditions.[29] The *p*-toluenesulfonyl derivative PhI=NTs **1** was used in the seminal study on metal-catalyzed alkene aziridination and is now regarded as the prototype reagent.[30] Iminoiodinanes have some drawbacks such as their troublesome preparation, as well as their limited stability, which might affect the yield of the aziridination. Efficiency of the latter has then been improved by the discovery of practical procedures for the *in situ* formation of iminoiodinanes, which involve the combination of an iodine oxidant with a nitrogen donor.[31–33] In addition to providing better conversions, these one-pot methods enhance the scope of catalytic nitrene transfers as they allow the use of sulfonamides, sulfamates, carbamates, or sulfonimidamides as nitrogen sources. In parallel, various metal complexes have been reported over the years as efficient catalysts for alkene aziridination. Among these numerous metallic species, simple copper(I) or (II) salts and dirhodium(II) tetracarboxylates proved to be exceptionally effective, their unique catalytic activity having been highlighted by several relevant synthetic applications.

7.19.2.2.1 Copper catalysis

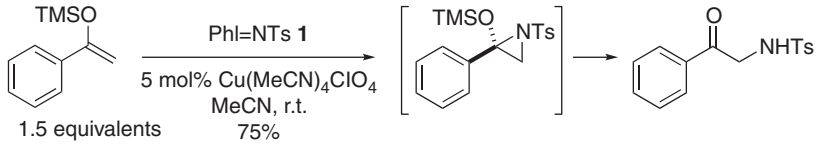
7.19.2.2.1.1 Methodological studies

The ability of copper complexes to efficiently catalyze alkene aziridination with iminoiodinanes was first demonstrated by the group of Evans. A comparative screening of various metals (Mn, Fe, Co, Rh, Ni, and Pd) revealed the higher activity of simple reagents such as $Cu(MeCN)_4ClO_4$ or $Cu(OTf)_2$.[34] Using these readily available complexes in the presence of PhI=NTs, aziridination of electron-rich and electron-deficient olefins occurs with yields of up to 92% (equation 1), whereas silyl enol ethers afford α-amino ketones after hydrolytic ring-opening of the aziridine (equation 2). The absence of products resulting from allylic C–H amination, a major side reaction frequently observed in alkene aziridination, illustrates the high chemoselectivity of the copper-mediated process.



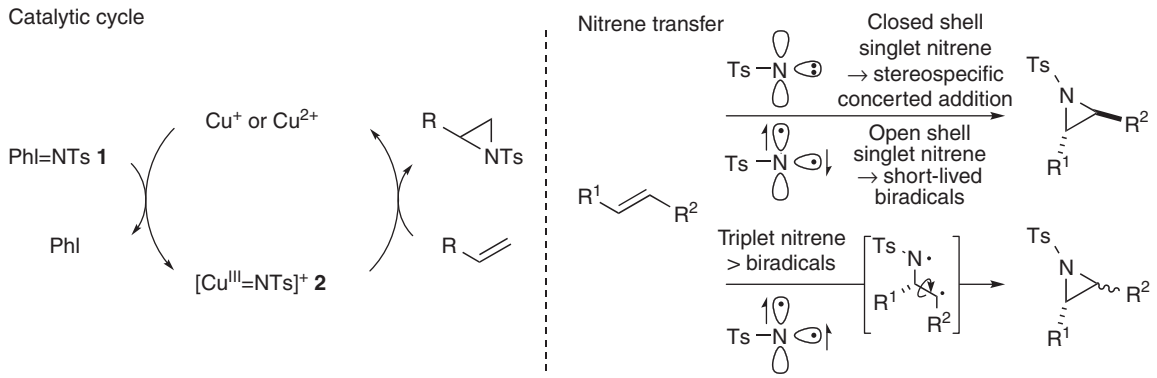
R^1	R^2	R^3	Cu	Yield (%)
Ph	H	H	$CuClO_4$	89
			$Cu(OTf)_2$	92
Ph	Me	H	$CuClO_4$	78
			$Cu(OTf)_2$	73
Ph	H	CO_2Me	$CuClO_4$	69
			$Cu(OTf)_2$	75
Bu^n	H	H	$CuClO_4$	66
			$Cu(OTf)_2$	62

(1)



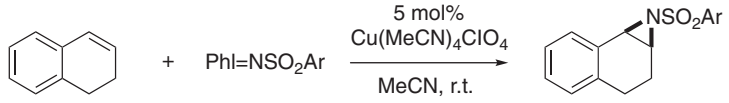
(2)

Mechanistic studies and density functional theory (DFT) calculations have allowed drawing a general catalytic cycle for the reaction (Scheme 2).[34–37] It has been proposed that the addition proceeds by a redox mechanism involving Cu(I) and Cu(III) species. Copper(I) or (II) salts are thus oxidized by **1** to release PhI and afford a copper(III)–nitrene species **2** though very recent results put into question its nature.[38] The mechanism of the subsequent metallanitrene transfer also remains a matter of debate. The stereospecific aziridination of *trans* olefins argues for the concerted addition of a singlet nitrene species. However, the formation of *cis*/*trans* aziridine mixtures, for example, from *cis*-stilbene, contradicts this hypothesis and is in agreement with the production of radicals arising from a triplet nitrene. Since the calculated energy difference for singlet and triplet copper intermediates is small,[37] a fair conclusion is that the mechanistic pathway will depend either on the nature of the copper complex or the substitution of the alkene.



Scheme 2

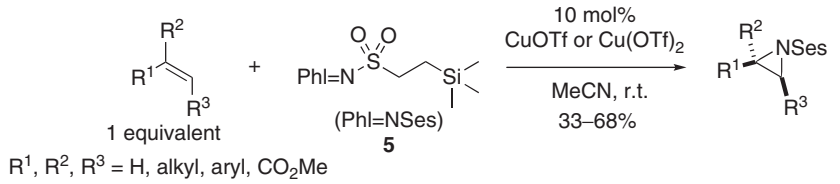
The efficiency and scope of copper-catalyzed olefin aziridination have been improved by the design of new iminoiodinanes. *p*-MeO-$C_6H_4SO_2N{=}$IPh **3** and *p*-NO_2-$C_6H_4SO_2N{=}$IPh **4** (PhI=NNs), both prepared according to the classical procedure,[29] have been found to be much more effective nitrene sources since they provide the corresponding aziridines in very good yields using alkene as the limiting agent (equation 3).[39] PhI=NNs, particularly, affords synthetically useful intermediates because of the versatility of the nosyl group which, in addition, can be easily removed under mild conditions.[40] The formation of the iminoiodinanes PhI=NSes **5** from 2-trimethylsilylethanesulfonamide ($SesNH_2$) also leads to the efficient preparation of versatile aziridines (equation 4).[41] However, the iminoiodinanes are rather capricious reagents since their preparation is difficult to reproduce. The possibility to generate *in situ* compounds **1**, **3**, or **5** by combining the starting sulfonamide with iodosylbenzene PhI=O circumvents this drawback and improves the practicability of the overall process (equation 5).[33]



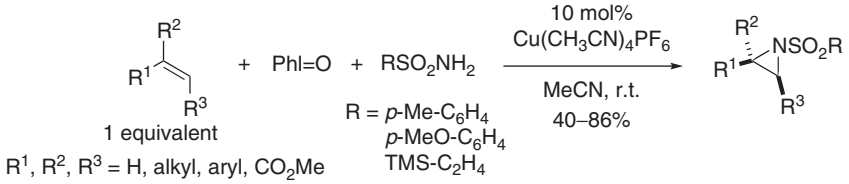
1: Ar = *p*-Tol
3: Ar = *p*-MeO-C_6H_4
4: Ar = *p*-NO_2-C_6H_4

Ar = *p*-Tol; 71% (5 equivalents of alkene)
Ar = *p*-MeO-C_6H_4; 95%
Ar = *p*-NO_2-C_6H_4; 89%

(3)

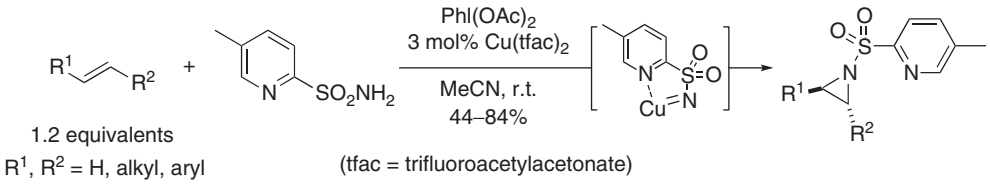


(4)

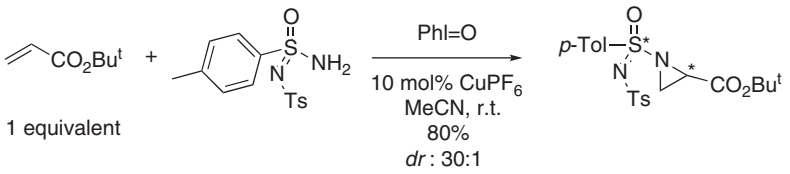


(5)

Thanks to the one-pot procedure, new nitrene precursors have been designed to perform high-yielding alkene aziridinations. Chang et al. have demonstrated that the use of 5-methyl-2-pyridinesulfonamide in the presence of $PhI(OAc)_2$ and $Cu(tfac)_2$ affords the expected aziridines in good yields via a chelation strategy.[42] An internal coordination provided by the 2-pyridinyl group stabilizes the copper nitrenoid intermediate (equation 6).[43] The simple copper salt CuI was reported to mediate efficiently the aziridination of styrene derivatives with PhI=O and trichloroethylsulfamate (see equation 14).[44] Excellent yields of up to 96% were also obtained from stoichiometric amounts of olefins by combining iodosylbenzene with the aza-analogs of sulfonamides: sulfonimidamides.[45] These chiral nitrogen sources add to alkenes with good levels of stereoselectivity. Interestingly, high levels of diastereoselectivity are observed with electron-deficient alkenes such as *tert*-butyl acrylate (equation 7).

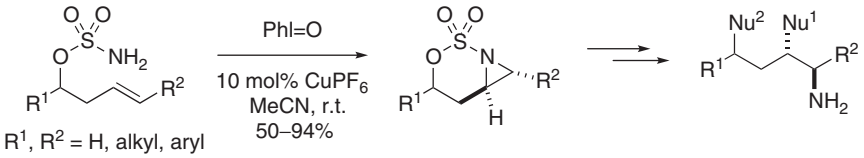


(6)



(7)

Iminoiodinanes, prepared from unsaturated sulfonamides, undergo intramolecular copper-catalyzed alkene aziridination in good yields.[46] The formation of cyclic sulfonamides can be improved by application of the one-pot procedure.[33] More interestingly, these conditions allow extending the intramolecular reaction to sulfamates with yields that are generally higher.[47] The resulting bicyclic aziridines are synthetically useful intermediates as they can undergo sequential regioselective nucleophilic ring openings to give polyfunctionalized amines (equation 8).



(8)

Modifications of the phenyliodine moiety of iminoiodinanes have also been investigated to determine their influence on the course of the reaction. Although this motif is clearly dissociated from the aziridinating species,[35] the introduction of an *ortho-tert*-butylsulfonyl or *ortho*-alkoxy group onto the PhI ring increases the solubility of the reagents. Their reactivity in alkene aziridination has been found comparable to that of PhI=NTs.[48,49]

In parallel to these studies, particular attention has been paid to the screening of copper complexes. Several ligands have been tailored to enhance their catalytic performance.[27,28] The family of nitrogen ligands has been thoroughly explored, often with excellent conversions being observed, for example, with copper–homoscorpionate complexes.[50] Some of the most spectacular

results have been reported with pyridine and pyridinophane ligands in the presence of $NaBAr^F_4$ (BAr^F_4 = tetra[3,5-di(trifluoromethyl)phenyl]borate) (Figure 1).[51,52] Aziridination of various alkenes, in some cases used as the limiting reagent, proceeds in minutes with very good yields and low catalyst loading. A recent report has provided evidence that *N*-heterocyclic carbene ligands can be useful alternatives. The readily available complex IPrCu(DBM) mediates the addition of a sulfamoyl-nitrene to a variety of olefins with yields of up to 88%.[53]

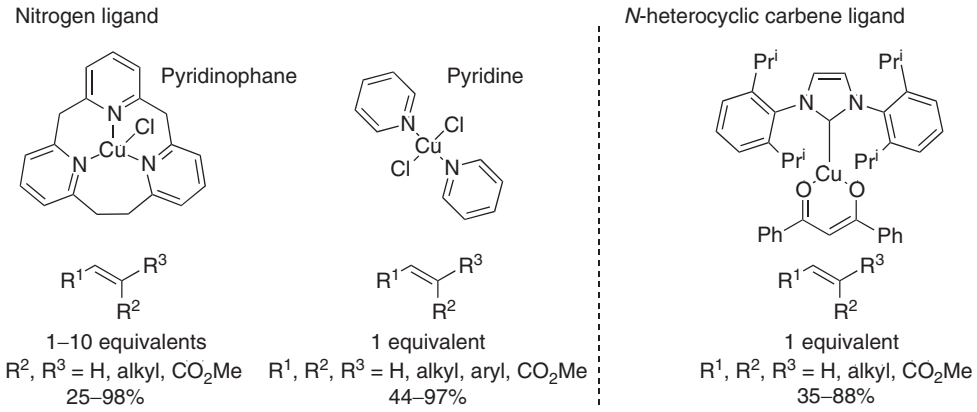
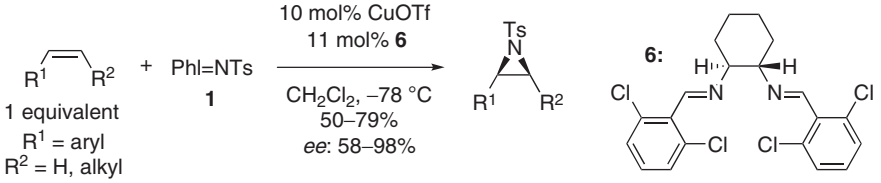
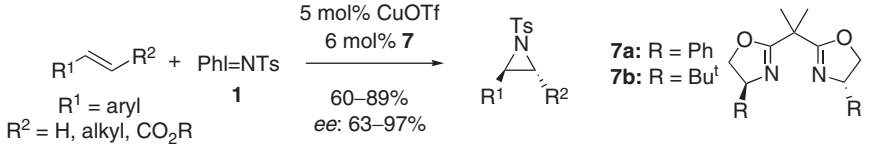


Figure 1 Ligands for the copper-catalyzed alkene aziridination.

Copper-catalyzed asymmetrical aziridination has been successfully developed with the design of chiral C_2-symmetrical ligands that fall into two main classes: the diimines and the bisoxazolines.[20,23] The first example of each ligand family was reported at the same time by the groups of Jacobsen[54] and Evans,[55] respectively. Chiral diimines derived from *trans* 1,2-diaminocyclohexane induce high enantioselectivities for the aziridination of *cis* olefins, the best enantiomeric excess being observed with the 2,6-dichlorobenzylidene derivative **6** (equation 9). The lack of reactivity of (salen)Cu(II) complexes reveals that the absence of open coordination sites on the metal is detrimental to its catalytic activity, hence the crucial effect of the *ortho*-chloro substituents that replace the former OH groups. By contrast, bis(oxazoline) ligands in combination with CuOTf are competent for the asymmetrical transformation of *trans* olefins, the *tert*-butyl, and phenyl analogs affording the best results (equation 10). However, in both cases, the asymmetrical alkene aziridination remains confined to styrenes, cinnamates, chromenes, or dihydronaphthalene.



(9)



(10)

These pioneering studies have been a source of inspiration to search for more discriminating ligands (Figure 2). Several chiral diimines have thus been developed by condensing 2,6-dichlorobenzaldehyde with various C_2-symmetrical diamines such as 6,6′-dimethylbiphenyl-2,2′-diamine (ligand **8**),[56] 1,1′-binaphthyl-2,2′-diamine (**9**),[57] or tetramethyloctahydro-2–2′-bifuranyl-3–3′-diamine (**10**).[58] In the case of **8**, the *ortho*-chloro substituents are crucial for the formation of highly active monometallic species. Very high levels of enantioselection are recorded for chromene and cinnamate derivatives but the enantiomeric excess remains low with other simple alkenes. However, chiral bis(oxazolines) with either an anthracenyl[59] (**11**) or a cyclohexyl[60] (**12**) backbone are efficient ligands for the asymmetrical aziridination of chalcones. Unexpectedly, the Cu-(**11**) complex affords aziridines with *ees* dependent on the substitution of the chalcones and an absolute configuration opposite to that provided by the analogous bis(oxazoline) **7a**. However, despite these studies, the parent bis(oxazolines) **7** remain the ligands of choice and their use in a one-pot protocol with 4-nitrobenzenesulfonamide as the nitrene source gives improved yields and enantioselectivities.[61] In addition, intramolecular aziridination of sulfamates (see equation **8**) with the Cu–(**7b**) complex proceeds efficiently with electron-deficient and electron-rich olefins.[62]

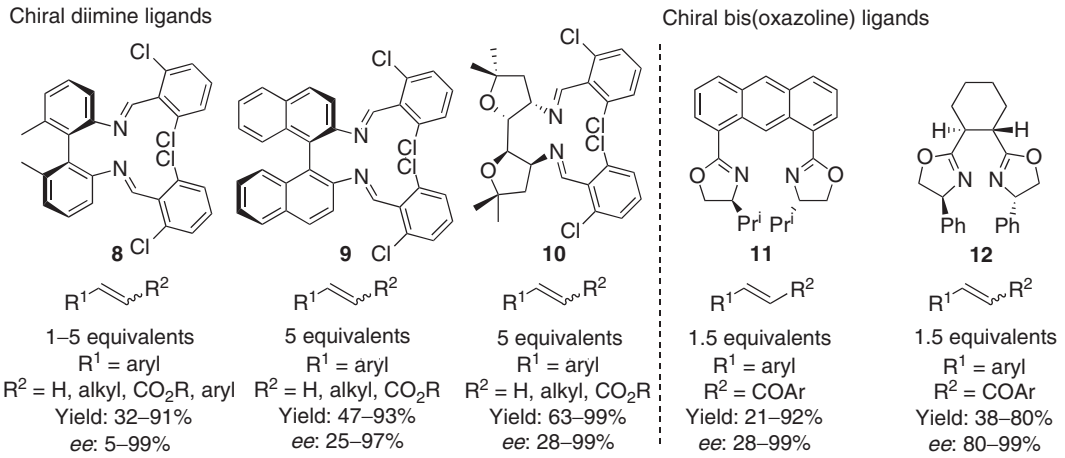
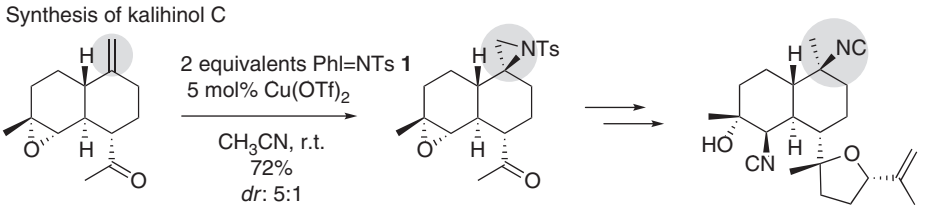


Figure 2 Chiral ligands for the asymmetric copper-catalyzed alkene aziridination.

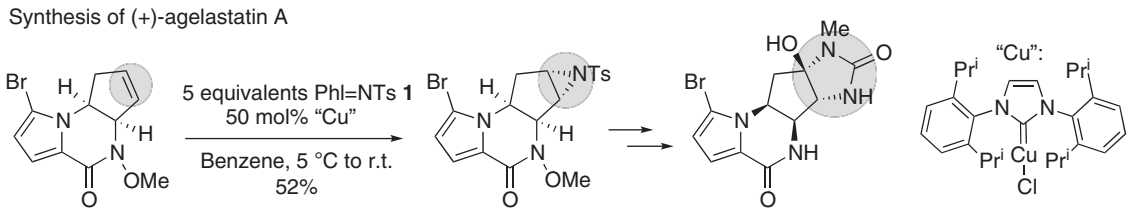
7.19.2.2.1.2 Synthetic applications

Early synthetic applications of the intermolecular copper-catalyzed aziridination are highlighted in the review focused on iminoiodinanes for C–N bond-forming reactions.[25] Relevant examples of its successful use in natural product synthesis have since been reported, including the total syntheses of Kalihinol C,[63] (+)-Agelastatin A,[64] or (+)-Lycoridine.[65] In the former case, aziridination of the *exo*-methylene proceeds efficiently to afford the expected spiro derivative in 72% yield and a diastereomeric ratio of 5:1 (**Scheme 3**). The subsequent aziridine ring-opening under reductive conditions allows introduction of the tertiary isonitrile of Kalihinol C.



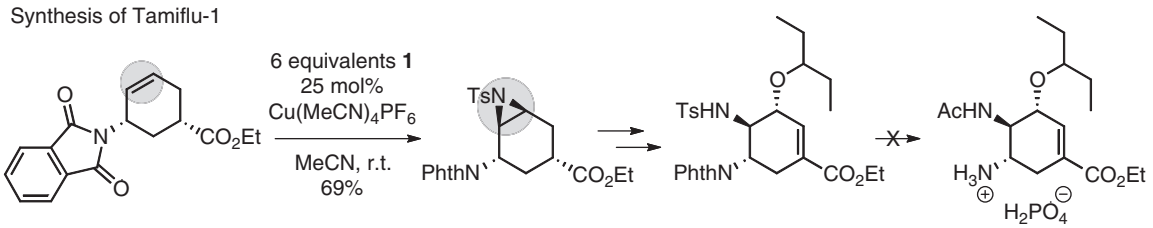
Scheme 3

Copper-catalyzed aziridination is the sole nitrene transfer effective for the elaboration of the D-ring of (+)-agelastatin A. But the poor reactivity of the electron-deficient olefin has required the development of an unprecedented copper–NHC complex that gives the expected aziridine in 52% yield and complete facial selectivity (**Scheme 4**).[63] The high catalyst loading reflects the need to search for more efficient catalyst to improve the scope of alkene aziridination. Intramolecular alkene aziridination has been applied to the synthesis of spisulosine.[66]



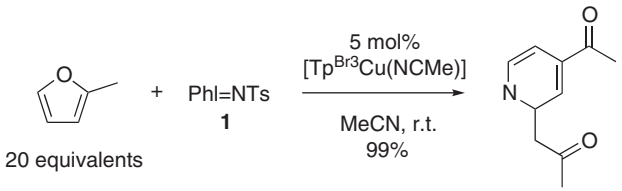
Scheme 4

Given the ubiquity of nitrogen in drugs, alkene aziridination provides unique opportunities in medicinal chemistry, as illustrated by its application to the preparation of Tamiflu.[67] The first strategy relied on the reaction of an allylic amine with PhI=NTs **1** to give an *N*-(tosyl)aziridine in good yield and complete stereoselectivity (**Scheme 5**). However, the frequently faced issue of tosyl deprotection led the authors to consider a different retrosynthetic scheme involving a diene and the more easily cleavable sulfonamide $SesNH_2$ as the nitrene source. Copper complexes afforded a mixture of regiosiomeric aziridines in this case, proving less selective than the dirhodium(II) catalysts (see **Scheme 7**).



Scheme 5

The ability of aziridines to react with a variety of nucleophiles makes catalytic aziridination a useful tool to produce libraries of bioactive compounds or functionalized materials. This is well illustrated by the preparation of an aziridinofullerene as a versatile platform for further functionalization.[68] Moreover, when applied to furans, aziridination catalyzed by a copper–scorpionate complex affords the rearranged products (equation 11).[69] This example, as many others, suggests that the scope of catalytic nitrene transfers is not just confined to aziridination and C–H amination.[70]

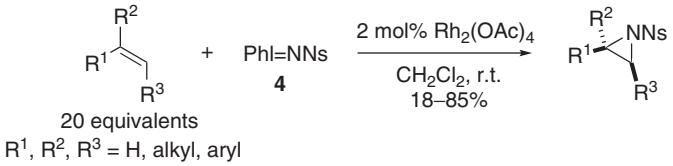


(11)

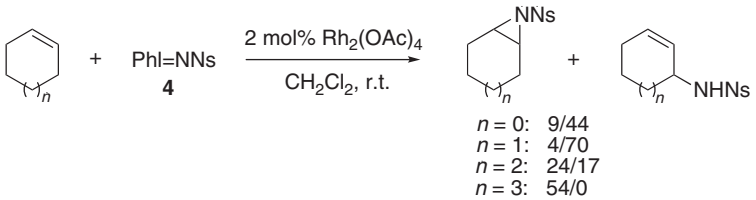
7.19.2.2.2 Rhodium catalysis

7.19.2.2.2.1 Methodological studies

In his seminal paper,[34] Evans already pointed out the capacity of $Rh_2(OAc)_4$ to catalyze alkene aziridination. However, the yield was lower than that obtained with copper, or that previously reported for a unique example of intramolecular nitrene C–H insertion.[71] Rhodium-catalyzed alkene aziridination was then investigated by the group of Müller. Optimized yields in the 18–85% range have been obtained by using PhI=NNs **4** instead of **1**, though in the presence of an excess of olefin (equation 12).[72] The reaction occurs stereospecifically starting from substituted styrenes and simple alkenes, however, allylic C–H amination is observed in the case of cycloalkenes with relative ratios dependent on the size of the cycle (equation 13).[73] This competitive process is often a side reaction in rhodium-catalyzed aziridination,[26] making it a major drawback. Mechanistic experiments such as Hammett studies and the use of radical clocks provide evidence in favor of the concerted addition of an electrophilic dirhodium(II)-nitrene species but the involvement of fast-recombining radicals cannot be ruled out, partly because of the nonstereospecific aziridination of *cis*-stilbene.[26,73]

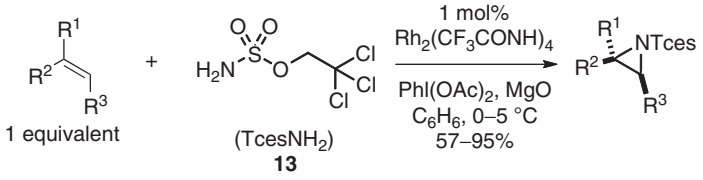


(12)



(13)

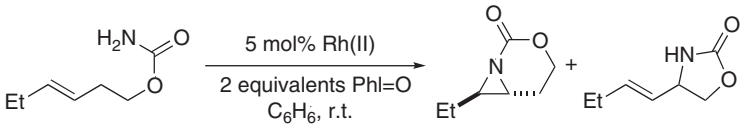
The emergence of a one-pot protocol for the formation of iminoiodinanes in the presence of rhodium(II) complexes[32] has led to major improvements. Intermolecular aziridination of olefins used in stoichiometric amounts thus proceeds in very good yields of up to 95% with only 1 mol% of readily available catalysts and trichloroethylsulfamate ($TcesNH_2$) **13** as the nitrene source (equation 14).[74,75]



R^1	R^2	R^3	Yield (%)
Ph	H	H	95
Ph	H	Me	85
H	Ph	Me	85
Me	H	C_6H_{13}	57
H	Me	C_6H_{13}	72
Bu^n	Me	H	72

(14)

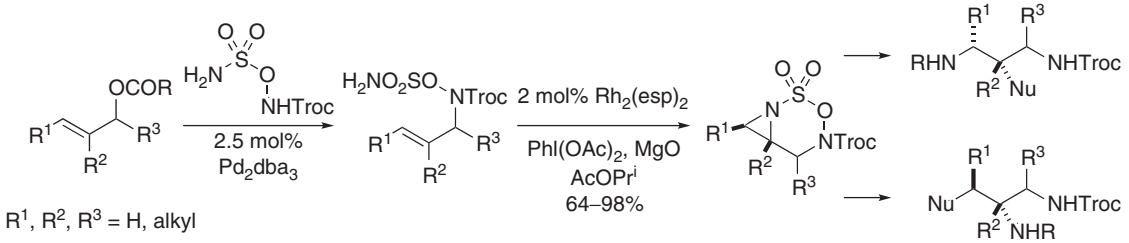
Under these conditions, highly efficient intramolecular aziridinations can be performed with a wide range of sulfonamides[76] and sulfamates,[77] the latter offering the opportunity to selectively prepare polyfunctionalized amines as previously described (see equation 8 and Scheme 8). Intramolecular aziridination also proceeds from allyl-[78] and homoallyl-carbamates.[79] The reaction, in the case of cycloalkenyl derivatives, occurs surprisingly even in the absence of the rhodium complex.[78] However, the use of homoallyl substrates raises once again the issue of chemoselectivity.[79] Mixtures of aziridines and allylic amines are generally obtained with the relative amounts dependent on the nature of the rhodium catalyst (equation 15), a trend confirmed in a recent study devoted to the synthesis of bicyclic methylene aziridines from allenes.[80]



	Aziridine/Allylic amine
Rh(II): $Rh_2(OAc)_4$	68/14
Rh(II): $Rh_2(oct)_4$	71/6
Rh(II): Rh_2(*S*-MEOX)$_4$	0/40

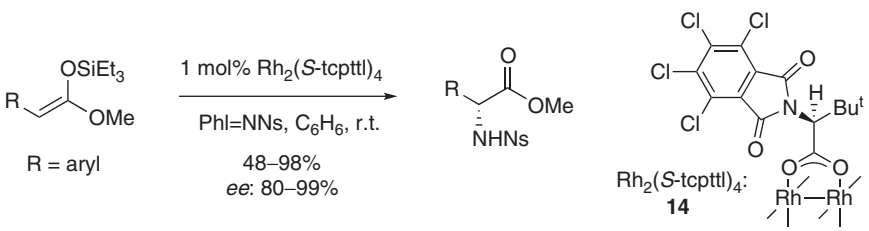
(15)

A relevant extension of the chemistry of sulfamates has been developed from hydroxylamines. Much of the success of the overall transformation relies on the careful choice of the protecting group for the hydroxylamine. An *N*4-Troc is optimal for isolation of the bicyclic aziridines obtained following the combination of palladium and rhodium catalysis (Scheme 6).[81] The regioselectivity of the subsequent aziridine ring-opening can be well controlled by the choice of the substituents, thereby leading to either 1,2- or 1,3-diamines.

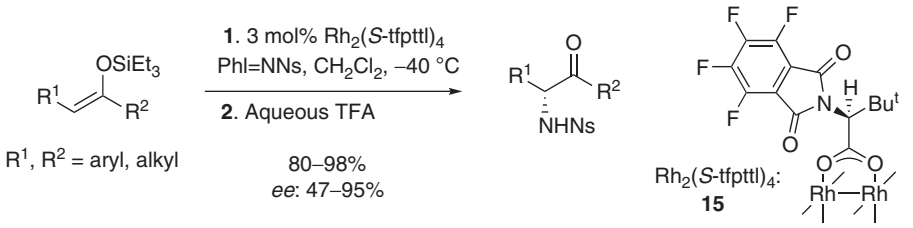


Scheme 6

A variety of chiral rhodium(II) complexes, generally commercially available, allows the performance of asymmetric intermolecular alkene aziridination, albeit with lower efficiency when compared to copper.[20,23] An optimized enantiomeric excess of 94% is obtained for the reaction with 2,2-dimethylchromene using Rh_2(*S*-tcpttl)$_4$ **14**, but the conditions did not apply efficiently to substituted styrenes.[82] **14** and its fluorous analog Rh_2(*S*-tfpttl)$_4$ **15**, by contrast, have proved more efficient for the aziridination of acyclic silylketene acetals[83] and silyl enol ethers,[84] affording phenylglycine derivatives and α-amino ketones, respectively (equations 16 and 17). Enantioselective intramolecular aziridination, with enantiomeric excesses of up to 76%, also takes place starting from various *o*-vinyl- and *o*-allyl-arenesulfonamides in the presence of Rh_2(4*S*-MEOX)$_4$.[85]



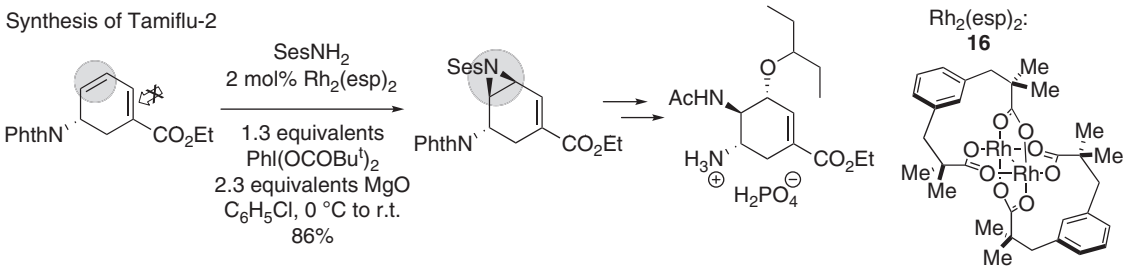
(16)



(17)

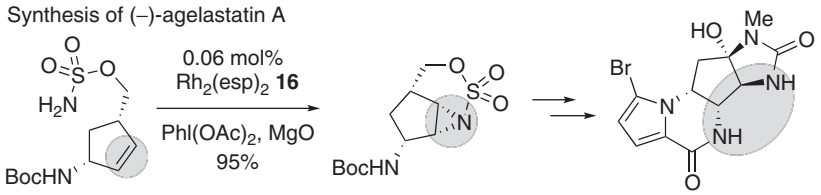
7.19.2.2.2 Synthetic applications

Rhodium-catalyzed alkene aziridination is one of the key steps in the recent asymmetrical synthesis of Tamiflu.[67] Careful optimization has found that use of the highly active and commercially available $Rh_2(esp)_2$ complex **16** (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid),[86] in combination with $SesNH_2$, $PhI(OCOBu^t)_2$, and MgO, affords the expected aziridine with a very good yield of 86% (Scheme 7). Importantly, this unprecedented reaction proceeds with complete regio-, chemo-, and stereoselectivities. The electron-withdrawing Ses group then allows the ring-opening of the aziridine to occur smoothly with 3-pentanol, before its cleavage that proceeds in 95% yield using the classical fluoride reagent tetra-*n*-butylammonium fluoride.



Scheme 7

The unique capacity of rhodium(II) complexes to mediate nitrene transfers is also illustrated by the application of intramolecular aziridination to the synthesis of (–)-agelastatin A.[87] By comparison with the previous strategy involving copper (see Scheme 4), a very small catalyst loading, 0.06 mol%, is sufficient to afford the tricyclic aziridine in excellent yield and, again, with a complete chemoselectivity (Scheme 8). In addition, the synthetic opportunities provided by bicyclic sulfamates are here exploited to elaborate the B- and D-rings of agelastatin A.

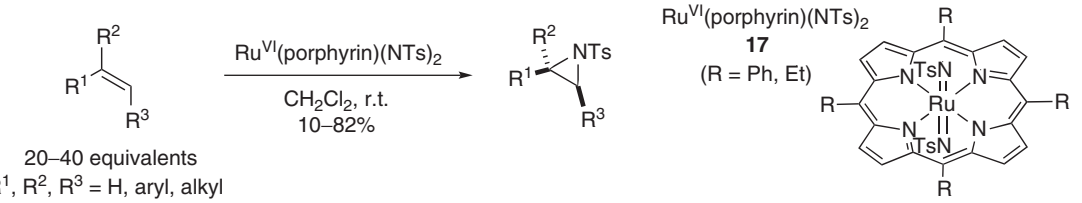


Scheme 8

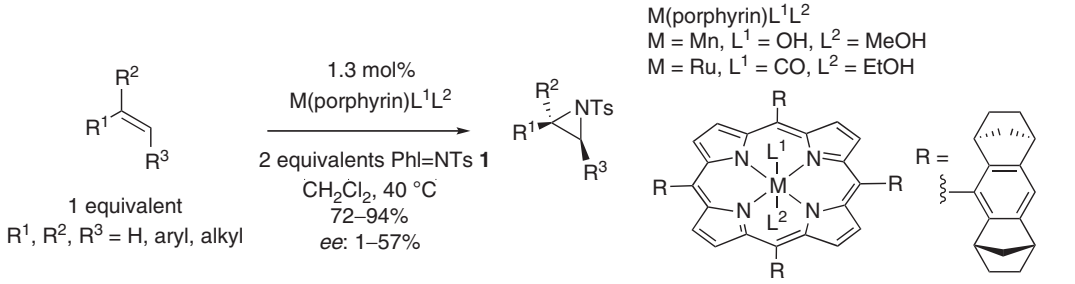
7.19.2.2.3 Other metal catalysis

7.19.2.2.3.1 Mn- and Ru-porphyrins

Following the seminal studies from the group of Mansuy,[30,88] various ruthenium and manganese porphyrins have been designed for alkene aziridination. Bis(tosylimido)ruthenium(VI) porphyrins **17**, prepared by reaction of porphyrins with PhI=NTs **1**, are able to transfer the imido group to several alkenes used in excess (equation 18).[89] Contrary to the case of copper or rhodium a collected body of experimental evidence, such as the nonstereospecific aziridination of *cis* alkenes, points to a stepwise mechanism involving the rate-determining formation of carboradical intermediates. The influence of the sulfonyl substituent on the imido function has revealed the higher reactivity of the Ns group, compared to that of the tosyl.[90] Subsequently, inter-[31] and intramolecular[91] porphyrin-catalyzed aziridinations have been developed, with imido species **17** being proposed as a competent intermediate in these nitrene additions.

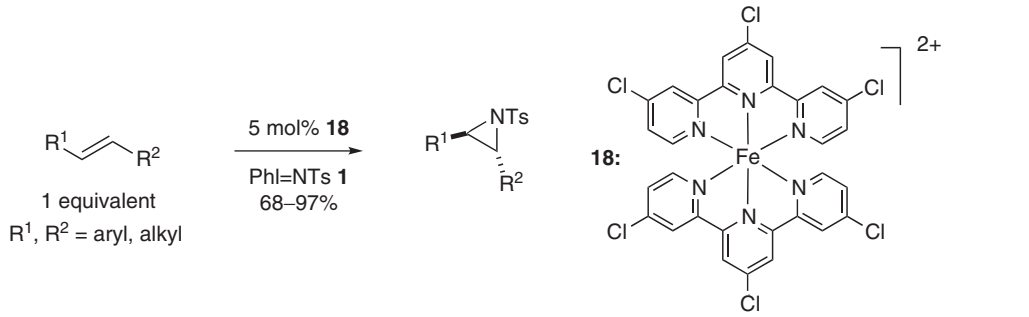


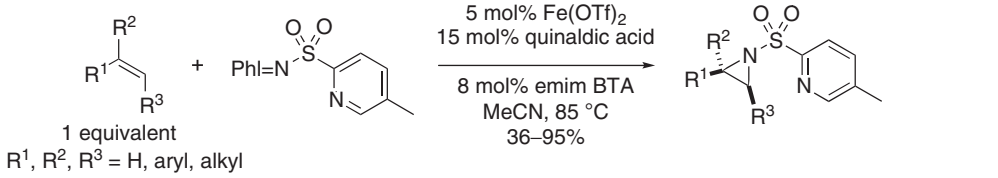
Chiral Ru- and Mn-porphyrins, which bear an octahydro-1,4:5,8-dimethanoanthracene unit at each methine of the ring, allow asymmetric intermolecular aziridination to be performed from styrene-type olefins though with moderate enantiomeric excesses of up to 57%. The manganese complex generally gives higher conversions and levels of stereoselectivity (equation 19).[92] It should be mentioned that chiral Ru(II)-[93] and Mn(III)–salen[94] complexes are also reported for catalytic asymmetric alkene aziridination using iminoiodinanes.



7.19.2.2.3.2 Iron complexes

The capacity of iron to catalyze alkene aziridination was demonstrated by the early studies of Mansuy with the use of iron(III)-porphyrins. The procedure, however, requires the addition of 100 equivalents of styrene.[30] A more synthetically useful procedure is mediated by the iron(II) complex **18** readily prepared by reaction between $Fe(ClO_4)_2 \cdot 6H_2O$ and 4,4′,4″-trichloro-2,2′:6′ 2″-terpyridine. Compound **18** acts as an efficient catalyst for the transformation of alkenes used in stoichiometric amounts (equation 20).[95] The simple iron(II) salt $Fe(OTf)_2$ is also able to catalyze the intermolecular aziridination of silyl enol ethers and styrene substrates.[96] The need to run the reaction with an excess of olefin is circumvented by the use of quinaldic acid and an ionic liquid additive, in the presence of the 5-methyl-2-pyridinesulfonamide-derived iminoiodinanes, allowing the aziridination to occur with yields of up to 95% (equation 21).[97]

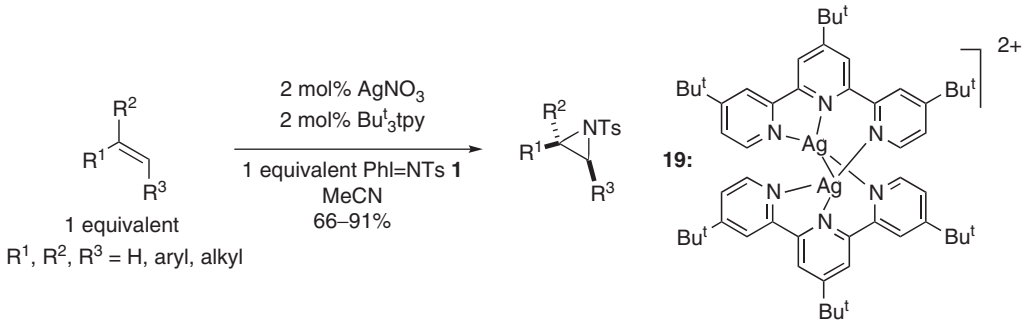




7.19.2.2.3.3 Silver and gold complexes

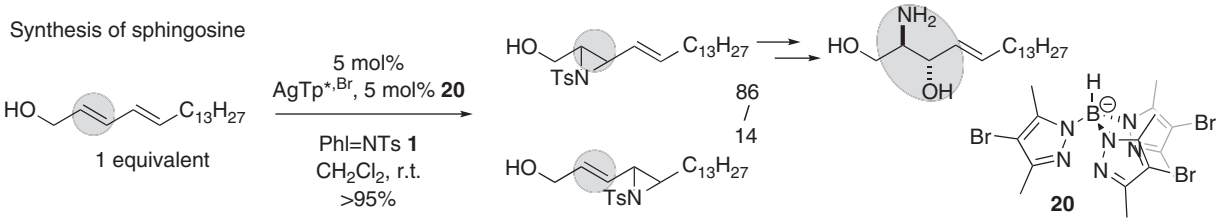
Alkene aziridination with iminoiodinanes can be mediated by silver(I)-[98] and gold(I)-complexes[99] combined with a tridentate pyridine ligand Bu^t_3tpy. Whereas the gold-catalyzed process operates under the one-pot conditions with $PhI(OAc)_2$ and several

sulfonamides, the use of silver in aziridination requires preformed iminoiodinanes such as **1**. The silver-catalyzed reaction takes place stereospecifically even with *cis*-stilbene and involves an unprecedented disilver(I) species **19** (equation 22). Each silver ion might offer potentially one electron for the catalytic two-electron nitrene transfer, hence avoiding the formation of radicals.



(22)

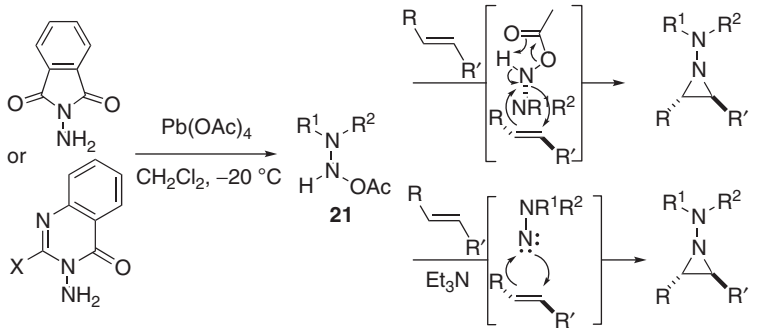
In combination with scorpionate ligands **20**, silver complexes prove more efficient than copper analogues for the aziridination of 1,3-dienes.[100] The reaction takes place stereospecifically and with excellent regioselectivity at the alkene unit vicinal to a hydroxyl group, which is believed to play a directing role in the nitrene addition. The synthetic utility of the method was then demonstrated by its application to the synthesis of sphingosine in 65% overall yield from a simple diene (Scheme 9).



Scheme 9

7.19.2.2.4 Metal-free alkene aziridination mediated by iodine(III) oxidants

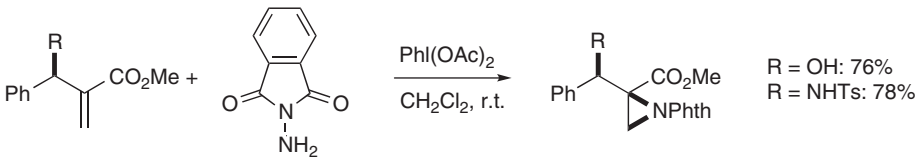
The preparation of aziridines from alkenes by reaction with *N*-aminoheterocycles is a well-known method pioneered at the end of the 1960s by the group of Rees and then intensively investigated by Atkinson.[1,101] A typical procedure involves the oxidation of *N*-aminophthalimide or *N*-aminoquinazoline in the presence of lead tetra(acetate) to produce the acetoxyamino derivative **21**. The latter has been identified as the aziridinating agent that adds to both electron-deficient and electron-rich olefins, according to a mechanism analogous to that proposed by Bartlett for the epoxidation with peracids (Scheme 10). The aziridination, however, can also proceed by a second distinct pathway involving the generation of an *N*-nitrene from **21** after base-induced α-elimination.



Scheme 10

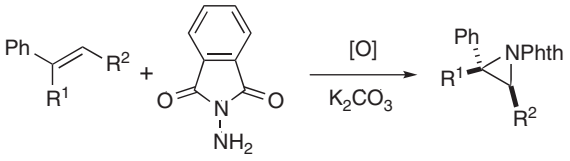
The use of $Pb(OAc)_4$ for the production of acetoxyamines raises the issues of toxicity and sustainability, thereby making the search for more eco-friendly oxidants necessary. The groups of Che[102] and Yudin[103] thus demonstrated the ability of $PhI(OAc)_2$ to mediate the aziridination of alkenes with *N*-aminophthalimide. The reaction occurs efficiently and stereospecifically with respect of the olefin geometry, under very mild conditions. It can be applied to either electron-poor or electron-rich olefins and tolerates various functional groups such as an hydroxyl group or an *N*-(tosyl)amine (equation 23). More importantly, the nitrene transfer

occurs in the absence of any metal catalyst. Detailed mechanistic studies have contradicted the initial hypothesis proposed by Yudin[21] suggesting the formation of the acetoxyamine. In contrast to the aziridination with $Pb(OAc)_4$, the reaction is believed to proceed through the formation of an iminoiodinane that adds to the alkene.[104]



(23)

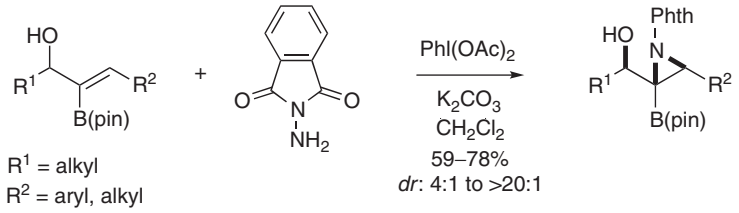
Further investigations have focused on reducing the production of PhI. The alkene aziridination occurs with comparable yields in the presence of stoichiometric amounts of an iodoarene and *meta*-chloroperbenzoic acid (*m*-CPBA) (equation 24).[105] The combination of these reagents allows the generation *in situ* of an iodine(III) oxidant, which then reacts with *N*-aminophthalimide to give the presumed iminoiodinane. However, all attempts to make the reaction catalytic in PhI have been unsuccessful due to the lack of an appropriate chemoselective oxidant.[104] Nevertheless, an intermolecular metal-free aziridination in the presence of catalytic quantities of tetrabutylammonium iodide, instead of PhI, and mediated by *m*-CPBA has been reported.[106] This reaction would not involve a nitrene, but rather the generation of hypoiodous acid HOI that would add to the olefin to afford a bridged iodonium subsequently attacked by $PhthNH_2$. Another noteworthy alternative that avoids the production of PhI is based on electroorganic synthesis with platinum electrodes in the presence of *N*-aminophthalimide, triethylamine, and acetic acid.[107]



R^1	R^2	Yield (%)[102] [O]: $PhI(OAc)_2$	Yield (%)[105] [O]: PhI +*m*CPBA	Yield (%)[106] [O]: Bu_4NI + *m*CPBA
H	H	84	81	76
H	Me	35	68	63
H	Ph	89	84	–
Me	H	–	57	69

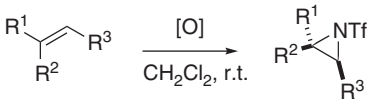
(24)

The scope of the alkene aziridination with *N*-aminophthalimide is wider than that of metal-catalyzed reaction involving classical iminoiodinanes. Contrary to the reaction described above, with a sulfamate, a sulfonamide, or a carbamate, the *N*-aminophthalimide-$PhI(OAc)_2$ system can be applied successfully to α-bromo-olefins,[108] affording α-bromoaziridines that rearrange under thermal conditions to α-bromohydrazones, and fluorinated alkenes.[109] Intermolecular aziridination of allylic amides and carbamates also takes place efficiently with high *syn* or *anti* diastereoselectivity according to the substituents installed on the vicinal nitrogen.[110] An analogous directing effect is observed in the case of boron-substituted allylic alcohols. The alkene aziridination proceeds with high diastereoselectivity and complete chemoselectivity since the B(pin) group withstands the oxidizing conditions of the reaction (equation 25).[111]



(25)

Metal-free alkene aziridination mediated by iodine(III) oxidants is not confined to *N*-aminoheterocycles. The use of (sulfonyl)iminoiodinanes has been reported by the group of Moriarty[112] in a study that complements the seminal work with carbamates.[78] Intramolecular aziridination can thus take place in the absence of a metal catalyst but the scope is limited to conformationally constrained sulfonamides.[112] By comparison, the recently described iminobromanes[113] are more versatile because their high reactivity, related to their increased hyperleaving character, allows intermolecular alkene aziridination to occur stereospecifically at room temperature. Very good yields are obtained from alkenes used as the limiting agent, either in the presence of the preformed iminobromane *p*-$CF_3C_6H_4Br{=}NTf$ (Tf: CF_3SO_2)[114] or by combining the corresponding (diacetoxybromo)arene with $TfNH_2$ (equation 26).[115] The low availability of bromine(III) oxidants, however, remains a major limitation for a general application of this efficient process.

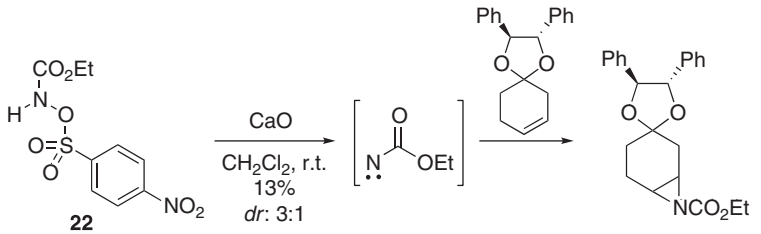


R^1	R^2	R^3	Yield (%)[114] [O]: ArBr=NTf	Yield (%)[115] [O]: $ArBr(OAc)_2$ + $TfNH_2$
Ph	H	H	84	76
Oct^n	H	H	65	73
Ph	H	Me	79	–
H	Ph	Me	–	84
Pr^n	H	Pr^n	53	73
H	Pr^n	Pr^n	–	87

(26)

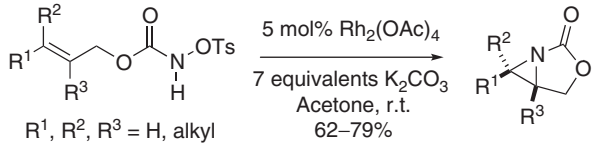
7.19.2.3 Alkene Aziridination with *N*-(Sulfonyloxy)Carbamates

N-(Sulfonyloxy)carbamates have recently emerged as a useful alternative to iodine(III) oxidants for the promotion of metal-catalyzed nitrene transfers in the context of sustainable chemistry. Yet, Lwowski pioneered the use of these species for the generation of nitrenes nearly 50 years ago.[116] Treatment of ethyl nosyloxycarbamate **22** with Et_3N allowed the generation of (ethoxycarbonyl)nitrene, which was shown to be a useful aminating agent. The group of Pellacani, in particular, has extensively investigated the chemistry based on this reagent with the addition of inorganic bases that are highly effective in inducing the required α-elimination.[117] Aziridination of chiral cyclohexenone ketals has been reported to proceed with moderate diastereoselectivity under these conditions (equation 27).[118] The process has been extended to a variety of electron-deficient olefins such as α,β-unsaturated ketones.[119] However, in this case, the mechanism may involve either a nitrene addition or a Michael-type addition followed by ring-closure (see Section 7.19.2.6).



(27)

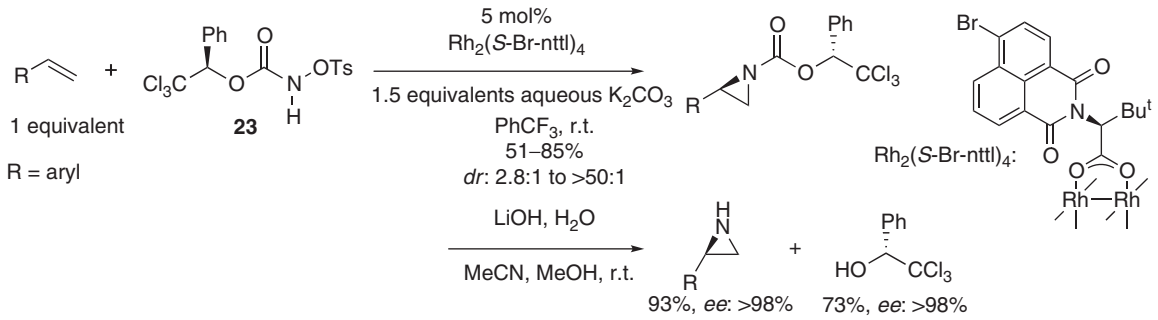
A noteworthy feature of the reaction is the release of a sulfonate salt as a polar by-product, which can be easily removed by simple filtration, unlike PhI. The group of Lebel thus capitalized on this observation to develop practical procedures for metal-catalyzed nitrene addition to alkenes using various tosyloxycarbamates. Intramolecular aziridination of allylic derivatives occurs stereospecifically in the presence of dirhodium(II) complexes to afford the corresponding bicyclic fused aziridines in very good yields (equation 28).[120,121] However, as previously observed with iodine oxidants (see equation 15), application of the reaction conditions to homoallylic substrates raises the issue of chemoselectivity and mixtures of aziridines and allylic amines are isolated.



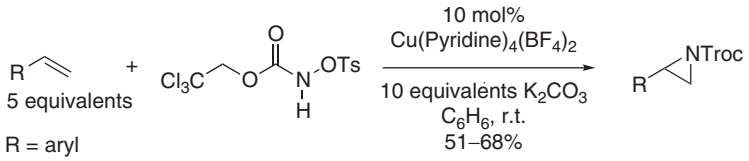
(28)

The matched combination of a chiral rhodium(II) complex with the well-designed chiral tosyloxycarbamate **23** allowed the development of the intermolecular stereoselective aziridination of alkenes under stoichiometric conditions. High levels of diastereoselectivity are observed but the reaction remains limited to styrene derivatives, as is the case with catalytic asymmetric aziridination with iminoiodinanes (**Scheme 11**).[122] Nevertheless, the Ph-Troc protecting group provides the advantage of being more easily cleaved than a tosyl substituent. The use of simple basic conditions leads to the free aziridines without side reactions of ring-opening. In addition, the chiral auxiliary is partially recovered in an optically pure form.

Intramolecular alkene aziridination of allylic *N*-(tosyloxy)carbamates is catalyzed by the copper salt CuOTf.[123] The yields are improved by replacing CuOTf with simple copper–pyridine complexes, as previously observed with iminoiodinanes.[52] Bicyclic aziridines, as described in equation 28, can therefore be isolated with yields ranging from 51% to 84%, which are comparable to those reported with rhodium(II) complexes.[124] More interestingly, the design of this copper catalyst allows extending the reaction conditions to intermolecular aziridination of substituted styrenes with a Troc *N*-tosyloxycarbamate (equation 29).

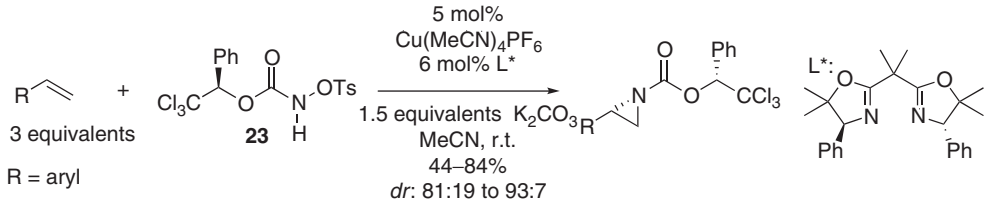


Scheme 11



(29)

The combination of the chiral phenyl-Troc **23** with a chiral copper-bis(oxazoline) complex affords various 2-arylaziridines with very good diastereomeric ratios (equation 30).[125] The efficient ring-opening of these aziridines with a variety of nucleophiles and the subsequent facile cleavage of the carbamate protecting group make this method useful for the synthesis of enantiopure amines. However, its overall practicability is somewhat thwarted by the need to use an excess of styrenic substrates.



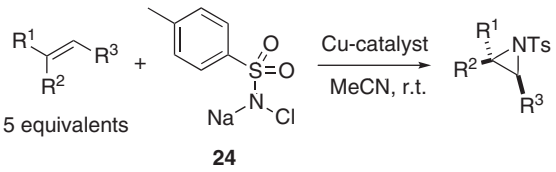
(30)

7.19.2.4 Alkene Aziridination with *N*-Haloamines

The addition of haloamines to alkenes for the formation of aziridines[126] provides unique opportunities in the framework of sustainable chemistry, best illustrated by the generation of innocuous sodium chloride as the only by-product from chloramine-T **24**. Use of the latter was formerly applied to osmium-mediated alkene aminohydroxylation (see Section 7.19.3.2). Pioneering studies[127] then demonstrated that chloramine-T combined with simple copper salts could be an efficient nitrogen donor for olefin aziridination. This transformation relies on the capacity of *N*-halo *N*-metallo reagents to behave as nitrenoids. However, *N*-halo *N*-metallo compounds can act as sources of both halonium cations and nitrogen anions, a property that has led to describe simple bromine-[128] and iodine-[129] catalyzed alkene aziridinations.

7.19.2.4.1 Metal-catalyzed alkene aziridination with haloamines

The seminal paper by Komatsu et al. describes the capacity of copper(I) chloride to catalyze olefin aziridination with anhydrous chloramine-T **24**, though with limited efficiency. Yields in the 18–75% range are obtained in the presence of five equivalents of alkenes.[127] An initial improvement came from the use of a pyridine-2-imine ligand in combination with copper(I) triflate. It allowed the reaction to be performed with slightly higher yields using commercially available chloramine-T trihydrate, thereby avoiding the hazardous drying of this reagent required for the initial procedure (equation 31).[130] Competitive allylic amination is observed with this copper complex in the case of cyclohexene. Mechanistic studies, albeit focused on copper-catalyzed C–H amination, revealed the involvement of an electrophilic metallanitrene species.[131] Chloramine-T also reacts with equimolar quantities of silver(I) nitrate to afford a radical nitrene species able to add to various types of olefins.[132] Worthy of note is the reaction with 1,6-dienes under these conditions that leads to the formation of bicyclic pyrrolidines.

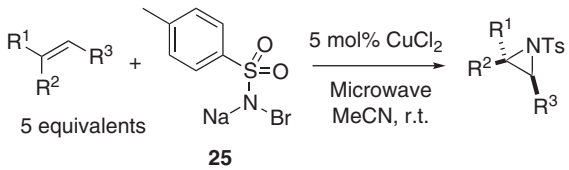


	Yield (%)[127] CuCl	Yield (%)[131] $(CuOTf)_2$ + Ligand
Ph	31	74
Ph	64	45
	67	76

Ligand: C_5H_{11}

(31)

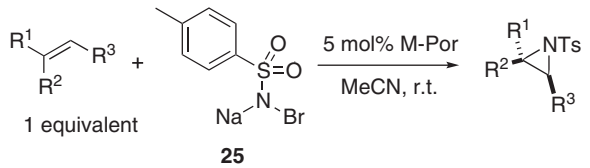
Further investigations have allowed a comparison to be drawn between chloramine-T **24** and bromamine-T **25**, the latter being found more effective in copper-catalyzed alkene aziridination. A screening of various metal halides has led to the identification of simple CuX_2 salts (X: Cl, Br) as the catalysts of choice for the aziridination with **25** under microwave irradiation.[133] Olefins used in excess are transformed with yields ranging from 36% to 88% (equation 32).

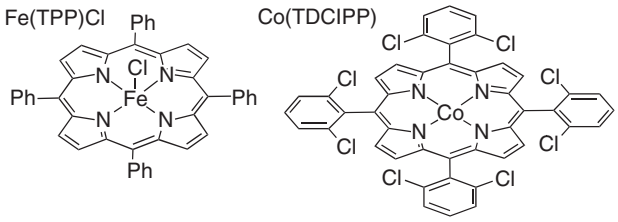


	Yield (%)[133]	Yield (%)[127] with **24**
Ph	70	31
Ph	88	75
$H_{17}C_8$	80	12

(32)

The higher reactivity of bromamine-T has been confirmed by various studies documenting the aziridination of alkenes catalyzed by different metals.[134–136] In particular, the group of Zhang has described highly efficient procedures based on the use of iron(III)[134] and cobalt(II) porphyrins.[135] They allow the transformation of a large variety of aromatic and aliphatic alkenes, used as the limiting agents, to afford the corresponding aziridines in good yields (equation 33). These reactions are assumed to occur via the addition of a metallanitrene intermediate with radical character, a conclusion that can be drawn from the mixtures of stereoisomers isolated from *cis* and *trans* 1,2-disubstituted alkenes.

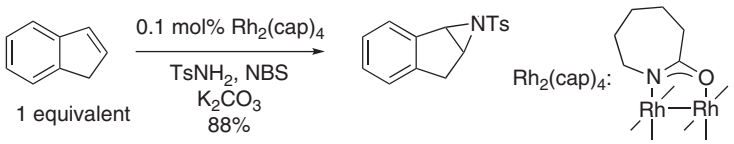




	Yield (%)[134] M-Por: Fe(TPP)Cl	Yield (%)[135] M-Por: Co(TDCIPP)
Ph	77	83
Ph	75	87
Ph	*cis*:*trans* 18:82 54	*cis*:*trans* 8:92 94
$H_{15}C_7$	*cis*:*trans* 56:44 60	*cis*:*trans* 9:91 56
	50	67

(33)

A practical procedure based on the combination of tosylamide with *N*-bromosuccinimide (NBS) to generate a bromamine *in situ* has been reported for alkene aziridination in the presence of very small amount of a dirhodium(II) complex (equation 34).[137] Unlike the previous reactions, this transformation would not involve the addition of nitrenes but rather the formation of a bromonium species followed by the addition of the bromamine formed. In this case, the dirhodium(II) catalyst serves as a Lewis acid.

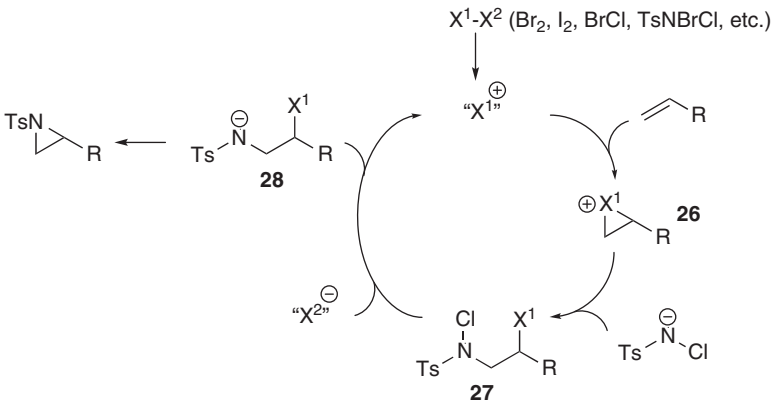


(34)

It should be mentioned that an environmentally friendly protocol, involving chloramine-T **24** and 12-phosphomolybdic acid as the catalyst, has been shown highly efficient for the production of aziridines from a stoichiometric amount of alkenes.[138]

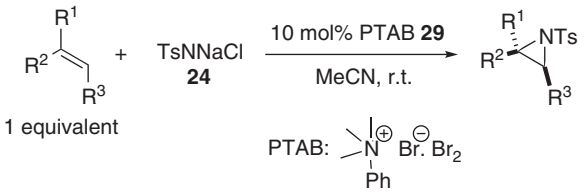
7.19.2.4.2 Metal-free catalytic alkene aziridination with haloamines

The ability to generate halonium cations from haloamines has been applied to develop several efficient and practical protocols for the formation of aziridines that avoid the use of transition metals. These reactions are catalyzed by bromine or iodine and are assumed to proceed according to an identical pathway regardless of the catalyst (Scheme 12). A halonium source would first react with the olefin to give a three-membered halonium species **26** subsequently ring opened by the haloamine to afford the intermediate **27**. Reaction with a halide would then induce the formation of the nitrogen anion **28** that could cyclize to the expected aziridine, and the regeneration of the halonium catalyst. Such a mechanism is in line with the stereospecificity observed in the case of *cis* and *trans* 1,2-disubstituted alkenes.



Scheme 12

Phenyltrimethylammonium tribromide (PTAB) **29** has been the first source of bromine reported by the group of Sharpless as a useful catalyst for the aziridination of olefins with chloramine-T.[128] When compared to the previous metal-catalyzed protocols, the reaction can be applied to a much wider range of olefins with excellent yields (equation 35). It proceeds, moreover, with equal efficiency using chloramine-T trihydrate. In some cases, however, allylic amines resulting from a competitive elimination process were isolated in small amounts. Worthy of note is the possibility to cleanly functionalize allylic alcohols under these conditions. Application of the latter to cyclic allylic alcohols thus affords preferentially *cis*-isomers.[139,140] Interestingly, the use of the copper–iminoiodinane system favors the formation of the *trans*-isomers, thereby illustrating the complementarity of both methods.

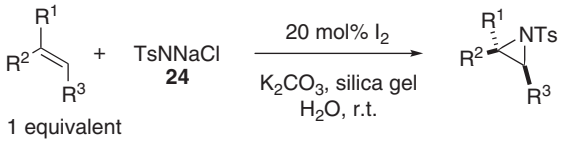


R^1	R^2	R^3	Yield (%)[128]
Ph	H	H	68
Ph	H	Me	76
H	Ph	Me	89
n-$C_{10}H_{21}$	H	H	54
n-C_5H_{11}	Me	H	76
H	Bu^n	Et	95
Pr^n	H	CH_2OH	97
H	Pr^n	CH_2OH	95
Me	CH_2OH	H	70
Me	Me	CH_2OH	94

(35)

Further studies have demonstrated that pyridinium hydrobromide perbromide ($Py \cdot HBr_3$),[141] or a combination of HBr and H_2O_2,[142] can be used as sources of bromonium cations, allowing extension of the reaction to electron-deficient olefins. The *N*-chloramine salt of *tert*-butylsulfonamide is also an efficient nitrogen source for alkene aziridination that should prove useful in synthetic applications since a *tert*-butylsulfonyl group can be cleaved under milder conditions by comparison with a tosyl.[143]

Iodine is also a very simple catalyst for the aziridination of alkenes with chloramine-T.[129] It allows performing the reaction in aqueous media in the presence of a phase-transfer catalyst or, more interestingly, using silica as a hydrophobic adsorbent (equation 36).[144] Under these conditions, the ring-opening of the resulting aziridine can also take place using NaN_3 or KCN as the nucleophile.



R^1	R^2	R^3	Yield (%)[144]
n-C_6H_{13}	H	H	49
n-C_5H_{11}	H	Me	42
H	n-C_5H_{11}	Me	70
Pr^n	H	CH_2OH	58
H	Pr^n	CH_2OH	61

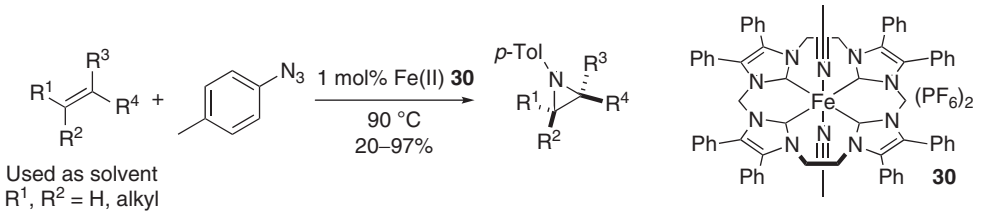
(36)

With the aim to enhance the variety of nitrogen sources for the functionalization of olefins, it has been demonstrated that a haloamine can be conveniently generated *in situ* from various sulfonamides such as $SesNH_2$. The protocol is based on the use of *tert*-butyl hypoiodite formed by reaction between *tert*-butyl hypochlorite (Bu^tOCl) and NaI.[145] These conditions are no longer catalytic in halonium reagents. Non-protected aziridines can also be directly isolated from styrene derivatives following reaction with aqueous ammonia and bleach in the presence of ammonium iodide as the catalyst.[146] Finally, it is worth mentioning relevant applications of alkene aziridination with haloamines. Iodine, for example, is an efficient catalyst for the diamination of glycals, leading to the formation of 2-amino-glycosylamines,[147] and for the selective functionalization of fullerenes for the production of photovoltaic cells.[148]

7.19.2.5 Metal-Catalyzed Alkene Aziridination with Azides

Azides are landmark reagents in the history of nitrene chemistry.[149] One of the first synthetically useful reactions with nitrenes was reported in 1951 with the photochemical conversion of *o*-azidobiphenyls to carbazoles. Photoinduced formation of nitrenes from azides has been widely used since then and is still applied today in organic synthesis as illustrated by the preparation of aminoglycosides through intramolecular alkene aziridination of an acyl azide.[150] The photoirradiation of Mn(III)-azide complexes also affords nitridomanganese(V) complexes,[151] which are efficient stoichiometric aminating agents. These have been shown to promote asymmetric alkene aziridination in good yields.[152]

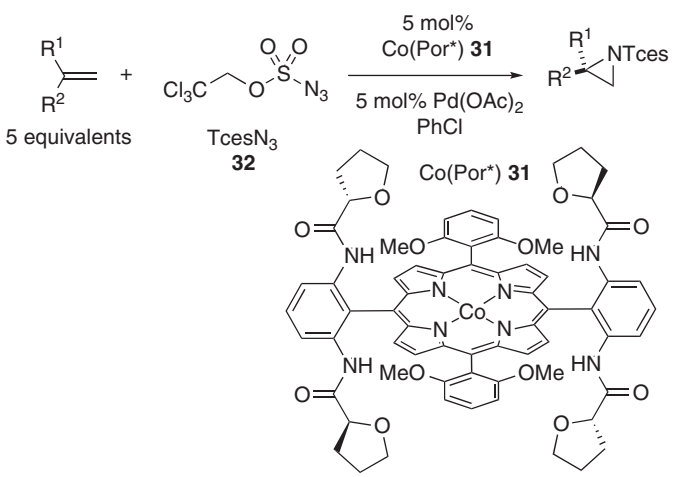
Use of benzenesulfonyl azide has allowed Kwart and Kahn to report the ability of a transition metal complex to catalyze nitrene transfers for the first time in 1967.[153] Surprisingly, despite azides providing an ideal solution in the context of sustainable chemistry, the only by-product generated by their decomposition is N_2, they have been only recently considered in metal-catalyzed alkene aziridination.[154] The use of ruthenium- and cobalt-porphyrins in catalytic aziridination using aryl azides as nitrogen sources, has been reported many years after the seminal studies involving copper powder.[153] *p*-Nitrophenyl azide proved optimal in combination with Ru(TPP)(CO) for the formation of aziridines starting from various aromatic alkenes[155] or 1,3-dienes[156] used in excess. The mechanism is believed to involve a Ru(TPP)–azide complex rather than a Ru–imido intermediate as the active species. The overall efficiency of the process, however, is sometimes limited by the competitive formation of triazolines under the thermal conditions of the reaction that deactivates the Ru catalyst.[155] Aryl azides have also been engaged successfully in catalytic alkene aziridination in the presence of a perfluorinated iron(III)–porphyrin[157] or, more recently, a new macrocyclic tetracarbene iron(II) complex **30**.[158] The latter is a recyclable catalyst that mediates the aziridination of di-, tri-, or tetrasubstituted aliphatic olefins, via the formation of a putative Fe(IV)–imido intermediate (equation 37). The low catalyst loading, however, is counterbalanced by the need to run the reaction with the alkene as the solvent.



(37)

It should be emphasized that the use of aryl azides in catalytic nitrene transfer is of high interest from an atom-economical point of view. It allows introduction of functional groups likely to be part of the final products, contrary to the case of classical azides substituted by an electron-withdrawing group. The latter is generally a sulfonyl substituent that often needs to be removed before the installation of an extra functional group. Nevertheless, sulfonyl azides have been widely applied in catalytic alkene aziridination, for example, in the presence of the aforementioned perfluorinated iron porphyrin[157] or cobalt(II) porphyrins. The careful design of porphyrins likely to interact with the sulfonyl group by hydrogen bonding has led to the development of an efficient aziridination of aromatic alkenes.[159] The scope of the reaction has also been greatly improved by the conception of a chiral D_2-symmetrical cobalt-porphyrin **31** and the use of trichloroethoxysulfonyl azide ($TcesN_3$) **32** as the nitrene source.[160]

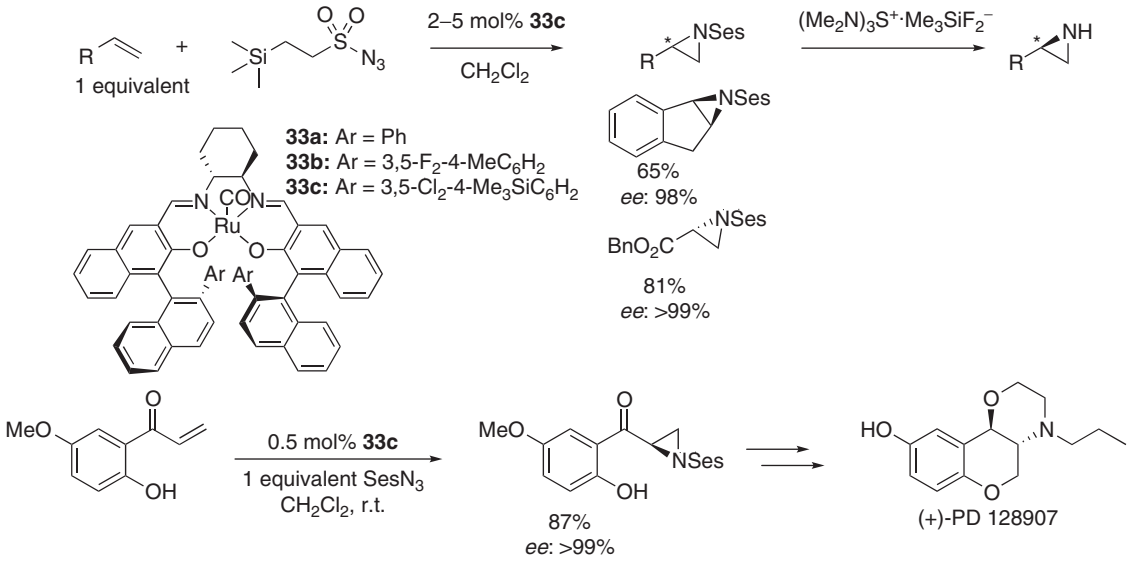
Under these conditions, and sometimes in the presence of palladium(II) acetate as an additive, the aziridination of a large variety of olefins proceeds in moderate-to-excellent yields and with very high enantioselectivities (equation 38). The involvement of a cobalt–nitrene radical species and the cooperative hydrogen bonding have been demonstrated by DFT calculations.[161] It should be mentioned that Co(II)–porphyrins are the catalysts of choice to perform alkene aziridination with diphenylphosphoryl azide (DPPA) as another nitrogen source, albeit with lower efficiency than that observed with the previous sulfonyl azides.[162]



R^1, R^2	Yield (%)[158]	*ee* (%)
Ph, H	91	94
Ph, Me	48	80
Bu^n, H	42	91
Ph, Ph	26	94
	53	87

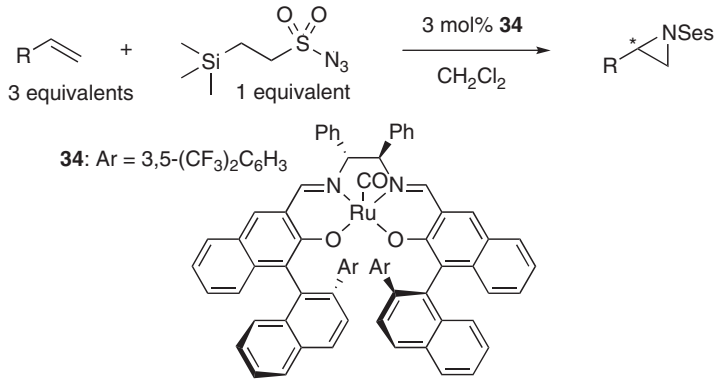
(38)

Chiral ruthenium(II)–salen complexes **33** are able to mediate efficiently the aziridination of a diverse range of alkenes that are used as the limiting agents, unlike the reactions with azides described in Scheme 13.[163] The activity of the first-generation catalyst **33a** has been improved by replacing the phenyl by a 3,5-difluoro-*p*-tolyl or a 3,5-dichloro-4-trimethylsilylphenyl group. In addition to increasing turnover numbers, complexes **33b,c** provide the opportunity to perform the reaction with azides substituted by easily cleavable protecting groups. $SesN_3$ in combination with **33c** thus affords the corresponding *N*-(Ses)aziridines in an enantiomerically pure form from indene and benzyl acrylate. These aziridines can be further deprotected in the presence of fluoride anions without racemization (Scheme 13). Under these reaction conditions, vinyl ketones are transformed with exceptionally high yields and enantiomeric excesses, a result that has been applied to the formal asymmetric synthesis of the dopamine receptor agonist (+)-PD 128907.[164]



Scheme 13

The third-generation catalyst **34**, with a 3,5-bis(trifluoromethyl)phenyl group, allows extending the scope of the aziridination to simple aliphatic alkenes (equation 39).[165] In addition, 0.5–1 mol% of complex **34** is sufficient to promote the reaction with aromatic olefins that leads to the corresponding *N*-(Ses)aziridines with yields in the 66–99% range and enantiomeric excesses of up to 99%.

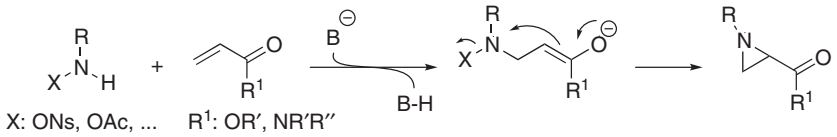


R	Yield (%)[164]	*ee* (%)
Bu^n	74	99
Cyclohexyl	45	99
But-2-en-1-yl	58	91
Bn	91	90
4-Br-C_4H_8	95	91

(39)

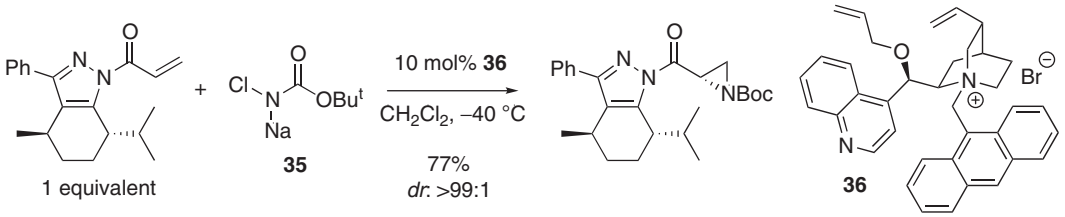
7.19.2.6 Organocatalyzed Aziridination of α,β-Unsaturated Carbonyl Derivatives

The design of aza-nucleophiles bearing a leaving group on the nitrogen has led to the development of many protocols for the Weitz–Scheffer-type aziridination. These reactions proceed according to the same pathway, sometimes referred to as aza-Michael initiated ring closure (MIRC), involving a first step of aza-Michael addition followed by a ring closing nucleophilic displacement (Scheme 14). Some of the aforementioned nitrogen reagents, such as *N*-nosyloxycarbamates **22**[117] or acetoxyamines **21**,[101] have been used in this process for the aziridination of α,β-unsaturated esters or amides. Diaziridines as a reagent have also proved fruitful to this end.[166] Recent investigations have culminated in the discovery of organocatalytic procedures involving quaternary, tertiary, secondary, or primary amines.



Scheme 14

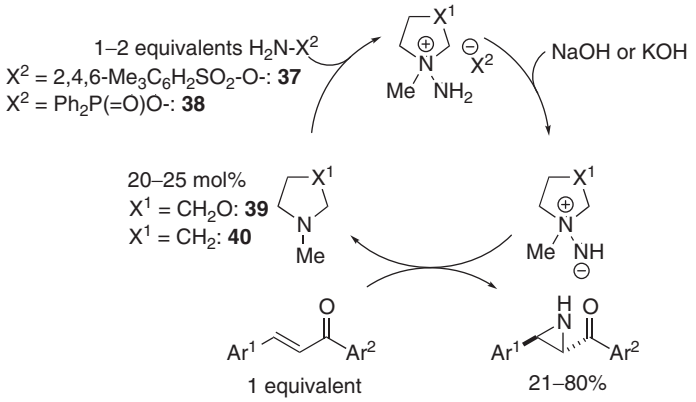
Chiral ammonium salts generated from Cinchona alkaloids are efficient phase-transfer catalysts for the stereoselective aza-MIRC additions to cycloalkenones,[167] as well as to esters, sulfones, and amides.[168] In the latter case, the reaction proceeds efficiently with *N*-chloro-*N*-sodio-carbamate **35** as the nitrogen source, whereas chloramine-T **24** does not react under these conditions. The matched combination of the cinchonidium salt **36** with a chiral menthol-derived auxiliary installed on the Michael acceptor allows the aziridination to occur with very good yields and excellent diastereoselectivity (equation 40).[169]



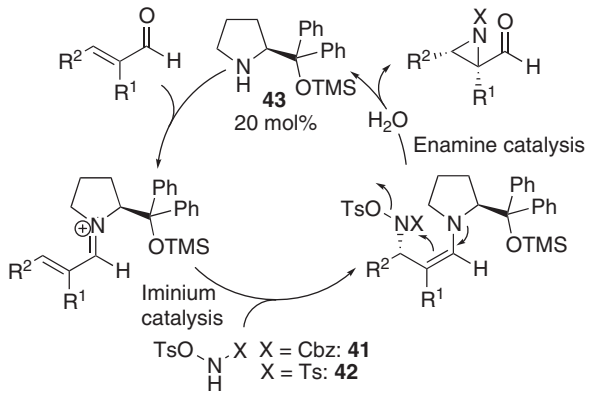
(40)

Organocatalyzed aziridination of chalcones can be performed with *N*-*N* ylides that are generated *in situ* following amination of tertiary amines with either *O*-(mesitylenesulfonyl)hydroxylamine (MSH) **37**[170] or *O*-(diphenylphosphinyl)hydroxylamine **38**.[171] *N*-methylpyrrolidine (NMM) **39** and *N*-methylpiperidine **40** are among the best catalysts to this end, affording the expected aziridines in good yields starting from electron-deficient or electron-rich enones (Scheme 15). The reaction can also be applied successfully to α,β,γ,δ-unsaturated carbonyl derivatives with complete regioselectivity for the α,β-alkene.[172] Chiral tertiary amines such as Tröger's base[170] or quinine[171] allow running asymmetrical aziridinations but the enantioselectivities remain moderate (*ee*s of up to 67%).

Primary and secondary amines induce activation of α,β-unsaturated aldehydes and ketones through covalent interactions. A tandem iminium–enamine process thus allows aziridination to take place with a wide scope. The enantioselective addition of *N*-(Cbz)-*O*-(Ts)-hydroxylamine **41** or its ditosylated equivalent **42** is efficiently mediated by the diaryl prolinol catalyst **43** and can be applied to a large variety of aliphatic and aromatic α,β-unsaturated aldehydes (Scheme 16).[173] The more atom-economic and eco-friendly *N*-acetoxycarbamates can also be used but they generally lead to lower diastereoselectivities when compared to *N*-tosyloxycarbamates. Very high enantioselectivities, in addition, are observed in the case of enones by combining **41** with the chiral primary amine salt **44** (equation 41).[174]

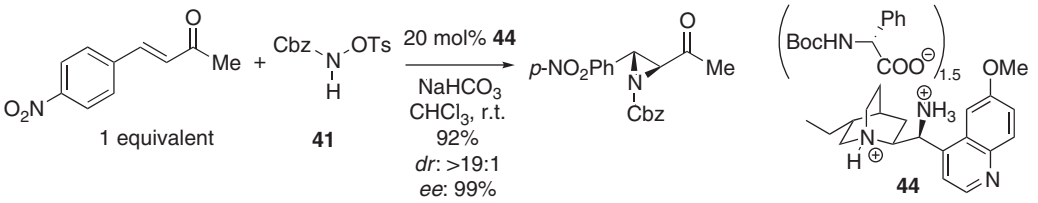


Scheme 15



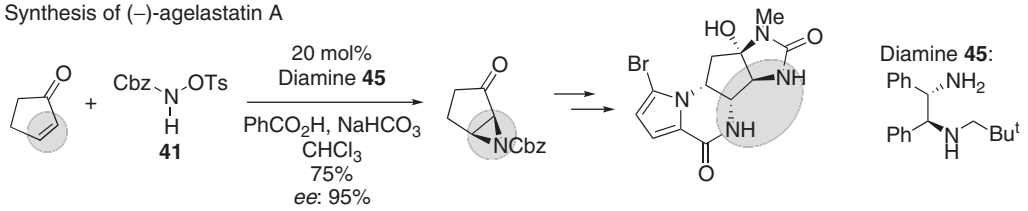
R^1	R^2	X	Yield (%)	*dr*	*ee* (%)
H	Me	Cbz	65	15:1	95
H	Pr^n	Cbz	72	15:1	97
H	CO_2Et	Cbz	57	5:1	91
H	Ph	Cbz	52	19:1	99
H	3-Pyr	Cbz	64	15:1	95
Bn	H	Cbz	88	–	94
n-C_5H_{11}	H	Cbz	64	–	95
Et	Pr^n	Ts	61	8:1	99
Me	Et	Ts	84	>25:1	99
Me	Ph	Ts	78	>25:1	98

Scheme 16



(41)

The application of organocatalytic aziridination of α,β-unsaturated carbonyl compounds to another asymmetric synthesis of (–)-agelastatin A[175] illustrates that these methods are complementary to those involving metal-catalyzed nitrene transfer. The diamine-catalyzed aziridination of cyclopentenone with **41** affords an optically pure aziridine (**Scheme 17**). Transformation of the latter leads to the construction of the B- and D-rings of the target product according to a strategy different from the one used in the synthesis through intramolecular aziridination of sulfamates (see **Scheme 8**).



Scheme 17

7.19.3 Alkene Oxyamination

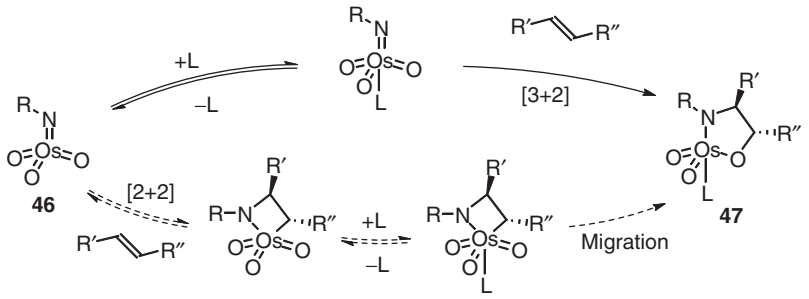
7.19.3.1 Introduction

The interest of the synthetic organic community for the 1,2-amino alcohol moiety results from the occurrence of this motif, as well as its derivatives, in a vast range of natural products, pharmaceutical agents, and ligands. Therefore, a number of methods have been designed for the direct oxyamination or aminohydroxylation of alkenes over the past 20 years.[176] This chapter is aimed at focusing only on the one-step procedures, therefore, sequential modifications of functional groups that are beyond the scope of this review will not be considered (*see* Chapter 7.16).

7.19.3.2 Sharpless Aminohydroxylation

7.19.3.2.1 Intermolecular reaction

The osmium(VIII)-based extension of the previously developed Sharpless dihydroxylation is one of the most powerful methods for the aminohydroxylation of alkenes.[177–180] The reaction involves an imidotrioxoosmium(VIII) species **46**, which adds in a *syn*-stereospecific manner to an alkene to generate the corresponding azaglycolate osmate(VI) ester **47** (Scheme 18). Two mechanistic pathways have long been proposed to explain the formation of this intermediate and to try to justify the chemio-, regio- and stereoselectivities observed in this reaction. A recent computational investigation of the mechanism tends to rule out the [2 + 2] cycloaddition of the imidotrioxoosmium(VIII) species **46** with the alkene and gives support to the [3 + 2] cycloaddition pathway.[181]

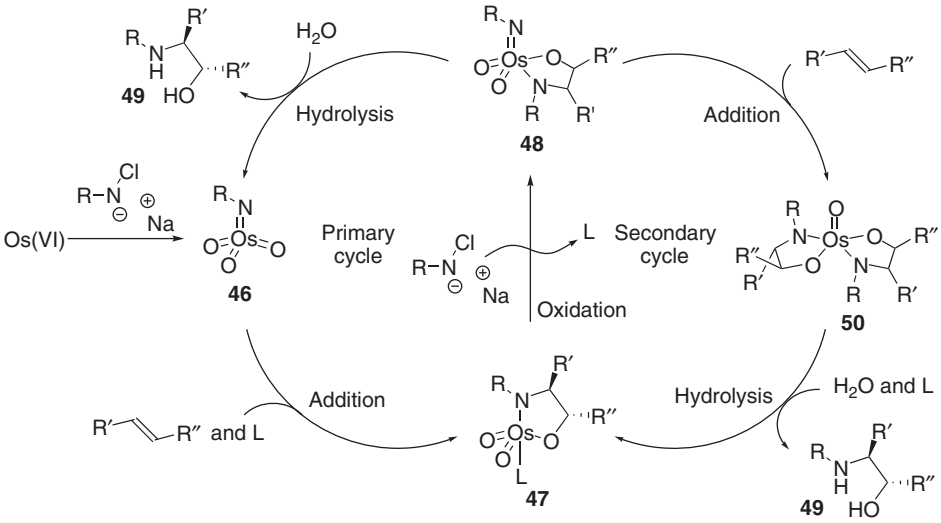


Scheme 18

In the earlier examples, the reaction was stoichiometric in osmium, but the process has been made catalytic by reoxidizing the osmium with a nitrogen oxidant.[182] The generally accepted mechanism involves two nested catalytic cycles to account for the experimental observations (see equation 46). The first catalytic cycle requires the initial formation of **46** through the oxidative addition of a nitrene equivalent to a catalytic osmium(VI) source, generally $K_2OsO_2(OH)_4$ (Scheme 19). Subsequent addition of a ligand and cycloaddition with an alkene generates the azaglycolate osmate(VI) ester **47**. At this stage, reoxidation of the osmium center with another nitrogen oxidant and liberation of the ligand furnishes the cornerstone intermediate **48** of the two competitive cycles. The latter can either be hydrolyzed to liberate the aminohydroxylated product **49** and regenerate **46** or undergo another cycloaddition with the alkene to initiate the competitive secondary cycle. Hydrolysis of the newly formed bis(azaglycolate)osmium(VI) species **50** and addition of a ligand finally liberate the product **49** as well as the intermediate **47**.

The early observation of the reaction rate acceleration in the presence of tertiary amine ligands like quinuclidine led to the evaluation of the effect of pseudoenantiomeric *Cinchona* alkaloid-derived ligands developed for the parent asymmetric dihydroxylation, on the aminohydroxylation. The 1,4-bis(9-*O*-dihydroquininyl)-phthalazine ($(DHQ)_2PHAL$) and the 1,4-bis(9-*O*-dihydroquinidinyl)-phthalazine ($(DHQD)_2PHAL$) have been the first two catalysts to give high enantioselectivities (Figure 3). The catalytic asymmetric aminohydroxylation was first reported with the oxidation of methyl cinnamate in an acetonitrile–water mixture.[183] In the presence of 4 mol% of $K_2OsO_2(OH)_4$, 5 mol% of ligand and 3 equivalents of chloramine-T, which acts as the nitrogen source and the oxidant, both enantiomers **51** and *ent*-**51** of the *N*-protected Taxol side chain are prepared in good yields and enantiomeric excesses (Scheme 20).

The aqueous mixed solvent promotes the hydrolysis of the intermediate **48**. The presence of the *Cinchona* alkaloids avoids the isolation of the diol by-product otherwise formed with similar reacting systems and improves the regioselectivity. The latter reaches a ratio of >5:1 in favor of the benzylic amine, whereas the original ligand-free version of the reaction, requiring silver nitrate, delivers racemic **51** only in a 2:1 ratio.[182] Importantly, the regioselectivity was found to depend on either the substrate, catalyst, solvent, or nitrogen source. Chloramine-T was initially used as the nitrogen oxidant because of its commercial availability and low cost. However, other chloramines are compatible, such as the easily prepared chloramine-M. This reagent tends to give better results in catalytic aminohydroxylation due to the decreased size of the sulfur substituent (equation 42).[184]



Scheme 19

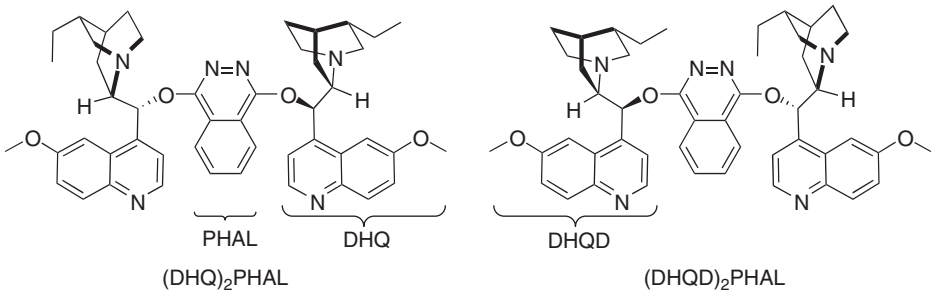
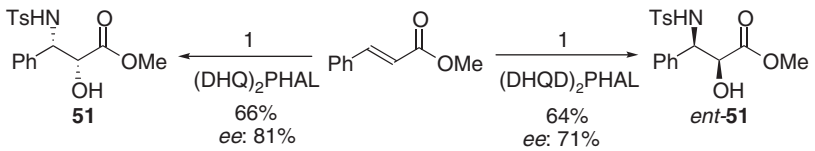
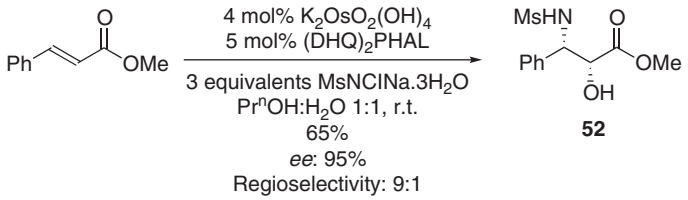


Figure 3 Chiral ligands for the catalytic asymmetric aminohydroxylation.



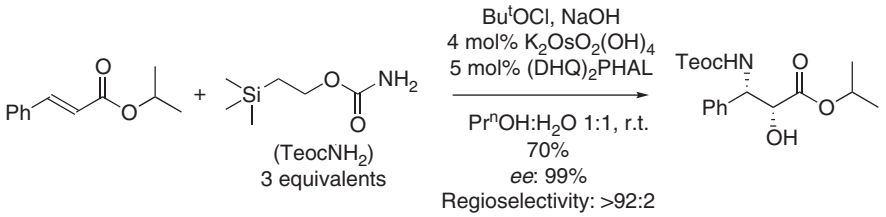
1. $K_2OsO_2(OH)_4$ (4 mol%), Ligand (5 mol%), TsNClNa·$3H_2O$ (3 equivalents), CH_3CN:H_2O 1:1, r.t.

Scheme 20

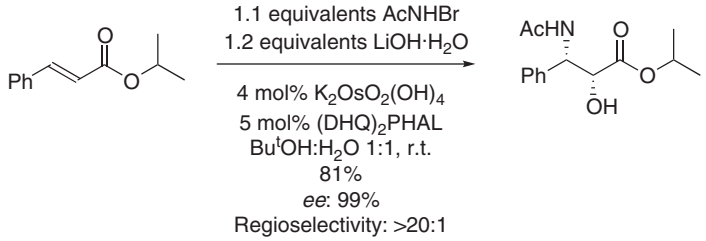


(42)

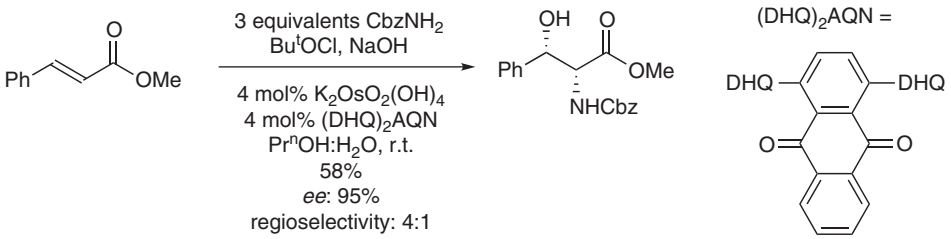
The formation of *N*-sulfonyl-1,2-amino alcohols raises the issue of the subsequent isolation of the free derivatives (see Scheme 5). In order to circumvent this problem, carbamate and amide derivatives have been designed and found suitable for the asymmetric aminohydroxylation. Chloramines can be generated from carbamates either *in situ* with *tert*-BuOCl and NaOH (equation 43)[185] or before the aminohydroxylation reaction. In the case of amides, the bromo–lithio analogues are generally used due to their lower propensity to undergo Hofmann rearrangement (equation 44).[186] Although catalytic asymmetric aminohydroxylation of cinnamate generally affords the β-amino-α-hydroxy product in the presence of $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$, replacing the phthalazine moiety with an anthraquinone (AQN) results in a reversal of the regioselectivity (equation 45).[187]



(43)

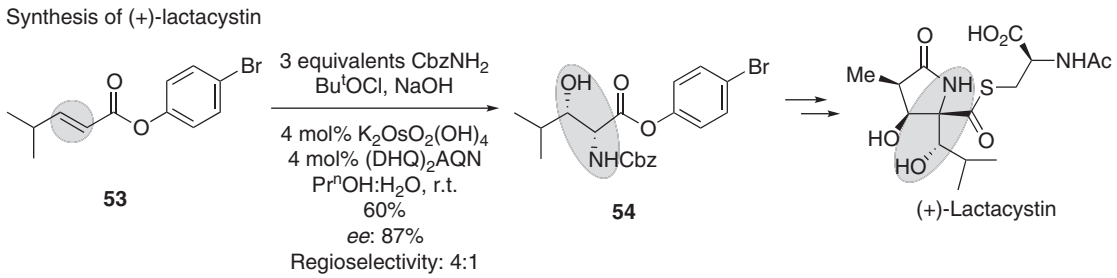


(44)



(45)

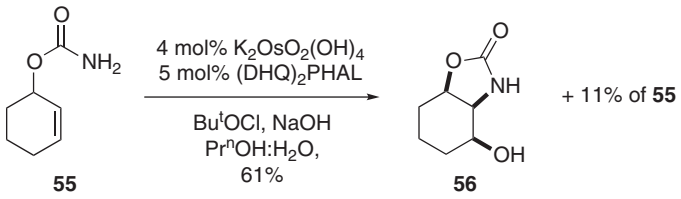
It has been found that aryl cinnamates still provide the *β*-amino-*α*-hydroxy derivatives as the major product in the presence of $(DHQ)_2AQN$.[188] It was hypothesized that the aromatic moiety of the cinnamyl derivative may interact with the AQN part of the ligand, thereby controlling the sense of the addition. Based on this hypothesis, aryl esters have been tested to reverse the regioselectivity. The *α*-amino-*β*-hydroxy product **54** is thus obtained in an optimal manner from the *p*-bromophenyl ester **53**. This strategy has been applied to the total synthesis of the (+)-lactacystin (**Scheme 21**).[189]



Scheme 21

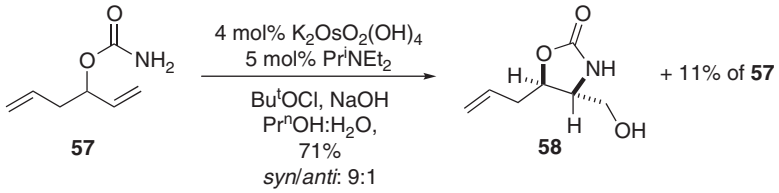
7.19.3.2.2 Tethered reaction

One of the issues of the Sharpless aminohydroxylation is the often poor and difficult to bias regioselectivity of the reaction. In response to this selectivity problem, Donohoe has elegantly proposed to completely control the regioselectivity by tethering the nitrogen atom to an allylic alcohol via a primary carbamate.[190] Rate acceleration is observed for the aminohydroxylation reaction in the presence of Hünig's base or Sharpless's catalyst, though the latter does not induce any enantioselectivity. This has led to the conclusion that the second catalytic cycle is here operative due to the favorable intramolecular [3 + 2] cycloaddition with the alkene in an intermediate of type **48**. When subjected to the optimized reaction conditions, **55** is converted to **56** in 61% yield with a complete regio- and diastereocontrol. However, 11% of unreacted starting material is recovered, and more complex mixtures of products are obtained when *tert*-BuOCl and NaOH are added in excess to reach completion (equation 46).



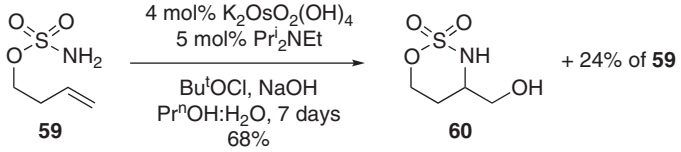
(46)

The reaction from the allylic/homoallylic substrate **57** demonstrates the higher tendency to form a five-membered ring over a six-membered ring.[191] The hydroxyoxazolidinone **58** is isolated in 71% yield with a 9:1 *syn*:*anti* ratio (equation 47).



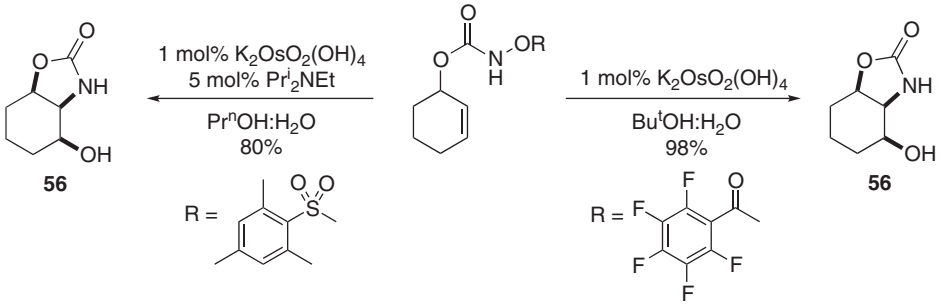
(47)

Inspired by previous results on catalytic C–H amination showing that carbamates lead to five-membered rings, whereas sulfamates afford 6-membered rings,[26] the tethered aminohydroxylation (TA) has been investigated with sulfamates and sulfonamides.[192] Under the same conditions, the tethered aminohydroxylation of **59** gives the expected oxathiazinane **60** but the reaction does not go to completion even after 7 days of stirring (equation 48). *iso*-Pr_2NEt is the optimum ligand while no asymmetric induction is observed with *Cinchona* alkaloid ligands. The scope of the sulfamate version appears to be highly substrate dependent and limited to monosubstituted alkenes.



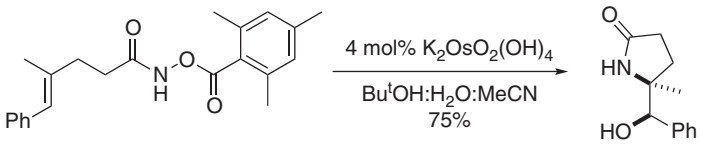
(48)

A new type of nitrogen reoxidant to replace the chloramine system has been developed to solve the issue of completion and develop the intramolecular aminohydroxylation of homoallylic derivatives. *N*-sulfonyloxy carbamates, previously described as nitrene precursors in rhodium-catalyzed C–H amination and aziridination,[120] have proved to be efficient nitrogen reoxidants for the catalytic-tethered aminohydroxylation, with *N*-mesitylsulfonyloxy carbamate giving the best results.[193] Under these conditions, product **56** is obtained with an improved 80% yield in the presence of 1 mol% of the osmium catalyst (**Scheme 22**). Analogous *N*-pentafluorobenzoyloxy carbamates have since been described as more general and reliable reagents delivering, for example, **56** in a nearly quantitative yield.[194]



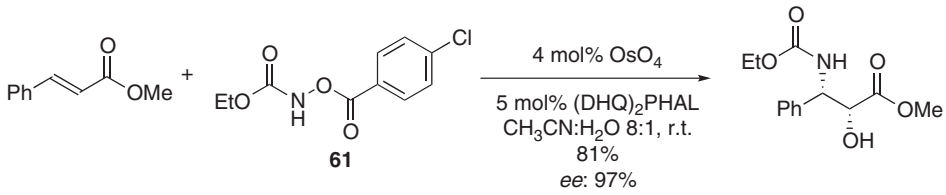
Scheme 22

Use of these neutral, hydroxylamine derivative-based procedures allows performing the tethered aminohydroxylation with amides.[195] The *N*-pentafluorobenzoyloxy leaving group, however, raises the issue of Hofmann rearrangement. It was thus successfully replaced by the *N*-trimethylbenzoyloxy moiety that affords the expected *N*,*O*-products from mono-, di-, tri-, or tetrasubstituted alkenes (equation 49).



(49)

It should be noted that intermolecular aminohydroxylation has benefitted from the development of the tethered reaction with the hydroxylamine derivatives. Use of ethyl *N*-(4-chlorobenzoyloxy)carbamate **61** as the oxidant nitrogen source leads to efficient base-free Sharpless catalytic asymmetric aminohydroxylation (equation 50).[196] In this procedure, the unusual replacement of $K_2OsO_2(OH)_4$ by OsO_4 results in moderate yields when the Boc analogue of **61** is introduced, due to competitive diol formation that is avoided by slight modification of the conditions.[197]



(50)

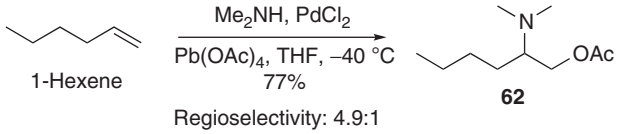
7.19.3.3 Alkene Nucleometallation with Carbophilic Metal Salts

The π-acidity of different transition metal salts has been utilized to activate carbon–carbon double bonds toward nucleophilic attack with heteroatom nucleophiles, particularly nitrogen reagents. The organometallic intermediates generated can undergo different reaction types to afford 1,2-difunctionalized products (see Sections 7.19.4.2 and 7.19.6.1).

7.19.3.3.1 High-valent transition metals

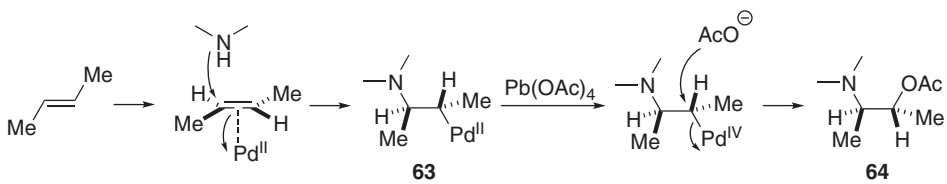
7.19.3.3.1.1 Palladium(II)/palladium(IV)

Most of the high-valent transition metal-catalyzed alkene oxyaminations are reported with palladium.[198] The intermolecular reaction, promoted by palladium(II) salts, was first described by Bäckvall in 1975.[199] The addition of dimethylamine to an alkene activated by stoichiometric $PdCl_2$ affords the vicinal aminoacetate product after oxidation with lead tetraacetate (equation 51).



(51)

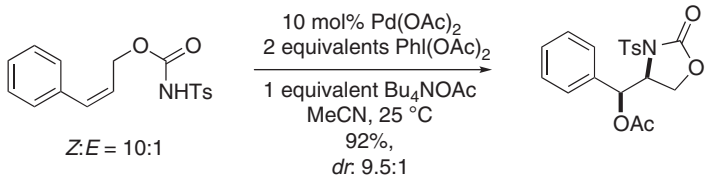
When 1-hexene is subjected to the reaction conditions, the internal aminated regioisomer **62** is obtained as the major product. However, various levels of regioselectivity are observed with other substrates. Subsequent studies have shown that bromine agents can be used as the oxidant NBS, giving the best yields in the presence of diethylamine.[200] Although primary amines lead to aziridines under normal conditions, addition of AgOAc allows the formation of the amino acetate, presumably by preventing the formation of transient haloaminated products.[201] Investigations carried out on (*E*)- and (*Z*)-2-butene have given some insights into the mechanistic pathway. Both alkenes afford the formal product of *cis*-aminoacetoxylation. The aminopalladation step occurs in a *trans* manner with this reacting system, forming **63** from (*E*)-2-butene.[202] Subsequent oxidation of the palladium(II) to palladium(IV) by $Pb(OAc)_4$ has been considered as a potential mechanism, which is consistent with more recent studies (see **Scheme 25**). Formation of the *cis* oxyamination product **64** requires that the reductive elimination step proceeds via the inversion of the stereochemistry at the carbon center, through an S_N2-type mechanism (**Scheme 23**).



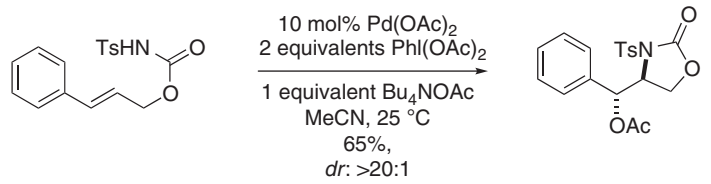
Scheme 23

The emergence of hypervalent iodine reagents, particularly their ability to oxidize smoothly palladium(II) intermediates, has led to the discovery of the first palladium-catalyzed intramolecular aminoacetoxylation of alkenes, more than 20 years after

Bäckvall's seminal studies. The reaction relies on the combination of sulfonamides with $PhI(OAc)_2$ and is tolerant to moisture and air.[203] Interestingly, the products of *trans*-aminohydroxylation are obtained from either (*Z*)- or (*E*)-olefins (equations 52 and 53), an observation that stands in contrast to those previously made by Bäckvall.

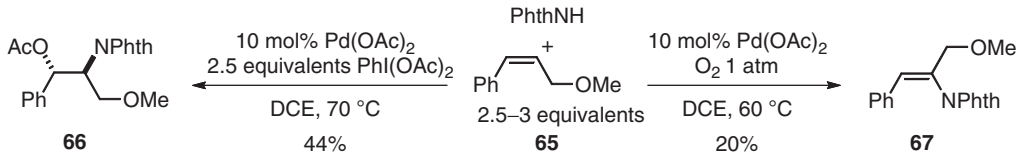


(52)



(53)

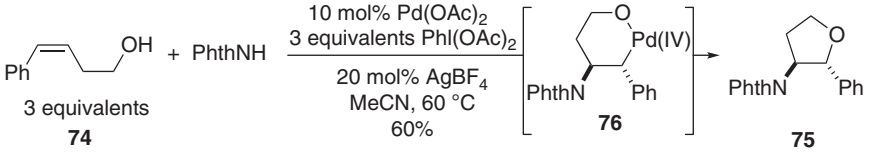
These results have been rationalized by a *trans*-aminopalladation of the alkene followed by the oxidation of palladium(IV) in palladium(IV), and, a final step of reductive elimination with retention of configuration. A *cis*-aminopalladation, however, cannot be ruled out, which means that the reductive elimination should take place with inversion of configuration in this case. Following this report, palladium(II) acetate and $PhI(OAc)_2$ have been found to mediate the intermolecular addition of phthalamide and acetate to alkenes, allylic ethers proving to be particularly good substrates due to the chelation with the metal (**Scheme 24**).[204] The high chemoselectivity for terminal alkenes and the complete regioselectivity, favoring the formation of primary acetates when terminal olefins are used, are however counterbalanced by the excess of alkene required in this procedure.



Scheme 24

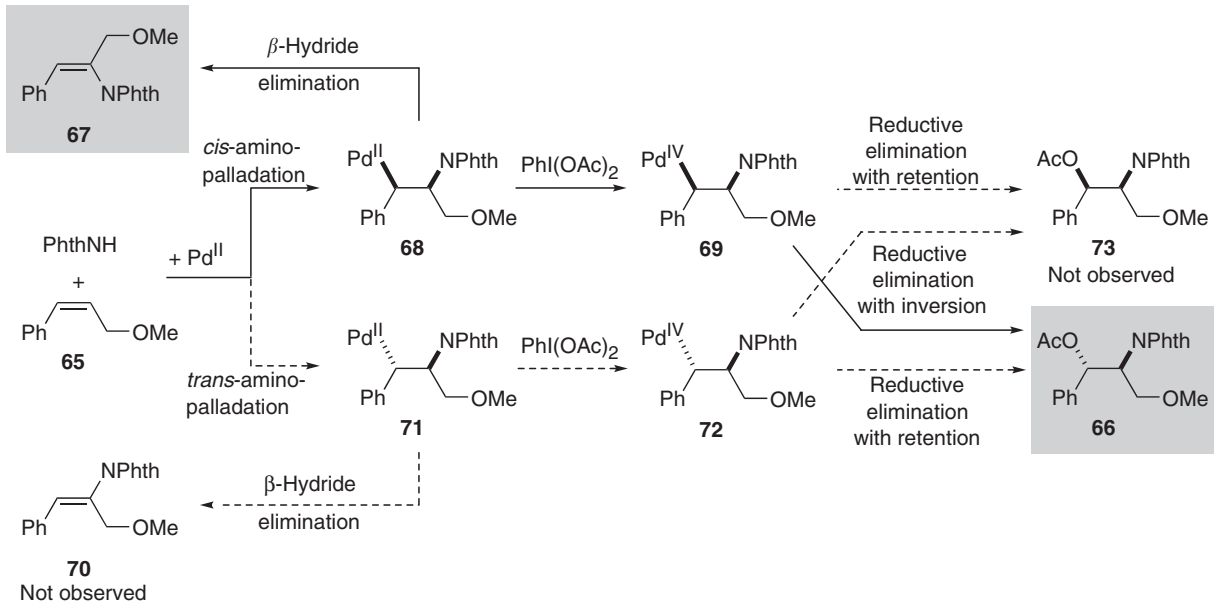
Mechanistic studies have been performed on **65** to understand the course of the reaction. When normal reaction conditions are applied, the *trans*-product **66** is obtained. Under conditions favoring the *β*-hydride elimination from the organopalladium intermediate, the alkene **67** is isolated, though in low yield. From these results, a mechanistic pathway has been designed. The formation of the *β*-hydride elimination product **67** instead of its regioisomer **70**, accounts for the intermediacy of a *cis*-aminopalladation compound **68**. Oxidation of the latter with the $PhI(OAc)_2$ leads to **69**. The exclusive formation of the *trans*-oxyamination product **66** requires that the final reductive elimination occurs with inversion of configuration. It should be mentioned that the (*E*)-isomer of **65** affords only traces of the corresponding oxyaminated product (**Scheme 25**).

Similar reaction conditions with phthalamide as the nitrogen source have been applied to homoallylic alcohols.[205] Compound **74** affords the *trans*-tetrahydrofuran (THF) product **75**, as a result of an overall *cis*-oxyamination process (equation 54). Careful analysis of the products obtained, when *β*-hydride elimination-inducing conditions are applied to **74**, demonstrates that the initial aminopalladation step proceeds in a *cis* manner leading to the intermediate **76**. The C–O bond-forming step, therefore, involves a reductive elimination with retention. The higher nucleophilicity of the alkoxide and/or the 'intramolecularity' of the last step would account for this scenario, which is different from the one depicted in **Scheme 25**.



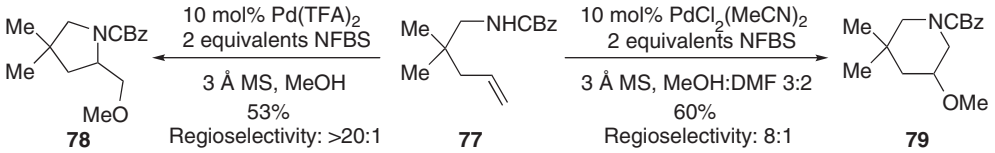
(54)

N-Fluorobenzenesulfonimide (NFBS, see equation 92) can promote the palladium(II)/palladium(IV) oxidation in the catalytic oxyamination of alkenes.[206] Carbamates add intramolecularly to alkenes activated by a Pd(II) source to give, in the presence of NFBS and an alcohol, either five- or six-membered rings, depending on the conditions. For example, **77** affords **78** in methanol in the presence of $Pd(TFA)_2$, whereas **79** is obtained with $PdCl_2(MeCN)_2$ in a 3:2 mixture of MeOH:*N*,*N*-dimethylformamide (DMF)



Scheme 25

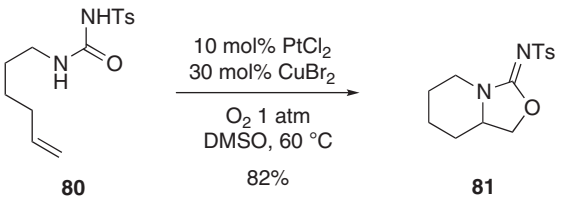
(Scheme 26). Both products are assumed to result from an initial nucleophilic addition of the carbamate to the alkene and oxidation of the resulting palladium(II) intermediate. Direct reductive elimination by displacement of the palladium(IV) by methanol affords **78**. However, modification of the catalyst and use of a highly polar solvent additive may induce the participation of the neighboring nitrogen to generate an aziridinium, subsequently opened to deliver **79**.



Scheme 26

7.19.3.3.1.2 Platinum(II)/(IV) and gold(I)/(III)

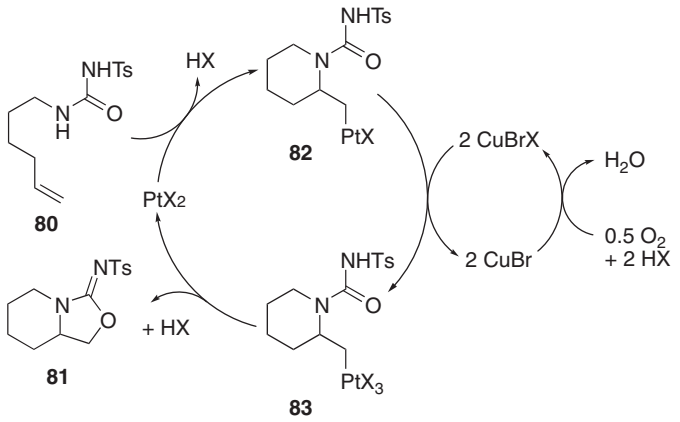
The use of platinum has allowed developing an appealing aerobic procedure for the catalytic intramolecular oxyamination of alkenes.[207] As a representative example, **80** affords **81** in 82% yield, in the presence of catalytic $PtCl_2$ and $CuBr_2$, and oxygen as the terminal oxidant (equation 55). Dimethylsulfoxide (DMSO) is unambiguously the best solvent for this reaction, whereas $CuBr_2$ is superior to its chloride and acetate analogues. However, the transformation is limited to terminal alkenes and the formation of [4.3.0] motifs.



(55)

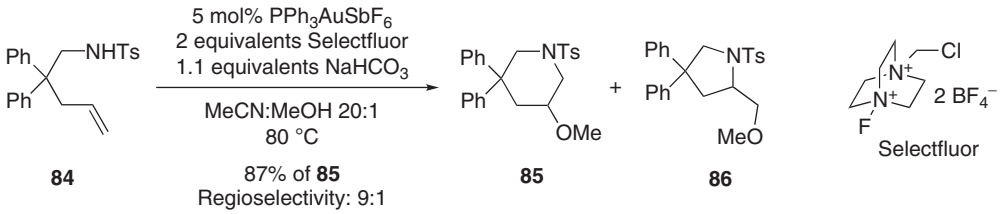
The results have been rationalized by a mechanism involving the transient formation of a π-alkene complex between the Pt(II) salt and **80**, which would be attacked intramolecularly by the urea nitrogen to lead to **82**. The rather low oxidation potential for platinum(II) salts then allows their oxidation by CuBrX to generate the platinum(IV) intermediate **83**. Reductive elimination through intramolecular C–O bond formation would deliver the product and regenerate the platinum(II) salts (Scheme 27). This result contrasts with urea diamination products obtained with other transition metals (see Section 7.19.4.2).

The cationic gold(I) catalyst ($(PPh_3)AuSbF_6$) promotes the intramolecular oxyamination, yielding mainly 3-oxygenated piperidine products, often accompanied by variable amounts of pyrrolidine analogues.[208] Selectfluor is used as the oxidant in alcoholic or aqueous acetonitrile, however, $PhI(OAc)_2$ can be utilized in 1,2-dichloroethane, which leads to the aminoacetoxylation products. When substrate **84** is subjected to a set of optimized conditions, products **85** and **86** are obtained in a 9:1 ratio



Scheme 27

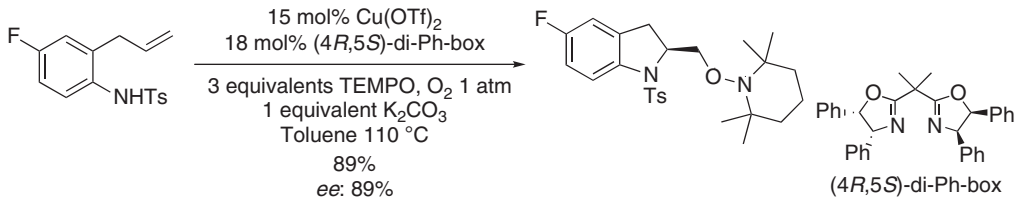
(equation 56). Slightly modifying the reaction conditions then leads to diamination products (see Section 7.19.4.2.2.3). Deuterium isotopic labeling of the alkene has allowed a mechanistic pathway for the formation of **85** that involves a 6-*endo*-cyclization via a *trans*-aminoauration to be drawn. Subsequent oxidation of the gold(I) intermediate to gold(III) by selectfluor and *cis*-reductive elimination concludes the catalytic cycle. Product **86** would arise from the analogous 5-*exo* cyclization.



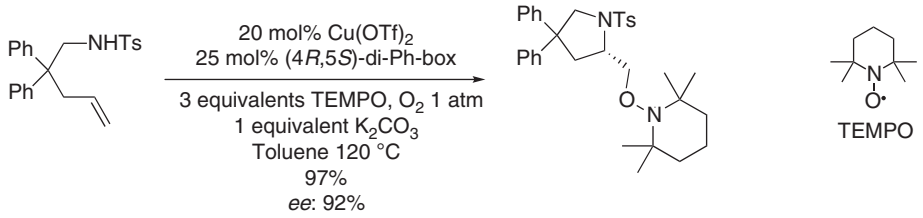
(56)

7.19.3.3.2 Nucleocupration

The π-acidity of relatively inexpensive copper(II) salts has been reported to induce oxyamination reactions through nucleocupration. Various substituted 2-allyl anilines and 4-pentenylamines, bearing an *N*-sulfonyl group (mostly Tosyl or Nosyl), can cyclize in the presence of copper(II) salts and (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) to afford indolines and pyrrolidines, respectively. A procedure involving 1.5 equivalents of the commercially available copper(II) 2-ethylhexanoate ($Cu(eh)_2$) in the presence of 3 equivalents of TEMPO and stoichiometric Cs_2CO_3 in xylenes at 130 °C allows the efficient preparation of 2,3-*trans*- and 2,5-*cis*-pyrrolidine in moderate-to-high diastereoselectivities, respectively.[209] The reaction has been made catalytic in copper by regeneration of the copper(II) via aerobic oxidation. Introduction of a chiral bisoxazoline ligand further improves the transformation that occurs on a multigram scale (equations 57 and 58).[210,211]



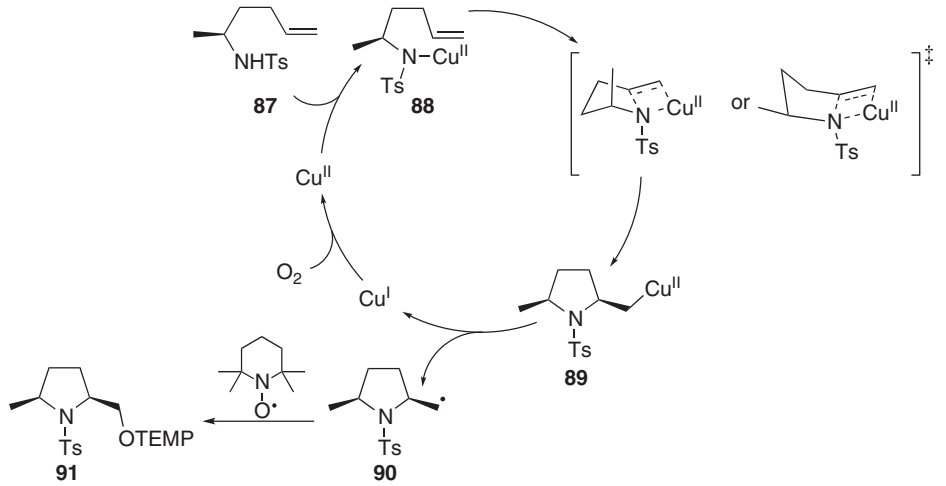
(57)



(58)

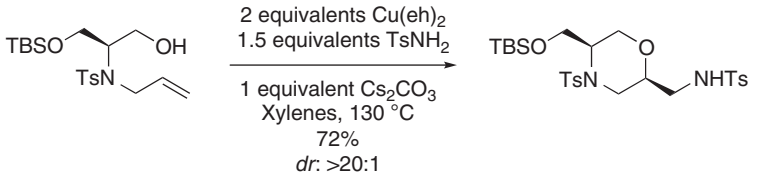
The mechanism of the reaction has been determined through kinetic experiments, ultraviolet-visible spectroscopy and electron paramagnetic resonance spectroscopy, and DFT calculations.[212] Initial complexation of the nitrogen in **87** to the copper(II) salt

leads to the formation of **88**. The addition of the N–Cu bond across the olefin is the rate-limiting step and occurs via two possible seven-membered transition states (chairlike or boatlike) separated by only 0.2 kcal mol^{-1} and both affording the *cis*-organocopper(II) intermediate **89**. A primary carbon radical **90** is then formed by the homolysis of the C–Cu(II) bond and a rapid recombination with the efficient radical trapping agent TEMPO finally affords the product **91**. Performing the reaction under an oxygen atmosphere allows regenerating the copper(II) catalyst from a copper(I) species (**Scheme 28**). This method can be applied to the preparation of 4,5-disubstituted cyclic ureas,[213] as well as to disubstituted isoxazolidines.[214]



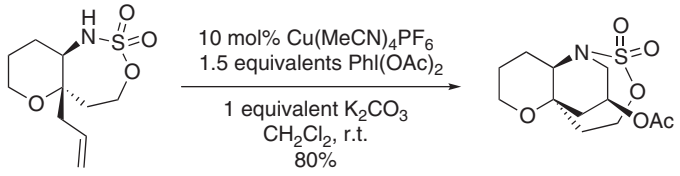
Scheme 28

Morpholines are accessible through the copper(II)-promoted oxyamination of alkenes albeit via a different mechanistic pathway (equation 59).[215] Although the previous examples involve an initial aminocupration, the copper(II)-mediated activation here induces a *cis*-oxycupration step. The organocopper thus generated would be converted to a primary carbon radical that recombines with a nitrogen-complexed copper(II) species to form a copper(III) intermediate. The latter undergoes reductive elimination to afford the product and release a copper(I) species.



(59)

The synthesis of piperidines and pyrrolidines via intramolecular alkene oxyamination is mediated by a copper(III)–nitrogen species generated from a copper(I) salt in the presence of an iodine(III) oxidant.[216] In the optimized procedure, $Cu(MeCN)_4PF_6$ catalyzes the formation of piperidines from γ-amino terminal olefins, in the presence of $PhI(OAc)_2$ (equation 60). Nosyl-protected nitrogen functional groups as well as sulfamates can be used. Although terminal olefins yield 6-*endo* products, 1,2-disubstituted alkenes afford pyrrolidines resulting from a 5-*exo* cyclization, with the nitrogen function and the acetate in an *anti*-disposition.



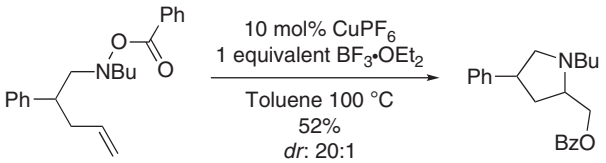
(60)

7.19.3.4 Radical-Mediated Reactions

Although some of the previously described reaction mechanisms involve radicals at some points, oxyamination purely mediated by radicals have also been reported. The frontier between these different pathways may be tenuous, however, this part summarizes procedures involving radicals in their rate-determining step.

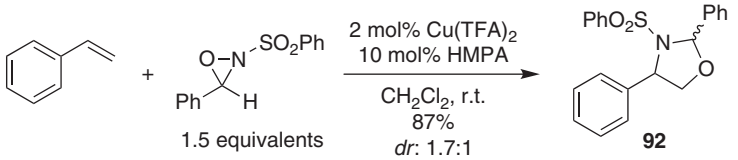
7.19.3.4.1 Copper-catalyzed reactions

Copper is an intriguing metal able to give rise to various classes of reagents with different properties. The copper(I) salt $CuPF_6$, combined with boron trifluoride, catalyzes the intramolecular addition of the N–O bond of *N*-benzoyloxylamine, to alkenes to afford pyrrolidines in moderate-to-good yields (equation 61).[217] Because a radical initiator (azobisisobutyronitrile) is not able to deliver the product in a decent yield, the mechanism is assumed to involve activation of the benzoyl moiety by the Lewis acid copper(I) salt thereby inducing the homolysis of the N–O bond. The aminyl radical generated adds to the alkene to form a primary carbon radical, which recombines with the previously released copper(II) benzoate.



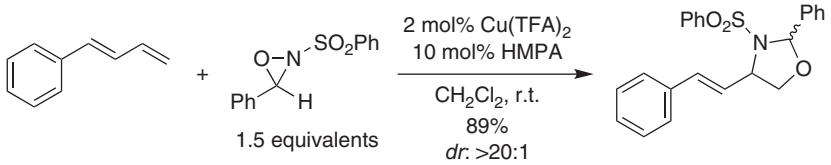
(61)

Intermolecular oxyamination of alkene can be performed efficiently with oxaziridines, allowing the formation of five-membered ring aminals via a highly regioselective process.[218] For example, styrene affords compound **92** in 87% yield as a mixture of *cis* and *trans* products under optimized conditions (equation 62).



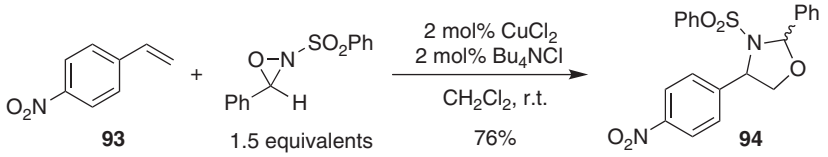
(62)

This reaction tolerates both electron-withdrawing and electron-donating groups located either on the *ortho*-, *meta*-, or *para*-position. Tri- and tetrasubstituted olefins also proved to be efficiently oxyaminated. When *Z*- and *E*-stilbenes are subjected to the reaction conditions, a stereoconvergence is observed in favor of the *trans* product. This oxaziridine-based oxyamination can be extended to dienes with a selectivity for the terminal double bond (equation 63).[219] Allysilanes and enol ethers are also good substrates for this reaction. This procedure offers an attractive alternative to the osmium-catalyzed aminohydroxylation, which often delivers poor regioselectivities with similar styrene and diene derivatives. The intermolecular asymmetric copper-catalyzed alkene oxyamination can be performed in the presence of chiral bis(oxazoline) ligand.[220] Although poor diastereoselectivities are observed, hydrolysis on the two diastereomeric aminals, which bear the same configuration at the benzylic center, affords the same product from the initial mixture.



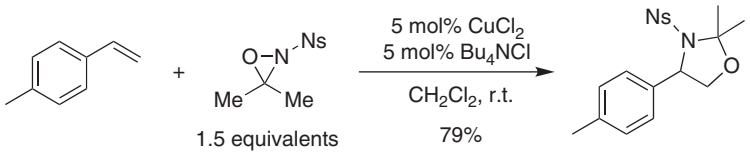
(63)

A halocuprate, formed from $CuCl_2$ and Bu_4NCl, is an even more efficient catalyst for the oxyamination of alkene with oxaziridines.[221] It induces acceleration of the reaction and extension of the scope to alkenes substituted by strong electron-withdrawing groups. Although **93** is converted to **94** with a moderate yield in 24 h using the original conditions, the $CuCl_2$/Bu_4NCl procedure affords **94** in 76% yield in only 4.5 h (equation 64).



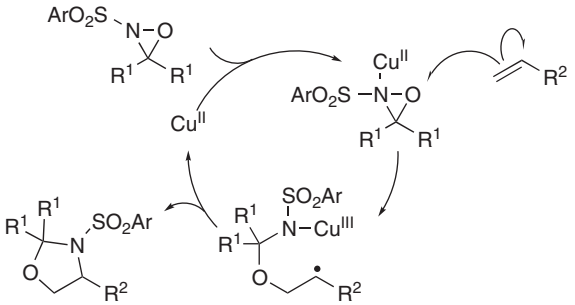
(64)

This electron-rich copper catalyst is able to promote the reaction with much less oxidizing dialkyloxaziridines, which are poorly reactive under the originally developed conditions. Symmetrical reagents, in addition, have the advantage to generate only one product, unlike the monosubstituted 1-aryloxaziridines (equation 65). Use of a nosyl substituent also proves more synthetically useful, the free 1,2-amino alcohols being easily obtained by sequential deprotection under mild conditions. These procedures have been applied to substituted indoles, producing the corresponding 2-oxy-3-aminoindoles in high yields.[222]



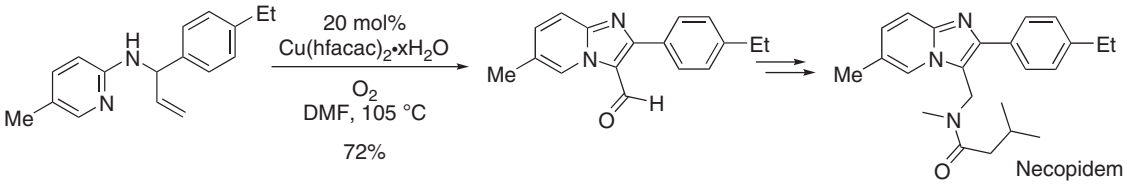
(65)

A mechanism has been drawn following experiments that involve either the radical trap CBr_4 or radical clocks. A body of evidence points to a radical pathway and a copper(II/III) catalytic cycle, a mechanism favored by the electron-rich halocuprate (Scheme 29). Copper(II) activation of the oxaziridine would induce reaction with the alkene by homolysis of the N–O bond, generating the more-stabilized radical and a transient copper(III)–sulfonamide complex. The latter would cyclize to release the cyclic aminal and regenerate the copper(II) catalyst. Worthy of note is that the uncatalyzed analogous reaction is reported to afford the other regioisomer with the oxygen in benzylic position, presumably via a cationic mechanism.[223]



Scheme 29

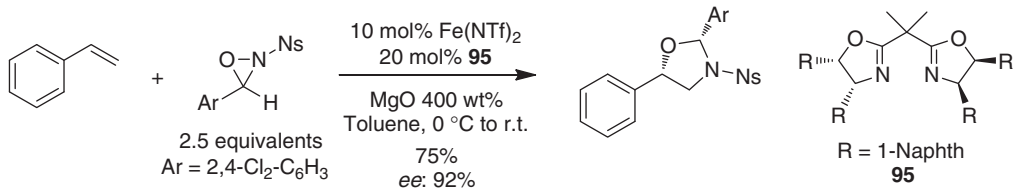
Aromatic heterocycles are accessible by radical-based oxyamination reactions. Copper(II)-catalyzed oxyamination of *N*-allyl-2-aminopyridines yield the corresponding imidazo[1,2-*a*]pyridine-3-carbaldehydes in moderate-to-good yields.[224] Although the scope of the reaction is relatively limited, it allows the rapid construction of structures otherwise more difficult to prepare. The synthetic utility of this reaction has been demonstrated by a synthesis of the anxiolytic drug necopidem (Scheme 30).



Scheme 30

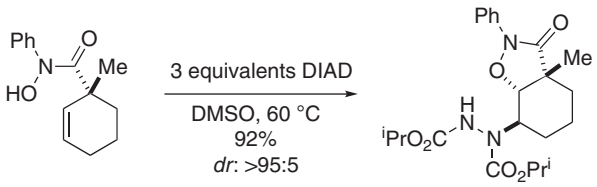
7.19.3.4.2 Other radical-mediated reactions

Iron salts are good substitutes for copper(II) salts in the catalytic alkene oxyamination with oxaziridines. Use of the iron(III) salt $Fe(acac)_3$ allows the formation of the oxyaminated products, principally as the regioisomers of the products obtained with copper(II) catalysts.[225] This unexpected result gives the opportunity to prepare selectively both regioisomers by careful choice of the metal catalyst. In addition, the asymmetric iron(III)-catalyzed reaction takes place efficiently using bis(oxazoline) ligands.[226] The oxyaminated product from styrene, for example, is isolated under the optimized reaction conditions in 75% yield and with an excellent 92% enantiomeric excess (equation 66). The excellent *cis* diastereoselectivity is the consequence of the selective conversion of one enantiomer of the racemic oxaziridine. Although the mechanism is still unclear, it is probable that the reductive N–O bond cleavage would generate a radical.



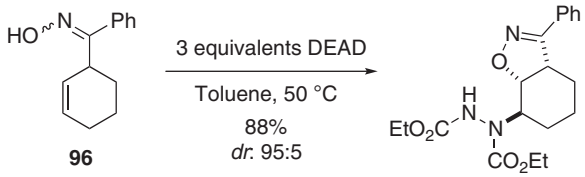
(66)

A metal-free tethered alkene oxyamination has been reported through the gentle heating of a hydroxamic acid in DMSO, in the presence of the radical initiator diisopropyl azodicarboxylate (DIAD).[227] It is assumed that an *O*-centered radical (amidoxyl) adds intramolecularly to the alkene. The newly formed carbon radical is then trapped by the DIAD to deliver the oxyamination product. When applied to linear substrates, the reaction gives the expected products in good yields but poor diastereoselectivities. By contrast, cyclic alkenes afford *trans*-compounds with nearly complete diastereoselectivities (equation 67). Formation of the five-membered ring is favored in the case of the competition with a six-membered ring. The N–O bond, or both N–O and N–N bonds, can be then cleaved selectively in good yields.



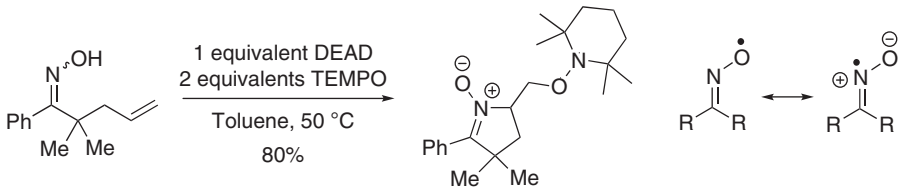
(67)

Heating β,γ-unsaturated ketoximines in the presence of the radical initiator diethyl azodicarboxylate (DEAD) generates an iminoxyl radical, which reacts through a sequence similar to the one suggested for equation 67. The products are obtained in high yields with an excellent *trans* diastereoselectivity starting from the cyclohexene derivative **96** (equation 68).[228]



(68)

When the reaction is applied to γ,δ-unsaturated ketoximines, a 5-*exo*-trig cyclization, instead of the expected 6-*exo*-trig reaction, is observed and leads to cyclic nitrone as a diamination product. The addition of TEMPO as the radical scavenger results in the formation of the oxyamination products (equation 69). The formation of the cyclic nitrone is explained by the resonance structures of the iminoxyl radical, which favors the 5-*exo*-trig cyclization due to a much lower energy of activation.



(69)

An electrochemically induced radical-mediated oxyamination reaction for the formation of *N*-heterocycles, in particular pyrrolidines, has been reported.[229] This procedure leads to *umpolung* bond formation between an anode-oxidized enol ether, enol thioether, or ketene thioacetal and a nitrogen nucleophile. The intermediate carbocation is then trapped by methanol. It was shown that addition of LiOMe was beneficial for the reaction and that a balance between pure methanol or a mixed MeOH/THF solvent has to be found depending on the substrate.

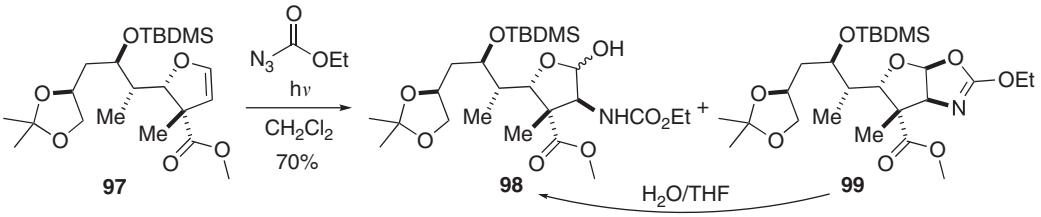
7.19.3.5 Nitrene-Mediated Oxyamination

Addition of nitrenes to alkenes generally affords aziridines that can then be opened by various nucleophiles (see Section 7.19.2). Although the aziridine ring-opening by an oxygen-nucleophile is beyond the scope of this chapter, nitrenes can react with olefins bearing a heteroatom to generate highly reactive transient species responsible for the observed oxyamination reactions (*see* Chapter 7.02).[70]

7.19.3.5.1 Photochemically generated nitrenes

A free nitrene generated by UV-light decomposition of ethyl azidoformate reacts with dihydropyran in the presence of water to afford the 1-hydroxy-2-carbamate derivative in 85% yield through a presumed transient aziridine.[230] This result has been applied to the preparation of aminosugars.[231] However, although the regioselectivity is excellent with the introduction of nitrogen at C2, the products are isolated as mixtures of diastereoisomers, with a preference for the formation of the *trans*-compounds. With the dihydrofuran derivate **97**,[232] the nitrene addition occurs on the less hindered face, but the 1-hydroxy-2-carbamate **98** is accompanied by the moisture-sensitive oxazoline **99**, assumed to derive from an aziridine rearrangement. Compound **99**, however, is easily hydrolyzed thereby allowing **98** to be isolated in 70% overall yield, as an anomeric mixture

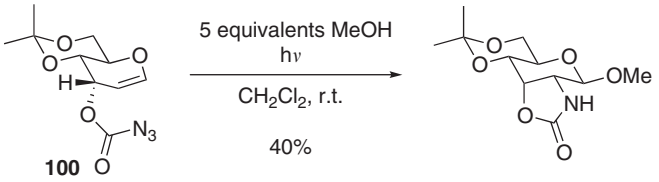
(equation 70). With more simple dihydrofurans, the reaction performed in the presence of water directly affords the amino-hydroxylated product.



(70)

TBDMS, *tert*-butyldimethylsilyloxy

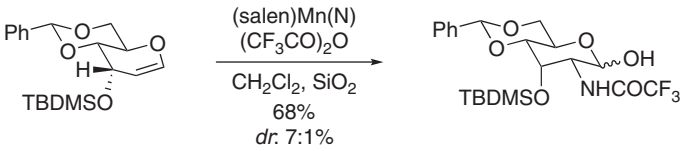
The intramolecular delivery of a tethered acyl nitrene controls the facial delivery of the nitrogen.[233] Photoirradiation of the azidoformate derivative **100** gives the corresponding oxyaminated product in moderate yields with low-molecular weight alcohols (equation 71). Because of the low performance of these transformations related to the high instability of the free nitrene, the oxyamination of electron-rich olefins has been developed through the application of the emerging methods for metal-catalyzed nitrene transfer.



(71)

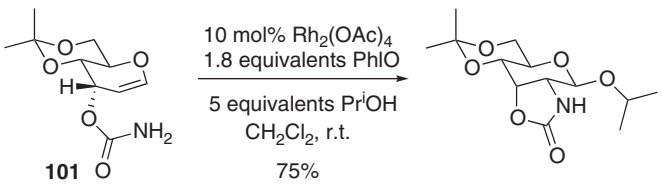
7.19.3.5.2 Oxyamination with metallanitrenes

Initial studies from the group of Carreira have demonstrated the capacity of a manganese nitride complex to react with trifluoroacetic anhydride to generate a nitrogen transfer agent that is able to add to different pyranoid and furanoid glycal derivatives. The resulting transient aziridine, or possibly oxazoline, is subsequently opened in the presence of water or silica to afford the oxyaminated product in good yields (equation 72).[234] As observed for the photochemical reactions, regioselective introduction of the trifluoroacetamide moiety occurs at C2, whereas a complete facial selectivity is obtained with C3-substituted substrates. However, the products are isolated as mixtures of epimers at the anomeric center.

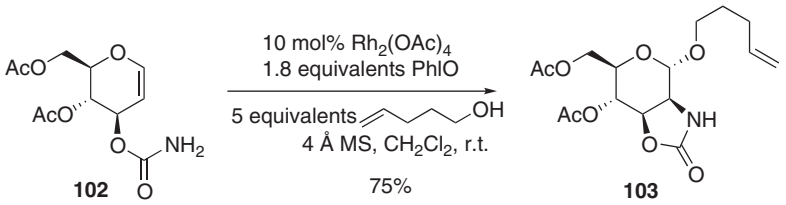


(72)

The oxyamination of glycal **101** can be performed through rhodium- or copper-mediated intramolecular nitrene transfer.[235] In the presence of $PhI(OAc)_2$ as the oxidant and the metal catalyst $Rh_2(OAc)_4$, 1-acetoxy-2-amino derivatives are isolated as mixture of anomers. When a five-fold excess of an alcohol additive and PhI=O instead of $PhI(OAc)_2$ are used, the alkoxy moiety is selectively introduced on the β-face (equation 73). The same reaction conditions applied to the C3 epimer glucal analogue lead to an anomeric mixture with the nitrogen selectively introduced on the β-face.[236] Use of more flexible substrates greatly improves the anomeric selectivity.[237] Thus, by replacing the acetal protection by two acetyl groups, the single α-anomer **103** is isolated from **102** in good yields (equation 74).

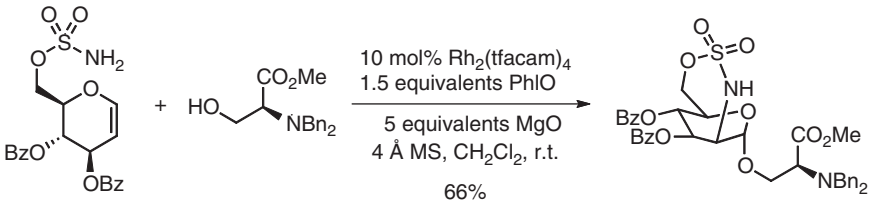


(73)



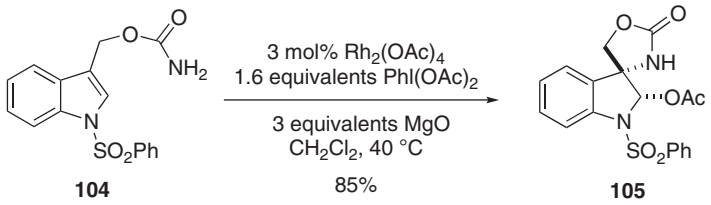
(74)

With the same objective of developing an efficient preparation of 2-aminosugars, tethering a sulfamate ester at different positions of the glycal derivatives allows the selective amination on the α- or β-face.[238–240] In the presence of either the $Rh_2(OAc)_4/PhI(OAc)_2$ or the $Rh_2(tfacam)_4/PhIO$ system, the transiently generated aziridine is opened *in situ* at the anomeric position by simple alcohols as well as amino acid or sugar derivatives. DFT calculations have revealed that the rhodium catalyst remains chelated to the nitrogen, thus activating the aziridine toward opening. This method is more synthetically useful than that involving carbamates because only *trans*-products are obtained in good yields in the presence of complex *O*-nucleophiles (equation 75).



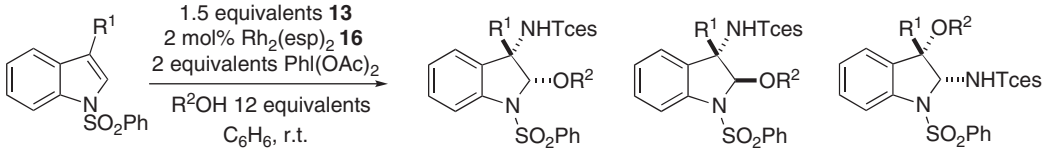
(75)

A metallanitrene, generated by rhodium-mediated decomposition of an iminoiodinanes formed from $PhI(OAc)_2$ and a carbamate tethered to the C3 carbon of an indole, can add intramolecularly to the C2–C3 double bond.[78] The resulting intermediate is then trapped by an acetate ligand released from $PhI(OAc)_2$ to afford **105** with a complete *cis*-selectivity (equation 76). The use of PhIO, instead of $PhI(OAc)_2$, allows introduction of different *O*-nucleophiles, still in a *cis* manner. This unexpected selectivity is explained by an initial nucleophilic addition of indole **104** to the metallanitrene, followed by the *cis*-delivery of the neutral nucleophile to the resulting *N*-sulfonyl iminium that would be directed by the negatively charged carbamate. When the analogous C2 tethered carbamate is subjected to the same conditions, a 5:2 mixture of products is obtained in favor of the *cis* isomer. An asymmetric version of the indole oxyamidation can be performed with a chiral rhodium complex, though with moderate enantioselectivities.[85]



(76)

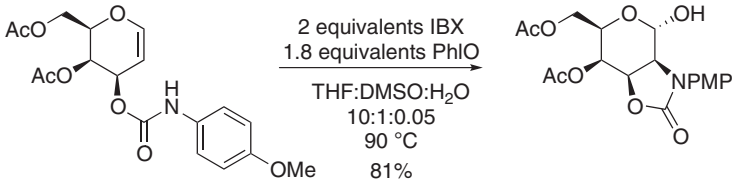
The analogous intermolecular indole oxyamination[241] efficiently takes place following application of the reaction conditions reported for C–H amination, that is, with $TcesNH_2$ **13** and $Rh_2(esp)_2$ **16**.[242] The reaction can be applied with equal success to the functionalization of other heterocycles such as benzoxazines and benzodioxine.[243] However, the course of the transformation depends either on the substitution of the substrate or nature of the nucleophile (equation 77). Although indole leads to the expected *cis*-aminoacetoxylated product, application of the conditions to the 3-ethyl derivative results in a reversal of the regioselectivity, with introduction of the acetate at the C3 position. Introduction of methanol as the nucleophile, in addition, affords the *trans*-product. The nature of the rhodium catalyst also plays a role in the *cis*:*trans* ratio. The transient formation of an aziridine, which would be subsequently opened through a S_N2- or S_N1-type mechanism according to the conditions, would account for these discrepancies.



(77)

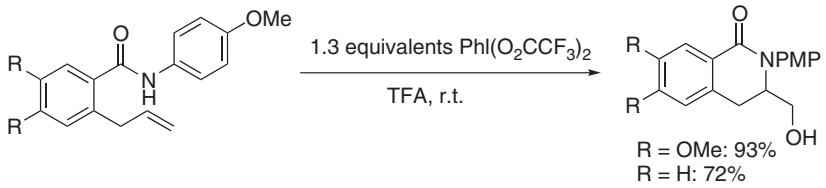
7.19.3.6 Hypervalent Iodine Reagents-Mediated Oxyamination

As previously reported for catalytic alkene aziridination (see Section 7.19.2.2.4), the use of commercially available hypervalent iodine reagents allows performing metal-free oxyamination reactions. A seminal paper describes the capacity of the hypervalent iodine(V) IBX (2-iodoxybenzoic acid) to mediate the oxyamination of glycal derivatives via a SET (single electron transfer) mechanism. The products are obtained in good-to-excellent yields and the removal of the *para*-Methoxyphenyl(PMP) group is possible (equation 78).[244] The reaction involves the formation of an *N*-centered radical that adds intramolecularly to the olefin. The newly created C1 radical is subsequently oxidized to an oxocarbenium ion trapped by water.



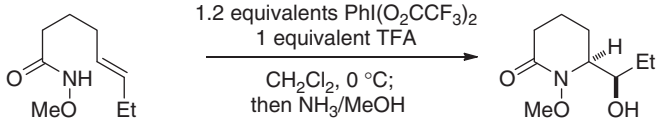
(78)

The intramolecular aminohydroxylation of *N*-(PMP)benzamides substituted in the *ortho* position by a vinyl or an allyl group is promoted by using phenyliodine bis(trifluoroacetate) (PIFA) in trifluoroacetic acid (TFA; equation 79).[245] The intermediacy of an acyl nitrenium species that reacts with the alkene to generate an aziridinium is suggested. The latter would be trapped by a trifluoroacetate in a 5-*exo* or 6-*exo*-trig manner, the hydroxyl group being formed by hydrolysis during the work-up of the reaction.

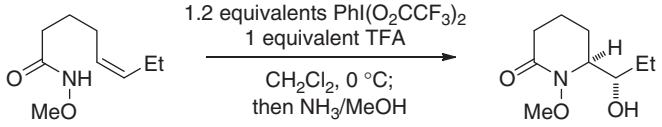


(79)

The formation of an acyl nitrenium intermediate is also described from an *O*-methyl hydroxamate by reaction with PIFA. This induces the production of a transient aziridinium species subsequently attacked by a trifluoroacetate through an S_N2-type mechanism the regioselectivity of which is governed by steric and electronic factors.[246] The addition of TFA to this PIFA-mediated reaction improves the conversion and a work-up with methanol/ammonia allows the removal of the trifluoroacetyl group (equations 80 and 81).



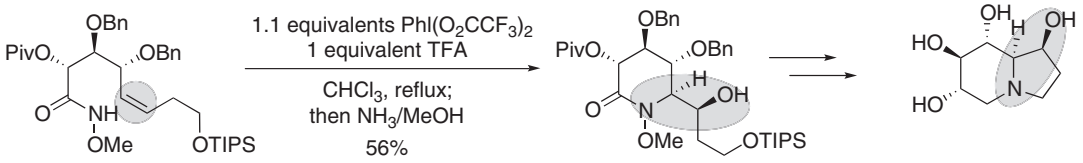
(80)



(81)

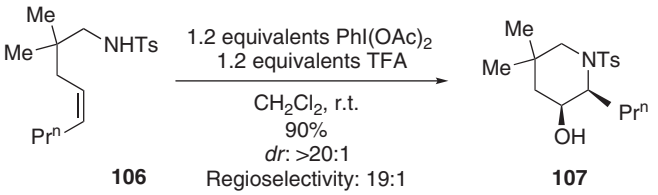
The method has been applied to the total synthesis of the polyhydroxylated natural products (+)-castanospermine[247] (**Scheme 31**) and (–)-swainsonine.[248]

Synthesis of (+)-castanospermine

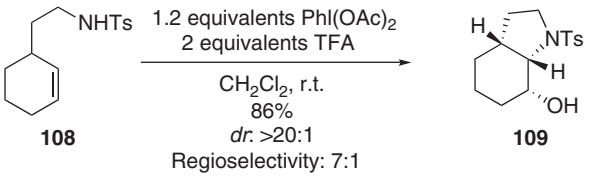


Scheme 31

Urea-tethered alkenes are potent substrates for metal-catalyzed cyclizing oxyamination (see Section 7.19.3.3.1.2) and diamination (see Section 7.19.4.2) reactions. Using strong Brønsted or Lewis acid activation, hypervalent iodine(III) reagents can induce their transformation to cyclic isoureas.[249] The reaction conditions have then been applied to unsaturated sulfonamides (equations 82 and 83).[250]

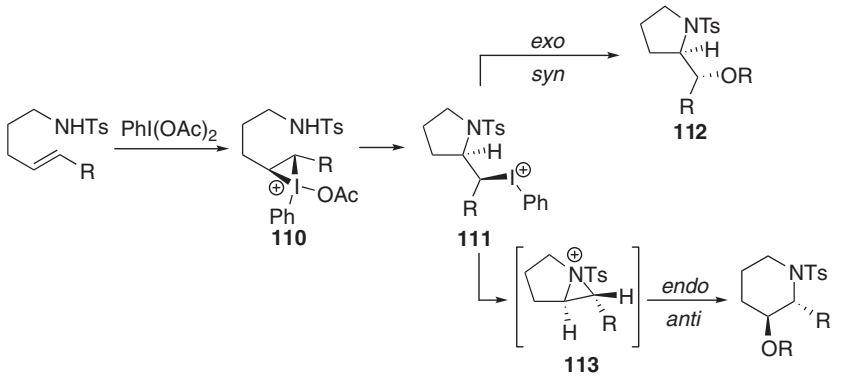


(82)



(83)

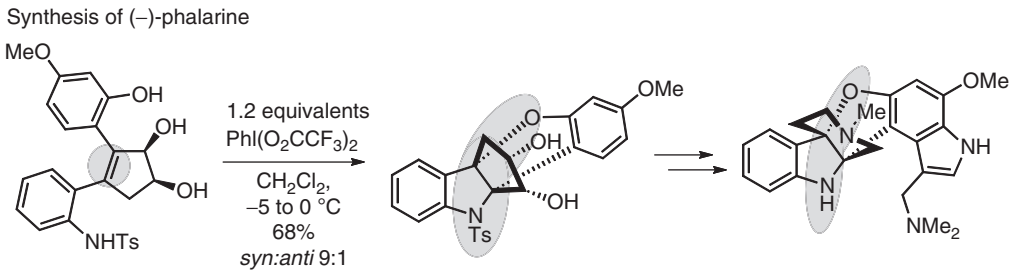
Several mechanisms can account for the *anti*-selectivity in flexible systems like **106** and for the *syn* addition in the more conformationally restricted structure **108**. Activation of the alkene through a halonium intermediate **110** has been proposed. Subsequent nucleophilic attack at the more stabilized position by the sulfonamide leads to **111**, which undergoes direct nucleophilic substitution in the conformationally restricted system to form the *syn* product **112**, or intramolecular nitrogen addition to form an aziridinium species **113** then opened to give a *trans*-product (**Scheme 32**).



Scheme 32

An asymmetric version of this transformation has been reported using chiral hypervalent iodine(III) reagents with the products being obtained in moderate-to-high enantiomeric excesses.[251] This contribution gives support to the previous mechanism pathway where the hypervalent iodine(III) reagent is in close contact with the substrate in the C–N bond-forming step. Should a nitrenium ion be involved, this will not be linked to the chiral iodine species and enantiomeric excesses will remain very low.

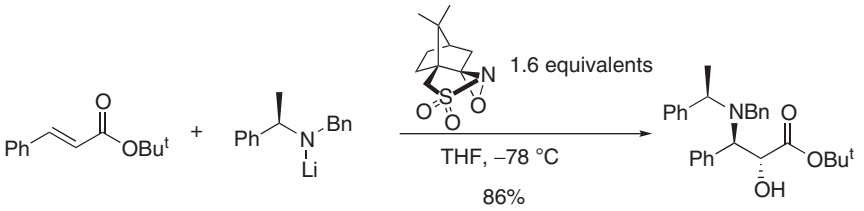
The iodine(III)-mediated alkene oxyamination with sulfonamides has been applied to the formal synthesis of (–)-phalarine (**Scheme 33**).[252]



Scheme 33

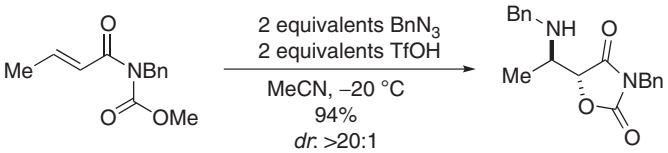
7.19.3.7 Miscellaneous Oxyamination Reactions

This paragraph is aimed at presenting some original isolated procedures for alkene oxyamination that do not belong to any of the previously described methods. An efficient method to access β-amino-α-hydroxy acid derivatives is based on the conjugate addition of a chiral lithium amide and subsequent trapping of the enolate by an electrophilic chiral oxaziridine (equation 84).[253]



(84)

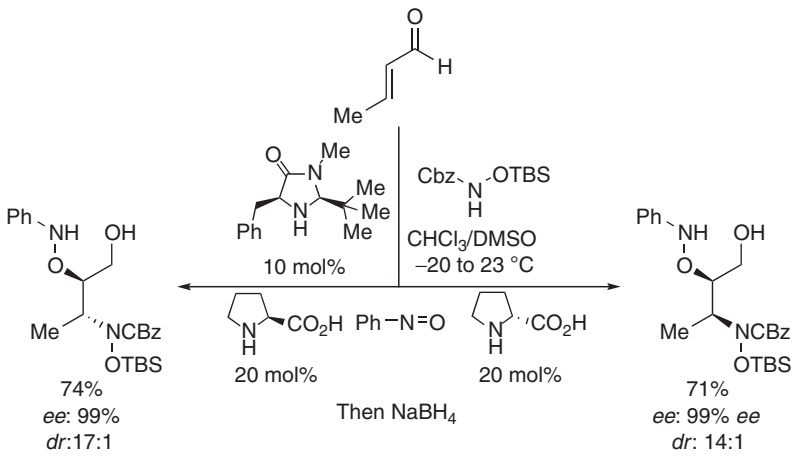
The oxyamination of the acryloyl derivative **114** is mediated by trifluoromethanesulfonic acid in the presence of benzyl azide (equation 85).[254] It is proposed that the amination of the olefin first proceeds to give a transient species subsequently attacked by the oxygen carbamate to afford the *anti*-addition product in moderate-to-excellent yields.



114 **115**

(85)

α,β-Unsaturated aldehydes undergo oxyamination using a dual organocatalytic system.[255] An initial imidazolidinone-mediated iminium catalysis, through LUMO activation, induces the Michael addition of the nitrogen nucleophile CbzNHOTBS. Subsequent addition of proline allows the enamine-mediated addition to the electrophilic oxygen donor PhNO. In the presence of the same imidazolidinone, use of proline enantiomers gives access to the *cis*- or *trans*-oxyaminated products in high yields and excellent enantioselectivities (**Scheme 34**).



Scheme 34

7.19.4 Alkene Diamination

7.19.4.1 Introduction

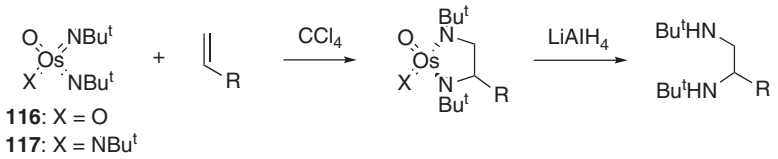
It is well known that diamines can be formed by a variety of two-step processes, that is, aziridination followed by nucleophilic attack, or oxyamination followed by conversion of the oxygen to a nitrogen moiety. However, the direct formation of diamines from C═C bonds is a very desirable goal in synthetic organic chemistry, and this section focuses on the advances made in this area over the past two decades. A number of recent reviews have addressed this domain as significant advances have been made in developing synthetically useful diamination reactions.[256–259] This addition to the literature outlines the advances made first by considering metal-mediated reactions and then those that proceed without the presence of a metal. Diazidination is also briefly covered (*see* Chapter 7.16).

7.19.4.2 Transition Metal-Mediated Diamination

7.19.4.2.1 Stoichiometric reactions

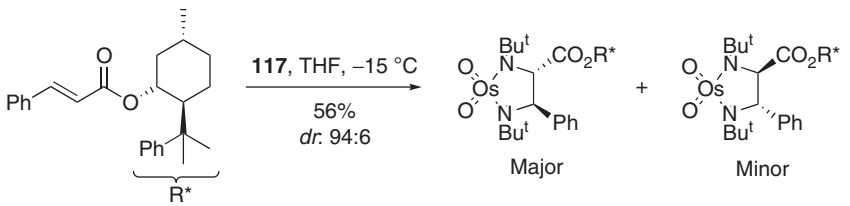
Historically a number of metals have been utilized in diamine synthesis including Os, Hg, Co, Tl, and Pb. Of these, only osmium has been further developed. Although the group of Barluenga did continue its work on the use of Hg,[260] the moderate yields and the toxic nature of mercury have not led to this work being adopted as a method for diamination. The studies describing Co-nitroso compounds as a reagent for the diamination of alkenes have also received little attention from the organic community until a recent article describing a novel ruthenium nitrosyl complex $[RuCl_2(NO)_2(THF)]$.[261] Current investigations are focusing on its use in asymmetric diamination.

Osmium bis- and tri-imido complexes **116** and **117** have been shown to react with alkenes by Sharpless in 1977 to give the diamines after treatment of the osmaindazolidines with metal hydrides (Scheme 35).[262] Although osmium(VIII) has successfully been used for asymmetric dihydroxylation and aminohydroxylation (see Section 7.19.3.2), the related diamination reaction has been relatively unexplored.



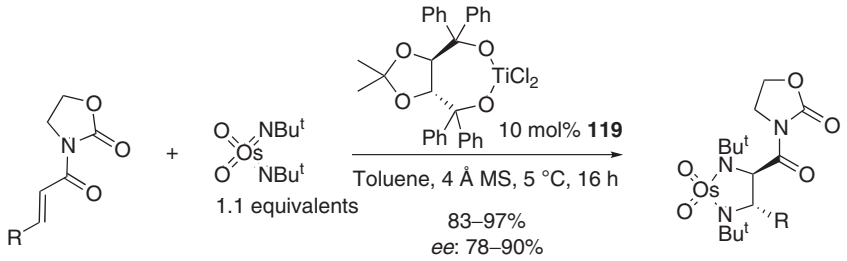
Scheme 35

A complete survey of the reaction was made in the mid 2000s,[177] shortly after the reaction to give the first asymmetric diamination of alkenes was described.[263] Although the development of an asymmetric reaction using the chiral ligands $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$ has been unsuccessful, the use of chiral acrylic esters derived from menthol (or its derivatives) gives the expected products in good yields and high diastereoselectivities (equation 86). When bis-esters are used, increased selectivity and yields are observed with the tris-imido osmium complex **117**. The products can be treated directly with $LiAlH_4$ to remove the osmium and reduce the ester. However, the chiral auxiliary can be cleaved without racemization by reaction with *tert*-butylamine and $ZnCl_2$, and the osmium removed by sodium borohydride. The reduced osmium can be recovered and recycled.



(86)

Although the reactions cannot be made catalytic in osmium, a complementary method that involves a stoichiometric osmium reagent utilized in the presence of a chiral catalyst can be used. The use of α,β-unsaturated aldehydes as substrates in the presence of proline as an organocatalyst gives low enantioselectivities even when used stoichiometrically.[264] However, the reaction with compounds **118**, although slow in the presence of solely osmium, is accelerated by the addition of Ti complexes. Thus, by using the Ti-TADDOLate complex **119** as a catalyst, the 1,2-diamination proceeds in high yield and good enantioselectivity (equation 87).[265] The chiral induction is explained by the model established by Seebach for other Ti-TADDOLate-catalyzed processes.

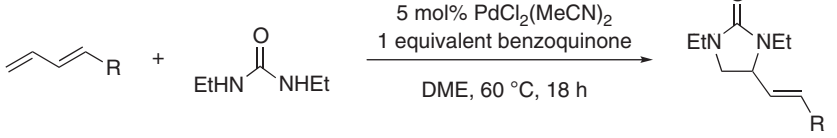


(87)

7.19.4.2.2 Catalytic reactions

7.19.4.2.2.1 Palladium and nickel

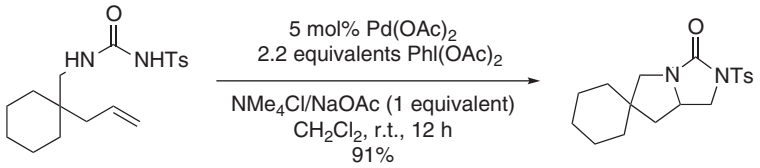
The ability of palladium to promote vicinal diamination of alkenes was already reported by Bäckvall in 1978.[266] The $PdCl_2(PhCN)_2$ complex combined with an oxidant such as *m*-CPBA or NBS, mediates the transformation of simple olefins into diamines, in the presence of dimethylamine. However, it was not until 2005 that catalytic conditions for the 1,2-diamination of dienes with palladium were reported (equation 88).[267] Use of urea as nitrogen donors is key to the success of the catalytic diamination because the resulting products do not deactivate the palladium through coordination. The reaction leads to the selective functionalization of the least substituted alkene with good yields. In the case of trisubstituted alkenes, the reaction yield and rate decrease.



R	Yield (%)[267]
Et	60
Ph	99
p-$MeOC_6H_4$	80
p-$CF_3C_6H_4$	99
2-naphthyl	73

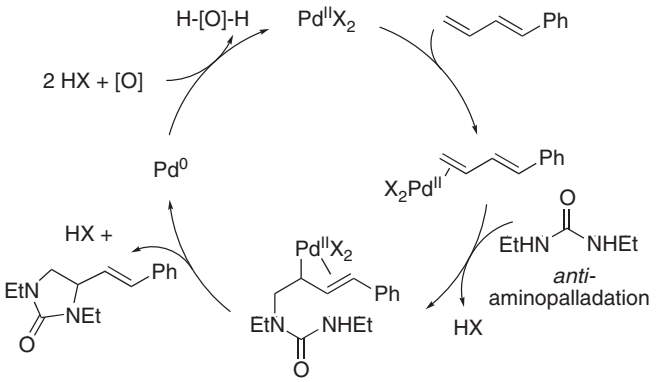
(88)

Intramolecular diamination of ω-alkenyl-substituted ureas was described concomitantly in the presence of $PhI(OAc)_2$ as the oxidant (equation 89).[268] Again, substituted ureas are the substrates of choice and lead to the bicyclic diamination products. Five-membered rings are efficiently prepared under these conditions, whereas the formation of the six- and seven-membered analogs is slower, high conversions being secured by increasing the catalyst loading to 10–25 mol%.



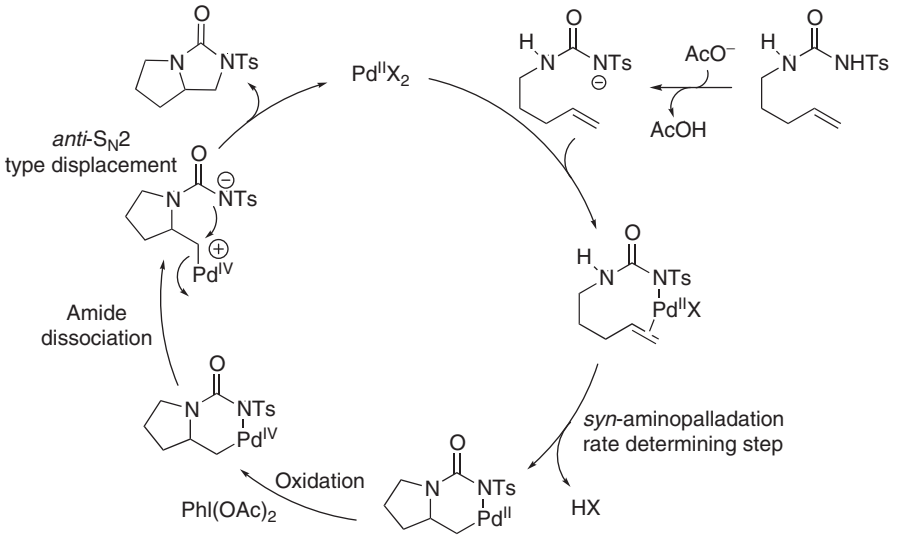
(89)

Although both methods use urea-derived substrates, the mechanism operating in each reaction is different. An *aza*-Wacker type process is suggested for the former diamination. The initial complexation of the diene to the palladium(II) would be followed by *anti*-aminopalladation. The resulting electrophilic Pd-π-allyl complex undergoes subsequent nucleophilic attack, in preference to β-hydride elimination, to give the cyclic urea. The palladium(0) species is then reoxidized by benzoquinone (Scheme 36).



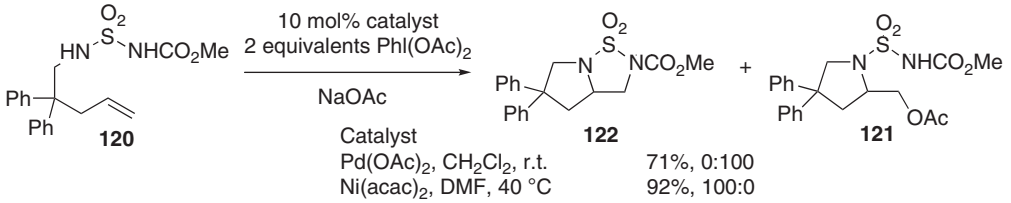
Scheme 36

In contrast, extensive mechanistic studies have led to the proposal of a palladium(II/IV) cycle for the intramolecular process (Scheme 37).[269] Base-mediated coordination of the urea to palladium initiates the reaction. Coordination of the alkene gives rise to *syn*-aminopalladation, followed by rapid oxidation of the palladium(II) to palladium(IV) by $PhI(OAc)_2$. This exacerbates the electrophilicity of the carbon, which is increased even further by amide dissociation from palladium. The cyclic urea is formed by an *anti*-S_N2-type amination.



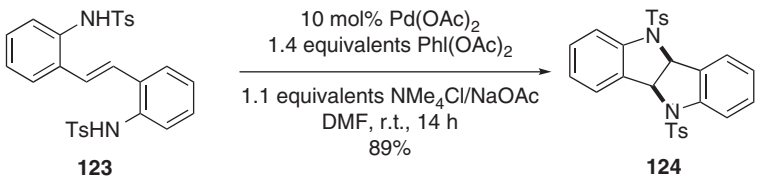
Scheme 37

The reaction has been extended to the synthesis of bicyclic guanidines.[270] This relies on the use of $CuBr_2$ as the oxidant because stronger oxidants, such as $PhI(OAc)_2$, give the aminoacetoxylation product. Copper bromide thus leads to the desired cyclic guanidines in good yields; however, the products gradually convert to the respective urea compounds under these conditions. This becomes the dominant product on moving to the six-membered ring formation. Simply changing the oxidant to $CuCl_2$ gives the desired cyclic guanidines as the sole products. The use of copper bromide also allows acrylates to be used as substrates.[271] In agreement with the previous diamination using iodine(III) oxidants, the reaction proceeds through *syn*-aminopalladation and Pd–N dissociation. Attempts to extend the palladium(II)/$PhI(OAc)_2$ method to the tethered sulfamide **120** led exclusively to the formation of the aminoacetoxylation product **121**.[272] The formation of diamine **122** can be favoured by replacing the palladium(II) catalyst with a nickel(II) catalyst (equation 90). Ureas and guanidines also react with complete selectivity for the diamination products.[272]



(90)

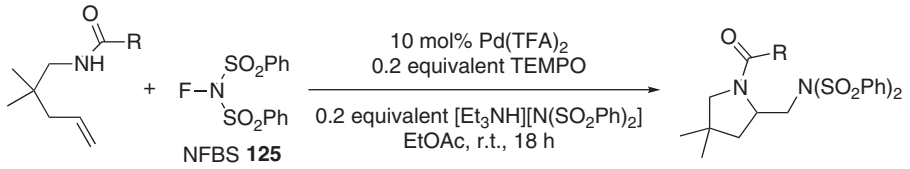
Intramolecular diamination of internal alkenes has been reported from stilbene substrates **123** and gives rise to C_2-symmetric bis-indolines **124** (equation 91).[273] Bis-pyrrolidines and annelated indoline heterocycles can also be prepared. The reaction is believed to occur through a mechanistic pathway similar to that depicted in Scheme 37, however, in this case the aminopalladation proceeds in an *anti*-manner due to geometric reasons.



(91)

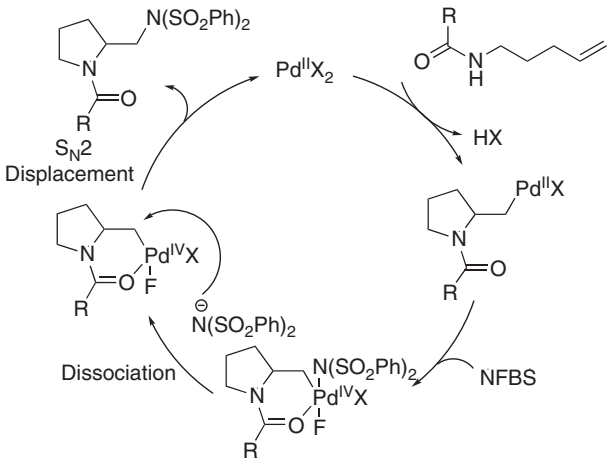
The examples of catalytic diamination with palladium highlighted so far involve substrates that give rise to doubly intramolecular reactions or intermolecular reactions that become intramolecular for the second C–N bond formation. A different strategy is based on an intramolecular aminopalladation followed by an intermolecular substitution. During investigations into haloamination of

amidoalkenes, NFBS **125** was shown to act as an electrophilic aminating agent.[274] Using this unusual reactivity, an efficient diamination process was developed. A number of different protecting groups on the tethered amine are tolerated, including carbamate and urea groups albeit with lower yields (equation 92). The addition of triethylammonium benzenesulfonimide is required to reduce the by-products formed from the addition of the palladium counterion. Palladium(IV) intermediates are postulated in the mechanism. Initial coordination of the substrate to the palladium(II) catalyst is followed by the *anti*-aminopalladation. The preference for *anti*-aminopalladation is in contrast to the previous studies (see Scheme 37) and would result from the relatively acidic conditions, as well as from the lower acidity of amides and carbamates. The oxidative addition of NFBS affords a Pd(IV) species. Dissociation of the nitrogen moiety and subsequent S_N2 displacement of the palladium gives the products (Scheme 38).



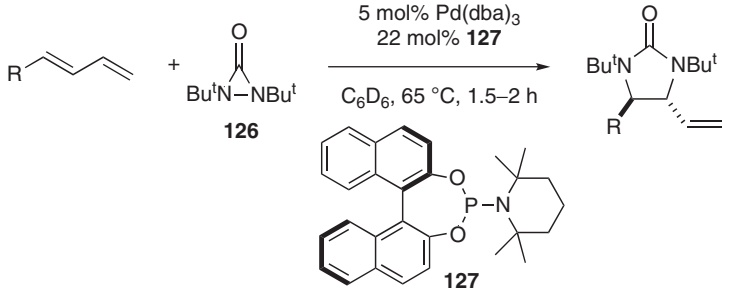
R	Yield (%)[274]
p-Tol	77
Ph	74
4-MeOC$_6$H$_4$	82
4-BrC$_6$H$_4$	73
OBn	59
OBu^t	30
NHBn	57
NHPh	49

(92)



Scheme 38

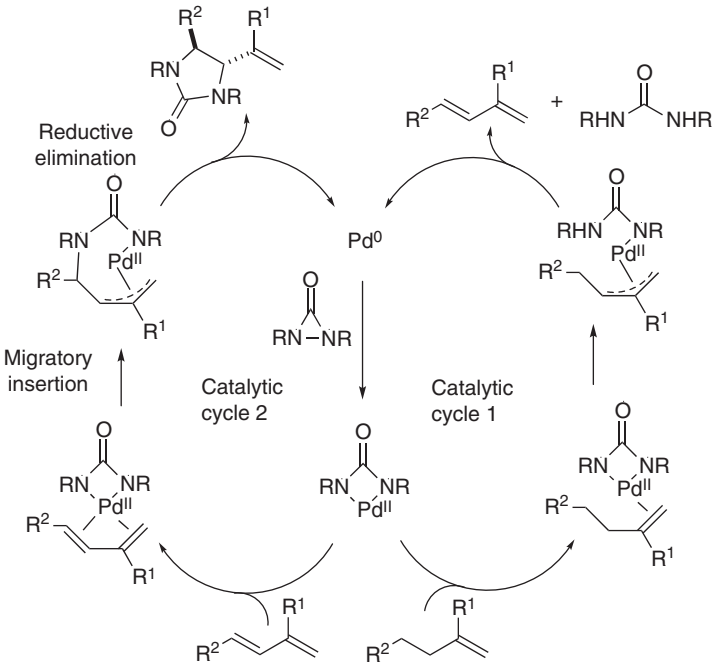
An alternative approach using Pd(0)-catalyzed protocols allows the regio- and stereoselective diamination of *trans*-dienes and *trans*-trienes. The reaction is based on the ability of palladium to insert oxidatively into the N–N bond of diaziridinones **126**. The resulting diamido species can insert into one of the double bonds of a diene and then reductively eliminate to give the diamination products.[275] This process is distinct from the former Pd(II)-catalyzed reaction (see equation 88) as shown by the regioselective diamination of the most substituted double bond (equation 93). In the case of trienes, the middle double bond is cleanly diaminated. The use of chiral phosphoramidite ligands derived from BINOL **127**, in addition, allows performing asymmetric diamination with high levels of enantiocontrol.[276] Either the mono- or di-deprotected products can be obtained merely by changing the temperature of the deprotection reaction (TFA at r.t. vs. TFA at 80 °C).



R	Yield (%)[276]	*ee* (%)
Me	91	91
Et	91	92
C_5H_{11}	90	92
Bn	94	92
c-C_6H_{11}	72	95
Ph	62	93
p-MeOPh	82	92

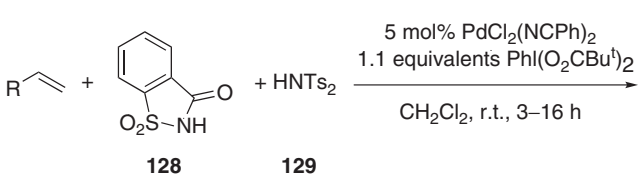
(93)

When the reaction is applied to a terminal alkene, the 1,2-diamination surprisingly occurs at the allylic and homoallylic positions affording the same product as that obtained above from a diene.[277] Extensive kinetic and nuclear magnetic resonance spectroscopic studies have led to the proposal of a palladium(0/II) catalytic cycle to account for this result.[278] It is assumed that the initial catalytic cycle generates the diene, through hydrogen transfer to the coordinated diaziridinone and β-H elimination (catalytic cycle one, Scheme 39). The diene would then enter a second catalytic cycle, which gives the diaminated product (catalytic cycle two, Scheme 39). Interestingly, simply replacing the diaziridinone by the *N*,*N*-di-*tert*-butylthiadiaziridine 1,1-dioxide (see equation 101) reverses the regioselectivity and gives the expected product of simple diamination of the terminal olefin.[279]



Scheme 39

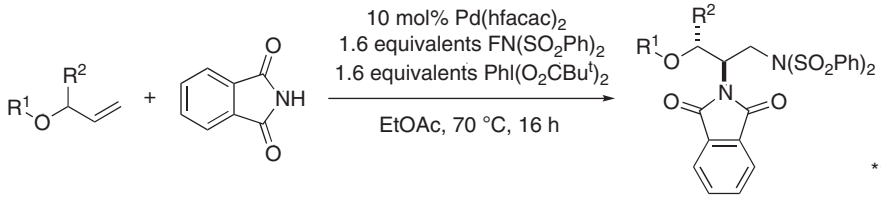
The first fully intermolecular diamination of terminal alkenes using two different nitrogen sources has been developed by combining saccharin **128**, a bis(tosyl)imide **129** and a palladium(II) salt under oxidative conditions.[280] The reaction tolerates a range of different functional groups in the alkene, including esters, amides, sulfones, azides, and halides (equation 94).



R	Yield (%)
Bu^n	73
C_6H_{13}	74
C_8H_{17}	76
$C_2H_4CO_2Me$	72
C_2H_4NPhth	67
C_2H_4Br	87
$C_2H_4N_3$	90

(94)

Modification of the reaction conditions, that is, using palladium bis(hexafluoroacetylacetonate) [Pd(hfacac)$_2$] with phthalimide and NFBS **125** as nitrogen sources, has led to the extension of the reaction to allylic ethers (equation 95).[281] Alkyl, benzyl, and benzoyl allylic ethers undergo clean 1,2-diamination with complete regio- and diastereoselectivity. Interestingly, the free alcohol is tolerated by the reaction conditions. It should be mentioned that, despite the use of iodosobenzene dicarboxylates, the diamination of alkenes and allylic ethers occurs without competitive aminooxygenation.

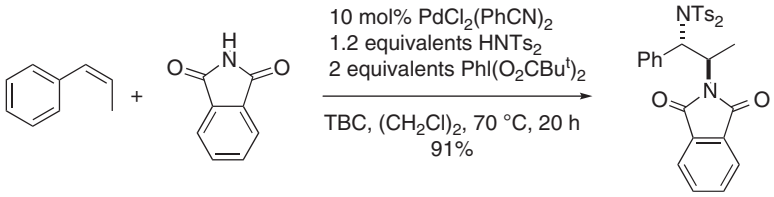


R^1	R^2	Yield, (%)
Bn	H	72
Bn	Ph	65*
Me	H	65
Me	Ph	55*

*100% diastereoselectivity

(95)

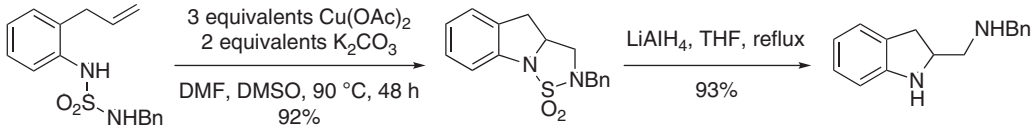
Both conditions described in equations 94 and 95 do not promote diamination of internal alkenes. However, combining $PdCl_2(PhCN)_2$, phthalimide, tosylimide **129**, and $PhI(OPiv)_2$ has overcome this limitation, providing that *tert*-butylcatechol (TBC) is added to the mixture.[282] This additive prevents polymerization of the alkene under the reaction conditions. Only (*Z*)-*β*-alkylstyrenes are suitable substrates, including those with electron-withdrawing substituents on the aryl group (equation 96). Low-catalyst loadings are required since competitive isomerization to (*E*)-olefins is observed at higher loadings (10 mol%). The products can be deprotected in high yields, generally affording the mono *N*-(sulfonyl)diamines.



(96)

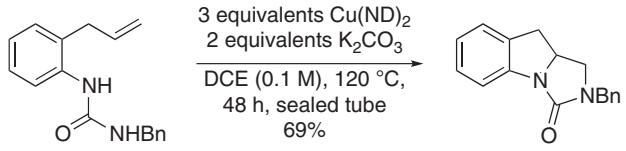
7.19.4.2.2.2 Copper

The first copper-mediated diamination involved stoichiometric amounts of the metal and focused on double intramolecular additions. Copper(II) acetate promotes the formation of bicyclic sulfamides from *γ*- and δ-alkenyl sulfamides.[283] Subsequent treatment of the cyclic sulfamides with $LiAlH_4$ yields the free diamines (equation 97).

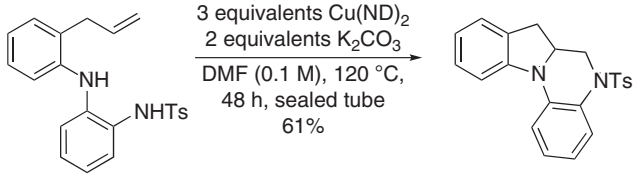


(97)

On optimization of the reaction conditions, including the utilization of other copper(II) carboxylates (e.g., copper(II) neodecanoate, $Cu(ND)_2$), the substrate scope could be expanded to include greater substitution of the substrates.[284] In the case of α-substituted sulfamides, these reactions proceeded with excellent diastereoselectivity (>20:1), to give the 2,5-*cis*-pyrrolidines. The reaction can also be applied to ureas and a 1,2-diaminobenzene tethered substrate (equations 98 and 99). The reaction is assumed to go through a sp^2-hybridized carbon radical intermediate (see **Scheme 28**), which on addition to another copper(II) complex forms a copper(III) species, which subsequently undergoes ligand exchange and either reductive elimination or S_N2 displacement to give CuND. The proposed mechanism requires at least two equivalents of copper(II) as the copper is lost from the reaction as copper(I) species. Unfortunately, this intramolecular diamination could not be rendered catalytic in copper with the addition of stoichiometric amounts of oxidant (MnO_2, O_2, and hypervalent iodine reagents).

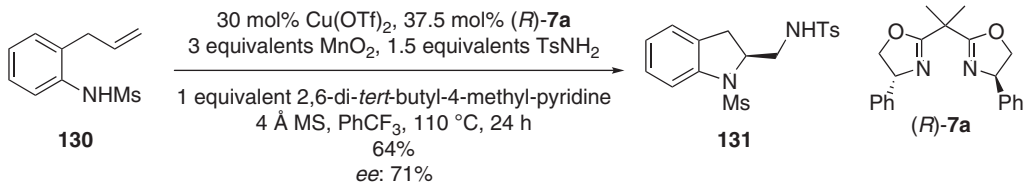


(98)



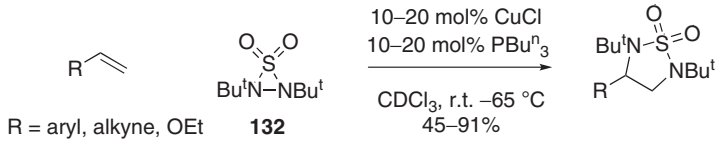
(99)

The synthetic utility of the reaction has been increased through the development of an 'intra/intermolecular' variant. The substrate scope includes *γ*-alkenyl-amides and *γ*-alkenyl-sulfonamides as well as *N*-allyl ureas.[285] A variety of different amine nucleophiles (anilines, azides, and amides) is tolerated in the second intermolecular C–N bond-forming reaction. In the case of sulfonamides as the nucleophile, the reaction has been rendered catalytic in copper. In addition, combined with the (*R*)-bis(oxazoline) **7a**, $Cu(OTf)_2$ catalyzes the asymmetric formation of diamine **131** from **130** in 64% yield and 71% *ee* (equation 100).



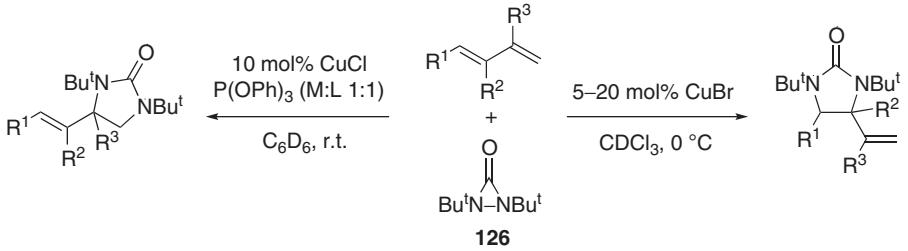
(100)

Alongside its work on palladium-catalyzed diamination, the group of Shi has developed the analogous copper(I)-catalyzed intermolecular diamination of terminal alkenes and dienes using the same cyclic nitrogen sources **126** and **132**. A range of styrene derivatives is successfully diaminated with **132** in good yields, in the presence of tri(butyl)phosphine (equation 101).[286] The free diamines can then be accessed following treatment of the cyclic products with concentrated HCl and $BaCO_3$. The reaction scope includes electron-donating and electron-withdrawing substituents on the styrene, though lower yields are obtained with electron-withdrawing substituents. Simple aliphatic olefins and ethyl acrylate are beyond the scope of the reaction.



(101)

By simply changing the phosphine ligand, the reaction can be extended to the cycloguanidination of terminal alkenes, using a diaziridinimine.[287] Conjugated dienes and trienes can also be transformed selectively at the terminal alkene unit when using a CuCl-PR_3 catalytic system and diaziridinone **126**.[287–289] On changing the copper source to CuBr, the complementary regioselectivity is observed and the internal double bond is diaminated (**Scheme 40**).[289,290] Isolated internal double bonds do not give appreciable quantities of diaminated products, thereby showing the terminal alkene is necessary for reactivity. Two pathways involving different mechanisms are suggested to account for the experimental results. The internal diamination would proceed according to the mechanism proposed for the Pd-catalyzed diamination (see **Scheme 39**). The addition of phosphine ligands may hinder the formation of the alkene complex, and thus make this pathway unlikely. A radical pathway is therefore assumed for the terminal diamination.

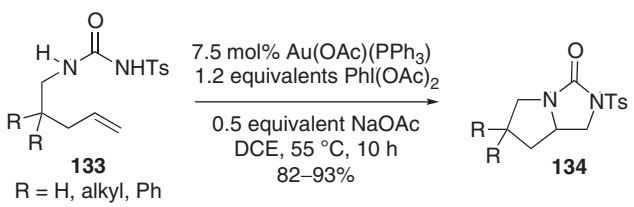


Scheme 40

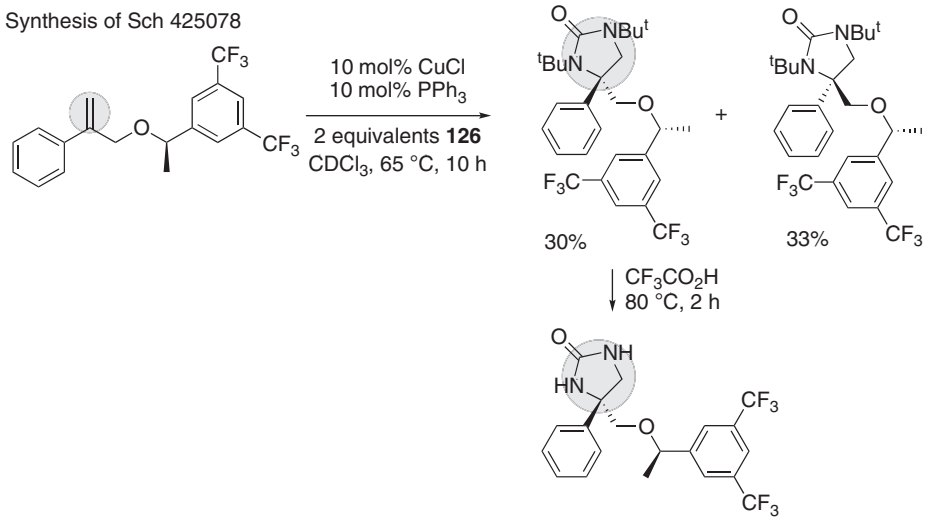
This approach has been utilized with disubstituted alkenes and di-*tert*-butyldiaziridinone **126**, for the successful synthesis of the potent NK_1 antagonist Sch 425078 (**Scheme 41**).[291]

7.19.4.2.2.3 Gold

There are very few examples of gold-catalyzed alkene oxyamination and diamination reported in the literature, though hydroamination reactions are well known. It was only in 2009 that a protocol emerged to intercept the hydroamination pathway leading to a gold-catalyzed diamination reaction.[292] Using the often-seen urea substrates of type **133**, a variety of bicyclic ureas are formed in excellent yields using $Au(OAc)(PPh_3)$ as the catalyst and substoichiometric quantities of a base under oxidative conditions (equation 102). Noticeably only five-membered rings are described starting from alkenes, whereas urea-tethered allenes afford both five- and six-membered bicyclic derivatives.[293] The base is required for the chemoselectivity because a mixture of diamination and oxyamination products is obtained without NaOAc. This method is complementary to the previous palladium-catalyzed reaction (see **Scheme 37**) giving the opposite diastereoslectivity, due to *anti*-aminoauration.

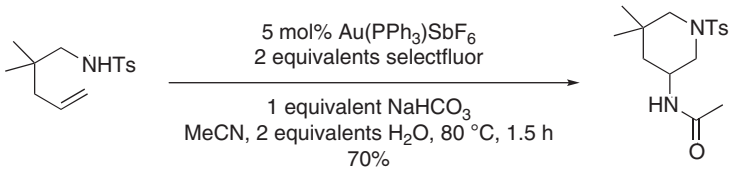


(102)



Scheme 41

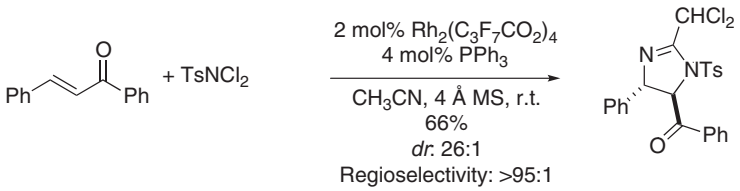
An intra-intermolecular gold-catalyzed aminoamidation has also been described in which acetonitrile acts as the second nitrogen source. Under the reaction conditions, the initial diaminated product is hydrolyzed to the amide giving access to *N*-piperidin-3-yl carboxamides (equation 103).[294]



(103)

7.19.4.2.2.4 Rhodium and iron

Rhodium and iron complexes have been used as the catalyst for electrophilic diamination reactions referred to as Ritter-type diaminations. A number of different α,β-unsaturated ketones can be transformed into imidazolines using $TsNCl_2$ and MeCN as the nitrogen sources in the presence of rhodium(II) carboxylates (equation 104).[295] The reaction proceeds in good yields and excellent diastereoselectivities (>20:1, *anti*:*syn*). The reaction also tolerates α,β-unsaturated esters albeit in lower yields (~50%). The drawbacks with the reaction are the handling difficulties associated with the hygroscopic nature of the catalyst system and the need to add the $TsNCl_2$ in two portions. These can be overcome by the use of a $FeCl_3/PPh_3$ catalyst system, which has the added advantage of involving a less expensive metal. Higher yields and stereoselectivities are obtained in most cases.[296] The same products can be formed under metal-free conditions albeit longer reaction times are required.[297]



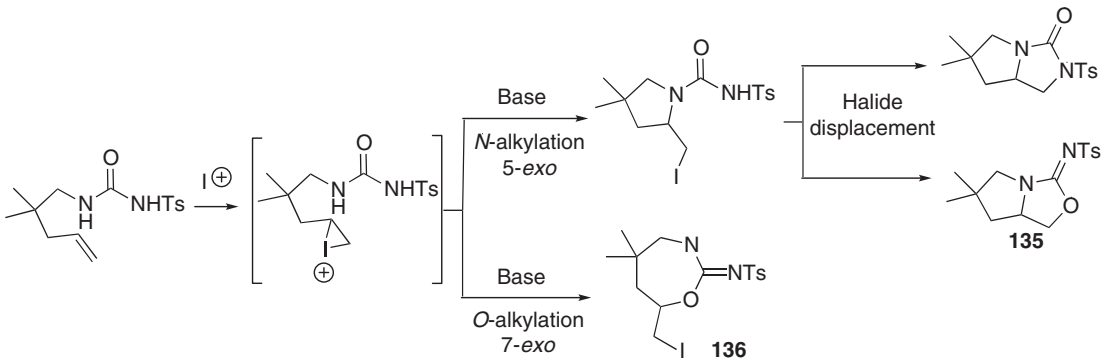
(104)

One example of diamination of a tethered indole using the rhodium(II) complex $Rh_2(esp)_2$ **16** has been reported.[241] The reaction is believed to proceed via a metallanitrene intermediate (see equation 77).

7.19.4.3 Metal-Free Reactions Toward Diamines

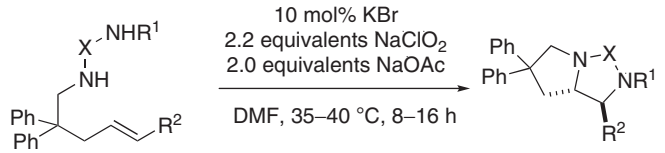
7.19.4.3.1 Methods involving halonium ion or aminohalogen intermediates

One-pot procedures have been developed that allow direct diamination of alkenes via halonium ions or aminohalogen intermediates (see Section 7.19.5). Starting from *N*-alkenyl urea substrates, a variety of different sources of electrophilic iodine including IPy_2BF_4,[270] *N*-iodosuccinimde (NIS),[298] and *in situ* generation of XOAc[299] mediates efficiently the double intramolecular process. Good-to-excellent yields are obtained in all cases and are similar to the yields obtained from the palladium-catalyzed reactions. Depending on the conditions, a number of side products can be obtained from competitive oxyhalogenation and aminohalogenation. When NIS is used, traces of the oxyamination product **135** are always observed, whereas with IPy_2BF_4 product **136** is obtained as a minor side product (Scheme 42).



Scheme 42

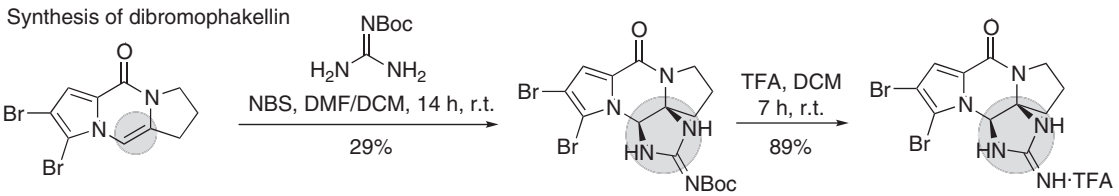
Although the above method avoids the need for expensive metal catalysts, it still involves stoichiometric quantities of halonium sources. A bromide-catalyzed variant has been described utilizing cheap and easily available reagents (KBr, $NaClO_2$, and NaOAc) and achieving excellent yields and chemoselectivity.[300] The substrate scope is wider and includes *N*-alkenyl sulfamides, internal alkenes, and acrylate derivatives, as well as the urea substrates (equation 105). A number of different carbamate protecting groups for the sulfamide are tolerated.



X	R^1	R^2	Yield (%)[300]
CO	Ts	H	90
CO	Ts	Ph	91, only *trans*
SO_2	Cbz	H	97
SO_2	Cbz	Ph	77, *dr* >15:1
SO_2	Cbz	CO_2Me	93, *dr* 4:1

(105)

Inter-intramolecular processes have also been developed using guanidine and urea derivatives as the nitrogen source, to give access to various intermediates for natural products synthesis. The addition of protected guanidines to 1,2-dihydropyridines and tetrahydropyridines in the presence of bromine gives a range of bicyclic products, which can be subsequently manipulated to give access to the 2-aminoimidazole products.[301] Racemic dibromophakellin, for example, has been synthesized using a Boc-protected guanidine in the presence of NBS as the Br^+ source (**Scheme 43**).[302]

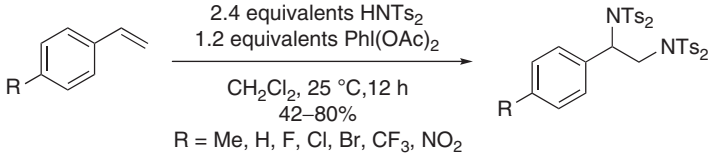


Scheme 43

Another noteworthy application involves catalytic quantities of iodine used in conjunction with chloramine-T 24 that allows the intermolecular diamination of glycals and disaccharide glycals for subsequent use either in *N*-glycopeptide synthesis or the development of selective inhibitors of α-galactosidase.[303]

7.19.4.3.2 Iodine(III)-promoted reactions

A highly versatile diamination procedure has been described with hypervalent iodine reagents.[304] This method represents the state of the art in terms of substrate scope and can be applied to styrenes, aliphatic terminal alkenes, and internal alkenes. A wide variety of substituents is tolerated in both the *para*- and *meta*- positions of styrene (equation 106). *Ortho*-substituents are not so well tolerated. The reaction is unsuccessful with *para*-methoxystyrene, instead the corresponding enamide is formed. Microwave heating at 80 °C leads to obtaining the dimesylated derivatives in good yields. Slightly higher temperatures are also needed to obtain good-to-excellent yields of the corresponding products from aliphatic alkenes (**Figure 4**). The reaction also works for internal alkenes such as stilbenes and those shown in **Figure 5**. For the aliphatic internal alkenes, $PhI(OAc)(NTs_2)$ is needed to obtain high yields. Cyclic alkenes can also be successfully diaminated.



(106)

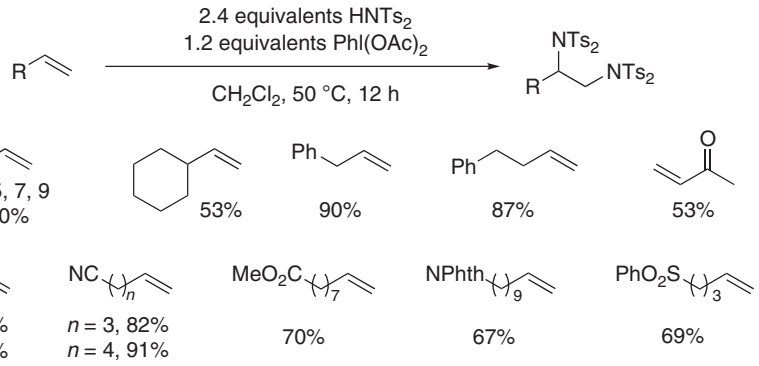
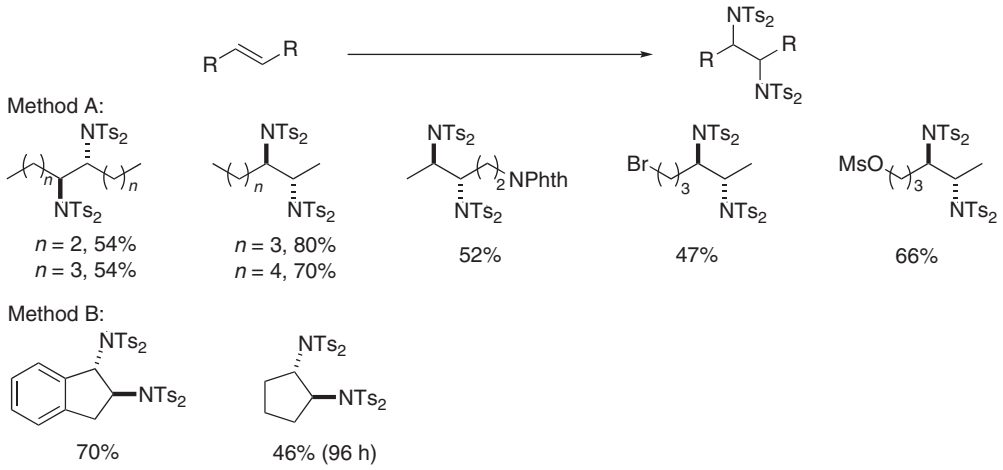


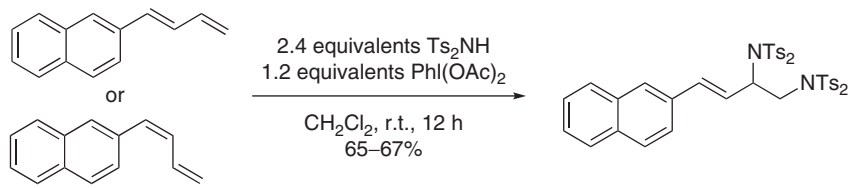
Figure 4 Iodine(III)-promoted diamination of terminal alkenes.



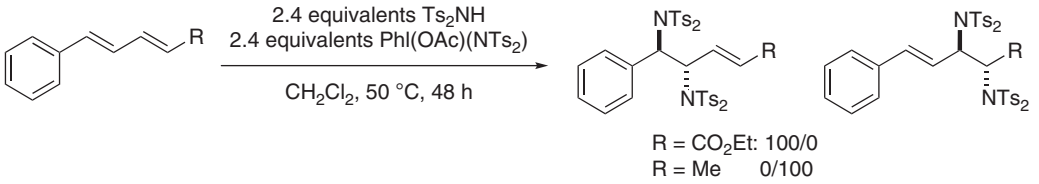
Method A: Ts_2NH 1.2 equivalents PhI(OAc)(NTs_2) 1.2 equivalents CH_2Cl_2, 50 °C, 18 h
Method B: Ts_2NH 1.5 equivalents PhI(OAc)(NTs_2) 1.4 equivalents CH_2Cl_2, 45 °C, 12 h

Figure 5 Iodine(III)-promoted diamination of internal alkenes.

The method can be utilized for the diamination of the terminal double bond of conjugated dienes and trienes.[305] The reaction is highly regioselective favoring the terminal alkene (equation 107). Both *E* and *Z* substrates give the same product under the reaction conditions allowing substrates that are a mixture of isomers to be utilized. In the case of an internal diene, the regioselectivity depends on the substitution (equation 108). In all cases, the *trans*-product is observed.

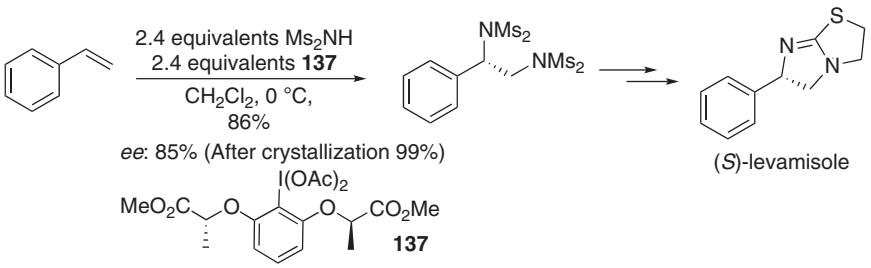


(107)



(108)

$PhI(OAc)_2$ also mediates efficiently the intra/intermolecular alkene diamination with bis(sulfonyl)imides as the external nitrogen source, to access 3-aminopiperidine products.[306] Interestingly, the reaction can be carried out at room temperature using catalytic PhI and 3-chloroperoxybenzoic acid as the oxidant. Finally, the chiral hypervalent iodine reagent **137** can be used to obtain chiral diaminated styrene derivatives in good enantioselectivities (74–95% *ee*, after one recrystallization 99% *ee*).[307] The utility of the reaction is illustrated by the synthesis of (*S*)-levamisole (Scheme 44).

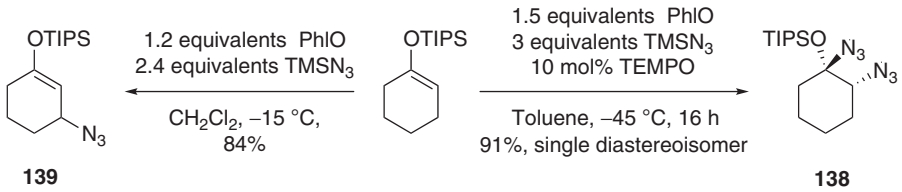


Scheme 44

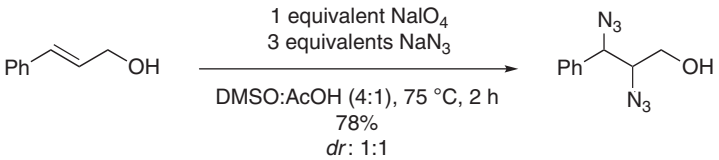
7.19.4.4 Miscellaneous Diamination Reactions

Application of the dual organocatalytic system previously described for the oxyamination of α,β-unsaturated aldehydes (see Scheme 34) allows the development of the analogous diamination.[255] The Michael addition of the nitrogen nucleophile BocNHOTBS is then followed by the trapping of electrophilic dialkyl azodicarboxylates. The combination of the imidazolidinone with either proline enantiomers, once again, gives access to the *cis*- or *trans*-diaminated products. The use of succinimide and diethyl azodicarboxylate is also efficient to perform diamination of α,β-unsaturated aldehydes.[308]

The reaction of PhIO and $TMSN_3$ with trimethylsilyl enol ethers affords products of 1,2-diazidation of alkenes **138**, provided catalytic amounts of TEMPO are added. In the absence of TEMPO, the β-azido adduct **139** is formed (Scheme 45).[309] Various styrenes and alkenes can also be converted to the diazido products by reaction with sodium metaperiodate $NaIO_4$ and sodium azide (equation 109).[310] Good-to-excellent yields are obtained, although a 1:1 mixture of diastereoisomers is obtained with internal alkenes. Although relatively underexplored, 1,2-diazidation has been shown to be useful to access a *syn*-diazido intermediate in the synthesis of (±)-dibromophakellstatin.[311]



Scheme 45



(109)

7.19.5 Alkene Aminohalogenation

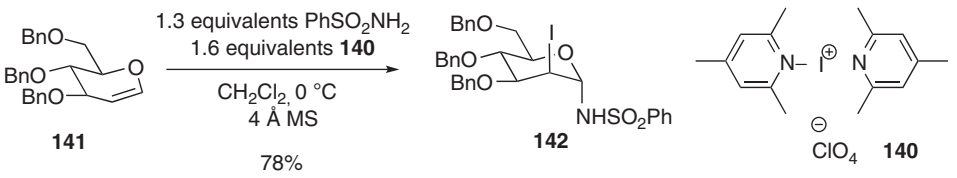
7.19.5.1 Introduction

The direct oxidation of a carbon–carbon double bond into vicinal haloamine derivatives allows the preparation of versatile building blocks and the rapid construction of valuable heterocycles. The potential of these compounds not only relies on their

ability to undergo intramolecular cyclization to form aziridines but also offers the possibility to conveniently functionalize various classes of alkenes. The increasing number of methods published over the past 20 years and recently reviewed[312] will be presented in this chapter, focusing on the principal examples (*see* Chapter 7.29).

7.19.5.2 Halosulfonamidation

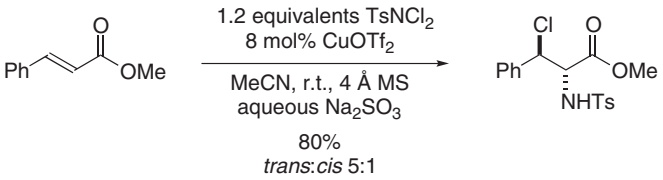
Among the numerous nitrogen sources available, the sulfonamides have probably been the most utilized in the aminohalogenation reactions. Different combinations of compounds of type RSO_2NH_2, RSO_2NMX (M = metal and X = halogen) and RSO_2NX_2 have been used as the nitrogen and/or halogen sources, in addition to other reagents. As an early example, the iodosulfonamidation of different glycal derivatives efficiently takes place in the presence of benzenesulfonamide and iodonium di-*sym*-collidine perchlorate **140**.[313] The protected glucal **141**, for example, is transformed to the *trans* diaxial **142** in 78% yield (equation 110). The stereoselectivity suggests the formation of an iodonium intermediate subsequently ring opened at the more stabilized positively charged anomeric position by the sulfonamide. The same reaction allows the difunctionalization of a galactal, an allal, and a disaccharide derivative in good yields.



(110)

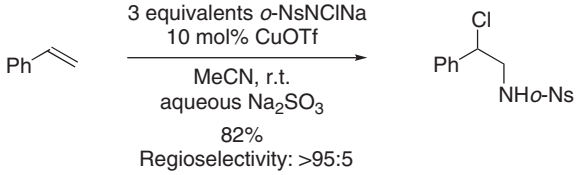
7.19.5.2.1 Metal salts

Cinnamic esters have been well studied in oxidative alkene difunctionalization. These substrates undergo aminochlorination with *N*,*N*-dichloro-*p*-toluenesulfonamide ($TsNCl_2$) in the presence of catalytic $CuOTf_2$ or $ZnCl_2$. The vicinal chloroamines are isolated in moderate-to-high yields with an excellent regioselectivity in favor of the α-amino-β-chloro products (equation 111).[314] A reductive work-up is necessary to reduce the N–Cl bond.



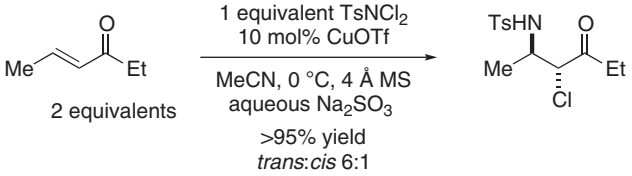
(111)

The use of *N*,*N*-dichloro-*o*-nitrobenzenesulfonamide (*o*-$NsNCl_2$) in combination with *o*-NsNClNa, in the presence of CuOTf, has been described as a method to form α-amino-β-chloro products with a more easily removable *N*-protecting group.[315] The products are obtained in good-to-high yields, generally with an excellent *trans*-diastereoselectivity. The diastereoselectivity and regioselectivity could be explained by the formation of a transient aziridinium, ring opened via an S_N2-type mechanism at the benzylic position. But, the intermediacy of a simple aziridine is ruled out by a control experiment showing the stability of such a compound in the reaction conditions.[316] The same study reveals that an excess of *o*-NsNClNa is sufficient to perform the aminochlorination of styrene (equation 112).



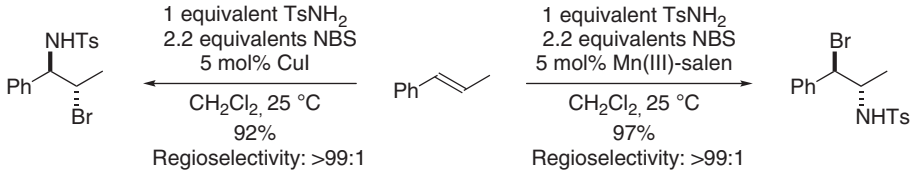
(112)

The combination of $TsNCl_2$ and CuOTf at 0 °C leads to the aminochlorination of α,β-unsaturated aromatic and aliphatic ketones.[317] The latter, unexpectedly, affords the products with the opposite regioselectivity (equation 113). The combination of *o*-$NsNCl_2$ and *o*-NsNClNa in the ionic liquid [bmim][BF_4] as the solvent allows increasing the reaction rate and the yields.[318] α,β-Unsaturated nitriles are also highly reactive substrates for the reaction, leading to the same regioselectivities as observed earlier with esters.[319]



(113)

The analogous bromoamination can be realized by using $TsNH_2$ and NBS with catalyst-controlled regioselectivity.[320] With CuI, the α-amino-β-bromo-styrene is obtained, whereas the use of a Mn(III)-salen induces the reverse regioselectivity (**Scheme 46**).

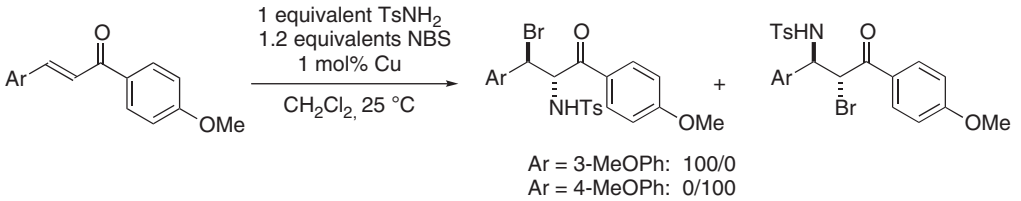


Scheme 46

Apart from copper salts and $ZnCl_2$, palladium acetate[321] and iron(III) chloride[322] have been reported to catalyze alkene aminohalogenation.

7.19.5.2.2 Elemental metals

The haloamination of alkene can be catalyzed not only by copper salts but also by copper powder. The latter efficiently mediates the aminobromination of α,β-unsaturated aromatic and aliphatic ketones with $TsNH_2$ and NBS.[323] The reactivity strongly depends on the substitution of the alkene (equation 114). Electron-rich substrates give high yields, whereas electron-deficient olefins remain unchanged. Interestingly, a PMP group induces a reversal of regioselectivity, an observation also made in the case of aliphatic ketones. Complete *trans*-selectivity is observed, independently of the regioselectivity.

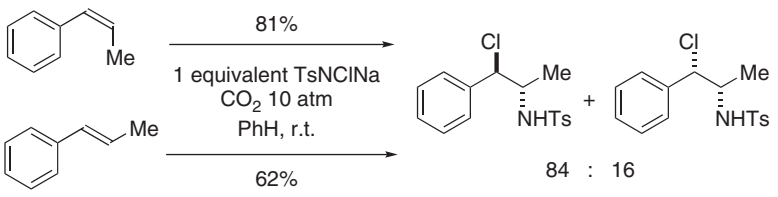


(114)

Higher yields are recorded when the reaction is performed in the presence of 1 mol% of aluminum powder.[324] Similar trends in selectivity are observed. The occurrence of two possible pathways, both involving the opening of an onium intermediate, is suggested to explain the *trans*-selectivity. In the presence of a PMP group, a bromonium ion would be initially produced before ring-opening by the nitrogen source via an S_N2 mechanism. The regioselectivity is explained by the attack at the more stabilized benzylic site. Otherwise, a nitrenium species would be involved. This reactive species would arise from the reaction of $TsNH_2$ with NBS to form $TsNBr_2$, followed by removal of one bromide by the metal. Opening of this nitrenium at the benzylic carbon would result in the *trans* product but with the opposite regioselectivity.

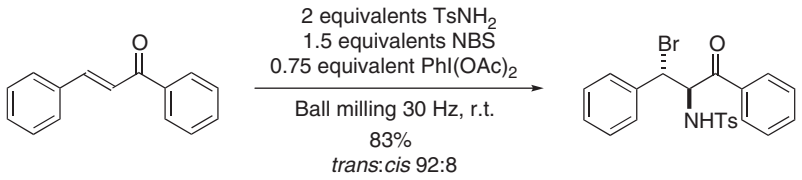
7.19.5.2.3 Metal-free aminohalogenation

The metal-free aminochlorination of alkenes using chloramine-T **24** has been reported under a pressurized CO_2 atmosphere.[325] A control experiment under a pressurized N_2 atmosphere confirms that CO_2 acts as a promoter for this reaction. The aliphatic alkenes only afford low yields of products but styrene derivatives are efficiently converted under these conditions. The reaction is stereoconvergent, affording the same ratio of *syn*/*anti* products from the *Z*- and *E*-β-methyl styrene substrates (equation 115). Once again, 4-MeO substitution leads to a reversal of the regioselectivity in the substituted styrene series. The chloramine T-mediated aminochlorination of α,β-unsaturated ketones can also be performed in water in the presence of sulfuric acid and a phase transfer agent, triethylbenzylammonium chloride (TEBAC).[326]



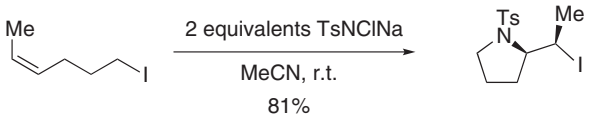
(115)

The use of hypervalent iodine reagents such as $PhI(OAc)_2$ allows the aminobromination of olefins to occur in good yields and high diastereoselectivities. An original procedure involves mechanical milling conditions in the presence of $PhI(OAc)_2$, with $TsNH_2$ and NBS as the nitrogen and bromine sources, respectively (equation 116).[327] The exact mechanism is still unclear but probably involves an aziridinium intermediate. In the context of sustainable chemistry, this aminobromination reaction can also be performed with the same reagents in water.[328]

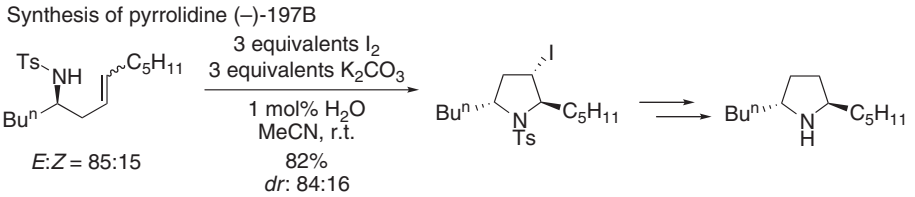


(116)

A synthetically useful application of alkene aminohalogenation involves the formation of heterocycles via cyclization reactions of γ-iodo-olefins following reaction with chloramine-T (equation 117).[329] This stereospecific transformation results from the initial displacement of the iodide by TsNClNa. The released NaI can then reduce the N–Cl bond, generating ICl that allows the formation of an iodonium intermediate. Subsequent 5-*exo* cyclization would afford the product. A similar reaction is possible from γ-*N*-(tosyl)-alkene, for example, the use of a combination of I_2 and K_2CO_3 has proved appropriate to form a 3-iodopyrrolidine for the total synthesis of pyrrolidine (–)-197B (**Scheme 47**).[330]



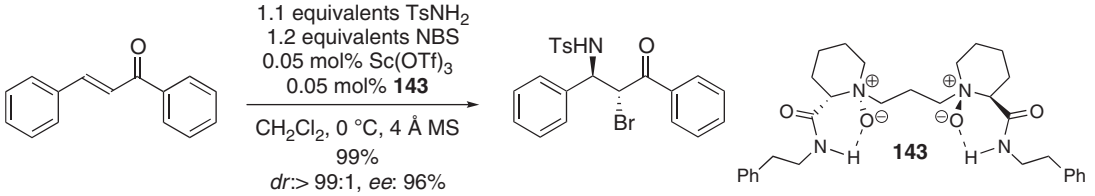
(117)



Scheme 47

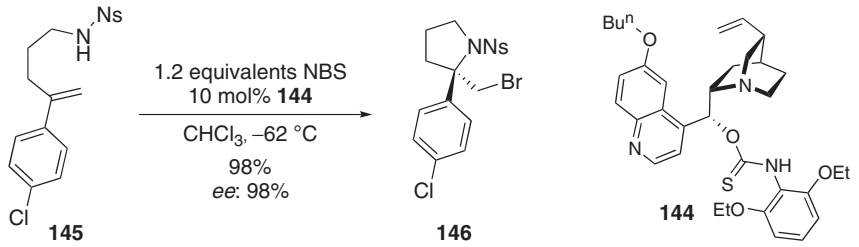
7.19.5.2.4 Asymmetric aminohalogenation

Diastereoselective aminohalogenation is reported with cinnamate derivatives bearing an Evans-type chiral auxiliary.[331] The reaction is catalyzed by CuOTf in an ionic liquid as the solvent, giving the products in good yields but often moderate diastereoselectivities. The catalytic asymmetric bromoamination of chalcones with a chiral scandium complex is more efficient since the compounds are isolated in high yields and with excellent diastereo- and enantioselectivities (equation 118).[332] It should be mentioned that the regioselectivity of the addition is reversed, an observation that implies the formation of a bromonium intermediate. A similar catalyst gives comparable high levels of efficiency and stereocontrol in the catalytic asymmetric alkene chloroamination, though with the $TsNCl_2/TsNH_2$ system.[333] More interestingly, in the presence of NIS and $TsNH_2$, the scandium complex allows performing the rarely described formation of vicinal iodosulfonamides in an asymmetric manner.[334] The chelation of TsNHX, formed by reaction between $TsNH_2$ and the halo source, and the substrate to the chiral scandium complex would account for the stereocontrolled delivery of the halogen. The resulting halonium ion would be instantaneously opened by the negatively charged nitrogen.



(118)

Cinchona alkaloid-derived thioureas are potent chiral promoters for bromoaminocyclization reactions.[335] Aromatic alkenes lead to higher enantioselectivities than the aliphatic derivatives. Quinine-derived catalyst **144**, for example, mediates the formation of **146** in excellent yield and enantioselectivity (equation 119). The pseudoenantiomeric quinidine-derivative gives the enantiomeric product.



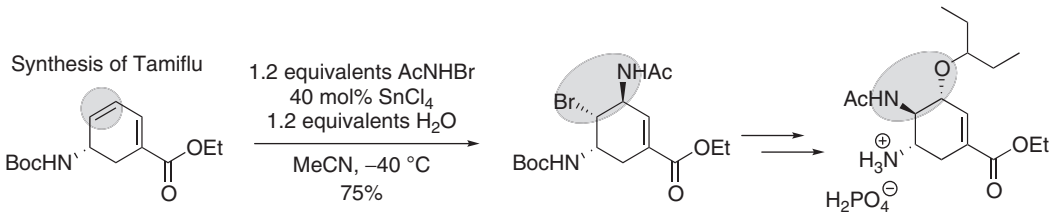
(119)

7.19.5.3 Halonium-Mediated Aminohalogenation

Some of the aforementioned methods involve the initial formation of halonium species for halosulfonamidation reactions. In this section, other types of aminohalogenation using a similar principle but with different nitrogen sources are presented. Due to the vast area potentially covered by this definition, only selected examples have been presented.

7.19.5.3.1 Intermolecular aminohalogenation

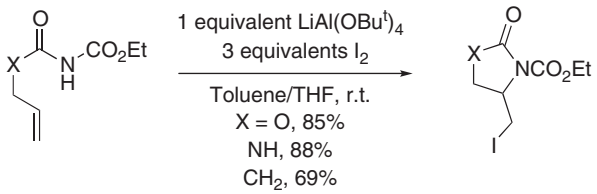
Benzamides can be employed for the bromoacetamidation of cycloalkenes. The reaction is catalyzed by $FeCl_2$ in the presence of NBS as the bromide source and allows the difunctionalization of styrene derivatives.[336] Vicinal haloazides are accessible from different types of alkenes by application of a method that combines $PhI(OAc)_2$, $TMSN_3$, and Et_4NX (with X = Br or I). The selectivities and yields depend on the nature of either the halide used or the olefin.[337] A more significant strategy relies on an efficient Ritter-type *trans*-amidohalogenation of cycloalkenes. This reaction performed in acetonitrile involves $SnCl_4$, $SnBr_4$, or $BF_3 \cdot OEt_2$ as a Lewis acid, and *N*-bromoacetamide as the bromonium donor.[338] The utility of this transformation is highlighted by the short total synthesis of the antiinfluenza neuramidase inhibitor Tamiflu (Scheme 48).[339] The reaction is believed to occur through the formation of a bromonium intermediate, which is opened by an acetonitrile molecule. Hydrolysis of the latter affords the acetamide product. Other nitriles can be used for the formation of different bromoamides.



Scheme 48

7.19.5.3.2 Cyclizing aminohalogenation reactions

Application of the haloamination reactions to the synthesis of nitrogen heterocycles raises the issue of the formation of either *O*- or *N*-cyclization products with ambident nucleophiles like amides. Several methods have been reported to avoid this problem but they require further transformations before the cyclization step.[340,341] A practical solution arises from the careful choice of a base promoter that induces the *N*-cyclization of unsaturated amides, carbamates, and ureas.[342] To this end, $LiAl(Ot\text{-}Bu)_4$ and *n*-BuLi give the best results among the tested bases (equation 120). *N*-Boc or *N*-CBz carbamates can be engaged successfully in this reaction.

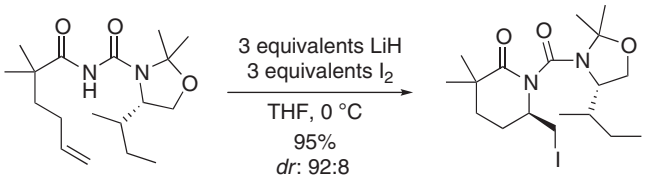


(120)

β-N-benzyl alkenes, when submitted to the action of I_2/$NaHCO_3$, afford 2-iodomethyl azetidines.[343] However, these unstable intermediates rearrange on silica gel to give 3-iodopyrrolidines.

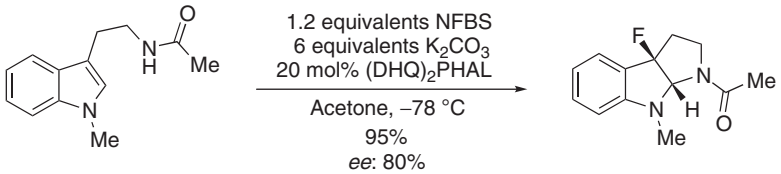
7.19.5.3.3 Asymmetric aminohalogenation reactions

Based on the study depicted in equation 120, an asymmetric iodolactamization has been developed through the use of an oxazolidine chiral auxiliary, and after optimization, LiH has been identified as the most effective base.[344] 2-iodomethyl γ- and δ-lactams are obtained with this method (equation 121).



(121)

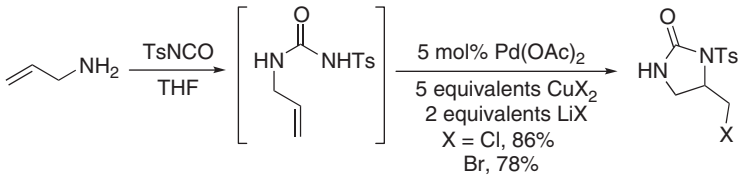
The dihydroquinine catalyst $(DHQ)_2PHAL$, aforementioned for aminohydroxylation reactions (see Section 7.19.3.2), promotes the asymmetric intramolecular fluoroamination of indole in the presence of selectfluor or NFBS as the F^+ donor (equation 122).[345] C3-tethered amides, carbamates, and sulfonamides can be used as nitrogen nucleophiles.



(122)

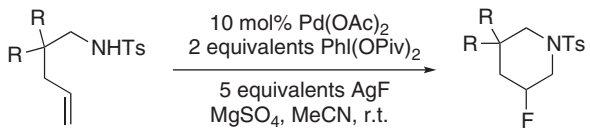
7.19.5.4 Nucleopalladation-Mediated Aminohalogenation

The electrophilicity of palladium(II) complexes has already been described in alkene aminohydroxylation and diamination (see Sections 7.19.3.3.1.1 and 7.19.4.2.2.1). It has been used to perform haloaminations from allylic carbamates and ureas, prepared *in situ* from the corresponding allylic alcohols and amines. Selective 5-*exo* aminochlorination and aminobromination take place with the $Pd(OAc)_2$/CuX_2/LiX (X = Cl, Br) system (equation 123).[346] Comparable results are obtained with $PdCl_2(MeCN)_2$, $AgBF_4$, and NCS,[347] whereas $Pd(OCOCF_3)_2$ in the presence of an excess of $CuBr_2$ affords *exo*/*endo* selectivities.[348]



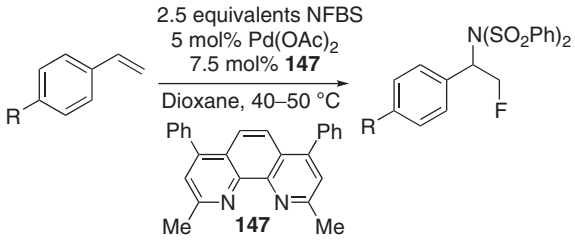
(123)

The more challenging aminofluorination proceeds in an intramolecular manner from γ-unsaturated *N*-tosylamine to give 3-fluoropiperidines in the presence of $Pd(OAc)_2$ (equation 124).[349] The reaction requires $PhI(OPiv)_2$ as an iodine(III) oxidant and AgF as the fluorine source. Although the mechanistic pathway is unclear, an initial alkene aminopalladation followed by oxidation of the metallic center to palladium(IV) has been proposed. The intermolecular aminofluorination of styrene derivatives is also possible by using NFBS, both as the fluorine oxidant and nitrogen source (equation 125).[350]



R	Yield (%)[349]
H	80
Me	84
Ph	83

(124)

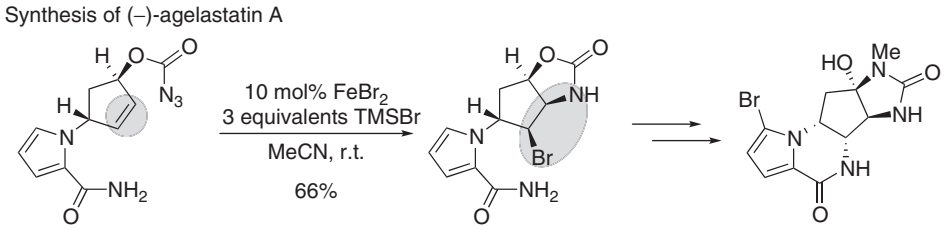


R	Yield (%)[350]
H	76
Me	80
Cl	79
OAc	67
OTs	62
CO_2Me	42
NO_2	37

(125)

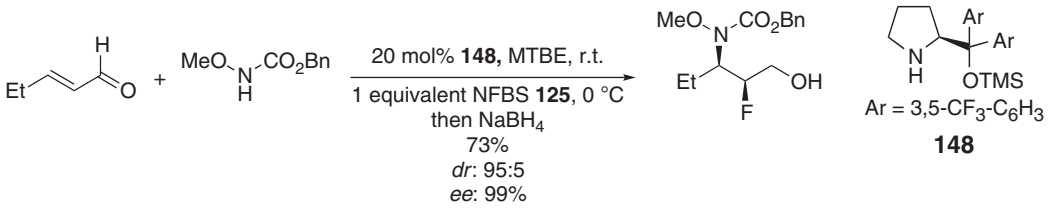
7.19.5.5 Miscellaneous Aminohalogenation Reactions

The thermolysis of *O*-allyl azidoformates in refluxing tetrachloroethane affords aminochlorination products through the formation of a transient aziridine subsequently opened by the hydrochloric acid generated *in situ*.[351] A more practical procedure involves a catalytic quantity of iron(II) salt $FeCl_2$ in the presence of trimethylsilyl chloride as a chlorine donor. Intramolecular reaction of carbamoyl azides leads specifically to the formation of five-membered rings.[352] The course of the metal-catalyzed reaction tends to involve radicals, even if such intermediates have not been trapped. This method has been applied to the total synthesis of the (–)-agelastatin A, by simply replacing $FeCl_2$ with $FeBr_2$ and using a different bromide donor (**Scheme 49**).[353]



Scheme 49

Based on the aminohydroxylation reported in equation 84, the replacement of the chiral oxaziridine by NFBS **125**, as the electrophilic agent trapped by the enolate, allows performing the aminofluorination of cinnamate esters.[354] Organocatalysis has also been used to target fluoroamines. The proline derivative **148** plays the dual role of iminium and enamine catalyst for the aminofluorination of unsaturated aldehydes then reduced into the corresponding alcohols (equation 126).[355]



(126)

7.19.6 Alkene Carboamination

7.19.6.1 Introduction

Reactions of alkenes allowing the concomitant formation of a C–N and a C–C bond can be referred to as carboamination reactions. The bond formation can occur in either order. In this chapter, the focus is on the addition of nitrogen to alkenes, so reactions where the C–N bond is, or believed to be, formed first will only be covered. Aminocarbonylation and aminohydroformylation reactions are also considered outside the purview of this chapter. For further information, the reader may refer to the recently published review on palladium-catalyzed alkene functionalization including Wacker-type processes and aminocarbonylation.[198]

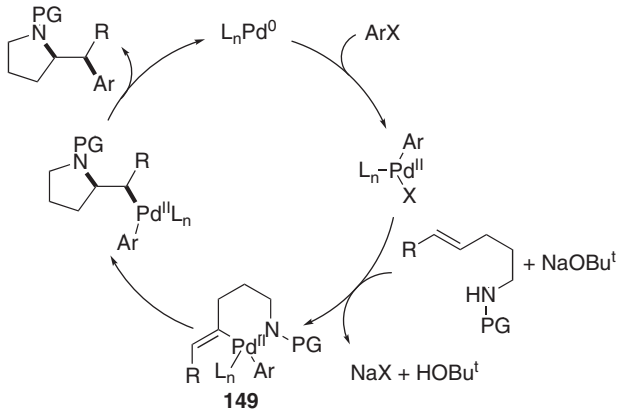
In the mid-2000s alongside the interest shown in metal-catalyzed diamination reactions of alkenes, attention turned toward the carboamination of alkenes. A number of groups have looked at both reactions simultaneously, presumably as the first steps of the two reactions are often very similar: the aminometallation of an alkene to form a new C–N bond. Attention has been focused primarily on palladium- and copper-mediated reactions. The majority of reactions fall under aminoarylation, utilizing aryl halides as the coupling partner for C–C bond formation. A few examples are also shown utilizing alkenyl and alkynyl halides. The

corresponding aminoalkylation has not been reported so far, and all the examples shown below are either fully intramolecular or intra-intermolecular processes (in most cases the aminometallation is intramolecular). No fully intermolecular process has been described. As a result the methodology is currently excellent for the synthesis of nitrogen heterocycles but lacks further diversity.

7.19.6.2 Transition Metal-Mediated Reactions

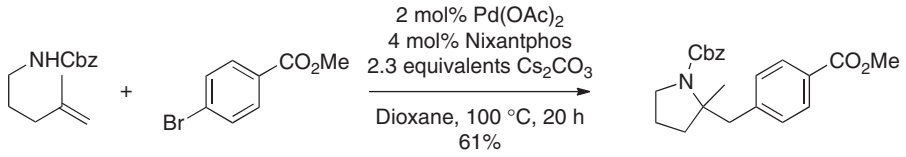
7.19.6.2.1 Palladium

The majority of work published on carboamination has been on the palladium-catalyzed method for the synthesis of heterocycles. Since a number of comprehensive reviews in this area have appeared,[356–358] this section will highlight some of the heterocyclic scaffolds that can be accessed in this way. In 2004, the group of Wolfe published its seminal paper that described the insertion of an alkene into a Pd-N bond to form both a new C–N and C–C bond, that is, the carboamination product.[359] This initial work provides a method to form *N*-aryl pyrrolidines. The following mechanism is proposed; the aryl halide oxidatively adds to the palladium(0), followed by reaction of the base and γ-(*N*-arylamino)alkene, to give intermediate **149**. *Syn*-alkene insertion and, then, reductive elimination gives the desired product (**Scheme 50**). Mechanistic studies and close examination of the side-products support this mechanism.[360]



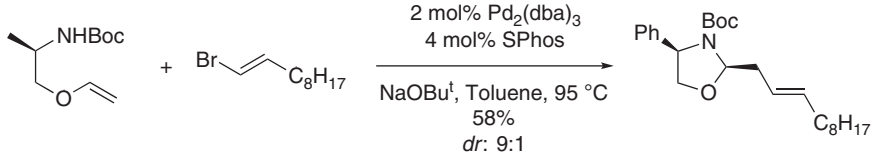
Scheme 50

Further work has shown that cesium carbonate can be used as the base allowing application of the reaction to triflates and more sensitive functional groups such as esters, nitro groups, and enolisable ketones (equation 127). A variety of different nitrogen-protecting groups, as well as a number of different substitution patterns on the alkene substrate, can be tolerated.[361]



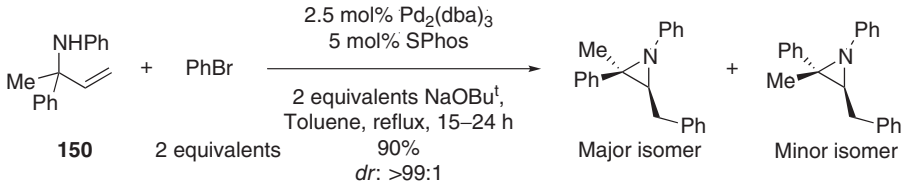
(127)

Using similar conditions, with only slight changes to the ligand, palladium source, and temperatures used, the reaction can be extended to the formation of various five-membered heterocycles such as pyrazolidines,[362] oxazolidines,[363] isoxazolidines,[364] and imidazolidin-2-ones.[365] Good yields and good-to-excellent diastereoselectivities are obtained. A few examples also show that alkenyl halides are viable coupling partners (equation 128).



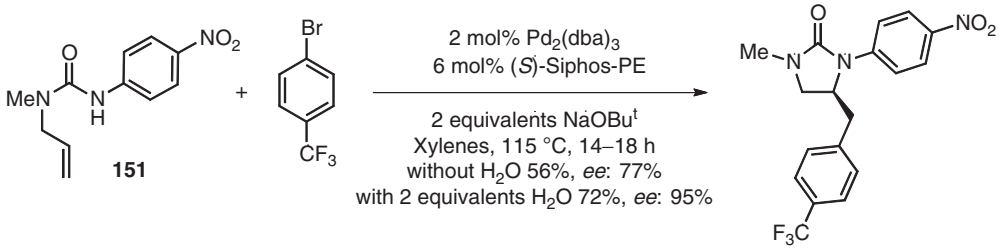
(128)

The reaction can be extended to create heterocycles of other sizes, for example, aziridines,[366] piperazines,[367] and morpholines.[368] Starting from *N*-phenylallylamines, high yields of aziridines are obtained with a variety of aryl and alkenyl bromides and chlorides (equation 129). However, the diastereoselectivity depends on sterical factors. When, for example, the phenyl group of **150** is replaced with the bulkier *tert*-butyl group, the diasteresoselectivity falls to 59:41.



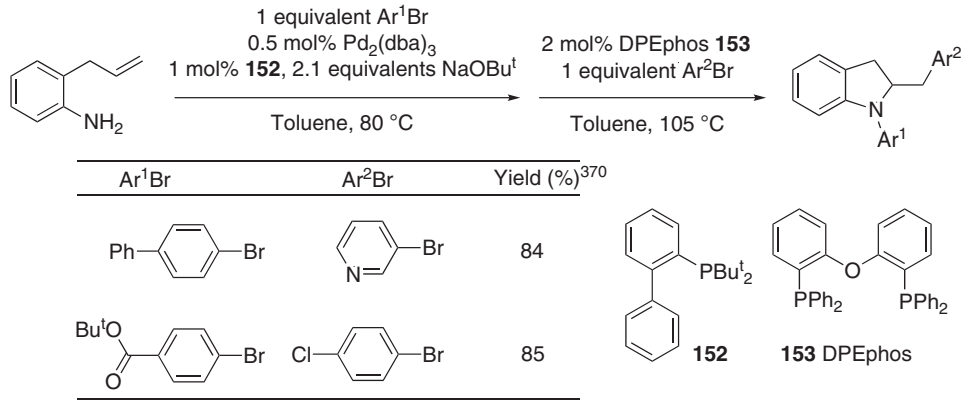
(129)

Enantioselective carboamination has been achieved from *N*-allyl urea **151** to give imidazolidin-2-ones with good-to-excellent enantiopurity (equation 130).[369] Electron-withdrawing groups on the aromatic group of the cyclizing nitrogen increased the level of enantioselectivity. The reaction can be performed with a number of aryl halides but *ortho*-substituents caused a slight lowering of yield. Interestingly, the addition of water improved the enantioselectivities and reproducibility of some of the examples. Using the same ligand, opposite stereoinduction is obtained for pyrrolidine formation, indicating that the enantiodetermining step changes between the two substrates even though the overall mechanisms appear to be very similar.

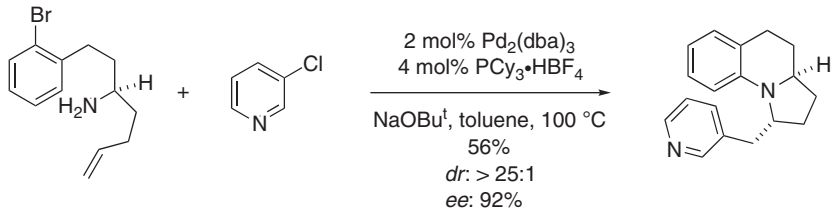


(130)

Development of the reaction has shown that a one-pot procedure can be developed in which *N*-arylation is performed before the carboamination step. In the case of 2-allylaniline, the carboamination has been performed *in situ* after *N*-arylation to give *N*-aryl-2-benzylindolines in good yields.[370] Key to the success of the reaction is the addition of a bisphosphine ligand bis(2-diphenylphosphinophenyl)ether (DPEphos) **153** to switch reactivity after the consumption of the first aryl bromide, and before addition of the second aryl bromide (**Scheme 51**). This allowed two different aryl groups to be used. The *N*-arylation can also be an intramolecular reaction giving access to tricyclic heterocyles (equation 131).[371]



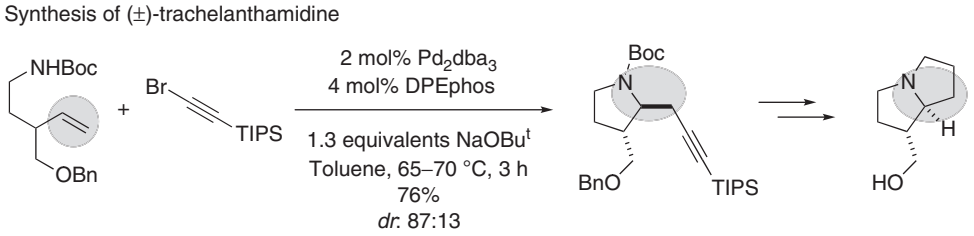
Scheme 51



(131)

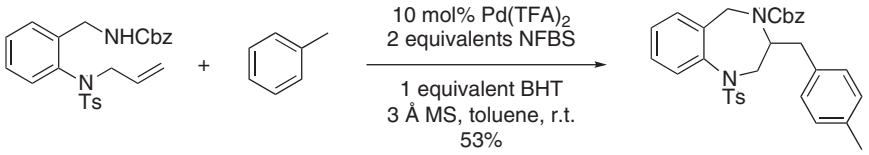
Carboamination with palladium has been extended to include aminoalkynylation using triisopropylsilyl ethynyl bromide.[372] Excellent diastereoselectivity is achieved for *cis*-2,5-disubstituted pyrrolidines. Natural product (±)-trachelanthamidine has been

synthesized to exemplify the method (Scheme 52). A similar reaction involving triisopropylsilyl ethynylbenziodoxolone can be utilized for the synthesis of the related lactams from *N*-tosyl amides and also works with alkenyl ureas and carbamates.[373] Good yields and reasonable diastereoselectivities are observed.



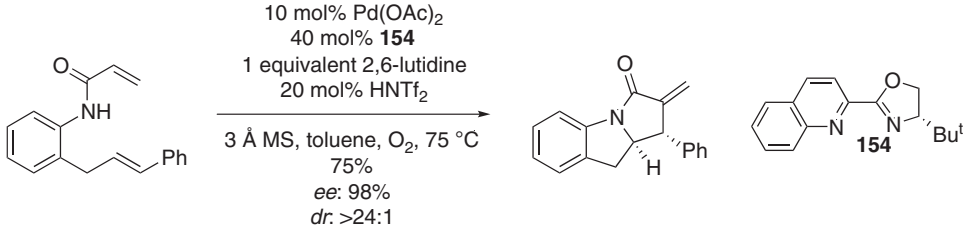
Scheme 52

A couple of other procedures have been reported in which the mechanism does not follow a 'classic' palladium(0/II) catalytic cycle. A number of products containing both pyrrolidine and indole heterocycles are accessible in reasonable yields and excellent enantio- and diastereoselectivity, under conditions in which the second carbon nucleophile is added outside the palladium cycle to a quinone methide intermediate.[374] However, a large excess of the second nucleophile is needed. Methods using high-valent palladium have also been studied. An NFBS-promoted palladium-catalyzed reaction, which is assumed to go through a palladium(II/IV) catalytic cycle,[274] allows the C–H activation of arenes, avoiding the need for aryl halides as the coupling partner. A variety of five-, six-, and seven-membered nitrogen heterocycles is formed (equation 132). Electron-rich arenes and halobenzenes are effective coupling partners, whereas electron-poor arenes, such as nitrobenzene, do not react. Worthy of mention is that with bromobenzene no participation of the Ar–Br bond is observed. The regioselectivity of the reaction is high with monosubstituted arenes giving exclusively the *para*-products. A number of different nitrogen-protecting groups are tolerated.



(132)

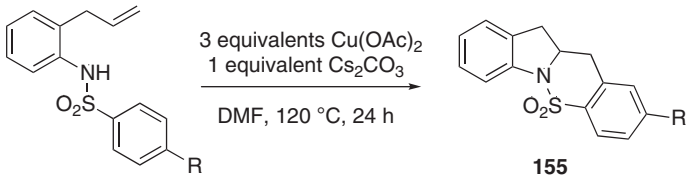
Oxidative aminations proceed via aminopalladation and then β-H elimination to give the aminoalkene. If this process can be interrupted by a coupling sequence (i.e., β-H elimination is disfavored) then C–C bond formation may occur. A typical example is the palladium(II)-catalyzed enantioselective tandem oxidative cyclization in which aminodialkene substrates undergo C–N and C–C bond formation to give a variety of indolines in good yield and high enantioselectivity (equation 133).[375] A number of different aryl substituents can be tolerated including halides, methyl, and methoxy groups.



(133)

7.19.6.2.2 Copper

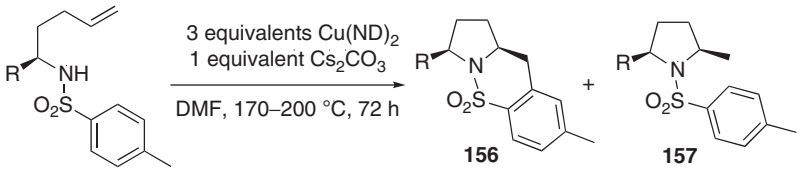
As with diamination (see Section 7.19.4.2.2.2), copper-mediated carboamination reactions were first reported with stoichiometric quantities of copper. Intramolecular carboamination occurs efficiently from tosyl-protected *o*-allylanilines to give tetracycles of type **155** under these conditions.[376] The reaction works best with electron-rich substrates. *Meta*-substituents on the arenesulfonamide moiety give regioisomeric mixtures with a preference for the *ortho*-isomer. DMSO can be added to increase the yields though the magnitude of the increase is dependent on the substrate (equation 134).



R	Yield (%) without DMSO	Yield (%)[376] with DMSO
Me	69	73
OMe	43	63
NO_2	–	24

(134)

The reaction has been extended to γ-alkenyl amides and imides for the formation of piperidines, through the use of different carboxylate ligands on copper (see equation 98) and increasing the temperature and time of the reaction.[377,378] In many of the examples, hydroamination products (e.g., **157**) have been isolated as significant side products (equation 135). The copper-mediated carboamination method has been further extended to the synthesis of pentacyclic sultams.[379]

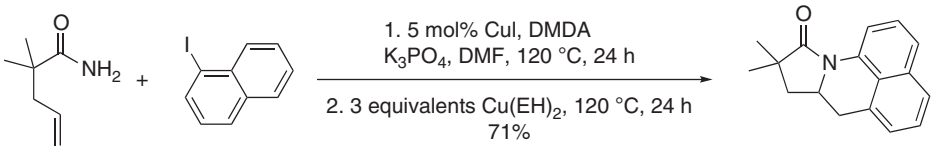


R	Yield **156** (%)	Yield **157** (%)[377]
Pr^i	49	25
Bu^t	34	15
Pr^iCH_2	49	20
Me	48	15
Bn	50	22

(135)

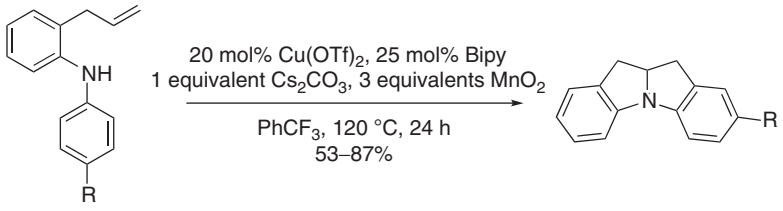
The authors have examined the mechanism and discounted a number of possible mechanistic pathways, such as the initial C–N formation occurring via addition of a nitrogen radical.[377] The current evidence points to a *syn*-aminocupration as the first step, generating the C–N bond and an unstable organocopper(II) species that homolyzes to give a carbon radical that cyclizes onto the arene. The achievement of an enantioselective catalytic variant (see **Scheme 54**) of the reaction indicates that the Cu is involved in the C–N bond-formation step. When TEMPO is added to the reaction, the oxyamination product corresponding to trapping the carbon radical is obtained. The preference for the *ortho*-regioisomeric product when *meta*-substituents are present on the sulfonamide also supports this. However, the possibility that organocopper species might be involved in the cyclization step has not been ruled out.

The preparation of the substrates via *N*-arylation leads to small amounts of the carboamination product, which has been exploited for the development of a one-pot procedure where the *N*-arylation is followed by carboamination (equation 136).[378]



(136)

All the above examples are stoichiometric and in some cases require up to three equivalents of copper. A catalytic version has been developed, allowing the amount of copper to be reduced to 0.2 equivalent.[380] Either MnO_2 or O_2 can be used as the oxidant. The functional group tolerance is broad, although once again *meta*-substituents on the cyclizing arene give regioisomers, with a slight preference for *ortho*-products. No difference in yields is observed if the substituents are switched to the other phenyl ring (equation 137). Once again a one-pot procedure has been used to first perform the *N*-arylation and then the carboamination.



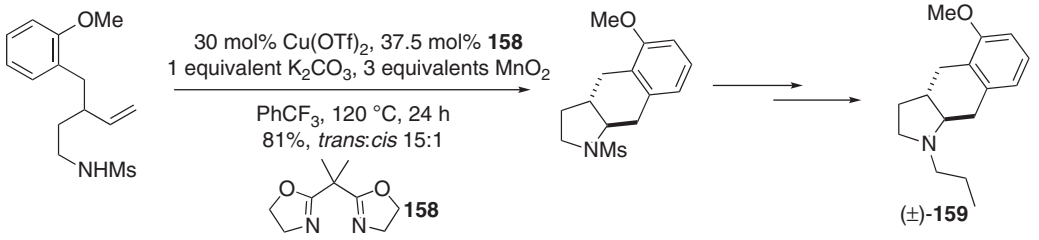
R = H, Me, OMe, SMe, F, NO_2

(137)

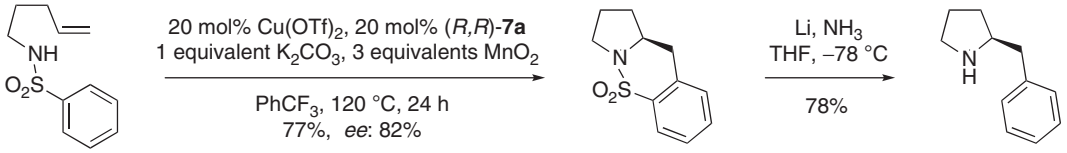
Diastereoselective carboamination can be achieved in the presence of the achiral bis(oxazoline) ligand **158**, allowing the synthesis of known 5-HT_{1A} receptor anatagonist **159**, in good overall yield (**Scheme 53**).[381]

The reaction has been rendered enantioselective by the use of chiral box-ligands (*R*,*R*)-**7a**. γ-Alkenyl arylsulfonamides have been cyclized in moderate-to-excellent yields (45–99%) and excellent enantioselectivities (80–97% *ee*) (**Scheme 54**).[381,382] The resulting cyclic sulfonamides can be reduced to the corresponding 2-benzylpyrrolidine. Allylaniline and allylbenzylamine derivatives gave reasonable yields but lower enantioselectivities.

The reactions with substrates disubstituted in the allylic position (**160**) gave excellent chemoselectivities. The aromatic ring in the allylic position cyclizes in preference to the *N*-arylsulfonyl ring, regardless of the substitution of the latter, giving rise to

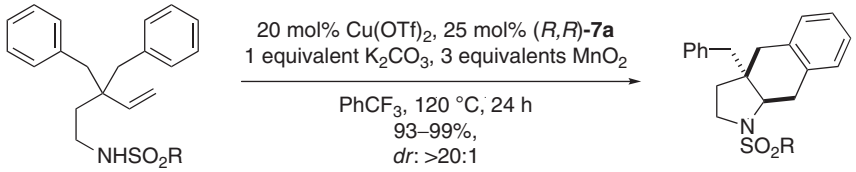


Scheme 53



Scheme 54

hexahydro-1*H*-benzo[*f*]indoles (equation 138).[381] As the aryl ring on the sulfonamide is no longer required for product formation, a number of protecting groups can be used.

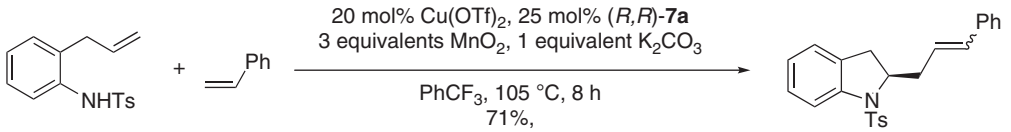


160

R = Me, Ph, *p*-Tol, *p*-NO_2Ph, *p*-MeOPh, *p*-ClPh

(138)

The reaction has been extended to an intra-intermolecular version by combining the γ-alkenyl sulfonamide with an external alkene, 1,1-diphenylethene being the most reactive coupling partner. This allowed the development of an intramolecular alkene amination/intermolecular Heck-type coupling cascade.[383] A variety of indolines and pyrrolidines has been accessed in good yields (62–88%) and enantioselectivities (71–95%) (equation 139). Tetrahydroisoquinolines have also been isolated albeit in lower yields.



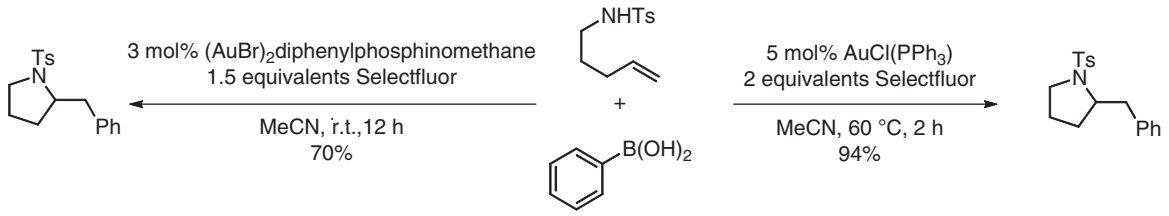
(139)

However, although significant progress has been made in the use of copper-catalyzed conditions for carboamination, the temperatures for the reactions remain high (> 100 °C) limiting the applicability of the reaction in more complex synthetic settings.

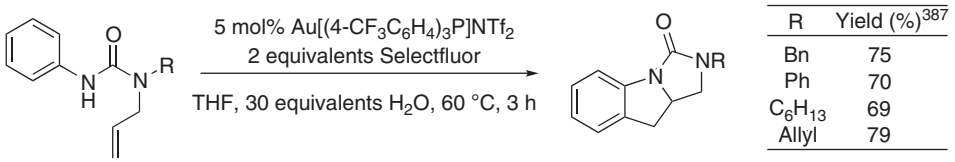
7.19.6.2.3 Gold

A couple of methods utilizing gold(I/III) catalysis for carboamination have recently emerged. A variety of substituted pyrrolidines have been obtained in an intra-intermolecular reaction from γ-alkenyl sulfonamides and arylboronic acids (**Scheme 55**).[384,385] The reaction tolerates *ortho*-substituents and a variety of different phenyl substituents (esters, aldehydes, and halides). However, electron-rich boronic acids such as those derived from anisole are incompatible with the reaction conditions as they are oxidized by Selectfluor. The reaction has been extended to the formation of piperidines. Two different mechanisms have been proposed depending on the type of gold catalyst used. A bimolecular reductive elimination pathway appears to be operative with bimetallic gold complexes,[386] whereas the reaction in the presence of mononuclear gold catalysts possibly follows a more traditional transmetallation/reductive elimination cycle.

A similar procedure has been applied to access tricyclic indolines from *N*-allyl-*N*-phenyl urea substrates via aminoauration followed by C–H functionalization (equation 140).[387] The use of water as an additive is essential for good yields. Methoxy, chloro, and bromo substituents are not tolerated, and *ortho*-substituents on the phenyl lead to lower yields. Low diastereoselectivity, in addition, is generally observed but the careful choice of reaction conditions allowed the formation of diastereomerically pure tricyclic 3-benzazepines in good yield via activation of one of the phenyl rings in the backbone of **161** (equation 141).[294]

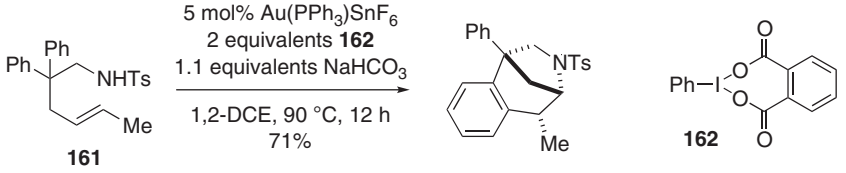


Scheme 55



R	Yield (%)[387]
Bn	75
Ph	70
C_6H_{13}	69
Allyl	79

(140)

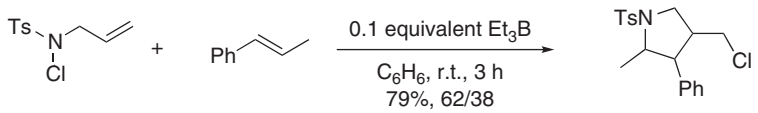


(141)

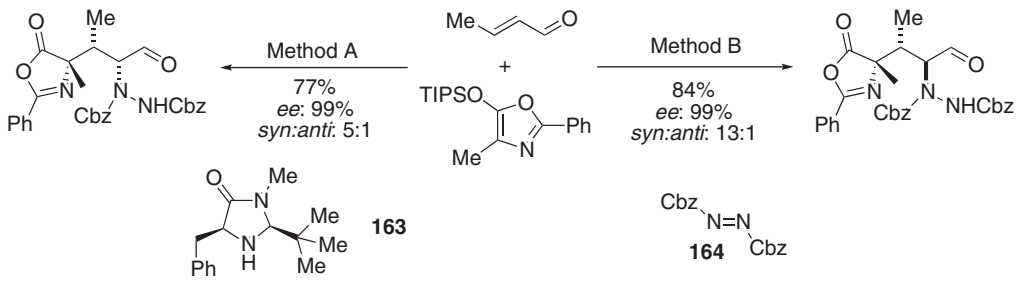
7.19.6.3 Metal-Free Reactions

7.19.6.3.1 Nitrogen radicals

Nitrogen radicals,[388] though not as widely used as carbon radicals in organic synthesis, are known to undergo cyclization with unsaturated systems such as C=C double bonds. The resulting carbon radical can then react in a number of ways such as H-abstraction leading to hydroamination products, trapping with an oxygen agent (see Section 7.19.3.4), or by the addition to another unsaturated carbon system before termination by H-abstraction/halide trapping. The latter process gives products where 1,2-carboamination of alkenes has occurred. Reactions of this type have often been used in natural product synthesis.[389] Rarely have these reactions been studied in a systematic fashion. One example where the reaction scope has been more systematically investigated is the radical [3 + 2] annulation of *N*-allyl-*N*-chlorotosylamide with alkenes reported by Oshima and coworkers (equation 142).[390]



(142)



Method A: 1. 10 mol% **163**, MeCN, H_2O, –40 °C, 12 h; 2. 20 mol% (*S*)-proline, **164,** MeCN, –40 to –15 °C, 10 h
Method B: The same as A except using (*R*)-proline

Scheme 56

7.19.6.3.2 Organocatalysis

Organocatalysis has not been widely utilized in carboamination, however, one example has been reported using the same catalytic system as seen in alkene oxyamination and diamination (see Scheme 34 and Section 7.19.4.4).[255] Although inherently limited to α,β-unsaturated aldehydes, the high selectivities and ease of diversification make it a promising method for the future (Scheme 56).

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7.20 Addition Reactions with Formation of Carbon–Sulfur and Carbon Selenium Bonds

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Glossary

Alcoxyselenenylation Addition reaction activated by an electrophilic selenium reagent in the presence of an alcohol (or water).

Anchimeric assistance The participation by a neighboring group in the rate-determining step of a reaction and in the stereochemical control.

Cyclofunctionalization Cyclization reaction of unsaturated substrates bearing, in a suitable position an internal nucleophile.

Hydrothiolation Addition reaction of a thiol to a double or triple bond.

Seleniranium ion Three membered ring including a positively charged selenium atom. It is the intermediate structure on the addition of electrophilic selenium reagents to carbon–carbon double bond.

7.20.1 Introduction

The addition reaction of electrophilic sulfur and selenium reagents represents a convenient methodology for the stereoselective functionalization of olefins affording the introduction of organosulfenyl and organoselenenyl moieties (*see* Chapter 4.06). The latter is generally used as versatile intermediate for the synthesis of much more complex molecules and can be considered suitable starting material for further stereoselective chemical manipulation.

Concerning the formation of carbon–sulfur bond, the hydrothiolations are currently largely studied protocols that, depending on the reaction conditions and on the nature of the substrates, can proceed with high chemo-, regio-, and stereoselectivity. Much more interesting, in the case of organoselenium analogs the inter and intramolecular electrophilic addition that are here reported including the discussion of their regio- and stereoselectivity.

During the past decades, a great effort has been directed toward the development of efficient procedures for the enantioselective functionalization of organic compounds. Some examples of reaction controlled by the chirality of the substrate as well as by the chirality of the reagents are reported and discussed here.

7.20.2 Addition Reactions to C═C Bonds with Formation of Carbon–Sulfur Bonds

7.20.2.1 Electrophilic Sulfur Addition to C═C Bonds

In comparison with organoselenium reagents, the electrophilic sulfur containing analogs have been only moderately applied in addition reactions to carbon–carbon double bonds. Electrophilic sulfur reagents are commonly divalent (e.g., sulfur alkyl or aryl monochlorides and sulfur dichloride) and only rare examples of hexavalent reagents have been reported.

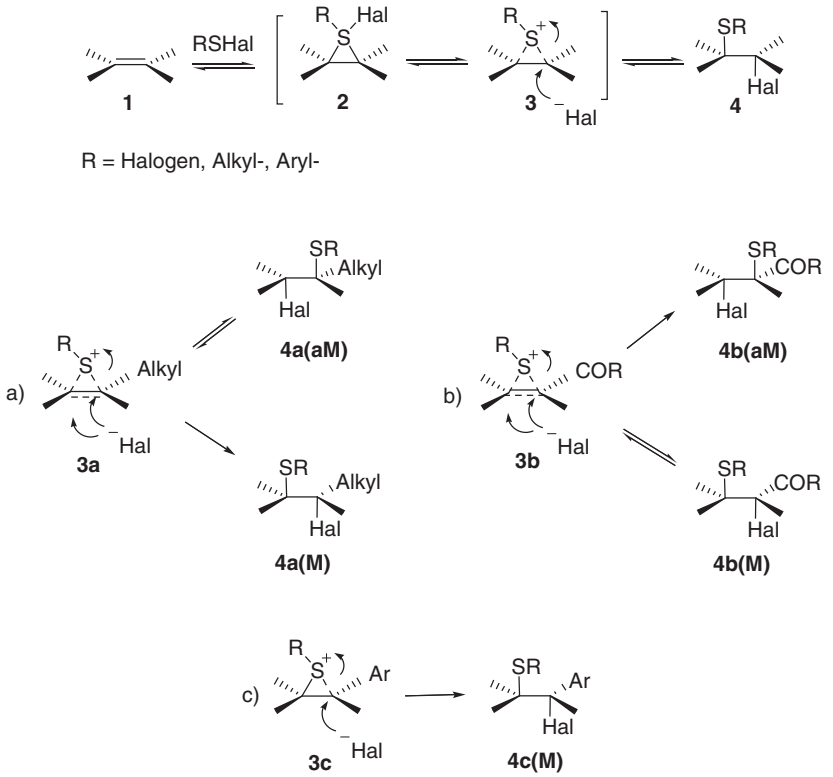
The main feature of these reactions is the stereospecific formation of the anti-addition products, rationalizable with a mechanism involving first the formation of cyclic cationic intermediates,[1] followed by the S_N2 nucleophilic attack of a nucleophile to the ring carbons of a thiiranium or thhiirenium ion occurring from the opposite side of the leaving group.[2]

The electrophilic addition of sulfenyl chlorides to alkenes **1** (or alkynes) may be regarded as a nucleophilic attack of the double (or triple) bond to the sulfur atom and the three classical mechanisms of a nucleophilic substitution could be envisioned S_N1,

S_N2, Ad_N-E. In the latter case, the formation of an episulfurane intermediate **2** has been demonstrated to be in equilibrium with a thiiranium ion **3** that is stereospecifically opened by the nucleophile leading **4**.[3]

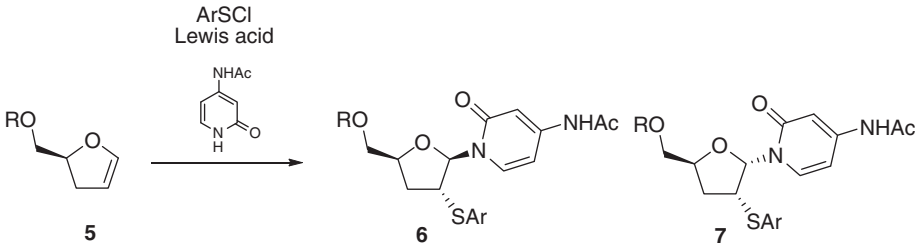
When the addition reaction occurs to unsymmetrical alkenes, two isomeric adducts could be obtained according to Markovnikov (M) and anti-Markovnikov (aM) orientations in a ratio that depends mainly on the nature of the used alkene.

Alkyl substituted olefins lead to a thiiranium ion (**3a**) that is predominantly opened affording the kinetic anti-Markovnikov products **4a**(aM) which rapidly undergo rearrangement to the thermodynamically favorite Markovnikov structure **4a**(M) (Scheme 1(a)). When the carbon–carbon double bond is conjugated to a phenyl or a vinyl group, the ring opening reaction of the cationic intermediate (e.g., **3c**) occurs directly with the Markovnikov orientation **4c**(M) (Scheme 1(c)). Only when the conjugation is with a carboxyl group (**3b**), the kinetically controlled Markovnikov oriented adduct **4b**(M) undergoes further rearrangement to the thermodynamically stable anti-Markovnikov derivative **4b**(aM) (Scheme 1(b)). DFT studies of the regioselectivity of addition of sulfenyl chloride to functionalized alkenes evidenced that when the substituent is an alkyl or carboxyl group the most likely intermediate is an episulfonium ion whereas it will be a carbonium ion when the substituent is a phenyl group.[4]



Scheme 1 Mechanism of electrophilic sulfenylation.

An electrophilic sulfenylation has been reported for the stereoselective glycosylation of furanoid glycals **5** with pyrimidine and purine bases. The use of *N*-acyl-cytosine as base afforded the products **6** and **7** in ratios and yields reported in Table 2 (Scheme 2).[5]



Scheme 2 Addition of ArSCl and N-Ac-cytosine to glycals.

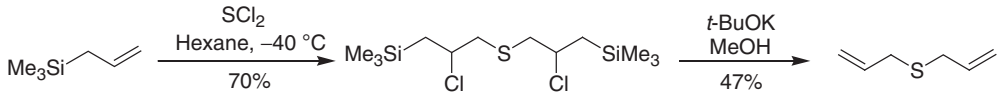
The stereoselectivity is not affected by the size of the aryl sulphenyl chloride (Table 1 entries 1 and 2 vs. 3 and 4) and the carbon sulfur bond formation occurs in the opposite site with respect to the substituent on the glycal ring. Differently much more important is the presence and the nature of the Lewis acid. The best results have been reported for tin tetrachloride (Table 1 entries 1 and 3) that was supposed to form a tin–sulfur complex, which increases the size of the intermediate blocking the face occupied by the sulfur. Nonthiophilic Lewis acids (such as TMS-OTf, Table 1 entries 2 and 4) showed a reduced stereoselectivity, confirming the hypothesis.

Table 1 Stereoselectivity of glycosylation (Scheme 2)

No.	*Ar-*	*Lewis acid*	*6:7*	*Yield (%)*
1	Phenyl-	$SnCl_4$	95:5	65
2	Phenyl-	TMS-OTf	83:17	60
3	2,4,6-Triisopropylphenyl-	$SnCl_4$	96:4	70
4	2,4,6-Triisopropylphenyl-	TMS-OTf	86:14	73

Sulfur dichloride (SCl_2) is a good electrophilic reagent and it was demonstrated that it reacts with two equivalents of unsaturated substrates giving a double chlorosulfenylation with the formation of a bis-(2-chloroalkyl)sulfide as valuable intermediate for the synthesis of diallyl or dialkenyl sulfides. The regioselectivity is mainly dependent on the nature of the substrate and of the solvent. For example, the electrophilic addition of SCl_2 to aryl allyl ethers in dichloromethane proceeds with anti-Markovnikov orientation whereas allylsulfides afforded a mixture of Markovnikov and anti-Markovnikov products. Allyltrimethylsilane **8** are selectively functionalized by treatment with SCl_2 in hexane affording the Markovnikov oriented bis(2-chloro-3-(trimethylsilyl)propyl sulfide **9**.

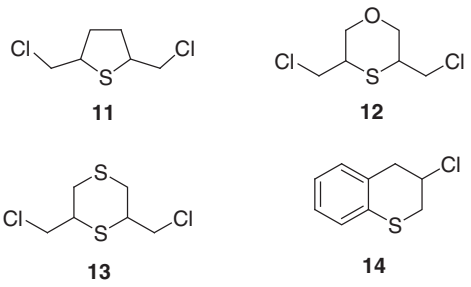
The halodesilylation by thermic treatment in the presence of a base leads to the diallyl sulfide **10** in moderate yield (Scheme 3).[6]



8 **9** **10**

Scheme 3 Addition of SCl_2 to allyltrimethylsilane and subsequent halodesilylation.

When the sulfur dichloride reacts with diallyl systems, the double addition reaction affords five- or six-membered saturated heterocycles. 1,5-Hexadiene, diallyl sulfide and diallyl ether showed anti-Markovnikov additions affording the cyclic compounds **11**, **12**, and **13**, respectively. In the case of allylbenzene derivatives, the regioselectivity is opposite (**14**) (Scheme 4).



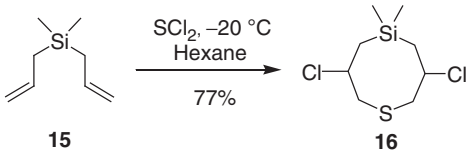
11 **12** **13** **14**

Scheme 4 Addition products of SCl_2 to different allyl systems.

Markovnikov orientation has been observed when sulfur dichloride is employed in the cyclization of diallyl dimethylsilane **15** to afford the uncommon height-membered heterocycle **16** (Scheme 5).[7]

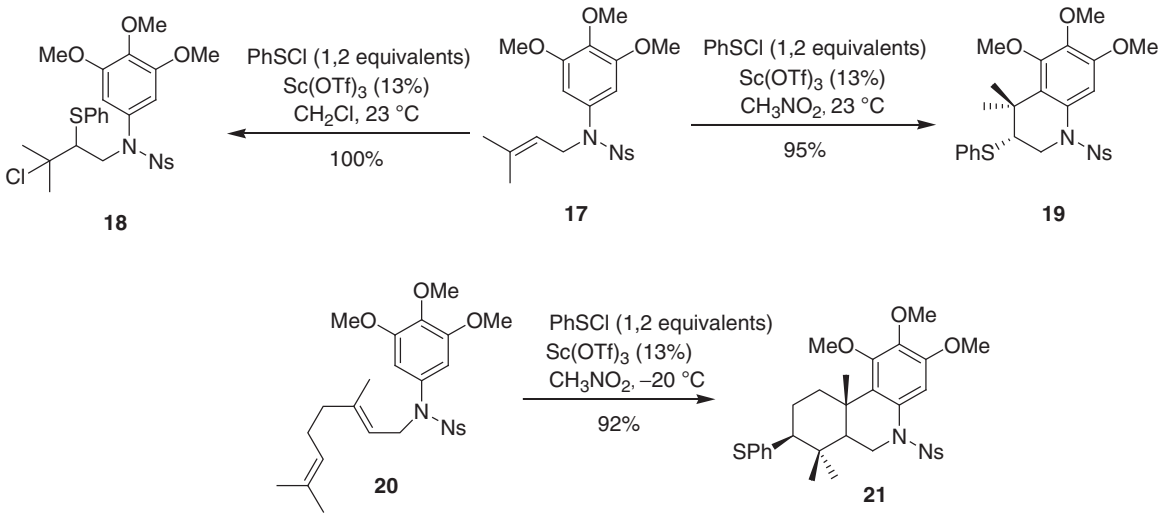
Recently Shav et al. reported the first catalytic alkene cyclization reaction mediated by sulfur-based electrophiles providing an excellent method for the synthesis of densely substituted tetrahydroquinolines, useful intermediates for the synthesis of natural products and nitrogen analogs of diterpenoids.

The reaction proceeds in the presence of a catalytic amount of $Sc(OTf)_3$ as precatalyst of the corresponding protic acid, and is strongly affected by the solvent polarity. Starting from **17** the acyclic addition product **18** was exclusively obtained when the reaction was effected in dichloromethane. Switching to a polar solvent the carbocyclization product **19** was obtained in 95% yield as the result of an intramolecular attack of the aromatic carbon to a thiiranium intermediate.



Scheme 5 Addition of SCl_2 to diallyl dimethylsilane **15.**

Using similar reaction conditions the same authors obtained the bicyclization of electron-rich geranylated aniline derivatives (e.g., **20**) affording stereoselectively and in excellent yield the corresponding *trans* fused tricyclic compounds (**21**) through 'chair–chair' conformations (Scheme 6). Similar results were obtained using the analog PhSeCl.[8]



Scheme 6 Carbocyclizations promoted by PhSCl.

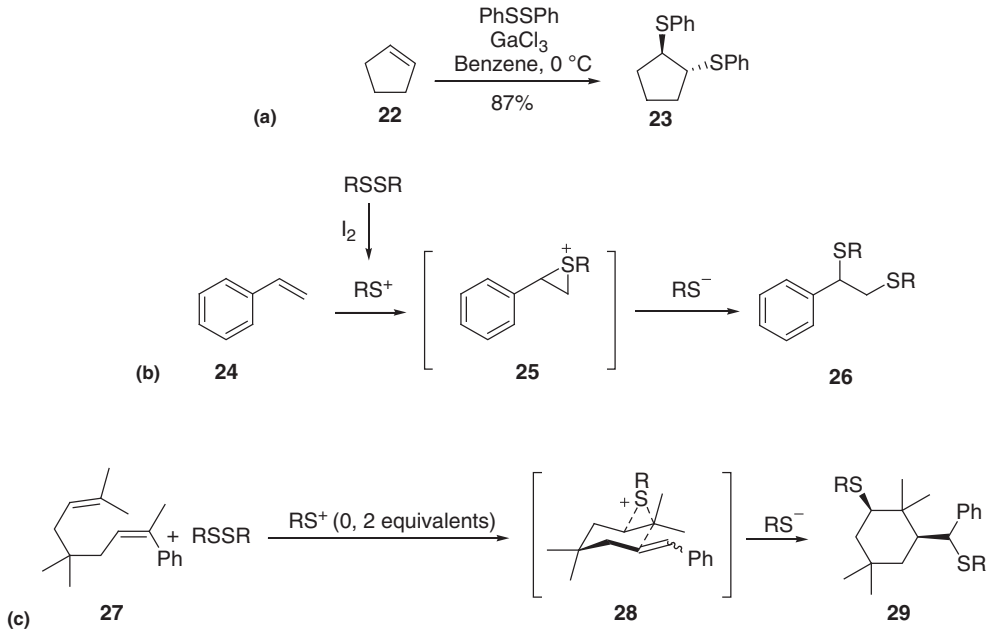
The disulfenylation reaction of unsaturated hydrocarbures is a useful strategy for the preparation of bis-alkyl- and aryl disulfides and a number of methods are known to affect this conversion. For this purpose, disulfides can be used in the presence of Lewis acids in order to increase the electrophilicity of the sulfur atom. The reaction that involves the formation of a thiiranium intermediate deriving from the nucleophilic attack of a carbon–carbon double bond to a thiosulfonium-like species, is highly stereoselective in favor of the *trans* addition-products. As an example the disulfenylation of cyclopentene **22** in the presence of diphenyl disulfide and gallium trichloride affording *trans*-1,2-di(phenylthio) cyclopentane **23** in good yield is reported in Scheme 7(a).[9]

More recently, Wang and Chen reported that this addition reaction can be effected using a catalytic amount of iodine to generate starting from dialkyl or diaryl disulfides, the electrophilic sulfenylating species RS^+ that, reacting with aryl substituted olefins **24**, affords the corresponding thiiranium ion **25**. This intermediate reacts with a second molecule of disulfide generating the adduct **26** and a molecule of sulfonium ion that continues the cycle allowing the use of a catalytic amount of iodine (Scheme 7(b)).[10] The reaction has been successfully performed in dichloromethane as well as in water and experimental evidences have dispelled the involvement of a radical mechanism. The yields and the reaction rate are not affected by the presence of radical trapping agents, such as 2,6-di-*tert*-butyl-4-methylphenol.

The disulfenylation of carbon–carbon double bonds in the presence of a disulfide can also be initiated by a catalytic amount of the electrochemically generated ArS^+. Using this procedure, the stereoselective carbocyclization of the diene **27** was directly realized under in-cell electrolysis conditions using a catalytic amount of electric energy. The electrophilic sulfenylating species attacks the more nucleophilic double bond giving the intermediate **28** and the other carbon–carbon double bond opens the episulfonium ion giving the cyclic adduct **29** as a mixture of diastereoisomers differing for the geometry of the exocyclic chiral center.[11]

7.20.2.2 Sulfur Additions in Asymmetric Synthesis

During the past ten years, some developments in asymmetric sulfur addition to carbon–carbon double bond have been reported in the literature. Following the success obtained in the field of organoselenium reagents, Wirth first reported the synthesis of new chiral sulfur containing electrophiles (**30, 31**) starting from the corresponding disulfides, describing their application in cyclofunctionalization reactions.



Scheme 7 Disulfenylation reactions.

Alkenoic acid (**32**) and alkenol (**34**) were cyclized into the corresponding lactone **33** and tetrahydrofuran (**35**) but the yields as well as the stereoselectivity are in both cases only moderate (Scheme 8(a) and (b)).[12]

More recently, Denmark optimized an asymmetric procedure based on the use of chiral Lewis bases for the thiofunctionalization of unactivated alkenes. Using a BINAM derived selenophosphoramide catalyst (**36**) and *N*-phenylsulfenyl-phthalimide (NPSPh) as electrophilic sulfur source inter- and intramolecular functionalizations were achieved in good yields and good facial selectivity for a variety of substituted olefins.[13]

The results reported in Scheme 8(c) and (d) are relative to the cyclofuntionalization of the alkenoic acid **37** and the alkenol **34** affording the heterocyclic adducts **38** and **39**, respectively. They clearly put in evidence that this method is superior if compared to the use of optically pure electrophilic sulfenylating reagents both in terms of yields and of stereoselectivity.

In a similar way, Bronsted acids can be employed to affect asymmetric oxysulfenylation of olefins and sulfoetherification of alkenols (e.g., **41**). In the latter cases, the use of a D-tartaric acid-based catalyst (**40**) and trifluoroethyl benzenesulfenate, as sulfur source, afforded the corresponding tetrahydrofurans (**42**) with up to 63% *ee* (Scheme 8(e)).[14]

Intramolecular acid catalyzed sulfamination is a convenient protocol for the synthesis of nitrogen containing heterocycles.[15] Pyrrolidines can be efficiently synthesized by cyclization of the corresponding amino-alkenes with PhSOMe. Using as catalyst a chiral phosphoric acid (**43**) the reaction can be effected in an asymmetric manner.

Cis-γ-aminoalkene **44** regioselectively cyclized to give the corresponding pyrrolidine **45** in 79% yield and 85% *ee* (Scheme 8(f)).[16]

7.20.2.3 Hydrothiolation Reactions

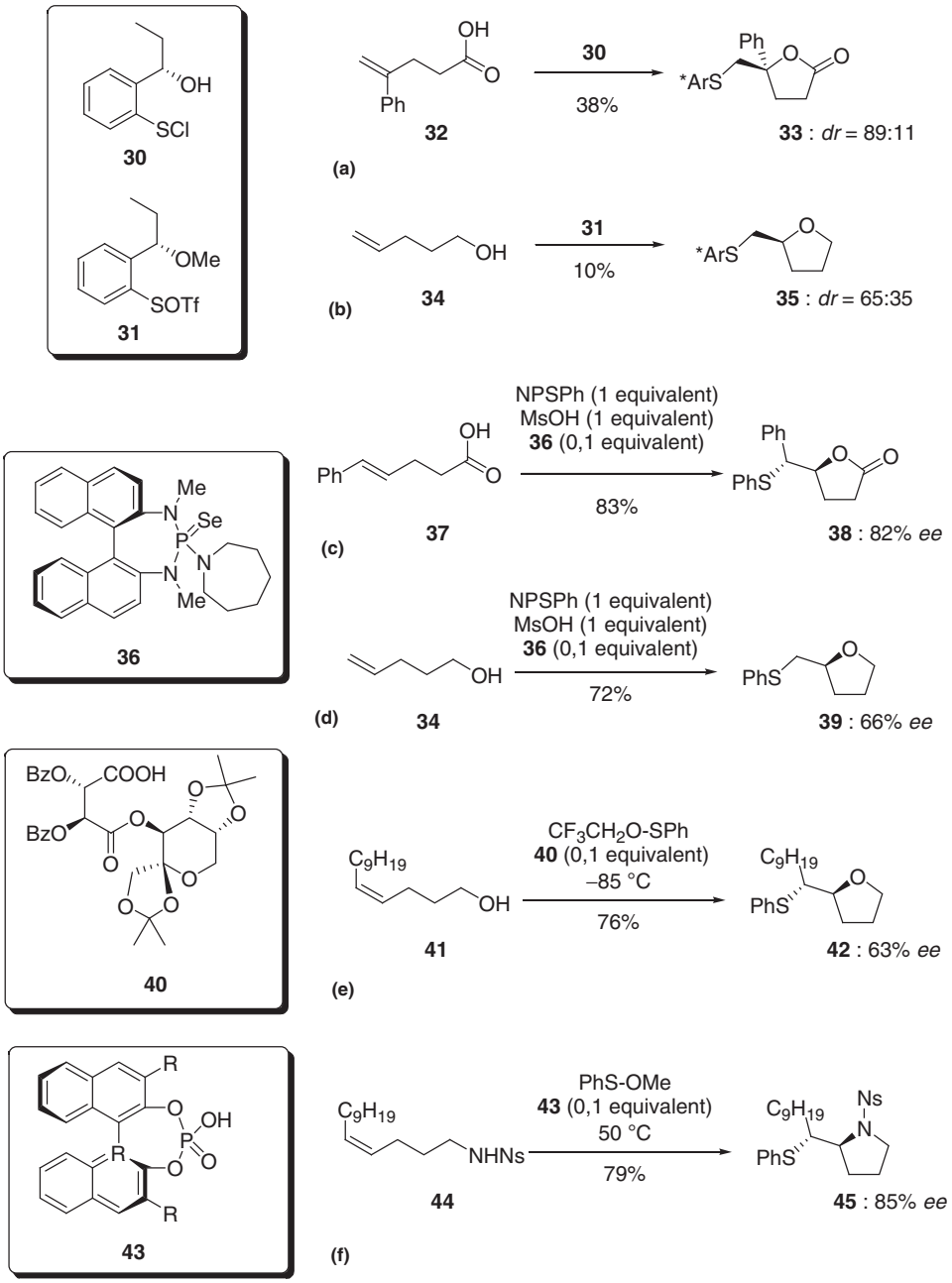
The addition of thiols to alkynes is one of the most important methods for the preparation of vinyl sulfides, commonly considered as useful synthetic intermediates. When the reaction is conducted under photochemical or basic conditions, usually there is no stereocontrol on the formation of the double bond. A mixture of *E* and *Z* anti-Markovnikov adducts is the result of these reactions that, in these cases, are also very slow even at high temperature.

Very recently a procedure catalyzed by ionic liquids has been reported. Using 1-*n*-butyl-3-methylimidazolium methylselenite, [bmim][$SeO_2(OCH_3)$], the hydrothiolation of terminal alkynes proceeds under mild and base-free conditions both with aromatic and aliphatic thiols. In all these cases, a mixture of the three possible isomers was obtained.[17]

The *E* anti-Markovnikov and the Markovnikov adducts are the main components of this mixture and they were always obtained in almost equimolar amount.

Similar conversions are much more selective when catalyzed by transition metals that control also the regioselectivity of the process. It has been reported that the regioselectivity mainly depends on the balance between a migratory insertion and the reductive elimination step.

Considering a terminal alkyne, after the activation of the sulfur–hydrogen bond mediated by a catalyst, the insertion into a metal–hydride bond affords anti-Markovnikov products whereas when the insertion occurs into metal–sulfur bond, the Markovnikov adduct is obtained in prevalence as *E* stereoisomer (Scheme 9). Because of these considerations, electronic and steric



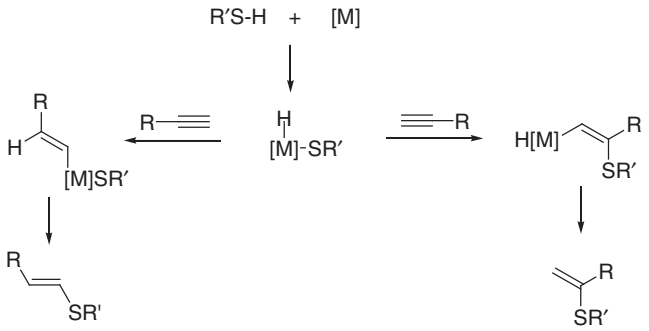
Scheme 8 Asymmetric cyclosulfenylations.

effects of both alkyne and catalyst are directly involved in determining the regio- and stereochemistry of the process. A comprehensive review on the C–S bond formation by metal catalyzed addition reaction of thiols to alkynes and alkenes has been very recently reported, including discussions on Pd-, Ni-, Rh-, Ir- and Pt-containing catalysts,[18] and for these reasons in this chapter only the most recent updates are reported.

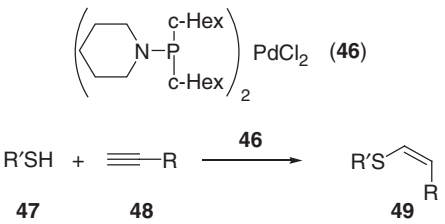
Dichloro bis[1-(dihexylphosphonyl)piperidine]palladium complex (**46**), already known as catalyst for C–C bond formation in coupling reactions, has been reported also as a surprising and versatile catalyst for alkyne hydrothiolation. Using 0.05 mol% of this complex, a number of aromatic alkynes and aromatic or aliphatic thiols were rapidly converted into the corresponding anti-Markovnikov thioethers in excellent yields and, for the first time, with *cis* configuration also in the presence of different funtionalities (Scheme 10).[19]

Some selected examples are reported in Table 2.

Indium(III) triflate has been proved to be a good catalyst for the hydrothiolation of terminal alkynes (**50**), and it is able to promote Markovnikov (**52**) and anti-Markovnikov (**54**) addition in the absence of any other cocatalysts.



Scheme 9 Metal catalyzed hydrosulfenylation.

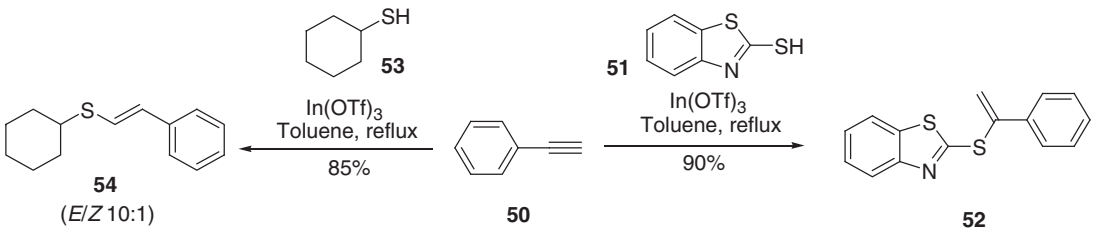


Scheme 10 Stereoselective *trans*-hydrothiolation.

Table 2 Hydrothiolation promoted by **46**

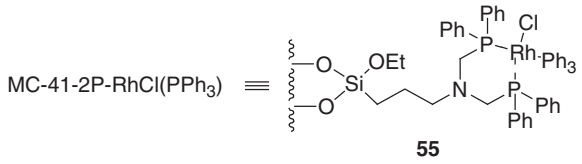
No.	*R*	*R′*	*Z/E*	*Yield (%)*
1	Phenyl-	Phenyl-	99:1	99
2	Phenyl-	*p*-MeO-C_6H_4	99:1	99
3	Phenyl-	*p*-NH_2-C_6H_4-	100:0	100
4	*p*-Br-C_6H_4	n-Octyl	96:4	100
5	2-Pyridyl	Phenyl-	100:0	100
6	Phenyl-	Benzyl	99:1	100

The key factor determining the regioselectivity is the nature of the thiol: Under the same reaction conditions heteroaromatic thiols (**51**) adds selectively according to the Markovnikov rule whereas the aromatic and aliphatic (**53**) ones show the opposite selectivity (Scheme 11).[20]

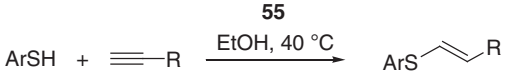


Scheme 11 Hydrothiolation catalyzed by In(III).

Rhodium *N*-heterocyclic carbene catalysts were reported for the hydrothiolation of alkynes under mild conditions. It was demonstrated that the regioselectivity could be strongly controlled by the nature of the ligand, offering a rational base for the design of regioselective and efficient new catalysts.[21] Wilkinson's catalyst [$RhCl(PPh_3)_3$] is known for its excellent activity toward the regio- and stereospecific anti-Markovnikov hydroselenenylation of terminal alkynes. Very recently, in order to overcome the problems deriving from the use of expensive and toxic transition metals as homogeneous catalysts, it was reported a new diphospino functionalized rhodium complex anchored to a mesoporous material (MC-41–2P-$RhCl(PPh_3)$) (**55**) (Scheme 12).[22]



55



Scheme 12 Stereoselective *syn*-hydrothiolation.

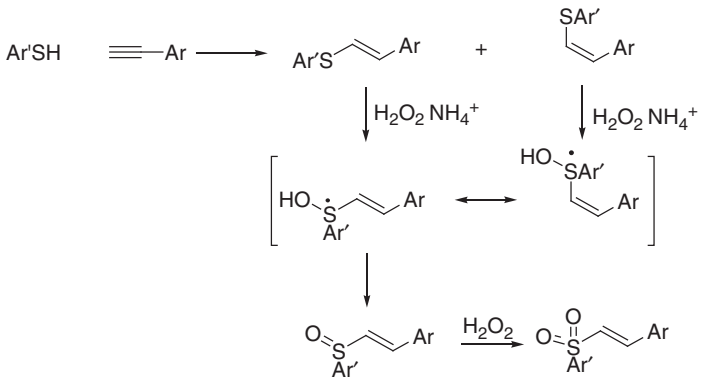
For a number of terminal alkynes, the reaction proceeds under very mild conditions and in good yields, affording the corresponding (*E*)-vinyl sulfides. Some selected examples are reported in Table 3.

Table 3 Hydrothiolation promoted by **55**

No.	*R*	*Ar′*	*Yield (%)*
1	Phenyl-	Phenyl-	95
2	*p*-Me-C_6H_4-	Phenyl-	93
3	Phenyl-	*p*-Cl-C_6H_4-	97
4	n-Hexyl-	Phenyl-	81
5	1-Cyclohexenyl-	Phenyl-	72

Under oxidative conditions, the reaction of an aryl or alkyl thiol with a terminal alkyne produces the synthesis of vinyl sulfones with a strong stereoselectivity in favor of the isomer *E*. The reaction proceeds in one-pot and involves a two-step radical mechanism that has been also proved by NMR experiments and by the evidence that, in the presence of radical inhibitors, the reaction rate was considerably decreased.

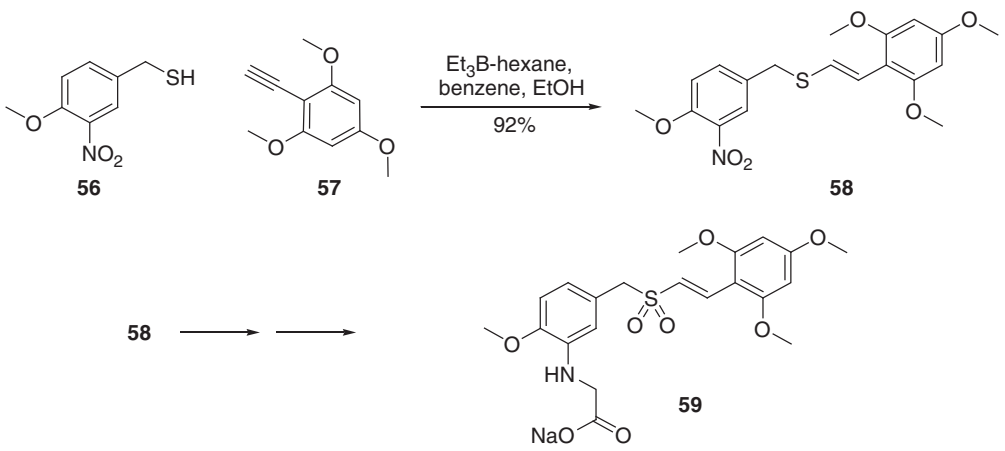
The success of the protocol depends on the presence of ammonium chloride as additive that was supposed to form with the hydrogen peroxide, an adduct similar to carbamide peroxide. The first step of the reaction consists in the anti-Markovnikov addition of the thiol to the alkyne followed by a radical oxidation of the sulfur to afford the *E*-vinyl sulfoxide that, by further oxidation, is converted into the corresponding sulfone (Scheme 13).[23]



Scheme 13 One-pot hydrothiolation and oxidation.

A free radical addition of benzyl thiol **56** to 2,4,6-trimethoxyphenylacetylene **57**, in the presence of Et_3B-hexane, has been proposed for the stereoselective synthesis of styryl benzyl sulfides **58**, a procedure successfully applied on the synthesis of the anticancer agent **59**. The hydrothiolation product **58** is subsequently subjected to the oxidation of the sulfur and the reduction of the nitro group to amine (Scheme 14).[24]

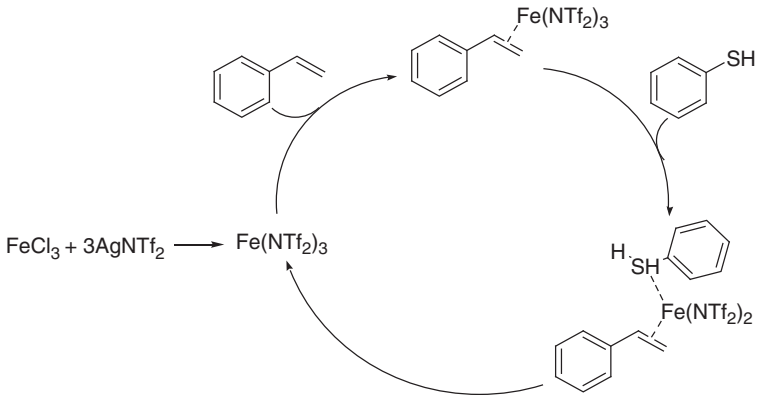
The hydrothiolation of carbon–carbon double bond can proceed according to two different mechanisms: a free radical or an electrophilic pathway. In the first case the anti-Markovnikov product is exclusively obtained and these procedures can be effected using mild reaction conditions whereas in the latter case over stoichiometric amount of Bronsted or Lewis acids is generally required.



Scheme 14 Synthesis of the anticancer agent Z(ON 01910Na).

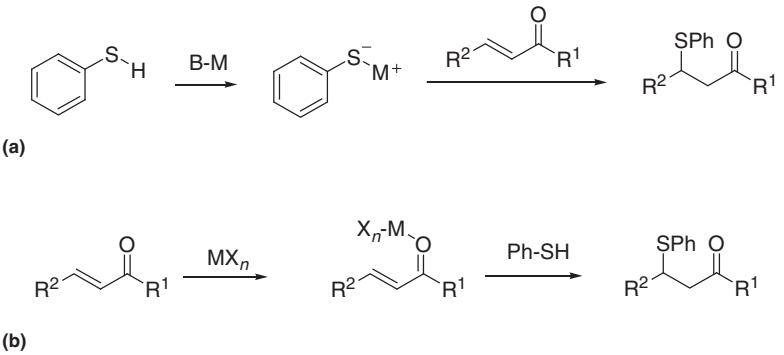
Very recently the Markovnikov hydrothiolation of styrene derivatives using bis(triflimide)iron(III) salt as catalyst has been reported.[25]

The iron(III) salt activates at the same time the benzylic position of the double bond and the nucleophile toward the addition, as depicted in Scheme 15. Using this procedure, a number of benzyl thioethers having a large number of different substituents have been synthesized in excellent yields and very mild conditions.



Scheme 15 Iron catalyzed Markovnikov hydrothiolation.

Carbon–sulfur bond formation can be also obtained by conjugate addition of thiols to α,β-unsaturated carbonyl compounds or nitriles that can be realized according to two different strategies: (1) nucleophilic activation in the presence of a base (Scheme 16(a)) and (2) electrophilic activation in the presence of Lewis acids (Scheme 16(b)).

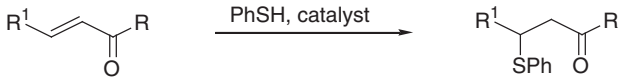


Scheme 16 1,4 Addition reaction to enones.

Under nucleophilic conditions, the base deprotonates the selenol producing a thiolate anion, which attacks the β-carbon of the conjugated system. Under electrophilic conditions, the coordination of a Lewis acid with the oxygen atom of the carbonyl group of the enone makes it more susceptible toward the attack of the selenol to the β-carbon of the carbon–carbon double bond.

As an efficient and reusable catalyst for the carbon–sulfur bond formation toward conjugate addition, it was recently reported the use of montmorillonite clays (K10/KSF) that produced very fast reactions on five membered enones and acyclic enones. The presence of a substituent on the β-carbon reduces considerably the rate of the reaction suggesting a mechanism involving the formation on this position of an incipient carbocation by the action of the catalyst. When this carbocation is stabilized by resonance with the substituent, the nucleophilic attack is retarded (Table 4 entries 1 and 4).[26]

Table 4 Catalyzed addition of benzenethiol to enones



No.	*R^1*	*R*	*Catalyst*	*Temperature (°C)*	*Time*	*Yield (%)*
1	H-	OMe-	(K10/KSF)	RT	15 min	92
2	H-	Methyl-	(K10/KSF)	RT	10 min	92
3	Phenyl-	Phenyl-	(K10/KSF)	50	6 h	82
4	Phenyl-	Methyl-	(K10/KSF)	50	3 h	83
5	Phenyl-	Phenyl -	NH_4Cl (saturated)	RT	3 h	85

A very simple and ecofriendly alternative has been proposed by Chen that used as catalyst a saturated aqueous solution of ammonium chloride to effect the thia-Michael addition on a number of Michael acceptors obtaining from moderate to very good yields. An example is reported in entry 5 of Table 4.[27]

7.20.3 Addition Reactions to C═C Bonds with Formation of Carbon–Selenium Bonds

7.20.3.1 Mechanism and Stereocontrol of Electrophilic Addition Reactions

Carbon–selenium bond can be conveniently generated by the reaction of electrophilic selenenylating reagents with unsaturated substrates and the process is generally highly chemo-, regio-, and stereoselective allowing the use of mild experimental conditions.

Some of the most common electrophilic reagents are nowadays commercially available (e.g., phenylselenyl chloride, phenylselenyl bromide, and *N*-phenylselenophthalimide) or alternatively, they can be prepared starting from the corresponding stable and mostly odorless diselenides. In order to avoid side reaction due to the presence of strongly nucleophilic anions some nonhalide electrophiles can be prepared *in situ* by reaction of the selenenyl halide with the appropriate silver salt (hexafluorophosphate, hexafluoroantimoniate, tolylsulfonate, triflate, *N*-saccharin).[28] A number of inorganic oxidants were described in the oxidative cleavage of the selenium–selenium bond and among these the ammonium persulfate, was reported in a number of synthetic applications to prepare, starting from a diselenide, the corresponding highly reactive selenyl sulfate.[29]

Even if the first example of a stereospecific addition reaction to a carbon–carbon double bond promoted by an electrophilic selenium reagent has been reported 60 years ago,[30] currently some mechanistic aspects of this widely used reaction are still under investigation and not completely clarified and explained in detail.

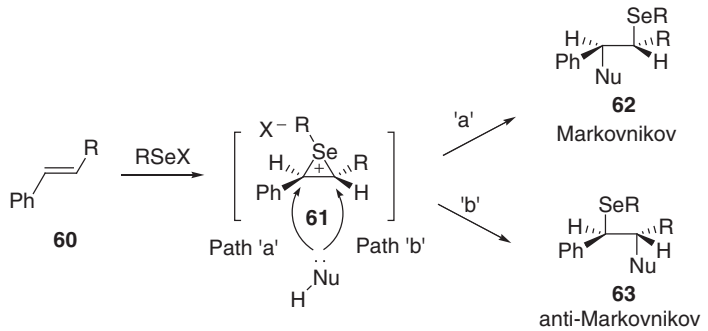
Electrophilic selenium reagents react with olefins (**60**) toward a stereospecific *anti*addition mechanism and the stereoselectivity is commonly supposed to be a consequence of the intermediate formation of a seleniranium ion (**61**) that is stereospecifically opened by a nucleophile.

The regiochemistry is usually dictated by the stability of the Markovnikov addition product (**62**) even if, in some cases, the presence of a coordinating heteroatom (e.g., a hydroxyl group in the allylic position) can modify this orientation leading to the preferential formation of the anti-Markovnikov regioisomer (**63** (Scheme 17)).[31]

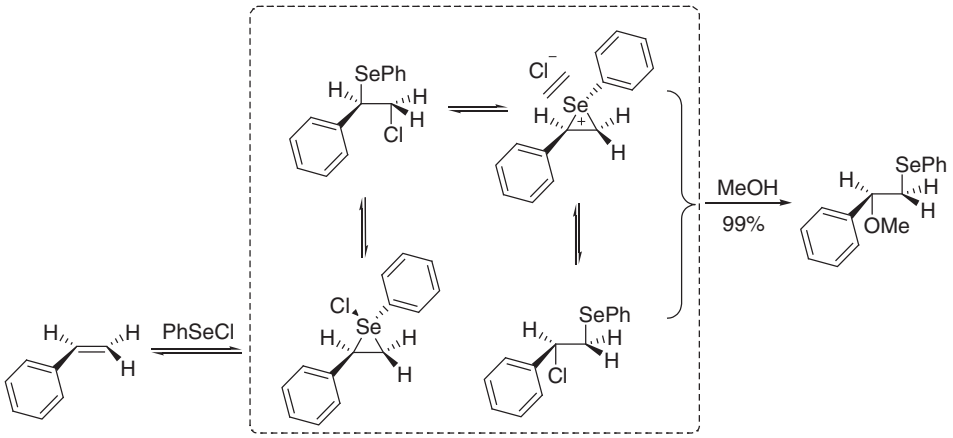
Based on kinetic and spectroscopic analysis it has been observed that PhSeCl reacts with styrene via initial formation of a three member ring episelenurane ion that rapidly evolves into the corresponding Markovnikov addition product. In the presence of polar stabilizing solvents, the Markovnikov adduct is in equilibrium with the anti-Markovnikov intermediate through a second three membered ring intermediate, the seleniranium ion that could exist as intimate or separate ionic pair.

The presence of an external oxygen containing nucleophile (e.g., methanol) moves the equilibrium leading to the quantitative formation of the Markovnikov β-alkoxyselenide as expected on the basis of the usually reported mechanism (Scheme 18).[29,32]

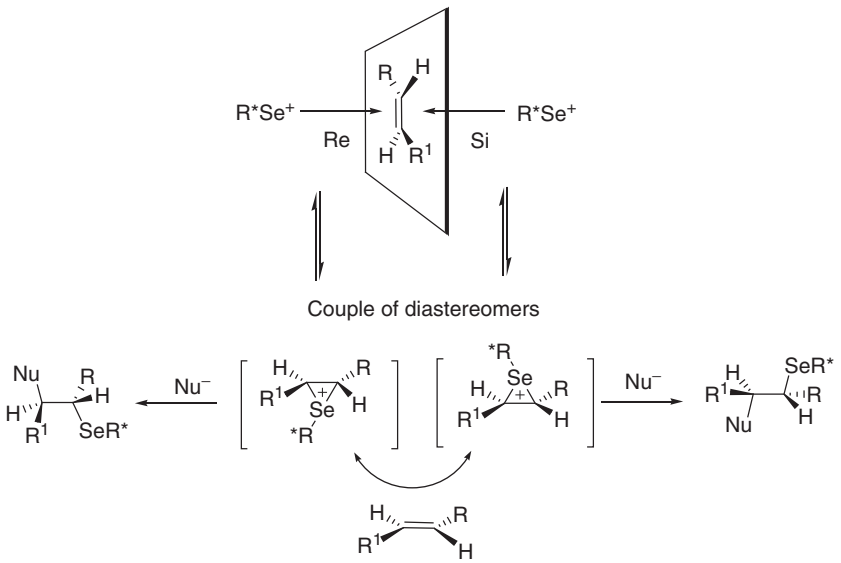
If the electrophilic reagent contains one or more optically pure chiral centers, the addition to the faces of an unsymmetrically substituted alkene leads first to a couple of diastereomeric seleniranium ions that are opened by the nucleophile affording a couple of diastereomeric adducts in a ratio that reflects the facial selectivity of the process (Scheme 19).



Scheme 17 Mechanism of electrophilic selenenylation.



Scheme 18 Addition of PhSeCl to styrene.



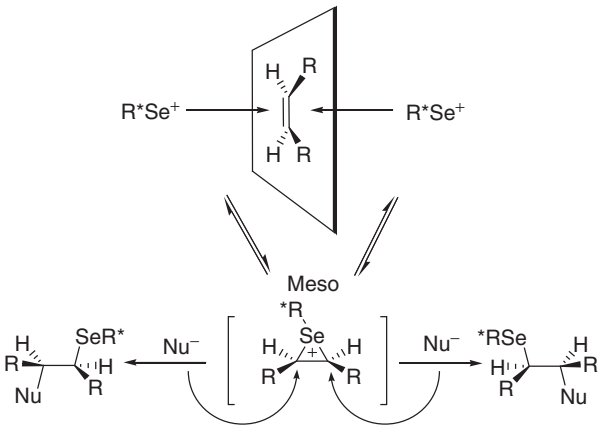
Scheme 19 Asymmetric electrophilic addition.

The preferential formation of one of the two possible seleniranium ions mainly depends on the reaction conditions as well as on the steric and electronic characteristics of both, the selenenylating reagent and the substrate.

Wirth et al.[33] demonstrated that the formation of seleniranium ion is a reversible process and, for this reason, the lower temperature will favor the formation of the kinetically controlled intermediate. It was also proven that a transfer of seleniranium from an olefin to another should be the cause of the stereoselectivity loss.[34]

A *meso* seleniranium ion is the intermediate when the addition occurs on a (*Z*) symmetrically substituted olefin. In this case, the stereoselective step consists in a desymmetrization of the seleniranium arising from the ring opening reaction mediated by the nucleophile.

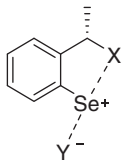
As a general consideration it can be highlighted that all these reactions normally produce only moderate level of stereoselectivity because of the distance between the chiral scaffold and the newly stereocenter formed (Scheme 20).



Scheme 20 Asymmetric electrophilic addition to (*Z*)-olefins.

A number of different optically pure diselenides were proposed as precursors of electrophilic reagents and applied in various asymmetric addition reactions.

The common characteristic of the most selective reagents is the possibility to establish a nonbonding interaction between positively charged selenium and a suitably positioned heteroatom such as oxygen, nitrogen, or sulfur (Figure 1).



X = OR, SR, NR_2

Figure 1 Se-heteroatom nonbonding interaction.

This interaction affects the facial selectivity leading to more rigid transition states and bringing the chiral moiety near to the reactive selenium center during the addition to the double bond.

Several authors combining the results of different techniques (X-ray crystallography, NMR, DFT calculations) have reported evidences of this interaction.[35]

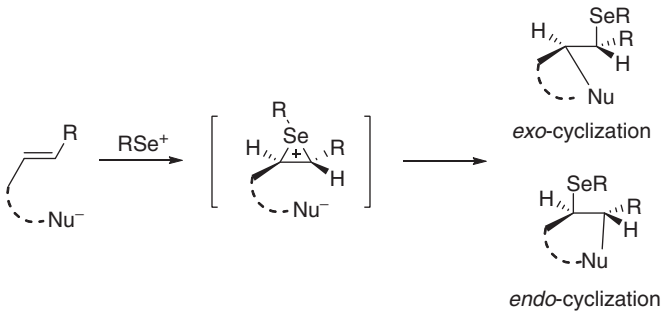
In the case of Se–S, the X-ray analysis showed a T-shaped geometry around the selenium atom with a distance between S and Se shorter than the sum of the corresponding van der Waals radii. This distance depends on the nature of the anion indicating a stronger interaction when it is a chlorine.

Overhauser correlation showed that this interaction exists also in solution and this result, combined with the evidence that the change of sulfur with a methylene group determines the complete loss of selectivity, evidenced the direct role of the Se–S interaction on driving the stereoselection of the process.[36]

When an unsaturated substrate contains, in a suitable position, an internal nucleophile (oxygen-, nitrogen-, or carbon-centered nucleophile), the electrophilic addition occurs as an intramolecular process resulting in a cyclofunctionalization reaction. The mechanism, as for the intermolecular addition, involves a seleniranium ion intermediate leading to functionalized heterocycles. Selenium mediated cyclofunctionalization proceeds normally with excellent control of both stereo- and regioselectivity, depending on the nature of the substrate as well as on the reaction conditions (Scheme 21).[37]

7.20.3.2 Intermolecular Electrophilic Addition to C═C Bonds

The electrophilic addition reaction starting from olefins in the presence of alcohol, water, or acetic acid affords the corresponding *β*- alkoxy-, hydroxyl-, and acetoxy-selenides, respectively. These processes, named oxyselenenylations, indicate the stereoselective

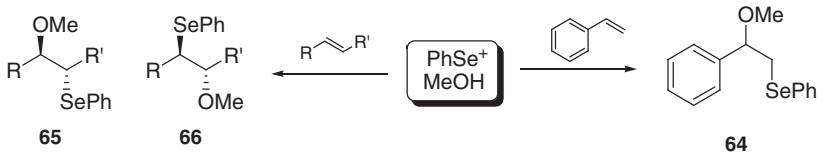


Scheme 21 Selenium mediated cyclofunctionalization.

formation of a new carbon–oxygen and carbon–selenium bond starting from carbon–carbon double bond and are nowadays commonly used for the functionalization of unsaturated substrates in consideration of their efficiency associated to the simple experimental conditions required.

As discussed in Section 7.20.3.1, when the electrophilic regent is PhSeCl, the reaction affords chemoselectively the β-methoxyselenide and the competitive formation of the corresponding chlorine derivatives could be observed only under kinetically controlled conditions.[38]

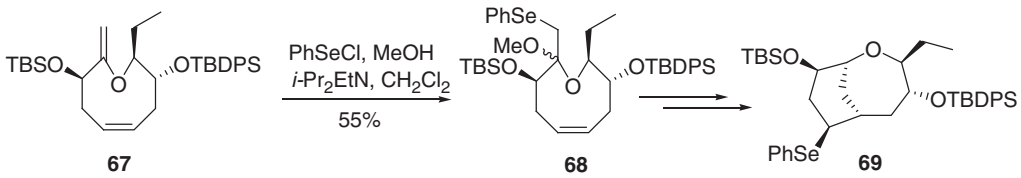
Terminal olefins lead exclusively to the formation of the Markovnikov adduct **64**[39] whereas the internal alkenes generally afford a mixture of regioisomers (**65**, **66**) (Scheme 22).[40]



Scheme 22 Regiochemistry on oxyselenenylation.

When the substrate is a conjugated diene, a 1,2-addition proceeds according to the Markovnikov orientation.[41]

Some interesting examples of methoxyselenenylation reaction are compared in the literature. In the synthesis of (+)-obtusenyne the reaction of the exocyclic enol ether **67** with PhSeCl gave a mixture of selenoacetal **68** in 55% yield. The latter is a convenient precursor of the 2-oxabicyclo[4.3.1]decane **69** (Scheme 23).[42]



Scheme 23 Synthesis of (+)-obtusenyne.

During the past decades, the introduction of new efficient and easily accessible optically pure selenenylating reagents allowed the access to the asymmetric functionalization of olefins for the synthesis of diastereomeric-enriched β-methoxyselenides.

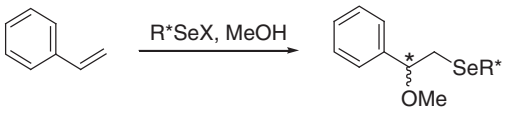
Selenenylating reagents based on terpenoid scaffolds[43] (Table 5, entry 1) are generally less efficient in comparison with similar aromatic derivatives.

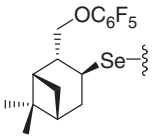
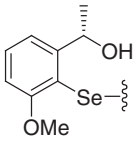
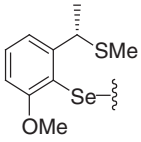
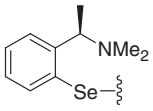
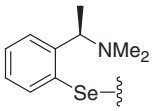
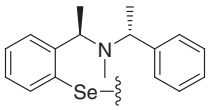
In the latter cases it was demonstrated that the presence of different coordinating heteroatoms produced different diastereomeric excesses and the sulfur[45] is the most efficient in terms of stereoselectivity with respect to oxygen[44] or nitrogen[46,47] nucleophiles (Table 5, entries 3 and 2 and 4–6, respectively).

For the nitrogen containing diselenides it was demonstrated that better results could be obtained when the anion is a sulfate (Table 5 entries 5 and 6)[46,47] allowing to reach excellent diastereomeric excesses even at room temperature.

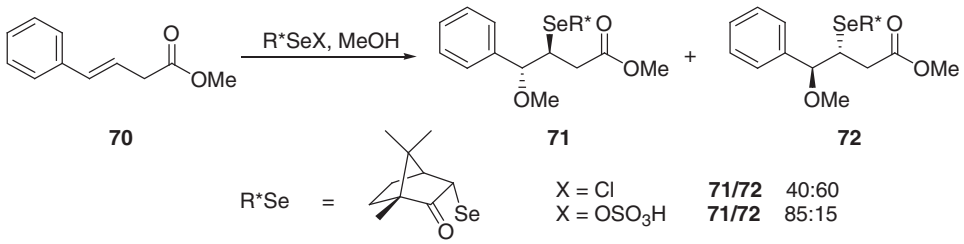
Several reports show that the counteranion could have a strong influence on determining the selectivity of the selenenylation reactions and all the results suggest that a decrease in anion nucleophilicity or an increase in the selenium electrophilicity produces an enhancement of the diastereomeric excess.[48]

Table 5 Asymmetric methoxyselenenylation of styrene



Entry	*R**	*X*	*Temperature (°C)*	*Yield (%)*	*de (%)*	*References*
1		OTf	−78	56	72	43
2		OTf	−100	55	96	44
3		OTf	−30	72	96	45
4		OTf	0	64	35	46
5		OSO_3H	25	80	94	46
6		OSO_3H	25	70	94	47

The effect of the anion was dramatically evident in the methoxyselenenylation of the olefin **70**. In this case, using chloride, a slight excess of the stereomer **72** was obtained whereas when the anion was a sulfate the process was strongly selective in favor of the isomer **71** (Scheme 24).[49]

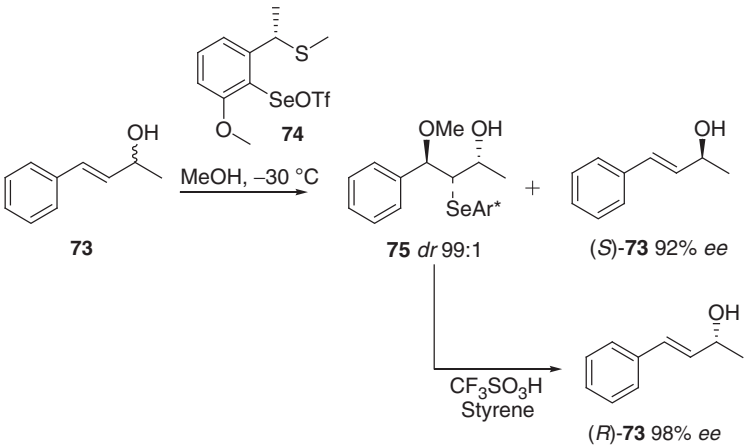


Scheme 24 Effect of the anion on the stereoselectivity of selenenylation reaction.

Freudendahl and Wirth investigated the possibility to affect the stereoselective oxyselenenylation of olefins using some chiral counteranions reaching however at least 3% of enantiomeric excess.[50]

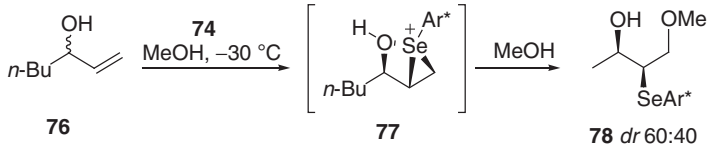
The optically pure sulfur containing selenenylating reagent **74** was applied in the first example of nonenzymatic kinetic resolution of racemic allylic alcohols through a methoxyselenenylation reaction.[31]

In the racemic mixture **73** the isomer (*R*) undergoes the methoxyselenenylation faster than its enantiomer (*S*) and the rate difference is enough to allow the almost quantitative conversion of (*R*)-**73** into the corresponding adduct **74** leaving the unreacted (*S*)-**73** in a 92% of *ee*. A reverse methoxyselenenylation can be obtained by treatment of **75** with trifluoromethanesulfonic acid in the presence of an excess of styrene as electrophile trapper, completing the resolution process (Scheme 25).



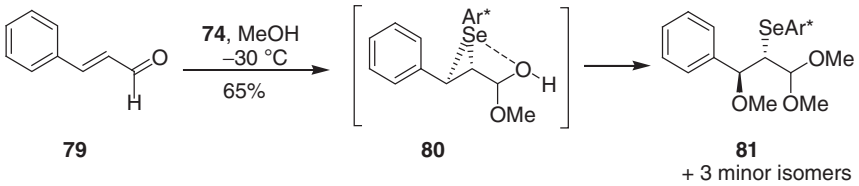
Scheme 25 Kinetic resolution of allylic alcohols.

When the same reaction was performed starting from a terminal olefin (e.g., **76**) the anti-Markovnikov adduct **78** was obtained as a unique product indicating that in the seleniranium intermediate **77** there is an orienting interaction between the positively charged selenium and the hydroxyl group (Scheme 26). A similar interaction was previously reported by Shimitzu et al. to explain the regiochemistry observed in the selenenylation of allyl ethers and allyl silyl ethers. They also described as this coordination resulted to be less effective in the cases of allyl benzoates, acetates and pivalates.[51]



Scheme 26 Anchimeric participation of the hydroxyl group.

A similar anchimeric participation has been proposed to drive the methoxyselenenylation on α,β-unsaturated aldehydes **79**. The process results in a one-pot carbonyl protection as dimethylacetal and electrophilic functionalization of the carbon–carbon double bond. The suggested intermediate is the hemiacetal **80** in which the coordination of the hydroxyl group with the seleniranium ion intermediate leading to **81** as major product (Scheme 27).[52] This coordination was supposed to be more efficient than that conceivable from the acetal that was proven to produce a less stereoselective reaction mixture.



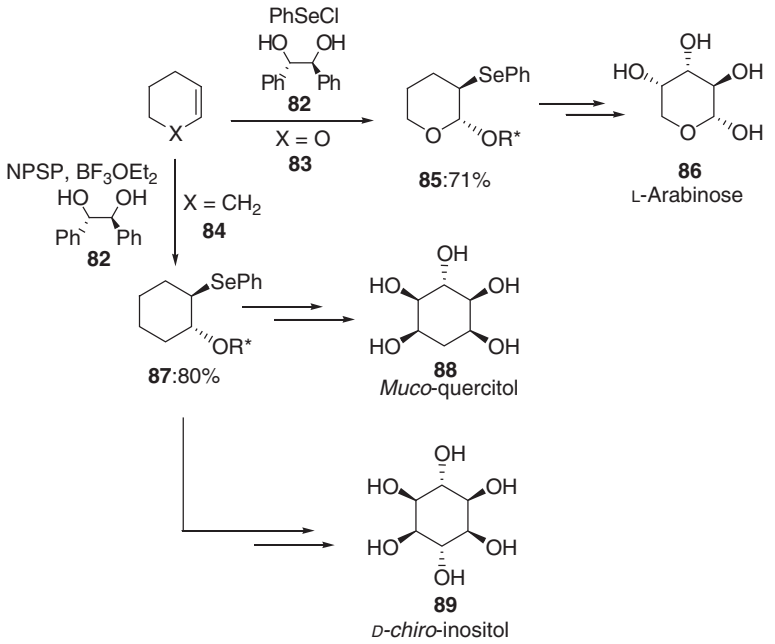
Scheme 27 Methoxyselenenylation of α,β-unsaturated aldehydes.

The stereocontrolled formation of carbon–selenium bond can be obtained, as well as with optically pure selenenylating reagents, also following two other main strategies: The selenenylation of alkenes in the presence of an enantiomerically pure alcohol and the functionalization of enantiomerically pure substrates.

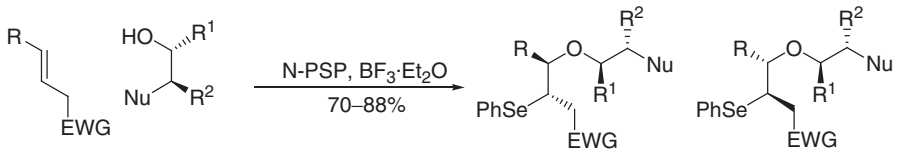
As an example, the 3,4-dihydro-2*H*-pyrane **83** reacts with the optically pure diol **82** in the presence of PhSeCl leading to the two diastereomeric addition adducts **85** in a quasi equimolar ratio (1.2:1). After chromatographic separation, the isomer with the appropriate absolute configuration was subjected to further manipulations affording the L-arabinose **86**. Starting from the other isomer it should be possible to prepare D-arabinose.[53]

Similarly cyclitols **88** and **89** were prepared starting with the alkoxymethoxylation of the cyclohexene **84** with alcohol **82**. The chirality of the selenide **87** drives the stereochemistry of the subsequent multistep reaction (Scheme 28).[54]

The alkoxyselenenylation of β,γ-unsaturated nitriles and esters promoted by *N*(phenylseleno)-phthalimide in the presence of enantiomerically pure diols or (*R*)-phenylglycinol affords key intermediates that, after chromatographic separation, were used by Tiecco and coworkers for the synthesis of enantiomerically pure tetrasubstituted 1,4 dioxanes[55] and 2,3,5-trisubstituted morpholines, (Scheme 29).[56]



Scheme 28 Stereoselective oxyselenenylation for the synthesis of cyclitols.



Olefin
EWG = COOMe, CN
R = Me, Ph

Nucleophiles
Nu = OH, $R^1 = R^2$ = Ph, Me; $R^1R^2 = -(CH_2)_4-$
Nu = NHBoc, R^1 = H, R^2 = Ph

Scheme 29 Stereoselective oxyselenenylation controlled by the nucleophile.

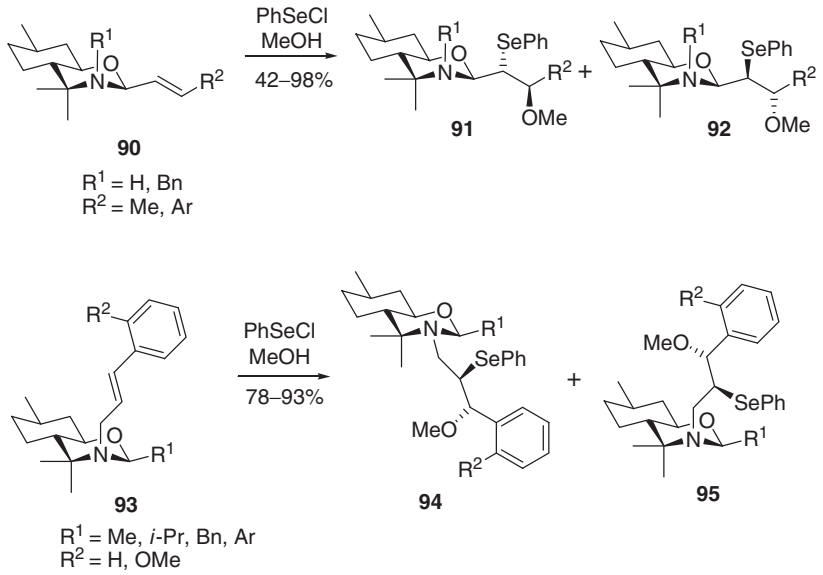
Perhydro-1,3-benzoxazines were demonstrated to be good chiral auxiliaries for the asymmetric synthesis controlled by the substrate. The reaction of the optically pure olefins **90** and **93**, with phenylselenyl chloride in methanol, afforded the corresponding *β*-methoxy selenides **91**, **92** and **94**, **95**, respectively, in high yields, and with very good regio- and stereoselectivity (Scheme 30).[57,58] The selectivity arises from the presence in the seleniranium intermediate of a nonbonding coordination between selenium atom and the oxygen of the heterocycle, in the first case, or to nitrogen, in the second case.

When water or aqueous organic solvents are used on the place of methanol, the electrophilic addition reaction affords the synthesis of *β*-hydroxyselenides that are demonstrated to be excellent intermediates for the preparation of allylic alcohols and epoxides.[59] A number of different protocols were proposed for these reactions. Among these, PhSeCl, *N*-(phenylseleno)phthalimide or *N*-(phenylseleno)succinamide in aqueous acetonitrile or methylene chloride,[60] PhSeBr in water/dimethylformamide or water/CF_3CH_2OH mixtures[61] are probably the most efficient and evaluable.

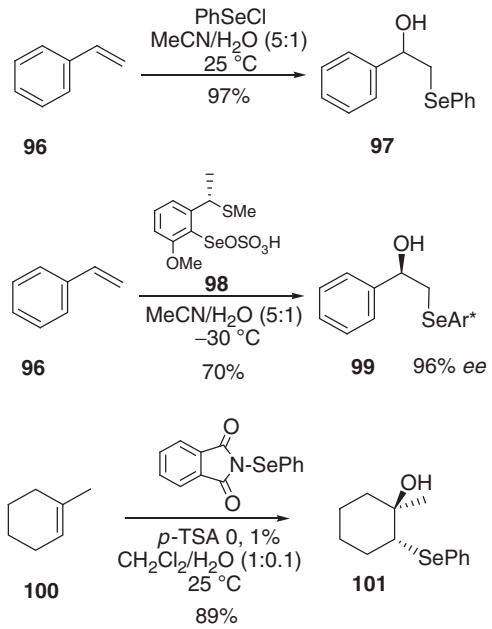
Selected examples are reported in Scheme 31. It is interesting to observe that also in these cases the use of chiral selenenylating reagents (e.g., **98**) in which the selenium can be coordinated by a neighboring sulfur atom produces very high levels of facial selectivity on the hydroxyselenenylation of styrene (**96**) affording the Markovnikov adduct **99** in 70% yield and 96% *ee*.[62]

Generally, asymmetric hydroxyselenenylations are affected using sulfate as counteranion. This is for two main reasons: (1) the selenenyl sulfate can be conveniently prepared directly in aqueous medium and (2) the reactions reach good level of selectivity at higher temperature (from $-30\,^{\circ}C$ to $+40\,^{\circ}C$) compared to that required by the corresponding triflates (from $-100\,^{\circ}C$ to $-78\,^{\circ}C$).

Phenylselenenyl triflate, generated *in situ* by treatment of the commercially available PhSeBr with silver triflate, has been successfully used for the regio- and stereospecific hydroxyselenenylation of terpenoid scaffolds containing endocyclic carbon–carbon double bonds. As an example in Scheme 32, the authors reported the functionalization of carene **102** and



Scheme 30 Methoxyselenenylation of substituted perhydro-1,3-benzoxazines.



Scheme 31 Hydroxyselenenylation of olefins.

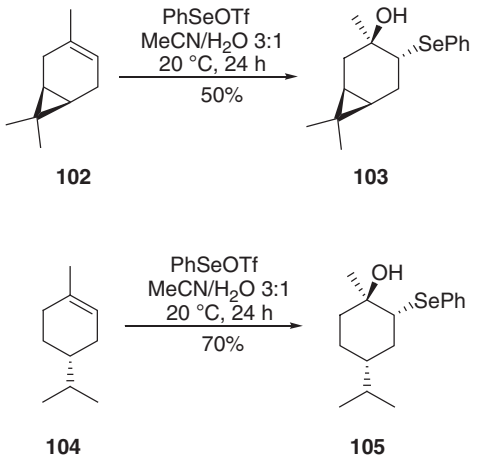
menthene **104** that occurs in both cases in moderate yields but with complete regio- and stereospecificity affording the adducts **103** and **105**, respectively.[63]

2-Phenylselenenyl-1,3-*syn*-diols are considered good intermediates for the synthesis of the corresponding 1,3-diols and should be obtained by electrophilic addition of benzeneselenenic acid to allylic alcohols[64] as well as by the electrophilic hydroxyselenenylation of the same substrates.[65] The reaction was promoted by phenylselenenyl chloride in a mixture of acetonitrile and water at room temperature.

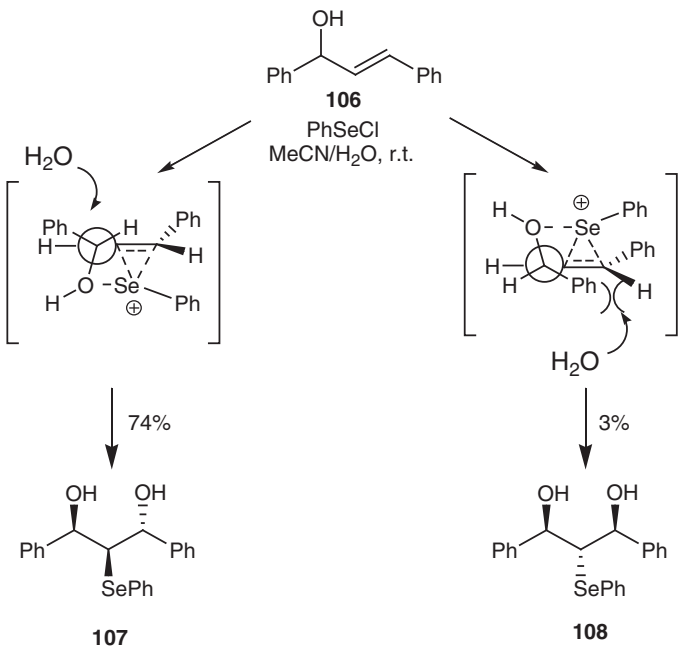
Under these conditions, the seleniranium ion, generated from the allylic alcohol **106**, is attacked by a molecule of water giving the diols **107** and **108**.

Considering different substrates, the yields are generally good with the alkyl-substituted substrates that proved to be less reactive in comparison with the aryl-substituted ones.

Diastereomeric ratios are in all the cases good and directly proportional to the size of the substituent. This could be rationalized taking in consideration a nonbonding interaction between the hydroxyl group and the selenium of the seleniranium ion that affords two different intermediates with different steric requirements on the carbon attached by the water (Scheme 33).



Scheme 32 Regio- and stereospecific hydroxyselenenylation of terpenes.



Scheme 33 Hydroxyselenenylation of allyl alcohols.

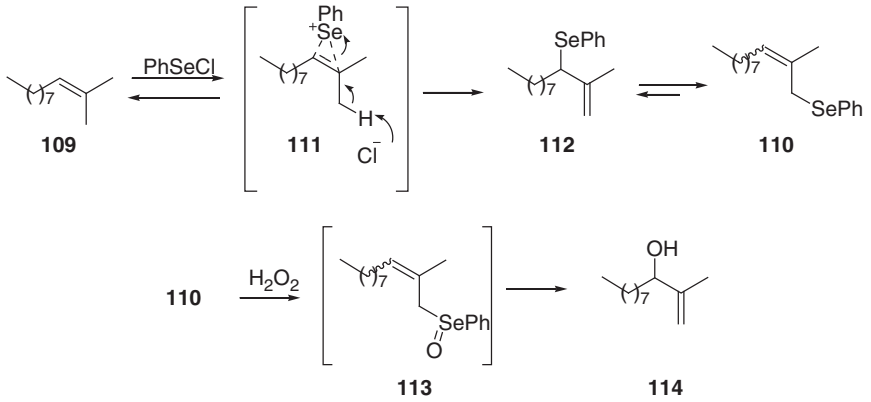
The treatment of a prenyl moiety (e.g., **109**) with PhSeCl in the presence of pyridine but in the absence of water, as well as other nucleophilic reagents, afforded, in good yield the phenylselenide **110**. This result was explained by suggesting a direct involvement of the chloride anion that, after the formation of the seleniranium ion **111**, attacks a methyl group, leading to the *exo*-alkenyl selenide **112** that rapidly equilibrates, according to a 1,3-sigmatropic rearrangement to the thermodynamically stable *endo*-alkenyl allylic selenide **113**. HCl, produced as a side product, could be trapped by the pyridine, and reasonably this is the driving force that moves the equilibrium toward the formation of **110**.

It is interesting to observe that the treatment of this intermediate with hydrogen peroxide affords the corresponding allylic alcohol **114** as result of a 2,3-sigmatropic rearrangement of the selenoxide intermediate **113** (Scheme 34).[66]

This sequence represents a convenient and general procedure to convert a prenyl group into a 3-isopren-2-ol unit, a protocol used in some interesting synthetic applications, such as the total synthesis of some natural compounds.[67]

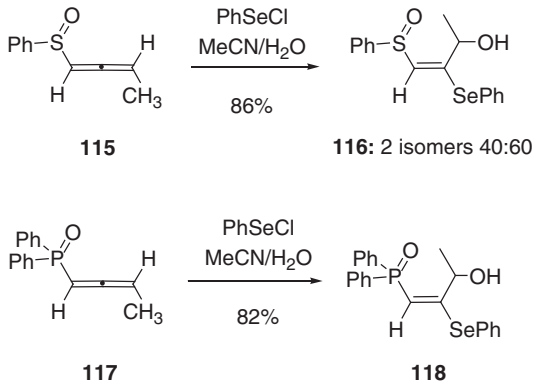
1,2-Allenes could be selectively functionalized using PhSeCl in $MeCN/H_2O$. The regio- and stereoselectivity of the process is strictly correlated to the presence of a sulfoxide (**115**)[68] or a phosphine oxide (**117**)[69] that participate in the ring opening reaction of the seleniranium intermediate affording the final allylic alcohols **116** and **118**, respectively (Scheme 35).

Aminoselenenylations of alkenes are less applied in synthesis in comparison to the above reported oxyselenenylation reactions, and this is probably due to the reduced nucleophilicity of some nitrogen-containing reagents. Nevertheless, in order to overcome this limitation, some activating additives can be used. For example, PhSeCl and silver tetrafluoroborate promoted the



109 111 112 110 110 113 114

Scheme 34 Synthesis of allylic alcohol from prenyl unit.

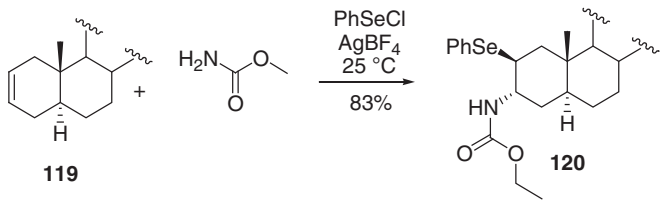


115 116: 2 isomers 40:60 117 118

Scheme 35 Hydroxyselenenylation of 1,2-allenyl sulfoxides and phosphine oxides.

intermolecular addition of carbamates, alternatively, in consideration to the high hygroscopicity of the silver salt, *N*-(phenylseleno)phthalimide and HBF_4 were conveniently used.[70]

As an example, the authors report here the amidoselenenylation of 5α-cholest-2ene **119**. The formation of the seleniranium ion is stereoselectively driven by the chirality of the substrate, and the nucleophile attacks this intermediate, affording the *trans* diaxial β-phenylseleno carbamate derivative **120** according the Furst–Plattner rule (Scheme 36).[71]



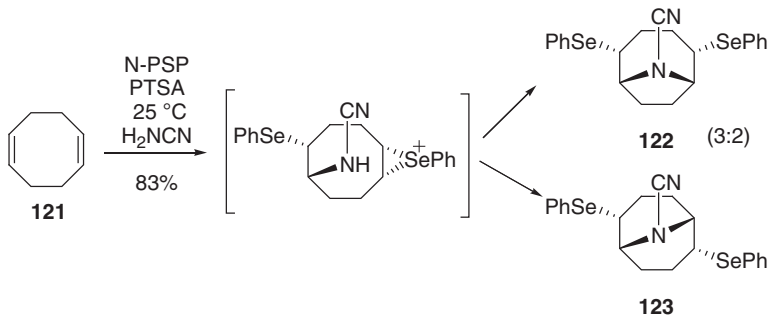
119 120

Scheme 36 Amidoselenenylation reaction.

Under kinetic conditions, the preferential formation of the hydroxyselenenylation adduct was observed as a result of a nucleophilic attack of the carboxylic oxygen of carbamate to the seleniranium ion, and subsequent hydrolysis of the resulting intermediate occurred during the workup. The results reported in the literature clearly demonstrate that this intermediate is in fast equilibrium with the seleniranium ion and that the reaction can be thermodynamically controlled in favor of the irreversible formation of a β-phenylselenocarbamate.

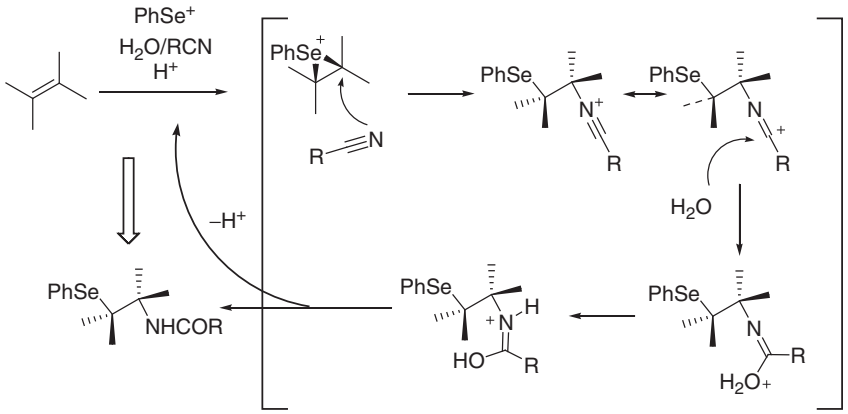
A further interesting example of nitrogen–selenium addition reaction to a carbon–carbon double bond involves the use of cyanamide as nucleophile. This reaction has a limitation only in the case of sterically hindered olefins and it could be efficiently affected starting from mono-, di-, and trisubstituted alkenes but not from the tetrasubstituted ones. The reaction of the cyclic nonconjugated diene cyclo-octa-1,5-diene (**121**) with *N*-(phenylseleno)phthalimide (*N*-PSP), PTSA and cyanamide gave two regioisomers, the 9-azabicyclo[3.3.1]-nonane (**122**) and the 9-azabicyclo[4.2.1]-nonane (**123**). This result can be explained

considering the combination of two processes, first an intermolecular electrophilic monoselenation followed by an intra-molecular electrophilic addition in which the nitrogen of cyanamido group is involved in a cyclization reaction[71] (Scheme 37).



Scheme 37 Cyanamidoselenenylation reaction.

Usually, acetonitrile is a convenient solvent for electrophilic reactions (e.g., hydroxyselenenylations) and the nucleophilicity of the nitrogen is not in competition with that of the desired nucleophile. Nevertheless, in the presence of water and with the catalysis of a strong acid, such as trifluoromethanesulfonic acid, the acylamino group can be introduced in a process of amidoselenenylation reaction that occurs according to a Ritter-type mechanism, as depicted in Scheme 38.



Scheme 38 Mechanism for the acylamidoselenenylation reaction.

This reaction can be obtained using electrophilic reagent PhSeCl,[72] 2-pyridylselenenyl chloride,[73] or $PhSeOSO_3H$.[74] In the latter case, the presence of the acid promotes also the formation of the electrophile from the corresponding diphenyldiselenide and ammonium persulphate.

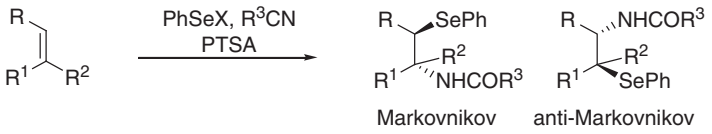
Selected results are reported in Table 6 evidencing that, in all the cases, the process consists in a stereospecific anti-addition and that, in the case of terminal olefins, only a minor amount of anti-Markovnikov adduct was obtained (entry 8). In addition, a number of different nitriles could be used affording differently substituted amides (entries 1–6).

Tiecco et al., using the enantiomerically pure camphorselenenyl sulfate,[75] reported the enantioselective version of this reaction. In contrast with other electrophilic additions previously described also in this chapter, the acylamidoselenenylations showed only moderate level of facial selectivity. Nevertheless, despite this limitation, the resulting diastereomeric *β*-acylamidoselenides (**125**, **126**) could be easily separated by flash chromatography affording enantiomerically pure intermediates that were used for the synthesis of oxazolines (**127**, **128**) or thiazoline (**129**, **130**)[76] in up to 99% *ee* (Scheme 39).

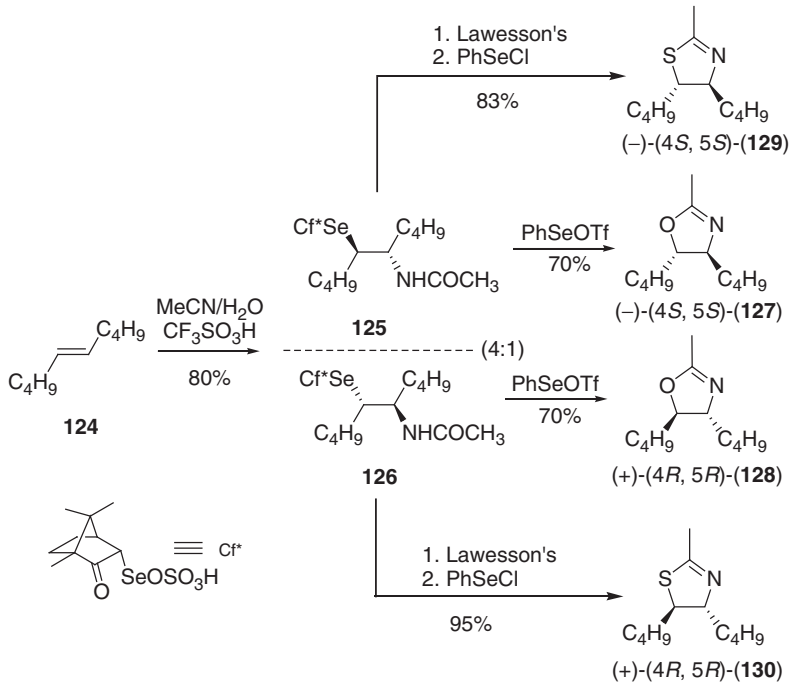
Further stereospecific transformations were reported demonstrating the synthetic relevance of this asymmetric acylamidoselenenylation reaction. Oxazolines (4*S*, 5*S*)-**127** and (4*R*, 5*R*)-**128** can be isomerized to the corresponding (4*S*, 5*R*) and (4*R*, 5*S*) diastereoisomers by acidic hydrolysis followed by a $SOCl_2$-promoted cyclization. Combining these synthetic strategies, the four enantiomerically pure 4,5-disubstituted oxazolines can be accessed and transformed into the corresponding enantiopure *β*-aminoalcohols. Furthermore, the reductive radical deselenenylation achieved by treatment of **125** and **126** with triphenyltin hydride and AIBN in refluxing benzene afforded the synthesis of enantiomerically pure amines.

β-Azidoselenides are synthetically useful intermediates because they combine the reactivity of the organoselenium moiety with the manipulations that can be effected on the azido group. They can react with both nucleophilic and electrophilic reagents as well as be involved in 1,3-dipolar addition reactions. After the seminal experiments reported by Krief and coworkers in 1979 using PhSeBr or MeSeBr as electrophilic reagents and sodium azide in methanol or lithium azide in DMF as nitrogen centered

Table 6 Synthesis of β-acylamidoselenenides



Entry	*R*	*R¹*	*R²*	*R³*	*X*	*Yield (%)*	*References*
1	$-(CH_2)_4-$		H	CH_3	Cl	98	72
2	$-(CH_2)_4-$		H	CH_2CH_3	Cl	95	72
3	$-(CH_2)_4-$		H	$CH_2CH_2CH_3$	Cl	85	72
4	$-(CH_2)_4-$		H	Ph	Cl	90	72
5	$-(CH_2)_4-$		H	$CH_2CO_2CH_2CH_3$	Cl	72	72
6	$-(CH_2)_4-$		H	CH_3	OSO_3H	81	74
7	CH_2CH_3	H	CH_2CH_3	CH_3	OSO_3H	78	74
8	H	H	C_6H_{13}	CH_3	OSO_3H	82 (m) 9 (aM)	74



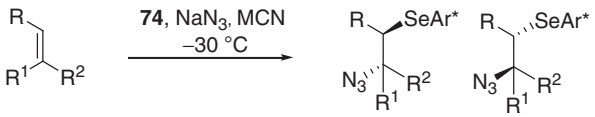
Scheme 39 Asymmetric acylamidoselenenylation and further transformations.

nucleophile,[61] the efficiency of the process was improved producing *in situ* the species phenylselenenyl azide ($PhSeN_3$). It can be realized in two main ways: by reaction of PhSeCl and sodium azide in DMSO[77] or, alternatively, reacting *N*-(phenylseleno)phthalimide and azidotrimethylsilane in methylene chloride.[78] Better regioselectivity in favor to the Markovnikov oriented isomer can be obtained using PhSeOTf and sodium azide at low temperature,[79] whereas the anti-Markovnikov selectivity was observed activating the reaction with an azido radical (PhSeSePh, NaN_3 and $PhI(OAc)_2$)[80] instead of a selenium electrophile. In the latter case the mechanism does not involve the formation of a seleniranium ion and there is not any particular stereocontrol in the formation of the carbon–selenium bond.

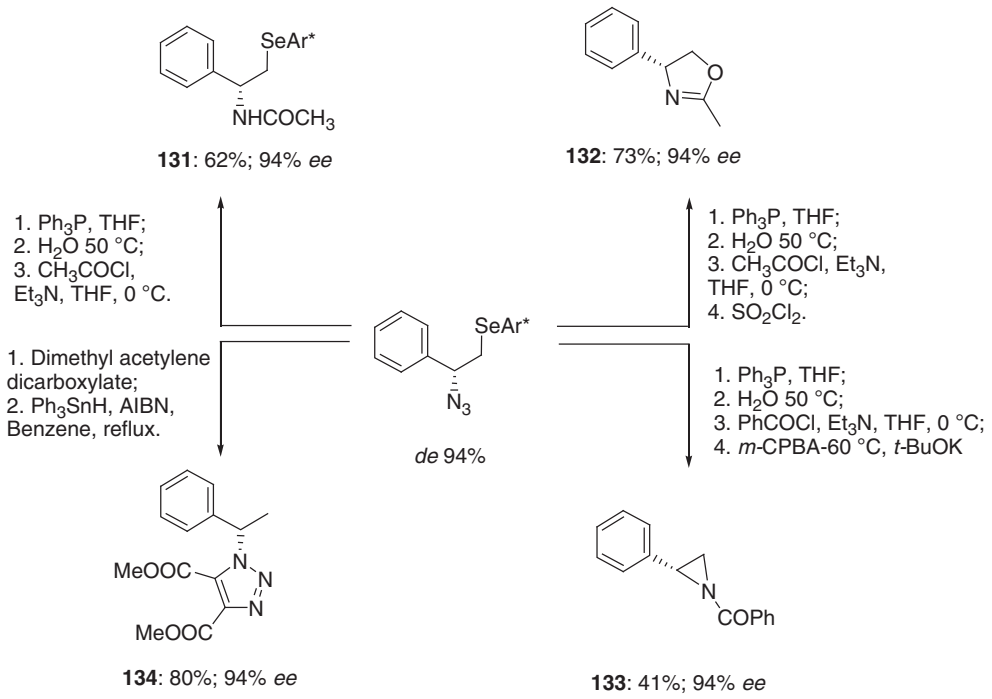
The absolute configuration of the chiral centers generated during the azidoselenenylation reaction can be controlled by the chirality of the reagent as well by the chirality of the substrates. In the first case the arylselenenyl triflate **74** has been successfully employed to prepare a number of highly enantiomerically enriched β-azidoselenides (Table 7).[81] These were subsequently employed in a number of stereospecific conversions affording enantiomerically enriched amides (**131**), isoxazolidines (**132**), aziridines (**133**) and triazoles (**134**) (Scheme 40).[81]

According to the 'chiral pool approach,' terpenes can be considered as convenient starting materials in asymmetric synthesis because they are commercially available, not expensive, and generally easily accessible in both enantiomeric forms.

Table 7 Synthesis of optically enriched β-azidoselenenides



Entry	*R*	*R*^{1}	*R*^{2}	*Yield (%)*	dr	*References*
1	H	H	Ph	90	97:3	74
2	Me	H	Ph	70	98:2	74
3	H	Me	Ph	60	99:1	74
4	C_3H_7	H	C_3H_7	95	95:5	74
5	C_4H_9	H	C_4H_9	95	95:5	74

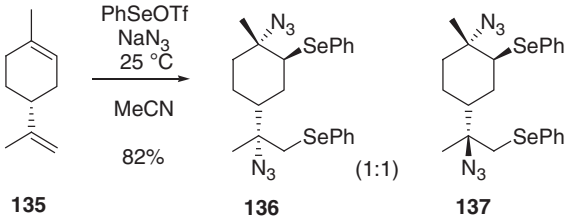


Scheme 40 Stereospecific manipulations of azidoselenides.

Starting from these substrates, the treatment with PhSeOTf and sodium azide affords the corresponding β-azidoselenides with a selectivity that mainly depends on the nature of the double bond. The addition is stereospecific when the carbon–carbon double bond is included in a cycle whereas it is less stereospecific in the case of double bond placed on a linear chain or exocyclic double bond such as in the (+)-aromadendrene. In the latter case, the addition afforded the two possible isomers in a ratio 4:1. An interesting example is that of limonene **135** that contains two double bonds. Affecting the double azidoselenenylation, only two isomers were obtained **136** and **137** as results of the different selectivity on the two olefins, one endocyclic and one isoprenylic (Scheme 41).[82]

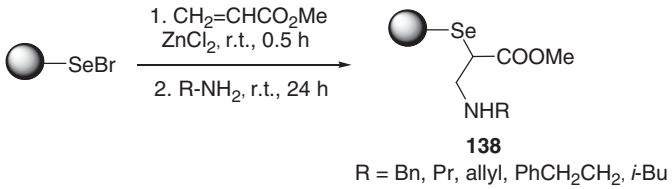
Using a supported selenenylating reagent, in the presence of a primary amine the synthesis of the functionalized resin **138** was realized. This resin has been successfully employed for the preparation of libraries of 2-pyridones, 1,4-diazepines, and 1,4-oxazepines (Scheme 42).[83]

Despite their synthetic relevance, intermolecular addition reactions with the involvement of a carbon-centered nucleophile are nowadays not extensively studied and only few examples were reported in the literature. For the first time, in 1996 Toshimitsu and coworkers reported that by treatment of a β-hydroxyselenide with a Lewis acid is possible to prepare a seleniranium ion that reacts with some carbon centered nucleophiles such as alkenyl silyl ethers, trimethylsilyl cyanide and allyltrimethylsilane.[84] Later it was reported that some aromatic nucleophiles such as anisole can be used in more efficient processes. Nishibayashi and coworkers, using a C_2-asymmetric electrophilic selenenyl triflate[85] described the first example of an asymmetric Friedel–Crafts such as



135 136 137

Scheme 41 Stereospecific azidoselenenylation of limonene.



138

R = Bn, Pr, allyl, $PhCH_2CH_2$, *i*-Bu

Scheme 42 Synthesis of nitrogen containing resins.

alkylation of an aromatic compound with an alkene. The asymmetric carboselenenylation of (*E*)-*β*-methylstyrene with a number of aromatic systems was reported and the results are summarized in Table 8.

The nature of the nucleophile considerably affected the stereoselectivity of the process and 2,4,6-trimethoxybenzene (entry 4) afforded the best selectivity (*de* of 90%) whereas *N*,*N*-dimethylaniline led to the addition product with 80% *de*.

Very recently, Wirth and coworkers presented the iodine-catalyzed selenenylation of alkenes with styrene nucleophiles.[86]

The authors suggest that the iodine first oxidizes diphenyl diselenide, generating the electrophilic reagent and, subsequently, activates the carbon–carbon double bond of the styrene toward nucleophilic attack to the seleniranium intermediate, leading to the formation of **139** (Scheme 43).

7.20.3.3 Electrophilic Promoted Cyclofunctionalization

Campos and Petragnani reported the first example of electrophilic selenium promoted cyclization of olefins bearing an internal nucleophile in 1960.[30] Nowadays this protocol is a useful and broadly applied procedure to obtain the synthesis of heterocyclic systems. Even if the mechanism is comparable to the thiocyclization or halocyclization reactions, the introduction of a selenium moiety offers a number of advantages, mainly correlated to a series of possible manipulations that can be realized thanks to the presence of a selenium atom: oxidative elimination of selenoxide, radical hydrogenation or nucleophilic substitution of the corresponding selenones.

The mechanism is closely related to that already described for the intermolecular addition reaction and proceeds stereospecifically through the formation of a seleniranium ion intermediate. Many factors could influence the course of the cyclization such as the substrate, the electrophilic reagent and its counterion, the solvent and the presence of additives.

The cyclization reaction can generate four, five, or six-membered rings according to, 4-*exo-trig*, 5-*endo-trig*, 5-*exo-trig*, or 6-*endo-trig* pathways (Scheme 44). The internal nucleophile could be an oxygen or a nitrogen, and in some cases, when both of these heteroatoms are present, the competitive nucleophilic attack can be controlled under kinetic or thermodynamic conditions.

It has been recently demonstrated that when the electrophilic reagent is PhSeCl the process passes through the kinetic formation of a haloselenenylation intermediate, subsequently converted into the thermodynamically stable product of cyclization.[87]

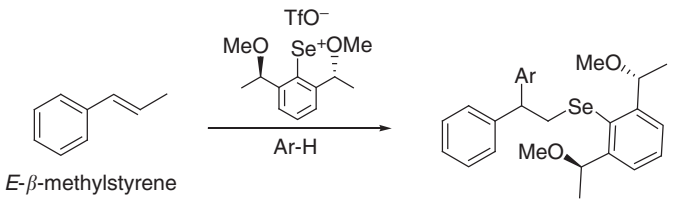
Selenium promoted cyclizations of alkenols and alkenoic acids are commonly named as selenoetherifications and seleno-lactonizations and produce cyclic ethers or lactones, respectively.

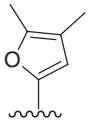
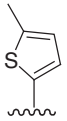
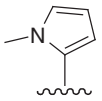
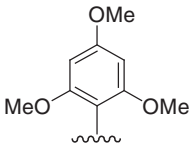
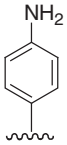
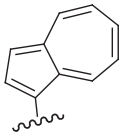
Tetrahydrofurans can be synthesized by electrophilic 5-*exo-trig* cyclizations as well as by 5-*endo-trig* processes even if, in this second case, the reaction should be unfavorable in accordance with the Baldwin rule. Selenocyclofunctionalizations are generally highly stereoselective, and the geometry of the heterocycle mainly depends on its thermodynamic stability.

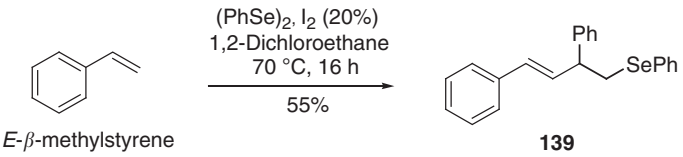
A series of 2-carbomethoxy-3-alkenols were cyclized using as the electrophilic reagent the phenylselenenyl sulfate. Starting from both the *erythro* and *threo* isomer (**140**), the reaction is stereoselective, leading, as major isomers, to **141** and **144** arising from electrophilic attack away from the carbomethoxy group (Scheme 45).[88]

When the anion of the electrophilic selenium is a chlorine or a bromine, the yields as well as the chemo- and stereoselectivity are normally reduced and, especially starting from secondary and tertiary alcohols, some additives can be used in order to obtain better results. The use of pyridine was first investigated by Mojslovic and Bugarcic in 2001 and later the same group reported that a catalytic amount of $SnCl_2$ promotes the selenoetherification of (*Z*)- and (*E*)-hex-4-en-1-ols (**145** and **148**) rapidly and in almost quantitative yield. The regiochemistry is driven by the geometry of the carbon–carbon double bond; '*E*' olefins gave a 6/*exo*

Table 8 Asymmetric carboselenenylation



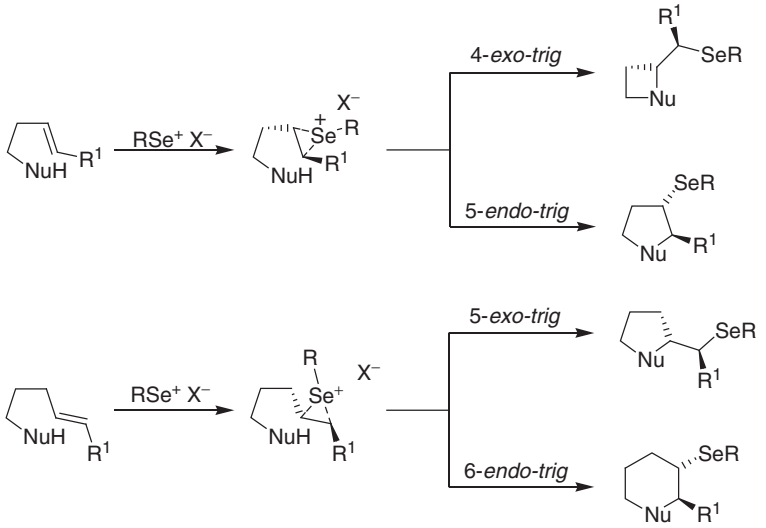
No.	Ar	Yield (%)	dr	References
1		63	92:8	85
2		52	91:9	85
3		48	89:11	85
4		77	95:5	85
5		51	90:10	85
6		34	91:9	85



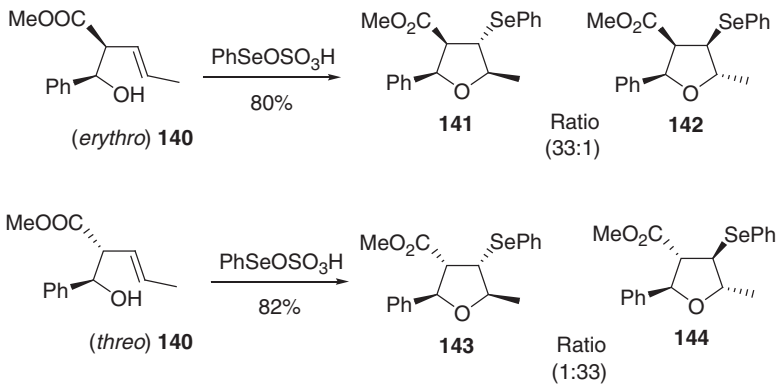
Scheme 43 Example of selenenylations of alkenes with styrene nucleophiles.

cyclization whereas '*Z*' olefins cyclized according to a 5-*exo* mechanism. They also observed that the stereoselectivity of the process is positively affected by the catalyst.[89] Selected examples are collected in Table 9.

The geometry of the carbon bearing the hydroxyl group as well as that of an additional hydroxyl group in the vicinal position do not provide an appreciable control on the stereochemistry of the cyclization. Starting from the optically pure alkenol **151**, accessible in two steps from the commercially available (*S*)-styrene oxide, the treatment with phenylselenenyl sulfate produced a mixture of two diastereomers with only a slight excess of **152** with respect to **153**.[90] In a similar way, the optically pure diols **154** and **157** were transformed into the corresponding tetrahydrofurans (**155**, **156** and **158**, **159**) with poor selectivity in favor of the isomer deriving by the seleniranium that was formed under the coordination of the hydroxyl group not involved in the cyclization (**156** and **159**).[91] Worth mentioning is the fact that in all the cases the mixture of diastereomers can be separated by



Scheme 44 Cyclofunctionalization promoted by electrophilic selenium reagents.



Scheme 45 Cyclofunctionalization of 2-carbomethoxy-3-alkenols.

chromatographic purification, affording enantiomerically pure compounds that were subjected to a series of stereospecific manipulations in order to afford different enantiomerically pure heterocycles (Scheme 46).

A hydroxyl group suitable for the cyclization reaction could be generated *in situ* starting from an aldehyde, a ketone or a *β*-dicarbonyl system, transforming these functional groups into the corresponding hemiacetal by the reaction with an external (**160**, **161**) or an internal oxygen-centered nucleophile[92] or into the corresponding enols (**162**, **163**) through a classical tautomerization[93] (Scheme 47).

By the reaction of (*E*)-2-(arylmethylene)cyclopropylaldehyde **164** with PhSeBr in acetonitrile/water mixture in the presence of K_2CO_3 the corresponding 3-oxabicyclo[3.1.0]hexan-2-ol (**166**), a structural motif frequently present in a number of biologically active compounds,[94] was obtained stereospecifically.

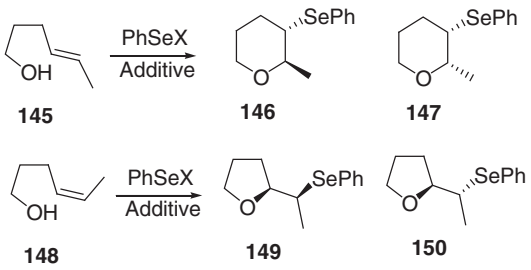
The mechanism involves the intermediate formation of the seleniranium ion (**165**) and the simultaneous hydration of the carbonyl group that generates the hydroxyl group necessary for the cyclization.

Selenolactonization reactions represent an important and efficient protocol for the synthesis of several natural intermediates. A number of electrophilic reagents have been reported for this purpose, and was generally used to convert unsaturated carboxylic acids into the corresponding lactones.

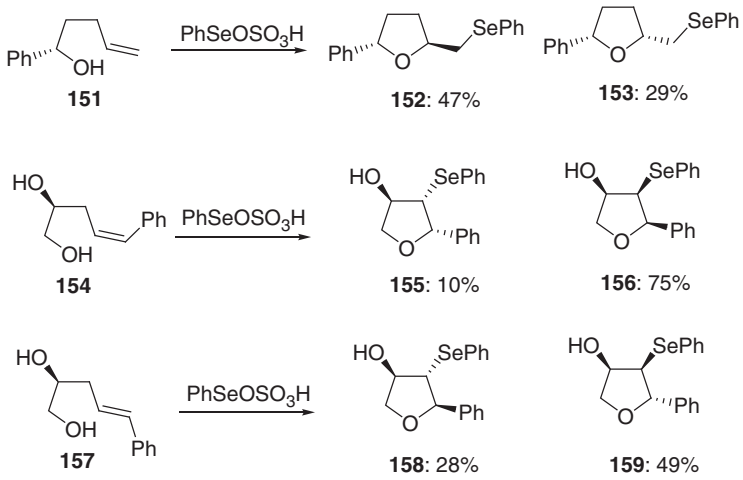
As an example, the cyclization of 3-alkenols (**167**), affording the lactones (**168**), can be realized using diphenyl diselenide and ammonium persulfate to generate, *in situ*, the electrophilic species $PhSeOSO_3H$. The latter activates the double bond toward the lactonization[95] reaction.

Polystyrene-supported selenium bromide reacts with *γ*,*δ*-unsaturated acids **169** leading, regioselectively, to the lactone **170** deriving from a 5-*exo-trig*-cyclization. The cleavage of the heterocycle from the polymer can be obtained by treatment with methyl iodide and sodium iodide and, from the resulting methylselenide, the electrophilic resin could be regenerated by treatment with bromine and reused several times.[96]

Table 9 Additives in cycloetherifications



No.	*Substrate*	*X*	*Additive*	*Ratio*	*Yield (%)*
1	145	Cl	None	69:31	81
2	145	Br	None	65:35	65
3	145	Cl	$SnCl_2$ cat	94:6	98
4	145	Br	$SnCl_2$ cat.	96:4	99
5	148	Cl	None	70:30	72
6	148	Br	None	70:30	75
7	148	Cl	$SnCl_2$ cat	87:13	99
8	148	Br	$SnCl_2$ cat.	82:18	98



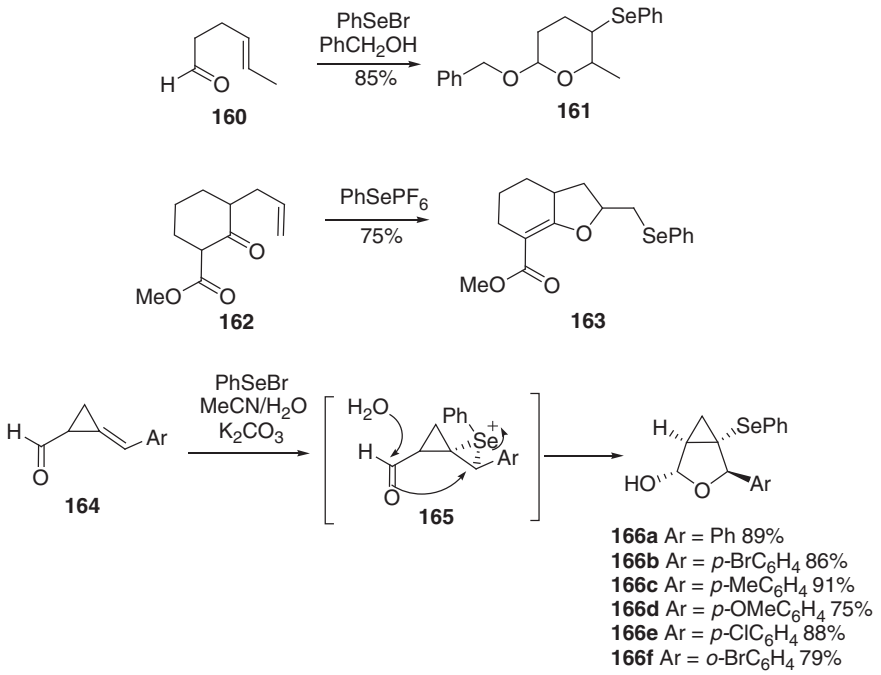
Scheme 46 Stereoselectivity controlled by the chirality of carbons bearing an hydroxyl group.

It was demonstrated that electrophilic cyclization of 2,3-allenoic acids with PhSeCl in acetonitrile proceeds in very poor yields, but better results can be obtained starting from the corresponding ethyl 2,3-allenoates **171** in a mixture of H_2O/MeCN (10:1). The product of the reaction is the vinyl selenobutenolide **172** (Scheme 48).[97]

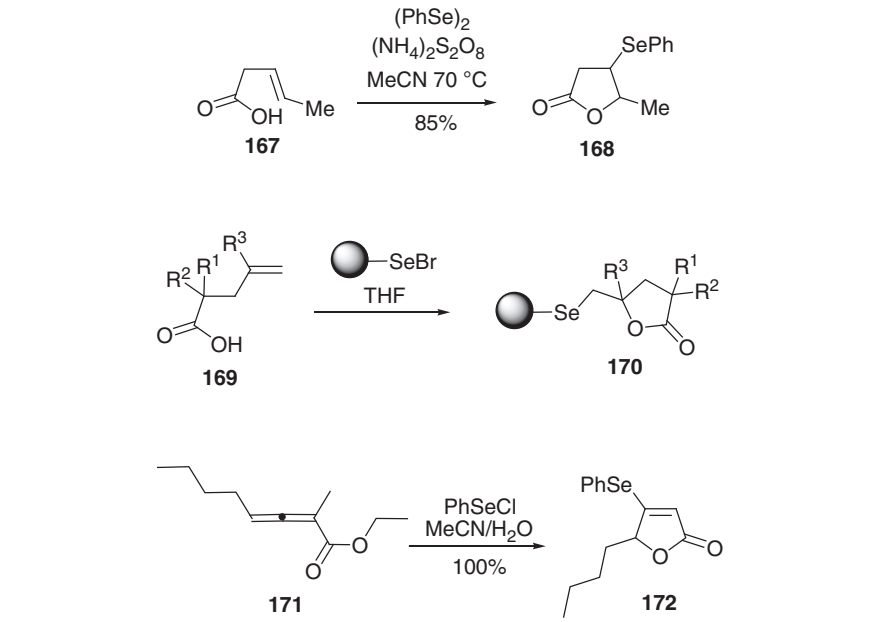
As already discussed in Section 7.20.3.2 for the intermolecular addition reactions, also the cyclofuntionalizations can be realized in enantioselective fashion. Among all the reagents, those containing a sulfur atom in a suitable position to stabilize the seleniranium ion intermediate by a nonbonding interaction are generally the best choice in terms of yields and facial selectivity, requiring also milder reaction conditions to achieve good enantiomeric excesses.

5-*Endo-trig*, 6-*endo-trig*, and 5-*exo-trig* cycloetherification as well as cyclolactonization can be realized starting from alkenols (**173**, **175**, **177**) or alkenoic acids (**179**) affording the corresponding heterocycles (**174**, **176**, **178** and **179**) in good yields and excellent diastereomeric excesses, from 84% to 96% (Scheme 49).[45,62]

Very recently Denmark and Collins[98] reported the first catalytic enantioselective selenoetherification reaction of alkenols (Scheme 50). The weak electrophilic *N*-arylselenophthalimide **181** combines with the chiral Lewis base 1,1′-binaphthalene-2,2′-diamine-derived (BINAM) thiophosphoroamide **183**, affording an ionic, strong electrophile that reacts with prochiral alkenes **182** to afford enantioenriched seleniranium ions. The ring closure reactions by the suitably positioned oxygen atom lead to the cyclic ether **184**, regenerating the Lewis base catalyst.



Scheme 47 *In situ* generated nucleophiles.

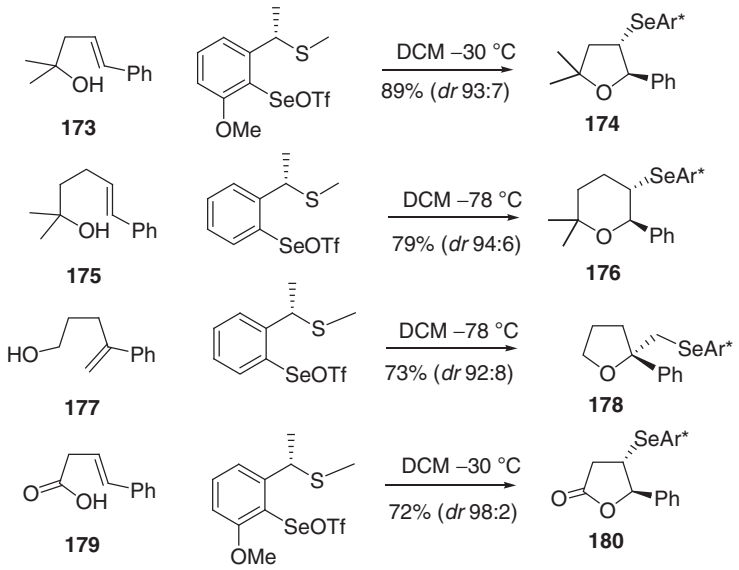


Scheme 48 Selenolactonizations.

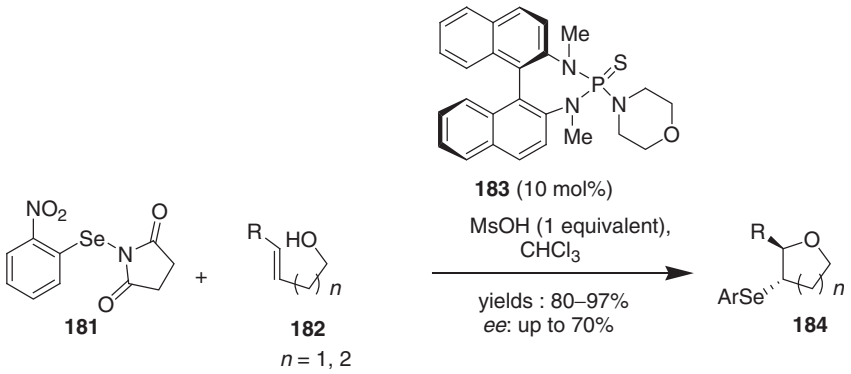
Exo selectivity in ring closure reactions is not always observed, and the use of an electrophilic reagent **181**, with a 2-nitrophenyl group linked to the selenium atom, significantly reduces the racemization of the seleniranium ion intermediates increasing the enantioselectivity of the process.[99]

The electrophilic cyclofunctionalizations of unsaturated substrates bearing an internal nitrogen nucleophile were largely studied in consideration of their synthetic relevance for the preparation of nitrogen containing heterocycles, especially in the total synthesis of alkaloids.

Primary amines are scarcely reactive in the presence of electrophilic reagents, whereas secondary amines or amines functionalized with an electron-withdrawing group, such as carbamates or tosylates, efficiently afford the corresponding heterocycles.[100] Selected examples are collected in Scheme 51.



Scheme 49 Asymmetric selenoetherification and lactonization.



Scheme 50 Catalytic enantioselective selenoetherification of alkenols.

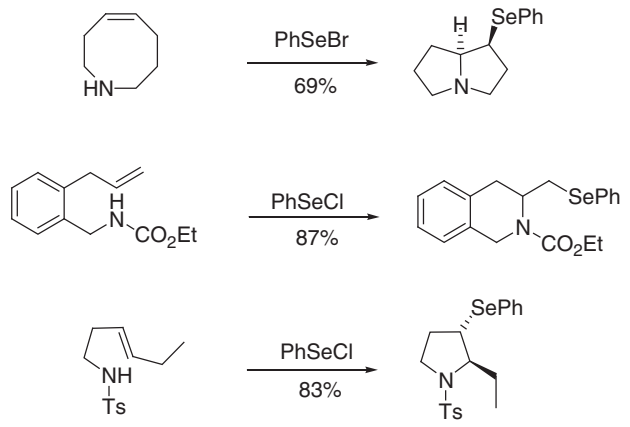
The processes are usually characterized by high stereoselectivity involving a seleniranium ion intermediate that drives the cyclization according to a *trans*-addition mechanism and, concerning the regiochemistry, it is mainly correlated to the nature of the substrate (Scheme 52).

Homoallylic secondary amines **185** showed a competition between a 5-*endo-trig* and a 4-*exo-trig* process, affording a mixture of azetidine **186** and pyrrolidine **187**. The regioselectivity depends on the nature of the substituents R^1 and R^2. In the case of unsubstituted substrates ($R^1=R^2=H$), the pyrrolidine was the major product (**186**/**187**=18:82) whereas in the case of a double substitution with a methyl group ($R^1=R^2=Me$), a larger amount of azetidine was obtained (**186**/**187**=83:17).[100,101]

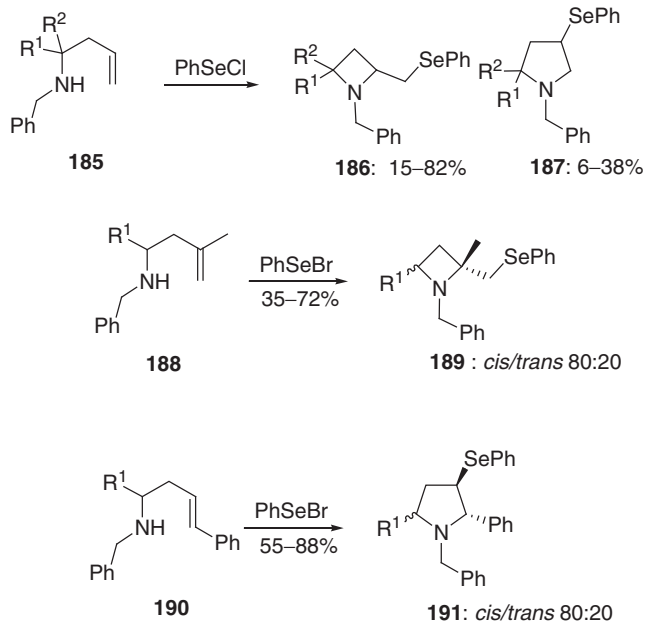
The presence of a methyl group in the γ-carbon of the homoallylic amine **188** afforded azetidine **189** as the only regioisomer in a mixture of *cis*/*trans* isomers with a large prevalence for the *cis*. Furthermore, when the substituent is a phenyl group in the δ-position (**190**), only the pyrrolidine **191** was obtained in a good yield and, also in this case, the 2,4-*cis* isomer was the major product. Increasing the size of the substituent R^1, a Thorpe Ingold effect is responsible for an appreciable enhancement of the yield, even if the effect on the stereoselectivity is not evident (Scheme 52).[102]

Similarly, isoxazolines can be prepared by cyclization of *O*-allylhydroxylamines with phenylselenenyl sulfate[103] or by cyclization of *O*-allyloximes with PhSeBr followed by reduction of the corresponding iminium salts intermediate.[104] The iminium salts could be alternatively hydrolyzed, affording the corresponding N–H oxazolines,[105] and when the reaction was activated by optically pure selenenylating reagents, the same heterocycle was obtained with a stereoselectivity up to 95% *de*.[106]

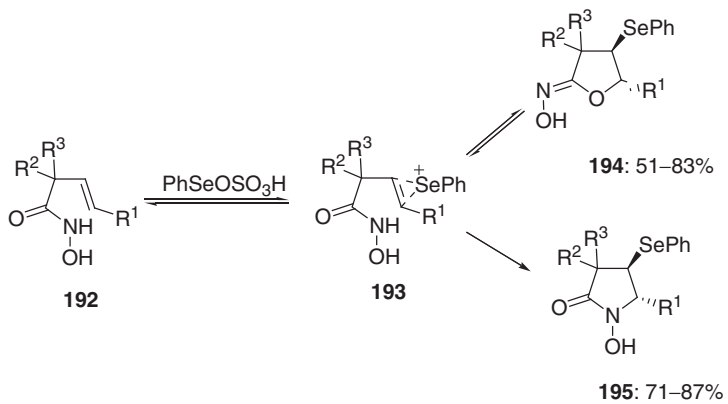
In some cases the nitrogen nucleophile is incorporated in a functional group together with other nucleophilic atoms, and two competitive cyclization mechanisms could be envisioned and controlled in different ways. As an example, alkenyl hydroxamic acids (**192**) can be cyclized using phenylselenenyl sulfate affording cyclic *N*-hydroxy imidates (**194**) when the nucleophile is the oxygen, or *N*-hydroxy γ-lactams (**195**) when the nucleophile is the nitrogen (Scheme 53).



Scheme 51 Synthesis of nitrogen containing compounds.



Scheme 52 Regio and stereoselectivity.



Scheme 53 Cyclization of alkenyl hydroxamic acids.

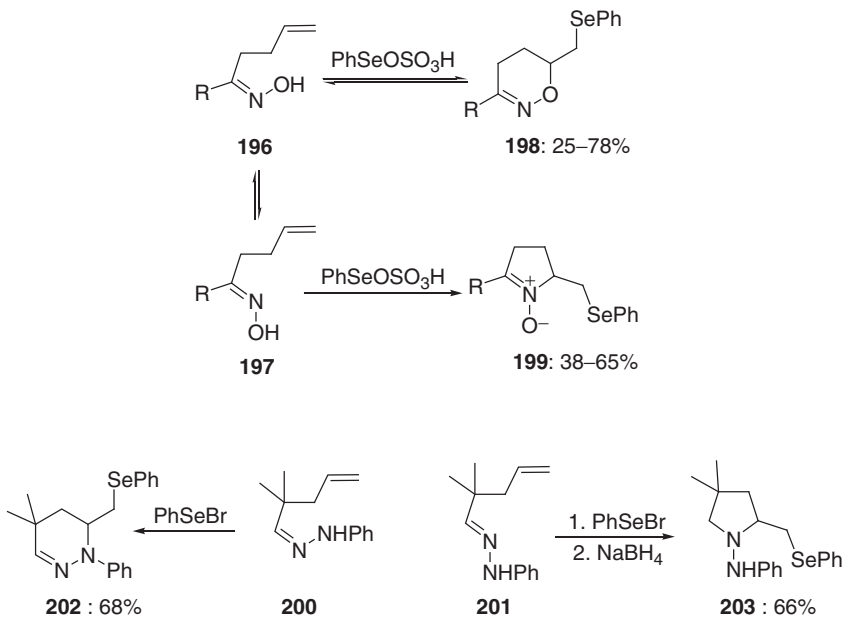
The chemoselectivity of the process can be controlled using kinetic conditions for the formation of **194** or thermodynamic conditions for the synthesis of **195** (Scheme 53).[105]

Differently, in the cases of alkenyl oximes and alkenyl phenylhydrazones, the chemoselectivity depends on the geometry of the functional group leading to a 5-*exo*-*trig* or a 6-*exo*-trig cyclization. Starting from the oximes **196** and **197**, the 1,2 oxazines **198** or alternatively the cyclic nitrones **199** should be obtained by the nucleophilic cyclization on the seleniranium ion of the oxygen or the nitrogen, respectively.[107]

The formation of 1,2-oxazones is a reversible process and, for long reaction times in the presence of the electrophilic phenylselenenyl sulfate, cyclic nitrones such as **199** are formed by isomerization between **196** and **197**.

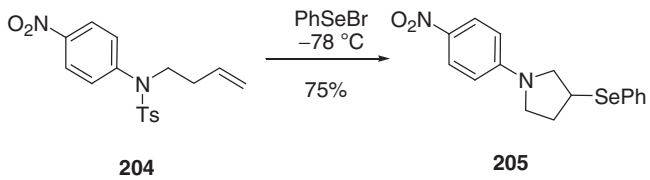
Optically pure electrophilic reagents were employed for the stereoselective synthesis of 1,2-oxazones as well as cyclic nitrones with a diastereomeric excess ranging from 50% to 92%.[106]

Both the amino and the imino nitrogen can be the internal nucleophile for the cyclization of phenylhydrazones **200** and **201**. Depending on the *syn*/*anti* geometry of the hydrazone, the process leads to the tetrahydropyrazine **202** or to an iminum salt that is reduced *in situ* by $NaBH_4$, affording **203** (Scheme 54).[108]



Scheme 54 Cyclization of oximes and phenylhydrazones.

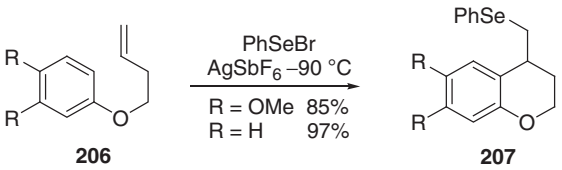
N-*p*-toluenesulfonamide **204** reacted at low temperature with $PhSeSbF_6$ leading to the *N*-arylpyrrolidine **205** according to an electrophilic promoted detosylative cyclization[109] (Scheme 55).



Scheme 55 Detosylative cyclization.

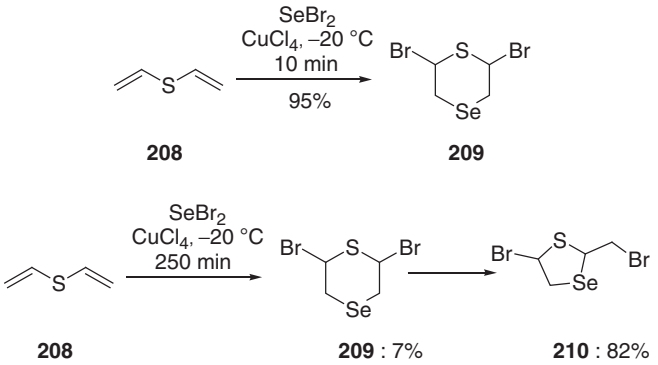
Recently, Lim and RajanBabu reported an updated version of the Friedel–Crafts like carbocyclization first proposed by Deziel and coworkers in 1998.[109] PhSeBr, in the presence of $AgOSbF_6$ in aqueous dichloromethane at $-80/-90\ ^{\circ}C$, converted **206** into the expected product **207** in 85% yield, and the reaction proceeds also with nonactivated aromatic carbon centered nucleophiles (97% yield) without competition with the hydroxyselenenylation process (Scheme 56).[110]

The synthesis of the selenium heterocycles can be realized by the addition reaction of selenium dibromide to divinyl sulfide **208**. The reaction proceeds in CCl_4 at room temperature and gives the thiaselenane **209** that, even at low temperature in chloroform solution, underwent spontaneous rearrangement to the 5-membered thiaselenolane **210** (Scheme 57).[111]



206 **207**

Scheme 56 Carbocyclization.



208 **209** **209** : 7% **210** : 82%

Scheme 57 Synthesis of selenium heterocycles.

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7.21 Addition Reactions with Formation of Carbon–Halogen Bonds

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Glossary

Aminohalogenation A reaction where an alkene is oxidized under the formation of a carbon–nitrogen and a carbon–halogen bond to give a vicinal difunctionalized haloaminoalkane.

Atom transfer radical addition (ATRA) The addition of a carbon–heteroatom bond across a carbon–carbon double bond to form a new carbon–carbon as well as a new carbon–heteroatom bond. Usually carried out as a radical reaction, often under transition metal catalysis.

Atom transfer radical cyclization (ATRC) The intramolecular addition of a carbon–heteroatom bond across a carbon–carbon double bond to form a new carbon–carbon as well as a new carbon–heteroatom bond and a new ring. Usually carried out as a radical reaction, often under transition metal catalysis.

Carbohalogenation A reaction where an alkene is oxidized under the formation of a carbon–carbon and a carbon–halogen bond to give a haloalkane.

Dihalogenation An oxidation of an alkene where two new carbon–halogen bonds are formed to give vicinal dihaloalkanes. Dihalogenations using electrophilic halogenating agents proceed via *anti*-addition of the two halogens onto the alkene.

Halocyclization A halogen-induced oxidative cyclization reaction of alkenes onto a tethered nucleophile such as a hydroxy (haloetherification), carboxy (halolactonization), or amino (aminohalogenation) group.

Haloetherification An oxyhalogenation reaction of an alkene where the oxygen nucleophile is an alkoxy group, usually carried out as intramolecular haloetherification on alkenol substrates.

Halolactonization An oxyhalogenation reaction of an alkene where the oxygen nucleophile is a tethered carboxylic acid group, leading to the formation of a lactone carrying a ω-(1-haloalkyl) substituent.

Oxyhalogenation A reaction where an alkene is oxidized under the formation of a carbon–oxygen and a carbon–halogen bond to give a vicinal difunctionalized haloalkanol.

The decades since the publication of the previous volume have seen an immense growth in the development of methods for selective carbon–halogen bond formation by addition reactions to unsaturated functional groups. The diversity of transformations and the sheer breadth of the topic thwart a comprehensive treatise. Restrictions will therefore apply, and the authors decided to limit themselves to either established methods that stand out in terms of generality and the number of reported applications or recent methods that hold future promise. As to the functional groups covered, the focus is on alkenes (usually not conjugated to a carbonyl/carboxyl group) as acceptors. Preformed or *in situ*-generated enamines and enol ethers are not included as these carbon–carbon double bonds are not alkenes in a strict sense. The exclusion of alkynes and allenes is in continuation to the previous chapter. The chapter is organized according to the bond being formed along with the carbon–halogen bond and that includes bond formations to halogens, hydrogen, oxygen, nitrogen, as well as carbon.

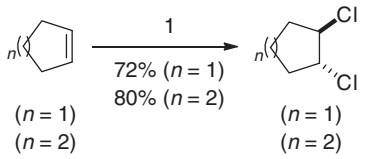
7.21.1 Dihalogenation Reactions

7.21.1.1 Dichlorination Reactions

7.21.1.1.1 Nonstereoselective and diastereoselective dichlorination reactions

7.21.1.1.1.1 Hypervalent iodine reagents

Hypervalent iodine reagents, such as (dichloroiodo)benzene, have been used as potent halogenation reagents. However, due to the low atom economy and the difficult separation of the by-product iodobenzene, their use is rather limited. As an alternative, biphasic[1] and polymer-supported[2] systems have been reported, which allow for easier handling and recycling of the iodo reagents. Using the latter method, cyclopentene and cyclohexene can react to the corresponding *trans*-dichlorocycloalkenes in good yields up to 80% (equation 1).



(n = 1) (n = 1)
(n = 2) (n = 2)

(1)

1. 1.5 equivalents $PhICl_2$ (polystyrene-supported), CH_2Cl_2, r.t., 2 h

7.21.1.1.1.2 Manganese-mediated dichlorination

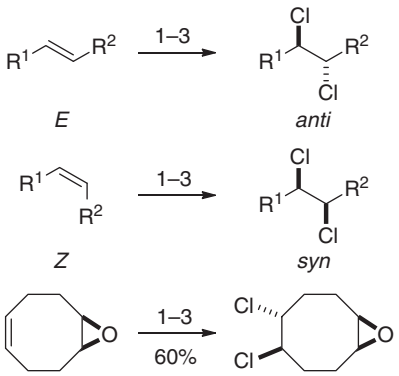
Another possibility for the *vic*-dichlorination of alkenes is the use of manganese reagents in the presence of a chloride source such as oxalyl chloride or acetyl chloride.[3] Unfortunately, these systems suffer from low stability of the manganese reagent and erratic results. Further development led to a reliable protocol, in which benzyltriethylammonium permanganate reacts with the alkene in the presence of Me_3SiCl in CH_2Cl_2 (Scheme 1).[4] The permanganese species is formed *in situ* by stirring powdered $KMnO_4$ with the phase-transfer reagent benzyl triethylammonium chloride. The resulting dichlorides are obtained in good to excellent yields (60–95%), where reaction of (*E*)-alkenes leads to the formation of the *anti*-dichlorides and reaction of (*Z*)-alkenes to the *syn*-dichlorides.

7.21.1.1.1.3 Tetraethylammonium trichloride

Mioskowski first introduced tetraethylammonium trichloride as a chlorinating agent.[5] This reagent is prepared by bubbling elemental chlorine through a solution of tetraethylammonium chloride in CH_2Cl_2. The resulting trichloride reacts with a range of different substrates including alkenes **1** in good to excellent yields. Based on these results, a diastereoselective protocol was developed for the synthesis of compounds of type **2**, precursors of a range of different chlorosulfolipids (Scheme 2).[6]

7.21.1.1.1.4 Organocatalytic diastereoselective dichlorination

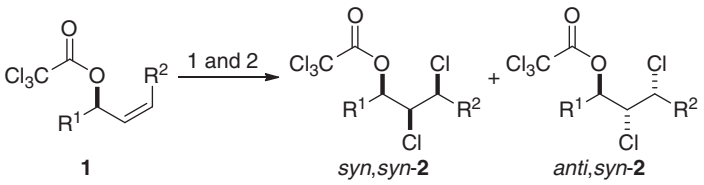
In the course of their study on the diastereoselective dibromination of unsaturated compounds, Barbas III also investigated the dichlorination of cyclohexene with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH, **4a**) in the presence of catalytic amounts of the thiourea **3** (Scheme 3).[7] The corresponding dichloride was obtained in 98% yield and a diastereoselectivity of 96:4 (*trans*/*cis*). Unfortunately, no other substrates are shown in this work, nor any comment is made about the general applicability of this system in the diastereoselective dichlorination.



R^1	R^2		Yield
$Pent^n$	H	–	86%
$(CH_2)_3OTBS$	H	–	82%
Ph	Ph	*E*	95%
Bu^n	Bu^n	*E*	94%
$Pent^n$	Me	*E*	84%
Bu^n	Bu^n	*Z*	81%
$–(CH_2)_4–$		*Z*	87%

1. 1.0 equivalent $KMnO_4$, 1.0 equivalent $BnEt_3N^+Cl^–$, 4.0 equivalents Me_3SiCl, CH_2Cl_2, 20 °C, 45 min; 2. alkene, CH_2Cl_2, 0 °C, 40 min; 3. aqueous $Na_2S_2O_3$

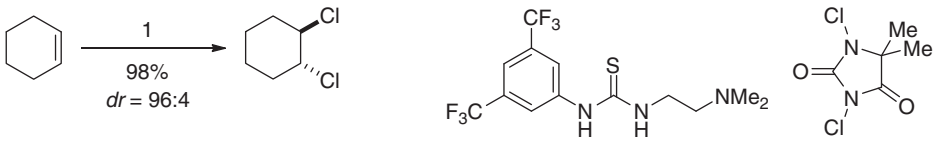
Scheme 1



R^1	R^2	*dr*	Yield
$Ph(CH_2)_2$	Bu^n	89:11	82%
$Ph(CH_2)_2$	CH_2OTBS	91:9	70%
Pr^i	Bu^n	88:12	77%
Me	$CH_2CH(OMe)_2$	89:11	78%
Bu^t	Bu^n	90:10	77%
CH_2OBn	Bu^n	82:18	67%

1. 10 equivalents $Et_4N^+Cl_3^–$, CH_2Cl_2, –90 °C, 90 min then –78 °C, 2 h;
2. Saturated aqueous $Na_2S_2O_3$:saturated aqueous $NaHCO_3$ (1:1)

Scheme 2



1. 20 mol% **3**, 1.5 equivalents **4a**, CH_2Cl_2, r.t., 3 h

3

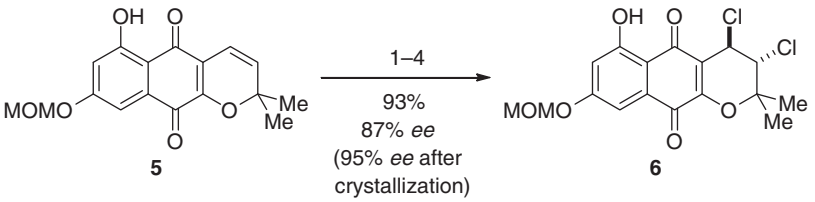
DCDMH (**4a**)

Scheme 3

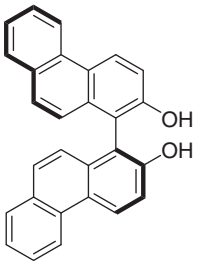
7.21.1.1.2 Enantioselective dichlorination reactions

7.21.1.1.2.1 Stoichiometric reactions

Snyder described a highly asymmetric dichlorination in the enantioselective total synthesis of (–)-Napyradiomycin A1 by using Cl_2 in the presence of 4 equivalents of a complex prepared from $BH_3 \cdot THF$ and the chiral diol (*S*)-**7** (Scheme 4).[8] The product **6** was obtained in 93% yield and 87% *ee* (95% *ee* after recrystallization). The use of a smaller amount of (*S*)-**7** was not possible, but the ligand can be recovered and recycled as long as the reaction is conducted in tetrahydrofuran (THF). In addition, the ligand also



1. 4.0 equivalents **7**, 4.0 equivalents BH_3·THF, 4.0 equivalents glacial AcOH, THF, r.t., 20 min;
2. Concentration; 3. **5**, THF, 25 °C, 1 h; 4. Cl_2 in CH_2Cl_2, 20 °C, –78 °C, 20 min



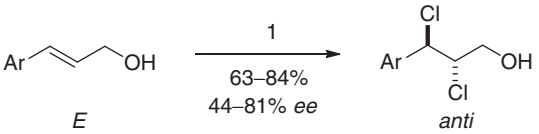
(*S*)-**7**

Scheme 4

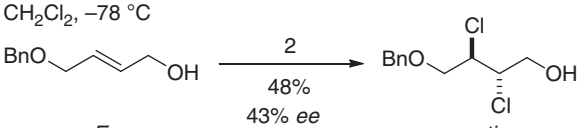
prevents chlorination of the aromatic ring, due to its steric bulk. In fact, no side products by over chlorination are observed. However, no other substrates are tested, giving no insight into the general applicability of the method.

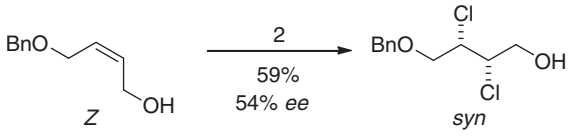
7.21.1.1.2.2 Enantioselective organocatalytic dichlorination reactions

Nicolaou developed the only organocatalytic protocol for the enantioselective dichlorination of alkenes (Scheme 5).[9] By using a catalytic amount of $(DHQ)_2PHAL$ (**8**) and hypervalent aryl iododichlorides, allylic alcohols react to yield the corresponding dichloro compounds. Depending on the substrate, different aryl iododichlorides are employed leading to the corresponding

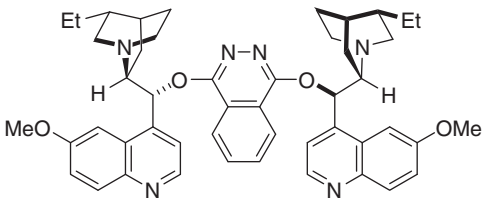


1. 20 mol% $(DHQ)_2PHAL$ (**8**), 1.6 equivalents 4-Ph(C_6H_4)ICl_2, CH_2Cl_2, –78 °C





2. 20 mol% $(DHQ)_2PHAL$ (**8**), 1.6 equivalents $PhICl_2$, CH_2Cl_2, –78 °C



$(DHQ)_2PHAL$ (**8**)

Scheme 5

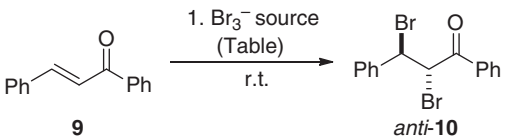
anti-dichloro adducts in good yields (up to 84%) and moderate to good enantioselectivity from 43% to 81% *ee*. The substrate scope is quite large, tolerating differently substituted cinnamyl substrates, naphthyl substrates, and sterically demanding allylic alcohols. However, very electron-deficient allylic alcohols failed to react. In the case of electron-rich cinnamyl compounds, the dichlorination was very fast but the corresponding products are prone to epimerization.

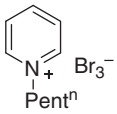
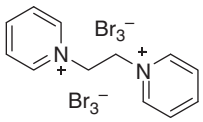
7.21.1.2 Dibromination of Alkenes

7.21.1.2.1 Nonstereoselective and diastereoselective dibromination reactions

7.21.1.2.1.1 Tribromide reagents

Ammonium and pyridinium tribromides are useful reagents for the bromination of organic molecules due to their lower toxicity and easy handling compared to elemental bromine. However, in many cases bromine is used in the synthesis of tribromides, which only shifts the use of this reagent to an earlier stage of synthesis. To avoid elemental bromine in the synthesis of ammonium tribromides, Chaudhuri used vanadium-catalyzed oxidation of the corresponding ammonium bromide with H_2O_2.[10] Tetrabutylammonium tribromide was then used in the dibromination of chalcone (**9**), styrene, and cinnamic acid. The moderate yields of 60–65% can be explained by phase-transfer properties of the resulting ammonium bromide, which lead to tedious purification of the products. In addition, due to these properties a substantial amount of the ammonium cations are lost, making recovery and recycling difficult. Another disadvantage is the generation of heavy metal waste due to the use of substoichiometric amounts of V_2O_5. A very elegant way to solve the extraction problems is the use of pentylpyridinium tribromide for the dibromination of alkenes.[11] The reactions are conducted without any additional solvent, leading to the precipitation of the products after addition of water, while the pentylpyridinium bromide dissolves in water. The dibromides are obtained in good yields up to 92%. A drawback of this method is again the use of elemental bromine for the synthesis of the tribromide. This problem was addressed by using a solvent-, metal-, and ionic liquid-free method, which makes use of a novel dibromide reagent.[12] This reagent has a higher bromine content per molecule and a better bromination efficiency and selectivity and is also devoid of phase-transfer properties. The tribromide is synthesized by oxidation of KBr with oxone, and the method allows for easy recovery and regeneration of the bromination reagent and exhibits a larger substrate scope. An overview of the different methods is given in Scheme 6.



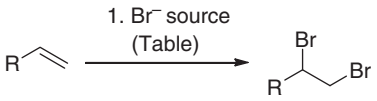
Br_3^- source	Equivalent	Yield	References
$Bu^n_4N^+Br_3^-$	1.0	65%	10
	1.0	85%	11
	0.5	92%	12

Scheme 6

7.21.1.2.1.2 Oxidative bromination using bromide reagents

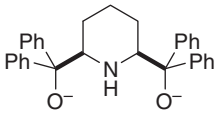
Oxidative bromination reactions using bromides are a very elegant way for the dibromination of alkenes due to the low toxicity, high atom economy, and easy handling compared to elemental bromine or other reagents. However, it is necessary to oxidize the bromide to the corresponding electrophilic bromine species. In fact, bromination *in vivo* is catalyzed by the naturally occurring enzyme vanadium bromoperoxidase (VBrPO). Several systems have been introduced to mimic this system using different catalysts and oxidation reagents. Ammonium metavanadate has been used as an efficient catalyst in the presence of H_2O_2 or atmospheric oxygen.[13] However, these systems suffer from high catalyst loadings and work only in the presence of a strong acid (either $HClO_4$ or CF_3COOH), hence limiting the substrate scope to compounds that are tolerant to these harsh conditions. To circumvent these limitations, new acid-free vanadium-based catalytic systems have been introduced. Mizuno showed that a divanadium-substituted phosphotungstate could act as an effective homogeneous catalyst in this transformation, with low catalyst loadings (0.05 mol%).[14] Unfortunately, despite the absence of any acid as a co-catalyst, the substrate scope for the dibromination presented in this study is limited to aliphatic alkenes. A larger substrate scope for a vanadium-catalyzed oxidative bromination was reported by Hartung. By using vanadium(V) complexes in the presence of β-bromo carboxylic acids as bromide sources, dibromination of different alkenes is possible even in the presence of an acid-labile acetal group with low catalyst loadings (1.0 mol%) in moderate yields from 59 to 73%.[15] As a transition metal-free alternative, a bromide/bromate (5:1) couple can be used, in which elemental bromine is formed *in situ* in the presence of hydrochloric acid.[16] This method allows dibromination of a reasonably broad substrate scope in good to high yields up to 98%, including esters, enones, and styrene derivatives. A drawback

of this reaction is the use of stoichiometric amounts of $NaBrO_3$ as oxidant and the formation of one equivalent of NaCl as the side product. This can be avoided by the use of sodium nitrite as catalyst. In this case, the catalytically active species is NO_2, which oxidizes HBr to elemental bromine. The resulting nitric oxide is then reoxidized by air, resulting in a catalytic cycle in which H_2O is the only side product. This catalytic system is applicable to various alkenes, alkynes, esters, and styrene derivatives.[17] An overview of the different methods is given in Scheme 7.

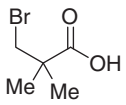


R	Catalyst	Oxidant	Br^- source	Solvent/*T*	Yield	References
Hex^n	100 mol% $NH_4^+VO_3^-$	2.0 equivalents H_2O_2	5.0 equivalents KBr	H_2O:$CHCl_3$ (1:1) 25 °C	95%	13a
Oct^n	5.0 mol% $NH_4^+VO_3^-$	1 atm O_2	3.0 equivalents $NH_4^+Br^-$	3.0 equivalents TFA 1,4-dioxane 80 °C	97%	13b
Hex^n	0.05 mol% $[NH_4^+]_4[\gamma\text{-}HPV_2W_{10}O_{40}]^{4-}$	1.0 equivalent H_2O_2	2.0 equivalents KBr	AcOH:1,2-$C_2H_4Cl_2$ (2:1) 20 °C	79%	14
Oct^n	1.0 mol% VO(**11**)(OEt)	1.6 equivalents Bu^tOOH	0.10 equivalent NaBr[a]	Propylene carbonate[b] 30 °C	71%	15
Hex^n	–	0.4 equivalent $KBrO_3$	2.0 equivalents KBr	AcOH r.t.	90%	16
Hex^n	5.0 mol% $NaNO_2$	1 atm air	2.0 equivalents aqueous HBr	MeCN 22 °C	92%	17

[a] 2.5 equivalents of **12** added as a catalytically activated Br^-source.
[b] Cyclohexa-1,4-diene added as co-solvent.



11

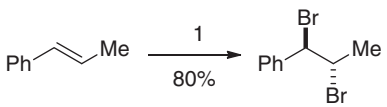


12

Scheme 7

7.21.1.2.1.3 Bromination using hypervalent iodine reagents as oxidant

The reaction of *β*-methyl styrene (**13**) with bisacetoxyiodobenzene (BAIB) and pyridine · HBr in CH_2Cl_2 leads to the *anti*-dibromo addition product **14** in 80% yield (equation 2).[18] It was shown that this reaction proceeds through a cationic intermediate and that halide addition to the cation is faster than an intramolecular nucleophilic attack. It was shown that the pyridine · HBr is oxidized by BAIB to generate an electrophilic bromine source, which reacts with the double bond, generating a carbenium ion, which then reacts with the bromide to form the dibromide. Interestingly, competition experiments with compounds bearing a nucleophilic heteroatom such as pent-4-en-1-ol did not lead to the corresponding heterocycle, which shows that the halide addition to the cation is faster than an intramolecular capture. A small substrate scope was examined as well, tolerating alcohols and protected amines.

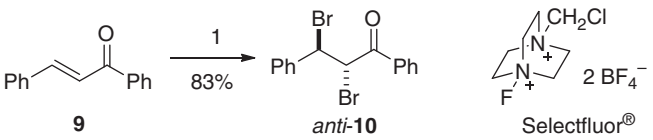


13 **14** (2)

1. 1.2 equivalents $PhI(OAc)_2$, 2.4 equivalents py·HBr, CH_2Cl_2, r.t., 6 h

7.21.1.2.1.4 Bromination using Selectfluor® as Oxidant

Besides being a versatile fluorination reagent for alkenes among others, Selectfluor® is also known to generate useful electrophiles, such as Cl^+ and Br^+.[19] By using Selectfluor® with KBr as bromide source in an MeCN:H_2O mixture, various enones such as chalcone (**9**) and styrenes undergo *trans*-dibromination in good yields up to 89% (equation 3).[20]



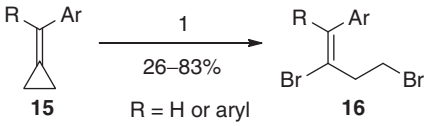
9 *anti*-**10** Selectfluor®

(3)

1. 2.5 equivalents KBr, 2.0 equivalents Selectfluor®, MeCN:H_2O(25:1), r.t., 2 h

7.21.1.2.1.5 Oxidative bromination using N-bromosuccinimide

N-Bromosuccinimide (NBS) in combination with LiBr can also be used in the dibromination of alkenes, alkynes, and allenes.[21] Even though NBS also serves as a bromination reagent via a radical pathway, it can also be a source of electrophilic Br^+. The dibromination reaction proceeds within minutes at room temperature in THF and leads to the products in good yields (up to 94%). In addition, the protocol can be used for the dibromination of a range of methylenecyclopropanes of type **15** to form the 2,3-dibrominated products 16 (equation 4).



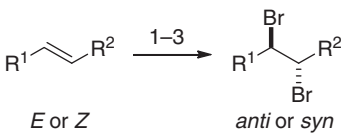
15 **16**

(4)

1. 2.0 equivalents LiBr, 2.0 equivalents NBS, THF, r.t., 2 min

7.21.1.2.1.6 Manganese-mediated reactions

Based on the previous work by Markó in the manganese-mediated dichlorination of alkenes,[3,4] *trans*-dibromination reactions with related systems have been reported.[22] In this case, tetradecyltrimethylammonium permanganate is used to overcome the low solubility of potassium permanganate, and bromotrimethylsilane is used as a bromine source. The dibromides are obtained in moderate to good yields of 60–91% (**Scheme 8**). In addition, it is possible to dibrominate internal and terminal alkenes selectively in the presence of α,β-unsaturated ketones.



E or *Z* *anti* or *syn*

R^1	R^2		Yield
Bu^t	H	–	62%
Ph	Ph	*E*	60%
$-(CH_2)_4-$		*Z*	79%

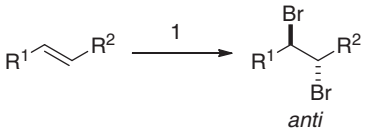
1. 1.0 equivalent $[n\text{-}C_{14}H_{29}Me_3N]^+[MnO_4]^-$, 2.05 equivalents Me_3SiBr, CH_2Cl_2, 0 °C; 2. alkene, CH_2Cl_2, 0 °C, 1.5 h; 3. aqueous $NaHSO_3$

Scheme 8

7.21.1.2.1.7 Organocatalytic dibromination

Zhao and Córdova has described the first organocatalytic method for the diastereoselective dibromination.[23] A range of alkenes and enones react with NBS in the presence of catalytic amounts of succinimide and pyrrolidine to afford the dibrominated *anti*-products in moderate to good yields (52–90%) and good diastereomeric ratios of >90:10 (**Scheme 9**). Remarkably, NBS acts in this reaction as a source of both Br^+ and Br^-. The substrate scope is limited to differently substituted *trans*-cinnamaldehydes, simple terminal and internal alkenes, and some styrene derivatives.

A milder version of this reaction with even higher diastereomeric ratios was reported by Barbas III. They were able to show that different thiourea derivatives are able to catalyze the diastereoselective dibromination of alkenes with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, **17**) as bromination reagent in CH_2Cl_2 at ambient temperature.[7] Especially the use of the amine-containing thiourea catalyst **3** leads to the corresponding *anti*-dibromoalkanes in high yields (74–99%) and high diastereoselectivities of >96:<4 (**Scheme 10**).

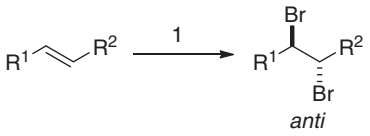


1. 2.2 equivalents NBS, 20 mol% succinimide, 20 mol% pyrrolidine, $CHCl_3$, 60 °C

R^1	R^2	*t*	*dr*	Yield
Ph	CHO	2 h	>96:<4	58%[a]
Bu^n	CHO	2 h	>96:<4	62%[a]
Ph	H	1.5 h	–	62%
Hex^n	H	4 h	–	47%
Ph	Ph	3 h	>91:<9	53%
Ph	Me	2 h	90:10	90%
$-(CH_2)_4-$		6 h	>91:<9	72%

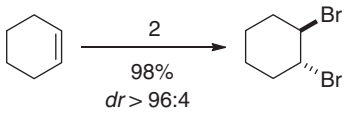
[a]Isolated yield after reduction with $NaBH_4$ in MeOH at 0 °C

Scheme 9

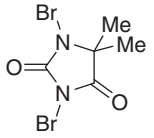


1. 20 mol% **3**, 2.0 equivalents **17**, CH_2Cl_2, r.t.

R^1	R^2	*t*	*dr*	Yield
Ph	CO_2Me	2 h	>96:<4	99%
Ph	C(O)Me	2.5 h	>96:<4	99%
$Pent^n$	C(O)Me	3 h	>96:<4	92%
Ph	NO_2	3 h	>96:<4	91%
Ph	CHO	12 h	>96:<4	78%
$Pent^n$	CHO	12 h	>96:<4	74%



2. 20 mol% **3**, 1.5 equivalents **17**, CH_2Cl_2, r.t., 4 h

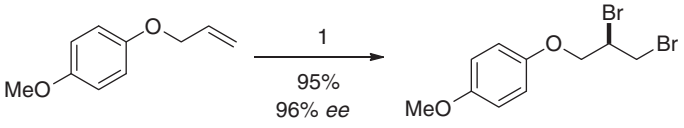


17

Scheme 10

7.21.1.2.2 Enantioselective dibromination

Despite the high interest in chiral dibromides as intermediates in the synthesis of bioactive compounds, there is to date only one report for the enantioselective dibromination of alkenes. Chiral *vic*-dibromo compounds can be synthesized by a reaction of the corresponding alkenes with $CuBr_2$ in the presence of catalytic amounts of a chiral palladium(II) complex (equation 5).[24] Interestingly, this reaction can be conducted in a mixture of H_2O and THF without the formation of the cognate bromohydrins, suggesting that the bromide anion is a better nucleophile than water. These results are interesting as the analogous reaction in the presence of $CuCl_2$ usually leads to the corresponding chlorohydrins.[25] The dibrominated products are obtained in high yields (up to 95%) and high enantioselectivities up to 97% *ee*. Enantioselectivities are poorer for internal alkenes such as cinnamyl alcohol (80% *ee*), and almost complete loss of enantioselectivity is observed when methyl *trans*-cinnamate is used. It is worth mentioning that the scope of chiral ligands and substrates presented in this study is rather small, leaving room for further improvement of this reaction.



(5)

1. 2.3 mol% $PdBr_2$, 2.3 mol% (*S*)-BINAP, 13.7 equivalents $CuBr_2$, 1.7 equivalents LiBr, 1 atm O_2, 20 ml $THF:H_2O$ (3:1), r.t., 6 days

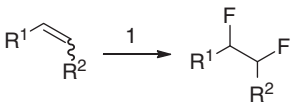
7.21.1.3 Difluorination Reactions

Despite the interest in fluorinated compounds and considerable progress in the field of (asymmetric) fluorination reactions, only little has been reported on the difluorination of alkenes. One of the most direct entries to vicinal difluorocompounds is the

addition of molecular fluorine to a carbon–carbon double bond.[26] But due to the high reactivity, high toxicity, and the cumbersome handling of fluorine gas, it is rarely used in organic synthesis. Therefore, other reagents that are able to perform this reaction are of high interest.

7.21.1.3.1 Xenon difluoride

As an alternative reagent, XeF_2 has been extensively studied in the difluorination of alkenes.[27] Although the reactions are generally quite slow, it has been shown that the use of XeF_2 in combination with a catalyst leads to better reaction performances.[28] Tamura reported the difluorination of styrene derivatives, stilbenes and 1,2-dihydronaphthalene with XeF_2 in the presence of catalytic amounts of SiF_4 (Scheme 11).[29] The corresponding difluorides were obtained in moderate to good yields of 64–87% but only in poor diastereoselectivity. Despite the advantages of XeF_2 compared to fluorine gas, XeF_2 is nevertheless a toxic compound and elemental fluorine is needed for its synthesis, only shifting the use of this toxic gas to an earlier stage of a synthesis.



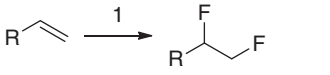
1. 1.2 equivalents XeF_2, 0.1 equivalent SiF_4, CH_2Cl_2, r.t., 3 h

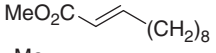
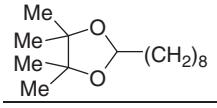
Alkene	Yield	*dr*
$Ph_2C{=}CH_2$	72%	–
E-PhCH=CHCH$_3$	64%	61:39
Z-PhCH=CHCH$_3$	71%	64:36
E-PhCH=CHPh	78%	66:34
Z-PhCH=CHPh	87%	55:45
1,2-Dihydronaphthalene	80%	25:75

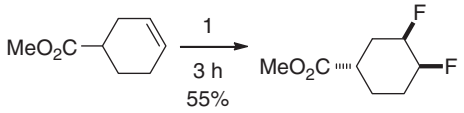
Scheme 11

7.21.1.3.2 Iodotoluene difluoride

A more versatile method was reported by Hara and Yoneda by using 4-iodotoluene difluoride (Scheme 12). In addition, this reagent can be prepared without the use of fluorine gas.[30] A mixture of 4-iodotoluene difluoride and 5 HF · Et_3N allows the difluorination of terminal and internal alkenes with a broad scope of substrates, such as alcohols, esters, acetals, and chlorides in moderate to good yields (53–70%).[31]



R	*t*	Yield
$C_{10}H_{21}$	2.5 h	65%
HO-$(CH_2)_9$	1 h	70%
AcO-$(CH_2)_9$	4 h	56%
Cl-$(CH_2)_9$	2 h	60%
AcO-$(CH_2)_4$	4 h	61%
MeO_2C–$(CH_2)_8$	2 h	68%
	1 h	55%
	4 h	53%



1. 1.3 equivalents 4-Me$C_6H_4IF_2$, 25 equivalents $Et_3N{\cdot}5HF$, CH_2Cl_2, –78 °C to 0 °C

Scheme 12

7.21.2 Hydrohalogenation Reactions

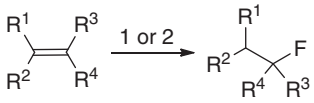
7.21.2.1 Hydrofluorination Reactions

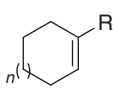
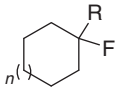
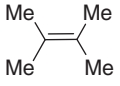
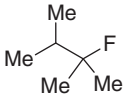
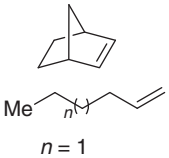
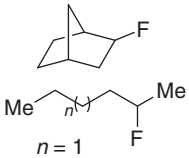
Despite the growing interest in fluorinated organic molecules and the broad spectrum of methods that can be used to introduce fluorine into organic molecules, the hydrofluorination of alkenes still remains a challenging transformation. This is mostly due to

the high reactivity and difficult handling of fluorinating reagents such as anhydrous HF, F_2, and other reagents.[32] As a less reactive alternative, Olah introduced the use of pyridinium/poly(hydrogen fluoride).[33] However, this method still suffers from drawbacks such as low functional group tolerance and difficulties in separation, handling, and stability. Therefore, more reliable and versatile methods are of high interest.

7.21.2.1.1 Poly(hydrogen fluoride) systems

As a further improvement to the poly(hydrogen fluoride)-based systems, Olah reported first the use of a poly(vinylpyridinium)/poly(hydrogen fluoride) complex[34] and later an even more stable dialkyl ether/poly(hydrogen fluoride) complex.[35] Both can be prepared by slowly adding condensed anhydrous hydrogen fluoride either to the commercially available cross-linked poly-4-vinylpyridine or to the ethers. The hydrofluorination with both complexes proceeds at 0–25 °C in 1–6 h, yielding the corresponding fluorinated compounds in good to excellent yields (72–94%, Scheme 13). Yet again, the substrate scope of both methods is rather limited and the authors do not comment on the functional group tolerance. However, it should be mentioned that both systems could also be used in the fluorination of alcohols and in the bromofluorination of alkenes.



Substrate	Product	Yield: Conditions 1	Yield: Conditions 2
			
n = 1, R = H	*n* = 1, R = H	76%	92%
n = 2, R = H	*n* = 2, R = H	81%	77%
n = 7, R = H	*n* = 7, R = H	60%	–
n = 1, R = Me	*n* = 1, R = Me	80%	–
		72%	94%
		79%	83%
n = 1	*n* = 1	–	73%[a]
n =7	*n* = 7	–	90%[a]

[a]Mixture of regioisomers.

1. Poly-4-vinylpyridinium poly(hydrogen fluoride) (PVP:HF (40%:60%)), CH_2Cl_2, 0–20 °C, 1–6 h; 2. Dimethyl ether/poly(hydrogen fluoride) (DME:PHF(1:5)), r.t., 1–3 h

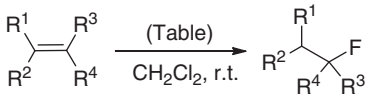
Scheme 13

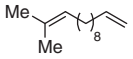
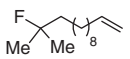
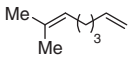
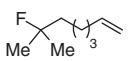
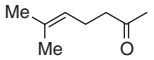
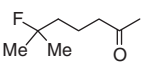
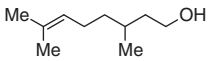
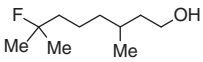
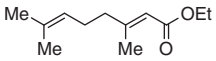
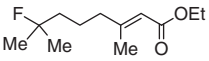
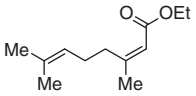
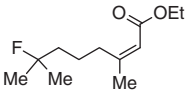
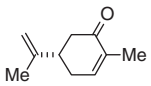
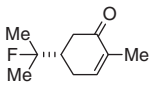
7.21.2.1.2 Hydrogen fluoride triethylamine complexes

A method with higher functional group tolerance to synthesize tertiary alkyl fluorides was reported by Hara and Yoneda.[36] By using the less reactive 5 or 6HF · Et_3N complexes, these authors were able to selectively hydrofluorinate branched alkenes in good yields (up to 82%) in the presence of a variety of functional groups (Scheme 14). However, the reaction times are rather long, and this method is limited to trisubstituted alkenes and cannot be used to prepare secondary or primary fluorides.

7.21.2.1.3 Iron-mediated hydrofluorination

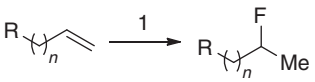
Recently, a versatile Fe(III)/$NaBH_4$-mediated hydrofluorination method was reported by Boger using Selectfluor® as a source of atomic fluorine.[37] The reaction can be conducted in the presence of air and uses water as a cosolvent and inexpensive reagents such as Fe(III) oxalate and $NaBH_4$. Due to the short reaction times and the possibility to use $NaBD_4$, the method can easily be applied for both ^{18}F- and deuterium-labeling experiments. The reaction proceeds with high regioselectivity, forming exclusively



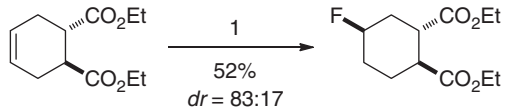
Substrate	Product	*n* HF·Et_3N	Time	Yield
		4.0 equivalents 5 HF·Et_3N	3 days	70%
		4.0 equivalents 5 HF·Et_3N	24 h	78%
		4.0 equivalents 5 HF·Et_3N	30 h	82%
		4.0 equivalents 6 HF·Et_3N	2 days	76%
		4.0 equivalents 5 HF·Et_3N	30 h	74%
		4.0 equivalents 5 HF·Et_3N	30 h	81%
		8.0 equivalents 6 HF·Et_3N	7 days	76%

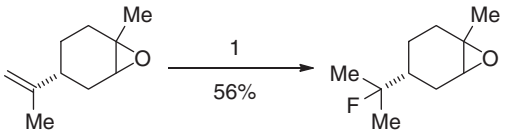
Scheme 14

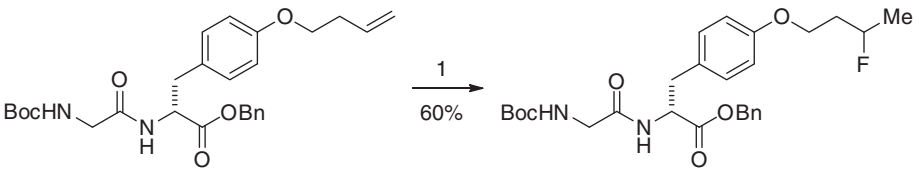
the Markovnikov products, and exhibits a quite general substrate scope, including protected and unprotected alcohols and amines, phenols, epoxides, ketals, acetals, carboxylic acids, carbamates, amide esters, peptides, and carbohydrates. Only styrenes proved to be ineffective under these reaction conditions, yielding the benzylic alcohols and the corresponding dimers of the benzylic radicals. Selected examples are shown in Scheme 15. Fluorolactonization is not observed under these conditions, but due to the radical mechanism of the reaction, it is possible to conduct a combined 5-*exo*-*trig*-cyclization/fluorination reaction by sequential addition of the reagents (not shown).



n = 8, R = OH, 75%
n = 8, R = OPMB, 70%
n = 3, R = COOH, 73%
n = 3, R = COOBn, 79%
n = 3, R = CONHBn, 75%
n = 2, R = COOH, 66%
n = 1, R = NHBz, 67%
n = 1, R = *o*-phenol, 60%
n = 1, R = NHBoc, 61%
n = 2, R = Ph, 55%







1. 2.0 equivalents $Fe_2(ox)_3$, 6.4 equivalents $NaBH_4$, 2.0 equivalents Selectfluor®, MeCN:H_2O (1:1), 0.0125 M, 0 °C, 30 min

Scheme 15

7.21.3 Oxyhalogenation

7.21.3.1 Intermolecular Oxyhalogenation

Intermolecular oxyhalogenation reactions of alkenes such as the halohydrin formation are well-established reactions for the heavier halogens chlorine, bromine, and iodine. Most electrophilic halogenating agents including the elemental halogens, *N*-haloamides and *N*-imides,[38] as well as oxidative halogenations[39] can be used in combination with a suitable oxygen nucleophile such as water, alcohols, or carboxylic acids[40] to achieve an oxyhalogenation. The formation of chlorohydrins and *β*-chloroethers from alkenes using an *N*-chloroimide, for example, *N*-chlorosuccinimide (NCS), is sometimes slow but can be catalyzed by thiourea.[41] Oxyfluorinations are much more difficult to achieve due to the lower reactivity of electrophilic fluorinating agents toward alkenes.

7.21.3.1.1 Oxyfluorination

In general, electrophilic oxyfluorinations have to be conducted on activated alkenes such as styrenes or allylic silanes to achieve acceptable yields. Stavber demonstrated that NFTh (also known as Accufluor®) is a convenient electrophilic source of fluorine for this type of reactions.[42] If used in acetonitrile together with water, an alcohol or a carboxylic acid as cosolvent, Accufluor® is effective in the oxyfluorinations of styrene derivatives (Scheme 16). The products, fluorohydrins, fluoroethers, or fluoroacetoxy derivatives, can be obtained with high yields (90–95%).



Accufluor®

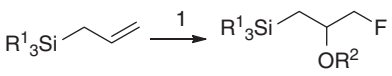
1. 1.0 equivalent. Accufluor®, MeCN:R^2OH (10:1), 35–80 °C, 30–60 min

R^1	R^2	Yield
H	H	90%
H	Me	92%
Me	H	93%
Me	Me	93%
Me	C(O)Me	90%
Ph	H	95%
Ph	Me	95%
Ph	C(O)Me	93%

Scheme 16

As an alternative to Accufluor®, the use of Selectfluor® is possible for electrophilic oxyfluorination reactions on styrene derivatives, again with good yields.[43] Selectfluor® is even compatible with water as the only solvent.[43b] An important difference between oxyfluorinations and oxyhalogenations with the heavier halogens is the stereochemistry of the addition. Because no cyclic fluoronium ion is formed, oxyfluorinations are not *anti*-selective and *syn*-additions are possible. In many cases, the stereoselectivity is low. For example, if Selectfluor® in water is used to oxidize *cis*-stilbene, the fluorohydrin is formed as a mixture of diastereomers (53:47).[43b]

Selectfluor® can also be applied in the oxyfluorination of allylic silanes.[44] The reaction was conducted in acetonitrile containing water or an alcohol as cosolvent (Scheme 17). When 1.5 equivalents of Selectfluor® were used, the products were obtained in moderate yields of 43–60%, largely independent of the substituents on the silicon atom or the oxygen nucleophile.



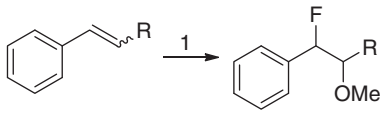
1. 1.5 equivalents Selectfluor®, MeCN:R^2OH (10:1), r.t., 24–36 h

R^1	R^2	Yield
Pr^i	H	60%
Pr^i	Et	61%
Pr^i	Pr^i	43%
Pr^i	Bu^n	60%
Pr^i	Allyl	61%
Ph	H	55%

Scheme 17

A different type of oxyhalogenation reagents are the hypofluorites such as methyl hypofluorite. It has been reported to methoxyfluorinate various alkenes including styrene derivatives (Scheme 18).[45] Interestingly, the fluorine atom in methyl hypofluorite is not electrophilic, resulting in a reversed regiochemistry of addition when compared to methods using electrophilic fluorinating agents.

The yields of the addition products are 75% for styrene and 70% for *β*-methylstyrene. However, for nonactivated alkenes such as cyclohexene, yields are often significantly lower and can be below 50%. Another problem is the synthesis of the reagent. Methyl hypofluorite has to be prepared from methanol and elemental fluorine, which causes significant handling problems.



R	Yield
H	75%
Me	70%

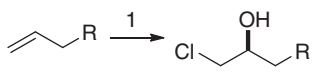
1. 1.4–4.0 equivalents MeOF, MeOH:MeCN:CH_2Cl_2, –40 °C to r.t., 5–25 min

Scheme 18

7.21.3.1.2 Asymmetric halohydrin synthesis

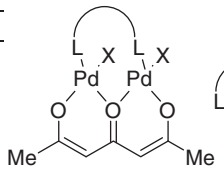
Despite the extensive developments in asymmetric intramolecular oxyhalogenations like the halolactonization, intermolecular asymmetric oxyhalogenations remain very challenging and difficult to achieve. Hajra investigated halohydrin formation on α,β-unsaturated carboxylic acid amides carrying a chiral auxiliary.[46] However, the stereoselectivities observed were in most cases only moderate (up to 64% *de*). Moderate enantioselectivities could also be achieved using chiral Brønsted acids to promote an intermolecular bromoesterification, but the reaction was not catalytic, the yields were low, and the valuable Brønsted acid was trapped by the substrate.[47]

A catalytic, asymmetric chlorohydrin synthesis related to the Wacker oxidation was reported by Henry.[25] These authors found that bimetallic palladium catalyst **18** is able to oxidize simple alkenes to the corresponding chlorohydrins with high enantioselectivity under high salt conditions (Scheme 19). The reaction medium consists of high amounts of copper chloride and lithium chloride dissolved in a THF/water mixture, and oxygen is used as terminal oxidant. On terminal alkenes such as propene or hex-1-ene turn-over-numbers of approximately 200 were observed and the chlorohydrin products were formed with enantioselectivities between 81 and 94% *ee*. Internal alkenes were not investigated, and only one example of a 1,1-disubstituted alkene was reported (2-methylbut-1-ene, 57% yield, 86% *ee*).[25b]

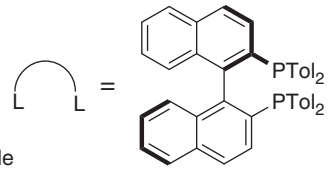


1. **18**, 3.0–5.0 M in $CuCl_2$, 0.1–2.2 M LiCl, O_2(atm), THF:H_2O, r.t.

R	*ee*
H	94%
Pr^n	81%
Bu^n	87%
OPh	93%



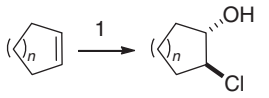
18



Tol-BINAP

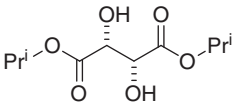
Scheme 19

Shibasaki described a rather general, catalytic chlorohydrin synthesis using tin Lewis acids as catalysts.[48] In combination with bis(trimethysilyl) peroxide (**20**) (stoichiometric oxidant) and trimethylsilyl chloride (chlorine source), internal alkenes can be efficiently oxidized to the chlorohydrins in 62–92% yield. On two occasions, the use of a chiral tin Lewis acid prepared from $SnCl_4$ and diisopropyl tartrate (**19**) was investigated (Scheme 20). The chlorohydrins of cyclopentene and cyclohexene were formed in good yield and with enantioselectivities of 56% and 58% *ee*, respectively. However, a more thorough investigation of this method is missing.

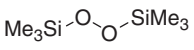


n = 1:76% yield, 56% *ee*
n = 2:86% yield, 58% *ee*

1. 10 mol% $SnCl_4$, 10 or 20 mol% **19**, 2.0 equivalents **20**, 2.0 equivalents Me_3SiCl, CH_2Cl_2, –20 °C



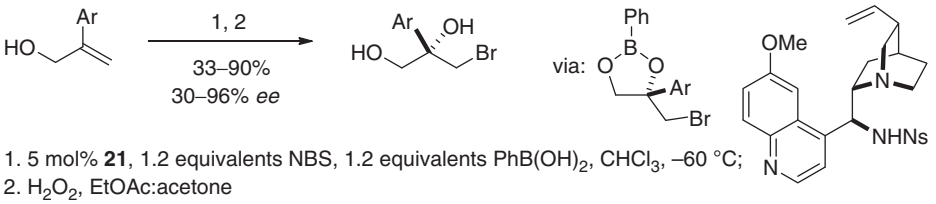
L-DIPT (**19**)



BTSP (**20**)

Scheme 20

The oxidation of allylic alcohols to bromohydrins is possible following a unique organocatalytic protocol.[49] Because the stereochemistry control in intermolecular oxyhalogenation is still difficult, the authors employed an esterification/cyclization strategy to establish the stereochemistry in an intramolecular reaction. The allylic alcohol is treated with phenyl boronic acid to form a boronate ester, which is cyclized in a one-pot procedure using NBS and a quinine-derived organocatalyst **21**. Subsequently, the boronate is hydrolyzed by H_2O_2 in ethyl acetate/acetone to give the bromohydrin. This strategy proved to be successful for allylic alcohols carrying an aromatic substituent in 2-position. The resulting bromohydrins were isolated in moderate to good yields and in most cases in high enantioselectivity (Scheme 21). However, this method is currently limited to a specific set of 2-substituted allylic alcohols whereas investigations on other substitution patterns are missing.



1. 5 mol% **21**, 1.2 equivalents NBS, 1.2 equivalents $PhB(OH)_2$, $CHCl_3$, –60 °C;
2. H_2O_2, EtOAc:acetone

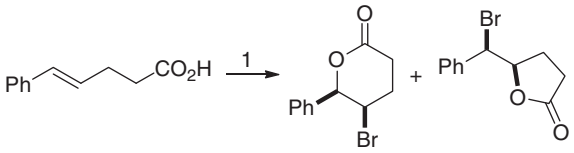
21

Scheme 21

7.21.3.2 Halolactonization

7.21.3.2.1 Nonstereoselective and diastereoselective halolactonizations

Chloro-, bromo-, and iodolactonization reactions can be induced by many electrophilic halogenating agents including the elemental halogens, Barluenga's reagent [$(Coll)_2IPF_6$], and *N*-haloamides and *N*-haloimides. The most commonly used reagents are the *N*-haloimides NBS and *N*-iodosuccinimide (NIS), respectively. Halolactonizations using NBS or NIS can be efficiently catalyzed by Lewis bases such as diphenyldiselenides,[50] amidines,[51] or guanidines.[52] An extensive study of Lewis base catalysis was conducted by Denmark, who could show that Lewis base catalysis does not only substantially accelerate halolactonization (and other alkene halogenations) but also influences the regiochemistry of the addition reaction (Scheme 22).[53] Lewis bases containing sulfur or selenium donor atoms are the most efficient catalysts and can be used in bromo- as well as iodolactonizations (not shown).



22 **23** **24**

1. 5 mol% Lewis base, 1.2 equivalents NBS, CH_2Cl_2, r.t.

Lewis base	$t_{1/2}$	t	**23:24**	Yield
none	>180	180	25:1	13%
$(Me_2N)_2C{=}O$	>180	180	23:1	36%
$Bu^n{}_3P{=}O$	>180	180	51:1	47%
$Bu^n{}_3P{=}S$	<0.5	8	75:1	89%
$(Me_2N)_3P{=}S$	<0.5	8	3.4:1	87%
$(CH_2)_4S$	<0.5	8	27:1	89%
$(PhSe)_2$	0.5–1	8	94:1	84%

Scheme 22

Only a few cases of fluorolactonization have been reported, which occur only on substrates containing activated alkenes (styrenes or norbornenes) and are rather low yielding.[54] For example, fluorolactonizations of norbornene carboxylic acids using Selectfluor® were described by Serguchev, resulting in the corresponding fluorolactones in 53–58% yield.[55]

7.21.3.2.2 Enantioselective chlorolactonization

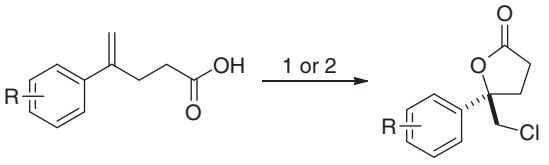
An organocatalytic method for the enantioselective chlorolactonization of 1,1-disubstituted alkenoic acids was developed by Borhan (Scheme 23).[56] Using a catalytic amount of the commercially available dimeric chinchona alkaloid derivative $(DHQD)_2PHAL$ (**8**) and 1,3-dichloro-5,5-diphenylhydantoin (DCDPH, **4b**), 4-arylsubstituted 4-pentenoic acids react via a 5-*exo* cyclization to the γ-lactone with generally high enantioselectivities (74–90% *ee*). With a electron-rich aryl group (R=OMe) or alkyl substituents on the alkene, only low enantioselectivies were achieved. The use of the commercially available halogenating agent (DCDMH, **4a**) leads to slightly lower enantioselectivity (less than 5% *ee* lower) but acceptable yields compared to **4b**.[57]

An alternative catalyst for this transformation was reported by Tang. Based on their previously developed catalyst for enyne halolactonizations,[58] these authors prepared a dihydroquinine-derived urea catalyst **25**. This catalyst was employed under convenient reaction conditions (commercially available **4a** as chlorinating agent) to promote the very same chlorolactonizations (Scheme 23).[59] The products were obtained in yields (76–99%) and with enantioselectivities (73–91% *ee*) comparable to those found with **8** as catalyst, whereas the limitations (alkyl- and electron-rich aryl groups on the alkene) remain the same.

7.21.3.2.3 Enantioselective bromolactonization

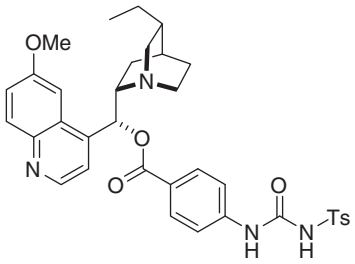
7.21.3.2.3.1 Organocatalytic approaches

A class of efficient thiocarbamate catalysts for asymmetric bromolactonizations has been developed by Yeung.[60] The catalysts are based on a cinchona alkaloid skeleton that is modified with a thiocarbamate group containing an electron-rich aryl ring. For example, thiocarbamate **26** based on cinchonidine can be used as catalyst (10 mol%) for asymmetric 5-*exo* bromolactonizations of 4-aryl-4-pentenoic acid-type substrates using cheap NBS as halogenating agent (Scheme 24).[60a] The reactions have to be conducted at low temperature and require the additive nosylamide. The products were obtained in good to excellent yields (67–99%) and generally with high enantioselectivities (70–99% *ee*). Even with bulky alkyl groups (*t*butyl and cyclohexyl) instead

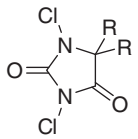


R	Conditions 1 Yield	*ee*	Conditions 2 Yield	*ee*
H	86%	89%	92%	–91%
4-Me	86%	80%	92%	–75%
4-Cl	80%	88%	92%	–84%
4-F	81%	89%	99%	–87%
4-OMe	99%	<5%	90%	–16%

1. 10 mol% **8**, 1.1 equivalents **4b**, 1.0 equivalent $PhCO_2H$, $CHCl_3$:*n*-hexane (1:1), –40 °C, 30–180 min;
2. 5 mol% **25**, 1.1 equivalents **4a**, $CHCl_3$:toluene (1:1), r.t.

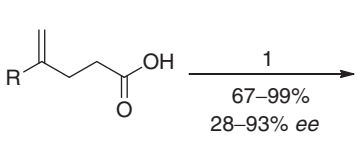


25

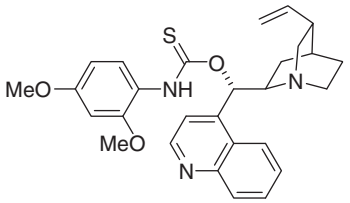


DCDMH (**4a** for R = Me)
DCDPH (**4b** for R = Ph)

Scheme 23



1. 10 mol% **26**, 1.2 equivalents NBS, 50 mol% $NsNH_2$, $CHCl_3$:toluene (1:2), –78 °C



26

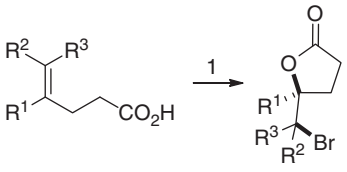
Scheme 24

of the aromatic ring, good enantioselectivities of 93 and 82% *ee* were observed. However, small alkyl groups (methyl, 41% *ee*) and electron-rich aryls gave only moderate selectivities.

Following the initial report, Yeung could show that this class of catalysts can be used in many related bromolactonizations if the chinchona alkaloid backbone and the substituents on the aromatic ring of the thiocarbamate group are carefully chosen. Enantioselective 6-*endo* bromolactonizations of 4-pentenoic acids with 1,2-disubstituted, (*E*)-configured alkenes are possible with quinidine-based thiocarbamate catalysts.[60b,c] Conversely, 1,2-substituted alkenes with *Z*-configuration react via the 5-*exo* mode, and a modification of the isochinoline ring of quinidine was necessary to obtain a highly enantioselective catalyst.[60d] One problem of chinchona alkaloid-based catalysts is their availability in only one enantiomeric form. If the other enantiomer is required, a pseudoenantiomer has to be used that can lead to significantly different selectivities in asymmetric halocyclization reactions. The chinchona alkaloid backbone of the thiocarbamate catalysts can also be replaced by simple prolinol derivatives. *S*- and *O*- alkyl prolinol thiocarbamates are active catalysts for 5-*exo* and 6-*endo* bromolactonizations, respectively.[60e] A clear advantage of these catalysts is their availability in both enantiomeric forms.

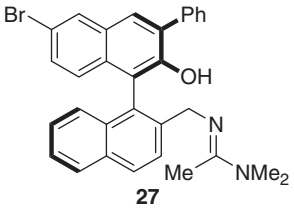
An alternative catalytic method for enantioselective bromolactonizations of 4-pentenoic acids was described by Martin.[61] They applied bifunctional catalyst **27** based on a 1,1′-bi-2-naphthol (BINOL) backbone that requires several steps to be prepared. Using **27** and the rather expensive halogenating agent 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) (**28**), alkyl-substituted (*Z*)-configured or 4-substituted pentenoic acids underwent 5-*exo* halolactonization with good to excellent enantioselectivities (70–97% *ee*, Scheme 25). However, (*E*)-configured alkenes reacted via the 6-*endo* mode, again with very good enantioselectivities (not shown). Interestingly, catalyst **27** is one of the very few that can be equally well applied in halocyclizations with a different halogen. **27** can be used in combination with NIS in iodolactonizations of the same substrates, leading to the formation of the iodolactonization products with very high enantioselectivities.[62]

An intriguing catalyst for the 6-*endo* bromolactonization of 5-hexenoic acids was reported by Fujioka. C_3-symmetric trisimidazoline **29**, which is proposed to activate the carboxyl group of the starting material, proved to be an efficient catalyst for this transformation in combination with the commercially available brominating agent DBDMH (**17**) (Scheme 26).[63] The reaction was preferentially conducted in toluene at low temperature (− 40 °C) on substrates containing an aryl substituent at the 5-position of the unsaturated carboxylic acid, leading to the products with generally high enantioselectivities (87–91% *ee*). Like in

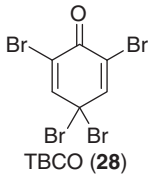


R^1	R^2	R^3	*ee*	Yield
H	H	Et	70%	90%
H	H	Pr^i	94%	94%
H	H	Cy	97%	94%
Ph	H	H	72%	99%
Me	Me	H	42%	89%

1. 10 mol% **27**, 1.2 equivalents **28**, CH_2Cl_2:toluene (1:2), –50 °C

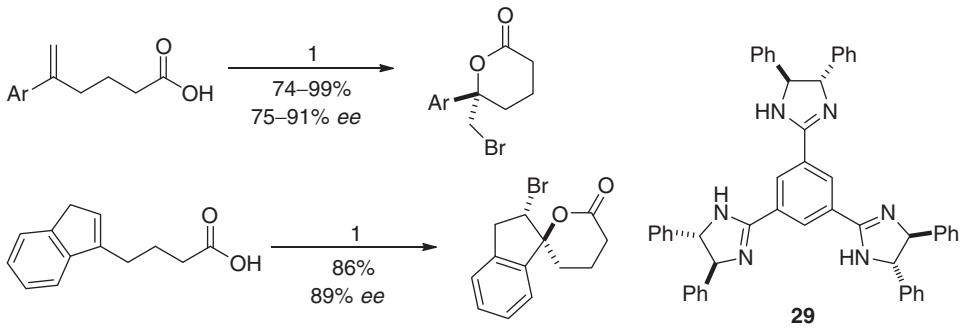


27



TBCO (**28**)

Scheme 25

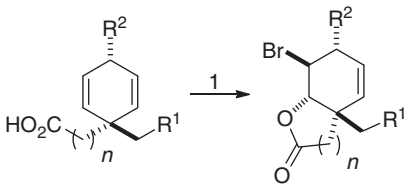


1. 10 mol% **29**, 1.0 equivalent **17**, toluene, –40 °C

Scheme 26

many related reactions, electron-rich aromatic and alkyl groups were detrimental to the enantioselectivity (72–80% *ee*). The cyclization of starting materials with a 1,1,2-trisubstituted alkene with (*Z*)-geometry was also possible and proceeded under the formation of two new stereocenters with high enantioselectivity (62–89% *ee*).

Bromolactonizations are also applicable to the desymmetrization of 1,4-cyclohexadiene carboxylic acid derivatives, easily available from benzoic acids by Birch reduction/alkylation. When treated with NBS and $(DHQD)_2PHAL$ (**8**), benzoic acid-derived cyclohexadienes underwent 4-*exo* cyclizations to the *β*-lactones, which were obtained with moderate to high enantioselectivity (47–92% *ee*, Scheme 27).[64] The scope of the reaction is intrinsically limited, but through homologation of the acid followed by 5-*exo* bromolactonizations, enantioenriched *γ*-lactones were accessible. An example of a kinetic resolution of a 1,4-dihydronaphthalene-1-carboxylic acid was also reported.



R^1	R^2	*n*	*ee*	Yield
OTBDPS	H	0	88%	93%
OTBDPS	Me	0	81%	89%
CO_2Bu^t	H	0	77%	49%
2-Np	H	0	47%	71%
OTBDPS	H	1	92%	90%

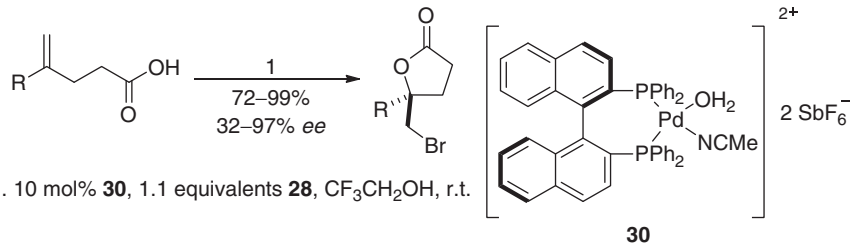
1. 10 mol% **8**, 1.2 equivalents NBS, $CHCl_3$:*n*-hexane (1:1), –40 °C

Scheme 27

7.21.3.2.3.2 Transition metal-catalyzed bromolactonization

Current methods for asymmetric halocyclizations are mostly based on nucleophilic organocatalysts. An alternative approach based on transition metal catalysis was reported by Kim and Lee. These authors showed that cationic palladium bisphosphine

complexes can be applied as catalysts in bromolactonizations of 4-pentenoic acids.[65] Using chiral bisphosphine ligands, asymmetric bromolactonizations are possible if TBCO (**28**) is used as a stoichiometric brominating agent instead of the more common *N*-bromoamide/imide derivatives. Highest enantioselectivities were observed if the reactions were conducted in trifluoroethanol at room temperature using BINAP as the bisphosphine ligand. Under these conditions, a range of 4-aryl-substituted 4-pentenoic acids underwent 5-*exo* bromolactonizations with moderate to very high enantioselectivities (32–97% *ee*, Scheme 28). Interestingly, derivatives with electron-rich aryl groups, substrates that are notoriously difficult in reactions using organocatalysts, led to the highest selectivities (85–95% *ee*). However, bromolactonizations of 4-alkyl-substituted 4-pentenoic acids remain difficult (32% *ee* for R=Me).

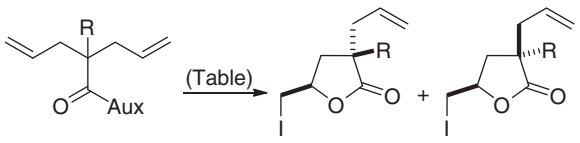


Scheme 28

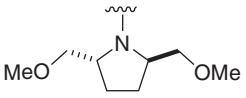
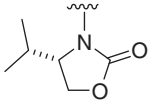
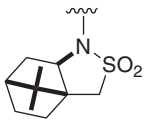
7.21.3.2.4 Enantioselective iodolactonization

7.21.3.2.4.1 Substrate-controlled asymmetric iodolactonization using chiral auxiliaries

Early attempts to render iodolactonizations asymmetric employed chiral auxiliaries on the carboxylic acid group. Several groups investigated desymmetrizing cyclizations on dialkene carboxylic acids carrying chiral amines or amides as auxiliary. For example, Fuji used bis(methoxymethyl)pyrrolidine as auxiliary in the iodolactonization of amide **31**.[66] Employing elemental iodine in aqueous THF, the reaction proved to be diastereoselective and the product was isolated with an enantiomeric excess of 91%, whereas the yield was only moderate (54%, Scheme 29, entry 1). Shibuya tested several other auxiliaries for this transformation. The common oxazolidin-2-one auxiliaries did not lead to satisfactory results, irrespective of the substituent on the ring. 5-Isopropyloxazolidin-2-one substituted **31** could be cyclized using NIS in aqueous THF, but the product **32a** was isolated only in low yield (35%) and with low enantiomeric excess (54% *ee*, Scheme 29, entry 2).[67] Much better results were obtained with camphor sultam auxiliaries. Amide **31** carrying this auxiliary had to be treated with the highly reactive iodinating agent I(collidine)$_2$ClO$_4$ to obtain high yield (87%), but under low temperature conditions, the product **32a** was formed with high enantiomeric excess (98% *ee*, Scheme 29, entry 3). These conditions were also applicable on more substituted substrates.



31 **32a** **32b**

Aux	R	Reagent	Conditions	Yield	*ee*	Ratio **32a**:**32b**	References
	H	I_2 (3 equivalents)	THF:H_2O (1:1), r.t.	54%	91% (**32a**)	1:0	66
	H	NIS (1.5 equivalents)	THF:H_2O (1:1) 0 °C to r.t.	35%	54% (**32a**)	1:0	67
	H	I(Collidine)$_2$ClO$_4$	CH_2Cl_2:MeOH, –40 °C	87%	98% (**32a**)	1:0	68
	Ph	I(Collidine)$_2$ClO$_4$	CH_2Cl_2:MeOH, –50 °C	65%	84% (**32b**)	1:5.5	68

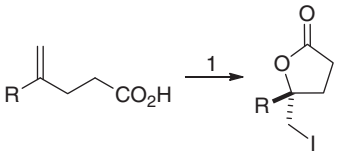
Scheme 29

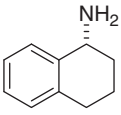
Iodolactonization of phenyl-substituted amide **31** led to the formation of iodolactone **32** with a chiral all-carbon quaternary stereocenter in acceptable yield and with high enantiomeric excess (84% *ee*) together with a minor diastereomer.[68]

Desymmetrizing iodolactonizations using chiral auxiliaries are also documented in isolated examples on cyclic dienes, for example, cyclohexadiene derivatives; however, results are mixed and depend on the structure of the diene.[66,69] Furthermore, chiral auxiliaries have also been employed in iodolactonizations of nonsymmetric alkenoic acids, but results are again mixed and these reactions have not been intensively investigated.[70]

7.21.3.2.4.2 Reagent-controlled asymmetric iodolactonization using stoichiometric amounts of reagent

Complexes of chiral amines with a suitable electrophilic halogen source were proposed by Grossmann as chiral halogenating agents for reagent-controlled asymmetric halogenations.[71] In initial experiments, two equivalents of a dihydroquinidine derivative were reacted with iodine and silver tetrafluoroborate to form *in situ* $(amine)_2I^+BF_4^-$-type reagents. However, the enantioselectivities observed in iodolactonizations using this reagent remained low (15% *ee*). Improved enantioselectivities using this concept were reported by Wirth. They used a combination of iodine monochloride and readily available chiral benzylamines such as **33** to induce iodolactonizations on 4-substituted 4-pentenoic acid-type starting materials (**Scheme 30**).[72]





33

R	*ee*
Ph	45%
4-$OMeC_6H_4$	27%
4-ClC_6H_4	49%
Me	0%
Pr^i	0%

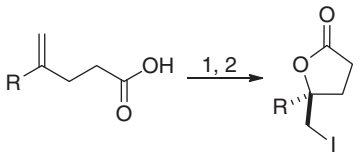
1. 4.0 equivalents **33**, 2.0 equivalents ICl, CH_2Cl_2, –78 °C

Scheme 30

Using two equivalents of reagent, 4-aryl-substituted 4-pentenoic acids underwent 5-*exo* cyclizations with moderate enantioselectivity (10–49% *ee*), whereas 4-alkyl-substituted derivatives led only to racemic mixtures. Further investigations by Rousseau showed that 5-*endo* iodolactonizations of 4-aryl-4-butenoic acids can also be accomplished using similar diamine iodonium salts. The enantioselectivities obtained were generally moderate (45% *ee*).[73]

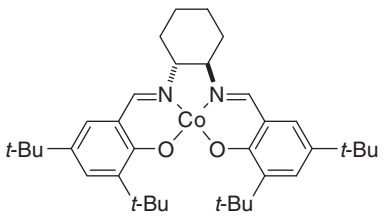
7.21.3.2.4.3 Reagent-controlled asymmetric iodolactonization using metal complexes

A single example of an asymmetric iodolactonization promoted by a stoichiometric amount of a titanium TADDOL complex had already been reported in 1992 by Taguchi.[74] The enantiomeric excess achieved was moderate, and the reaction had to be conducted with α-hydroxycarboxylic acid to allow for chelation in the metal complex. More efficient substoichiometric iodolactonizations are possible using chiral cobalt salen complexes, for example, **34** (originally introduced to asymmetric halocyclizations by Kang[87]). Gao showed that these complexes, if activated with NCS, promote iodolactonizations of 4-substituted 4-pentenoic acids using iodine as the halogenating agent (**Scheme 31**).[75] The iodolactone products were obtained in high yields (73–93%) with moderate to good enantioselectivities (22–86% *ee*) for most substituents. However, the reactions were not fully catalytic, and 40 mol% of the chiral metal complex were necessary to achieve these enantioselectivities.



R	*ee*	Yield
Ph	67%	87%
4-MeC_6H_4	70%	93%
2-Np	86%	83%
4-$OMeC_6H_4$	22%	89%
Me	55%	73%

1. 40 mol% **34**, 25 mol% NCS, toluene, r.t., 0.5 h; 2. 1.4 equivalents I_2, –18 °C, 20 h

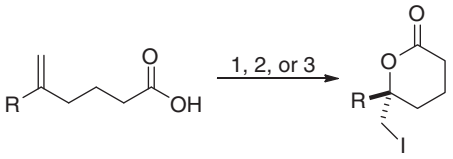


34

Scheme 31

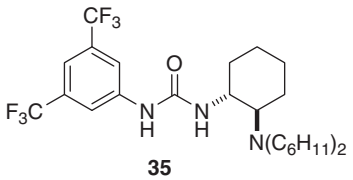
7.21.3.2.4.4 Reagent-controlled asymmetric iodolactonization using organocatalysts

Several structurally different organocatalysts have been developed for catalytic, asymmetric iodolactonizations. Jacobsen described the application of urea-based catalyst **35** in 6-*exo* cyclizations of 5-substituted 5-hexenoic acids.[76] **35** is best used in combination with *N*-iodo-4-fluorophthalimide (**36**) as stoichiometric halogen source and requires iodine (15 mol%) as additive. Under these conditions, 6-*exo* iodolactonizations generally proceeded in good yields and with high enantioselectivities (76–96% *ee*, Scheme 32). If the substituent on the alkene is an alkyl- or electron-rich aryl group, enantioselectivities were only moderate (48% *ee* for *p*-anisyl).

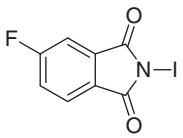


	Conditions 1		Conditions 2		Conditions 3	
R	Yield	*ee*	Yield	*ee*	Yield	*ee*
Ph	87%	94%	83%	87%	95%	97%
2-Np	92%	93%	91%	92%	96%	96%
4-ClC_6H_4	84%	96%	78%	96%	91%	97%
4-$OMeC_6H_4$	91%	48%	87%	12%	84%	85%
Pr^i	85%	76%	77%	16%	86%	81%

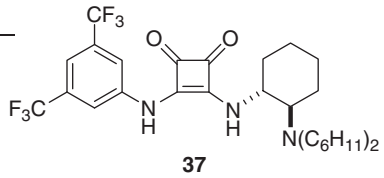
1. 15 mol% **35**, 1.0–2.0 equivalents **36**, 15 mol% I_2, toluene, –80 °C, 5 days; 2. 15 mol% **37**, 1.0 equivalent NIS, 15 mol% I_2, CH_2Cl_2:acetone (1:1), –78 °C, 24 h; 3. 5 mol% **38**, 1.1 equivalents NIS, toluene, –20 °C, 24 h



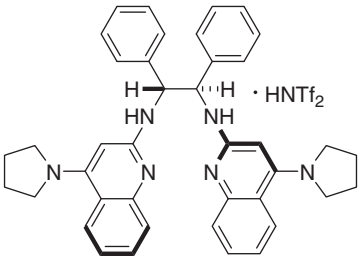
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36



37

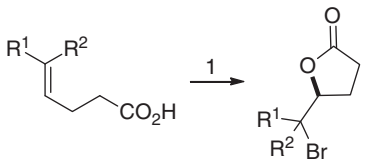


38

Scheme 32

Significant drawbacks of this method are the need for the noncommercially available halogenating agent *N*-iodo-4-fluorophthalimide (**36**) and the long reaction times (5 days) at low temperature (− 80 °C). If the urea group of the catalyst **35** is substituted by a square amide moiety, the new catalyst **37** can be used in combination with commercially available NIS as reported by Hansen (Scheme 32).[77] The reaction is now best conducted in an acetone:dichloromethane mixture, still at low temperature (− 78 °C) but with a shortened reaction time (24 h). Yields (77–91%) and enantioselectivities (12–96%) obtainable under Hansen's conditions were broadly comparable to Jacobsen's results, but critical substrates with alkyl- or electron-rich aryl groups showed only low selectivities. A completely different type of organocatalyst was developed by Johnston for this 6-*exo* iodolactonization.[78] These authors used a chiral bis(amidine) Brønsted base in combination with a strong Brønsted acid ($HNTf_2$) to generate the bifunctional catalyst salt **38**. Using 5 mol% of **38** in combination with NIS, the 6-*exo* iodolactonizations of the hexenoic acid substrates proceeded in very good yield (84–96%) and with high enantioselectivities (95–98% *ee*). Even the usually problematic alkyl-substituted alkenes were efficiently cyclized with good enantioselectivities (81% *ee* for Pr^i).

All three catalysts were optimized for 6-*exo* cyclizations and only applied to 5-*exo* iodolactonizations in isolated examples and with mixed results. However, asymmetric 5-*exo* iodolactonizations could be catalyzed by Martin's BINOL-derived catalyst developed for bromolactonizations.[61] If NIS is used instead of the brominating agent TBCO (**28**), iodolactonizations of (*Z*)-4-pentenoic acids are conducted in high yields (89–99%) and with excellent enantioselectivities (94–98% *ee*, Scheme 33).[62] Aryl as well as alkyl substituents on the alkene were well tolerated. Interestingly, the cyclization of (*E*)-configured 5-pentenoic acids using this method is not always regioselective, and 5-*exo* iodolactonization products were formed only with low enantioselectivity (34% *ee* for Pr^i). 6-*exo* Cyclizations of (*Z*)-configured 5-hexenoic acids were regioselective again and proceeded with high enantioselectivities (96–98% *ee*, not shown).[62]



R^1	R^2	Yield	*ee*
H	Pr^i	95%	95%
H	Ph	93%	97%
H	2-Np	94%	96%
Pr^i	H	78%	34%

1. 10 mol% **27**, 1.2 equivalents NIS, CH_2Cl_2:toluene (1:2), –20 °C, 14 h

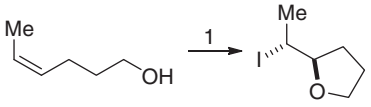
Scheme 33

7.21.3.3 Halocycloetherification

7.21.3.3.1 Nonstereoselective and diastereoselective halocycloetherifications

As is the case for halolactonizations, a range of different electrophilic halogenating agents such as elemental halogens, Barluenga's reagent, $((Coll)_2IPF_6)$, and *N*-haloamides and *N*-imides can be used to induce halocycloetherifications with the heavier halogens chlorine, bromine, and iodine. Fluorine is a special case, and fluorine-induced halocycloetherification can only be observed on specific types of starting materials (see the next section). Like halolactonizations, halocycloetherification can be catalyzed by Lewis bases.[53] However, no influence of the Lewis base on the regioselectivity of the cyclization is observed.

As an alternative to nucleophilic catalysis using Lewis bases, Morgan introduced palladium(II) salts with or without phosphine ligands as transition metal catalysts for iodocycloetherifications (**Scheme 34**).[79]



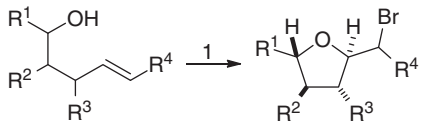
1. 1.2 equivalents NIS, 5 mol% catalyst, solvent, r.t., 1 h

Catalyst	Solvent	Yield
–	Toluene	13%
–	THF	95%
$(dppf)PdCl_2$	Toluene	95%
$(COD)PdCl_2$	Toluene	88%
$Pd(OAc)_2$	Toluene	71%

Scheme 34

Catalysis using palladium salts is possible only in apolar solvents (toluene) as the background reaction is too fast in more polar solvents such as THF. In toluene, the NIS-promoted haloetherification is significantly accelerated by various palladium salts, including $Pd(OAc)_2$ and $PdCl_2$ with ligands. The product is obtained in high yield (89–99%) and with high *anti*-selectivity. Interestingly, $(dppf)PdCl_2$ provided the highest catalytic activity. This could open the possibility to use chiral bisphosphine ligands to achieve enantioselective catalysis but no example has been described yet.

Another possibility to achieve catalytic bromoetherifications is the use of cobalt(II) catalysis in oxidative radical cyclizations. If $BrCCl_3$ is added to these reactions to trap carbon-centered radicals via a bromine transfer, oxybrominations result (**Scheme 35**).[80] The method is applicable to a range of homoallylic alcohols, and the THF products are often formed with high diastereoselectivity. However, large amounts of reagents (30 equivalents cyclohexa-1,4-diene, 10 equivalents $BrCCl_3$) are required for this method.



R^1	R^2	R^3	R^4	*dr*	Yield
Ph	H	H	H	>94:<6	85%
Ph	H	H	Me	>94:<6	87%
H	Ph	H	H	73:27	89%
H	H	Ph	H	>99:<1	84%

1. 15–40 mol% CoL_2, O_2(1 bar), 30 equivalents cyclohexa-1,4-diene, 10 equivalents $BrCCl_3$, toluene, 60–80 °C, L = 4-[3,5-bis(trifluoromethyl)phenyl]-4-oxybut-3-en-2-one

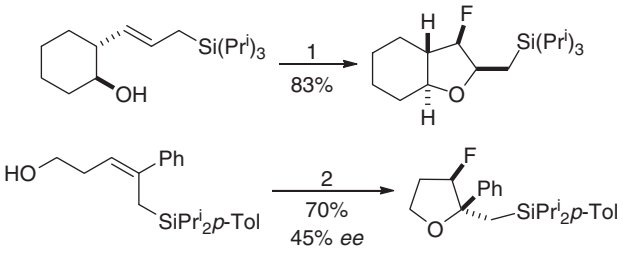
Scheme 35

7.21.3.3.2 Diastereoselective fluorocycloetherification

Electrophilic fluorocyclization reactions are much more difficult to achieve than halocyclizations with the heavier halogens because fluorine does not form cyclic fluoronium ions. This leads generally to much lower reactivity of electrophilic fluorinating agents toward alkenes and often to a lack of regio- and stereoselectivity.[81] However, stereoselective fluorocycloetherification can be achieved if the substrate is carefully chosen. Gouverneur showed that allylic silanes carrying a remote hydroxy group undergo

efficient fluorocyclizations if the silyl group is bulky, for example, triisopropylsilyl.[82] The silyl group is crucial in these cyclizations and activates the alkene toward electrophilic addition of fluorine. Using Selectfluor® in acetonitrile, regio- and diastereoselective 5-*exo* fluorocyclizations were observed (Scheme 36). The THF products were isolated in moderate to good yields (47–83%) depending on the size of the silyl substituent.

An asymmetric cyclization was attempted in one case. With a stoichiometric amount of $(DHQ)_2PHAL$ (**8**) as chiral ligand, the reaction proceeded with moderate enantioselectivity (45% *ee*) with the absolute configuration not assigned.

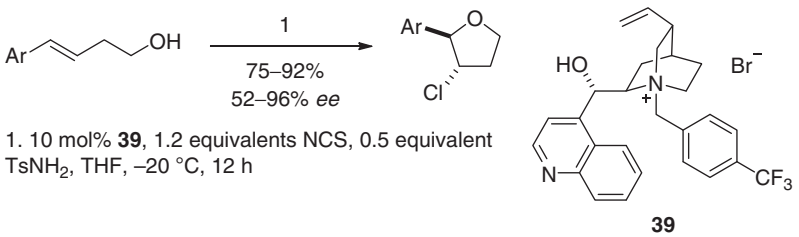


1. 1.0 equivalent Selectfluor®, 1.0 equivalent $NaHCO_3$, MeCN, r.t.;
2. 1.2 equivalents **8**, 1.2 equivalents Selectfluor®, 1.2 equivalents $NaHCO_3$, MeCN, –20 °C, 4 days

Scheme 36

7.21.3.3.3 Enantioselective chlorocycloetherification

An enantioselective chloroetherification reaction was reported by Sun.[83] These authors found that *N*-benzylcinchoninium bromides are good catalysts for 5-*endo* chlorocyclizations of styrene-derived homoallylic alcohols. Catalyst **39** carrying a 4-trifluorobenzyl substituent proved to be the most selective one and was best used in combination with NCS as a stoichiometric chlorine source (Scheme 37). The cyclization of various (*E*)-configured homoallylic alcohols delivered 1,2-*cis*-substituted tetrahydrofuran products in 75–92% yield and with high levels of enantiocontrol in most cases (52–96% *ee*). The highest enantioselectivities were observed on substrates with electron-deficient aromatic substituents. A (*Z*)-configured alcohol gave rise to a 1,2-*trans*-configured product, again in good yield (80%) and with good enantioselectivity (84% *ee*). Alkyl-substituted homoallylic alcohols did not react under these reaction conditions or gave low yields and selectivities.



1. 10 mol% **39**, 1.2 equivalents NCS, 0.5 equivalent $TsNH_2$, THF, –20 °C, 12 h

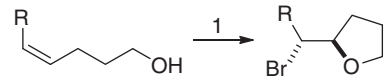
39

Scheme 37

7.21.3.3.4 Enantioselective bromocycloetherification

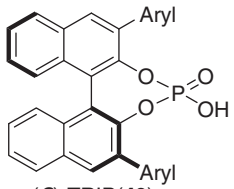
Successful asymmetric bromocycloetherifications using conventional Lewis basic organocatalysts are still elusive. However, BINOL-derived phosphoric acid diesters have been introduced as suitable catalysts for enantioselective bromoetherifications. This type of catalysts was first used in an asymmetric bromoetherification by Hennecke, who reported the desymmetrizing haloetherification of alkene diols.[84] This method is applicable to bromo- and iodoetherifications with better results observed in iodocyclizations. Consequently, the method is described in the next section. On nonsymmetrical substrates, asymmetric bromoetherifications using the sterically demanding phosphoric acid catalyst (*S*)-TRIP (**40**) were reported by Shi.[85] These authors showed that this catalyst in combination with NBS as halogenating agent is able to promote enantioselective 5-*exo* haloetherifications of (*Z*)-pent-5-en-1-ols (Scheme 38).

The THF products were isolated in high yields and with moderate to good enantioselectivities (61–81% *ee*) if the alkene is decorated with an alkyl substituent. (*E*)-configured, alkyl-substituted alkenes could also be cyclized, but the reactions were not fully regioselective (5-*exo*:6-*endo* = 12:1 to 33:1), whereas the enantioselectivities observed for the 5-*exo*-products were between 58% and 79% *ee* (not shown). The method is also applicable to bromoaminations if the hydroxyl group is replaced by a sulfonamide-protected amine.



1. 10 mol% **40**, 1.2 equivalents NBS, CH_2Cl_2, 0 °C,18 h

R	*ee*	Yield
Me	76%	81%
Et	81%	96%
C_5H_{11}	75%	95%
Bu^t	75%	86%
CH_2CH_2Ph	61%	84%

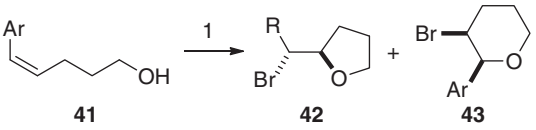


Aryl = 2,4,6-$(Pr^i)_3C_6H_2$

(*S*)-TRIP(**40**)

Scheme 38

A very similar protocol was developed by Denmark, but this time for alkenols carrying an aromatic substituent on the alkene.[86] The method employs the same catalyst **40** (5 mol%) but in combination with triphenylphosphine sulfide (5 mol%) as cocatalyst. NBS is again the halogen source, and the reaction is best conducted in toluene (instead of the dichloromethane used before) at 0 °C (Scheme 39). (*Z*)-5-arylpent-5-en-1-ols are preferentially yet not exclusively cyclized to THFs via a 5-*exo* cyclization (5-*exo*:6-*endo* > 90:10). The enantioselectivities observed (82–88% *ee*) are slightly higher than those seen for the alkyl-substituted starting materials. In (*E*)-configured substrates that ratio is strongly dependent on the aromatic ring, and mixtures are obtained. Interestingly, the 5-*exo* product is still formed with good enantioselectivity (70–94% *ee*), whereas the enantiomeric excess of the 6-*endo* products is rather low (up to 30% *ee*).



41 **42** **43**

1. 5 mol% **40**, 5 mol% Ph_3PS, 1.2 equivalents NBS, toluene, 0 °C, 12–14 h

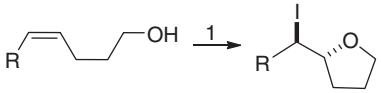
Ar	**42**:**43**	*ee* (**42**)	Yield
Ph	>95:<5	82%	77%
2-Np	95:5	84%	73%
3-MeC_6H_4	>95:<5	84%	86%
4-MeC_6H_4	90:10	88%	64%
4-FC_6H_4	95:5	80%	78%

Scheme 39

7.21.3.3.5 Enantioselective iodocycloetherification

7.21.3.3.5.1 Metal-catalyzed enantioselective iodocycloetherification

A transition metal-catalyzed intramolecular iodoetherification was reported by Kang. These authors found that salen metal complexes such as salen cobalt complex **34** can be used as catalysts for this type of reactions (Scheme 40).[87] **34** must be activated first by treatment with NCS and can then be used in combination with molecular iodine as the stoichiometric halogen source for the cyclization of (*Z*)-5-alkylpent-5-en-1-ols. Exclusive 5-*exo* iodoetherification was observed, and the products were isolated in very good yields (83–94%) and with high enantioselectivities between 73% and 90% *ee*.



1. 30 mol% **34**, 0.75 equivalent NCS, 1.2 equivalents I_2, toluene, –78 °C

R	*ee*	Yield
Me	67%	96%
Et	82%	89%
Pr^i	73%	83%
$(CH_2)OTr$	90%	89%
CH_2CH_2Ph	94%	84%

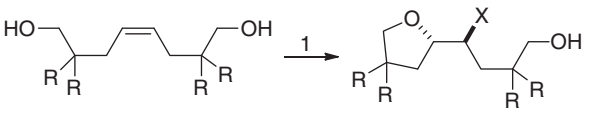
Scheme 40

(*E*)-configured or aryl-substituted starting materials were not investigated. A clear drawback of the method is the high catalyst loading of 30 mol% that is necessary to achieve high enantioselectivities. This problem was addressed by Kang in a subsequent

publication. If, instead of the cobalt salen complex **34**, the corresponding chromium salen complex is used under otherwise similar reaction conditions, the catalyst loading can be reduced to 7 mol%, whereas the yields and enantioselectivities obtained for the iodocyclization products are even slightly higher.[88]

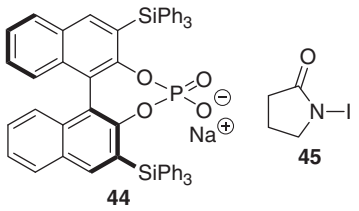
7.21.3.3.5.2 Organocatalytic enantioselective iodocycloetherification

An unusual approach to enantioselective iodocycloetherifications was disclosed by Hennecke. These authors investigated the desymmetrization of alkenediols via the opening of *meso*-halonium ion intermediates.[84] The sodium salt of a BINOL phosphoric acid diester **44** was identified as a suitable catalyst that could be used in enantioselective *5-exo* iodoetherifications of alk-4-ene-1,8-diols (Scheme 41). In this desymmetrization reaction, the 3,3′-triphenylsilyl-substituted BINOL salt **44** was superior to (*S*)-TRIP (**40**), which is more suitable for halocyclizations of nonsymmetrical substrates. The products were isolated in good yields (60–82%) and with moderate enantioselectivities between 62% and 71% *ee* when *N*-iodo-2-pyrrolidinone **45** was used as a halogenating agent with rather low reactivity.



	X = Br		X = I	
R	Yield	*ee*	Yield	*ee*
H	89%	44%	81%	62%
Me	68%	25%	60%	68%
Ph	82%	67%	82%	71%

1. 20 mol% **44**, 1.2 equivalents NBS or **45**, CH_2Cl_2, 0 °C



44

45

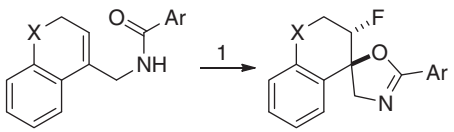
Scheme 41

When *N*-iodopyrrolidinone **45** was replaced by NBS as bromine source, asymmetric bromoetherifications were possible. The brominated products were isolated in good yields similar to the iodinated products, but the enantioselectivity of the bromocyclization is significantly lower (25–67% *ee*).

7.21.3.4 Other Halocyclization Reactions with *O*-Nucleophiles

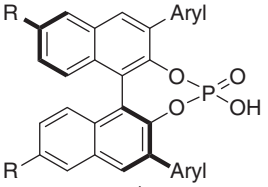
7.21.3.4.1 Enantioselective halocyclization under o-alkylation of amides

Halocyclization reactions can also involve unsaturated carboxylic acid amides. Depending on the length of the tether connecting the amide and the alkene as well as the substituent(s) at the amide, *N*- or *O*-alkylation is possible (for *N*-alkylation, see the next section). If the starting material is carefully chosen, only *O*-alkylation can be observed. For example, dihydronaphthalenes undergo selective *5-exo* fluorocyclization if treated with Selectfluor® and a suitable catalyst (Scheme 42). Toste developed an efficient phase-transfer method to render this transformation asymmetric.[89] Lipophilic phosphate **46** proved to be an ideal



Ar	X	*ee*	Yield
4-BrC_6H_5	CH_2	93%	87%
4-IC_6H_5	CH_2	93%	71%
2-Np	CH_2	96%	80%
2-Np	O	92%	70%

1. 10 mol% **46a**, 1.5 equivalents Selectfluor®, 1.25 equivalents Na_2CO_3, C_6H_5F:hexanes(1:1), r.t., 24 h

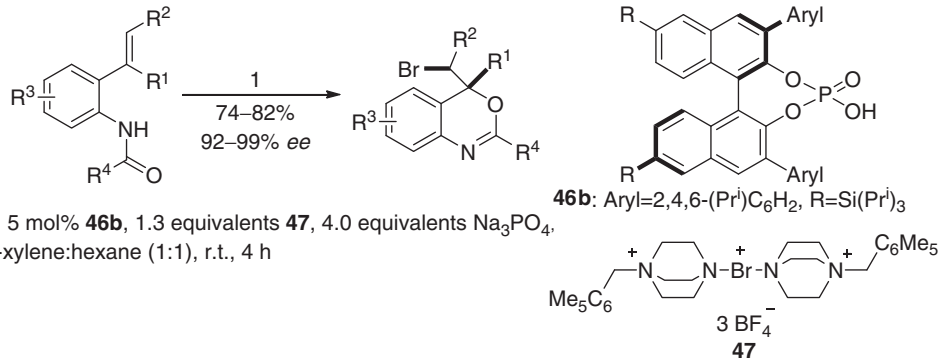


46a: Aryl = 2,4,6-(Pr^i)$_3C_6H_2$, R = C_8H_{17}

Scheme 42

catalyst in fluorobenzene:hexanes as solvent. Selectfluor® dissolves in this solvent mixture only after anion metathesis with **46a,** generating a chiral ion pair as fluorinating agent, which is able to induce the fluorocyclization of dihydronaphthalenes with yields between 70% and 87% and very high enantioselectivity (92–96% *ee*).

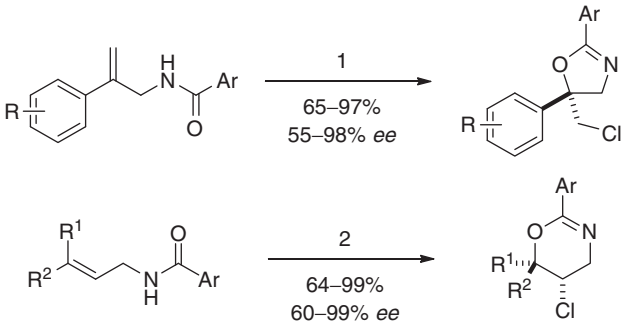
The reaction conditions were applicable not only to dihydronaphthalenes but also to cyclic enol ethers, benzothiophene derivatives, and even an acyclic alkene containing a benzamide group. Toste was able to extend this phase-transfer method to halocyclizations with the heavier halogens (bromine and iodine) as electrophile.[90] This required the preparation of new cationic halogenating agents that were insoluble under the applied reaction conditions. Bromonium salt **47** is such a reagent and can be used for the bromocyclization of styrene-derived amides (Scheme 43). This time, a silyl-substituted (*S*)-TRIP derivative **46b** was found to be the most selective phase-transfer catalyst enabling highly enantioselective bromoamidations in good yields (92–99% *ee* and 74–82%). A range of substituents on the starting material was well tolerated, and iodocyclizations were possible as well if the iodo-analog of salt **47** was used as halogenating agent.



1. 5 mol% **46b**, 1.3 equivalents **47**, 4.0 equivalents Na_3PO_4, *p*-xylene:hexane (1:1), r.t., 4 h

Scheme 43

An organocatalytic method for the halocyclization of carboxylic acid amides of allylic amines was described by Borhan. These authors found that their chlorolactonization method using $(DHQD)_2PHAL$ (**8**) and DCDPH (**4b**) is also applicable to the oxygen-selective chlorocyclization of these substrates if trifluoroethanol is used as solvent.[91] The highest enantioselectivities were obtained if the carboxylic acid was a *para*-substituted benzoic acid derivative. If the allylic amine carried an aromatic group at the 2-position, 5-*exo* cyclization occurred in 65–97% yields and with high enantioselectivities of 55–98% *ee*. If the allylic amine was mono- or disubstituted at the 3-position and (*E*)-configured, a 6-*endo* cyclization was observed and the enantioselectivities were even slightly higher (60–99% *ee*, Scheme 44).



1. 2 mol% **8**, 1.1 equivalents **4b**, 2,2,2-trifluoroethanol, –30 °C

Scheme 44

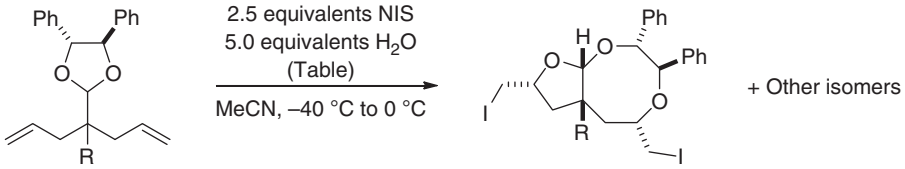
7.21.3.4.2 Halocyclization with cyclic ethers as nucleophile

Not only carboxylic acids (halolactonization), alcohols (haloetherification), and carboxylic acid amides (see Sections 7.21.3.2–7.21.3.4) are suitable nucleophiles in halocyclization reactions. Cyclic ethers such as epoxides and THFs can function as nucleophiles as well. However, in this case the alkylation of the ether by a halonium ion will generate a reactive cyclic oxonium ion, which will further react, most likely by trapping with another nucleophile. Such halocyclization/oxonium ion formation and trapping cascades have been used in biomimetic natural product synthesis. For example, numerous natural products from

Laurencia species have been prepared by bromocyclization reactions onto THFs followed by trapping of the resulting oxonium ion.[92] A bromonium-initiated epoxide opening cascade was employed by Jamison in the total synthesis of *ent*-dioxepandehydrothyrsiferol.[93] More general synthetic methods using cyclic ethers as nucleophile in halooxygenation reactions are rare. Braddock reported bromocyclizations of cyclooctadiene monoepoxide[94] and Yeung described intermolecular bromoaminoalkoxylations of alkenes.[95]

7.21.3.4.3 Halocyclization with acetals as nucleophile

Acetals are suitable nucleophiles in oxyhalogenations as well. More interestingly, if chiral acetals are employed, diastereoselective halocyclizations are possible. This enables the use of acetals as chiral auxiliaries. A powerful example of such a cyclization was reported by Fujioka.[96] These authors showed that symmetrical acetals containing two allyl groups can be efficiently desymmetrized using iodocyclizations. The iodocyclizations were preferentially induced by NIS in wet acetonitrile. An initial iodocyclization onto one of the acetal oxygens led to an oxonium ion, which is subsequently opened by water. This allows for a second iodocyclization to give the product containing four new stereocenters (Scheme 45). Depending on the size of the substituent, yields of cyclization were good, but a high diastereoselectivity was only observed for a large substituent (R=OTBS, *dr* 92:8).



R	*t*	Yield	*dr*
H	3 h	80%	78:22
Me	13 h	72%	60:40
Ph	3 h	72%	67:33
OMe	12 h	38%	n.d.[a]
OTBS	3 h	84%	92:8

[a]Not determined.

Scheme 45

7.21.4 Aminohalogenation

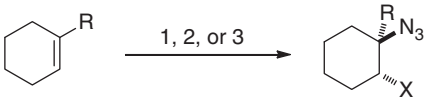
7.21.4.1 Intermolecular Aminohalogenation with Chlorine, Bromine, and Iodine

Like oxyhalogenation reactions, aminohalogenations are well-established reactions. Electrophilic aminohalogenations usually require an electrophilic halogenating agent and a suitable nitrogen nucleophile. In contrast to oxyhalogenations, this nucleophile must be chosen with care in aminohalogenations. Unprotected amines or amines with electron-rich protecting groups are sensitive toward oxidation by the halogenating agent. Furthermore, the aminohalogenation of alkenes leads to β-haloamines, which are prone to elimination of a halide, forming an aziridine or an aziridinium ion.[97] To avoid these problems, amine nucleophiles carrying electron-deficient protecting groups such as carboxamides or sulfonamides are frequently used.

A particular problem is the aminohalogenation using ammonia or protected ammonia equivalents. The use of elemental halogen and ammonia is not a viable option because, for example, iodine and ammonia form nitrogen triiodide, an explosive compound. Haloazides of the heavier halogens do react with alkenes in azidohalogenation reactions, but these are also explosive. To circumvent this problem, electrophilic halogenating agents can be used in combination with a suitable azide source, likely to form haloazides *in situ* (Scheme 46).

Barluenga employed IPy_2BF_4 as an electrophilic iodinating agent in combination with Me_3SiN_3 to achieve efficient azidoiodinations.[98] The yields were generally high on various alkenes including 88% yield on cyclohexene and 90% yield on 1-phenylcyclohexene. The electrophilic iodinating agent can also be prepared by oxidative methods as demonstrated by Nair.[99] The authors used ceric ammonium nitrate as convenient oxidant together with sodium iodide and sodium azide. Under these conditions, the azidoiodination proceeded with good yields (60% for cyclohexene); the reaction was not diastereoselective though (3:2 mixture of *trans*:*cis* isomers). A simple method for azidobrominations was reported by Olah.[100] The strongly acidic Nafion-H resin was found to catalyze azidobrominations of various alkenes employing NBS and Me_3SiN_3. The reactions gave selectively the *trans*-product in moderate to good yields, for example, 67% for cyclohexene and 55% for 1-methylcyclohexene.

Another possibility to introduce a protected primary amino group is aminohalogenation in acetonitrile under Ritter-type conditions (Scheme 47). Corey used *N*-bromoacetamide as halogenating agent in combination with $SnCl_4$ as Lewis acid to



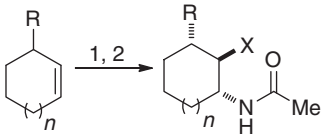
R	X	Conditions	Yield	References
H	I	1	88%	98
Ph	I	2	90%	98
H	I	2	60%[a]	99
H	Br	3	67%	100
Me	Br	3	55%	100

[a]3:2 mixture of *trans*:*cis* isomers

1. 1.5 equivalents IPy_2BF_4, 1.2 equivalents Me_3SiN_3, 1.5 equivalents $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C, 1.5–3 h;
2. 2.1 equivalents $Ce(NH_4)_2(NO_3)_6$, 1.0 equivalent NaN_3, 1.0 equivalent NaI, MeOH, 0 °C, 30 min;
3. Nafion-H, 0.9 equivalent NBS, 1.1 equivalents Me_3SiN_3, CH_2Cl_2:$MeNO_2$ (3:1), –30 °C–r.t., 2 h

Scheme 46

achieve bromoamidations on a wide range of cyclic alkenes.[101] The products were obtained as *trans*-isomers in generally very good yields. If the starting material already contained a stereocenter, the bromoamidations proceeded with high diastereoselectivity. Similar results for bromoamidations were reported by Hajra, who used NBS and $Cu(OTf)_2$.[102] Chloroamidations under Ritter-type conditions in acetonitrile are possible using silver nitrate and oxalyl chloride.[103]



R	X	*n*	Conditions	Yield	References
H	Br	3	1	85%	101
H	Br	1	1	91%	101
OBz	Br	1	1	74%	101
H	Br	1	2	68%	102
H	Br	3	2	69%	102
H	Cl	1	3	80%	103

1. 0.4 equivalent $SnCl_4$, 1.2 equivalents $CH_3CONHBr$, 1.2 equivalents H_2O, MeCN, 0 °C, 0.5–1 h;
2. 5.0 equivalents alkene, 5 mol% $Cu(OTf)_2$, 1.2 equivalents NBS, 1.2 equivalents $NaHCO_3$, 1.2 equivalents H_2O, MeCN, 20 °C; 3. 1.5 equivalents $AgNO_3$, 1.5 equivalents oxalylchloride, MeCN, –20 °C

Scheme 47

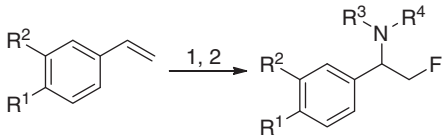
Haloamidations are possible using not only carboxamides but also carbamates and sulfonamides. For example, Zwierzak introduced *N*,*N*-dibromo-*tert*-butylcarbamate as a bromoamidation reagent containing a BOC-protected amine.[104] Aminobrominations are also often conducted with NBS and toluenesulfonamide introducing the amine in tosyl-protected form.[105] These reactions typically require a catalyst such as a transition metal[105a] or silicon powder.[105b]

7.21.4.2 Aminofluorination

Intermolecular aminofluorinations can be conducted using the electrophilic fluorination agent Accufluor® under Ritter-type conditions as demonstrated by Stavber (Scheme 48).[106] Reactions performed with Accufluor® in acetonitrile at 70 °C led to the formation of the Markovnikov products in good yields (70–81%) if the alkene was a styrene derivative. If 1,2-disubstituted styrene-derived alkenes were reacted, two diastereomers were observed in a 1:1 ratio. An alternative procedure for Markovnikov additions was developed by Liu.[107] These authors employed a palladium catalyst to promote the addition of the fluorinating agent NFSI (**49**) to the carbon–carbon double bond of styrene derivatives (Scheme 48). Yields were generally good (61–79%) for electron-neutral and electron-rich styrene derivatives but only moderate for electron-deficient derivatives (37% for R=NO_2). Alkenes carrying only alkyl substituents were unreactive under the reaction conditions. If the carbon–carbon double bond of the styrene was 1,2-substituted, the reactions were only moderately stereoselective (*dr* 2.1:1–4:1) favoring *anti*-addition.

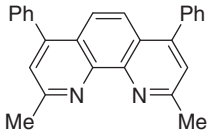
Anti-Markovnikov aminofluorinations are also possible and are achieved using hypervalent iodine reagents such as (difluoroiodo)xylene. Nevado reported the use of this reagent in combination with *N*-methyl toluenesulfonamide for the aminofluorination of various styrene derivatives (Scheme 49).[108] High yields between 68% and 80% were obtained but required the use of 6.0 equivalents of alkene. The unusual *anti*-Markovnikov selectivity was explained by the intermediate formation of an aziridinium ion, which is subsequently opened by a fluoride anion. This also explains the observed formation of diamines as by-products of the reaction.

Hypervalent iodine reagents are also readily applicable to intramolecular aminofluorinations. Liu reported a palladium-catalyzed intramolecular aminofluorination employing silver fluoride and $PhI(OPiv)_2$ as oxidant.[109] On tosylated 1-aminopent-4-ene derivatives, selective 6-*endo* cyclization was observed, and 3-fluoropipieridines were isolated in 55–89% yield (Scheme 50).

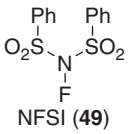


1. 1.1 equivalents Accufluor®, MeCN, 70 °C, 1–24 h;
2. 5 mol% $Pd(OAc)_2$, 7.5 mol% **48**, 2.5 equivalents **49**, dioxane, 40–50 °C, 10 h

Conditions	R^1	R^2	R^3	R^4	Yield	References
1	H	H	Ac	H	79%	106
1	Cl	H	Ac	H	81%	106
1	H	NO_2	Ac	H	70%	106
2	H	H	SO_2Ph	SO_2Ph	76%	107
2	Cl	H	SO_2Ph	SO_2Ph	79%	107
2	NO_2	H	SO_2Ph	SO_2Ph	37%	107
2	H	Me	SO_2Ph	SO_2Ph	70%	107

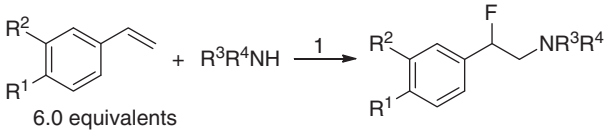


48



NFSI (**49**)

Scheme 48

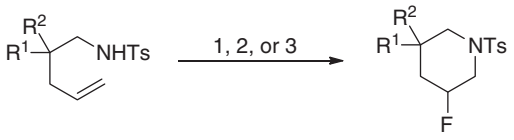


6.0 equivalents

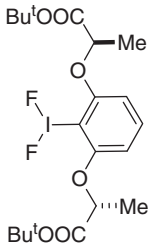
1. 2.0 equivalents xylene IF_2, M.S. (4 Å), CH_2Cl_2, 60 °C, 17 h

R^1	R^2	R^3	R^4	Yield
H	H	Ts	Me	77%
CF_3	H	Ts	Me	68%
H	F	Ts	Me	70%
H	CH_3	Ts	Me	80%
H	H	Ts	H	83%
F	H	SO_2Me	Me	68%

Scheme 49



Conditions	R^1	R^2	Yield	*dr* (*cis:trans*)	*ee*
1	H	H	80%	–	–
1	Me	Me	84%	–	–
1	Ph	Ph	83%	–	–
1	H	Ph	55%	33:67	–
2	H	H	90%	–	–
2	Me	Me	85%	–	–
2	Ph	Ph	81%	–	–
2	H	Ph	81%	>99:<1	–
3	Ph	Ph	79%	–	81%
3	4-MeC_6H_4	4-MeC_6H_4	69%	–	74%
3	2-MeC_6H_4	2-MeC_6H_4	73%	–	88%



50

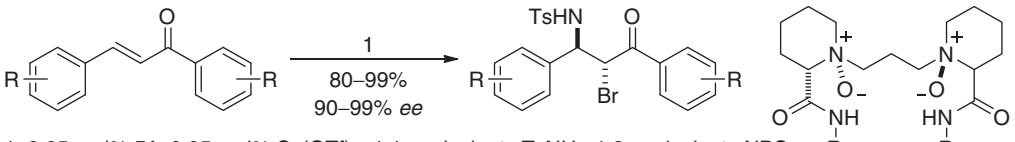
1. 10 mol% $Pd(OAc)_2$, 2.0 equivalents $PhI(OCOBu^t)_2$, 5.0 equivalents AgF, $MgSO_4$, MeCN, r.t.; 2. 10 mol% $BF_3{\cdot}OEt_2$, 1.2 equivalents $PhI(OCOBu^t)_2$, 10 equivalents HF·Py, CH_2Cl_2, r.t.; 3. 2.5 equivalents **50**, toluene, r.t., 17 h

Scheme 50

Monosubstituted aminopentenes reacted only with low diastereoselectivity with a preference for the *trans*-isomer (*dr* 2:1 for R^2 = Ph). The use of 5.0 equivalents of silver fluoride is certainly a drawback. As an alternative, Li reported a metal-free variant, employing boron trifluoride as activator and HF · pyridine as fluorine source, which was still required in large excess (10 equivalents) though.[110] Under these conditions, the 3-fluoropiperidine products were obtained in comparably high yields (59–90%) without the need for expensive transition metals. Interestingly, starting materials already containing a stereocenter reacted now with diastereoselectivities greater than 99:1 but in preference for the *cis*-isomer. Intramolecular aminofluorinations can also be conducted directly with (difluoroiodo)aryl reagents as demonstrated by Nevado.[108] This enables the use of chiral variants of these reagents making the cyclization asymmetric. Nevado showed that the chiral reagent **50** is capable of promoting the 6-*endo* cyclization to the 3-fluoropiperidines with enantioselectivities between 74% and 88% *ee* (Scheme 50). The substrate scope was not extensively explored, but related 7-*endo* cyclizations with moderate to good enantioselectivities were also reported. A drawback is the use of 2.5 equivalents of the hypervalent iodine reagent **50,** but recycling of the reagent is possible.

7.21.4.3 Intermolecular Enantioselective Aminohalogenation with the Heavier Halogens

General methods for the asymmetric intermolecular aminohalogenation with the heavier halogens chlorine, bromine, and iodine are currently not available. Only methods for electron-deficient alkenes in α,β-unsaturated carbonyl compounds have been reported. A chiral auxiliary approach was applied to the chlorosulfamidation of cinnamic acid derivatives; the diastereoselectivities were, however, only moderate (*dr* 3:1–7:1).[111] Much better results were obtained by Feng in catalytic asymmetric bromosulfamidations of chalcones (Scheme 51). These authors used a catalytic amount of a scandium Lewis acid with a sophisticated bis(amine oxide) ligand **51** in combination with NBS as brominating agent and tosylamide as nitrogen source to oxidize the carbon–carbon double bond of chalcones.[112] The bromosulfamidation products were formed in very high yields between 80% and 99% and with very high enantioselectivities from 90% to 99% *ee*. The substrate scope includes electron-rich and electron-deficient aromatic as well as heteroaromatic chalcones; alkyl derivatives were, however, not investigated. The method proved to be equally suited for chloro[112b] and iodo[112c] sulfamidations of chalcones.



1. 0.05 mol% **51**, 0.05 mol% $Sc(OTf)_3$, 1.1 equivalents $TsNH_2$, 1.2 equivalents NBS, CH_2Cl_2, 0 °C, 24 h

R = CH_2CH_2Ph

51

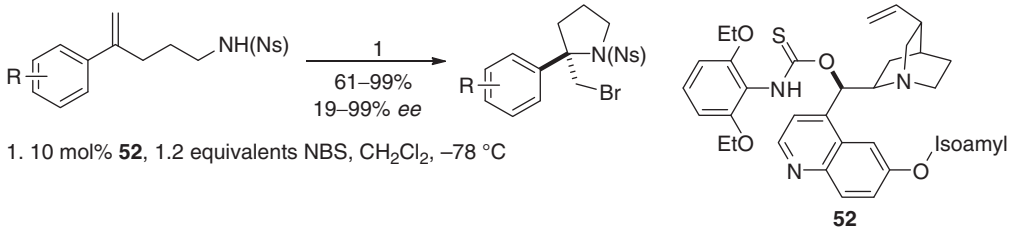
Scheme 51

7.21.4.4 Intramolecular Aminohalogenations with the Heavier Halogens

Intramolecular aminohalogenations can be conducted not only using electrophilic halogenating agents such as *N*-halo succinimides but also by radical methods and by transition metal catalysis.

7.21.4.4.1 Intramolecular aminohalogenations using electrophilic halogenating agents

Like halolactonizations and haloetherifications, intramolecular aminohalogenations can be catalyzed by Lewis bases via nucleophilic catalysis. Asymmetric intramolecular aminohalogenations were pioneered using a chiral auxiliary approach[113] but have been replaced by catalytic methods. Most of these organocatalytic methods for intramolecular aminocyclizations are derived from asymmetric intramolecular oxyhalogenation methods. For example, Yeung could show that their thiocarbamate catalysts, originally developed for halolactonizations,[60] are also applicable to enantioselective 5-*exo* bromosulfamidations of alkenes (Scheme 52).[114] The catalyst's structure and the reaction conditions had to be slightly adapted, but, then, 1-tosylamino-4-arylpent-4-enes could be



1. 10 mol% **52**, 1.2 equivalents NBS, CH_2Cl_2, –78 °C

52

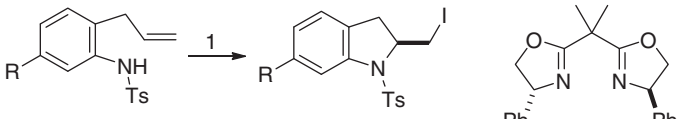
Scheme 52

cyclized to give 2,2-substituted pyrrolidines in yields between 61% and 99% with high enantioselectivities (66–99% *ee*). Like for halolactonizations, the aryl group was required to achieve high enantioselectivities, and electron-rich aryl groups (R = OMe, 19% *ee*) and alkyl substituents led only to low enantiomeric excesses. A similar thiocarbamate was reported as an enantioselective catalyst for 5-*endo* bromo aminocyclizations to give 2-substituted-3-bromopyrrolidines.[114b] A second-generation catalyst based on a cyclic selenoether was also described and can be employed in 5-*exo* bromosulfamidations.[114c]

Yeung's thiocarbamates are not the only oxyhalogenation catalysts useful for intramolecular bromoamidations. The BINOL-derived chiral Brønsted acid (*S*)-TRIP (**40**), a suitable catalyst for bromoetherifications, was also successfully applied in 5-*exo* bromosulfamidations.[85] If the starting material contains an Ns-protected amino group instead of a hydroxy group, the same reaction conditions were suitable for both types of cyclization and the enantioselectivities were even slightly higher for bromosufamidations than for bromoetherifications.

7.21.4.4.2 Intramolecular aminohalogenations using radical methods

Radical cyclizations are the least common method for haloaminations of alkenes. Radical precursors can be, for example, carbonyl azides, which have been used by Bach in chloroamidations promoted by $FeCl_2$ and Me_3SiCl.[115] An interesting asymmetric haloamidation involving halogen transfer was developed by Chemler (Scheme 53).[116] The reaction was promoted by 20 mol% of a copper catalyst, and isopropyl iodide was used as iodine atom donor. The 2-iodomethyl indoline products were obtained in good yields (72–85%) and with high enantioselectivity (80–90% *ee*). The substrate scope was not limited to indolines, and a range of substituted pyrrolidines could be prepared by this method if the reaction conditions were slightly modified.



1. 0.25 equivalent **53**, 0.2 equivalent $Cu(OTf)_2$, 6.0 equivalents Pr^iI, 3.0 equivalents MnO_2, 1.0 equivalent K_2CO_3, $PhCF_3$, 105 °C, 6 h

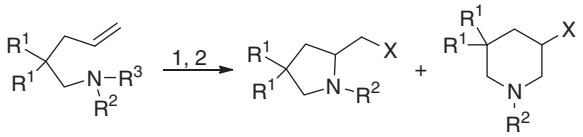
53

R	Yield	*ee*
CH_3	85%	90%
CN	85%	84%
F	80%	89%
Cl	83%	87%
OCH_3	72%	87%

Scheme 53

7.21.4.4.3 Transition metal-catalyzed intramolecular aminohalogenations

Intramolecular aminohalogenation can also be conducted using transition metal catalysis. The most common metal used for this reaction is palladium, and palladium-catalyzed halocyclizations of 1-amino-pent-4-enes have been studied under various reaction conditions (Scheme 54).



54 **55** **56**

R^1	R^2	R^3	Conditions	X	**55**:**56**	Yield	References
Me	Bu^n	Cl	1	Cl	<1:99	85%	117
Me	allyl	Cl	1	Cl	<1:99	51%	117
H	Ts	H	2	Br	37:63	72%	118
H	toluoyl	H	3	Cl	>99:1	90%	119
Me	toluoyl	H	3	Cl	>99:1	94%	119
Ph	toluoyl	H	3	Cl	>99:1	93%	119
Me	Ts	H	4	Cl	<1:99	78%	120
Bn	Ts	H	4	Cl	<1:99	75%	120

1. 1 mol% $Pd(PPh_3)_4$, THF, r.t.; 2. 10 mol% $Pd(TFA)_2$, 2.0 equivalents K_2CO_3, 3.0 equivalents $CuBr_2$, THF, 0 °C–r.t., 24 h; 3. 10 mol% $PdCl_2(MeCN)_2$, 1.2 equivalents NCS, CH_2Cl_2, r.t., 18 h; 4. 5 mol% $Pd(OAc)_2$, 2.0 equivalents 30% H_2O_2, 5.0 equivalents $CaCl_2$, HOAc, r.t.

Scheme 54

Göttlich investigated the palladium-catalyzed cyclization of *N*-chloro-1-aminopent-4-enes.[117] If these substrates were substituted with a *gem*-dimethyl group, 1 mol% $Pd(PPh_3)_4$ was sufficient to catalyze 6-*endo* cyclizations, selectively affording 3-chloropiperidines in 51–85% yield. Substrates without *gem*-dimethyl substitution also formed piperidines but only in lower yields (43–47%). Chemler studied the palladium-catalyzed bromosulfamidation of tosylated pentenylamines.[118] Using copper(II) bromide as oxidant and palladium trifluoroacetate as catalyst, 5-*exo* as well as 6-*endo* cyclization were observed, and only a product mixture was obtained. More selective reactions were achieved by Michael.[119] These authors switched to carboxamide-protecting groups on nitrogen (toluoyl) with NCS as oxidant and chlorine source. Palladium salts such as $PdCl_2(MeCN)_2$ as catalyst allow selective 5-*exo* cyclizations to give 2-chloromethyl pyrrolidines, and these products can be isolated in 90–94% yield. Carbamates such as Boc and Cbz could be employed as alternative protecting groups, and the synthesis of 2-chloromethylindolines by this method was also possible. Interestingly, the regioselectivity of cyclization can be inverted as demonstrated by Liu. Tosylated pentenylamines were cyclized selectively to the 3-chloropiperidines using palladium acetate as catalyst, H_2O_2 as oxidant, and calcium chloride as chlorine source.[120] The yields of 3-chloropiperidines are between 61% and 95%, and starting materials already containing a stereocenter reacted with high diastereoselectivities. 2-Chloromethylpyrrolidines were observed only in a few cases as minor side product. The exact reason(s) why and when 5-*exo* or 6-*endo* cyclizations are preferred are not yet known and further investigations are required.

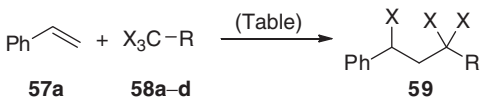
7.21.5 Carbohalogenation Reactions

7.21.5.1 Radical Carbohalogenation Reactions

The atom transfer radical addition (ATRA) describes the addition of a C–X bond across a C–C double or triple bond, leading to the formation of a new C–C as well as a C–X bond in a single transformation. This reaction was pioneered by Kharasch[121] and has since then been extensively studied. The key step is the homolytic cleavage of the C–X bond, which can be achieved among others by radical initiators, transition metal catalysts, or inorganic salts. Initially, the majority of the research focused on the intermolecular version of this transformation. However, as the intramolecular ATRA products exhibit greater synthetic value, the focus of this section will be placed here. Nonetheless, a brief selection of important and recent contributions to the field of intermolecular ATRA reactions will be given first.

7.21.5.1.1 Intermolecular atom transfer radical addition reactions

Snapper reported the use of $Cl_2(Cy_3P)_2RuCHPh$ as a mild catalyst for the ATRA of $CHCl_3$ to a wide range of substrates, including α,β-unsaturated ketones.[122] As a further development, these authors were able to show that the same reaction can be conducted with ethyl trichloroacetate **58a** and 1,1,1-trichloroethane **58b**.[123] With this method, Uozumi has developed a heterogeneous aqueous ATRA reaction by using an amphiphilic resin-supported ruthenium catalyst (Scheme 55).[124]

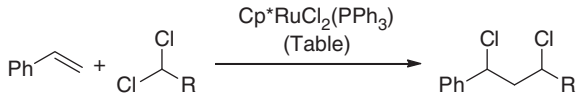


57a **58a–d** **59**

R	X	#	**58**	Catalyst	*t*	Solvent/*T*	Yield	References
CO_2Et	Cl	**58a**	20.0 equivalents	4.5 mol% $Cl_2(Cy_3P)_2RuCHPh$	48 h	neat/75 °C	57%	123
Me	Cl	**58b**	20.0 equivalents	5 mol% $Cl_2(Cy_3P)_2RuCHPh$	1.5 h	neat/75 °C	96%	123
Cl	Cl	**58c**	1.0 equivalent	0.33 mol% PS-PEG-PPh_2-Cp*$RuCl_2$	9 h	H_2O/60 °C	91%	124
Br	Br	**58d**	1.0 equivalent	0.33 mol% PS-PEG-PPh_2-Cp*$RuCl_2$	9 h	H_2O/60 °C	89%	124
CO_2Et	Cl	**58a**	1.0 equivalent	0.33 mol% PS-PEG-PPh_2-Cp*$RuCl_2$	9 h	H_2O/60 °C	89%	124

Scheme 55

Severin employed the half-sandwich ruthenium(III) complex $[Cp^*RuCl_2(PPh_3)]$ in catalytic amounts for the ATRA reaction of styrene with chloroform or ethyl dichloroacetate in the presence of various additives such as magnesium, azobisisobutyronitrile (AIBN), or manganese (Scheme 56).[125] The additives proved to be crucial in order to obtain high catalytic activity. Explanations for this are (1) activation of the catalyst precursor and/or (2) regeneration of the ruthenium(II) catalyst from ruthenium(III), formed as a result of a termination reaction.

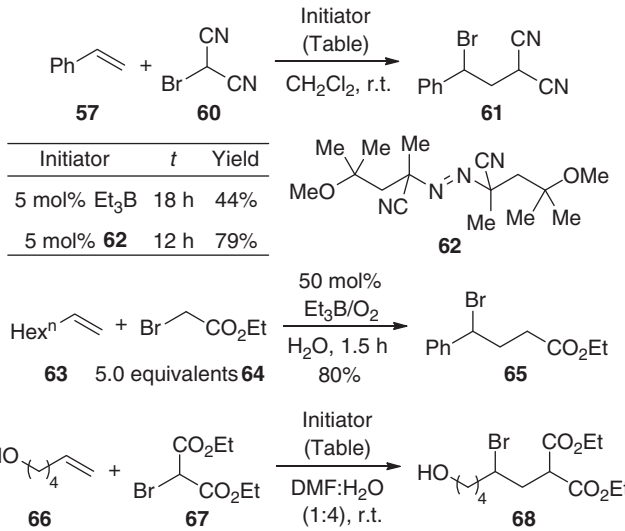


R	$Cp^*RuCl_2(PPh_3)$	Additive	*t*	Solvent/*T*	Yield	References
Cl	0.05 mol%	3 equivalents Mg, D_2O[a]	24 h	$CHCl_3$/r.t.	86%	125a
Cl	0.05 mol%	5 mol% AIBN	24 h	$CHCl_3$/60 °C	80%	125a
CO_2Et	0.1 mol%	5 equivalents Mn	1 h	THF/r.t.	86%	125b

[a] $CHCl_3$ saturated with D_2O was used as the solvent.

Scheme 56

Among the radical initiators used in ATRA reactions, AIBN has been extensively studied. However, it requires elevated temperatures for the generation of radicals, thus limiting its applicability. As an alternative, Kita examined more compatible radical initiators such as Et_3B and V-70 (**62**) in the addition of bromomalononitrile **60** to styrene **57** (Scheme 57).[126] The use of 5 mol% Et_3B as a standard room-temperature initiator led to the desired product **61** in only 44% yield, whereas under similar conditions, 5 mol% of V-70 yielded **61** in 79% yield in reduced reaction time. Later, Oshima was able to show that a combination of Et_3B and O_2 can be used as radical initiator in the ATRA of ethyl bromoacetate (**64**) to *n*-octene (**63**) in aqueous media (Scheme 57).[127] The method is also applicable to other substrates such as benzyl bromoacetate and bromomalonate, and the products are obtained within moderate reaction times (1.5 h) and good to excellent yields up to 99%. As a further improvement, Stephenson applied ruthenium- and iridium-based visible light photocatalysts **69** and **70** for the ATRA of bromomalonate (**67**) to 5-hexen-1-ol (**66**) in excellent yields (Scheme 57).[128] By changing the solvent system from DMF/H_2O to DMSO, it is possible to obtain product **68** in shorter reaction times with lower loadings of bromomalonate (**67**) and LiBr with only a slight reduction in yield. In addition to bromides, this method is also applicable to various perfluoroalkyl halides.



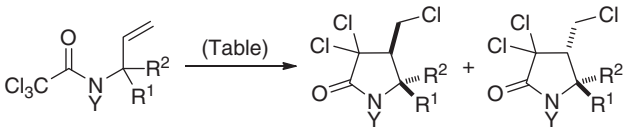
Scheme 57

7.21.5.1.2 Intramolecular atom transfer radical additions: atom transfer radical cyclization

The intramolecular version of ATRA, the atom transfer radical cyclization reaction (ATRC),[129] involves the transfer of a halogen atom from one carbon center to another with concomitant ring formation. The advantage of this reaction over other radical cyclization reactions is the retention of the halogen atom in the product, thereby allowing for further functionalization. In addition, the reaction opens access to a large variety of carbocyclic and heterocyclic ring systems, especially five- and six-membered rings, and exhibits a high functional group tolerance.

7.21.5.1.2.1 Transition metal-catalyzed ATRC

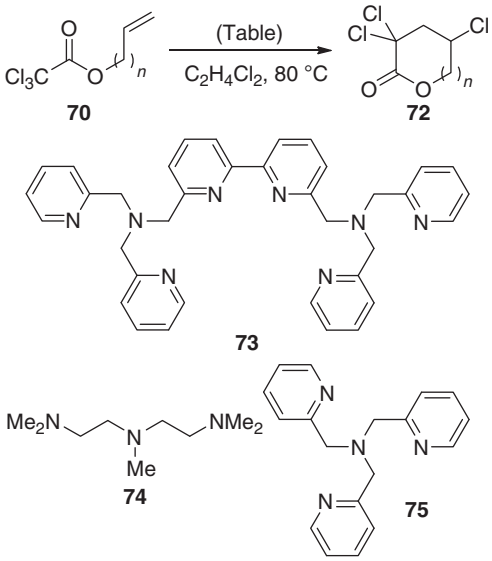
The first example of a transition metal-catalyzed ATRC was reported by Nagashima and Itoh. They were able to show that catalytic amounts of either CuCl[130] or $RuCl_2(PPh_3)_3$[131] can be used to cyclize allyl trichloroacetates or allyl trichloroacetamides to the corresponding lactones or lactams. However, these methods suffered from high reaction temperatures and only moderate yields in several cases. Later, the same group was able to show that using CuCl/bipy as catalytic system, the cyclization of allyl trichloroacetamides can be performed at room temperature in good to excellent yields and reduced reaction times.[132] In addition to the substrate scope, the stereochemistry of this reaction was studied with compounds having a substituent in the allylic position, which leads to the formation of β,γ-disubstituted γ-lactams. As a general trend, the stereochemical outcome of the reaction depends on the substitution on the nitrogen atom. If no protecting group is used, the diastereomeric ratios are in favor of the *trans*-product.[131b] However, if a protecting group is present the stereochemical outcome is strongly dependent on the nature of the protecting group (**Scheme 58**).[132]



R^1	R^2	Y	Catalyst	*t*	Solvent/*T*	Yield	Ratio *cis*:*trans*	References
Me	H	H	5 mol% $RuCl_2(PPh_3)_3$	2 h	Benzene/r.t.	64%	16:84	131b
Pr^n	H	H	5 mol% $RuCl_2(PPh_3)_3$	2 h	Benzene/r.t.	83%	11:89	131b
Ph	H	H	5 mol% $RuCl_2(PPh_3)_3$	1 h	Benzene/r.t.	60%	<1:>99	131b
CO_2Me	H	H	5 mol% $RuCl_2(PPh_3)_3$	1 h	Benzene/r.t.	89%	15:85	131b
Me	Me	Bn	30 mol% CuCl/bipy	1 h	CH_2Cl_2/r.t.	96%	–	132
Me	H	Bn	30 mol% CuCl/bipy	2 h	CH_2Cl_2/r.t.	98%	12:88	132
Me	H	Bn	30 mol% CuCl	13 h	MeCN/110 °C	84%	22:78	132
Me	H	Bn	5 mol% $RuCl_2(PPh_3)_3$	6 h	Benzene/140 °C	86%	29:71	132
Me	H	Me	30 mol% CuCl/bipy	1 h	CH_2Cl_2/–15 °C	98%	10:90	132
Me	H	Ts	5 mol% CuCl/bipy	6 min	CH_2Cl_2/r.t.	74%	78:22	132
Me	H	Boc	30 mol% CuCl/bipy	1.5 h	CH_2Cl_2/r.t.	98%	77:23	132

Scheme 58

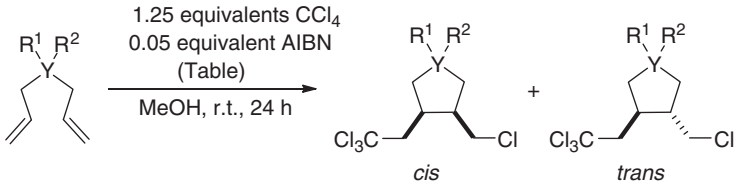
An improvement of the copper-based system in terms of catalyst loading and substrate scope was reported by Verlhac.[133] By using a range of polydentate nitrogen ligands, especially the branched oligopyridines **73** and **75** (TMPA), these authors were able to reduce the CuCl loading to 0.1 mol% whereas obtaining the lactons of type **72** in moderate to excellent yields of 47–99% (**Scheme 59**). It was also shown that the use of iron-based catalysts is also possible in several cases, even though with reduced yields. For example, using a slightly higher loading (0.3 mol%) of $FeCl_2$ in combination with inexpensive ligand **74**, the corresponding lactone was obtained in 62% yield.



n	Catalyst	Ligand	Yield
3	0.1 mol% CuCl	0.1 mol% **73**	99%
3	0.1 mol% CuCl	0.03 mol% **74**	18%
3	0.1 mol% CuCl	0.03 mol% **75**	90%
3	0.1 mol% CuCl	0.1 mol% bpy	47%
4	0.1 mol% CuCl	0.1 mol% **73**	53%
5	0.1 mol% CuCl	0.1 mol% **75**	70%
3	0.3 mol% $FeCl_2$	0.3 mol% **74**	62%

Scheme 59

A combination of copper(II) salts and ligand **75** (TMPA) was also applied in a sequential photoinitiated copper(II)-catalyzed ATRA and ATRC described by Pintauer.[134] By using different diallylamines, ethers, or 1,6-dienes, the corresponding five-membered rings were obtained in excellent yields (84–96%) and diastereoselectivities of >80:20 in favor of the *cis*-isomer (Scheme 60).



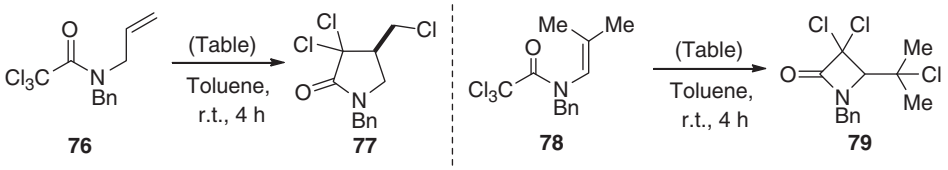
R^1	R^2	Y	Catalyst	Yield	Ratio *cis:trans*
–	–	O	–	0%	–
–	–	O	1 mol% [Cu^{II}(TMPA) Cl][Cl]	85%	82:18
–	–	O	0.05 mol% [Cu^{II}(TMPA) Cl][Cl]	96%	80:20
CO_2Bu^i	–	N	1 mol% [Cu^{II}(TMPA) Cl][Cl]	92%	80:20
$COCF_3$	–	N	1 mol% [Cu^{II}(TMPA) Cl][Cl]	84%	85:15
CO_2Et	CO_2Et	C	1 mol% [Cu^{II}(TMPA) Cl][Cl]	86%	85:15

Scheme 60

Also, other ruthenium-based catalytic systems, such as ruthenium amidinates **80** and **81,** were introduced. These were used for the synthesis of both β- and γ-lactams **77** and **79**, starting from either vinyl or allyl trichloroacetamides **76** and **78** in good to excellent yields (Scheme 61).[135]

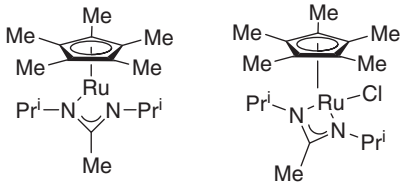
Based on work in the intermolecular ATRA reaction,[122] Quayle used the well-defined Grubbs I metathesis catalyst in the intramolecular version of this reaction due to the incompatibility of their substrates with the CuCl/bipy system.[136] However, the products were obtained only in moderate yields (25–70%) despite high reaction temperatures (Scheme 62, upper row). Using the same catalyst, Snapper reported a tandem ring-closing metathesis/ATRA reaction in good yields (Scheme 62, lower row).[137]

The CuCl/bipy system developed by Nagashima and Itoh[132] inspired further research in this field. Hiemstra and Speckamp used the same CuCl/bipy catalyst for the cyclization of several α-chloroglycine derivatives.[138] Depending on the substrate, either a mixture of the *endo*- and *exo*-cyclization products was obtained (internal alkenes), or in case of terminal alkenes, the five-membered ring was formed exclusively. Also, the synthesis of bicyclic structures is possible. The products are obtained in good yields (53–86%) and moderate to good diasteroselectivities depending on the substrate (Scheme 63).



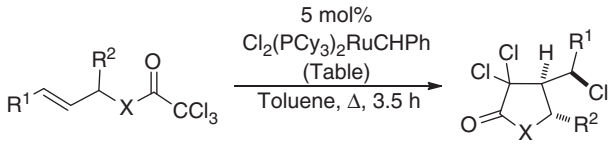
76 **77** **78** **79**

Substrate	Product	Catalyst	Yield
76	**77**	10 mol% **80**	85%
76	**77**	10 mol% **81**	88%
78	**79**	10 mol% **80**	35%
78	**79**	10 mol% **81**	82%

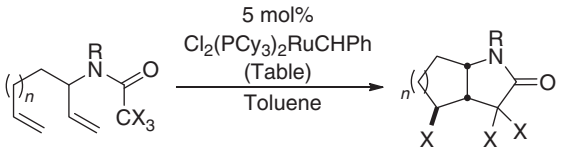


80 **81**

Scheme 61

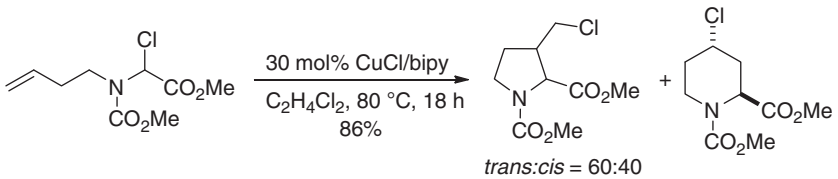


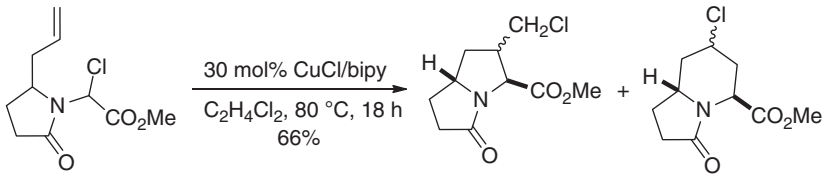
R^1	R^2	X	Yield
Ph	H	O	54%
Ph	Ph	O	25%
H	H	O	45%
H	H	NTs	70%



R	X	*n*	*t*	*T*	Yield
H	Cl	1	2.25 h	155 °C	75%
H	Cl	2	1.75 h	155 °C	85%
H	Cl	3	0.5 h	155 °C	55%
Bn	Cl	2	11 h	110 °C	85%
Bn	Br	2	2.5 h	r.t.	50%

Scheme 62

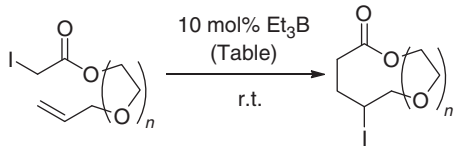




Scheme 63

7.21.5.1.2.2 Transition metal-free ATRC

A triethylborane-mediated ATRC of unsaturated α-iodoesters of type **82** was developed by Oshima.[139] By conducting the reaction in low concentrations in water as a solvent, it is possible to construct macrocycles up to a ring size of 18 in good to excellent yields. Performing the reaction in benzene led to low yields and recovery of up to 78% of the starting material (Scheme 64).



82 **83**

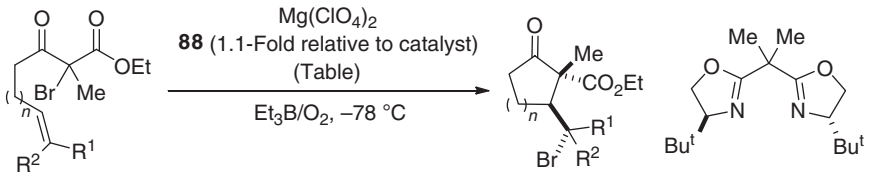
n	*t*	Solvent	Yield	*t*	Solvent	Yield
1	10 h	H_2O (Excess)	69%	10 h	Benzene	27%
2	8 h	H_2O (Excess)	84%	10 h	Benzene	22%
3	10 h	H_2O (Excess)	86%[a]	3 h	Benzene	41%
4	4 h	H_2O (Excess)	98%	6 h	Benzene	14%

[a] Et_3B added in two portions of 5.0 mol% each.

Scheme 64

7.21.5.1.2.3 Enantioselective ATRC

Yang reported an enantioselective Lewis acid-catalyzed ATRC in the presence of bisoxazoline ligand **88** and triethylborane and O_2 as radical initiators (Scheme 65).[140] The cyclopentanes **86** and cyclohexanes **87** were obtained in moderate yields and excellent enantioselectivities up to 94% *ee*. Later, these authors reported a similar reaction with chloro analogs of **85**.[141]



84, *n* = 1
85, *n* = 2

86, *n* = 1
87, *n* = 2

88

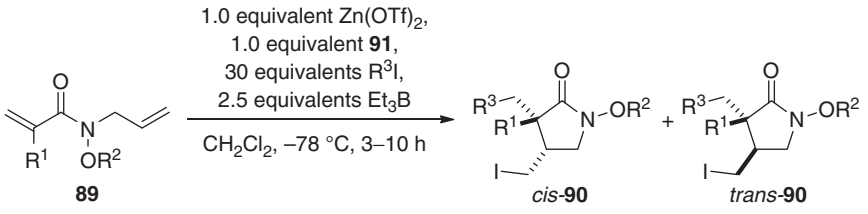
R^1	R^2	Catalyst	*t*	Solvent	Yield	*ee*
Me	Me	1.1 equivalents	7.5 h	CH_2Cl_2	68%	71%
Me	Me	1.1 equivalents	5 h	Toluene	67%	94%
Me	Me	0.3 equivalent	7 h	Toluene	68%	92%
Me	Me	1.1 equivalents	7.5 h	Toluene	62%	93%
Et	H	1.0 equivalent	9.5 h	Toluene	57% (1/1.2)[a]	68%/78%[b]
Et	H	1.0 equivalent	7 h	CH_2Cl_2	62% (1.3/1)[a]	44%/54%[b]
H	Et	1.0 equivalent	6.5 h	Toluene	62% (1/1.3)[a]	52%/78%[b]

[a] Ratio of R^1 = Et, R^2 = H and R^1 = H, R^2 = Et;
[b] The *ee* values for R^1 = Et, R^2 = H and R^1 = H, R^2 = Et, respectively.

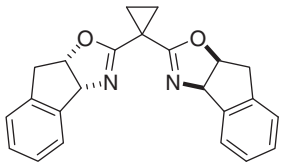
Scheme 65

As a further development of this reaction, Miyabe and Takemoto reported an enantioselective cascade radical addition-cyclization-trapping reaction.[142] In their case, the catalytic system consisted of $Zn(OTf)_2$ and the cyclopropane-containing bisoxazoline ligand **91,** whereas triethylborane is used again to initiate the radical reaction. With this system, these authors were able to show that different hydroxamate esters of type **89** can be reacted in the presence of different alkyl and aryl iodides to the corresponding 5-*exo* cyclization products *cis*- and *trans*-**90** in moderate to good yields (52–75%). The diastereoselective outcome of the reaction depends on the substitution pattern of the allyl moiety, whereas the enantioselectivity is high in most of the examples (up to 92% *ee*, Scheme 66).

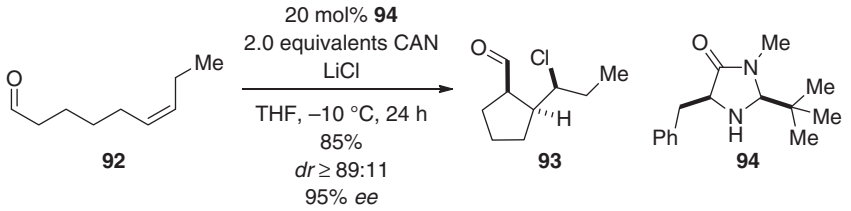
During their work in the enantioselective organocatalytic α-allylation of aldehydes using SOMO activation, MacMillan also presented an ATRC of the unsaturated aldehyde **92** in the presence of ceric ammonium nitrate and LiCl as halide source.[143] The product **93** was obtained in good yield and diastereoselectivity and high enantioselectivity (equation 6).



R^1	R^2	R^3	Yield	Ratio *cis:trans*	*ee*
Me	Me	Pr^i	75%	>98:<2	82%
Me	$CHPh_2$	Pr^i	52%	>98:<2	Racemic
H	Bn	Pr^i	52%	8:92	92%
H	Bn	Cy	57%	6:94	92%



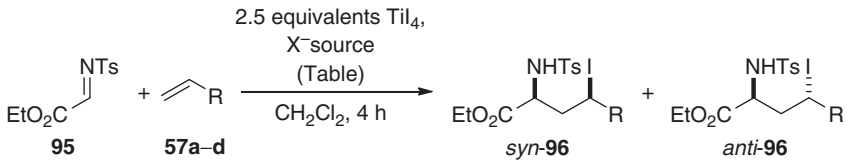
Scheme 66



(6)

7.21.5.2 Prins-Type Reactions

The Prins reaction is the electrophilic addition of an activated carbonyl or imine group to a carbon–carbon double or triple bond followed by the reaction of the resulting carbenium ion with a nucleophile.[144] The use of halides as nucleophiles leads to a formal carbohalogenation of the double bond. The majority of the examples of this halo-Prins reaction in literature focuses on the intramolecular variant, the Prins cyclization. Therefore, these transformations will be discussed exclusively in the following paragraph. However, as an intermolecular example from the laboratory of Shimizu, the aza-Prins reaction of imine **95** with different alkenes is shown in Scheme 67.[145]



R	#	*T*	X^- source	Yield	*dr syn:anti*
Ph	**57a**	0 °C	–	34%	64:36
Ph	**57a**	0 °C	1.0 equivalent I_2	74%	55:45
1-Naphthyl	**57b**	r.t.	1.0 equivalent I_2	58%	59:41
2-Furyl	**57c**	r.t.	1.0 equivalent I_2	42%	61:39
2-Thienyl	**57d**	r.t.	1.0 equivalent I_2	44%	62:38

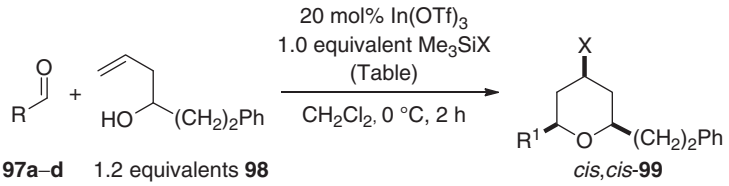
Scheme 67

7.21.5.2.1 Halo-Prins cyclization

The intramolecular Prins reaction, that is, Prins cyclization, leads to a variety of carbocyclic and heterocyclic compounds and has found numerous synthetic applications. The use of a homoallylic alcohol in this reaction leads to the facile construction of substituted tetrahydropyran (THP) derivatives and is, as a result, one of the most versatile methods for the synthesis of this oxygen heterocycle.

7.21.5.2.1.1 Halo-Prins cyclization for the formation of substituted THPs

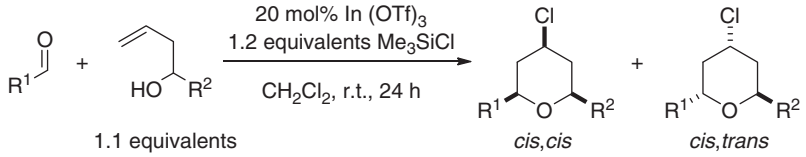
THPs are a common structural feature in a wide range of natural products. Generally, the reaction is Brønsted acid catalyzed, but over the past two decades, Lewis acid-catalyzed methods have been introduced. Despite the extensive research in halo-Prins cyclization, most of these methods were limited by the choice of the halide source, epimerization of the starting homoallylic alcohol, and the need to use a stoichiometric amount of Lewis acid.[146] Loh was able to overcome these limitations by using catalytic amounts of $In(OTf)_3$ and trimethylsilyl halides. The reaction of 1-phenylhex-5-en-3-ol (**98**) with a variety of aldehydes (including α,β-unsaturated) proceeded in moderate to excellent yields (61–94%) and proved to be highly diastereoselective with the products having all-*cis* configuration due to the all-equatorial arrangement of the substituents (Scheme 68). Moreover, the use of a chiral homoallylic alcohol leads to a transfer of chirality to the product when a weaker Lewis acid is applied. This asymmetric protocol was further employed in the synthesis of (–)-centrolobine.[147]



R	#	X	Yield
$CH(CH_2CH_3)_2$	**97a**	Cl	76%
$CH(CH_2CH_3)_2$	**97a**	Br	81%
$CH(CH_2CH_3)_2$	**97a**	I	91%
Et	**97b**	I	82%
Cy	**97c**	I	89%
$(CH_2CH_3)_2OBn$	**97d**	I	64%

Scheme 68

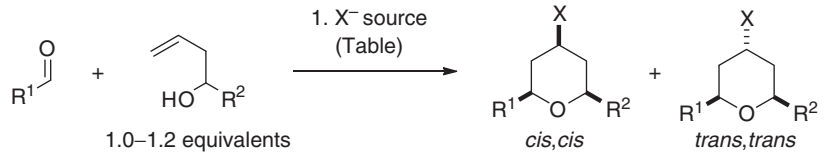
As mentioned in the preceding paragraph, the all-equatorial arrangement of the substituents is thermodynamically favored. However, access to other diastereomers of these trisubstituted THP-rings is also highly desired. This can be achieved by using the same catalytic system outlined in the previous paragraph with a carboxyl group attached to the carbinol carbon atom of the homoallylic alcohol, which leads to a mixture of all-*cis* and *cis*,*trans*-isomers (Scheme 69).[148] This was explained by the interaction of an oxygen lone pair of the ester functionality with the intermediate oxonium ion, which compensates the steric repulsion of the substituents.



R^1	R^2	Yield	*dr* *cis*,*cis*:*cis*,*trans*
Ph	$COOBu^n$	71%	51:49
Ph	CH_2OCOPh	69%	>99:<1
3-Pent	$COOPr^i$	57%	44:56
$(CH_2)_2Ph$	$COOPr^i$	62%	50:50
$CHCHCH_3$	$COOPr^i$	58%	51:49

Scheme 69

Other methods led to a mixture of the all-*cis* isomer and the *trans*,*trans*-isomer with the halide in the axial position (Scheme 70). Usually, the all-*cis* isomer is favored due to the equatorial arrangement of the substituents.[149] In addition, Fache was able to show that the reaction also proceeds under solvent-free conditions, resulting in an even higher diastereomeric ratio in favor of the all-*cis* diastereomer.[150] However, Saikia was able to obtain diastereoselectivities of higher than 99:1 for the *trans*,*trans*-isomer in this

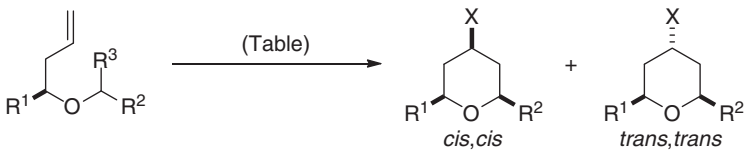


R^1	R^2	Promoter	X^- source	X	*t*	Solvent/*T*	Yield	*dr cis,cis: trans, trans*	References
Ph	$(CH_2)_2$-Ph	1.0 equivalent Me_3SiCl	1.0 equivalent NaI	I	3 min	MeCN/r.t.	96%	70:30	149
4-Br-C_6H_4	4-CH_3-C_6H_4	1.0 equivalent Me_3SiCl	1.0 equivalent NaI	I	5 min	MeCN/r.t.	83%	90:10	149
Cy	H	1.2 equivalents Me_3SiOTf	1.2 equivalents TBAB	Br	2 h	CH_2Cl_2/0 °C	65%	<1:>99	151
Cy	H	1.2 equivalents Me_3SiOTf	1.2 equivalents TBAI	I	30 min	CH_2Cl_2/0 °C	82%	<1:>99	151
Pr^n	Pr^n	1.2 equivalents Me_3SiOTf	1.2 equivalents TBAI	I	30 min	CH_2Cl_2/0 °C	80%	<1:>99	151
Ph-C_6H_4	H	1.5 equivalents Me_3SiCl	–	Cl	20 min–120 min	Neat/r.t.	83%	>99:<1	150
Ph-C_6H_4	H	1.5 equivalents Me_3SiBr	–	Br	20 min	Neat/r.t.	85%	85:15	150
Ph-C_6H_4	H	1.5 equivalents Me_3SiI	–	I	20 min	Neat/r.t.	70%	70:30	150

Scheme 70

transformation by using a mixture of Me_3SiOTf and TBAB or TBAI.[151] This method is applicable for a broad range of aldehydes and homoallylic alcohols in moderate to good yields (58–86%). Also, a mechanism for the formation of this axial-selective halo-Prins cyclization has been proposed.

Similar observations for the all-*cis* selectivity of this reaction were made in the halo-Prins cyclization of preformed ethers and acetals (Scheme 71).[152] Rychnovsky showed that this diastereoselectivity can be inverted by changing the Lewis acid from $SnBr_4$ to

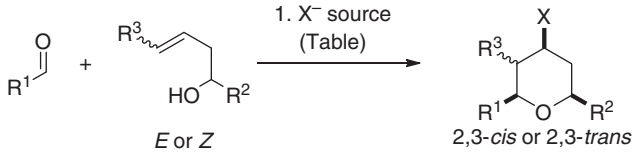


R^1	R^2	R^3	Lewis acid	X	*t*	Solvent/*T*	Yield	*dr cis,cis: trans:trans*	References
Me	4-MeO-C_6H_4	H	1.1 equivalents $SnBr_4$ 1.05 equivalents DDQ	Br	30 min	CH_2Cl_2/r.t.	89%	>99:<1	152a
Me	4-MeO-C_6H_4	H	1.1 equivalents $InCl_3$ 1.05 equivalents DDQ	Cl	6 h	CH_2Cl_2/r.t.	55%	>99:<1	152a
Hex^n	CH_2CO_2Et	H	1.0 equivalent $TiCl_4$	Cl	3 days	CH_2Cl_2/r.t.	63%	95:5	152b
Hex^n	CH_2CO_2Et	H	1.0 equivalent $TiBr_4$	Br	2 h	CH_2Cl_2/0 °C	64%	86:14	152b
$(CH_2)_2Ph$	Allyl	OAc	1.0 equivalent $SnBr_4$	Br	1 h	$MeNO_2$/0 °C	82%	92:8	153
$(CH_2)_2Ph$	Allyl	OAc	1.0 equivalent $SnCl_4$	Cl	1 h	CH_2Cl_2/0 °C	81%	79:21	153
$(CH_2)_2Ph$	Allyl	OAc	1.0 equivalent Me_3SiBr	Br	1 h	CH_2Cl_2/0 °C	85%	7:93	153

Scheme 71

Me_3SiBr.[153] These authors also studied the competing oxonia-Cope rearrangement and the chirality transfer when a chiral starting material was used.

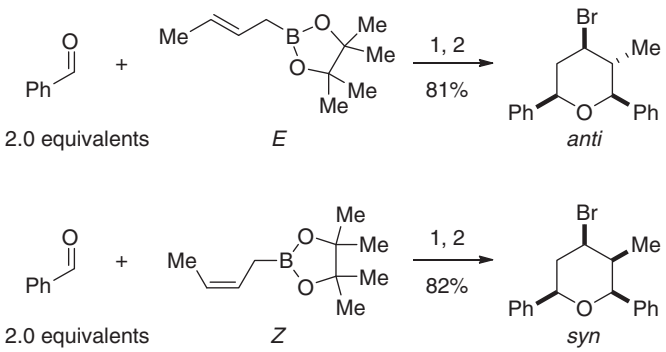
By using homoallylic alcohols with an internal double bond, an additional substituent can be introduced at the 3-position of the THP ring, thereby creating four stereogenic centers in one reaction step (Scheme 72). Yadav reported a metal-free halo-Prins cyclization by using iodine as reagent under mild reaction conditions leading to 4-iodo-substituted THP derivatives.[154] The reaction is diastereospecific, making 2,3-*cis*- or -*trans*-substituted THPs available from (*Z*)- and (*E*)-configured cyclization precursors, respectively. An entry into 3,4-bromo-substituted THPs is possible through a reaction of homoallylic alcohols bearing a bromine on the alkene.[155] The reaction proceeds in the presence of stoichiometric amounts of $InBr_3$ and Me_3SiBr as bromide source. Again, the stereochemical outcome of the reaction depends on the configuration of the alkene. As an alternative approach, these tetrasubstituted THP rings with similar configuration can be prepared starting from preformed acetals or ethers.[156]



R^1	R^2	R^3	Alcohol	Lewis acid	X^- source	X	*t*	Solvent/*T*	Yield		References
Pr^i	H	Et	*Z* 2.0 equivalents	–	1.0 equivalent I_2	I	60 min	CH_2Cl_2/r.t.	90%	2,3-*cis*	154
Pr^i	Me	Hex^n	*E* 2.0 equivalents	–	1.0 equivalent I_2	I	80 min	CH_2Cl_2/r.t.	93%	2,3-*trans*	154
Cy	$(CH_2)_2Ph$	Br	*Z* 1.2 equivalents	1.0 equivalent $InBr_3$	1.2 equivalents Me_3SiBr	Br	90 min	CH_2Cl_2/0 °C	95%	2,3-*cis*	155
Cy	$(CH_2)_2Ph$	Br	*E* 1.2 equivalents	1.0 equivalent $InBr_3$	1.2 equivalents Me_3SiBr	Br	90 min	CH_2Cl_2/0 °C	92%	2,3-*trans*	155

Scheme 72

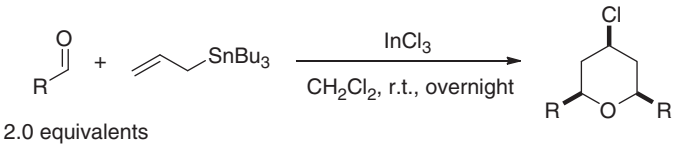
All examples so far presented were based on homoallylic alcohols or preformed related substrates. However, alternative reagents have been introduced in the halo-Prins cyclization to synthesize THP derivatives. Ramachandran used allyl and crotyl boronates, which first react with one equivalent of aldehyde, to form the homoallylic alcohol. The latter reacts in a second step in the presence of catalytic amounts of $In(OTf)_3$ and Me_3SiBr as halide source with the second equivalent of aldehyde to form the THP derivative in good yields (Scheme 73).[157] Again, the diastereochemical outcome of the reaction is dependent on the alkene geometry of the precursor.



1. 10 mol% $In(OTf)_3$, CH_2Cl_2, –78 °C; 2. 1.2 equivalents Me_3SiBr, –78 °C, 8 h

Scheme 73

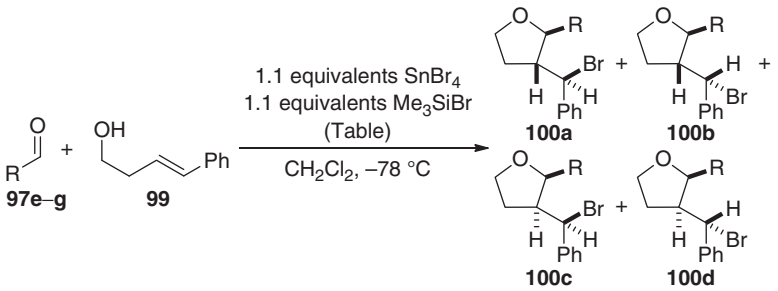
Li reported the reaction of tributylallylstannane and a broad range of aldehydes in the presence of $InCl_3$. The symmetric trisubstituted THP derivatives were obtained in good to excellent yields of 72–90% (Scheme 74). In addition to these examples, other reagents such as allylic silanes and bromides have been employed in this reaction.[158]



R	Yield
Ph	72%
2-F-C_6H_4	90%
3-F-C_6H_4	75%
4-F-C_6H_4	80%

Scheme 74

As shown above, the majority of the Prins cyclizations of homoallylic alcohols with aldehydes leads to the formation of THP rings. However, the formation of THFs is preferred when electron-donating substituents are located at the alkene, which leads to the stabilization of the exocyclic carbenium ion. Spivey was able to show that the alcohol **99** reacts with a range of aldehydes to form the THF derivatives **100a–d** (Scheme 75).[159] The ratio of the cyclic ethers depends on the aldehyde used. In addition, Padrón recently showed that the synthesis of seven-membered ethers is also possible via a Prins cyclization.[160]



R	#	*t*	Yield	Ratio **100a**:**100b**:**100c**:**100d**
Me	**97e**	1.5 h	55%	0:0:60:40
Pr^i	**97f**	3 h	92%	8:0:80:12
Ph	**97g**	1.5 h	60%	77:12:11:0

Scheme 75

7.21.5.2.1.2 Aza-halo-Prins cyclization

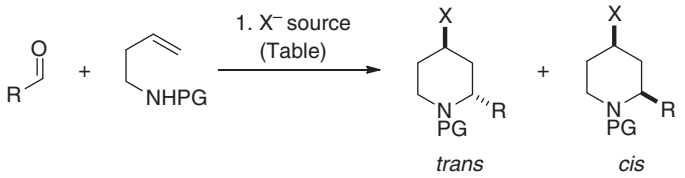
The use of homoallylic amines instead of alcohols in the Prins reaction is a simple and direct method for the preparation of substituted piperidine compounds. Martín and Padrón developed an iron(III)-mediated aza-halo-Prins cyclization of homoallylic tosylamides and various aldehydes in good to excellent yields (68–96%) and very high diastereoselectivities for the *trans*-isomer.[161] This somewhat unexpected diastereoselectivity in comparison to the oxygen analog is due to the steric interactions of the tosyl group at the iminium nitrogen atom with the R group of the aldehyde in the intermediate. To improve this reaction further, the authors used *p*-nitrobenzenesulfonyl (nosyl) protected homoallylic amines due to more efficient removal of this protecting group and were also able to develop a catalytic version of the reaction.[162] In addition, other groups have contributed to this field, resulting in different stoichiometric and catalytic variants of this transformation (Scheme 76).[163]

Dobbs reported the synthesis of trisubstituted piperidines by reacting tosylamide **101** containing a 1,2-disubstituted alkene with different aldehydes (Scheme 77).[164] Yields were relatively low in several cases despite long reaction times, and the piperidines were formed along with substantial amounts of the corresponding pyrrolidine.

Yadav was able to show that a similar transformation is possible by reacting homoallyic amines with various epoxides instead of aldehydes in the presence of a stoichiometric amount of $BiCl_3$.[165] The corresponding *trans*-piperidines are obtained in excellent yields (Scheme 78).

7.21.5.2.1.3 Mukaiyama-aldol–Prins cyclization

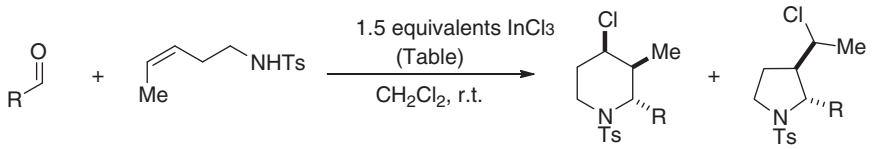
As a further development of the Prins cyclization, Rychnovsky reported a titanium halide-mediated Mukaiyama-aldol–Prins cyclization (MAP).[166] In this transformation, enol ether **105** can be reacted with different aldehydes or ketones in the presence of 2,6-di-*tert*-butylpyridine (2,6-DTBP) or 2,6-di-*tert*-butyl-4-methylpyridine (2,6-DTBMP) to yield the trisubstituted THP derivatives of type **106** in moderate to good yields (52–80%) and good diastereoselectivity in favor of the all-*cis*-substituted heterocycle (Scheme 79, upper). However, the formation of the secondary or tertiary alcohol was not diastereoselective. When an internal



R	Lewis acid	PG	X^- source	Aldehyde	X	*t*	Solvent/*T*	Yield	*dr trans:cis*	References
Bu^i	1.5 equivalents FeX_3	Tosyl	–	1.5 equivalents	Cl	1 h	CH_2Cl_2/r.t.	82%	>99:<1	161
Bu^i	1.0 equivalent FeX_3	Nosyl	–	1.0 equivalent	Cl	1 h	CH_2Cl_2/r.t.	96%	>99:<1	162
Bu^i	1.0 equivalent FeX_3	Nosyl	–	1.0 equivalent	Br	1 h	CH_2Cl_2/r.t.	84%	>99:<1	162
Ph	1.0 equivalent FeX_3	Nosyl	–	1.0 equivalent	Cl	1 h	CH_2Cl_2/r.t.	56%	85:15	162
Bu^i	0.1 equivalent FeX_3	Nosyl	1.0 equivalent Me_3SiX	1.5 equivalents	Cl	2–12h	CH_2Cl_2/r.t.	80%	>99:<1	162
Bu^i	0.075 equivalent $Fe(acac)_3$	Nosyl	1.0 equivalent Me_3SiX	1.0 equivalent	Cl	2–12h	CH_2Cl_2/r.t.	88%	>99:<1	162
Ph[a]	3.0 equivalents $FeCl_3$	Tosyl	–	1.5 equivalents	Cl	24 h	BTF/r.t.	82%	90:10	163a
Ph	0.1 equivalent GaI_3	Tosyl	1.0 equivalent I_2	1.0 equivalent	I	6.5 h	CH_2Cl_2/r.t.	91%	96:4	163b
Et	1.0 equivalent Me_3SiX	Tosyl	–	1.0 equivalent	I	2 h	MeCN/0 °C	88%	97:3	163c

[a] 1.5 equivalents $[Bmin]^+PF_6^-$ was used as an additive.

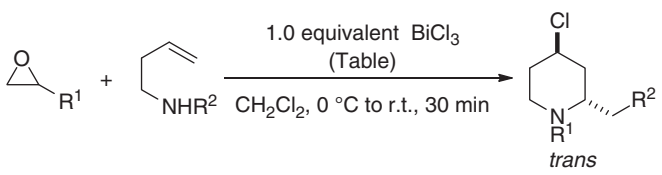
Scheme 76



1.5 equivalents **97c, g–j** **101** **102** **103**

R	#	*t*	Yield **102**	Yield **103**
CO_2Et	**97h**	1 h	20%	0%
Hep^n	**97i**	17 h	35%	35%
Ph	**97g**	144 h	15%	0%
Cy	**97c**	144 h	26%	50%
$(CH_2)_2Ph$	**97j**	17 h	40%	36%

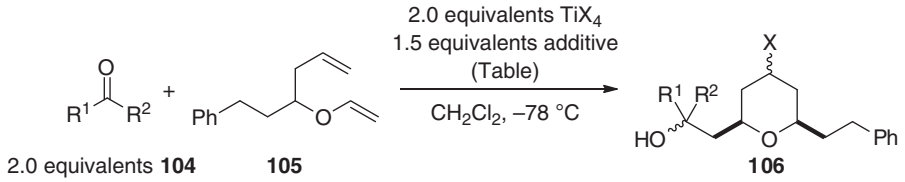
Scheme 77



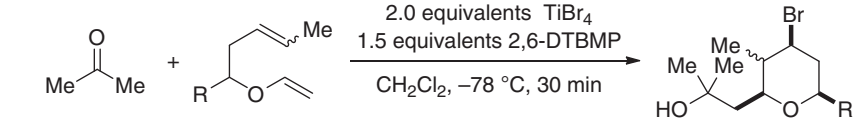
R^1	R^2	Yield
Ph	Ts	93%
Pr^i	Ts	88%
Ph	Ms	92%
Ph	Boc	93%

Scheme 78

alkene of type **108** is used, the stereochemistry in the product **109** is again dependent on the configuration of the alkene (Scheme 79, lower).



R^1	R^2	X	Additive	*t*	*dr* (OH)	*dr* (X) eq:ax	Yield	References
$(CH_2)_2Ph$	H	Cl	2,6-DTBP	n.r.	50:50	>95:<5	62%	166a
$(CH_2)_2Ph$	H	Br	2,6-DTBP	n.r.	52:48	>95:<5	72%	166a
$(CH_2)_2OBn$	H	Br	2,6-DTBP	n.r.	50:50	68:32	75%	166a
$(CH_2)_3OBn$	H	Br	2,6-DTBP	n.r.	50:50	85:15	75%	166a
Ph	Me	Br	2,6-DTBMP	30 min	57:43	87:13	52%	166b
$(CH_2)_2OTBDPS$	Me	Br	2,6-DTBMP	30 min	50:50	93:7	80%	166b



R		Yield		References
$(CH_2)_2OTBDPS$	*Z*	84%	2,3-*cis*-**109**	166b
Bn	*E*	89%	2,3-*trans*-**109**	166b

Scheme 79

The MAP cyclization can also be used to construct highly functionalized carbocycles such as hexasubstituted cyclohexanes[167] and pentasubstituted cyclopentanes.[168] This can be achieved by the reaction of the acetals **111** and **113** with silyl enol ethers of type **110** in the presence of 2 equivalents of $TiBr_4$ (Scheme 80). The presence of a substituent at the alkene of the acetal leads to the formation of the five-membered rings. Both reactions yield the corresponding products in good to excellent yields and in excellent diastereoselectivity for the cyclopentanes. It is worthy of note that in the case of the six-membered carbocycles, the use of a chiral acetal leads to very high enantioselectivities of both diastereomers obtained.

7.21.5.2.1.4 Bicyclic ethers via Prins-type cyclizations

Bicyclic ethers are also accessible via a Prins-type cyclization. Cho used an excess of $InCl_3$ to synthesize bicycle **116** in moderate yields.[169] In a related reaction, bicycle **118** is obtained in the presence of catalytic amounts of $PtCl_4$ by an internal hydroalkoxylation of the alkyne, followed by a Prins-type cyclization (Scheme 81).[170]

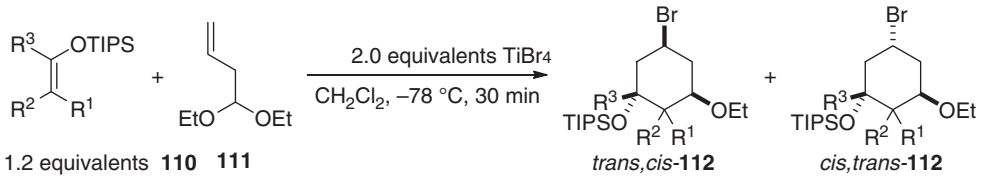
7.21.5.3 Transition Metal-Catalyzed Arylhalogenation (Carbohalogenation)

7.21.5.3.1 Oxidative palladium(II)-catalyzed arylhalogenation

Reports on palladium(II)-catalyzed arylhalogenation of alkenes are extremely scarce, yet the reported examples reveal the synthetic potential of such alkene functionalizations. One strategy is based on an oxidative intermolecular Heck-type arylation that is intercepted at the stage of the σ-alkylpalladium(II) intermediate by an oxidation–reductive elimination event. Another approach involves C–H bond activation followed by ring closure and substitution of the intermediate σ-alkylpalladium(II) complex.

7.21.5.3.1.1 Intercepted intermolecular Heck-type arylhalogenation

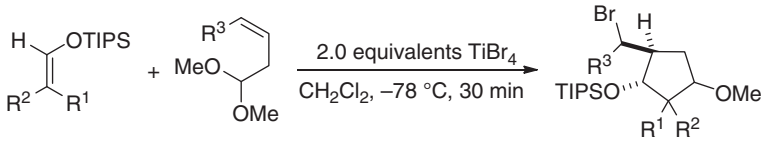
Sanford discovered a remarkable regiodivergent Heck-type arylhalogenation (Scheme 82).[171] The σ-alkylpalladium(II) intermediate of the oxidative Heck-type alkene arylation using stannane **120** is further oxidized with a halogen-containing oxidant to undergo reductive elimination with concomitant carbon–halogen bond formation. The choice of oxidant and solvent (and various other parameters) subtly controls the regiochemical outcome. Conventional 1,2-arylhalogenation is seen with CuX_2 in



1.2 equivalents **110** **111**

trans,cis-**112** *cis,trans*-**112**

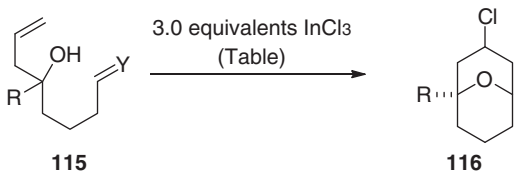
R^1	R^2	R^3	Yield	Ratio *trans,cis:cis,trans*	References
Me	Me	H	86%	63:37	167
$-(CH_2)_5-$		H	92%	79:21	167
H	$-(CH_2)_4-$		20%	–	167
Me	$-(CH_2)_4-$		81%	66:34	167



1.2 equivalents **110** **113** *trans*-**114**

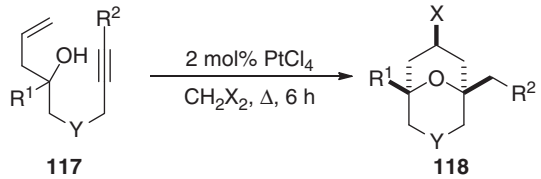
R^1	R^2	R^3	Yield	*dr*	References
Me	Me	Et	90%	>99:<1	168
$-(CH_2)_3-$		Et	86%	>99:<1	168
Me	Me	CH_2OBn	81%	>99:<1	168

Scheme 80



115 **116**

R	Y	*t*	Solvent/*T*	Yield
Me	O	6 h	CH_2Cl_2/0 °C	60%
Me	$(OCH_3)_2$	8 h	$CHCl_3$/r.t.	64%
H	$(OCH_3)_2$	5h	$CHCl_3$/r.t.	52%



117 **118**

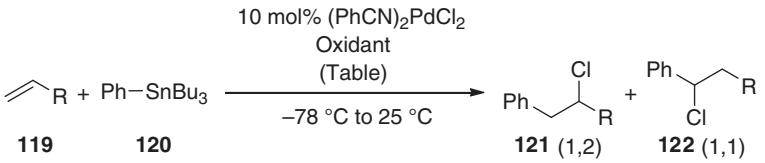
R^1	R^2	X	Y	Yield
Allyl	H	Cl	CH_2	92%
Allyl	H	Br	CH_2	76%
Allyl	H	Cl	O	78%
Et	H	Cl	CH_2	85%
Et	Ph	Cl	CH_2	83%

Scheme 81

Lewis basic THF; unusual 1,1-arylhalogenation is obtained using the same halogen source in less Lewis basic Et_2O. The latter regiochemistry is rationalized by *β*-hydride elimination and subsequent alkene (re)insertion with opposite regioselectivity. Both regioisomers are accessible from the same alkene with equally high selectivities.

7.21.5.3.1.2 Intramolecular arylhalogenation involving C–H bond activation (with an example of aminohalogenation)

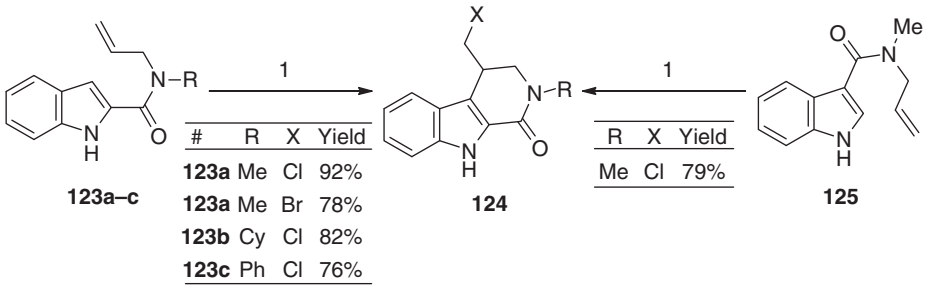
A typical intramolecular indole alkenylation might also be transformed into an arylhalogenation in the presence of CuX_2 as halide source (Scheme 83).[172] Broggini showed that unprotected C-2-substituted indoles cyclize cleanly to annulated indoles **124** with a halomethyl group (Scheme 83, upper left). The same constitutional isomer is formed starting from the corresponding C-3-substituted indole **125** (Scheme 83, upper right). Initial carbon–carbon bond formation at the C-3 carbon atom followed by a



119 **120** **121** (1,2) **122** (1,1)

R	Stannane	Oxidant	Solvent	Yield	Ratio **121**:**122**
$(CH_2)_4Br$	2.60 equivalents $PhSnBu_3$	4.0 equivalents $PhICl_2$	CH_2Cl_2	84%	93:7
$(CH_2)_4Br$	1.30 equivalents $PhSnBu_3$	4.0 equivalents $CuCl_2$	Et_2O	54%	<5:>95
$(CH_2)_4Br$	1.65 equivalents $PhSnBu_3$	4.0 equivalents $CuBr_2$	THF	54%	96:4
$(CH_2)_4Br$	1.30 equivalents $PhSnBu_3$	4.0 equivalents $CuBr_2$	Et_2O	54%	6:94
$(CH_2)_4OTs$	1.93 equivalents $PhSnBu_3$	4.0 equivalents $CuBr_2$	THF	64%	94:6
$(CH_2)_4OTs$	1.30 equivalents $PhSnBu_3$	4.0 equivalents $CuBr_2$	Et_2O	67%	<5:>95
$(CH_2)_4OC(O)Me$	1.90 equivalents $PhSnBu_3$	4.0 equivalents $CuBr_2$	THF	60%	93:7
$(CH_2)_4OC(O)Me$	1.30 equivalents $PhSnBu_3$	4.0 equivalents $CuBr_2$	Et_2O	68%	<5:>95

Scheme 82

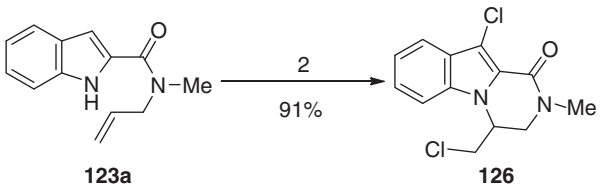


#	R	X	Yield
123a	Me	Cl	92%
123a	Me	Br	78%
123b	Cy	Cl	82%
123c	Ph	Cl	76%

R	X	Yield
Me	Cl	79%

123a–c **124** **125**

1. 5.0 mol% $(MeCN)_2PdCl_2$, 3.0 equivalents CuX_2, THF, Δ, 2 h



123a **126**

2. 5.0 mol% $(MeCN)_2PdCl_2$, 5.0 equivalents $CuCl_2$, 1.0 equivalent K_2CO_3, MeCN, Δ, 2 h

Scheme 83

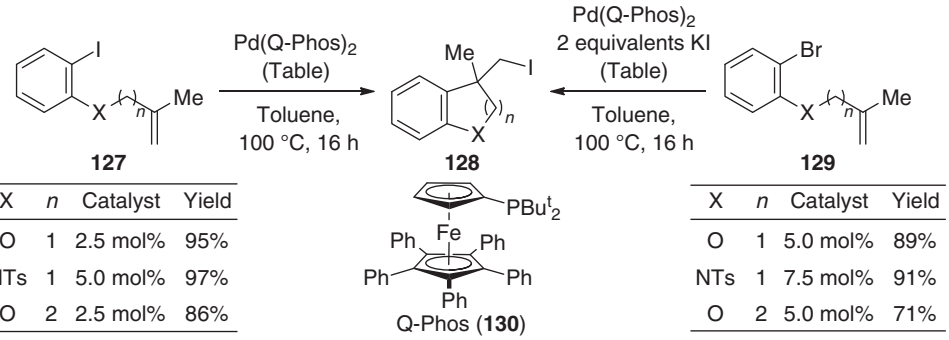
1,2-acyl migration is believed to be the origin of this rearrangement. These authors also reported that the same catalytic setup in basic medium results in aminohalogenation of the alkene with the indole nitrogen atom as nucleophile (Scheme 83, lower).

7.21.5.3.2 Palladium(0)-catalyzed arylhalogenation by intercepted Heck cyclization

Lautens has applied the intramolecular Heck reaction for the construction of all-carbon-substituted quaternary carbon atoms (Scheme 84).[173] By deliberate choice of the phosphine ligand (Q-Phos, **130**), the σ-alkylpalladium(II) intermediate lacking β-hydrogen atoms reductively eliminates to form a carbon–iodine bond (with aryl iodide **127** as cyclization precursor, left). The same transformation might be combined with a bromide-to-iodide exchange, again arriving at an iodomethyl group but now with aryl bromide **129** as the starting material (right).

7.21.5.4 Semipinacol Rearrangements

Pinacol and semipinacol rearrangements are powerful reactions especially suitable for the formation of quaternary carbon centers. Semipinacol rearrangements can be induced on allylic alcohols by the addition of an electrophile to the carbon–carbon double bond. The addition is followed by a (often *anti*-selective) 1,2-migration of a substituent from the allylic position onto the former double bond, yielding a carbonyl compound with the electrophile in the β-position. The use of halogen electrophiles in these



X	n	Catalyst	Yield
O	1	2.5 mol%	95%
NTs	1	5.0 mol%	97%
O	2	2.5 mol%	86%

X	n	Catalyst	Yield
O	1	5.0 mol%	89%
NTs	1	7.5 mol%	91%
O	2	5.0 mol%	71%

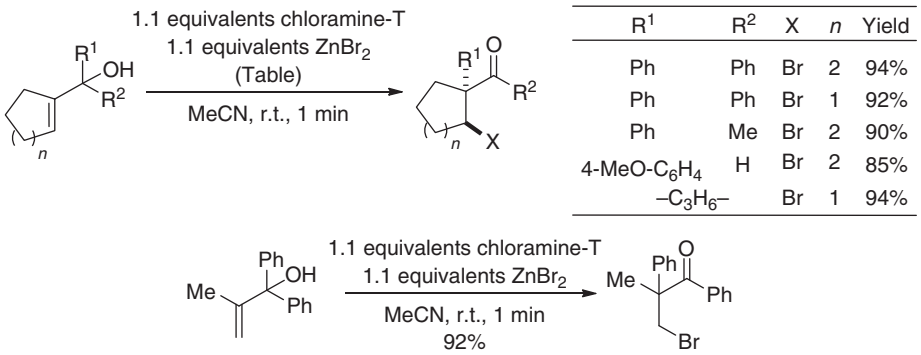
Scheme 84

reactions is very attractive because of their high reactivity compared to other suitable electrophiles (Brønsted acids, transition metals) thereby enabling the use of simple alkenes as substrates. In a formal sense, the use of a halogen electrophile leads to a carbohalogenation of the carbon–carbon double bond, grouping these reactions into this section.

7.21.5.4.1 Diastereoselective semipinacol rearrangements

Semipinacol rearrangements of alkenes can be induced by a range of different halogen electrophiles. A convenient method was reported by Tu, who used chloramine-T in combination with zinc salts to induce semipinacol rearrangements on secondary and tertiary allylic alcohols.[174]

Chloramine-T and zinc bromide induced a bromine-mediated rearrangement on cyclic as well as linear allylic alcohols (Scheme 85). Aryl groups migrated preferentially over alkyl groups, and the products were selectively obtained as *trans*-isomers. Yields were generally high (65–94%) even for secondary allylic alcohols when the product is an aldehyde. If the zinc bromide is replaced by zinc chloride or zinc iodide, the corresponding chlorinated or iodinated products were obtained. In a subsequent publication, Tu showed that the chloramine-T/zinc bromide induced rearrangement proceeds with moderately induced diastereoselectivity (53% yield, *dr* 75:25) if the starting material already contains a stereocenter.[175] In this instance, NBS was clearly the superior reagent and allowed for the formation of the product in high yield with almost complete simple and induced diastereoselectivity (93% yield, *dr* > 99:1). NBS-mediated semipinacol rearrangements have also been applied to other substrates, containing in most cases activated carbon–carbon double bonds such as tosylated enamines.[176]



R^1	R^2	X	n	Yield
Ph	Ph	Br	2	94%
Ph	Ph	Br	1	92%
Ph	Me	Br	2	90%
4-MeO-C_6H_4	H	Br	2	85%
–C_3H_6–		Br	1	94%

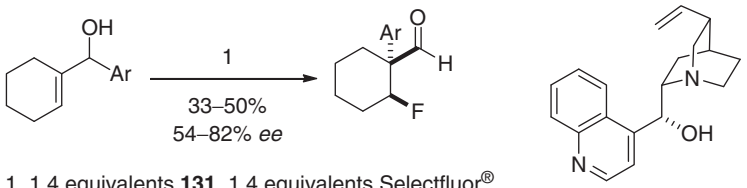
Scheme 85

7.21.5.4.2 Enantioselective semipinacol rearrangements

7.21.5.4.2.1 Fluorine-induced enantioselective semipinacol rearrangements

Compared to the other halogens, fluorine electrophiles have rarely been used in semipinacol rearrangements. Nevertheless, an asymmetric method for fluorine-induced semipinacol rearrangements of secondary allylic alcohols was developed by Tu.[177] Quinine (**131**) and Selectfluor® were combined in a ratio of 1:1 to generate an active chiral fluorinating agent that could be used in stoichiometric quantities to induce semipinacol rearrangements (Scheme 86)

The reaction required extended reaction times (6 days), and the products were isolated only in moderate yields (33–50%), whereas the observed enantioselectivities were moderate to good (54–82% *ee*). Only electron-neutral or electron-rich aryl substituents were reported as migrating groups, but some variation of the alkene moiety was possible, including a cycloheptene and an acyclic alkene derivative.



1. 1.4 equivalents **131**, 1.4 equivalents Selectfluor®, 0.6 equivalent K_2CO_3, MeCN, r.t., 6 days

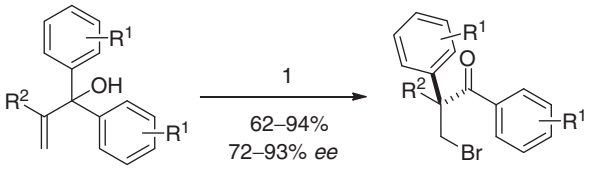
Quinine (**131**)

Scheme 86

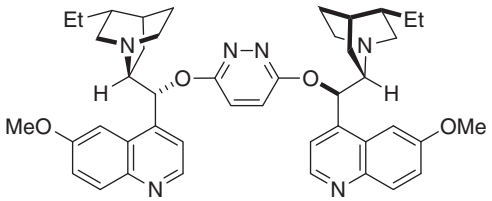
A related protocol was developed by Tu for asymmetric fluorine-induced semipinacol rearrangements of cyclic enol ethers.[178] This method requires only a substoichiometric amount of chiral ligand but is currently not applicable to simple alkenes.

7.21.5.4.2.2 Bromine-induced enantioselective semipinacol rearrangements

Catalytic, asymmetric bromine-induced semipinacol rearrangements of acyclic allylic alcohols were demonstrated by Tu. They showed that the dimeric cinchona alkaloid derivative $(DHQD)_2PYDZ$ (**132**) is a very efficient catalyst for this type of transformation.[179] In combination with NBS as stoichiometric halogen source, the rearrangement of a range of acyclic tertiary allylic alcohols was shown to proceed in good yields (62–94%) and high to very high enantioselectivity (72–93% *ee*, **Scheme 87**).



1. 5 mol% **132**, 1.2 equivalents NBS, 3.0 equivalents MeOH, 5 mol% 3,4-(OMe)PhCOOH, CCl_4, 50 °C



$(DHQ)_2PYDZ$ (**132**)

Scheme 87

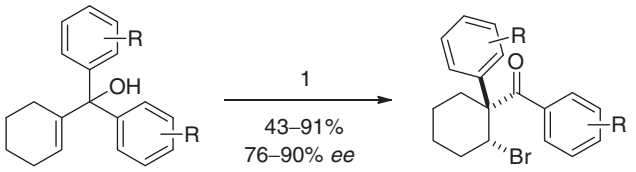
The products were selectively formed by an *anti*-addition of the halogen and the aromatic ring across the double bond and contained a quaternary carbon stereocenter. Substitution of the alkene with different alkyl groups (R^2 = alkyl) was tolerated, whereas the migrating group had to be an aryl ring. To obtain high enantioselectivities, the addition of additives (MeOH and a benzoic acid derivative) of unknown function was required.

A complementary method for cyclic alkenes was reported by Hennecke. For this type of starting materials, the use of $(DHQD)_2PYR$ (**133**) as catalyst was preferable. In combination with *N*-bromoacetamide (**134**) and a small amount of base (sodium carbonate), bromine-induced semipinacol rearrangements on cyclohexene derivatives could be conducted in good yields (44–91%) and with high enantioselectivities (76–90% *ee*, **Scheme 88**).[180] Again, the migrating group had to be an aryl ring and specific *anti*-addition was observed. Other cyclic alkenes such as cyclopentene derivatives reacted more slowly than cyclohexenes and were rearranged only in lower yield (43–52%) and enantioselectivity (37–40% *ee*).

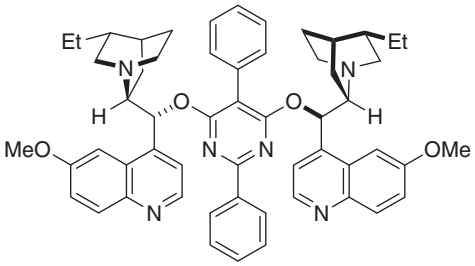
A related method for enantioselective bromine-induced semipinacol rearrangements of cyclic enol ethers is known as well.[181] However, the exact reaction conditions differ from the preferred conditions for unactivated alkenes and do not allow for the rearrangement of the latter with high enantioselectivities.

7.21.5.5 Intramolecular Carbohalogenations Using Electrophilic Halogenating Agents

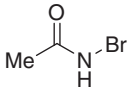
Compared to oxyhalogenation and aminohalogenation, electrophilic carbohalogenation usually proceeds much less readily due to the much weaker nucleophilicity of most carbon nucleophiles. This means that in many cases more reactive halogen electrophiles are required, and inducing this type of reactions with the weaker fluorine electrophiles is especially problematic.[182]



1. 5 mol% **133**, 1.2 equivalents **134**, 10 mol% Na_2CO_3, $CHCl_3$:toluene (1:1), –20 or 0 °C



(DHQD)$_2$PYR (**133**)



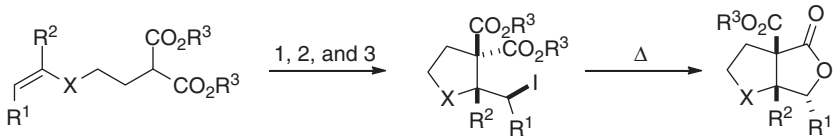
134

Scheme 88

Still, there is a range of methods available for carbohalogenation with the heavier halogens chlorine, bromine, and iodine, which will be presented according to the type of carbon nucleophile employed.

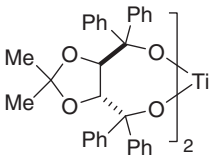
7.21.5.5.1 Carbohalogenation with malonate nucleophiles

Taguchi reported iodocarbocyclizations of pent-4-enyl-substituted malonic acid esters **135**.[183] Under the initially described conditions, 1.0 equivalent of Ti(OBu^t)$_4$ was used to activate the malonic acid ester moiety and 1.5 equivalents of iodine were used to induce the iodocyclization. The 5-*exo* cyclizations led to diastereoselective formation of iodomethyl-substituted cyclopentenes **136** (74–89% yield, Scheme 89). Depending on the reaction conditions or on heating, subsequent cyclization to bicyclic ester **137** was observed.



135 **136** **137**

R^1	R^2	R^3	X	Conditions	Yield	*ee*	References
H	H	Me	CH_2	1	74% **136**	–	183a
H	Me	Me	CH_2	1	89% **136**	–	183a
Me	H	Me	CH_2	1	86% **137**	–	183a
H	H	Me	CH_2	2	86% **137**	92%	184b
H	H	Bn	CH_2	2	86% **137**	94%	184b
H	H	Me	O	2	77% **137**	78%	184b
H	H	Bn	CMe_2	2	96% **137**	70%	184b
Me	H	Bn	CH_2	3	71% **137**	97%	184c



138

1. 1.0 equivalent Ti(OBu^t)$_4$, 1.5 equivalents I_2, CH_2Cl_2, r.t.; 2. 20 mol% **138**, 4.0 equivalents I_2, 2.0 equivalents 2,6-(OMe)$_2$Py, CH_2Cl_2, –78 °C to –35 °C; 3. 40 mol% **138**, 4.0 equivalents I_2, 2.0 equivalents 2,6-(OMe)$_2$Py, CH_2Cl_2:THF (4:1), –78 °C

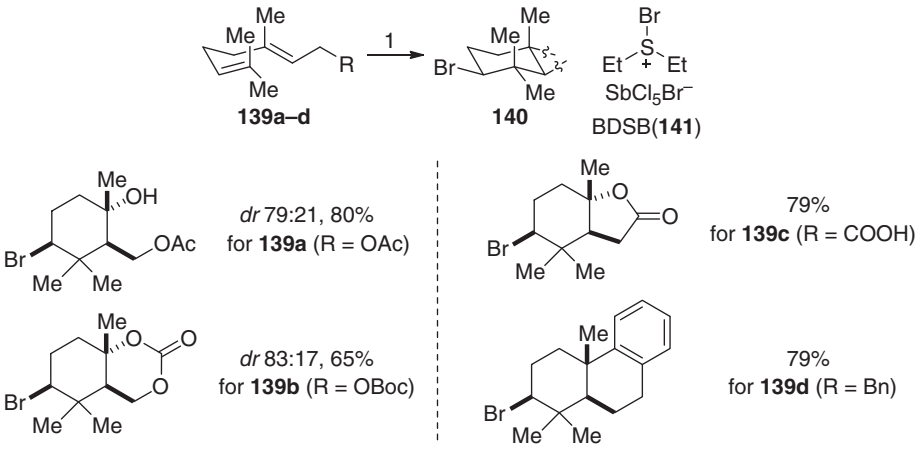
Scheme 89

Taguchi later showed that this method is also applicable to cyclizations of allyl-substituted malonic acid esters to give cyclopropanes.[183b] If the pent-4-enyl-substituted malonic acid esters already contained a stereocenter, reactions became diastereoselective with $dr \geq 99{:}1$.[183c] More importantly, reagent-controlled asymmetric iodocarbocyclizations were possible using

catalytic amounts of a chiral titanium Lewis acid. Titanium bis(TADDOLate) (**138**) proved to be a suitable catalyst for asymmetric iodocyclizations.[184] In the presence of a base such as 2,6-dimethoxypyridine, 20 mol% of this catalyst was sufficient to make the reactions enantioselective, and the bicyclic lactones **137** could be obtained in good yields (71–96%) and with enantioselectivities between 70% and 97% *ee*.

7.21.5.5.2 Halogen-induced polyene cyclizations

Halogen-induced polyene-type cyclizations require the use of very reactive halogenating agents. Standard electrophilic halogen sources such as *N*-haloimides are too unreactive, and only low yields of cyclization products are obtained. A highly reactive electrophilic brominating agent for this type of reactions was introduced by Snyder in the form of bromodiethylsulfonium bromopentachloroantimonate (BDSB, **141**).[185] This reagent is easily prepared from diethyl sulfide, bromine, and SbF_5 in a one-pot procedure.[185b] Cyclizations of dienes such as **139** were best conducted with 1.0 to 1.2 equivalents of **141** in nitromethane (Scheme 90). The bromocyclization products could be generally isolated in 56–80% yield. In many cases, the cyclization products were obtained as single diastereomers, and only in a few cases significant amounts of other diastereomers were formed.

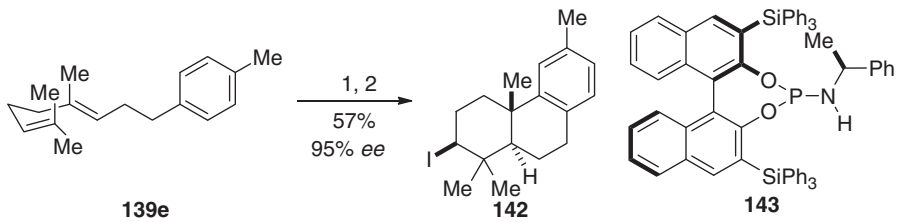


1. 1.0–1.2 equivalents **141**, CH_3NO_2, between –25 °C and r.t.

Scheme 90

Snyder also prepared related haloalkylsulfonium salts of chlorine and iodine and applied these salts in chlorine- and iodine-induced polyene cyclizations.[185c] The yields in chlorine-induced cyclizations were rather low; however, iodine-induced cyclization proceeded with yields comparable to bromine-induced cyclizations.

Enantioselective iodine-induced polyene cyclizations were reported by Ishihara.[186] These authors used a bulky BINOL-derived phosphoramidite as a stoichiometric promoter for such iodocarbocyclizations (Scheme 91). In combination with NIS as an electrophilic halogen source, diene **139e** could be cyclized at low temperature in toluene to the tricyclic product **142** with 95% *ee*. However, the low reactivity of the NIS was problematic, and a second acid-catalyzed cyclization step had to be introduced to achieve full conversion to the tricycle. NIS and the promoter **143** alone were not able to convert the whole material to the tricycle, and the bicyclic intermediate was isolated as well. Under the optimized two-step conditions, **142** was isolated in 57% yield and with 95% *ee*. High enantioselectivities above 90% *ee* were also observed in three more iodocarbocyclizations of a related diene, a triene, and a tetraene. However, the catalytic application of phosphoramidite **143** or bromine-induced cyclizations using NBS proceeded with only very low enantioselectivities.



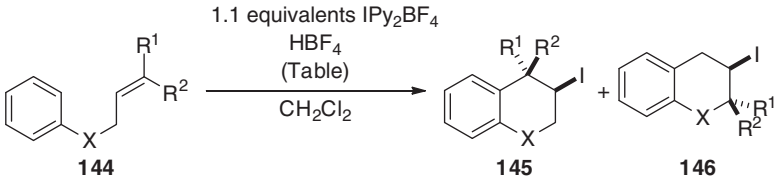
1. 1.0 equivalent **143**, 1.1 equivalents NIS, toluene, –40 °C, 24 h; 2. $ClSO_3H$, Pr^iNO_2, –78 °C, 4 h

Scheme 91

An alternative protocol for such polyene cyclizations was reported by Snyder.[187] These authors utilized a mercury-induced cyclization of dienes to form the bicyclic or tricyclic products in good yields and with moderate to good enantioselectivities. In a second step, the mercury complex could then be replaced by chlorine, bromine, or iodine. However, the requirement of stoichiometric amounts of highly toxic mercury salts and stoichiometric amounts of a chiral ligand does not make this protocol attractive for further use.

7.21.5.5.3 Electrophilic intramolecular arylhalogenation

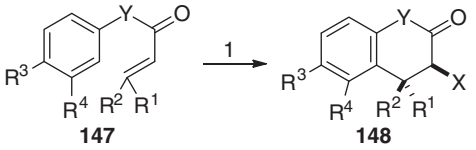
An alternative to palladium-catalyzed aryl halogenations of alkenes are arylhalogenations induced by electrophilic halogen species. Barluenga used IPy_2BF_4 as an iodonium ion source to mediate the intramolecular aryliodination of alkenes (Scheme 92).[188] The reaction generally proceeded via a 6-*endo* cyclization to give the iodoarylation products in good to very good yields. However, this reaction is unique in the sense that the reaction temperature (− 40 °C vs. − 90 °C) governs the formation of constitutional isomers **145** (expected) and **146** (unexpected) from the common precursor **144**. The authors proposed a reasonable mechanism for the unusual skeletal reorganization that is likely to proceed through a four-membered ring formed by ring opening of the iodonium ion by the heteroatom tether.



R^1	R^2	X	HBF_4	*t*	*T*	Yield (**145**)	Yield (**146**)
Me	H	O	1.0 equivalent	30 h	–40 °C	92%	–
Ph	H	O	1.5 equivalents	3 h	–40 °C	95%	–
Ph	H	O	1.5 equivalents	12 h	–90 °C	–	95%
Me	Me	O	3.0 equivalents	6 h	–90 °C	–	85%
Me	H	NMs	3.0 equivalents	15 h	–80 °C	80%	–

Scheme 92

Hajra reported related 6-*endo* haloarylations of alkenes using the simple *N*-haloimides NBS and NIS as halogenating agents.[189] A catalytic amount of the Lewis acid samarium triflate promoted even aryl halogenations of electron-deficient α,β-unsaturated alkenes at room temperature (Scheme 93). NBS and NIS reacted equally well and the products were formed in good yields. The substrate scope was rather broad and not only electron-deficient but also simple alkenes carrying an aryl or alkyl substituent could be cyclized to the *anti*-addition products.

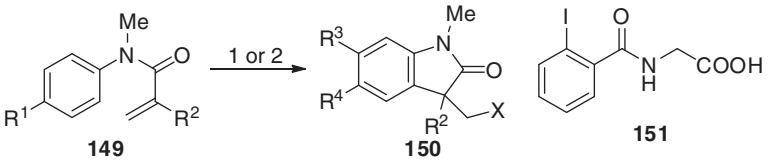


R^1	R^2	R^3	R^4	Y	X	Reagent	*t*	Yield
H	H	Ph	H	O	Br	NBS	4 h	94%
H	H	Ph	H	O	I	NIS	3 h	67%
H	H	Ph	H	NTs	Br	NBS	3 h	67%
H	H	Ph	H	NMs	Br	NBS	10 h	63%
Ph	H	$-C_4H_4-$		O	Br	NIS	3 h	66%
Me	Me	H	H	O	I	NIS	6 h	55%

1. 10 mol% $Sm(OTf)_3$, 1.1 equivalents reagent, MeCN, r.t.

Scheme 93

5-*exo* Aryl halogenations are also possible. If electron-deficient α,β-unsaturated alkenes **149** similar to **147** are treated with hypervalent iodine reagents and a suitable halogen source, the aryl halogenation proceeds via a 5-*exo* and not a 6-*endo* cyclization (Scheme 94).[190] Aryl iodinations were conducted using elemental iodine as halogen source and $PhI(OAc)_2$ as oxidant in acetonitrile. This procedure delivered the 5-*exo* cyclization products in 47–98% yield.[190a] Aryl brominations can be conducted under related conditions with NBS as bromine source and oxidant in combination with catalytic amounts of aryliodide **151** and ammonium chloride as demonstrated by Gulder.[190b] The yields (51–95%) under these conditions are comparable to those of the iodination.



149 **150** **151**

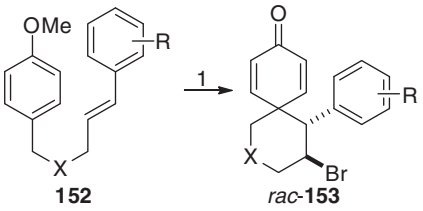
R^1	R^2	R^3	R^4	X	Conditions	Yield	References
I	Me	H	I	I	1	96%	190a
OMe	Me	H:I (82:18)	OMe	I	1	68%	190a
H	Ph	H	I	I	1	81%	190a
OMe	Me	Br	OMe	Br	2	94%	190b
I	Me	H	I	Br	2	66%	190b
H	Ph	H	Br	Br	2	95%	190b

1. 1.5 equivalents I_2, 1.5 equivalents $PhI(OAc)_2$, MeCN, r.t.; 2.10 mol% Aryliodide **151**, 10 mol% NH_4Cl, 2.4 equivalents NBS, CH_2Cl_2, r.t.

Scheme 94

However, both hypervalent iodine-promoted aryl halogenations suffer from rather low chemoselectivity. If the aryl group is electron neutral or electron rich, the aryl ring is also halogenated under the reaction conditions.

An interesting variation of this aryl halogenation was reported by You. These authors connected the alkene via a short tether to the *para*-position of an electron-rich anisyl ring. If this alkene was treated with the rather reactive halogenating agent 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, **17**), a bromoarylation of the alkene **152** via the 4-position of the anisyl ring occurred. However, in this case, no rearomatization of the aromatic ring was possible and the anisylmethyl group was cleaved instead, leading to the dearomatization of the aromatic ring (Scheme 95).[191]



152 *rac*-**153**

1. 1.0 equivalent **17**, 0.05 mL H_2O, CH_3CN, –20 °C

R	Z	Yield
2-Me	NTs	84%
4-Me	NTs	93%
4-MeO	NTs	68%
4-Cl	NTs	91%
4-Br	NTs	92%
3-NO_2	NTs	90%
H	NTs	91%
H	NNs	93%
H	O	89%

Scheme 95

This method proved to be quite general for (*E*)-configured alkenes carrying an aromatic substituent, and the corresponding products were isolated in 68–93% yield. Interestingly, (*Z*)-configured alkenes or alkenes without aromatic substituents did not undergo this reaction. The substrate scope is therefore somehow narrow, but this transformation nevertheless allows the simple construction of useful spirocyclic scaffolds.

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7.22 Oxidation of Carbon–Boron Bonds

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Glossary

1,2-Migration The migration of an s-bond to the neighbouring atom with expulsion of a leaving group.

Ate-complex A Tetrahedral boron with an overall negative charge.

Radical clock The existence of radical intermediates can be demonstrated by incorporation of a cyclopropane adjacent to the radical. Such radicals undergo fast ring opening of the strained cyclopropane to give the isomeric homoallylic radical. Thus, ring opened cyclopropanes provide evidence for radical intermediates.

Stereoselectivity The preferential formation of one stereoisomer over another during a reaction.

Stereospecificity The property of a reaction mechanism that converts stereoisomeric starting materials to stereoisomeric products.

7.22.1 Introduction

Organoboron compounds are versatile intermediates and as such are some of the most important classes of reagents in modern organic chemistry. This stems from their ease of preparation combined with their ability to undergo a broad range of chemical transformations.

Apart from C–C bond formation, the main transformation of organoboron compounds is oxidation. Indeed, some boranes are spontaneously flammable in air and thus have to be handled with caution. Nevertheless, oxidation offers a powerful platform with which new functional groups can be selectively introduced in a molecule.

Tricoordinate organoborons are Lewis acids because the B atom has an empty p orbital. Lewis bases can easily interact with this orbital, leading to (frequently stable) 'boron–ate' complexes. This peculiar electronic distribution around the B atom, combined with the relatively low thermodynamic stability of the B–C bond, makes its replacement by a more electronegative atom (overall an oxidative process) both kinetically and thermodynamically favored (Table 1).[1]

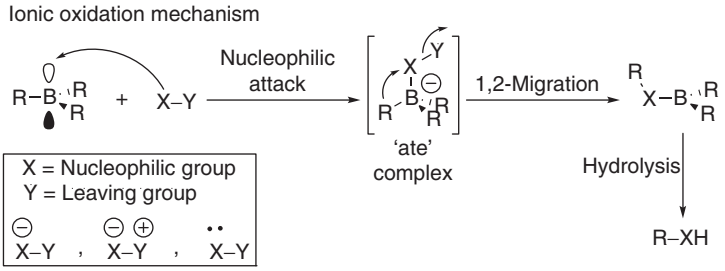
Table 1 B–X Bond dissociation energies

Bond	*ΔH (KJ mol^{-1})*	*Bond*	*ΔH (KJ mol^{-1})*
B–C	350.9	B–Cl	442.3
B–N	438.9	B–Br	366.6
B–O	519.2	B–I	269.7
B–F	644.6	B–S	357.4

 doi:10.1016/B978-0-08-097742-3.00726-6

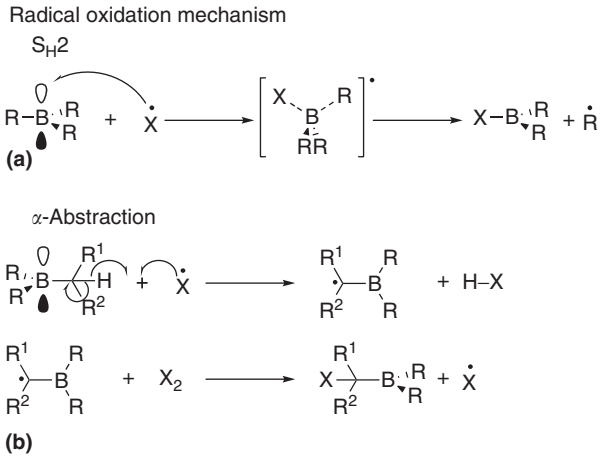
Oxidation of C–B bonds can be effectively promoted by a broad array of reagents and several mechanisms might be operative. In general there are three main mechanisms by which oxidation proceeds: (1) ionic, (2) radical, and (3) pericyclic.

The ionic mechanism involves the interaction of an organoboron with a bifunctionalized molecule containing a nucleophilic site (Lewis base) directly linked to a leaving group. The overall process consists of initial attack of the nucleophile into the empty p orbital generating a 'boron–ate' complex, followed by a 1,2-migration process and final hydrolysis of the B–X bond (Scheme 1). This pathway resembles the classical Wagner–Meerwein rearrangements and it is usually accompanied by stereoretention at the migrating center. However, due to the fact that a certain degree of negative charge is generated in the transition state that accompanies the reaction, the order of migratory aptitude primary > secondary > tertiary is frequently, but not exclusively, observed.



Scheme 1

There are two radical oxidation pathways of organoborons: (1) bimolecular homolytic substitution (S_H2) and (2) α-abstraction (Scheme 2). In both cases a chain process takes place and the stereochemistry of the oxidative product is generally lost. S_H2 reactions are particularly frequent during the handling of sensitive organoborons and traces of oxygen or UV light might be sufficient to initiate them.



Scheme 2

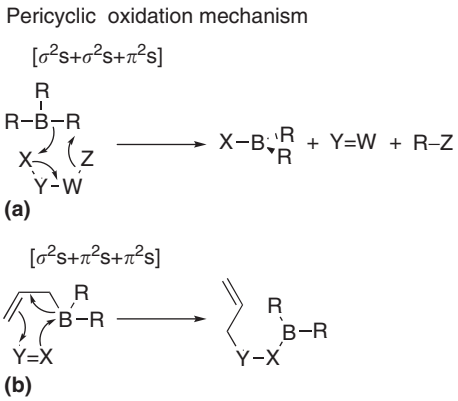
Pericyclic mechanisms can also be involved in the oxidation of organoboron compounds. In this case two general reaction pathways, both involving a 6-electron cyclic transition state, might be involved. In the first case the σC–B bond reacts as 2-electron partner in a [4 + 2]-like cycloaddition process (Scheme 3(a)). The second reaction manifold can be operative if a β–γ double bond is present on one of the B substituents. In this case the two electrons of the πC–C bond and the two electrons of the σC–B bond constitute the 4-electron component of the pericyclic system (Scheme 3(b)).

In this chapter the authors aim is to provide a critical discussion of oxidative processes where a general B–C bond is transformed into a B–X bond. Only transformation where X is a group bonded to the B through an atom more electronegative than carbon will be presented (X=O, N, halogen, S, Se, and P). Due to the presence of more comprehensive reviews on the oxidation of organoborons,[2] only synthetically useful methods and sophisticated examples that illustrate functional group compatibility will be discussed. The merits of each will be discussed where applicable.

7.22.2 Replacement of Boron by Oxygen

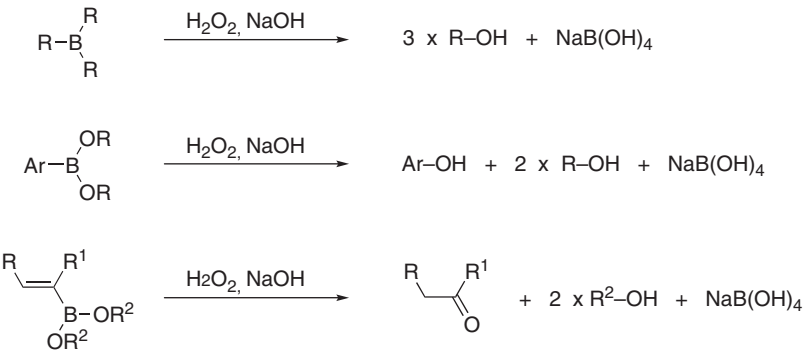
7.22.2.1 Oxidation with Alkaline Hydrogen Peroxide

Basic hydrogen peroxide is one of the oldest and most widely used reagents to perform the oxidation of organoboranes under mild conditions.[3,4] Since the reaction releases the organyl residues with retention of configuration, it has been particularly useful



Scheme 3

in the synthesis of enantioenriched alcohols. The oxidation of aryl or vinyl organoborons results in the formation of phenols and carbonyl-containing compounds, respectively (Scheme 4). Although a convenient reagent to use, particular care needs to be taken in order to avoid the explosive hazards associated with the use of hydrogen peroxide at high pH.[5]

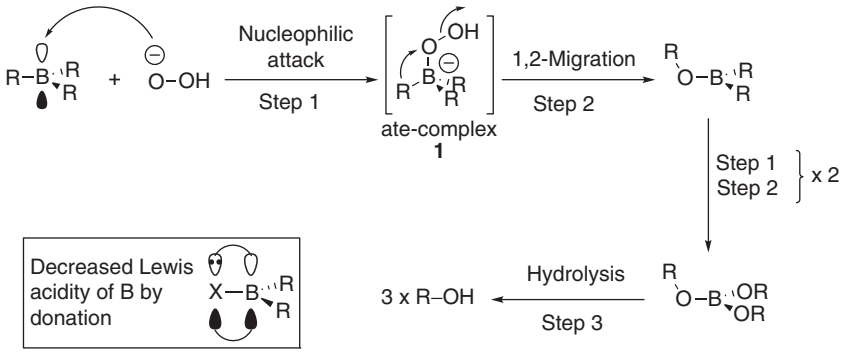


Scheme 4

The reaction mechanism consists of three steps (Scheme 5):

1. Initial nucleophilic attack of the *in situ* generated hydroperoxide anion onto the electron-deficient B atom, giving 'ate' complex **1**.[6,7]
2. Intramolecular 1,2-migration of one of the boron organyl substituents to the adjacent oxygen, and concomitant elimination of a hydroxide anion.
3. Hydrolysis of the B–O bond to deliver the desired oxidative product.

The order of reactivity $R_3B > R_2BX > RBX_2$ (R = aryl, alkenyl, and alkyl; X = OR, OH, and halogen) corresponds to the decreasing Lewis acidity of the B atom due to partial donation of the X lone pairs into the vacant p orbital of the B atom (Scheme 5).

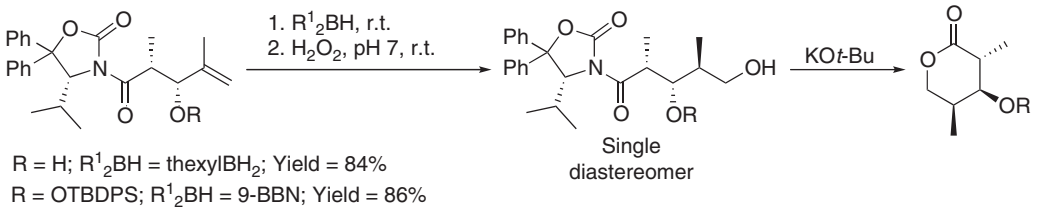


Scheme 5

One useful aspect of this method is the ability to tune the reaction conditions (in terms of base and H_2O_2 concentration) in order to maximize functional group tolerance, resulting in a broad functional group compatibility. Groups such as acetals, aldehydes, alkenes, alkynes, carboxylic acids, ethers, halogens, ketones, nitriles, silyls, and sulfonyls can all be present without requiring additional protection.

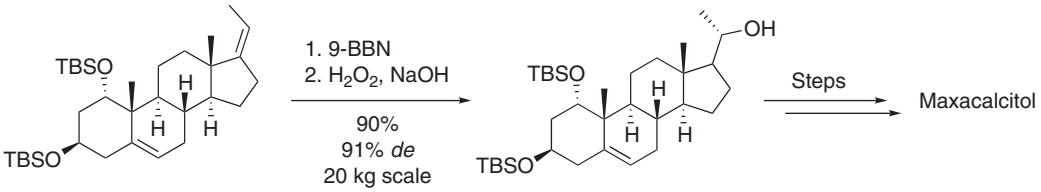
Since a number of methods have been developed that allow the preparation of organoboranes with exquisite levels of regio-, chemo-, and stereoselectivity, this oxidation procedure offers the potential for selective introduction of hydroxyl groups at specific positions of densely functionalized molecules. Although hydroboration is still one of the most commonly used methods to synthesize organoboranes, other protocols have also been developed: nucleophilic addition of organometallic reagents (mostly organolithiums and organomagnesiums) to boranes or boronic esters, addition of B nucleophiles to activated systems, and Pd-catalyzed cross couplings (Miyaura-type reactions). These methods are particularly useful for the preparation of organoborons that are challenging to construct by hydroboration, including many tertiary-, allyl-, vinyl-, and arylboranes/boronic esters. Selected examples will be briefly discussed.

The substrate-controlled hydroboration–oxidation of chiral allylic alcohols has been studied by Wagner during the synthesis of the polyketide discodermolide. A diastereoselective hydroboration of various differentially protected fragments was developed, in which the nature of the borylating agent proved critical in order to obtain high levels of selectivity. For example, hydroboration–oxidation of the *tert*-butyldiphenylsilyl-protected allylic alcohol required the use of 9-BBN borane, while the corresponding free alcohol underwent hydroboration most efficiently with thexylborane (Scheme 6).[8] After oxidation under neutral conditions, the strong chelation of the resulting boric acid with the newly formed 1,3-diol caused problems in the purification step. Treatment of the crude mixture with aqueous NaOH at pH > 11 followed by recrystallization solved this problem.[8]



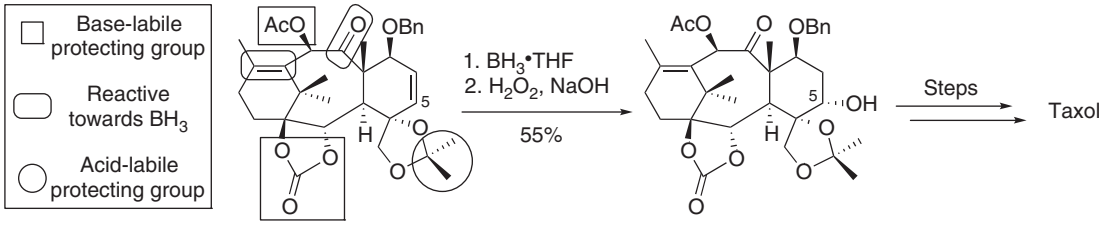
Scheme 6

Oxidation of organoborons with hydrogen peroxide has also been undertaken on a large scale. In the industrial synthesis of maxacalcitol, Shimizu described the regio- and stereoselective hydroboration–oxidation of a challenging steroidal intermediate (Scheme 7).[9] Under carefully optimized reaction conditions, the exocyclic olefin was selectively hydroborated. Further crystallization of the alcohol led to diastereomerically pure product.[9]



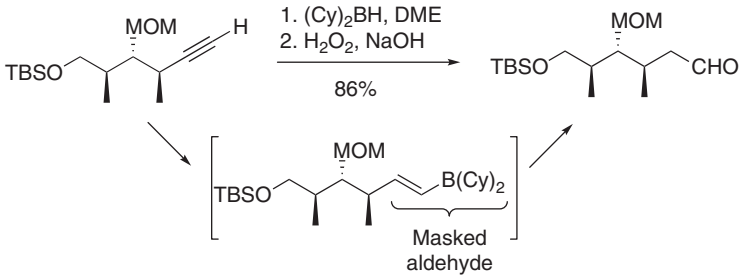
Scheme 7

Perhaps one of the most impressive examples of selectivity and functional group tolerance of hydrogen peroxide oxidation was demonstrated in the total synthesis of taxol in which Nicolaou reported a hydroboration–oxidation sequence to introduce the alcohol at C5 (Scheme 8).[10] The hydroboration took place chemo-, regio-, and stereoselectively on the disubstituted olefin over the ketone and the tetrasubstituted alkene. Oxidation with basic hydrogen peroxide gave the desired alcohol without affecting any of the other functional groups.[10]



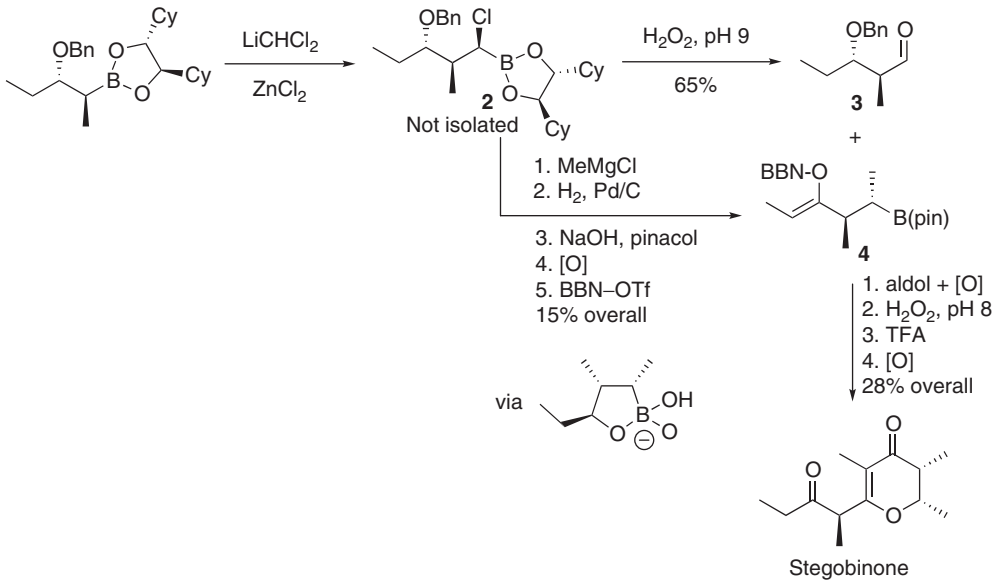
Scheme 8

In addition to alcohol synthesis, the oxidation of alkenylborons with basic hydrogen peroxide represents a convenient method to access carbonyl compounds. Based on this reactivity, a terminal alkyne can be carried through a synthetic sequence as a masked aldehyde. However, hydroboration–oxidation sequences of this particular class of compounds have to be performed under carefully optimized reaction conditions in order to minimize exposure of the newly formed aldehyde to borohydride-type species (e.g., $R_2B(H)OH^-$) that can be formed under basic conditions. Marshall found the use of freshly prepared dicyclohexylborane in dimethoxyethane (DME) ideal for the conversion of a functionalized terminal alkyne to aldehydes during the synthesis of bafilomycin V_1 (Scheme 9).[11,12]



Scheme 9

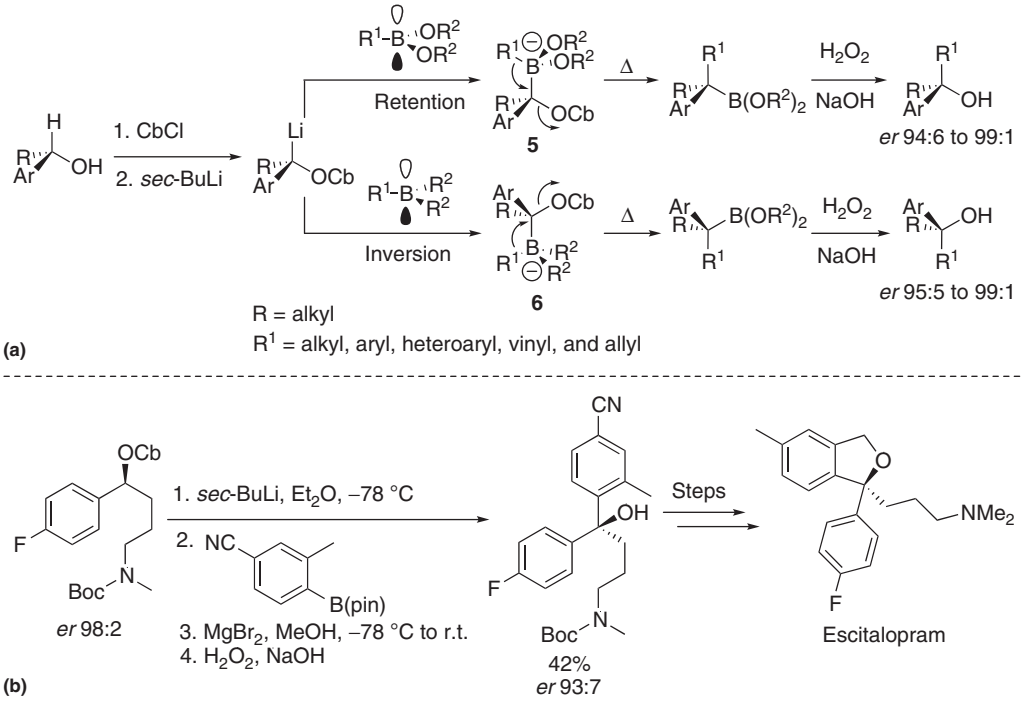
Another application of the oxidation of B–C bonds with basic hydrogen peroxide is found in the work of Matteson.[13] His asymmetric total synthesis of (2*S*,3*R*,1′*R*)-stegobinone makes extensive use of the manipulation and oxidation of organoborons. Taking advantage of the chiral director at B (*R*,*R*)-1,2-dicyclohexylethane-1,2-diol, all the stereogenic centers were selectively introduced by nucleophilic addition, followed by 1,2-migration of the resulting chiral α-chloroalkyl boronic esters. On arrival at the common intermediate **2**, basic oxidation afforded the enantiopure aldehyde **3**, while a five-step sequence gave the desired chiral boron-enolate **4** ready for aldol condensation. Following C–B bond oxidation under carefully adjusted basic conditions, cyclization and oxidation resulted in a highly enantioselective and convergent synthesis to the title natural product (Scheme 10).[13]



Scheme 10

Although a wide range of methods are available for the synthesis of primary and secondary chiral alcohols, only a limited number of protocols can be extended to the preparation of the more challenging chiral tertiary alcohols.[14–19] Aggarwal has developed a method to assemble tertiary alcohols efficiently with high levels of enantioselectivity. Starting from carbamoyl protected enantioenriched chiral secondary alcohols, deprotonation affords configurationally stable α-oxygen organolithium derivatives that were successfully quenched with a broad range of boronic esters and boranes to form boron–ate complexes **5** and **6**. On warming the ate-complex to room temperature, a 1,2-migration process with concomitant elimination of CbO^- afforded the tertiary boronic esters and boranes with no erosion of enantiopurity. Oxidative work-up resulted in the formation of the

highly enantioenriched tertiary alcohols in high yields (Scheme 11(a)).[20] One of the most intriguing aspects of this chemistry is the different stereochemical outcome of boranes versus boronic esters. Due to a possible precomplexation to the lithium cation of the lithiated carbamate, boronic esters react with essentially complete retention of configuration whereas boranes undergo complete invertive addition. This means that either enantiomer of the tertiary alcohol can be obtained from the same enantiomer of the secondary alcohol depending on the boron electrophile used.[20] This method was applied in the synthesis of escitalopram (Scheme 11(b)).[21]



Scheme 11

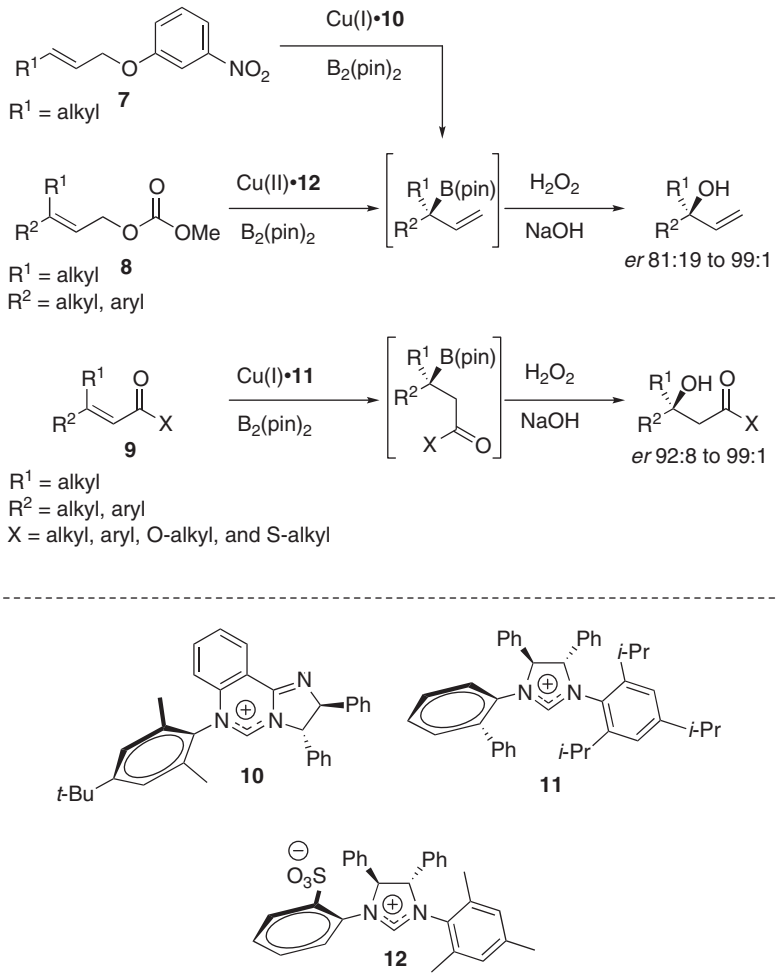
In the field of metal-catalyzed asymmetric borylations, the groups of Hoveyda and McQuade have recently developed a powerful approach for the preparation of highly enantioenriched secondary and tertiary boronic esters.[22–24] Both mono- and α,α-disubstituted allylboronic esters and β-boron substituted carbonyls can be obtained by nucleophilic addition of $B_2(pin)_2$ to allylic aryl ethers or carbonate esters **7** and **8** or (thio)esters/ketones **9**, respectively, in the presence of C_1-symmetric Cu(I)–*N*-heterocyclic carbene (NHC) complex or Cu(II)–NHC complex. Oxidative workup delivers the secondary or tertiary allylic alcohols and the β-hydroxy ketones/(thio)esters in good yields and with very high levels of enantioselectivity (Scheme 12).

Morken reported the enantioselective diborylation–oxidation sequence of terminal alkenes to the corresponding 1,2-diols (Scheme 13(a)).[25] Subsequent investigations by the same authors expanded the scope of this method to include prochiral allenes. After an initial enantioselective Rh-catalyzed diboration, the chemically distinct properties of the vinylic and allylic boronic esters of the intermediate **13** were exploited. Stereoselective allylation with an aldehyde followed by oxidation with basic hydrogen peroxide of the remaining vinyl boronic ester delivered the homologated β-hydroxy ketone in good yields and high levels of enantioselectivity (Scheme 13(b)).[26,27]

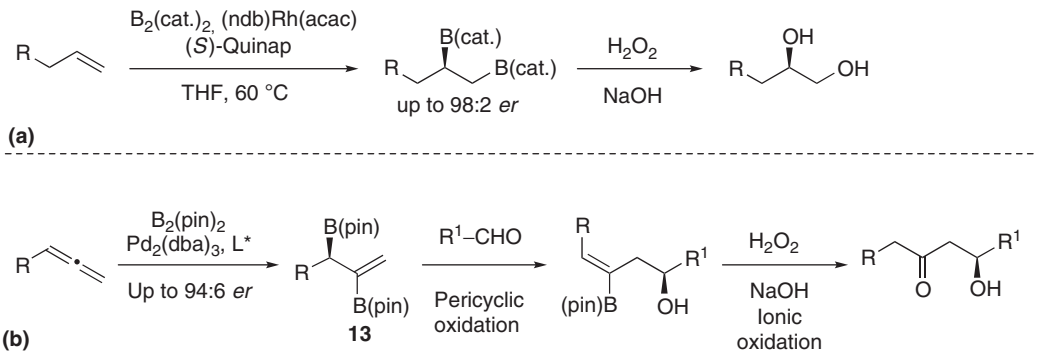
7.22.2.2 Oxidation with Sodium Perborate (SPB)

Introduced by McKillop, sodium perborate ($NaBO_3$) is a mild, inexpensive, and air-stable oxidizing agent.[28] Due to its high affinity for water it is usually found in its dimeric monohydrated form, $[NaBO_3 \cdot H_2O]_2$, which is more accurately represented as the disodium salt of the 1,4-diboratetroxane dianion (Scheme 14). SPB selectively oxidizes C–B bonds to C–O bonds, thus avoiding problems of overoxidation (see Scheme 16).[29,30] Alkyl-, aryl-, and vinylboranes are efficiently oxidized to alcohols, phenols, and carbonyl compounds, respectively. The oxidation process is proposed to occur by a mechanism similar to that of basic H_2O_2 (Scheme 14). Nucleophilic addition of a peroxyborate species onto the electron-deficient B atom and subsequent 1,2-migration of the R group from B to O with concomitant extrusion of boric acid gives intermediate **14**, hydrolysis of which generates the desired alcohol (Scheme 14).[29]

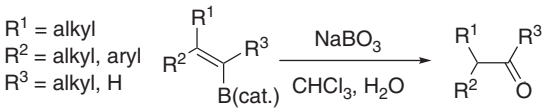
The use of SPB for the oxidation of C–B bonds is particularly effective for the conversion of alkenylborons to aldehydes or ketones. Under these mild reaction conditions, unwanted reactions such as C–C bond cleavage and aldehyde–H_2O_2 adduct formation can be significantly minimized (equation 1).[28]



Scheme 12

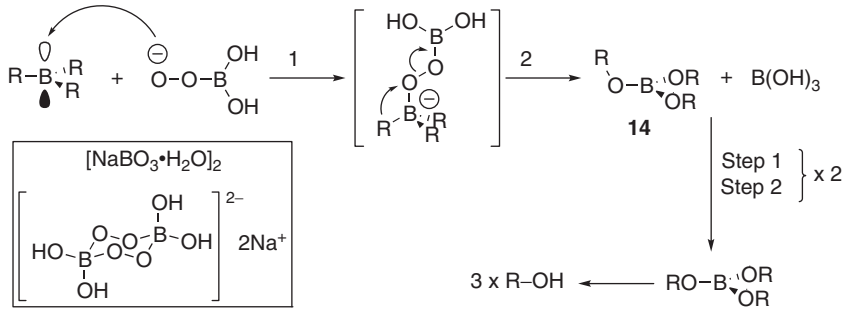


Scheme 13



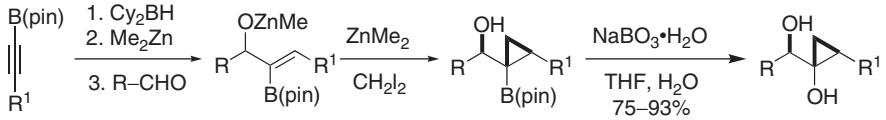
(1)

The use of SPB for the oxidation of diastereomerically pure cyclopropyl boronic esters was reported by Walsh (Scheme 15).[31] The use of SPB as oxidant gave the corresponding alcohols in good yield. In contrast, application of traditional oxidation methods



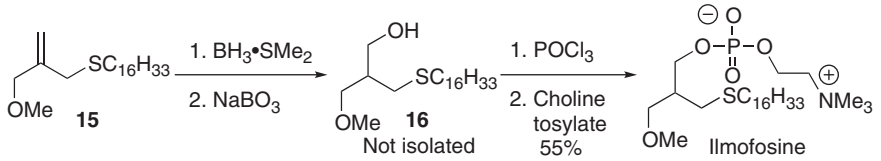
Scheme 14

onto these compounds, including H_2O_2/NaOH and Et_3NO, resulted in poor conversions and substantial amounts of unwanted C–C cleaved products.[31,32]



Scheme 15

The high functional group compatibility of SPB is highlighted in the synthesis of limofosine, a potent antineoplastic ether-linked phosphocholine derivative.[33] Borylation of the thio-functionalized terminal olefin **15** gave an organoboron, which was oxidized with SPB to the intermediate alcohol **16**. SPB selectively oxidized the borane despite the presence of a thioether functional group, which is also sensitive to oxidation (Scheme 16).[33]

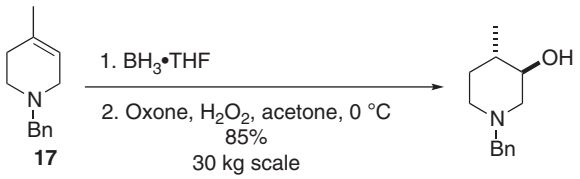


Scheme 16

7.22.2.3 Oxidation with Oxone

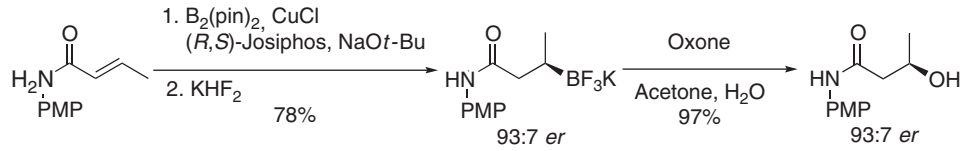
Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) represents a valuable reagent for the rapid oxidation of C–B bonds to C–O bonds. The reactions are usually conducted at low temperatures in the presence of a basic buffer and are characterized by extremely short reaction times. Alkyl- and arylboranes and boronic esters are efficiently oxidized to alcohols with retention of configuration.[34,35] The evidence that decreased yields are obtained when acetone is not used as solvent seems to suggest that dimethyl dioxirane is the active oxidizing agent.[36]

In an industrial synthesis of *cis*-*N*-benzyl-3-methylamino-4-methylpiperidine, problems were encountered during the oxidation of the intermediate borane resulting from hydroboration of dihydropiperidine **17** (equation 2).[37] The use of basic hydrogen peroxide led to a complex mixture of products, whereas the use of substoichiometric amounts of Oxone in the presence of H_2O_2 furnished the desired product in very high yield.[37]



(2)

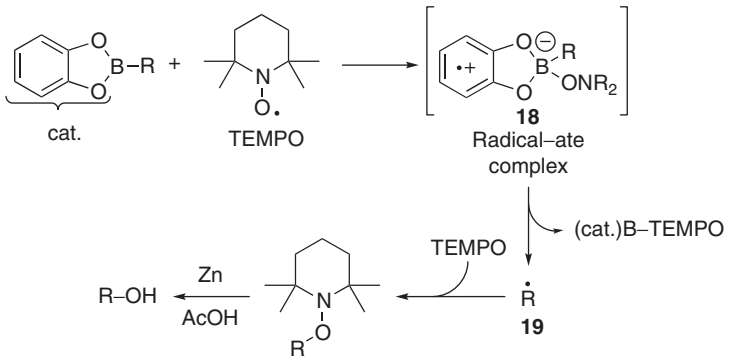
Molander has recently expanded the scope of boron reagents that can be oxidized by Oxone.[38] In their seminal contribution, a variety of aryl-, heteroaryl-, alkenyl-, and alkyltrifluoroborates were converted into the corresponding alcohols in excellent yields and with very short reaction times (Scheme 17). This method proved to be tolerant of a broad range of functional groups such as aldehydes, esters, ketones, and nitriles and afforded the hydroxylated products in a completely stereospecific manner.[38]



Scheme 17

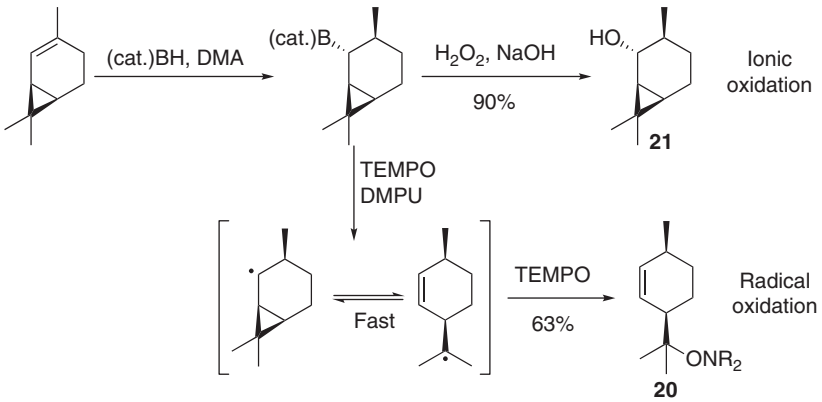
7.22.2.4 Oxidation with (2,2,6,6-Tetramethylpiperidin-1-yl)oxy (TEMPO)

TEMPO is a mild reagent that can oxidize C–B bonds to C–O bonds via a radical pathway.[39–41] B-Alkylcatecholboranes are usually the most reactive substrates and undergo homolytic substitutions with one equivalent of TEMPO leading to the electrophilic *C*-centered radical, which after intermolecular reaction with a second equivalent of TEMPO affords the corresponding alkoxyamines (Scheme 18). The formation of the initial stable perboryl radical–ate complex **18** has been clearly demonstrated by electron spin resonance studies and experimental evidence suggests that the use of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) as an additive can help the fragmentation of this intermediate to the alkyl radical **19**. Trapping of the radical by TEMPO followed by zinc-mediated reduction gave the alcohol. In attempts by Braslau to extend the TEMPO-mediated oxidation to trialkylboranes, the addition of the radical initiator di-*tert*-butylhyponitrite was found to be crucial in order to promote the oxidation reaction.



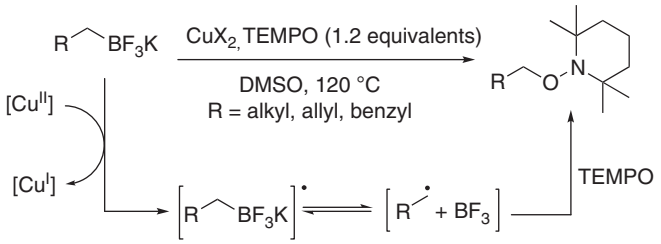
Scheme 18

Further evidence for the radical nature of this oxidation has been elegantly demonstrated by Renaud during his detailed study of this reaction mechanism.[41] When the reaction was performed on (+)-2-carene the ring-opened alkoxyamine **20** was obtained in good yield (Scheme 19). This indicates that the mechanism of oxidation is radical, since the bicyclic alcohol **21** would be obtained if an ionic oxidation mechanism was operational. It is well established that cyclopropyl methyl radicals undergo very rapid ring opening with relief of ring strain (classical radical clock experiment) to give a homoallylic alcohol.[41,42]



Scheme 19

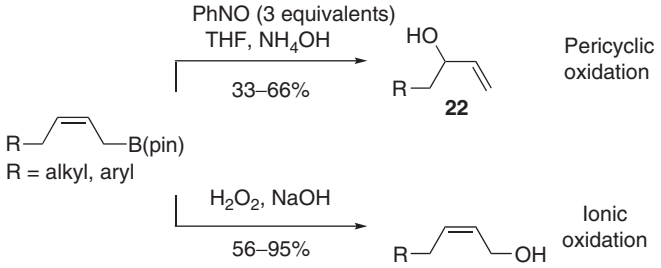
Fensterbank has recently reported the oxidation of organotrifluoroborates using Cu(II) salts and TEMPO.[43] The reaction has been extended to include densely functionalized alkyl and allyl substrates, but high reaction temperatures were required for good conversions. Although this reaction follows a radical pathway closely related to that depicted in Scheme 18, the use of Cu(II) as an external oxidant allows the direct formation of the *C*-centred radical that was subsequently trapped by TEMPO (Scheme 20).[43]



Scheme 20

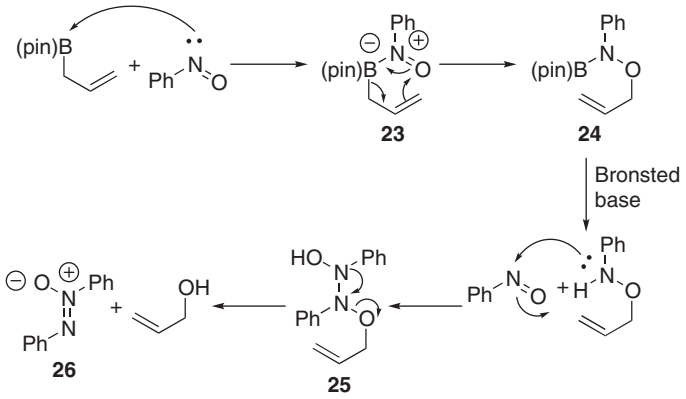
7.22.2.5 Oxidation with Nitrosobenzene

Reaction of allylboronic acid with nitrosobenzene proceeds via a pericyclic mechanism, giving rearranged allylic alcohol **22**. This method of oxidation has been developed to include a number of different alkyl- and aryl-substituted boronic esters, which give good-to-moderate yields of the rearranged secondary alcohols (Scheme 21).[44]



Scheme 21

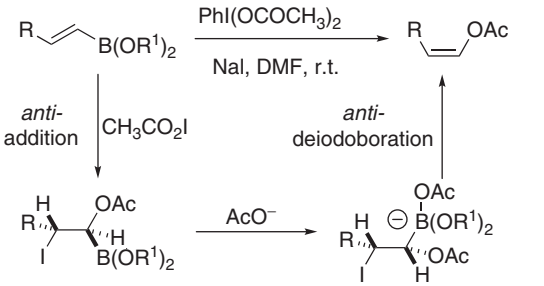
The reaction mechanism is thought to be related to a classical [3,3]-sigmatropic rearrangement, invoking the isoelectronic character of nitroso and carbonyl groups. After initial nucleophilic attack of the N onto the electron-deficient B, rearrangement delivers an oxygen to the terminal carbon of intermediate **23**, giving the allylic alkoxyamine **24**. At this stage the N–O bond can be cleaved by reaction with a second molecule of nitrosobenzene and a Brönsted base. The amine of the rearranged product is believed to attack a second molecule of nitrosobenzene forming intermediate **25**, which, after fragmentation, gives the desired alcohol and the byproduct **26** (Scheme 22).[44]

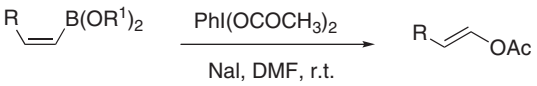


Scheme 22

7.22.2.6 Oxidation with (Diacetoxyiodo)benzene and Sodium Iodide

E- and *Z*-alkenylboronic acids and esters react with (diacetoxyiodo)benzene and sodium iodide to provide stereochemically pure *Z*- and *E*-enol acetates, respectively (Scheme 23).[45] The reaction mechanism has not been fully delineated, but it has been proposed to involve the formation of acetyl hypoiodite from NaI and (diacetoxyiodo)benzene, which undergoes stereospecific *anti*-addition to the olefin. Subsequent *anti*-deiodoboration aided by an acetoxy anion accounts for the formation of the geometrically pure enol acetate (Scheme 23).[45]



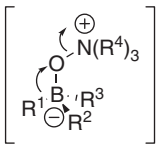


R = alkyl, aryl, and NR_2
R^1 = H, *i*-Pr

Scheme 23

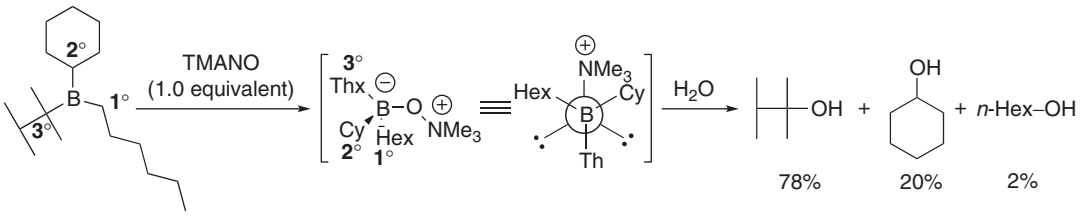
7.22.2.7 *N*-Oxide-Mediated Oxidation

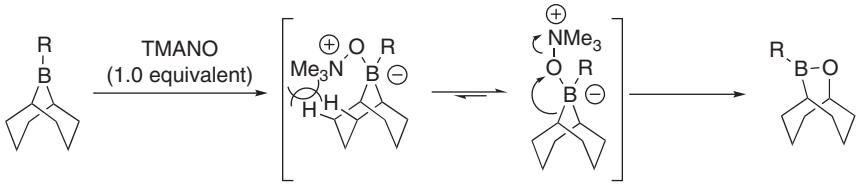
Commercially available *N*-oxides such as trimethylamine-*N*-oxide (TMANO), *N*-methyl morpholine-*N*-oxide, and *N*,*N*-dimethyl-4-toluidine-*N*-oxide are mild oxidizing agents that efficiently convert organoboranes and boronic esters to the corresponding alcohols/carbonyl compounds.[46–49] The reaction mechanism follows the classic ionic pathway proceeding via intermediate **27** (equation 3), resulting from nucleophilic attack of the *N*-oxide on the organoboron. The reaction proceeds in a stepwise fashion. The first group is normally oxidized at room temperature whereas the second and third groups need increasingly higher reaction temperatures.



27 (3)

TMANO is particularly efficient in the oxidation of a wide range of alkyl, aryl, and heterocyclic organoboron derivatives. One interesting aspect of this reaction manifold is the preferential migration of the most sterically demanding boron substituent (tertiary > secondary > primary).[47] This has been ascribed to the preferred conformation of the boron–ate complex, the main controlling factor in the migration. It should be noted that the observed order of migration observed with TMANO is the reverse of the usual migratory aptitude of boron substituents in boron–ate complexes (primary > secondary > tertiary) (Scheme 24).

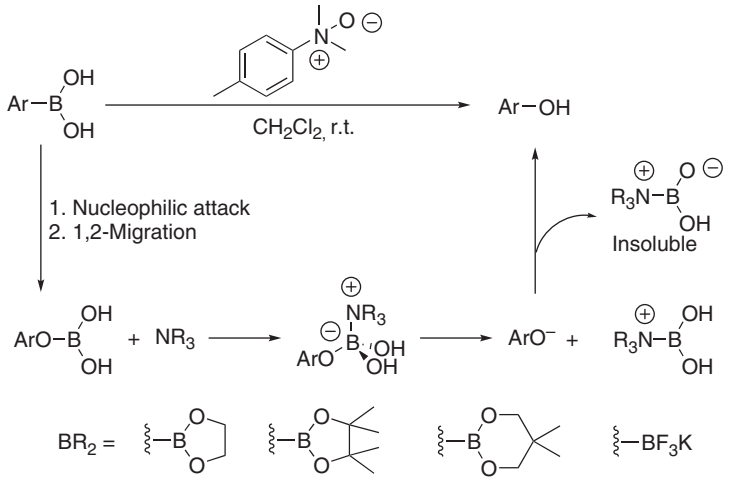




R = Me, *n*-Hex, Cy, and *t*-Bu

Scheme 24

The direct oxidation of arylboronic acids, esters, and trifluoroborates to the corresponding alcohols under mild reaction conditions was recently developed by Falck using *N*,*N*-dimethyl-4-toluidine-*N*-oxide. This reaction manifold is noteworthy due to the unusual reaction mechanism. After initial nucleophilic attack of the *N*-oxide and 1,2-migration of the resulting ate complex, the tertiary amine released is able to attack the B atom for a second time, thus facilitating the release of a phenoxide anion that can abstract a proton from the N–B complex, generating the desired alcohol along with an insoluble zwitterionic byproduct (Scheme 25).



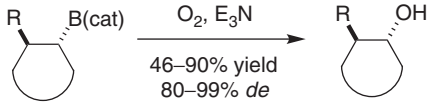
Scheme 25

7.22.2.8 Autooxidation

Simple trialkylboranes are extremely reactive compounds that undergo sometimes violent oxidative processes when exposed to air.[50,51] The mechanism of this spontaneous oxidation has been studied and all experimental evidence supports a radical pathway.[52–55] Brown was the first to report the oxidation of trialkylboranes with 1.5 equivalents of molecular oxygen (equation 4).[56,57] This protocol has, however, not found wide application in synthetic laboratories.

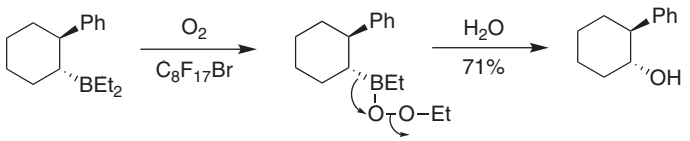
$$R_3B \xrightarrow[H_2O]{1.5 \times O_2} 3 \times R\text{–}OH \qquad (4)$$

Renaud has described the hydroxylation of alkyl catechol boronic esters in the presence of molecular oxygen and triethylamine (equation 5).[41] A wide range of alkyl and arylboronic esters was oxidized in good yields. Radical clock experiments confirmed the radical nature of the process, although the role of the tertiary amine is still unclear. Three possible explanations have been put forward: (1) Initial interaction of the amine with the boron–ate complexes could form an aminoborane intermediate, thus facilitating the homolytic fragmentation of the C–B bond. (2) Alternatively, the amine could quench the intermediate perborate, leading to the formation of the corresponding *N*-oxide. (3) Alternatively, the amine *N*-oxide might oxidize the starting material via a polar pathway.



(5)

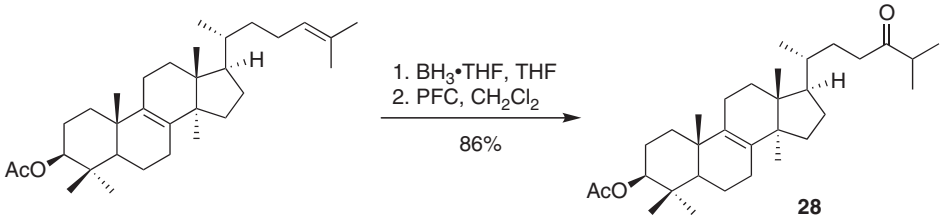
The use of perfluorinated hydrocarbons as solvents in molecular oxygen oxidations has been reported to have a beneficial effect due to their ability to dissolve oxygen. Bromoperfluorooctane has been employed by Knochel in the mild oxidation of chiral diethylboranes.[58] Almost complete retention of stereochemistry at the migrating C was observed (Scheme 26). Although this would normally rule out a radical pathway, in this case it has been accounted for on the basis of preferential initial oxidation of the B–Et bond leading to the hydroperoxide. Subsequent 1,2-migration followed by hydrolysis gave the alcohol with retention. Several functional groups, including ethers, halides, malonates, silicon ethers, and sulphonamides, were tolerated under the reaction conditions.



Scheme 26

7.22.2.9 Oxidation with Chromium Reagents

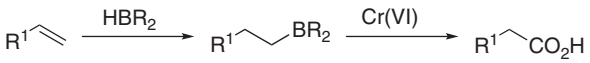
Pyridinium chlorochromate has been employed in the oxidative conversion of organoboranes to the corresponding ketones and aldehydes.[59,60] Parish has developed an improved protocol using pyridinium fluorochromate in a nonaqueous media.[61] A powerful application of this chemistry is the selective hydroboration–oxidation of the acyclic olefin of lanosterol acetate to give **28** (equation 6).[60]



Lanosterol acetate

(6)

Brown has developed an efficient method for the direct oxidation of terminal olefins to carboxylic acids (Scheme 27). This oxidation can be carried out using pyridinium dichromate in DMF, sodium dichromate in H_2SO_4 aqueous, or CrO_3 in 90% AcOH.[62]

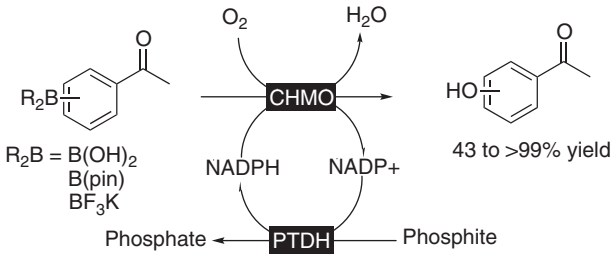


HBR_2 = $HBBr_2$•SMe_2
H_2BBr•SMe_2
H_2BCl•SMe_2
H_3B•SMe_2
$ThxBH_2$
Cy_2BH

Scheme 27

7.22.2.10 Baeyer–Villiger Monooxygenase (BVMO)

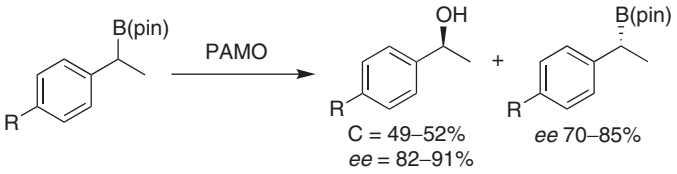
BVMOs are a class of flavin-containing and nicotinamide adenine dinucleotide phosphate-dependant enzymes that catalyze the nucleophilic incorporation of oxygen atoms into organic molecules.[63] BVMOs are mostly known for mediating epoxidations and oxidations of aldehydes, ketones, and heteroatoms (mainly B, N, P, S, and Se). Recently, Andrade reported the oxidation of aromatic boronic acids, esters, and trifluoroborates using BVMOs.[64] When the reaction using phenylacetone monooxygenase (PAMO) was carried out, a mixture of alcohol and Baeyer–Villiger oxidation products was obtained, whereas the use of cyclohexanone monooxygenases delivered the desired product in very high selectivity and with minimization of the unwanted second oxidation process (Scheme 28). This chemistry has been extended to vinylic boronic esters, circumventing the problem associated with the olefin epoxidation pathways.



R_2B = $B(OH)_2$
B(pin)
BF_3K

Scheme 28

Furthermore, the same group extended this method to the enantioselective oxidative kinetic resolution (OKR) of racemic boronic esters with PAMO.[65] The faster reacting enantiomer of the boronic ester was converted into the corresponding alcohol with excellent selectivity, the remaining slower reacting enantiomer being recovered with reasonable enantiopurity (equation 7). Extension of this OKR to β-boronate carboxylic esters has not been successful.

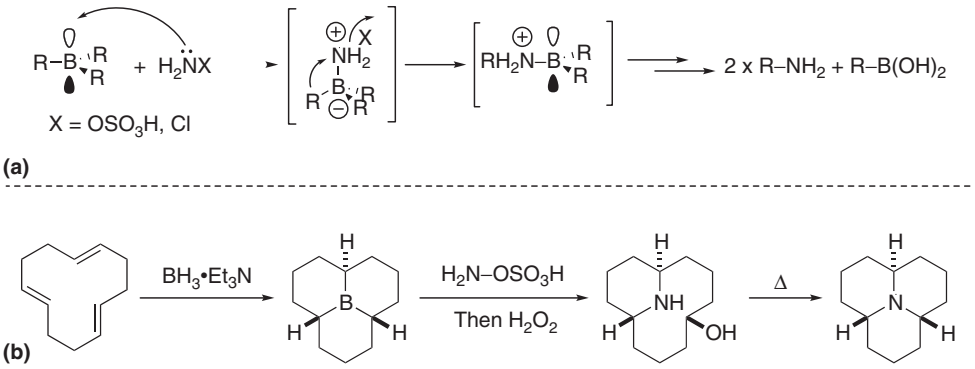


(7)

Although BVMO oxidations have limitations, they are considered to be a 'green' method of oxidizing C–B bonds, and current methods provide a platform for further development and application of biocatalysis in this area of chemistry.

7.22.3 Replacement of Boron by Nitrogen

The direct oxidation of B–C bonds to B–N bonds has been successfully applied to the synthesis of amines. Historically, the amination of organoborons follows a classic ionic pathway and involves the nucleophilic attack of an amine on the boron atom, followed by a 1,2-migration of one of the B substituents to the N atom with concomitant expulsion of a leaving group (Scheme 29(a)). Classic examples of this chemistry are the aminations of boranes and borinic esters with hydroxylamine-*O*-sulfonic acid or chloramine as developed by the groups of Brown[66] and Kabalka.[67] The reaction is, however, sensitive to both steric and electronic factors so that only two of the three alkyl groups of a borane can undergo the amination process, as highlighted in the synthesis of perhydro-9*b*-azaphenalenes (Scheme 29(b)).[66]



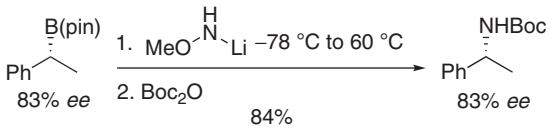
Scheme 29

Although this method is particularly powerful for the synthesis of primary amines from boranes, it suffers from the following:

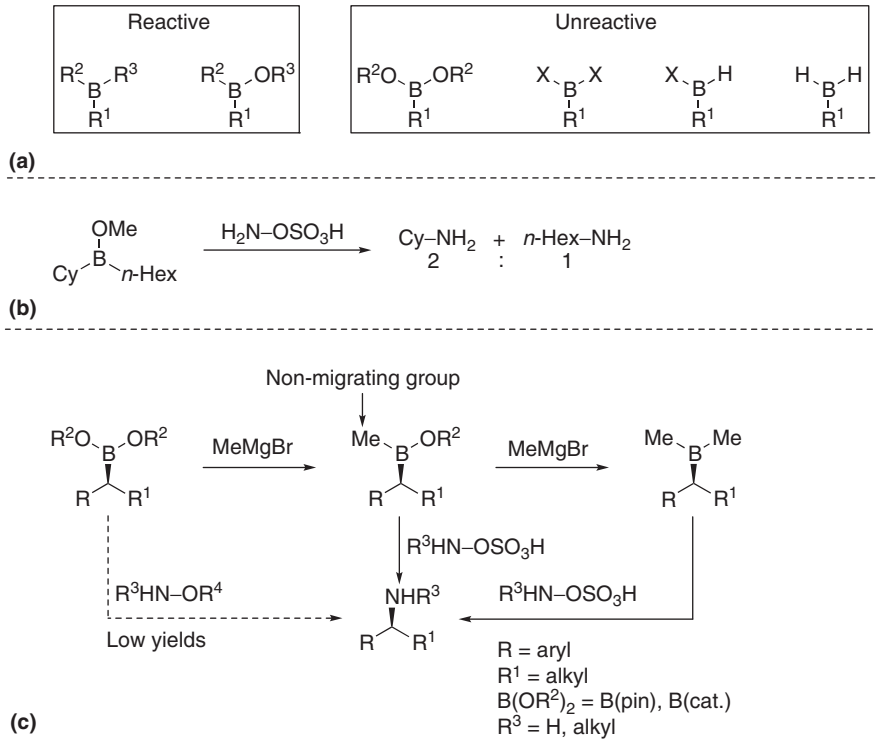
1. The reaction scope is limited to boranes and borinic esters (Scheme 30(a)).
2. A maximum yield of 67% can be obtained from homosubstituted boranes.
3. The use of differentially substituted boranes and borinic esters usually leads to mixture of products (Scheme 30(b)).

The poor migratory tendency of a methyl group makes it an ideal blocking group that can be strategically introduced into boronic esters (i.e., conversion to borinic esters) and boranes in order to solve chemoselectivity problems (Scheme 30(c)). The amination of enantioenriched secondary catechol boronic esters via dimethylborane intermediates was reported by Brown. The direct reaction of the cathecol boronic esters occurred in low yields.[68,69]

A recent development in the field of amination comes from Morken, who has developed a direct and stereoselective amination protocol of pinacol boronic esters to *N*-Boc-protected primary amines using lithiated methoxyamine (equation 8). The benefit of this method lies in its ability to use stable and easily accessible pinacol boronic esters, circumventing the necessity to convert them into more electrophilic species (*vide infra*). The reaction shows broad scope, including primary and secondary alkyl and aryl-boronic esters. However, tertiary boronic esters gave very low yields of the aminated products.[70]

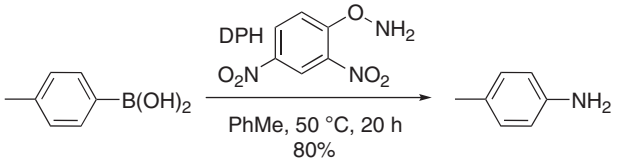


(8)



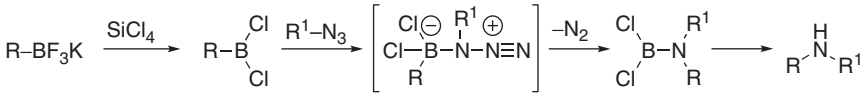
Scheme 30

Kürti and Falck have recently found that the aryl hydroxylamine derivative *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) can directly aminate arylboronic acids to the corresponding anilines (equation 9), presumably via an electrophilic addition and migration mechanism similar to that depicted in Scheme 29.[71]



(9)

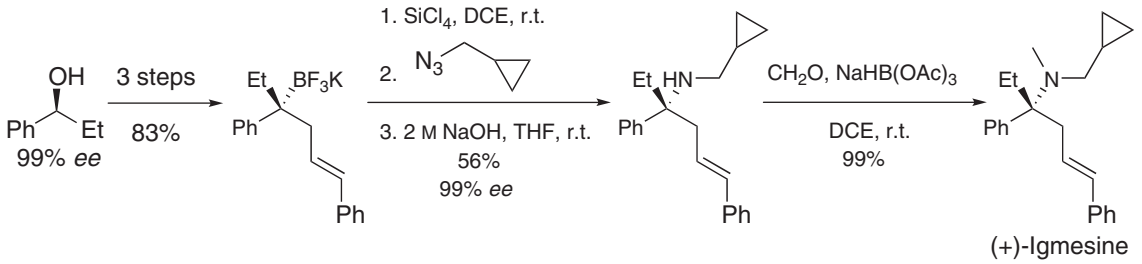
Secondary amines can be synthesized by the amination of potassium trifluoroborate salts with alkyl azides as developed by Matteson (Scheme 31).[72,73] In this case, the boron–ate complex formation is preceded by the formation of a much more electrophilic dichloroborane species, which can then undergo nucleophilic attack with a substituted azide. 1,2-Migration of the boron substituent and concomitant expulsion of nitrogen gas gives, after hydrolysis, the desired secondary amines.



Scheme 31

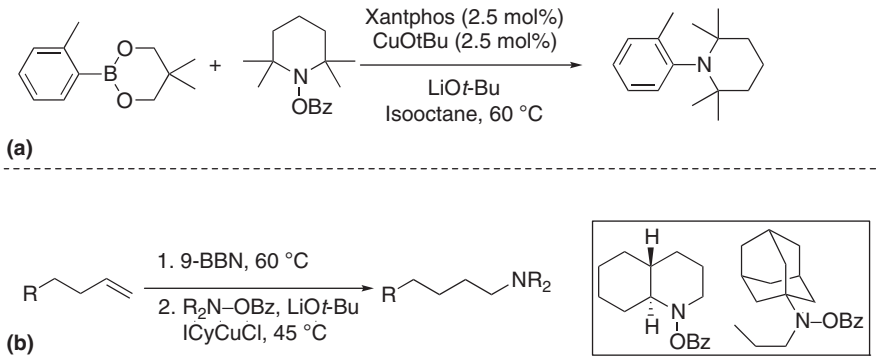
Aggarwal has extended Matteson's method and applied it to enantiomerically enriched tertiary trifluoroborates, illustrating that the amination proceeds with excellent retention of stereochemistry. The method was subsequently applied to the synthesis of the antidepressant drug (+)-igmesine (Scheme 32).[74]

A range of methods relating to the amination of aromatic organoborons exists, many based on copper catalyzed cross-couplings. In this manner, the boronic ester may often be used directly. This protocol has recently been used by Lalic for the synthesis of highly hindered anilines using benzoyl-derived aminating agents and aromatic neopentyl boronic esters (Scheme 33(a)).[75] Further reports from the same authors have focused on the development of a direct *anti*-Markovnikov



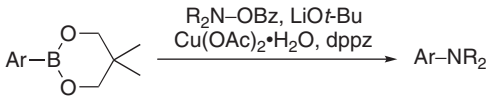
Scheme 32

amination of terminal olefins to form tertiary amines (Scheme 33(b)). In this case, after initial hydroboration with 9-BBN, treatment of the crude borane with *in situ* generated Cu(I)O*t*-Bu and an *O*-Bz-protected hydroxylamine gave the desired product in very good yields.[76]



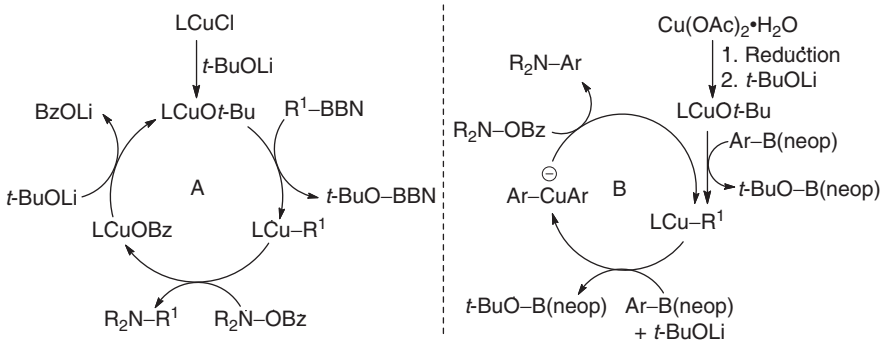
Scheme 33

A closely related protocol has been independently disclosed by Hirano and Miura.[77] In this case, a Cu(II) catalyst was employed for the direct amination of aryl neopentyl boronic esters (equation 10). Cruces has further expanded this Cu(II)-catalyzed process to include boronic acids and amines, which result in differentially substituted anilines.[78]



(10)

The proposed mechanisms of these Cu(I)- and Cu(II)-catalyzed processes are remarkably different and deserve some explanation. Lalic's protocol is most likely to involve an initial transmetalation of the 9-BBN borane with Cu(I)O*t*-Bu to generate a primary alkylcopper species. Reaction with the *O*-Bz-protected hydroxylamine gives the desired product along with Cu(I)OBz, which can be reconverted into Cu(I)O*t*-Bu by LiO*t*-Bu (Scheme 34A). The reaction manifold reported by Hirano and Miaura seems to involve a different pathway and has been supported by detailed mechanistic studies (Scheme 34B). First, the Cu(II) needs to be reduced *in situ* to Cu(I) in order to generate the catalytically active Cu(I)O*t*-Bu. Second, after formation of an



Scheme 34

arylcopper species, a second transmetallation occurs aided by the LiO*t*-Bu, which forms a Cu(I)–ate complex that is able to react with the *O*-Bz-protected hydroxylamine.

7.22.4 Replacement of Boron by Halogen

The selective introduction of a halogen atom in a molecule represents a valuable transformation as alkyl, vinyl, and aryl halides can undergo a wide range of chemical modifications.

7.22.4.1 Chlorinolysis of C–B Bonds

The direct chlorinolysis of C–B bonds has been extensively investigated and it mostly relies on electrophilic sources of chlorine atoms. Classical reagents include: nitrogen trichloride, copper(II) and iron(III) chloride, *t*-BuOCl, and dichloramine-T (DCT).[79] A critical comparison of these methods is presented.

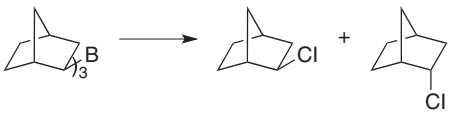
Nitrogen trichloride, a moderately difficult-to-handle reagent, reacts with trialkylboranes to give one equivalent of the alkyl chloride. This reagent is characterized by a weak N–Cl bond (N–Cl 47.7 kcal mol^{-1}; Cl–Cl 58.0 kcal mol^{-1}) and has a low basicity toward boron atoms and thus favors radical pathways. The free-radical nature of this process has been proven by Brown using radical clock experiments based on cyclopropylboranes. However, chlorination by NCl_3 is hampered by the fact that a large excess of the reagent has to be used in order to obtain good yields, and when differentially substituted boranes are present, mixtures of products are normally obtained (equation 11). The fact that the thexyl group is preferentially chlorinated indicates a free-radical pathway where a homolytic process forms the more stable tertiary radical.[79]



(11)

Reactions with *t*-BuOCl or DCT are accompanied by low yields and are thought to proceed through competing radical and polar pathways.[79] Copper(II) chloride and iron(III) chloride have been used as chlorinolysis reagents, and their mechanism is believed to involve electron-transfer reduction of the metal salts giving an alkyl radical from the organoborane. However, the long reaction times and the generation of HCl limit their use in synthetic chemistry. Nelson has reported a comparative study of these chlorinating agents in the reaction of diastereomerically pure tri-*exo*-norbornylborane.[80] The results of this study clearly demonstrate that almost all of these chlorinolysis reactions are sensitive to sterics and follow radical pathways. The variation of *exo*:*endo* ratios might be explained on the basis of the different selectivities of the norbornyl radical toward these reagents. Once the almost planar radical intermediate has been generated, the *exo* face is more accessible, and thus the *exo*:*endo* ratio depends on the steric bulk associated with the chlorinating reagents, DCT being the bulkiest as better selectivities are obtained (**Table 2**).[80]

Table 2 Chlorination of tri-*exo*-norbornylborane

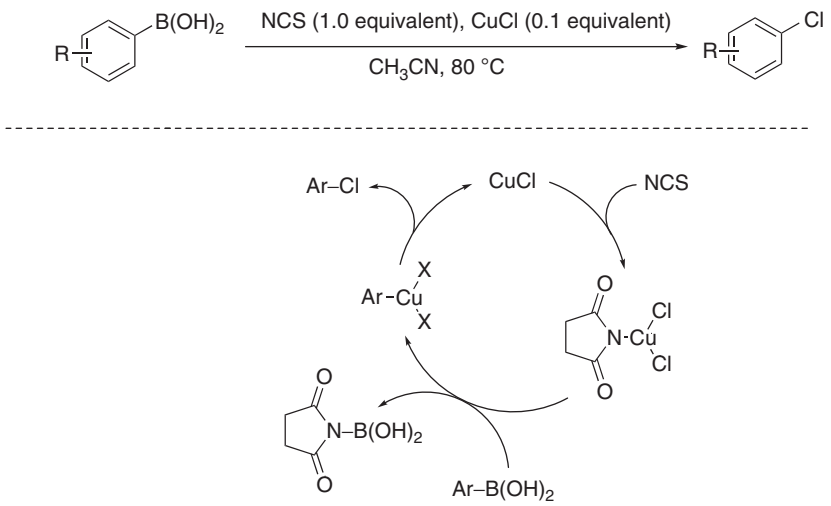


Chlorinating agent	*Solvent*	*Yield (%)*	exo:endo
t-BuOCl (3.0 equivalents)	Pentane	79.5	91:9
t-BuOCl (3.0 equivalents)	THF	26.2	91:9
$CuCl_2 \cdot H_2O$ (6.0 equivalents)	THF	55.4	92:8
$FeCl_3$ (6.0 equivalents)	THF	160	93:7
Dichloramine-T (1.0 equivalent)	CCl_4	69.1	99:1
NCl_3 (1.0 equivalent)	CCl_4	100	77:23

Abbreviation: THF, tetrahydrofuran.

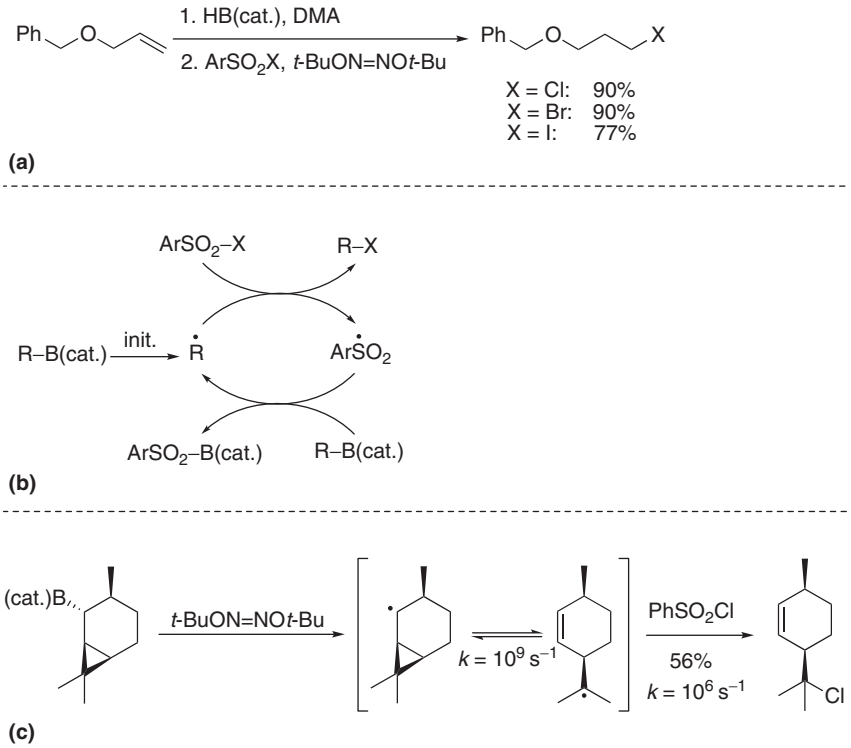
The direct chlorodeboronation of boronic acids and esters has been reported by the groups of Hynes and Renaud.[81,82] Hynes developed a Cu(I)-based chlorination using *N*-chlorosuccinimide (NCS) as chlorinating reagent. The process has been extended only to arylboronic acids, and it is thought to involve a classical ionic pathway based on the initial oxidative addition of Cu(I) on the N–Cl bond of NCS, transmetallation, and reductive elimination (**Scheme 35**).[81]

Renaud has reported a direct *anti*-Markovnikov chlorination of terminal alkenes. After DMA-catalyzed hydroboration with HB(cat.), the crude boronic esters were treated with a radical initiator and $PhSO_2Cl$ as a chlorine source to give the desired



Scheme 35

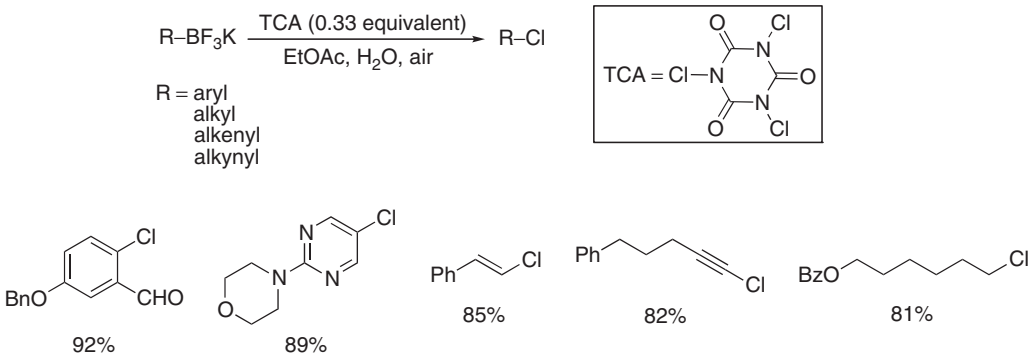
product in very good yields. The use of $PhSO_2Br$ and $TolSO_2I$ resulted in the corresponding alkyl bromides and iodides (Scheme 36(a)). The radical mechanism of this transformation (Scheme 36(b)) has been further demonstrated by radical clock experiments using (+)-carene and is supported by kinetic evidence (Scheme 36(c)).[82]



Scheme 36

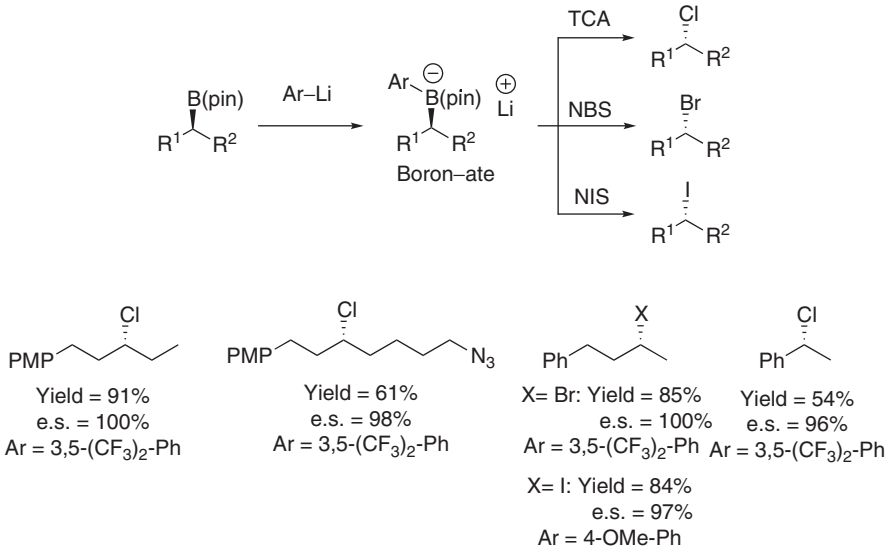
Trichloroisocyanuric acid (TCA), a widely available and inexpensive reagent, has recently been used by Molander to chlorinate aryl-, primary alkyl-, alkenyl-, and alkynyl trifluoroborates (Scheme 37).[83] Initial mechanistic studies seem to support an ionic pathway. Other reagents such as *t*-BuOCl and Chloramine-T/NaCl were tested, but were found to be susceptible to proto-deboronation and double chlorination.[83]

More recently, Aggarwal has expanded the chlorination of organoborons to chiral secondary boronic esters.[84] In this case, after formation of a 'boron–ate' complex a stereospecific S_E2 with inversion of configuration afforded the desired products in good yields and almost complete enantiospecificity (Scheme 38). TCA was found to be a superior electrophile to NCS, and the nature of



Scheme 37

the Ar group at B was critical (electron-deficient aromatics were optimal) in order to minimize unwanted single-electron transfer pathways, which eroded enantioselectivities. This method was also applied to the synthesis of highly enantioenriched secondary bromides and iodides.[84]



Scheme 38

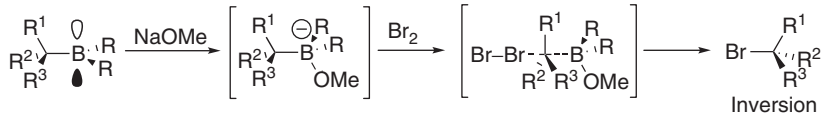
7.22.4.2 Brominolysis of C–B Bonds

Treatment of trialkylboranes with bromine and sodium methoxide affords the desired alkyl bromides, with inversion at the migrating carbon.[85–87] The mechanism is thought to proceed through a 'boron–ate' complex formed by initial nucleophilic addition of the methoxide to the electron-deficient B atom (Scheme 39(a)). This complex shows nucleophilic character and reacts with inversion of stereochemistry with bromine. Thus, the reaction with tri-*exo*-2-norbornylborane gives predominantly *endo*-2-norbornyl bromide. The small amount of the *exo*-product has been rationalized on the basis of a competing radical pathway (Scheme 39(b)).[85–87]

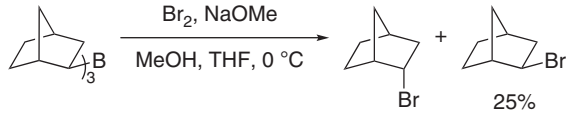
Brominolysis has also been achieved using sodium bromide and Chloramine-T (Scheme 40(a)).[88] This involves *in situ* oxidation of the bromide ion to the electrophilic bromine chloride (Scheme 40(b)). Primary trialkylboranes react more readily than secondary alkyl groups due to sterics. This method has been applied to potassium aryl-, alkenyl-, and alkynyltrifluoroborates with excellent yields (Scheme 40(c)).[89] The corresponding iodination reaction with NaI and Chloramine-T has been extended to aryltriolborates.[90]

Kabalka has recently identified tetrabutylammonium tribromide as a powerful and stereoselective bromodeboronation reagent for organotrifluoroborates.[91] Aryltrifluoroborates with a wide range of functional groups were converted into aryl bromides in good yields. The bromodeboronation of mono- and disubstituted alkenyltrifluoroborates was also achieved with retention of stereochemistry. This represents a powerful avenue for the otherwise challenging synthesis of (*Z*)-dibromoalkenes (Scheme 41).[91]

The bromodeboronation of arylboronic acids using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and catalytic NaOMe was achieved in high yields (equation 12).[92] DBDMH acts as an electrophilic brominating reagent, and the base is thought to aid the breakup of the less reactive trimeric boronic acid anhydrides to the more reactive monomeric form.

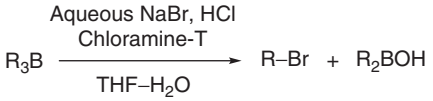


(a)

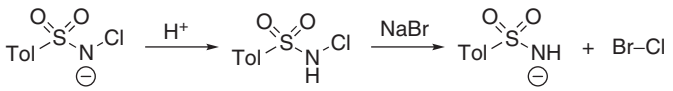


(b)

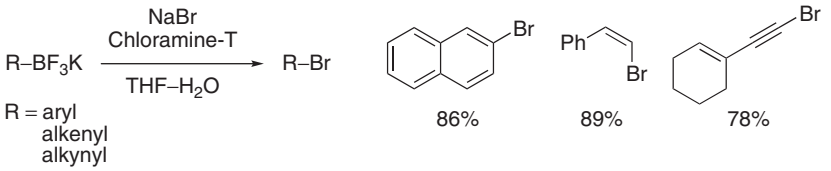
Scheme 39



(a)

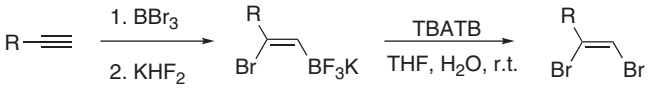


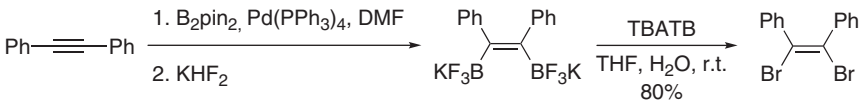
(b)



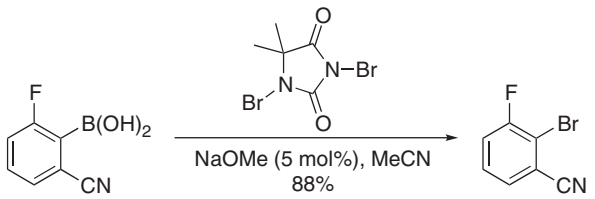
(c)

Scheme 40



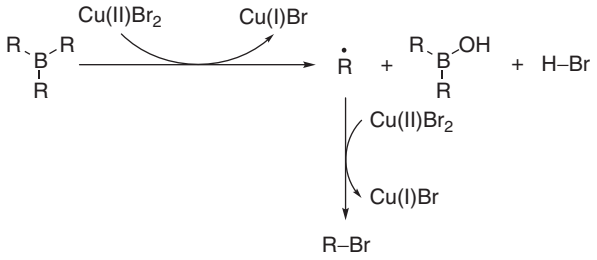


Scheme 41



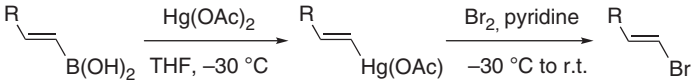
(12)

Copper(II)-mediated bromination of trialkylboranes gives 1 equivalent of alkyl bromide (Scheme 42). In analogy to the chlorinolysis of C–B bonds, the reaction occurs through an electron transfer reduction of the cupric salt, giving the alkyl radical. This then reacts with the second equivalent of $Cu(II)Br_2$ to give the alkyl bromide by a ligand transfer process (Scheme 42). This has also been applied to the bromination and iodination of arylboronic acids, with moderate-to-good yields.



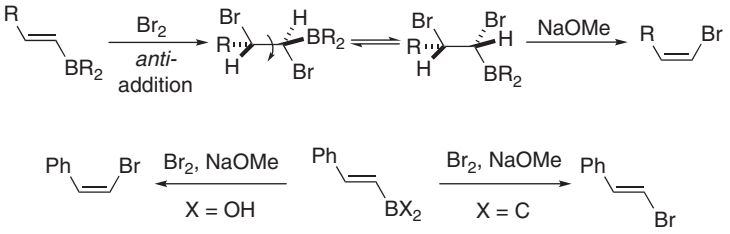
Scheme 42

Indirect brominolysis via initial reaction with mercury(II) acetate followed by bromination allows transfer of all three alkyl groups of trialkylboranes. This method has been used toward a one-pot, stereospecific synthesis of (*E*)-bromo-alkenes from (*E*)-alkenylboronic acids by Brown (Scheme 43).[93,94]



Scheme 43

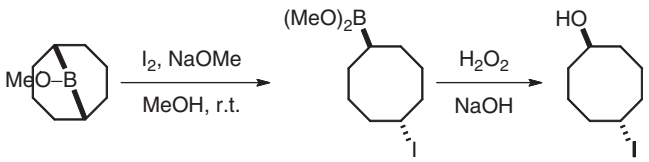
Brominolysis of alkenylboranes using bromine normally occurs with inversion of stereochemistry.[95–99] Bromine addition takes place through a bromonium ion, opened with a bromide ion – this gives overall *anti*-addition (Scheme 44). Base then promotes *anti*-elimination, resulting in overall inversion. This applies to alkenylboranes, boronic acids, and esters. However, with aryl and alkenylboranes retention of stereochemistry is observed (Scheme 44). This is thought to be a result of *syn*-addition of bromine to the alkene, due to stabilization from the aryl group. Base-mediated *anti*-elimination leads to the opposite isomer. Alkenylboronic acids react with bromine and base with inversion of stereochemistry, irrespective of the alkenyl group.[95–99]



Scheme 44

7.22.4.3 Iodinolysis of C–B Bonds

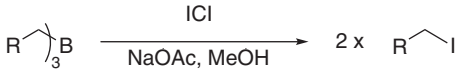
Iododeboronation of trialkylboranes occurs in an analogous fashion to bromodeboronation and usually results in inversion of stereochemistry in the migrating group. Initial reports from Brown focused on the use of iodine and a base for the iodinolysis of boranes and borinic esters (Scheme 45).[100]



Scheme 45

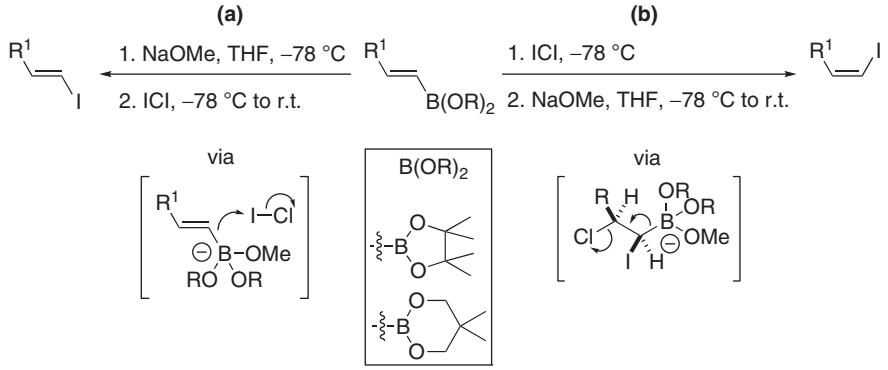
However, the use of strong bases is problematic due to functional group incompatibility. Kabalka was the first to identify iodine monochloride as a mild halogenating reagent, with sodium acetate used as a weak base (equation 13).[101] Primary

alkylboranes reacted more readily than secondary, presumably due to sterics, and for bulkier organoboranes there was transfer of only one alkyl group. The use of blocking groups such as 9-BBN has been reported where transfer of the boron substituent occurred in preference to the boracycle.



(13)

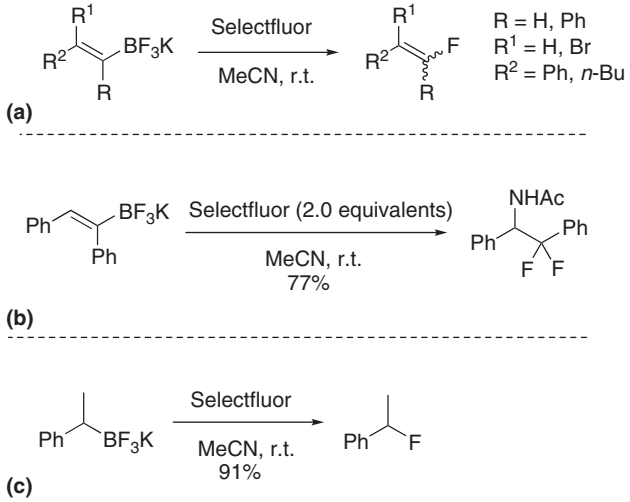
Cesium triiodide acts as an electrophilic iodinating reagent toward aryl and alkenyltrifluoroborates. Aryltrifluoroborates bearing electron-donating groups were shown to give higher yields than those bearing electron-withdrawing groups. Alkenyltrifluoroborates react with retention of stereochemistry. *N*-Iodosuccinimide has been utilized in the iodinolysis of arylboronic acids, resulting in *ipso*-substitution independent of the substituents on the aryl ring.[102] Reaction with alkenylboronic acids gives retention of stereochemistry.[103] It has been shown that in the iodinolysis of alkenylboronic esters, the stereochemistry of the product alkenyl iodide can be controlled by the order of addition of iodine monochloride (or iodine) and base (Scheme 46).[104] Addition of base at low temperatures should favor the formation of a 'boron–ate' complex, which then attacks the ICl with retention of stereochemistry (a). However, the addition of ICl to alkenylboronic esters affords an iodonium ion, which can be opened by chloride to give overall *trans*-addition. Base then leads to *trans*-elimination by attack at boron (b). Simultaneous addition of base and iodine leads to retention of stereochemistry – the opposite of brominolysis.[104]



Scheme 46

7.22.4.4 Fluorinolysis of C–B Bonds

Selectfluor is an electrophilic fluorinating reagent, shown to fluorinate alkenyltrifluoroborates in excellent yields.[105] However, while the reaction with NCS, NBS, and NIS proceeds with retention of configuration, with Selectfluor a mixture of *E* and *Z* isomers is obtained (Scheme 47(a)). This outcome is the result of a different reaction mechanism involving an addition–elimination

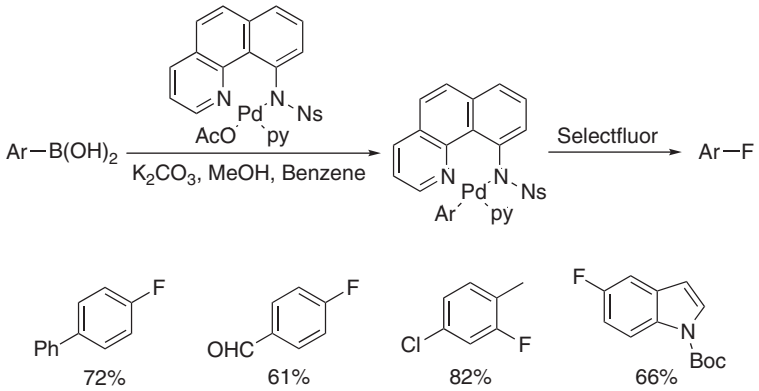


Scheme 47

process via a carbocationic intermediate. When 2 equivalents of Selectfluor are used, the alkenyl fluoride undergoes a second addition process revealing a putative carbocationic intermediate that can be trapped by the solvent in a Ritter-type process (Scheme 47(b)).[105] Recent investigations by Lemaire have expanded the scope of this transformation to arylboronic acids and benzylic trifluoroborates (Scheme 47(c)). In this case the stereoselectivity of the reaction manifold has not been evaluated.[106]

Indirect fluorinolysis of arylboronic acids has been reported, mediated by palladium.[107,108] Arylboronic acids are thought to undergo stoichiometric transmetallation with Pd(II) to give a Pd(IV) intermediate; fluorination with Selectfluor affords the aryl fluoride (Scheme 48). This method shows wide tolerance of functional groups, and is applicable to electron-poor, electron-rich, heterocyclic, and *ortho*-substituted arenes. The success of the reaction has been shown to rely on the ligand on the Pd atom, which has been designed on the basis of three main factors:[107,108]

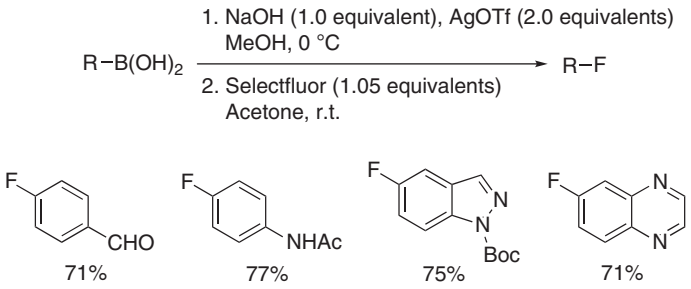
1. Can resist oxidation by electrophilic fluorinating agents.
2. Can support high-valent aryl–Pd–F for subsequent C–F reductive elimination.
3. Does not induce competing N–F reductive elimination.



Scheme 48

This method has recently been applied by Ritter to the synthesis of PET tracers for biomedical applications.[109]

Ritter also reported a stoichiometric silver(I)-mediated fluorinolysis of aryl- and alkenylboronic acids. This reaction proceeds with good yields, and complete retention of stereochemistry is generally observed (Scheme 49). This corresponds to a stereospecific transmetallation with silver triflate, fluorination, and subsequent stereospecific reductive elimination to give the alkenyl fluoride.[110]



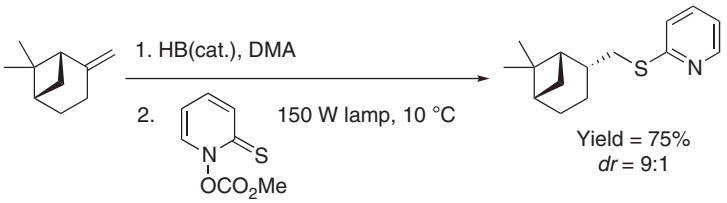
Scheme 49

7.22.5 Replacement of Boron by Sulfur or Selenium

Trialkylboranes readily undergo radical reactions with organodisulfides, giving dialkyl or alkyl aryl sulfides in good yields. The reaction is initiated by air or light, and shows higher reactivity for secondary alkyl groups than primary due to the formation of a more stable radical (equation 14).[111,112] The reaction of trialkylboranes with ferric thiocyanate affords alkyl thiocyanates in good yields.

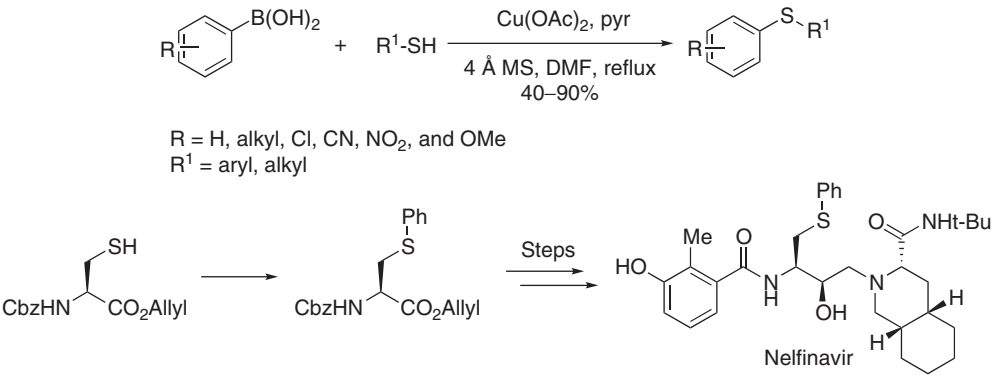
$$R_3B + 2\,Me_2S_2 \xrightarrow{\text{Air or } h\nu} 2\,R\text{–}SMe + RB(SMe)_2 \qquad (14)$$

A radical chain transfer reagent, pyridine-2-thione-*N*-oxycarbonyl, has been shown to react with *B*-alkylcatecholboranes to give C–S bonds (equation 15).[113,114]



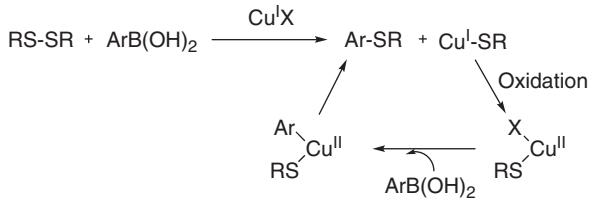
(15)

The reaction between arylboronic acids and alkyl sulfides can be mediated by stoichiometric $Cu(OAc)_2$ and pyridine (**Scheme 50**).[115,116] This reaction has been successfully applied to the synthesis of *S*-aryl cysteine derivatives, such as *N*-benzyloxycarbonyl-(*S*-phenyl)-L-cysteine, a key intermediate in the synthesis of nelfinavir (**Scheme 50**).[115]



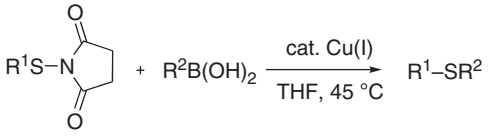
Scheme 50

The coupling of alkyl, alkenyl, and aryl disulfides with alkyl- or arylboronic acids can also be carried out using substoichiometric amounts of copper(I). In this case an oxidant is required to utilize the second RS moiety (**Scheme 51**).[115,116] This method was applied to diselenides and ditellurides with good results.[117,118]



Scheme 51

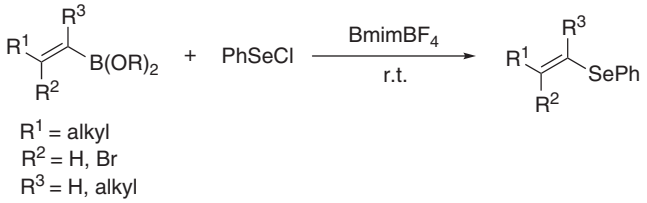
Copper catalysis was also employed in the coupling of organoboronic acids with thioimides, which are easily accessible from the organosulfide and NCS (equation 16).[115] This method allows a wide range of thioethers to be synthesized, and is thought to proceed through oxidative addition of *N*-thioimide to Cu, followed by transmetalation with the organoboronic acid and then reductive elimination to give the thioether. Similarly, alumina-supported copper was found to catalyze the electrophilic substitution of organoboranes by phenylselenium bromide, giving unsymmetrical diaryl and aryl alkyl selenides.



(16)

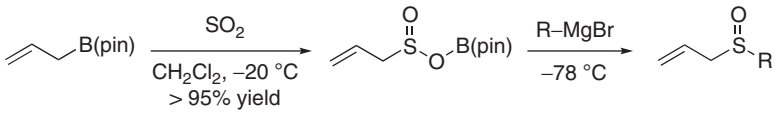
R^1 = alkyl, aryl, and heteroaryl
R^2 = aryl, alkenyl

Alkenyl selenides were prepared in good yields by the reaction of alkenylboronic acids and esters with phenylselenium chloride in ionic liquids such as $BmimBF_4$ (equation 17).[119] A range of alkenyl selenides was obtained with retention of stereochemistry, and after the reaction was complete, the products could be extracted into ether and the ionic liquid recycled.



(17)

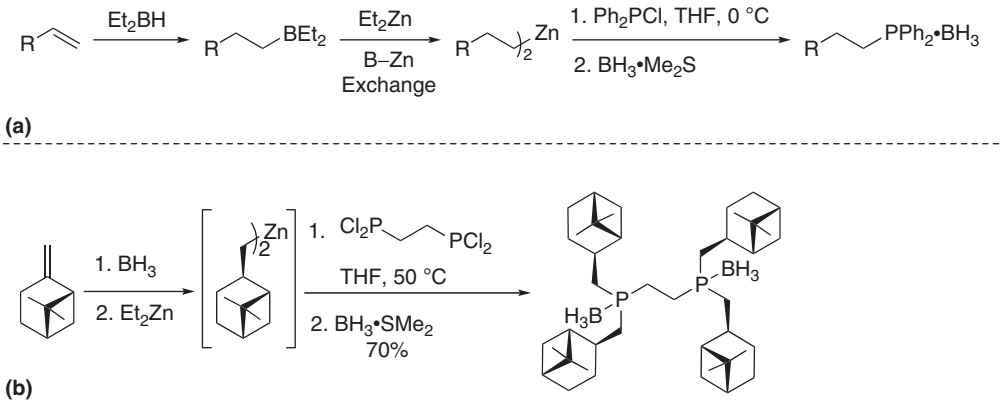
A pericyclic oxidation of boronic esters to sulfoxides has been reported by Vogel. This one-pot procedure relies on a bora-ene reaction of sulfur dioxide and allylboronic esters, giving mixed anhydride intermediates that react *in situ* with Grignard reagents to give the desired allylsulfoxide (Scheme 52).[120]



Scheme 52

7.22.6 Replacement of Boron by Phosphorus

Organoboranes undergo transmetallation with zinc to give diorganozinc compounds as described by Knochel (Scheme 53(a)).[121] These then act as mild nucleophiles toward chloroorganophosphines, creating valuable substituted phosphines. Chiral phosphines and diphosphines can be prepared using chiral organozinc reagents, derived from naturally occurring terpenes (Scheme 53(b)).



Scheme 53

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7.23 Oxidation of Carbon–Metal Bonds

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Glossary

Ligand-centered redox Oxidation of organometallic complexes in which the HOMO is predominantly ligand- or M–L-bond-centered proceeds via redox chemistry centered at the ligand.

Metal-centered redox Oxidation of organometallic complexes in which the HOMO is predominantly metal-centered proceeds via redox chemistry centered at the metal to generate higher-valent complexes.

Outer-sphere oxidation An oxidation in which electron transfer is not coupled to bond-making between the organometallic complex and the oxidant.

Oxidative addition Reaction between a metal-containing compound and a molecule, generically X–Y, in which the metal fragment is oxidized by two electrons, new M–X and M–Y bonds are formed, and the original X–Y bond is broken.

Reductive elimination The formal reverse of oxidative addition reactions. A molecule X–Y is formed from a metal complex (X–M–Y), M–X and M–Y bonds are cleaved, and the metal is reduced by two electrons.

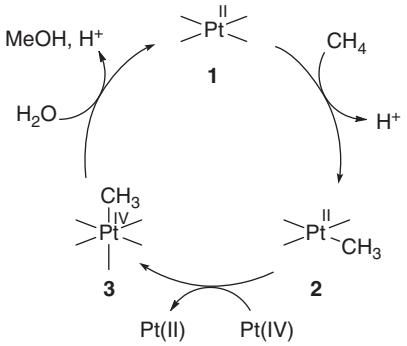
S_E(ox) pathway An oxidation pathway in which the initial interaction is between the oxidant and the metal center. Discrete metal-centered oxidation affords a higher-valent intermediate from which M–C bond oxidation products are obtained by subsequent reaction steps.

S_E2 pathway An oxidation pathway in which oxidant and M–C bond directly interact. Oxidative M–C bond cleavage is accomplished without redox chemistry at the metal center.

Single-electron transfer Redox reaction in which one electron is transferred between the two redox-active reagents.

7.23.1 Introduction

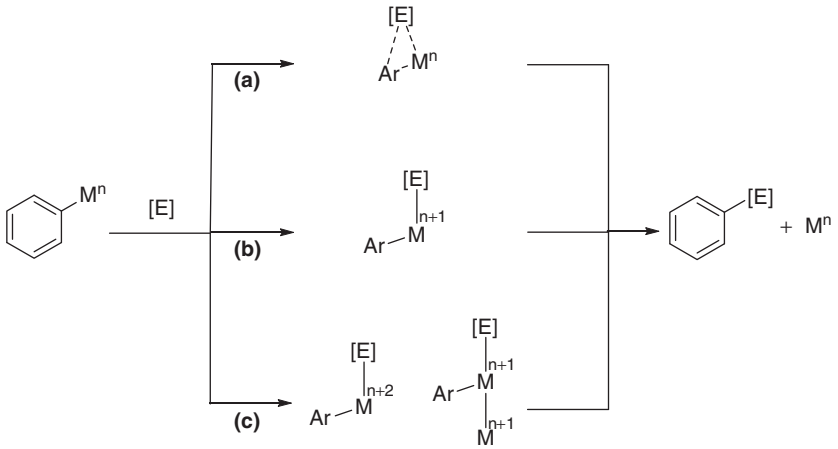
Oxidative metal–carbon (M–C) bond cleavage is the product-forming step in many transition metal-catalyzed organic reactions that proceed via organometallic intermediates. Transition metal-catalyzed reactions such as partial hydrocarbon oxidation and arene C–H bond oxidation can proceed via the oxidative cleavage of the M–C bonds of organometallic intermediates. For example, the Shilov reaction has been developed for the partial oxidation of methane to methanol (Scheme 1).[1] In this reaction, a Pt(II) catalyst (**1**) participates in C–H metallation to afford a methyl Pt(II) intermediate (**2**).[2] In the presence of a stoichiometric amount of a Pt(IV)-based oxidant and water, methanol is generated. The mechanism of oxidation during the Shilov reaction is proposed to proceed by oxidation of Pt(II) alkyl intermediate **2** to afford Pt(IV) alkyl intermediate **3**, followed by nucleophilic attack by water on the methyl ligand to afford methanol. One of the major challenges in Shilov chemistry, and the topic of substantial continuing research, is finding a more economically viable oxidant than Pt(IV) to accomplish the oxidation of Pt(II)



Scheme 1 The proposed catalysis cycle for partial oxidation of methane to methanol by the Shilov reaction involves platination, oxidation of the resulting alkyl Pt(II) to generate a Pt(IV) intermediate, and nucleophilic attack on the electrophilic methyl ligand by water to afford methanol and regenerate Pt(II). Ligands are not drawn for the intermediates of the cycle because the primary coordination sphere is not known; ligands may be Cl, OH, or H_2O.

methyl intermediate **2** to Pt(IV) methyl intermediate **3**.[3,4] The oxidant must oxidize organoplatinum(II) intermediate **2** without oxidizing Pt(II) catalyst **1**. The search for new oxidants for application in partial hydrocarbon oxidation reactions has been informed by studies of the mechanism of Pt–C bond oxidation.[3b]

Depending on the electronic structure of the organometallic intermediate and the nature of the oxidant being used, various mechanisms of oxidative M–C bond functionalization are available. The HOMO of the organometallic complex can be metal-centered, ligand-centered, or metal–ligand bond-centered.[5] For organometallic complexes in which the HOMO is predominantly ligand-centered, M–C bond functionalization can proceed by direct electrophilic substitution without participation of redox chemistry at the metal center (**Scheme 2(a)**). Alternatively, for organometallic intermediates that feature metal-centered HOMOs, oxidation may proceed at the metal center to afford higher-valent organometallic intermediates. Subsequent reaction chemistry, such as reductive elimination, can release the products of formal M–C bond oxidation from high-valent intermediates (**Scheme 2(b)** and **(c)**).[6] Reductive elimination is frequently more facile from high-valent complexes, and thus high-valent intermediates have been targeted in many challenging C–heteroatom bond-forming reactions.[7]



Scheme 2 Oxidation of M–C bonds can be initiated by direct interaction of the oxidant with the M–C σ-bonding orbital (S_E2) path (a) or by either one-electron path (b) or two-electron path (c) oxidation of the metal center. C–[E] bond-forming reactions following initial metal-centered redox chemistry can proceed via numerous mechanisms, as discussed below.

This chapter will present examples of oxidative M–C bond functionalization reactions, which have been selected to highlight the diversity of mechanisms by which oxidative M–C bond cleavage can proceed. This chapter does not comprehensively discuss synthetic examples of M–C bond oxidation, but instead illustrates issues of oxidation mechanisms through selected examples. Discussion is organized by the extent to which metal-centered redox chemistry participates in M–C bond activation. The authors will begin by examining cases of M–C bond oxidation in which metal-centered redox is not operative during oxidative M–C bond cleavage, and will then examine the mechanistic alternatives available to organometallic complexes in which the metal center can participate in redox chemistry. Stoichiometric organometallic transformations will be discussed in order to illustrate well-defined examples of various organometallic oxidation mechanisms. The relationship of these stoichiometric studies to the mechanism of

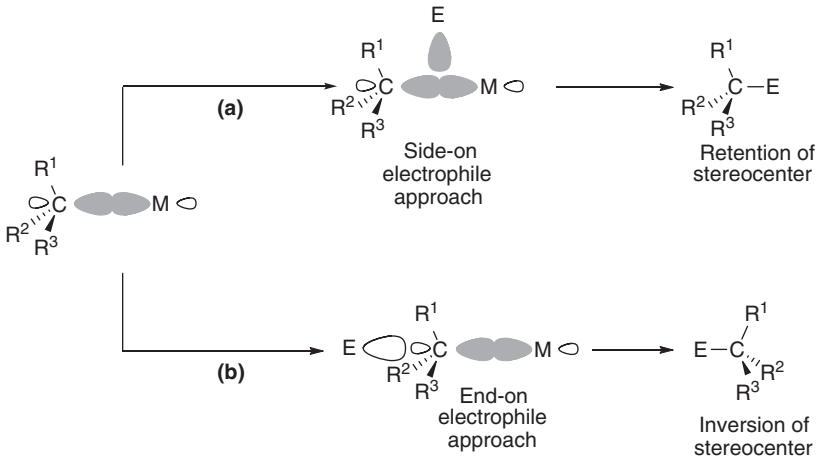
M–C bond oxidation in metal-catalyzed organic reactions will be discussed when possible. Oxidation reactions that do not proceed via organometallic intermediates (i.e. intermediates with an M–C σ bond) will not be discussed.

7.23.2 Electrophilic Substitution of M–C Bonds without Metal-Centered Redox

In electrophilic M–C bond cleavage reactions in which the HOMO of the organometallic reactant is either ligand-centered or predominantly centered on the metal–ligand bond, electrophilic M–C bond cleavage can proceed by direct interaction of the electrophile with the M–C bond. For example, the reaction of a Grignard reagent with an electrophile proceeds via interaction of the electrophile with a highly polarized M–C bond to afford oxidation products via ligand-centered redox. Such oxidative M–C bond cleavage proceeds without metal-centered redox chemistry.

7.23.2.1 Oxidative Functionalization of M–C Bonds in Main-Group Organometallics

Main-group organometallic compounds containing highly polarized M–C bonds, such as in organolithium compounds, can react with a variety of electrophiles to afford substitution products. The stereochemical outcome of electrophilic substitution reactions at M–C bonds provides information regarding the geometry of the substitution transition state. In contrast to S_N2 reactions, which necessarily proceed with inversion at the carbon center, S_E2 reactions of alkyl metals can proceed with either inversion or retention (Scheme 3). Interaction of an electrophile with the M–C σ-bonding orbital can proceed via a side-on geometry, resulting in retention of configuration, or via an end-on geometry, resulting in inversion of configuration.[8]



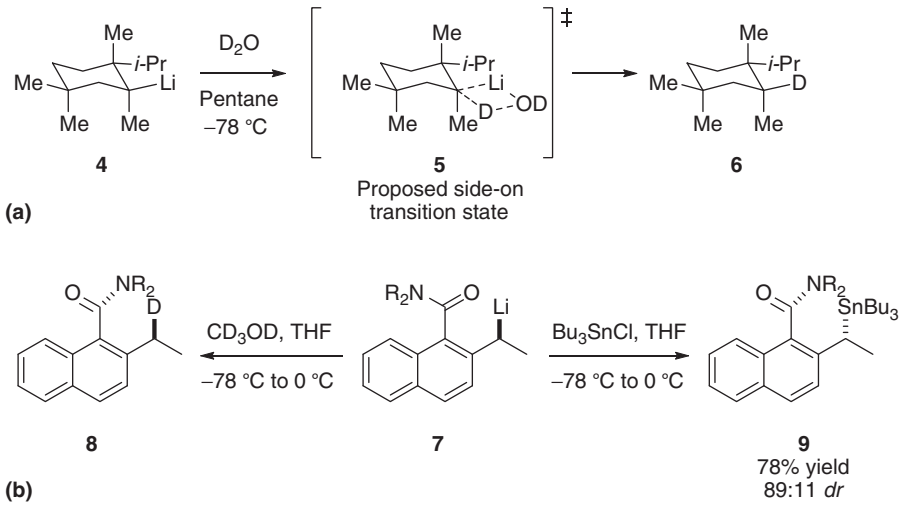
Scheme 3 Frontier orbital interactions that are relevant to electrophilic substitution reactions of alkyl metal compounds with either retention (a) or inversion (b) of configuration.

The high degree of polarization of C–Li bonds leads to a predominantly ligand-centered HOMO. Studies of electrophilic substitution reactions of configurationally stable alkyllithium compounds have revealed examples of substitution reactions with both retention and inversion of configuration.[9] For example, protonation of cyclohexyllithium derivative **4** affords cyclohexane derivative **6**, the product of substitution with retention of configuration (Scheme 4(a)).[10] The observed retention of configuration, which is fairly general for electrophilic substitution reactions of organolithium reagents, has been rationalized with transition states such as **5**, in which side-on protonation of the Li–C bond is invoked. In contrast, whereas protonation of configurationally stable alkyllithium **7** with deuterated alcohols proceeds with retention of configuration to afford compound **8**, stannylation of **7** with Bu_3SnCl proceeds with inversion to generate stannane **9** (Scheme 4(b)), presumably through end-on approach of the electrophile.[11] Regardless of the specific transition state geometry, electrophilic substitution reactions of organolithium reagents proceed by direct interaction of the electrophile with the ligand-centered HOMO.

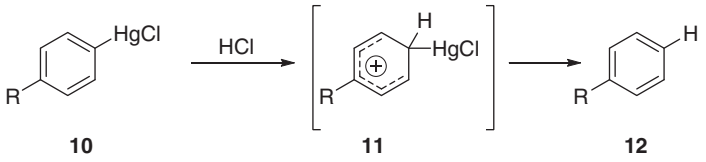
Protonation of some main-group arylmetal species is proposed to proceed at carbon instead of at the M–C σ-bond.[12] In the protolytic cleavage of Hg–C bonds in arylmercuric chloride compounds (i.e., **10**), protonation proceeds at the *ipso*-carbon to afford a Wheland-type intermediate (**11**; Scheme 5). Subsequent demetallation of the Wheland intermediate affords the observed C–H bond-containing products.

7.23.2.2 Oxidation of M–C Bonds of d^0 Organotransition Metal Complexes

Electrophilic substitution of d^0 organotransition metal compounds also proceeds by interaction of electrophiles with ligand-based HOMOs. Stereochemical information regarding the products of M–C bond cleavage is available in a number of cases. For

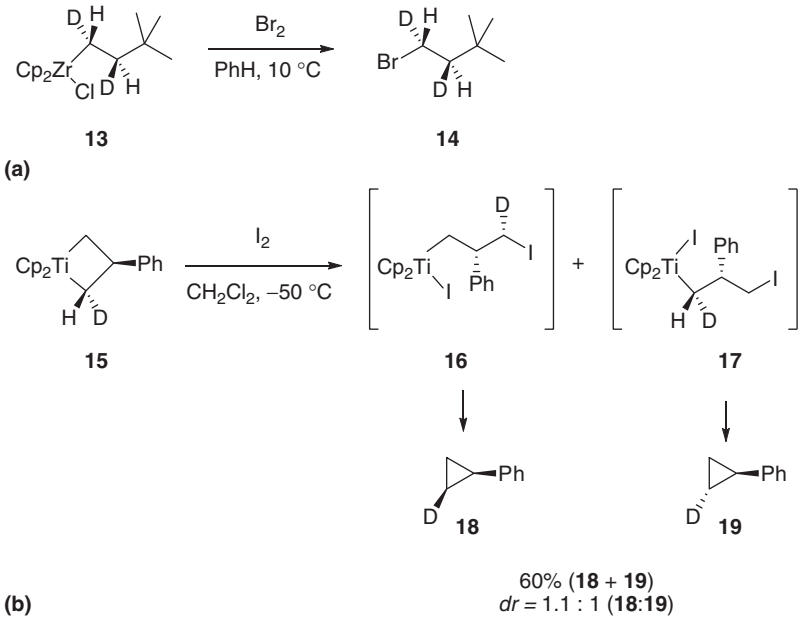


Scheme 4 (a) Protonation of configurationally stable organolithium **4** results in deuterium incorporation with retention of configuration. The observed stereochemical outcome is consistent with side-on protonation of the Li–C bond, as shown in transition structure **5**. (b) Electrophile-dependent stereoselectivity has been observed. Protonation of organolithium **7** affords **8** with retention of configuration, whereas treatment of **7** with Bu_3SnCl affords **9** with inversion of configuration (R = *i*-Pr).



Scheme 5 Oxidation of main-group aryl metals, such as organomercurial **10**, has been proposed to proceed via Wheland-type intermediates (i.e., **11**).

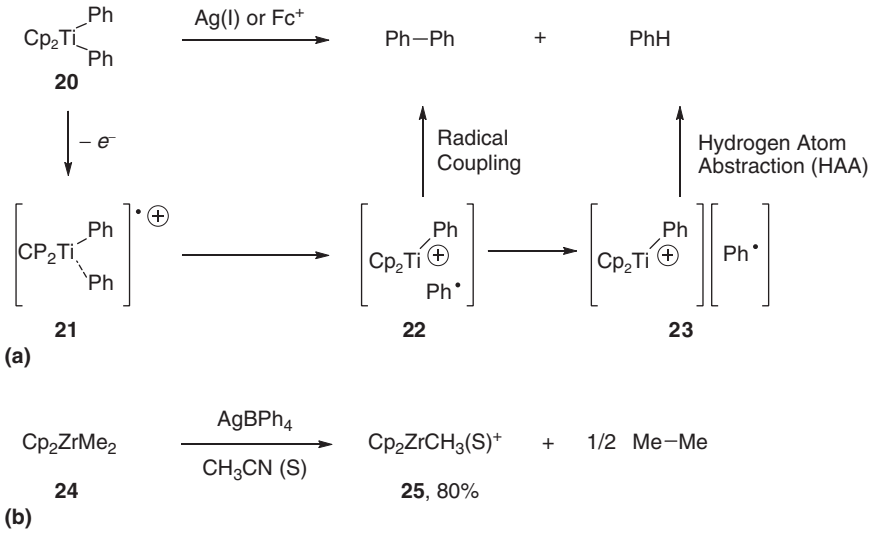
example, bromination of Zr(IV) complex **13** affords alkyl bromide **14** with retention of configuration (Scheme 6(a)).[13] Similarly, the oxidation-induced elimination of cyclopropanes from titanacyclobutanes has been shown to proceed with retention of configuration; treatment of complex **15** with I_2 at –50 °C affords complexes **16** and **17**, in which the Ti–C bond has been cleaved



Scheme 6 (a) Bromination of zirconocene complex **13** proceeds with retention of configuration at carbon. (b) Initial cleavage of a Ti–C bond in the elimination of cyclopropanes from titanacyclobutane **15** proceeds with retention of configuration.

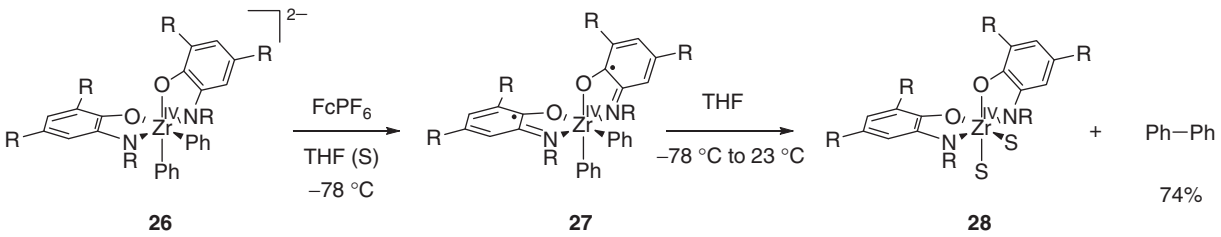
with retention of configuration (Scheme 6(b)).[14] Subsequently, intramolecular S_N2 displacement of the alkyl iodide affords the observed cyclopropanes **18** and **19**. The observed retention of configuration is consistent with side-on interaction of the electrophile with the M–C σ-bond.

One-electron oxidants have also been used to effect oxidative M–C bond cleavage of d^0 organometallic complexes. Because d^0 organometallic complexes have no M-centered, valence d-electrons, oxidation of d^0 organometallic complexes occurs by removal of M–C bonding electrons (see below for an exception based on redox-active ancillary ligands).[15] For example, treatment of d^0 Ti(IV) diphenyl complex **20** with one-electron oxidants such as Ag(I) or Fc^+ affords a mixture of biphenyl and benzene. Oxidation is proposed to remove an electron from the Ti–C(Ph) σ-bond (Scheme 7).[15] Ti–C bond homolysis generates solvent-caged radical **22**, and the observed biphenyl has been proposed to arise from radical coupling within a solvation cage (i.e., **22**), whereas the observed formation of benzene has been proposed to proceed by formation of a solvent-separated radical-cation pair (**23**) followed by hydrogen atom abstraction (HAA). Similarly, oxidation of dialkyl zirconocene complex **24** has been shown to afford cationic, monoalkyl zirconocene complex **25** and ligand-coupling products.[16] This reaction, which presumably proceeds via a similar mechanism to the oxidation of titanium complex **20**, has been rationalized as due to the highly carbanionic nature of the organometallic ligands of **24**, which facilitates ligand-based oxidation.



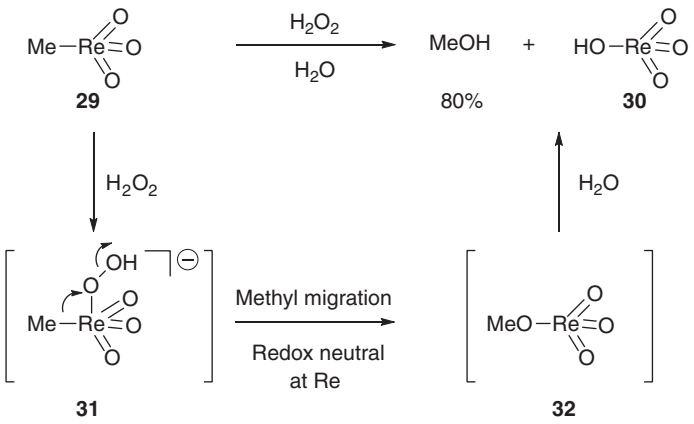
Scheme 7 (a) One-electron oxidation of d^0 Ti(IV) complex **20** proceeds by oxidation of the Ti–C(Ph) σ-bond. The observation of biphenyl and benzene is proposed to arise from radical coupling and HAA pathways, respectively. (b) Treatment of dimethyl Zr(IV) complex **24** with $AgBPh_4$ affords ethane, the product of alkyl radical coupling, and cationic Zr(IV) complex **25**.

By definition, either ligand-based or metal–ligand-bonding electrons are removed during oxidation of d^0 organometallic complexes. The oxidation of Zr(IV) complex **26** demonstrates that oxidative cleavage of M–C bonds can be achieved by oxidation of redox-active ancillary ligands (Scheme 8).[17] Two-electron oxidation of **26** proceeds to afford complex **27** in which the Zr(IV) center is supported by two one-electron-oxidized ligands. Subsequent C–C reductive elimination affords biphenyl and Zr(IV) complex **28**. Both reaction steps, oxidation of **26** and C–C reductive elimination from **27**, proceed without metal-centered redox, and are enabled by the presence of redox-active ligands.



Scheme 8 Two-electron oxidation of Zr(IV) complex **26** affords Zr(IV) complex **27** in which each of the supporting ligands has been oxidized by one electron. The ligand-based oxidizing equivalents facilitate subsequent formal C–C reductive elimination to generate biphenyl and Zr(IV) complex **28** (R = *t*-Bu).

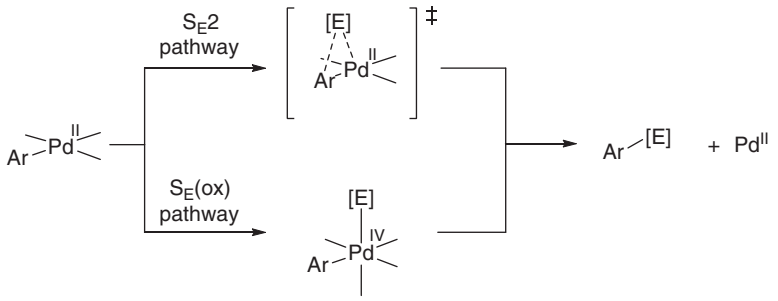
The oxidation of methyl trioxorhenium (MTO, **29**) with H_2O_2 demonstrates a different mechanism for redox-neutral-at-metal cleavage of M–C bonds. Treatment of MTO with oxidants such as H_2O_2 and IO_4^- results in Re–C bond oxidation to liberate MeOH (Scheme 9).[18] Computational investigation of the mechanism of oxidative cleavage in d^0 MTO has revealed that oxidation proceeds by an organometallic Baeyer–Villiger-type mechanism, in which two-electron oxidation of the Re–C bond proceeds without metal-centered redox. In proposed transition state **31**, methyl migration and IO_3^- expulsion proceed simultaneously.



Scheme 9 Oxidation of the Re–C bond in methyl trioxorhenium (**29**) is suggested to proceed via a Baeyer–Villiger-type reaction mechanism without redox chemistry at the Re center.

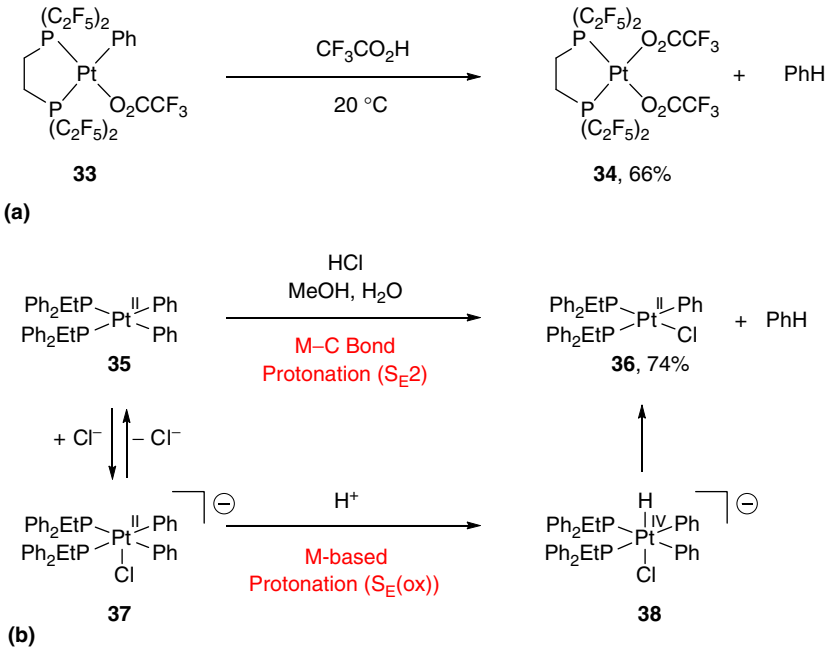
7.23.2.3 Oxidative Functionalization of M–C Bonds with Valence d-Electrons

Oxidative functionalization of M–C bonds in organometallic complexes with partially filled d-orbital manifolds present potential mechanistic complexity that is not present in the oxidative cleavage of main-group M–C bonds. Although oxidation can still proceed via direct interaction of an oxidant with the M–C σ-bonding orbital, it can also potentially proceed via initial metal-centered oxidation (Scheme 10). For example, oxidation of a generic aryl Pd(II) complex could proceed via direct substitution of the M–C σ-bond (S_E2 pathway) or by metal-based oxidation to afford a higher-valent metal complex, such as a mononuclear Pd(IV) complex, as an oxidation intermediate (S_E(ox) pathway). The nature of the oxidized intermediate will be discussed in greater detail in Sections 7.23.3.1 and 7.23.3.2.



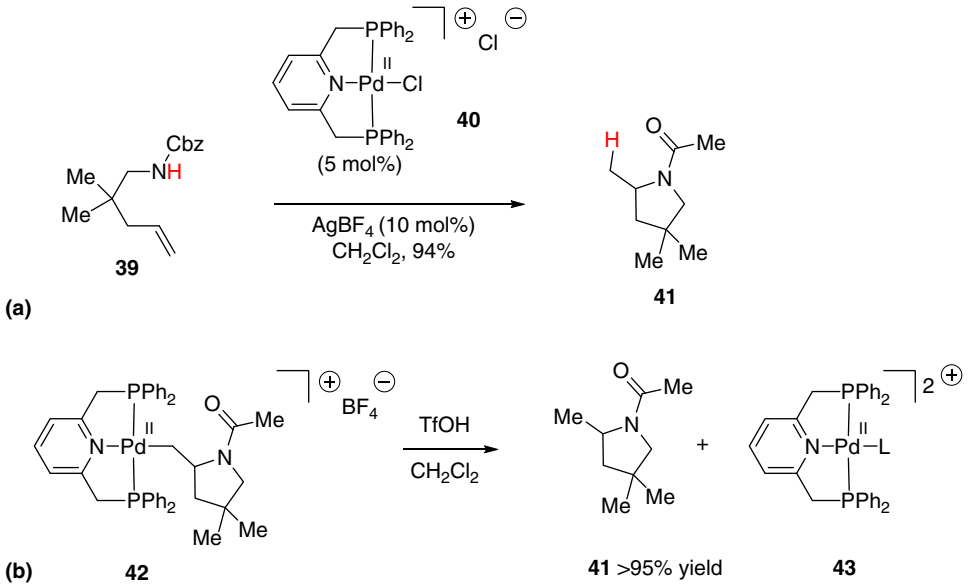
Scheme 10 Oxidative M–C bond functionalization of organopalladium(II) complexes can proceed by either direct electrophilic substitution (S_E2) or an oxidation-reductive elimination sequence (S_E(ox)).

Due to the relevance of Pt–C bond protonation as the microscopic reverse of C–H platination, significant effort has been directed toward the study of Pt–C protonation mechanisms.[19] Depending on the complex in question, both S_E2 and S_E(ox) pathways have been implicated in these studies. Protonation of Pt(II) aryl complex **33**, supported by an electron-deficient bidentate phosphine ligand, is proposed to proceed via S_E2 chemistry.[19d] Large kinetic isotope effects ($k_H/k_D \approx 7$) have been reported for protonation reactions and have been interpreted as consistent with S_E2 reaction pathways (Scheme 11(a)).[20] In other cases, competition between S_E2 and S_E(ox) pathways has been observed; for example, in the protonation of Pt(II) complex **35**, a two-term rate law – rate $= k\,[35]\,[H^+] + k'\,[35]\,[H^+]\,[Cl^-]$ – was observed, which suggests that both S_E2 and S_E(ox) pathways are operative (Scheme 11(b)).[19c,21] The observation of halide ion dependence has been used as an indicator of S_E(ox) pathways because an expanded valence is required to accommodate the additional ligand.[21]



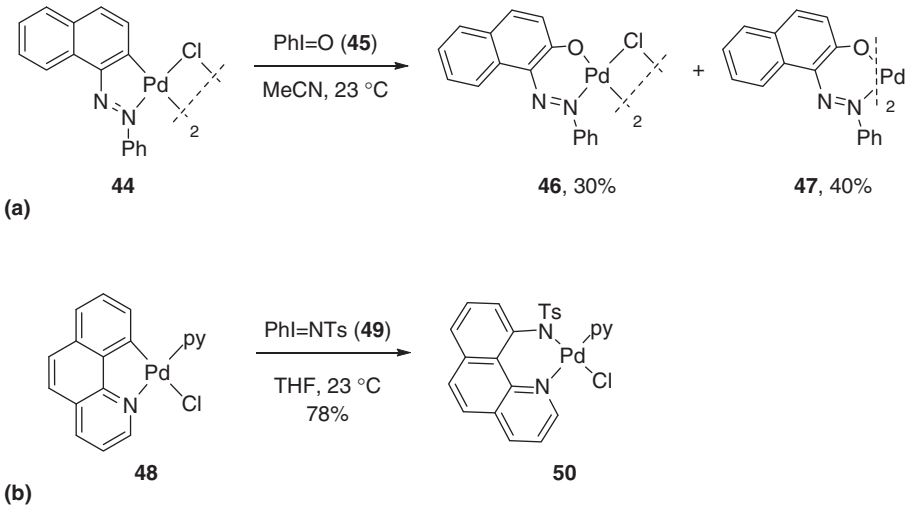
Scheme 11 (a) Protonation of Pt(II) complex **33** has been proposed to proceed via direct Pt–C σ-bond protonation (S_E2). (b) The reaction of Pt(II) complex **35** with HCl to afford Pt(II) complex **36** and PhH has been shown to proceed via two pathways, with both S_E2 and $S_E(ox)$ reaction pathways occurring in parallel.

Although protonation of organopalladium(II) intermediates is an important step in a variety of Pd-catalyzed reactions, compared with the protonation chemistry of organoplatinum complexes, the mechanisms of protonation reactions of organopalladium complexes are less well described. For example, the turnover-limiting step of hydroamination of terminal olefins catalyzed by cationic Pd pincer complex **40** is proposed to be the protonation of Pd(II) alkyl complex **42** (Scheme 12).[22] In part because no intermediates were observed on treatment of **42** with TfOH at low temperature, the authors proposed that protonation of complex **42** proceeds via an S_E2 pathway, without the intermediacy of a Pd(IV) hydride. Based on the available evidence, an alternative $S_E(ox)$ pathway, with rate-determining metal-centered protonation followed by fast C–H reductive elimination, could not be excluded.



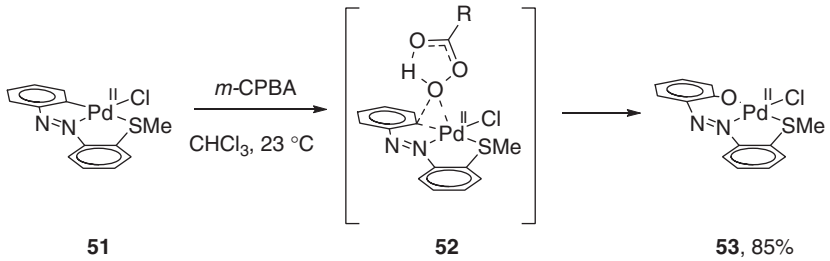
Scheme 12 (a) Cationic Pd(II) complex **40** has been developed as a catalyst for hydroamination of olefins. (b) The turnover-limiting step in catalysis is proposed to be the protonation of organopalladium intermediate **42**, which is proposed to proceed via an S_E2 mechanism (L = **41**).

Oxygen and nitrogen atom-transfer reactions to organometallic complexes can result in formal insertion of the heteroatom into the M–C bond.[23,24] Treatment of organopalladium(II) complex **44** with iodosylbenzene (**45**), for example, results in oxygen-atom insertion into the Pd–C bond to afford the new palladacycles **46** and **47** (Scheme 13(a)).[23a] Similarly, treatment of cyclometallated Pd(II) complex **48** with PhI=NTs (**49**) affords Pd(II) sulfonamide complex **50** (Scheme 13(b)).[23b]



Scheme 13 (a) Treatment of organopalladium(II) complex **44** with iodosylbenzene (**45**) affords complexes **46** and **47**, in which an oxygen atom has been inserted into the Pd–C bond. (b) Treatment of palladacycle **48** with PhI=NTs (**49**) affords **50**, the product of formal nitrene insertion.

Similar to the protonation chemistry discussed in Schemes 11 and 12, both direct insertion reactions via 3-membered transition states with no redox change at the metal center (S_E2 pathways) and S_E(ox) pathways have been discussed to account for the observed chemistry, and the precise mechanism of insertion has not yet been generally resolved. Direct electrophilic substitution via transition state **52** has been proposed for the oxidation of **51** with *m*-CPBA based on both rate law and the large negative entropy of activation (−47±5 e.u.) of oxidation (Scheme 14).[24] The available data are also consistent with a metal-centered oxidation pathway.

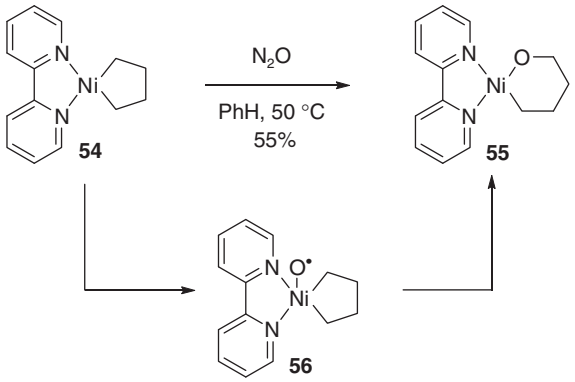


Scheme 14 Oxidation of Pd(II) complex **51** with *m*-CPBA has been proposed to proceed via transition state **52**, in which the oxygen-atom insertion proceeds without redox chemistry at the metal center.

Oxygen-atom insertion into an Ni–C bond of dialkylNi(II) complex **54** has been observed to result from treatment with N_2O (Scheme 15).[25] Conceptually, the observed Ni–C cleavage chemistry could proceed by direct Ni–C bond oxidation via an S_E2 transition state or with metal-centered redox chemistry. Investigation of the insertion by DFT computations has led to the suggestion that a variant of S_E(ox) chemistry, via an Ni(III) oxyl radical intermediate (**56**), is operative. The C–O bond-forming step in this reaction has been suggested to proceed by migration of one of the alkyl ligands to the pendant oxyl radical ligand (Scheme 15).

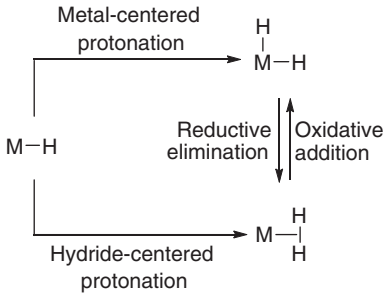
7.23.2.4 Comparison of Hydridic and Carbanionic Ligands in Protonation Reactions

Although three-centered transition states in which no metal-centered redox chemistry is involved are proposed for some electrophilic substitution reactions of M–C bonds, in many cases, metal-centered redox chemistry is operative (*vide infra*). In contrast, protonation of metal hydrides (M–H), which is an important step in the reduction of protons to H_2, generally proceeds with



Scheme 15 Oxygen-atom insertion into an Ni–C bond in **54** has been proposed to proceed via Ni(III) oxyl radical intermediate **56**.

ligand-centered protonation.[26] Metal-centered protonation of metal hydrides affords dihydride complexes whereas ligand-centered protonation of metal hydrides affords dihydrogen complexes (Scheme 16).



Scheme 16 Protonation of metal hydride complexes can proceed via protonation at either the metal center or the hydride ligand. Protonation at metal affords metal dihydrides as the initial products of protonation, whereas protonation of the hydride ligand affords dihydrogen complexes. Metal dihydrides and dihydrogen complexes can interconvert by oxidative addition or reductive elimination reactions, which complicates the assignment of reaction mechanism.

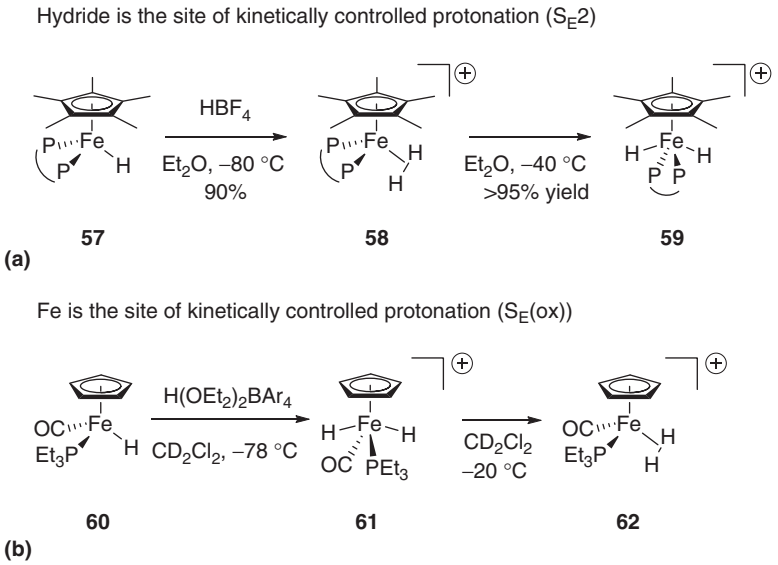
Identification of the protonation site is complicated by interconversion of dihydrogen and dihydride complexes via oxidative addition and reductive elimination reactions, which are frequently facile (Scheme 16).[26] In addition, evolution of H_2 from dihydrogen complexes complicates interrogation of the product of protonation of metal hydride complexes.[27,28] Ligand- versus metal-centered protonation mechanisms have been differentiated in reactions in which the kinetic and thermodynamic products of protonation are distinct chemical species. Protonation of Fe hydride complex **57** at $-80\ ^{\circ}C$ led to observation of dihydrogen complex **58**, which, on warming, evolved to dihydride complex **59** (Scheme 17(a)).[29] In this reaction, the dihydrogen adduct **58** (product of S_E2 protonation) is the kinetic product whereas dihydride complex **59** is the thermodynamically preferred product. In contrast, protonation of Fe(II) hydride **60** with $H(OEt_2)_2BAr_4$ at $-78\ ^{\circ}C$ proceeds with initial metal-centered redox chemistry to afford Fe(IV) dihydride **61** (Ar = 3,5-*bis*-trifluoromethylphenyl; Scheme 17(b)).[30] Subsequent reductive elimination of dihydrogen affords cationic Fe(II) dihydrogen complex **62**. The difference in protonation site between **57** and **60** demonstrates that relatively minor perturbations of the ligand field of the transition metal complex can have a significant effect on the mechanism that is operative in oxidative cleavage of M–L bonds.

The tendency for protonation of metal hydride complexes to proceed at the hydride ligand has been proposed to be due to minimization of electronic reorganization energy.[31] In addition, electrophilic attack at hydride ligands is not encumbered by steric effects that are present during protonation of M–C bonds.

7.23.3 Electrophilic Cleavage of M–C Bonds via Two-Electron, Metal-Centered Redox

7.23.3.1 Mononuclear S_E(ox) Reactions

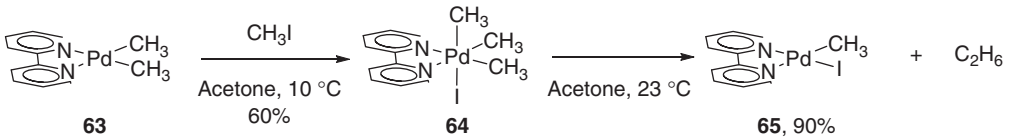
In the preceding sections, M–C bond oxidation reactions in which oxidation proceeds at the ligand (S_E2) have been discussed. Oxidative functionalization reactions of M–C bonds can also proceed by initial M-centered redox chemistry (i.e., Scheme 2(b) and (c)). Two-electron, metal-centered oxidation of Pd(II) organometallics affords mononuclear Pd(IV) complexes, which can participate in C–X bond-forming reductive elimination chemistry to afford the product of M–C bond oxidation as well as Pd(II).



Scheme 17 (a) Protonation of Fe(II) hydride **57** at −80 °C affords dihydrogen complex **58** as the kinetic product of protonation. Subsequent isomerization of **58** on warming affords Fe(IV) dihydride complex **59**, as the thermodynamic product of oxidation (bidentate phosphine = dppe). (b) Protonation of Fe(II) hydride **60** occurs via protonation of the metal center to afford Fe(IV) dihydride **61**. Subsequent warming leads to the formation of Fe(II) dihydrogen complex **62**, the thermodynamic product of protonation (Ar = 3,5-*bis*-trifluoromethylphenyl).

Two-electron, S_E(ox) pathways were briefly introduced in the above discussion of protonation chemistry (Section 7.23.2.4), but will be more fully discussed in Scheme 16.

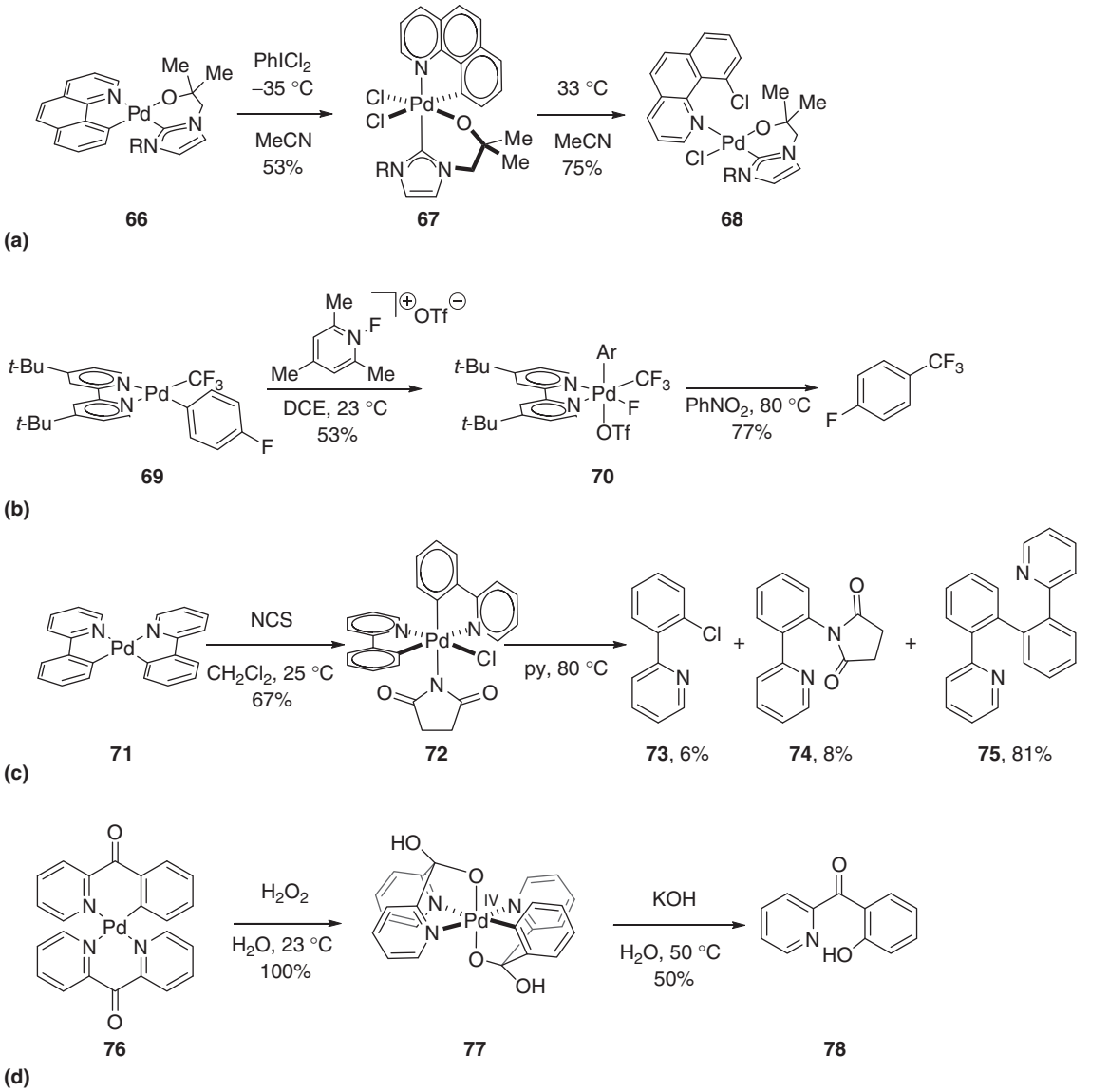
Organopalladium(IV) complexes were first prepared in 1975; however, these early complexes were not reported to participate in reductive elimination chemistry, which is required for product release in an S_E(ox) reaction pathway.[32] In 1986, Canty and co-workers reported that treatment of dimethyl Pd(II) complex **63** with CH_3I afforded mononuclear Pd(IV) complex **64**, which was characterized by X-ray crystallography (Scheme 18).[33] On warming to 23 °C, Pd(IV) complex **64** evolved ethane, as well as mononuclear Pd(II) complex **65**. The observation of ethane elimination from complex **64** was the first report of organometallic chemistry originating from a well-defined mononuclear Pd(IV) compound, and the sequence of **63** → **64** → **65** was the first demonstration of S_E(ox) pathways from Pd(II) complexes.[33,34]



Scheme 18 Oxidation of dimethyl Pd(II) complex **63** with MeI affords mononuclear Pd(IV) complex **64**, which on warming participates in reductive elimination of ethane to afford Pd(II) methyl iodide complex **65**. Elimination of ethane from mononuclear Pd(IV) complex **64** was the first report of reductive elimination from a characterized Pd(IV) complex.

Since the original report of C–C reductive elimination from mononuclear Pd(IV) complexes, a wide variety of C–C and C–heteroatom reductive elimination reactions have been documented from isolated mononuclear Pd(IV) complexes. C–X reductive elimination chemistry from well-defined Pd(IV) complexes has been pioneered by Sanford and co-workers. The chelating alkoxycarbene ligand that supports Pd(IV) dichloride **66** has been used to demonstrate the potential for carbenes to support Pd(IV) centers while allowing C–Cl reductive elimination to be observed (Scheme 19(a)).[35] *N*-fluoropyridinium salts have been demonstrated to be competent oxidants for the preparation of Pd(IV) fluoride complexes, such as **70** (Scheme 19(b)).[36] C–CF_3 reductive elimination from **70** is observed in preference to potential C–F reductive elimination. In other cases, such as Pd(IV) chloride **72**, multiple reductive elimination reactions are observed from a given Pd(IV) complex; C–C, C–N, and C–Cl reductive elimination products have all been observed from Pd(IV) complex **72** (Scheme 19(c)).[37] Verdernikov and co-workers have reported the synthesis of Pd(IV) complex **77** by oxidation of mononuclear Pd(II) complex **76** with H_2O_2 and have shown that complex **77** participates in C–OH reductive elimination to afford phenol **78** (Scheme 19(d)).[38]

Following oxidation to Pd(IV), C–C or C–X reductive elimination affords the organic fragment of M–C bond cleavage, as well as a Pd(II) fragment. A variety of mechanisms are potentially available for reductive elimination. For example, direct reductive elimination from a hexacoordinate octahedral complex, such as C–H reductive elimination from Pt(IV) complex **79** (Scheme 20(a)), is possible.[39] Although C–H reductive elimination from octahedral metal complexes has been proposed in some

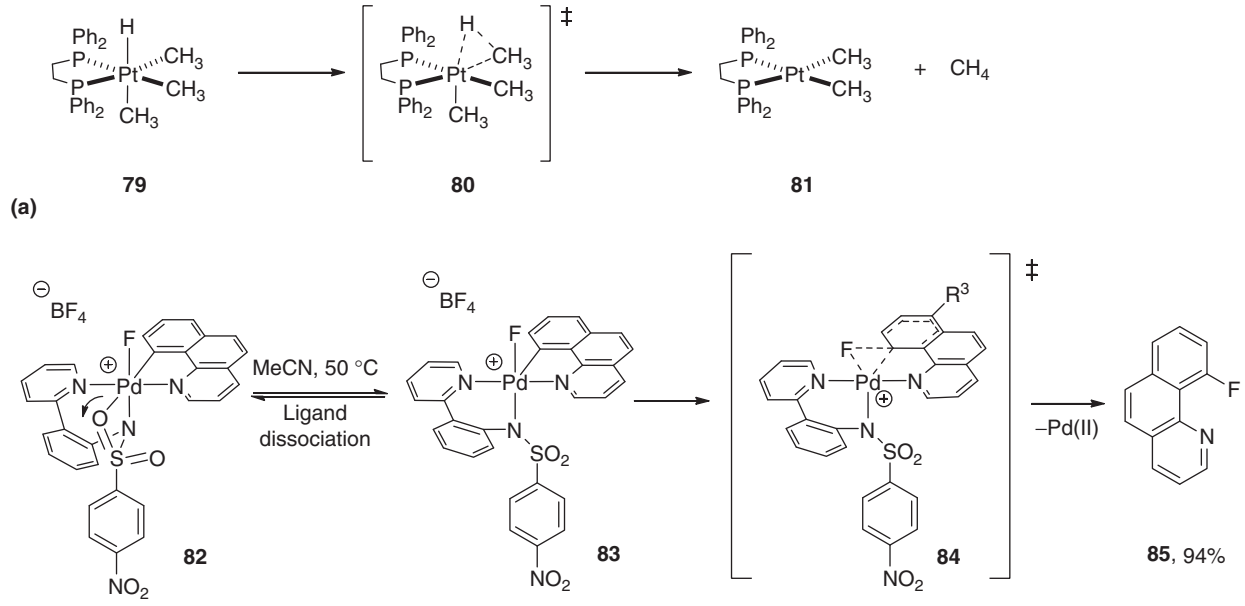


Scheme 19 Many mononuclear Pd(IV) complexes have been isolated by oxidation of organopalladium(II) complexes with external oxidants. A variety of C–X bond-forming reductive elimination reactions, such as C–Cl (a), C–CF_3 (b), C–Cl, C–N, and C–C (c), and C–O (d) bond-forming reactions, have been identified from these complexes.

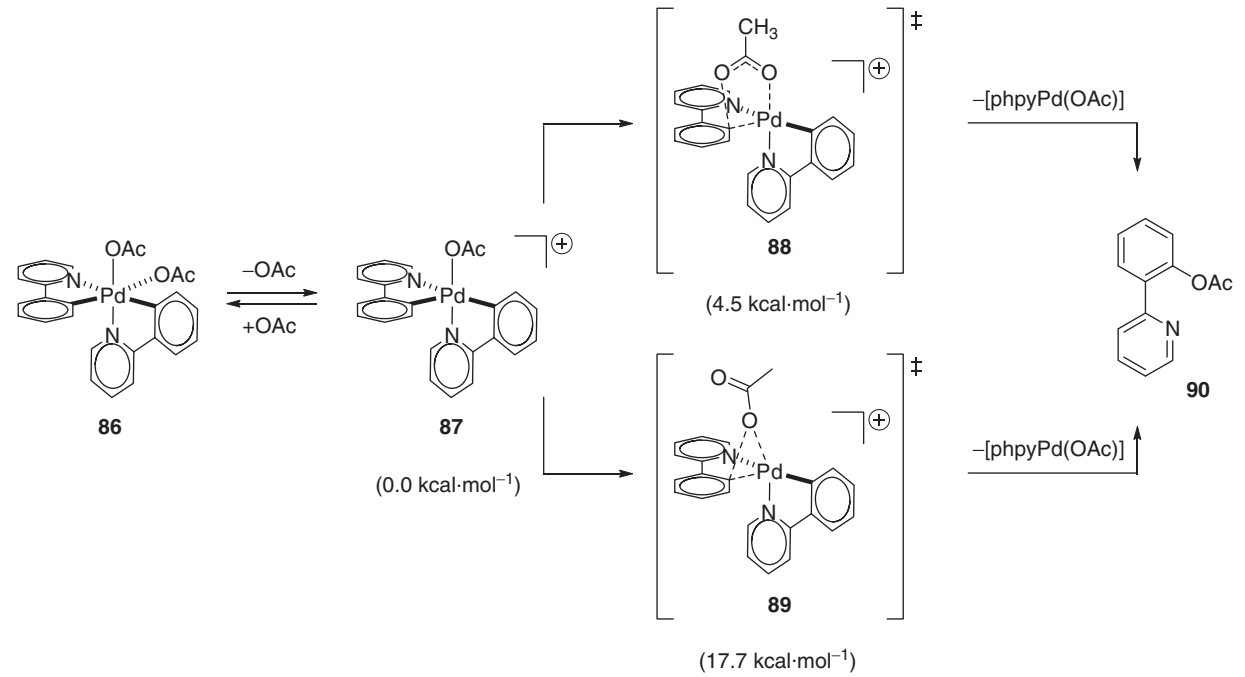
cases, more commonly, ligand dissociation to afford a pentacoordinate intermediate precedes reductive elimination via three-centered, distorted trigonal-bipyramidal transition states.[40] An example of a three-centered transition state for reductive elimination from a pentacoordinate Pd(IV) center can be seen in C–F reductive elimination from Pd(IV) fluoride complex **82**, in which dissociation of a sulfonamide oxygen ligand affords a pentacoordinate Pd(IV) intermediate from which reductive elimination proceeds.[41]

Reductive elimination from pentacoordinate Pd(IV) intermediates need not proceed via a three-centered transition state.[42] Based on DFT calculations, C–O reductive elimination from Pd(IV) acetate complex **86** was proposed to proceed by transition state **88**, in which the carbonyl oxygen, not the Pd-bound oxygen, participates in C–O bond formation (**Scheme 21**). Transition state **88** was calculated to be 13.2 kcal · mol^{-1} lower in energy than three-centered transition state **89**. C–OAc reductive elimination transition states were also computed for reductive elimination reactions from Pd(II) and binuclear Pd(III) complexes, and in each case, participation of the carbonyl oxygen in C–O bond-forming reductive elimination was preferred over reductive elimination of the Pd-bound oxygen.

Alternatively, C–X bond-forming reductive elimination can proceed via an S_N2-like mechanism, in which one of the ligands dissociates from the metal center to afford a cationic, pentacoordinate Pd(IV) followed by nucleophilic attack of the dissociated ligand onto the M–C bond. Goldberg and co-workers have demonstrated that S_N2-like mechanisms are operative in C–I,[43] C–O,[44]



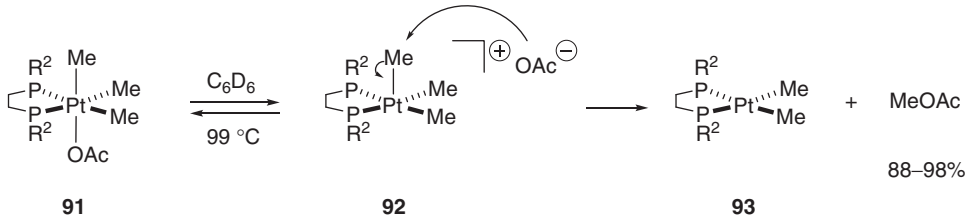
Scheme 20 (a) Direct three-centered transition states for C–H reductive elimination from hexacoordinate Pt(IV) complexes have been supported in some reactions by both theory and experiment. (b) More common than reductive elimination from hexacoordinate, octahedral complexes, is reductive elimination from pentacoordinate intermediates following dissociation of a ligand, as is demonstrated in C–F reductive elimination from Pd(IV) fluoride **82**.



Scheme 21 Based on DFT calculations, transition state **88**, in which the carbonyl oxygen of the acetate ligand participates in C–O bond-forming reductive elimination, is preferred over a three-centered transition state in which the Pd-bound oxygen participates in C–O reductive elimination (phpy = 2-phenylpyridyl).

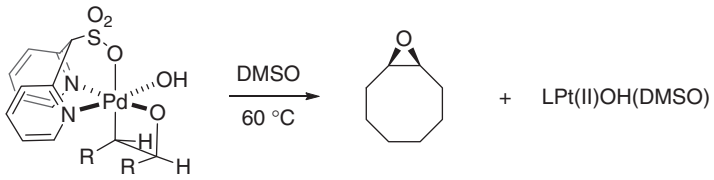
and C–N,[45] reductive elimination reactions from Pt(IV) complexes supported by bidentate phosphine ligands, as seen in the reductive elimination of methyl acetate from mononuclear Pt(IV) complex **91** (Scheme 22).

Although many C–X reductive elimination reactions from mononuclear Pt(IV) complexes proceed via S_N2-like transition states, examples of concerted, three-centered transition states are also known. For example, experimental and computational



Scheme 22 C–OAc reductive elimination from Pt(IV) complex **91** has been proposed to proceed via an S_N2-like pathway, in which the C–OAc bond is formed by nucleophilic attack of dissociated acetate on the Pt–C bond of cationic, pentacoordinate Pt(IV) intermediate **92**.

results regarding the elimination of epoxides from metallooxetanes, such as Pt(IV) complex 94, are consistent with a three-centered reductive elimination transition state (Scheme 23).[46]



Scheme 23 Reductive elimination of epoxide **95** from metallooxetane **94** has been proposed to proceed via a concerted three-membered transition state, not via S_N2-like chemistry (R = $-C_6H_{12}-$).

7.23.3.2 Binuclear S_E(ox) Reactions

In the M–C bond functionalization reactions discussed in Section 7.23.3.1, S_E(ox) mechanisms proceed via initial two-electron oxidation of a single metal center to afford an oxidized, mononuclear intermediate, which subsequently participates in C–X bond-forming reductive elimination. In principle, the two electrons of redox chemistry need not be localized at a single metal center, but instead could be shared among two, or more, metal centers.

Oxidation of polynuclear complexes, in which oxidation is shared among multiple metal centers, has been observed with a wide variety of metals.[47] Binuclear Pd(III) complexes are, in principle, binuclear analogs of mononuclear Pd(IV) S_E(ox) intermediates. Oxidation of binuclear Pd(II) complexes by either one or two electrons has been known since 1988,[48] and a small, but growing, number of binuclear Pd(III) complexes have been characterized (Scheme 24).[49] Although early examples of binuclear Pd(III) complexes provided structural information regarding Pd–Pd bonding, organometallic transformations were not observed from these complexes. The lack of reactivity from structures such as 99 may be due to the orientation of the aryl ligand, which is held in a bridging position, and thus the π-face is inaccessible to the apical ligand for potential C–X bond-forming reductive elimination.

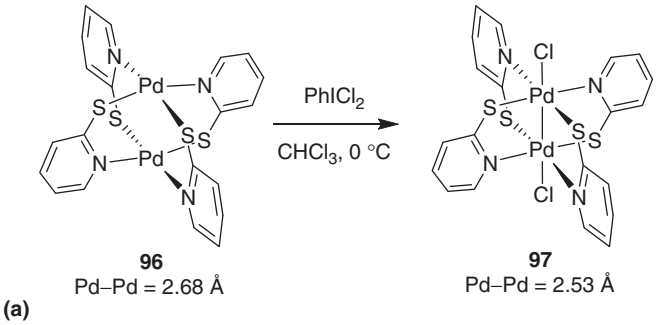
Binuclear S_E(ox) reaction pathways were demonstrated for C–Cl bond-forming reactions in 2009.[50] Oxidation of binuclear Pd(II) complex **101** with $PhICl_2$ affords binuclear Pd(III) complex **102**, which on warming undergoes C–Cl reductive elimination to generate **103** and Pd(II)-containing products (Scheme 25).[50a] Experimental and theoretical investigations of the mechanism of C–Cl bond formation are consistent with reductive elimination proceedings without cleavage of the binuclear core.[51] These observations constituted the first examples of organometallic transformations from isolated Pd(III) complexes, and were the first observations of C–heteroatom bond-forming reductive elimination from a binuclear transition metal complex.

7.23.3.3 Difference Between Mono- and Bimetallic S_E(ox) Pathways

7.23.3.3.1 M–M interactions during oxidation

It is interesting to consider potential roles for the binuclear core during oxidative M–C bond cleavage: What effect does a second metal have on the metal-centered redox chemistry during oxidative M–C bond functionalization? Recent studies of $Pd(OAc)_2$-catalyzed C–H arylation[52] and chlorination[53] reactions have implicated binuclear intermediates in redox chemistry (Scheme 26). It is interesting to note that, although the resting state of the arylation catalyst is a mononuclear Pd(II) complex, which in principle could undergo direct oxidation to afford mononuclear Pd(IV) intermediates, binuclear oxidation intermediates are implicated by kinetics measurements.

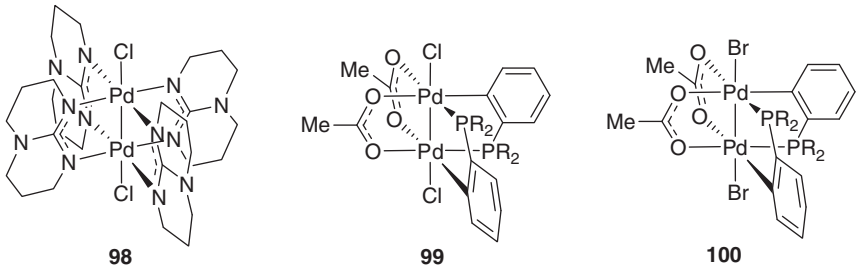
Mixing of $4d_{z^2}$ orbital of each Pd center results from the ligand-enforced proximity of two metal centers, and gives rise to an M–M molecular orbital manifold featuring both an M–M σ-bonding orbital and a σ^* antibonding orbital, which is raised in energy relative to the parent $4d_{z^2}$ orbital (Scheme 27).[47] Removing electrons from the HOMO of a binuclear complex should



96
Pd–Pd = 2.68 Å

97
Pd–Pd = 2.53 Å

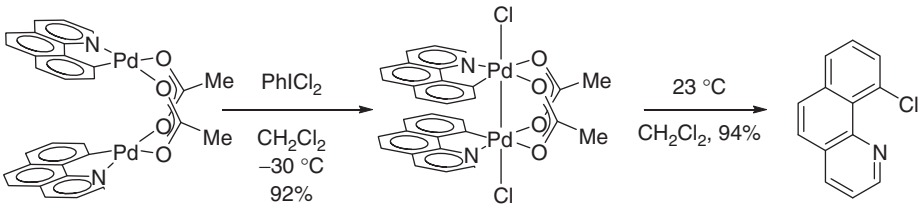
(a)



98 **99** **100**

(b)

Scheme 24 (a) Treatment of tetra-bridged binuclear Pd(II) complex **96** with $PhICl_2$ affords binuclear Pd(III) complex **97**. (b) Tetra-bridged binuclear Pd(III) complexes **98–100** were prepared by oxidation similar to the reaction in (a). C–X reductive elimination of the apical ligands and the bridging arylphosphines was not reported (R = Ph).



101
Pd-Pd: 2.84 Å

102
Pd-Pd: 2.57 Å

103

Scheme 25 Oxidation of binuclear Pd(II) complex **101** with $PhICl_2$ affords binuclear Pd(III) complex **102**. Thermolysis of **102** affords **103** and Pd(II)-containing products, the products of C–Cl reductive elimination. The sequence of **101** → **102** → **103** demonstrates $S_E(ox)$ chemistry of binuclear transition metal complexes.

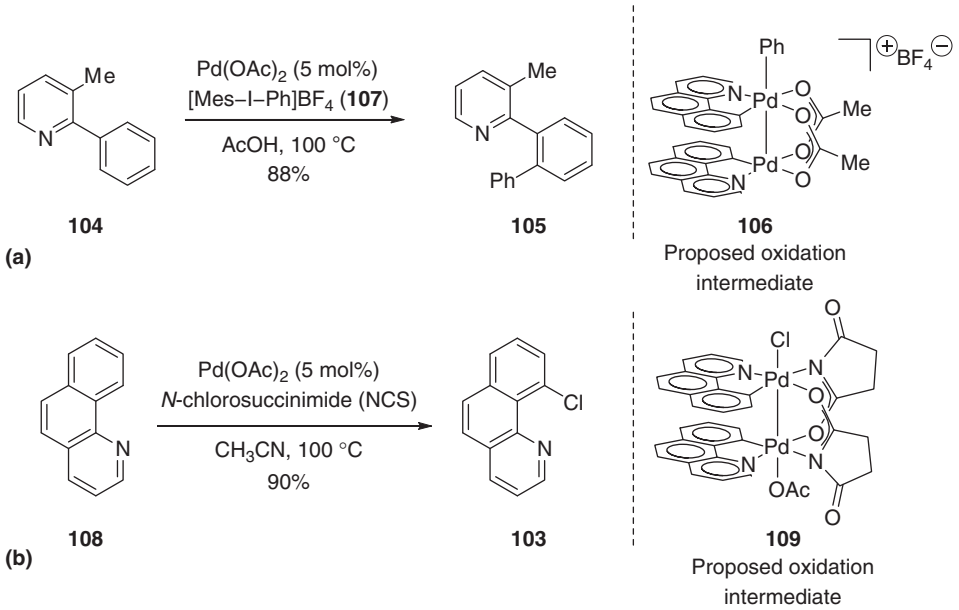
therefore be more facile than oxidation of a mononuclear complex.[48] In addition, nascent Pd–Pd bonding interactions in the transition state of oxidation could lower the activation barrier to oxidation.

7.23.3.3.2 Role of M–M interactions during reductive elimination

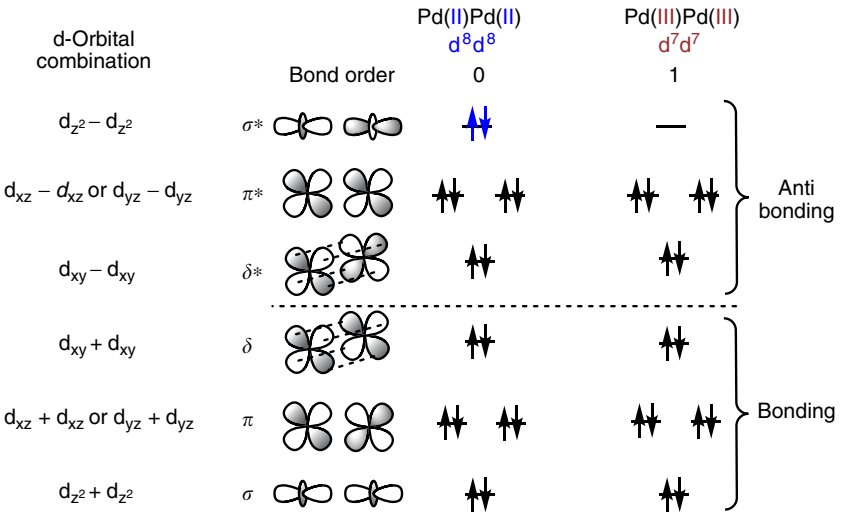
The role of the binuclear Pd core of **102** in C–Cl reductive elimination was investigated by examination of the barrier to reductive elimination as a function of Pd–Pd distance.[51] Computationally forced elongation of the Pd–Pd bond attenuates the overlap of the $4d_{z^2}$ orbitals and thus decreases electronic communication between the metals as compared to low-energy structure **A** (equation in Scheme 28). Elongation of the Pd–Pd bond of **A** results in monotonic increase in the reductive elimination activation barrier, consistent with Pd–Pd cooperation facilitating reductive elimination. The facilitating effect of the binuclear core of **102** on reductive elimination has been rationalized as due to either the strong *trans* influence of the M–M bond[54] on the apical ligand during reductive elimination, or the ability to delocalize charge during reductive elimination from the binuclear core to avoid high-energy intermediates.[55]

7.23.3.4 Oxidative M–C Bond Cleavage by M–M Cleavage

During efforts to understand the generality of binuclear $S_E(ox)$ pathways in Pd-catalyzed C–H oxidation reactions, the chemistry of binuclear Pd(II) complex **101** with electrophilic trifluoromethylating reagent **113** has been explored.[56] Unlike the oxidation of **101** with $PhICl_2$, which affords binuclear Pd(III) complex **102**, oxidation with **113** affords mononuclear Pd(IV) complex **111**



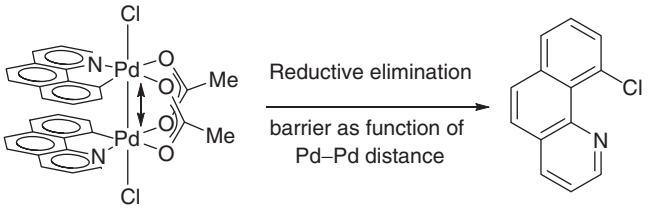
Scheme 26 During studies of the mechanisms of $Pd(OAc)_2$-catalyzed C–H arylation (a) and chlorination (b) reactions, binuclear intermediates (i.e. **106** and **109**) have been implicated in oxidation.



Scheme 27 Molecular orbital diagram for M–M bonding based on mixing of d-orbitals only. Mixing of the $4d_{z^2}$ orbitals provides both σ-bonding and σ-antibonding orbital. The σ^* orbital is destabilized as compared to a mononuclear parent complex, which can lower the oxidation potential of a binuclear complex.

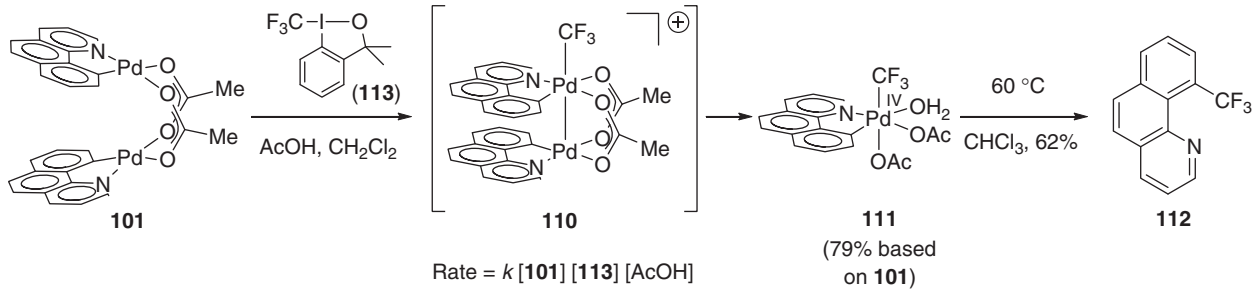
(Scheme 29). Examination of the reaction kinetics of oxidation of binuclear Pd(II) complex **101** to afford mononuclear Pd(IV) complex **113** revealed that oxidation is rate-determining, and that oxidation proceeds from binuclear Pd(II) complex without fragmentation.[57] The experimentally determined rate law suggests binuclear Pd(III) cation **110** as the initial product of oxidation and suggests that mononuclear Pd(IV) complex is formed by formal Pd–Pd heterolysis from **110**. DFT calculations indicate that fragmentation pathways from **110** proceed through lower activation barriers than potential C–CF_3 reductive elimination from **110**. Prolonged heating of **111** does afford **112**, the product of C–CF_3 reductive elimination, but the available experimental data do not allow the identity of the complex from which this reductive elimination proceeds to be elucidated.[57]

The ligand-dependent reactivity observed for **102** and **110** has been rationalized by examining the effect of apical ligand identity on the $4d_{z^2}$ orbital population.[58] As the $4d_{z^2}$ is predominantly responsible for Pd–Pd bonding, population of this orbital is likely important for Pd–Pd cleavage. DFT calculations revealed a correlation between the σ-donating strength of the apical



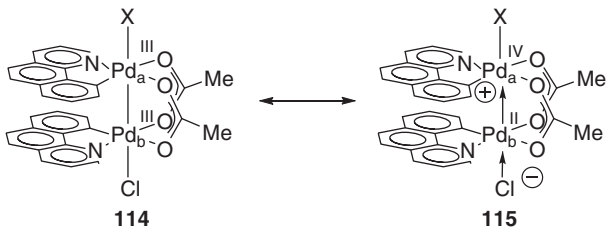
Pd–Pd Distance (Å)	Ground State Energy [kcal·mol^{-1}]	Activation Energy [kcal·mol^{-1}] relative to A
2.62	0.0 (A)	17.1
2.95	6.2	21.8
3.30	20.5	33.3
3.65	35.3	46.0

Scheme 28 The activation barrier to C–Cl reductive elimination from **102** (**A**) increases as the Pd–Pd distance is elongated.



Scheme 29 Oxidation of binuclear Pd(II) complex **101** to mononuclear Pd(IV) complex **111** proceeds via initial oxidation to binuclear Pd(III) cation **110** followed by Pd–Pd heterolysis.

ligand and $4d_{z^2}$ population (Scheme 30). Based on the computed $4d_{z^2}$ orbital population, and the effect of apical ligand identity on the heterolytic Pd–Cl dissociation energy, it was proposed that binuclear Pd(III) complexes bearing a strongly σ-donating apical ligand should be formulated as mixed-valence Pd_2(II,IV) dimers.

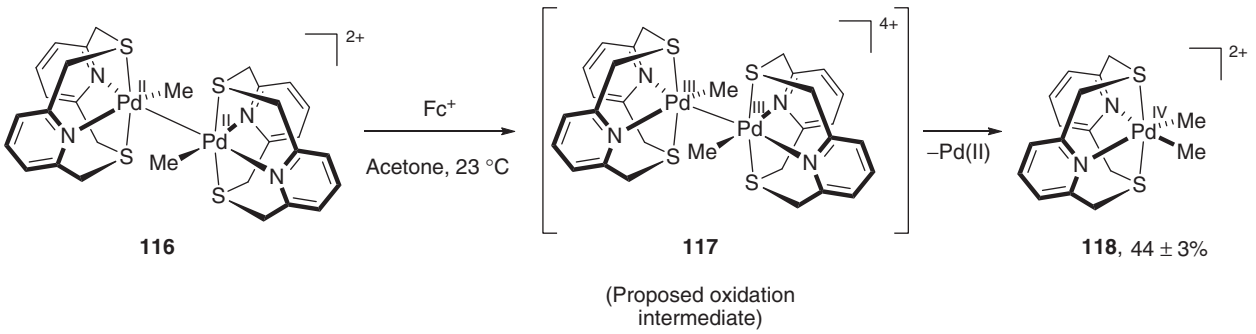


Scheme 30 DFT calculations have shown a positive correlation between the sigma-donating ability of apical ligands on Pd_a and population of the $4d_{z^2}$ orbital of Pd_b. These data suggest that increasingly sigma-donating ligands favor a mixed-valence Pd_2(II,IV) electronic structure over valence symmetric binuclear Pd(III) formulations.

Pd–Pd cleavage has also been proposed as operative in the oxidation of Pd(II) complex **116** to Pd(IV) complex **118** (Scheme 31).[59,60] Pd(II) complex **116** shows unusually strong Pd–Pd interaction for a binuclear Pd(II) complex, which was the basis of the suggestion of Pd–Pd bond formation on oxidation.

7.23.4 Electrophilic Cleavage of M–C Bonds via One-Electron, Metal-Centered Redox

Although oxidative cleavage of M–C bonds to generate new C–C or C–X bonds is a two-electron transformation, electrophilic M–C bond cleavage can be initiated by one-electron, metal-centered oxidation. Such a reaction at organopalladium(II) complexes, for example, would be initiated by one-electron oxidation to generate a mononuclear Pd(III) complex, which would undergo subsequent chemistry to afford M–C bond oxidation products. Following one-electron oxidation of mononuclear Pd(II)

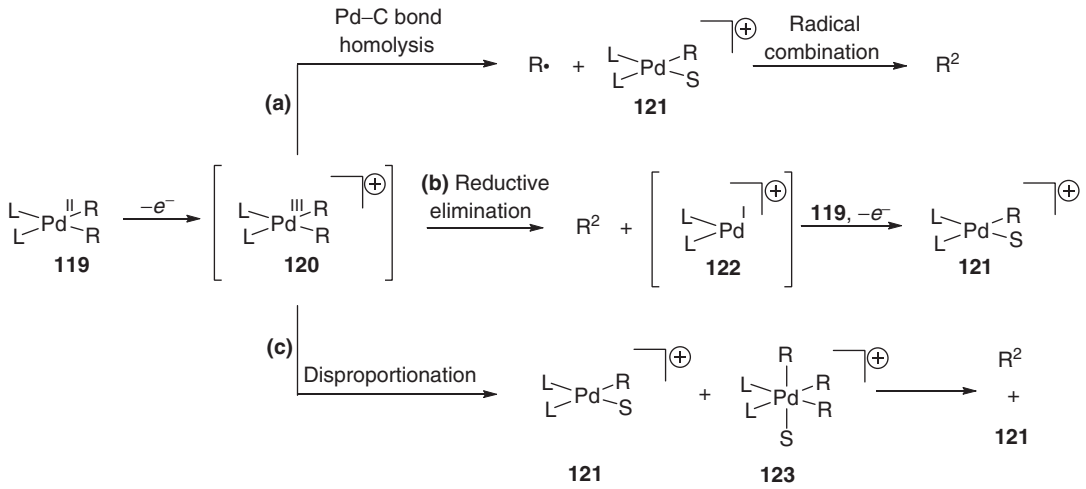


Scheme 31 Oxidation of binuclear Pd(II) complex **116** to mononuclear Pd(IV) complex **118** has been proposed to proceed via binuclear Pd(III) complex **117**.

complexes to afford mononuclear Pd(III) species, various reaction pathways could, in principle, lead to the formation of C–C and C–X bonds. Among the mechanisms that are available are:

1. Pd–C bond homolysis to generate an organic radical and a Pd(II) complex, with C–C or C–X bond formation occurring by subsequent radical coupling (Scheme 32(a));
2. Two-electron reductive elimination to generate the observed organic fragment and a Pd(I) intermediate, which would be subsequently oxidized to a Pd(II) complex (Scheme 32(b)); and
3. Disproportionation of two Pd(III) complexes to generate Pd(II) and Pd(IV) complexes, with bond-forming reductive elimination proceeding from the Pd(IV) complex (Scheme 32(c)).

In the following sections, reactions in which each of these pathways is proposed to be operative will be presented.

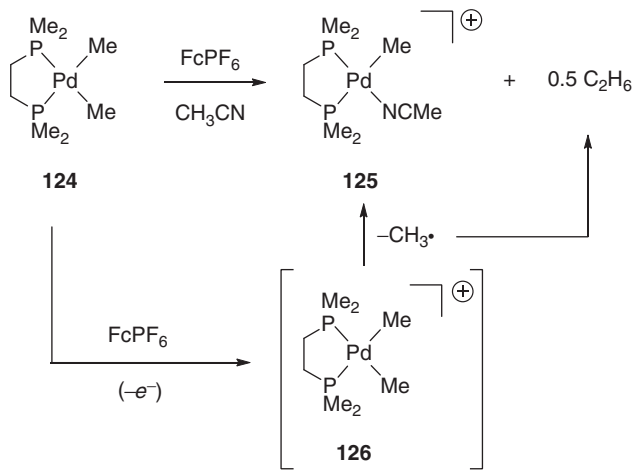


Scheme 32 Oxidative Pd–C bond functionalization can proceed via initial one-electron oxidation of mononuclear Pd(II) complexes to afford mononuclear Pd(III) complexes. Subsequent C–C or C–X bond formation can proceed via various mechanisms, including Pd–C bond homolysis to generate a Pd(II) complex and an alkyl radical, which subsequently participates in bond-forming chemistry (a), direct reductive elimination from the mononuclear Pd(III) complex to afford the observed organic fragment and a Pd(I) complex (b), or disproportionation of two mononuclear Pd(III) complexes to afford Pd(II) and Pd(IV) complexes, with subsequent bond-forming reductive elimination from the Pd(IV) complex (c).

7.23.4.1 M–C Homolysis Pathways for Oxidative M–C Bond Cleavage

One pathway for single-electron-oxidation-induced oxidative M–C bond functionalization is Pd–C bond homolysis from an initially formed Pd(III) intermediate to generate an organic radical and a Pd(II) fragment, followed by radical coupling chemistry. Reaction mechanisms based on Pd(III)–C bond homolysis have been proposed for both C–C and C–X bond-forming reactions.

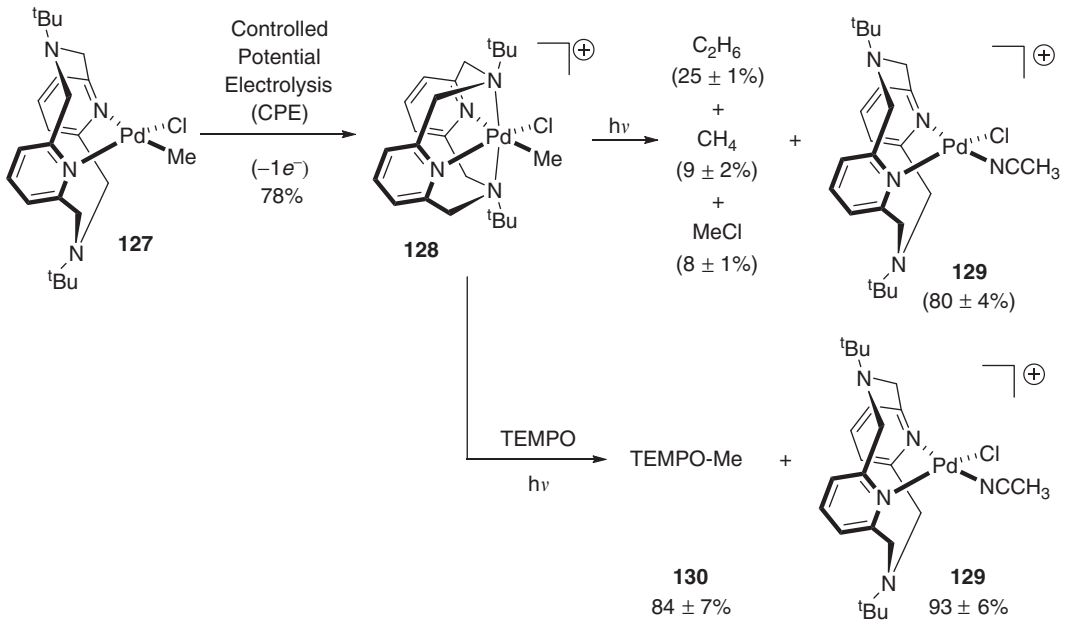
In 1992, Trogler and co-workers reported that treatment of dimethyl Pd(II) complex **124** with ferrocenium hexafluorophosphate ($FcPF_6$), a one-electron, outer-sphere oxidant, resulted in the liberation of ethane and the formation of cationic Pd(II) methyl complex **125** (Scheme 33).[61] Electrochemical measurements and bulk electrolysis of **124** revealed that the overall



Scheme 33 One-electron oxidation of dimethyl Pd(II) complex **124** affords monomethyl Pd(II) complex **125** and ethane. Formation of ethane has been proposed to arise from a sequence of initial oxidation of **124** to a dimethyl Pd(III) complex (**126**), homolytic cleavage of the Pd–C bond to generate **125** (after solvent coordination) and a methyl radical, and, finally, coupling of the methyl radicals.

transformation illustrated in Scheme 33 is a one-electron transformation. Furthermore, measurement of the reaction rate either as a function of applied electrolysis potential or as a function of redox potential of the chemical oxidant employed (by using variously substituted ferrocenium oxidants) revealed that the reaction proceeds via rate-determining, outer-sphere electron transfer. The observed reaction products were rationalized by a mechanism in which initial one-electron oxidation of **124** affords a mononuclear Pd(III) complex (**126**), from which homolytic Pd–C cleavage affords Pd(II) complex **125**, as well as methyl radicals, which subsequently couple to form the observed ethane. No Pd(III) intermediates were observed in these studies.

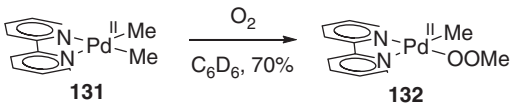
Mirica has reported organometallic transformations of isolated and well-defined mononuclear Pd(III) complexes (Scheme 34).[62] One-electron oxidation of mononuclear Pd(II) complex **127** afforded mononuclear Pd(III) complex **128**, stabilized by a chelating, tetradentate ligand. Photolysis of complex **128** affords methane, ethane, and methyl chloride, as well as Pd(II) complex **129**. The observed organic products are consistent with product expected of photochemical extrusion of methyl radical from complex **128**. Further evidence of this proposed pathway was obtained by carrying out the photolysis in the presence of TEMPO, as a radical trap. In this experiment, the only organic product that was observed was TEMPO-Me (**130**). The observed



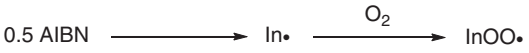
Scheme 34 One-electron oxidation of Pd(II) complex **127** affords mononuclear Pd(III) complex **128**. Photolysis of complex **128** affords a mixture of methane, ethane, and methyl chloride, as well as cationic Pd(II) complex **129**. Consistent with photochemical extrusion of methyl radical from **128**, photolysis in the presence of potential radical trap TEMPO affords only Pd(II) complex **129** and TEMPO-Me (**130**).

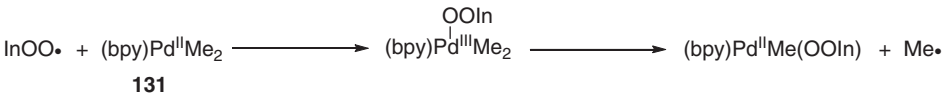
reactions of Pd(III) complex **128** represent the first M–C bond functionalizations that are initiated from isolable mononuclear Pd(III) complexes.

During a study of O_2 insertion into the Pd–C bond of dimethyl Pd(II) complex **131** in 2009, Goldberg and co-workers proposed mononuclear Pd(III) intermediates in a radical chain mechanism (Scheme 35).[63] In the proposed reaction manifold, which was supported by extensive reaction kinetics measurements, Pd–C bond homolysis from structure **132** affords Me•, which propagates the radical chain mechanism.

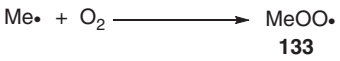


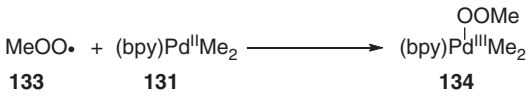
Initiation

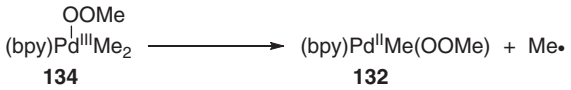




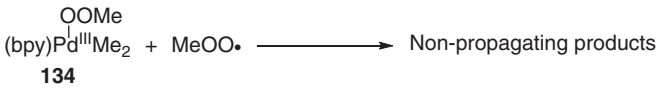
Propagation







Termination



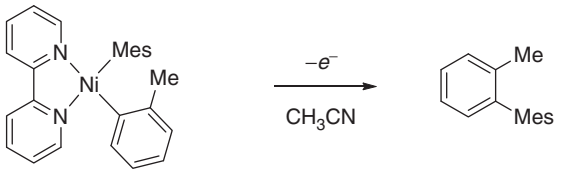
Scheme 35 Treatment of dimethyl Pd(II) complex **131** with O_2 leads to the formation of methyl peroxide **132**. Based on extensive measurements of reaction kinetics, a radical chain mechanism has been proposed in which methyl radical, the proposed radical chain carrier, is generated by Pd–C homolysis from an intermediate Pd(III) complex.

7.23.4.2 Two-Electron Reductive Elimination Pathways for Oxidative M–C Bond Cleavage

An alternative to the Pd(III)–C bond homolysis pathways described in Section 7.23.4.1 would be two-electron reductive elimination to generate a new organic fragment and a mononuclear Pd(I) complex. No well-defined Pd-based examples of this mechanism have been reported;[64] however, both C–C and C–X bond-forming reactions have been proposed to proceed via two-electron reductive elimination from a mononuclear Ni^{III} complex to afford a mononuclear Ni^{I} complex.[65]

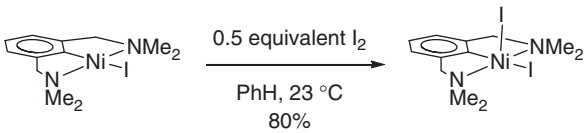
One-electron oxidation of Ni(II) diaryl complex **135** results in selective intramolecular ligand coupling to afford **136**, with no homocoupling products observed (Scheme 36).[65a,b] This observation has been rationalized by invoking a two-electron reductive elimination reaction from an initially formed Ni(III) complex without the intermediacy of organic radicals.

Seminal work by van Koten showed that organonickel(III) complexes are generated by oxidation of Ni(II) complexes with $CuBr_2$, and obtained X-ray crystallographic characterization of Ni(III) complex **141**, which was generated by oxidation of Ni(II) complex **137** with I_2 (Scheme 37(a)).[66] C–Br bond formation has been observed on oxidation of mononuclear Ni(II) complex **142** with Br_2, and has been proposed to proceed by reductive elimination from an Ni(III) intermediate (Scheme 37(b)).[65b,c,67]



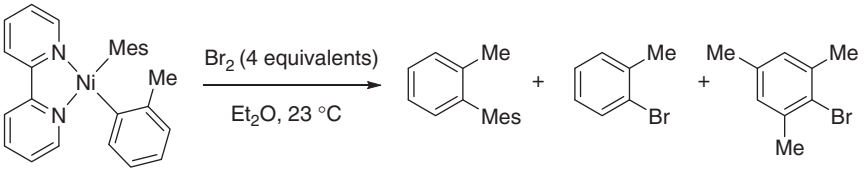
135 **136**

Scheme 36 One-electron oxidation of diaryl Ni(II) complex **135** results in the selective crosscoupling to afford biaryl **136**. No homocoupling products were observed, inconsistent with a radical-mediated reaction pathway.



137 **138**

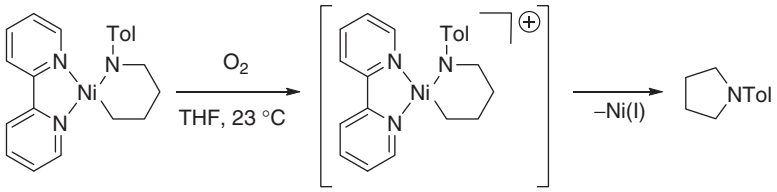
(a) X-ray, EPR



(b) **139** 30% 35% 35%

Scheme 37 (a) Treatment of *N,C,N*-pincer Ni(II) complex **137** with 0.5 equivalent of I_2 affords square pyramidal Ni(III) complex **138**, which has been characterized by both EPR and single-crystal X-ray diffraction. (b) The ratio of organic product obtained following treatment of **139** with Br_2 is invariant with $[Br_2]$, consistent with the intermediacy of an Ni(III) complex, from which C–Br reductive elimination proceeds.

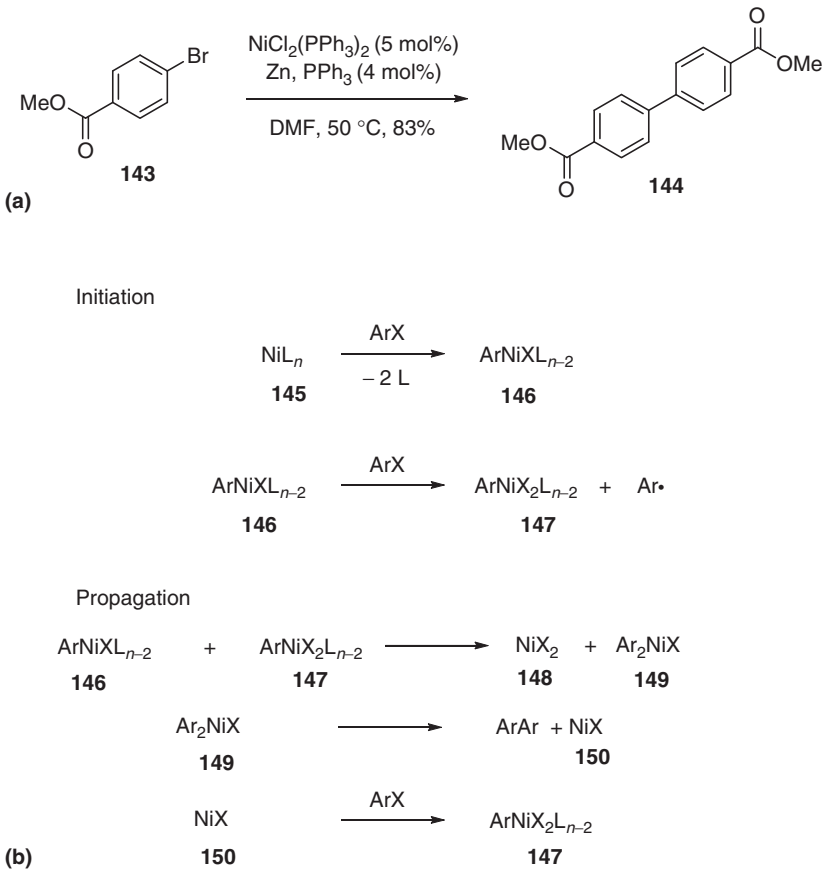
Similar oxidation-induced reductive elimination chemistry has been suggested in C–O and C–N bond-forming reactions from nickelacycles, such as **140** (Scheme 38).[68] Hillhouse and co-workers have reported that treatment of metallacycle **140** with oxidants such as ferrocenium, iodine, or O_2 resulted in formation of pyrrolidine **142**. The observed chemistry has been proposed to proceed by one-electron oxidation of Ni(II) complex **140** to Ni(III) intermediate **141**. Following C–N reductive elimination, the resulting Ni(I) intermediate would be oxidized to Ni(II) under the reaction conditions.



140 **141** **142**, 18%

Scheme 38 Treatment of metallacycle **140** with oxidants, such as O_2, initiates in C–N bond-forming reactions. The observed bond-forming reaction has been proposed to proceed by reductive elimination from Ni(III) intermediate **141**.

Two-electron C–C bond-forming reductive elimination from Ni(III) intermediates has been proposed in the reductive coupling of aryl halides as well as in Ni-catalyzed cross-coupling reactions of aryl halides with organometals. In the cross-coupling of aryl halides,[69a] initial oxidative addition of aryl halide to Ni(0) (**145**) affords an Ni(II) aryl halide complex (i.e. **146**; Scheme 39).[69b] Although complex **146** is stable to thermolysis, biaryls are observed on treatment with aryl halides. The observed aryl halide-induced C–C bond-forming chemistry has been rationalized by a mechanism in which single-electron transfer from an organometallic Ni(II) complex **146** to an aryl halide affords an Ni(III) intermediate (**147**) and aryl radicals. Subsequent aryl ligand exchange between Ni(III) (**147**) and an aryl Ni(II) complex (**146**) affords a diaryl Ni(III) intermediate (**149**). Two-electron

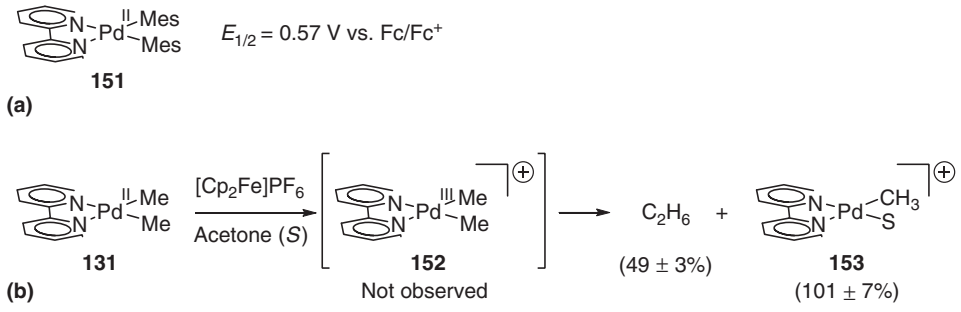


Scheme 39 (a) Ni-catalyzed reductive coupling of aryl halides has been developed. (b) A radical chain mechanism based on Ni(I) and Ni(III) chain carriers has been proposed for the homocoupling of aryl halides as well as crosscoupling of aryl halides and organometals.

reductive elimination of biaryls from Ni(III) affords the observed C–C coupling products and Ni(I) intermediate (**150**), which propagates the chain reaction.

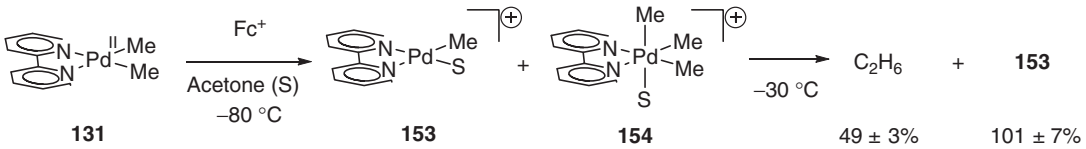
7.23.4.3 Disproportionation Pathways for Oxidative M–C Bond Cleavage

Following initial oxidation to a mononuclear Pd(III) complex, bimolecular disproportionation can occur, resulting in the formation of mononuclear Pd(II) and Pd(IV) complexes, respectively. Sanford and Mayer have reported the coupling of methyl ligands of Pd(III) dimethyl complex **131** induced by treatment of **131** with ferrocenium hexafluorophosphate (Scheme 40).[70] Based on electrochemical investigation of related *bis*-mesityl Pd(II) complex **151**,[71] which displays a reversible Pd(II)/Pd(III) redox couple but does not participate in oxidation-induced C–C bond-forming chemistry, presumably due to the steric demand of the mesityl ligands, treatment of **131** with Fc^+ was proposed to result in initial oxidation to Pd(III).



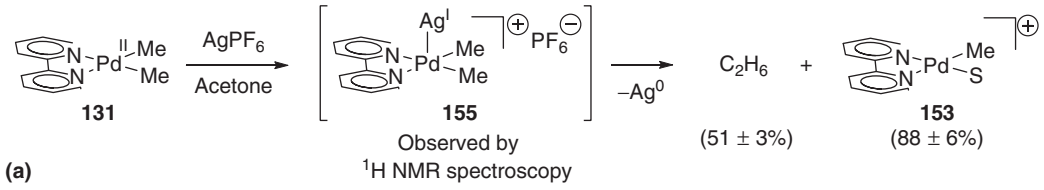
Scheme 40 (a) *Bis*-mesityl Pd(II) complex **151** exhibits reversible one-electron electrochemical behavior. (b) Treatment of dimethyl Pd(II) complex **131** with outer-sphere, one-electron oxidants, such as Fc^+, results in the evolution of ethane. The observed oxidation chemistry is proposed to proceed by initial oxidation of **131** to mononuclear Pd(III) complex **152**.

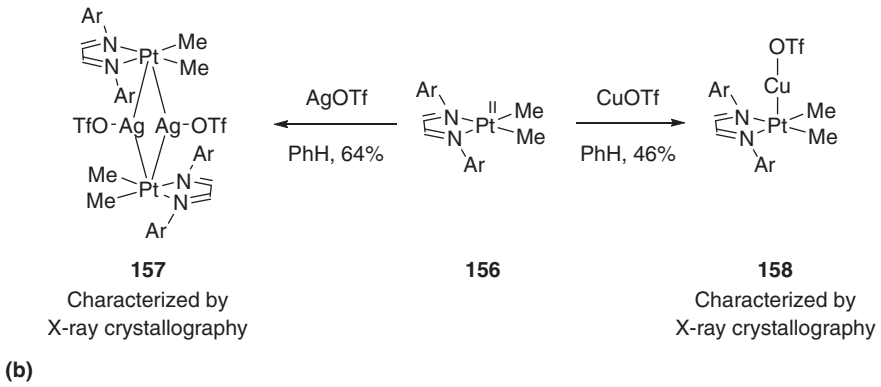
The critical C–C bond-forming reaction was proposed to proceed via disproportionation to afford Pd(II) and Pd(IV) complexes, followed by reductive elimination from Pd(IV). Consistent with this proposal is the observation that treatment of **131** with Fc^+ at –80 °C resulted in the formation of Pd(IV) solvento complex **154** (Scheme 41).



Scheme 41 Treatment of **131** with Fc^+ under cryogenic conditions resulted in the observation of mononuclear Pd(IV) complex **154**, consistent with disproportionation of **152** en route to ethane formation.

Sanford and Mayer also found that oxidation-induced coupling of methyl ligand could be initiated by Ag(I) reagents (Scheme 42(a)), and observed an association complex between **131** and $AgPF_6$, which was proposed to be intermediate **155**, featuring a metallophilic Pd–Ag interaction.[70] As silver is a common additive in C–H coupling reactions, the observation of Ag-mediated oxidation of Pd(II) suggests that higher-valent intermediates may be more prevalent than is generally appreciated. Similar metallophilic interactions have been observed by Chen and co-workers in compounds **157** and **158**, by treatment of Pt(II) complex **156** with coinage metal triflate salts (Scheme 42(b)).[72]

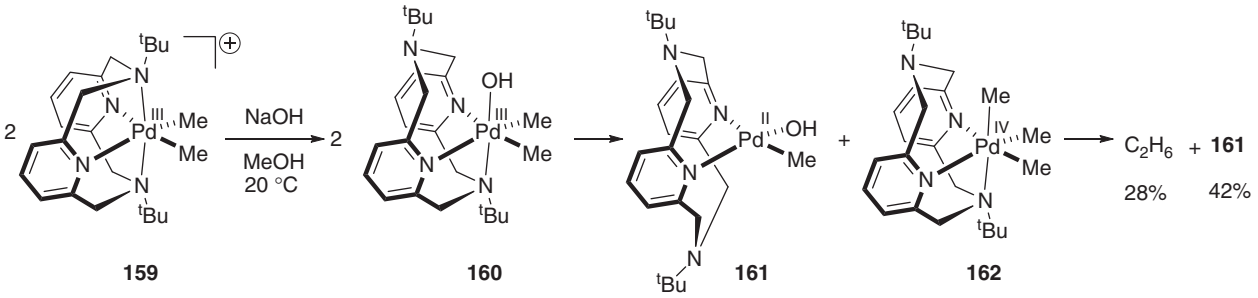




Scheme 42 (a) An intermediate assigned as **155** was observed on treatment of Pd(II) complex **131** with $AgPF_6$. (b) Treatment of dimethyl Pt(II) complex **156** with CuOTf or AgOTf affords adducts **157** and **158**, respectively. Complexes **157** and **158** are Pt-based analogs of complex **155** proposed in the reaction of **156** with $AgPF_6$ (Ar = 2,6-dichlorophenyl).

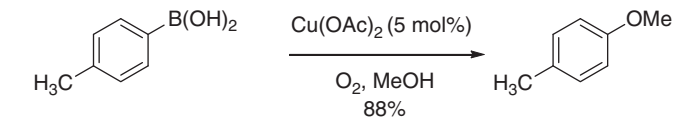
Mirica et al. has proposed ligand-induced disproportionation of isolable Pd(III) complexes (Scheme 43).[73] Treatment of mononuclear Pd(III) complex **159**, with anionic donors, such as hydroxide, affords mononuclear Pd(II) complex **161** and ethane. The observed reactivity has been proposed to proceed by anion binding to **159** to generate **160**, followed by disproportionation to afford mononuclear Pd(IV) complex (**162**) and Pd(II) complex **161**, followed by C–C reductive elimination from Pd(IV) complex **162**.

A similar disproportionation-based mechanism has been proposed for Cu-catalyzed coupling reactions of arylboronic acid with alcohols to generate aryl ethers.[74] Originally developed by Chan, Evans, and Lam, Cu-catalyzed coupling of arylboronic acids has been developed for the synthesis of a variety of C–O and C–N bond-containing products.[75] In 2009, Stahl and co-workers reported an investigation of the mechanism of methoxylation of *p*-tolylboronic acid (Scheme 44(a)) in which it was established that O_2 serves as a four-electron oxidant and that two equivalents of Cu(II) are consumed during the formation of each equivalent of ethereal product.[74] Based on these observations, a mechanism involving disproportionation of two Cu(II) species to generate Cu(I) and Cu(III) intermediates, with subsequent C–O reduction elimination from the Cu(III) intermediate, was proposed.

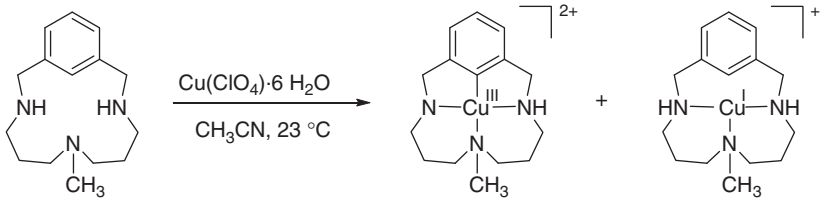


159 160 161 162

Scheme 43 Treatment of mononuclear Pd(III) complex **159** with anionic donors, such as hydroxide, induces disproportionation. The Pd(IV) complex **162**, generated by disproportionation, undergoes reductive elimination to afford ethane and Pd(II) complex **161**.



(a)



163 164 ~50% 165 ~50%

(b)

Scheme 44 (a) The Cu-catalyzed methoxylation of arylboronic acids has been proposed to proceed through reductive elimination from a Cu(III) intermediate, generated by disproportionation of two equivalents of Cu(II). (b) Treatment of triamine **163** with Cu(II) results in the formation of equimolar amounts of Cu(III) complex **164** and Cu(I) complex **165.**

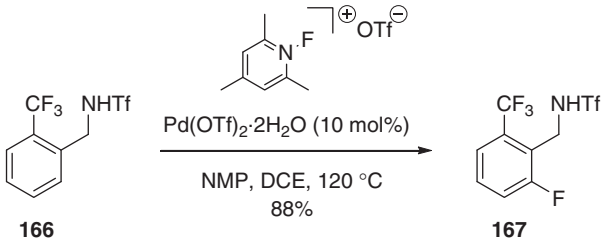
Consistent with this proposal is the observation that treatment of triamine **163** with $Cu(ClO_4)_2$ resulted in the formation of 0.5 equivalent of Cu(III) complex **164** and 0.5 equivalent of Cu(I) complex **165** (Scheme 44(b)).[76]

7.23.5 Conclusion

In the above sections, a variety of potential pathways for M–C bond oxidation have been described. Depending on the electronic structure of the organometallic partner and the identity of the oxidant employed, M–C bond oxidation can proceed with no redox chemistry at the metal center, or via pathways where initial oxidation of the metal center initiates oxidative M–C bond cleavage. Examples of both one- and two-electron, metal-centered oxidation initiate M–C bond oxidation have been discussed. By studying the chemistry of well-defined oxidative M–C cleavage reactions, the intimate details of these reaction pathways have been elucidated.

Although well-defined, stoichiometric studies of M–C bond oxidation have provided information regarding the diversity of oxidation mechanisms available in oxidation of organometallic species, the course of M–C oxidation reactions relevant to many transition metal-catalyzed reactions is less clear. As an example, the mechanism of oxidation during directed Pd-catalyzed C–H oxidation reactions has received a great deal of attention recently.[55,77] It is frequently difficult to elucidate the nature of the oxidation step in catalysis because C–H metallation is commonly turnover-limiting, and thus information regarding the redox chemistry is obscured to kinetics investigations. In a few cases of catalysis, the nature of the oxidation step has been elucidated; in both $Pd(OAc)_2$-catalyzed C–H oxidation reactions binuclear $S_E(ox)$ reaction pathways have been suggested.

In other Pd-catalyzed C–H oxidation reactions, bridging ligands, such as acetate, are not available and highly electron-deficient Pd catalysts are employed. These reaction conditions may favor S_E2 M–C bond oxidation pathways. For example, the $Pd(OTf)_2$-catalyzed fluorination reactions developed by Yu are carried out under reaction conditions that may not support metal-based oxidation mechanisms (Scheme 45).[78] The rich diversity of organometallic oxidation mechanisms that have been encountered in



166 167

Scheme 45 $Pd(OTf)_2$-catalyzed C–H fluorination. Detailed information is not available regarding the oxidation mechanism in catalysis; however, based on the lack of strong field ligand available, S_E2 oxidation pathways may be operative.

this chapter suggests that an increasing diversity of M–C oxidation mechanisms will be encountered as additional catalytic reactions are studied.

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7.24 Oxidation of Carbon–Halogen Bonds

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Glossary

1,3-Diaxial interaction The steric interaction between two axial hydrogen or substituent, which are relatively close each other, on the same side of the ring, resulting in a steric destabilization.

Nucleofugacity If the leaving group of the substrate has high nucleofugacity in the reaction, such as nucleophilic substitution and nucleophilic aromatic substitution, then the leaving group will have high electron dense and easily leave the substrate.

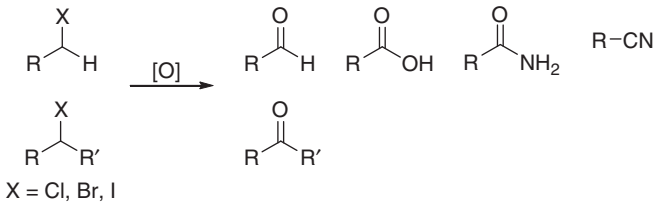
Tandem reaction A consecutive series of intramolecular organic reactions without the isolation of reaction intermediate that allows the efficient synthesis of complex organic compounds from a single acyclic precursor.

Ylide A compound that has opposite charges on adjacent covalently bonded atoms that have complete octets; normally written X^{-}–Y^{+}. Usually X is carbon and Y is a hetero atom (nitrogen, phosphorus, or sulfur).

7.24.1 Introduction

Halides are extremely versatile intermediates. One of the valuable and interesting transformation is their oxidation to carbonyl compounds. In many cases, these reactions are reliable routes to relatively inaccessible carbonyl compounds, such as heterocyclic aldehydes and 1,2-diketones, being combined with halogenations of methyl arenes or α-alkyl carbonyl compounds. As will be seen below, there are many, often complementary, synthetic methods for the oxidation of organic halides. This chapter deals with oxidation of carbon–halogen bond to carbonyl compounds such as aldehydes, ketones, 1,2-dicarbonyl compounds, 1,2,3-tricarbonyl compounds, carboxylic acid, amides, and nitriles (Scheme 1), concentrating mainly on highly selective methods using chemical oxidizing agents, except for multistep oxidation via alcohol and electrochemical oxidation, and mainly covering the literature from the first edition[1] to the middle of 2012.

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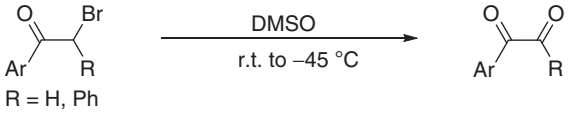


Scheme 1

7.24.2 Kornblum Oxidation and Related Methods

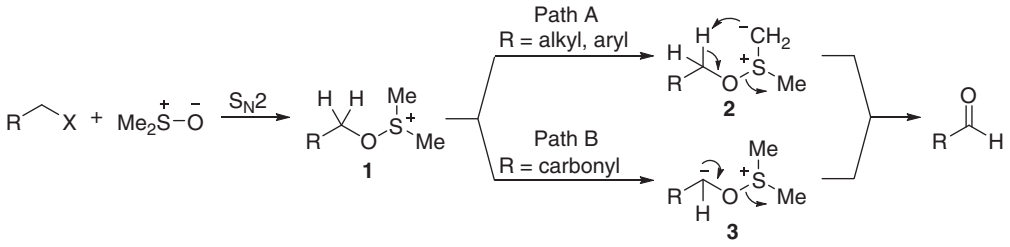
7.24.2.1 Oxidation with Dimethyl Sulfoxide

The Kornblum oxidation is perhaps one of the most widely used and best-known methods for the oxidation of halides.[2,3] In 1957, Kornblum et al. reported that α-bromoketones were oxidized to 1,2-oxoaldehydes and 1,2-diketone by dissolving in dimethyl sulfoxide (DMSO) (Scheme 2).[4] In the majority of cases, the reactions proceed at room temperature. In addition, oxidation of 4-nitrobenzyl bromide to 4-nitrobenzaldehyde proceeded in moderate yield by raising the temperature and using acetonitrile as a solvent.



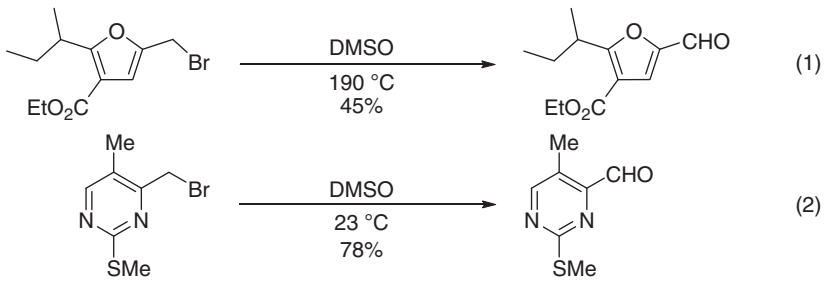
Scheme 2

The reaction proceeds through an S_N2 displacement of halide by the oxygen atom of the DMSO to form sulfonium salt **1** (Scheme 3).[5,6] When sulfonium salts **1** are obtained from alkyl and benzyl halide, the proton is removed to generate a sulfur ylide (**2**), affording the oxidized product (Path A). However, **1** obtained from α-halocarbonyl compounds loses an α-proton to generate carbonyl groups since the protons adjacent to it are now more acidic than those of the methyl groups of the sulfonium salt **1** (Path B).



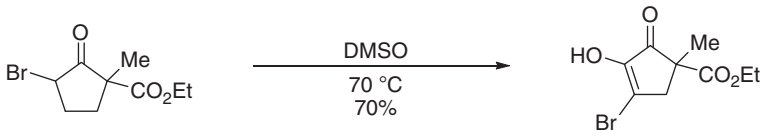
Scheme 3

Recent examples are presented in Scheme 4. Some benzyl bromides, including bromomethyl heteroarenes such as furan and pyrimidine, can be oxidized to the corresponding aldehydes (equations 1 and 2).[7,8] Furthermore, microwave irradiation allows a quick and convenient oxidation of 1,2-dibromides to give 1,2-diketones.[9]



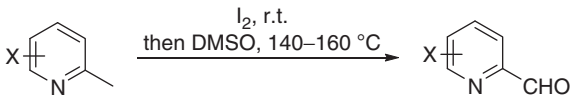
Scheme 4

In some cases, bromine, which is produced by the oxidation of the liberated hydrogen bromide (HBr) by DMSO,[10] leads to bromination of the primary oxidation product in good yield (Scheme 5).[11,12]



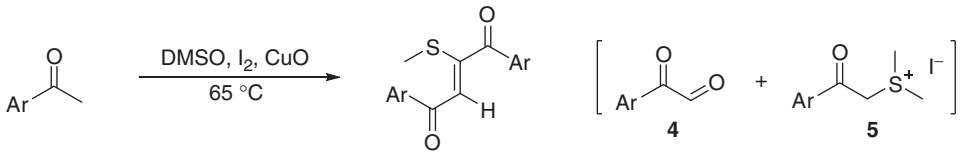
Scheme 5

Interestingly, acetophenones and cyclic 1,3-diones were directly converted to aryl glyoxals and 1,2,3-triones, respectively, through bromination and oxidation with DMSO in the presence of HBr.[13,14] Furthermore, Kornblum oxidation can be combined with iodination to provide a very convenient synthesis of 2-pyridinecarbaldehydes from the corresponding picolines (Scheme 6).[15]



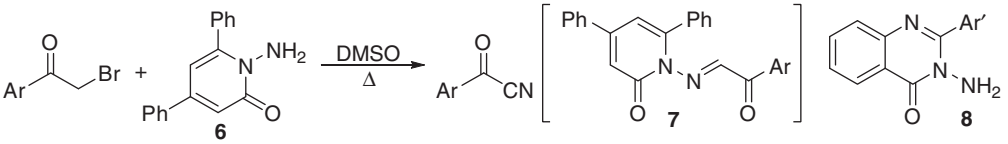
Scheme 6

Kornblum oxidation was also used for carbon–carbon double-bond formation via self-sorting tandem reaction (Scheme 7).[16] Aryl glyoxal **4**, which is generated by iodination and oxidation of acetophenones, and sulfonium iodide **5** are reaction intermediates.



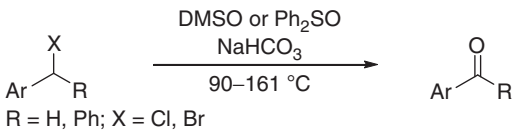
Scheme 7

However, phenacyl bromides can be oxidized to aroyl cyanide by using 1-amino-4,6-diphenyl-2-pyridone **6** in DMSO (Scheme 8).[17] Under the reaction conditions, the aldimine intermediate **7** was formed and pyrolyzed to give aroyl cyanide. Under these conditions, aliphatic substrates did not give satisfactory yields. 2-Aryl-3-amino-4-oxo-3,4-dihydroquinazoline **8** can also be used.[18]



Scheme 8

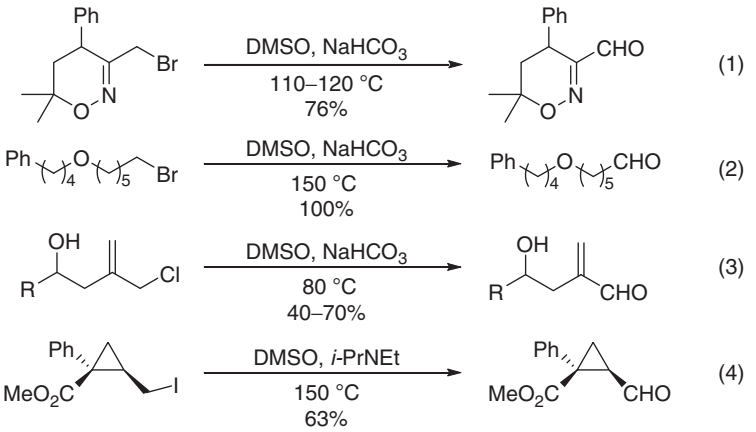
In the presence of sodium bicarbonate ($NaHCO_3$), benzyl chloride and bromide can be oxidized to aldehydes with DMSO at high temperature in fair yields (Scheme 9).[19] Diphenylmethyl chloride, which cannot be structurally eliminated, was oxidized to benzophenone in moderate yield. Note that 1,2-epoxy-3-phenoxypropane can be used for nonalkaline HBr scavenger.[20]



Scheme 9

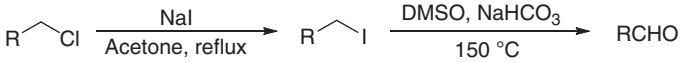
Generally, secondary halides are prone to elimination, as would be expected for a reaction relying on an S_N2 displacement as the first step. If the approach of the DMSO is hindered, for example, by a 1,3-diaxial interaction, the oxidation of α-haloketone proceeds poorly, and elimination of HBr proceeds preferentially.[21,22]

Scheme 10 shows some recent examples. Primary benzyl, allyl, and alkyl bromides were oxidized to aldehydes (equations 1 and 2).[23,24] Furthermore, benzyl and allyl chloride and alkyl iodide can be also oxidized to aldehydes (equations 3 and 4).[25,26]



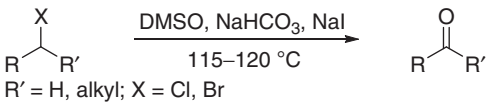
Scheme 10

Primary alkyl chlorides can also be oxidized to the aldehydes by Kornblum oxidation through the corresponding alkyl iodide, which is generated with sodium iodide (NaI) (Scheme 11).[27] Although 2-iodooctane, a secondary iodide substrate, is oxidized to the ketone in 32% yield, iodocyclohexane remains intact under these conditions.



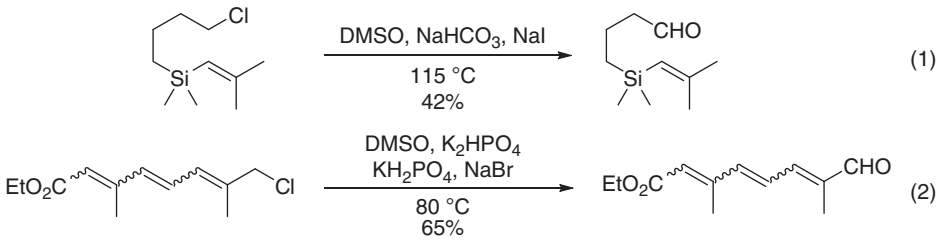
Scheme 11

Furthermore, it was found that primary alkyl chlorides and bromides were directly oxidized to aldehydes in the presence of NaI (Scheme 12).[28] Under these conditions, secondary bromides can be oxidized to the corresponding ketones in modest to good yields, and *p*-nitrobenzyl chloride was also oxidized to the corresponding aldehyde in good yield.



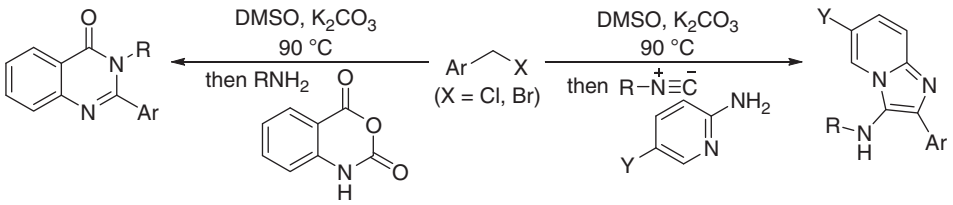
Scheme 12

Recent examples are presented (Scheme 13).[29,30] For some substrates, the combination of sodium bromide (NaBr) and buffer (K_2HPO_4, KH_2PO_4) was used instead of NaI and $NaHCO_3$ (equation 2).



Scheme 13

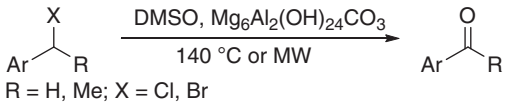
Kornblum oxidation is used for one-pot synthesis of 4(3*H*)-quinazolines and imidazo[1,2-a]pyridine from benzyl chlorides and bromides (Scheme 14).[31,32] In the first step, treatment of benzyl halides with DMSO yields aldehyde intermediates in both reactions.



Scheme 14

As primary halides and DMSO are strongly polar reagents that absorb microwave radiation very well, benzyl and aliphatic halides (Cl, Br, and I) are converted to the corresponding aldehydes and ketones with DMSO in the presence of $NaHCO_3$ or $KHCO_3$ under microwave irradiation.[33–36] Remarkably, alkyl chlorides can also give the corresponding products in moderate yield.

However, Mg–Al hydrotalcite [$Mg_6Al_2(OH)_{24}CO_3$] was used as the heterogeneous basic catalyst (Scheme 15).[37] The Mg–Al hydrotalcite could be easily recovered and reused successfully. This reaction was complete in a short period of time using microwave irradiation.[38] $Ba(OH)_2$ is also used as heterogeneous base.[39]



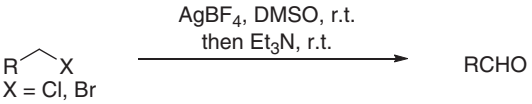
Scheme 15

One way to increase the nucleofugacity of alkyl halides is to activate them with silver salts. Primary unactivated chlorides, bromides, and iodides could be oxidized by prior conversion to the tosylate with silver tosylate, followed by reaction in DMSO (Scheme 16).[40]



Scheme 16

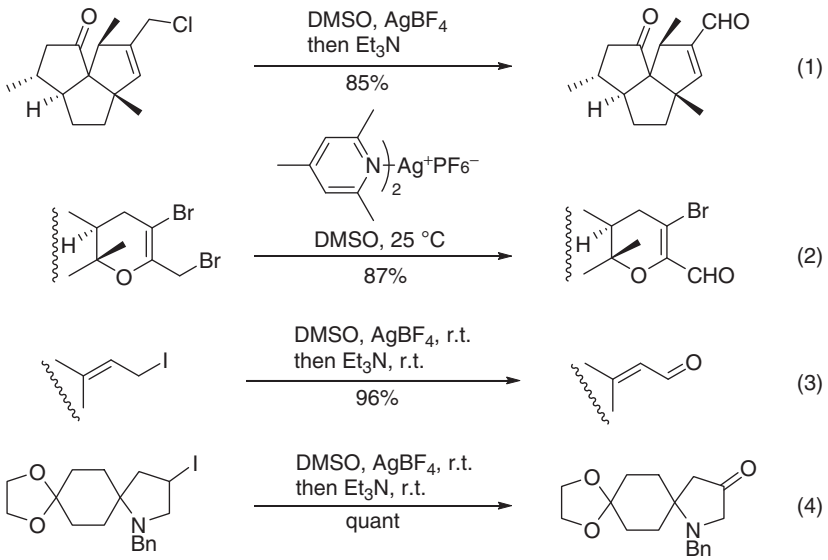
Later, it was found that addition of a silver salt to the DMSO solution was equally effective (Scheme 17).[41,42] In many cases, triethylamine was added as a base after formation of the sulfonium salt. Although simple alkyl bromides and allyl chloride were oxidized to aldehydes in moderate to high yields, the method fails for unactivated chlorides, for deactivated bromides, and for substrates where solvolytic reactions are possible. Silver perchlorate was also used.[43]



Scheme 17

Recent examples are presented in Scheme 18. Allyl chlorides, bromides, and iodides can be oxidized in the presence of silver salt in high yields (equations 1–3).[44–46] Furthermore, a secondary alkyl iodide was also oxidized to the corresponding ketone (equation 4).[47]

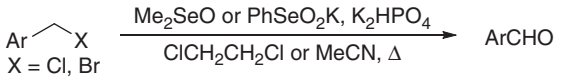
Benzyl bromide is converted to benzaldehyde or acetophenone in good yields in the presence of zinc salts ($ZnCO_3$, ZnS).[48] The zinc is moderately electropositive, thus it is expected to increase the nucleofugacity of halides, besides acting as HX scavengers. When *tert*-β-bromo alcohol is used as substrate, the oxidative product is a minor product and rearranged product is obtained as the major product.[49]



Scheme 18

7.24.2.2 Oxidation with Selenoxides and Telluroxides

Benzyl chloride and *p*-nitrobenzyl bromide can be oxidized to aldehyde using SeO_2.[50,51] Furthermore, dimethyl selenoxide or potassium benzeneselenite also convert the benzyl chlorides and bromides, which include polysubstituted or base-sensitive ones, to the corresponding aldehydes under mild conditions (Scheme 19).[52] Di(4-anisyl) selenoxide is also known for benzyl bromide oxidation to aldehyde.[53]

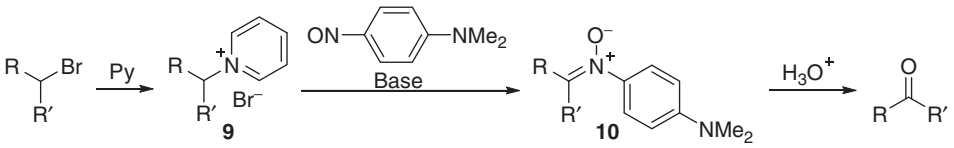


Scheme 19

Oxidation of organotelluriums to aldehydes by molecular oxygen has been known, and benzyl chloride was converted to aldehyde using potassium tellurocyanate (KTeCN) through benzyl tellurocyanate.[54,55] Tellurium dioxide (TeO_2),[56] sodium phenyl telluride (NaTePh),[57–59] and sodium hydrogen telluride (NaTeH)[60] are also used for the oxidation of benzyl halides.

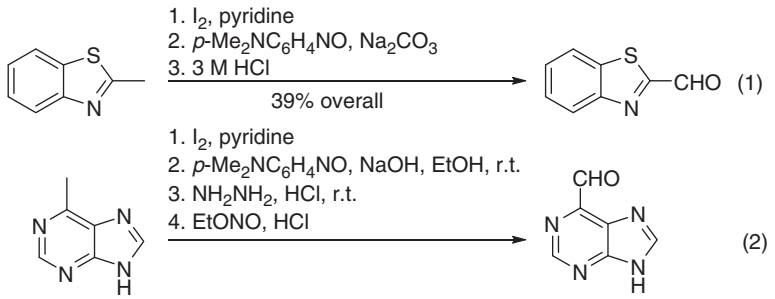
7.24.3 The Kröhnke Oxidation

One of the oldest and most popular methods for oxidizing activated halides is the three-step Kröhnke oxidation.[61] The individual steps are (1) substitution of the halide with pyridine; (2) reaction of the pyridinium ylide, generated by deprotonation of **9** with base, with *N*,*N*-dimethyl-4-nitrosoaniline; and (3) acid hydrolysis of the nitrone **10** to the carbonyl compound (Scheme 20).



Scheme 20

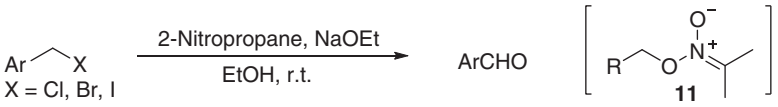
The method is limited to activated halides, which are stable to alkoxide bases and aqueous acids. According to the authors,[61] the Kröhnke oxidation is inferior to the Sommelet reaction for benzyl halides, especially those bearing electron-withdrawing groups. This oxidation is an excellent method for the preparation of heterocyclic aldehydes, which are difficult to synthesize.[62–66] Activated methyl groups have been transformed into carbaldehyde through iodination and oxidation (Scheme 21).[67,68] For acid-sensitive substrates, the nitrone can be removed by hydrazinolysis, followed by diazotization (equation 2).[68]



Scheme 21

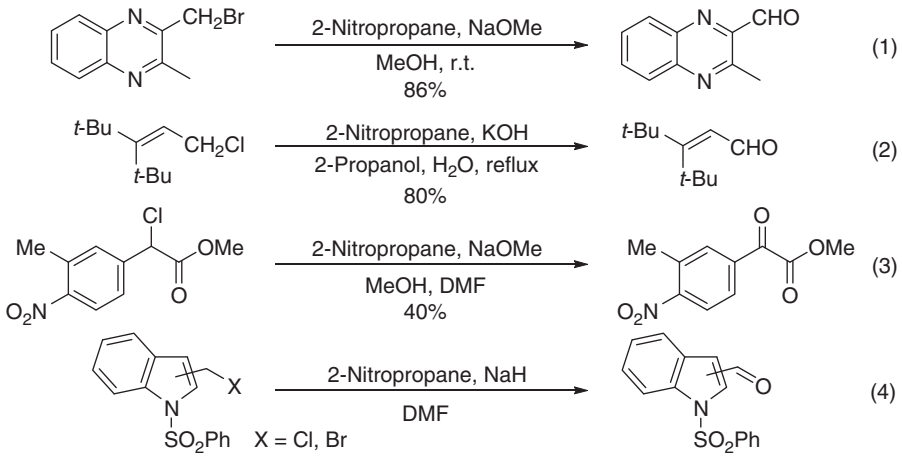
7.24.4 The Hass–Bender Oxidation

Hass and Bender have reported the oxidation of benzylic halides to aldehydes (Scheme 25).[69] This reaction proceeds by the displacement of the halide ion by nitronate oxygen to **11**, followed by liberation of the oxime (Scheme 22). It is often competitive with other methods.[70,71] The sodium salts of phenylnitromethane and phenylnitroacetonitrile were also used for the oxidation of benzyl chloride.[72] There is a limitation to the method: 4-nitrobenzyl chloride gives the aldehyde in only 1% yield. The major product is the alkylated product resulting from single-electron transfer and radical coupling, which is greatly influenced by thermal effects.[73,74]



Scheme 22

Representative examples of the reaction are shown in Scheme 23. The method works well for primary allyl and benzyl chlorides and bromides (equations 1 and 2).[75,76] α-Chloroesters can be oxidized to α-oxoesters in modest yield (equation 3).[77] *N*-Protected bromo and chloro methylindoles can be oxidized to indolaldehyde using NaH/*N*,*N*-dimethylformamide (DMF) conditions in reasonable yields (equation 4).[78,79]

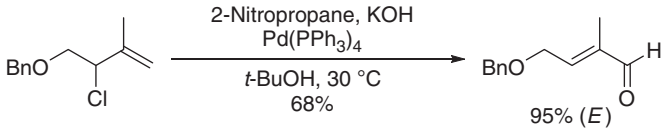


Scheme 23

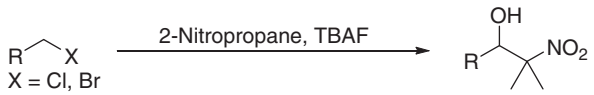
A palladium catalyst has been used to isomerize a secondary allylic halide before oxidation (Scheme 24).[80] In this case, it is possible that the reaction is occurring by attack of the nitronate anion on the π-allylpalladium complex rather than on the chloride itself.

Dimethylnitro alcohols are constructed from benzyl chloride and bromide in a one-pot reaction (Scheme 25).[81] The use of tetrabutylammonium fluoride (TBAF) as the promoter is essential for this tandem Hass–Bender/Henry reaction to proceed.

A TBAF solution possesses an intermediate basicity that is strong enough to promote the Hass–Bender oxidation but moderate enough so that the retro-Henry is not favored. Nonactivated halides are feasible substrates for this transformation.



Scheme 24

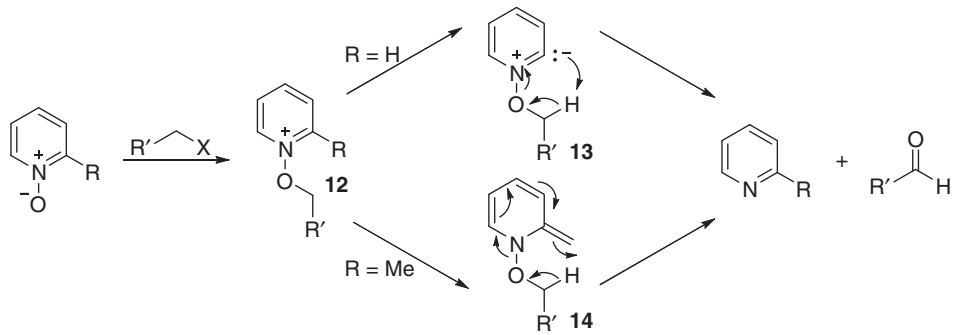


Scheme 25

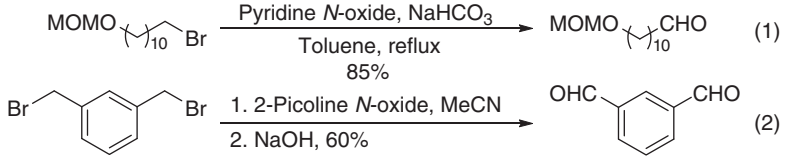
7.24.5 *N*-Oxides, *N*-Hydroxypyridones, Nitrones, and Hydroxylamines

7.24.5.1 Pyridine *N*-Oxides and Derivatives

The oxidation of alkyl halides to carbonyl compounds with pyridine or 2-picoline *N*-oxide is a popular and general method, applicable even to unreactive substrates. The reaction may be performed in two ways. In the first, the halide is heated with the *N*-oxide in the presence of a base such as $NaHCO_3$. In the second, the intermediate *N*-alkoxypyridinium salt **12** is isolated before base treatment. The reaction has been shown by labeling to proceed via the pyridinium ylide **13**,[82] or, in the case of picoline *N*-oxide, through anhydrobase **14** (Scheme 26).[83] Some typical examples are shown in Scheme 27.[84,85] Alkyl and benzyl bromide are oxidized to aldehydes. Note that an ester is tolerated under these conditions, but a 2-tetrahydropyranyl ether is cleaved to some extent.[86,87]



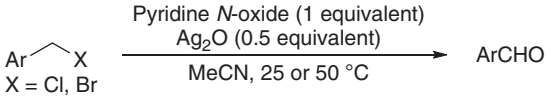
Scheme 26



Scheme 27

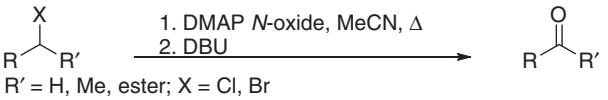
It is curious that under thermal conditions, α-bromo acids preferentially undergo oxidative decarboxylation rather than oxidation to the α-keto acid.[88] Under microwave irradiation, benzyl bromides can be oxidized to aldehydes without solvent and base.[89] However, oxidation of benzyl and alkyl halides (bromide, chloride) with cellulose-grafted *N*-oxide was also reported recently.[90] In the presence of silver nitrate, 1,2-oxoesters and 1,2-oxoacids are prepared in a one-pot procedure with pyridine *N*-oxide, followed by addition of triethylamine.[91] Furthermore, benzyl chloride and bromide are conveniently oxidized to aldehydes

and ketones by pyridine *N*-oxide in the presence of Ag_2O in acetonitrile under mild conditions (Scheme 28).[92] Silver oxide assists the heterolysis of the carbon–halogen bond in the substitution reaction with pyridine-*N*-oxide. The resulting hydroxide ion from the reaction between silver oxide and halogen then functions as the base in the elimination reaction to produce the carbonyl group. The substituent effects indicate an S_N1-like mechanism for the first step in the reaction pathway.

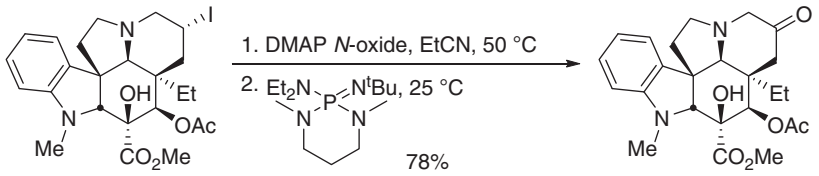


Scheme 28

The *N*-oxide of 4-dimethylaminopyridine (DMAP *N*-oxide) would be expected to be a more powerful nucleophile than the parent compound. DMAP *N*-oxide is able to displace bromide even from secondary unactivated substrates (Scheme 29)[93]; however, the method still fails due to elimination with cyclohexyl bromide. A modified method with DMAP *N*-oxide is used for oxidation of secondary iodide (Scheme 30).[94]



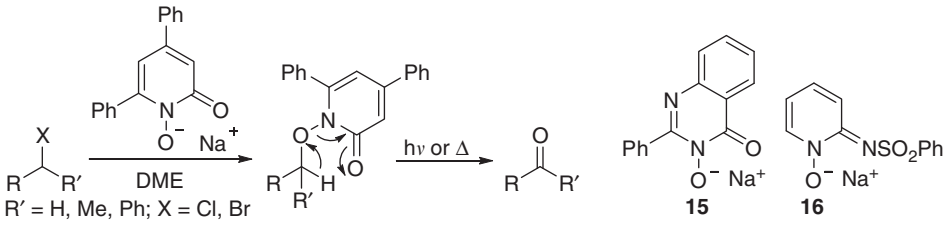
Scheme 29



Scheme 30

7.24.5.2 *N*-Hydroxypyridones

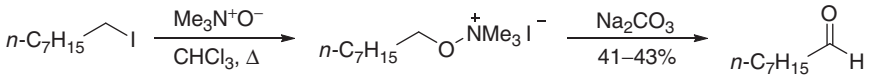
The use of *N*-hydroxypyridone salts offers some advantages over the procedures using pyridine *N*-oxides; specifically, the second step can be done under nonhydrolytic conditions either thermally or photochemically (Scheme 31).[95,96] Thus, this reaction can be used for base-sensitive substrates; however, these methods are unsuitable for aliphatic halides, and there appear to be no α-halocarbonyl examples. The *N*-hydroxy salts **15** and **16** offer some advantages.[97,96]



Scheme 31

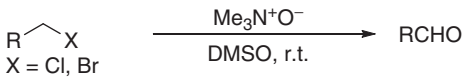
7.24.5.3 Amine Oxides

Trimethylamine *N*-oxide (TMANO) can be used in place of pyridine *N*-oxide for the oxidation of activated and unactivated bromides and iodides (Scheme 32).[98,99]



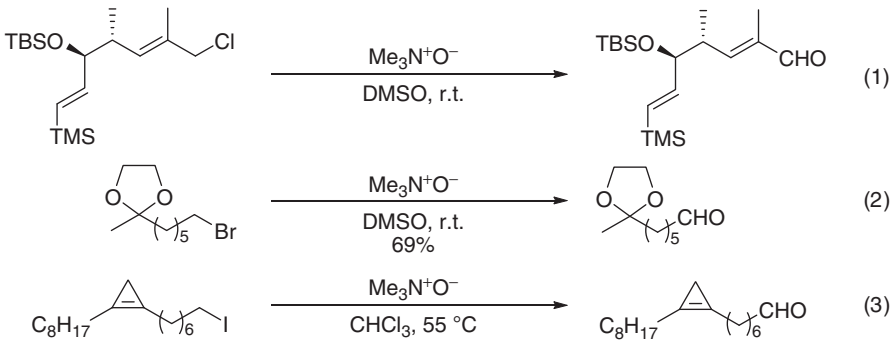
Scheme 32

Furthermore, by using DMSO as solvent, benzyl and allyl halides (X=Cl, Br) and aliphatic bromides can be oxidized to aldehydes with anhydrous TMANO (Scheme 33).[100] Under these conditions, reactions proceed with a shorter reaction time and at a lower temperature. Alkyl chlorides are not oxidized, and elimination-prone halides, such as phenethylbromide, tend to form alkenes.



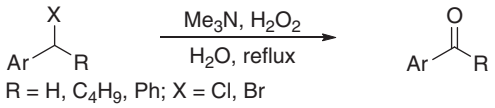
Scheme 33

Recent examples are presented in Scheme 34. Allyl chlorides, alkyl bromides, and iodides are oxidized to aldehydes in good yields (equations 1–3).[101–103]



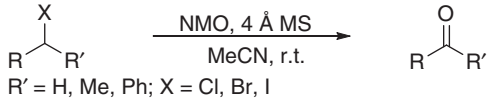
Scheme 34

Oxidation of benzyl chlorides and benzyl bromides to the corresponding aldehydes and ketones was achieved by refluxing in H_2O using TMANO, generated from triethylamine and H_2O_2 *in situ*, in high yields (Scheme 35).[104] When the reaction is conducted on a large scale, the product is separated from the water layer after cooling to room temperature. Generally, primary halides are oxidized faster than secondary halides.



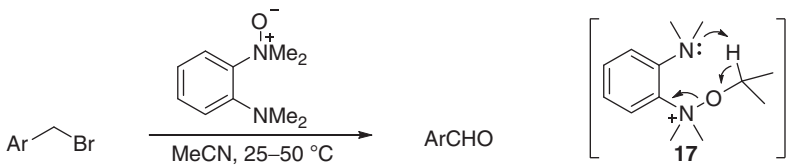
Scheme 35

N-methylmorpholine-*N*-oxide (NMO) has also been used for the oxidation of benzyl and allyl halides to ketones and aldehydes (Scheme 36).[105] In this reaction aliphatic iodides are also oxidized. Oxidation of allyl chlorides to aldehydes with *N*-ethylmorpholine-*N*-oxide in DMF was also reported.[106]



Scheme 36

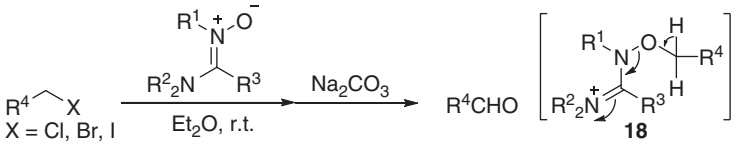
2-Dimethylamino-*N*,*N*-dimethylaniline *N*-oxide, which possesses an *N*-oxide and the basic dimethylamino moieties, ensures that the elimination step occurs via the putative cyclic seven-membered transition state **17** (Scheme 37).[107] Benzyl bromide, phenacyl bromide, and cinnnamyl bromide are oxidized to the corresponding aldehydes under relatively mild conditions in high yields. In this reaction benzyl chloride and alkyl bromides cannot be oxidized at all.



Scheme 37

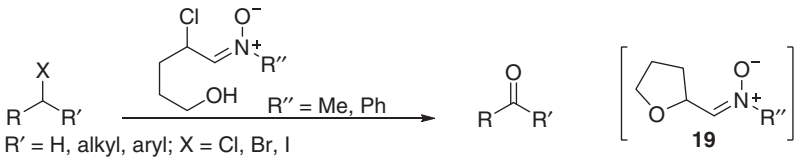
7.24.5.4 Nitrones and Hydroxylamines

α-Amino nitrone has been used successfully as an oxidizing reagent for the synthesis of aldehydes from various alkyl and benzyl halides (X=Cl, Br, and I) in good yields (Scheme 38).[108] Nitrone readily undergoes an S_N2 reaction with alkyl halides to afford an intermediate compound **18**, which is not isolated, and the N–O bond of the intermediate **18** breaks to give aldehydes when the reaction mixture is stirred with solid sodium carbonate.



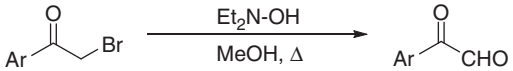
Scheme 38

Alkyl and benzyl halides can be oxidized to aldehydes and ketones using α-chloronitrones (Scheme 39).[109–113] Nitrone **19** is formed and reacts very quickly with alkyl halides.



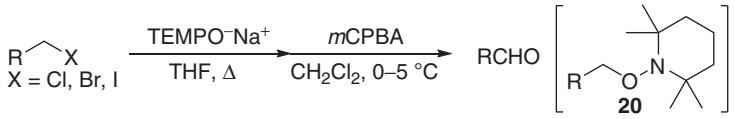
Scheme 39

There is one report with *N*,*N*-dialkylhydroxylamines oxidizing phenacyl bromides to aryl glyoxals (Scheme 40).[114] This method is not applicable to other α-halocarbonyl compounds such as 2-chlorocyclohexanone and α-bromopropiophenone. However, when 1,1-dimethylhydrazine is used, phenacyl bromides are converted to arylglyoxaldimines.[115]



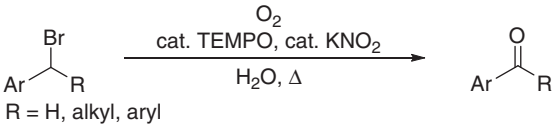
Scheme 40

Alkyl halides can be oxidized to aldehydes with sodium 2,2,6,6-tetramethylpiperidine-*N*-oxide ($TEMPO^-Na^+$), generated by reduction of TEMPO with sodium naphthalenide in THF, and *m*-chloroperbenzoic acid (*m*CPBA) (Scheme 41).[116] Primary alkyl halides react with the TEMPO anion to give the corresponding alkoxyamines **20** in good to excellent yields. Secondary halides are less reactive, and a moderate yield is obtained with benzyl halide.



Scheme 41

Various benzylic bromides are successfully oxidized to the corresponding aldehydes and ketones in aqueous media with molecular oxygen as the stoichiometric oxidant in the presence of catalytic amounts of TEMPO and KNO_2 (Scheme 42).[117]



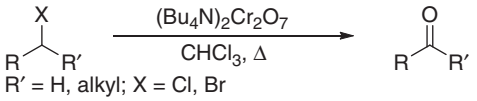
Scheme 42

4-Nitrobenzyl bromide is a poor substrate, and oxidation of aliphatic bromides cannot be achieved in the catalytic process. In the absence of TEMPO, further oxidation of aldehyde to carboxylic acid occurs. It appears likely that the hydrolysis of the halides to alcohol is the rate-determining step. Secondary halides are oxidized faster, since the hydrolysis of secondary ones is faster than that of primary ones.

7.24.6 Transition-Metal Salts

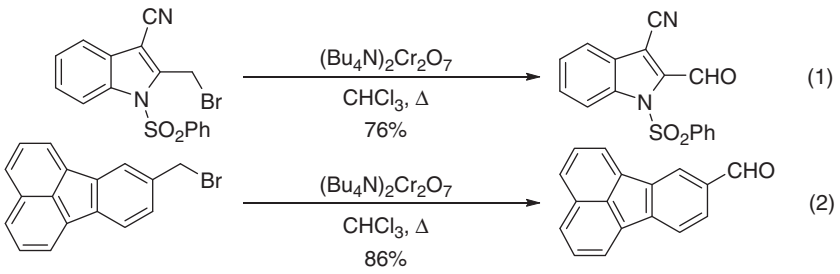
7.24.6.1 Chromium

Oxidation of benzyl chloride and allyl bromide to ketone with chromium trioxide (CrO_3) has been known.[118–120] Potassium chromate (K_2CrO_4) also has been used for oxidation of benzyl bromide and chloride to aldehyde or ketone.[121,122] Furthermore, quaternary ammonium salts have been used in an aprotic solvent (Scheme 43).[123] Under these conditions, an aliphatic bromide, 2-bromooctane, is oxidized to the corresponding ketone in good yield. Use of polymer-supported hydrogen chromate salt was also reported.[124]



Scheme 43

Recent examples are shown in Scheme 44. Benzyl bromides can be oxidized to the corresponding aldehydes.[125,126]

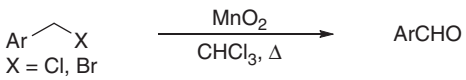


Scheme 44

Tetrakis-pyridino-cobalt(II) dichromate $Py_4Co(HCrO_4)_2$ (TPCD) also can oxidize the benzyl chloride and bromide to aldehyde and ketone.[127] In this reaction, α-chlorocarbonyl compounds also can be oxidized to 1,2-diketones.

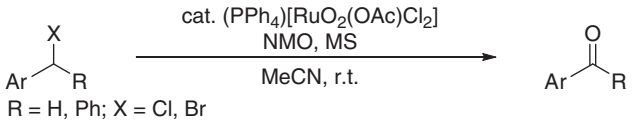
7.24.6.2 Other Metals

Benzyl bromide and chloride can be oxidized to aldehyde using manganese dioxide (MnO_2) (Scheme 45).[128] Interestingly, in the case of 1,4-bis(bromomethyl)benzene, only one bromomethyl group can be oxidized. This reaction probably proceeds through a benzyl radical by activated interaction with MnO_2. Oxidation with barium permanganate [$Ba(MnO_4)_2$] was also reported.[129]



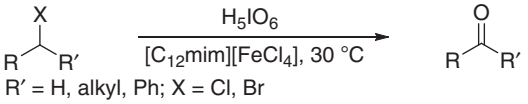
Scheme 45

Benzyl halides (X=Cl, Br) can be oxidized to aldehydes and ketones using $(PPh_4)[RuO_2(OAc)Cl_2]$ in the presence of powdered molecular sieves in MeCN (Scheme 46).[130] Geranyl bromide can also be oxidized to aldehyde without competing double-bond cleavage. This reaction proceeds both stoichiometrically and catalytically in the presence of NMO as a cooxidant.



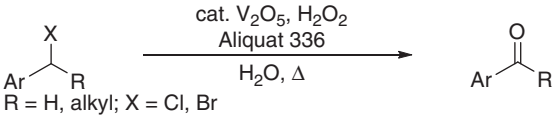
Scheme 46

When using an ionic liquid $[C_{12}mim][FeCl_4]$ as solvent, benzyl chlorides and bromides and alkyl chlorides can be oxidized to aldehydes and ketones with H_5IO_6 in high yields (Scheme 47).[131] The ionic liquid can be recovered and reused for subsequent reactions. However, using iron chloride ($FeCl_3$) and pyridine under an oxygen atmosphere, enolizable ketones can be converted directly to 1,2-diketones through chlorination and oxidation.[132]



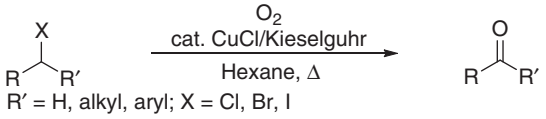
Scheme 47

Furthermore, benzyl and alkyl chlorides and benzyl bromides are converted to aldehydes and ketones using H_5IO_6 and V_2O_5 in the ionic liquid [bmpy][PF_6].[133] However, in the presence of catalytic amounts of V_2O_5 and aliquot 336 in water, benzyl bromides and benzyl chlorides can be oxidized to ketones and aldehydes using hydrogen peroxide (H_2O_2) as the stoichiometric oxidant (Scheme 48).[134] The reaction of benzyl chlorides is faster than that of benzyl bromides, probably because $^{-}OV(O_2)_2$, a good leaving group, is substituted by the bromide more easily, being a better nucleophile than the chloride ion.



Scheme 48

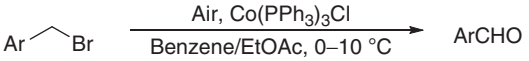
Alkyl halides and benzyl halides (Cl, Br, and I) are oxidized to aldehydes and ketones using catalytic amounts of CuCl/Kieselguhr and molecular oxygen (Scheme 49).[135] This catalyst is reusable 5 times.



Scheme 49

The allyl iodide, 3-iodomethyl-3-cephem, can be oxidized to the corresponding aldehyde in the presence of $P_2O_5 \cdot 24MoO_3 \cdot xH_2O$ in *N*-methyl-2-pyrrolidinone under bubbling oxygen conditions.[136,137] A superoxide anion was formed *in situ* by one-electron reduction of molecular oxygen. Furthemore, $RhCl_3$/Al, $VO(acac)_2$, or $VOSO_4$ can also be used for the same oxidation.[138]

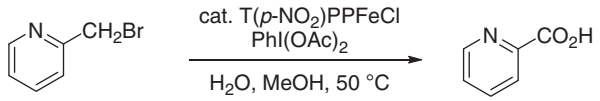
Benzyl bromides can be oxidized to aldehydes using $Co(PPh_3)_3Cl$ under air bubbling (Scheme 50).[139] In this reaction, some traces of carboxylic acids are also obtained as minor side products. $Co(PPh_3)_3Cl$ works for facile formation of the benzylic radical from the benzyl bromides. Benzyl chlorides and bromides can also be oxidized to aldehydes or ketones with Co(salen)–polyoxometalate (POM), Keggin type POM, or polyacrylamide-supported cobalt complex in the presence of H_2O_2.[140,141] Oxidation of allyl bromides to ketones in the presence of silver trifluoroacetate ($AgOCOCF_3$) can be used for the oxidation of allyl



Scheme 50

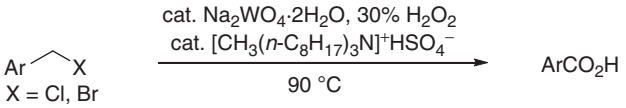
bromides to ketones in air for the synthesis of himandridine.[142] Furthermore, secondary α-bromoketimines are oxidized to α-imidoketones cleanly in the presence of silver carbonate (Ag_2CO_3) in acetonitrile under reflux condition.[143]

Direct oxidation of benzyl halides to carboxylic acids is also known. Oxidation of benzyl chlorides and benzyl bromides to carboxylic acids with potassium permanganate ($KMnO_4$) in the presence of base has been reported.[144–146] Furthermore, oxidation of benzyl halides with nitric acid (HNO_3) is known,[147] and in the presence of $NaVO_3$ and 65% aqueous HNO_3 at reflux, tetrakis(bromomethyl)benzene was oxidized to a tetracarboxylic acid.[148] However, bromomethyl pyridine can be directly oxidized to the corresponding carboxylic acid using catalytic amounts of T(*p*-NO_2)PPFeCl and $PhI(OAc)_2$ (Scheme 51).[149] Benzyl bromides and chlorides and alkyl iodides were oxidized to ketones and aldehydes or carboxylic acids using transition-metal periodate complexes such as $[M(OH)_2\{IO_5(OH)\}_2]^{6-}$ (M = Ni or Pt).[150] Benzyl bromides and chlorides were oxidized to carboxylic acids using OsO_4 with $K_3[Fe(CN)_6]$ or $NaBrO_3$ in aqueous NaOH solution.[151] In this reaction, *cis*-$[OsO_4(OH)^2]^{2-}$ was generated *in situ*. Furthermore, both aqueous $[RuO_4]^-/BrO_3^-$ and *trans*-$[Ru(OH)_2O_3]_2^-/S_2O_8^{2-}$ can convert the benzyl and allyl halide (bromide and chloride) to carboxylic acid.[152] In this reaction 1-iodobutane was a poor substrate. On the contrary, primary alkyl iodides can be oxidized to carboxylic acids using catalytic amounts of $RuCl_3 \cdot xH_2O$ and H_5IO_6 in H_2O.[153]



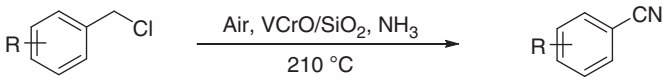
Scheme 51

Using $Na_2WO_4 \cdot 2H_2O$ and $[CH_3(n\text{-}C_8H_{17})_3N]^+HSO_4^-$, benzyl chlorides and bromides can be oxidized to carboxylic acids with 30% H_2O_2 as stoichiometric oxidant without any organic solvents (Scheme 52).[154] The substrates bearing electron-withdrawing groups can be more easily oxidized to the corresponding aromatic acids than those having electron-donating ones. Aliphatic chlorides remained intact under the reaction conditions. In this reaction, benzyl halides were first hydrolyzed to the corresponding benzyl alcohol. In addition, $(NH_4)_7Zn_{0.5}[\alpha\text{-}ZnO_4W_{11}O_{30}ZnO_5(OH_2)] \cdot nH_2O$, water-soluble heteropolyoxotungstate, can be used.[155]



Scheme 52

Interestingly, tolunitriles can be efficiently synthesized by selective ammoxidation of benzyl chlorides with $VCrO/SiO_2$ and NH_3 in the presence of air at high temperature (Scheme 53).[156–158] 2,6-Difluorobenzyl chloride also can be converted to 2,6-difluorobenzonitrile with vanadium–titanium oxide catalyst and NH_3 in a flow reactor.[159]



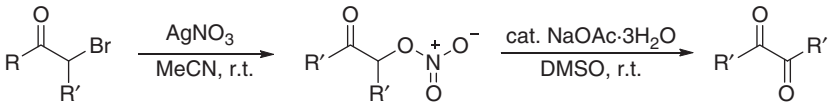
Scheme 53

7.24.7 Metal Nitrates and Nitrites

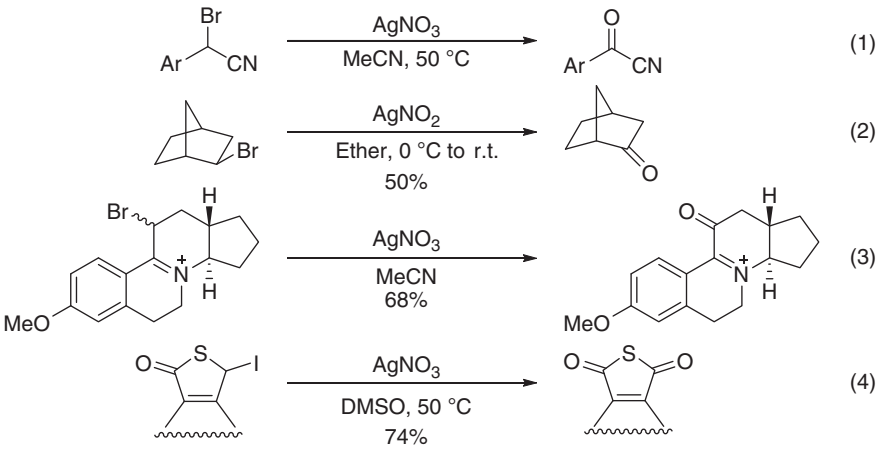
7.24.7.1 Silver Nitrate

Reaction of halides with silver nitrate to give nitrate esters has been known, and Kornblum showed that the nitrate esters derived from α-bromocarbonyl compounds decompose smoothly with catalytic sodium acetate in DMSO to give the 1,2-dicarbonyl compounds in high yield (Scheme 54).[160] Unfortunately, the method gave variable results with benzyl halides.

Some related oxidations are shown in Scheme 55.[161] Oxidation of secondary alkyl bromides proceeds in moderate yield (equation 2).[162] Furthermore, oxidation of an iminium salt is notable (equation 3)[163]; 5-iodothiobutenolide was also oxidized to thiomaleic anhydride (equation 4).[164]



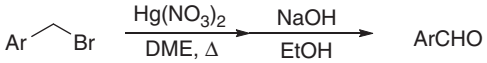
Scheme 54



Scheme 55

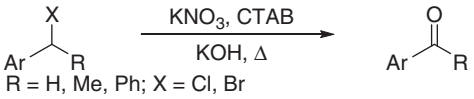
7.24.7.2 Other Metal Nitrates and Nitrites

The difficulty experienced by Kornblum in the oxidation of benzyl halides (*vide supra*) can be solved by using mercury(II) nitrate [$Hg(NO_3)_2$] (Scheme 56).[165] Under these conditions, 2- and 4-methoxybenzyl halides and nitrobenzyl halides are poor substrates because of difficulties with hydrolysis of the nitrate esters. Copper(II) nitrate[166] and lead(II) nitrate[167] have also been used. Furthermore, benzyl bromides can be oxidized to aldehydes using copper(II) nitrate on montmorillonite K10 clay (claycop) and H_2O_2 under microwave conditions.[168]



Scheme 56

Benzyl chlorides and bromides are oxidized to aldehydes and ketones using potassium nitrate (KNO_3) and 10% aqueous KOH using cetyltrimethylammonium bromide (CTAB), a phase-transfer catalyst, without any organic solvents (Scheme 57).[169] A 10% aqueous KOH solution is added dropwise with a dropping funnel to keep the pH value at 10–11 because aldehyde may decompose under the strongly basic conditions. Benzyl halides with strong electron-withdrawing nitro and electron-donating methoxy groups are poor substrates. No aliphatic aldehydes could be produced. Benzyl bromides can be oxidized to aldehydes using $NaNO_3$ in the presence of aqueous NaOH.[170] Furthermore, benzyl chloride oxidation to aldehyde with $NaNO_3$ catalyzed by PEG-600 in aqueous media was also reported.[171]

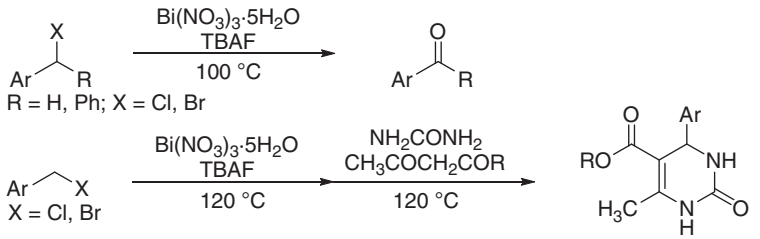


Scheme 57

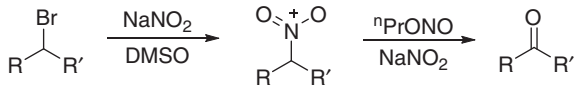
Benzyl bromides and chlorides can be oxidized to ketones and aldehydes using bismuth nitrate [$Bi(NO_3)_3$] in TBAF as an ionic liquid (Scheme 58).[172] Also, an efficient one-pot synthesis of 3,4-dihydropyridin-2(1*H*)-one from benzyl halide was reported. Aliphatic alkyl halides give the dihydropyrimidinones in less than 30% yields under the present reaction conditions.

Sodium nitrite ($NaNO_2$) in DMSO is a powerful nitrogen nucleophile, and this property has been used in a very mild, nonhydrolytic oxidation method for activated and unactivated bromides (Scheme 59).[173] A particularly impressive feature is the successful oxidation of secondary unactivated bromides prone to elimination.[174]

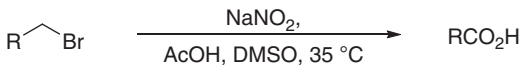
Furthermore, direct oxidation of benzyl and alkyl bromide to carboxylic acids was achieved using $NaNO_2$ in the presence of acetic acid in DMSO (Scheme 60).[175,176]



Scheme 58



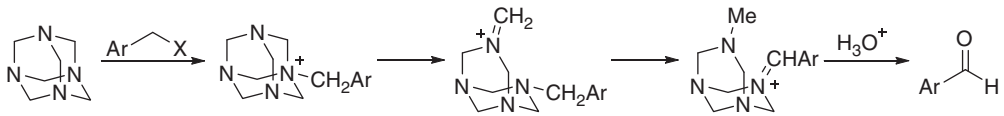
Scheme 59



Scheme 60

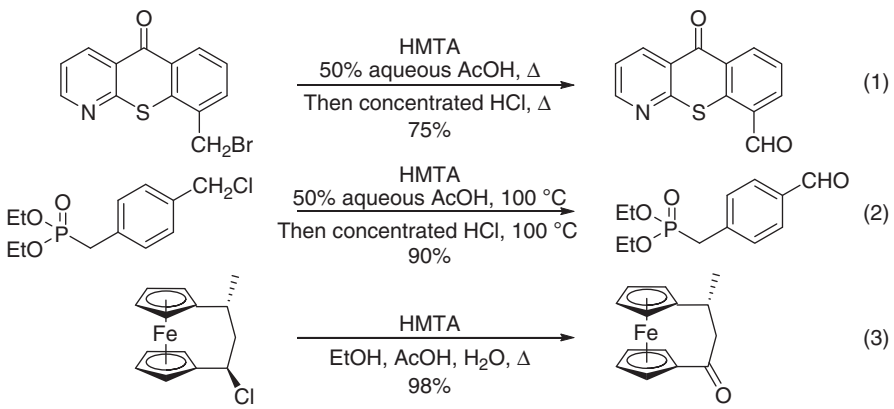
7.24.8 The Sommelet Oxidation

This is one of the oldest methods for the oxidation of halides, and has been used quite widely for the preparation of benzaldehydes and heteroaromatic aldehydes from halomethyl compounds.[177,178] Unactivated aliphatic alkyl halides give reduced yields. The reaction is experimentally simple: halide is heated with hexamethylenetetramine in a polar solvent such as aqueous acetic acid. With unreactive halides, the quaternary salt is first prepared in chloroform and then decomposed in a protic medium. At the end of the reaction it is normal to add hydrochloric acid to ensure the hydrolysis of the Schiff base. The reaction is believed to proceed as shown in Scheme 61.



Scheme 61

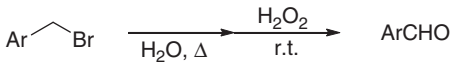
Scheme 62 shows some recent examples.[179–181] Benzyl chlorides and benzyl bromides are oxidized to aldehydes or ketones.



Scheme 62

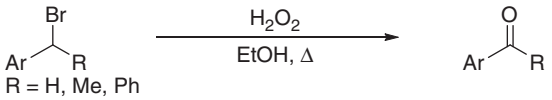
7.24.9 Hydrogen Peroxide

Hydrogen peroxide is an excellent oxidant due to the production of water as the only byproduct. One-pot oxidation of benzyl bromides to aldehydes was reported using H_2O_2 as an oxidant in H_2O without a catalyst (Scheme 63).[182] In this system, the reactive species BrOH, generated *in situ*, will affect the oxidation of benzylic alcohols to aldehydes. Unfortunately, aliphatic bromides remain intact under the reaction conditions.



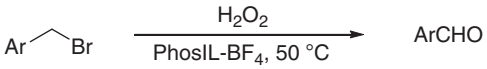
Scheme 63

Direct oxidation of benzyl bromides to aldehydes and ketones using H_2O_2 in EtOH was reported (Scheme 64).[183] In other solvents such as THF, $CHCl_3$, and CH_2Cl_2, a much longer time is required, and the conversion is poorer. Note that the reaction rate of secondary bromides is faster than that of primary bromides.



Scheme 64

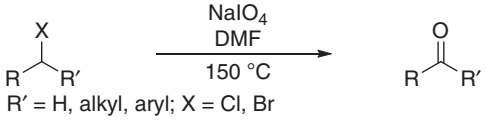
Benzyl bromides can be oxidized to aldehydes using H_2O_2 in trihexyl(tetradecyl)phosphonium tetrafluoroborate (PhosIL-BF_4), a highly basic phosphonium ionic liquid, in high yields (Scheme 65).[184] The ionic liquid can be recycled and reused approximately 10–20 times with only a slight change in its efficiency (0.5–1%). As phosIL-BF_4 is less dense than water, the product is separated by just decanting the aqueous layer. Benzyl chlorides and bromides can also be oxidized to aldehydes and ketones using 30% H_2O_2 under solvent-free conditions with microwave irradiation.[185]



Scheme 65

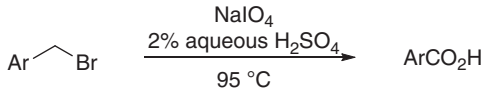
7.24.10 Halogen and Halogen Compounds

Alkyl and benzyl halides (X=Cl, Br) can be oxidized to ketones and aldehydes using $NaIO_4$ in DMF for short time periods (Scheme 66).[186] In this reaction alkyl bromides, such as octyl bromide and cyclohexyl bromide, can be oxidized in good yields. However, phenacyl bromide is converted to benzaldehyde via phenyl glyoxal. When a DMF-like ionic liquid is used, these reactions proceed even at lower temperatures.[187] Furthermore, benzyl chlorides and benzyl bromides are converted to aldehydes by 1-butyl-3-methyl imidazolium periodate ($[BMIM]^+IO_4^-$) at room temperature in high yields.[188] In addition, benzyl halides (X=Cl, Br, and I) can be oxidized to aldehydes or ketones with iodic acid (HIO_3) supported by montmorillonite K10 under microwave irradiation without solvent.[189]



Scheme 66

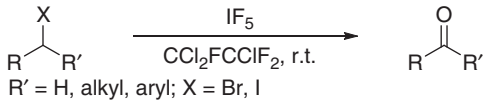
Oxidation of benzyl halides with sulfuric acid (H_2SO_4) has been known,[190] and in the presence of $NaIO_4$ and 2% aqueous H_2SO_4, benzyl bromides can be directly oxidized to carboxylic acids (Scheme 67).[191] In this reaction, benzylic bromides are



Scheme 67

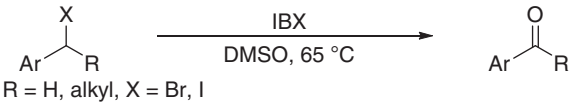
hydrolyzed in the presence of $NaIO_4$ in acidic medium to give alcohols, which are directly oxidized to the corresponding carboxylic acids with Br_2 through a free radical pathway. Benzyl chloride is resistant to oxidation under the reaction conditions.

Alkyl iodides and benzyl bromides can be oxidized to aldehydes or ketones using iodine pentafluoride (IF_5) (Scheme 68).[192] Alkyl bromides react only slightly, and benzyl and alkyl chlorides are unreactive under the reaction conditions. The reaction proceeds through an intermediate iodine(III) or bromine(III), respectively.



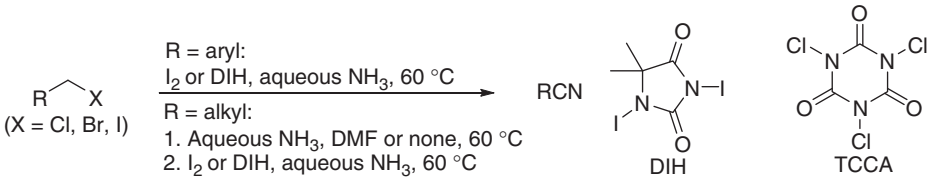
Scheme 68

2-Iodoxybenzoic acid (IBX) also has been used for oxidation of benzyl bromides and iodides to aldehydes and ketones in DMSO (Scheme 69).[193] Cinnamyl bromide as well as sterically hindered mesityl bromide undergo smooth conversion to the corresponding aldehyde in reasonable yields. Although benzyl chlorides are converted to aldehydes in 30% isolated yield, 1-bromooctane was unreactive. The conversion of olefins to bromohydrins using *N*-bromosuccinimide (NBS)-H_2O in DMSO can be nicely adapted to IBX oxidation, and olefins are converted to the corresponding 1,2-diketones in one pot. Furthermore, benzyl bromides are converted to benzimidazoles by oxidation of benzyl bromides to aldehydes with IBX, followed by oxidative cyclization with *o*-phenylenediamine in a one-pot procedure in moderate yields.[194] However, when phosphonium ionic liquid (PhosIL-BF_4) is used, benzyl chloride is also oxidized to aldehyde in high yield.[195]



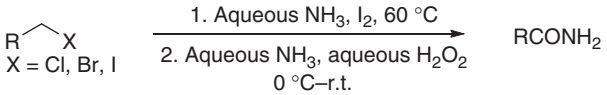
Scheme 69

Interestingly, benzyl halides (X=Cl, Br, and I) can be oxidized to nitriles using molecular iodine (I_2) or 1,3-diiodo-5,5-dimethylhydantoin (DIH) in aqueous ammonia (Scheme 70).[196,197] Alkyl halides are converted to nitriles in one pot. The initial nucleophilic reaction of ammonia with halides occurs to generate the corresponding amines. The amine is oxidized with molecular iodine or DIH through the aldimines to the nitriles. Trichloroisocyanuric acid is also used for the same reaction.[198] In this reaction, aliphatic nitriles cannot be observed. Furthermore, direct oxidation of benzyl bromides to nitriles is also accomplished using catalytic amounts of I_2, pyridine, *tert*-butyl hydroperoxide, and K_2CO_3 in aqueous ammonia.[199]



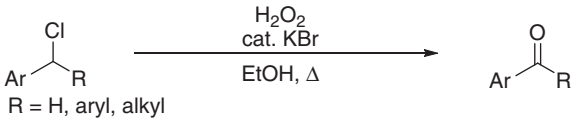
Scheme 70

One-pot oxidative conversion of benzyl halides (X=Cl, Br, and I) to aromatic amides proceeds when using (1) molecular iodine in aqueous ammonia and (2) hydrogen peroxide in aqueous ammonia (Scheme 71).[200] Alkyl halides provide the corresponding amides in low yields, along with the starting alkyl halides and amines.



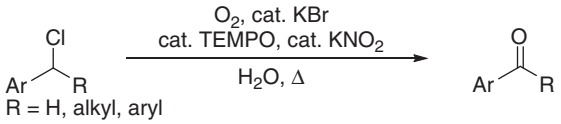
Scheme 71

Benzyl chlorides can be oxidized to aldehydes and ketones with catalytic amounts of KBr using H_2O_2 as the stoichiometric oxidant in EtOH (Scheme 72).[183] The actual oxidizing agent is hypobromous acid.



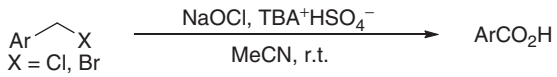
Scheme 72

Various benzyl chlorides are successfully oxidized to the corresponding aldehyde and ketone in aqueous media with molecular oxygen as the oxidant in the presence of catalytic amounts of TEMPO, KBr, and KNO_2 (Scheme 73).[117] KBr is helpful for this reaction by producing HBr, which plays an essential role in the catalytic cycle. It appears likely that the hydrolysis of the halides is the rate-determining step. Since secondary halides are hydrolyzed faster than primary ones, the former are oxidized faster. Furthermore, benzyl chlorides and bromides can be oxidized to aldehydes with $(n\text{-Pr})_4NBrO_3$ or $(n\text{-Bu})_4NBrO_3$ in EtOH.[201] Additionally, 2-bromo-1,3-dicarbonyl compounds can be oxidized to 1,2,3-tricarbonyl compounds by bromination with bromides, and hydrolysis with sodium ethoxide.[202]



Scheme 73

However, benzyl bromides and benzyl chlorides can be directly oxidized to carboxylic acids with sodium hypochlorite (NaOCl) in the presence of $TBA^+HSO_4^-$ (Scheme 74).[203] Secondary benzyl halides are also converted to ketones. Oxidation of *p*-fluorobenzyl chloride to the corresponding carboxylic acid as a major product using NaOCl in water is also reported.[204] Under ultrasonic irradiation conditions, secondary benzyl bromides are oxidized to ketones in high yield.[205] Primary benzyl chlorides and bromides give a mixture of aldehydes and carboxylic acids. With this reaction, cyclohexyl bromide is not oxidized at all.

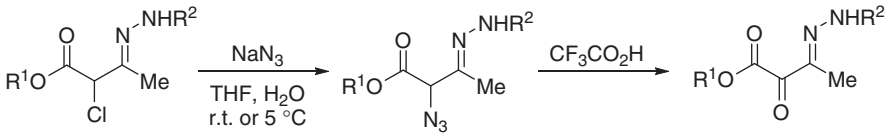


Scheme 74

Secondary alkyl bromides are oxidized to ketones using Selectfluor.[206] Bromide is displaced even at room temperature to afford the alcohol. Selectfluor oxidizes bromide ions to bromine, which oxidizes alcohols to ketones. Furthermore, secondary alkyl iodides can be oxidized to ketones with moist mercuric fluoride by heating in nitromethane.

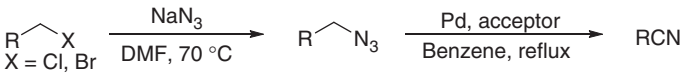
7.24.11 Azides

Azidation of α-halocarboxyl compounds with sodium azide (NaN_3), followed by decomposition of the intermediate α-azidocarbonyl compounds to 1,2-dicarbonyl compounds has been reported.[207–212] For instance, 2-chlorohydrazone can be oxidized through a 2-azidohydrazone intermediate, which hydrolyzes to 2-oxohydrazone with CF_3CO_2H (Scheme 75).[213]



Scheme 75

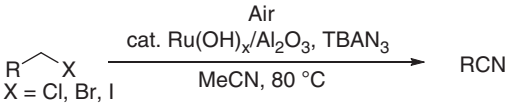
Furthermore, synthesis of nitriles from alkyl and aryl halides (X=Cl, Br) was demonstrated through azidation of halides, and conversion to the nitriles in the presence of Pd (Scheme 76).[214] In the presence of hydrogen-acceptors [$HOC(CH_3)_2C{\equiv}CC(CH_3)_2OH$, $PhC{\equiv}CPh$], yields of the nitriles are increased. Bromine trifluoride (BrF_3), which requires special care, was also used



Scheme 76

for conversion of azides to nitriles.[215] Furthermore, a one-pot reaction of benzyl and allyl halides (X=Cl, Br) to aryl and vinyl nitriles using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone as an oxidant was also reported.[216]

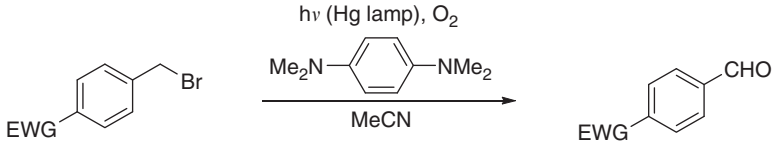
The direct synthesis of nitriles from primary halides, including benzyl, allyl, and alkyl ones, using $TBAN_3$ could be realized with $Ru(OH)_x/Al_2O_3$ in moderate to high yields (Scheme 77).[217] The $Ru(OH)_x/Al_2O_3$-catalyzed transformation of primary azides to nitriles possibly proceeds via the concerted activation of primary azides by the Lewis acid and Brønsted base sites to form imide intermediates. The catalyst can be reused for the transformation of benzyl azide without an appreciable loss of its high performance.



Scheme 77

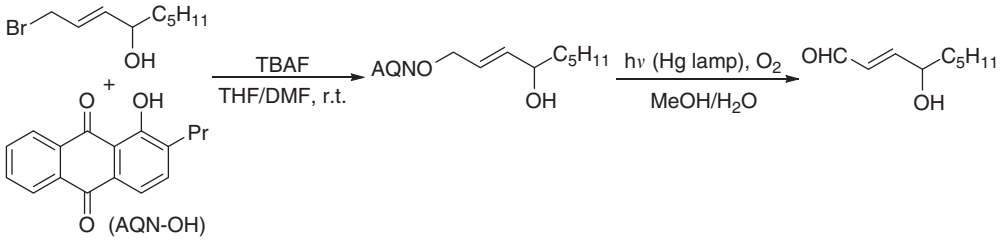
7.24.12 Photooxidation

Electron-poor benzyl bromides can be oxidized to aldehydes using *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine under photoirradiation by a 400 W Hg lamp with O_2 bubbling (Scheme 78).[218] In its excited state the photosensitizer gives an electron to the substrate.



Scheme 78

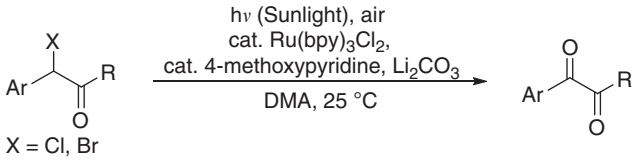
Benzyl bromides and alkyl iodides can be oxidized to aldehydes via anthraquinone derivatives, which are prepared by reaction of 1-hydroxyanthraquinone with halides (Scheme 79).[219] For instance, 4-hydroxy-2-nonenal can be synthesized from 1-bromo-2-nonen-4-ol via 1-alkoxyanthraquinone.[220] Furthermore, benzyl bromides can be oxidized to aldehydes using resin-supported 1-hydroxyanthraquinone.[221] However, the oligomers [d(GCNiTA)] and [d(CANiGT)] are transformed into new oligonucleotides, accompanied by the 7-nitrosoindole.[222]



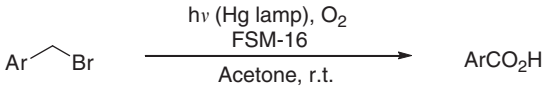
Scheme 79

α-Haloarylacetic acid esters (chloride and bromide) are oxidized smoothly to produce the corresponding carbonyl products in good yields using $Ru(bpy)_3Cl_2$ and 4-methoxypyridine and Li_2CO_3 under natural sunlight and air (Scheme 80).[223] Oxidation of benzyl halides is not effective under these optimized conditions, and the products are obtained in moderate yields. However, bis(di-imine) copper(I) complex, a redox photocatalyst, can be used for the oxidation of *p*-nitrobenzyl bromide to *p*-nitrobenzaldehyde under photoirradiation conditions in the presence of triethylamine through electron transfer.[224]

Benzyl bromides can be oxidized to carboxylic acids and ketones directly using FSM-16, mesoporous silica, as a promoter under photoirradiation by a 400 W Hg lamp at room temperature (Scheme 81).[225] When a substrate that possesses a nitro group



Scheme 80

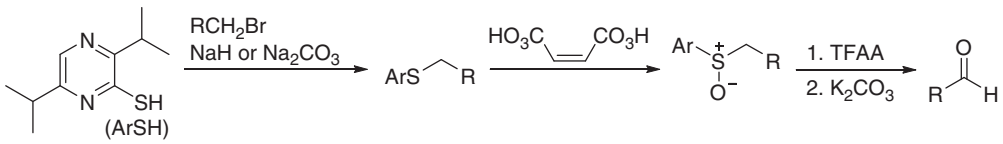


Scheme 81

is used, aldehydes are the main products. In this reaction, benzyl chloride is much less reactive than the corresponding bromide. Aliphatic bromides remain intact under the reaction conditions. Interestingly, methyl benzoate is obtained as the main product instead of the carboxylic acid when methanol is used as the solvent. FSM-16 was found to be a recyclable photocatalyst. Oxidation of benzyl chlorides to carboxylic acids or aldehydes by photobromination with NBS or Br_2 and hydrolysis was also reported.[226,227]

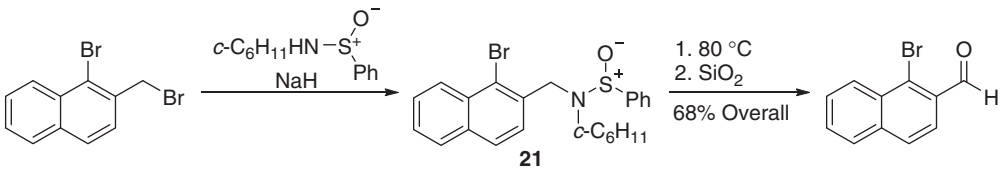
7.24.13 Pummerer Rearrangement

A general oxidation method for activated and unactivated bromides through a Pummerer rearrangement of a pyrazinyl sulfoxide was reported (Scheme 82).[228] This is an improvement of an earlier procedure in which benzenethiol was used as the precursor.[229] Benzyl and aliphatic bromides and chlorides can be oxidized to aldehydes using a Merrifield resin-supported sulfide linkage as a safety-catch linker.[230] A related method based on the chlorination of sulfides was also reported.[231]



Scheme 82

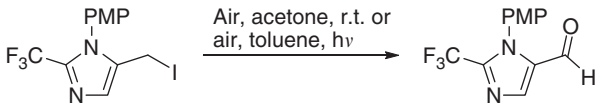
In these reactions, problems can arise at the last stage due to difficulties in the isolation of the aldehyde and/or preferential vinyl sulfide formation. Sulfoxides are prone to thermal elimination, and this has been used by Trost in his method, wherein benzyl chlorides and allyl bromides are oxidized to aldehydes using sulfinamide through nucleophilic substitution of halides, thermal dehydrosulfenylation of **21** to imine, and hydrolysis (Scheme 83).[232]



Scheme 83

7.24.14 Miscellaneous Methods

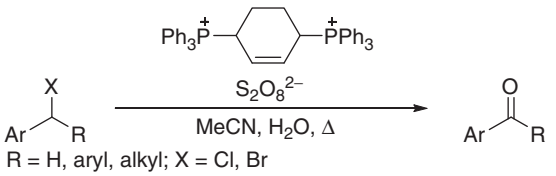
2-Bromo-1,3-dicarbonyl compounds can be oxidized to 1,2,3-tricarbonyls using dimethyldioxirane in the presence of DMAP.[233] This reaction proceeds at ambient temperature in good yields. However, α-chloroesters can be oxidized to 1,2-oxoesters using sodium cyanate (NaOCN), albeit in low yield.[210] 5-Iodomethyl imidazole is oxidized to the corresponding aldehyde under an atmosphere of air in polar or nonpolar solvent (Scheme 84).[234] The C–I bond dissociates into a radical intermediate and an iodine radical. In the presence of O_2, the radical intermediate is converted to a peroxy intermediate. The aldehyde forms by means



Scheme 84

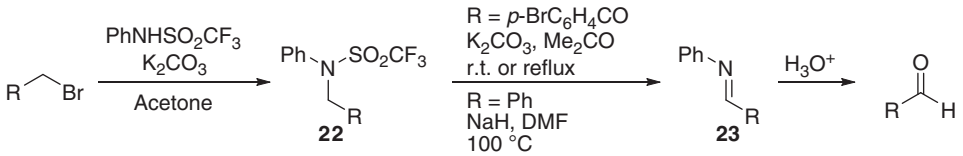
of removal of a hydroxyl radical in acetone, a polar solvent. In toluene, a nonpolar solvent, light plays a significant role in the C–I bond cleavage step.

However, benzyl chlorides and bromides can be oxidized to aldehydes and ketones with 3,6-bis(triphenylphosphonium)cyclohexene peroxodisulfate under mild and neutral conditions (Scheme 85).[235] Allyl and alkyl halides are resistant toward this transformation and remained intact. This reaction probably proceeds though an single electron transfer mechanism. Benzyl chlorides and benzyl bromides also can be oxidized to aldehydes with tetrakis(pyridine)silver(II) peroxodisulfate in modest yield.[236]



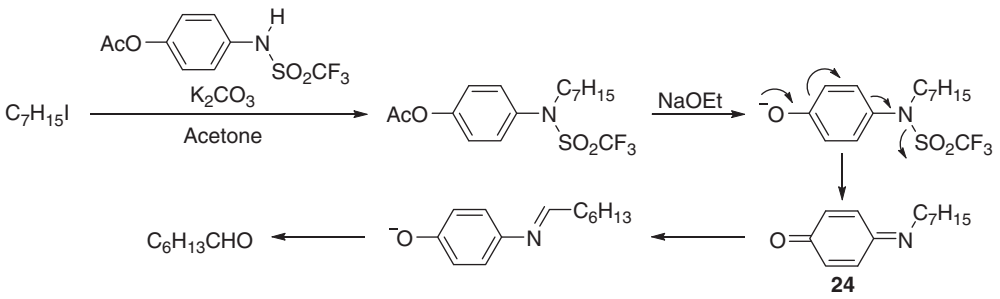
Scheme 85

The anion of *N*-phenyltriflamide is nucleophilic enough to react with activated and unactivated halides under mild conditions. Treatment of the adduct **22** with base eliminates trifluoromethanesulfonate to give the imine **23**, which is then hydrolyzed to the aldehyde in acid (Scheme 86).[237] The method works quite well with phenacyl bromide.[238] With benzyl bromide, the elimination requires sodium hydride in hot DMF, whereas aliphatic substrates do not undergo elimination at all.



Scheme 86

This drawback was surmounted by the use of *N*-4-acetoxyphenyltriflamide (Scheme 87).[238] Elimination now occurs through the quinoneimines **24** under mild conditions, even with aliphatic substrates.

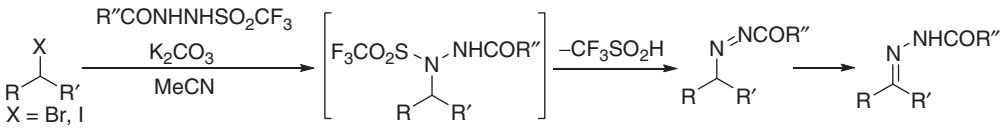


Scheme 87

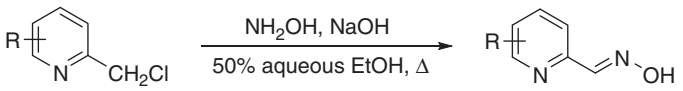
Despite the ingenious chemistry, there appear to be few advantages over other methods (Scheme 88).[239] A procedure exists for the synthesis of hydrazones from halides.

Interestingly, 2-chloromethyl pyridine can be converted to aldoximes directly with NH_2OH in the presence of base (Scheme 89).[240] Under these conditions, *p*-chlorobenzyl chloride gave dialkyl hydroxylamine as the only product.

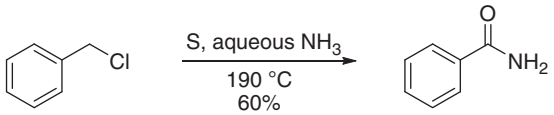
Benzyl chloride can be converted to benzamide in the presence of sulfur and aqueous ammonia, the Willgerodt condition, at 190 °C in 60% yield (Scheme 90).[241]



Scheme 88

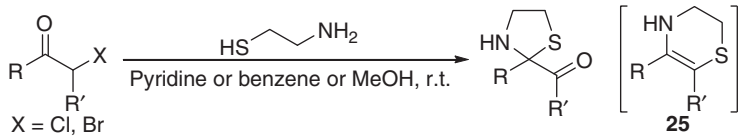


Scheme 89



Scheme 90

Cyclic and acyclic α-haloketones are converted to spirothiazolidin-2-ones with 2-aminoethanethiol (**Scheme 91**).[242] The conversion of α-haloketones presumably involves the autooxidation of 1,4-thiazine intermediate **25**. The use of microwave irradiation can shorten significantly the reaction time.



Scheme 91

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7.25 The Beckmann and Related Reactions

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Glossary

Dynamic path bifurcation The phenomenon in which two reactions share a common transition state, representing a fundamental departure from conventional transition state theory. In the context of the Beckmann reactions, according to 'dynamic path bifurcation' the rearrangement and fragmentation pathways pass through a 'nodal' transition state, on either side of which the paths diverge.

One-pot This indicates that a number of independent reactions or conversions are carried out in the same flask, without work-up at the intermediate stages. In the context of the Beckmann reaction, this usually implies starting from a ketone or an aldehyde to prepare the corresponding amide, without isolating the intermediate oxime.

Quasi-Beckmann reaction A reaction that employs an oxime analog as a substrate and mimics the overall bonding changes characteristic of a classical Beckmann reaction. An example is the photolysis of a cyclic nitrone leading to a lactam.

Second-order Beckmann reaction The fragmentation of an oxime leading to a nitrile and a carbocationic intermediate. In this process, one of the C–C bonds at the oxime carbon atom is broken in concert with the cleavage of the N–O bond.

Self-propagating A term proposed for a catalyzed Beckmann reaction in which a catalytic cycle reproduces the intermediate nitrilium cation, which reacts with the oxime substrate and thus acts as the *de facto* catalyst. This cycle acts alongside the catalytic cycle involving the original catalyst, although at a different rate.

7.25.1 Introduction

The continuing importance of the classical Beckmann reaction into the third century after its initial discovery not only indicates its practical significance but is also interesting in a general conceptual sense.[1] Thus, it parallels the importance being enjoyed by the analogous Baeyer–Villiger reaction, and indeed several other classical reactions, e.g., Cannizzaro, Hofmann, and Perkin. This indicates that the patterns of bond-breaking and bond-making established during the era of the pioneers represent a fundamental basis of chemical reactivity – a blueprint that can never be supplanted.

The synthetic utility of the Beckmann reaction stems from several inherent advantages. Operationally, it is a thermodynamically driven rearrangement, which implies excellent atom efficiency and an equilibrium overwhelmingly favoring the amide product. (This derives from the resonance stabilization enjoyed by the carboxylic amide group, via conjugation of the

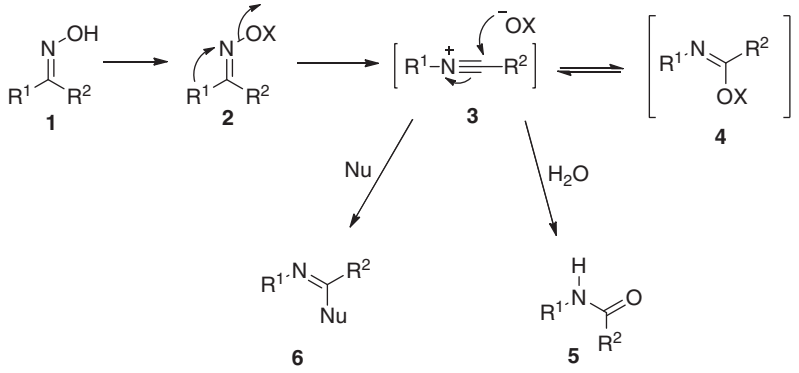
 doi:10.1016/B978-0-08-097742-3.00730-8

nitrogen lone pair with the carbonyl group, and believed to be worth ~20 kcals mol^{-1}.)[2] A reasonably well-established mechanism also indicates that there would be few surprises in the case of complex substrates. Essentially, however, the structural transformations that the reaction accomplishes constitute its forte: the oxime substrates derive from ketones that are more versatile and easily modified than the amide product.

The structural diversity that is carried over to the product is particularly invaluable in the case of the nitrogen substituent in the amide, there being few methods that can rival this feature of the Beckmann reaction. Thus, the α-alkylaktion of a ketone enolate followed by the Beckmann reaction (via the 'anti-oxime') is a *de facto* α-alkylation of the nitrogen center in the product amide. (Carbon-nucleophilic addition to iminium ions is an alternative 'umpolung' version of this transformation.)[3] Similarly, the potential of the Beckmann reaction to provide access to a variety of *N*-aryl derivatives is also noteworthy, and is a feature almost unique to the family of reactions occurring via migration to electrophilic nitrogen (which includes the Hofmann and related rearrangements).

Although the Beckmann reaction is thermodynamically driven, the oxime substrates possess considerable kinetic stability. Thus, the activation of the oxime hydroxyl group, thereby enhancing its nucleofugacity, is not only necessary but also the key to designing newer versions that enable the reaction under milder conditions. Classical *O*-activation procedures generally employed strong electrophiles, e.g., PCl_5 and RSO_2Cl, and a few effected the reaction at low temperatures. Recent studies have been motivated by the need to develop catalytic *O*-activation, and by environmental concerns. To this end solvent-free methods, and nonconventional techniques (ultrasound, microwave, supercritical water, etc.), have been investigated.

The mechanism of the Beckmann reaction is now well established (**Scheme 1**), and most chemists are aware of its broad features. Thus, the reaction is 'triggered' by the heterolysis of the *N*–*O* bond in the oxime (**1**), via an activated oxime derivative (**2**), which draws the anti (alkyl or aryl) group to migrate nucleophilically to the developing electron-deficient nitrogen center (one of the earliest demonstrations of a stereoelectronic effect). The process is essentially concerted, the migration being stereospecific with retention, and leads to the formation of a cationic nitrilium intermediate (**3**). This is trapped by an available nucleophile, most often the nucleofuge in the rearrangement (to form **4**, possibly reversibly), that is subsequently hydrolyzed during work-up to the amide **5**; however, trapping by other external or internal nucleophiles is indeed possible (to form **6**) and has greatly enhanced the scope and versatility of the reaction.[1]

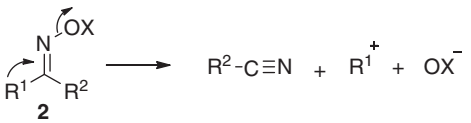


Scheme 1

The transition state of the key migration step is thus believed to be highly polarized, and therefore the reaction would be accelerated in polar solvents. This is supported by the observation that the reaction generally occurs in a nucleophilic solvent. (However, water – an environmentally desirable solvent – is generally ruled out because of the ready hydrolysis of oximes.)

The ready availability of caprolactam, the monomeric precursor for the manufacture of Nylon-6, via the Beckmann rearrangement of cyclohexanone oxime, remains one of the most important industrial applications of the reaction. (Analogous conversions, particularly of cyclododecanone oxime to laurolactam, have also been studied.) The conversion of substituted acetophenone oximes to corresponding acetanilides has been of interest vis-à-vis the preparation of paracetamol (acetaminophen). Such applications continue to serve as an important driving force for the study of various aspects of the Beckmann reaction.

This chapter reviews developments since the first edition,[1] avoiding repetition of earlier material and focusing on new trends and applications. Thus, the literature from around the mid-1990s onwards is covered, the treatment being exemplary rather than exhaustive. In addititon, the 'second-order' Beckmann fragmentation reaction (equation 1) is discussed toward the end, in Section 7.25.4 dealing with complex molecules. This is because the fragmentation mode is often an unwanted side reaction of the rearrangement mode, and finds its most important applications in relatively complex systems.



(1)

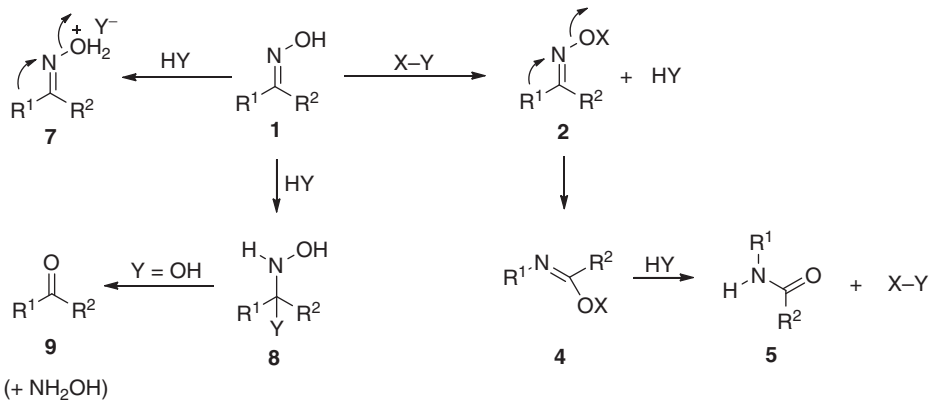
7.25.2 Rearrangement Reactions

7.25.2.1 Ketoximes

A veritable plethora of reagents, both stoichiometric and catalytic, has been reported to effect the Beckmann reaction of ketoximes. Indeed, it would not be much of an exaggeration to state that every conceivable electrophilic activator is being thrown at the oxime function in order to coax it to rearrange – in fact, the Beckmann reaction has served as an important probe for testing the strength of 'designer electrophiles.'

7.25.2.1.1 Catalytic methods

The development of catalytic activators has understandably received particular attention. Intriguingly, the catalyst-driven Beckmann reaction is not as straightforward as it may appear, essentially because of a number of possible competing processes. In particular, the hydrolysis of the oxime substrate and the regeneration of the catalyst via cleavage from the rearranged product can be major hurdles. These complications are set out in Scheme 2.



Scheme 2

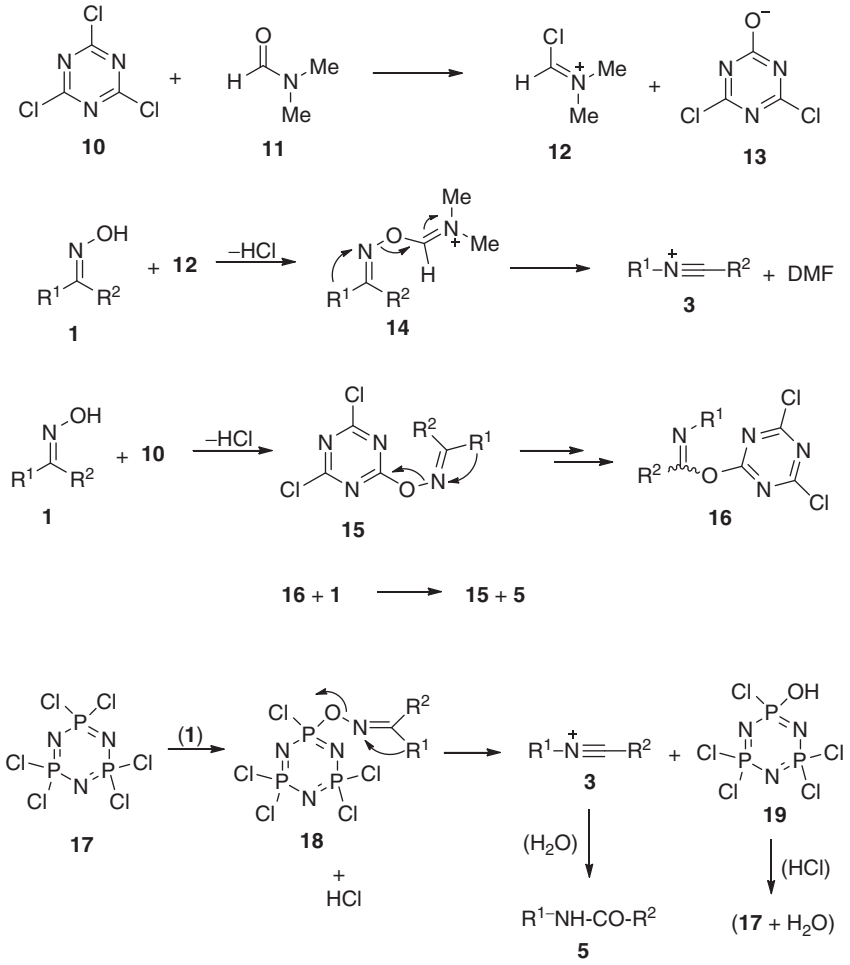
Attack of the oxime **1** by the electrophile X–Y forms the activated species **2** along with the acid HY. This may protonate unreacted **1** to form **7**, which could undergo the Beckmann rearrangement as indicated, generating water in the process; this, of course, would add to the nitrilium cation **3** (Scheme 1) formed alongside, but could also competitively hydrolyze **1** in the increasingly acidic medium. The HY may also add to unreacted **1** to form **8**, which may suffer hydrolysis to the corresponding ketone (**9**), particularly if Y is a hydroxyl group (or **8** may also react with water). It is also possible that the formation of **8** is to some extent irreversible, thus inhibiting the main rearrangement process. Furthermore, the rearrangement of **2** leads to **4**, which would need to react with HY to form the amide (**5**), concurrently regenerating X–Y. If this process is inefficient, it will adversely affect the overall catalytic function of X–Y.

Clearly, an efficient catalyst for the Beckmann reaction, apart from being a strong electrophilic activator, would not only avoid the formation of **7** and **8**, but also be easily regenerated from **4**. It is noteworthy, however, that X–Y being a strong electrophilic activator implies that Y is a strongly electronegative group and also that the O–X bond is relatively strong; this implies that HY is a relatively strong acid (and thus the formation of **8** is not easily reversed), and that the O–X bond in **4** is not easily cleaved. (Although this cleavage would be thermodynamically driven, a strong O–X bond in **5** represents a corresponding kinetic barrier to the regeneration of X–Y.) Thus, the success of X–Y as a catalyst hinges on striking a fine balance between conflicting reactivity trends.

7.25.2.1.1.1 Organocatalytic methods

A number of catalytic (including organocatalytic) Beckmann reactions have been claimed in recent years. Particular mention should be made here of the 1,3,5-triazine-based systems, first reported in the stoichiometric form by Giacomelli and coworkers in 2002,[4] and later in the catalytic version by Yamamoto and coworkers in 2005.[5] In these procedures, the oxime (**1**) is reacted with 2,4,6-trichloro[1,3,5]triazine (cyanuric chloride, **10**, Scheme 3). The conditions, are however, different for the two versions, and interesting mechanistic differences are also manifested.

The stoichiometric version employs dimethylformamide (DMF, **11**) as the solvent at room temperatures, whereas the catalytic version employs refluxing acetonitrile (MeCN).[4] The reaction in DMF is believed to involve a Vilsmeier – Haack iminium intermediate (**12**), which activates the oxime hydroxyl group via the formation of **14**. The subsequent rearrangement process forms nitrilium cation **3**, and regenerates DMF but not **10**, which has suffered hydrolysis (thus forming the conjugate acid of **13** as byproduct). A range of ketoxime substrates undergo the reaction in generally high yields in 3–12 h, although sterically hindered substrates need 24 h. (Aldoximes furnished corresponding nitriles in quantitative yields, under similar conditions.)



Scheme 3

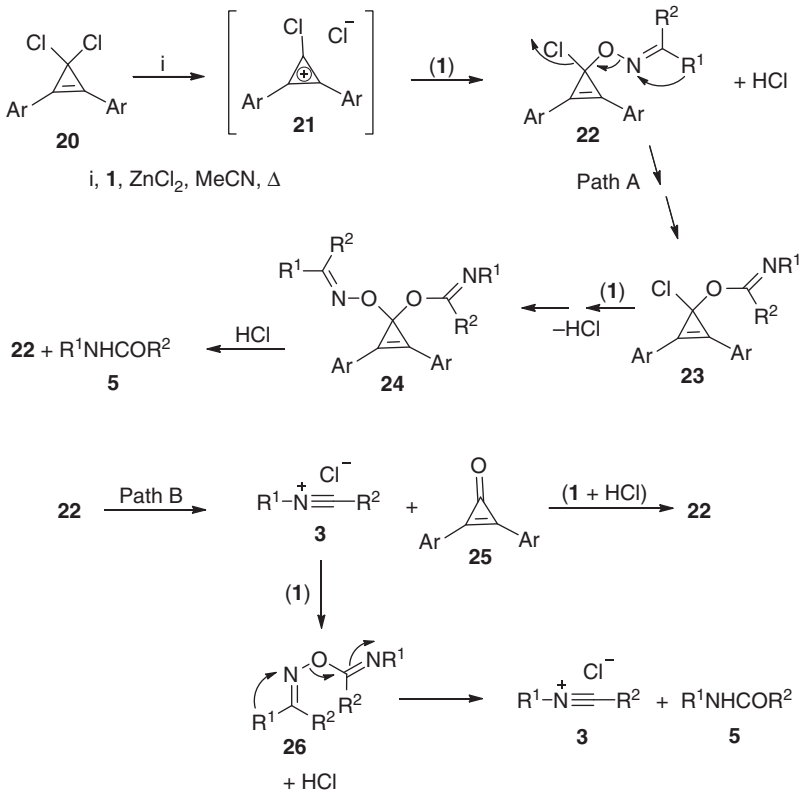
The catalytic version is believed to occur via nucleophilic displacement of chloride in **10** by the oxime hydroxyl group in **1** to form the activated derivative **15**.[5] Rearrangement of this leads to the nitrilium adduct **16**, which reacts with another molecule of oxime to form **15** and the amide product (**5**). This propagates the reaction without regenerating the original cyanuric chloride (**10**). Reaction times are shorter than for the stoichiometric case, with yields being generally comparable. The catalytic process is also promoted by acidic cocatalysts (preferably $ZnCl_2$), which also decrease the amount of **10** needed (from 5 mol% to 2 mol%).

An interesting triphosphazene analog **17** was subsequently reported by Ishii and coworkers as an effective catalyst for the Beckmann reaction.[6] The preferred solvent was hexafluoroisopropanol (HFIP) or MeCN, the reactions being carried out for 2 h at reflux, with 1 mol% of **17**. The yields were also comparable to those with **10**, although a smaller range of substrates was employed. The postulated reaction mechanism is analogous to the case of catalytic **10** discussed in Section 7.25.2.1.1.1, and involves initial nucleophilic displacement of chloride at the phosphorus center in **17** by the oxime hydroxyl group. The resulting activated oxime derivative (**18**) undergoes rearrangement. Subsequently, however, **17** is regenerated by reaction of the hydroxytriphosphazene byproduct (**19**) with the hydrochloric acid byproduced in the Section 7.25.2.1.1.1 activation step.

All these procedures lead to clean rearrangement, i.e., without any accompanying fragmentation, although this may reflect the set of oxime substrates chosen. Moreover, a later report by the Ishii group indicates that the reactions with catalytic **10** or **17** may be accomplished at much lower relative catalyst concentrations (0.5 mol%) in a 3:2 mixture of trifluoroacetic acid (TFA) and toluene as solvent.[7]

An interesting organocatalytic Beckmann reaction reported relatively recently employs the cyclopropenium cation, a 2π electron aromatic system, as electrophilic activator. An initial study by Yadav and coworkers employed 3,3-dichloro-1,2-diphenylcyclopropene (**20**, Ar = Ph, **Scheme 4**) as the precursor for generating the 1-chloro-2,3-diphenylcyclopropenium cation (**21**, Ar = Ph).[8] Thus, treating various ketoximes in refluxing acetonitrile with **20** and $ZnCl_2$ (3 mol% each) effected the Beckmann reaction, generally in high yield within 1–2 h. The authors proposed a catalytic cycle (cf. Path A) in which the activated oxime (**22**) rearranged to **23**, which underwent nucleophilic substitution of chloride by another molecule of oxime (**1**) to form **24**. This served to activate the oxime toward rearrangement, and enabled the propagation of the catalytic cycle via the reaction of **24** with

HCl, thus regenerating **22** and releasing amide **5**. (The $ZnCl_2$, among several other metal halides, presumably assists the ionization of **20** to **21**.)



Scheme 4

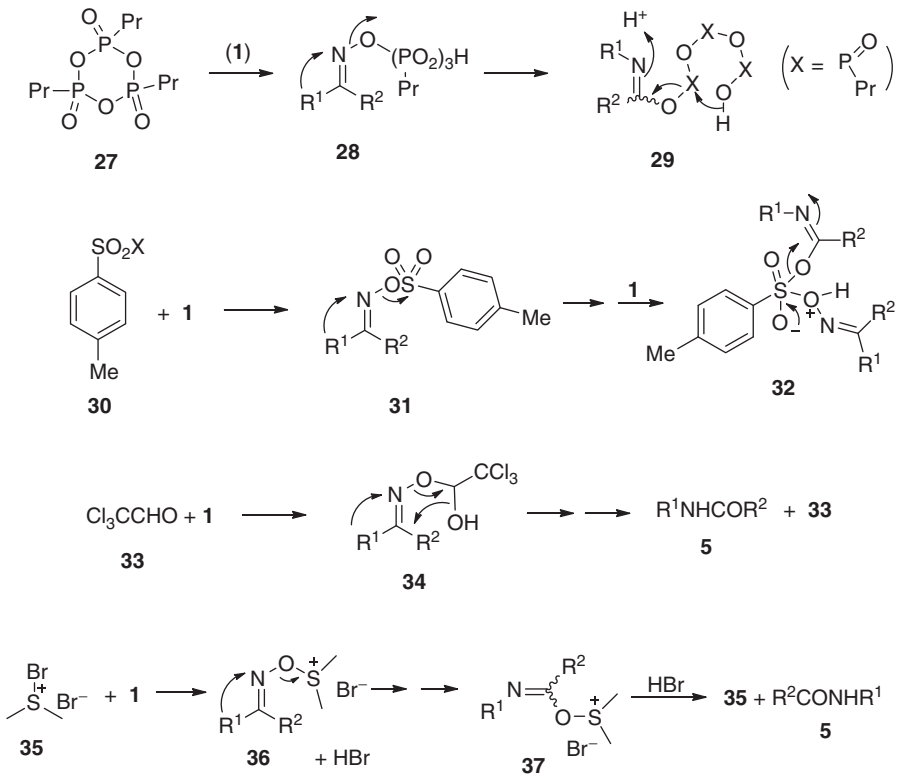
A subsequent report by Vanos and Lambert essentially confirmed the preparative value of the above cyclopropenium ion-catalyzed Beckmann reactions.[9] This study also employed a variety of disubstituted chlorocyclopropenium cations (**21**), generated from the corresponding cyclopropenones (**25**) in $MeNO_2$ as solvent. Employing **21** in stoichiometric amounts effected the reaction at ambient temperatures in 0.5–1.5 h. However, the catalytic version required heating at 60 °C for up to 1.5 h. Yields were generally high with 5–10 mol% catalyst loading. A positive correlation was also observed between the substituent-induced stability of the cyclopropenium system in **21** and the reaction efficiency. Optimal results in terms of yield, reaction time, and catalyst loading were obtained with xylyl and mesityl-substituted systems.

These authors, however, also raise intriguing mechanistic questions.[9] In particular, they make a distinction between genuine catalysis and self-propagation, based on a 'subcycle' involving catalysis by the nitrilium cation intermediate (cf. Path B). This latter self-propagation mode may become dominant as the reaction proceeds and the nitrilium intermediate concentration builds up. It is noteworthy that this would represent a special case of autocatalysis, involving the intermediate formed in the rate-limiting step (rather than the final product).

These arguments are supported by the finding that stable imidoyl chlorides (adducts of the nitrilium cation and Cl^-) effect the Beckmann reaction as efficiently as does cyanuric chloride (**10**).[9] These authors essentially claim that there exist no genuine cases of catalysis in the case of the Beckmann reaction. However, further analysis of this interesting mechanistic controversy, which is still evolving, is clearly beyond the scope of this chapter.

A few other organocatalytic approaches that have been claimed recently are noteworthy. (The key steps in the proposed catalytic cycles for these procedures are indicated in **Scheme 5**.) Augustine and coworkers have employed 15 mol% propylphosphonic anhydride (**27**) in THF at 70 °C (1–3 h), to obtain excellent yields of the amide products across a wide range of ketoxime substrates.[10] Aldoximes furnished the corresponding nitriles under similar conditions. The authors propose a viable catalytic cycle, via the oxime propylphosphonate (**28**), and the regeneration of the original catalyst as indicated in **29**. It is particularly noteworthy that this is one of the few organocatalytic protocols to afford high yields in the conversion of cyclohexanone oxime to caprolactam.

Deng and coworkers report the Beckmann rearrangement of several ketoximes with a mixture of *p*-toluenesulfonyl (tosyl) chloride (**30**, X = Cl) and $ZnCl_2$ (1–5 mol% each) in refluxing MeCN.[11] The procedure is characterized by a short reaction time



Scheme 5

(1 h) and close to quantitative yields in almost all cases. (It is remarkable that tosyl chloride was previously employed as a stoichiometric reagent for the Beckmann reaction.) The authors propose a catalytic cycle in which the oxime *p*-toluenesulfonate (tosylate, **31**) undergoes the rearrangement to yield a tosyl (*p*-toluenesulfonyl) imidate intermediate (cf. **4**, X = tosyl); this transfers its tosyl group to a molecule of the oxime substrate (as indicated in **32**), thus reforming **31** and releasing a molecule of the amide product (**5**).

Xia and coworkers report the Beckmann rearrangement of several ketoximes with a mixture of *p*-toluenesulfonic acid (PTSA, **30**, X = OH) and $ZnCl_2$ (10 mol% each) in refluxing acetonitrile over 5 h.[12] Other organic acids and metal salts were less effective. Excellent yields were generally observed, although a catalytic cycle was not proposed. (The reaction with PTSA has also been reported in the solid state with a few substrates.)[13]

Another report employs a substoichiometric quantity of chloral (**33**, 50 mol%) in a solvent-free procedure, in which the reactants were generally heated in the neat melt at 120–140 °C for 3–5 h.[14] The procedure is based on the known electrophilic reactivity of chloral, which is presumed to react with the oxime hydroxyl group to form an intermediate hemi-acetal adduct (**34**). Rearrangement occurs from this intermediate with subsequent release of the amide product (**5**) and chloral (**33**).

Yadav and coworkers report that bromodimethylsulfonium bromide (**35**), in combination with either an ionic liquid ([bmim]PF_6) or $ZnCl_2$, catalyzes the rearrangement of a wide variety of ketoximes.[15,16] The $ZnCl_2$ reactions were generally accomplished in refluxing acetonitrile in 1–5 h, at a catalyst loading of 12 mol%. The reactions in the ionic liquid were complete in 1–3 h, at 80 °C and a catalyst loading of 20 mol%. The yields of the expected amide products were generally high, and a straightforward catalytic cycle, based on the initial formation of an oxime *O*-sulfonium intermediate (**36**), was proposed. The rearranged nitrilium adduct (**37**) underwent nucleophilic displacement at the sulfur atom by the hydroxyl group of a molecule of the oxime (**1**), effectively regenerating **36** and releasing the amide product (**5**).

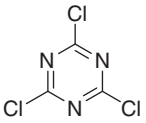
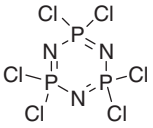
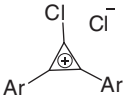
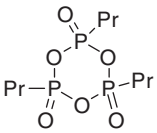
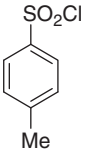
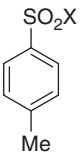
Among several other procedures, the Beckmann rearrangement has been reported with sulfamic acid/$ZnCl_2$,[17] phosphoric acid under microwave irradiation,[18] chlorosulfonic acid in toluene,[19] PEG-SO_3H,[20] and citric acid under solvent-free conditions.[21] The reaction with sulfamic acid/$ZnCl_2$ was carried out in refluxing MeCN at a catalyst loading of ~3 mol% over 1–3 h. Yields of the amide product were generally high, and it is noteworthy that satisfactory results were obtained in the case of cyclopentanone and cyclohexanone oximes.

The results of the major organocatalytic approaches discussed in Section 7.25.2.1.1.1 have been summarized in **Table 1**.

7.25.2.1.1.2 Metal-ion and related catalytic methods

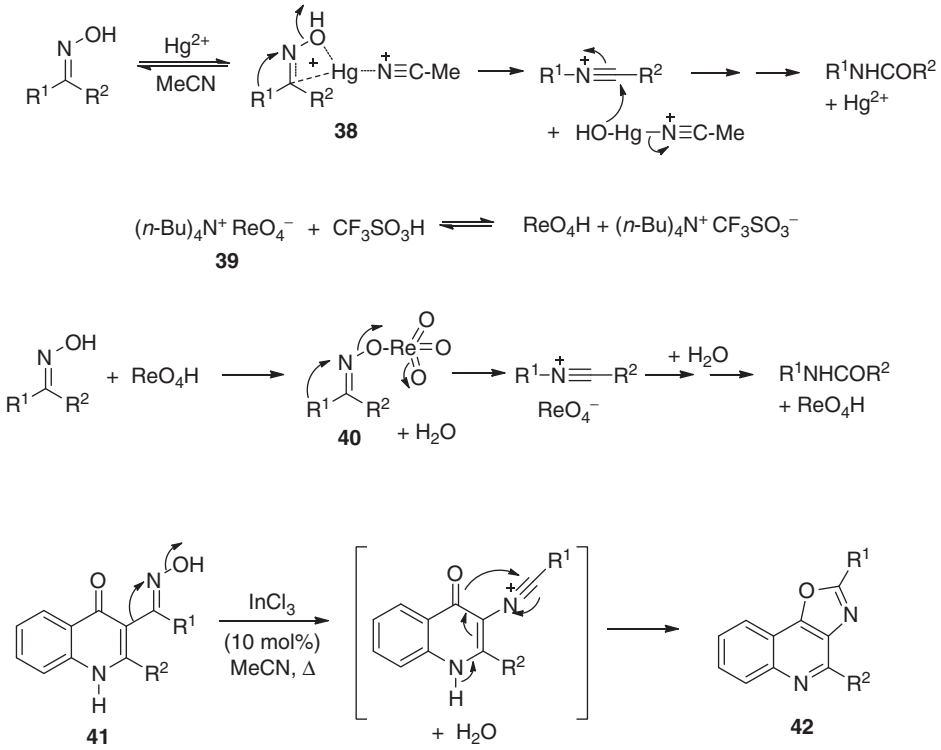
A very large number of inorganic catalysts have been reported to effect the Beckmann rearrangement, many being transition metal (including several lanthanide) ions. These can provide useful and interesting alternatives to the organocatalysts, in terms of availability, stability, and handling, as well as reactivity.[22]

Table 1 Comparison of various organocatalytic methods for the Beckmann rearrangement

Catalyst	*Concentration (mol%)*	*Solvent*	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*References*
 **10** Cyanuryl chloride (+2 mol% $ZnCl_2$ in MeCN)	2	MeCN	Reflux	1–2	>95	4,5
	0.5	3:2 TFA/Toluene	70			
 **17** Triphosphazene	1	$(CF_3)_2CHOH$	Reflux	2	>99	6
	1	MeCN	Reflux	2	>99	
	0.5	3:2 TFA/Toluene	70			7
 **21** Chlorodiarylcyclopropenium	3	MeCN	Reflux	2	>86	8
	10	$MeNO_2$	80	0.5–2	>85	9
 **27** Propylphosphonic anhydride	15	THF	70	1–3	>84	10
 **30** (X = Cl)	10	MeCN	Reflux	5	>90	11
30 (X = Cl) *p*-Toluenesulfonyl chloride (+12 mol% $ZnCl_2$)						
 **30** (X = OH) *p*-Toluenesulfonic acid (+10 mol% $ZnCl_2$)	10	MeCN	Reflux	5	>92	12
Cl_3CCHO **33** Chloral	50	None	120–140	2.5–7.5	>67	14
$[Me_2SBr]^+Br^-$ **35**	12[a]	MeCN	Reflux	1–5	>71	15
	20	$[bmim]PF_6$	80	2	>97	16
Bromodimethylsulfonium bromide						

[a]With 12 mol% $ZnCl_2$.

Ramalingan and Park report the mercury-catalyzed Beckmann reaction of a variety of ketoximes in acetonitrile solution.[23] Employing $HgCl_2$ at 12 mol% in MeCN at 80 °C for 8 h, generally high yields of the expected amide products were obtained. (However, the yield of carpolactam from cyclohexanone oxime was mediocre and required a higher catalyst loading of 30 mol%. This is similar to the results generally obtained with organocatalysts.) The authors propose a plausible catalytic cycle, based on a mechanism involving the coordination of a mercury cation with both the oxime function and a molecule of the MeCN solvent (**38**, Scheme 6). This is based on the observation of a pronounced solvent effect in the reaction.



Scheme 6

A rhodium-catalyzed rearrangement of several ketoximes has been reported by Arisawa and Yamaguchi.[24] These authors employed a mixture of $RhCl(cod)_2$, tris(*p*-tolyl)phosphine, and trifluoromethanesulfonic acid in the ratio 1:3:5, at a Rh loading of 1–5 mol%. The reactions were conducted in refluxing dichloroethane over 3 h. A substrate set of several diaryl and alkylaryl ketoximes was employed, the yields of the amide products approaching quantitative levels in several cases. In general, however, the yields were variable, the reactions being under 'migratory-aptitude control' in the case of unsymmetrical ketoximes. This is because both possible amide products were observed, regardless of the original oxime geometry. Thus, although antimigration predominated generally, in the case of *p*-fluoropropiophenone oxime preferential aryl migration (~55%) was observed with both *E* and *Z* oxime isomers (attributed to their isomerization by trifluoromethanesulfonic acid). However, neither a detailed mechanism nor a catalytic cycle was proposed.

The $AlCl_3$-catalyzed rearrangement of ketoximes has been reported in refluxing MeCN over 2 h, in generally high yields at a catalyst loading of 10 mol%.[25] The reaction, however, practically failed with cyclohexanone oxime, and several unsymmetrical diaryl oximes furnished mixtures of both possible amide products.

Gallium(III) triflate has been reported to catalyze the Beckmann rearrangement of ketoximes in generally high yields.[26] The reactions were performed in MeCN solution, although the catalyst loading (5–50 mol%), reaction temperature (40–120 °C), and reaction time (20 min–16 h) depended on the reactivity of the substrate ketoxime. Cyclic substrates were relatively sluggish, although high yields were obtained in the case of cyclohexanone oxime. Mixtures of isomeric amide products were observed in a few cases. A mechanism, based on the coordination of the oxime oxygen atom with the Ga^{3+} center, was proposed.

De has reported the Beckmann rearrangement of ketoximes with yttrium triflate [$Y(OTf)_3$], neodymium triflate [$Nd(OTf)_3$], and ruthenium trichloride ($RuCl_3$).[27–29] The reactions in all three cases were performed under similar conditions, viz., refluxing MeCN for 1–4 h, and led to generally high yields of the expected amide products. However, the yttrium and neodymium triflate reactions suffered from high catalyst loading (40–50 mol%), although the recovery and reuse of the yttrium catalyst was demonstrated. The $RuCl_3$ procedures employed reduced catalyst loading (10 mol%), although cyclopentanone and cyclohexanone oximes afforded only moderate yields of the corresponding lactams (in contrast to the yttrium and neodymium cases). Similar results had been reported earlier by Yadav and coworkers by employing ytterbium triflate [$Yb(OTf)_3$].[30]

Tetrabutylammonium perrhenate [$(n\text{-Bu})_4N^+$ ReO_4^- (**39**)] in combination with trifluoromethanesulfonic acid (20 and 21 mol%, respectively) was reported to catalyze the rearrangement of several ketoximes (including cyclohexanone oxime) in high yields.[31] The reactions were performed in refluxing nitromethane solvent with azeotropic removal of water. The addition of $NH_2OH.HCl$ (20 mol%) resulted in significantly improved yields by compensating for competitive hydrolysis of the ketoxime substrate. This observation, in fact, led to a 'one-pot' procedure for the conversion of ketones into amides in moderate yields. The proposed mechanism involved the *in situ* generation of perrhenic acid ($HReO_4$) and its reaction with the ketoxime, the resulting oxime *O*-perrhenate (**40**) rearranging further.

Several groups have reported the In(III)-catalyzed Beckmann rearrangement, particularly in the heterocyclic series.[32–35] Pak and coworkers report the $InCl_3$-catalyzed rearrangement of 3-acylquinolone oximes (**41**), and the *in situ* trapping of the resulting nitrilium ion intermediate by the endocyclic enolic group, to form the corresponding oxazoloquinolines (**42**).[32] The reaction occurred with 10 mol% catalyst in refluxing MeCN, and also produced minor amounts of the corresponding isoxazoloquinolines. Several heterocyclic oximes have been reported to rearrange in the presence of $InBr_3$ and AgOTf in refluxing acetonitrile in excellent yields.[33] The rearrangement of several ketoximes with $InCl_3$ and $In(OTf)_3$ in acetonitrile has been reported earlier (aldoximes furnishing corresponding nitriles by dehydration).[34,35]

An early report describes the Beckmann rearrangement of ketoxime *O*-trimethylsilyl ethers with a combination of $SbCl_5$ and $AgSbF_6$ (20 mol% each), in a refluxing mixture of dichlomethane and dichloroethane.[36] Reactions occurred over 3 h to furnish generally high yields of the corresponding amide products.

The Ce(III)-promoted Beckmann rearrangement of a variety of oximes has been reported with the $CeCl_3.7H_2O$-NaI/SiO_2 system, under solvent-free and microwave-irradiation conditions.[37] An interesting study of certain heterobimetallic complexes, with a Co^{3+} center and a peripheral Zn^{2+} ion, has been reported.[38] In these complexes, the Zn^{2+} occupies an exposed cleft, and its electrophilic reactivity has been employed to catalyze the Beckmann reaction of several oximes in moderate yields.

The important metal-ion-catalyzed procedures discussed in Section 7.25.2.1.1.2 have been summarized in Table 2.

Table 2 Comparison of metal-ion-catalyzed procedures for the Beckmann rearrangement

Catalyst	*Concentration (mol%)*	*Solvent*	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*References*
$HgCl_2$	12	MeCN	80	8	>80	23
$RhCl(cod)_2$ [+ (*p*-Tolyl)$_3$P + CF_3SO_3H]	1–5	$(ClCH_2)_2$	Reflux	3	>65	24
$AlCl_3$	10	MeCN	Reflux	2	>60	25
$Ga(OTf)_3$	5–50	MeCN	40–120	0.3–16	>68	26
$Y(OTf)_3$	50	MecN	Reflux	1.5–5	>80	27
$Nd(OTf)_3$	40	MeCN	Reflux	1–4	>80	28
$RuCl_3$	10	MeCN	Reflux	1.5–8	>72	29
$In(OTf)_3$						34

7.25.2.1.1.3 Supported catalysts

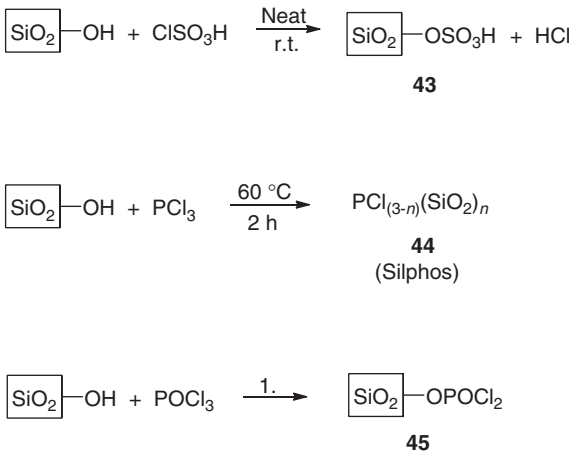
A number of electrophilic reagents supported on relatively inert materials, primarily silica and alumina, have been reported to catalyze the Beckmann reaction. These often involve microwave irradiation, and although it is not always clear that their action is truly catalytic, the results are impressive in terms of yield and substrate scope. Several of the catalysts can be recovered and reused, while a few of them perform the conversion of ketones and hydroxylamine hydrochloride directly into the Beckmann-rearranged amides.

Silica sulfate (**43**, Scheme 7), prepared from silica gel and chlorosulfonic acid,[39] has been employed for effecting the Beckmann reaction of a wide range of oximes.[40] The reaction was conducted in acetone solution under microwave irradiation at 450 W for 3–6 min, depending on the substrate. (A catalyst loading of ~25 mol% was implied.) Very high yields were generally observed, including the cases of cyclohexanone and cyclopentanone oximes. The catalyst could also be recovered, regenerated, and reused several times.

Silica-supported dichlorophosphine ('Silphos', **44**), prepared from silica gel and PCl_3, is reported to effect the rearrangement of several ketoximes.[41] The reactions were conducted in MeCN at room temperature for 8–10 h, and the yields of the amide products were generally high. The same reagent was later reported to effect the Beckmann reaction under microwave irradiation (195 W) in THF for 3–6 min, at a loading of 20 mol%.[42] Yields of the amide products with a range of ketoximes were very high (including with cyclopentanone and cyclohexanone oximes).

The related silica-supported dichlorophosphate (**45**) was prepared from silica gel and $POCl_3$ under microwave irradiation.[43] At 25 mol% loading in THF, and under microwave irradiation (445 W) for 5–6 min, **45** effected the Beckmann rearrangement of a wide range of ketoximes in very high yields (this included cyclopentanone and cyclohexanone oximes). It was also demonstrated that the catalyst could be recovered and reused several times.

A 1:1 M mixture of $AlCl_3$-$ZnCl_2$ supported on silica gel was reported to catalyze the rearrangement of several acetophenones and benzophenones in generally high yields.[44] The reactions were conducted under solvent-free conditions under microwave irradiation (1550 W) for 4–7 min, at a catalyst loading of 20 mol%. (The yield in the case of cyclohexanone oxime was very low.)



Scheme 7

A solid mixture of silica gel and P_2O_5 was reported to effect the Beckmann rearrangement of a range of oximes.[45] This reagent also effected the one-pot conversion of ketones to amides in the presence of hydroxylamine hydrochloride. Both procedures required microwave irradiation for several minutes. Although yields were impressive, it is unclear whether the method is catalytic. However, it is noteworthy that cyclohexanone oxime furnished caprolactam in very high yields, and that camphor oxime furnished the corresponding lactam rather than the usual nitrile product via the fragmentation mode.

Silica-supported $NaHSO_4$ has been reported to effect a 'one-pot' conversion of ketones to amides, via the Beckmann rearrangement of intermediate oximes.[46] The reactions were conducted with a mixture of ketone and hydroxylamine hydrochloride under microwave irradiation. Two related methods employ silica-supported formic acid,[47] and silica-supported sulfamic acid,[48] both under microwave irradiation.

A few alumina-supported reagents have also been reported for effecting the Beckmann reaction. A 'one-pot', solvent-free conversion of ketones to amides with Al_2O_3.$NaHSO_4$ has been reported[49] (analogous to the silica-supported case mentioned in Section 7.25.2.1.1.3).[46] The reactions were conducted on a mixture of the ketone and hydroxylamine hydrochloride under microwave irradiation (320 W) over 1–3 min, and effected the Beckmann rearrangement of the *in situ* generated oxime. The yields of expected amides were generally high (including caprolactam from cyclohexanone). The catalyst could be recovered and reused. A similar conversion has been reported with alumina sulfuric acid,[50] and with alumina methanesulfonic acid.[51]

A few of these supported catalysts are listed in **Table 3** along with conditions and typical yields.

Table 3 Supported catalysts reported to effect the Beckmann rearrangement

Catalyst	*Concentration (mol%)*	*Solvent*	*Temperature (°C)*	*Time (h)*	*Yield (%)*	*References*
SiO_2—OSO_3H	25	Acetone	Microwave irradiation	3–6 min	>84	39,40
43 Silica sulfate						
$PCl_{(3-n)}(SiO_2)_n$	–	MeCN	Room Temp.	8–10 h	>87	41
44 'Silphos'	20	THF	Microwave irradiation	3–6 min	>79	42
SiO_2—$OPOCl_2$	25	THF	Microwave irradiation	5–6 min	>72	43
45						
SiO_2 ($AlCl_3$-$ZnCl_2$)	20		Microwave irradiation	4–7 min	>65	44
$NaHSO_4$-Al_2O_3	30		Microwave irradiation	1–3 min	>70	49

7.25.2.1.1.4 Other inorganic catalysts

The Beckmann rearrangement has been effected with catalytic I_2 in refluxing MeCN over 1–4 h.[52] Very high yields were observed for the conversion of a variety of ketoximes, including cyclopentanone and cyclohexanone oximes. The Beckmann reaction has also been reported with a mixture of P_2O_5 and trifluoromethanesulfonic acid as the catalyst, in DMF at 60–120 °C over 1 h.[53] Although nearly quantitative conversion of cyclohexanone oxime to caprolactam was obtained, yields were variable with other ketoximes.

7.25.2.1.2 Noncatalytic methods

The use of at least a stoichiometric amount of an electrophilic reagent to effect the Beckmann rearrangement is as old as the reaction itself. Although catalytic methods are generally preferable, noncatalytic methods can be useful if the reaction conditions are mild, and if the reagent is inexpensive or recoverable. Indeed, noncatalytic approaches continue to be pursued vigorously, and a wide variety of stoichiometric reagents have been reported.

Several of these reagents are metal salts, notably $AlCl_3$, $ZnCl_2$, $FeCl_3$, and TiO_2. Among nonmetallic electrophiles, mention should be made of metaboric acid, and several phosphorus-centered ones, e.g., $POCl_3$/DMF (Vilsmeier – Haack reagent), PhO-$POCl_2$, $(EtO)_2POCl$, and Ph_3P/*N*-chlorosuccinimide. Electrophiles with organic moieties include mesitylenesulfonyl chloride, tosylbenzotriazole/*t*-butoxide, tosylimidazole/Cs_2CO_3/SiO_2, pivaloyl chloride, bis-(trichloromethyl)carbonate, and oxalic acid.

The $AlCl_3$-based conversions occur in the solid state with a reagent loading of 2–4 times the oxime substrate at 35–80 °C.[54] Nearly quantitative conversions have been claimed in several cases (including cyclohexanone oxime), although a mixture of amide products has been observed with unsymmetrical oximes. The reactions with $ZnCl_2$ were reported under solvent-free and microwave irradiation conditions to afford high conversions in a limited number of cases.[55]

A number of studies with anhydrous ferric chloride, whether by itself or on an inert support, have been reported. Anhydrous $FeCl_3$ was reported to effect the rearrangement of a range of ketoximes under solvent-free conditions, at a reagent loading of 3–4 times the substrate, at 80–90 °C over 1.5–3 h.[56] High yields (~90%), and excellent selectivity in the unsymmetrical cases, were generally observed. $FeCl_3$ supported on silica gel ('Silferc') was reported to act at catalytic levels (60 mol%) in refluxing dichloroethane, but on a limited set of acetophenone and benzophenone oximes.[57] $FeCl_3$ supported on the acidic clay Montmorillonite K10 was reported to rearrange several diaryl ketoximes in refluxing toluene; although the overall yields were excellent, mixtures of amide products were observed in several unsymmetrical cases.[58]

TiO_2 was reported to effect the 'one-pot' conversion of several (mostly aromatic) ketones, with added hydroxylamine hydrochloride, to the corresponding Beckmann-rearranged products.[59] The solvent-free reactions were performed at a substrate: NH_2OH:TiO_2 ratio of 1.0:4.3:2.0, and a temperature of 140–170 °C over 1–9 h. Excellent yields of the amide products (70–90%), including caprolactam (78%), were reported.

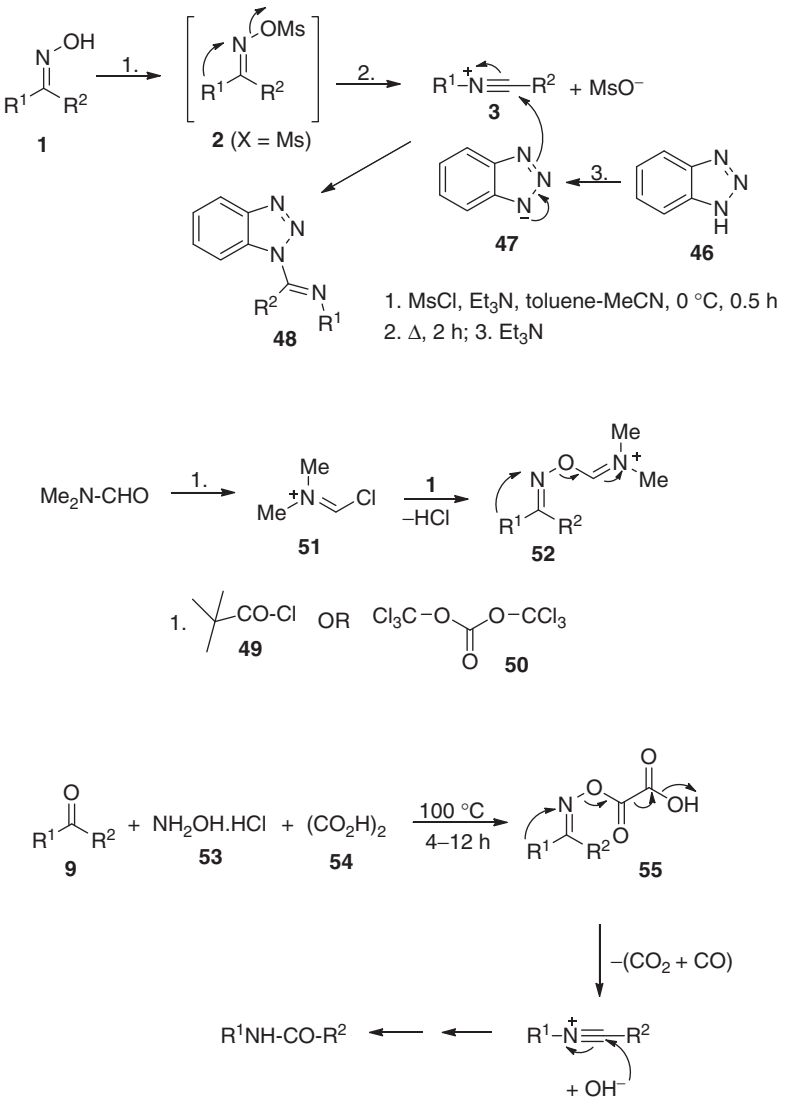
Metaboric acid (from the dehydration of boric acid) was reported to effect the Beckmann reaction of a range of oximes under solvent-free conditions.[60] The reactions were conducted at ~140 °C over (usually) extended periods of time (7–58 h), the yields of the amide products being generally good. The reactions are believed to be mediated by the oxime *O*-borate derivative.

The Vilsmeier–Haack reagent, prepared from $POCl_3$ in DMF, has been reported to effect the Beckmann rearrangement of a few ketoximes in reasonable yields.[61] Detailed studies, however, have been reported on the phosphorus-centered reagents diethyl chlorophosphate [$(EtO)_2POCl$] and phenyl dichlorophosphate [$(PhO)POCl_2$]. Expectedly, the latter is the more reactive, effecting the conversion of a range of ketoximes in MeCN solution at ambient temperatures.[62] Typical reaction times of 5–10 h and yields of the amide products of ~75% were observed. The reactions with the diethyl phosphate were typically conducted in refluxing toluene, over relatively shorter periods of time (<30 min). Generally good yields of several aryl ketoximes were observed (~80–90%).[63] (Reaction in both the cases presumably involves an activated oxime *O*-phosphate intermediate.)

An interesting report describes the Beckmann reaction of a few ketoximes with a combination of Ph_3P and *N*-chlorosuccinmide in CH_2Cl_2 at room temperature.[64] Reaction was completed almost 'instantaneously' in good yields, and is believed to involve a $(Ph_3PCl)^+$ species as the electrophilic activator of the oxime hydroxyl group.

There are several essentially organic – although not necessarily carbon-centered – electrophiles that have been reported for the Beckmann reaction. An extensive study by Ramalingan and Park reports the utility of mesitylenesulfonyl chloride in effecting the rearrangement of a wide range of keoximes.[65] The reactions were performed in THF with added LiOH as base, although heating at 60 °C for extended periods of time (typically 7–10 h) was required. Yields of the amide products were often close to quantitative, even for caprolactam (although the method essentially failed for cyclopentanone oxime). The reaction is believed to be sterically accelerated by the *ortho* methyl groups in the oxime mesitylenesulfonate intermediate (implying that steric effects in its formation are minimal). The method was employed to prepare several diazepam-5-ones from the corresponding piperidin-4-one oximes.

Two other oxime *O*-sulfonate-based methods that are noteworthy employ activated sulfonyl derivatives. Following an earlier report by Katritzky and coworkers, the conversion of a range of ketoximes (**1**) to *N*-imidoylbenzotriazoles (**48**, **Scheme 8**) has been reported.[66] The reaction was performed by treating **1** in a mixture of toluene and acetonitrile with methanesulfonyl chloride (MsCl) and excess triethylamine at 0 °C; this was followed by the addition of benzotriazole (**46**) and refluxing the mixture for 2 h. The reaction presumably occurs via the attack of the benzotriazolyl anion (**47**) on the nitrilium intermediate (**3**), **48** being formed in generally fair yields. (The *E* isomer of **48** was exclusively formed in general, possibly indicating a measure of steric control in the addition of the benzotriazolyl anion to the nitrilium ion.)



Scheme 8

An analogous method employs 1-tosylimidazole in DMF, in the presence of cesium carbonate and silica gel.[67] The mixture was refluxed for 1–2 h, and excellent yields of amide products were reported for a range of ketoximes.

Among several carbon-centered electrophilic reagents for the Beckmann transformation, two employ DMF as solvent. These generate the Vilsmeier–Haack chloroiminium ion **51**, which adds the oxime to form **52** as the key reactive species. These procedures employ either pivaloyl chloride (**49**)[68] or bis-(trichloromethyl)carbonate (**50**)[69] as the reagent. However, the latter requires refluxing for various periods of time in DMF/MeCN (typically 1 h with 0.3 equivalent of the reagent),[69] whereas the former effects the reaction at room temperature.[68] The yields are somewhat comparable in the two methods (although the pivaloyl procedure reports quantitative yields for caprolactam).

The Beckmann reaction has been effected by employing oxalic acid (**54**) as the activating reagent, in a 'one-pot,' solvent-free procedure involving the ketone (**9**) and hydroxylamine hydrochloride (**53**).[70] The reaction requires heating the mixture at ~100 °C for 4–12 h, and generally good yields of the expected amide products were reported. The reaction is believed to be driven by the decomposition of the oxime *O*-oxalate intermediate (**55**), generating CO and CO_2 as gaseous byproducts. As no provision was made for the removal of water formed during the formation of the oxime, a mechanism analogous to the Schmidt reaction was also proposed.

The reaction of ketoximes with gaseous HCl results in the formation of the corresponding hydrochloride salts, which undergo the Beckmann rearrangement on heating below their melting points (typically 5–12 h).[71] This solvent-free procedure, employing an inexpensive reagent, is particularly expeditious.

The major noncatalytic methods discussed in Section 7.25.2.1.2 are shown in Table 4.

Table 4 Noncatalytic methods for the Beckmann rearrangement

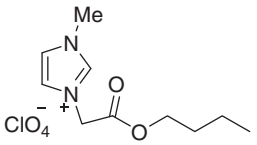
Reagent	*Equivalent*	*Solvent*	*Temperature (°C)*	*Time*	*Yield (%)*	*References*
$AlCl_3$	2–4	–	35–80	30 min	97	54
$FeCl_3$	3–4	–	80–90	1.5–3 h	>70	56
Tio_2 ('One-pot' from ketone + $NH_2OH.HCl$)	2	–	140–190	1–9 h	>70	59
Metaboric acid	3	–	140	7–58 h	>62	60
$(PhO)POCl_2$	1.5	MecN	r.t	5–10 h	>75	62
$(EtO)_2POCl$	1	Toluene	Reflux	<30 min	>80	63
Mesitylene sulfonyl chloride (+ 1.2 equivalents LiOH)	1	THF	60	7–10 h	>90	65
MsCl + benzotriazole (**46**)	1	Toluene	Reflux	–	>80	66
Pivaloyl chloride (**49**)	1.5	DMF	r.t	2.5–14 h	>72	68
Oxalic acid (**54**) ('One-pot' from ketone + $NH_2OH.HCl$)	2.5	–	100	4–12 h	>67	70
HCl (gas)	–	–	70–130	5–48 h	>67	71

7.25.2.1.3 The use of ionic liquids

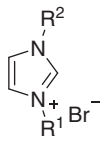
The transition state for the migration step in the Beckmann reaction has considerable ionic character, as it leads to the nitrilium cation intermediate (Scheme 1). Consequently, polar media accelerate the reaction (acetonitrile was the solvent of choice in many of the cases reviewed in Section 7.25.2.1). In recent years, there has been much interest in the use of ionic liquids (ILs) to effect the Beckmann reaction, for several reasons.[72–81] Primarily, of course, ILs are highly polar, but they also (generally) possess low viscosity and vapor pressure, apart from chemical and thermal stability. Many of these properties are highly beneficial in the case of large-scale industrial processes, and facilitate work-up, waste disposal, etc. In addition, ILs that possess additional catalytic or other functions that can take part in the reaction (task-specific ionic liquids), as well as ILs that are easily removed during work-up, are of low toxicity and are biodegradable, are much sought after.[72]

The Beckmann rearrangement has been reported to be accelerated by the presence of ILs in the reaction medium, leading to improved yields under milder reaction conditions. The IL does not supplant the conventional electrophilic catalyst, which is generally present. However, the IL can be present in catalytic quantities, or be employed as the solvent, with or without a cosolvent. Interestingly, it is now believed that the industrial-scale rearrangement of cyclohexanone oxime leads, in fact, to the hydrogen sulfate of caprolactam, itself an IL under the reaction conditions.[73]

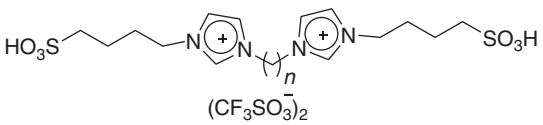
A recent report by Maia and coworkers describes the rearrangement of several ketoximes in the biodegradable imidazolium-based IL 3-methyl-(1-*n*-butoxycarbonylmethyl)imidazolium perchlorate ([BuOCOmmim][ClO_4], **56**).[74] The reaction was catalyzed by cyanuryl chloride (**10**, typically 5.6 mol%) at 60 °C for varying time periods (typically 0.68 h), affording the expected amide products generally in excellent yields (except in the case of caprolactam). The recovery and reuse of **56** was also demonstrated.



56



57



58 (*n* = 1,6,10)

Zicmanis and coworkers report an extensive study, involving 17 different ILs and 4 Lewis acids, of the Beckmann reaction of 5 aromatic ketoximes.[75] The Lewis acids employed were $AlCl_3$, $TiCl_4$, $SnCl_4$, and BF_3. The ILs were, for the most part, derived from 1,3-dialkylimidazolium systems (**57**), but also included a few alkylpyridinium and a dodecylammonium system; the inorganic counterion was also varied (halides, BF_4^-, and PF_6^-). Reaction was accomplished by heating the reactants for varying periods of time (typically, 40–120 °C/0.5–3 h). High conversions and isolated yields, often approaching quantitative levels, of the expected amide products were generally realized. The preferred combination was $AlCl_3$ or $TiCl_4$ with tetrabutylammonium bromide as the IL.

The use of novel Brønsted-acidic ILs, in combination with $ZnCl_2$, to effect the Beckmann reaction of a range of ketoximes has been reported by Chinese workers.[76] The ILs employed were of the bis-imidazolium type (**58**), as well as the 'monomeric' analogs. Reaction was typically performed with 5 mol% each of IL and $ZnCl_2$ in refluxing MeCN over 5 h. Excellent yields of amide products were generally realized (typically >90%, except for caprolactam).

Anantharaman and coworkers report a comparative study involving several *N*-alkylimidazolium-based room temperature ILs, of the rearrangement of a limited set of ketoximes.[77] Reactions were typically conducted with 20 mol% each of the IL and PCl_5 at

80 °C over 3 h. Best yields depended on the appropriate IL-substrate combination; a 78% yield of caprolactam, for example, was realized with cyclohexanone oxime and *N*-isopropylimidazolium hexafluorophosphate.

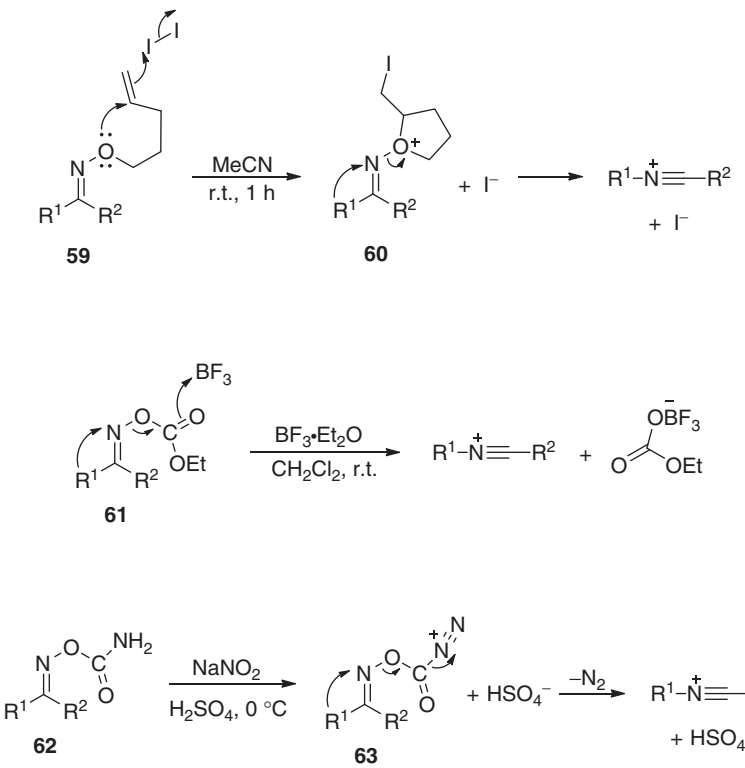
The $In(OTf)_3$-catalyzed rearrangement of several ketoximes in the IL 1-butyl-2,3-dimethylimidazolium hexafluorophosphate has been performed under microwave irradiation.[78] Generally good yields of the expected amide products were obtained, the reaction time being typically <1 min.

Other reports with ILs involve (as electrophilic catalysts) metaboric acid,[79] PCl_5,[80] P_2O_5,[81] etc. This is a rapidly evolving area and the future is expected to unfold novel and fascinating developments.

7.25.2.2 Ketoxime Derivatives

There are only a few reports of the Beckmann reaction having been performed on ketoxime derivatives in recent years; effecting the rearrangement from the ketoximes themselves is viewed as more interesting and challenging. The following reports are noteworthy.

Taguchi and coworkers report an interesting tactic in which the Beckmann rearrangement is 'remotely triggered' in a ketoxime *O*-4-pentenyl substrate (**59**, Scheme 9).[82] Electrophilic attack at the remote C=C group by I_2, NBS, etc., induces nucleophilic participation by the oxime oxygen atom to form a tetrahydrofuranium cation (**60**). This activates the oxime functional group toward rearrangement. The reactions with **59** were carried out with several ketoximes in MeCN at room temperature over 1 h, to obtain the rearranged amides in fair yields.

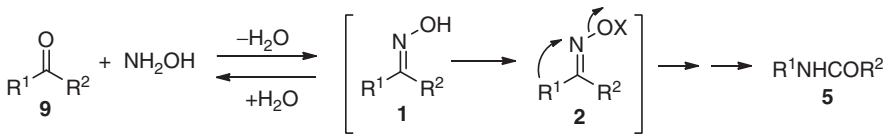


Scheme 9

The rearrangements of ketoxime carbonates (**61**) and ketoxime carbamates (**62**) have been reported.[83,84] The reaction with **61** was performed with BF_3 etherate in dichloromethane at room temperature over (typically) 4–12 h, excellent yields of the expected amide products being generally realized; a polymer-supported version was later reported by Cossy and coworkers.[83] The rearrangement of the carbamates **62** was induced by diazotization of the terminal amine function with iso-amyl nitrite or sodium nitrite in concentrated H_2SO_4, at 0 °C over (typically) 4–8 h.[84] The resulting diazonium ion (**63**) suffers loss of nitrogen, which provides the kinetic driving force for the reaction. Good-to-excellent yields of the amide products were obtained.

7.25.2.3 Conversion of Ketones to Amides

The reaction of a ketone (**9**) with hydroxylamine (NH_2OH) leading to an amide (**5**), via the Beckmann rearrangement of an *in situ* generated ketoxime (**1**), is a particularly attractive variant of the Beckmann reaction (Scheme 10).

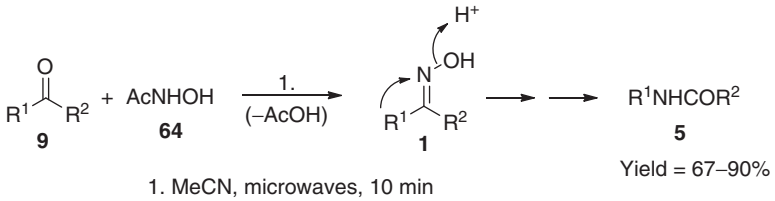


Scheme 10

This procedure clearly obviates the need to isolate the intermediate oxime (**1**); in fact, it even obviates the need to remove the water formed in the oxime formation step, as the rearrangement step displaces the initial equilibrium between ketone and oxime. In the absence of other competing reactions (involving other functional groups sensitive to the reaction conditions), this 'one-pot' procedure would indeed be the method of choice. Interestingly, there are an increasing number of studies reporting such an approach to the Beckmann reaction.

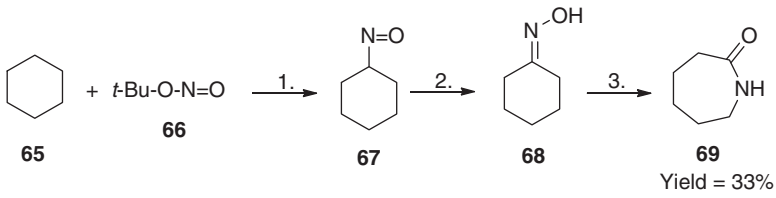
In fact, several of the methods discussed in Sections 7.25.2.1.1.3, 7.25.2.1.1.4, and 7.25.2.1.2 start from the ketone. These include SiO_2/P_2O_5,[45] SiO_2/HCO_2H,[47] SiO_2/NH_2SO_3H,[48] $Al_2O_3/NaHSO_4$,[49] Al_2O_3/H_2SO_4,[50] $Al_2O_3/MeSO_3H$,[51] TiO_2,[59] and oxalic acid.[70] Other noteworthy methods that have been reported are $SiO_2/NaHSO_4$/microwave,[85] PCl_3,[86] and ZnO.[87] It is particularly interesting that most of these methods involve supported reagents and several are solvent-free. (It is possible that the solid supports absorb the water formed in the oximation step, cf. Scheme 10, and displace the equilibrium toward the oxime.)

Among other methods, Sridhar and coworkers report an interesting procedure involving acetohydroxamic acid (**64**) and catalytic sulfuric acid (Scheme 11).[88] The reactions were conducted in refluxing MeCN under microwave irradiation over ~10 min. (but needed several hours under conventional heating). A variety of ketones (**9**) was thus converted to the corresponding amides (**5**) generally in good yields (67–90%). The conversion is believed to be mediated by the oxime (**1**), formed *in situ* from the ketone and acetohydroxamic acid. The oxime subsequently rearranges under the reaction conditions. The method was also successfully adapted to the synthesis of several benzoxazoles starting from (2-hydroxyaryl) ketones, via intramolecular trapping of the nitrilium cation by the *ortho* hydroxyl group.



Scheme 11

In a remarkable report, Ishii and coworkers describe the conversion of cycloalkanes to corresponding lactams in 'one-pot' (Scheme 12).[89] This was typically accomplished by treating cyclohexane (**65**) with catalytic *N*-hydroxyphthalimide (NHPI) and *t*-butyl nitrite (**66**) in fluorobenzene with a trace of acetic acid (72 °C/2 h), followed by the isomerization of the resulting nitrosocyclohexane (**67**) to cyclohexanone oxime (**68**) with Et_3N in EtOAc (80 °C/1 h). The oxime was rearranged with cyanuryl chloride (**10**, 5 mol%) in hexafluoroisopropanol (HFIP; 70 °C/2 h), to obtain caprolactam (**69**) in 33% yield. (Cyclododecanone similarly furnished the ring-expanded lactam in 72% yield.)

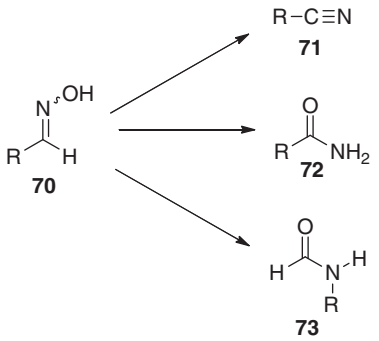


Scheme 12

7.25.2.4 Aldoximes

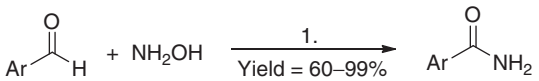
Treating aldoximes (**70**, Scheme 13) to Beckmann reaction conditions generally leads to the corresponding nitriles (**71**), but rarely to the two rearranged amide products that are possible in principle (**72** and **73**). (We note, however, that primary amide **72** is both the product of the hydration of nitrile **71** and the product of hydrogen migration to nitrogen in the rearrangement of **70**.) Indeed, many

of the methods for ketoximes reviewed in Section 7.25.2.1 have been reported to convert aldoximes to corresponding nitriles, often in high yields. The reagents effecting this conversion include cyanuryl chloride (**10**),[4] propylphosphonic acid (**27**),[10] chloral (**33**),[14] chlorosulfonic acid,[19] Silphos (**44**),[41] silica-PCl_3,[42] $FeCl_3$-Montmorillonite K 10,[58] metaboric acid,[60] diethyl chlorophosphate,[63] Ph_3P/*N*-chlorosuccinimide,[64] $(Cl_3CO)_2CO$,[69] HCl (heating oxime hydrochlorides),[71] and $AlCl_3$/KI/H_2O/MeCN.[90]



Scheme 13

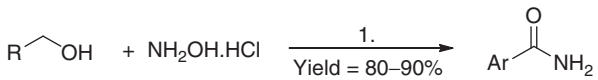
However, there has been a surge of interest in the conversion of aldoximes into primary amides in recent years.[22] In a remarkable study, Ramón and coworkers describe the Cu (II)-catalyzed conversion of aldehydes into primary amides, via reaction with hydroxylamine in water (equation 2).[91] The reactions were performed with 2 mol% $Cu(OAc)_2$ in water at 110 °C over 48 h. A variety of mostly aromatic aldehydes furnished the corresponding primary amide (cf. **72**) in excellent yields. The 'one-pot' procedure is believed to involve the *in situ* generation of the aldoxime. (After extraction of the product, the aqueous reaction medium with the catalyst could be recycled for subsequent batches.)



(2)

1. $Cu(OAc)_2$ (2 mol%), H_2O, 110 °C, 48 h

In another interesting study, Das and Chakraborty report the 'one-pot' conversion of a variety of primary alcohols to the corresponding primary amides (equation 3).[92] The 'one-pot' procedure employed a mixture of I_2-TEMPO, $NH_2OH.HCl$, K_2CO_3, and $FeCl_3$, reactions being conducted in 1,2-dichloroethane at 90 °C for (typically) 12 h. Aliphatic and alicyclic substrates required longer periods (than aromatic ones); the yields, however, were generally excellent. The reaction is believed to involve the *in situ* oxidation of the alcohol by I_2-TEMPO, the resulting aldehyde then reacting with the hydroxylamine to form the aldoxime; the rearrangement of this was catalyzed by $FeCl_3$ at 10 mol% loading.



(3)

1. I_2-TEMPO, K_2CO_3 + $FeCl_3$, $ClCH_2CH_2Cl$, 90 °C, 12 h

A string of metal-based catalysts, involving Ni, Rh, and Ru, have been reported to effect the Beckmann conversion of aldoximes to primary amides in recent years.[22] (These include several 'one-pot' conversions starting from the aldehyde.) Interestingly, the conversions generally involve the reaction of the corresponding nitrile intermediate with water or amines. Thus, they do not formally represent a Beckmann rearrangement, and the reader is referred to an excellent review[22] and key original reports for details.[93,94]

7.25.2.5 Catalysis by Zeolites and Mesoporous Materials

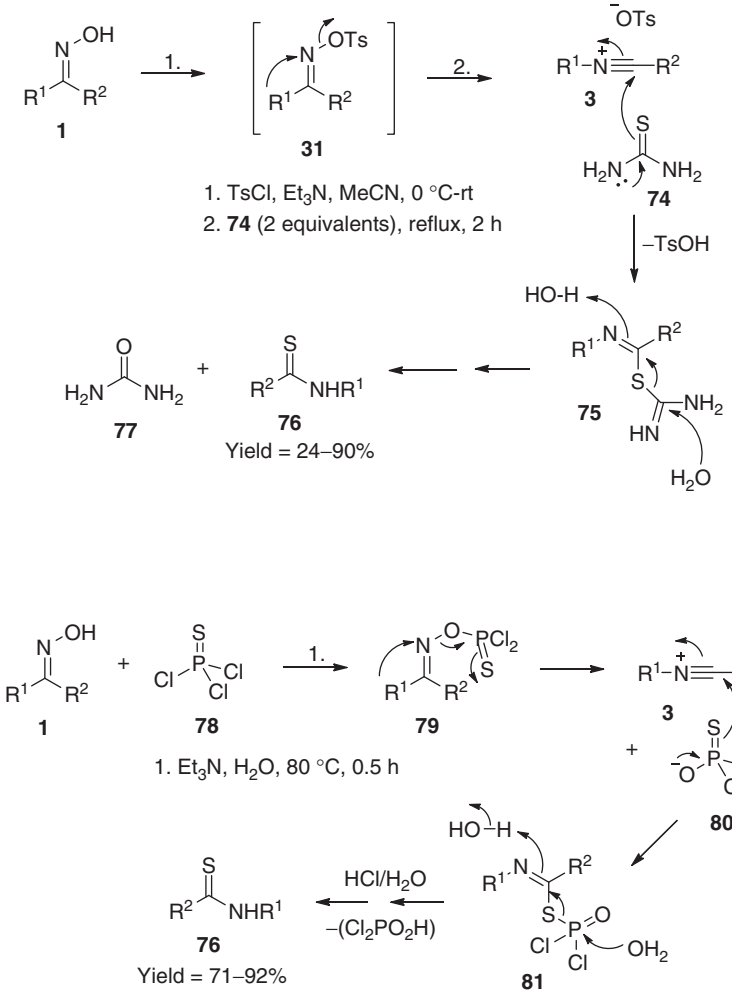
A very important application of the Beckmann rearrangement lies in the conversion of cyclohexanone oxime to ε-caprolactam (precursor for the manufacture of Nylon-6). The conventional industrial process involves treating cyclohexanone oxime with concentrated sulfuric acid or oleum; however, this leads to problems of corrosion, as well as the build-up of very large quantities of ammonium sulfate byproduct on neutralization and work-up. In view of the enormous commercial importance of Nylon-6, a great deal of work is thus being directed toward developing alternative mild catalysts, particularly for effecting the conversion in the vapor phase.

A large number of zeolites and mesoporous materials have thus emerged as viable catalysts in recent decades, and have indeed been employed for the manufacture of ε-caprolactam. These solid catalysts function by providing acidic sites within nanoscale cavities, at which the oxime binds and is thus activated toward rearrangement. Efforts are being directed toward developing specific catalysts for the rearrangement of cyclohexanone oxime, and hence their scope and applicability in general synthesis are often unclear. In any case, a discussion of this topic is beyond the scope of this chapter, and the interested reader is referred to select recent reports for further study.[95–97]

7.25.2.6 Extensions of the Beckmann Reaction

Two interesting variations that extend the scope of the Beckmann reaction have been reported and are briefly discussed below.[98–100] These involve (i) employing the Beckmann reaction to prepare thioamides and (ii) the Beckmann reaction in which the migrating group is phosphorus-centered.

(1) The Beckmann rearrangement has been employed for the preparation of thioamides, essentially by trapping the nitrilium intermediate with a sulfur nucleophile. Deng and coworkers report that refluxing ketoxime tosylates (**31**, formed *in situ* as shown in Scheme 14) with a two-fold excess of thiourea (**74**) in MeCN over 2 h afforded the corresponding thioamides (**76**) in generally good yields.[98] The mechanism is believed to involve the trapping of the nitrilium ion (**3**) by thiourea (**74**) to form the thioimidate intermediate **75**, which is hydrolyzed to **76** and urea (**77**).

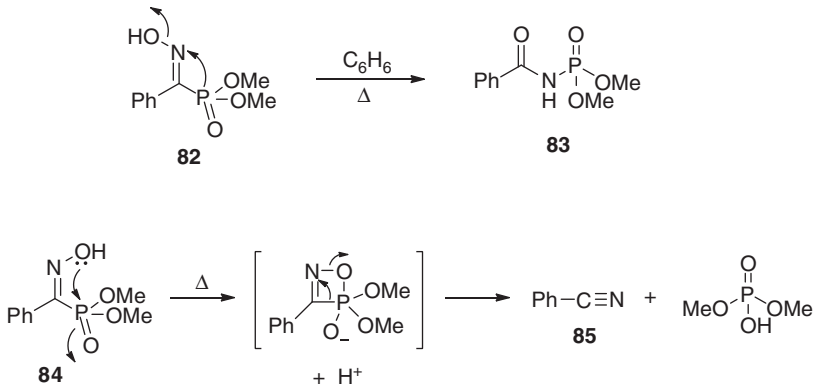


Scheme 14

The same conversion has been accomplished with $PSCl_3$ (**78**) by Pathak and coworkers.[99] The reaction, in fact, was performed in water, with an excess of **78** and triethylamine (Et_3N), at (typically) 80 °C over 0.5 h. The reaction is believed to involve the oxime *O*-dichlorothiophosphate intermediate (**79**), which rearranges to the nitrilium ion (**3**) and dichlorothiophosphate anion

(**80**). Ions **3** and **80** recombine, but at the carbon and sulfur centers, respectively, to form the thioimidate (**81**). This is hydrolyzed to the thioamide product (**76**), generally in excellent yields from a large variety of oximes (**1**).

(2) Breuer has reported several cases of the Beckmann reaction in which the migrating group is phosphorus-centered.[100] Thus, for example, the (*E*)-α-hydroxyiminobenzylphosphonate **82** (Scheme 15) rearranges to the *N*-benzoylphosphoramidate **83** in refluxing benzene. The corresponding (*Z*) isomeric oxime **84**, however, undergoes fragmentation to benzonitrile (**85**) and dimethyl hydrogen phosphate (Me_2HPO_4), as indicated. (Oximes **82** and **84** can be prepared by reacting the corresponding benzoylphosphonate with hydroxylamine.)



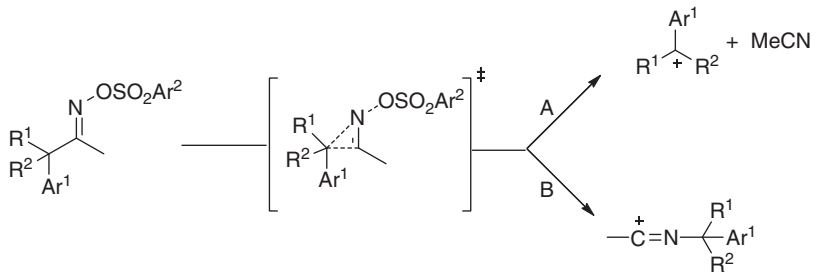
Scheme 15

7.25.3 Mechanistic and Theoretical Studies

In view of its importance both in synthetic practice and in industry, the Beckmann reaction continues to be subjected to various mechanistic and theoretical studies. However, as this chapter primarily addresses the synthetic aspects of the reaction, only a brief mention of certain key developments is possible herein.

An interesting development, possibly of far-reaching practical significance, involves conducting the Beckmann reaction in supercritical water (scH_2O). This refers to water beyond its critical point ($T_c = 647$ K, $P_c = 22$ MPa), which is believed to possess significantly different structure, as well as different physical and chemical properties.[101,102] In view of the great interest in developing a 'green' alternative to the conventional process for the manufacture of caprolactam (cf. Section 7.25.2.5), scH_2O has been proposed as a relatively benign solvent that also catalyzes the Beckmann reaction. The conversion of cyclohexanone oxime has indeed been accomplished in scH_2O in the absence of added catalysts, although in a microreactor. High yields (80%), in fact, were realized in as little as 3 min. Further developments would indeed be interesting.

The Beckmann reaction has been the subject of an intriguing theoretical proposal in recent years. Yamataka has argued that the two competing modes of the Beckmann reaction, viz., rearrangement and fragmentation (paths A and B, respectively, Scheme 16), share a common transitions state.[103] This proposal ('dynamic path bifurcation') represents a fundamental departure from conventional transition state theory, which forbids a common transition state for two different pathways. The proposal is based both on theoretical and experimental studies. (The latter is based on the observation of a linear relationship between the reactivities of certain substituted phenylpropanone oxime naphthalenesulfonates.) This proposal, of course, is not to be confused with the idea that the two modes share a common nitrilium cation intermediate, examples of which will be mentioned further in Section 7.25.4.1.2.

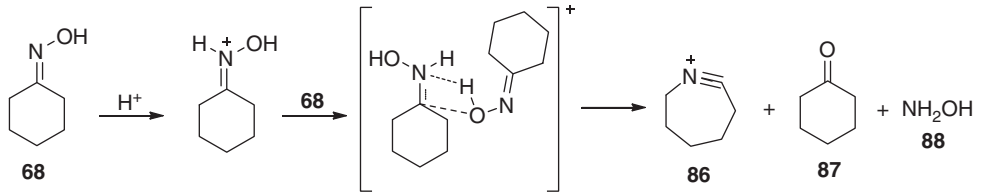


Scheme 16

A computational study addresses the question of the concertedness of the Beckmann rearrangement.[104] The study concludes that the reaction of cyclohexanone oxime is concerted, whereas the reactions of acetone and acetophenone oximes are multistep and involve various σ and π complexes.

Ab initio theoretical studies have indicated a strong solvent effect on the acid-catalyzed Beckmann rearrangement reaction.[105] In the case of formaldoxime in the gas phase, initial *N*-protonation of the oxime occurs, which is followed by a slow and rate-determining 1,2 proton shift to form the *O*-protonated oxime. This step is considerably accelerated by active solvent participation.

A DFT computational study has unearthed a possible competing pathway in the Beckmann reaction of cyclohexanone oxime (**68**), which leads to the formation of cyclohexanone even under anhydrous conditions.[106] (This is in support of experimental observations.) The path involves the reaction of the *N*-protonated oxime with another molecule of oxime (**Scheme 17**) leading to the nitrilium cation **86**, cyclohexanone (**87**), and hydroxylamine (**88**).

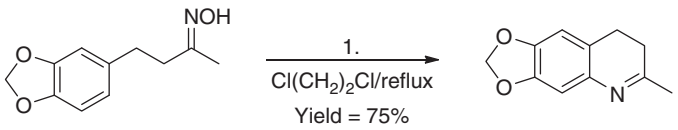


Scheme 17

An extensive kinetic and crystallographic study has revealed that oximes add to nitrilium salts, the resulting adducts subsequently undergoing the Beckmann rearrangement to the expected amide products.[107] These, however, react further with the nitrilium salts leading to mixtures of products, indicating that catalysis of the Beckmann rearrangement with nitrilium salts is not feasible. (This is significant in light of recent proposals that the Beckmann reaction can be 'self-propagating', via reaction of the oxime substrate with the nitrilium cation intermediate produced on rearrangement.)[9]

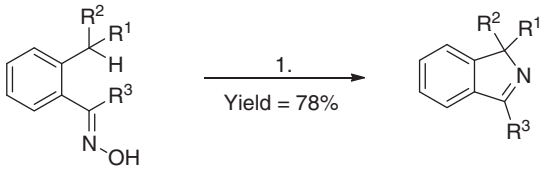
X-ray crystallographic studies of several ketoxime derivatives have revealed bond distortions that indicate that the molecules are 'predisposed' to undergo the Beckmann rearrangement.[108,109] Thus, the relevant bond distances and bond angles indicate that the atomic displacements characteristic of the reaction are manifested in the molecular ground state, which represent the early stages of the Beckmann rearrangement. (The bond distances and angles involve the atomic centers undergoing change during the transformation.)

Among several reactions of oximes that can out-compete the Beckmann reaction, two are noteworthy. One involves initial S_N2 attack at the oxime nitrogen (equation 4), several such examples being now known.[110] The other (equation 5) likely involves intramolecular C–H insertion by a nitrenium species.[111] Both occur under electrophilic conditions, and indicate that effecting the Beckmann reaction is not always straightforward.



(4)

1. 20 mol% *n*-Bu_4NReO_4, 1.0 equivalent CF_3SO_3H, 0.5 equivalent chloranil



(5)

1. Ac_2O, xylene, microwave, 0.5 h

Two reports describe stereospecific Beckmann rearrangements of homochiral oximes, taking advantage of the known retention of configuration of the migrating center, to prepare homochiral lactams.[112,113] Also noteworthy are reports describing the coupling of ketoxime isomer equilibration (between *E* and *Z* forms) with the Beckmann rearrangement, which leads to a breakdown of the stereoelectronic requirement of the migration.[113,114]

7.25.4 Complex Molecules and Natural Products

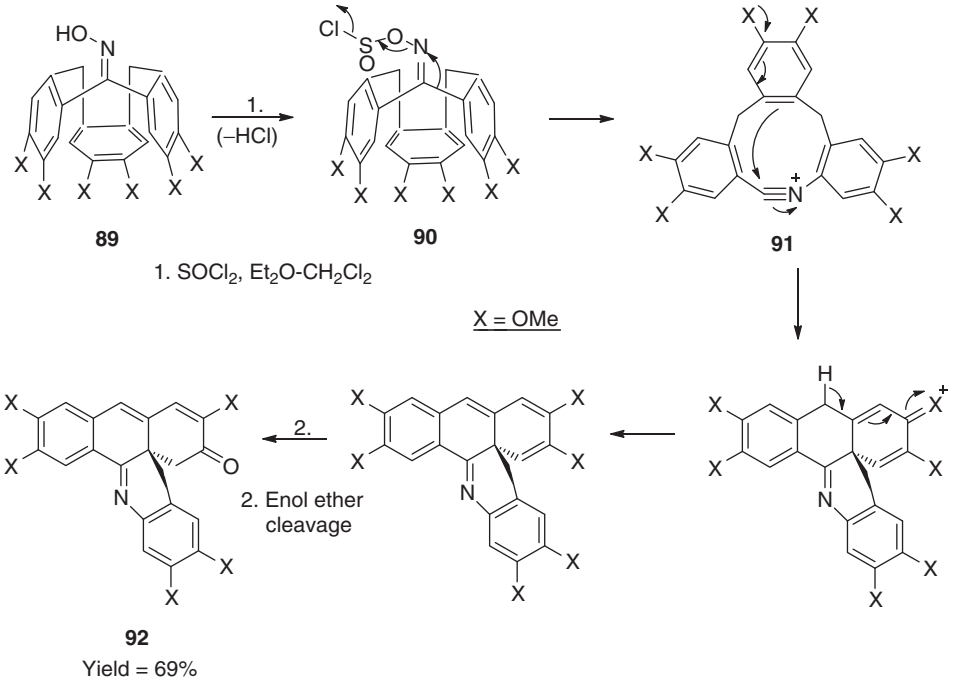
The Beckmann reaction – in both the rearrangement and 'second-order' fragmentation modes – continues to be an important element in the synthetic armory of the modern chemist, finding widespread application in the construction of various complex molecules, particularly natural products of biological importance. Exhaustive coverage of these is clearly beyond the scope of this chapter; however, the examples found below have been culled from the vast literature essentially for their conceptual interest and significance, and hopefully provide useful insight into the scope and extent of the Beckmann reaction.

7.25.4.1 The Beckmann Rearrangement

The rearrangement reaction has been employed for the incorporation of the carboxamide or lactam unit in the construction of a diverse range of molecular frameworks. In several cases, the intermediate nitrilium cation (**3**, Scheme 1) has been intercepted by a variety of nucleophilic species, sometimes leading to tandem reactions involving other well-known synthetic reactions. The rearrangement has also been selectively effected in the presence of other reactive functional groups.

7.25.4.1.1 Additions to the nitrilium ion

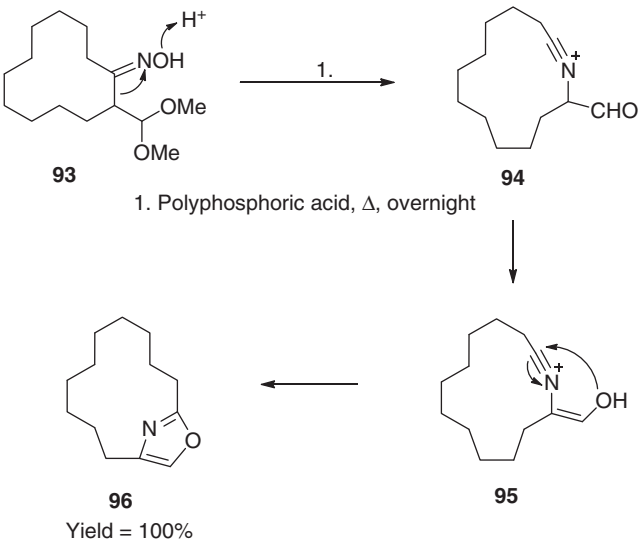
Although examples in which the rearrangement introduces the carboxamide or lactam unit in straightforward fashion are far too numerous to mention, the creative interception of the intermediate nitrilium ion has evolved into a fascinating and useful synthetic tactic. An interesting (if serendipitous) example was reported by Becker and coworkers in the cyclotriveratrylene (CTV) series.[115] In this case, a nitrilium ion intramolecularly attacks an electron-rich aromatic ring (Scheme 18). Thus, the CTV ketoxime **89**, on treatment with $SOCl_2$, forms the chlorosulfonate **90**, which rearranges to the nitrilium ion **91;** this suffers electrophilic attack by the distal aromatic ring, leading finally to ketone **92** as shown.



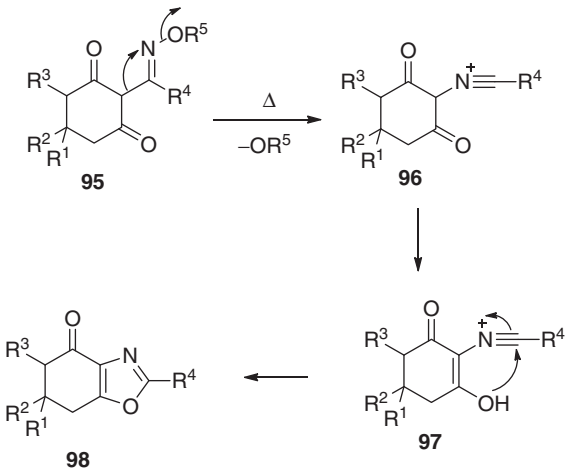
Scheme 18

Among several examples of the trapping of the nitrilium intermediate with an internal enolate species, two may be mentioned. Uemura and coworkers report that α-formyl cyclododecanone oxime dimethyl acetal (**93**) rearranged on heating with polyphosphoric acid in toluene, to furnish the oxazole **96** in quantitative yield (Scheme 19).[116] The reaction likely occurs via the nitrilium aldehyde **94**, formed by rearrangement of the oxime function and hydrolysis of the dimethyl acetal moiety. Enolization of **94** generates **95**, in which the enol can add across the nitrilium triple bond as shown, to form the macrocyclic ring-fused oxazole **96**.

Rubinov and coworkers report that ketoximes of the type **95** rearrange to furnish the dihydrobenzoxazolones **98**, presumably via the initially formed nitrilium ion **96**. Enolization of one of the ketone groups in **96** leads to **97**, in which the enol function adds intramolecularly to the nitrilium moiety to form the oxazole ring in **98** (Scheme 20, R^1 through R^5 are generally hydrogen or alkyl).[117]



Scheme 19



Scheme 20

It is known that the reaction of ketoximes with organometallic reagents can induce the Beckmann rearrangement, and can finally lead to products derived from the addition of hydride or alkyl anions to the nitrilium ion intermediate. (The rearrangement step is possibly induced by coordination of the activated oxime moiety with the metal center involved in the reaction.) Among several new examples two are noteworthy.

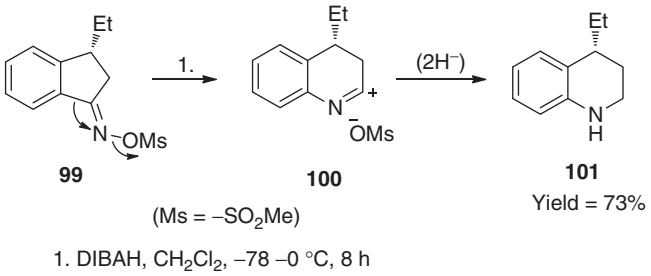
Mani and Wu report that treating the indanone oxime methanesulfonate (mesylate) **99** with diisobutylaluminum hydride (DIBAH) in dichloromethane at low temperatures led to the formation of the tetrahydroisoquinoline **101** in 73% yield (Scheme 21).[118] The reaction presumably occurs via the transfer of hydride from DIBAH to the nitrilium ion intermediate **100**, as shown.

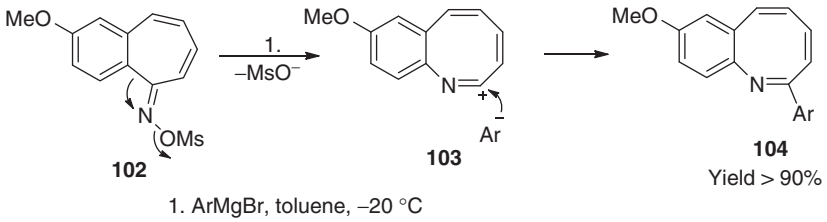
Yu and coworkers have induced the rearrangement of the benzocycloheptenone oxime mesylate **102** with various aryl Grignard reagents, to obtain the 2-aryl-1-benzazocines **104**, likely via the addition of aryl anion to the nitrilium ion intermediate **103**.[119]

Shibuya and coworkers report the $TiCl_4$-mediated rearrangement of α-tetralone oxime mesylates (**105**) in the presence of triethylphosphite [$P(OEt)_3$], leading to the unsaturated aminophosphonates **107**.[120] The reaction presumably involves the reaction of $P(OEt)_3$ with the nitrilium ion **106** generated in the rearrangement (Scheme 22), in a manner reminiscent of the Arbuzov reaction. (This reaction is an interesting example of the interception of the nitrilium ion intermediate by a phosphorus-centered nucleophile.)

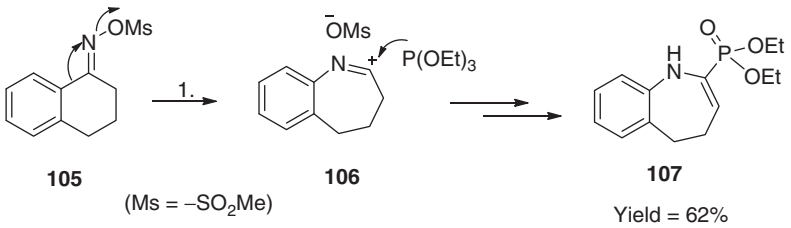
7.25.4.1.2 Novel variations and synthetic protocols

Several ingenious modifications of the Beckmann rearrangement have led to novel synthetic protocols with significantly extended applications in complex syntheses.



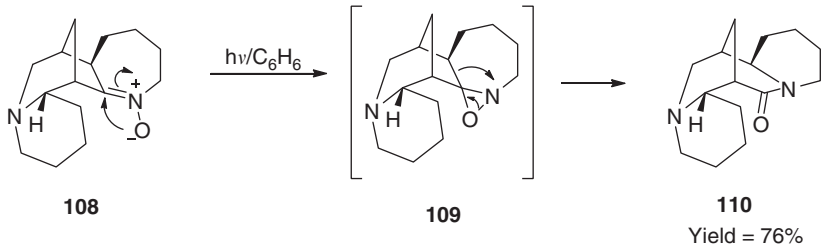


Scheme 21



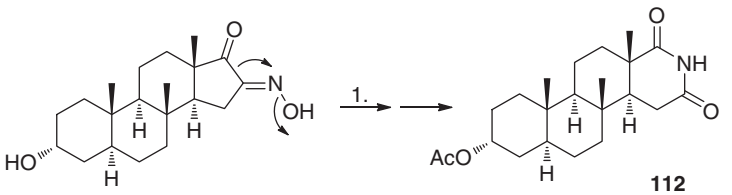
Scheme 22

An interesting photochemical variant has been reported by Aubé and coworkers, as employed in their total synthesis of the alkaloid (+)-sparteine.[121] Thus, photolysis of the nitrone **108** in benzene at 254 nm afforded the lactam **110** in 76% yield, presumably via the oxaziridine intermediate **109**. (Scheme 23. This may be considered a 'quasi-Beckmann' reaction, inasmuch as a nitrone is an *N*-alkylated oxime, and the reaction leads to a lactam via a Beckmann-type migration.)



Scheme 23

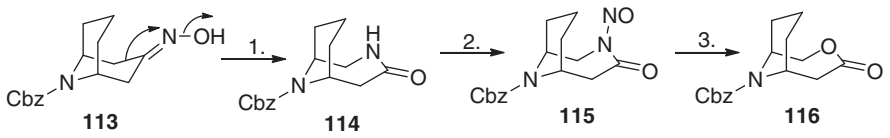
Hu and coworkers have reported an interesting rearrangement of a steroidal oxime in which the migrating center is a carbonyl group.[122] Thus, heating the 3-hydroxyandrostane-16,17-dione 16-oxime **111** in an acid medium led to expansion of the D ring to form the corresponding six-membered cyclic imide **112** (Scheme 24).



111 **112**

Yield = 65%

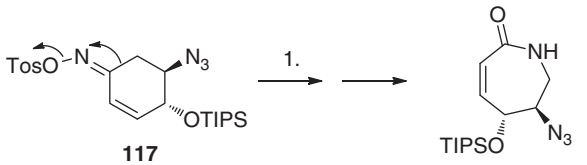
1. AcOH-H_2SO_4-H_2O, 80–90 °C, 1.5 h



113 **114** **115** **116**

1. TsCl, K_2CO_3, DME-H_2O, 80 °C, 3 h; 2. N_2O_4, DME, 0 °C, 15 min; 3. K_2CO_3, 80 °C, 2 h

(Cbz = $PhCH_2OCO$-; DME = dimethoxyethane)



117 **118**

1. Excess $TiCl_3(OPr^i)$, CH_2Cl_2, r.t.

Yield = 66%

[TIPS = $Si(OPr^i)_3$]

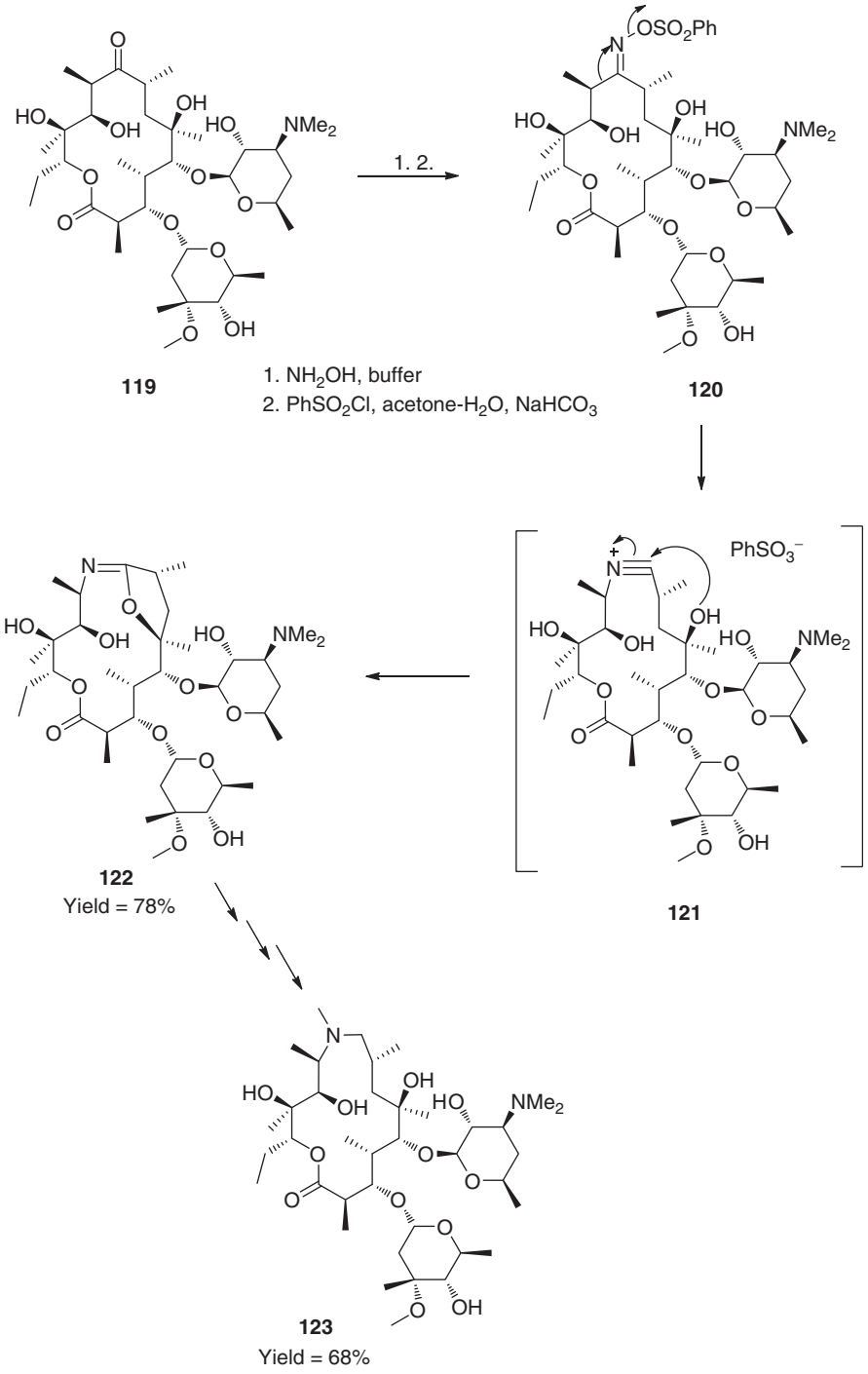
Scheme 24

An interesting extension of the Beckmann rearrangement involves the Huisgen–White conversion of carboxamides to corresponding esters. Muraoka and coworkers have performed the Beckmann–Huisgen–White sequence in the course of their asymmetric synthesis of (–)-dihydropalustramic acid.[123] Beckmann rearrangement of the bicyclic ketoxime **113** to lactam **114** was accomplished with tosyl chloride and potassium carbonate. Lactam **114** was treated with N_2O_4 to form the *N*-nitroso derivative **115**, which on heating furnished the lactone **116** in 85% yield. The overall sequence provides an alternative to the Baeyer–Villiger oxidation of ketones, and can be applied to substrates that fail to undergo this reaction (as, in fact, did the ketone precursor of **113**).

The utility of the Beckmann reaction is, of course, greatly enhanced by its applicability in complex syntheses. For this, the rearrangement needs to be selectively effected in the presence of possibly interfering functional groups. The following examples are particularly noteworthy.

Wu and Jacobsen report the rearrangement of the α,β-unsaturated azido ketoxime **117** (Scheme 24) with excess $TiCl_3(OPr^i)$ in dichloromethane at room temperature.[124] The corresponding caprolactam derivative **118** was obtained in 66% yield (despite competing oxime stereoisomerization).

An important impetus for the Beckmann reaction in recent decades was provided by the discovery of the semisynthetic antibiotic azithromycin (insightfully reviewed by Mutak).[125] Azithromycin is a member of the azalide class of antibiotics, which are structurally related to the erythromycin group (Scheme 25). The key step in the conversion of erythromycin (**119**) to azithromycin (**123**) involves the Beckmann rearrangement of erythromycin oxime, which was accomplished with bezenesulfonyl chloride in acetone-water, in the presence of $NaHCO_3$. The intermediate oxime benzenesulfonate (**120**) rearranged to furnish the imino ether **122**, via the capture of the nitrilium moiety in the intermediate **121** by a neighboring hydroxyl group, as indicated. (Ether **122** can be converted to **123** via hydrogenation followed by *N*-methylation.)

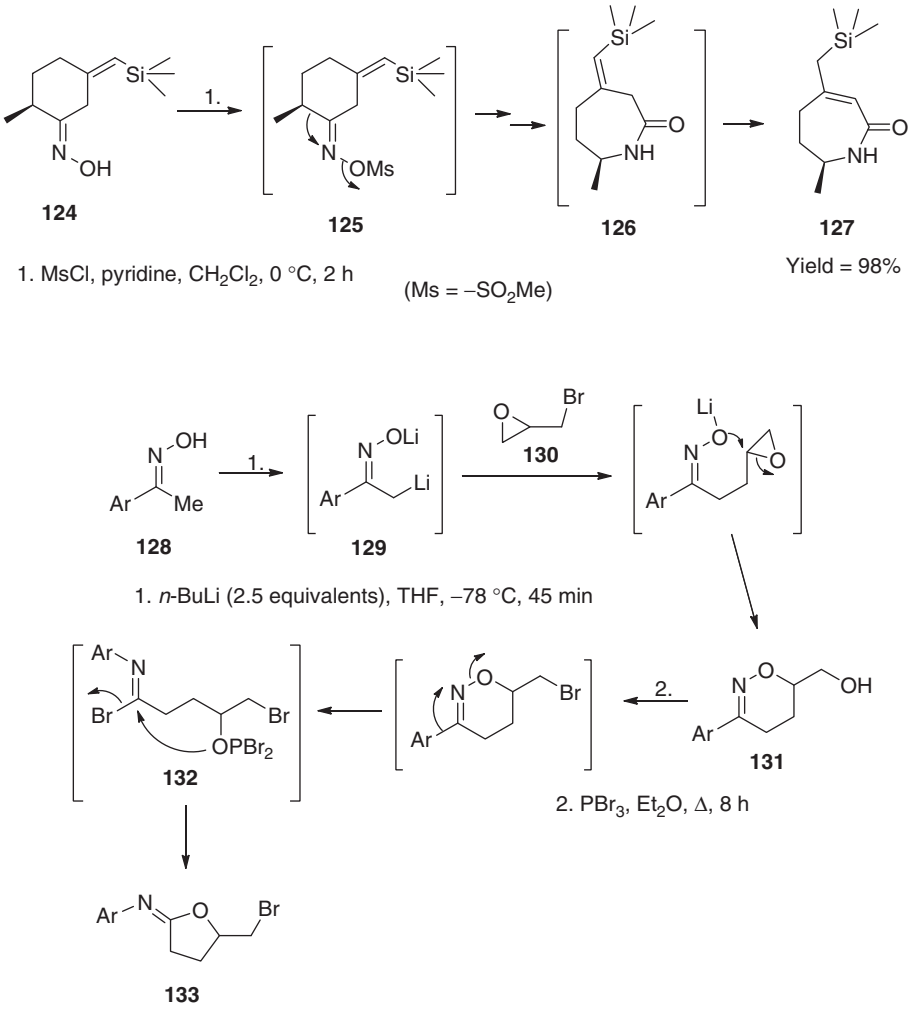


Scheme 25

In this sequence, the Beckmann reaction has been effected in a dense and sensitively functionalized skeleton. The macrocyclic lactone moiety and the two anomeric centers in the pyranose units are particularly noteworthy, as these are sensitive to acid media (normally used for the Beckmann rearrangement). The intramolecular capture of the nitrilium moiety in **121** is also interesting, and has proved advantageous to the overall objective.

The Beckmann rearrangement has been effected in the presence of a vinylsilane moiety by Ishikawa and coworkers (Scheme 26).[126] Thus, the α-methylcyclohexanone oxime **124**, bearing a remote vinylsilane function, rearranged via the mesylate **125** to the caprolactam derivative **126**, which isomerized to the allylsilane **127**.

An ingenious adaptation of ketoxime reactivity, for subsequent Beckmann rearrangement, has been reported by Langer and coworkers.[127] In this strategy (Scheme 26), an aryl alkyl ketoxime (**128**) was dilithiated at the oxygen and α-carbon centers, and



Scheme 26

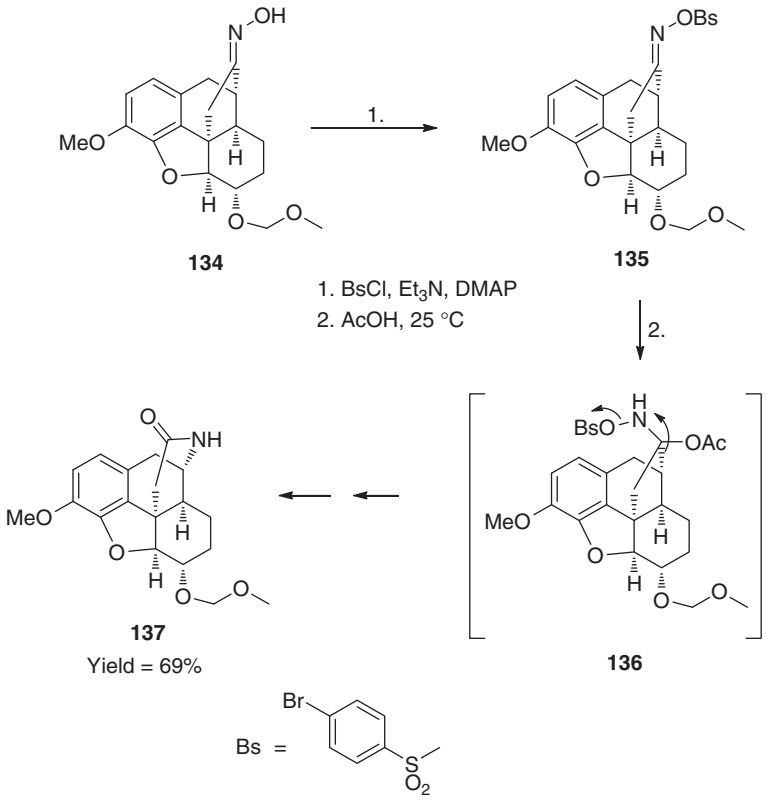
the resulting dianion (**129**) reacted with epibromohydrin (**130**) to obtain corresponding 1,2-oxazines **131**. These cyclic oxime derivatives underwent Beckmann rearrangement on treatment with PBr_3 to furnish the vinyl bromide intermediate **132**. Intramolecular displacement of the vinylic bromine atom as indicated furnished the iminotetrahydrofurans **133**. Although yields were only moderate, this is a novel application of the Beckmann rearrangement involving a cyclic *O*-alkyl derivative of an oxime.

Effecting the Beckmann rearrangement in complex systems has also led to interesting mechanistic insight. Thus, in their asymmetric total synthesis of (+)-codeine, White and coworkers observed that the Beckmann rearrangement of the pentacyclic ketoxime **134** (Scheme 27) was unusually sluggish under the normal reaction conditions.[128] (These included activating **134** with tosyl chloride or carbonyl diimidazole.) This was attributed to the rigidity of the molecular framework, leading to a stereoelectronic impediment to the rearrangement. The authors then reasoned that converting the oxime carbon atom to a tetrahedral center would possibly remove the impediment; accordingly, the rearrangement could be effected on the oxime brosylate derivative **135** in glacial acetic acid, presumably via the adduct **136**, to furnish lactam **137** in good yields. (The possibility that the oxime carbon center needs to be tetrahedralized has been considered in the reaction of oximes with oxalic acid.)[70]

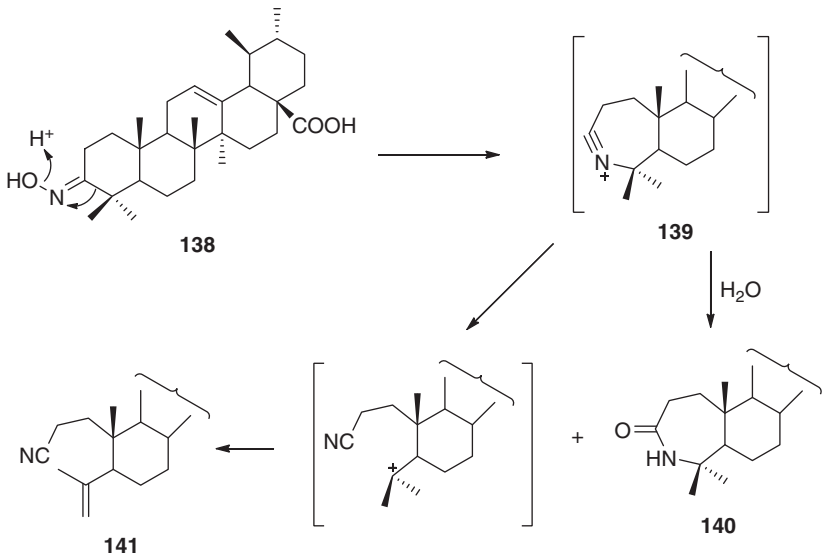
The Beckmann reaction of ketoxime **138** derived from ursolic acid (not shown) furnishes a mixture of the rearrangement and fragmentation products **140** and **141**, respectively, in varying amounts depending on the reaction conditions (Scheme 28). Gnoatto and coworkers explain their observations on the basis of the common intermediate **139**, which is partitioned between the two products at different relative rates depending on the conditions.[129] (A common intermediate for rearrangement and fragmentation was also proposed in the case of the Beckmann reaction of 3-nortricyclanone oxime, on the basis of experimental and theoretical studies.)[130]

7.25.4.2 The Beckmann Fragmentation

This mode of the Beckmann reaction (equation 1) accompanies the main rearrangement mode as a side reaction in several cases. However, under certain conditions, this 'second-order' mode can predominate to varying extents; it can either be driven by relief



Scheme 27

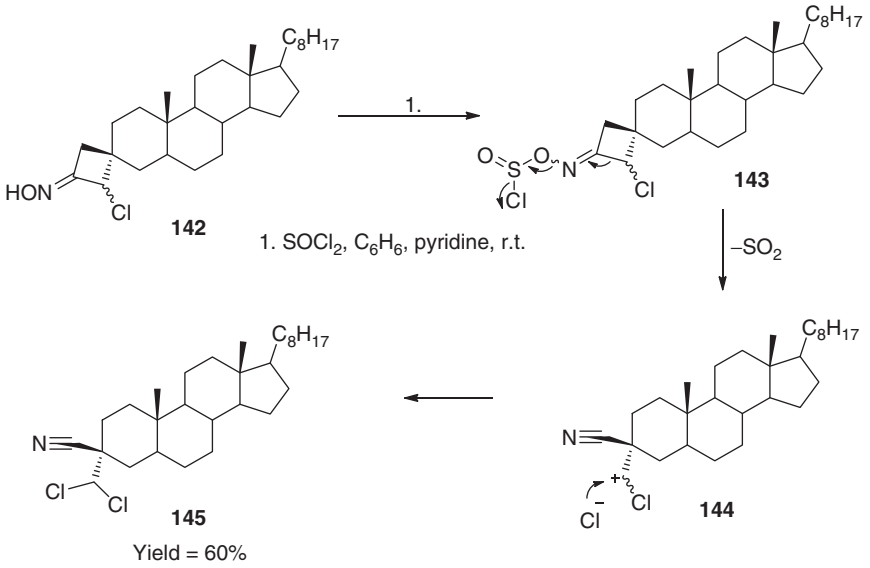


Scheme 28

of strain or be assisted electronically by an α heteroatom lone pair. Generally, of course, the formation of a stable carbocation byproduct (R^{1+}) would facilitate the fragmentation. Examples of both strain relief and electronic assistance continue to be reported, particularly in complex systems. The following selection is intended to convey recent trends and developments.

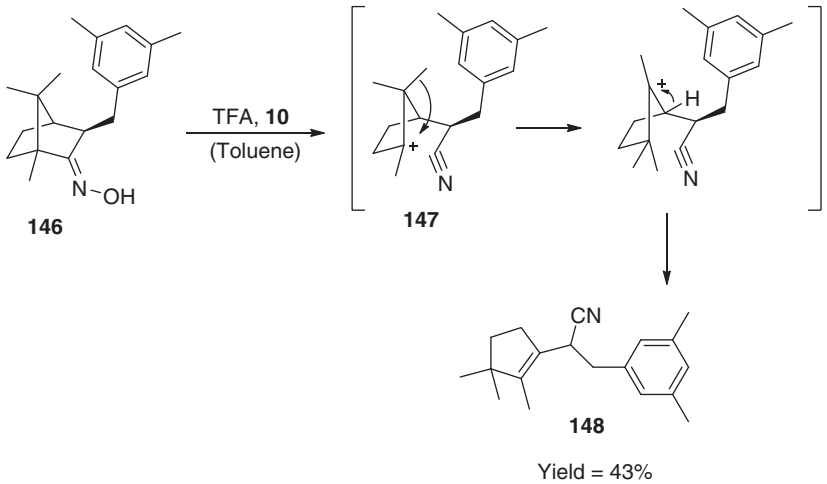
The fragmentation of several steroidal α-chlorocyclobutanone oximes, reported by Paryzek and coworkers, reveals interesting structure-reactivity trends.[131] Thus, the spirocyclic oxime **142** fragmented to furnish the dichloronitrile **145** as the major product, on treatment with thionyl chloride (**Scheme 29**). The fragmentation is driven by the stability of the intermediate chloromethyl

cation **144**, as suggested by theoretical calculations. (The reaction of cyclobutanone oximes generally furnishes both rearrangement and fragmentation products in varying relative yields, depending on structural features and reaction conditions.)



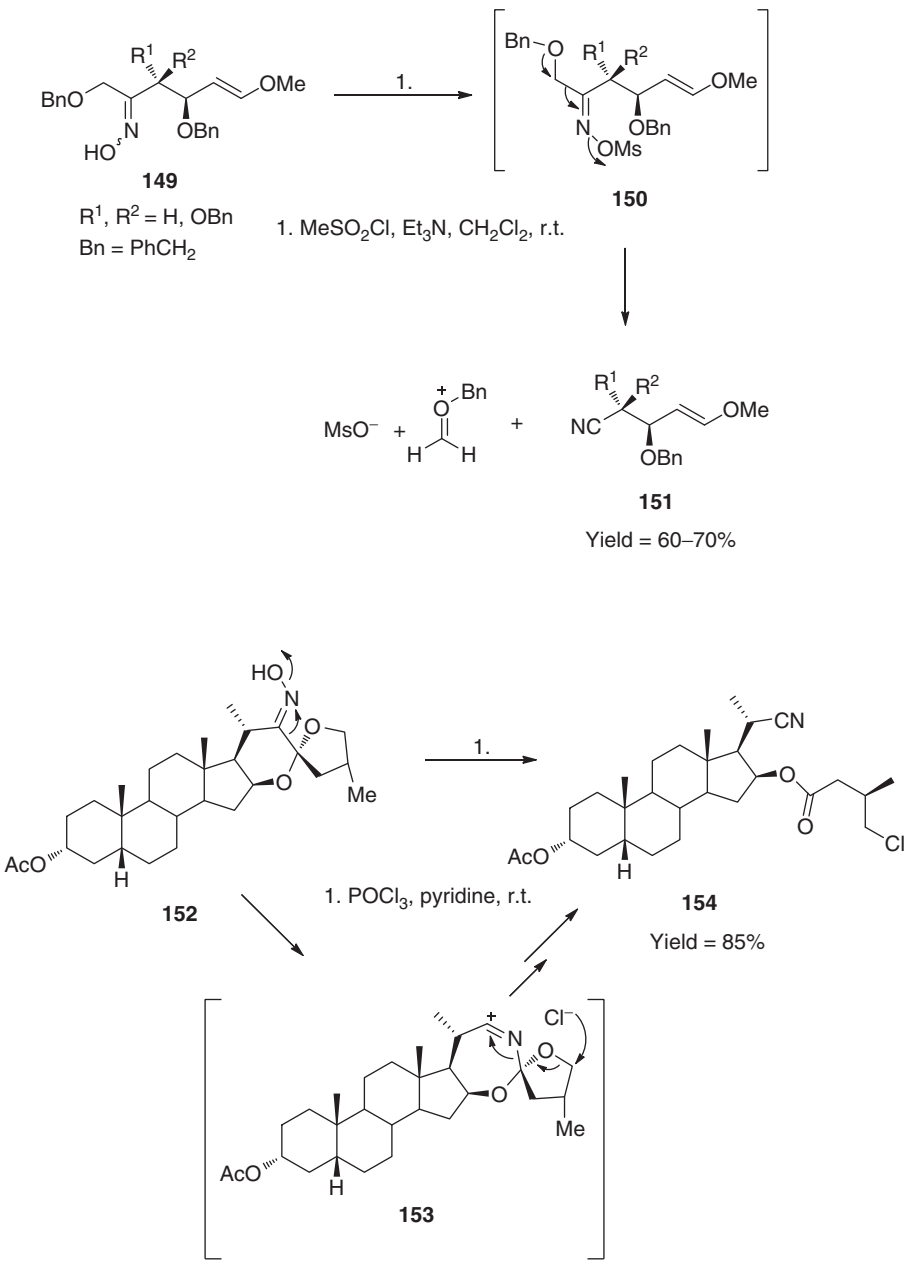
Scheme 29

The Beckmann reaction of camphor oximes continues to attract the attention of synthetic chemists, in view of the potential of the camphor framework in asymmetric synthesis. Grošelj and coworkers report that treating the benzyl-substituted camphor oxime **146** with TFA in toluene, along with catalytic quantities of cyanuryl choride (**10**) and pyridine, yielded the *β,γ*-unsaturated nitrile **148** almost exclusively (Scheme 30).[132] A mechanism involving the preferential formation of the tertiary carbocation **147**, which subsequently undergoes a 1,2-methyl shift followed by proton loss (as shown), was proposed. The reaction is probably driven by relief of both steric and bond angle strain in the highly substituted bicyclic framework, apart from the stability of the tertiary cation **147**.



Scheme 30

However, the Beckmann reaction of oximes in which the fragmentation mode can be assisted by an α-hetero atom is being actively pursued, with novel examples continuing to be reported. Piancatelli and coworkers report an extensive study of the fragmentation of several multifunctional ketoximes, aimed at the asymmetric synthesis of functionalized pentenenitriles.[133] Thus, treating the acyclic ketoxime **149** with mesyl chloride and triethylamine in dichloromethane at room temperature effected its fragmentation to the nitrile **151** in fair yields (Scheme 31). The ease of formation of **151** indicates the assisted mechanism shown in the intermediate mesylate **150,** involving the electron pair on the neighboring oxygen atom.

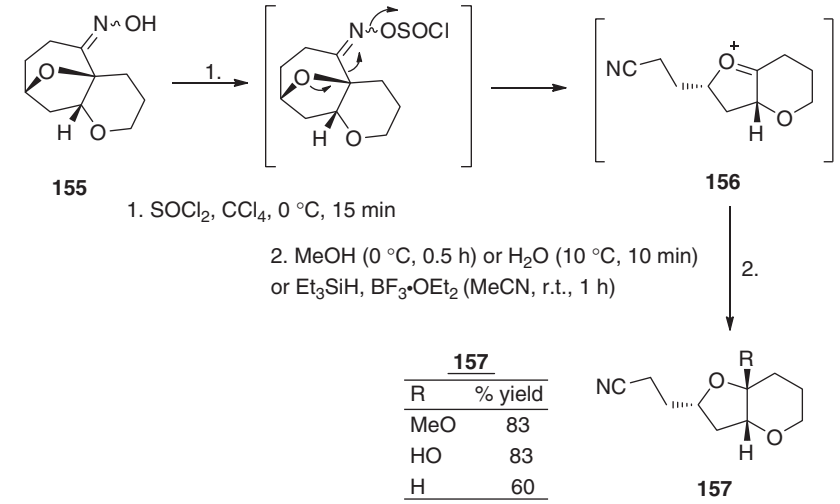


Scheme 31

An intriguing steroidal system involving two α oxygen atoms has been reported by Iglesias-Arteaga and coworkers.[134] It was observed that the spirocyclic *E* oxime **152** underwent fragmentation to nitrile **154,** whereas its *Z* isomer underwent rearrangement (competitively with isomerization to **152**). Interestingly, a mechanism involving an initial rearrangement to the nitrilium cation **153,** rather than the oxygen-assisted fragmentation (cf. **150**), was proposed.

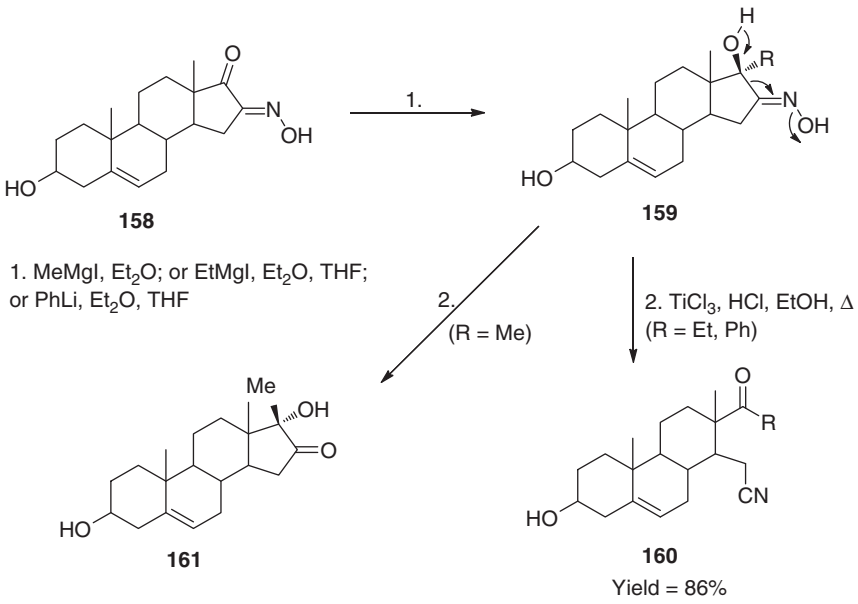
The fragmentation of the tricyclic oxime **155** under very mild conditions has been reported by Murali Krishna, aimed at the construction of furopyans for synthetic elaboration (Scheme 32).[135] The reaction was effected in two stages, initial treatment of **155** with thionyl chloride in CCl_4 at 0 °C followed by a selection of three nucleophilic reactants. These were methanol, water, and triethylsilane (Et_3SiH), which added to the oxacarbenium intermediate **156** produced by the fragmentation. The resulting nitriles **157** were isolated in 60–83% yields.

The interesting fragmentation of the steroidal α-keto oxime **158,** on addition of various carbon nucleophiles to the carbonyl group, has been reported by Penov Gaši and coworkers (Scheme 33).[136] The initially formed **159** cleaved to the nitrile **160** with $TiCl_3$ and HCl in boiling ethanol (in the case of the ethyl and phenyl derivatives). Under these conditions, the methyl derivative hydrolyzed to the epimeric ketone **161,** although the fragmentation to **160** (R = Me) could be achieved with acetic anhydride in pyridine.



157	
R	% yield
MeO	83
HO	83
H	60

Scheme 32



Scheme 33

In conclusion, a large number of other studies of much interest have been reported in the recent literature, and the above selection is meant to provide an overview of the synthetic possibilities of the second-order Beckmann fragmentation reaction.

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7.26 Glycol Cleavage Reactions

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Glossary

Aldol reaction An addition reaction between two aldehydes (or an aldehyde and a ketone) resulting in a β-hydroxy aldehyde. Similar reaction between two ketones gives a β-hydroxy ketone. Subsequent dehydration produces an α,β-unsaturated aldehyde or ketone. The combination of an aldol reaction with subsequent dehydration is an aldol condensation which can be promoted by base or acid.

α-Glycol A diol with two hydroxyl groups bonded to two adjacent carbons.

INOC Intramolecular nitrile oxide cycloaddition. A 1,3-dipolar cycloaddition between a nitrile oxidation and an alkene.

Ionic liquid A salt in liquid state which are largely made of ions and short-lived ion pairs.

Oxidative fission The oxidative splitting of an atomic nucleus into two or more lighter nuclei accompanied by energy release.

Spiro A molecule containing two or more rings where two adjoined rings share exactly the same atom.

7.26.1 Introduction

This chapter discusses the development of oxidative carbon–carbon bond cleavage of vicinal diol (α- or 1,2-glycols) and related functional groups after the 1990s. The glycol fission reactions usually are very rapid, clean quantitative, and specific. Nowadays, sodium periodate is the most common reagent of choice because of its reactivity under neutral and mild conditions which is compatible with a wide range of functional groups, its stability, and its low cost. The studies of other reagents have been mainly exploratory or mechanistic. Some have shown promise for specific application but none has been as popular as lead tetraacetate (LTA) or periodate in organic synthesis. Several reviews of glycol cleavage were published.[1–7]

7.26.2 Metallic Reagents

7.26.2.1 Bismuth(V) and Bismuth(III) Derivatives

The synthetic potential of sodium bismuthate for cleavage of vicinal diols and conversion of acyloins to α-diketone was discovered first by Rigby in 1950. Arylbismuth(V) reagents has been known for many years with their oxidizing ability. However, no further development of this reagent was carried out after the twentieth century. For details, please refer back to the review reported before.[5]

7.26.2.2 Calcium Hypochlorite

Calcium hypochlorite, $Ca(OCl)_2$, is an inexpensive and easily stored oxidizing agent, which is able to cleave α-glycols to its corresponding carbonyls. Apart from α-glycols, it is also feasible to fragmented α-diones, α-hydroxy ketones, and α-hydroxy and α-keto acids. However, it is not popular in synthetic application nowadays and no development anymore nowadays.[5]

7.26.2.3 Cerium(IV) Reagents

Cerium(IV) is an efficient reagent for α-glycol cleavage. Recently, Tandon et al. has reported that addition of rhodium(III) chloride and further enhance the cleavage rate of propane-1,2-diols and butane-2,3-diols under acidic medium.[8]

7.26.2.4 Chromium(VI) Reagents

Chromic acid and pyridinium chlorochromate (PCC) are two reagents usually employed for glycol cleavage oxidation. However, chromic acid receives less attention because of its harsh conditions used as well as the newly formed aldehydes easily further oxidized to its corresponding carboxylic acids.[5] Apart from PCC, Maki et al. also reported using pyridinium dichromate to cleave the vicinal diols.[9] It is believed that the intermediate should consist of a chromate ester.

7.26.2.5 Cobalt(II) Reagents

Cobalt(II) salts are effective catalysts for glycol cleavages with molecular oxygen in aprotic polar solvents. The aldehydic products are usually further oxidized to carboxylic acids, so it is very useful to convert vicinal diols into carboxylic acids industrially.[10]

7.26.2.6 Lead Tetraacetate (LTA)

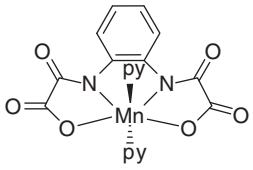
LTA is one of the most widely used reagents for the oxidative cleavage of vicinal diols nowadays. It was first discovered by Criegee, and has been demonstrated to cleave the carbon–carbon bond of 1,2-diols efficiently in 1931.[11] The reactions are very clean, efficient, and give high yields. A stoichiometric amount of the oxidant is required for each mole of carbon–carbon cleaved. The carbonyl compounds generated are inert toward further oxidation. The reaction is usually conducted in acetic acid or aprotic solvents such as benzene, ethyl acetate, and dichloromethane. For mechanistic details, please refer to the review published by Shing.[5]

7.26.2.7 Manganese Dioxide

Excess activated manganese dioxide can cleave α-glycols to their corresponding carbonyls smoothly under neutral conditions.[12] The reaction conditions are extremely mild (stirring at room temperature in dichloromethane) and neutral. However, only 1,2-*cis*-diols and *trans*-diols with flexible backbones are able to be cleaved. No further development is reported on the oxidative fission using MnO_2 after the 1990s.

7.26.2.8 Manganese(III) Complexes

In recent years, the oxidative fission of vicinal diols by molecular oxygen accompanied by catalytic amount of manganese(III) complexes has been investigated. Barroso et al. reported that using *trans*-dipyridine manganese(III) complex (**1**) with a tetradentate *o*-phenylenedioxamate ligand to cleave the mono-, di-, tri-, and tetra-substituted vicinal diols.[13] The complex catalyzes the oxidative cleavage of α,β-disubstituted diols such as 2-phenyl-1,2-propanediol, 1,1-diphenyl-1,2-ethanediol, and 1-*p*-nitrophenyl-1-phenyl-1,2-ethanediol to the corresponding ketones, acetophenone, benzophenone, and *p*-nitrobenzophenone, respectively, with very good yields. Besides, Fernández et al. have discovered the positive effect of ionic liquid toward the manganese(III)-catalyzed oxidative cleavage of vicinal diols.[14]



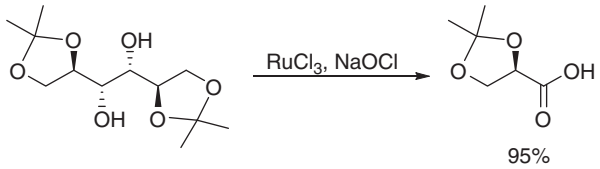
7.26.2.9 Potassium Permanganate

Ferreira et al. used the silica-gel supported potassium permanganate for the oxidative carbon–carbon bond cleavage of vicinal diols to give either ketonic compounds or carboxylic acids. The advantages of this reaction includes: (1) mild conditions, efficient and

simple work-up procedures; (2) the ketone compounds formed are eluted with the solvent which makes its isolation exceeding easy; and (3) the reagent is cheap.[15]

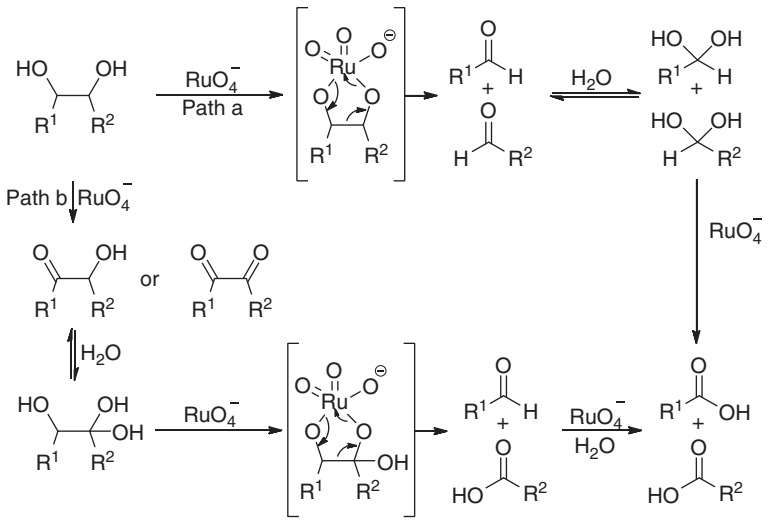
7.26.2.10 Ruthenium Reagents

Ruthenium pyrochlore oxide is a well-known catalyst for glycol cleavage reactions with oxygen gas as oxidant. It was first reported by Felthouse which 1,6-hexanediol, 1,2-*cis*-cyclohexanediol and its *trans*-isomer were successfully converted into their corresponding carbonyl compounds with high conversions.[16] Ruthenium(III) chloride catalyzed hypochlorite oxidation of cyclohexane-1,2-diols were also reported by Wolfe in 1970.[17] Later on, Emons et al. modified the method, making it become useful to a wide range of acetal-protected sugars (Scheme 1).[18]



Scheme 1

In 1999, Takezawa discovered the usage of a catalytic amount of the commercially available dichlorotris(triphenylphosphine) ruthenium(II) loaded on the activated charcoal ($Ru(PPh_3)_3Cl_2/C$), with molecular oxygen to perform the oxidative fission of various kinds of vicinal diols. Good conversion and selectivity was observed when treating of 1,2-octanediol and 1,2-cyclooctanediol with dioxygen in the presence of the catalyst in benzotrifluoride at 60 °C for 15 h to furnish 1,8-octanedial in 77% and 76% yield, respectively.[19] Recently, Schmidt et al. discovered the cleavage of vicinal diols by tetrapropylammonium perruthenate (TPAP) with *N*-methylmorpholine *N*-oxide (NMO). However, this method is only useful to synthesize ketonic compounds or carboxylic acids as the aldehydic products would be further oxidized.[20] Two mechanistic pathways are proposed for the cleavage by TPAP. The first involves initial formation of a cyclic perruthenate diester (path a)[21] which then oxidatively collapses under cleavage of the C–C bond to give the corresponding carbonyl compounds (Scheme 2). Hydration of the latter and subsequent oxidation give the desired carboxylic acid (or diacid).[22] It is also conceivable that the diol is first oxidized to the hydroxy ketone (or diketone) which, after hydration, could also form a cyclic perruthenate diester (path b). The oxidative fragmentation of this Ru(VII) diester would result in a carboxylic acid (two carboxylic acids in the case of a diketone precursor) and an aldehyde which could then be oxidized further.[22]

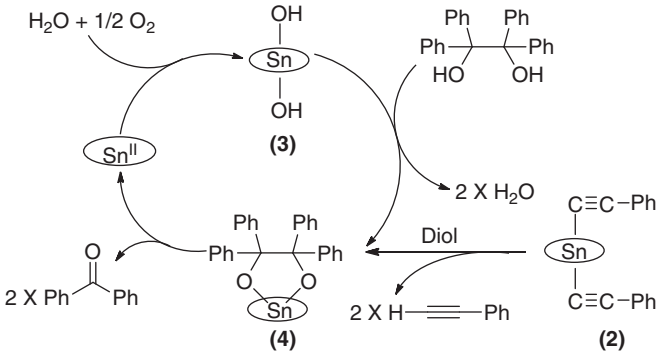


Scheme 2

7.26.2.11 Tin(IV) Porphyrin Complexes

Tin(IV) porphyrin complexes have been reported by Du et al. to cleave vicinal diols. They used a catalytic amount of the tin phophyrin complexes with air as oxidant and examined the reactivity of the catalysts toward the oxidative fission reaction. It was found that $(TTP)Sn(CCPh)_2$ (**2**) and $(TTP)Sn(OH)_2$ (**3**) gave good to excellent yields of benzophenone from benzopinacol.[23]

The mechanism starts with (TTP)Sn(CCPh)$_2$ (**2**), with which the diols reacted to form the cyclic tin intermediates (**4**), which breaks down to provide the desired carbonyl compounds. The inactive tin(II) porphyrins complex is oxidized back to active tin(IV) phophyrin complex (**3**) by air (Scheme 3).



Scheme 3

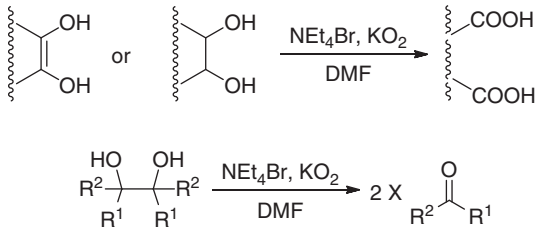
7.26.2.12 Vanadium Reagents

In recent years, Kirihara et al. has reported the effective cleavage of ditertiary glycols via vanadium(V) catalyzed aerobic oxidation. $VOCl_3$ was selected as a catalyst to furnish good to excellent yields of the carbonyl compounds. However, this reaction does not proceed for secondary-tertiary glycols as only the ketonic products can be obtained quantitatively, but the aldehydic compound would lead to a complex mixture.[24]

7.26.3 Nonmetallic Reagents

7.26.3.1 Ammonium Type Reagents

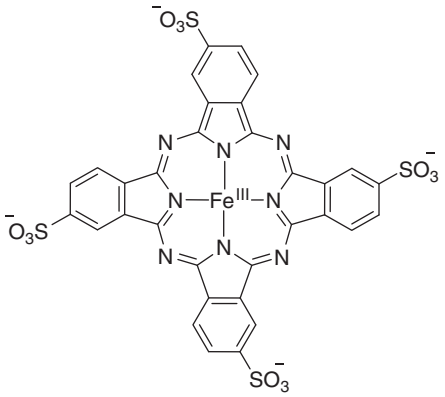
Tetrabutylammonium tribromide (TBATB) has been used for the bromination of some selected organic substrates, but only a few reports regarding their use as oxidizing and brominating agents in synthetic chemistry have been reported. This reagent is more suitable than molecular halogens because of its solid nature, ease of handling, stability, selectivity, and excellent product yields. There were no reports on the oxidation of diols by TBATB until the discovery by Gosain. TBATB can oxidize ethanediol, propane-1,2-diol, butane-2,3-diol, butane-1,2-diol, and pinacol to their corresponding carbonyl compounds in excellent yields. The reaction conditions are mild and efficient as well.[25] Tetraethylammonium superoxide, generated *in situ* by the phase-transfer reaction of potassium superoxide and tetraethylammonium bromide in dimethylformamide (DMF) efficiently cleaved carbon–carbon bond of vicinal diols and related dihydroxy arenes under mild conditions at room temperature (Scheme 4).[26]



Scheme 4

7.26.3.2 Hydrogen Peroxide

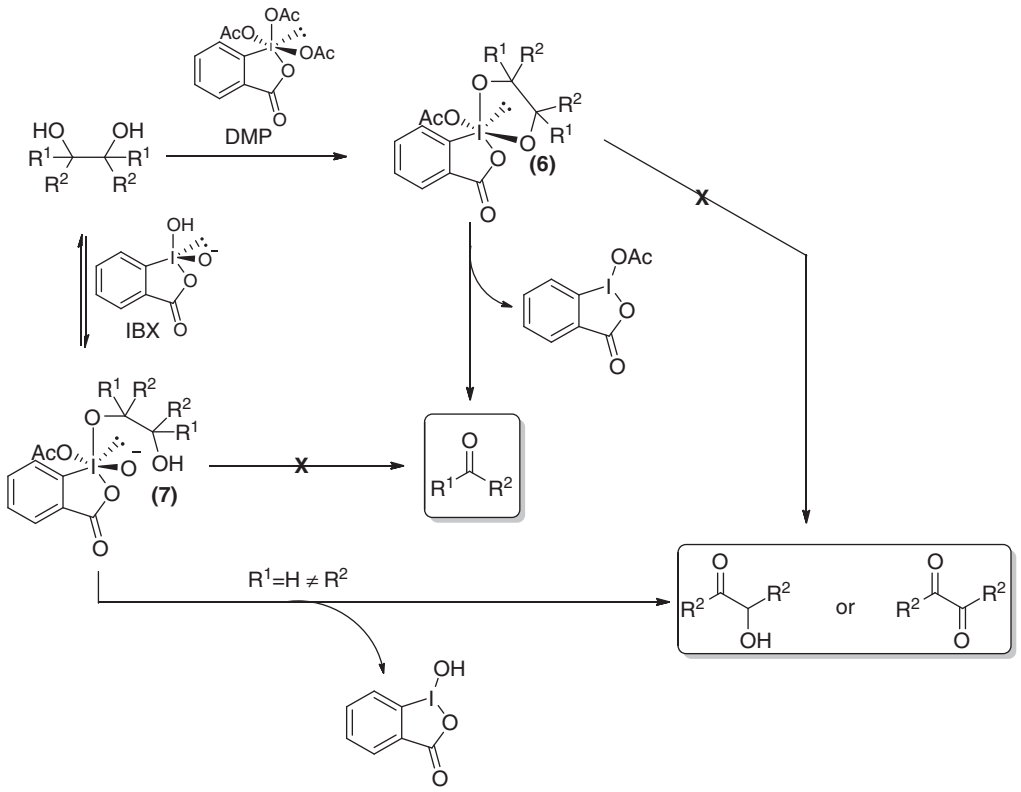
This method employs an inexpensive catalyst and readily available, cheap, and nonpolluting oxidizing agent, which is particularly useful in large-scale experiments. Recently, the presence of iron tetrasulfophthalocyanine (FePcS) catalyst (**5**) with H_2O_2 was employed for oxidative fission of vicinal diols in polysaccharides to give their carbonyl and carboxylic derivatives.[27]



7.26.3.3 Iodo Reagents

Beebe has shown that vicinal diols are cleaved to their corresponding carbonyl compounds on treatment with *N*-iodosuccinimide (NIS) and UV light. Products produced from this oxidation are ketones, aldehydes, iodine and succinimide.[28] However, the iodine produced may pose some complication with substrates with sensitive functional groups. McDonald has extended the application of NIS to cleave vicinal and monoprotected diols to a mixed acetal and carbonyl compounds.[29]

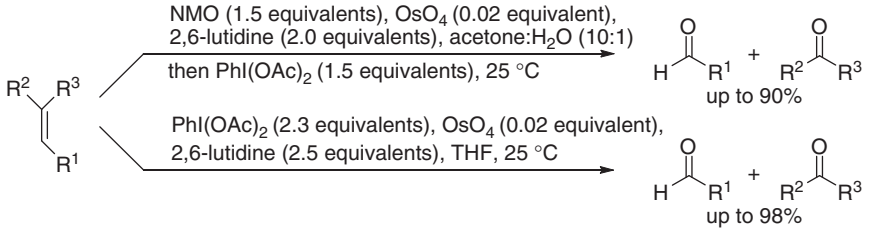
Dess–Martin periodinane (DMP) is a well known oxidant to cleave vicinal diols into the corresponding carbonyl compounds. This high reactivity is because of the irreversible formation of intermediate (**6**) when the diol reacts with DMP and rapidly undergo decomposition into dicarbonyl compounds (Scheme 5).[30]



Scheme 5

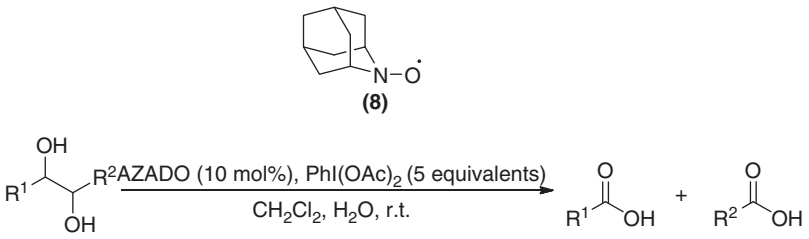
IBX has been found to have the same effect as DMP by Moorthy if trifluoroacetic acid (TFA) was used as solvent. TFA can promote the formation of intermediate (**16**) rather than intermediate (**7**) for all types of 1,2-diols, leading to effective oxidative fragmentation.[30]

The use of phenyliodiodiacetate [$PhI(OAc)_2$] to cleave 1,2-diols was rare until Nicolaou's extensive study on it.[31,32] The reaction conditions are very mild by mixing the 1,2-diols and $PhI(OAc)_2$ in dichloromethane at room temperature. He further extended the use of $PhI(OAc)_2$ to cleave olefinic bond in the presence of osmium tetraoxide OsO_4 (cat.) and 2,6-lutidine to yield the corresponding carbonyl compounds, albeit, in some cases, with α-hydroxy ketones as a byproduct. A more practical and clean protocol to effect oxidative cleavage of olefinic bonds involves NMO, OsO_4 (cat.), 2,6-lutidine, and $PhI(OAc)_2$ (Scheme 6).



Scheme 6

The addition of a catalytic amount of AZADO (**8**) with $PhI(OAc)_2$ can cleave the α-glycols to their corresponding carboxylic acids. The advantages of this reaction are that large amounts of NMO are unnecessary as compared to TPAP (reported before), and a wider scope of substrates are applicable (Scheme 7).[33]



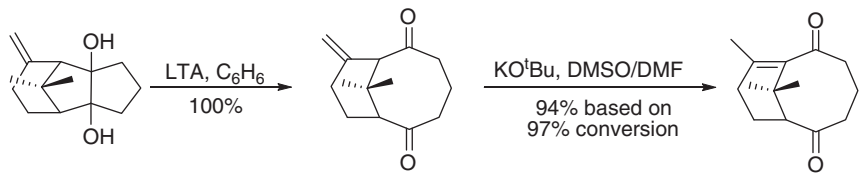
Scheme 7

7.26.3.4 Periodate

Periodate reagents are by far the most widely used reagent for oxidative fission of vicinal diols. The reactions are usually rapid, efficient, clean, specific, and quantitative. Periodic acid was before the first choice but because of its high acidity, it is not useful for broad synthetic applications. However, mild sodium and potassium periodate are now more popular. Shing et al. improved the silica-gel supported metaperiodate reagent in powder form for the efficient and facile preparation of aldehydes from vicinal glycols, which is by far the most popular method. The powder is easy to prepare and stable. Nonpolar solvents such as dichloromethane can also be used.[34] Later on, Dakdouki introduced the solvent-free oxidative cleavage of vicinal diols in solid phase using alumina/potassium metaperiodate. It permits preparation of the corresponding carbonyl compounds with high purity and good to excellent yields requiring only short reaction times.[35] Mechanistic aspects are discussed in a previously published review.[5]

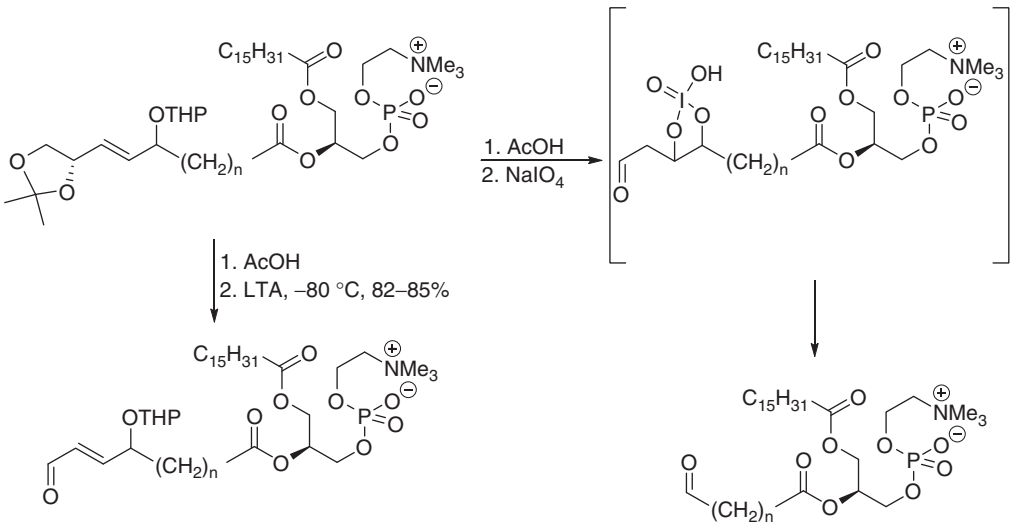
7.26.4 Applications in Organic Syntheses

Shimada et al. also used LTA to cleave the angular *trans*-diol to complete the synthesis of AB-ring core of taxol (Scheme 8).[36]



Scheme 8

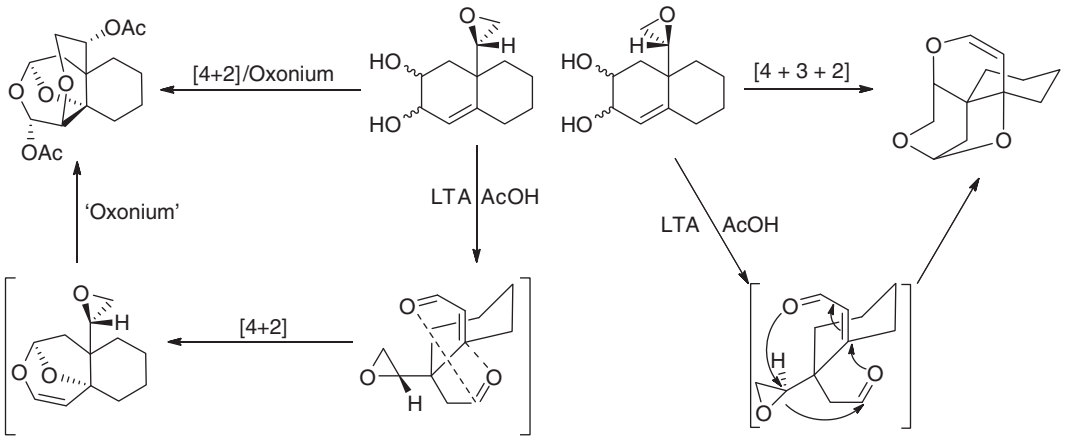
Another interesting example from Deng reported that exposure of the esters to aqueous acetic acid and periodate failed to give any of the desired γ-hydroxy-α,β- unsaturated carboxaldehydic esters (Scheme 9). Rather, shorter chain aldehydes were produced,



Scheme 9

presumably by Michael addition of periodate to the target α,β-unsaturated aldehydes followed by oxidative fragmentation of intermediate periodate esters. Some of the target aldehyde was obtained on hydrolytic removal of the THP and acetonide-protecting groups with aqueous acetic acid, followed by evaporation of the aqueous acetic acid and treatment of the resulting diol with LTA in methylene chloride in the presence of a suspension of sodium carbonate at room temperature. The yield was improved to 37% when the oxidative cleavage was conducted at 0 °C and was improved further (82–85%) by performing the oxidative cleavage at −80 °C.[37]

The developments of modular domino reactions are very challenging and attractive. Recently, unsaturated vicinal diols with different epoxides configuration at angular position have been discovered to give different structural products by oxidative cleavage of LTA.[38] It is possible to modify the regiochemical outcome of the domino process in such a way as to create a different pathway, [4+2] versus [4+3+2], and control product distribution by using the configuration bias (Scheme 10).

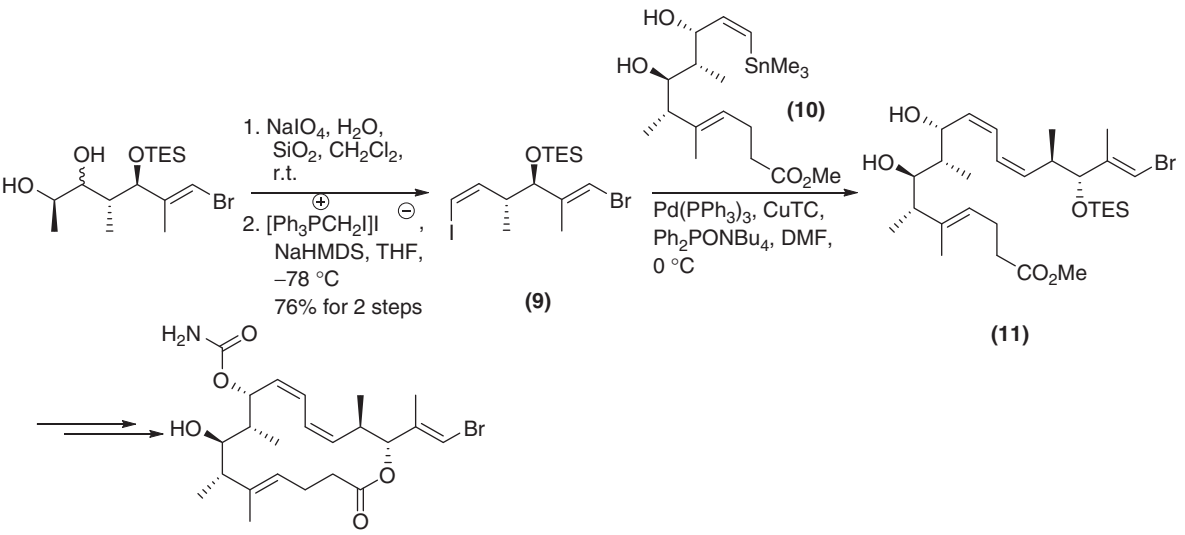


Scheme 10

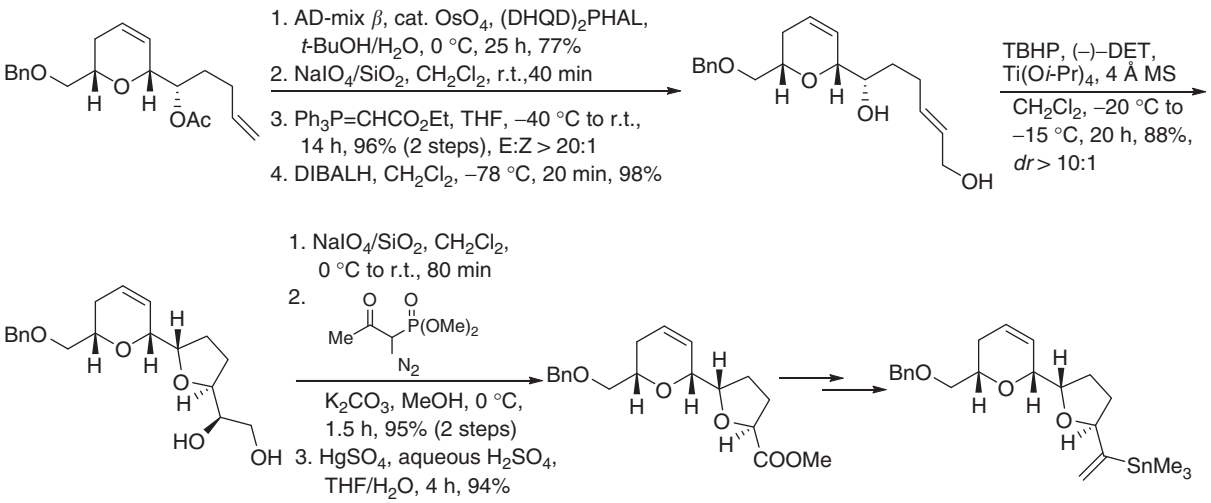
The silica-gel supported glycol cleavage has drawn a lot of attention from synthetic chemists in recent years because of its clean, efficient, specific, and quantitative properties. It has been fully utilized in natural products syntheses, drugs syntheses, and methods research.

The synthesis of leiodermatolide began with the synthesis of its macrocyclic core followed by cross-coupling with the δ-lactone. Paterson used the silica-gel supported glycol cleavage to generate the *bis*-vinyl halide (**9**), which was used in Stille coupling with stannane (**10**) to obtain diene (**11**) as shown in Scheme 11.[39]

In the total synthesis of goniodomin A, Saito et al. utilized the silica-gel supported oxidative cleavage of 1,2-diols followed by Wittig reaction and Horner-reaction to synthesize the key stannane for Liebeskind–Srogl cross-coupling. The C15–C36 segment of goniodomin A was successfully synthesized (Scheme 12).[40]



Scheme 11



Scheme 12

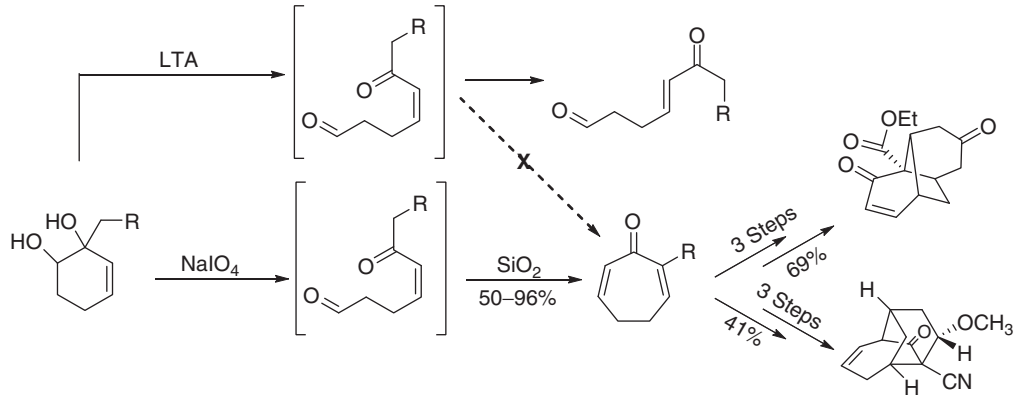
In the synthetic studies of some dihydrotropones, a ring-expansion protocol was employed by Do (Scheme 13). The seven-membered conjugated carbonyl compounds would be synthesized by the ring-expansion strategy from the same 3-cyclohexene-1,2-diols utilizing the intramolecular aldol condensation of the immediate oxidative ring-opening products with *Z*-configuration. It is therefore crucial to control the *Z*/*E*-configuration in the oxidative ring opening reaction of 3-cyclohexene-1,2-diol. However, LTA was not able to give the desired *Z* product because acetic acid was, formed, which isomerized the *Z*-isomer to its *E*-isomer. Periodate, which is acetic acid free, produced the *Z*-isomer predominantly. Silica-gel supported sodium periodate could even be used to carry out one-pot cyclization from the various 3-cyclohexene-1,2-diols to form the dihydrotropones.[41]

In the total synthesis of guanacastepenes N and O Gampe carried out the oxidative cleavage of an olefin with osmium tetraoxide followed by silica-gel supported glycol cleavage reaction to provide an aldehyde, which by a following intramolecular aldol reaction furnishes the key *β*-hydroxyketone (**12**) for further transformations (Scheme 14).[42]

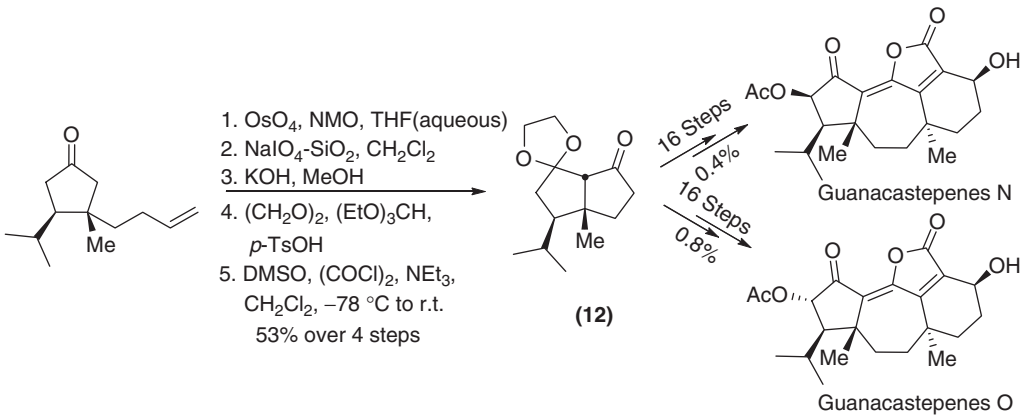
In the synthetic studies of highly substituted cyclopentanes by the N-heterocyclic carbene (NHC) catalyzed addition, the mild oxidative cleavage of the *α*-glycol maintained the stereochemistry of the cyclopentanes and tolerated multiple functional groups (Scheme 15).[43]

In the improved synthesis of the key intermediate of (+)-biotin from D-mannose, Chen used the silica-gel supported oxidative cleavage to obtain the intermediate aldehyde (**13**) quantitatively, which was followed by Horner–Emmons olefination. Further modification led to the formation of the key intermediate (Scheme 16).[44]

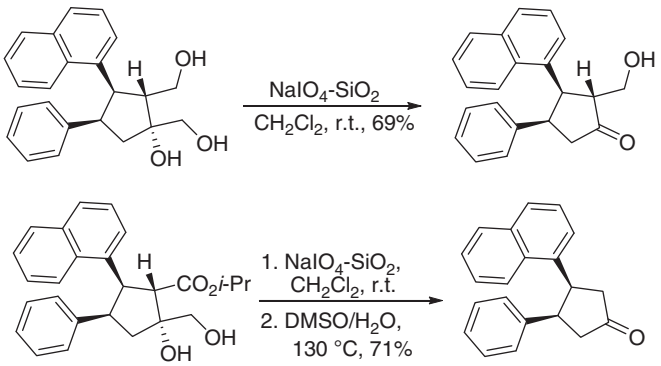
In the total synthesis of (+)-rishirilide, the clean and reliable character of silica-gel supported glycol cleavage gave the desired intermediate (**14**). Excess periodate would lead to lactone (**15**) and reverted back to the starting material (Scheme 17).[45]



Scheme 13



Scheme 14

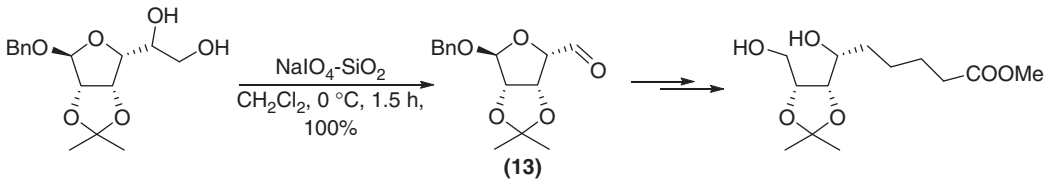


Scheme 15

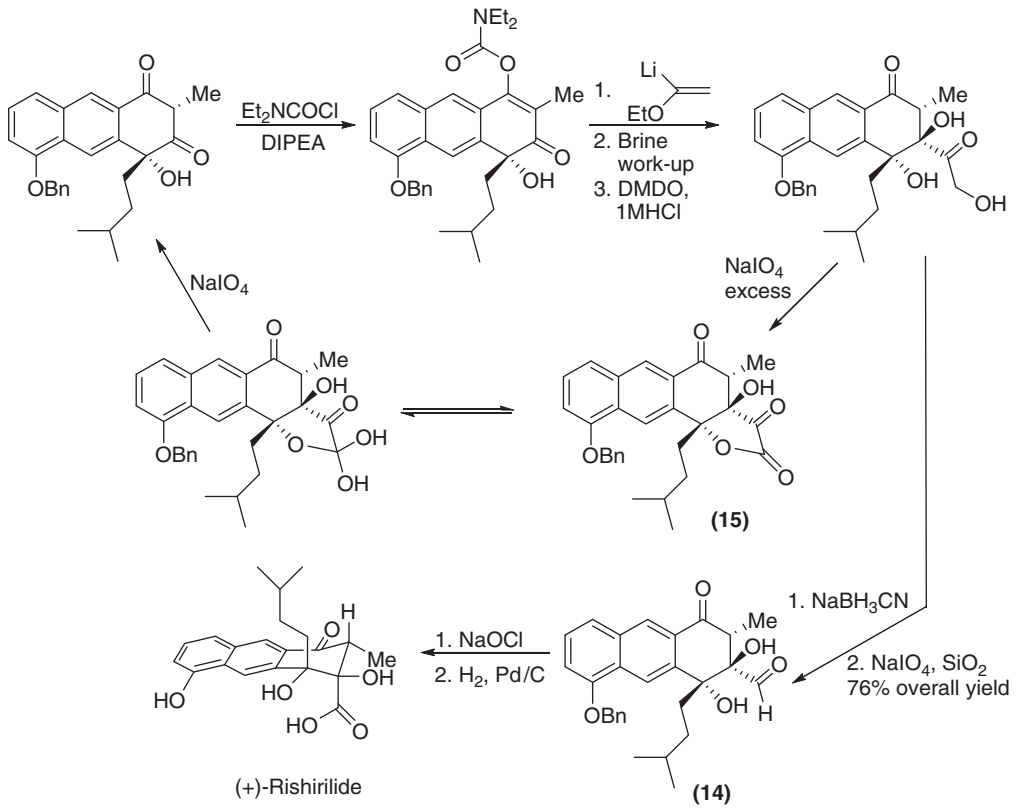
The effective silica-gel supported periodate oxidative cleavage and further reduction successfully provided the key intermediate diol quantitatively in the synthesis of the mixed acetal segment of *S*-glyceroplasmalopsychosine. The diol could be used directly without purification (Scheme 18).[46] More examples of silica-gel supported periodate oxidative cleavage in natural products syntheses are illustrated from Schemes 19–23.[47–51]

In the development of the synthesis of chiral aminoalcohol from carbohydrates and amino acids, Dunlap et al. utilized the silica-gel supported glycol cleavage on various kinds of carbohydrates so as to obtain the key aldehydic intermediate, which was further converted into the corresponding amide in one step. The amide was fully converted into the desired chiral amino alcohol (Scheme 24).[52]

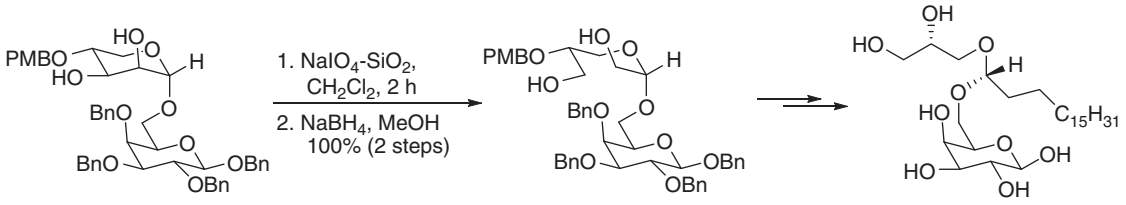
Shibuya et al. further extended the use of silica-gel supported periodate with TEMPO for rearrangement of tertiary allylic alcohols to β-substituted and α,β-unsaturated ketones (Scheme 25).[53] The reaction is mild, efficient and gives high yields. The reaction proceeds well with all acyclic, medium-size, and macrocyclic tertiary alcohols.



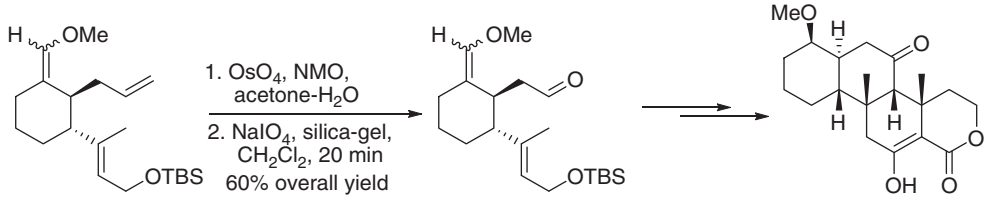
Scheme 16



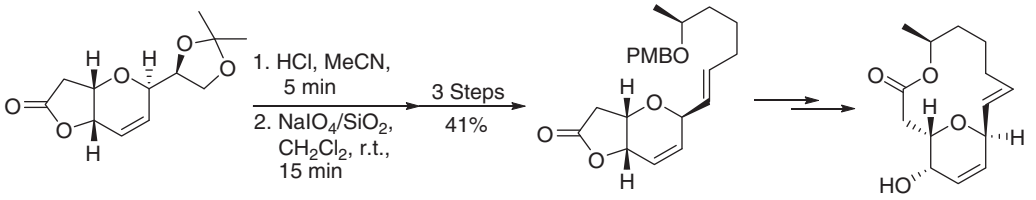
Scheme 17



Scheme 18

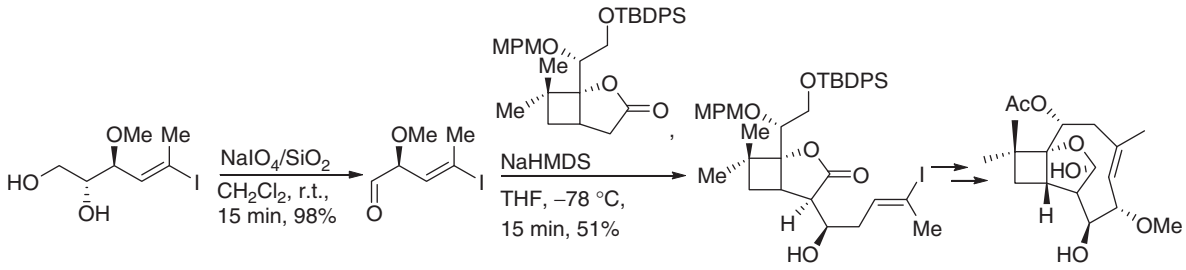


Scheme 19



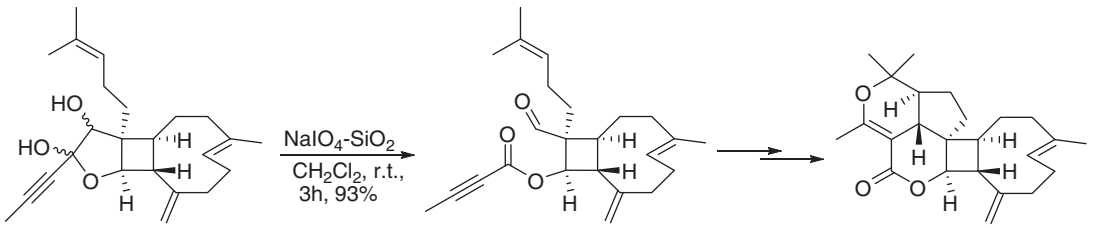
(+)-Aspergillide

Scheme 20



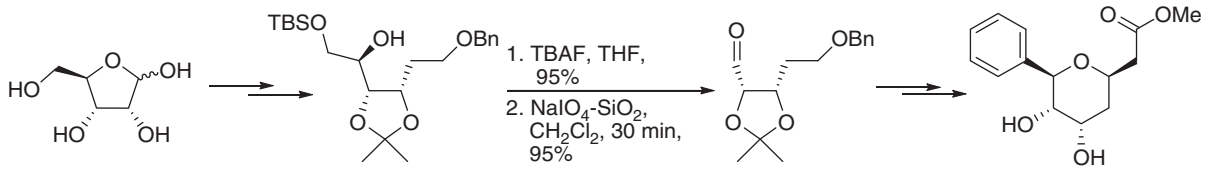
(–)-Pestalotiopsin A

Scheme 21



Antheliolide A

Scheme 22

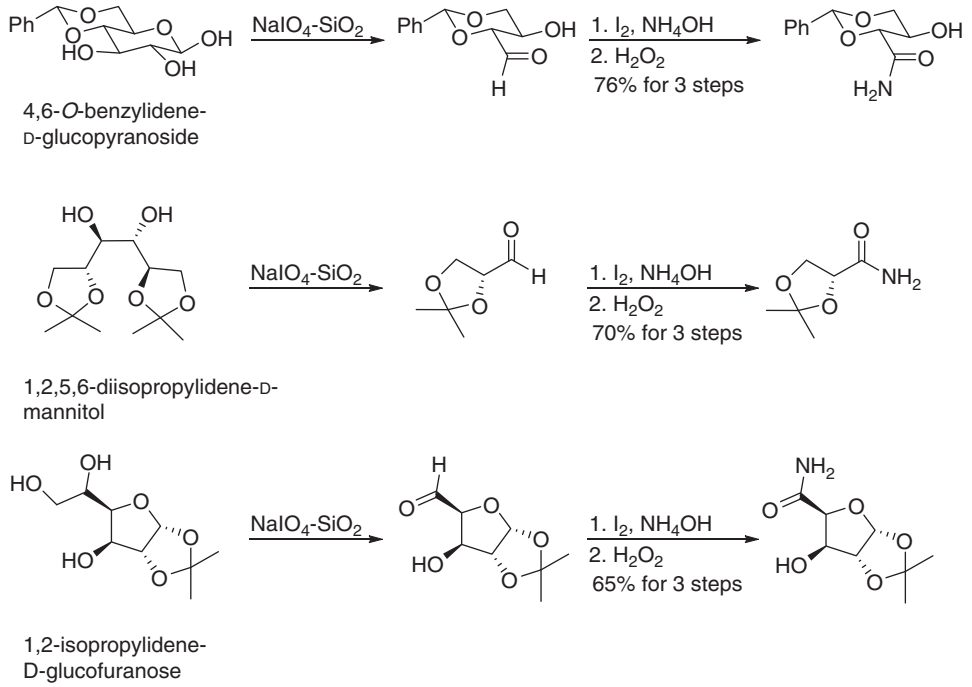


Goniothalesdiol A

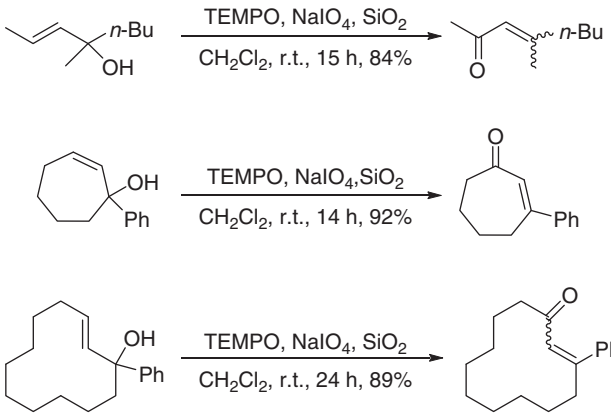
Scheme 23

In the synthesis of novel [3.3.1]bicyclic sulfonamide-pyrazoles, which serve as potent γ-secretase inhibitors, oxidative cleavage of intermediate (**16**) gives the key intermediate dialdehyde, which was then subjected to Mannich reaction to obtain the core of [3.3.1]bicyclic sulfonamide-pyrazole (Scheme 26). Further modification gave a series of novel drugs. The series is not only potent, metabolically stable, and exhibits >190-fold selectivity for inhibition of APP versus Notch processing by γ-secretase, but is also efficacious in reducing the cortical Abx-40 levels in wild-type FVB mice via a single pharmaceutically relevant oral dose.[54]

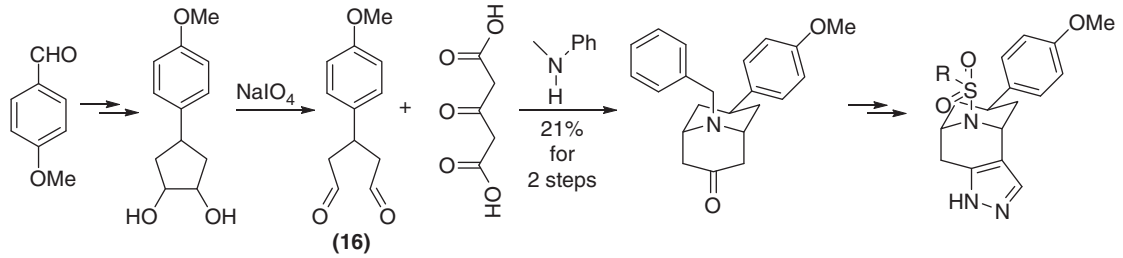
In the synthesis of ezetimibe, a powerful cholesterol inhibitor, silica-gel supported $NaIO_4$ oxidative cleavage allows the cleavage of 1,2-diols (**17**). When the Schering–Plow method is employed, decomposition products always accompany the desired aldehyde during isolation. It is suspected that the formation of the hydrate by the aldehydic product lead to the difficulties of the isolation. Such problems can be avoided by using Shing's method (Scheme 27).[55]



Scheme 24

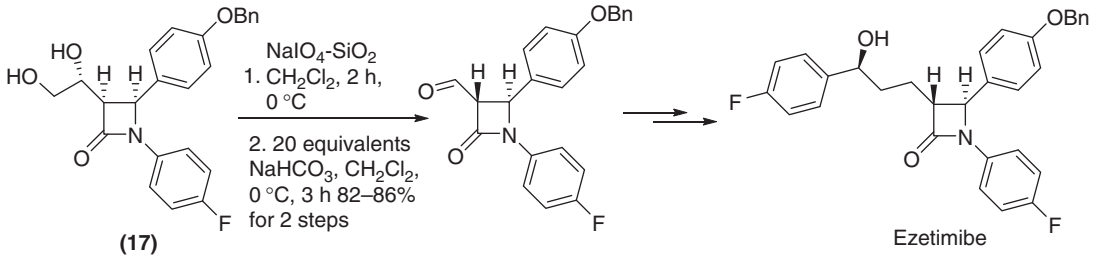


Scheme 25

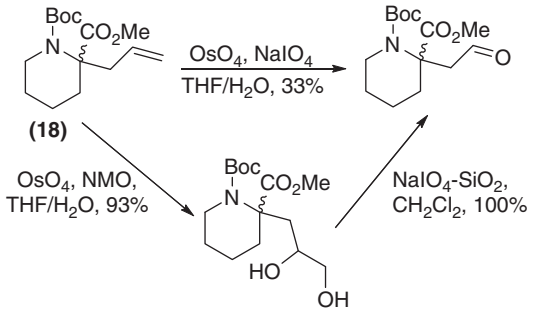


Scheme 26

In the synthesis of pipecolic acid-based spiro bicyclic lactam scaffolds as β-turn mimics, Shing's method does improve the oxidative cleavage of the olefin (**18**). If OsO_4 and $NaIO_4$ were used, the yield of the desired product was only 33%. However, a modified procedure involving first the dihydroxylation followed by silica adsorbed with $NaIO_4$ gave a superior yield (>90% over two steps) of the desired aldehyde without the need for column chromatography (Scheme 28).[56]

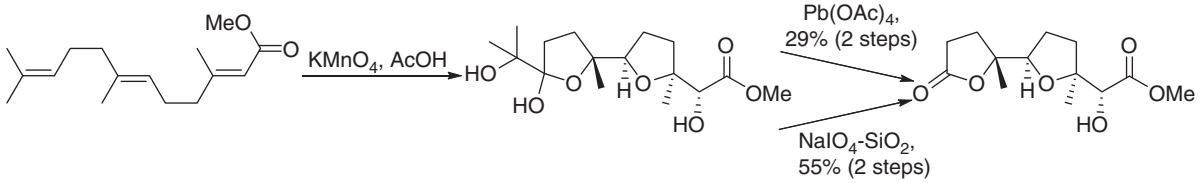


Scheme 27



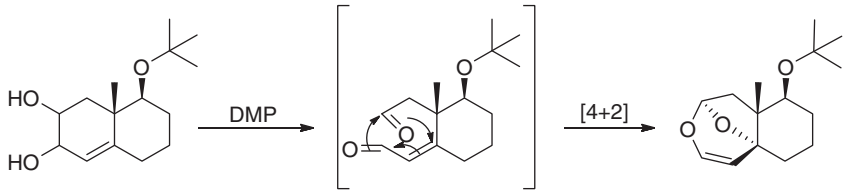
Scheme 28

The milder silica-gel supported periodate gave a better yield of the desired lactone for the oxidative cleavage of the corresponding diols comparing with LTA. The overall yield was 26% higher if Shing's method was chosen for cleavage (Scheme 29).[57]



Scheme 29

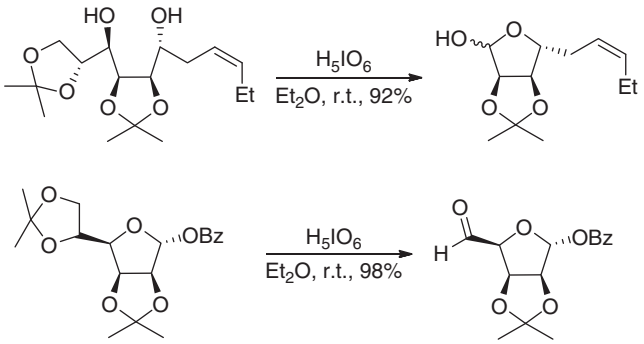
The oxidative cleavage of vicinal diols by DMP is illustrated in Scheme 30. The oxidative cleavage of the glycol carbon–carbon bond leads to the intramolecular cycloaddition to form the tricyclic enol.[58]



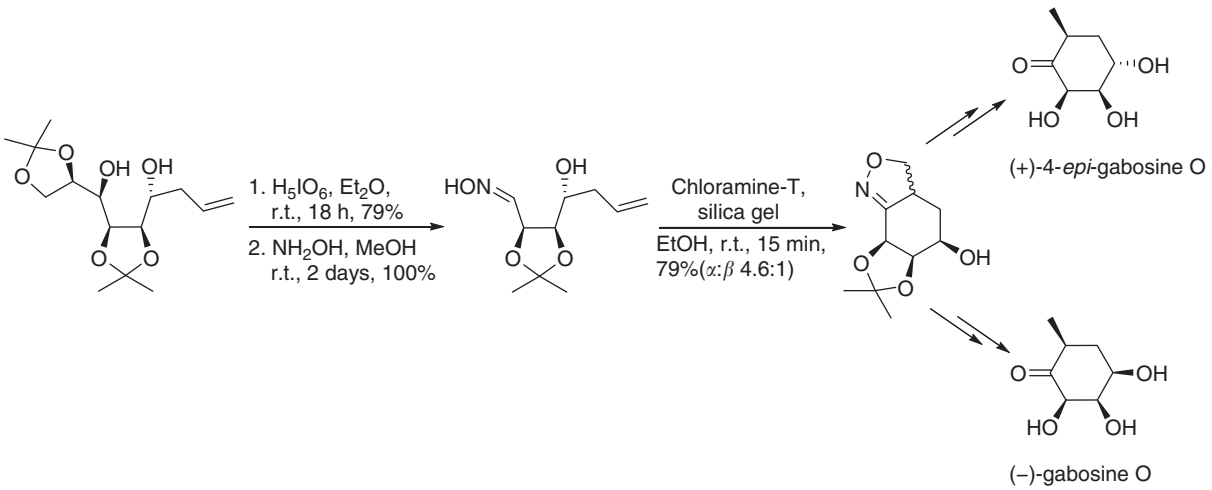
Scheme 30

Periodic acid is now one of the most useful tools to cleave vicinal acetals. Such a transformation is very crucial in synthetic chemistry. The traditional way to cleave an acetal is to hydrolyze the acetal by acid followed by cleavage of the vicinal diols. However, this sequence is not entirely chemoselective and usually suffers from tedious workup, providing the product in moderate yield. Especially, the application of this strategy has limited value in some cases, such as in the presence of acid-sensitive groups (e.g., TBDMS) or of a protecting group (Ac) susceptible of migrations. Ethereal periodic acid can cleave a *vic*-glycol or epoxide smoothly, especially in the case of water-insoluble compounds or where a cleavage product is sensitive to aqueous acid. A hydrated form of periodic acid can affect the selective hydrolytic cleavage of terminal isopropylidene acetals in one pot as shown in Scheme 31.[59]

In the total synthesis of (−)-gabosine O and (+)-4-epi-gabosine O, Shing used periodic acid to cleave the vicinal acetal, which was then converted into an oxime bearing free hydroxyl groups and perform an INOC to generate the key hydroxylated cycloadduct. The cycloadduct was further functionalized to synthesize the (−)-gabosine O and (+)-4-epi-gabosine O (Scheme 32).[60]

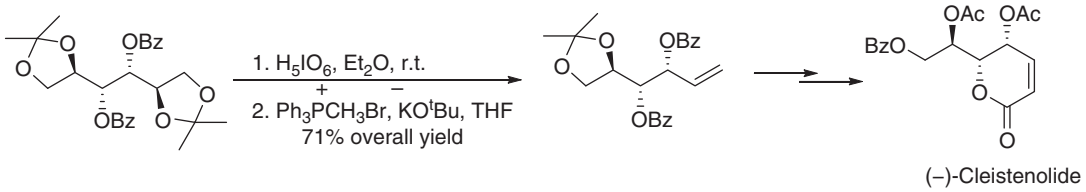


Scheme 31



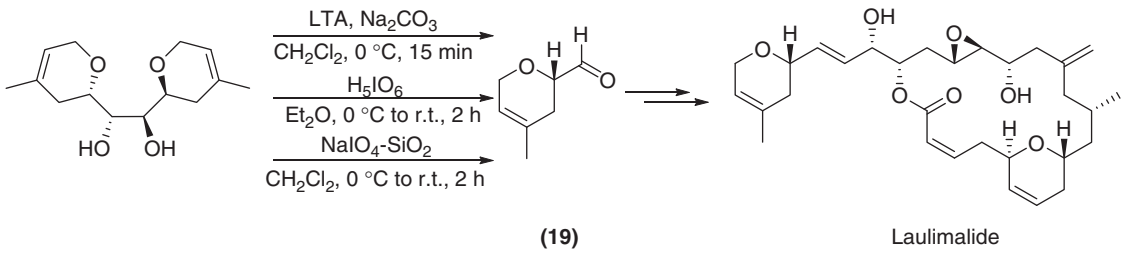
Scheme 32

In the total synthesis of (–)-cleistenolide, periodic acid was employed to cleave one terminal vicinial acetal selectively, followed by Wittig olefination to afford a key alkene intermediate (**Scheme 33**).[61]



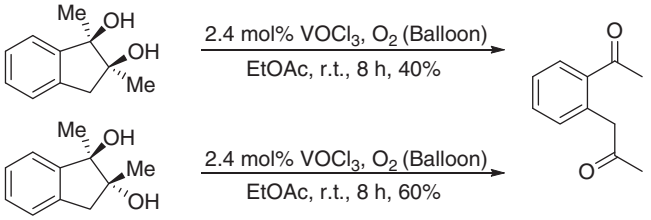
Scheme 33

In the total synthesis of laulimalide and its nonnatural analogs, all LTA, silica-gel supported glycol cleavage and periodic acid were employed to synthesize the key intermediate aldehyde (**19**), which was highly volatile. The low boiling solvent employed in all methods facilitated the isolation of the aldehyde (**Scheme 34**).[62]



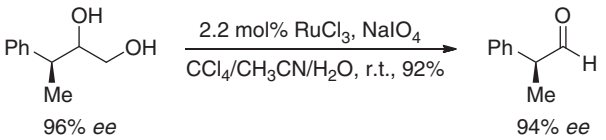
Scheme 34

Compared to nonmetal reagents, metallic reagents are less frequently applied in synthetic chemistry, whereas vanadium(V) and ruthenium species are relatively more popular. Kirihara et al. used $VOCl_3$ with molecular oxygen to cleave the cyclic ditertiary glycols and interestingly, both the *cis*- and *trans*-glycols reacted similarly (Scheme 35).[24] In the study of oxidative cleavage of pinacol by vanadium(V) dipicolinate complex, Hanson discovered that the vanadium(V) was reduced to vanadium(III) after the reaction. The complex is easily oxidized back to vanadium(V) by air.[63]

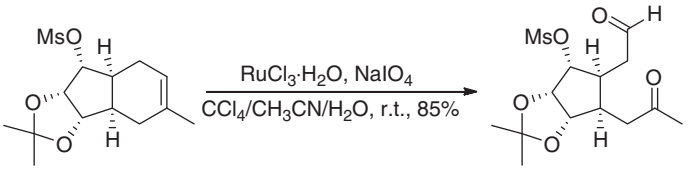


Scheme 35

Sharpless used catalytic amounts of $RuCl_3$ in the presence of periodate as the cooxidant to successfully cleave vicinal diols to their corresponding aldehydes. It is interesting to note that the stereochemistry of the chiral center can be retained (Scheme 36).[64] Such a method is also employed by Ivanova to synthesize cyclopentane derivatives, which can be further functionalized for natural products syntheses (Scheme 37).[65]

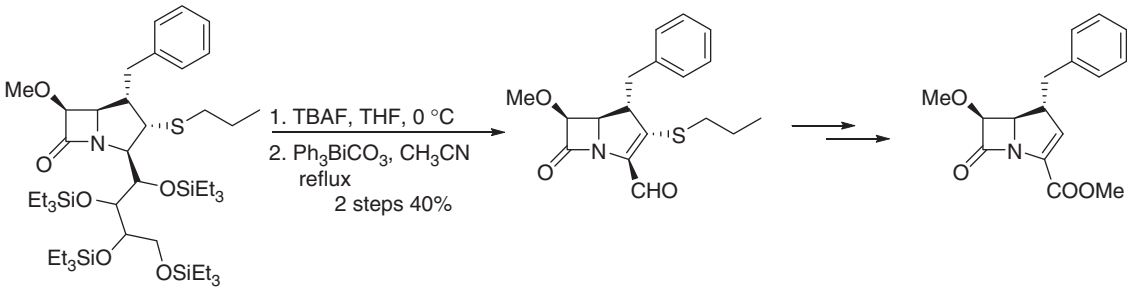


Scheme 36



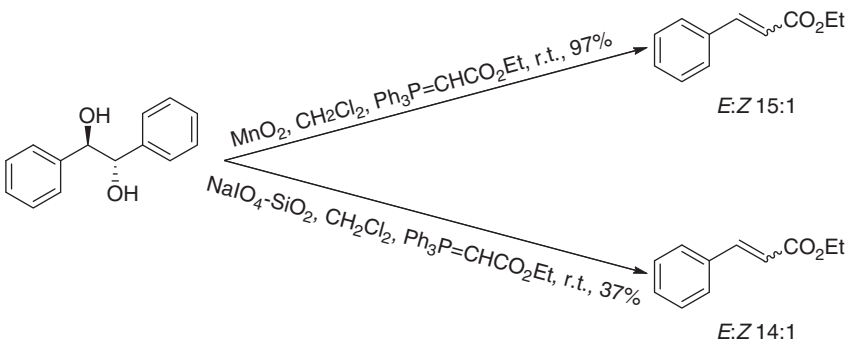
Scheme 37

Anaya et al. used the triphenylbismuthcarbonate to cleave a glycol to yield the corresponding aldehyde. The aldehyde was further transformed to the methyl ester carbapenam, which can act as an antibiotic precursor (Scheme 38).[66]



Scheme 38

Outram has compared the reactivity of MnO_2 and silica-gel supported $NaIO_4$ in the *in situ* oxidative diol cleavage-Wittig reaction. In most cases, the silica-gel supported periodate gave a better yield than manganese dioxide except for the hydroxybenzoin synthesis (Scheme 39).[67]



Scheme 39

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7.27 The Hunsdiecker and Related Reactions

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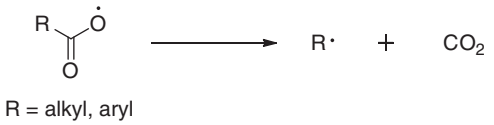
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Glossary

Alkynylation Formation of a carbon–alkyne bond.
Amination Formation of a carbon–nitrogen bond.
Chalcogenation Formation of a carbon–chalcogen bond.
Decarboxylation Loss of carbon dioxide from a carboxyl radical.
Phosphorylation Formation of a carbon–phosphorus bond.

7.27.1 Introduction

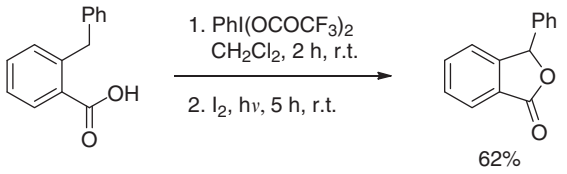
Formally, the Hunsdiecker reaction is that of dry silver carboxylate salts with halogens leading to the formation of the noralkyl halides with loss of a molecule of carbon dioxide. The reaction involves the *in-situ* formation of acyl hypohalites, which then decompose by a radical chain process involving as key step to the decarboxylation of intermediate carboxyl radicals (equation 1). This chapter, like its precursor in COS-I,[1] uses a broader definition of the Hunsdiecker reaction and focuses on those reactions that involve decarboxylation of chemically generated carboxyl radicals, as opposed to electrochemical ones and the Kolbe electrolytic coupling, whatever the trapping reagent employed. As such, in addition to decarboxylative formation of carbon–heteroatom bonds, the chapter includes reductive decarboxylation to give noralkanes and also decarboxylation with subsequent carbon –carbon bond formation, although they are not formally oxidations.



R = alkyl, aryl (1)

The loss of carbon dioxide from aliphatic carboxyl radicals is an extremely rapid process with rate constants in the order of 10^9–10^{10} s^{-1} (k $MeCO_2\bullet$ to $Me\bullet = 1.9 \times 10^9$ s^{-1} at room temp in MeOH),[2,3] such that once generated decarboxylation can be considered to be instantaneous and trapping of the carboxyl radicals by all but the most potent traps, such as benzeneselenol,[4] is not a consideration. With aryl and vinyl carboxyl radicals, however, decarboxylation is considerably slower (k $PhCO_2\bullet$ to $Ph\bullet = 2 \times 10^6$ s^{-1} at 24 °C in CCl_4),[5] such that alternative inter- and intramolecular processes can intervene. One such example of a process arising from the slow decarboxylation of an arylcarboxyl radical is the use of a carboxyl radical in an intramolecular hydrogen atom abstraction process described by Togo and coworkers (equation 2).[6]

 doi:10.1016/B978-0-08-097742-3.00732-1

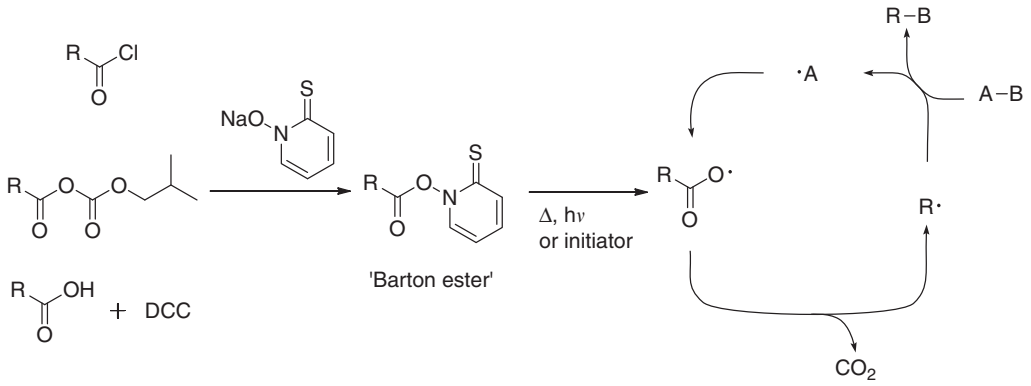


(2)

7.27.2 Generation of Carboxyl Radicals

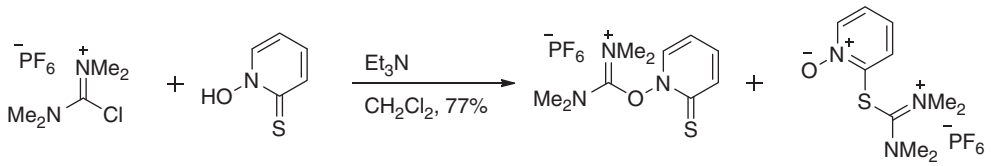
As discussed in COS-I,[1] the need for dry, stoichiometric silver carboxylates in the original version of the Hunsdiecker reaction spurred the development of alternative silver-free methods for decarboxylation and resulted in variations based on mercury,[7] thallium, and lead salts.[8–10]

These methods, which suffer from the use of heavy metals and the oxidizing conditions that limit the range of applicable substrates, are covered in COS-I.[1] Methods based on the thermolysis of peroxides, both diacyl and alkyl acyl, have also found useful but are not in widespread application owing to the need to prepare potentially unstable peroxides. The use of hypervalent iodine reagents in conjunction with iodine has seen increasing use in recent years, but without a doubt the most versatile method has been Barton's decarboxylation process that employs mixed anhydrides of carboxylic acids and thiohydroxamic acids, known as the *O*-acyl thiohydroxamates or Barton esters.[11,12] In this method which has been reviewed numerous times, recently in 2009,[13] following initiation a thiophilic radical A• from the trap A–B adds to the thiocarbonyl group of the Barton ester resulting in the formation of a pyridylthio byproduct and the carboxyl radical. After decarboxylation, the alkyl radical combines with the trap A–B to give the product R–B and regenerate the chain transfer radical A• (**Scheme 1**). The wide variety of compatible traps A–B and the numerous possible permutations on the general theme, coupled with the mild conditions (white light photolysis or heating typically below 100 °C) combine to render the Barton decarboxylation a very versatile and widely employed process.



Scheme 1

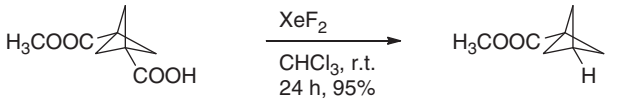
An essential first step in the employment of the Barton decarboxylation is the preparation of the *O*-acyl thiohydroxamate. As mixed anhydrides, these species are relatively potent acylating agents ($\gamma \sim 1810\ cm^{-1}$) and accordingly are most frequently made and used *in situ*, although they have been isolated and characterized on numerous occasions. The original and most widely employed thiohydroxamic acid is *N*-hydroxypyridine-2-thione, which gives pale yellow Barton esters activated by white light but which must be shielded from the light to avoid premature decomposition. Numerous alternative thiohydroxamic acids have been developed to avoid the sensitivity to ambient light,[14–16] but *N*-hydroxypyridine-2-thione continues to be the most widely employed because of its widespread commercial availability (both the free acid and the Na salt, sodium omadine, are widely available; the zinc salt, zinc pyrithione, is the active constituent of certain antidandruff products). Barton esters were originally and continue to be prepared by the reaction of activated carboxylic acid derivatives (acyl chlorides, mixed anhydrides, etc.) with thiohydroxamic acids, but a number of other methods, based on the activation of the thiohydroxamic acid, have been developed for application with sensitive acids. These include the commercially available phosgene adduct of *N*-hydroxypyridine-2-thione,[12] the combination of 2,2′-dipyridyl disulfide bis-*N*-oxide and tributylphoshine,[17] and the highly reactive HOTT reagent (equation 3), all of which react directly with the carboxylic acid substrate without the need for prior activation.[18] A polymer-supported thiohydroxamic acid also has been developed to facilitate purification.[19]



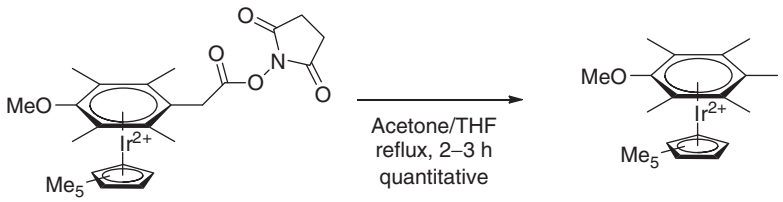
(3)

7.27.3 Reductive Decarboxylation

Reductive decarboxylation requires the generation of the carboxyl radical in the presence of a suitable hydrogen donor. The pyrolysis of *tert*-butyl esters in the presence of hydrogen donor solvents is a classical solution to this problem.[20,21] Heating of carboxylic acids with lead tetraacetate in chloroform is another solution to this problem.[22] Silver-catalyzed decarboxylation of aliphatic carboxylic acids in the presence of persulfate in $CHCl_3$ also provides the noralkane.[23] The photolysis of *O*-acyl benzophenone oximes in ^{i}PrOH leads to reductive decarboxylation in the presence of *tert*-butyl thiol.[24] Other processes of limited applicability reported in recent years include reaction of the carboxylic acid with XeF_2 in $CHCl_3$ (equation 4),[25] and the thermolysis of an *N*-hydroxy succinimide ester in a hydrogen-donor solvent mixture (equation 5).[26]

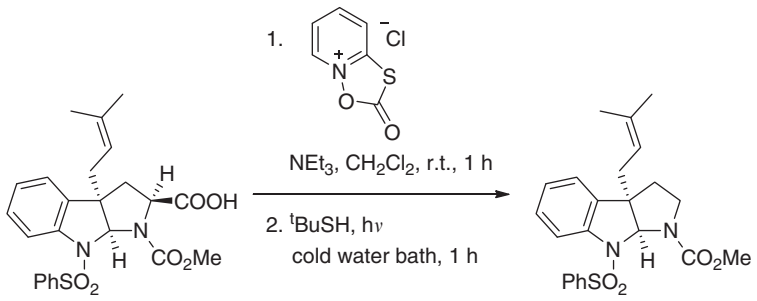


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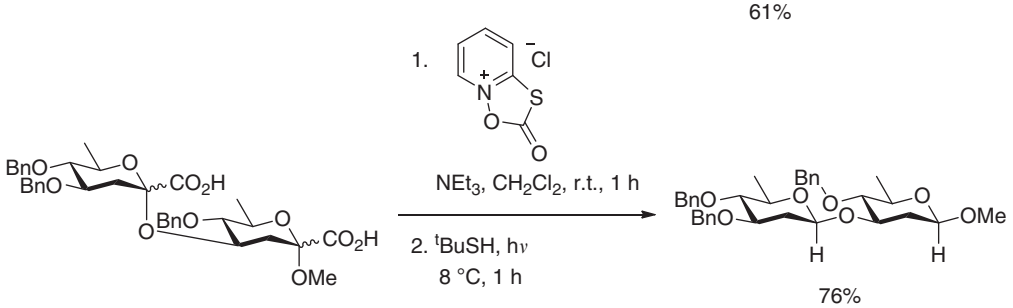


(5)

The application of the Barton decarboxylation in the presence of a sterically hindered tertiary thiol (*tert*-dodecanethiol is a cheap and relatively odorless alternative[27] to the original *tert*-butylthiol) is, however, the most widely applied method. Examples illustrating substrate scope include the removal of the original stereodirecting carboxyl group in a later stage of the asymmetric synthesis of (+)-debromoflusramine B from tryptophan (equation 6),[28] and application to the control of anomeric stereochemistry in a synthesis of the olivomycin A CD-disaccharide (equation 7).[29]

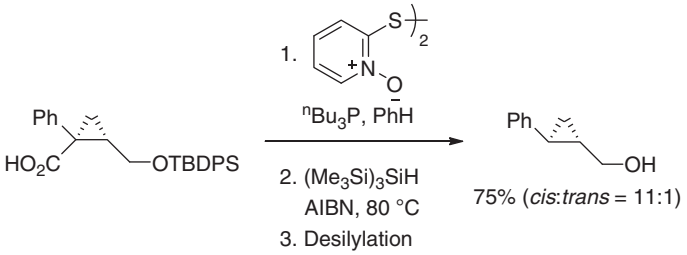


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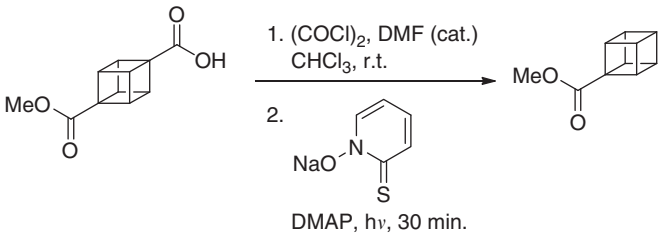


(7)

Tris(trimethylsilyl)silane (TTMS) has also proven itself to be a worthy hydrogen atom donor in the Barton decarboxylation as illustrated by the example of equation 8,[30] as has chloroform (equation 9).[31]



(8)

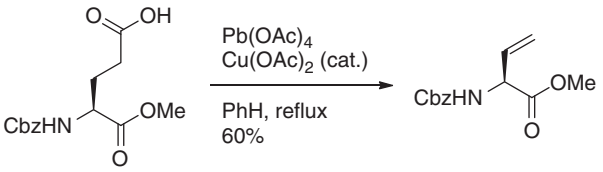


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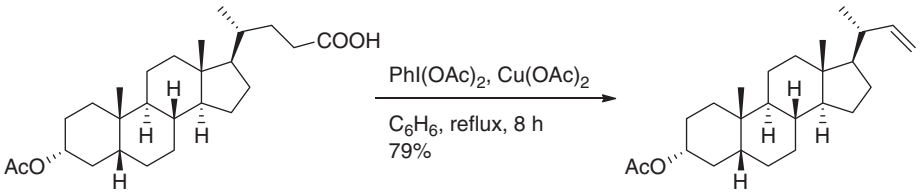
7.27.4 Oxidative Decarboxylation

7.27.4.1 Carboxylic Acids to Olefins

Terminal olefins can be introduced by the generation of carboxyl radicals in the presence of copper(II) acetate which serves to oxidize the alkyl radical formed on loss of carbon dioxide. Lead(IV) salts of primary carboxylic acids in benzene are heated with catalytic $Cu(OAc)_2$ to afford the noralkenes, of which an important example is Hanessian's synthesis of optically pure of L-vinylglycine from L-aspartic acid (equation 10).[32] Carboxyl radicals generated by other systems, such as $Na_2S_2O_8$ with catalytic $AgNO_3$,[23] or $PhI(OAc)_2$,[33] can also be transformed into the nor-olefins in the presence of copper(II) (equation 11).

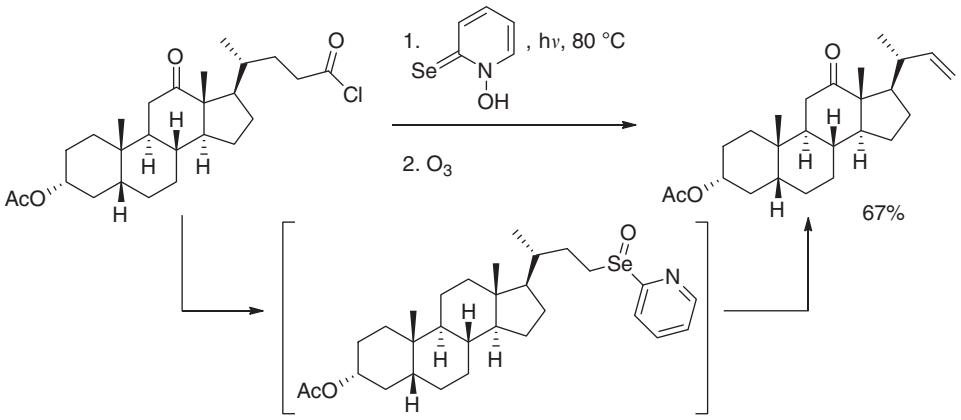


(10)



(11)

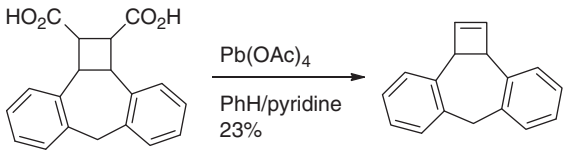
An alternative approach to the problem employs a modification of the Barton decarboxylation in which an *O*-acyl selenohydroxamate is photolysized to give a 2-pyridylselenide, which undergoes *syn*-elimination to the alkene on oxidation to the selenoxide (equation 12).[34]



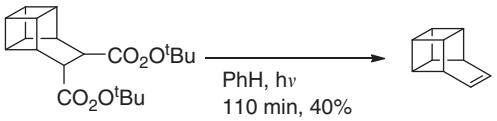
(12)

7.27.4.2 1,4-Dicarboxylic Acids to Olefins

Treatment of 1,4-dicarboxylic acids with lead tetraacetate gives olefins via double decarboxylation (equation 13).[35,36] Similarly, peresters of 1,4-diacids give the bisnor-alkenes on photolysis (equation 14).



(13)



(14)

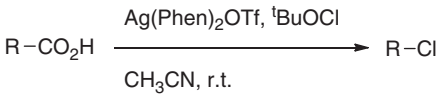
7.27.5 Decarboxylative Halogenation

7.27.5.1 Decarboxylative Chlorination, Bromination, and Iodination

The classical Hunsdiecker decarboxylative halogenation of silver carboxylates and molecular halogen was fraught with difficulties in preparation of dry silver carboxylates and its stoichiometric nature with respect to silver. For this reason, variations employing mercury and thallium salts enjoyed popularity for a number of years but must be considered obsolete in the modern era.[7,8]

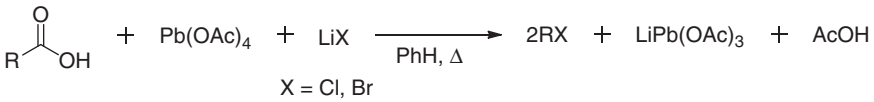
Recent work from the Li group, however, promises a renaissance in silver ion-mediated Hunsdeicker reactions. Thus, it has been shown that the decarboxylative chlorination of alkanoic acids can be achieved with *tert*-butyl hypochlorite as halogen source in the presence of only 5 mol% of bis(1,10-phenanthroline)silver triflate. A number of primary, secondary, and tertiary acids were converted into the noralkyl chlorides in high yield in this manner (**Table 1**).[37]

Table 1 Decarboxylative halogenation mediated by a catalytic silver salt



R		*Time (h)*	*Yield (%)*
$^{n}H_{21}C_{10}$		1	89
Ph, O		2	92
Ph		20	84
R′	R′ = Ph	5	93
	R′ = NO_2	26	85
N, O, O		18	90
Br, 8		2	80

Decarboxylative halogenation with lead tetraacetate in the presence of lithium halides is known as Kochi reaction (equation 15). Both lithium chloride and bromide can be employed leading to the chlorides and bromides, respectively.[9,10] The use of molecular iodine as halogen donor in tetrachloromethane provides the corresponding iodides.[38] NCS can also be used as a chlorine source.[39]



(15)

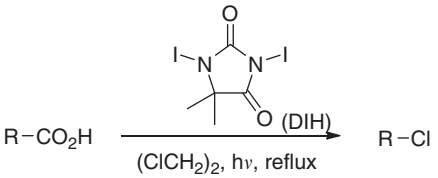
An alternative method for the preparation of acyl hypoiodites involves the treatment of the free acids with *tert*-butyl hypoiodite (Scheme 2).[38] Subsequent photolysis affords the corresponding alkyl iodides. This method, which is applicable to the primary, secondary, and tertiary acids, but which is not compatible with free alcohols, provides a convenient metal-free variant on the Hunsdiecker reaction.



Scheme 2

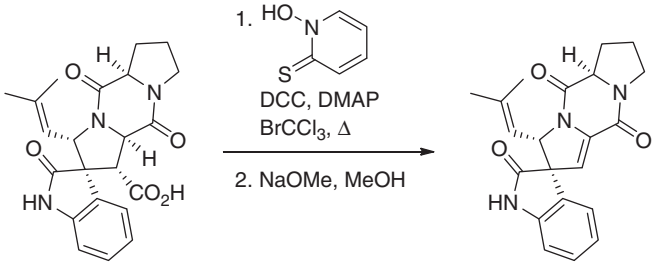
A recent variation on the metal-free Hunsdiecker reaction relies on the weakness of the N-I bond and makes use of either *N*-iodosuccinimide or 1,3-diiodo-5,5-dimethylhydantoin (DIH) as a dual initiator and iodine donor. In addition to a range of primary, secondary, and tertiary alkanoic acids, the authors also demonstrated the applicability of the reaction to simple aryl carboxylic acids (Table 2).[40]

Table 2 Decarboxylative halogenation with 1,3-Diiodo-5,5-dimethylhydantoin

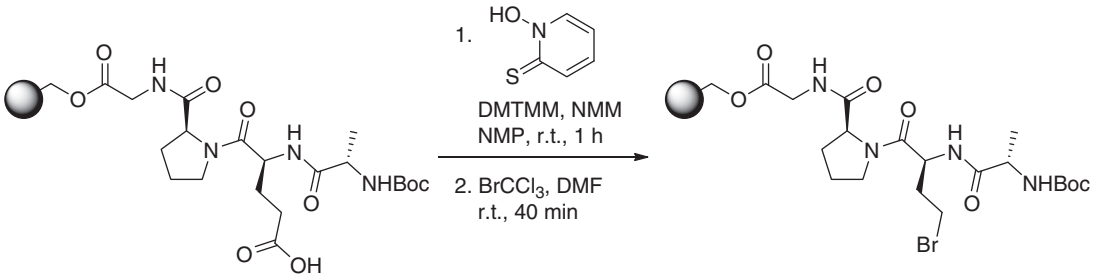


R	*RCO₂H:DIH*	*Time (h)*	*Yield (%)*
Ph	1:1	6	85
O_2N	1:0.5	8	84
BocN	1:1.2	2	80
BocN	1:1.2	3	75
MeO, O	1:2.5	2	93
Ph	1:1.5	24	61
CO_2Me	1:1.5	24	80

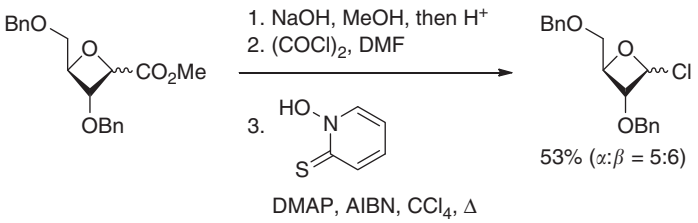
Heating or photolytic decomposition of Barton esters in either tetrachloromethane or bromotrichloromethane leads to the formation of the noralkyl chloride and bromides, respectively.[33,41,42] Many examples of the Barton Hunsdiecker have been reported testifying to its broad functional group tolerance and nonoxidative conditions. Examples include the final stages of William's synthesis of spirotryptystatin (equation 16), for which it was noted that neither the lead tetraacetate nor the iodobenzene diacetate methods were successful,[43] the decarboxyative bromination of a polymer-supported glutamic acid derivative (equation 17),[44] and the formation of oxetanyl chlorides in the course of Fleet's synthesis of noroxetanocin (equation 18).[45]



(16)

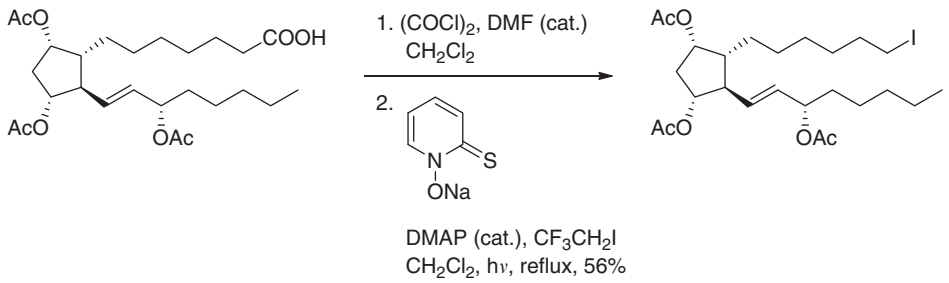


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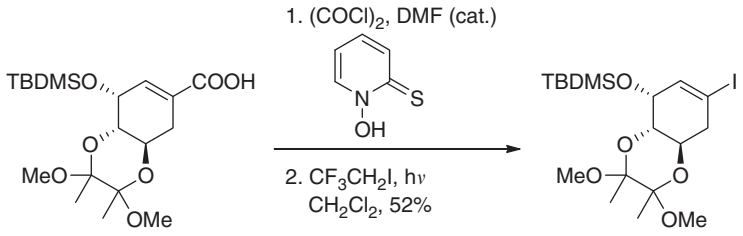


(18)

When the formation of alkyl iodides is required, iodoform originally served as iodine source, but this required the addition of a sacrificial alkene such as cyclohexene.[41] Later, Eaton et al. advocated the use of trifluoroethyl iodide as an iodine source.[46] This procedure has been applied to iododecarboxylation of prostaglandins $F_{1\alpha}$ and $F_{2\alpha}$ (equation 19),[47] and in the synthesis of phospha-shikimic acids (equation 20),[48] with the latter providing a rare example[49,50] of the application of the Barton Hunsdiecker to an alkenoic acid or aryl acid.



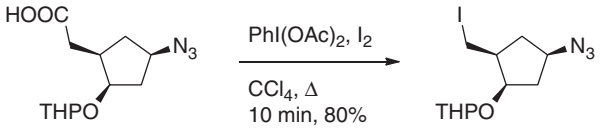
(19)



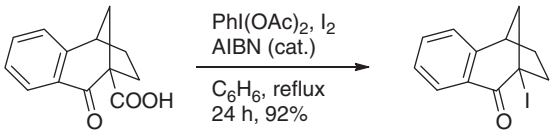
(20)

Hypervalent iodine reagents and particularly iodobenzene diacetate have been widely employed in decarboxylative halogenation processes. Thus, Suárez et al. demonstrated that the treatment of alkanoic acids with $PhI(OAc)_2$ and I_2 in

terachloromethane at reflux gives the corresponding primary, secondary, and tertiary iodides in good yield (equation 21).[51] This method is mild and tolerant for many functional groups with the exceptions of alcohols. The use of AIBN as initiator for this sequence has been described by Moriarty (equation 22).[52]

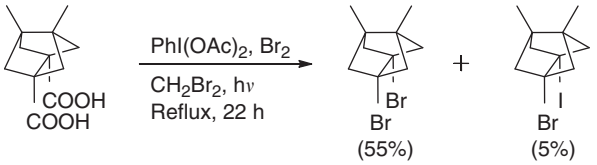


(21)



(22)

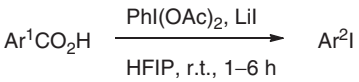
The combination of $PhI(OAc)_2$ and molecular bromine has been employed in decarboxylative bromination under irradiation by tungsten lamp (equation 23).[53] The method is efficient for 1,2-dicarboxylic acids, which are not good substrates for the Barton protocol owing to their ready dehydration to the corresponding anhydrides.

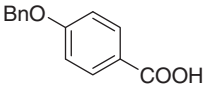
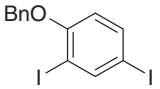
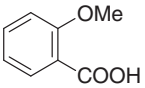
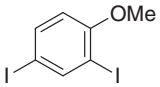
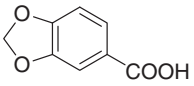
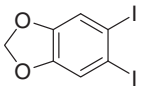
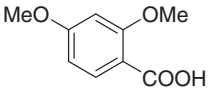
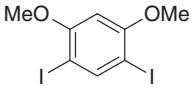
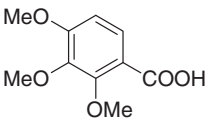
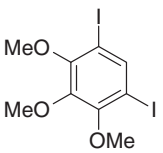


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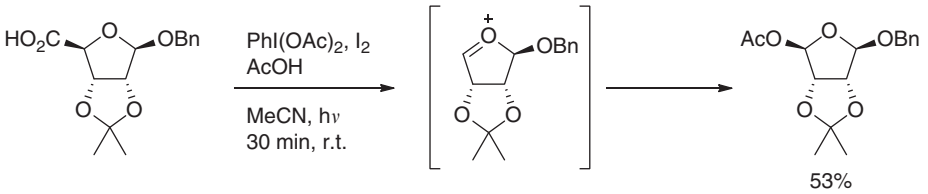
Although the use of iodobenzene diacetate and iodine does not bring about Hunsdiecker reaction of aryl acids, it has been reported that the combination of iodobenzene diacetate and lithium halides is effective for electron-rich aryl acids, provided the reaction is conducted in the presence of fluorinated alcohol such as hexafluoroisopropanol (**Table 3**).[54]

Table 3 Decarboxylative halogenation of arenecarboxylic acids in hexafluoroisopropanol

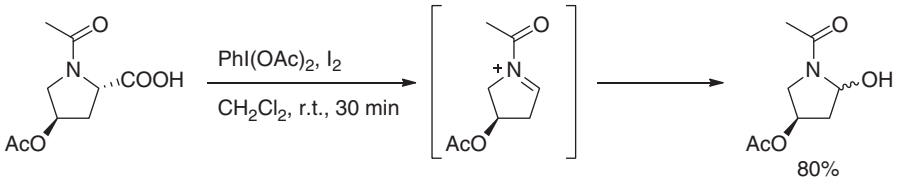


Ar^1COOH	*Ar^2I*	*Yield (%)*
		89
		74
		88
		91
		81

Application of the Suarez hypervalent iodine protocol to α-alkoxy and α-amino acids results overall in the generation of oxocarbenium or iminium ions that may be trapped by suitable nucleophiles (equations 24 and 25).[55–59]



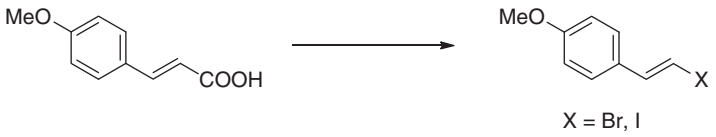
(24)



(25)

The oxidative decarboxylation of alkenoic acids, particularly cinnamic acids, to β-halostyrenes attracts wide attention. Considerable effort has been extended to develop suitable reagents and conditions as summarized in Table 4. A nitrone trapping experiment for the conditions using LiOAc as catalyst supports the dominance of an ionic pathway over the radical route.[60]

Table 4 Conversion of the cinnamic acids to β-halostyrenes



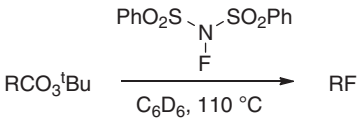
Halogen source	*Initiator*	*Conditions*	*Yield (%)*	*References*
NBS	$PhI(OAc)_2$ or PhIO	CH_3CN/H_2O, 60°C, 30 min	67	61
	LiOAc (cat.)	CH_3CN/H_2O, r.t., 12 min	91	62–66
		CH_3CN/H_2O, r.t., MW	96	63
	$Mn(OAc)_2$ (cat.)	CH_3CN/H_2O, r.t., 16 h	91	67
	$^nBu_4N(CF_3COO)$	$(ClCH_2)_2$, r.t., 2 h	94	68–71
	Et_3N	CH_3CN/H_2O, r.t., 1–2 min	90	72
Et_4NBr	P_2I_4	CS_2, r.t., 9 h	90	73
	$PhI(OAc)_2$	CH_2Cl_2, r.t., 4 h	92[a]	74
	DMP	CH_2Cl_2, r.t., 5 min	92	75
KBr	Selectfluor®	CH_3CN/H_2O, r.t., 5 h	84[a] (*E*:*Z*=95:5)	76
	H_2O_2-Na_2MoO_4	H_2O, 30–80°C, 40 min	85	77
	H_2O_2, Mg-Al-LDH molybdate	H_2O, r.t., 20 min	90	78
LiBr	CAN	CH_3CN/H_2O, r.t., 1 h	81	79
NaX	Oxone®	Na_2CO_3, CH_3CN/H_2O, r.t.	97	80
$Br(coll)_2PF_6$		CH_2Cl_2, r.t., 30 min	88[a] (*E*:*Z*=96:4)	81–83
Br_2		CH_2Cl_2/AcOH, 0°C, 1 h	67[b]	84
HBr	$NaNO_2$	CH_3CN/H_2O, r.t., 2 h	90	85

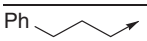
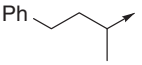
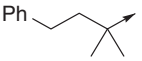
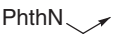
[a]Cinnamic acid was used as a substrate.
[b]*o*-Methoxycinnamic acid was used as a substrate.

7.27.5.2 Decarboxylative Fluorination

For many years decarboxylative fluorination was limited to very simple substrates owing to the nature of the reagents: fluorine gas,[86] or xenon difluoride/HF.[86] Two recent developments in this area, however, have opened the door to more practical versatile approaches to fluorine transfer to alkyl radicals. In the first, Sammis et al. studied the thermolysis of peresters in the presence of an *N*-fluorosulfonimide, NFSI, which was chosen as a fluorine atom source based on its computed N–F homolytic bond dissociation energy.[87] The method was successful with a number of primary, secondary, and tertiary alkanoic acids (Table 5).[87] The second development is that of Li et al., and involves the silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids with Selectfluor® in aqueous solution (Table 6).[88] Attempts at the use of bidentate silver complexes such as $Ag(Phen)_2OTf$ and of anhydrous organic solvents were not productive. Although the detailed mechanism of this reaction is yet to be determined, the oxidation of Ag(I) by Selectfluor® into Ag(III)-F, which then initiates decarboxylation and fluorine atom transfer has been proposed.

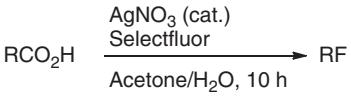
Table 5 Decarboxylative fluorination of peroxyesters

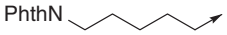
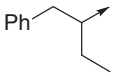
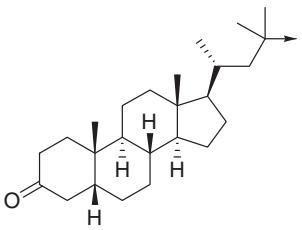
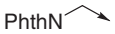
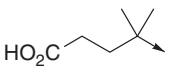


R	*Time*	*Yield (%)*
	12 h	24
	19 min	98
	15 min	98
	6 min	45[a]
	10 min	57

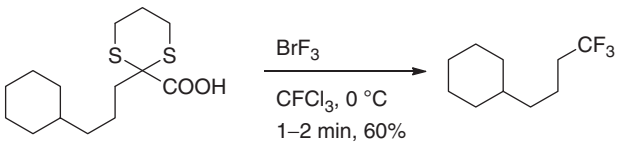
[a]Reaction was carried out in CD_3CN.

Table 6 Catalytic silver-mediated decarboxylative fluorination



R	*Solvent*	*Temperature (°C)*	*Yield (%)*
	H_2O	55	80
	H_2O/acetone	45	77
	H_2O/acetone	Reflux	80
	H_2O	55	97
	H_2O/acetone	r.t.	95

The construction of CF_3 groups by treatment of the 1,3-dithiane derivatives of α-ketoacids with BrF_3 has been reported by Rozen et al. (equation 26). The method is considered to proceed by initial formation of the α,α-difluoroacid followed by the radical decarboxylative fluorination.[89]

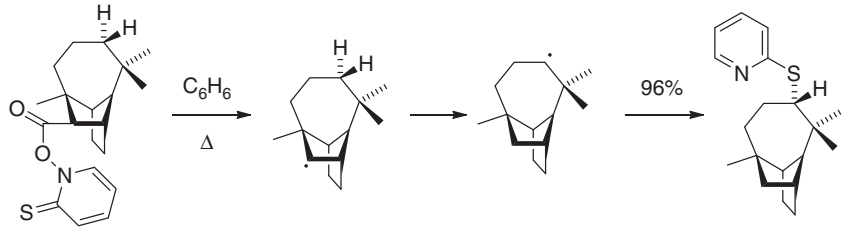


(26)

7.27.6 Decarboxylative Chalcogenation

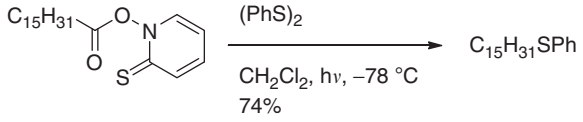
The simplest case of decarboxylative chalcogenation involves the photolysis or thermolysis of an *O*-acyl thiohydroxamate in the absence of other traps and leads, via a radial chain mechanism,[15] to alkyl 2-pyridyl sulfides.[12] Many examples of this process are

known in the literature, but the example illustrated stands out because of the transannular hydrogen atom abstraction that intervenes before C–S bond formation (Scheme 3).[90] The identical process may also be conducted with *O*-acyl selenohydroxamates leading to the formation of alkyl pyridyl selenides (equation 12).[34]

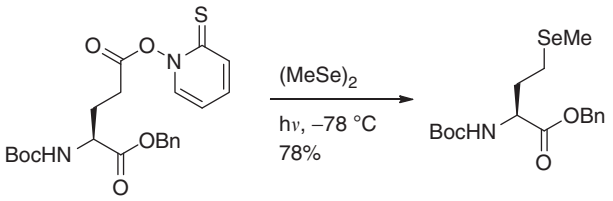


Scheme 3

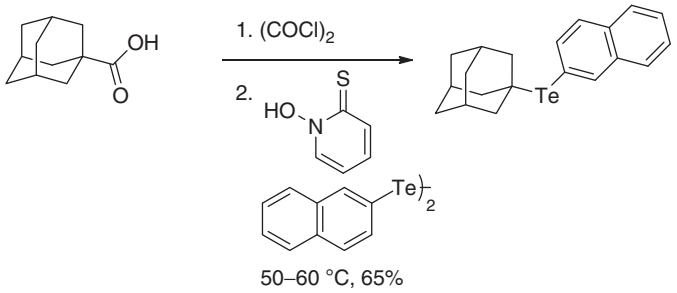
More versatile in terms of the substituent introduced is the photo-induced fragmentation of *O*-acyl thiohydroxamates in the presence of disulfides, diselenides, or ditellurides which affords the corresponding sulfides, selenides, and tellurides, respectively (equations 27–29).[91,92] Decarboxylative selenylation of cinnamic acids may be achieved with iodosobenzene diacetate and diphenyl diselenide, although this is presumably not a radical process (equation 30).[93]



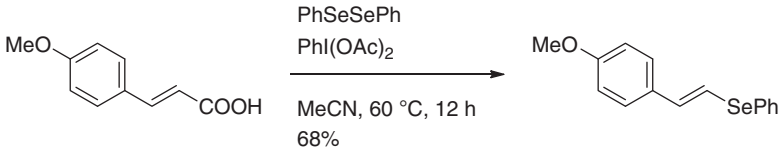
(27)



(28)

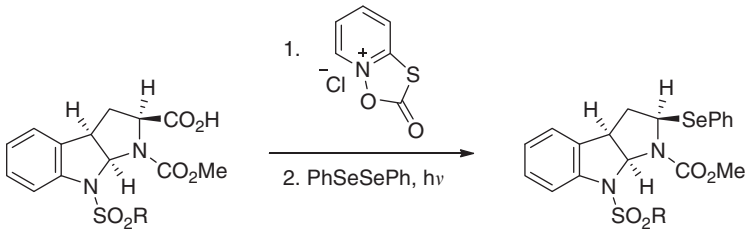


(29)



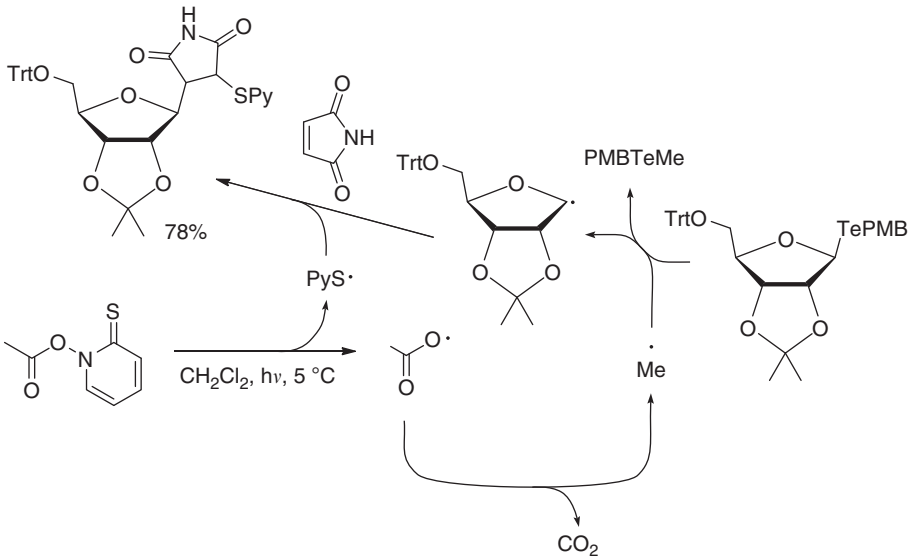
(30)

The reaction provides an easy access to α-phenylthio and α-phenylseleno carbamates from the corresponding protected α-amino acids and so affords a practical entry into functionalized *N*-acyl iminium ions (equation 31).[94,95]



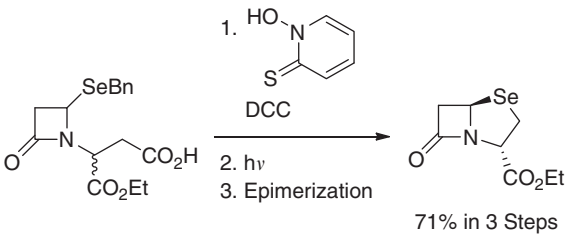
(31)

In addition to dichalcogenides the noralkyl radical can also be trapped by alkyl aryl tellurides with displacement of a new, more stable alkyl radical for subsequent use in a synthetic protocol. An elegant demonstration of this principle is included in Barton's synthesis of showdomycin in which the key glycosyl radical was generated from a glycosyl anisyl telluride by photolysis in the presence of *O*-acetyl thiohydroxamte (**Scheme 4**).[96]



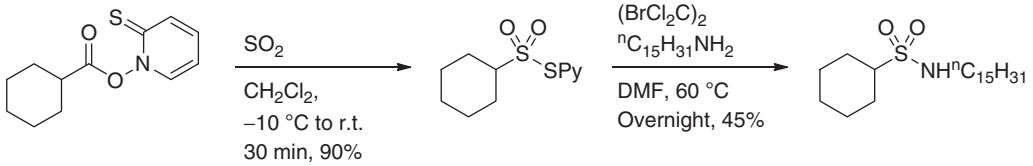
Scheme 4

The intramolecular variant of the process involves cyclization of *O*-acyl thiohydroxamte-derived alkyl radicals onto benzyl selenides with expulsion of a benzyl radical and formation of selenocycles.[97,98] The method is beautifully illustrated by the synthesis of a selenopenam (equation 32).[99]



(32)

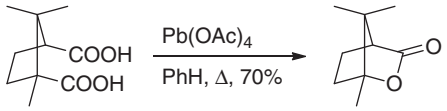
The trapping of *O*-acyl thiohydroxamate-derived alkyl radicals with sulfur dioxide provides a useful entry into sulfonic acid derivatives (**Scheme 5**).[100]



Scheme 5

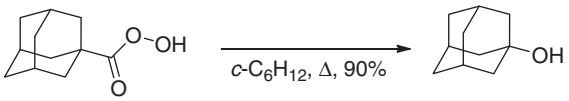
7.27.7 Decarboxylative C–O Bond Formation

Selective monodecarboxylation of 1,3- and 1,4-decarboxylic acids with lead tetraacetate takes place with formation of γ- and δ-lactones, respectively, in moderate to good yield (equation 33).[101]



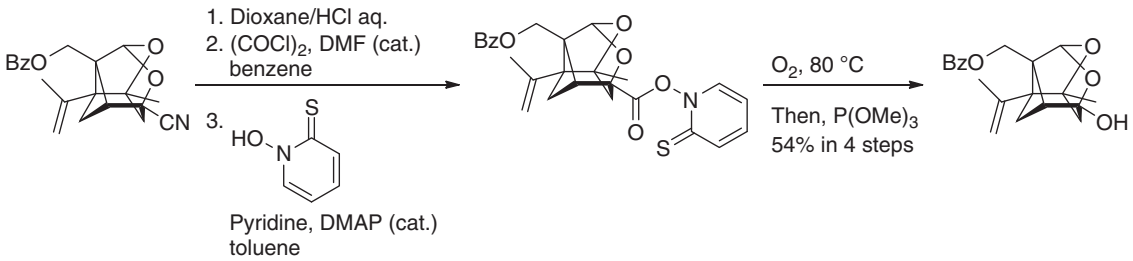
(33)

Simple alcohols can be obtained from decomposition of the peracids in cyclohexane or benzene at reflux (equation 34).[102]



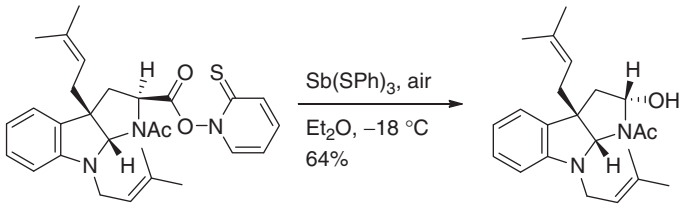
(34)

Decomposition of *O*-acyl thiohydroxamates in the presence of triplet oxygen and a *tert*-thiol as hydrogen donor, provides the noralkyl hydroperoxides, which can be converted into the corresponding alcohols by treatment with $P(OMe)_3$ *in situ*.[41,103–105] Alternatively, workup with TsCl and pyridine results in the carbonyl compound.[41,103,104] The use of $^{18}O_2$ in this protocol enabled the formation and isolation of an ^{18}O-labeled hydroperoxide for the first time.[106] In the total synthesis of (–)-paeoniflorin by Takano et al., acidic hydrolysis of a nitrile provided a carboxylic acid, which then was converted directly into a hemiacetal by decarboxylative radical oxygenation (Scheme 6).[107]



Scheme 6

In an alternative sequence, although indirect, alkyl radicals from *O*-acyl thiohydroxamates are trapped with tris (phenylthio)antimony to give the corresponding alkylbis(phenylthio)antimony derivative. This substance undergoes insertion of oxygen into the C–Sb bond on exposure to air followed by rearrangement to give an alkoxyantimonate which provides the alcohol on hydrolysis (equation 35).[108–110]



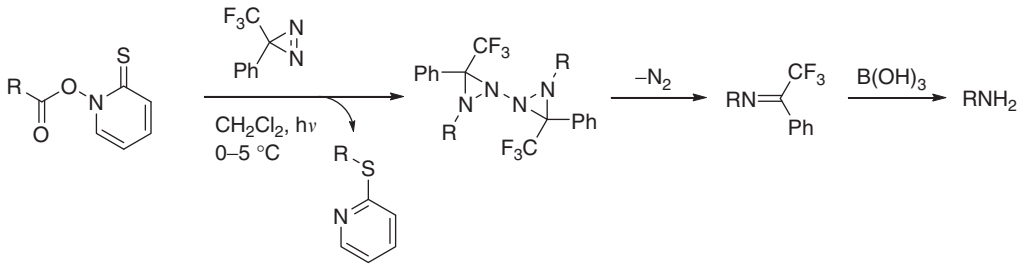
(35)

7.27.8 Decarboxylative C–N and C–P Bond Formation

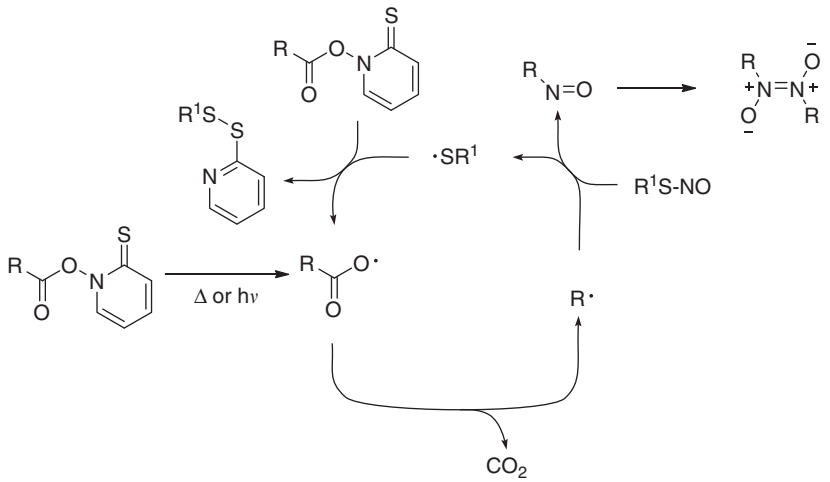
Barton et al. demonstrated that *O*-acyl thiohydroxamate-derived alkyl radicals can add to the N═N double bond of 3-phenyl-3-(trifluoromethyl)diazirine to furnish, ultimately, an imine (Scheme 7). Subsequent treatment with boric acid yields the amination product. This nonchain C–N bond formatting reaction is accompanied by the formation of alkyl 2-pyridyl sulfides reflecting the relatively low reactivity of the diazirine toward alkyl radicals and the radicophilic nature of the thiopyridone moiety inherent in the *O*-acyl thiohydroxamates.[111]

An alternative sequence developed by Motherwell et al. (Scheme 8) is a chain process and involves photolysis of the Barton ester in the presence of trityl thionitrite. The immediate product of the reaction, a nitrosoalkane undergoes spontaneous dimerization in the usual manner.[112,113]

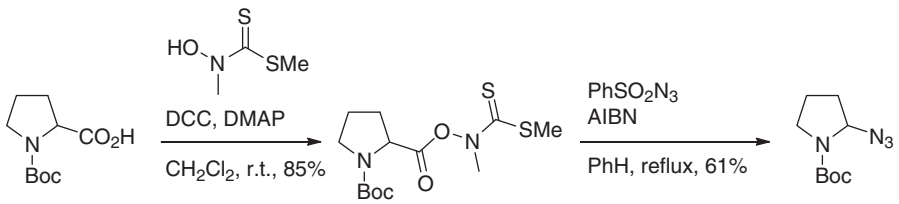
A more practical method was developed by Nyfeler and Renaud and employs sulfonyl azides as radical traps and source of chain propagating radical, and provides alkyl azides (Scheme 9). A second example illustrates the use of the method in the context of a cyclization reaction (equation 36).[114]



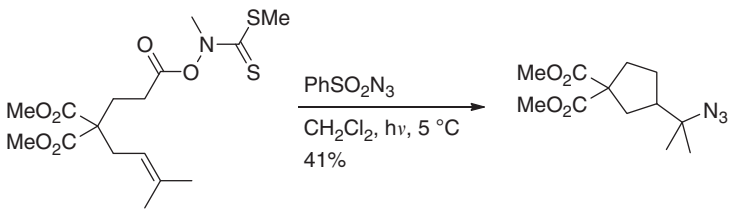
Scheme 7



Scheme 8

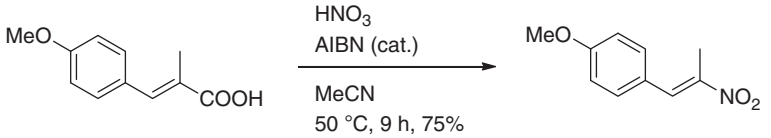


Scheme 9



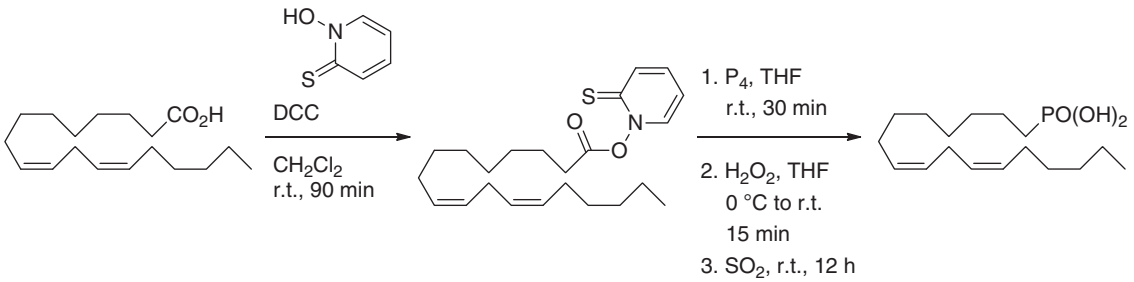
(36)

The decarboxylative nitration of cinnamic acids may be achieved with nitric acid under catalysis of AIBN,[115] acetic acid,[116] or a wide range of nitrate salts[117] (equation 37).



(37)

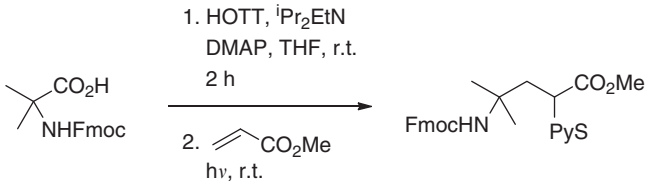
Phosphoric acid derivatives may be prepared by the decomposition of *O*-acyl thiohydroxamates in the presence of tris(phenylthio)phosphorus,[118] but an experimentally more convenient phosphorylation protocol employs white phosphorus with subsequent workup with hydrogen peroxide (Scheme 10).[119]



Scheme 10

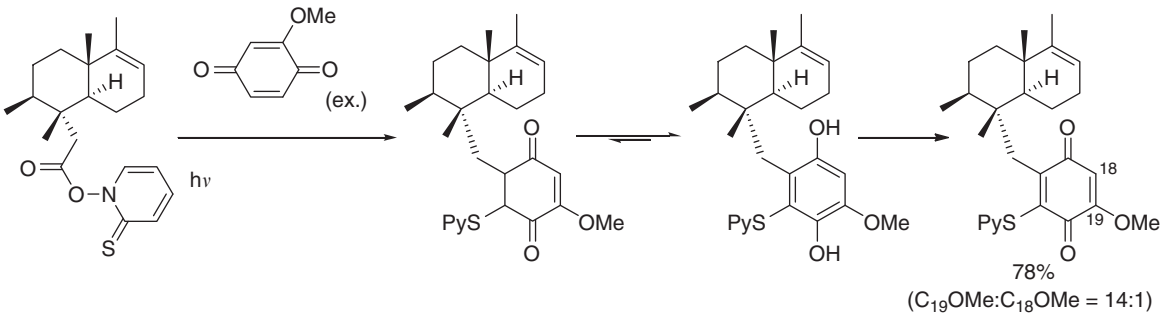
7.27.9 Decarboxylative C–C Bond Formation

The full range of the Barton decarboxylation, coupled with carbon–carbon bond forming processes, particularly when radical cyclizations and tandem processes are included, is vast and beyond the scope of this chapter. As such only a limited number of simple, illustrative examples are provided here. Alkyl radicals derived from *O*-acyl thiohydroxamates undergo addition to a wide range of electron-deficient terminal alkenes. The overall result, after chain transfer, is the addition of the alkyl radical and the 2-pyridylthio radical, or its equivalent, across the alkene.[14] The method is illustrated for α-aminoisobutyric acid (equation 38).[18]



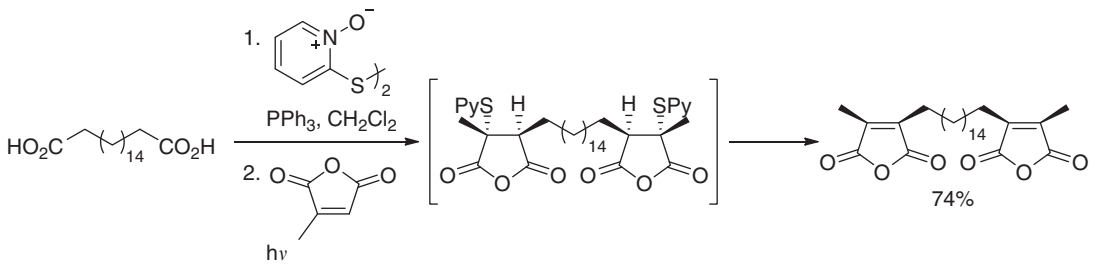
(38)

Alternatively, an activated allyl sulfide may be employed as the trap resulting overall in the transfer of a 2-substituted allyl moiety to the alkyl radical.[120] When the use of a nonterminal alkene is required, with the exception of the highly electron-deficient nitroalkenes, a double activated system must be employed in order to overcome the facile competing process of decarboylxative rearrangement to give the alkyl pyridyl sulfides; quinones and cyclic anhydrides serve this function well. For example, Theodorakis et al. demonstrated the addition reaction of alkyl radical generated from a Barton ester to a 1,4-quinone (Scheme 11). After addition of the radical and thiopyridine, the semiquinone rapidly tautomerizes to the hydroquinone, which protects the other double bond from further radical addition. The excess quinone slowly oxidizes the hydroquinone to the quinone.



Scheme 11

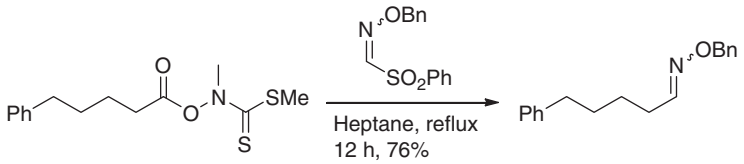
When the trap is maleic anhydride, or a maleimide the immediate product, a *trans*-2-alkyl-3-arylthiosuccinic anhydride or imide undergoes spontaneous elimination of the arylthio moiety to give the 2-alkylsuccinic anhydride or imide. An example of such a process, the synthesis of tyromycin A, is given in Scheme 12.[121]



Scheme 12

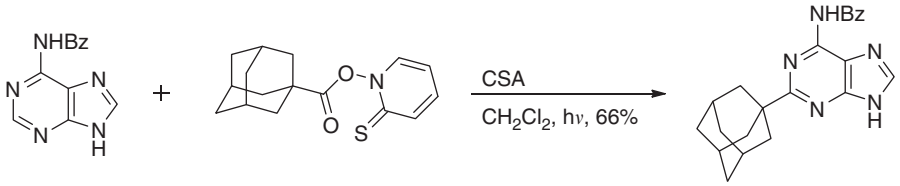
When overall homologation of the initial carboxylic acid by one carbon is required, the trap must be a two carbon alkene and nitroethene and phenylvinyl sulfone are the systems of choice.[122,123]

Trapping of decarboxylation-derived alkyl radicals by a one-carbon trap results in products with the same overall carbon skeleton as the initial carboxylic acid. When the trap is isotopically labeled, this provides a ready means of access to mono-labeled carboxylic acids. The method was initially developed using isonitriles as traps in conjunction with Barton esters as radical source,[124] but the sulfonyl oxime ethers introduced by Kim (equation 39) are probably the more practical solution.[16]



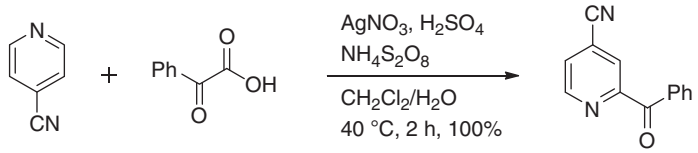
(39)

Photolysis of *O*-acyl thiohydroxamates in the presence of protonated heteroaromatic bases is an efficient means of generation of alkylated heterocycles (equation 40).[125]



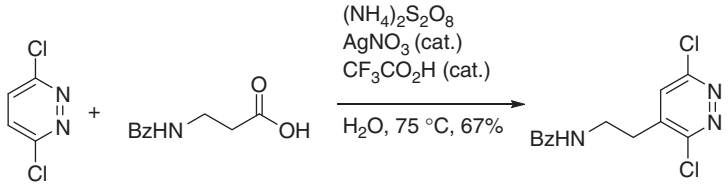
(40)

The Ag(I)-catalyzed peroxydisulfate oxidative decarboxylation of α-keto acids provides a useful means of acylation of protonated heteroarenes (pyridine, quinoxaline, and pyrazine) (equation 41).[126,127]



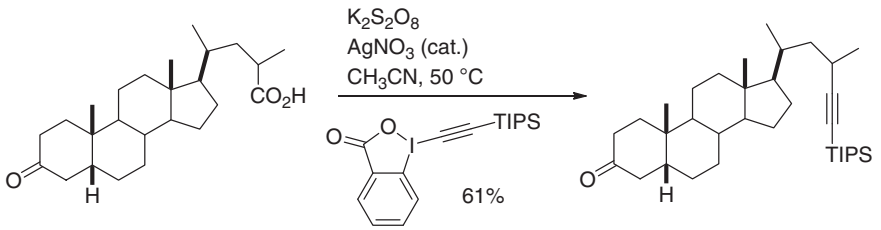
(41)

Application of the Minisci conditions to *N*-protected amino acids provides a useful entry into amino alkyl heterocycles (equation 42).[128]



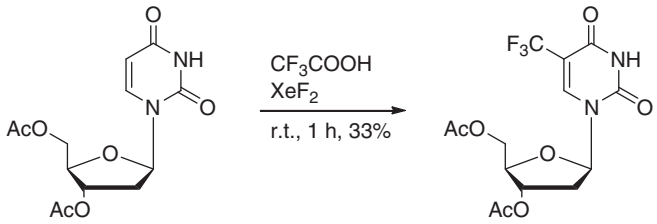
(42)

A recent development involves the alkynylation of noralkyl radicals generated by the catalytic silver nitrate/peroxydisulfate combination in the presence of the alkynyliodonium species (equation 43).[129]



(43)

Perfluoroalkylation of aromatic and heterocyclic rings has been demonstrated by Matsuo et al. (equation 44)[130] following the oxidation of perfluoro acids with xenon difluoride in CH_2Cl_2.



(44)

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7.28 Oxidation of Sulfur, Selenium, and Tellurium

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Glossary

Active site-directed mutagenesis It is a molecular biology method used to make specific changes to the DNA sequence of a gene.

Mechanical milling It is the reactivity of species modified under ball-milling conditions due to more efficient mixing and increase in reagent surface, temperature, and/or pressure.

Microreactor These are tubings or channels which serve as reactor for flow chemistry. The channel widths or tube diameters should be less than a few millimeters to be considered as microreactors.

Microwave irradiation A wave of electromagnetic radiation between far infrared and radio waves.

Ultrasound irradiation The effects of direct interactions of sonic waves with molecular species.

7.28.1 Introduction

Organo-sulfur and selenium-containing compounds at different oxidation states have found extensive application in organic chemistry. Accordingly, oxidations of a variety of organo-sulfur, selenium, and tellurium compounds have been intensively investigated in the past two decades to develop selective, mild, and environmentally benign procedures. Thiols, selenols, and tellurols are the most sensitive compounds as they increasingly suffer facile oxidation to the corresponding disulfides, diselenides, and telluronides (equation 1). These products are themselves susceptible to further oxidation according to the reaction conditions to afford a variety of products.

$$RMH \xrightarrow{[O]} RM\text{–}MR \quad (1)$$

Disulfides and diselenides are particularly useful reagents in the α-heterofunctionalization of carbonyl compounds (*see* Volume 6, Chapter 6.04). The oxidation of sulfides **1** (M = S), selenides **1** (M = Se), and tellurides **1** (M = Te) to sulfoxides **2** (M = S), selenoxides **2** (M = Se), and telluroxides **2** (M = Te) and further oxidation to sulfones **3** (M = S), selenones **3** (M = Se), and tellurones **3** (M = Te) represents a vast section in the general field of oxidation of organic compounds (equation 2). The presence of sulfur and selenium groups at different oxidation states stabilizes a vicinal carbanion useful to form a new carbon–carbon bond (*see* Volume 3, Chapter 3.03). Elimination of the selenoxide and telluroxide groups gives alkenes (*see* Volume 6, Chapter 6.18). The [2,3]-sigmatropic rearrangement of allylic sulfoxides and selenoxides affords the allylic alcohols (*see* Volume 6, Chapter 6.16).

$$\underset{\mathbf{1}}{R^1\text{–}M\text{–}R^2} \xrightarrow{[O]} \underset{\mathbf{2}}{R^1\text{–}M(=O)\text{–}R^2} \xrightarrow{[O]} \underset{\mathbf{3}}{R^1\text{–}M(=O)_2\text{–}R^2} \quad (2)$$

M = S, Se, Te

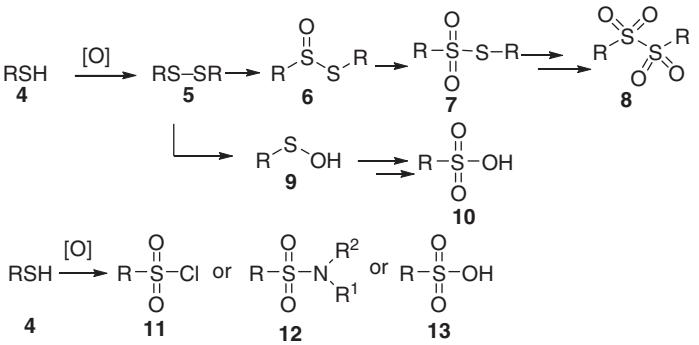
This chapter will focus on the most effective and selective methods reported for the oxidation of representative organic sulfur, selenium, and tellurium compounds (equations 1 and 2) under chemical and enzymatic conditions. Highly stereoselective oxidative processes will also be included for the synthesis of compounds **2**. Literature from 1990 to mid-2012 is covered, whereas previously reported oxidative methods can be found in (*see* Chapter 6.01) of Comprehensive Organic Synthesis, first edition.

7.28.2 Oxidation of Organic Sulfur Compounds

7.28.2.1 Oxidation of Thiols to Disulfides by Dioxygen and Chemical Reagents

Symmetrical and unsymmetrical disulfides are an important class of compounds recognized in biologically active peptides and peptide mimetics,[1] as cleavable linkages in drug delivery systems,[2] or as vulcanizing agents for rubber and elastomers and in a variety of macrocyclic compounds.[3]

The oxidation of thiols to disulfides occurs easily, with an increasing rate from tertiary to primary alkyl derivatives and the aromatic thiols being the most reactive. The need to stop the process of oxidation selectively at the disulfide level without obtaining species at a higher oxidation state (compounds **6–10**) has stimulated intensive research into selective methods in recent years.[4] The most effective reagents developed so far for the oxidation of thiols to disulfides are based on the use of dioxygen or air, halogen sources of Br_2, I_2, metal salts, and complexes such as Mn(IV), V(V), Fe(III), Ti(IV), Re(III), and peroxides. Direct procedures for the full oxidation of thiols to derivatives of type **11–13** have also been developed (**Scheme 1**).



Scheme 1

7.28.2.1.1 By dioxygen

The use of dioxygen or air with metal complexes, salts, or Brønsted base catalysts has been reported as one of the most effective and practical ways to effect thiol oxidation to disulfides. Moreover, in view of the environmental concerns, dioxygen is a highly appealing oxidant that is regarded as a green and sustainable reagent. Mo(VI),[5] V(V),[6] Mn(III)-Schiff base,[7] and Fe(III)-metal organic frameworks (MOF)[8] complexes recently proved to be useful catalysts in this process. Substrates less prone to be oxidized are tertiary alkyl thiols, which are generally isolated in moderate yield after prolonged reaction time.

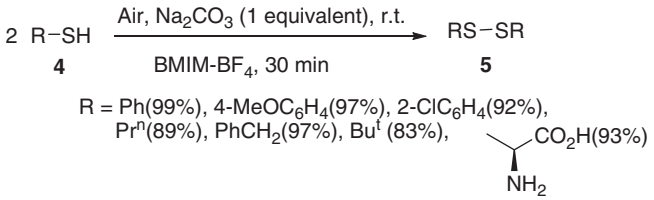
Mechanistically, the oxidation of thiols to disulfides can proceed either via a radical (equation 3) or an ionic pathway (equation 4) (Scheme 2).

$$2\ RSH + 1/2\ O_2 \longrightarrow 2\ RS^{\bullet} + H_2O \longrightarrow RSSR \qquad (3)$$

$$RSH + 1/2\ O_2 \longrightarrow RS^{+} + RSH \longrightarrow RSSR + H_2O \qquad (4)$$

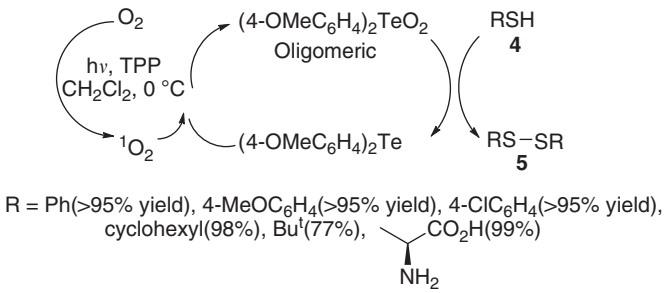
Scheme 2

It has been observed that the oxidation of thiols can be subjected to base catalysis.[9] Under heterogeneous conditions and exposure to dioxygen or air, hydrotalcite clay,[10] CsF-Celite,[11] and anhydrous K_3PO_4[12] were able to selectively oxidize aromatic and alkyl thiols to disulfides in good yield. Common bases such as Et_3N in *N*,*N*-dimethylformamide (DMF) at reflux or at room temperature under sonication provided the disulfides within short reaction times.[13] A practical and simple procedure to rapidly access a good variety of symmetrical disulfides in high-to-excellent yield relies on the use of a stoichiometric amount of Na_2CO_3 in recyclable ionic liquid 1,3-dialkylimidazolium tetrafluoroborate (BMIM-BF_4) as solvent working at room temperature, bubbling air into the reaction vessel (Scheme 3).[14] Notably, the sterically demanding tBuSH is also converted into the product in very good yield.



Scheme 3

The same reaction conditions are suitable for the oxidation of heteroaromatic thiols and functionalized thiols of biological interest, such as L-cysteine. The BMIM-BF_4 medium can be recovered and reused for five oxidative cycles, with a slight decrease in the product yield observed. This system proved to be significantly more efficient that the previously reported aerobic oxidation of thiols catalyzed by Co(II)-phthalocyanines dissolved in BMIM-BF_4.[15] A base-free BMIM-SeO_2(OMe) protocol for the aerobic oxidation of symmetrical aryl, alkyl, and functionalized thiols under microwave irradiation has been found to be suitable for reuse up to five cycles affording the products in good-to-high yield.[16] Gold nanoparticles supported on CeO_2 were recently reported to smoothly promote the oxidation of aromatic and heterocyclic thiols to disulfides under air in the absence of solvent or in neutral water solution. However, unbranched alkyl thiols were unreactive under these conditions.[17] The oxidation of thiols to disulfides can also be performed in less than 1 h under aerobic photochemical conditions by employing 1 mol% loading of bis(4-methoxyphenyl)telluride irradiated with a 500-W halogen lamp in the presence of tetraphenyl porphyrin (TPP) at 0 °C in dichloromethane or polar protic solvents (Scheme 4).[18] Excellent yields of aromatic, heteroaromatic, alkyl, and functionalized disulfides are generally observed. However, this system affords a complex reaction mixture when starting from α,ω-dithiol. Cyclic disulfides derived from intramolecular oxidative coupling are obtained in low yield. The active species involved in the oxidation was suggested to be the tellurone oligomer produced by reaction of the telluride with singlet dioxygen.

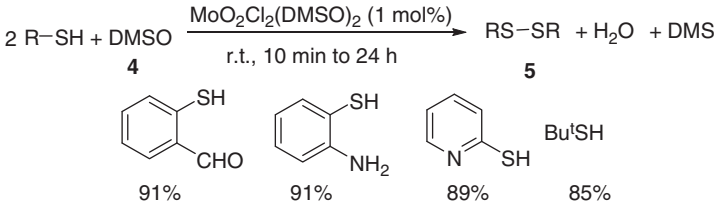


Scheme 4

A rapid and efficient method for the selective intermolecular oxidative coupling of some α,ω-dithiols to cyclic bis-disulfides and hindered ortho-substituted aromatic thiols under aerobic oxidation is achievable by using catalytic loadings of silica gel treated with thionyl chloride ($SOCl_2$-SiO_2) (5 mol%) in dichloromethane at 0 °C.[19]

7.28.2.1.2 By metal complexes/dioxygen source, inorganic salts, and peroxides

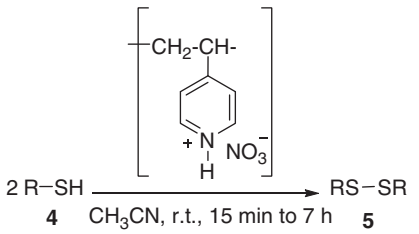
A variety of metal complexes in the presence of oxidants other than dioxygen were reported for the oxidation of thiols to disulfides, e.g., Mn(III)-Salen/urea-hydrogen peroxide (UHP),[20] $VO(acac)_2$/tert-butyl hydroperoxide (TBHP),[21] and Re(V)/dimethyl sulfoxide (DMSO).[22] DMSO is known to be able to oxidize thiols to disulfides, although long reaction times and high temperature are required.[23] More effective systems have also been developed by adding trimethylchlorosilane, cyanuric chloride,[24] or hexamethyldisilazane to DMSO.[25] A selective method of oxidation under mild reaction conditions of a variety of thiols has been developed by means of 1 mol% of $MoO_2Cl_2(DMSO)_2$ in DMSO working at room temperature (Scheme 5).[26]



Scheme 5

The oxidation is fast and selective for aromatic thiols, and also bear sensitive functional groups, which are obtained in high yield, whereas prolonged reaction times and higher temperatures (70 °C) are necessary to oxidize sterically more demanding alkyl thiols. The role of DMSO is to reoxidize $MoOCl_2(DMSO)_2$ to $MoO_2Cl_2(DMSO)_2$, which is formed after the oxidation of the thiol to disulfide. The system is not affected by the water produced during the process and it can be successfully scaled up to multigram quantity, although one major disadvantage is the production of foul-smelling dimethyl sulfide waste product.

Inorganic salts, most of them commercially available, such as $Bi(NO_3)_3 \cdot 5H_2O$,[27] $Al(NO_3)_3 \cdot 9H_2O$/silica sulfuric acid,[28] and $NaNO_2$/silica phosphoric acid,[29] selectively oxidize at room temperature or at higher temperature aromatic, heteroaromatic, and alkyl thiols to disulfides in high yield. The most attractive features of these heterogeneous systems are the easy availability of the reagents and the clean work-up, which often consists of filtering the reaction mixture to remove the inorganic residue and then evaporation of the solvent to give almost pure product. Recently, a supported version of poly(4-vinylpyridinium nitrate) was found to be active in the oxidative coupling of thiols to disulfides working at room temperature in acetonitrile (Scheme 6).[30]



Scheme 6

An advantage of this system is the recoverability of the poly(4-vinylpyridine) after filtration. It can be reconverted to the active reagent after treatment with nitric acid and reuse for oxidation. The formation of unstable thionitrites is believed to occur, and these then decompose to thiyl radicals involved in the coupling.

Gaseous dinitrogen tetraoxide N_2O_4, a highly reactive and harmful reagent, is known to react under controlled conditions with thiols to provide thionitrite intermediates that then decompose to furnish disulfides.[31] However, further oxidized species are often observed such as thiosulfonates **7** and sulfonic acids **10** when working in excess of dinitrogen tetraoxide. Easy-to-handle and more controlled sources of N_2O_4 have been developed by immobilizing it onto polyvinylpyrrolidone (PVP-N_2O_4)[32] or impregating it onto charcoal.[33] These solid reagents are effective in the selective oxidative coupling of thiols to difulfides in organic solvents.

Several methods of oxidation of thiols to disulfides based on chromate reagents such as pyridinium chlorochromate,[34] tetramethylammonium chlorochromate,[35] quinolinium fluorochromate,[36] cetyltrimethylammonium dichromate,[37] n-butyl-triphenylphosphonium dichromate,[38] 2,6-dicarboxypyridinium chlorochromate,[39] 3-carboxypyridinium trichloroacetatochromate,[40] ethylenebis(N-methylimidazolium)chlorochromate,[41] and silica-supported bis(trimethylsilyl) chromate have been developed.[42] Although most of these reagents are inexpensive and generally afford symmetrical disulfides in high yield, limited tolerance of other

oxidable functional groups in the starting material and the high environmental impact of the metal residue are the major disadvantages.

Solvent-free oxidations of thiols to disulfide can be carried out with $KMnO_4/CuSO_4$ mixture, adding the thiol to the solid oxidant at room temperature under stirring. After a few minutes the disulfides are almost quantitatively recovered with acceptable purity after washing the reaction mixture with a minimum volume of organic solvent followed by evaporation.[43] A solvent-free oxidation of thiols to disulfides satisfactorily proceeds under microwave irradiation by using the heterogeneous system Al_2O_3/KF.[44] High-valent iron salt K_2FeO_4 in the presence of acid support K-10 montmonillorite clay has proven effective in the oxidative coupling.[45]

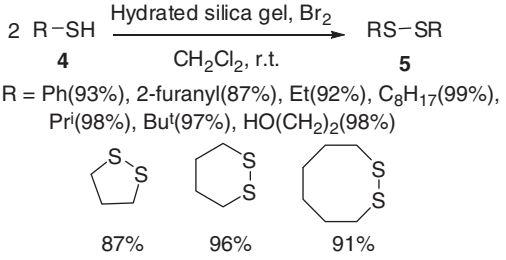
Hydrogen peroxide and peroxyacids are commonly used reagents to oxidize thiols to disulfides, although it is easy to observe byproducts at various oxidation states.[46] A number of selective protocols of oxidation such as water solution of hydrogen peroxide in alcohols as media,[47] 1,4-diazabiciclo[2.2.2]octane-di-*N*-oxide-di-perhydrate,[48] and catalytic NaI with a stoichiometric amount of 30% hydrogen peroxide[49] have been developed. The hydrogen peroxide urea adduct, UHP, is activated toward the oxidative coupling of thiols by maleic anhydride, whereas aromatic cyclic seleninate esters and spirodioxyselenuranes mediate the oxidation of thiols to disulfides in the presence of H_2O_2.[50] Solid-state oxidation of thiols with ammonium persulfate,[51] or tetrabutyl ammonium persulfate,[52] benzyl triphenyl phosphonium monoperoxysulphate,[53] and sodium perborate[54] in solution, has also been reported.

7.28.2.1.3 By halogens and halogen-containing compounds

The use of halogens is attractive because of their low cost, but some disadvantages include their toxicity and use in aqueous-organic biphasic reaction media. The formation of hydrogen halide byproducts can cause further acid-catalyzed side reactions.

The oxidation of thiols with iodine is known to proceed to disulfides under various reaction conditions with high tolerance of different functional groups on the starting thiols.[55] More recently, this oxidation has been performed simply using I_2 in a range of different solvents,[56] in the presence of bases,[57] or with cerium(III) chloride heptahydrate in graphite and ethyl acetate as solvent.[58] Symmetrical and cyclic disulfides, some of them showing interesting biological activity, have been recovered in satisfactory yield.[59] Fast and selective oxidation can be performed with easily available $NaIO_3$ or $NaIO_4$ reagents.[60]

Bromine in organic media has been used for the oxidative coupling of thiols. A system based on bromine effectively oxidizes thiols in the presence of silica gel, which is proposed to facilitate the process, serving as a heat sink and an acid scavenger. A good variety of disulfides are isolated in high-to-excellent yield after simple filtration of the reaction mixture and evaporation of the solvent (Scheme 7).[61]



Scheme 7

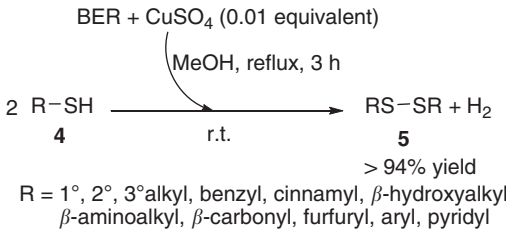
The most striking feature of the process is the successful synthesis of cyclic disulfides, even of large size, in excellent yield, without the requirement of diluted reaction conditions to suppress the competitive intermolecular oxidative coupling. Several procedures based on bromo-containing reagents such as *o*-xylylenebis(triphenylphosphonium tribromide),[62] bipyridinium hydrobromide perbromide,[63] *N*,*N*′-dibromo-*N*,*N*′-1,2-ethanediylbis(*p*-toluenesulfonamide),[64] *N*-bromophthalimide,[65] 1,3-dibromo-5,5-dimethylhydantoin,[66] and [K.18-crown-6]Br_3[67] of nanotube-like structure have been developed. Trichloroisocyanuric acid (TCCA),[68] sulfuryl chloride in dichloromethane,[69] and monochloro poly(styrenehydantoin) beads in water[70] have been found to be effective reagents for the oxidation of symmetrical thiols to disulfides.

7.28.2.1.4 By chemical reagents, enzymatic systems, and other methods

Different chemical and enzymatic systems are also effective for the oxidative coupling of thiols. A simple system, based on copper deposited on borohydride exchange resin (BER) by reduction of $CuSO_4$ with BER in methanol, catalyzes the disproportion of symmetrical thiols to disulfides and molecular hydrogen (Scheme 8).[71]

The formation of products **5** occurs at room temperature in a few hours in excellent yield. Laser-prepared Cu nanoparticles have been found to be effective for the same purpose, although this protocol appears less practical.[72]

Diethyl azodicarboxylate (DEAD), an electrophilic nitrogen reagent, has been found to be effective in the oxidative coupling of thiols since the 1960s.[73] Diazenecarboxamides can also accomplish this type of oxidation.[74] In addition to the access to symmetrical disulfides in fairly good yield, the most relevant application of DEAD concerns the oxidative coupling to unsymmetrical disulfides. This reagent and derivatives thereof such as diisopropyl azodicarboxylate (DIAD),[75] tetramethylazodicarboxamide (TMAD),[76] and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[77] have been used to generate unsymmetrical glycosyl- and vancomicin analogs bearing disulfide bonds.[78] These reagents are of general application, although the presence of hydroxy and carboxyl



Scheme 8

groups in compounds **4** is not tolerated. Another method for the preparation of unsymmetrical disulfides has been accomplished via anodic oxidation of symmetrical disulfides to sulfenyl cation RS^+ intermediates trapped by different thiols.[79]

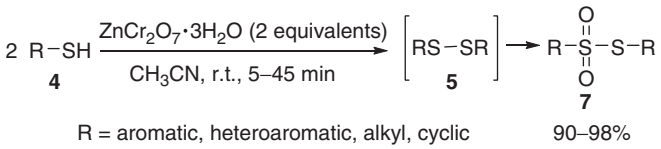
An alternative approach to disulfides **5** has been developed by reacting primary and aromatic thiols with the Burgess reagent at room temperature.[80] Sterically demanding secondary and tertiary disulfides are obtained in modest yield and the formation of trisulfides is observed.

Different classes of enzymes such as baker's yeast, horseradish peroxidase (HRP), and mushroom tyrosinase in phosphate buffer and organic solvent biphasic mixtures are able to convert aromatic and alkyl thiols to disulfides in good-to-high yield.[81]

7.28.2.2 Oxidation of Thiols to Thiosulphonates, Sulfonyl Chlorides, Sulfonamides, and Sulfonic Acids

Thiosulfonates **7** serve as useful compounds in the industry,[82] show some biological activity,[83] and are employed as strong sulfenylating agents.[84] Several pharmaceutically active compounds used in the prevention and treatment of important diseases contain the sulfonamide group.[85] Moreover, sulfonamides and sulfonic acids are used industrially for applications as pesticides, dyes, surfactants, and acid catalysts.[86]

The preparation of thiosulfonates, sulfonyl chlorides, sulfonamides, and sulfonic acids can be conveniently accomplished starting directly from thiols via one-pot oxidation, and disulfides are generally intermediates of the process. Few methods of oxidation of thiols to thiosulfonates have been developed in comparison to those reported for the oxidation of thiols to other derivatives. PVP-N_2O_4[32] or dinitrogen tetraoxide absorbed on charcoal[33,87] easily oxidizes aromatic and alkyl thiols to thiosulfonates in high yield in halogenated solvents at room temperature. Phenyliodine(III) bistrifluoroacetate (PIB) can provide the same oxidation, although with inferior efficiency.[88] Controlled ratios of tetrabutylammonium peroxymonosulfate in the presence of manganese meso-TPP and imidazole selectively allow symmetrical disulfides **5** or thiosulfonates **7** in high yield starting from aromatic or alkyl thiols to be obtained.[89] A simple and rapid one-pot oxidation of thiols mediated by zinc dichromate trihydrate affords the thiosulfonates in excellent yield (Scheme 9).[90] Disulfides are formed as intermediates.



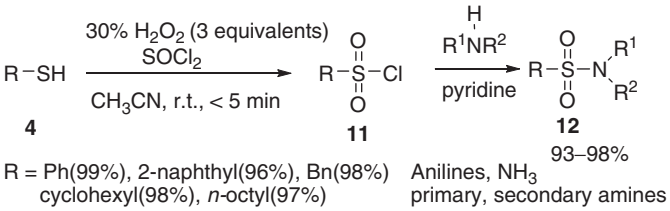
Scheme 9

Easily available ceric ammonium nitrate (CAN) is used under catalytic conditions in wet poly(ethylene glycol) (PEG-400), with I_2 as stoichiometric co-oxidant to regenerate Ce(IV). Under these conditions, thiols or disulfides are efficiently oxidized to thiosulfonates.[91]

Different procedures of oxidation are mediated by hydrogen peroxide in the presence of metal complexes or other reagents. According to the reagent ratios, the oxidation of a variety of thiols in acetonitrile with $TiCl_4$ and a 30% H_2O_2 system[92] affords the thiosulfonates **7**. When working in excess of $TiCl_4$ or alternatively with $ZrCl_4$[93] as promoter, sulfonyl chlorides **11** are obtained in fairly good yield. $ZrCl_4/H_2O_2$ is also a suitable system for the one-pot synthesis of sulfonamides **12** by adding a solution of a primary or secondary amine in pyridine to the previously generated sulfonyl chlorides **11**.[94] The methyltrioxorhenium/H_2O_2 system oxidizes aromatic and aliphatic thiols at room temperature to the corresponding sulfonic acids **13** in high yield.[95] The combination of H_2O_2 and thionyl chloride ($SOCl_2$) is one of the most effective methods for the oxidative chlorination of thiols to sulfonyl chlorides or to sulfonyl amides after adding in the reaction vessel a proper amine to the firstly formed compounds **11** (Scheme 10).[96] However, heteroaromatic thiols led to byproducts, likely due to the instability of the corresponding sulfonyl chlorides.

Protocols using $POCl_3$ as promoter with H_2O_2 in water as solvent using sodium dodecyl sulfate (SDS) or $HOF \cdot CH_3CN$ complex are effective for the oxidation of thiols or disulfides to sulfonyl chlorides, or sulfonic or sulfinic acids.[97] A similar protocol is also useful for the synthesis of sulfonamides and sulfonic esters.[98]

Sulfenamides or sulfonamides can be produced by the use of a copper catalyst in air or under dioxygen atmosphere in the presence of amines.[99]



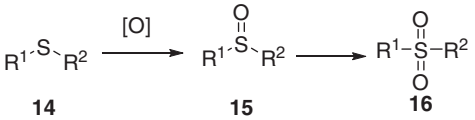
Scheme 10

Commercially available TCCA[100] or 1,3-dichloro-5,5-dimethylhydantoin (DCH)[101] is used in combination with the chlorinating agent $BnMe_3NCl$ to convert thiols to sulfonyl chloride and, subsequently, to sulfonamides using various amines in organic solvents. A more environmentally benign and cheaper oxidation of thiols or disulfides to sulfonamides is provided by TCCA in water followed by the addition of K_2CO_3 and the proper amine.[102]

The one-pot oxidative halogenation of thiols to sulfonyl chlorides and sulfonyl fluorides can be performed by other systems such as $TMSCl/KNO_3$,[103] *N*-chlorosuccinimide (NCS),[104] ClO_2,[105] or $NaOCl/KHF_2$.[106] A useful application of the $NaOCl/KHF_2$ system is the selective synthesis of difficult-to-access heteroaryl sulfonamides from heteroaryl thiols.[106a]

7.28.2.3 Oxidation of Sulfides to Sulfoxides

The oxidation of sulfides **14** to sulfoxides **15** can be accomplished by conventional oxidants including meta-chloroperoxybenzoic acid (MCPBA), TBHP, H_2O_2, PhIO, NaClO, and $KMnO_4$. However, the selectivity of the oxidation is an important issue to address and reaction conditions, the stoichiometry of the reagents need to be controlled to prevent the over-oxidation to sulfones **16** (equation 5).



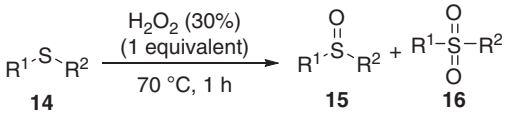
(5)

A plethora of methods has been developed in recent years for the oxidation of sulfides to sulfoxides, particularly focused on the use of benign oxidants, recyclable solvents, and catalytic systems or under metal-free conditions.

7.28.2.3.1 By hydrogen peroxide, peroxides, peroxyacids, and dioxygen

7.28.2.3.1.1 By hydrogen peroxide, peroxides, peroxyacids, and dioxygen under metal-free conditions

The oxidation of sulfides with H_2O_2 in various solvents such as acetone and acetic acid or in methanol is a practical and chemoselective procedure of oxidation of sulfides to sulfoxides also bearing unsaturations in their scaffolds.[107] More nucleophilic alkyl sulfides are oxidized at a faster rate than aryl sulfides since the process involves an electrophilic attack of the oxygen atom of the oxidant on the sulfur. Acceleration of the oxidation has been observed in methanol, although this medium is not compatible with functionalized sulfides.[108] Interestingly, protic solvents such as hexafluoro-2-propanol (HFIP)[109] and phenol[110] provide fast, highly chemoselective, and complete oxidation to aryl and alkyl sulfoxides bearing sensitive groups. Functionalized glycosyl and electron-poor 1-trifluoromethyl vinyl sulfides are also good substrates for the oxidation when using HFIP as solvent.[111] It has been proposed that hydrogen bonding of the acidic OH group of the solvent with H_2O_2 increases the electrophilicity of the peroxy oxygen atom facilitating the oxidation of sulfides, whereas hydrogen bonding of the solvent with the sulfoxide would suppress its nucleophilicity, preventing further oxidation. Hydrogen peroxide rapidly oxidizes a variety of aryl and alkyl sulfides to sulfoxides in high yield under solvent-free conditions at 70 °C (**Scheme 11**).[112]

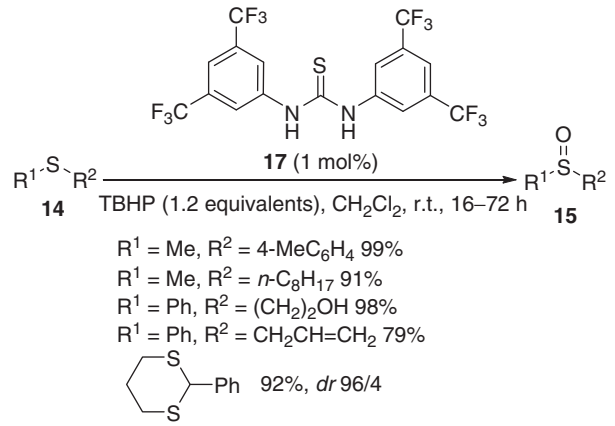


R^1 = Me, R^2 = 2-$MeOC_6H_4$ 98%
R^1 = Me, R^2 = 4-$NH_2C_6H_4$ 90%
$R^1 = R^2 = Bu^n$ 87%
$R^1 = R^2$ = Ph 80%
R^1 = Ph, $R^2 = (CH_2)_3OH$ 87%

Scheme 11

Good chemoselectivity is observed with products **15**/**16** ratio ranging from 99/1 to 83/17. This convenient and environmentally benign procedure is an example of a self-catalyzed process by the sulfoxide product, since a small amount of sulfoxide added initially significantly accelerates sulfide oxidation. Chemoselective oxidation of sulfides to sulfoxides can be achieved using H_2O_2 in acetonitrile in a microreactor, which allows for a rapid mixing of reagents in small quantities, thus enhancing reactivity and reducing risks when employing explosive compounds by simpler control of the reaction parameters.[113] Ionic liquids can also be used as recyclable medium to activate H_2O_2 in the chemoselective oxidation of sulfides to sulfoxides at room temperature.[114] Although a certain influence of the sulfide structure and nucleophilicity is observed, sulfoxides are obtained in good-to-high yield after reasonable reaction times. UHP is a valuable reagent for the solid-state oxidation of some alkyl and aryl sulfides to either sulfoxides or sulfone at 85 °C.[115]

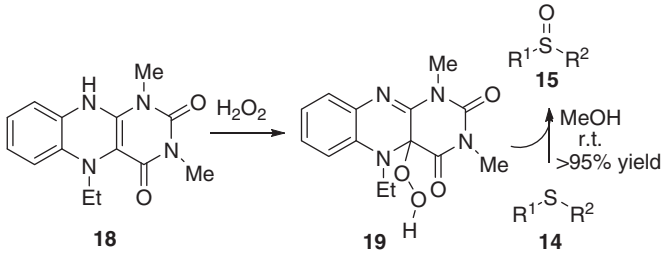
Organic acids such as camphorsulfonic acid (CSA)[116] or *in situ* generated dodecylhydrogenosulfate[117] catalyze at 10 or 5 mol% loading the highly chemoselective oxidation of sulfides to sulfoxides either in organic medium with TBHP or under solvent-free conditions with H_2O_2 as oxidant, respectively. Solid acids, in the form of silica sulfuric acid, Amberlite IR 120 H, carbon-based solid acid, and sulfamic acid catalyze the oxidation of sulfides to sulfoxides by one equivalent of H_2O_2.[118] Working with an excess of the oxidant in some examples enables the formation of sulfones. Simple silica gel and alumina are also suitable promoters of sulfide oxidation by using TBHP or oxone.[119] Less acidic molecules, such as thiourea **17**, are able to activate TBHP at only 1 mol% loading for the highly chemoselective oxidation of sulfides to sulfoxides (Scheme 12).[120]



Scheme 12

Alkyl, aryl, and functionalized sulfides are converted into sulfoxides in good-to-high yield at room temperature. The diastereoselectivity observed in the oxidation of 2-phenyl-dithiane and dithiolane is comparable to that reported in metal-catalyzed oxidations. Thioureas, including recoverable fluorous derivatives and other organic promoters such as N-formyl proline, have been reported to efficiently activate TBHP[121] and H_2O_2[122–123] for the same process under mild reaction conditions.

Flavins/H_2O_2 systems are known to effect sulfoxidation via the *in situ* formation of an intermediate hydroperoxide of type **19** (Scheme 13).[124]



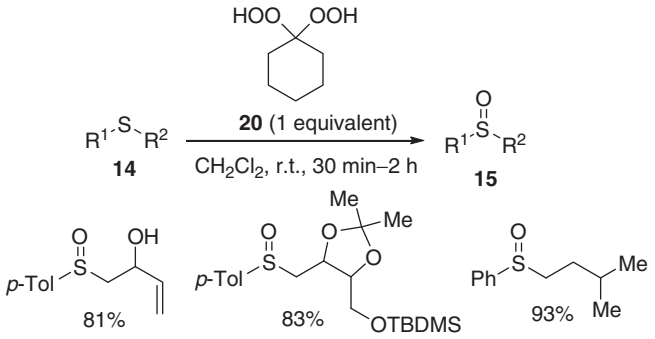
Scheme 13

Kinetic studies showed that the flavin hydroperoxides are up to 10 times[4] more reactive than H_2O_2 in the highly chemoselective and effective oxidation of alkyl aryl and dialkyl sulfides to sulfoxides also bearing sensitive functional groups. The reaction is generally carried out in methanol at room temperature with less than 2 mol% of flavin precursor **18** and 1.75 equivalents of H_2O_2. Electron-withdrawing groups on the aromatic ring of the hydroperoxide is beneficial for the stability of the flavin derivatives, which undergo oxidation to the real oxidant **19** during the catalytic cycle. Flavin catalysts immobilized onto ionic liquids have been developed showing a good recyclability of the catalyst up to seven times.[125] Amphiphilic flavinium salts in micellar systems are also applicable in the sulfoxidation using hydrogen peroxide as the terminal oxidant.[126] Moreover, synthetic flavins

have been reported as catalysts for the oxidation of sulfides in water with the assistance of ascorbic acid as a reductant with molecular oxygen as terminal oxidant.[127] Alternatively, the photooxidation of sulfides under dioxygen atmosphere with coenzyme NAD^+ type derivatives as catalysts is a feasible oxidative process.[128] The oxidation is chemoselective, although aromatic sulfides bearing electron-withdrawing groups are rarely converted into the product. Trimethylsilyl chloride has been reported as an activator of H_2O_2 in the oxidation of a variety of sulfides to sulfoxides. Under stoichiometric loadings of TMSCl, fast and complete oxidation of functionalized sulfides occurs in acetonitrile at room temperature.[129]

Hydroperoxy sultams, derived from the oxidation of isothiazolium salts[130] and 3-hydroperoxy-4,4,5,5-tetramethyl-3-phenyl-1,2-dioxolane,[131] are stoichiometric recyclable hydroperoxides used for the chemoselective oxidation of a variety of sulfides including acid-sensitive sulfides, such as allylic sulfides at room temperature in the absence of any additive. Their activity is superior to that observed by TBHP and H_2O_2 under the same conditions.

Cyclohexylidene bishydroperoxide **20**,[132] easily obtained from cyclohexanone, and similar derivatives[133] are successfully used as safe and stable reagents for the chemoselective oxidation of sulfides to sulfoxides (**Scheme 14**).

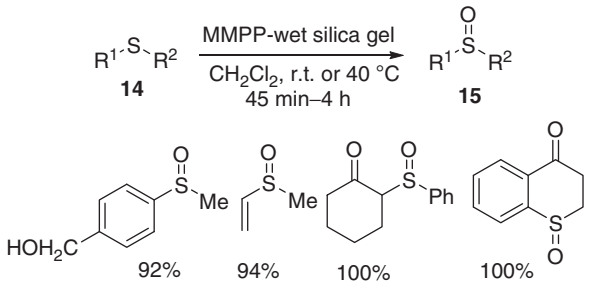


Scheme 14

Sulfoxides bearing sensitive groups are isolated in good-to-high yield within short reaction times.

Organic peracids are stronger oxidants than H_2O_2 and alkyl hydroperoxides, and hence less selective reagents to apply in the sulfide oxidation. The readily available MCPBA is often used at stoichiometric loading and controlled temperatures ($T \leq 0\ ^\circ C$) to minimize over-oxidation to sulfone and to preserve other acid-sensitive groups on the starting material.

Inexpensive and easily available monoperoxyphthalate (MMPP) has been known as a suitable reagent for the oxidation of sulfides to sulfoxides since the 1980s.[134] However, severe limitations prevented its employment, including the necessity of protic solvents for solubility reasons and the low chemoselectivity when carbon–carbon double bonds and carbonyl groups are present on the sulfide. The applicability of this reagent has been markedly improved by using wet silica gel as solid support in dichloromethane as solvent.[135] This practical system enables the isolation, after filtration, of different types of sulfoxides in excellent yield and chemoselectivity (**Scheme 15**).



Scheme 15

A convenient system for the oxidation of sulfides either to sulfoxides **15** or to sulfones **16** relies on the use of a catalytic loading of borax (10 mol %) and H_2O_2 as terminal oxidant in methanol as solvent.[136] The effective oxidants are peroxoborate species and the major advantages of this system are the recyclability of the catalyst and the relatively large volume of sulfide (5 g) that can be converted. Inorganic peroxides, such as sodium percarbonate and sodium perborate under solvent-free conditions or in water, respectively, work well as convenient oxidants of sulfides to sulfoxide or to sulfone.[137] Easy-to-handle, stable, and commercially available oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) has also been reported to effect the oxidation of sulfide to sulfoxides when working in ethanol as solvent or in the absence of any solvent by mechanical milling.[138] Sulfones are obtained employing water as medium.

Similarly to hydrogen peroxide, dioxygen is an advantageous oxidant from an economic and environmental point of view. Dioxygen, in the triplet ground state, has been used with N-hydroxyphthalimide (NHPI) as catalyst in the presence of an excess of

cyclohexanol in benzonitrile at 90 °C for the oxidation of sulfides to sulfoxides. The suggested oxidant derives from an NHPI-mediated radical oxidation of the alcohol to give the α-hydroxy hydroperoxide. Aromatic sulfides, bearing electron-withdrawing groups, are not converted into the product and lower yields are observed for sterically hindered sulfides.[139] *N*-hydroxysuccinimide (NHS) is similarly used in excess as promoter with H_2O_2 to generate the postulated α-hydroxy hydroperoxide as the oxidant for the chemoselective oxidation of spirolactone-related sulfides to sulfoxides.[140]

Mesoporous graphitic carbon nitride has been used as a heterogeneous photocatalyst for the oxidation of sulfides to sulfoxides with dioxygen in combination with an aldehyde under visible light irradiation.[141] Singlet dioxygen in ionic liquids provides fast oxidation of methyl phenyl sulfide likely via persulfoxide intermediate formation, although a mixture of various compounds is obtained when using common solvents.[142] A nafion membrane doped with a lead ruthenate pyrochlore catalyst and a ruthenium-based photosensitizer has been used for the chemoselective oxidation of methyl aryl sulfides to sulfoxides with dioxygen under 500 W halogen lamp irradiation and acidic conditions.[143] This heterogeneous system is able to generate H_2O_2 as the effective oxidant.

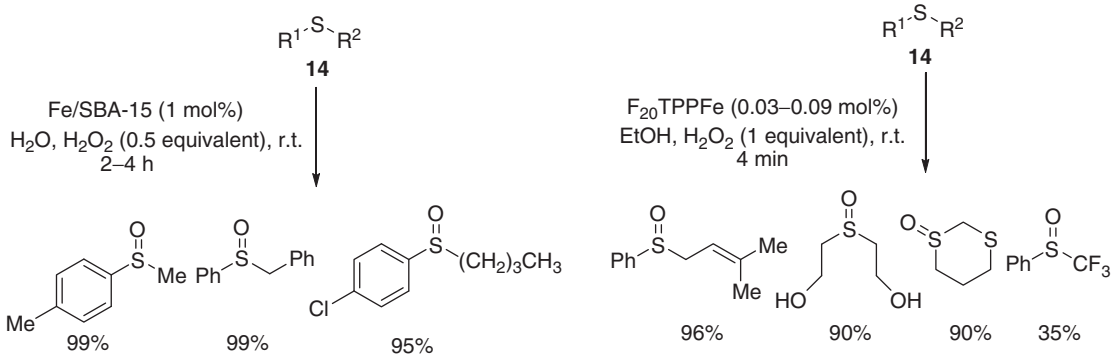
7.28.2.3.1.2 By hydrogen peroxide, peroxides, and dioxygen under metal conditions

Several metal salts and complexes are known to activate H_2O_2.[46b,107c] More recently, novel metal sources have been demonstrated to be useful activators and more convenient and environmentally friendly protocols have been developed by improving previous catalysts. As a general trend, good-to-high chemoselectivity to sulfoxides is observed in the metal-catalyzed oxidations. However, excess of the oxidant is often sufficient to obtain sulfones as the exclusive products.

Recyclable immobilized $VO(acac)_2$,[144] vanadyl phosphonates,[145] and other vanadium complexes onto different supports or unsupported tantalum(V) and niobium(V) complexes catalyze the chemoselective oxidation of sulfides to sulfoxides using H_2O_2 or TBHP in different solvents, including water.[146] Good-to-high efficiency has been observed by reuse of the supported catalyst for various oxidative cycles. However, in some examples significant leaching of the metal complex into the solution has been detected. The production of sulfones can also be achieved under modified conditions, and when using tantalum-and niobium-catalyzed oxidations either sulfoxides or sulfones are selectively produced.[146c–e]

Heterogeneous Ti-doped zeolites, silicalites, and Ti-complexed ionic liquids have been used to promote the oxidation of sulfides to sulfoxides or sulfones in the presence of H_2O_2, UHP, or TBHP.[147] According to the pore size of the channels, the oxidation of sterically more demanding sulfides is not observed, demonstrating that the process largely occurs inside the channels. Different Ti(IV)-based complexes,[148] solids,[149] and Mo- based complexes,[150] oxides,[151] and $ZrCl_4$[152] can provide the oxidation of sulfides to sulfoxides with good-to-high chemoselectivity and tolerance of functional groups on the sulfide in the presence of H_2O_2 or TBHP. Peroxo complexes of tungsten[153] and recoverable tungstate-based catalysts[154] are active in the oxidation of sulfides to sulfoxides or to sulfones employing H_2O_2 as terminal oxidant. Aryl, alkyl, cyclic, and heteroaromatic sulfides are efficiently converted into either sulfoxides or sulfones by employing 0.1 mol% of selenium-containing dinuclear peroxotungstate and H_2O_2 as oxidant.[155]

Several additional transition metal-based methods are useful for the catalytic oxidation of sulfides to sulfoxides with different oxygen donors such as Cr(III),[156] Co(II),[157] Au(III),[158] Cu(II),[159] Mn(III),[160] and Re(IV) complexes.[161] In view of the environmental and economic concerns, oxidation reactions of sulfides to sulfoxides catalyzed by cheap and nontoxic iron-based catalysts appears to be particularly attractive. Fe(III) oxide nanoparticles, supported on mesoporous silica-type materials (SBA-15), provide a clean and complete oxidation of aryl alkyl sulfides to sulfoxides in water with H_2O_2 as terminal oxidant at room temperature (Scheme 16).[162]



Scheme 16

Negligible leaching of the metal is observed and the heterogeneous catalyst, recovered after filtration, can be used for up to eight cycles of oxidation with the same efficiency.

Commercially available iron tetrakis-(pentafluorophenyl)porphyrin ($F_{20}TPPFe$) is a highly effective catalyst at low loading in the chemoselective and rapid oxidation of sulfides to sulfoxides in ethanol with H_2O_2 as terminal oxidant at room temperature (Scheme 16).[163] The method has wide scope and different functional groups are tolerated on the starting sulfide, although the catalytic activity is strongly reduced when an electron-withdrawing group is directly bonded to the sulfur atom. Sulfones can also be prepared under slightly modified reaction conditions. A convenient and chemoselective oxidation of dialkyl and alkyl aryl

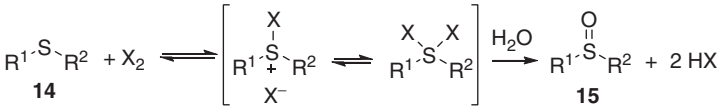
sulfides can be accomplished by using 1 mol% of readily available $Fe(acac)_2$ in polyethylene glycol under dioxygen atmosphere at 100 °C. Fe(IV)-oxo species are supposed to be involved in the oxidation.[164]

Ni(II)-complexes of perflourinated 1,3-diketones have been used in the presence of an excess of isobutyraldehyde under dioxygen atmosphere in the oxidation of representative alkyl and aryl sulfides to either sulfoxides or sulfones in perfluorinated solvents. The products are isolated by simple phase separation and the recyclability of the metal catalyst has been studied.[165]

Polyoxometallates such as $H_5PV_2Mo_{10}O_{40}$ are known to oxidize sulfides to sulfoxides at different dioxygen pressures and reaction temperatures (up to 110 °C) in various media.[166] The chemoselectivity is variable, as mixtures of sulfoxides and sulfones are generally obtained. The catalysts are recycled and applied for different oxidative runs.

7.28.2.3.1.3 By halogens and halogen-containing compounds

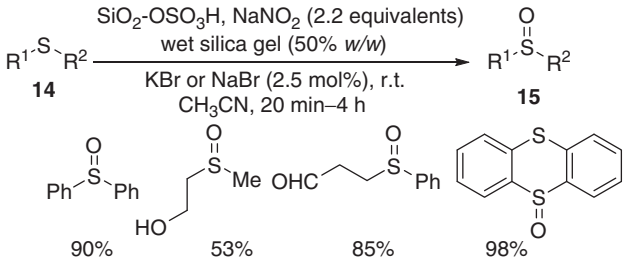
Molecular halogens are known to form halosulfonium salts with organic sulfides, which in the presence of water are hydrolyzed to sulfoxides (Scheme 17).[46b,167]



Scheme 17

Side reactions occur when using these reagents and sulfonic or sulfinic acid byproducts are observed. Halogenations of the aromatic residues and cleavage of the C–S bond are competitive reactions.[168] The acid released in the hydrolysis to sulfoxide **15** is thought to be responsible for the side reactions. The addition of basic additives[169] or working under two-phase basic conditions can partially prevent some of these drawbacks as reported when using Br_2 and H_2O_2 in a two-phase system (CH_2Cl_2/H_2O). Whereas dialkyl sulfides are converted into sulfoxides, the aryl alkyl sulfides afford the sulfoxide contaminated with the brominated sulfide and other side products. Less reactive diaryl sulfides are not converted into sulfoxides under these conditions.[170]

Molecular bromine on hydrated silica gel is a practical solution to eliminate HBr produced during the oxidation of sulfides, affording the sulfoxides chemoselectively in moderate-to-high yield.[171] Silica sulfuric acid and sodium nitrite in the presence of catalytic amounts of KBr or NaBr and wet SiO_2 in acetonitrile is a mild system for the oxidation of a wide range of sulfides to sulfoxides. Products **15** are chemoselectively obtained in moderate-to-high yield (Scheme 18).[172] The generation of a bromosulfonium ion intermediate, undergoing hydrolysis to the sulfoxide, has been proposed.



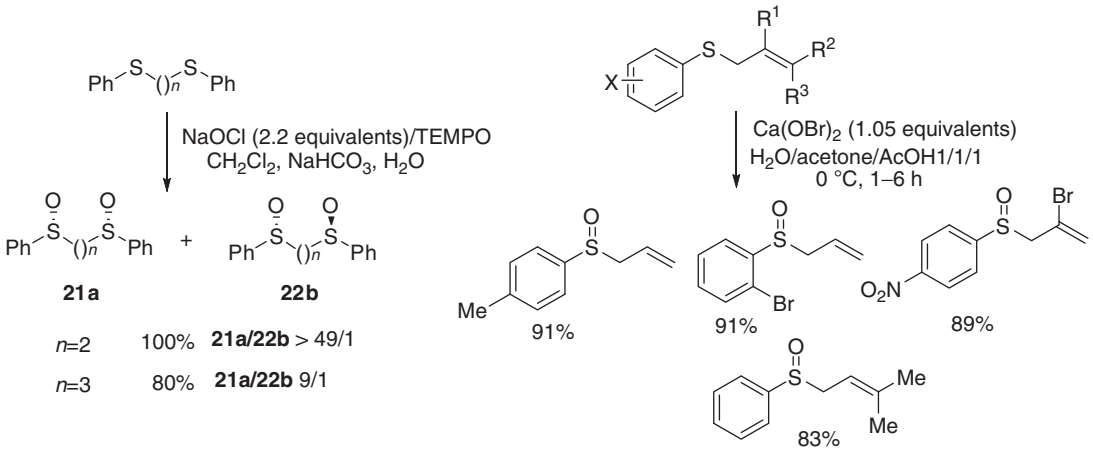
Scheme 18

An efficient and selective oxidation of sulfides to sulfoxides is attainable by using the $Br_2/NaNO_2/H_2O/O_2$ system working in acetonitrile at room temperature.[173] Cetyltrimethylammonium tribromide (CTMATB) is a stoichiometric reagent to be used in mixed acetonitrile-water to selectively oxidize sulfides to sulfoxides without affecting hydroxy or acetate groups.[174] The HgO-I_2 system accomplishes the oxidation of more reactive dialkyl and aryl alkyl sulfides to sulfoxides in dichloromethane.[175] Aqueous solutions of chlorine dioxide can be used for the chemoselective synthesis of γ-oxo sulfoxides in moderate-to-good yield.[176]

Active halogen sources such as NCS or *N*-bromosuccinimide (NBS),[177] *N*-chloroacetamide (NCA),[178] chloramines,[179] and bromamines[180] are well-known reagents for the oxidation of sulfides to sulfoxides. More recently, 4,4-dibromo-3-methylpyrazol-5-one in acetic acid,[181] TCCA[182] in acetonitrile-dichloromethane-pyridine, and NBS/β-cyclodextrin[183] in water mixture have been reported to selectively oxidize sulfides to sulfoxides in good-to-high yield.

Aryl, cyclic, and vinyl sulfides are converted into sulfoxides by NaClO in various solvents, although the oxidation of dialkyl sulfides is unselective and sulfone is also significantly formed.[184] The selectivity of this reagent is affected by the pH of the solution, with the HClO being able to effect the oxidation of sulfides in organic media.[185] A practical application of easily available NaClO oxidant has been developed under phase-transfer conditions. Interestingly, the process enables a stereoselective oxidation of bis-(phenylthio)alkanes to meso-bis-sulfoxides **21** in high yield (Scheme 19).[186] Oxidation of sulfides with tert-butyl hypochlorite (tBuOCl) serves to prepare cyclic or acyclic sulfoxides[187] and it has been reported to provide sulfoxides in a stereoselective manner.[188] However, propargyl or (methoxycarbonyl)methyl sulfides react with tBuOCl in an alcoholic solvent to

give the corresponding α-alkoxy sulfides rather than the sulfoxides.[189] Easy-to-handle calcium hypochlorite has been used with moist alumina to conveniently accomplish the chemoselective oxidation of sulfides to sulfoxides bearing various functional groups, such as carbonyl groups in aldehydes and ketones, nitriles, halides, ethers, hydroxyls, olefinic, and allylic double bonds.[190] Under controlled reaction conditions, $Ca(OBr)_2$ serves as an effective oxidizing agent for the selective oxidation of differently substituted allylic sulfides to the sulfoxides in high yield without observing bromination of the aromatic ring or oxidation of the C–C double bond to give epoxides or halohydrins (**Scheme 19**).[191]

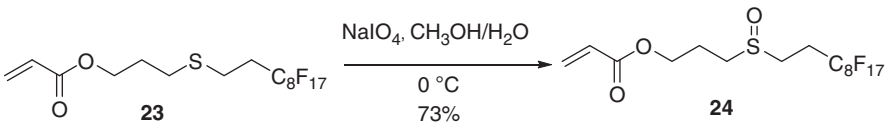


Scheme 19

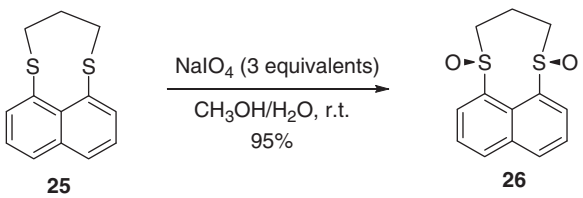
Sodium chlorite $NaClO_2$ in the presence of catalytic loading of a (salen)manganese(III) complex and alumina[192] or sodium bromite, especially in the presence of inorganic support materials,[193] such as aluminas, zeolites, silica gel, and clays, are useful reagents in the chemoselective oxidation of sulfides to sulfoxides. $NaBrO_3$-$Mg(HSO_4)_2$ in acetonitrile or under solvent-free conditions accomplishes the oxidation of alkyl aryl sulfides to sulfoxides in good-to-high yield.[194]

Periodic acid HIO_4, periodic acid hydrate (H_5IO_6),[195] and aqueous HIO_3[196] have been applied with success in the oxidation of sulfides to the corresponding sulfoxides, although the latter cannot be used in case of unsaturated sulfides as the starting compounds. Sodium periodate is the most representative reagent among the periodates to employ in the oxidation of sulfides to sulfoxides. The reactions are generally carried out in water/methanol mixture under a stoichiometric amount of the oxidant and temperature-controlled conditions to avoid sulfone formation. The oxidation of fluoroalkylsulfenyl acrylate **23** with $NaIO_4$ furnishes the corresponding sulfoxide **24** in good yield as a monomer for synthesis of water- and oil-repellent polymers (equation 6).[197] The oxidation of naphtho[1,8-b,c]-1,5-dithiocin **25** with an excess of $NaIO_4$ at room temperature results in the selective formation of the cis-1,5-disulfoxide **26** in high yield (equation 7).[198] Potentially active cardiac modulator and antifungal agent **28** has been obtained in fairly good yield by oxidation of the corresponding methylsulfinylalkanoic acid **27** with $NaIO_4$ (equation 8).[199] A range of alkyl aryl and dialkyl sulfides are rapidly converted into sulfoxides without traces of sulfone, by adsorbing the sulfides on wet silica-supported $NaIO_4$ and exposing the mixture to microwave irradiation.[200] Working with an excess of the supported oxidant leads to the formation in good-to-high yield of the corresponding sulfones.

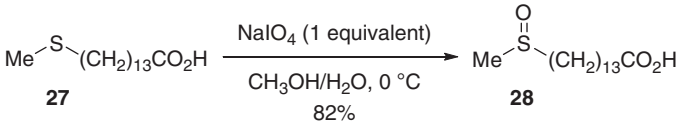
Tetrabutylammonium periodate (TBAPI) is an effective oxidant in organic solvents with the advantage of easy purification of sulfoxides by simple silica gel filtration.[201] TBAPI supported on clays[202] and a TBAPI/$AlCl_3$ mixture[203] are other modified systems suitable for the oxidation of typical sulfides to sulfoxides, although the former is more effective.



(6)

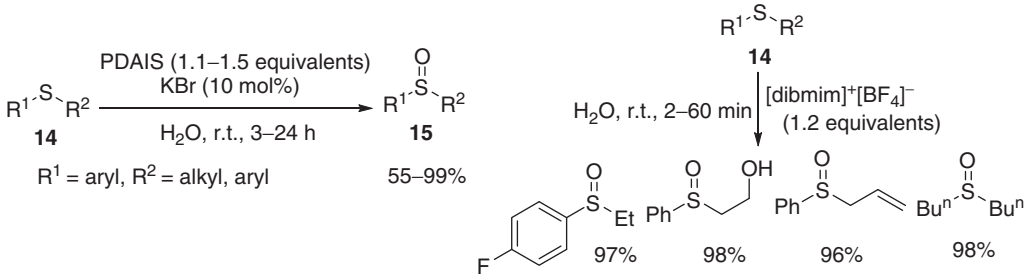


(7)



(8)

Low-toxic and easy-to-handle hypervalent iodine(III) reagents have been extensively used in the oxidation of organic compounds.[204] Iodosobenzene ($C_6H_5I{=}O$) needs to be activated with Lewis acidic additives to provide the oxidation of sulfides to sulfoxides. Numerous hypervalent iodine (III) reagents can be used in the oxidation of sulfides to sulfoxides in different media, such as $C_6H_5I{=}O$-$(RCO)_2$,[205] $C_6H_5I{=}O$-C_6H_5SeOOH,[206] $C_6H_5I{=}O$-metalloporphyrin of Fe(III), and Mn(III) complexes.[207] The latter systems are less selective as over-oxidation to the corresponding sulfone and C–S bond-cleavage are observed. However, improvements have been observed with silica gel-supported systems.[208] $C_6H_5I{=}O$-metallosalen,[209] $C_6H_5I{=}O$-clays,[210] alumina-supported iodobenzene diacetate [$PhI(OAc)_2$, PIDA],[211] $C_6H_5IOTsOH$,[212] and $C_6H_5I{=}O$-cetyltrimethylammonium bromide (CTAB)[213] have also been reported. An environmentally friendly process has been developed by employing poly(diacetoxyiodo)styrene (PDAIS) in the presence of catalytic loadings of KBr in water as solvent. The oxidation of alkyl aryl sulfides to sulfoxides smoothly proceeds in a chemoselective manner (Scheme 20).[214] After filtration of the reaction mixture, the iodinated resin can be recycled.

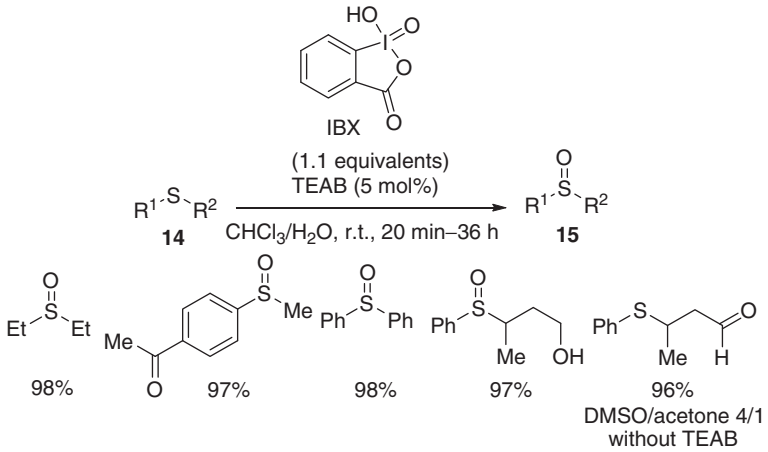


Scheme 20

An ion-supported hypervalent iodine reagent $[dibmim]^+[BF_4]^-$ is efficiently used in water to selectively oxidize a variety of sulfides bearing different functional groups to sulfoxides in short reaction times (Scheme 20).[215] The sulfoxides are extracted with diethyl ether and the ion-supported iodobenzene precipitate can be easily recovered by filtration.

In situ prepared iodobenzene dichloride $C_6H_5ICl_2$ converts aliphatic, aromatic, or heterocyclic sulfides to sulfoxides.[216] Interestingly, an excess of the oxidant leads to the α-halogenation of the aliphatic sulfoxides, instead of over-oxidation to sulfone. *o*-Iodosylbenzoic acid in the presence of acid additives and 1-(tert-butylperoxy)-1,2-benziodoxol-3(1H)-one [(tert-butylperoxy)-iodane] are efficient oxidants of various sulfides to sulfoxides.[217]

Among the hypervalent iodine(V) reagents, iodoxybenzene ($C_6H_5IO_2$) and other derivatives are used with Brønsted or Lewis acid as additives in the oxidation of sulfides to sulfoxides, although the process sometimes appears to be unselective.[218] An efficient, chemoselective, and rapid procedure for the oxidation of sulfides bearing different functional groups is mediated by *o*-iodoxybenzoic acid (IBX) as the oxidant in the presence of catalytic amounts of tetraethylammonium bromide (TEAB) (Scheme 21).[219]



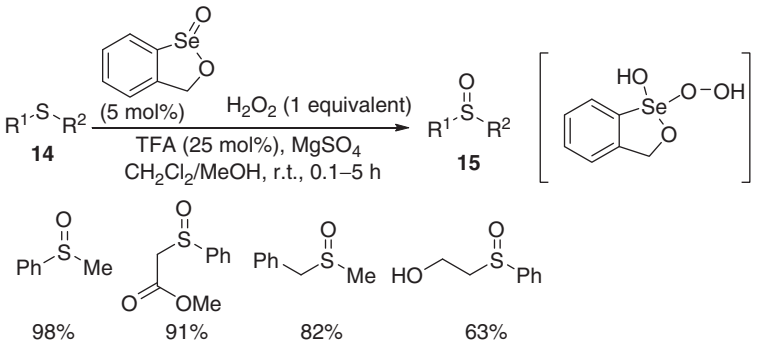
Scheme 21

The chemoselectivity is completely shifted from sulfide to alcohol oxidation by changing the solvent.

7.28.2.3.1.4 By other chemical reagents and other methods

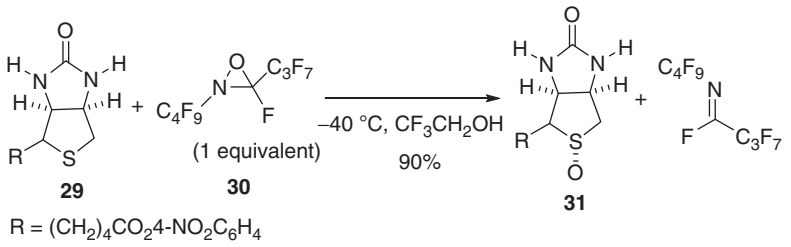
Other chemical reagents are useful for the selective oxidation of simple and functionalized sulfides to the corresponding sulfoxides, such as nitric acid,[220] nitronium salts,[221] N_2O_4 absorbed on charcoal,[87] CAN on hydrated silica gel,[222] NaOCl/succinimide,[223] cerium (IV) triflate/H_2O_2,[224] thallium(III) nitrate,[225] bismuth(III) nitrate,[226] $BiBr_3$-$Bi(NO_3)_3 \cdot 5H_2O$,[227] $POCl_3/H_2O_2$[228] triflic anhydride, or trifluoroacetic anhydride(TFAA)/H_2O_2.[229] Chemoselective oxidation of sulfides to either sulfoxides or sulfones can be successfully achieved by using catalytic loadings of 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-tetrachloride (TAPC) with H_2O_2 as the terminal oxidant.[230] In most of the methods reported, *in situ* generated peroxy intermediates were suggested to be the active oxygen donors.

Different selenium compounds have been used in the sulfoxidation such as diaryl diselenides,[231] selenoxides,[232] and areneselenonic ($ArSeO_3H$) and areneseleninic acids ($ArSeO_2H$).[233] Cyclic seleninate esters, in addition to being able to catalyze the oxidation of thiols to disulfides in the presence of H_2O_2,[234] promote the chemoselective oxidation of alkyl aryl sulfides to sulfoxides in good-to-high yield via intermediate selenoperoxy species (**Scheme 22**).[235]



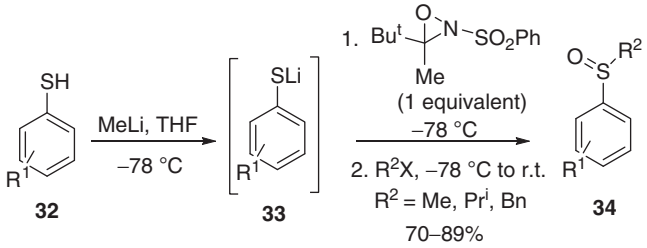
Scheme 22

N-sulfonyl aziridines, *in situ* generated by reacting imines with oxone, are known to oxidize sulfides to sulfoxides under phase-transfer conditions.[236] A perfluoro oxaziridine **30** has been reported to oxidize sulfides to sulfoxides under controlled reaction conditions in excellent yield.[237] These fluorinated oxaziridines are stronger oxidants than formerly reported *N*-sulfonyl aziridines. Biologically important sulfides such as 4-nitrophenyl ester of (+)-biotin (vitamin H) **29** (equation 9) are oxidized by oxaziridine **30** in high yield and a completely diastereoselective manner to sulfoxide **31**. When using an excess of reagent **30**, sulfones are obtained as products.



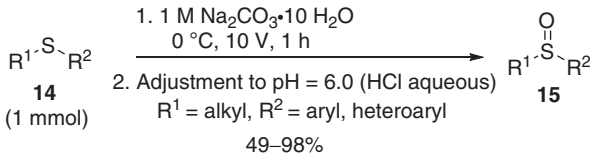
(9)

The employment of oxaziridines as reagents to obtain sulfoxides has been successfully applied in a one-pot strategy starting from aromatic thiols **32** as compounds (**Scheme 23**).[238] Highly nucleophilic thiolate anions are smoothly oxidized by *N*-sulfonyl aziridines to give sulfenate anions able to undergo S_N2 displacement with an alkyl halide to afford aryl alkyl sulfoxides **34** in good yield.



Scheme 23

Electrochemical oxidation of sulfides is not a selective process since mixtures of sulfoxide and sulfone are usually observed.[239] Moreover, products derived from Cα-H deprotonation or C–S bond cleavage are detected.[240] An undivided cell, fitted with a boron-doped diamond anode working electrode and a platinum wire cathod as the counter electrode, has been used with water, Na_2CO_3, and HCl at an applied potential to *in situ* generate NaOCl as the effective oxidant. Some alkyl aryl sulfides are chemoselectively converted into sulfoxides in good-to-high yield (Scheme 24).[241]



Scheme 24

This simple system has notable potential for scale-up applications, and the electrolyte solution can be recycled and reused with no loss in activity. Ultrasound irradiation has been applied to enhance the oxidation rate of aryl methyl sulfides to sulfoxides either by using recyclable β-cyclodextrin[242] or metal complexes[243] and H_2O_2 as the oxidant in water or methanol as solvent. The chemoselectivity is high when adding the oxidant portionwise. The presence of poly(ethyleneglycol) dimethyl ether ($PEGDME_{500}$) as recyclable reaction media has been found to be useful in ultrasound irradiation-promoted oxidation of sulfides to sulfoxides or sulfones with H_2O_2 as the oxidant.[244]

7.28.2.4 Oxidation of Sulfides and Sulfoxides to Sulfones by Chemical Reagents

The oxidation of sulfoxides usually proceeds to sulfones, although under particularly harsh conditions sulfonic acids can be isolated.[245] Sulfones are frequently obtained by direct oxidation of sulfides via the intermediate formation of sulfoxides (equation 5). Several reagents reported for the oxidation of sulfides to sulfoxides have been further exploited to obtain sulfones. In order to achieve this goal, reaction conditions have been tuned by using an excess of the oxygen source, prolonging the reaction time, or working at higher reaction temperatures in order to facilitate the second oxidation of sulfoxides to sulfones. Some of the oxidative systems used for the oxidation of sulfides to sulfones have been highlighted in the previous section: H_2O_2 under acidic conditions,[118] or in the presence of V-,[144] Ti-,[147,149b] Ta-,[146c–e] Mo-,[150,151] W-,[153–155] Re-[161] Fe-based[163]- complexes, borax,[136] sodium percarbonate,[137] $KHSO_5$ (Oxone),[89,138] oxaziridines,[236] $NaIO_4$,[199] NaOCl,[222,223] and others.[165,195,230,244] The oxidation rate of sulfoxides to sulfones with peroxy acids is lower than that of sulfides to sulfoxides as the former are less nucleophilic species than sulfides. In contrast, when using nucleophilic oxidants such as periodates and $KMnO_4$ an opposite trend is observed.

7.28.2.4.1 Oxidation of sulfides to sulfones by hydrogen peroxide, peroxides, peroxyacids, and dioxygen

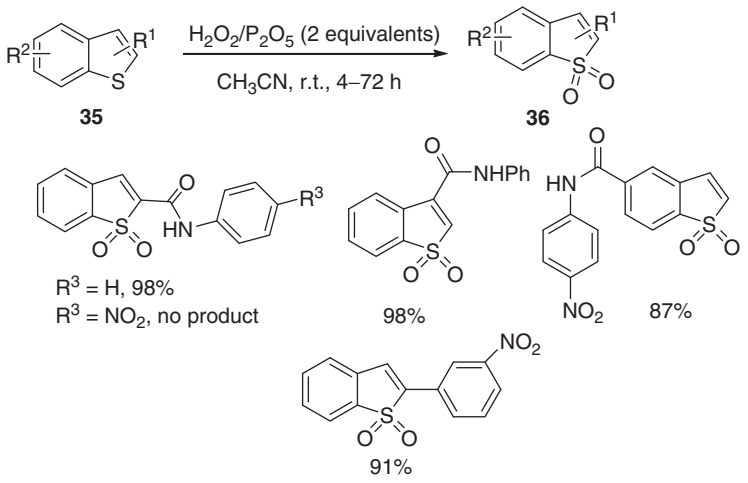
The oxidation of sulfides to sulfones, although less investigated than the oxidation of sulfides to sulfoxides, can be accomplished by a variety of oxidative systems. Sulfones are important synthetic targets due to the possibility of further manipulation and also as compounds of pharmaceutical interest.[246]

A convenient and high atom-economy oxidation of sulfides to sulfones concerns the use of H_2O_2 under solvent-free conditions at 75 °C.[247] Electron-rich and electron-poor alkyl aryl, dialkyl, heteroaryl alkyl-, and cyclic sulfides irrespective of the aggregate state are converted into the corresponding sulfones in good-to-high yield. A facile conversion of difficult-to-oxidize compounds such as benzo[b]thiophenes **35** to the corresponding sulfones has been accomplished by using the H_2O_2/P_2O_5 system in acetonitrile at room temperature (Scheme 25).

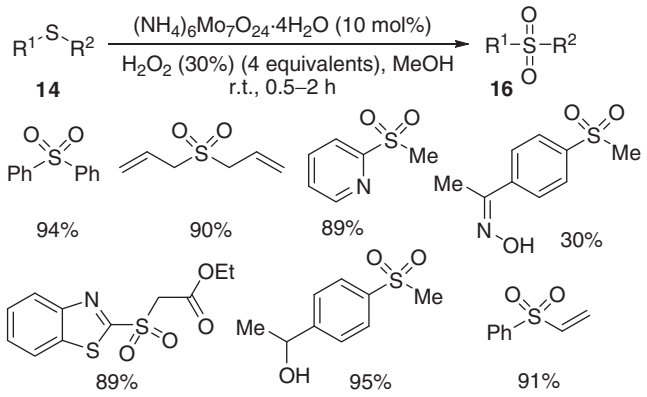
The TFAA/H_2O_2 system[229b] and dimethyl dioxirane[248] are alternative reagents for the oxidation of compounds of type **35** to sulfones or to sulfoxides, although they are less practical than the H_2O_2/P_2O_5 system. Heterogeneous systems such as SiO_2-TiO_2 mesoporous xerogels,[249] nanocrystalline TiO_2 particles,[250] Pd/Ti based nanoparticles,[251] or tetrameric titanium alkoxide/ionic liquid[252] have been successfully used with H_2O_2 in the oxidation of sulfides to sulfones. Commercially available and stable ammonium heptamolybdate catalyzes the oxidation of alkyl aryl and alkyl heteroaryl sulfides to sulfones in excellent yield with H_2O_2 as oxygen source at room temperature in methanol (Scheme 26).[253] A range of sensitive groups on the starting sulfides are tolerated. W-, V-, and Mo-containing layered double hydroxides,[254] polymeric phosphotungstate,[255] polyoxometallate type catalysts,[256] and $MnSO_4$[257] have been developed for facile oxidation of sulfides to sulfones with hydrogen peroxide or UHP as the oxidant.

Vinyl sulfones are easily obtained with high E-selectivity and yield, via the one-pot oxidative approach, reacting thiols **4** with terminal alkynes **37** under oxidative conditions employing H_2O_2 as the oxidant (Scheme 27).[258] The corresponding vinyl sulfoxides can be isolated when working at room temperature.

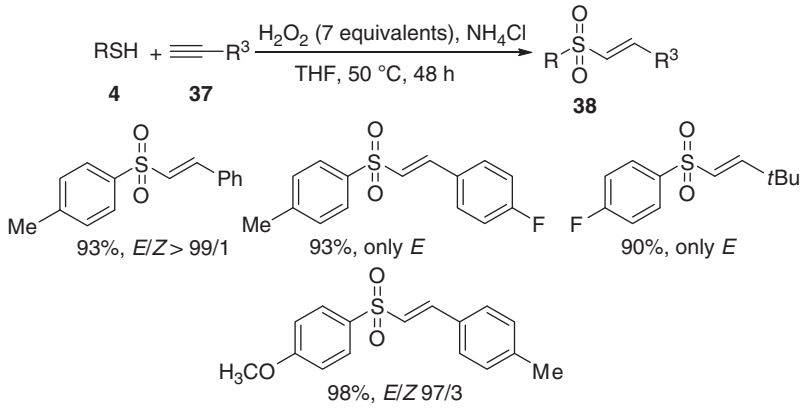
Peroxy acids such as MCPBA,[259] MMPP on hydrate silica gel,[260] silica-supported peracid in supercritical carbon dioxide under flow conditions,[261] tetrabutylammonium, and other hydrogen monopersulfates have also been used in the preparation of



Scheme 25



Scheme 26



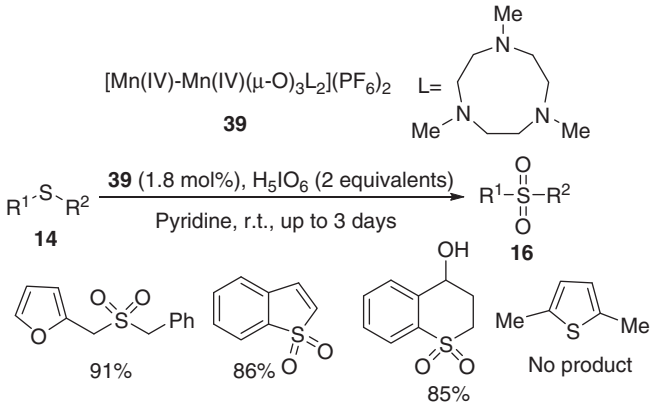
Scheme 27

sulfones from sulfides.[262] Dioxygen has been employed as the oxygen source in oxidations of sulfides to sulfones under metal[263] and metal-free conditions.[264] Cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) is a commercially available compound used at stoichiometric loading for the rapid and effective oxidation of a variety of alkyl aryl, dialky, and cyclic sulfides to sulfones in the presence of an excess of H_2O_2 as the terminal oxidant.[265]

7.28.2.4.2 Oxidation of sulfides to sulfones by halogens and halogen-containing compounds

A number of halogen-containing compounds have been developed for the chemoselective oxidation of sulfides, and NaOCl[266] and pyridine solution of $PhICl_2$[267] are among the most general to produce sulfones. However, aromatic sulfides bearing electron-withdrawing groups are not converted into sulfoxides.[46b]

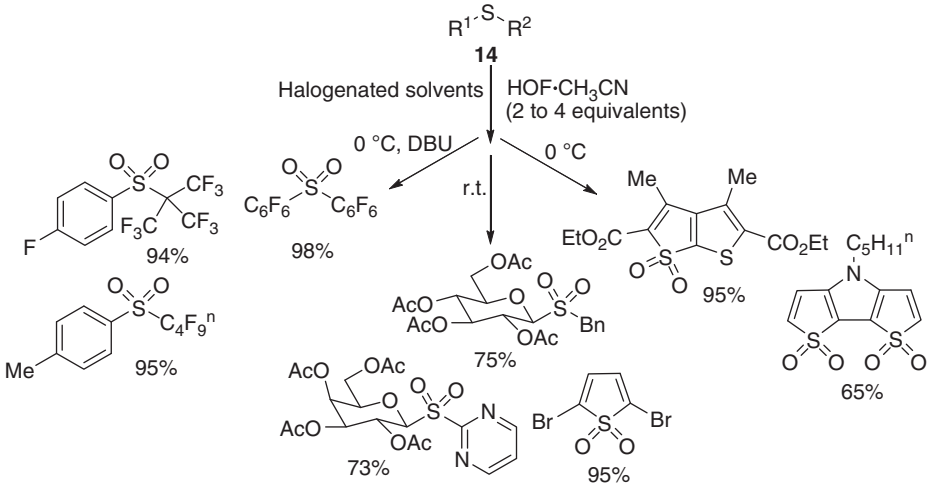
Binuclear manganese complex **39** has turned out to be useful in the catalytic oxidation of diaryl, dialkyl, and sterically hindered and less common sulfides to sulfones in the presence of H_5IO_6 as the oxidant in pyridine at room temperature (Scheme 28).[268] High chemoselectivity is observed in the presence of various sensitive functional groups in the sulfide.



Scheme 28

A variety of alkyl aryl, alkyl heteroaryl, and cyclic sulfides bearing sensitive and electron-withdrawing groups are easily oxidized to sulfone in high yield by using 3 mol% of CrO_3 and H_5IO_6 as the oxidant in acetonitrile at $-35\ ^\circ C$.[269] Polymer-micelle-incarcerated ruthenium catalysts are effective recyclable promoters for the oxidation of representative alkyl aryl and dialkyl sulfides to the corresponding sulfones with $PhI(OAc)_2$ as the oxidant.[270]

The $HOF \cdot CH_3CN$ complex, prepared by passing F_2 through aqueous acetonitrile, is a highly efficient oxygen transfer agent for a variety of transformations.[271] This strongly electrophilic oxidant, used at low temperature, is extremely useful for the synthesis of a variety of sulfones, including electron-poor sulfur derivatives and thiophenes that are difficult to oxidize by alternative reagents. The oxidations generally proceed in a few minutes and products are obtained in high yield (Scheme 29).[272]



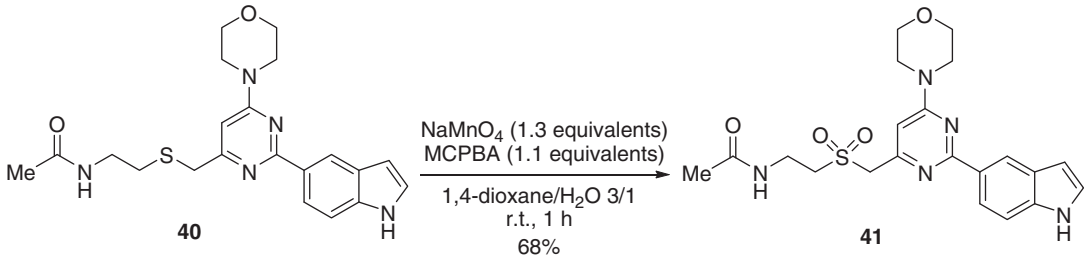
Scheme 29

Except unprotected amines, other functional groups such as hydroxyls, ketones, ethers, and aromatic rings are tolerated. Sulfoxides can eventually be isolated when working at $-75\ ^\circ C$.

7.28.2.4.3 Oxidation of sulfides to sulfones by transition metal salts and other reagents

The oxidation of alkyl aryl, dialkyl, and cyclic sulfides to sulfones can be carried out under heterogeneous or solvent-free conditions by cheap $KMnO_4$ supported on active manganese dioxide.[273] The reactions are almost complete after short reaction

time and the product can be obtained by extracting the solid mixture with an organic solvent. Ultrasonic irradiation of the solvent-free mixture further accelerates the conversion to the product. Other heterogeneous systems such as $KMnO_4$/ion exchange resin[274] and $KMnO_4/MnSO_4$ show similar performances.[275] Glycosyl sulfones are obtained under mild conditions from the corresponding sulfides by using 1–5 mol% loading of OsO_4 and an excess of *N*-methyl morpholine *N*-oxide[276] or mixtures of $KMnO_4/CuSO_4 \cdot 5H_2O$.[277] The oxidation of sulfoxides to sulfones proceeds faster than the oxidation of sulfides to sulfoxides.[278] Consequently, a satisfactory degree of selectivity for compounds bearing sulfoxide and sulfide moieties can be achieved in the oxidation by using these nucleophilic or electrophilic reagents, such as MCPBA.[46b] In this regard, the coupling of both reagents solves problems of chemoselectivity as reported in the synthesis of pharmaceutically interesting sulfones of type **41** (Scheme 30).[279]



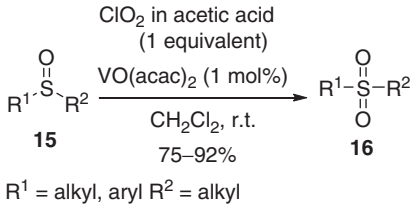
Scheme 30

The same oxidation performed with MCPBA or oxone leads to easy formation of sulfoxide intermediate, but further oxidation with these reagents is not chemoselective, as byproducts of *N*-oxidation of the pyrimidine ring are observed. Tetra *n*-propylperruthenate (TPAP) has been used at 5 mol% loading in the presence of an excess of *N*-methyl morpholine *N*-oxide as co-oxidant in acetonitrile at 40 °C to oxidize functionalized sulfides to sulfones.[280] This reagent is highly tolerant of carbon–carbon double bonds in the sulfide. Another effective system for the oxidation of a variety of sulfides, also bearing electron-withdrawing groups, to sulfones consists of 0.05 mol% of $RuCl_3$ and $NaIO_4$ (3 equivalents).[281]

In an approach similar to that reported in Scheme 23, the employment of 2 equivalents of 2-(phenylsulfonyl)-3-phenyloxaziridine enables the oxidation of aryl thiols to the corresponding sulfinate salts, via preliminary deprotonation of the thiol at −78 °C. The salts are isolated and then subjected to phase-transfer-catalyzed alkylation to give alkyl aryl sulfones in good yield.[282] Extension of the same protocol to alkyl thiols to obtain dialkyl sulfones has been reported.[283]

7.28.2.4.4 Oxidation of sulfoxides to sulfones by miscellaneous methods

In addition to the methods cited in the Section 7.28.2.4, further systems have been developed for the oxidation of sulfoxides to sulfones. Peroxide intermediates obtained when reacting KO_2 with diethyl chlorophosphate [$(EtO)_2POCl$] or 2-nitrobenzenesulfonyl chloride oxidize sulfoxides to sulfones.[284] Among the halogen-based reagents, sulfuryl chloride,[285] and bromine[286] can oxidize some sulfoxides to sulfone in aqueous solvents, although side halogen-containing products are observed, limiting their application. The $ClO_2/VO(acac)_2$ is a suitable system for the oxidation of some representative alkyl aryl and dialky sulfides to sulfones (Scheme 31).[287]

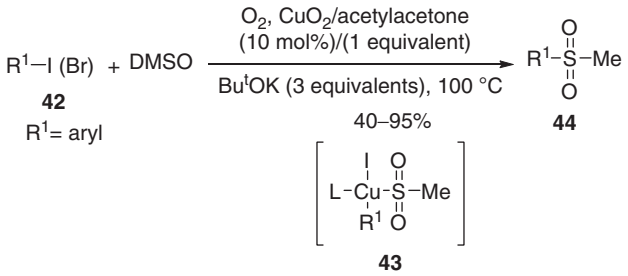


Scheme 31

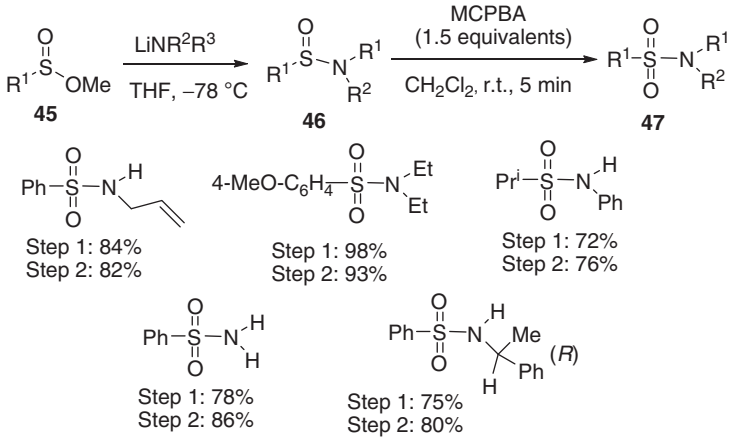
Aryl methyl sulfones **44** are obtained via CuO_2-catalyzed oxidation and cleavage/formation of carbon–sulfur bond from aryl halides and DMSO (Scheme 32).[288]

After first oxidation of DMSO to the corresponding sulfone, the reactive complex **43** has been suggested to be involved in the formation of sulfone **44**. Sulfoxides undergo photochemical oxidation to sulfones in variable yield.[289]

A mild oxidative one-pot process has been developed for the synthesis of sulfonamides starting from methyl sulfinates.[290] Primary, secondary alkyl, and aryl litium amides treated with methyl sulfinate **45** at −78 °C afford sulfinamides **46** in good yield. The crude product **46** undergoes fast oxidation with MCPBA at room temperature to sulfonamides **47** in good yield (Scheme 33).



Scheme 32



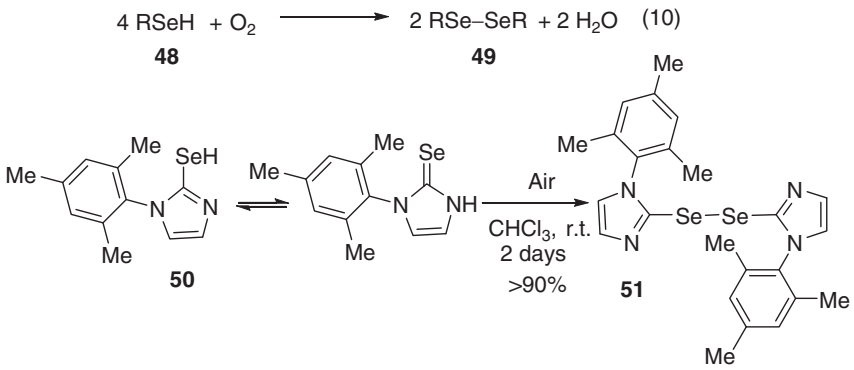
Scheme 33

Methyl pyridine-2-sulfinates are not converted into the final products **47** in appreciable yield. Primary amide equivalent, lithium hexamethyldisilazanide, is exploited for the synthesis of primary sulfonamides. *In situ* generated optically pure amides from the corresponding amines are compatible without observing appreciable racemization in the product.

7.28.3 Oxidation of Organic Selenium Compounds[291]

7.28.3.1 Oxidation of Selenols to Diselenides and Further Oxidized Species by Chemical Reagents

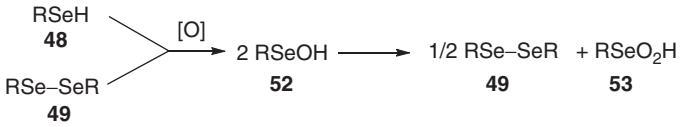
Selenols are more easily oxidized to diselenides than are thiols to disulfides (Scheme 34, equation 10). The oxidation occurs faster on alkyl selenols than on aryl counterparts under air at room temperature.[292] Given their limited stability, selenols are generally *in situ* prepared via reduction of diselenides to generate nucleophilic RSe groups or use them as reducing agents. The synthesis of diselenides **49** is carried out by bubbling dioxygen or air into the reaction vessel containing selenol **48**, as illustrated with representative derivative **50** to diselenide **51** (Scheme 34).[293] This procedure has been applied to the synthesis of optically pure bisferrocenyl diselenides.[294]



Scheme 34

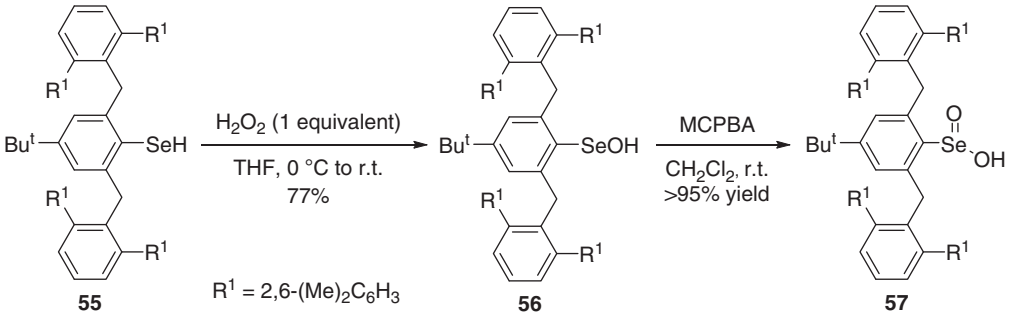
The oxidation of a variety of selenols to diselenides can be accomplished by using H_2O_2,[295] DMDO,[296] $K_3Fe(CN)_6$,[297] tris[trinitratocerium(IV)]-paraperiodate $[(NO_3)_3Ce]_3$-H_2IO_6,[298] TCCA/pyridine/benzoic acid,[299] and bipyridinium hydrobromide perbromide.[300]

Selenenic acids **52** are the products of oxidation of selenols or diselenides.[301] They are important molecules from a biological viewpoint as they are involved as intermediates in the catalytic cycle of glutathione peroxidase (GPx), a selenium-containing enzyme involved in the protection of cells by oxidative stress.[302] Selenenic acids are highly unstable compounds and they rapidly undergo a disproportionation to form the corresponding diselenides **49** and seleninic acids **53** (equation 11).



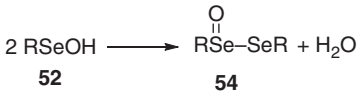
(11)

Disproportionation has been observed even for sterically demanding 2,4,6-tri-tert-butylbenzene selenenic acid.[303] Some areneselenenic acids have been observed in solution.[304] The oxidation of bowl-type substituted selenol **55** with H_2O_2 affords the selenenic acid **56**, as a stable compound (**Scheme 35**).[305]

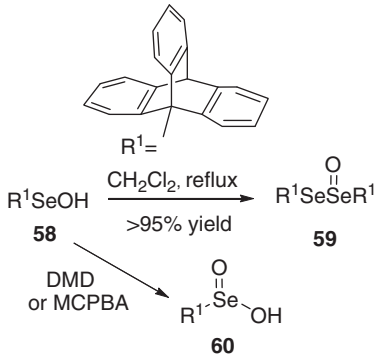


Scheme 35

The corresponding seleninic acid **57** can be obtained via oxidation with MCPBA. Alternatively, the oxidation of sterically calixarene-based alkyl selenide with MCPBA followed by thermolysis allowed the isolation of the corresponding selenenic acid.[306] This compound is further oxidized with MCPBA to the seleninic acid. Selenenic acids **52** suffer self-condensation to give selenoseleninates **54** (equation 12). On warming, selenenic acid **58** quantitatively condenses to the selenoseleninate **59** (**Scheme 36**).[296] Both DMDO and MCPBA are useful reagents for the oxidation of compound **58** to seleninic acid **60**.

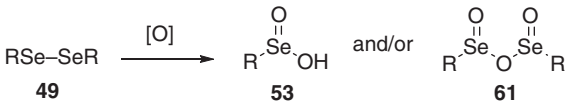


(12)



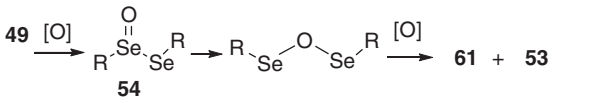
Scheme 36

The oxidation of diselenides **49** affords the formation of seleninic acids **53** and/or seleninic anhydrides **61** and it occurs in the presence of various oxidants such as $PhIO_2$,[307] TBHP,[308] H_2O_2,[304] HNO_3,[309] and ozone[310] (equation 13).

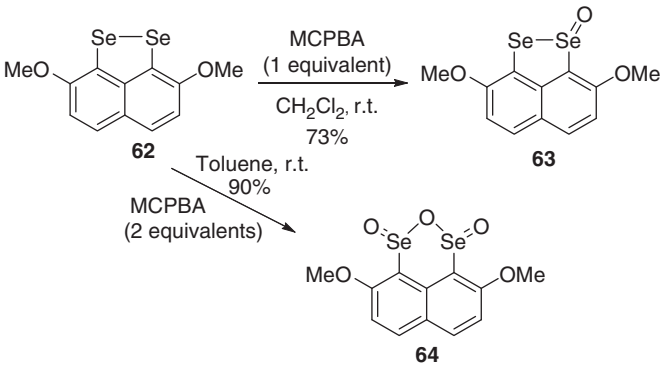


(13)

Different intermediates have been detected in the oxidation of diselenides to seleninic acids carried out with common oxidants such as H_2O_2 or MCPBA (equation 14). Selenoseleninates **54** are formed and in some examples anydrides **55** were also detected.[296,311] When using an excess of oxidant, seleninic acids **53** or anydrides **61** are obtained as observed in the oxidation of conformationally restricted naphthalene diselenide **62** with MCPBA (Scheme 37).[312]

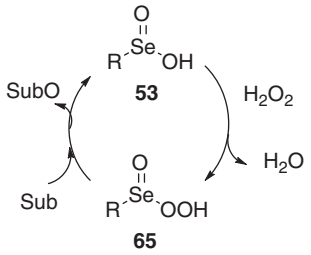


(14)



Scheme 37

Diselenides **49**, seleninic acids **53,** and seleninic anhydrides **61** are known to catalyze a number of oxidations.[233,308,313] The real oxidant involved in the catalytic cycle, when using seleninic acids as the promoter and H_2O_2 as the terminal oxidant, has been suggested to be an *in situ* generated perseleninic acid **65** (Scheme 38).



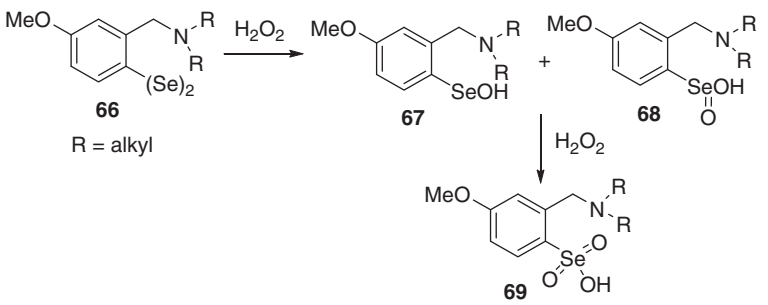
Scheme 38

The use of hydrogen peroxide as the oxidant with amine-based diselenides **66** affords mixtures of selenenic **67** and seleninic acids **68** (Scheme 39).[314] In excess of H_2O_2, the formation of selenonic acids **69** occurs, and these generally show low thermal stability and high acidity. A selective oxidation of similar selenides to seleninic acids has been reported.[315] DMDO has been successfully employed in the oxidation of biomimetic seleninic acid to the corresponding selenonate salts.[316] $KMnO_4$ is a more general reagent to synthesize selenonic acid starting from seleninic acids.[317]

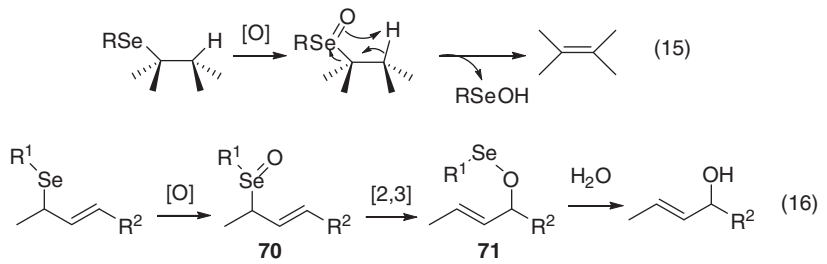
Phenylselenenyl cation ($PhSe^+$), obtained via oxidation of the corresponding diselenide with $(NH_4)_2S_2O_8$,[318] is a useful electrophilic reagent involved in the oxyselenylation of alkenes (*see* Volume 7, Chapter 7.20).[319]

7.28.3.2 Oxidation of Selenides to Selenoxides by Chemical Reagents

A variety of oxidants are suitable for the oxidation of selenides to selenoxides. When these compounds bear a β-hydrogen atom, a fast *syn*-elimination of selenenic acid occurs even at low temperature ($T < 0\ ^\circ C$) to afford alkenes and selenenic acid byproduct (Scheme 40, equation 15).



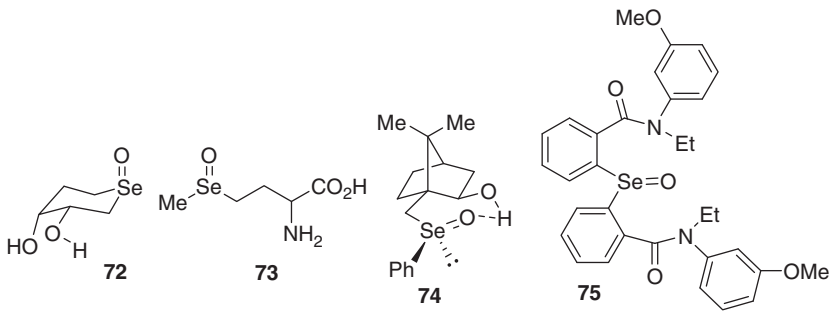
Scheme 39



Scheme 40

This sequence is frequently applied, especially for the synthesis of α,β-unsaturated carbonyl compounds. Conversely, allylic selenoxides **70** undergo [2,3]-sigmatropic rearrangement leading to a selenenic ester intermediate **71** (Scheme 40, equation 16). This product is easily hydrolized to the corresponding allylic alcohol. Numerous synthetic applications of the chemistry illustrated in Scheme 40 have been reported and these will be described in Volume 6, Chapters 6.16 and 6.18 of this series.

Selenoxides that do not bear β-hydrogen atoms, such as methyl, benzyl, vinyl, aryl selenoxides, and diaryl selenoxides, are stable compounds. In general, alkyl selenoxides are not thermally stable enough to be isolated, although in some reports they have been characterized especially when stabilized by hydrogen bonding or when bearing a β-alkoxy group.[320] Selenosugar oxide **72**,[321] biologically important selenomethionine selenoxide **73**,[322] and selenoxides of type **74** and **75** are representative examples (equation 17).[323] Compounds **74** and **75** gain additional stabilization through hydrogen bonding or intramolecular coordination of amide groups.

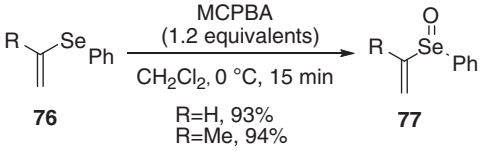


(17)

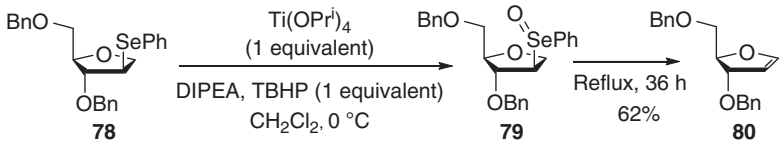
7.28.3.2.1 By peroxides, peroxyacids, DMDO, ozone, and dioxygen

The most selective and convenient reagent to oxidize selenides is the use of a stoichiometric amount of 30% H_2O_2 in THF or dichloromethane as solvent at 0 °C.[321–324] Several functional groups present in the selenide are tolerated when using this oxidant. UHP can be applied as alternative reagent.[325] Although less chemoselective, MCPBA can be successfully used in the oxidation of selenides to selenoxides under controlled conditions,[323,326] as illustrated in the case of vinyl phenyl selenides[326d] (Scheme 41).

TBHP is a suitable and mild oxidant alone[313b,327] or in the presence of metal catalysts such as $Ti(OiPr)_4$ and $VO(acac)_2$.[328] Selenoxide **79** is rapidly formed when using the stoichiometric system $Ti(OiPr)_4$/TBHP/diisopropylethylamine (DIPEA) (Scheme 42).[328b] Being particularly stable, compound **79** has to be refluxed to undergo β-elimination to glycal **80**.

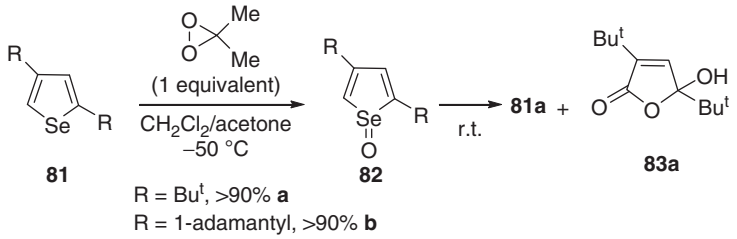


Scheme 41



Scheme 42

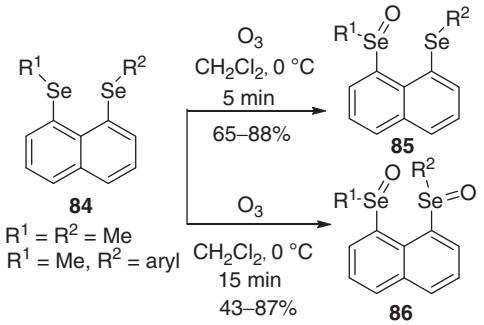
DMDO has been successfully employed in the oxidation of different sterically demanding selenophenes **81** to the corresponding selenophene 1-oxides **82** under controlled conditions (Scheme 43).[329]



Scheme 43

The stability of compound **82a** in solution at room temperature is limited, and decomposition to the starting selenide **81a**, furanone **83a**, and SeO_2 occurs on standing. Selenoxides **82** can be isolated, although they are hygroscopic and decompose on warming. The same oxidation does not lead to the formation of the expected selenoxide when using less demanding selenophenes, and instead a mixture of ring-oxidation byproducts with extrusion of the selenium atom is observed. The oxidation of sterically hindered *n*-butyl 9-triptycyl selenides, performed under similar reaction conditions, gives the intermediate selenoxide, which undergoes β-elimination at room temperature to the corresponding selelenic acid.[296]

Ozone is generally a highly chemoselective reagent to use in the facile oxidation of selenides to selenoxides.[295,330] In order to avoid oxidation of other sensitive functional groups present in the molecule and to prevent the over-oxidation to selenone, the reactions are generally performed at -78 °C. According to the reaction time, ozone enables the oxidation of bis-selenides **84** to mono- **85** or bis-selenoxides **86** working at 0 °C in CH_2Cl_2 as solvent (Scheme 44).[331]



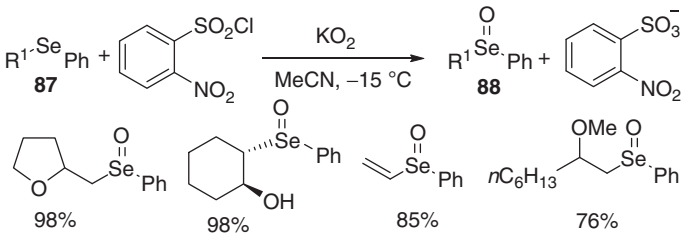
Scheme 44

The singlet dioxygen/rose bengal system in water/alcohol solutions was found to be useful for the oxidation of aryl benzyl and aryl methyl selenides to the corresponding selenoxides.[332] Similarly, selenides are also converted into selenoxides by autoxidation with dioxygen in the presence of a catalytic amount of NO_2 under acidic conditions.[333]

7.28.3.2.2 By other reagents

The oxidation of selenides has often been accomplished by using sodium metaperiodate in methanol/water mixtures or acetone/water mixtures.[295a,326a,328a,334] $KMnO_4$ in acetic acid oxidizes polyfluorinated diaryl selenides to the corresponding selenoxides in satisfactory yield.[335]

Alkyl phenyl selenoxides **88** are obtained in high yield by oxidation of the corresponding selenides **87** with 2-nitrobenzenesulfonyl chloride and potassium superoxide in acetonitrile at $-15\,^{\circ}C$ (Scheme 45).[336]

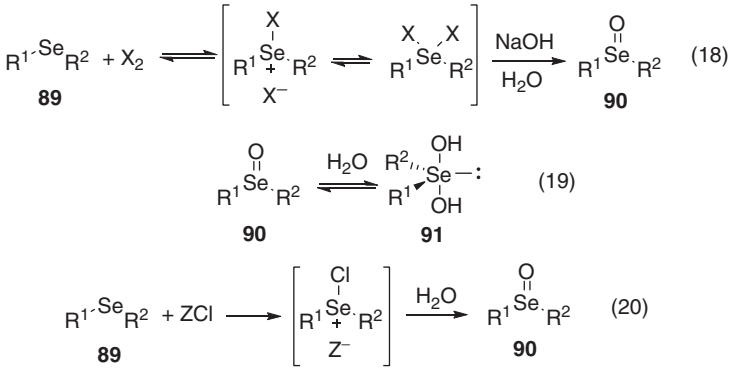


Scheme 45

The active oxidant is suggested to be the *in situ* formed 2-nitrobenzenesulfonyl peroxy intermediate.

N-4-nitrobenzenesulfonyloxaziridine chemoselectively oxidizes methyl phenyl selenide to the selenoxide in excellent yield at room temperature in halogenated solvents.[337] However, stoichiometric loading of oxaziridines and controlled reaction temperatures have to be used for chemoselectivity purposes. Soluble and recyclable polymer-supported *N*-benzenesulfonyl-3-phenyloxaziridine has been prepared and used in the oxidation of selenides, followed by β-elimination to alkenes.[338]

Oxidative addition of halogens (Cl_2, Br_2, I_2) to selenides **89** is an old reaction (Scheme 46, equation 18).[339] The corresponding dihalogen adducts are hydrolized under basic conditions to selenoxides **90**.[340] By contrast to sulfoxides, selenoxides easily add water to afford dihydroxy selenanes **91** in a dynamic equilibrium (equation 19). In some examples, both compounds **90** and the hydrates **91** have been isolated and interconverted by stirring in wet solvents.[341]



Scheme 46

The halogenation/hydrolysis/elimination procedure has been applied as an alternative approach to that reported in Scheme 40 (equation 15) for the synthesis of functionalized alkenes.[342]

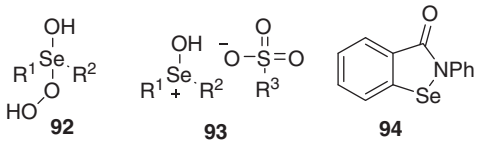
Diaryl and aryl benzyl selenides are oxidized with $PhICl_2$ at $-40\,^{\circ}C$ in aqueous pyridine to selenoxides.[334a] Other common reagents such as NCS[343] and NBS[344] oxidize functionalized selenides to the corresponding selenoxides in good yield. Hydrolysis with $NaHCO_3$/10% NaOH leads to the products. The formal oxidation step is believed to be the formation of a chloroselenonium intermediate, followed by hydrolysis (Scheme 46, equation 20). Similarly, tBuOCl can be used to prepare selenoxides, being more practical than NCS, as the byproduct formed is t-butanol.[343]

Aryl methyl and diaryl selenides, bearing electron-withdrawing groups, react with tBuOCl in acetonitrile at $-25\,^{\circ}C$ in the presence of methanol/pyridine.[345,323a] After hydrolysis, selenoxides are isolated in high yield. Diaryl selenides are converted into the selenoxide by using NaOCl supported on neutral alumina under microwave irradiation.[346] (tert-Butylperoxy)-iodinane is also an effective reagent in the oxidation of diphenyl selenide.[347] Dess–Martin periodinane rapidly oxidizes alkyl 2-pyridylselenides in halogenated solvents. Treatment of the intermediate tetravalent selenanes formed, with aqueous $NaHCO_3$, gives rise after hydrolysis and elimination to terminal alkenes.[348]

The electrochemical oxidation of benzo[b]selenophene,[349] dialkyl, and diaryl selenides in acetonitrile at various potentials gives the selenoxides, which are not stable enough under the reaction conditions to give coupling products of the oxidized material. Confirmation of the process was achieved through the isolation of the hydrate form of diaryl selenoxides.[350]

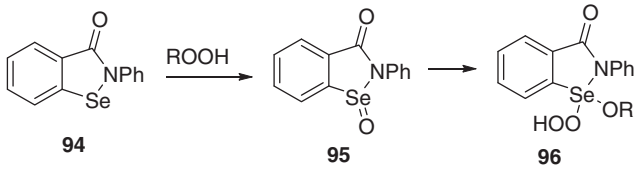
The oxidation of organoselenium acetophenones to selenoxides has recently been accomplished by phenylacetone monooxygenase (PAMO) in high yield.[334c] Interestingly, the process is highly chemoselective and the ester formation, derived from Baeyer–Villiger oxidation, is not observed.

Dialkyl and diaryl selenoxides are known as mild reagents or catalysts for the oxidation of a variety of organic compounds such as alkenes, thiols, sulfides, phosphines, amines, benzyl alcohols, and halomethylarenes.[313a,351] The formation of hydroxy perydroxy selenane of type **92** has been suggested as the active oxygen donor, when using H_2O_2 as the oxidant.[351f] Selenoxides are more basic than sulfoxides, and adducts of selenoxides with sulfonic acids **93** have been characterized and used as oxidants (Scheme 47).[352]



Scheme 47

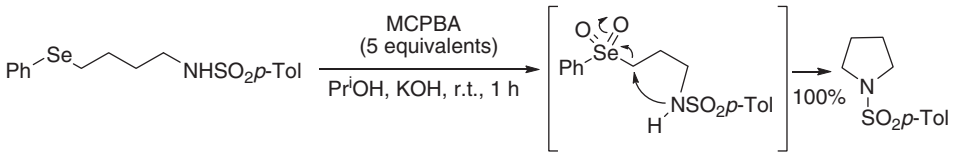
Cyclic selenenamide **94**, named ebselen, and related compounds have been intensively investigated as scavengers of radical oxygen species including peroxides having protective properties against oxidative stress in cells of various organisms, mimicking the enzymatic action of GPx.[353] Ebselen **94** and similar selenenamides promote the oxidation of different organic compounds in the presence of 30% H_2O_2 or TBHP as terminal oxidant.[334c,354] In some of these processes the formation of selenoxide **95** followed by further oxidation to hydroperoxyselenurane **96** as the active oxidant has been suggested (Scheme 48). A free radical mechanism seems to be an alternative pathway in other oxidative processes.[334c,355]



Scheme 48

7.28.3.3 Oxidation of Selenides and Selenoxides to Selenones

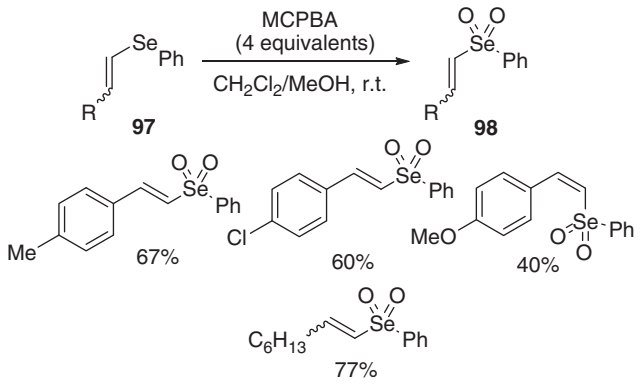
Selenones are versatile compounds employed in tandem Michael-type reactions to give cyclic products, thanks to the electron-withdrawing nature and leaving group ability of the selenone group.[356] A number of oxidants such as MCPBA, $KMnO_4$, ozone, and other peracids can oxidize with variable efficiency the selenides to the selenoxides according to the groups present in the starting selenide.[357] Reactions with milder oxidants such as H_2O_2, TBHP, and $NaIO_4$ afford selenoxides as major products. The most effective and widely used oxidant of selenides and selenoxides to selenones is MCPBA.[358] The second oxidation requires strong reaction conditions to proceed, and in alcoholic solvents the oxidation is faster than in halogenated solvents (Scheme 49).[358d] Ethereal solvents are also suitable media.[358c,f]



Scheme 49

Vinyl selenones are generally prepared in high yield by using an excess of MCPBA.[358a,b,359] The oxidation is carried out at room temperature and better yields are observed when starting from E-isomers (Scheme 50).[360] Using an excess of MCPBA

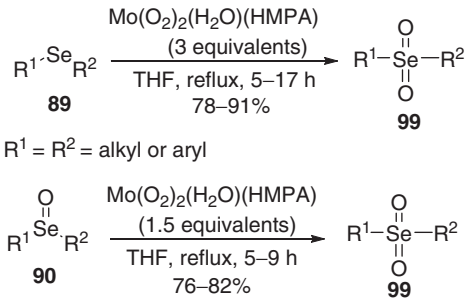
(2 to 5 equivalents) with alkyl phenyl selenides in alcoholic solvents such as methanol leads to the formation of dialkyl ethers via phenylselenonyl nucleophilic substitution.[361]



Scheme 50

Some alkyl aryl selenides are oxidized to the corresponding selenones only in the presence of a large excess of H_2O_2, since the oxidation of selenoxide to selenones is a slow process.[324d] The oxidation is easily performed in the presence of benzenseleninic acid as a stoichiometric promoter in CH_2Cl_2 or trifluoroethanol as the solvent at room temperature with a large excess of H_2O_2 (10 equivalents).[362] Different alkyl phenyl and dialkyl selenides are converted into the corresponding selenoxides in moderate-to-good yield. The active oxidant is suggested to be the perseleninic acid **65** (Scheme 38).

Oxone is a mild and convenient reagent to convert phenyl alkyl selenides to selenoxides in good to high yield, under buffered reaction conditions, in methanol at room temperature.[363] Treatment of tetraaryl-substituted selenophenes with DMDO (2 equivalents) in acetone at 0 °C leads to the clean formation of the selenophene-1,1-dioxides in good-to-high yield.[364] The isolation of the corresponding selenoxides when using 1 equivalent of DMDO was unfruitful as these compounds are labile, except in the case of benzo[b]selenophene.[365] Diaryl, alkyl aryl, and some dialkyl selenides and selenoxides are rapidly oxidized by aqueous NaClO in DMF at room temperature in satisfactory yield.[366] The same system supported on silica gel or allumina successfully provides the selenones under microwave irradiation.[346] Readily prepared peroxo complex of molybdenum $[MoO(O_2)_2(H_2O)(HMPA)]$ has been employed in the oxidation of either diaryl or dialkyl selenides to selenones by refluxing in THF. The oxidation of selenoxides requires a half molar ratio of the Mo-complex (1.5 equivalents) to proceed to selenones (Scheme 51).[367]



Scheme 51

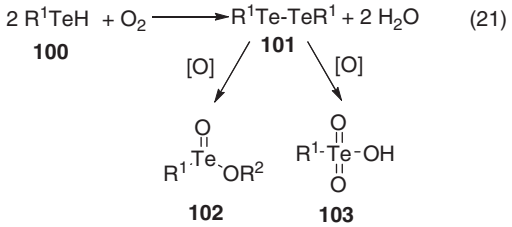
Selenoxides are unreactive with singlet dioxygen. Photooxidation of diaryl selenoxides with a stoichiometric amount of dimethyl sulfide in CH_2Cl_2 with methylene blue at 0 °C using a 300 W Xenon lamp affords the selenones in high yield.[368] The oxidation of selenoxides is indirectly mediated by the *in situ* formed persulfoxide intermediate.[142]

7.28.4 Oxidation of Organic Tellurium Compounds[291a,b,339b]

7.28.4.1 Oxidation of Tellurols to Ditellurides and Further Oxidized Species by Chemical Reagents

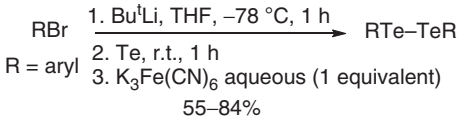
Tellurols are highly air-sensitive compounds, and due to their labile nature and thermal instability only a limited number of compounds has been isolated.[369] Tellurols are easily oxidized to ditellurides under dioxygen atmosphere, which represents the

most exploited approach to ditellurides (Scheme 52, equation 21).[370] Aryltellurols are generally prepared by *in situ* reduction of the corresponding ditellurides with $NaBH_4$ or other reducing agents[370a,371] to form the sodium tellurolates, which after acidification afford tellurols or are used for other transformations. Sterically demanding silyl tellurols have been demonstrated to be significantly more stable compounds.[372]



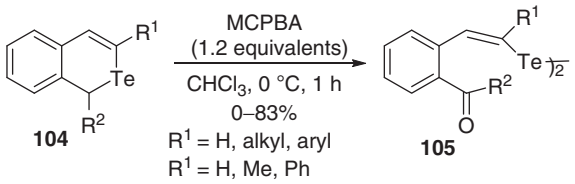
Scheme 52

An alternative reagent for the oxidation of diaryltellurols is aqueous potassium ferricyanide ($K_3Fe(CN)_6$), which enables the isolation of the corresponding ditellurides in good-to-high yield (Scheme 53).[373]



Scheme 53

A specific example of the oxidative approach to ditellurides is illustrated in the oxidation of 1-unsubstituted or 1-phenyl-1H-isotellurochromenes with MCPBA, which resulted in a ring-opening reaction to afford the corresponding *o*-formyl or benzoyl distyryl ditellurides (Scheme 54).[374]



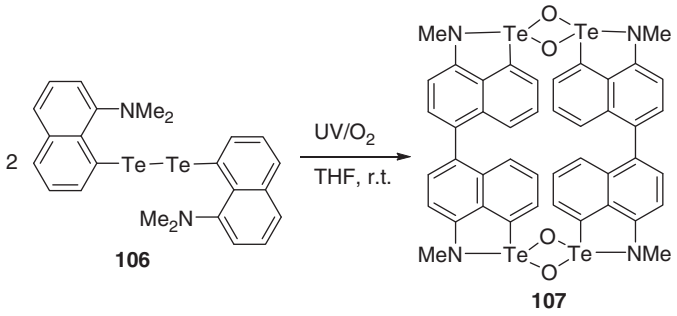
Scheme 54

Unidentified products were originally obtained when treating diaryl ditellurides with H_2O_2.[375] Diaryl ditellurides bearing chelating amino groups undergo oxidation with H_2O_2 affording diaryl ditelluronic acids **103** or cyclic ester derivatives of type **102** (Scheme 52).[376] TBHP oxidizes diaryl ditellurides to tellurinic esters **102** (Scheme 52).[377] Dialkyl ditellurides dissociatively adsorb on gold (111) surfaces to form tellurium-gold covalent bonds, which are subsequently autooxidized at room temperature, providing dialkyl ditelluride autooxidized monolayers with network structures.[378] The photooxidation of diorgano ditellurides occurs rapidly on irradiation with UV light, leading to the formation of solids, likely polymeric tellurinic acids [RTe(O)OH]n or related anhydrides. Although complex reaction mixtures are generally obtained, in the photooxidation of compound **106**, a telluroxane cluster **107** has been identified (Scheme 55).[379]

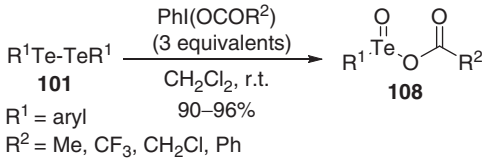
Arene tellurinic acids having bulky substituents can be obtained from the corresponding diaryl ditellurides by oxidation with ozone followed by hydrolysis.[380]

Phenyliodine(III) dicarboxylate (DIP) is a highly efficient oxidant for the oxidation of diaryl ditellurides to arene tellurinic mixed anhydrides in CH_2Cl_2 at room temperature (Scheme 56).[381]

Various organotellurium trihalides (R^1TeX_3) are obtained via oxidation of ditellurides **101** with chlorine,[382] bromide,[370c,382a,383] iodine,[382a,384] and fluorine or XeF_2[385] at room temperature.[339b,386] Under stoichiometric conditions of bromine, the tellurenyl halide (RTeX) is isolated.[387] Alternative reagents to synthesize organotellurium trichlorides are sulfuryl chloride[383a] (SO_2Cl_2) and thionyl chloride ($SOCl_2$).[382a,b] Diaryl ditellurides are oxidized by lead tetraacetate [$Pb(OAc)_4$] to give aryltellurium triacetates, which suffer easy hydrolysis.[388] Oxidation of dialkyl and diaryl ditellurides by nitrosyl salts such as NO^+X^- ($X^- = BF_4^-$, ClO_4^-, and $CF_3SO_3^-$) generates tellurenyl cations (R^1Te^+).[389] Ditellurides are effective antioxidants since they show thiol peroxidase activity in the presence of H_2O_2 as the oxidant.[390] The formation of intermediate telluroxides in these processes has been demonstrated.



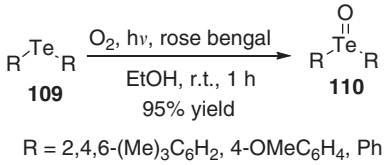
Scheme 55



Scheme 56

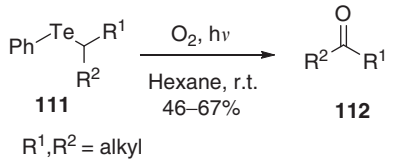
7.28.4.2 Oxidation of Tellurides to Telluroxides

The oxidation of diaryl or dibenzyl tellurides to the corresponding telluroxides with dioxygen is a slow process.[391] The same oxidation performed with singlet oxygen is an effective transformation as illustrated in the quantitative oxidation of diaryl tellurides carried out with rose bengal in ethanol at room temperature (Scheme 57).[392a]



Scheme 57

According to the reaction conditions and structure of the diaryl telluride a high conversion to the corresponding tellurone has been observed.[393] Diaryl tellurides are oxidized to dicationic Te–O–Te-bonded species by using nitrosyl tetrafluoroborate ($NOBF_4$) or the $(CF_3SO_2)_2O/O_2$ system.[394] Interestingly, functionalized alkyl aryl tellurides are easily photooxidized by sunlight to the corresponding carbonyl compounds (Scheme 58).

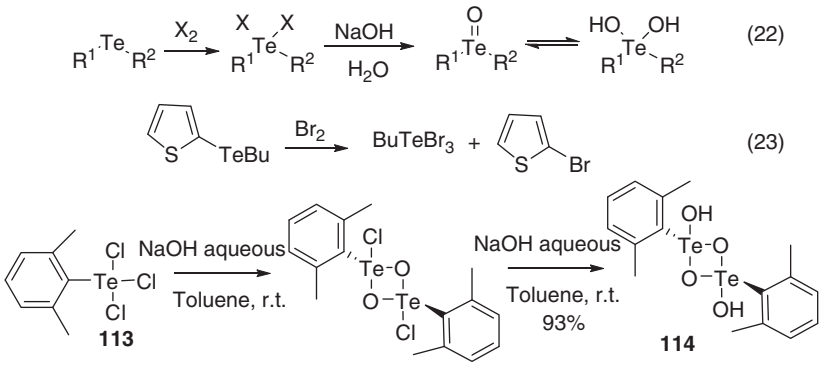


Scheme 58

Aldehydes and ketones **112** are expected to be formed by carbon radicals generated by photochemical alkyl–Te bond cleavage. Ozone has also been employed as oxidant to obtain Te-oxide dimers.[395] Dihydroxytellurane (hydrates of telluroxides) is obtained via photooxidation of tellurapyrylium dyes with singlet oxygen.[396]

Telluroxides are usually prepared via halogenation[339b,386,397] of tellurides with different common halogen sources such as Br_2, Cl_2, I_2, $SOCl_2$, and SO_2Cl_2, followed by basic hydrolysis of the corresponding diorganotellurium dihalides (equation 22, Scheme 59).[398] Telluroxides are isolable hygroscopic compounds, and in solution containing water are in equilibrium with the hydrated form (equation 22). The reaction of some alkyl aryl tellurides with dihalogens gives rise to cleavage of one of the C–Te bonds to form organotellurium trihalides, as illustrated in equation 23 (Scheme 59).[399] Organotellurium trihalide **113** is

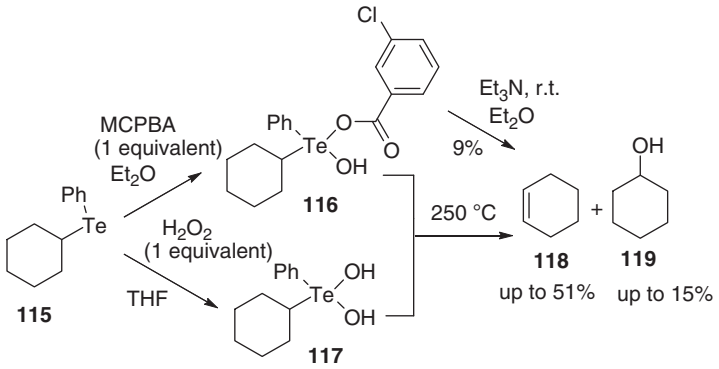
hydrolized under basic conditions to the corresponding tellurinic acid dimer **114** in a stepwise process with the formation of the acid chloride (ArTeOCl) intermediate (Scheme 59).[400] The corresponding anhydrides [$(ArTeO)_2O$] are indeed observed under mild acid hydrolysis.



Scheme 59

Basic hydrolysis of 2-phenylazophenyltellurium trihalides allowed the formation of organotellurium oxide clusters.[401] Treatment with NBS and tBuOCl followed by basic hydrolysis provides an effective oxidation of tellurides to telluroxides.[343] $NaIO_4$ has been reported to oxidize sterically encumbered diaryl tellurides to telluroxides in EtOH–water mixtures in good yield.[402]

The oxidation of various tellurides occurs in the presence of H_2O_2, TBHP, and MCPBA, and according to the structure of the starting material, telluroxides are not always isolable compounds and their identity has been confirmed after reduction of the crude reaction mixture giving back the starting reagent.[232d,390,403] *n*-Alkyl aryl telluroxides are stable compounds and alkenes are obtained via *syn*-elimination[404] of tellurenic acid (RTeOH) refluxing the mixture in a similar manner as observed for selenoxides (Scheme 40, equation 15). *sec*-Alkyl phenyl telluroxides are prone to give elimination to the corresponding alkenes under milder conditions.[405] The observed reduced ability of telluroxides to give *syn*-elimination with respect to selenoxides has been ascribed to the presence of the dihydroxytellurane form, significantly present in solution (equation 22, Scheme 59), which bears less basic oxygen to undergo the elimination process. *sec*-Alkyl phenyl telluroxides treated with MCPBA and triethyl amine as a stoichiometric additive are easily converted into alkenes in higher yield (Scheme 60).[406a]

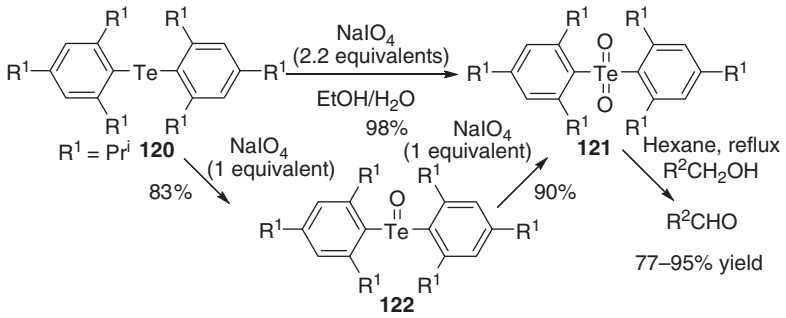


Scheme 60

The oxidation of telluride **115** proceeds with the formation of stable dihydroxytellurane **117** when using H_2O_2 as oxidant or the ester adduct **116** when using MCPBA. The pyrolysis at high temperature of compounds **116** or **117** gives cyclohexene **118** in poor-to-modest yield contaminated by cyclohexanol **118**. In the presence of Et_3N as additive, the intermediate **116** is converted faster into cyclohexene at room temperature, likely favoring the formation of the telluroxide, which then more easily eliminates to cyclohexene **118**. The geometry of the final alkenes is influenced by the nature and amount of oxidant used, and lower selectivity has been observed compared to the organoselenenium analogs.[406b] Allylic aryl tellurides after oxidation with H_2O_2, TBHP, and $NaIO_4$ undergo [2,3]-sigmatopic rearrangements of the intermediate telluroxide to give the allylic alcohol as the product, in analogy to the selenide counterparts (equation 16, Scheme 40).[407] $Pb(OAc)_4$ is a suitable oxidant of diaryl tellurides to generate diorganotellurium diacetates.[388] Diaryl and alkyl aryl tellurides behave as antioxidants, mimicking the GPx activity via telluroxides formation.[302d,403b,408]

7.28.4.3 Oxidation of Tellurides to Tellurones

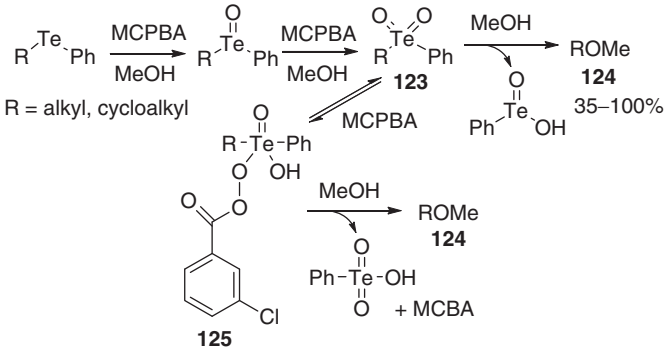
The first accurate report on the identity of a tellurone product has been illustrated in the oxidation of bis(4-methoxyphenyl) telluride perfomed with $NaIO_4$ in water/MeOH mixture at room temperature.[409] The same reagent was found to be very efficient in the oxidation of sterically hindered diaryl tellurides such as compound **120**, whose tellurone **121** was obtained in 98% yield (Scheme 61).[402]



Scheme 61

A stepwise oxidation of telluride **120** to telluroxide **122** and then to tellurone **121** proceeds efficiently by using the same oxidant. Tellurone **121** turns out to be a good reagent (2 equivalents) to oxidize benzylic, allylic, and aliphatic primary alcohols to aldehydes (Scheme 61).

Diaryl and dialkyl tellurides or telluroxides are oxidized by NaClO to the corresponding tellurones in good yield.[346,366] However, a chemoselective oxidation of tellurides to telluroxides is not feasible with this reagent, due to the rapid oxidation of telluroxides to tellurones. Diaryl tellurones can be generated by photooxidation[393] and they are *in situ* used to promote the oxidation of thiols to disulfides.[18] $[MoO(O_2)_2(H_2O)(HMPA)]$ is another useful oxidant to produce diaryl tellurones starting from either tellurides or telluroxides.[367] Similarly to the leaving group ability shown by selenones with nucleophiles (Scheme 49), alkyl aryl tellurides when treated with an excess of MCPBA (up to 5 equivalents) in alcoholic solvents at room temperature are converted into dialkyl ethers according to the mechanism illustrated in Scheme 62.[361a] Tellurone **123** evolves to product **124** by an S_N2-type reaction or, alternatively, the addition of MCPBA to tellurone gives the adduct **125**, which then eliminates telluronic acid to give the product. Organotellurium trihalides are oxidized by TBHP to unstable organotellurium oxyhalides, which decompose to organic halides as the product.[410]



Scheme 62

7.28.5 Synthesis of Enantioenriched Sulfoxides by Chemical and Biological Oxidation

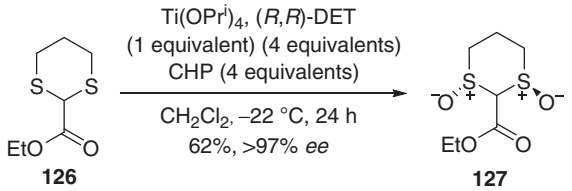
7.28.5.1 Synthesis of Enantioenriched Sulfoxides by Oxidation

Enantiomerically enriched sulfoxides are widely exploited as starting materials or versatile chiral auxiliaries in asymmetric synthesis.[411] Several effective methods are available to obtain alkyl aryl and dialkyl sulfoxides by using metal-catalyzed, organocatalyzed, and enzyme-catalyzed asymmetric oxidations of sulfides.[412]

7.28.5.1.1 Oxidation by using chiral ligand-metal complexes

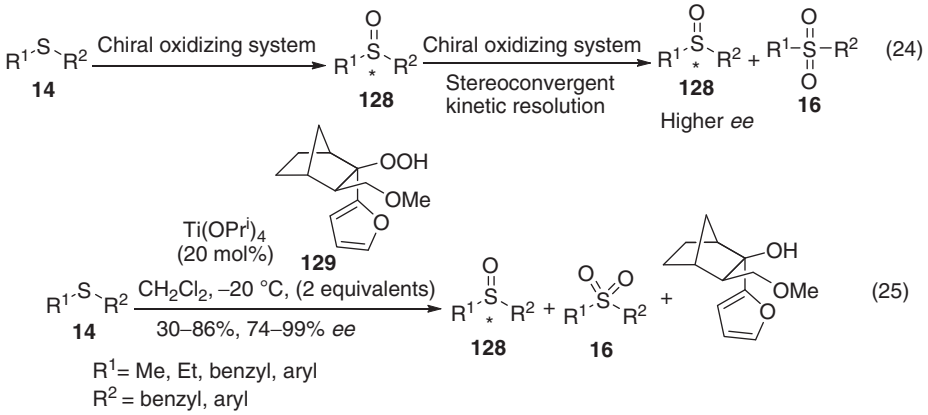
Stoichiometric or catalytic chiral ligand metal-based protocols represent the most investigated systems over the past two decades to use in the asymmetric oxidation of sulfides. The well-known oxidation based on the $Ti(OiPr)_4$/L-diethyl tartrate/TBHP/H_2O system[413] was reported in 1984 as a modification of the Sharpless – Katsuki reagent for the asymmetric epoxidation of allylic alcohols.[414] The nature of the oxidant, the presence of additives, and in general different reaction conditions have been thoroughly investigated in the oxidation of aryl methyl sulfides, whose sulfoxides are obtained chemoselectively in good yield and good–to-high enantioselectivity (*ee* 75–95%).[415] Dialkyl sulfoxides are obtained with lower asymmetric induction (<71% *ee*).

The Ti/tartrate/TBHP system has also been applied, under stoichiometric conditions, in the oxidation of α-substituted 1,3-dithiane or dithiolane derivatives to access the mono- or bis-sulfoxides in high enantioselectivity,[416] as illustrated in the double oxidation of compound **126** to trans-1,3-dioxide **127** using cumyl hydroperoxide (CHP) as the oxidant (Scheme 63).[416b]



Scheme 63

Immobilization of (R,R)-tartaric acid onto soluble-polymers and its use as recyclable ligand for the Ti-catalyzed asymmetric sulfoxidation has been also accomplished.[417] Other successful ligands, such as (R)-1,1′-bi-2-naphthol (BINOL),[418] optically active 1,2-diols,[419] and chiral C_3-symmetric trialkanol amines,[420] are used in the enantioselective oxidation of alkyl aryl and also some functionalized sulfides to sulfoxides. Catalytic loadings of 5–10 mol% of the $Ti(OiPr)_4$/ligand system are used with TBHP as the oxidant, achieving high levels of enantiocontrol (*ee* > 80%). Heterogeneous immobilized BINOL-based ligands have been developed and employed in the enantioselective Ti-catalyzed oxidation of aryl methyl sulfides to sulfoxides with success.[421] In some of these oxidations,[418–421] the chemoselectivity was not complete since sulfone **16** was detected (equation 24, Scheme 64). A deeper analysis showed that in many examples a process of stereoconvergent kinetic resolution occurs during the oxidation of sulfoxides to sulfones, which enhances the enantiomeric excess of sulfoxides **128** to an extent related to the conversion to sulfone **16**. The combined oxidative processes are useful to improve the level of enantioselectivity of sulfoxides at the expense of the yield.[422]

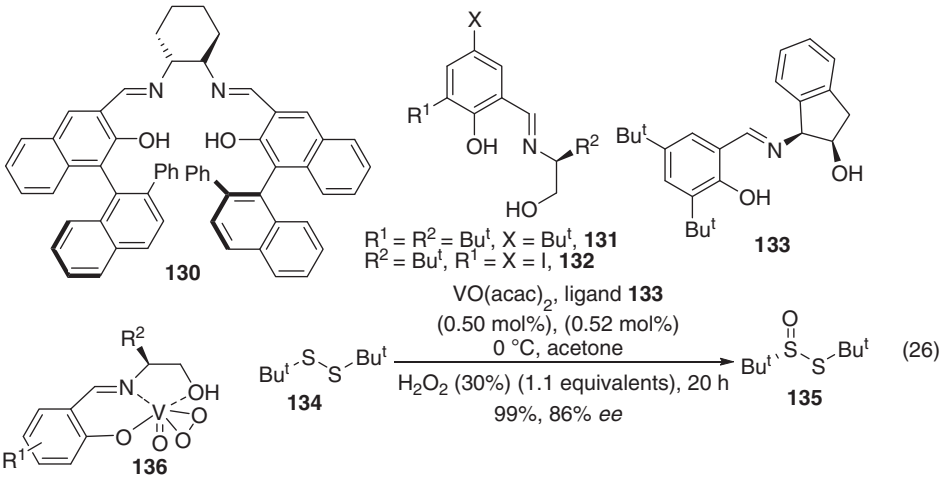


Scheme 64

Optically pure alkyl hydroperoxides are alternative stoichiometric reagents in the asymmetric sulfoxidation with $Ti(OiPr)_4$ as the catalyst in the absence of any ligand.[423] The combined stereoconvergent oxidation and kinetic resolution approach using norcamphor-derived hydroperoxide **129** with 20 mol% of metal catalyst gives enantioenriched sulfoxides in modest-to-good yield and good-to-excellent *ee* (equation 25, Scheme 64).

More environmentally friendly procedures for the enantioselective oxidation of aryl methyl sulfides to sulfoxides have been developed using H_2O_2 or UHP as the oxygen source and catalytic loadings (≤5 mol%) of chiral complexes based on Ti(IV),[424] V(IV),[425] Fe(III),[426] Al(III),[427] Nb(III),[428] and different enantiomerically pure Schiff bases **130–133**.

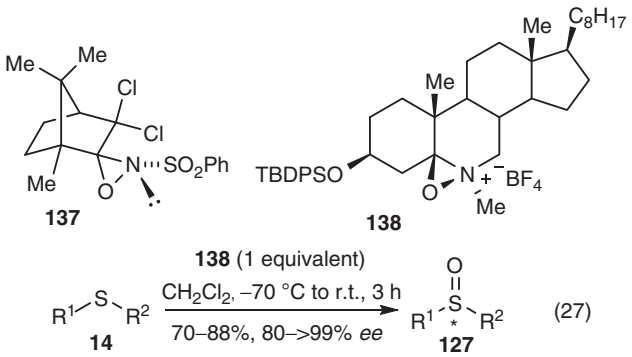
The vanadium system has been additionally applied in the oxidation of di-tert-butyl disulfide **134** affording the thiosulfinate **135** in excellent yield and good enantioselectivity using only 0.5 mol% of bis(acetylacetonato)oxovanadium(IV) and 0.52 mol% of ligand **133** (Scheme 65, equation 26).[425d] NMR studies suggest the involvement of complex **136** as the catalytically active species (Scheme 65).[425b] Chiral platinum diphosphine complexes proved to be effective in the sulfide oxidation with H_2O_2 as oxidant in water as solvent.[429] Zr(IV)-[420b] and Mo(VI)[430]-based chiral complexes have been successfully reported with CHP as the oxidant in the combined oxidation/kinetic resolution approach to alkyl aryl sulfoxides starting from the corresponding sulfides.



Scheme 65

7.28.5.1.2 Oxidation by using organocatalysts

The organocatalytic methods suitable for the asymmetric oxidation of sulfides are significantly underdeveloped when compared to chiral metal-based catalysis, and only very recently have impressive results been achieved.[431] The use of chiral peroxyacids or cyclodextrins, with MCPBA and bovine serum albumin in the asymmetric sulfoxidation, has met with modest success.[432] The first optically pure effective organic compound able to mediate the enantioselective stoichiometric oxidation of a variety of alkyl aryl, dialkyl, and functionalized sulfides at room temperature in CCl_4 as solvent is oxaziridine **137** (Scheme 66).[433]



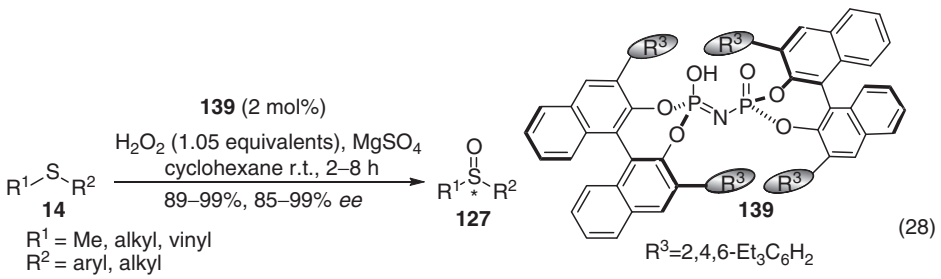
Scheme 66

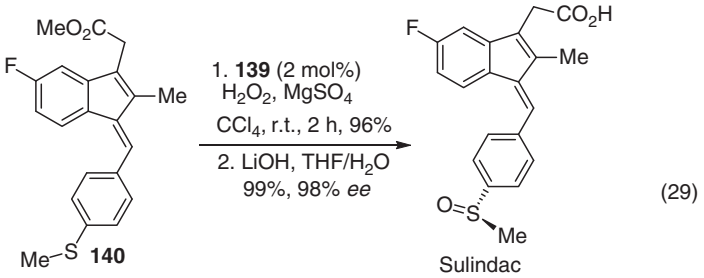
The sulfoxides are isolated with high yield and enantioselectivity (*ee* >90%). Reagent **137** oxidizes sulfenylimine to sulfinylimines in high yield and *ee*.[434] Oxaziridinium salt **138** is an efficient electrophilic oxygen transfer reagent for the oxidation of alkyl aryl sulfides in CH_2Cl_2 (equation 27, Scheme 66).[435] A stoichiometric amount of camphor-derived sulfonylimines with an excess of H_2O_2 (4 equivalents) under basic conditions is a suitable system for the enantioselective oxidation of α-substituted dithianes to the trans-mono-oxide.[436] D-fructose-derived ketone (30 mol%) with oxone in acetonitrile/dimethoxymethane mixture promotes the asymmetric oxidation of functionalized sterically hindered symmetric disulfides to thiosulfinate esters obtained with up to 96% *ee*.[437] The active oxygen donor is the *in situ* formed dioxirane.

Optically active flavinium salts/H_2O_2 are particularly attractive systems for the oxidation of methyl aryl sulfides in view of their low catalyst loading (≤1 mol%) and the solvents used such as water or water/MeOH mixtures.[438] Unfortunately, in addition to a limited substrate scope, a moderate level of enantioselectivity is observed (up to 80% *ee*). The asymmetric oxidation of some alkyl

aryl sulfides has been accomplished with moderate enantiocontrol by using iodoxybenzene ($PhIO_2$) as the oxidant with a variable amount of CTAB and a chiral tartaric acid additive.[439] Recently, optically pure phosphoric acids derived from BINOL[440] and more hindered confined imidodiphosphoric acid **139** has shown to catalyze, at only 2 mol% loading, the enantioselective sulfoxidation of alkyl aryl and dialkyl sulfides to sulfoxides with H_2O_2 in cyclohexane at room temperature with excellent enantiocontrol (equation 28, Scheme 67).[441] The sulfoxides are recovered in excellent yield and *ee*.

The method illustrated in Scheme 67 competes well with the chiral metal-catalyzed methods in terms of catalyst loading, level of asymmetric induction, and simple and environmentally benign reaction conditions. Application of this catalytic system to the synthesis on a large scale of the anti-inflammatory drug sulindac led to 3 g of the (*R*)-sulfoxide in excellent yield and *ee* (equation 29, Scheme 67).





Scheme 67

7.28.5.2 Synthesis of Enantioenriched Sulfoxides by Biological Oxidation

The employment of enzymes for the oxidation of sulfides has increased over the past two decades.[442] The processes are highly advantageous thanks to the environmentally friendly conditions used in the oxidation and the high chemo- and stereoselectivity observed. However, the high substrate specificity of enzymes and their variable activity according to the experimental conditions limit the scope of their application. The asymmetric oxidation of sulfides can be accomplished by more expensive purified enzymes or by whole-cell systems.

7.28.5.2.1 Oxidation by isolated enzymes

A variety of peroxidases catalyze the oxidation of alkyl aryl and some functionalized sulfides under buffered conditions with H_2O_2 as the oxidant. The most studied are HRP,[443] chloroperoxidase (CPO) isolated from the marine fungi Caldariomyces fumago,[444] and vanadium-containing bromoperoxidase (VBrPO) from the alga Corallina officinalis.[445] A slow addition of H_2O_2 to the reaction mixture helps to suppress the uncatalyzed oxidation (equation 30, Scheme 68).[446]

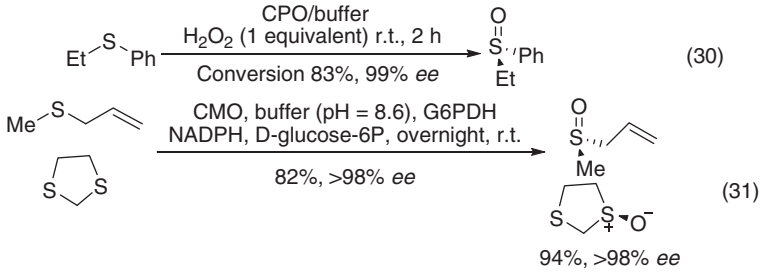
Microencapsulated CPO into a solid matrix has been developed for biocatalyst recycling.[447] Nicotinamide adenine dinucleotide phosphate-dependent cyclohexanone monooxygenase (CMO) is another useful system for the oxidation of alkyl aryl, dialkyl sulfides, and 1,3-dithiane or 1,3-dithiolane (equation 31, Scheme 68).[448b]

Active site-directed mutagenesis or random mutagenesis is applicable to improve the activity and stereoselectivity of these enzymes.[449]

7.28.5.2.2 Oxidation by whole-cell systems

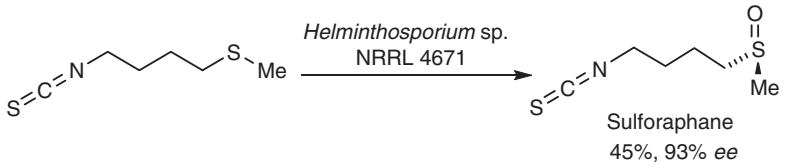
Whole-cell biocatalysis is attractive due to the fact that the enzymes do not need to be purified and it does not require the addition of cofactors or oxidant. Bacteria, yeast, and fungi are directly employed in the process, although unpredictable results in terms of yield and enantiocontrol are observed given the complexity of the system.

Several studies have focused on the oxidation of a variety of sulfides by the fungus *Helminthosporium* sp. NRRRL 4671.[450] In addition to methyl aryl sulfoxides obtained in good-to-high enantiomeric excess, ω-methylthioalkylphthalimides are oxidized to the corresponding sulfoxides in excellent enantioselectivity.[451] These compounds are important precursors of biologically active



Scheme 68

isothiocyanate-containing methyl sulfoxides, such as (*S*)-sulforaphane, a molecule showing anticancer activity. This compound is also obtained by direct oxidation of the sulfide by the fungus *Helminthosporium* sp. NRRRL 4671 and the opposite enantiomer by using the fungus *Mortierella isabellina* ATCC 42613 (Scheme 69).[451b]

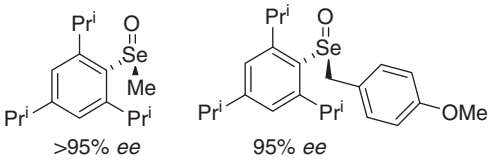


Scheme 69

7.28.6 Synthesis of Enantioenriched Selenoxides and Telluroxides by Chemical Oxidation

7.28.6.1 Synthesis of Enantioenriched Selenoxides by Chemical Oxidation

Organic selenoxides are configurationally unstable compounds, and the racemizazion of enantioenriched selenoxides has been ascribed to the formation of achiral hydrates when water is present (equation 19, Scheme 46), a process that has been demonstrated to be acid-catalyzed.[339b,452] Asymmetric oxidations of alkyl aryl selenides, carried out under anhydrous reaction conditions with oxaziridine **137**, lead to moderate levels of asymmetric induction when working at $-20\ ^{\circ}C$ (up to 83% *ee*).[453] However, when using sterically demanding alkyl aryl selenides high enantioselectivity is observed for the selenoxides using oxaziridine **137** (1 equivalent) at 0 °C in $CHCl_3$ (Scheme 70).[454]

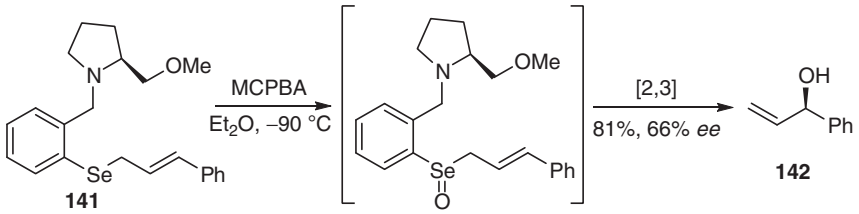


Scheme 70

O-protected *β*-oxyalkyl selenides are oxidized to the corresponding selenoxides with the $Ti(OiPr)_4$/L-diisopropyl tartrate (DIPT)/TBHP in modest *ee*.[455]

Enantiomerically enriched allenic sulfones or cyclohexylidenemethyl ketones are obtained via asymmetric oxidation of the corresponding aryl vinyl selenides with the oxaziridine **137** or Ti/tartate system, followed by elimination in modest-to-good enantiocontrol (up to 83% *ee*).[456] Diastereoselective oxidation of an allylic selenide **141**, bearing a tertiary amine as stereocontrol element, with MCPBA followed by [2,3]-sigmatropic rearrangement leads to allylic alcohol **142** in good yield and 66% *ee* (Scheme 71).[457] A similar approach has been reported by using the $VO(aca)_2$/TBHP system.[458]

Optically pure diselenides bearing a chiral oxazoline group have been used in the presence of Lewis acids and H_2O_2 as oxidant in the Baeyer–Villiger oxidation of cyclobutanones to *γ*-lactones. However, the formation of a chiral seleninic acid intermediate, followed by a peroxyseleninic acid suffering racemization, gives the product in low *ee*.[459] Biological oxidations of selenides to selenoxides with whole-cell systems proved to be unsuccessful.[460] Optical resolution of racemic seleninic acids and selelenamides via chiral HPLC analysis demonstrated that sterically demanding aromatic enantiomers, once separated, are less prone to racemization.[461]



Scheme 71

7.28.6.2 Synthesis of Enantioenriched Telluroxides by Chemical Oxidation

The oxidative approach to the synthesis of enantioenriched telluroxides has been poorly investigated, as they equilibrate with the hydrate form, thus suffering facile racemization (equation 22, Scheme 59). However, the oxidation of some enantiomerically pure allylic ferrocenyl tellurides with TBHP followed by [2,3]-sigmatropic rearrangement of the intermediate allylic telluroxides afforded the allylic alcohols in slightly enantioeriched form (up to 22% *ee*).[462]

Demonstration of the configuration lability of enantioenriched telluroxides and tellurinic acids has been achieved by optical resolution of the racemic compounds and isolation of both enantiomers via chiral HPLC analysis.[463]

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7.29 Oxidative Functionalization with Hypervalent Halides

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Glossary

Domino reactions Domino reactions are the result of two or more subsequent synthetic transformations. These reactions are also called 'tandem reactions' or 'cascade reactions.'

Hypervalent iodine reagents Compounds in which the iodine atom is having an oxidation state of +3, +5, or +7.

Oxidation reactions These reactions are explained on the basis of electron transfer from one molecule to another. The reactions in which the loss of electrons or increase in oxidation states occurs are called oxidation reactions.

Oxo-bridged hypervalent iodine reagents Reagents in which two trivalent iodine atoms are linked through oxygen.

Pseudo-hypervalent iodine reagents Hypervalent iodine reagents having planar pseudobenziodoxole moieties that arise from intramolecular nonbonding iodine–oxygen interactions.

Rearrangement Rearrangement can be defined as 'one-step' or 'multistep' migration of a hydrogen atom or a larger molecular fragment within an intermediate of lower stability.

Ring contractions Ring contractions are rearrangements which lead to the formation of a new ring with one or more carbon atom less than in the original molecule.

Ring expansions Ring expansions are rearrangements which lead the formation of new ring with one or more carbon atom more than in the original molecule.

7.29.1 Introduction

The first hypervalent iodine reagent was reported in 1886,[1] but the progress of hypervalent iodine chemistry was slow until the late 1970s. The real development of hypervalent iodine chemistry started in the early 1980s with the discovery of the Dess–Martin periodinane (DMP) as an extremely mild and versatile oxidant.[2] In the past two decades, different hypervalent iodine reagents have been investigated and been successfully used in oxidative transformations. Hypervalent iodine-mediated reactions have been part of significant applications in natural products chemistry.[3,4] Hypervalent iodine chemistry is now a well-established area of organic chemistry, and several books,[5] book chapters,[6] and review articles[7–10] have appeared to describe various aspects of this chemistry. This chapter highlights the developments of oxidative functionalizations using hypervalent iodine reagents.

7.29.2 Reagents

Hypervalent iodine reagents have received particular attention because of their low toxicity, a favorable safety profile, easy handling, and an environmentally friendly nature. The scope of hypervalent iodine reagents is not limited to their oxidative properties, and they have been used as powerful electrophiles. The search for novel oxidizing agents, especially for reagents showing a high degree of selectivity by tolerating a variety of other functional groups, is a high priority in current research. These reagents can be divided into various classes.

7.29.2.1 Noncyclic Hypervalent Iodine Reagents

The hypervalent iodine chemistry began with the discovery of the hypervalent iodine reagent (dichloroiodo)benzene by Willgerodt and Prakt in 1886.[1] After that discovery, various acyclic hypervalent iodine reagents have been reported as oxidants including powerful electrophilic derivatives.

7.29.2.1.1 Noncyclic hypervalent iodine(III) reagents

Recently, hypervalent iodine(III) reagents have received particular attention of synthetic organic chemists. Various hypervalent iodine(III) reagents **1–13** as shown in Figure 1 have been investigated as oxidants. (Dichloroiodo)arenes such as **1** and (difluoroiodo)arenes such as **2** have been reported as effective chlorinating and fluorinating reagents.[11] Iodosobenzene **3** is a polymeric reagent $(PhIO)_n$, but it depolymerizes in alcohols or acids. The scope of reagent **3** in oxidation reactions is limited because of its polymeric nature. (Bisacetoxyiodo)benzene **4** (phenyliodine diacetate (PIDA)) and [bis(trifluoroacetoxy)iodo] benzenes **5** (PIFA) are the most commonly used hypervalent iodine(III) reagent in different oxidation reactions including rearrangements.[12] Furthermore, reagents **4** and **5** were electronically modified as shown with reagents **6–8**, where the benzene moiety has been replaced by a heteroaromatic system. The modified reagents **6–8** have been used for oxidations of hydroquinones and sulfides as well as for rearrangements.[13] [Hydroxy(tosyloxy)iodo]benzene **9** was first reported in 1970[14] and is often called Koser's reagent.[15,16] It can be easily synthesized from **4** and **5** through a ligand exchange reaction. In 2005, Kita and his research group have reported hypervalent iodine(III) reagents **10a–c** based on the tetraphenylmethane moiety.[17] In 2008, Zhdankin and his research group modified the reagents **5** and **9** and reported 3-[bis(trifluoroacetoxy)iodo]benzoic acid **11a** and 3-[hydroxy(tosyloxy)iodo]benzoic acid **11b**, respectively.[18] In the literature, there are several methods described for the synthesis of hypervalent iodine(III) reagents **1–11**.[10] In 2010, Wirth and coworkers reported the synthesis of highly reactive polyfluorinated hypervalent iodine(III) reagents **12a–c** and their applications in oxidation reactions.[19] Recently, the same research group reported the *in situ* formation of hypervalent iodine reagent **13** by reaction of **4** or **5** with TMSOTf and its use as electrophile.[20]

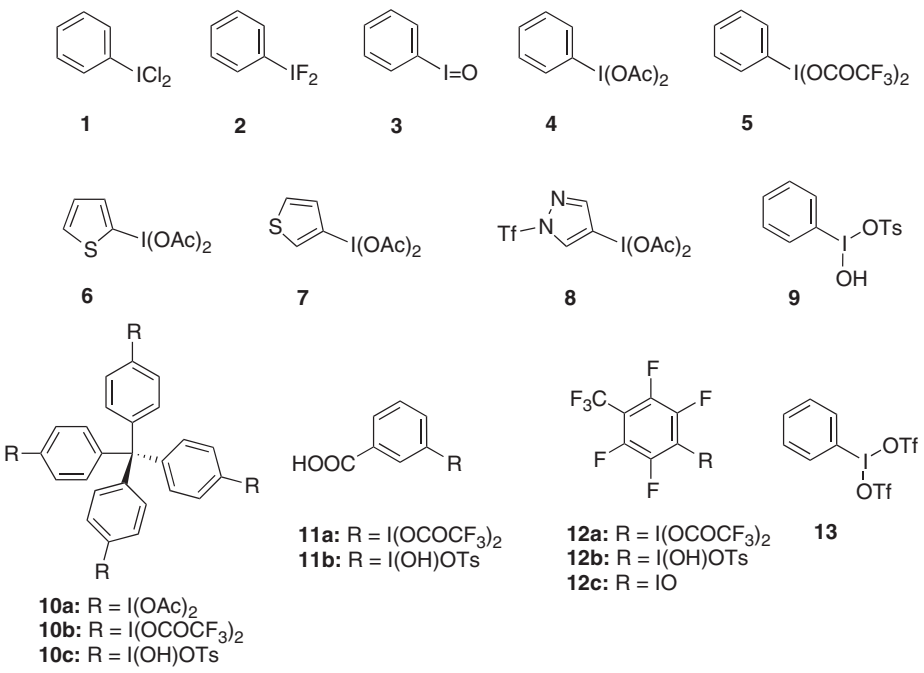


Figure 1 Acyclic hypervalent iodine(III) reagents **1**–**13**.

7.29.2.1.2 Noncyclic hypervalent iodine(V) reagents

As shown in Figure 2, different hypervalent iodine(V) reagents **14**–**17** have been reported as oxidants. Iodylbenzene **14** is the simplest hypervalent iodine(V) reagent and has no functional group.[21] 2-Iodylphenol ether derived hypervalent iodine reagents **15a–d** were synthesized by oxidation of the corresponding 2-iodophenol ethers with dimethyldioxirane. The X-ray diffraction analysis of 1-iodyl-2-isopropoxybenzene **15c** and 1-iodyl-2-butoxybenzene **15d** revealed pseudopolymeric arrangements in the solid state formed by intermolecular interactions between IO_2 groups of different molecules. These reagents have been reported for oxidation of sulfides to sulfoxides and alcohols to the respective carbonyl compounds.[22] Pyridine-based hypervalent iodine(V) reagents **16a–c** were also synthesized by using the same synthetic method. These reagents can be used effectively as recyclable oxidants.[23] Very recently, hypervalent iodine(V) reagents **17a**,**b** have been reported by Zhdankin and his research group. These reagents have been employed as effective reagents for the oxidative iodination of aromatic functional groups.[24]

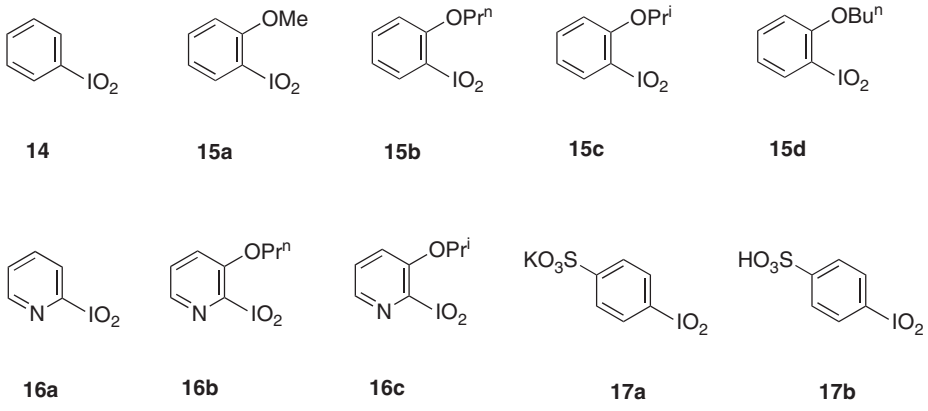


Figure 2 Noncyclic hypervalent iodine(V) reagents **14**–**17**.

7.29.2.2 Cyclic Hypervalent Iodine Reagents

Many cyclic hypervalent iodine reagents have been investigated in detail. Generally, cyclic hypervalent iodine reagents are usually more stable in comparison to their noncyclic counterparts and their use for oxidation reactions is well established. Although these reagents are popular for oxidative functionalizations, they have recently also been used in carbon–carbon bond-forming reactions.[7,25]

7.29.2.2.1 Cyclic hypervalent iodine(III) reagents

Many cyclic hypervalent iodine(III) reagents **18–32** have been developed (Figure 3). Cyclic hypervalent iodine(III) reagents are more stable reagents than other hypervalent iodine reagents. 2-Iodosobenzoic acid (IBA) **18** (X=OH) is a simple reagent of this class that can be synthesized by the oxidation of 2-iodobenzoic acid. The reactions of **18** are much less common in organic synthesis due to its very low reactivity.[26] In 2007, Wirth and his research group reported the hypervalent iodine reagent 2,3,4,5-tetrafluoro-6-iodosobenzoic acid (FIBA) **19** with increased reactivity compared with **18** and can be used advantageously in several oxidation reactions.[27] The diphenyl diselenide-catalyzed oxidative cyclization of unsaturated acid to lactones has been achieved with **19**, whereas **18** is not reactive enough in this reaction.[28] In 2006, a thia-analog of IBA **20** was synthesized and used in oxidation reactions.[29] There are several other reagents **21–25** of this class that have been developed and employed successfully in various transformations.[30–33]

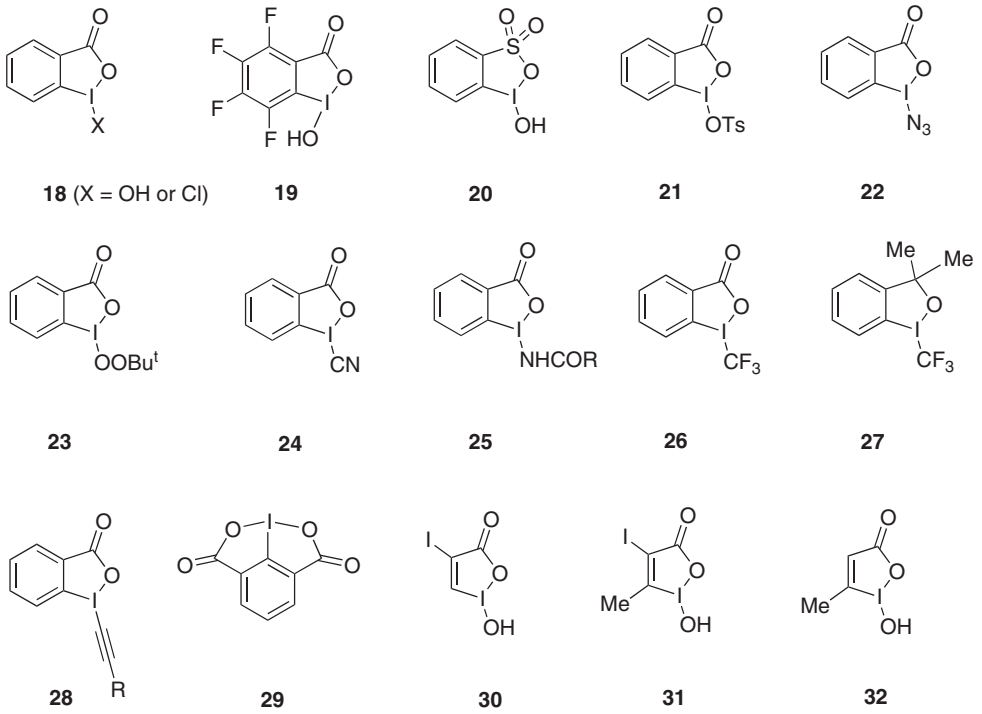


Figure 3 Cyclic hypervalent iodine(III) reagents **18–32**.

Togni and coworkers developed the synthesis of trifluoromethyl benziodoxolone **26** (Togni's reagent) and **27** and successfully used **26** for trifluoromethylation of various aliphatic and aromatic substrates.[34,35] Alkynyl hypervalent iodine reagents of type **28** (R=H, $SiMe_3$, Si^iPr_3) have been reported as efficient acetylene group transfer reagents to various heterocycles.[36,37] Zhang and colleagues developed a recyclable tricyclic hypervalent iodine reagent (iodosodilactone) **29** as an efficient coupling reagent for the direct condensation of carboxylic acids and alcohols or amines.[38] Some iodoxolone-based hypervalent iodine reagents **30–32** can be synthesized by the oxidation of (*Z*)-3-iodo acrylic acids and are already known for a long time, others have been developed recently.[39] These reagents have been used for various reactions with superior or similar reactivity as conventional cyclic hypervalent iodine(III) reagents.[39]

7.29.2.2.2 Cyclic hypervalent iodine(V) reagents

Usually, cyclic hypervalent iodine(V) reagents are more powerful oxidizing agents in the comparison of cyclic iodine(III) compounds. There are several cyclic iodine(V) reagents **33–44** described in the literature (Figure 4) with the most representative cyclic iodine(V) reagents being 2-iodoxybenzoic acid (IBX, **33**) and DMP **34**.[5–7,40,41] The first cyclic hypervalent iodine(V) reagent (IBX, **33**) was reported in 1893,[42] but its use was quite limited in reactions, probably due to its low solubility in most organic solvents and some other drawbacks.[27] In recent years, IBX **33** has received remarkable attention as oxidant particularly for the oxidation of alcohols despite its solubility issues.[43] Furthermore, Dess and Martin reported the synthesis of a more soluble reagent DMP **34** by the acetylation of IBX **33**.[2] Currently, DMP **34** is used frequently as an oxidant in many valuable synthetic transformations. After the recent success of IBX as oxidant, the synthesis of derivatives **35–41** has been reported. Vinod and Thottumkara reported the synthesis of a more soluble reagent **35** using 3-nitrophthalic acid as starting material which was used to oxidize allylic or benzylic alcohols selectively.[44] In 2008, the same research group reported the synthesis of reagent **36** from commercially available 2-aminoterephthalic

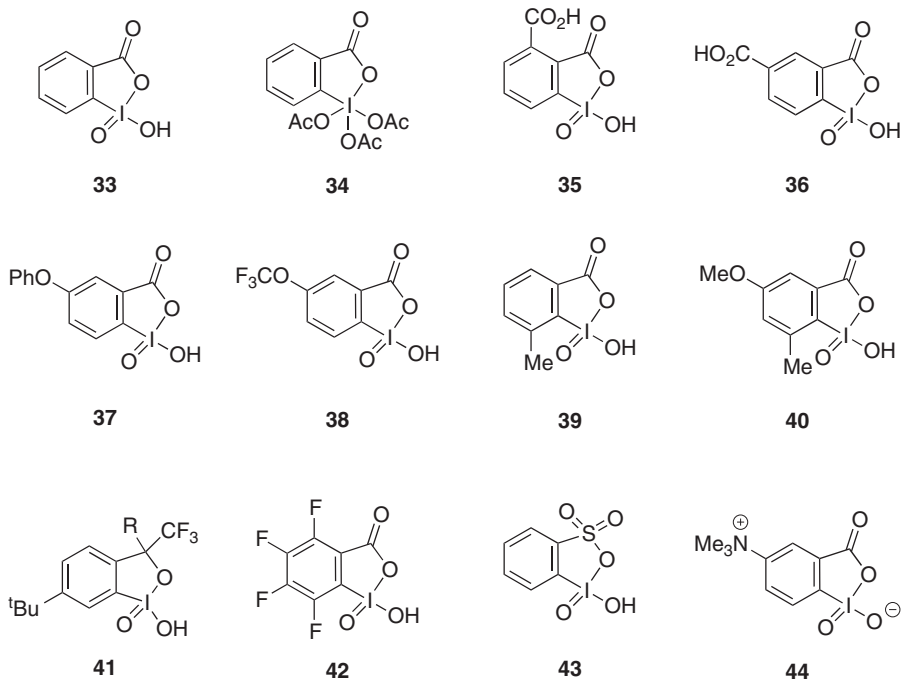


Figure 4 Cyclic hypervalent iodine(V) reagents **33–44**.

acid in two steps, which can be used for the oxidation of alcohols.[45] Both of these reagents are soluble in water and dimethylformamide (DMF). The substituted IBX reagents **37** and **38** have also been synthesized by oxidation of the corresponding iodobenzene derivatives.[46] Goddard and his research group modified IBX **33** as 3-Me-IBX **39**.[47] After Goddard's report, Moorthy reported the synthesis of the more soluble 2-Me-4-MeO-IBX **40**, which can be applied to the oxidation of alcohols and sulfides at room temperature in short reaction times.[48] Other cyclic hypervalent iodine reagents of type **41** have been introduced as highly soluble and nonexplosive oxidants, although their synthesis involves several steps.[49] Wirth and his research group reported the synthesis of 2,3,4,5-tetrafluoro-6-iodoxybenzoic acid (FIBX) **42** by the oxidation of 2,3,4,5-tetrafluoro-6-iodobenzoic acid using potassium bromate as oxidant. FIBX **42** has been shown to have higher reactivity than IBX **33** in common organic solvents.[27]

In 2006, Zhdankin and his research group reported the synthesis of 2-iodoxybenzenesulfonic acid (IBS) **43** by direct oxidation of 2-iodobenzenesulfonic acid with oxones. IBS **43** was not thermally stable in various organic solvents such as acetonitrile, dimethyl sulfoxide (DMSO), and methanol and decomposed into the more stable reagent **20**. Unfortunately, the authors could not investigate the oxidative ability of **43** due to its low stability in organic solvents.[29] Recently, Zhang and coworkers reported the synthesis of a water-soluble IBX analog **44** (AIBX), which was employed in the oxidation of cyclic β-keto esters to the corresponding dehydrogenated products.[50]

7.29.2.3 Pseudocyclic Hypervalent Iodine Reagents

Although 1-hydroxy-1,2-benziodoxol-3-(*1H*)-one (IBX, **33**) and DMP **34** are frontline oxidants, both are suffering from a number of drawbacks, as DMP is highly sensitive toward moisture[2b] and unstable to storage for long time, whereas IBX can explode by heating to more than 200 °C.[51] The reagents have limited solubility in most organic solvents except DMSO. As pointed out above, several research groups have made remarkable efforts to resolve these complications by modifications in functionalizing the IBX aromatic core. Other research groups investigated the synthesis of various pseudocyclic hypervalent iodine reagents based on planar pseudo-benziodoxole moieties that arise from intramolecular nonbonding iodine–oxygen interactions. These nonbonding iodine–oxygen interactions can lead to a partial disruption of the polymeric network, and, consequently, enhance their solubility and reactivity. Initially, the synthesis of pseudocyclic iodine(V) reagents of type **45** was reported.[52,53] In 2003, Zhdankin and coworkers synthesized pseudo-benziodoxoles of type **46** and their structure is similar to IBX amides because of noncovalent intramolecular iodine–oxygen interactions.[54] In 2004, the same research group developed IBX esters **47** as reusable reagents.[55] In the same year, the synthesis of IBX sulfonate esters **48** and IBX sulfonamides **49** have been achieved.[56] The iodine(V) reagent **47** (R=Me) can be further converted to the diacetate or bis(trifluoroacetate) derivatives **50** (R=Ac or CF_3CO) by treatment with acetic anhydride or trifluoroacetic anhydride, respectively.[57] Single-crystal X-ray diffraction analysis of **50** (R=Ac) reveals a pseudobenziodoxole structure with three relatively weak intramolecular iodine–oxygen interactions.

To increase the solubility and reactivity, the synthesis of C_2 symmetrical iodine(V) reagents **51** (R=Me or Pr^i) was achieved by oxidation of the respective iodoarenes with dimethyldioxirane. The reason for the synthesis of compound **51** was to provide the

intramolecular coordination of the iodine(V) center with two carbonyl oxygens so that solubility and reactivity could improve. Interestingly, the single-crystal X-ray diffraction analysis of diisopropyl 2-iodoxyisophthalate clearly showed an intramolecular iodine–oxygen interaction with only one carbonyl oxygen of the two carboxylic groups, whereas nuclear magnetic resonance spectra in solution indicated equivalency of both ester groups. These pseudocyclic iodine(V) reagents **45–51** were chemically more stable and soluble in common organic solvents. They possess the identical reactivity to IBX and DMP and are used as useful oxidizing reagents for the oxidation of alcohols[57] and sulfides (Figure 5).[58]

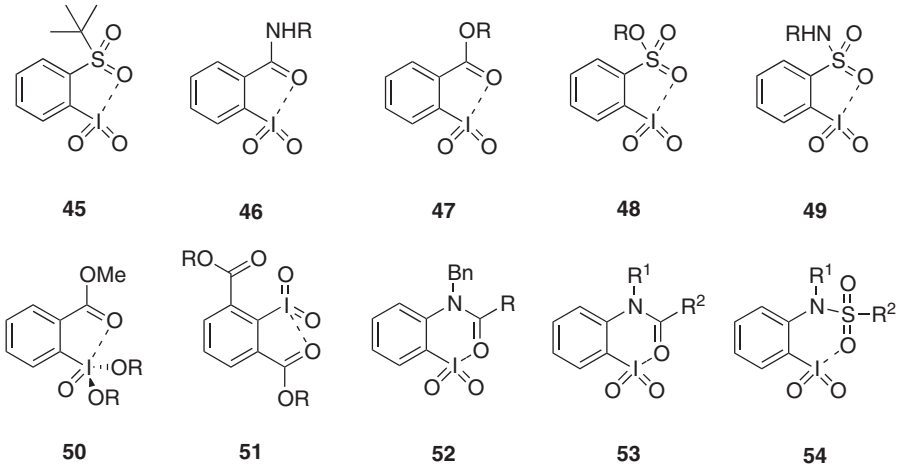


Figure 5 Pseudocyclic hypervalent iodine(V) reagents **45–54**.

In 2005, Zhdankin and his research group reported the synthesis of novel *N*-(2-iodylphenyl)acylamides (NIPA) **52** and **53** starting from *ortho*-iodoaniline in three steps.[59] The X-ray analysis of **54** (R^1 = Me, R^2 = ^{t}Bu) revealed a unique pseudo-benziodoxazine structure, which was the first report on six-membered pseudocyclic iodine(V) reagents with noncovalent intramolecular I···O interactions. Reagents **53** and **54** (except R^1 = H) have been successfully used as oxidants to oxidize alcohols and sulfides into corresponding carbonyl moiety and sulfones, respectively, whereas the reactivity largely depends on the substitution pattern of the amide group adjacent to the iodyl functional group.[59] In 2009, the same research group has reported the synthesis and applications of new six-membered pseudocyclic iodine(V) reagents *N*-(2-iodylphenyl)tosylamides in oxidation reactions.[60]

7.29.2.4 Oxo-Bridged Hypervalent Iodine reagents

Oxo-bridged hypervalent iodine reagents have a long history,[61] but unlike other hypervalent iodine reagents their development was quite limited. Oxo-bridged hypervalent iodine reagents are reagents in which two trivalent iodine atoms are linked through an oxygen atom (Figure 6).

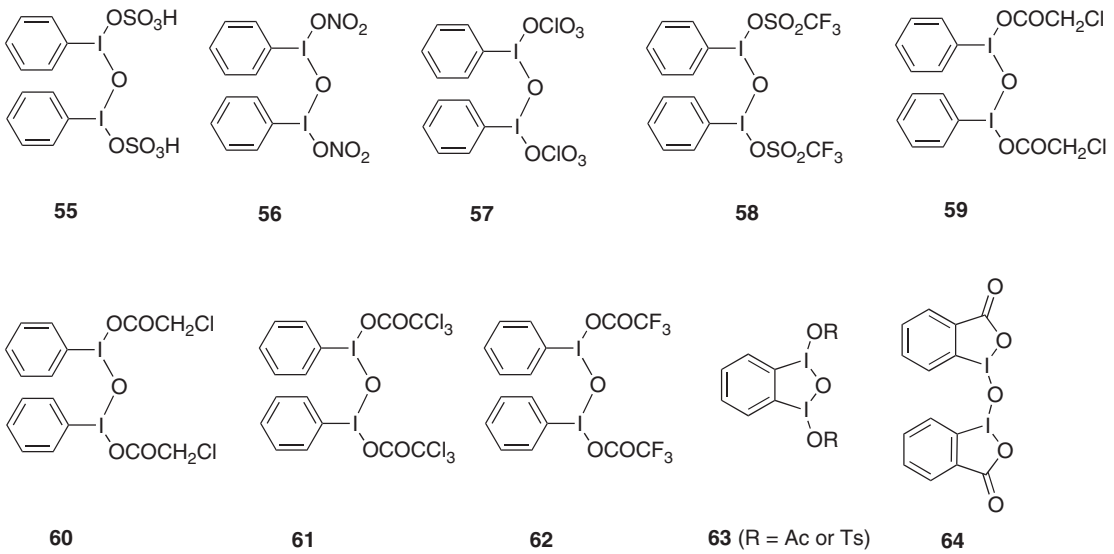


Figure 6 Bridged-hypervalent iodine(III) reagents **55–64**.

The synthesis of various acyclic (**55–62**) and cyclic bridged iodine(III) reagents **63** and **64** has been reported (Scheme 6).[61,62] By considering the reactivity of bis(trifluoroacetoxy)iodo]benzenes **5**, Varvoglis reported the synthesis of μ-oxo-bis[trifluoroacetato (phenyl)iodine] **62** by treatment of compound **5** with a strong base in dichloromethane in excellent yield.[63] Recently, **62** was used as oxidant for the oxidation of phenols to the corresponding spiro compounds[64,65] and showed better reactivity than bis (trifluoroacetoxy)iodo]benzene **5**. The reagent **62** can also be used as an alternative for **5** in the oxidation of phenols and other oxidation reactions.

7.29.2.5 Polymer-Supported Hypervalent Iodine Reagents

Polymer-supported hypervalent iodine reagents have also found synthetic applications in organic chemistry,[66] although the first synthesis of polymer-supported hypervalent iodine reagent was reported in the early 1970s.[67] The attachment of hypervalent iodine reagents to an insoluble polymer matrix provides an easy reaction work-up accompanied by fast reaction optimization, simple filtration, and automated parallel synthesis.[68–70] The chemistry of these species is now well recognized by organic chemists and used in both, academic and industrial laboratories.[71] Iodine(III) and iodine(V) reagents have been reported in the literature.

7.29.2.5.1 Polymer-Supported iodine(III) reagents

A number of polymer-supported hypervalent iodine(III) reagents **65–72** have been synthesized (Figure 7). The synthesis of polystyrene-supported (diacetoxyiodo)benzene (PS-DIB) **65**[72] and polystyrene-supported [bis(trifluoroacetoxy)iodo]benzene (PS-PIFA) **66**[73] was achieved by different research groups. Both reagents **65** and **66** have been successfully used in rearrangements and coupling reactions including oxidation processes.[7c,74–76] Polymer-supported derivative **67** was also synthesized and used for similar reactions.[77] Polymer-supported (dichloroiodo)benzene (DCIB) **68** was used as chlorinating and oxidizing reagent.[78] In 2004, Huang and Chen reported the synthesis of polymer-supported Koser reagent (PS-HTIB) **69**.[79] Recently, Zhdankin and his colleagues reported the synthesis of polystyrene-supported iodosylbenzene sulfate (PS-IBS) **70** by reaction of PS-DIB **65** with sodium bisulfate, which can be used for the oxidation of alcohols and sulfides.[80] Very recently, the same research group described the synthesis of novel polystyrene-supported iodosylbenzene (PS-ISB) **71** from **65** under solvent-free conditions.[81] The same research group also reported the synthesis of polystyrene-supported hydrated iodosylbenzene (hydrated PS-ISB) **72** from **65**.[81] Polystyrene-supported alkenyl(phenyl) iodonium salts have been also reported in the literature and used as synthons of alkenyl cations.[82] All these polymer-supported reagents can be very easily removed after the reaction by filtration. Furthermore, it is possible to reoxidize them and to reuse them with almost no loss of activity. Zhu and Wie have reported the synthesis of various nanoparticle-supported (diacetoxyiodo)benzene reagents from 4-iodobenzoic acid, which were used in different oxidation reactions.[83] In 2005, Zhang and coworkers reported the synthesis of ion-supported hypervalent iodine(III) reagents and their use in the selective oxidation of alcohols.[84]

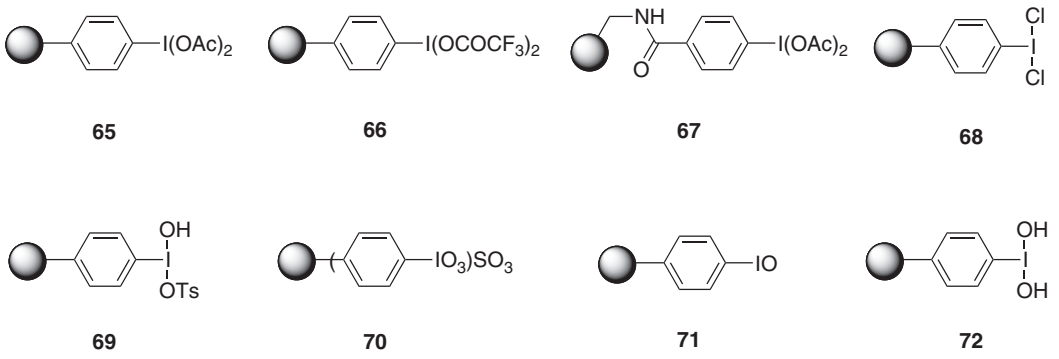


Figure 7 Polymer-supported hypervalent iodine(III) reagents **65–72**.

7.29.2.5.2 Polymer-Supported iodine(V) reagents

Despite the availability of various polymer-supported iodine(III) reagents, a number of polymer-supported iodine(V) reagents **73–81** have been reported in the literature (Figure 8). As mentioned earlier, the solubility of IBX is low in many organic solvents[42]; to overcome the solubility issue, the several research groups have reported polymer-supported IBXs of type **73** that can be used in common organic solvents such as dichloromethane, tetrahydrofuran, etc.[85–90] The presence of a functional group in the *ortho*-position of pseudocyclic iodine(V) reagents provides an opportunity to generate polymer-supported pseudocyclic iodine(V) reagents **74–79** (Figure 8). Lee and coworkers have reported the synthesis of polymer-supported IBX-ester **74** and IBX-amides **75** and **76** starting from commercially available hydroxy- or amino-polystyrene, which have been used for the oxidation of alcohols.[91] Polymer-supported IBX-amide **76** showed efficient results than **74** and **75** during the oxidation of alcohols under mild reaction conditions.[91] The reagent **76** is also an efficient oxidant for the oxidative bromination of activated aromatic compounds using tetraethylammonium bromide (TEAB).[92] In 2005, Linclau and coworkers reported an improved synthesis of polymer-supported

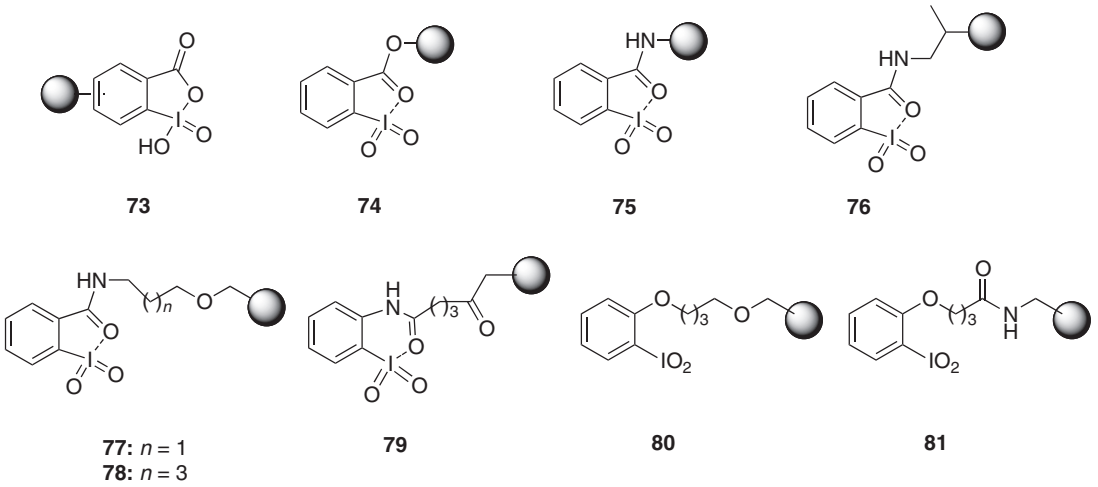


Figure 8 Polymer-supported hypervalent iodine(V) reagents **73–81**.

IBX-amides **77** and **78** using commercially available starting materials 2-iodobenzoyl chloride and Merrifield resin,[93] which have shown promising reactivity during the oxidation of alcohols into corresponding carbonyl functional groups. The advantage of these reagents is the recycling of the resin with a minimal loss of activity after two reoxidations.[93] In 2006, Zhdankin and researchers developed pseudo-benziodoxazine cored polymer-supported iodine(V) reagents **79** by starting with inexpensive commercially available 2-iodoaniline in three steps.[94] Only a moderate decrease in the oxidative activity of **79** was observed after multiple recovery steps and this reagent represents a good alternative to previously reported reagents **74–78**. Furthermore, Zhdankin reported the synthesis of polymer-supported 2-iodylphenol ethers **80** and **81** from easily assessable starting materials 2-iodophenol and stable IBX analogs having a pseudocyclic four-membered ring motif.[22] These reagents **80** and **81** have been successfully applied for the oxidation of primary and secondary alcohols after multistep recovery even only slight decrease in oxidative activity was observed, possibly, due to iodine loss in the course of resin reoxidation.[95] All polymer-supported iodine(V) reagents **74–81** have the advantage of easy reaction work-up by simple filtration, and they can find practical applications in the solid phase and combinatorial high-throughput synthesis.

7.29.2.6 Chiral Hypervalent Iodine Reagents

Asymmetric transformations induced by chiral hypervalent iodine reagents have found the specific attention of various research groups.[96] By using chiral hypervalent iodine reagents, various asymmetric transformations have been developed such as oxidative dearomatization of phenols,[97,98] α-functionalization of ketones,[99,100] alkene dioxygenations,[101] and oxyaminations.[20a] In recent years, various chiral hypervalent iodine reagents **82–93** have been reported (Figure 9). The first optically active hypervalent iodine compound was reported in 1907 by the reaction of diphenyliodonium hydroxide and tartaric acid.[102] In 1997, Wirth and his research group reported chiral hypervalent iodine(III) reagents of type **82** and used them in various asymmetric functionalizations of alkenes and ketones.[103] The *ortho*-substituted Koser-type reagent **83** (R^1 = Me, Et) was also made and similar reactions have been investigated.[100,104]

In 2007, Fujita and coworkers reported the synthesis of lactic acid-based chiral hypervalent iodine(III) reagents **84** (R = Me or ^{i}Pr) by Mitsunobu reaction of 2-iodophenol with optically active methyl lactate followed by oxidation with sodium perborate in acetic acid. Reagents **84** were used in highly stereoselective cyclization reactions.[105] Lactate-based reagents **84** have been modified into *ortho*-disubstituted reagents **85** and used in similar reactions.[106] Furthermore, the same research group developed lactate-based chiral iodine(III) reagents having C_2 symmetry **86** (R = Me or Pr^i)[107] which can be used in oxidative lactonization of 2-alkenyl benzoic esters.[107] Kita and coworkers reported the synthesis of a chiral-bridged iodine(III) reagent **87** and applied this reagent in enantioselective dearomatization reactions of phenols.[97] Zhdankin introduced novel chiral iodine(V) reagents of type **88**, which were efficient in the asymmetric oxidation of sulfides.[108,109] In 2006, the same research group reported the synthesis of chiral hypervalent iodine(V) reagents **89** based on the benziodoxazine functional group by using inexpensive and readily available (*S*)-proline.[110] These reagents have been employed as asymmetric reagents for the oxidation of alcohols and sulfides with moderate selectivities.[110] In 2009, Boppisetti and Birman developed aryliodooxazoline-based chiral iodine(V) reagents **90** by using amino alcohols as starting material and used them for the asymmetric dearomatization of phenols.[111] Recently, Ishihara and coworkers investigated conformationally flexible C_2-symmetric chiral hypervalent iodine(III) reagents **91**, which were employed in enantioselective spirolactonizations with high selectivities.[112] Various reagents of type **91** have been synthesized *in situ* during enantioselective spirolactonization of phenols.[112] Recently, bicyclic chiral iodine(V) reagents of type **92** were reported and used in

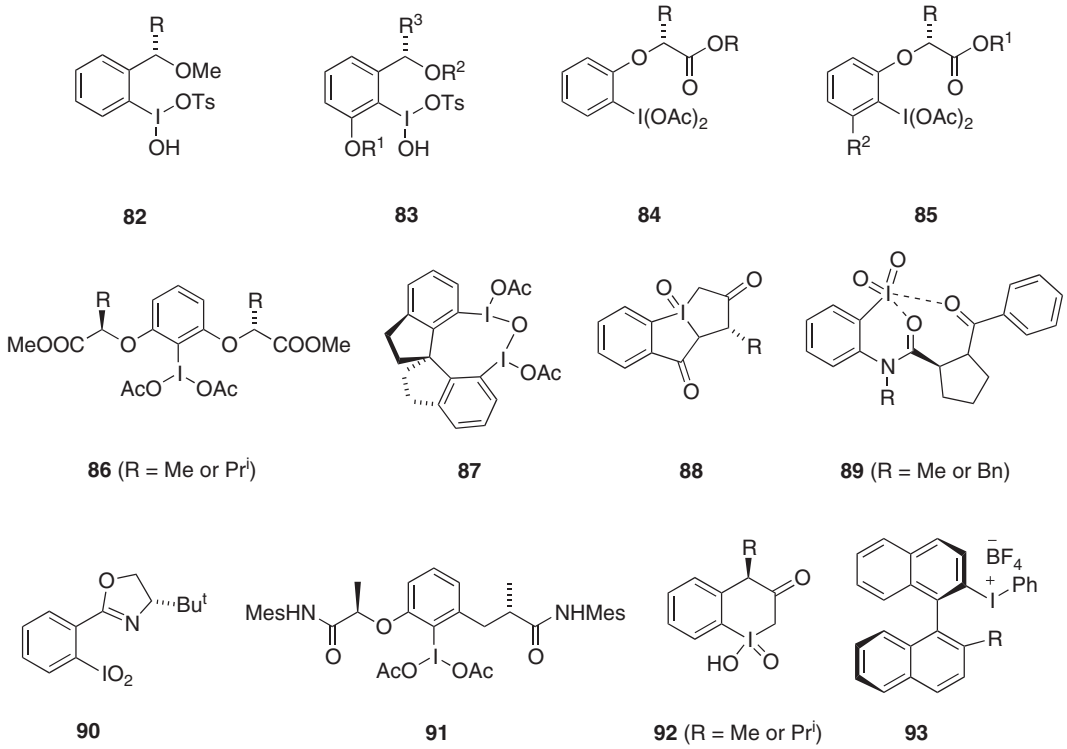


Figure 9 Chiral hypervalent iodine reagents **82–93**.

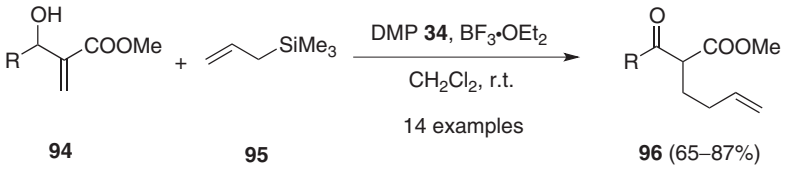
the enantioselective dearomatization of phenols, but the products were obtained with moderate to poor selectivities.[99a] Ochiai and his research group reported chiral diaryliodonium salts **93**, which were used for the phenylation of β-keto esters with moderate selectivity.[113] Furthermore, to expand the scope chiral hypervalent salts, Jalalian and Olofsson synthesized three new chiral diaryliodonium salts and applied them successfully in asymmetric α-phenylations of carbonyl compounds.[114] Few other optically active hypervalent iodine reagents were also synthesized but did not show high selectivities in asymmetric transformations.[105,113,115,116]

7.29.3 Oxidations

Oxidation reactions are one of the most important transformations in organic chemistry. Oxidation reactions can be achieved by using hypervalent iodine reagents under mild reaction conditions. This chapter highlights the most important transformations and is restricted to those transformations, where a new oxygen atom is attached to the substrate. To include all the references would be beyond this chapter and only recent work is being highlighted.

7.29.3.1 Oxidations of Alcohols

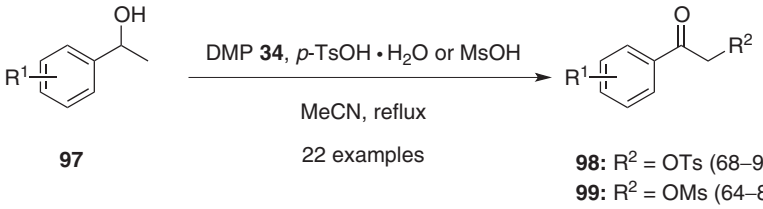
The oxidation of alcohols to the corresponding carbonyl functional groups is one of the most fundamental and important transformations in synthetic organic chemistry.[117–119] Particularly, selective oxidative transformations of alcohols to carbonyl compounds are attractive, since the target molecules can be obtained directly in a one-pot sequence. Various hypervalent iodine reagents have been employed for the oxidation of alcohols to the corresponding carbonyl compounds. DMP **34** and its cyclic precursor, *o*-iodosylbenzoic acid (IBX) **33**, are commonly used for the oxidation of alcohols.[7b] In 1994, IBX **33** was used for first time for the oxidation of alcohols in DMSO.[120] Although IBX can be used for the oxidation of alcohols[121] but is more commonly employed in the oxidation of 1,2-diols.[120,122] Generally, DMP **34** can be used to cleave the carbon–carbon bond of 1,2-diols.[43,122] The application of DMP **34** is not limited to the oxidation of alcohols, oxidative additions and oxidative substitution reactions can be achieved successfully as well. Yadav and his coresearchers described a one-pot oxidative conjugate addition of Morita–Baylis–Hillman adducts **94** with allyltrimethylsilane **95** in the presence of DMP/boron trifluoride–diethyl ether complex under mild reaction conditions. The reaction products **96** were obtained in 65–87% yield (equation 1).[123]



94 **95** **96** (65–87%) (1)

Oxidative conjugate addition of Morita–Baylis–Hillman adducts **94**

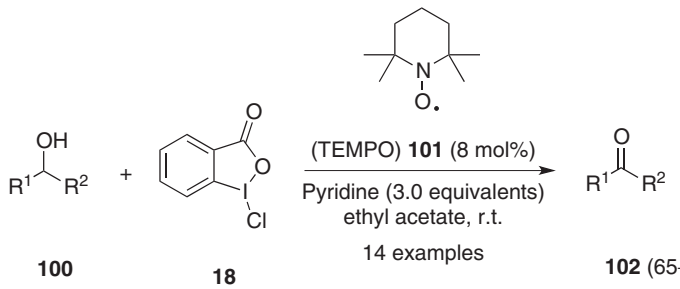
Recently, DMP **34** has been applied for the direct conversion of secondary alcohols to α-organosulfonyloxyketones. The α-tosyloxyketones **98** and α-mesyloxyketones **99** were directly synthesized from the corresponding alcohols **97** in a single flask by treatment with hypervalent iodine(V) reagents in combination with *p*-toluenesulfonic acid and methanesulfonic acid, respectively. The oxidation products were obtained in moderate to good yields (equation 2). These oxidation reactions could be achieved under solvent-free conditions.[124]



97 **98:** R^2 = OTs (68–92%) **99:** R^2 = OMs (64–88%) (2)

Direct conversion of secondary alcohols **97**

In 2007, Wirth and coworkers used the polyfluorinated IBX analog **42** (FIBX) for the oxidation of 1,2-diols and one hydroxyl was selectively oxidized into a carbonyl moiety.[27] It was mentioned earlier that IBX has received limited applications as an oxidant because of solubility issues.[26] Recently, Li and Zhang developed the combination of IBA analog **18** with 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO) **101** as a catalyst for various oxidation reactions (equation 3).[125] They have achieved the oxidation of alcohols **100** to the corresponding carbonyl compounds **102** in high yields. The important aspect of this reaction was the tolerance of many functional groups and reusing capability of **18**.[125]

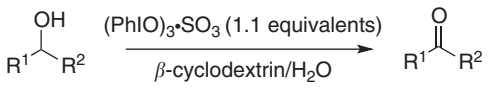


100 **18** **102** (65–87%) (3)

R^1 = alkyl, aryl, heteroaryl, or allyl
R^2 = H, alkyl, or aryl

TEMPO-catalyzed oxidation of alcohols **100** using IBA analogue **18**

Also acyclic hypervalent iodine reagents have been tested in the oxidation of alcohols. Zhu and Wei developed a highly efficient oxidation of alcohols **100** to the corresponding carbonyl compounds **102** with iodine(III) reagents catalyzed by β-cyclodextrin.[126] The oxidation reactions proceeded in water to afford oxidation products **102** in excellent yields and high selectivity without overoxidation to carboxylic acids (equation 4). Selective oxidation of primary alcohols in the presence of secondary alcohols was also achieved.[126]

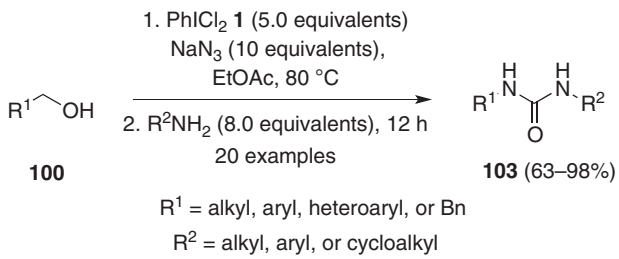


100 13 examples **102** (37–94%) (4)

R^1 = alkyl, aryl, heteroaryl, Bn, or allyl
R^2 = H, alkyl, or aryl

β-Cyclodextrin-catalyzed oxidation of alcohols **100**

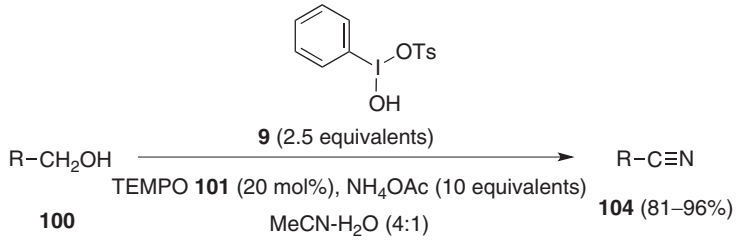
Zhang and coworkers used [bis(acetoxy)iodo]benzenes **4** with the combination of sodium azide for the oxidation of benzylic primary alcohols to symmetrical 1,3-diarylureas or substituted benzamides in a one-pot reaction.[127] In addition, the same combination of reagents can be employed for the oxidation of various secondary alcohols to their corresponding ketones in excellent yields.[127] Furthermore, secondary alcohols can be oxidized preferentially to the corresponding ketones in a mixture with primary alcohols under similar reaction conditions.[127] Very recently, Zhang and coworkers reported a one-pot synthesis of functionalized ureas **103** directly by oxidation of primary alcohols **100** using the combined reagent of iodobenzene dichloride **1** and sodium azide in ethyl acetate using primary amines as nucleophiles. The reaction products **103** were obtained in moderate to excellent yields via initial formation of acyl azides (equation 5).[128] By using the same combination of reagents, primary alcohols can be oxidized into the corresponding carbamoyl azides in high yields.[128] Recently, Kita and coworkers developed a TEMPO **101** catalyzed green approach for the selective oxidation of alcohols using tetraphenyladamantane-based iodine(III) reagents in moderate to excellent yields.[129]



(5)

Oxidation of alcohols **100** to functionalized ureas **103**

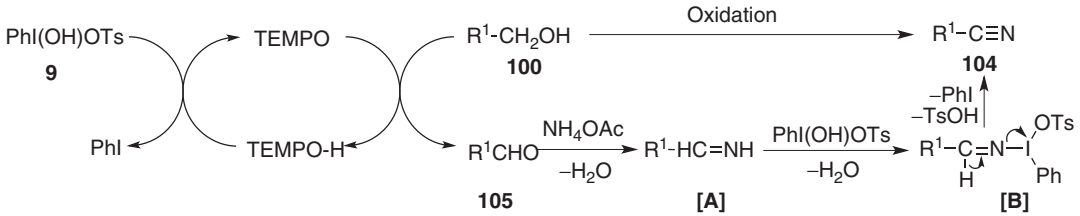
In 2010, Wirth and coworkers used the more reactive polyfluorinated hypervalent iodine(III) reagent **12a** for the oxidation of 1,2-diols.[19] Wei and coworkers employed the combination of Koser reagent **9** (hydroxy(tosyloxy)iodobenzene, HTIB) with ammonium acetate for the oxidation of alcohols **100** directly into corresponding nitriles **104** in excellent yields (equation 6).[130]



(6)

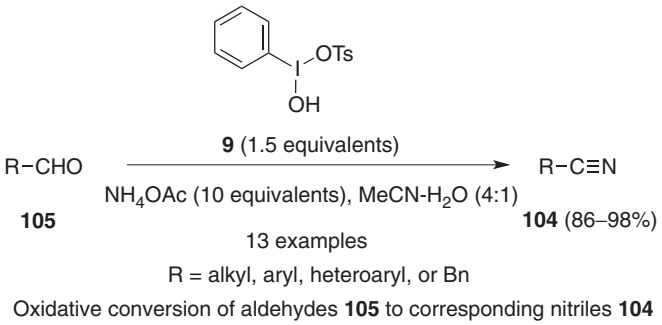
Oxidation of alcohols **100** to corresponding nitriles **104**

The reaction mechanism for the oxidation of primary alcohols **100** to the corresponding nitriles **104** is depicted in Scheme 1.[130] According to this mechanism, the reaction initiates with the oxidation of primary alcohol into corresponding aldehydes by oxidant TEMPO, whereas the role of Koser reagent **9** is to regenerate TEMPO from TEMPO-H. In the next step, the aldehyde reacts with ammonium acetate to form an aldimine intermediate **[A]**, which undergoes oxidation by HTIB to afford another *N*-I(OTs)Ph aldimine intermediate **[B]**. Elimination of HOTs from the *N*-I(OTs)Ph aldimine **[B]** gives nitrile **104** as final products. Iodobenzene was detected at the end of the reaction.



Scheme 1 Reaction mechanism for oxidation of alcohols **100** to corresponding nitriles **104**.

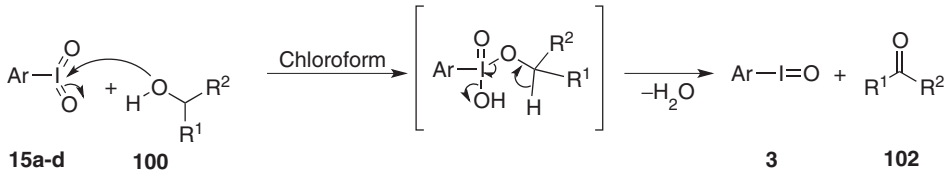
It is clear from the mechanism of oxidation of primary alcohols that alcohol is oxidizing initially into corresponding aldehyde intermediate **105**. Furthermore, the oxidative conversion of aldehydes **105** into corresponding nitriles **104** have been achieved under the same combination of reagents in the absence of TEMPO in 86–98% yields (equation 7), which could also support the above mechanism.[130]



(7)

Oxidative conversion of aldehydes **105** to corresponding nitriles **104**

Recently, the synthesis of *β*-enamino ketones was achieved by reaction of *endo* glycals with primary or secondary amines by using Koser reagent **9** as oxidant in a one-pot operation. The reaction products were isolated in moderate yields.[131] Iodylbenzene **14** is the simplest iodylarene(V) reagent without any functional group and used for the oxidation of benzyl alcohols to the corresponding bezaldehyde.[21] Zhdankin and coworkers reported the oxidation of alcohols **100** to their corresponding carbonyl compounds **102** with more than 99% conversion by using iodine(V) reagents **15a–d** as oxidant (**Scheme 2**).[22] In 2011, the same research group developed the oxidation of alcohols by iodylpyridines **16a–c** in high yields.[23]

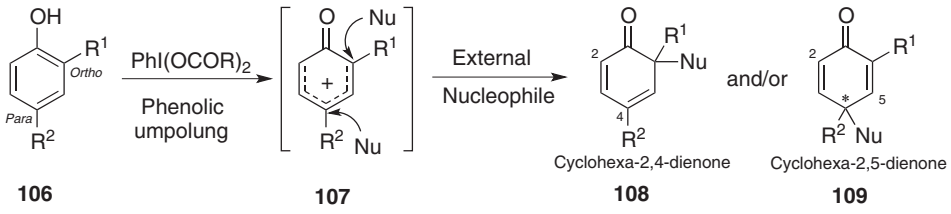


Scheme 2 Oxidation of alcohols using iodine(V) reagents **15a–d**.

In 2003, Kirschning and coworkers used polymer-supported hypervalent iodine reagent for the oxidation of alcohols in the presence of catalytic amount TEMPO **101**.[132] These reagents are advantageous because they can be recycled and reused in oxidation reactions. Various polymer-supported hypervalent iodine reagents have been used successfully in oxidation of alcohols to corresponding aldehydes and ketones.[7b,7c,80,81,83,84,91,93,95]

7.29.3.2 Oxidations of Phenols

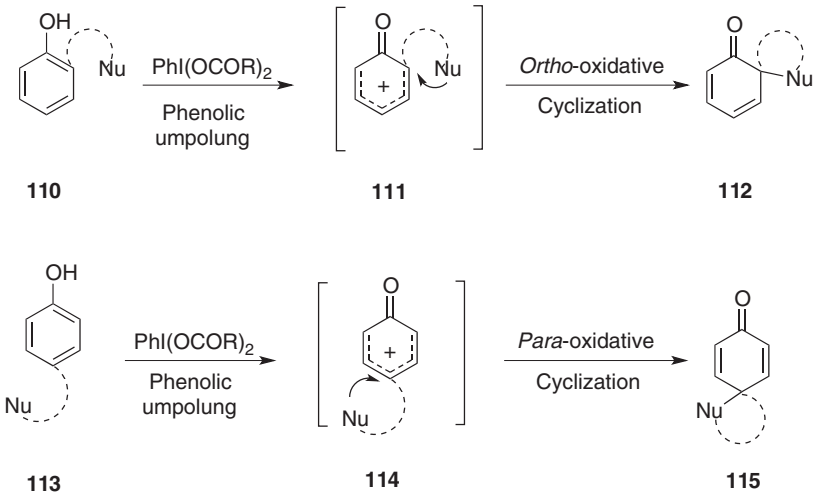
Oxidation of phenolic scaffolds has been developed as an important tool of synthetic and natural product chemistry.[9a,b] By using hypervalent iodine reagents, phenols **106** can be oxidized to corresponding quinone derivatives **107**, which can perform addition reactions with external nucleophiles. The formation of addition products **108** or **109** is dependent on the position of substitution on the phenol, *ortho*-and *para*-substituted phenols could lead to products **108** and **109**, respectively (**Scheme 3**).



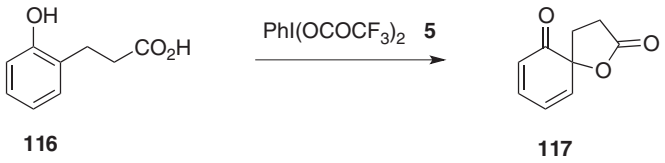
Scheme 3 Hypervalent iodine reagents-mediated oxidation of phenols **106**.

Phenolic compounds with internal nucleophiles can undergo oxidative cyclization reactions. The phenolic compounds **110** and **113** can form cyclic products **112** and **115** by using hypervalent iodine reagents (**Scheme 4**). Depending on the nature of the nucleophile, various spiro compounds have been synthesized using this approach.

Functionalized phenols such as **116** have been oxidized by hypervalent iodine reagent **5**, and depending on the substitution pattern, cyclizations have taken place as shown in equation 8.[133,134] Product **117** is unstable and undergoes a subsequent Diels–Alder reaction leading to polycyclic addition products in good yields. Some quinone oxidation products have also been used in subsequent Michael additions[135–139] or in Diels–Alder reactions.[140] Recently, Ciufolini and Liang reported an oxidative cyclization of dienic sulfonamides mediated by (diacetoxyiodo)benzene in trifluoroacetic acid (TFA), followed by a tandem intramolecular Diels–Alder reaction. The cyclized products lead to valuable synthetic intermediates for the himandrine alkaloids.[141]



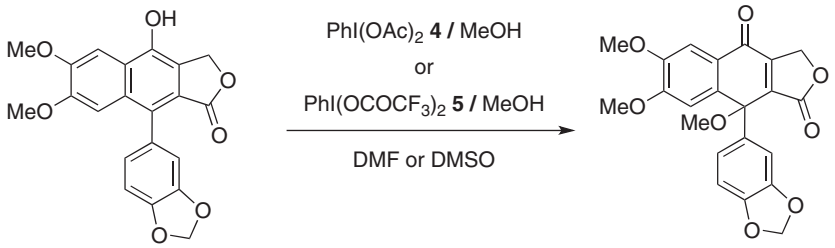
Scheme 4 Oxidative cyclizations of phenols **110** and **113** having internal nucleophiles.



(8)

Oxidative cyclization of *ortho*-substituted phenol **116**

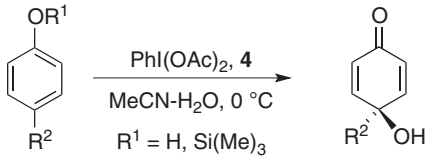
In 2005, Kita and coworkers reported the synthesis of dienone lactones through oxidation of nonphenolic alkanoic acid derivatives followed by an intramolecular cyclization using a combination of hypervalent iodine(III) reagent and heteropoly acid. This approach was applied for the preparation of highly oxygen-substituted dienone lactone scaffolds.[142] Oxidation of aromatic ring of diphyllin **118** bearing a free phenolic group was achieved by iodine(III) reagents **4** or **5** in methanol to 1-methoxy-1-aryl-4-oxonaphthalene lactone **119** in high yields (equation 9). The reaction products **119** have been used as important intermediates for the synthesis of various valuable compounds.[143] The phenolic compound diphyllin **118** is a natural product, which was isolated from the plant *Cleistanthus collinus*.



(9)

Oxidation of aromatic ring of diphyllin **118** using **4** or **5**

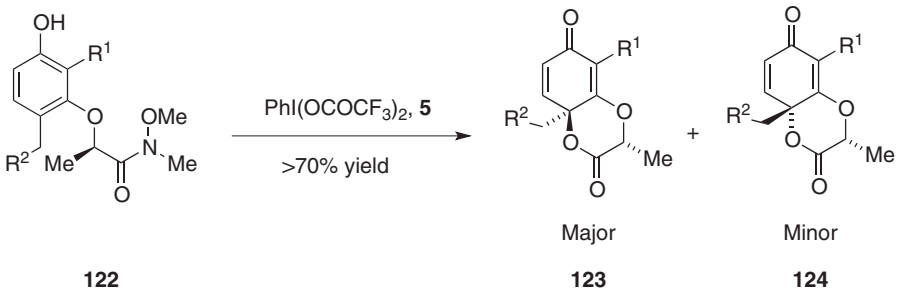
In 2007, Felpin reported an efficient synthesis of *p*-arylquinols **121** by the oxidation of 4-arylphenol trimethylsilyl ethers **120** with (diacetoxyiodo)benzene **4** in a MeCN–H_2O solvent combination (equation 10). Interestingly, the trimethylsilyl protected phenols **120** ($R^1 = SiMe_3$) showed better yields of *p*-quinols by minimizing side products compared with the oxidation of free phenols **120** ($R^1 = H$) with hypervalent iodine(III) reagents.[144]



(10)

(Diacetoxyiodo)benzene **4** mediated dearomatization of protected phenols **120**

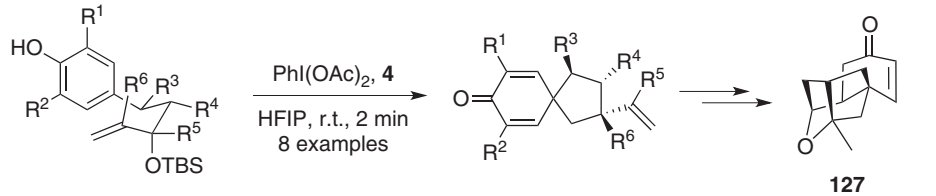
The hypervalent iodine reagents IBX **33** and [bis(trifluoroacetoxy)iodo]benzene **5** have been used for the regiocontrolled oxidation of polycyclic aromatic phenols to specific isomers of polycyclic aromatic quinones. The reaction products were obtained in good to moderate yields.[145] Pettus and researchers developed an iodine(III)-mediated oxidative dearomatization of resorcinol derivatives **122** to stable chiral cyclohexadienones **123** and **124** as useful building blocks for the construction of many highly functionalized chiral six- and seven-membered ring systems (equation 11).[146]



122 **123** **124** (11)

Oxidative dearomatization of resorcinols **122** using iodine(III) reagent **5**

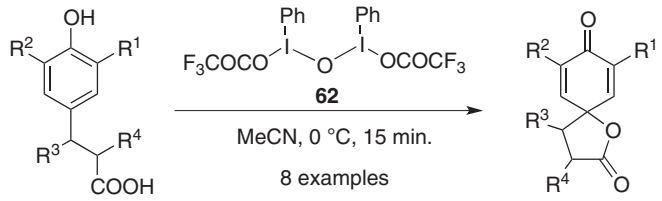
In 2011, Canesi and coworkers reported an oxidative prins-pinacol tandem process mediated by (diacetoxyiodo)benzene **4**. This oxidative version of the famous tandem process fits within the concept of 'aromatic ring umpolung' and allows the stereoselective transformation of simple phenols to highly elaborated spirocyclic dienone cores containing several quaternary carbon centers. In this process, the phenolic compounds **125** were oxidized into spirocyclic dienones **126** in moderate yields. Furthermore, the products **126** have been used in the synthesis of the antibiotic agent platensimycin main fragment **127** in two chemical steps (Scheme 5).[147a] Recently, the same group reported the activation of phenol derivatives with hypervalent iodine reagent **4** promoting the formation of polycyclic compounds via a cationic cyclization process. The method is applicable for the synthesis of various naturally occurring compounds.[147b]



125 **126** (30–84%) **127** (–)-Platensimycin main core

Scheme 5 (Diacetoxyiodo)benzene-mediated oxidation of phenols **125** to spirocyclic dienones **126**. HFIP, hexafluoro-2-propanol.

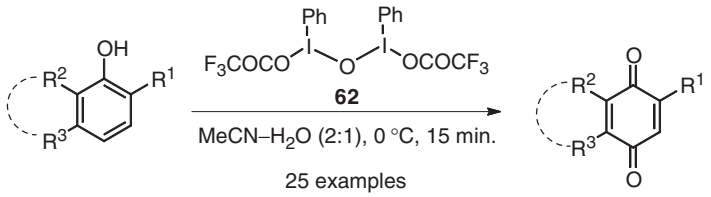
Recently, Kita and his coworkers used the bridged hypervalent iodine(III) reagent **62** for the oxidation of phenols. By using **62** as oxidant, the functionalized phenols of type **128** can be oxidized to the corresponding spirocyclohexadienone derivatives **129** in excellent yields. In these reactions, the bridged iodine(III) reagent **62** showed better reactivity than **5** (equation 12).[64a] Furthermore, Coelho and coworkers developed an iodine(III)-induced synthesis of highly functionalized spirocyclohexadienones from Morita–Baylis–Hillman adducts.[64b]



128 **129** (80–98%) (12)

Bridged iodine(III) reagent **62** induced oxidative cyclization of phenols **128**

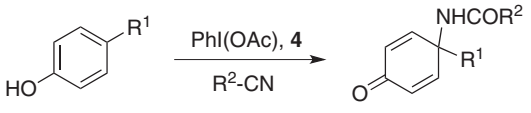
The same research group developed the approach for oxidative dearomatization of phenols **130** by using the highly reactive bridged iodine(III) species **62**. The reactions were carried out in MeCN–H_2O mixture in 2:1 ratio and dearomatized 1,4-quinones **131** were isolated in high yields (equation 13).[65] The reagent **62** has shown more promising results than **4** or **5**.



130 **131** (70–98%) (13)

Oxidative dearomatization of phenols **130**

The oxidative amidation of phenols affects the conversion of appropriately substituted phenols into 4-amidodienones ('*para*-oxidative amidation') or 2-amidodienones ('*ortho*-oxidative amidation') by the action of hypervalent iodine reagents. The hypervalent iodine(III) reagent **4** is especially effective in these transformations. The bimolecular oxidative amidation of 4-substituted phenols **132** has been achieved successfully in good yields (equation 14).[148]



132 **133** (50–85%) (14)

(Diacetoxyiodo)benzene-induced oxidative amidation of *p*-substituted phenols **132**–**133**

Oxidative amidation reactions of phenolic amines such as the cyclization of phenolic oxazolines **134** and **134a**,[149,150] and of *ortho*- and *para*-phenolic sulfonamides **137** and **137a**[151,152] have been reported by using iodine(III) reagent **4** (Scheme 6).

These cyclization reactions have been used for the synthesis of azaspirocyclic natural products such as FR-901683[153] and TAN-1251C.[154] The oxidative cyclizations of phenolic secondary amines **140** and **142** have been also achieved and employed in total synthesis of FR-901683 and of TAN-1251 compounds (Scheme 7).[155–159]

The treatment of various functionalized phenols in the presence of iodine(III) reagent **4**, perfluorinated alcohols and furan produced tricyclic heterocyclic compounds via a formal [2+3] cycloaddition. The addition products **146** were obtained in moderate yields (Scheme 8).[160]

Canesi and coresearchers have reported the synthesis of dihydrobenzofurans by treatment of various substituted phenols in the presence of allyltrimethylsilane, (biacetoxyiodo)benzene **4**, in perfluorinated alcohols via formal [2+3] cycloaddition in moderate to useful yields (Scheme 9).[161]

Furthermore, various other heterocyclic systems such as dihydrofuranobenzofurans, tetrahydrofuranobenzofurans, tetrahydropyranofurans, etc., could be obtained by using similar oxidative annulation processes.[162]

7.29.3.3 Oxidation of Aromatic Amines

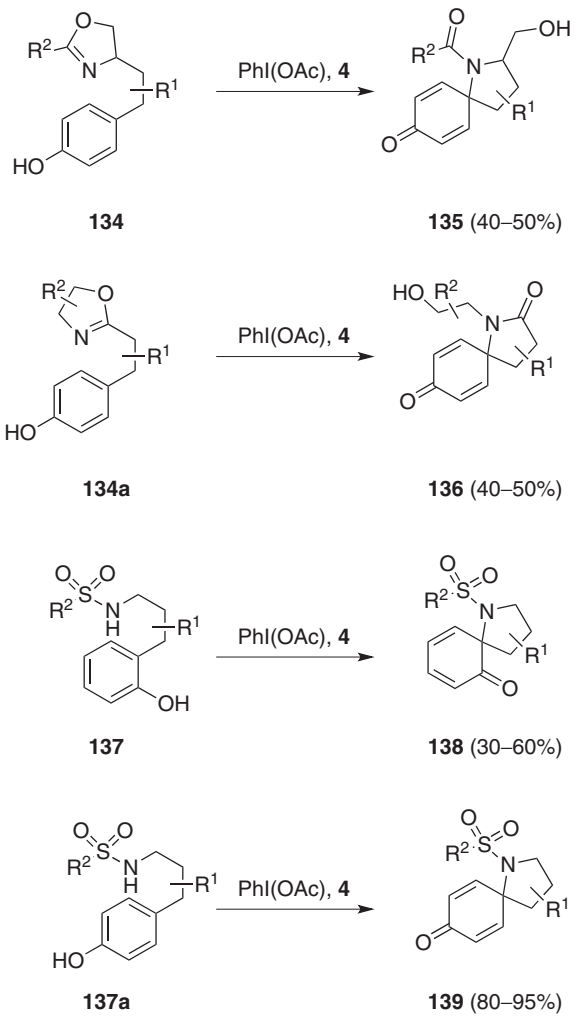
Like dearomatization of phenols, the oxidative dearomatization of aromatic amines can be achieved using hypervalent iodine reagents. Recently, Peddinti and coworkers have developed the oxidation of various functionalized *p*-methoxyanilides **149** with (diacetoxyiodo)benzene **4** to dearomatized carbamate-protected *p*-quinone monoimine ketals **150** (Scheme 10).[163] If the reaction is carried out in the presence of silica gel, the monoketals **152** are obtained directly.

Using the same hypervalent iodine(III) reagent **4**, the cyclization of indolic oxazolines **153**[164] and sulfonamides **155**[165] has been achieved. The cyclized products **154** and **156** were isolated in good to moderate yields (Scheme 11). Recently, Ma and coworkers have developed the oxidative dearomatization of primary and secondary amines with hypervalent iodine reagent DMP **34** in moderate to excellent yields.[166]

The synthesis of benzimidazole-fused heterocycles has been achieved by intramolecular oxidative cyclization of secondary amines. The secondary amines of type **157** and **159** can be converted to benzimidazole-fused heterocycles **158** and **160** by reaction with the Koser reagent **9** in moderate yields (Scheme 12).[167] The DMP-mediated oxidative cyclization of unsaturated anilides has also been reported and applied successfully in the total synthesis of phomoidrides A and B.[168]

7.29.3.4 Oxidation of Aliphatic Amines

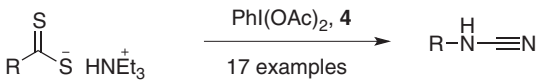
Similar to the oxidation of alcohols, the oxidation of amines has been achieved successfully. Kuhakarn and coworkers reported the oxidation of amines **161** to the corresponding nitriles **104** and aldehydes **105** using cyclic iodine(V) reagent IBX **33**. Nitriles **104** were isolated as major products with up to 85% yield, whereas the aldehydes **105** were obtained as minor products. The mechanism for the formation of nitriles and aldehydes is also indicated in Scheme 13.[169]



Scheme 6 Oxidative amidation of phenols.

Recently, Wei et al. developed an elegant procedure for the direct oxidation of primary, secondary, and tertiary amines **161** into the corresponding nitriles **104** using the hypervalent iodine(III) reagent hydroxy(tosyloxy)iodobenzene **9** (Scheme 14). To check the competitive oxidation of primary, secondary, and tertiary amines, the reaction was performed using a mixture of all three types of amines. The results suggest that a chemoselective oxidation of primary amines in the presence of secondary and tertiary amines is possible using this system.[130]

In 2009, Patel and coworkers reported an efficient synthesis of cyanamides **163** from dithiolates of type **162** promoted by the hypervalent iodine(III) reagent **4**. The reaction products **163** were obtained in moderate yields (equation 15).[170]



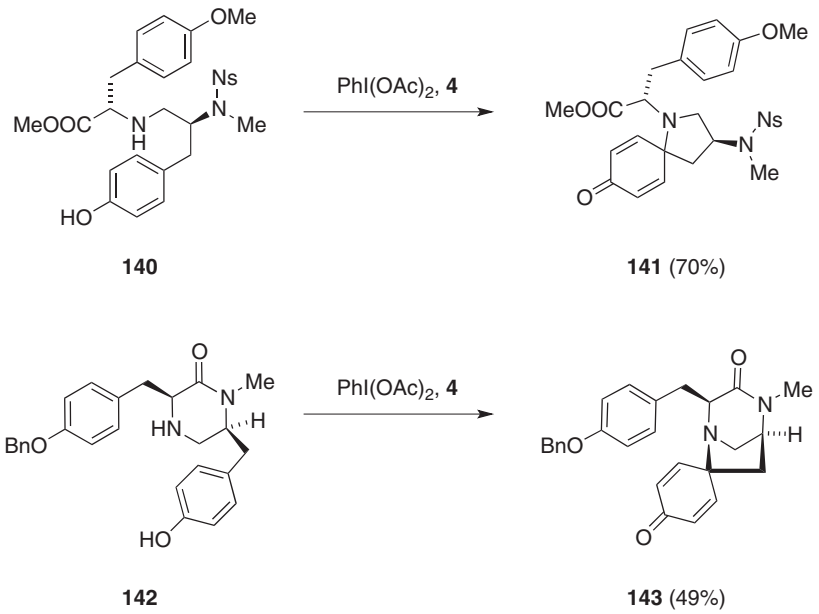
(15)

R = aryl, alkyl, or benzyl groups

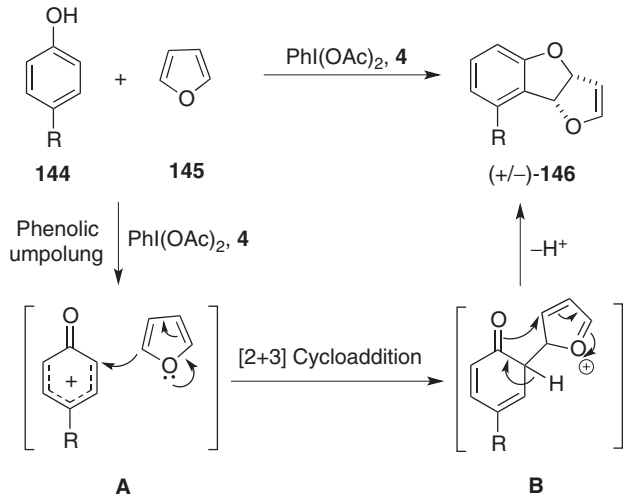
(Diacetoxyiodo) benzene-induced oxidation of dithiolates **162** to cynamides **163**

Kumar and researchers have reported a hypervalent iodine-mediated oxidation of 1,2-diaminobenzimidazole **164** and its Schiff bases **167**. The reaction produces 3-amino-1,2,4-benzotriazine **166** and 2-aryl-1,2,4-triazolo 1,5–a benzimidazoles **169** in moderate yields (Scheme 15).[171]

In 2008, Bao and coworkers investigated the metal-free oxidative amidation of aromatic aldehydes **170** with primary amines **171** by using hypervalent iodine(III) reagent **4**. The reaction products **172** were isolated in good to moderate yields. Various

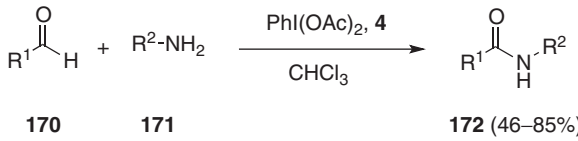


Scheme 7 Oxidative cyclizations of phenolic secondary amines **140** and **142**.



Scheme 8 (Diacetoxyiodo)benzene-mediated synthesis of tricyclic heterocyclic compounds **146** via a formal [2+3] cycloaddition.

aromatic moieties in the aldehydes were tolerated (equation 16).[172] Recently, Bernini and coworkers have shown some useful and efficient applications of IBX **33** in the oxidative chemistry of flavonoids to obtain bioactive compounds in high yields.[173]

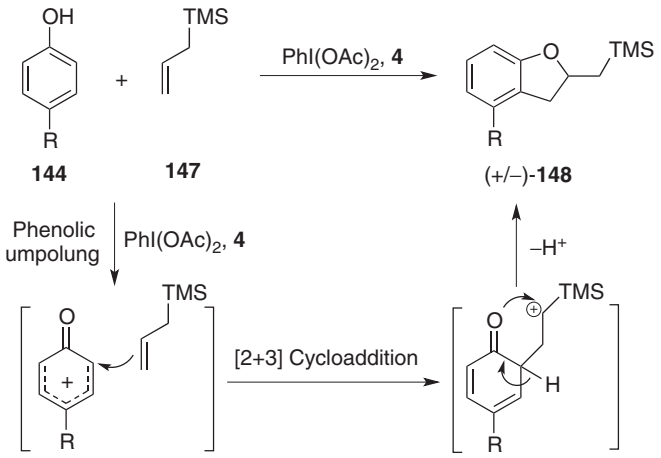


(16)

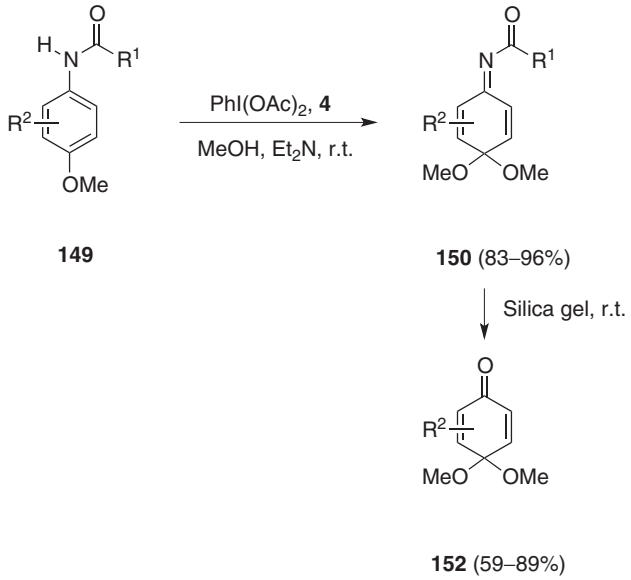
Oxidative amidation of aldehydes **170** with primary amines **171** using **4**

7.29.3.5 Oxidation of Amides

Similar to oxidation of alcohols and amines, the oxidation reactions of amides have received particular attention in past few years.[7f] In 2005, Nicoloau and Mathison reported a DMP **34**-mediated oxidation of amides **173** and **175** to the corresponding



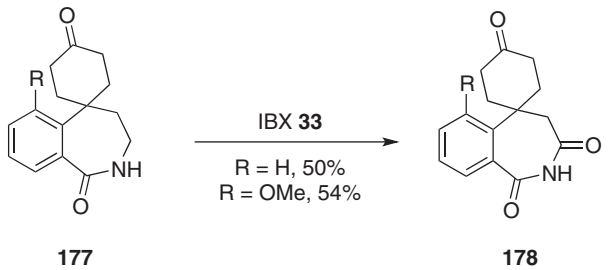
Scheme 9 (Diacetoxyiodo)benzene-induced synthesis of dihydrobenzofurans.



Scheme 10 (Diacetoxyiodo)benzene-mediated oxidative dearomatization of *p*-methoxyanilides **149**.

imides **174** and **176** in excellent yields. Various functional groups such as aromatic halides, ether, and double bonds are being tolerated in this oxidation reaction (Scheme 16).[174]

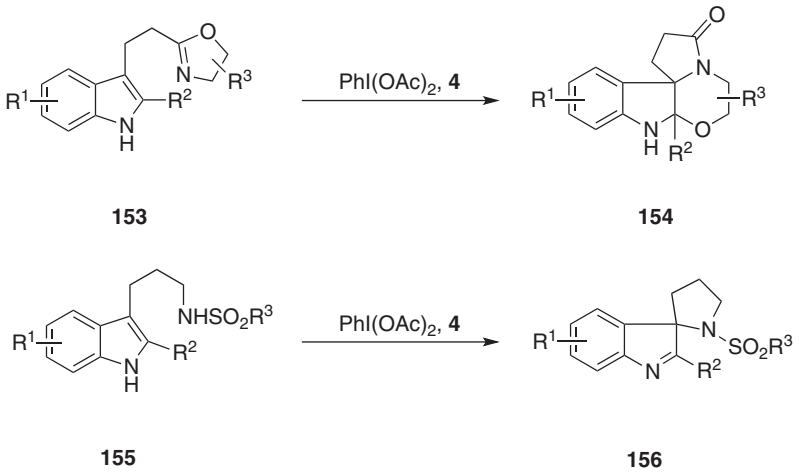
Later, Szántay and coworkers reported the IBX **33**-mediated oxidation of lactams **177** to imides **178** in good yields. The same research group also used this oxidation approach for the total synthesis of galanthamine-type *Amaryllidaceae* alkaloids (equation 17).[175,176]



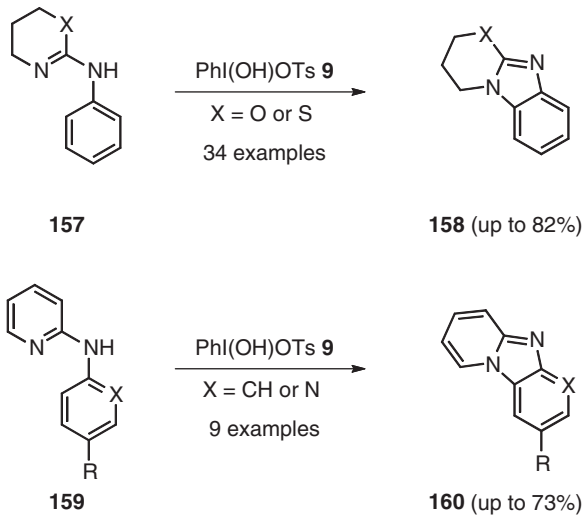
(17)

177 **178**

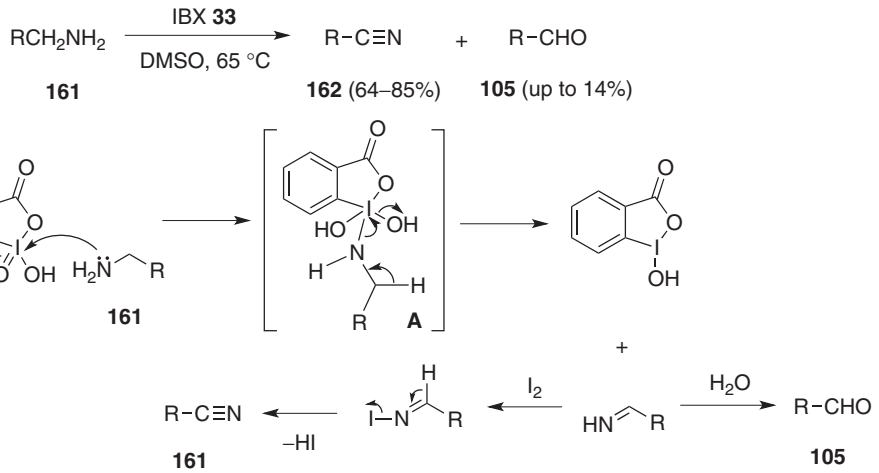
IBX-mediated oxidation of lactams **177** to imides **178**



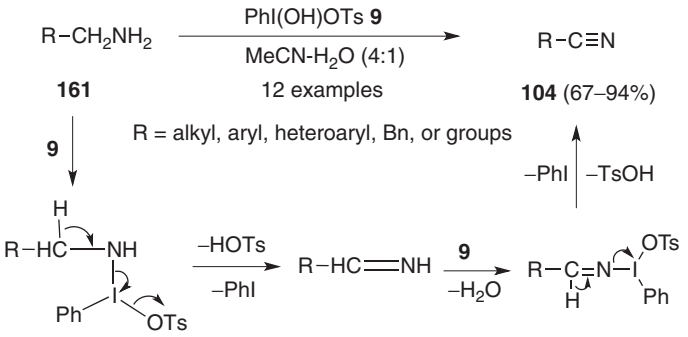
Scheme 11 (Diacetoxyiodo)benzene-mediated cyclization of indolic oxazolines **153** and sulfonamides **155**.



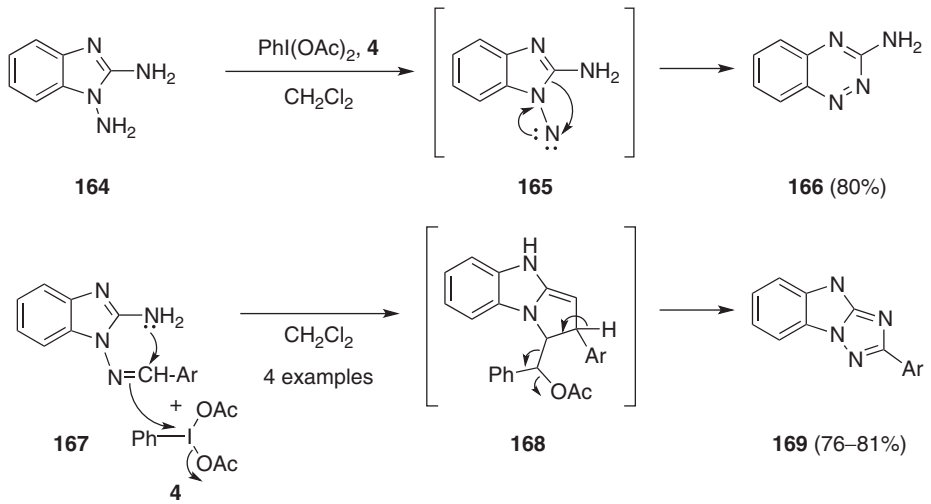
Scheme 12 Koser reagent-mediated cyclization of amines **157** and **159**.



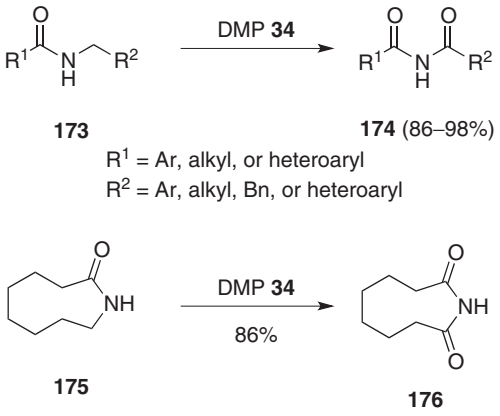
Scheme 13 IBX-mediated oxidation of amines **161**.



Scheme 14 Koser reagent-mediated oxidation of amines **161**.



Scheme 15 (Diacetoxyiodo)benzene-mediated oxidation of 1,2-diaminobenzimidazole **164** and its Schiff bases **167**.

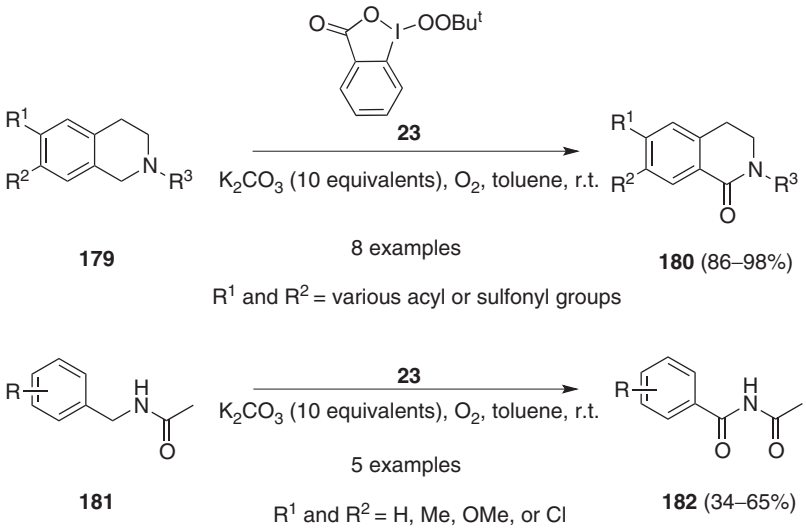


Scheme 16 DMP-mediated oxidation of amides **173** and **175**.

The radical oxidation of various amides **179** and **181** has been achieved with hypervalent *tert*-butylperoxyiodinanes **23** in the presence of molecular oxygen using potassium carbonate as a base. The reaction products **180** and **182** were isolated in good yields as shown in Scheme 17.[177,178]

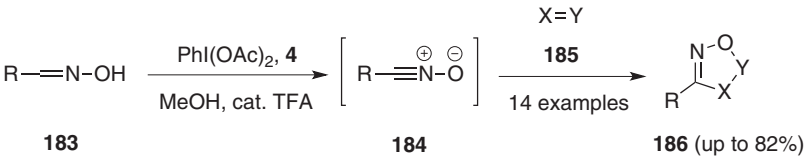
7.29.3.6 Oxidation of Oximes

Recently, Ciufolini and his research group emphasized his efforts toward the oxidation of oximes using hypervalent iodine reagents. They have achieved a (diacetoxyiodo)benzene 4-mediated oxidation of oximes **183** to the corresponding nitrile oxides



Scheme 17 The radical oxidation of various amides **179** and **181** using cyclic iodine(III) reagent **23**.

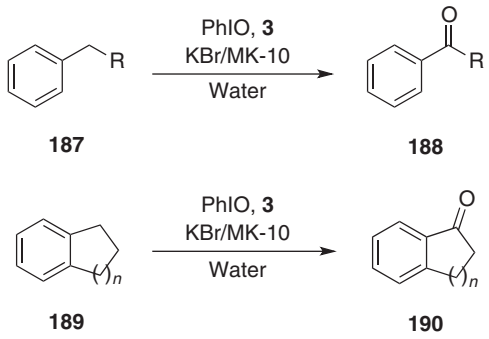
184 via the oxidative cleavage of the carbonyl-imino σ bond. Furthermore, the nitrile oxides **184** thus formed were trapped with various olefins **185** and formed various heterocyclic compounds of type **186** in good yields (Scheme 18).[179,180] The reaction was working well with both α-oxo-aldoximes and oxo-ketoximes.



Scheme 18 (Diacetoxyiodo)benzene **4**-mediated oxidation of oximes **183** to nitrile oxides **184**.

7.29.3.7 Oxidation of Benzylic C–H Bonds

Recently, hypervalent iodine(III) reagents **3** and **5** have been successfully used for the oxidation of benzylic C–H bonds. In 2008, Kita et al. reported the oxidation of benzylic C–H bonds of compounds type **187** and **189** using unreactive and insoluble polymeric iodosobenzene **3** in water in the presence of KBr and montmorillonite-K10 (M-K10) clay. The oxidized products **188** and **190** were isolated in moderate to excellent yields (Scheme 19).[181]



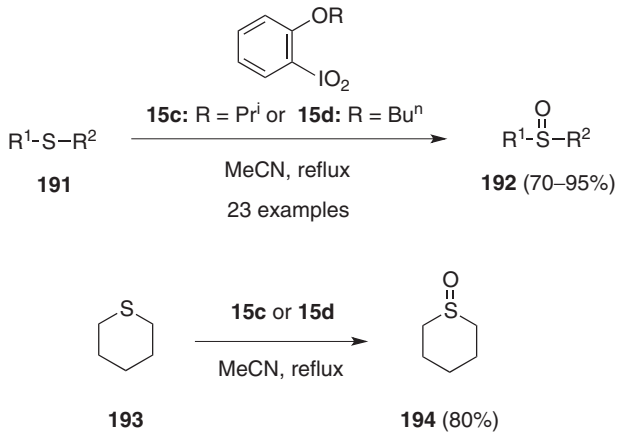
Scheme 19 PhIO-induced oxidation of benzylic C–H bonds.

Kilic and Catir have reported a similar type of benzylic C–H oxidations using reagents **5** and TBHP **23**.[182] This approach was also applicable for the oxidation of allylic C–H bonds.

7.29.3.8 Oxidation of Sulfides

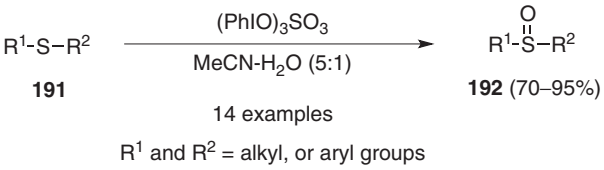
Hypervalent iodine reagents are frequently used for the oxidation of chalcogen compounds. The oxidation of sulfides leads often to mixtures of sulfoxides and sulfones under drastic conditions. By using hypervalent iodine reagents, generally only sulfoxides are

formed in excellent yields.[183] Recently, several hypervalent iodine reagents have been successfully applied in the oxidation of sulfides to sulfoxides.[13,19,48,57–59] In 2006, Zhdankin and coworkers used iodine(V) reagents such as 1-iodyl-2-isopropoxybenzene **15c** and 1-iodyl-2-butoxybenzene **15d** for the selective oxidation of sulfides **191** and **193** to the corresponding sulfoxides **192** and **194**. The oxidation products **192** and **194** were isolated in high yields (Scheme 20).[22] Later, iodine(III) reagent **11a** was used for the oxidation of thioanisole to thioacetophenone in 86% yield.[18] Wirth and coworkers achieved the oxidation of thioanisole to thioacetophenone in 90% yield using cyclic iodine(V) reagent **42**.[27]



Scheme 20 Hypervalent iodine-mediated oxidation of sulfides **191** and **193**.

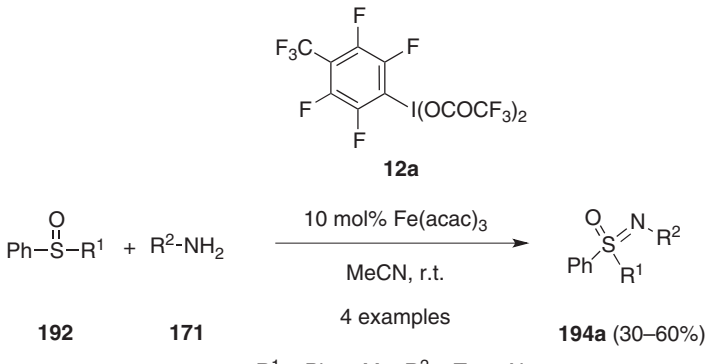
In 2009, Zhdankin et al. developed oligomeric iodosylbenzene sulfate-mediated oxidation of sulfides **191** to **192** in high yields in water (equation 18).[184] Recently, the same research group has achieved the oxidation by using pyridine-based iodine(V) reagents in excellent yields.[23]



(18)

Oxidation of sulfides **191** to sulfoxides **192** using oligomeric iodosylbenzene sulfate

Hypervalent iodine reagents are not only limited for the oxidation of sulfides but they can be used for the oxidation of the sulfoxides to provide sulfoximines. Sulfoximines are highly valuable compounds and used as ligands, auxiliaries, and chiral building blocks in organic chemistry.[185–188] The synthesis of sulfoximines **193** can be achieved by the oxidation of sulfoxides **192** using iodine(III) reagent **12a** in the presence of 10 mol% of [Fe(acac)$_3$] in moderate yields. The amines **161** were used as source of nitrogen (equation 19).[19] The other hypervalent iodine reagents can also be used for this reaction.[189]

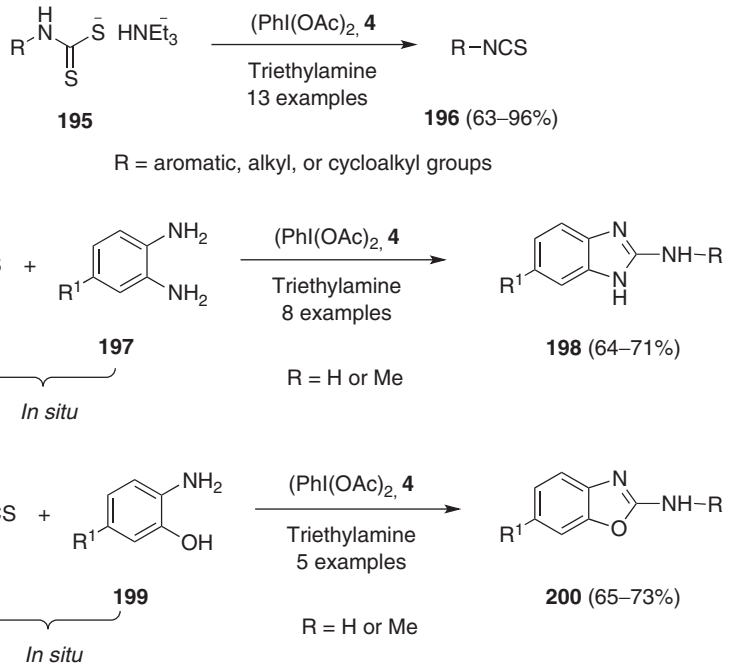


(19)

R^1 = Ph or Me; R^2 = Ts or Ns

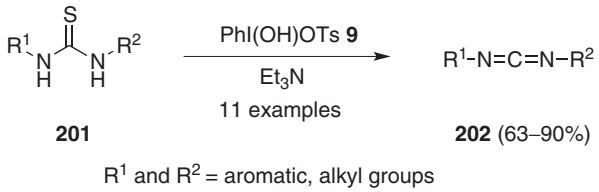
Iodine(III)-mediated synthesis of sulfoximines **194a**

Hypervalent iodine reagents can be used for desulfurization reactions. In 2008, Patel and coworkers explored the ability of **4** in the preparation of isothiocyanates **196** from the corresponding dithiocarbamate salts **195**. Furthermore, *in situ* generated **196** reacted with *o*-phenylenediamine **197** and *o*-aminophenol **199** to form benzimidazoles **198** and aminobenzoxazoles **200**, respectively, under similar reaction conditions. The products **196**, **198**, and **200** were isolated in good yields (Scheme 21).[190]



Scheme 21 (Diacetoxyiodo)benzene-mediated desulfurization reactions of **195**.

Recently, an efficient synthesis of symmetrical and unsymmetrical carbodiimides **202** has been achieved from the corresponding thioureas **201** via dehydrosulfurization using Koser's reagent **9**. The oxidation afforded carbodiimides in excellent yields with high selectivity (equation 20).[191] Furthermore, the oxidative desulfurization approach can be utilized for the construction of oxadiazole and thiadiazole heterocycles using iodobenzene and oxone.[192]

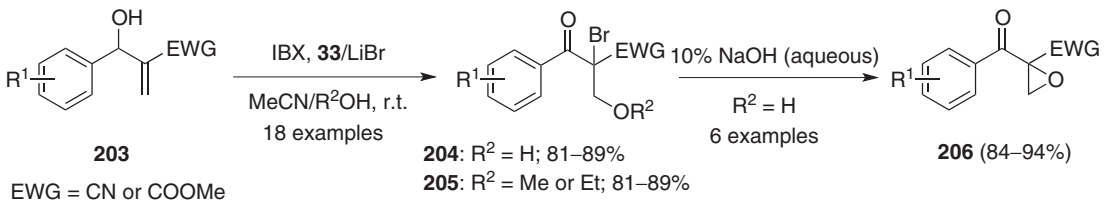


(20)

Koser's reagent induced dehydrosulfurization of thioureas **201**

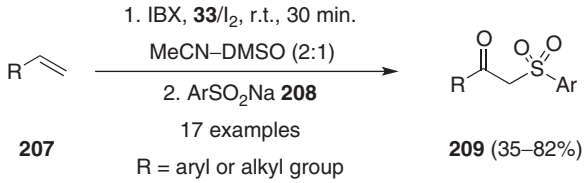
7.29.3.9 Oxidation of Alkenes

Various oxidation reactions of alkenes have been achieved by using hypervalent iodine reagents.[193–197] The oxidative anti-Markownikov bromohydroxylation and bromoalkoxylation of Baylis–Hillman (BH) adducts (olefins) has been reported using LiBr as the bromine source and IBX **33** as the oxidant. The process involves oxidation of BH adducts with IBX **33** to give *β*-ketomethylene compounds *in situ*, which undergo highly regioselective vicinal functionalization with LiBr/H_2O or LiBr/ROH in the same vessel to afford *α*-bromo-*β*-hydroxy compounds **204** or *α*-bromo-*β*-alkoxy compounds **205**, respectively, in excellent yields. Furthermore, the *α*-bromo-*β*-hydroxy compounds **204** can be transformed to epoxides in excellent yields (Scheme 22).[198]



Scheme 22 Synthesis of *β*-epoxyketones **206**. EWG, electron withdrawing group.

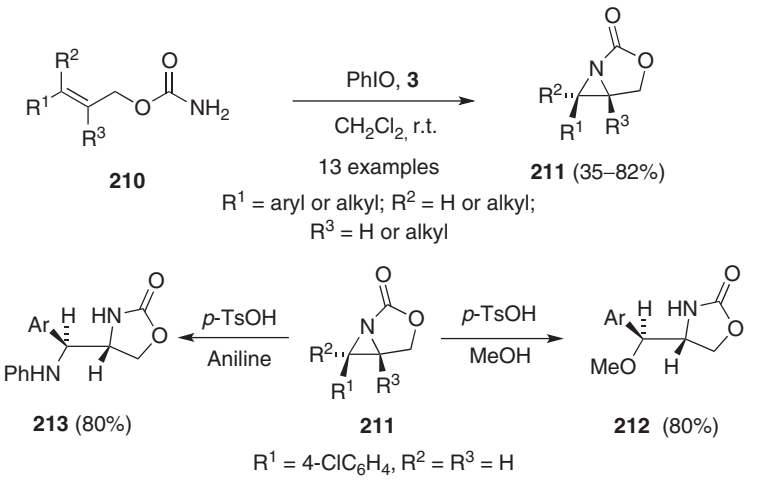
Recently, the synthesis of β-keto sulfones has been reported by the oxidation of olefins using combination of IBX **33**/I_2 followed by the addition of arenesulfinates. The oxidized products were isolated in moderate yields (equation 21).[199]



(21)

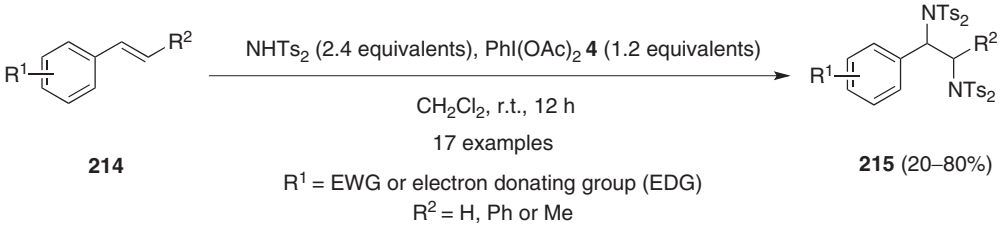
IBX-mediated synthesis of β-keto sulfones **209**

In 2007, Wirth and coworkers reported a detailed study of hypervalent iodine-mediated aziridination of alkenes.[200] Recently, PhIO-mediated metal-free intramolecular aziridination reaction of allylic carbamates **210** was developed as shown in Scheme 23.[201] Analytically pure aziridines **211** were obtained in high yields by simple filtration of the reaction mixture.



Scheme 23 Hypervalent iodine-mediated aziridination of alkenes **210**.

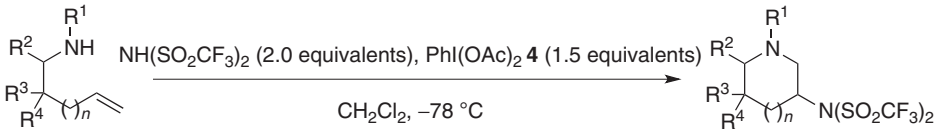
Furthermore, *in situ* ring opening of the aziridines provides an easy access to useful vicinal amino alcohol derivatives **212** and diamine compounds **213** (Scheme 23).[201] Recently, hypervalent iodine reagent-mediated diamination of alkenes have received particular attention from various organic chemists. In 2011, Muñiz and coworkers reported an unexpected enantioselective 1,2-diamination reaction of styrenes that proceeds in the presence of a defined chiral hypervalent iodine(III) reagent and bissulfonimides as nitrogen sources.[202] The same research group has reported a procedure for vicinal diamination of alkenes **214** using **4** as oxidant and bissulfonimides as source of nitrogen. The reaction products **215** were obtained in variable yields (equation 22).[203] Various alkenes such as terminal, internal, and cyclic alkenes have been employed in this reaction. Furthermore, the asymmetric version of this reaction have been achieved up to 63% enantiomeric excess (*ee*) using chiral hypervalent iodine reagent **86** (R=Me).[203]



(22)

Vicinal diamination of alkenes **214** using **4** as oxidant

Very recently, Blakey and Kong introduced a direct intramolecular diamination of terminal olefins **216** to functionalized six-membered cyclic amines of type **217** using **4** as oxidant. The reaction products **217** have been isolated in moderate to excellent yields (equation 23).[204] The synthesis of five-membered cyclic amines can be also achieved by using same reaction and conditions by changing the alkenes.[204]



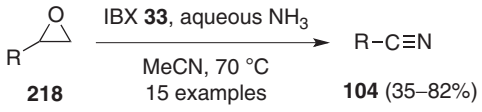
(23)

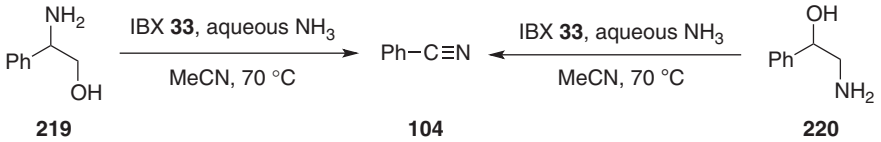
(Diacetoxyiodo)benzene-mediated intramolecular diamination of terminal olefins **216**

7.29.3.10 Oxidation of Epoxides

The oxidation of epoxides using hypervalent iodine reagents is not a very popular reaction in synthetic organic chemistry. In 2011, Akamanchi and coworkers reported that oxiranes of type **218** undergo oxidative fragmentation when treated with cyclic hypervalent iodine(V) reagents, particularly with IBX **33**, in aqueous ammonia to yield the corresponding nitriles **104**. The formation of nitriles **104** could be explained via the formation of 1,2-amino alcohols as intermediates followed by carbon–carbon bond cleavage.

Furthermore, the mechanism was supported by carrying out the reaction of 2-amino-2-phenylethanol **219** and 2-amino-1-phenylethanol **220** with IBX in aqueous ammonia, and the expected benzonitrile **104** was obtained in very high yields and as a single product (Scheme 24).[205] In addition, hypervalent reagents can be used for iodo-functionalization of alkenes and alkynes.[206]





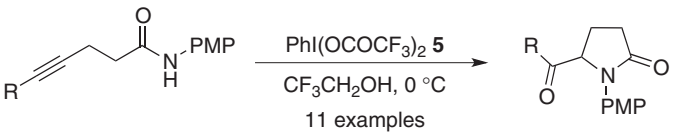
Scheme 24 Oxidative fragmentation of oxiranes **218** using IBX **33** as oxidant.

7.29.4 Cyclization Reactions

A multitude of cyclization reactions has been developed using hypervalent iodine reagents as oxidants or as electrophiles. Some cyclization reactions have been discussed in Sections 7.29.3.2, 7.29.3.3, and 7.29.3.9, particularly the oxidation of phenols, anilines, and alkenes. Generally, hypervalent iodine-mediated cyclizations can lead to cyclic compounds having different ring sizes. On the basis of formation of various ring sizes, the cyclization reactions have been categorized further.

7.29.4.1 Monocyclic Heterocycles

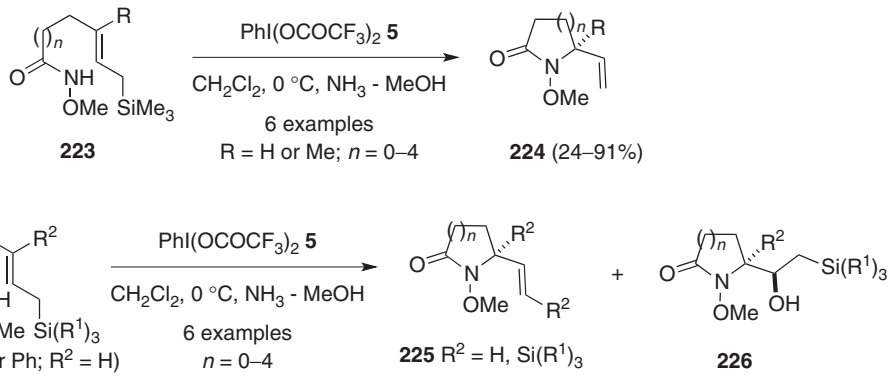
Various hypervalent iodine-mediated cyclization reactions led to monocyclic compounds, particularly nitrogen- and oxygen-based heterocycles. In 2005, Tellitu and coworkers investigated a novel (diacetoxyiodo)benzene-mediated alkyne amidation to achieve the synthesis of 5-aroyl-pyrrolidinones.[207a] The oxidation of functionalized amides **221** by **5** provides the generation of a nitrenium ion that can react intramolecularly with a triple bond, leading to the construction of 5-aroyl-pyrrolidinones **222** in moderate yields (equation 24).[207a] This type of cyclization was also reported to lead to *N*-alkylated derivatives of **222**.[207b]



(24)

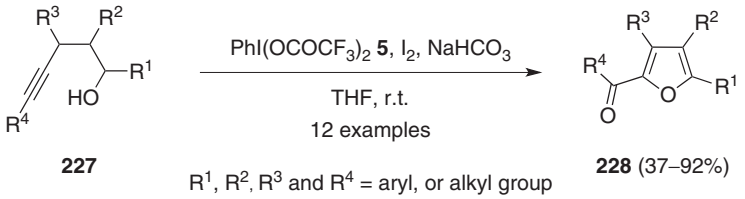
(Diacetoxyiodo)benzene-mediated oxidation of functionalized amides **221**

Wardrop and researchers developed a versatile method for the synthesis of various four- to eight-membered α-vinyl and α-(2-silylvinyl) lactams **224–226** involving the oxidative cyclization of unsaturated *O*-alkyl hydroxamates **223**. The course of reaction can be effectively controlled by variation of the substitution pattern at the silicon center. Although allyltrimethylsilanes **223** undergo ring closure with desilylation to form α-vinyl lactams **224**, the corresponding triisopropyl and triphenylsilanes cyclize without loss of the larger silyl group to form *E*-vinylsilanes **225** with excellent stereoselectivity with side product **226** (Scheme 25).[208]



Scheme 25 [Bis(trifluoroacetoxy)iodo]benzene-mediated oxidative cyclization of unsaturated *O*-alkyl hydroxamates **223**.

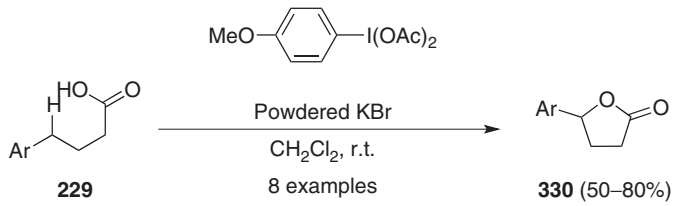
The oxidative cycloisomerization of *cis*-enynols **227** was reported by using combination of **5**, molecular iodine, and $NaHCO_3$ as base. This approach offers an efficient synthesis of 2-acyl furans **228** with diverse substitution patterns in a regioselective manner under mild reaction conditions. The 2-acyl furans **228** were isolated in good to moderate yields (equation 25).[209] Fujita and coworkers developed the synthesis of highly functionalized tetrahydrofurans by using hypervalent iodine(III) reagent **3** as oxidant.[210]



(25)

The oxidative cycloisomerization of *cis*-enynols **227** using **5**

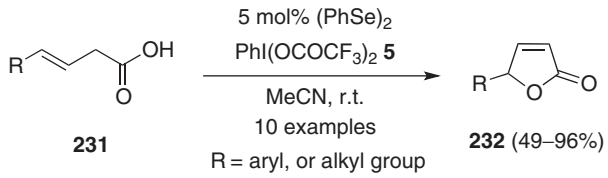
In 2007, Kita and coworkers reported the oxidative cyclization of carboxylic acids of type **229** to biologically important lactones **330** using a combination of hypervalent iodine(III) reagents with KBr. The reaction products were obtained in moderate yields (equation 26).[211] Furthermore, six- and seven-membered lactones were also assembled using same strategy. The reaction proceeded by formation of benzylic radical via a selective C–H abstraction.



(26)

Oxidative cyclization of carboxylic acids **229** using acyclic iodine(III) reagent

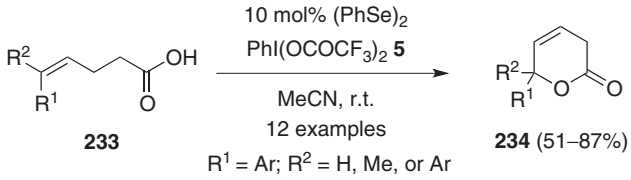
In 2007, Wirth and his research group used iodine(III) reagent **5** to activate diaryl diselenides. They have reported the synthesis of functionalized butenolides **232** by selenium-catalyzed cyclization of β,γ-unsaturated carboxylic acids **231** using [bis(trifluoroacetoxy)iodo]benzene **5** as oxidant. The cyclized products **232** were isolated in moderate to excellent yields (equation 27).[28b,212] The asymmetric variant of this reaction using chiral diselenides has also been developed.



(27)

Selenium-catalyzed cyclization of β,γ-unsaturated carboxylic acids **231**

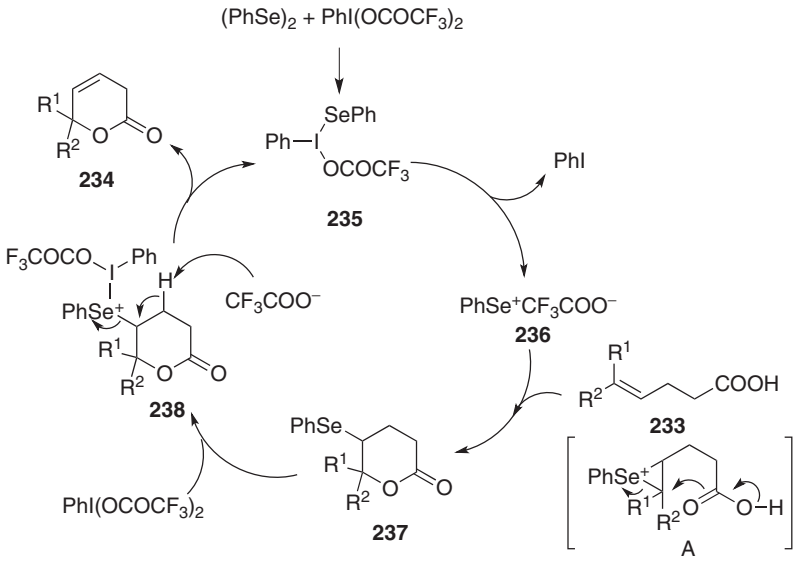
Furthermore, Singh and Wirth reported the synthesis of six-membered lactones **234** by the cyclization of γ,δ-unsaturated carboxylic acids **233** in the presence of 10 mol% diphenyl diselenide and [bis(trifluoroacetoxy)iodo]benzene **5** as oxidant. The reaction products **234** were isolated in moderate yields (equation 28).[28a]



(28)

Selenium-catalyzed cyclization of γ,δ-unsaturated carboxylic acids **233**

The plausible mechanism for these cyclization reactions is depicted in Scheme 26. The reaction is initiated by the formation of phenylselenenyl trifluoroacetate **236**, which reacts with γ,δ-unsaturated pentenoic acid **233** to yield a selenolactone **237**. The selenide functional group of lactone **237** is then activated for elimination by [bis(trifluoroacetoxy)iodo]benzene via intermediate **238** to finally yield the 3,6-dihydro-2*H*-pyran-2-ones **234** as reaction products. The selenium electrophile **236** is regenerated by this process, leading to the catalytic cycle as shown in Scheme 26.

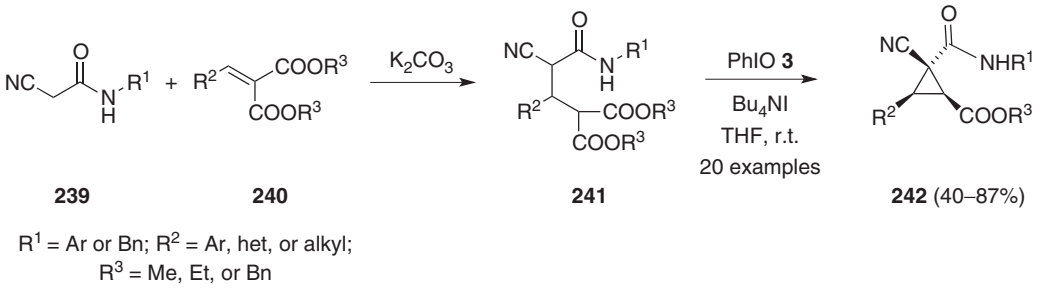


Scheme 26 Reaction mechanism for selenium-catalyzed cyclization of **233**–**234**.

Cyclopropane rings can be assembled by cyclization reactions using hypervalent iodine reagents. Recently, Wang and Fan have reported the synthesis of 2-carbamoyl-2-cyanocyclopropanecarboxylates **242** through a tandem iodosobenzene/tetrabutylammonium iodide-induced oxidative cyclization and a subsequent neighboring group-assisted decarboxylation of the Michael adducts **241** of 2-cyanoacetamides **239** with α,β-unsaturated malonates **240**. This approach offers highly functionalized cyclopropanes in moderate to good yields and with excellent diastereoselectivities (Scheme 27).[213] The cyclopropanation of alkenes can be achieved by using iodonium ylides.[214]

7.29.4.2 Fused Heterocycles

Fused heterocyclic compounds are known to have interesting biological and pharmaceutical properties, particularly when they contain nitrogen and oxygen heteroatoms.[215] Until 2003, the synthesis of few fused heterocyclic compounds have been achieved

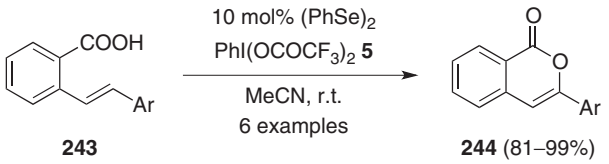


Scheme 27 Synthesis of 2-carbamoyl-2-cyanocyclopropanecarboxylates **242** using PhIO **3**.

by using hypervalent iodine reagents such as [bis(trifluoroacetoxy)iodo]benzene **5**.[215–219] In order to reduce the complexity, the fused heterocycles are categorized into bicyclic and polycyclic heterocyclic compounds.

7.29.4.2.1 Bicyclic-Fused Heterocycles

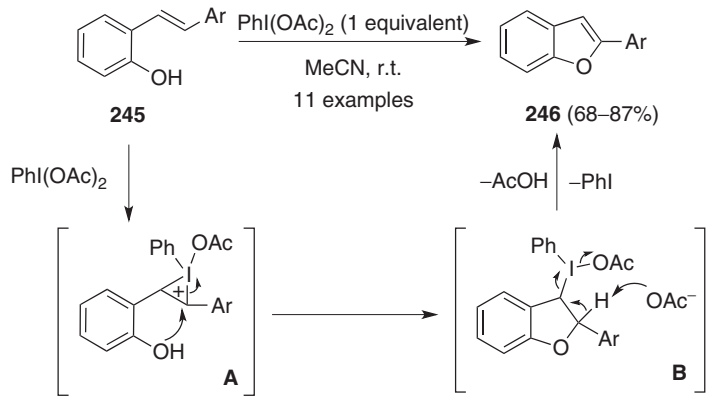
The synthesis of isoquinolinone- and isoindolinone-fused heterocycles has been reported by [bis(trifluoroacetoxy)iodo]benzene-mediated amidohydroxylation of alkenes.[220,221] The synthesis of tetrazole-fused glycosides can be achieved by a tandem fragmentation–cyclization reaction using hypervalent iodine reagents in high yields.[222] In 2010, Wirth and coworkers developed the cyclizations of stilbenecarboxylic acids **243** to the corresponding isocoumarin derivatives **244** in excellent yields by using diselenide or disulfide reagents as catalyst and [bis(trifluoroacetoxy)iodo]benzene **5** as oxidant (equation 29).[223]



(29)

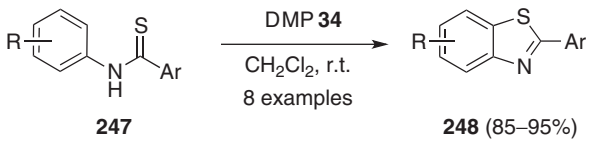
Selenium-catalyzed cyclizations of stilbenecarboxylic acids **243**

Recently, Singh and Wirth reported an oxidative cyclization of *ortho*-hydroxystilbenes **245** to arylated benzofurans **246** in excellent yields (**Scheme 28**).[224] The same approach can be applied for the synthesis of naphthofurans in high yields. A plausible mechanism for the cyclization of stilbenes **245** to benzofurans **246** is shown in **Scheme 28**. According to mechanism, the electrophilic iodine activates the double bond of stilbene **245** forming a three-membered iodonium intermediate **A**. This undergoes intramolecular reaction with the phenolic oxygen atom leading to intermediate **B**. Finally, elimination of the hypervalent iodine then gives product **246**. Furthermore, benzofurans can be synthesized by Pummerer-type reactions using hypervalent iodine reagents in ionic liquids.[225]



Scheme 28 (Diacetoxyiodo)benzene-mediated cyclizations of stilbenes **245** to benzofurans **246**.

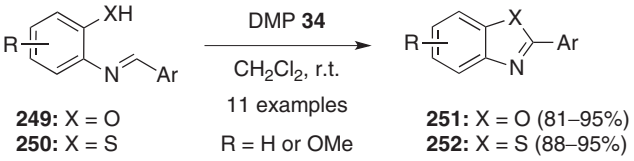
Bose and Idrees developed the synthesis of 2-arylbenzothiazoles **248** via an intramolecular cyclization of thioformanilides **247** by using DMP **34** in dichloromethane at ambient temperature (equation 30).[226] The reaction proceeds via a thiyl radical in excellent yields.



(30)

DMP-mediated intramolecular cyclizations of thioformanilides **247** to benzothiazoles **248**

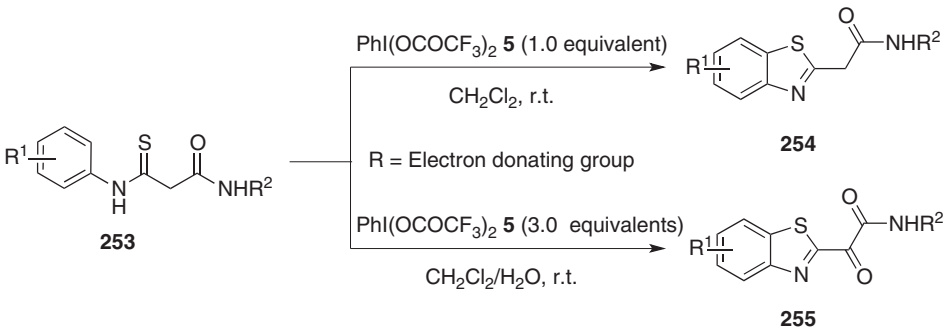
In 2010, the same research group reported a DMP-mediated intramolecular cyclization of phenolic azomethines **249** or thiophenolic azomethines **250** to substituted benzoxazoles **251** and benzothiazoles **252**, respectively. The cyclized products were obtained in excellent yields (equation 31).[227]



(31)

DMP-mediated intramolecular cyclization of azomethines **249** and **250**

Recently, the synthesis of various benzo[*d*]thiazoles of type **254** and **255** was developed by intramolecular cyclization of readily available *β*-oxo thioamides **253** mediated by **5**. The formation of products **254** or **255** is depending on the equivalent of hypervalent iodine reagent **5** used in the reaction (Scheme 29).[228]



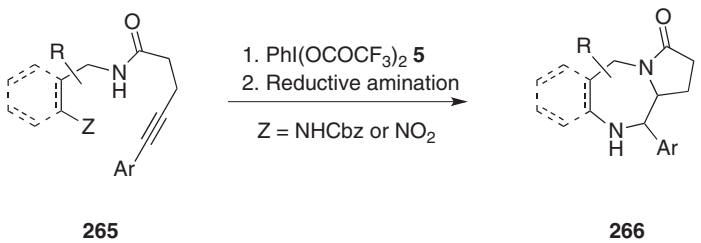
Scheme 29 Intramolecular cyclizations of *β*-oxo thioamides **253–254** and **255**.

7.29.4.2.2 Polycyclic-Fused Heterocycles

The synthesis of different tricyclic-fused heterocycles such as phenanthridines **257**, phenanthridinones **259**,[229] and phenanthrenoids **261**[230] has been achieved by oxidative cyclization of *N*-arylbenzylamines **256**, *N*-arylbenzamides **258**, and stilbenoids **260**, respectively, mediated by [bis(trifluoroacetoxy)iodo]benzene **5** (Scheme 30). Furthermore, [bis(trifluoroacetoxy)iodo]benzene has been used for the construction of N-, O-, and S-containing heterocyclic-fused quinolinones.[218]

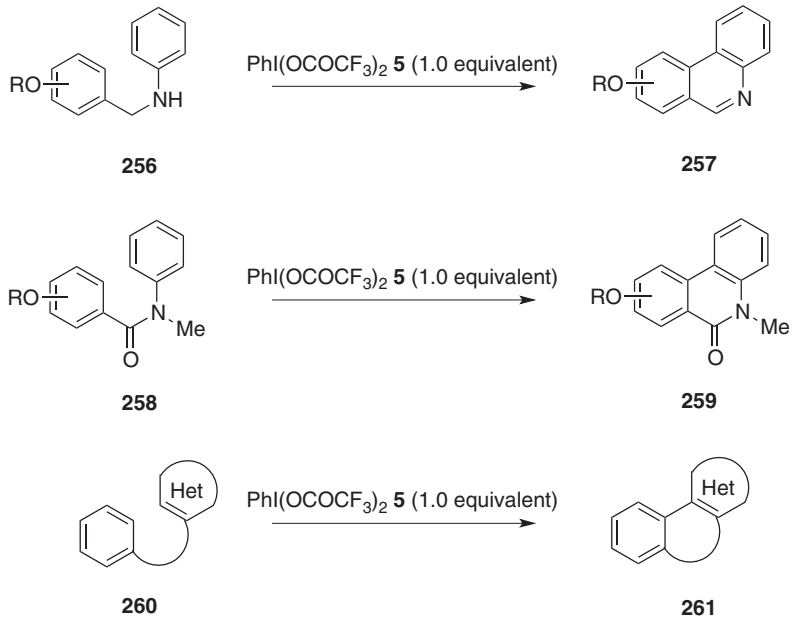
In 2005, the synthesis of benzo-, naphtho-, and heterocycle-fused pyrrolo [2,1–c][1,4] diazepines using [bis(trifluoroacetoxy) iodo]benzene was reported. The advantage of this approach was the cyclization of **262** to the tricyclic hetercycle **263**, which can be converted into antibiotic (−)-DC-81 **264** in two further steps (Scheme 31).[231]

Recently, the same research group reported an approach to structurally diverse pyrrolo(benzo)diazepines **266** from linear alkynylamides **265**. The tricyclic products **266** were isolated in moderate yields (equation 32).[232] The approach for the formation of **266** was based on an intramolecular double addition of a diamino fragment across both positions of a triple bond assisted by **5**.

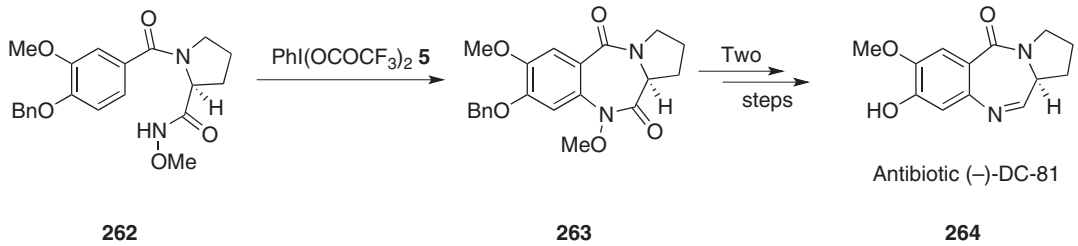


(32)

Synthesis of pyrrolo(benzo)diazepines **266**



Scheme 30 [Bis(trifluoroacetoxy)iodo]benzene-mediated oxidative cyclization of *N*-arylbenzylamines **256**, *N*-arylbenzamides **258**, and stilbenoids **260**.



Scheme 31 [Bis(trifluoroacetoxy)iodo]benzene-mediated synthesis of antibiotic **264**.

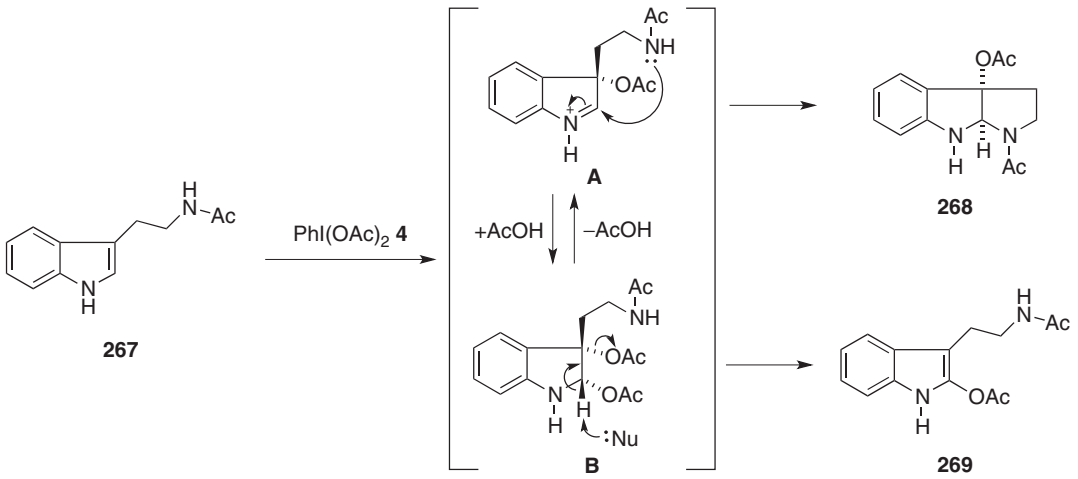
Recently, Nishiyama and coworkers developed an oxidative cyclization of *N*-acetyltryptamine **267** with (diacetoxyiodo)benzene **4** providing the corresponding 1,2,3,3a,8,8a-hexahydropyrrolo 2,3–bindol-3a-ol derivative **268**, which could be derivatized following appropriate protection of the two amino and *tert*-hydroxyl groups. In some reactions, 2-acetoxytryptamine derivatives **269** were isolated as minor products. According to the reaction mechanism, the reaction initiates with the formation of an iminium intermediate **A** bearing an acetoxyl group at C-3, which could led the formation of cyclized product **268** using terminal amide functional group. In competition during the cyclization process, addition of acetate to the C-2 position of iminium intermediate **A** gives another intermediate **B**, which could lead to the formation of the minor product **269** by elimination. Furthermore, the product **268** was employed for the synthesis of naturally occurring compounds CPC-1 and debromoflustraminol B in moderate yields (Scheme 32).[233]

7.29.5 α-Functionalization of Carbonyl Compounds

α-Functionalized carbonyl compounds are an important class of synthetic intermediates in medicinal and natural product chemistry. Different areas of organic chemistry provide elegant solutions to the challenges of α-functionalization of carbonyl compounds. Despite the availability of organocatalysis, hypervalent chemistry is continuously providing novel approaches for the α-functionalization of carbonyl compounds in recent years.

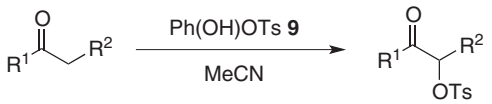
7.29.5.1 α-Tosyloxylation of Carbonyl Compounds

Several research groups have developed approaches for the α-tosylation of carbonyl compounds. In 1982, Koser and his research group reported the use of Koser's reagent **9** as oxytosylating agent. They have developed the synthesis of α-oxytosylated carbonyl compounds **271** in moderate to excellent yields (equation 33).[234] This approach was extended by Lodaya and Koser to include



Scheme 32 Oxidative cyclization of *N*-acetyltryptamine **267** using **4** as oxidant.

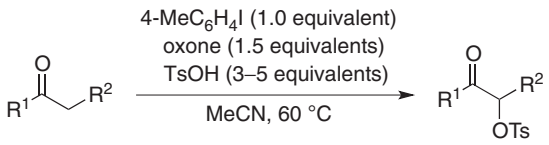
α-oxymesylation of ketones using [hydroxy(mesyloxy)iodo]benzene (HMIB).[235] Nabana and Togo developed the α-oxytosylation and α-oxyphosphorylation of ketones in 2002.[236] Also in 2002, Lee and coworkers reported the same α-oxytosylation approach using microwave as a source of energy.[237] Several other research groups have also investigated the α-oxytosylation of carbonyl compounds using Koser's reagent **9**.[238–243]



(33)

Synthesis of α-tosyloxylated carbonyl compounds **271** using Koser reagent **9**

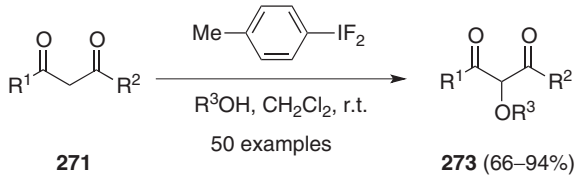
Recently, Tanaka and Togo prepared the Koser reagent *in situ* and used it successfully in α-oxytosylations of ketones in which a stoichiometric amount of 4-iodotoluene was oxidized using oxone in the presence of *p*-toluenesulfonic acid (equation 34).[244] In 2005, Wirth and Yusubov reported (diacetoxyiodo)benzene-mediated α-oxygenation reactions of carbonyl compounds under solvent-free conditions.[245]



(34)

α-Oxytosylation of ketones **270** by *in situ* generated Koser reagent

Furthermore, Zhang and coworkers emphasized the synthesis of Koser type reagents *in situ* and used them in similar α-oxygenation reactions. They have reported a detailed study of $TolIF_2$-mediated α-oxygenation of β-dicarbonyls using various oxygen-containing nucleophiles, including *p*-toluenesulfonic acid, methanesulfonic acid, acetic acid, diphenyl phosphate, methanol, ethanol, and isopropyl alcohol. The reaction with all oxygen-containing nucleophiles was proceeding smoothly and α-oxygenated β-dicarbonyl products **273** were isolated in good to excellent yields (equation 35).[246] The combination of iodosylbenzene and *p*-toluenesulfonic acid can also be used as precursors for the α-oxytosylation of carbonyl compounds.[247]

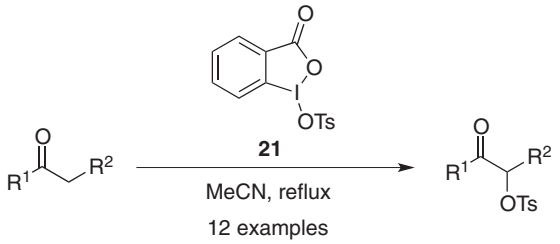


271 **273** (66–94%) (35)

R^1 = Ar, het. or alkyl; R^2 = Ph, Me or OEt;
R^3 = Ts, Ms, Ac, Me, Et, Pr^i, $(PhO)_2PO$

α-Oxygenation of β-dicarbonyls **273** using various nucleophiles

Wirth and coworkers have used FIBA **19**[27] and iodoxolone-based iodine(III) reagents **30–32**[39] in α-oxytosylations of carbonyl compounds. In 2008, Karade and coworkers reported iodine(III) reagent **21** as α-oxytosylating agent for carbonyl compounds and α-oxytosylation was achieved in moderate to excellent yields (equation 36).[30] In the majority of α-oxytosylation reactions, iodine (III) reagents have been reported, but Mahajan and Akamanchi achieved the same α-oxytosylations using iodine(V) reagents.[248]



270 **271** (63–88%) (36)

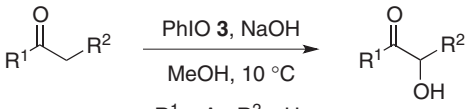
R = Ar, het; R = H or alkyl group

α-Oxytosylation of carbonyl compounds **270** using IBA analogue **21**

More recently, several research groups have successfully achieved the α-oxytosylation of carbonyl scaffolds with different polymer-bound[249–251] other recyclable iodine(III) and iodine(V) reagents.[17,244,252–254] Furthermore, Wirth[100a,100b,101b,104,105,255] and others[256–258] developed the asymmetric α-tosyloxylation of carbonyl compounds using hypervalent iodine reagents in stoichiometric or catalytic amounts with limited success.

7.29.5.2 α-Hydroxylation of Carbonyl Compounds

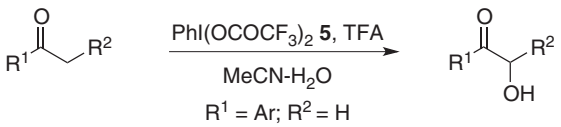
Similar to the α-oxytosylation of ketones, the history of α-hydroxylation of carbonyl compounds using hypervalent iodine reagents is long. The α-hydroxylation of carbonyl compounds **270** was reported for the first time in 1981 by Moriarty and coworkers (equation 37).[259]



270 **274** (37)

Synthesis of α-hydroxylation of carbonyl compounds **274** using PhIO **3**

In 1992, Moriarty and coworkers developed the α-hydroxylation of ketones under acidic conditions using **5** and TFA in acetonitrile–water. The α-hydroxylated ketones **274** were obtained in excellent yields (equation 38).[259]

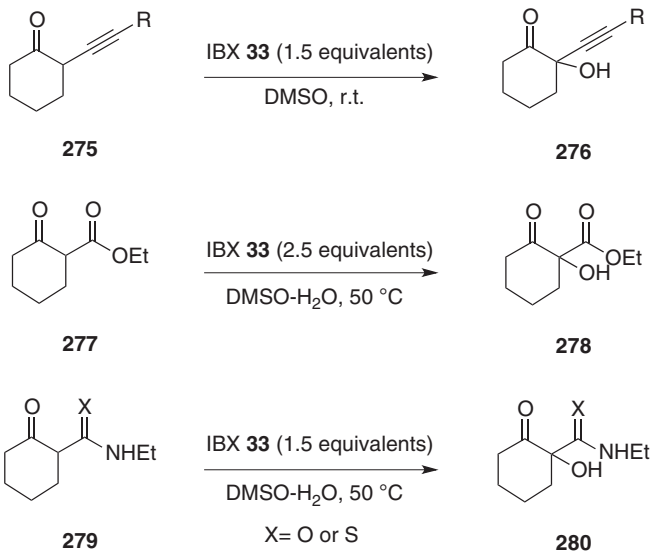


270 **274** (up to 94%) (38)

Synthesis of α-hydroxylation of carbonyl compounds **274** using **5**

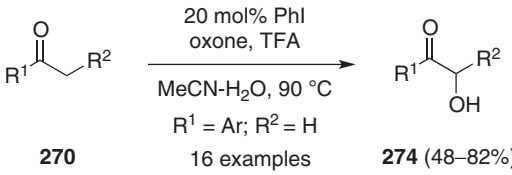
The cyclic iodine(V) reagent IBX **33** has been applied in the synthesis of α-hydroxy ketones **276** from α-alkynyl carbonyl compounds **275** (Scheme 33).[260] The same approach was then used for the α-hydroxylation of β-keto esters **277** and β-keto

amides **279** as shown in Scheme 33.[261] Some other hypervalent iodine reagents for the α-hydroxylation of carbonyl compounds have been developed.[262–266]



Scheme 33 IBX-mediated α-hydroxylation of cyclic ketones **275**, **277**, and **279**.

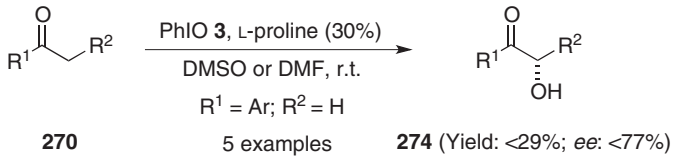
In 2008, Huang and coworkers developed an iodobenzene-catalyzed α-hydroxylation of aromatic ketones using oxone as the stoichiometric oxidant. Various α-hydroxy ketones were synthesized in moderate yields (equation 39).[267]



(39)

Iodobenzene-catalyzed α-hydroxylation of ketones **270**

Furthermore, the catalytic asymmetric α-hydroxylation of ketones **270** has been achieved using L-proline as catalyst and iodosylbenzene as oxidant. Chiral α-hydroxy ketones **274** were obtained in up to 77% *ee* (equation 40).[268]

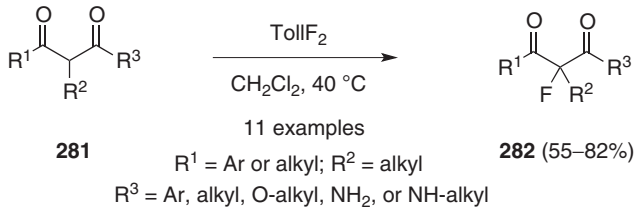


(40)

Enantioselective α-hydroxylation of ketones **270**

7.29.5.3 α-Halogenation of Carbonyl Compounds

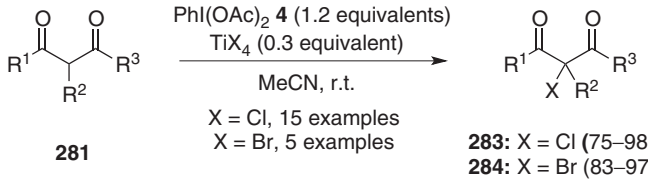
Standard reagents for halogenation reactions are often aggressive, unstable, toxic, and corrosive. The introduction of hypervalent iodine reagents has enabled mild reaction conditions, selective reactions, and nontoxic waste in such reactions. 4-(Difluoroiodo) toluene ($TolIF_2$) is an efficient α-fluorination reagent for various carbonyl compounds. The α-fluorination of 1,3-dicarbonyl compounds has been achieved using $TolIF_2$ in the presence of HF–amine complex.[269] Hara and coworkers reported the α-fluorination of β-keto esters, β-keto amides, and diketones **281** to the fluorinated products **282** in high yields (equation 41).[270]



(41)

α-Fluorination of 1,3-dicarbonyl compounds **281** using $TolIF_2$

In 2009, Ibrahim and coworkers developed a (diacetoxyiodo)benzene-mediated chlorination and bromination of 1,3-dicarbonyl compounds using substoichiometric amounts of titanium(IV) chloride and titanium(IV) bromide as the chloride and bromide source, respectively. Using this approach the synthesis of α-halogenated diketones, β-keto esters, and β-keto amides has been achieved in excellent yields (equation 42).[271]



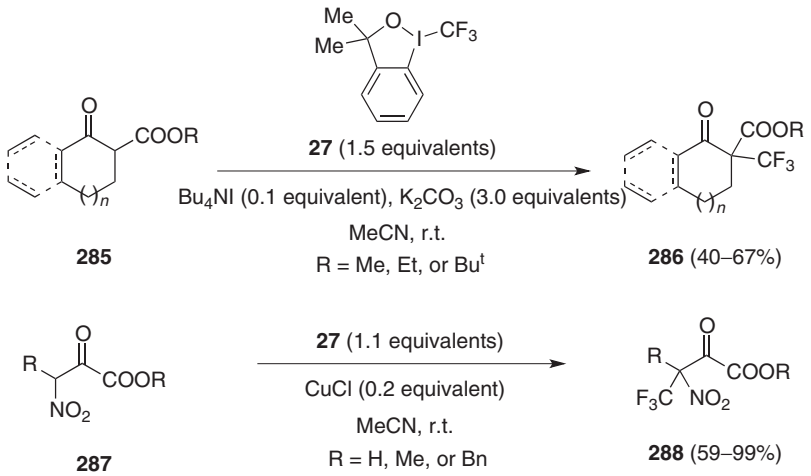
(42)

(Diacetoxyiodo)benzene-mediated chlorination and bromination of 1,3-dicarbonyl compounds **281**

Various other research groups have also investigated hypervalent iodine reagents for the α-halogenations of carbonyl compounds.[272–277]

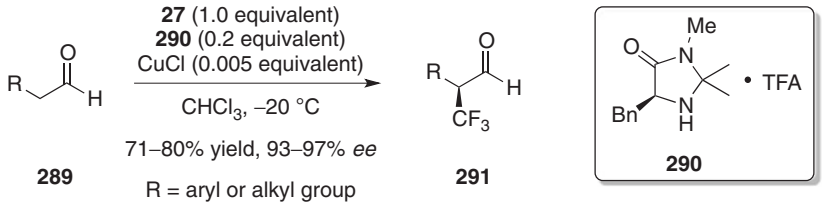
7.29.5.4 α-Trifluoromethylation of Carbonyl Compounds

The trifluoromethyl functional group is frequently found in synthetic drugs and agrochemicals, as it can favorably alter uptake, metabolism and mode of action. Recently, cyclic iodine(III) reagent **27** (Togni's reagent) has been used as trifluoromethylating agent. Compound **27** has been used for α-trifluoromethylation of cyclic β-keto esters **285** in good yields (Scheme 34).[228] This reaction was not proceeding with less reactive, open chain β-keto esters. However, the α-trifluoromethylation of α-nitro esters **287** has been achieved only by using 20 mol% of CuCl. The reaction products were isolated in moderate to excellent yields (Scheme 34).[278]



Scheme 34 α-Trifluoromethylation of ketones **285** and **287** using Togni's reagent **27**.

Recently, MacMillan and coworkers used Togni's reagent **27** in organocatalytic enantioselective α-trifluoromethylations of aldehydes **289**. The α-trifluoromethylated aldehydes **291** were obtained in excellent yields with up to 97% *ee* using the imidazolidinone catalyst **290** as chiral source (Scheme 35).[279]

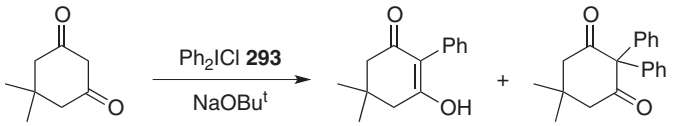


Scheme 35 Enantioselective α-trifluoromethylation of aldehydes **289**.

7.29.5.5 α-Arylation of Carbonyl Compounds

α-Arylated carbonyl compounds are important scaffolds found in various biologically active compounds having pharmaceutical importance.[280] The introduction of an aryl functional group at the α-position of carbonyl compounds, particularly in an asymmetric fashion, is an ongoing challenge in organic synthesis.[280] Although there are several metal-catalyzed approaches available for α-arylations of carbonyl compounds, these are associated with some drawbacks such as the use of expensive heavy metals and sometimes harsh reaction conditions.[281] In recent years, the α-arylation of carbonyl compounds has been successfully achieved using hypervalent iodine reagents.

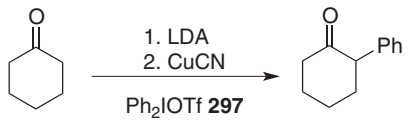
The first α-arylation of carbonyl compounds was reported by Beringer and coworkers in 1960 using diaryliodonium salts.[282] The phenylation of a cyclic 1,3-dione **292** with diphenyliodonium chloride **293** was achieved, and α-phenylated carbonyl compound **294** was obtained in 22% yield with 23% of bis-phenylated product **295** (equation 43).[282] Since this report, the same research group has successfully developed the α-arylation of various carbonyl compounds such as 1,3-indanediones,[283] malonates,[284] esters and β-keto esters,[285] and 1-indanones.[286]



292 **294** **295** (43)

α-Arylation of cyclic ketones **292** using Ph_2ICl **293**

In 1997, Ryan and Stang used lithium diisopropylamide (LDA) to generate the lithium enolate of cyclohexanone **296**, which was treated with diphenyliodonium triflate **297**. The arylated product was observed in less than 5% yield, which was improved to 50% yield after addition of one equivalent of copper(I) cyanide (equation 44).[287] Interestingly, five-membered cyclic ketones furnished diarylated products, whereas larger rings were only monoarylated. Various other diaryliodonium triflates can be synthesized by easily accessible starting materials.[288] Other strategies for the α-arylation of various acyclic and cyclic carbonyl compounds have also been developed.[289]



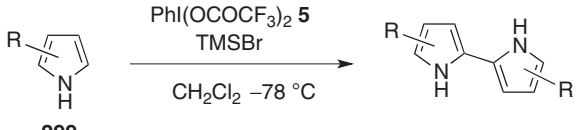
296 **298** (50%) (44)

α-Phenylation of cyclic ketone **296** using diphenyliodonium triflate **297**

Hypervalent iodine reagents can also be used for other α-functionalizations of carbonyl compounds such as alkynylation,[37c,290] alkenylation,[290d,291] oxidative homocoupling,[195,292] and azidation.[293] Synthetically valuable α-functionalized derivatives can be synthesized using these approaches.

7.29.6 Oxidative Coupling Reactions

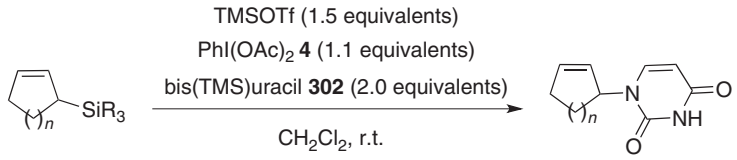
In recent years, hypervalent iodine reagents have been successfully used in coupling reactions. In 2006, Kita and coworkers developed an effective oxidative coupling reaction of pyrroles to give α-linked bipyrroles selectively in the presence of bromotrimethylsilane. This approach provided 2,3′-bipyrroles by the choice of substitution in the pyrrole ring. The reaction products **300** were obtained in good yields (equation 45).[294] The indoles have been used in this reaction successfully. In 2011, Kita and coworkers also developed the synthesis of bithiophenes using $BF_3{\cdot}Et_2O$ or TMSOTf.[295]



299 **300** (52–82%) (45)

An effective oxidative coupling reaction of pyrroles **299**

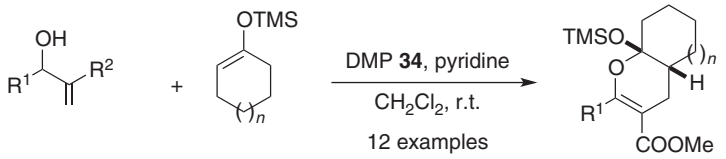
Yoshimura and coworkers reported the synthesis of carbocyclic nucleosides **303** by oxidative coupling reaction of cycloalkenylsilanes **301** with a silylated nucleobase **302** using iodine(III) reagents as oxidant (equation 46).[296] The same approach has been used for the synthesis of carbocyclic cytidine derivatives, which were investigated as potential anti-HIV agents. Recently, the same research group has reported on the synthesis of N^1-substituted uracil derivatives.[297]



301 **303** (46)

Synthesis of carbocyclic nucleosides **303** by coupling **301** and **302** using **4**

Yadav and coworkers used DMP **34** for an oxidative coupling of Baylis–Hillman adducts **304** with silyl enol ethers **305** to a new class of dihydropyrans **306** in high yields. The reaction proceeded by oxidative Mukaiyama–Michael addition followed by cyclization in the presence of the DMP and pyridine under mild reaction conditions (equation 47).[298]

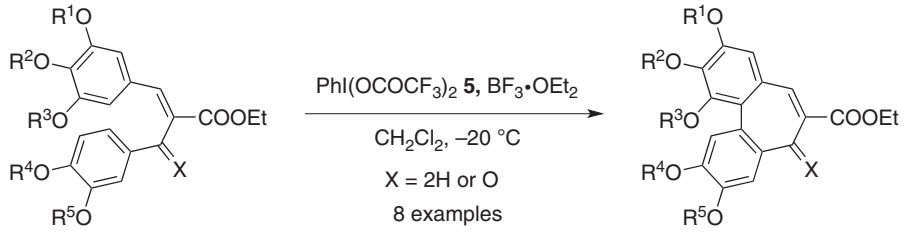


304 **305** **306** (78–86%) (47)

R^1 = Ar or alkyl; R^2 = COOMe, COOEt or CN; n = 0 or 1

DMP-induced coupling of Baylis–Hillman adducts **304** with silyl enol ethers **305**

The synthesis of dibenzo[*a*,*c*]cycloheptenes **308** can be achieved in moderate yields by intramolecular oxidative coupling reactions of various 1,3-diarylpropene derivatives **307** using **5** in combination with $BF_3{\cdot}OEt_2$ under mild reaction conditions as depicted in equation 48. Furthermore, the same approach has been employed in the synthesis of natural product metasequirin-B.[299]

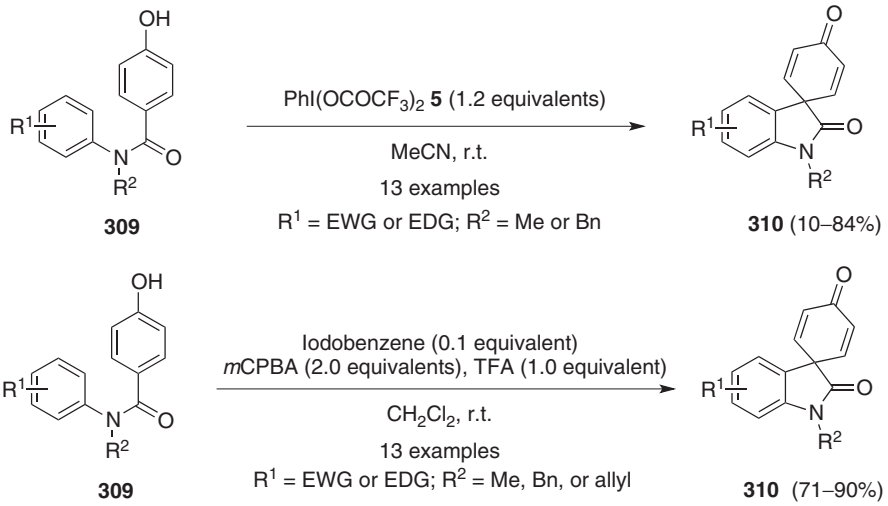


307 **308** (10–84%) (48)

R^1 = Me; R^2 = H or Me; R^3 = H or Me; R^4 = Me; R^5 = H or Me

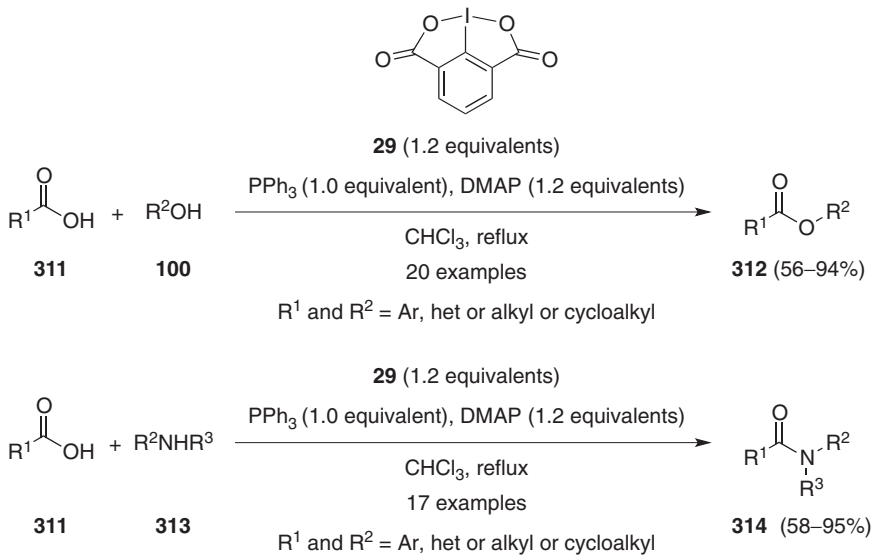
Intramolecular coupling of 1,3-diarylpropene derivatives **307**

Recently, the synthesis of spirooxindoles **310** has been developed by the [bis(trifluoroacetoxy)iodo]benzene-induced intramolecular oxidative coupling of functionalized 4-hydroxyphenyl-*N*-phenylbenzamides **309** in excellent yields. Furthermore, oxidative coupling reactions were achieved by using 10 mol% of iodobenzene as catalyst and *m*-chloroperoxybenzoic acid or urea·H_2O_2 as terminal oxidant (**Scheme 36**).[300]



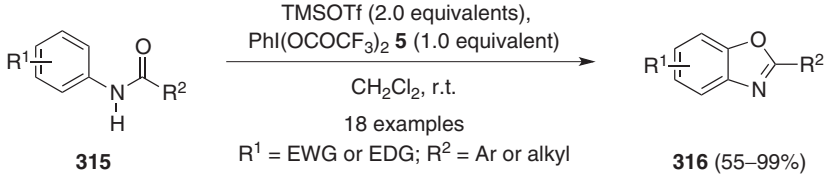
Scheme 36 Intramolecular coupling of **309** using iodine(III) reagents in stoichiometric or catalytic amounts.

Recently, Zhang and coworkers developed the cyclic iodine(III) reagent **29** as an efficient coupling reagent to promote the direct condensation between carboxylic acids **311** and alcohols **100** or amines **313** to provide esters **312** and amides **314**, respectively, in excellent yields (Scheme 37).[38] This approach has also been applied in the synthesis of peptides.



Scheme 37 Condensation between carboxylic acids **311** and alcohols **100** or amines **313**.

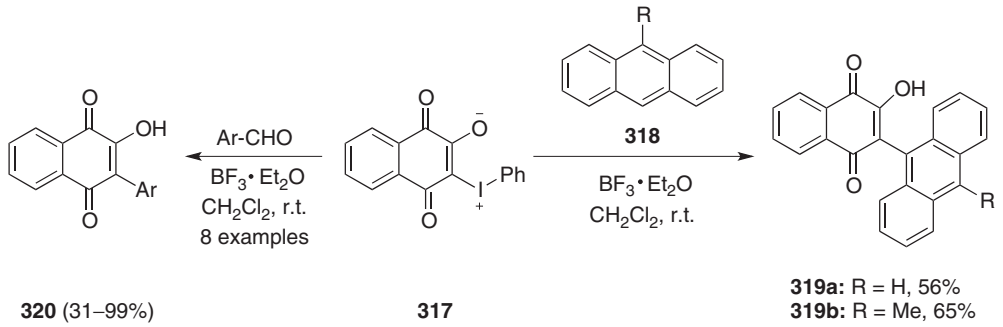
Yu and coworkers reported an intramolecular oxidative C–O coupling of *N*-(4-alkoxy-phenyl) and *N*-(4-acetamido-phenyl) benzamides **315** using the combination of **5** with TMSOTf under mild reaction conditions. The benzoxazole derivatives **316** were obtained as a result of oxidative C–O coupling reactions in variable yields (equation 49).[301]



(49)

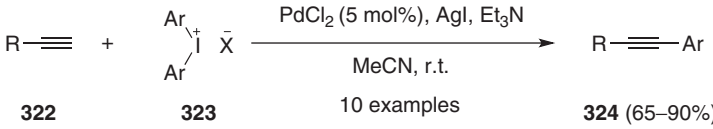
Intramolecular oxidative C–O coupling of **315** using **5** with TMSOTf

Malamidou-Xenikaki and coworkers have been used phenyliodonium ylide **317** in coupling reactions with electron-rich arenes **318** to afford 2-aryl-3-hydroxy-1,4-naphthoquinones **319** in moderate yields. Products **320** were obtained in good yields by the coupling reaction of **317** with aromatic aldehydes as shown in Scheme 38.[302]



Scheme 38 The coupling of ylides **317** with anthracenes **318** and aromatic aldehydes.

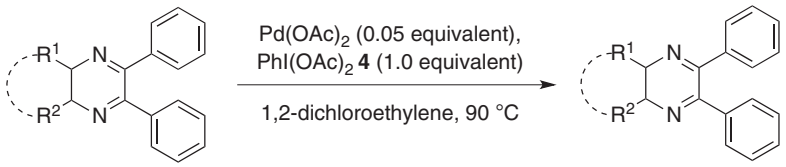
Hypervalent iodine reagents can be used in palladium-catalyzed reactions. In 2008, Zhu and coworkers reported a palladium-catalyzed Sonogashira coupling reaction of terminal alkynes **322** with hypervalent iodonium salts **323**. The arylalkynes **324** were isolated in excellent yields as indicated in equation 50.[303]



(50)

Pd-catalyzed Sonogashira coupling reaction of terminal alkynes **322** with hypervalent iodonium salts **323**

Recently, Reddy and coworkers developed the palladium-catalyzed acetoxylation of 2,3-diarylquinoxalines **325** using PhI $(OAc)_2$ **4** as oxidant via C–H activation. The acetoxy-susbstituted quinoxaline derivatives **326** were obtained in excellent yields in high regioselectivity (equation 51).[304] The same research group extended the reaction to the acetylation of 2-aryl-4-quinazolinones.[305]



(51)

Pd-catalyzed acetoxylation of 2,3-diarylquinoxalines **325** using PhI$(OAc)_2$ **4**

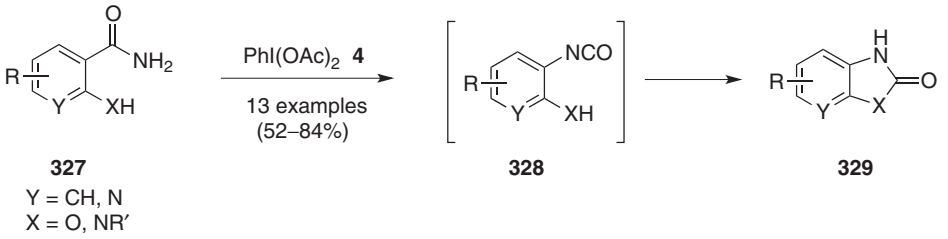
7.29.7 Rearrangements

In the past years, a dramatic increase in the development of hypervalent iodine reagent-mediated oxidative rearrangements has been observed. Hypervalent iodine reagents have a unique property to react first as an electrophile and then act as a good leaving group. This property has been used in different cationic rearrangements for the construction of highly functionalized architectures.

7.29.7.1 Rearrangement of Amides

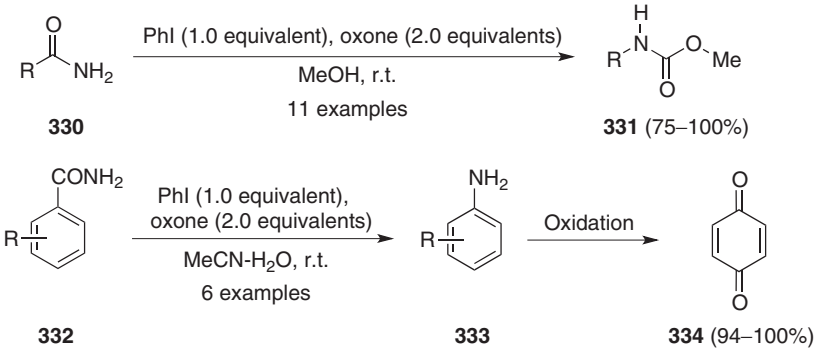
Various iodine(III) reagents such as PhI$(OAc)_2$ **4**,[306] **5**,[307] Koser's reagent **9**,[308] and their recyclable analogs[309] have been used in the rearrangement of amides. In 2001, Moriarty and coworkers reported the synthesis of heterocyclic compounds **329** by direct cyclization of aromatic amides **327** with a nucleophile in the *ortho*-position. The reaction products **329** were isolated in good to

moderate yields. The reaction occurs via an initial Hofmann-type rearrangement followed by intramolecular cyclization of the intermediate isocyanate **328** (Scheme 39).[310]



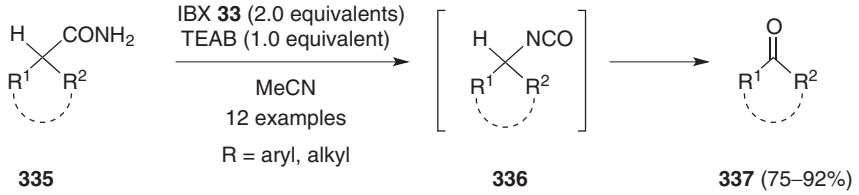
Scheme 39 Synthesis of heterocyclic compounds **329** by direct cyclization of aromatic amides **327**.

According to Zhdankin, alkylcarboxamides **330** can be converted to the corresponding amines **331** by a Hofmann rearrangement using hypervalent iodine species generated *in situ* from PhI and Oxone in aqueous acetonitrile. Furthermore, the functionalized benzamides **332** were treated under similar reaction conditions, and reaction products were isolated as dearomatized quinone derivatives **334**; anilines **333** were not observed as products (Scheme 40). Compounds **334** were probably formed via an oxidative dearomatization of anilines **333**.[311]



Scheme 40 Hofmann rearrangements of amides **330** and **332** using hypervalent iodine species generated *in situ*.

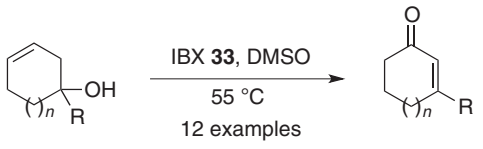
Akamanchi and coworkers reported that α,α-disubstituted acetamides **335** undergo oxidative dehomologation to yield ketones **337** when treated with IBX **33** in combination with TEAB. All the reactions were working smoothly and ketones **337** were isolated in excellent yields. The reaction is proceeding via the formation of Hofmann-type rearrangement intermediates **336** (Scheme 41).[312]



Scheme 41 IBX-mediated oxidative dehomologation of α,α-disubstituted acetamides **335**.

7.29.7.2 Rearrangement of Tertiary Alcohols

Some oxidative rearrangements of tertiary alcohols have been reported in the literature. In 2004, Iwabuchi reported the IBX-mediated oxidative rearrangement of five- and six-membered cyclic tertiary allylic alcohols **338** to β-disubstituted α,β-unsaturated ketones **339** in DMSO. The rearranged products **339** were isolated in excellent yields (equation 52).[313] Alkylic tertiary alcohols can be rearranged into α,β-unsaturated ketones in poor yields under similar reaction conditions. Several conventional protecting groups (e.g., Ac, $MeOCH_2$, and TBDPS) are compatible with the reaction conditions.



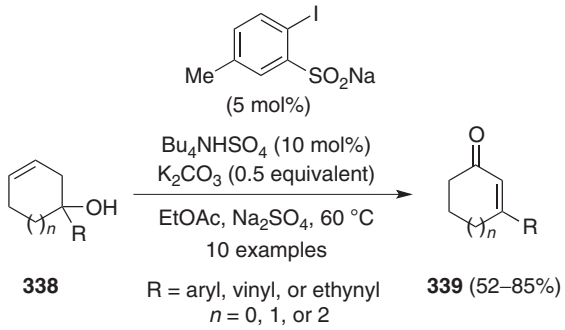
338 **339** (38–88%) (52)

R = aryl or alkyl; n = 0 or 1

IBX-mediated oxidative rearrangement of cyclic tertiary allylic alcohols **338** to unsaturated ketones **339**

Furthermore, the Lewis acid-promoted oxidative rearrangement of tertiary allylic alcohols **338** to β-disubstituted enones **339** can be achieved by using catalytic amounts of TEMPO with iodosylbenzene (PhIO) as a cooxidant. Bismuth triflate was found to be the most-efficient catalyst for the majority of the substrates tested except for tertiary vinyl carbinols.[314]

Recently, the 2-IBS acid-catalyzed oxidative rearrangement of tertiary allylic alcohols of type **338** to enones **339** was developed by Ishihara et al. with powdered oxone in the presence of potassium carbonate and tetrabutylammonium hydrogen sulfate. The reaction products **339** were formed in good to moderate yields as shown in equation 53.[315]

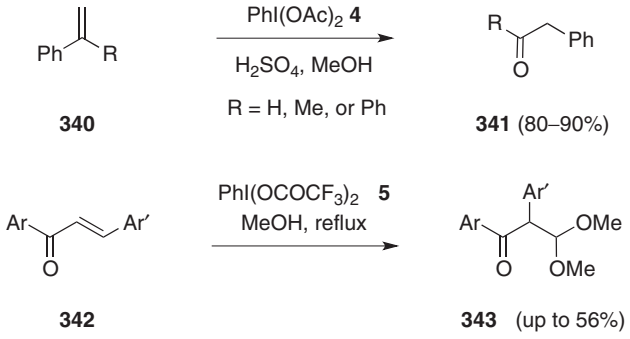


338 R = aryl, vinyl, or ethynyl; n = 0, 1, or 2 **339** (52–85%) (53)

Iodoarene-catalyzed oxidative rearrangement of cyclic tertiary allylic alcohols **338** to unsaturated ketones **339**

7.29.7.3 1,2-Aryl Migration Rearrangement

Oxidative rearrangements due to aryl group migration using hypervalent iodine reagents have received particular attention in recent years. The reaction of alkenes with hypervalent reagent is a well-documented reaction in synthetic organic chemistry. α-Substituted styrenes **340** can be rearranged oxidatively to corresponding arylacetones **341** using (diacetoxyiodo)benzene **4** in a H_2SO_4/MeOH combination. The reaction proceeds via a 1,2-aryl migration. The reaction products **341** were isolated in excellent yields (Scheme 42).[316] The chalcones **342** can be rearranged into compounds of type **343**, which could be used in the synthesis of isoflavones (Scheme 42).[317,318]

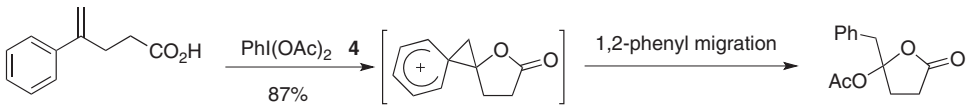


340 **341** (80–90%)

342 **343** (up to 56%)

Scheme 42 Oxidative rearrangements of styrene **340** and chalcones **342**.

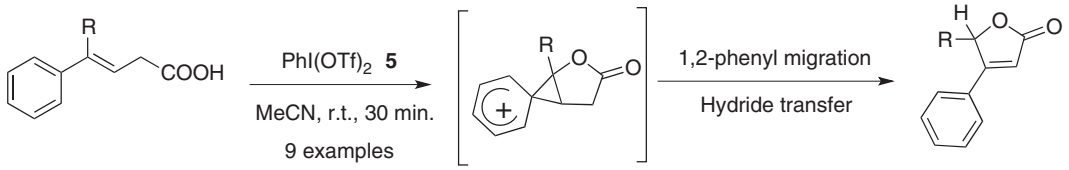
Treatment of aryl-substituted alkenes with hypervalent iodine compounds can lead to the formation of phenyliodinated intermediates, which can be stabilized by the aryl substituent via the formation of phenonium ions. Subsequent nucleophilic attack might then lead to rearranged products. The substrate **344** can be rearranged into lactone **346** via formation of an intermediate phenonium ion **345** followed by a 1,2-phenyl migration (Scheme 43).[319]



344 345 346

Scheme 43 Oxidative rearrangements of acid **344**.

Recently, Wirth and coworkers developed the oxidative cyclization of unsaturated acids of type **347** to highly functionalized furanones **349** via formation of an intermediate phenonium ion **348** followed by a 1,2-phenyl migration and hydride transfer. The reactions were completed in few minutes and products **349** were isolated in excellent yields. Furthermore, this rearrangement has been employed for the synthesis COX-2 inhibitor rofecoxib in 83% yield (Scheme 44).[20b]

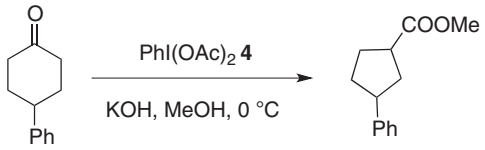


347 348 **349** (78–95%)

Scheme 44 Oxidative rearrangement of β,γ-unsaturated acids **347** to furanones **349**.

7.29.7.4 Ring Contractions

The ring contraction of cycloalkenes and cycloalkanones mediated by iodine(III) compounds, especially by iodobenzene diacetate **4** and by [hydroxy(tosyloxy)iodo]benzene (Koser´s reagent) **9**, has been achieved successfully. In 2006, Silva has published a review article in which the various aspects of iodine(III) reagents induced ring contraction of cycloalkenes and cycloalkanones is discussed.[320] The ring contraction of 4-arylcyclohexenone **350** was achieved by using iodine(III) reagent **4** in 40% yield (equation 54).[321]

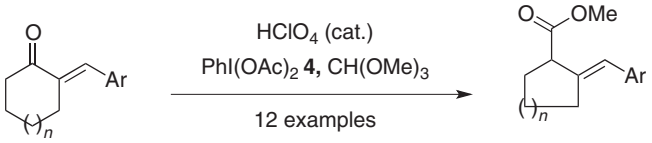


(54)

350 **351** (40%)

Ring contraction of 4-arylcyclohexenone **350** with reagent **4**

2-Arylidenecycloalkanones **352** can be rearranged to 2-arylidenecycloalkane carboxylates **353** by treatment with (diacetoxyiodo)benzene **4** in moderate yields (equation 55).[322] The synthesis of five-, six-, and seven-membered ring esters can be achieved using this approach.



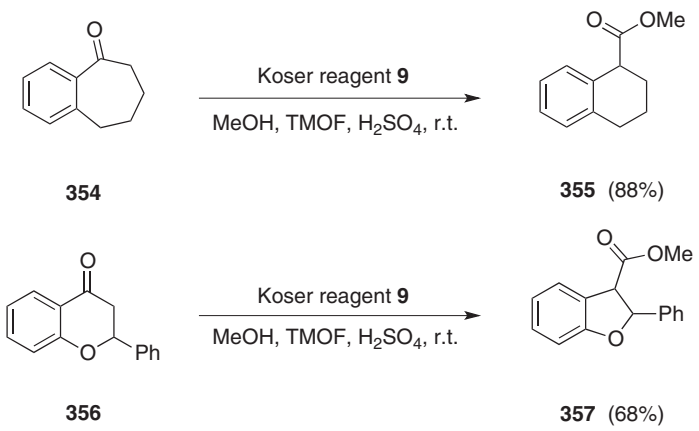
(55)

352 **353** (58–74%)

PIDA-mediated ring contraction of 4-arylcyclohexenone **352**

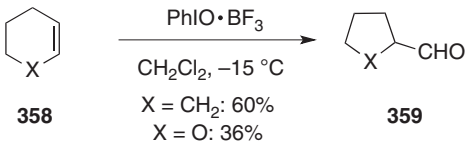
The ring contraction of 1-benzosuberone **354** to methyl 1,2,3,4-tetrahydronaphthalene-1-carboxylate **355** has been achieved in 88% yield using *1H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (HMBI) as oxidant, although a similar ring contraction product was not observed with 1-indanone or 1-tetralone (Scheme 45).[323] In contrast, flavanone **356** affords methyl 2,3-dihydro-2-phenyl-3-benzofurancarboxylate **357** in 68% yield under similar reaction conditions (Scheme 45).[323] There are a few ring contractions of other cyclic ketones that have been reported in the literature.[324–326]

Hypervalent iodine-mediated ring contractions are not only limited to cyclic ketones, but contraction of cycloalkenes also have been reported. Treatment of such cycloalkenes with iodosobenzene–BF_3 complex led to the ring contraction product in reasonable



Scheme 45 Koser reagent-mediated ring contraction of 1-benzosuberone **354** and flavanone **356**.

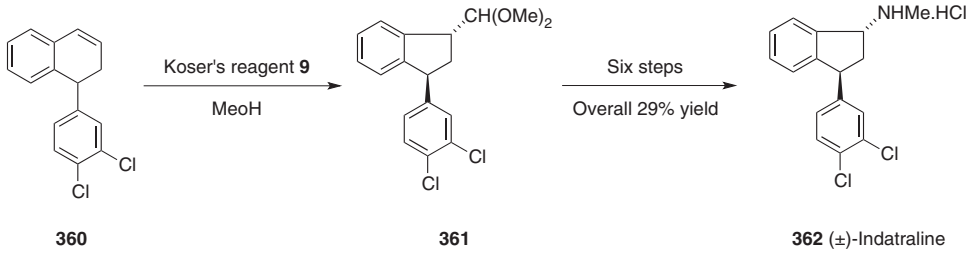
yields. Furthermore, dihydropyran **358** rearranged to the corresponding tetrahydrofuran **359** using iodosobenzene–BF_3 complex (equation 56).[327] Few other research groups have achieved similar type of ring contraction of cycloalkenes.[328–330]



(56)

The ring contraction of cycloalkenes **358** to five-membered rings **359**

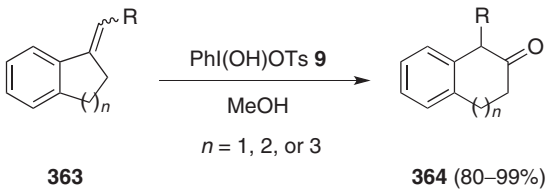
Recently, Silva and coworkers developed a Koser's reagent-mediated diastereoselective ring contraction of a 1,2-dihydronaphthalenes **360** to the indan ring systems **361**. Furthermore, these indan ring systems **362** can be used for the synthesis of (±)-indatraline, which is a 3-phenyl-1-indanamine that displays several biological activities (Scheme 46).[331]



Scheme 46 Koser's reagent-mediated diastereoselective ring contraction of a 1,2-dihydronaphthalenes **360**.

7.29.7.5 Ring Expansions

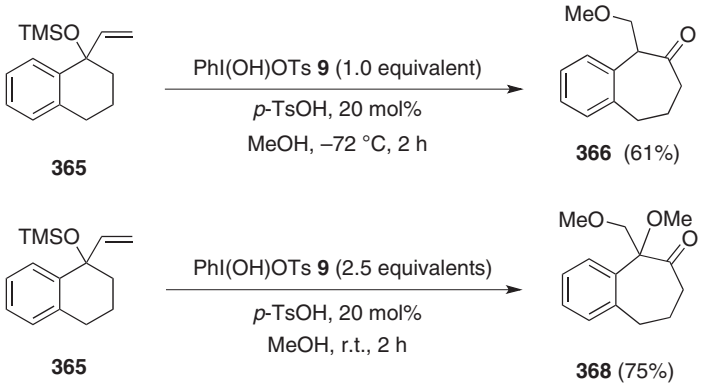
Various hypervalent iodine reagents induced ring expansions have been reported. In 2005, Koser and coworkers demonstrated the synthesis of *β*-benzocycloalkenones **364** containing six-, seven- and eight-membered rings by oxidative ring expansion of alkylidenebenzocycloalkenes **363** using [hydroxy(tosyloxy)iodo]-benzene (Koser's reagent) **9** under mild reaction conditions in excellent yields (equation 57).[332] Furthermore, Hara and coworkers developed the stereoselective synthesis of five- to seven-membered cyclic ethers by iodine(III) reagents-mediated ring expantions.[333]



(57)

Koser reagent-mediated oxidative ring expansion of alkylidenebenzocycloalkenes **363**

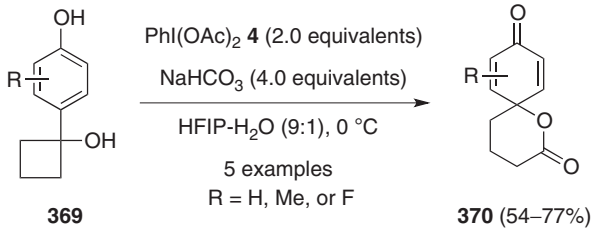
In 2008, Silva applied the same approach for the ring expansion of 1-vinyltetralol derivatives **365** under different reaction conditions to 5-(methoxymethyl)-8,9-dihydro-5*H*-benzo[7]annulen-6(7*H*)-one derivatives **366** and **368**, respectively (Scheme 47).[334]



Scheme 47 Koser reagent-mediated ring expansion of 1-vinyltetralol derivative **365**.

7.29.7.6 Domino Reactions

Recently, Kita and coworkers developed the domino reaction of 1-(*p*-hydroxyaryl)cyclobutanols **369** and [bis(acetoxy)iodo] benzene **4** in hexafluoroisopropanol and water. The reaction products, spirocyclohexadienone lactones **370** were isolated in good to moderate yields (equation 58).[335] The interesting aspect of this reaction is the one-pot four-step reaction. The sequence was as follows: (1) oxidation of the phenolic hydroxyl group forming a carbocation at the *p*-position, (2) rearrangement reaction producing a spiro diene dione compound, (3) water attack on the ketone affording a carboxylic phenol, and (4) intramolecular cyclization giving the spiro cyclodienone lactone, proceeding in a domino sequence.



(58)

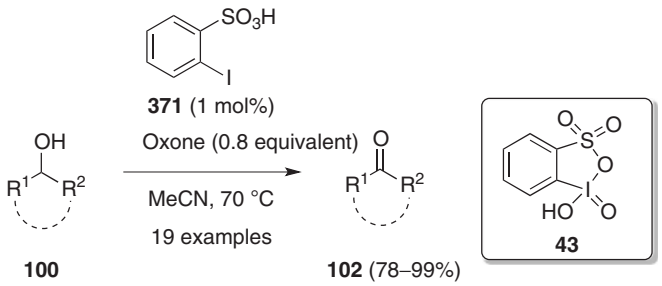
Domino reaction of 1-(*p*-hydroxyaryl)cyclobutanols **369**

7.29.8 Catalytic Reactions

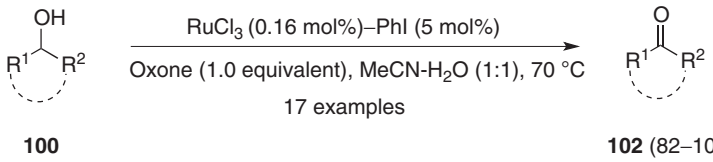
In the past years, iodoarene-mediated catalytic transformations have received particular attention of various hypervalent iodine chemists. During these years, various oxidative transformations have been successfully achieved using the catalytic amount of iodine(III) or iodine(V) reagents. Common oxidants such as *m*-chloroperbenzoic acid (*m*CPBA) or oxone have been used for generation of active hypervalent iodine(III) or (V) species from iodoarenes *in situ*. In 2009, Kita and Dohi published an excellent review article addressing the history and developments until 2009.[336] In 2009, Uyanik and Ishihara also published a review article including various oxidation reactions of alcohols using both stoichiometric and catalytic use of hypervalent iodine reagents, particularly cyclic iodine(V) reagents.[7b] This section highlights the developments in this area after 2009.

Ishihara and coworkers reported that 2-iodoxybenzensulfonic acid **43** (IBS), which is generated from 2-iodobenzenesulfonic acid *in situ*, is an extremely active and mild catalyst for the highly chemoselective oxidation of various alcohols with powdered oxone to carbonyl compounds such as aldehydes, carboxylic acids, ketones, and cycloalkenones under nonaqueous conditions (Scheme 48).[337] Interestingly, the application of pure **43** was limited because of stability issues in various solvents.[50]

Zhdankin and coworkers developed an efficient PhI/$RuCl_3$-cocatalyzed oxidation of various alcohols **100** to the corresponding carbonyl compounds **102** using oxone as stoichiometric oxidant. The reaction tolerated different functional groups and oxidation products were isolated in high yields (equation 59).[338] The same approach can be used for the oxidation of the benzylic position of aromatic hydrocarbons.[338]



Scheme 48 *In situ* generation of **43** for alcohol oxidation.



(59)

PhI/$RuCl_3$-cocatalyzed oxidation of various alcohols **100** to the corresponding carbonyl compounds **102**

Furthermore, the same research group developed recyclable bifunctional catalysts bearing ionic liquid supported (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (**Figure 10**) and employed them in the oxidation of alcohols **100** in peracetic acid. The oxidation products **102** were obtained in high yields.[339] The ionic liquid supported bifunctional catalysts were easily recovered and reused.

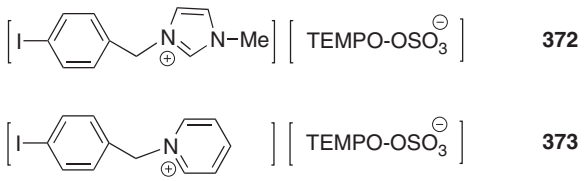
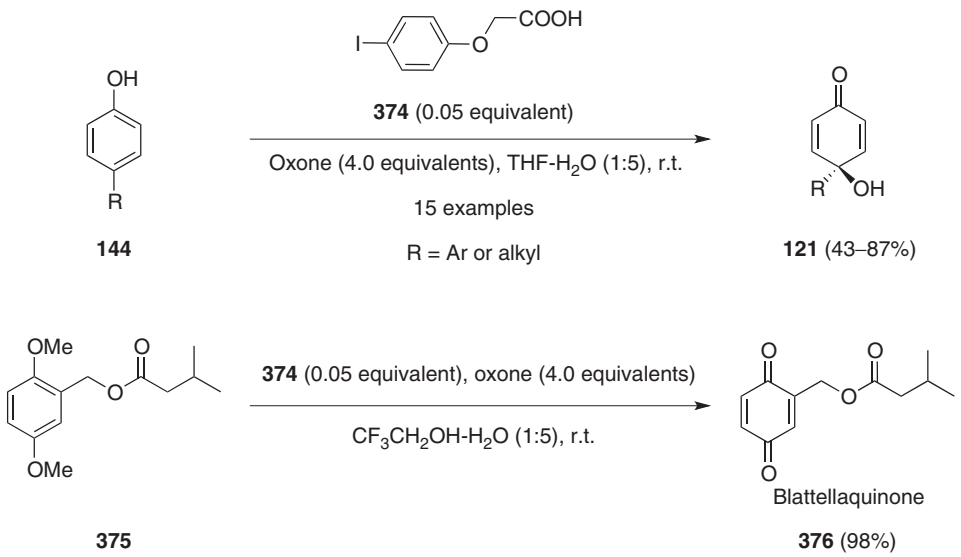


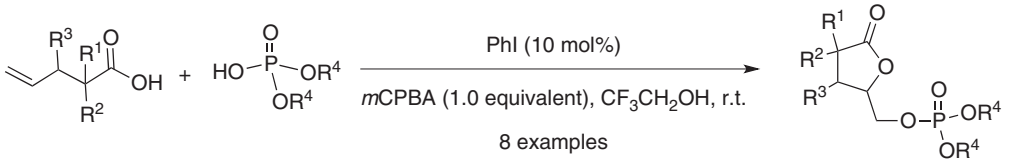
Figure 10 Ionic liquid-supported iodoarene–TEMPO bifunctional catalysts **372** and **373**.

Yakura and coworkers reported the oxidation of phenols **144** to the corresponding *p*-quinols **121** with 5 mol% of 4-iodophenoxyacetic acid **374** in the presence of oxone. The reaction products **121** were isolated in moderate to excellent yields. Furthermore, the same oxidative aromatization approach was applied in the synthesis of blattellaquinone **376**, the sex pheromone of the German cockroach *Blattella germanica* (**Scheme 49**).[340]



Scheme 49 Oxidation of phenols **144** to *p*-quinols **121** with 5 mol% of 4-iodophenoxyacetic acid **374**.

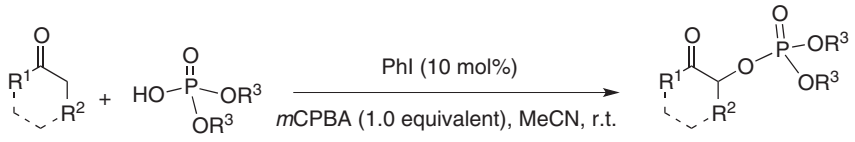
The iodobenzene-catalyzed phosphoryloxylactonization of pentenoic acids **377** has also been achieved using *m*CPBA as the terminal oxidant in CF_3CH_2OH at room temperature. The phosphoryloxylactons **379** were obtained in good yields (equation 60).[341]



377 **378** **379** (58–73%) (60)

Iodobenzene-catalyzed phosphoryloxylactonization of pentenoic acids **377**

Yan and coworkers developed the iodobenzene-catalyzed approach for the α-phosphoryloxylation of ketones **102** using *m*CPBA as the terminal oxidant in acetonitrile at room temperature. The reactions were proceeding smoothly and keto phosphates **380** were obtained in moderate to good yields (equation 61).[342] Recently, Rodriguez and Moran have been reported the enantioselective catalytic oxidative cyclization of 5-oxo-5-phenylpentanoic acid in moderate yields with up to 51% *ee*.[343]

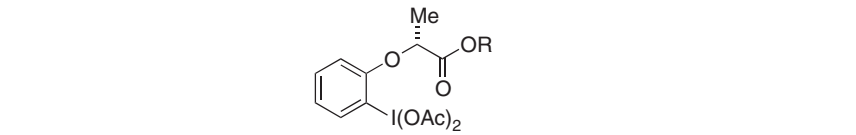


102 **378** **380** (18–71%) (61)

Iodobenzene-catalyzed approach for α-phosphoryloxylation of ketones **102**

7.29.9 Stereoselective Reactions

Stereoselective transformations using chiral hypervalent iodine reagents are a comparatively new phenomenon in hypervalent iodine chemistry. Hypervalent iodine-induced stereoselective reactions have received particular attention especially asymmetric oxidative cyclizations. The chiral Koser-type reagents of **82** and **83** (Figure 9) were used in asymmetric functionalizations of alkenes and ketones but could provided up to 65% *ee*.[101a,104,105] Fujita and coworkers used lactic acid-based chiral λ^3-iodanes **84** in the tetrahydrofuranylation of acyloxybutenes **381**, leading to products **382** in up to 64% *ee* (equation 62).[106]

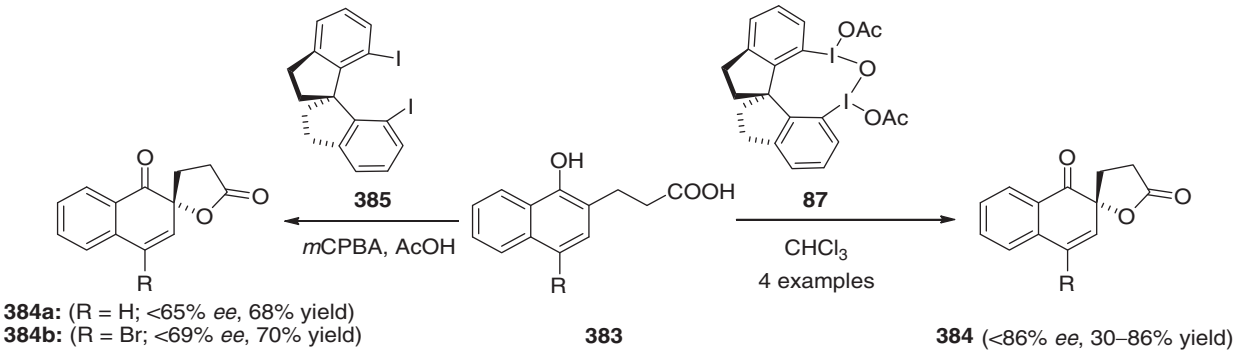


381 **382** (<64% *ee*, 44–59% yield) (62)

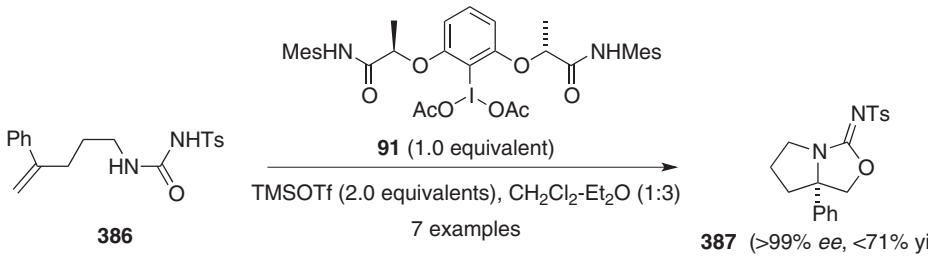
Tetrahydrofuranylation of acyloxybutenes **381** using chiral iodine(III) reagent **84**

Kita and coworkers have developed enantioselective oxidative spirolactonizations of naphthols **383** by using chiral hypervalent iodine reagent **87** with selectivities of up to 86% *ee*. Furthermore, asymmetric catalytic enantioselective oxidative spirolactonizations were also developed using chiral iodoarene **385** with up to 69% *ee* (Scheme 50).[97] Later, Ishihara and his research group used C_2-symmetric chiral iodoarene (precursor of **87**) and catalytic spirocyclizations were achieved with selectivities of up to 92% *ee*.[112,344]

Recently, Farid and Wirth reported stereoselective oxyamination reactions using various chiral hypervalent iodine reagents **91** with up to 99% *ee* (equation 63).[20a] The reaction products were isolated in up to 76% yield.



Scheme 50 Enantioselective oxidative spirolactonizations of naphthols **383** by using chiral hypervalent iodine reagent **87** catalytic or stoichiometric amounts.



(63)

Stereoselective aminohydroxylations using chiral reagent **91**

Various other stereoselective transformations have been reported using different chiral hypervalent iodine reagents but most of them were associated either with moderate or low selectivities. Recently, Liang and Ciufolini as well as Farid and Wirth have published reviews highlighting stereoselective reactions using chiral hypervalent iodine reagents.[96]

7.29.10 Hypervalent Bromine Reagents

Unlike hypervalent iodine chemistry, the chemistry of hypervalent bromine reagents is still not well explored despite the first report on the hypervalent bromine reagent **388** in 1952.[345] In 2009, Wirth and coworkers have published a short review about the progress of hypervalent bromine reagents (Figure 11).[346]

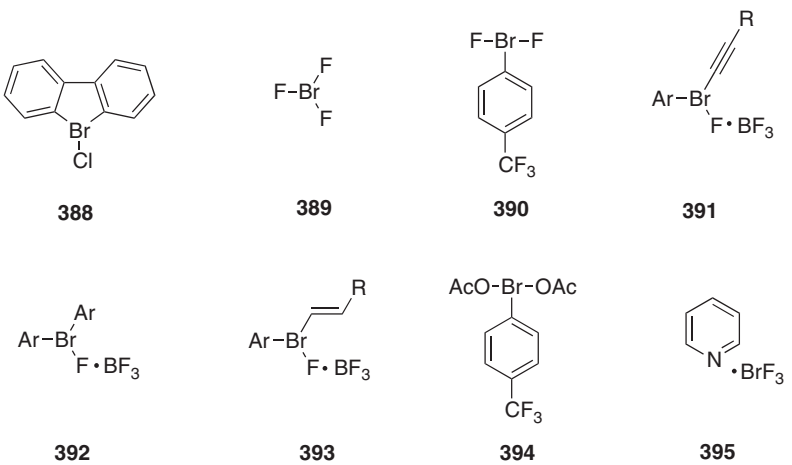
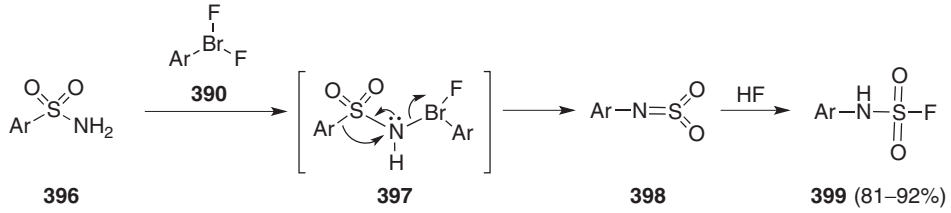


Figure 11 Hypervalent bromine reagents **388–395**.

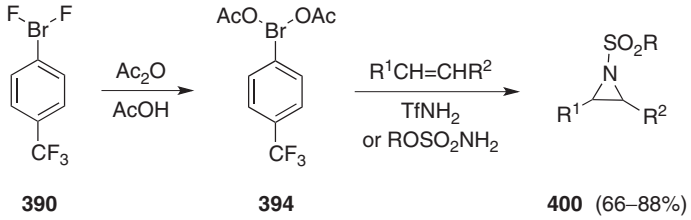
Only very few research groups have made serious contributions in the development of this chemistry. Various hypervalent bromine reagents **388–395** have been reported and most of them can be synthesized by ligand-exchange reactions using bromine trifluoride **389**.[347,348] Hypervalent bromine reagents **389**[349–352] and **393**[353] can be used in various substitution reactions. Very recently, Hagooly and Rozen have used the pyridine–BrF_3 complex **395** for the fluorination of aromatic compounds.[354]

Ochiai and coworkers reported the difluoro-λ^3-bromane **390**-mediated Hofmann rearrangement of sulfonamides **396**, and rearranged products **399** were isolated in excellent yields (Scheme 51).[355] The reaction was initiated with formation of intermediate **397**, which was rearranged to **398** via 1,2-shift. Furthermore, compound **398** can be converted to corresponding aryl sulfamoyl fluorides **399** by the reaction with HF.



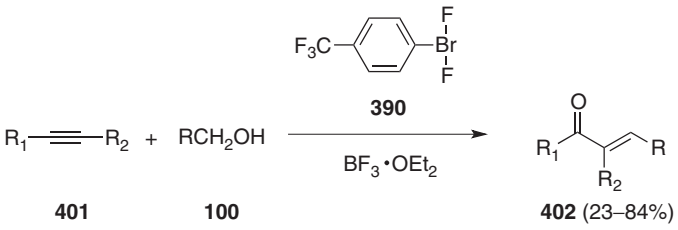
Scheme 51 Hofmann rearrangement of sulfonamides using hypervalent bromine(III) reagent **390**.

In 2011, the same research group has reported the synthesis of (diacetoxybromo)benzene **394** by ligand exchange of *p*-$CF_3C_6H_4BrF_2$ **390** with acetoxy groups using AcOH and Ac_2O, which performs aziridination of alkenes in the presence of $TfNH_2$ and sulfamate esters in a one-pot reaction under mild conditions. The reaction products **400** were isolated in moderate yields (Scheme 52).[356] Furthermore, a similar one-pot aziridination approach was applied to intramolecular reactions.



Scheme 52 Hypervalent bromine-mediated aziridination of alkenes.

Also other oxidation reactions have been successfully achieved using hypervalent bromine reagent **390**. In 2008, Ochiai and coworkers have developed the oxidative coupling of alcohols **100** and alkynes **401** using bromine(III) reagent **390**. The reaction products are α,β-unsaturated ketones **402**, which were isolated in good yields (equation 64).[357]



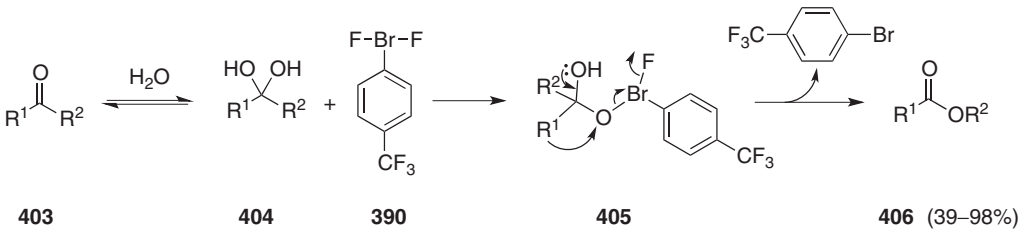
(64)

Synthesis of α,β-unsaturated ketones **402** using hypervalent bromine reagent **390**

In 2010, the Ochiai research group has successfully achieved the Baeyer–Villiger oxidation of carbonyl compounds **403** with hypervalent bromine(III) reagent **390** in excellent yields. This reaction involves the initial hydration of carbonyl compounds **403**, followed by ligand exchange on the hypervalent aryl-λ^3-bromane **390** with the resulting hydrate **404**, yielding a new type of activated Criegee intermediate **405**. Finally, the intermediate **405** undergoes Baeyer–Villiger rearrangement and produces an ester **406** via facile reductive elimination of an aryl-λ^3-bromanyl group because of its hypernucleofugality (Scheme 53).[358]

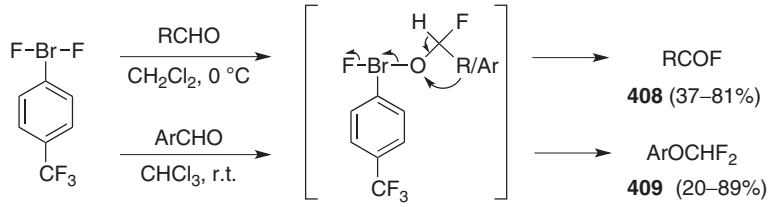
The oxidation of primary aliphatic aldehydes with *p*-trifluoromethylphenyl(difluoro)-λ^3-bromane **390** in dichloromethane at 0 °C afforded acid fluorides **408** selectively in good yields, whereas the aromatic aldehydes produced aryl difluoromethyl ethers **409** in chloroform at room temperature (Scheme 54).[359] A larger migratory aptitude of aryl groups compared with primary alkyl groups during a 1,2-shift from carbon to an electron-deficient oxygen atom in bromane(III) Criegee-type intermediates such as **407** is causing these differences in the reaction course.

Recently, Ochiai and coworkers reported a metal free highly regioselective amination of unactivated alkanes **410** based on hypervalent sulfonylimino-λ^3-bromane **411** via C–H insertion of a nitrogen functional group. The reaction produces triflyl-substituted amines **412**, which were obtained in moderate to high yields (equation 65).[360] Tertiary C–H bonds have shown higher selectivity than secondary C–H bonds.



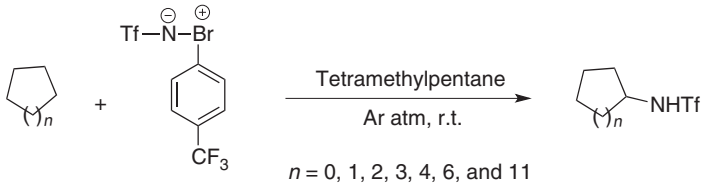
403 **404** **390** **405** **406** (39–98%)

Scheme 53 Baeyer–Villiger reaction using bromine(III) derivative **390**.



390 **407**

Scheme 54 Rearrangements from Criegee intermediates **407**.



410 **411** **412** (54–92%) (65)

Amination of C–H bonds using bromine(III) reagent **411**

Similar to iodonium ylides, the corresponding bromonium ylides have been synthesized and used in various synthetic transformations.[361–364]

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