INTRODUCTION TO VOLUME 3: CARBON–CARBON BOND FORMATION

Since the pioneering work of Friedrich Wöhler in 1828 on the synthesis of urea, organic chemists have, by essence, been interested in developing ingenious approaches for the creation of carbon–carbon bonds. Under the leadership of the previous volume editor Gerald Pattenden, most of the useful methods developed for the creation of carbon–carbon bond were described in volume 3 of Comprehensive Organic Synthesis. However, considering the pace of advancements of the field, the increasing degree of sophistication that needs to be addressed and the tools that were developed to reach these target molecules, it became clear that an update of the volume was needed. For instance, the area of C–C bond formation promoted by catalysts started to grow exponentially in the 1990s with the general appreciation of opportunities offered by organometallic chemistry and metal catalysis for organic synthesis. So, from the 32 initial chapters published in the previous edition in 1991, most of them have been updated and now cover the most modern aspects of synthetic transformations for the creation of C–C bonds with a special emphasis on catalysis leading to regio-, diastereo- and enantioselective transformations. This gigantic task would not have been possible without the exceptional talents of authors, who have spent many precious hours working on this update. I am deeply indebted to this truly international group of authors. Without their efforts, this new volume would not have been possible. It is their expertise that will familiarize the reader with the essence of the topic. I will also be grateful to readers who draw my attention to mistakes or missing information in the present volume.

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3.01 Alkylations of Enols and Enolates

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3.01.1 Introduction 2
3.01.1.1 A Historical Perspective 2
3.01.2 Formation and Reactivity of Enolates 4
3.01.2.1 Group I Metal Enolates 4
3.01.2.1.1 Formation of group I metal enolates 4
3.01.2.1.1.1 Deprotonation of carbonyl compounds 4
3.01.2.1.1.2 Alternate methods to form group I enolates 6
3.01.2.1.2 Alkylation of group I metal enolates 6
3.01.2.2 Group II Metal Enolates 8
3.01.2.3 Boron Enolates 9
3.01.2.4 Silyl Enol Ethers 10
3.01.2.4.1 Formation of silyl enol ethers 10
3.01.2.4.2 Alkylation of silyl enol ethers 13
3.01.2.5 Transition Metal Enolates 14
3.01.2.5.1 Formation and structure of transition metal enolates 14
3.01.2.5.2 Reactions of transition metal enolates 14
3.01.2.5.3 Transition metal and main group Lewis acids 15
3.01.3 Diastereoselective Enolate Alkylations 16
3.01.3.1 Substrate Control in Asymmetric Alkylation 16
3.01.3.1.1 Stereoelectronic effects 18
3.01.3.1.2 Steric effects 20
3.01.3.1.2.1 Impact on molecular conformation 20
3.01.3.1.2.1.1 Allylic strain 21
3.01.3.1.2.2 Electrophile accessibility 21
3.01.3.1.2.3 Intramolecular alkylation 25
3.01.3.1.3 Chelation effects 25
3.01.3.1.4 Memory of chirality 26
3.01.3.2 Chiral Auxiliaries 28
3.01.3.2.1 Amino alcohol-derived auxiliaries 28
3.01.3.2.2 Terpenoid-derived auxiliaries 32
3.01.3.2.3 Carbohydrate-derived auxiliaries 32
3.01.4 Enantioselective Enolate Alkylation 34
3.01.4.1 Group I and II Metal Enolates 34
3.01.4.1.1 Enantioselective deprotonation 34
3.01.4.1.2 Enantioselective alkylation of prochiral enolates 34
3.01.4.2 Transition Metal Enolates 36
3.01.4.2.1 Transition metal catalyzed asymmetric allylic alkylation 36
3.01.4.2.1.1 Palladium-catalyzed allylic alkylation 36
3.01.4.2.1.1.1 Stabilized enolates 36
3.01.4.2.1.1.2 Nonstabilized enolates 38
3.01.4.2.1.2 Iridium-catalyzed allylic alkylation 40
3.01.4.2.1.3 Other transition metal catalyzed allylic alkylation 41
3.01.4.2.2 Other transition metal catalyzed asymmetric α-alkylations 41
3.01.4.2.2.1 Copper-catalyzed amide α-alkylation 41
3.01.4.2.2.2 Nickel-catalyzed amide α-alkylation 41
3.01.4.2.2.3 Chromium-based alkylations 41
3.01.5 Miscellaneous 43
3.01.5.1 Phase Transfer Catalysis 43
3.01.5.2 Phosphazene Superbase-Promoted Alkylations 45
3.01.5.3 Radical Alkylations 46
3.01.5.4 Lewis Acid Mediated Alkylations 48
3.01.6 Conclusion 48
References 49

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Glossary

Allylic strain Strain resulting from a steric interaction between a substituent located at a vinylic position and another substituent at an allylic position around a double bond. $A^{1,2}$ strain refers to the steric clash between substituents attached to the same carbon of the double bond, whereas $A^{1,3}$ strain encompasses interactions between functionality on opposite sides of the double bond.

Chiral auxiliary A molecular fragment that is temporarily incorporated in a substrate to direct the stereochemical outcome for a chemical transformation and is subsequently removed.

Phase transfer catalysis A chemical reaction that incorporates a catalytic charged organic molecule to facilitate the interaction of reagents between the organic and aqueous phases of the reaction.

Phosphazene A molecule that incorporates a phosphorus atom covalently connected to a nitrogen atom through a double bond and to three other substituents (also often nitrogen atoms) through single bonds.

Stereoelectronics The geometrical orientation a compound adopts due to the electronic elements found within the molecule.

3.01.1 Introduction

Enolate alkylation, the nucleophilic substitution of electrophilic alkylating reagents by carbon nucleophiles generated from the α-deprotonation of carbonyl compounds, is one among the most fundamental and important methods for the construction of carbon–carbon bonds adjacent to a carbonyl group. Over the past fifty years, this methodology has evolved into a highly selective, efficient, and essential technique integral to the practitioners of pharmaceutical industry, chemical biology, and academic organic synthesis.

Since the previous publication of Comprehensive Organic Synthesis in 1991,[1] a field-wide explosion of interest in catalysis has sparked the development of numerous metal and metal-free catalytic alkylation methods. These advances have introduced new methods for enolate formation, expanded substrate scope, and enabled highly stereoselective α-alkylations. New techniques allow elaboration of a diverse array of small molecules and have made enolate alkylation one of the most important methods for asymmetric carbon–carbon bond formation.

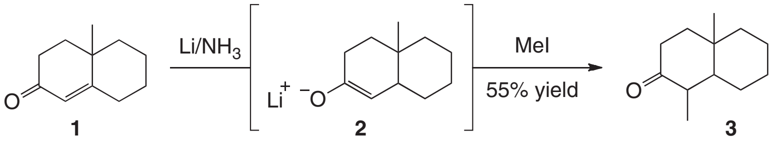
Owing to the overwhelming wealth of literature on carbonyl chemistry, attempt has been made to narrowly define 'enolate alkylation' to encompass only the reactions of enolates with sp^3-hybridized carbon electrophiles. Aldol reactions, conjugate additions, arylations, and functionalizations of enamines and metalloenamines will be addressed in other chapters of this compendium.

3.01.1.1 A Historical Perspective

In principle, enolate alkylation is a fundamentally and mechanistically simple transformation: enolate generation by some means (typically by α-deprotonation of the parent carbonyl compound) is followed by nucleophilic attack on an alkyl halide or pseudohalide via S_N2-displacement to form a carbon–carbon bond. However, in practice, α-alkylations suffer from several endemic side reactions (Scheme 1). Enolates may dimerize with their carbonyl precursor to form aldol products or alkylate at oxygen instead of carbon. Alternatively, enolates may act as bases that cause undesired over-alkylation, elimination of electrophiles, and epimerization of stereocenters in diastereoselective transformations. In ketones, positional infidelity in enolate generation or subsequent isomerization can create broad product distributions.

These undesired side reactions plagued chemists until the middle of twentieth century. Reliance on strong ionic bases and polar solvents made many alkylations low yielding or impossible. They, instead, chose substrates with occluded or activated α-positions. Most versatile are the stabilized enolates of 1,3-dicarbonyl compounds like diethylmalonate, which react smoothly and can be subsequently decarboxylated. However, the applications of these transformations were inherently limited and their procedures often quite involved.

Direct alkylation of ketones remained difficult until 1961, when Stork et al. demonstrated the regioselective generation and alkylation of the thermodynamic enolate of *trans*-10-methyl-2-decalone (**3**, equation 1).[2] Reduction of the appropriate octalone (**1**) by lithium metal in liquid ammonia affords only one enolate (**2**), but transfer of the solution to more polar solvents like DMSO results in complete loss of selectivity. Use of other group I metals has the same effect. These observations established that a stronger metal–oxygen association of lithium enolates in nonpolar media mitigates reactivity and suppresses the proton transfer associated with enolate isomerization.



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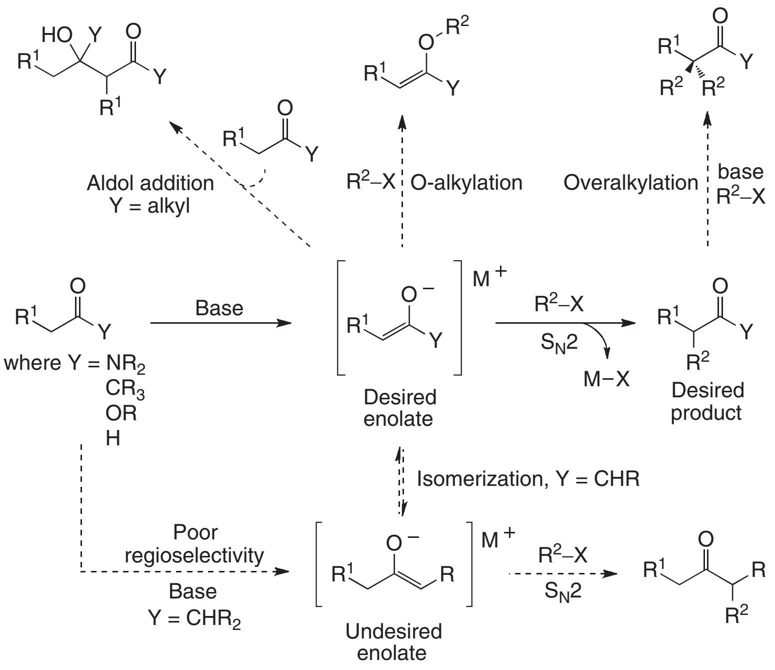


Scheme 1 Side reactions of enolates.

Stork's discoveries heralded the modern era of enolate functionalization. Over the next two decades, studies by House et al.,[3] Seebach,[4] and others produced 'standard conditions' for enolate alkylation: low temperature deprotonation by a nonnucleophilic, lithium amide bases like lithium diisopropylamide (LDA) in a nonpolar ethereal solvent such as THF, followed by addition of an alkyl halide electrophile.

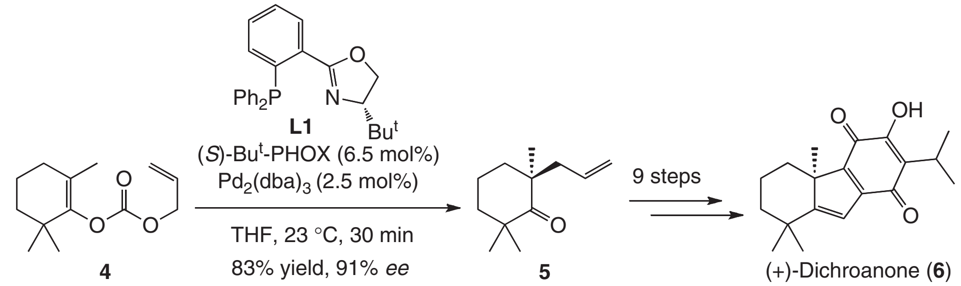
Introduction of the concepts of thermodynamic and kinetic deprotonation control gave chemists acute selectivity in enolate generation.[5,6] It was quickly found that more highly substituted enolates were formed under equilibrating conditions, whereas nonequilibrating conditions favored less-substituted species. These observations are rationalized in terms of thermodynamics: the most sterically accessible proton is abstracted faster forming the 'kinetic enolate,' but can be converted over time to the more energetically stable 'thermodynamic enolate' if dynamic isomerization is allowed to occur. This new found selectivity, in turn, permitted high yielding alkylations including regioselective functionalization of ketones. These advances bestowed predictability and control on alkylations via subtle manipulation of temperature, solvent, additives, and stoichiometry.[4]

As enolate substitution became more reliable, the increasing need for optically enriched small molecules in chemical biology and medicine shifted focus to asymmetric transformations. Detailed studies on diastereoselectivity produced a number of predictive stereochemical models for alkylations of chiral molecules. However, it was not until Corey and Ensley introduced chiral auxiliaries based on menthol in 1975 that reliable and practical methods began to emerge for asymmetric synthesis.[7] This work was expanded upon in the enolate alkylation area by Evans, Meyers, Oppolzer, Myers, and many others to yield a library of well-studied, chiral pool derived addends for the control of alkylation stereochemistry.[1,8,9]

Concurrently, burgeoning study on the reactivity of enolates stabilized by nongroup I metals contributed unique chemistry to the repertoire of alkylation methodology. By the 1970s, stable silyl enol ethers and enol stannanes had enabled the purification of enolates for alkylations with isomerically pure nucleophiles.[3a] The enolates of Lewis acidic transition metals, like titanium, exhibit strong chelation effects that augment stereoinduction in chiral substrates. Others, such as tin, promote unusual S_N1 or radical processes for substitutions of bulky tertiary and secondary alkyl halides.[10]

However, transition metal chemistry would ultimately make the greatest impact in catalysis. Before the twenty-first century, few general methods existed for catalytic generation of enriched stereocenters through enolate alkylation (for an exception, see Section 3.01.5.1). Building on the work of Tsuji and others, chemists such as Trost,[11] Stoltz,[12] and Jacobsen[13] developed highly enantioselective, catalytic α-alkylations using chiral ligands and metals such as palladium or chromium. For the first time, spontaneous generation of stereocenters – including synthetically challenging, all-carbon quaternary stereocenters – became possible for a wide range of carbonyl containing substrates. These catalysts also introduced a new generation of stable enolate precursors, such as enol carbonates and β-ketoesters, which are metal-activated *in situ* without the need for a strong base.[12]

Today, these landmark discoveries stand at the frontier of enolate alkylation research. New procedures have permitted novel synthetic strategies and rapid access to a bevy of targets ranging from unnatural polypeptides to complex secondary metabolites. Scheme 2 depicts one such example: the palladium-catalyzed decarboxylative asymmetric allylic alkylation of enol carbonate 4



Scheme 2 Stoltz's palladium-catalyzed decarboxylative asymmetric allylic alkylation.

developed in the Stoltz group.[12] Ketone **5** was advanced in a protecting group free sequence to the norditerpenoid natural product (+)-dichroanone (**6**) in nine further steps.[14]

We have organized this chapter around this variegated history. Our treatment of the topic begins with a primer of groups I and II metal enolate alkylations (Section 3.01.2), which introduces the essentials of this integral technique and reviews the state-of-the-art technologies. Paralleling the field as a whole, our discussion turns to diastereoselective alkylation (Section 3.01.3), including an examination of stereocontrol with chiral auxiliaries (Section 3.01.3.2). Finally, we trace this trajectory to the most recent developments in transition metal enolate chemistry and asymmetric catalysis (Section 3.01.4). In proceeding, this chapter strives not only to sketch the fundamentals of this powerful mode of carbon–carbon bond construction, but also to illustrate the contemporary landscape of a synthetic method vital to innumerable chemists in academia, medicine, and industry.

3.01.2 Formation and Reactivity of Enolates

3.01.2.1 Group I Metal Enolates

The formation of carbon–carbon bonds at the α-carbonyl position by alkylation of group I metal enolates has been a crucial technique in organic chemistry since its inception.[4,15] The reactivity of these enolates depends on a number of factors such as solvent choice, presence of metal-chelating co-solvents, and salt additives.

3.01.2.1.1 Formation of group I metal enolates

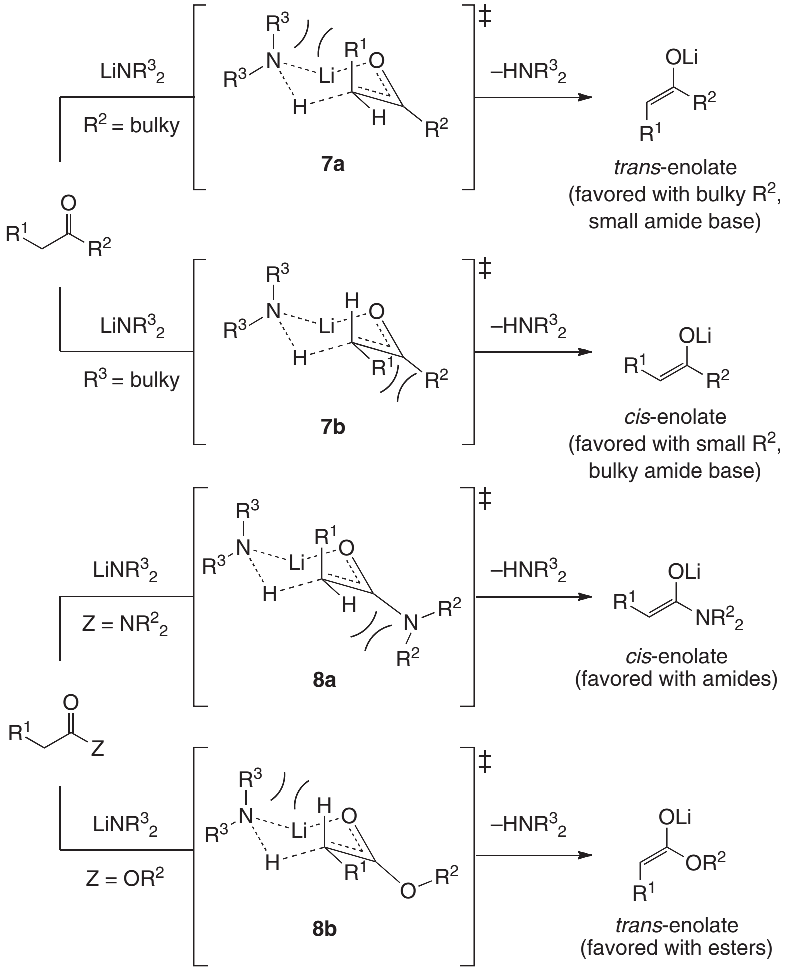
3.01.2.1.1.1 Deprotonation of carbonyl compounds

One of the most prominent methods for forming group I metal enolates is by deprotonation of carbonyl compounds with bases such as metal alkoxides, metal hydrides, alkyl metal species (especially trityllithium), and metal amide bases (*see* Volume 2, Chapter 2.06). Of these bases, the last are the most prominently used in modern research. Common bases include lithium diisopropylamide (LDA),[16] lithium hexamethyldisilylamide (LHMDS),[17] lithium 2,2,6,6-tetramethylpiperidide (LTMP),[18] and lithium *t*-butyl-*t*-octyl amide (LOBA),[19] as well as their sodium and potassium equivalents. Cesium and rubidium enolates, although known, are not commonly employed in synthesis, and to the best of our knowledge there are no reports of francium enolates.

To obviate undesired reactions such as aldol condensation and enolate equilibration, low temperatures and polar aprotic solvents are typically used for enolate formation. Such solvents include monodentate *n*-donating ethereal solvents such as THF and diethyl ether, di- and polydentate *n*-donating ethereal solvents such as DME and higher glymes, and occasionally other polar aprotic solvents or co-solvents such as HMPA and DMF. The choice of solvent and co-solvent affects the aggregation state of the resulting enolate, thus influencing reactivity.

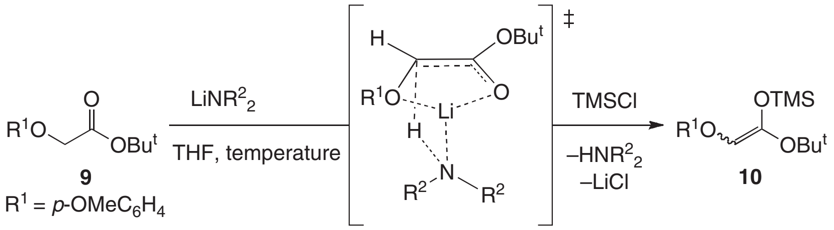
In unsymmetrical ketones with protons at both α-positions, kinetic and thermodynamic factors in the deprotonation step can favor one isomeric enolate over the other.[5] Generally speaking, the kinetically favored enolate results from deprotonation at the position with the least steric hindrance at the α- and *β*-positions, whereas the more-substituted enolate is thermodynamically favored. Reaction conditions favoring kinetic deprotonation usually make use of a bulky amide base and are conducted at low temperatures. Thermodynamic enolization usually results from enolate equilibration at higher temperatures with excess ketone. Kinetic deprotonation of α,*β*-unsaturated ketones (normally in aprotic solvents with a lithium amide base) favors deprotonation at the α′-position resulting in cross-conjugated metal dienolates, whereas thermodynamic deprotonation (most often in protic solvents with alkoxide bases or in aprotic solvent with a metal hydride base) favors deprotonation at the *γ*-position resulting in extended metal dienolates.

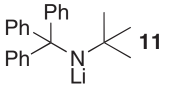
In the case of linear ketones, in addition to thermodynamic and kinetic considerations, the enolization conditions may favor either the *cis*- or *trans*-enolate isomer (**Scheme 3**). Whereas increasing the steric bulk of the metal amide base generally favors the *trans*-isomer (**7a**), the presence of a bulky group at the α′-position favors formation of the *cis*-enolate (**7b**), and is rationalized by a chair-like six-membered transition state of the deprotonation step.[20] Lithium *N*-cyclohexylisopropylamide, LHMDS, LTMP, and LOBA are more sterically hindered bases than LDA, that are used to obtain greater *trans*-selectivity. In the formation of enolates with α-chelating groups (as in the case of oxyacetate esters, **Table 1**), the existence of a mechanism favoring deprotonation to form the *cis*-enolate isomer can reduce this selectivity, and the especially bulky amide base lithium



Scheme 3 Factors influencing enolate geometry.

Table 1 Selectivity in enolate formation with amide bases[19b]



Entry	*Base*	*Temperature (°C)*	trans-:cis-***10***
1	LDA	−78	2:1
2	LTMP	−78	3.5:1
3	LOBA	−100	5:1
4	 **11**	−78	14:1

N-*tert*-butyl-*N*-tritylamide (**11**) has been developed by the Corey group for this purpose.[19] In their studies, a 14:1 ratio of *trans*- to *cis*-products was formed from the silylation of *t*-butyl 4-methoxyphenylacetate (**10**) using this base, compared to 5:1, 3.5:1 and 2:1 ratio using LOBA, LMTP and LDA, respectively. Owing to the low steric hindrance on the oxygen atom of esters, these substrates typically favor the *trans*-isomer. As a result of the high barrier of rotation about the carbon–nitrogen bond of amides, these substrates almost invariably favor the *cis*-isomer.

As already alluded to, the methods described above for forming enolates from ketones by deprotonation also apply to carboxylic acid derivatives such as esters, lactones, *N*,*N*-dialkylamides, *N*-alkyllactams, and nitriles.[21] The enolate dianions of nonfully substituted amides, lactams, and carboxylic acids can be formed by the addition of two or more equivalents of base.[22] Addition of two equivalents of potassium or sodium amide to β-dicarbonyl compounds in liquid ammonia, or the addition of a second equivalent of a strong base (such as LDA or *n*-butyllithium) can form the dienolate dianion.[23] In the case of 1,3-diketones, the second deprotonation occurs selectively at the less-substituted position in the absence of an activating group at the more-substituted position.[24]

Aldehydes are poor substrates for alkylation via group I metal enolates.[25] Although it is possible with extremely sterically hindered aldehydes, generally the rate of self-aldol condensation is competitive with that of deprotonation.[25] Alternate methodologies for the α-alkylation of aldehydes have proven to be more fruitful, such as alkylation of the corresponding enamine or deprotonated Schiff base, as discussed in chapter 2 of this text. An exception to this rule is α,β-unsaturated aldehydes, which can be deprotonated (typically with potassium hydride in THF) at the γ-position resulting in extended dienolates, which are less prone to self-aldol condensation than simple aldehyde enolates.[26]

3.01.2.1.1.2 Alternate methods to form group I enolates

Another commonly employed method for forming lithium enolates is the cleavage of silyl enol ethers or enol acetates.[1,27] Silyl enol ethers may be cleaved by methyllithium, metal fluoride salts such as KF[28] (with or without 18-crown-6) or CsF,[29] lithium amide,[30] or potassium *tert*-butoxide.[31] The major advantage of these methods is that the enolate isomer formed reflects the composition of the silyl enol ether or enol acetate starting material. As it is possible to purify silyl enol ethers and enol acetates, this technique is a useful method to obtain a single lithium enolate isomer that would be difficult to access by selective deprotonation.

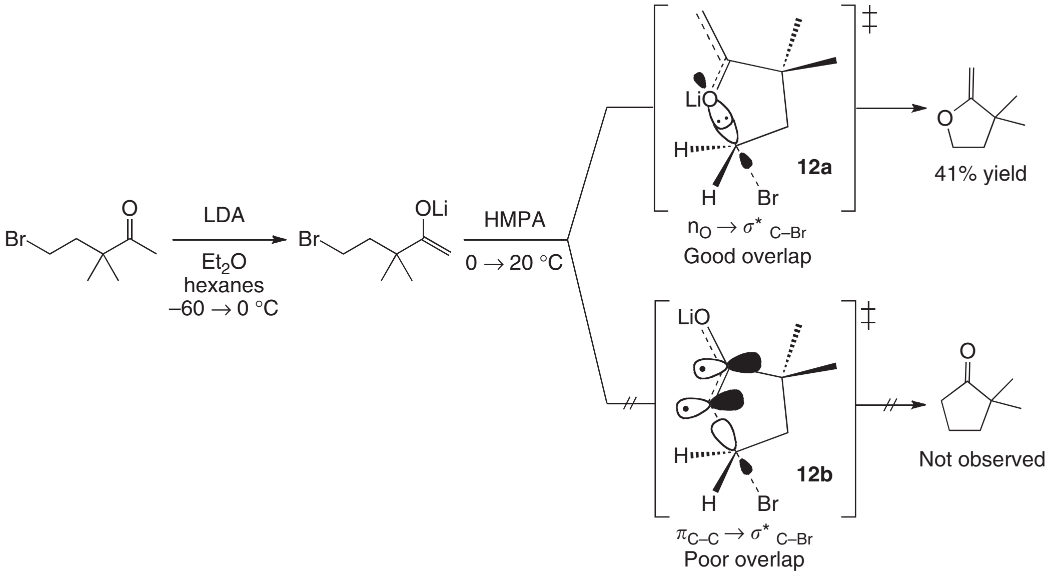
Lithium–ammonia reduction of α,β-unsaturated ketones is another method for the selective formation of a single lithium enolate isomer.[32] The enolate isomer formed directly reflects the position of the carbon–carbon double bond in the starting enone. Similarly, organocuprate reagents may be added to α,β-unsaturated ketones to selectively form β-substituted lithium enolates, which may be used *in situ* in alkylation reactions.[33] In these reactions, copper(I) salts remain and affect the reactivity of the lithium enolate, even in small amounts. Typically, the conjugate addition steps are conducted in THF or ether, while a cosolvent such as HMPA must be added during the alkylation step in order to increase reactivity of the resulting enolate.[33a]

3.01.2.1.2 Alkylation of group I metal enolates

In alkylation reactions, group I metal enolates follow general reactivity trends for S_N2 reactions. Alkyl iodides and sulfonates react more rapidly than the corresponding bromides, which all react more quickly than the analogous chlorides. Alkylation with benzyl and allyl halides or pseudohalides usually proceeds rapidly, and primary halides and pseudohalides are also excellent substrates for alkylation. The reactivity of the electrophile is attenuated by β-substitution, and α-substitution dramatically reduces the rate of alkylation. Tertiary halides and pseudohalides undergo elimination almost exclusively, as do other substrates prone to elimination, for example, homoallyl halides and β-halocarbonyl compounds. O-alkylation of simple group I metal enolates is not a typical side-reaction, except with extremely reactive alkylating agents such as dialkylsulfates and trialkyloxonium salts. However, in the *endo*-cyclizations of terminal enolates, O-alkylation is seen as the exclusive product for the formation of five-membered rings due to the geometric constraints of S_N2 reactions (i.e., **12a** vs. **12b**, **Scheme 4**).[34] The lone pair of electrons in the sp^2 orbitals of oxygen is able to achieve colinearity with the C–X $\sigma*$ orbital to affect the transformation, whereas the electrons in the C–C π-bond are not. In *exo*-cyclizations or cyclizations forming rings of larger sizes, C-alkylation again predominates.

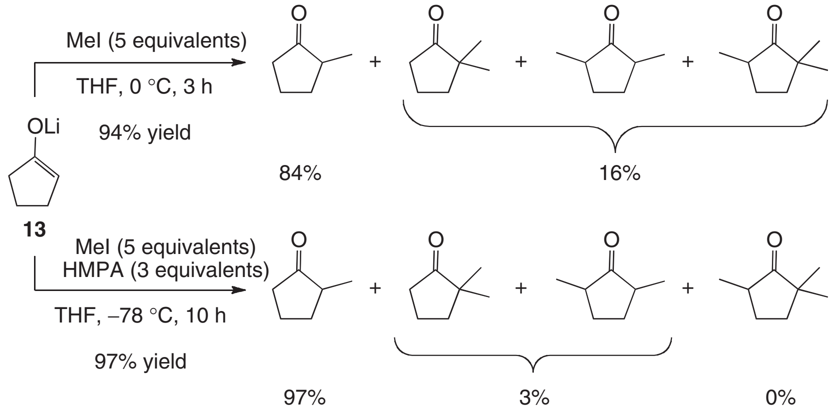
Extensive research has been conducted to determine the aggregation state of group I metal enolates, with lithium enolates being the most well-studied class.[35] Crystal structures of lithium enolates have been solved as dimers, tetramers, and hexamers.[36] The enolates and lithium counterions have been found in the solid state either alone or with coordinated solvent and/or cosolvent molecules, according to the conditions of crystal growth. NMR studies have suggested that, in solution, lithium enolates exist as dimers and tetramers, and that mixed aggregates are formed with LDA, diisopropylamine, and salt additives such as LiCl, LiBr, and $LiClO_4$.[37] Underscoring the complexity of these studies, the lithium enolate of pinacolone in the solid state grown from heptane was found to be a hexamer whereas the sodium enolate was seen to be a tetramer; with THF as a cosolvent, the lithium enolate was found to be tetrameric with four coordinated THF molecules whereas the potassium enolate was observed as a hexamer with six coordinated THF molecules.[38,39] Recent UV-visual spectroscopic methods have suggested that lithium enolates exist in equilibrium between monomer and tetramer favoring the tetramer,[40] whereas cesium enolates exist in an equilibrium favoring tetramer over dimer over monomer.[41] Kinetic studies suggest, however, that the monomer is the reactive species in alkylations of both enolate species.[40–42]

Over-alkylation represents the major byproduct-forming side-reaction accompanying metal enolate alkylation. Evidence has shown that less-substituted enolates favor aggregation as compared with more-substituted enolates, leading to the formation of such byproducts.[3b] As such, proton transfer between the starting enolate and the alkylated products can result in significant over-alkylation. Excess base in solution can deprotonate an alkylation product, which can subsequently alkylate again, leading to the formation of undesired polyalkylated byproducts. A number of techniques have been developed to prevent or diminish the extent of over-alkylation in reactions with metal enolates. Addition of a metal-chelating cosolvent is one of the most frequently used



Scheme 4 Exclusive O-alkylation during five-membered ring formation.

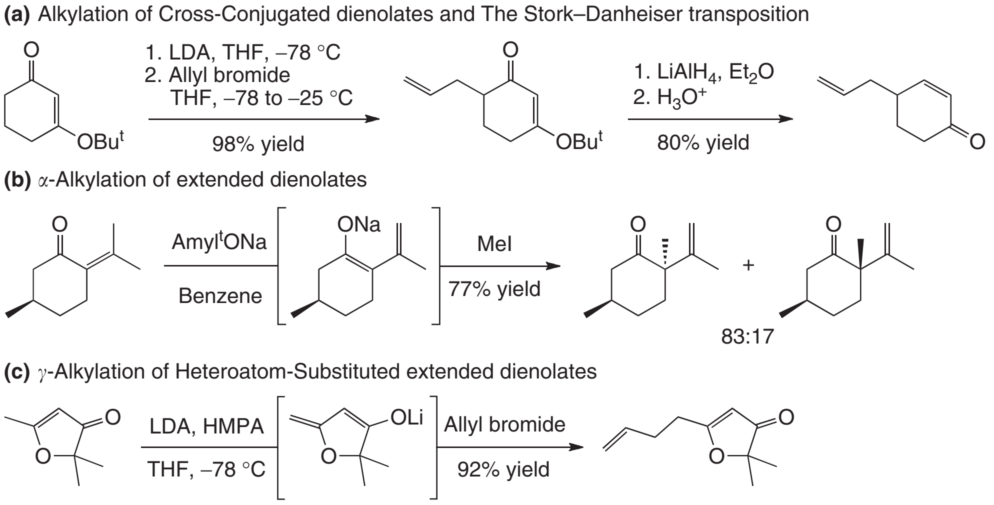
methods developed to date for preventing this side-reaction. The cosolvent of choice is typically HMPA, though other polar aprotic solvents such as NMP, DMF, and DMSO are also occasionally used, along with tetramethylethylenediamine (TMEDA) and crown ethers.[1,43] Coordination of the metal by a cosolvent or additive causes dissociation of enolate aggregates, resulting in less competition with background reactions. For example, in the alkylation of the lithium enolate of cyclopentanone (**13**) with methyl iodide, employing three equivalents of HMPA at −78 °C resulted in a 97:3 ratio of mono- to bis-methylated products, as opposed to the 84:16 ratio obtained in THF at 0 °C (Scheme 5).[44] However, such conditions can also result in higher ratios of O- versus C-alkylation due to the separation of the O-bound metal counter-ion.



Scheme 5 Suppression of over-alkylation by HMPA.

The addition of metal salts and Lewis acidic species can also affect the amount of over-alkylation side-products observed.[45] Addition of excess lithium halide salt can cause the dissociation of dimeric and tetrameric aggregates, having a similar effect on the reactivity and selectivity of alkylation reactions as the addition of metal-chelating co-solvents.[35a] Other examples of Lewis acidic species added to reduce over-alkylation include triethylboron, as discussed in Section 3.01.2.3, and transition metal species such as triethylaluminum and dimethylzinc, as discussed in Section 3.01.2.5.2. The strength of the metal–oxygen interaction and/or the extent of enolate aggregation is also reflected in the relative reactivity of enolates within a group, as lithium enolates are less reactive than sodium enolates, which are in turn less reactive than potassium enolates.

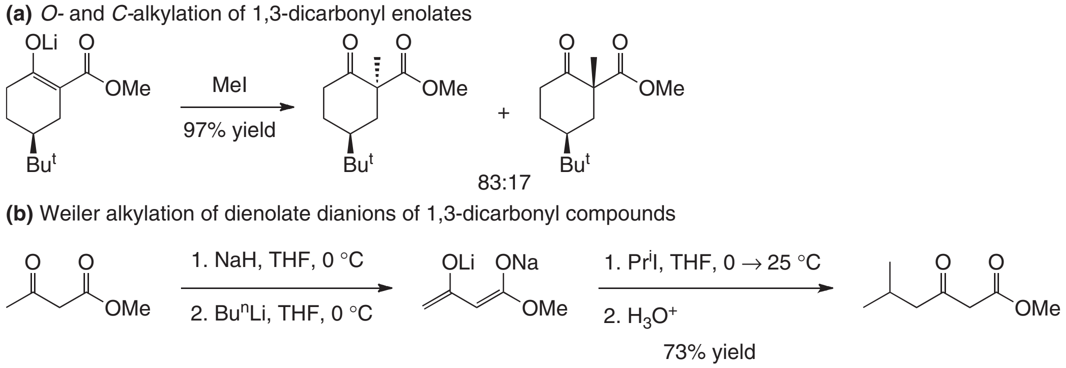
The cross-conjugated metal dienolates of α,β-unsaturated ketones can be mono-alkylated selectively without isomerization to the thermodynamically favored extended enolate.[1,5] The products of alkylation of the cross-conjugated dienolate of vinylogous esters are highly useful in the synthesis of γ-substituted cyclohexenones via the Stork–Danheiser transposition: reduction of the carbonyl group followed by hydrolysis of the enol ether yields the corresponding enone (Scheme 6(a)).[46] Except in cases of extreme steric hindrance, the extended metal dienolates of α,β-unsaturated ketones, aldehydes and the dianion of α,β-unsaturated



Scheme 6 Position-selective alkylation of cross-conjugated metal dienolates.

carboxylic acids typically undergo alkylation at the α-position due to greater electron density at this position (Scheme 6(b)),[47] though in the case of γ-heteroatom-substituted extended dienolates alkylation at the γ′-position may be observed, presumably due to an increased electron density at this carbon (Scheme 6(c)).[48]

O-alkylation predominates in reactions of the metal enolate of 1,3-dicarbonyl compounds with electrophiles. Use of less electropositive metal counterions (i.e., lithium) and nonpolar or protic solvents, as well as more polarizable electrophiles such as alkyl iodides or allylic and benzylic halides can improve the selectivity for C-alkylation; improved selectivities may also be obtained with trialkylammonium salts as counterions (Scheme 7(a)).[49] More practical modern methods, however, have taken advantage of transition metal catalysis to provide a more general and practical solution to this selectivity problem, as will be discussed in Sections 3.01.2.5 and 3.01.4.2. The dienolate dianion of 1,3-dicarbonyl compounds undergoes Weiler alkylation selectively at the γ-position (Scheme 7(b)).[23,50]



Scheme 7 Selective C-alkylation of metal enolate of 1,3-dicarbonyl compounds.

Asymmetric methods of forming and alkylating lithium enolates will be discussed in Section 3.01.4.1.

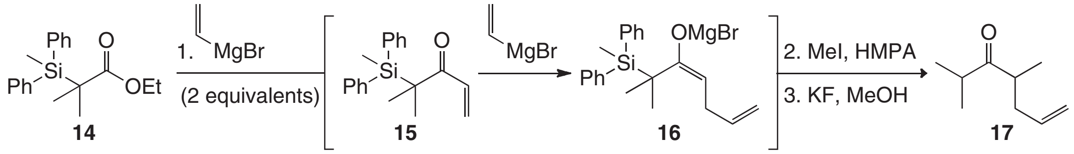
3.01.2.2 Group II Metal Enolates

The use of group II metal enolates is far less common in organic synthesis than their group I counterparts; furthermore, the only widely synthetically utilized group II metal enolates are those of magnesium.[51] Beryllium[52] and calcium[53] enolates have been reported, but are not frequently used as reagents. Strontium[54] and barium[55] enolates have been reported, but only in rare cases; to the best of our knowledge, there have been no reported radium enolates.

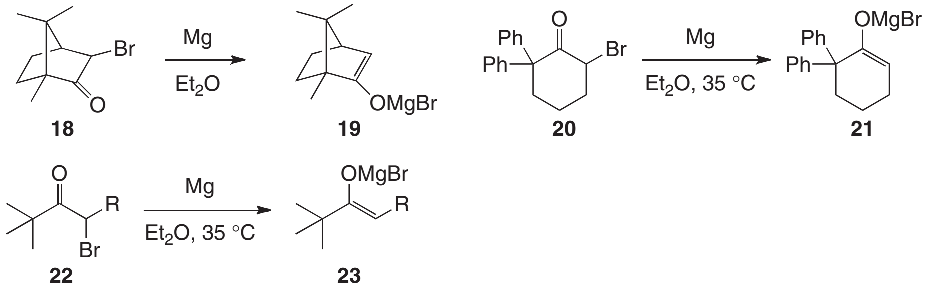
There are several useful methods for the formation of magnesium enolates (*see* Volume 2, Chapter 2.06). Addition of a magnesium(II) salt such as magnesium chloride or magnesium bromide to a lithium enolate effects a transmetallation to form the corresponding magnesium enolate.[56] Amide bases of magnesium such as bromomagnesium diisopropylamide (BMDA),[57] chloromagnesium diisopropylamide (CMDA),[58] bromomagnesium hexamethyldisilylamide (BMHMDS),[59] and bromomagnesium dicyclohexylamide (BMDCA)[60] may be formed from the addition of an alkylmagnesium halide species to the corresponding amine. These bases are more thermally stable and less reactive than their corresponding lithium bases, and have been used to deprotonate ketones (typically in DME–HMPA mixtures) with good selectivity for the formation of the kinetic enolate product.[61] Grignard reagents can also be used to deprotonate ketones to form the corresponding enolate. Addition of methylmagnesium bromide in glyme at reflux[62] and magnesium(II) bromide etherate in toluene at − 19 °C[63] to silyl enol ethers has been reported to form the corresponding magnesium enolate. Addition of methylmagnesium bromide or iodide to enol acetates can also afford the corresponding magnesium enolate.[64]

Analogous to their lithium counterparts,[33c,65] the copper(I)-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated ketones has been reported, resulting in the regioselective formation of the corresponding magnesium enolate.[66,67] In a cascade reaction, the addition of two equivalents of vinylmagnesium bromide to ethyl 2-methyl-2-(diphenylmethylsilyl)propionate (**14**) resulted first in the formation of α,β-unsaturated ketone **15** from the ester, followed by a second conjugate addition to form the extended magnesium dienolate (**16**, Scheme 8(a)).[68] Magnesium metal in diethyl ether or diethyl ether–benzene mixtures has been used to insert into the carbon–halogen bond of α-bromo and α-iodo ketones, resulting in the regioselective formation of a magnesium enolate in both cyclic and acyclic systems. This method is often plagued by reduction side-products as well as self-coupling between the resulting enolate and the electrophilic starting material; as such, this technique is typically only applied to sterically hindered substrates such as 2-bromocamphor (**18**),[69] 2-bromo-6,6-diphenylcyclohexanone (**20**),[70] and α-bromo-α′-*tert*-butyl ketones (**22**),[71] which results in selective formation of the *cis*-enolate (**23**, Scheme 8(b)).

(a) Conjugate addition of grignard reagents



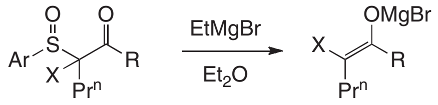
(b) Insertion into α-bromo ketones



R = Me, Et, Pr^i, Bu^i

Scheme 8 Formation of magnesium enolates.

A method for forming α-halogenated magnesium enolates is by the addition of ethylmagnesium bromide to α-halo α-sulfinyl ketones. This reaction proceeds regioselectively to form halogenated trisubstituted enolates, which in turn yield α-halo ketone products.[72] Ethylmagnesium bromide has also been used in the desulfinylation of α-sulfinyl amides, esters, ketones, and carboxylic acids to afford the corresponding enolate product (equation 2).[73]



R = Ph, (CH$_2$)$_2$Ph
Ar = Ph, *p*-Tol
X = F, Cl, Br

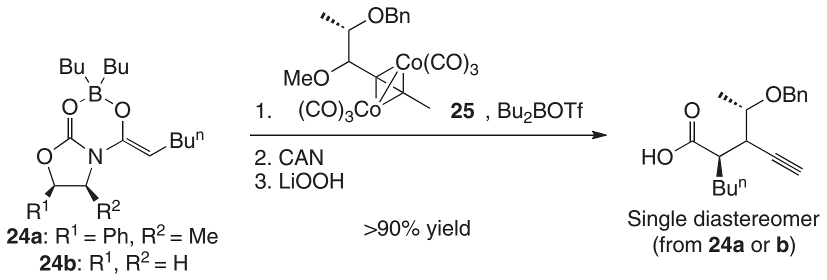
(2)

Magnesium enolates can be competent substrates in alkylation reactions, though due to their reduced reactivity as compared with group I metal enolates, an excess of HMPA must almost always be added. Like their lithium counterparts, except with extremely reactive alkylating agents, C-alkylation is favored over O-alkylation.

Asymmetric methods of forming magnesium enolates will be discussed in Section 3.01.4.1.

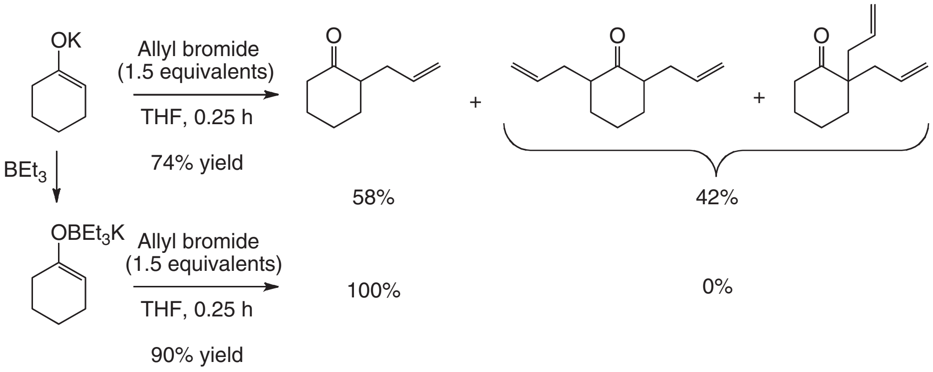
3.01.2.3 Boron Enolates

Generally speaking, boron enolates are not reactive toward alkylation, and are primarily used in aldol-type chemistry. A rare example of alkylation of a boron enolate is found in the asymmetric syntheses of (+)- and (−)-blastmycinolactol by Jacobi and coworkers.[74] The boron oxazolidinone enolate **24** is alkylated by methyl ether **25** in the presence of dibutyl boron triflate, a strong Lewis acid (equation 3). Interestingly, the diastereoselectivity of the reaction was entirely dependent on the stereochemistry of the electrophile, as substitution on the oxazolidinone moiety did not affect the diastereomeric ratio.



(3)

The addition of triethylboron to group I metal enolates has been shown to yield much higher selectivity for mono-alkylation products. For example, the potassium triethylboron enolate of cyclohexanone provides mono-allylation with allyl bromide with complete selectivity in 90% yield, in contrast to the potassium enolate, which affords a 58:42 ratio of the mono-alkylated product to a mixture of 2,2- and 2,6-di-alkylated products in 74% overall yield (Scheme 9).[75]



Scheme 9 Selective mono-alkylation of boron enolates.

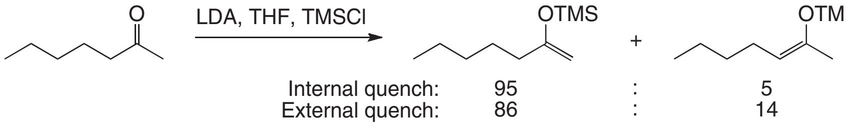
3.01.2.4 Silyl Enol Ethers

Silyl enol ethers are a versatile intermediate in alkylation reactions of enolates. They are often stable and can be purified (typically by fractional distillation, or occasionally by chromatography on deactivated silica), allowing a single enolate to be used in a reaction that would otherwise be difficult to form selectively. Silyl enol ethers usually store well without decomposition when protected from water and acid, depending on both the enolate and silyl group. Silyl enol ethers can be converted to various metal (e.g., lithium, sodium, potassium, magnesium) enolates, a 'naked' enolate (with a noncoordinating counterion, such as a tetralkylammonium cation), or alkylated directly with an electrophile in the presence of a Lewis acid.

3.01.2.4.1 Formation of silyl enol ethers

The formation of silyl enol ethers has been reviewed extensively in an excellent review by Kobayashi.[27] The predominant method for the formation of silyl enol ethers is addition of a silylating agent to a metal enolate, typically of a group I or II metal. Standard silylating reagents include trimethylsilyl chloride (TMSCl), trimethylsilyl iodide (TMSI), trimethylsilyl trifluoromethylsulfonate (TMSOTf), *t*-butyldimethylsilyl chloride (TBDMSCl), *t*-butyldimethylsilyl trifluoromethylsulfonate (TBDMSOTf), triisopropylsilyl chloride (TIPSCl), and triisopropylsilyl trifluoromethylsulfonate (TIPSOTf).

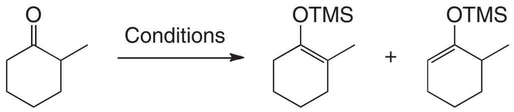
The considerations of kinetic versus thermodynamic and *cis*- versus *trans*-enolate formation discussed in Section 3.01.2.1.1.1 apply to the formation of silyl enol ethers, including generation of the silyl enol ethers of α,β-unsaturated ketones and 1,3-dicarbonyl substrates. An important consideration in the trapping of kinetically generated lithium enolates is the use of an internal or external quench. In an internal quench, the silylating agent is present in the reaction mixture before enolate generation, whereas in an external quench, the silylating agent is added following enolate formation. Internal quenching typically results in better selectivity for the kinetic silyl enol ether, as the enolate is trapped before equilibration can occur. For example, an internal quench with TMSCl of the enolate generated by the addition of LDA to heptan-2-one results in a 95:5 product mixture of terminal:internal silyl enol ether, as opposed to the 86:14 mixture obtained with an external quench (equation 4).[3a,19a,76]



(4)

Although trapping of a lithium enolate with an internal quench is typically the best method of forming a kinetic silyl enol ether directly from a ketone, it has been found that a mixture of bromomagnesium diisopropylamide (BMDA), triethylamine, and TMSCl in HMPA at 25 °C yields the thermodynamic silyl enol ether with good selectivity (Table 2, entry 2).[57b] Alternatively, use of a metal hydride at warmer temperatures also provides the thermodynamic enolate, albeit with lower selectivity (entry 3).[77]

Table 2 Regioselectivity in silyl enol ether formation

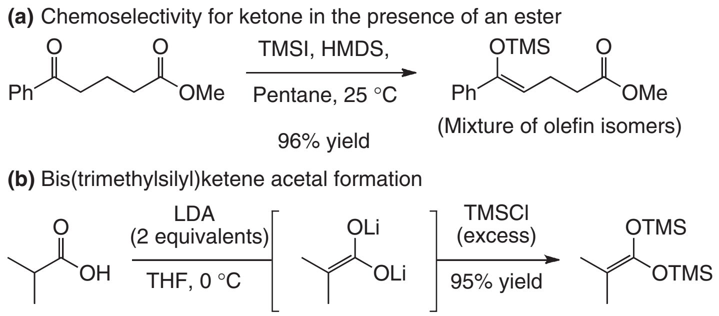


26a **26b**

Entry	*Conditions*	***26a:b***	*References*
1	LDA, DME, 0 °C; TMSCl	1:99	3a
2	BMDA, TMSCl, NEt_3, HMPA, 25 °C	93:7	57b
3	KH, THF, 20 °C; TMSCl	67:33	77

In addition to silylation of metal enolates, silylation of ketones by the House method (TMSCl, triethylamine, DMF, reflux) is popular for substrates in which only one product may be formed.[3a,27] Use of the trialkylsilyl iodides[78] or triflates[79] allows the reaction temperature of this method to be decreased significantly, typically to room temperature. Silylation with bulkier trialkylsilyl groups is slower, but these substrates are usually much more stable to harsh reaction conditions and storage than their less-bulky counterparts.

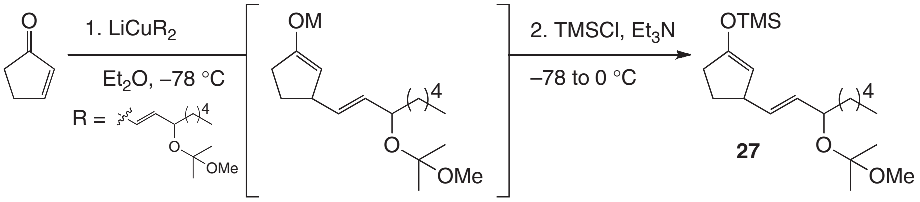
Ketones may be selectively converted to silyl enol ethers in the presence of esters by the use of TMSI and hexamethyldisilazane (HMDS) (Scheme 10(a)).[78a] In the synthesis of silyl ketene acetals from esters, C-silylation can be a major side-product formed.[80] Conditions favoring O-silylation include the use of a nonbulky O-substituent as in the case of a methyl, ethyl, or phenyl ester, increasing steric bulk on the nucleophilic carbon, and using TBDMSCl instead of TMSCl as a silylating agent.[80a,c] The bis(trimethylsilyl)ketene acetal of carboxylic acids may be formed by reaction of the dianion of the carboxylic acid with two equivalents of silylating agent (Scheme 10(b)).[81]



Scheme 10 Chemoselective formation of silyl enol ethers and silyl ketene acetals.

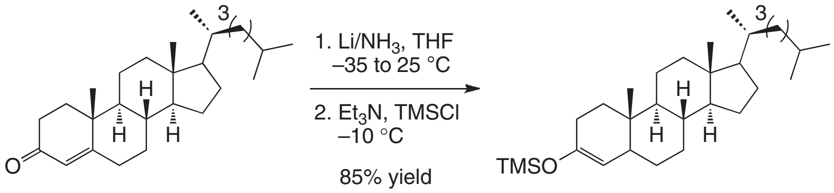
Like their group I and II metal enolate counterparts, formation of silyl enol ethers from α,β-unsaturated ketones can be an effective technique to achieve regioselectivity. Trapping the intermediate of a copper-mediated conjugate addition with a silylating reagent results in the formation of a single silyl enol ether, according to the position of the C–C double bond in the starting material.[82] Patterson and Fried employed this approach to generate silyl enol ether **27** on route to the prostaglandin core (Scheme 11(a)).[83] In addition to trapping the intermediate of a lithium–ammonia reduction (Scheme 11(b)),[84] hydrosilylation is another prominent method for reductive formation of silyl enol ethers from α,β-unsaturated ketones. In these procedures, the α,β-unsaturated ketone may be treated with a silane and a catalytic amount of a transition metal complex, typically palladium,[85] platinum,[86] copper,[87] or rhodium[80c,88] to yield the silyl enol ether resulting from the reduction of unsaturated ketone (Scheme 11(c)). Montgomery and coworkers have reported the nickel-catalyzed reductive three-component coupling of an

(a) Patterson's trapping of cuprate addition

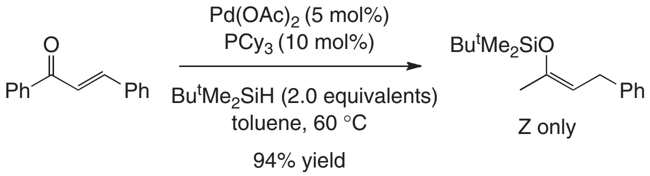


27

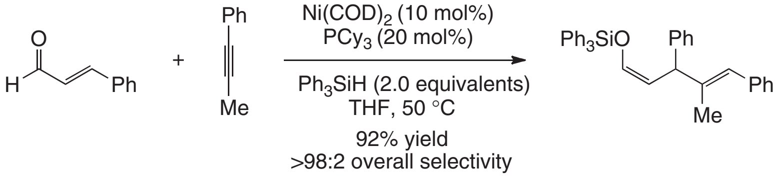
(b) Knölker's trapping Li/NH$_3$ reduction



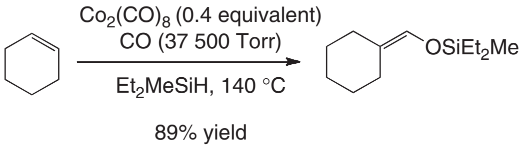
(c) Palladium-catalyzed hydrosilylation



(d) Montgomery Ni coupling



(e) Carbonylation/hydrosilylation

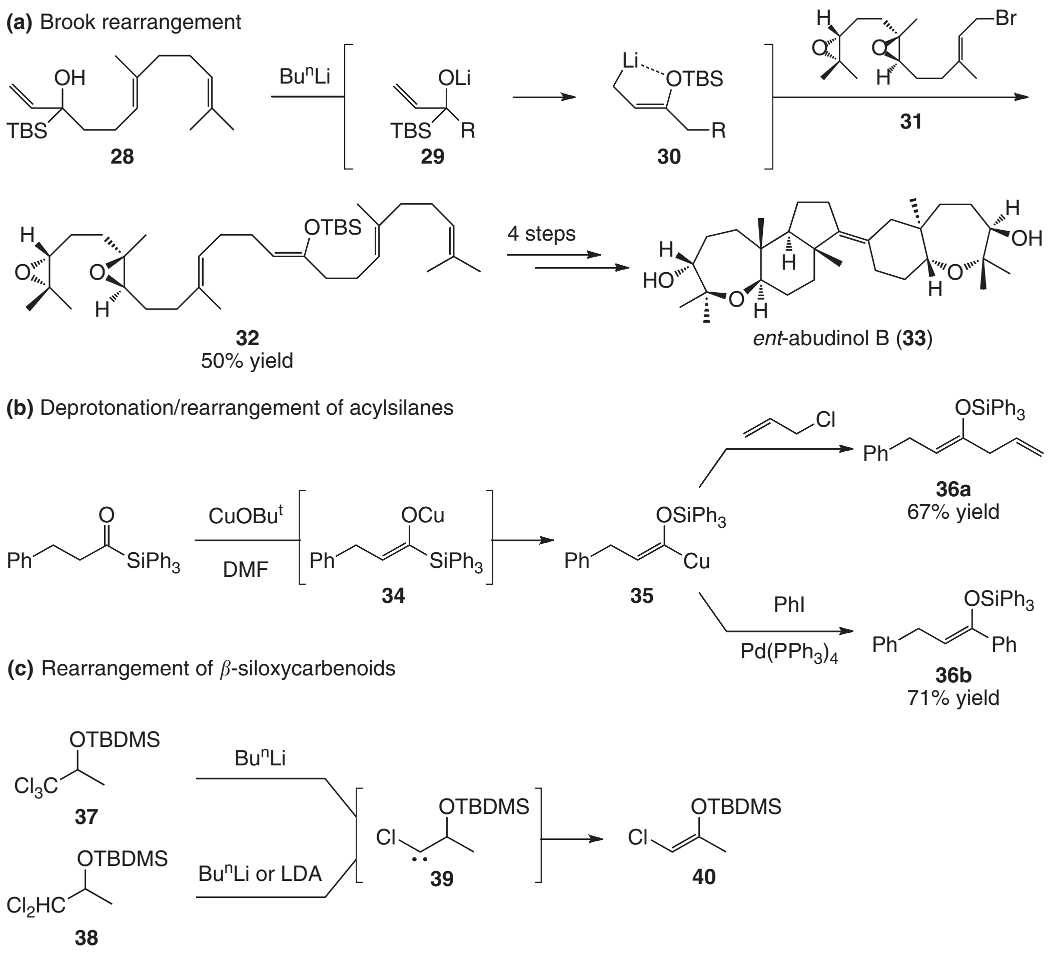


Scheme 11 Formation of silyl enol ethers under reductive conditions.

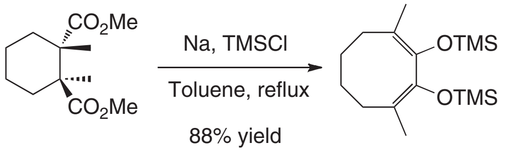
α,β-unsaturated aldehyde with an alkene and a silane, resulting in highly functionalized *cis*-silyl enol ethers with excellent selectivities (**Scheme 11(d)**).[89] Under a carbon monoxide atmosphere, Murai and Sonoda were able to affect a reductive carbonylation–hydrosilylation of cyclohexene to the diethylmethylsilyl enol ether of cyclohexanecarbaldehyde (**Scheme 11(e)**).[90]

Silyl enol ethers may be produced via rearrangements. Deprotonation of 1-trimethylsilyl allyl alcohols (**28**) with *n*-butyllithium provides an intermediate α-silyl alkoxide (**29**), which can undergo a Brook rearrangement (**29** to **30**) to form the corresponding silyl enol ether (**32**) following trapping of the intermediate allyllithium with an electrophile (**31**, **Scheme 12(a)**).[91] This strategy is employed in McDonald's total synthesis of *ent*-abudinol B (**33**).[92] Alternatively, Takeda and coworkers have found that deprotonation of acylsilanes with copper(I) *t*-butoxide results in a copper enolate **34**, which rearranges to form the alkenyl copper species **35**, which can be used in alkylation or palladium-catalyzed coupling reactions to obtain functionalized silyl enol ethers (**Scheme 12(b)**).[93] Rearrangement of β-siloxycarbenoids can also furnish silyl enol ethers. For example, treatment of the β-*t*-butyldimethylsiloxy trichloromethyl compound **37** with *n*-butyllithium results in an intermediate carbene (**39**), which on rearrangement yields the *cis*-chlorinated silyl enol ether **40** (**Scheme 12(c)**).[94] Similarly, deprotonation of β-*t*-butyldimethylsiloxy dihalomethyl compounds of type **38** with LDA or *n*-butyllithium results in carbenes that rearrange to form the corresponding *cis*-halogenated silyl enol ethers.[94,95]

Silyl trapping of the product generated by an acyloin condensation results in 1,2-bis(silyloxy)alkenes,[96] which is usually accomplished by adding sodium to a mixture of the diester starting material and TMSCl in a solvent such as toluene or xylenes. Trapping of this intermediate can prevent the occurrence of unwanted side reactions, such as Claisen or Dieckmann condensations, due to the sodium alkoxide produced in the reaction. The silyl enol ether may be isolated, whereas an acidic workup furnishes the acyloin product cleanly. Furthermore, if the resulting product is a 1,2-bis(siloxy)cyclobutene, the product undergoes an electrocyclic ring-opening reaction, yielding a 2,3-bis(siloxy)butadiene moiety (equation 5).[97]

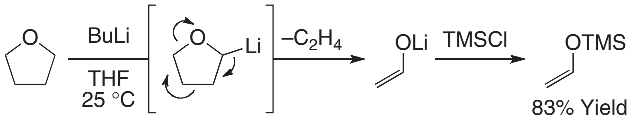


Scheme 12 Formation of silyl enol ethers via rearrangements.



(5)

Though many other specialized and somewhat exotic methods for forming silyl enol ethers exist, one final method that will be discussed here is the synthesis of the trimethylsilyl enol ether of acetaldehyde from tetrahydrofuran. Deprotonation of tetrahydrofuran with *n*-butyllithium at 25 °C effects a rearrangement to form the lithium enolate of acetaldehyde and ethylene gas. The resulting enolate can be trapped with TMSCl to form the silyl enol ether of acetaldehyde in an overall 83% yield (equation 6).[98] This methodology is useful because other methods of enolization of acetaldehyde result mostly in undesired side reactions such as aldol condensations.



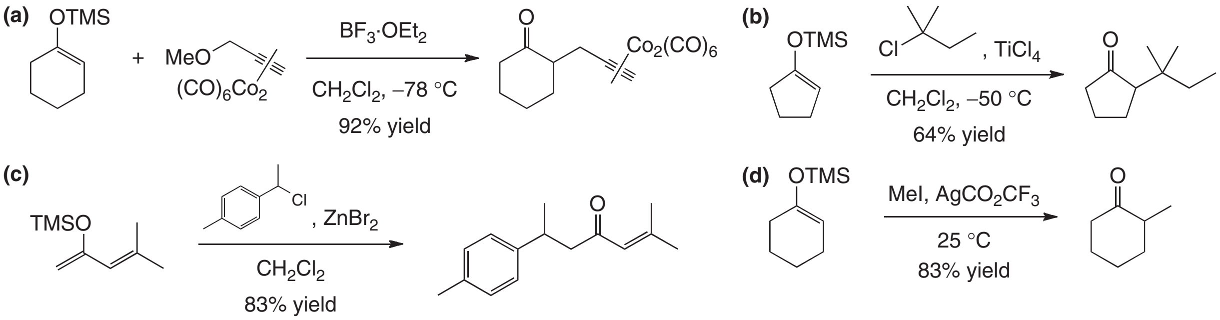
(6)

3.01.2.4.2 Alkylation of silyl enol ethers

The primary mode of alkylation of silyl enol ethers is by conversion to a metal enolate and subsequent reaction of this enolate with an electrophile.[99] Alternatively, the 'naked' enolate may be formed by addition of a tetraalkylammonium fluoride such as tetrabutylammonium fluoride (TBAF),[99] benzyltributylammonium fluoride (BTAF),[100] or another source of nucleophilic fluorine with a noncoordinating counter-ion such as tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF).[101] Addition of these reagents results in the cleavage of the Si–O bond (~110 kcal mol^{-1}) due to the strength of the Si–F bond (~135 kcal mol^{-1}).[102]

Owing to the bulk of the cation of these species, there is only an ionic interaction between the enolate and the cation resulting in a highly reactive 'naked' enolate. These enolates typically are more reactive and selective than their metal enolate counterparts, resulting in fewer side-products.[99]

Addition of a Lewis acid to a mixture of silyl enol ether and a latent electrophile can affect the alkylation of a silyl enol ether without first forming a metal or 'naked' enolate. For example, $BF_3 \cdot OEt_2$ has been shown to catalyze the alkylation of silyl enol ethers with cobalt-complexed prop-2-ynyl ethers (**Scheme 13(a)**).[103] An especially important transformation in this reaction regime is the *tert*-alkylation of silyl enol ethers catalyzed by $TiCl_4$, $ZnBr_2$, and $ZnCl_2$. Addition of one of these Lewis acids results in alkylation with S_N1-type electrophiles. Reetz and coworkers have shown that $TiCl_4$ in particular catalyzes the addition of silyl enol ethers to acyclic, branched, and cyclic tertiary halides, as well as secondary allylic and benzyl halides and α-heteroatom-substituted halides (such as methyl chloromethyl ether (MOMCl) and chloromethyl phenyl sulfide ($PhSCH_2Cl$)) in excellent yields without rearrangement of the electrophile (**Scheme 13(b)**).[10,104] In the reaction of more sensitive silyl enol ethers, $ZnCl_2$ may be used instead of $TiCl_4$, albeit with slower reaction rates and lower yields. $ZnBr_2$ in particular has been shown to lead to the alkylation of silyl enol ethers with secondary benzyl bromides (**Scheme 13(c)**).[105] These Lewis acids are not competent in affecting the alkylation of non-S_N1-type electrophiles. However, Jefford and coworkers have shown that silyl enol ethers may be alkylated by *n*-alkyl iodides in the presence of $Ag(CO_2CF_3)$, albeit in modest yields (**Scheme 13(d)**).[106]



Scheme 13 Lewis acid-catalyzed alkylation of silyl enol ethers.

3.01.2.5 Transition Metal Enolates

Over the course of the past 50 years, extensive investigations have been devoted to developing α-alkylations of transition metal enolates.[107] Given the length of the present chapter and the vigor of the investigation, the topic coverage within this section is by no means exhaustive. Rather, emphasis is placed on key findings and advances in the state of the art methods. This section will begin with an overview of known transition metal enolate complexes followed by an outline of the applications of these complexes in the context of stoichiometric nonasymmetric α-alkylation of carbonyl compounds.

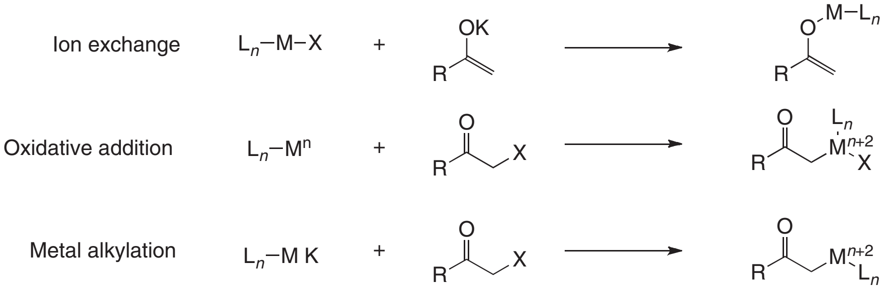
3.01.2.5.1 Formation and structure of transition metal enolates

A wide variety of transition metal enolate complexes have been isolated and characterized, including cobalt,[108] copper,[109] iron,[110] gold,[111] zinc,[112] palladium,[113] platinum,[114] nickel,[115] rhodium,[116] mercury,[117] molybdenum,[118] ruthenium,[119] iridium,[120] and others (*see* Volume 2, Chapter 2.06).[121] One important consideration, with respect to the reactivity of these complexes, is whether the metal adopts an η^1-O-bound, η^3-oxa-π-allyl, or η^1-C-bound bonding motif. The presence, absence or shifting of key spectroscopic data, such as carbonyl IR stretch, vinylic C–H resonance in ^1H NMR, carbonyl ^{13}C NMR resonance, or M–C coupling in ^{13}C NMR, typically help to determine the bonding pattern of a transition metal enolate. Although ligands about the metal bear influence on the binding mode, the general trend observed in this regard is for main group metals and early transition metals to favor the O-bound form whereas late transition metals tend to favor the C-bound form.[122] A number of methods for generating transition metal enolates have been elucidated; selected examples are shown in **Scheme 14**.

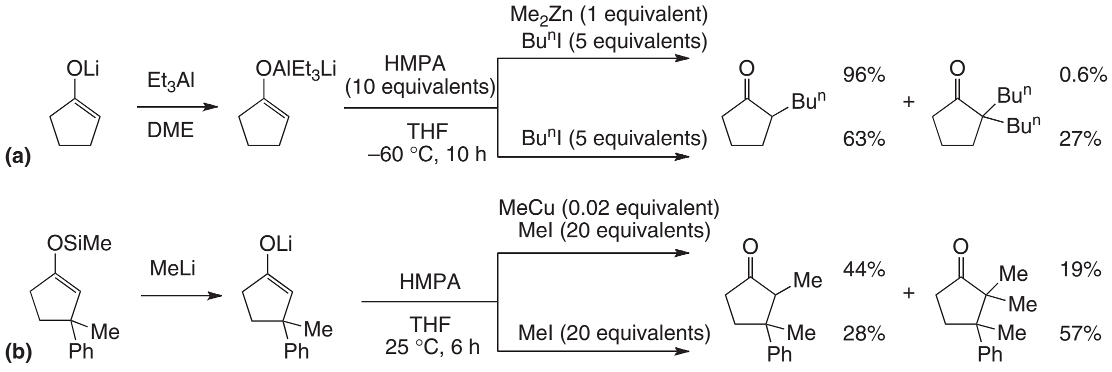
3.01.2.5.2 Reactions of transition metal enolates

Early examples of transition metal mediated enolate alkylation demonstrated the capability of transition metal additives to suppress polyalkylation of multiply enolizable ketones with alkyl halide electrophiles. Noyori and coworkers found that the addition of dimethylzinc to a lithium aluminate of cyclopentanone dramatically reduced the amount of polyalkylation (**Scheme 15(a)**).[44b] Similar results were obtained with the addition of copper(I) salts (**Scheme 15(b)**).[123]

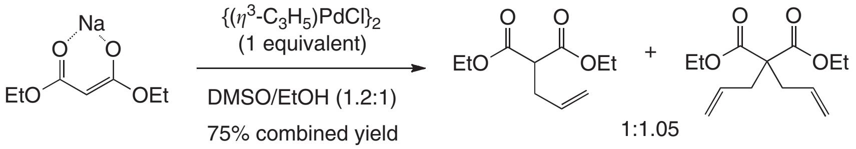
Transition metal catalyzed allylic alkylation of enolates ranks among the most successful and most widely studied methods for the α-functionalization of carbonyl containing compounds.[236c] Within this realm of catalysis, palladium has seen the most development.[124] Early examples of this reaction primarily utilized stabilized enolates,[125] such as malonate derivatives, as nucleophilic partners in allylic substitution reactions that were stoichiometric in palladium (equation 7).[126]



Scheme 14 Generation of transition metal enolates.



Scheme 15 Suppression of polyalkylation by transition metal additives.

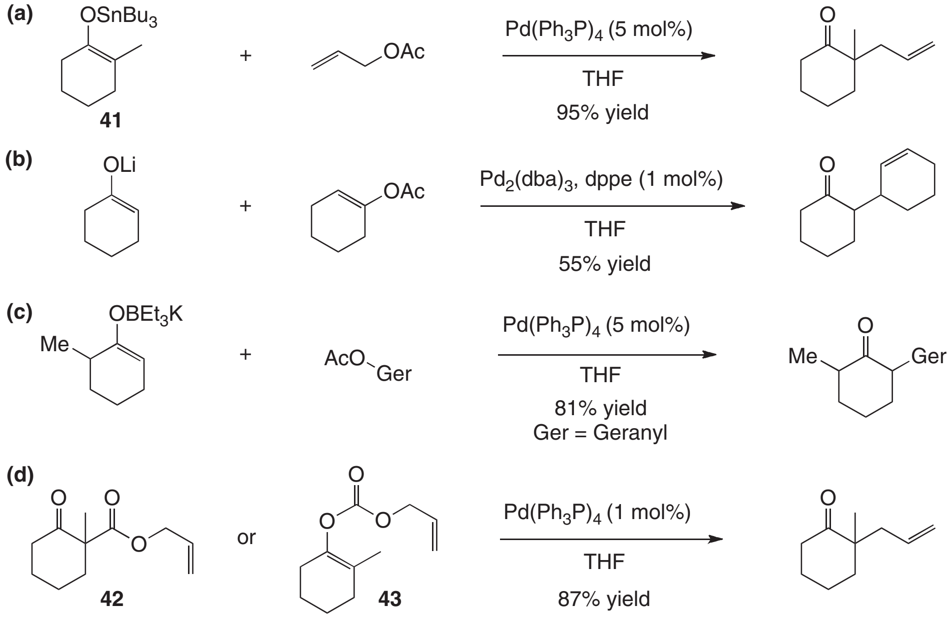
 (7)

In 1980, Trost and Keinan disclosed the first example of a nonstabilized nucleophilic enolate undergoing allylic alkylation; in their case, an enol stannane (**41**) underwent positionally selective mono-alkylation under palladium catalysis (Scheme 16(a)).[127] Many reports followed this initial disclosure, expanding the substrate scope for palladium-catalyzed allylic alkylation to include lithium (Scheme 16(b)),[128] boron (Scheme 16(c))[129] and zinc enolates.[130] Contemporary with these findings, Tsuji and coworkers revealed a powerful method that eliminated the need to generate an enolate species *in situ* and employed allyl enol carbonates (**42**) or allyl β-ketoesters (**43**) as masked enolate precursors (Scheme 16(d)).[131] These latent enolates undergo facile decarboxylation following formation of a palladium π-allyl species and subsequently generate enolates *in situ*, which may participate in palladium catalysis.

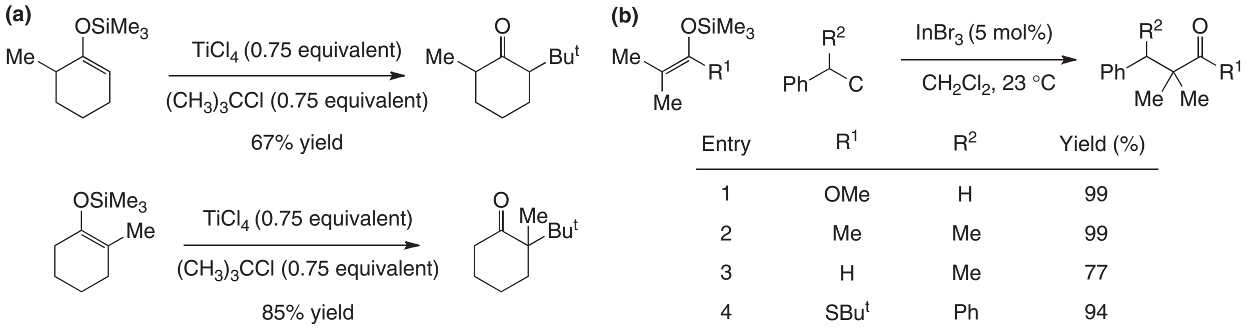
Rhodium, tungsten, molybdenum, nickel, and iridium complexes have also proven to be competent catalysts for the allylic alkylation of both stabilized and nonstabilized enolates, including allyl carbamates.[132] Catalytic enantioselective variants of transition metal catalyzed allylic alkylation of prochiral enolates will be treated extensively in Section 3.01.4.2.1.

3.01.2.5.3 Transition metal and main group Lewis acids

A number of main group and transition metal Lewis acids have been shown to efficiently induce α-alkylation of carbonyl containing compounds.[133] Carbonyl preactivation by conversion to the silyl enol ether is followed by Lewis acid activation of the halogen electrophile to deliver α-tertiary or α-quaternary ketones, aldehydes, esters, and lactones with excellent positional selectivity (for selected examples, see Scheme 17(a)). Reports by Reetz and coworkers demonstrate the utility of $TiCl_4$, $SnCl_4$, and zinc halide salts in such transformations.[104b] Activation of the carbonyl eliminates the need for strong base, and positional specificity in silyl enol ether formation is often excellent. Importantly, where alkylations of alkali and alkaline earth metal enolates often require S_N2 active electrophiles, Lewis acid activation of halogen electrophiles allows for alkylation by more hindered, S_N1 active groups. Recent findings by Baba and coworkers have shown indium-based Lewis acids to be efficient activators of primary and secondary benzyl chlorides for α-alkylation of enol silanes, providing a valuable expansion of electrophile substrate scope for this methodology (Scheme 17(b)).[134]



Scheme 16 Palladium-catalyzed position-selective allylic alkylation.



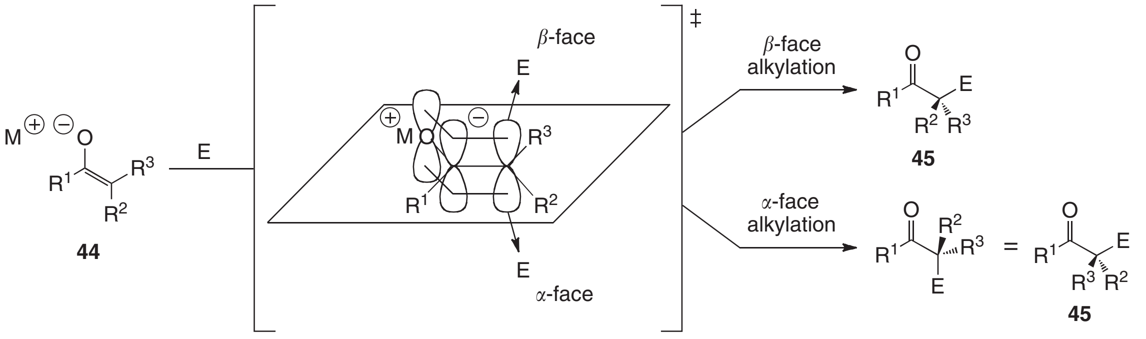
Entry	R^1	R^2	Yield (%)
1	OMe	H	99
2	Me	Me	99
3	H	Me	77
4	SBu^t	Ph	94

Scheme 17 Lewis acid-catalyzed alkylation with secondary and tertiary alkyl halides.

3.01.3 Diastereoselective Enolate Alkylations

3.01.3.1 Substrate Control in Asymmetric Alkylation

Alkylation of di- (R^1=H and either R^2 or R^3=H), tri- (R^1, R^2, or R^3=H), and tetrasubstituted (R^1, R^2, and $R^3 \neq$H) enolates (44) with an electrophile (E) results in the formation of a new stereocenter (Scheme 18). In the alkylation transition state, the



Scheme 18 Facial selectivity and product stereochemistry.

electrophile approaches the nucleophile from one of the enolate π-faces,[135] generating one of the two enantiomeric products (**45β** or **45α**). A diastereoselective alkylation occurs when the enolate molecule already possessed a stereocenter before the alkylation (R^1, R^2, and/or R^3 is chiral). This chiral center (*) can influence the π-facial selectivity of the approaching electrophile, leading to a diastereotopic bias for one of the enolate faces.[123,136]

Evans[137] has proposed three scenarios where substrate asymmetric induction may exist: (i) endo- and exocyclic enolates with annular chirality (Figure 1(a)); (ii) acyclic enolates with chirality off the enolate (Figure 1(b)); and (iii) enolates where chirality is imparted through metal chelation (Figure 1(c)). In each scenario, stereoinduction through substrate control is only achieved if the enolate structure is rigid or limited to predominantly one conformation and if the molecular components differentiate the enolate diastereotopic π-faces.[138] It is also important to note that the *E*/*Z*-enolate orientation can affect alkylation selectivity for acyclic and larger cyclic enolates.

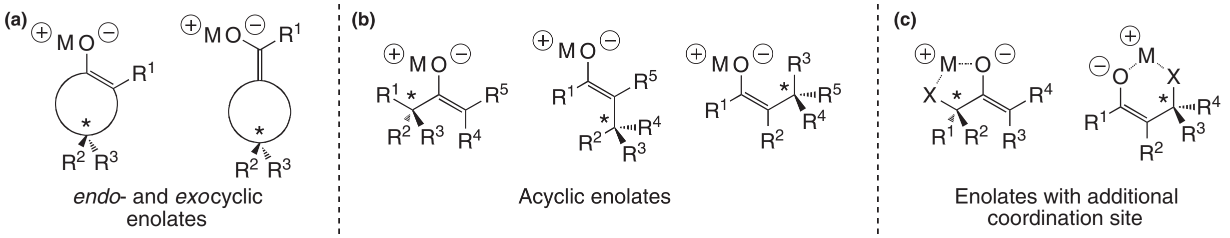
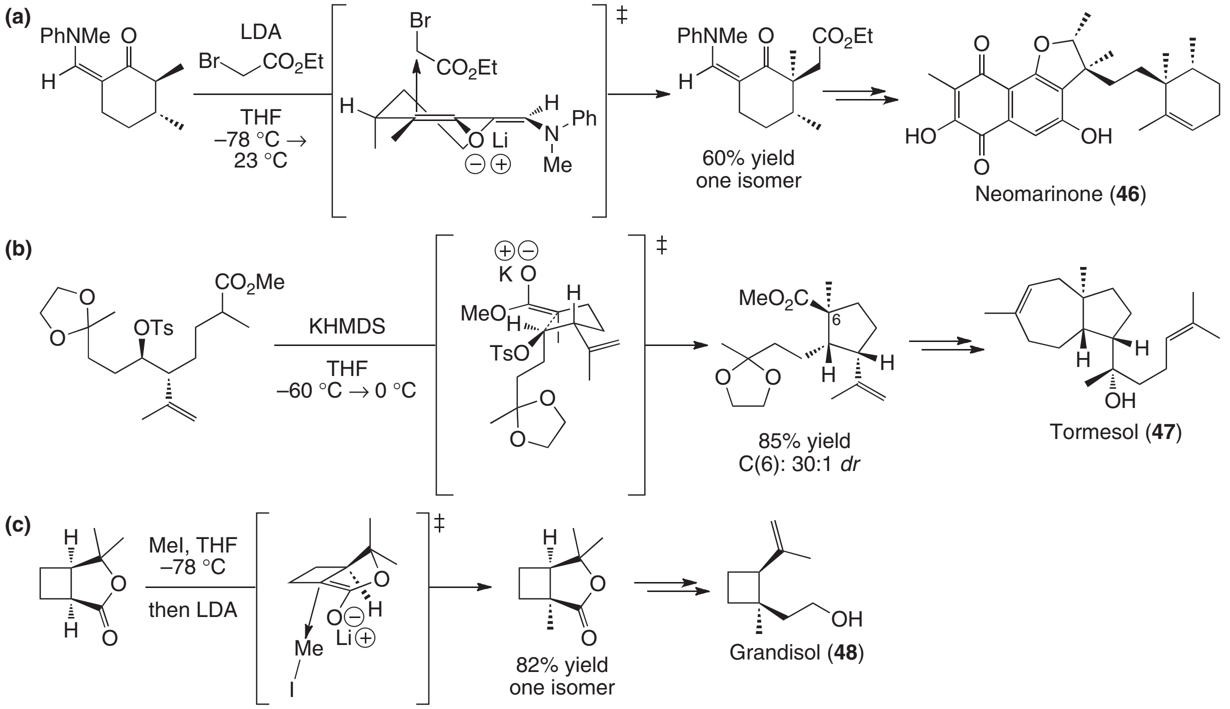


Figure 1 Evans' proposal of substrate-controlled asymmetric induction.

Many of the molecular aspects that affect substrate control (predominantly stereoelectronic and steric forces) were elucidated in foundational studies performed primarily during 1950–80,[139] where numerous examples were investigated to rationalize alkylation trends.[140] Analysis of these trends suggests information about the alkylation transition state and provides a starting point in predicting selectivity for many enolate substrates. However, the extrapolative process can be challenging for systems with less precedent, multiple contributing factors, and many available conformations (e.g., medium and large rings[141]). Ultimately, stereoinduction is best anticipated by analyzing related enolates and determining the relative significance of the stereoelectronic and steric factors within the molecule (i.e., analyze by analogy).

Although the foundational work was performed more than 20 years ago, substrate control remains relevant today. In fact, many modern synthetic endeavors depend on molecular bias for the stereoselective introduction of functionality, as illustrated with the alkylations depicted in Scheme 19 on route to the natural products neomarinone[142] (**46**), tormesol[143] (**47**), and

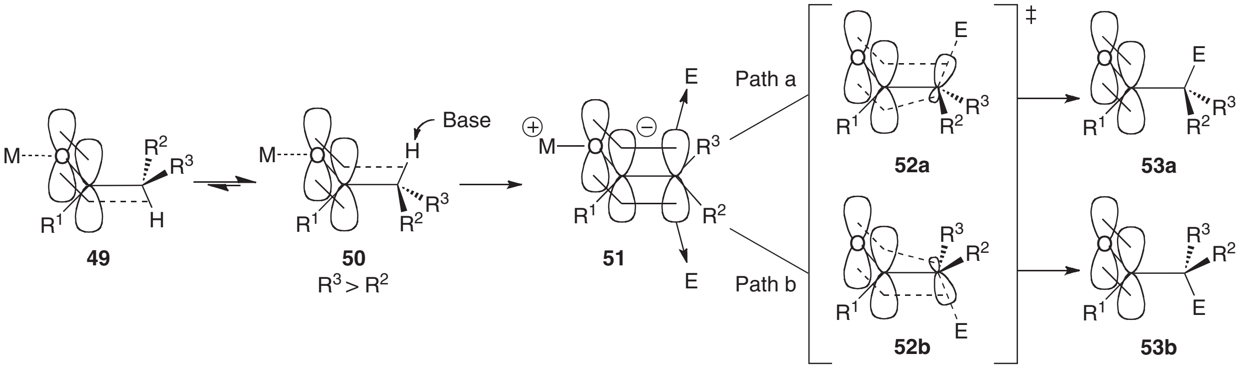


Scheme 19 Substrate-controlled stereoselective alkylation in total syntheses.

grandisol[144] (**48**). Given the importance and relevance of substrate control, this section covers a number of diastereoselective trends, but does not provide an exhaustive listing of substrate class examples. The reader is directed to other sources for more information.[1,135b,137,145]

3.01.3.1.1 Stereoelectronic effects

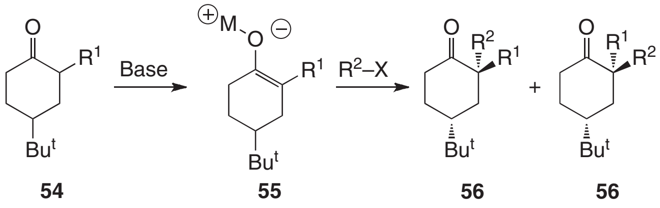
Stereoelectronics reflects the geometrical orientation a compound adopts due to the electronic elements found within the molecule. In enolate alkylation, this refers to the three-dimensional molecular changes experienced as the enolate orbitals interact with the approaching electrophile in the transition state (Scheme 20). During this event, the developing electrophile σ-orbital must overlap with the carbonyl π-orbital (**52a** and **b**) just as the α-hydrogen σ-bond overlaps during deprotonation (**50**) on route to enolate formation (**51**).[137] The implication of this orientation on diastereoselectivity is demonstrated in a classic study that follows.



Scheme 20 Stereoelectronic effects in enolate alkylation.

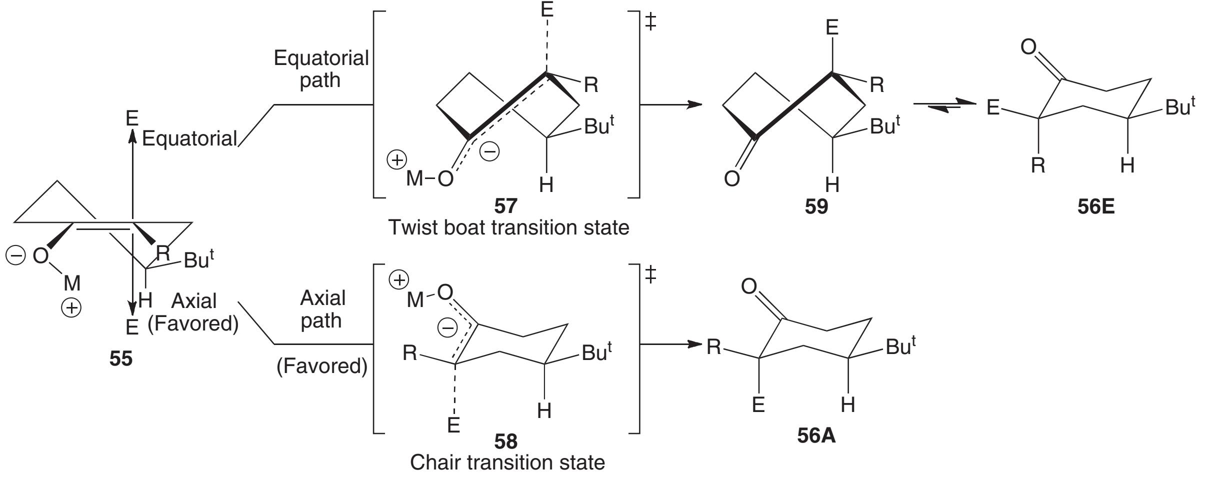
The alkylation of 4-*t*-butylcyclohexanone derivatives was studied extensively during the 1960–70 to determine the basic substrate control exerted in a conformationally locked six-membered ring (Scheme 21(a)).[49,136c,146] Cyclohexanone **54** is

(a) Classical stereoelectronic study



Entry	M	R^1	R^2–X	**56 E:A**
1	Li	H	MeI	45:55
2	Li	H	EtI	46:54
3	Li	Me	CD_3I	30:70
4	Na	Me	Pr^iBr	41:59
5	Li	CO_2Me	MeI	17:83

(b) Transition state comparison



Scheme 21 Stereoelectronic studies on the alkylation of 4-*t*-butylcyclohexanone.

deprotonated to generate enolate **55**, which adopts energy-minimized half-chair conformation. In this configuration, maintaining overlap between the developing σ-bond and carbonyl orbital results in a twist boat transition state (**57**) due to alkylation from above (equatorial) and a more stable chair transition state (**58**) with electrophile approach from below (axial).[146] (The electrophile approach (equatorial or axial) refers to the alkylation substituent orientation in the product) The relative stabilities of these transition state conformations favor formation of the axial isomer **56A**, however the effect is often small with little diastereoselectivity when $R^1 = H$ (21A, entries 1 and 2). The diastereoselective impact of the proposed transition states is minimal due to the strongly exothermic nature of enolate alkylation,[137,145] which as described by the Hammond postulate[147] leads to an earlier transition state with more reactant than product character. For less exothermic alkylations, one would expect these product-like intermediates (**57** and **58**) to play a larger diastereoselective role.

The increased facial selectivity with larger α-substituents (Scheme 21(a), entries 3–5) could be ascribed to a later transition state; however, House et al.[148] have proposed a more logical alternative that focuses on resolving the eclipsing strain within the molecule. In their model, the cyclohexanone enolate adopts a skewed configuration (**60a** and **60b** for Newman projection depiction) that limits eclipsing between the enolate oxygen, α-substituent (R), and corresponding adjacent pseudoequatorial groups such that $\theta \neq 0°$ (Figure 2). The researchers suggest that this conformational adjustment diminishes steric hindrance along the axial electrophile approach and leads to a rehybridization of the p orbital to sp^3, which increases orbital overlap on the axial π-face. These aspects combined with the disfavored torsional strain for equatorial approach (O/R eclipse) leads to high levels of axial alkylation, yielding product **56A** preferentially.

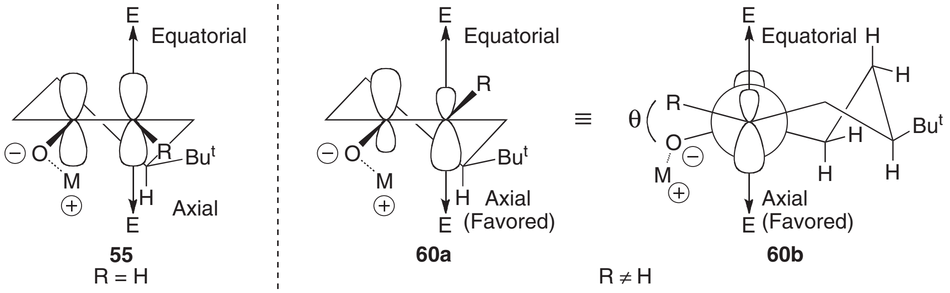
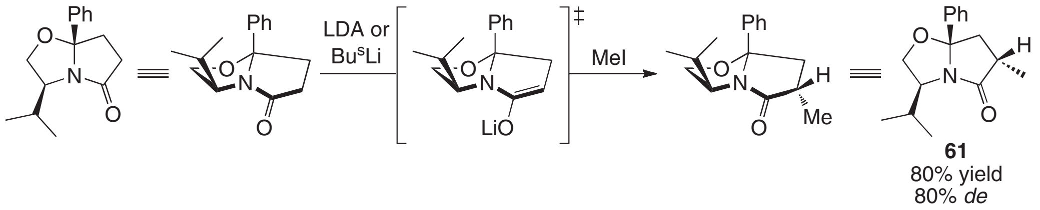


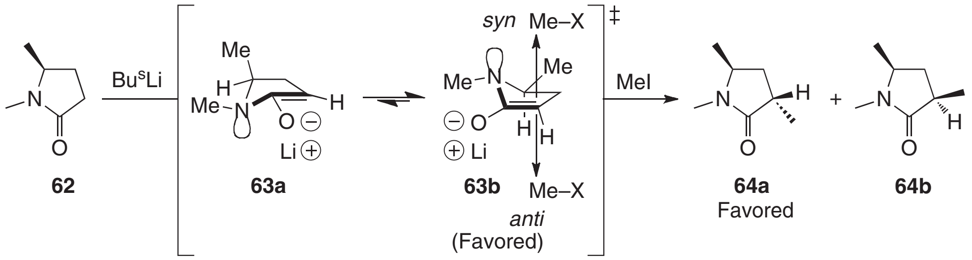
Figure 2 House's enolate configuration model.

Another stereoelectronic trend is observed in the alkylation of lactam enolates. To understand the observed selectivity of their bicyclic lactams (e.g., **61**, Scheme 22(a)),[149] Meyers and coworkers performed *ab initio* calculations on simplified 2-pyrrolidinone **62** (Scheme 22(b)).[150] Their results indicate that methylation of the lowest energy conformation **63b** (2.95 kcal mol^{-1} less than the related **63a**) is preferred on the β-face (0.99 kcal mol^{-1}) due to orbital increase anti to the nitrogen lone pair in the HOMO.[151] This stereoelectronic effect consequently favors formation of lactam **64a**, and in practice, the facial bias is generally high (Table 3, entries 1–5). Pilli et al.[152] have found a related trend for 2-piperidinone substrates (entries 6 and 7). For more information on these systems, see Section 3.01.3.2.1.

(a) Example of bicyclic lactam

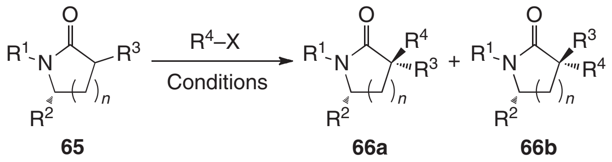


(b) 2-Pyrrolidinone *ab in/tio* model



Scheme 22 Stereoelectronic trends in the alkylation of lactam enolates.

Table 3 Alkylation of 2-pyrrolidinone and 2-piperidinone substrates[151,153]

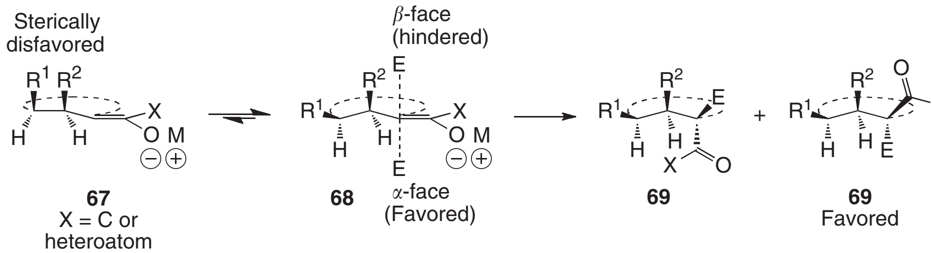


Entry	n	R^1	R^2	R^3	R^4	Yield (%)	**66a:b**	References
1[a]	1	Me	Me	H	Bn	95	99:1	150
2[a]	1	Me	Me	Bn	allyl	95	99:1	150
3[b]	1	Boc	Ph	H	Me	83	86:14	152
4[b]	1	Boc	Me	H	allyl	52	> 95:5	152
5[b]	1	Boc	Ph	H	Bn	60	> 95:5	152
6[c]	2	Boc	Me	H	allyl	44	93:7	152
7[c]	2	Boc	Me	H	Bn	57	> 99:1	152

[a] Conditions: Substrate **65** (1 equivalent), Bu^sLi (1 equivalent), R^4–X (1.05 equivalents) in THF, − 78 °C.
[b] Conditions: Substrate **65** (1 equivalent), LDA (4 equivalents), DMPU (20 equivalents), R^4–X (4 equivalents) in THF, − 78 °C.
[c] Conditions: Substrate **65** (1 equivalent), LDA (1.1 equivalents), DMPU (4 equivalents), R^4–X (4 equivalents) in THF, − 78 °C.

3.01.3.1.2 Steric effects

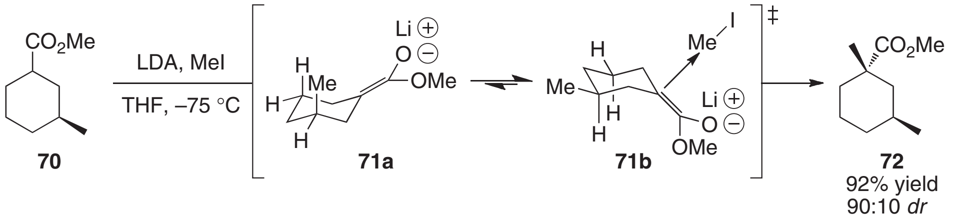
In comparison, steric factors typically play a larger role in determining enolate diastereomeric bias, as stereoelectronic facial considerations are often approximately equivalent in competing transition states. Steric forces contribute to substrate control by inducing a preferred geometrical configuration within a molecule (**68** over **67**) and by directing the reaction between molecules to a less hindered position or face (α-face of enolate **68**, Scheme 23). The impact of steric interactions on conformation and electrophile accessibility as well as additional factors for intramolecular alkylations are discussed in the following subsections.



Scheme 23 Steric effects in substrate control.

3.01.3.1.2.1 Impact on molecular conformation

Steric repulsion contributes to the geometrical orientation adopted by conformationally flexible molecules. Some substituents contribute primarily to this energy minimizing process and have limited influence on the electrophile trajectory. In such cases, the role of other steric and stereoelectronic forces must be considered in determining stereoinduction. For example, the major steric contribution of the methyl group in ester **70** is to bias the transition state toward one resembling enolate **71b**, where alkylation occurs *syn* to avoid 1,3-diaxial interactions on the opposite face (equation 8).[153] The methyl group may block the electrophile approach in the alternative configuration (**71a**), but the contribution of this effect is minor. The remote *t*-butyl group plays a similar conformation-stabilizing role for 4-*t*-butylcyclohexanone derivatives as discussed previously, where stereoelectronic effects ultimately determine the diastereoselectivity (Scheme 21). In contrast to these examples, substituents can alternatively affect determine approach in addition to molecular conformation, and this is frequently the case with functionality located proximally to the enolate. The influence of these neighboring groups is described in the subsequent discussion on allylic strain.



(8)

3.01.3.1.2.1.1 Allylic strain

There are two types of allylic strain[138,154] that result from steric interactions between groups located adjacent to the enolate. $A^{1,2}$ strain refers to the steric clash between substituents attached to the same carbon of the enolate (**Figure 3(a)**), whereas $A^{1,3}$ strain encompasses interactions between functionality on opposite sides of the enolate (**Figure 3(b)**). These steric interactions do not exclusively exist between enolate carbon functionality, but also occur with the attached heteroatom groups. The impact of allylic strain is illustrated in the following examples.

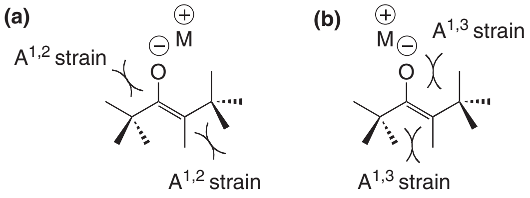
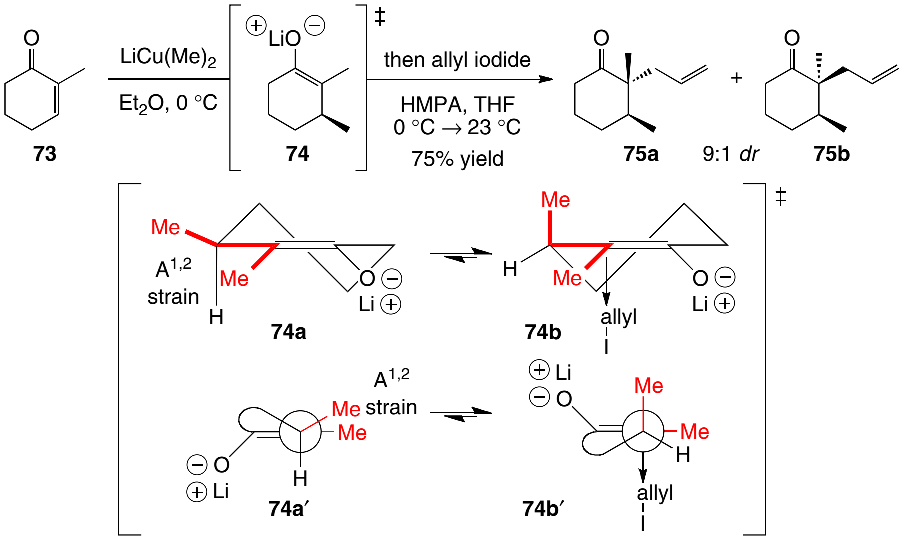


Figure 3 $A^{1,2}$ and $A^{1,3}$ strain.

$A^{1,2}$ strain is the prevalent guiding force for selectivity in the alkylation of enolate **73** (**Scheme 24**).[33a] In this case, the methyl group introduced through the cuprate addition sterically clashes with the enolate methyl when in pseudoequatorial conformation **74a**. The unfavorable substituent proximity is particularly evident in the Newman projection (**74a′**). $A^{1,2}$ strain is minimized through a rotation to structure **74b,** which places the adjacent methyl group at the pseudoaxial position and subsequently directs alkylation to provide the antiproduct (**75a**). Another example of $A^{1,2}$ directed alkylation was portrayed previously in **Scheme 19(a)** en route to neomarinone (**46**).

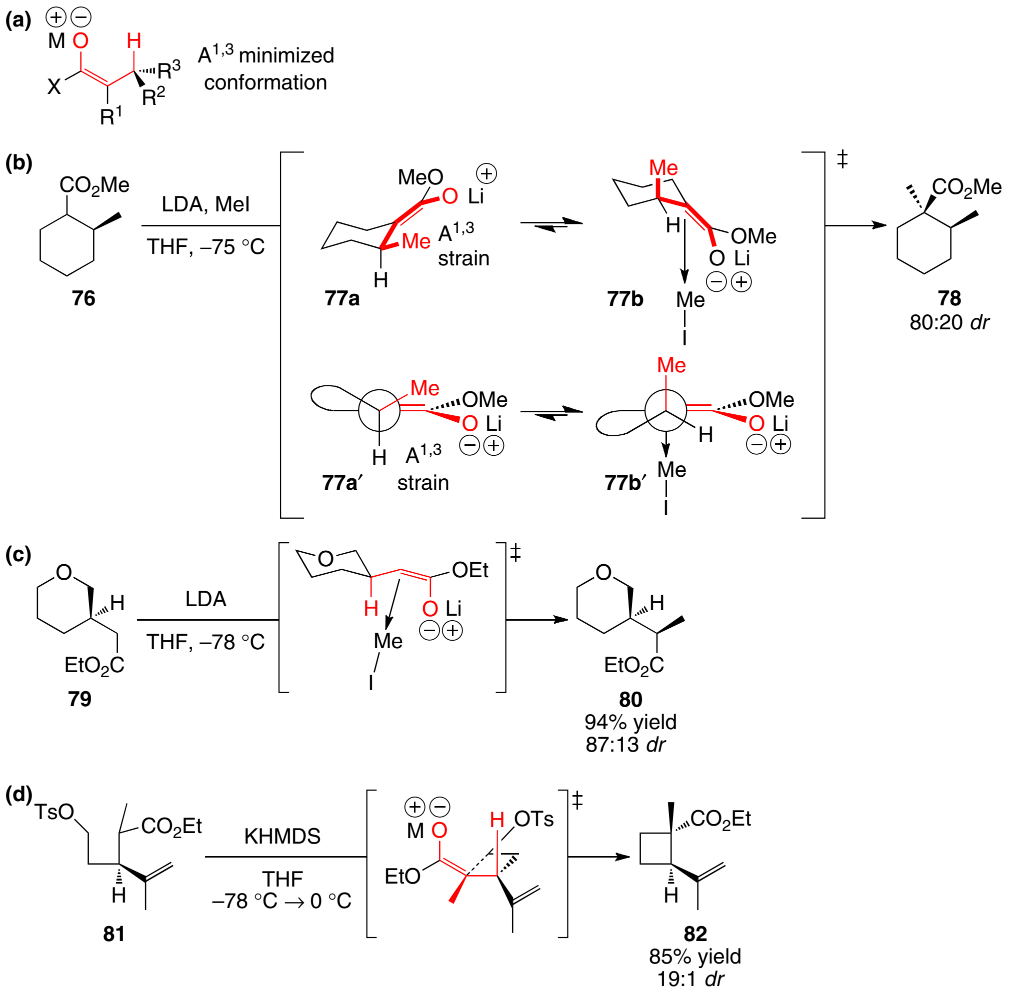


Scheme 24 Stereoselectivity guided by $A^{1,2}$ strain.

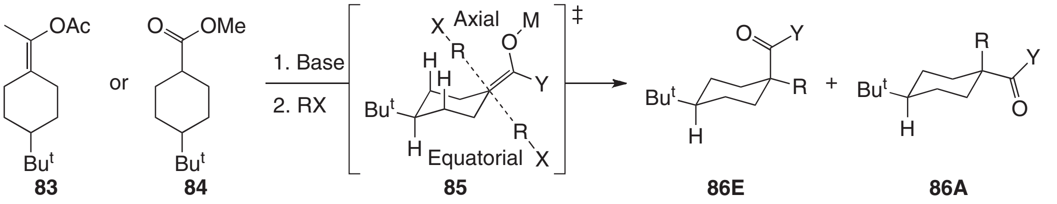
$A^{1,3}$ strain is minimized in enolate systems by positioning the smallest substituent (H) parallel to the adjacent enolate group (**Scheme 25(a)**).[137,155] This energy-minimized orientation is manifested in the axial methyl transition state (**77a** and **a′**) that directs the alkylation of ester **76** to proceed chiefly anti to the methyl substituent (**Scheme 25(b)**).[153] The preferred configuration is also present in acyclic enolate **79**, where methylation is favored anti to the ether group by stereoelectronic direction of this functionality (**Scheme 25(c)**).[156] Additionally, this model is frequently invoked for intramolecular reactions, as seen with ester **81** (**Scheme 25(d)**).[157] $A^{1,3}$ strain also guides the alkylation depicted in **Scheme 19(b)** on route to tormesol (**47**).

3.01.3.1.2.2 Electrophile accessibility

In the lowest energy molecular conformation, the relative inhibition substituents pose to electrophile approach along the π-facial trajectory determines product distribution. Ultimately, the extent of stereoinduction imparted by the substrate depends on how well the substituents differentiate each side of the enolate (i.e., the extent of steric dissymmetry). For example, the alkylation of exocyclic cyclohexane enolates (e.g., **83** and **84**) occurs predominantly from the α-face due to 1,3-diaxial steric interactions along the β-face trajectory (**85**), favoring the formation of the equatorial alkylated product (**86E**, **Scheme 26**).[153,158] Increasing steric repulsion at the diaxial positions decreases electrophile accessibility to the axial face, and as seen with the alkylation of aldehyde



Scheme 25 Stereoselectivity guided by $A^{1,3}$ strain.

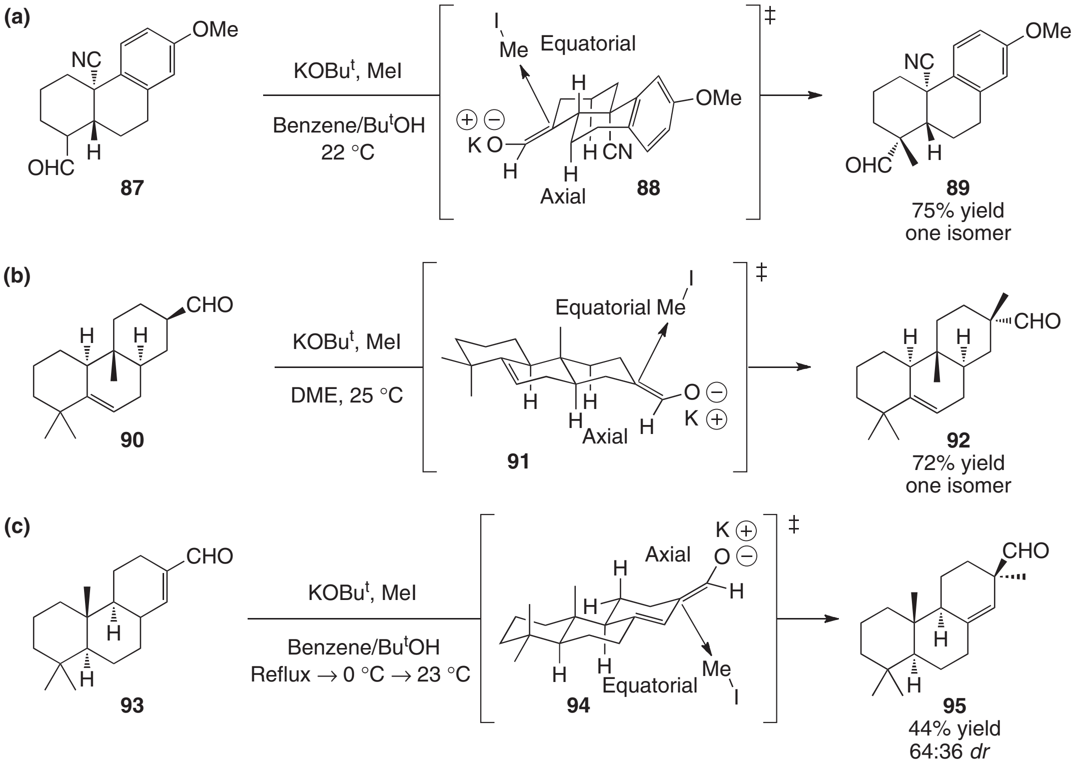


Entry	Reactant	Base	R–X	**86E**:**A**	References
1	**83**	MeLi	MeI	85:15	159
2	**84**	LDA	MeI	84:16	154
3	**84**	LDA	Bu^{n}Br	87:13	154

Scheme 26 Stereoselectivity guided by 1,3-diaxial steric interactions.

87, the process occurs with high selectivity (Scheme 27(a)).[159] The opposite is also true; weaker steric repulsion leads to approximately equal π-facial exposure and decreased selectivity. Comparison of the alkylation of aldehydes **90** and **93** illustrates this point, where the conjugated olefin in transition state **94** removes one diaxial interaction (in contrast to **91**) and decreases facial discrimination, subsequently providing aldehyde **95** with a lower diastereomeric ratio (Scheme 27(b) and (c)).[160]

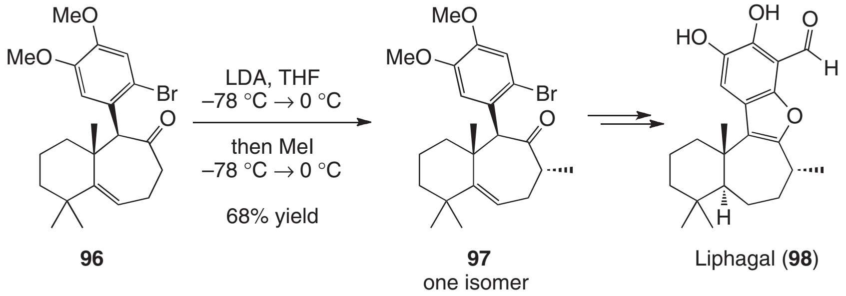
Multiple substituents on a molecule can cooperatively direct alkylation to occur at one enolate face. This principle is illustrated in route to liphagal (**98**) with the alkylation of cycloheptanone **96**, where the methyl and aryl groups direct anti-methylation



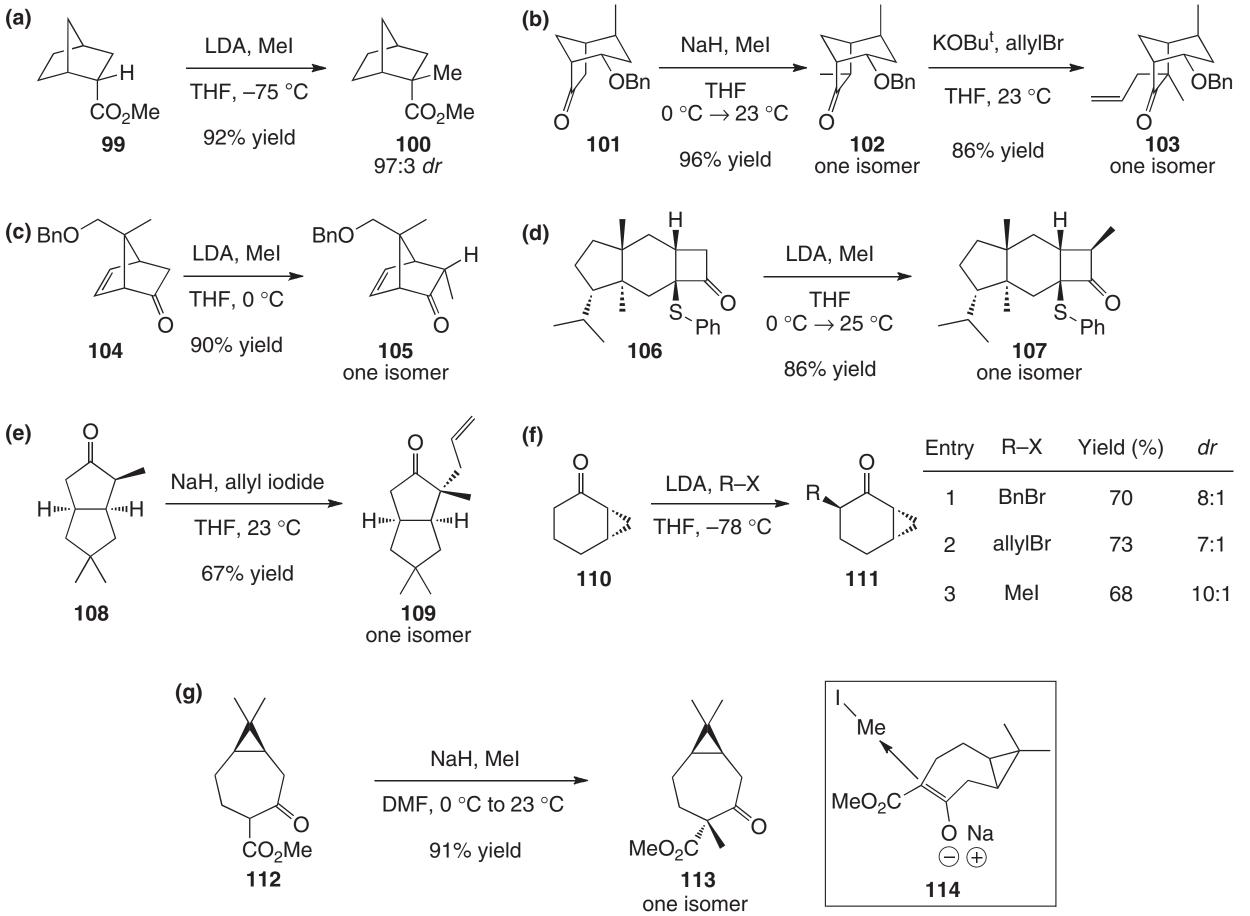
Scheme 27 Steric repulsion and facial accessibility.

(Scheme 28). The cooperative effect is also seen with bridged and polycyclic enolates where substituents are tethered together, creating a rigid structure that impedes electrophile approach from one side. For bridged molecules, such as exocyclic ester **99**[153] and ketone **101**,[161] *exo*-alkylation is favored due to a decreased steric requirement side (Scheme 29(a) and (b)). The presence of functionality on a bridging carbon can block the *exo*-face and reverse the normal selectivity, illustrated by the *endo*-methylation of norbornyl ketone **109** (Scheme 29(c)).[162] The fused cycles have a concave structure where alkylation preferentially occurs on the convex side, as seen with tricycle **106**[163] and bicycle **108**[164] (Scheme 29(d) and (e)). The cupped nature of ketone **110** directs alkylation with a number of electrophiles although the bicycle is on the α′-side of the enolate (Scheme 29(f)).[165] Although there are a number of trends for the alkylation of polycyclic molecules, predicting facial selectivity with larger ring sizes can be challenging given the conformational flexibility of these systems. For example, the seven-membered ring in [7–3] bicycle **112** creates an additional concave arrangement (**114**) that guides alkylation syn to the cyclopropane ring (Scheme 29(g)).[166]

Alkylation of bicycles at the ring juncture produces predominantly *cis*-fused products. Smaller bicycles follow this trend well, as seen in the angular alkylation of tricycles **115**[167] and **117**[168] (Scheme 30(a) and (b)). Larger fused rings also tend to favor the *cis*-conformer, but are often less selective (as decalin **119**[169]) without additional reinforcing functionality, as seen with tricycle **122**[170] (Scheme 30(c) and (d)). In addition, bulky substituents can competitively divert selectivity to the *trans*-product, as observed in the reductive methylation of enone **124** (Scheme 30(e)).[171]

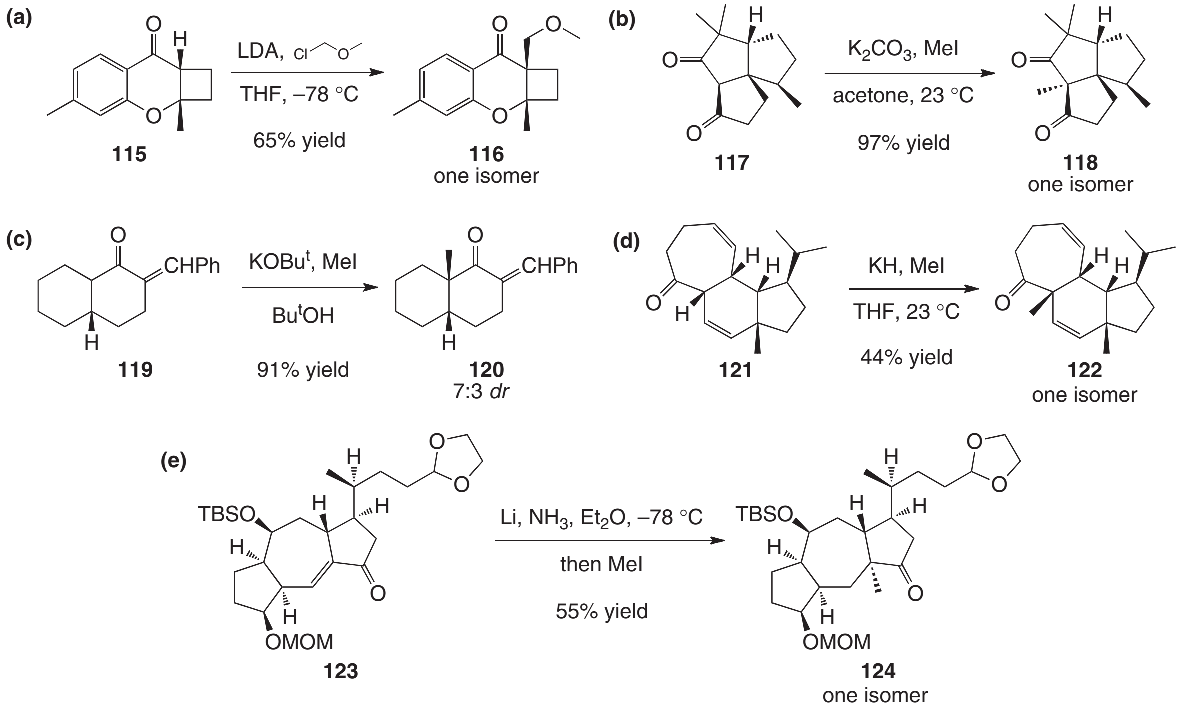


Scheme 28 Cooperative steric effects of multiple substituents.



Entry	R–X	Yield (%)	*dr*
1	BnBr	70	8:1
2	allylBr	73	7:1
3	MeI	68	10:1

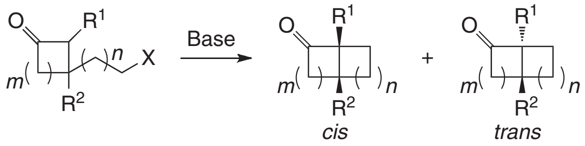
Scheme 29 Cooperative steric effects in bridged and polycyclic enolates.



Scheme 30 Selective formation of *cis*- and *trans*-fused rings by alkylation.

3.01.3.1.2.3 Intramolecular alkylation

The key factors that influence diastereoselectivity in intramolecular annulative alkylation are the flexibility of the molecular carbon core, length of the electrophilic tether, and steric interactions experienced while orienting the leaving group LUMO with the enolate HOMO. These molecular characteristics determine if the compound can adopt conformations where alkylation can occur at either of the enolate π-faces. If the carbon core is particularly rigid ($m \leq 2$) and/or the electrophilic chain is short ($n \leq 2$), alkylation favors generation of a *cis*-ring fusion (equation 9). These effects are illustrated in the formation of [5–5] bicycle **125**[172] and [5–6] bicycle **127**[173] (Scheme 31(a) and (b)).



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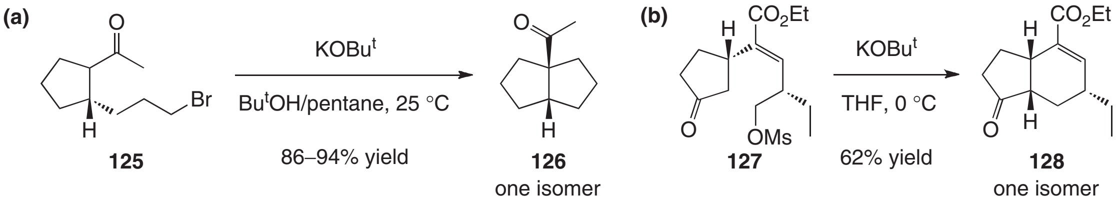
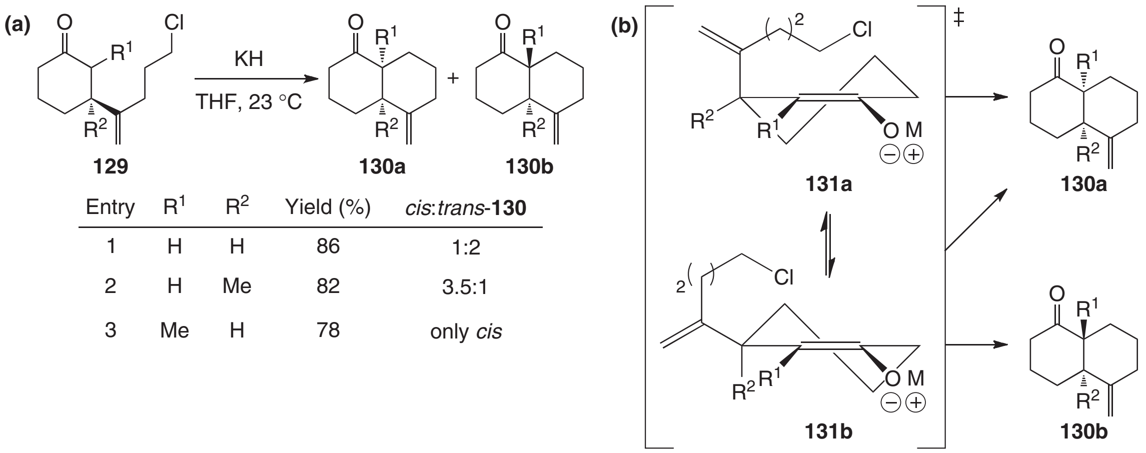


Scheme 31 *Cis*-ring fusion favored in [5–5] and [5–6] bicycles.

Larger molecules typically access several conformations and are consequently capable of producing both *syn-* and *anti*-alkylated products. For example, the intramolecular alkylation of cyclohexanone **129** occurs with varying *cis*/*trans*-selectivity depending on the substituents (Scheme 32(a)).[174] Two half-chair transition states can contribute to the selectivity, however conformer **131a** can only afford the *cis*-product (**130a**) due to tether flexibility restrictions, whereas enolate **131b** allows formation of either isomers due to the pseudoequatorial orientation of the electrophile chain (Scheme 32(b)). In entry 1 ($R^1/R^2 = H$), the annulation produces primarily the *trans*-ketone (**130b**), although Piers and coworkers attribute this selectivity to *in situ* epimerization. Inclusion of β-functionality ($R^2 = Me$, entry 2) favors the *cis*-bicycle (**130a**) as the major product. This *cis*-fused ketone is predicted to be the kinetically favored isomer,[175] however, the impact of epimerization on the level of selectivity is unclear in this example. When the α-position is substituted ($R^1 = Me$, entry 3), epimerization is not possible and the reaction generates the *cis*-ketone (**130a**) exclusively. The high selectivity of this transformation is ascribed to the allylic strain in conformer **131b** that favors half-chair transition state **131a**, which exclusively produces the *cis*-bicycle.

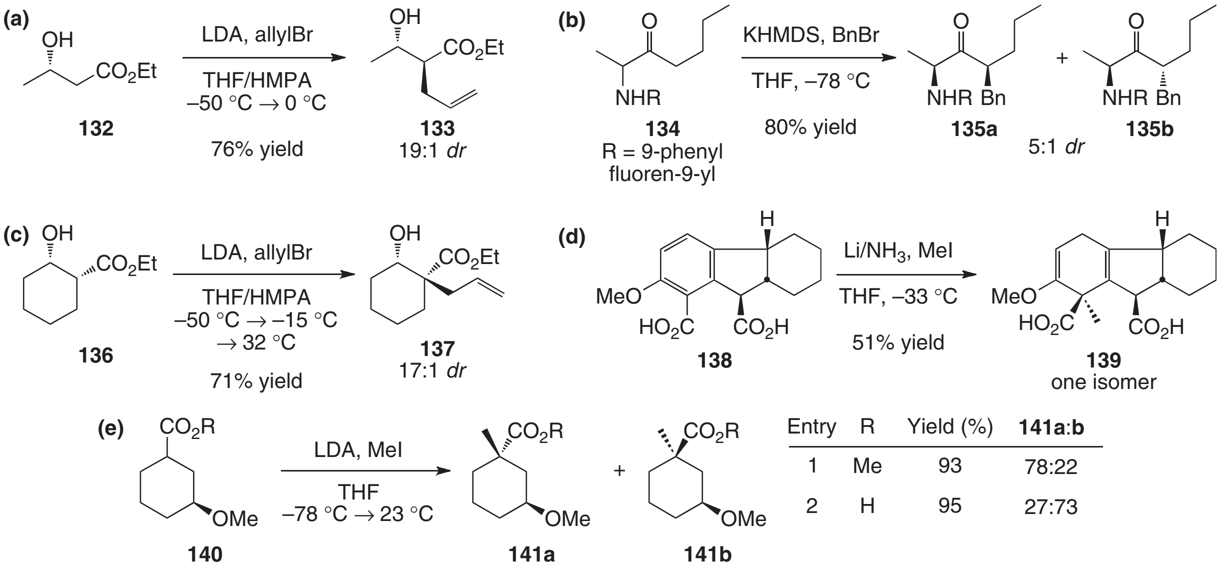


Entry	R^1	R^2	Yield (%)	*cis*:*trans*-**130**
1	H	H	86	1:2
2	H	Me	82	3.5:1
3	Me	H	78	only *cis*

Scheme 32 Substituent effects on *cis/trans*-selectivity.

3.01.3.1.3 Chelation effects

Chelation of metal counterions between the enolate and other heteroatom functionality can enforce a nucleophile conformation that directs alkylation diastereoselectively. This directing effect has been observed with both acyclic and cyclic enolates, where selectivity can be imparted by chelation that occurs on the same side (α) or opposite side (α') of the enolate, as seen respectively with *β*-hydroxyester **132**[176] and α-aminoketone **134**[177] (Scheme 33(a) and (b)). In the alkylation transition state, facial bias is established through the chelating functionality that either directly block one π-face (Scheme 33(c) and (d))[178,179] or subsequently orients the other functionality to impede electrophilic approach (Scheme 33(a) and (b)). In some cases, the coordinating effect may provide the opposite selectivity observed from steric interactions, as seen with the differences in alkylation between the ester and carboxylic acid of **140** (Scheme 33(e)).[153] Metal chelation also plays a significant role in asymmetric induction for many chiral auxiliaries (see Section 3.01.3.2).



Entry	R	Yield (%)	**141a**:**b**
1	Me	93	78:22
2	H	95	27:73

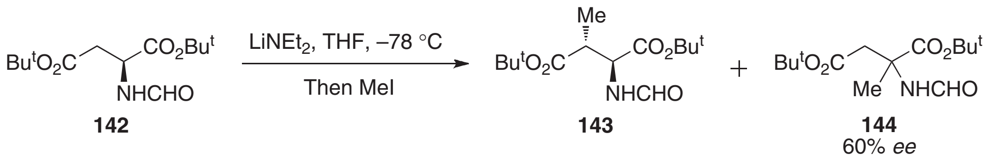
Scheme 33 Chelation effects.

3.01.3.1.4 Memory of chirality

Usually, enolate formation at a tertiary stereocenter results in the loss of the stereochemical information at that position. Without other chiral centers in the same molecule to direct diastereoselectivity, the reaction of this enolate with an achiral electrophile will proceed without facial bias and generate racemic product. Nevertheless, under certain circumstances, stereochemical information can be transferred from a starting material with a single stereocenter to a product through the course of an enolate alkylation event at that center. Fuji and coworkers were the first to use the term 'memory of chirality' (MoC) to describe this effect.[180]

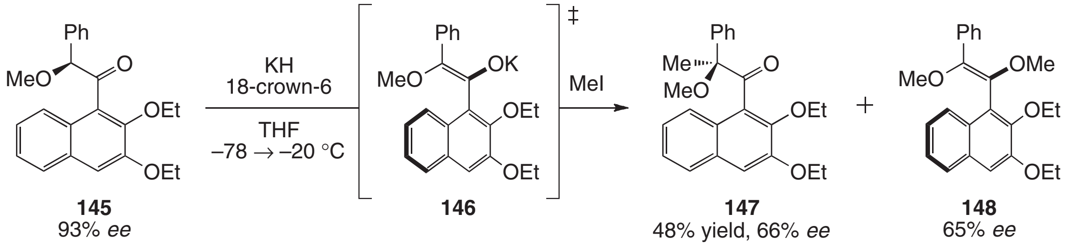
A reaction with MoC is broadly defined in a review by Carlier as a 'formal substitution at an sp^3 stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system.'[181] Although there are several examples of this phenomenon in carbocation and radical reactions, MoC has been studied in the most depth in the realm of enolate chemistry, and Fuji and Kawabata have published two reviews specifically on this subject.[182,183]

In 1981, Seebach reported the first reaction exhibiting MoC.[184] Treatment of dilithiated aspartic acid derivative **142** with methyl iodide produced a mixture of α- and *β*-substituted products. Surprisingly, the α-alkylated product (**144**) was obtained in approximately 60% *ee* (equation 10).



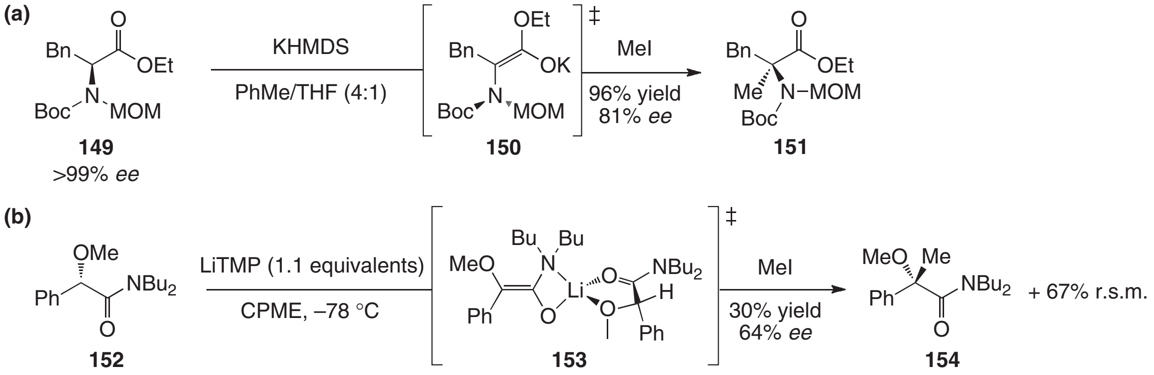
(10)

Ten years later, Fuji and coworkers coined the term MoC when they designed enantio-enriched ketone **145**, which on deprotonation with potassium hydride, generates axially chiral enolate **146** (equation 11).[180] Treatment of the potassium enolate with methyl iodide provides C-alkylated ketone **147** in 66% *ee*, in addition to optically active O-alkylated enol ether **148**, which has a half-life of racemization of 53 min at 21 °C.



(11)

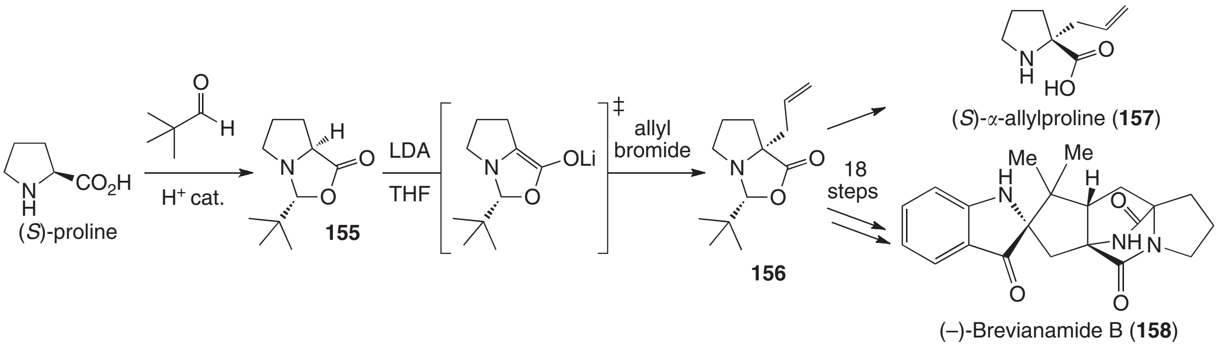
Since Fuji's seminal publication, numerous applications of MoC have been demonstrated for enolate alkylation, most notably in the α-alkylation of amino acid derivatives.[185] Several substrate-dependent mechanisms for chirality transfer have been shown to be operative. In certain cases, axially chiral enolate intermediates have been inferred by trapping the enolate as an optically active enol ether (*vide supra*). This was shown to be the case with phenylalanine derivative **149** (Scheme 34(a)); potassium enolate **150** has hindered rotation about the C–N bond with a half-life of racemization of 22 h at −78 °C. In other circumstances (e.g., glycolate **152**), evidence has been found for mixed enolate aggregates (i.e., **153**) based on results from crossover experiment (Scheme 34(b)).[186]



Scheme 34 Substrate-dependent mechanisms for chirality transfer.

Related to MoC is an similar strategy pioneered in 1981 by Seebach, 'self-regeneration of stereocenters' (SRS).[187] Though MoC relies on the transfer of chirality of a single stereogenic center to form a chiral enolate, SRS is a stepwise strategy that uses the single stereogenic center to direct a diastereoselective acetalization, imparting a second stereocenter. On enolization, the original stereocenter is trigonalized and the acetal stereocenter imparts stereoselectivity in the alkylation. After the alkylation, the acetal auxiliary may be cleaved to provide an optically active product.

In one of the first examples of this strategy, proline was condensed with pivaldehyde, forming bicyclic acetal **155** as a single diastereomer (Scheme 35).[188] Deprotonation with LDA planarizes the original stereocenter, and subsequent treatment with allyl bromide affords alkylated product **156** as a single diastereomer with overall retention of stereochemistry. Proline derivative **156** was used in Williams' total synthesis of brevianamide B (**158**).[189]



Scheme 35 MoC strategy in the allylation of a proline derivative.

Although the strategy requires a multistep sequence, the diastereomeric purity of intermediates may be enriched by ordinary means; therefore, products of higher enantiomeric purity are more easily obtained than the corresponding compounds prepared using MoC. In addition, MoC alkylations often require the use of specific protecting groups, which can render the step efficiency of the strategy equivalent to that of SRS.

3.01.3.2 Chiral Auxiliaries

In the interest of preparing natural products and drug candidates in single enantiomer form, a variety of methods have been developed for diastereoselective alkylation of enolates bearing removable chiral auxiliaries. Although there have been considerable advances in catalytic enantioselective enolate alkylation, the use of chiral auxiliaries bears certain advantages.[190,191] First, there are few methods for catalytic enantioselective alkylation in linear systems and the scope of these reactions remains limited. Second, reaction mechanisms associated with chiral auxiliaries are typically well understood, and therefore the reactivity and selectivity is predictable and reliable. Finally, in cases where selectivity is not perfect, the use of a chiral auxiliary allows for the removal of the undesired diastereomer using standard separation techniques, which is particularly useful in cases where the auxiliary bound product is crystalline.

Chiral auxiliaries commonly employed in stereoselective α-alkylation of carbonyl compounds largely fall into two categories. Nitrogenous derivatives of ketones and aldehydes (imines, hydrazones, sulfonimides, etc.) represent an important class of auxiliaries that are addressed elsewhere in this compilation. Carboxylate derivatives (i.e., esters, amides, imides, etc.) are particularly amenable for stereoselective alkylation of enolates in linear systems and constitute the focus of this section.

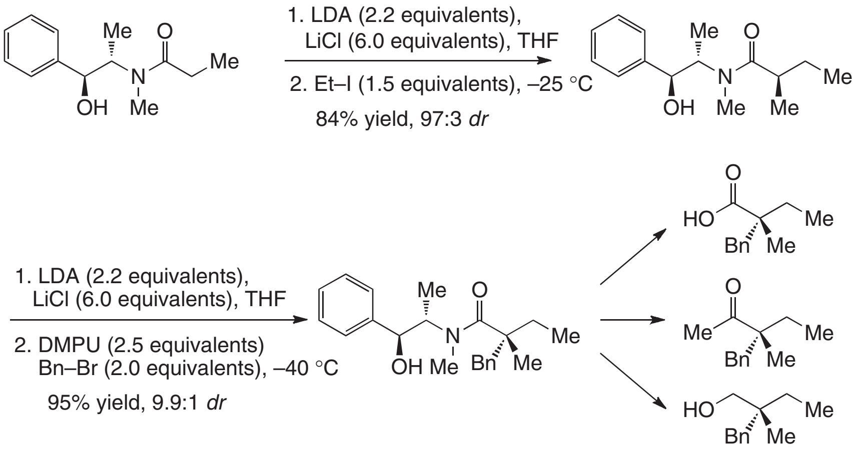
Whereas several applications have been found for many of the chiral auxiliaries discussed below, including stereoselective aldol reactions, conjugate additions, and Diels–Alder reactions (*see* Volume 5, Chapter 5.09), this section will only highlight their use in enolate alkylation. In addition, the breadth of the literature on this topic is such that an emphasis must be placed on those auxiliaries that have demonstrated the greatest practical synthetic utility, or those that underscore important concepts. For a comprehensive discussion on chiral auxiliaries and many of their applications, a recent review by Gnas and Glorius is recommended.[192] In addition, a review by researchers at Boehringer Ingelheim on the asymmetric synthesis of active pharmaceutical ingredients provides an excellent treatment of auxiliary strategies that are amenable to large-scale synthesis.[193] In addition, focused reviews on specific classes of auxiliaries and reliable multigram-scale preparations of important compounds are referenced throughout this section that may provide further guidance.

3.01.3.2.1 Amino alcohol-derived auxiliaries

Chiral amino alcohols are ubiquitous in nature, and are often easily derived from abundant natural sources, particularly α-amino acids. They serve as an important and inexpensive precursor for numerous chiral ligands and auxiliaries.[192,193]

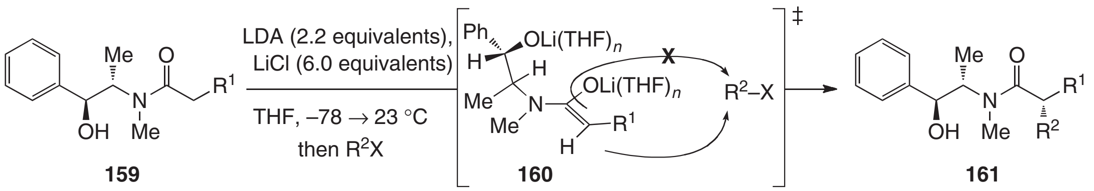
In 1994, Myers disclosed the use of pseudoephedrine as a chiral auxiliary for enolate alkylation.[194] Tertiary amides were formed by the reaction of pseudoephedrine with an acid chloride or anhydride, which were doubly deprotonated by LDA and then treated with an alkyl halide to generate tertiary stereocenters with high *dr* (>50:1) in most cases (Scheme 36).[195] In addition, the methodology was recently extended to the synthesis of quaternary stereocenters.[196]

Myers' auxiliary can be cleaved under acidic or basic conditions; however, tertiary stereocenters can epimerize under basic conditions, particularly with electron-withdrawing substituents at the α-position. Conditions have also been developed for the direct conversion of the pseudoephedrine amides to ketones, aldehydes, and alcohols.[8,197]



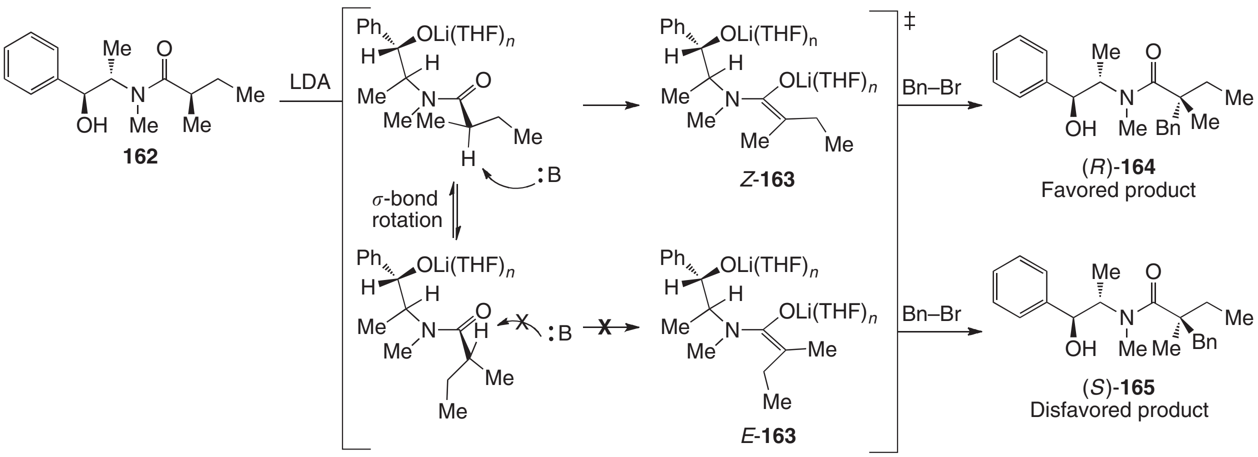
Scheme 36 Myers' pseudoephedrine auxiliary.

From a mechanistic perspective, Myers and coworkers propose that dianionic intermediate **160**, generated via deprotonation with LDA to stereoselectively form a *Z*-enolate, adopts an energy-minimized conformation with respect to allylic strain, where the C–H bond adjacent to nitrogen rests in a coplanar conformation with respect to the oxyanion (equation 12).[197] The lithium alkoxide and associated solvent cage block nucleophilic attack from the *β*-face of the enolate, and consequently the electrophile is delivered to the unencumbered *α*-face with excellent selectivity.



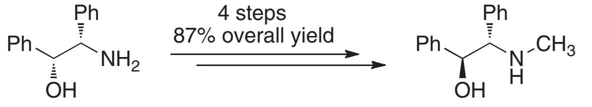
(12)

The extension of Myers' chiral auxiliary methodology to the synthesis of quaternary stereocenters hinged on their discovery, disclosed in 2006, that the diastereomeric configuration at the tertiary alpha-position directly influences the geometry of the enolate generated upon treatment with base.[196] On the basis of enolate trapping experiments, Myers and coworkers propose that the chiral auxiliary blocks deprotonation from the *β*-face of the amide (Scheme 37). Kinetic deprotonation from the *α*-face preferentially generates a single enolate geometry, which is then alkylated from the same face. The net result is a selective alkylation of an *α*-tertiary pseudoephedrine amide (e.g., **162**) occurs selectively with retention of configuration under the reported conditions. A notable exception occurs with *α*-phenyl substituents, where the enolate isomerizes to the thermodynamically favorable geometry, and the same product diastereomer is obtained from either diastereomer of the starting material.



Scheme 37 Myers' auxiliary in the synthesis of quaternary stereocenters.

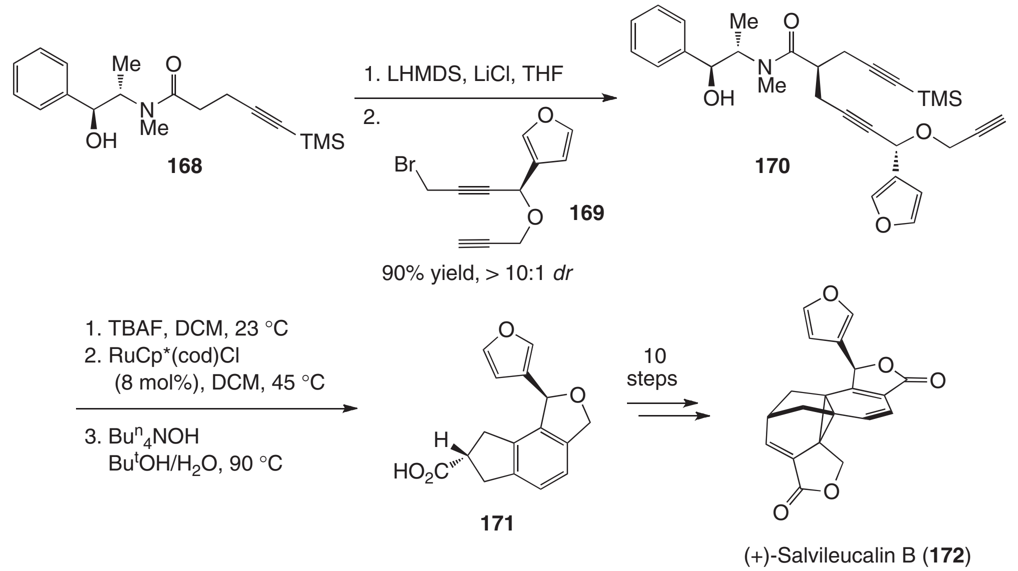
A notable drawback of this methodology is the availability of pseudoephedrine, whose sale is often controlled because it is a precursor to illegal drugs including methamphetamine. To address this problem, the Myers group recently reported the use of pseudoephenamine (**167**), available in four steps from commercial materials without chromatography, as a chiral auxiliary that shows an efficacy similar to pseudoephedrine in the asymmetric alkylation of enolates (equation 13).[198] Although the precursor is more expensive than pseudoephedrine, there are no regulatory restrictions to its purchase.



166 Pseudoephenamine (**167**)

(13)

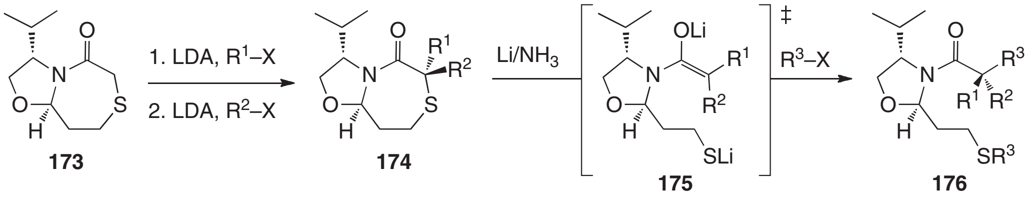
Overall, Myers' auxiliary enables the practical construction of synthetically useful chiral building blocks. In particular, Myers and coworkers extended this method to the synthesis of *α*-amino acids and protected derivatives.[199,200] This auxiliary has found use in numerous natural product syntheses, including a recent synthesis of salvileucalin B (**172**) by Reisman and coworkers (Scheme 38).[201] In their synthesis, the auxiliary served as a lynchpin to connect two complex fragments (**168** and **169**) in good diastereoselectivity. Furthermore, Myers' methodology is amenable to large-scale synthesis[191] due to the crystallinity of many pseudoephedrine amides and also has broad electrophile compatibility, making the auxiliary arguably the most versatile for the stereoselective enolate alkylation of linear systems.



Scheme 38 Myers' auxiliary in the synthesis of salvileucalin B.

In 2006, Gleason and coworkers reported a bicyclic thioglycolate lactam auxiliary (**173**), derived in three steps from valine, capable of generating quaternary stereocenters with high selectivity (Table 4).[202] The thioglycolate may be iteratively deprotonated and alkylated using LDA to afford tertiary thioethers **174**; reductive C–S cleavage stereoselectively affords dianionic enolate **175**, which can be alkylated with a third electrophile, to yield an α-quaternary amide (**176**). Notably, either antipode of a desired chiral building block can be generated from a single enantiomer of the auxiliary simply by altering the order of electrophile addition. Although this relatively new technology has not yet seen widespread use, the Gleason auxiliary is commercially available, and extensions of this methodology by Gleason and others have been reported since the initial publication of this work.[203]

Table 4 Generation of quaternary stereocenters using Gleason's auxiliary

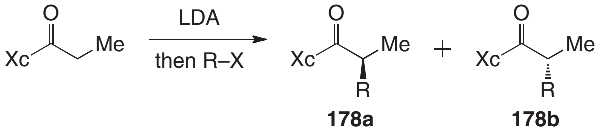


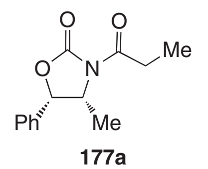
Entry	*R^1*	*R^2*	*R^3*	*Yield (%)*	dr
1	Et	Me	Bn	92	93:7
2	Me	Et	Bn	85	93:7
3	Bn	Me	Et	87	97:3
4	Et	Me	Pr	88	99:1
5	Et	Me	TBSO(CH$_2$)$_3$	86	96:4
6	Et	Me	Cl(CH$_2$)$_4$	79	95:5

Evans' oxazolidinones, first reported in 1981, constitute another class of amino alcohol-derived chiral auxiliaries that has found widespread use.[204] These oxazolidinones are most commonly used to direct enantioselective aldol reactions, but have also proven to be useful for the preparation of tertiary stereocenters via enolate alkylation.[205] Oxazolidinones derived from valinol, phenylalanol, or norephedrine can be acylated with an appropriate acyl chloride.[206] The imide (e.g., **177a** and **b**), on deprotonation with a base, can subsequently be treated with a reactive alkyl halide, such as methyl iodide, allyl bromide, or benzyl bromide (Table 5). These imide enolates are less reactive than Myers' pseudoephedrine amide enolates, and unactivated alkyl halides often suffer from poor yields.

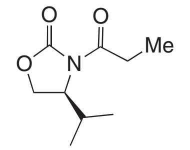
Evans' oxazolidinones have been used for asymmetric alkylations in the syntheses of several natural products and drug candidates.[191] Shindo and coworkers used phenylalanine derived oxazolidinone **177c** in a recent synthesis of sundiversifolide

Table 5 Examples of alkylation with Evans' oxazolidinones

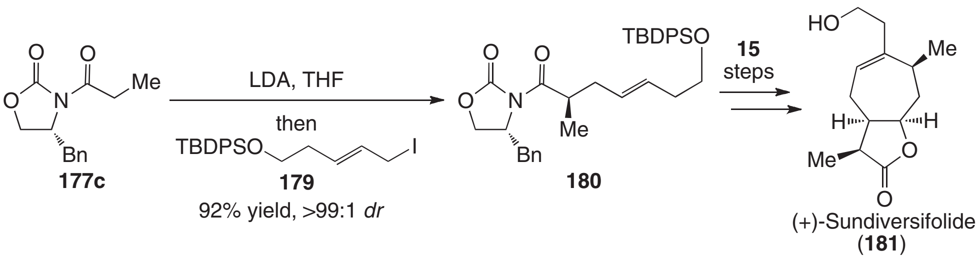



177a

Entry	Imide	Electrophile	Yield (%)	178a:b
1	**177a**	PhCH$_2$Br	78	>99:1
2	**177b**	PhCH$_2$Br	92	>1:99
3	**177a**	CH$_2$=CHCH$_2$Br	75	>99:1
4	**177b**	CH$_2$=CHCH$_2$Br	71	>1:99
5	**177a**	Et-I	53	>99:1
6	**177b**	Et-I	36	<1:99

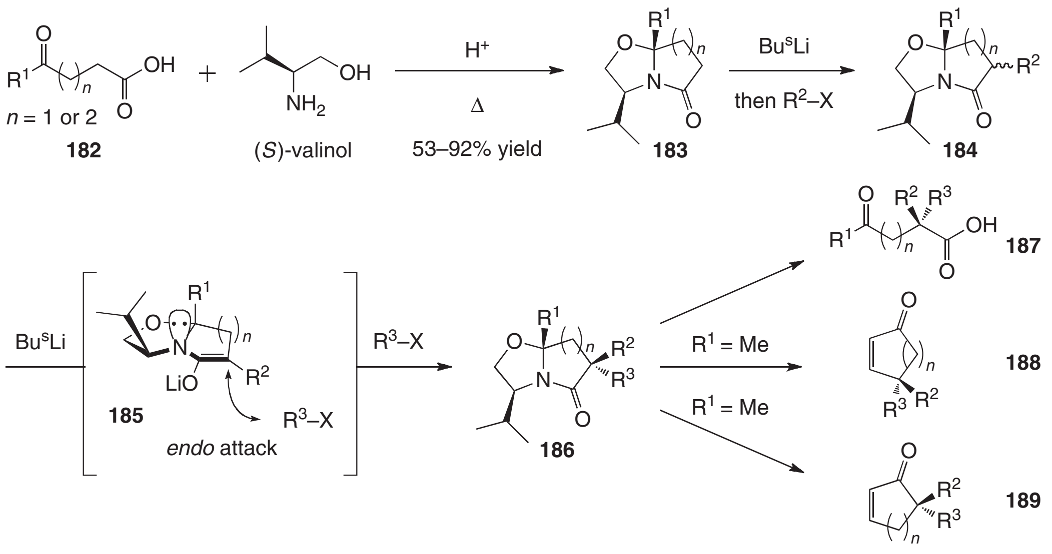

177b

(**181**), alkylating the propionate imide with an allylic iodide in excellent yield and diastereoselectivity (Scheme 39).[207] Numerous related chiral auxiliaries have been developed and are discussed in a recent review.[208]



Scheme 39 Evans' oxazolidinones in the synthesis sundiversifolide.

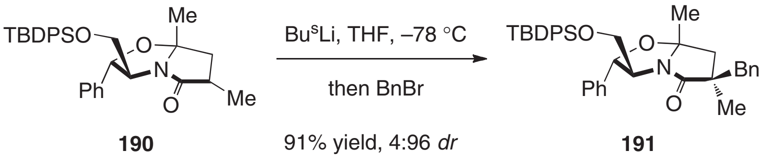
In 1984, Meyers reported one of the first strategies for the enantioselective synthesis of quaternary stereocenters using a chiral auxiliary (Scheme 40).[209] Condensation of valinol with a γ- or δ-ketoacid (**182**) provided bicyclic lactams (**183**) in moderate to excellent yields.[149a] Deprotonation with *sec*-butyllithium ($\mathrm{Bu^sLi}$) followed by treatment with an alkyl halide afforded monoalkylated lactams (**184**) in varying degrees of diastereoselectivity, and acidic hydrolysis of the chiral auxiliary at this stage results in epimerization of the tertiary stereocenter. However, a second deprotonation of the diastereomeric mixture provides a fully



Scheme 40 Meyers' chiral lactam alkylation.

substituted enolate (**185**), which is alkylated on the endo face with excellent diastereoselectivity to form a quaternary stereocenter. These products (**186**) have been derivatized to a variety of synthetically useful building blocks (e.g., **187–189**) and applied in several natural product syntheses.[149a]

The observed stereoselectivity has been attributed to the electronic repulsion from the nitrogen lone pair, which directs an antiapproach of the electrophile (see Section 3.01.3.1.1). This stereochemical preference can be overridden by the incorporation of a steric bulk on the concave face of the bicyclic lactam.[151] In this way, a reversal of selectivity may be obtained with lactam **190**, and exo-substituted product **191** is obtained (equation 14).



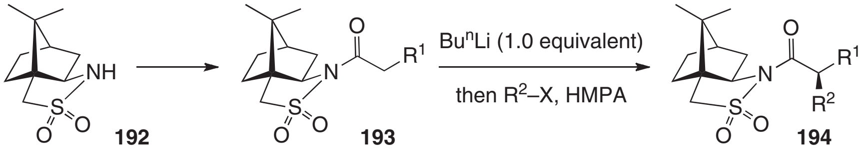
190 **191**

(14)

3.01.3.2.2 Terpenoid-derived auxiliaries

In addition to amino acids and alkaloids, terpenoids such as camphor[210] and menthol[211] have proven to be fertile ground for chiral auxiliary development. The most prominent of these is Oppolzer's sultam (**192**), which is available in three steps from camphor sulfonyl chloride.[212] It was found to be an effective chiral auxiliary for asymmetric Diels–Alder reactions,[213] and was later extended to asymmetric α-alkylations to form tertiary stereocenters (Table 6).[214] Notably, many of the alkylation products can be purified by recrystallization, and the auxiliary can be cleaved by saponification or LAH reduction and recovered via aqueous extraction. In addition, the scope of compatible electrophiles is broad, and includes aliphatic, allylic, and benzylic halides. The use of an equivalent of HMPA is necessary; reactions run without the additive provide diminished selectivity.

Table 6 Stereoselective alkylation of Oppolzer's sultam derivatives



192 **193** **194**

Entry	*R^1*	*R^2–X*	*Crude* dr	*Yield (%)*[a]	dr[a]
1	Me	BnI	98:2	89	99:1
2	Me	$HC{\equiv}C{-}CH_2Br$	99:1	78	>99.5:0.5
3	Me	$C_5H_{11}I$	99:1	81	99:1
4[b]	Me	$CH_2{=}CH{-}CH_2I$	98:2	74	98:2
5	Me	$Me_2C{=}CHCH_2Br$	>99.5:0.5	70	>99.5:0.5
6	Bn	MeI	97:3	88	>99.5:0.5

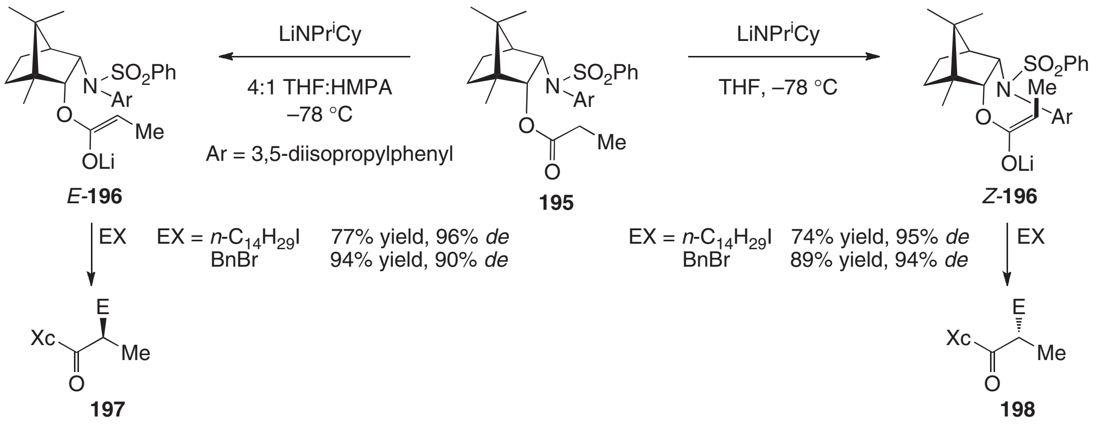
[a] After crystallization.
[b] 1.0 equivalent Bu^{n}Li + 0.1 equivalent isopropylcyclohexylamine.

Prior to Oppolzer's work, a report from Helmchen and coworkers outlined the use of several camphor-derived ester auxiliaries for enolate alkylation.[215] Deprotonation of ester **195** in THF generated an *Z*-enolate, whereas the use of a 4:1 mixture of THF:HMPA resulted in an *E*-enolate (Scheme 41).[216] In both cases, alkylation occurs on the unencumbered β-face. The net result is that either enantiomer of α-tertiary carboxylic acid can be obtained from a single enantiomer of the auxiliary simply by altering the solvent mixture during the alkylation step. Accordingly, this case highlights the influence of enolate geometry on stereoselectivity. This auxiliary was applied in the synthesis of Vitamin E (**199**), setting the two tertiary stereocenters of the aliphatic sidechain in two stages (Scheme 42).[217]

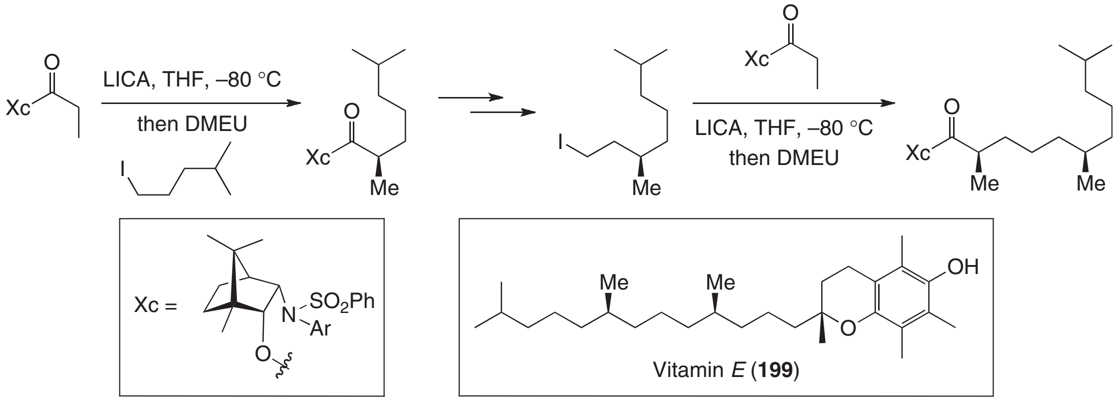
3.01.3.2.3 Carbohydrate-derived auxiliaries

Carbohydrates are also a useful natural source of chirality and their derivatives have found numerous applications as auxiliaries, catalysts, additives, and reagents in asymmetric synthesis.[218] They bear multiple stereocenters and are widely commercially available. In addition, they have multiple functional handles, allowing for steric and electronic tuning as well as variation of the point of attachment when used as a chiral auxiliary.

Reports of carbohydrate-based auxiliaries for enolate alkylation are relatively limited. Tadano and coworkers have developed a series of sugar derivatives for stereoselective conjugate additions, Diels–Alder reactions, and enolate alkylations.[219] The most broadly useful auxiliary is 6-deoxy-glucose derivative **200**, which has been used in enolate alkylations to generate tertiary[220] and quaternary[221] stereocenters with high diastereoselectivity (Table 7). Notably, in the case of the propionate esters, a reversal in

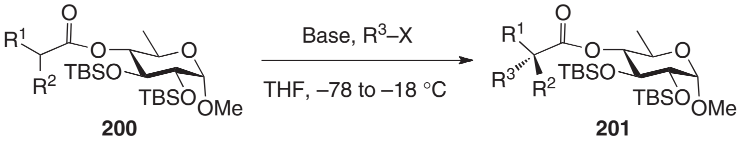


Scheme 41 Control of enolate geometry on camphor-derived esters.



Scheme 42 Camphor-based auxiliary in the synthesis of Vitamin E.

Table 7 Tadano's carbohydrate-based auxiliary



Entry	*R^1*	*R^2*	*Base*	*R^3–X*	*Yield (%)*	dr
1	Me	H	NaHMDS	BnBr	97	95:5
2	Me	H	NaHMDS	$CH_2{=}CHCH_2Br$	85	>95:5
3	Me	H	NaHMDS	Bu^nI	90	>95:5
4	Me	H	LDA	BnBr	17	16:84
5[a]	Ac	Me	NaOMe	BnBr	75	>97:3
6[a]	Ac	Me	NaOMe	$CH_2{=}CHCH_2Br$	80	>97:3

[a] – 78 °C to r.t.

diastereoselectivity was observed when bases with lithium counterions were used, although the diastereomeric excess was only moderate in these cases (Table 3, entry 4). The practicality of this procedure is limited due to the fact that the auxiliary-bound esters are oils and that diastereomeric separations are difficult.

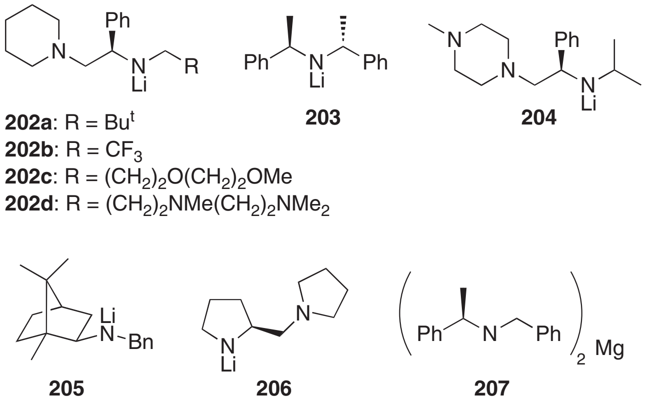
3.01.4 Enantioselective Enolate Alkylation

3.01.4.1 Group I and II Metal Enolates

In the area of enantioselective formation and alkylation of group I and II metals, only lithium and magnesium enolates have been researched extensively. This research falls roughly into two categories: enantioselective deprotonation of prochiral ketones by metal amide bases, and enantioselective alkylation of prochiral enolates by complexation to a chiral lithium amide aggregate.

3.01.4.1.1 Enantioselective deprotonation

The use of chiral lithium amide bases to enantioselectively deprotonate prochiral ketones was reported independently by Koga[222] and Simpkins.[222c,223] A wide array of chiral amine backbones have been explored (Figure 4). These bases have been used to desymmetrize 4-substituted[222b,224] and 2,6-disubstituted[222b,c] cyclohexanones, tropinone derivatives and similar bridged bicyclic compounds,[222b,225] 3-substituted and di-substituted cyclobutanones,[226] and other miscellaneous substrates. The chiral lithium enolate obtained is trapped with TMSCl (either with an internal quench or in the presence of LiCl with an external quench), and the silyl enol ether is usually isolated before further use in reactions.



202a: R = Bu^t
202b: R = CF_3
202c: R = $(CH_2)_2O(CH_2)_2OMe$
202d: R = $(CH_2)_2NMe(CH_2)_2NMe_2$

203 **204** **205** **206** **207**

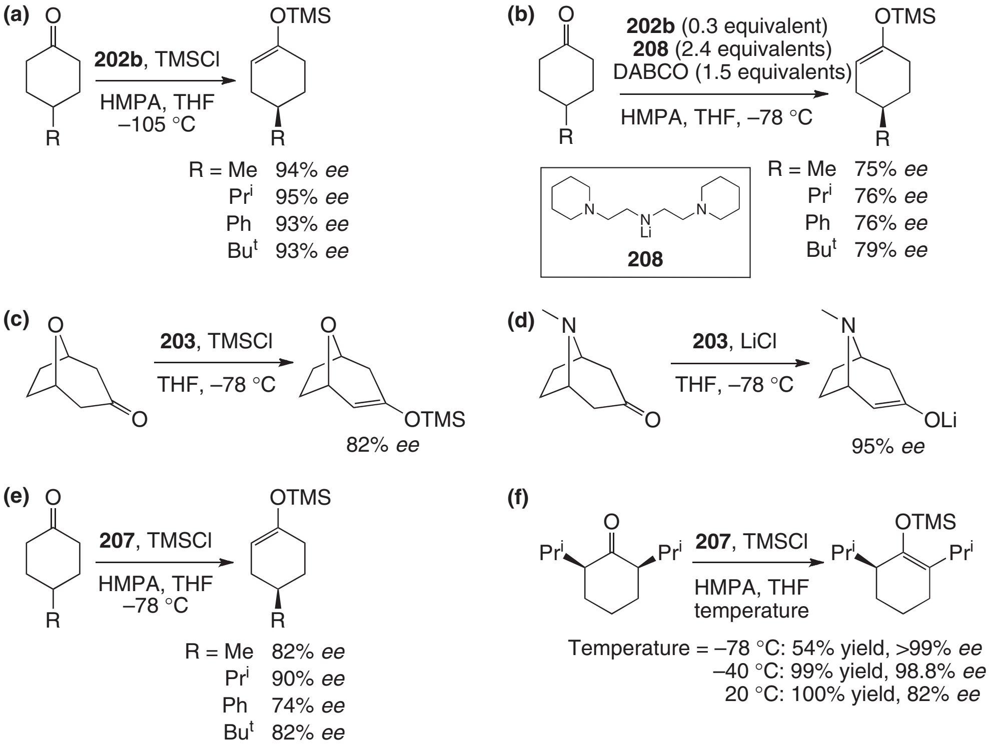
Figure 4 Chiral lithium and magnesium amide bases.

The most effective chiral lithium amides were found to be those of types **202**–**204** (Scheme 43(a–d)). With these amides and similar species, enantiomeric excesses between 80 and 95% are typically obtained, with some examples significantly lower and a few substrates proceeding with an enantiomeric excess greater than 99%. In particular, Koga and coworkers have found the *β*-*tert*-butyl and *β*-trifluoromethyl groups of amides **202a** and **b** to be critical to achieving good enantioselectivities (Scheme 43(a) and (b)). Tetrahydrofuran was found to be the optimal solvent, with the addition of 1.2 equivalents of HMPA and between 0.5 and 1.1 equivalents of LiCl or LiBr greatly increasing the enantioselectivity in almost all cases and increasing the yield in most.[222b,227] Importantly, Koga and coworkers have reported efforts toward the use of a catalytic amount of chiral amide.[222b] By using 0.2–0.3 equivalents of chiral amide **202a** or **b** with 2.4 equivalents of achiral amide **208**, they were able to affect the enantioselective deprotonation of 4-substituted cyclohexanones, albeit in slightly lower enantiomeric excess (Scheme 43(b)). The reseachers theorize that the excess of achiral amide base acts to regenerate the chiral amide after deprotonation of the ketone, as well as to prevent catalyst inactivation by forming aggregates with lithium bromide salts. These processes have also been used in the chiral resolution of racemic 2-substituted[222b,224] and 2,6-disubstituted[222b,c] cyclohexanones.

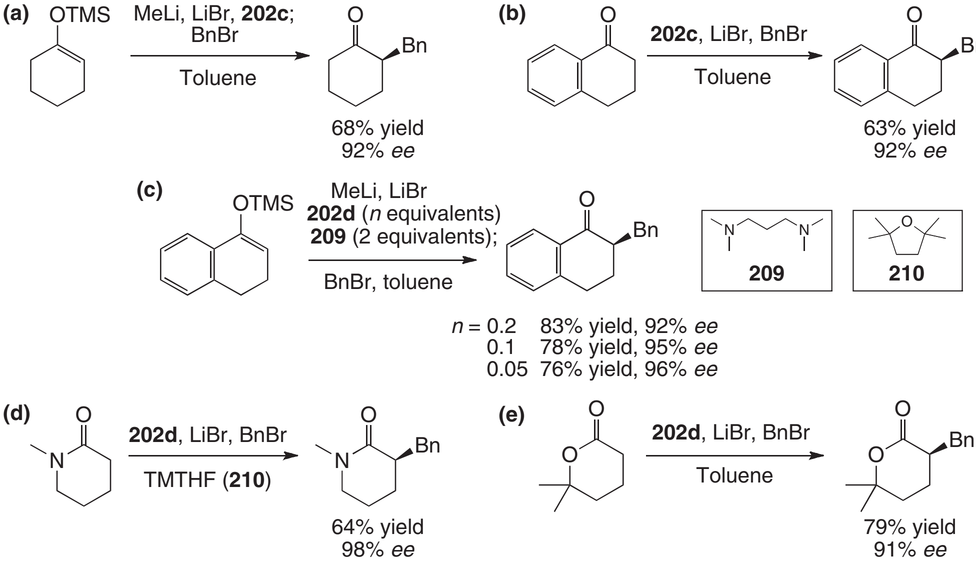
Kerr, Henderson, and coworkers have extended this methodology to the use of similar backbones to form chiral magnesium diamide bases (Scheme 43(e)).[228] These bases are less reactive than their lithium counterparts. At low temperatures, the deprotonations proceed with excellent enantioselectivity, but are plagued by low conversion. At warmer temperatures, enantioselectivity is reduced significantly, whereas excellent yields are obtained (Scheme 43(f)).[229] These bases have been used in the desymmetrization of 4-substituted and 2,6-*cis*-di-substituted cyclohexanones, as well as in the chiral resolution of racemic *trans*-2,6-disubstitued cyclohexanones (Scheme 43(f)).[228,229]

3.01.4.1.2 Enantioselective alkylation of prochiral enolates

Koga and coworkers have also reported the use of similar chiral amides as ligands for the asymmetric alkylation of prochiral enolates. Using lithium amide **202c** as a base, the alkylation of cyclohexanone and tetralone with benzyl bromide, cinnamyl bromide, allyl bromide, methyl bromoacetate, and methyl iodide could be accomplished in good to excellent yields and enantioselectivities (Scheme 44(a) and (b)).[222b,c,230] Moreover, the silyl enol ether of both of these ketones could be converted to the corresponding lithium enolate with MeLi · LiBr, to which the chiral amine ligand could be added followed by alkylating agent. In these reactions, toluene is the ideal solvent, and 10 equivalents of an alkylating agent and 1 equivalent of lithium bromide are necessary to achieve optimal yields and enantioselectivities. As in the deprotonation methodology, catalytic amounts of chiral



Scheme 43 Enantioselective deprotonation using chiral amide bases.

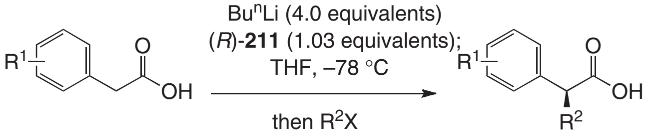


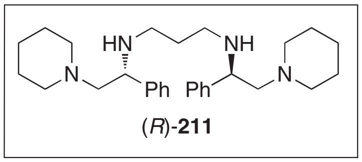
Scheme 44 Koga's symmetric alkylation of prochiral enolates.

amine **202d** could be used, when supplemented with an excess of achiral amine **209** (Scheme 44(c)).[222b,231] In this case, catalytic loadings of chiral amine **202d** as low as 0.05 equivalent were found to be effective with 2 equivalents of achiral amine **209**. More recently, Koga and coworkers have reported the asymmetric alkylation of five- and six-membered lactams and lactones using this methodology (Scheme 44(d) and (e)).[232] Interestingly, 2,2,5,5-tetramethyltetrahydrofuran (TMTHF, **210**) was found to be the ideal solvent for alkylation of lactams, whereas alkylation of lactones was still optimal in toluene.

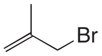
Zakarian has recently disclosed the alkylation of the dianion of prochiral benzyl carboxylic acids using the lithium diamide base derived from C_2-symmetric tetraamine **211** (Table 8).[233] The alkylation performs optimally with 4.0 equivalents of *n*-butyllithium and 1.03 equivalents of amine **211** in THF at −78 °C. Though the reaction requires stoichiometric amounts of chiral amine, the amine can be nearly quantitatively recovered by recrystallization with HCl. The carboxylic acid dianion was

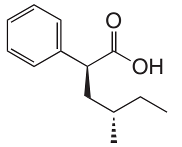
Table 8 Zakarian's asymmetric alkylation of carboxylic acids



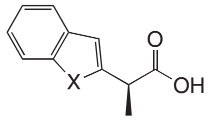


(*R*)-**211**

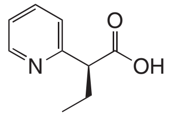
Entry	*R^1*	*R^{2}X*	*Yield (%)*	*ee (%)*
1	H	MeI	83	88
2	H	Pr^{i}I	89	98
3	H	BnBr	85	92
4	H		80	91
5	H	TBSOC$_4$H$_8$I	93	87
6	4-F	EtI	84	93
7	4-Br	EtI	65	96
8	4-OMe	EtI	71	89
9	2-Me	EtI	82	94



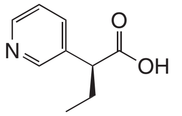
67% yield, 99:1 *dr*
(1.3:1 *dr* with LDA)



X = O: 62% yield, 92% *ee*
X = NMe: 71% yield, 84% *ee*



212
12% yield, 0% *ee*



61% yield, 95% *ee*

found to be competent in alkylation reactions with allylic, benzylic, primary, and secondary bromides and iodides. The reaction was tolerant of both electron donating and withdrawing substitution on the aromatic ring. Heteroaromatic substrates such as pyridine, indole, furan, benzofuran and thiophene analogs of benzoic acid are also competent nucleophiles, with the exception of 2-pyridyl substrate **212**, which underwent racemic alkylation with iodoethane in poor yields. For all other substrates, the reaction proceeds in fair to excellent yields (60–96% yield) with good to excellent enantioselectivities (84–98% *ee*). With chiral electrophiles, diastereomeric ratios as high as 99:1 are obtained. The researchers propose stereoinduction by a chiral lithium aggregate bound to both anionic oxygens of the enolate dianion, noting that due to the equivalency of the two oxyanions the resulting enolate is symmetric, thus obviating the necessity for considerations of *cis*- and *trans*-enolate isomerization.

3.01.4.2 Transition Metal Enolates

3.01.4.2.1 Transition metal catalyzed asymmetric allylic alkylation

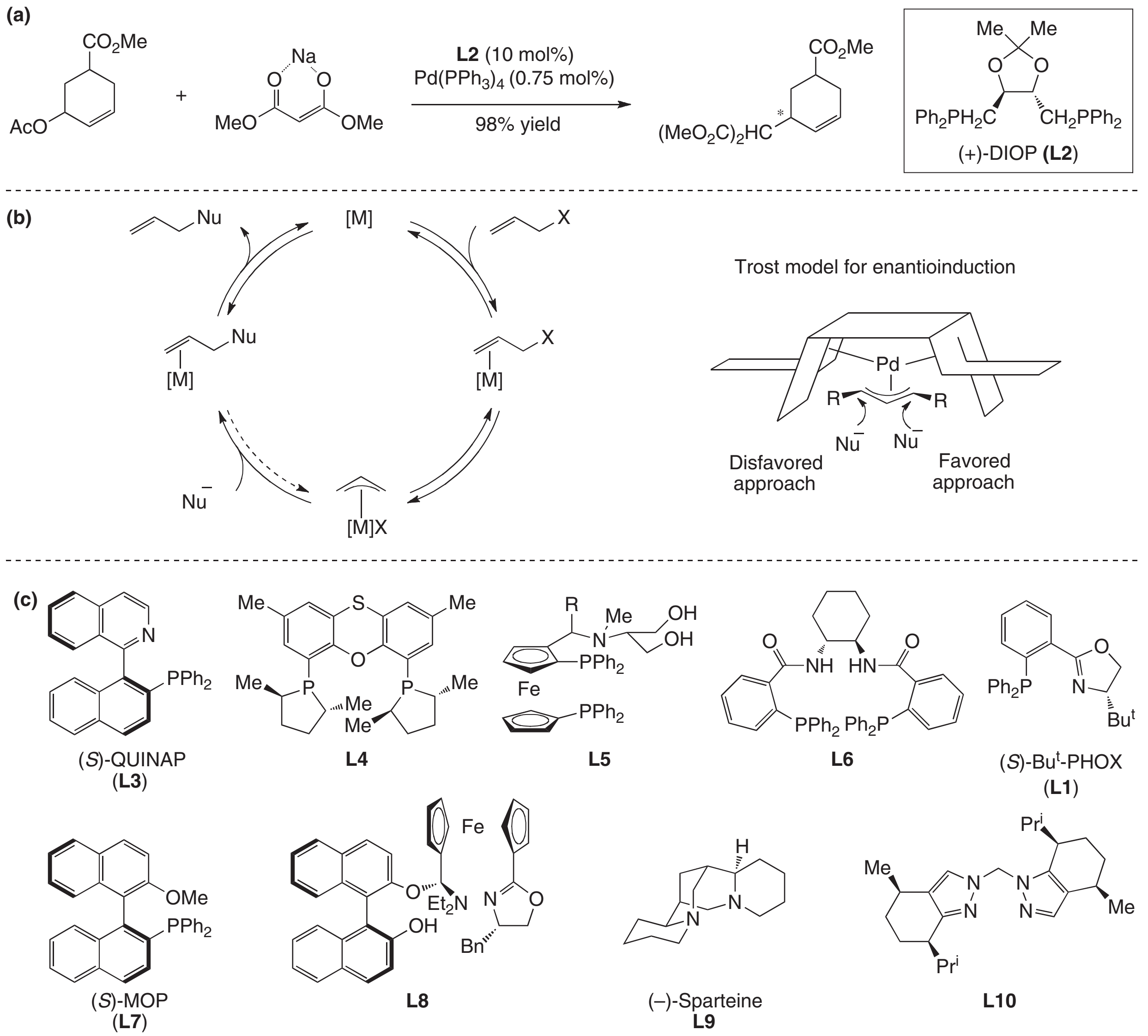
In the domain of transition metal catalyzed asymmetric enolate alkylation, catalytic asymmetric allylic alkylation represents perhaps the most powerful method for the stereoselective construction of C–C bonds.[234] This technology has facilitated a vast number of total synthetic efforts and enabled crucial C–C bond formation in the assembly of novel compounds.[235] A focus on substrate class will help divide this section. It begins with an exploration of allylic alkylation of stabilized enolate nucleophiles ($pK_a = \sim 11–15$) and subsequently examines nonstabilized enolate nucleophiles ($pK_a \geq \sim 21$) (*see* Volume 4, Chapter 4.11). Finally, more recently developed methods that employ more traditional electrophiles, such as alkyl halides, as well as transition metal enolate electrophiles will be discussed.

3.01.4.2.1.1 Palladium-catalyzed allylic alkylation

3.01.4.2.1.1.1 Stabilized enolates

Pioneering studies by Trost and Tsuji revealed the power of palladium catalysis in α-alkylation of carbonyl-containing compounds and helped to establish a burgeoning field of chemical research.[107j,236] Early examples involved stabilized enolates acting as nucleophiles in allylic alkylation reactions. In 1977, Trost and Strege reported the first instance of asymmetric induction in this methodology.[237] Employing 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane (DIOP, **L2**) as a chiral ligand for palladium, they obtained 37% optical yield (Scheme 45(a)).

Interest in this area expanded quickly, and improvements to the modest enantioselectivity observed in Trost's initial experiments soon followed. Scheme 45(b) depicts the general catalytic cycle for the allylic substitution transformation. Privileged ligand scaffolds for this methodology include ferrocene-derived diphosphines (**L5**),[238] sparteine (**L9**),[239] bis(pyrazolyl)methanes (**L10**),[240] phosphinooxazoline (**L1**),[241] and many others (Scheme 45(c)).[242,243] Trost and coworkers suggest that once decorated with a ligand, the palladium-ligand complex displays a chiral pocket that imparts the catalyst with sterically differentiated approach trajectories capable of inducing asymmetry (Scheme 45(b)).[244]

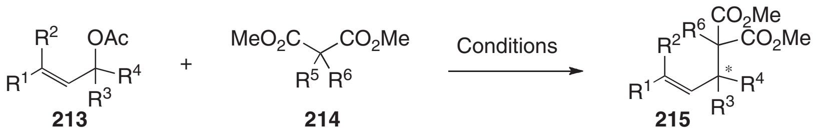


Scheme 45 Trost's asymmetric allylic alkylation of stabilized enolates.

Table 9 compares the performance of selected ligands, using the alkylation of (*E*)-allyl acetate derivatives (**213**) with dimethyl malonate derivatives (**214**) as a model reaction. Early studies demonstrated that sterics greatly influence the position of nucleophilic attack, with mono-substituted allyl fragments preferentially giving rise to linear products (entry 2).[243a] Similarly, in the case of 1,1,3-trisubstituted allyl fragments, the less hindered position of the allyl fragment is more susceptible to attack (entry 3). Hayashi and coworkers pioneered aminoalkyl ferrocene-derived diphosphines (**L5**) capable of directing allylation via pendant hydroxyl groups.[238] Allylic alkylation employing xantphos derived ligands (**L4**) proceeds in excellent yields and good to excellent enantioselectivities for allyl fragments bearing small alkyl substituents (entry 5).[245] In 1992, Trost introduced the diphenylphosphino benzoic acid (DPPBA) ligand scaffold (**L6**),[246] which is immensely successful and widely used in palladium-catalyzed allylic alkylation reactions across a range of substrate classes (Scheme 45(c)).[247] The DPPBA based ligands provide excellent enantioinduction for allyl substrates bearing small alkyl groups (entry 8). However, aromatic-substituted allyl substrates often undergo allylation with modest stereoselectivity and in poor yields (entry 7).[248] The DPPBA ligand is also highly positionally selective, favoring the branched isomer for allyl substrates bearing gem-diacetoxy substituents (entry 6).[247c] These ligand scaffolds are most compatible with allyl carbonates.

Positional control in allylation reactions has been an area of intense investigation since the conception of the field.[249] Hayashi et al. have shown that the monodentate ligands such as MeO–MOP (**L7**) preferentially give rise to branched products when starting with branched allyl acetate substrates (Table 9, entries 11 and 12).[250] Perhaps the most successful ligand scaffold disclosed toward the goal of positional control is Dai's ferrocene-derived diamine ligand (**L8**).[251] Monosubstituted alkyl or aryl linear allylic acetates undergo substitution to give the branched products in excellent yield, positional selectivity and enantioselectivity (entries

Table 9 Ligand performance in palladium-catalyzed asymmetric allylic alkylation reactions



Entry	R^1	R^2	R^3	R^4	R^5	R^6	Pd (mol%)[a]	Ligand	Solvent	Additive	Yield (%)	ee (%)	References
1	Ph	H	Ph	H	Na	H	2	**L3**	MeCN	15-C-5	95	98	243a
2	Ph	H	H	H	Na	H	2	**L3**	MeCN	15-C-5	85[b]	–	243a
3	Ph	H(Ph)[c]	Ph	Ph(H)[c]	Na	H	2	**L3**	MeCN	15-C-5	60	47	243a
4	Ph	H	Ph	H	H	H	1	**L4**	CH$_2$Cl$_2$	BSA, KOAc	100[d]	97	245
5	Me	H	Me	H	H	H	1	**L4**	CH$_2$Cl$_2$	BSA, KOAc	100[d]	68	245
6	Ph	H	OAc	H	Na	Me	5	**L6**	THF	–	92	95	247c
7[e]	Ph	H	Ph	H	H	H	2	**L6**	CH$_2$Cl$_2$	Cs$_2$CO$_3$	9	52	248
8[e]	Me	H	Me	H	H	H	2	**L6**	CH$_2$Cl$_2$	Cs$_2$CO$_3$	98	92	248
9	Ph	H	Ph	H	H	H	1	**L1**	CH$_2$Cl$_2$	BSA, KOAc	94	95	238
10[f]	Ph	H	Ph	H	Na	H	0.5	**L5**	THF	–	97	90	238
11[g]	H	H	Ph	H	Na	Me	1	**L7**	THF	–	97[i]	86	250
12[g]	H	H	An[h]	H	Na	Me	1	**L7**	THF	–	96[j]	87	250
13	Ph	H	H	H	H	H	2	**L8**	CH$_2$Cl$_2$	BSA, KOAc	98[k]	95	251
14	An[h]	H	H	H	H	H	2	**L8**	CH$_2$Cl$_2$	BSA, KOAc	97[l]	97	251
15	Me	H	H	H	H	H	2	**L8**	CH$_2$Cl$_2$	BSA, KOAc	83[m]	94	251
16	Ph	H	Ph	H	H	H	10	**L10**	CH$_2$Cl$_2$	BSA, Et$_4$NCl	85	83	240
17	Ph	H	Ph	H	Na	H	5	**L9**	THF	–	77	75	252c
18	Me	H	Me	H	Na	H	5	**L9**	THF	–	83	69	252c

[a] Pd source used {(η^3-C$_3$H$_5$)PdCl}$_2$.
[b] 100% conversion, 15% of branched isomer observed.
[c] Parenthetical entry describes product.
[d] Conversion (%).
[e] Allyl carbonate used in place of allyl acetate.
[f] Pre-formed sodium acetylacetonate ion used in place of dimethylmalonate.
[g] 2-Methyl-sodiodimethylmalonate used in place of dimethylmalonate.
[h] Anisole.
[i] 82:18 branched to linear (b/l).
[j] 90:10 (b/l).
[k] 95:5 (b/l).
[l] 93:7 (b/l).
[m] 97:3 (b/l).

13–15). Diamine ligands are competent scaffolds for allylic alkylation of stabilized enolate nucleophiles (entries 16–18); however, many of these catalysts suffer modest activity and limited stability.[252]

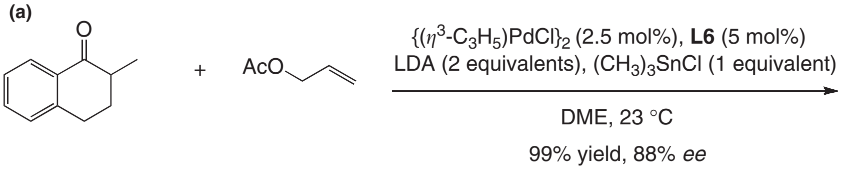
In addition to the allylic acetate and allyl carbonate derivatives described above, a host of alternative allyl fragments have been shown to serve as effective π-allyl precursors. Popular allyl partners include vinyl epoxides,[253] allylic sulfones,[254] phosphates,[255] nitro groups,[256] and halides.[257]

Azalactones,[258] α-amino esters,[259] β-ketoesters, and β-dicarbonyls,[247b] among others, are all competent nucleophiles for allylic alkylation chemistry. Such prochiral nucleophiles are useful as they offer the opportunity to set multiple stereocenters simultaneously. Furthermore, in the case of azalactones, α-amino esters, and α-amino ketones, the allylic alkylation products are valuable precursors for the construction of amino acid derivatives, both natural and unnatural.[260] α-Aryl-stabilized ketones[261] have also succumbed to asymmetric allylic alkylation with a high degree of enantioinduction.

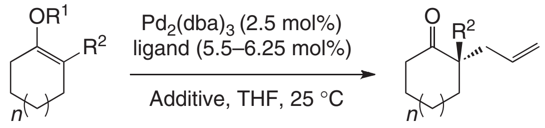
3.01.4.2.1.1.2 Nonstabilized enolates

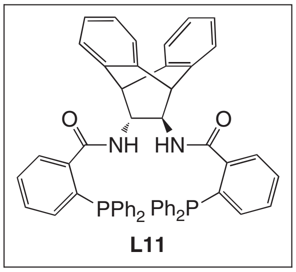
Inherent differences in the chemical properties of stabilized and nonstabilized enolates, in particular the much lower acidity of nonstabilized enolate α-protons (p$K_a = \sim 25$) relative to stabilized enolate α-protons (p$K_a = \sim 11$–15), forestalled the development of asymmetric variants of allylic alkylation methodologies put forward nearly 20 years ago. In 1999, Trost and coworkers disclosed the first example of palladium-catalyzed allylic alkylation of a nonstabilized enolate with induction of asymmetry.[11] They found the inclusion of Lewis acid additives to be critical, with chlorostannanes performing optimally (Scheme 46(a)). Although restricted to singly enolizable ketones, this report constituted a significant step in broadening the substrate scope of available allylic alkylation methodologies. In 2004, the Stoltz group disclosed an asymmetric variant of Tsuji's palladium-catalyzed decarboxylative allylic alkylation protocol,[12] employing a chiral phosphinooxazoline[262] (PHOX) ligand (**L1**). As the palladium triggered decarboxylation leads to *in situ* generation of the desired prochiral enolate, these reactions do not require strong base – a

(a)



(b)

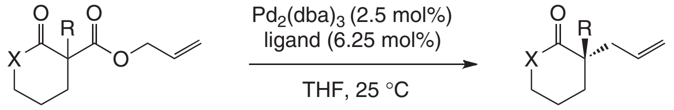


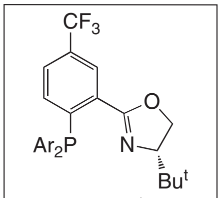


L11

Entry	*n*	R^1	R^2	Ligand	Additive	Yield (%)	*ee* (%)
1	1	$CO_2CH_2CH{=}CH_2$	Me	**L1**	–	90	89
2	1	$CO_2CH_2CH{=}CH_2$	Et	**L1**	–	96	92
3	2	$CO_2CH_2CH{=}CH_2$	Me	**L1**	–	81	87
4	1	TMS	Et	**L1**	diallyl carbonate, $Bu_4NSiF_2Ph_3$	96	92
5	1	$CO_2CH_2CH{=}CH_2$	H	**L11**	–	78	78
6	1	$CO_2CH_2CH{=}CH_2$	Me	**L11**	–	88	85

(c)

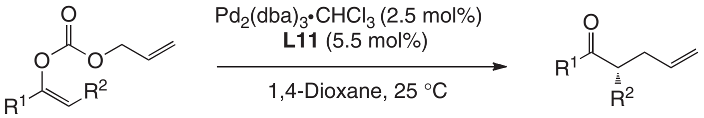




(*S*)-$(CF_3)_3$-Bu^t-PHOX
(**L12**)
Ar = 4-$CF_3C_6H_4$

Entry	X	R	Ligand	Yield (%)	*ee* (%)
1	CH_2	Me	**L1**	85	88
2	CH_2	Et	**L1**	96	92
3	CH_2	Bn	**L1**	96	85
4	NBz	Et	**L12**	92	99
5	NBz	F	**L12**	89	99
6	NBz	Bn	**L12**	85	99

(d)



Entry	R^1	R^2	Yield (%)	*ee* (%)
1	Ph	Et	94	94
2	Ph	Pr^i	30	32
3	Ph	CH_2Ph	75	88
4	Pyridyl	Me	95	73
5	2-Furyl	Me	89	88
6[a]	Mesityl	Me	99	96
7[a]	Cy	Me	94	97

[a] (*E*)-enol carbonate used in place of (*Z*)-enol carbonate.

Scheme 46 Trost's and Stoltz's asymmetric allylic alkylation of nonstabilized enolates.

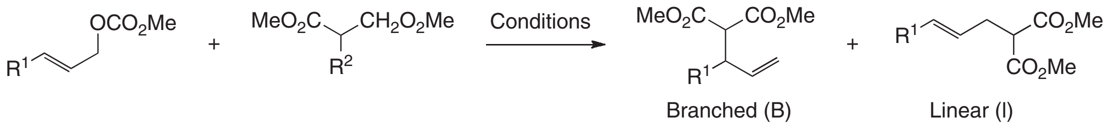
reaction component that made α'-blocking groups prerequisite in earlier methods. Asymmetric allylic alkylation of multiply enolizable nonstabilized enolates, as developed by the Stoltz group, functions equally well with a suite of substrates, including allyl enol carbonates (Scheme 46(b)), silyl enol ethers (Scheme 46(b), entry 4),[12] and allyl β-ketoesters and allyl β-carboxylactams (Scheme 46(c)).[263,264] These reactions proceed in uniformly excellent yields and good to excellent enantioselectivities for a variety of prochiral nucleophiles including heteroatoms (Scheme 46(c), entries 4–6).

Subsequent publications by Trost report similar asymmetric variants of the Tsuji protocol for both cyclic (Scheme 46(b))[265] and acyclic substrates (Scheme 46(d)).[266] Excellent acyclic substrates for palladium-catalyzed allylic alkylation include allyl enol carbonates bearing simple primary or secondary alkyl groups at position 1 (Scheme 46(d), entries 1–3). Aromatic, heteroaromatic, and alkyl groups are also well tolerated at position 1 (Scheme 46(d), entries 4–7).

3.01.4.2.1.2 Iridium-catalyzed allylic alkylation

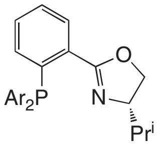
The Takeuchi group reported the first iridium-catalyzed allylic alkylation of stabilized enolates in 1997.[267] Since then, numerous reports of similar transformations, including asymmetric variants, have come to light.[268] Iridium-catalyzed allylic alkylation reactions furnish enantioselectivities similar to those reported for palladium-based systems; however, an advantage offered by iridium over the palladium variant is complementary positional selectivity.[269] Whereas palladium-based catalysts can isomerize via a η^1–η^3–η^1 equilibrium,[270] iridium-based catalysts isomerize more slowly and offer improved selectivity in favor of the branched product isomer. $\{\mathrm{Ir[cod]Cl}\}_2$ has proven to be a uniquely successful precatalyst due to the low level of catalytic activity before complexation.[271] Though a variety of ligand frameworks for iridium offer enantioinduction to an excellent degree, the two most well-studied so far have been the PHOX and phosphoramidite scaffolds (Table 10).[272] The PHOX ligands (e.g., **L13**) were among the first to be investigated in the context of iridium-catalyzed allylic alkylation and are robust ligands for aryl-substituted linear allylic acetates (entries 1 and 2).[273] However, these ligands fail to provide good enantioinduction for alkyl-substituted allyl partners. Phosphoramidite-ligated iridium catalyzes allylic alkylations of nonsymmetrical allyl groups with malonate-derived nucleophiles in excellent yields and with exquisite levels of positional- and enantioselectivity. Helmchen et al. have shown that phosphoramidite ligand **L14** provides excellent enantioinduction for reactions involving both aryl (entry 3) as well as alkyl-substituted allylic acetates (entries 4 and 5).[272a] Additional examples of both phosphoramidite and DIAPHOX (**L16**, entry 7)[272d] ligands in iridium-catalyzed allylic alkylation are given in Table 10. Salt-free reaction conditions, recently disclosed by Helmchen, eliminate difficulties with scale-up and catalyst stability to base over prolonged periods of time, which previously limited the generality of these reactions.[274]

Table 10 Ligand performance in iridum-catalyzed asymmetric allylic alkylation reactions

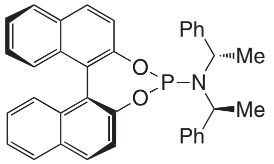


Entry	*R*^{1}	*R*^{2}	*Base*	*Ir*[a] *(mol%)*	*Ligand*	*Solvent*	*Additive*	*b:l*	*Yield (%)*[b]	*ee (%)*	*References*
1	Ph	Na	–	2	**L13**	THF	–	95:5	99	91	273
2	An[c]	Na	–	2	**L13**	THF	–	99:1	98	95	273
3	Ph	Na	TBD	4	**L14**	THF	THT[d], CuI	99:1	88	96	272a
4	CH_2Bn	Na	TBD	4	**L14**	THF	THT, CuI	81:19	92	96	272a
5	$CH_2OTBDPS$	Na	TBD	4	**L14**	THF	THT, CuI	88:12	88	97	272a
6	Ph	Na	–	4	**L15**	THF	LiCl	99:1	82	98	272c
7	Ph	H	BSA	5	**L16**	CH_2CL_2	LiOAc, $NaPF_6$	99:1	92	90	272d
8	Ph	H	Bu^nLi	10	**L17**	THF	$ZnCl_2$	93:7	99	96	272b

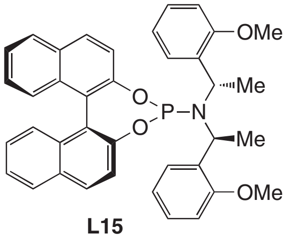
[a] $\{\mathrm{Ir(cod)Cl}\}_2$.
[b] Combined branched/linear.
[c] An = anisole.
[d] THT = tetrahydrothiophene.



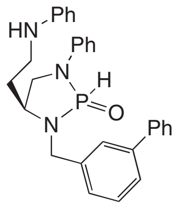
L13
Ar = 4-$CF_3C_6H_4$



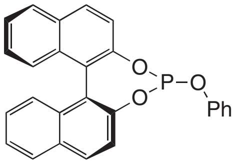
L14



L15



L16

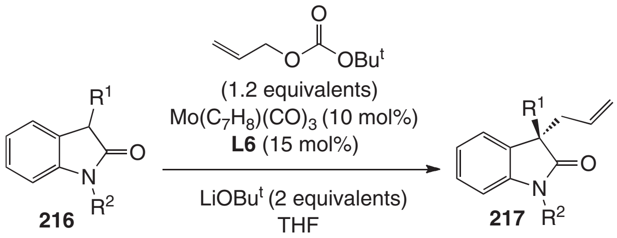


L17

3.01.4.2.1.3 Other transition metal catalyzed allylic alkylation

Recently, molybdenum-catalyzed asymmetric allylic alkylations of stabilized enolates have been developed[275] as a powerful strategy for the stereoselective construction of C–C bonds. Similar to iridium-catalyzed allylic alkylation reactions, molybdenum-catalyzed reactions complement the relatively more developed palladium variants by providing access to branched allylation products.[276] Molybdenum catalysts exhibit high levels of positional selectivity as well as enantioselectivity.[277] In addition to alkylation of linear allyl carbonates with malonate derivatives, molybdenum catalysts have been shown to alkylate 3-alkyloxindole nucleophiles (**216**) to generate 3-quaternary oxindoles (**217**), an important motif ubiquitous in natural products (**Table 11**).[278]

Table 11 Molybdenum-catalyzed allylic alkylation with oxindole nucleophiles



Entry	*R^1*	*R^2*	*Yield (%)*	*ee (%)*
1	Me	Me	99	81
2	Bn	Me	95	93
3	Bn	MOM	95	87
4	Pr^i	Me	96	91
5	CH_2CN	Me	99	93
6	CH_2CH_2OTBS	Me	94	75

The allylic alkylation chemistry of tungsten has been investigated largely in parallel to that of molybdenum.[279] Although similar patterns of product distribution are observed, preliminary results indicate that tungsten based catalysts are less reactive relative to other transition metals.[280,281]

3.01.4.2.2 Other transition metal catalyzed asymmetric α-alkylations

3.01.4.2.2.1 Copper-catalyzed amide α-alkylation

Although copper-catalyzed allylic alkylations have been extensively investigated over the past several decades,[282] the great majority of these investigations have been in the context of harder, nonstabilized nucleophiles (such as organometallics). Although not an allylic alkylation, a notable example of alkylation of stabilized enolate nucleophiles with prochiral 3-alkyl-3-halooxindole electrophiles under copper catalysis was reported by Stoltz and coworkers.[283] In this methodology, bisoxazoline-ligated copper catalyzes the coupling of a 3-halooxindole (**218**) electrophilic partner with a malonate ion nucleophile (**Table 12**). A variety of substitution patterns are tolerated at the C3-position, including various heteroatoms, and the reaction proceeds in moderate to good yields with good to excellent enantioselectivities.

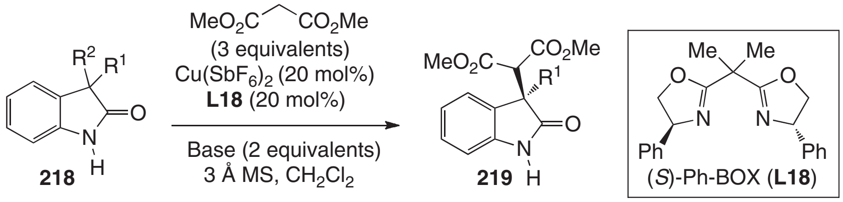
3.01.4.2.2.2 Nickel-catalyzed amide α-alkylation

As nickel-bound π-allyl groups are excellent electrophiles for attack by hard, nonstabilized nucleophiles,[284] it follows that the majority of the chemistry described to date in this category deals with relatively hard nucleophiles, such as Grignard reagents,[285] borates,[286] and boronic acids.[287] Fu and Fischer have developed a protocol for Negishi-type sp^3–sp^3 cross coupling of organozinc nucleophiles with nickel enolate electrophiles.[288] In this methodology, nickel enolates are generated from secondary α-bromo amide compounds (**220**). The coupling proceeds with excellent yields and enantioselectivities and tolerates primary and secondary alkyl, ethereal, and cyanide containing nucleophiles (**Table 13**).

3.01.4.2.2.3 Chromium-based alkylations

Jacobsen and Doyle have identified a novel methodology that allows access to α-quaternary ketones in excellent enantioselectivities and good to excellent yields.[13] Utilizing a chiral Cr(salen) catalyst (**Cr-L20**), this method couples preformed cyclic tin enolate nucleophiles with a range of sp^3-hybridized S$_N$2 active electrophiles (**Table 14**). The observation that tin enolates isomerize between *E*- and *Z*-enol stannanes via the C-stannyl tautomer led Jacobsen and Doyle to hypothesize a dynamic process in which the more reactive isomer would be preferentially alkylated.[289] Indeed, a silylanol derivative of their previously employed

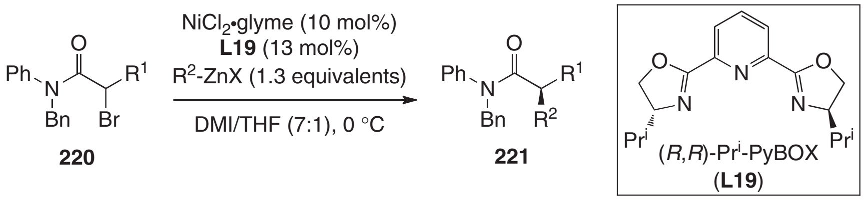
Table 12 Copper-catalyzed alkylation of halooxindole electrophiles



Entry	R¹	R²	Base	Yield (%)	ee (%)
1	CH_2CH_2OTIPS	Br	Pr^iEt_2N	77	88
2	Bu^n	Br	Pr^iEt_2N	44	84
3	$CH_2CH_2C_8H_4NO_2$[a]	Br	Pr^iEt_2N	63	94
4	$CH_2CH_2OTBDPS$	Br	Pr^iEt_2N	78	88
5	Ph	Cl	Et_3N	76	−76
6	4-Br-C_6H_4	Cl	Et_3N	84	81

[a] Phthalimide.

Table 13 Nickel-catalyzed alkylation of α-bromo amides



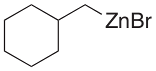
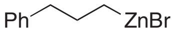
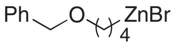
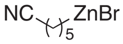
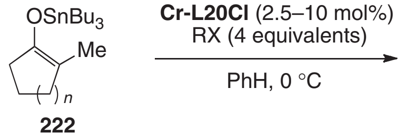
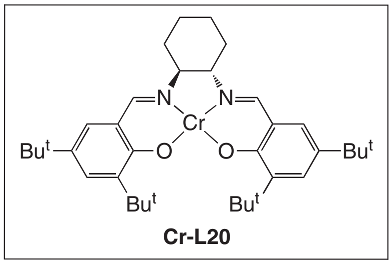
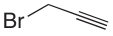
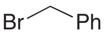
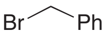
Entry	R¹	R²-ZnX	Yield (%)	ee (%)
1	Et	Hex^n–ZnBr	90	96
2	Et	 ZnBr	58	92
3	Bu^n	 Ph ZnBr	79	96
4	Et	 Ph O ZnBr 4	77	96
5	Et	 NC ZnBr 5	70	93

Table 14 Chromium-catalyzed alkylation of cyclic enol stannanes

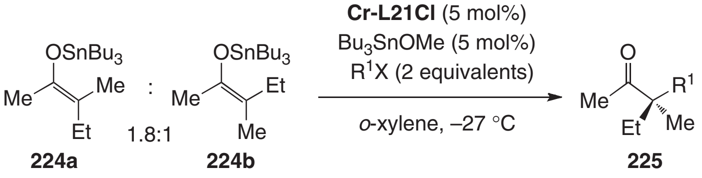




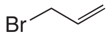
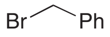
Entry	n	RX	Yield (%)	ee (%)
1	1	 Br	81	96
2	1	 I CO₂Et	73	96
3	1	 Br Ph	91	93
4	2	 I CO₂Et	67	95
5	2	 Br Ph	80	85

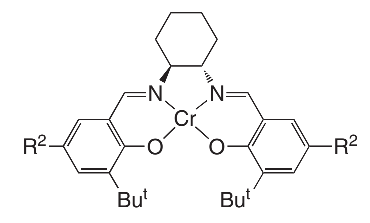
ligand combined with a chromium catalyst, a similar range of electrophiles, and a thermodynamic mixture of *E*- and *Z*-tin enolates furnished acyclic α-quaternary ketones products in good yields and enantioselectivities (Table 15).

Table 15 Chromium-catalyzed alkylation of acyclic enol stannanes



224a **224b** **225**

Entry	*R¹X*	*Yield (%)*	*ee (%)*
1		80	79
2		73	76
3		86	81



Cr-L21

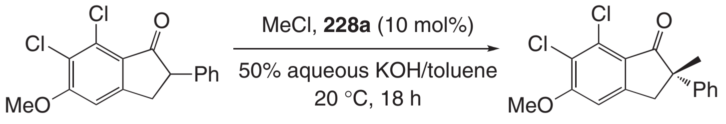
$R^2 = –OSiThMe_2$, Th = Thexyl

3.01.5 Miscellaneous

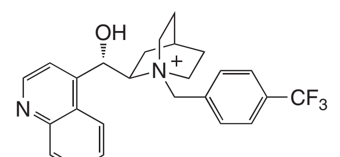
Several significant methods for enolate functionalization do not fit well into previous sections and are consequently covered here. These alternatives address specific challenges in alkylation methodology. For example, phase transfer catalysis was developed for asymmetric synthesis of α-amino acid derivatives.[290] Organic superbases offer milder conditions for base-sensitive enolates that cannot be reliably deprotonated by conventional means.[291] Radical and Lewis acid-mediated alkylations extend electrophile scope to normally unreactive 2° and 3° alkyl halides substrates.[104a,292]

3.01.5.1 Phase Transfer Catalysis

Since the technique was first introduced,[293] asymmetric phase transfer catalysis has provided a reliable avenue for the stereoselective alkylation of enolates, especially in the construction of natural and unnatural α-amino acids.[294] In 1984, the Merck group demonstrated that indanone **226** could be stereoselectively methylated under phase transfer conditions using 10 mol% N-((4-trifluoromethyl)-benzyl)cinchodinium bromide (**228a**) in 95% yield and 92% *ee* (equation 15).[295] Today, elaboration of this seminal work has enabled facile asymmetric alkylations with scalable procedures, mild conditions, and inexpensive, safe reagents.[296]



226 **227**



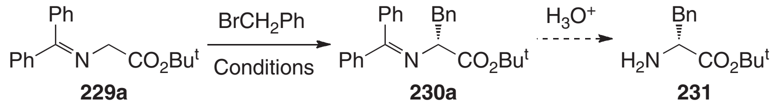
228a

(15)

Phase transfer catalysis occurs between an organic phase and an alkali aqueous phase. Deprotonation of the substrate at the phase interface generates an enolate and, on association with a cationic phase transfer catalyst (PTC), the produced anion is extracted into the organic phase for alkylation.[297] Typically, base is introduced as a concentrated aqueous NaOH or KOH solution, and popular organic solvents are toluene, methylene chloride, chloroform, or mixtures thereof. Under these conditions, a chiral PTC can exert strong stereocontrol through the close association of the generated contact ion-pair in nonpolar media. Such is the scope of the literature committed to the mechanism, catalyst design, and synthetic utility that comprehensive coverage is not possible in this document.[298]

Asymmetric phase transfer alkylation has made its greatest contributions to peptide synthesis. In 1989, O'Donnell introduced acetophenone Schiff base derivatives of glycinate esters (**229**) as peptide precursors (Table 16). These substrates can be asymmetrically alkylated with cinchonidine-derived quaternary ammonium salts, and may subsequently be acid hydrolyzed to generate the desired peptide ester (**231**). O'Donnell showed that the system tolerated a variety of electrophiles, giving decent yields and

Table 16 Alkylation of Schiff base **229a**[295a,e]



Entry	*PTC*	*Conditions*[a]	*Product*	*Yield (%)*	*ee (%)*
1	**228b**	A	(*S*)-**230a**	84	94
2	**228c**	B	(*S*)-**230a**	93	94
3	**232**	C	(*R*)-**230a**	90	99
4	**233**	D	(*R*)-**230a**	55	90
5	**234**	E	(*R*)-**230a**	>95	95

[a] Conditions: (A) **228a** (10 mol%), CsOH, H_2O, CH_2Cl_2, −78 °C, 23 h; (B) **228c** (5 mol%), 50% CsOH (aqueous), PhMe:CH_2Cl_2 (7:3), 0 °C; (C) **232** (1 mol%), 50% KOH (aqueous), PhMe, 0 °C; (D) **233** (30 mol%), 1 M KOH (aqueous), CH_2Cl_2, 0 °C; (E) **234** (20 mol%), 50% KOH (aqueous), CH_2Cl_2, 0 °C.

enantioselectivities in the sixties.[294d] Modern PTCs (Figure 5) developed in the past decade improve on this work, and can afford exceptional stereoselectivity in enolate alkylations with low catalyst loadings (Table 16).[294e]

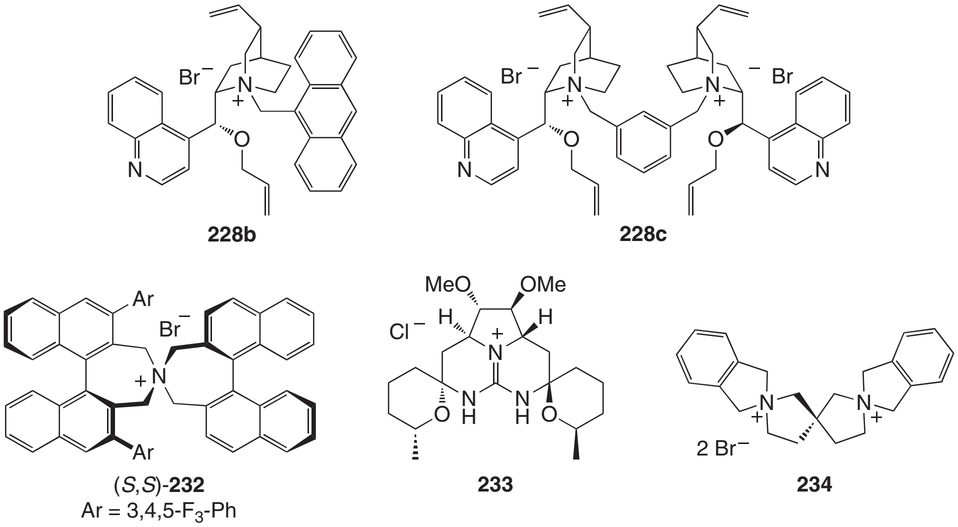
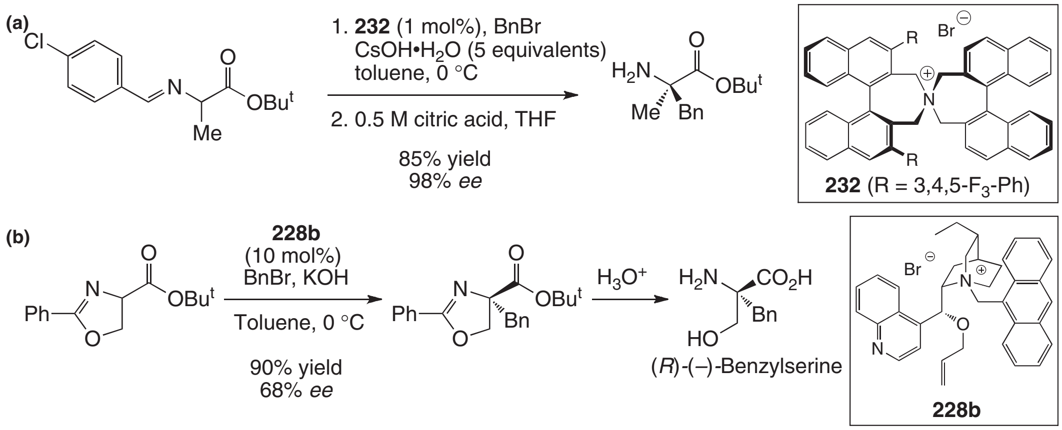


Figure 5 Chiral phase transfer catalysts.

Quaternary ammonium salts are the preferred PTCs for enolate alkylations. Most prolific among them are the *N*-alkyl-O-alkyl ammonium salts of *Cinchona* alkaloids (**228**, Figure 5).[294a,e] Although the first generation of chiral PTCs (e.g., **228a**) lacked O-substituents, studies by Corey,[299] Cahard and Plaquevent,[300] Lygo,[301] and others state that O-alkylation increased catalyst stability under the reaction conditions.[294d,302] Combined with an increase in the bulk of *N*-benzyl substitutions, these modifications augmented enantioselectivities and produced the 'second-generation PTCs' (e.g., **228b**, Figure 5). In the past decade, further optimization has yielded tethered *bis*-dihydrocinchonidinium species (**228c**), which afford enantiomeric excesses in the high nineties (Table 16, entry 2).[303] Other structural motifs based on the atropoisomeric binaphthyl-backbone (**232**),[304] tartrate salts (**233**),[305] and fused spirocycles (**234**)[306] have also enjoyed recent success, though lengthy syntheses diminish their utility.

Over the past 20 years, improvements in catalyst design have enabled the enantioselective synthesis of fully substituted stereocenters and broadened substrate scope. Introduced by Maruoka in 1999, binapthol-derived, spiro ammonium PTCs ((*S*,*S*)-**232**) give exceptional *ee*'s in the one-pot, asymmetric double alkylation of almidine Schiff bases (Scheme 47(a)).[307] These binapthyl ammonium salts also afford enantioselectivities up to 92% *ee* in the benzylation of cyclic *β*-ketoesters.[304,308] Jew and Park employed catalyst **228b** in their synthesis of optically active α-alkyl serines and cysteines via functionalization of 2-phenyl-oxazolines and -thiazolines (Scheme 47(b)).[296]

Phase transfer catalysis is one of the few dependable methods for the direct, asymmetric, organocatalytic α-functionalization of enolates. PTCs enable the installation of nearly enantiopure tertiary and quaternary stereocenters using inexpensive materials and low catalyst loadings. These qualities offer phase transfer catalysis an environmentally benign alternative to transition metals in enantioselective catalysis.

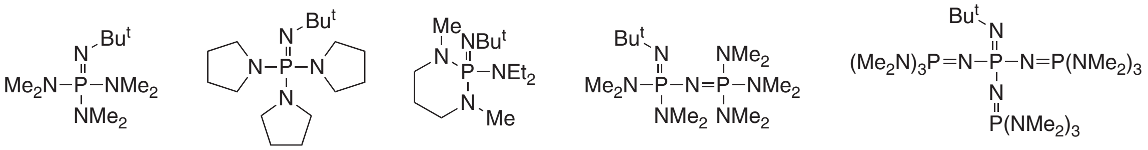


Scheme 47 Synthesis of fully substituted stereocenters by phase transfer catalysis.

Drawbacks to phase transfer enolate alkylation include the lack of regiocontrol in enolate generation and a strong rate dependence on the speed of stirring, which can limit scale. Additionally, substrate scope has not significantly extended beyond peptide precursors. Finally, since root asymmetric induction and suppression of background racemization often benefit from catalyst bulk, PTCs are generally massive and therefore undesirable in some industrial processes.

3.01.5.2 Phosphazene Superbase-Promoted Alkylations

The discovery of phosphorus/nitrogen containing organic superbases by Schwesinger, Verkade, and others in the 1980s has led to the development of alternative, neutral reagents for the generation of enolates.[309] Monomeric and oligomeric iminophosphoranes (i.e., the phosphazene superbases, **235–239**, Figure 6) exhibit a high proton affinity stemming from nearly complete charge delocalization in their corresponding phosphazenium conjugate acids. These protonated species form weak ion pairs and produce reactive 'naked' enolates under appropriate conditions.[310] Phosphazenes are organic soluble and can offer a milder, more selective alternative to canonical metal-amide bases.[310,311]



Name	P1-Bu^t (**235**)	BTPP (**236**)	BEMP (**237**)	P2-Bu^t (**238**)	P4-Bu^t (**239**)
rel. pK$_{BH}$ (MeCN)	26.9	26.98	27.63	33.49	42.7

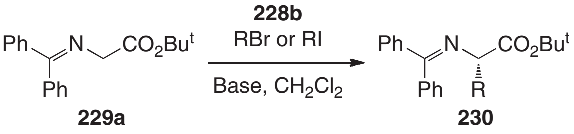
Figure 6 Phosphazene superbases.

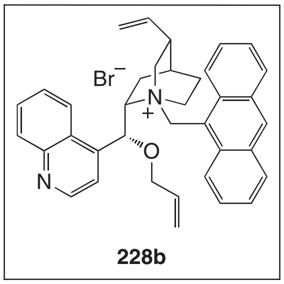
O'Donnell and Schwesinger have shown that monomeric iminophosphoranes, such as BEMP (**235**) and BTPP (**236**), promote alkylations of glycine Schiff bases in the presence of PTC (**228b**, Table 17). Under homogeneous conditions, this system affords unnatural α-amino acid precursors in high yields (87–96%) and enantioselectivities (84–97% *ee*) comparable to phase transfer conditions for a variety of electrophiles.[312]

The tetrameric P4-iminophosphoranes (i.e., **239**) are exceptionally strong, nonionic bases, but extensive conjugation attenuates nucleophilicity and the Lewis acidity of P4-phosphazenium conjugates. Side reactions common with ionic bases are frequently not observed with P4-bases. P4-Bu^t benzylation of substituted dioxanone **240** proceeds well, whereas use of LDA leads only to decomposition (Scheme 48).[310] Effective in both mono-alkylation and polyalkylation reactions, P4-phosphazenium enolates achieve high diastereoselectivities (83% *de*) in the presence of enriched stereocenters.[311]

Organic superbase-promoted alkylations remain relatively esoteric despite several decades of development. Their utility has suffered from a dearth of methods, availability, and general obscurity. However, the mild reactivity profile, ease of handling, and high regiochemical fidelity make superbases excellent alternatives to lithium bases in some cases.

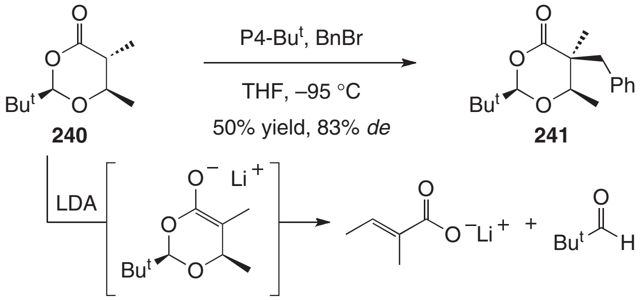
Table 17 Alkylation of Schiff base **229a**





Entry	*R*	*Base*	*Yield (%)*	*ee (%)*
1	Me	BEMP^a	92	94
2	Bu^n	BTPP^b	88	91
3	Bn	BEMP^a	88	91
4	isoprenyl	BEMP^a	91	94

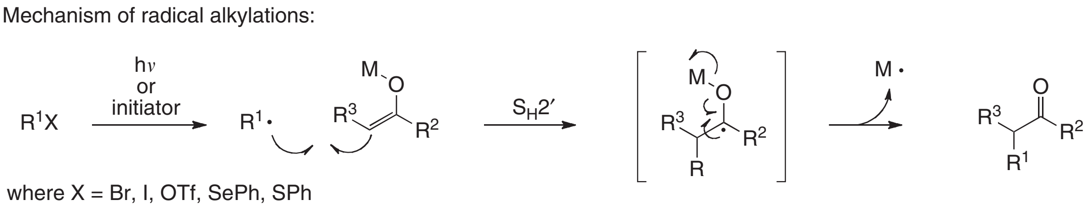
^{a}Run at –78 °C.
^{b}Run at –50 °C.



Scheme 48 P4-Bu^t benzylation of dioxanone 240.

3.01.5.3 Radical Alkylations

Substitutions on sterically encumbered, polyhalogenated, and carbonyl containing substrates are often low yielding under strongly basic alkylating conditions. However, radical conditions can promote efficient couplings between otherwise poor electrophiles and silicon, zinc, titanium, or tin enolates via a homolytic substitution (S_H2') pathway (**Scheme 49**).[313] Leaving groups for these substitutions include not just halides and pseudohalides, but phenylseleno- and phenylthioethers as well. Radical alkylations are most successful with amide, ester, alkylphenone, and cyclic ketone derived enolates.[314]



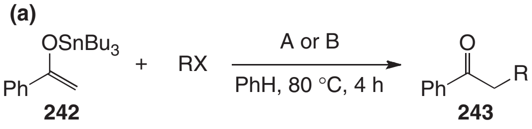
Scheme 49 Radical alkylation via S_H2' pathway.

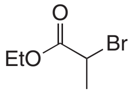
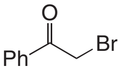
Like allyl stannanes, stannyl enolates are effective radical-alkylating agents. Tin enolates couple particularly well with the electron-deficient radicals generated from photostimulation of α-phenylseleno or α-halocarbonyl species to form 1,4-dicarbonyl compounds.[315] Hosomi and coworkers have more recently extended this methodology to chemical initiators like AIBN or triethylborane (BEt_3). This system showed success in the introduction of bulky Bu^t and Pr^i substitutions to acetophenone-derived silyl enol ethers (**Table 18(a)**).[313a] The Kim group has shown that silyl and phosphonate N,O-acetals (**244**) undergo similar alkylations using either catalytic tin or tin-free conditions, reducing reliance on toxic organostannanes (**Table 18(b)**).[316]

Although polyhaloalkyl substitutions have important pharmaceutical and materials properties, their corresponding electrophiles frequently decompose by elimination in the presence of metal amide bases.[317,318] Historically, radical perfluoroalkylations of silicon, germanium, and tin enolates have addressed this problem.[313b,d,319] More recently, titanium and zinc metal enolates prepared *in situ* have proven to be higher yielding and more broadly applicable.[317,322]

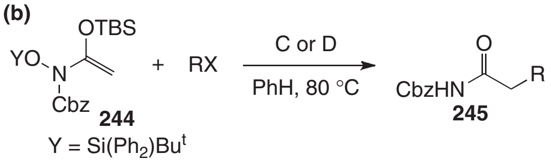
Although there are few examples of catalytic, asymmetric perhaloalkylations, radical substitutions are strongly influenced by existing stereocenters. Diastereoselective, triethylborane-mediated, radical trifluoromethylations using the lithium enolates of

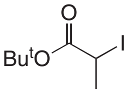
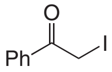
Table 18 Examples of radical alkylation



Entry	RX	Conditions[a]	Yield (%)
1	Pr^i-I	A B	61 97
2	Pr^i-I	A B	65 99
3		A	95
4		A	85

[a]Conditions: A) **242** (1 mmol), RX (0.5 mmol), AIBN (2.5 mol%). B) **242** (2 mmol), AIBN (5 mol%).

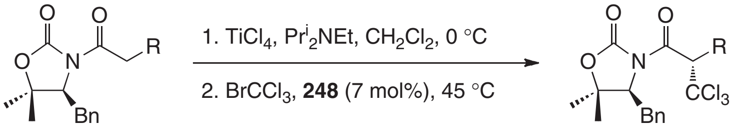


Entry	RX	Conditions[a]	Yield (%)
1	Ad-I	D	47
2	Cy-I	D	56
3		C	84
4		C	71

[a]Conditions: C) AIBN (10 mol%), 6 h. D) $(Me_3Sn)_2$ (30 mol%), 300 nm, 8 h.

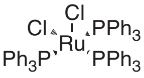
chiral imides were developed in the mid-nineties.[320] Zakarian and coworkers later exploited the biradical character of titanium enolates in the trichloromethylation of *N*-acyl oxazolidinones using a $(PPh_3)_3RuCl_2$ initiator **248** (Table 19).[321] This approach was both selective and high yielding in the synthesis of enriched **247a**, which was advanced to intermediates **249** and **250** in a convergent synthesis of the trichloroleucine derived marine natural product, neodysidenin (Scheme 50).[322]

Table 19 Radical alkylation of oxazolidinones

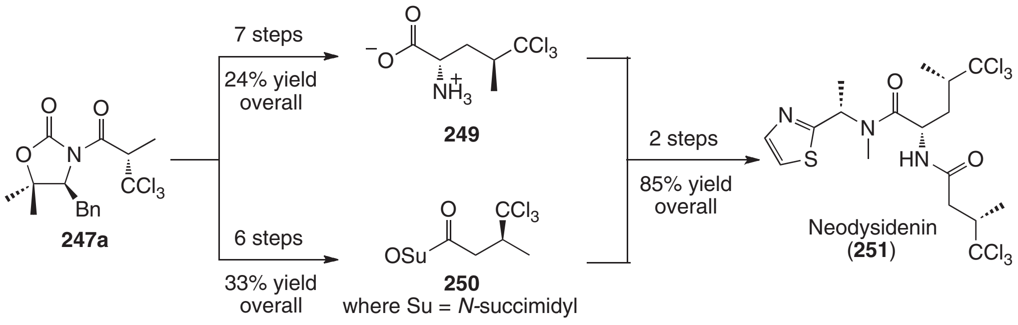


246a–d **247a–d**

Entry	R	Product	Yield (%)	dr
1	Me	**247a**	95	>98:2
2	Bu^n	**247b**	99	>98:2
3	Ph	**247c**	91	>98:2
4	3′-(*N*-tosyl-indolyl)	**247d**	61	>98:2



248



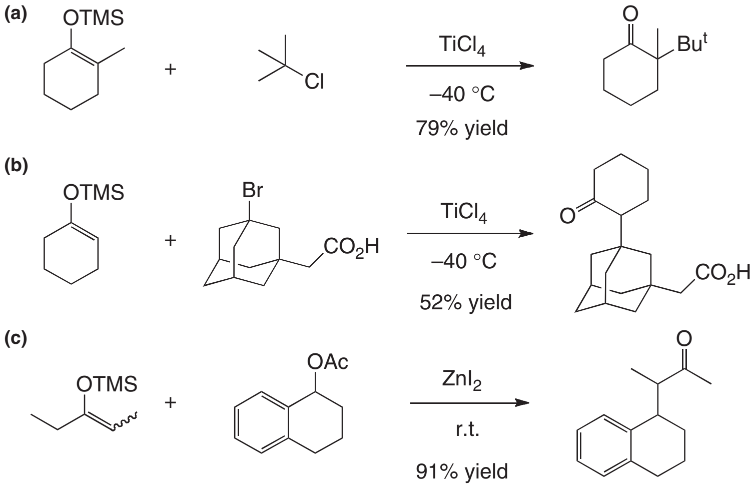
Scheme 50 Radical alkylation product in the synthesis of neodysidenin.

Radical mediated alkylation cascades can offer chemists a rapid path to complex α-functionalization, but do not strictly qualify as enolate alkylation under our definition and will not be covered here.[323]

The versatility and strength of radical alkylations are balanced by substrate-dependent yields. Methods are less successful with linear, aliphatic ketones or with tetrasubstituted enolates. However, they offer a powerful, alternative approach to alkylation that appears ripe for future development.

3.01.5.4 Lewis Acid Mediated Alkylations

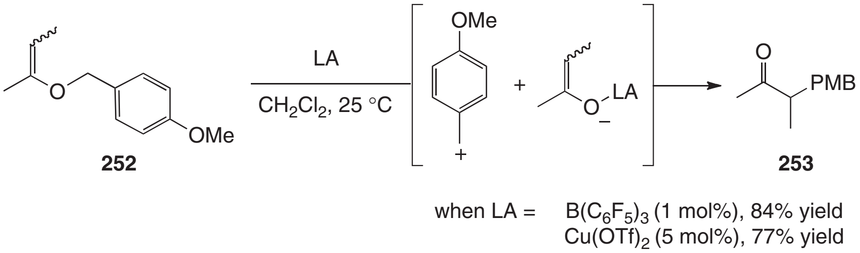
Another strategy for substitution of S_N2 inactive electrophiles is Lewis acid-mediated enolate alkylation. Although true Lewis acid alkylations proceed through an S_N1 pathway, often radical processes cannot be ruled out (Scheme 51).[104b]



Scheme 51 Lewis acid-mediated alkylations.

Reetz and coworkers have demonstrated the Lewis acid-promoted addition of enol silanes to highly substituted alkyl halides.[10] Enol silanes and silyl ketene acetals (both cyclic and acyclic) combine rapidly and regioselectively with tertiary alkyl halides in dichloromethane. The strong acid titanium(IV) tetrachloride ($TiCl_4$) and weaker species such as tin(IV) tetrachloride ($SnCl_4$) or zinc(II) halides efficiently mediated *tert*-butylations, 1-adamantylations, and similar *tert*-alkylations in good yields (Scheme 51(a and b)). Whereas unactivated secondary halides are largely inert, allyl and aryl-activated substrates react smoothly. Further, alkylations of secondary benzylic acetates (Scheme 51(c)) can be achieved in high yields (91%) at room temperature. An attractive feature of this chemistry is a broad functional group tolerance. Even tertiary chlorides bearing distal primary alkylbromide functionality yield products without loss of chemoselectivity.[10]

More recently, Gansäuer et al. disclosed an ingenious system for Lewis acid-catalyzed S_N1 alkylations.[324] Aliphatic or benzylic enol ethers (**252**) are cleaved in the presence of strong acids to provide both a metal enolate and a carbocationic electrophile, which then recombine as the α-benzylated product (**253**, equation 16). The reaction proceeds with low loadings of $Cu(OTf)_2$ or boron-based Lewis acids to give good yields for the handful of substrates examined. Despite the elegance of this regime, further investigations into substrate scope are needed.



252 **253** (16)

3.01.6 Conclusion

As can be determined from the pages and examples outlined above, the area of enolate and enol alkylation is one rich with both intellectual and practical appeal. Although it is truly impossible to be comprehensive, attempt has been made to provide the reader with a thorough overview of the field with an emphasis on major developments since the previous iteration of this treatise.

The advances of the recent past notwithstanding, there are undoubtedly still many advances yet to be discovered. Future chapters dealing with this topic are likely to be equally rife with new chemistry as can be seen in the current version. For those who are fortunate to perform research in this area, it will be interesting and amazing to witness the dazzling progress of the next 20 years and beyond. For those who are sophisticated users of the methods described herein, the discoveries of the future will continue to make the impossible seem more feasible and attainable.

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3.02 Organolithium Compounds Bearing a Phenyl-, a Vinyl-, and/or a Seleno Group on their Carbanionic Centers: Synthesis by Se/Li Exchange and Unusual Synthetic Applications

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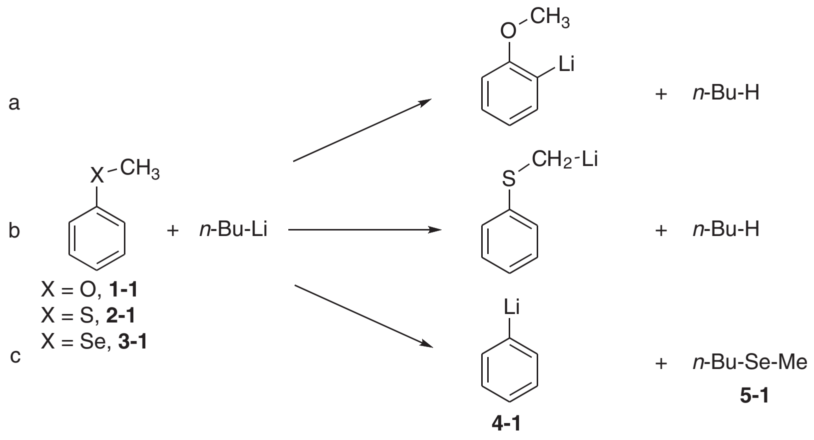
3.02.1 Generalities 57
3.02.2 Reactivity of Selenides and Functionalized Selenides toward Organolithiums 58
3.02.2.1 Reactivity of Selenides toward Organolithiums 58
3.02.2.2 Reactivity of Functionalized Alkyl Selenides toward Organolithiums 61
3.02.2.2.1 Synthesis of allyllithiums from allyl selenides 61
3.02.2.2.2 Synthesis of benzyllithiums from benzyl selenides 63
3.02.2.2.2.1 Reactivity of benzyl selenides 63
3.02.2.2.2.2 Insight on the configurational stability of benzyllithiums 67
3.02.2.2.3 Reactivity of organolithiums toward α-heterosubstituted selenides in which the heteroatoms do not belong to a cycle 70
3.02.2.2.3.1 Synthesis of α-alkoxy-alkyllithiums from α-alkoxyselenides (O,Se acetals) 70
3.02.2.2.3.2 Synthesis of α-thioalkyllithiums from α-thio-selenides (S,Se acetals) 71
3.02.2.2.3.3 Synthesis of α-selenoalkyllithiums from α-seleno-selenides (Se,Se acetals) 72
3.02.2.2.4 Reactivity of organolithiums toward α-heterosubstituted selenides in which two heteroatoms are part of a cycle 76
3.02.2.2.4.1 Reactions of organolithiums with Se,Se acetals 76
3.02.2.2.4.2 Reactions of organolithiums with O,Se acetals 80
3.02.2.2.4.3 Reactions of organolithiums with seleno-orthoesters 81
3.02.2.2.5 On the mechanism of the Se/Li exchange involving organolithiums 82
3.02.2.2.6 Selenoacetal structure–reactivity relationships 83
3.02.2.2.7 Reactivity couple butyllithium-solvent towards selenoacetals 83
3.02.3 Reactivity of Selenides and Functionalized Selenides toward Elemental Lithium and Metal Arenides 83
3.02.3.1 Reactivity of Selenides toward Elemental Lithium and Metal Arenides 84
3.02.3.1.1 Reactivity of alkyl-methylselenides toward lithium and lithium arenides 85
3.02.3.1.2 Reactivity of diarylselenides toward lithium and lithium arenides 85
3.02.3.1.3 Reactivity of alkyl-aryl selenides toward lithium and lithium arenides 85
3.02.3.2 Reactivity of Selenoacetals toward Lithium and Lithium Arenides 89
3.02.4 Reactivity of Benzyllithiums: Exceptional Family of Organometallics 90
3.02.4.1 Access to Benzyllithiums: An Overview 90
3.02.4.2 Physical Properties of Benzyllithiums 91
3.02.4.3 Reactivity of Benzyllthiums 91
3.02.4.3.1 Reactivity of benzyllthiums toward carbonyls and α,β-unsaturated carbonyl compounds 91
3.02.4.3.2 Reactivity of benzyllithiums toward alkyl-, benzyl-, and allyl-halides 93
3.02.4.3.3 Reactivity of benzyllithiums toward heterocyclic compounds 94
3.02.4.3.4 Reactivity of benzyllithiums toward carbon–carbon double bonds of alkenes and heterosubstituted alkenes 97
3.02.4.4 Syntheses of Aryl Alkanes Involving the Di-alkylation of the Carbonyl Group of Aromatic Aldehydes and Ketones and Aryl-alkylation of the Carbonyl Group of Aliphatic Aldehydes and Ketones 98
3.02.4.4.1 Syntheses producing noncyclic aryl alkanes 98
3.02.4.4.1.1 Syntheses involving aliphatic carbonyl compounds and aromatic organometallics 98
3.02.4.4.1.2 Syntheses involving aromatic carbonyl compounds and aliphatic or aromatic organometallics 100
3.02.4.4.1.3 Syntheses involving aromatic carbonyl compounds and aryl selenoacetals 100
3.02.4.4.1.4 Selection of the best reagents and methods for the synthesis of aryl alkanes from carbonyl compounds 101
3.02.4.4.1.4.1 Syntheses of aryl selenoacetals and benzyl selenides 101
3.02.4.4.1.4.2 Syntheses of α-selenobenzyllithiums 101
3.02.4.4.1.4.3 Synthesis of α-metallo selenoacetals and of α-metallo-benzyl selenides by H/Li exchange 102
3.02.4.4.2 Synthesis of arylcycloalkanes by di-alkylation of the carbonyl group of aromatic aldehydes and ketones 102
3.02.4.4.2.1 Synthesis of aryl cyclopentanes and aryl cyclohexanes involving dihalogenoalkanes and sulfonates 102
3.02.4.4.2.2 Synthesis of arylcyclopropanes involving dihalogenoalkanes 104
3.02.4.4.2.3 Synthesis of arylcyclopropanes involving epoxides 104
3.02.4.4.2.4 Synthesis of arylcyclopropanes involving carbon–carbon double bonds 108
3.02.4.4.2.5 Synthesis of aryl cyclopentanes and cyclohexanes involving carbon–carbon double bonds 108
3.02.4.4.2.5.1 Synthesis of aryl cyclopentanes and cyclohexanes involving methylene terminated carbon–carbon double bonds 108

3.02.4.4.2.5.1.1 Scope and limitations 108
3.02.4.4.2.5.1.2 Substitution at the benzylic carbon 113
3.02.4.4.2.5.1.3 Length of the alkenyl side chain 116
3.02.4.4.2.5.1.4 Substitution on the carbon–carbon double bond 116
3.02.4.4.2.5.1.5 The nature of the aromatic ring 118
3.02.4.4.2.5.2 Synthesis of aryl-aryl cycloalkanes involving carbon–carbon double bonds substituted by a phenyl or a thiophenyl group 121
3.02.4.4.2.5.2.1 Synthesis of aryl-aryl cycloalkanes involving carbon–carbon double bonds substituted by a phenyl 121
3.02.4.4.2.5.2.2 Synthesis of aryl cycloalkanes involving carbon–carbon double bonds substituted by a thioorganyl or a tetraorganylsilyl group 125
3.02.4.4.2.5.2.3 Reaction of ω-alkenyl benzyl selenides bearing a phenyl or a thiophenyl group in the ω position on the vinylic carbon 126
3.02.4.4.2.5.2.4 Stereochemistry at the exocyclic carbon resulting from carbocyclization reactions 127
3.02.4.4.2.5.2.5 Isomerization of ω-alkenyl benzylselenides involving a carbocyclization reaction 130
3.02.4.4.2.5.2.6 Beyond and about the mechanism of the carbocyclization involving unsaturated benzyllithiums 132
3.02.4.4.2.5.3 Synthesis of alkylidene cyclopentanes involving carbon–carbon triple bonds 135
3.02.4.4.2.5.4 Synthesis of vinyl cyclopentanes involving allyl ethers and related reactions involving propargyl ethers 135
3.02.4.4.2.6 Enantioselective syntheses of 1-phenyl-2-alkyl and 1-phenyl-2-alkenyl cyclopentanes 137
3.02.4.4.2.7 Syntheses of 1-ethyl-2-phenyl cyclopentanes as model for the synthesis of 1-alkyl-2-aryl cyclopentanes 142
3.02.4.4.2.7.1 Syntheses of 1-ethyl-2-phenyl cyclopentanes by methylation of (2-methyl-2-phenylcyclopentyl)methyllithium 143
3.02.5 Conclusion 147
References 153

3.02.1 Generalities

The selenium atom when present in organic molecules confers exceptional properties related to its membership with the chalcogen family and to the fourth row elements of the periodic table of elements.[1,2] Thus the reactivity of divalent selenium is expected to take advantage of the presence of highly polarizable lone pairs and of low lying unoccupied 4d orbitals which are prone to produce hypervalent intermediates or compounds such as onium salts and ate complexes. Thus, though a related type of reactivity is expected between ethers, sulfides, and selenides, and all members of the chalcogen family, some differences can be perceived. This is effectively the case with methyl phenyl ether **1-1**, methyl phenyl sulfide **2-1,** and methyl phenyl selenide **3-1** when reacted with *n*-butyllithium in tetrahydrofurane (THF); since the former is ortho-metallated,[3–5] the second is metallated laterally on the methyl group (for an extension to isopropyl phenyl sulfide, see Ref. 7),[6–9] and the latter is cleaved (**Scheme 1**).[10,11] To review articles on this topic see Ref. 12–17.



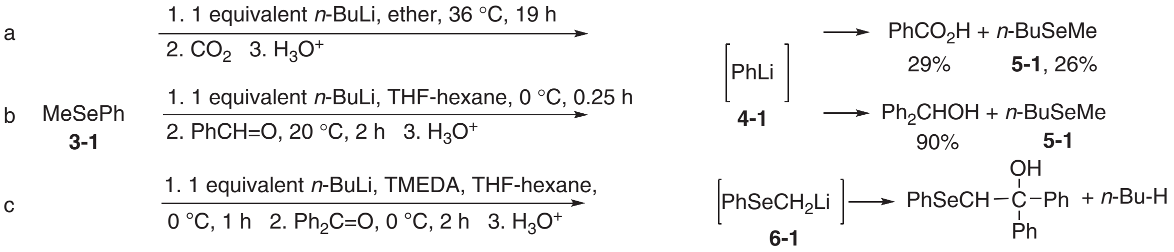
Scheme 1

The authors describe in this review the reactivity of selenides including functionalized ones toward lithium and organolithiums.

3.02.2 Reactivity of Selenides and Functionalized Selenides toward Organolithiums

3.02.2.1 Reactivity of Selenides toward Organolithiums

Selenides exhibit a high propensity to be cleaved by organolithiums. The selenium/lithium (Se/Li) exchange has been first described by Gilman who reported that *n*-butyllithium in ether reacts rapidly with diphenylselenide **8-1** to produce phenyllithium **4-1** and *n*-butyl phenyl selenide **3-2**.[10] He also extended the reaction to methyl phenyl selenide **3-1** that proved to be more difficult and selectively produces phenyllithium **4-1** and *n*-butyl methyl selenide **5-1** rather than methyllithium and phenyl butyl selenide (Scheme 2, entry a).[11]



Scheme 2

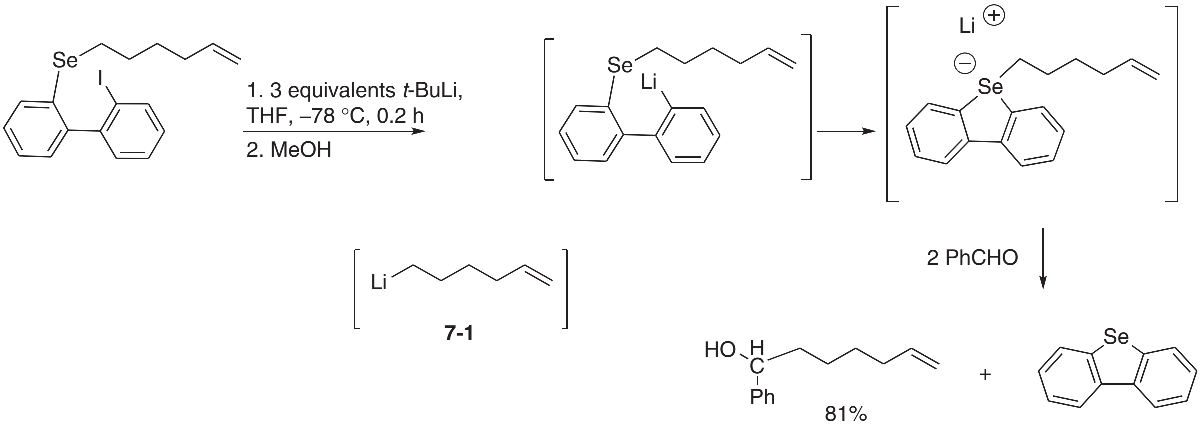
It was later found that this reaction was more efficiently achieved when carried out in THF (Scheme 2, compare entry b to entry a)[18] and that its course was altered if performed in the presence of *N,N,N,N*-tetramethylethylene diamine (TMEDA) since metallation rather than Se/Li exchange takes place (Scheme 2, entry c).[19]

The Se/Li exchange has been successfully extended to the synthesis of α-seleno-alkyllithium,[20] benzyllithiums,[21–23] and allyllithiums[24] from the corresponding functionalized selenides and butyllithiums which proved, at least from those cases, superior to existing methods. This is due to

1. easy access to the starting materials such as selenoacetals[25] and selenides, which take advantage of the high nucleophilicity of selenols[26] and selenolates toward aldehydes and ketones, benzyl and allyl halides, and related alcohols, respectively;
2. selectivity of the exchange that provides among the two possible organolithium compounds the one which possesses the more stabilized carbanion; and
3. inertness of the by-products under the conditions used for the cleavage.

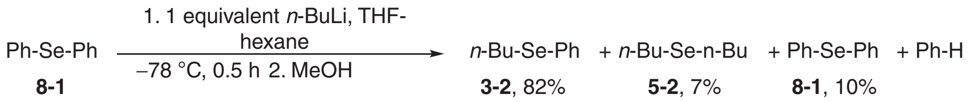
Furthermore, the reaction is usually carried out in a homogeneous medium with the commercially available series of butyllithiums in ether or THF and in the case of benzyl selenides in alkanes. As it will be disclosed, the proper choice of the butyllithium-solvent system allows one to properly tune the efficiency of the Se/Li exchange.

The formation of an ω-alkenyl lithium from an aryllithium is one of the rare examples in which the C–Se bond cleavage provides the least stabilized carbanion (Scheme 3).[27]



Scheme 3

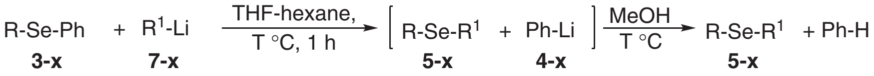
Otherwise, it was found that *n*-butyllithium selectively cleaves at −78 °C, diphenyl selenide **8-1** but not the resulting butyl phenyl selenide **3-2** (Scheme 4).[28]



Scheme 4

It was also found that, although the cleavage of methyl phenyl selenide **3-1** by *n*-butyllithium in THF-hexane is readily achieved at 0 °C (Scheme 2, entry b), it is slower at −50 °C (1.75 h). Under those conditions *n*-butyllithium in ether cleaves methyl phenyl selenide **3-1** to an extent of 10%, whereas *s*-butyllithium and *t*-butyllithium generate phenyllithium **4-1** in 57 and 81%, respectively.[18]

The reactivity of alkyl phenyl selenides toward butyllithiums in THF-hexane decreases by increasing the length and the branching of the alkyl chain. Thus methyl phenyl selenide **3-1** is more reactive that *n*-butyl phenyl selenide **3-2** (Scheme 5 and Table 1, entries a–c compared to Scheme 2, entry b).[28,29] *s*-Butyl phenyl selenide is even less reactive (Scheme 5 and Table 1, entries d–f compared to entries a–c),[29] and *t*-butyl phenyl selenide is inert toward all organolithiums (Scheme 5 and Table 1, entries g–i).[29]



Scheme 5

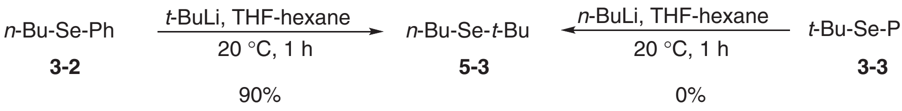
Table 1 Reactivity of alkyl phenyl selenides toward butyllithiums

			A: T = −78 °C		*B: T = 0 °C*	
Entry	*R*	*R¹*	*Bu-Se-R¹* ***5-x*** *(%)*	*Bu-Se-Ph* ***3-x*** *(%)*	*Bu-Se-R¹* ***5-x*** *(%)*	*Bu-Se-Ph* ***3-x*** *(%)*
a	*n*-Bu	*n*-Bu	23	71	88	0
b	*n*-Bu	*s*-Bu	84	12	90	0
c	*n*-Bu	*t*-Bu	32	65	90	0
d	*s*-Bu	*n*-Bu	0	90	24	72
e	*s*-Bu	*s*-Bu	6	92	39	55
f	*s*-Bu	*t*-Bu	0	89	36	61
g	*t*-Bu	*n*-Bu	0	89	0	93
h	*t*-Bu	*s*-Bu	0	87	0	95
i	*t*-Bu	*t*-Bu	0	89	0	90

It was also found that methyllithium in THF-hexane does not react with primary alkyl phenyl selenides, whereas *s*-butyllithium and *t*-butyllithium both efficiently react. They proved to be far more efficient than *n*-butyllithium (Scheme 5 and Table 1).[29]

Finally, as already pointed out for methyl phenyl selenide **3-1**, the reaction discussed above is much faster when carried out at 0 °C than at −78 °C (Scheme 5 and Table 1, compare entry b to entry a).

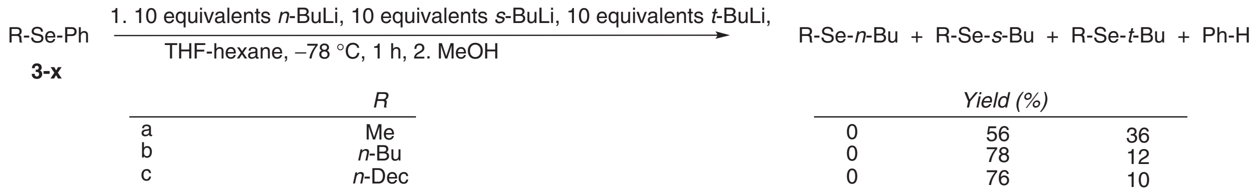
Accordingly, the synthesis of *n*-butyl *t*-butyl selenide **5-3** cannot be achieved from *t*-butyl phenyl selenide **3-3**. However, it can be produced in almost quantitative yield from *n*-butyl phenyl selenide **3-2** (Scheme 6).[28,29]



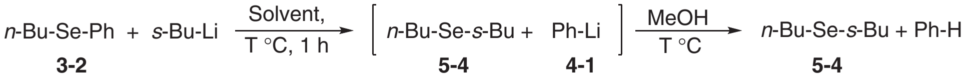
Scheme 6

It has been confirmed that in competing experiments involving methyl-, *n*-butyl-, and *n*-decyl phenyl selenides and a 10-fold excess of a mixture *n*-, *s*-, *t*-butyllithiums that among the series of butyllithiums used *s*-butyllithium is the one that cleaves the C–Se bond more efficiently in primary alkyl phenyl selenides (Scheme 7).[28]

The authors have gathered in Scheme 8 and Table 2 results concerning the reactivity of *n*-butyl phenyl selenide **3-2**, used as a model, for *s*-butyllithium in THF, ether, and pentane.[29] It clearly shows that the reaction carried out in THF is, as already suggested, by far more efficient than the ones performed in ether or pentane (Scheme 8 and Table 2, entry a compared to entry b), especially if the reaction is performed at −25 °C (Scheme 8 and Table 2, entry c).



Scheme 7

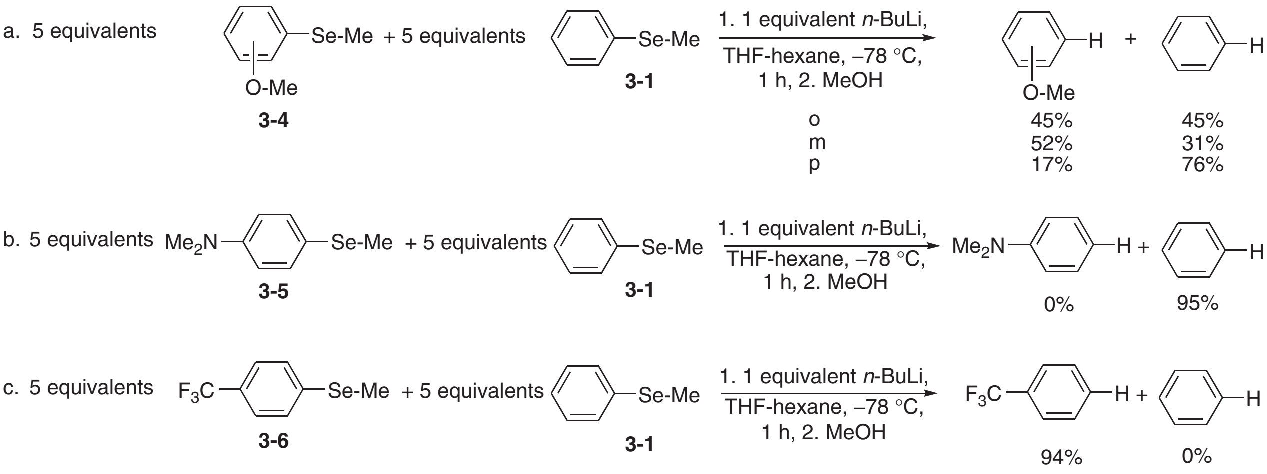


Scheme 8

Table 2 Reactivity of *n*-butyl phenyl selenide **3-2** toward *s*-butyllithium

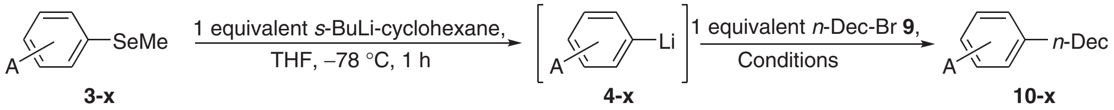
Entry	*Solvent*	*A: T = – 78 °C*		*B: T = – 25 °C*	
		n-*Bu-Se-*s-*Bu* ***5-4*** *(%)*	n-*Bu-Se-Ph* ***3-2*** *(%)*	n-*Bu-Se-*s-*Bu* ***5-4*** *(%)*	n-*Bu-Se-Ph* ***3-2*** *(%)*
a	THF	84	12	86	0
b	Ether	0	94	53	40
c	Pentane	0	89	0	92

The nature of the substituents on the aromatic ring of alkyl aryl selenides has an impact on their reactivity. Thus, competing experiments involving *n*-butyllithium and a fivefold excess of a one to one mixture of methyl phenyl selenide **3-1** and one of the aryl methyl selenide **3-4** to **3-6** whose structures are disclosed in Scheme 9 have been carried out. Surprisingly, methyl *o*-methoxy-phenyl selenide does not have a higher propensity to be cleaved than methyl phenyl selenide **3-1** (Scheme 9, entry a) as it would be expected in correlation with the high propensity of methoxy benzene to be *ortho*-metallated (Scheme 9, entry a compared to Scheme 1, entry a). It was also found that phenyllithium is more efficiently produced than *p*-methoxy-phenyllithium from related methyl selenides (Scheme 9, entry a) and similar results are obtained with *p*-dimethylamino-phenyl **3-5** (Scheme 9, entry b). The reverse is, however, observed with the *p*-trifluoromethyl-substituted derivative **3-6** (Scheme 9, entry c), which is more easily cleaved than the parent compound.[28,29] Thus the presence of an electron-withdrawing group on the aromatic ring favors the cleavage of the C–Se bond producing the more stabilized *p*-trifluoromethylphenyllithium and the reverse reactivity is observed when an electron-donating substituent is present on the aromatic ring.



Scheme 9

Nevertheless, the cleavage of the whole series of aryl methyl selenides **3-x** bearing electron-withdrawing or electron-donating substituents on the phenyl ring, disclosed above, has been quantitatively achieved at – 78 °C using *sec*-butyllithium in THF–cyclohexane (Scheme 10 and Table 3).[29] Alkylation of the resulting aryllithium with decyl bromide **9** takes place at approximately 0 °C and produces, except for *p* trifluoromethyl phenyllithium (Scheme 10 and Table 3, entry d), 1-aryl-decanes **10-x** in yield ranging between 60% and 70% (Scheme 10 and Table 3). Similar yields have been obtained from *p*-trifluoromethylphenyllithium when the alkylation is carried out in the presence of hexamethyl phosphoramide (HMPA) (Scheme 10 and Table 3, entry e compared to entry d).[29] The whole process offers, over a related one involving aryl halides, the advantages to avoid concomitant butylation of the aryllithium that occurs on reaction of the butyl halide resulting in halogen/lithium exchange. This side reaction does not take place on the *s*-butyl methyl selenide generated concomitantly to the aryllithium in the reaction described in Scheme 10 and Table 3.[29]



Scheme 10

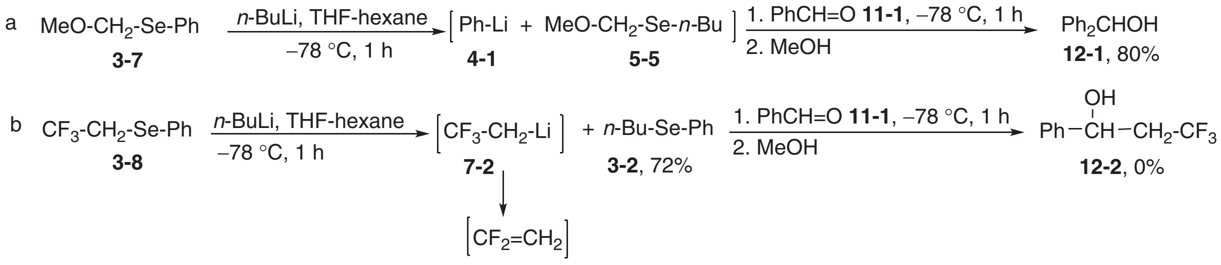
Table 3 Cleavage of substituted aryl methyl selenides

Entry	*R*	*Conditions*	*Aryl decanes **10-x** (%)*
a	*m*-MeO	THF, 0–25 °C, 10 h	73
b	*p*-MeO	THF, 0–25 °C, 10 h	70
c	*p*-Me_2N	THF, 0–25 °C, 10 h	61
d	*p*-F_3C	THF, 0–25 °C, 10 h	33
e	*p*-F_3C	1 equivalent HMPA, − 78 °C, 1 h; 0–25 °C, 10 h	64

3.02.2.2 Reactivity of Functionalized Alkyl Selenides toward Organolithiums

The cleavage of the C–Se bond reported below has been extended to alkyl selenides bearing at their alpha carbons a carbon–carbon double bond such as allyl- (see Section 3.02.2.2.1) and benzylselenides (see Section 3.02.2.2.2) or an heteroatom such as (O,Se)-acetals (see Section 3.02.2.2.3.1), (S,Se)-acetals (see Section 3.02.2.2.3.2), and (Se,Se)-acetals (selenoacetals) (see Section 3.02.2.2.3.3).

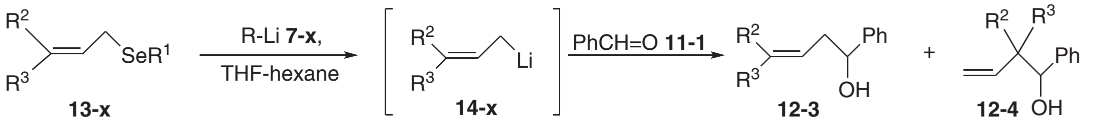
It has thus been reported that methoxymethyl phenyl selenide **3-7** reacts with *n*-butyllithium to produce phenyllithium **4-1** and methoxymethyl *n*-butyl selenide **5-5** (Scheme 11, entry a)[30] and that 2,2,2-trifluoroethyl phenyl selenide **3-8** produces *n*-butyl phenyl selenide **3-2** but not the 1-phenyl 3,3,3-trifluoropropanol **12-2** on further reaction with benzaldehyde **11-1** and methanol.[28] This is probably due to the decomposition of the intermediate 2,2,2-trifluoroethyllithium **7-2** probably through a *ββ*-elimination reaction (Scheme 11, entry b).



Scheme 11

3.02.2.2.1 Synthesis of allyllithiums from allyl selenides

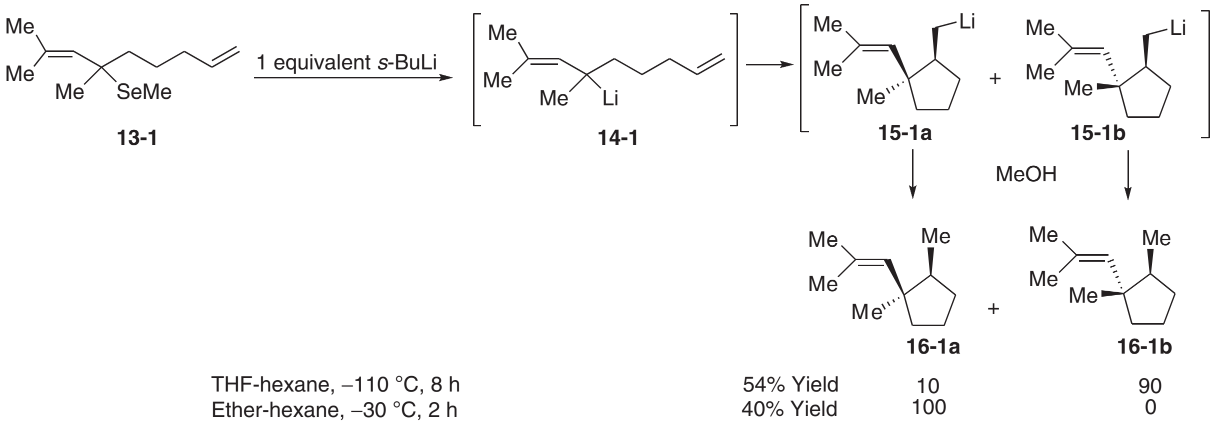
The cleavage of the C–Se bond has been successfully achieved on various phenyl and methyl allyl selenides using usually *n*-butyllithium in THF-hexane at approximately − 78 °C. It provides allyllithiums in very good yields (Schemes 12–16 and Tables 4 and 5).[13,24,31–35]



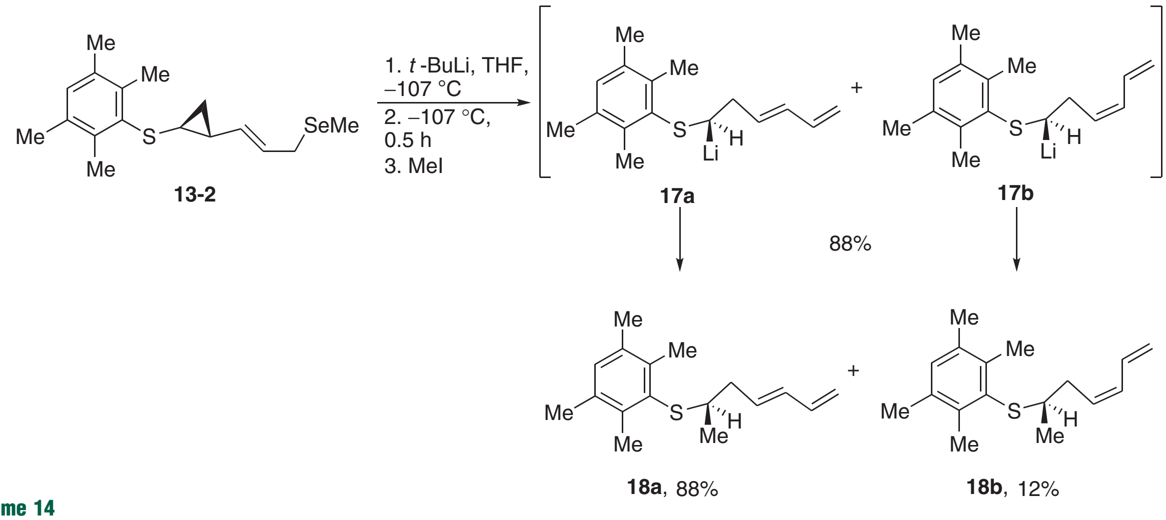
Scheme 12

Table 4 Cleavage of phenyl and methyl allyl selenides

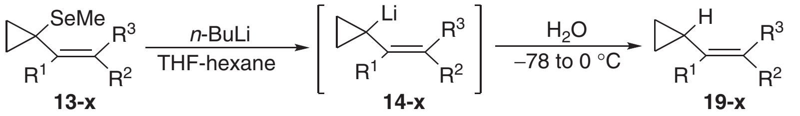
Entry	*R^1*	*R^2*	*R^3*	*R*	*Conditions*	*Yield (%)*	***12-3/12-4***
a	Ph	H	H	*n*-Bu	− 78 °C, 0.1 h	86	
b	Me	H	H	*n*-Bu	− 78 °C, 0.1 h	95	
c	Me	H	H	Me	0 °C, 0.1 h; 20 °C, 0.2 h	81	
d	Me	H	Hex	*n*-Bu	− 78 °C, 1 h	81	30/70
e	Ph	Me	Me	*n*-Bu	− 78 °C, 0.5 h	82	34/66
f	Me	Me	Me	*n*-Bu	− 78 °C, 0.5 h	76	36/64



Scheme 13



Scheme 14

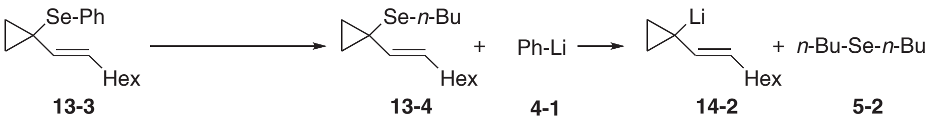


Scheme 15

In the case of the parent methyl allyl selenide **13-x**, the cleavage has been successfully achieved using methyllithium in ether but takes place at much higher temperatures (Scheme 12 and Table 4, entry c).[24] The exceptional stabilization by delocalization of the lone pair of the carbanion on the allylic system is probably responsible for the unusual C–Se bond cleavage which does not even occur on benzyl selenides.

Table 5 Cleavage of methyl allylselenides **13-x** whose allylic carbon is part of a cyclopropane ring

Entry	R^1	R^2	R^3	*Conditions*	*Yield (%)*
a	H	H	Hex	– 60 °C, 0.1 h	80
b	H	Hex	H	– 60 °C, 0.1 h	84
c	Hex	Pent	H	– 45 °C, 0.5 h	80
d	H	Ph	H	– 78 °C, 0.5 h	75
e	H	H	Ph	– 78 °C, 0.5 h	80



	13-4	4-1	14-2	5-2
a. 1 equivalent *n*-BuLi, THF-Hexane, –78 °C	100%	100%	0%	0%
b. 2 equivalents *n*-BuLi, THF-Hexane, –78 °C	0%	0%	100%	100%

Scheme 16

The case of the allylic selenide **13-1** bearing an extra-alkenyl side chain is interesting (Scheme 13). The cleavage has been efficiently achieved in both THF and ether at low temperature but the resulting allyllithium **14-1** whose carbanion is tertiary, adds almost instantaneously at low temperature across the extra carbon–carbon double bond to produce by carbocyclization the cyclopentylmethyllithiums **15-x** in modest yield but with good stereocontrol that is solvent dependent (Scheme 13).[32] It must be recalled that the same process occurs at a much higher temperature if performed with Grignard reagents instead.[36] A related reaction using 1-*N*,*N*-dimethylaminonaphthalenide (LDMAN) has been disclosed by Cohen.[37]

On the contrary, the allyl selenide **13-2** whose carbon–carbon double bond is part of a 1-thioaryl-2-vinyl cyclopropane, reacts with *t*-butyllithium even at very low temperature (– 107 °C) to produce the mixture of scalemic α-thiohomoallyllithiums **17** (Scheme 14).[38] This process involves fragmentation of the cyclopropane ring that allows the release of the strain and the formation of the most stabilized carbanion.

Se/Li exchange has been extended to the subgroup of methyl allylselenides **13-x** whose allylic carbon is part of a cyclopropane ring (Scheme 15 and Table 5).[31] It produces the corresponding allyllithium **14-x,** which is protonated at the place where the selenomethyl group was previously attached. It has been interestingly observed that the stereochemistry of the carbon–carbon double bond is not affected in the process (Scheme 15 and Table 5, entries a and b), that increasing the number of alkyl substitution on the carbon–carbon double bond decreases the rate of cleavage (Scheme 15 and Table 5, compare entries a–c), whereas the presence of an aryl group on the carbon–carbon double bond favors the reaction (Scheme 15 and Table 5, entries d and e).[31]

The reaction takes another course when carried out on the related phenylselenide **13-3** with 1 equivalent of *n*-butyllithium. The formation of phenyl lithium **4-1** competes with that of the allyllithium derivative **14-2** (Scheme 16, entry a).[31] The latter is produced quantitatively, besides phenyllithium **4-1**, when the reaction is carried out with two equivalents of *n*-butyllithium (Scheme 16, entry b).

It can be argued that the carbon–carbon double bond attached to the α-cyclopropyllithium **14-2** provides an extra stabilization to the carbanion, although its delocalization on the double bond is hampered by the formation of an alkylidene cyclopropane that implies an extra-strain. Addition of a second equivalent of *n*-butyllithium allows the complete cleavage of the *n*-butyl selenide **13-4** intermediate that leads to the allyllithium **14-2** besides phenyllithium **4-1** (Scheme 16, entry b).[31]

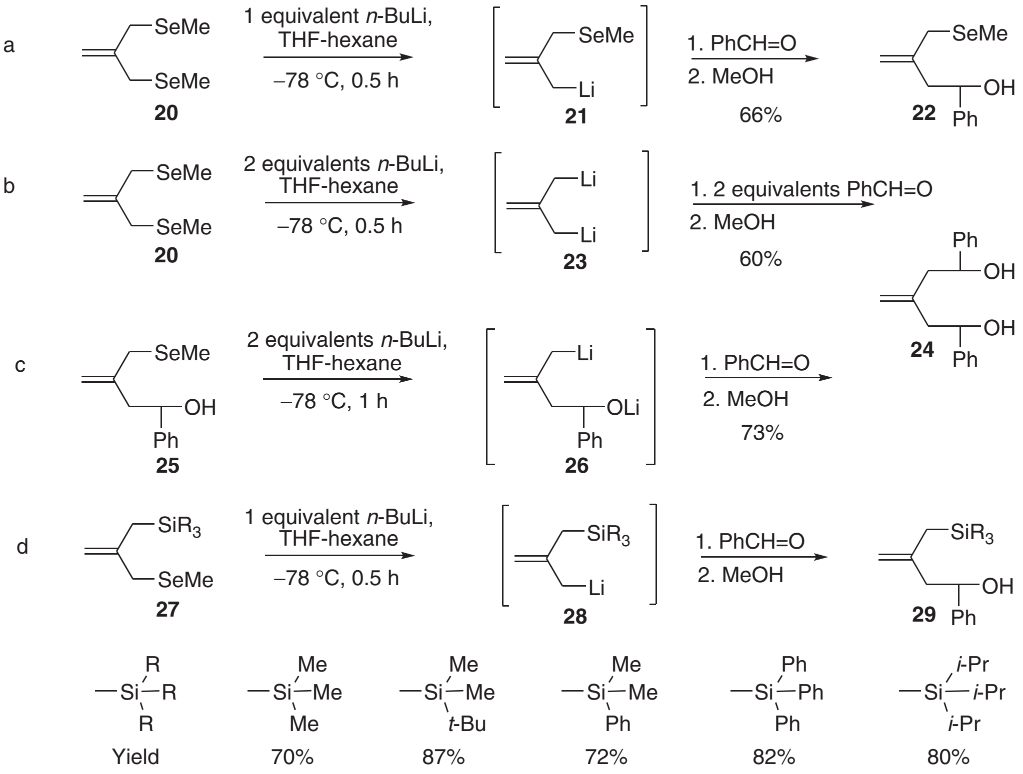
3-Methylseleno-2-[methylselenomethyl] propene **20** is a versatile reagent able to transfer a four-carbon unit as trimethylenemethane and isobutene dianion synthons (Scheme 17, entries a and b).[34] The cleavage of the C–Se bond in **20** is chemoselectively achieved using 1 equivalent of *n*-butyllithium in THF-hexane at – 78 °C and produces the allyllithium **21** (Scheme 17, entry a), whereas the related dilithio derivative **23** is easily generated at the same temperature if **20** is instead reacted with 2 equivalents of *n*-butyllithium (Scheme 17, entry b).[34] The allylic selenide bearing an extra hydroxyl group on a homoallylic carbon **25** whose structure is disclosed in Scheme 17, entry c, is also transformed to the corresponding allyllithium **26** on reaction with 2 equivalents of *n*-butyllithium.

3-Methylseleno-2-[methylselenomethyl] propene **20** is a valuable precursor of a series of 3-methylseleno-2-[silylmethyl] propenes **27**, which are precursors of 2-silylmethylallyllithiums **28** (Scheme 17, entry d).[35] They play a pivotal role in the construction of Milbemycin β.[33]

3.02.2.2.2 Synthesis of benzyllithiums from benzyl selenides

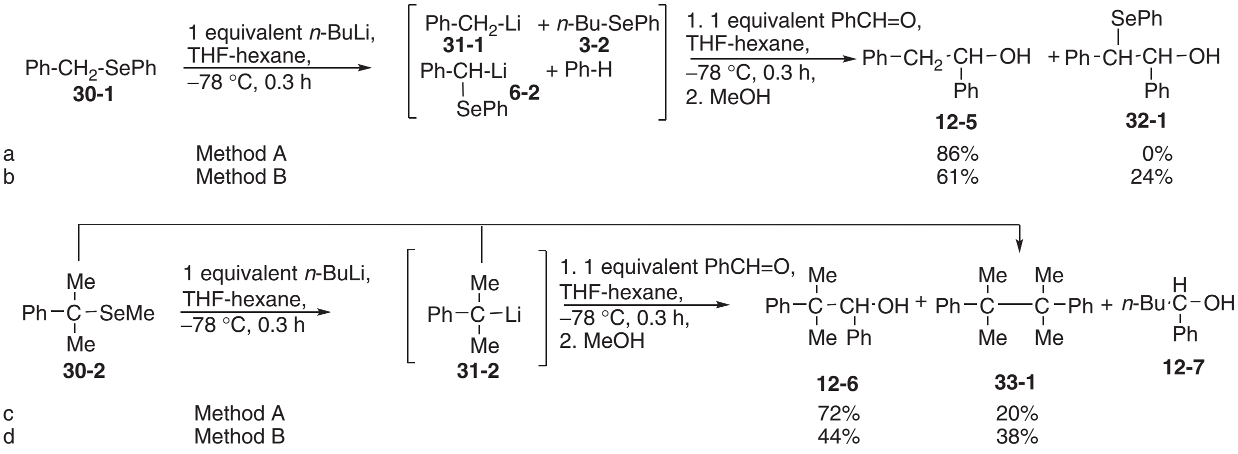
3.02.2.2.2.1 Reactivity of benzyl selenides

Benzyl selenides are very good precursors of benzyllithiums. They are usually regioselectively formed from phenyl- (Scheme 18) or methyl- (Scheme 19, entry a) benzyl selenides and *n*-butyllithium in THF-hexane. Selenides should be added to a solution of



Scheme 17

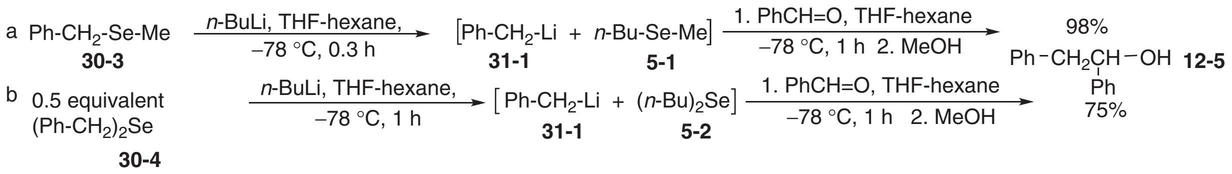
n-butyllithium in THF-hexane maintained at – 78 °C (Method A) to get optimum yields and to avoid the concomitant formation of by-products observed especially when *n*-butyllithium is added to the first members of the series (Method B) (Scheme 18, entries b and d; compared to entries a and c, respectively; Scheme 19).[21,39] These side reactions are especially observed on the primary members of the series bearing a methylene, a hydrogen, and a methyl or two methyl groups at their benzylic carbon and more rarely with homologs bearing longer or branched alkyl chains. It takes place efficiently when benzylphenyl selenides are reacted with *n*-butyllithium.



Scheme 18

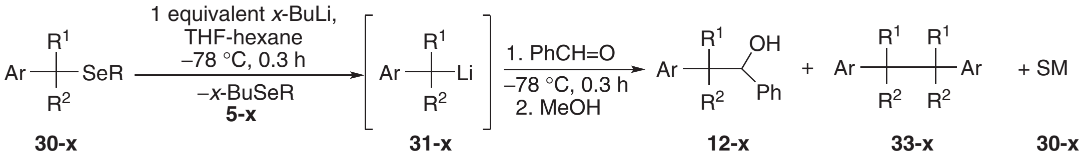
The synthesis of benzyllithium from benzyl selenide reported above has been successfully extended to dibenzyl selenide that delivers 2 equivalents of benzyllithium besides dibutyl selenide on addition to a solution of 2 equivalents of *n*-butyllithium in THF-hexane (Scheme 19, entry b).[40]

The Se/Li exchange reaction is one of the most efficient methods of synthesis of benzyllithiums since other methods require the use of lithium, lithium arenides, (lithium naphtalenides (LiN), or lithium di-*tert*butylbiphenylide (LiDBB)) on the corresponding benzyl ethers[41] or benzyl sulfides[42] (see references cited in Ref. 21 for other methods).[21]



Scheme 19

The reaction occurs on a wide range of benzyl selenides including those whose benzylic carbon bears a methylene group (Scheme 18, entries a and b; Scheme 20 and Table 6, entries k–m) or is mono- (Scheme 20 and Table 6, entries a, b, and n), or dialkylsubstituted (Scheme 20 and Table 6, entries c–j), and those whose aromatic ring is substituted by halogens or alkoxy groups (Scheme 20 and Table 6, entries k–n).[21] It is interesting to mention that competing heteroatom/lithium exchange on the heteroatoms attached to the aromatic ring does not take place.[41,42]



Scheme 20

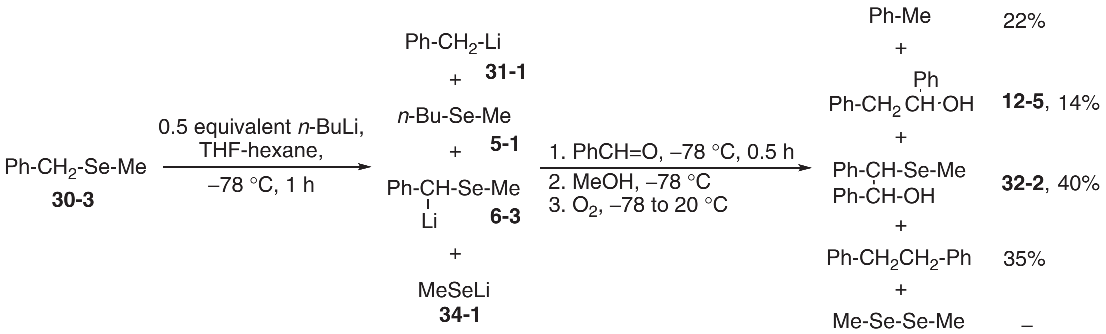
Table 6 Synthesis of benzyllithiums from benzyl selenides

Entry	*R*	*Ar*	*R^1*	*R^2*	x	***12-x*** *(%)*	***33-x*** *(%)*
a	Me	Ph	H	Me	*n*	79	
b	Ph	Ph	H	Me	*n*	83	
c	Ph	Ph	Me	Me	*n*	5	74
d	Me	Ph	Me	Me	*t*	81	0
e	Me	Ph	Me	*i*-Pr	*n*	80	
f	Me	Ph	Pr	*i*-Pr	*n*	78	
g	Me	Ph	Me	*t*-butyl	*n*	0	
h	Me	Ph	Me	*t*-butyl	*s*	86	
i	Me	Ph	*i*-Pr	*i*-Pr	*n*	0	
j	Me	Ph	*i*-Pr	*i*-Pr	*s*	92	
k	Me	*o*-Cl-Ph	H	H	*n*	94	
l	Me	*p*-Cl-Ph	H	H	*n*	91	
m	Me	*p*-F-Ph	H	H	*n*	83	
n	Me	*p*-MeO-Ph	H	Me	*n*	82	

Method B favors competing (1) metallation (H/Li exchange) of the parent compounds bearing a benzylic methylene group, that competes with the Se/Li exchange and provide the corresponding α-selenoalkyllithiums (Scheme 18 compare entry b to entry a),[21] it also favors (2) coupling of the carbon framework leading to biscumyl derivatives (Scheme 20 and Table 6, compare entry d to entry c).[21] Therefore, condition A has to be used every time those side reactions have to be avoided (Scheme 20 and Table 6, entry e compared to entry c and to Scheme 18, entry a).

n-Butylllithium in THF-hexane is the usual reagent-solvent couple (Scheme 18 and Scheme 20 and Table 6, entries a, b, e, f, and k–n); nevertheless, in the case of cumyl derivatives (Scheme 18 entries c and d; Scheme 20 and Table 6, entry c) and those benzyl selenides bearing bulky alkyl groups on the benzylic carbon (Scheme 20 and Table 6, entries g and i), the related benzyllithiums cannot be used further because either coupling occurs (Scheme 20 and Table 6, entry c)[21] or the C–Se bond cleavage does not take place (Scheme 20 and Table 6, entries g and i),[21] respectively. In those cases *s*- or *t*-butyllithiums allow efficient reaction (Scheme 20 and Table 6, entries d, h, and j), they also allow very efficient synthesis of the whole series of benzyllithiums from benzylselenides even in ether (Scheme 25 and Table 7, entries c–h)[21] or pentane (Scheme 25 and Table 7, entries i–l).[43] This cleavage is inefficient when carried out with *n*-butyllithium in ether or pentane (Scheme 25 and Table 7, entry i).[22,23]

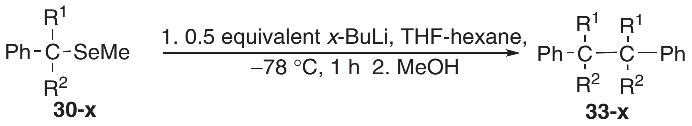
Coupling occurs every time the benzylselenide is not readily transformed to the corresponding benzyllithium, so the benzyllithium formed in the process can react with the starting benzylselenide. This is why it occurs more efficiently (1) when conditions B are used intead of conditions A (2) when the least reactive *n*-butyllithium is used instead of the more reactive *t*-butyllithium (3) on the less reactive phenyl compared to methyl cumyl selenide (4) or when the selenides are reacted with half an equivalent of butyllithium (see below, Scheme 21).



Scheme 21

Results reported in Scheme 21 show that when half an equivalent of *n*-butyllithium is reacted with benzyl methyl selenide, the resulting benzyllithium in turn reacts with an excess of starting material to produce the (1) α-selenobenzyllithium by metallation (see also Scheme 18, entry a), (2) the dibenzyl and lithium methylselenolate resulting formally from substitution of its methylseleno moiety (see also Scheme 18, entries c and d). For convenience the methylselenolate has been in turn oxidized to the diselenide (Scheme 21).[40]

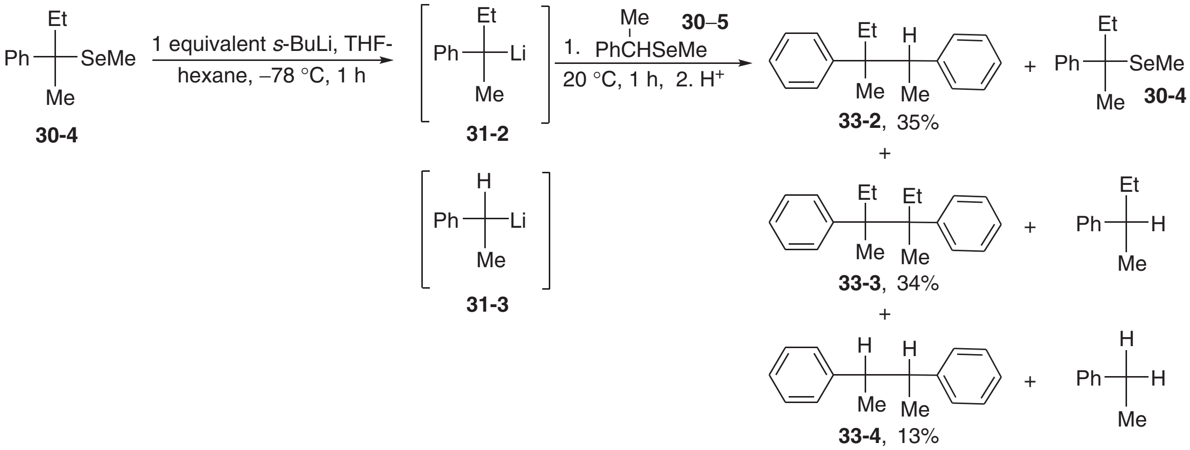
Scheme 22 widens the scope of the coupling reaction (Scheme 22, entries a–c) and discloses its limitation to only those benzyl selenides which do not bear a bulky substituent on the benzylic carbon (Scheme 22, compare entries a–c to entries d and e).[40]



Entry	*R^1*	*R^2*	x-*BuLi*	*Yield (%)*
a	H	Me	*n*-BuLi	81
b	Me	Me	*n*-BuLi	89
c	Me	Et	*s*-BuLi	79
d	Me	*i*-Pr	*t*-BuLi	0
e	Me	*t*-Bu	*t*-BuLi	0

Scheme 22

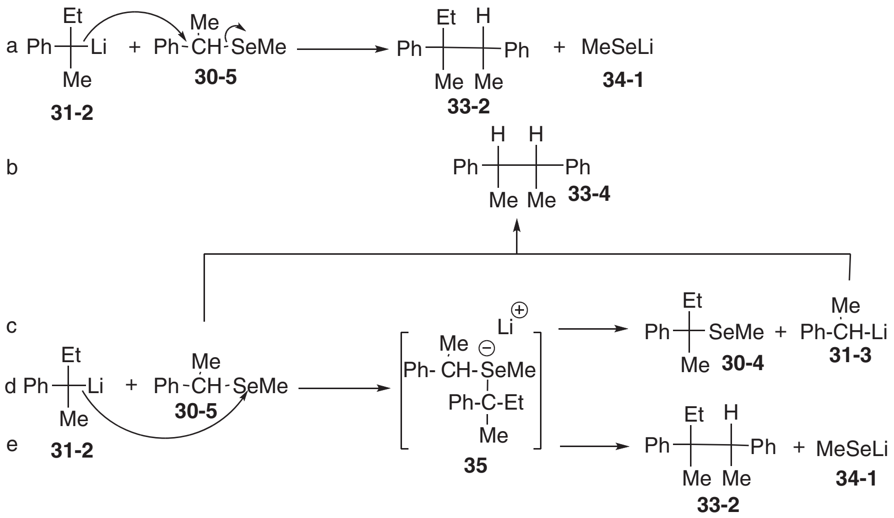
It is finally interesting to note that 2-phenylbutyl-2-lithium **31-2** reacts with 1-methylseleno-1-phenylethane **30-5** to deliver the whole set of possible bibenzyls **33-2** to **33-4** (Scheme 23).[40]



Scheme 23

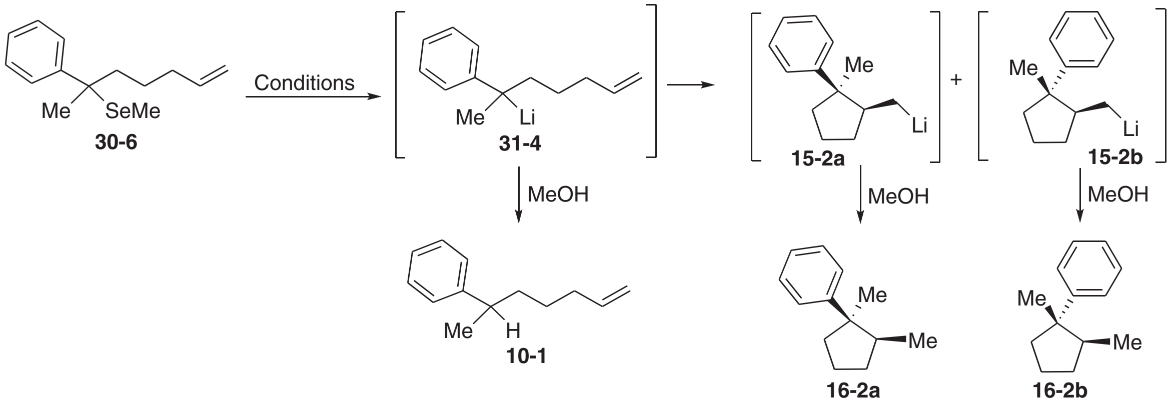
There is no clear-cut evidence to discriminate between a simple substitution reaction between the benzyllithium **31-2** and the benzylselenide **30-5** (Scheme 24, entry a) or the formation of an ate complex intermediate **35** which then collapses (Scheme 24, entry d).

The formation of 2,3-diphenylbutane **33-4** in the experiment disclosed in Schemes 23 and 24, entry b, suggests the formation of a mixed ate complex **35** or a very closely related species (Scheme 24, entry d).



Scheme 24

Benzyl selenide **30-6** bearing an ω-alkenyl substituent produces benzyllithium **31-4** on reaction with n-butyllithium in ether or THF. However **31-4** is unstable and possesses a high propensity to add across the extra carbon–carbon double bond to produce alkyllithiums **15-2a** and **15-2b** resulting from a carbocyclization reaction whose stereochemistry is dependent on the solvent used (Scheme 25 and Table 7, entries a and b).[44] The C–Se bond cleavage in **30-6** has been also carried out in alkanes (pentaneor hexane) (Scheme 25 and Table 7, entries i–l). n-Butyllithium in hexane cleaves very slowly the C–Se bond of **30-6** (Scheme 25 and Table 7, entry i) whereas s-butyllithium (Scheme 25 and Table 7, entry j) and especially t-butyllithium in pentane (Scheme 25 and Table 7, entries e–g) are more efficient.[43]



Scheme 25

It is interesting to note that in alkanes, protonation of the benzyllithium by the solvent is prevented so the reaction can be achieved at a much higher temperature than in THF or ether.

Benzyllithiums bearing two alkyl groups on the benzylic carbon are able to metallate, as butyllithium does, THF or diethyl ether at 20 °C. They are subsequently protonated and lead to the corresponding benzyl selenides (Scheme 26).[43] These metallated ethers decompose rapidly and generate ethylene[43] which in turn reacts very consequently with remaining benzyllithium (Scheme 26).[43]

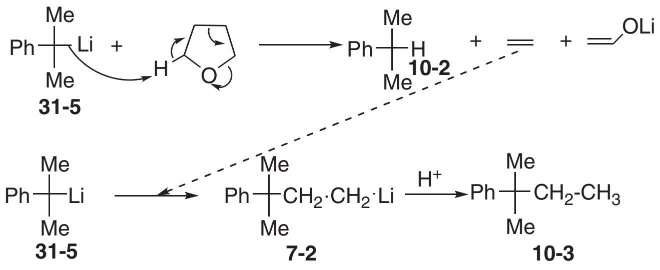
3.02.2.2.2.2 Insight on the configurational stability of benzyllithiums

Benzyllithiums proved to be configurationally unstable. This is the case of 4-terbutyl-1-phenylcyclohexyllithium **31-6** (Scheme 27)[45] and of the α-methyl benzyllithium **31-3**, which has been generated by Se/Li exchange at a temperature even lower than − 78 °C.[46] The rate of enantiomerization of the latter at − 78 °C was found to be faster than its addition to Weinreb amides, ketones, or aldehydes.[47]

This property has been used to control the stereochemistry of intramolecular alkylation of the ω-bromo-benzyllithium **31-7** disclosed in Scheme 28. Thus reaction of the diastereoisomeric mixture of ω-bromo-benzylselenides **30-8** with n-butyllithium

Table 7 Carbocyclization of benzyl selenide **30-6** bearing an ω-alkenyl substituent

Entry	*Conditions*	***30-6** (%) Recovery*	***10-1** (%)*	***16-2** (%)*	***16-2a***	***16-2b***
a	1. *n*-BuLi, THF-hexane, −78 °C, 0.5 h 2. MeOH, −78 °C	0	0	85	2	98
b	1. *n*-BuLi, THF-hexane, −78 °C, 0.5 h 2. −78 to 20 °C 3. 20 °C, 24 h 4. MeOH, 20 °C	0	0	85	15	85
c	1. *t*-BuLi, Et_2O-pentane, −110 °C, 0.3 h 2. MeOH, −110 °C	0	97	3	0	100
d	1. *t*-BuLi, Et_2O-pentane, −78 °C, 0.3 h 2. MeOH, −78 °C	0	75	25	25	75
e	1. *t*-BuLi, Et_2O, −78 °C, 7 h 2. MeOH, −78 °C	0	6	94	25	75
f	1. *t*-BuLi, Et_2O-pentane, −78 °C, 7 h 2. −78 to −30 °C, 0.5 h 3. −30 °C, 0.3 h 4. MeOH, −30 °C	–	4	96	35	65
g	1. *t*-BuLi, Et_2O-pentane, −30 °C, 0.3 h 2. MeOH, −78 °C	–	0	85	98	2
h	1. *t*-BuLi, Et_2O-pentane, 0 °C, 0.3 h 2. 0–20 °C, 0.5 h 3. 20 °C, 24 h 4. MeOH, 20 °C	4			97	3
i	1. *n*-BuLi, hexane, 20 °C, 24 h 2. MeOH, 25 °C	51	0	13	100	0
j	1. *s*-BuLi, hexane, 20 °C, 0.25 h 2. MeOH, 25 °C	84	0	16	100	0
k	1. *s*-BuLi, hexane, 25 °C, 0.75 h 2. MeOH, 20 °C	43	0	57	100	0
l	1. *t*-BuLi, pentane, 25 °C, 0.75 h 2. MeOH, 20 °C	10	0	90	100	0

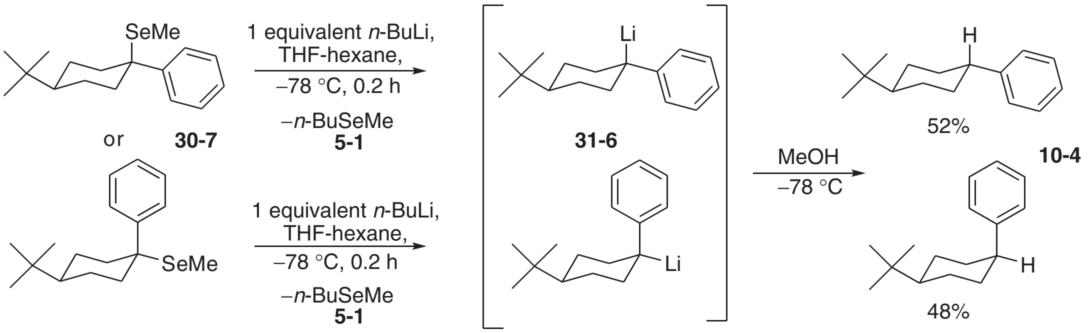


Scheme 26

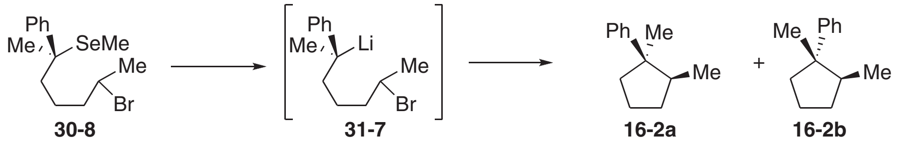
leads to the formation of a mixture of **16-2a**/**16-2b** in which **16-2a** prevails in ether (Scheme 28, entry a) and **16-2b** in pentane (Scheme 28, entry b).[45]

It has been, however, found[45] that each of the two stereoisomeric benzyl methyl selenides **30-9** bearing a sulfonyl group in γ-position reacts with *n*-butyllithium to specifically produce each of the two stereoisomeric cyclopropane **10-5** derivatives shown in Scheme 29. Carbocyclization formally involves retention of configuration at each reacting carbon atom or double inversion according to different postulated mechanisms which have been proposed.[45]

Nevertheless, each of the two related diastereoisomeric selenides **30-10** bearing a hydroxy group in the γ-position reacts with 2 equivalents of *n*-butyllithium to provide, after sequential reaction with trimethylsilyl chloride and aqueous potassium

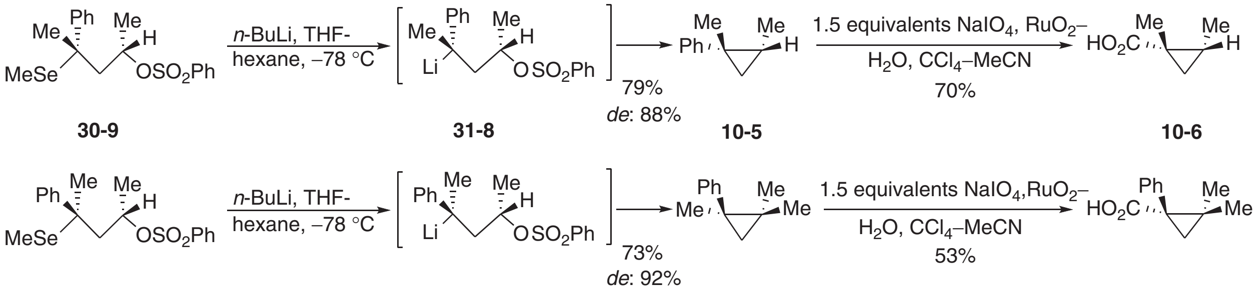


Scheme 27



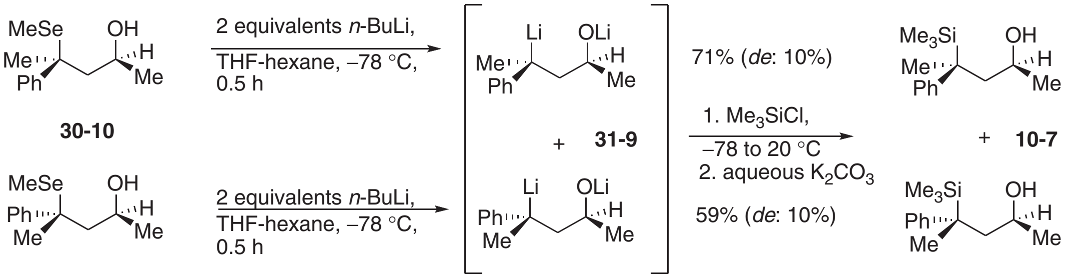
			16-2a	16-2b
a	n-BuLi, THF or s-BuLi, ether or s-BuLi, ether-HMPA	80%	80	20
b	s-BuLi, pentane	73%	19	81

Scheme 28



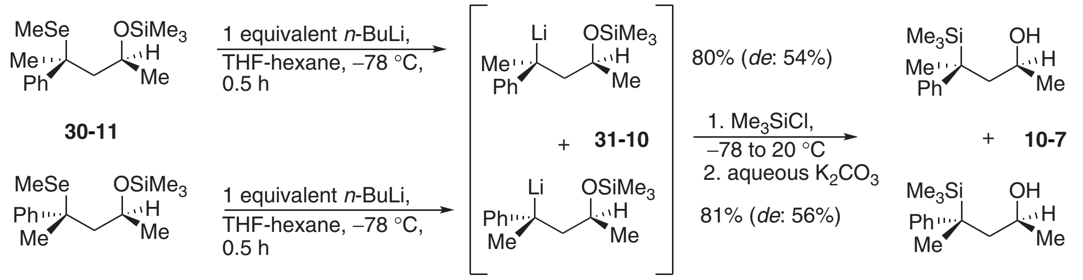
Scheme 29

carbonate, the same diastereoisomeric mixture of **10-7** (*de*: 10%), suggesting that there is no intramolecular complexation of the organolithium intermediates by the γ-alkoxide-group either to keep the original stereochemistry or to give one of the two stereoisomers predominantly (Scheme 30).[48]



Scheme 30

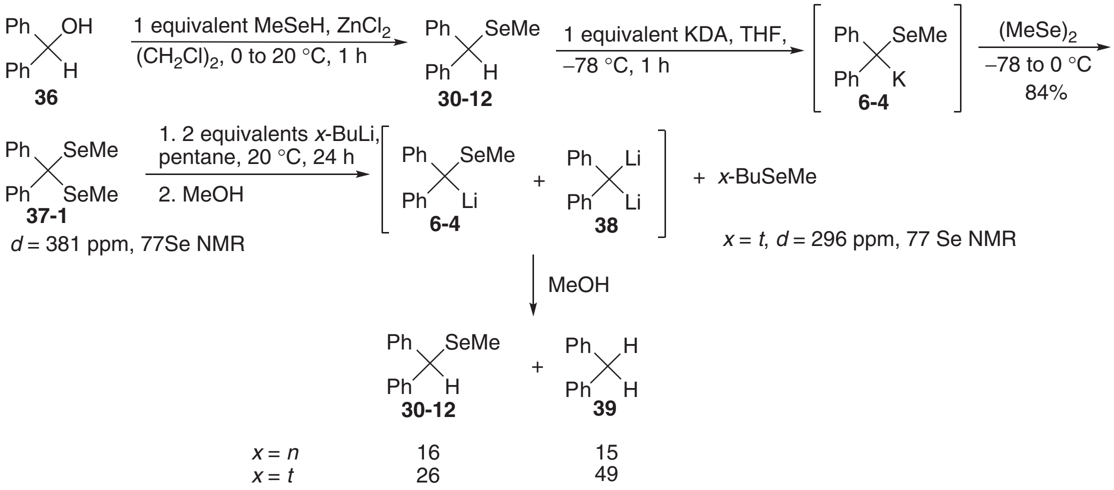
The same stereoisomeric mixture, but with a different ratio of stereoisomers has been produced on reaction of *n*-butyllithium with each of the related diastereoisomeric selenides **30-11** bearing a silyloxy-group in the γ-position, suggesting that the retro-Brook rearrangement, involved in this process, is not stereospecific (Scheme 31),[48] suggesting that those benzyllithiums are not configurationally stable.



Scheme 31

This rearrangement does not occur intramolecularly since the triethylsilyl derivatives have been exclusively isolated if the reaction described in Scheme 31 is instead carried out in the presence of an excess of triethylsilyl chloride.[48]

Finally, there is some evidence that diphenyldilithiomethane **38** is generated from diphenyl-di(methylseleno)methane **37-1** and alkyllithiums especially *t*-butyllithium (Scheme 32).[49] The synthesis of diphenyl-di(methylseleno)methane **37-1** is unusual for a selenoacetal. It takes advantage of the easy metallation of diphenyl-(methylseleno)methane **30-12** by potassium diisopropylamide (KDA) and its selenenylation using dimethyldiselenide (Scheme 32).[49]

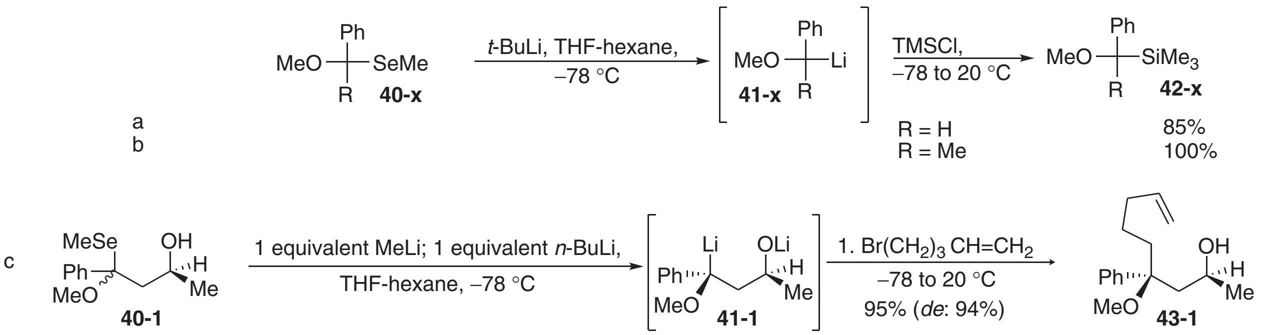


Scheme 32

3.02.2.2.3 *Reactivity of organolithiums toward α-heterosubstituted selenides in which the heteroatoms do not belong to a cycle*

3.02.2.2.3.1 Synthesis of α-alkoxy-alkyllithiums from α-alkoxyselenides (O,Se acetals)

α-alkoxyselenides or (O,Se)-acetals do not produce α-organyloxyalkyllithiums on reaction with butyllithiums[30,50,51] and instead produces phenyllithium (Scheme 11, entry a). The presence of an aryl substituent on their α-carbon favors the C–Se bond cleavage[48,52,53] resulting in the synthesis of the related α-alkoxy benzyllithiums. *t*-Butyllithium in THF-pentane has proved by far to be the most efficient combination (Scheme 33, entries a and b),[53] although *n*-butyllithium in the same solvent mixture has been successfully used with the parent compound.[52]

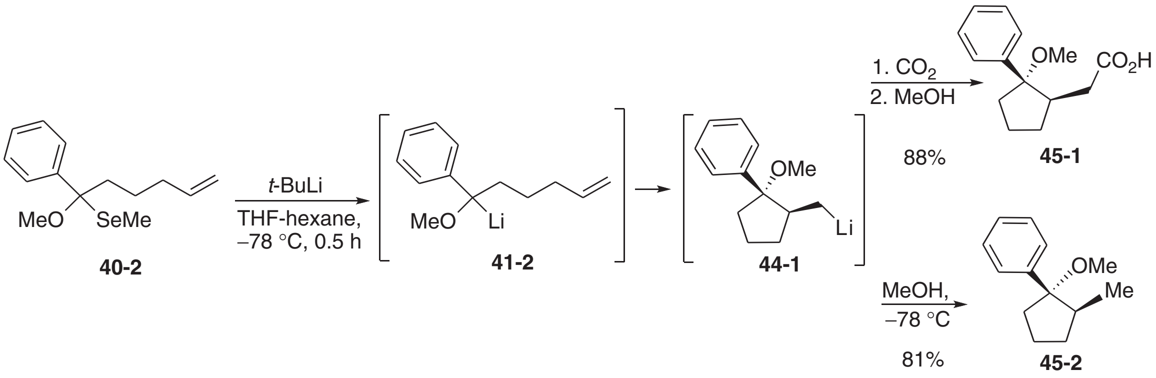


Scheme 33

Cleavage of the C–Se bond of γ-hydroxy mixed O,Se acetal **40-1** requires an extra equivalent of *n*-butyllithium to transform the alcohol present to the corresponding lithium alkoxide **41-1** (Scheme 33, entry c). Since the first equivalent of *n*-butyllithium does not selectively achieve the O–H/OLi exchange and partly cleaves the C–Se bond of the mixed selenoacetal, the alcohol still present is able to achieve *in situ* the protonation of the benzylic carbanion.[48] In order to overcome this inconvenience, the H/Li exchange on the hydroxyl of the alcohol has been first selectively achieved using methyllithium that is unable to achieve the Se/Li exchange. Under such conditions, subsequent addition of *n*-butyllithium on the resulting α-alkoxy-benzyl selenide produces an α-alkoxy-benzyllithium which on further alkylation produces almost a single stereoisomer of the alkylated product **43-1** (Scheme 33, entry c). These results suggest that an epimerization has taken place at the benzylic site.[54]

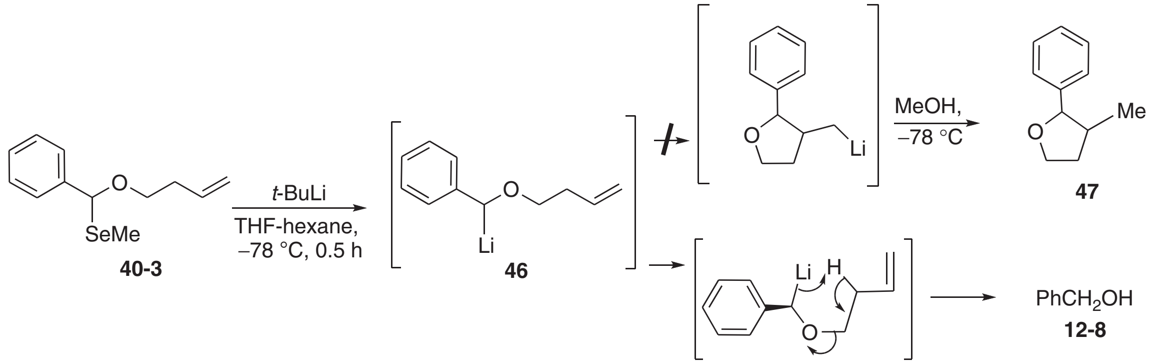
This reaction has been extended to the case of stereoisomerically pure γ-silyloxy O,Se selenoacetals which produce in each case the same diastereoisomeric mixture of γ-hydroxy benzylsilanes in quite high diastereoselection (*de*: 76%) through a retro-Brook rearrangement.[48]

Related compound **40-2** bearing an alkenyl side-chain rapidly cyclizes to produce (1-phenyl-1-methoxy-cyclopentyl)methyllithium **44-1** (Scheme 34)[53] implying a process related to that already described in Scheme 25. In such cases, the C–Se bond cleavage has been successfully achieved by *t*-BuLi not only in THF-hexane (−78 °C, 0.5 h) but also in ether-pentane (−40 °C, 5 h) and in pentane (20 °C, 48 h).[53] Contrary to the reactions described in Scheme 25, the same stereoisomer is formed in each of the cases. The benzyllithium kept for a long time (148 h) at room temperature, leads in small amounts, to products resulting from a Wittig rearrangement (15%).[53] This cyclization has been extended to the formation of (1-phenyl-1-methoxy-cyclohexyl) methyllithium.[53]



Scheme 34

The cyclization, reported in Scheme 34, cannot be extended to the synthesis of the THF derivative **47**. The reaction of *t*-BuLi on the unsaturated α-alkoxy selenide **40-3** instead produces benzyl alcohol **12-8** after hydrolysis (Scheme 35).[52] This result suggests that the intramolecular elimination depicted in Scheme 35 and involving an allylic hydrogen is taking place on the α-alkenyloxy-benzylithium intermediate **46** rather than the cyclization which would have led to **47** (Scheme 35).[52]

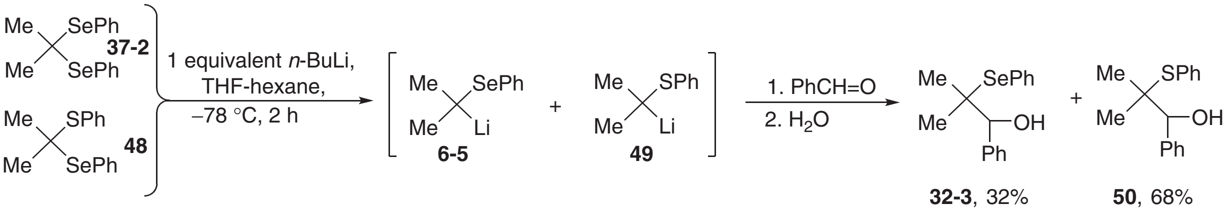


Scheme 35

3.02.2.2.3.2 Synthesis of α-thioalkyllithiums from α-thio-selenides (S,Se acetals)

The stabilization of a carbanion by an adjacent thioorganyl moiety has been debated for long.[55,56] The cleavage of the C–Se bond in mixed (S, Se) acetals has been used to synthesize α-phenylthioalkyllithiums, even those possessing two alkyl groups on their carbanionic center. They are not available using conventional H/Li exchange from the corresponding *s*-alkyl phenyl sulfides.[17]

They have been found using competing experiments involving the reaction of (1) *n*-butyllithium on a one-to-one mixture of 2-phenylthio-2-(phenylseleno)propane **48** and 2,2-bis-(phenylseleno)propane **37-2** (Scheme 36), (2) 2-phenylthio-2-propyllithium **49** and 2,2-bis-(phenylseleno)propane **37-2** used in stoichiometric amounts, and (3) 2-phenylseleno-2-propyllithium **6-5** and 2-phenylthio-2-(phenylseleno)propane **48**. The 2-phenylthio-2-propyl carbanion derived from **49** is only slightly more stable than 2-phenylseleno-2-propyl carbanion derived from **6-5** (70/30 ratio at equilibrium),[57] although the difference was expected to be much more important as predicted on theoretical grounds.[56]



Scheme 36

3.02.2.2.3.3 *Synthesis of α-selenoalkyllithiums from α-seleno-selenides (Se,Se acetals)*

Since the pioneer work of D. Seebach describing the transformation of bis(phenylseleno)methane and bis(phenylseleno)ethane into phenylselenomethyl- and phenylselenoethyl-lithium on reaction with *n*-butyllithium in THF-hexane,[19,58] this reaction has been extended to various alkyl-, cycloalkyl-, and aryl-substituted phenylseleno and methylseleno acetals **37-x**. The reaction has been carried out in THF-hexane, ether-hexane, and in some cases pentane and summarized in scientific articles[20,22,23,26] and in a few reviews.[13,17,59–62] Some representative selenoalkyllithiums **6-x**, generated by cleavage of the C–Se bond of the related selenoacetals **37-x** by butyllithiums, are disclosed in Scheme 37.[20]

As general trends, in this reaction, butyllithiums are by far more reactive than methyl- or phenyllithium. The latter exclusively produces α-selenoalkyllithiums in which the α-carbon bears a phenyl or a vinyl group. In order to avoid extensive destruction of the α-selenoalkyllithiums, the reaction has to be carried out at −78 °C since substantial decomposition (elimination of lithium hydride) and metallation of the ether solvents have already taken place at approximately −50 °C.[20] Although the synthesis of α-selenoalkyllithiums has been routinely achieved using *n*-butyllithium in THF-hexane,[20] *s*-butyllithium in the same solvent proved to be the best combination for the most difficult cases (Scheme 37).[20] *s*-Butyllithium also cleaves efficiently selenoacetals in diethyl ether, but this cannot be achieved by *n*-butyllithium unless the reaction is performed on selenoacetals derived from formaldehyde or aromatic aldehydes (Scheme 37).[20] The resulting α-selenoalkyllithiums are more stable, more nucleophilic, and less basic in that solvent than in THF.

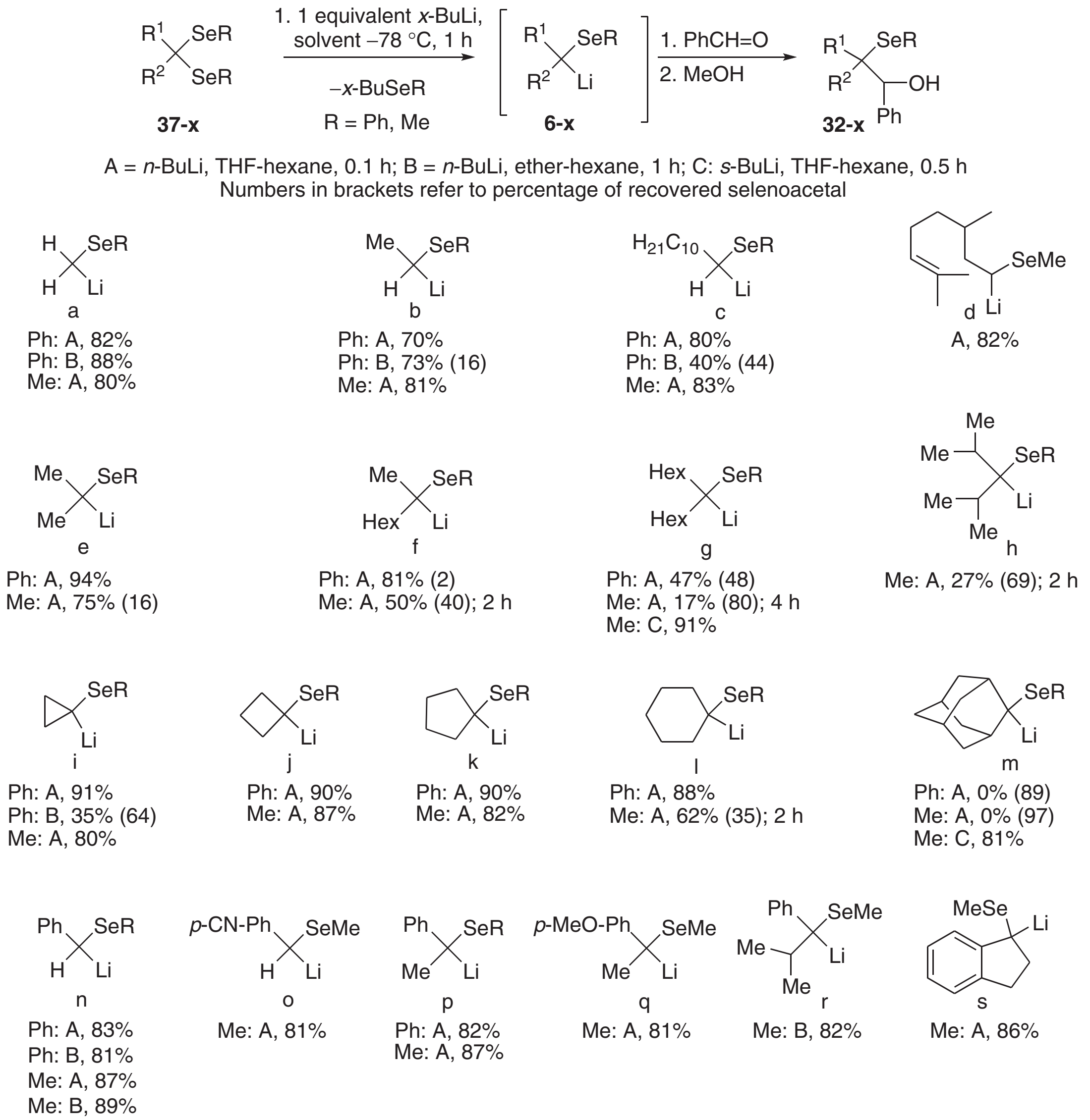
Otherwise, selenoacetals leading to the more stabilized carbanions are usually more easily cleaved (Schemes 37 and 38).[20,57] Thus,

1. phenylselenoacetals are more easily cleaved than methylseleno acetals because a phenylseleno moiety stabilizes a carbanion much more than the methylseleno one.[20,22,63]
2. selenoacetals bearing hydrogens on their α-carbons or derived from aromatic carbonyl compounds are cleaved more easily than those derived from dialkyl ketones, especially those that possess bulky alkyl substituents.[19,20,58]
3. selenoacetals derived from a three- to five-membered cyclic ketones and especially the three-membered cyclic ones are more efficiently cleaved than those parts of a six-membered cycle.[13,20,64,65] Selenoacetals derived from adamantanone are the most difficult to cleave (Scheme 37, entry m).[20]

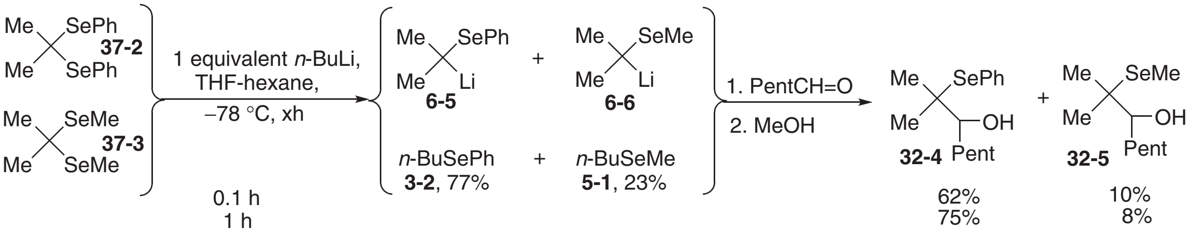
It is interesting to note that

1. the C–Se bond cleavage mainly occurs on 2,2-bis(phenylseleno)propane **37-2** in competing experiments involving 2,2-bis(phenylseleno)propane **37-2** and 2,2-bis(methylseleno)propane **37-2** (Scheme 38).[57] This result suggests that an α-phenylseleno carbanion is more stable than an α-methylseleno carbanion.
2. C–SeMe bond cleavage occurs in the mixed 2-methylseleno-2-phenylseleno-propane **37-4** to produce 2-phenylseleno-2-propyllithium **6-5**, which possesses the most stable of the two carbanions (Scheme 39, entry a). This result suggests that, all being equal, butyllithiums react more efficiently on the selenium atom of a methylseleno than of a phenylseleno moiety.[20] This is supported by the fact that C–SeMe bond cleavage selectively occurs in a competing experiment in which one equivalent of each 2-methylseleno-2-phenylseleno-propane **37-4** and 2,2-bis(phenylseleno)propane **37-2** are reacted with 1 equivalent of *n*-butyllithium (Scheme 39, entry b).[20]

It has to be stressed, however, that the reaction of a seleno-alkyllithium and a selenoacetal can take another course if carried out with those derived from aldehydes since they are prone to be metallated to produce the α-bisselenoalkyllithium instead (Scheme 40).[20] This reaction is particularly efficient with the first members of the series and therefore the C–Se bond cleavage in those types of selenoacetals should be achieved rapidly to consume all the selenoacetal extremely rapidly avoiding such process to take place.[20]



Scheme 37

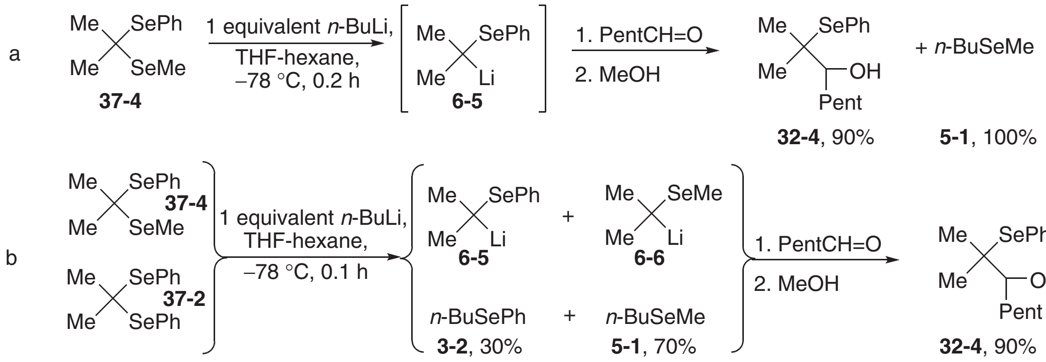


Scheme 38

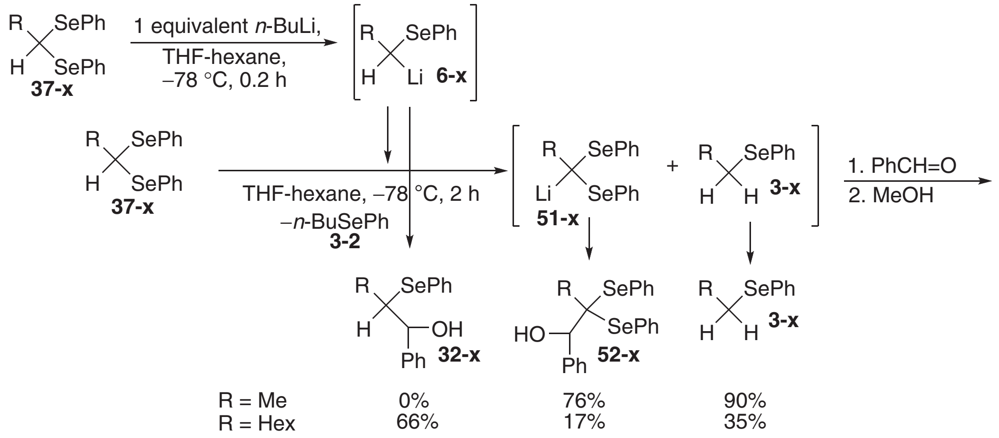
It has been observed that *n*-butyllitium cleaves selectively the axial seleno group of phenylselenoacetals **37-5** as well as methylselenoacetals **37-6** derived from conformationally rigid 4-*tert*-butyl cyclohexanone leading, under kinetic control, to the corresponding selenoalkyllithium whose lithium lies in the axial position (Scheme 41).[66]

It has also been observed that *n*-butyllithium in THF cleaves with quite good control (80/20) the C–SeMe bond of the mixed (SePh, SeMe) selenoacetal **37-7** derived from *t*-butyl-cyclohexanone which lies in an equatorial position.

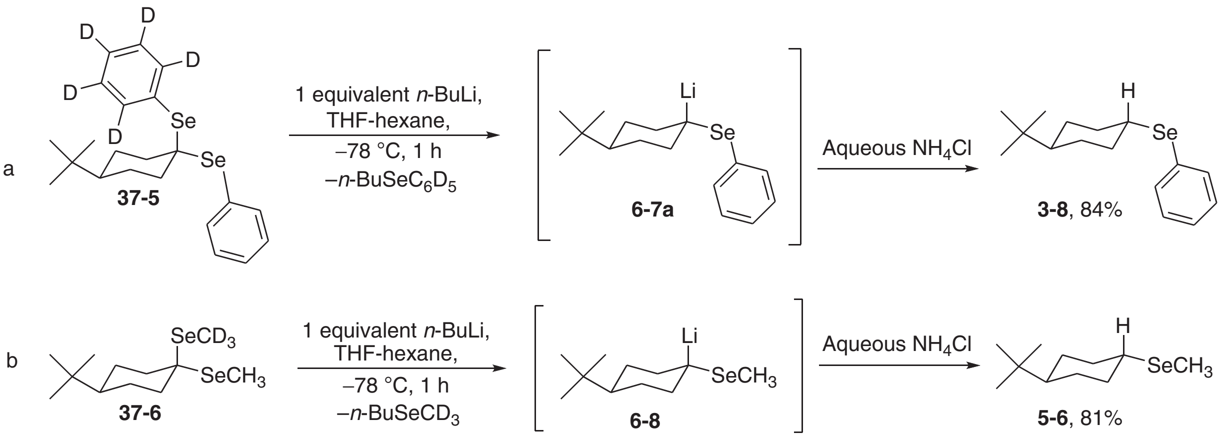
The resulting phenylselenoalkyllitium **6-7e** whose lithium is expected to lie in the equatorial position epimerizes, however, to its axial isomer **6-7a** almost instantaneously at −78 °C (axial/equatorial: 96/4).[66] In such a case, the great capacity of



Scheme 39



Scheme 40

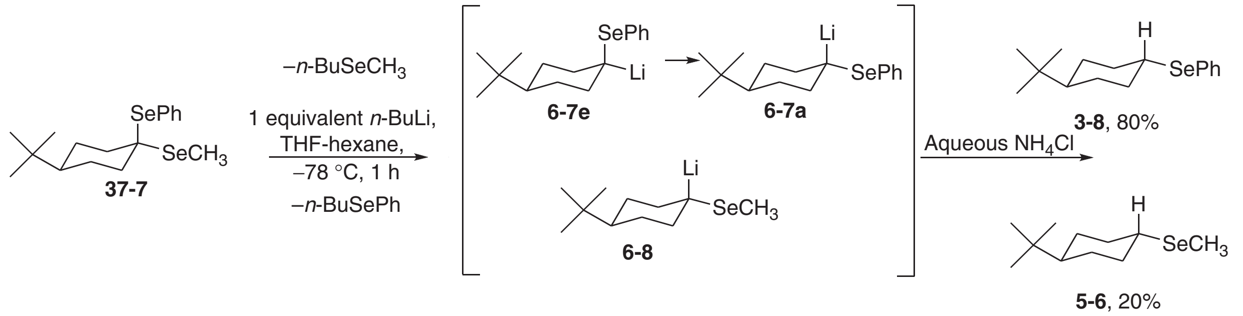


Scheme 41

n-butyllithium to cleave the axial C–Se bond in those selenoacetals,[66] is balanced by its aptitude to produce the α-phenylselenoalkyllithium whose carbanion is more stabilized than that of its α-methylselenoalkyllithium (Scheme 42).[57]

Facile epimerization of α-selenoalkyllithiums has also been reported by Reich[67] and by Hoffmann.[68–72] Similar observations have also been disclosed on α-selenobenzyllithiums.[73]

A tentative explanation of the high propensity of those organolithiums to lie in axial position may be proposed. It can be assumed that the conformation of the first incipient carbanion and even more of the presumed ate-complex intermediate is similar to that of the starting material. According to that proposal, the axial carbanion, from the cyclic compound, is better



Scheme 42

stabilized than its equatorial epimer, due to more favorable delocalization of the negative charge of the carbanion lone pair in the sigma Se–R bond (Figure 1). Both the presence of the polarizable selenium atom and an antiperiplanar arrangement are without doubt crucial for this purpose.[56]

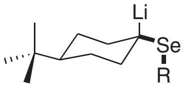
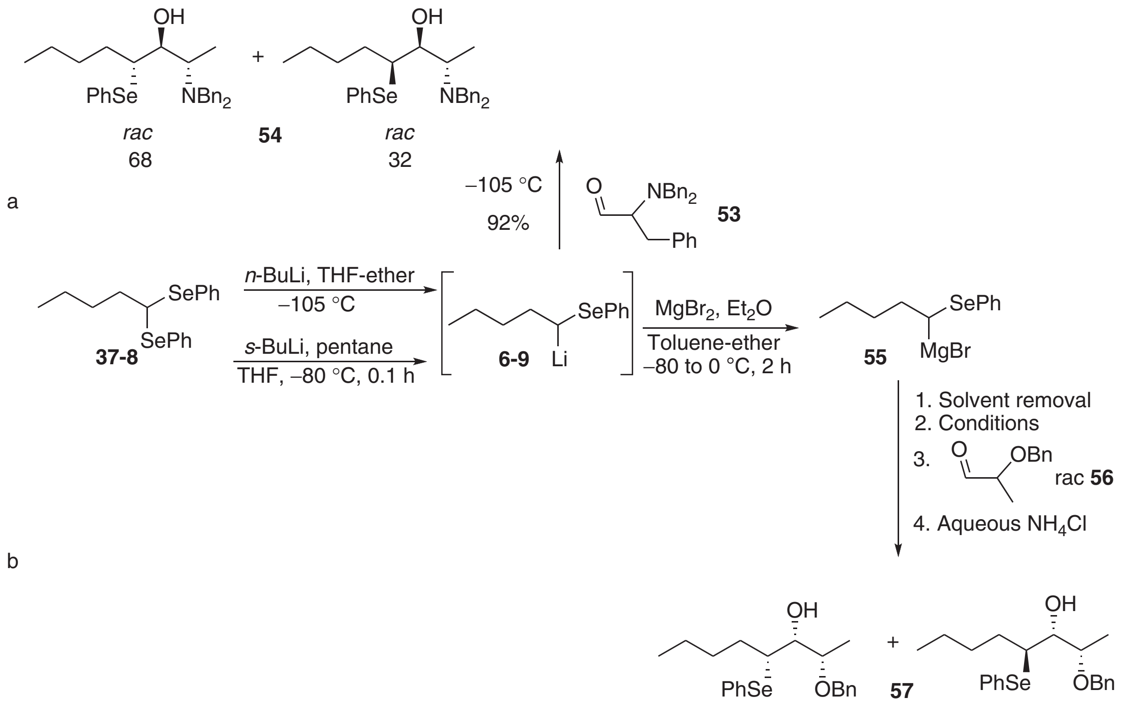


Figure 1 Stabilization of the axial carbanion.

Using a test based on kinetic resolution, the 1-phenylseleno-alkyllithium, **6-9** has been shown to undergo enantiomer equilibration at $-105\,°C$ with a rate comparable to that of its addition to aldehydes (Scheme 43, entry a).[68] The related bromo-magnesium derivative **55** prepared from **6-9** by Li/Mg exchange using magnesium dibromide, shows significant degrees of kinetic resolution, on reaction with α-benzyloxypropionaldehyde **56** especially when the reaction is run

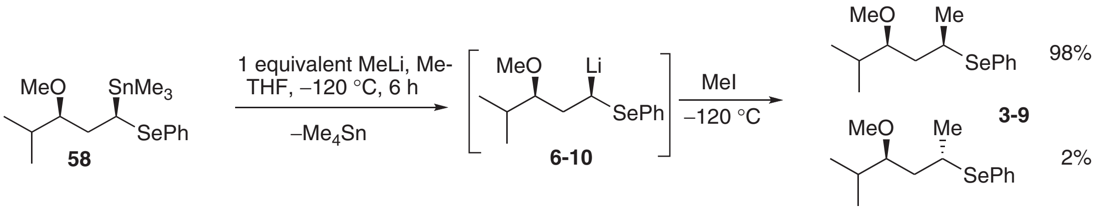


		rac	rac
THF, 0 °C, 1 h	62%	70	30
Et_2O, –78 °C, 5 h	46%	82	18
Toluene, –78 °C, 5 h	57%	93	7
CH_2Cl_2, –20 °C, 5 h	72%	95	5

Scheme 43

in CH_2Cl_2 (Scheme 43, entry b). Under these conditions, racemic **55** was resolved by reaction with 0.59 equivalent of α-benzyloxypropionaldehyde **56** at temperatures below − 20 °C. The remaining **55** prove to have an enantiomer enrichment of 80 –86% *ee* (as found by trapping with benzaldehyde). Hence, **55** has a considerably higher configurational stability than its lithium counterpart **6-9**.[72]

Interestingly, scalemic α-phenylseleno-alkyllithium compound **6-10**, resulting from tin/lithium exchange, from the corresponding scalemic α-tin alkyl phenyl selenide **58** and methyllithium was found to be configurational stable for at least 6 h at − 120 °C in methyl-THF (Scheme 44).[68]



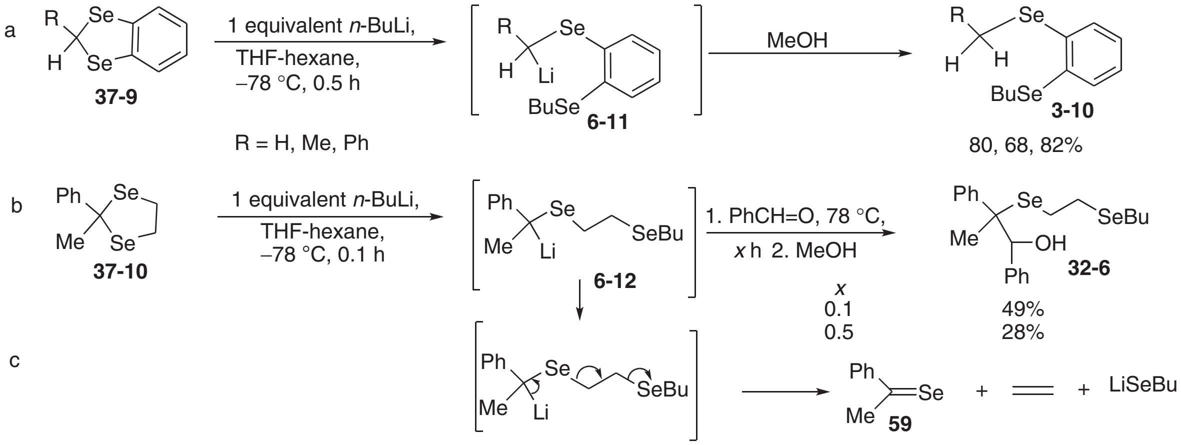
Scheme 44

Finally, it has been reported by Hoffmann[70] that the complex between diastereoisomeric 1-phenylseleno-3-methyl-butyllithium and scalemic chiral *trans*-1,2-dimethylamino cyclohexene is trapped by benzaldehyde and 2-dibenzylamino-3-phenyl propionaldehyde more rapidly than it equilibrates.

3.02.2.2.4 Reactivity of organolithiums toward α-heterosubstituted selenides in which two heteroatoms are part of a cycle

3.02.2.2.4.1 Reactions of organolithiums with Se,Se acetals

The reactivity of selenoacetals whose selenium atoms are part of a cycle, is far more complex than that of their alicyclic analogues. Thus 1,3-dibenzoselenolanes **37-9** react efficiently with *n*-butyllithium in THF-hexane at − 78 °C to produce the corresponding selenoalkyllithiums **6-11** in good yield (Scheme 45, entry a).[74] The related 1,3-selenolanes **37-10** provide modest yields of the corresponding α-selenoalkyllithiums **6-12** (Scheme 45, entry b).[75] This could be due to the instability of the intermediate carbanion **6-12** that decomposes through a cyclic mechanism leading to the unstable selenacetophenone **59** (Scheme 45, entry c). This proposal is supported by the observation that the yield of the alcohol **32-6** resulting from trapping the organolithium with benzaldehyde at − 78 °C but at different intervals of time decreases substantially on increasing the temperature (Scheme 45, entry c).[75] There is no clear cut evidence on the intimate mechanism by which **59** is formed. It can be also produced by fragmentation of the 'ate-complex intermediate' resulting from the attack of benzyllithium on the selenium atom of the SeBu moiety.

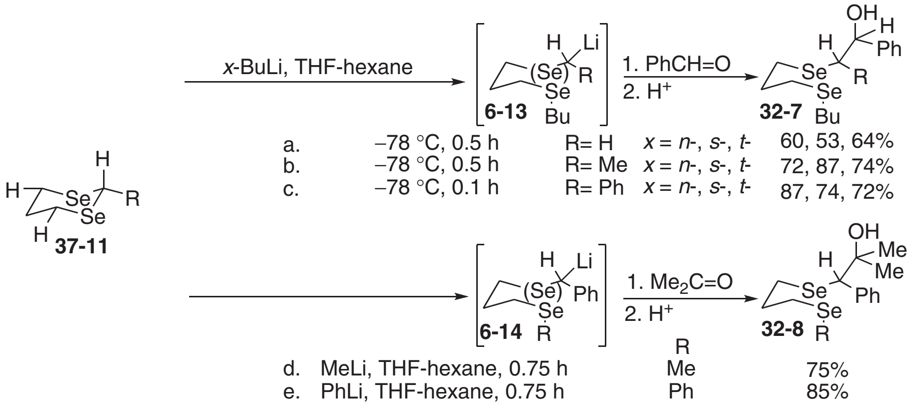


Scheme 45

The reaction of 1,3-diselenanes **37-11** with organolithiums is quite puzzling:

1. The parent compound as well as those substituted at the 2-position by a methyl or a phenyl are cleaved by the whole set of butyllithiums very rapidly in THF-hexane at − 78 °C to produce, in reasonably good yields, the corresponding α-selenoalkyllithiums **6-13** possessing in their structures a built-in butylseleno moiety (Scheme 46, entries a–c).[76,77]

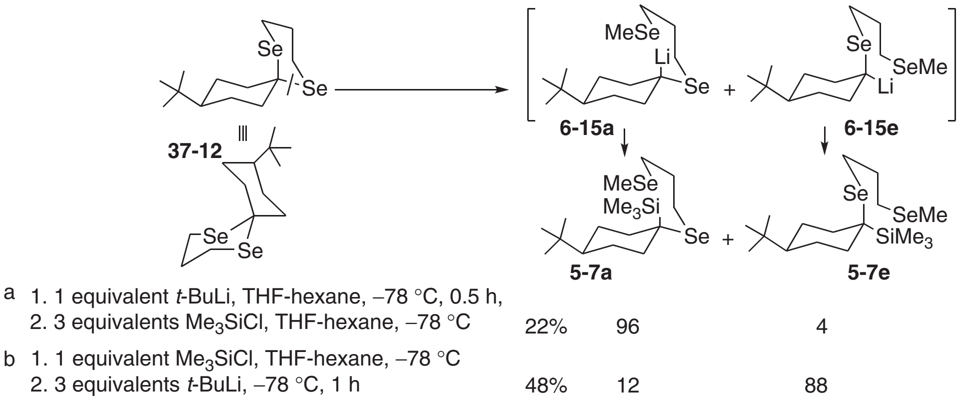
   None of them reacts with *n*-butyllithium in ether under similar conditions. 2-Phenyl-1,3-diselenane reacts faster than the others with butyllithiums in THF-hexane solution (Scheme 46, entry c compared to entries a and b) and is even cleaved, which is quite exceptional, by methyl- and phenyllithium in the same solvent mixture (Scheme 46, entries d and e). The authors have



Scheme 46

not detected products resulting from metallation of **37-11**, which takes place efficiently between related 1,3-dithianes and organolithiums allowing their use as masked acylanion equivalents.[78,79] Interestingly *n*-butyllithium-TMEDA complex, which usually has a higher propensity than *n*-butyllithium to act as a base, does not metallate 2-phenyl-1,3-diselenane which is expected to be one of the most acidic selenoacetals.

The C–Se bond cleavage also takes place with the spiro selenoacetal **37-12** whose structure is displayed in Scheme 47. It nevertheless requires the use of a threefold excess of the more reactive *t*-butyllithium to deliver, in modest yields, the related 4-*t*-butyl-1-trimethylsilyl-1-seleno cyclohexane **5-7a** in which the trimethyl silyl moiety is axial (kinetic product) if the reaction is carried out in the presence of trimethylsilyl chloride (Scheme 47, entry a).[75] Its epimer **5-7e** (thermodynamic product) is, however, mainly produced if the α-selenoalkyllithium **6-15e** is trapped after 0.5 h with trimethylsilyl chloride (Scheme 47, entry b).[75] Similar behavior has been previously reported by Reich for a related 1,3-diselenane derived from *cis*-3,5-diphenyl cyclohexanone.[67]

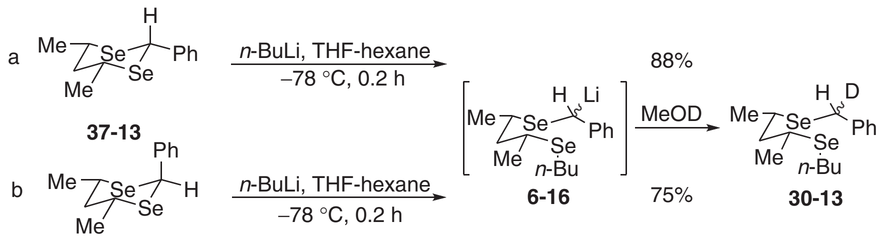


Scheme 47

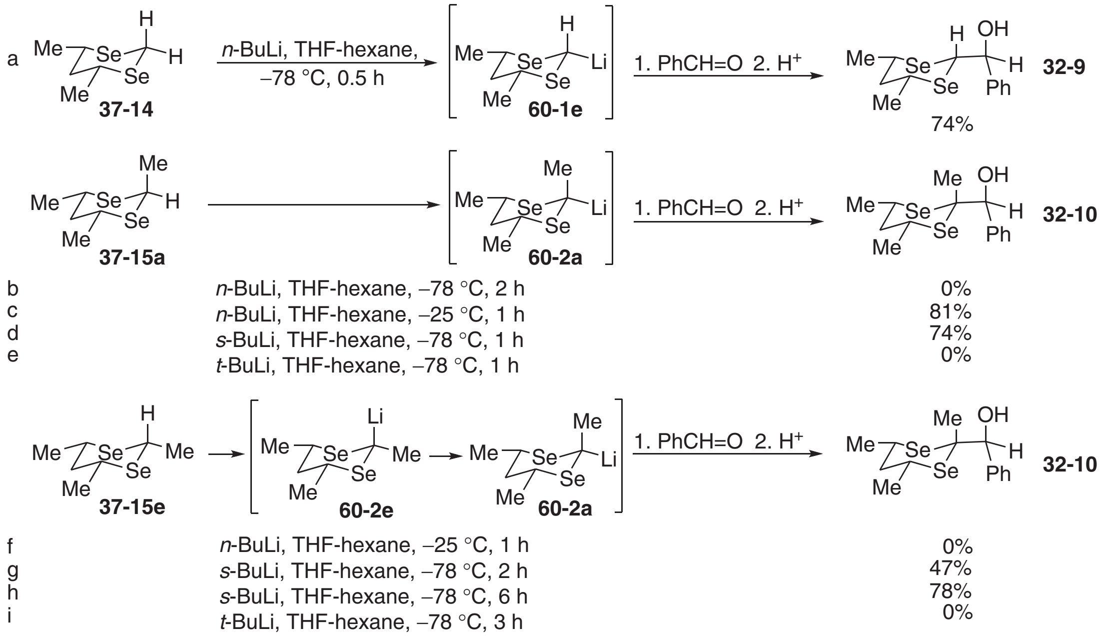
2. 2-Phenyl-4,6-dimethyl-1,3-diselenanes **37-13**, which possess rigid structures with the phenyl group either in equatorial or in axial position, react with butyllithiums in THF-hexane, the same way as 2-phenyl-1,3-diselenane. Each stereoisomers produce the same (80/20) stereoisomeric mixture of deuterated α-selenobenzylselenides **30-13** on further reaction with deuteromethanol (Scheme 48).[76,77]
3. Related 4,6-dimethyl-1,3-diselenane **37-14** and the epimeric 2,4,6-trimethyl-1,3-diselenanes **37-15** whose structures are disclosed in Scheme 49 behave differently toward butyllithiums.[76,77]

n-Butyllithium in THF-hexane efficiently metallates 4,6-dimethyl-1,3-diselenane **37-14** at C-2 already at − 78 °C (Scheme 49, entry a),[76] whereas the same reaction takes only place at higher temperature (− 25 °C) with 2,4,6-trimethyl-1,3-diselenane **37-15a** whose methyl group at C-2 is axially oriented (Scheme 49, entry c compared to entry a). Interestingly, its C-2 epimer **37-15e** does not react with *n*-butyllithium (Scheme 49, entry f compared to entry c).

Both epimeric 2,4,6-trimethyl-1,3-diselenane at C-2 **37-15** are, however, metallated with *s*-butyllithium in THF-hexane, although a marked difference of reactivity has been observed between them. Thus, the reaction already takes place efficiently after 1 h at − 78 °C on the epimer **37-15a** bearing the methyl group at C-2 in axial position (Scheme 49, entry d),[76] whereas it requires a much longer time on 2,4,6-trimethyl-1,3-diselenane **37-15e** bearing the methyl group in the equatorial position



Scheme 48



Scheme 49

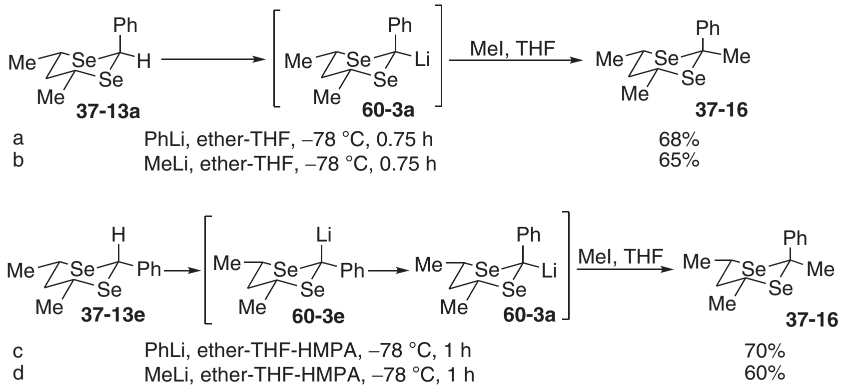
(Scheme 49, entries h and g compared to entry d).[76] It is interesting to note that trapping the resulting organolithiums **60-1e** and **60-2** with benzaldehyde produces exclusively and in all cases the alcohols **32-9** and **32-10** in which the benzylic group is in the equatorial position (Scheme 49).[76] It should be finally pointed out that *t*-butyllithium does not react with 2,4,6-trimethyl-1,3-diselenanes **37-15** under conditions which successfully allow their metallation by *s*-butyllithium (Scheme 49, entries e and i compared to entries d and h).[76]

Thus, butyllithiums do not behave similarly with 4,6-dimethyl-1,3-diselenane **37-14** and 2,4,6-trimethyl-1,3-diselenanes **37-15** than with other 1,3-diselenanes[76] and selenoacetals,[20] which are usually cleaved. *s*-Butyllithium in THF-hexane allows the synthesis of those 1-lithio-2,3-diselenanes which are not accessible from the same 1,3-diselenanes and LDA.[80] The stereochemistry of the resulting 2-lithio-1,3-diselenanes, however, resemble that of their potassio analogs which are efficiently produced on metallation of those 1,3-diselenanes by KDA instead.[80]

The results reported above for 4,6-dimethyl-1,3-diselenane **37-14** and 2,4,6-trimethyl-1,3-diselenanes[70] **37-15** are reminiscent of those already published by Eliel for the related 1,3-dithianes,[81–86] which do not usually exhibit[87] the high propensity of selenoacetals to be cleaved by butyllithiums.[20]

Metallation of 2-phenyl-4,6-dimethyl-1,3-diselenane **37-13**, which cannot be achieved by *n*-, *s*-, or *t*-butylllithium in THF-hexane (Scheme 48)[76] due to competing C–Se bond cleavage, has been efficiently achieved using phenyl- or methyllithium instead, which do not exhibit such a type of reactivity (Scheme 50).[20] Metallation proceeds at −78 °C in THF-hexane for the epimer **37-13a**, which bears the phenyl group in an axial position (Scheme 50, entries a and b). It is more difficult for its epimer at C-2 **37-13e**, and requires the use of HMPA to be successful (Scheme 50, entries c and d). Methylation has been achieved by methyl iodide and delivers in both cases the same 2-phenyl-2-methyl-4,6-dimethyl-1,3-diselenane **37-16** in which the phenyl group lies in the axial position (Scheme 50).[76]

Figure 2 tentatively visualizes the difficulties for butyllithiums, due to steric interactions with the methyl group lying in an equatorial position, to reach the selenium atom of 4,6-dimethyl-1,3-diselenane to achieve the C–Se bond cleavage.



a	PhLi, ether-THF, −78 °C, 0.75 h	68%
b	MeLi, ether-THF, −78 °C, 0.75 h	65%
c	PhLi, ether-THF-HMPA, −78 °C, 1 h	70%
d	MeLi, ether-THF-HMPA, −78 °C, 1 h	60%

Scheme 50

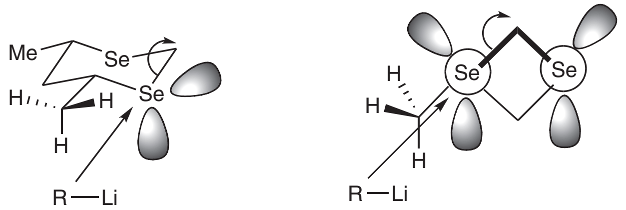


Figure 2 Steric interactions in 4,6-dimethyl-1,3-diselenane.

Figure 3 tentatively rationalizes the preferential attack of bases on the equatorial hydrogen on rigid 1,3-diselenanes. This reaction produces the equatorial carbanion in which the lone pair is suitably oriented to delocalize over the antiperiplanar carbon framework of the heterocycle through the polarizable soft selenium atom.

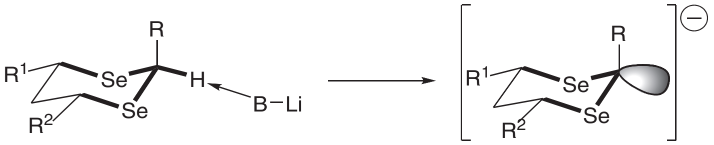


Figure 3 Preferential attack on rigid 1,3-diselanes.

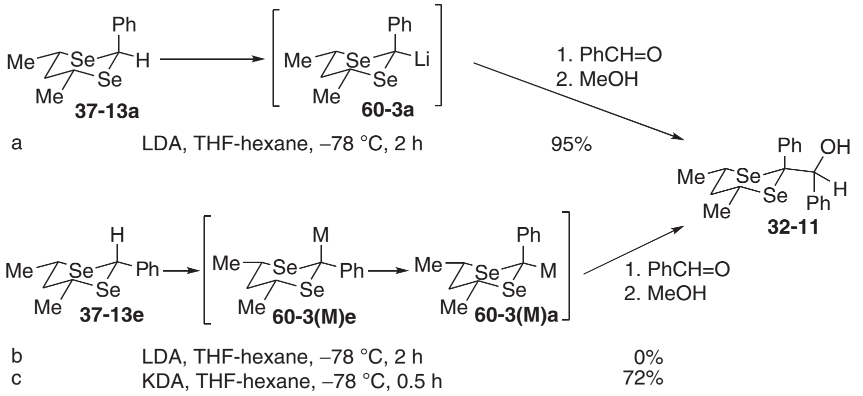
Epimers bearing an axial hydrogen at C-2 are much more difficult to metallate since the resulting axial carbanion is unable to accommodate the antiperiplanar arrangement. This is why it epimerizes so rapidly to the more stable isomer in which the carbanion lies in an equatorial position and reacts with electrophiles along this direction (Schemes 49–51).[76,80,88] This sort of argumentation has been originally disclosed by Eliel to rationalize the behavior of related rigid 1,3-dithianes with bases.[81–86]

Accordingly, it was found that lithium diisopropylamide (LDA) is able to metallate efficiently 2-phenyl-4,6-dimethyl-1,3-diselenane **37-13a** in which the benzylic hydrogen lies in the equatorial position (Scheme 51, entry a).[80] LDA is, however, unable to metallate the epimeric 2-phenyl-4,6-dimethyl-1,3-diselenane **37-13e** whose benzylic hydrogen lies in the axial position (Scheme 51, entry b).[80] Successful metallation has been nevertheless achieved, as already pointed out using the extremely basic KDA (Scheme 51, entry c).[80] Trapping of the resulting organometallics **60-3(K)a** with benzaldehyde produces exclusively the same benzyl alcohol **32-11** in which benzaldehyde has been inserted in the equatorial position (Scheme 51).[80]

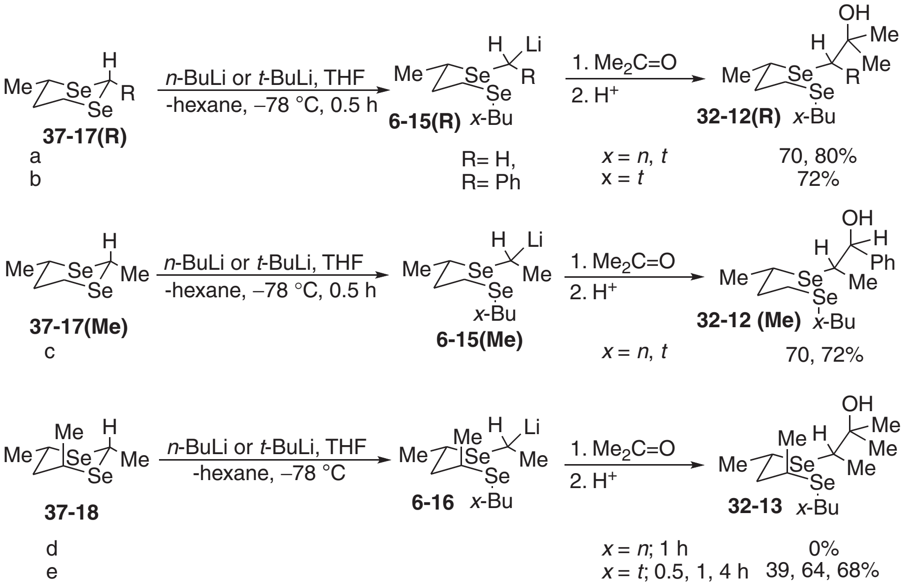
4-Methyl-1,3-diselenane **37-17(R)** (R=H) (Scheme 52, entry a) as well as its 2-phenyl- **37-17(R)** (R=Ph) (Scheme 52, entry b) and 2-methyl- **37-17(Me)** (Scheme 52, entry c) homologs in which all the substituents are *cis* to each other are cleaved on reaction with *t*-butyllithium.[77]

n-Butyllithium as well as *t*-butyllithium apparently selectively react with the selenium atom which is the farthest from the 4-methyl group and cleave the related C–Se bond quite rapidly at −78 °C (Scheme 52, entries a–c).[77]

2,4,6-Trimethyl-1,3-diselenane **37-18**, in which the methyl groups at C-4 and C-6 are *cis* to each other is far less reactive than its 4-desmethyl analogs toward butyllithiums (Scheme 52, entries d and e).[77] It is inert toward *n*-butyllithium at −78 °C (Scheme 52, entry d) and requires 4 h at the same temperature to be cleaved by *t*-butyllithium (Scheme 52, entry e). Those results are puzzling since *t*-butyllithium does not react with related 2,4,6-trimethyl-1,3-diselenane stereoisomers **37-15** (Scheme 49, entries e and i), whereas *s*-butyllithium metallates them instead (Scheme 49, entries d and h).



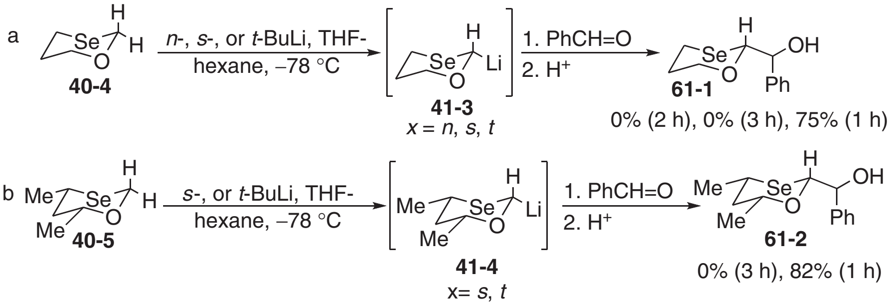
Scheme 51



Scheme 52

3.02.2.2.4.2 Reactions of organolithiums with O,Se acetals

Cyclic O,Se-acetals **40-4** and **40-5** only react with *t*-butyllithium which selectively metallate them (Scheme 53).[77] It is interesting to point out that the reaction toward *t*-butyllithium of the parent O,Se-acetals **40-4** is different from that of the parent selane **37-11**, which is instead cleaved (Scheme 53, entry a compared to Scheme 46, entry a). Both 4,6-dimethyl O,Se- **40-5** and its Se,Se analog **37-14** are, however, metallated by butyllithiums (Scheme 53, entry b compared to Scheme 49, entry a).



Scheme 53

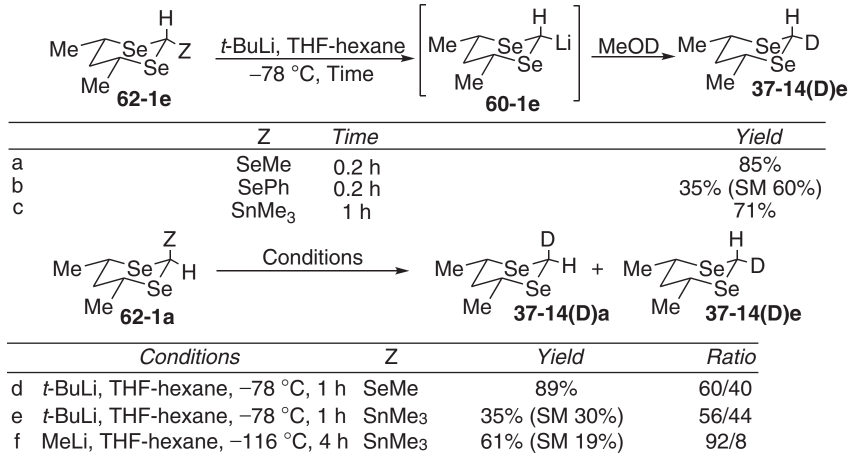
3.02.2.2.4.3 Reactions of organolithiums with seleno-orthoesters

Seleno-orthoesters are very easily cleaved by *n*-butyllithium in THF-hexane or in ether-hexane at −78 °C. Thus tris-(phenylseleno)ethane produces under those conditions 1,1-bis(phenylseleno)-1-ethyllithium[19,58] and tri(methylseleno)-orthoesters behave similarly and produce 1,1-bis(methylseleno)-1-alkyllithiums.[17,64,89,90]

2-Lithio-2,6-dimethyl-1,3-diselenanes have been efficiently synthesized, via a Se/Li exchange, from 2-seleno-2,6-dimethyl-1,3-diselenanes and butyllithium.[77] The reaction proceeds without competing hydrogen/lithium exchange at C-2 or Se/Li exchange at one of the endocyclic selenium, which would have otherwise led to the destruction of the heterocycle.[88] This method proved to be far more general for the synthesis of 2-lithio-2,6-dimethyl-1,3-diselenanes than those involving the metallation of the corresponding 2,6-dimethyl-1,3-diselenanes by lithium diisopropylamine[77] or by organolithiums.[76,77]

Se/Li exchange can be performed at −78 °C with *n*-butyllithium in THF-hexane, but can be achieved very rapidly at much lower temperature (−130 °C), if instead carried out with *t*-butyllithium in a similar solvent mixture.

The reaction carried out at −78 °C on the rigid 2-seleno-4,6-dimethyl-1,3-diselenane **62-1e** bearing the seleno moiety in the equatorial position, delivers stereoselectively 2-deutero-4,6-dimethyl-1,3-diselenane **37-14(D)e**, whose deuterium atom lies exclusively in the equatorial position, on further reaction with MeOD. The reaction proceeds more efficiently with the methylseleno derivative (Scheme 54, entry a)[77,88] than with its phenylseleno analog (Scheme 54, entry b).[77,88]



	Z	Time	Yield
a	SeMe	0.2 h	85%
b	SePh	0.2 h	35% (SM 60%)
c	$SnMe_3$	1 h	71%

	Conditions	Z	Yield	Ratio
d	*t*-BuLi, THF-hexane, −78 °C, 1 h	SeMe	89%	60/40
e	*t*-BuLi, THF-hexane, −78 °C, 1 h	$SnMe_3$	35% (SM 30%)	56/44
f	MeLi, THF-hexane, −116 °C, 4 h	$SnMe_3$	61% (SM 19%)	92/8

Scheme 54

Reaction of 2-methylseleno-4,6-dimethyl-1,3-diselenane **62-1a** bearing the seleno moiety in axial position requires more longer time at −78 °C (Scheme 54, entry d). It delivers a 60/40 mixture of epimeric 2-deutero-4,6-dimethyl-1,3-diselenanes **37-14(D)a** and **37-14(D)e** suggesting that epimerization at the anomeric carbon as taken place prior deuteration, although it is slow enough to allow to trap the least stable axial carbanion in quite high ratio even after 1 h at −78 °C (Scheme 54, entry d).

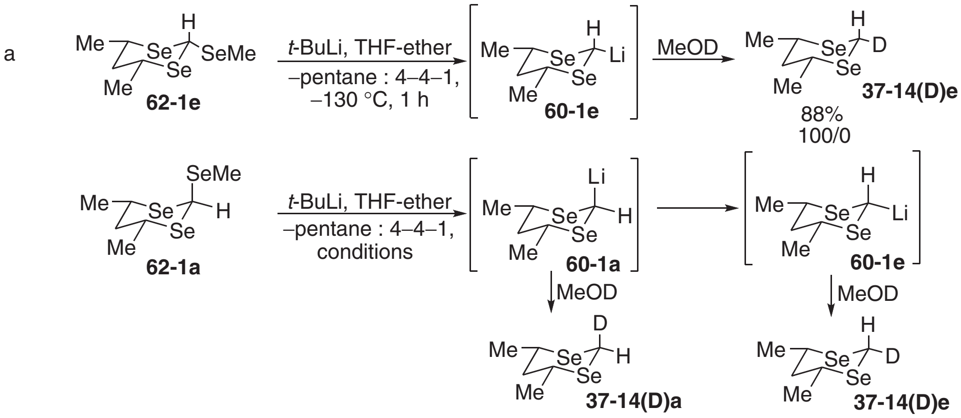
The related 2-trimethyltin-4,6-dimethyl-1,3-diselenane **62-1** is less reactive toward *t*-butyllithium owing probably the steric hindrance implied in the process (Scheme 54, entries c and e). Interestingly, methyllithium is more reactive than other alkyllithiums (Scheme 54, entry f) and works at even lower temperature (−116 °C) to allow access to the 2-lithio-1,3-diselenane whose deuteration provides 2-deuterio-4,6-dimethyl-1,3-diselenane **37-14(D)a** with the deuterium atom in axial position.[77]

2-Methylseleno-4,6-dimethyl-1,3-diselenanes **62-1** also efficiently react with *t*-butyllithium in the Trapp mixture of solvents (THF–ether–pentane: 4–4–1) (Scheme 55).[91,92] Under those conditions the cleavage can be achieved at much lower temperature (around −130 °C or −116 °C, 0.1 to 0.5 h).[88]

The reaction involving 2-methylseleno-4,6-dimethyl-1,3-diselenane **62-1a** bearing the selenomethyl group in axial position is rather slow at −130 °C, requires at least one hour to go to completion and by quenching the organolithium intermediate **60-1a** with deuterated methanol after 1 h provides 2-deutero-4,6-dimethyl-1,3-diselenanes **37-14(D)a**, in which the deuterium atom has been stereoselectively introduced at the axial position (Scheme 55, entry b).[88] The Se/D exchange occurs, therefore, with complete retention of configuration.

Thus, the organolithium derivative **60-1a** bearing the lithium atom in axial position proved to be remarkably configurationally stable as it retains its stereochemistry for a reasonably long period of time between −130 and −116 °C (Scheme 55, entries b and c).[88] Those results are remarkable since epimerization to the more stable 2-lithio-4,6-dimethyl-1,3-diselenane **60-1e** with the lithium lying in equatorial position occurs slowly until −98 °C and extremely rapidly at −78 °C (Scheme 55, entries e and f).[80,88]

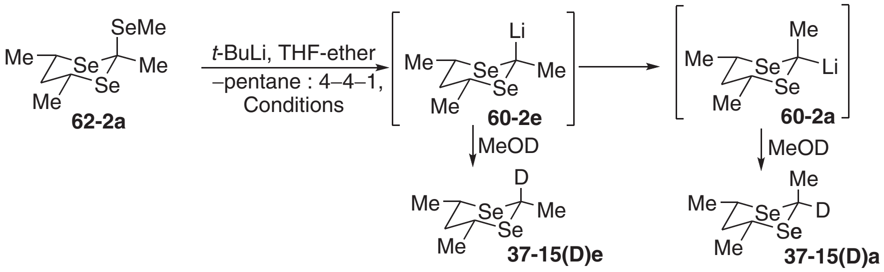
The reaction has been successfully extended to 2-methylseleno-2,4,6-trimethyl-1,3-diselenanes **62-2a** (Scheme 56).[88] 2-Methylseleno-2,4,6-trimethyl-1,3-diselenane **62-2a** bearing the methylseleno moiety in axial position provides on reaction of *t*-butyllithium at −116 °C, stereoselectively 2-lithio-2,4,6-trimethyl-1,3-diselenane **60-2e** then 2-deutero-2,4,6-trimethyl-1,3-diselenane **37-15(D)e** bearing the lithium and deuterium atom in axial position after deuterolysis at the same temperature



	Conditions	Overall yield (%)	Ratio D-axial/D-equatorial
b	–130 °C, 0.2 h	25	99/1
c	–130 °C, 1 h	85	98/2
d	–98 °C, 1 h	90	95/5
e	–78 °C, 0.1 h	90	70/30
f	–78 °C, 1 h	80	40/60

Scheme 55

(Scheme 56, entry a). Epimerization of 2-lithio-2,4,6-trimethyl-1,3-diselenane **60-2e** bearing the lithium in axial position is quite rapid even more rapid at − 78 °C than that of the related 2-lithio-4,6-dimethyl-1,3-diselenane **60-1a** (Scheme 56, entries b and c compared to Scheme 55, entries d and e).[88]



	Conditions	Overall yield (%)	Ratio D-axial/D-equatorial
a	–116 °C, 1 h	90	100/0
b	–78 °C, 0.6 h	80	50/50
c	–78 °C, 1 h	90	35/65

Scheme 56

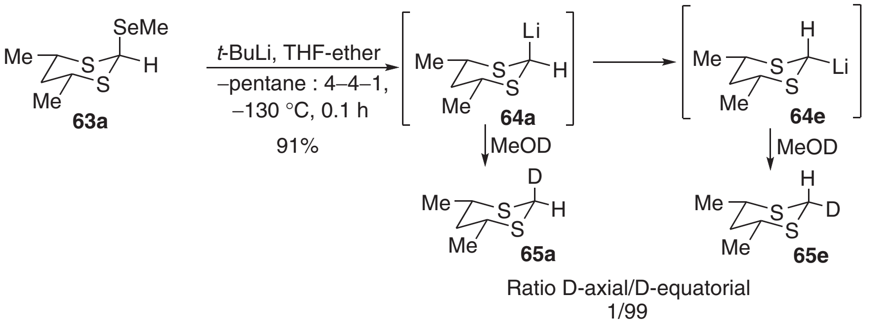
The cleavage of the C–Se bond, reported above in the case of 2-methylseleno-4,6-dimethyl-1,3-diselenane **62-1**, has been successfully extended to 2-methylseleno-4,6-dimethyl-1,3-dithiane **63a**.[88] It is extremely rapid at − 130 °C with the stereoisomer **63a** that bears the methylseleno moiety in the axial position, but epimerization of the resulting 2-lithio-4,6-dimethyl-1,3-dithiane **64a** is extremely rapid and almost exclusively leads after deuterolysis to 2-deutero-4,6-dimethyl-1,3-dithiane **65e** in which the deuterium atom lies almost exclusively in equatorial position (Scheme 57).[88]

A higher thermodynamic stability of 1-lithio-1,3-dithianes **64** compared to their selenium analogs **60-1** was expected. The results disclosed in Schemes 57 and 55 entries a and b suggest that this is apparently not the case. Our results, however, match those recently reported by Hoffmann[93] (and references cited therein).

The lower configurational stability of 2-lithio-4,6-dimethyl-1,3-dithiane **64** compared to 2-lithio-4,6-dimethyl-1,3-diselenane **60-1** can be due to the higher destabilizing effect on the carbanion of the unshared electrons localized on the axial 3sp^3 orbitals of sulfur in 1,3-dithianes compared to the more diffuse 4sp^3 orbitals of selenium in 1,3-diselenolanes.

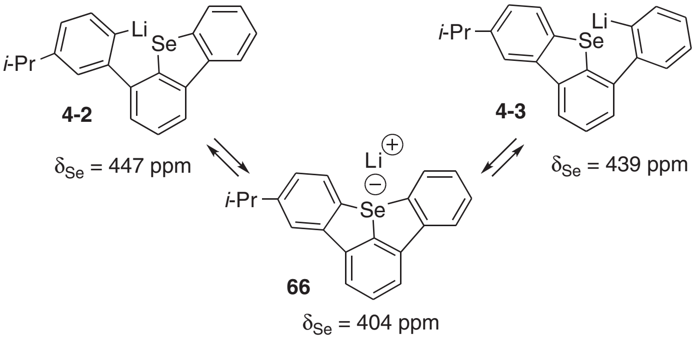
3.02.2.2.5 On the mechanism of the Se/Li exchange involving organolithiums

Ate complexes, first proposed by Wittig and Schollkopf,[94] have been postulated as presumptive intermediates in chalcogen/metal exchange reactions.[95,96] Those having only alkyl and aryl ligands have been characterized in solution and in the solid state, and probed by high-level calculations.[97–99]



Scheme 57

Reich[100,101] has tentatively set up DNMR experiment, on the compounds whose structures are disclosed in Scheme 58, to probe the presence of the ate complex **66**. He reported that the very fast intramolecular Li/Se exchange between **4-2** and **4-3** does not proceed appreciably through the observable separated ion pairs ate complex **66**. He, therefore, proposes that the interconversion of separated ion pairs/contact ion pairs is slower than the Li/Se exchange rate, which allows the intramolecular substitution to bypass the separated ion pairs of ate complex **66**.[100,101]



Scheme 58

3.02.2.2.6 Selenoacetal structure–reactivity relationships

Relationships between structure of selenides and their reactivity toward organolithiums can be summarized as follows:

1. Benzyl and allylselenides, even those bearing two alkyl-substituents on the benzylic carbon, react with alkyllithiums much more rapidly than related methyl or phenyl selenides.
2. Phenylselenoacetals are more easily cleaved than methylseleno ones.[17]
3. Selenoacetals derived from formaldehyde reacts faster than those derived from other aldehydes themselves reacting faster than those derived from ketones. However, selenoacetals derived from cyclopropanone are more easily cleaved than those derived from cyclobutanones, cyclopentanone, and cyclohexanones, which are the least easily cleaved.[17]
4. Selenoacetals derived from aromatic aldehydes and ketones react faster than those derived from alkyl-susbtituted aldehydes and ketones, respectively.

3.02.2.2.7 Reactivity couple butyllithium-solvent towards selenoacetals

The cleavage of the C/Se bond has been tested with various organolithiums such as methyllithium, phenyllithium, *n*-, *s*-, or *t*-butyllithiums as well as with Grignard reagents in THF-hexane, ether-hexane, or hexane. Selenoacetals do not react with Grignard reagents in diethyl ether or in THF. Methyllithium and phenyllithium have only been successfully used when reacted with selenoacetals derived from aromatic carbonyl compounds, which are the most reactive. *s*-Butyllithium in THF-hexane is probably the most efficient combination. It should be used any time as *n*-butyllithium in THF, if it is not able to cleave the C/Se bond rapidly at − 78 °C.

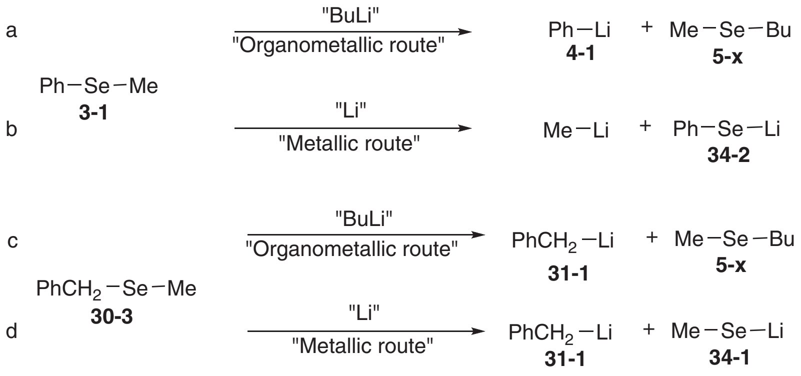
3.02.3 Reactivity of Selenides and Functionalized Selenides toward Elemental Lithium and Metal Arenides

Reaction of selenides with elemental lithium or lithium arenides has attracted much less attention than that involving butyllithiums. It requires in all the cases to carry out at one stage of the process a heterogeneous reaction involving either the reaction of lithium with the selenide or the synthesis of the lithium arenides. They are unstable at room temperature and have to be prepared just before use. The best conditions involve the use of a slight excess of lithium powder,[102] lithium shaving, chunk or lithium wire,[28] or a stoichiometric amount of lithium naphtalenide (LiN),[42,103,104] lithium amino-naphtalenide (LDMAN), which offers the advantage to remove from the medium, at the end of the process, the metal carrier by acid washing[105–107] or the more efficient lithium di-*t*-butyl biphenyl (LiDBB) (reduction potential half wave toward Hg electrode: naphtalene $E_0 = -1{,}98$ V, DBB $E_0 = -2{,}05$).[107–109] In the latter cases, use of catalytic amounts of di-*t*-butyl biphenyl (DBB) as lithium carrier proved to be beneficial[102] (for controversial results, see Ref. 106).[110]

The resulting organolithium compounds have been usually trapped with benzaldehyde either after the reaction between the selenide and lithium or lithium arenide is over (Grignard-type conditions)[111,112] or by *in situ* trapping by benzaldehyde present in the medium (Barbier-type conditions).[113,114] The latter conditions cannot usually be carried out in the presence of carbonyl compounds when the Se/Li exchange is performed with alkyllithium reagents.

3.02.3.1 Reactivity of Selenides toward Elemental Lithium and Metal Arenides

The mechanism of the reactions involving the cleavage of the C–Se bond by butyllithiums (the 'organometallic route,' two-electron transfer) or lithium or lithium arenides (the 'metallic route,' involving one electron transfer) markedly differs and provides the same or different compounds depending on the relative stabilization, in the transition states, of the anion and radical intermediates. Thus, each of the two processes provide a different class of products from methyl-phenylselenide (Scheme 59, entry b compared to entry a), whereas they deliver the same benzyllithium from benzylmethyl- or benzylphenyl selenides (Scheme 59, compare entry d to entry c).



Scheme 59

This is not the only difference between the two approaches: in fact butyl selenide is generated as by product in the 'organometallic route' (Scheme 59, entries a and c) whereas a lithium selenolate (Scheme 59, entries b and d) is concomitantly formed in the 'metal route.'

The 'metal route' offers the advantage to:

1. Carry the Se/Li exchange in the presence of a carbonyl compound with *in situ* reaction with the extremely reactive or unstable organometallics (Barbier process).
2. Use of a cheap reagent in the case of lithium or when involving catalytic amounts of DBB.
3. Generate alkyllithium rather than aryllithiums from alkyl-arylselenides as obtained using the 'organometallic route' instead.

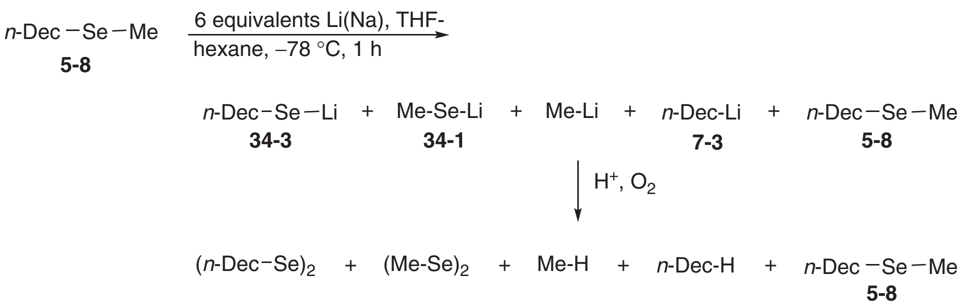
The 'metal route' presents the following drawbacks:

1. Competing cleavage of the carbon–selenium bond of the selenide by the organometallic resulting from the reaction of the metal on the same selenide.
2. Concomitant production of lithium selenolates as powerful nucleophiles that react competitively to the organolithium on reaction with an alkyl halide.
3. The amount of arene by-product formed on completion of the reaction involving the use of stoichiometric amount of lithium arenide which is difficult to separate from the medium especially if naphtalene is used.
4. Furthermore, alkyllithiums produced from alkyl-phenylselenides through the radical process tend to initiate a competing 'ionic cleavage' of the unreacted selenide, finally leading to a complex mixture of products.

The reactivity of selenides toward lithium and lithium arenides largely depends on the structure of the selenide. The most difficult to cleave are without doubt dialkylselenides whereas diarylselenides are the most easy to cleave.

3.02.3.1.1 Reactivity of alkyl-methylselenides toward lithium and lithium arenides

Lithium does not react with *n*-decyl-methylselenide **5-8** at − 78 °C in THF (Scheme 60, entry a), but reacts if the reaction is carried out at 20 °C instead to cleave each of the two C–Se bonds to provide methyllithium and lithium decylselenolate in slight (57/43) excess over decyllithium and lithium methylselenolate (Scheme 60, entry b). For conveniences the medium has been sequentially reacted with (1) aqueous hydrochloric acid solution to protonate the organolithiums and the selenolate and (2) then with oxygen to oxidize the selenols to the corresponding diselenides (work-up A) (Scheme 60).[28,115]

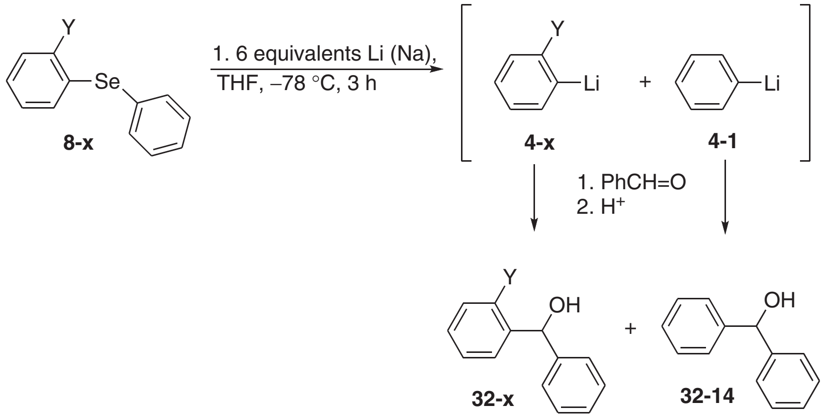


		$(n\text{-Dec-Se})_2$	$(\text{Me-Se})_2$	Me-H	*n*-Dec-H	*n*-Dec−Se−Me **5-8**
a	−78 °C, 3 h	–	–		–	92%
b	20 °C, 24 h	45%	34%		29%	0%

Scheme 60

3.02.3.1.2 Reactivity of diarylselenides toward lithium and lithium arenides

As already point out, diaryl selenides are easily cleaved at − 78 °C in THF, by elemental lithium in shanks containing 1% sodium. The reaction is completely regioselective for dissymmetric derivatives bearing a methoxy- or a dimethylamino group in the *ortho* position known as *ortho*-directing groups which produce the *ortho*-substituted phenyllithium rather than phenyllithium (Scheme 61, entries a and b). It is modestly selective with *ortho*-trifluoromethyl-phenyl-phenylselenide (Scheme 61, entry d), and unselective with aryl-phenylselenides whose aryl group bears an *ortho*-methyl group (Scheme 61, entry c), methoxy- or dimethylamino groups in *para* or *meta* position. It suggests that inductive or mesomeric effects do not play a crucial role in the process.[28]

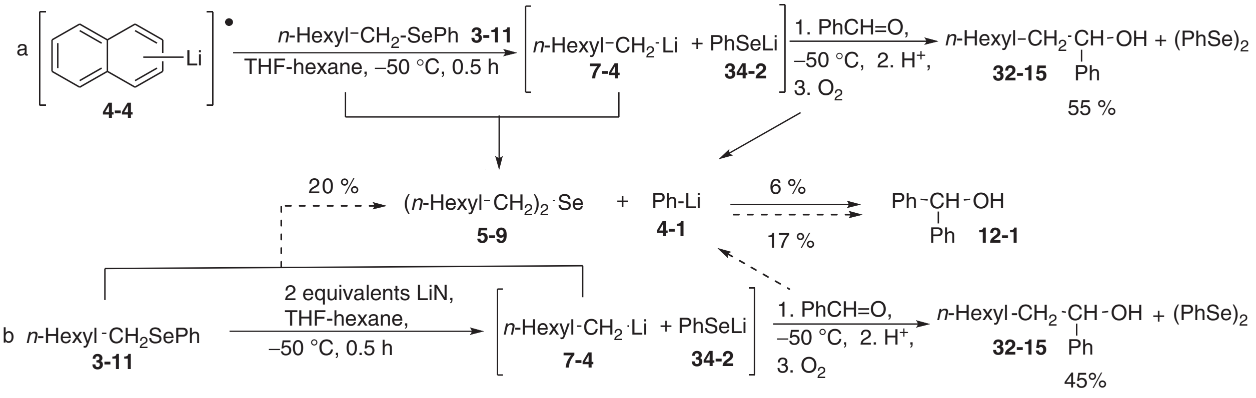


	Y	Yield (%)	Yield (%)
a	OMe	63	0
b	NMe_2	59	0
c	Me	36	26
d	CF_3	47	15

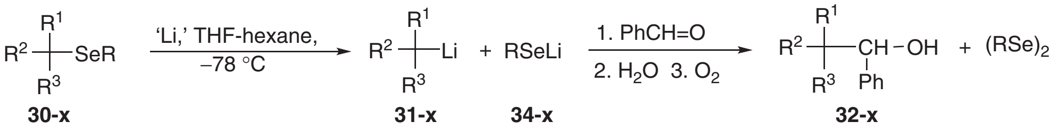
Scheme 61

3.02.3.1.3 Reactivity of alkyl-aryl selenides toward lithium and lithium arenides

The reactions between alkyl-phenyl selenides and lithium or lithium arenides have been carried out between − 50 and − 78 °C according to different procedures that are disclosed below and involve trapping of the generated organometallics with benzaldehyde, then quenching with hydrochloric acid followed by an oxygen treatment (work-up A).[28,115] The reactions have been carried out either with lithium (Scheme 63 and Table 8, entries a, b, e, h, i, n, o, q, t, and u Scheme 64 and Table 9) or lithium arenides (Schemes 62 and 63 and Table 8, entries c, d, f, g, j, m, p, r, s, and v) under Grignard- (Scheme 62; Scheme 63 and Table 8) or Barbier- (Scheme 64 and Table 9) conditions. Under Grignard conditions, the reaction of LiN 4-4 on heptyl-phenylselenide 3-11, performed by adding the selenide on to a preformed solution of LiN maintained at −5 to 0 °C (protocol A; Scheme 62, entry a) gives a better yield of the benzyl alcohol 32-15 over that involving the reverse order of addition (protocol B; Scheme 62, entry b compared to entry a).[28,115,116]



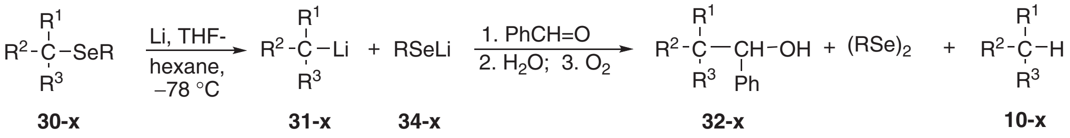
Scheme 62



Scheme 63

Table 8 Reaction between alkyl-phenylselenides and lithium or lithium arenides

Entry	*R*	*R¹*	*R²*	*R³*	*Reagent*	*Yield (%)*		
						Alcohol	*Diselenide*	*Coupling*
a	Ph	H	H	H	Li	77	89	–
b	Ph	H	H	*n*-Pr	Li	64	87	–
c	Ph	H	H	*n*-Hept	LiDBB	75	–	–
d	Ph	H	H	*n*-Hept	LiN	46	–	–
e	Ph	H	H	*n*-Nonyl	Li	61	92	–
f	Ph	H	Me	*n*-Hept	LiDBB	76	–	–
g	Ph	H	Me	*n*-Hept	LiN	51	–	–
h	Ph	H	H	*n*-Nonyl	Li	50	86	–
i	Ph	Me	Me	Me	Li	39	90	–
j	Ph	Me	Me	Me	LiDBB	63	–	–
k	Ph	Me	Me	Me	LiN	27	–	–
l	Ph	4-MeOPh	H	H	LiDBB	78	–	0
m	Ph	4-MeOPh	H	H	LiN	55	–	0
n	Ph	Ph	H	H	Li	0	90	35
o	Me	Ph	H	H	Li	18	85	55
p	Ph	Ph	H	Me	LiN	48	–	52
q	Ph	Ph	H	Me	Li	0	94	82
r	Me	Ph	H	Me	LiDBB	63	–	–
s	Ph	Ph	Me	Me	LiN	9	–	91
t	Ph	Ph	Me	Me	Li	0	95	87
u	Me	Ph	Me	Me	Li	0	89	91
v	Me	Ph	Me	*n*-Hept	LiDBB	72	–	0



Scheme 64

Table 9 Reaction between alkyl-phenylselenides and lithium

Entry	*R*	*R¹*	*R²*	*R³*	*Yield (%)*		
					Alcohol	*Diselenide*	*Arylalkane*
a	Ph	H	H	H	75	92	
b	Ph	H	H	*n*-Pr	65	92	
c	Ph	H	Me	Et	62	90	
d	Ph	Me	Me	Me	40	91	
e	Ph	Nonyl	Me	Me	33	90	
f	Ph	Ph	H	H	69	90	26
g	Me	Ph	H	H	81	87	0
h	Ph	Ph	H	Me	58	88	25
i	Me	Ph	H	Me	73	80	8
j	Ph	Ph	Me	Me	52	90	28
k	Me	Ph	Me	Me	62	85	20

The formation of diphenylcarbinol **12-1** in up to 17% yield besides 1-phenyloctanol **32-15** (Scheme 62, entry b) suggests that the formation of phenyllithium, which is expected to arise beside di-heptylselenide **5-9**, from the cleavage of heptyl-phenylselenide **3-11** by the heptyllithium **7-4** intermediate can be minimized (6%, Scheme 62, entry b) by adding the selenide to the LiN solution avoiding the presence of a large amount of heptyl-phenylselenide **3-11** besides the heptyllithium **7-4** just formed.

It is imperative to carry out the cleavage at − 78 °C and not at higher temperatures to avoid the competing reaction described above. Thus, performing the reaction between heptyl-phenylselenide **3-11** and LiN **4-4** (2.1 equivalents) at 0 °C for 0.5 h produces in complement to the expected 1-phenyloctanol **32-15** (18%), diphenylcarbinol **12-1** (18%), and diphenyldiselenide (18%) resulting from the cleavage of the heptyl-phenylselenide **3-11** by the heptyllithium intermediate **7-4** (compared to Scheme 63 and Table 8, entries d and f).

Consequently, the reactions disclosed in Scheme 63 and Table 8 have all been carried out at − 78 °C using protocol A (the selenide being added to the lithium or the arenyllithium). The cleavage is already effective at that temperature as attested by the high yield of diphenyldiselenide recovered. It delivers either the methyllithium (Scheme 63 and Table 8, entry a), the primary-alkyl- (Scheme 63 and Table 8, entries b–e and h), the secondary-alkyl- (Scheme 63 and Table 8, entries f and g), as well as the tertiary-alkyl-lithiums (Scheme 63 and Table 8, entries i–k) in reasonably good yields whatever the reagent used.

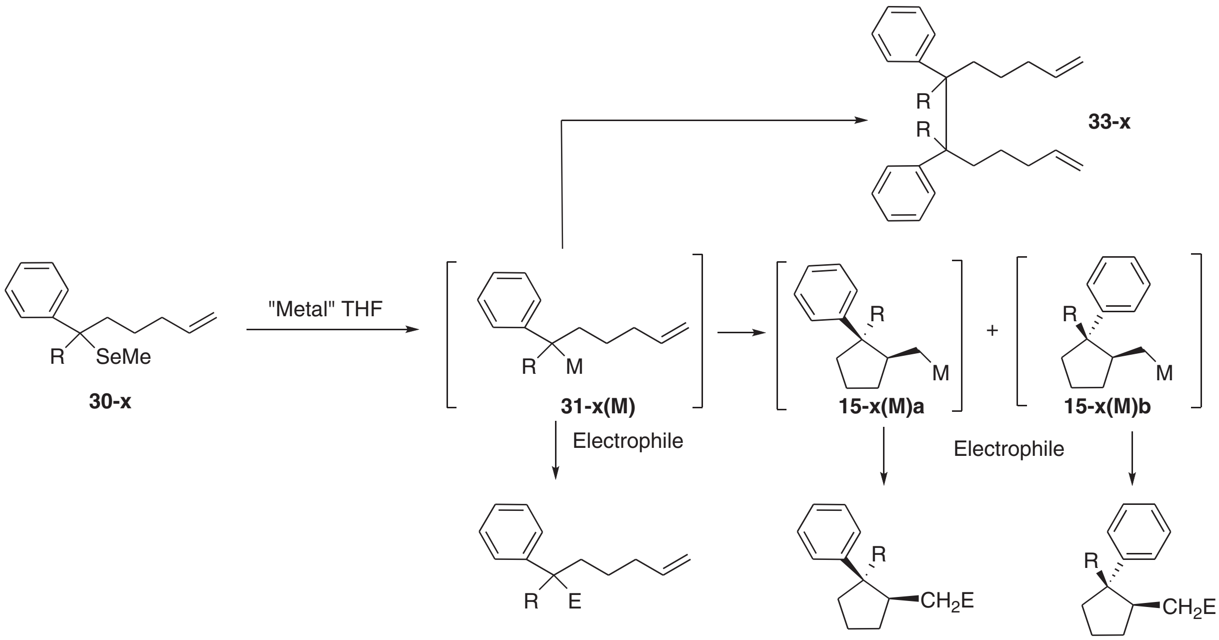
The method involving lithium is probably the most convenient, since it does not require separation of the arene, which is otherwise present in stoichiometric quantities when lithium arenides are used instead. It should be, however, noted that the use of elemental lithium is not optimum for the synthesis of tertiary alkyllithiums for which LiDBB proved to be by far superior even than LiN **4-4** (Scheme 63 and Table 8, entry j compared to entries i and k).[115]

Methyl- (Scheme 63 and Table 8, entries o, r, u, v) and phenyl- (Scheme 63 and Table 8, entries l–n, p, q, s, t) benzylselenides are both efficiently cleaved by lithium and lithium arenides (Scheme 63 and Table 8, entries l–v). The cleavage occurs regioselectively to produce, benzyllithiums and dimethyldiselenide and diphenyldiselenide resulting from the oxidation of the corresponding selenolates benzylic carbanion.[28,115] However, except LiDBB that allows the synthesis of the whole set of benzyllithiums (Scheme 63 and Table 8, entries l, r, v), other reagents such as LiN and especially elemental lithium mainly led to bibenzyl resulting from the substitution of benzylselenide with the benzyllithium just formed, which is apparently more reactive, than lithium naphthalenide (Scheme 63 and Table 8, entries p and s) and elemental lithium (Scheme 63 and Table 8, entries n, o, q, t, u).[28,115]

To avoid such competing coupling reactions, benzyl-methylselenides as well as benzyl-phenylselenides have been reacted with elemental lithium in the presence of benzaldehyde, under Barbier type conditions (Scheme 64 and Table 9, entries f–k). Alkyl-phenylselenides have been also reacted under the same conditions for comparison purposes (Scheme 64 and Table 9, entries a–e), but for that series of compounds 'Barbier conditions' do not offer substantial advantages over those involving 'Grignard conditions' (Scheme 64 and Table 9, entries a–e compared to Scheme 63 and Table 8, entries a–k).[28] 'Barbier conditions' proved, nevertheless, beneficial for the transfer of a benzylic residue to benzaldehyde used as the model.

Elemental lithium allows the synthesis of the whole range of benzyllithiums in very good to good yields [(H, H; Ph: Scheme 64 and Table 9, entry f; 69% compared to Scheme 63 and Table 8, entry n; 0%), (H, H; Me: Scheme 64 and Table 9, entry g; 87% compared to Scheme 63 and Table 8, entry o; 18%), (H, Me; Ph: Scheme 64 and Table 9, entry h; 58% compared to Scheme 63 and Table 8, entry q; 0%), (H, Me; Me: Scheme 64 and Table 9, entry i; 73%), (Me, Me; Ph: Scheme 64 and Table 9, entry j; 52% compared to Scheme 64 and Table 9, entry t; 0%), (Me, Me; Me: Scheme 64 and Table 9, entry k; 62% compared to Scheme 63 and Table 8, entry t; 0%)].

The reaction of LDMAN with the benzyl-methylselenides **30-x** bearing an ω-alkenyl side chain and a methyl group on the benzylic carbon, provides when carried out at −78 °C in THF, the cyclopentylmethyllithium **15-x(M)b** with high stereocontrol and yields[28,115] related to that using butyllithium instead[43] (Scheme 65, entry a compared to Scheme 25 entry a).



	10-x	33-x	16-x	16-xa	16-xb
a R = Me; 1. 5 equivalents LDMAN, –78 °C, 2 h 2. MeOH	-- -----	------	78%	2	98
b R = H; 1. 5 equivalents LDMAN, –78 °C, 2 h 2. MeOH	95%	------	------	----	---
c R = H; 1. 5 equivalents LDMAN, –78 °C, 0.1 h 2. CO$_2$ 3. H$^+$	95%	------	------	----	---
d R = H; 1. 5 equivalents LDMAN, –78 to –20 °C, 1 h 2. MeOH	69%	------	------	----	---
e R = H; 1. 2.5 equivalents LiN, –78 °C, 1 h 2. MeOH	95%	------	------	----	---
f R = H; 1. 2.5 equivalents LiN, –20 °C, 1 h 2. MeOH	- -----	------	68%	35	65
g R = H; 1. 2.5 equivalents NaN, –78 °C, 1 h 2. MeOH	61%	37%	------	----	---
h R = H; 1. 2.5 equivalents NaN, –78 to –20 °C, 1 h 2. MeOH	2%	6%	78%	50	50

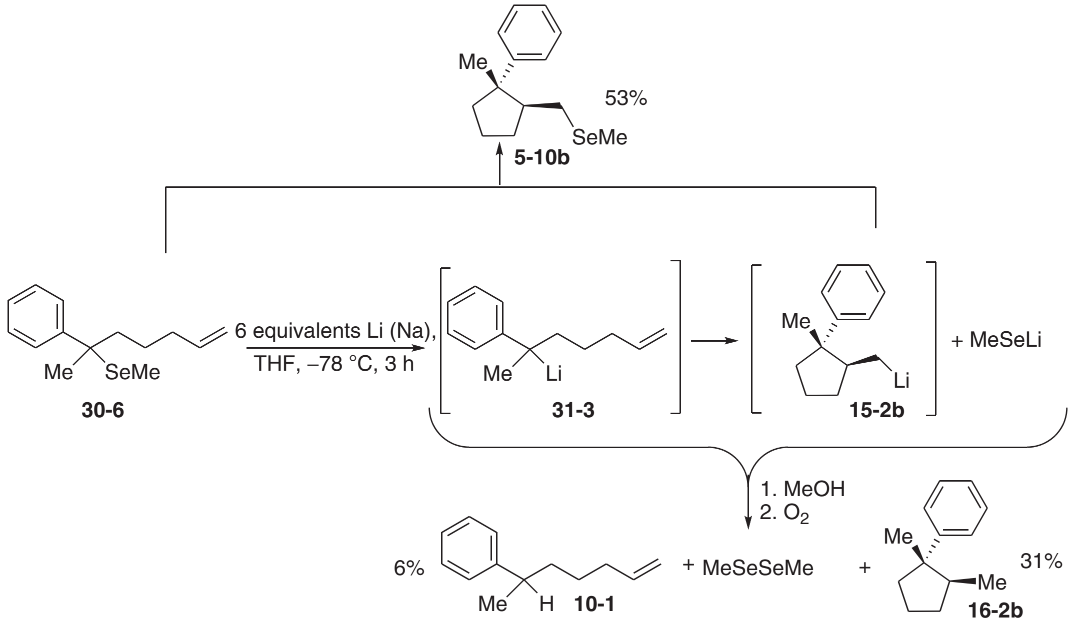
Scheme 65

The reaction's rate of **30-x** (R=H) missing the methyl group at the benzylic position is much lower and the stereocontrol is poorer.[28] It allows trapping the benzyllithium intermediate **31-x(Li)** (R=H) (Scheme 65, entries b–d). The reaction of **30-x** with lithium- (Scheme 65, entries e and f)[117] and sodium naphthalenide (Scheme 65, entries g and h)[117] parallels that of LDMAN and that of *n*-butyllithium.[43]

Se/M exchange takes already place at −78 °C and cyclization occurs in both cases at approximately −78 °C leading to a diastereoisomeric mixture of **16-xa**/**16-xb** in roughly the same ratio after protonation. Two striking differences have been noticed between the reactions involving LiN and NaN: (1) The higher propensity of NaN to promote the coupling of the carbon containing subunit leading to **33-x** (R=H) (Scheme 65, entry g compared to entry e) and (2) the fact that sequential addition of carbon dioxide and methanol allows the carbonation of **15-xa** (M= Li) but not of the related sodium derivative **117**.[117]

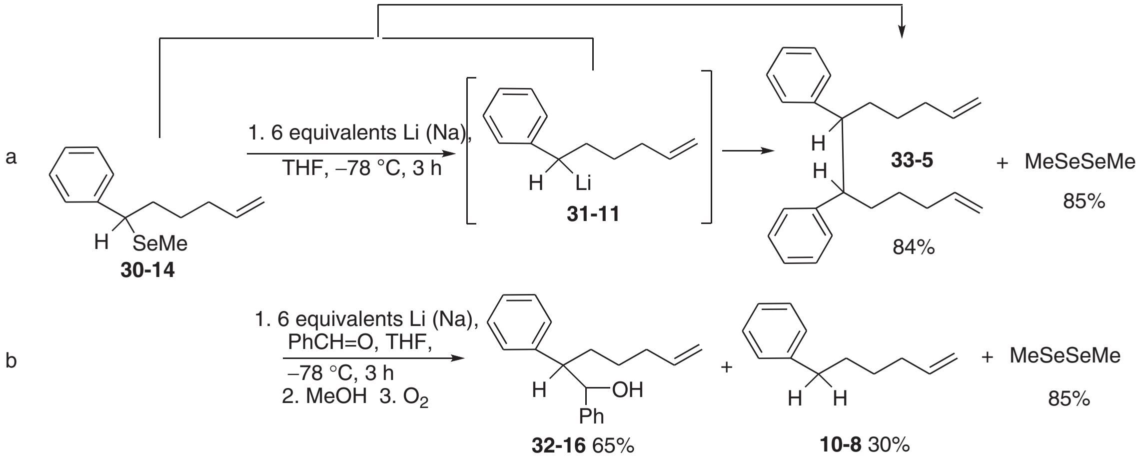
The situation is quite different when elemental lithium, doped by sodium, is instead used since cyclization still occurs in extremely high yield (>85%), but after acid hydrolysis the main product is the selenide **5-10b** (Scheme 66).[28] This product results from the reaction of the cyclopentylmethyllithium **15-2b** on the selenium atom of **30-6**, which regenerates **31-3** (see below Scheme 101).[28] It has been already observed in even higher yield when **30-6** is reacted with catalytic amounts of *n*-butyllithium in THF (see below Scheme 101).[43] Therefore, the **16-2b**/**5-10b** ratio is reminiscent of the two competitive processes. It clearly shows the importance of the experimental conditions on the outcome of the reactions and the higher reactivity of the THF-soluble LDMAN over that of the elemental lithium which involves a heterogeneous process (Scheme 66 compared to Scheme 65, entry a).[28]

The reaction of the benzylselenide **30-14** unsubstituted by a methyl group at the benzylic position with elemental lithium takes another course and provides **33-5** resulting from the coupling of the two benzylic units in high yield (Scheme 67, entry a). In this



Scheme 66

case the benzyllithium intermediate **31-11** reacts on the benzylic carbon of **30-14** as already reported for benzylselenides whose side chains are saturated (Scheme 20 and 24 and Table 6, entry a).[21,40]



Scheme 67

The low reactivity of elemental lithium coupled with the more accessible carbon of **30-14** compared to **30-6** is probably responsible for the different outcomes of those reactions involving different experimental conditions (compare Scheme 67, entry a to Scheme 66 and Scheme 65).[28]

As expected, performing the same reaction in the presence of benzaldehyde suppresses the formation of **33-5** by trapping the benzyllithium intermediate **31-11** to produce **32-16** (Scheme 67, entry b).[28]

3.02.3.2 Reactivity of Selenoacetals toward Lithium and Lithium Arenides

Phenylseleno and methylselenoacetals have been reacted with LiN in THF and are easily cleaved at − 78 °C to deliver the corresponding α-selenoalkyllithiums in modest yield (34–74%). It is interesting to note that the cleavage of 2,2-bis(methylseleno)undecane by LN (0.5 h, 74%) is faster than that of *n*-butyllithium under the same conditions instead.[116]

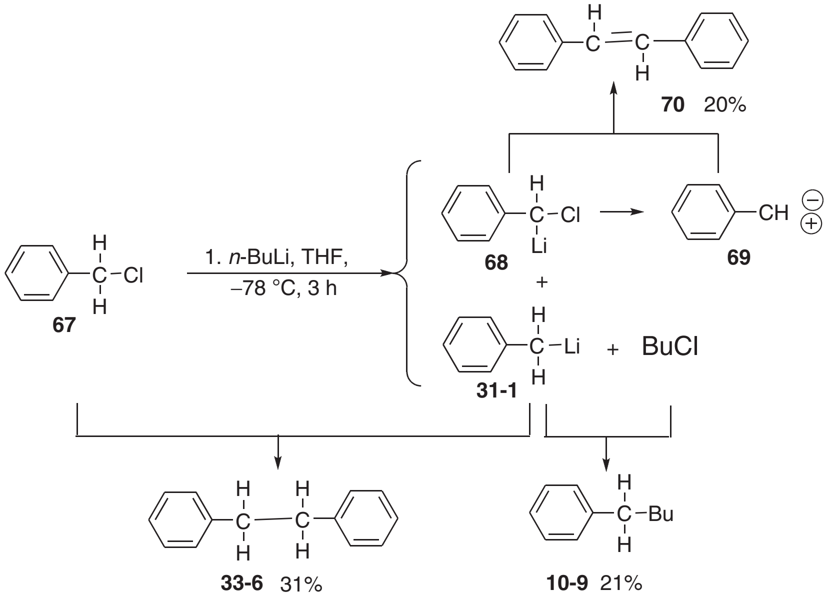
3.02.4 Reactivity of Benzyllithiums: Exceptional Family of Organometallics

Benzyllithiums proved to be valuable synthetic intermediates. Their synthesis from selenides and butyllithiums as reported above, open an easy access to the whole series of these organometallics (primary, secondary, and tertiary) in a wide range of solvents (diethyl-ether, THF, alkanes) and temperatures (– 110 to 0 °C) which offers the occasion to modulate their reactivity and their stability.

3.02.4.1 Access to Benzyllithiums: An Overview

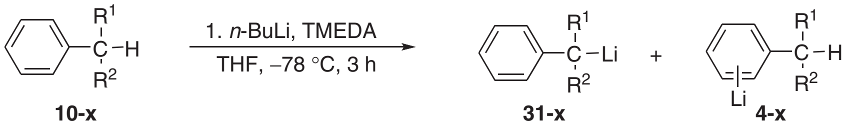
Benzyllithiums, exceptional members of the organometallics family have attracted over the last 80 years constant theoretical and synthetic interest. The presence of an aromatic ring on the carbanionic center of an organolithium dramatically affects its physical and chemical properties as well as its synthesis. In fact, before our work, convenient syntheses of benzyllithiums were scarce.

Halogen/lithium exchange, using elemental lithium or butyllithiums, which is the usual method for the synthesis of alkyllithiums is no longer effective with benzyllithiums.[118–121] Thus the reaction of benzylchloride 67 with butyllithium does not lead to benzyllithium, but instead to a mixture of bibenzyl 33–6 and stilbene 70 resulting from the coupling of two units (Scheme 68). The former product results from competing coupling between the starting benzyl halide 67 and the expected benzyllithium 31–1, both more reactive than their alkyl counterparts.[118,119] The formation of stilbene 70 probably results from the intermediate formation of a phenylcarbene 69 resulting from a hydrogen/metal exchange on the more acidic benzylic hydrogen (Scheme 68).



Scheme 68

Benzyllithium, whose carbanion is stabilized both by inductif and mesomeric effects, can be synthesized by metallation of toluene, the corresponding carbon acid. Successful metallation requires a strong base such as *n*-butyllithium–TMEDA complex (Scheme 69, entry a) but competing metallation also takes place on the aromatic ring and produces some lithio-toluenes.[122–124] Hydrogen/lithium exchange reaction cannot be extended to higher homologs on which ring metallation largely prevails over lateral metallation (Scheme 69, entries b and c).



R^1	R^2	*Ratio*
H	H	88/12
H	Me	37/63
Me	Me	3/97

Scheme 69

Since the usual halogen/lithium as well as hydrogen/lithium exchange proved inefficient for the synthesis. The whole family of benzyllithiums remained almost unknown till recently. Thus, the parent benzyllithium was unknown in 1913[125] and in 1955 the best yield so far reported was, despite intensive research, only 1.4% (by halogen/metal exchange on benzylchloride).[118] It was first synthesized, in 1958, in more than 90% yield by Gilman who used benzyl ethers and elemental lithium to achieve the oxygen/lithium exchange.[126] The reaction involving elemental lithium was then extended successfully to benzylsulfides including those possessing one or two methyl groups on the carbanionic center and references cited in Refs.[42,127–129] Limitations have been, however, reported: for example, the O/Li exchange does not allow the synthesis of benzyllithiums bearing an halogen on the aromatic ring[41] and S/Li that of benzyllithiums bearing a methoxy group on the aromatic ring.

Although those methods allow access to the parent benzyllithium as well as those compounds bearing one or two methyl groups on their carbanionic center, they produce concomitantly lithium alcoholates or thiolates, which are basic/nucleophilic enough to compete with the original benzyllithiums in alkylation reactions, for example.

Benzyllithiums have also been prepared by addition of alkyllithiums across the carbon–carbon double bond of aryl-alkenes (styrenes) but polymerization competes.[130–132]

As general trends, the addition is solvent dependent and (1) does not take place in the alkane,[132] (2) is favored in diethyl ether[132] or isooctane-TMEDA,[133] and (3) leads to polymerization in THF.[131]

The synthesis of benzyllithiums from benzyl selenides and alkyllithiums (Section 3.02.2.2.2) compares well with the methods reported above. It allows the synthesis of the whole series of benzyllithiums including the parent compound (not accessible by addition to styrene) and those bearing an halogen or an alkoxy group on the aromatic ring (not accessible by O/Li or S/Li exchange).[22,63] It allows their synthesis in hydrocarbon (not possible using all other methods instead). Furthermore, benzyllithiums are usually produced concomitantly to butyl selenides which are inert and allows inter alias their efficient alkylation.[23] which is not the case of the reactions involving benzyl ethers and sulfides and lithium and which instead concomitantly produce lithium chalcogenates prone to be alkylated.

3.02.4.2 Physical Properties of Benzyllithiums

The reactivity[134,135] as well as the structure of benzyllithiums, especially the location of the lithium cation raised the interest of chemists, particularly for the determination of the geometry of the benzylic carbon.

It has been proved by X-ray that the lithium cation in benzyllithium complexes usually lies out of the plane of the aromatic ring and that η^1-[$PhCH_2Li$–THF–TMEDA complex] possesses a pyramidal benzylic carbon,[136–140] whereas dihapto- ($PhCH_2Li$–DABCO)[141,142] or trihapto[138] derivatives possess planar chirality.

The nature of the benzylic carbon–lithium bond in benzyllithiums[39,130,131,143–147] has been studied by ^{13}C NMR in solvents of different polarities (alkanes, benzene, ether, THF) and in the presence of external ligands,[144] such as amines, diamines (such as 1,2-dipiperidylethane or TMEDA), or built-in cation complexing agents.[145] These studies as well as MNDO calculations,[148,149] suggest that the carbon–lithium bond in the parent benzyllithium is a tight ion-pair or even partially covalent (different ^{13}C NMR shifts at the benzylic carbon) in different solvents, such as diethyl ether and THF, heat, and in the presence of different external ligands.[145,150]

α,α-Dialkylsubstituted benzyllithiums, however, exhibit properties expected for delocalized carbanions. The ^{13}C NMR shift at the benzylic carbon has been recorded.[39] It is identical in different solvents such as diethyl ether and THF, heat, and in the presence of different external ligands,[143,144] and very similar to that of cumylpotassium that involves loose ion pairs.[144]

The parent benzyllithium as well as benzyllithiums bearing amino-, thio-, or seleno moieties on the benzylic carbon including α-thio- and α-selenobenzyllithiums bearing a crown ether proved to be contact ion pairs,[151] whereas α-silyl benzyllithiums, internally coordinated or not, have partially delocalized structures.[136,138] (**Scheme 70**)

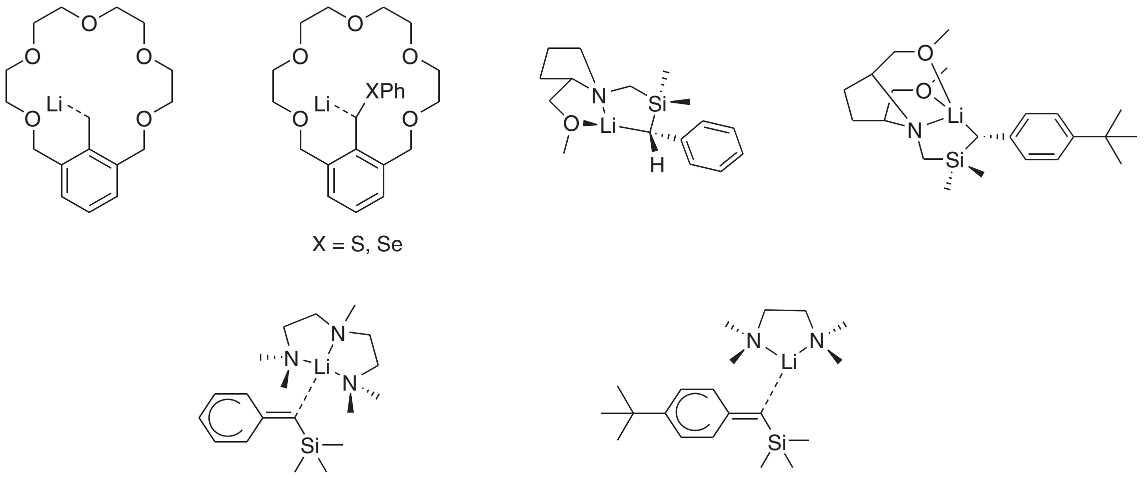
Benzyllithiums, including those bearing seleno moieties or two alkyl groups on their benzylic carbons, proved to be valuable reagents acting as powerful nucleophiles in alkylation reactions.

Alkylation has been achieved either with alkyl halides[22,23,63] including secondary alkyl ones (see Sections 3.02.4.3.2, 3.02.4.4.2.1 and 3.02.4.4.2.2), epoxides[152] (see Sections 3.02.4.3.3 and 3.02.4.4.2.3) or by addition across carbon–carbon double bonds (see Sections 3.02.4.3.4 and 3.02.4.4.2.4).[43,44]

3.02.4.3 Reactivity of Benzyllthiums

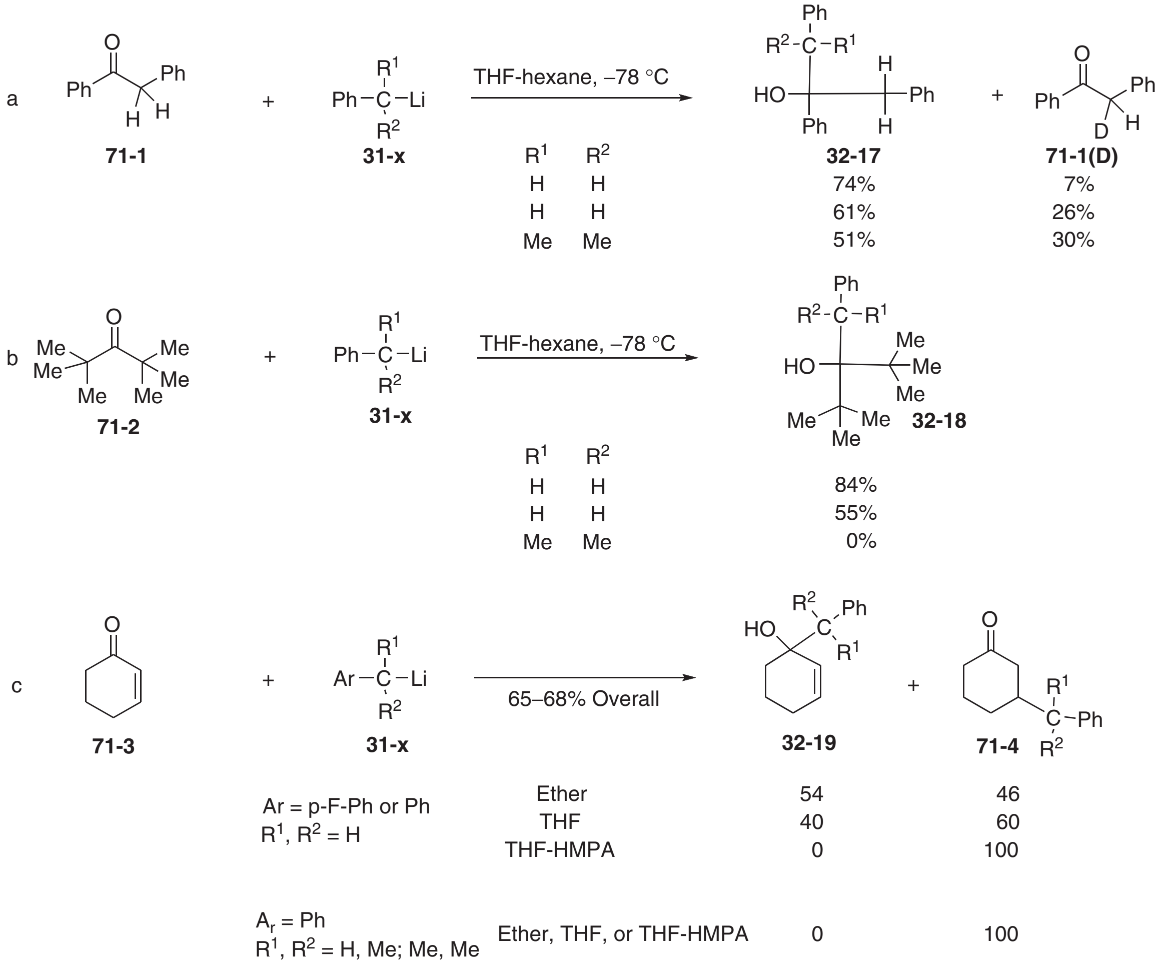
3.02.4.3.1 Reactivity of benzyllthiums toward carbonyls and α,β-unsaturated carbonyl compounds

Benzyllithiums are quite good nucleophiles toward carbonyl compounds and α,β-unsaturated carbonyl compounds (**Scheme 71**). They are, nevertheless, far less nucleophilic toward them than the related α-selenoalkyllithiums. Although alcohols are produced on sequential reaction with deoxybenzoin **71-1**, which belongs to the 'highly enolizable' class of carbonyl compounds, enolization also takes place to quite a large extent especially when the benzyllithium bears two methyl substituents on the benzilic carbon (**Scheme 71**, entry a).[21] Benzyllithium and α-methyl-benzyllithium react with di-*tert*-butyl ketone **71-2**, which belongs to the 'highly hindered' class of carbonyl compounds, but whatever the conditions used 2-phenyl-2-propyllithium, does not react (**Scheme 71**, entry b).[21] Thus, whereas benzyllithium, which possesses a tight ion pair or even partially covalent C–Li bond, adds substantially to



Scheme 70

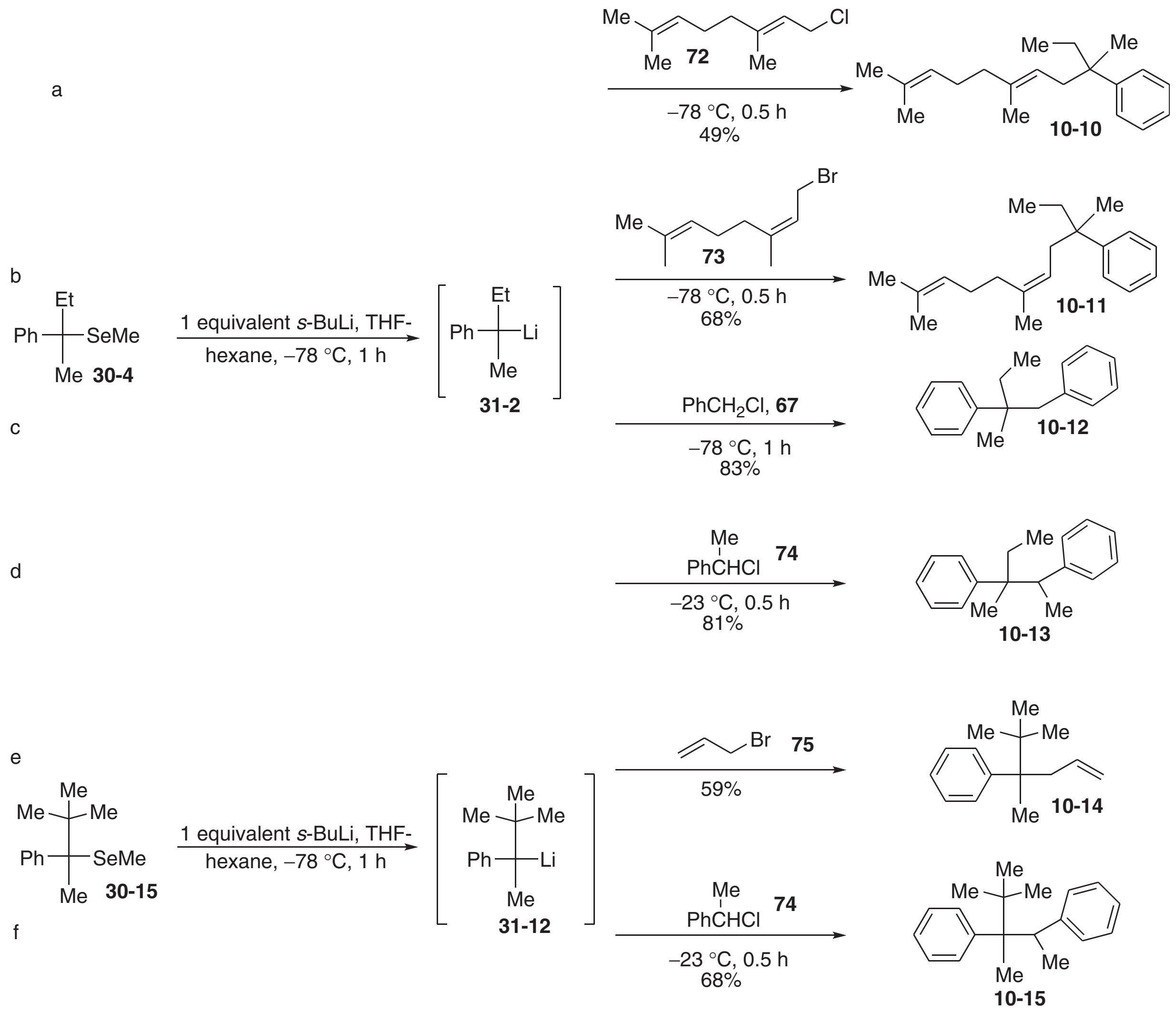
the carbonyl group of cyclohexenone **71-3** when the reaction is carried out in ether (Scheme 71, entry c),[21] 1-phenyl-ethyllithium and 2-phenyl-2-propyllithium which exhibit properties expected for delocalized carbanion exclusively react with their carbon–carbon double bond (Scheme 71, entry c).[21] Interestingly, the use of HMPA in conjunction with ether enhances the 1,4-addition of the three benzyllithiums to cyclohexenone **71-3** (Scheme 71, entry c).[21]



Scheme 71

3.02.4.3.2 Reactivity of benzyllithiums toward alkyl-, benzyl-, and allyl-halides

The whole series of benzyllithiums reacts efficiently with alkyl-, benzyl-, and allyl-halides (Schemes 72–74).



Scheme 72

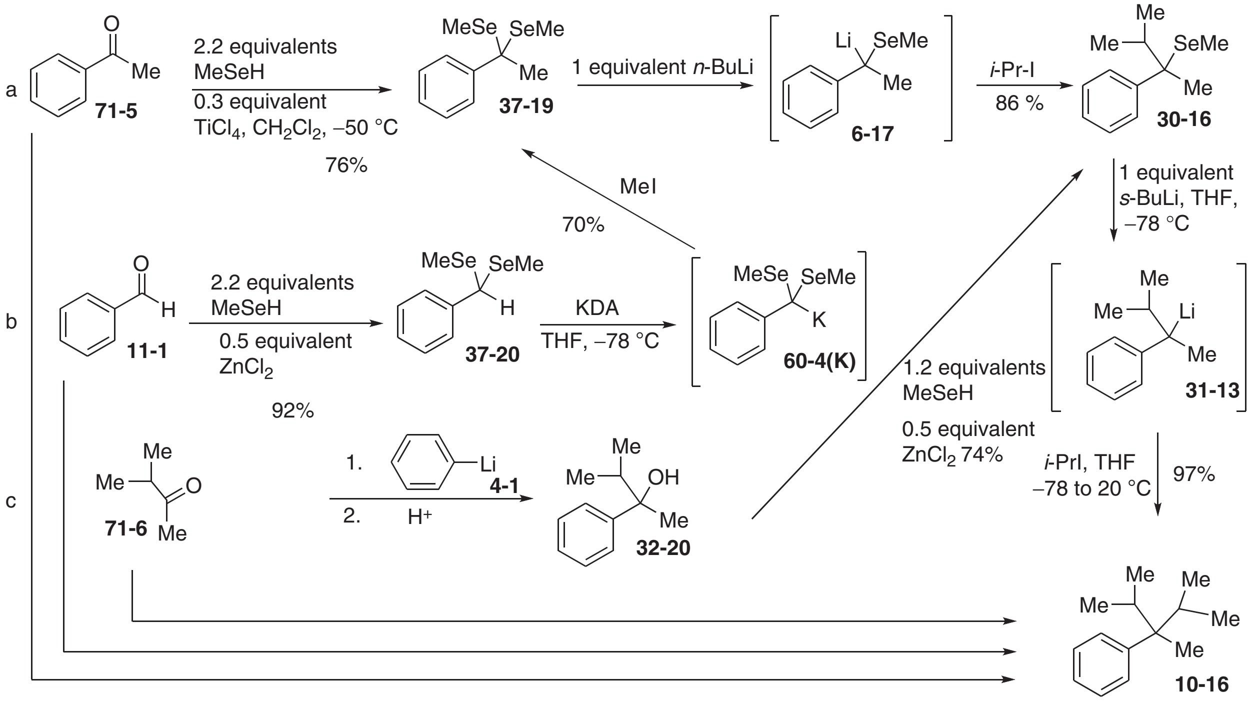
The reaction occurs regioselectively at the primary carbon of primary allyl halides and stereoselectively with geranyl chloride **72** or neryl bromide **73** with conservation of the stereochemistry of their carbon–carbon double bonds (Scheme 72, entries a and b).[40]

Benzyllithiums react very efficiently with benzyl halides (Scheme 72, entries c, d, and f)[40] and lead to products resulting from their heterocoupling in high yields. Products resulting from homocoupling of the benzyl halide or of the benzyllithium are not observed. It is to be recalled that reaction of benzyllithiums with a different benzylselenide leads to a mixture of products resulting from hetero- and homo coupling (compare Scheme 72, entry d, to Scheme 23).[40]

Interestingly, both benzylation and allylation have been successfully achieved on benzylselenide **30-4** (Scheme 72, entry e) and **30-15** (Scheme 72, entry f) that bears a dialkylsubstituted benzylic carbon with a quite bulky substituent there.[40]

Alkylation has been carried out, as a crucial step in the transformations described in Schemes 73–75.[22,23] It takes place on the whole set of alkyl halides except the tertiary alkyl ones, on the whole series of benzyllithiums including those bearing two alkyl groups on their carbanionic center (Schemes 73–75), in particular, those that possess a methyl and an isopropyl- (**31-13**, Scheme 73), a methyl-, and a *t*-butyl- (**31-12**, Schemes 72 and 75), or even two isopropyl- (**31-14**, Scheme 74, entry d) groups at the benzylic carbon as well as with α-seleno-benzylmetals (Scheme 73, entries a and b; Scheme 74, entries c and d).[22,23]

In some rare cases products **10-24** resulting from the protonation of the benzyllithiums are formed in low yields besides the alkylated compounds (Scheme 75).[23]



Scheme 73

3.02.4.3.3 Reactivity of benzyllithiums toward heterocyclic compounds

α-Seleno-benzyllithiums also have a high propensity to react with ethylene oxide and oxetane in THF (Scheme 76, entries a and b).[116,152] They do not, however, react with the least strained THF[153] or tetrahydropyran.[116] In the latter cases, successful ring opening has been achieved using the heterocycle as the solvent and boron tri-halides (BF_3-OEt_2 or BCl_3) as catalyst (Scheme 76, entries c and e).[153] Acid-catalyzed ring opening of THFs and tetrahydropyrans has also been successfully achieved using only five equivalents of THF in ether solvent (Scheme 76, entry d). A successful process involves mixing the heterocycle and the benzyllithium in ether before the addition of the acid catalyst. This procedure avoids decomposition of both reactants.[153] This reaction has been successfully extended to α-methoxy-benzyllithium and THF (Scheme 77, entry d).[154]

The reaction involving α-seleno benzyllithiums has been extended to THFs and epoxides differently alkyl substituted on their α-carbon atom but not to tetra-alkyl- substituted epoxides.[116,153,155] It takes place at the least alkyl-substituted carbon of 2-methyl-THF **76-5** (Scheme 77, entry b) and of epoxides.[116,152,155]

Most of the work involving epoxides has been achieved with α-methylselenobenzyllithiums[45,152,156] as well as α,α-bis(methylseleno)benzyllithiums.[45,116,152,156] The results are on the line of those already reported for α-selenoalkyllithiums,[155,157] but α-selenobenzyllithiums proved by far more nucleophilic.

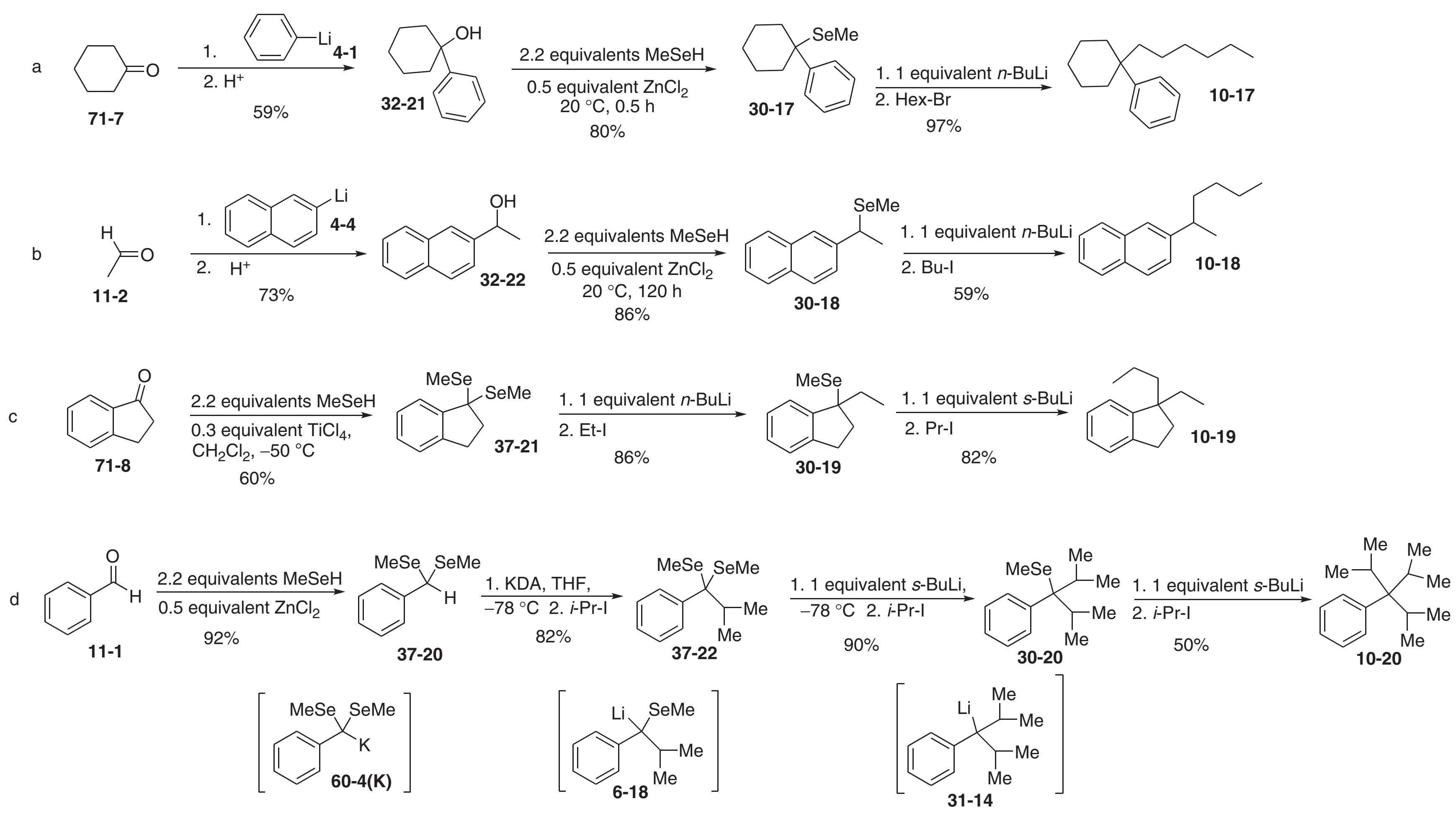
Thus, 1-methylseleno-1-phenyl ethyllithium **6-17** in THF exclusively reacts on the least hindered carbon atom of methyl oxirane **76-7** delivering regioselectively a 1/1 mixture of stereoisomeric γ-hydroxy-alkyl selenides **32-32** on further hydrolysis (Scheme 78, entry a).[152]

The reaction of methylseleno-phenyl methyllithium **6-19**, its lower homolog, is by far less regioselective and provides a 1/1 regioisomeric mixture of γ-hydroxy-alkyl selenides **32-33** and **32-34** (Scheme 78, entry b).[152]

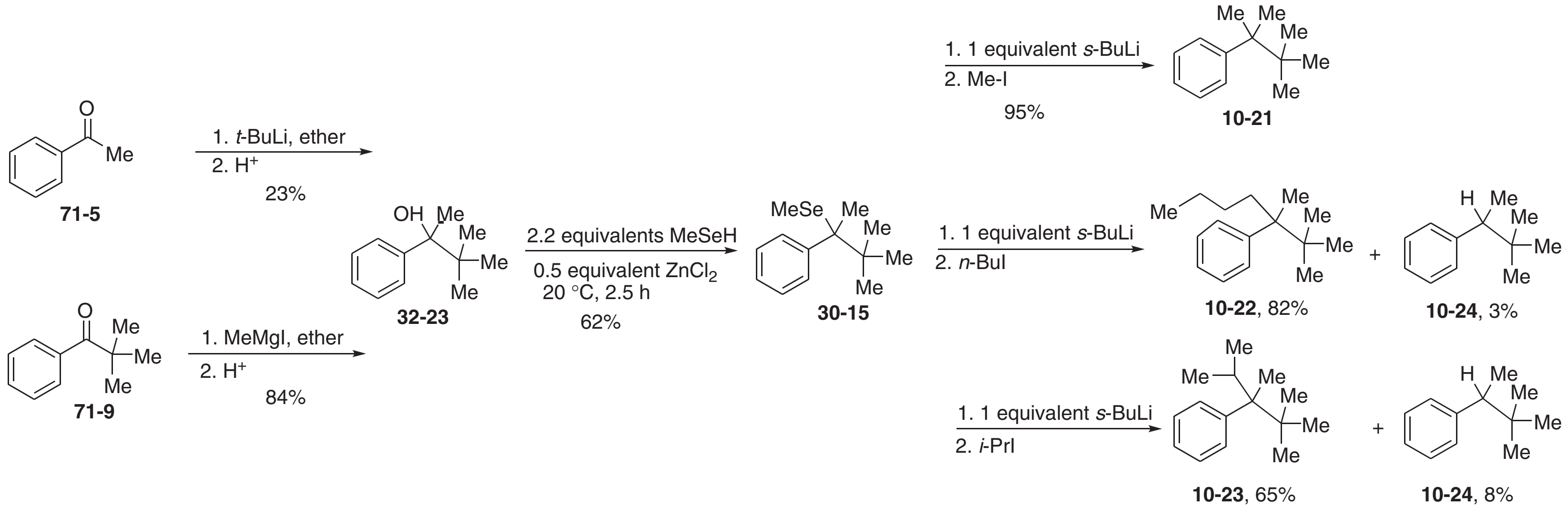
The same trends have been observed on reaction of oxido-styrene **76-8** with 1-methylseleno-1-phenyl ethyllithium **6-17** and methylseleno-phenyl methyllithium **6-19** in THF. It provides a 81/19 and 60/40 ratio of regioisomers in which the major one arises from the epoxide ring opening at the least hindered carbon of oxido-styrene. Performing the reaction in such a case with HMPA increases, in some cases, the amount of **32-35a** (Scheme 78, compare entries f to e).[152]

Ring opening of oxido-styrene **76-8** by methylseleno-phenyl methyllithium **6-19** leads to **32-35b** with complete inversion of configuration at the substituted carbon (see Scheme 78, entry e). It, however, leads to a mixture of stereoisomeric γ-hydroxy-alkyl selenides **32-35** epimeric at the benzylic carbon. They are usually very easily separated by chromatography on silica gel. The reaction has been successfully extended to 2,3-oxido butene, 1,2-oxido-2-methyl-1-heptene, oxido-cyclohexene, and 1,2-oxido-butadiene.[152] The latter produces a mixture of regioisomers (56/44) even when the reaction is performed in the presence of HMPA.[152]

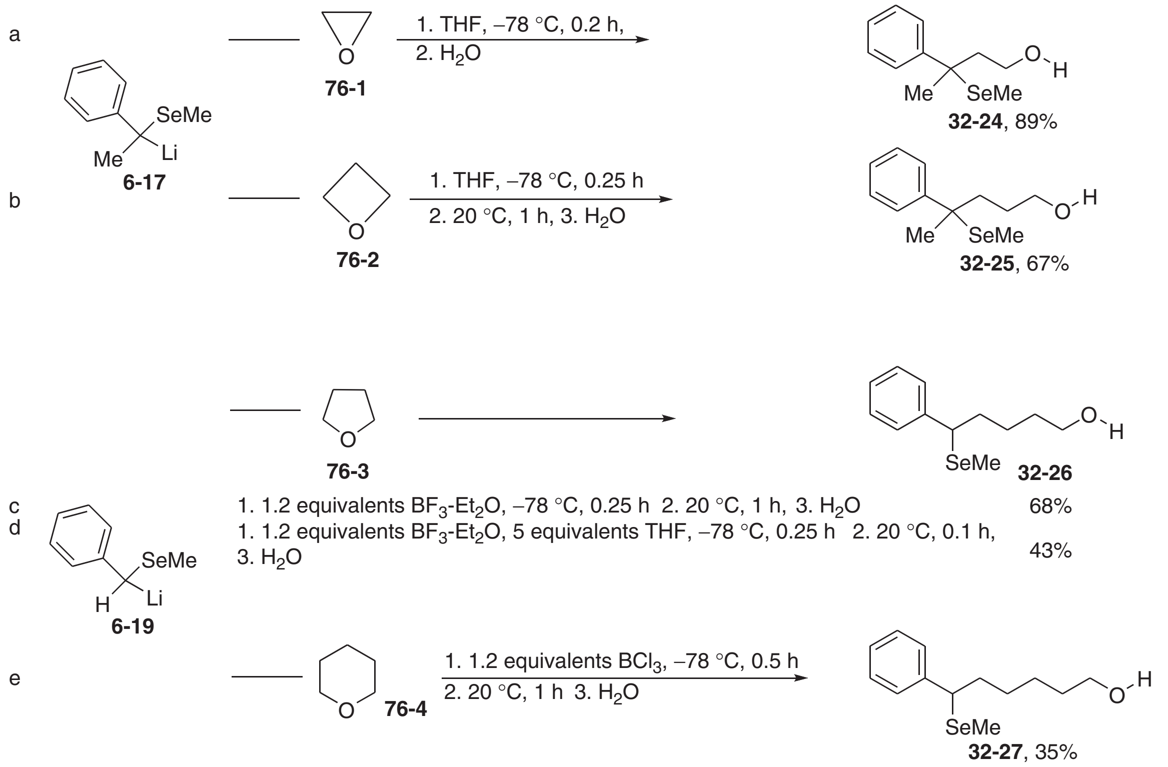
Reactions have also been performed with scalemic oxido-propylene **76-7** and oxido-styrene **76-8** (Scheme 78).[156]


a
71-7
1. 4-1
2. H+
59%
32-21
2.2 equivalents MeSeH
0.5 equivalent ZnCl2
20 °C, 0.5 h
80%
30-17
1. 1 equivalent n-BuLi
2. Hex-Br
97%
10-17
b
11-2
1. 4-4
2. H+
73%
32-22
2.2 equivalents MeSeH
0.5 equivalent ZnCl2
20 °C, 120 h
86%
30-18
1. 1 equivalent n-BuLi
2. Bu-I
59%
10-18
c
71-8
2.2 equivalents MeSeH
0.3 equivalent TiCl4,
CH2Cl2, –50 °C
60%
37-21
1. 1 equivalent n-BuLi
2. Et-I
86%
30-19
1. 1 equivalent s-BuLi
2. Pr-I
82%
10-19
d
11-1
2.2 equivalents MeSeH
0.5 equivalent ZnCl2
92%
37-20
1. KDA, THF,
–78 °C 2. i-Pr-I
82%
37-22
1. 1 equivalent s-BuLi,
–78 °C 2. i-Pr-I
90%
30-20
1. 1 equivalent s-BuLi
2. i-Pr-I
50%
10-20
60-4(K)
6-18
31-14

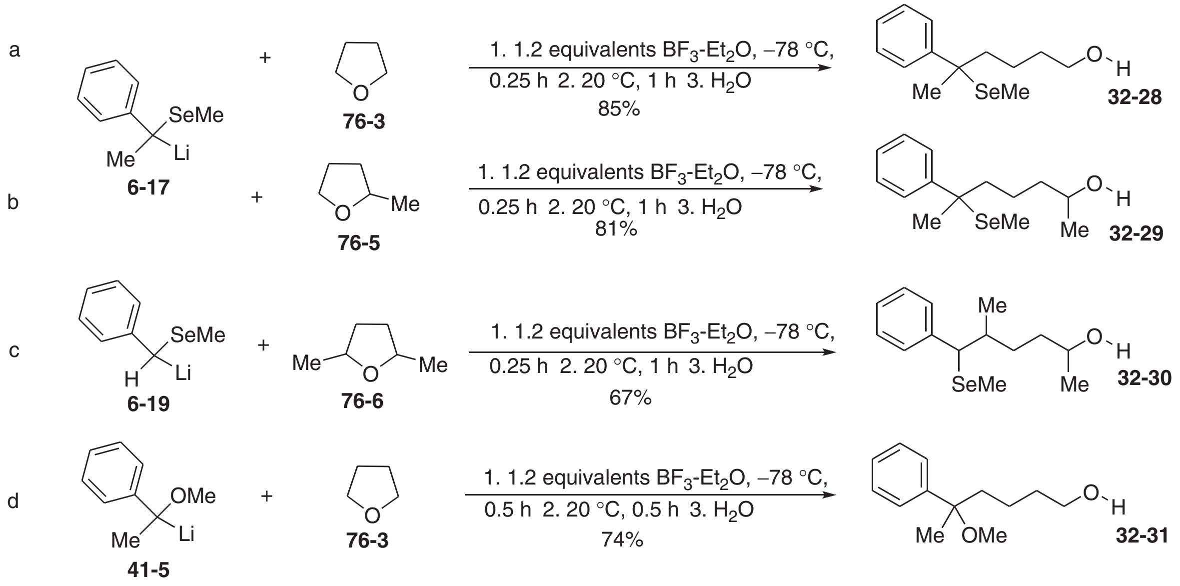
Scheme 74


71-5
1. t-BuLi, ether
2. H+
23%
71-9
1. MeMgI, ether
2. H+
84%
32-23
2.2 equivalents MeSeH
0.5 equivalent ZnCl2
20 °C, 2.5 h
62%
30-15
1. 1 equivalent s-BuLi
2. Me-I
95%
10-21
1. 1 equivalent s-BuLi
2. n-BuI
10-22, 82%
10-24, 3%
1. 1 equivalent s-BuLi
2. i-PrI
10-23, 65%
10-24, 8%
O
Me
OH
MeSe
H
+

Scheme 75



Scheme 76

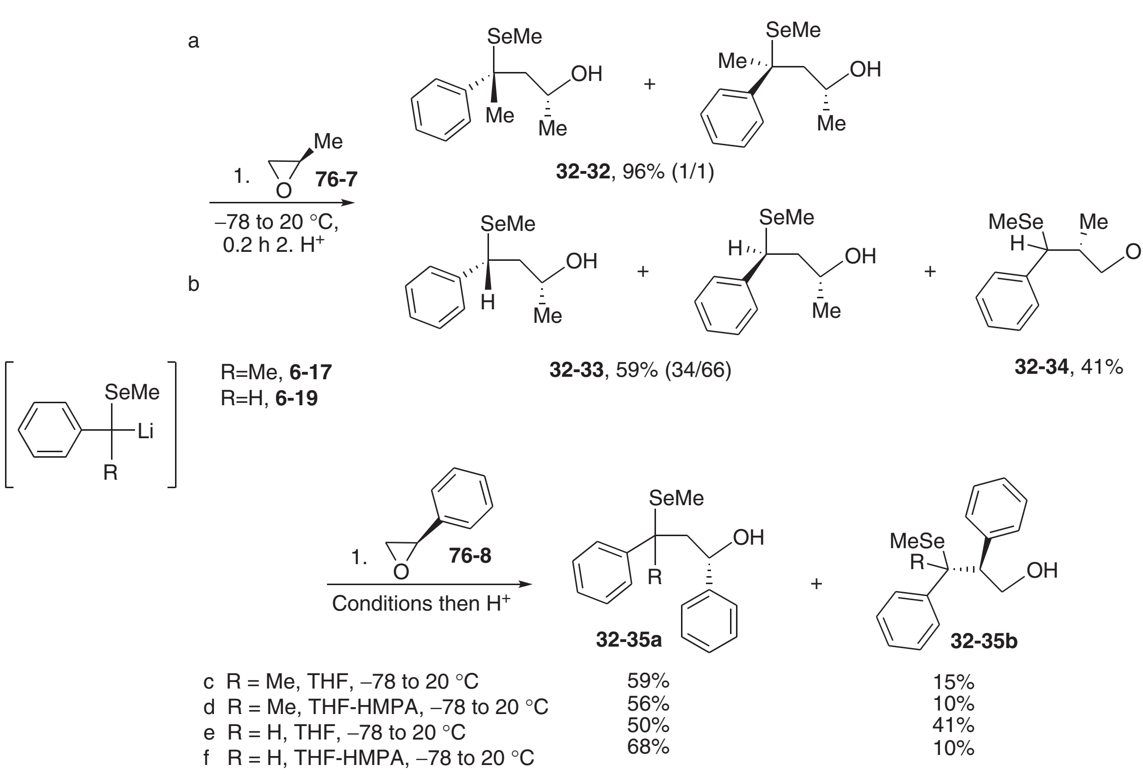


Scheme 77

3.02.4.3.4 Reactivity of benzyllithiums toward carbon–carbon double bonds of alkenes and heterosubstituted alkenes

Benzyllithiums possess a higher propensity to add across the carbon–carbon double bond of unactivated alkenes. Those possessing the more substituted carbanion are the most reactives.

It has, for example, reported that benzyllithiums bearing two alkyl groups on the benzylic carbon, are able to metallate THF or diethyl ether at 20 °C producing ethylene. The latter is, in turn, trapped by the remaining benzyllithiums (Scheme 26).[43] It has also been reported that benzyllithiums possessing an alkenyl side chain suitably located generates five- and six-membered carbocycles already at low temperature (Scheme 25 and Table 7, Schemes 34, 65 and 66).[28,44,53,115]



Scheme 78

Alkylation of the benzyllithiums bearing one or two methyl groups on their carbanionic center has been achieved using ethylene or trimethylsilylethylene as the alkylating agent (Scheme 79).[43] Protonation of corresponding adducts allows the substitution of the methylseleno moiety of the methylseleno benzylselenide by an ethyl group (Scheme 79, entry a) or a 2-trimethylsilyl-ethyl group (Scheme 79, entry c), respectively. Addition of carbon dioxide, before acid hydrolysis, allows the synthesis of the corresponding carboxylic acids by insertion of an ethylene moiety between the benzylic carbon and the carboxyl group (Scheme 79, entries b and d).[43]

This reaction does not take place with homologuous alkenes but has been successfully extended to heterosubstituted carbon–carbon double bonds and will be discussed later in this review.[158]

3.02.4.4 Syntheses of Aryl Alkanes Involving the Di-alkylation of the Carbonyl Group of Aromatic Aldehydes and Ketones and Aryl-alkylation of the Carbonyl Group of Aliphatic Aldehydes and Ketones

3.02.4.4.1 Syntheses producing noncyclic aryl alkanes

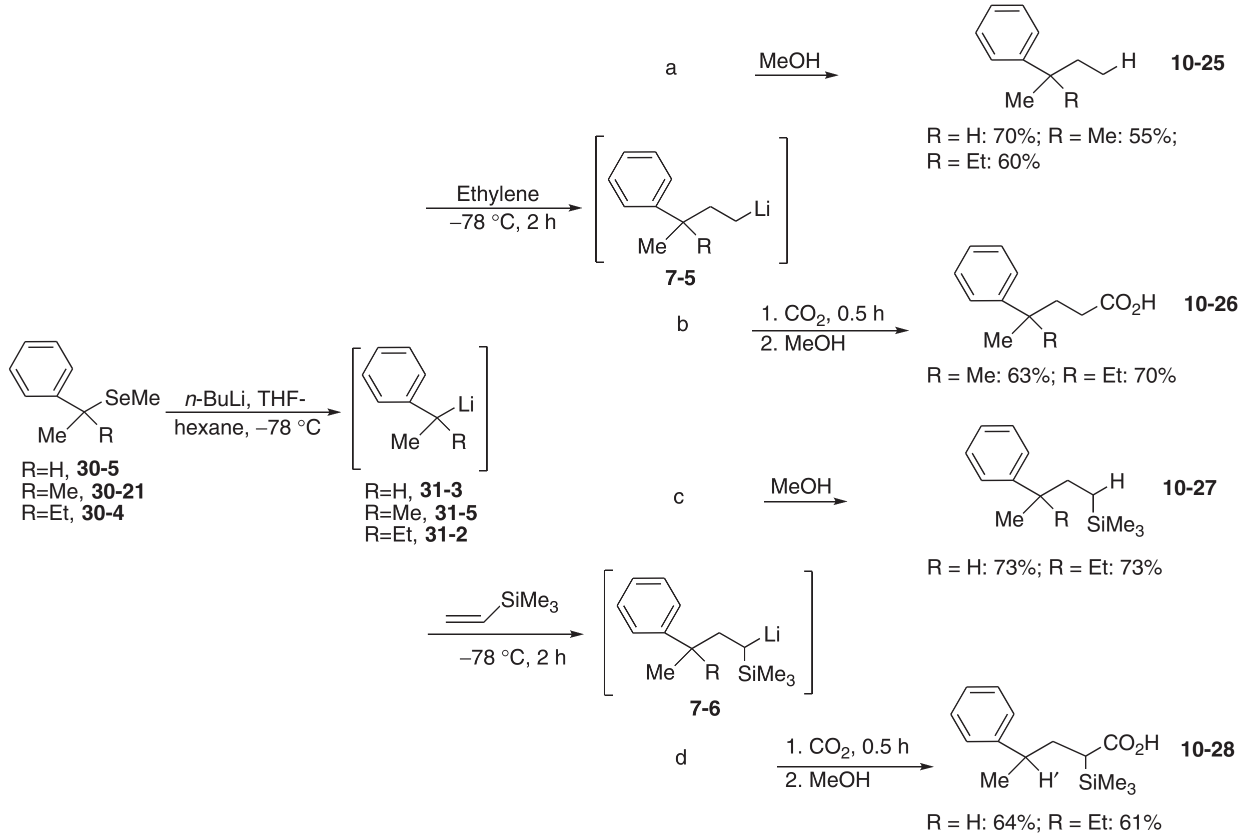
The exceptionally efficient cascade metallation-alkylation reactions of aromatic selenoacetals and benzylselenides, disclosed in the synthetic way Schemes 73–75 and in the retro synthetic way Schemes 80–82,[22,23,63] have been used as a key step for the synthesis of aryl alkanes **10-x** from aromatic or aldehydes and ketones and with a little variation has been extended to aliphatic carbonyl compounds **71-x** and **11-x** (Scheme 80).

3.02.4.4.1.1 Syntheses involving aliphatic carbonyl compounds and aromatic organometallics

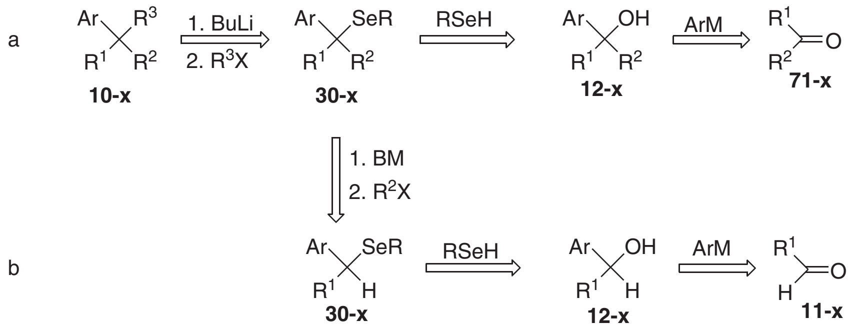
The former approach involves sequential arylation and alkylation of the carbonyl group of aliphatic carbonyl compounds and is disclosed in Scheme 80, entry a.

It implies sequentially:

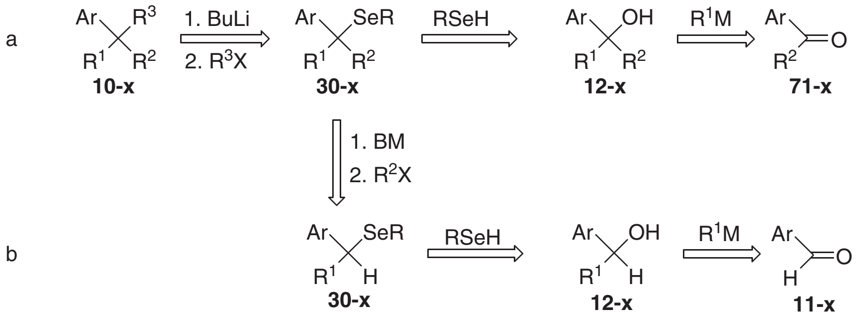
1. Addition of aromatic Grignard or Gilman reagents on to the carbonyl group of aldehydes or ketones (Scheme 73, entry c; Scheme 74, entries a and b).[23]
2. Transformation of the resulting alcohols to the corresponding selenides on reaction of selenol in the presence of an acid catalyst,[22,23] or alternatively transformation to the corresponding sulfonates or halides and substitution by a selenolate (Scheme 73, entry c; Scheme 74, entries a and b; Scheme 75).[2,16,159]
3. Se–Li exchange on the benzylselenide followed by *in situ* alkylation involving alkyl halides or sulfonates (Scheme 73, entry a; Schemes 74 and 75)[22,23,63] or reaction with ethylene followed by protonation (Scheme 79, entry a).[43]



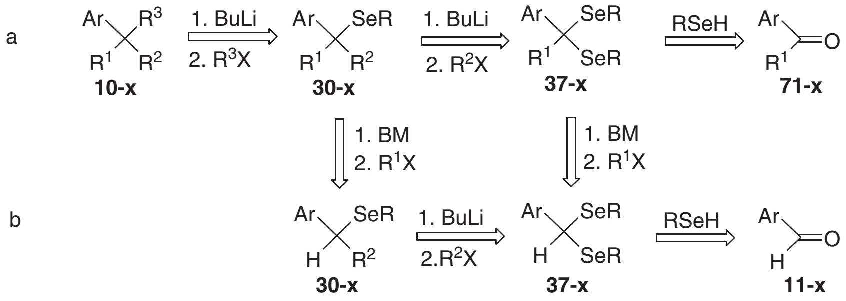
Scheme 79



Scheme 80



Scheme 81



Scheme 82

3.02.4.4.1.2 Syntheses involving aromatic carbonyl compounds and aliphatic or aromatic organometallics

The second approach involves the dialkylation of the carbonyl group of ***aromatic*** aldehydes and ketones (Scheme 81, entry a). This transformation implies alkyl-magnesium or -lithium derivatives as nucleophilic alkylating agents of aryl carbonyl compounds and a second alkylation involving an electrophilic alkylating agent (Schemes 75).

3.02.4.4.1.3 Syntheses involving aromatic carbonyl compounds and aryl selenoacetals

The previous approach implies the synthesis of aromatic selenoacetals from carbonyl compounds and formal dialkylation of their carbonyl groups (Scheme 82).

It involves:

1. Selenoacetalization of aromatic ketones (Scheme 82, entry a).[22,63]
2. Two sequential Se/Li exchange-alkylation which deliver the aryl alkane (Scheme 82, entry a; Scheme 73, entries a and b; Scheme 74, entries c and d).[22,63]

Each of the three approaches reported above for the sequential dialkylation of the carbonyl group of aromatic aldehydes and ketones or the sequential arylation, alkylation of their aliphatic counterparts can be extended to the sequential trialkylation of the carbonyl carbon of aromatic aldehydes (Scheme 81, entry b). Specific example disclosed in Scheme 73, entry b and Scheme 74, entry d; or Scheme 82, entry b) or the sequential arylation, dialkylation of their aliphatic counterparts (Scheme 80, entry b). These transformations involve an extra sequential metalation, alkylation step that can be achieved either on the prim- or sec-benzylselenide **30x** (Scheme 80, entry b; Scheme 81, entry b; Scheme 82, entry b) or the acetal **37x** derived from aromatic aldehydes (Scheme 82, entry b).

The results disclosed in Schemes 73–75 unambiguously demonstrate that all the approaches have been successfully achieved providing high yields of aryl alkanes even those possessing extremely hindered alkyl groups on the benzylic carbon of their side chains.[22,23,63]

In Scheme 73 three different routes have been described to (2,3,4-trimethylpentan-3-yl) benzene **10-16** bearing a methyl and two isopropyl groups on the benzylic carbon, from either acetophenone **71-5**, benzaldehyde **11-1** or 3-methyl-butan-2-one (isopropyl methyl ketone) **71-6**.

Thus, acetophenone **71-5** has been transformed to the corresponding methylselenoacetal **37-19** whose sequential reactions, at −78 °C, with *n*-butyllithium in THF and isopropyl iodide provides the selenide **30-16**. Se/Li exchange on this quite hindered selenide requires the use of *s*-butyllithium and delivers the extremely crowded benzyllithium **31-13** whose alkylation with quite hindered isopropyl iodide provides the aryl alkane **10-16** in extremely good yield (Scheme 73).[23]

The same aryl alkane **10-16** has been synthesized from benzaldehyde **11-1**. Transformation to the corresponding acyl anion equivalent **60-4(K)** requires the use of KDA to avoid the unusual competing Se/Li exchange observed if LDA is instead used. Methylation of **60-4(K)** provides **37-19** in reasonably good yield (Scheme 73, entry b). The transformation of **37-19** to **10-16** has been then achieved according to the description described above (Scheme 73).

Interestingly, **10-16** has also been synthesized from isopropyl methyl ketone **71-6**. Its transformation to the benzyl alcohol **32-20** has been achieved using phenyllithium and the synthesis of the quite hindered benzyl selenide **30-16** has been routinely achieved from alcohol **32-20** using methylselenol in acidic media (Scheme 73, entry c).

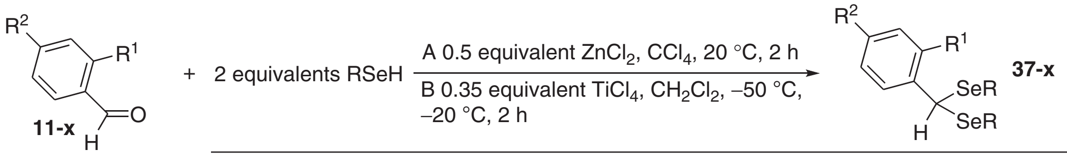
To be successful, the strategies reported above not only require efficient alkylation reactions but also efficient syntheses of the aryl selenoacetals and benzylselenides, which are the key intermediates on which the sequential Se/Li exchange and alkylation reactions take place.

As general trends those reactions are best achieved using methylseleno derivatives which (1) are easier to synthesize than their phenylseleno analogs and the related (2) benzyl-methylselenides that are more easily cleaved than their benzyl-phenylselenides analogs.

3.02.4.4.1.4 Selection of the best reagents and methods for the synthesis of aryl alkanes from carbonyl compounds

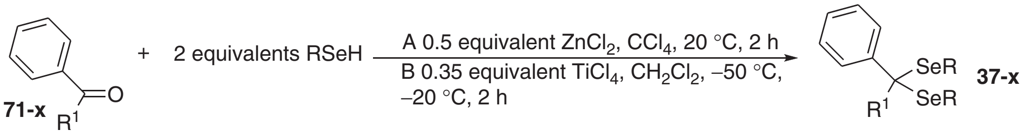
3.02.4.4.1.4.1 Syntheses of aryl selenoacetals and benzyl selenides

The synthesis of selenoacetals is usually achieved, at room temperature, by reacting carbonyl compounds with stoichiometric amounts of a selenol (2 equivalents) in the presence of 0.5 equivalents of zinc chloride (Conditions A).[22] Those conditions are, however, limited to methylselenol and aromatic aldehydes **11-x** (Scheme 83). It applies efficiently to aliphatic carbonyl compounds and methyl- and phenylselenols and applies to aromatic aldehydes and methyl selenol. It cannot be extended to related phenylselenoacetals and does not apply to the synthesis of methylselenoacetals derived from aromatic ketones.



11-x **37-x**

R^1	*R^2*	*R = Me*	*R= Ph*
H	H	92% (A), 89% (B)	0% (A), 64% (B)
MeO	H	71% (A), –	–
H	MeO	78% (A), 84% (B)	19% (B)
H	CN	78% (A)	–
H	Cl	78% (A)	55% (B)



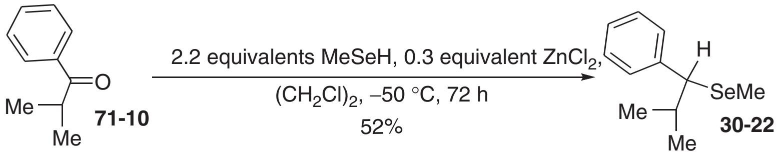
71-x **37-x**

R^1 = Me, R = Ph	A: 1%, B: 39%
R^1 = Me, R = Me	B: 72%
R^1 = *n*-Pr, R = Me	B: 71%

Scheme 83

Selenoacetalization of aromatic ketones **71-x** is not as easy as their aliphatic analogs. It is quite poor with phenylselenol and is more conveniently achieved at low temperature (–30 °C) with methylselenol using titanium tetrachloride (0.33 equivalent) instead of zinc chloride as acid catalyst.[22] These conditions also apply to the synthesis of bis methylseleno derivatives from aromatic aldehydes (Scheme 83; Conditions B).

Furthermore, the reaction is limited to those ketones whose carbonyl group is not too hindered. It does not apply to isopropyl phenyl ketone **71-10**, which instead of the selenoacetal **37-22** leads to methyl-(2-methyl-1-phenylpropyl)selenide **30-22** resulting from a reductive substitution reaction (Scheme 84).[22]



71-10 **30-22**

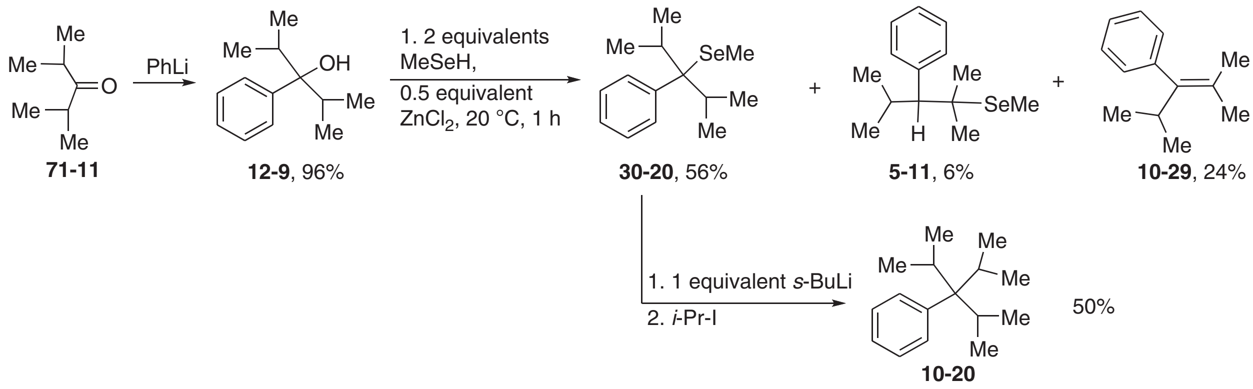
Scheme 84

The synthesis of the selenoacetal **37-22** can be, however, achieved from phenyl-bis(methylseleno)methane **37-20** and isopropyl iodide taking advantage of the easy alkylation of phenyl-bis(methylseleno)methyl potassium (Scheme 74, entry d).

The synthesis of selenides is efficiently achieved from benzyl alcohols and methylselenol in the presence of zinc chloride and only in rare occasions, such as the one involving the benzyl alcohol **12-9** bearing two isopropyl groups **12-9** at the benzylic carbon, selenides resulting from skeletal rearrangements are formed besides those resulting from the direct substitution of the hydroxyl by the methylseleno moiety (Scheme 85).[23] The easy access of the selenide **30-20** from diisopropyl ketone allows a novel synthesis of triisopropylmethyl benzene (Scheme 85)[23] that favorably compares to that involving benzaldehyde **11-1** instead (Scheme 74, entry d).

3.02.4.4.1.4.2 Syntheses of α-selenobenzyllithiums

α-Selenobenzyllithiums have been efficiently synthesized at –78 °C by cleavage of the C–Se bond of the related methylseleno acetals and *n*-butyllithium in THF. The reaction takes place efficiently even on those acetals that bear a bulky alkyl group at their benzylic carbon (Scheme 73, entry a; Scheme 74, entry d).

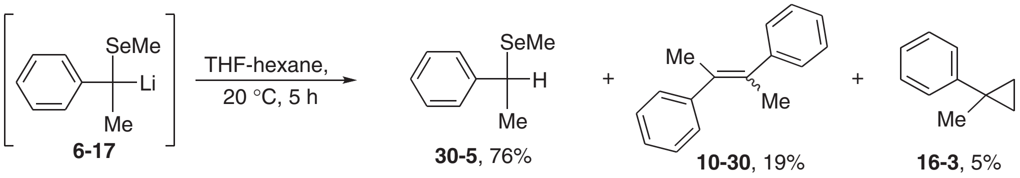


Scheme 85

Alkylation of aryl selenoacetals has been efficiently achieved with methyl, *n*-alkyl, and *i*-propyl bromides or iodide (Scheme 73, entry b; Scheme 74, entry d) but does not occur with *t*-butyl halides.[22]

The reaction is usually carried out from −78 °C to room temperature, and one should have in mind that those organometallics are able to react with the solvent or decompose at room temperature and, therefore, raising the temperature to 20 °C is always risky.

Thus 2-phenyl-2-methylseleno-ethyllithium **6-17**, which is stable for a prolonged period of time at −78 °C in THF solution is protonated by THF when stirred at room temperature for 5 h (Scheme 86). The concomitant formation of 1-methyl-1-phenylcyclopropane **16-3** probably results from the reaction of 2-phenyl-2-methylseleno-ethyllithium **6-17** with ethylene itself resulting form the decomposition of 2-lithio-THF (Scheme 26).[43]



Scheme 86

The formation of 1,2-dimethyl stilbene **10-30** suggests the decomposition of the benzylic carbanion to produce the corresponding phenyl carbine, which further reacts with its precursor.

3.02.4.4.1.4.3 Synthesis of α-metallo selenoacetals and of α-metallo-benzyl selenides by H/Li exchange

Metallation of seleno-acetals derived from aromatic aldehydes is not an easy task unless KDA (a mixture of potassium *t*-butoxide and LDA in THF)[160] is used (Scheme 73, entry b; Scheme 74, entry d; Scheme 87, entry a).[63] Neither LDA nor LiTMP[161] are able to achieve it quantitatively (Scheme 87, entries b–e) and even the latter reagent exhibits a surprisingly high propensity to act as a nucleophile toward bis(methylseleno)-phenyl methane **37-20** (Scheme 87, entries d and e).

Similarly, KDA more efficiently metallates benzyl-methyl selenide **30-3** than LDA and LiTMP (Scheme 87, entry f). Surprisingly, the reaction takes another course when performed on 1-phenyl-1-methylseleno-1-ethane **30-5**, its higher homolo,g and produces styrene **10-31** instead (Scheme 87, entry g).[19,58,63,89,162–165]

3.02.4.4.2 Synthesis of arylcycloalkanes by di-alkylation of the carbonyl group of aromatic aldehydes and ketones

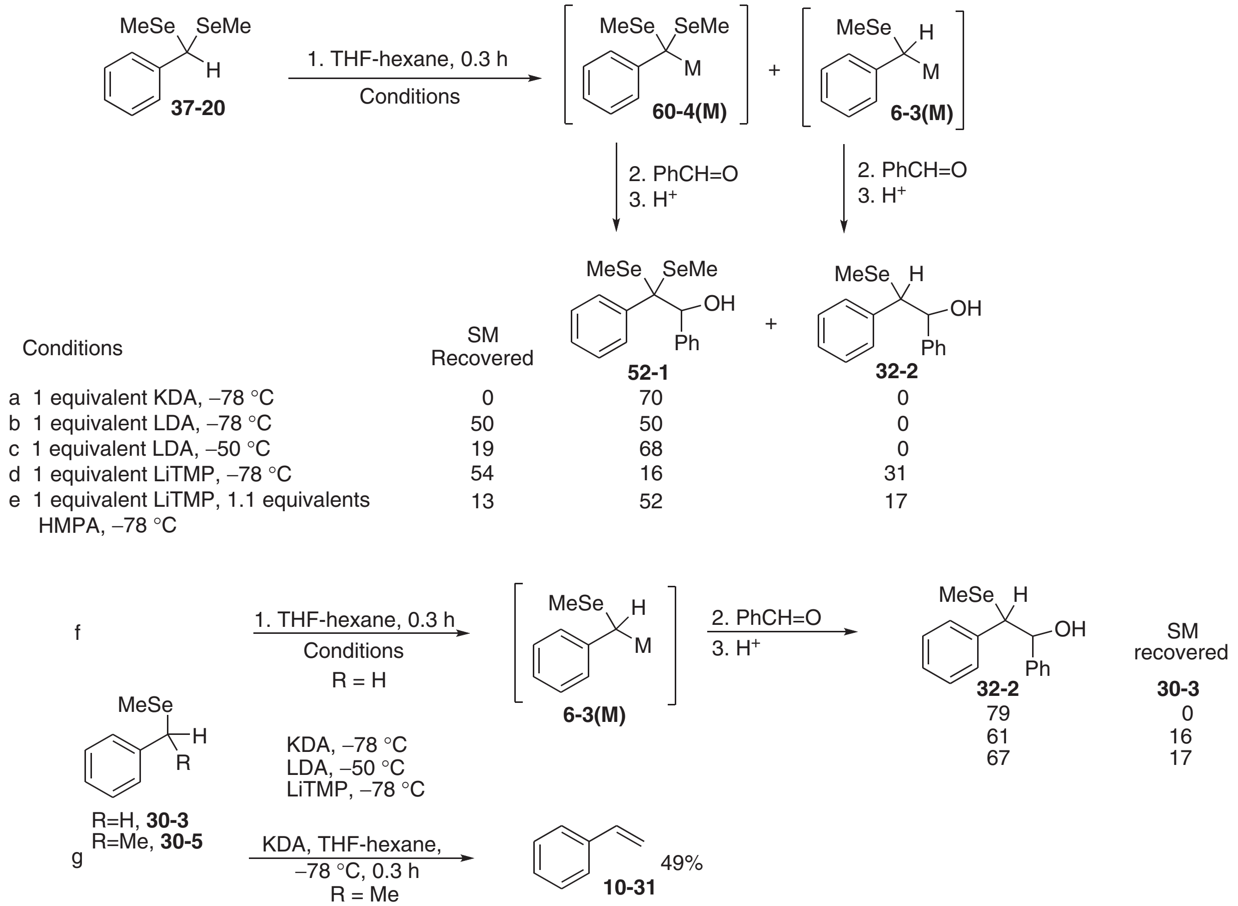
The strategy implying the dialkylation of the carbonyl group of aromatic aldehydes and ketones and involving selenoacetals as intermediates, has been successfully extended with, in some cases, substantial variations to the synthesis of aryl cycloalkanes especially arylcyclopropanes,[152,156] arylcyclopentanes,[44] and aryl-cyclohexanes.[166]

3.02.4.4.2.1 Synthesis of aryl cyclopentanes and aryl cyclohexanes involving dihalogenoalkanes and sulfonates

The first approach involves the use of ω-halogeno-primary-alkylhalides. The reaction can be carried out stepwise or in a single pot using 2 equivalents of butyllithium at first.

Mono-alkylation of α-selenobenzyllithiums with 1,*n*-dihalo alkanes only produces the ω-halogenoalkyl benzylselenides when the benzyllithium is added to the dihalide and not the reverse since the latter conditions lead to the formation of diaryl alkanes.

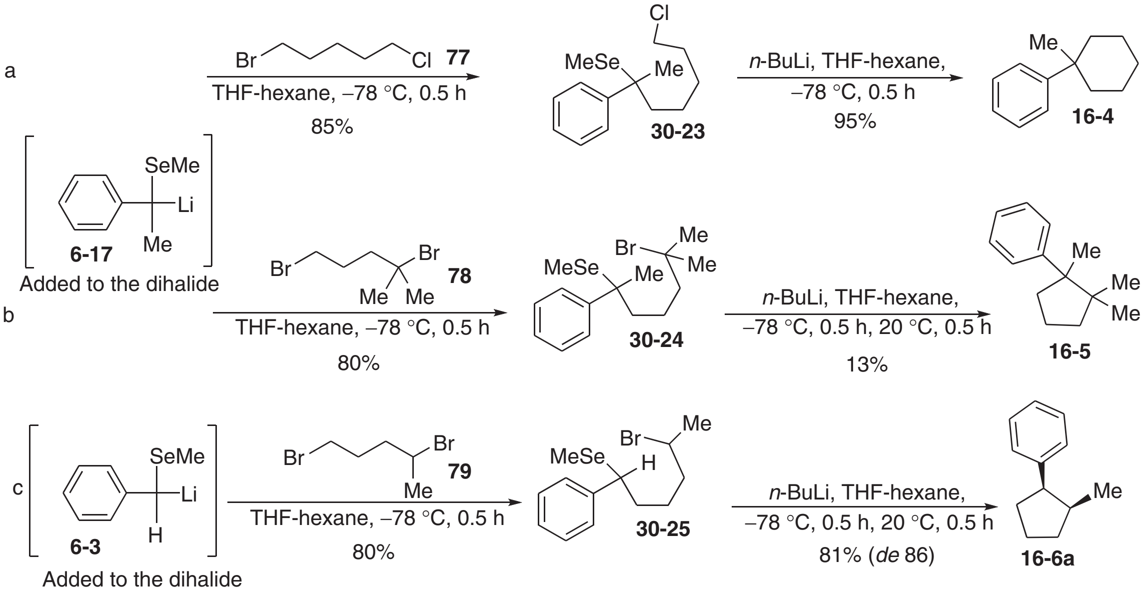
Under proper conditions, the reaction selectively occurs at the methylene carbon bearing the bromine atom of 1-bromo-5-chloro-pentane **77** (Scheme 88, entry a)[166] and at the least substituted carbon of 1,4-dibromo-pentane **79** (Scheme 28; Scheme 88, entry c),[152] and 2,5-dibromo-2-methyl-pentane **78** (Scheme 28; Scheme 88, entry b).[152]



	Conditions	SM Recovered	52-1	32-2
a	1 equivalent KDA, –78 °C	0	70	0
b	1 equivalent LDA, –78 °C	50	50	0
c	1 equivalent LDA, –50 °C	19	68	0
d	1 equivalent LiTMP, –78 °C	54	16	31
e	1 equivalent LiTMP, 1.1 equivalents HMPA, –78 °C	13	52	17

f Conditions	32-2	SM recovered 30-3
KDA, –78 °C	79	0
LDA, –50 °C	61	16
LiTMP, –78 °C	67	17

Scheme 87



Scheme 88

Reaction of those ω-halogeno-benzyl methyl selenides **30-8** and **30-23** to **30-25** with *n*-butyllithium delivers smoothly aryl-cyclohexane **16-4** (Scheme 88, entry a)[166] and aryl cyclopentanes **16-2**, **16-5**, and **16-6a** (Scheme 28; Scheme 88, entries b and c).[116,152] The synthesis of cyclopentane derivatives merits further comments since the most hindered stereoisomer of 1-methyl-2-phenyl cyclopentane **16-6a** (Scheme 88, entry c) and 1,2-dimethyl-1-phenyl cyclopentane **16-2a** (Scheme 28, entry a) are stereoselectively produced if the reactions are performed in THF-hexane, whereas the more stable stereoisomer of 1,2-methyl-1-phenyl cyclopentane **16-2b** is formed if the cyclization is carried out in pentane (Scheme 28, entry b).[152]

The synthesis of 1,2-dimethyl-1-phenyl cyclopentane **16-2** is high yielding and involves the formation of a new bond between a quaternary and a tertiary carbon (Scheme 28)[152] and that of 1,2,2-trimethyl-1-phenyl cyclopentane **16-5**, which proceeds in low yield (13%, Scheme 88, entry b),[152] is remarkable since it involves the exceptional formation of a new bond between two contiguous quaternary carbons.[152]

The formation of cyclic compounds has been carried out on benzylselenides bearing a sulfonate at their terminus and resulting from the reaction of α-selenobenzyllithiums with ω-alkoxyalkyl halides or THFs (see Schemes 76 and 77).[153] It has been reported that cyclization is more efficient using bromides or chlorides rather than sulfonates (Scheme 88, entry a; Scheme 89, entries c and e compared to Scheme 89, entries a and d).[116]

Otherwise, formation of cyclopropanes (Scheme 29, see also Section 3.02.4.4.2.3) and cyclopentanes (Scheme 28) via an exo-tet process is more efficient as usually reported, than cyclohexanes (Scheme 89, entries a and c) and especially cyclobutanes (Scheme 89, entries d, e and f).[167,168]

3.02.4.4.2.2 Synthesis of arylcyclopropanes involving dihalogenoalkanes

It would have been suitable to produce, according to the strategy reported above, the parent 1-methyl-1-phenyl cyclopropane **16-3** by reacting 2,2-bis(methylseleno)-2-phenyl-propane **37-19** sequentially with *n*-butyllithium and 1-bromo-2-chloro-ethane **84**. In fact, this reaction takes another course and delivers instead a stereoisomeric mixture of 2,3-diphenyl-2-butene **10-30** (Scheme 90, entry a).[152]

The formation of 2,3-diphenyl-2-butene **10-30** can be rationalized by reaction of the carbanion **6-17** on the bromine atom of 1-bromo-2-chloro-ethane **84** leading first to 1-bromo-1-phenyl-1-methylseleno-ethane **30-27** and ethylene in a process related to the reaction of *n*-butyllthium and 1,2-dibromo-ethane.[169] Coupling of 1-bromo-1-phenyl-1-methylseleno-ethane **30-27** with 1-methylseleno-1-phenylethyllithium **6-17** and elimination of the two adjacent methylseleno groups is expected to generate 2,3-diphenyl-2-butene **10-30** (Scheme 90, entry b).[152]

Interestingly, the vinylogous 1,4-dichloro-2-butene **85** reacts with a mixture of 2,2-bis(methylseleno)-2-phenyl-propane **37-19** and 2 equivalents of *n*-butyllithium to generate the corresponding vinyl cyclopropane **16-9b** in reasonably good yield and with very high diastereoselection (Scheme 90, entry c).[170] The cyclization step involves the intermediate formation of a benzyllithium **31-25** bearing a chloro allyl side chain and its cyclization via an exclusive S_N2' process.[170]

It is interesting to note that neither the *E*- nor the *Z*-1,4-dichloro butene **85** produces the isomeric cyclopentene derivative **16-10** and that this reaction cannot be extended to the 1,4-dibromo-2-butene.[170]

3.02.4.4.2.3 Synthesis of arylcyclopropanes involving epoxides

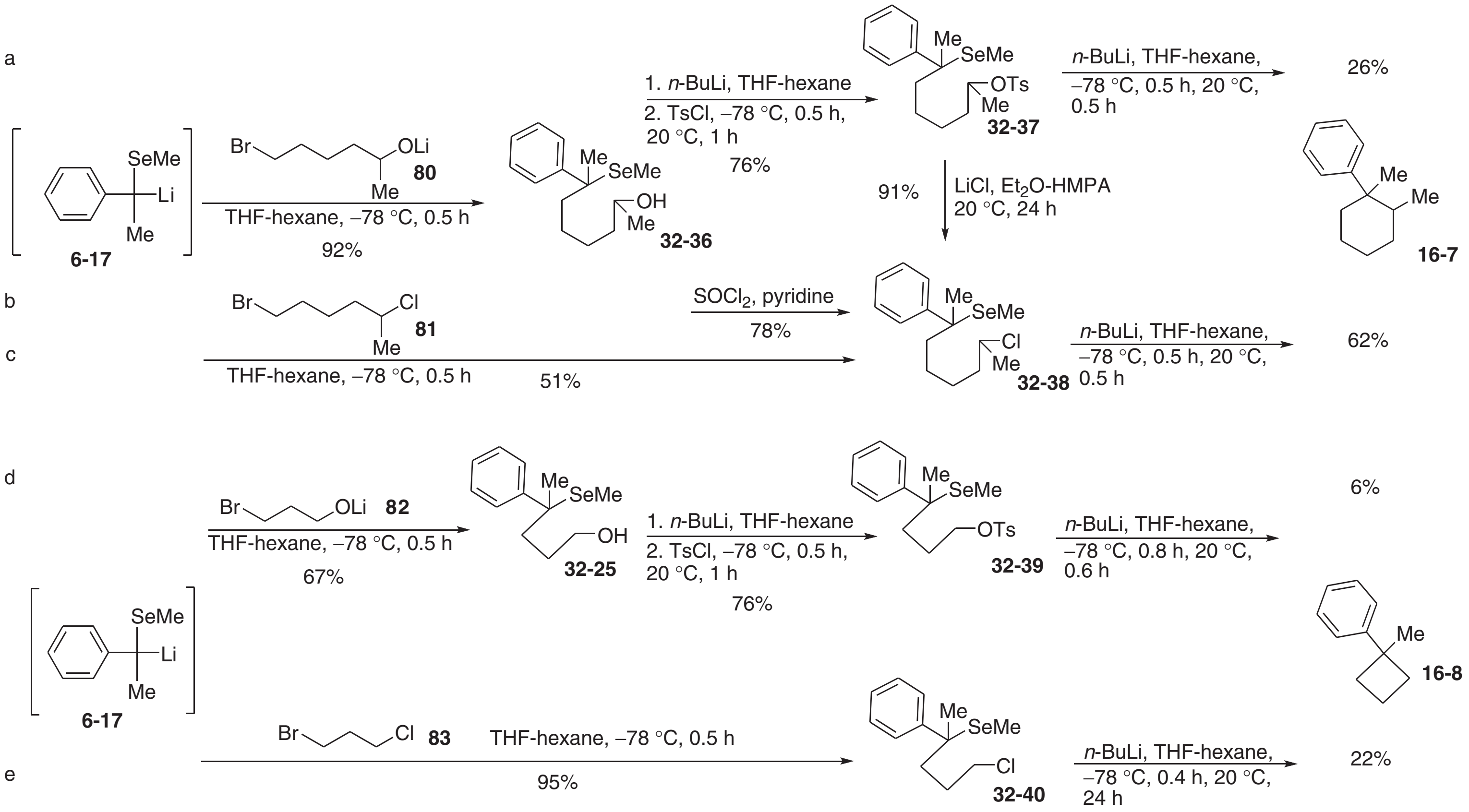
The synthesis of 1-methyl-1-phenyl cyclopropane **16-3** unavailable from 1,2-dihalogeno-ethylenes has been achieved very conveniently from 1-methylseleno-1-phenylethyllithium **6-17** and ethylene oxide **76-1**. It involves the sequential *in situ* activation of the resulting alcoholate **30-30** with phenylsulfonyl chloride and reaction of the resulting phenyl sulfonate **30-31** with *n*-butyllithium (Scheme 91, entry a).[152] The reaction has also been carried out with mesylsulfonyl chloride, but it requires 2 equivalents of *n*-butyllithium to produce the cyclopropane ring (Scheme 91, entry c).[152] This is due to the propensity of *n*-butyllithium to metallate the methyl group of the mesylate rather than to cleave the C–Se bond of 3-(methylselanyl)-3-phenylbutyl methanesulfonate **30-32** (Scheme 91, entry b).[152]

The transformation described above has been extended to other benzyllithiums and epoxides[152] such as methyl oxirane **76-7**, oxido-styrene **76-8**, vinyl oxirane, and oxido-cyclohexene including some scalemic ones that have allowed the synthesis the related aryl cyclopropane derivatives.[152,156]

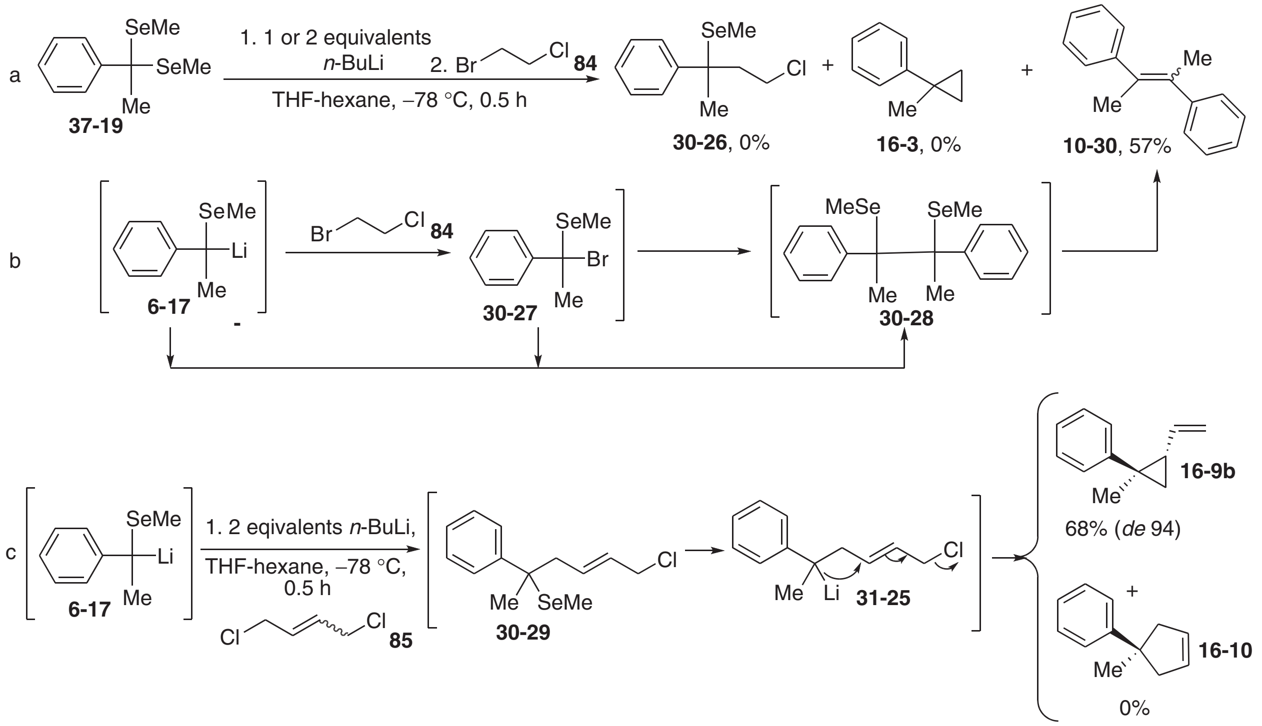
Although cyclizations are very efficient even from benzyllithiums, fully alkylated at their benzylic sites, they cannot be achieved with tertiary alkyl tosylates. The latter reaction instead delivers several isomeric olefinic compounds in addition to some residual starting material (Scheme 92).[116]

Cyclization to the cyclopropane ring proved to be completely stereoselective starting from the mixture of the two regioisomeric γ-hydroxyselenides derived from methylseleno phenyl methyllithium **6-3** and 1-(*R*)-oxidostyrene **(*R*)-76-8** (Scheme 93).[156] The formation of a single diastereoisomer starting from a mixture of regioisomeric γ-hydroxyselenides, therefore, implies epimerization at the benzylic carbanion. The formation of a single enantiomer (1*R*,2*R*)-*trans*-oxido-stilbene **(*R*,*R*)-16-12** (*ee*: 99.9%) confirms that the epoxide ring opening in THF-hexane occurs with inversion of configuration (Scheme 78). It has been, however, found that styrene epoxide **76-8** ring opening is less stereoselective if it is carried out in pentane instead of THF (*ee*: 67%).[156]

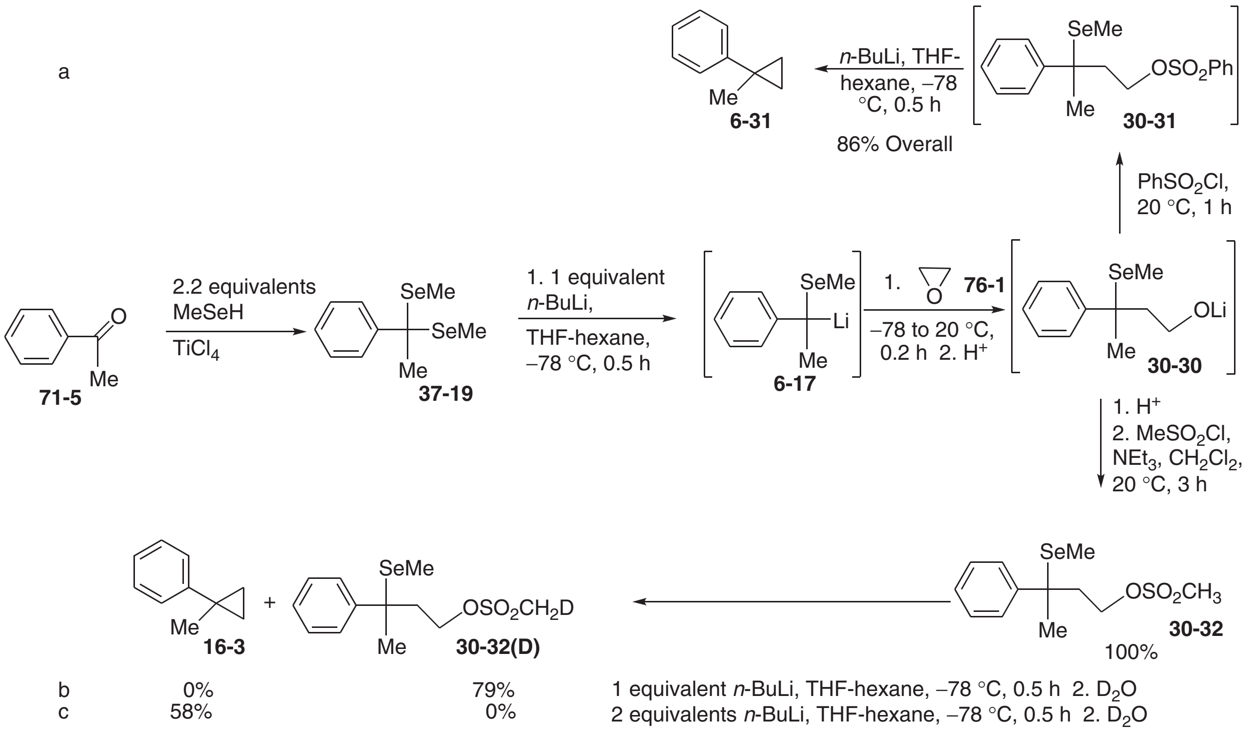
Cyclizations leading to di- and tri-substituted arylcyclopropanes from γ-benzylselenide sulfonates as described in Schemes 29 and 89 are stereospecific and occurs either by double inversion or retention of configuration. Those outcomes are compatible with the formation of a tetracoordinated cyclic selenurane **86** leading to a racemic cyclopropane derivative **rac-16-12** (Scheme 94, route a) a W-conformation on an open chain, leading to a scalemic cyclopropane derivative **(*S*,*S*)-16-12** (Scheme 94, route b) as already proposed to rationalize a related stereochemical outcome involving cyclization of 1,3-dibromoalkanes instead.[171]


a
b
c
d
e
SeMe
Li
Me
6-17
Br
OLi
Me
80
THF-hexane, –78 °C, 0.5 h
92%
Me
SeMe
OH
Me
32-36
1. n-BuLi, THF-hexane
2. TsCl, –78 °C, 0.5 h, 20 °C, 1 h
76%
Me
SeMe
OTs
Me
32-37
n-BuLi, THF-hexane, –78 °C, 0.5 h, 20 °C, 0.5 h
26%
91%
LiCl, Et$_2$O-HMPA 20 °C, 24 h
Me
Me
16-7
Br
Cl
Me
81
SOCl$_2$, pyridine
78%
THF-hexane, –78 °C, 0.5 h
51%
Me
SeMe
Cl
Me
32-38
n-BuLi, THF-hexane, –78 °C, 0.5 h, 20 °C, 0.5 h
62%
Br
OLi
82
THF-hexane, –78 °C, 0.5 h
67%
Me
SeMe
OH
32-25
1. n-BuLi, THF-hexane
2. TsCl, –78 °C, 0.5 h, 20 °C, 1 h
76%
Me
SeMe
OTs
32-39
n-BuLi, THF-hexane, –78 °C, 0.8 h, 20 °C, 0.6 h
6%
SeMe
Li
Me
6-17
Me
16-8
Br
Cl
83
THF-hexane, –78 °C, 0.5 h
95%
Me
SeMe
Cl
32-40
n-BuLi, THF-hexane, –78 °C, 0.4 h, 20 °C, 24 h
22%

Scheme 89

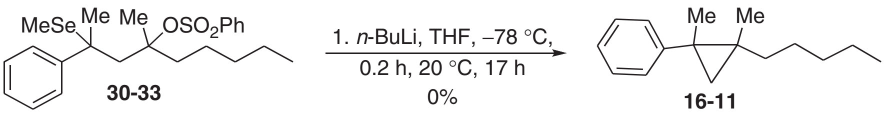


Scheme 90

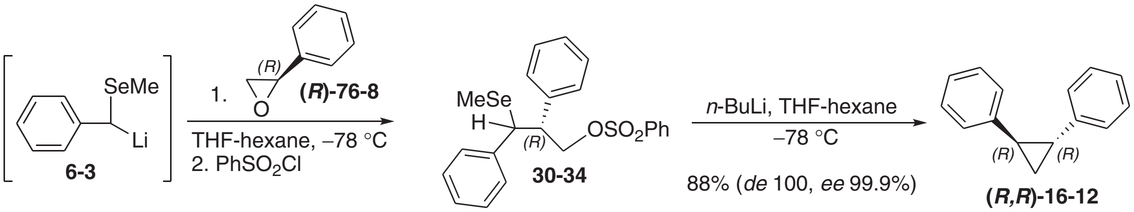


Scheme 91

The formation of the (1*S*,2*S*)-1,2-diphenylcyclopropane **(*S*,*S*)-16-12** with 46% enantiomeric excess from scalemic (1*S*,3*S*)-3-(methylselanyl)-1,3-diphenylpropyl benzenesulfonate (Scheme 94) suggests that the reaction takes place mainly through a W-conformation on the starting material (Scheme 94, route b, X=$SnBu_3$), although part also involves route b.[156]

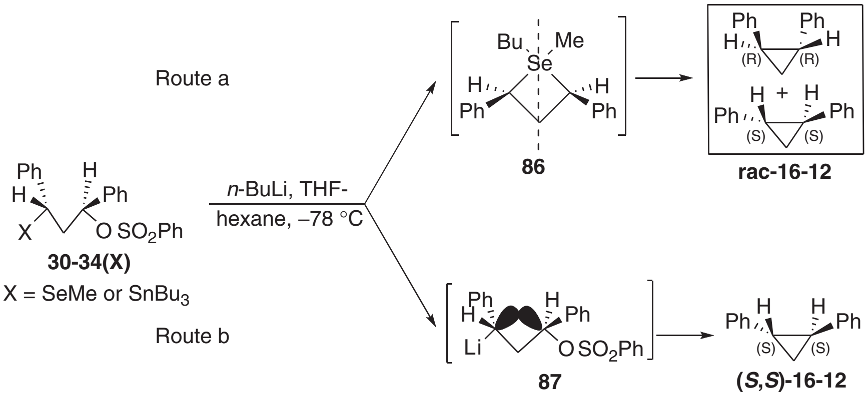


Scheme 92



Scheme 93

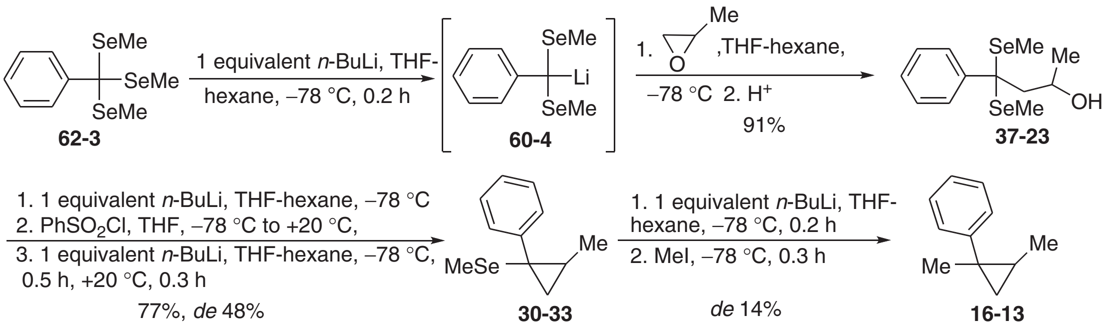
Interestingly (1*S*,2*S*)-1,2-diphenylcyclopropane **(*S*,*S*)-16-12** is produced as the only enantiomer when the reaction is carried out on the related (1*S*,3*S*)-1,3-diphenyl-3-(tributylstannyl)propyl benzenesulfonate which is unable to produce a four-membered cyclic intermediate (Scheme 94).[156]



Scheme 94

The sequence of reaction described in Schemes 29, 93, and 94 allows not only the enantioselective synthesis of aryl cyclopropane derivatives, but when coupled to the reaction involving sodium periodate-ruthenium dioxide oxidation also allows the stereospecific synthesis of scalemic cyclopropane carboxylic acids (Scheme 29).

An interesting approach to 1,2-dimethyl-1-phenyl cyclopropane **16-13** involves benzonitrile as the starting material and its sequential transformation to phenyl-tris(methylseleno) methane **62-3**, phenyl bis(methylseleno)methyllithium **60-4,** and the corresponding γ-hydroxy-selenoacetal **37-23** (Scheme 95).[116] The latter generates 2-methyl-1-phenyl-1-methylseleno cyclopropane **30-33** by *in situ* transformation to the corresponding benzene sulfonate and further reaction with *n*-butyllithium. Finally, sequential reaction with *n*-butyllithium and methyl iodide produces 2-methyl-1-phenyl-1-lithio cyclopropane and then



Scheme 95

1,2-dimethyl-1-phenyl cyclopropane **16-13** (Scheme 95). The last transformation, which is carried out on a single stereoisomer of 2-methyl-1-phenyl-1-methylseleno cyclopropane **30-33** (the minor one), produces a mixture of 1,2-dimethyl-1-phenyl cyclopropane **16-13** showing that epimerization has taken place under the reported conditions.[116]

3.02.4.4.2.4 Synthesis of arylcyclopropanes involving carbon–carbon double bonds

An even more interesting and straightforward route to arylcyclopropanes involves the reaction of 2,2-bis(methylseleno)-2-phenylalkanes, *n*-butyllithium, and ethylene, butadiene, or styrene (Scheme 96).[158] This one-pot reaction takes advantage of the high propensity of α-methylseleno-alkyllithiums **6-17** to add across a carbon–carbon double bonds and the capacity of the resulting alkyllithium expel, by a process not fully understood, the methylseleno moiety. Thus, the α-methylseleno-alkyllithiums **6-17** act as a carbene equivalent.[43]

This reaction has been successfully extended to heterosubstituted olefins that produce a large array of heterosubstituted arylcyclopropanes with very high stereocontrol including those bearing a trimethylsilyl-, thiophenyl-, selenomethyl-, selenophenyl-substituent (Scheme 97).[158] The surprising formation of 1-methyl-1-phenyl-2-methylseleno cyclopropane **30-34b** in place of the expected 1-methyl-1-phenyl-2-phenylseleno cyclopropane **30-35b** (Scheme 97, entry d compared to entries c and e) suggests, at least for this case, the intermediate formation of the ate complex **88** (Scheme 97, entry f), which collapses to provide first the benzyllithium **89** bearing in γ-position both the SePh and SeMe groups, then the methylseleno cyclopropane **30-34b** by kicking the selenophenyl group that possesses the higher leaving group ability (Scheme 97, entry f).[158] A related case is disclosed in Scheme 97, entry b.

The synthesis of cyclopropane derivatives disclosed in Schemes 96 and 97 and is probably the shortest, most convenient, and most versatile dialkylation of the carbonyl group of aromatic aldehydes and ketones. It occurs with excellent relative stereocontrol (Schemes 96 and 97).

Another approach could involve ω-unsaturated benzylselenides as versatile precursors of arylcycloalkanes owing the exceptional capacity of benzyl selenides to generate carbanions (butyllithiums), carbon radical (metals, tin-hydrides, silicon hydrides) or carbocations ($TiCl_4$, Lewis acids), which are stabilized by the attached aromatic ring (Scheme 98). The addition of carbon radicals[172–174] and carbocations across the carbon–carbon double bonds are well-established processes,[175–177] whereas addition of carbanion to carbon–carbon double bonds is less documented, although involved in polyethylene synthesis.[130–133]

It is interesting to note that the usual strategy to build aryl alkanes involves the Friedel–Craft reaction and the formation of a bond between the aromatic ring and the alkyl chain. It takes advantage of the stabilization of the carbocation on the six-member ring.[178–180]

The Friedel–Craft reaction cannot be extended to the synthesis of arylcyclopropanes owing the high propensity of cyclopropyl carbinyl anions, cations, and radicals to release the strain by rearrangement to the related homoallyl species.[38,181–186] The reaction disclosed in Scheme 14 and designed to produce enantioselectively scalemic α-arylthio-alkyllithium supports the behavior of cyclopropyl carbinyl carbanions reported in Scheme 98, entry a.[38]

Nevertheless, the synthesis of cyclopropane derivatives can be achieved by combining an elimination reaction and thus avoiding equilibration that favors the destruction of the cyclopropane ring. This has been achieved by producing benzyllithium derivatives bearing in suitable position an allyl chloride (Scheme 90, entry c)[170] or allyl phenylsulfonate (Scheme 99, entry a).[170] It is interesting to point out that the synthesis of the vinyl cyclopropane derivative even occurs by kicking of dilithium oxide, a quite poor leaving group as compared to the chloride (Scheme 99, entry b).

3.02.4.4.2.5 Synthesis of aryl cyclopentanes and cyclohexanes involving carbon–carbon double bonds

The strategies disclosed in Scheme 98 have been tested systematically on the ω-alkenyl benzylselenide **30-6** (Schemes 100 and 101).

Thus **30-6** is efficiently reduced with tributyltin hydride, but the radical intermediate further reacts to deliver, besides the product resulting from selenium/hydrogen exchange **10-1** (23%), a mixture of all the possible carbocycles **16-4** and **16-2** in which the five-membered ones **16-2b** and **16-2a** prevail (42%, *de* 71%) (Scheme 100, entry a).[44]

Reacting with the ω-alkenyl benzylselenide **30-6** with $TiCl_4$, as Lewis acid catalyst, promotes the exclusive cyclization leading to 4-chloro-1-methyl-1-phenyl-cyclohexane **16-21**. The latter, on subsequent reduction with tributyltin hydride in the presence of catalytic amounts of AIBN, delivers 1-methyl-phenylcyclohexane **16-4** as the sole hydrocarbon (Scheme 100, entry b).[166]

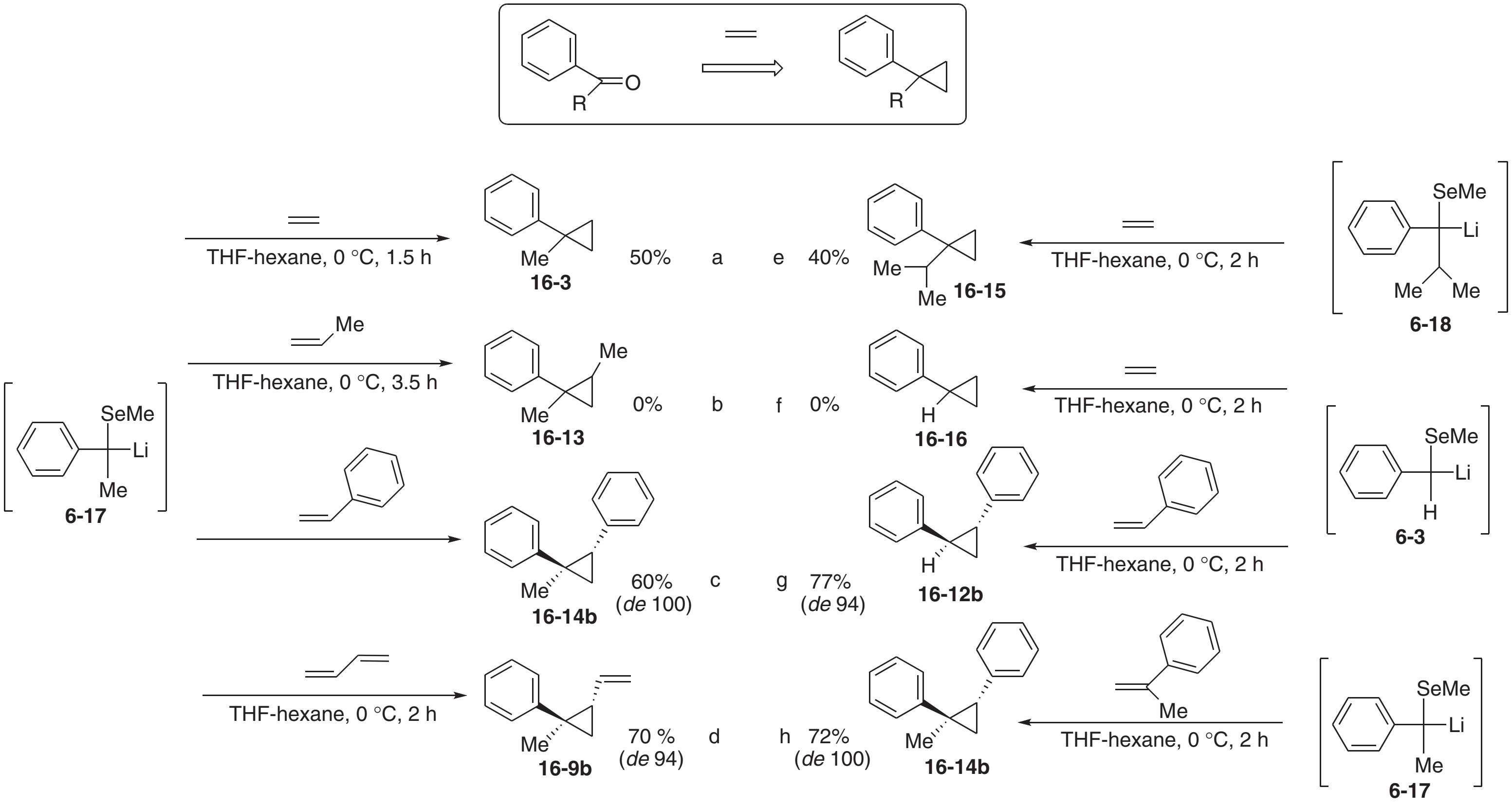
The transformations disclosed in Scheme 25 and Table 7, that involve the intermediate formation of ω-alkenyl benzyllithium **31-3** schematized in Scheme 98, entry a, proved by far to be more efficient than the others for the synthesis of aryl cyclopentane derivatives (Scheme 98, entries b and c).[43] It allows not only the efficient carbocyclization reaction, but also the solvent-dependent formation of each of the two possible diastereoisomers. The scope and limitations of this unusual reaction is discussed in Section 3.02.4.4.2.5.1.

3.02.4.4.2.5.1 Synthesis of aryl cyclopentanes and cyclohexanes involving methylene terminated carbon–carbon double bonds

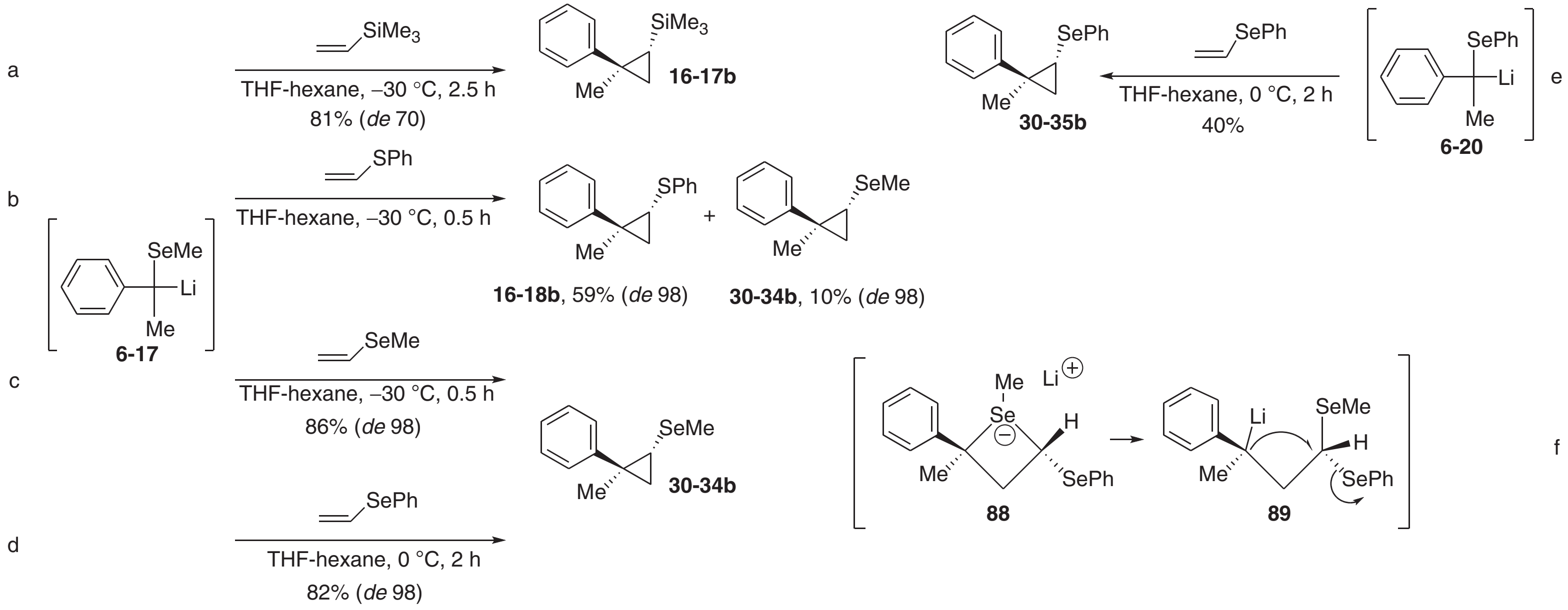
3.02.4.4.2.5.1.1 Scope and limitations

The authors have have already reported that the ω-alkenyl benzylselenides **30-6** and related derivatives (Scheme 34)[53] react with lithium or lithium arenides (Schemes 65 and 66)[28,115] or butyllithiums (Scheme 25 and Table 7)[43] to produce ω-alkenyl benzyllithium **31-3** that cyclizes rapidly to produce after methanolysis aryl cycloalkanes.

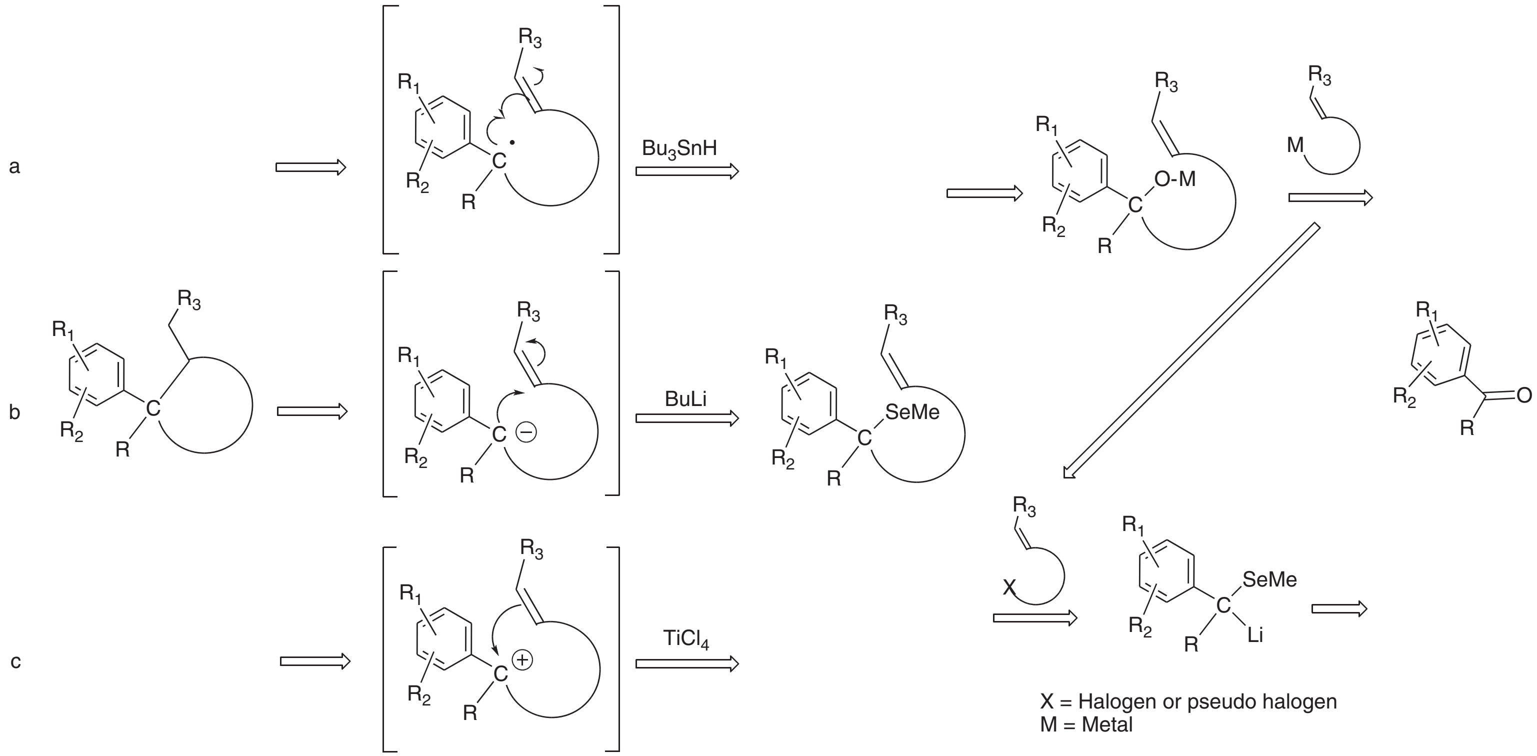
In fact, when this work started, the carbocyclization reactions were expected to occur via radical processes,[187] or in the case of ω-alkenyl allylmagnesium through a concerted ene reaction.[188] Baily had just shown that carbocyclization could process through


R
O
R
SeMe
Li
Me
6-17
THF-hexane, 0 °C, 1.5 h
Me
16-3
50%
a
e
40%
Me
Me
16-15
THF-hexane, 0 °C, 2 h
SeMe
Li
Me
Me
6-18
Me
THF-hexane, 0 °C, 3.5 h
Me
Me
16-13
0%
b
f
0%
H
16-16
THF-hexane, 0 °C, 2 h
SeMe
Li
H
6-3
Me
16-14b
60%
(de 100)
c
g
77%
(de 94)
H
16-12b
THF-hexane, 0 °C, 2 h
THF-hexane, 0 °C, 2 h
Me
16-9b
70 %
(de 94)
d
h
72%
(de 100)
Me
16-14b
Me
THF-hexane, 0 °C, 2 h
SeMe
Li
Me
6-17

Scheme 96

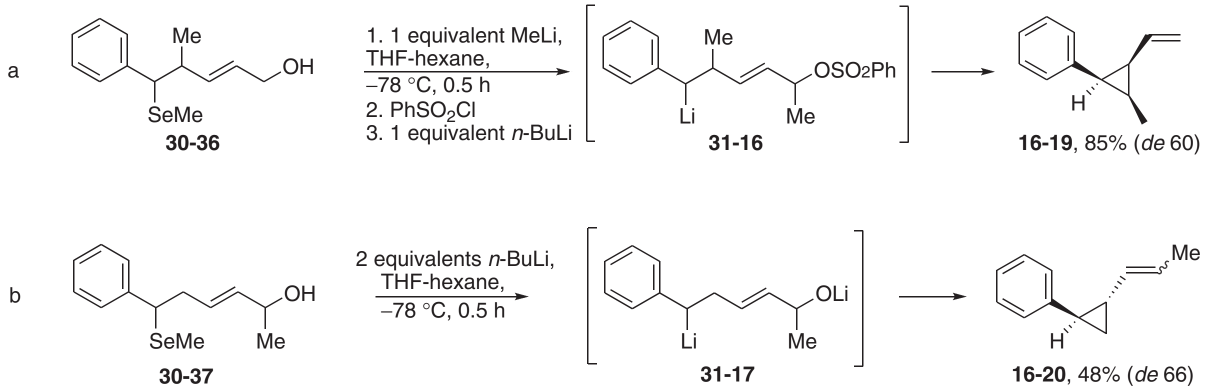

a
SiMe3
THF-hexane, –30 °C, 2.5 h
81% (de 70)
SiMe3
Me
16-17b
b
SPh
THF-hexane, –30 °C, 0.5 h
SPh
Me
+
SeMe
Me
16-18b, 59% (de 98)
30-34b, 10% (de 98)
SeMe
Li
Me
6-17
c
SeMe
THF-hexane, –30 °C, 0.5 h
86% (de 98)
SeMe
Me
30-34b
d
SePh
THF-hexane, 0 °C, 2 h
82% (de 98)
SePh
Me
30-35b
SePh
THF-hexane, 0 °C, 2 h
40%
SePh
Li
Me
6-20
e
Me
Li⊕
Se
⊖
H
Me
SePh
88
Li
SeMe
H
Me
SePh
89
f

Scheme 97

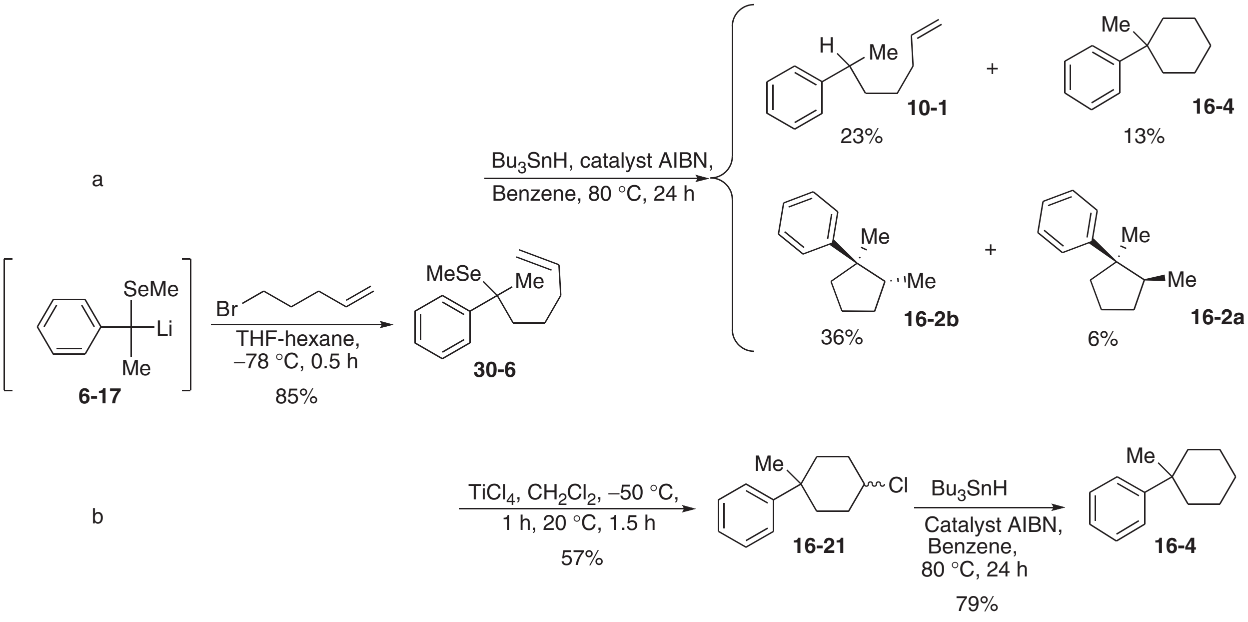


X = Halogen or pseudo halogen
M = Metal

Scheme 98



Scheme 99



Scheme 100

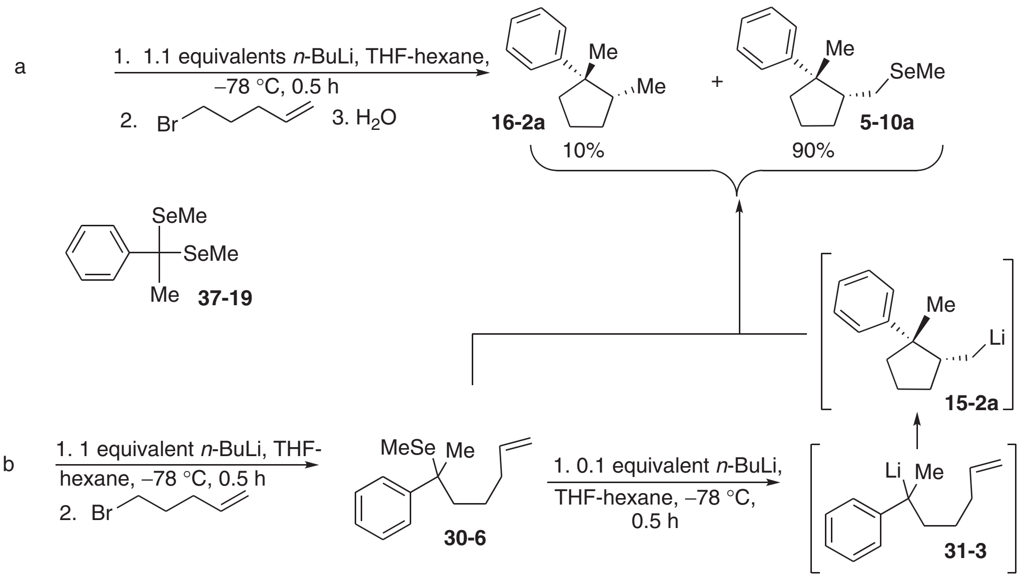
a two-electron transfer.[189,190] Later, several papers appeared involving lithium-mediated carbocyclization reactions, inter alia the work of Cohen.[37,191–193]

In the course of the synthesis of methyl-(2-methylhept-6-en-2-yl)selane **30-6,** by reacting 2-phenylseleno-2-phenyl-2-propyllithium with 5-bromopent-1-ene, it was rather surprising to observe, after acid hydrolysis, the formation instead of its five-membered cyclic isomer methyl-(2-methyl-2-phenylcyclopentyl)methylselane **5-10a** with extremely high stereocontrol (*de*: 95%) (Scheme 101, entry a)[44] besides 10% of 1,2-dimethyl-1-phenyl cyclopentane **16-2a**.

This surprising isomerization of **30-6** to **5-10a** was accounted to the presence of 10% excess of *n*-butyllithium, which remains in the medium after complete cleavage of the C–Se bond of 2,2-bis(methylseleno)-2-phenyl-propane **37-19** and subsequent alkylation of the resulting 2-methylseleno-2-phenyl-2-propyllithium.

It was rationalized that the cleavage of the C–Se bond of the resulting ω-alkenyl benzylselenide **30-6**, by the small amount of remaining *n*-butyllithium, initiates an extremely fast cyclization of the resulting ω-alkenyl benzylic carbanion **31-3** across its terminal C–C double bond leading to the cyclopentylmethyllithium **15-2a**, which in turn cleaves the C–Se bond of the ω-alkenyl benzylselenide **30-6** and initiates the catalytic isomerization process leading to **10-5a**. Protonation of the remaining cyclopentylmethyllithium **15-2a** leads selectively to **16-2a** in 10% yield, exactly what is expected from the excess of *n*-butyllithium used.[44] This reaction has been extended to other ω-alkenyl selenides and the results are reported below in Scheme 127 and Table 10.[154]

The hypothesis disclosed above has been supported by producing independently the same compounds **5-10a** and **16-2a** in the same ratio by reacting the ω-alkenyl benzylselenide **30-6** with only 10% of *n*-butyllithium in THF-hexane (Scheme 101, entry b)[44]



Scheme 101

Table 10 Butyllithium catalyzed isomerisation of ω-alkenyl benzylselenide **30-x**

Entry	*SM*	*R^1*	*R^2*	*Conditions*	*5-x*	*Yield 5-x (%)*	*a/b Ratio*
1	**30-6**	Me	H	0.1 equivalent *n*-BuLi, THF, 20 °C, 3 h	**5-10**	70	
2	**30-6**	Me	H	0.1 equivalent *t*-BuLi, Et_2O, 20 °C, 3 h	**5-10**	67	
3	**30-6**	Me	H	0.1 equivalent *t*-BuLi, Et_2O, − 25 °C, 4 h	**5-10**	54	
4	**30-6**	Me	H	0.1 equivalent *t*-BuLi, pentane, 20 °C, 72 h	**5-10**	58	
5	**30-6**	Me	H	0.1 equivalent *t*-BuLi, pentane, 40 °C, 5 h	**5-10**	58	
6	**30-6**	Me	H	0.1 equivalent *t*-BuLi, benzene, 80 °C, 5 h	**5-10**	70	
7	**30-57**	Me	SPh	0.2 equivalent *n*-BuLi, THF, 20 °C, 48 h	**5-13**	75	90/10
8	**30-65**	Me	SC_6H_{11}	0.2 equivalent *n*-BuLi, THF, 20 °C, 16 h	**5-14**	72	64/34
9	**30-54**	Me	Ph	0.2 equivalent *n*-BuLi, THF, 20 °C, 24 h	**5-15**	80	52/48
10	**30-54**	Me	Ph	0.2 equivalent *t*-BuLi, Et_2O, 20 °C, 24 h	**5-15**	56	62/38
11	**30-66**	H	SPh	0.2 equivalent *n*-BuLi, THF, 20 °C, 48 h	**5-16**	0	
12	**30-67**	H	Ph	0.2 equivalent *n*-BuLi, THF, 20 °C, 24 h	**5-17**	58	56/64
13	**30-68**	Me	$SiMe_3$	0.2 equivalent *n*-BuLi, THF, − 78 °C, 3.75 h	**5-18**	80	66/34
14	**30-69**	Me	$SiMe_2Ph$	0.2 equivalent *n*-BuLi, THF, 20 °C, 24 h	**5-19**	80	63/37
15	**40-2**	OMe	H	0.2 equivalent *t*-BuLi, THF, − 78 °C, 7 h	**5-20**	82	

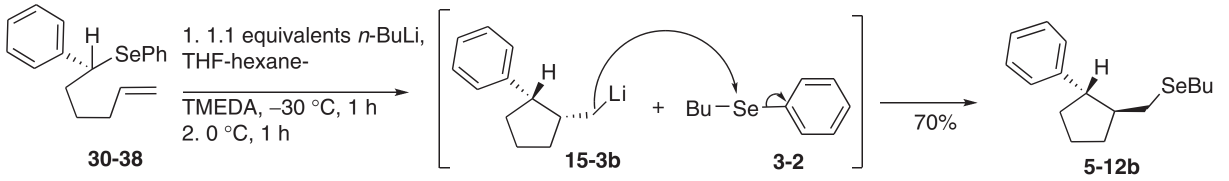
(compared to the reaction implying the same selenide and elemental lithium, Scheme 66).[28,115] It was also found that the stereoisomeric ratio observed in THF can be inverted by carrying out the C–Se bond cleavage in hexane at room temperature (Scheme 25 and Table 7, entry l) or in ether at − 30 °C (Scheme 25 and Table 7, entry g).[44]

3.02.4.4.2.5.1.2 Substitution at the benzylic carbon

Accordingly **30-4** has been selectively prepared by reacting the selenoacetal **37-19** with a slight default of *n*-butyllithium then with 5-bromo-pent-1-ene. It has been found that the substitution at the benzylic carbon influences the rate, the stereochemistry, and even the outcome of the carbocyclization reaction.

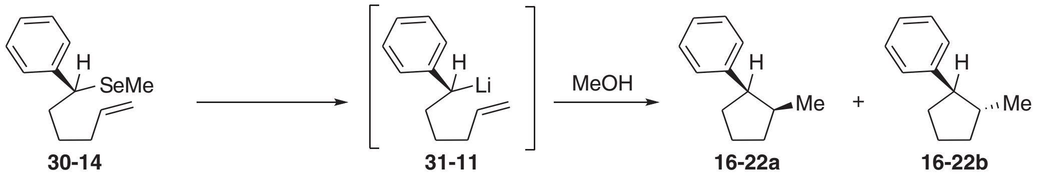
Thus, the reaction with *n*-butyllithium of **30-38** the ω-alkenyl benzyl selenide bearing a phenylseleno instead of a methylseleno substituent at the benzylic carbon clearly shows the importance of the methylseleno over the phenylseleno moiety to produce by carbocyclization a novel organolithium compound (Scheme 102 compared to Scheme 25 and Table 7). The formation of **5-12b** suggests that the organolithium **15-3b** resulting from the carbocyclization of the benzyllithium reacts on the butyl phenyl selenide **3-2** produced concomitantly by cleavage of the C–Se bond of **30-38** by *n*-butyllithium (Scheme 102).

Otherwise, methyl-(hept-6-en-2-yl)selane **30-14**, which bears a hydrogen at the benzylic position, produces a five-membered cycle on reaction with butyllithiums in THF or ether, but the reaction is slower than that of the related benzylic selenide **30-6** bearing a methyl group at the benzylic position (Scheme 103 compared to Scheme 35). Although the carbocyclization of **30-14**



Scheme 102

parallels that of **30-6** in ether, providing after hydrolysis, the cyclopentane derivative **16-22a** in which the phenyl and the methyl group are *cis* to each other, with extremely high stereocontrol (Scheme 103, entry a compared to Scheme 25 and Table 7, entry g).[44] **16-22b** is, however, produced from **30-14** with a poorer stereocontrol than that involving **30-6** instead when the reaction is performed in THF under similar conditions (Scheme 103, entry b compared to Scheme 25 and Table 7, entry g).[44] A reasonably good stereocontrol has been restored by carrying out the reaction at higher temperature (+20 °C instead of −78 °C) for a longer time that suggests a thermodynamic control. (Scheme 103, entry c compared to entry b).[44]

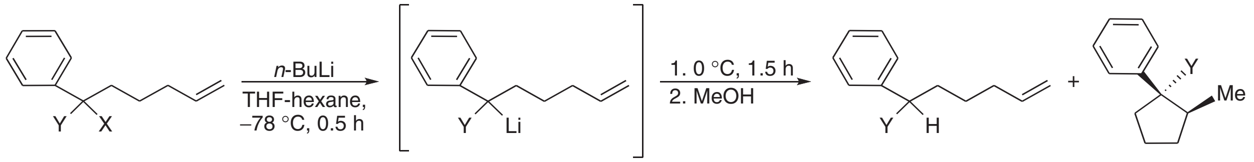


			16-22a	16-22b
a	t-BuLi, ether-hexane, 0 °C, 0.5 h	88%	100	0
b	n-BuLi, THF-hexane, –38 °C, 0.5 h	75%	45	55
c	n-BuLi, THF-hexane, 20 °C, 1 h	71%	10	90

Scheme 103

The behavior of ω-alkenyl benzyllithiums bearing a chalcogeno substituent at the benzylic carbon is strictly dependent on the nature of this substituent. Thus, the methoxy-substituted ω-alkenyl benzyllithium **41-2** cyclizes extremely rapidly and after protonation leads to 1-phenyl-1-methoxy-2-methyl cyclopentane **45-2** in very good yield and with extremely good stereocontrol. Nevertheless, the stereoisomer bearing the phenyl and the methyl group in *cis*-position is the only one obtained, whatever the solvent used (Scheme 104, entry a; Scheme 34).[53] Its phenylthio analog **91** does not cyclize under similar or forced conditions (Scheme 104, entry b).[87]

The related methylseleno-substituted benzyllithium reacts differently and produces around room temperature, through a tandem cyclization-substitution reaction, the bicyclo-[3.1.0] cyclohexane **16-24** bearing a phenyl substituent at bridgehead position (Scheme 105, entry b).[194] This reaction has been successfully extended to the synthesis of bicyclo-[4.1.0] cycloheptane **16-23** (Scheme 105, entry c).[194]

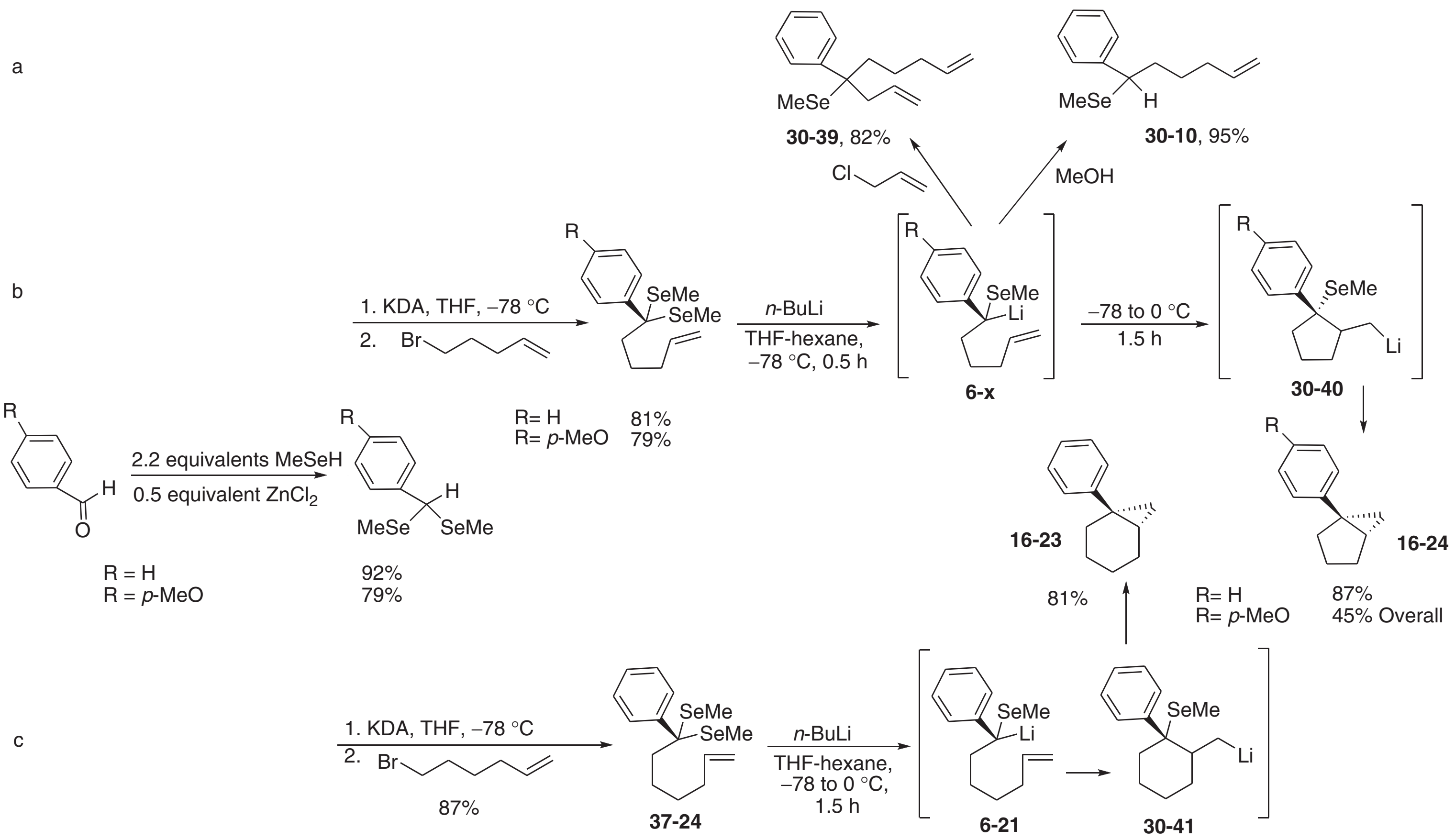


a	X = SeMe, **40-2**	Y = OMe, **41-2**	0%	**45-2**, 81%
b	X = SPh, **90**	Y = SPh, **91**	**92**, 90%	0%

Scheme 104

It seems that the organometallics that bear the more stabilized carbanion is the least prone to achieve a carbocyclization reaction. It has been, however, reported that a related α-phenylthioallyl potassium adds intramolecularly across a carbon–carbon double bond to provide a bicyclic derivative in a process related to the reactions disclosed in Scheme 105.[37]

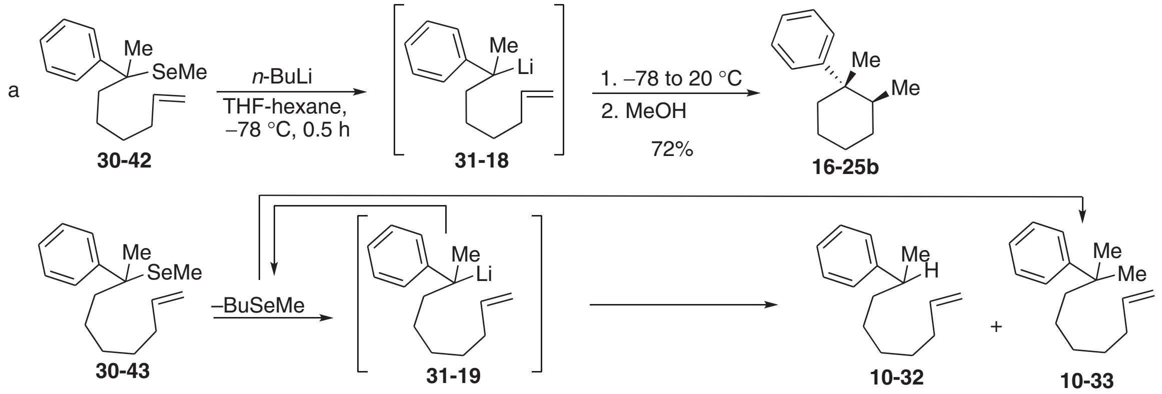
The results reported in Scheme 104, entry b, that involves the S/Li exchange is reminiscent of the C/Se exchange. It is unusual and apparently occurs not only because the resulting carbanion is well stabilized by the thiophenyl group and the phenyl ring, but also because the dithioacetal is missing hydrogen at the benzylic carbon which would have otherwise produced the corresponding acyl anion equivalent by H/Li exchange.[78,195]


a
b
c
30-39, 82%
30-10, 95%
MeSe
H
Cl
MeOH
R
SeMe
Li
6-x
1. KDA, THF, –78 °C
2. Br
n-BuLi
THF-hexane, –78 °C, 0.5 h
–78 to 0 °C
1.5 h
30-40
R= H 81%
R= p-MeO 79%
2.2 equivalents MeSeH
0.5 equivalent ZnCl2
R = H
R = p-MeO
92%
79%
16-23
16-24
81%
R= H 87%
R= p-MeO 45% Overall
87%
37-24
THF-hexane, –78 to 0 °C, 1.5 h
6-21
30-41

Scheme 105

3.02.4.4.2.5.1.3 Length of the alkenyl side chain

The carbocyclization reaction described above allows the synthesis of the cyclohexane derivative **16-25b** consisting of a single stereoisomer possessing a *trans* relationship between the adjacent phenyl and methyl groups. This stereocontrol is neither solvent (THF or ether) nor temperature dependent (Scheme 106).[194]



b	1. *t*-BuLi, pentane, 20 °C,	2. 20 °C, 3h 3. MeOH	64%	100	0
c	1. *t*-BuLi, pentane, 20 °C	2. 20 °C, 360 h 3. MeOH	48%	62	24
d	1. *t*-BuLi, *i*-octane, 20 °C, 1 h	2. 90 °C, 17 h 3. MeOH	–	33	26
e	1. *n*-BuLi, THF, –78 °C, 0.5 h	2. MeI	65%	6	94

Scheme 106

The carbocyclization described above cannot, however, be extended to the formation of

1. cycloheptane derivatives from the homologous alkenyl benzyllithiums **31-19** even if the benzyllithium is heated up to 90 °C for 17 h (Scheme 106, entry d),[194,196,197]
2. cyclopropane derivative **10-4** from (2-phenylpent-4-en-2-yl)lithium **31-20** (Scheme 107, entry a).

Reacting (2-phenyl non-8-en-2-yl)lithium **31-19** in pentane for a longer period of time (360 h instead of 3 h, Scheme 106, compare entries b and c) or at a higher temperature (Scheme 106, compare entries d and c) provides besides the product resulting from protonation of **31-19**, another one implying its methylation. It might result from the unexpected reaction between **31-19** and butyl methyl selenide, concomitantly produced,[197] and has been produced in better yield on reacting (2-phenyl non-8-en-2-yl)lithium **31-19** with methyl iodide (Scheme 106, entry e).

(2-Phenylpent-4-en-2-yl)lithium **31-20** does not produce **10-4**, but instead the open chain 4-phenyl-1-pentene **10-34** on hydrolysis. It reacts, however, with ethylene to produce after hydrolysis the aryl cyclopentane **16-26** whose structure is disclosed in Scheme 107, entry b.[194] Its formation probably results from a cascade of addition reactions, which involves sequential formation of the alkyllithium **7-7** whose structure is disclosed in Scheme 107, entry b.[194]

Reaction of *n*-butyllithium on the benzyl selenides **30-39** bearing two carbon–carbon double bonds in adequate positions also initiates a highly regioselective tandem carbocyclization leading finally to the fused [3.3.0] bicyclooctane **16-27** bearing the phenyl ring at one of the fused junctions as shown in Scheme 107, entry c.[194]

The absence of cyclopropane derivatives **10-4**, and **16-28** disclosed in Scheme 107 (entries a and c) could be explained by the great aptitude of cyclopropylcarbinyllithiums to fragment as disclosed in Scheme 14.

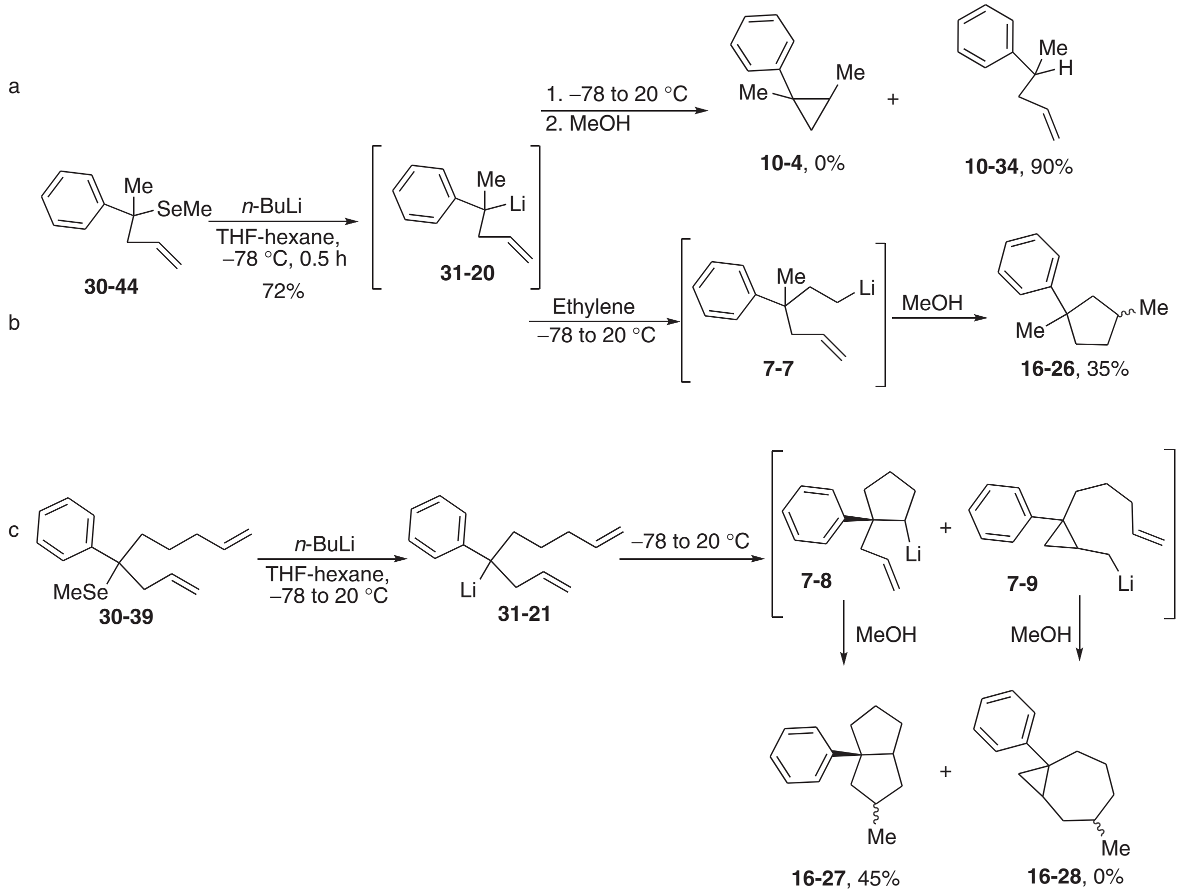
3.02.4.4.2.5.1.4 Substitution on the carbon–carbon double bond

6-Methyl-2-methylseleno-2-phenyl-6-heptene **30-45** is also cleaved, at − 78 °C, by *n*-butyllithium in THF-hexane, but cyclization of the resulting 6-methyl-2-lithio-2-phenyl-6-heptene **31-22** is quite slow at that temperature and takes place at approximately 20 °C (Scheme 108, entry a).[43] It produces after work-up 1-phenyl-1,2,2-trimethyl-cyclopentane **16-5** in low yield (13%), which results from the protonation of **15-4**.

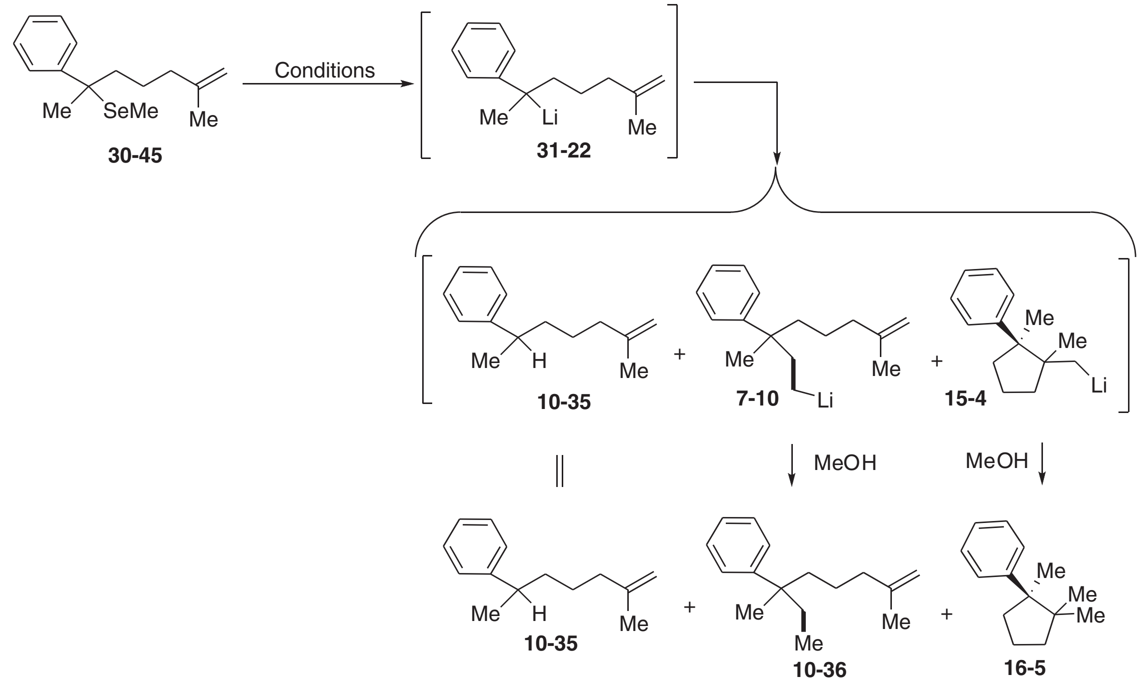
6-Methyl-2-phenyl-6-heptene **10-35** (23%) results from the protonation of **31-22** and 3,7-dimethyl-3-phenyl-7-octene **10-36** that bears an ethyl group at the benzylic position results from the protonation of **7-10**. The latter is formed by addition of **31-22** to ethylene produced by decomposition of 2-lithio-THF (Scheme 108).[43]

1-Phenyl-1,2,2-trimethyl-cyclopentane **16-5** is, however, formed in very high yield if the reaction is carried out at 25 °C in pentane (Scheme 108, entry b).[43]

The latter conditions are suitable for the three steps–two pots synthesis of cuparene **16-29**, a naturally occurring terpene, from *p*-methyl-acetophenone **71-12** (Scheme 109, entry a).[43] This transformation is not only very efficient due to the few steps involved and the high yields of each of them, but also because it produces at the same time two adjacent quaternary carbons that is among the most difficult tasks to achieve in organic synthesis (Scheme 109, entry a).[43] The strategy used is related to that described in Scheme 98 and clearly discloses an original, short, and efficient method of dialkylation of the carbonyl group of



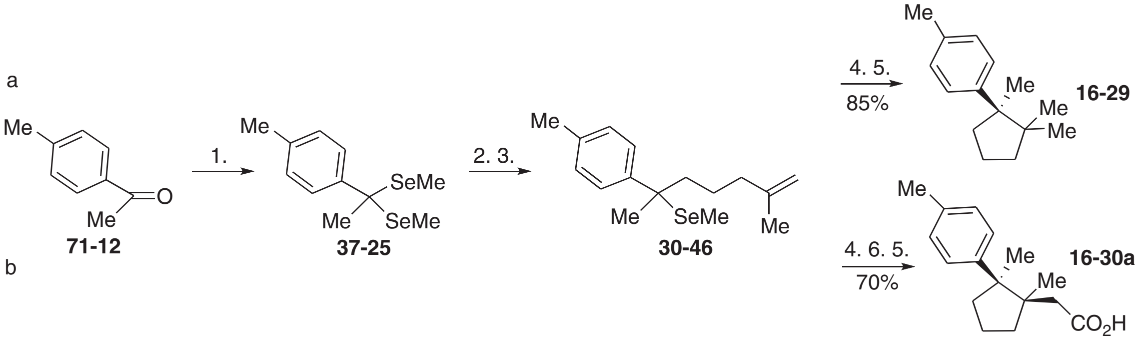
Scheme 107



		10-35	10-36	16-5
a	*n*-BuLi, THF-hexane, 0 °C, 0.5 h, 25 °C, 2.5 h	23%	13%	13%
b	*t*-BuLi, pentane, 20° C, 0.3 h			82%

Scheme 108

p-methyl-acetophenone **71-12**. Carbonation before acidic hydrolysis produces the corresponding acid **16-30a** in high yield in which the phenyl group and methylenecarboxyl group are in a *cis*-relationship (Scheme 109, entry b).[43]



1. 2 equivalents MeSeH, 0.33 equivalent $TiCl_4$, –50 °C, 0.25 h, 20 °C, 2 h; 2. *n*-BuLi, THF-pentane, –78 °C, 0.5 h;
3. 5-chloro-4-methyl-4-pentene; 4. *t*-BuLi, pentane, 20 °C, 0.3 h; 5. MeOH; 6. CO_2

Scheme 109

The reaction of butyllithiums with the isomeric *ω*-alkenyl benzylselenide **30-47** bearing an *α*,*β*-disubstituted carbon–carbon double bond provides the corresponding benzyllithium **31-23** its cyclization is far less easy than the related compound **31-4** bearing a terminal carbon–carbon double bond (Scheme 110, compared to Scheme 25 and Table 7).[43,44,166] Warming the temperature from − 78 to 20 °C provides in THF, after methanolysis, a mixture of compounds that include the products resulting from (1) the protonation **10-37** (40%) (2) the ethylation **10-38** (20%) of the related benzylic carbanion **31-23** as well as (3) 1-phenyl-1,2-dimethyl cyclohexane **16-31** (27%) and (4) 2-ethyl-1-methyl-1-phenyl-cyclopentane **16-32** (6% Ph/Et *trans*/*cis* 84/16) resulting from carbocyclization reactions leading to a six-membered and a five-membered cycle (Scheme 110, entry a).[166] It has been reported that the stereochemistry of the carbon–carbon double bond on **30-47** has no impact on the outcome of this transformation.[166]

The reaction carried out in ether provides the five-membered cycle **16-32b** (12%, as a 1/1 ratio of *cis*/*trans* stereoisomers) and cyclopent(a)indene **93-1** (37%, Scheme 110, entry b).[166] The latter is almost exclusively formed if the reaction is performed in pentane (Scheme 110, entry c).[166]

Cyclopent(a)indenes are produced in very good yields under the above described conditions with related *ω* alkenyl selenides which bears an isopropyl group (Scheme 110, entry d) or an hydrogen (Scheme 110, entry e) at their benzylic carbon.

Those results are quite exceptional since (1) the addition of organometallics to *α*,*β*-dialkylsubstituted olefins usually only occurs on strained derivatives;[198] (2) it produces cyclopent(a)indene **93-1** which is expected to involve a tandem of two unusual additions of organolithiums **31-23** and **15-6** accross the carbon–carbon double bonds of a dialkylsubstituted alkene and of a phenyl ring, respectively, followed by a *β*-elimination reaction of lithium hydride allowing the recovery of the aromatic ring (Scheme 110);[166] and (3) it involves formal synthesis of the intermediate **15-6**, which should obviously possess the *cis*-geometry between the aryl group and the methyllithium group to promote the last carbocyclization.

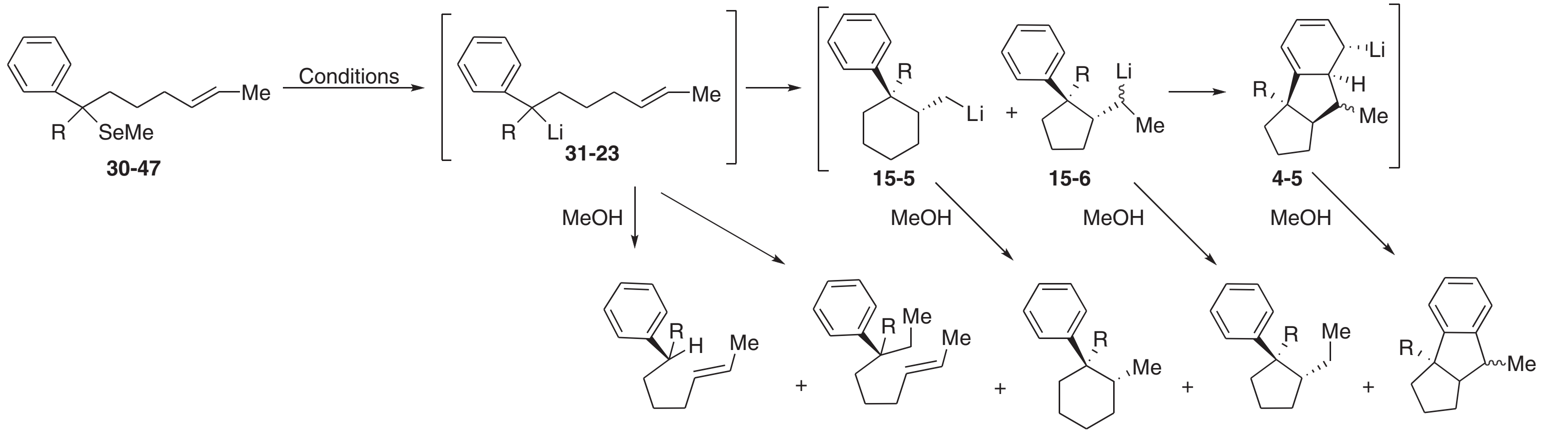
The C–Se bond of 2-methyl-7-methylseleno-7-phenyl-2-octene **30-48** is cleaved efficiently by butyllithiums, but the resulting benzyllithium **31-24** has an extremely low propensity to cyclize (Scheme 111).[166] Performing the reaction in THF provides after acid hydrolysis a one-to-one mixture of products resulting from the protonation **10-39** and ethylation **10-40** of the corresponding carbanion **31-24** (Scheme 111, entry a)[197] that probably result from the metallation of THF and the addition of ethylene resulting from the decomposition of the metallated THF as disclosed in Scheme 26.

When the reaction is instead carried out in pentane carbocyclization is extremely slow, slower than in THF since **31-24** is still present after 720 h, it leads to **10-39** in almost 50% yield after hydrolysis (Scheme 111, entry b).[197] It also produces **10-41**, probably resulting from the methylation of **31-24** by butyl methyl selenide, and cyclopent(a)indene **93-2** both in low yields (Scheme 111, entry b).[197]

The synthesis of cyclopent(a)indene **93-2** has been, however, successfully achieved using instead tin tetrachloride or better titanium tetrachloride (Scheme 111, entries c and d).[166]

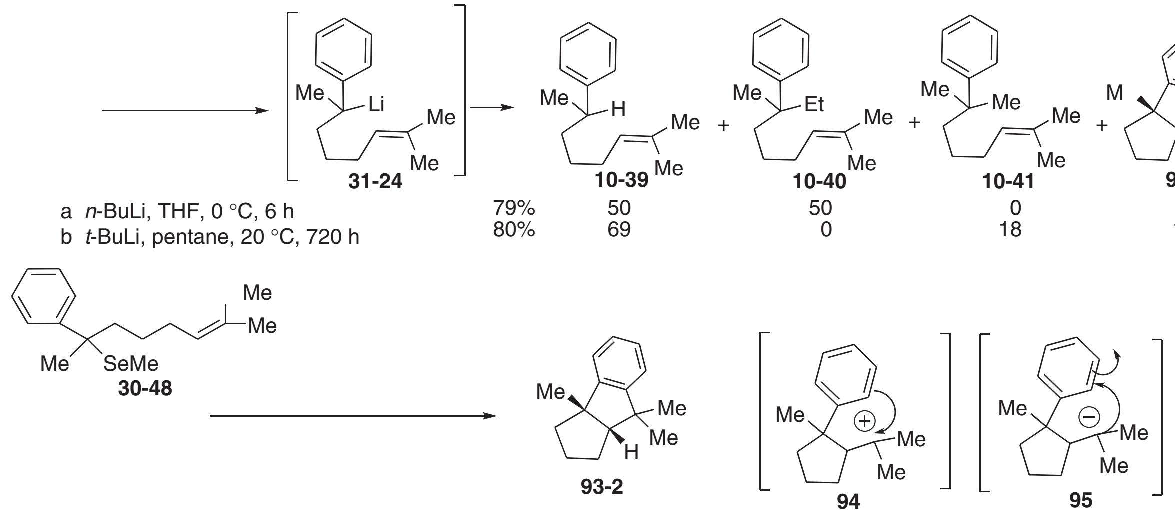
3.02.4.4.2.5.1.5 The nature of the aromatic ring

It has been already shown for the synthesis of cuparene **16-30a** that the transformation that involves a benzylselenide, disclosed in Scheme 109, applies similarly to its *p*-methyl-phenyl analog (Scheme 109).[43] Similar features have been observed when 6-methylseleno-6-(2,5-dimethyl-phenyl)-1-heptene **30-49** **(R^1=Me)** (Scheme 112, entries a and b), 6-methylseleno-6-(3,5-dimethyl-phenyl)-1-heptene **30-49** **(R^2=Me)** (Scheme 112, entries c and d), and 6-methylseleno-6-(4-methoxy-phenyl)-1-heptene **30-50** (Scheme 112, entries e and f) are reacted with *t*-butyllithium in THF (Scheme 112, entries a, c, and e) or pentane (Scheme 112, entries b, d, and f). Substitution of the aromatic ring by methyl or methoxy groups does not affect the rate of the carbocyclization reactions, but eventually the stereochemistry of the resulting cyclopentane derivatives.



		10-37	**10-38**	**16-31**	**16-32**	**93-1**
a *n*-BuLi, THF-hexane, −78 °C, 0.5 h, 20 °C, 24 h	R= Me	40%	20%	27%	6%	7%
b *s*-BuLi, ether-hexane, −30 °C, 0.5 h, 20 °C, 24 h	R= Me	15%	24%	0%	12%	37%
c *t*-BuLi, pentane, 20 °C, 0.3 h, 20 °C, 24 h	R= Me	4%	0%	0%	3%	93%
d *t*-BuLi, pentane, 20 °C, 0.3 h, 20 °C, 24 h	R= *i*-Pr	10%	0%	0%	2%	90%
e *t*-BuLi, pentane, 20 °C, 0.3 h, 20 °C, 24 h	R= H	–	0%	0%	–	86%

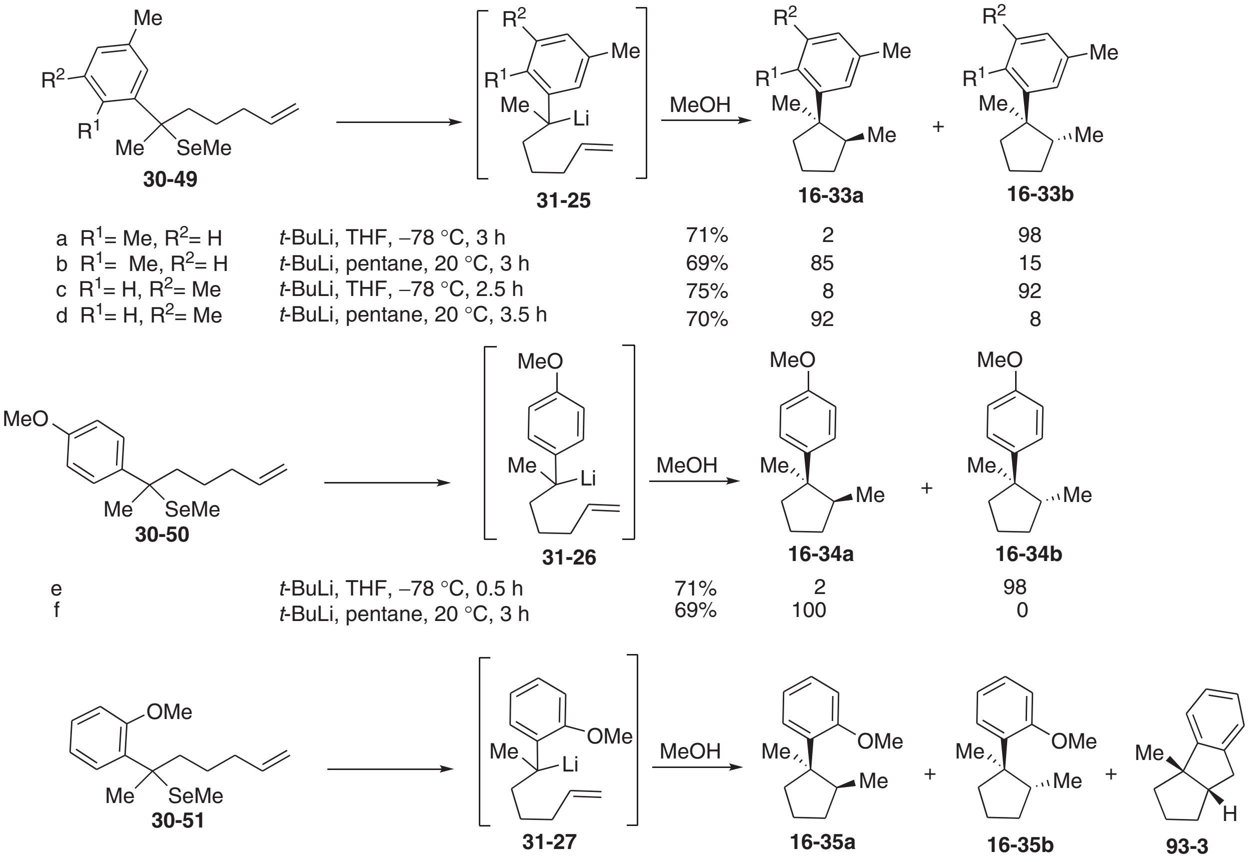
Scheme 110



a	*n*-BuLi, THF, 0 °C, 6 h	79%	50	50	0	0
b	*t*-BuLi, pentane, 20 °C, 720 h	80%	69	0	18	13

c	$SnCl_4$, CH_2Cl_2, –50 °C, 1 h, 20 °C, 1.5 h	62%
d	$TiCl_4$, CH_2Cl_2, –50 °C, 1 h, 20 °C, 1.5 h	89%

Scheme 111



a	R^1= Me, R^2= H	*t*-BuLi, THF, –78 °C, 3 h	71%	2	98
b	R^1= Me, R^2= H	*t*-BuLi, pentane, 20 °C, 3 h	69%	85	15
c	R^1= H, R^2= Me	*t*-BuLi, THF, –78 °C, 2.5 h	75%	8	92
d	R^1= H, R^2= Me	*t*-BuLi, pentane, 20 °C, 3.5 h	70%	92	8

e	*t*-BuLi, THF, –78 °C, 0.5 h	71%	2	98
f	*t*-BuLi, pentane, 20 °C, 3 h	69%	100	0

g	*t*-BuLi, THF, –78 °C, 0.75 h	76%	0	100	
h	*t*-BuLi, pentane, 20 °C, 1 h	78%	27	73	
i	*t*-BuLi, ether, –30 °C, 1 h	88%	15	85	
j	*t*-BuLi, THF, 20 °C, 1 h	–	0	53	47

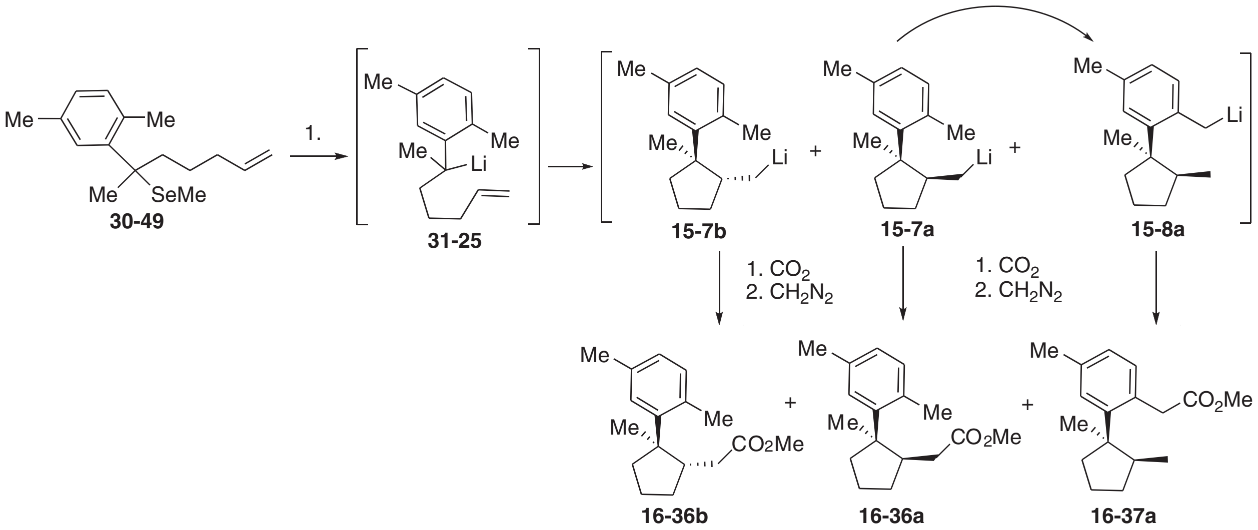
Scheme 112

Thus, the cyclopentane derivatives **16-33** and **16-34** in which the aryl and the methyl group are *trans* (**16-33b** and **16-34b**) are formed when the reactions are carried out in THF-hexane (**Scheme 112**, entries a, c, and e) and *cis* (**16-33a** and **16-34a**) when the reaction was carried out in pentane (**Scheme 112**, entries b, d, and f). 6-Methylseleno-6-(2-methoxy-phenyl)-1-heptene **30-51** behaves differently since the *trans* adduct (**16-35b**) is exclusively (**Scheme 112**, entry g) or mainly produced whatever is the solvent used (**Scheme 112**, entries h and i).

It is interesting to note that cyclopent(a)indene **93-3** is also produced from **30-51** if the reaction is carried out in THF at 20 °C instead of −78 °C (**Scheme 112**, compare entries j and g).

This result implies that (1) an epimerization takes place to produce the cyclopentane with the aryl- and lithiomethylene groups *cis* to each other from the first formed *trans*-stereoisomer (**Scheme 112**, compare entries j and g). (2) Addition of the lithiomethylene moiety on the aromatic ring exclusively takes place at the carbon–carbon bond bearing the methoxy group with subsequent elimination of methoxylithium rather than addition of the unsubstituted aromatic carbon–carbon double bond followed by lithium hydride elimination (**Scheme 112**, entry j compared to **Scheme 110**).

The reaction of ω-alkenyl benzylselenides **30-49** with *t*-butyllithium in pentane, followed by addition of carbon dioxide and hydrolysis after 3 h as described in **Scheme 113**, entry a, is similar to the reaction reported in **Scheme 110**, entry b, that was quenched with methanol. The former, even after longer reaction time (120 h instead of 3 h) does not provide a significant improvement in products resulting from the carbocyclization reaction, but it produces after carbonation a mixture of carboxylic esters **16-36** and **16-37** (**Scheme 113**, compare entries b and a).[197] It involves the isomerization of the *cis*-stereoisomer **15-7a** to **15-8a** by intramolecular metalation of the *ortho*-aromatic methyl group by the lithiomethylene moiety of **15-7a** (**Scheme 113**, compare entries b and a).[197]



			16-36b	16-36a	16-37a
a	1. *t*-BuLi, Pentane, 20 °C, 3 h	62%	15	85	0
b	1. *t*-BuLi, Pentane, 20 °C, 120 h	50%	15	35	50

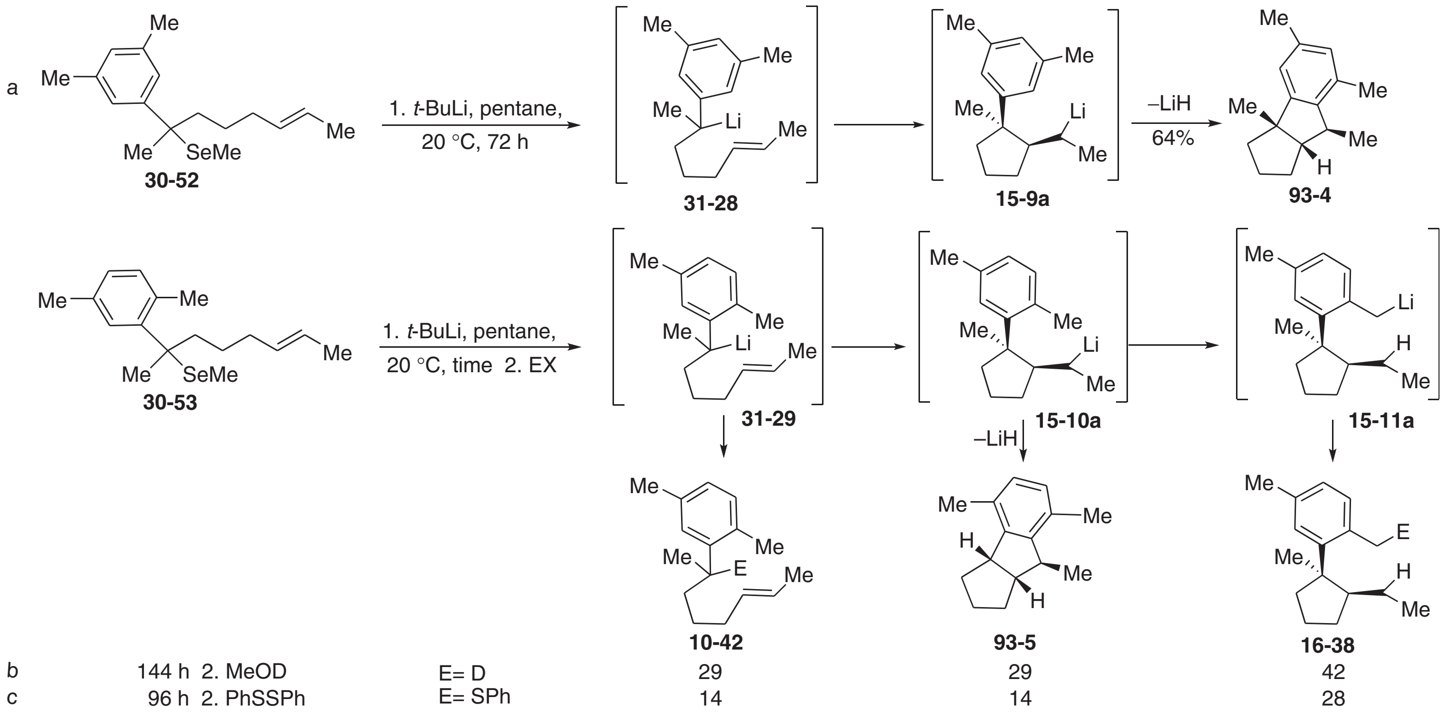
Scheme 113

The reaction of ω-alkenyl benzylselenides **30-52** and **30-53** with *t*-butyllithium in pentane is reminiscent of the ω-alkenyl benzylselenides **30-47** possessing a dialkyl substituted carbon–carbon double bond (**Scheme 114** compared to **Scheme 110**, entry c) and to **30-49** that bears a methyl group on the aromatic ring (**Scheme 114** compared to **Scheme 113**, entry b).[197] This is particularly the case of **30-53** that bears an *ortho* methyl group (compare **Scheme 114**, entry b, with **Scheme 113**, entry b). The latter produces the *cis*-cyclopentane **16-38** in surprisingly high yield (**Scheme 114**, entry b) compared to **30-47** or **30-52** missing the *ortho* methyl group, which instead systematically leads the indano-cyclopentane derivatives **93-x** (**Scheme 110**, entries c–e; **Scheme 114**, entry a).[197] In fact, trapping the carbanion with deuteromethanol or diphenyldisulfide provides **16-38** $E=D$ (**Scheme 114**, entry b) and $E=SPh$ (**Scheme 114**, entry c), respectively, where the electrophile is introduced selectively at the 'ortho' aromatic methyl group (**Scheme 114**, entries b and c compared to entry a).[197] It is the first time that the cascade of the two consecutive carbocyclizations is interrupted in a competing process in which the secondary alkyllithium generated by the first carbocylization metallate intramolecularly the benzylic hydrogen of the *ortho* methyl group on the aromatic ring.

3.02.4.4.2.5.2 Synthesis of aryl-aryl cycloalkanes involving carbon–carbon double bonds substituted by a phenyl or a thiophenyl group

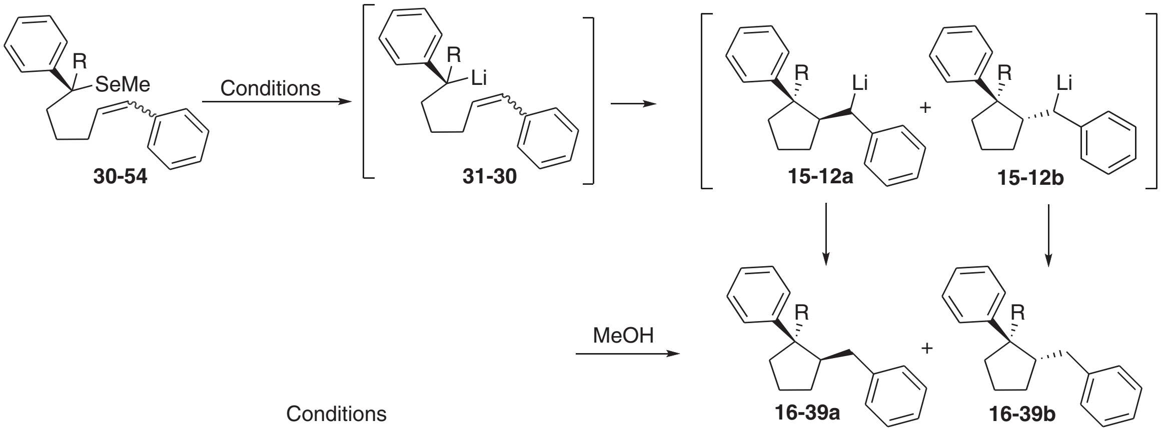
3.02.4.4.2.5.2.1 Synthesis of aryl-aryl cycloalkanes involving carbon–carbon double bonds substituted by a phenyl

The reaction involving (2,7-diphenyl-hept-6-en-2-yl)(methyl)selane **30-54** is particularly interesting since the cyclization is expected to produce a more stabilized carbanion **15-12** than that of its open chain isomer **31-30** (**Scheme 115**).[190] The reaction outcome is related to that of 6-methylseleno-6-(phenyl)-1-heptene **30-6** (**Scheme 25**) and produces after methanolysis the


a
30-52
1. t-BuLi, pentane, 20 °C, 72 h
31-28
15-9a
–LiH
64%
93-4
30-53
1. t-BuLi, pentane, 20 °C, time 2. EX
31-29
15-10a
–LiH
15-11a
10-42
93-5
16-38
b 144 h 2. MeOD E= D 29 29 42
c 96 h 2. PhSSPh E= SPh 14 14 28

Scheme 114

cyclopentane derivative **16-39** in which the phenyl and the benzyl group on the adjacent carbon are *trans* to each other (**16-39b**) when the reaction is carried out in THF at –78 °C (Scheme 115, entry a). The *cis*-diastereoisomer **16-39a** is instead obtained when the reaction was performed at 20 °C in pentane (Scheme 115, entry d).

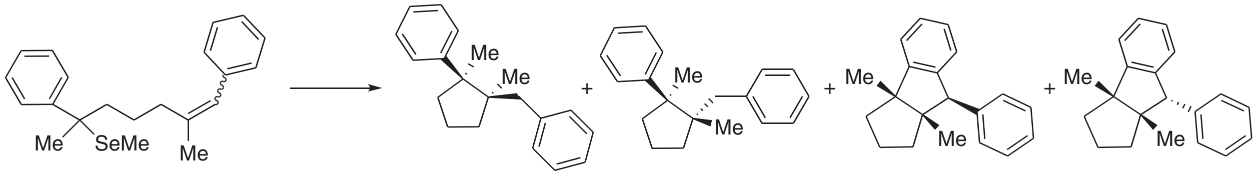


		Conditions		16-39a	16-39b
a	R = Me	*n*-BuLi, THF-hexane, –78 °C, 0.5 h	83%	3	97
b	R = Me	*n*-BuLi, THF-hexane, 0 °C, 1 h	75%	27	73
c	R = Me	*t*-BuLi, pentane, 20 °C, 1 h	82%	100	0
d	R = Me	*s*-BuLi, ether-hexane, 0 °C, 1 h	72%	98	2
e	R = Me	*t*-BuLi, ether-hexane, –100 °C,1 h	70%	8	92
f	R = H	*n*-BuLi, THF-hexane, –78 °C, 0.5 h	51%	6	94
g	R = H	*t*-BuLi, pentane, 20 °C, 1 h	73%	95	5
h	R = H	*t*-BuLi, ether-hexane, 0 °C, 1 h	70%	83	17

Scheme 115

The reaction carried out in ether produces the *cis*-stereoisomer **16-39a** (*de*: 96% at 0 °C; *de*: 80% at − 45 °C) (Scheme 115, entry d) and the *trans*-stereoisomer **16-39b** (*de*: 94% at − 100 °C) whose synthesis takes place under kinetic control (Scheme 115, entry e).[199] The outcome of this carbocyclization reaction, is similar to the one that involves (2-phenylhept-6-en-2-yl)(methyl)selane **30-6** (Scheme 25 and Table 7, compare entries c and f).

The presence of the phenyl group on the carbon–carbon double bond greatly increases the rate of the carbocyclization reaction (compare Scheme 115, entry f, with Scheme 25 and Table 7, entry c). This is corroborated by the easy cyclization at − 78 °C of methyl-(6-methyl-2,7-diphenylhept-6-en-2-yl)selane **30-55** (Scheme 116, entry a)[200] compared with the cyclization of methyl(6-methyl-2-phenylhept-6-en-2-yl)selane **30-45** (Scheme 108, entry a).[43] Similarly, when (2,7-diphenyloct-6-en-2-yl)(methyl)selane **30-56** is heated with *s*-butyllithium in ether (Scheme 117)[201] it cyclizes more rapidly that (2-phenyloct-6-en-2-yl)(methyl)selane **30-47** (Scheme 110).[166]



30-55

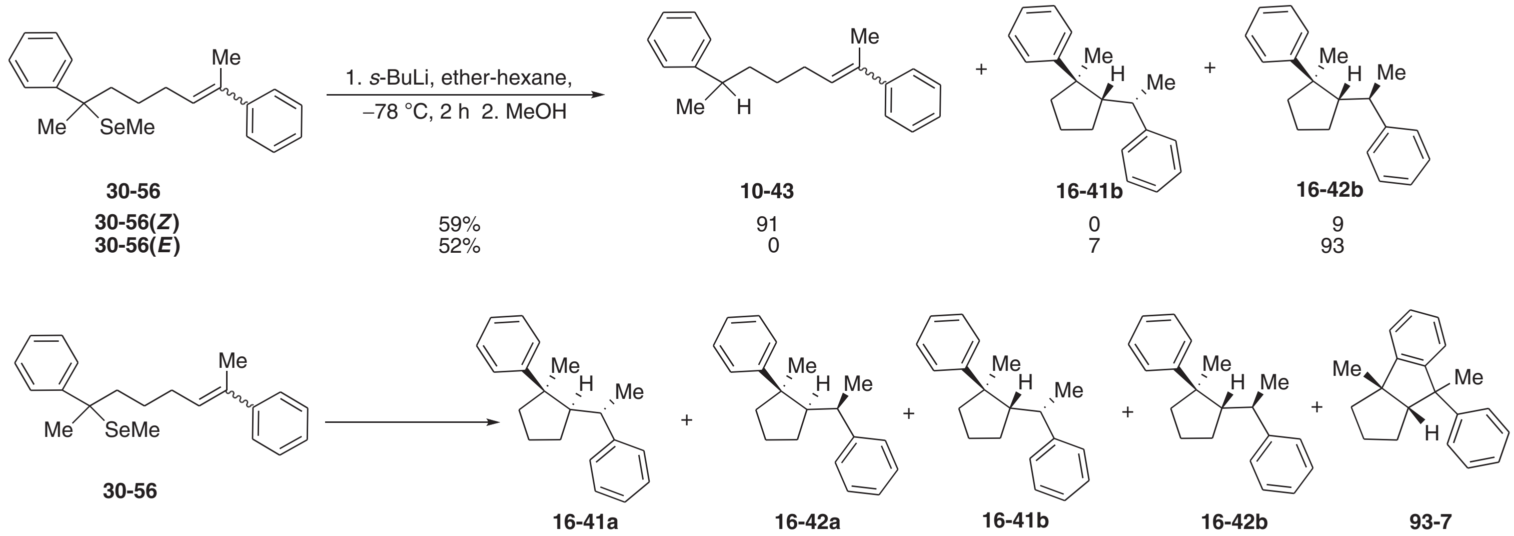
	Conditions		16-40a	16-40b	93-6a	93-6b
a	1. *n*-BuLi, THF-hexane, −78 °C, 2 h 2. MeOH	66%	5	95	70	30
b	*t*-BuLi, pentane, 20 °C, 24 h	34%				

The stereochemical assignments have not been securely assessed

Scheme 116

It has been found, however, that the rate of carbocyclization of the *E*-stereoisomer of (2,7-diphenyloct-6-en-2-yl)lithium resulting from the reaction of (2,7-diphenyloct-6-en-2-yl)(methyl)selane **30-56(*E*)** with *s*-butyllithium in ether is faster than of its *Z*-stereoisomer **30-56(*Z*)** (Scheme 117, compare entries b and a).[153] It surprisingly produces at − 78 °C almost exclusively **16-42b** in which the phenyl and benzyl group are *trans* to each other (Scheme 117, entry b) and a 60/40 (**16-41b** + **16-42b**/**16-41a** + **16-42a**) mixture when performed in the same solvent but at 0 °C instead (Scheme 117, entry c).

The *cis*-stereoisomer is surprisingly formed when the reaction is carried out in THF (Scheme 117, entry d) and cascade cyclizations leading to cyclopent(a)indene **93-7** occurs if (2,7-diphenyloct-6-en-2-yl)(methyl)selane **30-55** and



	30-56		10-43	16-41b	16-42b
a	**30-56(*Z*)**	59%	91	0	9
b	**30-56(*E*)**	52%	0	7	93

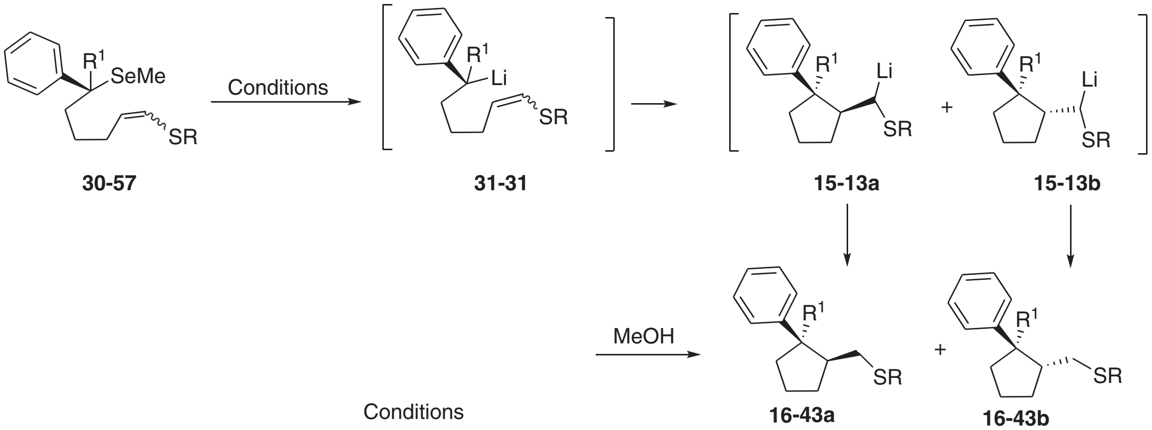
	30-56		16-41a	16-42a	16-41b	16-42b	93-7
c	1. *s*-BuLi, ether-hexane, 0 °C, 2 h 2. MeOH	56%	3	37	7	53	
d	1. *n*-BuLi, THF-hexane, –78 °C, 2 h 2. MeOH	56%	11	61	6	16	
e	1. *t*-BuLi, pentane, 20 °C, 24 h 2. MeOH	58%	2	15	2	20	61

Scheme 117

methyl(6-methyl-2,7-diphenylhept-6-en-2-yl)selane **30-56** are reacted with *t*-butyllithium at 20 °C in pentane (Scheme 116, entry b; Scheme 117, entry e).

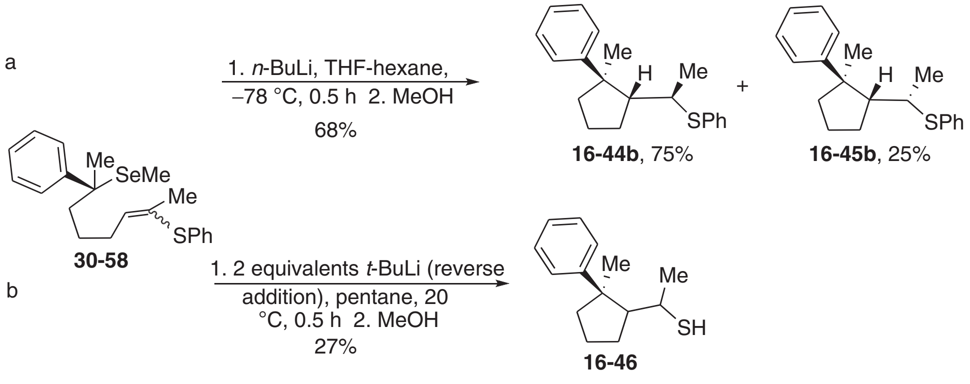
3.02.4.4.2.5.2.2 Synthesis of aryl cycloalkanes involving carbon–carbon double bonds substituted by a thioorganyl or a tetraorganylsilyl group

ω-alkenyl-benzyl selenides bearing a organylthio or a triorganylsilyl group on the carbon–carbon double bond react with butyllithiums to efficiently produce 1-aryl-cyclopentanes derivatives bearing at the adjacent carbon 1-organylthio-1-alkyllithiums[189,193] and 1-triorganylsilyl-1-alkyllithiums,[194] and the related 1-organylthio-1-alkyl group (Schemes 118 and 119) and 1-triorganylsilyl-1-alkyl group (Scheme 120) after methanolysis.



		Conditions		16-43a	16-43b
a	R = Ph, R^1= Me	*n*-BuLi, THF-hexane, –78 °C, 0.5 h	89%	5	95
b	R = Ph, R^1= Me	*t*-BuLi, pentane, 20 °C, 1.5 h	79%	96	4
c	R = Ph, R^1= Me	*t*-BuLi, Et_2O, 20 °C, 1 h	70%	70	30
d	R = Ph, R^1= Me	*t*-BuLi, Et_2O, –110 °C, 1 h	59%	51	49
e	R = C_6H_{11}, R^1= Me	*n*-BuLi, THF-hexane, –78 °C, 0.5 h	92%	5	95
f	R = C_6H_{11}, R^1= Me	*t*-BuLi, pentane, 20 °C, 1.5 h	80%	95	5
g	R = C_6H_{11}, R^1= Me	*t*-BuLi, Et_2O, 20 °C, 1 h	64%	97	3
h	R = C_6H_{11}, R^1= Me	*t*-BuLi, Et_2O, –78 °C, 1 h	50%	96	4
i	R = Ph, R^1= H	*n*-BuLi, THF-hexane, –78 °C, 2.5 h	83%	40	60
j	R = Ph, R^1= H	*t*-BuLi, pentane, 20 °C, 1.5 h	61%	100	0

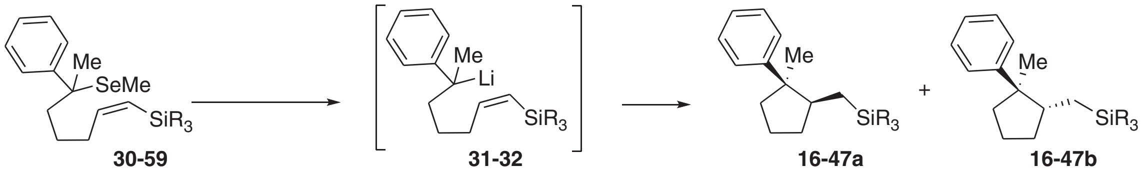
Scheme 118



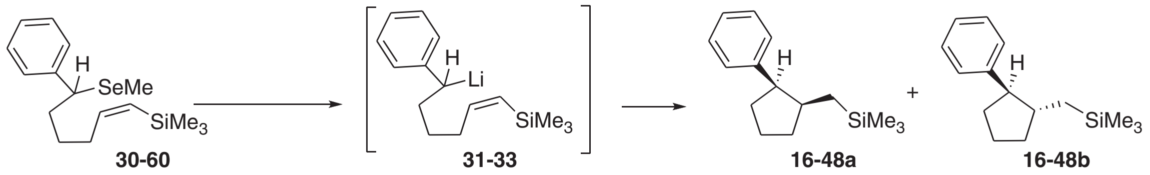
Scheme 119

Carbocyclization provides the cyclopentane derivatives **16-43b**, **16-44b**, **16-45b**, **16-47b**, and **16-48b** on which the phenyl group and the adjacent thio- or silyl-alkyl groups are *trans* to each other when the reaction is carried out in THF-hexane.[202–204] The selectivity is very high when the benzylic carbon bears a methyl group with compounds bearing both a sulfur and silicon substituents on the carbon–carbon double bond (Scheme 118, entries a and e; Scheme 119, entry a; Scheme 120, entries a and b). This stereocontrol is unusually high with the trimethylsilyl derivative **30-60** when the benzylic carbon bears a hydrogen (Scheme 120, entry i).[204] The selectivity is much lower with the thiophenyl derivative **30-57** (Scheme 118, entry i).[202,203]

The stereoisomer **16-43a** in which the phenyl and the adjacent thio-alkyl groups are *cis* is selectively generated if the reaction is carried out in pentane (Scheme 118, entries b and f). The *cis*-stereoisomer cannot be synthesized under the same conditions



a	$SiR_3 = SiMe_3$	*n*-BuLi, THF-hexane, –78 °C, 0.5 h	54%	5	95
b	$SiR_3 = SiMe_2Ph$	*n*-BuLi, THF-hexane, –78 °C, 0.5 h	70%	3	97
c	$SiR_3 = SiMe_3$	*t*-BuLi, pentane, 20 °C, 1 h	80%	50	50
d	$SiR_3 = SiMe_2Ph$	*t*-BuLi, pentane, 20 °C, 1 h	65%	35	65
e	$SiR_3 = SiMe_3$	*t*-BuLi, Et_2O, 0 °C, 1 h	78%	74	26
f	$SiR_3 = SiMe_3$	*t*-BuLi, Et_2O, –25 °C, 1 h	68%	10	90
g	$SiR_3 = SiMe_2Ph$	*t*-BuLi, Et_2O, 0 °C, 1 h	82%	12	88
h	$SiR_3 = SiMe_2Ph$	*t*-BuLi, Et_2O, –25 °C, 1 h	65%	11	89

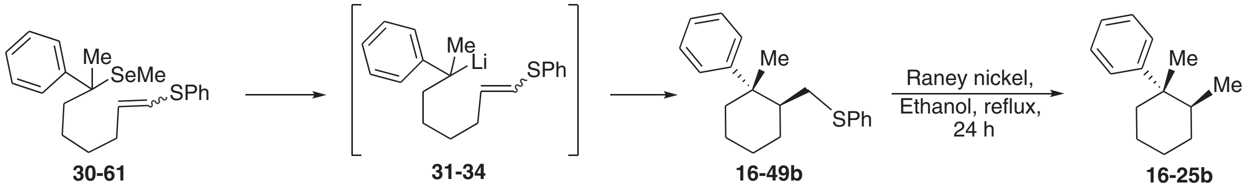


i	*n*-BuLi, THF-hexane, –78 °C, 0.5 h	77%	4	96
j	*t*-BuLi, pentane, 20 °C, 1 h	60%	8	92
k	*t*-BuLi, Et_2O, 0 °C, 1 h	36%	5	95

Scheme 120

with (1) the homologous derivative **30-58** bearing a phenylthio and a methyl group on the same olefinic carbon which surprisingly deliver the thiol **16-46** (Scheme 119, entry b) and (2) with the silyl derivatives **30-59** and **30-60** owing probably to the unfavorable interaction in the transition state due to the presence of the bulky triorganosilyl group (Scheme 120, entries c, d, and j). The same apply if the reaction is performed in ether (Scheme 120, entries f–h and k). The higher propensity of cyclohexylthio derivatives to deliver the *cis*-derivative **16-43a** over its phenylthio derivative is noteworthy (Scheme 118, entries g and h, compared to entries c and d).

The reaction of (7-(methylselanyl)-7-phenyloct-1-en-1-yl)(phenyl)sulfane **30-61** with butyllithium in THF or pentane provides the same single diastereoisomeric cyclohexane derivative **16-49b** possessing the *trans*-stereochemistry between the phenyl group and the methylthiophenyl group on the adjacent carbon (Scheme 121). Those results parallel that of the related selenide missing the thiophenyl moiety on the carbon–carbon double bond (Scheme 121 compared to Scheme 106, entry a). Reduction of **16-49b** with Raney nickel produces 1,2-dimethyl-cyclohexyl-benzene **16-25b** identical to the one reported (Scheme 121; Scheme 106, entry a).



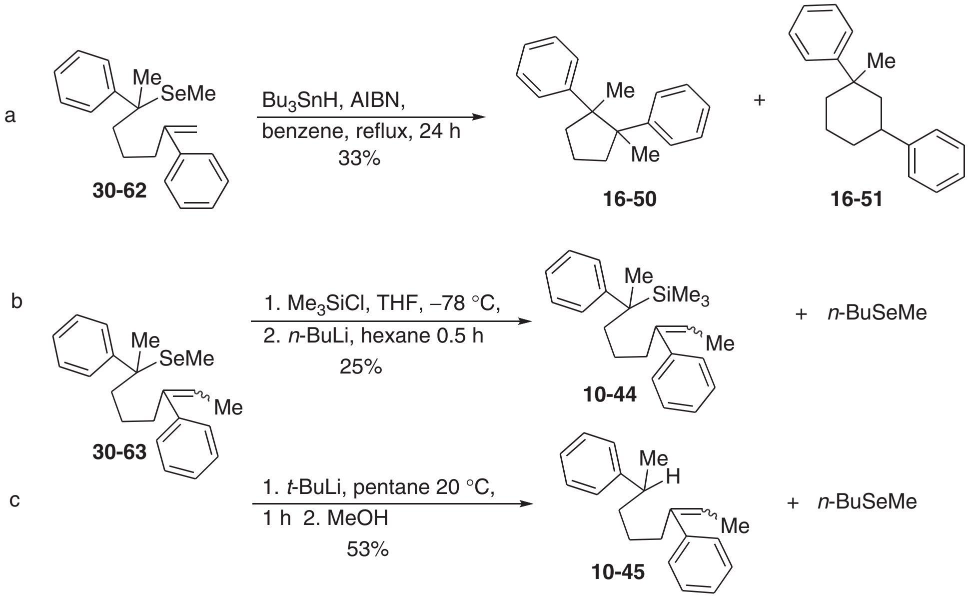
a	1. *n*-BuLi, THF-hexane, –78 °C, 1 h 2. MeOH	64%	60%
b	1. *t*-BuLi, pentane, 20 °C, 1.5 h 2. MeOH	40%	

Scheme 121

3.02.4.4.2.5.2.3 Reaction of ω-alkenyl benzyl selenides bearing a phenyl or a thiophenyl group in the ω position on the vinylic carbon

ω-alkenyl benzyl selenides **30-62** bearing a phenyl or a thiophenyl group in the ω position on the vinylic carbon and possessing a terminal carbon–carbon double bond, react with butyllithiums in THF or pentane to produce oligomeric materials whose structures have not been assessed.[204] Interestingly however, a mixture of two regioisomers 1,2-diphenyl-cyclopentane **16-50** and 1,3-diphenyl cyclohexanes **16-51** is produced by reaction with tributyl tin hydride in the presence of AIBN (benzene, reflux, 24 h) (Scheme 122, entry a).

Related compound **30-63**, bearing a vinylic methyl group react with butyllithiums but does not oligomerize.[204] The protonated product **10-45** is not formed when the reaction, carried out in THF at −78 °C, is trapped with methanol. The trimethylsilyl derivative **10-44** is, formed in low yield when *n*-butyllithium in hexane is added to a mixture of **30-63** and excess of trimethylsilyl chloride in THF (Scheme 122, entry b).[204] Protonated compound **10-45** is, however, generated if the reaction is instead performed in pentane (Scheme 122, entry c).[204]



Scheme 122

3.02.4.4.2.5.2.4 Stereochemistry at the exocyclic carbon resulting from carbocyclization reactions

In several instances, methanolysis or alkylation of the products resulting from carbocyclization produces a new exocyclic stereogenic center. It has been found that the major stereoisomers **16-42b** (Scheme 117, entries b and d) and **16-44b** (Scheme 119, entry a) resulting from the protonation of the benzyllithium and α-phenylthiomethyllithium formed by carbocyclization from the related ω-alkenyl benzyllithiums, possess the same configuration at the protonated carbon (Scheme 117, entries b and d, compared to Scheme 119, entry a).[202,203]

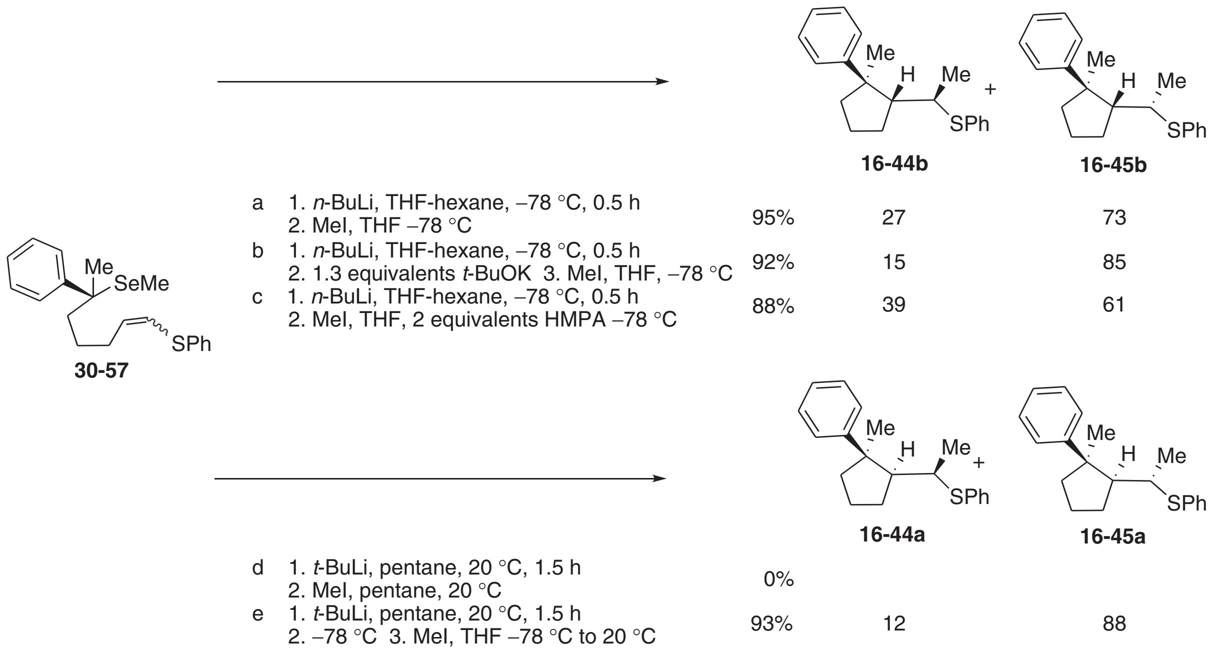
It has been, however, found that the major products **16-45b** and **16-44b** resulting, respectively, from the methylation of the intermediates formed by carbocyclization of (6-(methylselanyl)-6-phenylhept-1-en-1-yl)(phenyl)sulfane **30-57** in THF (Scheme 123, entry a) or in pentane (Scheme 123, entry e) possess the same configuration at the carbon bearing the thiophenyl group and that **16-45b** is epimeric to **16-44b** (Scheme 123, entry a, compared to Scheme 119, entry a).[188,189] Similar results have been observed by reacting (2,7-diphenyloct-6-en-2-yl)(methyl)selane **30-56** bearing a phenyl group on the carbon–carbon double bond with *s*-butyllithium in ether (Scheme 117, entry b).[153]

Alkylation has been carried out in the presence of potassium *t*-butoxide (Scheme 123, entry b)[197] or HMPA as additive. Better stereocontrol has been observed if the methylation is carried out in the presence of potassium *t*-butoxide (Scheme 123, entry b),[197] whereas poorer stereoselectivity is found if the reaction is carried out in the presence of HMPA (Scheme 123, entry c). It has also been found that methylation does not proceed in pentane (Scheme 123, entry d). It is very efficient if carried out in pentane but in the presence of a few equivalents of THF (Scheme 123, entry e). Interestingly, in none of the cases epimerization has taken place on the cycle, which means that fragmentation does not take place under those conditions (Scheme 123, entries b, c, and e).[197]

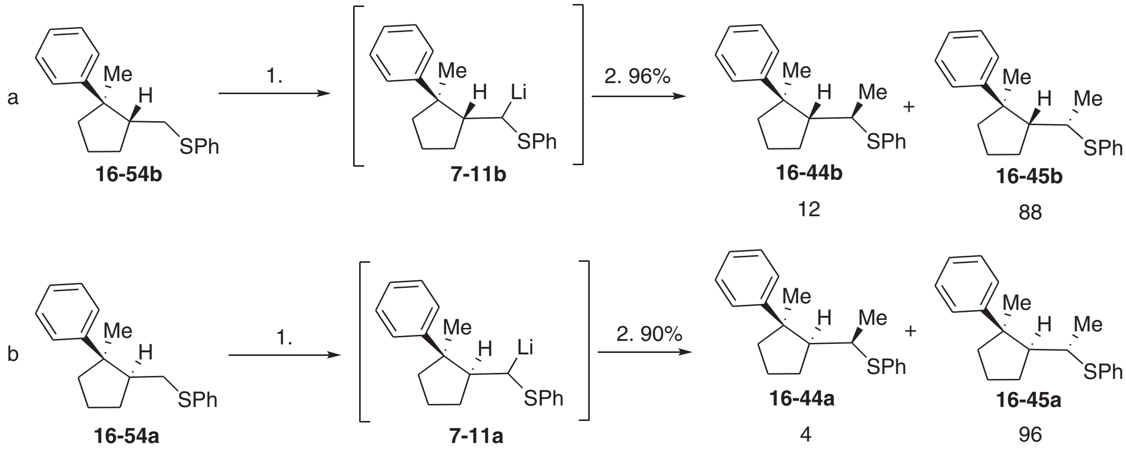
The same cyclopentane derivatives **16-45b** + **16-44b** and **16-45a** + **16-44a** have been synthesized by selective sequential metallation/methylation of 2-methyl-2-phenylcyclopentyl)methyl)(phenyl)sulfane **16-54** in which the phenyl and the phenylthiomethylene group are in *trans*- (**16-54b**, Scheme 124, entry a) or *cis*-relationships (**16-54a**; Scheme 124, entry b).[184] The metallation has been successfully achieved by using *n*-butyllithium/potassium *t*-butoxide mixture in THF,[195,196] which proved by far more efficient than the published method which uses *n*-butyllithium in THF-HMPA.[8]

In order to rationalize those results 6-(methylselanyl)-6-phenylhept-1-en-1-yl)(duryl)sulfane **30-64** has been sequentially reacted, at −106 °C, with *t*-butyllithium in THF and *O*-deuteromethanol. It was expected that the presence of the bulky duryl (2,3,5,6-tetramethylphenyl) substituent and the extremely low temperature used could avoid epimerization of the α-thioalkyllithium resulting from the carbocyclization reaction of the benzyllithium intermediate on either the *Z*- and *E* built-in carbon–carbon double bonds (Scheme 125).[205]

It was found that carbolithiation occurs in THF at −105 °C, in essentially a stereoselective manner, when starting from a sample enriched in **30-64(*Z*)** (Scheme 125, entry a). Carbolithiation in the *E*-series **30-64(*E*)** leads to a 6/4 mixture of the two cyclopentane derivatives **16-56b**/**16-55b** epimeric at the exocyclic carbon (Scheme 125, entry c). The differences between the two



Scheme 123



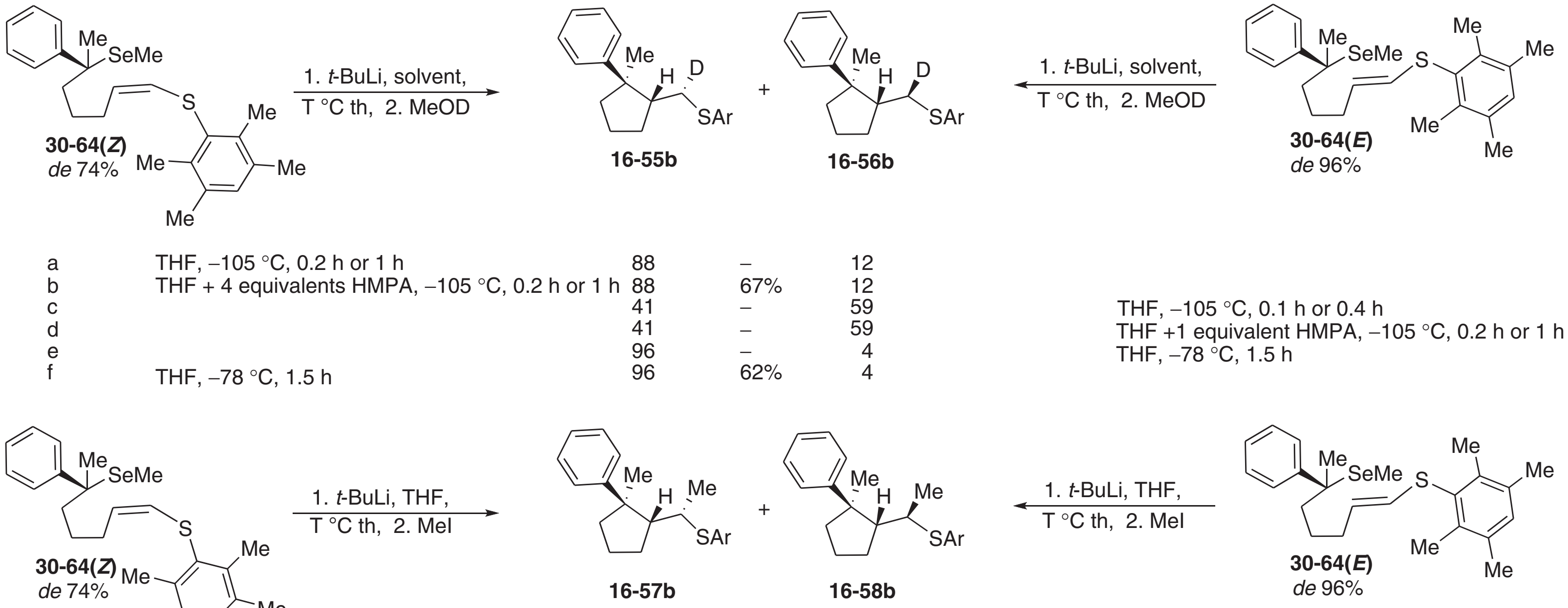
1. *n*-BuLi-1.3 equivalents *t*-BuOK, THF-hexane, −78 °C, 0.75 h; 2. MeI, THF, −78 °C

Scheme 124

series of experiments and the fact that the time between carbolithiation and trapping has no influence on the **16-56b**/**16-55b** epimers ratio indicates that the α-durylthioalkyllithium intermediates are configurationally stable under the reaction conditions. The diastereoisomer ratio is, therefore, kinetically controlled. Warming of the reaction mixture to −78 °C before quenching leads to equilibration of the two epimeric organolithium. Subsequent trapping then reflects the thermodynamic ratio of the corresponding organolithium compounds (Scheme 125, entries e, f, and i).[205] Moreover, dilution or trapping with methyl iodide to give **16-57b** and **16-58b** had no effect on the **16-57b**/**16-58b** ratio (Scheme 125, entries g and i).[205]

The carbolithiation of vinyl sulfides in THF was found to be nonstereospecific regarding formation of the new lithium bearing stereocenter. This suggests that carbolithiation proceeds in a nonconcerted fashion, in which collapse of an ion pair determines the configuration of the lithium-bearing center at the migration terminus.

A more detailed representation of the intimate mechanism of this process is disclosed in Scheme 126. It suggests that, in lithium coordinating cosolvents, such as THF, the C–Li bond at the migration origin has to be broken first, in the extreme with the formation of a solvent separated ion pair **31-35**, a process favored at lower temperatures (Scheme 126).[206,207] The carbon–carbon bond formation implying the carbocyclization step, proceeds in the carbanion part of the lone pair to give the two stereoisomeric ions pairs **96** and **98** in which the carbanion lone pair, the sulfur, and the aromatic carbon C_i attached to sulfur are initially

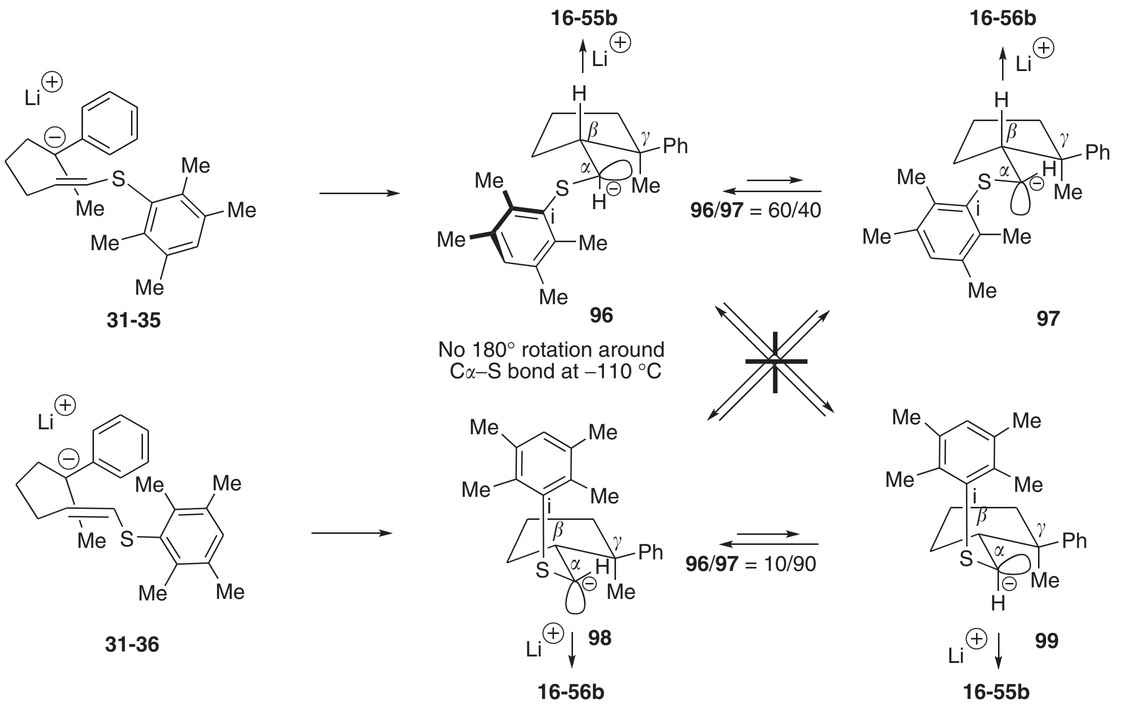


a	THF, –105 °C, 0.2 h or 1 h	88	–	12	
b	THF + 4 equivalents HMPA, –105 °C, 0.2 h or 1 h	88	67%	12	
c		41	–	59	THF, –105 °C, 0.1 h or 0.4 h
d		41	–	59	THF +1 equivalent HMPA, –105 °C, 0.2 h or 1 h
e		96	–	4	THF, –78 °C, 1.5 h
f	THF, –78 °C, 1.5 h	96	62%	4	

g	–106 °C, 0.5 h	90	–	10	
h		43	70%	57	T–105 °C, 0.3 h
i	–78 °C, 1.5 h	94	81%	6	

Scheme 125

antiperiplanar in **96** and **98** in order to stabilize the transition state of the cyclization by delocalization of the negative charge intio the C_i–S sigma* orbital (Scheme 126). Rotation about the $C\alpha$–$C\beta$ bond generates the antiperiplanar S–$C\alpha$–$C\beta$–$C\gamma$ conformation.

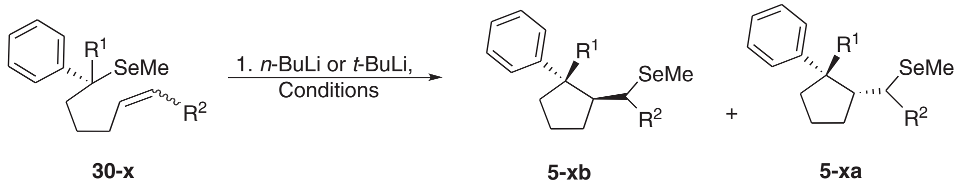


Scheme 126

Thus, the cyclization of **30-64(*E*)** and **30-64(*Z*)** leads to two distinct ion pairs **96** and **98**. Interconversion between the ion pairs would require carbanion inversion and rotation about the $C\alpha$–S bond, a process which should be slow at −110 °C,[89] but could be viable at −78 °C. The change in the stereochemistry of the carbolithiation reaction is then attributed to an inversion at the carbanion center, which is calculated to have a rather low (<2.5 kcal mol^{-1}) activation barrier.[93] This inversion to give **97** and **99** could, therefore, be competitive with or faster than the collapse of the ion pairs **96** and **98** to the configurationally stable organolithium compounds **16-55b** and **16-56b**. It should be noted that the same stereoselectivity is observed in the absence or presence of HMPA (Scheme 125, entries b and d).[197]

3.02.4.4.2.5.2.5 Isomerization of ω-alkenyl benzylselenides involving a carbocyclization reaction

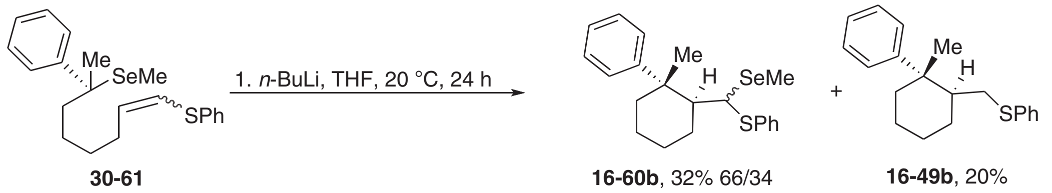
Butyllithium-catalyzed isomerisation of ω-alkenyl benzylselenide **30-6** to the carbocyclized product **5-10a**, first disclosed by Ph. Barbeaux (Scheme 101),[44] has been successfully extended to various ω-alkenyl benzylselenides **30-x** (Scheme 127 and Table 10).[204,208]



Scheme 127

It has been applied to ω-akenyl benzylselenides whose carbon–carbon double bond is located three carbons away from the benzylic carbon and that bears hydrogens (Scheme 127 and Table 10, entries 1–6 and 15),[44,154,208] a phenylthio- (Scheme 127 and Table 10, entries 7 and 11),[204] a cyclohexythio- (Scheme 127 and Table 10, entry 8),[204] a phenyl- (Scheme 127 and Table 10, entries 9–10 and 12),[199,204] or a silyl group (Scheme 127 and Table 10, entries 13 and 14)[204] at the terminus of the carbon–carbon double bond and a methyl (Scheme 127 and Table 10, entries 1–10, 13, and 14), a hydrogen (Scheme 127 and Table 10, entries 11 and 12), or a methoxy group[154] (Scheme 127 and Table 10, entry 15) at the benzylic carbon.

This isomerization has also been extended to the formation of six-membered carbocycle (Scheme 128).[204]



Scheme 128

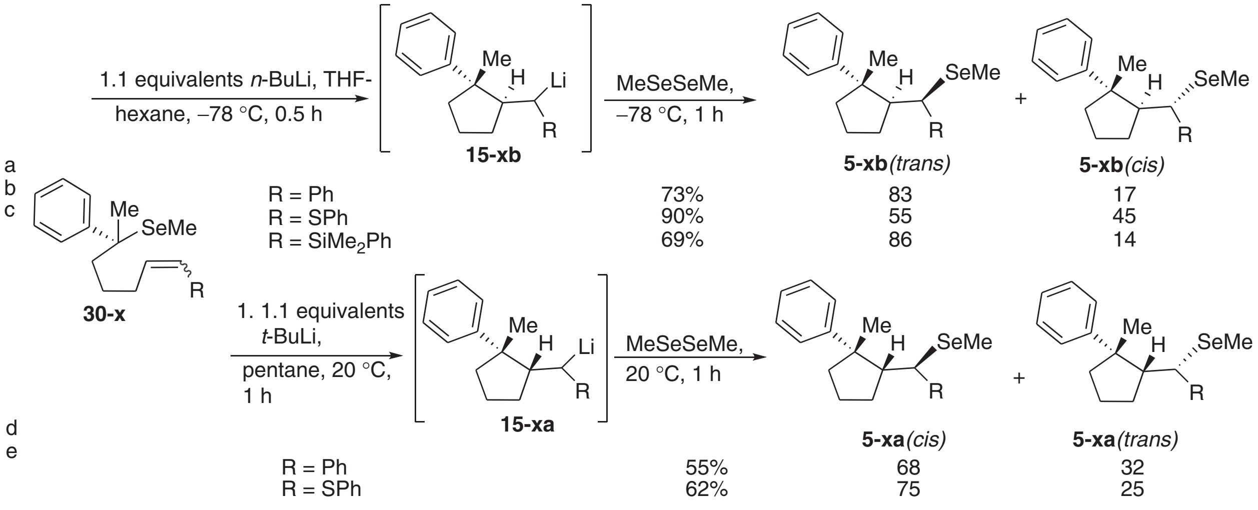
As general trends:

1. The reactions leading to a five membered cycle are faster than those producing a six-membered cycle,
2. Starting materials bearing a hydrogen at their benzylic carbon cyclize less efficiently than those bearing a methyl or a methoxy,
3. The presence of a group such as a thio, a phenyl, or a silyl group on the vinylic carbon, able to stabilize a carbanion after carbocyclization lowers the reaction rate (Scheme 127 and Table 10, entries 7–14 compared to entries 1–6 and 15). In the same series the reaction is faster with the groups that stabilize the least the carbanion resulting from the carbocyclization. Thus, the reaction is faster with the compound bearing on their carbon–carbon double bond (a) cyclohexylthio- instead of phenylthio group (Scheme 127 and Table 10, entry 8 compared to entry 7) and (b) trimethylsilyl instead of dimethylphenylsilyl group (Scheme 127 and Table 10, entry 13 compared to entry 14),

   These results apparently contradict those involving the rate of the carbocyclization reaction reported above for ω alkenyl benzylselenides. Lowering of the rate of formation of **5-x** when the olefinic carbon bears a carbanion stabilizing group strongly suggest that the rate of the reaction involving the cleavage of the benzylic selenide by the organolithium is responsible for this reverse order of reactivity (Scheme 127 and Table 10, entries 9, 10, and 12, compared to Scheme 115, entry f, and to Scheme 25 and Table 7, entry c (compared to Section 3.02.4.4.2.5.2)).[204]

   The remarkable case of **30-54** that produces alternatively the most stabilized (carbocyclization) and the least stabilized (generation of the open chain benzyllithium) benzyllithium intermediates is to be noted (Scheme 127 and Table 10, entries 9 and 10).[204]
4. The reaction producing a five membered cycle provides mainly the diastereoisomer bearing the phenyl- and the methylselenomethyl-group when carried out in pentane at room temperature or in ether around −30 °C whereas its stereoisomer is produced if the reaction is instead carried out in THF at −78 °C. However, the stereoisomer bearing the phenyl and methylselenomethyl in the *cis*-position is obtained, whatever the solvent used, if the starting material bears a methoxy group at the benzylic carbon (Scheme 127 and Table 10, entry 15),[53]
5. Although the reaction provides a mixture of compounds epimeric at the carbon bearing the methylseleno moiety, the stereoisomer bearing the methylseleno group in the α orientation is often the major one (Scheme 127 and Table 10, entries 7–14) (Scheme 128).

The same compounds **5-x** have been prepared by reaction of the carbocyclized organolithium compounds **15-x**, prepared from **30-x** and stoichiometric amount of butyllithiums, reacting then with dimethyl diselenide (Scheme 129).[204]



	30-x	Yield	5-xb(*trans*)	5-xb(*cis*)
a	R = Ph	73%	83	17
b	R = SPh	90%	55	45
c	R = SiMe$_2$Ph	69%	86	14

	30-x	Yield	5-xa(*cis*)	5-xa(*trans*)
d	R = Ph	55%	68	32
e	R = SPh	62%	75	25

Scheme 129

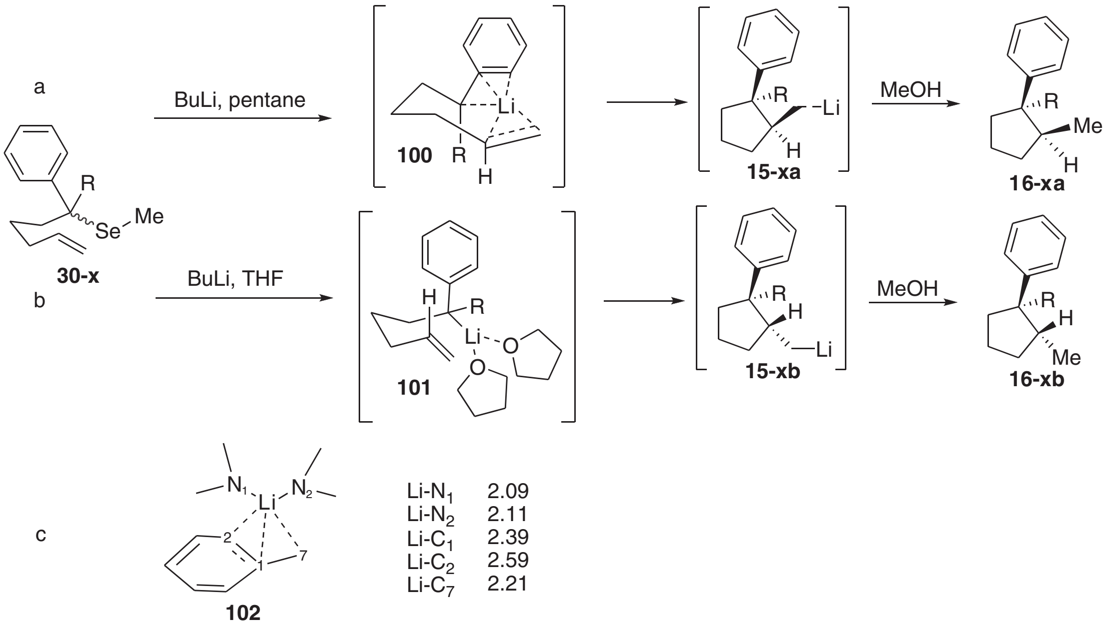
3.02.4.4.2.5.2.6 Beyond and about the mechanism of the carbocyclization involving unsaturated benzyllithiums

Kinetic versus thermodynamic control in reactions implying alkenyl benzyllithiums bearing a terminal carbon–carbon double bond: As reported above, benzyllithiums possess a high propensity to add across built-in unactivated carbon–carbon double bonds to produce a novel organolithium compound by exo-tet cyclization (Schemes 25, 34, 65, 66, 79, 96, 97, 101, and 105).

Reaction of benzylmetals to olefinic compounds, ethylene especially, trace back to the work of Ziegler.[206,207] It works particularly well with those benzyllithiums, whose carbanion bears methoxy or alkyl groups especially those that bear two methyl groups there that are expected to be the least stabilized ones. The best results are observed when carbocyclization implies the formation of a five-membered cycle involving an *exo–tet* process[164,208,209] (Scheme 110, entry a for an exception) especially when the carbon–carbon double bond bears on the other carbon two hydrogens or groups able to stabilize the resulting carbanions such as an aryl or thioorganyl substituent.

Many reports which involve carbolithiation reactions have appeared in the literature and even some computational study on the stereochemistry of intramolecular carbolithiation has been recently published.[193] However, very little has been published to provide advice to control the stereochemistry at will of the resulting compounds.

The *cis*-stereochemistry on the cyclopentane between the phenyl group and the group on the adjacent carbon bearing the lithium was accounted to the lower chelating property of hydrocarbon or ether, used as solvent, that favors a transition state in which the lithium cation is coordinated at the same time by the carbon–carbon double bond as well as the aromatic moiety (Scheme 130, entry a; Scheme 70)[21,43,53,87,166,194] (Scheme 25 and Table 7, entries j and g; Scheme 34; Scheme 103, entry c; Scheme 104; Scheme 107; Scheme 108, entry b; Scheme 109; Scheme 110, entries b–e). A similar behavior has been observed with ω-alkenyl allyllithiums (Scheme 13).[32]



Scheme 130

The *trans*-relationship between the same groups might be the result of chelation of the lithium cation, by THF, which increases its size and at the same time weakens the interaction with the carbon–carbon double bond (Scheme 130, entry b; Scheme 25 and Table 7, entry a compared to entry b; Scheme 110, entry a).

It is interesting to note that the formation of the *cis*-stereoisomer is independent of the choice of the solvent with the benzylselenide bearing a methoxy group at the benzylic position (Scheme 34)[53] and that the formation of the cyclopent(a)indene **93-1** whose structure is disclosed in Scheme 110 is detrimental to the synthesis of **16-32** which is its precursor. In the last event, if the conditions involve an equilibrium, the latter should be withdrawn toward the formation of **93-1** since it requires the elimination of lithium hydride that restores the aromaticity through a nonreversible process (**4-5** to **93-1**, Scheme 110).

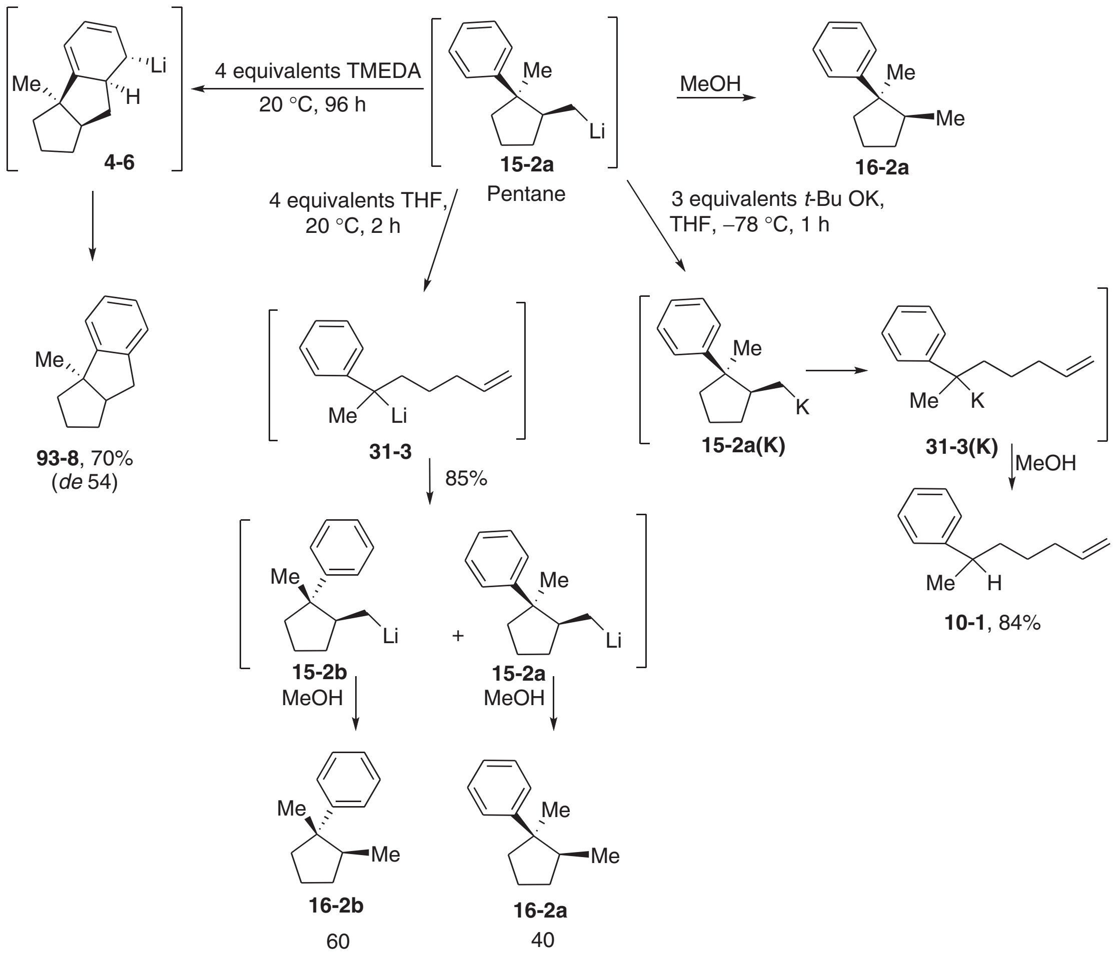
Since the solvent is so important for the control of the stereochemistry of **16-2**, the role of various ethers on the stereochemical outcome of the carbocyclization of **30-6** has been tested (Scheme 25). It has been found that the stereoisomer **16-2a** in which the phenyl and the adjacent methyl group are *cis* to each other is produced in up to 80% yield, from **30-6** when the reaction is carried out with *t*-BuLi in (1) pentane (20 °C, 1 h; **16-2a** *de* 96%), (2) 2,2,5,5-tetramethyl-THF (−78 °C, 4 h or −30 °C, 4 h; **16-2a** *de* 98%), diethyl ether (−30 °C, 0.5 h or 1 h, **16-2a** *de* 98%), and di-*n*-butyl ether (−30 °C, 1 h, **16-2a** *de* 98%).[195]

It is interesting to note that the stereocontrol is highly temperature dependent when the reaction is carried out in diethyl ether and di-*n*-butyl ether since poorer selectivity is observed in these solvents if the reaction is carried out at − 78 °C instead of − 30 °C (− 78 °C, 7 h, **16-2a** *de* 50% instead of *de* 98%).

It has been also found that the other stereoisomer **16-2b** is produced, in up to 80% yield when the reaction is carried out in THF (− 78 °C, 0.5 h, **16-2b** *de* 96%) or 2-methyl-THF (− 78 °C, 1 h; **16-2b** *de* 90%; − 30 °C, 0.5 h, **16-2b** *de* 86%) instead. 2,5-Dimethyl-THF, however, provides **16-2** as a mixture of stereoisomers (− 40 °C, 0.5 h, **16-2b** *de* 30%).

In order to have a better insight on the factors involved in the cyclization reaction, several reactions have been carried out on the preformed cyclopentane derivative **15-2a** bearing the phenyl and the lithiomethylene groups *cis* to each other (Scheme 25 and Table 7, entry j missing the addition of methanol).

Addition of 4 equivalents of THF on preformed **15-2a** in hexane for 2 h at 20 °C changes the ratio of **16-2b**/**16-2a** from 98/2 to 60/40 (compared to Scheme 25 and Table 7, entry b compared to entry a) suggesting that fragmentation takes place under those conditions and that the addition is reversible at least at that temperature (Scheme 131).[197]

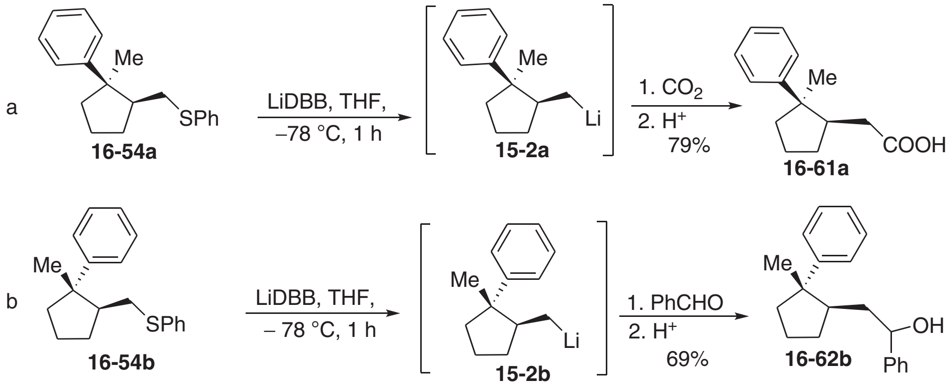


Scheme 131

Addition of TMEDA to the preformed **15-2a**, at low temperature, does not change the ratio of **16-2b**/**16-2a** but favors the slow addition of the primary alkyllithium **15-2a** possessing the '*cis*-stereochemistry' on the carbon–carbon bond of the aromatic ring leading to the tricyclic derivative shown in Scheme 131 after rearomatization.[197] These conditions allow the synthesis of the cyclopent(a)indene **93-8** bearing two hydrogens at the newly formed benzylic carbon, which is unavailable otherwise (compared to Scheme 110).[166]

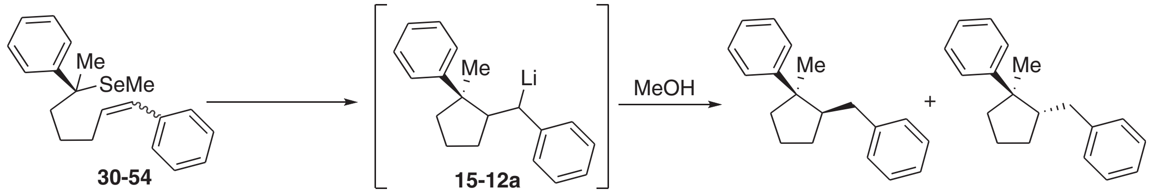
The authors finally found that lithium is crucial in the process since addition of *t*-BuOK in THF to preformed **15-2a** in pentane leads to the recovery of **10-1** in high yield suggesting that **15-2a(K)** reverts rapidly to **31-3(K)**. Similarly, **10-1** also is produced if *n*-BuLi is reacted at − 78 °C on a mixture of 2-phenyl-2methylseleno-6-heptene **30-6** and *t*-BuOK in THF-hexane suggesting that **31-3(K)** apparently does not exhibit the high propensity of its lithium analog **31-3** to carbocyclize (Scheme 131).[197]

Finally, each of the two 1,2-dimethyl-1-phenyl-cyclopentanes **15-2a** and **15-2b** have been prepared stereospecifically at −78 °C from the corresponding phenyl sulfides **16-54a** and **16-54b** and LiDBB in THF. Trapping the organolithium by CO_2 (Scheme 132, entry a) or benzaldehyde (Scheme 132, entry b) provides the carboxylic acid **16-61a** and the benzylic alcohol **16-62b** in good yields (Scheme 132).[197,202] These results clearly show that the cyclopentylmethyllithium **15-2b** generated in THF from **16-54b**, that produces **16-2b** after protonation, does not epimerize after being kept at −78 °C for at least 1 h to **15-2a**. Therefore the latter should be formed, under kinetically controlled conditions, on reaction of 2-phenyl-2-methylseleno-6-heptene **30-6** with *n*-butyllithium in THF-hexane (Scheme 25 and Table 7, entry a).[197]



Scheme 132

Kinetic versus thermodynamic control in reactions implying alkenyl benzyllithiums bearing a phenyl or phenylthio group on their carbon–carbon double bond: The benzyllithium intermediate **15-12a** resulting from the reaction at −78 °C, of the *ω*-alkenyl benzylselenide **30-54** with *n*-butyllithium in THF, epimerizes when the temperature reaches 0 °C (Scheme 133, entry c compared to entries a and b). Isomerization does not take place, however, when the reaction is instead carried out in ether and the temperature raised from −110 °C to 0 °C (Scheme 133, entry d compared to Scheme 115, entry e).



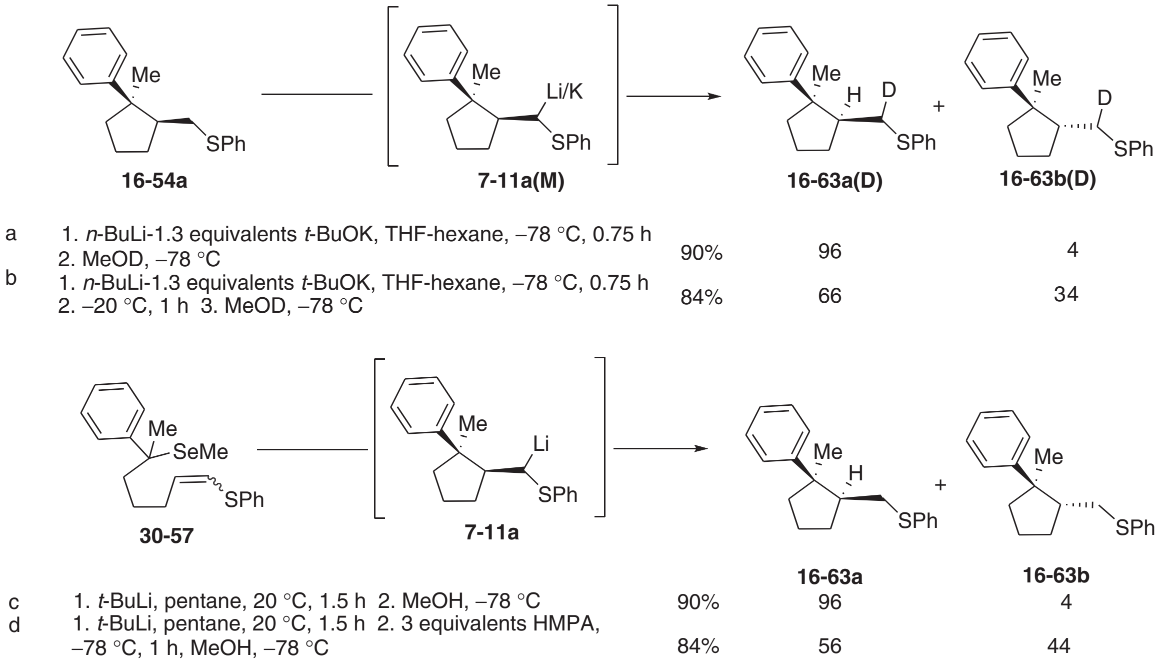
			16-39a	16-39b
a	1. *n*-BuLi, THF-hexane, –78 °C, 0.5 h	83%	3	97
b	1. *n*-BuLi, THF-hexane, 0 °C, 1 h	75%	27	73
c	1. *n*-BuLi, THF-hexane, –78 °C, 1 h, 2. –78 to 0 °C, 1 h	60%	26	74
d	1. *n*-BuLi, ether-hexane, –100 °C, 1 h, 2. –100 to 0 °C, 1 h	70%	4	96

Scheme 133

It has been found that the organometallic species **7-11(M)** resulting from the metallation of **16-54a**, which bears the phenyl and the phenylthiomethyl substituent in *cis*-relationship with *n*-BuLi/*t*-BuOK mixture in THF does not epimerize at −78 °C (see Scheme 124 entry b; Scheme 134, entry a).[197] It, however, epimerizes to produce quite a large amount of its stereoisomer **16-63b** in which the phenyl and the phenylthiomethyl substituents are in *trans*-relationship when the temperature rises to −20 °C (Scheme 134, entry b).[197] Both epimers have a 95% of deuterium content if deuteromethanol is used to quench those reactions (Scheme 134).[197]

Epimerization also takes place when HMPA is added to the reaction implying *t*-butyllithium in ether (Scheme 134, entry d compared to entry c).[197,199]

It has been also found that the open chain *ω*-alkenyl benzylpotassium (Scheme 114) is produced from the related *β*-potassiocarbinyl phenyl cyclopentane bearing a methylene carbanion, whereas at the same temperature and solvent, the *α*-thio alkyl potassium **7-11a(K)** does not revert to the open chain benzyl potassium suggesting that it is due to the extra stabilization of the carbanion brought by the phenylthio moiety (Scheme 134, entry b).



16-54a **7-11a(M)** **16-63a(D)** **16-63b(D)**

a	1. *n*-BuLi-1.3 equivalents *t*-BuOK, THF-hexane, –78 °C, 0.75 h 2. MeOD, –78 °C	90%	96	4
b	1. *n*-BuLi-1.3 equivalents *t*-BuOK, THF-hexane, –78 °C, 0.75 h 2. –20 °C, 1 h 3. MeOD, –78 °C	84%	66	34

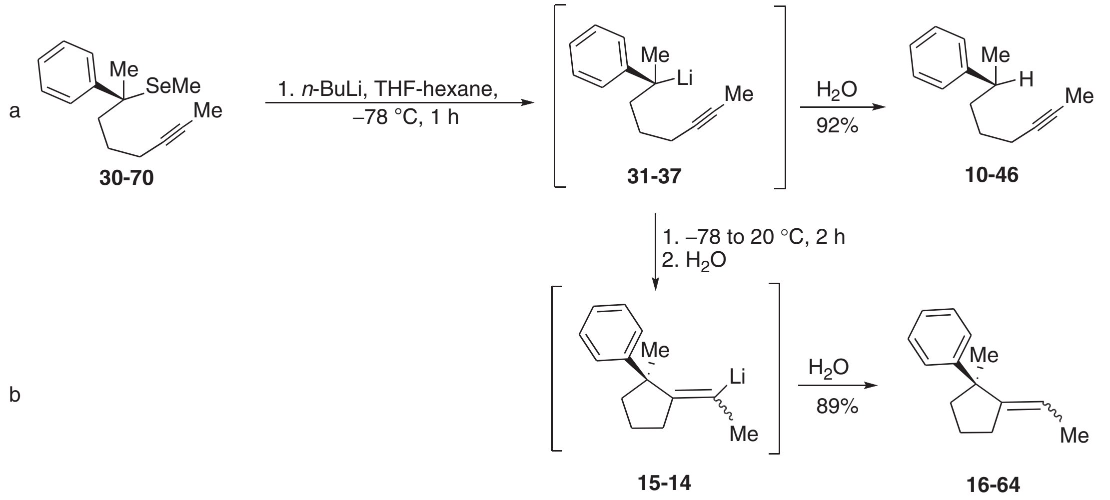
30-57 **7-11a** **16-63a** **16-63b**

c	1. *t*-BuLi, pentane, 20 °C, 1.5 h 2. MeOH, –78 °C	90%	96	4
d	1. *t*-BuLi, pentane, 20 °C, 1.5 h 2. 3 equivalents HMPA, –78 °C, 1 h, MeOH, –78 °C	84%	56	44

Scheme 134

3.02.4.4.2.5.3 Synthesis of alkylidene cyclopentanes involving carbon–carbon triple bonds

Finally, the benzyllithium **31-37** bearing a carbon–carbon triple bond which results from the cleavage of methyl(2-phenyloct-6-yn-2-yl)selane **30-70** by *n*-butyllithium in THF is less prone than its olefinic analog to cyclize. In fact, the open chain compound **10-46** is obtained in high yield after quenching the reaction at – 78 °C with methanol (Scheme 135, entry a) but efficiently cyclizes at 20 °C (Scheme 135, entry b) producing, in extremely good yield, 2-ethylidene-1-methylcyclopentyl)benzene **16-64**, whose stereochemistry has not yet been determined through the intermediate formation of the vinyllithium **15-14** (Scheme 135, entry b).

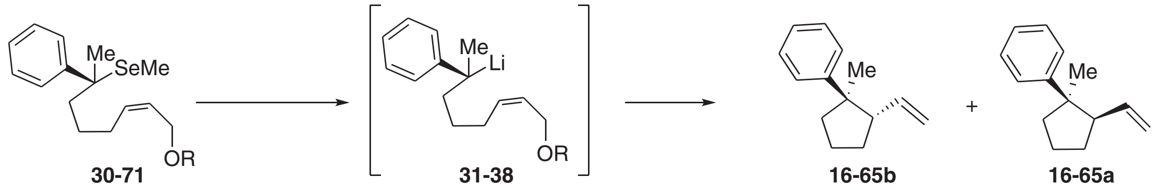


30-70 **31-37** **10-46** **15-14** **16-64**

Scheme 135

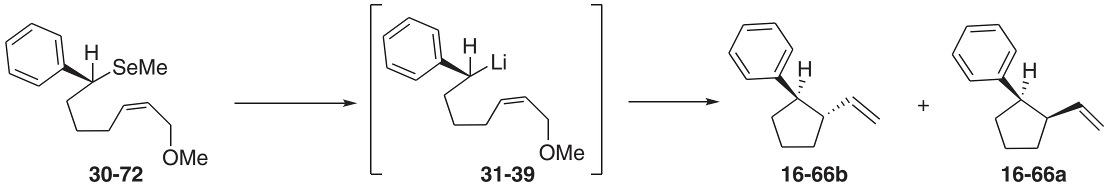
3.02.4.4.2.5.4 Synthesis of vinyl cyclopentanes involving allyl ethers and related reactions involving propargyl ethers

Benzyl selenides bearing a side chain possessing in suitable position an allyl chloride (Scheme 90, entry c),[170] allyl sulfonate (Scheme 99, entry a),[170] allylic ether (Scheme 136, entries a–c; Scheme 137; Scheme 138),[209] or even allylic alcohol (Scheme 99, entry b), react with butyllithiums to produce, via the corresponding benzyllithiums, 1-aryl-2-vinylcycloalkanes releasing concomitantly a chloride, a sulfonate, an alcoholate, or even a lithium alkoxide ion, respectively.



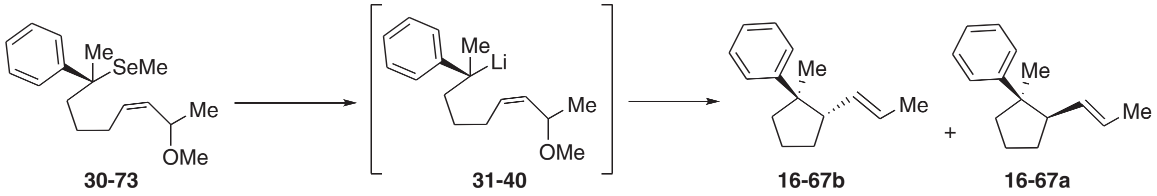
a	Me	1. *n*-BuLi, THF-hexane, –78 °C, 1 h 2. MeOH	83%	95	5
b	Me	1. *t*-BuLi, pentane, 22 °C, 1 h 2. MeOH	94%	8	92
c	Me	1. *t*-BuLi, Ether, –45 °C, 0.5 h 2. MeOH	74%	4	96
d	MEM	1. *n*-BuLi, THF-hexane, –78 °C, 1 h 2. MeOH	83%	97	3
e	MEM	1. *t*-BuLi, pentane, 22 °C, 1 h 2. MeOH	83%	7	97
f	MEM	1. *t*-BuLi, Ether, –45 °C, 0.5 h 2. MeOH	76%	60	40

Scheme 136



a	1. *n*-BuLi, THF-hexane, –78 °C, 1 h 2. MeOH	75%	20	80
b	1. *t*-BuLi, pentane, 20 °C, 1 h 2. MeOH	76%	3	97

Scheme 137



a	1. *n*-BuLi, THF-hexane, –78 °C, 3 h 2. MeOH	75%	98	2
b	1. *t*-BuLi, pentane, 20 °C, 3 h 2. MeOH	76%	9	91

Scheme 138

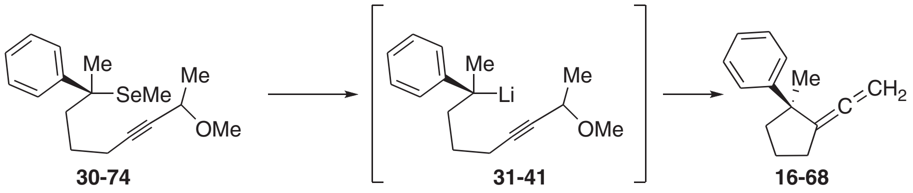
The reaction which has some precedent[160,203–208,210] allows the perfect control of the relative stereochemistry in the case of arylcyclopentane derivatives bearing a methyl group at the benzylic position (Schemes 136 and 138). In such cases the reaction produces with high stereocontrol the stereoisomer in which the phenyl and the vinyl groups on the adjacent carbons are *trans* to each other when carried out, at − 78 °C, in THF-hexane (Scheme 136, entries a and d; Scheme 138, entry a). The stereoisomer with the *cis*-stereochemistry is almost exclusively produced when performed in pentane (Scheme 136, entries b and e; Scheme 138, entry b). The selectivity concerning the reaction carried out in ether is often closely related to that performed in pentane (Scheme 136, compare entries c and b), but this is not always the case (Scheme 136, compare entries f and e).[199]

The formation of *cis*-stereoisomer **16-66a** is efficiently achieved from the *ω*-alkenyl selenide **30-72** missing the methyl group at the benzylic position (Scheme 137, entry b). The formation of the *trans*-stereoisomer **16-66b** is less selective when the reaction is carried out in THF (Scheme 137, entry a).[209] The reported behavior is closely related to that involving instead the related *ω*-alkenyl benzyllithiums (Scheme 25 and Table 7).

Furthermore, only those products **16-67b** and **16-67a** possessing the (*E*)-carbon–carbon double bond are formed by carbocyclization of **30-73** whatever the solvent used (Scheme 138).[209]

The reaction has been successfully extended to the *ω*alkynyl benzyllithium **30-74** bearing a methoxy group at the propargylic carbon and produces the related allene derivative **16-68** whether it is performed in THF or pentane (Scheme 139).[209]

These reactions can proceed in two consecutive steps implying the addition of the benzyllithium across the carbon–carbon double or triple bond followed by a *β*-elimination reaction leading to the formation of the vinyl moiety or in a single step through an S_N2' process. All the efforts to trap a potential intermediate cycloalkane carbinyllithium by carrying out the reaction of



a	1. *n*-BuLi, THF-hexane, −78 °C, 3 h 2. MeOH	72%
b	1. *t*-BuLi, pentane, 20 °C, 3 h 2. MeOH	71%

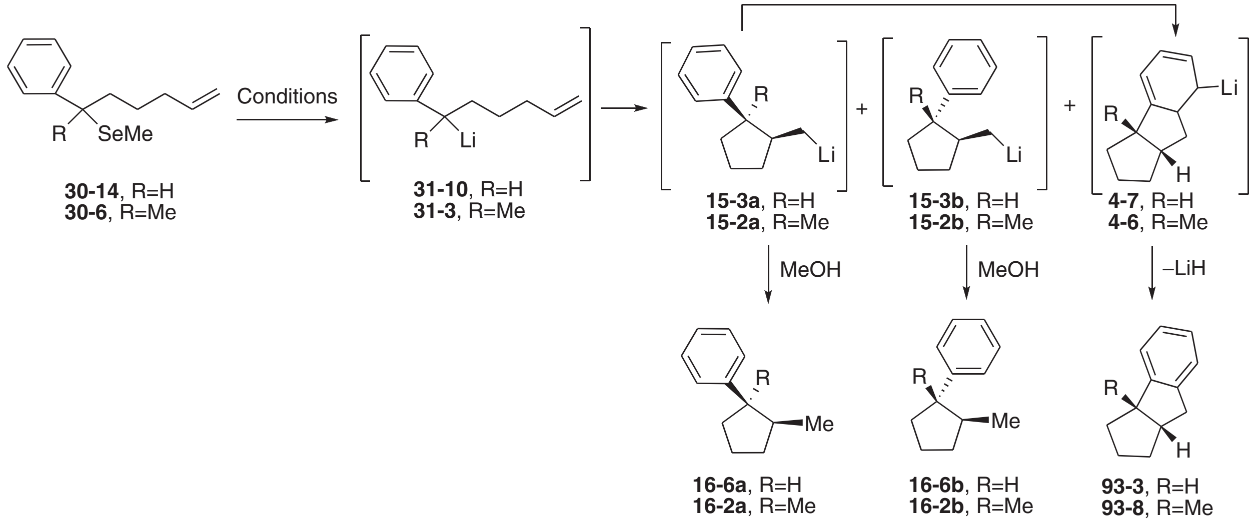
Scheme 139

butyllithium on **30-73** in the presence of trimethylsilyl chloride for example, has only led instead to the silylation of the benzyllithium before its cyclization.[209]

3.02.4.4.2.6 Enantioselective syntheses of 1-phenyl-2-alkyl and 1-phenyl-2-alkenyl cyclopentanes

The reaction implying the carbocyclization of ω-alkenyl benzyl selenides allows the synthesis of each of the two diastereoisomers of β-substituted derivatives but as a racemic mixture. Therefore efforts have been undertaken to prepare ideally each of the 4 enantiomers.

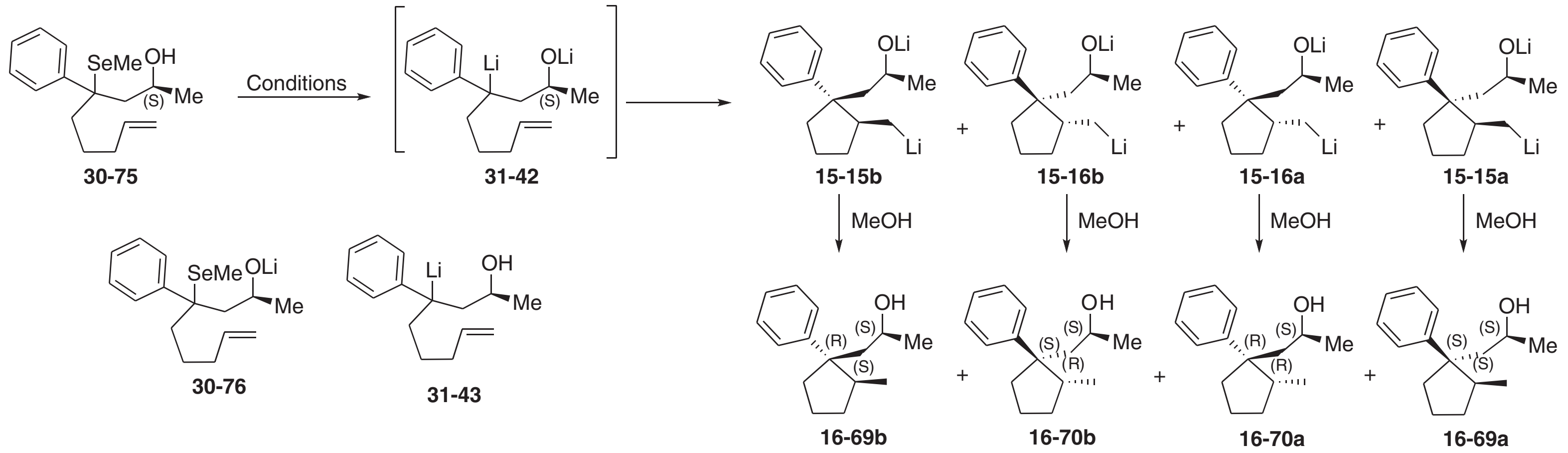
Thus *t*-butyllithium complexed to sparteine has been reacted with the ω-alkenyl benzyllithiums **30-14** and **30-6** expecting that complexation of the lithium cation with sparteine will induce diastereoselective carbocyclization leading finally to the formation of scalemic cyclopentane derivatives.[211–213] We, however, found that the presence of sparteine in the reaction of **30-6** (R=Me) favors in pentane the formation of the diastereoisomer **16-2b** (R=Me) in which the phenyl and the methyl groups on the adjacent carbon are *trans* as well as the cyclopent(a)indene **93-8** (R=Me) (Scheme 140, entries a and b). The latter has been produced in the racemic version when TMEDA, a diamine whose chelating properties of lithium cation is similar to those of sparteine, is added to the pentane solution of **30-6** (R=Me) in pentane (Scheme 131).[184] Related results have been observed when the same conditions are used with **30-14** (R=H) except that the cyclopent(a)indene **93-3** (R=H) is not formed at the expense of **16-6a** (R=H) (Scheme 140, entries c and d). Furthermore, it has not beenpossible to find conditions that allow the separation of the enantiomeric mixtures.[145]



			16-6a / 16-2a	16-6b / 16-2b	93-3 / 93-8
a	1. *t*-BuLi-sparteine, pentane, 0 °C, 2 h 2. 20 °C, 72 h 3. MeOH (R=Me)	69%	14	54	32
b	1. *t*-BuLi-sparteine, Et_2O, −78 °C, 2 h 2. 20 °C, 12 h 3. MeOH (R=Me)	61%	53	21	26
c	1. *t*-BuLi-sparteine, pentane, 0 °C, 2 h 2. 20 °C, 48 h 3. MeOH (R=H)	69%	85	15	0
d	1. *t*-BuLi-sparteine, pentane, −78 °C, 2 h 2. 20 °C, 24 h 3. MeOH (R=H)	52%	88	12	0

Scheme 140

Another approach implies the reaction of **30-75** with organolithiums expecting that the remote chiral center bearing the hydroxyl group will induce the asymmetric induction once the alkoxide would complex the lithium cation squeezing it between the benzylic carbon of the aromatic and the carbon–carbon double bond (Scheme 141).[214] The reaction of 2 equivalents of



			16-69b	16-70b	16-70a	16-69a
a	1. 1.1 equivalents MeLi-ether-Et_2O, 2. *t*-BuLi, pentane, –20 °C, 1 h 3. MeOH	90%	13	52	22	13
b	1. 1.1 equivalents MeLi-LiBr-ether-Et_2O, 2. *t*-BuLi, pentane, –20 °C, 1 h 3. MeOH	90%	8	82	8	2

Scheme 141

butyllithiums on **30-75** expected to produce sequentially the alcoholate **30-76** then the β-alkoxide benzyllithium **31-42**. The reaction proceeds differently since Se/Li exchange leading to **31-43** occurs at a competitive rate with that of the H/Li exchange on the hydroxyl group. It finally leads to a mixture of compounds in which some protonation of the benzylic carbanion has occurred.

Methyllithium which is unable to cleave the C–Se bond effects the selective hydrogen metal exchange on (2*S*)-4-(methylselanyl)-4-phenylnon-8-en-2-ol **30-75** derived from scalemic (*S*)-2-methyloxirane (see Section 3.02.4.3.3) and subsequent addition of *t*-butyllithium in pentane produces **31-42** very efficiently at −78 °C. Carbocyclization takes then place at approximately −20 °C and leads to a mixture of the four stereoismers of (*S*)-1-((1*R*,2*S*)-2-methyl-1-phenylcyclopentyl)propan-2-ol **16-69** and **16-70** in which the stereoisomers **16-69b** and **16-70b** that possess the *trans*-stereochemistry between the phenyl and the adjacent methyl prevails (*de*=30%) (Scheme 141, entry a).[203] Much better *trans*/*cis* (90/10) ratio has been observed if the reaction is carried out still in pentane but in the presence of lithium bromide (1.1 equivalents, *de*=80%). In such case the stereoisomer **16-70b** proved to be by far the major (82%) (Scheme 141, entry b compared to entry a).[203] The formation of the compound possessing the *trans*-stereochemistry as the major compound instead of the *cis* usually produced when the reactions are carried out in ether shows the importance of the alkoxy group to control the stereochemistry especially when lithium bromide is used.[203]

The ω-alkenyl benzylselenide **30-75** required for the above synthesis has been prepared stepwise from benzaldehyde **11-1** through the intermediate formation of phenyl-di(methylseleno)methyl potassium **60-4(*K*)** by sequential alkylation/Se/Li exchange and alkylation. The first approach in which 1-bromo-4-pentene and 2-(S)-oxido propene **(*S*)-76-7** are sequentially reacted instead of the reverse 2-(*S*)-oxido propene **(*S*)-76-7** then 1-bromo-4-pentene clearly show the crucial role of the pending alkoxy group in **37-27** which produce **30-75** in a very high yield and with extremely high diastereoselection (*de*=96%) (Scheme 142, entry b).[214] The same compound **30-75** is, however, produced as a 1:1 diastereoisomeric mixture when the reverse order of addition is used (Scheme 142, entry a).

Note that in the first approach the sequential use of methyllithium and butyllithium for the transformation of **37-27** to **30-75** is reminiscent of the problem already discussed for the transformation of **30-75** to **16-70b** (compare Scheme 141 to Scheme 142).

The second approach to scalemic cyclopentane derivatives use a completely different strategy that allows the synthesis of 1-phenyl-1-methyl-2-vinyl-cyclopentanes **16-67** and **16-71** in extremely high yield and with extremely high enantioselection (Scheme 144) from the 8-(benzyloxy)-2-phenylnon-6-en-2-yl)(methyl)selanes **107(*E*)** and **107(*Z*)** whose syntheses are described in Scheme 143.

They use (*S*)-but-3-yn-2-ol **103** as exceptional scalemic precursor that possesses in addition to the chiral propargylic carbon (the inductor) the acetylenic hydrogen which allows to build the side chain via a metallation/alkylation sequence and the carbon–carbon triple bond precursor of the *Z*- or *E*-allylic alcohols by catalytic hydrogenation or using the aluminium hydride Red-Al, respectively (Scheme 143).

8-(Benzyloxy)-2-phenylnon-6-en-2-yl)(methyl)selanes **107(*Z*)** and **107(*E*)** are isomeric. They possess (1) the same functional groups (allyl alcohol and benzylselenide) (2) the same (*S*)-stereochemistry at the allylic carbon bearing the hydroxyl group, and (3) both involve an epimeric mixture at their C-2 benzylic site.

Compounds **107(*Z*)** and **107(*E*)** differ, however, from the stereochemistry of their carbon–carbon double bond.

Reaction of the ω-alkenyl benzylselenide **107(*Z*)**, which possesses a *Z*-carbon–carbon double bond with butyllithiums produces 1-methyl-2-prop-1-en-1-yl)cyclopentyl)benzene **16-71b** in which the phenyl and the vinyl groups on the cyclopentane ring are *trans* to each other when the reaction is carried out in THF at −78 °C (Scheme 144, entry a) and its *cis*-stereoisomer **16-71a** when the reaction is instead performed in ether at 0 °C (Scheme 144, entry b). **16-71b** and **16-71a** are both formed in high yield, with good diastereoselectivity (>88%) and very high enantioselectivity (>95%) (Scheme 144, entries a and b). They share (1) the same gross structure, (2) the same (*S*)-stereochemistry at the benzylic carbon C-1, and (3) the same *E*-stereochemistry of their carbon–carbon double bond but are epimeric at C-2.

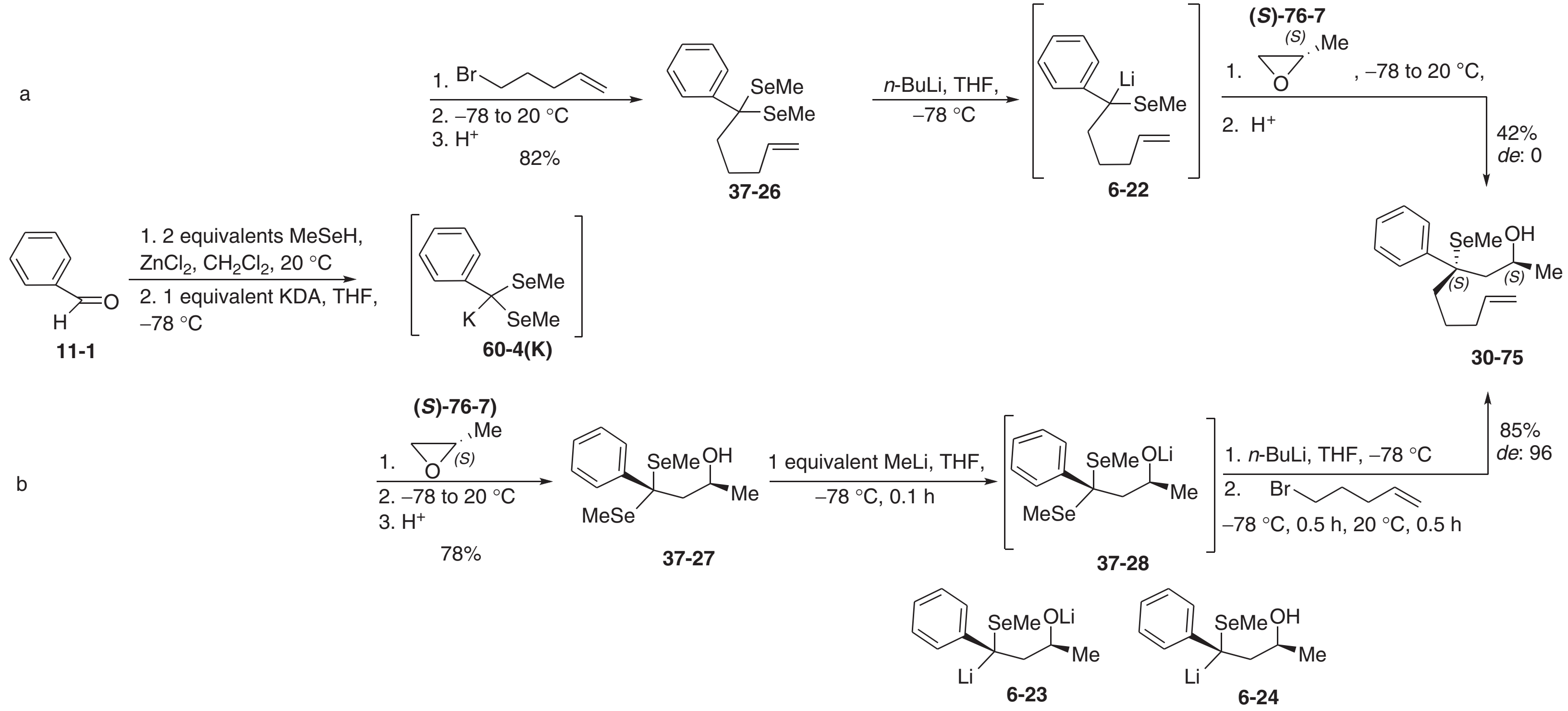
The stereochemistry at the benzylic carbons of both **16-71b** and **16-71a** is remarkable since it arises from an epimeric mixture at the C-2 benzylic site of **107(*Z*)** and implies epimerization of the benzyllithium intermediates **31-44(*Z*)** and **31-45(*Z*)**.

Reaction of the ω-alkenyl benzylselenide **107(*E*)** possessing a *E*-carbon–carbon double bond with butyllithiums (Scheme 144, entries c and d) parallels that of **107(*Z*)** which has been reported above (Scheme 144, entries a and b). Thus **16-67b** in which the phenyl and the vinyl groups on the cyclopentane ring are *trans* to each other is mainly formed when the reaction is carried out in THF at −78 °C (Scheme 144, entry c), and its *cis*-stereoisomer **16-67a** is generated when the reaction is instead performed in ether at −78 °C (Scheme 144, entry d).

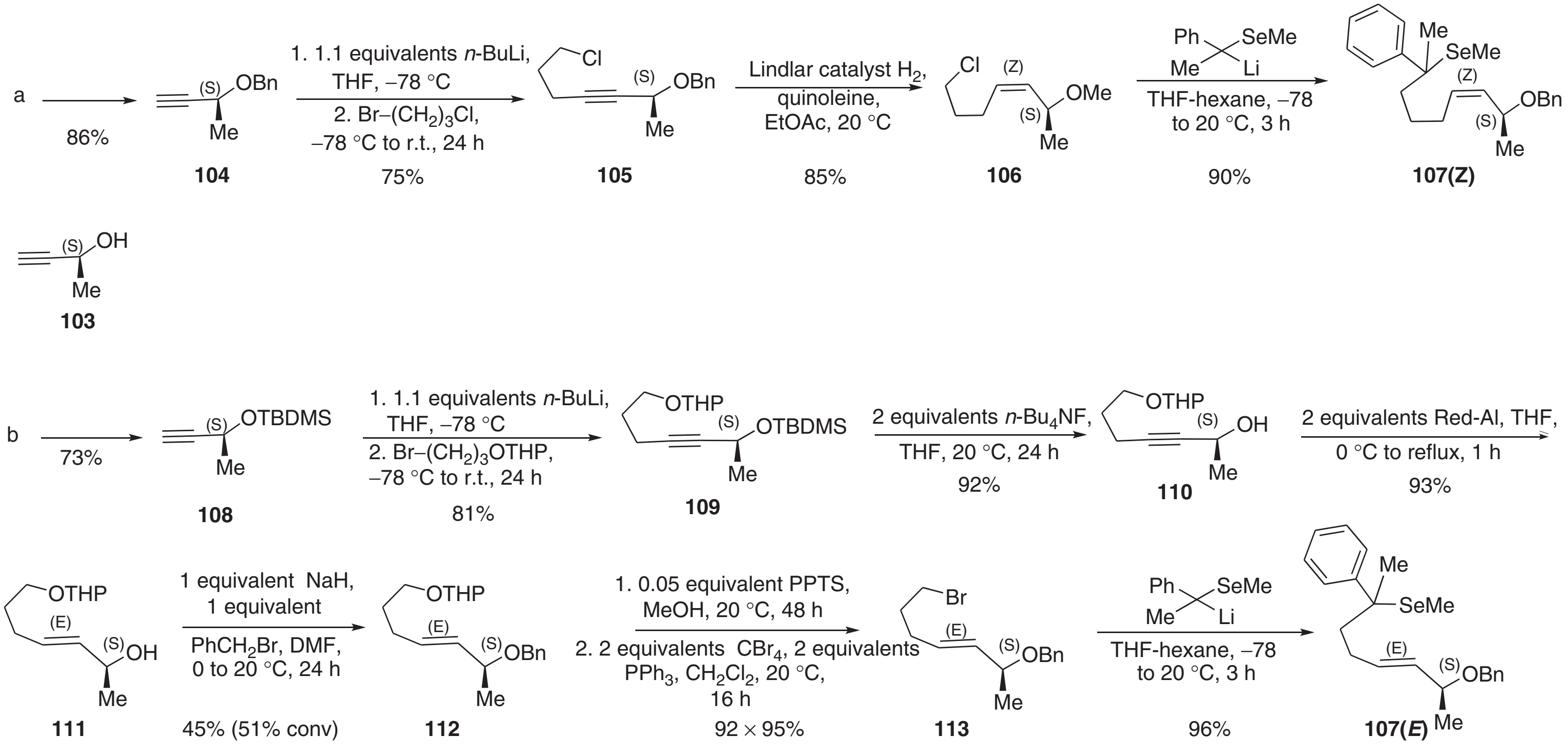
Stereoisomers **16-67a** and **16-67b** are both formed in high yield, with high diastereoselectivity (> 86%) and enantioselectivity (>95%) (Scheme 144, entries c and d). They share (1) the same gross structure, (2) the same (*R*)-stereochemistry at the benzylic carbon C-1, and (3) the same *E*-stereochemistry of the propenyl group but are epimeric at C-2.

The relation between the structures of the starting materials **107(*Z*)** and **107(*E*)** and that of the resulting products **16-71b**, **16-67b**, **16-67a**, and **16-71a** suggests that the reactions carried out in:

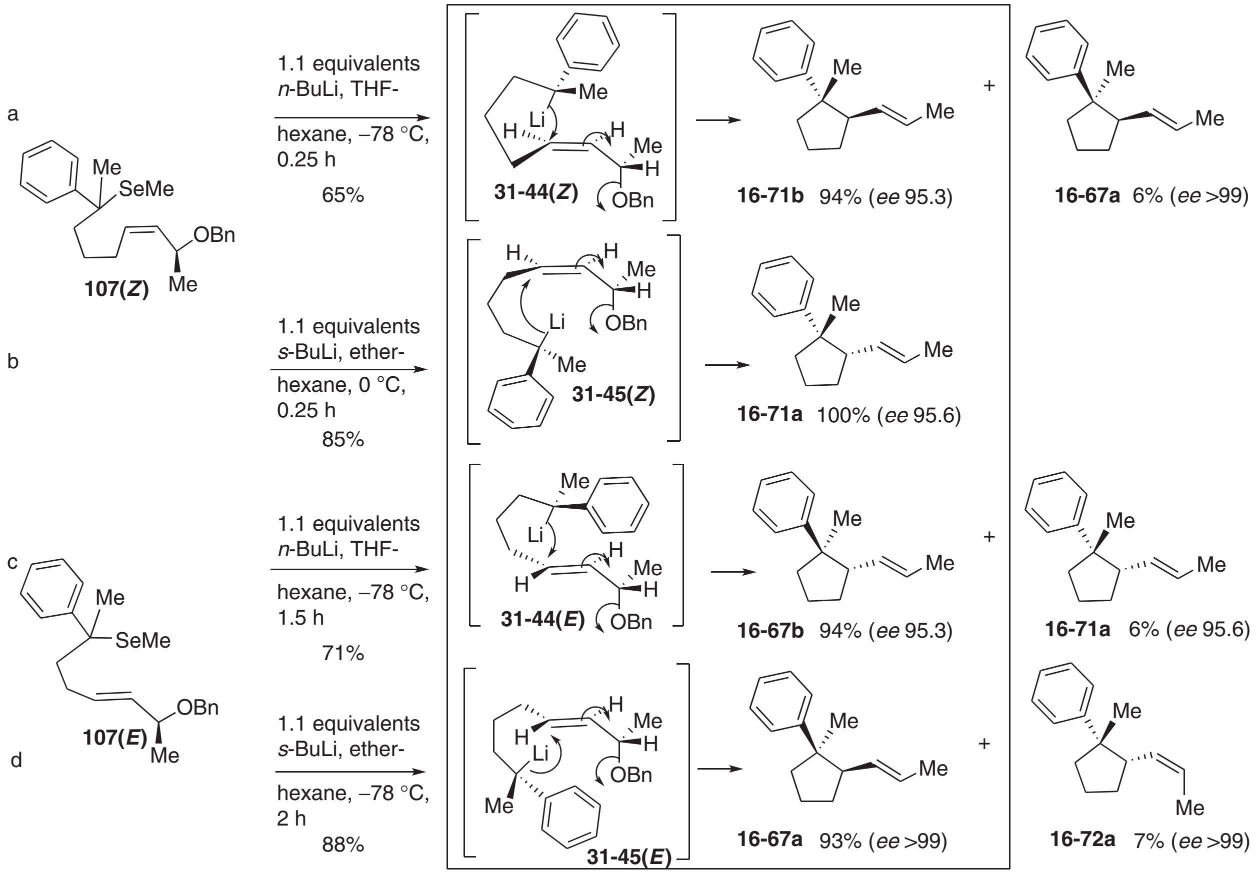
1. ether and leading to **16-67a** and **16-71a**, respectively, involve the intermediates **31-45(*E*)** and **31-45(*Z*)** in which the entering benzylic carbanion, the pi-bond, and the alkoxy leaving group are in a *syn*-coplanar conformation in the transition state. It suggests that the lithium cation interacts not only with the benzylic carbon, the aromatic ring, and the carbon–carbon double bond to favor the *cis*-geometry between the phenyl- and the vinylgroup, as often found in related cases (Scheme 25 and Table 7, entry h; Scheme 103, entry c; Scheme 109, entry b; Scheme 115, entry e; Scheme 118, entries c and h; Scheme 119, entry e; Scheme 136, entry c), but also with the alkoxy group (Scheme 144, entries b and d),


a
b
1. Br
2. –78 to 20 °C
3. H+
82%
SeMe
SeMe
37-26
n-BuLi, THF,
–78 °C
Li
SeMe
6-22
(S)-76-7
(S)
Me
O
1.
, –78 to 20 °C,
2. H+
42%
de: 0
SeMe
OH
(S)
(S)
Me
30-75
H
O
11-1
1. 2 equivalents MeSeH,
ZnCl2, CH2Cl2, 20 °C
2. 1 equivalent KDA, THF,
–78 °C
SeMe
K
SeMe
60-4(K)
(S)-76-7)
Me
(S)
O
1.
2. –78 to 20 °C
3. H+
78%
SeMe
OH
Me
MeSe
37-27
1 equivalent MeLi, THF,
–78 °C, 0.1 h
SeMe
OLi
Me
MeSe
37-28
1. n-BuLi, THF, –78 °C
2. Br
–78 °C, 0.5 h, 20 °C, 0.5 h
85%
de: 96
SeMe
OLi
Me
Li
6-23
SeMe
OH
Me
Li
6-24

Scheme 142


a
86%
(S)
OBn
Me
104
1. 1.1 equivalents n-BuLi,
THF, –78 °C
2. Br–(CH2)3Cl,
–78 °C to r.t., 24 h
75%
Cl
(S)
OBn
Me
105
Lindlar catalyst H2,
quinoleine,
EtOAc, 20 °C
85%
Cl
(Z)
OMe
(S)
Me
106
Ph
SeMe
Me
Li
THF-hexane, –78
to 20 °C, 3 h
90%
Me
SeMe
(Z)
OBn
(S)
Me
107(Z)
(S)
OH
Me
103
b
73%
(S)
OTBDMS
Me
108
1. 1.1 equivalents n-BuLi,
THF, –78 °C
2. Br–(CH2)3OTHP,
–78 °C to r.t., 24 h
81%
OTHP
(S)
OTBDMS
Me
109
2 equivalents n-Bu4NF,
THF, 20 °C, 24 h
92%
OTHP
(S)
OH
Me
110
2 equivalents Red-Al, THF,
0 °C to reflux, 1 h
93%
OTHP
(E)
(S)
OH
Me
111
1 equivalent NaH,
1 equivalent
PhCH2Br, DMF,
0 to 20 °C, 24 h
45% (51% conv)
OTHP
(E)
(S)
OBn
Me
112
1. 0.05 equivalent PPTS,
MeOH, 20 °C, 48 h
2. 2 equivalents CBr4, 2 equivalents
PPh3, CH2Cl2, 20 °C,
16 h
92 × 95%
Br
(E)
(S)
OBn
Me
113
Ph
SeMe
Me
Li
THF-hexane, –78
to 20 °C, 3 h
96%
Me
SeMe
(E)
(S)
OBn
Me
107(E)

Scheme 143



Scheme 144

2. THF that leads to **16-71b** and **16-67b**, respectively, involve the intermediate formation of **31-44(*Z*)** and **31-44(*E*)** in which the entering benzylic carbanion, the pi-bond, and the alkoxy leaving group are in a *anti*-coplanar conformation in the transition state. This approach is suspected to minimize steric interactions between the 'bulky' phenyl- and the vinyl-group as often found in related cases (Scheme 25 and Table 7, entry a; Scheme 103, entry b; Scheme 112, entry a; Scheme 115, entry d; Scheme 117, entry d; Scheme 118, entries a and e; Scheme 119, entries a and b; Scheme 125, entries a and g; Scheme 136, entries a and d), as well as with compounds bearing an alkoxy group (Scheme 144, entries a and c).

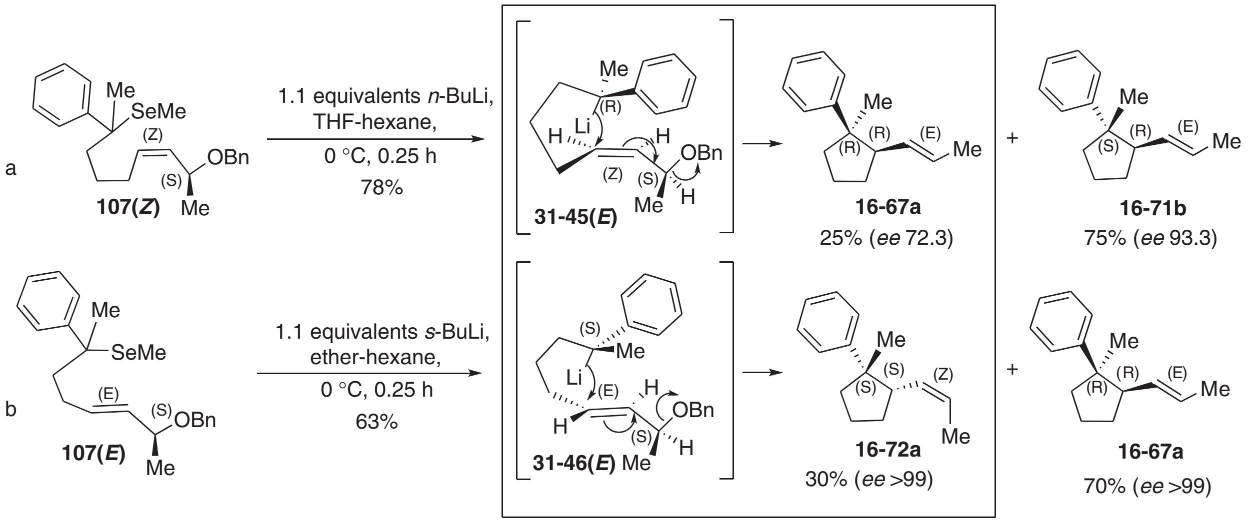
The reaction implying **107(*Z*)** in ether (Scheme 144, entry b) is completely stereoselective, providing **16-71a** as a single diastereoisomer under the conditions used. All others produce a mixture of diastereoisomers in which one mainly prevails and the other stereoisomers are formed in minor quantities (Scheme 144, entries a, c, and d). The reaction involving **107(*E*)** in ether is worthwhile to comment since it is the only one which leads to **16-72a** the only member of phenyl vinyl cyclopentane series which possess a *Z*-propenyl moiety, although in low yield, but with high enantioselectivity in these carbocyclization reaction.

Performing the reaction of **107(*Z*)** in THF at higher temperature (0 instead of −78 °C) leads to an increase of the minor isomer **16-67a** that possesses a *cis*-stereochemistry between the phenyl and the propenyl moiety at the expense of **16-71b** (Scheme 130, entry a, compared to Scheme 144, entry a). The formation of **16-67a** can be rationalized by assuming that the formation of the **31-45(*E*)** intermediate involves a *syn*-coplanar S_N2' process (Scheme 145, entry a).

Increasing the temperature (0 instead of −78 °C) in the reaction involving **107(*E*)** in ether leads to an increased formation of **16-72a** bearing the *cis*-stereochemistry between the phenyl and the *Z*-propenyl moiety at the expense of **16-67a** (Scheme 145, entry b, compared to Scheme 144, entry d). The postulated intermediate **31-46(*E*)** involves a *syn*-coplanar process (Scheme 145, entry b) in which the benzylithium approaches the other face of the π-bond as compared as **31-45(*E*)** (Scheme 144, entry d).

3.02.4.4.2.7 Syntheses of 1-ethyl-2-phenyl cyclopentanes as model for the synthesis of 1-alkyl-2-aryl cyclopentanes

The methods described above allow the synthesis of 1,2-dimethylcyclopentyl)benzene **16-2** from 6-bromo-(2-phenylheptan-2 yl)(methyl)selane **30-8** (Scheme 28) and methyl-(2-phenylhept-6-en-2 yl)selane **30-6** (Scheme 25 and Table 7; Scheme 65), as a mixture of diastereoisomers (*de* 60 or 96%, respectively) which is highly solvent dependent.



Scheme 145

Extension of the latter reaction to produce 2-ethyl-(1-methylcyclopentyl)benzene **16-32** with high stereocontrol is not feasible since methyl(2-phenyloct-6-en-2 yl)selane **30-47** on reaction with butyllithiums provides little amount of the desired product besides phenyl cyclohexane **16-31** or cyclopent(a)indene **93-1** when the reaction is carried out in THF-hexane and in pentane, respectively, (Scheme 110, entries a and c).[166]

Other strategies to produce 2-ethyl-(1-methylcyclopentyl)benzene **16-32** involve (1) formal methylation of (2-methyl-2-phenylcyclopentyl)methyllithium **15-2** (Scheme 146, entry c), (2) reduction of (1-(2-methyl-2-phenylcyclopentyl))ethyl (phenyl)sulfane **16-52a** or **16-52b** or their mixture or **16-53a** or **16-53b** or their mixture prepared by (a) methylation of ((2-methyl-2-phenylcyclopentyl)(phenylthio methyllithium **15-13** (Scheme 146, entry b) or (b) protonation of 1-(2-methyl-2-phenylcyclopentyl(phenylthio)methyllithium **15-17** (Scheme 146, entry c), or (3) hydrogenation of 1-methyl-1-phenyl-2-vinyl cyclopentane **16-65** itself prepared (a) from **30-77** as the result of a carbocyclization reaction (Scheme 146, entry d) or (b) on Wittig reaction on the aldehyde **114** resulting from the ozonolysis of **16-67** or **16-71** (Scheme 146, entry e).

The latter is particularly interesting since it not only allows the diastereoselective synthesis of *cis*- or *trans*-1-methyl-1-phenyl-2-ethyl cyclopentane **16-32**, but in each case to reach each of the two enantiomers selectively.

3.02.4.4.2.7.1 Syntheses of 1-ethyl-2-phenyl cyclopentanes by methylation of (2-methyl-2-phenylcyclopentyl)methyllithium

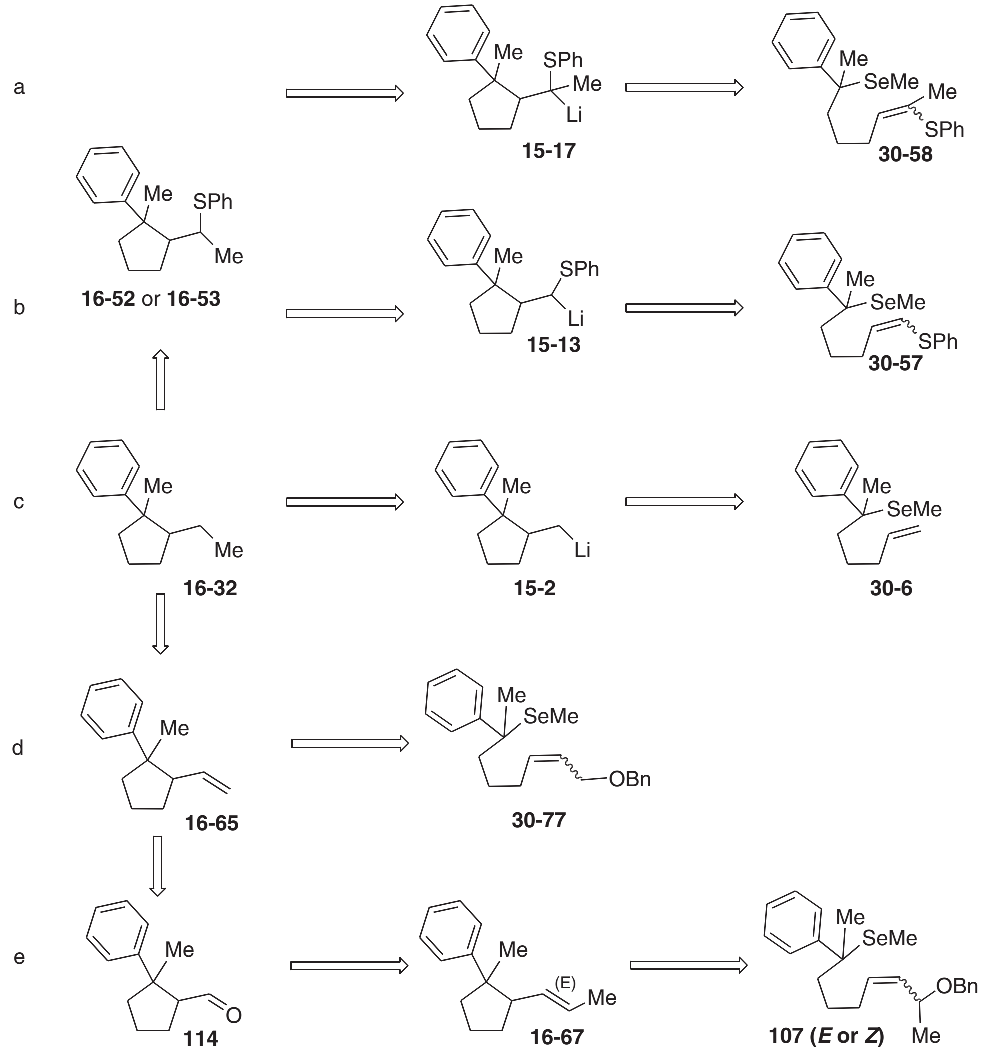
Reaction of (2-methyl-2-phenylcyclopentyl)methyllithium **15-2b** generated from methyl(2-phenylhept-6-en-2 yl)selane **30-6** and *t*-butyllithium in THF or ether, with a single equivalent of methyl iodide, does not lead to 1-phenyl-1-methyl-2-ethyl cyclopentane **16-32**, but instead to the product **33-7** resulting from the coupling of the related carbon framework (Scheme 147, entry a).[215] It suggests that the formation of the (2-methyl-2-phenylcyclopentyl)methyl iodide intermediate **16-73b(I)** is slow enough to allow its coupling with its precursor **15-2b**. This coupling can be prevented by reacting **15-2b** with a fourfold excess of methyl iodide which increases the rate of the lithium/iodine exchange producing (2-methyl-2-phenylcyclopentyl)methyl iodide **16-73b(I)** (Scheme 147, entry b).[215] Apparently the stereoisomeric (2-methyl-2-phenylcyclopentyl)methyllithium **15-2a** generated in ether at room temperature, reacts faster with methyl iodide to produce (2-methyl-2-phenylcyclopentyl)methyl iodide **16-73a(I)** with good stereocontrol (*cis* between the phenyl and the adjacent iodomethyl group), even if one equivalent of methyl iodide is used (Scheme 147, entry c).[215]

This Li/I exchange is probably due to the concomitant formation of insoluble methyllithium that move the equilibrium toward its formation and that of **16-73(I)**.[215–217]

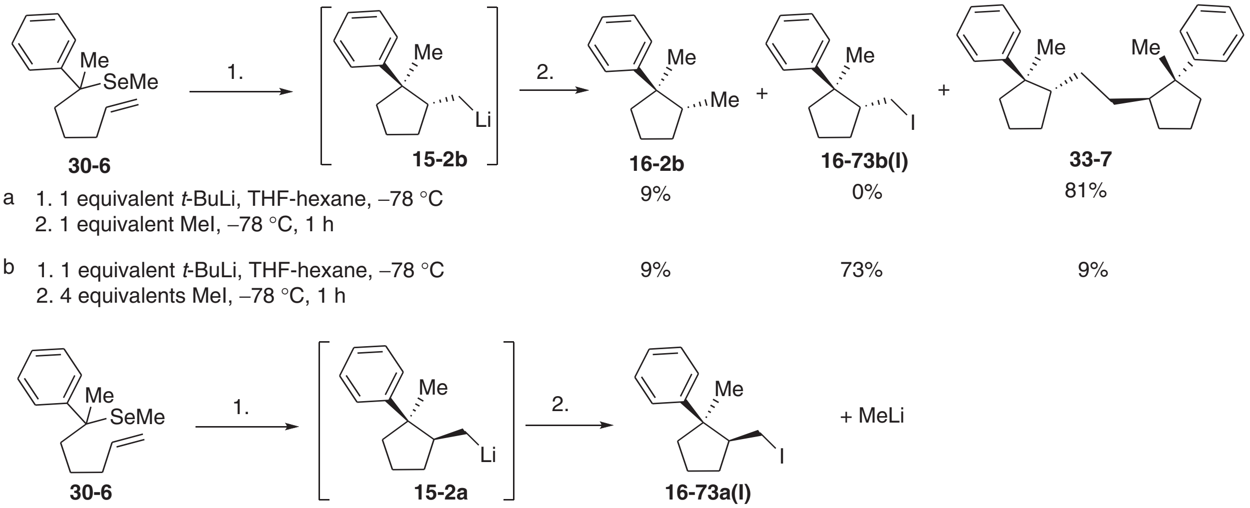
Performing the methylation on the corresponding cyano-cuprate **16-74a** leads to **16-32a** in extremely good yield (Scheme 148).[204]

Otherwise, lithium/halogen exchange has even been more efficiently achieved using dibromomethane instead of methyl iodide.[215,217] Reaction of (2-methyl-2-phenylcyclopentyl)methyl bromides **16-73(Br)** with lithium dimethyl cuprate allows the synthesis of each of the two stereoisomers of 1-phenyl-1-methyl-2-ethyl cyclopentanes **16-32** in good yield with very good stereocontrol depending on the solvent used to generate **15-2** (Scheme 149).[215]

Another and straightforward approach to each of the two stereoisomers of **16-32** was successfully achieved by trapping the organolithium compound **15-2** resulting from the carbocyclization of **30-6** carried out in THF (Scheme 150, entry a) or ether (Scheme 150, entry b) by dimethyl sulfate instead of methyl iodide (compared to Scheme 147).[215] It is effectively known that dimethyl sulfate does not exhibit the propensity of methyl iodide to exchange its leaving group with the metal of the organometallics.



Scheme 146

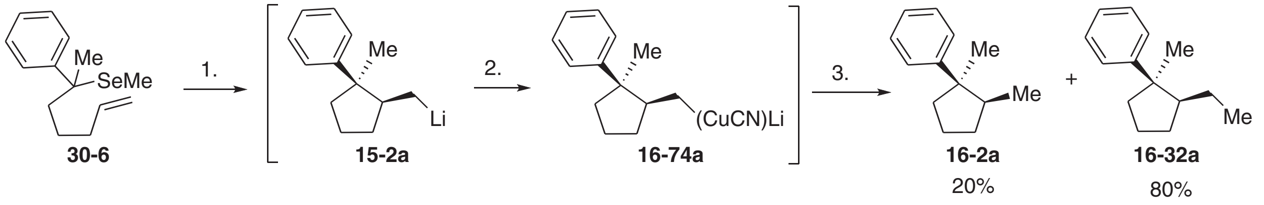


a 1. 1 equivalent *t*-BuLi, THF-hexane, –78 °C
2. 1 equivalent MeI, –78 °C, 1 h
9% 0% 81%

b 1. 1 equivalent *t*-BuLi, THF-hexane, –78 °C
2. 4 equivalents MeI, –78 °C, 1 h
9% 73% 9%

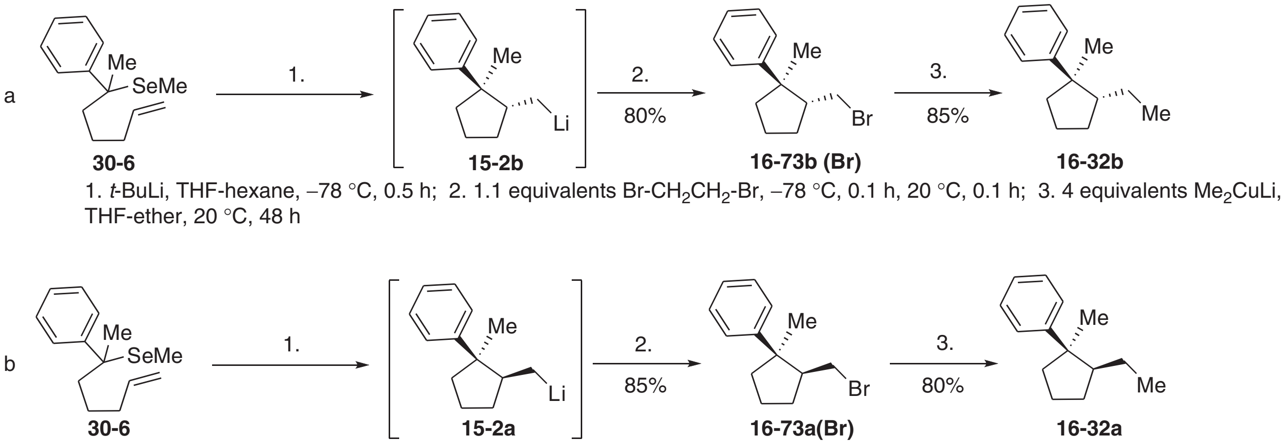
c
1. 1 equivalent *t*-BuLi, ether-hexane, –25 °C, 0.5 h
2. 1 or 4 equivalents MeI, –78 °C, 1 h
50%

Scheme 147



1. 1 equivalent *t*-BuLi, hexane, –20 °C, 1 h; 2. 1 equivalent CuCN, THF, 20 °C to –25 °C, 0.2 h; 3. 2 equivalents MeI, –25 °C, 1 h

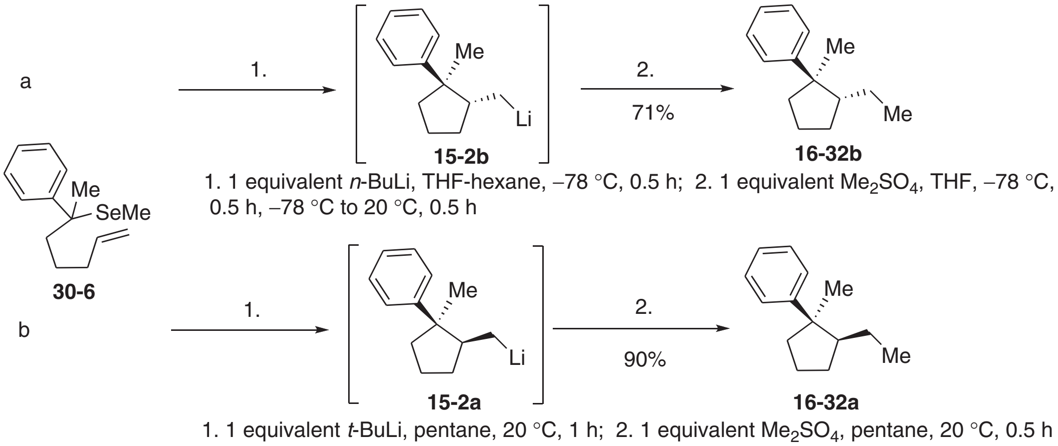
Scheme 148



a: 1. *t*-BuLi, THF-hexane, –78 °C, 0.5 h; 2. 1.1 equivalents Br-CH_2CH_2-Br, –78 °C, 0.1 h, 20 °C, 0.1 h; 3. 4 equivalents Me_2CuLi, THF-ether, 20 °C, 48 h

b: 1. *t*-BuLi, ether-hexane, –30 °C, 0.5 h; 2. 1.1 equivalents Br-CH_2CH_2-Br, –78 °C, 0.1 h, 20 °C, 0.1 h; 3. 4 equivalents Me_2CuLi, THF-ether, 20 °C, 48 h

Scheme 149

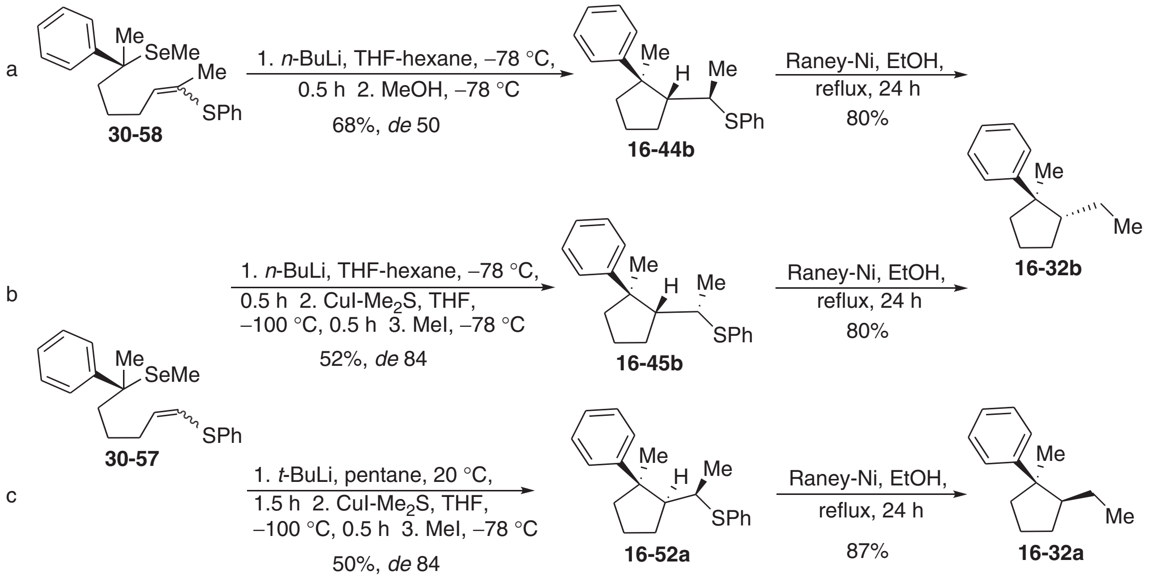


a: 1. 1 equivalent *n*-BuLi, THF-hexane, –78 °C, 0.5 h; 2. 1 equivalent Me_2SO_4, THF, –78 °C, 0.5 h, –78 °C to 20 °C, 0.5 h

b: 1. 1 equivalent *t*-BuLi, pentane, 20 °C, 1 h; 2. 1 equivalent Me_2SO_4, pentane, 20 °C, 0.5 h

Scheme 150

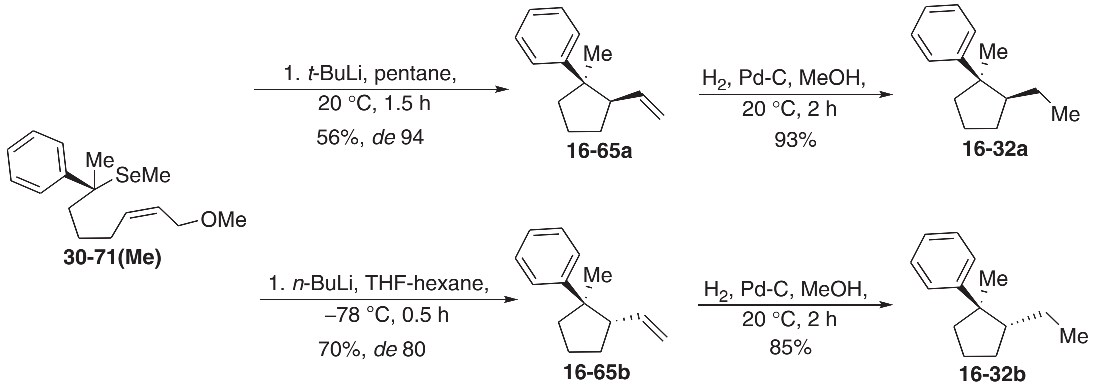
Another approach involves the use of ω-alkenyl benzylselenides bearing a thiophenyl group on the carbon–carbon double bond and ideally a methyl group such as in **30-58** (Scheme 151, entry a). Carbocyclization carried out in THF, followed by protonation leads to the corresponding racemic phenyl sulfide **16-52b** with good stereocontrol at each of the chiral centers. Hydrogenation of **16-52b**, using Raney-nickel, allows the high yield synthesis of **16-32b** (Scheme 151, entry a).[202,215] However, this strategy does not apply to the synthesis of its stereoisomer **16-32b** since the same protocol applied to **30-58** does not provide **16-53** if the reaction is carried out in pentane instead of THF (Scheme 119, entry b).[202,215]



Scheme 151

An alternative method disclosed in Scheme 151 allows the synthesis of the missing stereoisomer **16-32a** possessing the *cis*-stereochemistry between the phenyl and the ethyl group on the cyclopentane ring. It takes advantage of the stereoselective formation of **16-52a** by carbocyclization in pentane of **30-57** that misses the vinylic methyl group present in **30-58**. The desired synthesis then requires the methylation of the carbanion resulting from the carbocyclization followed by reaction with Raney-nickel (Scheme 151, entry c).[188,204] This approach has been successfully extended to the synthesis of **16-32b** as disclosed in Scheme 151, entry b.[188,204] The stereochemistry at the carbon bearing the methyl group and the thiophenyl group is different depending on the nature of the group introduced (Scheme 151, compare entry a to b), but this has not to be taken into account for the purpose of this study since the stereochemistry at the *exo*-carbon is destroyed during the reduction step.

Another synthesis implies the use of the benzylselenide **30-71(Me)** bearing a methoxy group at the allylic position, which lead to each of the two stereoisomeric 1-phenyl-2-vinyl cyclopentanes **16-65a** and **16-65b** depending on the solvent used (Schemes 136 and 152). Those are then efficiently and stereoselectively transformed to **16-32a** and **16-32b** by palladium catalyzed hydrogenation of their carbon–carbon double bond (Scheme 152).



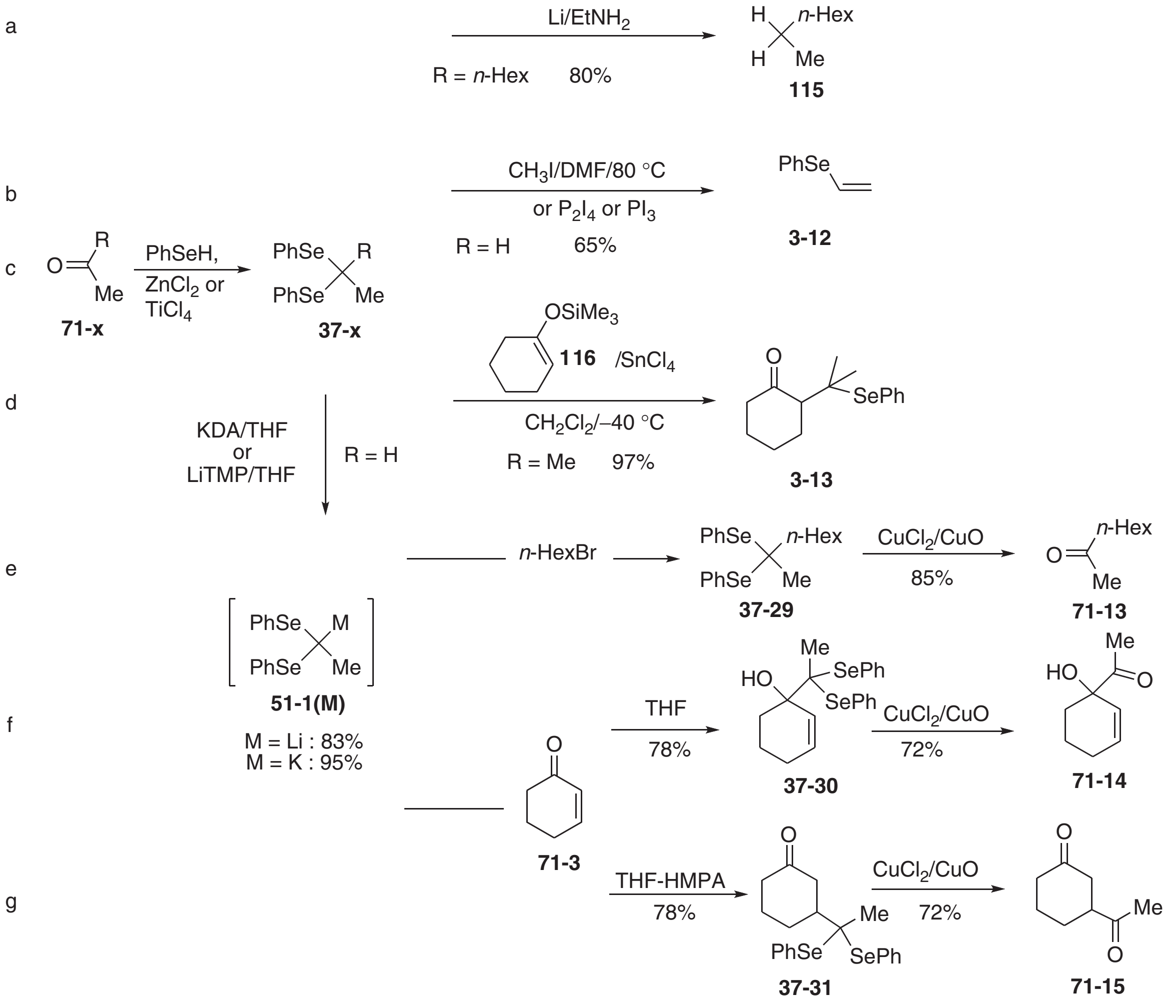
Scheme 152

Application of this reaction to **16-71** or **16-67** (Scheme 144) implies ozonolysis of the resulting **16-67** and **16-71** followed by a Wittig reaction involving ethylidenetriphenylphosphorane or a metathesis reaction which should allow the synthesis of each of the four enantiomers of **16-32**.

3.02.5 Conclusion

The authors have mainly described the reactivity of selenides and selenoacetals with special emphasis to benzyl selenides and selenoacetals derived from aromatic carbonyl compounds, toward butyllithiums, elemental lithium, and related lithium arenides. Some stereoelectronic features related to the kinetic formation of resulting organolithium compounds in the 1,3-diselenane series have been also described. The reactivity of benzyllithiums and related α-seleno-benzyllithiums has also been extensively described.

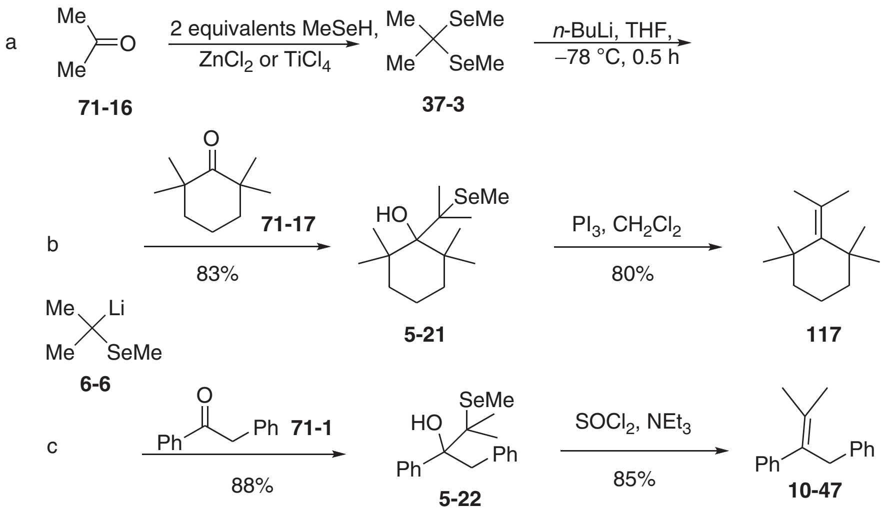
α-Selenoalkyllithiums are available in high yielding two steps from aldehydes or ketones which involves (1) the synthesis of selenoacetals from aldehydes or ketones using an acid catalyst such as zinc chloride or titanium tetrachloride (Scheme 153, entry c; Scheme 154, entry a)[25] and (2) their cleavage by alkyllithiums (Scheme 154, entry a).[12,20]



Scheme 153

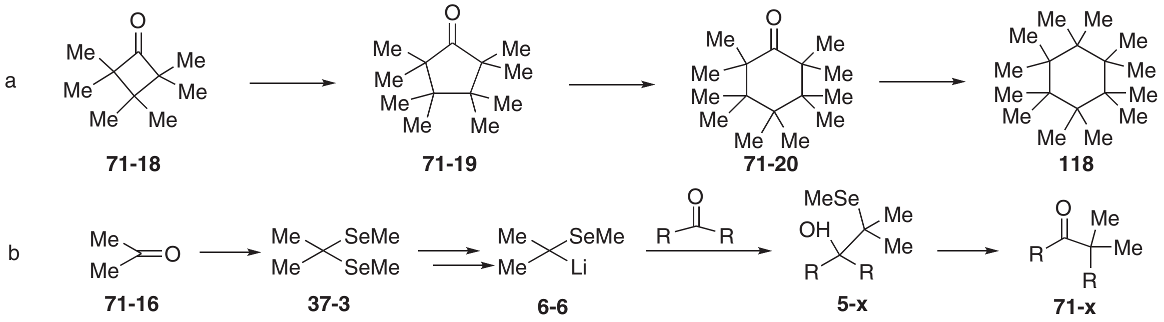
Selenoacetals can be produced alternatively by alkylation of bis(seleno)alkylmetals themselves prepared by Se/Li exchange from orthoselenoesters and butyllithiums[90] or by metallation of selenoacetals derived from the first members of aliphatic aldehydes and all the aromatic ones with LiTMP or KDA (Scheme 153, entry e).[19,58,63,89,162–165]

Selenoacetals (1) are reduced to alkanes by lithium in liquid ammonia[218] or tributyltin hydride[219,220] (Scheme 153, entry a), (2) are transformed to vinylselenides using methyl iodide acting as an alkylating agent and β-elimination on the resulting selenonium intermediate (Scheme 153, entry b),[221] (3) play the role of alkylating agent toward trimethylsilyloxy cyclohexene **116** (Scheme 153, entry d),[222] and (4) are transformed to carbonyl compounds on reaction with Lewis acids or oxidants in the presence of water (Scheme 153, entries e–g).[223,224] Therefore α-selenoalkylmetals can play the role of acyl anion equivalents' in the reaction which involve their alkylation or reactions with enones which can be directed selectively, by proper selection of the solvent (THF or THF-HMPA), either on their carbonyl group or on their carbon–carbon double bond, respectively (Scheme 153, entries e–g).[90,225–228]



Scheme 154

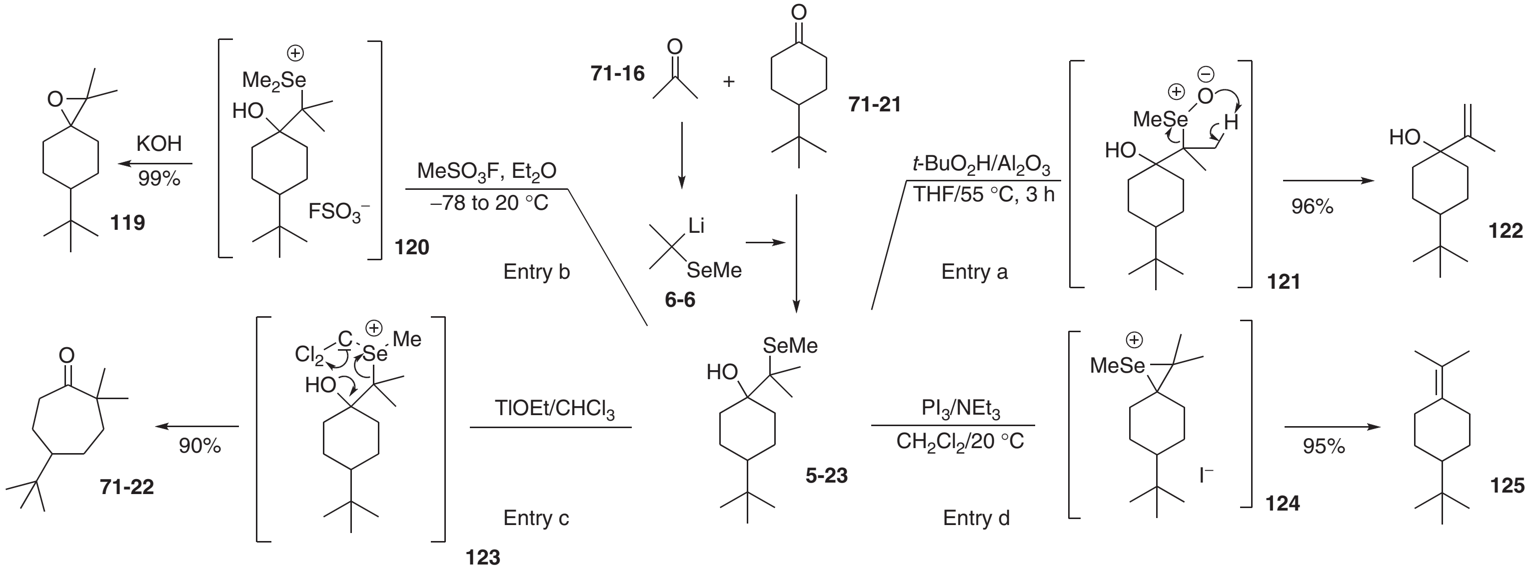
α-Selenoalkyllithiums possess an exceptional aptitude to add across the carbonyl group of carbonyl compounds, even those that possess (1) hindered carbonyl groups such as 2,2,6,6-cyclohexanone **71-17** (Scheme 154, entry b)[213] or permethyl cyclohexanone **71-18** (Scheme 155, entry a)[229] or (2) highly enolizable carbonyl compounds such as deoxybenzoine **71-1** (Scheme 154, entry c).[230]



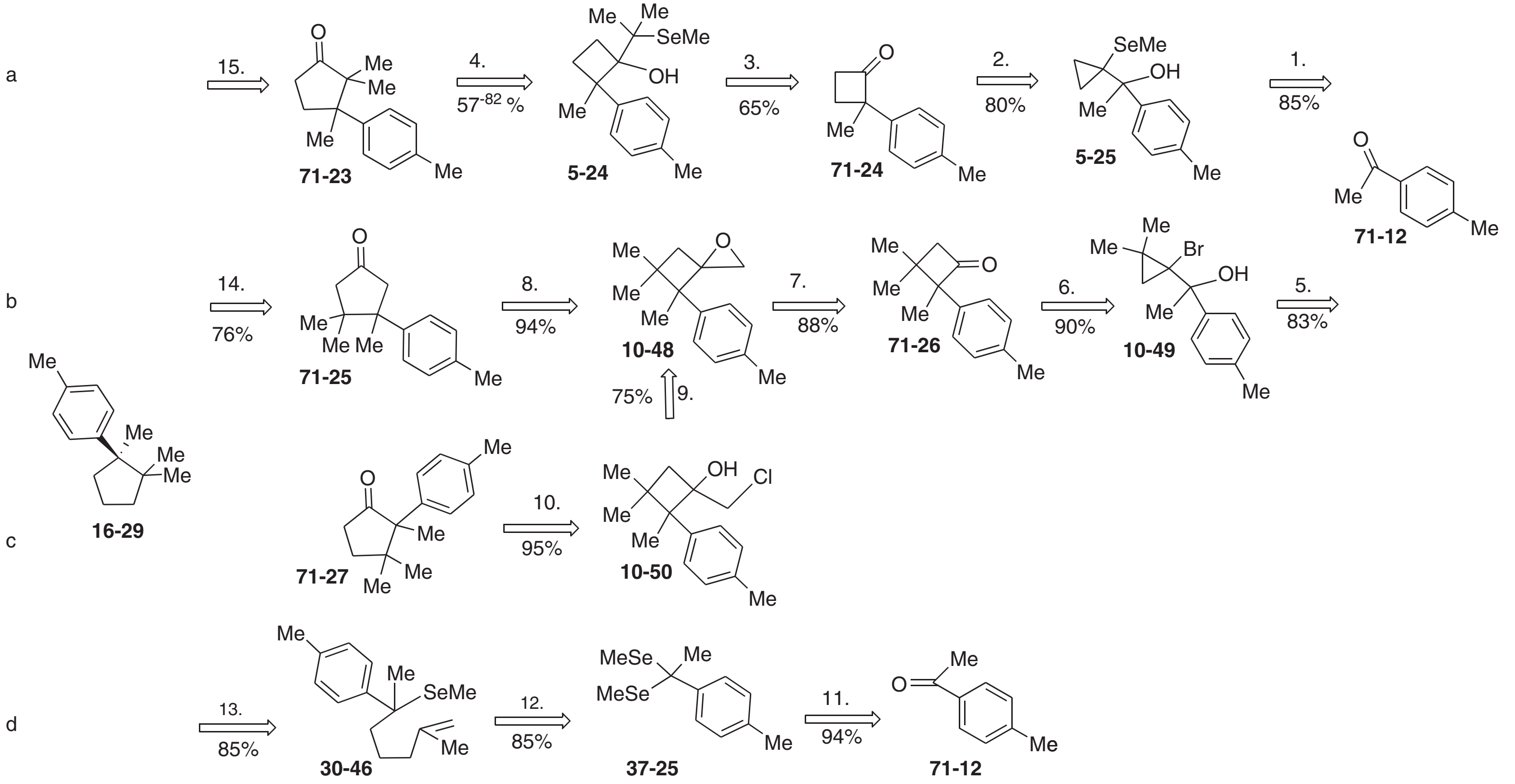
Scheme 155

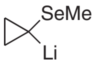
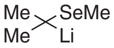
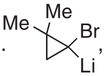
The value of the exceptional reactivity reported above is enhanced by the exceptional reactivity of the resulting β-hydroxyalkyl selenides,[219,231] especially those belonging to the methylseleno series which is summarized in Scheme 156. This is directly related to the possibility to selectively activate the soft methylseleno or the hard hydroxyl- moiety of β-hydroxyalkyl methylselenides. Thus, β-hydroxyalkyl methylselenides have been transformed to (1) allyl alcohols by selective tandem selenoxide formation-elimination reaction (Scheme 156, entry a),[219,231] (2) epoxide synthesis through tandem selenonium formation and intramolecular substitution promoted by reaction of potassium hydroxide[219] or thalium ethoxide in chloroform (Scheme 156, entry b and Scheme 157, entry b),[232] (3) ketone formation through a pinnacolic type rearrangement implying dichlorocarbene (produced, for example, from thallium ethoxide and chloroform (Scheme 155, entry b; Scheme 156, entry c; Scheme 157, entries a and b),[233–235] and to (4) olefins on reaction with phosphorus triiodide or diphosphorous tetraiodide which transform the hydroxyl moiety to a better leaving group and favor the iodide reaction selectively on the soft selenium atom of the methylseleniiranium intermediate (Scheme 154, entries b and c; Scheme 156, entry d).[219,236–239]

Benzyllithiums and α-selenobenzyllithiums are not as nucleophilic toward carbonyl compounds as α-selenoalkyllithiums (Scheme 71, entries a and b) and exhibit a higher propensity to add 1,4 than 1,2 toward cyclohexanone (Scheme 71, entry c).[21] Benzyllithiums and α-selenobenzyllithiums are, however, by far more nucleophilic toward alkyl halides including sec-alkyl derivatives and epoxides than α-selenoalkyllithiums. They also possess the exceptional propensity to add to 'unactivated carbon –carbon double bond.' Scheme 157 discloses three competing syntheses of cuparene **16-29** and four syntheses of three isomers of cuparenone **71-23** (Scheme 157, entry a), **71-25** (Scheme 157, entry b), and **71-27** (Scheme 157, entry c) all of which use *p*-methyl acetophenone **71-12** as an electrophilic- (Scheme 157, entries a and b) or nucleophilic- (Scheme 157, entries d) starting material and involves at one or several occasions α-selenoalkyl- or benzyllithiums.[43,240,241]

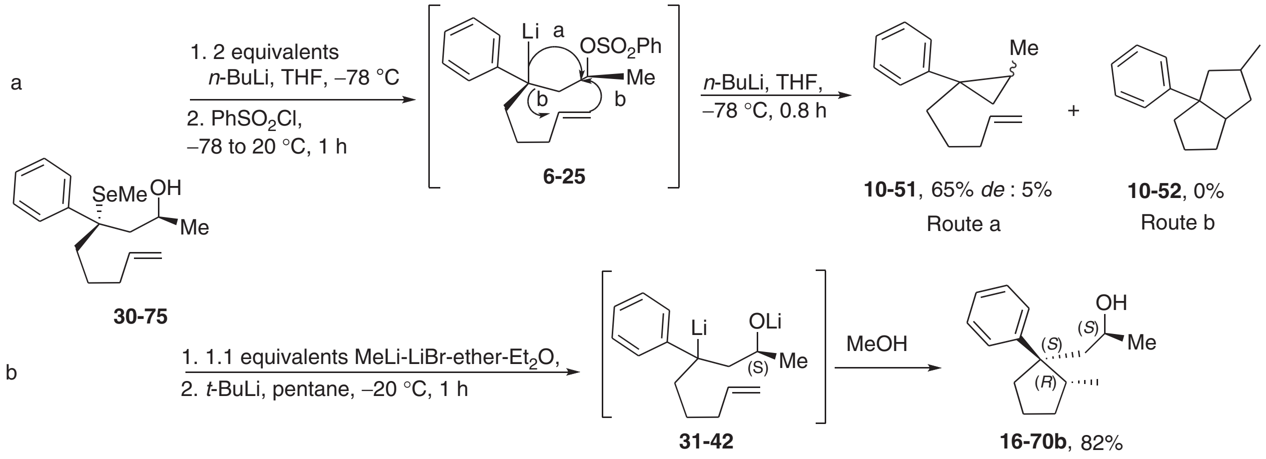

71-16
71-21
6-6
5-23
Li
SeMe
HO
t-BuO2H/Al2O3
THF/55 °C, 3 h
Entry a
MeSe
O
H
121
96%
122
MeSO3F, Et2O
−78 to 20 °C
Entry b
Me2Se
FSO3−
120
KOH
99%
119
TlOEt/CHCl3
Entry c
Cl2
C
Se
Me
123
90%
71-22
PI3/NEt3
CH2Cl2/20 °C
Entry d
I−
124
95%
125

Scheme 156

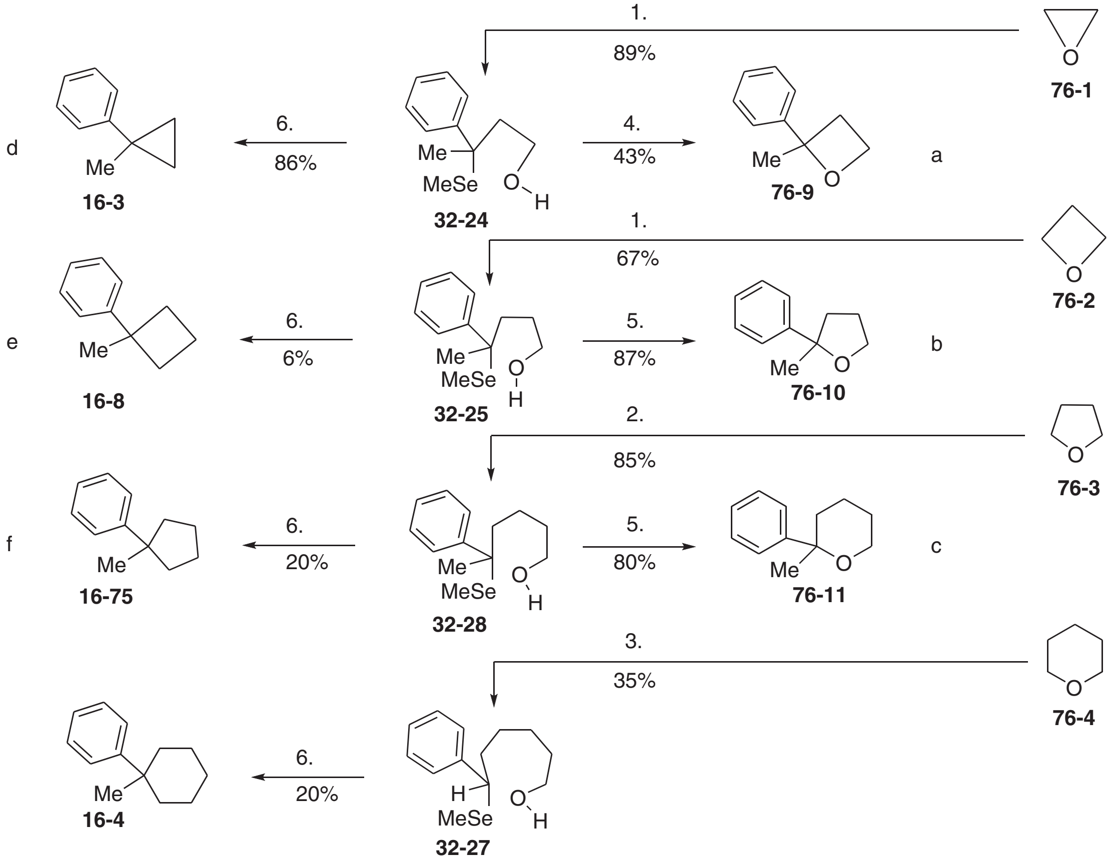


1.  THF, –78 °C; 2. ptoluene sulfonic acid, benzene, reflux; 3. , THF, –78 °C; 4. (a) $MeSO_3F$, ether, 82%, (b) EtOTl, $CHCl_3$, 57%, (c) $AgBF_4$-Al_2O_3, CH_2Cl_2, 69%; 5. , THF, –78 °C; 6. (a) *t*-BuOK, THF 7, (b) $MeSeCH_2Li$; 7. EtOTl, $CHCl_3$, 20 °C, 15 h; 8. LiI-12-crown-6, dioxane, 80 °C; 9. $BeCl_2$, THF, 20 °C, 20 h; 10. $AgBF_4$-Al_2O_3, 20 °C, 15 h; 11. 2 equivalents MeSeH, 0.33 equivalent $TiCl_4$, –50 °C, 0.25 h, 20 °C, 2 h; 12. (a) *n*-BuLi, THF-pentane, –78 °C, 0.5 h (b) 6-chloro-2-methyl-1-hexene, –78 to 20 °C; 13. (a) *t*-BuLi, pentane, 20 °C, 0.3 h (b) MeOH; 14. NH_2NH_2, –2 HCl, NH_2NH_2-H_2O, ethylene glycol; 125 °C, 2 h, 220 °C, 3 h; 15. NH_2NH_2, ethylene glycol, 185 °C, 2 h, 80 °C, 4 h.

Scheme 157



Scheme 158



1. (a) 1-phenyl-1-methylselenoethyllithium, THF-hexane, –78 °C, 0.25 h, (b) 20 °C, 1 h, (c) H_3O^+; 2. (a) 1-phenyl-1-methylselenoethyllithium, (b) 1.2 equivalents BF_3-Et_2O, –78 °C, 0.25 h (b) 20 °C, 1 h, (c) H_2O; 3. (a) 1-phenyl-1-methylselenomethyllithium, 1.2 equivalents BCl_3, –78 °C, (b) 0.5 h, 20 °C,1 h, (c) H_2O; 4. SO_2Cl_2, CH_2Cl_2, 20 °C, 65 h; 5. 1.3 equivalents $(CF_3CO_2)_2Hg$, CH_2Cl_2, 20 °C, 18 h; 6. (a) *n*-BuLi, THF-hexane, –78 °C, $PhSO_2Cl$, THF, 20 °C, 1 h (b) *n*-BuLi, THF-hexane, –78 °C, 0.5 h; (c) 20 °C, 0.5 h.

Scheme 159

The first three approaches imply the stepwise incremental ring expansion reactions from 'no cycle' to three-, four-, and five-membered cycles as described in Scheme 155 and Scheme 156, entry c.[242] They produce cyclopentanones whose carbonyl has been reduced to a methylene group by Huang-Milon modified Wolf-Kishner reaction to produce cuparene (Scheme 157, entries a–c).[243–245]

Alternative methods, disclosed in Scheme 157, use the aptitude of heterosubstituted benzyllithiums and benzyllithiums to be (1) alkylated using an alkylhalide and (2) by a addition across a carbon–carbon double bond. The reaction produces in the same step a new carbon–carbon bond substituted by two quaternary carbons (Scheme 157, entry d).[43]

As disclosed above, benzyllithiums possess a great aptitude to react on a carbon–carbon double bond at ω-position to produce aryl cylopentanes and on alkylsulfonates at γ position to produce arylcyclopropanes. The formation of the latter is exclusively observed if both opportunities are available competitively[116] (Scheme 158).

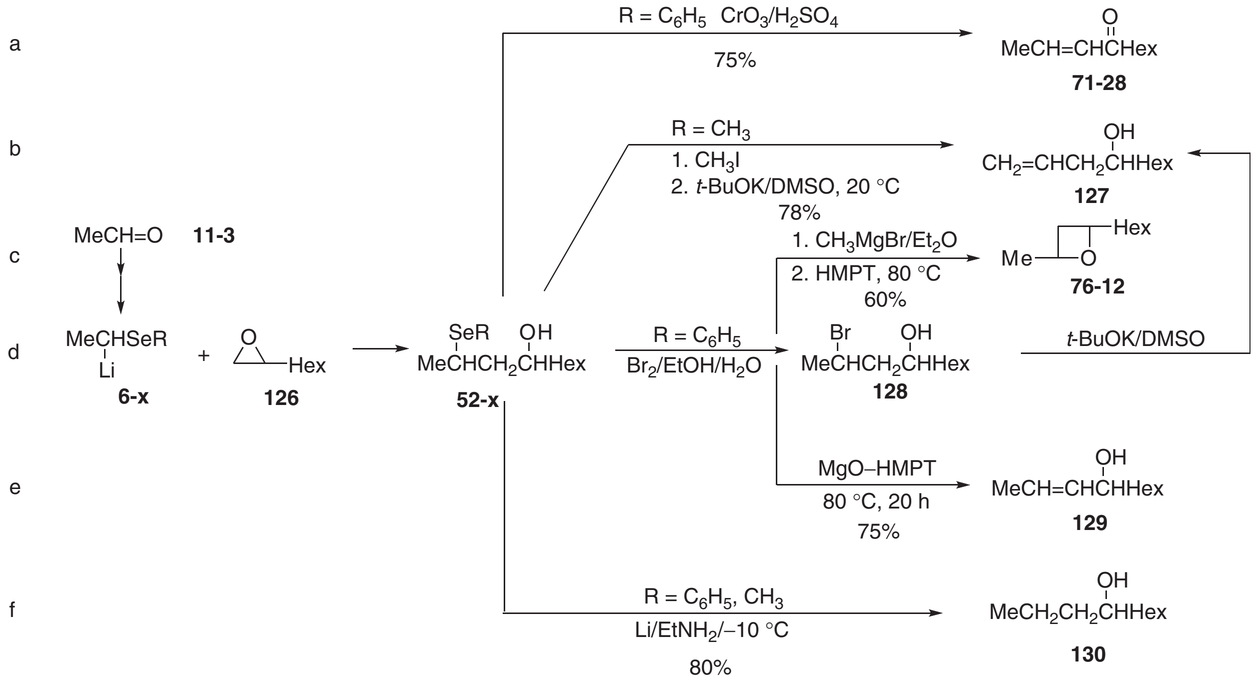
Benzyl methyl selenides bearing an alkoxy group on the side chain and available by reaction of α-methylseleno-benzyllitiums with (1) carbonyl compounds, (2) epoxides,[152,156] (3) oxetanes,[116] and for related results,[157] (4) THFs have been used to produce (1) epoxides, (2) oxetanes,[116] (3) tetrahydrofurans,[153] (4) tetrahydropyrans,[153] respectively (Scheme 159, entries a–c) or (1′) cyclopropanes, (2′) cyclobutanes, (3′) cyclopentanes and (4′) cyclohexanes by carbocyclization of their sulfonates, respectively (Scheme 159, entries d–f).

Heterocycle synthesis has been achieved by:

1. (a) sequential alkylation of the selenium atom of hydroxyl-alkyl selenides with methyl iodide in the absence or in the presence of silver tetrafluoroborate or on reaction of methyl fluorosulfonate (Magic methyl) followed by (b) treatment of the resulting hydroxyalkyl selenonium salt with a base such as potassium hydroxide of potassium *t*-butoxide.[1,2,12–14,16,219,230,244,246] This method has been used for the synthesis of epoxides[1,2,12–14,16,219,230,246,247] and more rarely for that of THFs[112,157,204] or tetrahydopyrans,[153]
2. reacting a carbene generated from chloroform and potassium hydroxide, under phase transfer catalyst or thallium ethoxide.[232] Those reactions may present some limitations due to competing pinacolic type rearrangement, which occurs when the carbon bearing the seleno moiety is fully alkyl substituted,[232]
3. reacting mercury bis(trifluoroacetate) ($((CF_3CO_2)_2Hg))$) which has been successfully used for the synthesis of THFs and tetrahydropyran from the related hydroxyalkyl benzylselenides (Scheme 159, entries b and c).[153]

The carbocyclization reactions involving benzene sulfonates proved, except those producing cyclopropanes,[152,156] by far less efficient than those involving the related halides (Scheme 159, entries d–f compare to Scheme 89, entries c and e).[116]

Finally, Scheme 160 summarizes some reactions implying γ-hydroxyalkyl selenides as a pendant to the reactions disclosed in Scheme 156 for β-hydroxyalkyl selenides.[61,155,157,248]



Scheme 160

These results clearly show the potentiality of selenium compounds in organic synthesis.

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3.03 Alkylation of α-Sulfur-Containing Carbanions

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3.03.1 **Introduction** 157
3.03.2 **Alkylation of α-Thiocarbanions** 157
3.03.2.1 Alkyl and Allyl α-Sulfenyl Carbanions 157
3.03.2.2 Vinyl α-Sulfenyl Carbanions 163
3.03.3 **Alkylation of α-Sulfinyl Carbanions** 164
3.03.3.1 Alkyl and Allyl α-Sulfinyl Carbanions 164
3.03.3.2 Vinyl α-Sulfinyl Carbanions 168
3.03.4 **Alkylation of α-Sulfonyl Carbanions** 170
3.03.4.1 α-Metalloalkyl Sulfones 171
3.03.4.2 α-Metalloallyl Sulfones 176
3.03.4.3 α-Metallo α-Heterosubstituted Alkyl Sulfones 184
3.03.4.4 α-Metallovinyl Sulfones 185
3.03.5 **Alkylations of Sulfoximinoyl Carbanions** 187
3.03.5.1 α-Metalloalkyl Sulfoximines 187
3.03.5.2 α-Metallovinyl Sulfoximines 190
3.03.6 **Alkylation of Sulfonates, Sulfonamides, and Sulfur Ylides** 191
3.03.6.1 Sulfonates and Sulfonamides 191
3.03.6.2 Sulfur Ylides 191
3.03.7 **Alkylation of Carbanions Bearing Two Geminal Sulfur Atoms** 193
3.03.7.1 Dithioacetals and Dithioketals 193
3.03.7.2 Compounds Bearing Sulfoxides and Sulfoximines 199
3.03.7.3 Compounds Bearing Sulfones 200
References 203

3.03.1 Introduction

The chemistry of α-sulfur stabilized carbanions has suffered a continuous expansion in the past 20 years.[1] There are excellent reviews and books that cover general aspects either of the preparation or the reactivity of compounds bearing sulfur moieties (*see* Chapters 6.04, 6.17, 7.28, and 8.15).[2–6]

α-Sulfur carbanions are versatile intermediates[7–9] and have found applications in the synthesis of many natural and bioactive products (*see* Chapter 1.12). In particular, the chemistry of sulfoxides,[10–18] sulfones,[19–23] sulfoximines,[24,25] as well as geminal disulfur compounds[26–29] such as dithianes[30,31] has been widely exploited. Their extensive use has brought about the commercial availability of some simple compounds precursors of α-sulfur carbanions and some of them are gathered in common data bases of organic reagents.[32]

The scope of this chapter is the alkylation of α-sulfur-containing carbanions primarily with alkyl halides and sulfonates, epoxides, and aziridines, as well as, some transition metal-catalyzed alkylations with allylic systems from 1990 to 2011. The chapter excludes alkylations of substrates that can be view as α-thioenolates. This review is not intended to be an exhaustive summary of all the existing examples of the covered material. Apologies to the authors of the valuable contributions that have not been included in the chapter.

3.03.2 Alkylation of α-Thiocarbanions

3.03.2.1 Alkyl and Allyl α-Sulfenyl Carbanions

One of the more useful reactivities of alkyl sulfides is based on their easy deprotonation to form α-sulfenyl carbanions that are trapped with electrophiles. Detailed computational studies support this behavior.[33,34] In particular, the alkylation of simple aryl alkyl sulfides with alkyl halides is a robust tool that has been used in different contexts such as in the construction of a library of serotonin reuptake transporter ligands (**Scheme 1**).[35] Comprehensive studies on the competitive lithiation at the alkyl chain versus ortho-metallation of the aromatic ring of alkyl aryl thioethers have demonstrated its utility.[36] Thus, treatment of (methylthio)benzene in Hexane/*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine (TMEDA) at 0 °C with excess of Bu^nLi produces the doubly lithiated species that is trapped by different electrophiles (E=MeI, MeOH) with no regioselectivity (**Scheme 1**).

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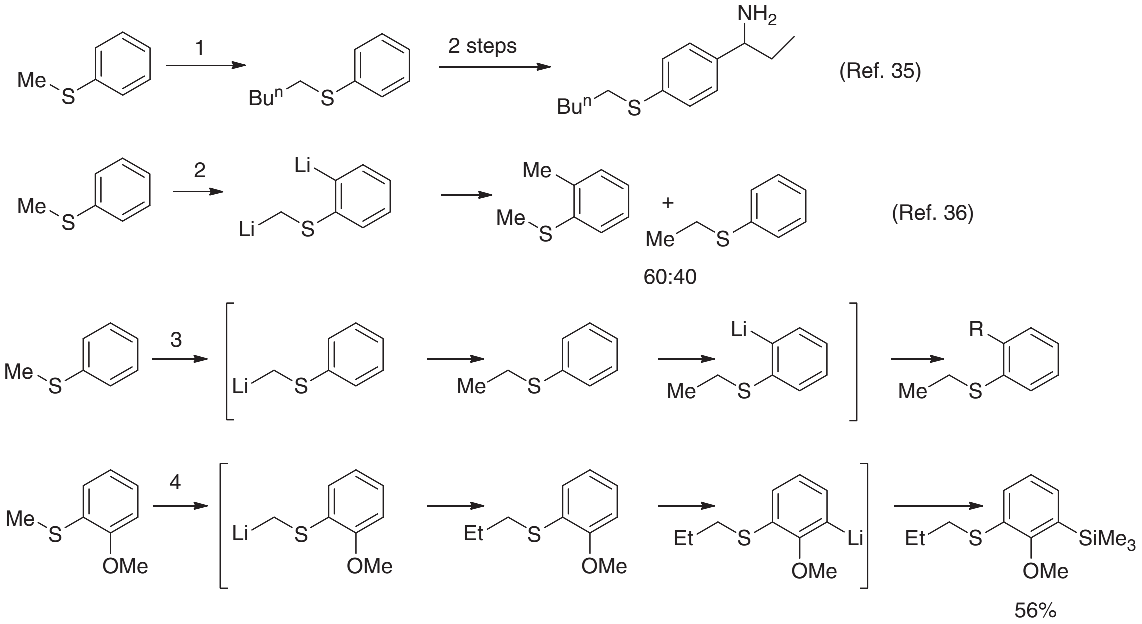
This problem can be overcome by two successive one-flask mono-metallations allowing for the introduction of two different electrophiles (MeI and RX) with complete regiocontrol. Different substitution at the aryl group of the starting thioether, such as in 2-(methylthio)-1-methoxybenzene, can alter the position of the ortho-metallation while maintaining the competitive pattern of both metallations (EtI, Me_3SiI). Alternatively, placing a branched alkyl group in the starting aryl alkyl thioether (Pr^iSAr instead of MeSAr) prevents the formation of the α-thiocarbanions under these conditions since alkyl substitution decreases the acidity of the alpha hydrogen. This decrease in reactivity of the higher alkyl thioethers homologs can be circumvented by using superbases as Bu^nLi/Bu^tOK mixtures for the deprotonation.[37]

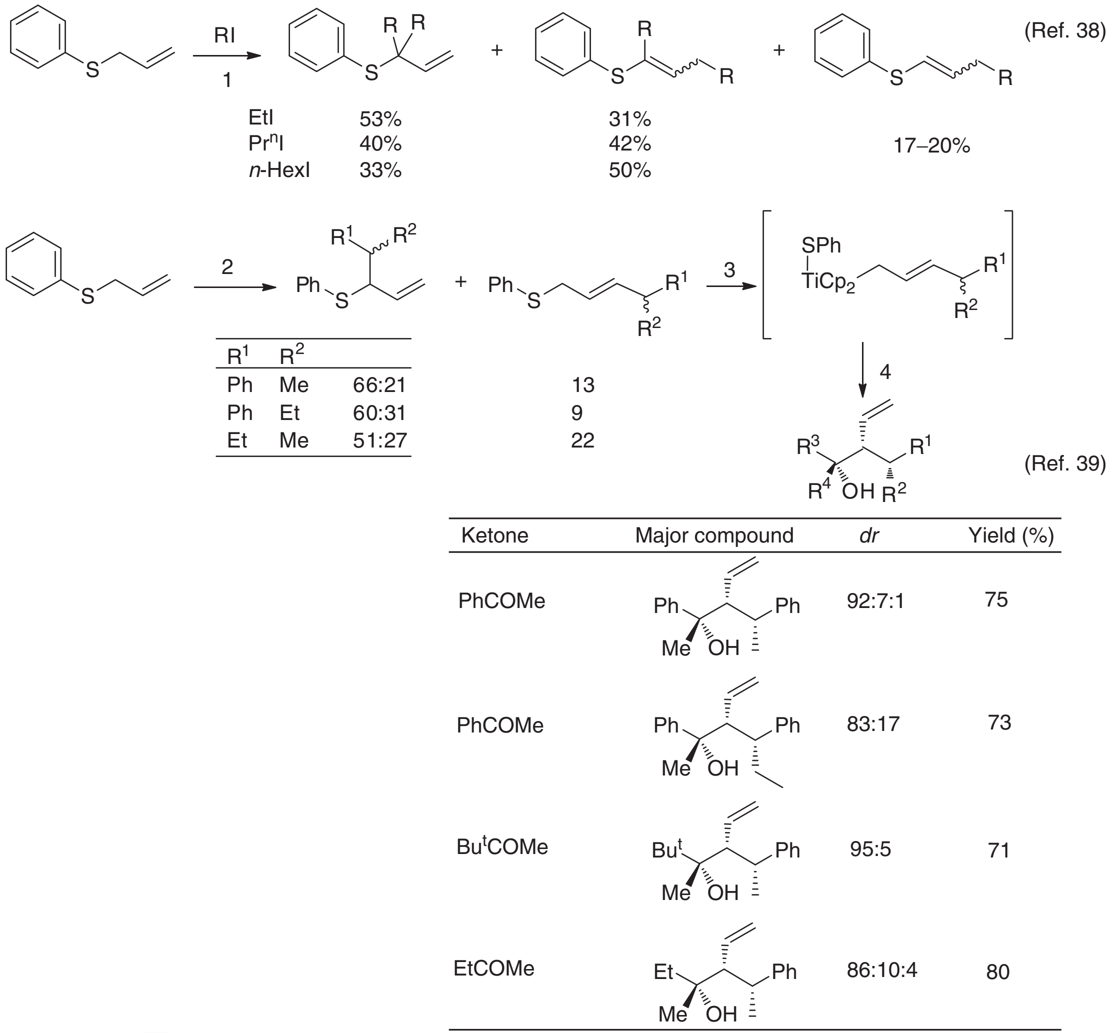


1. Bu^sLi, Bu^nI, THF, −78 °C, 3.5 h, 76%. 2. (a) 2 equivalents Bu^nLi, Hex/TMEDA, 0 °C. (b) MeI, 0 °C to r.t. 12 h, then MeOH. 3. (a) 1 equivalent Bu^nLi, Hexane/TMEDA, 0 °C. (b) MeI. (c) 1 equivalent Bu^nLi, Hex/TMEDA, 0 °C. (d) RX: MeI 75%, EtI 71%, PhSSPh 61%. 4. (a) 1 equivalent Bu^nLi, Hexane/TMEDA, 0 °C. (b) EtI. (c) 1 equivalent Bu^nLi, Hex/TMEDA, 0 °C. (d) $SiMe_3I$.

Scheme 1

Simple allyl aryl thioethers can be alkylated using alkyl halides and aminoalkoxide-activated $NaNH_2$. The use of these types of superbases allows for two consecutive deprotonations alpha to the sulfide albeit with low 1,3-regioselectivity for the subsequent alkylations (Scheme 2).[38] Bu^nLi as base also leads to alkylation with low regioselectivity[39]; however, in this latter example the mixture of alkylated sulfides was submitted to a regioselective desulfurizative titanation with a titanocene complex that rendered a regio- and diastereoselective addition to ketones giving finally tertiary homoallylic alcohols with multiple chiral centers in good yields (Scheme 2). Aryl propargylic thioethers can also be alkylated under similar conditions and the alkylated compounds have served as starting materials in the synthesis of functionalized heterocycles.[40]

Epoxides are among the electrophiles more frequently used to trap α-thiocarbanions[41] (Scheme 3). An example involves the addition of methyl or benzyl sulfide anions, generated with Bu^nLi or Bu^tLi, to simple epoxides.[42] Refluxing the resulting alcohols with *p*-toluenesulfonic acid in toluene led to thiochromans through an intramolecular electrophilic aromatic substitution strongly influenced by the substitution in the carbinol chain. Epoxide alkylation of sulfide-derived carbanions has been frequently applied to the synthesis of natural products. Thus, the first total synthesis of (±)-sinulariol-B, a marine cembranoid relays in an intramolecular epoxide opening by a thioether-stabilized carbanion to create the macrocyclic structure.[43] Similarly, the synthesis of terpenoid (±)-norartemeseol has been accomplished by addition of an allyl thioether anion to ethylene oxide followed by acid induced cyclization to give a sulfide substituted tetrahydrofuran (THF).[44] Subsequent sulfide oxidation to sulfoxide, elimination, and epoxidation of the double bond produced a bicyclic oxirane that is converted into (±)-norartemeseol in two additional steps. The above allyl thioether alkylation has also been used in an approach to *cis*-sabinene and related structures that involves the creation of a cyclopropane fused to a cyclopentane skeleton.[45] Thus, the thioether resulting from the opening of ethylene oxide is transformed in two steps, iodide substitution and iodide/lithium exchange followed by addition to acrolein, in an acyclic allylic sulfide containing two double bonds. At this point, deprotonation at the allylic carbon with Bu^tOK/Bu^nLi and transmetallation with LiBr trigger an ene reaction with the distal double bond followed by an intramolecular displacement of the thiophenoxide anion to generate the cyclopropane ring. Finally, hydrogenation of the remaining double bond led diastereoselectively to (±)-*cis*-sabinene. Likewise, a



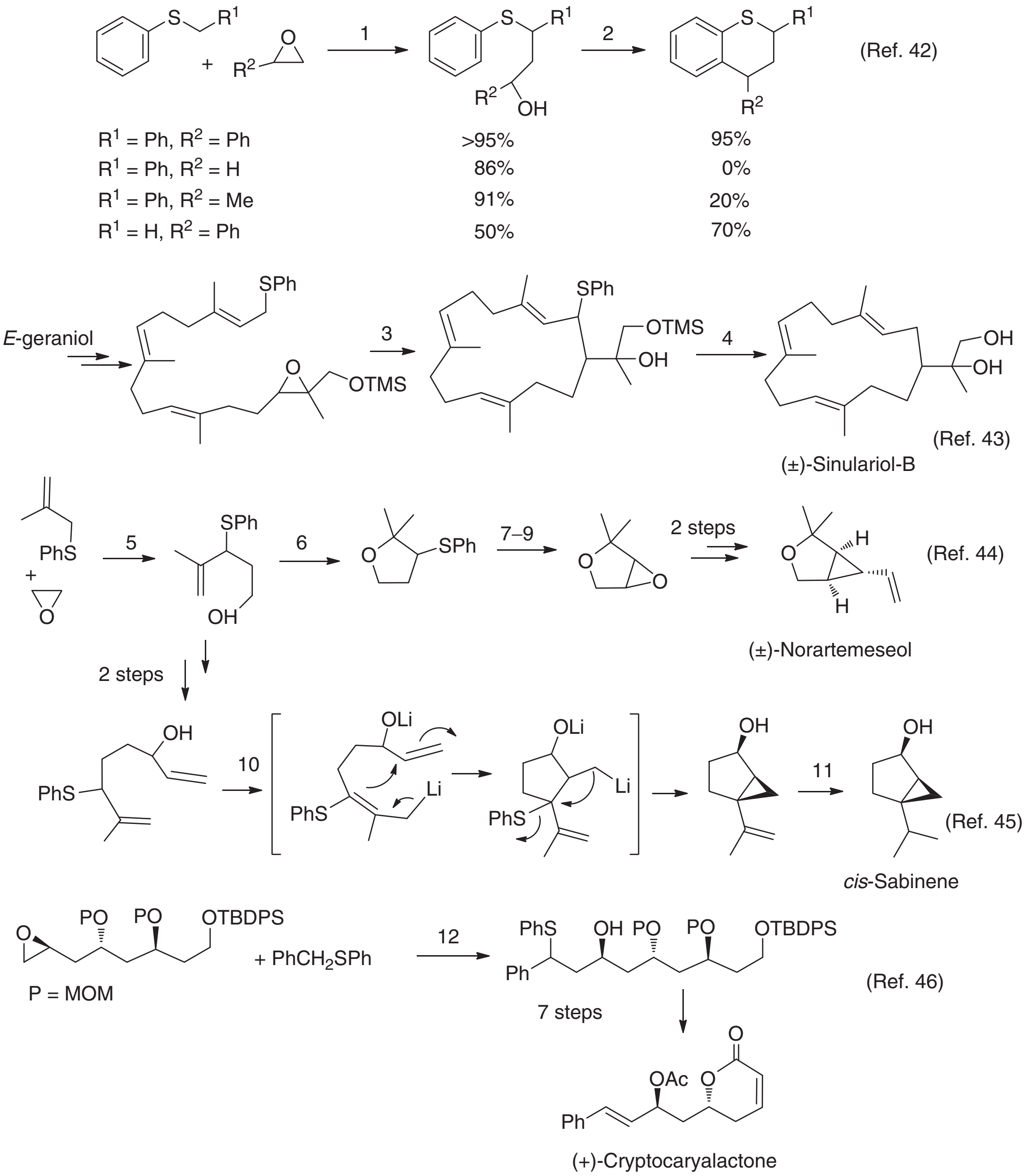
1. $NaNH_2$, piperidine-N–$(CH_2)_2OH$, THF, 45 °C, 2 h. 2. (a) Bu^nLi, –30 °C, THF, 1 h. (b) R^1R^2CHBr, –30 °C, THF, 2 h, 59% for R^1 = Ph, R^2 = Me. 3. Cp_2TiCl_2, Bu^nLi, –78 °C, 15 min, then 0 °C, 2 h. 4. ketone (R^3COR^4), –78 °C, THF, 18 h.

Scheme 2

diastereoselective approach to (+)-cryptocaryalactone implies the regioselective addition of the anion of benzyl phenyl sulfide, prepared with Bu^nLi to an optically active epoxide, bearing a polyhydroxylated chain.[46] The benzylic sulfide, thus generated was transformed into (+)-cryptocaryalactone in seven additional steps.

Carbanionic species alpha to sulfides have also been generated in more functionalized sulfides such as benzotriazolylalkyl methyl thioethers in the context of the synthesis of functionalized ketones. In particular, 1-(benzotriazol-1-yl)methyl methyl thioether,[47] prepared by a Pummerer reaction of dimethyl sulfoxide (DMSO)/Ac_2O and benzotriazol (BtH), was deprotonated with Bu^nLi in THF and reacted with a number of alkyl halides, R^1X (Scheme 4). The primarily alkylated products could suffer a second deprotonation and further react with a second alkyl halide (R^2I) as well as other electrophiles, such as aldehydes, ketones, esters, and isocyanates. The doubly alkylated thioethers were submitted to hydrolysis furnishing dialkyl ketones in good yields.

Alternatively, tin–copper transmetallation has been used to generate carbanion species alpha to sulfides.[48] In particular, when α-(2-pyridylthio)allyl stannanes react with allyl halides in the presence of CuI and in DMSO–THF as solvents (Scheme 4). The allylation proceeds with high γ-regioselectivity (from 82:18 to 100:0) and yields (70–90%). An example is shown in Scheme 4. In contrast, under the same conditions the related arylthio analog produces a 100% of α-allylation with only 28% of yield therefore the intramolecular coordination of pyridine nitrogen and Sn or Cu atoms can explain this increase in reactivity. The vinyl sulfides resulting of this transmetallation/alkylation protocol were submitted to a vinylic alkylation alpha to the sulfide by reacting with Bu^nLi/TMEDA or lithium diisopropylamide (LDA) and alkyl iodides. Further conversion to the corresponding ketones implies the transformation of 2-pyridyl thioethers into methyl thioethers (TsOMe/dimethylformamide (DMF)/NaOH) and subsequent hydrolysis.



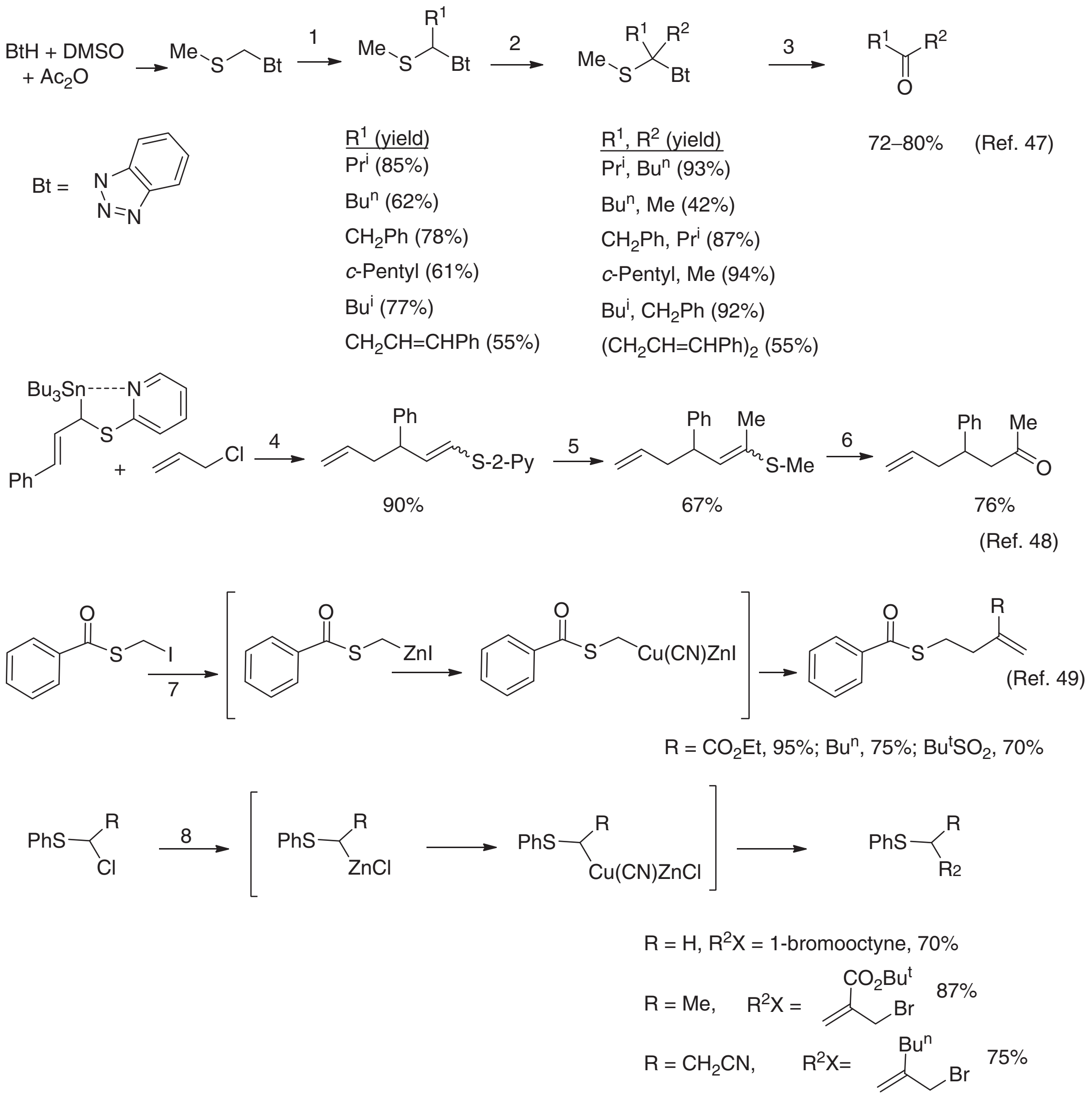
	1	2
R^1 = Ph, R^2 = Ph	>95%	95%
R^1 = Ph, R^2 = H	86%	0%
R^1 = Ph, R^2 = Me	91%	20%
R^1 = H, R^2 = Ph	50%	70%

1. Bu^nLi, THF, –78 °C. 2. HOTs, Toluene, reflux. 3. LDA, –78 °C, DABCO, 48%. 4. (a) Bu^nNF, –100 °C. (b) Li, $EtNH_2$, –78 °C, 67 %. 5. Bu^nLi, THF, –78 °C then ethylene oxide, 1 h, 86%. 6. HOTs, benzene, 70 °C, 75%. 7. $NaIO_4$, MeOH-H_2O, 12 h, 91%. 8. K_2CO_3, 180–200 °C, 55%. 9. *m*-CPBA, CH_2Cl_2, 12 h, 81%. 10. (a) Bu^tOK, Bu^nLi, THF, –50 °C. (b) LiBr, r.t., 2 h, 88%. 11. NH_2NH_2, H_2O_2, $Cu(OAc)_2$, 68%. 12. Bu^nLi, TMEDA, –40 °C, 99%.

Scheme 3

Finally, zinc insertion in carbon–halide bonds has found use in the formation of carbanions alpha to sulfides.[49] Thus, iodomethyl thiobenzoate and α-chloroalkyl phenyl sulfides smoothly react with zinc dust in THF to give the corresponding α-zinc thioorganometallic intermediates (Scheme 4). In both cases, the proximity of the sulfur atom facilitates the organozinc formation in comparison with simple alkyl halides. Further zinc–copper transmetallation renders organocopper intermediates that are able to react with electrophiles such as, alkyl and allyl halides, aldehydes, and acid chlorides.

One of the major challenges in the alkylation of α-thiocarbanions is to overcome the configurational lability of the chiral α-thioorganolithium species[50–52] more prone to racemization than the α-oxycarbanions so many efforts have been devoted to understand the structural requirements as well as the experimental conditions necessary for their asymmetric reaction with electrophiles. Selected examples will be disclosed below.[53–61] Two main factors to increase the barrier of racemization of

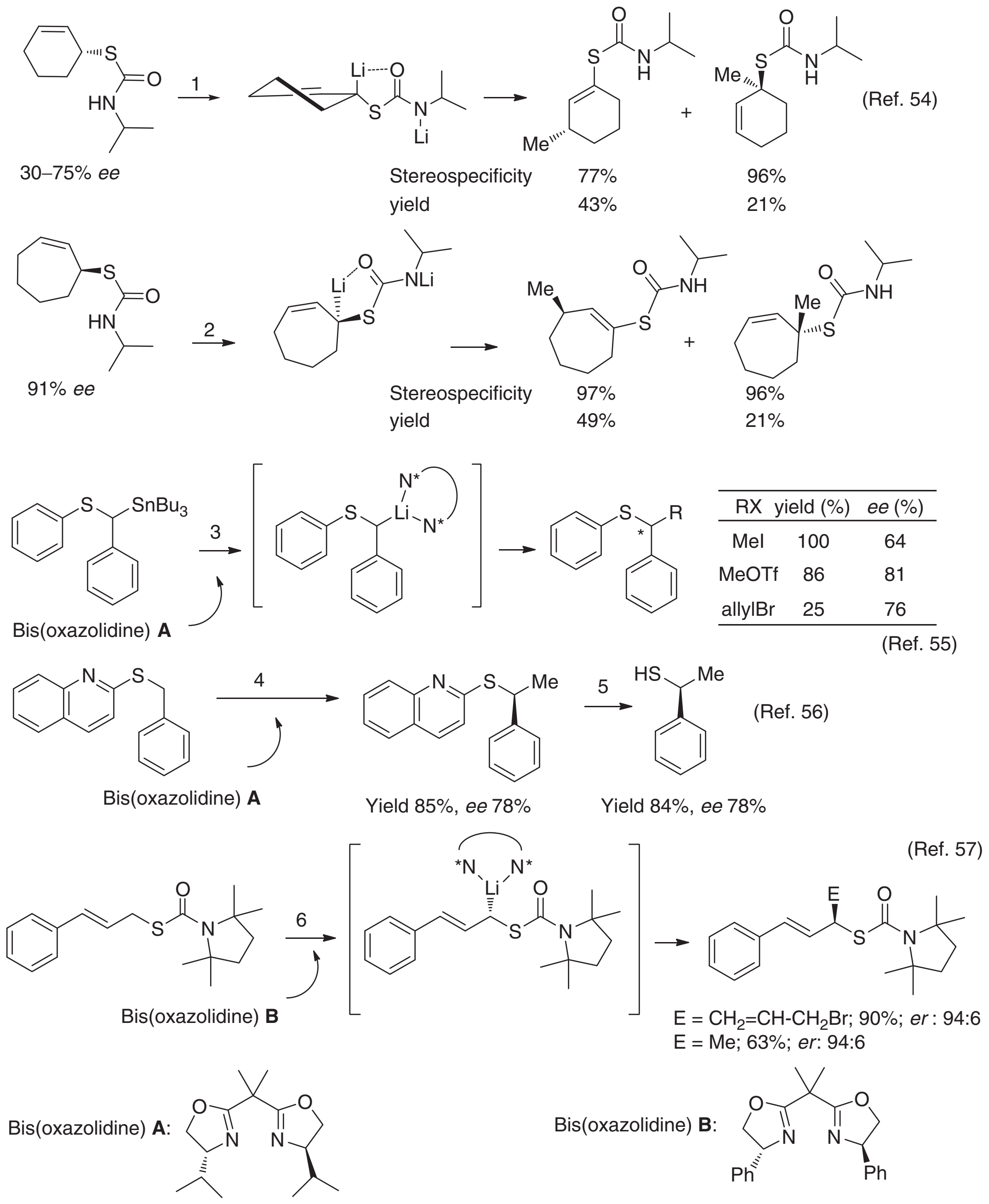


1. Bu^nLi, R^1I, THF, –78 °C. 2. Bu^nLi, R^2I, THF, –78 °C. 3. MeOH, H_2SO_4, r.t. or 60 °C. 4. CuI, DMSO-THF, r.t. 5. (a) Bu^nLi, TMEDA or LDA, MeI. (b) TsOMe, DMF. 6. $HgCl_2$, MeCN, H_2O. 7. (a) Zn activated, THF, 8 °C. (b) CuCN LiCl, –60 °C, THF. (c) $CH_2=C(R)-CH_2Br$, –70 °C to 0 °C or 25 °C. 8. (a) Zn activated, THF, 25 °C. (b) CuCN LiCl –60 °C, THF. (c) R^2X, –70 °C to –60 °C, 0 °C or 25 °C.

Scheme 4

α thio carbanions are bulkiness of substituents at the sulfur atom and branching at the carbanionic center. Guided by these requirements the group of Hoppe has designed several enantioenriched α thio carbanions.[53] In particular they have examined the alkylation, among other reactions with electrophiles, of α-thioallyllithium species generated from enantioenriched *S*-allyl *N*-isopropylthiocarbamates[54] (**Scheme 5**) for the asymmetric transformation of cyclohexene and cycloheptene thiocarbamates. The α-thioallyllithium compounds produced were stable in THF at -78 °C and alkylations proceed antarafacially with a high degree of chiral transmission (stereospecificity), secured by X-rays, though low α,γ-regioselectivity.

An alternative approach to configurationally stable α-thioorganolithiums was examined by the group of Toru (**Scheme 5**).[55] Thus, α-lithio benzyl phenyl sulfide was generated from α-stannyl benzyl phenyl sulfide by treatment with Bu^nLi and a chiral bis(oxazolidine). Further reaction with alkyl iodides and triflates produces the alkylated sulfides in moderate to good enantiomeric excesses (*ee*'s) and yields. Changing the phenyl group at the sulfur atom by a heterocycle, either 2-pyridyl or 2-quinolyl[56] allows for the simpler base-induced deprotonation of the sulfide, instead of the Sn/Li exchange, to generate the α-thio carbanion species. Alkylation, as well as reaction with ketones and aldehydes, render moderate to good *ee*'s and yields. In particular, the conversion to enantioenriched thiols is easily achieved for benzyl 2-quinolyl sulfides by treatment with $NaBH_3CN$. A parallel strategy has been



RX	yield (%)	*ee* (%)
MeI	100	64
MeOTf	86	81
allylBr	25	76

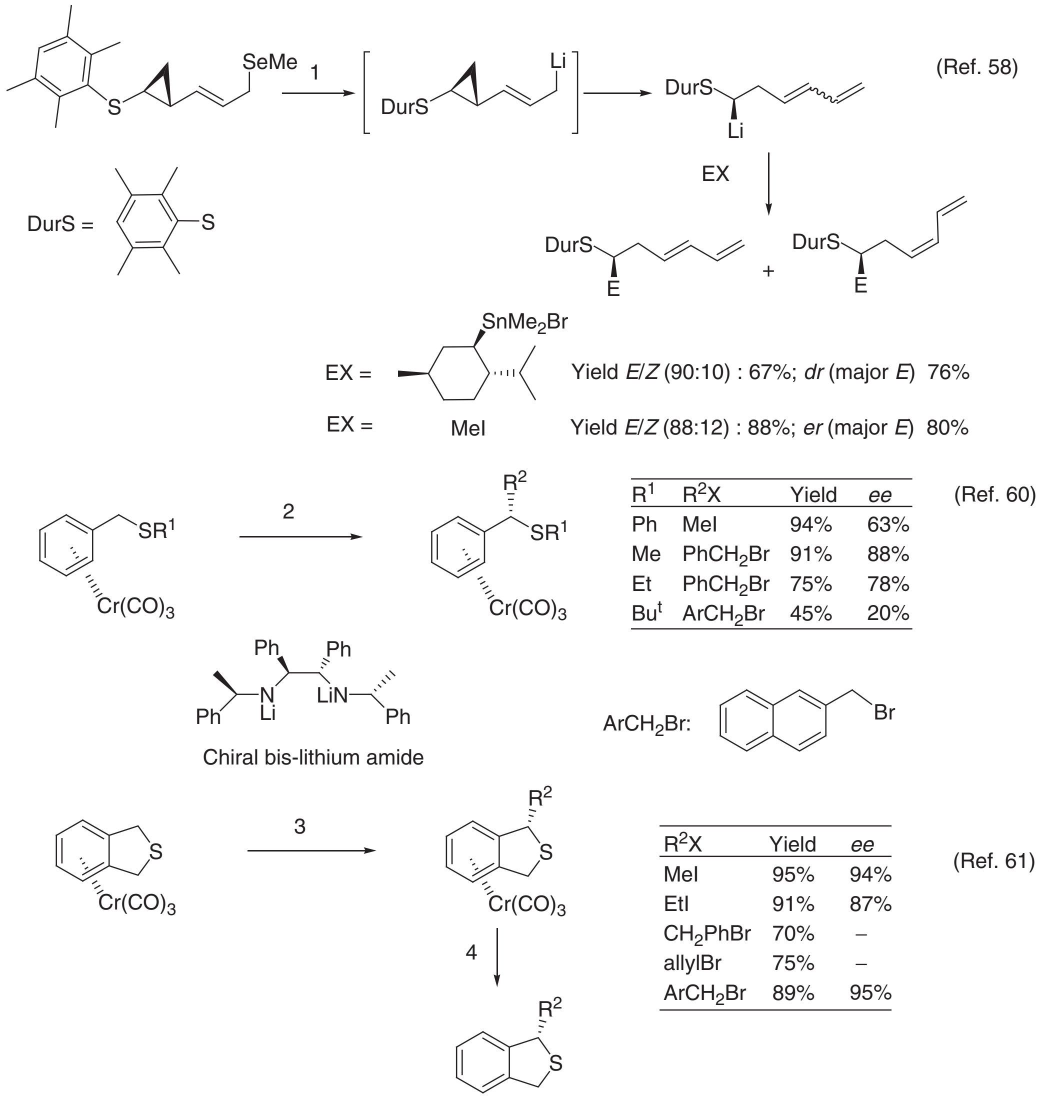
E = CH_2=CH-CH_2Br; 90%; *er*: 94:6
E = Me; 63%; *er*: 94:6

1. Bu^sLi, TMEDA, THF –78 °C, MeI, 5 min. 2. Bu^sLi, TMEDA, THF –78 °C, MeI, 30 min. 3. Bu^nLi, bis(oxazolidine), cumene, –78 °C, RX. 4. Bu^nLi, bis(oxazolidine), cumene, –50 °C, MeOTf. 5. $NaBH_3CN$, AcOH, r.t. 6. Bu^nLi, bis(oxazolidine), toluene, –30 °C, MeOTf or allyl bromide.

Scheme 5

employed by the group of Hoppe for the enantioselective alkylation of α-thio allyl carbanions derived from *S*-cinnamyl thiocarbamates.[57] Deprotonation of the thiocarbamate with Bu^nLi in the presence of chiral ligands provides after alkylation (allylBr, methyl triflate, and other electrophiles) enantioenriched thioamides in good yields and enantiomeric ratios. For both examples, benzyl phenyl sulfides and *S*-cinnamyl thiocarbamates, differences in energy of the two diastereomeric carbanions formed after deprotonation of the chiral ligand–sulfide complex are responsible for the high enantioselectivities found.

A particular methodology to generate an α-thiocarbanion that reacts in a stereochemically defined manner consists of the ring opening of a cyclopropyl allyllithium bearing a bulky thioduryl substituent (DurS).[58] Thus, treatment of cyclopropyl allyl seleno ether with Bu^tLi, at low temperature (Scheme 6) provides an allyllithium intermediate that undergoes a retro-carbolithiation reaction that implies the cyclopropyl opening. The configurational stability of the α-duryl thio alkyllithium species[59] at low temperature allows for their trapping with (–)-menthyl(dimethyl)tin bromide or MeI with a fair degree of stereocontrol, with retention of configuration at the sulfur bearing carbon atom for the major *E* diene (*E*:*Z*, 90:10). A different approach entails the use of thioethers bearing tricarbonyl(η^6-arene)chromium complexes that are deprotonated with chiral bis-lithium amide bases. The approach has been explored by different groups for acyclic benzyl thioethers[60] and benzothiophene[61] derivatives obtaining good yields and *ee*'s for the alkylation products (**Scheme 6**).



R^1	R^2X	Yield	*ee*
Ph	MeI	94%	63%
Me	$PhCH_2Br$	91%	88%
Et	$PhCH_2Br$	75%	78%
Bu^t	$ArCH_2Br$	45%	20%

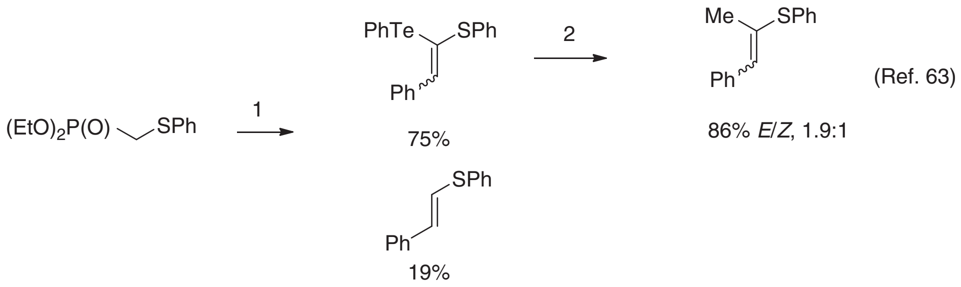
R^2X	Yield	*ee*
MeI	95%	94%
EtI	91%	87%
CH_2PhBr	70%	–
allylBr	75%	–
$ArCH_2Br$	89%	95%

1. (a) Bu^tLi, THF, –107 °C, 30 min. (b) EX. 2. (a) Chiral bis-lithium amide, THF, –78 °C. (b) R^2X. 3. (a) Chiral bis-lithium amide, THF, LiCl, –100 °C. (b) R^2X. 4. light, CH_2Cl_2, 70–88%.

Scheme 6

3.03.2.2 Vinyl α-Sulfenyl Carbanions

Similarly to alkyl thioethers, vinyl thioethers are also susceptible of deprotonation with bases and capture of the vinyl lithium intermediate with electrophiles, however, the competitive addition of Bu^nLi to the double bond is a drawback that can be circumvented by using more hindered bases such as LDA and tuning the experimental conditions.[62] An alternative to direct deprotonation protocols is the use of (*E*,*Z*)-ketene thio(telluro)acetals,[63] readily available by reaction of thiomethyl phosphonates with LDA and aryl tellurenyl bromides, followed by a second equivalent of LDA and capture with aldehydes (**Scheme 7**). A small amount (19%) of vinyl sulfide from the reduction of the tellurium atom is also produced in these reactions. The ketene thio(telluro)acetals, so generated, suffer Te/Li transmetallation on treatment with Bu^nLi and then react with methyl iodide to provide vinyl sulfides as mixtures of *Z* and *E* stereoisomers. Similarly, (*E*)-α-stannylvinyl sulfides undergo Stille coupling reactions with allyl bromides to afford the corresponding vinyl sulfides in good yield and stereoselectivity.[64]



1. (a) LDA, THF, –78 °C. (b) PhTeBr. (c) PhCHO. 2. (a) Bu^{n}Li, –78 °C, THF, MeI.

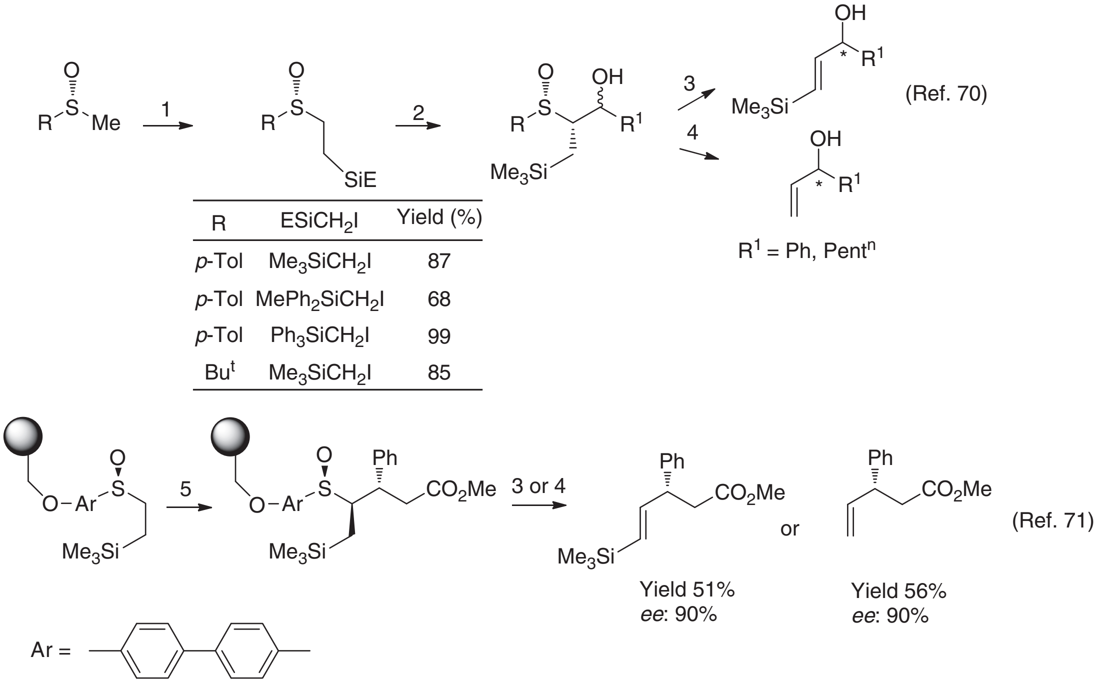
Scheme 7

3.03.3 Alkylation of α-Sulfinyl Carbanions

3.03.3.1 Alkyl and Allyl α-Sulfinyl Carbanions

Sulfoxides are commonly employed in asymmetric synthesis as chiral auxiliaries. Their configurational stability joint to their versatile reactivity have made available a plethora of examples to illustrate their usage.[7–18] The α-carbanions generated from optically active sulfoxides maintain the configuration at sulfur;[65] therefore the reactions with electrophiles and in particular the alkylations with halides,[66,67] trimethylphosphate,[68] and epoxides[69] are methods to increase the functionality of simple sulfoxides.

The use of β-trialkylsilyl ethyl sulfoxides is found among the synthetic strategies that involve alkylation of sulfoxides (Scheme 8).[70] These versatile compounds are prepared in a single step from aryl methyl sulfoxides, LDA, and iodomethyl trialkylsilanes (R_3SiCH_2I). After taking advantage of their reactivity, through Michael addition or addition to carbonyls of the α-lithium sulfinyl carbanions, the resulting β-trialkylsilyl ethyl sulfoxides can suffer elimination reactions to provide a vinylsilane or a terminal double bond in the final molecules. This approach has been applied to solid-phase synthesis.[71]

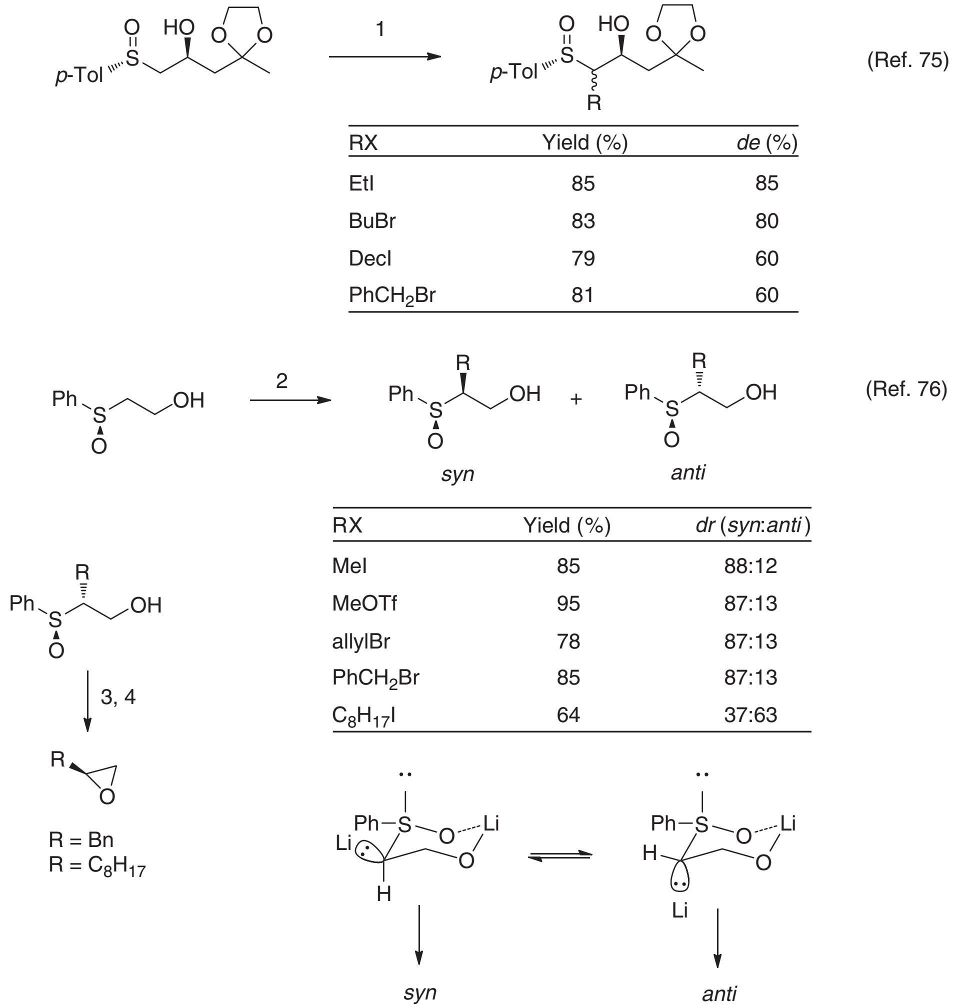


R	$ESiCH_2I$	Yield (%)
p-Tol	Me_3SiCH_2I	87
p-Tol	$MePh_2SiCH_2I$	68
p-Tol	Ph_3SiCH_2I	99
Bu^t	Me_3SiCH_2I	85

1. (a) LDA, THF, –78 °C. (b) $ESiCH_2I$. 2. (a) LDA, THF, –78 °C. (b) R^1CHO. 3. Benzene, reflux, 1 h, 80–89%. 4. Bu$^n{}_4$NF, THF, r.t., 91–97%. 5. (a) LDA, THF, –78 °C. (b) PhCH=CHCO$_2$Me.

Scheme 8

Nevertheless, the most interesting applications of alkylation reactions are those in which a new stereogenic center is created taking advantage of the chiral induction of the sulfinyl group.[72] In this context, several groups have independently examined the alkylations of β-hydroxysulfoxides. Similarly to previous studies from Tanikaga[73] and Fujisawa,[74,1] the group of Blase has submitted to alkylation *β*-hydroxy δ-dioxolane sulfoxides[75] by treatment with MeLi as base and simple alkyl halides (**Scheme 9**). In spite of the good yields, the diastereoselectivities were moderate ranging from 85% for EtI to 60% for *n*-$C_{10}H_{21}I$ and BnBr and the absolute configuration for the newly created stereocenters was not determined. Furthermore, the single contribution of the sulfinyl group to the asymmetric alkylation has been also evaluated by the group of Ohta in enantiopure 2-phenylsulfinyl ethanol.[76] In this case (**Scheme 9**), deprotonation with LDA affords a dilithium species that is then alkylated with alkyl halides or triflates with good yields and *syn*:*anti* ratios approximately 87:13. The absolute configuration for the newly created stereocenter was determined by transformation into known epoxides. The diastereoselectivity observed was interpreted by the authors in terms of the formation of a chelated six-membered ring intermediate in which the phenyl group adopts an equatorial position. The more reactive electrophiles would react preferentially with the most populated conformation of the dianion (C–Li equatorial), with inversion, giving the *syn*-alkylated product and reflecting the conformational ratio of the chelate intermediate. However the bulkier electrophiles (octyl iodide) would reverse the *syn*:*anti* ratio by the approach to the anion from the less hindered *exo* site of the dianion anion (C–Li axial) giving a lower diastereoselectivity (*syn*:*anti*, 37:63).



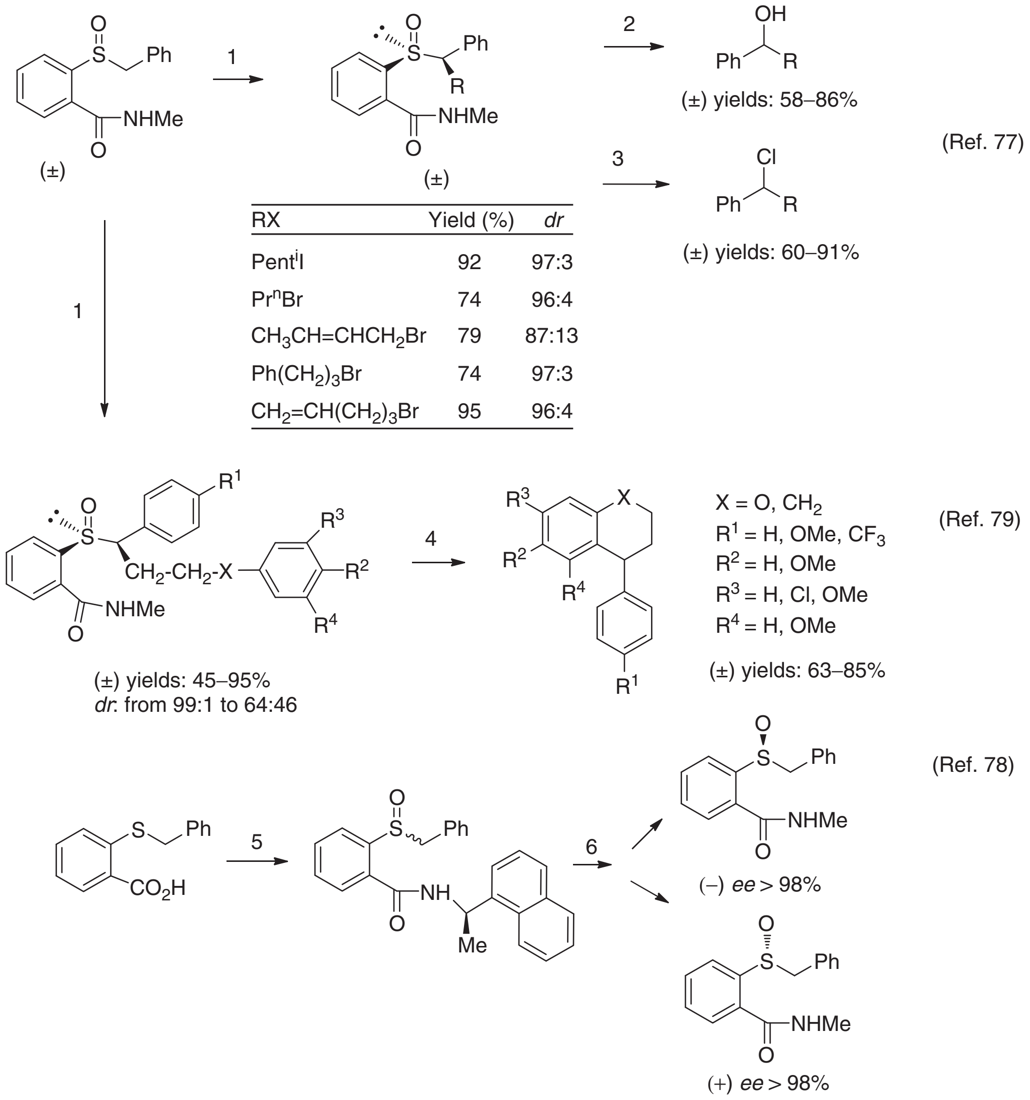
RX	Yield (%)	*de* (%)
EtI	85	85
BuBr	83	80
DecI	79	60
$PhCH_2Br$	81	60

RX	Yield (%)	*dr* (*syn*:*anti*)
MeI	85	88:12
MeOTf	95	87:13
allylBr	78	87:13
$PhCH_2Br$	85	87:13
$C_8H_{17}I$	64	37:63

1. (a) 2 equivalents MeLi, THF, 0 °C. (b) RX, −78 to 0 °C, 4 h. 2. 2.2 equivalents LDA, −78 to −20 °C,THF. (b) RX, −78 °C to r.t. 3. $TiCl_4$, CH_2Cl_2, $NaBH_4$, DME, 0 °C. 4. (a) Me_3OBF_4, CH_2Cl_2, r.t. (b) NaOH.

Scheme 9

In a similar context, moderate to high diastereoselectivities were obtained in the reaction of bis-lithiated ortho-(*N*-methylcarbamoyl)phenyl benzyl sulfoxides and alkyl, allyl, and benzyl halides[77] (**Scheme 10**). Two equivalents of Bu^nLi along with HMPA were needed to deprotonate the starting racemic benzylic sulfoxides and except for MeI, which gave mixtures of *C*- and *N*-alkylation, all the reactions took place with high selectivity for *C*-alkylation. The absolute configuration for the major diastereomer was determined by X-ray diffraction of one of the alkylated compounds. Under Pummerer or chloro-Pummerer conditions, the alkylated benzylic sulfoxides were transformed into racemic secondary alcohols or chlorides. This methodology has also been improved using enantiopure sulfoxides, available through coupling with chiral (+)-2-*β*-naphthyl ethylamine, rendering enantioenriched secondary alcohols and chlorides.[78] The scope of this two steps alkylation-Pummerer sequence was increased with the synthesis of 1-aryl tetralines and 4-aryl benzopyrans when 1-bromo-3-arylpropyl derivatives are used for the alkylation step.[79]



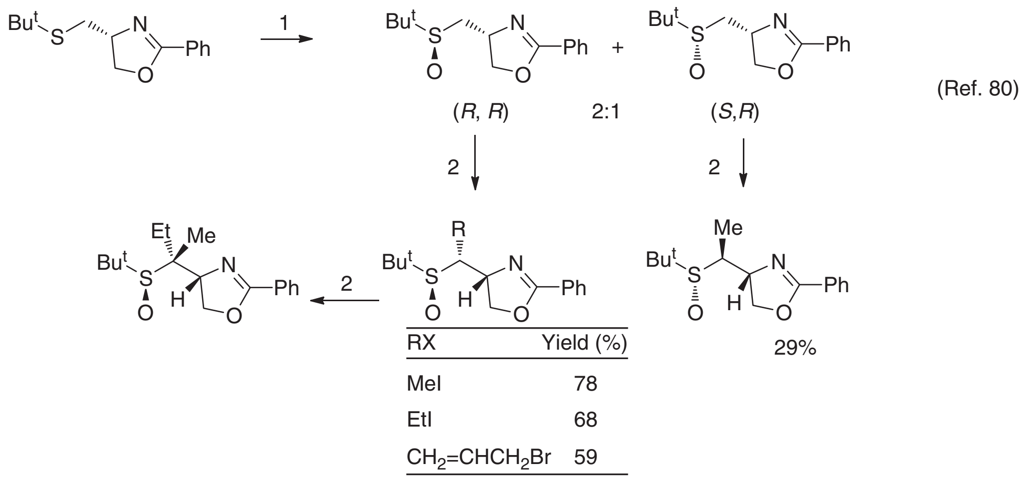
RX	Yield (%)	*dr*
Pent^{i}I	92	97:3
Pr^{n}Br	74	96:4
$CH_3CH{=}CHCH_2Br$	79	87:13
$Ph(CH_2)_3Br$	74	97:3
$CH_2{=}CH(CH_2)_3Br$	95	96:4

1. (a) Bu^{n}Li (2 equivalents), HMPA (5 equivalents), THF, –78 °C. (b) RX. 2. TFAA, TMP, CH_2Cl_2, 0 °C. 3. $(COCl)_2$, TMP, CH_2Cl_2, –78 °C. 4. Tf_2O, TMP or DTBMP, CH_2Cl_2, –78 °C or 0 °C. 5. (*R*)-2-β-naphthyl ethylamine, BOP, DIPEA, DMF. (b) MCPBA, $CHCl_3$, 0 °C. 6. (a) separation. (b) KOH, EtOH. (c) $MeNH_2$, BOP, DIPEA, DMF.

Scheme 10

An interesting example of diastereoselective alkylation takes place in a sulfoxide derived from (*R*)-cysteine (Scheme 11).[80] First, (*R*)-cysteinol was protected as an oxazoline derivative and was oxidized providing two diastereomeric sulfoxides (*R*,*R*) and (*S*,*R*) in 2:1 ratio. When the (*R*,*R*)-sulfoxide was deprotonated with LDA and treated with MeI, a single alkylated product, assigned by X-ray analysis, was obtained in 78% yield. EtI and allyl bromide also provided satisfactory yields and selectivities. The same high diastereoselectivity was observed for the methylation of the (*S*,*R*)-sulfoxide, however, only with 29% yield of alkylated compound. A chelate six-membered ring intermediate could be responsible for the high diastereoselectivity found. In addition, quaternary centers can be diastereoselectively created by a second alkylation with EtI albeit the yield decreases significantly.

Alkylation of α-sulfinyl carbanions also occurs in cyclopropyl derivatives.[81] In particular, the cyclopropenyl sulfoxide prepared by reaction of cyclopropenyl lithium (generated from 1,1,2-tribromocyclopropane) and (–)-menthyl-(*S*)-*p*-toluenesulfinate suffers

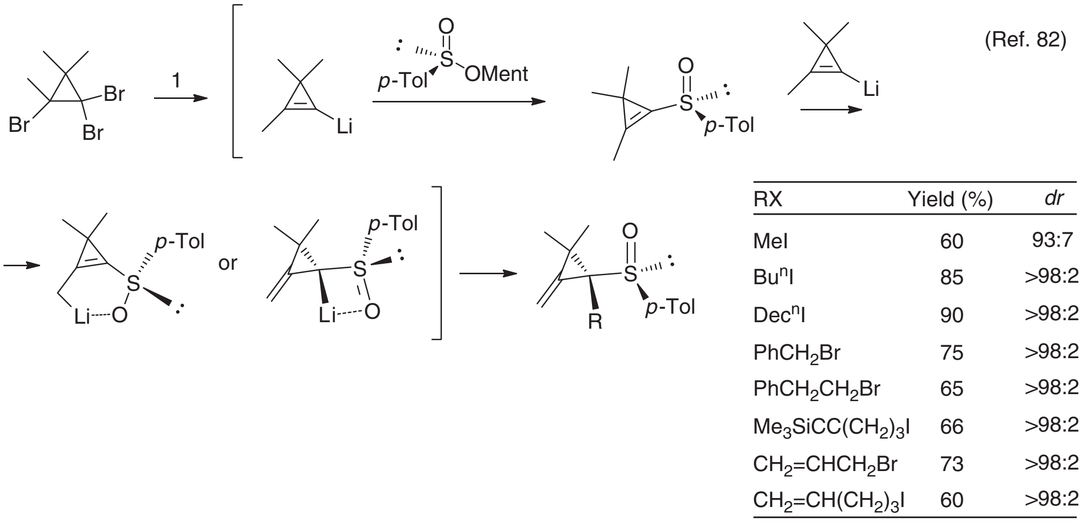


RX	Yield (%)
MeI	78
EtI	68
CH_2=$CHCH_2Br$	59

1. MCPBA (1 equivalent), CH_2Cl_2, r.t., 4–5 h, 95%. 2. (a) LDA, –78 °C, THF.
(b) RX, 4 h at –78 °C and 12 h to r.t.

Scheme 11

an *in situ* allylic deprotonation followed by capture with a broad range of halides (Scheme 12).[82] The one-pot reactions take place with good yields and diastereoselectivities leading to strained chiral methylene cyclopropanes.

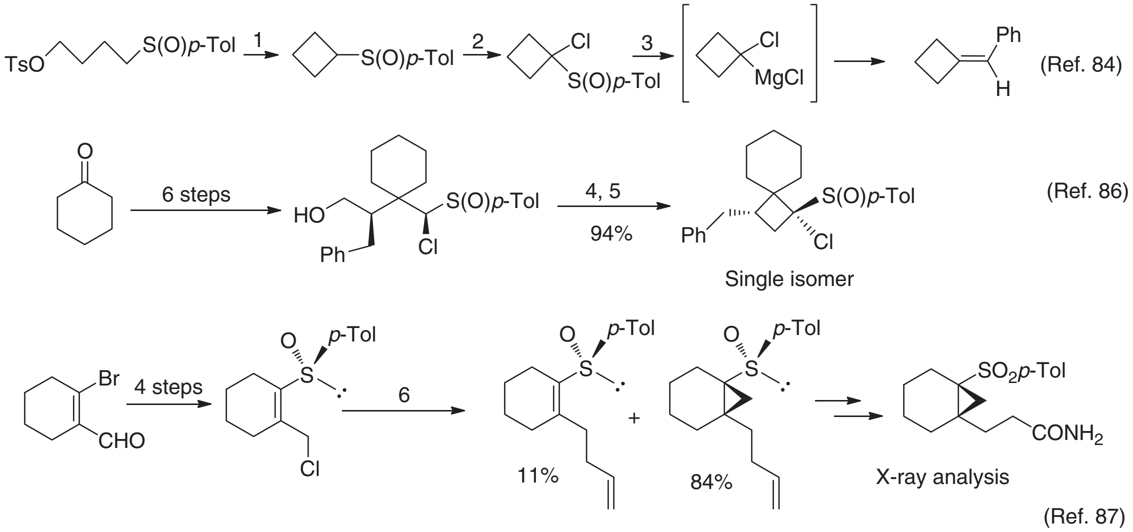


RX	Yield (%)	dr
MeI	60	93:7
Bu^{n}I	85	>98:2
Dec^{n}I	90	>98:2
$PhCH_2Br$	75	>98:2
$PhCH_2CH_2Br$	65	>98:2
$Me_3SiCC(CH_2)_3I$	66	>98:2
CH_2=$CHCH_2Br$	73	>98:2
CH_2=$CH(CH_2)_3I$	60	>98:2

1. (a) 4 equivalents Bu^{t}Li, Et_2O –80 °C to 20 °C. (b) 0.5 equivalent (–)-menthyl-(*S*)-*p*-toluenesulfinate, THF, –78 °C to –20 °C. (c) 1.7 equivalents RX, warming to 25 °C, overnight.

Scheme 12

When both, an electrophile and a sulfoxide, coexist in an alkyl chain intramolecular alkylation can take place as side reaction of the α-sulfinyl carbanion.[83] However, sometimes this approach has been efficiently used for the synthesis of cyclopropane and cyclobutane rings (Scheme 13). Thus, racemic 4-tosyloxybutyl sulfoxide cyclizes to cyclobutyl *p*-tolyl sulfoxide on treatment with LDA, at 0 °C.[84] Further reaction with NCS provides 1-chlorocyclobutyl sulfoxide that undergoes a sulfoxide–magnesium exchange producing a cyclobutylmagnesium carbenoid. *In situ* reaction with lithium α-sulfonyl carbanions, finally rendered alkylidene cyclobutanes. Also cylopropyl sulfoxides have been obtained by this approach.[85] In a different example of the intramolecular alkylation, an alkyl iodide can act as electrophile. In particular, in six steps from cyclohexanone was generated a racemic hydroxymethyl chloro sulfoxide[86] that underwent iodination followed by diastereoselective cyclization to render 1-chlorocyclobutyl *p*-tolylsulfoxide as a single isomer in good yield. An alternative strategy for the intramolecular alkylation implies the generation of the α-sulfinyl carbanion employing a diastereoselective Michael addition.[87] Namely, treatment of an enantiopure chiral vinyl sulfoxide, bearing a leaving group (Cl) at the γ-position, with allylmagnesium bromide gives an α-sulfinyl carbanion that undergoes intramolecular alkylation affording a bicyclic cyclopropane as major product (84%) along with minor amounts of the coupling product. Other nucleophiles (MeMgBr, $Me_2CuCNLi_2$) or leaving groups (OMs) did not provide cyclopropanes in reasonable yields. The absolute stereochemistry of the cyclopropane was determined by X-ray analysis of a sulfone derivative.



1. LDA, THF, 0 °C to r.t., 98%. 2. NCS, THF, 0 °C to r.t., 99%. 3. (a) 2.5 equivalents EtMgCl, THF, −78 °C. (b) $PhCHLiSO_2Ph$, −78 °C to −20 °C, 83%. 4. Ph_3P, imidazole, I_2, THF, r.t., 15 min. 5. KHMDS, 0 °C, THF:Tol (90:10), 15 min, 94% overall yield (4 and 5). 6. allylMgBr, −78 °C, THF.

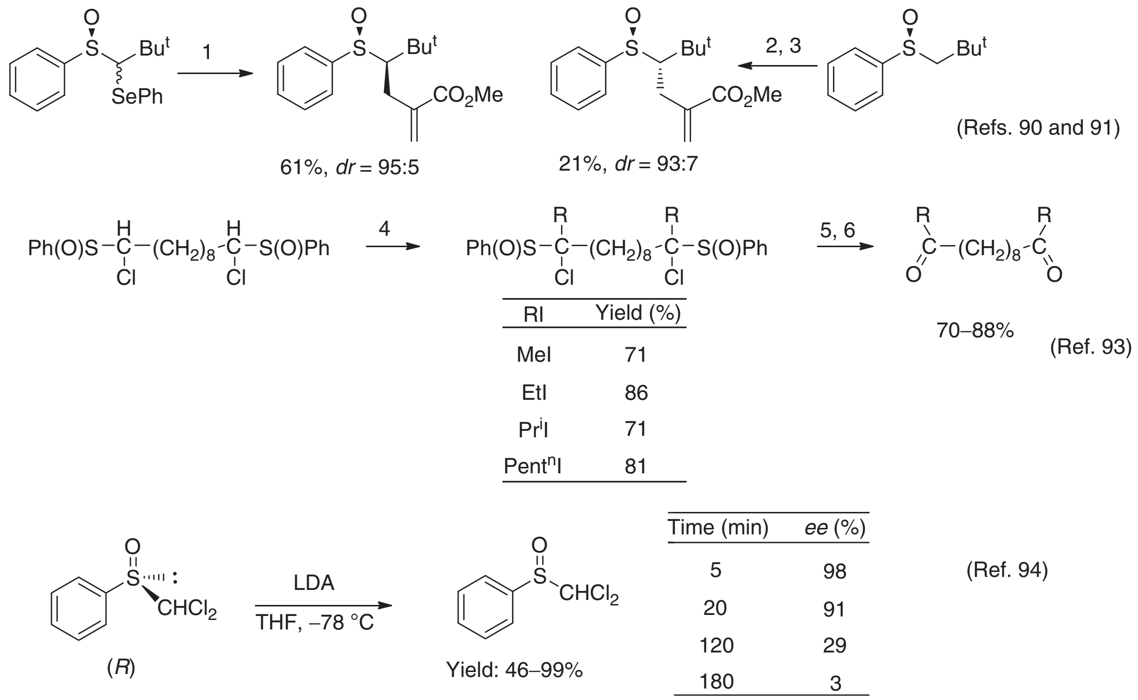
Scheme 13

Alkyl sulfoxides with additional heteroatoms located alpha to the sulfinyl group are involved in processes to transform the alkyl chain in different ways. This is the case of α-bromomethyl sulfoxides that participate in palladium-catalyzed Suzuki cross-coupling α-arylations[88] and α-selenoalkyl sulfoxides that are involved in the α-allylation by a radical mechanism.[89] In particular cases, the radical allylation of aryl α-selenoalkyl sulfoxides with allyl stannanes provides a complementary stereoselectivity to the ionic alkylation procedure (Scheme 14).[90,91] Nevertheless, within the context of alkylation of α-sulfinyl carbanions, there are several examples that used α-alkoxy[92] and α-chloro[93] sulfoxides as starting materials. Particularly, the synthesis of symmetrical aliphatic diketones has been accomplished by treatment of bis-chloro sulfoxides with LDA and alkyl iodides (Scheme 14). The doubly alkylated chloro sulfoxides thus obtained were transformed into the corresponding diketones by treatment with triflic anhydride/NaI followed by hydrolysis with aqueous perchloric acid. Finally, the use of carbanions derived from dichloromethyl sulfoxides in alkylation reactions could be limited to nonasymmetric methodology, since the treatment with strong bases such as LDA, LHMDS, NaHMDS, and KHMDS resulted in racemization of the sulfur stereogenic center even at low temperatures (Scheme 14).[94]

3.03.3.2 Vinyl α-Sulfinyl Carbanions

The acidity of α-protons in vinylic sulfoxides allows for their abstraction with strong bases such as MeLi or LDA to render α-lithium vinyl sulfoxides that can be trapped with electrophiles. This strategy has been widely employed in spite of the configurational instability of (*Z*)-α-sulfinyl carbanions that rapidly isomerize to the (*E*)-α-sulfinyl carbanions which have restrained the application of trisubstituted vinyl sulfoxides in this context. Interestingly, the intramolecular version of this reactivity has revealed the value of di- and trisubstituted vinyl sulfoxides for the synthesis of 1-cycloalkenyl sulfoxides (Scheme 15).[95] In particular, on treatment of β-(ω-haloalkyl) substituted vinylic sulfoxides with LDA at low temperature (−78 °C), the α-sulfinyl vinyl carbanions produced undergo intramolecular alkylation to render five- to seven-membered rings. Any of *Z*, *E*, or mixtures of *Z*/*E* disubstituted vinyl sulfoxides can be used as starting materials with comparable yields of cycloalkenyl sulfoxides. Alkyl bromides and iodides are preferably used as leaving groups and the cyclization proceeds even with secondary iodides. *Z* and *E* β,β-disubstituted vinylic sulfoxides also suffer α-deprotonation; however the close energy difference between the *E*/*Z* sulfinyl carbanions for these substrates along with the nature of the intramolecular alkylation, effective for only one of the isomers, produce a 50% as highest conversion. This methodology has been successfully applied to the synthesis of indene and cyclitol derivatives.

An alternative approach to generate α-metallo vinyl sulfoxides consists of a highly *syn*-selective Cu-catalyzed addition of organozinc compounds to 1-alkynyl sulfoxides (Scheme 16).[96] This method allows for the stereoselective synthesis of trisubstituted vinylic sulfoxides by trapping the carbanion intermediates generated with allylic bromides. Thus, 1-alkynyl sulfoxides

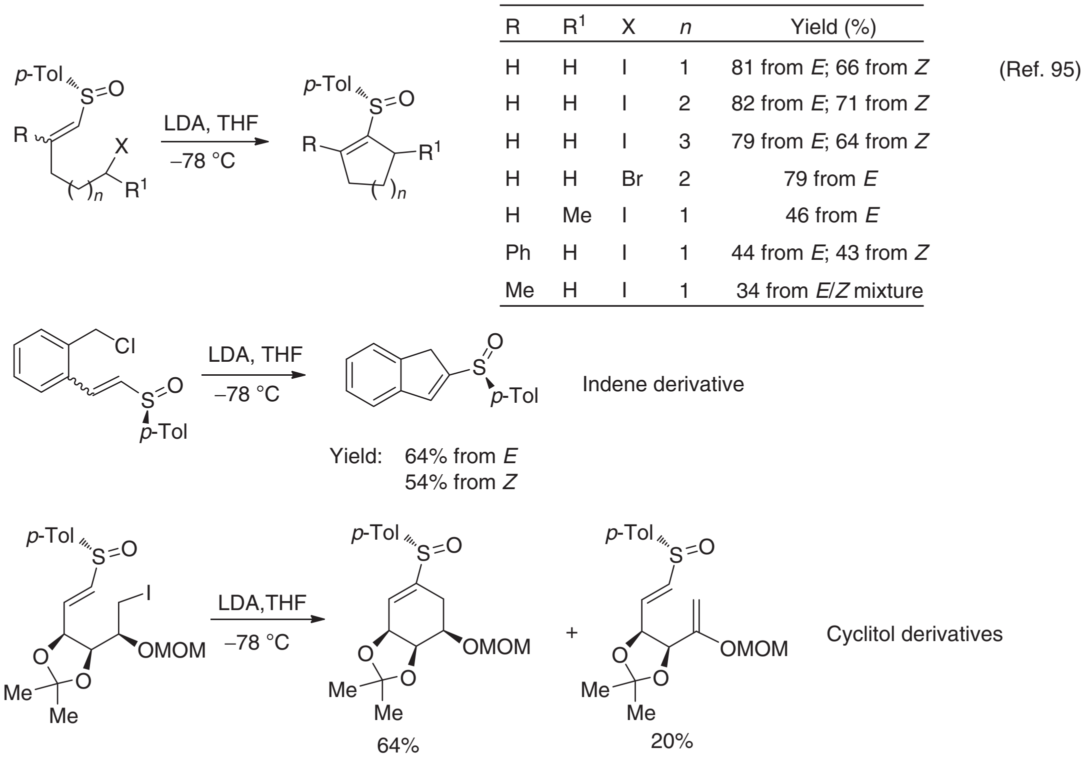


RI	Yield (%)
MeI	71
EtI	86
Pr^iI	71
$Pent^nI$	81

Time (min)	*ee* (%)
5	98
20	91
120	29
180	3

1. Bu_3SnCH_2-$C(CO_2Me)=CH_2$, AIBN, C_6H_6, 10 °C, sun lamp. 2. (a) LDA, THF. (b) $BrCH_2$-$C(CO_2Li)=CH_2$. 3. CH_2N_2. 4. LDA, HMPA, THF, RI, –60 °C to –25 °C. 5. Tf_2O, NaI, acetone, –55 °C. 6. 10% $HClO_4$, dioxane, reflux, 1.5 h.

Scheme 14

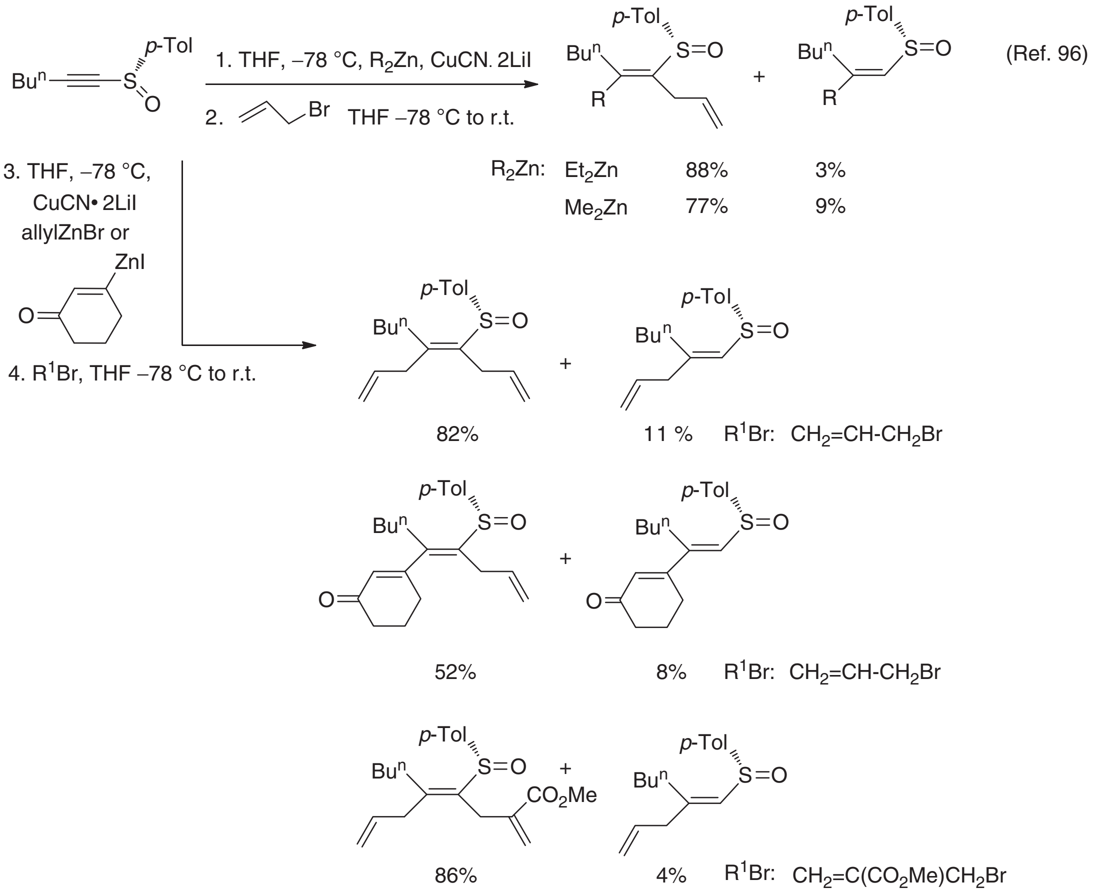


R	R^1	X	*n*	Yield (%)
H	H	I	1	81 from *E*; 66 from *Z*
H	H	I	2	82 from *E*; 71 from *Z*
H	H	I	3	79 from *E*; 64 from *Z*
H	H	Br	2	79 from *E*
H	Me	I	1	46 from *E*
Ph	H	I	1	44 from *E*; 43 from *Z*
Me	H	I	1	34 from *E*/*Z* mixture

Yield: 64% from *E*
54% from *Z*

Scheme 15

undergo stereospecific carbozincation on treatment of with Et_2Zn or Me_2Zn in the presence of copper salts generating vinylzinc intermediates that react with allyl bromide. More functionalized allylic and vinylic groups can be introduced in the carbozincation step as well as in the final electrophilic capture providing more complex trisubstituted vinylic sulfoxides as single isomers.

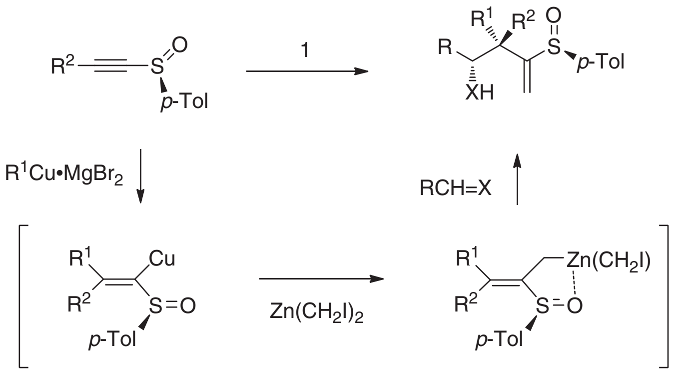


Scheme 16

Another strategy that also relays on carbometallation of alkynyl sulfoxides to generate α-metallo vinyl sulfoxides involves the regio and stereospecific *syn*-carbocupration of various 1-alkynyl sulfoxides with organocopper reagents, obtained from alkyl magnesium halides and copper salts as CuBr or CuI (Scheme 17).[97] Then, the α-copper *β*,*β*-dialkylated ethylenic sulfoxide reacts with bis(iodomethyl)zinc (prepared from Et_2Zn and CH_2I_2 or formed *in situ*) generating a chelated allylzinc species that is finally trapped with aldehydes and sulfonyl imines with high regio- and stereoselectivity. Under these conditions, neither the vinylcopper nor the zinc carbenoid, $Zn(CH_2I)_2$, reacts with the final electrophile (RCH=O or RCH=NTs). Several alkyl groups can be introduced in the carbocupration (Me, Et, Bu) as well as functionalized aldehydes can also be used.[98] Further optimization of the reaction sequence has provided a four-component reaction protocol where alkynyl sulfoxide, aldehyde, dialkylzinc, and CH_2I_2 are added simultaneously to the organocopper species providing homoallylic alcohols in excellent yields and diastereoselectivities.

3.03.4 Alkylation of α-Sulfonyl Carbanions

Sulfones are the most popular functional group containing sulfur. Sulfonyl compounds have been used in a myriad of instances since their fruitful reactivity allows for numerous transformations. The reactions of α-sulfonyl carbanions with electrophiles and in particular, alkylations belong to the cluster of methods available for organic synthetic chemists. For that reason detailing every case of the literature would exceed the extension of this review and consequently an array of interesting examples has been selected to show the advances in this area in the past years.



(Refs. 97 and 98)

R^1	R^2	RCH=X	*dr*	Yield (%)
Et	Bu^n	PhCHO	99:1	78
Bu^n	Et	PhCHO	99:1	68
Me	Et	Bu^nCHO	30:1	58
Et	Bu^n	*p*-ClC_6H_4CHO	99:1	70
Et	Me	*p*-$MeOCOC_6H_4CHO$	98:2	60
Et	Bu^n	2-(thiophenyl)CHO	99:1	83
Et	Bu^n	2-(furyl)CHO	99:1	70
Bu^n	Et	PhCHNTs	99:1	70

1. (a) CuI, R^1MgBr, THF, –50 °C to –30 °C. (b) THF, alkynyl sulfoxide, –30 °C. (c) THF, –30 °C, RCH=X, CH_2I_2, Et_2Zn.

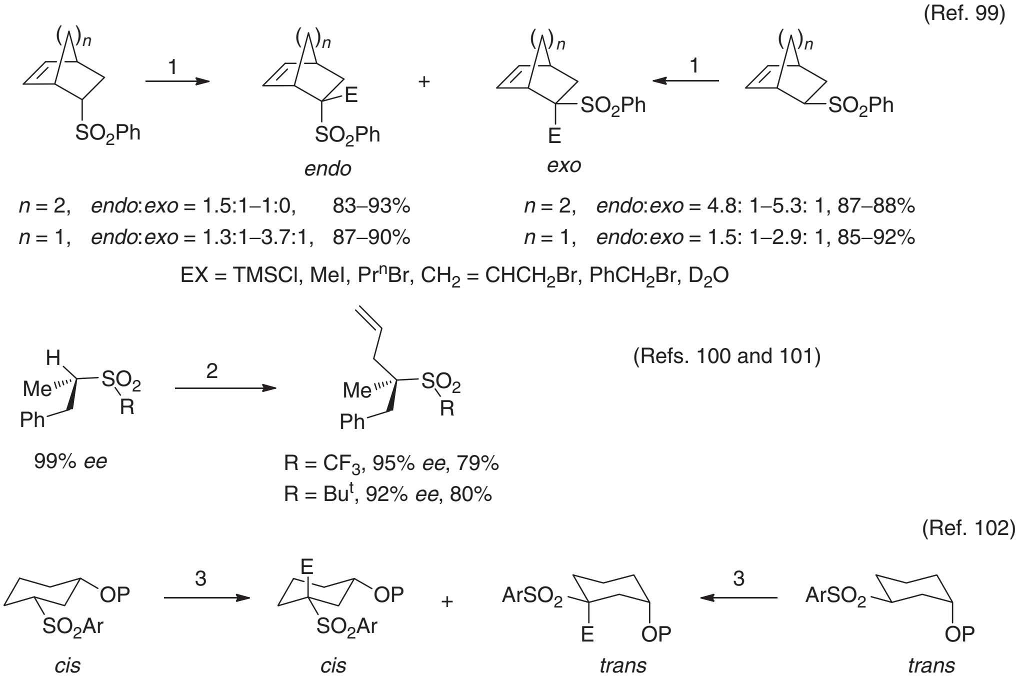
Scheme 17

3.03.4.1 α-Metalloalkyl Sulfones

α-Sulfonyl carbanions of simple alkyl sulfones have been generated with moderate to high stereoselectivity in a number of examples. The electrophilic quench of the carbanions derived from a variety of bridged bicyclic sulfones[99] (Scheme 18) takes place with varying stereoselectivity depending on the electrophile used, the presence of additives and, to a lesser extent the stereochemistry of the starting material with *endo* sulfone isomers always predominating. Likewise, the stereochemistry of the lithiation and allylation of enantiopure acyclic trifluoromethyl and *tert*-butyl sulfones has been studied. In these cases, configurationally stable sulfonyl carbanions are formed with very high enantioselectivity that is maintained in the ensuing allylation[100] (Scheme 18). Recently, the synthesis, configurational stability and reactivity toward alkylation of a variety of lithium α-*tert*-butylsulfonyl carbanion salts have been investigated in detail.[101] In a similar context, the reactions of α-arylsulfonyl carbanions derived from 3-hydroxy and 3-alkoxy-1-(arylsulfonyl)cyclohexane with electrophiles have been investigated.[102] For the hydroxyl derivatives, both *cis* and *trans* dianions are deuterated with high selectivity in favor of the *trans* isomer, suggesting a rapid isomerization of the chelated *cis*-derived dianion; allylation then would proceed with inversion of configuration at the carbanionic center. The more reactive silyloxy monoanion provided an almost equimolar mixture of isomers on deuteration and a highly diastereoselective allylation with predominant inversion of configuration.

The alkylation of methyl phenyl sulfone with a lithium base leads to significant polyalkylation, presumably by equilibration processes between the initial carbanion and the monoalkylated product.[103] The use of a potassium base enhances the product of monoalkylation for simple alkyl halides but is less effective for more reactive allyl and benzyl bromides. Finally, reaction of α-silyl phenyl sulfones with *n*-butyllithium also produces an α-sulfonyl anion by migration of the $SiMe_3$ group to the ortho-position of the phenyl sulfones[104] (Scheme 19).

Within the examples of alkylation of benzylsulfonyl carbanions (Scheme 20), the use of a new Mitsunobu reagent, cyanomethylene trimethylphosphorane (CMMP), allows for the efficient alkylation of arylmethyl phenyl sulfones with primary and secondary alcohols.[105] Also, the α-sulfonyl carbanions of *o*- and *p*-halobenzyl sulfones may be efficiently generated with the phosphazene base P_2-Et providing the desired alkylation products with higher yields than standard conditions.[106] It was also possible to carry out sequential cross-coupling (Heck, Suzuki–Miyaura) and α-alkylation-*β*-elimination sequence by alkylation with ethyl bromoacetate in the presence of P_2-Et. However, optically active allyl sulfonyl acetic esters undergo a highly stereospecific palladium-catalyzed decarboxylative allylation to produce optically active tertiary homoallylic sulfones. These reactions entail mild conditions and allylation of the intermediate sulfonyl anion is faster than racemization.[107]



n = 2, *endo*:*exo* = 1.5:1–1:0, 83–93% *n* = 2, *endo*:*exo* = 4.8: 1–5.3: 1, 87–88%
n = 1, *endo*:*exo* = 1.3:1–3.7:1, 87–90% *n* = 1, *endo*:*exo* = 1.5: 1–2.9: 1, 85–92%
EX = TMSCl, MeI, Pr^nBr, $CH_2 = CHCH_2Br$, $PhCH_2Br$, D_2O

R = CF_3, 95% *ee*, 79%
R = Bu^t, 92% *ee*, 80%

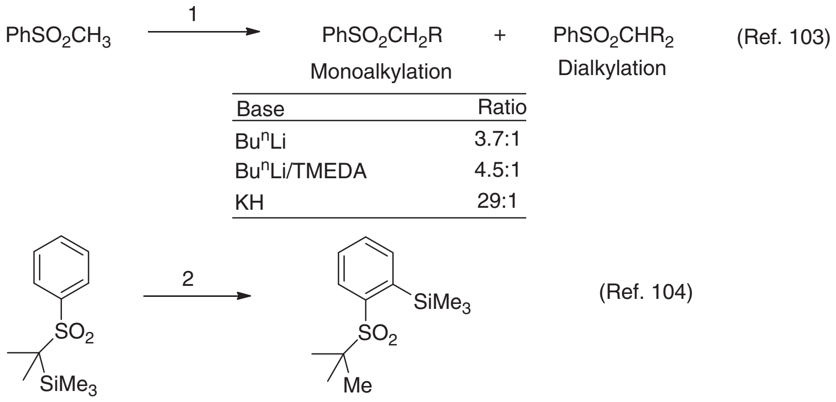
Ar = *p*-Bu^t-C_6H_4
P = H, EX = D_2O, *cis:trans* = 4:96, 92%
P = H, EX = allylBr (in Et_2O), *cis:trans* = 80:20, 84%

Ar = Ph
P = TBDMS, EX = D_2O, *cis:trans* = 46:53, 82%
P = TBDMS, EX = allylBr (in Et_2O), *cis:trans* = 7:93, 92%

Ar = *p*-Bu^t-C_6H_4
P = H, EX = D_2O, *cis:trans* = 0:100, 98%

1. (a) 1.1 equivalents Bu^nLi, THF, –78 °C, 15 min. (b) 1.2–6 equivalents EX, –78 °C to r.t., 1.5 h. 2.(a) Bu^tLi, THF. (b) $CH_2 = CHCH_2I$. 3. (a) Bu^nLi, THF or Et_2O. (b) EX.

Scheme 18



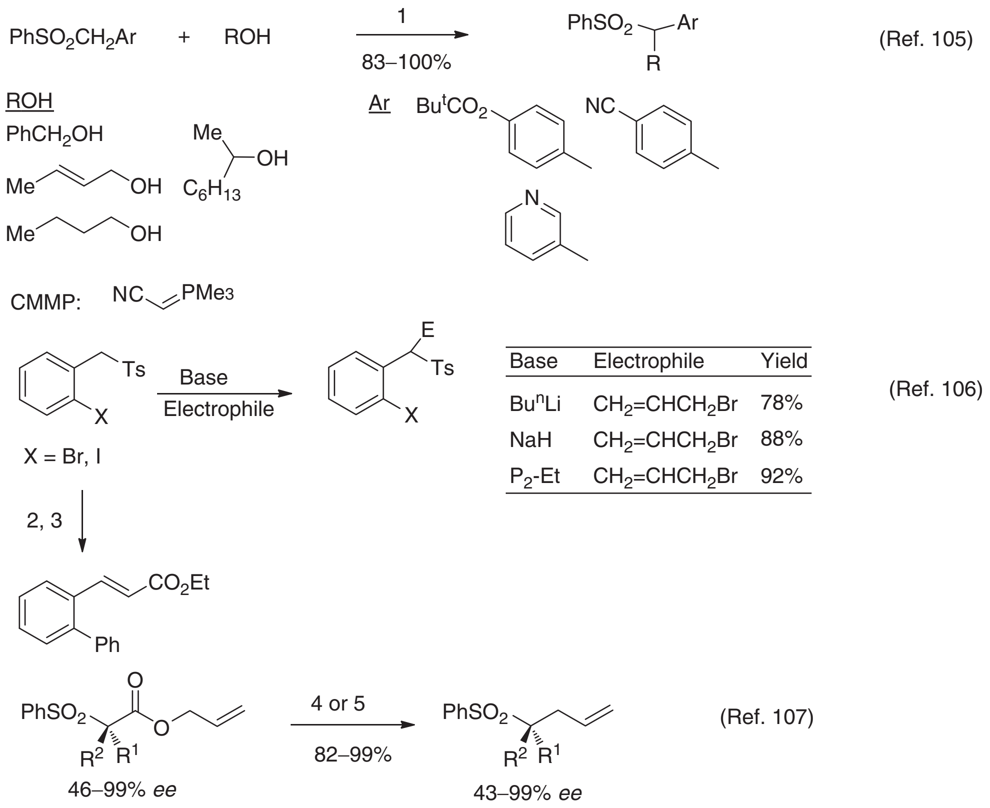
$PhSO_2CH_3$ → $PhSO_2CH_2R$ + $PhSO_2CHR_2$
Monoalkylation Dialkylation

Base	Ratio
Bu^nLi	3.7:1
Bu^nLi/TMEDA	4.5:1
KH	29:1

1. (a) Base, THF. (b) Pr^nBr. 2. (a) Bu^nLi, Et_2O, 0 °C. (b) MeI, 93%.

Scheme 19

The intramolecular alkylation of α-sulfonyl carbanions has been widely used to prepare three- to six-membered carbocycles. Thus, enantiopure sulfonyl alcohols have been transformed into sulfonyl cyclopropanes by tosylation and cyclization at low temperature with LDA (Scheme 21). Interestingly, lithiation of a 35:65 mixture of a more substituted substrate with a methyl group α to sulfur leads to a single isomer of a trisubstituted sulfonyl cyclopropane.[108,109] Alkylation of cyclopropyl derivatives is an alternative approach to these compounds. So, although the reaction of cyclopropyl α-sulfonyl carbanions derived from *trans*



Base	Electrophile	Yield
Bu^nLi	$CH_2=CHCH_2Br$	78%
NaH	$CH_2=CHCH_2Br$	88%
P_2-Et	$CH_2=CHCH_2Br$	92%

R^1 = Me, *p*-Cl-C_6H_4, CH_2CH_2O-*p*-$MeOC_6H_4$, Bn
R^2 = *p*-F-Ph, Me, *p*-Br-Ph, Ph, $CH_2CH_2OTBDMS$, CH_2CH_2O-*p*-$MeOC_6H_4$

1. CMMP, THF or toluene, 80–120 °C, 24 h. 2. $PhB(OH)_2$, DMF, 120 °C, K_2CO_3, $Pd(OAc)_2$, PPh_3. 3. $BrCH_2CO_2Et$, P_2-Et, THF, 0 °C to r.t., 69% (2 steps). 4. 2% $Pd(PPh_3)_4$, toluene, r.t. 5. 5% Pd_2dba_3, 10% (±)-binap, toluene, 95 °C.

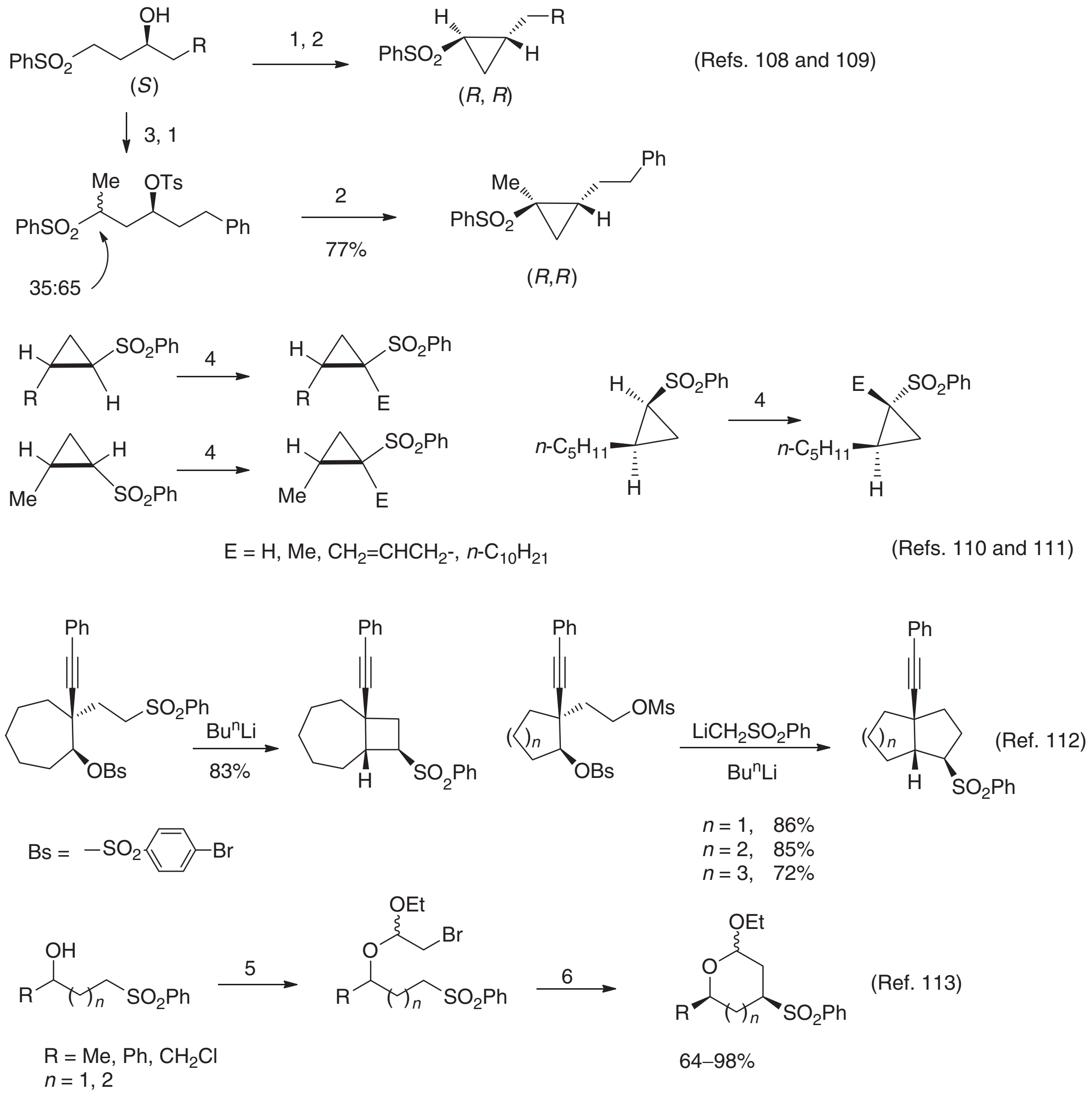
Scheme 20

substituted cyclopropanes takes place with retention of the configuration, the isomeric *cis* cyclopropane led to a rapid isomerization at the carbanion center (**Scheme 21**).[110] This inversion of configuration in favor of the anion that places the sulfone and C_5H_{11} group *trans* to each other has also been noted in the alkylation of enantiopure *cis*-substituted sulfonyl cyclopropanes.[111]

In addition a simple route to *cis*-carbocyclic scaffolds relies on the regioselective cleavage of bicyclic oxiranes bearing an alkynyl moiety followed by functional group manipulations that allow for an intramolecular ring closure mediated by α-sulfonyl carbanions.[112] Interestingly, pyranosyl sulfones can be obtained from a number of bromoacetal derivatives of γ- and δ-hydroxysulfones that undergo highly stereoselective intramolecular alkylation of the α-sulfonyl carbanion on treatment with lithium hexamethyldisilazane (**Scheme 21**).[113] Finally the application of this reactivity to the synthesis of natural products is illustrated with the macrocyclization between sulfonyl carbanions and allylic halides, one of the latter steps of the synthesis of phomactin D,[114] and of the preparation of advanced intermediates for the phomactins.[115]

In a related context, the lithiation and reaction with mono- and dielectrophiles of *N*-benzyl β-amino sulfones has been investigated in detail. For the substituted examples (R=Ph) the *anti* isomers are predominant (**Scheme 22**). With appropriate dielectrophiles, interesting nitrogen heterocycles are produced. Treatment with 1,2-diiodoethane brings about a stereoselective dimerization of the anion to produce *anti* disulfonyl diamines. The lithiation of *N*-benzyl-3-tosylpiperidine, obtained by reaction with a dielectrophile as described above, and axial alkylations take place smoothly.[116] In related research, the alkylation of a variety of enantioenriched *N*,*N*-dibenzylated β-amino sulfones has been described with excellent yields and variable diastereoselectivities.[117]

In several cases β-amino sulfones have been used to build heterocycles (**Scheme 23**). Thus, readily available (*S*)-5-(tosylmethyl)-2-pyrrolidinone is dialkylated on treatment with NaH and dielectrophiles, allowing for a synthesis of the indolizidine alkaloid (–)-coniceine.[118] Also, the sequential alkylation with dielectrophiles of readily available sulfonyl piperidines and pyrrolidines takes place smoothly and has been employed to prepare a variety of polyhydroxylated indolizidines and quinolizidines, as well as medium-sized cyclic amines.[119] Similarly, the chlorination of sulfonyl aminoalcohols takes place with a stereospecific rearrangement via aziridinium intermediates with chloride ion attack to the tertiary carbon atoms. Subsequent intramolecular alkylation provides a convenient route to substituted pyrrolidines.[120] However, the stereoselective alkylation of tert-butyl sulfones



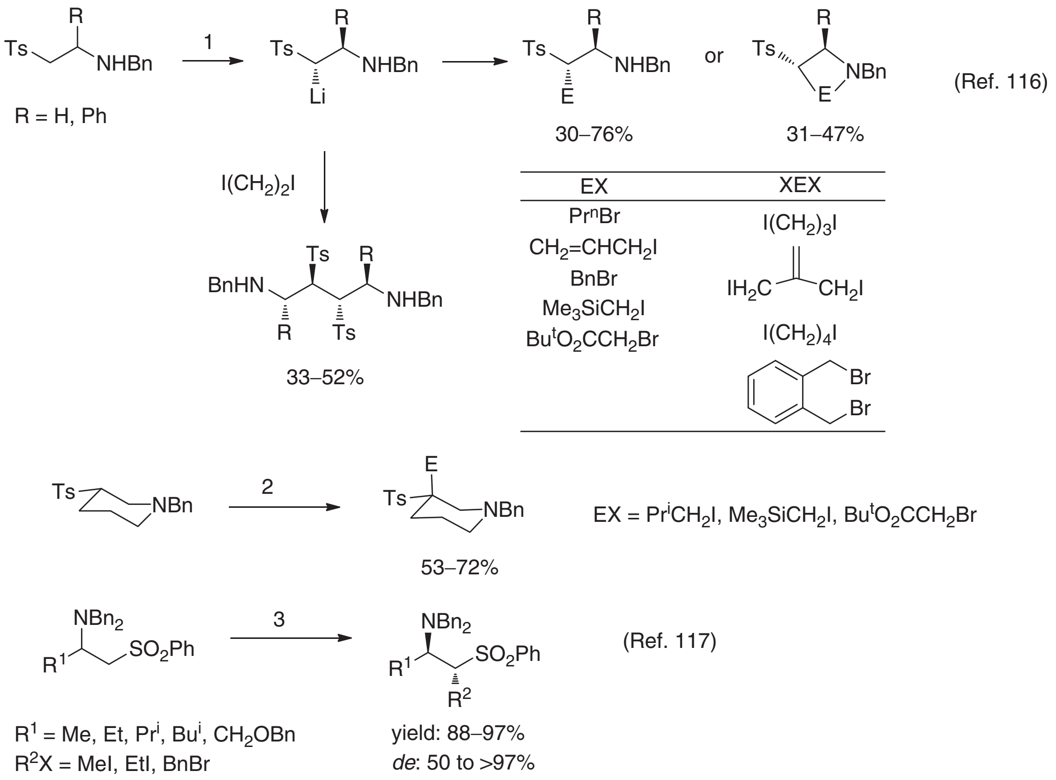
1. TsCl, pyr, 80–96%. 2. LDA, THF, –78 °C, 64–98%. 3. Bu^{n}Li, MeI, THF, (35:65), 72%. 4. Bu^{n}Li, TMEDA, EX, 52–86%. 5. NBS, ethylvinylether, 61–70%. 6. LiHMDS, THF, –78 °C to r.t.

Scheme 21

derived from (*R*)-cysteine has been studied (Scheme 23).[80] These alkylations take place under chelate control with high selectivity except for allyl bromide and are very sensitive to the bulk of alkylating agent. A chiral sulfonyl pyrrolidinopyridine was lithiated and alkylated with substoichiometric amounts of benzyl bromide.[121]

More complex alkyl halides can be used in the alkylation. Actually, alkylations of α-sulfonyl carbanions with funtionalized alkyl halides are employed very often in synthesis of natural products and analogs such as the secoester of reicifeiolide,[122] the trienomycins,[123] pheromones,[124] the calicogorgins,[125] mycotrienol,[126] the epothilones,[127] antascomicin A,[128] and latanoprost.[129]

The Ramberg–Bäcklund reaction continues to attract considerable attention (*see* Chapter 3.18).[130,131] A useful protocol entailing a Horner–Wadsworth–Emmons (HWE)/ conjugate addition/ Ramberg–Bäcklund sequence has been applied to a concise synthesis of unnatural (–)-varitriol.[132] Olefination of the lactol shown in Scheme 24 with the appropriate phosphonate produces a transient vinyl sulfone that undergoes conjugate addition to produce the sulfone in 88% yield. The key halogenation α to the sulfone followed by intramolecular alkylation and extrusion of SO_2 took place in a single step to afford a 1:3 mixture of alkenes that were separated and deprotected to produce (–)-varitriol and its 3′-epimer. In a related context, the synthesis of trisubstituted double bonds from sulfones is possible (Scheme 24).[133] Thus, 3,3-dilithio-1,1-dimethoxy-3-tosylpropane reacts with mono and dielectrophiles to give dialkylated products and carbocyclic derivatives in good yields. These acetals were transformed into aldehydes and further treatment with DBU afforded unsaturated aldehydes.



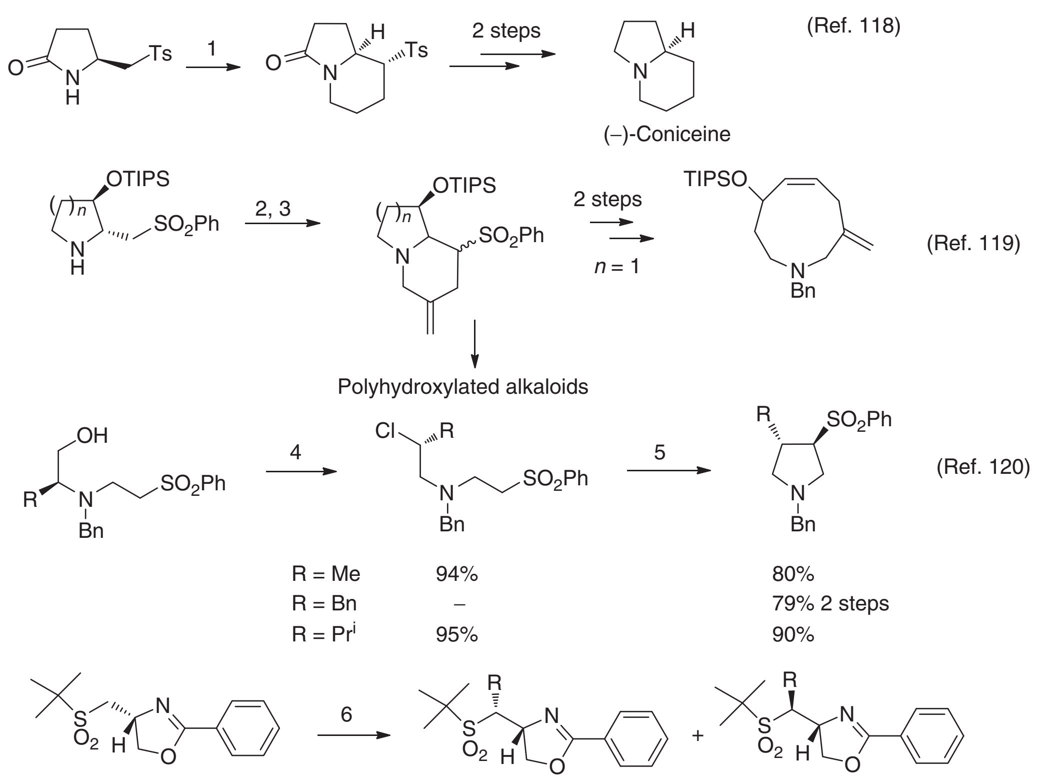
1. (a) 1.1 equivalents Bu^nLi, 1.0 equivalent DMPU, THF, −78 °C, 10 min. (b) 1.1 equivalents EX or XEX. 2. (a) 1.1 equivalents Bu^nLi, 1.1 equivalents DMPU, THF, −78 °C, 10 min. (b) EX. 3. (a) 1.3 equivalents LDA, THF, 1.3 equivalents TMEDA, −78 °C, 4 h. (b) 1.4 equivalents R^2X, −78 °C, 1 h, then r.t. overnight.

Scheme 22

Finally, in some cases, α-sulfonyl carbanions generated by conjugate addition to a vinyl sulfone may be efficiently alkylated (Scheme 25); thus, allylpotassium added to a functionalized vinyl sulfone to produce a carbanion that was quenched in excellent yields with MeI or TMSCl to produce single diastereomers at the α-sulfonyl center.[134] The α-silyl sulfone was utilized then as a latent anion and ultimately allowed for a subsequent ring closure. A related conjugate addition followed by allylation was an important step in a synthesis of cephalotaxine.[135] This protocol is also viable by intramolecular conjugate addition of a vinyl lithium generated by transmetallation and trapping with MeI to produce the bicyclic adduct as a single isomer.[136] Addition of phenyldimethylsilyllithium to vinyl sulfones followed by alkylation affords good yields of the alkylated products.[137]

In the same context, cyclopropane rings can be formed using this approach (Scheme 26). Thus, treatment of 2-sulfonyl 1,3-dienes with a sulfoxonium ylide results in a regiospecific cyclopropanation at the electron deficient alkene in high yields for cyclic dienes and in moderate to good yields for acyclic dienes.[138] Also, pentose and hexose-derived vinyl sulfones with a suitable leaving group react with a variety of nucleophiles to produce a transient α-sulfonyl carbanion that undergoes a highly stereoselective ring closure to produce sulfonyl cyclopropanes in good yields.[139] In related research, the nucleophilic addition of carbon-based nucleophiles to a 4-sulfonylhex-3-enopyranoside with a leaving group at C-6 gives rise to a mixture of sulfonyl cyclopropane and uncyclized adduct. Chromatographic separation and further treatment with base lead to excellent combined yields of the desired sulfonyl cyclopropanes.[140]

Epoxides are among the more versatile electrophiles in alkylation of α-sulfonyl carbanions and some examples are gathered in Scheme 27. The reaction between lithiated β-trimethylsilylalkyl sulfones and oxiranes, followed by treatment with sodium hydride affords predominantly *Z* *O*-trimethylsilyl homoallylic alcohols in good yields. In the absence of NaH, the expected adducts are produced in excellent yield.[141] In another example, the pheromone grandisol was prepared by a sequence of steps that includes the condensation of a lithiated cyclobutyl phenyl sulfone with a sulfanyl oxirane and subsequent oxidation to produce a ketodisulfone that was further transformed into (±)-grandisol.[142] Similarly, the reaction of lithiated (phenylsulfonyl)methane in THF-1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) with a variety of 2-substituted oxiranes followed by quenching with TBDMSCl gave the expected sulfonyl silyl ethers that were transformed into hydroxy vinyl sulfones, within a study on their cyclization to THFs.[143] This reactivity is also available for solid-phase synthesis. Thus, the monoalkylation of polymer-bound sulfonyl carbanions is efficiently carried out with dimsyl anion at r.t. When terminal oxiranes are used as electrophiles, the subsequent Swern oxidation of the adducts cleaves the linker and produces unsaturated ketones in excellent yields.[144]



R		
R = Me	94%	80%
R = Bn	–	79% 2 steps
R = Pr^i	95%	90%

RX		
MeI	72%	–
EtBr	65%	–
PrBr	14%	–
CH_2=$CHCH_2Br$	24%	13%

1. 2 equivalents NaH, 1,3-diiodopropane, DMF, 0 °C to r.t., 60%. 2. 3-chloro-2-chloromethylpropene, K_2CO_3, cat. LiI, CH_3CN, r.t., 72% ($n = 1$). 3. LiHMDS, THF, 0 °C, 97% ($n = 1$); 80% ($n = 2$, two steps). 4. 1.5 equivalents $SOCl_2$, Δ, 2 h, $CHCl_3$; then aqueous KOH. 5. 1.4 equivalents LDA, THF, –78 °C, 2 h. 6. (a) 1.5 equivalents LDA, THF, –78 °C, 1 h. (b) 2.0 equivalents RX, 4 h, –78 °C, 12 h, r.t.

Scheme 23

There are interesting examples of intramolecular epoxide alkylations (Scheme 28) such as the intramolecular alkylation of a lithiosulfone with an epoxide, a key step in an approach to tetrasubstituted oxocanes,[145] and the stereocontrolled synthesis of cyclobutanes[146] by a sequence that entails an heteroatom-directed conjugate addition to a vinyl sulfone followed by intramolecular oxirane opening of the resulting α-sulfonyl carbanion.

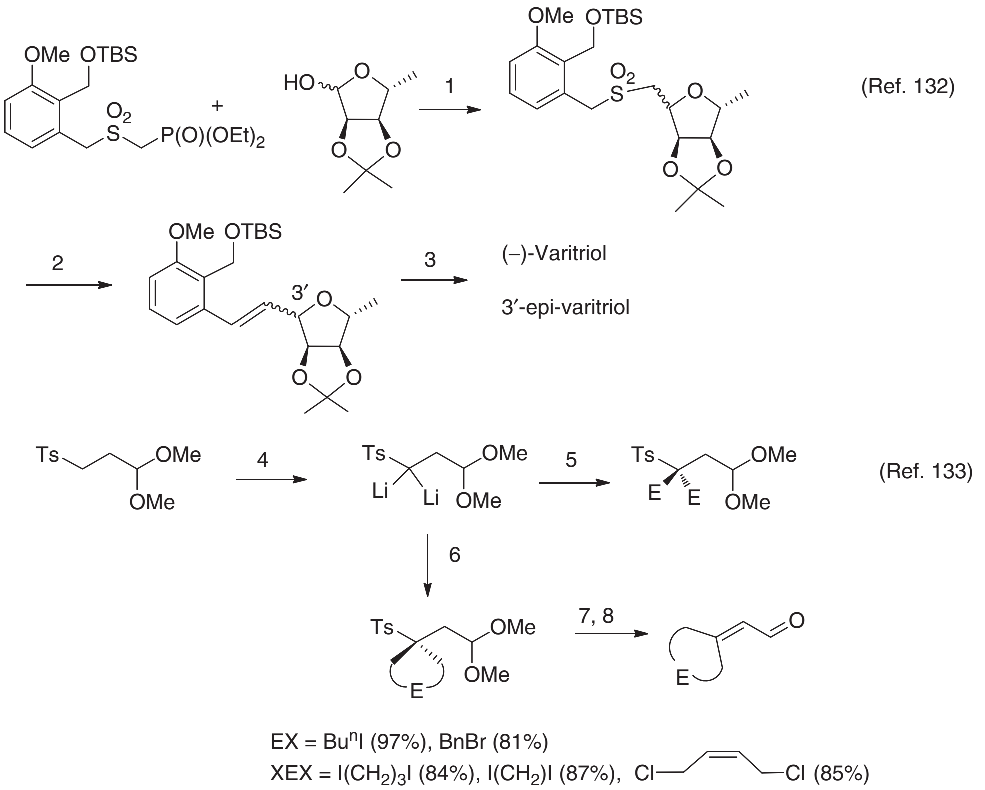
Finally, aziridines are also susceptible of acting as electrophiles in alkylation reactions (Scheme 29). In particular, the nucleophilic cleavage of a spiro-aziridine with an α-sulfonyl carbanion to produce a sulfonyl sulfonamide in excellent yield is a key step in a recent synthesis of (±)-lepadiformine.[147] Also, 1,2,3-trisubstituted aziridines bearing vinyl or hydroxymethyl substituents undergo highly regioselective ring opening with α-sulfonyl carbanions.[148]

3.03.4.2 α-Metalloallyl Sulfones

α-Metalloallylic sulfones have become a useful instrument in organic synthesis and consequently have been used in a variety of synthetic approaches to natural products, such as (+)-ambrein,[149] taxol fragments,[150] (±)-sinulariol-B,[43] coenzyme Q_{10},[151] acyclic terpenoids,[152] and lycopene.[153]

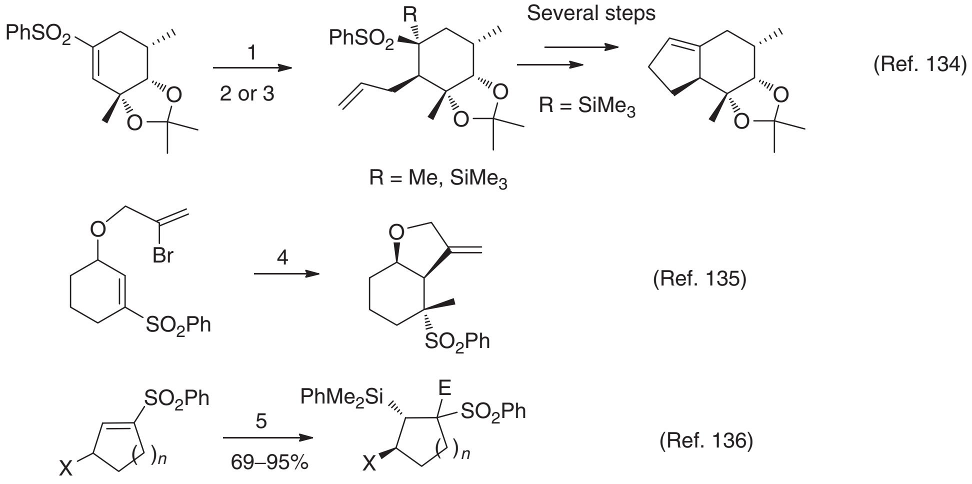
The lithiation and trapping with electrophiles of bicyclic *tert*-butyl sulfones has been investigated in detail from a structural point of view (Scheme 30).[154] The stereochemical outcome of the process is dependent on the period of time between the end of addition of the base and addition of the electrophile; at short times, good levels of selectivity may be recorded.

In some cases, vinyl sulfones can be efficiently metallated to produce the related allylic sulfonyl carbanions (Scheme 31). Thus, a sulfonyl cyclopropene with a methyl substituent at the *β*-position is metallated with *n*-butyllithium and trapped with a variety of



1. NaH, THF, 0 °C to r.t., 88% (α:β = 2:3). 2. KOH, Al_2O_3, CBr_2F_2, 78% (α:β = 1:3). 3. 1 M aqueous HCl, THF, 72% and 83%. 4. 2 equivalents Bu^nLi, THF, –78 to 0 °C. 5. 2 equivalents EX, then H_2O. 6. XEX, then H_2O. 7. cat. HCl, acetone/H_2O. 8. DBU, CH_2Cl_2.

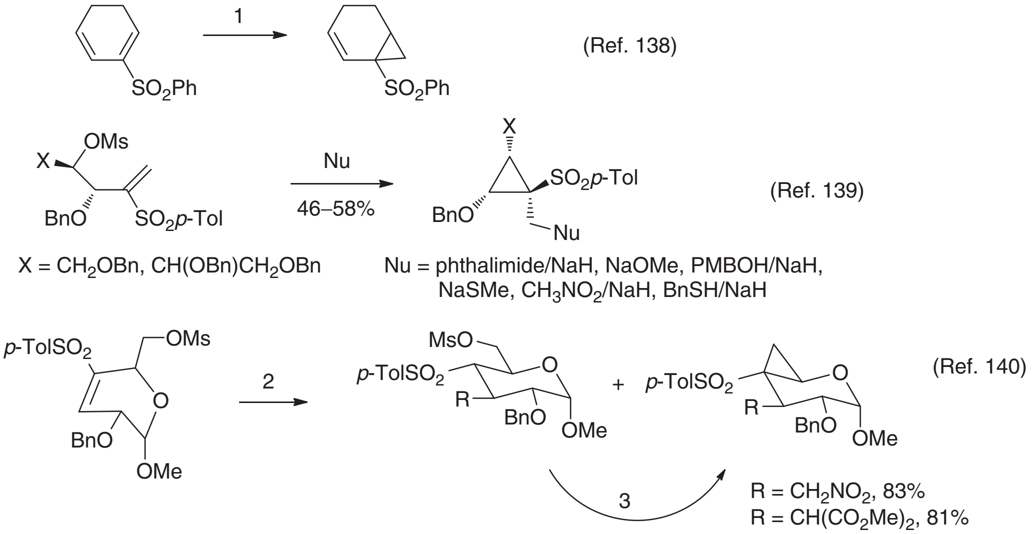
Scheme 24



n = 1, 2, 3
X = OTBDMS, OTBDPS, OMe, OMOM, H

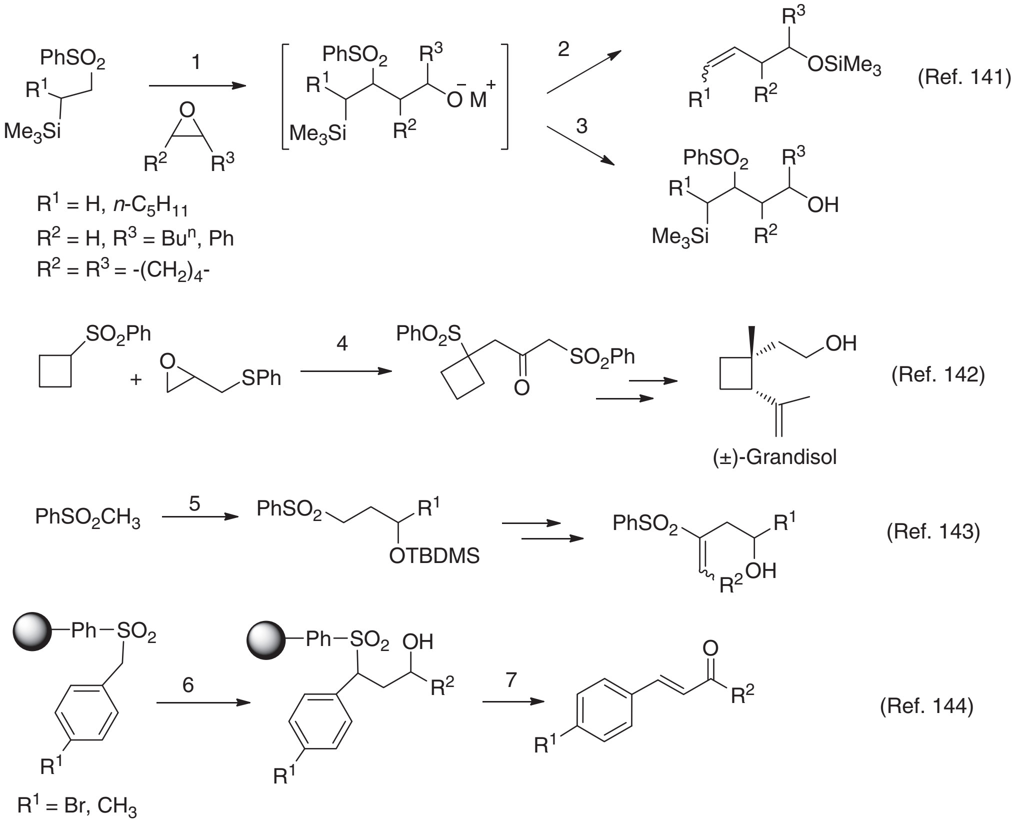
1. Allylpotassium, Et_2O, –78 °C. 2. MeI, –78 °C to r.t., 91%. 3. TMSCl, –78 °C to r.t., 92%. 4. (a) 1.1 equivalents Bu^tLi, THF, –78 °C. (b) excess MeI, –78 °C to r.t., 69%. 5. (a) $PhMe_2SiLi$, THF, –78 °C. (b) Electrophile (AllylBr, BnBr), HMPA.

Scheme 25



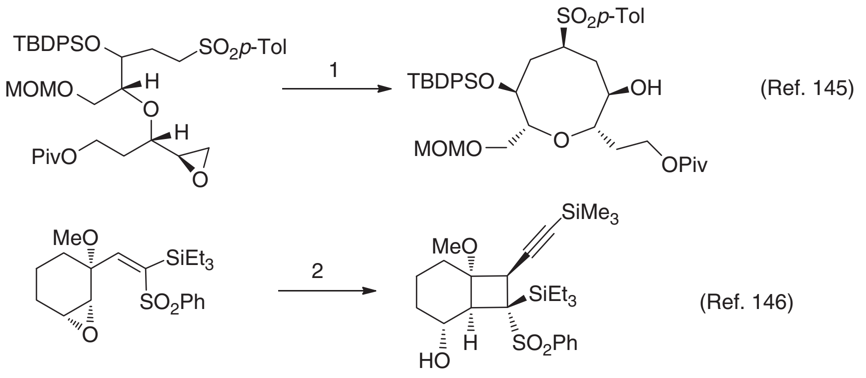
1. Me_3SOI, NaH, 95%. 2. CH_3NO_2 or $CH_2(CO_2Me)_2$, $KOBu^t$, THF, 70 to 80 °C, 8 h. 3. $KOBu^t$, THF, 70 to 80 °C, 2 h.

Scheme 26



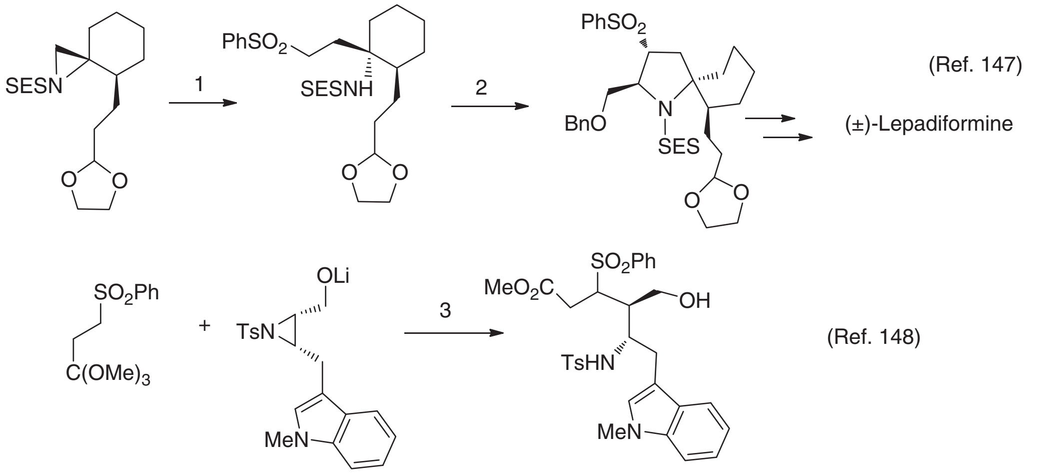
1. Bu^nLi, DME, –78 °C then oxirane, –78 °C to r.t., 1–3 h. 2. NaH (1.5–3.0 equivalents), Δ, 85–92%. 3. H_2O, 80–90%. 4. (a) MeLi, THF, –15 °C, then oxirane. (b) H_2O_2, HOAc. (c) Jones, r.t., 87% overall. 5. Bu^nLi, THF, –78 °C to r.t.; add DMPU, then oxirane; add TBDMSCl, 70–96%. 6. 5 equivalents $CH_3S(O)CH_2Li$, THF, r.t.; 7 equivalents propylene or styrene oxide. 7. Swern, 82–90% overall.

Scheme 27



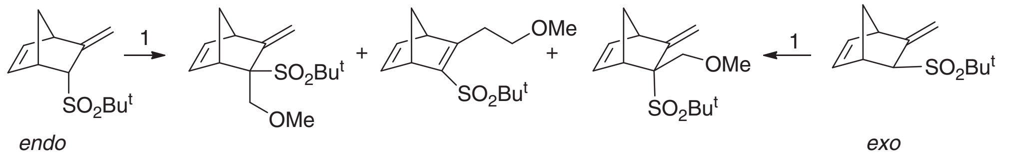
1. 4 equivalents LDA, THF, -65 °C, 71%. 2. 5.5 equivalents $HCCSiMe_3$, 5 equivalents MeLi, hexane-Et_2O, -40 °C to r.t., 75%.

Scheme 28



1. $PhSO_2Me$, Bu^nLi, THF, 97%. 2. 2 equivalents Bu^nLi, THF, -78 °C, then $BnOCH_2CHO$, then PhCOCl, 60%. 3. Bu^nLi, THF, then O-Li-aziridine, -78 °C to r.t., then aqueous NH_4Cl, 90%.

Scheme 29



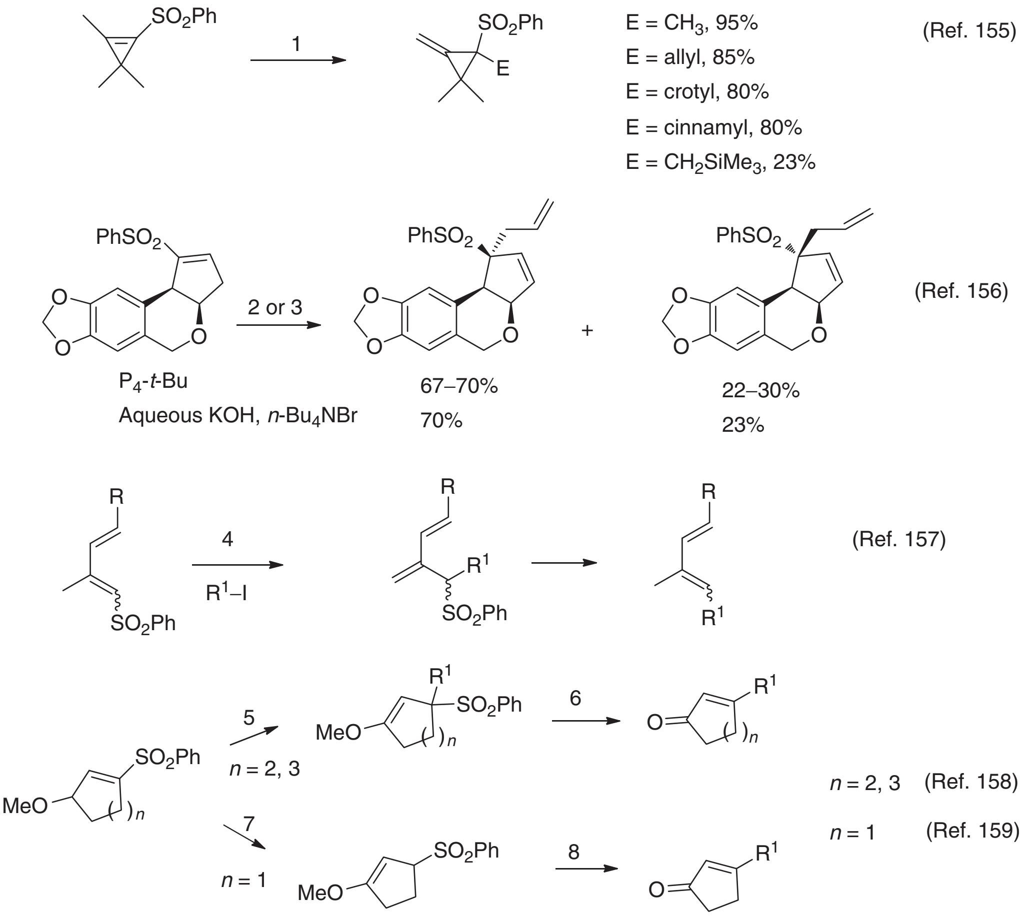
SM	Time (min)	Ratio	Yield (%)
endo	5	72:15:13	98
endo	120	30:27:43	98
exo	5	14:27:59	98
exo	120	22:35:43	98

(Ref. 154)

1. Bu^nLi, THF, -105 °C, 5 or 120 min; then $MeOCH_2$ I, -105 °C.

Scheme 30

alkylating agents to afford methylene cyclopropanes.[155] Similarly, α-alkylation with allyl bromide of functionalized cyclic vinyl sulfones may be carried out with the phosphazene base P_4-*t*-Bu or under basic phase-transfer catalysis without any anion-promoted β-elimination.[156] Dienyl sulfones can also serve as starting materials for these reactions. Thus, alkylation of a variety of dienyl sulfones with a methyl substituent at C-2 is α-selective in the presence of NaHMDS and 18-c-6. The resulting products may



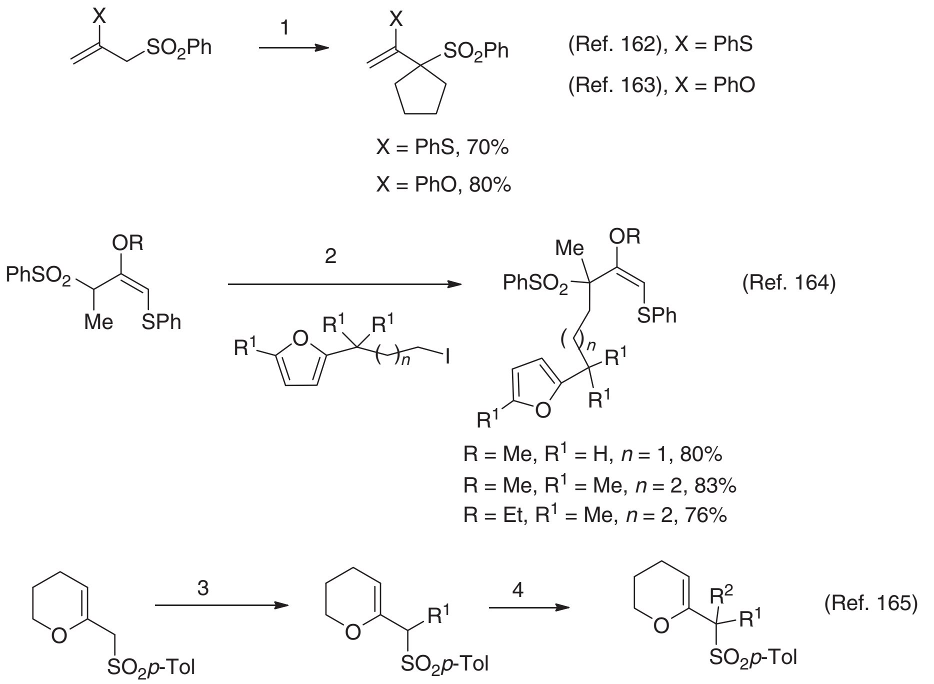
1. 1.1 equivalents Bu^nLi, THF; then EBr or Me_3SiCH_2Cl or CH_3I. 2. 1.05 equivalents P4-*t*-Bu, 3–5 equivalents allyl bromide, THF, –78 °C, 5 min. 3. 50% aqueous KOH, 0.2 equivalent n-Bu_4NBr, 10 equivalents allyl bromide, THF, r.t., 5 min. 4. 1.5 –2.5 equivalents NaHMDS, 1.55–2.55 equivalents 18-c-6, 2–4 h, THF, –78 °C to r.t., 85–99%.
5. Bu^tLi, THF, –78 °C, R^1Br or R^1I. 6. Saturated $NaHCO_3$, 91–98%. 7. P_2-Et, 50–55 °C, 65–70 h, >90%. 8. Bu^nLi, R^1Br, then moist SiO_2, CH_2Cl_2, r.t., 12 h, 76–86%.

Scheme 31

undergo stereocontrolled desulfonylation to produce *E,E* or *E,Z* derivatives.[157] Finally, the vinyl to allyl isomerization on lithiation and α-sulfonyl alkylation takes place smoothly for γ-methoxy cyclohexenyl and cycloheptenyl vinyl sulfones, affording β-substituted enones in excellent yields.[158] Successful extension to the cyclopentenyl series requires previous isomerization to sensitive γ-methoxy allyl sulfone followed by metallation, alkylation, and mild hydrolysis.[159] In related chemistry, substituted tosylaziridines are also adequate electrophiles.[160] The methodology was later extended to the preparation of 3-substituted-4-alkyl cyclohex-2-en-1-ones that required the use of HMPA in some cases.[161]

In a similar context, allylic sulfones with a heteroatom at C-2 can undergo alkylation in different situations (Scheme 32). For example, the alkylation of acyclic sulfones bearing heteroatomic phenylthio[162] and phenoxy[163] substituents at C-2 with alkyl halides takes place at the α-position and affords cyclic products from 1,w-dihalides. Likewise, the alkylation of related systems with heteroatomic substituents at C-2 and C-3 required the use of HMPA to afford exclusively *E* alkylated products in good yields.[164] In addition, allylic sulfones with a heteroatomic substituent at C-2 embedded in a ring are also adequate substrates for α-alkylation. In the case of sulfonyl 2*H*-pyrans, monoalkylation takes place smoothly even for isopropyl bromide, whereas that is not possible for a second alkylation.[165] A related sulfonyl 2,3-dihydro-1*H*-pyrrole may also be successfully monoalkylated similarly.[166]

Aside the above examples of optimization of the alkylation protocols in different contexts, the base-catalyzed alkylation has been an important tool allowing the study of a number of useful methodologies. These include the molybdenum-catalyzed nucleophilic substitution of an allylic sulfone,[167] a novel route to substituted cyclic 1,3-dienes by base-induced elimination of benzenesulfinic acid from alkylated cyclic allylic sulfones,[168] and the mono- and sequential dialkylation of 1-(phenylsulfonyl)-4-(trimethylsilyl)-2-butenes that ultimately lead to 1,1-disubstituted-1,3-butadienes.[169]



(Ref. 162), X = PhS

(Ref. 163), X = PhO

X = PhS, 70%

X = PhO, 80%

(Ref. 164)

R = Me, R^1 = H, *n* = 1, 80%

R = Me, R^1 = Me, *n* = 2, 83%

R = Et, R^1 = Me, *n* = 2, 76%

(Ref. 165)

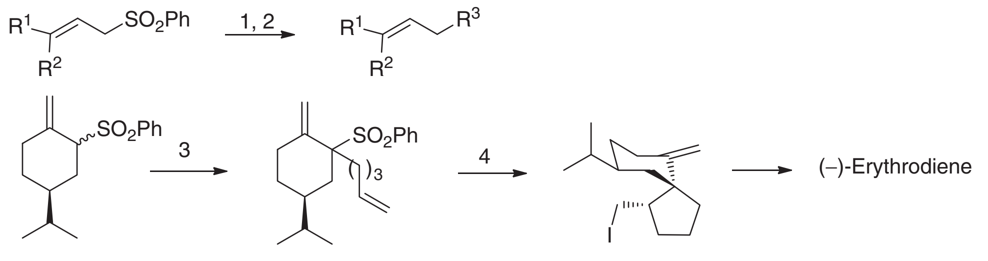
R^1X	Yield (%)
$TMSCCCH_2Br$	47
$CH_2{=}CHCH_2Br$	90
MeI	83
$PhCH_2Br$	84
Bu^nBr	70
Pr^iBr	60
Bu^tBr	0

R^1	R^2X	Yield (%)
Bu^n	$CH_2{=}CHCH_2Br$	90
Bu^n	Bu^nBr	72
Bu^n	Pr^iBr	0
$CH_2{=}CHCH_2$	Bu^nBr	82

1. 2.2 equivalents NaH, DMF, 1 equivalent 1,4-dibromobutane, 0°C to r.t. 2. 1.1 equivalents Bu^nLi, THF; 20% HMPA, –78 °C to –50 °C. 3. 0.9 equivalent Bu^nLi, THF, 1 equivalent HMPA, 1 equivalent R^1X. 4. 1.1 equivalents Bu^nLi, THF, 1 equivalent HMPA, 1 equivalent R^2X.

Scheme 32

In some occasions, the alkylation of allylic α-sulfonyl carbanions is followed by a desulfonylation process (Scheme 33). This is the case of an 'integrated chemical process' consisting of a series of alkylations of allylic sulfones and one-pot Pd-catalyzed reductive desulfonylations with $LiBHEt_3$ which provide higher yields that the stepwise procedure.[170] Also, readily available allylic phenyl sulfones that allow for a straightforward introduction of an alkene chain, are superior to allylic acetates in the Pd-catalyzed



dr = 80:20

dr = 95:5

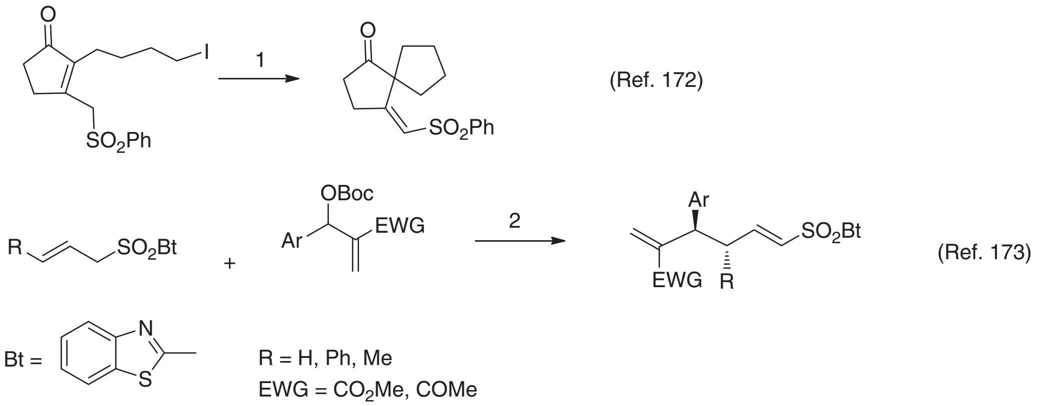
(Ref. 171)

1. 1.05 equivalents Bu^nLi, 1.0 equivalent R^3Br, THF –78°C to r.t. 2. 0.1 equivalent $Pd(OAc)_2$, 0.1 equivalent dppp, 2.0 equivalents $LiBHEt_3$, 0 °C, 2–4 h, 57–93%, 9 examples. 3. Bu^nLi, $CH_2{=}CH\text{-}(CH_2)_3\text{-}I$, 89%. 4. $Pd(PPh_3)_4$, Et_2O, $ZnEt_2$, 25 °C, 27 h; then I_2 in THF, 94%.

Scheme 33

Zn-ene cyclization.[171] The methodology is general for several types of substrates and has been applied successfully to the synthesis of erythrodiene.

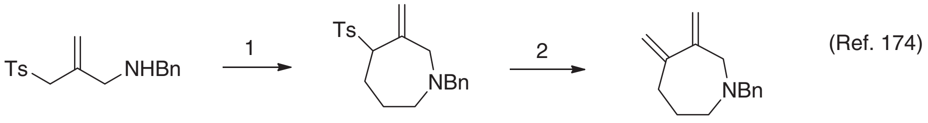
Although the vast majority of alkylations to allylic sulfones are α-selective, there are cases in which γ-alkylation is predominant or even exclusive (**Scheme 34**). Intramolecular alkylation of a cyclopentenyl allylic sulfone leads to an excellent yield of a spirocyclic vinyl sulfone by alkylation at the γ-position.[172] In an interesting work, a Lewis base assisted Brønsted base catalysis (LBABB) strategy for the direct asymmetric γ-alkylation of allylic sulfones with Morita– Baylis–Hillman (MBH) carbonates has been described.[173]



1. 1.1 equivalents NaH, Et_2O, 0°C, 2 h, 83%. 2. 5% $(DHQD)_2AQN$, $PhCF_3$, 40 °C, 53–82%, 89–98% *ee*, 17 examples.

Scheme 34

Allylic sulfonyl carbanions have been used in the synthesis of azepane rings (**Scheme 35**). In particular the chemistry of mono- or dilithio derivatives of γ-tosyl substituted benzylmethallylamine has been studied finding that in most cases, the monolithio derivatives are alkylated exclusively α- to the sulfone.[174] When dielectrophiles are used cyclic allylic sulfones are obtained in moderate yields. Subsequent alkylation of a lithiated perhydroazepine thus produced with (chloromethyl)magnesium chloride resulted in electrophilic substitution followed by β-elimination to render an exocyclic diene in excellent yield.



1. 2.2 equivalents Bu^nLi, 2.2 equivalents DMPU, 1.1 equivalents $I(CH_2)_3I$, THF, –78 °C to r.t., 43% (52% from monoanion). 2. Bu^nLi, THF, 2 equivalents $ClCH_2MgCl$ (from $ClCH_2I$ and Pr^iMgCl), –78 °C to –30 °C, 90%.

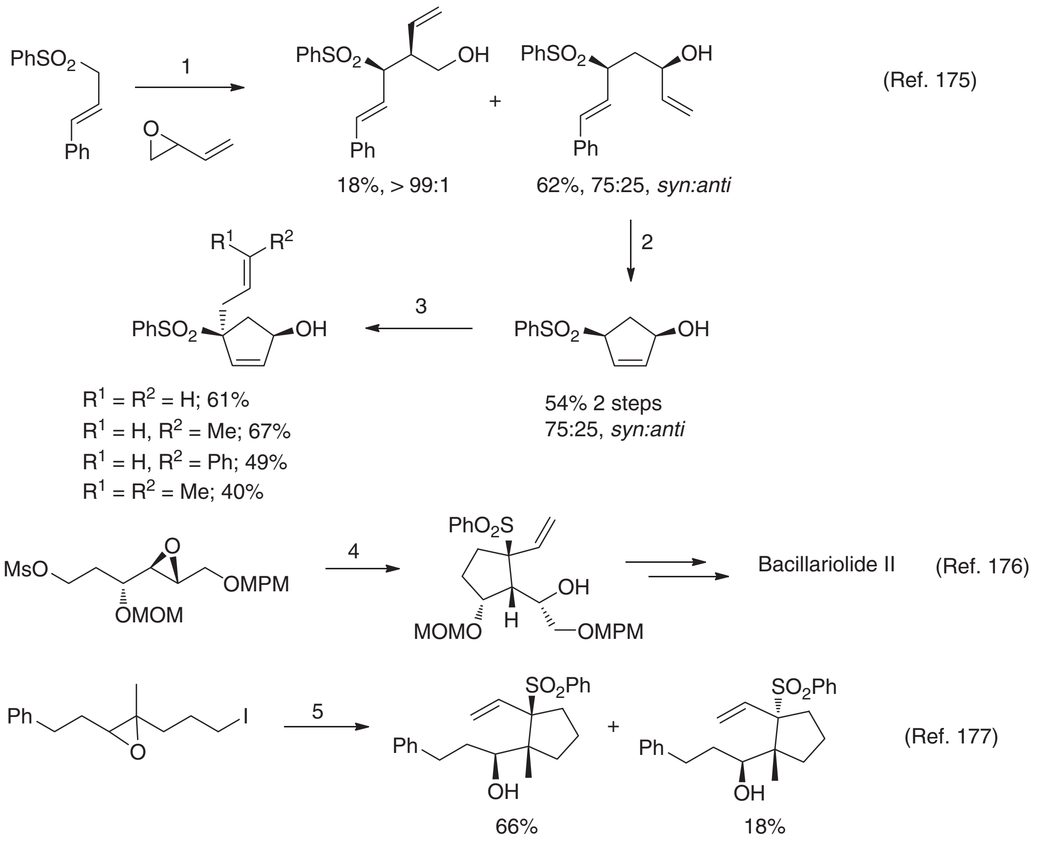
Scheme 35

Epoxides can be used as electrophiles in the alkylation of allylic sulfonyl carbanions (**Scheme 36**). The alkylation of lithiated cinnamylsulfonyl benzene with vinyl oxirane takes place with fair regioselectivity and with moderate *syn* stereocontrol. Ring-closing metathesis leads to a hydroxy cyclopentenyl sulfone that undergoes a completely selective allylation on treatment with *n*-butyllithium.[175] A particularly interesting development is the one-pot construction of carbocycles from epoxy mesylates and lithiated allyl phenyl sulfones. This protocol allows for the synthesis of three- to six-membered carbocycles and it has been applied to the synthesis of the bacillariolides.[176] In an extension of the method, the synthesis of cyclopentane derivatives with a quaternary carbon has been reported; this modification is best performed from epoxy iodides, in a stepwise one-pot fashion and with the aid of a Lewis acid (Me_3Al) to facilitate the intramolecular oxirane cleavage.[177]

Alcohols have also been used as electrophiles (**Scheme 37**). In an example, CMMP mediates the Mitsunobu alkylation of allylic sulfones with primary and secondary alcohols. The methodology has been applied to the synthesis of norfaranal, an analog of a Pharaoh's ant pheromone.[178]

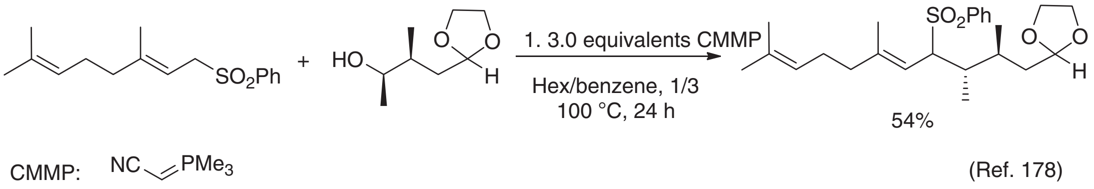
In a similar context, the solid-phase synthesis of isoxazolocyclobutanones and related substrates has been reported (**Scheme 38**). This protocol involves the sulfinate-sulfone alkylation, formation of a four-membered ring by sulfone dianion alkylation, regioselective nitrile oxide 1,3-dipolar cycloaddition and Swern oxidation to a cyclobutanone with concomitant cleavage of the linker and double-bond migration to produce an isoxazole.[179]

Parallel to allyl sulfones, there are examples of alkylation of other related sulfonyl compounds (**Scheme 39**). In particular the treatment with base of sulfonyl allenes triggers an isomerization to the propargyl anions that undergo efficient cyclization to

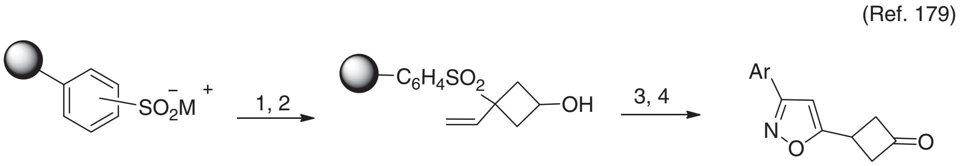


1. 1.0 equivalent Bu^{n}Li, THF, then oxirane, –20 °C to r.t., 2.5 h. 2. 0.005 equivalent Grubbs' 2nd gen. catalyst, CH_2Cl_2, Δ, 30 min. 3. 2.0 equivalents Bu^{n}Li, THF; then $R^1R^2C = CHCH_2Br$, –20 °C to r.t., 1.5–2.5 h. 4. 2.5 equivalents allyl phenyl sulfone, 2.4 equivalents Bu^{n}Li, THF, –78 °C to r.t., 99%. 5. 2.4 equivalents allyl phenyl sulfone, 2.3 equivalents Bu^{n}Li, THF, –78 °C to –20°C, then 2.1 equivalents Bu^{n}Li and 2.2 equivalents $AlMe_3$, THF, –78°C to 0 °C.

Scheme 36



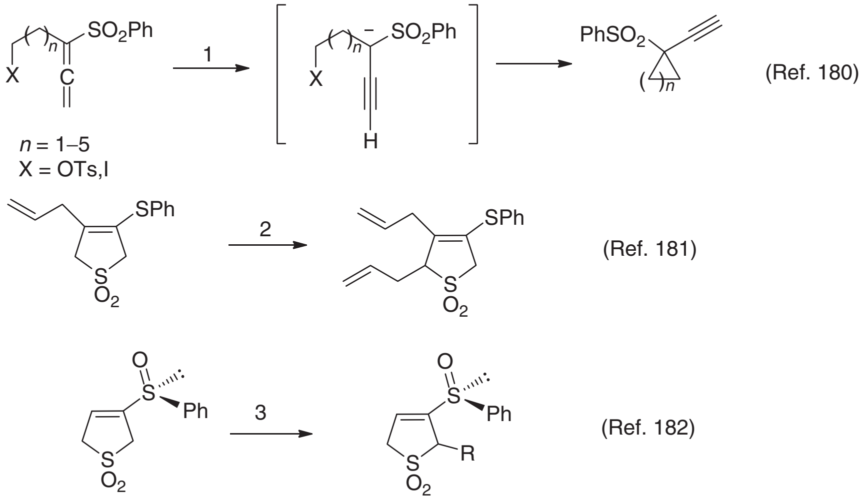
Scheme 37



1. Allyl bromide, THF/DMF. 2. 8 equivalents Bu^{n}Li, THF, 10 equivalents epichlorohydrin, r.t., 24 h. 3. Ar-CH=NOH, aqueous NaOCl, CH_2Cl_2/THF (1:1). 4. Swern oxidation, 32–36% four steps.

Scheme 38

produce three- to seven-membered 1-ethynyl-1-(phenylsulfonyl)substituted carbocycles.[180] Sulfolenes are among this type of compounds. The regiochemical outcome of the alkylation of metallated sulfolenes is dependent on the nature of the substituents. Thus the allylation of a phenylthio substituted sulfolene took place exclusively at the distal position relative to the sulfide substituent.[181] In contrast, the alkylation of the dianion derived from a 3-phenylsulfinyl sulfolene takes place exclusively at C-2 and with moderate to high diastereoselectivity; both isomers were converted into the same diene by thermal extrusion of SO_2.[182]



RX	Yield (*S*,*S*:*S*,*R*)
CH_3I	88% (6:1)
CH_2=$CHCH_2Br$	84% (100:0)
$PhCH_2Br$	75% (5:1)
CH_2=$CH(CH_3)I$	80% (4:1)
CH_2=$CH(CH_2)_4I$	82% (4:1)

1. NaH, DMF, 0 °C or TBAF, DMF, 0 °C (0.1–0.01 M), 51–97%.
2. 1.7 equivalents Bu^nLi, 4.0 equivalents HMPA, 4.0 equivalents allyl bromide,
THF, −78 °C, 54%. 3. 2.2 equivalents Bu^nLi, 4.0 equivalents HMPA, 1.0 equivalent RX, THF, −105°C.

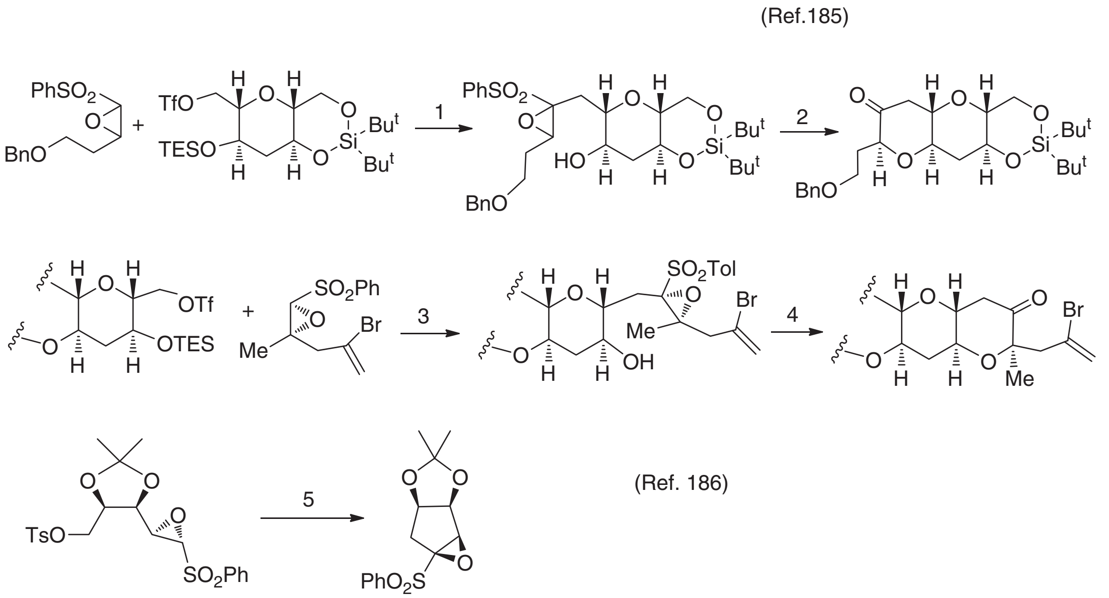
Scheme 39

3.03.4.3 α-Metallo α-Heterosubstituted Alkyl Sulfones

The alkylation of sulfones bearing α-oxygen substituents has received considerable attention.[183,184] An interesting and useful iterative approach to the synthesis of polycyclic ether natural products based on the coupling of oxiranyl sulfonyl anions with triflates, followed by a cyclization has been developed (Scheme 40).[185] The coupling is best effected by addition of Bu^nLi to a cold mixture of the triflate and the sulfonyl oxirane in the presence of HMPA. Subsequent cyclization aided by a Lewis acid with concurrent loss of the sulfone gives rise to highly substituted ketones. Alternatively, treatment of the alkylated sulfonyl oxirane with $MgBr_2$ gives rise to a bromo ketone that cyclizes with DBU with epimerization to the equatorial isomer if appropriate; this mode of cyclization allows for the use of racemic sulfonyl oxiranes, more readily available, for the alkylation step. This cyclization can also be affected in an intramolecular fashion with excellent results.[186] In contrast, the base-promoted cyclization of the alkenyl sulfone precursor (not shown) with a tosylate or iodide leaving group was much lower yielding (10–19%).

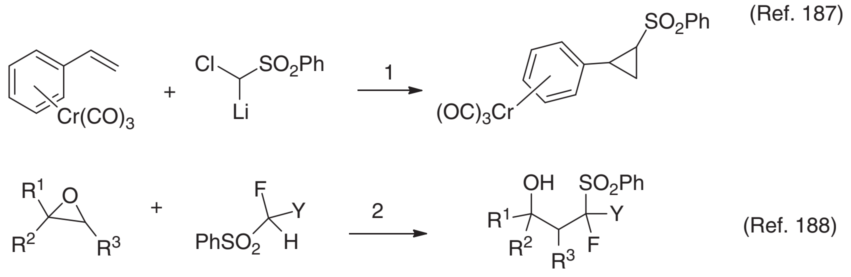
Within the same context sulfones bearing α-halide substituents can be alkylated (Scheme 41). Tricarbonyl(styrene)chromium (0) reacts with a lithiated α-chlorosulfone to give the complex of a disubstituted cyclopropane as a single diastereomer.[187] Also the nucleophilic fluoroalkylation of epoxides with fluorinated sulfones has been explored. Although the difluorinated carbanion was unreactive, the monofluoro species had moderate reactivity under optimized conditions and the related disulfone had a better reactivity profile. The reactivity of these fluorinated sulfones was substantially different to that of the chlorinated analogs.[188]

Finally, sulfones bearing α-nitrogen substituents have also received considerable attention (Scheme 42). The alkylation of fused sulfonyl lactams takes place in good yields.[189] Phenylsulfonyl(nitro)methane is a useful nucleophile for Pd(0)-catalyzed allylic alkylations within the context of the enantioselective synthesis of carbanucleosides.[190] Tosylmethyl isocyanide (TosMIC) allows for a sequential alkylation by treatment under varying conditions with alkyl iodides. Subsequent reductive elimination of tosyl and isonitrile groups with Li in liquid NH_3 gives rise to sex pheromones of the apple leafminer.[191]



1. (a) Bu^{n}Li, THF, HMPA, –100 °C, 90%. (b) *p*-TsOH·H_2O, CH_2Cl_2, MeOH, r.t., 99%. 2. (a) MgBr·OEt_2, LiBr, CH_2Cl_2, –15 °C to 0°C, 99%. (d) DBU, CH_2Cl_2, 0 °C, 90%. 3. (a) Bu^{n}Li, THF, HMPA, –100 °C, 91%. (b) *p*-TsOH·H_2O, CH_2Cl_2, MeOH, r.t., 91%. 4. BF_3·OEt_2, CH_2Cl_2, –80 °C, 98%. 5. 2.2 equivalents LiHMDS, THF, –78 °C, 1 h, 87%.

Scheme 40



Y = F, 0%
Y = H, 10–78%
Y = SO_2Ph, 70–91%

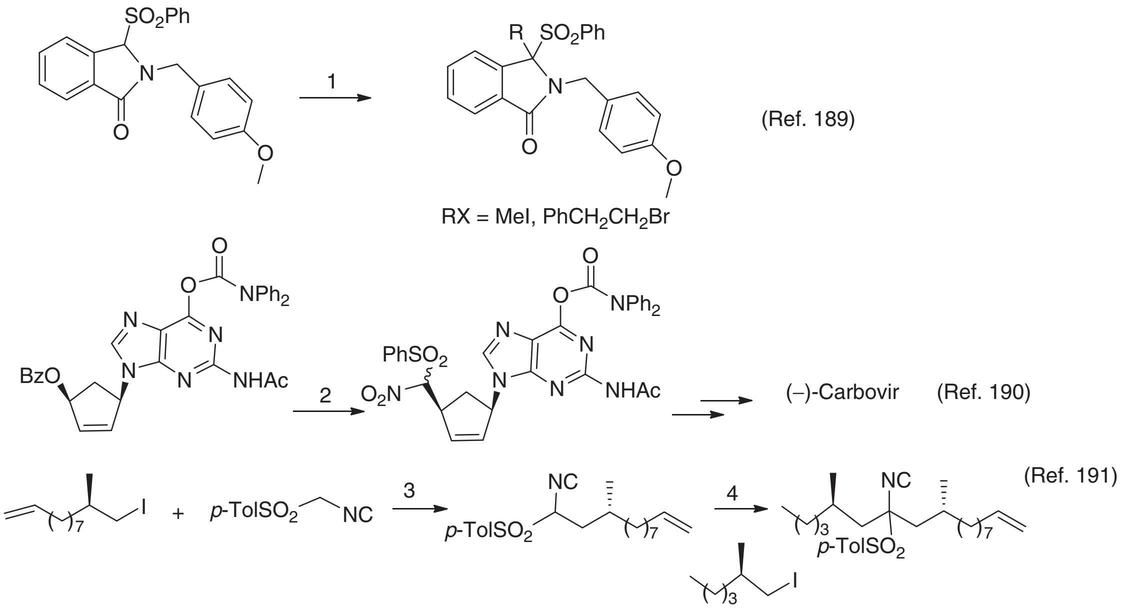
1. THF, 91%, >95% *de*. 2. Bu^{n}Li, Et_2O, –78 °C, 30 min; then BF_3·Et_2O, 5 min; then epoxide, 2–12 h, –78 °C to r.t.

Scheme 41

3.03.4.4 α-Metallovinyl Sulfones

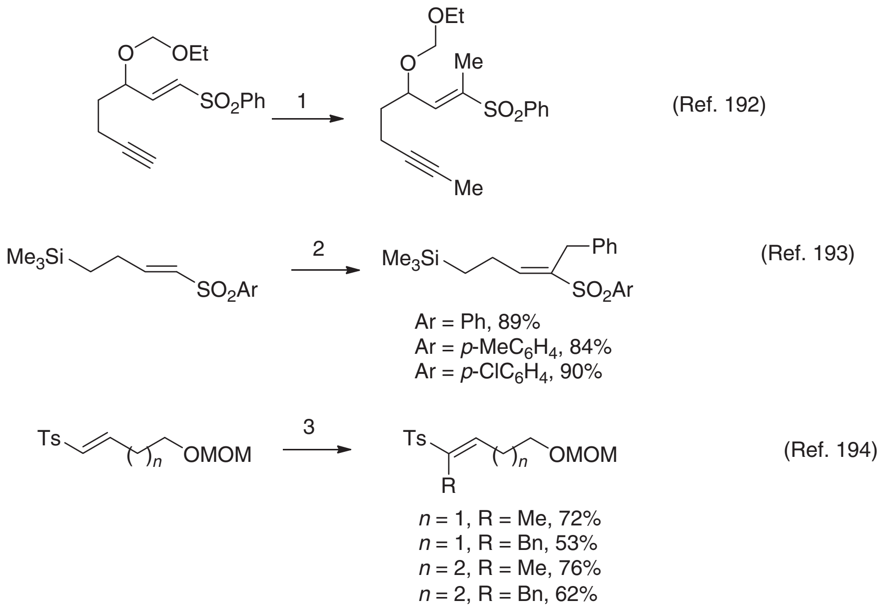
As in the case of vinyl sulfoxides, the alkylation of α-metallo vinyl sulfones has found interesting applications (Scheme 43). The dilithiation of α-sulfonyl enyne and trapping with MeI results in smooth dimethylation at the vinyl sulfone and the terminal alkyne.[192] Also the lithiation and benzylation accelerated by HMPA of vinyl sulfones with a distal trimethylsilyl substituent at the alkyl chain, takes place with excellent yields.[193] Similarly the MOM derivatives of tosyl butenol and pentenol can be lithiated with *n*-butyllithium and undergo smooth reaction with a variety of electrophiles including methyl iodide and benzyl bromide.[194]

Alternatives to base-induced deprotonation have been used to generate α-metallovinyl sulfones (Scheme 44). Interestingly, the *syn*-copper-catalyzed addition of alkyl zinc derivatives to alkynyl sulfones leads to organometallic species that react with typical electrophiles.[195] The allylzincation of an acetylenic sulfone affords a vinyl zinc intermediate that undergoes smooth Negishi cross-coupling with allyl and benzyl bromides, as well as, with aromatic bromides and iodides.[196] A useful sulfonyl vinyl Grignard reagent can arise by metal–halogen exchange from a bromosulfone and Pr^{i}MgBr; the reaction of this species with allylic bromides required Cu(I) catalysis.[197] The palladium-catalyzed hydrostannylation of alkynyl sulfones followed by coupling in the presence of CuI with allylic bromides leads to 1,4-dienyl sulfones.[198]



1. NaH, THF/DMSO (9:1) or THF/HMPA (4:1), MeI or $PhCH_2CH_2Br$, 55–75%. 2. 1% $Pd_2dba_3{\cdot}CHCl_3$, 8% PPh_3, 1.2 equivalents $PhSO_2CH_2NO_2$, 2.5 equivalents Et_3N, THF, r.t., 97%. 3. 0.3 equivalent TBAI, 40% aqueous NaOH, CH_2Cl_2, 0 °C, 2 h, r.t., 12 h, 80%. 4. 3.0 equivalents NaH, DMSO/Et_2O (1:5), 3 h, 90%.

Scheme 42

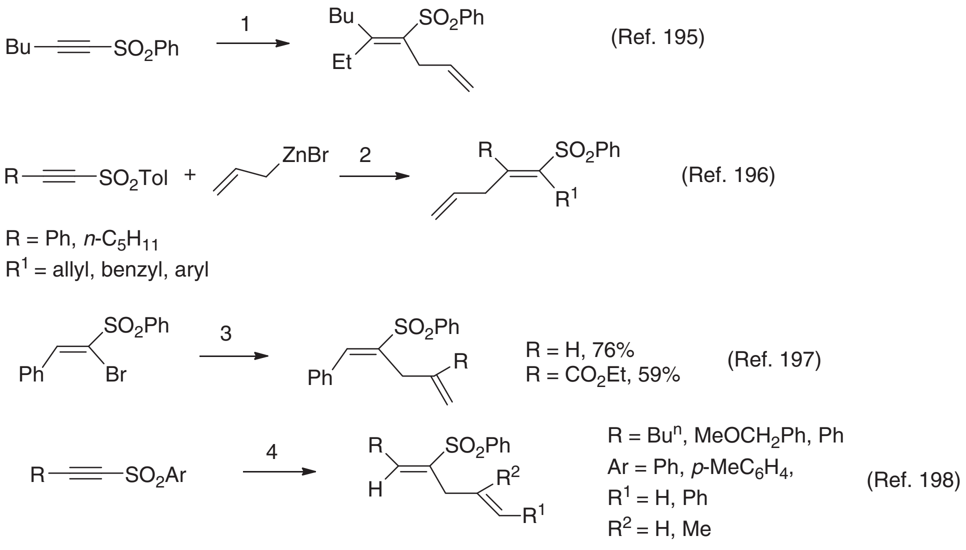


1. 2.0 equivalents Bu^nLi, THF, –78 °C, 2.0 equivalents MeI, 79%. 2. 2.0 equivalents Bu^nLi, 2 equivalents BnBr, 2.1 equivalents HMPA, THF, –78 °C to r.t. 3. 1.2 equivalents Bu^nLi, 1.2 equivalents MeI or BnBr, THF, –78 °C to –50 °C.

Scheme 43

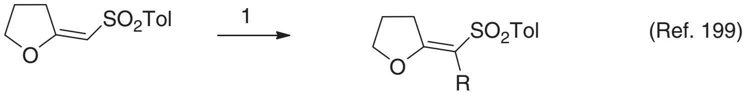
The lithiathion and alkylation of vinyl sulfones with heteroatomic substituents is often a useful tool to prepare alkylated vinyl sulfones (Scheme 45). The alkylation of a 2-methylene THF derivative in the presence of HMPA takes place in fair yields for several alkyl halides, except for isopropyl bromide and with good selectivity for alkylation α- to the alkenyl sulfone.[199]

Intramolecular cyclizations of alkenyl sulfones is also a practical method for the synthesis of functionalized heterocycles (Scheme 46). The use of oxiranes is quite general and on lithiation with LDA, cyclization takes place with inversion at the



1. Et_2Zn, 10% CuI, THF, 0 °C, 3 h; then allylbromide. 2. THF, reflux, 2 h; then 1 equivalent R^1X, 10% $NiCl_2(PPh_3)_2$, THF, 50 °C, 12 h, 40–93%. 3. 1.2 equivalents Pr^iMgBr, THF, –40 °C; 10% CuCN, 1.3 equivalents allylic bromide, –40 °C to r.t. 4. 5% $Pd(PPh_3)_4$, benzene, 1.05 equivalents Bu_3SnH, r.t., 4 h; exchange solvent to DMF, 0.9 equivalent allylic bromide, 0.7 equivalent CuI, r.t., 8 h, 69–81%.

Scheme 44



RX	Yield (%)
MeI	48
$CH_2{=}CHCH_2Br$	61
$PhCH_2Br$	49
Bu^nBr	48
Pr^iBr	14

1. 1.0 equivalent Bu^nLi, THF, –78 °C, 1.0 equivalent HMPA, 1.0 equivalent RX.

Scheme 45

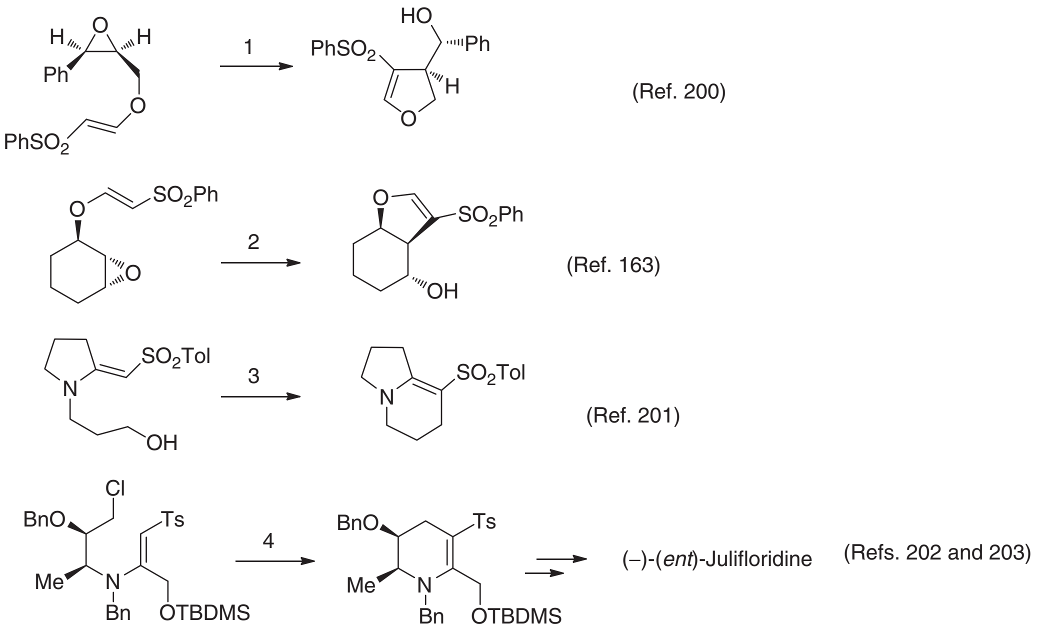
electrophilic carbon generating dihydrofurans,[200] or dihydropyrans and fused bicyclic dihydrofurans.[163] In the case of vinylogous sulfonamide, the 'enamine' character is sufficient to participate in a cycloalkylation under mild conditions via a detectable iodide intermediate.[201] Finally, a novel route to piperidines, pyrrolizidines, indolizidines, and quinolizidines that entails the LDA promoted cyclization of amino vinyl sulfones, produced from acetylenic sulfones and chloroamines, has been described.[202] The methodology has been also applied to the synthesis of (*ent*)-julifloridine.[203]

Lastly, cyclic α-vinyl amines undergo a rate-limiting conjugate addition to acetylenic sulfones, followed by a 3-aza-Cope rearrangement of the resulting zwitterionic intermediate to afford a ring expanded heterocycle in good yields (Scheme 47).[204] To extend the scope of the methodology, the reactivity of tertiary amines with an α-vinyl group embedded in an aromatic system was examined. For indole derivatives, the outcome of the process was remarkably dependent on the protecting group of the indole nitrogen. The benzylated indole did not follow an aza-Cope pathway but instead afforded a product of dissociation and subsequent recombination. In contrast, the benzenesulfonyl indole underwent an aza-Cope pathway followed by subsequent cyclization to afford a tetracyclic product presumably by deprotonation, anionic electrocyclic ring closure, and reprotonation.[205]

3.03.5 Alkylations of Sulfoximinoyl Carbanions

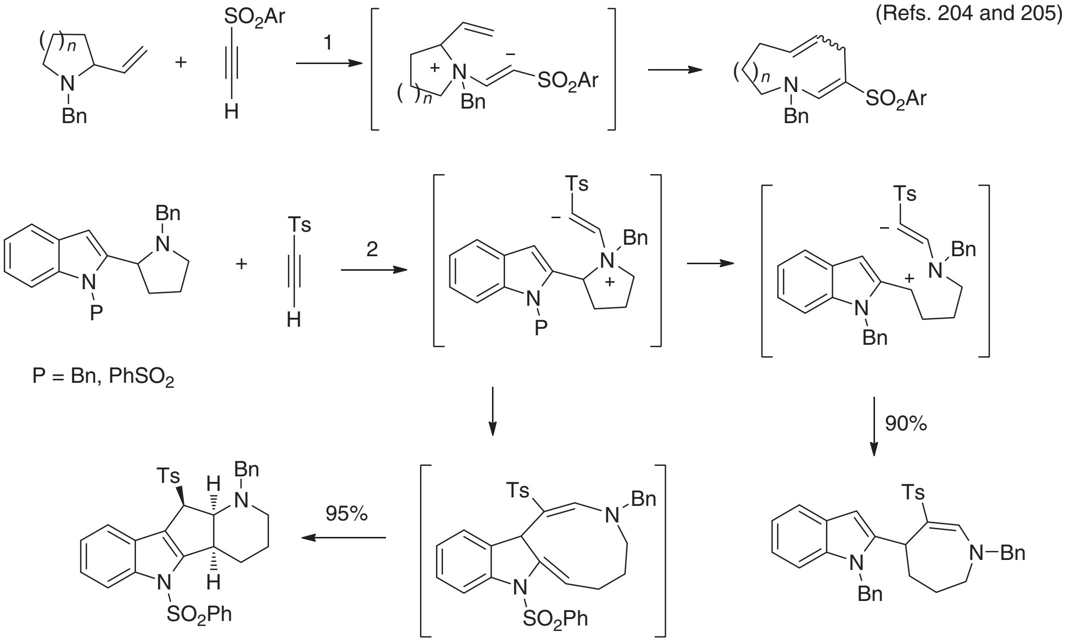
3.03.5.1 α-Metalloalkyl Sulfoximines

Sulfoximines are useful sulfur reagents in asymmetric synthesis. Deprotonation at the α-position is facile and leads to metallated species that react with a variety of electrophiles (Scheme 48). Thus, *N*-TMS protected *S*-methyl-*S*-phenyl sulfoximine was lithiated,



1. 1.3 equivalents LDA, THF, –78 °C to 0 °C, 68%. 2. 1.1 equivalents LDA, THF, –78 °C to 0 °C, 44%. 3. 3.0 equivalents PPh_3, 5.0 equivalents imidazole, 2.0 equivalents I_2, MeCN, Δ, 2 h, 80%. 4. 2.0 equivalents LDA, THF, –78 °C, 91%.

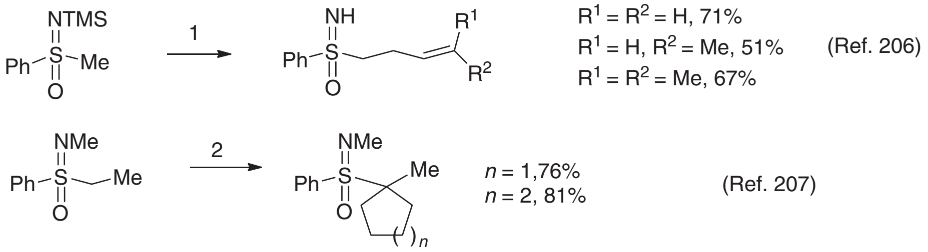
Scheme 46



1. CH_2Cl_2, or MeOH, 0 °C or r.t., 58–91%. 2. CH_3CN, 14–24 h, r.t.

Scheme 47

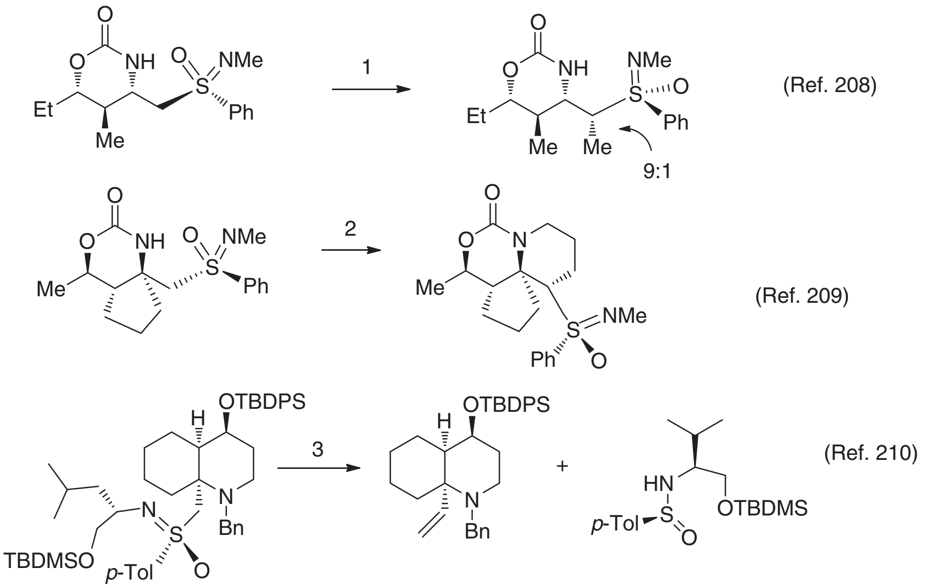
allylated, and N-deprotected in a simple fashion. Subsequent N-functionalization gave valuable precursors for metathesis processes.[206] The dilithiation of S-ethyl-N-methyl-S-phenyl sulfoximine to produce an ortho-, α-dilithiated species has been studied. On reaction with an excess of MeI, α,α-dimethylated sulfoximines are produced, presumably by initial α-alkylation followed by *trans*-lithiation, and a second α-alkylation; with bis-electrophiles, five- and six-member rings are formed smoothly.[207]



1. (a) 1.0 equivalent Bu^{n}Li, THF, –78 °C; then allylic bromides. (b) NH_4Cl, MeOH, r.t. 2. (a) 1.0 equivalent Bu^{n}Li, THF, –78 °C to 0 °C; then 1.0 equivalent $I(CH_2)_nI$.

Scheme 48

Sulfonimidoyl substituted oxazinones can undergo a double lithiation and alkylation at the α-position with good stereoselectivity (**Scheme 49**).[208] This methodology has been extended successfully to the cycloalkylation of bicyclic carbamate-sulfoximine dianions to produce a variety of azaspirocycles with excellent diastereoselectivity.[209] In contrast, the somewhat related sulfonimidoylmethyl substituted azabicycles could be lithiated but failed to react with common electrophiles (allyl bromide, etc.). However, addition of the lithiated sulfoximine to a preformed carbenoid solution (from diiodomethane and *iso*-propylmagnesium iodide) and allowing the mixture to warm up to rt, resulted in a *β*-elimination of the sulfur moiety to afford angular vinyl substituted products.[210]

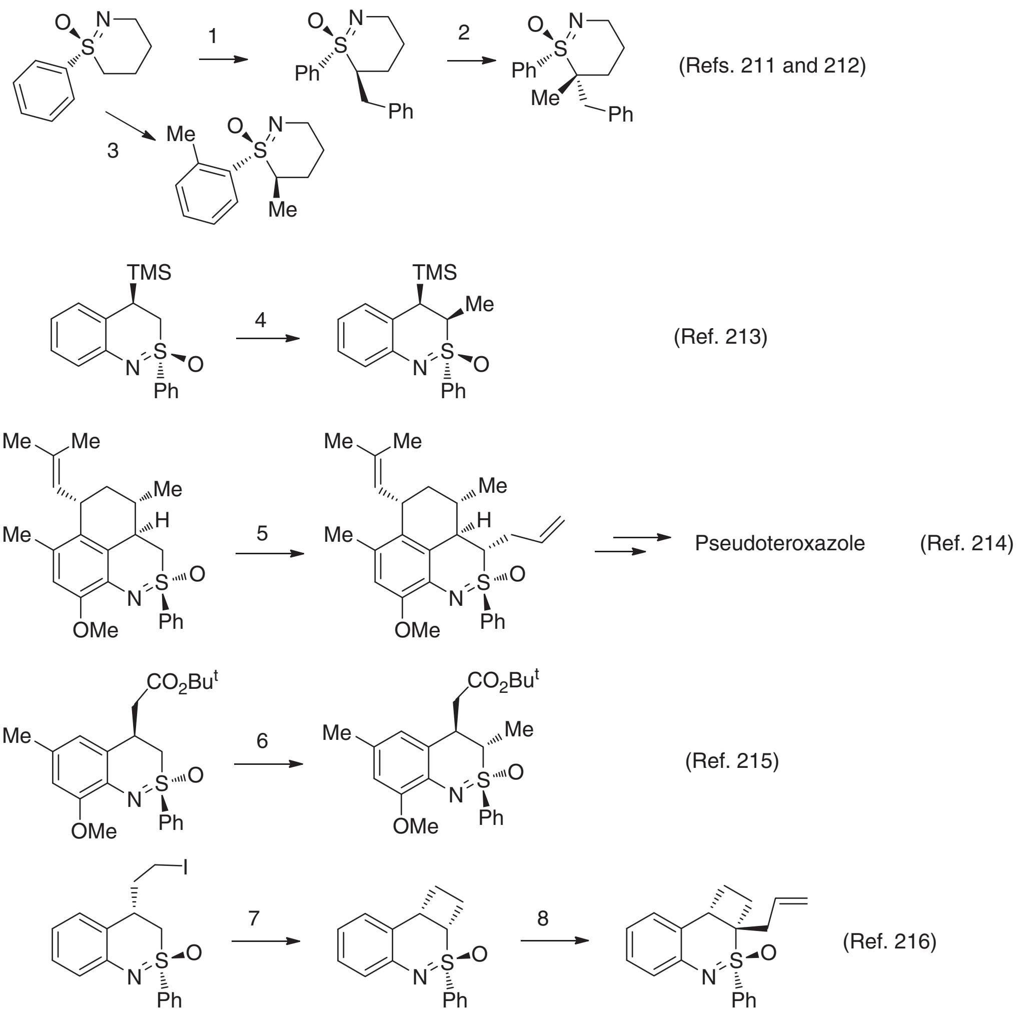


1. 2.1 equivalents Bu^{n}Li, THF, –10 °C; then MeI, 68% (diastereomerically pure).
2. 2.2 equivalents Bu^{n}Li, THF, –50 °C to –10 °C; then TsO $(CH_2)_3$OTs, –50 °C to r.t., 75%, >98% *de*.
3. 1.0 equivalent Bu^{n}Li, THF, –78 °C; then Pr^{i}MgI and CH_2I_2 (10 equivalents each), THF, –78 °C, 1 h; then add lithiated sulfoximine to carbenoid solution, –78 °C to r.t., 16 h, 66%.

Scheme 49

Within the same context, the allylation of cyclic α-sulfonimidoyl carbanions takes place in good to excellent yields and diastereoselectivities (**Scheme 50**). Subsequent lithiation and alkylation yields α,α-dialkyl substituted sulfoximines in a highly stereoselective manner.[211] The use of 2.2 equivalents of Bu^{n}Li results in double α-, ortho-lithiation, and trapping of the dianion with MeI affords an ortho, α-dimethylated product,[212] in clear contrast with the behavior of an acyclic sulfoximine (see before).[211] Also, the α-alkylation of a silyl benzothiazine and reaction with several alkyl, benzyl, and allyl halides took place with good yields (55–79%) and varying diastereoselectivities (1.5:1 to 25:1).[213] The allylation of an enantiopure tricyclic benzothiazine in quantitative yield and complete selectivity is one of the steps of a synthesis of the diterpene pseudopteroxazole.[214] It was also possible to perform related alkylations in the presence of a *t*-butyl ester with good yields (44–83%) and selectivities

(5.1:1 to 28.8:1).[215] A simple route to fused cyclobutanes by base-induced intramolecular cyclization of iodoethyl substituted benzothiazines has been developed (58–96%). Lithiation and electrophilic trapping of these cyclobutanes is also feasible.[216]

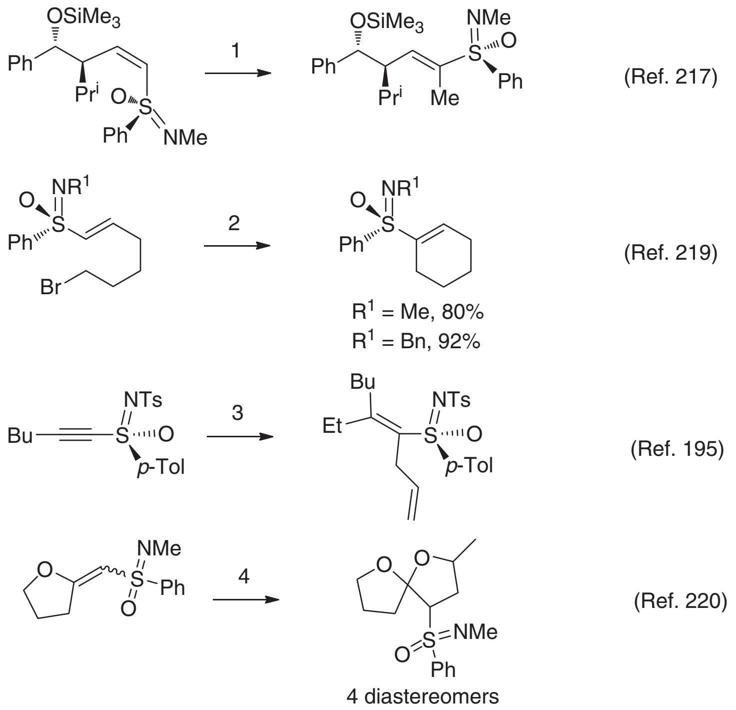


1. 1.1 equivalents Bu^nLi, THF, –50 °C to r.t.; then 1.1–1.5 equivalents BnBr, –78 °C, 3 h, 71%, (*de* > 98%). 2. Bu^nLi, THF, –78 °C; then MeI, 3 h, 96%, (*de* > 98%). 3. 2.2 equivalents Bu^nLi, THF, –50 °C; then MeI –78 °C, 76%, (*de* > 95%). 4. 1.1 equivalents Bu^nLi, THF, –78 °C, then MeI, –78 °C to r.t., 88% (*dr* = 25:1). 5. LiHMDS, THF, –45 °C, 1 h; then allyl bromide, –45 °C, 1 h, 100%. 6. 1.1 equivalents LiHMDS, THF, –50 °C, 1 h; then MeI, 1 h, 80%, (*dr* = 16.3:1). 7. 1.5 equivalents KH, THF, –78 °C to r.t., overnight, 88%. 8. 1.5 equivalents Bu^nLi, THF, –78 °C, 45 min; then allyl bromide, 57%.

Scheme 50

3.03.5.2 α-Metallovinyl Sulfoximines

The facile lithiation of (*Z*)-alkenyl sulfoximines, on warming to −30 °C resulted in complete isomerization to the (*E*) isomers that were trapped with MeI in excellent yields (Scheme 51).[217] Under similar conditions, the high-yielding reaction with allyl bromide has also been described.[218] Cycloalkenyl sulfoximines were prepared in high yield by metallation of 6-bromo alkenyl sulfoximines with LDA.[219] The copper-catalyzed *syn* carbozincation of alkynyl sulfoximines affords a single isomer of a vinyl metal intermediate that undergoes allylation in good yield.[195] Lithiation of racemic 2-(sulfonimidoylmethylene)THFs, followed by reaction with racemic terminal oxiranes affords hydroxy vinyl sulfoximines in good yields, as 1:1 mixture of diastereomers. Addition of HMPA to the reaction mixture before quenching leads to a smooth cyclization to produce 5,5-spiroketals as mixtures of four diastereoisomers and in high yields; alternatively treatment of the alcohols with NaH leads also to the spiroketals.[220]



1. 1.2 equivalents MeLi, Et_2O, –78 °C to –30 °C; then MeI, THF, –78 °C, 98%.
2. 1.0 equivalent LDA, THF, –78 °C to r.t. 3. 1.8 equivalents Et_2Zn, 10% CuI, THF, 0 °C, 3 h; then 1.5 equivalents allyl bromide, –20 °C to r.t., overnight, 65%. 4. 1.0 equivalent MeLi, THF, –80 °C, 30 min, 2-methyloxirane, –80 °C to –24 °C over 1.5 h, then –24 °C for 48 h; 2.0 equivalents HMPA, r.t., 24 h, 84%.

Scheme 51

3.03.6 Alkylation of Sulfonates, Sulfonamides, and Sulfur Ylides

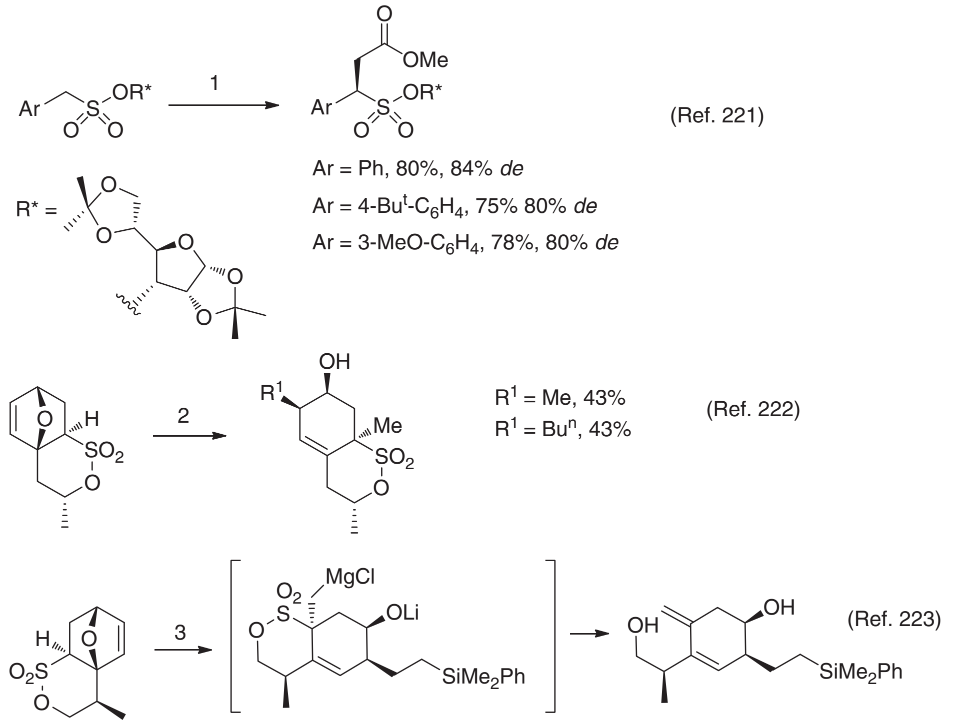
3.03.6.1 Sulfonates and Sulfonamides

The α-alkylation of sulfonates and sulfonamides is also possible. Within this context (Scheme 52), the alkylation of metallated benzylic sulfonates bearing an allofuranose auxiliary takes place in good yields and selectivities to afford pure stereoisomers after recrystallization.[221] The treatment of oxatricyclic sultones with an excess of alkyllithiums results in ring opening followed by alkoxide directed conjugate addition of the lithium reagent to produce an allylic anion that is trapped with MeI exclusively α to sulfur.[222] Similarly, the intermediate allylic anions may be trapped with (iodomethyl magnesium) chloride at low temperature to afford a β-metallosultone that undergoes β-elimination on warming at room temperature to produce methylenecyclohexenes in good yield. This methodology has been applied to the synthesis of (–)-eriolanin and (–)-eriolangin.[223]

The α-alkylation of sulfonamides is also a viable process (Scheme 53). Treatment of a Boc protected methane sulfonamide with an excess of LDA produced a dianion that underwent smooth α-alkylation with terminal oxiranes.[224] The alkylation of sultams with (iodomethyl)trimethylsilane followed by treatment with fluoride afforded unsaturated amines by desulfurization and methylenation, as observed for the related sultones. The *N*-THP substituted substrates lead to successful alkylations, presumably due to chelation of the lithiated intermediate, in contrast to *N*-benzyl or *N*-phenylethyl substituted substrates.[225]

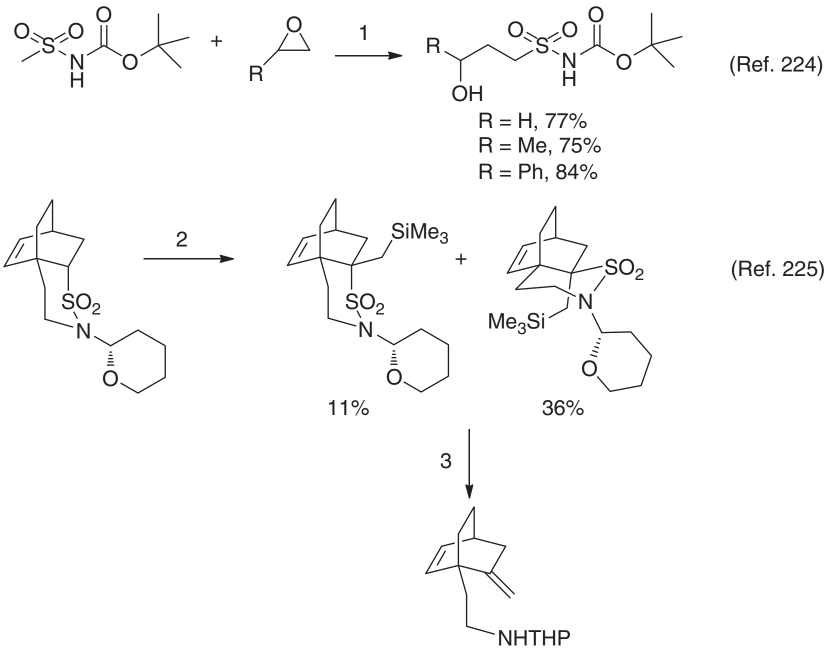
3.03.6.2 Sulfur Ylides

Alkylation of sulfonium ylides with alkyl halides are relatively rare (Scheme 54). A one-pot protocol for the one carbon homologation of benzylic, allylic, propargylic, and primary halides or mesylates with an excess of dimethylsulfonium methylide has been described.[226] Similarly, terminal allylic or benzylic epoxides lead to one carbon homologated allylic alcohols.[227] This homologation of terminal oxiranes, coupled with Sharpless asymmetric epoxidation provides an iterative process to polyoxygenated compounds.[228] Within the context of a synthesis of epothilones, the homologation methodology was extended to the use of a sulfonium triflate precursor to the ylide and diethyl ether that led to a substantial increase of yield in that example.[229] In the case of dialkyl 1,2-disubstituted epoxides, the *trans* isomers are completely unreactive; in contrast, the *cis*-epoxides react with



1. 1.1 equivalents Bu^nLi, THF, –95 °C, 45 min; then 1.5 equivalents methyl bromoacetate, THF, –95 °C, 1 h, then –78 °C 16 h. 2. 2 equivalents alkyllithium, THF, –78 °C (Bu^nLi) or –78 °C to 0 °C (MeLi), then MeI, –78 °C, 30 min. 3. 1.0 equivalent MeLi, THF, –78 °C, 20 min; then $LiCH_2CH_2SiMe_2Ph$ –78 °C to –20 °C; then ICH_2MgCl, THF, –78 °C to r.t., 61%.

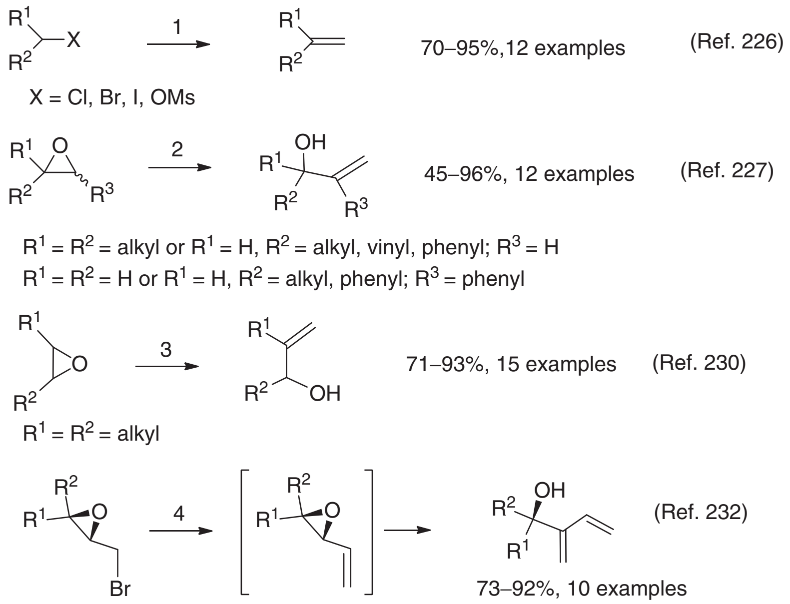
Scheme 52



1. 2 equivalents LDA, THF, –78 °C then 1.25 equivalents oxirane, –78 °C to r.t.
2. 1.2 equivalents MeLi, THF, –78 °C to r.t.; then 3 equivalents ICH_2SiMe_3, –78 °C to r.t.
3. 5 equivalents Bu_4NF, powdered 3 Å MS, THF, 0 °C to reflux, nearly quantitative.

Scheme 53

an excess of ylide to produce allylic alcohols in good yields. Although in asymmetric acyclic substrates the regioselectivity can only be modulated to some extent by varying steric bulk around the epoxide, some cyclic systems led to complete regioselectivity controlled by steric hindrance and conformational aspects.[230,231] The treatment of chiral *trans*-disubstituted and trisubstituted 2,3-epoxy-1-bromides with an excess of dimethylsulfonium methylide affords 1,3-butadienyl-2-ylmethanols by a double one-carbon homologation via initial formation of epoxyalkenes, isolated in some cases, followed by regioselective cleavage of the activated oxirane.[232] The reaction between a variety of *N*-*tert*-butylsulfonyl and *N*-tosyl aziridines and dimethylsulfonium methylide leads to a one-carbon homologation to produce protected allylic amines in good to excellent yields.[233]



1. 4 equivalents Me_3SI, 3.7 equivalents LiI, 3.7 equivalents Bu^nLi, THF, 0 °C, then add substrate, 0 °C to r.t., overnight. 2. 3 equivalents Me_3SI, 2.9 equivalents Bu^nLi, THF, –10 °C, 30 min; then add oxirane, –10 °C to r.t., 2 h.
3. 4 equivalents Me_3SI, 3.7 equivalents Bu^nLi, THF, –10 °C, 30 min; then add oxirane, –10 °C to r.t., 2 h.
4. 6.5–10 equivalents Me_3SI, 6–9 equivalents Bu^nLi, THF, –10 °C, 20 min; then add oxirane, –10 °C to r.t., 3 h.

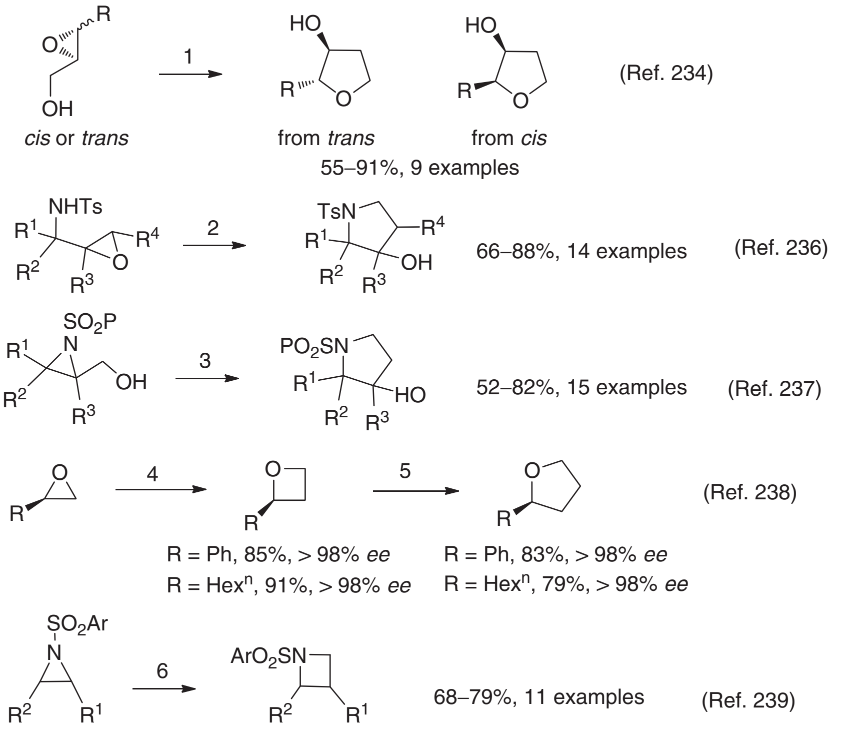
Scheme 54

Treatment of a variety of epoxy alcohols with an excess of dimethylsulfoxonium ylide resulted in a Payne rearrangement to produce a terminal oxirane that undergoes regioselective opening at C-1 with the ylide followed by ring closure to yield 2,3-disubstituted THFs with defined stereochemistry dependent on that of the starting material (Scheme 55).[234] In related work, *cis*-1,2-disubstituted epoxides with an α-OTBDMS group undergo ring opening with sulfoxonium ylide, followed by silyl migration and ring closure to afford 3,4-disubstituted THFs.[235] Epoxysulfonamides, available from allylic alcohols by a Sharpless aziridination followed by aza-Payne rearrangement, undergo oxirane cleavage with dimethylsulfoxonium methylide followed by cyclization to produce 2-substituted-3-hydroxypyrrolidines with high stereocontrol. In one case (R^1=H, R^2=C_5H_{11}, R^3=H, R^4=*p*-ClC_6H_4) the methodology was successfully extended to the preparation of a 2,3,4-trisubstitued pyrrolidine in 77% yield.[236] In related but independent work, a number of epoxy amines have been transformed into 2,3-substituted pyrrolidines in good to excellent yields (52–99%) on treatment with dimethylsulfoxonium methylide. Furthermore, conditions to promote the one-pot, aza-Payne followed by oxirane cleavage and cyclization have been developed.[237] Alternatively two consecutive ring expansions of simple epoxides with dimethylsulfoxonium methylide yielding first oxetanes and then tetrahydrofurans have been examined.[238] Thus, four- and five-membered oxacycles are available with complete preservation of the stereochemistry of the starting epoxide. Microwave irradiation of 1-arenesulfonylaziridines and dimethylsulfoxonium methylide under solvent-free conditions results in the stereoselective formation of sulfonylazetidines in good yields.[239]

3.03.7 Alkylation of Carbanions Bearing Two Geminal Sulfur Atoms

3.03.7.1 Dithioacetals and Dithioketals

During several decades dithioacetals and dithioketals have occupied an important place within the areas of carbanion chemistry and carbon–carbon bond formation. The success of their usage is based on the umpolung reactivity available through deprotonation of the central carbon allowing for the introduction of electrophilic partners onto a carbon atom that later will be

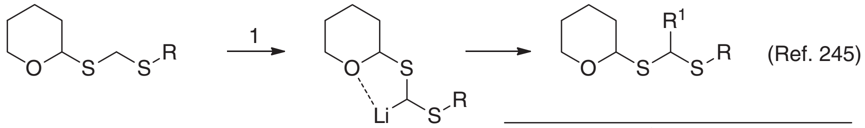


1. 3.0–10 equivalents Me_3SOI, NaH, DMSO, or THF, 80 °C, 36 h, 17–85%. 2. 2.95 equivalents Me_3SOI, 3.2 equivalents Bu^nLi, THF, –78 °C, 15 min; then add epoxy sulfonamide, 20 equivalents DMPU, –78 °C, to r.t., then 2 hreflux. 3. 8.0 equivalents NaH, DMSO, 8.0 equivalents Me_3SOI, r.t., 30 min; then add aziridinol, r.t., 4 h; then 80–85 °C, 24 h. 4. 1.6 equivalents Me_3SOI, 1.6 equivalents NaH, DMSO, 70–80 °C, 18 h. 5. 6 equivalents Me_3SOI, 10 equivalents NaH, diglyme, 120–130 °C, 0.5 h (R=Ph), 23 h (R=Hex^n). 6. 3 equivalents Me_3SOI, 3 equivalents KOH, Al_2O_3, MW, 160 W, 90 °C, 7 min.

Scheme 55

transformed into a carbonyl or a methylene unit. Even focusing only in alkylation reactions, a complete revision of the widespread chemistry of thioacetals in the past years would be beyond the extension of this review therefore selected and/or recent examples will be included to illustrate their applications.

The alkylation of acyclic thioacetals with alkylic and allylic halides[240–242] and epoxides[243,244] have been examined in different contexts. In particular diastereoselectivities up to 95:5 were obtained on alkylation of lithiated 2-(phenylthiomethylthio)-tetrahydropyrans, generated by deprotonation with Bu^{n}Li, with alkyl and benzyl halides (Scheme 56).[245]

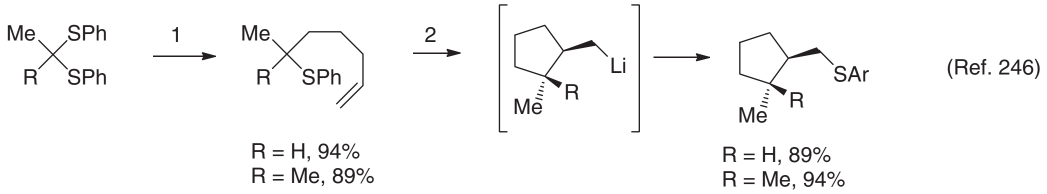


R	R^1X	Yield (*dr*)
Ph	CH_3I	80% (87:13)
Ph	Bu^nBr	85% (90:10)
Ph	$PhCH_2Br$	64% (87:13)
2-Naphth	Bu^nBr	70% (95:5)
Me	Bu^nBr	58% (70:30)

1. 1.1 equivalents Bu^nLi, THF, –78 °C, 1 h; then 1.0 equivalent R^1X, –78 °C to r.t., overnight.

Scheme 56

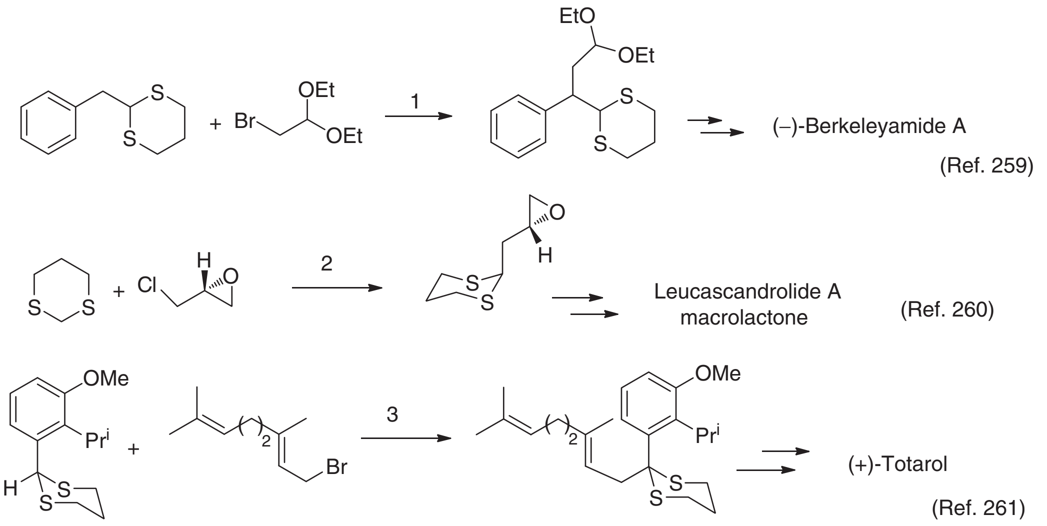
Alternatively, reductive metallation of thioacetals and thioketals using aromatic radical anions is a useful strategy in the formation of substituted cyclopentane rings (Scheme 57).[246] Thus, treatment of 2,2-bis(phenylthio)propane with lithium 1-(dimethylamino)naphthalenide (LDMAN) generates 2-phenylthio-2-lithiopropane that can be quenched with 5-bromo-1-pentene. Subsequent treatment with lithium 4,4′-di-*tert*-butylbiphenylide (LDBB) generates a second organolithium that cyclizes at the suitable temperature. The method is also applied to dithioketals. Similarly, the methylation through reductive metallation using $NiCl_2$(dppe) and MeMgI of cinnamaldehyde dithioacetals has been described.[247]



1. LDMAN, THF, –78 °C; then CH_2=CH$(CH_2)_3$Br, –78 °C to –20 °C, 30 min. 2. (a) LDBB, THF, –78 °C, 10 min for R = H; –78 °C to –45 °C, 2 h for R = Me; then (p-MeOC_6H_4S$)_2$.

Scheme 57

Undoubtedly the most widespread carbanions bearing two geminal sulfur atoms are 2-metallo 1,3-dithianes which have been extensively employed in the synthesis of natural products.[30] Detailed studies focused on their structure,[248,249] their enthalpies of formation,[250] and the mechanism of alkylation[251,252] have been published. Reliably, simple 1,3-dithiane as well as 2-subtituted dithianes undergo base-induced deprotonation followed by alkylation with alkyl tosylates[253] or halides.[254] Most of the cases described used primary,[255] benzylic,[256] or allylic[257] halides. These protocols have been used in the synthetic approaches to natural products such as the following selected examples: (–)-jimenezin,[258] (–)-berkeleyamide A,[259] leucascandrolide A,[260] (+)-totarol,[261] and methyl sarcophytoate[262] (**Scheme 58**).



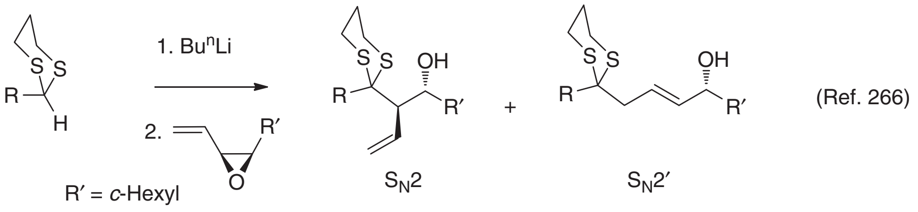
1. Bu^{n}Li, THF, –78 °C; then RBr, warm to 0 °C, 78%. 2. Bu^{n}Li, THF, –78 °C; then (R)-epichlorohydrin, warm to r.t., 78%. 3. Bu^{n}Li, THF, 0 °C; then geranyl bromide, 78%.

Scheme 58

Alkylation with more sophisticated electrophiles has been also described such as cyclic sulfamidates for the synthesis of functionalized amines[263] and vinylselenonium salts for the synthesis of cyclopropane rings[264]; however, epoxides are by far the most frequently used electrophiles with this reactivity extend to aziridines as well.[265] Interestingly, the alkylation of 2-lithium 1,3-dithianes with α,β-unsaturated epoxides have been studied in detail finding a high chemoselectivity (S_N2 vs. S_N2') mainly based on the steric hindrance exerted by substituents at C-2 (R) (**Scheme 59**).[266]

Some examples of the reaction of 2-lithium 1,3-dithianes with epoxides and aziridines directed to the synthesis of natural products are the approaches to SHC351448,[267] leucascandrolide A,[268] (6*R*,4′*S*,6′*R*)-cryptofolione,[269] cyanolide A,[270] lytophilippine,[271] spirastrellolide B,[272] jerangolid,[273] ambruticin S,[274] myrtine,[275] C-1–C-20 fragment of tetrafibricin,[276] and tedanolide[277] (**Scheme 60**).

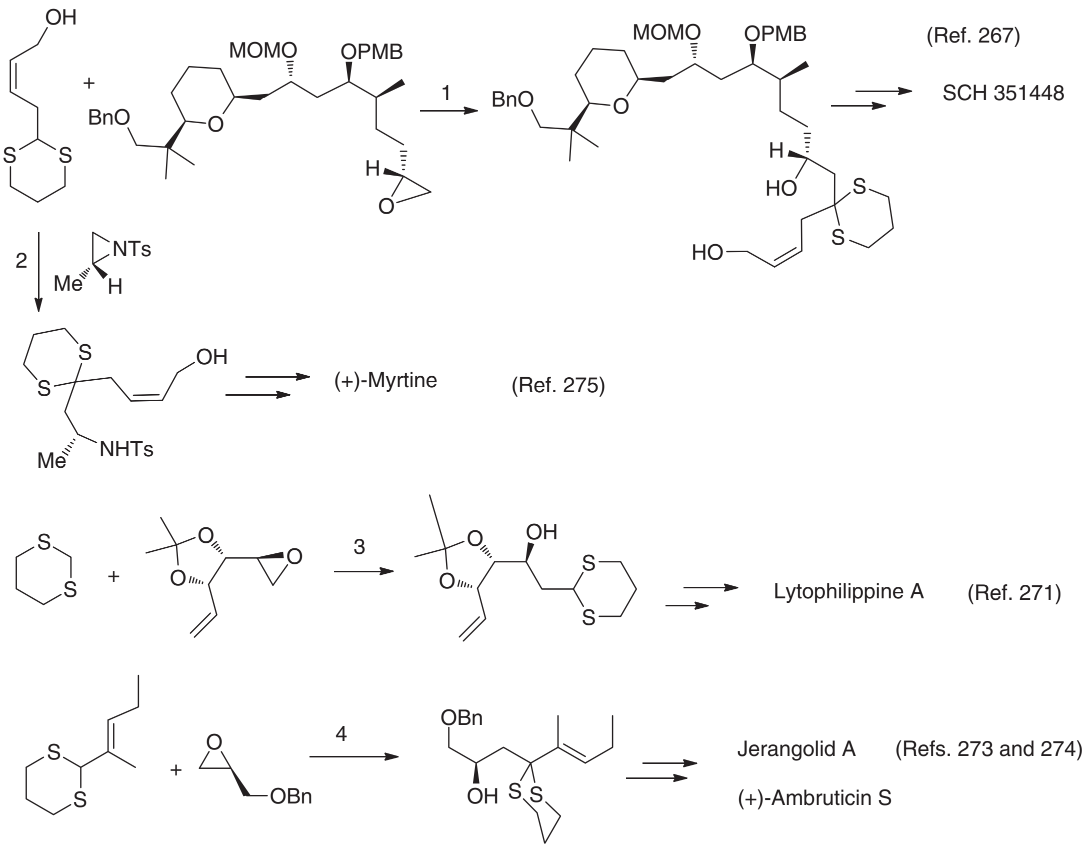
Within 1,3-dithiane rings, glyoxylate dithioacetals have been used in the synthesis of lumazine derivatives[278] and a manzamine A fragment.[279] Also 1,3-dithianes bearing a silyl group attached to the central carbon, represent a particular case whose chemistry has been developed in the past years.[280] Thus, 2-trialkylsilyl thioacetals easily undergo base-induced deprotonation followed by alkylation with alkyl halides[281,282] and epoxides.[283] In most cases, the alkylated products are transformed into functionalized



R	Yield (%)	Ratio S_N2:S_N2'
H	74	100(*anti*):0
Ph	82	100(*anti*):0
TMS	85	100(*anti*):0
Et	78	0:100
Pr^i	84	0:100
TIPS	86	0:100

1. Bu^{n}Li, THF, HMPA, –78 °C to –25 °C, 1 h. 2. (±)-epoxide, THF, –78 °C to –25 °C, 3 h.

Scheme 59

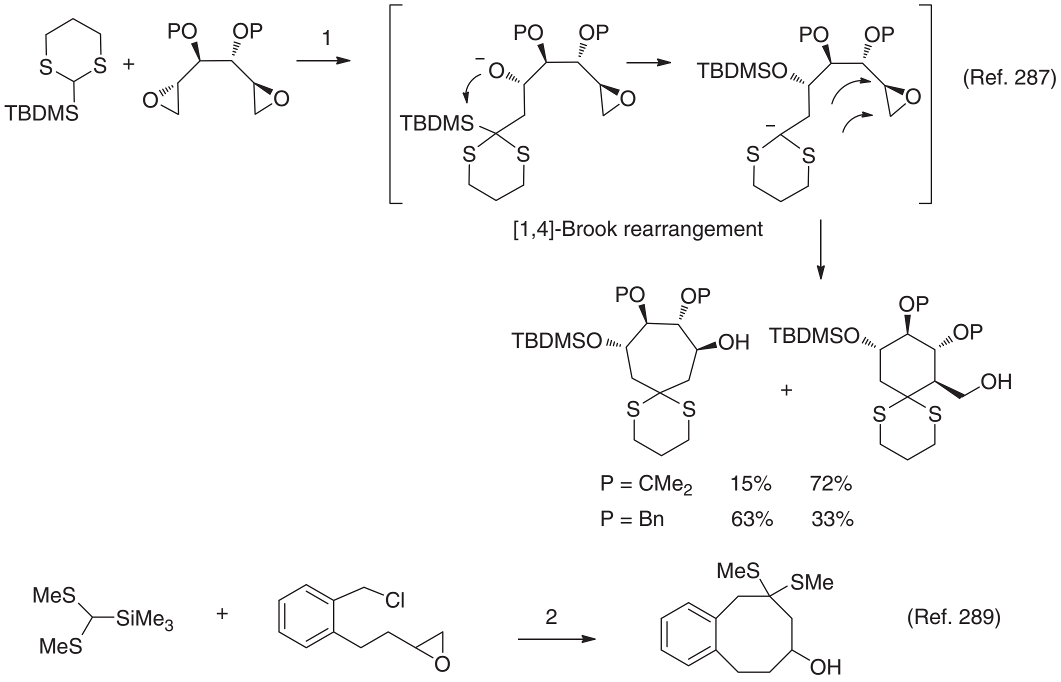


1. Bu^{t}Li, THF/HMPA (4:1), 5 min; then epoxide, –78 °C, 1 h, 80%. 2. Bu^{t}Li, THF/HMPA (10:1), 5 min; then aziridine –78 °C, 1 h, 75%. 3. Bu^{n}Li, THF, 73%. 4. Bu^{n}Li, THF, –78 °C, 97%.

Scheme 60

acylsilanes that readily undertake radical cyclizations useful for the synthesis of natural products such as (+)-swainsonine [284] and (+)-lentiginosine[285] among others.

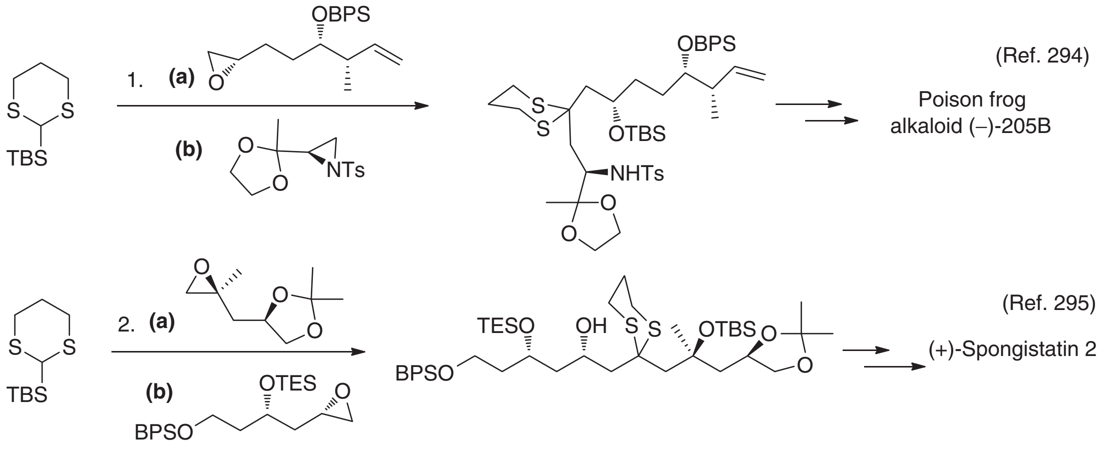
Aside of the above reactivity, when lithiated silyl-substituted dithioacetals react with epoxides an alkoxide is generated that can suffer a carbon to oxygen silyl migration ([1,4]-Brook rearrangement) producing *in situ* a second dithioacetal carbanion capable for a second alkylation (Scheme 61). This methodology is particularly convenient for the synthesis of carbocycles when bis-electrophiles such as bis-epoxides,[286,287] epoxi-tosylates,[288] halo-epoxides,[289] and bromo-esters[290] are used.



1. (a) 1.0 equivalent Bu^{t}Li, THF, HMPA, −78 °C; then bis-epoxide, 15 min for P = CMe$_2$ or 1.0 equivalent Bu^{n}Li, 0.25 equivalent Bu$^n_2$Mg, THF, HMPA, r.t. then bis-epoxide, 15 min for P = Bn. 2. 1.0 equivalent Bu^{n}Li, THF, −78 °C to −50 °C, then chloro-epoxide,18 h. (b) TBAF 3 H$_2$O, THF, r.t., 30 min, 46% over 2 steps.

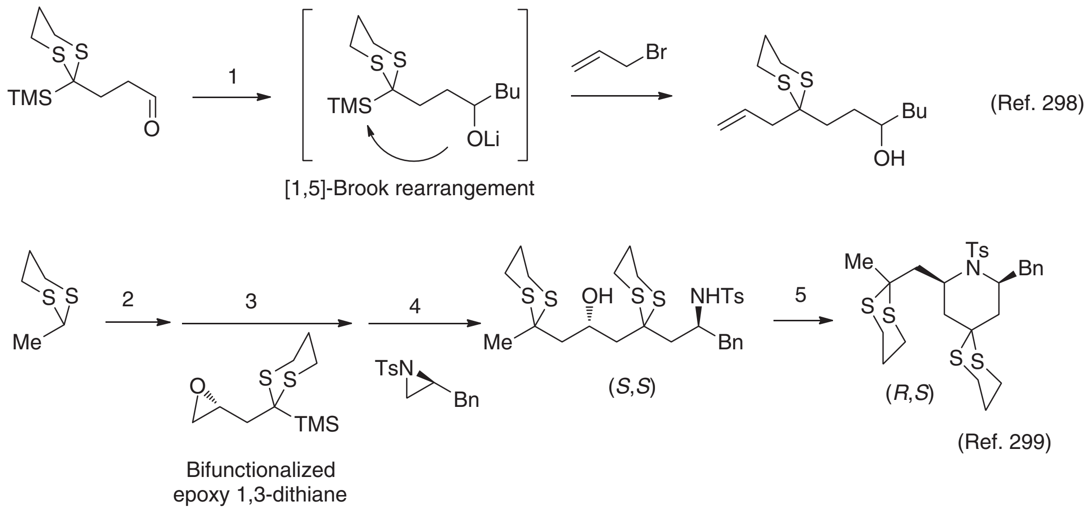
Scheme 61

Alternatively, early attempts to carry out tandem bis-alkylation of 2-lithio 2-silyated-1,3-dithianes with two molecules of electrophiles took place in good yields using two equivalents of a single chiral epoxide and a crown ether to afford enantiopure 1,5-diols.[291] Detailed studies of similar reactions revealed a strong solvent effect on the silyl migration step. Accordingly, the Brook rearrangement does not occur in THF but proceeds readily on addition of HMPA or DMPU.[292] This observation has opened the scope of these protocols allowing for multicomponent reactions with two different epoxides or an epoxide and an aziridine where 2-silyl-1,3-dithianes act as linchpin (Scheme 62), thus assembling highly complex molecules.[293–297]



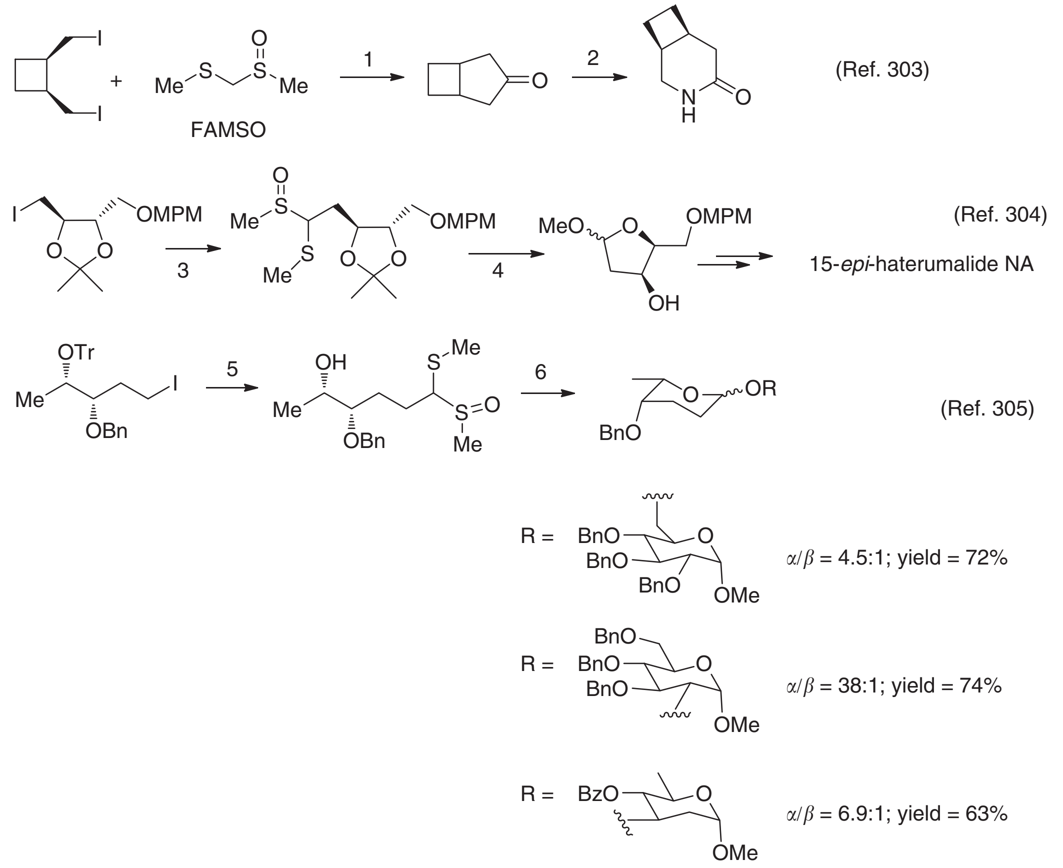
1. (a) Bu^{t}Li, Et$_2$O, −78 °C to −45 °C, 1 h; then epoxide, Et$_2$O −78 °C to −20 °C, 2 h. (b) aziridine, THF/DME, −78 °C to 0 °C, 53% overall. 2. (a) Bu^{t}Li, Et$_2$O, −78 °C to −45 °C, 1 h; then epoxide, −78 °C to −25 °C, 1 h. (b) epoxide, Et$_2$O/HMPA (9:1), −78 °C to r.t., 65% overall.

Scheme 62



1. (a) 1.05 equivalents $\mathrm{Bu^nLi}$, THF –78 °C. (b) 1.1 equivalents $\mathrm{Bu^tOK}$, –30 °C to –20 °C; then allyl bromide. (c) acidic work-up, 62%. 2. $\mathrm{Bu^nLi}$, $\mathrm{Bu^tOK}$, THF –78 °C. 3. bifunctionalized epoxy 1,3-dithiane, THF –78 °C. 4. (a) aziridine, THF –78 °C to 0 °C. (b) TBAF, THF or HCl (cat.) MeOH, 74% overall yield (2–4). 5. (a) MsCl, TEA, THF, 0 °C. (b) NaH, THF, r.t., 87%.

Scheme 63



1. (a) 1.0 equivalent FAMSO, 3.4 equivalents KH, THF, 0°C; then 1.0 equivalent diiodide, 4 h, r.t. (b) 9 M H_2SO_4, acetone, reflux, 3 h. 2. HCO_2H (solvent), NH_2OSO_3H, reflux, 3 h, 9% overall yield 3 steps. 3. FAMSO, $\mathrm{Bu^nLi}$, THF-hexanes, 87%. 4. Concentrated HCl, MeOH, (8:92), 58%. 5. (a) FAMSO, NaH, THF, 57%. (b) CSA, MeOH, 70% two steps. 6. 1.0–3.0 equivalents ROH, Tf_2O, CH_2Cl_2, MS 4 Å, –78 °C to –50 °C or to r.t.

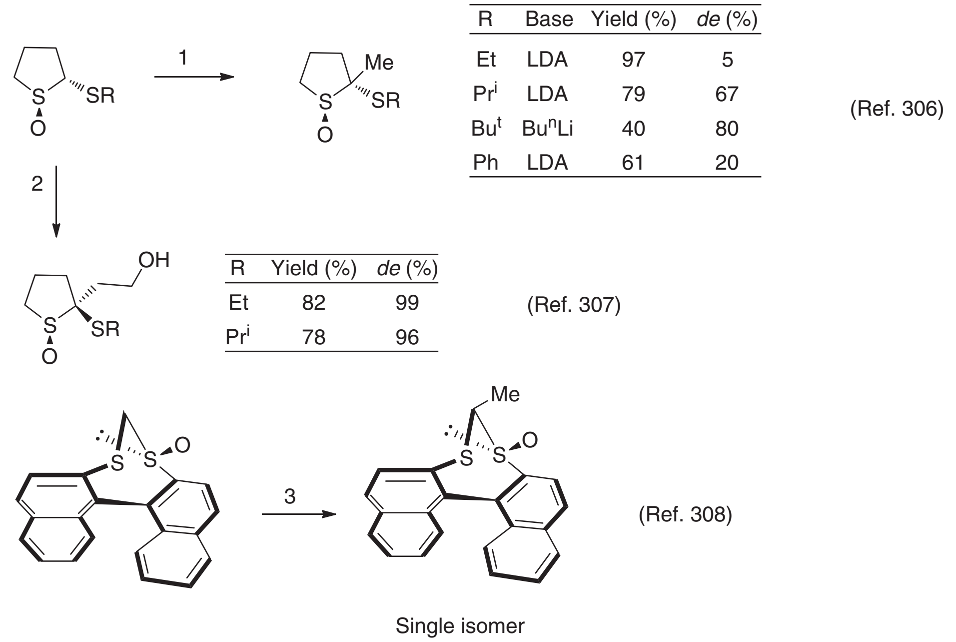
Scheme 64

Seeking to expand the utility of this strategy the viability of long range [1,5]-Brook rearrangements has been successfully examined.[298] In addition, related bifunctional 2-silylated-1,3-dithianes bearing an epoxide have been designed to act as linchpin for multicomponent alkylations in the context of diversity oriented synthesis of piperidines[299] and the synthesis of natural products[300] (**Scheme 63**).

3.03.7.2 Compounds Bearing Sulfoxides and Sulfoximines

Commercially available methyl (methylsulfanyl)methyl sulfoxide, known as MMTS or FAMSO (formaldehyde mercaptal sulfoxide) is found among the most commonly used sulfinyl–sulfide compounds (**Scheme 64**). Generally, bis-alkylation of FAMSO carbanions with alkyl halides is used in the synthesis of symmetric ketones.[301,302] In a particular example, deprotonation of FAMSO with KH followed by alkylation with bis(iodomethyl)cyclobutane renders after acidic treatment a bicyclic cyclopentanone that after Beckmann rearrangement leads to bicyclic 2-piperidinone in an efficient sequence.[303] Interestingly, the alkylation of FAMSO carbanion with a suitable functionalized iodoalkane bearing a 3-alkoxide substituent provides after hydrolysis a furanoside derivative used in the synthesis of an analog of haterumalide NA.[304] In a similar approach a glycosylation reaction is carried out to remove the sulfur moiety thus creating a disaccharide.[305]

In terms of stereochemistry (**Scheme 65**), the diastereoselectivity in alkylation of the carbanion of 2-(methylthio)thiolane sulfoxide has been examined using MeI. The lithium carbanions react with MeI at low temperature with moderate to good diastereomeric excesses increasing with the bulkiness of the exocyclic substituent (SR).[306] Similarly epoxides can alkylate these sulfur-stabilized carbanions with almost complete *trans* diastereoselectivity with ethylene oxide.[307] Diastereoselective alkylations have also been described for dithiepine *S*-oxides derived from C_2-chiral binaphthodithiol.[308]



R	Base	Yield (%)	*de* (%)
Et	LDA	97	5
Pr^i	LDA	79	67
Bu^t	Bu^nLi	40	80
Ph	LDA	61	20

(Ref. 306)

R	Yield (%)	*de* (%)
Et	82	99
Pr^i	78	96

(Ref. 307)

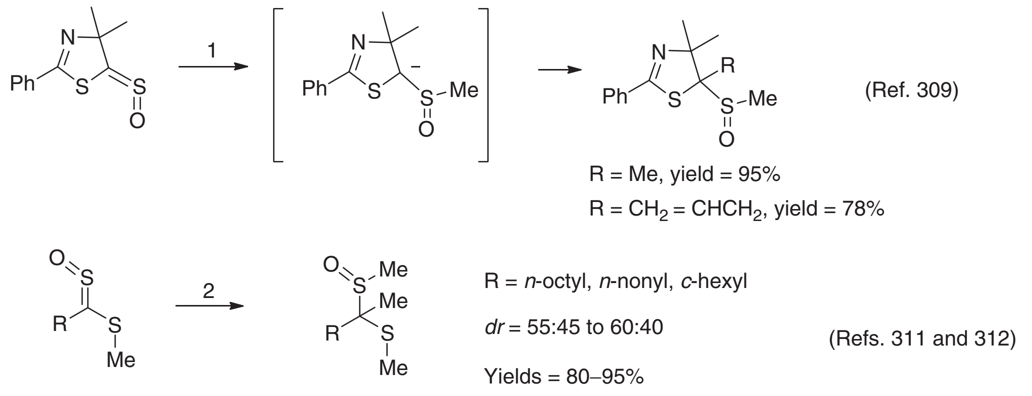
(Ref. 308)

1. (a) 1.1 equivalents base, THF, –30 °C, 1 h, then MeI warm up to r.t., 3 h. 2. 1.9 equivalents LDA, THF, –30 °C to –78 °C, then excess of epoxide, and warm up to r.t. 12 h. 3. 1.2 equivalents, Bu^nLi, THF, –78 °C, 2 h; then MeI, warm up to –40 °C, 95%.

Scheme 65

An alternative approach for this alkylation entails the reaction of sulfines, readily available by *m*-CPBA oxidation of thiocarbonyl esters, with organolithium compounds generating a sulfinyl-sulfide stabilized carbanion that is quenched with an alkyl halide (**Scheme 66**). This reactivity has been examined in heterocycles bearing sulfines, such as 1,3-thiazoles[309] and pyridines,[310] and in simpler aliphatic compounds.[311,312]

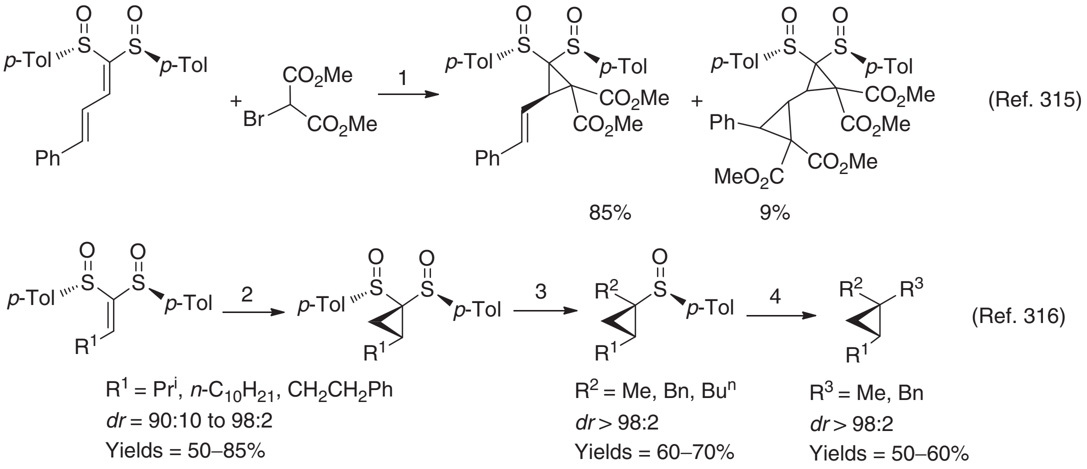
Likewise, bis-sulfinylmethane derivatives can undergo base-induced deprotonation and alkylation under standard conditions, however frequently the bis-sulfinyl stabilized carbanion is indirectly generated by a Michael addition to alkylidene bis(*p*-tolylsulfoxides) (**Scheme 67**).[313] In an example, the addition of the enolate from dimethyl bromomalonate produces a carbanion that is trapped intramolecularly by the leaving group present in the molecule, leading to a single isomer of a spiro cyclopropane.[314] This reaction can be applied onto dienyl bis-sulfoxides.[315] Within the context of the synthesis of cyclopropanes, sulfur ylides



1. MeLi, THF, –78 °C, 10 min, then MeI or allyl bromide, –78 °C to r.t., 3 h. 2. MeLi, THF, –78 °C, 5 min, then MeI.

Scheme 66

generated *in situ* by deprotonation of trimethyloxosulfonium iodide with NaH in DMSO react with alkylidene bis(sulfoxides) rendering the corresponding bis(*p*-tolylsulfinyl)cyclopropanes in good yields and excellent diastereomeric ratios. Further *syn*-selective sulfoxide/lithium exchange followed by electrophilic quenching provides enantiomerically pure polyalkylated cyclopropane derivatives.[316] This type of reactivity has also been applied to (diethoxyphosphoryl)vinyl *p*-tolylsulfoxides.[317]



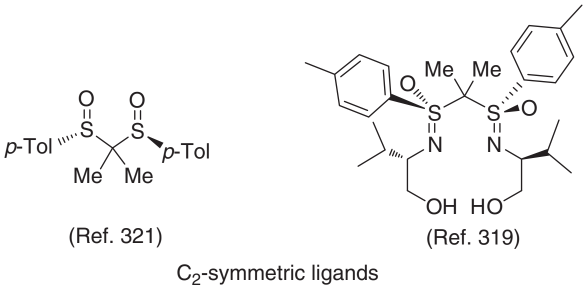
1. NaH, THF, –50 °C, 2 days. 2. $Me_2S(O)MeI$, NaH, DMSO. 3. Bu^nLi, THF, –80 °C, then R^2Br or R^2I.
4. Bu^nLi, THF, –80 °C, then CuCN, then BnBr or MeI, –80 °C.

Scheme 67

Finally, bis-sulfinyl methane[318] as well as bis-sulfoximidoylmethane derivatives have been considered as chiral ligands in the context of asymmetric metal catalysis with moderate success[319] (Scheme 68). Methylation of these compounds onto the central methylene unit has been carried out to limit the conformational flexibility of the ligand in the catalytic metal complexes. Thus, in spite of the lack of configurational stability found for α,α-disubstituted bis-sulfoxides in the presence of strong bases,[320] these catalyzed the Diels–Alder reaction of cyclopentane and 3-acryloyl-1,3-oxazolidinone with excellent yield and diastereoselectivity although moderate *ee*.[321]

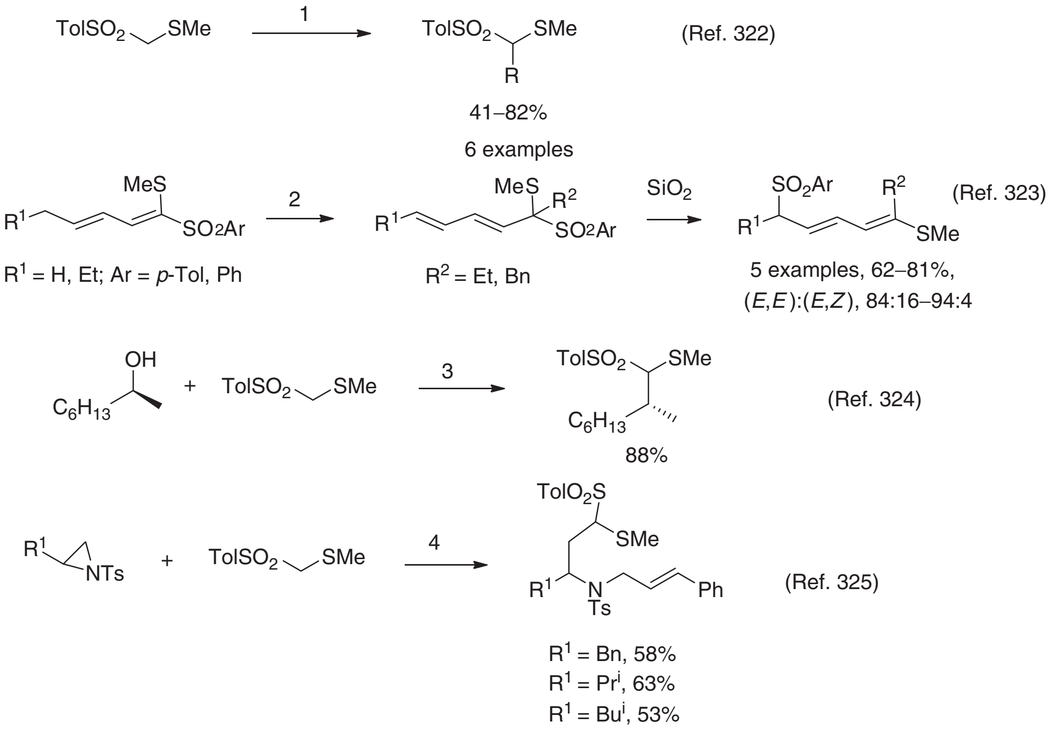
3.03.7.3 Compounds Bearing Sulfones

Methylthiomethyl *p*-tolyl sulfone (Scheme 69) undergoes standard alkylation with alkyl, allyl, and benzyl bromides on treatment with LDA in fair to excellent yields.[322] Treatment of 1-arylsulfonyl-1-methylthio-1,3-alkadienes with potassium *tert*-butoxide and ethyl or benzyl iodide resulted in diene isomerization and α-alkylation; purification by chromatography on silica gel resulted in smooth 1,5-rearrangement of the sulfonyl group.[323] Methylthiomethyl phenyl sulfone undergoes Mitsunobu alkylation in good to high yields with primary, allylic, benzylic, and secondary alcohols by treatment with cyanomethylenetributylphosphorane



Scheme 68

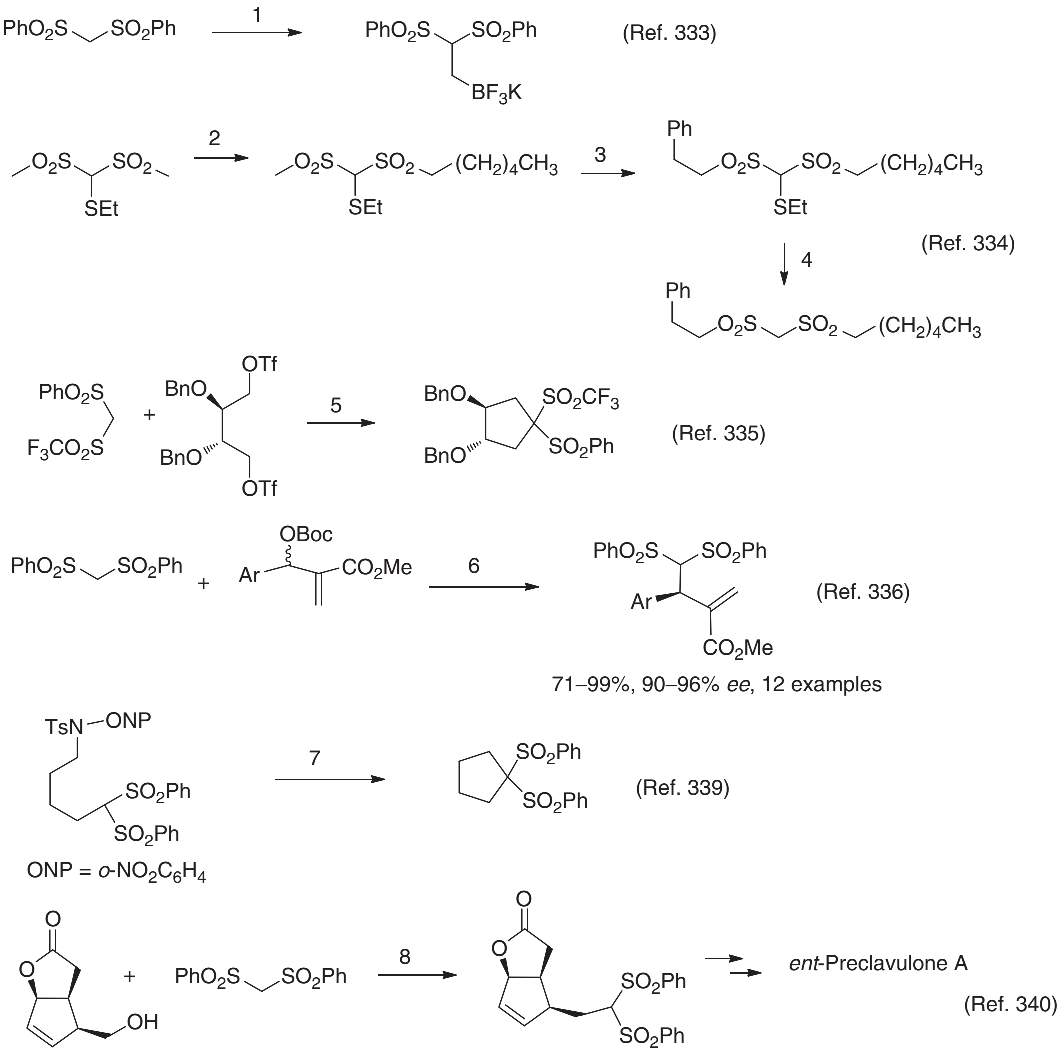
(CMBP).[324] Lithiated methylthiomethyl *p*-tolylsulfone adds smoothly to terminal *N*-tosyl aziridines to afford tosylamides that are further alkylated with an allylic bromide.[325] The related tolylsulfinyl tolylsulfonyl methane is alkylated with KH/ RCH_2I in high yield, and undergoes palladium-catalyzed allylic alkylation under biphasic conditions in low yield.[326]



1. 1.1 equivalents LDA, THF, –78 °C, 1 h; then add RBr, –78 °C. 2. Bu^tOK, R^2I, THF, –20 °C.
3. 1.5 equivalents cyanomethylenetributylphosphorane, benzene, 150 °C, 24 h.
4. (a) 1.0 equivalent Bu^nLi, THF, –78 °C, then add aziridine. (b) NaH, $PhCH{=}CHCH_2Br$, DMF, r.t.

Scheme 69

Alkylations of bis-phenylsulfonyl methane and related species are nowadays very common in synthetic organic chemistry both with halides,[327–331] and oxiranes.[188,332] Scheme 70 gathers some more unusual alkylations of these gem-disulfones. Pinacol iodomethylboronate gives rise to the alkylated trifluoroborates in good yields by treatment with stabilized anions followed by KHF_2.[333] Protection of the central acidic hydrogens of bis(methylsulfonyl)methane as a thioether followed by dianion formation, regioselective alkylation at the methyl group and removal of the thioether moiety allows even for alkylation of both methyls with different groups.[334] Phenyl sulfonylmethyl triflone undergoes bis-metallation and dialkylation to afford α-phenylsulfonyl triflones in high yields.[335] There are several examples in which bis(phenylsulfonyl)methane and fluoro bis(phenylsulfonyl)methane undergo allylic alkylation with racemic MBH carbonates under catalysis with the cinchona alkaloid $(DHQD)_2AQN$ in good yields and enantioselectivities.[336–338] Readily available aryl(sulfonyl)amino groups are good leaving groups in intramolecular substitutions for a variety of nucleophiles including vicinal disulfones.[339] Bis-sulfonyl methylenes undergo dehydrative alkylation under Mitsunobu conditions with a variety of alcohols. This methodology has been recently applied to the synthesis of *ent*-preclavulone A,[340] and to the synthesis of *C*-glycosides.[341]

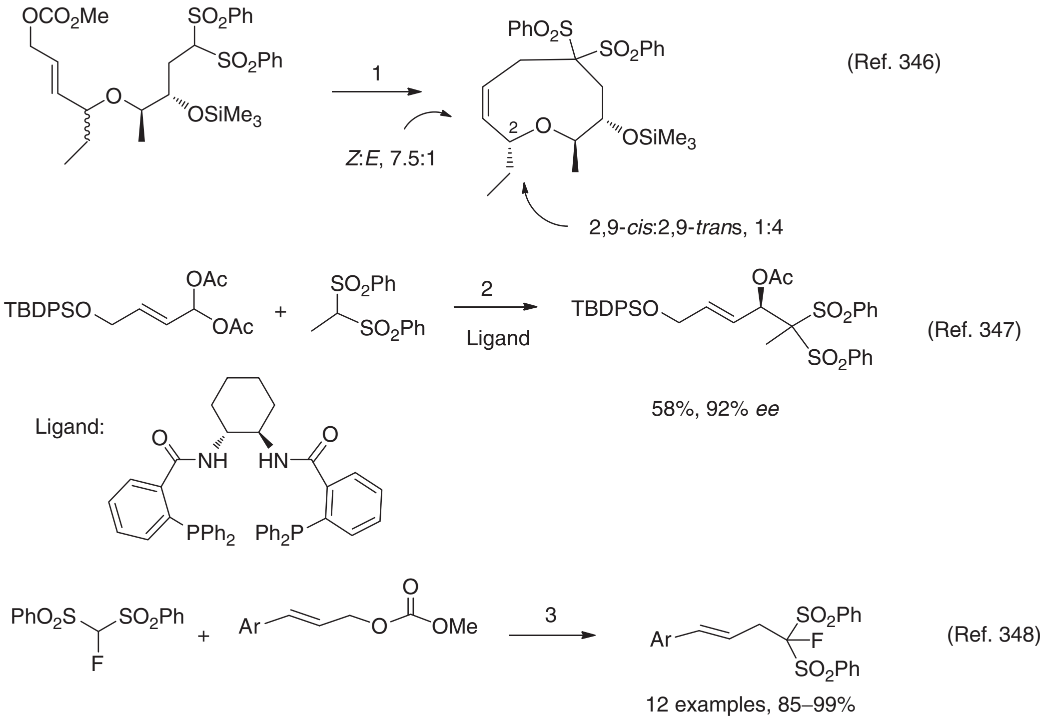


1. (a) 1.0 equivalent NaH, THF, 0 °C to r.t., 2 h. (b) ICH_2BPin, THF, r.t., 12 h. (c) 3 equivalents KHF_2, MeOH-H_2O (5.25-1), r.t., 4 h, 70%. 2. 2.0 equivalents Bu^nLi, iodopentane, 76%. 3. 2.0 equivalents Bu^nLi, BnBr, 87%. 4. NaSEt, EtSH, EtOH, quantitative. 5. 2.3 equivalents Bu^nLi, HMPA/toluene, –78 °C, then add ditriflate, –78 °C to r.t., 10 h, 95%. 6. 1.5 equivalents allylic carbonate, 10% hydroquinidine (anthraquinone-1, 4-diyl) diether, $(DHQD)_2AQN$, mesitylene, 30 °C. 7. 2 equivalents K_3PO_4, DMF, 150 °C, 30 h, 84%. 8. Ph_3P, bis-(phenylsulfonyl)methane, 3.0 equivalents DEAD, benzene, r.t., 1.5 h, 87%.

Scheme 70

The use of gem-disulfones in palladium-catalyzed processes on vinyl oxiranes,[342] allylic acetates,[343] alkynes,[344] and diallyldiacetates,[345] is increasingly frequent. A few representative examples are gathered in Scheme 71. The palladium-catalyzed synthesis of medium-ring ethers has been investigated. In the case of nine-membered rings, the use of an *E* allylic carbonate with dppe and long reaction times results in predominantly *Z* rings presumably under thermodynamic control and with moderate to high diastereoselectivity at C-2, rationalized by Pd-catalyzed allylic ether cleavage and recyclization. From the isomeric *Z* allylic carbonate and with $P(OEt)_3$ a faster reaction affords almost exclusively the *E* cyclic ether presumably under kinetic control.[346] The asymmetric alkylation of allylic gem-dicarboxylates produces allylic esters under palladium catalysis with a chiral ligand. Although malonate nucleophiles display high regio- and enantioselectivities, the less reactive bis(phenylsulfonyl)ethane requires a slow addition of a solution of diacetate, palladium catalyst, and chiral ligand to improve the enantioselectivity.[347]

The palladium-catalyzed allylic alkylation of fluorobis(phenylsulfonyl)methane with a variety of acyclic carbonates takes place with very high regioselectivity and excellent yields.[348]



1. (a) 10% $Pd_2(dba)_3(CHCl_3)$, 45% dppe, THF, reflux, slow addition of substrate (13 h), then 17 h, 67%.
2. 1% π-allylpalladium chloride dimer, 3% (*R*,*R*)-1,2-di(2'-diphenylphosphinobenzamido) cyclohexane, 1.5–2.0 equivalents NaH, THF, 0 °C slow addition, 6 h. 3. 2% $Pd(OAc)_2$, 4% dppe, 1.05 equivalents allylic carbonate, 1 equivalent K_2CO_3,THF, r.t.

Scheme 71

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3.04 Alkylations of Nonstabilized Carbanions

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3.04.1	**Introduction**	209
3.04.2	**Generation and Nucleophilic Displacement of Alkyl and Alkenyl Polar Organometallics**	210
3.04.2.1	Introduction	210
3.04.2.2	Alkyl Organometallic Reagents	210
3.04.2.3	Alkenyl Organometallic Reagents	216
3.04.3	**Allylation of Nonstabilized (Hard) Nucleophiles**	218
3.04.3.1	Introduction	218
3.04.3.2	Regio- and Stereoselective Allylic Substitutions With Nonstabilized Nucleophiles	219
3.04.3.2.1	Copper-mediated and -catalyzed transformations	219
3.04.3.2.2	Other regio- and stereoselective allylic substitutions	222
3.04.3.3	Enantioselective Allylic Substitutions With Nonstabilized Nucleophiles	223
3.04.3.3.1	Copper-catalyzed transformations	223
3.04.3.3.1.1	Copper-catalyzed transformations with organomagnesium reagents	223
3.04.3.3.1.2	Copper-catalyzed transformations with organozinc reagents	227
3.04.3.3.1.3	Copper-catalyzed transformations with organoaluminum and organolithium reagents	230
3.04.3.3.1.4	Kinetic resolutions and related processes	232
3.04.3.3.2	Other transition metal-catalyzed transformations	234
3.04.3.3.3	Transition metal-free, Lewis base-catalyzed transformations	234
3.04.3.4	Ring-Opening Reactions of Bicyclic Alkenes	236
3.04.3.4.1	Ring-opening of oxabicyclo[2.2.1]- and [3.2.1]-systems, and related structures	236
3.04.3.4.2	Ring-opening of 2,3-*bis*-heteronorbornenes, and related structures	240
3.04.4	**Carbometalations and Related Reactions**	241
3.04.4.1	Introduction	241
3.04.4.2	Carbometalation of Cyclopropene Derivatives	242
3.04.4.3	Carbometalation of Other Unsaturated Substrates	245
3.04.5	**Transition Metal-Catalyzed Cross-Coupling Alkylations with Zn- and Mg–Alkyl Carbanions**	246
3.04.5.1	Introduction	246
3.04.5.2	Alkylations of Organo Zinc Reagents	246
3.04.5.2.1	Pd-catalyzed transformations	246
3.04.5.2.2	Ni-catalyzed transformations	250
3.04.5.2.3	Cu-catalyzed transformations	252
3.04.5.3	Alkylations of Organomagnesium Reagents	253
3.04.5.3.1	Ni-catalyzed transformations	253
3.04.5.3.2	Pd-catalyzed transformations	255
3.04.5.3.3	Co-catalyzed transformations	256
3.04.5.3.4	Fe-catalyzed transformations	259
3.04.5.3.5	Cu and Zn-catalyzed transformations	260
References		261

Glossary

Direct enantioconvergent transformation Chemical reaction in which two enantiomers of the same starting material, forming a racemic mixture, react with a chiral enantiopure reagent (or in the presence of a chiral enantiopure catalyst) according to the two different pathways, giving rise to the same enantiomer of the final product without any racemization or equilibration process taking place.

Leaving group-directed substitution Chemical process in which a leaving group placed on the substrate exerts also the function of directing group for the incoming nucleophile, thereby dictating the regio- and stereochemical outcome of the transformation.

Parallel kinetic resolution Chemical reaction in which two enantiomers of the same starting material, forming a racemic mixture, react with a chiral enantiopure reagent (or in the presence of a chiral enantiopure catalyst) to form two different products in enantioenriched form.

Superbase An equimolar mixture of an organolithium reagent (e.g., butyllithium) and an alkali metal alkoxide (e.g., potassium *tert*-butoxide) endowed with high reactivity and good selectivity.

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3.04.1 Introduction

According to the pioonering publication by Cram,[1] carbanions can be stabilized by the presence of several different functional groups and/or unsaturations. This means that in practice only those lacking any substituent can be considered as nonstabilized carbanions even if the presence of simple oxygen or nitrogen containing groups provides little stabilization. Following this general principle, the authors have focused, in this chapter, on the reactions involving polar organometallic compounds (alkali metals, magnesium and zinc) with little if no stabilization. In particular the authors have examined recent advances on the preparation and subsequent reactions with alkylating agents, of alkyl and alkenyl polar organometallic reagents.

Reviews and books on related topics have been published in the past dealing with the chemistry of lithium,[2–4] sodium and potassium,[5–7] magnesium, and zinc reagents.[8–12] A comprehensive overview on organoalkali chemistry has been very recently edited by Schlosser covering all main aspects of the preparation and synthetic applications of polar organometallics.[13]

Because a large number of publications deals with the alkylation of nonstabilized carbanions, the authors decided to restrict their review to some more representative topics. The authors illustrate, with literature examples mainly dated after 2003 (year of publication of the previous edition of the Comprehensive Organic Synthesis), the general aspects of nucleophilic substitutions/addition by polar organometallics (Section 3.04.2), and more in details the allylation (Section 3.04.3), carbometalation (Section 3.04.4), and cross-coupling reactions involving alkyl organometallic reagents (Section 3.04.5).

3.04.2 Generation and Nucleophilic Displacement of Alkyl and Alkenyl Polar Organometallics

3.04.2.1 Introduction

There are a few general methods to prepare nonstabilized carbanions: metalation (hydrogen–metal exchange), direct insertion of the metal on a carbon–halogen bond, permutational displacement by an organometallic species on a carbon–halogen or a carbon–metal bond. Metalation is the preferred method when one has to deal with the preparation of stabilized carbanions, whereas it becomes less performing if the hydrogen to be exchanged comes from unactivated positions. Simple alkanes are unreactive toward any polar organometallics species (except for the metalation of cyclopropyl derivatives with superbasic mixtures like alkyllithiums/potassium *tert*-butoxide)[14] while aromatic substrates carrying activating and directing substituents are largely used in metalation reactions.[15]

Both the halogen (or sometimes sulfur)[3]–metal exchange and the direct metal insertion are instead general and reliable methods to get access to nonstabilized carbanionic species. Countless organic halides have been converted into their corresponding zinc, magnesium, lithium, sodium and potassium compounds by direct metal insertion. The method suffers from problems related to the stability/reactivity of the generated organometallic species in the reaction medium and, except for magnesium and, better, zinc, cannot be used for substrates carrying functional groups. However, after the discovery by Wittig et al.[16] and Gilman et al.[17] of the bromine–lithium and iodine–lithium permutation, and the analogous bromine–magnesium exchange reported by Prevost,[18] the method has been considered mature for a while until a marked revival mainly due to the use of organomagnesium and zinc reagents.[19]

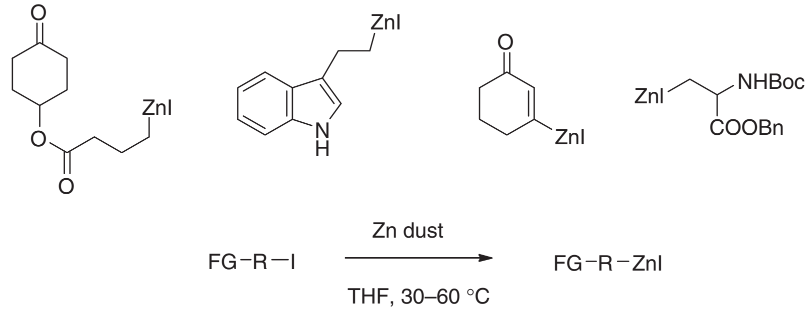
3.04.2.2 Alkyl Organometallic Reagents

As already said above (see Section 3.04.2.1), metalation of simple alkanes is practically impossible and the only way to get access to alkylmetallic compounds is by direct metal insertion onto the carbon–halogen bond or halogen–metal exchange. The former is certainly the most-used method to access alkylmetallic compounds but the conditions used to perform direct metal insertion with lithium and magnesium prevent the generation of functionalized organometallic species. This problem is partially solved by the use of highly activated Rieke magnesium (Mg*), obtained by the reduction of a soluble magnesium salt with lithium naphthalenide,[20] but it still cannot be of general use with substrates containing highly reactive functional groups. Organozinc reagents, however, can be prepared by direct reaction of zinc dust with organic iodides and the method, due to the low reactivity of the resulting organometallic, allows for the preparation of a broad range of functionalized intermediates (**Scheme 1**).[21]

Their low reactivity is a 'bonus' for the preparation of functionalized organometallic species but, of course, makes them not very attractive for applications in reactions with carbon electrophiles unless activated by transition metals.

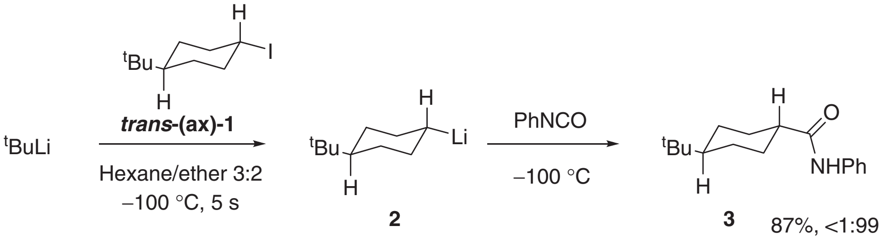
Halogen–metal exchange is largely used both for Csp^3- and Csp^2-halogenated substrates and, despite some limitations, is probably the most straightforward and hence the most-used method to generate reactive organometallic intermediates. Alkyllithium species are easily generated by bromine or iodine–lithium exchange with butyllithium or *tert*-butyllithium at low temperature and react with a large array of electrophiles.[7] Instead, examples of halogen–magnesium exchange for the preparation of alkylmagnesium species are less numerous, since the method is mainly used for accessing alkenyl and aromatic organometallics.

Very recently,[22] secondary alkyllithium compounds have been prepared by a very low temperature treatment (−100 °C) of *cis*- and *trans*-4-*tert*-butylcyclohexyl iodide, ***cis*-(ax)-1** and ***trans*-(ax)-1**, with *tert*-BuLi. The resulting organolithium species is stable enough to be trapped with several electrophiles among which PhNCO, affording the corresponding functionalized cyclohexyl derivative in good yields and selectivities, the latter being higher for the thermodynamically more stable ***trans*-(eq)-2** (**Scheme 2**).



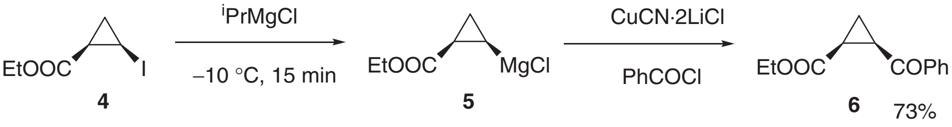
FG = COOR, CN, X, $(RCO)_2N$, $(TMS)_2N$, RNH, NH_2, RCONH, $(RO)_3Si$, $(RO)_2PO$, RS, RSO, RSO_2, PhCOS
R = alkyl, aryl, benzyl, allyl

Scheme 1 Preparation of functionalized organozinc reagents.



Scheme 2 Stereoselective generation of cyclohexyllithium.

Iodine–magnesium exchange has been employed, for example, for the stereoselective preparation of cyclopropyl magnesium halides **5** which afford, after benzoylation, ketone **6** in 73% yield. The same procedure has been also applied to the *trans* isomer to give the *trans* ketone in 65% yield (Scheme 3).[23]



Scheme 3 Stereoselective generation of cyclopropylmagnesium.

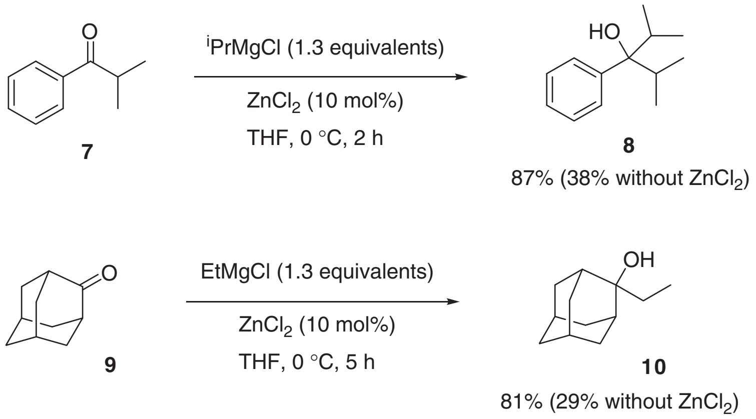
Addition to carbonyl compounds is a widely used way of introducing functional groups on alkyl metallic species. Enolization competes with addition every time when a basic organometallic reagent is used. To avoid or decrease this undesired reaction, addition of zinc chloride and lithium chloride to the alkylmagnesium reagent proved to be quite effective: yields of alcohols **8** and **10** increase significantly on addition of the two chlorides (Scheme 4).[24]

Alkylzinc reagents themselves react only sluggishly with carbonyl compounds and a Lewis acid activator is usually required. First typical examples date back to the late 1980s and the methodology has been later extended to the synthesis of enantiomerically enriched alcohols making use of chiral auxiliaries. 1,2-Bis-sulfonamide[25] and TADDOL-ligands[26] have displayed a remarkable enantioselectivity in addition of alkylzinc to aldehydes.

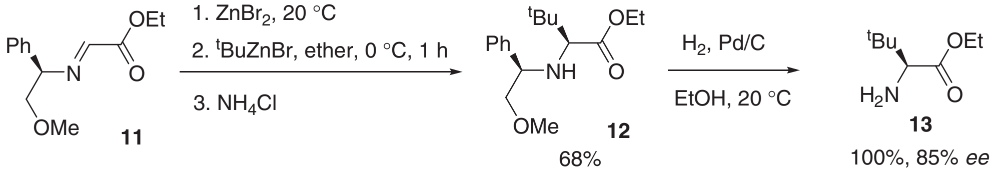
A more recent example of alkylzinc reactivity with carbon electrophiles is the addition to imine as a tool for the preparation of chiral amino acids.[27] The addition of *tert*-BuZnBr to chiral α-imino-ester **11** gives the corresponding adduct **12** with a good diastereoselectivity (96:4). After removal of the auxiliary by hydrogenolysis, the corresponding amino-ester **13** is obtained in 85% *ee* (Scheme 5).

It is well known that alkylmagnesium derivatives can add to Michael acceptors in 1,4-fashion. The topic has been recently reviewed.[28] Recent examples concern the addition of simple alkylmagnesium chlorides to substituted acrylic acids **14** and amides **16** in the presence of an excess of MeLi at −15 °C. An excess of the magnesium reagent is also required to obtain the acid and amide **15** and **17**, respectively (Scheme 6).[29]

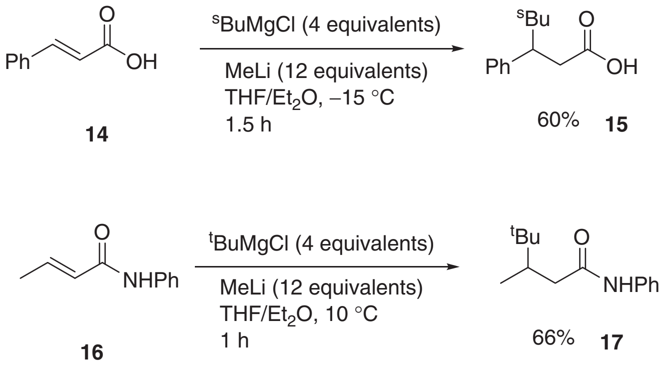
The conjugated addition can be done also with chiral auxiliaries thus allowing for the preparation of enantiomerically enriched carbonyl compounds. In a pioonering work, Kanai and Tomioka reported the use of a proline-derived phosphine as auxiliary for the addition of alkylmagnesium to enones in the presence of copper iodide.[30] More recently the ferrocene-derived ligand



Scheme 4 Addition of organozinc reagents to carbonyl coumpounds.



Scheme 5 Addition of organozinc reagents to imines.



Scheme 6 Addition of organomagnesium reagents to α,β-unsaturated compounds.

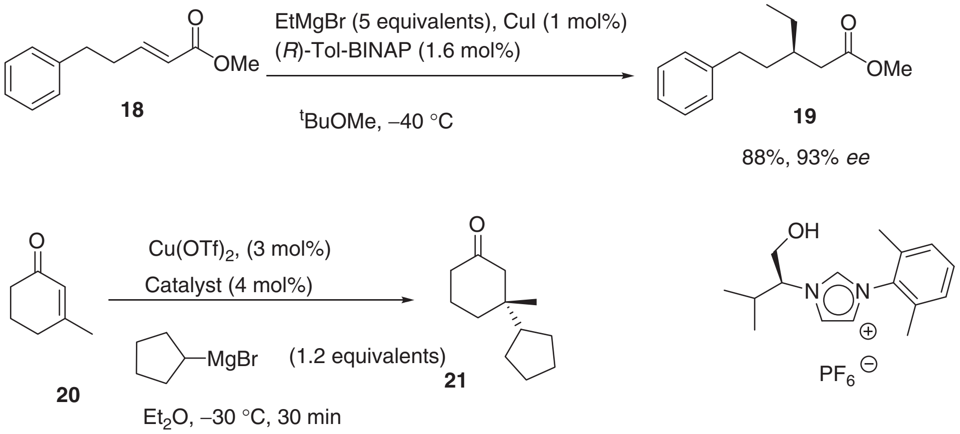
(*R*,*S*)-Josiphos has been employed in the copper-catalyzed 1,4-addition of alkyl Grignard reagents with very high levels of enantioselectivity. Also BINAP[31] and carbene ligands[32] have been used in the same process giving very good results in terms of both yield and selectivity of ketones **19** and **21** (Scheme 7).

Conjugated addition of organozinc reagents in the presence of copper salts is also a well-established reaction. It works better if activation by Me_3SiCl is provided. A typical example is the addition of zinc–copper reagent **23** to cyclohexanone in the presence of Me_3SiCl which gives 1,4-addition product **24** in 97% yield (Scheme 8).[33]

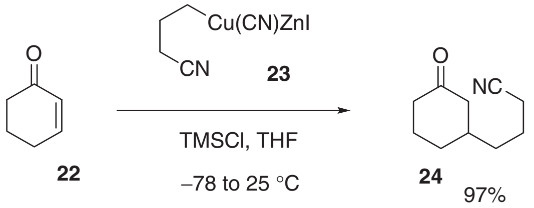
The enantioselective version of this process has been investigated by Feringa et al.[34] and Alexakis et al.[35] in the late 1990s to early 2000s. Very good enantiomeric excesses (up to 93% *ee*) of the addition products have been obtained by using a phosphoramidite ligand as shown by an example in which a pivaloyloxy alkylzinc reagent is used to afford product **26** (Scheme 9).

Activation by heterosubstituents is sometimes crucial for the selective functionalization of poorly reactive substrates. It is well known that *N*-activated heterocycles (*N*-Boc pyrrolidines[36,37] and analogs,[38] piperidines,[39] piperazines[40]), and *O*-alkyl carbamates[41] can be conveniently lithiated and alkylated to give both racemic and enantiomerically enriched compounds, depending on the base used (Scheme 10).

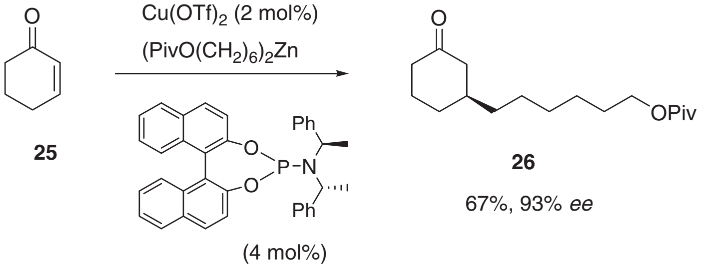
The method has been widely used for the preparation of enantiomerically enriched compounds via lithiation with organolithium reagents in the presence of chiral diamine ligands.[42,43] Important milestones and examples are the preparation of the



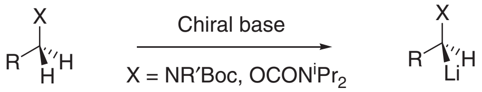
Scheme 7 Enantioselective addition of organomagnesium reagents to α,β-unsaturated compounds.



Scheme 8 Addition of organozinc reagents to α,β-unsaturated compounds.

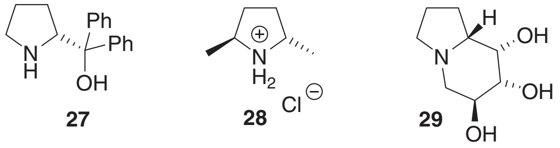


Scheme 9 Enantioselective addition of organozinc reagents to α,β-unsaturated compounds.



Scheme 10 Enantioselective lithiation of *N*-activated heterocycles and *O*-alkyl carbamates.

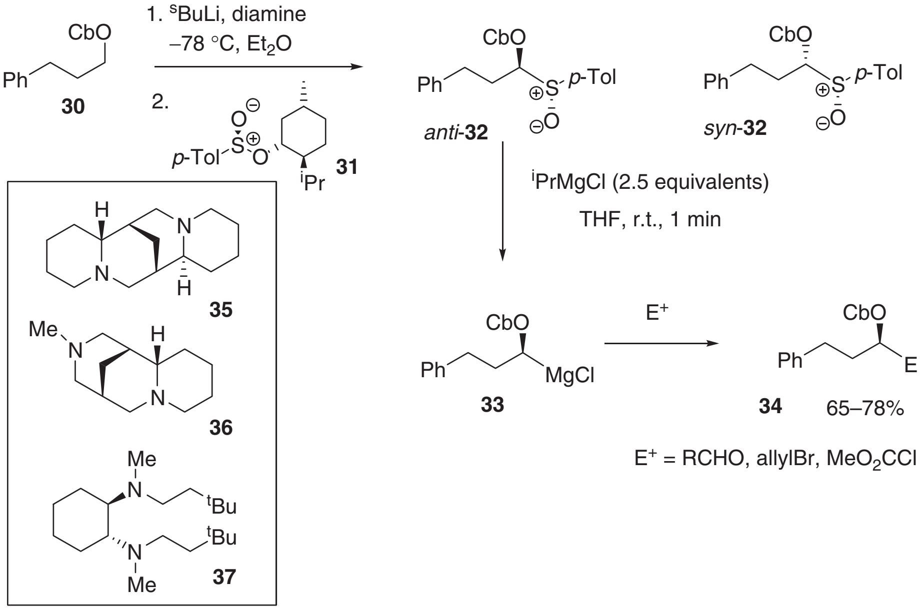
amino alcohol **27** (>99.5% *ee*) (precursor to Corey's CBS reagent), the hydrochloride salt of 2,5-dimethylpyrrolidine **28** (>99% *ee*) (a well-used chiral auxiliary), 8-epi-1-deoxycastanospermine **29** (Scheme 11).



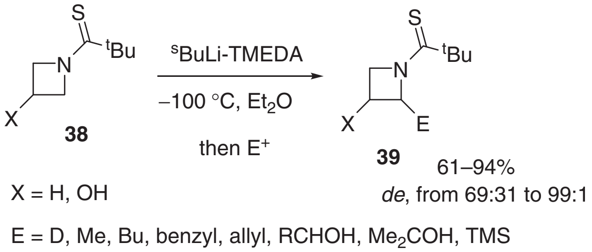
Scheme 11 Synthesis of enantiomerically enriched pyrrolidines through lithiation.

Recent application of this strategy has been reported for the synthesis of alkaloids[44,45] and potential pharmaceuticals[46,47] and the general methodology has also been revised making it simpler and avoiding the use of amine ligands.[48]

A very promising approach for the enantioselective functionalization of pyrrolidine and *O*-alkyl carbamates has been very recently described by O'Brien and coworkers.[49] They have reported the enantioselective deprotonation with butyllithium/chiral diamines of both *N*-activated heterocycles and *O*-alkyl carbamates, followed by lithium–magnesium exchange through the formation of sulfoxides and final reaction with electrophiles. The reaction scheme is illustrated for *O*-alkyl carbamate **30**. The lithiated species is transformed into the sulfoxides *syn*-**32** and *anti*-**32** by reaction with Andersen's sulfinate **31**. Good diastero- and enantioselectivities for both isomers are obtained by a careful choice of the reaction conditions and by using different chiral diamines. When the lithiation is performed in the presence of (−)-sparteine **35**, *anti*-**32** is produced whereas the *syn*-isomer is formed by using spartein surrogate **36** or diamine **37**. Both diastereomers are obtained in a 99:1 ratio and in enantiomerically pure form. The sulfoxide *anti*-**32** is then submitted to treatment with *iso*-propylmagnesium chloride and reaction with electrophiles giving the final products **34** in good yields and as a single stereoisomer (Scheme 12). The four-membered ring azetidines have been also the subject of investigations concerning the possibility of introducing C-electrophiles through a lithiation/substitution process. Azetidine itself (**38**, X=H) can be lithiated, provided nitrogen is protected with a thiopivaloyl group, with *sec*-butyllithium/TMEDA at −78 °C and then the lithiated intermediate can be trapped with different electrophiles. Interestingly only the *N*-thiopivaloyl azetidine is suitable for this purpose, since any other protecting group tested gave rise to extensive decomposition (Scheme 13).[50]



Scheme 12 Enantioselective synthesis via lithium-sulfonate-magnesium exchange.

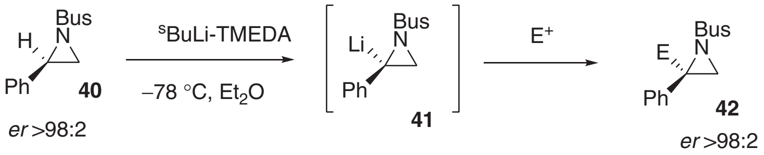


Scheme 13 Metalation/functionalization of azetidines.

The analog 3-hydroxy-*N*-thiopivaloylazetidine (**38**, X=OH) has also been lithiated and intercepted with electrophiles with very good yields.[51]

The more strained oxiranes and aziridines can also be lithiated on the ring carbons and the subsequent reaction with electrophiles allows for the preparation of functionalized heterocycles. This methodology has been the subject of several review articles.[52]

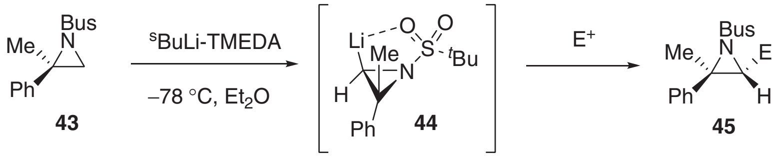
A recent example concerns the *N*-activated aziridine **40** which, on treatment with *sec*-BuLi/TMEDA at low temperature, is selectively lithiated at the α-benzylic position and then trapped with alkylating agents (Scheme 14).



E = D, Me, Me_2COH, PhCHOH

Scheme 14 Metalation/functionalization of aryl-substituted aziridines.

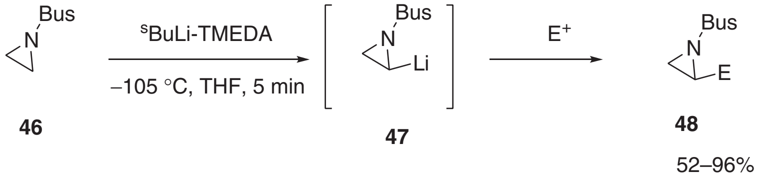
When the α-benzylic postion is methylated as in substrate **43**, lithiation does occur at the β-position to give the chelated species **44** which is then trapped with electrophilic reagents with good stereocontrol (Scheme 15).[53]



E = D, Me, TMS

Scheme 15 Metalation/functionalization of disubstituted aziridines.

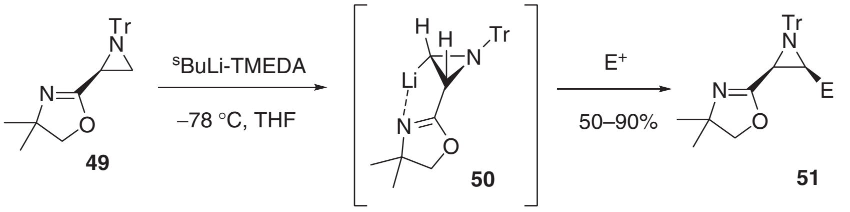
Even the unsubstitued *N*-Bus aziridine **46** can be lithiated with a careful choice of the reaction conditions: treatment with *sec*-butyllithium/TMEDA at −105 °C and then trapping with C-electrophiles, gives the functionalized terminal aziridines **48** in good yields (Scheme 16).[54]



E⁺ = CD_3OD, TMSCl, PhCHO, ᵗBuCHO, EtCHO, PrCHO, Et_2CO

Scheme 16 Metalation/functionalization of unsubstituted aziridines.

If the aziridine ring carries a heterocyclic substituent, an additional stabilization of the lithiated species can be envisaged. Indeed when the aziridine **49** is submitted to lithiation and electrophilic quenching, the corresponding β-alkylated products **51** are obtained with good yields and selectivities (Scheme 17).[55]



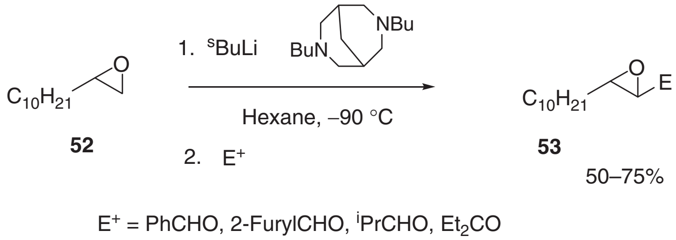
E = D, Et, allyl, PhCO, TMS

Scheme 17 Metalation/functionalization of oxazolinyl aziridines.

Interestingly, the less hindered *N*-benzyl substituted aziridine analog, undergoes lithiation at the α-position thus affording α-substituted regioisomeric derivatives.[55]

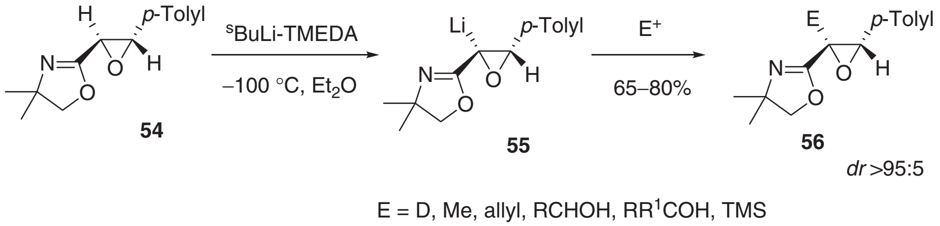
Oxiranes can undergo similar α-lithiation reactions and trapping with electrophiles. The unstabilized oxirane **52** can be metalated with *sec*-butyllithium and *N*,*N*-dibutylbispidine (DBB) and the intermediate organolithium species can be functionalized with a variety of external electrophiles (Scheme 18).[56]

In analogy with aziridines, oxiranyl lithium derivatives are also stabilized in the presence of a heterocyclic substituent. The lithiated oxazolinyloxirane **55**, generated from the *trans* precursor **54**, reacts regio- and stereospecifically with a series of



Scheme 18 Metalation/functionalization of monosubstituted oxiranes.

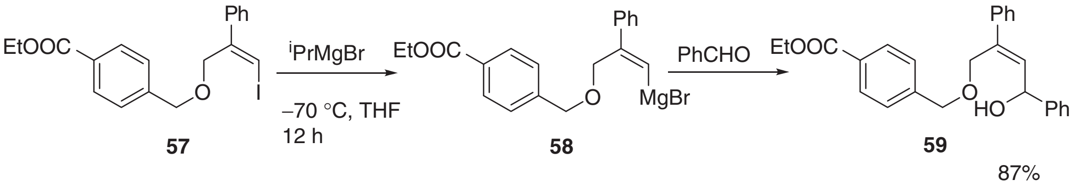
electrophiles with complete retention of configuration at the *α*-carbon to give **56**. The *cis*-isomer is instead configurationally unstable and gives mixtures of diastereoisomers (Scheme 19).



Scheme 19 Metalation/functionalization of oxazolinyl oxiranes.

3.04.2.3 Alkenyl Organometallic Reagents

Some alkenes lacking allylic activated positions can be deprotonated by strong bases at vinylic positions[57–59] but the halogen–metal exchange procedure is far more general and reliable. Halogen–metal exchange is certainly more versatile for the selective preparation of alkenyl metallic reagents. Several examples of magnesium–iodine exchange on alkenyl iodides on reaction with ^{i}PrMgBr and ^{i}Pr$_2$Mg were reported by Knochel and Cahiez in the 1990s.[60] The exchange in such case is slower than with aryl iodides but can be accelerated if the double bond is activated by the presence of a chelating heteroatom or an electron-withdrawing functional group. So, for example, the alkenyl iodide **57**, undergoes exchange with ^{i}PrMgBr and the resulting vinylmagnesium intermediate **58** is trapped with aldehydes in very good yields (Scheme 20).



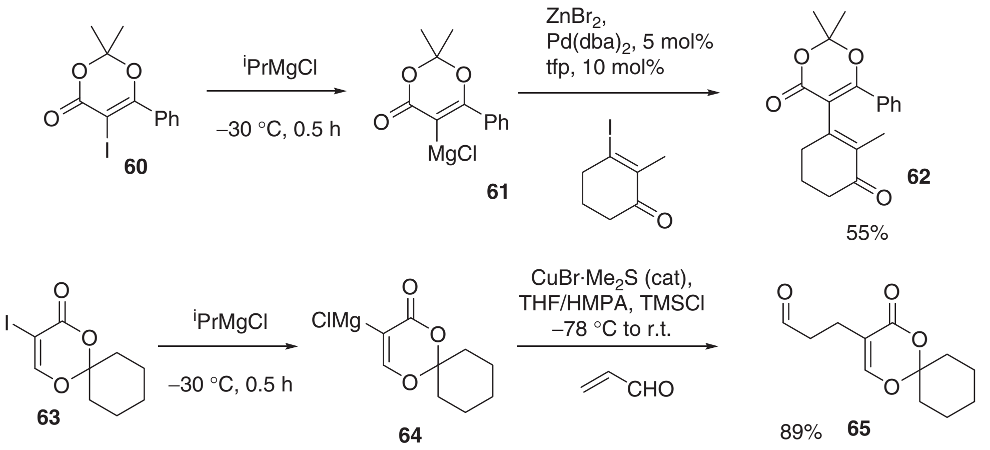
Scheme 20 Iodine–magnesium exchange on alkenes.

The presence of an electron-withdrawing group on the double bond facilitates the exchange as in the case of alkenyl iodides **60**[61] and **63**[62] which are converted into the functionalized products **62** and **65** through Pd and Cu-catalyzed reactions, respectively (Scheme 21).

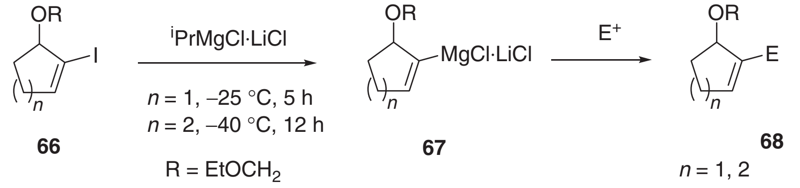
The rate of iodine–magnesium exchange increases dramatically when the complex ^{i}PrMgCl·LiCl is used.[63] By this approach, 2-iodo cycloalkenyl derivatives **66** are easily converted into the corresponding functionalized cycloalkenes **68** after reaction with aldehydes, acylchlorides, tosylated aziridines, and allyliodides.[64] The reaction is quite general and, being performed at −25 °C, can tolerate functional groups on the alkene moiety and allows to maintain the double bond configuration (Scheme 22).

Alkenyl iodides **69** are converted into alkenes **71** at low temperature with high yields and a perfect stereocontrol. Halogen-, cyano and ester functionalities are tolerated and electrophilic reagents such as aldehydes, allyl bromide and tosyl cyanide can be employed (Scheme 23).[65]

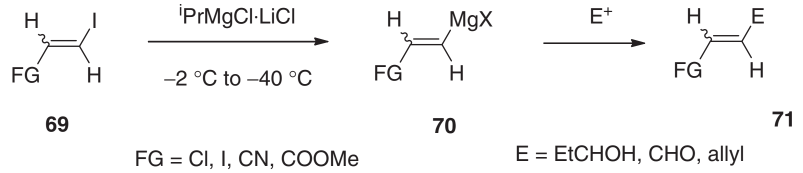
Functional groups in olefins cannot survive conditions usually required for metalation with polar organometallics but their magnesiation and zincation are possible making use of a family of 2,2,6,6-tetramethylpiperidyl bases. TMPMgCl·LiCl, TMP$_2$Mg·2LiCl, TMPZnCl·LiCl, and TMP$_2$Zn·2MgCl$_2$.LiCl have been proven to be very versatile: the high kinetic basicity allows



Scheme 21 Iodine–magnesium exchange on activated alkenes.

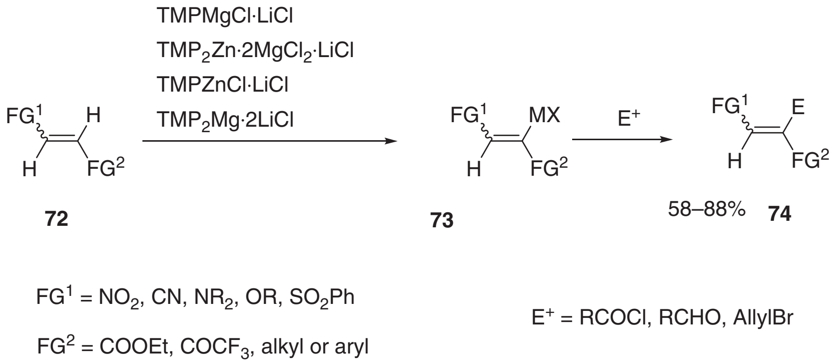


Scheme 22 Iodine–magnesium exchange with ^{i}PrMgCl·LiCl complex.



Scheme 23 Iodine–magnesium exchange/functionalization of alkenes.

them to replace hydrogen from olefins **72** containing groups which normally do not survive in the presence of bases at temperature higher than −80 °C (Scheme 24).



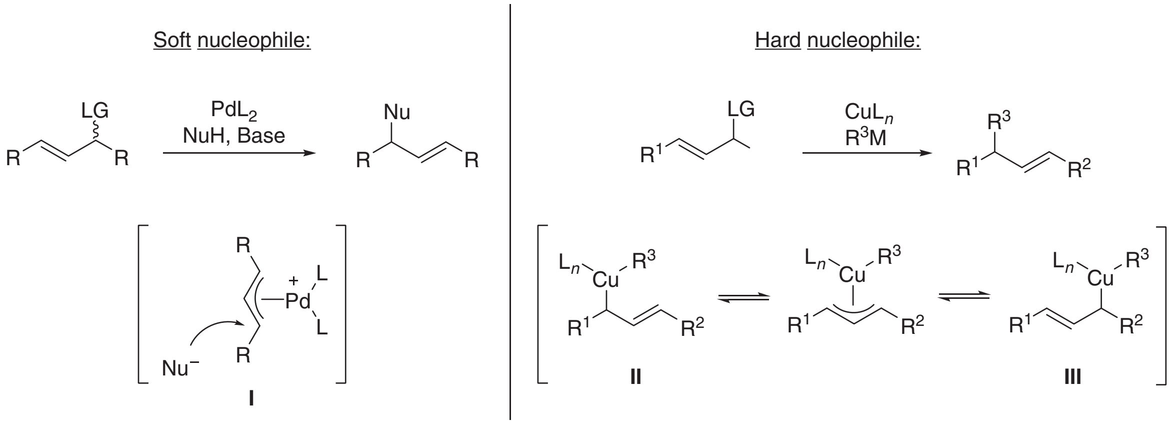
Scheme 24 Metalation of alkenes with magnesium- and zinc-amides.

Most of these reactions are carried out at room temperature and, remarkably, the method allows the synthesis of zincated nitro olefins as well as esters under practical reaction conditions (between −30 and 25 °C).[66]

3.04.3 Allylation of Nonstabilized (Hard) Nucleophiles

3.04.3.1 Introduction

Allylic substitution is one of the most useful transformations currently available for the selective formation of carbon–carbon σ bonds, and involves reaction of a nucleophile with a suitable allylic electrophile (Scheme 25). Such reaction is often facilitated by the use of transition metal (TM)-based mediators or catalysts,[67,68] but employment of TM-free promoters has also been reported. Catalysts containing a variety of different metals, including Pd,[69] Mo,[70] Ir,[71] and Ru,[72] are typically associated with the use of 'soft' stabilized nucleophiles, such as malonates and heteroatom-centered nucleophiles; on the contrary, employment of 'hard' non-stabilized nucleophiles, such as polar organometallic species (RMgX, R_2Zn, R_3Al, RLi), has been mostly accomplished by the application of Cu-based catalysts,[73,74] although examples detailing the use of different metals exist.

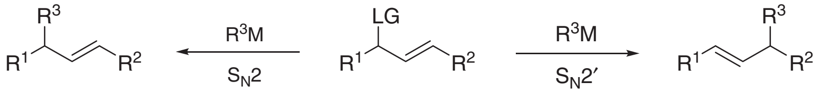


LG = OAc, Cl, Br, $OP(O)(OEt)_2$ etc.
NuH = RNH_2, ROH, $CH_2(CO_2Me)$ etc.
M = Li, MgX, ZnX, AlX_2 etc.

Scheme 25 Different mechanistic pathways for the allylic substitution by soft and hard nucleophiles.

The mechanism of transition metal-catalyzed allylic substitutions has been the subject of extensive studies, and two main mechanistic pathways are currently accepted, depending not only on the particular metal catalyst employed, but also on the nature of the nucleophile (Scheme 25). In the case of soft nucleophiles (exemplified by the Pd-catalyzed reaction on the left) formation of a π-allylic metal complex is usually followed by a nucleophilic attack from the opposite site of the coordinated metal ion.[75] Conversely, for hard nucleophiles (as in the case of the Cu-catalyzed reaction of a polar organometallic reagent on the right) C–C bond formation takes place following a reductive elimination from one of the interconverting organometallic intermediates **II** or **III**.[76,77]

As can be already deduced from Scheme 25, one of the most important parameters to be controlled in an allylic substitution reaction is the regioselectivity. Indeed, displacement of an allylic leaving group can proceed according to two different routes (Scheme 26): direct nucleophilic attack on the carbon bearing the leaving group gives rise to the so-called S_N2 reaction, whereas attack at the γ-position causes an additional allylic shift of the double bond and is usually termed the S_N2' reaction. Therefore, in the case of substrates having two different groups at the α and γ positions of the allylic system ($R^1 \neq R^2$ in the scheme), two different products can be formed. The regioselectivity of an allylic substitution reaction can be influenced by many different parameters, such as leaving group, nucleophile, nature and loading of the catalyst, solvent, temperature and so on.[78] Careful choice of the reaction conditions can thus allow controlling the regiochemistry of the reaction.



LG = OAc, Cl, Br, $OP(O)(OR)_2$ etc.
M = MgX, ZnX, Li, AlX_2 etc.

Scheme 26 Possible regioselectivity of the allylic substitution reaction.

In this paragraph, the authors survey important results recently described for catalyzed allylic substitution of hard, nonstabilized nucleophiles, either in the presence of transition metal catalysts or of activating Lewis bases. Both regio- and stereoselective, albeit nonasymmetric, protocols and enantioselective reactions published in the years 2000–2013 will be considered.

3.04.3.2 Regio- and Stereoselective Allylic Substitutions With Nonstabilized Nucleophiles

3.04.3.2.1 Copper-mediated and -catalyzed transformations

In recent years, several groups have contributed to the development of efficient copper-catalyzed allylic substitutions with polar organometallics. Such reactions can proceed with high regio- and stereochemical control: in particular, it has been long known that Cu-catalyzed processes are usually *anti*-stereoselective. The reason of such preference was first rationalized by Corey and Boaz, who observed that the reaction of an incoming organocuprate with an allylic electrophile requires the carbon–nucleofuge bond to be roughly orthogonal to the carbon–carbon double bond, making the corresponding σ^* and π^* orbitals coplanar and thus allowing the overlap of both of them with the nucleophilic copper d orbitals in the transition state (Figure 1).[79]

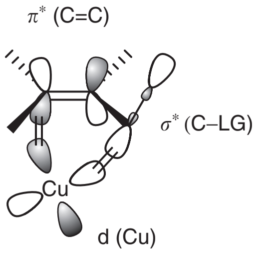
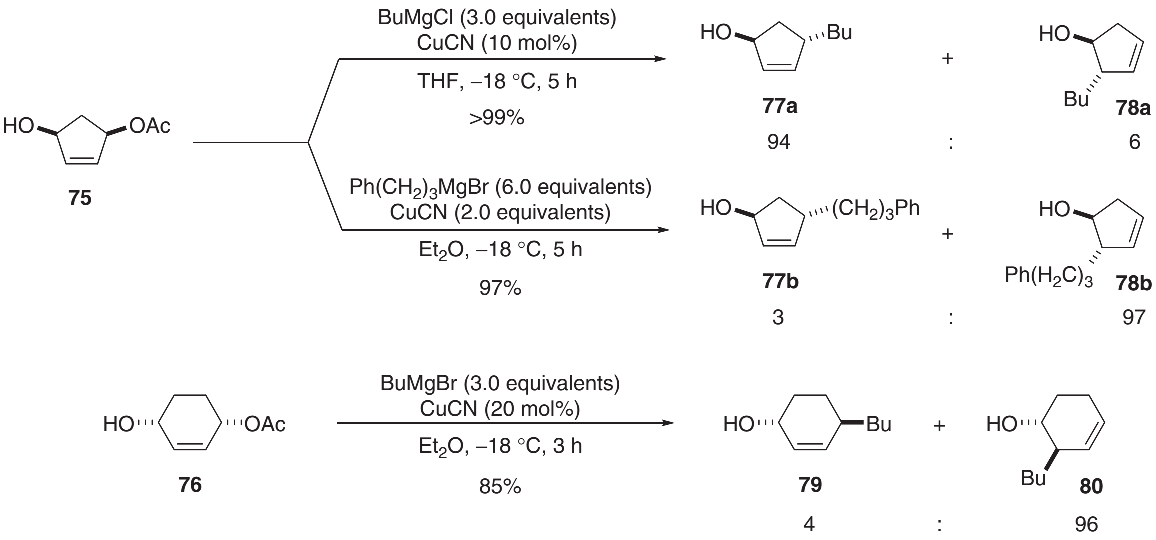


Figure 1 Orbital overlap for the addition of an organocuprate to an allylic electrophile.

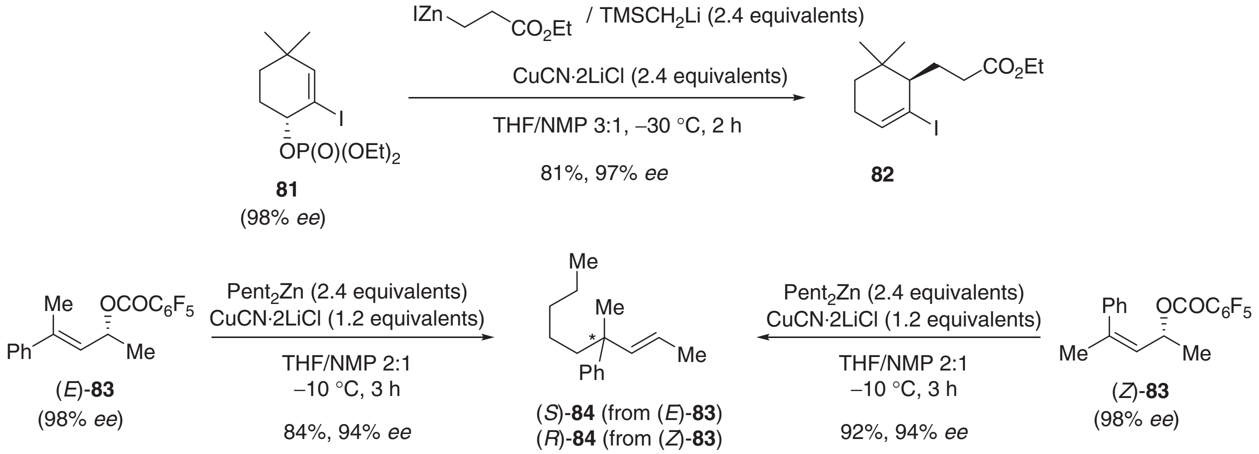
In a series of papers, Kobayashi and coworkers addressed the problem of the regio- and stereoselective alkylation of cyclic 1,3-diol monoacetates **75**–**76** and derivatives thereof, using Grignard reagents in combination with copper salts. In the case of cyclopentene derivatives, it was found that the S_N2:S_N2' product ratio could be completely reversed by variation of the reaction stoichiometry, the solvent and the copper salt employed (Scheme 27, top).[80,81] Conversely, in the case of cyclohexene derivatives the selectivity could be somewhat affected by a change in the reaction conditions, but the product of γ-substitution was always preferred (Scheme 27, bottom).[82] In both cases, *anti*-addition products were obtained exclusively.



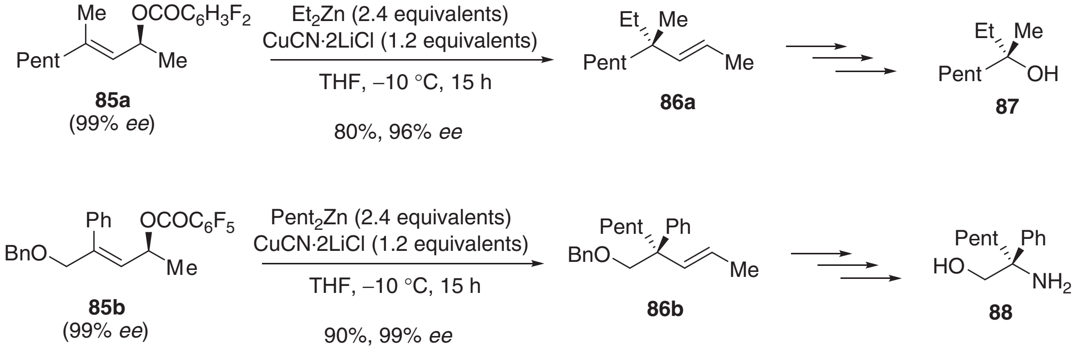
Scheme 27 Selectivity of the Cu-mediated alkylation of cyclic 1,3-diol monoacetates.

Interestingly, it was later found that a modification of the reaction conditions could also lead to selective reactions using aryl and vinyl Grignard reagents, instead of the alkyl derivatives employed above, but in this case the products of *anti*-S_N2 substitution were formed preferentially.[83] In a separate work, the same group showed that compounds of structure **77**, after conversion to the corresponding acetates, could also be alkylated, and it was found that an excellent control of the regio- and stereochemistry was possible also in this case, with reactions in THF favoring the formation of the S_N2 product whereas those in Et_2O brought to the formation of the other regioisomer. The synthetic utility of this chemistry was demonstrated by the preparation of the brown algae pheromone dihydromultifidene.[84]

An important contribution to the development of stereoselective Cu-mediated allylic alkylations was given by Knochel's group, who studied in detail the enantiospecific transformations of chiral allylic esters, which are easily obtained from the corresponding alcohols, in the presence of functionalized organozinc reagents; highly enantioenriched allylic alcohols can in turn be prepared by a number of synthetic methodologies.[85] The authors demonstrated the use of allylic phosphates as substrates for the reaction (Scheme 28, top),[86,87] and introduced also penta- and difluorobenzoates as new leaving groups, which enabled an outstanding transfer of chiral information.[86] All reactions proceeded with complete *anti*-selectivity and afforded exclusively products deriving from γ-alkylation. This methodology allowed also for the formation of quaternary stereogenic centers with remarkable conservation of the stereochemical integrity of the substrates;[88] strikingly, use of either the (*E*)- or (*Z*)-diastereomer of starting material **83** led to the selective formation of both enantiomers of product **84** (Scheme 28, bottom). Later, Knochel and coworkers reported an impressive application of the same chemistry, describing the preparation of chiral tertiary alcohols and amines in high enantiomeric excess starting from an enantiospecific and diastereoselective Cu-mediated allylic alkylation with diorganozinc reagents (Scheme 29).[89] The alcohols were obtained from olefins **86** through a sequence comprising ozonolysis with reductive work-up, Bayer–Villiger oxidation and hydrolysis with alcoholic KOH; on the contrary, amine synthesis from compounds **86** included ozonolysis with oxidative work-up, Curtius rearrangement and finally isocyanate hydrolysis under acidic conditions.



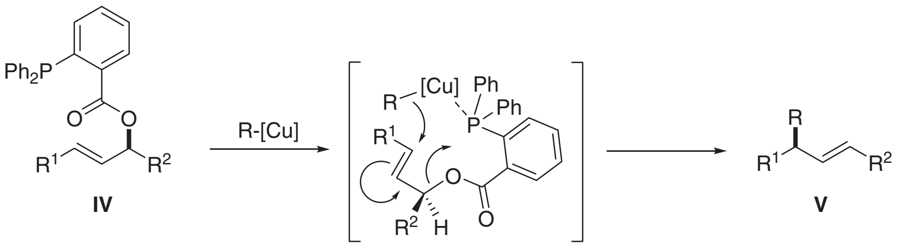
Scheme 28 Enantiospecific copper-mediated allylic alkylations according to Knochel et al.



Scheme 29 Stereoselective synthesis of tertiary alcohols and amines via Cu-mediated allylic substitution.

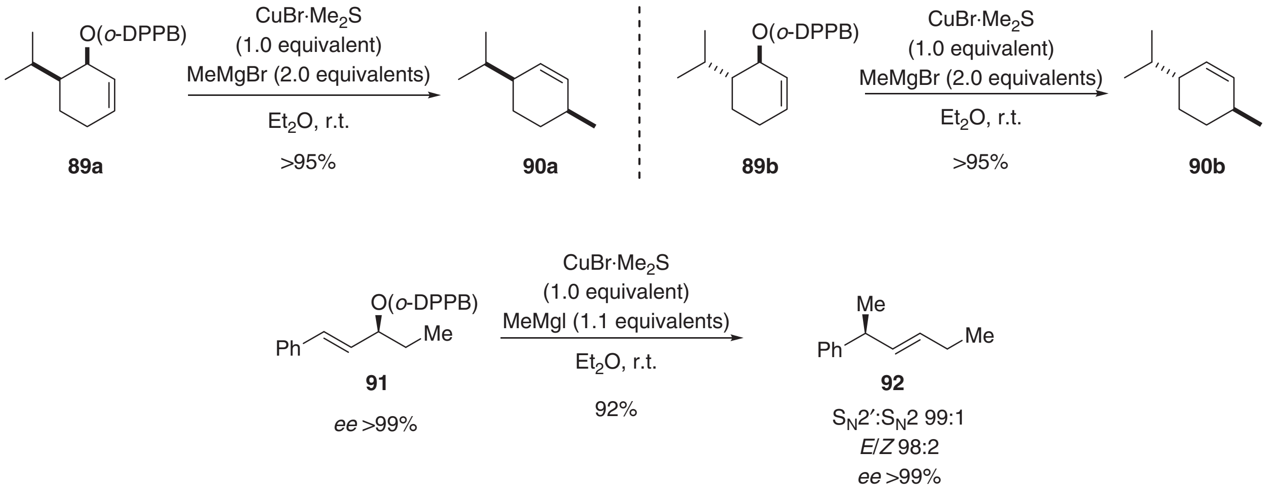
Extensions of the same methodology were later reported, which allowed access to other classes of interesting chiral compounds, including ketones[90,91] and (*E*)-alkenyl silanes[92] bearing a stereogenic center at the α-position, as well as α,β-unsaturated nitriles with a stereogenic center at the γ-position.[93] In spite of the synthetic utility of these protocols, it should be pointed out that they all required employment of a stoichiometric amount of complex CuCN·2LiCl to proceed. An exception was constituted by the reaction of functionalized Grignard reagents with simple allylic halides, which was later found to take place in the presence of a catalytic quantity (5 mol%) of the same metal complex.[94]

Even considering the successful examples shown above, achievement of complete regio- and stereoselectivity in Cu-mediated allylic alkylations can still represent a challenging goal. A possible solution to this problem is constituted by the use of a directing leaving group, which can coordinate the incoming organocopper nucleophile and thus influence its trajectory, leading to a selective γ-substitution; moreover, such a leaving group could also reverse the typical stereochemistry of copper-mediated transformations, giving rise to a selective *syn*-addition.[95] This strategy has been investigated in detail by Breit et al., who introduced the *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB) moiety as a multifunctional reagent-directing group (**Scheme 30**).



Scheme 30 Regio- and stereoselectivity of allylic substitution with *o*-DPPB esters.

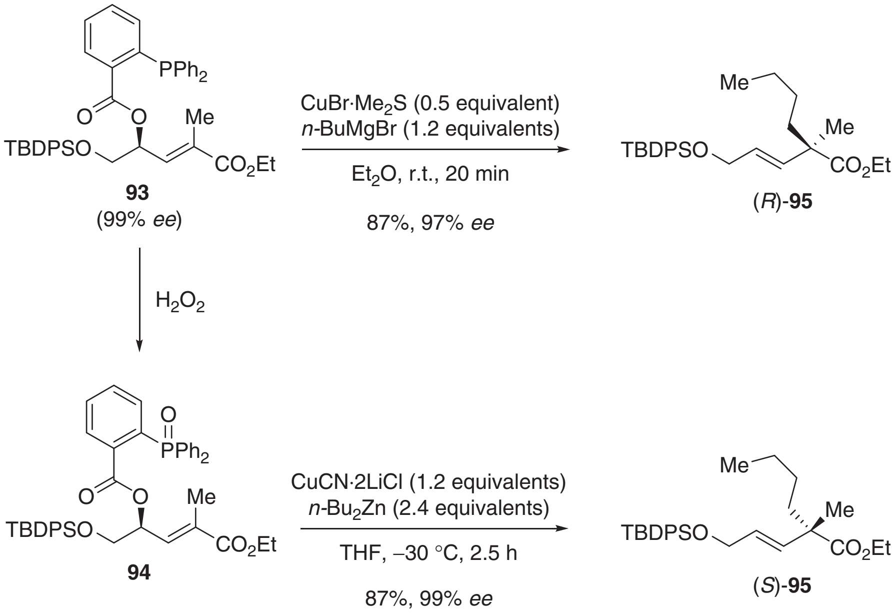
Employment of allylic *o*-DPPB esters in the Cu-mediated reaction with alkyl Grignard reagents afforded exclusively the products of *syn* γ-substitution, as demonstrated by the results obtained with cyclic substrates **89a–b** (**Scheme 31**, top).[96] The excellent control of stereochemistry was further shown by the conversion of chiral ester **91**, which yielded the corresponding product with no erosion of enantiomeric excess (**Scheme 31**, bottom).[97] Later, the same research group demonstrated that a complete reversal of the reaction stereochemical outcome was possible starting from a single substrate, by means of a simple 'on/off switch' of the leaving group directing ability. Oxidation of the phosphorous atom in *o*-DPPB derivative **93** with aqueous H_2O_2 afforded the corresponding phosphine oxide, which was unable to coordinate copper and therefore could not direct the nucleophilic substitution; thus, by treatment of compound **94** with organozinc reagents in the presence of a different copper salt, formation of the product of *anti*-addition was observed in high selectivity; importantly, in the directed reactions the authors showed the possibility to use the copper source in substoichiometric (0.5 equivalent) amount (**Scheme 32**).[98,99]



Scheme 31 Examples of stereoselective allylic substitutions with *o*-DPPB esters.

The synthetic utility of the Cu-mediated allylic alkylation of *o*-DPPB esters was demonstrated by the development of a unified, iterative procedure for the stereoselective preparation of deoxypropionate scaffolds, by means of which all the possible diastereomers of a C-10 tris(deoxypropionate) building block could be accessed starting from the same precursor.[100,101] Interestingly, such synthetic sequence is complementary to the classic approaches involving enolate alkylation chemistry, since here the growing propionate chain is introduced as a nucleophile and not as an electrophile. Subsequent application of the same methodology to a series of different substrates led to the development of efficient strategies for the stereoselective construction of useful building blocks, such as acetate–propionate and propionate units[102] and trisubstituted olefins,[103] as well as trisubstituted alcohols and amines.[104]

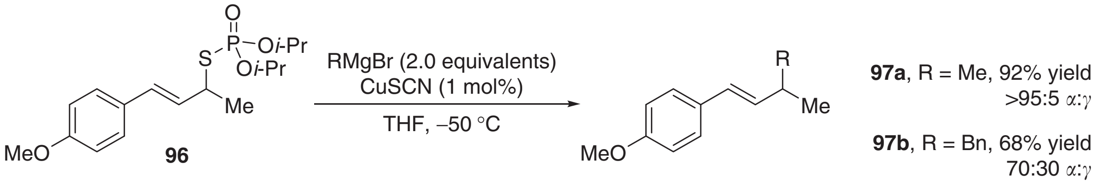
The Cu-mediated directed allylic alkylation of *o*-DPPB esters was exploited by Breit's group to perform the stereoselective total synthesis of several natural compounds such as borrelidin,[101] the 4,6,8,10,16,18-hexamethyldocosane from cane beetle



Scheme 32 Stereospecific enantiodivergent formation of quaternary stereocenters with an 'on/off' oxidative switch.

Antitrogus parvulus,[105,106] (+)-bourgeanic acid,[107] and (*R*,*R*,*R*)-α-tocopherol.[108] The latter synthesis is particularly remarkable, since the *o*-DPPB directed allylic substitution represented the final fragment-coupling step, taking place between two large functionalized building blocks. In addition, other groups have also applied Cu-mediated allylic alkylations to the synthesis of peptide mimetics.[109–112]

Finally, an intriguing study was recently published by Wu and coworkers, who identified suitable conditions to carry out Cu-catalyzed allylic substitutions with high α-selectivity, as opposed to the typical γ-selectivity usually displayed by such processes. Key to obtain this peculiar regioselectivity was the use of allyl phosphorothioate esters **96** as substrates, whose employment in metal-catalyzed substitutions was previously unknown.[113] Use of primary alkyl- and arylmagnesium halides as nucleophiles in combination with CuSCN resulted in highly selective reactions, whereas employment of sterically encumbered reagents and benzylic derivatives occasionally gave inferior results (Scheme 33); performing the reaction on an enantiomerically enriched substrate showed that the process took place with good *anti*-diastereoselectivity as well.



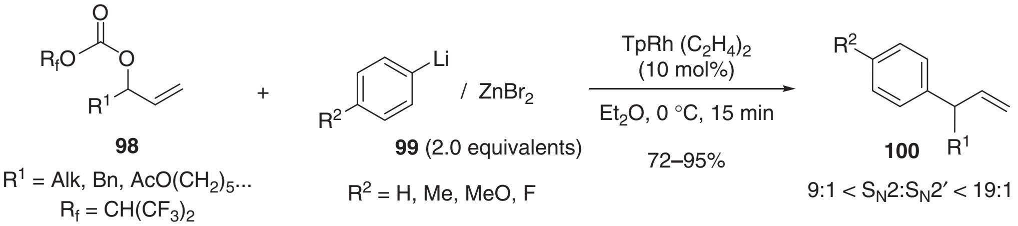
Scheme 33 Regioselective Cu-cat. α-alkylation of allyl phosphorothioate esters.

According to the authors, the phosphorothioate leaving group, after its displacement by the incoming organocopper nucleophile, could act as an electron-rich ligand to copper, slowing down reductive elimination and favoring interconversion between the two σ-allyl complexes (**II** and **III** in Scheme 25), thus leading to the selective formation of the more stable α-adduct.

3.04.3.2.2 Other regio- and stereoselective allylic substitutions

Compared to copper-mediated processes, regio- and stereoselective allylic substitutions conducted in the presence of other promoters have been much less investigated. Despite that, the few studies reported in recent years disclosed useful synthetic protocols and highlighted the possibility to carry out reactions as selective as the Cu-mediated transformations described above (see Section 3.04.3.2.1).

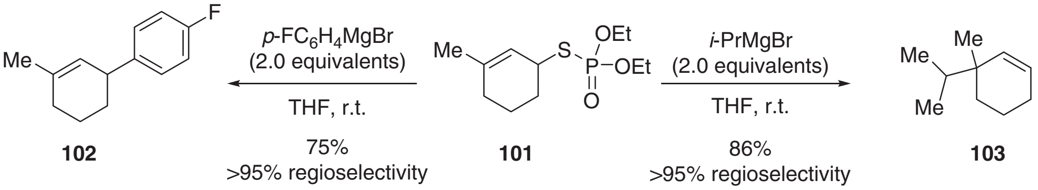
In 2003, the group of Evans described a Rh-catalyzed, regio- and enantiospecific arylation of fluorinated allylic carbonates.[114] This peculiar class of leaving groups was selected because it ensured higher levels of regioselectivity compared to traditional leaving groups such as acetate and carbonate in the conversion of secondary substrates. Thus, treatment of compounds **98** with several arylzinc bromides, in turn obtained from the corresponding organolithium reagents and $ZnBr_2$, under the influence of metal catalyst $TpRh(C_2H_4)_2$ (Tp=hydrotris(pyrozolyl)borate)[115] led to the clean formation of secondary S_N2-products **100** with high selectivity (Scheme 34). Application to a chiral enantioenriched substrate showed that the reaction proceeded with net inversion of the absolute configuration in an enantiospecific fashion. Its synthetic utility was proved by an enantioselective preparation of the famous analgesic drug (*S*)-ibuprofen.



Scheme 34 Rh-catalyzed allylic arylation of secondary fluorocarbonates.

As far as transition metal-free protocols are concerned, a few interesting transformations have been recently reported. Kondo and coworkers showed that the well-known *t*BuP4 base[116] could be used to catalyze (10 mol%) the allylic substitution of activated α,β-unsaturated-γ-chloro esters by diethylzinc with high S_N2' selectivity, provided that LiCl was used as an additive; the selectivity was reversed only when a phenyl group was present at α-position relative to the ester moiety.[117] Preliminary ^{1}H-NMR studies suggested that the high reactivity of Et_2Zn under these conditions was due to coordination by the base, which enhances the nucleophilicity of the organometallic reagent.

Parallel to their studies on Cu-catalyzed reactions (see previous paragraph, Scheme 33),[113] Wu and coworkers also developed a procedure for the metal-free allylic substitution of cyclic phosphorothioate esters with Grignard reagents.[118] Interestingly, the reactions were found to take place cleanly in the presence of 2.0 equivalents of the organometallic reagent without the need for additives; in addition, reactions could also be run at room temperature, as opposed to −50 °C required for the Cu-catalyzed protocol. A significant difference with the metal-catalyzed transformation was nevertheless found, in that reactions conducted with aryl- and vinyl-Grignard derivatives gave high α-selectivity, whereas those employing alkyl Grignard reagents afforded preferentially the product of γ-substitution, albeit with reduced selectivity (Scheme 35).



Scheme 35 Regioselective, transition metal-free allylic alkylation of cyclic phosphorothioate esters.

3.04.3.3 Enantioselective Allylic Substitutions With Nonstabilized Nucleophiles

Among the methods available to prepare optically active building blocks and intermediates, enantioselective catalysis is particularly attractive, due to the possibility to use readily available prochiral starting materials, access both enantiomers of a product starting from the same substrate and introduce the chiral information by means of just a small quantity of an enantioenriched catalyst.[119] Several examples of catalytic enantioselective allylic substitutions with hard nonstabilized organometallics have been recently published, both in the presence and in the absence of a transition metal complex as the chiral promoter.

3.04.3.3.1 Copper-catalyzed transformations

As it is the case for nonasymmetric, regio- and stereoselective allylic substitutions with nonstabilized carbon nucleophiles (see Section 3.04.3.2), the vast majority of enantioselective reactions have also been reported to work in the presence of copper promoters. In this instance, the catalysts are typically constituted by complexes of Cu(I) with mono- or bidentate chiral ligands, either preformed or prepared *in situ*. Copper-catalyzed enantioselective allylic substitutions have already been extensively reviewed:[73,74,120] for this reason, the most significant results obtained in recent years will be briefly recalled, whereas the latest important developments will be discussed in more detail. Reactions will be classified according to the nature of the particular organometallic reagent employed.

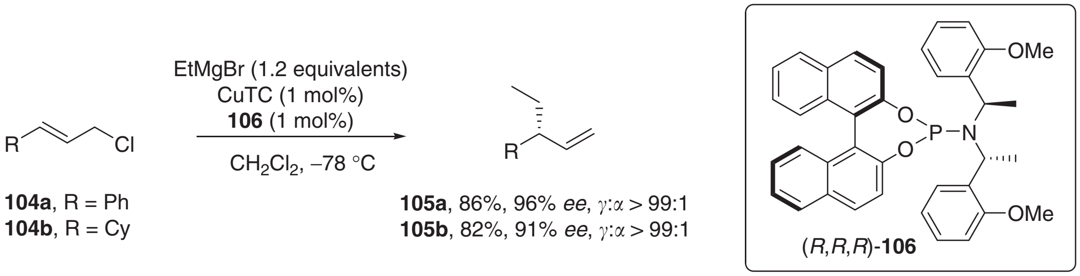
3.04.3.3.1.1 Copper-catalyzed transformations with organomagnesium reagents

Historically, Grignard reagents have been the first organometallic nucleophiles to be used in Cu-catalyzed enantioselective allylic substitutions: indeed, already in 1995 Bäckvall and van Koten reported such a reaction in which allylic acetates were used as the substrates and the catalyst was a chiral arenethiolatocopper(I) complex, achieving complete γ-regioselectivity but only moderate enantioselectivities up to 42%.[121] Later, further optimization and employment of a bulky organomagnesium nucleophile allowed a small increase in enantioselectivity, up to 53% *ee*, while retaining high regioselectivity.[122]

After these initial results, the development of this kind of transformations has been investigated by several research groups, who focused on different classes of chiral ligands, combining them with various copper sources.

The group of Alexakis was particularly successful in pioneering the application of chiral monodentate phosphoramidate ligands; in a first report, it was already reported that TADDOL-derived ligands in combination with CuCN or CuTC were able to catalyze the reaction of alkyl Grignard reagents with γ-aryl-substituted allylic (cinnamyl) chlorides to yield the corresponding products with high γ-regioselectivity and good enantiomeric purity (up to 73% *ee*).[123] A major breakthrough was achieved when monodentate phosphoramidates bearing biphenol and binaphthol units were introduced.[124,125] In particular, ligand **106** (featuring *o*-methoxy substituents on the phenyl rings) proved to be very effective, allowing conversion of both cinnamyl and (for the first time) alkyl-substituted substrates with high regioselectivity and 91–96% *ee* (Scheme 36).[125,126] Interestingly, the reaction worked also with Grignard reagents having terminal double bonds; the resulting products could therefore undergo ring-closing metathesis (RCM) and cross-metathesis (CM) reactions with Grubbs catalyst[127] to give cyclic and acyclic olefins in good yields.

Following these reports, monodentate phosphoramidate ligands have been subsequently applied to an ever increasing number of substrate–nucleophile combinations, often with remarkable results.[73,74]



Scheme 36 Cu-phosphoramidate-catalyzed enantioselective allylic alkylations.

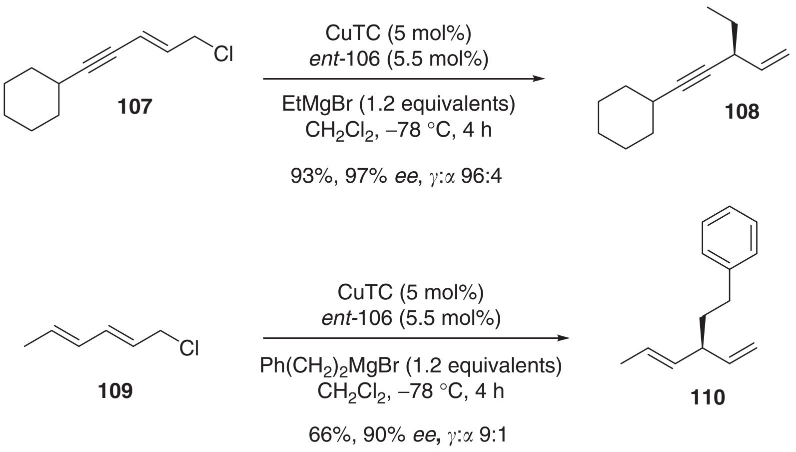
Alexakis established optimal conditions for the transfer of a methyl group, which was previously regarded as a challenging process; slow addition of the nucleophile MeMgBr was found to be crucial to convert a series of substituted cinnamyl chlorides with high regio- and stereoselectivity.[128] This result illustrates how the selectivity of these reactions can be affected by the particular procedure employed, and explains why research groups routinely explore the slow addition of the nucleophile as a way to boost the regioselectivity of their allylic alkylations.

Use of Cu(I)–phosphoramidate complexes was then extended to the alkylation of various other substrates, such as β- and γ-disubstituted alkenes[129,130] as well as 1,4-dihalo-2-butenes (X=Cl, Br):[131,132] the latter process is particularly interesting, since the resulting homoallylic halides could be used either as electrophiles or nucleophile precursors in subsequent reactions. Alkylation of 1,4-dibromo-2-butene with a Grignard reagent was also reported in conjunction with the employment of 'SimplePhos' ligands, a new class of promoters also developed by Alexakis and coworkers.[133] Another category of substrates that were converted under Cu(I)-phosphoramidate catalysis were ω-ethylenic allylic halides. The resulting dienes, having two terminal double bonds at both extremities of the carbon chain, could directly undergo RCM with Grubbs 2nd generation catalyst to produce cyclic olefins with good to high *ee* (67–93%).[134] Thus, such protocol constitutes an alternative to the employment of alkyl Grignard reagents with a terminal double bond mentioned above.[124,125]

In 2007, Carosi and Hall described the enantioselective Cu(I)-catalyzed asymmetric allylic alkylation of 3-chloropropenylboronates with EtMgBr in the presence of ligand **5,5′,6,6′,7,7′,8,8′-octahydro-*ent*-106**. The products α-substituted allylboronates were useful synthetic intermediates, since they could be directly treated with aldehydes and ketones under Lewis base catalysis to give, after a highly stereospecific reaction, homoallylic alcohols with 85–94% *ee*.[135]

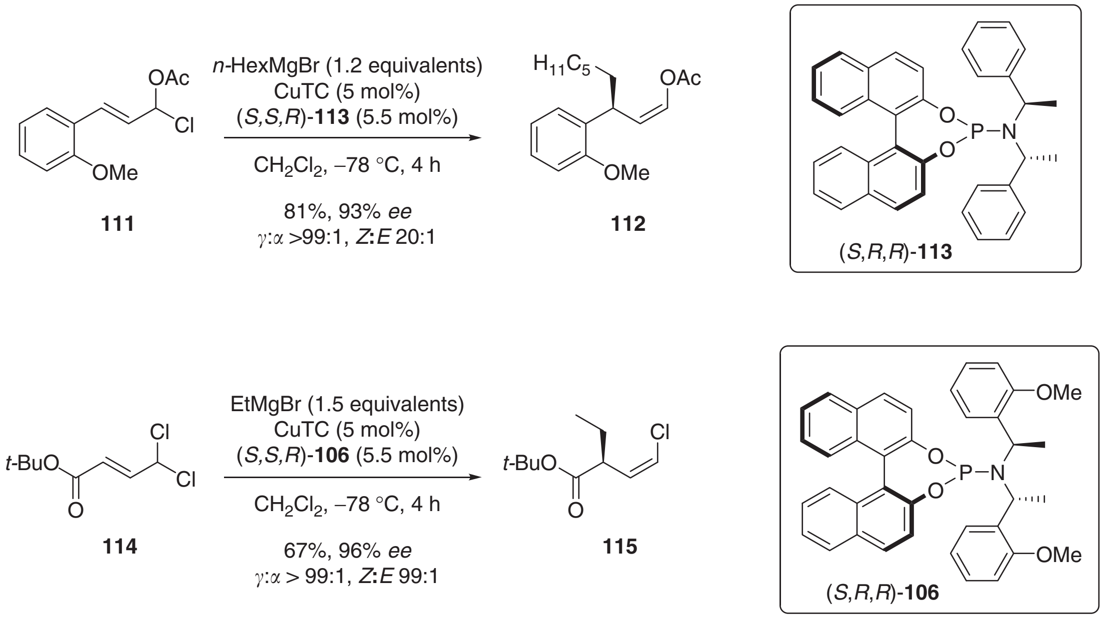
Very recently, the enantioselective alkylation of substrates characterized by extended π-systems, such as enyne and diene chlorides, has been described. In the presence of CuTC and ligand ***ent*-106**, substrates **107** and **109** could be efficiently reacted with a number of alkyl Grignard reagents giving the corresponding products **108** and **110** with high *ee* and γ-selectivity (Scheme 37).[136] The only exception was MeMgBr, which gave an almost equimolar mixture of the S_N2 and S_N2' products, albeit the latter was obtained with 93% *ee*; in addition, employment of PhMgBr gave almost exclusively the achiral S_N2 adduct.

Two further remarkable examples have been reported by Feringa et al., who explored the reactivity in allylic alkylations of *gem*-α,α-disubstituted substrates. In a first study, the transformation of α-chloroallylic acetates **111**, in turn easily prepared from the corresponding unsaturated aldehydes, was investigated.[137] The authors found that, under the influence of the CuTC/(*S*,*R*,*R*)-**113** combination, (*Z*)-vinylacetates **112** were formed smoothly in good to high *ee*'s, with the exception of those derived from bulky organomagnesium reagents (Scheme 38); compounds **112** could then be converted into the corresponding β-branched aldehydes simply by basic hydrolysis. In a subsequent investigation, the reactivity of α,α-*gem*-dichlorides **114** was assessed: it was found that, under optimized conditions, no product of multiple substitution was formed, and (*Z*)-vinylchlorides **115** could be obtained with



Scheme 37 Examples of Cu-cat., enantioselective allylic alkylations of enyne and diene chlorides.

very high regio-, stereo- and enantioselectivity (Scheme 38).[138] Derivatives **115** are valuable synthetic intermediates because they can be converted into a number of other compounds by cross-coupling processes.



Scheme 38 Asymmetric allylic alkylations of chloroallyl acetate **111** and *gem*-allyldichloride **114**.

Employment of bidentate phosphorous ligands has been investigated in particular by Feringa and coworkers, who managed to obtain high selectivity especially with axially chiral, ferrocene-based diphosphines.[120d] It should be pointed out that few of these ligands had also been tested by Alexakis et al. in the course of their studies (see above in this section), but were usually found to give inferior results compared to C_2-symmetric phosphoramidates: this observation underlines the importance of finding the right conditions to match the reactivity of the particular chiral catalyst employed, and shows that excellent results can be obtained with different classes of ligands provided that a sufficiently optimized protocol is employed.

Initially, it was shown that axially chiral ligands Josiphos (**116–117**, Figure 2) and especially Taniaphos (**118**) could be used to efficiently convert γ-monosubstituted allylic bromides (up to 99% yield, 99% *ee*),[139] also bearing protected alcohol and amine moieties;[140] interestingly, the preferred copper source was CuBr·Me$_2$S, in contrast with the typical procedure of Alexakis using CuTC.[125] Remarkably, the procedure was highly regio- and enantioselective also for the introduction of a methyl group, which was usually regarded as particularly challenging.[128]

An extension of this work established that the allylic alkylation products could then be elaborated through a multistep sequence leading to natural products (−)-lasiol and (+)-faranal.[141] A similar protocol for the preparation of chiral compounds with two adjacent stereogenic centers was described a few years later by Marsden and coworkers, who carried out an asymmetric allylic alkylation of γ-monosubstituted allylic bromides with Cu(I)/(*R*,*R*)-**118** followed by Ru-catalyzed cross-metathesis and

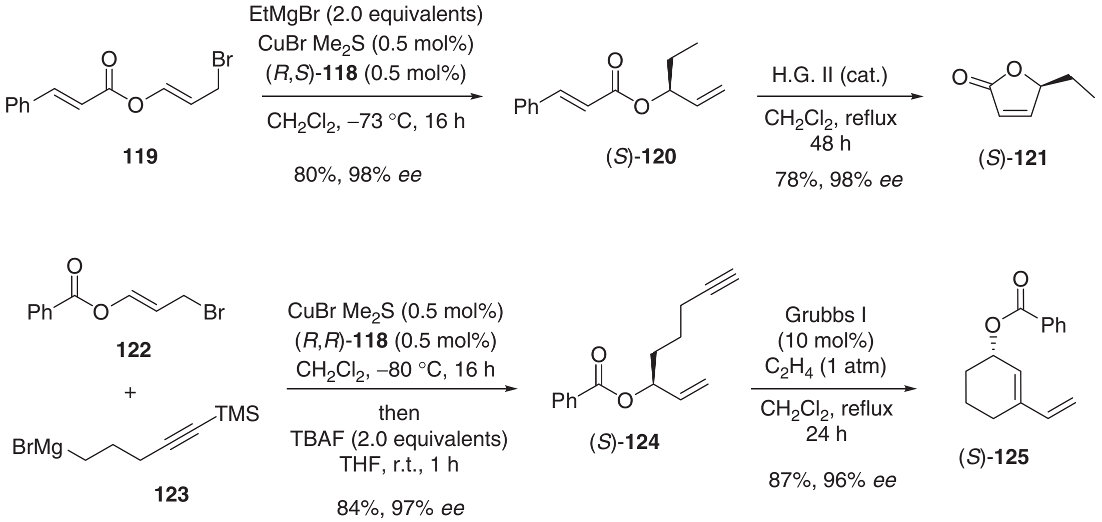
(*R*,*S*)-**116**, R^1 = Cy, R^2 = Ph
(*R*,*S*)-**117**, R^1 = Ph, R^2 = Cy

(*R*,*S*)-**118**

Figure 2 Ferrocene-based bidentate diphosphine ligands.

Ir-catalyzed asymmetric allylic substitution with amines; this allowed the isolation of functionalized allylamines with good diastereomeric purity.[142]

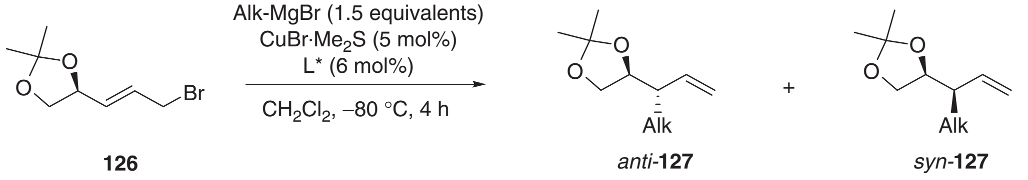
As in the case of monodentate phosphoramidates, also bidentate bisphosphines **116–118** were applied to the conversion of several other substrates. Reaction of 3-bromopropenylesters with alkylmagnesium bromides in the presence of CuBr·Me_2S and (*R*, *S*)-**118** gave rise to protected allylic alcohols in excellent yields with 95–98% *ee*.[143] Selective transformation of cinnamic acid derivative **119** gave chiral ester **120**, which underwent RCM with Hoveyda–Grubbs catalyst II[144] to yield naturally occurring butenolide (*S*)-**121** (Scheme 39, top). This chemistry was later exploited as a platform for the asymmetric syntheses of several chiral *γ*-butyrolactones such as (−)-whiskey and (−)-cognac lactones, as well as biologically active (−)-nephrosteranic acid and (−)-roccelaric acid.[145] Furthermore, employment of Grignard reagents carrying a terminal double bond or a TMS-protected triple bond allowed preparing chiral dienes and enynes, which could be then further elaborated: for example, compound **124** underwent enyne metathesis with Grubbs I catalyst to give cyclic diene **125** in high *ee* (Scheme 39, bottom).[146]



Scheme 39 Alkylation of 3-bromopropenyl esters and subsequent synthetic elaboration.

A strategy similar to that used by Alexakis for the alkylation of *ω*-ethylenic allylic halides (see Section 3.04.3.3.1.1)[134] was applied for the conversion of substrates containing a protected nitrogen atom within the linear carbon chain: after ring-closing metathesis with Hoveyda–Grubbs second generation catalyst chiral cyclic amines were formed with enantiomeric excesses up to 99%.[147] Methylation of 3-halocrotonate substrates was also noteworthy, since after optimization the reaction selectively proceeded through only one of the four conceivable pathways (1,2- and 1,4-additions, S_N2 and S_N2' substitutions), giving cleanly the *γ*-alkylation product in high yield with up to 99% *ee*.[148] The resulting *α*-chiral homoallylic esters where then subjected to a variety of transformations (hydroboration, dihydroxylation, cross-metathesis, etc.) to give useful enantioenriched intermediates.

A further variation in terms of substrates was reported by Feringa et al., who studied the alkylation of protected allylic diol **126** (Scheme 40),[149] accessible in enantiopure form starting from D-mannitol. This transformation was especially interesting, since preferential formation of one of the two possible diastereomers of the *γ*-substitution product, ***anti*-127** and ***syn*-127**, was dependent on the possibility by the chiral catalyst to overcome the intrinsic selectivity of the reaction, dictated by the existing stereogenic center. After optimization, it was observed that by carrying out the reaction at low temperature (−80 °C) an almost complete reversal of diastereoselectivity was possible depending on the particular ligand used: (*R*,*R*)-**118** led to exclusive formation of ***anti*-127** with a range of nucleophiles, while its diastereomer (*R*,*S*)-**118** produced mixtures with *syn*/*anti* ratios up to 9:1. In this latter case, the transformation retained its synthetic utility since the minor diastereomer could readily be removed by flash column chromatography.



126 *anti*-**127** *syn*-**127**

L* = (*R*,*R*)-**118**, 80–91% yield 100 : 0

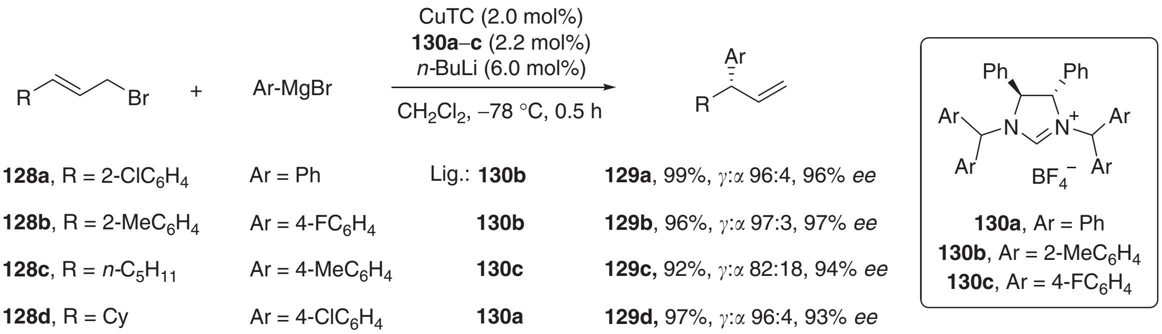
L* = (*R*,*S*)-**118**, 72–85% yield 10–13 : 87–90

Scheme 40 Stereodivergent synthesis of *anti*- and *syn*-1,2-diol building blocks.

Besides ferrocenyl-derivatives **116–118**, a small number of other phosphine-containing ligands have been reported. In 2008, the group of Tomioka proposed the use of chiral cyclic amidophosphines, previously employed for various other Cu- and Rh-catalyzed asymmetric reactions. Ethylation of *trans*-cinnamyl bromide proceeded in general with good to high enantioselectivities but moderate γ:α regioselectivity (up to 73:27). On the contrary, arylations with aryl Grignard reagents were sometimes characterized by high regioselectivity, but the *ee*'s did not exceed 81%.[150] A few years later, Schmalz and coworkers reported a detailed study concerning the synthesis and application of 14 different bidentate phosphine–phosphite ligands: the chirality was embedded in the phosphite portion, and derived either from a binaphthol or a TADDOL-based moiety. After careful optimization, it was found that reaction of various *trans*-cinnamyl chlorides with MeMgBr proceeded with high efficiency and selectivity (87–97% *ee*); transfer of other alkyl moieties was occasionally less satisfactory, but gave the products still with acceptable to high *ee*'s (66–99%).[151] The alkylation procedure was subsequently applied to the asymmetric total synthesis of bioactive compounds helioporins C and E.[152]

The last class of ligands employed in Cu-catalyzed enantioselective allylic alkylations with Grignard reagents is that of *N*-heterocyclic carbenes (NHCs).[153] Early reports in this area were published by Okamoto and coworkers, who reported the use of C_2-symmetric NHCs with chiral benzylic substrates,[154,155] and by Hong and coworkers, who employed bisisoquinoline-based ligands.[156] Despite extensive optimization and substrate screening, which involved testing substrates with different leaving groups, alkylation products were obtained in both cases with only moderate enantioselectivities (up to 70% and 77% *ee*, respectively).

Shortly after, a significant breakthrough was achieved when Tomioka and coworkers reported the first γ-selective Cu-catalyzed asymmetric allylic substitution with aromatic Grignard reagents. Use of NHC-ligand precursor **130b**, bearing bulky *o*-tolyl substituents, in combination with CuTC allowed the reaction of several cinnamyl bromides with variously substituted arylmagnesium bromides to proceed in high regio- and enantioselectivity (Scheme 41).[157] A further study from the same group showed that γ-alkyl substituted allylic bromides gave in general inferior results compared to their aromatic counterparts, but use of ligand precursors **130a,c** instead of **130b** led nevertheless to respectable *ee*'s and good regioselectivity. In particular, cyclohexyl-substituted substrate **128d** could be reacted with several aryl Grignard reagents to give products with up to 96:4 S_N2':S_N2 selectivity and 86–96% *ee* (Scheme 41).[158]



130a, Ar = Ph
130b, Ar = 2-MeC$_6$H$_4$
130c, Ar = 4-FC$_6$H$_4$

128a, R = 2-ClC$_6$H$_4$	Ar = Ph	Lig.: **130b**	**129a**, 99%, γ:α 96:4, 96% *ee*
128b, R = 2-MeC$_6$H$_4$	Ar = 4-FC$_6$H$_4$	**130b**	**129b**, 96%, γ:α 97:3, 97% *ee*
128c, R = *n*-C$_5$H$_{11}$	Ar = 4-MeC$_6$H$_4$	**130c**	**129c**, 92%, γ:α 82:18, 94% *ee*
128d, R = Cy	Ar = 4-ClC$_6$H$_4$	**130a**	**129d**, 97%, γ:α 96:4, 93% *ee*

Scheme 41 Selective arylation of allylbromides mediated by chiral Cu-NHC complexes.

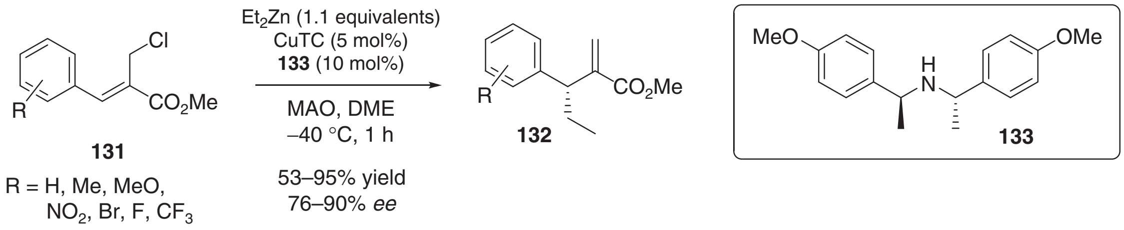
Finally, a very recent report by Mauduit et al. described the use of aminoalcohol-derived, C_1-symmetric NHC ligands bearing an additional hydroxyl group for the selective γ-alkylation of allylic phosphates. Satisfactory results were obtained for monosubstituted starting materials, which gave up to 94% *ee* with good S_N2' selectivity; the only exception was represented by the products of substitution with sp^2-hybridized nucleophiles, which gave overwhelming S_N2 selectivity. Remarkably, the reaction took place also starting from γ,γ-disubstituted substrates: products containing quaternary stereocenters were thus isolated with 82–87% *ee*.[159]

3.04.3.3.1.2 Copper-catalyzed transformations with organozinc reagents

The second most-used class of polar organometallic reagents in copper-catalyzed enantioselective allylic substitutions is represented by organozinc reagents. After the initial disclosure of Bäckvall and coworkers regarding Grignard reagents,[121] organozinc compounds have been for a few years the nucleophiles of choice, due to their lower reactivity, which suppressed unwanted noncatalyzed transformations, and superior functional group tolerance. Later, refinement of the reaction conditions allowed the productive use of organomagnesium reagents (see previous paragraph), which were ultimately preferred thanks to their wider availability and ease of preparation: organozinc compounds remain nevertheless useful nucleophiles for this transformation and can give excellent results provided that the right reaction conditions are found.

The first reports on an enantioselective allylic alkylation with R_2Zn were described by Dübner and Knochel, who employed chiral ferrocenylamines together with $CuBr{\cdot}Me_2S$ as the catalysts for the conversion of cinnamyl chlorides.[160,161] Despite the high level of regioselectivity generally observed, this method had a fundamental limitation in that high enantioselectivities (up to 98%) could be reached only by using bulky dineopentylzinc as the nucleophile.

Almost at the same time, Woodward et al. reported their studies on the alkylation of cinnamyl halides having an ester substituent at the β-position. The authors found that, in the presence of a catalyst generated *in situ* from $[Cu(MeCN)_4]BF_4$ and a bulky 2,2′-disubstituted BINOL, clean formation of S_N2' substitution products took place with moderate *ee*'s up to 64%.[162] On the basis of these results, it was later discovered that simple C_2-symmetric amine **133** could act as an efficient ligand for the same transformation. When using diethylzinc, it was found that the enantiomeric excess would decrease as the reaction proceeded, due to the progressive formation of the EtZnCl species in the reaction medium. Thus, addition of a halide scavenger such as methylaluminoxane (MAO $[-Al(Me)O-]_n$) drove the zinc-Schlenk equilibrium in favor of the dialkylzinc species, thereby helping to substantially increase the enantioselectivity (**Scheme 42**).[163]



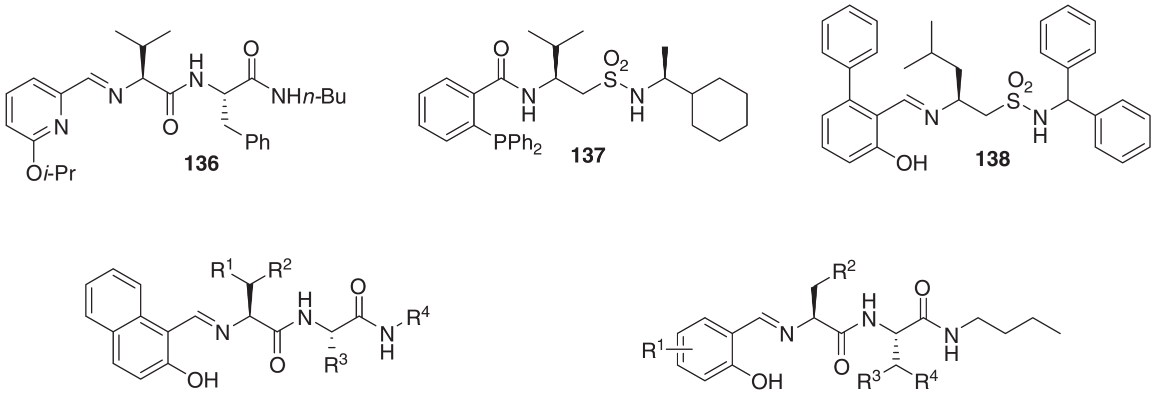
Scheme 42 Enantioselective allylic ethylation with MAO as an halide scavenger.

As in the case of reactions employing organomagnesium reagents, also those involving organozinc species were carried out using a few main classes of chiral ligands, among which monodentate phosphoramidates featured once again prominently (see Section 3.04.3.3.1.1). In a preliminary study on cinnamyl bromide alkylation it was found that the $CuBr{\cdot}Me_2S$/(*S*,*R*,*R*)-**113** (see **Scheme 38**) catalytic system was able to give an *ee* of 77% for the reaction with Et_2Zn (together with 85% formation of the S_N2' product), but transfer of other alkyl moieties gave inferior selectivity.[164] In a subsequent investigation, refinement of the reaction conditions was carried out and use of (*S*,*R*,*R*)-**5,5′,6,6′,7,7′,8,8′-octahydro-113** as the ligand allowed to convert several cinnamyl bromides with high regioselectivity and enantiomeric excesses consistently in the 86–88% range.[165,166]

Pineschi and coworkers used the phosphoramidate–Cu(I) catalytic systems to mediate the enantioselective ring-opening/desymmetrization of cyclic epoxides, in particular arene oxides.[167] In the case of benzene oxide, the catalyst was composed by CuOTf in combination with (*R*,*R*,*R*)-**113**. Reaction with Me_2Zn gave predominantly the α-substitution product, but the γ-substitution product was obtained in excellent 93% *ee*; when Et_2Zn was used, however, the regioselectivity was reversed, but the enantiomeric excess of the γ-adduct was much lower (64%).[168] In a following study, the same group examined the desymmetrization of cyclooctatetraene oxide and found that, under similar reaction conditions, use of ligand (*S*,*R*,*R*)-**113** together with CuOTf cleanly led to formation of S_N2' substitution products with various organozinc reagents in good yield and *ee* (82–90%).[169]

A different kind of desymmetrization was reported by Piarulli, Gennari, and coworkers, who studied the alkylation of cyclic *meso*-bisphosphates **134a–c**. This investigation was actually a follow-up of a previous report in which modular sulfonamide ligands had been employed (see **Figure 3**, compounds **137** and **138**).[170] Depending on the substrate, both diastereomers of compound **113** were the ligands of choice, which in this case were used with $[Cu(OTf)_2{\cdot}C_6H_6]$ as the copper source. Desymmetrization of 5, 6 and 7-membered rings **134a–c** (and of one disubstituted analog of **134b**) with Et_2Zn proceeded with high enantioselectivities, provided that the reaction was run at low temperature (−60 to −40 °C);[171] remarkably, substitution of **134a** with Me_2Zn at low temperature was extremely slow but produced the desired cyclic phosphate with 92% *ee*; running the reaction at 0 °C allowed to obtain an acceptable conversion and still gave the product with 87% *ee* (**Scheme 43**).[172] Unfortunately, use of different dialkylzinc reagents resulted in much lower enantioselectivities.[171,172]

A second category of important chiral ligands that have been used in the asymmetric Cu-catalyzed allylic substitutions with organozinc reagents is constituted by modular structures containing amino acid-derived stereogenic centers (**Figure 3**). The first report on the use of such compounds was published by Hoveyda, who employed pyridinyl-peptide ligands for the alkylation of cinnamyl phosphates with diethylzinc. After an extended ligand-screening effort, optimal structure **136**, based on the three building blocks *o*-*i*Pr-pyridine, L-Val and L-Phe, was identified. Use of this promoter together with CuCN led to formation of products with tertiary stereogenic centers in 66–87% *ee*; strikingly, the reaction worked even better on γ,γ-disubstituted allylic

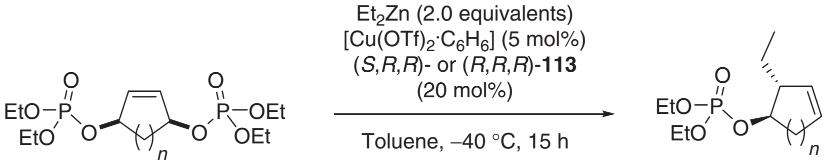


136 **137** **138**

139a, R^1 = H, R^2 = Cy, R^3 = R^4 = *n*-Bu
139b, R^1 = H, R^2 = Cy, R^3 = *i*-Pr, R^4 = *n*-Bu
139c, R^1 = Me, R^2 = O*t*-Bu
R^3 = 3-(*N*-Boc-Imidazolyl), R^4 = Bn

140a, R^1 = 3-MeO, R^2 = Cy, R^3 = R^4 = Me
140b, R^1 = R^3 = H, R^2 = CH$_2$CONHTrt, R^4 = 4-BnO-Ph
140c, R^1 = 4-MeO, R^2 = CH$_2$CONHTrt, R^3 = H, R^4 = 4-BnO-Ph

Figure 3 Chiral modular ligands used in Cu-catalyzed enantioselective allylic alkylations.



134a, *n* = 1
134b, *n* = 2
134c, *n* = 3

135a, >98% yield, 87% *ee*
135b, 69% yield, 94% *ee*
135c, 86% yield, >98% *ee*

Scheme 43 Desymmetrization of cyclic 5, 6 and 7-membered *meso*-bisphosphates.

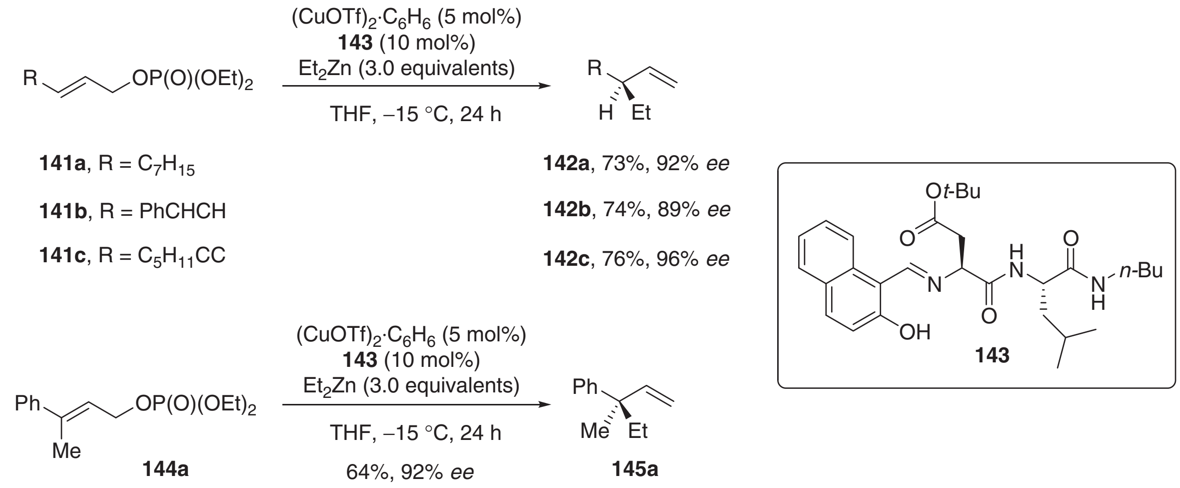
phosphates, giving products bearing quaternary stereocenters with 78–90% *ee*. Finally, its synthetic utility was demonstrated by the total synthesis of fish deterrent (*R*)-(−)-sporochnol in 82% *ee*.[173]

Shortly after, Gennari, Piarulli, and coworkers investigated the use of modular sulfonamide-containing ligands to promote the same transformation. Extensive ligand screening was carried out, but, even under optimized conditions, the combination between CuCN and the best ligand **137** promoted the reaction of diethylzinc with cinnamyl phosphate with only 40% *ee* (9:1 γ:α ratio).[174]

As mentioned above, Gennari's group applied a similar class of ligands to the alkylation of cyclic *meso*-bisphosphates **134** (see Scheme 43);[170] compared to phosphoramidate ligands, sulfonamide-containing structures such as **138** displayed a narrower substrate scope, since they were effective only for the conversion of 5-membered ring compound **134a**; with this particular substrate, however, transfer of a methyl or butyl group took place with high yield (75–98%) and enantioselectivity (88–94%), which was not the case with ligands **113**; even reaction with Ph$_2$Zn gave the product with good 78% *ee*, albeit with lower yield.[172]

Ligands **139a–b** and **140a** were applied in combination with (CuOTf)$_2$·C$_6$H$_6$ to the alkylation of α,β-unsaturated esters bearing a primary γ-phosphate. Reactions with Et$_2$Zn were usually highly selective, leading to products with up to 97% *ee* and >20:1 S$_N$2′:S$_N$2 ratio. Reaction with Me$_2$Zn was equally successful, although it required a long time to give an acceptable yield of the product, and even a functionalized organozinc reagent bearing an acetate group could be employed giving similar results. The utility of the protocol was demonstrated by the enantioselective synthesis (90% *ee*) of topoisomerase II inhibitor (*R*)-elenic acid.[175] Later, the same protocol was adapted to the formation of products with quaternary stereogenic centers; depending on the nature of the substrate, either **139c** or **140b–c** were the ligands of choice, and products were obtained with good to high *ee*, except for those stemming from transfer of a secondary alkyl moiety.[176]

Hoveyda and Kacprzynski reexamined the reaction of dialkylzinc derivatives with simple allylic phosphates, and introduced improved ligand **143**, which, together with (CuOTf)$_2$·C$_6$H$_6$, was able to give better results than pyridine-based compound **136**.[173] Cinnamyl derivatives were converted with *ee*'s ≥84% also with functionalized alkylzinc reagents, although sterically encumbered substrates gave unsatisfactory regioselectivity. More interestingly, the system worked also for alkyl, alkenyl and alkynyl-substituted allylic phosphates, and even γ,γ-disubstituted substrates were efficiently converted to give products with quaternary stereocenters (Scheme 44).[177]



Scheme 44 Enantioselective allylic alkylation with chiral ligand **143**.

A thorough investigation of all possible ligand variations revealed that the enantioselectivity was mostly dictated by the stereogenic center on the second amino acid moiety, but that a good match with the stereocenter on the first amino acid residue was required to have a high *ee*. In addition, a secondary amide was required on the molecule *N*-terminus, and the –OH group on the naphthyl ring was also essential. Based on this information, the authors elaborated a model of the reaction transition state, which involved formation of a chiral Cu–**143**-complex, but also coordination of the phosphate moiety of the substrate through a Lewis acidic zinc center, giving rise to a highly ordered tridimensional assembly.[177]

The last category of chiral ligands to have been applied in the Cu-catalyzed asymmetric allylic alkylation with R_2Zn is represented by *N*-heterocyclic carbenes, which were extensively studied by Hoveyda's group. In a first report, it was found that use of the dimeric Ag(I) complex of the ligand stemming from precursor **146 · HCl** (Figure 4) together with $(CuOTf)_2{\cdot}C_6H_6$ promoted the addition of a few organozinc reagents to allylic phosphates with complete regioselectivity and good to high enantioselectivity;[178] interestingly, this gave much better results than the use of the ligand itself.

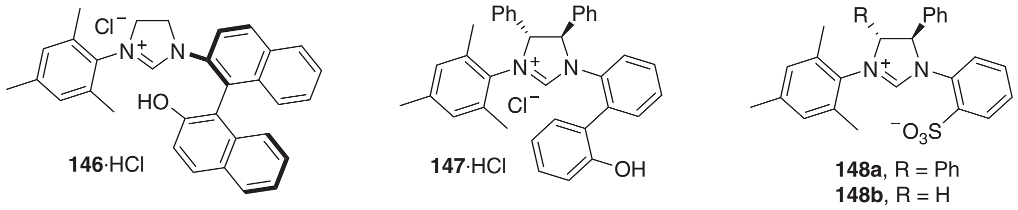


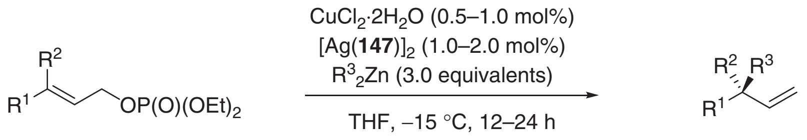
Figure 4 Precursors of chiral *N*-heterocyclic carbene ligands.

The employment of an Ag(I) complex was motivated by the previous disclosure of a facile exchange reaction between Ag-based complexes of NHCs and Cu salts. Notably, catalyst loadings could be greatly reduced in comparison with previous methods using amino acid based ligands[173,175–177] and reactions were generally faster, which allowed running them at −78 °C, thus further improving enantiomeric excesses.

In a later study, the synthesis and application of ligand precursor **147 · HCl** (Figure 4) was reported; compared to structure **146**, compound **147** had a simpler biphenyl backbone, which made it more easily accessible; the source of chirality was in this case located in the diamine moiety, which was also able to control the conformation of the biphenyl portion on complexation of a metal. The catalytic system formed from the dimeric Ag(I) complex of **147** in combination with air-stable $CuCl_2{\cdot}2H_2O$ proved competent to promote alkylation of several allylic phosphates with 1–2% catalyst loading (which, in some cases, could be further reduced).[179] The system was particularly powerful for the formation of quaternary stereocenters, and even γ,γ-diaryl substituted substrates could be converted with good *ee*'s (Scheme 45). The same catalytic system was then applied to the conversion of γ-silyl substituted allylic phosphates. The resulting chiral allylsilanes were useful building blocks, which could be used for example for the construction of chiral 1,3-diols with high enantiomeric excess.[180]

3.04.3.3.1.3 Copper-catalyzed transformations with organoaluminum and organolithium reagents

Compared to organomagnesium and organozinc reagents, other hard organometallic nucleophiles, such as those based on aluminum and lithium, have been much less exploited in Cu-catalyzed allylic alkylations. However, especially in recent years, various selective protocols have been reported which make use of these compounds.

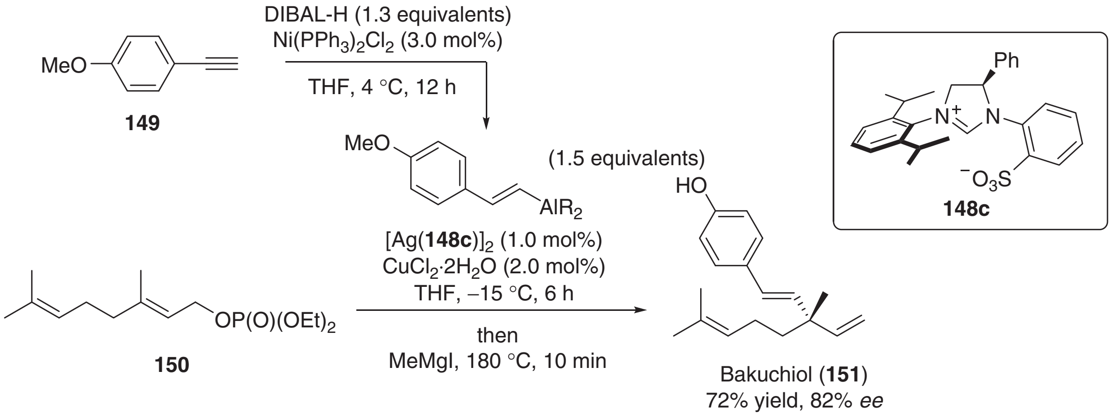


144a, R^1 = Ph, R^2 = Me	R^3 = *i*-Pr	**145b**, 74% yield, γ only, 98% *ee*
144b, R^1 = Cy, R^2 = Me	R^3 = Et	**145c,** 76% yield, γ only, 97% *ee*
144c, R^1 = Ph, R^2 = 4-NO_2-Ph	R^3 = Et	**145d**, 79% yield, γ only, 85% *ee*

Scheme 45 Cu-catalyzed enantioselective allylic alkylation with Ag(I)–NHC complexes.

One of the first protocols using alkylaluminum reagents in Cu-catalyzed asymmetric allylic alkylations was reported by Hoveyda in the context of the enantioselective total synthesis of unusual siphonariid metabolite baconipyrone C: conversion of a symmetric β,γ-disubstituted allylic phosphate with Me_3Al in the presence of $CuCl_2 \cdot 2H_2O$ and $[Ag(\mathbf{148a})]_2$ (see Figure 4) afforded a key triene intermediate in good yield and diastereoselectivity with almost perfect enantioselection.[181]

Organoaluminum reagents have proved particularly valuable for the selective transfer of sp^2- and sp-hybridized moieties, which, with a few exceptions,[157,180] proved particularly challenging with organomagnesium and organozinc derivatives. The addition of vinylaluminum reagents, in turn obtained from the corresponding alkynes via simple reaction with DIBAL-H, to β,γ-disubstituted allylic phosphates was studied using the $CuCl_2 \cdot 2H_2O/[Ag(\mathbf{148a\text{–}b})]_2$ catalyst system. Interestingly, **148a–b** were the only active NHC precursors, since no reaction was obtained with the less activating species **146–147**. Thanks to this procedure, a series of dienes featuring tertiary stereogenic centers was readily obtained with high yields and *ee*'s, although, curiously, slightly worse results were recorded for simple γ-substituted allylic substrates, which required the use of NHC precursor **148b**.[182] Later, the protocol was extended to the formation of products with quaternary stereogenic centers: reactions with alkyl-substituted vinylaluminums proceeded smoothly in the presence of $CuCl_2 \cdot 2H_2O/[Ag(\mathbf{148a})]_2$ (1.0–5.0 mol%) giving the desired products with complete regioselectivity and 80–96% *ee*.[183] In the case of aryl- and alkenyl-substituted vinylaluminums, however, a relatively large amount of alkynyl addition product was detected. The problem was circumvented by introducing a new procedure for the generation of the vinylaluminum species, which was carried out under catalysis by $Ni(PPh_3)_2Cl_2$; under these conditions, and employing NHC precursor **148c**, the desired products could be obtained with high chemo- and regioselectivities and satisfactory enantiomeric excesses (e.g., see Scheme 46).



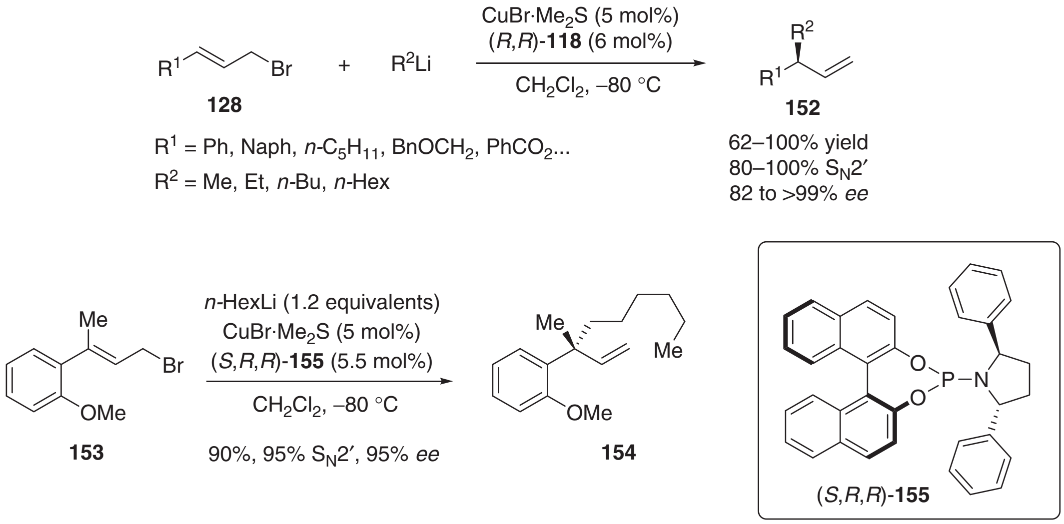
Scheme 46 Asymmetric synthesis of bakuchiol (**151**) via enantioselective vinylaluminum addition.

Application of a similar protocol to disubstituted alkynes bearing a trimethylsilyl group (rather than terminal alkynes as in Scheme 46) made it possible to obtain organometallic reagents with the aryl and dialkylaluminum moieties on the same side of the double bond: accordingly, synthesis of 1,4-dienes containing *E* or *Z* alkenes, at will, was made possible. The protocol was applied to the first enantioselective synthesis of natural compound (−)-nyasol.[184]

Hoveyda's group then proceeded to complete the range of possible organoaluminum nucleophiles. First, it was demonstrated that (hetero)aryl aluminum reagents, obtained by transmetalation of the corresponding organolithium compounds with Et_2AlCl, could be applied to the reaction with allylic phosphates;[185] subsequently, the first enantioselective allylic substitution was recently reported which made use of alkynylmetal reagents as the nucleophiles. Alkynylaluminum derivatives were generated *in situ* from terminal alkynes and DIBAL-H, and were then reacted with a series of γ,γ-disubstituted allylic phosphates under the influence of the $CuCl_2 \cdot 2H_2O/[Ag(\mathbf{148c})]_2$ catalytic system: 1,4-enynes bearing quaternary stereocenters were obtained with high selectivity.

Remarkably, the latter compounds could be further elaborated through a short synthetic sequence including an Au(III)-catalyzed cyclization, to provide valuable enantiomerically enriched heterocycles.[186]

Organolithium reagents have long been considered too reactive to be used in catalytic enantioselective transformations, due to their high propensity to undergo nonselective, uncatalyzed side-reactions. For this reason, until recently enantioselective reactions employing organolithium reagents have been mostly limited to processes making use of stoichiometric chiral ligands.[187] In 2011, a breakthrough in this area of research was achieved by Harutyunyan, Feringa, and coworkers, who reported the first highly enantioselective alkylation of allylic halides using organolithium compounds.[188] The authors found that performing the reactions at low temperature (−80 °C) with the careful exclusion of ethereal solvents was key to obtain high selectivities. Reactions were catalyzed by phosphorous-containing ligands (*S*,*S*,*S*)-**106**, (*S*,*S*,*S*)-**113** or (*R*,*R*)-**118** in combination with a copper salt: $CuBr{\cdot}Me_2S$ gave the best regio- and enantioselectivity, but other copper sources gave only slightly inferior results. Various linear alkyllithium reagents could be used, but employment of PhLi resulted in low yield and preferential formation of the S_N2 substitution product (although the S_N2' product was formed with 99% *ee*); several allylic chlorides and bromides were tested as substrates resulting in product formation with 80–100% regioselectivity and 82–99% *ee* (Scheme 47).



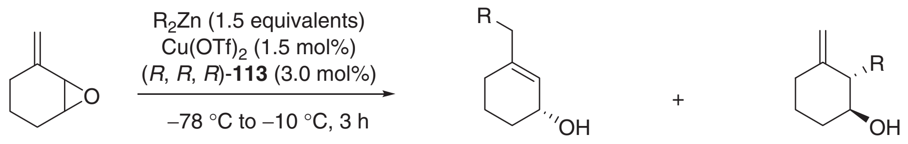
Scheme 47 Enantioselective alkylation of allylic bromides using organolithium reagents.

Further extension of this methodology included the challenging substitution with secondary alkyllithium reagents, which gave rise to mixtures of diastereomers, albeit with good enantiomeric purity (up to 82% *ee*), and the conversion of γ,γ-disubstituted substrates to generate quaternary stereogenic centers (72–90% *ee*), which found the only serious limitation in the use of starting materials featuring the bulky, noncoordinating 2-MePh substituent.[189] Finally, use of highly reactive organolithium reagents could be exploited to convert usually inert substrates, such as allylic ethers; indeed, in the presence of the catalytic system constituted by CuTC, (*S*,*S*,*S*)-**113** and TMSOTf/$BF_3{\cdot}OEt_2$ (acting as Lewis acidic activators), both allylmethyl- and allylbenzylethers could be transformed in the corresponding chiral terminal olefins with a high degree of regio- and diastereoselectivity.[190]

3.04.3.3.1.4 Kinetic resolutions and related processes

The enantioselective alkylation of allylic electrophiles by means of polar nonstabilized organometallics has been applied also to kinetic resolutions and related processes,[191] starting from racemic mixtures of chiral substrates. In this context, an early striking example was reported by Pineschi and Feringa, who identified suitable conditions to carry out a regiodivergent parallel kinetic resolution (PKR) of racemic cyclic epoxides. Differently from a classical kinetic resolution, in a PKR the two enantiomers of the substrate react giving rise to two different products: thus, full conversion of the substrate becomes possible (although separation of the two products at the end of the reaction is required).[192] In the process reported by Pineschi and Feringa and coworkers, it was found that reaction of the two enantiomers of vinyl epoxide **156** with alkylzinc reagents under the influence of the $Cu(OTf)_2$/(*R*,*R*,*R*)-**113** catalytic system would afford the two regioisomers **157** and **158** with good to high enantioselectivity.[193] The reaction with Me_2Zn was particularly remarkable, affording a 1:1 mixture of the two products, each with >90% *ee* (Scheme 48). Detailed kinetic studies revealed that one of the two enantiomers of **156** was quickly processed by the chiral catalyst, giving rise to the S_N2' products **157a–b** with high *ee*; reaction of the second enantiomer was much slower and proceeded through the S_N2 pathway giving the other products **158a–b**. Such mechanistic picture was confirmed by the fact that use of racemic ligand (*S*,*S*,*S*)/(*R*,*R*,*R*)-**113** afforded exclusively the S_N2' product as a racemic mixture.[193]

Later, extension of the same protocol to other cyclic substrates was also described.[167] Although the 5-membered ring analog of **156** gave the products with reduced enantioselectivity (72% *ee* for the S_N2' adduct), the corresponding 7-membered ring afforded



(*rac*)-**156**

157a, R = Et, 80% *ee* **158a**, R = Et, 99% *ee*

S_N2':S_N2 = 55:45

157b, R = Me, 96% *ee* **158b**, R = Me, 92% *ee*

S_N2':S_N2 = 49:51

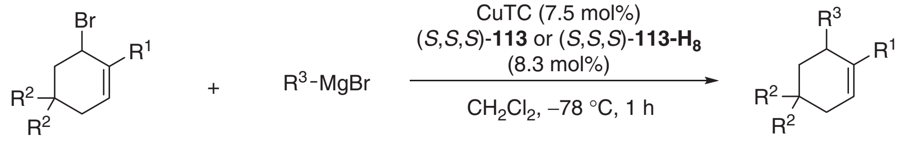
Scheme 48 Parallel regiodivergent kinetic resolution of a chiral racemic epoxide.

better results (reaction with Bu_2Zn, S_N2':S_N2 ratio of 52:48 with 82% and 90% *ee*, respectively).[194] The outcome of the reaction carried out on cyclic 1,3-diene oxides (with an endocyclic double bond) depended on the size of the ring: thus, conversion of (*rac*)-1,3-cycloheptadiene oxide with three different alkylzinc reagents gave always equimolar mixtures of regioisomers in high *ee*'s (90–95%). Reaction of 5-, 6- and 8-membered analogs, however, usually afforded the S_N2' adduct as the main product, due to insufficient kinetic discrimination between the two pathways: as a consequence, only the minor S_N2 product could be recovered in high *ee*.[193–195]

Application to acyclic vinyl epoxides was also challenging, due to their conformational flexibility, and good results could be obtained only with selected substrates.[194] Unfortunately, the PKR protocol could not be extended to the corresponding *N*-Cbz aziridines: a classical kinetic resolution, carried out using a substoichiometric amount of Et_2Zn, was nevertheless operative, and enantioenriched allylamines could be obtained at less than 50% conversion with up to 83% *ee*.[196]

Cu-catalyzed kinetic resolutions of cyclic 1,3-diene oxides with Grignard reagents as the nucleophiles were also reported. In a first study, chiral Josiphos-type ferrocenyl diphosphines were utilized as ligands, giving S_N2' products with high regioselectivity and up to 91% *ee* at 45% conversion.[197] Later, application of Simplephos ligands[133] to the same process was described, and in that case a PKR of 1,3-cyclohexadiene oxide was also attempted with *i*PrMgCl (1.5 equivalents): similarly to what previously observed,[193] the S_N2' product was obtained as the major regioisomer in moderate *ee*, but the minor S_N2 adduct was instead recovered with very high enantiomeric excess (>99% *ee*).[198]

An interesting example of a reaction converting a racemic mixture into an enantioenriched product was recently reported by Langlois and Alexakis, who examined the alkylation of racemic cyclic allylic electrophiles. After optimization, they found that (*rac*)-3-bromocyclohexene **159a** could be completely converted into the corresponding 3-alkyl olefin **160a** by treatment with primary alkyl Grignard reagents in the presence of CuTC/(*S*,*S*,*S*)-**113** with up to 92% *ee*.[199] Further experimentation led to the development of a few alternative preparative procedures (also utilizing ligand (*S*,*S*,*S*)-**113-H$_8$**), by means of which various racemic 3-bromocyclohexenes **159** could be converted into the desired products in high yields and *ee* (Scheme 49).[200]



159a, $R^1 = R^2 = H$	R^3 = *n*-Bu	**160a**, 81%, 92% *ee*
159b, R^1 = H, R^2 = Me	$R^3 = PhCH_2CH_2$	**160b**, 94%, 97.5% ee
159c, R^1 = Ph, R^2 = H	R^3 = Me	**160c**, 80%, 97% *ee*
159d, R^1 = Me, R^2 = H	$R^3 = PhCH_2CH_2$	**160d**, 95%, 18% *ee*

Scheme 49 Enantioselective allylic alkylation of racemic 3-bromocyclohexenes.

Unfortunately, at this stage the reaction still presented some limitations: not all the substituents on the 6-membered ring were well-tolerated (see Scheme 49), transformations of the corresponding 5- and 7-membered substrates proceeded with modest enantioselectivities, and also transfer of bulky alkyl groups could not be performed with more than 74% *ee*.[200] Initially, the reaction was classified as a dynamic kinetic asymmetric transformation (DYKAT),[201] and, based on previous results by Bäckvall,[202] its mechanism was interpreted in terms of an equilibration via a common η^3-allyl-Cu intermediate followed by rate-determining reductive elimination.[200] On the basis of some internal inconsistencies, however, this hypothesis was questioned, and a re-examination of the reaction mechanism was carried out by means of DFT calculations. This work revealed that the reaction is indeed a rare example of a direct enantioconvergent transformation (DET), in which the two enantiomers of the substrate give the same product following two distinct reaction pathways: thus, under the conditions described above, enantiomer (*R*)-**159a** would react through an *anti*-S_N2' pathway, while (*S*)-**159a** would undergo reaction according to an *anti*-S_N2 pathway, in both cases leading to the same enantiomer of product **160a**.[203] This revised mechanistic interpretation led to a further optimization of the reaction conditions: use of a very reactive leaving group such as trifluoroacetate in place of bromine increased the rate of oxidative addition, resulting in improved enantioselectivities (e.g., transfer of a cyclopentyl group took place with 90% *ee*).[203]

Finally, an interesting example of a stereodivergent kinetic resolution, reported once again by Langlois and Alexakis, should be mentioned. In this case, it was found that a racemic mixture of acyclic 1,3-disubstituted allylic halides, on reaction with alkyl Grignards in the presence of Cu(I)–phosphoramidate complexes, would yield a mixture of the (*E*)- and (*Z*)-diastereomers of the product alkenes, both with good to high enantioselectivity (up to 91%). This phenomenon was explained taking into account an attack of the intermediate organocopper species from the same prochiral face of the two enantiomeric substrates, each of them, however, reacting in a different conformation.[204] Despite that, the transformation was still considered synthetically very useful, since simple synthetic manipulations of the double bond, such as ozonolysis, reduction or cross-metathesis, allowed erasing the dichotomy between the two diastereomers, thus leading to the formation of a single enantioenriched product from a racemic mixture.

3.04.3.3.2 Other transition metal-catalyzed transformations

Compared to copper-catalyzed processes, enantioselective allylic substitutions with hard organometallic nucleophiles promoted by other transition metals have been scarcely described. However, a few interesting protocols have been reported, dealing mostly with the transfer of aryl groups, which was often challenging under copper catalysis.

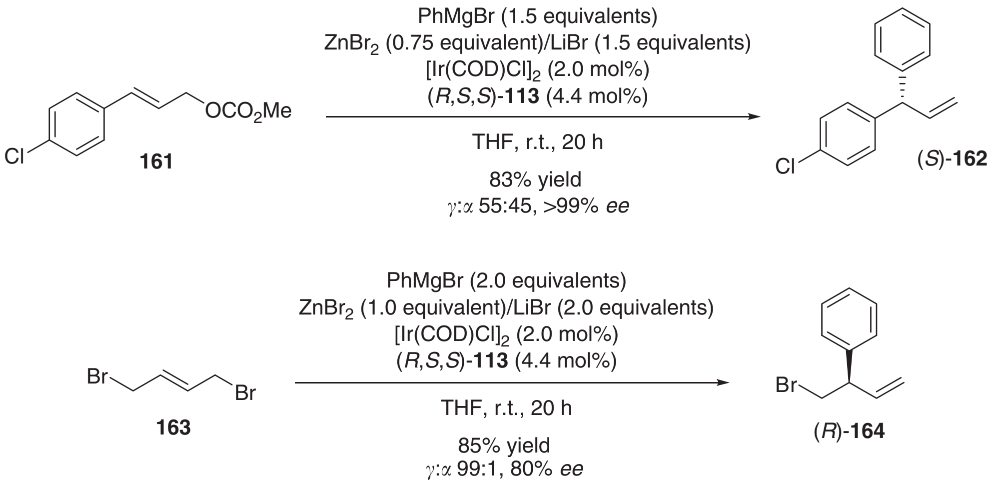
An early report on the use of chiral nickel catalysts to mediate the reaction of 3-substituted cyclohexenes (similar to **159a**, see Scheme 49) with aryl Grignard reagents was published by Uemura and coworkers. Interestingly, it was found that a Ni(0)–phosphine-oxazoline catalytic system was able to promote reaction of 3-methoxy- and 3-phenoxycyclohexene (usually considered unreactive substrates, see Ref. 190) with a small range of substituted arylmagnesium bromides with moderate to good yields and 64–95% *ee*.[205] Unfortunately, however, conversion of a 5-membered analog as well as of acyclic substrates was much less effective (up to 47% *ee* with low regioselectivity, where possible).

Another study making use of Ni-based catalysts was published a few years later by Woodward, who investigated the methylation of cinnamyl electrophiles of type **131** (see Scheme 42) by means of $AlMe_3$. It was found that use of ferrocenyl-based phosphonites having biphenol or binaphthol backbones in combination with $Ni(acac)_2$ gave γ-methylation products with the best *ee*'s (up to 93%): despite that, reactions were extremely slow and were sometimes affected by unsatisfactory $\gamma:\alpha$ regioselectivity.[206] The mechanism of the reaction was investigated computationally, and it was found that in the absence of the chiral ligand, S_N2 reaction should have been the predominant process. Accordingly, an α-selective $Ni(acac)_2$-catalyzed allylic methylation of chlorides **131** under ligand-free conditions was developed, giving products in up to 77% yield.[207]

The last example of transition metal-catalyzed substitution of allylic electrophiles with polar organometallic nucleophiles concerns the employment of iridium-containing chiral catalysts. The nucleophiles were constituted by arylzinc halides, which were prepared *in situ* by mixing the corresponding Grignard reagent with $ZnBr_2$ in the presence of an equimolar amount of LiBr. After extensive optimization, it was found that $[Ir(COD)Cl]_2$ in the presence of (*S*,*S*,*S*)-**106** was able to promote the reaction of the nucleophiles with linear cinnamyl carbonates **161** with high efficiency; although good to high enantioselectivity was recorded (*ee* ≥90% for eight substrate–nucleophile combinations), $\gamma:\alpha$ ratios did not exceed 73:27 and were often just slightly above 50:50.[208] It should be pointed out that these were nevertheless the best results obtained to that date for such a reaction (see Ref. 157 for later improvements based on Cu-catalysis). Further studies allowed expanding the reaction scope, and thus the protocol could be used also for the conversion of racemic 3-substituted cyclohexenes[199,200] and 1,4-dibromo-2-butene:[131,132] in this latter case, the regioselectivity was much improved compared to the previous reaction, and products with up to 80% *ee* were obtained (Scheme 50).[209] A preliminary study on the mechanism of the first reaction was carried out, which suggested that two distinct mechanistic pathways could be operative, each one leading to a different regioisomer, thus explaining the moderate $\gamma:\alpha$ ratios.

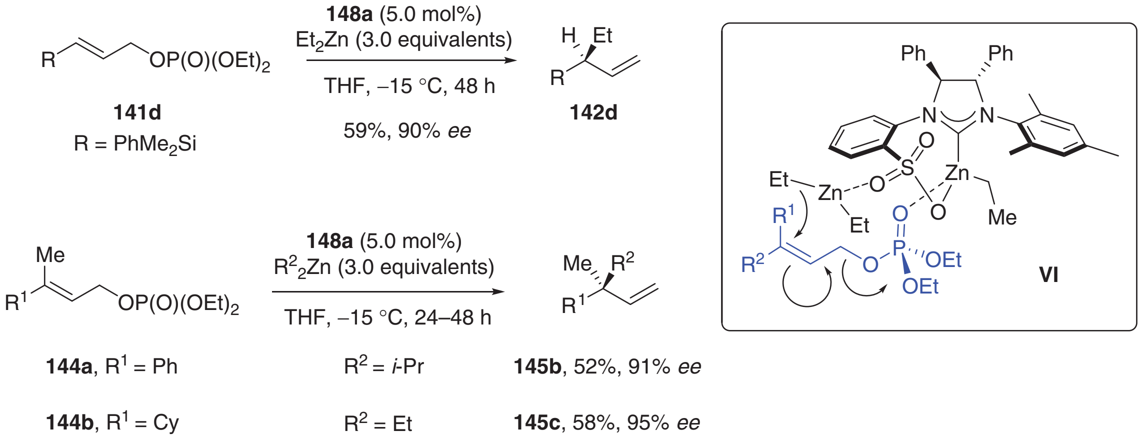
3.04.3.3.3 Transition metal-free, Lewis base-catalyzed transformations

One of the most intriguing recent developments in the field of asymmetric allylic substitution reactions is represented by the discovery of highly enantioselective processes which do not make use of transition metals in the active catalysts. The first results in this area were disclosed by Hoveyda, whose approach was based on the hypothesis that association of a Lewis base with a polar organometallic reagent, such as a Grignard species, may cause a redistribution of the electron density, giving a Lewis base·RMgX complex exhibiting improved nucleophilicity; this speculation was supported by the experimental observation of an elongation of the C–Mg bonds, compared to the parent dialkylmetal, in the X-ray structure of an $NHC{\cdot}MgEt_2$ complex.[210] Indeed, after some experimentation it was found that complex $[Ag(\mathbf{147})]_2$ was a competent catalyst for the reaction of *i*PrMgCl with an activated γ-chloro-α,β-unsaturated ester; even more interestingly, precursor **147 · HCl** (deprotonated *in situ* by the excess Grignard reagent) gave rise to an even better catalyst, yielding the product with almost full conversion, 90% regioselectivity and 97% *ee*.[211] Based on this result, the scope of the reaction was briefly examined, and it was found that linear Grignard reagents gave worse results than branched ones; moreover, slow addition of the electrophile was reported to efficiently limit the formation of undesired side-products.



Scheme 50 Asymmetric phenylation of allylic electrophiles with an Ir-based catalyst.

At this point, the problem of converting simple allylic electrophiles, such as phosphates, was considered. In this instance, it was found that the Zn–NHC complex formed from **148a** in combination with an excess of dialkylzinc reagent was the catalyst of choice: products bearing a tertiary stereogenic center were formed with perfect regioselectivity and in good to high *ee*, although reactions required 24–60 h at −15 °C to give a good yield. Strikingly, substitutions of allylic phosphates having a trisubstituted olefin proceeded even better, and products with a quaternary stereocenter were thus formed with higher enantioselectivity (Scheme 51).[212]

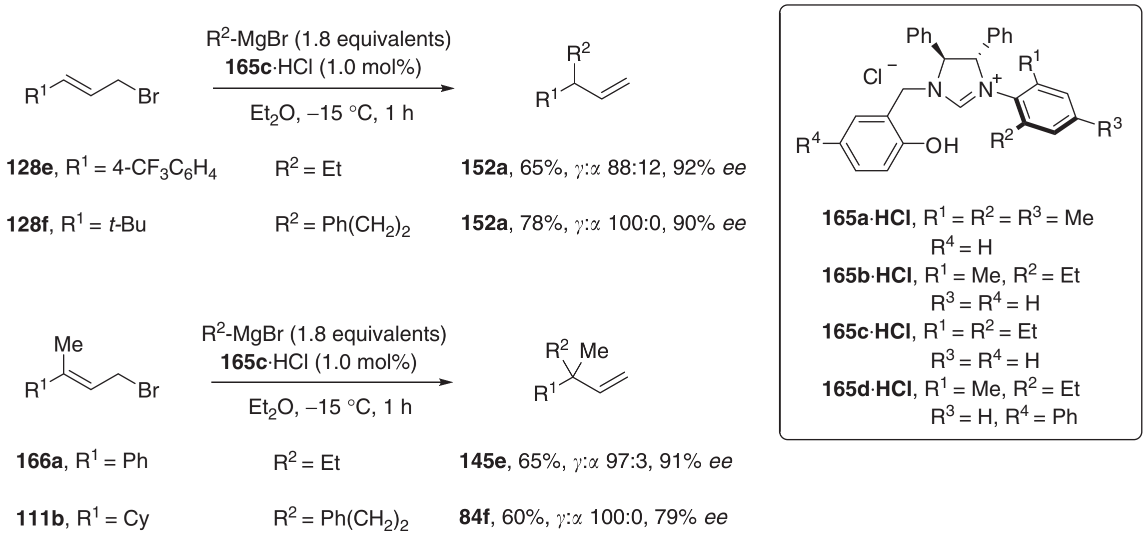


Scheme 51 TM-free enantioselective alkylation of allylic phosphates.

The authors hypothesized a mechanism involving the formation of a Zn–NHC complex acting as a bifunctional catalyst, activating the phosphate substrate by means of the Lewis acidic Zn-center and, at the same time, promoting the addition of the nucleophile $ZnEt_2$ through coordination with the Lewis basic sulfonate moiety (see complex **VI**, Scheme 51). In the same work, the possibility to carry out methylation reactions using $AlMe_3$ as the nucleophile was also examined: reactions were found to take place easily with an enhanced rate compared to those involving Zn-based reagents, but *ee*'s did not exceed 82%.[212]

A different kind of NHCs, derived from chiral substituted aminoindanols, has been described by Fuchter and coworkers. Three different ligand precursors, in the form of their HBr or HI salts, were prepared through a multistep synthetic sequence starting from commercially available 4-chromanone. They were tested in the alkylation reaction of cinnamyl bromides with EtMgBr as the nucleophile: unfortunately, the products were obtained with low regioselectivity (often favoring the *α* regioisomer), but good levels of asymmetric induction were recorded, giving tertiary stereogenic centers with up to 87% *ee*.[213] A further study analyzed the behavior in the same reaction of NHC-precursors similar to **148b**, but having one extra methylene unit between the imidazole and the phenyl ring. Results showed that the resulting catalysts were remarkably active, with the best one having a rather good TON of approximately 100. Reactions of alkyl Grignard compounds with cinnamyl bromides under the influence of the new catalysts gave the products with fair enantioselectivities (up to 82%), although regioselectivities were usually not satisfactory.[214]

A final class of NHC catalysts for enantioselective allylic alkylations has been described by Alexakis and coworkers, who examined structures having a phenol group connected to the imidazole ring through a flexible methylene linkage; the authors focused on the use of Grignard reagents as nucleophiles due to their superior characteristics of availability and atom economy compared to diorganozinc compounds.[215,216] First, it was observed that the reaction of cinnamyl halides with EtMgBr in the presence of NHC-precursor **165a · HCl** proceeded in the same fashion with and without a Cu salt; this surprising observation was followed by an extensive optimization of the reaction conditions, at the end of which, allylic bromides were identified as the substrates of choice, and the three most effective catalyst precursors resulted compounds **165a–c · HCl**, with the latter usually giving the best results. Under optimized conditions, conversion of allylic bromides **128** proceeded smoothly to give products with good regioselectivity and good to high enantiomeric excess (Scheme 52), although linear alkyl substituents on the substrate were not well-tolerated. The reaction worked also with trisubstituted electrophiles, and quaternary stereocenters were obtained in good *ee*'s and with consistently high regioselectivity for the γ-product, which was superior to that normally observed for copper-catalyzed reactions (Scheme 52).[215,216]



Scheme 52 Asymmetric alkylations of allylic bromides with NHC precursors **165**.

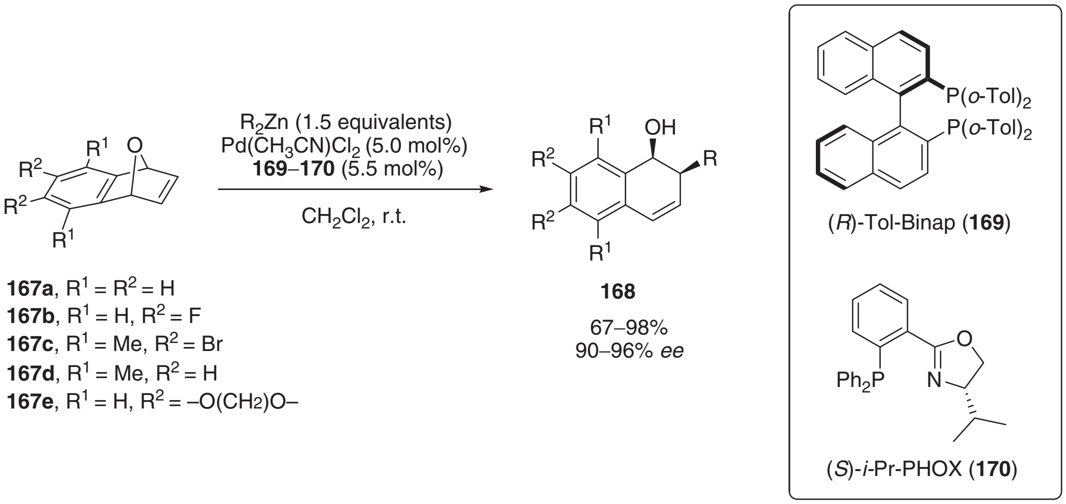
From the mechanistic point of view, the authors invoked the formation of an NHC–Mg–alkyl complex, which would coordinate the incoming substrate: transfer of the alkyl group would then take place directly from this complex without the intervention of a further nucleophile molecule, as in Hoveyda's model for diorganozinc reactions (see Scheme 51). A further application of the same chemistry to affect asymmetric alkylations of β-halo substituted allylic bromides was later reported, which made use of compound **165d · HCl** as the catalyst precursor. The products chiral vinylbromides featured a further C(sp^2)-Br bond, which could undergo subsequent reactions, such as cross-coupling transformations. Most importantly, for this reaction results provided by the transition metal-free protocol were consistently superior to those furnished by the corresponding copper-catalyzed process.[217]

3.04.3.4 Ring-Opening Reactions of Bicyclic Alkenes

A further transformation related to the allylic substitutions examined above is the ring-opening reaction of rigid heterobicyclic structures. Such process is synthetically useful, since it provides easy access to a number of intermediates that can be employed in natural products synthesis.[218] Usually, the substrates used in this kind of reactions possess an allylic leaving group within a strained cycle, and thus the ring-opening process corresponds, at least formally, to an allylic substitution reaction. However, depending on the particular metal promoter employed, the reaction of heterobicyclic compounds with hard organometallics can proceed through different mechanistic pathways, which are reflected also by the diverging stereochemistry of the products formed (see Section 3.04.3.4.1).[167,219]

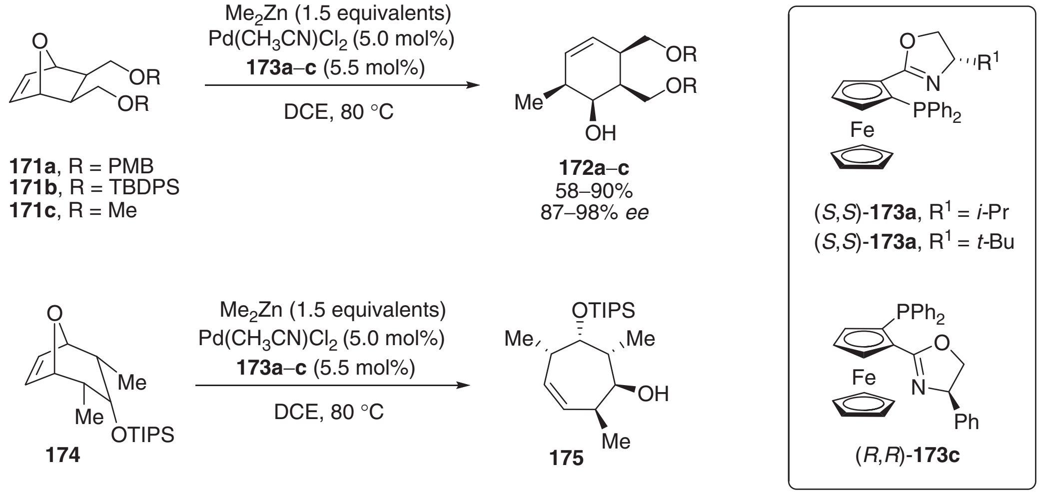
3.04.3.4.1 Ring-opening of oxabicyclo[2.2.1]- and [3.2.1]-systems, and related structures

One of the most common class of substrates used in this kind of transformations is constituted by oxabicyclo[2.2.1]- and [3.2.1]-systems, among which 7-oxabenzonorbornene and related compounds are predominant due to their superior reactivity. The chemistry of such systems has been extensively studied by Lautens and coworkers,[219] who examined their ring-opening reactions under Pd-catalysis. In 2000, they reported the first highly enantioselective Pd-catalyzed alkylative ring-opening of a series of oxabenzonorbornenes **167a–e** using diorganozinc reagents (Scheme 53). The catalyst was generated *in situ* by mixing a suitable Pd (II) salt with either a bis-phosphine or a phosphine–oxazoline chiral ligand, and the products were obtained with complete regioselectivity and *syn*-stereoselectivity in 90–96% *ee*.[220] Later, a further extension of the reaction scope including branched alkyl- and benzylzinc reagents was reported, and an acceleration of the reaction using cationic Pd(II) catalysts was demonstrated.[221]



Scheme 53 Pd-catalyzed enantioselective ring-opening of oxabenzonorbornenes.

The same group reported the results of additional studies conducted on the less reactive [2.2.1]- and [3.2.1]-oxabicyclic compounds. A change in the chiral ligand was required, with ferrocenyl-based DIPOF structures (**173**) often giving the best results, and in some cases promotion of the reaction by addition of a suitable Lewis acid such as Zn(OTf)$_2$ was also necessary.[222] Unfortunately, the method found a serious limitation in the fact that only transfer of a methyl group was possible (Scheme 54), although later extension to the use of Et$_2$Zn as a nucleophile was described.[221]

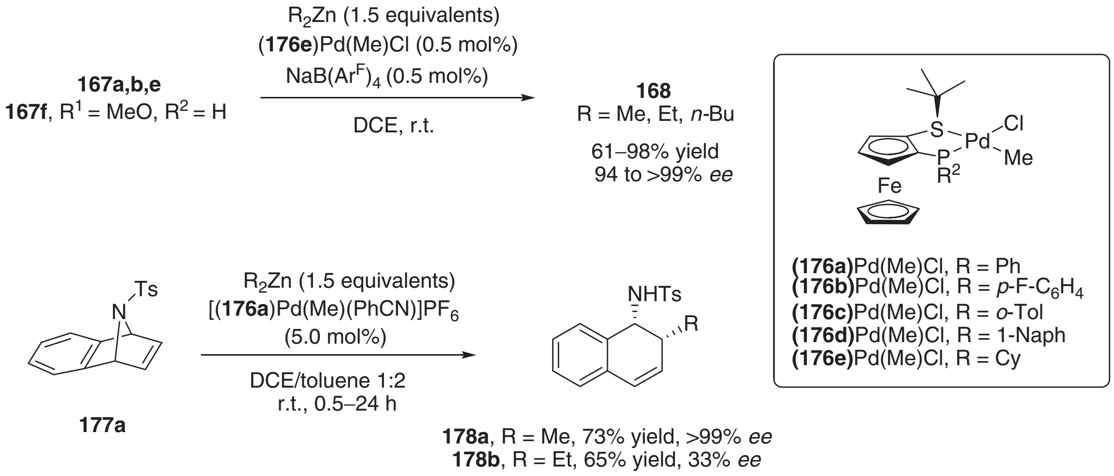


Scheme 54 Pd-catalyzed enantioselective ring-opening of [2.2.1]- and [3.2.1]-oxabicyclic compounds.

Ring-opening of nitrogen-containing analogs such as azabenzonorbornadienes was also demonstrated using (*S*)-*i*Pr-PhOX ligand (**170**). The catalytic system used in these studies was then employed for the same ring-opening reactions using more reactive organozinc halides: in general, good to high enantioselectivities (up to 95%) were obtained with BINAP or ligand **170**, but occasionally low yields were recorded and the effects of Lewis acidic additives were not studied.[223,224]

To explain the origin of the high regio- and *syn*-stereoselectivity displayed by the above transformations, Lautens' group conducted a series of studies to elucidate their mechanism; based on experiments carried out on unsymmetrical substrates, a π-allyl mechanism was quickly ruled out. The authors convincingly demonstrated that, after initial formation of an organopalladium intermediate, the reaction proceeds through carbopalladation of the double bond on the less hindered *exo*-face (which, in the case of an asymmetric reaction constitutes the enantioselective step) followed by *β*-oxygen elimination, thus giving the ring-opened product.[225] The chemistry developed during these studies was used in the stereoselective preparation of natural compounds, such as polyether antibiotic ionomycin.[226]

After the initial studies of Lautens, several other groups examined the ring-opening reaction of 7-oxabenzonorbornadiene (**167a**) and related structures with hard organometallic nucleophiles. Carretero and coworkers introduced the use of axially chiral 1-phosphino-2-sulfenylferrocenes (Fesulfos) as highly selective ligands for the above transformation. Although the use of these ligands together with $Pd(CH_3CN)_2Cl_2$ could induce methylation and ethylation of compound **167a** with up to 93–94% *ee*, respectively, the reactions were relatively slow and good yields of the products could be obtained only after 24 h.[227] Based on these results, and on the evidence gathered by previous mechanistic work,[225] the authors reasoned that cationic methylpalladium complexes of the Fesulfos ligands could serve as very active catalysts for the transformation under study: accordingly, complexes of the kind (**176**)Pd(Me)Cl (**Scheme 55**) were prepared and employed in the reaction of Me_2Zn with substrate **167a** in the presence of chloride scavenger $NaB(Ar^F)_4$ (used to generate the cationic complex). A spectacular rate enhancement was observed, and reactions were complete within 30 min: this allowed to reduce the catalyst loading and to work at lower temperatures, thus improving the enantioselectivity.[228] The scope of the reaction was examined and it was found that substituted oxabenzonorbornenes **167** could be alkylated with linear organozinc reagents to give the corresponding dihydronaphthols **168** in good yields and up to >99% *ee*. The transformations were also effective with less reactive substrates of type **171** (90–99% *ee*), as well as with azabenzonorbornadienes **177** (**Scheme 55**), although longer reaction times were required: moreover, in the last case, although transfer of a methyl group took place with perfect enantioselectivity (>99% *ee*), the corresponding ethylation surprisingly proceeded with a modest 33% *ee*.[229] The authors explain the excellent activity and selectivity displayed by this catalytic system by the synergistic effect of the strong *trans*-effect of the phosphorous moiety, which contributes to the activation of the alkene substrate, coupled with the great steric control exerted by the stereogenic sulfur atom bearing the very bulky *tert*-butyl substituent.[229]



Scheme 55 Enantioselective ring-opening of heteronorbornenes with Fesulfos–Pd complexes.

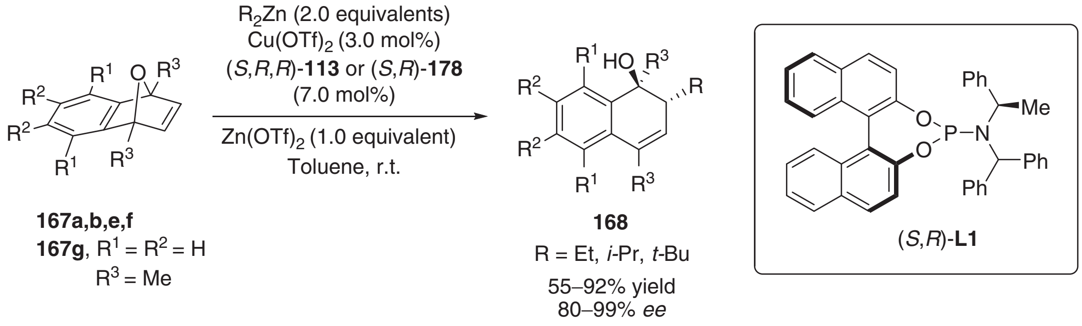
Other ligands have been reported to induce high enantioselectivity in the asymmetric Pd-catalyzed ring-opening reaction of 7-oxabenzonorbornene and related bicyclic structures, all giving rise to 1,2-substituted products with exclusive *syn*-stereoselectivity. Among them, especially good results were obtained with axially chiral 3,5-tBu_2-MeO-Biphep (up to 98% *ee*),[230] as well as with biphosphines with stereogenic phosphorous atoms bearing either quinoxaline or alkylnyl moieties (up to >99% *ee*).[231,232]

Besides palladium, other transition metal have been employed to catalyze the ring-opening reaction of oxanorbornenes with *syn*-stereoselectivity: based on this stereochemical preference and on the selective production of 1,2-disubstituted products, the same mechanism, comprising carbometalation and *β*-oxygen elimination,[225] is likely to operate also in these cases.

In 2000, Waymouth and coworkers described the use of Ti- and Zr-containing catalysts to effect the ring-opening of [2.2.1]- and [3.2.1]-oxabicyclic compounds **171**, **174** with trialkylaluminum and Grignard reagents; interestingly, use of a zirconium complex (5 mol%) having a menthol-derived chiral backbone allowed to open compound **171c** with Me_3Al in 64% yield and 96% *ee*, although further variations both in the substrate and in the organometallic reagent led to much lower selectivities.[233] The catalytic system constituted by $FeCl_3$ and TMEDA was also used to promote the reaction of substrates of type **167**, **171** and **174** with Grignard reagents. In this case, use of aryl- or vinylmagnesium halides was successful, affording the ring-opened products with moderate to good yields: alkylmagnesium halides, however, failed to deliver the desired compounds, producing either the corresponding vinylated cyclohexenols or the products of hydride addition. The authors explained this peculiar behavior invoking the intervention of a *β*-hydride elimination step after formation of the intermediate organoiron species.[234] The research group of Chen and coworkers have applied nickel-based catalysts to the ring-opening of several 7-oxa- and 7-azabenzonorbornenes **167**,**177** with organozirconium reagents. Vinylzirconium reagents were subjected to reaction in the presence of $Ni(PPh_3)_2Cl_2$ and

Zn powder to give products with 59–89% yield (although in some cases aromatization to naphthalene was observed);[235] alkyl- and allylzirconium compounds, in turn, were reacted under the influence of Ni(dppe)Br_2 and Zn powder to give comparably good results (52–85% yield).[236]

A different stereochemical outcome compared to that of Pd-catalyzed reactions is obtained when the ring-opening transformations are carried out under copper catalysis. In such case, 1,2-disubstituted products with *anti*-stereochemistry are formed preferentially. The first example of Cu-catalyzed alkylative ring-opening of 7-oxabenzonorbornenes **167** was described by Pineschi, Feringa et al., who used $Cu(OTf)_2$ in combination with their binaphthol-derived phosphoramidate ligands. Reactions required the additional employment of a Lewis acidic promoter such as $Zn(OTf)_2$ to activate the substrate and reach good conversions: products **168** were isolated with ≥58% yield (except for the transfer of a methyl group, which proved sluggish) and 80–99% *ee* with good *anti*-selectivity (Scheme 56).[237] The results were explained in terms of a classic S_N2' allylic alkylation, in which oxidative addition of an alkylcopper intermediate and subsequent reductive elimination take place on the opposite side of the leaving group (in this case, the bridging C–O bond).[76]



Scheme 56 Enantioselective Cu-catalyzed ring-opening of 7-oxabenzonorbornenes.

To avoid the need for an additional Lewis acid catalyst, the possibility to use more reactive Grignard reagents in place of diorganozinc compounds was evaluated. Carretero and coworkers found that use of a simple CuCl–PPh_3 combination (10 mol%) in toluene at r.t. would allow conversion of a series of bicyclic substrates **167** with several alkyl- and aryl Grignard in good yield and excellent *anti*-stereoselectivity. Furthermore, the less reactive compound **171c** easily underwent ring-opening as well, although application of a higher temperature was required.[238] Based on these results, the procedure was extended to the conversion of 7-azabenzonorbornenes of type **177**. It was established that a phosphine ligand was not necessary in this case and that CuCN was the most effective copper source: more importantly, it was also determined that the best substrate for the reaction was compound **177b**, bearing a (2-pyridyl)sulfonyl substituent on the bridging nitrogen instead of the more common tosyl (**177a** in Scheme 55), nosyl or Boc groups. Under these conditions, products were isolated in 53–98% yield with ≥85% *anti*-stereoselectivity.[239]

The first copper-catalyzed enantioselective ring-opening of bicyclic oxanorbornenes with Grignard reagents was reported shortly after by Zhou, who employed chiral phosphoramidates with a spirocyclic backbone (**179**, Figure 5): reactions carried out on substrates **167** with a few linear alkylmagnesium halides provided compounds **168** with up to 99:1 *anti*/*syn*-selectivity 88% *ee*. Unfortunately, the ring-opening reaction with a branched nucleophile, *i*BuMgBr, afforded a racemic product.[240] Later, the same group moved to a different, albeit structurally related, class of ligands, namely spirocyclic phosphines **180**, which were employed together with $Cu(OTf)_2$ in the presence of $NaB(Ar^F)_4$, whose role was to generate a cationic metal catalyst as previously indicated by Carretero.[228,229] After optimization, transfer of various alkyl Grignard reagents on 7-oxabenzonorbornenes **167** proceeded with good to high yields, perfect diastereoselectivity and 86–99% *ee*, also for the formation of quaternary stereocenters and when

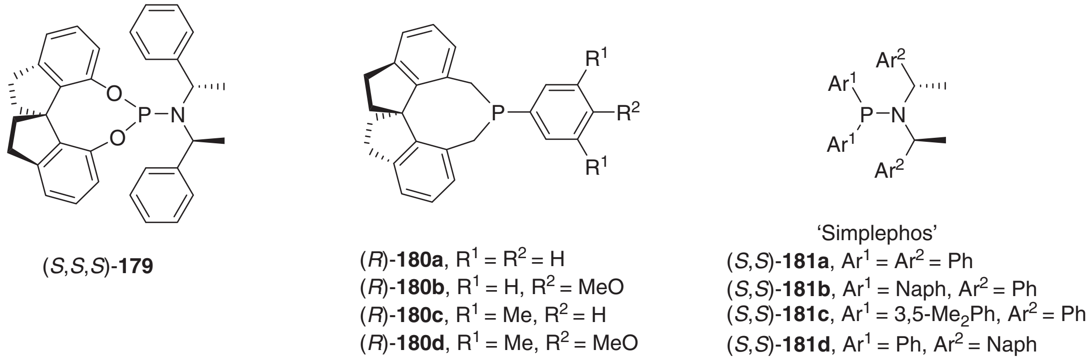


Figure 5 Chiral phosphines used in the Cu-cat. Enantioselective ring-opening of substrates **167**.

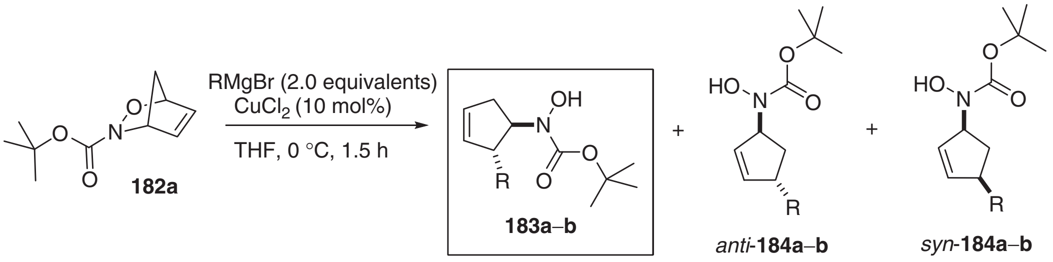
branched aliphatic nucleophiles were used. Methyl group was transferred efficiently although with slightly diminished *ee* (80%), whereas use of aromatic Grignard reagents returned racemic products.[241]

Use of Grignard reagents as the nucleophiles was described also by Alexakis, who made use of chiral 'Simplephos' ligands **181** (Figure 5).[133] After extensive optimization conducted on substrate **167a**, CuTC was identified as the preferred copper source and ligand **181a** proved to be the most effective among those tested. Despite these efforts, good enantioselectivities (72–82%) were registered only for the transfer of linear alkyl groups on compound **167a**: use of branched alkyl or phenyl Grignard as well as of substituted 7-oxabenzonorbornenes resulted in lower enantiomeric excesses (≤64%).[242] Due to the limited substrate scope demonstrated by the reaction with Grignard reagents, the authors turned their attention to the use of organoaluminum derivatives. Ring-opening reactions carried out with such nucleophiles under the influence of the CuTC–**181a** catalytic system in MTBE as the solvent afforded products of type **168** in good yields with 93–99% *anti*-diastereoselectivity and 87–94% enantiomeric excess; formation of quaternary stereocenters (substrate **167g**) was also possible in high *ee*, but was accompanied by formation of aromatic by-products.[242,243] Transfer of a phenyl group from $PhAlR_2$ (R=Me, Et, *i*Bu), in turn generated by transmetalation of PhLi with the appropriate dialkylaluminum chloride, was also attempted: products were obtained with good enantiomeric excess (up to 84%), but unfortunately they were always formed in mixture with the products stemming from the transfer of the alkyl group.[242,243]

3.04.3.4.2 Ring-opening of 2,3-bis-heteronorbornenes, and related structures

A further class of bridging bicyclic compounds that have been considered in ring-opening reactions, due to their simple preparation and high potential synthetic value, is represented by 3-aza-2-oxabicyclo[2.2.1]hept-5-enes and 2,3-diazabicyclo[2.2.1]hept-5-enes. Such compounds are easily accessible in multigram scale by hetero-Diels-Alder reactions between cyclopentadiene and either acylnitroso compounds or azodicarboxylates, respectively.[244]

In 2002, Miller and coworkers reported the copper-catalyzed ring-opening of some 3-aza-2-oxabicyclo[2.2.1]hept-5-enes **182** by means of Grignard reagents. It was found that in the presence of $CuCl_2$ as a catalyst, reactions with vinyl or alkyl Grignard could be driven to produce preferentially the *anti*-1,2-substitution product **183** over the other possible regio- and diastereomers (Scheme 57), although with phenylmagnesium bromide such selectivity was not observed.[245] The methodology developed in this study was extended to the use of benzylic Grignard reagents, which were applied to the synthesis of a series of cyclopentenyl hydroxamic acid-based inhibitors of 5-lipoxygenase enzyme.[245,246] Compounds of type **182** are chiral: their kinetic resolution was attempted using organozinc reagents (0.55–0.60 equivalent) in the presence of the $Cu(OTf)_2$/(*R*,*R*,*R*)-**113** catalytic system, giving ring-opened products **183** (R=Me, Et) with 56–58% *ee* at 46–52% conversion.[247]

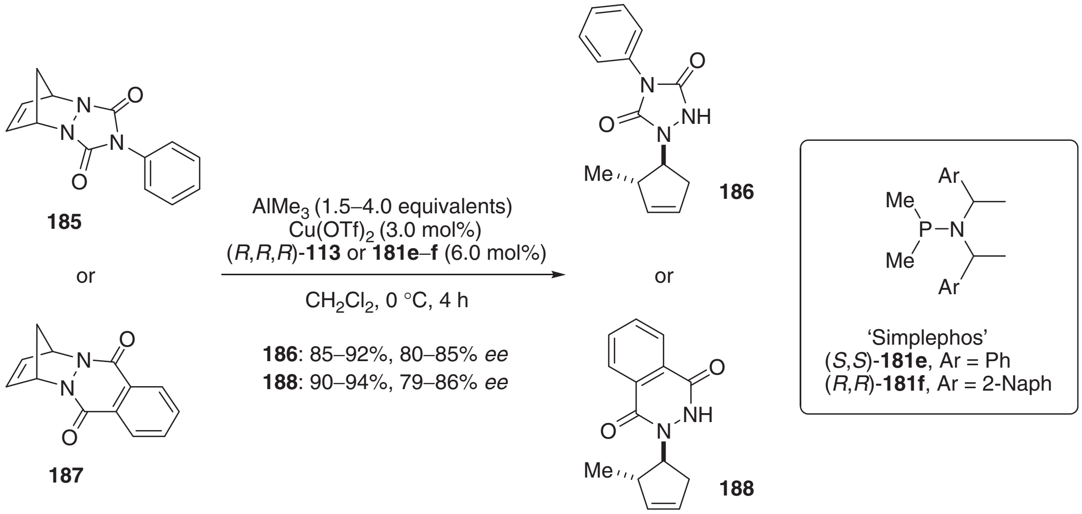


R = CH_2=CH 71% yield **183a** : *anti*-**184a** : *syn*-**184a** = 8.4:3:1
R = Et 93% yield **183b** : *anti*-**184b** : *syn*-**184b** = 18:2:1

Scheme 57 Cu-catalyzed ring-opening of 3-aza-2-oxabicyclo[2.2.1]hept-5-enes with Grignard reagents.

The ring-opening reaction of the homologated [2.2.2]-acylnitroso cycloadducts (analogs of **182** with an ethylene instead of a methylene bridge) was studied by Pineschi et al., who employed different kinds of organometallic reagents to effect the transformation. In the presence of $Cu(OTf)_2$ and either BINAP or ligand **113**, it was found that $ZnMe_2$ and trialkylaluminum reagents were able to induce formation of the desired *anti*-1,2-diastereomer with good regioselectivity, but conversions were low and the use of $Sc(OTf)_3$ as a Lewis acidic additive was required. Therefore, the authors switched to the use of Grignard reagents: whereas reactions employing alkylmagnesium chlorides or bromides produced preferentially the 1,4-substitution products, deriving from a S_N2 process, it was surprisingly observed that the corresponding iodides gave the 1,2-regioisomers with high selectivity. Such a halide effect was unprecedented in ring-opening reactions.[248]

In 2005, the first enantioselective ring-opening reaction of 2,3-diazabicyclo[2.2.1]hept-5-enes with organometallic reagents was described. It was observed that, using trialkylaluminum reagents in the presence of the $Cu(OTf)_2$/(*R*,*R*,*R*)–**113** catalytic system, symmetrical derivatives **185** and **187** could be converted into the corresponding cyclopentenes **186** and **188** (Scheme 58) with high conversion, perfect regio- and diastereoselectivity and enantiomeric excesses up to 80% and 86%, respectively. Surprisingly, dialkylzinc reagents proved totally ineffective in the reaction; moreover, employment of diastereomeric ligand (*R*,*S*,*S*)-**113**, bearing the enantiomeric chiral amine, resulted in products having the opposite absolute stereochemistry. This result was particularly puzzling, since usually in allylic substitution reactions it was the binaphthol part of the ligand to dictate the sense of enantioinduction in the formation of the products.[247,249]



Scheme 58 Enantioselective Cu-catalyzed ring-opening of 2,3-diazabicyclo[2.2.1]hept-5-enes.

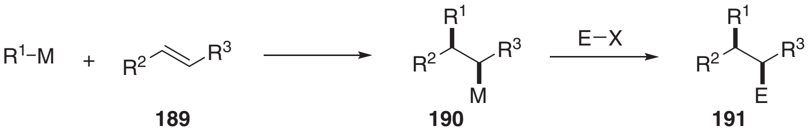
These surprising observations prompted Alexakis, Micouin, and coworkers to analyze the reaction in more detail: by analysis of the ^{31}P-NMR spectrum of a **113**–$AlMe_3$ mixture in dichloromethane, they realized that the organoaluminum reagent reacted with the phosphoramidate ligand, causing cleavage of the Binol moiety and formation of an aluminum complex of a 'Simplephos'-type ligand **181**, thus explaining the observed dependence of the sense of enantioinduction on the chirality of the amine part. Optimization studies led to the preparation of more efficient 'Simplephos' ligands, which were able to induce the formation of **186** with up to 85% *ee*.[250]

Finally, the group of Pineschi studied in detail the copper-catalyzed reaction of 2,3-diazabicyclo[2.2.1]hept-5-enes with organomagnesium halides. In 2009, they found that by application of the $Cu(OTf)_2$/*rac*-BINAP catalytic system, a double Boc-protected derivative could be induced to undergo a rearrangement-allylic substitution sequence to afford *anti*-1,3-disubstituted cyclopentenes with good to high regioselectivity, in lieu of the *anti*-1,2-products usually observed in the presence of copper (see Scheme 58).[251] Reaction on the [2.2.2]-analog of compound **182** with methylmagnesium chloride also displayed a peculiar regiochemistry: indeed, in the presence of the $CuCl_2$/*rac*-BINAP catalytic system, a mixture of products was obtained, in which the *anti*-1,4-adduct was the major one, in a 3:1 ratio to the canonical 1,2-substitution product.[252]

3.04.4 Carbometalations and Related Reactions

3.04.4.1 Introduction

Another class of transformations that has been widely employed in recent years to promote the alkylation of hard, nonstabilized organometallic nucleophiles is represented by carbometalation reactions. Such processes are defined as the addition of the carbon–metal bond of an organometallic species to a carbon–carbon multiple bond, leading to the formation of a new organometallic compound, which can in turn react with a suitable electrophile to yield the final product.[9,253] As shown in Scheme 59, if the species undergoing carbometalation is an olefin, a single carbon–carbon bond will be formed after the addition, resulting in the alkylation of the original organometallic reagent.



Scheme 59 General scheme for the carbometalation of an olefin substrate.

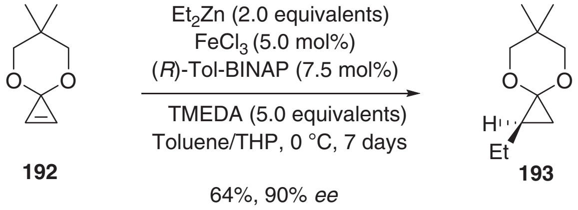
Despite their large potential, carbometalation reactions face a series of selectivity issues, which must be overcome to make these transformations synthetically useful: in the case of an unsymmetrical olefin, for example, two different regioisomers of compound **190** could be formed. Carbometalations often proceed by forming the new carbon–carbon bond on the most substituted end of the alkene system, but such selectivity can be altered depending on the substrate and on the particular organometallic used. In addition, enantioselective carbometalation reactions are complicated by the difficulty of enantiofacial differentiation of unactivated alkenes, and as a consequence such reactions have been described only in few cases.

In this paragraph, the authors present several results recently disclosed for carbometalations using hard, nonstabilized nucleophiles, sometimes performed in the presence of transition metal-based catalysts. In particular, the authors focus on reports published in the year 2000–2013 dealing with the conversion of selected important substrates.

3.04.4.2 Carbometalation of Cyclopropene Derivatives

Among the various classes of substrates that can be subjected to carbometalation reactions, cyclopropenes and related alkenes have been one of the most extensively studied. Indeed, carbometalation of such compounds[254] can provide access to substituted cyclopropanes, which are important synthetic intermediates,[255] and are also structural components of several biologically active species.[256] In addition, cyclopropenes are especially reactive due to the large strain caused by their endocyclic double bond and, for this reason, can undergo a series of transformations which extend far beyond the typical reactivity of alkenes.[257]

In 2000, Nakamura and coworkers published a very interesting report describing the iron-catalyzed carbometalation of cyclopropenone acetal **192** (CPA). The reaction could be performed either with Grignard or diorganozinc reagents as nucleophiles, and employed $FeCl_3$ as the catalyst. The authors found that an enantioselective version of the reaction could be developed by the addition of a diphosphine ligand and a diamine additive such as TMEDA (Scheme 60).[258]

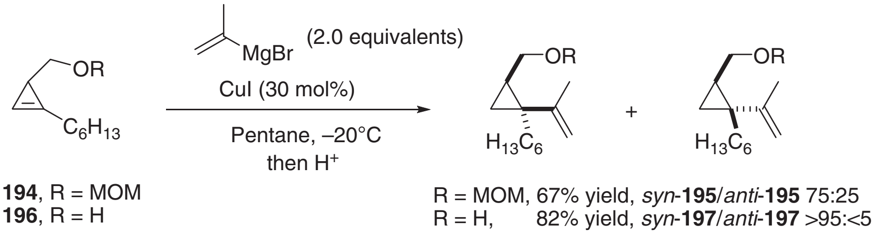


Scheme 60 Enantioselective iron-catalyzed carbozincation of CPA **192**.

(*R*)-*p*-Tol-BINAP proved to be the best ligand, whereas changing the co-solvent from THP to THF caused a loss in yield, but did not affect the *ee* of the final product significantly. Finally, the presence of TMEDA in the reaction mixture was essential: indeed, although it decreased the reaction rate, a racemic product was obtained in the absence of this additive.

Based on this protocol, the same group shortly after described an asymmetric allylzincation of substituted CPAs, employing a preformed chiral allylzinc derivative and demonstrating the formation of quaternary stereogenic centers with very high *ee*'s.[259] Both procedures were then applied to the synthesis of open-chain derivatives, in which they were followed by an oxidative cleavage of the three-membered ring that used MnO_2 or PbO_2 as the final oxidants.[260]

The first general procedure for the addition of several Grignard reagents to cyclopropenes was reported by Liao and Fox, who discovered that copper (I) salts could act as useful catalysts for this transformation. Thus, treatment of MOM-protected cyclopropenes **194** with alkyl- or alkenylmagnesium halides in the presence of CuI (30 mol%) afforded the corresponding cyclopropanes in good yields and perfect regioselectivity, albeit with sometimes unsatisfactory *syn*/*anti*-selectivity (Scheme 61). Interestingly, the authors found that use of the unprotected substrates **196** with a free OH group led to much better stereoselectivities, probably due to substrate coordination of the organometallic nucleophile (Scheme 61).[261]



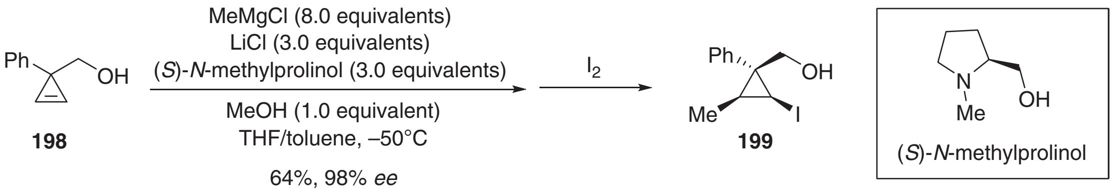
194, R = MOM
196, R = H

R = MOM, 67% yield, *syn*-**195**/*anti*-**195** 75:25
R = H, 82% yield, *syn*-**197**/*anti*-**197** >95:<5

Scheme 61 Cu-catalyzed carbomagnesiation of cyclopropenes.

Notably, the reaction was not productive when arylmagnesium derivatives were used as the nucleophiles. It was eventually found that switching the solvent from pentane to THF and running the reaction in the presence of a stoichiometric amount (1.2 equivalents) of tri-*n*-butylphosphine as a ligand for copper could help to overcome this problem: under such conditions, a range of substituted aryl Grignard reagents could be added to 3-hydroxymethylcyclopropenes with good yields and stereoselectivities (usually favoring the *syn*-isomer).[262]

In a significant development of their original work,[261] Fox's group also reported conditions for an enantioselective addition of methylmagnesium chloride to the same class of cyclopropene derivatives. In this case, a copper catalyst was not required, but the reactions had to be run in the presence of a large excess of the organometallic reagent, together with LiCl and a chiral ligand (*N*-methylprolinol, used in excess).[263] Remarkably, the authors found that the enantioselectivity of the reaction could be largely improved by the presence of 1 equivalent of MeOH, although the exact role of such additive was not discussed. As already reported in previous cases, quenching the reaction with electrophiles different than H^+ gave rise to products substituted on all ring positions (**Scheme 62**).

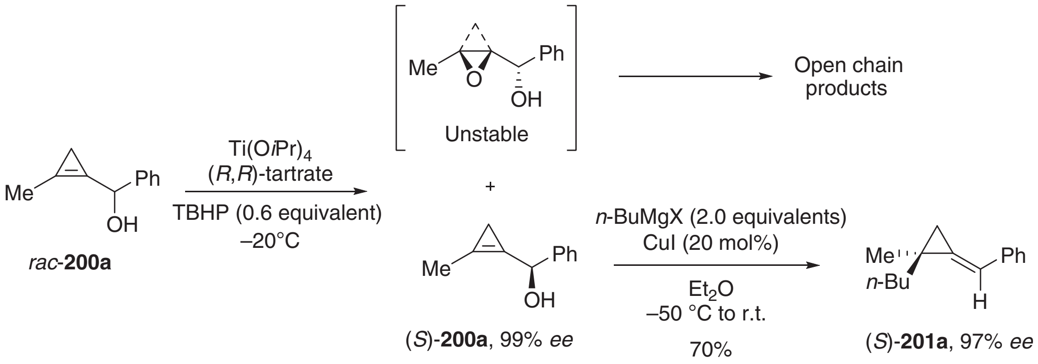


Scheme 62 Enantioselective methylmagnesiation of cyclopropenes.

Unfortunately, the protocol was limited to the introduction of a methyl group, as the addition of different nucleophiles gave rise to products with only low to moderate *ee*'s (20–64%).

A different reactivity pattern for the reaction of cyclopropene derivatives with Grignard reagents was identified both by the groups of Fox and Marek, who described the preparation of methylenecyclopropanes (having an exocyclic double bond) from different substrates. In the first case, it was found that reaction of 3-hydroxymethylcyclopropenes carrying an ethereal substituent at position 2 with various Grignard reagents afforded, in the absence of any copper catalyst, methylenecyclopropanes in good yields with excellent facial selectivity; the reaction was formally similar to an allylic alkylation, although it was best described by a carbometalation–elimination sequence.[264] Interestingly, the outcome of the reaction was dependent on the halide ion present in the Grignard reagent, with alkylmagnesium bromides giving better results compared to the corresponding chlorides.

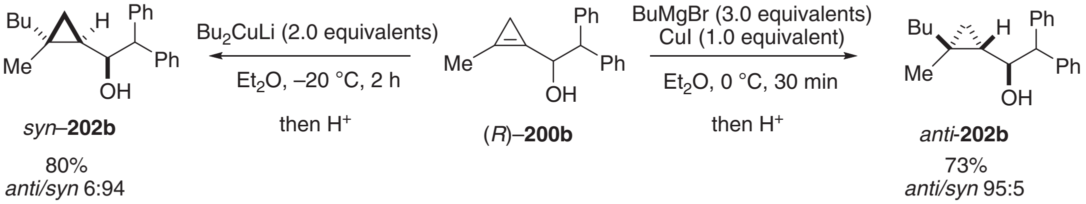
In the second example, the preparation of alkylidenecyclopropanes was described starting from enantiomerically pure cyclopropenylcarbinols **200**. The latter were easily obtained from the corresponding racemic materials, in turn prepared from 1,1,2-trihalocyclopropanes,[265] thanks to an ingenious application of Sharpless kinetic resolution (**Scheme 63**).[266,267] When treated with both alkyl- and arylmagnesium halides in the presence of a catalytic quantity of copper (I) iodide, compounds **200** were readily converted into methylenecyclopropanes **201** with almost complete conservation of the stereochemical information; the *E*/*Z* stereoselectivity in the formation of the double bond was usually very high, although it decreased slightly when arylmagnesium derivatives were used (**Scheme 63**).[268]



Scheme 63 Synthesis of enantiomerically pure alkylidenecyclopropanes from cyclopropenylcarbinols.

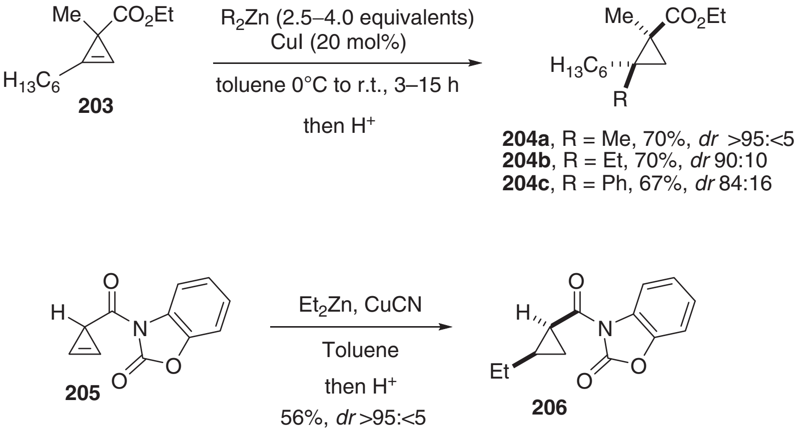
In analogy with the previous report by Fox,[264] also in this case the authors observed a halide effect, with alkylmagnesium iodides giving better *E*/*Z* stereoselectivities compared with chlorides and bromides.[269] The above observations were explained on the basis of a mechanistic hypothesis involving three subsequent steps: (1) a *syn* copper-catalyzed carbomagnesiation reaction, leading to a cyclopropylcopper intermediate, (2) a transmetalation reaction into the corresponding cyclopropylmagnesium compound and, finally, (3) a *syn* β-elimination yielding the final product.[268,269]

The authors reasoned that, if the contra-thermodynamic transmetalation from copper to magnesium could be avoided, then the cyclopropylcopper intermediate would be more stable toward β-elimination,[270] thus allowing to trap it with an electrophile and obtain access to cyclopropylcarbinol derivatives. To this end, reactions were performed under the same conditions as above, but using a stoichiometric amount of copper (**Scheme 64**): after treatment with acid or other electrophiles, cyclopropylcarbinols **202** were indeed obtained in good yields and up to 95:5 *anti*/*syn* ratios.[271,269] Surprisingly, when the reaction was conducted using an organocuprate stemming from BuLi and CuI, a complete reversal of selectivity was observed, with the *syn*-isomer being strongly favored (**Scheme 64**): the two protocols are therefore of high synthetic interest, given the possibility of forming two diastereomers of the same product starting from a common precursor.



Scheme 64 Stereodivergent synthesis of cyclopropylcarbinol derivatives.

The selective carbometalation of cyclopropene derivatives was extended by Fox and coworkers to a new class of substrates, namely cyclopropene-3-carboxylates. Such compounds were shown to be incompatible with the use of Grignard reagents, and as a consequence their conversion was attempted using diorganozinc reagents. The addition of organozinc species to cyclopropenes had been previously described in the initial works of Nakamura,[258–260] as well as in a report by Smith and Richey,[272] but this was the first example in which such reaction was conducted with facial selectivity. As shown in **Scheme 65**, cyclopropenyl esters **203** were treated in toluene with various diorganozinc compounds in the presence of CuI or CuCN (20 mol%); the resulting carbometalated intermediates were captured with suitable electrophiles (H^+, I_2, allyl bromide) to provide cyclopropyl esters **204** in good yields and usually high diastereoselectivity (*dr* up to $>95:<5$).[273] The reactions proceeded well also when the ester functionality was replaced by an oxazolidinone moiety, which could therefore act as an efficient directing group as well: this was especially interesting for compounds derived from the parent cycloprop-2-ene carboxylic acid, as its ester derivatives are known to be unstable.

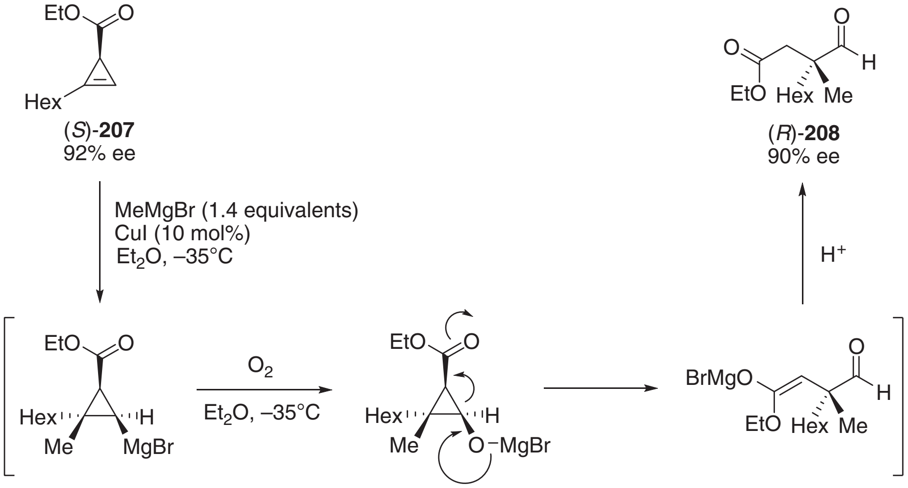


Scheme 65 Stereoselective Cu-catalyzed carbozincation of cyclopropene carboxylates and oxazolidinones.

The method found a limitation in the use of commercially available diorganozinc reagents. To overcome this problem, the authors investigated the *in situ* formation of such species from the corresponding Grignard reagents, with good results.[273] In a further development, the same group reported the generation of functionalized arylzinc derivatives from the corresponding iodides according to a sequential I/Mg/Zn exchange, and their addition to substrates of type **203**; the product cyclopropyl esters were formed with good yields and stereoselectivities; in this context, treatment of the *in situ*-generated organozinc compounds with dioxane was found to be essential to remove magnesium salts from the solution, in the presence of which poor diastereoselectivities were observed.[274]

A further example of diorganozinc addition to cyclopropenes was recently disclosed by Lautens and coworkers, who described the first enantioselective palladium-catalyzed carbozincation of symmetrical 3,3-disubstituted cyclopropenes. After optimization, it was found that treatment of the substrates with Et_2Zn in the presence of a chiral complex generated from $Pd(MeCN)_2Cl_2$ and (*R*)-Tol-BINAP, followed by aqueous quench, afforded usymmetrical cyclopropanes with moderate to high enantioselectivity (up to 91%); in addition, transmetalation to copper bofore quenching allowed trapping with various electrophiles, thus generating a series of products in enantioenriched form (90–93% *ee*).[275] Despite these encouraging results, the method was limited both in terms of substrates, with a fluorenyl derivative being the only one to give high *ee*'s, and of nucleophiles, since only the use of diethylzinc was demonstrated.

In conclusion of this paragraph, a very recent work by Marek's group should be mentioned, which dealt with the stereoselective preparation of chiral aldehydes bearing a quaternary stereocenter at the α-position, starting from the carbometalation of cyclopropene esters.[276] In contrarst to previous reports, the authors found suitable conditions to perform such transformation using a mixture of Grignard reagents and a copper (I) salt: (as pointed out previously, Grignard reagents were considered not suitable for the clean carbometalation of cyclopropene esters: see Ref. 271.) *syn*-cyclopropane esters were obtained with good selectivity (Scheme 66). Once again, use of a cuprate stemming from an organolithium reagent and a copper salt provided the same product with inverted facial selectivity. Oxidation of the intermediate organomagnesium species resulted in a fragmentation sequence that ultimately yielded the ring-opened product: starting from enantiomerically enriched substrate **207**,[277] chiral aldehyde **208** could be obtained with remarkable conservation of the stereochemical information (Scheme 66).



Scheme 66 Synthesis of chiral aldehydes bearing a quaternary stereocenter starting from cyclopropene esters.

3.04.4.3 Carbometalation of Other Unsaturated Substrates

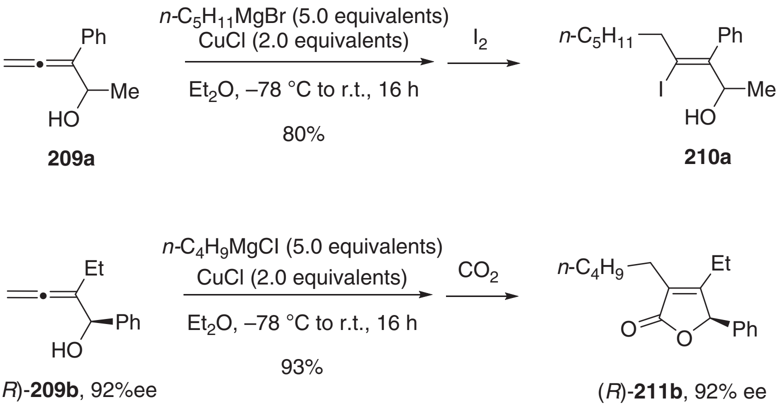
Apart from cyclopropenes, a series of other unsaturated substrates have been involved in carbometalation reactions resulting in the net alkylation of the organometallic species, among which dienes and allenes are particularly noteworthy.

Kambe's group worked extensively on the three-component reactions of dienes with organometallics and suitable electrophiles. In 2003, they reported a procedure for the one-pot, nickel-catalyzed dimerization/carbosilylation of 1,3-butadienes with Grignard reagents and chlorosilanes: the reaction afforded 1,6-dienes bearing an allylsilane functionality with good yields and high regioelectivities, which decreased only when substituted butadienes were employed as the substrates.[278] In a related investigation, the same group examined the nickel-catalyzed, three-component reaction of organomagnesium and organozinc derivatives with butadienes and alkyl halides: no dimerization was observed in this case, and therefore the reaction led to the formation of a series of tetrasubstituted olefins, which were obtained in moderate to high yields but often with unsatisfactory E/Z selectivity.[279]

An interesting example of a diastereo- and enantioselective intramolecular carbometalation reaction has been reported in 2010 by the research group of Marek. In such work, treatment of suitable acylsilanes bearing a terminal double bond with an alkynylzinc reagent (in turn obtained from diethylzinc and a terminal alkyne) resulted in a reaction cascade consisting of: (1) zinc-mediated addition to a C=O double bond; (2) Zn-Brook rearrangement; (3) isomerization to a Zn-allene species; (4) Zn-ene-allene cyclization. Trapping of the resulting alkylzinc species with electrophiles yielded functionalized cyclopentanes in good yields with up to 72% *ee*.[280]

Finally, an efficient protocol for the regioselective carbomagnesiation of 2,3-allenols was described by Ma and coworkers, who also employed copper (I) halides as promoters. When substrates of type **209** were reacted with various alkyl- and arylmagnesium bromides in the presence of a stoichiometric amount of CuCl, a clean transformation took place, in which the new carbon–carbon bond was formed at the allene terminal position; trapping of the organometallic intermediate with I_2 afforded the final products **210** (Scheme 67).[281]

Very recently, this procedure was extended to the synthesis of substituted 2(5*H*)-furanones by employment of CO_2 as the terminal electrophile. In that context, it was observed that the nature of the halide anion of the Grignard reagent had once again a dramatic effect on the reaction outcome, with chlorides giving a much higher yield than bromides and iodides. Conversion of enantiopure substrates provided the five-memebered rings **211** in good yields with complete retention of their stereochemical integrity (Scheme 67).[282]



Scheme 67 Cu-catalyzed regioselective carbometalation of 2,3-allenols.

3.04.5 Transition Metal-Catalyzed Cross-Coupling Alkylations with Zn- and Mg–Alkyl Carbanions

3.04.5.1 Introduction

Transition metal-catalyzed cross-coupling reactions between organic electrophiles and organo-metallic reagents constitute one of the most straightforward methods for the formation of carbon–carbon bonds.[283–285] Numerous examples of useful catalytic reactions have been developed and exploited as a powerful tool to assemble complex molecular frameworks useful in a range of fields, including total synthesis of natural products, medicinal chemistry, industrial process development as well as chemical biology, materials science, and nanotechnology. Such value has been recognized in 2010 by the awarding of the Nobel prize in chemistry to Richard Heck, Ei-ichi Negishi, and Akira Suzuki "for palladium-catalyzed cross-couplings in organic synthesis."

Studies of reactions between Grignard reagents and organic halides in the presence of transition metal such as Co, Mn, Cr, Fe, Ni salts date back to the 1940s.[286,287] However, such reactions were performed in the absence of ligands and often resulted in homocoupling and/or disproportionation of organic moieties.[288,289] Breakthrough discoveries in cross-coupling were made in the early 1970s using Fe,[290] Ni,[291,292] and Pd[293] catalysts, which prompted a rapid growth in the area of the cross-coupling of aryl or vinyl halides. In particular, the use of phosphine complexes of nickel and palladium provided excellent yields of coupling products in reactions with Grignard or organolithium reagents.[292,293]

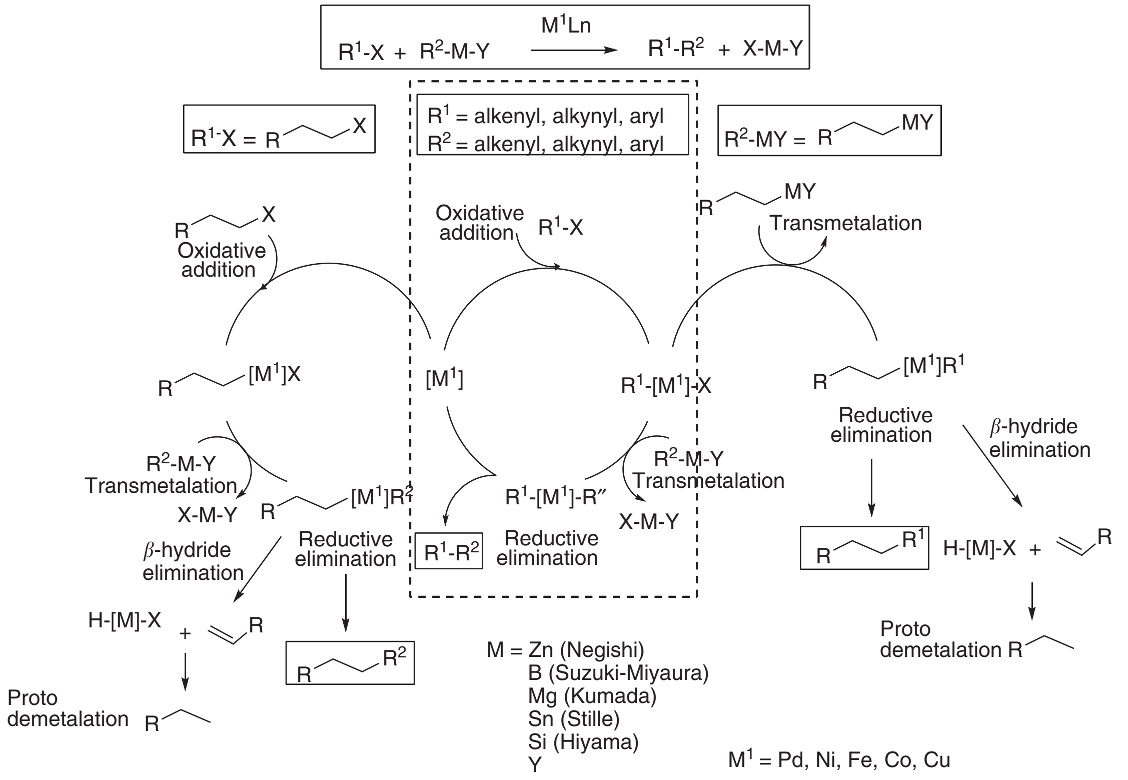
Since then, a variety of organometallic reagents and catalysts have been studied whereas the scope of the coupling partners had long been limited to C(sp^2)–C(sp^2) bonds.

The general catalytic cycle for metal-catalyzed cross-couplings is depicted in Scheme 68 and involves oxidative addition to a coordinatively unsaturated metal complex [M^1], transmetalation of the organometallic nucleophile to the catalyst species, and reductive elimination. Different pathways are dependent from the coupling partners used. Alkyl halides, especially those with β-hydrogen atoms, represented a difficult class of electrophiles for cross-coupling reactions due mainly to slow oxidative addition to transition metal catalysts, fast β-elimination from the σ-alkyl metal intermediates and slower reductive elimination of alkyl groups compared with C(sp^2) units. Likewise the use of C(sp^3) organometallics in cross-coupling reactions has suffered from several serious problems, expecially those that can undergo β-hydride elimination. The necessity to prepare *in situ* the organometallic reagents (as they are not air-stable), the spontaneous decomposition of alkyl organometallics via β-elimination or by proto-demetalation,[294] the often slow transmetalation (thus requiring various additives), made their development much slower than that of related C(sp^2) organometallics. However, during the past decade, remarkable progress has been achieved by many groups also with these coupling partners.[295] The use of suitable ligands or ligand precursors such as bulky trialkylphosphines, *N*-heterocyclic carbenes (NHC), bidentate or tridentate amines, olefins, and dienes has allowed various transition metals to play important roles as catalysts in such reactions. Among these metals Fe, Ni, Co, Cu as well as Pd have been extensively studied and successfully used in synthetic applications. Nevertheless, to identify an efficient combination of ligands (Figure 6), metals, and conditions to effectively promote cross-coupling reactions, especially when C(sp^3)-organometallics or C(sp^3)-electrophiles are involved, can still be challenging.

3.04.5.2 Alkylations of Organo Zinc Reagents

3.04.5.2.1 Pd-catalyzed transformations

Organozinc reagents of type R_2Zn or RZnX are some of the most widely used organometallic reagents in cross-coupling reactions.[296] Because of the low reactivity in addition reactions, which is due to the highly covalent character of the carbon–metal bond, and the mild Lewis acidic nature of zinc, they are tolerant of a wide range of functional groups. Additionally, the empty low-lying p orbitals of zinc make these reagents susceptible to transmetalation reactions with various transition metals, leading to a reactive intermediate **212** which readily undergoes reductive elimination to provide the final products (Scheme 69).



Scheme 68 General catalytic cycle for metal-catalyzed cross-couplings.

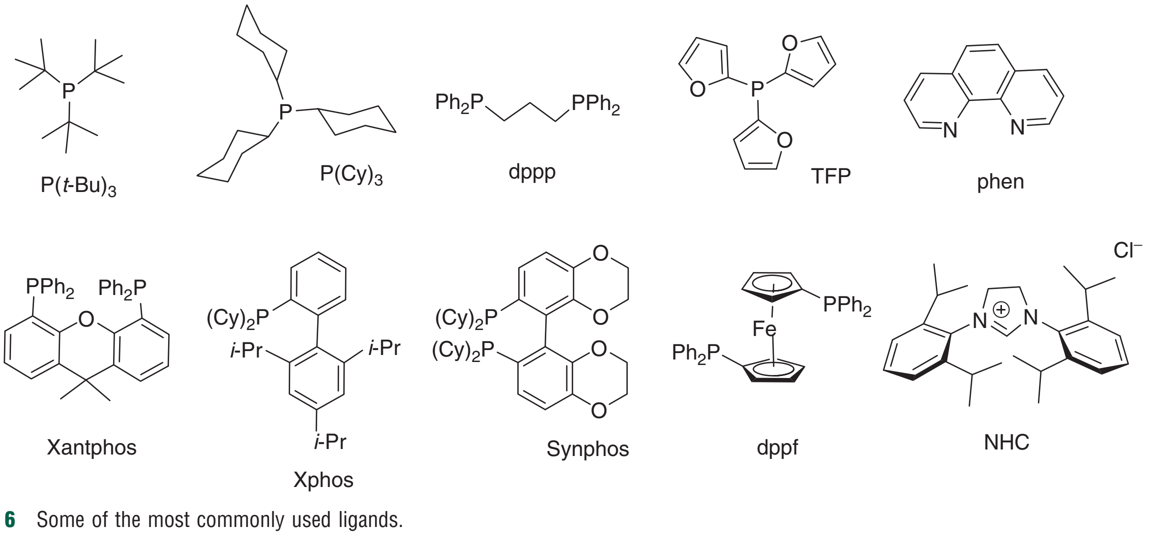
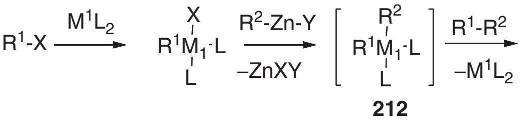
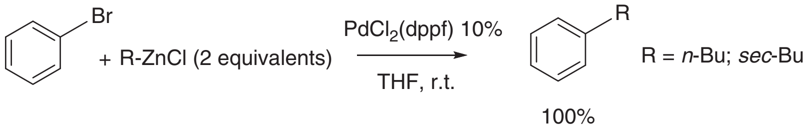


Figure 6 Some of the most commonly used ligands.



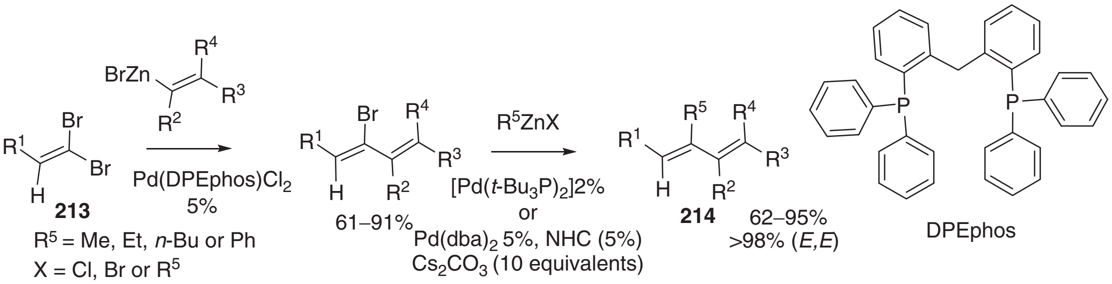
Scheme 69 Cross-coupling with alkylzinc reagents.

In 1977, Negishi et al. reported that organozinc reagents undergo Ni- or Pd-catalyzed cross-coupling reactions, providing a general and mild procedure for the synthesis of biaryls and diarylmethines with high chemo- and regioselectivity and opening the way to the application of organozing reagents in cross-coupling reactions.[297] This transformation has come to be named Negishi reaction. Indeed cross-coupling reactions of alkylzinc reagents with aryl and alkenyl,[298] acyl,[296] or alkyl halides[299–301] or pseudohalides[302] have been successfully used, whereas those with alkyl groups containing β-hydrogen(s) have not always given satisfactory results. In particular, the cross-coupling of secondary or tertiary alkyl reagents has been found to be difficult because it can be accompanied by isomerization of the alkyl group and/or reduction of the halide.[303] Such undesired side reactions can be suppressed by an appropriate choice of catalyst which could potentially accelerate the reductive elimination pathway[304–308] and favor the isomerization of the coupling partners from a *trans* arrangement to *cis*, which is necessary for reductive elimination to occur.[309] For instance, $PdCl_2$ in the presence of (dppf) (**Figure 6**), a bidentate phosphine ligand with a large bite angle (P–Pd–P=99.07°), was found to be an excellent catalyst for cross-coupling since it enforces the coupling partners into a *cis* geometry within a square-planar Pd(II) complex, thereby increasing the rate of reductive elimination. Using this catalytic system excellent product selectivity in the cross-coupling of bromobenzene and primary or secondary butylzinc chloride were obtained (**Scheme 70**).[310]



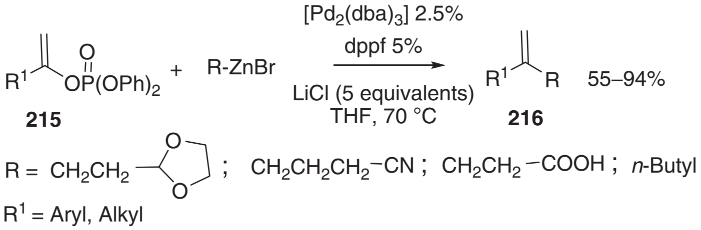
Scheme 70 Cross-coupling of bromobenzene and primary or secondary butylzinc chloride.

Very important results have been achieved in the past decade in the $C(sp^2)$–$C(sp^2)$ Negishi coupling of vinyl electrophiles. Stereoselective synthesis of dienes **214** and ene-ynes from the corresponding 1,1-dibromo-1-halides **213** has been performed by two subsequent Negishi coupling. Pd-catalyzed *trans*-selective monoalkenylation of 1,1-dibromo-1-alkenes was followed by a stereospecific methylation or ethylation with dimethylzinc/methylzinc halide or diethylzinc/ethylzinc halide, respectively (**Scheme 71**). Two different ligands were used, (DPEphos) in the first step and the bulky phosphine, $P(t\text{-}Bu)_3$ in the second (**Figure 6**). Alternatively, a $[Pd_2(dba)_3]$–NHC ligand combination could be used.[311,312]



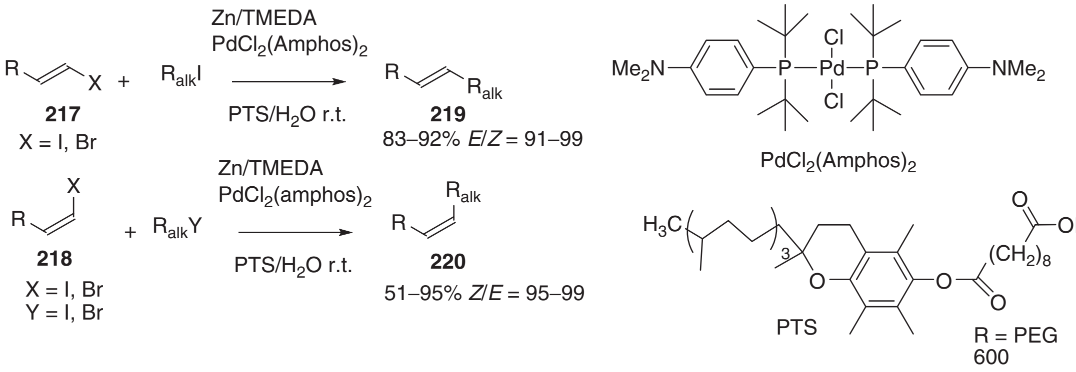
Scheme 71 Stereoselective synthesis of dienes.

$C(sp^3)$–$C(sp^2)$ bond formation has been obtained using alkyl vinyl phosphates **215**,[313] which have been shown to undergo Negishi cross-coupling using dppf (**Figure 6**) as ligand and Pd_2dba_3 as pre-catalyst (**Scheme 72**). The corresponding 1,1-aryl,alkyl or 1,1-alkyl,alkyl disubstituted alkenes **216**, respectively, are obtained in good yields. In this coupling, as already observed by Buchwald and coworkers,[314] the addition of an excess (5 equivalents) of lithium chloride was found to be essential.



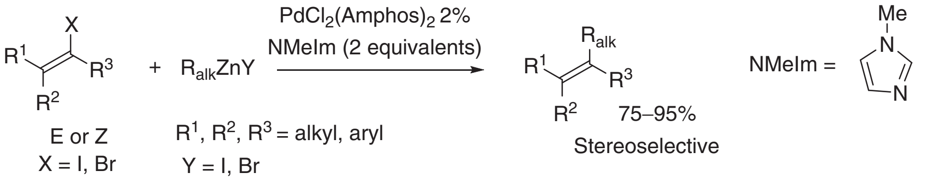
Scheme 72 Pd-catalyzed Negishi cross-coupling with vinyl phosphates.

The nonionic amphiphile PTS (Scheme 73) enables a simple approach to Pd-catalyzed stereoselective cross-couplings by simply combining an alkenyl halide **217**, **218** with an alkyl iodide in the presence of zinc powder. Cross-coupling products **219**, **220** are recovered in good yields without prior formation of the organozinc reagents. Crucial to the success of this technology are the following points: the use of TMEDA as additive, the employment of palladium(II) precursor $PdCl_2(Amphos)_2$, as other sources of Pd (0) or Pd(II) catalysts led to inferior results, the use of amphiphile PTS which presumably supplies the hydrophobic pocket in which the *in situ* generated water-sensitive organozinc halide reacts and the use of Zn dust, rather than powder. The reaction is conducted at room temperature, tolerates various functional groups and allows replacement of organic solvents with water as the only medium.[315]



Scheme 73 Pd-catalyzed stereoselective cross-couplings of alkenyl halides in water.

Negishi couplings at olefinic centers do not always occur with the anticipated maintenance of stereochemistry. Lipshutz and coworkers have reported that the stereochemical outcome using *Z*-alkenyl halides substrates could vary, contrary to prevailing thinking, as a function of the ligand(s) on the Pd catalyst.[316] Thus a modified method has been developed that solves the stereochemical issue and significantly improves yields of the reaction. Indeed, the ligand effects on both stereoselectivity and reaction pathway could be fully overcome using catalytic $PdCl_2(PPh_3)$ in the presence of an equivalent of TMEDA. These reaction conditions could be successfully applied to a variety of functionalized reaction partners, even sterically hindered vinyliodides and vinylbromides. These results suggest that additional new insights regarding mechanistic details associated with Pd-catalyzed C–C bond-forming reactions can be discovered. The same group also reported an efficient technology for high yielding Pd-catalyzed cross-couplings which provides consistent maintenance of both *E*- and *Z*-olefin geometry in the products. This was obtained using a combination of catalytic $PdCl_2(Amphos)_2$ with the aid of N-methylimidazole (NMeIm) as the key additive in THF at room temperature (Scheme 74).[317]



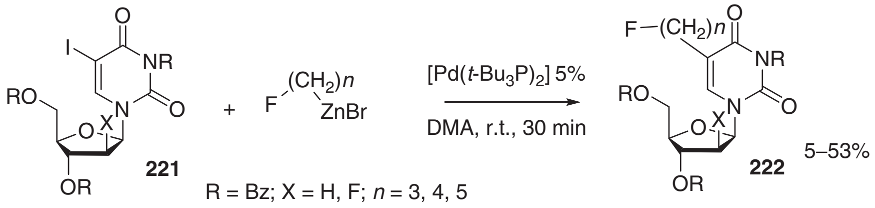
Scheme 74 N-methylimidazole as additive for stereoselective synthesis of *E*- and *Z*-olefines.

Alkenyl iodides and bromides together with primary and secondary alkylzinc iodides can be used as substrates. The functional group, together with the exceptionally mild conditions developed allowed for the synthesis of a variety of functionalized isomerically pure alkenes.

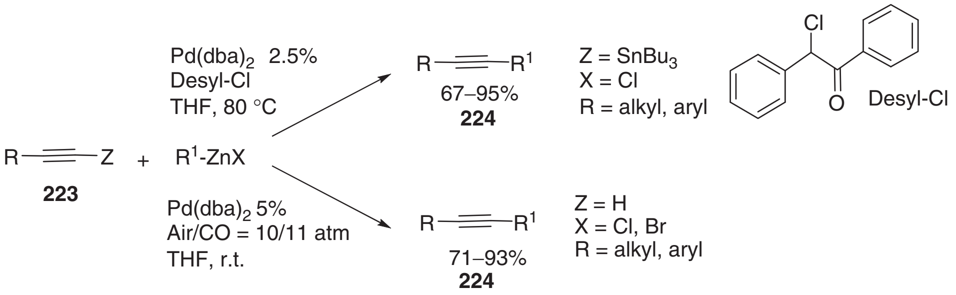
Negishi cross-coupling has been applied to the functionalization of unsaturated heterocycles. A library of biologically active 5-fluoroalkylated pyrimidine nucleosides **222** was synthesized by a $[Pd(t\text{-}Bu_3P)_2]$ catalyzed alkylation of protected 5-iodo-20-deoxyuridine nucleosides **221** (Scheme 75).[318] This methodology provides a direct route to synthesize F18-radiolabeled nucleosides that could be used as probes for non invasive *in vivo* molecular imaging.

$C(sp^3)$–C(sp) coupling have also been reported. Pd-catalyzed oxidative cross-coupling of terminal alkynyltin **223** reagents with alkylzincs in the presence of desyl chloride allowed to obtain unsymmetrically disubstituted alkynes **224** in good yields (Scheme 76)[319] The reaction occurs through a double transmetalation. Similarly $C(sp^3)$–C(sp) coupling of terminal alkynes (Z=H) could be accomplished using $Pd(dba)_2$ and a (10:1) mixture of air–CO as the oxidant[320](Scheme 76).

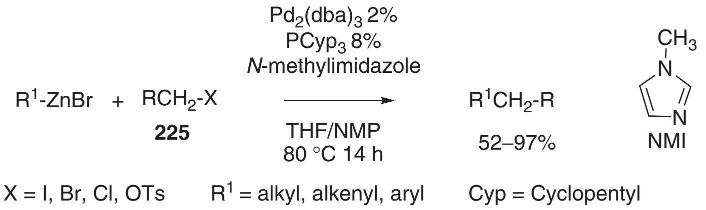
In the past decade significant progress has been achieved in the area of $C(sp^3)$–$C(sp^3)$ cross-coupling between alkyl organometallics and alkyl electrophiles (Scheme 77). To promote oxidative addition of the saturated C-halogen bond an electron-rich Pd center is required and that can be obtained by using electron-rich phosphines or N-heterocyclic carbenes (NHCs) as ligands.



Scheme 75 Alkylation of protected 5-iodo-20-deoxyuridine nucleosides.



Scheme 76 Synthesis of unsymmetrically disubstituted alkynes.



Scheme 77 C(sp^3)–C(sp^3) cross-coupling with Pd$_2$(dba)$_3$–PCyp$_3$–*N*-methylimidazole.

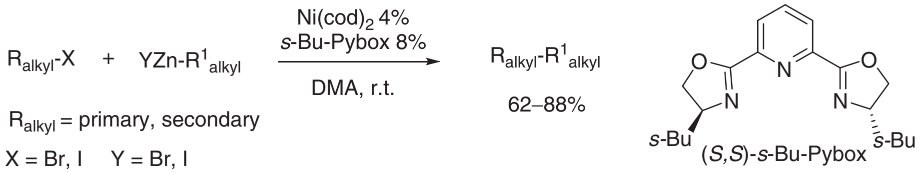
Fu's group has made key contributions in this area by identifying a set of electron-rich hindered ligands capable of promoting cross-coupling with alkyl halydes. A single catalytic system that is effective for a range of unactivated alkyl electrophiles **225** has been selected. Pd$_2$(dba)$_3$–PCyp$_3$–*N*-methylimidazole (NMI) was found to be an effective catalytic system that can cross-couple a spectrum of substrates.[302] The addition of NMI improved yields, perhaps through activation of alkylzinc halides toward transmetalation.

Sterically hindered NHC proved to be efficient ligand for promoting high yielding cross-coupling of unactivated alkyl bromides possessing *β*-hydrogens with alkylzinc halides in mild conditions[321] using a variety of Pd sources. An investigation on different NHC precursors showed that bulky 2,6-diisopropylphenyl moiety (**Figure 6**) was necessary to achieve high yields even with *β*-substituted alkyl bromides and alkylzinc halides. Alkyl chlorides were unaffected in these conditions.[322]

3.04.5.2.2 Ni-catalyzed transformations

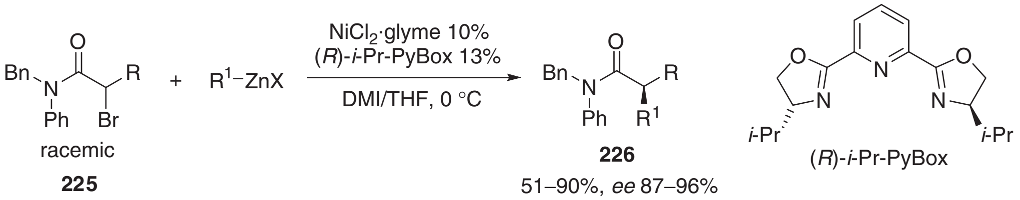
Although Negishi reaction is catalyzed by Ni or Pd complexes, the latter have been much more developed. Nevertheless Ni-catalyzed processes have become important in recent years, especially for their activity in the formation of alkyl–alkyl bonds. Conditions for the Ni-catalyzed cross-coupling of alkylzinc reagents with alkenyl and aryl halides were established some years ago and after then they have shown a broad scope with respect to both coupling partners.[323] In 1996, Knochel and coworkers reported the first Ni-catalyzed alkyl–alkyl Negishi cross-coupling.[324] The key to the success of this reaction is suggested to be the formation of intermediate Ni(II)–olefin complexes, which further undergo easy transmetalation and reductive elimination reactions. The methodology was further developed and efficient and fast couplings between polyfunctional primary iodoalkanes and primary diorganozinc compounds in the presence of *m*-trifluoromethylstyrene or acetophenone as promoters[325] were obtained. In particular, the presence of Bu$_4$NI and *m*-trifluoromethylstyrene as a promoter, greatly enhances reaction efficiency[326] and also allows cross-coupling of benzyl, primary and secondary zinc reagents.[327] Recently the formation of Pd-nanoparticles from Pd(OAc)$_2$ and Bu$_4$NBr was inferred.[328] It is possible that the alkylzinc reagent reduces Pd(OAc)$_2$ to Pd(0) which is suspended as nanoparticles (PdNPs) and stabilized by Bu$_4$NBr. Such nanoparticles could provide a more accessible and active surface area to interact with substrates thus increasing the catalytic activity. Several experiments support that Pd(NPs) are formed, including the observation that PPh$_3$ acts as a catalyst poison.[329]

Since the pioneering work of Knochel[324,330,331] new ligands and conditions have been reported for this type of coupling catalyzed by Ni complexes. In 2003, Zhou and Fu reported that Ni(COD)$_2$ in the presence of (*s*-Bu)-Pybox in DMA (*N,N*-dimethylacetamide) catalyzes cross-coupling of a range of secondary alkyl bromides and iodides with alkylzinc halides. The reaction conditions used are compatible with functional groups such as sulfonamides, ethers, acetals, esters, and amides (Scheme 78). The same catalyst was also employed with primary alkyl halides.[332]



Scheme 78 Ni-catalyzed cross-coupling of secondary alkyl bromides and iodides.

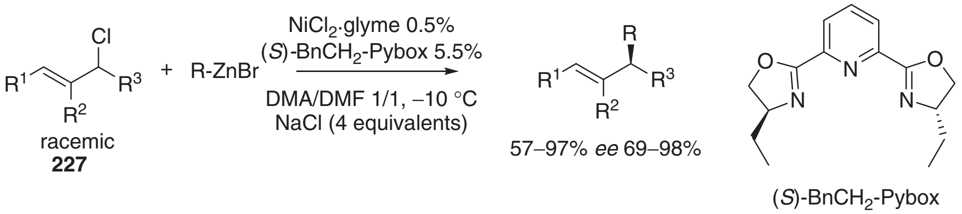
Fu's group has published several articles in which the scope of Ni-catalyzed alkyl–alkyl bond formation has been significantly broadened. The asymmetric Ni/(*i*-Pr)-Pybox-catalyzed Negishi cross-coupling of a range of secondary α-bromoamides **225** with an array of functionalized and unfunctionalized organozinc reagents has been shown to proceed in good yield to give the corresponding α-alkylated amides with very good enantiomeric excess (Scheme 79). A mixture of DMI (1,3-dimethyl-2-imidazolidinone) and THF as solvent and very mild conditions were used.[333]



Scheme 79 Asymmetric Negishi cross-coupling of of secondary α-bromoamides.

The same conditions could be applied to a second family of reaction partners, racemic secondary benzylic halides which could be coupled in good *ee* and chemical yields.[334]

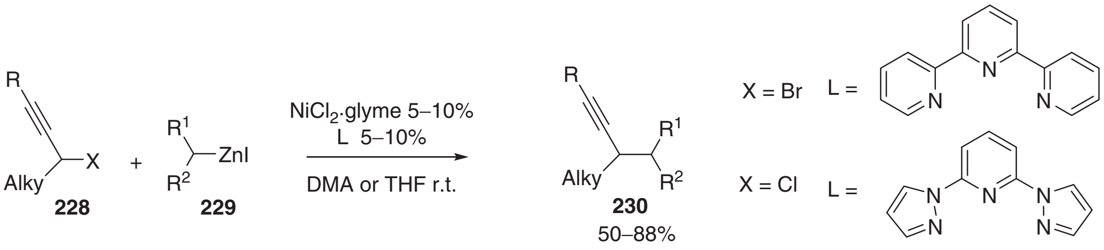
A similar catalytic system was reported for the regioselective asymmetric Negishi cross-coupling of racemic secondary allyl chlorides **227** with readily available organozinc halides.[335] Both symmetrical ($R^1{=}R^3{=}CH_3$) and unsymmetrical allyl chlorides coupled in high yields and with high enantioselectivities. The process was stereoconvergent as the two enantiomers of the racemic substrate were transformed into the same enantiomer of the product with good stereoselectivity (Scheme 80). The method was applied in two-key steps of a formal total synthesis of fluvirucinine A.



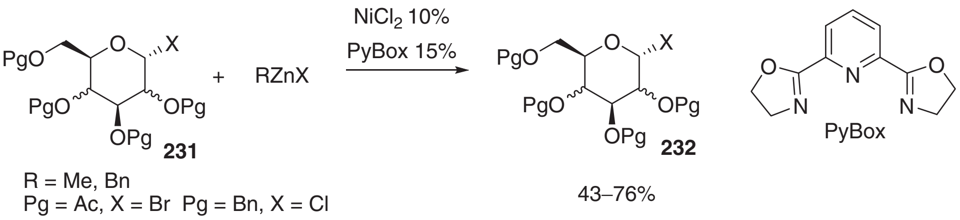
Scheme 80 Negishi cross-coupling with secondary allyl chlorides.

The Ni-catalyzed Negishi cross-coupling between secondary alkylzinc reagents **228** and secondary propargylic bromides and chlorides **229** can be performed at room temperature using a combination of a 10 mol% Ni-complex with tridentate ligands and 10 mol% terpyridine in DMA (Scheme 81)[336] Bulky substituents on the alkyne were found to be crucial to obtain compounds **230** avoiding diyne formation via homocoupling. This methodology has been applied to the formal total synthesis of R-cembra-2,7,11-triene-4,6-diol.

Negishi coupling could be used to synthesize fully oxygenated, fully saturated C-glycosides **232** starting from glycosyl halides **231** and functionalized alkylzinc reagents as reaction partners (Scheme 82).[337] NiCl$_2$ together with unsubstituted PyBox ligands provided good yield of products. In the case of acetyl-protected glycosides, bromine was the preferred living group whereas benzyl-protected ones where best matched to chloride living group. Mannosyl halides were found to be particularly diastereoselective with retention of configuration at C1.

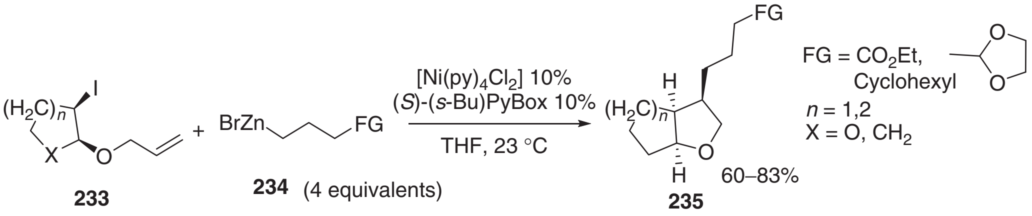


Scheme 81 Negishi cross-coupling between secondary alkylzinc reagents and secondary propargylic halides.



Scheme 82 Synthesis of fully saturated C-glycosides.

Two different C(sp^3)–C(sp^3) bonds could be formed from alkyl iodide and organozinc reagent in a process that is triggered by the formation of radicals in the reaction of iodides with Ni(I) complexes. Alkyl halides are known to undergo oxidative addition to Ni-catalysts via a radical pathway.[338] This led to the successful construction of substituted cyclic ethers **235** via cascade cyclization–cross-coupling reaction.[339] The reaction was carried out using the Ni(py)$_4$Cl$_2$/(S)-*sec*-BuPybox-based catalyst and secondary alkyl bromides and iodides **233** with commercially available alkylzinc bromides **234** at room temperature in good yields (Scheme 83).

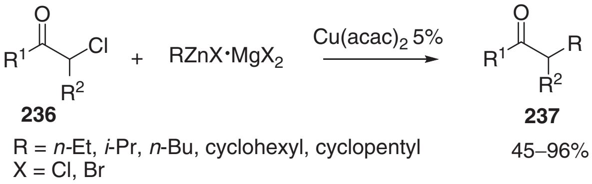


Scheme 83 Synthesis of substituted cyclic ethers via cascade cyclization–cross-coupling reaction.

Mechanistic, experimental, and computational studies support the radical pathway, and that Ni(I) complexes are the catalytically active species. Evidence for a Ni(I) active species in the catalytic cross-coupling of alkyl electrophiles has been reported by isolation of a paramagnetic monomethylated terpyridine complex which was able to promote cross-coupling in the presence of ZnI$_2$. This was proposed to proceed via a single electron transfer from the ligand to the alkyl halide generating an alkyl radical.[340] Further DFT calculations also suggest the involvement of a single-electron process in Ni-catalyzed alkyl–alkyl Negishi couplings showing that the traditional two-electron redox mechanism is energetically unfavorable. Moreover, the halogen atom transfer to the metal center was found to be the rate-determining step.[341]

3.04.5.2.3 Cu-catalyzed transformations

Organozinc halides, generated *in situ* from the corresponding Grignard reagents by reaction with Zn halides, undergo cross-coupling reaction with α-haloketones **236** under Cu catalysis (scheme 84).[342] The procedure represents a general strategy for the



Scheme 84 Cu-catalyzed alkylation of α-chloro ketones.

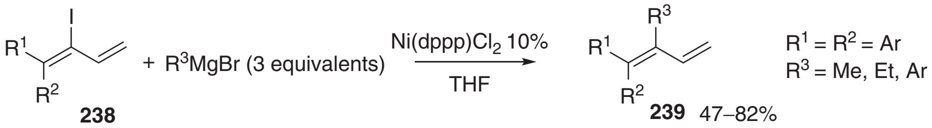
synthesis of α-branched ketones **237**. Secondary zinc reagents can be successfully used providing compounds which would be difficult to access using conventional enolate alkylation. Using optically active chloroketones, enantiomerically enriched substituted ketones have been obtained.

3.04.5.3 Alkylations of Organomagnesium Reagents

3.04.5.3.1 Ni-catalyzed transformations

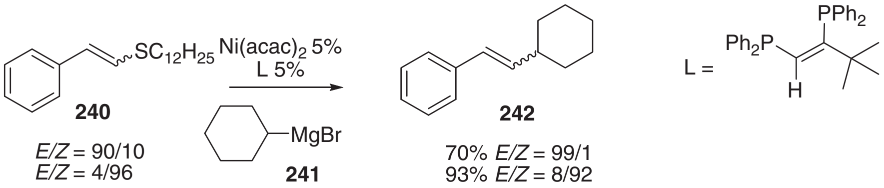
Organomagnesium reagents were first discovered by Grignard in 1900,[343] and since then, they have been a powerful synthetic tool for synthetic organic chemists. Despite their wide use, the main focus of these reagents has remained for long time on nucleophilic addition and substitution reactions, but in 1943 the pioneering work of Kharasch and Fuchs[289] opened the way for using such reagents in cross-coupling reactions. In 1972, Kumada and coworkers[292,344] and Corriu and Masse[291] reported independently the Ni-catalyzed coupling reaction with organomagnesium reagents, demonstrating the synthetic utility of Grignard reagents in cross-coupling reactions and describing the catalytic cycle which has become a model for many Pd-catalyzed cross-coupling reactions. This transformation has come to be known as the Kumada–Corriu cross-coupling. Many applications have been reported, especially where aryl Mg reagents are used,[284] however the modest functional groups tolerance of Grignard reagents has limited their use in synthesis.

C(sp^3)–C(sp^2) Kumada–Corriu cross-coupling has been reported to alkylate vinyl iodides **238** for the synthesis of polysubstituted butadienes **239**. The reaction was carried out in the presence of Ni(dppp)Cl_2 under mild conditions (Scheme 85).[345]



Scheme 85 Synthesis of polysubstituted butadienes via Kumada–Corriu cross-coupling.

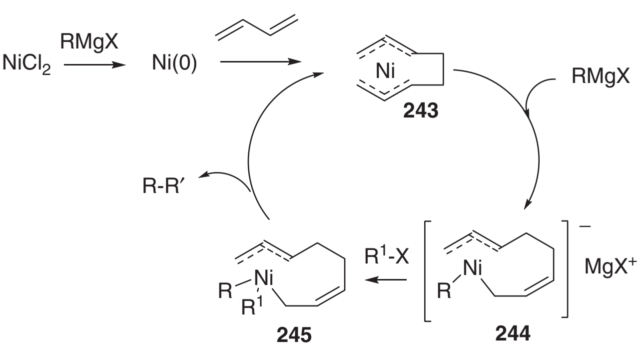
Notably, it was found how the use of a substrate with an isolated double bond resulted only in dehalohydrogenation suggesting that the diene moiety is necessary to promote the Kumada coupling reaction under these conditions. Activation of C (sp^2)–S and C (sp^2)–O bonds has also been reported. For instance, a combination of nickel(II) acetylacetonate and (*Z*)-3,3-dimethyl-1,2-bis(diphenylphosphino)but-1-ene catalyzes cross-coupling reactions of alkenyl–alkyl sulfides **240** with primary and secondary alkyl Grignard reagents **241** (Scheme 86)[346] to give alkenes **242** with retention of the double bond configuration.



Scheme 86 Cross-coupling of alkenyl alkyl sulfides with primary and secondary alkyl Grignard reagents.

It was not until 2002, almost 30 years after the report of Kumada and Corriu, that the first successful Ni catalyzed C(sp^3)–C (sp^3) cross-coupling between alkyl Grignard reagents and alkyl electrophiles was reported by Kambe and coworkers[347] who developed a unique cross-coupling reaction of alkyl halides with organomagnesium reagents using 1,3-butadiene as additive. No phosphine ligands were required and under the optimized conditions using $NiCl_2$ (1–3 mol%) and butadiene (10 mol%), the coupling products were obtained in good to excellent yields at 0 °C in 30 min. Unsubstituted 1,3-butadiene showed the highest activity for this cross-coupling reaction which could be performed also using aryl and secondary alkyl Grignard reagents, or alkyl tosylates and chlorides as coupling partners. The catalytic system was shown to be capable to promote cross-coupling also using organo zinc reagents or Pd as catalyst.[301] This reaction follows a new catalytic pathway which is shown in Scheme 87. $NiCl_2$ is reduced by Grignard reagent to Ni(0) which reacts with 2 equivalents of 1,3-butadiene to afford a bis(π-allyl)–nickel(II) complex **243**. Thus 1,3-butadiene plays an important role to convert Ni(0) to Ni(II) π-complex, which is inert toward organic halides but readily reacts with Grignard reagents to form an anionic complex **244**. Such complex, being coordinatively saturated, does not undergo the β-hydrogen elimination process but reacts with alkyl halides to give dialkylnickel(II) complex **255** from which the coupling product is obtained by reductive elimination.

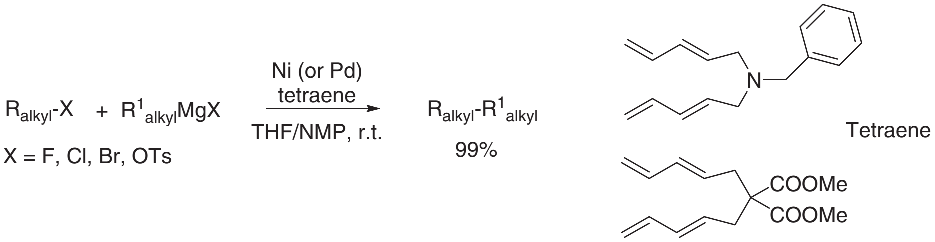
Pd and Ni complex bearing simple allyl ligands were also found to catalyze coupling of alkyl bromides and alkyl tosylates with alkyl Grignard reagents.[348] Two allyl ligands are essential in this case to obtain high yields of the coupling product. DFT calculations were performed on a model substrate for Ni(allyl)$_2$-catalyzed cross-coupling suggesting the existence of a weak but



Scheme 87 Catalytic pathway of butadiene-activated Ni catalyzed Kumada–Corriu cross-coupling.

persistent interaction between Mg and the allyl moiety throughout the catalytic cycle. Oxidative addition is proposed to be the turnover-limiting step, and competing β-hydride elimination is confirmed to be much higher in energy compared to reductive elimination.[349]

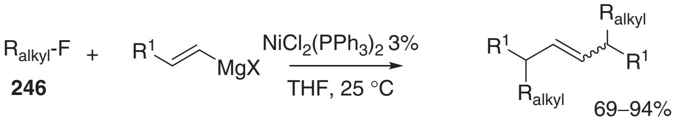
The same catalytic system allowed to disclose the first example of C–C bond forming reaction using nonactivated alkyl fluorides, a class of compound which are recognized as very inert substrates due to their strong C–F bond.[350] The use of copper salts as additives was necessary in order to achieve high yields. The efficiency of cross-coupling of alkyl fluoride with Grignard reagents was further improved using 1,3,8,10-tetraene as additive (Scheme 88). High yields were thus obtained using of only 0.6 mol% of Ni catalyst and 15 mol% of 1,3,8,10-tetraene.[351]



Scheme 88 Cross-coupling of alkyl fluoride with Grignard reagents.

The catalytic system was efficient also with bromides, chlorides, and tosylates and using primary or secondary alkylzinc reagents in the presence of $MgBr_2$. Several functional groups were tolerated in these reaction conditions.

Ni-catalyzed alkylative dimerization of vinyl Grignard with alkylfluorides **246**, under mild conditions was also reported (Scheme 89).[352] The reaction proceeds exclusively in the case of alkyl fluorides whereas the corresponding chlorides, bromides, and iodides undergo reduction, elimination or cross-coupling with vinyl Grignard reagents, demonstrating the superiority of alkyl fluorides as alkylating agents in this condition.

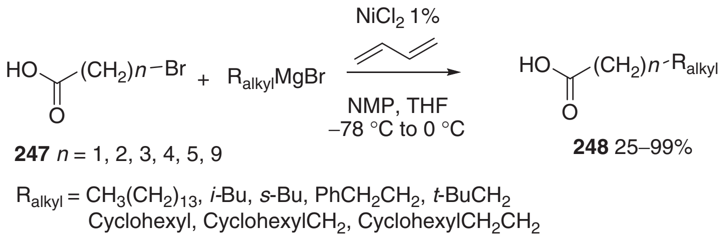


Scheme 89 Alkylative dimerization of vinyl Grignard with alkylfluorides.

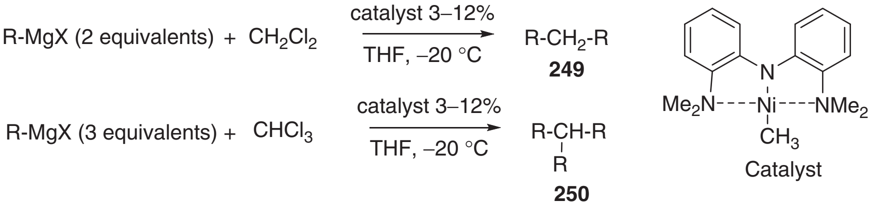
A good functional group tolerance was also found by the use of catalytic amounts of nickel salt and 1,3-butadiene in the primary and secondary alkyl Grignard reagents cross-coupling with alkyl bromides, iodide and tosylates, amide, ester or ketone moieties.[353] The reaction is carried out in mild conditions and provides a practical method for the construction of functionalized carbon chains. As an interesting application of this procedure a convenient and efficient one-pot procedure for the construction of carbon framework of fatty acids **248** using alkyl bromides that contain a carboxy functionality **247** as substrates has been reported, in combination with an *in situ* protection procedure (Scheme 90).[354]

The cross-coupling reaction proceeds efficiently and various fatty acids have been prepared. The regioisomers of elaidic acid were synthesized through an iterative cross-coupling procedure.

A Ni-catalyzed Kumada–Corriu coupling using a pincer amido-bis-(amine) ligand was reported in 2008 by Hu and coworkers who observed an unusual reaction of CH_2Cl_2 and $CHCl_3$ with *n*-BuMgBr to give the dialkylated **249** or trialkylated products **250**, respectively[355] (Scheme 91).



Scheme 90 Synthesis of fatty acids using carboxy alkyl bromides.



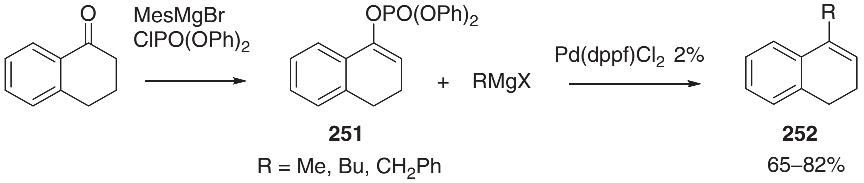
Scheme 91 Pincer amido-bis-(amine) ligand for Ni-catalyzed Kumada–Corriu coupling.

The reaction involves cleavage of up to three C–Cl bonds to form three new C–C bonds at the same carbon center and is proposed to follow a radical pathway. The scope of this reaction was further extended to include other alkyl Grignard reagents. Long chain primary alkyl Grignard reagents could be successfully coupled. Good yields were obtained for the coupling of primary and secondary alkyl mono iodides and chlorides using this pincer Ni complex.[356] The complex was also effective for a highly efficient and mild catalytic coupling of nonactivated and functionalized alkyl bromides and iodides, including esters, amides, ethers, acetals, ketones.[357]

3.04.5.3.2 Pd-catalyzed transformations

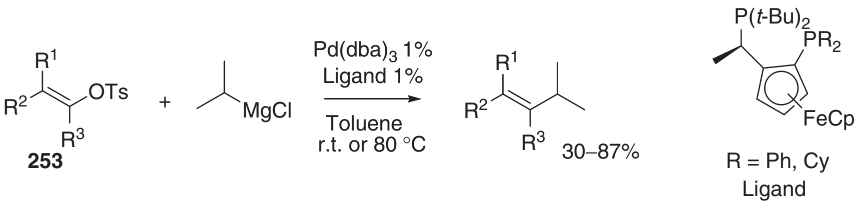
Pd-catalyzed cross-coupling reactions using alkyl Grignard reagents are limited. This could be due to the high reactivity of alkyl Mg reagents and to the higher tendency of Pd alkyl species to undergo β-hydride elimination if compared with the corresponding Ni species.

C(sp^3)–C(sp^2) cross-coupling was reported using enolphosphonates **251** and Grignard reagents. Phosphonates were formed *in situ* from the corresponding ketones (Scheme 92) and Pd(dppf)Cl$_2$ was used as catalyst.[358] Good yield were reported in the alkylation of 3,4-dihydronaphthalen-1(2H)-one **252**.



Scheme 92 C(sp^2)–C(sp^3) cross-coupling with enolphosphonates.

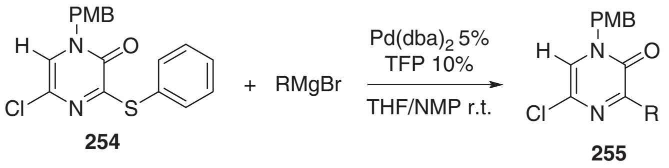
Vinyl tosylates **253** can also be coupled in the presence of an electron-rich phosphine as ligand (Scheme 93).[359]



Scheme 93 C(sp^2)–C(sp^3) cross-coupling with vinyl tosylates.

Previous couplings of aryl and vinyl sulfonates have been conducted predominantly with triflates, but in this case the less expensive and more easily handled tosylates could be reacted under mild conditions.

Pd-catalyzed desulfinative Kumada cross-coupling was used for generating a library of 3-alkylated-2-(H)-pyrazinones **255** (**Scheme 94**) from the corresponding thiovinylethers **254** using the electron-rich trifurylphosphine (TFP) (**Figure 6**) as ligand. In this case the catalytic system was better performing compared with Fe or Ni catalysts.[360]



R = CH_2CH_3 (63%), $(CH_2)_7CH_3$ (68%)

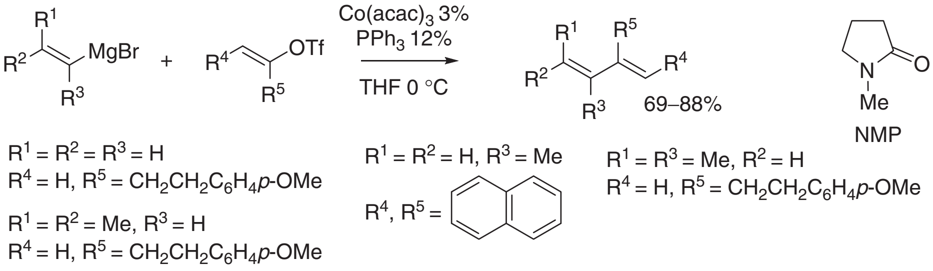
Scheme 94 Synthesis of substituted 2-(H)-pyrazinones.

The first Pd-catalyzed C(sp^3)–C(sp^3) coupling with alkyl Grignard was reported in 2003 by Kambe and coworkers.[361] Likewise to the nickel-catalyzed transformation 1,3-butadiene as ligand was found crucial for obtaining good yields. Interestingly Pd-catalyzed reaction was found to be selective when chloro alkyl tosylates were used as substrates by reacting exclusively with tosyl leaving group. Recently the same group has demonstrated that Ni- and Pd-containing perowskites, $LaFe_{0.8}Ni_{0.2}O_3$ (LFNO) and $LaFe_{0.95}Ni_{0.05}O_3$ (LFPO) can be used as useful catalyst sources for the cross-coupling of primary alkyl halides or tosylates with Grignard reagents in the presence of dienes. LFNO showed slightly higher reactivity than LFPO. The reaction is catalyzed by trace amount of Ni or Pd in solution leached by perowskites. Very high TON (107) were found and the remaining bulk perowskite could be reused.[362]

3.04.5.3.3 Co-catalyzed transformations

Cobalt-catalyzed cross-coupling reactions have received particular attention in the middle of the 20th century. The scope of these reactions is different from that of the Pd- and Ni-mediated procedures, for instance, they are very efficient for the elaboration of C(sp^2)–C(sp^2). Good results have also been obtained in the arylation of alkyl Mg reagents. Such reactions have been recently reviewed[363] and will not be reported herein.

Very few C(sp^2)–C(sp^2) cross-coupling reaction have been described. One example was reported by Cahiez using an alkenyl Grignard reagents and alkenyl halides in the presence of $CoCl_2$ and *N*-methylpyrrolidone (NMP) which gave stereospecifically the corresponding pure *trans* diene in moderate yield.[364] Recently the cobalt-catalyzed cross-coupling between alkenyl triflates and alkenyl Grignard reagents was described. Good yields were obtained from *α*-monosubstituted or *α*,*β*- and *β*,*β*-disubstituted alkenyl Grignard reagents in the presence of PPh_3 as ligand (**Scheme 95**).[365]



$R^1 = R^2 = R^3 = H$
$R^4 = H, R^5 = CH_2CH_2C_6H_4p\text{-}OMe$

$R^1 = R^2 = Me, R^3 = H$
$R^4 = H, R^5 = CH_2CH_2C_6H_4p\text{-}OMe$

$R^1 = R^2 = H, R^3 = Me$
$R^4, R^5 =$

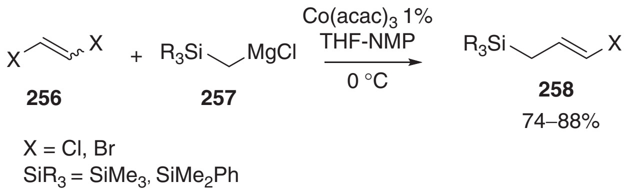
$R^1 = R^3 = Me, R^2 = H$
$R^4 = H, R^5 = CH_2CH_2C_6H_4p\text{-}OMe$

Scheme 95 C(sp^2)–C(sp^2) Co-catalyzed cross-coupling with alkenyl triflates.

C(sp^3)–C(sp^2) bond formation using vinyl electrophiles and alkyl Grignard reagents has been more developed. After the discovery[364] that the use of NMP as co-solvent allows to couple stereospecifically alkenyl iodides, bromides and chlorides in high yields, the procedure has been applied to the synthesis of several olefins. The coupling of silylated Grignard **257** reagents with 1,2-dihalogenoethylenes **256** was reported.[366] As previously shown,[364] the formation of the disubstituted products was not observed (**Scheme 96**). Stereodifferentiation between (*E*)- and (*Z*)-1,2-dihaloethylene is possible, thus reacting an excess of a mixture of (*E*)- and (*Z*)-1,2-dibromoethylene the only product recovered is the (*E*)-1-bromoalkene.

The reaction has been extended to the very efficient synthesis of differently substituted allylsilanes **258** by reaction of *α*- or *β*-monosubstituted or *β*,*β*-disubstituted vinylhalides.[367]

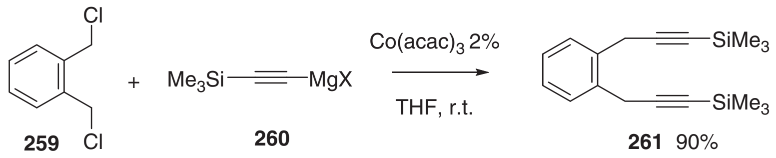
Alkylation of acetylenic Grignard reagents allows C(sp)–C(sp^2) or C(sp)–C(sp^3) bond formation and has been performed efficiently under Co catalysis using ethynylmagnesium halides. Moderate to excellent yields are obtained in the benzylation with



X = Cl, Br
SiR$_3$ = SiMe$_3$, SiMe$_2$Ph

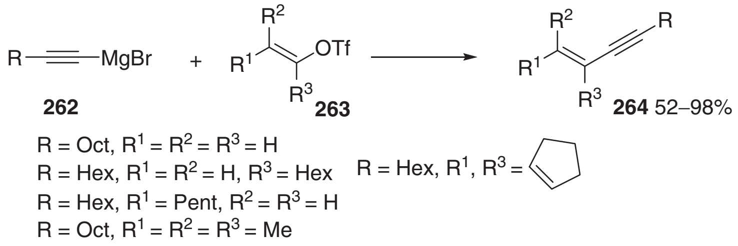
Scheme 96 Co-catalyzed cross-coupling of silylated Grignard reagents with 1,2-dihalogenoethylenes.

benzyl bromides or chlorides with trimethylsilylmagnesium halides **260**, even in the presence of *ortho* substituents.[368] The reaction allowed the preparation of diynes **261** from 1,2-bis(chloromethyl)benzene **259** (Scheme 97).



Scheme 97 Synthesis of diynes from 1,2-bis(chloromethyl)benzene.

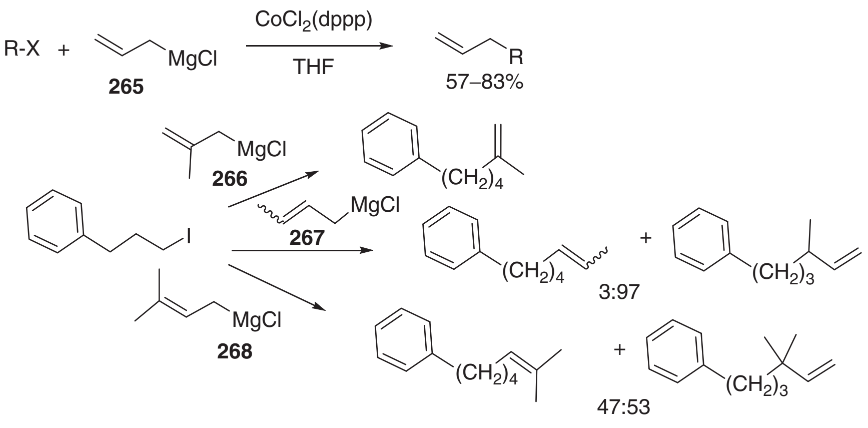
The cobalt-catalyzed coupling between alkynylmagnesium **262** halides and alkenyl triflates **263** has been described.[369] Good to excellent yields of ene-ynes **264** were obtained from a wide range of substrates (Scheme 98). No additional ligands were used in this case. Some examples of chemoselective couplings in the presence of an alkenyl, an alkyl, or an aryl bromide are reported.



R = Oct, R^1 = R^2 = R^3 = H
R = Hex, R^1 = R^2 = H, R^3 = Hex
R = Hex, R^1 = Pent, R^2 = R^3 = H
R = Oct, R^1 = R^2 = R^3 = Me
R = Hex, R^1, R^3 =

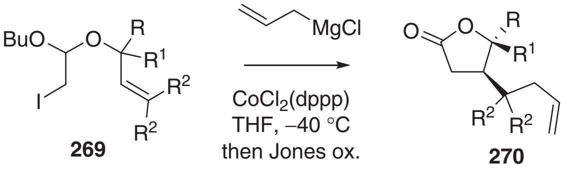
Scheme 98 C(sp)–C(sp^2) cross-coupling between alkynylmagnesium halides and alkenyl triflates.

In recent years excellent procedures have been developed for coupling reactions involving alkyl halides, since decomposition by *β*-hydrogen elimination of alkyl-cobalt intermediates is not a limitation. Thus, alkylation of alkylmagnesium reagents has been exploited for C(sp^3)–C(sp^3) bond formation. An important contribution in this area was given by Oshima. In 2002 he reported the Co-catalyzed cross-coupling between unactivated alkyl halides and allyl Grignard reagents **265** in the presence of dppp (Figure 6) as ligand.[370] Not only primary alkyl halides but also secondary and tertiary alkyl halides undergo allylation, in the latter case to give quaternary carbon centers (Scheme 99). With substituted allyl Grignard reagents **266–268** the regioselectivity was found to be highly dependent on the structure of the allyl moiety.



Scheme 99 Co-catalyzed cross-coupling between unactivated alkyl halides and allyl Grignard.

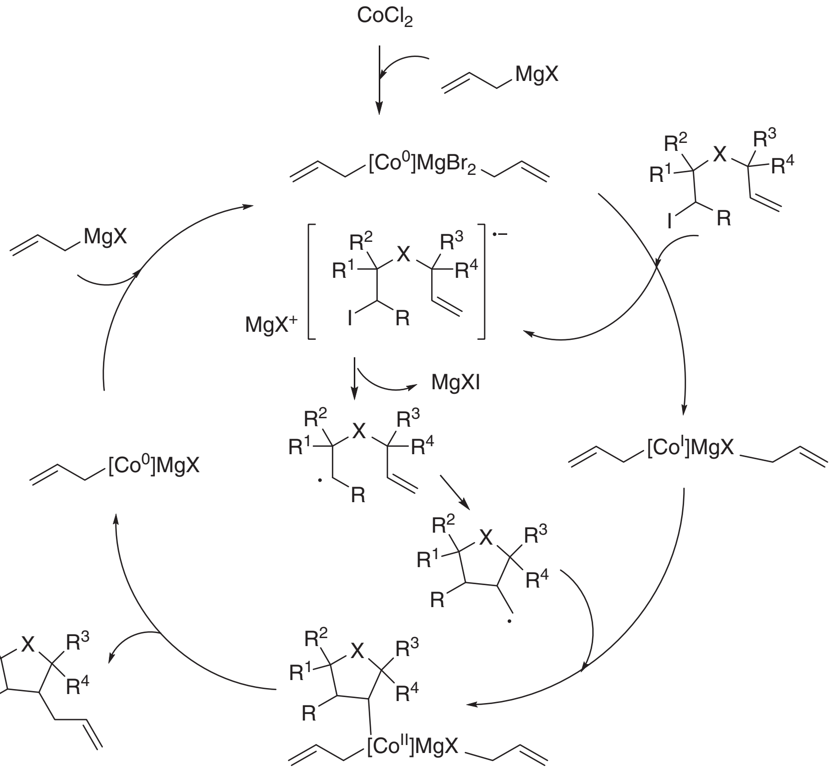
The cobalt-mediated transformation proceeds via a radical pathway allowing an interesting application in the tandem cyclization/allylation cascade reaction. Some 3-butenyl-substituted lactones **270** (Scheme 100) have been obtained from ε-unsaturated alkyl halides **269** through this pathway.



R = R^1 = R^2 = H; 77%
R = R^1 = Me, R^2 = H; 100%
R = R^1 = H, R^2 = Me; 98%
R = Pentyl, R^1 = R^2 = H; 77%

Scheme 100 Synthesis of 3-butenyl-substituted lactones via tandem cyclization/allylation reaction.

The mechanism proposed for such transformation is shown in Scheme 101.



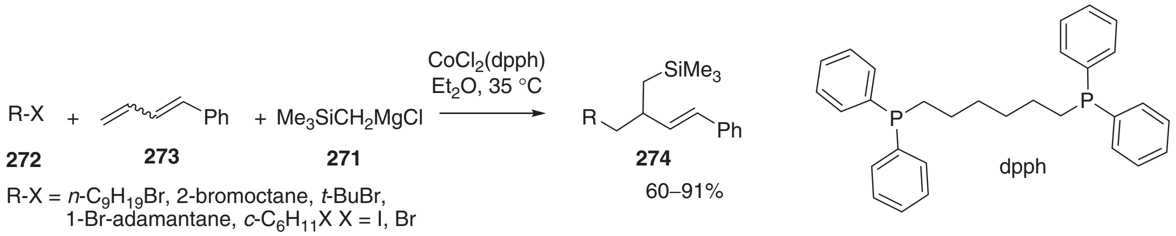
Scheme 101 Mechanism proposed for the tandem cyclization/allylation reaction.

Similar conditions were used also to perform the cross-coupling between alkyl halides and benzyl Grignard reagent.[371]

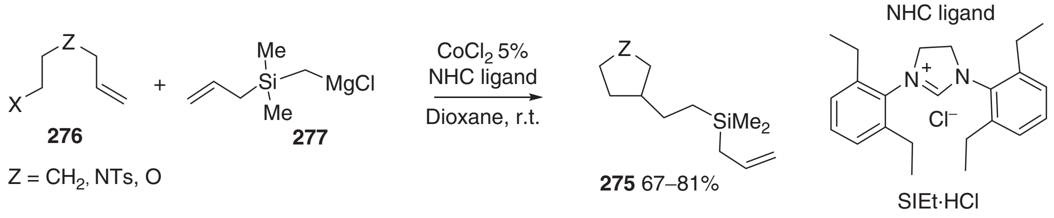
Trimethylsilylmethyl-,[372] ethenyl, and ethynylmagnesium reagents[373] have been investigated. Unactivated secondary as well as primary halides can be employed as substrates. Sequential cyclisation/alkenylation or alkynylation are reported. Trimethylsilylmethyl Grignard reagent **271** was also employed in a cobalt-catalyzed three-component coupling with alkyl bromides **272** and 1,3-dienes **273**.[374] Among the ligands that were examined, 1,6-bis(diphenyl)phosphino hexane (dpph) provided the best yields of compounds **274** (Scheme 102). Primary, secondary, and tertiary bromides could be used. The presence of functional groups on the dienes is well-tolerated.

Cobalt-catalyzed cross-coupling reactions of alkyl halides with Grignard reagents and sequential intramolecular cyclization were reported to proceed only with the aid of NHC ligands. Good yields of silylated compounds **275** were obtained starting from differently substituted **276** and allyldimethylsilylmethylmagnesium chloride **277**. The latter was chosen in consideration of the importance of this silyl moiety as a hydroxy equivalent (Scheme 103).[375]

In 2008 Cahiez reported the first example of cobalt-catalyzed chemoselective alkyl–alkyl coupling reaction. The best results were obtained by adding TMEDA and LiI and that was the first example of the beneficial influence of iodide anion in such reactions. Secondary and tertiary alkyl Grignard could not be used.[376]



Scheme 102 Three-component coupling with alkyl bromides, 1,3-dienes and trimethylsilylmethyl Grignard reagent.

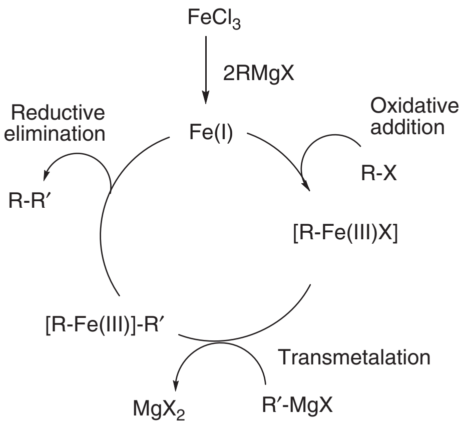


Scheme 103 Cross-coupling and intramolecular cyclization with cobalt(II) chloride and NHC ligands.

3.04.5.3.4 Fe-catalyzed transformations

Since the first report by Koichi and coworkers[377] describing the coupling of vinyl bromides with alkyl Grignard reagents catalyzed by $FeCl_3$, the use of cheap, nontoxic, and environmentally benign iron compounds as catalysts in Kumada–Corriu cross-couplings has received a great interest, motivated by the search of 'greener' and cheap catalysts. Both C(sp^2)–C(sp^2) and C(sp^3)–C(sp^2) couplings have been obtained in synthetically useful yields, especially those involving arylation of aryl and alkyl Grignard reagents. The latter reactions have been reviewed and will not be discussed here.[378,379]

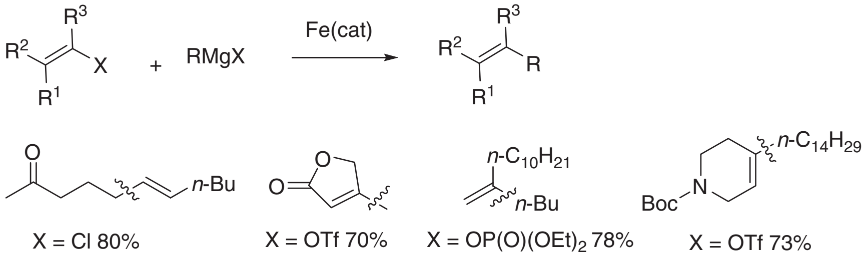
Successful C(sp^3)–C(sp^2) bond formation was reported employing tris(dibenzoylmethido)Fe(III) as the catalyst[380] and the proposed reaction mechanism implies the catalytically active Fe(I) species which is formed *in situ* by reduction of Fe(III) with 2 equivalents of RMgX. The resulting Fe(I) species undergoes oxidative addition of R-X followed by transmetalation with RMgX to give a dialkyl–Fe(III) intermediate which upon reductive elimination yields the coupling product and regenerates the catalyst (Scheme 104). Recently, Norrby and coworkers supported this mechanism by computational studies. The authors found unfavorable thermodynamics for reductive elimination of Fe(II) to Fe(0), whereas the energy barrier for reductive elimination in the case of Fe(III) to Fe(I) was only 10 kJ mol^{-1}. Moreover, the energy barrier for reductive elimination of Fe(II) to Fe(0) was found to be extremely high.[381]



Scheme 104 Proposed reaction mechanism for Fe-catalyzed Kumada–Corriu cross-coupling.

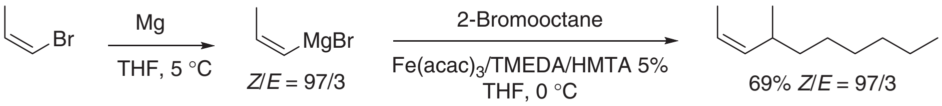
Almost 30 years passed from the original report before the development of synthetically useful protocols. In 1989 Cahiez reported that the reaction of a vinyl bromide with octylMgBr in the presence of 3 mol% $Fe(acac)_3$ in THF afforded stereospecifically the desired alkene in good yields in the presence of *N*-methyl-2-pyrrolidinone (NMP) as a cosolvent.[382] In addition to alkenyl halides, related electrophiles such as alkenyl sulfones, sulfides, phosphates, and triflates are also suitable coupling partners

(Scheme 105).[383–385] In some cases a TMEDA–HMTA mixture (HTMA=hexamethylenetetramine) replaced NMP as additive. The iron-catalyzed bond formation usually works better than the uncatalyzed addition of the Grignard reagent to other electrophilic sites in the substrate, thus rendering functional groups such as esters, ketones, enones, carbamates, or acetals compatible.



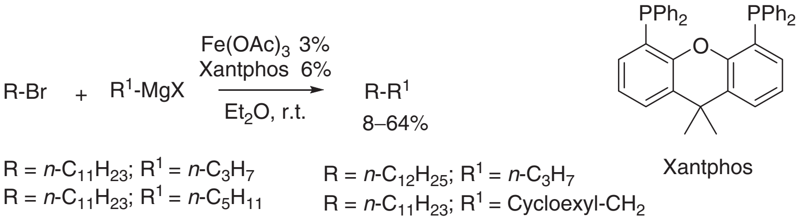
Scheme 105 Iron-catalyzed $C(sp^2)$–$C(Sp^3)$ bond formation with alkenyl electrophiles.

$FeCl_3$ was found to catalyze efficiently cross-coupling reactions between various alkyl halides and alkenyl Grignard reagents in the presence of TMEDA.[386] Secondary alkyl halides could be used successfully, moreover the conditions used are compatible with the presence of polar functional groups on the substrate. The first Fe-catalyzed cross-coupling between alkenyl Grignard reagents and secondary alkyl halides was described in 2007 by Cahiez,[387] using $Fe(acac)_3$–TMEDA–HMTA in a 1:2:1 ratio (Scheme 106). Very mild conditions are required and the reaction is highly stereo- and regioselective.



Scheme 106 $C(sp^2)$–$C(sp^3)$ bond formation with secondary alkyl halides.

A careful optimization of the ligand and reaction conditions was necessary until appropriate conditions were found to allow iron-catalyzed $C(sp^3)$–$C(sp^3)$ cross-coupling of Grignard reagents with unactivated alkyl electrophiles. In 2007, Chai and coworkers found that using $Fe(OAc)_2$ in the presence of Xantphos various alkylbromides could be coupled with alkyl Grignard reagents in moderate yields (Scheme 107).[388]



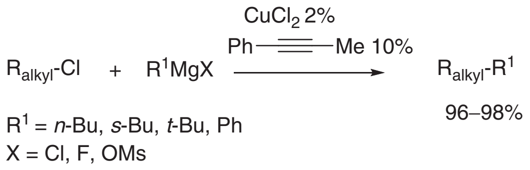
Scheme 107 $C(sp^3)$–$C(sp^3)$ Fe-catalyzed cross-coupling with unactivated alkyl electrophiles.

The reaction is proposed to proceed via a radical pathway. However, the mechanism of iron-catalyzed alkyl–aryl cross-coupling remains largely unknown. Evidence has accumulated that radical intermediates may play a role, at least in certain cases. Whether this is general, however, remains to be elucidated. In contrast with the catalytic cycle proposed by Kochi (Scheme 104), Furstner et al. proposed recently a catalytic cycle in which the active catalytic specie is formally in the -2 oxidation state. A full account concerning this studies has been recently reported.[389]

3.04.5.3.5 Cu and Zn-catalyzed transformations

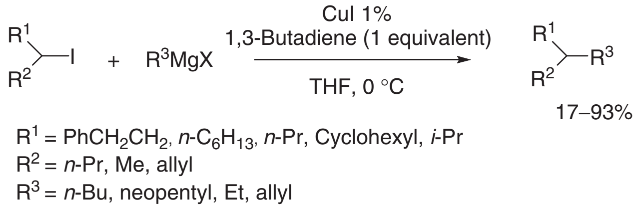
The formation of C–C bonds by alkylation of organocopper reagents has been extensively studied and is considered a classical tool in organic synthesis leading to high yields and chemoselectivity.[390] However, such reagents present some disadvantages, especially for large-scale applications. The more attractive alternative is the Cu-catalyzed alkylation of Grignard reagents.[391] In 2000, Cahiez et al. reported that the presence of NMP dramatically improves the yield and chemoselectivity of such reaction when alkyl bromides or iodides are used. The reaction is carried out with primary alkyl bromides and *n*-BuMgCl, *t*-BuMgCl or *i*-PrMgCl using 4 equivalents of NMP and 3 mol% of Li_2CuCl_4. Secondary and tertiary alkyl halides do not react in these conditions.[392] Later on Kambe and coworkers reported that the Cu-catalyzed cross-coupling reaction of nonactivated alkyl fluorides could be performed under mild conditions in the presence of 1,3-butadiene.[350] More recently the same group has reported the first example of a

Cu-catalyzed cross-coupling reaction using alkyl chlorides, which are very useful alkylating agents because of their wide availability and low cost. The procedure requires the presence of 1-phenylpropyne as additive.[393] The reaction can also be performed using alkyl fluorides, mesylates and tosylates (Scheme 108).



Scheme 108 Cu-catalyzed cross-coupling reaction with alkyl chlorides.

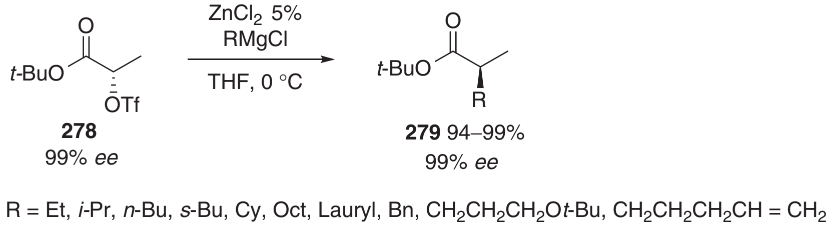
Although the role of the additive in this reaction has not been fully clarified, it is possible that the coordination of the alkyne to the Cu(I) species prevents the decomposition of the thermally unstable of the alkylcopper intermediate formed by exchange with Mg. As a further development of such reaction, copper-catalyzed coupling reaction of alkyl Grignard reagents with secondary alkyl iodides has been developed by the same group. In this case CuI was used as catalyst together with 1,3-butadiene as an additive.[394] A variety of substrates were reacted to give the coupling products in good yields (Scheme 109).



Scheme 109 Cu-catalyzed cross-coupling reaction with secondary alkyl iodides.

The method was applied to the synthesis of 1,*n*-dienes o enynes.

A zinc-catalyzed stereospecific C(sp^3)–C(sp^3) coupling has been recently reported.[395] Readily available enantiomerically pure *α*-hydroxyesters **278** were coupled with primary, secondary acyclic and secondary cyclic Grignard reagents in mild conditions (Scheme 110) to give *α*-alkylated esters **279** in excellent yields with complete inversion of configuration.



Scheme 110 Zn-catalyzed Stereospecific C(sp^3)–C(sp^3) coupling of enantiomerically pure *α*-hydroxyesters.

α-Hydroxy esters with linear, *β*-branched alkyl chains or benzyl substituents could be used. Protected hydroxyl and ester functional groups are tolerated.

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3.05 Polyene Cyclizations

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3.05.1 Introduction 268
3.05.2 Brønsted Acid-Catalyzed Cyclizations 268
3.05.2.1 Lewis Acid-Assisted Brønsted Acid (LBA)-Mediated Cyclizations 269
3.05.2.2 Lewis Base-Assisted Brønsted Acid (LBBA)-Mediated Cyclizations 270
3.05.3 Epoxide-Based Openings 272
3.05.3.1 Use of Enol Silane Terminating Groups in Synthesis 272
3.05.3.2 Use of Other Terminating Groups in Epoxide-Based Polyene Cyclizations 274
3.05.3.3 Unusual Transformations 275
3.05.4 Other Functional Groups for Initiation 276
3.05.5 Metal-Mediated Polyene Cyclizations 278
3.05.5.1 Polyene Cyclizations onto Simple Olefins 278
3.05.5.2 Heck-like Reactions of Polyenes 279
3.05.5.3 Reactions of Alkynes 280
3.05.6 Halonium-Initiated Cyclizations 284
3.05.6.1 Iodonium-Initiated Cyclizations 284
3.05.6.2 Bromonium- and Chloronium-Initiated Cyclizations 284
3.05.6.3 Asymmetric Halonium-Initiated Cyclizations 285
3.05.7 Radical-Initiated Cyclizations 287
3.05.7.1 Cyclizations of 1,3-Dicarbonyl Compounds 287
3.05.7.2 Other Modes of Radical Activation 288
References 291

3.05.1 Introduction

Ever since the polycyclization of terpenes through electrophilic activation was first explored in the middle of the twentieth century as a means to synthesize steroids (among other frameworks), these processes have captivated the attention of the synthetic community as a tool of unique power, one capable of rapidly and stereoselectively forging molecular complexity. Indeed, as evidenced by the previous polyene cyclization chapter in the first edition of this volume,[1] as well as several recent and excellent review articles,[2] chemists have been able to develop myriad variants of the general reaction process based on the initiating group, alkene/alkyne patterning within the cyclization substrate, and the ultimate terminating group, accessing diverse materials as a result. In some cases, these events may have biomimetic relevance, whereas in others they reflect solely the creativity and ingenuity of the chemists who developed them based on patterns of reactivity that should result based on first principles when reagents of appropriate chemoselectivity are applied.

Given the wealth of coverage of this process, particularly in terms of the key factors which determine the ring size, stereochemistry (as governed largely by the Stork–Eschenmoser hypothesis), and functional patterning of products based on the mode of specific initiation and chain termination, the goal of this chapter is to focus specifically on recent advances made in the polyene cyclization field in the past 15 years. Indeed, as the ensuing sections will reveal, chemists have been able to develop several highly novel variants of the process, particularly in terms of chiral reagents and catalysts, that are reaching (and in some cases potentially exceeding) levels of selectivity that nature can accomplish with enzymes. Moreover, new activating groups and reagents have been added to the repertoire of available tools, allowing for highly productive metal- and halonium-mediated cyclizations, among others, that were not previously achievable even in a racemic sense. Finally, entirely distinct mechanistic modes outside of the traditional electrophilic activation pathway, such as radical chemistry, have been explored as well as means to access similar frameworks; in some cases, these approaches offer products with altered stereocontrol, ring size, and/or order of ring formation. However, it should be noted that many frontiers remain, and it is hoped that this chapter might inspire the solutions needed to further extend the profound synthetic power of cation-π chemistry into new realms.

3.05.2 Brønsted Acid-Catalyzed Cyclizations

Chemists have long known that nature can deploy 'cyclase' enzymes to deliver a proton selectively to the terminal olefin of polyisoprenoids, forming complex, polycyclized products as single enantiomers as a result. One significant example of such a process is the bacterial conversion of squalene into hopene.[2e] Inspired by such events, synthetic chemists, too, have utilized such

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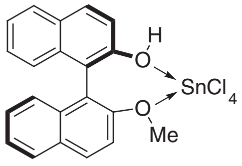
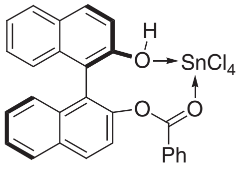
proton-initiated cyclizations with unfunctionalized polyene starting materials to fashion an array of materials. Of note, though, the majority of these efforts have proceeded to deliver racemic products. Indeed, it is only in the previous decade that simple synthetic tools have begun to compete with the power of Nature's cyclases and afforded laboratory examples of enantioselective, proton-induced polyene cyclizations. Given the small size of a proton that exists even when it is associated with its conjugate base and the high conformation flexibility of most substrates, it should not be too surprising that asymmetric protonation has proven challenging to achieve. In this section, we will cover recent examples of the chiral form of this chemistry, highlighting the critical design elements and synthetic tools that have taken this polyene cyclization variant to its current, powerful state.

3.05.2.1 Lewis Acid-Assisted Brønsted Acid (LBA)-Mediated Cyclizations

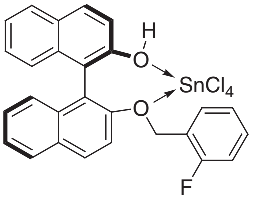
Many of the early, and critical, discoveries in the area of enantioselective proton-induced cyclizations were pioneered by Yamamoto. In a series of seminal publications, his research team showed that the coordination of a chiral Brønsted acid to a Lewis acid, species termed as 'LBAs,' possesses the capability to serve as artificial cyclases and enantioselectively protonate appropriate polyenes. Several examples of such complexes are shown below (**1**–**4**), where in each the coordination of a chiral 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) derivative to a Lewis acid such as tin(IV) chloride both constricts the conformational flexibility of the O–H bond within a chiral surrounding and increases the acidity of that proton.



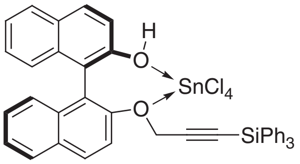
1: (*R*)-BINOL-Me•SnCl$_4$



2: (*R*)-BINOL-Bz•SnCl$_4$



3: (*R*)-BINOL-*o*-FBn•SnCl$_4$



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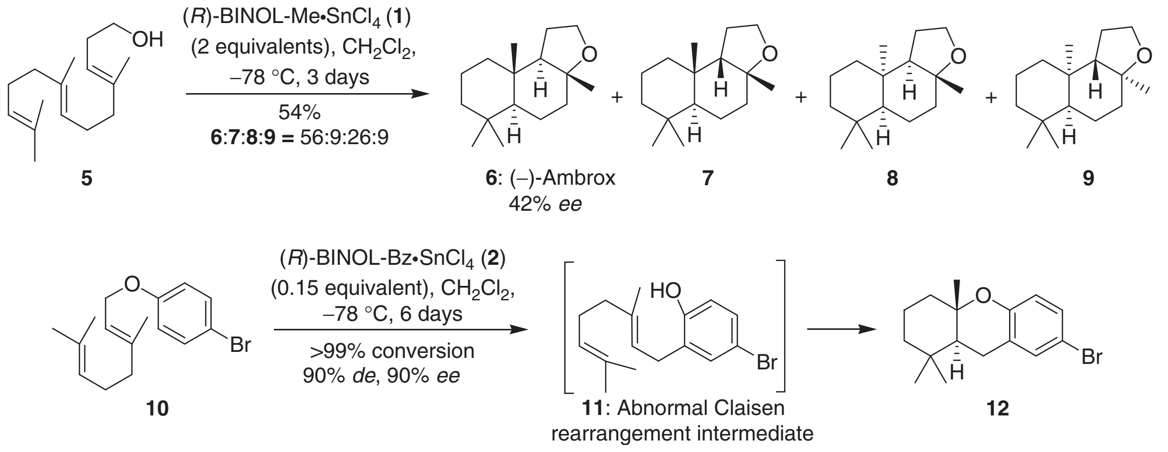
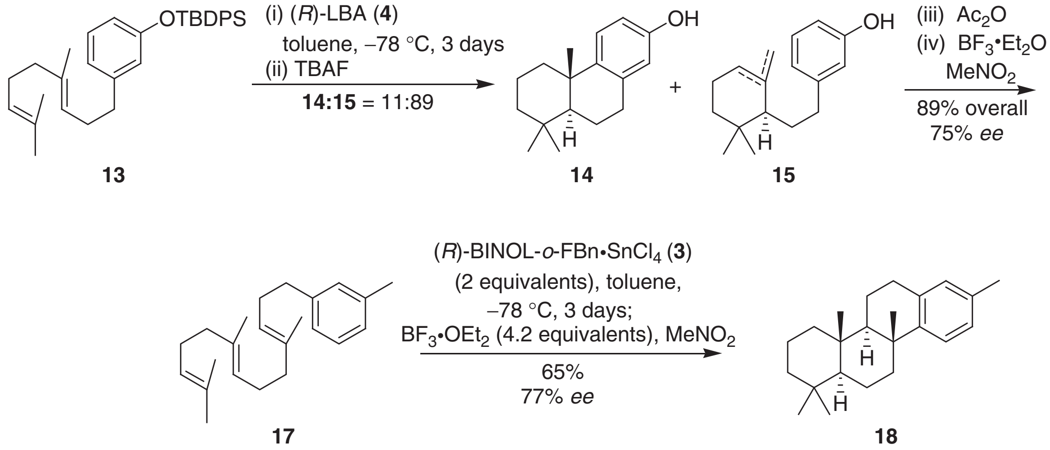
The earliest examples of LBA-initiated cyclizations showed that geranyl alcohols and *o*-geranyl phenols could be efficiently cyclized using stoichiometric loadings of LBA, favoring *trans*-fused products with modest enantioselectivity.[3] The promising utility of these reagents was showcased in a total synthesis of enantioenriched (–)-ambrox (**6**, Scheme 1), a relatively popular synthetic target due to its use in the fragrance industry. As indicated, it was the major product formed from the cyclization of **5**, obtained in 42% *ee* along with a few other diastereoisomers (**7**–**9**) using LBA **1**. Interestingly, catalytic amounts of LBA **2** have also been shown to effect the cyclization of geranyl phenolic ethers such as **10** to give the same products as *o*-geranyl phenols with much higher enantioselectivity and overall selectivity for *trans*-fused products; mechanistically, however, this process is a distinct one, likely proceeding first via an abnormal Claisen-rearrangement followed by the key polyene cyclization step.



Scheme 1

Enantioselective bi- and tricyclizations of polyolefins terminated by aromatic rings can also be achieved with LBA complexes, though generally these reagents are not sufficient to drive the material to complete cyclization (i.e., form more than one ring), as evidenced by the conversion of **13** (Scheme 2) into a mixture of **14** and **15** favoring the latter material using **4**.[4] Fortunately, such mixtures can usually be converted into fully cyclized products in an additional step, one typically involving a final diastereoselective cyclization promoted either by a protic or Lewis acid (such as $BF_3 \cdot Et_2O$). The latter was utilized in this case, with the mixture of **14** and **15** being converted into **16** in 89% overall yield and 75% *ee*. It is worth noting here that acetate protection of the phenol proved critical in ensuring that the initial enantioselectivity set by LBA **4** translated into diastereoselective formation of **16** in the final cyclization of **15**, thereby enabling this material to be eventually converted into (+)-podocarpa-8(14)-en-13-one, a versatile synthetic intermediate (structure not shown) for accessing multiple terpenes. The same overall approach was used in the total synthesis of **18**, a natural product isolated from Tasmanian tasmanite sediment, with high efficiency (65% yield) and enantioselectivity (77% *ee*).[5] Previous synthetic efforts toward this target by Corey et al. utilized a chiral epoxide at the terminus of the polyene chain to initiate the cyclization event, affording an alcohol functionality which had to be removed postcyclization[6]; thus, the ability to effect a direct, enantioselective proton-based cyclization, as likely achieved in nature, afforded a more efficient solution to this particular challenge.



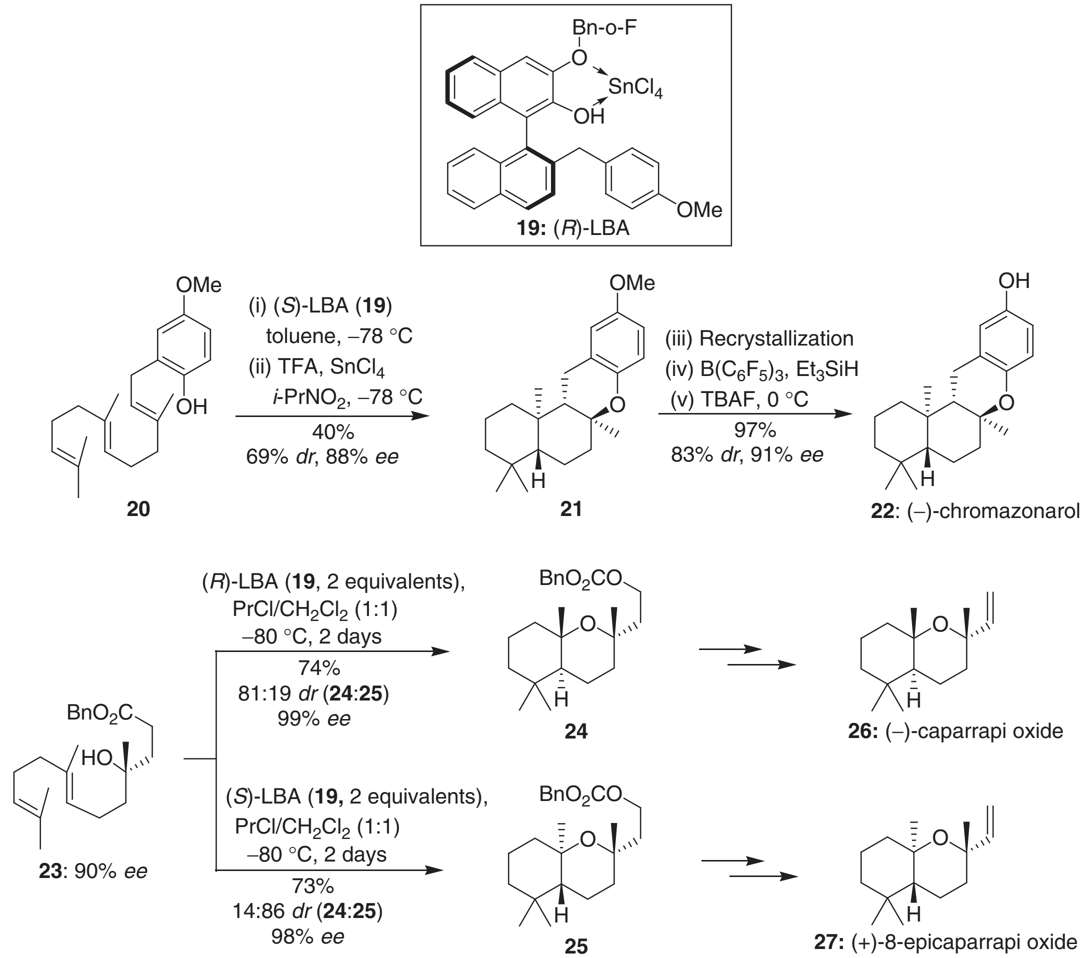
Scheme 2

Critical to the success of these processes in terms of enantioselection, however, is the nature of the terminating group. Indeed, initial efforts to use BINOL-derived LBA complexes to effect similar polyene cyclizations terminated by alcohols or phenols tended to provide only modest stereoselectivity, likely due to these functionalities effecting undesired and/or nonproductive coordination with the Lewis acid. Fortunately, it was found that catechol-derived LBA complex **19** (Scheme 3), which has a tighter five-membered coordination sphere, could efficiently cyclize polyenes terminated by a nucleophilic alcohol group as well as by arenes to form tri-, tetra-, and pentacyclic structures with improved enantioselectivity.[7] For example, this reagent was used to efficiently cyclize **20** to **21** in a two-step sequence with moderate diastereoselectivity and in 88% *ee*. Subsequent recrystallization afforded enhanced optical purity with a final deprotection of the aromatic methyl ether affording (–)-chromazonarol (**22**) in excellent yield. Interestingly, LBA **19** also proved capable of enantiodifferentiation when starting materials containing chiral centers were used.[8] For instance, starting with enantioenriched **23**, the separate enantiomers of LBA **19** favored different stereoisomers with nearly matched levels of overall control, revealing its ability in this case to effectively override any substrate bias. This ability was exploited in an elegant and enantiodivergent synthesis of (–)-caparrapi oxide (**26**) and (+)-8-epicaparrapi oxide (**27**) from a common intermediate.

3.05.2.2 Lewis Base-Assisted Brønsted Acid (LBBA)-Mediated Cyclizations

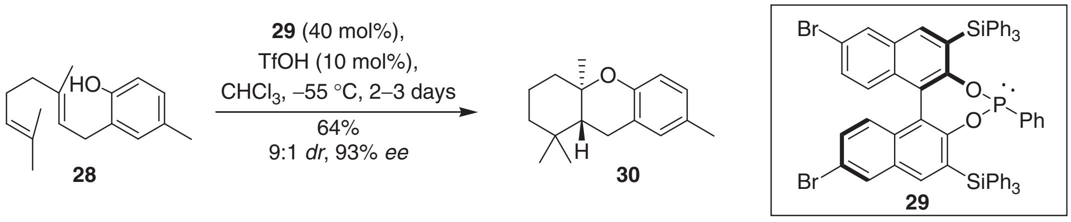
Although LBA-promoted cyclizations clearly have great power, there is certainly room for additional solutions to this problem. In this vein, Ishihara and coworkers have developed a related, but distinct, group of chiral phosphorous(III) Lewis basic complexes; these materials combine species such as **29** (equation 1) with an achiral Brønsted acid like TfOH to form chiral phosphonium salts that are capable of catalyzing biomimetic cyclizations of *o*-geranyl phenol derivatives.[9] Such complexes are termed chiral LBBAs, with the cyclization of **28** to **29** being representative of the power of these reagents where *trans*-fused products are typically obtained with high enantioselectivity. In this case, the result was an overall yield of 64% for **30**, generated with 9:1 *dr* and 93% *ee*.

Yet, despite the enormous successes of chiral LBA and LBBA complexes that have been registered to date, several challenges still remain in effecting asymmetric proton-initiated polyene cyclizations. Most notably, nearly all available techniques require multiple days at cryogenic temperatures to reach completion, and enantioselectivity seems to plateau consistently at, and more typically below, 90% *ee*. Additionally, as already noted on several occasions, the bi-, tri-, and higher-order cyclizations of polyenes terminated by aryl rings usually requires an additional step to forge the final rings, one not necessarily compatible with all functional groups. In a recent effort to address these issues, Corey and coworkers discovered that a chiral BINOL complex ligated to $SbCl_5$ (i.e., **32**, equation 2) is capable of cyclizing polyenes with high yields and stereoselectivity.[10] Key, though, is that this reagent leads to reaction times that are of the order of hours (at – 78 °C) and there is no need for a terminating treatment with a protic or Lewis acid to close the final ring system. In fact, (*R*)-*o*,*o*-dichloro BINOL•$SbCl_5$ (**32**) proved capable of fully cyclizing

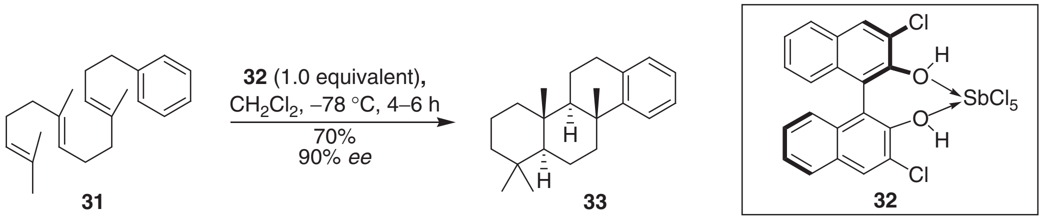


Scheme 3

several substrates containing both electron-rich as well as unactivated aryl rings with excellent diastereoselectivity in upwards of 70% yield and 84–92% *ee*. Other Lewis acids screened with this ligand showed much slower reaction times and diminished enantioselectivity. The efficiency of the ideal complex (i.e., **32**) can be explained by the fact that $SbCl_5$ is both a bulkier and stronger Lewis acid than $SnCl_4$, and time will tell what additional advantages this design has for this and related classes of polyene cyclizations.



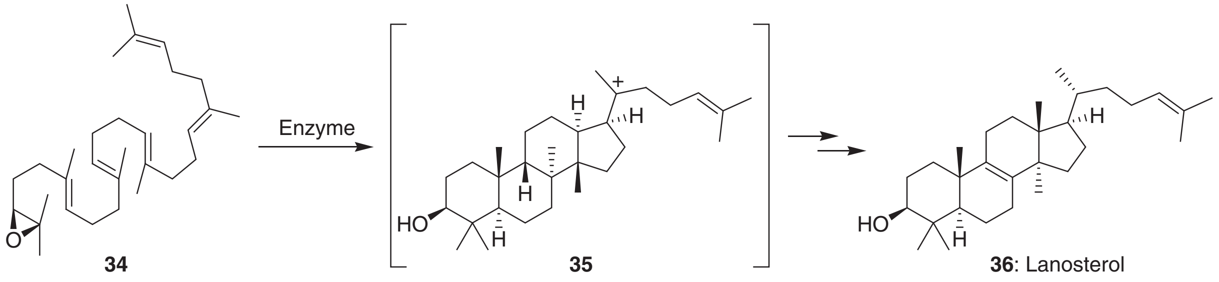
(1)



(2)

3.05.3 Epoxide-Based Openings

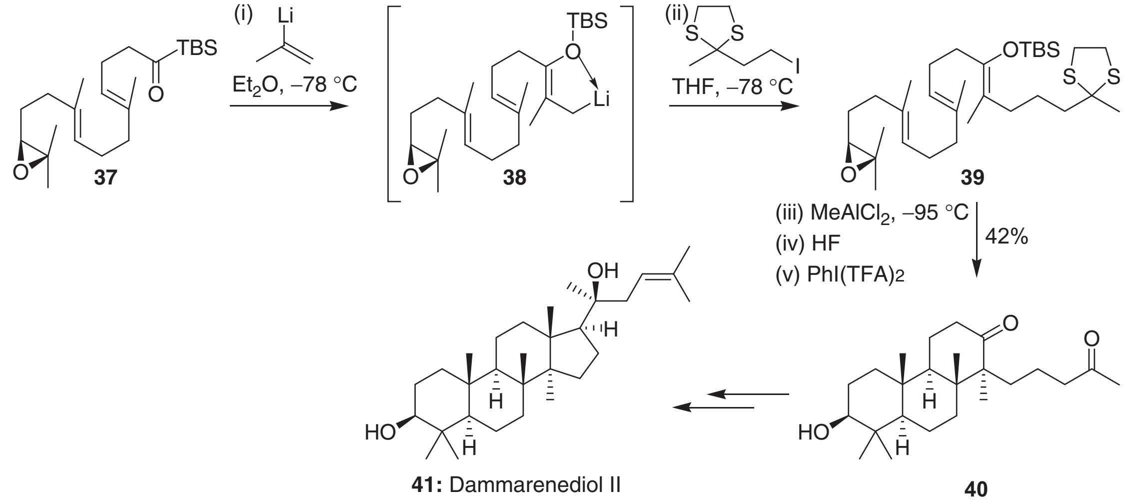
Outside of proton-based cyclizations, the one-step cyclization of 2,3-oxidosqualene (**34**) to lanosterol (**36**) by epoxidosqualene cyclase as shown in equation 3 is an equally elegant and key step in the biosynthesis of various steroids.[2e] Many examples of such activation and subsequent cyclization exist in nature, and the process has certainly been honed for numerous and significant applications. As such, it is of little surprise that events such as these have also inspired synthetic chemists to utilize the same key transformation in their own efforts at biomimicry, and excellent results have been achieved.



(3)

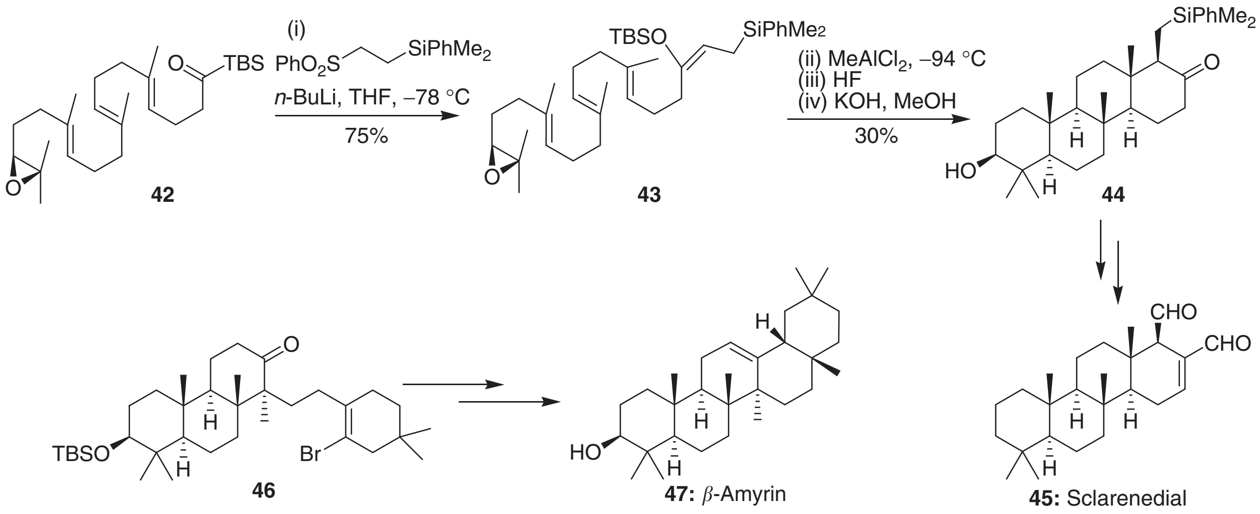
3.05.3.1 Use of Enol Silane Terminating Groups in Synthesis

Critical for the ability of organic chemists to match Nature's stereoselective oxidation ability with enzymes has been the array of well-developed tools that allow for similar asymmetric epoxidation of olefins in a laboratory flask in a highly enantio- and diastereoselective manner (whether direct or through multistep processes such as asymmetric dihydroxylation, leaving group formation, and cyclization). Yet, with this problem of initial prefunctionalization largely solved through a number of methodological advancements, one longstanding challenge in terms of the polyene cyclization step, at least in a biomimetic fashion for tricyclizations of squalene derivatives without the aid of enzymes, is the tendency for the C-ring to be generated in a five-membered form rather than the needed six-membered alternative. In the mid-1990s, Corey et al. developed a solution to this problem in Markovnikov selectivity by terminating the tricyclization with a nucleophilic enol silane, one that ensured six-membered ring formation.[11,12] An example of this process is shown in Scheme 4, where the chiral epoxide within starting material **37** had been formed via an enantioselective dihydroxylation reaction followed by selective mesylation and epoxide formation. Subjecting that acyl silane (**37**) to a novel three-component addition/Brook-rearrangement/substitution sequence afforded (*Z*)-enol silane **39** in 60% overall yield. Subsequent cyclization using Me_2AlCl as a Lewis acid, followed by silyl deprotection and hydrolysis of the dithiane group, yielded tricyclic **40** in 42% overall yield with high stereoselectivity. Because of the well-designed orientation of functional groups as a result of the creative termination of the sequence, the resultant material was readily elaborated to dammarenediol II (**41**), the primary product of the cyclization of 2,3-epoxidosqualene in plants.



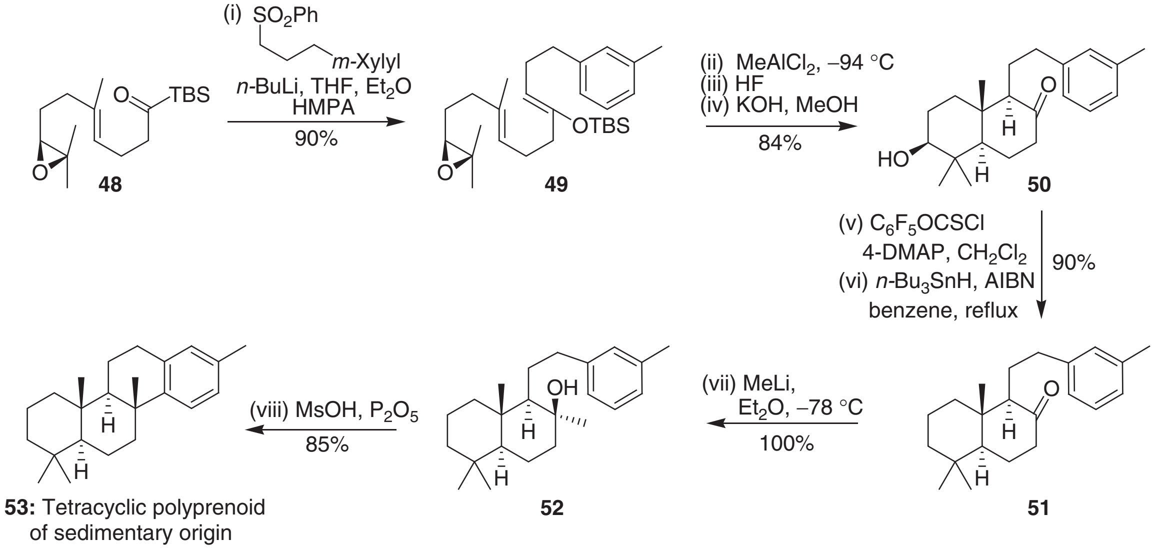
Scheme 4

Use of an enol silane terminating group has also proven useful in the direct synthesis of structures containing more than three rings. For instance, compound **43** (Scheme 5, synthesized using a similar three-component sequence as above) underwent tetracyclization on exposure to Me_2AlCl.[13] Subsequent selective silyl deprotection and equilibration of the stereocenter adjacent to the carbonyl completed the synthesis of **44** in 30% overall yield. Further elaboration of this key intermediate through standard reactions yielded sclarenedial (**45**). It is noteworthy in this synthesis that the chiral epoxide was strategically used as a functional handle to govern both the enantio- and diastereoselectivity of the cation-π cyclization, but that the resultant alcohol was later removed from the product by radical deoxygenation.



Scheme 5

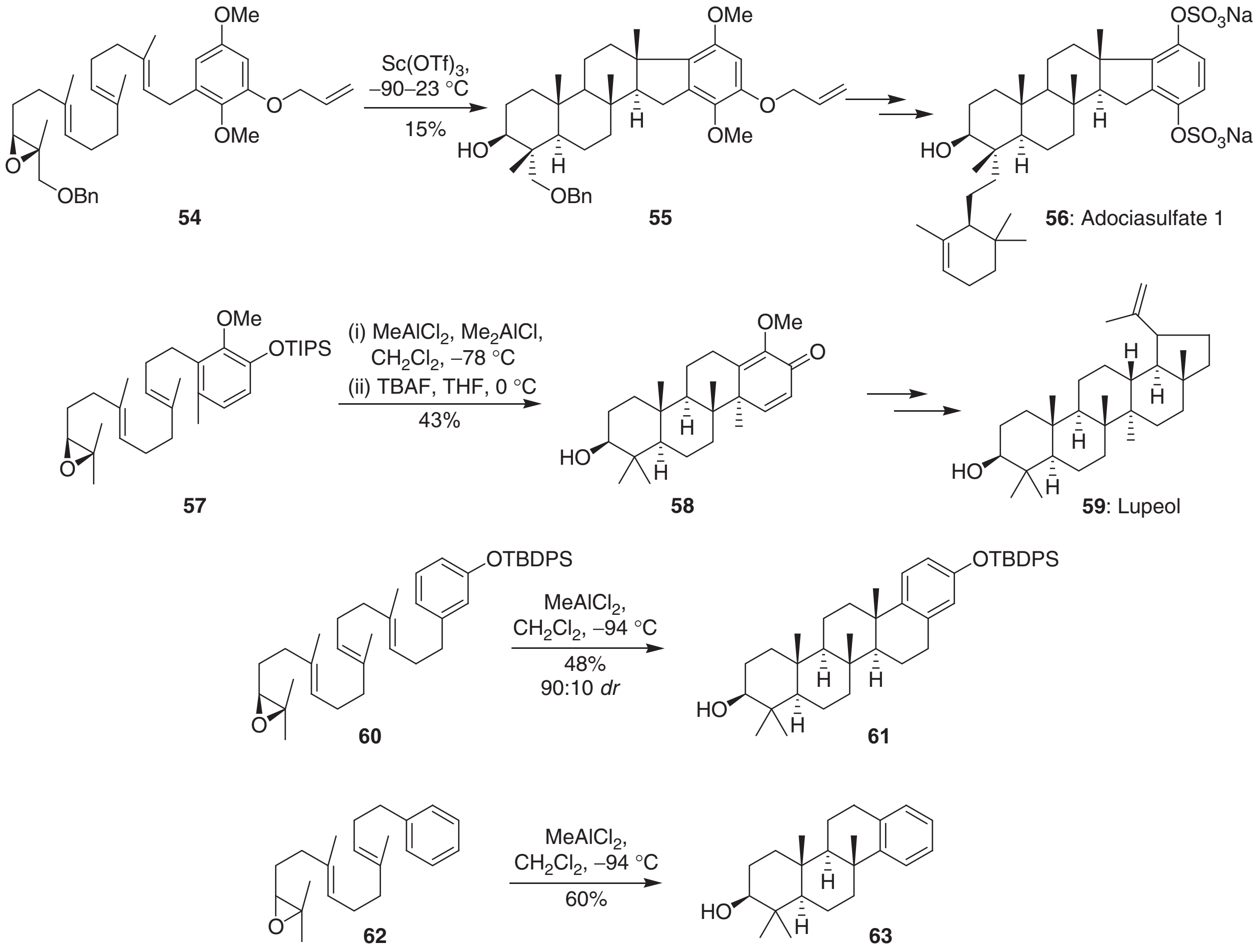
Several additional variants on this overall theme have enabled the Corey group to prepare a number of additional complex targets from the final cyclization materials, using either similar aldol condensation chemistry as deployed to forge the final ring system of dammarenediol II[11] (**41**, cf. Scheme 4), cross-coupling chemistry as used to access β-amyrin (**47**)[14] from **46**, or as shown in more detail in Scheme 6, electrophilic aromatic substitution to access a tetracyclic natural product of sedimentary origin (**53**) following the formation of **52**.[6]



Scheme 6

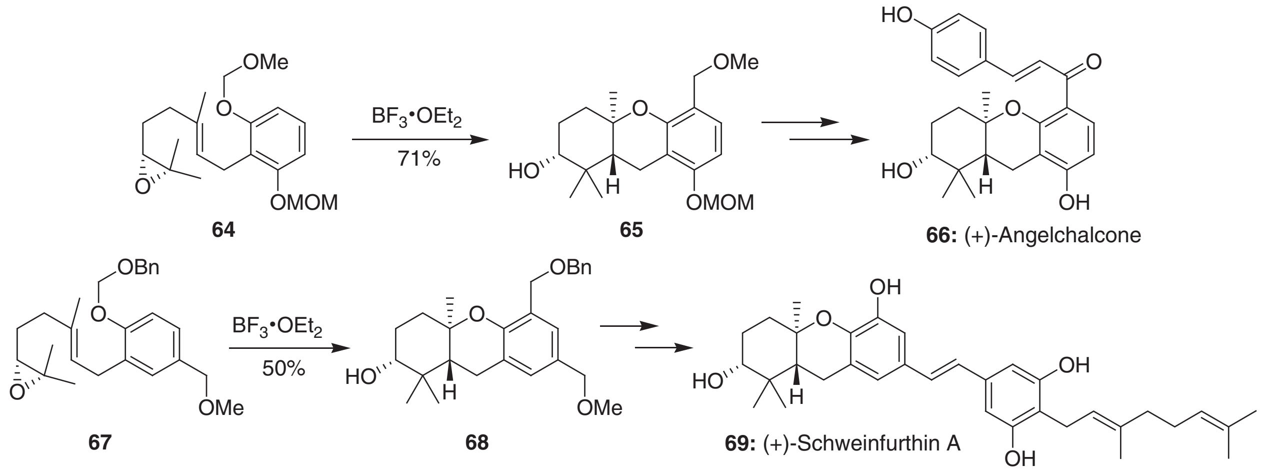
3.05.3.2 Use of Other Terminating Groups in Epoxide-Based Polyene Cyclizations

Recent work has also shown that terminating groups for epoxide opening-initiated polyene cyclizations can include aryl rings and styrenyl alkenes. For instance, the Overman group used an epoxide-initiated tetracyclization terminated by an aryl ring in an enantioselective synthesis of adociasulfate 1 (**56**, Scheme 7), a kinesin motor protein inhibitor extracted from the *Haliclona* family of sea sponges.[15,2d] In this work, the chiral epoxide group within **54** was readily installed in 95% *ee* using a standard Sharpless asymmetric epoxidation procedure. Subsequent exposure of **54** to $Sc(OTf)_3$ then afforded pentacycle **55** in 15% yield (accounting for an impressive 62% yield per step in this cyclization cascade), where the electron-donating phenyl allyl ether proved essential for the completion of the final cyclization; in its absence, only mixtures of partially cyclized products were obtained. Equally interesting, the use of Me_2AlCl, a stronger and more commonly used Lewis acid for epoxide opening cascades, gave only trace **55** ($<5\%$) in this case. Nevertheless, this result may be substrate specific, given that Corey and coworkers have shown that Me_2AlCl is, in fact, capable of initiating epoxide opening of certain tri- and tetracyclizations terminated by arenes or styrenyl olefins.[16] In the case of tricyclizations, both activated and unactivated arenes efficiently proceeded to the desired products in high yield; such methodology is shown in Scheme 7 through three examples, including the enantioselective synthesis of lupeol (**59**).[17]



Scheme 7

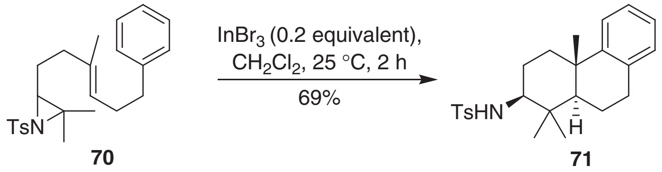
Outside of these events, where arguably the anticipated (or standard) product was formed in each case as long as the right initiator was used, Wiemer et al. have recently reported an interesting cascade reaction where unexpected products were cleanly formed instead due to rearrangement chemistry. These cases all involved $BF_3 \cdot Et_2O$-catalyzed epoxide opening-based cyclizations terminated by a phenolic acetal; here, hydrolysis of that acetal moiety generated a potent carbon-based electrophile that was trapped via electrophilic aromatic substitution. The first example where this alternate terminating pathway was observed occurred in the cyclization of **64** terminated by a methoxymethyl ether protected phenol, which delivered aromatic acetal **65** in 71% yield.[18] Elaboration of this key intermediate then enabled the total synthesis of (+)-angelichalcone (**66**) in 21% overall yield; arguably, it would have been difficult to imagine how such a domain might have otherwise been incorporated with such efficiency on this framework had this rearrangement not occurred during the polyene cyclization. Further exploration revealed that this acetal-based process has some generality and could also extend to BOM-protected intermediates, with **67** being efficiently cyclized to give hexahydroxanthine derivative **68** in 50% yield.[19] In this case, this intermediate served as a key synthon by which to ultimately access (+)-schweinfurthin A (**69**) in a stereoselective manner by converting that new alkyl group into a phenol (Scheme 8).



Scheme 8

3.05.3.3 Unusual Transformations

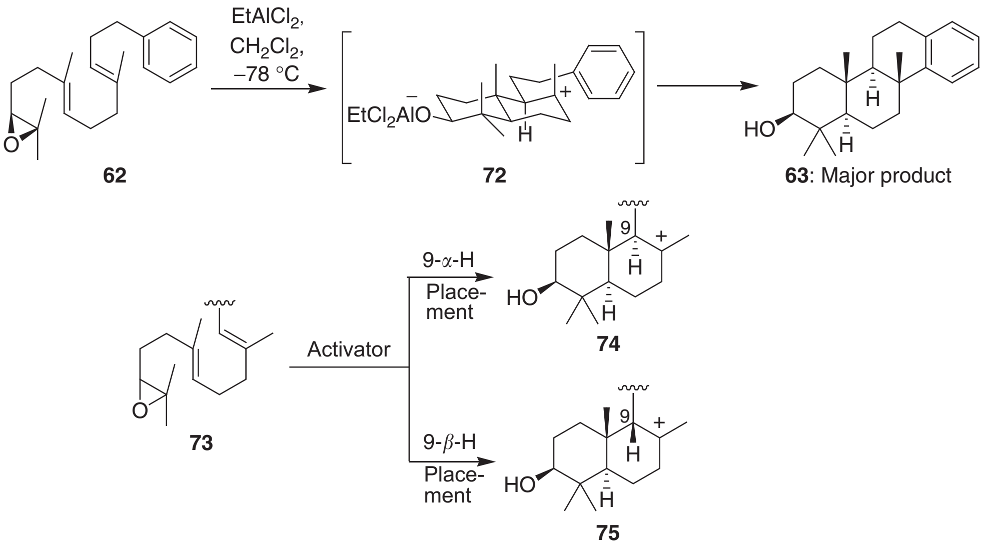
Finally, it is worth noting as well that the general principles of epoxide-based polyene cyclizations have been extended in a few cases to aziridine-opening cascade reactions as well.[20] It was Loh et al. who reported the first example of such a reaction in 2009, showing cases where aziridine opening as initiated by $InBr_3$ at ambient temperature led to bi- and tricyclizations of polyenes with high efficiency and diastereoselectivity. In contrast to most examples of epoxide openings where stoichiometric loadings of Lewis acid are needed to effect complete conversion, it is worth noting that in these cases (such as the conversion of **70** to **71**, equation 4) catalytic loadings of Lewis acid proved sufficient.



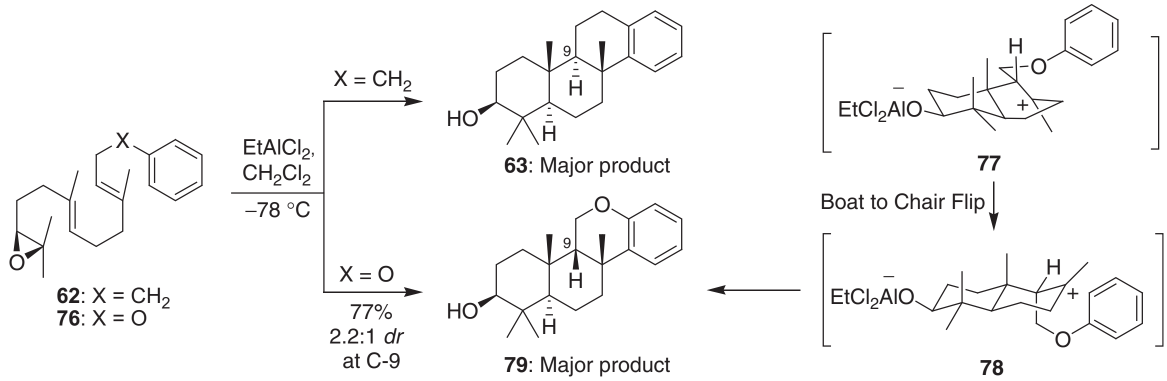
(4)

Before ending this section, however, the authors of this chapter would be remiss if they fail to note a key component of the stereochemistry observed within typical epoxide-based frameworks following cyclization, one which might appear to be a subtlety, but one which is of potential significance if additional frameworks are to be accessed through such processes. The facet is that although the *trans–anti-trans* geometry of **63** obtained from the Lewis acid catalyzed tricyclization of **62**[16] is commonly observed in the case of polyprenoids containing all *E*-configured olefins (resulting from an all chair-like transition state such as **72**), this outcome is not universal. Indeed, based on the orientation of the olefin involved in the formation of the second ring (B ring), two modes of cyclization (9-α-H and 9-β-H) are possible.[21] In principle, appropriate understanding of the subtleties in how π-facial selectivity in B-ring formation is determined could enable one to access either material, at will, from the same starting point (Scheme 9).

Recent work by Corey et al. has provided a key discovery along this direction, one which showed that the generally favored 9-α-H pathway as observed in the cyclization of **62** can actually be switched to favor the 9-β-H transition state by replacing the benzylic carbon with oxygen, allowing access to bent polycycles. Presumably, the initial cyclization proceeds through a boat-like transition state in the B-ring, which is followed by a ring flip converting **77** to **78**, ultimately yielding **79**. This phenomenon appears to be general for reactions of phenolic ethers, likely due to participation of the oxygen lone pairs in influencing π-facial selectivity. Although this result is preliminary, further understanding of what determines π-facial selectivity in cation-induced polyene cyclizations may lead to greater reaction control and access to natural products once thought difficult and/or impossible to obtain via laboratory-based polyene cyclizations executed without enzymes (Scheme 10).



Scheme 9

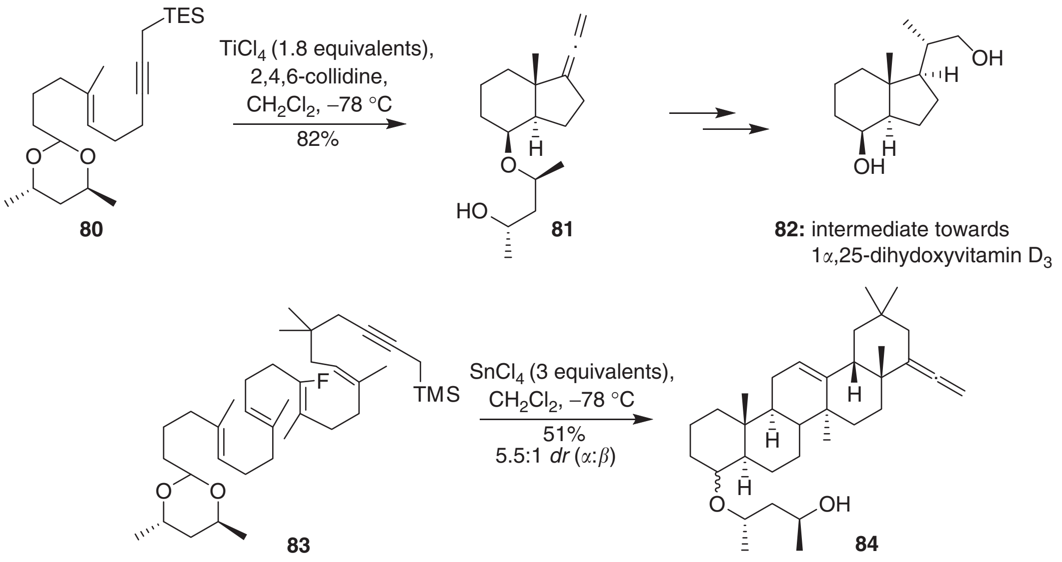


Scheme 10

3.05.4 Other Functional Groups for Initiation

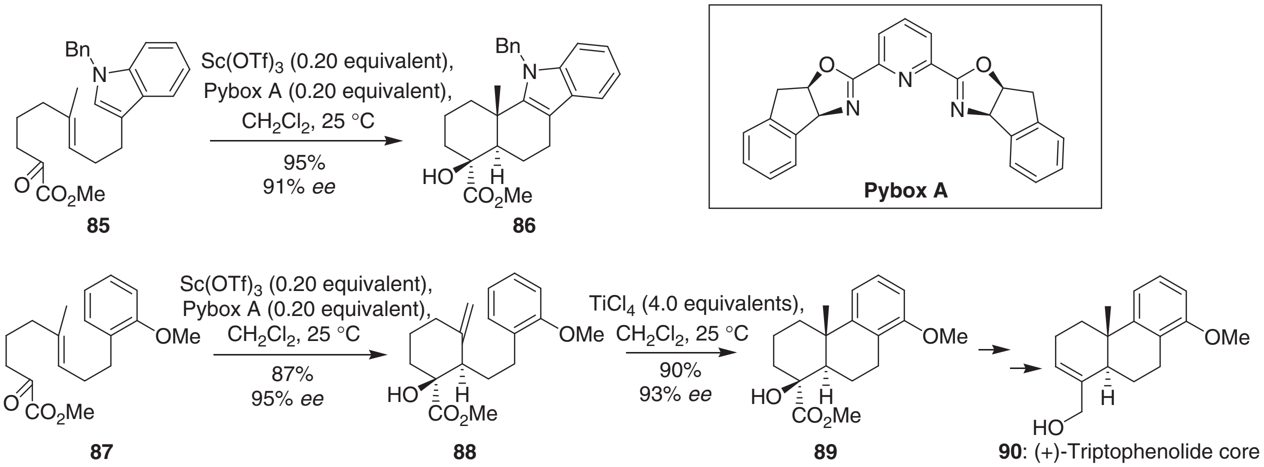
In this section, some examples of other modes of activation using potentially more unique, and arguably less biomimetic, electrophilic activators are provided. Several are worth consideration, and the most important for consideration is the use of oxocarbenium and *N*-acyl iminium ions to activate the C-1 position of a polyene chain for cyclization. This mode of activation has been long explored; for example, extensive studies by Johnson et al. nearly half a century ago established the viability for initiating asymmetric polyene cyclizations by Lewis acid opening of optically active acetals.[22] As shown in Scheme 11, this methodology is exemplified in Johnson's synthesis of a key intermediate toward vitamin D metabolites (**82**), where upon exposure to Ti(IV) chloride, acetal **80** cyclized to optically pure **81** with high yield and diastereoselectivity.[23] Here, termination by a propargylic silane was used to ensure five-membered ring formation. A second classic example of this methodology is Johnson's Sn(IV)-catalyzed pentacyclization of **83** to generate **84** with 5.5:1 *dr* in favor of the C-1 α-disposed product.[24] Use of the fluorine atom helped to stabilize positive charge in the transition state, driving the pentacyclization to completion, while also directing the regioselective synthesis of the C-ring as a six-membered moiety rather than its five-membered alternative.

Building on these studies in terms of generating similar activation at C-1, recent work by Loh and coworkers has further developed the overall process by finding that 1,2-dicarbonyls under appropriate conditions can create effective C-1 electrophiles and undergo asymmetric cyclizations with appropriate chiral ligands. For instance, exposure of an indole-terminated polyene with a C-1 dicarbonyl function (**85**) to catalytic $Sc(OTf)_2$ and chiral ligand pybox A yielded **86** in 95% yield and 91% *ee*.[25] It is worth noting, however, that polyenes terminated with an aryl ring are likely to undergo a different mechanism for cyclization in this approach. For example, as shown in the case of **87**, a competing carbonyl-ene mechanism is most likely the cause for exclusive



Scheme 11

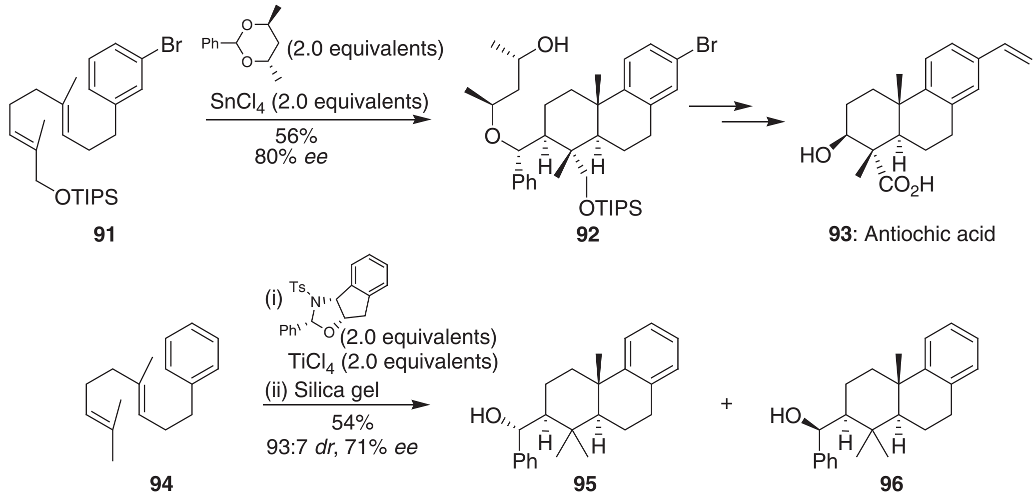
monocyclization leading to **88** rather than bicyclization. In any event, subsequent treatment with TiCl$_4$ successfully completed the tricycle (**89**) with retention of absolute configuration, leading to an asymmetric synthesis of the triptophenolide core (i.e., **90**) (Scheme 12).



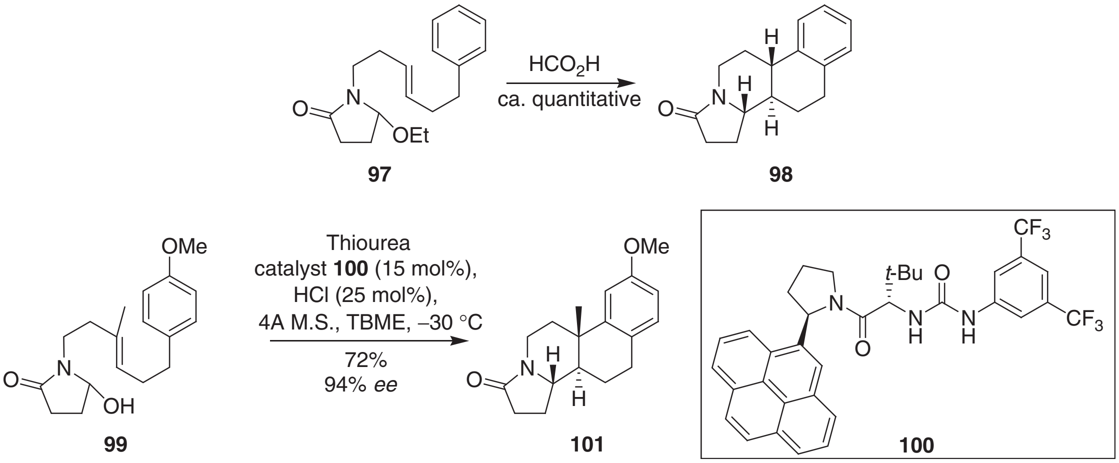
Scheme 12

It is equally significant that whereas Johnson's classic acetal work requires the placement of a chiral auxiliary within the polyolefin starting material to effect stereoselective polyene cyclizations, the Loh group has also developed an intermolecular polyene cyclization initiated by a chiral acetal promoter with an achiral polyene starting material (Scheme 13).[26] In this case, Lewis acid generation of a chiral oxocarbenium ion *in situ* effected cyclization to chiral products in high yield and good enantioselectivity. The utility of this methodology was exemplified in Loh's asymmetric synthesis of antiochic acid (**93**), where **91** was converted into **92** in 56% yield and in 80% *ee*.[27] Similarly, this process has also been extended to the use of chiral amino alcohol derivatives, as evidenced by the predominant formation of **95** from **94** in 54% yield in 93:7 *dr* and 71% *ee*.[28]

As a final unique form of C-1 electrophilic activation, the authors turn to *N*-acyl iminium ions (Scheme 14). It was Speckamp and coworkers who first showed the viability of such species for initiating polyene cyclizations in the late 1970s, where treatment of **97** with formic acid led to a quantitative yield of **98** as a single diastereomer.[29] This mode of activation is mentioned here since recent work by Jacobsen and coworkers has discovered how to extend it to an enantioselective variant by catalyzing polyene cyclizations of iminium ions using a chiral hydrogen-bonding thiourea catalyst (such as **100**).[30] Chiral thioureas containing a 2-aryl pyrrolidine motif were found to be crucial to promote the enantioselectivity of this reaction, suggesting that the catalyst stabilizes positive charge buildup within the polyene through a cation-π interaction. Pyrene-containing thiourea **100** was found to be optimal overall, producing cyclized products such as **101** in high yield as single diastereomers with exceptional enantioselectivity (here 94% *ee*).



Scheme 13



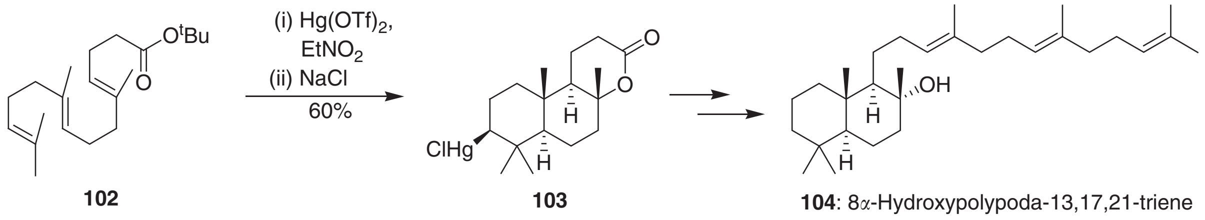
Scheme 14

3.05.5 Metal-Mediated Polyene Cyclizations

Outside of traditional, biomimetic modes of electrophilic activation, there has been a tremendous surge in interest in the past two decades in effecting transition metal-based activation as well. This mode of reactivity has been explored in several different formats: stoichiometric incorporation of metals within cyclized products, catalytic activation of polyenes, and carbometallation-induced cyclizations.

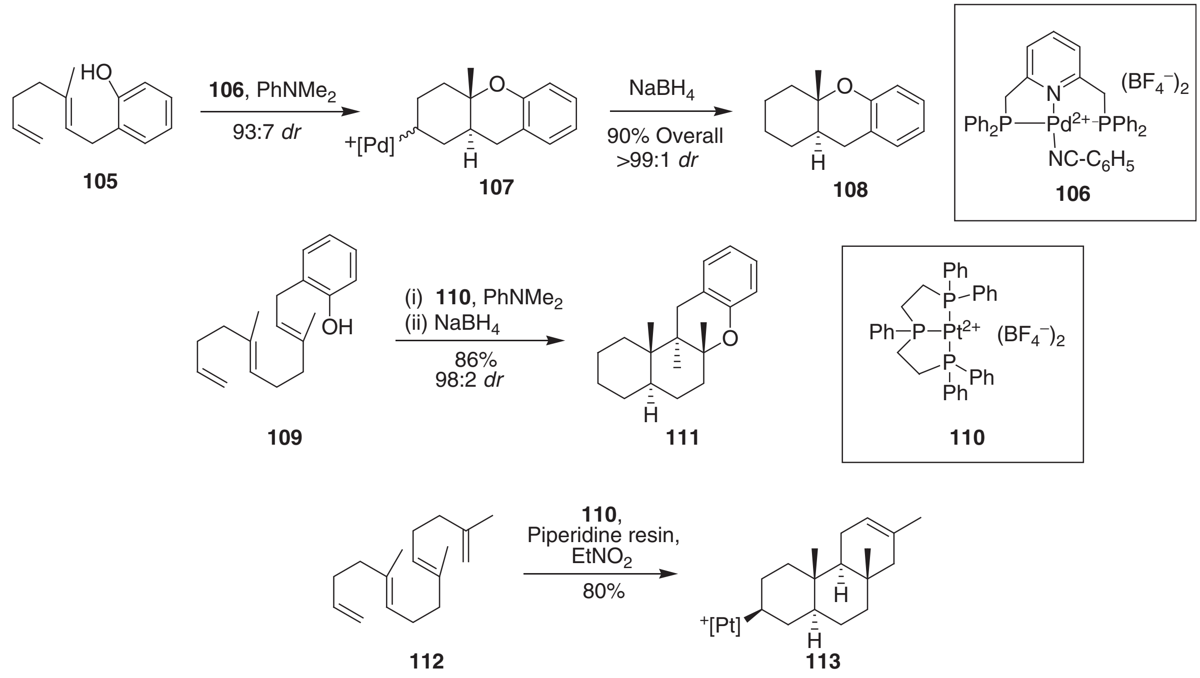
3.05.5.1 Polyene Cyclizations onto Simple Olefins

As a means to begin exploring this chemistry in its various forms, an early example of this mode of activation is seen in Nishizawa's stoichiometric Hg(II)-catalyzed cyclizations of polyolefins.[31] As shown in equation 5, treatment of **102** with $Hg(OTf)_2$ yielded **103** in 60% yield, which could be further elaborated to complete a synthesis of 8α-hydroxypolypoda-13,17,21-triene (**104**).[32] Intermediate organomercurial cyclized products such as **103** are easily isolated as stable crystalline solids, and can be easily demetallated using $NaBH_4$ and other nucleophiles as well (including selenium and halogens, vide infra). Some of the main advantages of this metal include the ability to: (a) cyclize polyenes that terminate with electron-deficient alkenes, such as that within **102** since there is a neighboring ester moiety which is deactivating through induction and (b) replace the organomercurial with other nucleophiles with retention of configuration (something not shown here). The price is the need to use a stoichiometric amount of a fairly toxic metal to achieve this chemistry.



(5)

Outside of Hg(II), Gagné and coworkers have demonstrated the utility of Pt(II) and Pd(II) pincer-ligand complexes in polyolefin cyclizations terminated by alcohols, phenols, amines, and simple olefin nucleophiles.[33,34] Unlike other transition metals, as well as simple Brønsted acids, Pd(II) and Pt(II) cationic complexes prefer to coordinate to less substituted alkenes, allowing access to polycyclic compounds otherwise unobtainable via standard polyene cyclization using naturally derived terpene patterning.[35] For example, cationic Pd complex **106** (Scheme 15) effected polyene cyclization of **105** with good diastereoselectivity, yielding **108** in 90% yield upon demetallation with $NaBH_4$. The presence of two epimers around the alkylpalladium center is attributed to competing chair–chair and boat–chair transition states, an issue that was not observed when Pt(II) complex **110** was used instead.



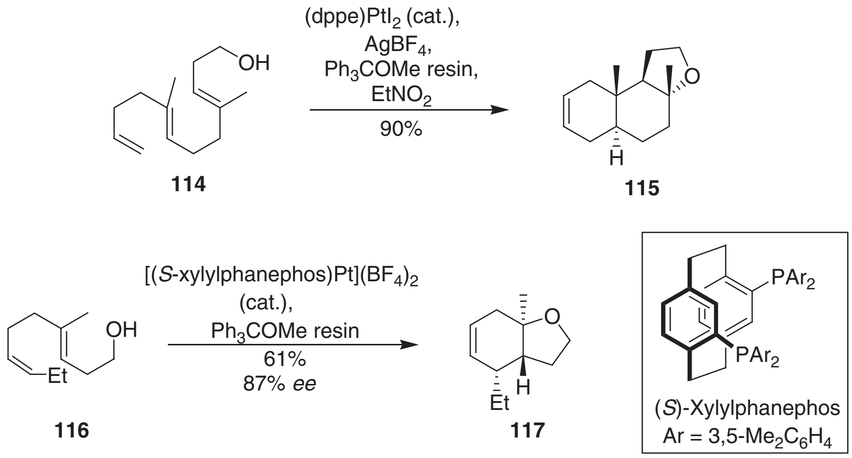
Scheme 15

Pleasingly, Pt(II)-initiated polyene cyclizations can also be rendered catalytic in the presence of an oxidant such as resin-bound trityl methyl ether.[36] For instance, use of a bidentate phosphine ligand rather than a (PPP)-pincer ligand creates a vacant coordination site on the metal to facilitate regioselective β-hydride elimination of the alkyl platinum complex resulting from polyene cyclization. Furthermore, use of appropriate chiral phosphines can render this reaction enantioselective, as seen in the cyclization of **116** to form **117** in 87% *ee* (Scheme 16).[37]

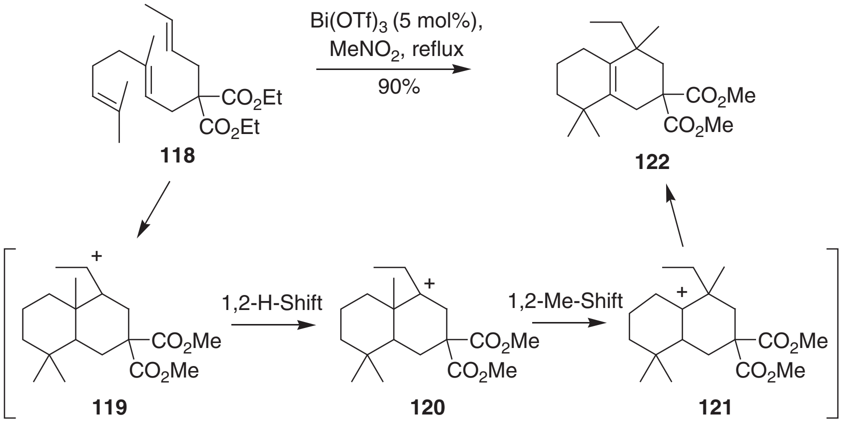
Other metals also work well in polyene cyclization chemistry. Indeed, a recent report by Dunach and coworkers described a highly efficient $Bi(OTf)_3$-catalyzed cyclization of simple polyenes, where the terminating groups can either be aryl rings or simple olefins.[38] Scheme 17 provides one example, where treatment of **118** with catalytic $Bi(OTf)_3$ generated bicycle **122** in 90% yield. Presumably, the product results from an initial 1,2-hydride shift of the initial 2° carbocation generated in the polyene cyclization process. Subsequent 1,2-methyl shift and elimination would then account for the observed product. The role of the metal in this reaction mechanism is still unclear, and it is possible that the cyclizations could result entirely from TfOH generated by the presence of adventitious water.

3.05.5.2 Heck-like Reactions of Polyenes

Outside from a metal itself serving as an electrophile, or facilitating the acid-based cyclization of polyenes, chemists have also used other modes of traditional metal-based reactions to effect cyclizations to afford polyene cyclization-like materials. Perhaps the



Scheme 16



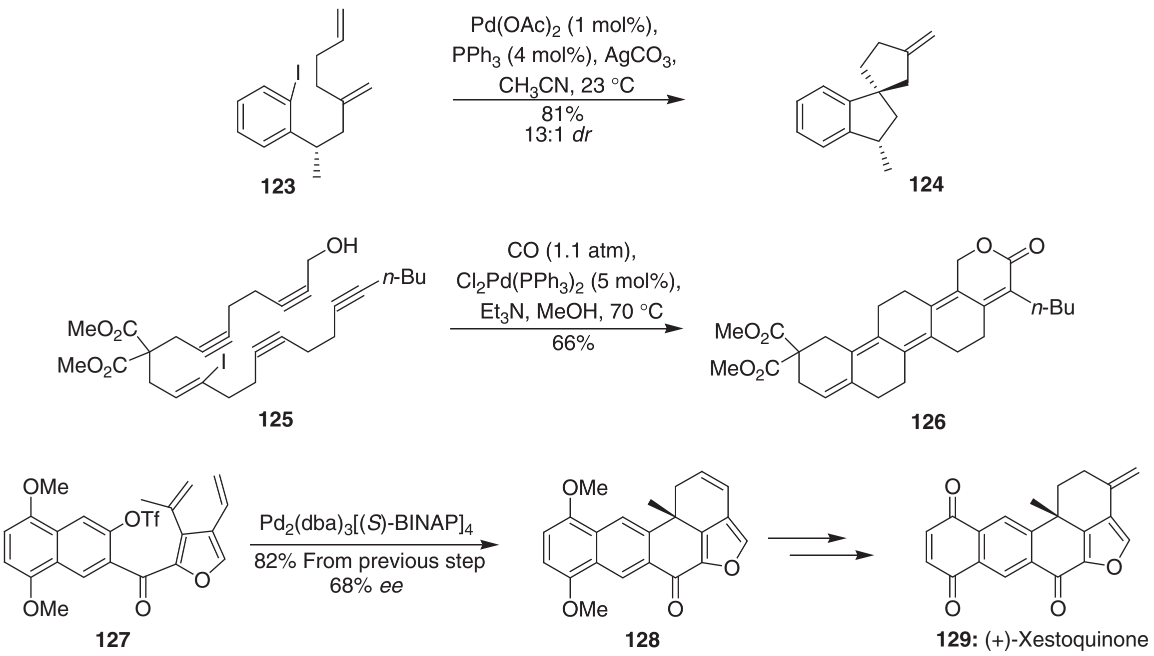
Scheme 17

most significant body of work in this direction involves Heck-based sequences. For instance, early work by Overman and Negishi in the early 1990s showed that palladium-catalyzed Heck reactions, where oxidative addition of Pd(0) into an aryl- or vinyl-halide or triflate bond followed by successive intramolecular carbopalladation events within a polyene framework is a highly efficient method to access polycycles, albeit through a vastly different mechanism from biomimetic polyolefin cyclizations.[39,40] The powerful utility of this method is exemplified in Scheme 18, where one example includes the asymmetric synthesis of (+)-xestoquinone (**129**), a polyketide isolated from the Pacific sponge *Xestospongia sapra* that possesses anticancer and antiviral properties.[41] In this case, treatment of aryl triflate **127** with catalytic Pd(0) in the presence of (*S*)-BINAP effected bicyclization to **128** in 68% *ee*.

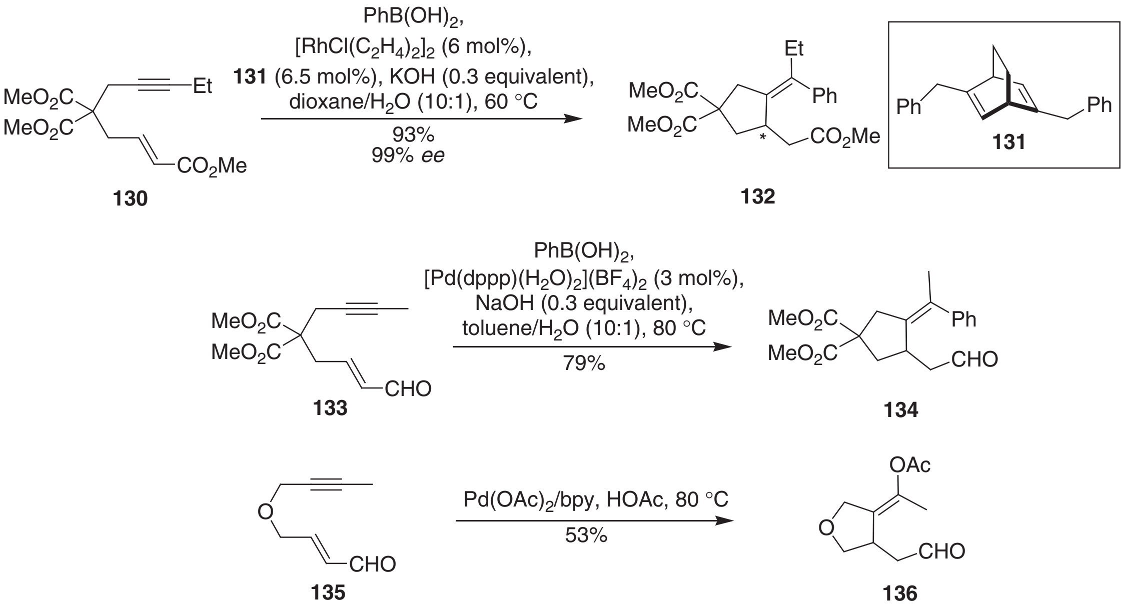
More recent examples exhibiting similar reactivity are those of cationic palladium(II) or rhodium(I) catalyzed intramolecular alkyne/α,β-unsaturated carbonyl coupling. In 2005, Hayashi and coworkers showed that chiral Rh(I) complexes could catalyze arylative cyclizations of alkyne-tethered α,β-unsaturated esters using arylboronic acids with exceptional stereoselectivity (**130**→**132**, Scheme 19).[42] Lu and coworkers recently reported a similar cationic Pd(II)-catalyzed arylative cyclization onto enals and enones, which can be rendered highly enantioselective with the use of a chiral phosphine ligand (**133**→**134**).[43] The mechanism for this reaction most likely involves carbopalladation of the alkyne followed by alkene insertion and protonolysis, yielding cyclopentane derivatives in good yield and enantioselectivity. Aside from arylboronic acids, nucleophiles can also include acetate and halogens, as illustrated for the formation of **136** from **135**.[44]

3.05.5.3 Reactions of Alkynes

Although all of the previous cases have begun either with alkenes or prefunctionalized alkene derivatives (such as epoxides) as sites for initial reaction in the critical polycylization event, selective activation of alkynes through various pi-acids such as Pt(II) and Au(I) has enabled the advent of eneyne cycloisomerization reactions as equally valuable approaches to access highly complex



Scheme 18

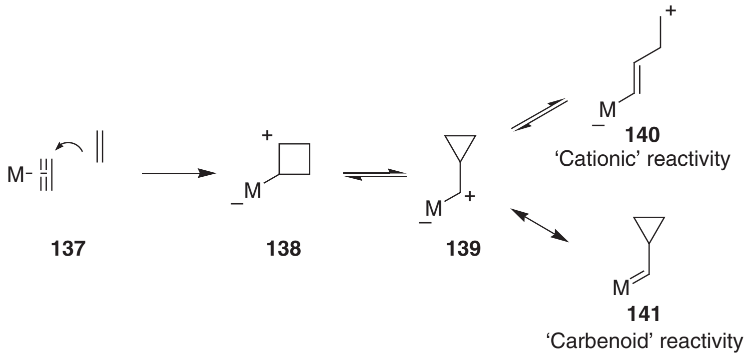


Scheme 19

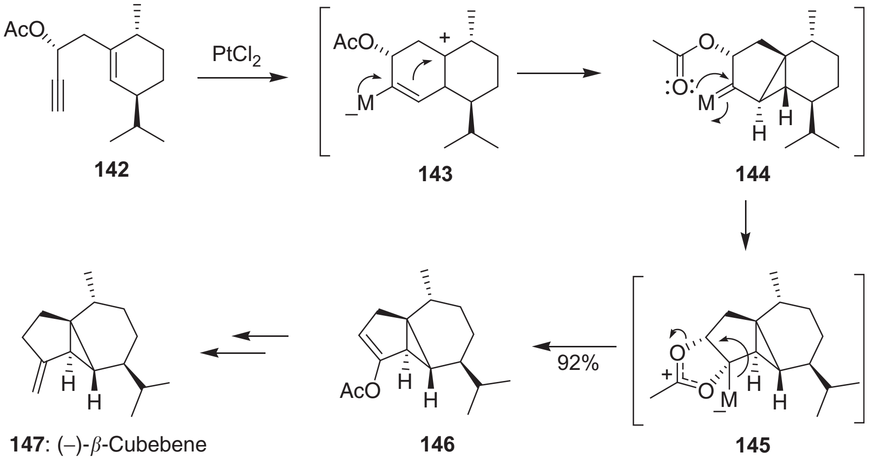
polycycles from relatively simple polyunsaturated starting materials. The key component of reactivity is that metal-complexed intermediates in such reactions are capable of reacting in both a 'cationic' (**140**) and 'carbenoid-like' sense (**141**, Scheme 20).[2c]

Fürstner's total synthesis of (–)-β-cubebene, for example, is a classic example of pi-acid carbenoid type reactivity in the impressive Pt(II)-catalyzed conversion of propargylic acetate **142** to **146** in 92% yield as shown in Scheme 21.[45] Several other groups, such as those of Malacria and Sarpong, have also taken advantage of such chemistry to rapidly and stereoselectively access complex frameworks of both natural and designed origin.[46]

Both Au(I) and Pt(II) complexes are also capable of catalyzing polyene cyclizations of 1,6-enynes in a biomimetic, 'cationic' sense terminated by intermolecular (example 1, Table 1) or intramolecular nucleophiles (examples 2 and 3) in a 6-*exo* fashion.[47,48] For instance, Toste and coworkers recently showed that cationic gold complexes using a sterically bulky chiral phosphine ligand are capable of effecting highly enantioselective cation-π cyclizations (**164**→**165**, equation 6).[49] Michelet and coworkers

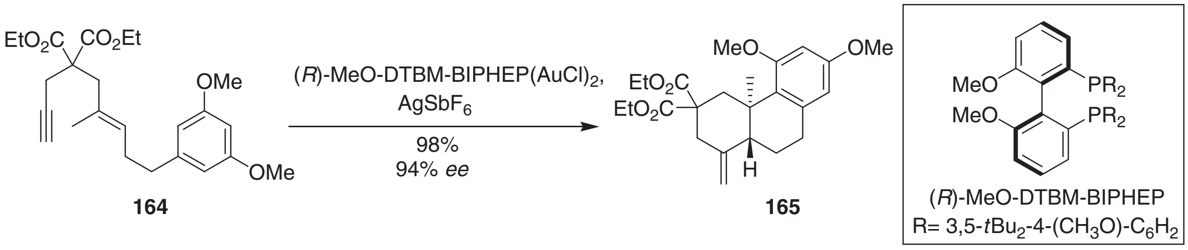


Scheme 20



Scheme 21

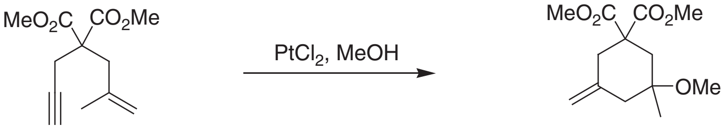
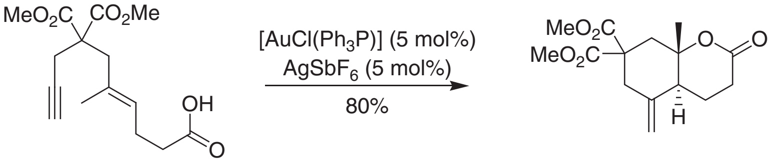
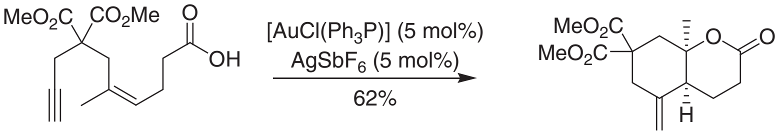
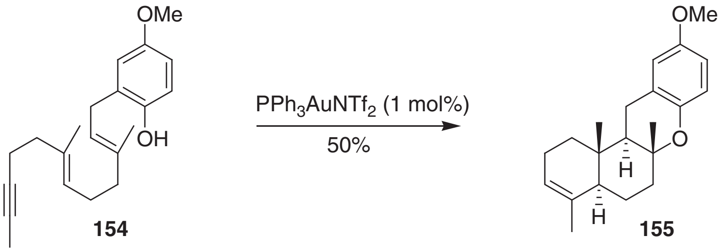
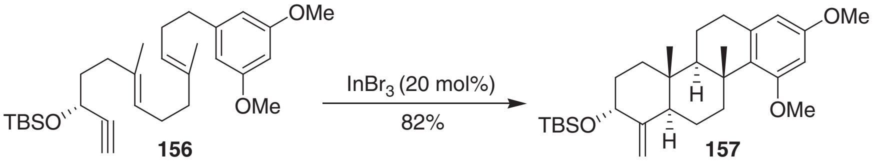
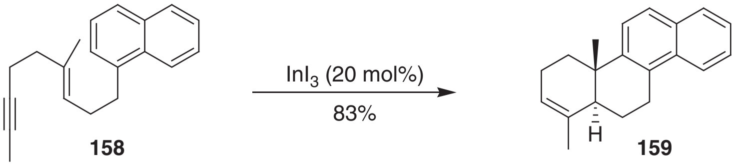
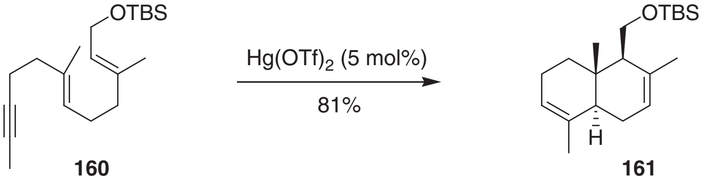
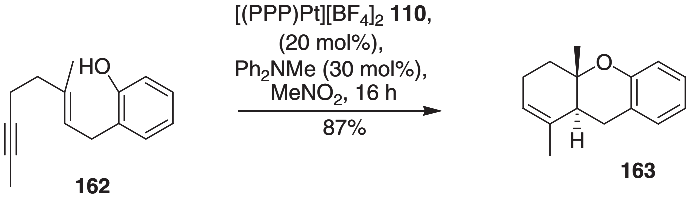
also recently described Au(I)-catalyzed phenoxy-terminated bi- and tricyclizations of 1,5-enynes in a 6-*endo* fashion (example 4),[50] whereas Nishizawa and coworkers also described a $Hg(OTf)_2$-catalyzed cyclization onto alkynes in a 6-*endo* fashion, which can be terminated by either an aryl ring or simple olefins (example 7).[51] In the latter case, a vinylmercurial intermediate is presumably initially formed, which is followed by demetallation due to catalytic TfOH generated *in situ*. Similarly, Gagné and coworkers demonstrated that a pincer-ligated Pt(II) complex previously used for polyene cyclizations with alkene terminals is also capable of effecting the cyclization of 1,5-enyne **162** terminated by an intramolecular phenoxy nucleophile.[52]



(6)

More recently, Corey and coworkers have reported an In(III)-induced polyene cyclization of propargylic silyl ethers in a 6-*exo* fashion (example 5, Table 1).[53] These researchers postulated that the vacant 5*s* and 5*p* orbitals on In(III) allow its selective bidentate coordination to p_x and p_y orbitals on the acetylenic subunit as well as the propargylic oxygen lone pairs. Bi-, tri-, and tetracyclizations of polyenes are possible using $InBr_3$ as a catalyst, and terminating groups can be either aryl rings or Boc-protected alcohols. This method is complementary to epoxide opening cascades in that the protected propargylic alcohol can be easily synthesized in an asymmetric fashion using Carreira's recently disclosed method.[54] Moreover, it is worth noting that whereas epoxide opening cascades catalyzed by $MeAlCl_2$ are highly sensitive to substrates containing coordinating heteroatoms, this method offers a far more general method to access a wide variety of polycycles since it is much milder. In(III) reagents have also

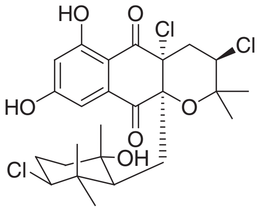
Table 1 Selected examples of alkyne-initiated cyclizations

	Example	Reference
 **148** **149**	1	47
 **150** **151**	2	48
 **152** **153**	3	48
 **154** **155**	4	50
 **156** **157**	5	53
 **158** **159**	6	55
 **160** **161**	7	51
 **162** **163**	8	52

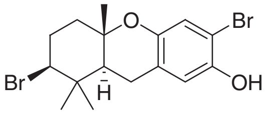
proven capable of catalyzing alkyne-initiated polyene cyclizations in a 6-*endo* fashion at ambient temperature in high yields with high diastereoselectivity (example 6, Table 1).[55] Both acetylenic arenes as well as polyunsaturated acetylenes are suitable substrates for this method. Thus, these examples hopefully illustrate the overall utility of alkynes as an alternate starting point for metal-mediated cyclizations, one that will likely only expand in the future.

3.05.6 Halonium-Initiated Cyclizations

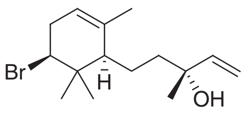
Although the preceding sections reveal a very high state of the art for a number of distinct polyene cyclizations, both in racemic and enantioselective forms, one significant area which has traditionally lagged behind in development are cyclizations initiated by halonium electrophiles, even though initial explorations of the process occurred in the 1960s.[56,57] Nature takes advantage of such events with some frequency, particularly in the construction of marine-based natural products containing chlorine and bromine such as **166–168**, among dozens of others, where it is vanadium- or heme-based chloro- and bromoperoxidases that install the electrophilic halogen atom with high chemo- and facial selectivity onto terpene precursors.[58] However, most laboratory efforts to execute similar chemistry in racemic form have not proven nearly as successful, with many simple halonium sources (such as molecular halogens and halosuccinimides) affording either poor conversion, multiple side products in addition to the desired material, and/or products of intermolecular chemistry rather than intramolecular cyclizations (where some species in solution behaves as either nucleophile or base).[59] In the past decade, though, the first useful tools have begun to emerge which can address the incorporation of any halogen atom onto terpenes and other related materials, initiating highly productive polyene cyclizations.



166: Napyradiomycin B4



167: 4-Isocymobarbatol



168: α-Snyderol

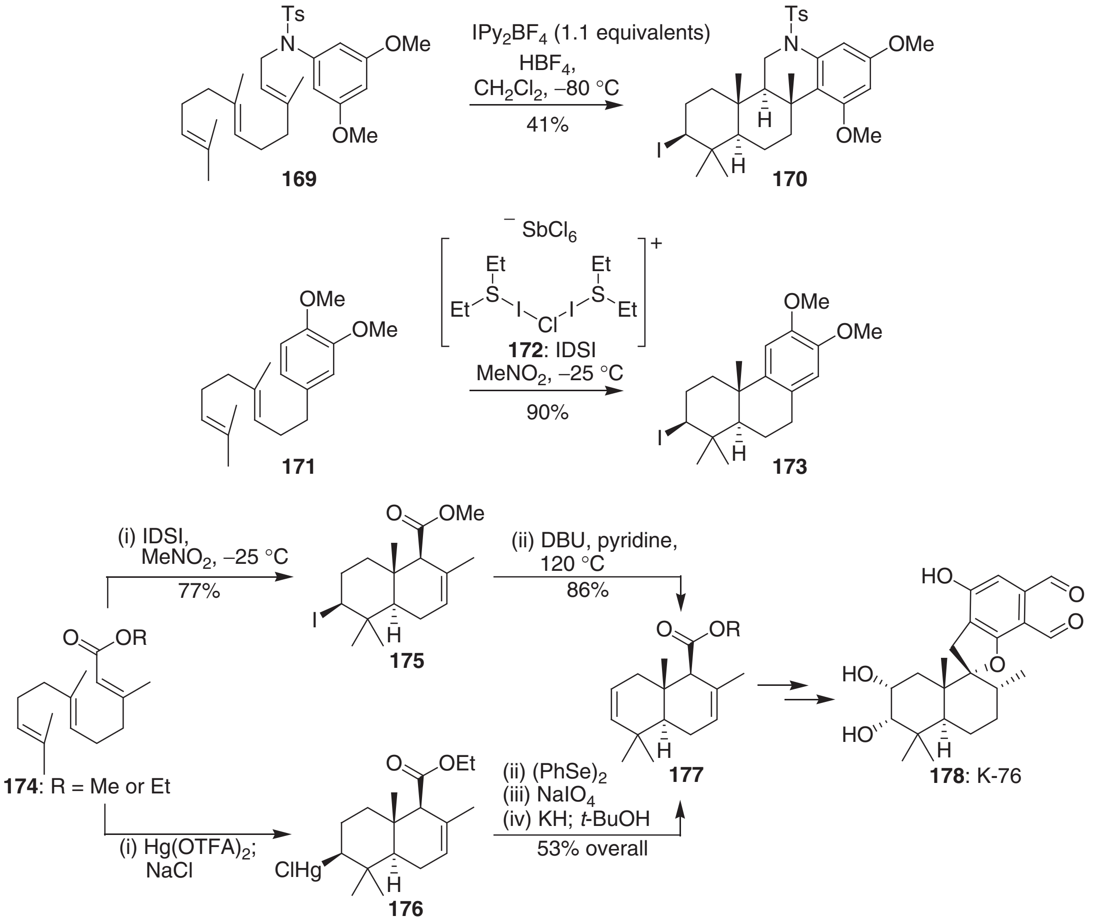
3.05.6.1 Iodonium-Initiated Cyclizations

One of the first major advances occurred with the disclosure by Barluenga et al. in 2004 that the reagent formed by the combination of IPy_2BF_4 with HBF_4 could smoothly initiate iodonium-based cation-π cyclizations of electron-rich frameworks.[60] Scheme 22 provides one example in the form of a tricyclization of **169** into **170** which proceeded in 41% yield (74% per ring formed), showing that appropriate tuning of the electrophile source could initiate chemistry where other simple iodonium sources failed. Of note is that the electron-rich aromatic ring was not substituted in this event, a side-reaction that can occur with other reagents.

The second reagent which possesses similar reactivity was developed by the Snyder group in 2010, which they have termed as IDSI (**172**); it combines both a Lewis base in the form of Et_2S and a Lewis acid ($SbCl_5$) with molecular iodine to generate a crystalline form of iodonium which can also smoothly cyclize electron-rich systems such as **171** without effecting electrophilic aromatic substitution.[61] However, one advantage of IDSI over the Barluenga alternative, at least based on published examples, is that it can also cyclize systems that terminate with an electron-withdrawing group, such as the ester possessed by **174**. In this case, exposure to IDSI for just a few minutes at $-25\ ^\circ C$ provided *trans*-decalin framework **175** in 77% yield; historically, only reagents such as Hg(II) salts have been able to effectively cyclize such materials in good yield, as highlighted by the conversion of **174** into **176** using $Hg(OTFA)_2$ and subsequent manipulation into alkene **177** through three additional operations.[62] Here, though, an advantage of the iodine atom within **175**, although not found in any materials in nature, is that it can be eliminated through exposure to DBU at elevated temperatures to provide the same product (i.e., **177**). Thus, with the right tool and the ability to alter that iodine atom (something not readily achieved with other halogens), a more efficient sequence which avoids toxic metals could be achieved to afford an alternate formal total synthesis of K-76 (**178**); similar strategies and tactics have also been used for several other natural products as well which do not possess halogen atoms.[61]

3.05.6.2 Bromonium- and Chloronium-Initiated Cyclizations

Intriguingly, the same design used by the Snyder group to create a novel iodonium source has also provided tools to broadly effect bromonium-initiated cyclizations.[63] Before that discovery, no single halonium source worked broadly for all terpene classes, and most product yields were quite low with perhaps the best reagent overall being 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCD).[64] That new tool, **179** (Scheme 23), is known as bromodiethylsulfonium bromopentachloroantimonate (BDSB) ($Et_2SBr \cdot SbBrCl_5$),[63] and though it has a slightly different structure than IDSI, it behaves in the same way for diverse substrates, typified here by its ability to convert **181** into **182** via a tricyclization as well as the use of terpenes with non-*E* geometry to afford a highly strained *cis*-decalin framework en route to completing a synthesis of the proposed structure of peysonnol A (**183**).[61] One particular advantage of these reagents in these cases is that they form a highly acidic by-product (presumed to be protonated Et_2S) which helps to drive these cyclizations to completion; typically in the formation of materials such as **182**, a separate acid-based treatment step is needed to close the final ring system as has been highlighted several times in earlier sections. As a final example, and what may constitute the most complex case explored to date for a bromonium-induced polyene cyclization, the Krauss group



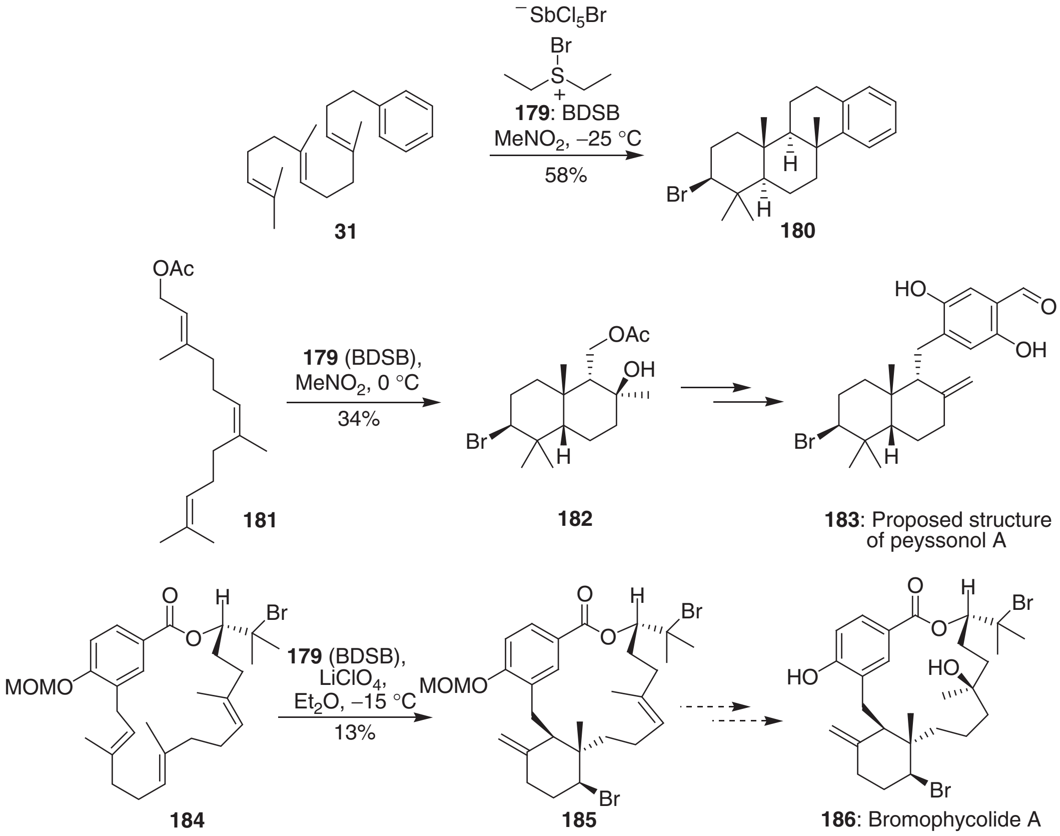
Scheme 22

attempted to effect a chemoselective cyclization within a 19-membered macrocyclic framework to form the core of bromophycolide A (**186**) in what may be a biomimetic event.[65] Using starting material **184** and BDSB in the presence of $LiClO_4$, they successfully formed **185** in 13% yield. Although not as efficient as might be desired, other tools did not afford this material in any significant quantity.

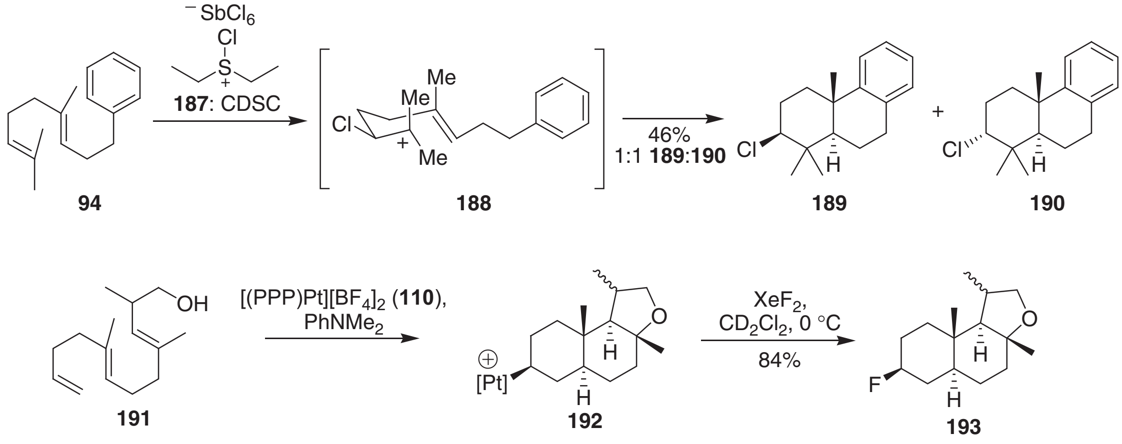
Outside of iodine and bromine incorporation, approaches to directly install both chlorine and fluorine have proven even more challenging. The first example of any direct chloronium-induced polyene cyclization appears to have come in 2010 with the chlorinated version of the IDSI and BDSB reagents mentioned above (i.e., **187**, CDSC).[61] However, as noted in the cyclizations achieved with this reagent to date, such as the conversion of **94** into **189** and **190**, not only are yields modest but also the reactions possess no diastereocontrol. This outcome suggests that the challenge derives, in part if not in whole, in intermediates such as **188** being active where it is a true tertiary carbocation, not a chloronium species, which prevents reaction occurring through the tight, chair-like transition states of the Stork–Eschenmoser stereoselection model.[66] For fluorine, there are no direct cyclization examples known, though it has proven possible to effect a stoichiometric platinum-mediated cyclization of substrates such as **191** into **192**; a terminating treatment with XeF_2 could then replace that metal atom, with retention, for fluoride to afford **193** in 84% overall yield.[67] Again, there are no natural products known which possess such fluorine atoms, though these analogs may possess improved physicochemical properties, especially for pharmaceutical applications (Scheme 24).

3.05.6.3 Asymmetric Halonium-Initiated Cyclizations

Each of the above examples, however, constitutes racemic events, and although these processes are beginning to reach more advanced stages, the same cannot be said of enantioselective variants. Only one report of such a process has been published to date. This work, from Ishihara and coworkers, used NIS in combination with chiral ligand **195** to effect highly enantioselective iodonium-based cyclizations of a few electron-rich frameworks, including **194**.[68] Although unquestionably a major discovery, at present the process has only limited substrate scope, requires prolonged times at cryogenic temperatures, and unfortunately has not successfully translated to either direct bromonium- or chloronium variants (though the chiral iodine could be lithiated and replaced with the other halogens in a second step). The major reason for this state of affairs, especially for direct bromonium-based processes, is likely



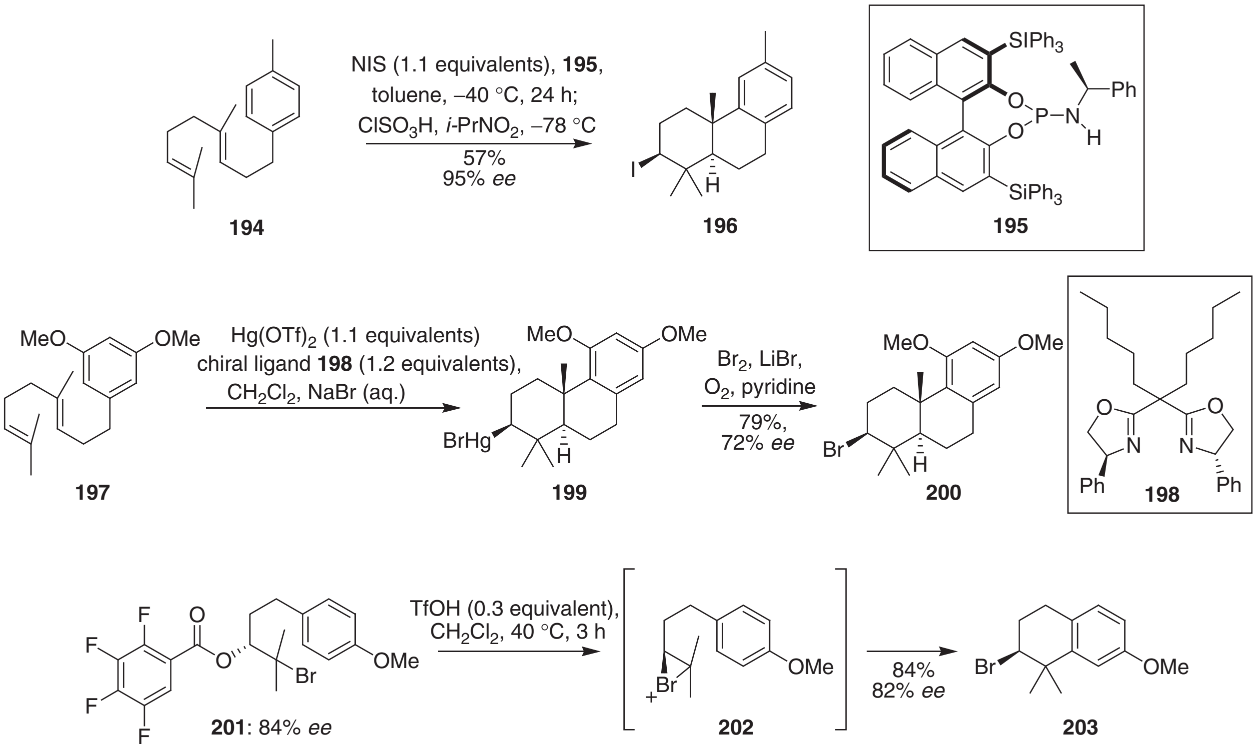
Scheme 23



Scheme 24

the known ability of a halonium to transfer rapidly between alkenes and thereby erode any reagent-induced asymmetry before productive cyclization.[69] Perhaps as a result, the only other successful approaches for enantioselective generation of halogenated products of polyene cyclizations have had to rely on more indirect approaches that can avoid this potential problem (Scheme 25).

For instance, the Snyder group was able to show that several substrates, such as **197**, could be converted into chiral materials such as **200** with modest to fairly good enantioselectivity (here 72% *ee*) by way of chiral organomercurials such as **199**, formed by the combination of Hg(OTf)$_2$ with chiral ligand **198**.[70] Although the use of stoichiometric mercury obviously is far from ideal, particularly for large-scale synthesis, advantages include the fact that the intermediate organomercurials are crystalline, allowing for recrystallization as a means to improve optical purity, and the ability to use conditions developed originally by Jensen, Hoye,



Scheme 25

and Kurth to replace that mercury atom with any halogen, largely with retention.[71] A second multistep solution comes from the Braddock group, who used several steps to create **201** via a chiral diol precursor formed via Sharpless dihydroxylation, showing that on its exposure to an acid source they could generate a chiral bromonium species without loss of stereochemial integrity.[72] As a result, they obtained chiral materials such as **203**. The key is the absence of any alkenes within these reactants, thereby preventing chiral erosion via halonium transfer. It will be interesting to see if such approaches can be extended to more complex systems. Clearly, however, much work remains in the arena of enantioselective variants of these processes in a more global sense, particularly in direct reactions, if chemists are to fully mirror the power of nature's haloperoxidases.

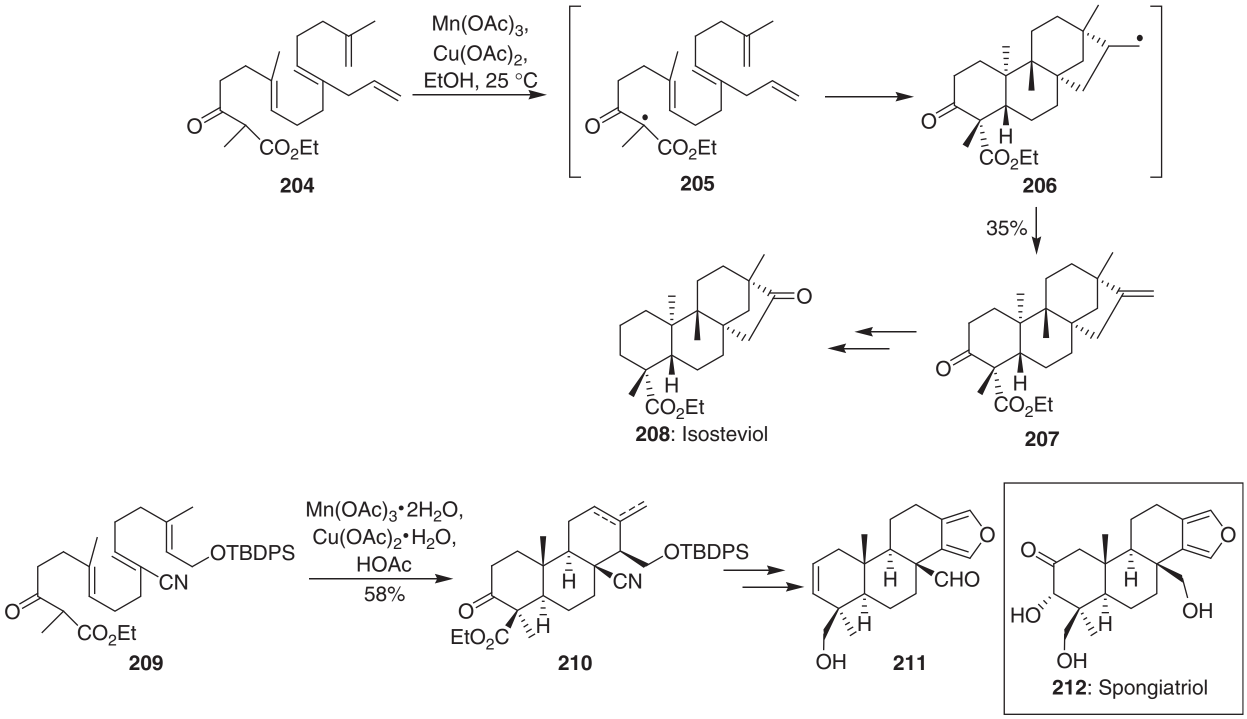
3.05.7 Radical-Initiated Cyclizations

3.05.7.1 Cyclizations of 1,3-Dicarbonyl Compounds

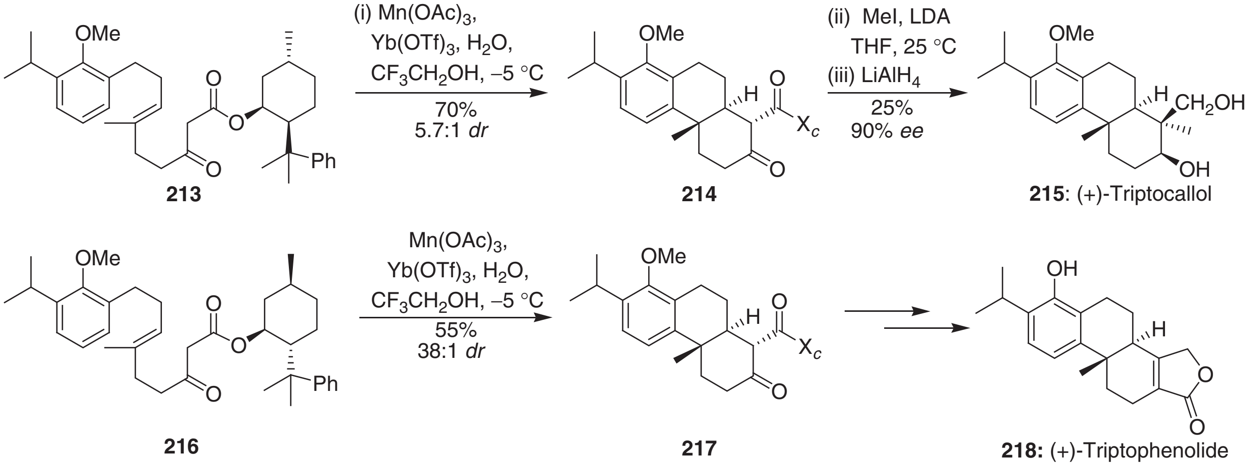
Although all examples in the preceding sections follow the classical pattern of electrophilic activation to initiate polyene cyclization, save for the substrates cyclized through Heck-like processes, there are other mechanistic possibilities that can account for the formation of similar products. Indeed, as early as 1962, Breslow postulated that radical-initiated pathways might also be a viable alternative, though evidence collected at the time seemed to indicate that such events may not have biogenetic relevance.[73] Whether used in nature or not, chemists have utilized radical-based processes with much success to generate polycyclic products with core structures matching those obtained with more standard approaches, most within the past 15 years. In some cases, unique functionalization patterns, stereochemistry, and ring sizes can result that would otherwise be difficult to obtain.

Among the earliest and most successful radical-based polyene cyclization approaches are those pioneered by Snider (Scheme 26). Here, radicals generated from 1,3-dicarbonyl compounds through exposure to a mixture of $Mn(OAc)_3$ and $Cu(OAc)_2$ initiate polycyclizations affording complex frameworks, as illustrated in the conversion of **204** into **207**.[74] Although the overall yield for this process was modest in terms of raw number (35%), the yield per cyclization (77%) is certainly quite good, and in this case afforded a framework that could be readily advanced into the natural product isosteviol (**208**) in just a few additional steps. Indeed, related approaches have been utilized in several cases to fashion complex terpenes, with a particular advantage of the approach being that the 1,3-dicarbonyl function maps well onto several targets and affords functional handles for further manipulation. The conversion of **209** into the core structure of spongiatriol (**211**) by Zoretic et al. serves as an additional expression of this overall concept.[75]

It is only recently, however, that this process has been rendered enantioselective. As shown by the Yang group, incorporation of an appropriate chiral auxiliary onto the 1,3-dicarbonyl portion (as in **213** and **216**, Scheme 27) was sufficient to enable highly diastereoselective formation of both **214** and **217**, in one case with 38:1 *dr*.[76] Cleavage of the auxiliary then could afford single



Scheme 26

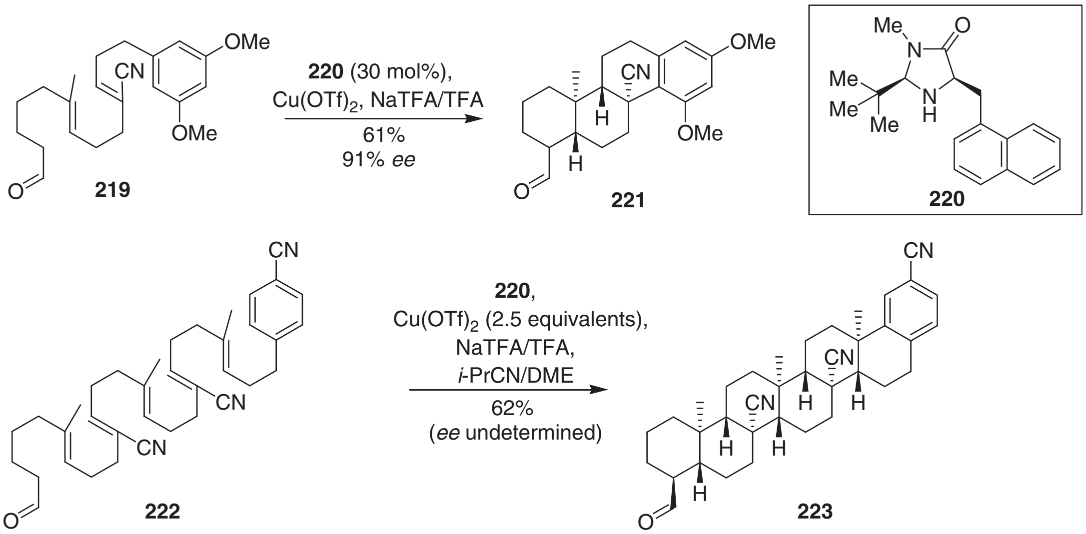


Scheme 27

enantiomers of cyclization products. Of note in these processes is that subtle alteration of stereochemistry within the auxiliary did have an impact on the diastereoselection observed, indicating that careful matching of substrate and auxiliary is critical. Equally significant, these researchers observed that the use of Yb(OTf)$_3$ (and other lanthanides in general) actually catalyzed the Mn(OAc)$_3$ radical cyclization reactions, suggesting that chiral Lewis acids on their own, without the presence of an auxiliary, might be able to render such reactions enantioselective; in their absence, yields and diastereoselectivities were poorer in these particular examples.

3.05.7.2 Other Modes of Radical Activation

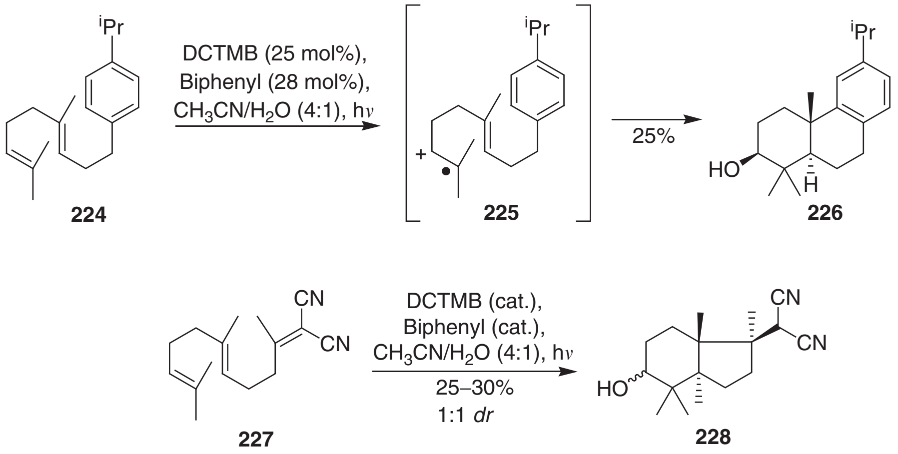
Outside of dicarbonyls, a recent report from Rendler and MacMillan showed that radical-based polycyclizations could be initiated with only a single carbonyl in the form of an aldehyde as catalyzed by **220** (Scheme 28).[77] Here, what has been termed singly occupied molecular orbital (SOMO) catalysis is initiated by iminium formation between the aldehyde and secondary amine catalyst followed by single-electron transfer. Optimal yields and stereoselection are achieved by alkene/aromatic ring patterning



Scheme 28

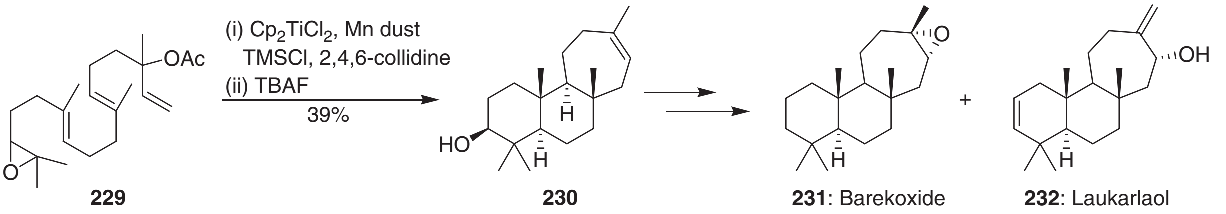
that alternates from electron-rich to electron-poor; the good yield and enantioselection observed for the conversion of **219** into **221** is typical of the method, with examples of a pentacyclization and hexacyclization (**222**→**223**) also achieved to afford frameworks reminiscent of terpene-derived steroids.

Equally difficult to achieve are cyclizations starting purely from terpenes without prefunctionalization. For instance, Demuth has been able to show, in multiple cases, that use of photo-induced electron transfer using 1,4-dicyanotetramethylbenzene (DCTMB) in the presence of biphenyl can lead to the formation of radical-cation intermediates such as **225**.[78] These reactive species can then go on to form functional frameworks such as **226** via attack of water at the carbocation and cyclization through the radical. The conversion of **227** into **228** is a second example of the process, with some cases of tetracycles being generated as well (not shown) and remote chiral auxiliaries being able to afford diastereoselection to the process as a whole. Yields, however, tend to be modest, likely due to challenges in fully controlling the initiating site of such reaction pathways, particularly as additional alkenes are added into the polyene starting material chain (Scheme 29).



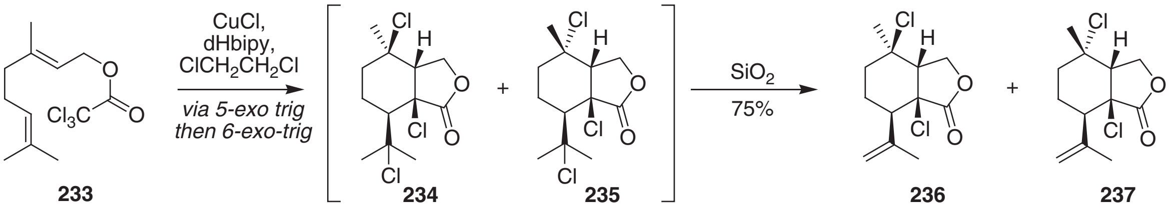
Scheme 29

As a result, more common is to begin with a prefunctionalized framework such as epoxide **229**, where use of a Lewis acid (Cp_2TiCl_2) to help coordinate and direct the site of radical generation in this case led to the synthesis of **230** (equation 7).[79] Critical to note in this example is a terminating 7-*endo* cyclization, which was able to outcompete the alternate 6-*exo* pathway; such control in ring formation had been noted before with other systems, but highlights here a valuable use of radical chemistry to access a framework, one elaborated to the natural products barekoxide (**231**) and laukarlaol (**232**), that would otherwise have been difficult to obtain through more classical polyene cyclization manifolds.



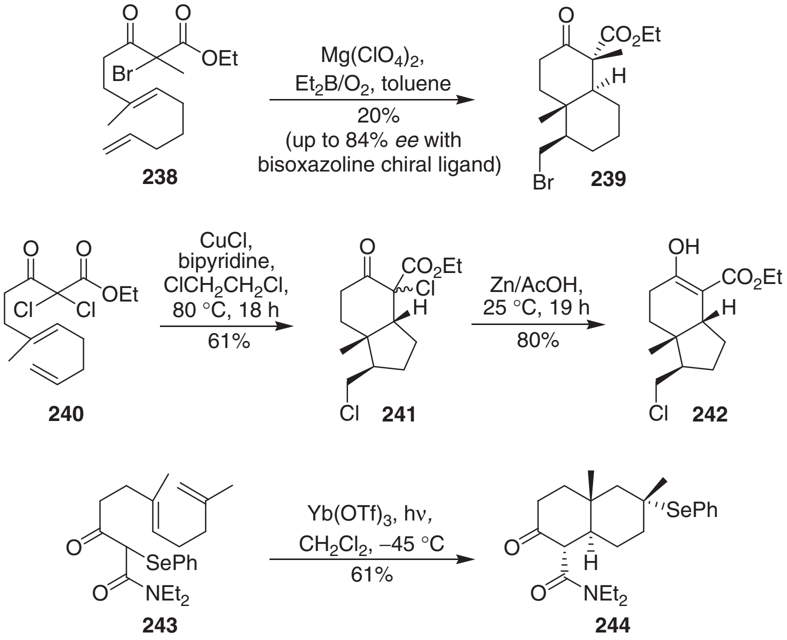
(7)

Similar trends have been observed for other efforts to initiate radical-based polycyclizations with other initiators. For instance, use of radical halogenation conditions from nonfunctionalized starting materials typically leads to products where halogen atoms have been incorporated at every possible site; in some instances, as in work from Quayle (equation 8),[80] creative use of those atoms postcyclization can afford access to highly functionalized frameworks pertinent to natural product synthesis, where it is worth noting that these rings were formed in the opposite order typical of standard polyene cyclizations.



(8)

However, potentially more readily deployed, and of greater synthetic generality, are radical-based reactions where the functional atom is already present, with atom-transfer processes being able to incorporate the initiating group at the end of the radical chain for use in further chemistry. The Yang group has been a major developer of such chemistry, with the three examples in Scheme 30 highlighting how appropriate Lewis acids can allow for not only bromine but also chlorine and selenium-based systems to undergo polycyclizations, with the initiating atom incorporated and subsequently modified in the final polyene cyclization-like frameworks.[81] Enantioselection has only been moderately investigated with these processes, but it is encouraging to note that in the initial bromine-based example (238 → 239), use of a simple bisoxazoline ligand was able to afford the desired product in 84% *ee*, despite the overall modest yield of the reaction itself.



Scheme 30

Overall, these examples have hopefully illustrated that radical chemistry has quite a bit to offer in the way of generating functionalized products similar to those formed under more classical manifolds; the future will show whether Nature uses such processes as well and what other creative approaches chemists can develop to use other initiating groups and radical species as part of these events.

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3.06 Transannular Electrophilic Cyclizations

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3.06.1	**Introduction**	293
3.06.2	**Eight-Membered Rings**	295
3.06.2.1	Endocyclic Alkenes	295
3.06.2.2	Exocyclic Alkenes	298
3.06.3	**Nine-Membered Rings**	302
3.06.3.1	Dienes and Related Systems	303
3.06.3.2	Enones	305
3.06.3.3	Miscellaneous	306
3.06.4	**Ten-Membered Rings**	308
3.06.4.1	Dienes	308
3.06.4.2	Epoxyalkenes	309
3.06.4.3	Enones	309
3.06.4.4	Alkynes	311
3.06.5	**Eleven-Membered Rings**	313
3.06.5.1	Humulene Derivatives	313
3.06.5.1.1	Humulene-1,2- epoxide and humulene-4,5-epoxide	313
3.06.5.1.2	Humulene-8,9-epoxide	314
3.06.5.2	Zerumbone and its Derivatives	315
3.06.5.3	Miscellaneous	317
3.06.6	**Other Rings**	319
3.06.6.1	Alkenes and Epoxides in Large Rings	319
3.06.6.2	Alkynes in Large Rings	322
3.06.6.3	Transannular Cascades	325
3.06.6.4	Cyclophanes	325
3.06.7	**Formation of Carbon–Heteroatom Bonds**	326
3.06.7.1	C–N Bonds	327
3.06.7.2	C–O and C–S Bonds	329
References		335

Glossary

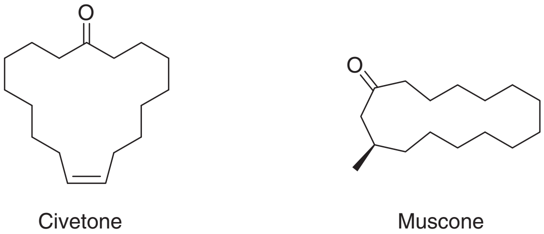
Antiperiplanar Specific conformation (ap) in which two coplanar groups make a torsion angle of 180° (±30°).
Cascade reactions Sequence of multiple reactions occurring sequentially without the need of purifying the intermediates (often referred to as one-pot reactions).
Chalcogens Group VIA elements.
Lewis acid Electron pair acceptor.
Nonclassical carbocations Delocalized and electron-poor (e.g., with 3-center, 2-electron bonds) cationic intermediates and transition states (some stable species are also known).
Planar chirality Stereoisomerism resulting from the arrangement of out-of-plane groups with respect to a planar region (e.g., amide, alkene, and aryl) of the molecule.
Shift Reaction consisting in a movement of an alkyl group or a hydrogen atom, from one center to another (adjacent or not).

3.06.1 Introduction

The structures of the first known large natural macrocycles civetone and muscone, 17- and 15-membered rings, respectively, have been elucidated around 1930 (Scheme 1).[1]

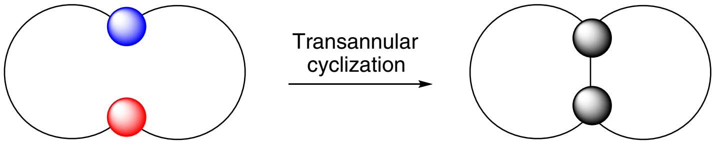
This discovery heralded a novel branch of chemistry devoted to the synthesis, use, and properties of this structurally wealthy class of compounds. It was soon realized that many such macrocycles experience strain owing to unfavorable noncovalent interactions between ring substituents on nonadjacent atoms. These so-called transannular interactions generate transannular strain also known as Prelog strain.[2] This effect is particularly strong in medium-sized ring systems, for example, of 8–11 atoms. Accordingly, these rings are more difficult to obtain by direct macrocyclization of their corresponding linear precursors.[3] However,

doi:10.1016/B978-0-08-097742-3.00310-4



Scheme 1

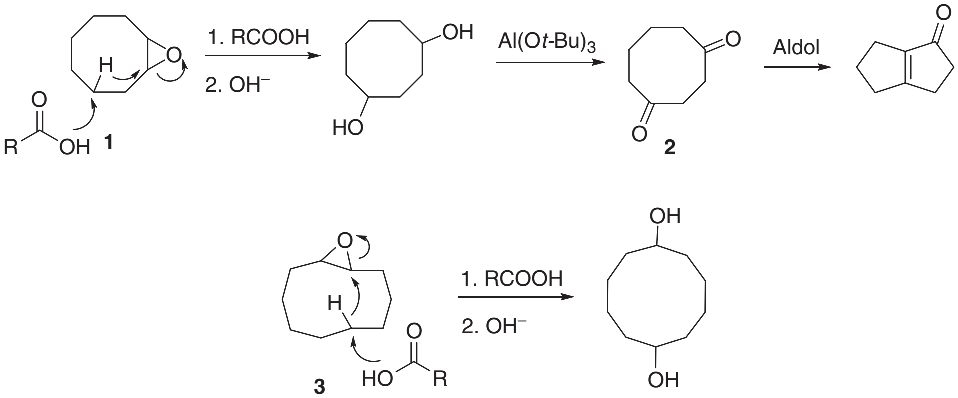
strained macrocycles easily undergo transannular reactions (across the ring) when reactive partners are located on opposite sides of the circle (Scheme 2).[4]



Scheme 2

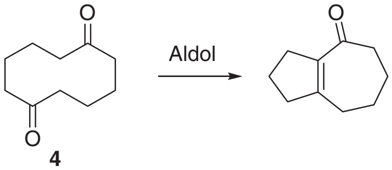
To some extent, the restricted and confined geometry of macrocyclic molecules compares well with the constraints enzymes impose on their substrates. As a result, reactivity is enhanced because 'the closer we hold reagents together, the more likely they are to react' and 'we all know that enforced propinquity often leads to greater intimacy.'[5] As for enzymes, much control (regio- and stereo-control) is expected as the two tethers control the trajectory approach of the reactive centers.

The first transannular reactions were observed in the middle of the twentieth century. They involved 1,3-hydrogen shift and aldol condensation[6] inside 8-membered medium rings **1** and **2** as well as 1,5-hydrogen shift[7] in a 10-membered congener **3** (Scheme 3).

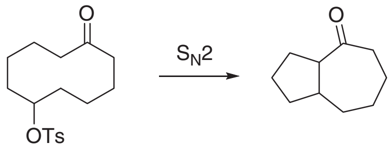


Scheme 3

Aldol condensation of cyclodecane-1,6-dione **4** (equation 1) and S_N2 alkylation of tosyl protected 6-hydroxycyclodecan-1-one **5** (equation 2) were also studied around the same period.[8] Since that time many other transforms have been also studied and used in transannular environments. The approach is now so widespread that it constitutes an important synthetic tool.



4 (1)



5

(2)

The most common transannular processes[9] can be divided into two classes: (1) those leaving the macrocycles untouched as in H-transfer reactions ([1,5]sigmatropic hydrogen shifts);[10] and (2) those involving ring closure reactions by cycloaddition (Diels–Alder[11,12] and ene[13] reactions, dipolar,[14] [2 + 2][15] and other cycloadditions),[16] Michael additions[17] aldol condensations (under basic conditions),[18] Mannich[19] and miscellaneous addition reactions[20] and radical cyclizations.[21,22]

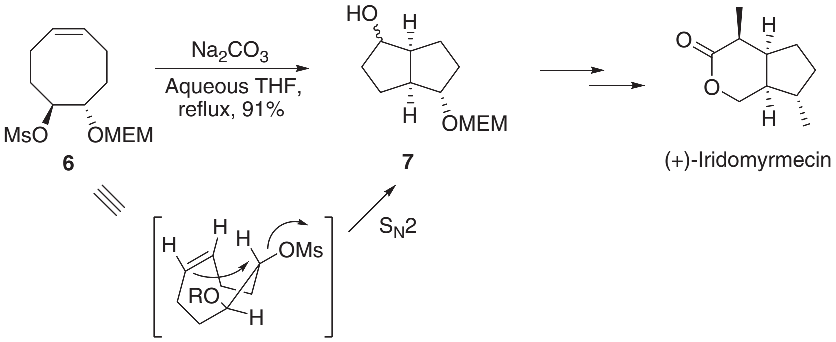
This chapter is particularly devoted to ring closure reactions involving electrophilic species such as carbocations or related intermediates. As such it constitutes an extension of chapters covering (Friedel–Crafts alkylations) and *see* Chapter 3.05. The chapter is simply divided according to the size of the starting macrocycles from 8 till 11 atoms within the rings, to facilitate retrieval of information. Systems involving more atoms within the ring and heteroatoms as nucleophilic counterparts are reviewed separately.

3.06.2 Eight-Membered Rings

3.06.2.1 Endocyclic Alkenes

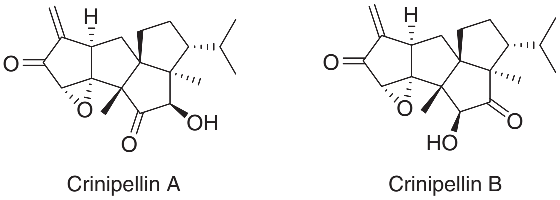
Following early observations of Cope et al. on transannular H-transfer reactions in cyclooctenes,[6b,23] many studies were carried out to explore transannular processes in endocyclic cyclooctene systems. Since 1990, attempts have been made to develop these transannulations in quest of efficient synthetic routes to complex structures or natural compounds.

Thus, a newer synthesis toward (+)-iridomyrmecin by Suemune et al. has been achieved starting from the mesylate **6** via the bicyclic species **7** (Scheme 4).[24] From **6** to **7**, the reaction proceeds through an S_N2 displacement of the mesylate leaving group by the facing alkene. The resulting secondary carbocation is then quenched by water.



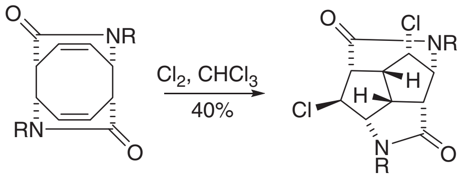
Scheme 4

In recent years, some studies have been designed to approach the challenging tetraquinane natural products crinipellins A and B (Scheme 5) by means of transannular cyclizations.



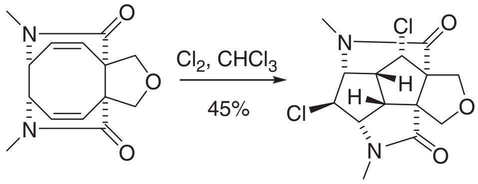
Scheme 5

Initial experiments have been investigated with pyridone dimers as rigid polycyclic compounds containing a 1,5-cyclooctadiene.[25] Surprisingly, chlorination of **8** produced the bicycle[3.3.0]octane **9** as a result of transannular closure and migration of one amide nitrogen (equation 3). Similarly, molecule **10** underwent the same process to give **11** (equation 4).



8 **9**

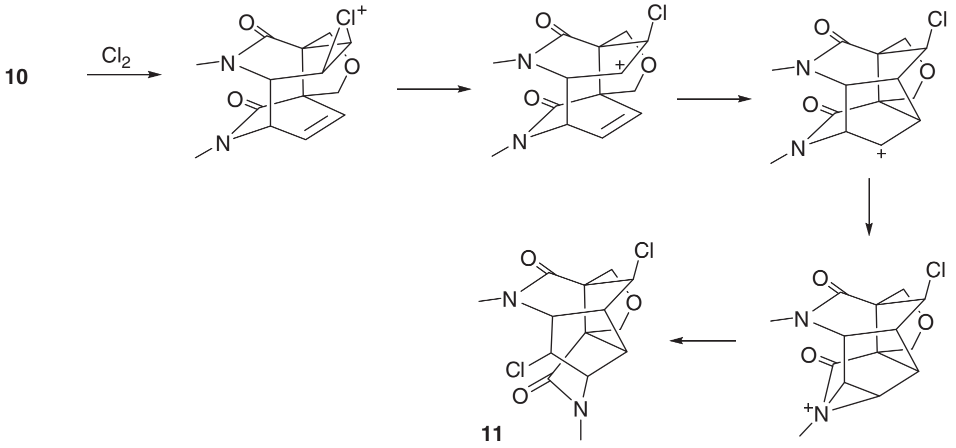
(3)



10 **11**

(4)

The cascade mechanism of such stereoselective reactions could be rationalized as in Scheme 6.



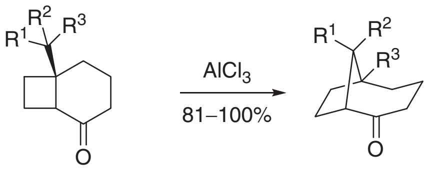
Scheme 6

Following these promising preliminary results, structure **12** was designed and synthesized in the hope of obtaining a bicyclo[3.3.0] skeleton as potential precursor of crinipellins.[26] However, chlorination of **12** produced only two unexpected products **13** and **14**, whose structures are based on a [4.2.0] ring system, as shown in Scheme 7.

It was therefore desirable to replace the alkene in **12** by an enone (**15**) with the purpose of preventing these unexpected pathways. This strategy did really work but unfortunately led to a new rearranged system **16**, as depicted in Scheme 8.

As cyclooctadiene systems seemed not to be an appropriate candidate for the expected transannular cyclization into the skeleton of crinipellins, an alternative exocyclooctene structure **17** was investigated.[27] Effectively, this compound reacted with a Lewis acid to form exactly the desired bicyclo[3.3.0] framework **18**, reminding the 5–5-5-5 fused ring system of crinipellins with three contiguous quaternary carbons, in excellent yield (Scheme 9).

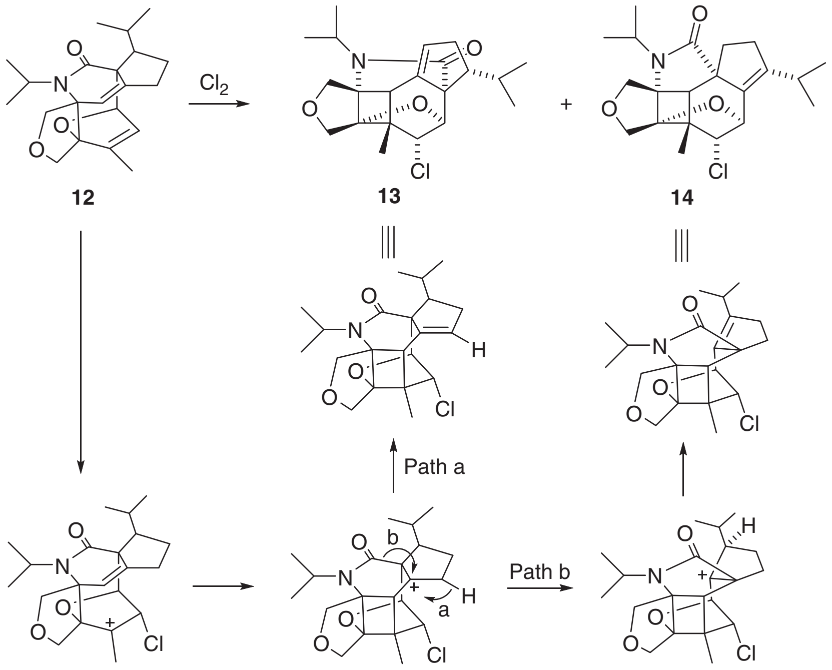
As a key structure of several terpenoids, the construction of bicyclo[4.2.1] frameworks via transannulation has taken interest in organic chemistry. Thus, the eight-membered ring cations **21** generated by ring opening of 6-substituted bicyclo[4.2.0]octanones **19**, under acid conditions, underwent an alkyl shift and subsequent cyclization to afford bicyclo[4.2.1]nonanes **20** in good yields (equation 5, Scheme 10).[28]



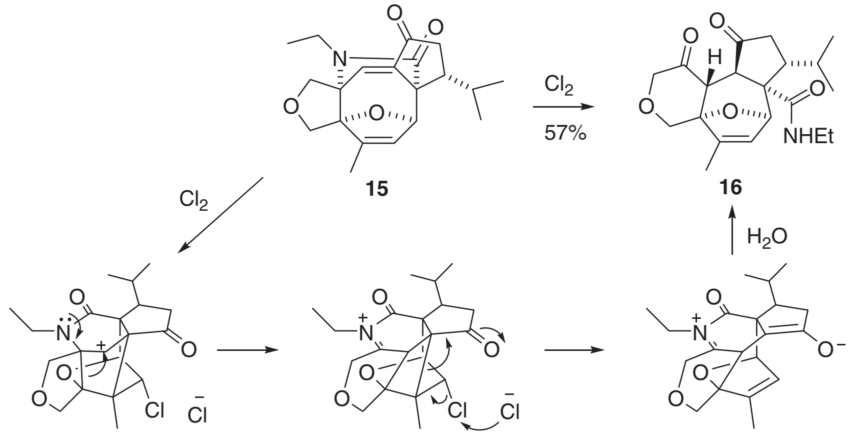
19a R^1, R^2, R^3 = Me
19b R^1, R^2 = Me, R^3 = H
19c R^1, R^2 = $-(CH_2)_5-$, R^3 = H

20

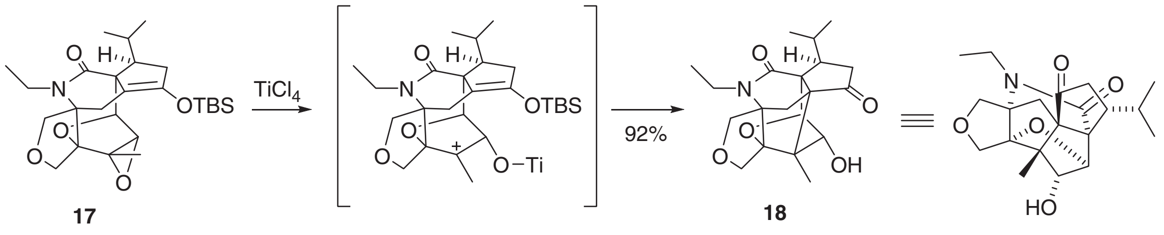
(5)



Scheme 7



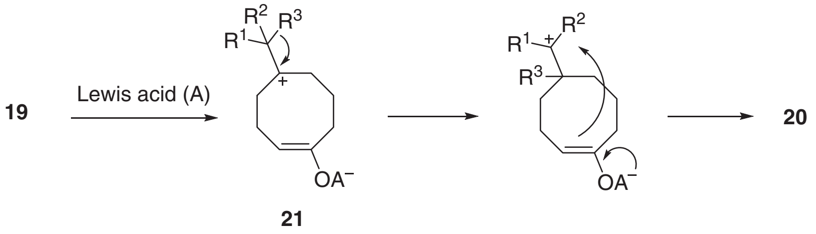
Scheme 8



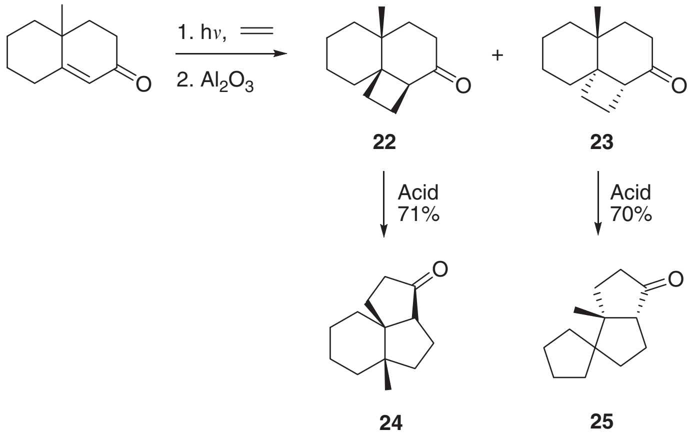
Scheme 9

The acid-catalyzed rearrangement of the two isomeric 5,6-disubstituted bicyclo[4.2.0]octanones **22** and **23** led to dissimilar results: the '*cis,cis*' ketone **22** gave an angularly fused ketone **24** whereas the '*trans,cis*' ketone **23** gave the spiroannulated triquinane ketone **25** as the major product (Scheme 11).[29]

On complexation with a Lewis acid, **22**, whose geometry is shown in Scheme 12, the cyclobutane ring decompresses by breaking apart across its weakest bond. This movement of electron toward the oxygen atom of the carbonyl is eased by the

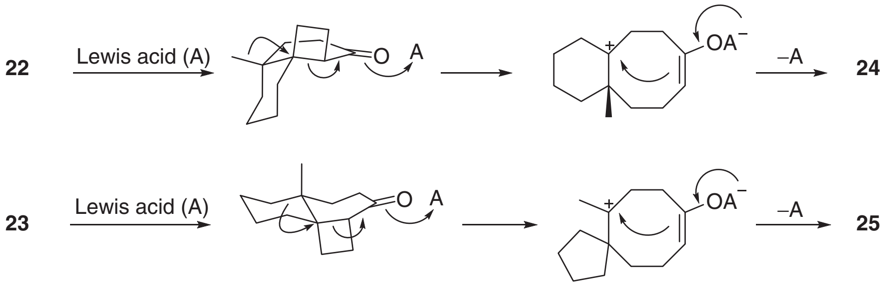


Scheme 10



Scheme 11

migration of the only group antiperiplanar to the bond experiencing cleavage, namely the methyl group. The resulting tertiary carbocation, located at the ring junction reacts with the enolate across the eight-membered ring, yielding product **24**. In the case of **23**, the story is much the same. However, the only antiperiplanar group now capable of migrating during concomitant collapse of the cyclobutane is a methylene from the adjacent cyclohexane (Scheme 12). As in the case of **22**, the resulting tertiary carbocation further react with the enolate located on the opposite side of the eight-membered carbocycle to finally afford product **25**.

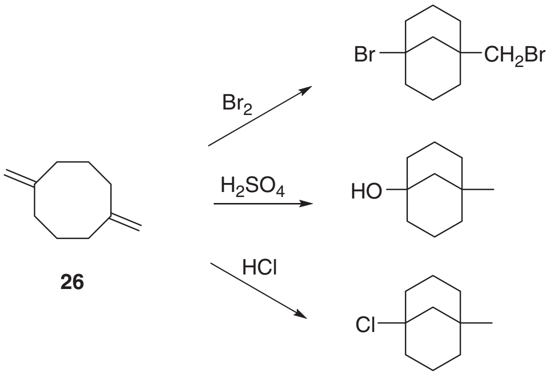


Scheme 12

3.06.2.2 Exocyclic Alkenes

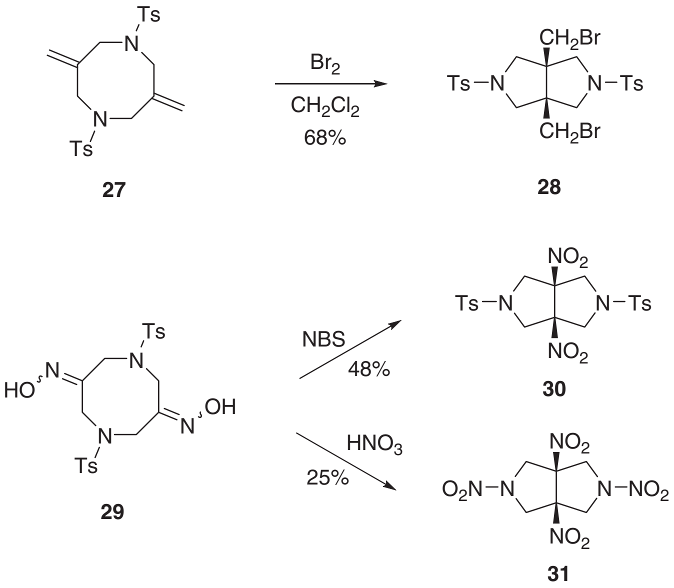
Like endocyclic dienes, exocyclic dienes are also good substrates for various transannular transforms. To date though, very few studies on these systems have been carried out. Early examples are the transannular additions of bromine, hydrochloric acid, or water (strongly acidic aqueous solution) to 1,5-dimethylenecyclooctane **26** giving the corresponding bicyclic products in acceptable to good yields (Scheme 13).[30]

At first glance, it appears surprising that the introduction of nitrogen atoms inside the ring might modify completely the outcome of the transannular electrophilic cyclizations of compounds related to **26**. Thus, diaza-analogs of **26** such as 3,7-bismethylene-1,5-diazacyclooctane **27** offer a facile entry into the previously inaccessible (although apparently simple)



Scheme 13

3,7-diazabicyclo[3.3.0]octane ring **28**, precursor of various heterocyclic propellanes.[31] Diene **27** is prone to undergo transannular addition but unlike the case of **26**, the bicyclo[3.3.0]octane **28** was obtained instead of a bicyclo[3.2.1]nonane skeleton. This quite different behavior of **27** from carbonium ion considerations guided the preparation of 1,5-dinitro-3,7-diazabicyclo[3.3.0]octane derivatives **30** and **31** from dioxime **29** in moderate yields (Scheme 14).



Scheme 14

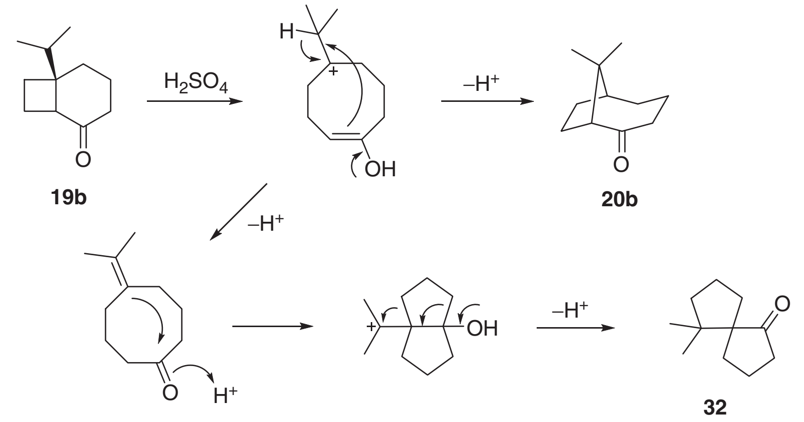
It has already been discussed that compound **19b** reacts with Lewis acids to yield ketone **20b** (equation 5 and Scheme 10). When treating **19b** with sulfuric acid, **20b** is again one of the resulting products (Scheme 15). It is, however, remarkable that a small amount of spiroannulated diquinane ketone **32** is also isolated as a byproduct.

Following these observations, some 5-cyclopentylidenecyclooctanone derivatives **33**, **35**, and **37** were envisaged and synthesized in an attempt to generate helical polyspiroquinanes. However, only **33** showed the desired cascade rearrangement leading to the spiroquinane structure **34**, whereas the two others afforded propellane- or polyquinane-type compounds (**36** and **38**–**41**) (Schemes 16, 17, and 18).

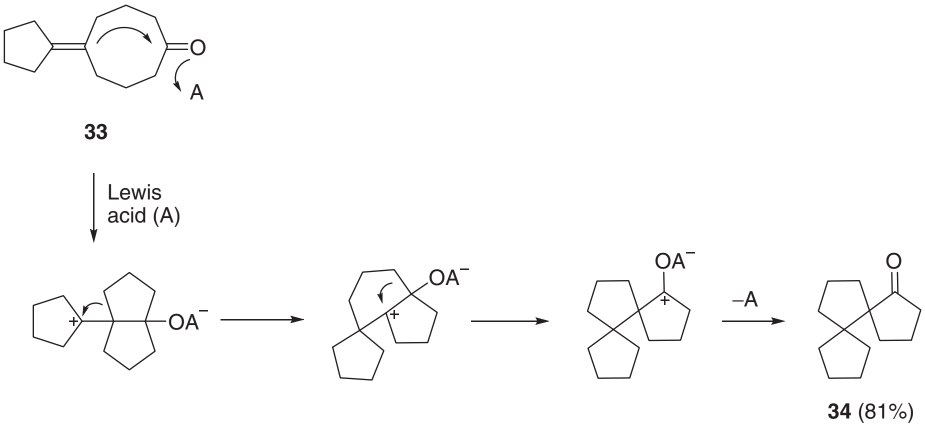
The different behavior of **37** (Scheme 18) in sulfuric acid and in the presence of a Lewis acid inducing various product mixtures may be due to kinetic control on the formation of its intermediate carbocations during the reaction.[32]

Other attractive studies on transannulation in exocyclic polyene systems involve the formation of adamantane derivatives. Early synthesis of this skeleton were realized via the ring closure of 1,5-dimethylenecyclooctane systems such as 1,3,5,7-tetramethylenecyclooctane **42** and 3,7-dimethylenebicyclo[3.3.1]nonane **43** (Scheme 19).[30b]

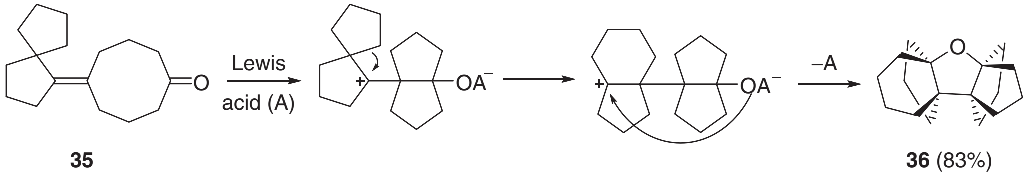
Diene **43** reacts with N-halogenosuccinimides (NXS with X=Cl, Br, and I) to yield carbocations **44** (Scheme 20), which proved to be much more stable than equivalent norbornyl carbocations.[33]



Scheme 15



Scheme 16



Scheme 17

Once formed, **44** can then further react with a plethora of external nucleophiles such as halide anions or solvent molecules in the final step to give various halomethyladamantanes. Some examples are shown in Scheme 21 to illustrate the scope of the sequence starting from N-bromosuccinimide and **43**.[34]

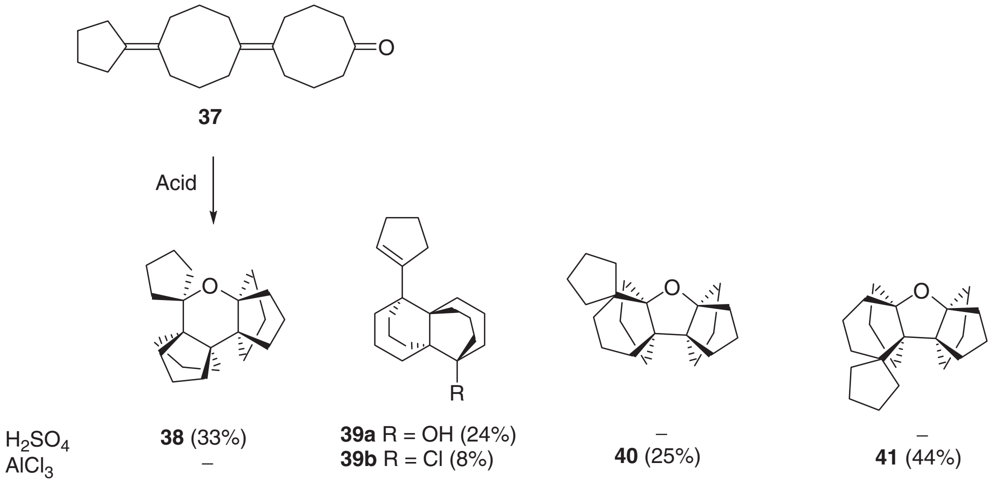
This method is very versatile and works well with substituted alkenes like **45** (Scheme 22).

Ring system **43** has also been efficiently used to prepare diverse novel functionalized fluoroadamantanes of pharmaceutical interest (Scheme 23).

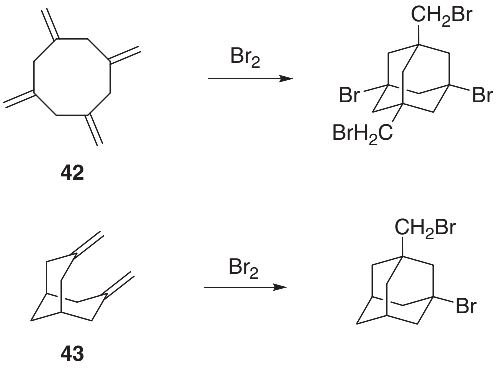
Enone **46** built around the exocyclic cycloctenone fragment was synthesized in order to study the stereochemistry of electrophilic substitution (S_E) reactions.[35] While investigating its cyclization, a number of cyclized products **47–51** were obtained according to the amount of *para*-toluenesulphonic acid (in toluene) used (Scheme 24).

The formation of these compounds could be conceived by an '*ene*' mechanism or acid-catalyzed S_E reaction of enone **46** (Scheme 25).

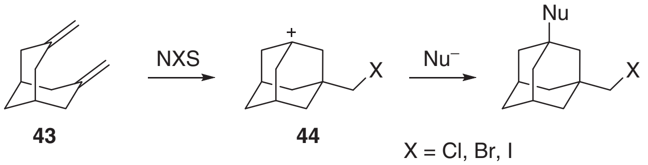
In another powerful transannular cyclization, the complex and congested tetraquinane systems **55** and **56** were obtained when tricycle **52** was treated with triethylaluminum with or without trimethylsilyl cyanide (Scheme 26). The formation of the non-classical carbocations **53** and **54**, which have only the *β*-face available for nucleophile attack could account for the stereoselectivity of these reactions.[36]



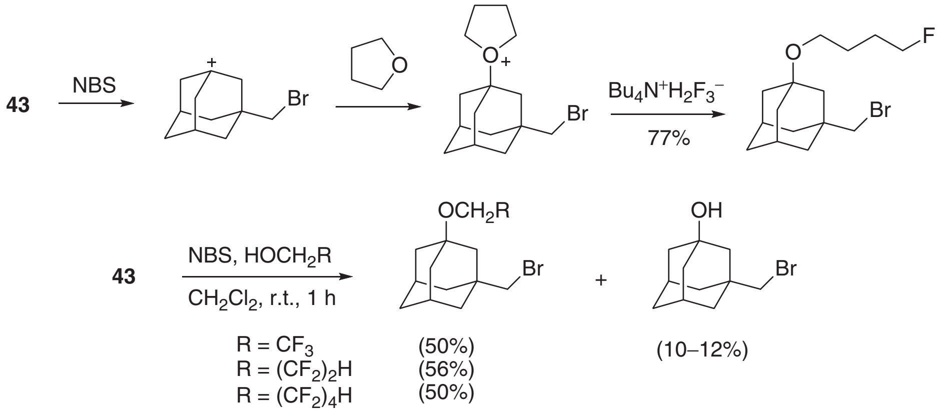
Scheme 18



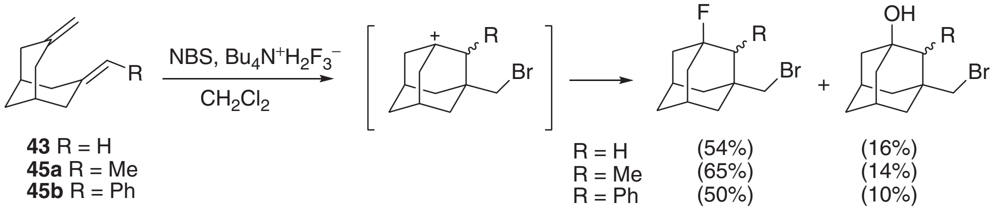
Scheme 19



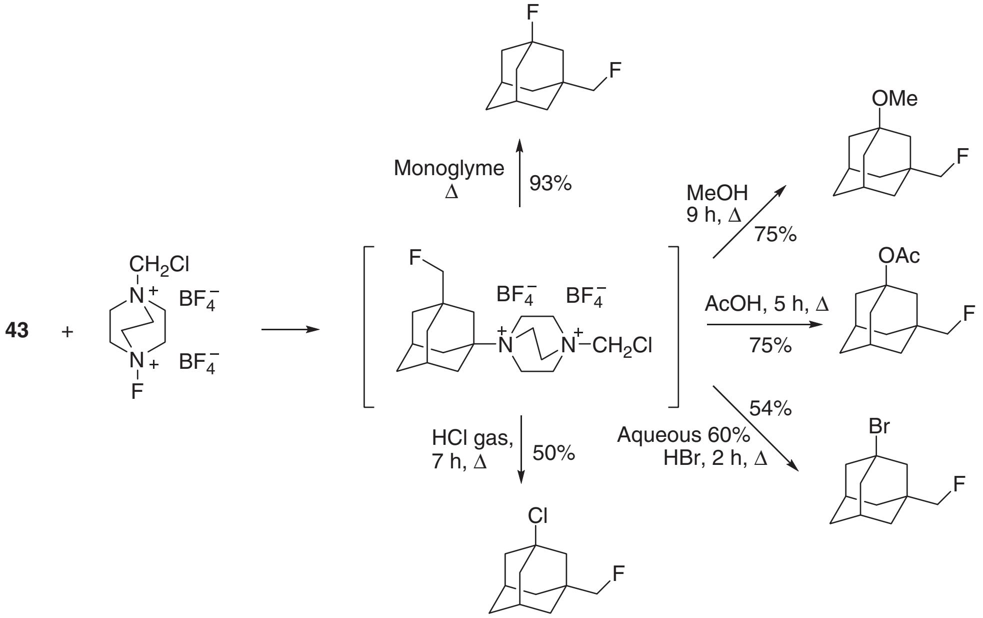
Scheme 20



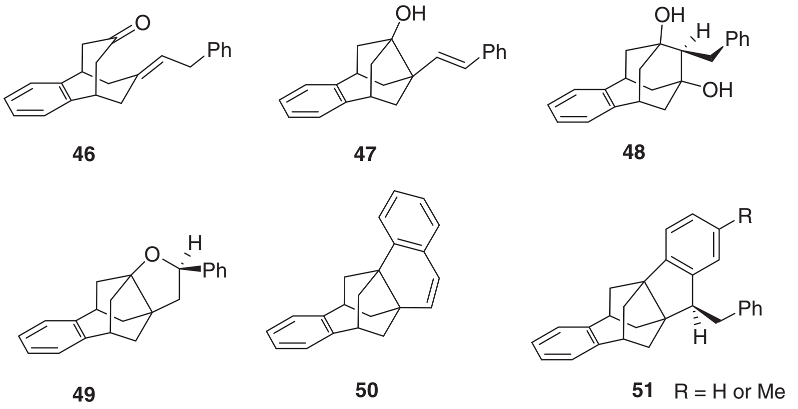
Scheme 21



Scheme 22



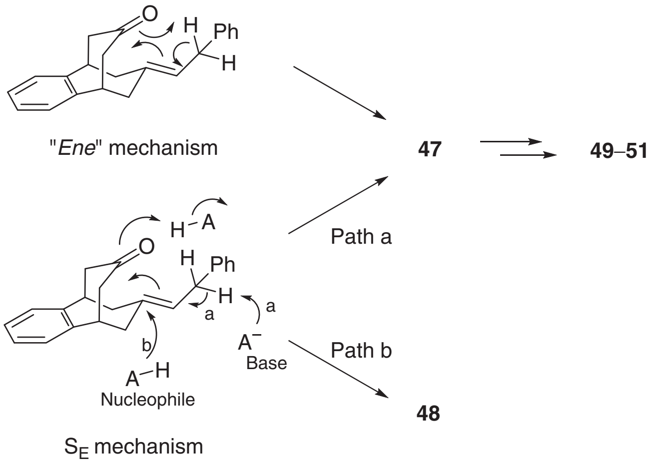
Scheme 23



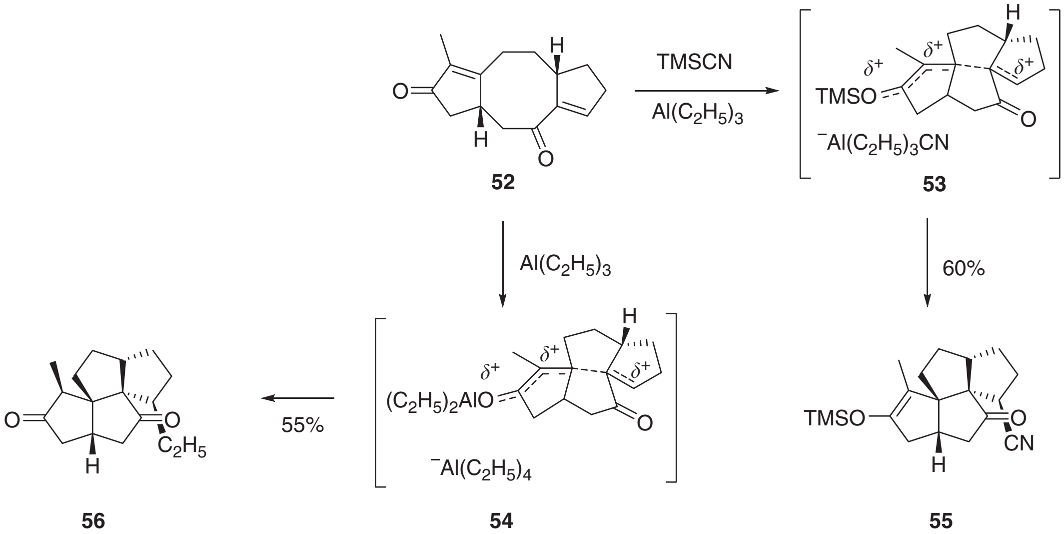
Scheme 24

3.06.3 Nine-Membered Rings

Transannular reactions in the nine-membered rings concern various ring contraction and ring expansion to produce smaller and larger ring systems, respectively, or, in some specific cases, bicyclic compounds. Scheme 27 shows an interesting example of such transformation. In the event, the 9-membered lactone **57** undergoes a ring expansion under mild desilylation conditions to produce 10–12-membered lactones **58**.[37] The mechanism obviously involves an alkoxy group, which attacks the carbonyl group

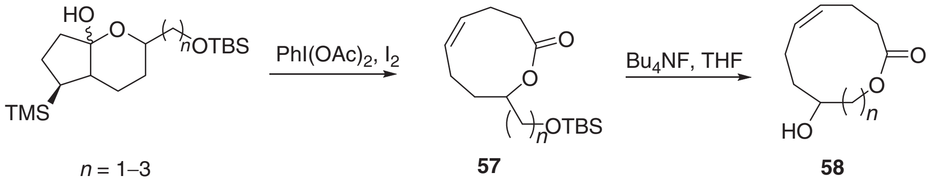


Scheme 25



Scheme 26

as a nucleophile and in a transannular approach. The driving force is likely the relief of tension within the nine-membered starting lactone **57** because both the starting materials **57** and the products **58** bear the same functionalities.

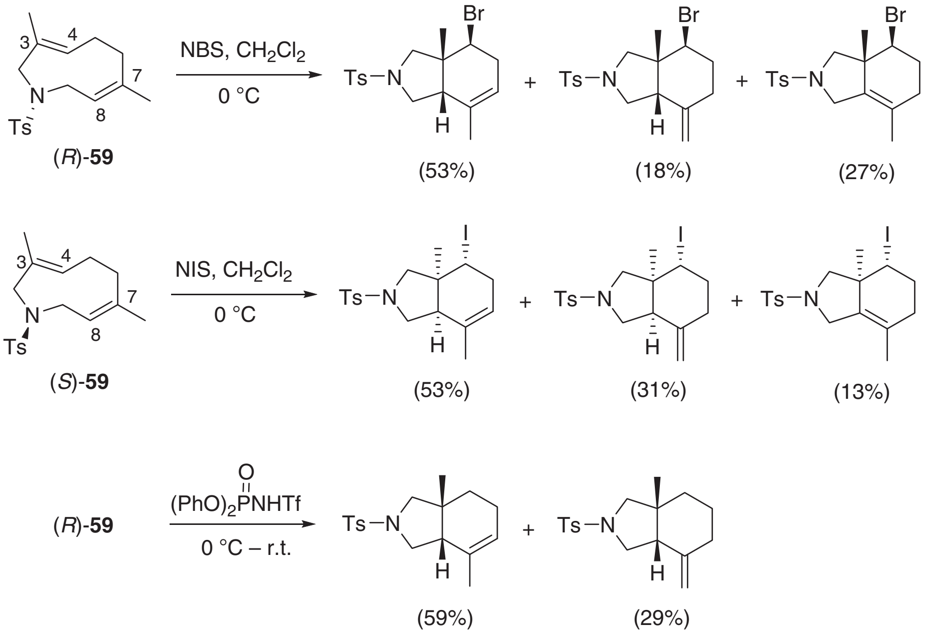


Scheme 27

Numerous reviews involving the synthesis, structure, reactivity, and applications of nine-membered heterocycles have been published.[38] This section covers some studies on the transannular cyclizations in nine-membered systems leading to the creation of carbon–carbon covalent bonds.

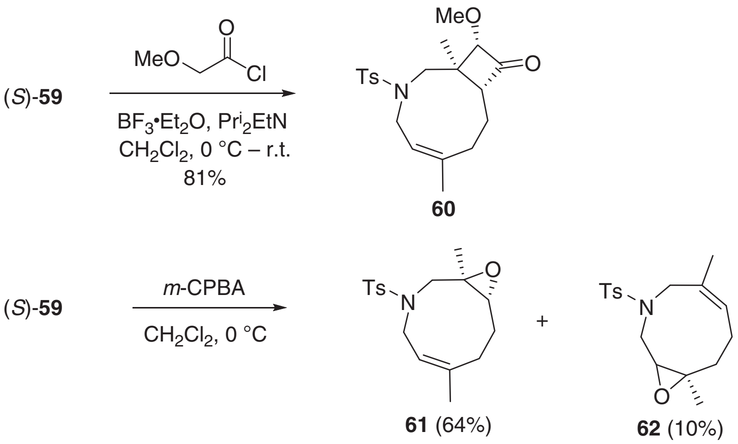
3.06.3.1 Dienes and Related Systems

The nine-membered diallylic amide **59**, consisting of two stable planar conformers (atropisomerism is common in constrained nine-membered rings, e.g., caryophyllene), was reported as a good substrate for transannular stereoselective transformation due to the perpendicular arrangement of its two olefins toward the ring.[39] Indeed, direct transannular reactions of its two mirror image atropisomers (*R*)-**59** and (*S*)-**59** provided several bicyclo[4.3.0] derivatives as mixtures of olefinic regioisomers in good yields and with high stereoselectivity (Scheme 28).



Scheme 28

These reactions could be rationalized by a cationic activation at the C3–C4 olefin of **59** from the outer face followed by a transannular C4–C7 or C3–C7 bond formation. Furthermore, the [2 + 2]cycloadduct **60** and epoxides **61** and **62** formed from **59** (Scheme 29) also underwent stereoselective transannular transformations.

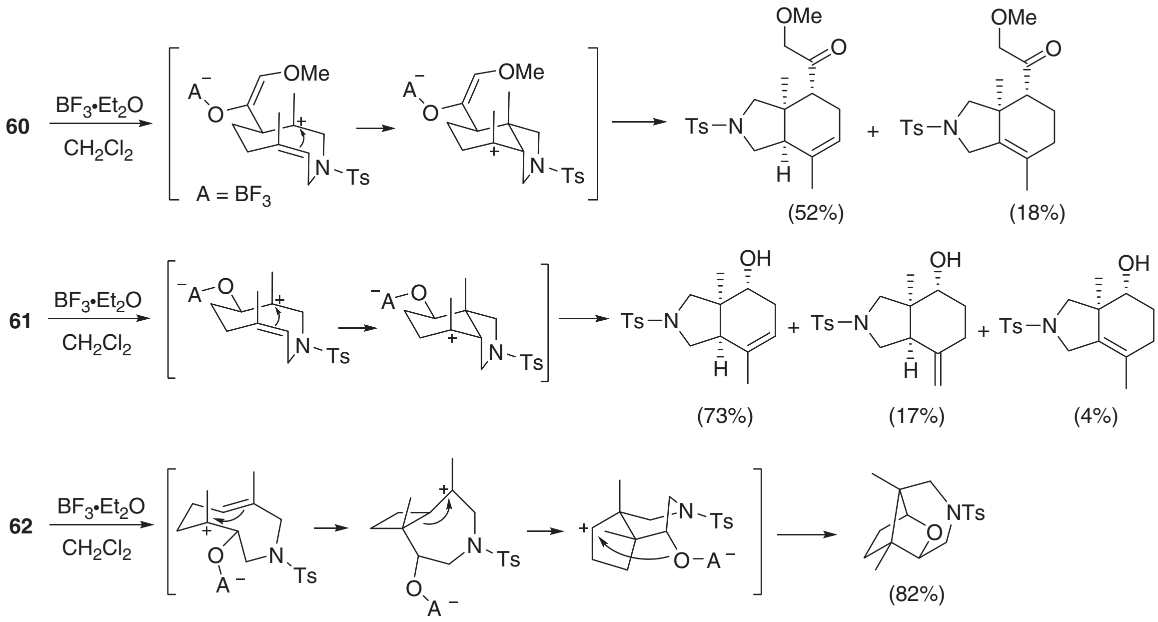


Scheme 29

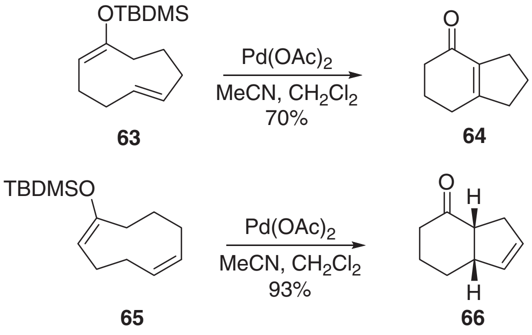
Lewis acid complexation of the carbonyl in **60** and the epoxide oxygen in **61** and **62** triggered ring opening of the four- and three-membered strained rings, respectively. The resulting tertiary carbocations underwent electrophilic transannulation with the facing alkenes to give a variety of bicyclic products in good yields (Scheme 30).[39]

Under palladium(II)-mediated cycloalkenylation conditions, the nine-membered ring enolsilanes **63** and **65** transformed into bicyclic ring products **64** and **66** in good to high yields (Scheme 31).[40]

The regioselectivity in these reactions are dependent on the geometry of the olefin in the starting compounds. Namely, (*E*)-cycloalkene **63** and (*Z*)-cycloalkene **65** produce two different sigma-bonded palladium intermediates **67** and **68**, respectively.



Scheme 30



Scheme 31

These intermediates give different *syn*-palladium β-hydride elimination products **64** and **66** due to the different orientation of hydrogen atoms available for elimination (Scheme 32). In principle, **67** could *syn*-eliminate to form two alkenes. However, only the most substituted, hence more stable, product is observed experimentally.

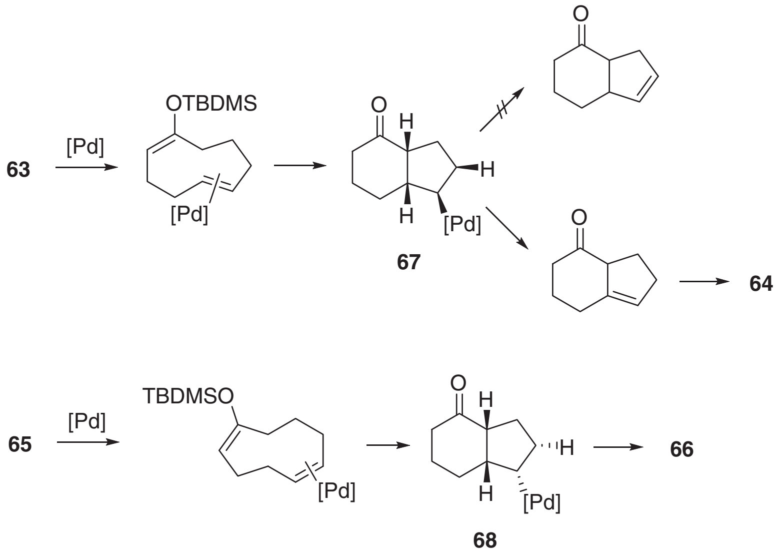
3.06.3.2 Enones

Recently, the enantioselective synthesis of the bicyclo[4.3.0]nonane ring system (Scheme 33) of pinguisane-type sesquiterpenoids (like pinguisenol, acutifolone A, and norpinguisanolide) and austrodorane sesquiterpenoids (like austrodoral, austrodoric acid, norrisolide, and chromodorolide) has been achieved by means of a Bronsted acid-promoted transannulation.[41]

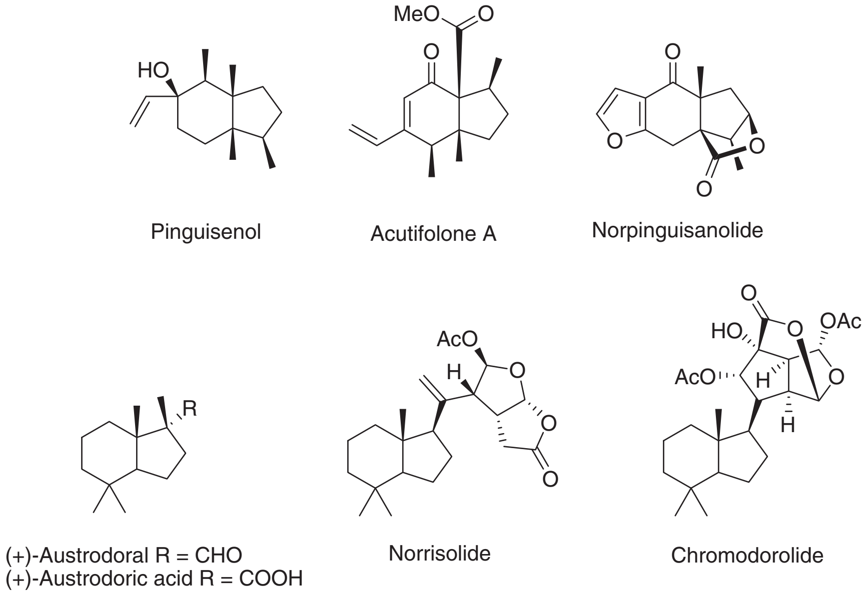
Thus, the compounds **69** and **72** underwent transannular cyclization to yield the bicycles **71** and **74** matching the desired pinguisane and austrodorane skeletons, respectively (Scheme 34).

There exist two competing mechanisms for these reactions depending on which group gets protonated first, the ketone or the alkene. Protonation of the alkene following path a (Scheme 35) turns the alkene into an electrophilic group to which the opposing enol form of the ketone donates electrons. On the contrary, when the carbonyl moiety is protonated (path b), the flow of electrons is reverted, as in a Prins reaction. The most substituted (R=Me) hence more nucleophilic alkene favors the Prins reaction. As a result **69** follows path a (R=H); whereas, macrocycle **72** follows path b (R=Me).

Furthermore, while carried out in nonnucleophilic solvents, the cyclization of **73** tended toward the formation of **75** by loss of a proton from the intermediate carbocation (Scheme 36). Additional transformations on **75** gave aldehyde **76**, which offers a potential entry into the highly functionalized bicyclo[4.3.0]nonane core of the austrodorane sesquiterpenoids (Scheme 33). In both **70** and **73** cases, the lactone bridge, which is formed from the transannular lactonization of the nine-membered rings **69** and **72**, accomplished its task of preventing cyclization via the oxygen and enolization between C1 and C2.



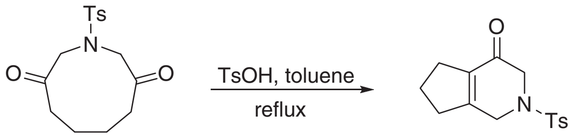
Scheme 32



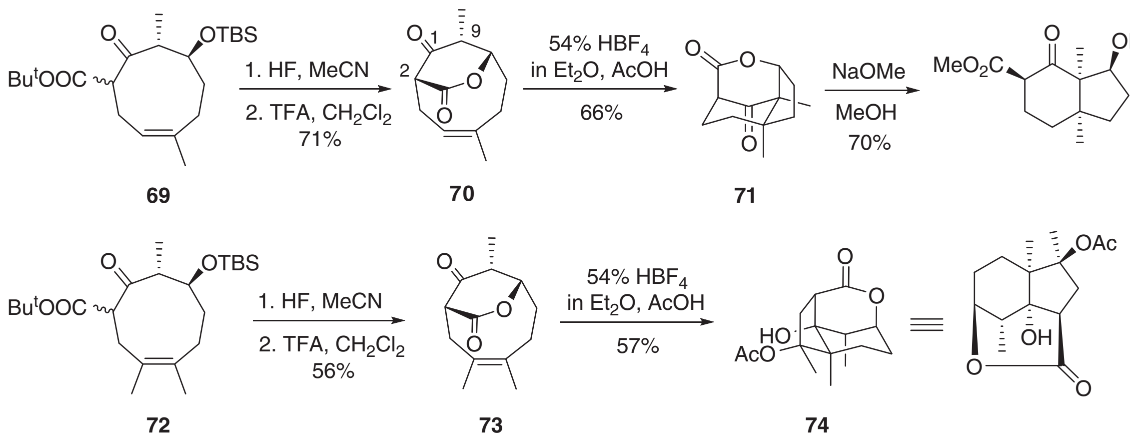
Scheme 33

3.06.3.3 Miscellaneous

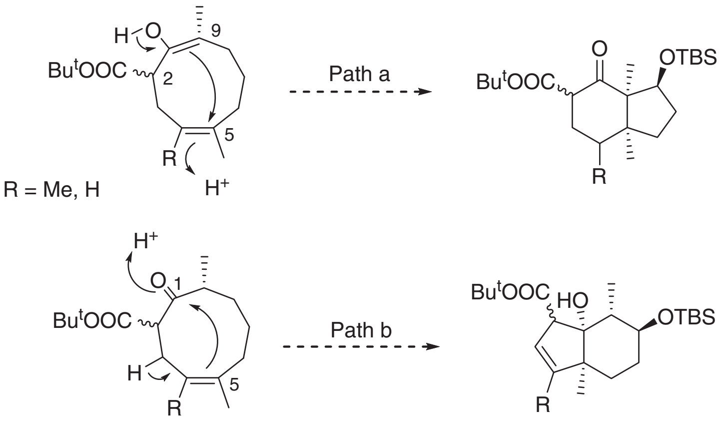
Other examples of transannular electrophilic cyclization in nine-membered rings are illustrated below. These reactions involve obviously intramolecular aldol condensations to afford bicyclic compounds (equations 6[42] and 7[43]) or a transannular keto-alkyne cyclization (equation 8[44]). It is worth noting that the crystal structure of **77** shows the perpendicular orientation of the ketone to the alkyne as well as the lack of conjugation between the carbonyl group and the aromatic ring, which could explain why the transannular cyclization displayed in equation 8 occurred successfully in a quantitative conversion.



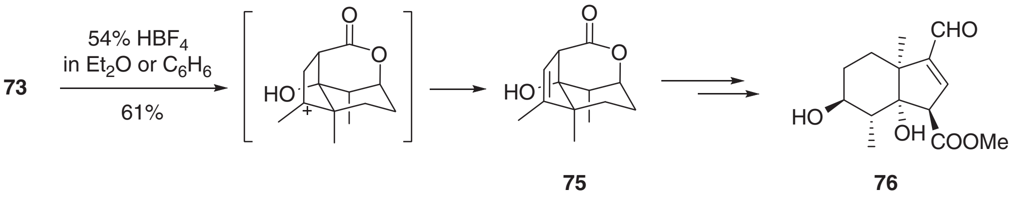
(6)



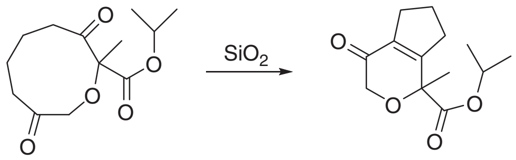
Scheme 34



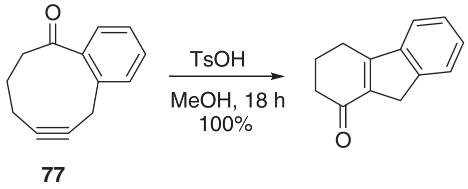
Scheme 35



Scheme 36



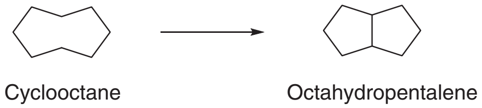
(7)



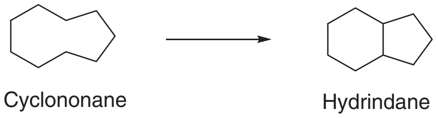
(8)

3.06.4 Ten-Membered Rings

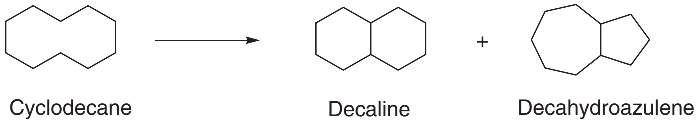
Bicyclic frameworks are ubiquitous in nature either as isolated systems or as part of larger entities. For example, bicyclo[3.3.0]octane is a portion of hirsutanes and capnellanes[45] and bicyclo[4.3.0]nonane is the core of many natural products (see Sections 3.06.2 and 3.06.3). These important bicycles, also known as octahydropentalene[46] and hydrindane, respectively, can be synthesized following transannular processes, particularly electrophilic additions, from cyclooctane-based (equation 9) and cyclononane-based (equation 10) precursors, respectively. Likewise, adequately decorated cyclodecanes can react to produce bicyclo[4.4.0]decanes and bicyclo[5.3.0]decanes, also named decalins and decahydroazulenes (equation 11). The decalin ring system is a prevalent structural backbone contained within the natural products, particularly terpenoids.[47] Conceptually, dienes, epoxyalkenes, enones, diynes, and ynones can be used in transannular strategies to produce bicyclodecanes. All these five types of compounds have been actually studied and utilized in total synthesis over the last two decades.



(9)



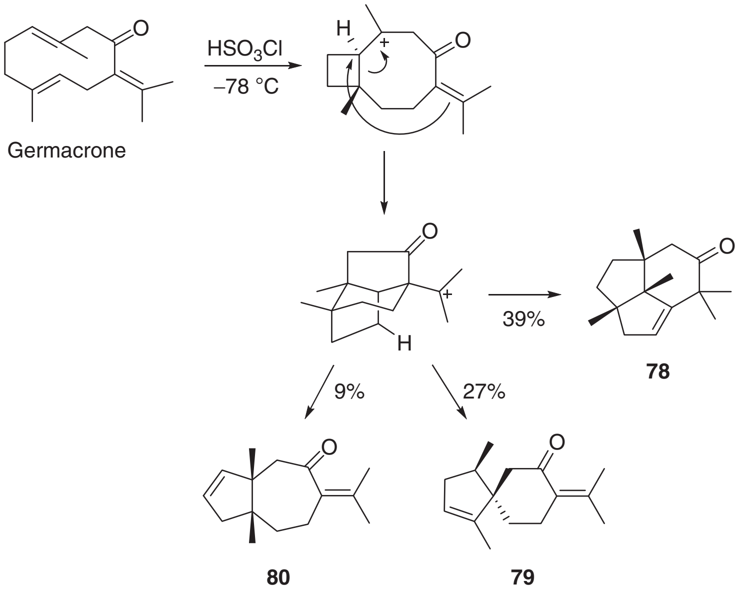
(10)



(11)

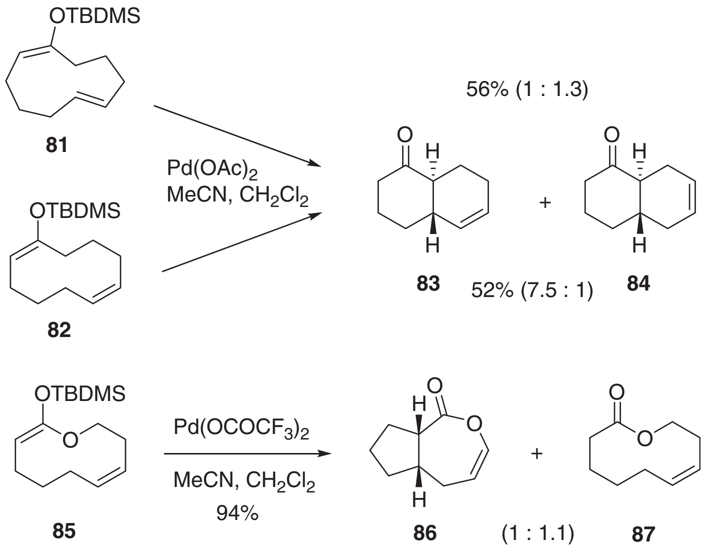
3.06.4.1 Dienes

The electrophilic transannular cyclization of germacrone, a 1,5-diene (Scheme 37),[48] gives rise to a strained bicyclo[6.2.0]decan-2-ylium reactive intermediate ion, which evolves to produce several unusual skeletons through subsequent cyclization and Wagner–Meerwein rearrangements. However, the method may prove synthetically unreliable as shown by the results obtained when germacrone was treated with chlorosulfonic acid in 1-nitropropane at −78 °C. The addition of 4 equivalents of acid to 1 equivalent of germacrone gave a mixture of three compounds **78** (39%), **79** (27%), and **80** (9%).



Scheme 37

When treated with Pd(II), the 10-membered enolsilanes **81** and **82** give the same two *trans*-decalines **83** and **84** with reasonable yields (Scheme 38). Both reaction products **83** and **84**, differ from each other by the position of the alkene moiety, are obtained with different ratios depending on the geometry (either *E*- or *Z*-) of the alkene in the starting materials **81** and **82**.

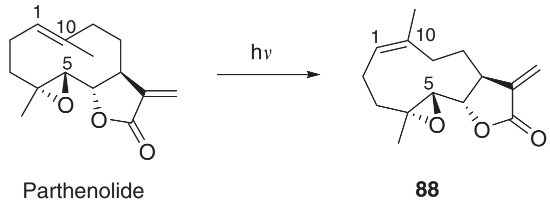


Scheme 38

Under similar conditions the 10-membered ketene acetal **85** is obviously unable to produce lactones isoteric to **83** and **84**. Instead the *cis*-fused bicyclic enol lactone **86** is formed together with an equivalent amount of lactone **87**, the latter corresponding to simple silyl deprotection of **85** (Scheme 38).[40]

3.06.4.2 Epoxyalkenes

A study was conducted to account for the biological reactivity of parthenolide, a sesquiterpene lactone. The work was destined to unravel the parameters of the electrophilic cyclization in the transannular environment of the 10-membered rings. The 1(10) *trans* double bond of parthenolide was isomerized with light to produce its *cis* isomer **88** (equation 12).[49]

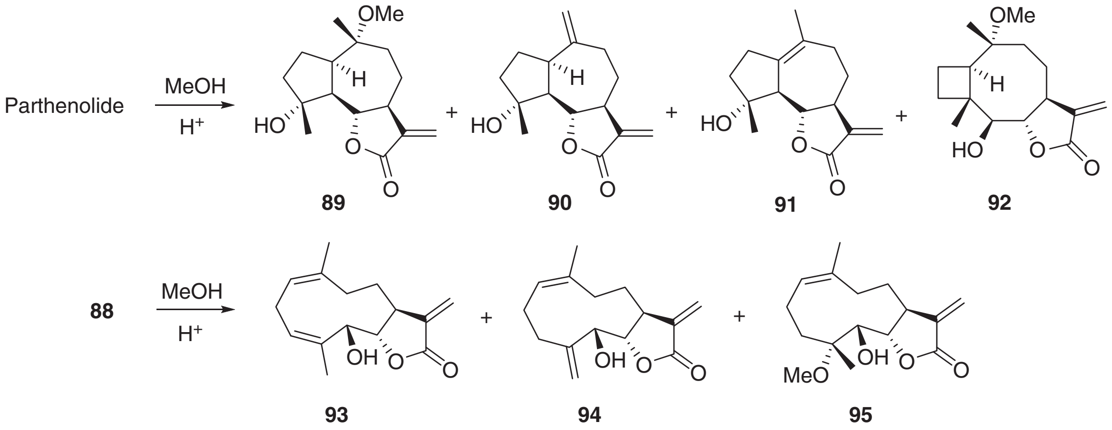


(12)

Although parthenolide reacted readily under acidic conditions to produce mostly guaiane derivatives **89**, **90**, and **91** and a bicyclo[6.2.0]decane system **92**, its *cis* isomer **88** remained stubbornly unreactive under the same conditions (Scheme 39), none of the products **93**–**95** being a transannular adduct. A computational conformational search revealed that the 1(10)-(*trans*) double bond dictates the overall molecular shape of parthenolide and **88**. The crucial C1–C5 transannular distance is particularly affected, being as short as 2.92 Å in parthenolide. The same C1–C5 distance remains rather long (3.33 Å) in the case of its *cis* isomer **88**, preventing the occurence of electrophilic cyclization across the 10-membered ring. On the contrary, parthenolide and related systems can undergo facile electrophilic transannular cyclization.

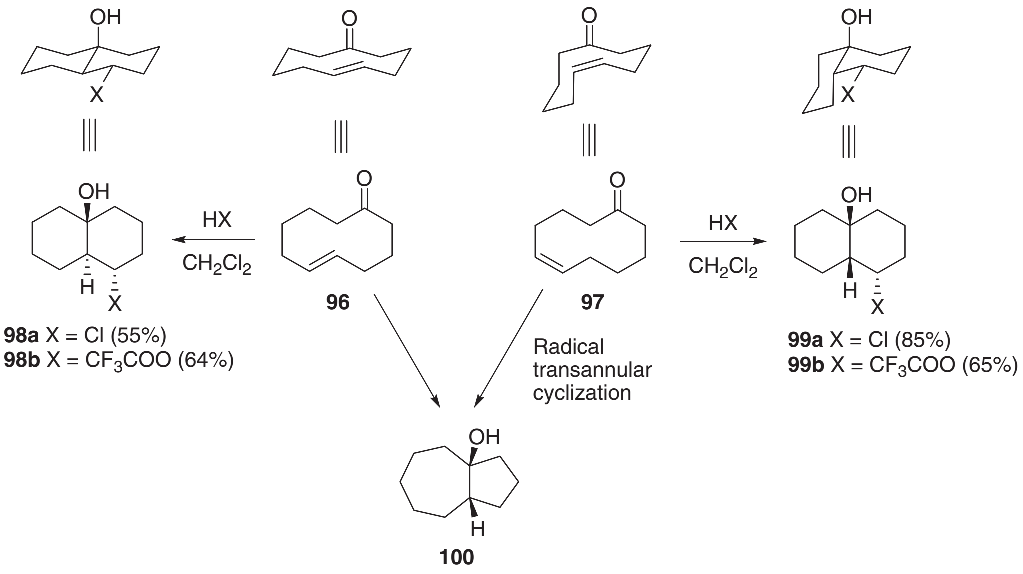
3.06.4.3 Enones

As reactive partners an alkene and a ketone can undergo Prins reaction under acidic conditions and in the presence of a nucleophile. The process has been studied in the transannular environment of 10-membered rings and without substituents (Scheme 40). It was then possible to uncover the natural outcome of the reaction without any other influences but the macrocycle itself and the geometry of the alkene. It first appeared that the 5-cyclodecenones **96** and **97** lead only to bicyclo[4.4.0]decane products by electrophilic cyclization. The other possible product **100** based on the decahydroazulene framework (equation 11) can be prepared through a radical transannular cyclization.[50]



Scheme 39

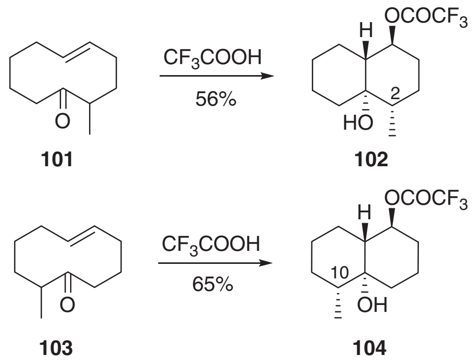
The stereochemistry at the ring junction in the products is fully determined by the geometry of the alkene in the starting macrocylic keto-alkene. The (*E*)-5-cyclodecenone **96** yields *trans*-fused decalinols **98**, whereas its (*Z*)-isomer **97** produces only *cis*-fused decalinols **99**. The acid used (HX, either hydrogen chloride or trifluoroacetic acid) simply behaves as a nucleophile attacking one end of the alkene, whereas the other end develops a bond with the carbon atom of the protonated ketone. Its nature does not influence the way the alkene and the ketone adopt their relative positions at the transition state. Consequently, both hydrogen chloride and trifluoroacetic acid give the same geometry and also similar yields (see **98a**, **98b**, and **99a** and **99b** in Scheme 40).



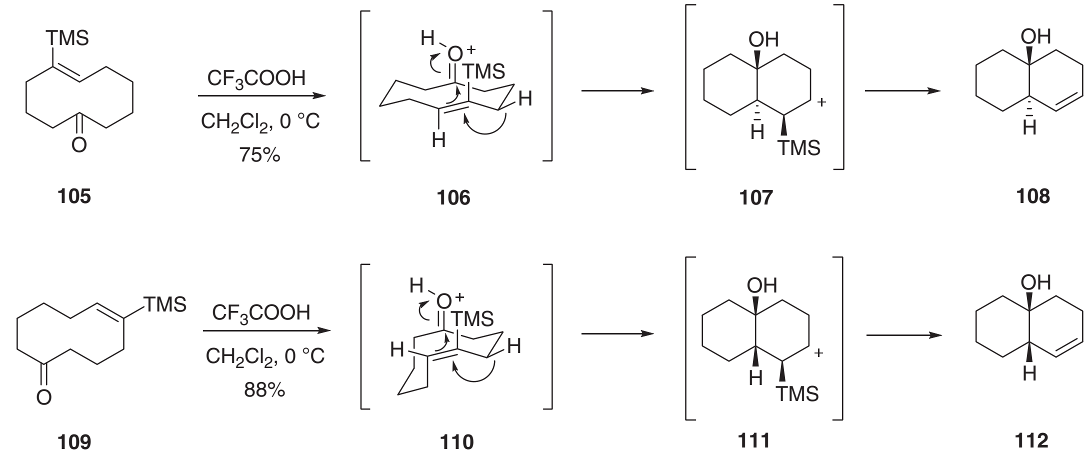
Scheme 40

Methyl and trimethylsilyl substituents were later added to macrocycles **96** and **97**. The modified macrocycles **101** and **103** behaved exactly in the same way as their parent model **96**; only *trans*-fused decaline derivatives were obtained from (*E*)-5-cyclodecenones (Scheme 41). Thus, the trifluoracetic acid-induced transannular cyclization of (*E*)-2-methyl- and (*E*)-10-methyl-5-cyclodecenone (**101** and **103**) afforded the expected *trans*-fused decalinols **102** and **104**, respectively.[51]

In the same way, the trifluoroacetic acid triggered electrophilic cyclization of 5-cyclodecenones functionalized with a vinylsilane moiety was studied (Scheme 42).[52] Although the bulky trimethyl silyl group was directly located on the reacting alkenes, it did not disturb at all the natural trend previously described. In the case of (*E*)- and (*Z*)-5-(trimethylsilyl)-5-cyclodecenones **105** and **109**, the protonated macrocyles adopted the conformations **106** and **110** before cyclization as expected. Nevertheless, trifluoroacetic acid did not add to the alkenes as before. Instead, concomitant hydride migrations occurred to yield the intermediate *β*-silylcarbocations **107** and **111** well suited for elimination. The resulting alkenes **108** and **112** were again the expected products, their backbones being *trans*- and *cis*-fused decalines, respectively.



Scheme 41



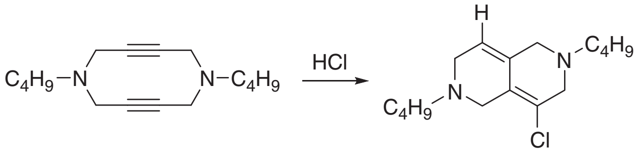
Scheme 42

It proved that it is eventually possible to force a 5-cyclodecenone to produce hydroazulenols instead of decalinols. This was made possible by using an alkene adequately substituted, which would favor the appearance of a transient tertiary β-silylcarbocation during the course of the reaction. When the 5-cyclodecenone **113** was subjected to Prins reaction conditions, by means of trifluoracetic acid in tetrahydrofuran, the *trans*-fused hydroazulenol **119** was the main product together with its *cis*-fused isomer **118** (Scheme 43). Both products have the same relative antistereochemistry for the alcohol and the ethoxy ether as found in the reactive conformations **115** and **114**, respectively, in which the orientation of the alkoxy substituent is *anti* to the keto oxygen. After transannular electrophilic ring closure leading to the most stable tertiary carbocations **117** and **116**, *exo* elimination involving the silyl groups takes place and afford the observed products.[53]

3.06.4.4 Alkynes

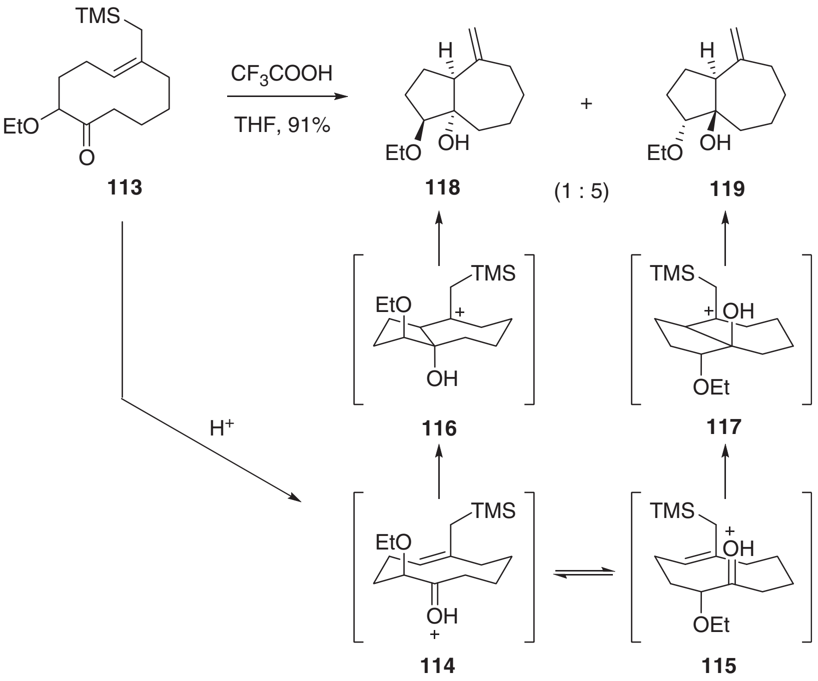
The close proximity of two alkynes results in bond formation between them. The simplest example one might think of in a 10-membered ring is 1,6-cyclodecadiyne (Scheme 44).

The easily built symmetrical diamine **120** (equation 13), topologically equivalent to 1,6-cyclodecadiyne, produced the bicyclic compound **121** when submitted to acidic conditions (HCl).[54]

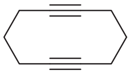


120 **121** (13)

The acid-catalyzed transannular rearrangement of 5-cyclodecynone **122** into the bicyclic enone **126** has been the subject of much debate since its discovery in 1971 (Scheme 45).[55] More recent studies support the idea that the electrophilic protonated



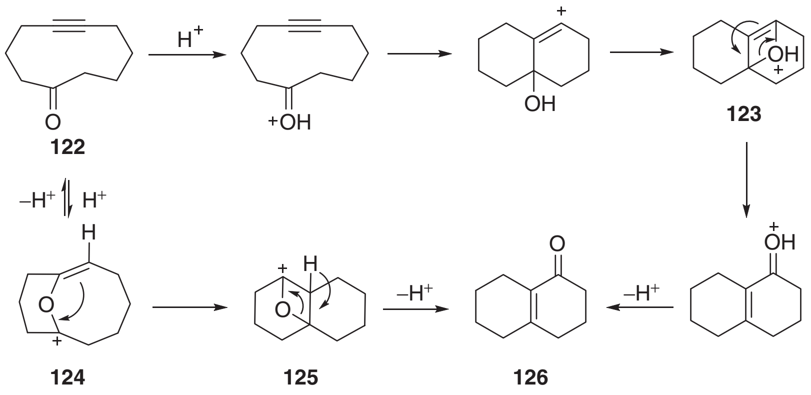
Scheme 43



1,6-Cyclodecadiyne

Scheme 44

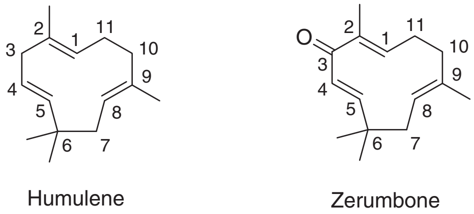
ketone is attacked by the opposite triple bond.[56] The resulting vinyl cation could then rearrange into the protonated form of **126** via the oxetene intermediate **123**. Three years later, this first explanation was challenged considering that the strained anti-Bredt oxetene intermediate **123** was indeed much too unstable to be real.[57] The double bond in **123** is truly horribly twisted. A way around this major snag was to consider an alternate path in which protonation of the alkyne would occur first. This first step would be followed immediately (or concurrently) by transannular attack of the ketone through its oxygen atom to afford the eight-membered enol ether carbocation **124**. This [5.3.1] bicyclic system would rearrange into oxetane **125**, a lot less strained than oxetene **123**. Finally, a last rearrangement would produce the bicyclic enone **126**.



Scheme 45

3.06.5 Eleven-Membered Rings

Transannular cyclizations are of much importance in the synthesis of polycyclic complex molecules such as the polycyclic sesquiterpene systems. The transannulations related to carbocations generated from cycloundecapolyenes have been the subject of considerable research.[58] A majority of studies on transannular electrophilic cyclizations in 11-membered rings have been realized around humulene (Scheme 46).[59] Zerumbone, as the 3-ketone form of humulene, has also taken interest of some researchers. This section reports some novel transannular cyclizations in humulene derivatives as well as in zerumbone and its derivatives. An additional part presents transannular processes in some other 11-membered ring systems.

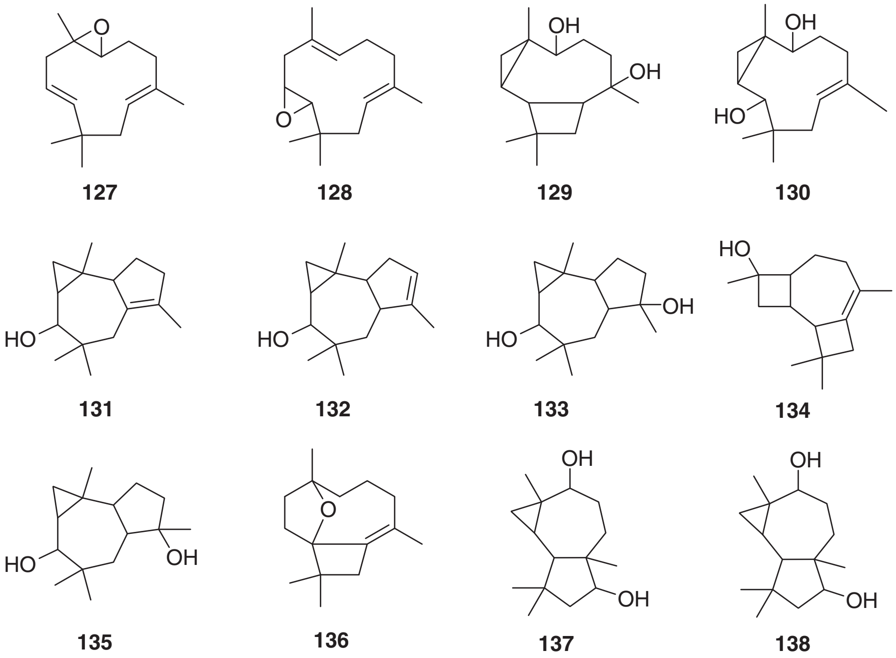


Scheme 46

3.06.5.1 Humulene Derivatives

3.06.5.1.1 Humulene-1,2- epoxide and humulene-4,5-epoxide

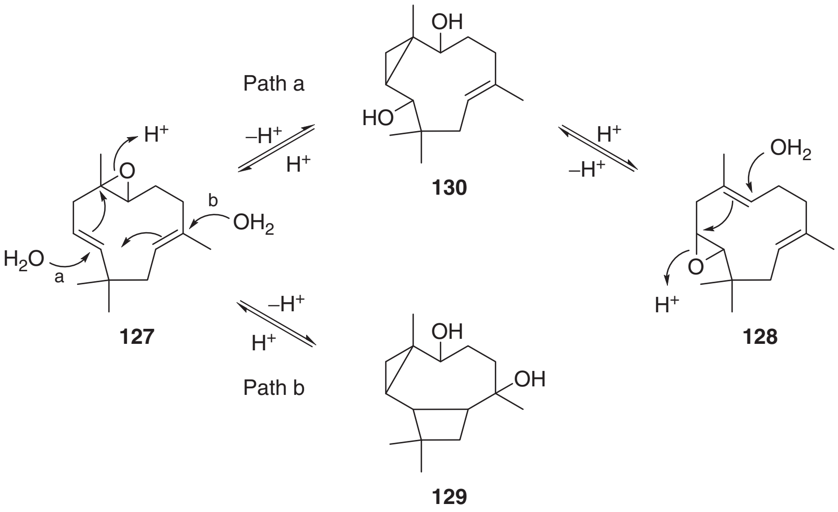
The hydrolysis of humulene-1,2-epoxide **127** and humulene-4,5-epoxide **128** (Scheme 47) conducted in buffer solutions at pH 4 produced complex product mixtures. Twelve compounds from **127** and sixteen from **128** accounted for 83% and 93%, respectively, of the whole mixtures. All the products issued from the hydrolysis of **127** were also present in the product mixture of **128**. Among all these compounds, 10 of them, **129–138**, are bicyclic and tricyclic ring systems resulting from transannular cyclizations.[60]



Scheme 47

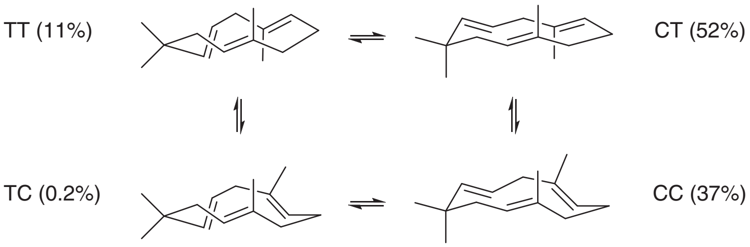
Further experiments and analyses suggested that **127**, **128**, and **129** exist in equilibrium in aqueous solution at pH 4 and the compound **130** might be the key intermediate to establish this equilibrium (Scheme 48).

In addition, humulene (and its epoxides **127** and **128** in particular) is known to adopt four minimally strained conformations abbreviated by CC, CT, TC, and TT (Scheme 49).[61] A thorough investigation could demonstrate that the equilibrium set up



Scheme 48

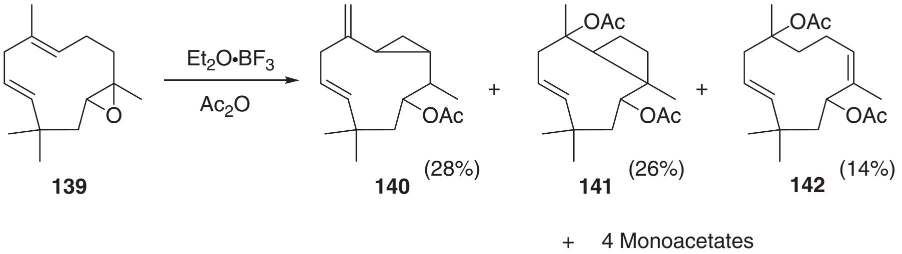
among **127**, **128**, **129**, and **130** can be rationalized by considering only the two most stable conformers CC and CT of humulene epoxides **127** and **128**.



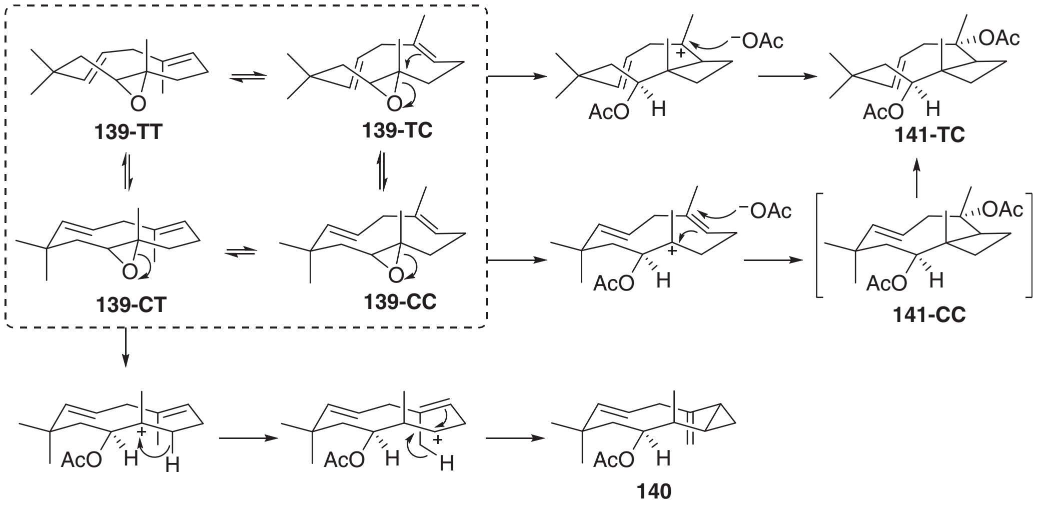
Scheme 49

3.06.5.1.2 Humulene-8,9-epoxide

Lewis acid treatment of humulene-8,9-epoxide ring **139** activated the epoxide and triggered its transannular ring opening by the most substituted alkene. As acetic anhydride was also present in the reaction medium, all free alcohols could be transformed into the corresponding acetates and acetate anions could also trap all carbocations formed during the reaction. As a result seven products were generated, five monoacetates and two diacetates. Three compounds **140**–**142** accounted for as much as 68% of the whole reaction mixture. Among these three compounds, two, **140** and **141**, were bicyclic transannular adducts (equation 14). Assuming that epoxide **139** exists as a mixture of four conformers **139-TT**, **139-CT**, **139-TC**, and **139-CC** directly related to the related humulene conformers (inside dashed box of Scheme 50),[60b,61] a thorough analysis was carried out in order to determine how and why **140** and **141** might have been preferentially formed. Further analyses showed that **139** adopts the preferred CT conformation of humulene (**139-CT**). It is therefore reasonable to believe that **139** reacts preferentially under this conformation. Starting from **139-CT**, the path leading to **140** is indeed straightforward. Regarding **141**, it was originally thought that it was coming from the next favored (after the CT conformer) **139-CC** conformer. However, after newer nuclear magnetic resonance and nuclear Overhauser effect spectroscopic data had revealed that the conformation of **141** is **141-TC**, it was then concluded that **141** might have been generated starting from **139-TC**. This is indeed rather surprising and unexpected, considering that the TC conformation is very little populated with only 0.2% of the whole mixture of humulene conformers (Scheme 49).[62]



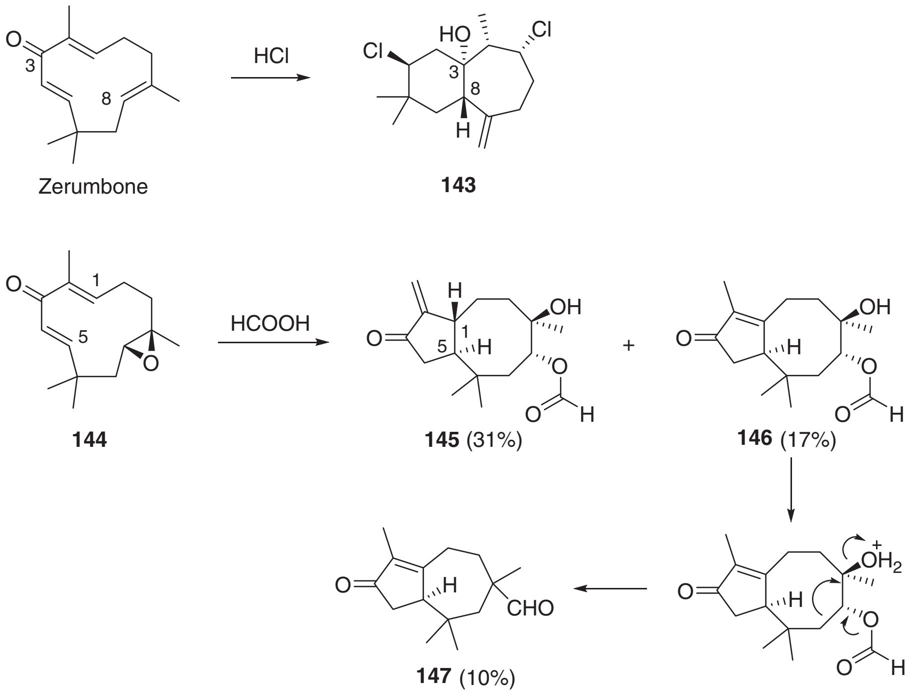
(14)



Scheme 50

3.06.5.2 Zerumbone and its Derivatives

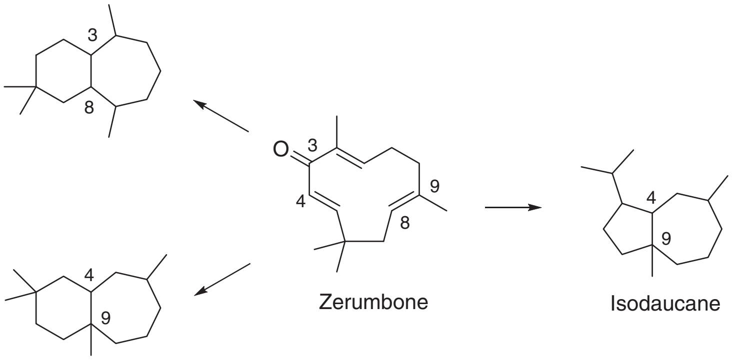
Early acid-catalyzed transannular cyclizations of zerumbone and its epoxide **144** to produce bicyclic skeletons have been reported (Scheme 51). On the whole, the chemistry of these compounds is ruled by the reactivity of the cross-conjugated dienone under acidic conditions. Thus, hydrochloric acid adds twice to zerumbone and the resulting protonated ketone reacts with the remaining unconjugated alkene in a transannular Prins reaction to yield the bicyclo[5.4.0]undecenol **143**.[63]



Scheme 51

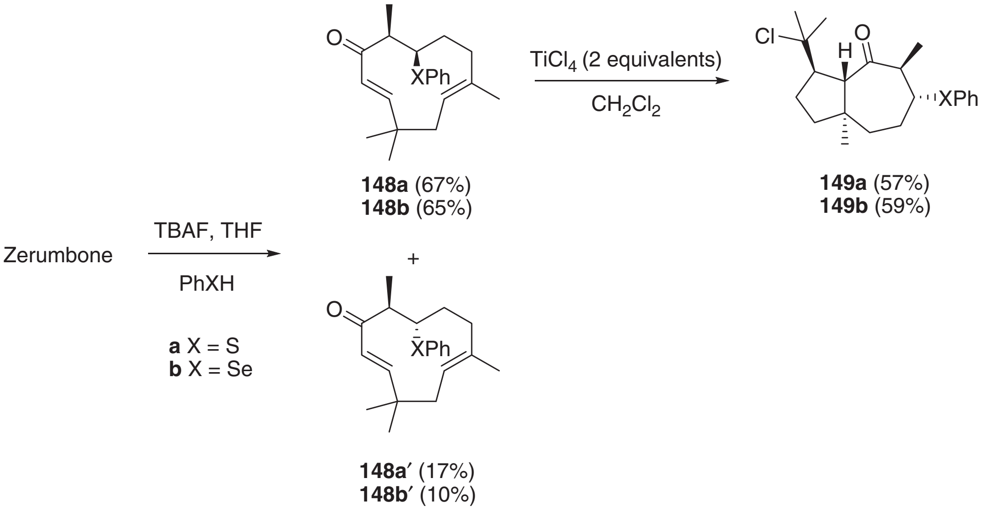
In the case of **144**, its epoxide first opens up in the presence of formic acid. The ensuing reaction then involves the yet untouched cross-conjugated dienone. Its transannular electrophilic cyclization yields two 5,8 bicyclic compounds **145** and **146**, of which **146** experiences ring contraction to give a 5,7 bicycle **147**.[64]

Some other chemical transformations of zerumbone ring systems have been described including selective conjugate additions and transannular electrophilic cyclizations providing several polycyclic compounds such as 6,7- and 5,7-carbocycles, of which the 5,7-bicyclic products constitute the structural unit of natural sesquiterpenes such as isodaucane, as illustrated in Scheme 52.[65]



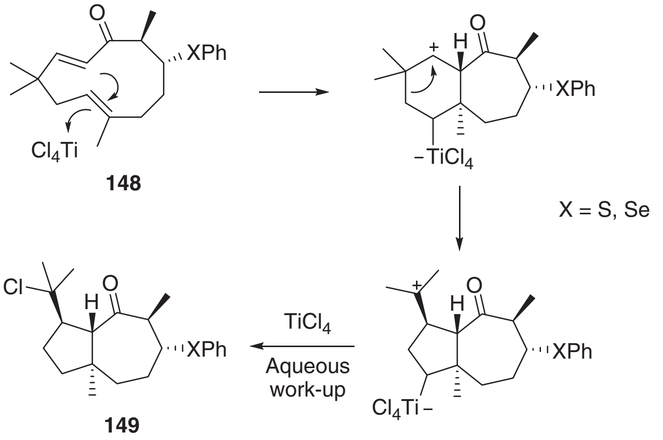
Scheme 52

Thus, Lewis acid treatment of sulfide **148a** or selenide **148b** (easily available by Michael addition on zerumbone) gave the substituted bicyclo[5.3.0]decanes **149a** and **149b** with fair yields (Scheme 53).



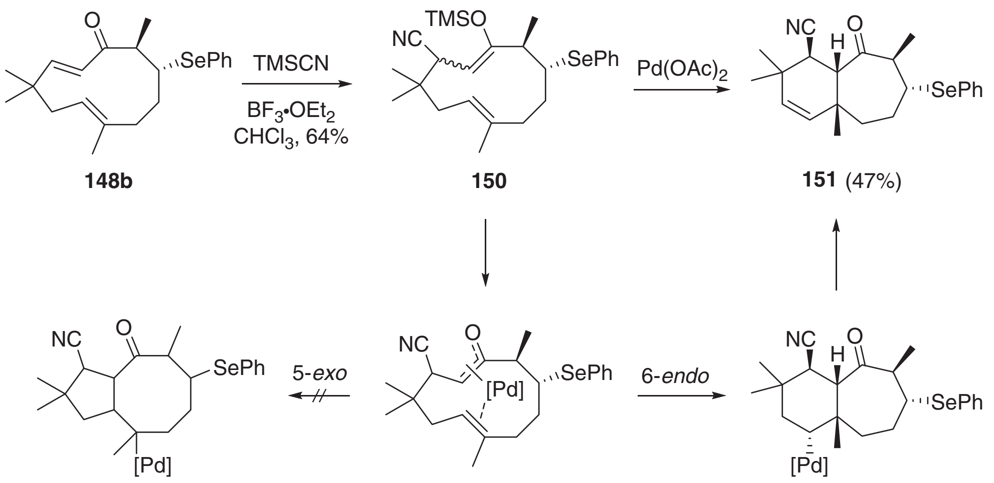
Scheme 53

The most plausible route to **149** is shown in Scheme 54.



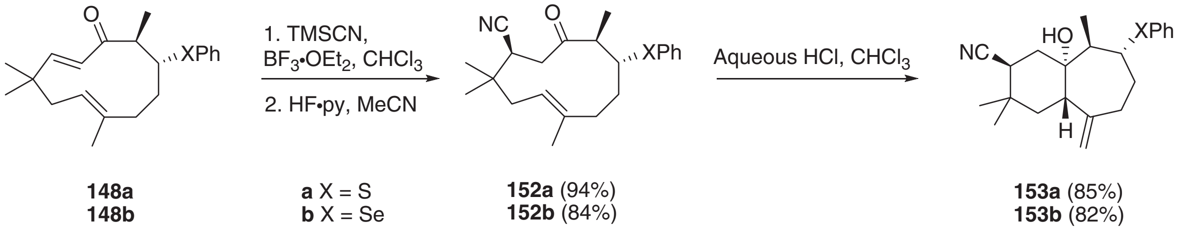
Scheme 54

In another experiment with a divalent palladium complex, the zerumbone derivative **150** (obtained by Michael addition of cyanide to **148b**, then trimethylsilyl protection of the resulting enolate), led to the bicyclo[5.4.0]undecene system **151** (Scheme 55). In this case, the oxy-π-allylpalladium species seemed to undergo carbopalladation in 6-*endo* fashion rather than 5-*exo* fashion to give a 6,7-bicyclic intermediate, whose subsequent elimination of palladium produced **145**.[65,66]



Scheme 55

Derivatives **152a** and **152b** (prepared by Michael addition of cyanide to **148a** and **148b**, then trapping of the resulting enolate with trimethylsilyl and finally removal of the silyl protective group with fluoride) gave also 6,7-bicyclic products **153** by acid-catalyzed transannular cyclizations (Scheme 56).[65]



Scheme 56

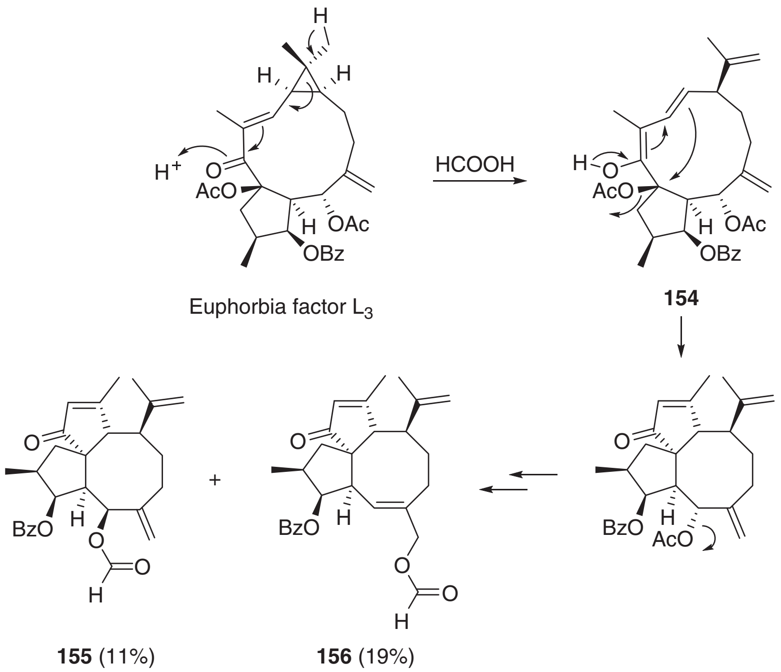
3.06.5.3 Miscellaneous

Transannular cyclizations in lathyrane diterpenes have been reported, providing access to a series of highly functionalized diterpenoids of unnatural skeletal type. For instance, treatment of the euphorbia factor L_3 (available from the seeds of the caper spurge, *Euphorbia lathyris* L.) with formic acid promoted the opening of the cyclopropane ring, leading to a dienol **154**, which provoked transannular ejection of an acetate leaving group. A few more steps afforded the two tricyclic compounds **155** and **156** in very moderate yields (Scheme 57).[67]

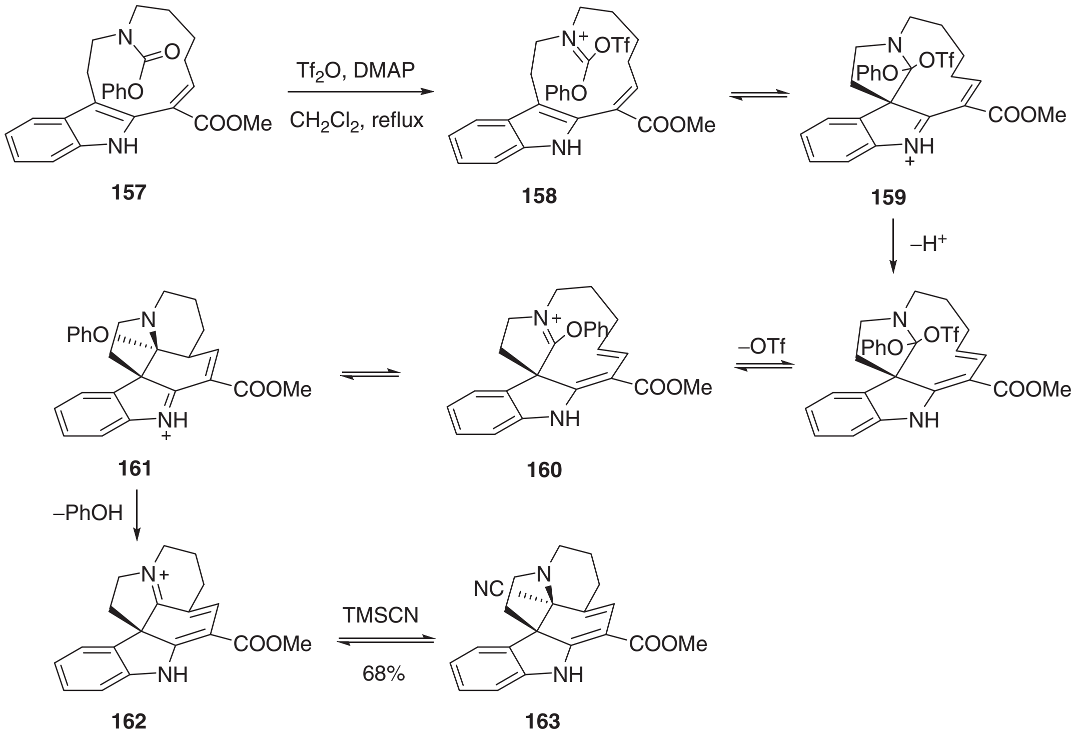
Transannulation processes were also utilized in the synthesis of the kopsia alkaloid ring systems (Scheme 58). In the presence of a powerful electrophile-like triflic anhydride, **157** was first transformed into the electrophilic iminium ion **158**. Then, **158** underwent its first transannular cyclization, a transannular electrophilic Mannich reaction giving **159**. Loss of triflic acid yielded another iminium ion **160** ready for still another transannular Mannich reaction (vinylogous this time) to give **161**. Elimination of phenol yielded yet another iminium ion **162**. Subsequently, **162** was quenched by trimethylsilyl cyanide leading to the desired framework of the kopsia alkaloids **163** in one pot and in good yields.[68]

The first examples of transannular $PtCl_2$-catalyzed cycloisomerizations in 1,5-cycloundecenynes opened a new route to cyclopropanic tricyclic systems.[69] As shown in Scheme 59, after an initial electrophilic π-complexation of alkyne **164** with Pt(II), the resulting complex **165** experiences a 1,2-hydride migration to form the oxocarbenium ion **166**, a resonance form of the allylic carbene **167**. Transannular cyclization follows suit to yield the enol ether **168**, which is finally deprotected into the final ketone **169**.

When benzoate **170** was used in the same sequence of reactions instead of ether **164** (Scheme 60), the final outcome was substantially different as the isomeric ketone **175** was obtained rather than **169**. The participation of the ester carbonyl in **171**

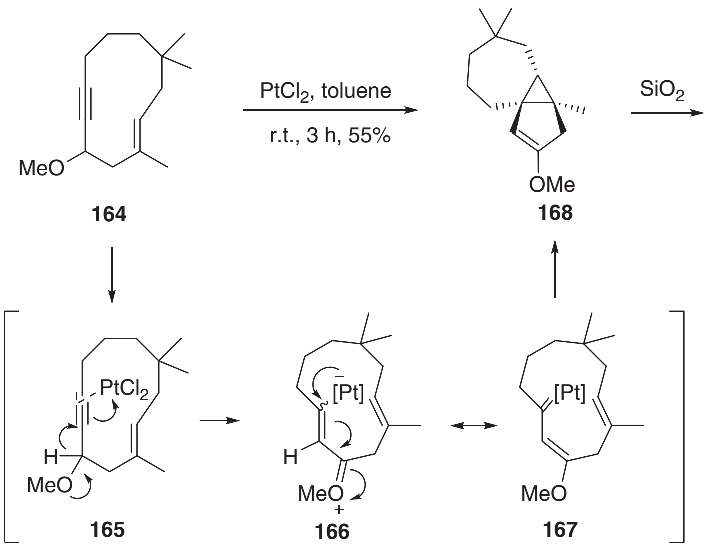


Scheme 57

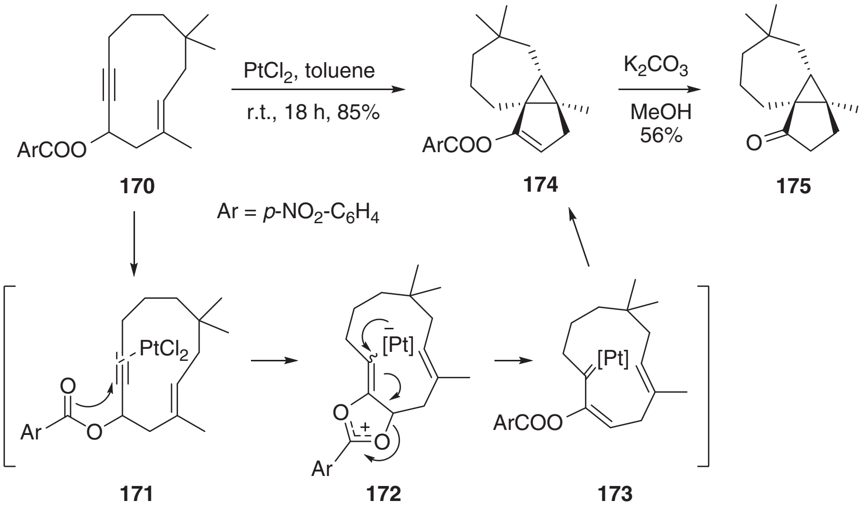


Scheme 58

triggered 1,2-benzoate migration rather than hydride shift as formerly seen in **165**. The resulting oxocarbenium ion **172** opened up to complete the ester migration to yield the allylic carbine **173**. Transannular cyclization took place to give the complexe ring system **174**. Hydrolysis of the benzoate finally gave ketone **175**.



Scheme 59



Scheme 60

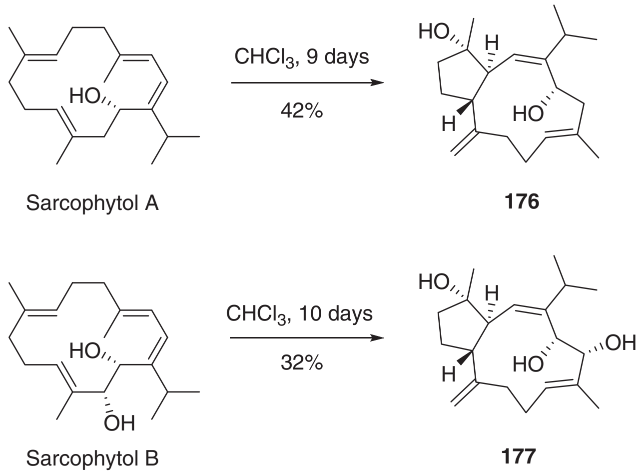
3.06.6 Other Rings

Transannular electrophilic cyclizations in medium-sized ring systems have been reviewed in the above sections. However, less strained much larger rings with alkenes and alkynes can also constitute interesting and reactive precursors to electrophilic transannulations. Other systems are prone to undergo several transannular electrophilic cyclization steps in cascades. Finally, some cyclophanes may provide a suitable environment for transannulations as well. All these orphan cases make the topic of this section.

3.06.6.1 Alkenes and Epoxides in Large Rings

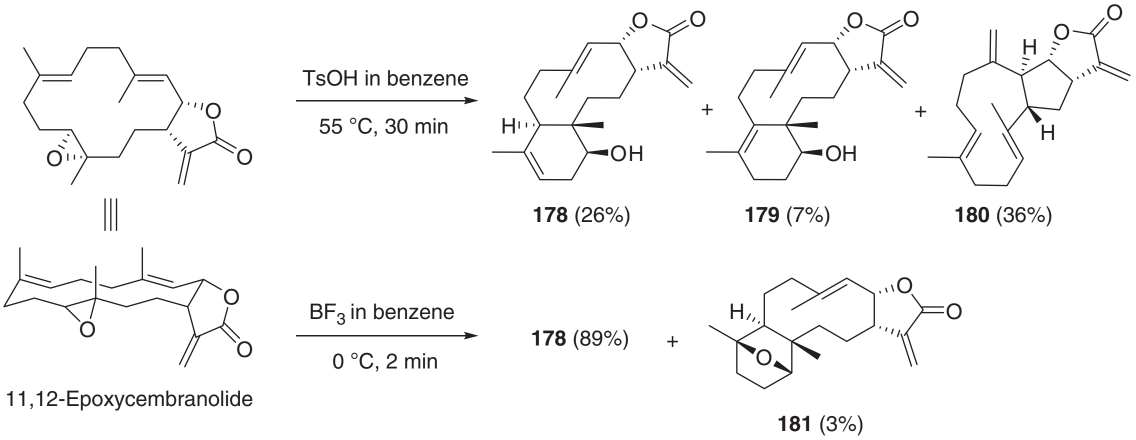
Some studies have demonstrated that 14-membered rings such as cembranoids could be as reactive in transannular cyclizations as 10- and 11-membered rings. Cyclizations in these macrocycles of natural origin were observed earlier while keeping sarcophytols A and B standing in chloroform at room temperature for several days, affording bicyclic compounds **176** and **177**, respectively, as their major products (Scheme 61).[70]

The global shape of 11,12-epoxycembranolide in solution was determined by nuclear Overhauser effect spectroscopy.[71] As shown in Scheme 62, three methyl groups are located on the same face with respect to the average plane of the cembranolide



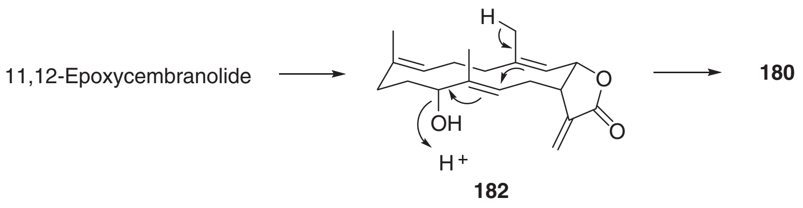
Scheme 61

14-membered ring. This favored ground state conformation is likely analogous to the transition state geometry found in the following transannular process. The acid-induced cyclizations of 11,12-epoxycembranolide was investigated under protic acid and Lewis acid catalysis (Scheme 62). Cyclized products were rapidly obtained in good yield with BF_3 in benzene after only 2 min. The reaction was slower and less clean with sulfonic acid. The epoxide ring opens up under acid conditions with concomitant transannular attack of the closest alkene. A tertiary carbonium intermediate results from this first step; and is subsequently deprotonated to yield alkenes **178** and **179**.



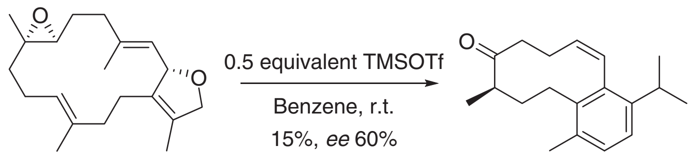
Scheme 62

As for the formation of **180**, epoxide ring opening with *para*-toluenesulfonic acid gives the allylic alcohol **182**, which further reacts in a transannular fashion with departure of water (Scheme 63).



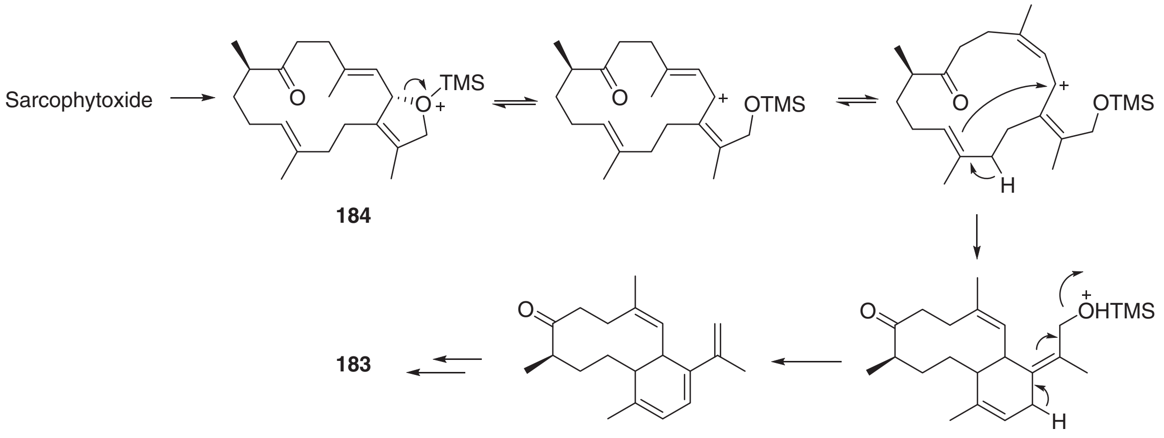
Scheme 63

Interestingly, treatment of sarcophytoxide, another 14-membered marine cembranoid, with a Lewis acid formed an aromatic ketone **183** as an unsual cyclization product (equation 15). It should be rationalized via the formation of ketone **184** by acid-catalyzed rearrangement of sarcophytoxide as illustrated in Scheme 64.[72]



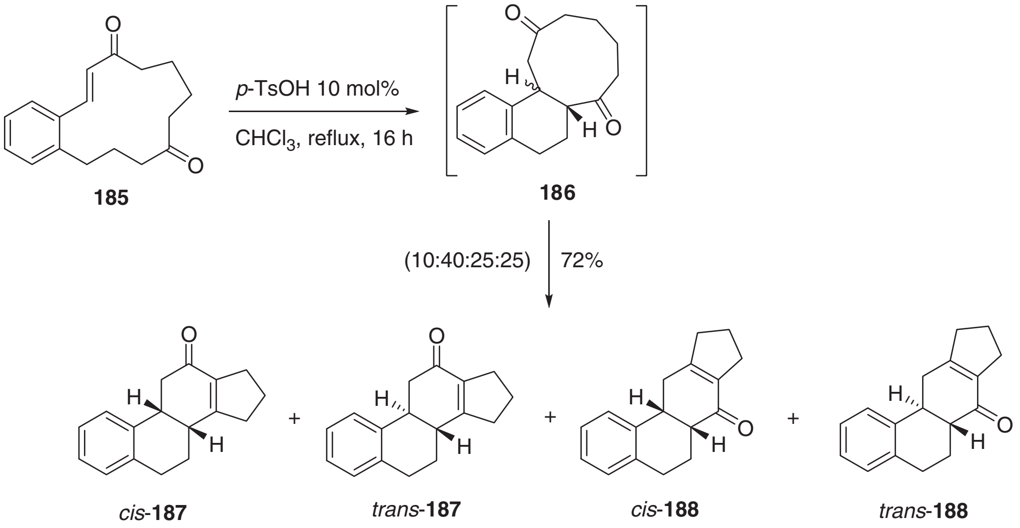
Sarcophytoxide **183**

(15)



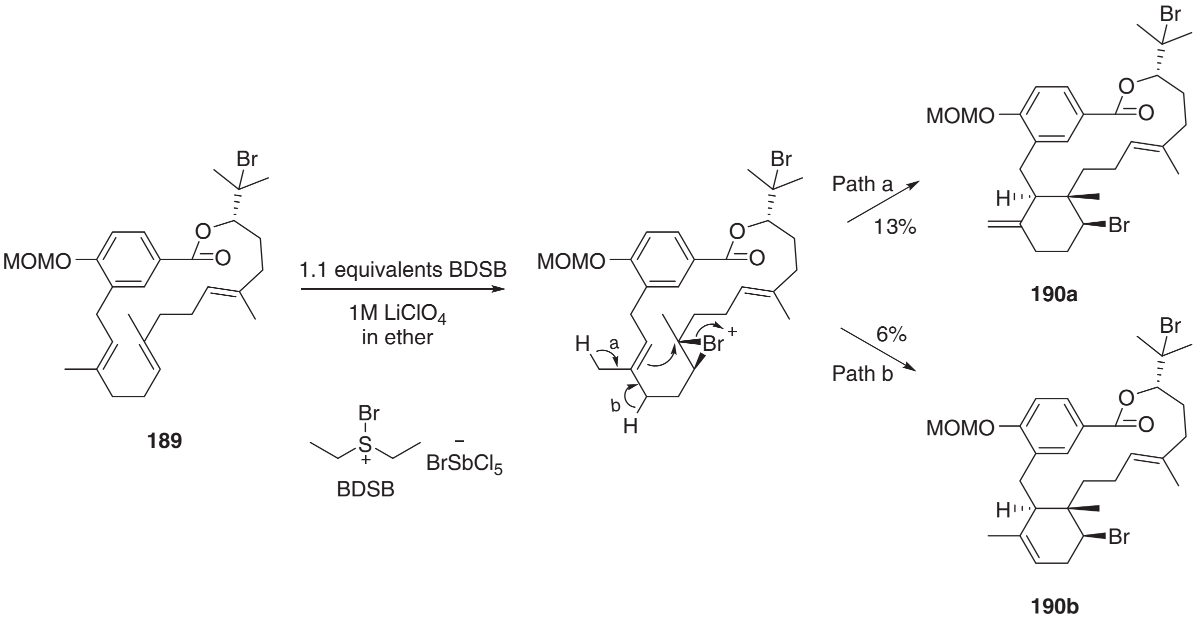
Scheme 64

Other examples of transannulation in large olefinic rings are summarized in Schemes 65 and 66. These include the formation of the steroid frameworks *cis*-**187** and *trans*-**187** via an acid-induced double transannular cyclization of the 14-membered ring precursor **185**. Under the conditions of reaction, a Michael addition occurred first, immediately followed by an aldol condensation on the resulting nine-membered dione **186** (Scheme 65). However, the selectivity is poor because there is basically no way to avoid the appearance of the competing aldol adducts *cis*-**188** and *trans*-**188**. In fact, these undesired tetracycles account for as much as 50% of the whole mixture of products.[73]



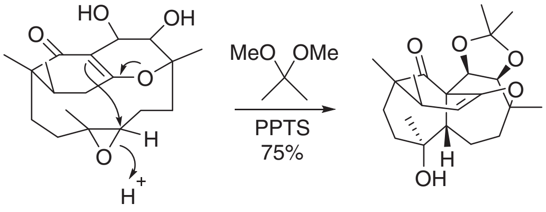
Scheme 65

A crucial step in the synthesis of the ring system **190** as found in bromophycolide A starts with the 19-membered triene lactone **189**. Its treatment with a bromodiethylsulfonium salt (bromopentachloroantimonate counterion, BDSB) provoked selective bromination of the central alkene. Then, bromonium-promoted transannular cyclization ensued, leading to 19% of the two desired 15-membered macrolactones **190a** and **190b** (Scheme 66).[74]



Scheme 66

When the 12-membered ring diol epoxide **191** was subjected to the usual conditions used to protect a diol as an acetonide (equation 16), an acid-promoted transannular addition of the enol ether occurred. The less substituted side of the epoxide was selectively attacked for reasons of proximity. A tetracycle was obtained in the process.[12o]



191

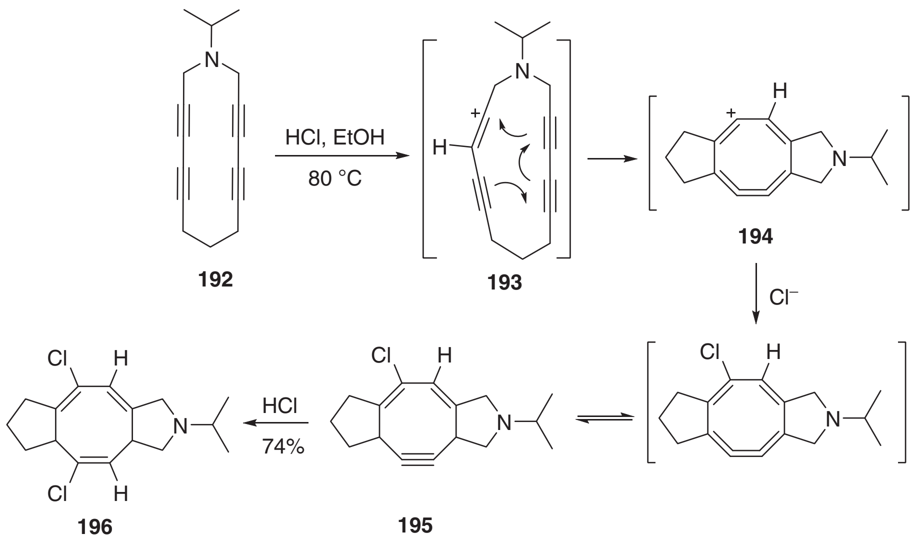
(16)

3.06.6.2 Alkynes in Large Rings

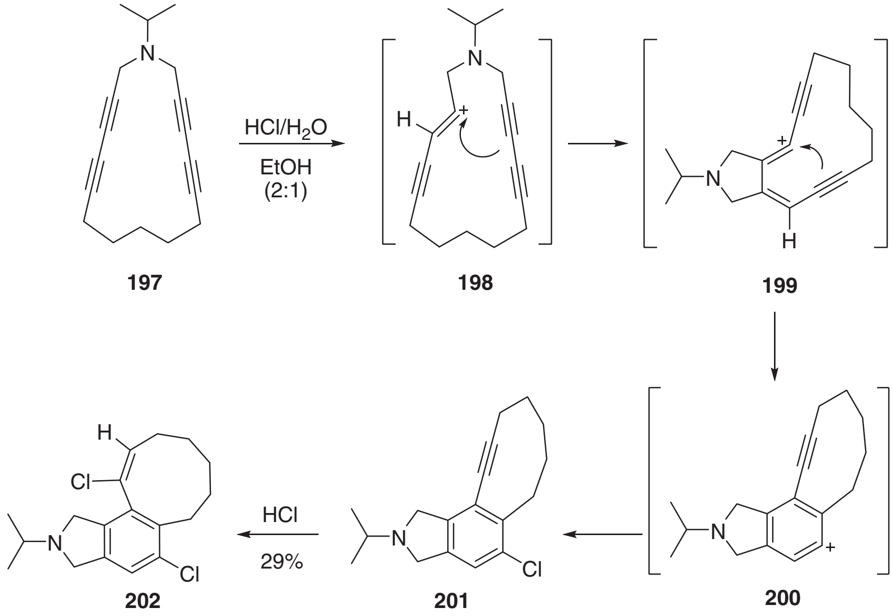
Transannular interactions among conjugated triple bonds also constitute a fascinating part. Some examples have been already presented in the Section 3.06.4. Other studies on transannulation between two parallel or not so parallel 1,3-butadiyne units in large rings are summarized below. The first examples involve the acid-catalyzed cyclizations of some aza-macrocycles containing two 1,3-butadiyne units in their structures, leading to several tricyclic products, as shown in Schemes 67[54] and 68.[75] The crystal structure of the 14-membered tetrayne ring **192** (Scheme 69) has revealed that the distances between pairs of peripheral sp centers are much shorter (3.06–3.11 Å) than the distances between the inner sp centers (3.35–3.41 Å). Consequently, **192** reacts favorably with hydrochloric acid to yield the strained cumulene **194**, via the vinyl cation **193**. As **194** itself is a reactive vinyl cation, addition of a chloride anion is straightforward. A second molecule of hydrochloric acid later adds up to the resulting strained alkyne **195** to produce **196**.

The larger parent molecule **197** reacts also with hydrochloric acid (Scheme 68). Like **192**, the reactivity of the different C(sp) atoms can be related to their mutual distances. The crystal structure of the large 16-membered ring **197** shows that the distance between pairs of sp centers increases rapidly as we move away from the nitrogen atom (Scheme 69). Logically the two C(sp) atoms facing each other and whose distance is shorter (3.12 Å) are more prone to react with each other and this is exactly what happens experimentally. Protonation of **197** leads to the vinyl cation **198**. Two successive transannular electrophilic additions ensue to yield the phenyl cation **200**, via the vinyl cation **199**. The obviously very reactive species **200** adds a chloride anion then a second molecule of hydrochloric acid reacts with alkyne **201** to afford **202**.

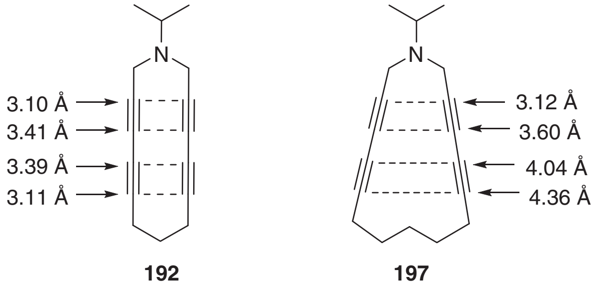
The synthesis of some indenofluorene analogs have been reported via multiple halogen-induced transannular cyclization processes (Scheme 70 and equation 17). Thus, the macrocycle **203** containing two parallel 1,3-butadiyne units undergoes two electrophilic cyclizations with iodine, leading to a bicyclo[7.3.0] ring system **204** as the initial intermediate. According to



Scheme 67

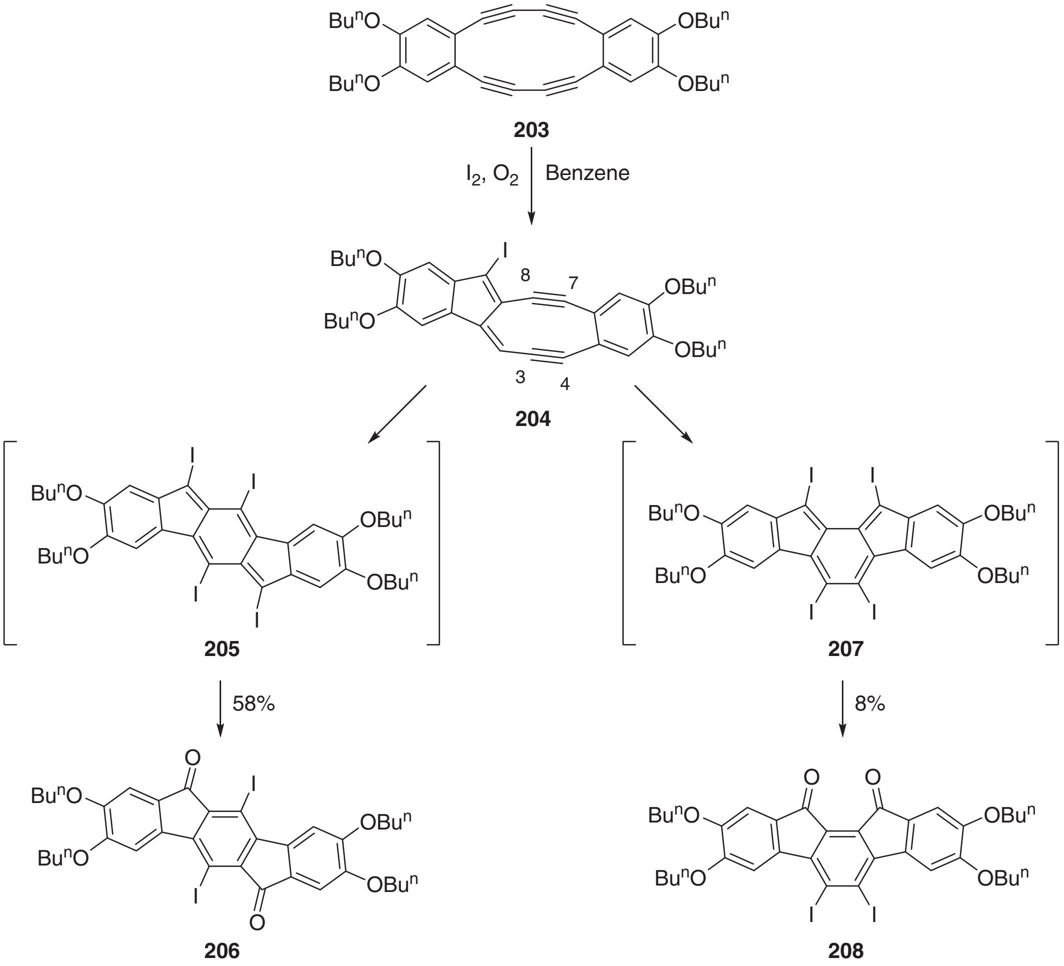


Scheme 68



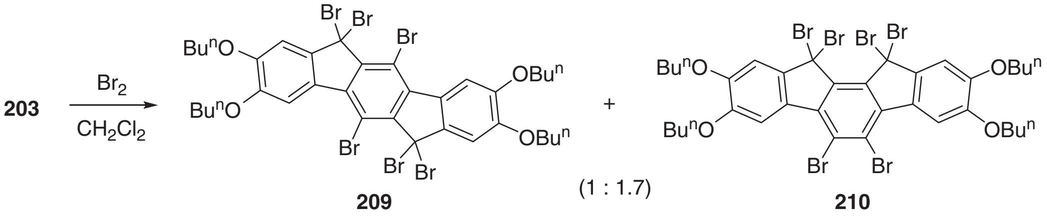
Scheme 69

calculations, the highest occupied molecular orbital coefficient at atoms C7 and C8 are larger than those at positions 3 and 4. Accordingly, a second electrophilic addition of iodine can then take place at C8, followed by transannular C3–C7 bond formation. This first path leads to the *anti*-indenofluorene analog **206** (via the nonisolated tetraiodo compound **205**). Alternatively, the second favored electrophilic addition of iodine can take place at C7. Transannular C4–C8 bond formation then gives the *syn*-indenofluorene analog **208** (via **207**). The result was much the same under anaerobic conditions.[76]



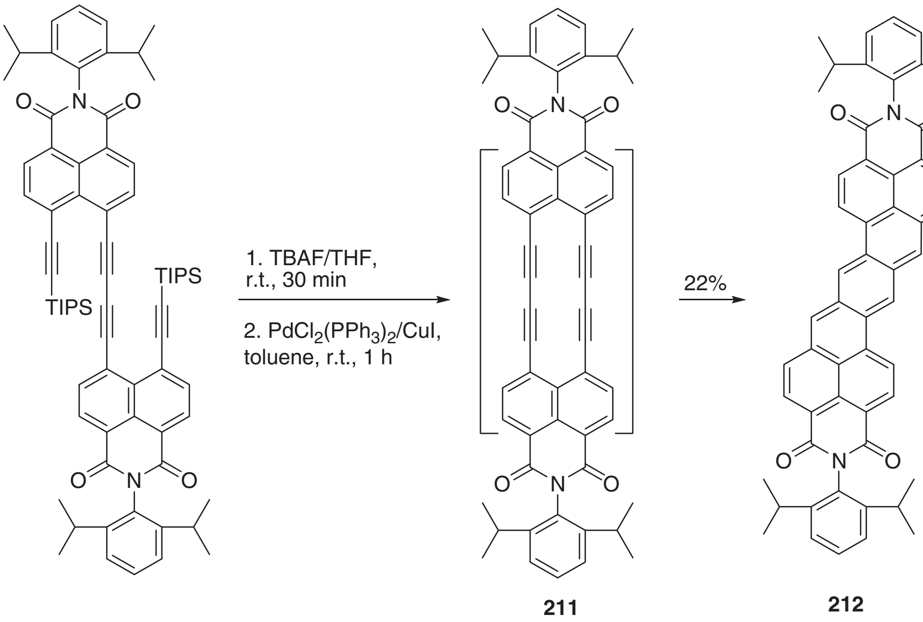
Scheme 70

When treated in a similar way with bromine instead of iodine, **203** yielded the two products **209** and **210** (equation 17). It is noteworthy that diketone products (equivalent to **206** and **208**) were not obtained in the reaction of **203** with bromine, even under aerated conditions.



(17)

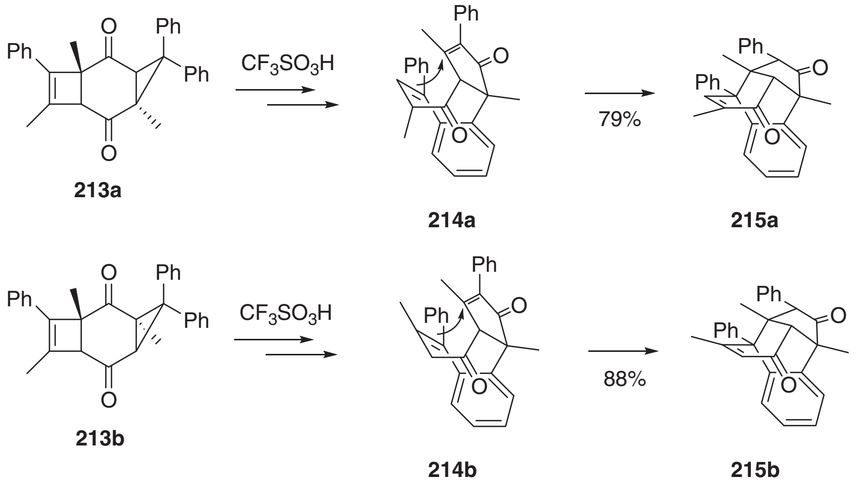
The final example on acetylenic ring systems is the synthesis of a soluble and stable heptazethrene derivative **212** via the Pd-catalyzed transannular cyclization of the intermediate **211** in acceptable yield over two steps (Scheme 71).[77]



Scheme 71

3.06.6.3 Transannular Cascades

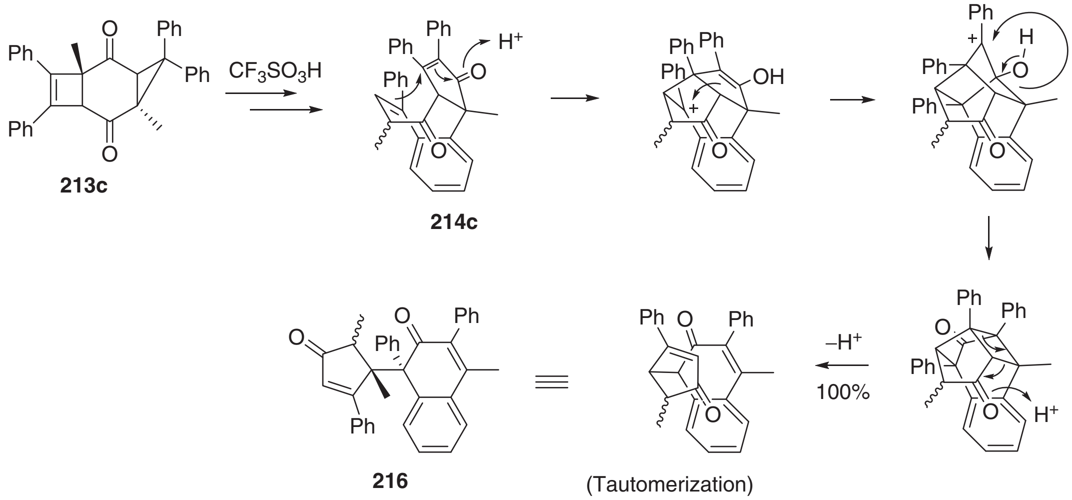
Acid-catalyzed rearrangements of highly strained cyclobutenes **213** were investigated. Compounds **213** underwent consecutive skeletal rearrangements, as shown in Schemes 72–74 to afford bicyclic diones **214**. These diones exhibited three types of different transannular cyclizations: (1) Michael additions (5-*exo-trig* or 6-*exo-trig*) leading to the tetracyclic diones **215** (Schemes 72), (2) [3 + 2] cycloaddition followed by sequential rearrangement to 2-naphthalenone derivatives leading to **216** (Schemes 73), or (3) *ipso*-Friedel–Crafts alkylation accompanied by rearomatization and loss of water leading to **217** (Scheme 74). These reactions depended much on the cyclopentenone ring substituents and the position of the [8]annulenone methyl group.[78]



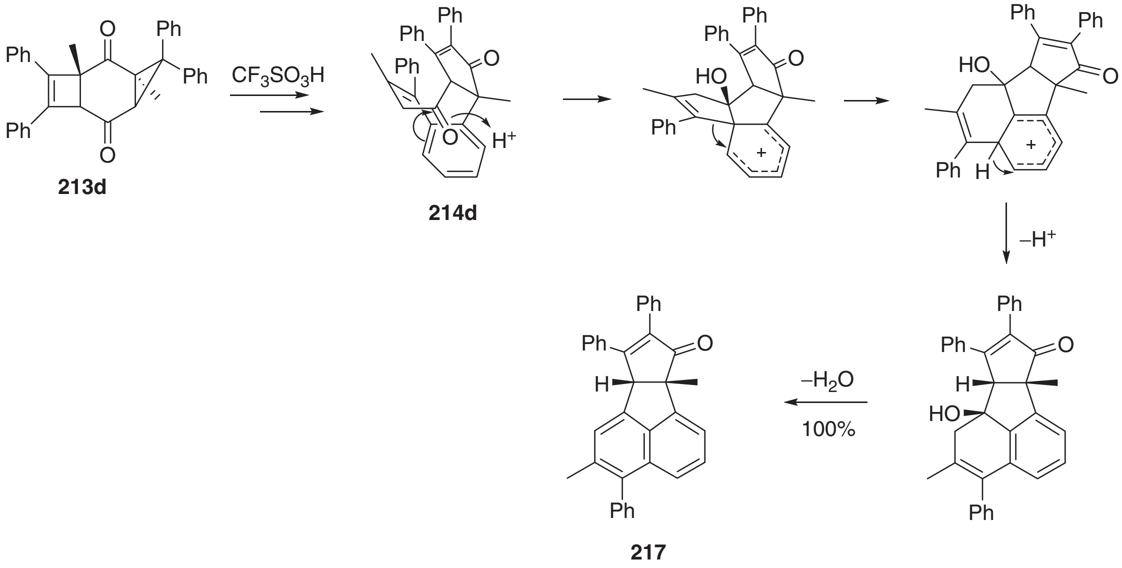
Scheme 72

3.06.6.4 Cyclophanes

Some transannular electrophilic reactions have been investigated in medium-sized cyclophanes. Thus, the [2.2]metacyclophane **218**, while treated with benzyl trimethylammonium tribromide (BTMA Br$_3$), induced a transannular cyclization to yield the tetrahydropyrene-type product **220** exclusively (Scheme 75). After the initial transannular step from **218** harboring two phenyl



Scheme 73



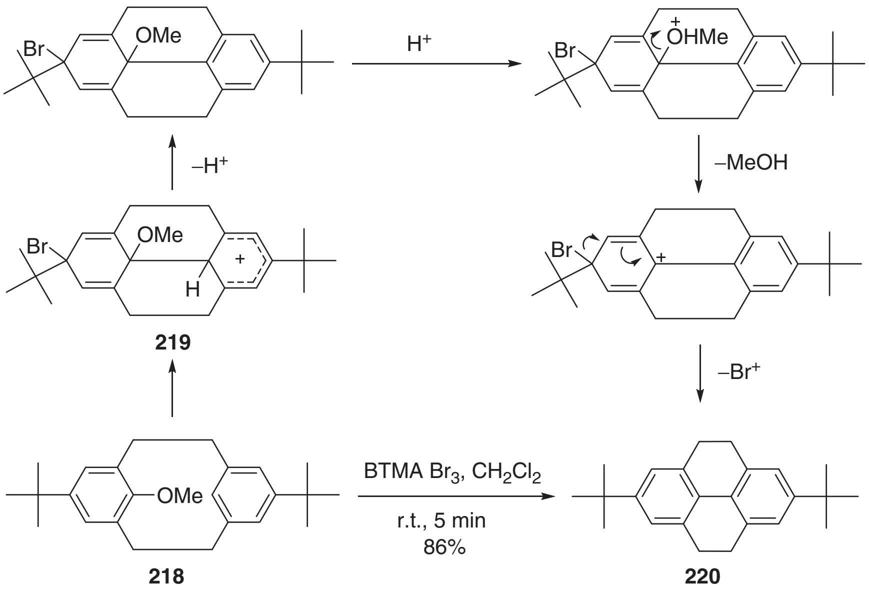
Scheme 74

rings, the resulting product **219** is on the contrary no more aromatic. All subsequent steps are in fact aimed at recovering the lost aromaticity. This goal is finally achieved via 'biphenyl' **220**.[79]

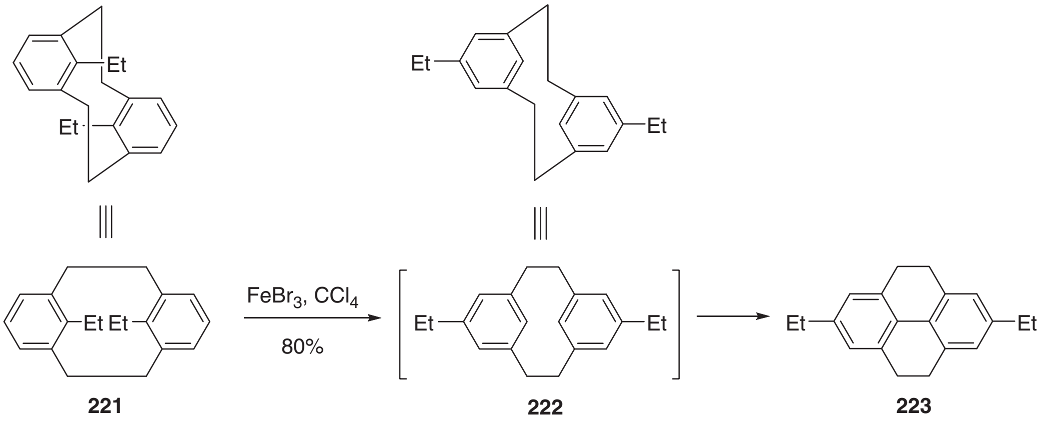
The following case is rather surprising and impressive; it concerns the transannular cyclization of a very similar cyclophane, a [2.2]metacyclophane **221** (Scheme 76). At first glance this cyclophane should not be able to cyclize in the same way that **218** did, because two ethyl groups mask the carbon centers that should normally react. However, transannulation really occurs and yields the unexpected tetrahydropyrene compound **223**. In fact, everything goes as if the two ethyl groups had undergone rearrangement to give the intermediate, and not isolated, cyclophane **222**. The reaction is very fast with iron tribromide but fails with other Lewis acid catalysts like $TiCl_4$ and $FeCl_3$.[80]

3.06.7 Formation of Carbon–Heteroatom Bonds

Transannular cyclizations are not only used in the preparation of carbocyclic systems but also of heterocyclic systems. In this section, some examples of C-heteroatom (such as N, O, and S) bond formation via transannular interactions are collected.



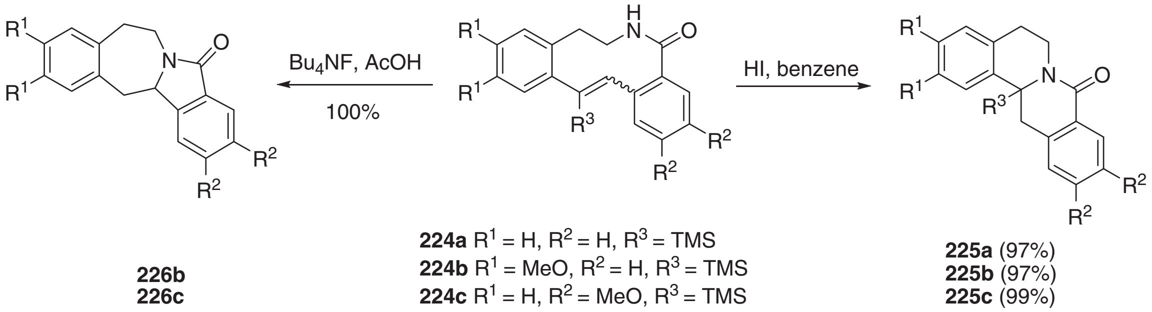
Scheme 75



Scheme 76

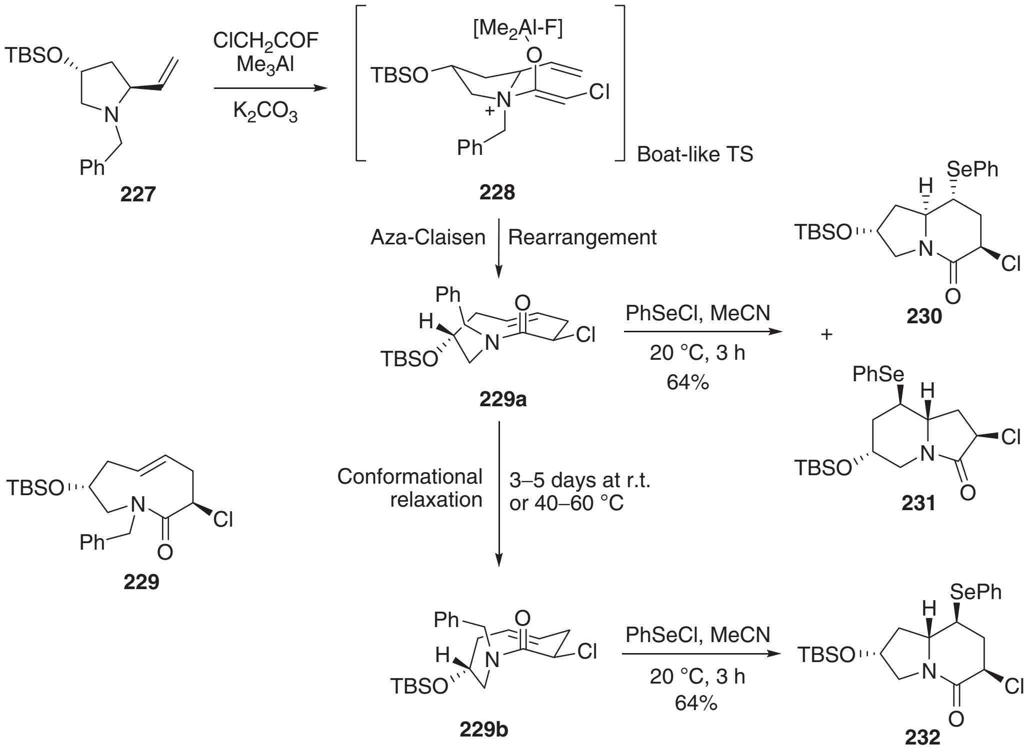
3.06.7.1 C–N Bonds

Treatment of 10-membered ring lactams **224** with hydroiodic acid or fluoride led to tetrahydroprotoberberines **225** or isoindolobenzazepines **226**, respectively, in almost quantitative to quantitative yields (Scheme 77).[81]



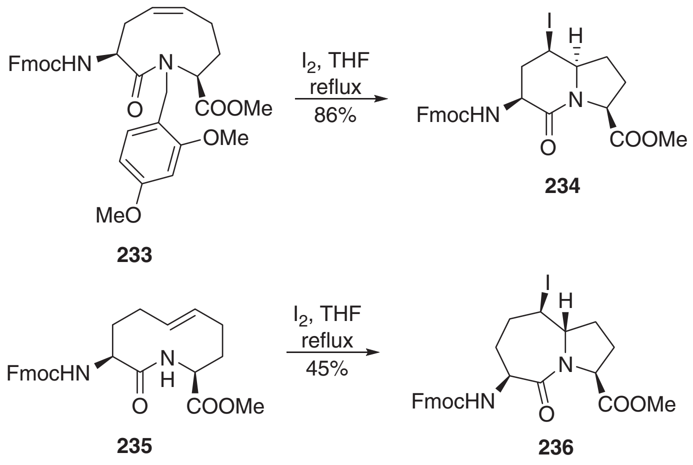
Scheme 77

An approach to optically active indolizidinones has been also developed from unsaturated optically active azoninones bearing *E*-olefins, featuring transannular electrophilic cyclizations (Scheme 78). When chloroacetyl fluoride, trimethylaluminum, and potassium carbonate were successively added to the vinyl pyrrolidine **227**, an aza-Claisen rearrangement took place to yield azoninone **229** having the planar chirality **229a**. This pure atropisomer **229a** corresponds to the frozen geometry of the preferred boat-like zwitterionic aza-Claisen transition state **228**. However, **229a** is not the most stable atropisomer of **229**. When left at room temperature for a few days or heated at 40–60 °C for a short while, **229a** relaxes to its more stable planar conformer **229b**. With the two separate pure atropisomers **229a** and **229b** in hand, transannular electrophilic cyclizations were carried out to yield the bicyclic products **230**–**232**.[82]



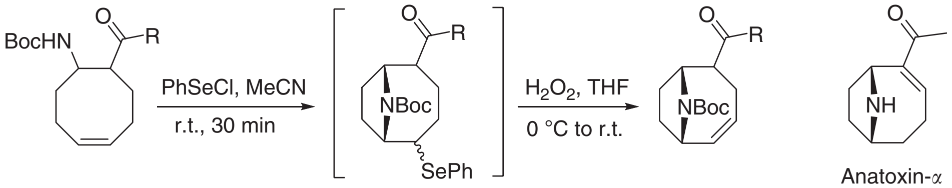
Scheme 78

Other 9- and 10-membered ring lactams such as **233** and **235** served as precursors for the synthesis of bicyclic aminoesters **234** and **236** (Scheme 79), offering potential in peptide mimicry.[83]



Scheme 79

Transannular C–N formations are also of interest in the synthesis of natural products. For instance, anatoxin-α and several of its analogs **238** were constructed by selenocyclization of a carbamate nitrogen across the cyclooctene rings **237** (Scheme 80).[84]



Anatoxin-α

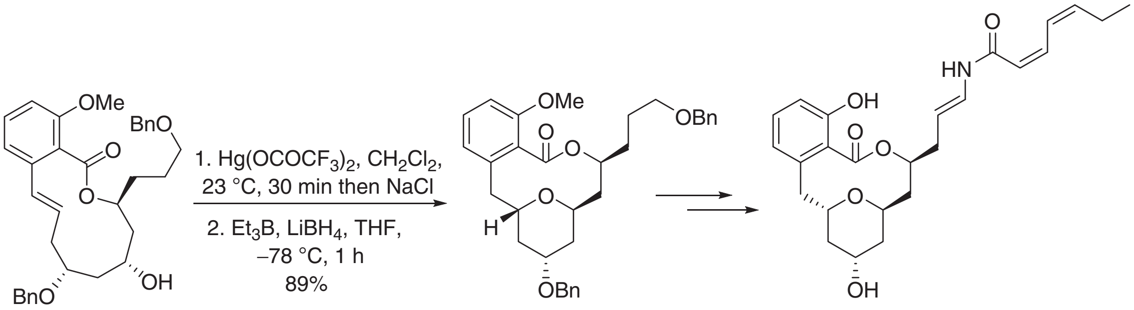
237a R = Me
237b R = Ph
237c R = *n*-Bu

238a (55%)
238b (42%)
238c (36%)

Scheme 80

3.06.7.2 C–O and C–S Bonds

The total synthesis of (–)-apicularen A skeleton **240** has been achieved through a transannular pyran formation from the precursor **239** (Scheme 81). On treatment with mercuric trifluoroacetate, **239** yielded the cyclized organomercurial intermediate within minutes. Reductive demercuration then gave the desired pyran **240** *en route* to (–)-apicularen A.[85]



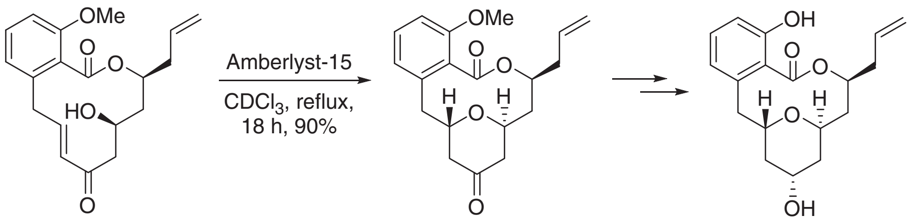
239

240

(–)-Apicularen A

Scheme 81

In an alternate approach, the formation of the pyran ring was tackled through another transannular process: an oxy-Michael addition from enone **241** yielding pyranone **242** (Scheme 82). A few additional chemical transforms gave alkene **243**, a known precursor of (–)-apicularen A.[86]



241

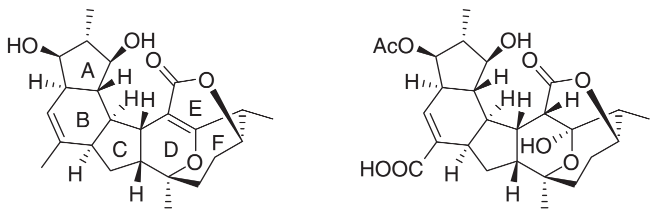
242

243

Scheme 82

Two natural products FR182877 and hexacyclinic acid (Scheme 83) share remarkable similarities in structure and also biological activities.[87] Intramolecular and transannular Diels–Alder reactions have been used successfully in the synthesis of FR182877.[12f,12i,12j,88]

Another approach has been investigated to get access to the DEF framework of these natural products. The novel route features a transannular cationic cyclization reaction from the nine-membered ring **244** (Scheme 84). In the presence of iodine and silver acetate, alkene **244** is transformed into its corresponding iodonium ion **245**. This intermediate undergoes a transannular

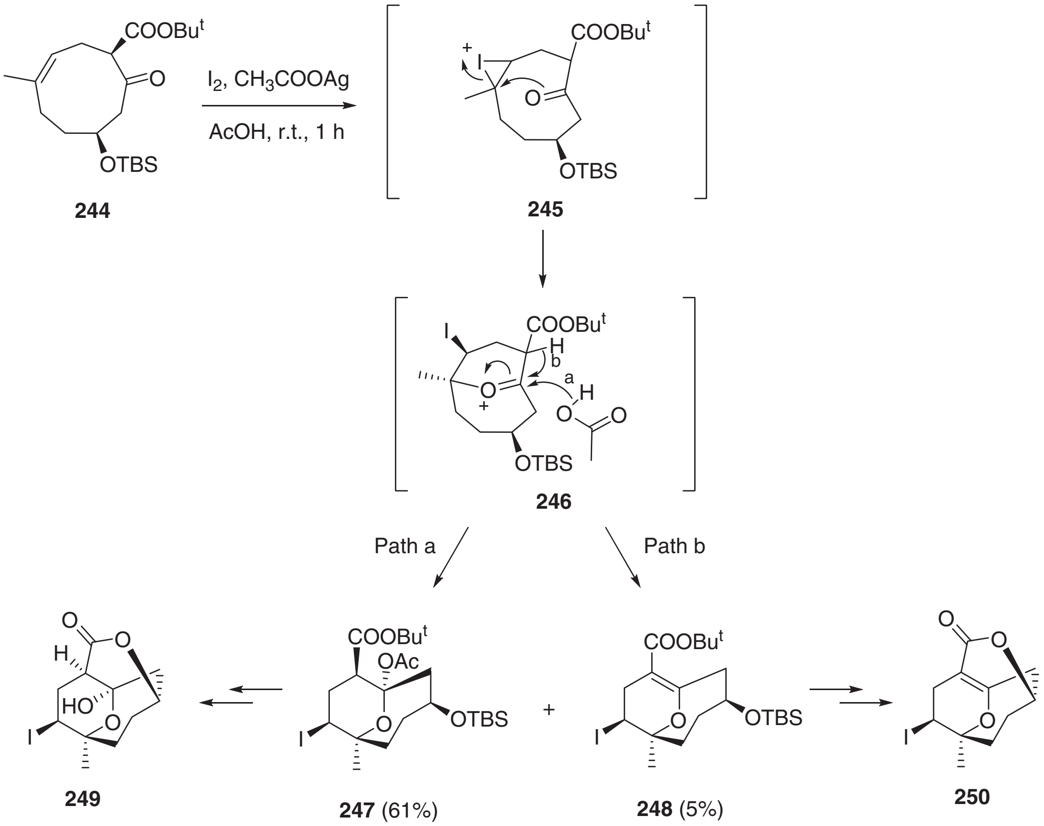


FR182877

Hexacyclinic acid

Scheme 83

iodocyclization of the ketone carbonyl group, leading possibly to the intermediate oxocarbenium ion **246**. This latter transient species can be quenched following path a by the addition of the acetic acid solvent, producing the final cyclized compound **247**, or deprotonated following path b leading to another cyclize compound **248**. Both bicycles **247** and **248** can be lactonized to generate the tricycles **249** and **250**, whose resemblance with the DEF part of hexacyclinic acid and FR182877 is striking (Scheme 81).[41c,89]

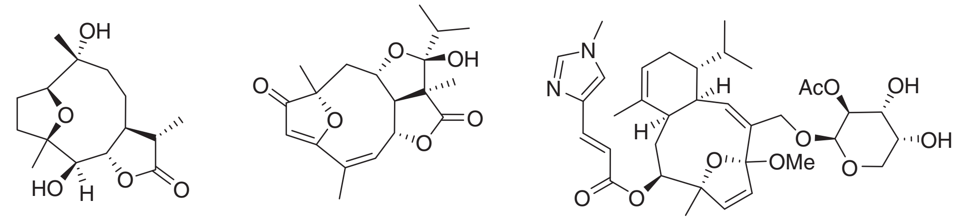


Scheme 84

The attractive family of germacrolides has demonstrated a great capacity for transannular cyclizations providing a diversity of bicyclic carbocycle systems as already discussed in Section 3.06.4. This accessible family has also proved to be a suitable source of starting materials for the enantiospecific synthesis of both 1,4-epoxycyclononane and 1,4-epoxycyclodecane frameworks, which exist in several naturally occuring terpenoids such as dihydroparthenolide diol, eremantholide A, and eleutherobin (Scheme 85).[90]

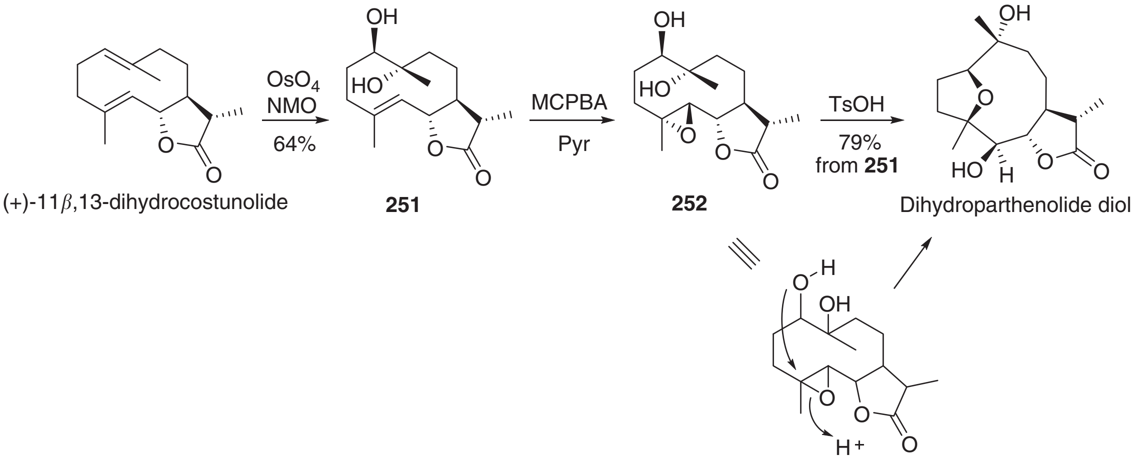
For example, selective oxidation of one alkene of (+)-11β,13-dihydrocostunolide afforded diol **251** (Scheme 86). The remaining alkene was then epoxidized to give **252**. Its acid-induced transannular cyclization as the final step provided exactly dihydroparthenolide diol in good yield.

Diol **251** was selectively oxidized to produce ketone **253**, which was epoxidized like **251** (Scheme 87). The resulting 10-membered ring **254** system underwent a new tandem reaction combining a transannular cyclization and a ring contraction opening a new avenue to 9-membered rings related to **255**.[90]

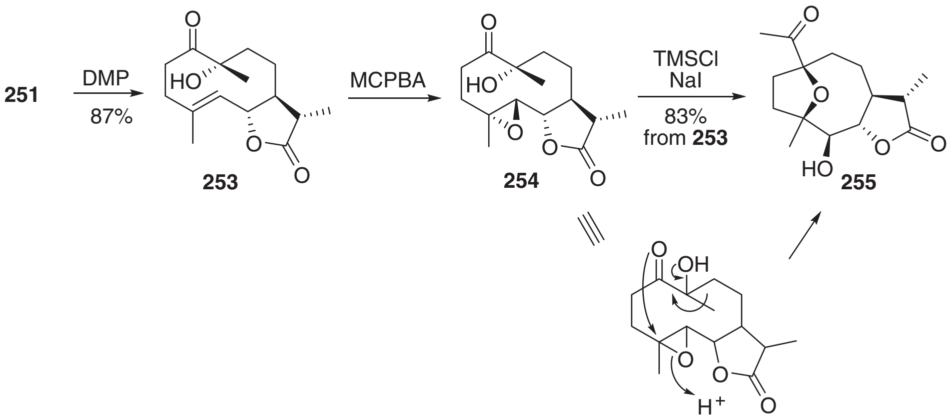


Dihydroparthenolide diol Eremantholide A Eleutherobin

Scheme 85



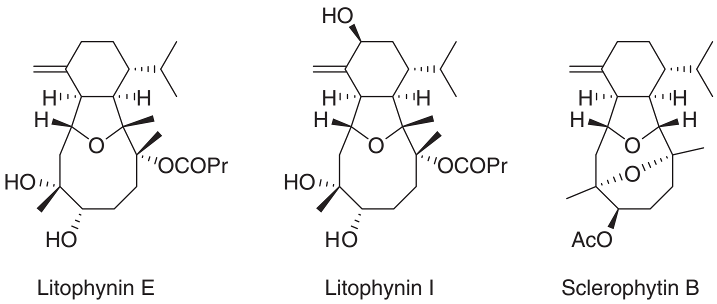
Scheme 86



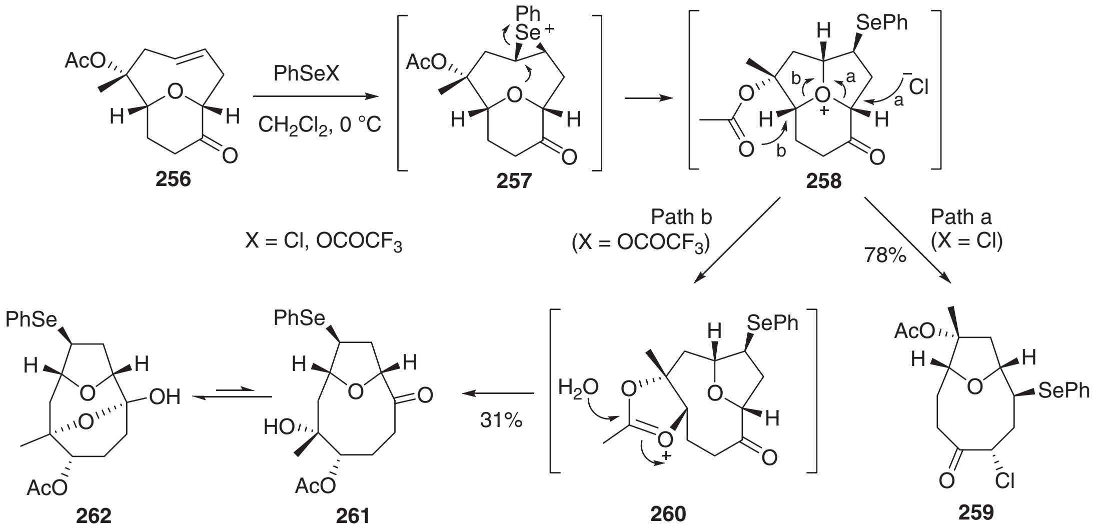
Scheme 87

A new approach to the stereoselective synthesis of the 11-oxabicyclo[6.2.1]undecane skeleton found in the cladiellin (eunicellin) family has been developed.[91] Members of this family include litophynin E, litophynin I, and sclerophytin B (Scheme 88).

The novel strategy involves a transannular rearrangement of the (*E*)-oxabicyclo[5.3.1]undecene system **256** (Scheme 89). On treatment with phenylselenium chloride or phenylselenium trifluoroacetate, selenonium ion **257** is formed selectively. The bridge ether oxygen is then practically forced to attack the electrophilic selenonium ion in a transannular way to give the tricyclic oxonium ion **258**. At this stage, only the counterion makes a difference. Following path a, the chloride ion attacks the most electrophilic site located α to the carbonyl group to produce the bridge bicyclic ether **259**. In the presence of trifluoroacetate ions no intermolecular attack occurs as before, because the trifluoroacetate anion is too weak as a nucleophile. Rather, the acetate group participates in opening the tricyclic oxonium intermediate, following an intramolecular S$_N$2 reaction (path b). The resulting



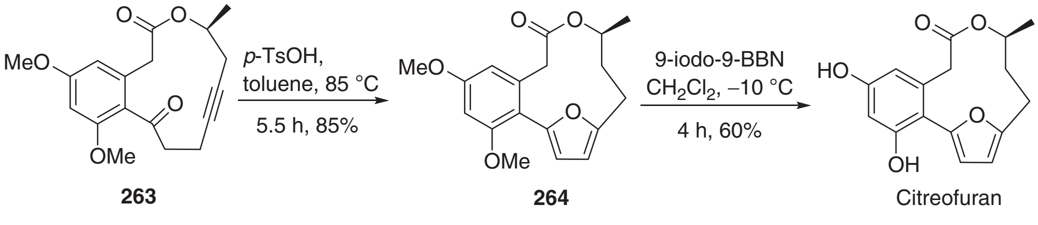
Scheme 88



Scheme 89

oxonium ion **260** reacts with water during the workup, giving hydroxy-ketone **261**. Like a sugar, the hydroxyl-ketone **261** is in equilibrium with its cyclized hemiketal form **262**; the latter being the core of sclerophytin B (Scheme 88).

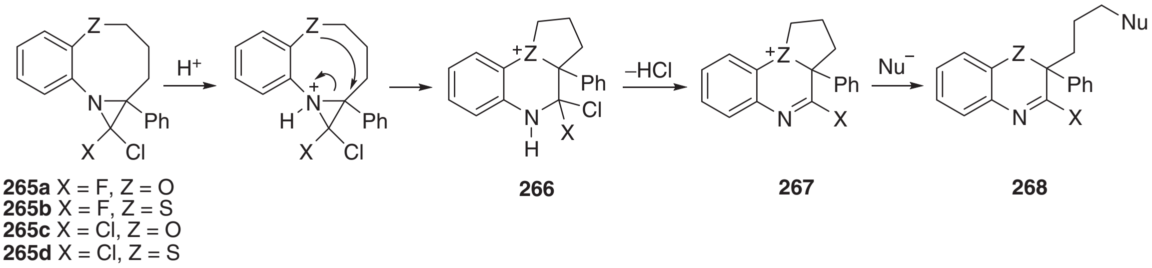
A total synthesis of citreofuran was completed involving some key steps, one of which is a transannular cycloaromatization of a strained cycloalkyne **263** (Scheme 90). When treated with *para*-toluenesulfonic acid, its triple bond becomes susceptible to nucleophilic attack by the adjacent carbonyl group to form furan **264**. Treatment of the latter with 9-iodo-9-borabicyclo[3.3.1]nonane (BBN) to cleave the methyl ethers furnishes citreofuran.[92]



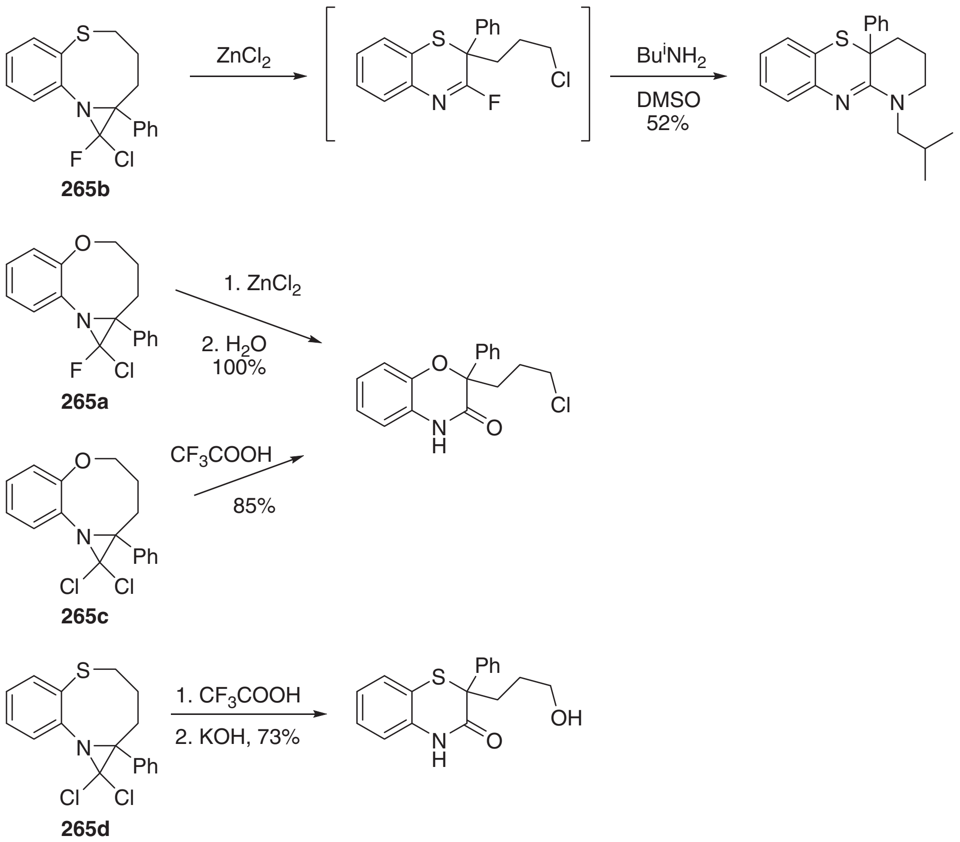
Scheme 90

Some examples of transannular ring transformations in azirino-fused eight-membered *O*,*N*- or *S*,*N*-heterocycles **265** involving selective aziridine ring opening and medium-sized ring contraction were realized (Scheme 91). On addition of a strong protic acid, the aniline nitrogen atom of **265** gets protonated and a transannular attack forming an oxygen or sulfur heteroatom is then favored. The resulting bicyclic salt **266** can eliminate hydrochloric acid to form **267**. An external nucleophile can attack **267** on the carbon atom linked to the positively charged chalcogen atom with concomitant opening of the five-membered ring. Some representative examples are shown in Scheme 92.[93]

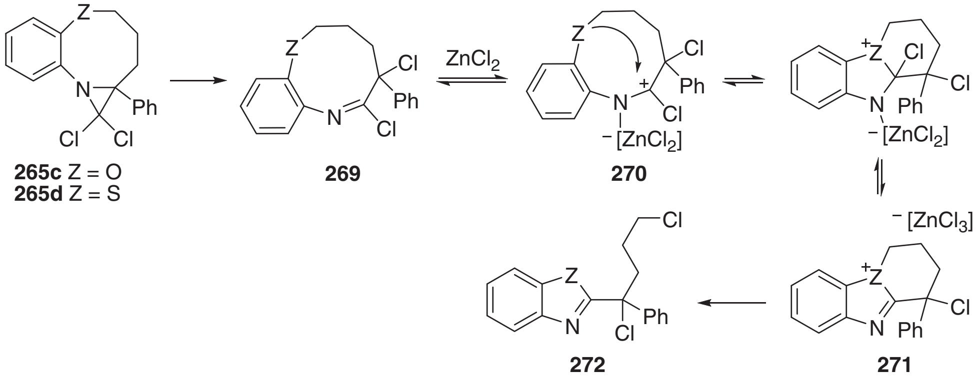
The use of dichloro derivatives **265** under Lewis acid-catalyzed conditions favor another route leading to functionalized 1,3-benzoxazoles and 1,3-benzothiazoles (Scheme 93). In the absence of strong protic acids, the aziridine ring breaks apart



Scheme 91

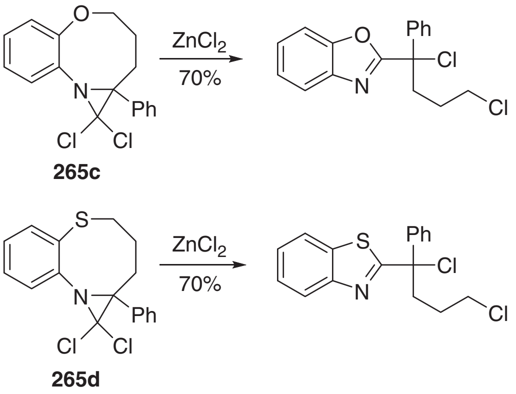


Scheme 92



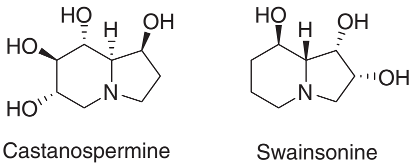
Scheme 93

thermally to afford the nine-membered imidoyl halogenide **269**. The Lewis acid catalyzes the transformation of **269** into the onium salt **271**, via transannular attack of the chalcogen atom on the positively charged carbon atom of **270**. The onium salt is finally attacked by chloride anions to yield **272**. Two examples are displayed in Scheme 94.[93,94]

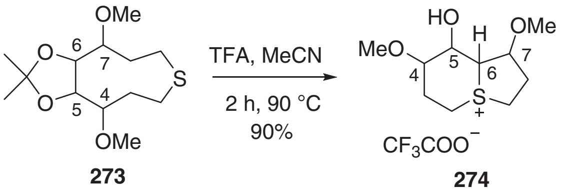


Scheme 94

Glycosidase inhibitors like castanospermine and swainsonine are important therapeutic agents (Scheme 95). A route was developed to prepare sulfonium derivatives of these nitrogen-based bicycles (equation 18).[95]



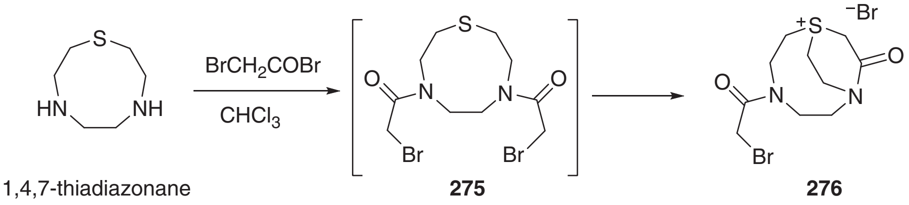
Scheme 95



(18)

The functionalized thioswainsonine **274** was obtained from the C_2 symmetric nine-membered derivative **273**. Simple addition of trifluoroacetic acid provoked the transannular attack of the nucleophilic sulfur atom onto one of the electrophilic centers located across the ring. The strength of the approach comes from the perfect regio- as well as stereoselectivity of the transannular cyclization: there exists only one product **274**, irrespective of what position the sulfur atom attacks, either C5 or C6.

When another nine-membered thioether 1,4,7-thiadiazonane was bromoacetylated with bromoacetyl bromide, the expected product **275** could not be isolated. The reaction went further to produce the tricycle sulfonium salt **276** by transannular attack of the sulfur atom onto one of the electrophilic centers located α to the amide carbonyl groups (Scheme 96).[96]



Scheme 96

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3.07 Coupling Reactions Between *sp*^{3}-Carbon Centers

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3.07.1	**Introduction**	337
3.07.2	**Homocoupling Reactions**	338
3.07.2.1	The Classical Wurtz Reaction	338
3.07.2.2	Catalytic Reductive Homocoupling of Alkyl Halides	341
3.07.2.3	Catalytic Oxidative Homocoupling of Organometallic Reagents	343
3.07.3	**Direct Cross-Coupling**	346
3.07.3.1	Alkylation of Alkyl Halides with Transition Metal Reagents	346
3.07.3.1.1	Using alkyl cuprates	346
3.07.3.1.2	Using nickelalactones	348
3.07.4	**Transition Metal-Catalyzed Cross-Coupling**	350
3.07.4.1	Copper Catalysts	351
3.07.4.1.1	Using Grignard reagents	351
3.07.4.1.1.1	Reaction with alkyl Grignard reagents	351
3.07.4.1.1.2	Reaction with allylic Grignard reagents	354
3.07.4.1.1.3	Synthetic application	355
3.07.4.1.2	Using other organometallic reagents	355
3.07.4.1.2.1	Reaction with organomanganese reagents	356
3.07.4.1.2.2	Reaction with organozinc reagents	356
3.07.4.1.2.3	Reaction with organoborane reagents	357
3.07.4.1.2.4	Reaction with organosamarium reagents	357
3.07.4.2	Nickel Catalysts	358
3.07.4.2.1	Using Grignard reagents	358
3.07.4.2.1.1	π-Carbon ligands	358
3.07.4.2.1.2	Amine ligands	360
3.07.4.2.1.3	Phosphine Ligands	362
3.07.4.2.2	Using alkylzinc reagents	363
3.07.4.2.3	Using alkylborane reagents	365
3.07.4.2.4	Asymmetric cross-coupling	366
3.07.4.3	Palladium Catalysts	372
3.07.4.3.1	Using alkylborane and alkylzinc reagents	372
3.07.4.3.1.1	Phosphine ligands	372
3.07.4.3.1.2	NHC ligands	375
3.07.4.3.2	Using Grignard reagents	378
3.07.4.3.3	Using alkylstannane reagents	379
3.07.4.4	Silver Catalysts	379
3.07.4.5	Iron Catalysts	382
3.07.4.6	Cobalt Catalysts	384
References		387

3.07.1 Introduction

An excellent review of homocoupling reactions of alkyl halides and cross-coupling of allylic and benzylic carbons covering the progress up to 1991 is available in the first edition of this series. Therefore, this chapter deals with coupling reactions between *sp*^{3}-carbons that have been reported mainly after the early 1990s, with a focus on newly developed cross-coupling reactions as well as historically important homocoupling reactions. The alkylation of stabilized carbanions such as enolates and metalated sulfonates or dithioacetals is not covered in this chapter. For alkylation of stabilized and nonstabilized carbanions, *see* Chapters 3.01, 3.02, 3.03, and 3.04, respectively.

Coupling reactions between two *sp*^{3}-carbon centers are one of the most important and straightforward transformations for constructing saturated hydrocarbon frameworks in the field of organic synthesis. The classical method for this coupling is the Wurtz reaction, which results in the formation of symmetrical homocoupling products from alkyl halides with the aid of powerful reducing reagents such as metallic sodium. The same transformation promoted by a mild reducing reagent has also been developed using transition metals as catalysts (equation 1). The oxidative homocoupling of organometallic reagents in the presence of an appropriate oxidant is also an attractive alternative to the classical Wurtz reaction (equation 2). From the synthetic viewpoint,

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the more important reaction is cross-coupling reaction between sp^3-hybridized carbon centers that connects two different alkyl groups to construct carbon frameworks (equation 3). The simplest strategy for this transformation might be the reaction of alkyl halides as carbon electrophiles with alkyl metal reagents as carbon nucleophiles by an S_N2 mechanism. However, this reaction does not always proceed satisfactorily and occasionally halogen–metal exchange occurs leading to disproportionation of the reagents with the production of by-products. Additional problems can arise when the coupling of alkyl groups is attempted using transition metal catalysts for the following reasons. The oxidative addition of sp^3-carbon–X bonds to transition metals is, in general, less efficient in comparison with reactions of unsaturated carbon–X bonds, that is, sp^2- or sp-carbon–X. The reductive elimination of dialkyl transition metal intermediates to form C–C bonds is slower than the corresponding process including unsaturated carbon units such as aryl, vinyl, and alkynyl groups. Alkylmetal intermediates tend to undergo homolysis to generate alkyl radicals and/or β-elimination, leading to homocoupling, reduction, and elimination products. Thus, cross-coupling reactions between sp^3-carbon centers is more difficult to achieve and less developed than the corresponding reactions at sp- and sp^2-carbon centers. From the late 1990s, however, the usefulness of alkyl halides as a promising partner in cross-coupling reactions was recognized and attracted considerable interest. In the 2000s, a variety of useful methods for alkyl–alkyl cross-coupling, including asymmetric versions, were developed, based on a combination of appropriate ligands and transition metals, and this field continues to grow.

$$2\ \mathrm{R{-}X} \xrightarrow{\text{Reductant}} \mathrm{R{-}R} \tag{1}$$

$$2\ \mathrm{R{-}m} \xrightarrow{\text{Oxidant}} \mathrm{R{-}R} \tag{2}$$

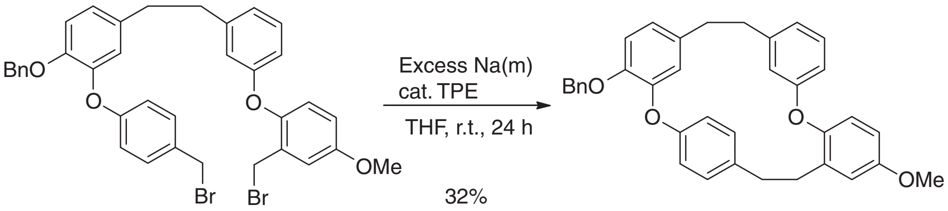
$$\mathrm{R{-}X} \quad + \quad \mathrm{R'{-}m} \xrightarrow{\text{Catalyst}} \mathrm{R{-}R'} \tag{3}$$

3.07.2 Homocoupling Reactions

Homocoupling reactions can be employed for the synthesis of symmetrical carbon frameworks that contain an even number of carbons, numerous examples of which have been reported. A main side reaction is β-elimination to give olefins. Homocoupling reactions can be classified into two types: (1) the coupling of organic halides in the presence of reducing agents (equation 1) and (2) the coupling of organometallic reagents using oxidizing agents (equation 2). Classically, a stoichiometric or excess amount of a strong oxidizing or reducing agent is employed in these reactions. The use of mild oxidizing or reducing agents in the presence of transition metal catalysts is more preferable in terms of functional group tolerance. This chapter consists of three sections: (1) classical Wurtz reactions, (2) catalytic variants of the Wurtz-type reductive coupling of alkyl halides using mild reducing agents, and (3) its reverse-type coupling, namely, the oxidative homocoupling of organometallic reagents.[1] Cross-coupling between two different alkyl moieties is discussed in Sections 3.07.3 and 3.07.4.

3.07.2.1 The Classical Wurtz Reaction

Homocoupling reactions of alkyl halides in the presence of elemental Na are known as Wurtz coupling[2,3] and is utilized to synthesize cyclic and acyclic alkanes. The relative reactivity of alkyl halides decreases in the order of I > Br > Cl. As classical reaction conditions are heterogeneous, the use of a catalytic amount of a homogenizer such as tetraphenylethylene (TPE) to solubilize the Na metal (Muller's method) gives better results.[4] Muller's method has been used for the construction of macrocycles including Marchantin I (equation 4)[5] and a key intermediate **3** for Garugambin-1 (Scheme 1)[6]. The Na–K alloy, which is usually liquid at room temperature, is highly reactive and employed for reactions between congested tertiary alkyl iodides.[7]

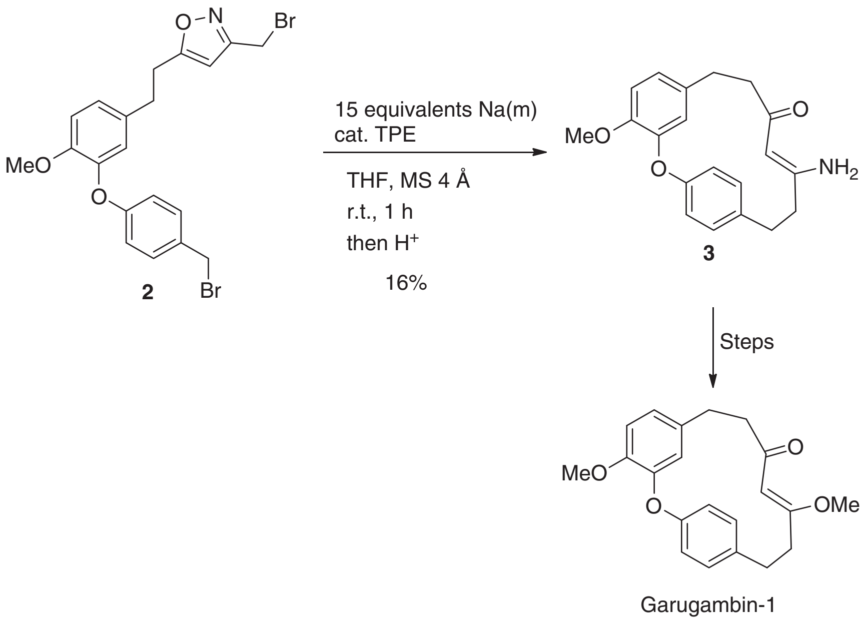


1

Marchantin I

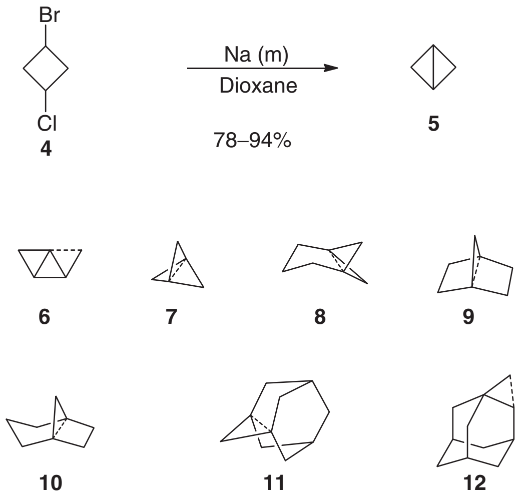
(4)

Another typical application of homocoupling is the construction of small cyclic compounds, such as cyclopropanes and cyclobutanes, by intramolecular cyclization. For example, 1-bromo-3-chlorocyclobutane (4) undergoes intramolecular coupling in

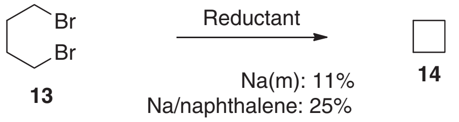


Scheme 1

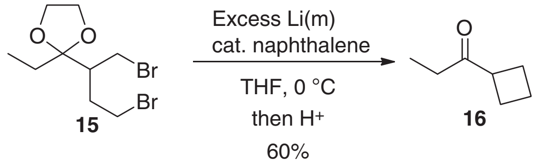
the presence of elemental Na in refluxing dioxane to give bicyclo **5** (**Scheme 2**).[8,9] This intramolecular cyclization can be used for the syntheses of fused hydrocarbon frameworks[10] such as tricyclo[2.1.0.0^{1,3}]pentane (**6**),[11] tricyclo[1.1.1.0^{1,3}]pentane (**7**),[12,13] tricyclo[3.1.1.0^{1,5}]heptane (**8**),[14] tricyclo[2.2.1.0^{1,4}]heptane (**9**),[15,16] tricyclo[3.2.1.0^{1,5}]octane (**10**),[17] tetracyclo[3.3.1.1^{3,7}.0^{1,3}]decane (**11**),[18,19] and 1,2-methanoadamantane (**12**)[20,21] as shown in **Scheme 2**, where the newly formed C–C bond produced by Wurtz coupling is indicated by the dashed line. The intramolecular Wurtz coupling of 1,4-dibromobutane (**13**) using Na under classical Wurtz reaction conditions was not efficient and the addition of naphthalene improved the yield of cyclobutane (**14**) slightly (equation 5).[22] The use of Li instead of Na resulted in better results for the cyclization of **15** (equation 6).[23]



Scheme 2

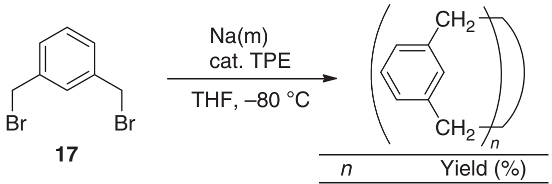


(5)



(6)

The selectivity of this type of cyclization is not always satisfactory. For example, when 1,3-bis(bromomethyl)benzene (**17**) was treated with Na in the presence of TPE in tetrahydrofuran (THF) at −80 °C, the cyclized dimer, [2.2]metacyclophane, was obtained in 33–35% yield along with a series of oligomeric [2.*n*]metacyclophanes up to the 50-membered [2.10]metacyclophane as shown in equation 7.[24]



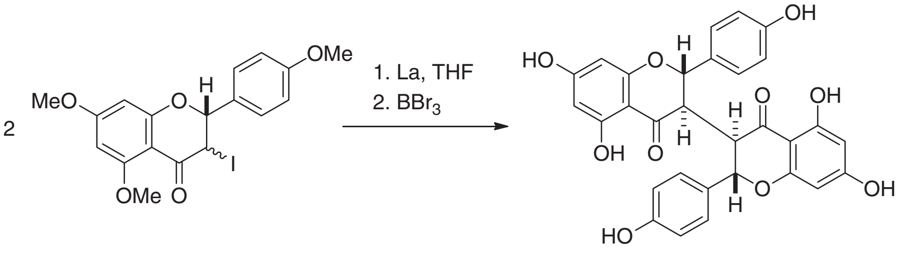
n	Yield (%)
2	33–35
3	7.5–8.9
4	1.7
5	4.8–5.1
6	3.1–4.4
7	0.5
8	0.6
9	0.4–0.5
10	0.3

(7)

The yields for classical Wurtz reactions are not universally high, and this represents a drawback to the reaction. To improve the synthetic utility of the reaction, various modifications have been attempted in which various reducing reagents are used in place of Na. Sonication has been reported to be effective for accelerating Li-mediated Wurtz coupling reaction.[25,26] Magnesium–graphite shows good reactivity for the dimerization of halogenated sugars.[27] The use of activated Cu gives good yields of homocoupling products from various alkyl iodides; however, side reactions cannot be completely suppressed in the case of an unactivated alkyl iodide derivative.[28]

The homocoupling of allylic and benzylic halides can be achieved, when transition metals such as CuI/lithium amide,[29] Cu (0)–isonitrile,[30] Rieke Ni,[31,32] $CoCl(PPh_3)_3$,[33,34] Fe,[35] $Fe_3(CO)_{12}$/pyridine *N*-oxide,[36] CpFe(cod)·Li(TMEDA),[37] $Mn_2(CO)_{10}$,[38] $CrCl_2$,[39] $CrCl_3/LiEt_3BH$,[40–42] $VCl_2(py)_4$,[43] $VCl_3/LiAlH_4$,[44] Ti(II),[45] and SmI_2,[46] as well as typical element compounds such as Et_3B/O_2,[47] $Bu_3SnSnBu_3/h\nu$,[48] aryl Grignard reagent,[49,50] Te(−II),[51] and indium[52] are used.

^{t}BuBr underwent homocoupling in a reaction with $CrCl_3/LiEt_3BH$ to give the dimerized product in 84% yield.[40] Metallic indium was also reported to promote the homocoupling of simple alkyl iodides as well as α-iodoketones.[52] When simple alkyl iodides are treated with elemental lanthanum, homocoupling products are obtained in moderate to good yields.[53] This homocoupling is triggered by the one-electron reduction of the alkyl iodides by La to generate alkyl radical intermediates, which undergo subsequent recombination to give coupling products. This La-mediated Wurtz coupling was used for the synthesis of the 3,3′-biflavanone natural product, Chamaejasmine, as shown in equation 8.[54]



Chamaejasmine

(8)

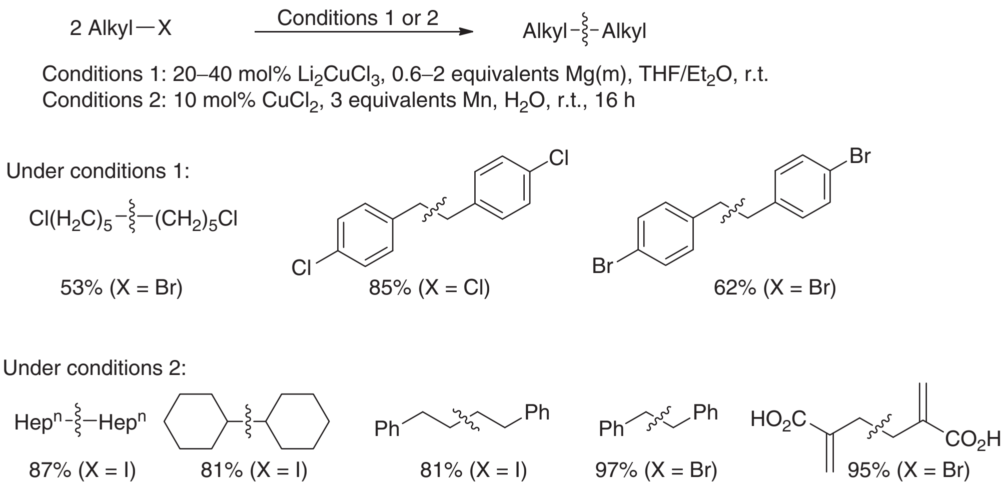
As a nonmetal technique, excellent yields of coupling products were obtained by the homocoupling of unactivated alkyl halides promoted electrochemically using a silver–palladium cathode.[55–58] The laser-induced intramolecular homocoupling of benzyl halides[59] and the photo-induced dimerization of iodoalkanes with rare earth metals have also been reported.[60]

3.07.2.2 Catalytic Reductive Homocoupling of Alkyl Halides

As shown in Section 3.07.2.1, classical Wurtz-type reactions require a stoichiometric or an excess amount of a strong reducing agent and are applicable to only simple compounds without functionalities that are prone to react with electron transfer reagents or with carbon nucleophiles that are generated *in situ*. Alternatively, to overcome these problems, a combination of mild reducing reagents and transition metals can be employed for homocoupling reactions, as shown in equation 9. This method has been successfully applied to unsaturated compounds such as alkynyl, vinyl, and aryl compounds to provide functionalized conjugated systems for conductive and optical materials, dyes, medicinal drugs, and related materials.[61,62] However, there are inherent difficulties associated with the transition metal-catalyzed homocoupling of alkyl halides (equation 9), as mentioned in Section 3.07.1. However, several useful synthetic methods have been developed, as shown below.

$$2\ \text{Alkyl–X} \xrightarrow{\substack{\text{Catalyst}\\ \text{Reductant}}} \text{Alkyl–Alkyl} \qquad (9)$$

The use of a catalytic amount of Li_2CuCl_3 and a stoichiometric amount of Mg metal promotes the homocoupling of alkyl halides in moderate to good yields. When dihalides are employed under optimized conditions, site selective homocoupling can be achieved, where the alkyl–Br bond is preferentially reduced to give homocoupling products in which alkyl–Cl and Ar–Br bonds remain intact under the reaction conditions (**Scheme 3**).[63] $CuCl_2$ catalyzes the homocoupling of primary and secondary alkyl iodides and bromides in aqueous media using metallic manganese as a reducing agent.[64] Carboxylic acid groups survive this coupling reaction (**Scheme 3**). Similarly, the Zn-mediated Cu-catalyzed homocoupling of alkyl halides proceeds in aqueous media.[65]

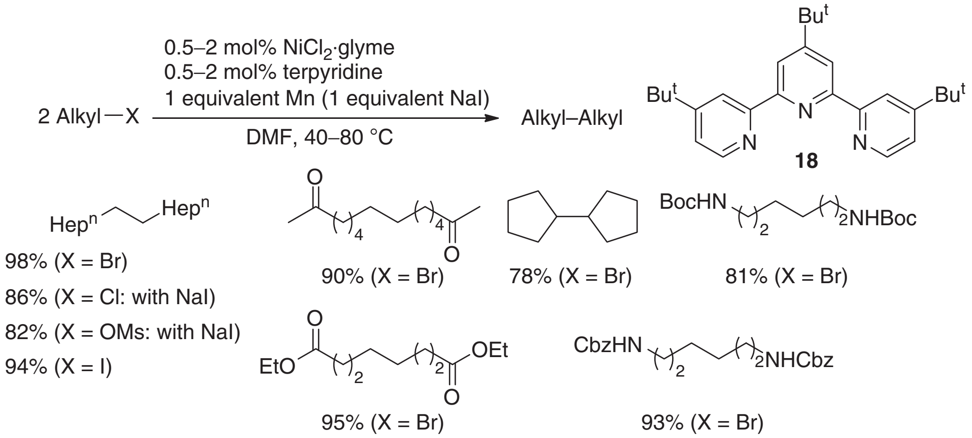


Scheme 3

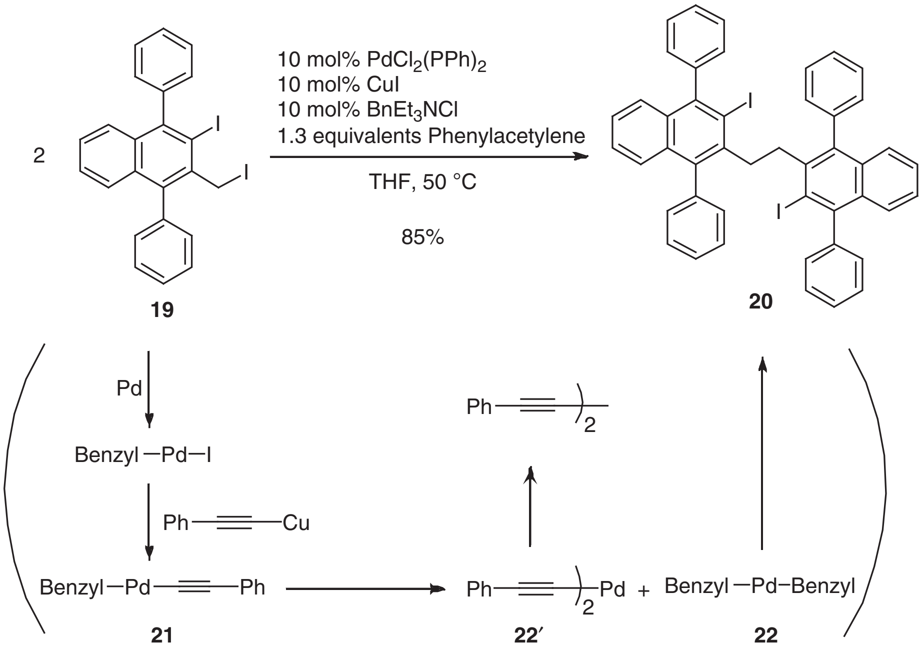
Benzyl halides underwent homocoupling in a Cu/Zn system under neat conditions in the presence of a catalytic amount of an ionic liquid.[66] Powdered elemental iron,[67] more preferably iron nanoparticles,[68] also served as a viable reducing agent for the Cu-catalyzed homocoupling of benzylic halides.

Although Ni(0)[31,32] and Cr(II)[39,40] promote Wurtz-type coupling as mentioned above, the use of these metals as catalysts is also possible. Catalytic systems of Ni/Zn[69,70] Ni/Mn[71], and Cr/electrochemical reduction[72] are effective for the homocoupling of allyl and benzyl halides. The use of tridentate nitrogen ligands such as **18** expanded the scope of the Ni-catalyzed system to the homocoupling of unactivated alkyl halides carrying a carbonyl functionality (**Scheme 4**).[70,71] The addition of NaI enhanced the reactivity of alkyl chlorides and mesylates, probably due to halogen exchange reactions.[71]

Pd was found to catalyze the homocoupling of 2-iodo-3-iodomethyl-1,4-diarylnaphthalene derivatives **19** to give **20** under standard conditions of the Sonogashira coupling reaction (equation 10). On the basis of evidence showing that CuI and phenylacetylene are both essential and that the dimerization of phenylacetylene proceeds concomitantly, it is proposed that a Pd intermediate having benzyl and alkynyl groups disproportionates, aided by an alkynylcopper generated *in situ*, to afford dialkynyl and dibenzyl Pd complexes **22**′ and **22**. The bulkiness of the fused aromatic rings of substrate **19** played an important role in this reaction because 1-iodo-2-iodomethylbenzene, a simple analog of **19**, gave a complex mixture.[73]



Scheme 4



(10)

The Pd-catalyzed intermolecular homocoupling of benzylic bromides proceeds in the presence of hexaalkylditin, which functions as a suitable reducing agent.[74] Hydrazine was used as a reducing reagent in the palladium-catalyzed homocoupling reaction of alkyl iodides.[75]

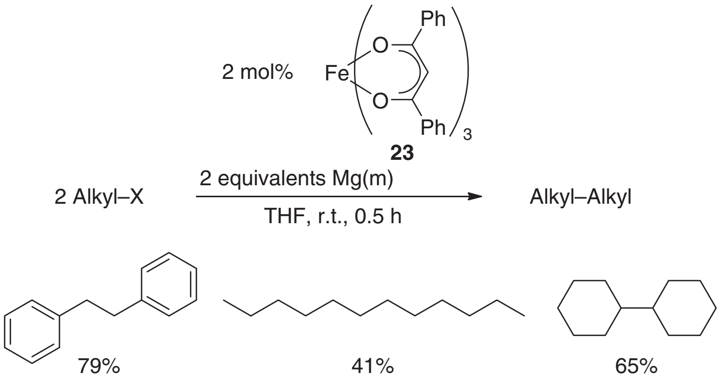
Titanium and zirconium complexes catalyze homocoupling of benzylic and allylic halides at ambient temperatures.[76–79]

Trivalent iron complex, Fe(DBM)$_3$ (**23**), was found to be an effective catalyst for the homocoupling reaction of alkyl bromides by metallic Mg (Scheme 5).[80] Benzyl bromide couples to afford dibenzyl in 79% yield at room temperature, although the reaction of bromohexane results in only a 41% yield of product probably due to β-hydride elimination. The secondary alkyl bromide, bromocyclohexane, also couples to give the corresponding dimer in 65% yield.

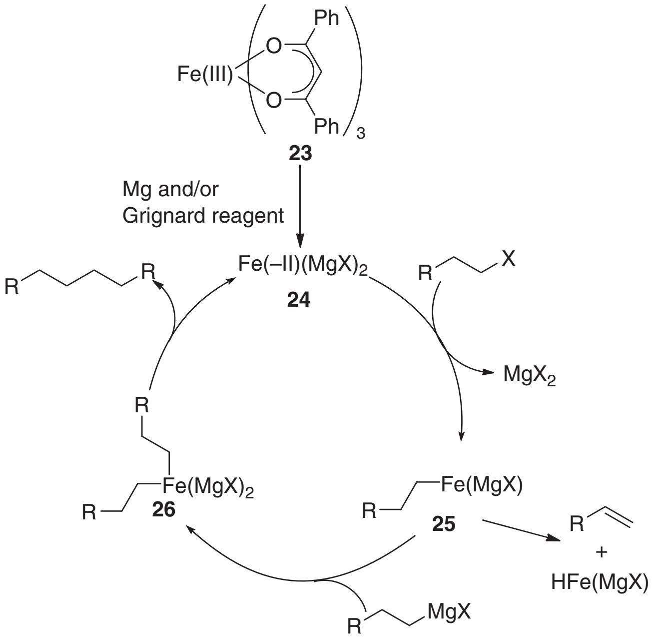
A possible reaction mechanism is shown in Scheme 6. Reduction of Fe(DBM)$_3$ (**23**) to Fe(–II) by Mg metal or Grignard reagent, generated by the reaction of alkyl halide with Mg, initiates the reaction and generates catalytically active species **24**, which reacts with alkyl halides to generate alkyl iron complex **25**. Then complex **25** reacts with Grignard reagents to give dialkyl iron **26**. Subsequent reductive elimination gives coupling products and regenerates **24**.

Iron acetylacetonate also catalyzes the electrochemical homocoupling of alkyl halides, although reduction to alkanes and elimination to alkenes compete to afford mixtures of products.[81]

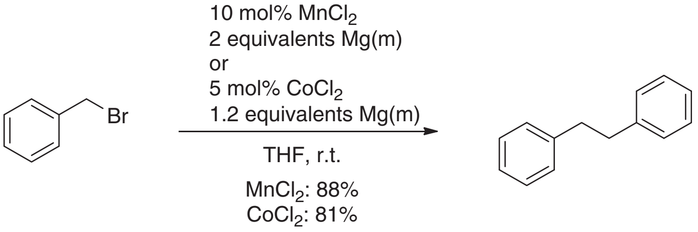
Manganese chloride[82] and cobalt chloride[83] also act as catalysts for the homocoupling of alkyl bromides as well as aryl and vinyl halides under similar conditions (equation 11).



Scheme 5



Scheme 6



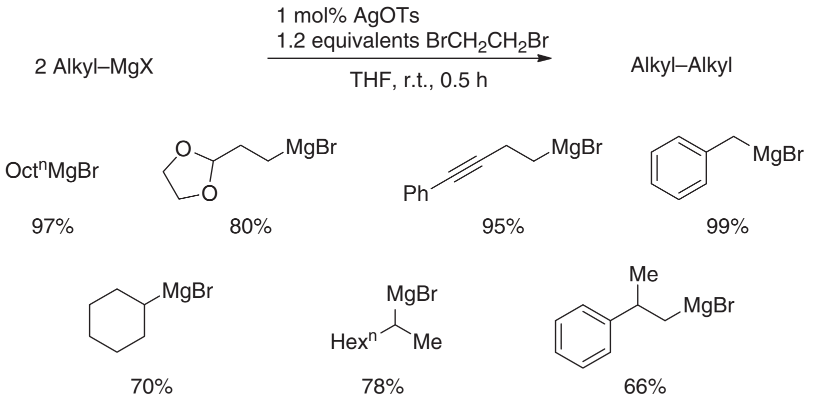
(11)

3.07.2.3 Catalytic Oxidative Homocoupling of Organometallic Reagents

Alkyl metal reagents undergo homocoupling by reactions with oxidizing reagents in the presence of catalysts (equation 12).

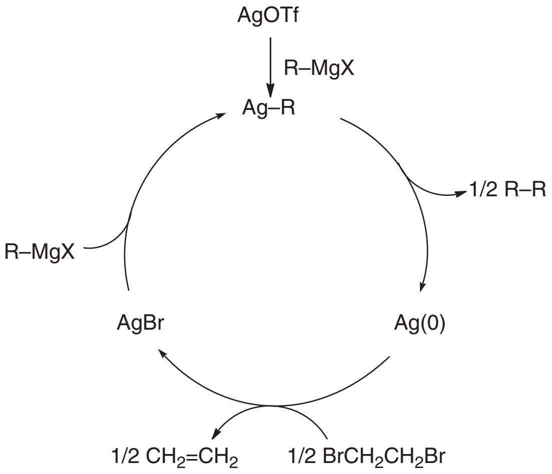
$$2\ \text{Alkyl–(m)} \xrightarrow{\substack{\text{Catalyst}\\ \text{Oxidant}}} \text{Alkyl–Alkyl} \qquad (12)$$

The pioneering work directed to the homocoupling of Grignard reagents by AgBr as an oxidant was reported in 1929 demonstrating that aryl and benzyl Grignard reagents afforded homocoupling products in good yields, although ^{n}BuMgBr resulted in a moderate yield and no pure products were obtained in the case of ^{i}Bu- and ^{s}BuMgBr.[84] This stoichiometric silver-mediated homocoupling was applied to alkylboranes.[85,86] Dialkylcuprate, generated by the reaction of a Cu(I) salt with 2 equivalents of alkyllithium, is known to result in homocoupling products of the alkyl group on treatment with oxygen.[87] These results suggest that, if the transition metal can be reoxidized by an appropriate oxidant, these reactions would proceed catalytically. Indeed, the use of a catalytic amount of a silver salt as well as Fe, Co, Ni, and Cu salts was found to be effective for the homocoupling of EtMgBr in the presence of $LiNO_3$ as an oxidant, albeit with low turnover numbers (TONs) of the catalyst and poor selectivities.[88] Hayashi et al. utilized 1,2-dibromoethane as a mild oxidant for the silver-catalyzed homocoupling reaction of alkyl Grignard reagents, as shown in Scheme 7. [89] Remarkable features of the catalyst are as follows: (1) the reaction is rapid and efficient, giving good yields of products under mild conditions, (2) it is applicable to various primary and secondary alkyl Grignard reagents that contain a β-hydrogen, and (3) only ethylene is formed as the sole by-product.



Scheme 7

Scheme 8 shows the proposed mechanism. Alkylsilver intermediate generated by transmetalation of AgX with Grignard reagent undergoes disproportionation to form coupling products and Ag(0), which is reoxidized by 1,2-dibromoethane to regenerate AgX.

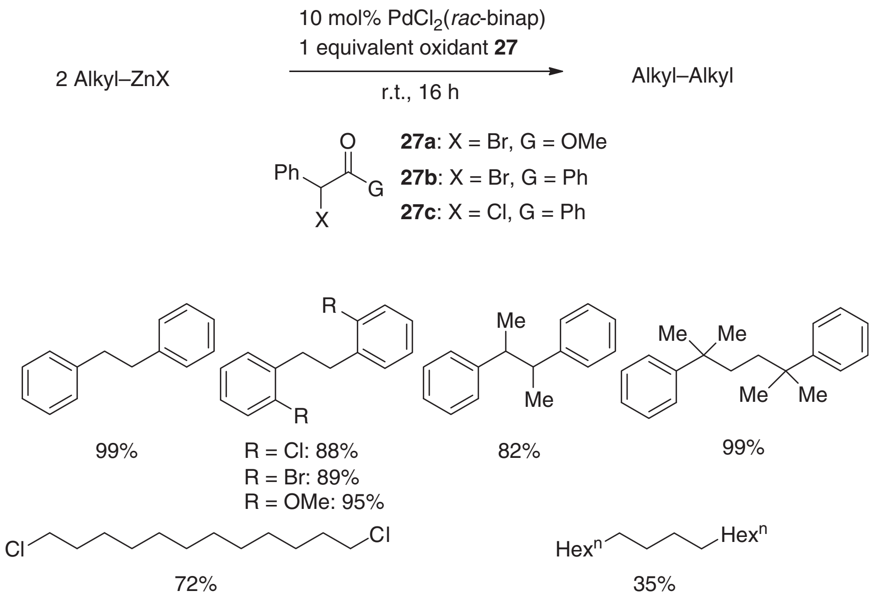


Scheme 8

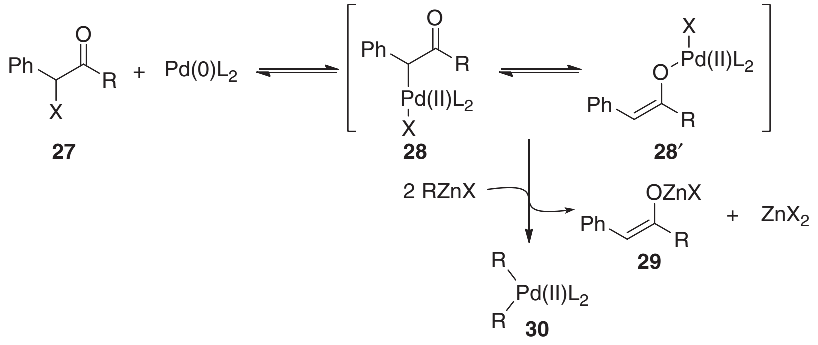
Other oxidants that promote homocoupling of alkyl Grignard reagents include Tl salts[90] and Tf_2O.[91]

α-Halocarbonyl compounds **27** were successfully employed as suitable oxidants for the Pd-catalyzed homocoupling of alkylzinc, -magnesium, and -borane reagents.[92] Although this reaction proceeds nicely in the case of the homocoupling of benzyl and alkyl groups having no β-hydrogen, simple alkylzinc reagents bearing β-hydrogens result in lower yields (Scheme 9).

The α-halocarbonyl oxidants, also applicable to homocoupling of *sp*- and sp^2-carbon nucleophiles,[93,94] react as shown in Scheme 10. The first step involves the oxidative addition of the C–X bond of **27** to Pd(0) to form the Pd(II) intermediate **28**, which



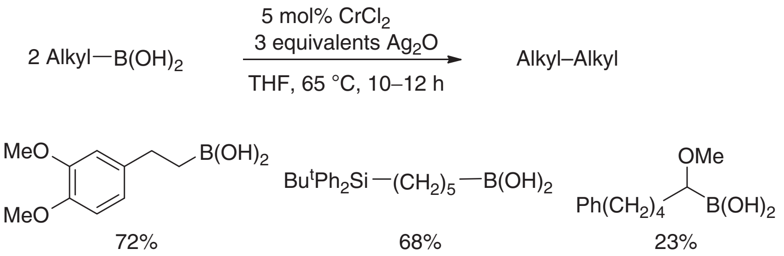
Scheme 9



Scheme 10

is in equilibrium with its enolate form **28**′. A double transmetalation yields ZnX_2, zinc enolate **29**, and dialkyl Pd intermediates **30**, which readily undergo reductive elimination.

Chromium chloride catalyzes the homocoupling of alkyl boronic acids in the presence of a stoichiometric amount of Ag_2O as an oxidant, where primary alkylboronic acids as well as vinyl and aryl derivatives couple in good to moderate yields, although the coupling of α-methoxyalkylboronic acids results in poor yield (Scheme 11).[95]



Scheme 11

Rhodium-catalyzed homocoupling of diorganomercury proceeds without oxidizing reagents,[96] giving the homocoupling products in good yields from dialkynyl and diarylmercury, in moderate yields from dibenzylmercury, and no reaction took place when dibutylmercury was used.

3.07.3 Direct Cross-Coupling

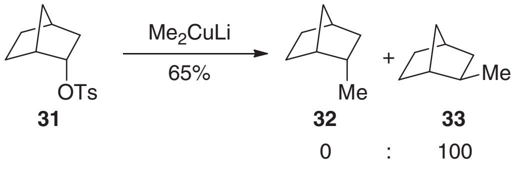
A simplest method for forming carbon–carbon bonds involves the reaction of carbon nucleophiles with carbon electrophiles by an S_N2 mechanism. Although alkyl halides represent the most straightforward and versatile type of carbon electrophile, this reaction does not always proceed effectively in cases in which nonstabilized carbon nucleophiles are involved. For example, the reaction of organolithium reagents and alkali metal analogs with alkyl halides often results in mixtures of products arising from competing metal–halogen exchange, α-metalation, β-elimination, and coupling reactions. Organomagnesium, -zinc, and -aluminum reagents are much less reactive and do not react with nonactivated alkyl halides efficiently. However, some alkyl transition metal complexes, including Cu and Ni, react with alkyl halides to give cross-coupling products as the result of a reaction between two different alkyl groups. From the synthetic point of view, this cross-coupling has the following drawbacks: (1) stoichiometric or even excess amounts of organotransition metal complexes are required; (2) these complexes are usually generated by the reaction of a transition metal salt with the corresponding alkyllithiums or alkylmagnesium halides, resulting in a narrow functional group tolerance; (3) alkyl metal complexes produced from transition metals are not kinetically stable, especially when a hydrogen or heteroatom substituent is present on an sp^3-carbon at the β-position. However, such stoichiometric cross-coupling has occasionally been employed for constructing saturated carbon chains.

3.07.3.1 Alkylation of Alkyl Halides with Transition Metal Reagents

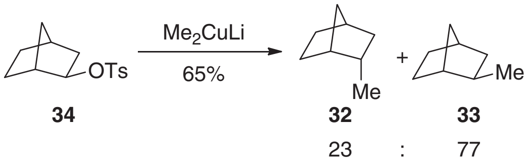
3.07.3.1.1 Using alkyl cuprates

Gilman et al. reported that the reaction of CuCl with 1 equivalent of methyllithium or -magnesium gave a bright yellow ether-insoluble methyl copper derivative, which was stable at temperatures below 0 °C but underwent decomposition with the evolution of ethane and methane at room temperature, leaving metallic Cu as a residue.[97] The addition of an additional equivalent of methyllithium resulted in the formation of the ether-soluble dimethylcuprate. Similar reactions were also observed in the case of ethylmagnesium bromide, although the resulting ethyl copper was much less stable than methyl copper and decomposed even at temperatures below 0 °C.[97] Corey et al. utilized dimethylcuprates generated by the reaction of CuX with 2 equivalents of MeLi or MeMgX in ether for the methylation of alkyl iodides and bromides. These reactions proceeded at ambient temperature or temperatures down to −15 °C to give methylated products in good yields.[98] Diethyl or dibutylcuprates react faster with halides than dimethylcuprate, albeit they are less stable. Therefore, butylation was performed successfully at lower temperatures, for example, at 0 °C for heptyl chloride and at −45 °C for decyl iodide.[99] Further investigations into the coupling of dialkylcuprates with alkyl halides revealed that (1) the addition of Li salts slightly improved the reactivity of cuprates, (2) the coupling reactions were enhanced significantly when a polar coordinating solvent such as THF was used and the reaction was suppressed when a hydrocarbon medium was used, (3) a large excess of cuprate (approximately 3 equivalents) to alkyl halide was required to attain high yields, (4) secondary alkyl halides react with dialkylcuprates much slower than primary halides, (5) di-*n*-butylcuprate reacts with primary iodides, bromides, and chlorides to give coupling products in excellent to good yields, and (6) di-*sec*-butyl cuprate couples moderately with primary alkyl chlorides and much less efficiently with iodides but di-*tert*-butyl cuprate does not give the coupling product with either halides. The addition of P^nBu_3 dramatically improved the yields.[100] In coupling reactions with dialkylcuprates, only one of the two alkyl groups on the cuprates is transferred to the electrophile. Therefore, to improve the atom efficiency of the coupling reaction, cuprates in which one alkyl group is replaced with a heteroatom ligand are often employed. Some representative examples are shown in **Table 1**.[101–105]

Mechanistic studies of these coupling reactions revealed that (1) kinetically, the reaction is generally first order in both electrophiles and organocuprates,[106,107] (2) the rate-limiting step is the oxidative addition step, (3) the oxidative addition step proceeds via a nucleophilic substitution mechanism and the successive reductive elimination step obeys a concerted mechanism in the case of primary alkyl electrophiles, and (4) the reaction of secondary alkyl iodides proceeds predominantly via a radical pathway.[108,109] The formation of an alkyl radical from the secondary alkyl iodide **35** was also supported by the formation of cyclopentane **37** probably via 5-*exo* radical cyclization (**Scheme 12**).[108] As shown in equation 13, *endo*-2-norbornyl tosylate (**31**) coupled with dimethylcuprate in 65% yield with complete stereo inversion. However, the same reaction of the *exo*-2-norbornyl tosylate (**34**) gave a coupling product with 23% inversion and 77% retention, suggesting the possibility of competing E1 and/or E2 mechanisms (equation 14).[106]



(13)

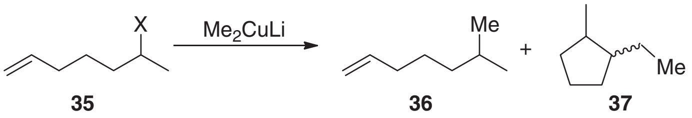


(14)

Table 1 Reaction of alkyl halides with alkyl cuprates

$$\text{Alkyl–X} + \text{R(X)CuLi·L} \longrightarrow \text{Alkyl–R}$$

Substrate	*Cuprate*	*Solvent*	*Yield (%)*
Pen^nI	$Bu^n{}_2CuLi$	THF	98
Pen^nBr	$Bu^n{}_2CuLi$	THF	98
Pen^nBr	$Bu^n{}_2CuLi$	Pentane	<2
Pen^nBr	$Bu^n{}_2CuLi$	Et_2O	68
Pen^nCl	$Bu^n{}_2CuLi$	THF	80
Pen^nOTs	$Bu^n{}_2CuLi$	THF	98
2-PenBr	$Bu^n{}_2CuLi$	THF	12
Pen^tBr	$Bu^n{}_2CuLi$	THF	<10
Pen^nI	$Bu^s{}_2CuLi$	THF/hexane	7
Pen^nBr	$Bu^s{}_2CuLi\ PBu^n{}_3$	THF/hexane	94
Pen^nI	$Bu^t{}_2CuLi$	THF/pentane	<1
Pen^nBr	$Bu^t{}_2CuLi\ PBu^n{}_3$	THF/pentane	92
Oct^nI	$PhS(Bu^s)CuLi$	THF	67
Oct^nI	$PhS(Bu^t)CuLi$	THF	98
Oct^nI	$Bu^tO(Bu^s)CuLi$	THF	52
Oct^nI	$Bu^tO(Bu^t)CuLi$	THF	82
Oct^nI	$Ph_2P(Bu^n)CuLi$	THF	64
Oct^nI	$Bu^t{}_2P(Bu^n)CuLi$	THF	69
Oct^nI	$Cy_2N(Bu^n)CuLi$	THF	71



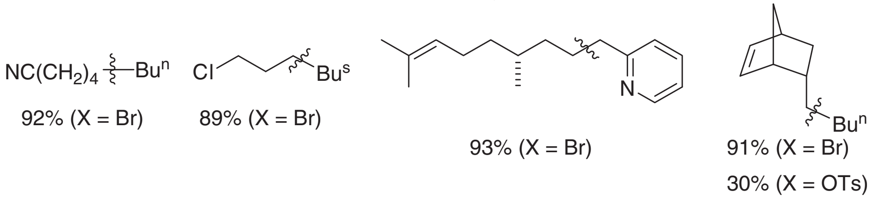
X	Yield of **36** (%)	Yield of **37** (%)
OTs	24	0
Br	68	0
I	18	65

Scheme 12

Investigations of the stereochemistry in the cuprate-mediated substitution of enantiomerically pure secondary alkyl halides revealed that stereo inversion occurred in the case of bromides, and racemic coupling products were formed when iodides were used.[110] These results suggest that both S_N2 substitution and radical mechanisms are possible and that the reaction mechanism depends on the reaction conditions used, the structure of the organo moiety, as well as the leaving group.

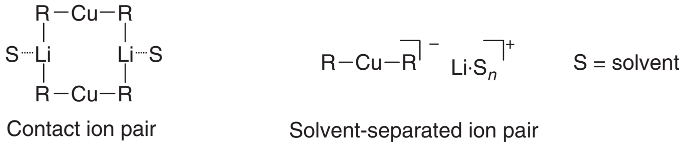
$R_2Cu(CN)Li_2$, generated from CuCN and 2 equivalents of RLi, which are referred to as 'higher-order cuprates' or 'Lipshutz cuprates,'[111] are known to be potent nucleophilic reagents and have been used successfully for alkylation toward secondary alkyl iodides but reacted less efficiently with alkyl chlorides and tosylates (Scheme 13).[110,112,113]

$$\text{Alkyl–X} + R_2Cu(CN)Li_2 \xrightarrow[\text{THF, –78 °C to r.t.}]{} \text{Alkyl–R}$$



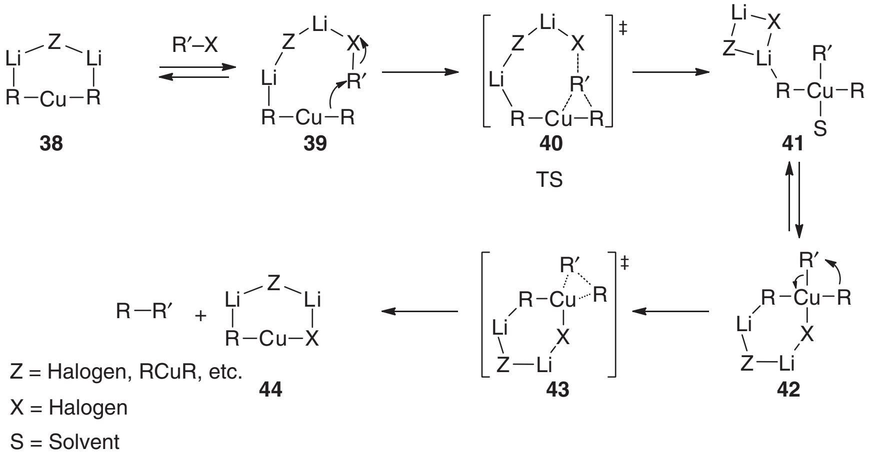
Scheme 13

The structures of cuprates in solution vary depending on the ligands, solvents, additives, etc., and may exist in an equilibrium mixture of different structures. The higher reactivity of the Lipshutz cuprates was once ascribed to a dianionic tricoordinated copper(I) $R_2Cu(CN)\ Li_2$ ('higher order') structure, but numerous structural studies have shown that the Lipshutz cuprate exists as a 'cyano-Gilman' ($R_2CuLi{\cdot}LiCN$) cuprate.[114,115] The crystal and solution structures of the diorganocuprate complexes were examined using various experimental techniques and two types of structures, namely, a contact ion pair (CIP) and a solvent-separated ion pair (SSIP) as shown in Scheme 14 have been proposed as the active species.[116] X-ray analyses of both CIP[105,117] and SSIP[118,119] of dialkylcuprates indicate that they exist in the form of a linear array. For $R_2Cu(CN)Li_2$,[111] an SSIP structure R_2Cu^{-}+$Li_2CN(L)_n^{+}$ was reported in solid state.[120] Generally, CIP and SSIP exist in equilibrium and the solvation of the lithium cation by the highly coordinating solvent such as THF shifts the equilibrium in favor of a solvent-separated ion pair.



Scheme 14

Extensive theoretical calculations have been made on the structures of cuprates and their reactivity.[121,122] Density functional theory (DFT) calculations assuming an S_N2 alkylation mechanism showed that the rate-determining step of this coupling reaction is the bond scission process of C–X associated with an incoming R–Cu moiety (**39–41**) via the TS **40**, where the lithium atom activates the leaving group by coordination (Scheme 15). As a result, no substitution reaction occurred in the presence of crown ether.[123] From the resulting Cu(III) species **42**, reductive elimination occurs. A long-standing question regarding cuprate-mediated alkylation revolved around why cross-coupling between R and R′ predominates over homocoupling to form an R–R structure. This can be explained by the *trans*-orientation of the two alkyl groups R in intermediate **42**, a situation that is not favorable for homocoupling to proceed.[123]



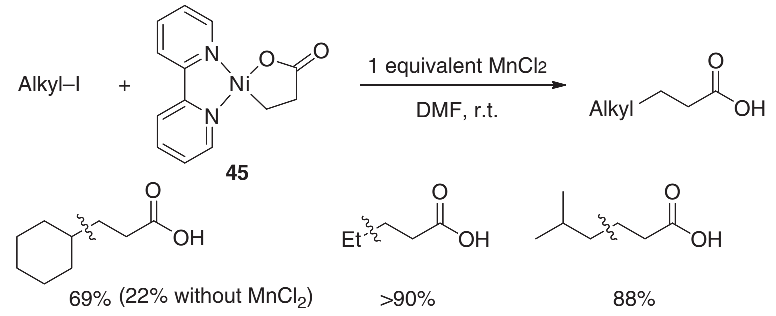
Scheme 15

3.07.3.1.2 Using nickelalactones

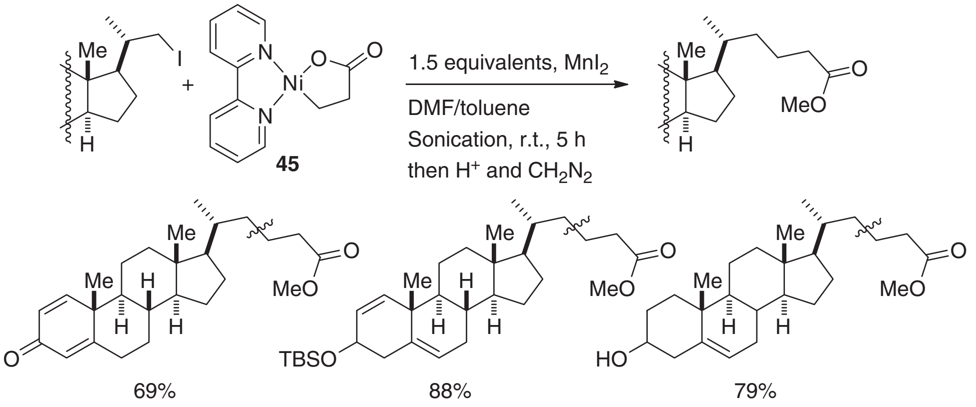
It is known that π-allylnickel complexes, being in equilibrium with σ-allyl structures, are substantially stable and are frequently used in allylation reactions, which were reviewed in the first edition of this series.[124] Another interesting strategy for inhibiting β-hydrogen elimination is the use of metalacycles. As a synthetically useful example, nickelalactones were utilized as useful alkylating reagents that contain a carboxyl group in coupling reactions with alkyl iodides.[125] The addition of 1 equivalent of an Mn(II) salt improved the yield of coupling products (Scheme 16). In the absence of the Mn salt, the coupling of nickelalactone **45** with cyclohexyl iodide gave the corresponding carboxylic acid in only 22% yield.

The nickelalactone **45** was used for introducing a propionic acid moiety into steroids having various functionalities on the A and/or B rings as shown in Scheme 17.[126]

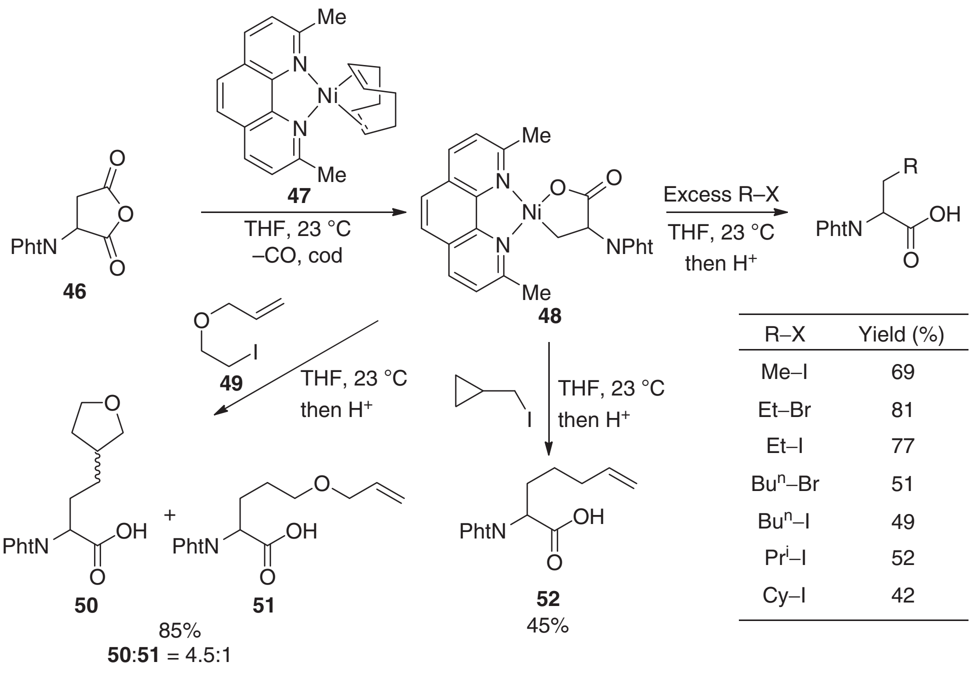
A nickelalactone **48** derived from the *N*-protected aspartic acid anhydride **46** and Ni(0) complex **47** reacts with alkyl bromides and iodides to afford a series of amino acid derivatives in moderate yields (Scheme 18). When 6-iodo-4-oxa-1-hexene (**49**) was used as a substrate, the cyclized product **50** was obtained as a major product. In addition, the reaction of cyclopropylmethyl iodide gave the ring-opening product **52** as the sole product. These results suggest that this reaction proceeds via alkyl radical intermediates.[127]



Scheme 16



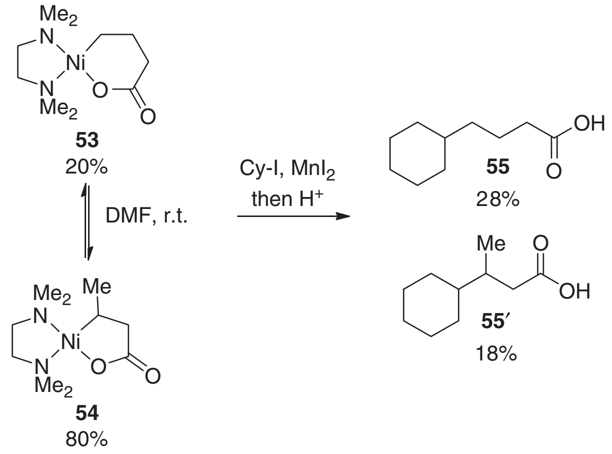
Scheme 17



R–X	Yield (%)
Me–I	69
Et–Br	81
Et–I	77
Bu^n–Br	51
Bu^n–I	49
Pr^i–I	52
Cy–I	42

Scheme 18

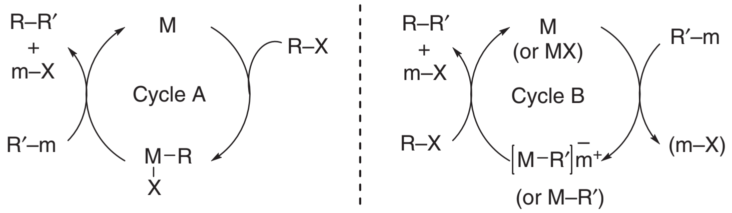
In some cases, however, nickelalactones undergo isomerization via *β*-hydrogen elimination and insertion. For example, nickelalactones **53** and **54** present as an equilibrium mixture with a ratio of 2:8 in *N*,*N*-dimethylformamide (DMF) at room temperature and a mixture of alkylated products was obtained when alkyl iodide and MnI_2 were added (Scheme 19).[128]



Scheme 19

3.07.4 Transition Metal-Catalyzed Cross-Coupling

Transition metal-catalyzed cross-coupling reactions of organohalides and organometallic reagents are one of the most useful and powerful methods for the creation of new C–C bonds between two carbon centers and are widely employed in the synthesis of various classes of organic compounds both in laboratories and in industrial processes.[129–133] In these reactions, *sp*- and sp^2-hybridized substrates have mainly been used as coupling partners,[133,134] with some early exceptions by Kharasch[135,136] and Kochi,[137] due to the difficulty in the utilization of alkyl halides[138] and/or alkylmetal reagents.[139] These difficulties arise from (1) the slow oxidative addition of alkyl halides to low valent transition metals in comparison to the case of unsaturated carbon halides, (2) facile *β*-hydrogen elimination from alkylmetal intermediates, (3) single-electron transfer from metal catalyst to substrates to generate alkyl radicals, (4) homolysis of metal–alkyl bonds, and (5) slow reductive elimination from alkylmetal intermediates.[140,141] Since the epoch making discoveries of cross-coupling reaction of unsaturated substrates in the 1970 s,[142] three decades were required to overcome such problems to achieve catalytic sp^3–sp^3 cross-coupling efficiently. In the late 1990s, employment of appropriate ligands and transition metal catalysts opened a new era of the coupling reaction which emerged extensively in the 2000s using various metals including Cu, Ni, Pd, Fe, Co, and Ag, realizing various coupling reactions of alkyl halides as well as asymmetric variants.[143,144] Although mechanistic details are not known in many cases, the reaction pathway can be classified into the following two types of catalytic cycles (Scheme 20). The catalytic cycle A, a common mechanism for the cross-coupling of aryl and vinyl halides, is triggered by oxidative addition to the metal. Subsequent transmetalation with organometallic reagents followed by reductive elimination gives coupling products. In cycle B, as exemplified by the Cu-mediated reaction as shown in Section 3.07.3.1, metal catalysts first react with the organometallic reagent, followed by the alkyl halide via S_N2 or radical mechanisms.



R, R′ = Organic group

X = (Pseudo)halide

M = Transition metal catalyst

m = Typical element

Scheme 20

This section focuses on the catalytic cross-coupling of alkyl halides and pseudohalides with alkyl nucleophiles being organized according to transition metal catalysts.

3.07.4.1 Copper Catalysts

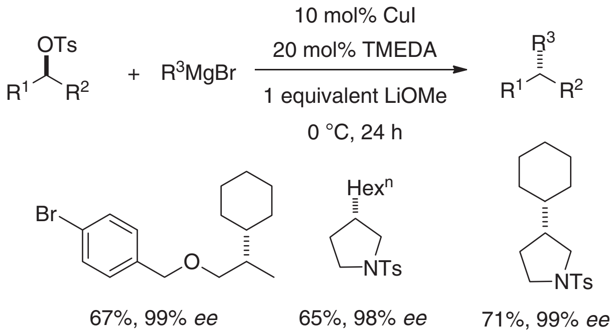
Various cuprates ($R_2CuLi{\cdot}LiX$) have been employed as useful alkylating reagents for cross-coupling reactions as shown in Section 3.07.3.1.1. A serious drawback of this transformation is the low atom economy of the reagents, that is, large excesses of cuprates are needed to achieve high yields of coupling products and only one of the organo group on Cu is transferred to the reacting partners. To overcome these problems, Cu-catalyzed cross-coupling reactions of alkyl halides have been developed using alkylmagnesium, -zinc, -lithium, -boron, and –samarium as carbon nucleophiles.

3.07.4.1.1 Using Grignard reagents

3.07.4.1.1.1 Reaction with alkyl Grignard reagents

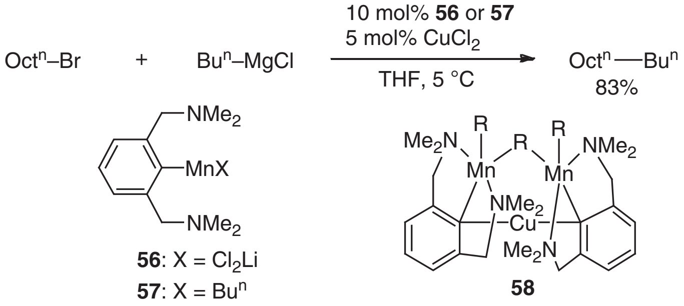
In the early 1970s, Kochi utilized catalytic amounts of simple Cu salts for the reaction of primary alkyl halides with alkyl Grignard reagents and observed that cross-coupling proceeded catalytically following first-order kinetics with respect to Cu catalyst.[145–147] A few years later, Schlosser demonstrated the Cu-catalyzed cross-coupling of alkyl tosylates with alkyl Grignard reagents.[148] In 1997, Burns reported that a soluble copper salt adduct, CuBr–LiSPh–LiBr–THF, efficiently catalyzed cross-coupling of alkyl halides and tosylates with alkyl Grignard reagents.[149] This catalytic system is compatible with ester groups and efficiently promoted cross-coupling reaction of secondary alkyl tosylates with primary alkyl Grignard reagents as well as the cross-coupling of primary alkyl tosylates with secondary and tertiary alkyl Grignard reagents. It was proposed based on nuclear magnetic resonance (NMR) studies that the active species were Cu aggregates ligated by LiBr, thiophenol, and THF.

In a recent study, Liu et al. reported that the addition of a stoichiometric amount of LiOMe enhanced the catalytic activity of the Cu catalyst and enabled coupling reaction at unactivated secondary carbon centers with complete inversion of stereochemistry as shown in Scheme 21.[150]



Scheme 21

The combined use of Cu salts and manganese(II) complexes (**56** and **57**) having an NCN tridentate pincer ligand was found to be effective for the cross-coupling of primary alkyl bromides with alkyl Grignard reagents including sterically hindered tertiary alkyl Grignard reagents. Trinuclear organometallic reagents $[CuMn_2R_3(NCN)_2]$ **58** were proposed as the catalytically active species (Scheme 22).[151]



Scheme 22

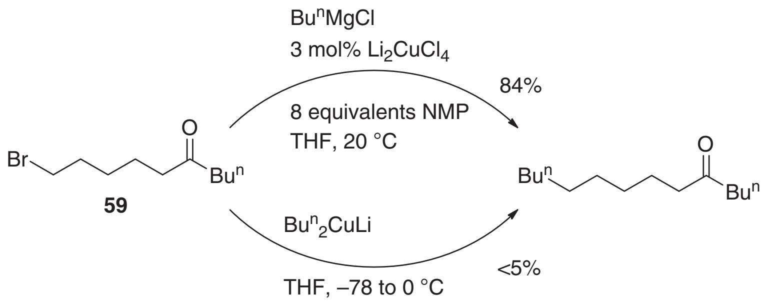
When the Grignard reagents were slowly added using a syringe pump,[152] a remarkable effect was observed on the cross-coupling of alkyl bromides with alkyl Grignard reagents using $CuCl_2$ as catalyst in THF to furnish coupling products in high yields (Scheme 23).

$$\text{Oct}^n\text{–Br} \quad + \quad \underset{\text{Slow addition}}{\text{Bu}^n\text{–MgCl}} \xrightarrow[\text{THF, 0 °C}]{\text{3 mol\% CuCl}_2} \text{Oct}^n\text{–Bu}^n$$

Addition over	
15 min	32%
30 min	80%
60 min	94%

Scheme 23

The addition of *N*-methylpyrrolidinone (NMP) improved both the yield and the chemoselectivity of Cu-catalyzed cross-coupling reaction.[153] For example, the reaction of ^{n}OctBr with ^{t}BuMgCl and ^{i}PrMgCl in the presence of Li_2CuCl_4 (3 mol%) and 4 equivalents of NMP in THF afforded 85% and 76% yields of coupling products, respectively, whereas no reaction was observed in the absence of NMP, with yields of only 8% and 5%, respectively. Moreover, an alkyl bromide **59** having a keto group reacted with ^{n}BuMgCl selectively to achieve the coupling product in the presence of a catalytic amount of Cu and 8 equivalents of NMP, whereas a reaction with a stoichiometric amount of lithium dibutylcuprate under similar conditions did not afford the coupling product (Scheme 24). Ester, nitrile, and carboxylic acid can survive in this catalytic system.



Scheme 24

Simple and highly chemoselective cross-coupling with sterically congested secondary and tertiary alkyl Grignard reagents has been achieved under mild conditions as shown in Scheme 25, where various functional groups including amides, esters, thioethers, heterocycles, and ketones remained intact.[154]

The use of less reactive alkyl electrophiles like alkyl fluorides and chlorides was realized by the addition of unsaturated hydrocarbons.[155] The Cu-catalyzed coupling reaction of alkyl fluorides is facilitated by 1,3-butadiene at ambient temperature (equation 15).[156] The relative reactivities of alkyl halides under the reaction conditions were estimated by competitive reaction to be Br > F >> Cl (equation 16). This unusual order of reactivities between fluorides and chlorides can be attributed to the higher affinity of fluorine atoms toward the magnesium cation.

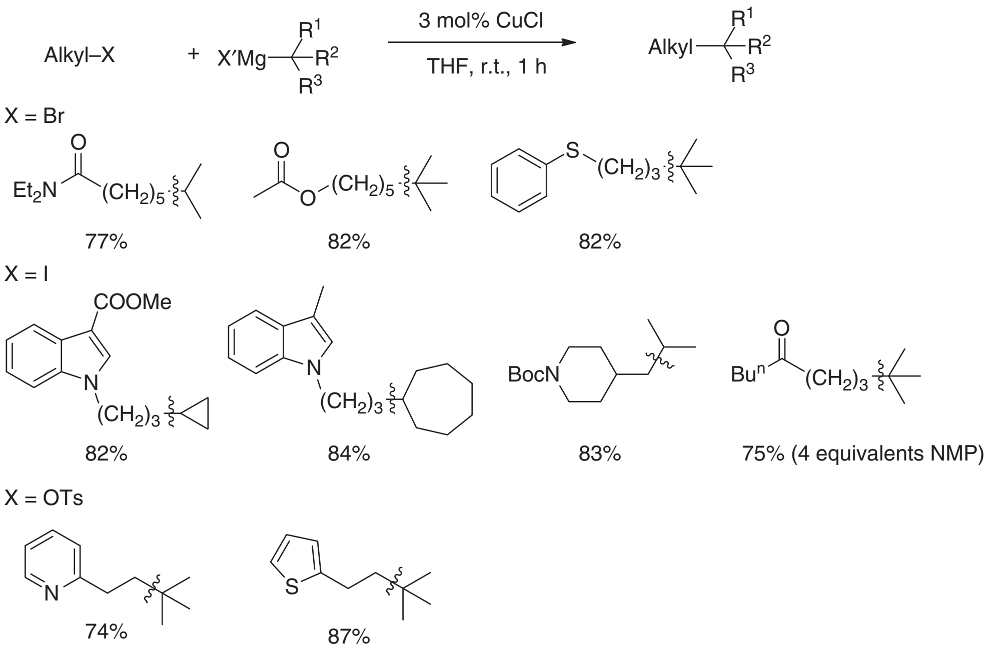
$$\text{Oct}^n\text{–X} \quad + \quad \text{Pr}^n\text{–MgBr} \xrightarrow[\text{THF, 25 °C}]{\substack{\text{3 mol\% CuCl}_2\\ \text{10 mol\% 1,3-butadiene}}} \text{Oct}^n\text{—Pr}^n \qquad (15)$$

X = F: 94%
X = Cl: 3%
X = Br: 97%

$$\text{Pen}^n\text{–MgBr} + \text{Non}^n\text{–F} + \text{Oct}^n\text{–Cl} + \text{Dec}^n\text{–Br} \xrightarrow[\text{THF, 25 °C}]{\substack{\text{3 mol\% CuCl}_2\\ \text{10 mol\% 1,3-butadiene}}} \qquad (16)$$

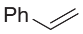
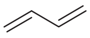
$$\underset{16\%}{\text{Non}^n\text{—Pen}^n} + \underset{0\%}{\text{Oct}^n\text{—Pen}^n} + \underset{40\%}{\text{Dec}^n\text{—Pen}^n}$$

Cross-coupling of alkyl chlorides with alkyl Grignard reagents was found to be catalyzed by Cu in refluxing THF more efficiently by use of 1-phenylpropyne rather than 1,3-butadiene (equation 17).[157] Under the same conditions, sterically hindered secondary and tertiary alkyl Grignard reagents as well as aryl Grignard reagents afforded the corresponding coupling products in excellent yields.[157]

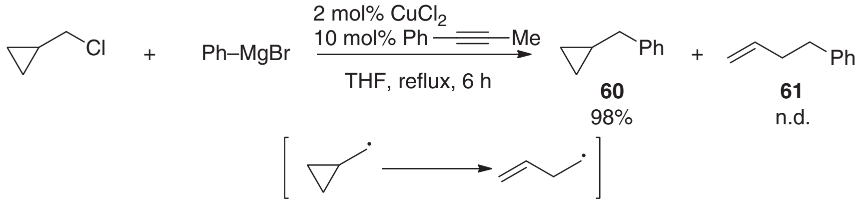


Scheme 25

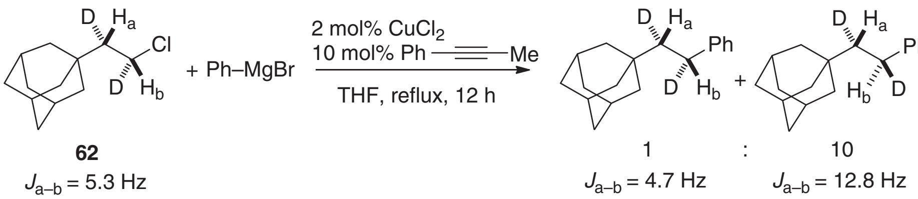
$$\mathrm{Non^n{-}Cl} + \mathrm{Bu^n{-}MgCl} \xrightarrow[\text{THF, reflux, 6 h}]{\text{2 mol\% CuCl}_2,\ \text{10 mol\% additive}} \mathrm{Non^n{-}Bu^n} + \text{nonane} + \text{nonenes} \tag{17}$$

Additive	Non^n—Bu^n	Nonane	Nonenes
none	3%	2%	0%
	4%	10%	2%
	16%	26%	4%
Ph—≡—Me	>98%	<1%	0%

When the cyclopropylmethylchloride was subjected to these reaction conditions, benzylcyclopropane (**60**) was obtained as the sole coupling product without the formation of 4-phenyl-1-butene (**61**) (equation 18), which can arise from ring opening of the cyclopropylmethyl radical.[158] Further mechanistic studies of the stereochemistry of this reaction using deuterated substrate **62** revealed that primary alkyl chlorides undergo substitution with inversion of the stereochemistry at the reacting carbon. These results are consistent with an S_N2 mechanism (equation 19).



(18)

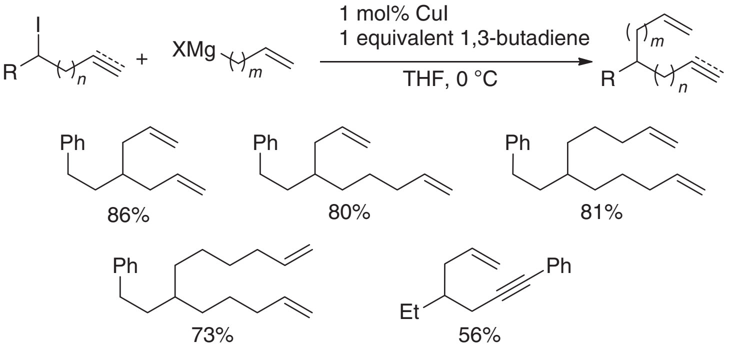


62
J_{a-b} = 5.3 Hz

J_{a-b} = 4.7 Hz J_{a-b} = 12.8 Hz

(19)

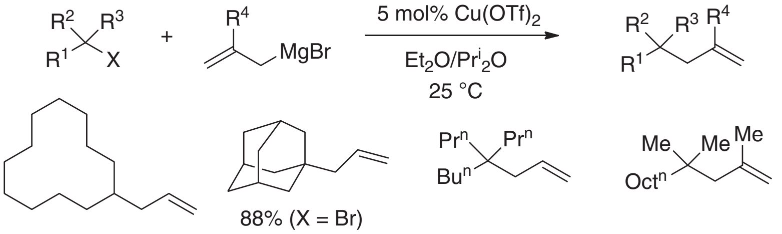
The Cu/butadiene catalytic system can be successfully applied to the coupling of unactivated secondary alkyl iodides.[159] This reaction proceeds via nonradical mechanism and was applied to the synthesis of various nonconjugated dienes and enynes (Scheme 26).



Scheme 26

3.07.4.1.1.2 Reaction with allylic Grignard reagents

Allylic Grignard reagents are highly reactive and can be coupled with sterically hindered secondary and tertiary alkyl halides and sulfonates in the presence of a Cu catalyst under mild conditions as shown in Scheme 27.[160]



89% (X = Br)

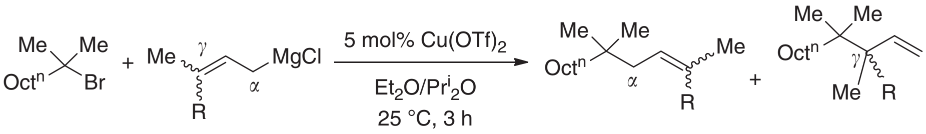
88% (X = Br)
69% (X = Cl, reflux)
78% (X = I)

49% (X = Br)

92% (X = Br)

Scheme 27

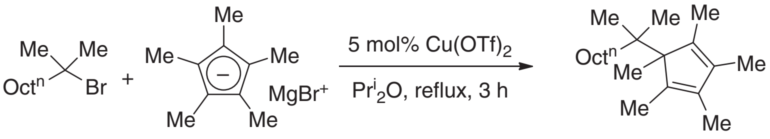
A drawback of this reaction is poor regioselectivity. As shown in Scheme 27, symmetric allylic Grignard reagents afford terminal olefins in good yields; however, mixtures of regioisomers were obtained when allyl Grignard reagents having a γ-substituent(s) are employed (equation 20). Mechanistic studies of this reaction imply that the actual copper species is likely diallylcuprate(I).



(20)

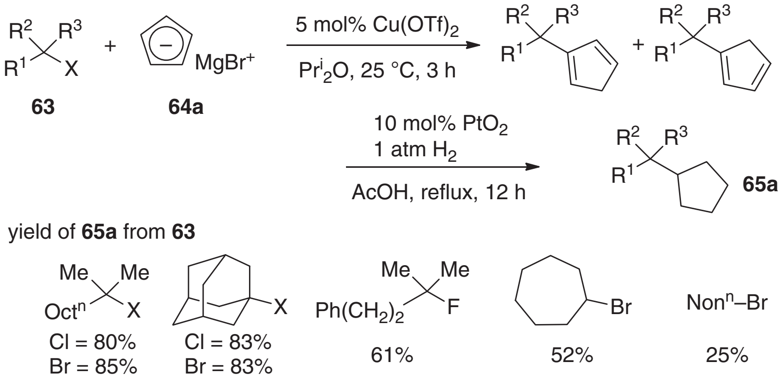
58%, α:γ = 65:35 (R = H)
53%, α:γ = 72:28 (R = Me)

Cyclopentadienylmagnesium bromide (**64a**), a family of allylic Grignard reagents, also reacted with alkyl halides **63** to give a mixture of alkylated cyclopentadienes, which on subsequent reduction afforded cyclopentanes **65a**.[161] Various tertiary alkyl halides including fluorides provided **65a** in good yields (Scheme 28). A similar reaction of pentamethylcyclopentadienyl magnesium reagent **64b** yielded the corresponding coupling product **65b** bearing consecutive quaternary carbon centers in 41% yield (equation 21).



63 **64b** **65b** 41%

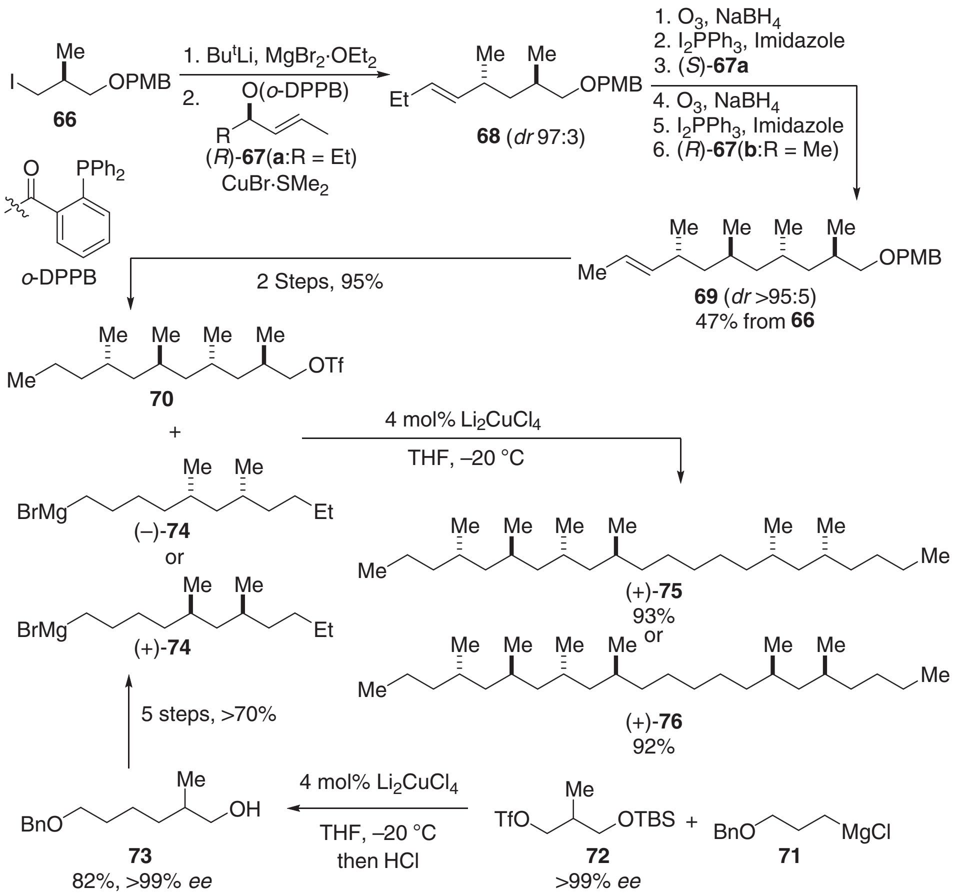
(21)



Scheme 28

3.07.4.1.1.3 Synthetic application

Cu-catalyzed sp^3–sp^3 coupling reaction has been employed for enantioselective total synthesis and determination of the absolute configuration of the 4,6,8,10,16,18-hexamethyldocosane, which was isolated from cane beetle *Antitrogus parvulus* as its sex pheromone. The strategy for the synthesis of two regioisomers of 4,6,8,10,16,18-hexamethyldocosane **75** and **76** includes stereoselective allylic substitution to form methyl-substituted tertiary carbon centers in **70** and **74** and sp^3–sp^3 cross-coupling to construct carbon frameworks of **73**, **75**, and **76** as shown in Scheme 29.[162,163]



Scheme 29

3.07.4.1.2 Using other organometallic reagents

Cu-catalyzed alkyl–alkyl cross-coupling using other organometallic reagents is rarely discussed relative to Grignard reagents probably due to their poor nucleophilicity toward Cu center to form catalytic active cuprates. Alkyl lithium reagents are powerful carbon nucleophiles and often used in preparing alkyl cuprates. However, only limited examples have been reported for catalytic reactions using alkyllithiums as a coupling partner.[152] This section summarizes examples of cross-coupling reaction using less reactive organometallic reagents.

3.07.4.1.2.1 Reaction with organomanganese reagents

Organomanganese derivatives, which are readily prepared from $MnCl_2$ and the corresponding organolithium or -magnesium reagents, are known to be mild nucleophilic reagents.[164] Cahiez et al. utilized the alkylmanganese reagents for the Cu-catalyzed alkyl–alkyl coupling reaction and found that reaction of bromides, iodides, and sulfonates gave excellent to good yields of products, although chlorides were found to be sluggish (Scheme 30).[165]

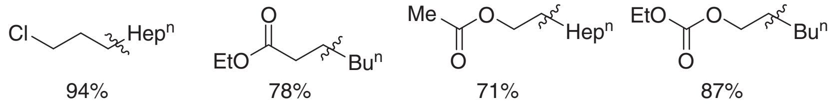
$$CH_3(CH_2)_{11}\text{–}X \quad + \quad Bu^n\text{–}MnCl \xrightarrow[\text{THF/NMP, r.t.,1 h}]{\text{3 mol\% }Li_2CuCl_4} CH_3(CH_2)_{11}\text{—}Bu^n$$

X	Yield (%)
Cl	7
Br	91
I	90
OSO_2Ph	76

Scheme 30

As can be expected, various functional groups remain intact during the reaction (Scheme 31).

$$\text{Alkyl–Br} \quad + \quad \text{Alkyl′–MnCl} \xrightarrow[\text{THF/NMP, r.t., 1 h}]{\text{3 mol\% }Li_2CuCl_4} \text{Alkyl—Alkyl′}$$



Scheme 31

Both RMnCl and RMgCl coupled with alkyl bromides efficiently when primary alkyl metals were employed; however, the former afforded better yields when secondary alkylmetals were used under similar conditions (Scheme 32).

$$\text{Hex}^n\text{–Br} \quad + \quad \text{Bu}^n\text{–m} \xrightarrow{\text{3 mol\% }Li_2CuCl_4} \text{Hex}^n\text{—Bu}^n$$

m	Conditions	Yield (%)
MgCl	THF, 0 °C, 3 h	78
MnCl	THF/NMP, 20 °C, 1 h	90

$$\text{Oct}^n\text{–Br} \quad + \quad \text{Pr}^i\text{–m} \xrightarrow{\text{3 mol\% }Li_2CuCl_4} \text{Oct}^n\text{—Pr}^i$$

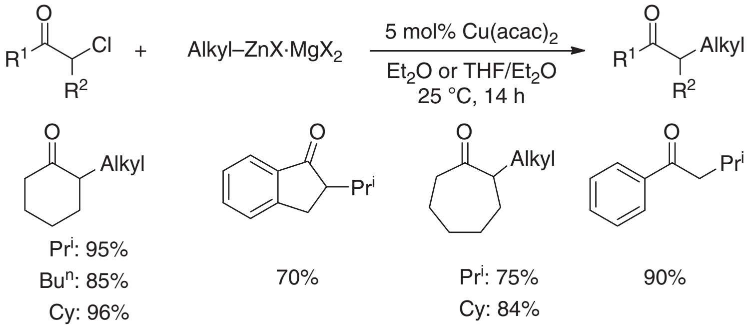
m	Conditions	Yield (%)
MgCl	THF, 20 °C, 16 h	24
MnCl	THF/NMP, 20 °C, 1 h	85

Scheme 32

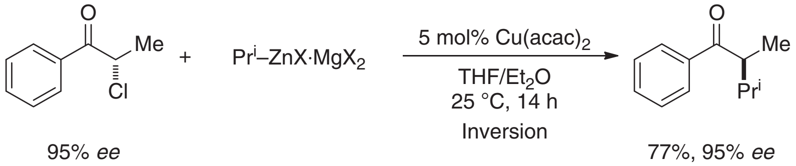
3.07.4.1.2.2 Reaction with organozinc reagents

Cu catalyzes cross-coupling reaction of alkylzinc reagents with activated alkyl chlorides bearing a keto group at the α-position. Under mild conditions, various cyclic and acyclic α-chloroketones coupled with primary and secondary alkylzinc halides

(Scheme 33).[166] Although this transformation can possibly be explained by reaction of enolates with alkyl chlorides generated *in situ* by Zn–Cl exchange, this was not the case. The present Cu-catalyzed cross-coupling was not affected by overalkylation and enabled introduction of secondary alkyl groups with inversion of stereochemistry as shown in equation 22.



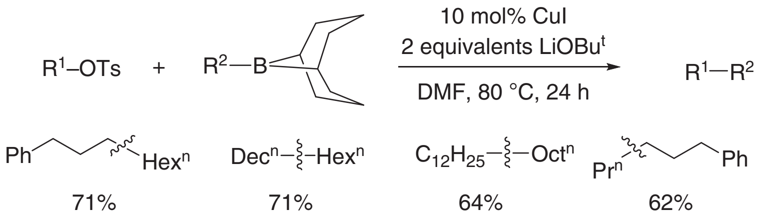
Scheme 33



(22)

3.07.4.1.2.3 Reaction with organoborane reagents

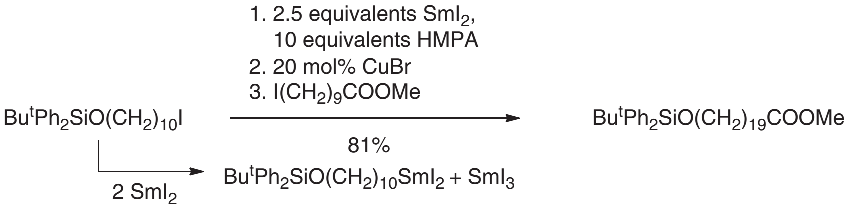
Alkylboranes can be employed as promising coupling partners in Pd- or Ni-catalyzed cross-coupling reaction; however, utilization of alkylboranes for the Cu-catalyzed alkyl–alkyl coupling is still limited. Liu et al. demonstrated the cross-coupling of alkyl tosylates with alkyl-9-borabicyclo[3.3.1]nonanes (9-BBNs) in the presence of 10 mol% of CuI and 2 equivalents of LiO^{t}Bu, although the yields were moderate (Scheme 34).[167]



Scheme 34

3.07.4.1.2.4 Reaction with organosamarium reagents

Cross-coupling of alkylsamarium(III), prepared by reaction of 2 equivalents of freshly prepared SmI_2 or $Sm(OTf)_2$ with alkyl halides, with alkyl iodides is also possible in the presence of catalytic amounts of CuBr. This reaction was successfully applied to the alkyl iodide having a methyl ester group, whereas the reaction of alkyl bromides, benzyl bromide, and secondary alkyl iodides gave moderate yields (equation 23).[168]



(23)

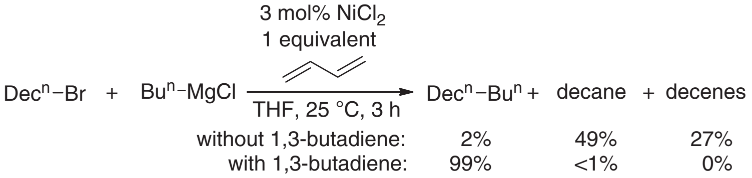
3.07.4.2 Nickel Catalysts

Development of Kumada–Tamao–Corriu cross-coupling between sp^2-carbon centers was one of the most important scientific milestones in the history of cross-coupling, and nickel was originally employed as the catalyst.[169,170] Thereafter, Murahashi reported a Pd variant of the reaction[171] and various types of cross-coupling reactions were developed using Pd catalysts due to the wide adaptability of Pd in comparison to Ni. However, since the pioneering work on cross-coupling between sp^3-carbon centers using Ni catalysts by Knochel in the late 1990s,[172–174] Ni has again attracted attention as a promising cross-coupling catalyst,[175–177] and a new era of asymmetric cross-coupling reactions was opened using Ni catalysts employing secondary alkyl electrophiles.[178] This section deals with Ni-catalyzed C(sp^3)–C(sp^3) coupling reaction using various organometallic reagents and its application to asymmetric synthesis.

3.07.4.2.1 Using Grignard reagents

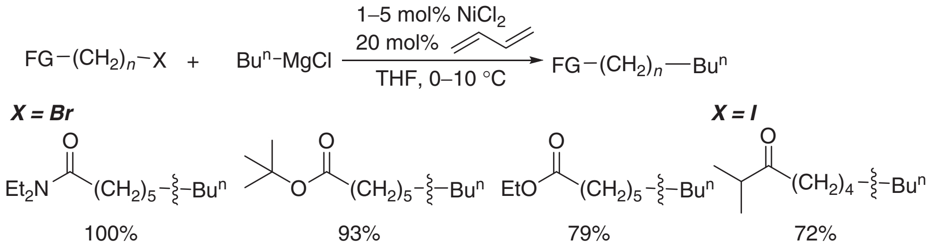
3.07.4.2.1.1 π-Carbon ligands

Ni-catalyzed cross-coupling reactions of simple alkyl chlorides, bromides, or tosylates with alkyl Grignard reagents were reported by Kambe et al., where 1,3-butadiene showed significant additive effects regarding high yield and selectivity.[179] For example, in the absence of 1,3-butadiene, the reaction of ^{n}DecBr with ^{n}BuMgCl provides only 2% of coupling product accompanied by decane in 49% yield and decenes in 27% yield; however, the addition of 1,3-butadiene to the reaction suppressed unwanted side reactions and yielded the coupling product, tetradecane, as a sole product (equation 24).[180]

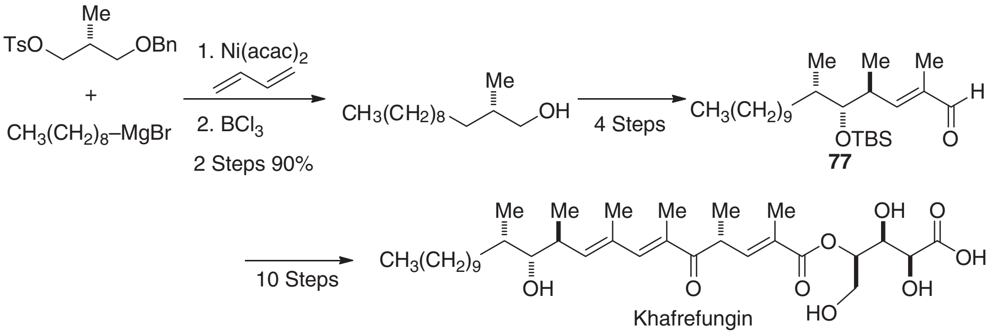


(24)

The present Ni–butadiene system successfully catalyzed cross-coupling reaction of alkyl halides carrying a functional group such as ketone, ester, and amide groups demonstrating the synthetic usefulness of this coupling reaction (Scheme 35).[181] As a synthetic application, this coupling reaction was employed for the construction of the C7–C22 fragment of the antifungal agent, khafrefungin 77 (Scheme 36).[182]

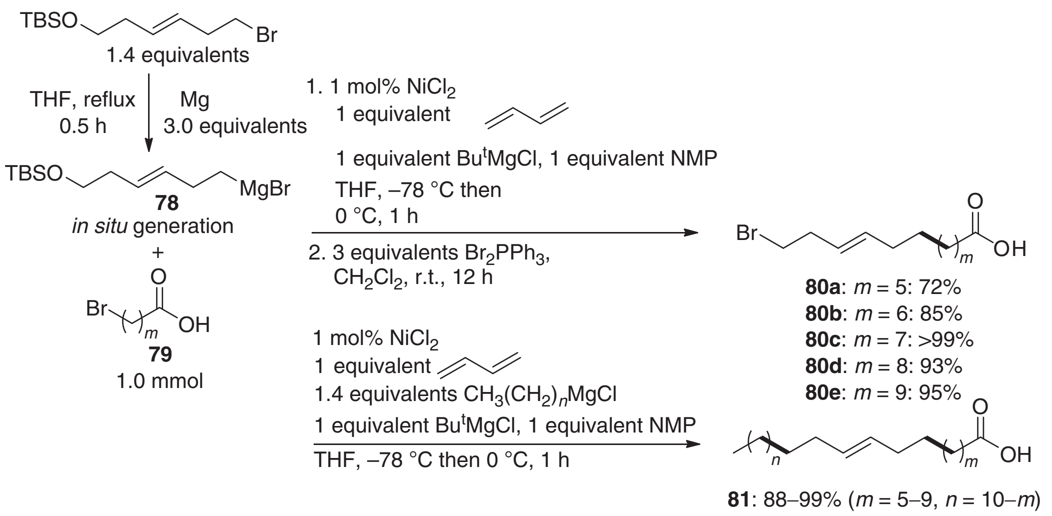


Scheme 35



Scheme 36

Another application of the Ni–butadiene system to cross-coupling was demonstrated by synthesizing bioactive unsaturated fatty acid and its regioisomers as shown in Scheme 37.[183] As a simple method for the protection of the carboxylic acid moiety, **79** was treated with ^{t}BuMgCl to convert into magnesium carboxylate. The subsequent cross-coupling by Ni–butadiene catalytic system

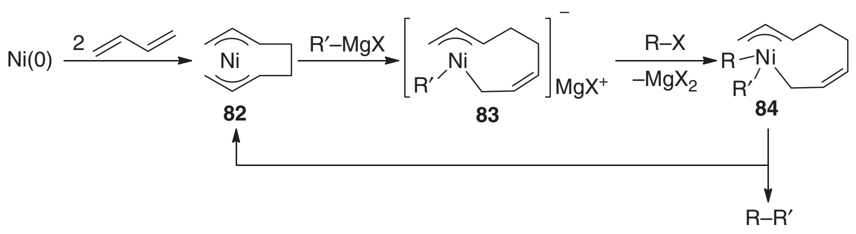


Scheme 37

afforded various fatty acids **80** in a one-pot operation. Iterative cross-coupling of **80** by this one-pot procedure provided elaidic acid **81** having a *trans*-olefin moiety at the ω-9 position and its regioisomers in excellent yields (Scheme 37).

Cross-coupling can be run using perovskite ($LaFe_{0.8}Ni_{0.2}O_3$ (LFNO)) as a reusable catalyst source for the Ni–butadiene system without significant loss of its catalytic activity. Control experiments suggested that the reaction is catalyzed by trace amounts of Ni in solution leached from LFNO with a quite high TON of Ni up to approximately 10^7.[184]

The reaction mechanism for this Ni–butadiene catalytic system is depicted in Scheme 38. Bis(π-allyl)nickel complex **82** delivered from Ni(0) and two butadiene reacts with Grignard reagents to form the ate complex **83** by shifting the coordination mode of one of two ally ligands from η^3 to η^1 to retain d^{16} electron state at the Ni center. RX reacts with **83** at the anionic Ni center to form Ni(IV) intermediate **84**, which readily undergoes reductive elimination to give coupling product with concomitant regeneration of bis(π-allyl)nickel complex **82** (Scheme 38). Theoretical calculations supported this pathway.[185,186]

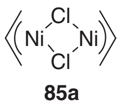
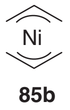


Scheme 38

This proposed mechanism was also supported by the evidence that the cross-coupling of ⁿDecBr with ⁿBuMgCl proceeded successfully with the Ni complex having two π-allyl ligands, bis(π-allyl)nickel complex **85b**, whereas $NiCl_2$ and monoallylnickel complex **85a** failed to catalyze this reaction (Table 2).[187]

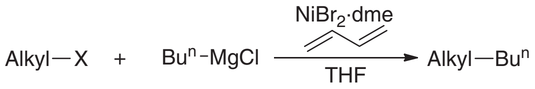
Table 2 An effect of π-allyl ligand on Ni-catalyzed cross-coupling

$$\mathrm{Dec^n{-}Br} + \mathrm{Bu^n{-}MgCl} \xrightarrow[\text{THF, –30 °C}]{\text{Ni cat.}} \mathrm{Dec^n{-}Bu^n} + \text{decane} + \text{decenes}$$

Ni cat.			*Decⁿ–Buⁿ*	*Decane*	*Decenes*
 **85a**	 **85b**	$NiCl_2$	5%	33%	18%
		$[(C_3H_5)NiCl]_2$ **85a**	7%	33%	24%
		$(C_3H_5)_2Ni$ **85b**	94%	4%	2%

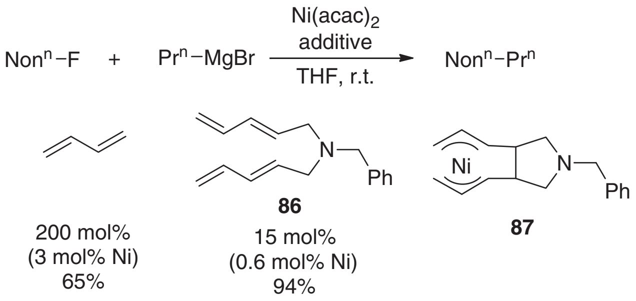
Kinetic studies of this Ni–butadiene catalytic system suggested that the rate-determining step is the reaction of ate complex **83** with RX (Scheme 38, **83** and **84**) for alkyl bromides, tosylates, and iodides. This was also supported by DFT calculations.[186] The relative reactivities of primary alkyl iodides, bromides, and tosylates toward ^{n}BuMgCl were estimated to be 1000:50:1 at 0 °C with activation free energy $\Delta G^{\ddagger}$ of 55.3 ± 6.0, 61.9 ± 8.6, and 71.1 ± 9.8 kJ mol^{-1}, respectively (Table 3).[188]

Table 3 Activation free energies and activation parameters of Ni-catalyzed cross-coupling



Alkyl-X	$\Delta G^{\ddagger}_{273}$ *(kJ mol^{-1})*	$\Delta H^{\ddagger}$ *(kJ mol^{-1})*	$\Delta S^{\ddagger}$ *(JK^{-1} mol^{-1})*
Hep^n-OTs	71.1 ± 9.8	52.7 ± 4.9	-67.6 ± 18.0
Non^n-Br	61.9 ± 8.6	57.3 ± 4.0	-16.9 ± 16.7
Hex^n-I	55.3 ± 6.0	51.2 ± 2.6	-14.8 ± 12.3

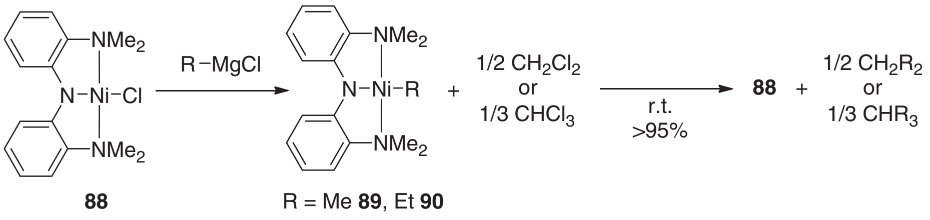
The cleavage of C(sp^3)–F bonds and subsequent functionalization is a challenging theme in organic syntheses. This Ni–butadiene system can catalyze the coupling reaction of unactivated alkyl fluorides though yields were moderate even in the presence of a large excess of butadiene.[156] The yield was dramatically improved when a 1,3,8,10-tetraene such as **86** was used in place of 1,3-butadiene, which readily forms the bis(π-allyl)nickel complex **87** by the reaction with Ni(0) (equation 25).[189]



(25)

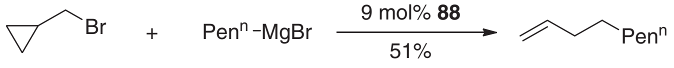
3.07.4.2.1.2 Amine ligands

Nitrogen-based pincer ligands retard β-hydrogen elimination of alkylnickel intermediates as suggested by DFT calculation that this process is thermodynamically disfavored.[190] Hu et al. demonstrated that the nickel complexes having Me (**89**) or Et (**90**) group on the Ni center, prepared by the reaction of the corresponding Cl complex **88** with alkyl Grignard reagents, readily reacted with CH_2Cl_2 or $CHCl_3$ to give double or triple alkylation products, respectively, along with the regeneration of **88** (equation 26).[191] This procedure can be applied to the cross-coupling of alkyl iodides and bromides, as well as *gem*-di- and trichlorides with alkyl Grignard reagents at the reaction rates following the order of RI > RBr > RCl and benzyl > octyl > cyclohexyl.



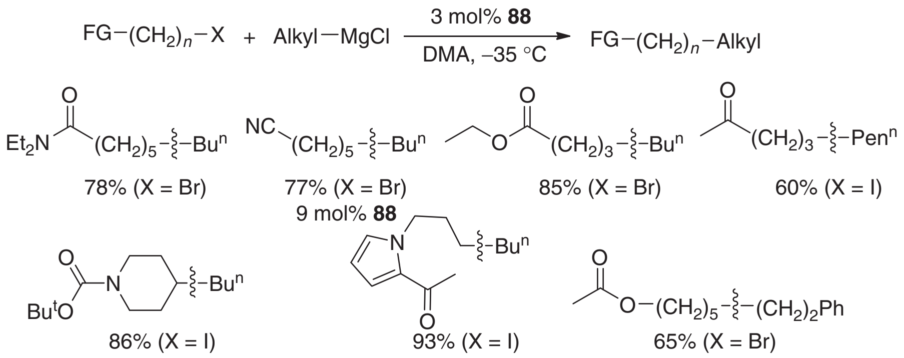
(26)

When cyclopropylmethyl bromide was used as a coupling partner, ring opening of cyclopropane ring was observed (equation 27), suggesting the involvement of an alkyl radical intermediate.[192]



(27)

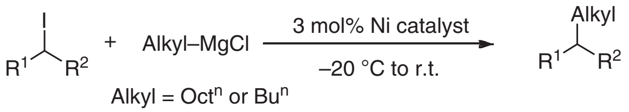
Grignard reagents are known to tolerate a wide range of functionalities at low temperatures (less than −35 °C)[193,194] and the catalyst **88** shows high reactivity under such conditions. Thus, alkyl iodides and bromides bearing various functional groups including ester, amide, nitrile, and ketone can be coupled with alkyl Grignard reagents in the presence of **88** (Scheme 39).[195]

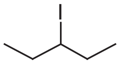
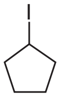
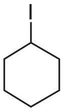
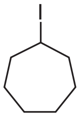
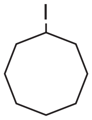


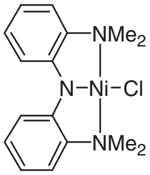
Scheme 39

The Ni catalyst **88** was not very effective for the cross-coupling of congested nonactivated secondary alkyl halides. This problem has been solved by the combined use of a monoanionic bidentate *o*-phenylenediamine and a pyridine derivative as the ligands **93–95**, which enabled the use of acyclic and cyclic secondary alkyl iodides and bromides (Table 4).[196]

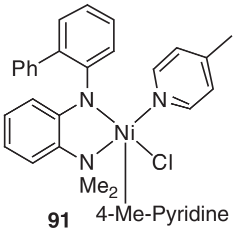
Table 4 Ni complexes-catalyzed cross-coupling of secondary alkyl iodides



	Yield of coupling product (%)					
Cat.						
88	8	Trace	38	46	Trace	0
91	43	3	47	57	13	7
92	58	50	43	61	65	52
93	69	53	69	84	87	82
94	75	38	68	77	81	61
95	68	31	69	80	65	54



88



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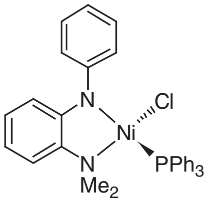

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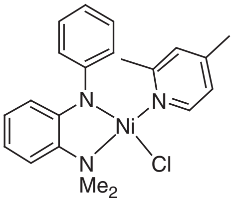

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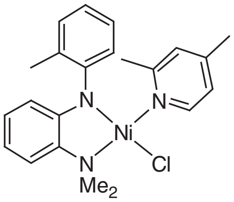

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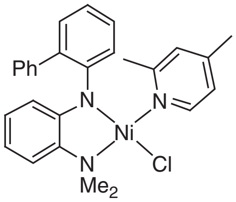
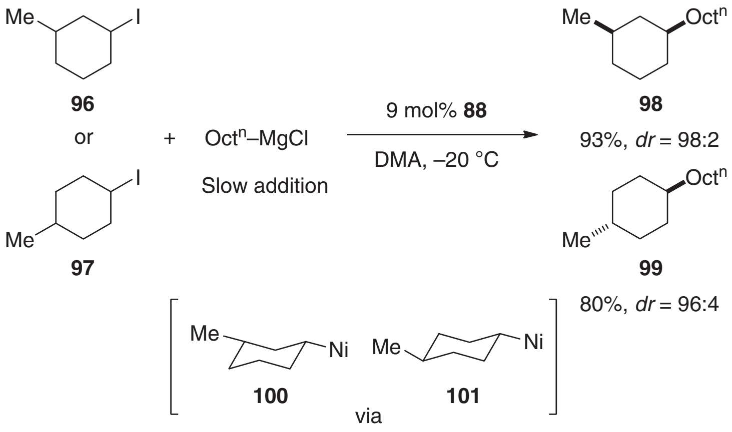


95

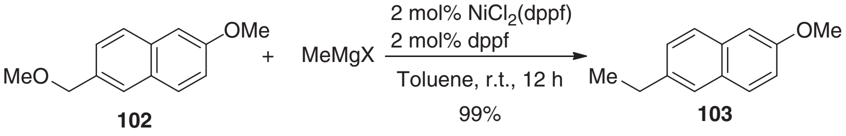
When 3- or 4-substituted cyclohexyl halides **96** and **97** were subjected to the Ni catalyst **88**, high diastereoselectivities were observed (Scheme 40).[197] This can be explained by the formation of intermediacies **100** and **101** by a radical mechanism, which prefers the more stable diequatorial conformation.



Scheme 40

3.07.4.2.1.3 Phosphine Ligands

Benzylic ethers can be employed as suitable electrophiles for Kumada–Tamao–Corriu type cross-coupling reactions in the presence of bidentate phosphine ligands. Site-selective coupling at sp^3-carbons over sp^2-carbons was achieved. For example, ether **102** selectively underwent cross-coupling at the benzylic carbon rather than at the aromatic carbon in 99% yield (equation 28).[198] When the secondary benzylic ether **104** was used as an electrophile, complete stereo inversion at the α-carbon was observed to give **105** in 94% *ee* (equation 29).[199] Introduction of a methoxyethoxy group as the leaving group facilitated the Ni-catalyzed coupling reaction of Grignard reagents with benzylic ethers, where oxygen atoms played an important role as a directing group by coordinating to the magnesium cation (Scheme 41).[200]



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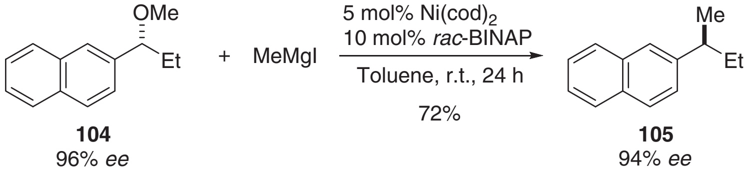
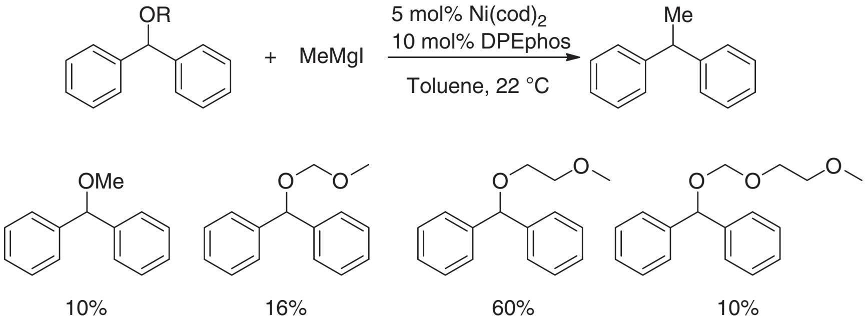


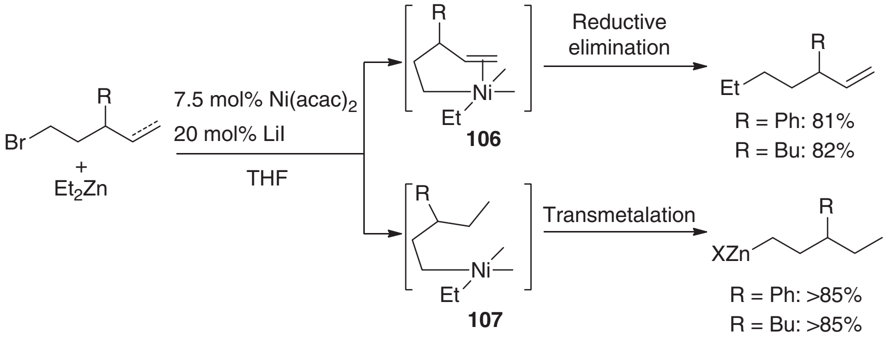
(29)



Scheme 41

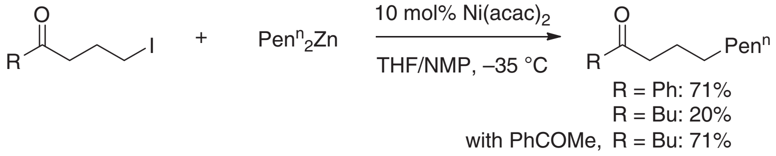
3.07.4.2.2 Using alkylzinc reagents

An important feature of organozinc reagents is their high functional group tolerance which is essential for practical applications in the synthesis of desired organic compounds.[201] In 1995, Knochel et al. found that when 5-bromo-1-pentene and 1-bromopentane derivatives were treated with Et_2Zn in the presence of a catalytic amount of $Ni(acac)_2$ and LiI in THF, cross-coupling products were obtained from the former and transmetalated products were formed from the latter (**Scheme 42**).[172] Intramolecular coordination of an olefinic moiety at an appropriate position depicted as **106** might exert a significant effect to promote cross-coupling by facilitating reductive elimination.



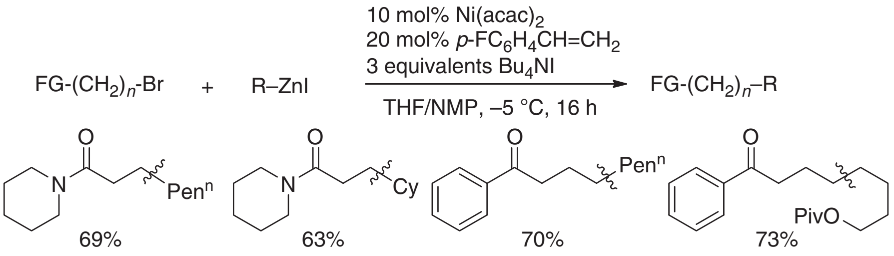
Scheme 42

Interesting additive effect of electron-deficient unsaturated organic molecule was also observed for the nickel-catalyzed cross-coupling of alkyl iodides with dialkylzinc.[173,174] When the reaction of phenylpropyl iodide with dipentylzinc was conducted in the presence of $Ni(acac)_2$ as a catalyst, the reaction was sluggish (25 °C, 40 h) and provided only a 34% yield of the coupling product. The addition of electron-deficient olefin, ethyl crotonate, enhanced the yield to 64% even after 24 h at −25 °C. Another interesting additive effect was demonstrated by an electron-deficient carbonyl group as shown in equation 30. The cross-coupling reaction of alkyl iodide having a phenyl ketone group proceeded smoothly even at −35 °C. However, similar alkyl halides carrying a more electron-rich alkyl ketone group gave only a 20% yield of coupling product and a significant amount (57%) of the corresponding organozinc iodide was formed by iodine–zinc exchange reaction. When acetophenone was added as an external ligand, the yield of the coupling product was again improved to 71% and no iodine–zinc exchange was observed. Fluoro- and trifluoromethylstyrenes also worked as external ligands. These results suggest that electron-deficient olefin or ketone groups, either at an appropriate position in the molecule or added externally, accelerate the reductive elimination of dialkylnickel intermediates by coordination to nickel.[174,202]



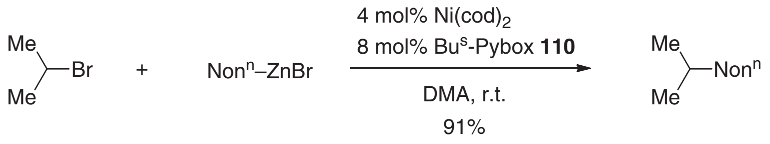
(30)

These reactions required dialkylzinc reagents and failed when alkylzinc halides were used. The addition of Bu_4NI to the catalytic system using 10 mol% of $Ni(acac)_2$ and 20 mol% of *p*-fluorostyrene enables cross-coupling of primary alkyl bromides or iodides with various functionalized alkylzinc halides including benzyl and secondary alkylzinc iodides (**Scheme 43**).[203,204]



Scheme 43

Nitrogen-based tridentate ligands, pyboxs (**110**), are suitable ligands for the Ni-catalyzed $C(sp^3)$–$C(sp^3)$ coupling, enabling the reaction of less reactive secondary alkyl bromides and iodides with primary alkylzinc bromides (equation 31).[205] This protocol using *N–N–N* ligands also catalyzed cross-coupling between secondary alkyl carbons (equation 32).[206] For example, the coupling of a cyclohexylzinc reagent with the secondary propargyl bromide **108** efficiently proceeded when terpyridine (**111**) was used as a ligand at ambient temperature. Although more sterically hindered cycloheptylzinc was sluggish under the same conditions using **111** (20% yield), the desired product was formed in a good yield using the more compact ligand **112** in THF.[206]



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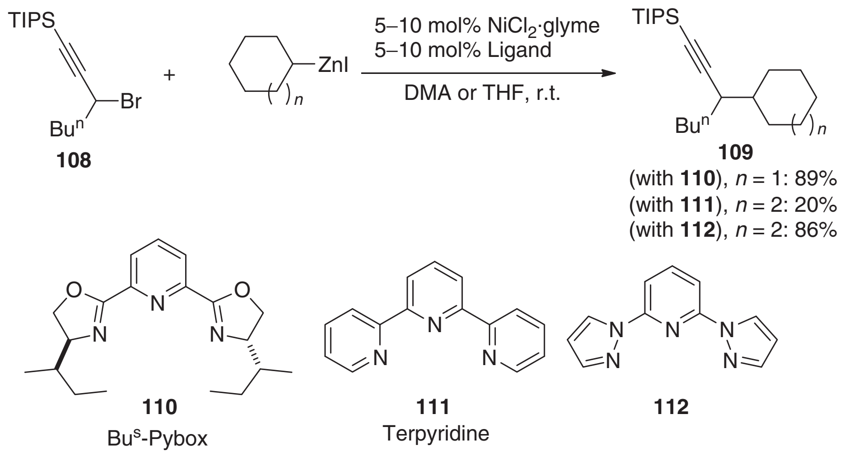
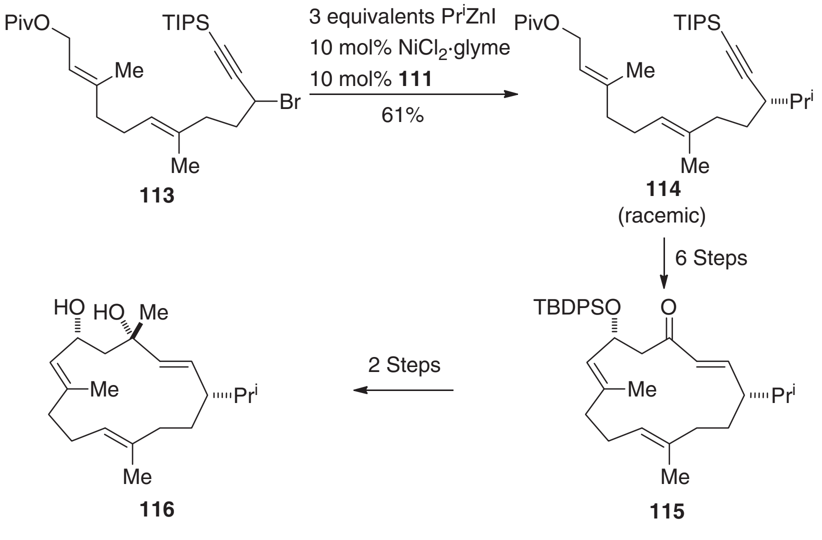


(32)

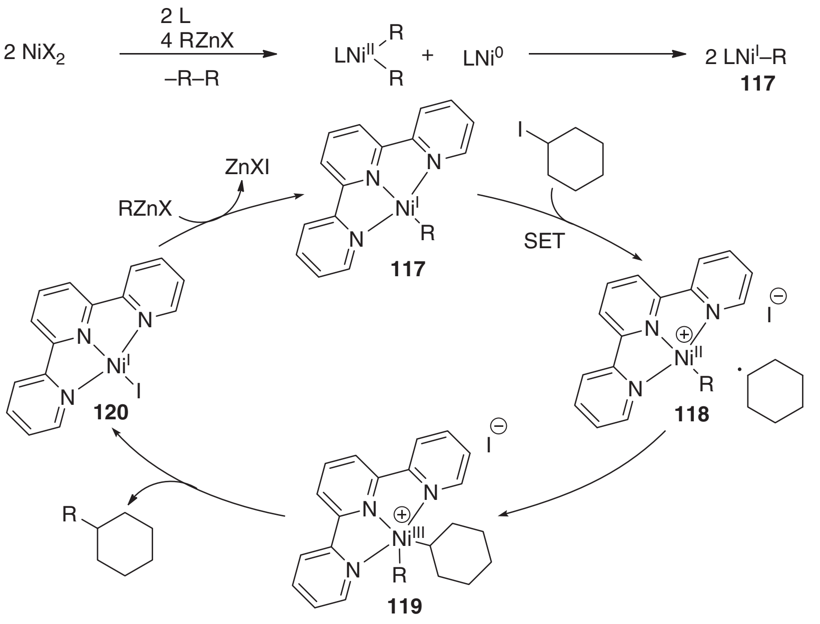
This secondary–secondary coupling protocol using terpyridine was successfully applied to the formal total synthesis of an antitumor-active cembranoid diterpene, (±)-α-cembra-2,7,11-triene-4,6-diol (**116**) (Scheme 44).[206]



Scheme 44

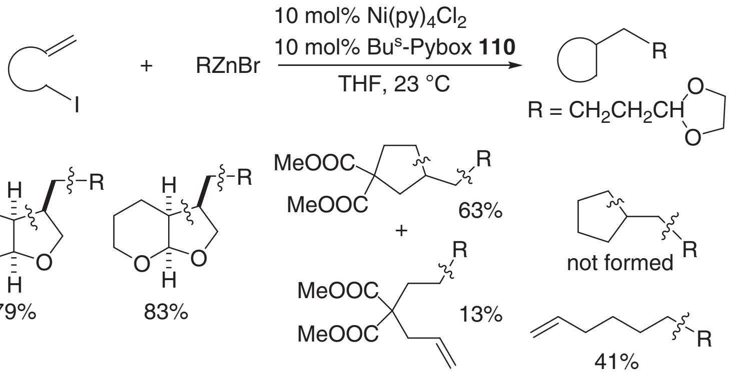
Mechanistic studies along with theoretical calculations of the cross-coupling reaction using terpyridines suggested that an Ni (I)–Ni(III) catalytic cycle is involved as shown in Scheme 45.[207–210] Active Ni(I) species **117** are formed from dialkyl Ni(II) and Ni (0) being generated via transmetalation of Ni salts with alkylzinc reagents followed by reductive elimination. The catalytic cycle is triggered by single-electron transfer (SET) from **117** to alkyl iodides and subsequent recombination forms dialkyl Ni(III) **119**, which undergoes reductive elimination to yield cross-coupling products with regeneration of alkyl Ni(I) **117** via **120**. A computational study suggested that this Ni(I)–Ni(III) pathway is more feasible than the conventional Ni(0)–Ni(II) pathway.[210]

As carbon–halogen bond cleavage induced by SET is involved in the catalytic cycle as shown in Scheme 45, a radical cyclization or ring-opening process can possibly be incorporated into this cross-coupling.[211] Selectivities between direct cross-coupling and



Scheme 45

cascade reaction varied depending on the rates of competing radical cyclization or ring opening, suggesting that the rate of cross-coupling is comparable to intramolecular cyclization and falls within the range of 0.9×10^7–6.7×10^7 s^{-1} (Scheme 46).



Scheme 46

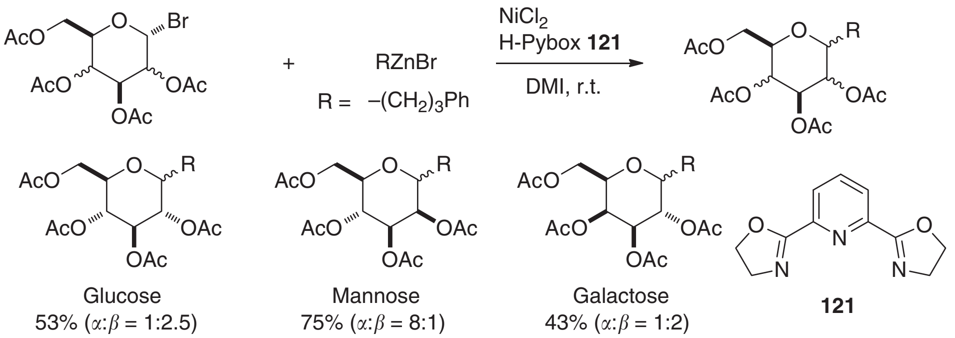
A nitrogen-based pincer ligand **121** was successfully applied to Negishi cross-coupling of α-halo sugars catalyzed by Ni to form C-alkyl glycosides, which are an important class of bioactive compounds. The difficulties of utilizing sugars in metal-catalyzed cross-coupling reactions arise from β-O elimination from C1–metal intermediates and poor diastereoselectivities; however, the former problem could be overcome by employing pincer-ligated Ni catalyst. As shown in Scheme 47, aceto-α-1-bromo-sugars when coupled with alkylzinc halides resulted in good yields but poor diastereoselectivities in the case of glucose and galactose derivatives. In contrast, when α-halomannose derivatives were subjected to the reaction, the α-anomer became major products (Scheme 47).[212,213]

1,3-Butadiene ligand system is also useful for Negishi coupling of alkyl halides though a long reaction time is required. The addition of catalytic amount of 1,3,8,10-tetraene **122** instead of butadiene significantly improved catalytic activity and reaction was completed within 1 h (Scheme 48).[189]

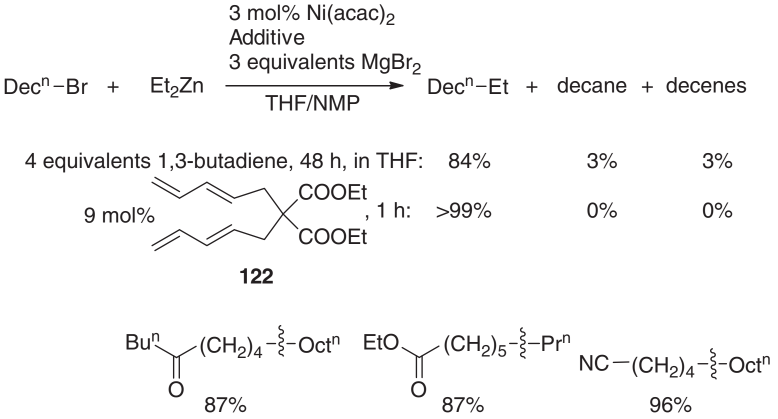
3.07.4.2.3 Using alkylborane reagents

Diamine ligands are also effective for Suzuki–Miyaura alkyl–alkyl coupling. As shown in Scheme 49, the coupling reaction of bromocyclohexanes with alkyl-9-BBNs is efficiently catalyzed by Ni salt in the presence of *N*,*N*′-dimethyl-1,2-cyclohexanediamine (**123**), KO^tBu, and ^iBuOH in dioxane.[214]

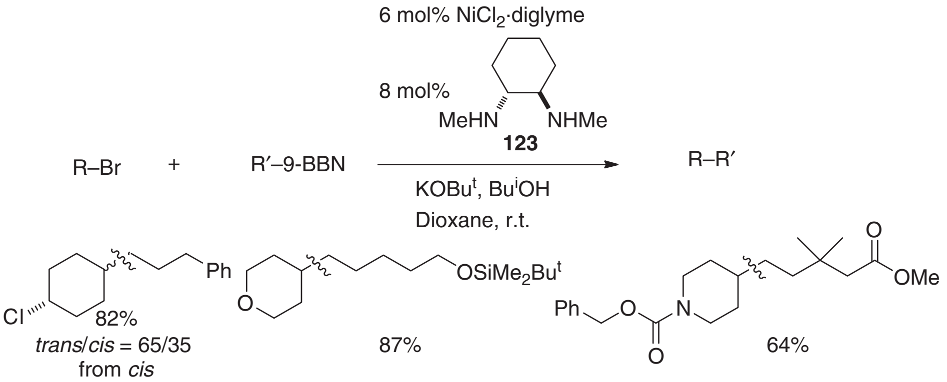
Under optimized conditions using diamine **124** as a ligand, cyclohexyl iodide and bromide undergo cross-coupling at comparable rates, and the corresponding chloride reacts relatively slowly with approximately fourfold half-life time when conducted



Scheme 47



Scheme 48

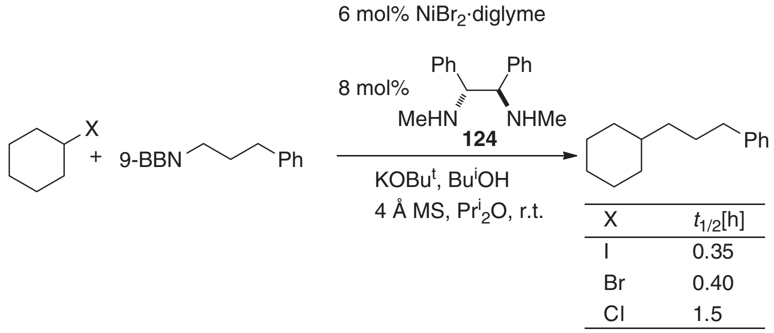


Scheme 49

separately (Scheme 50). However, competitive experiments revealed that cyclohexyl iodide reacts more than 15 times faster than the corresponding bromide and the bromide reacts more than 15 times faster than the chloride (Scheme 51). These results suggest that oxidative addition is not the rate-determining step of the catalytic cycle in the case of cyclohexyl iodide and bromide.[215]

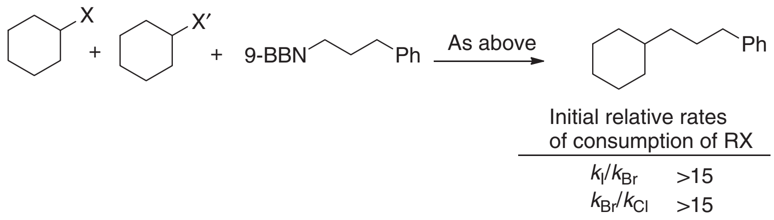
3.07.4.2.4 Asymmetric cross-coupling

Successful cross-coupling of secondary alkyl halides achieved by Ni catalysts as described in Section 3.07.4.2 [216] brought about a possibility of asymmetric cross-coupling leading to the construction of chiral carbon frameworks.[176] The first report of enantioselective alkyl–alkyl cross-coupling was the reaction of racemic α-bromoamides with alkylzinc halides catalyzed by Ni employing a chiral Pybox ligand **125**.[217] Substituents on the amide moiety, but not the substituent at the α-position, affected both the enantioselectivity and yield of products (Scheme 52). This catalyst system selectively promoted cross-coupling at the



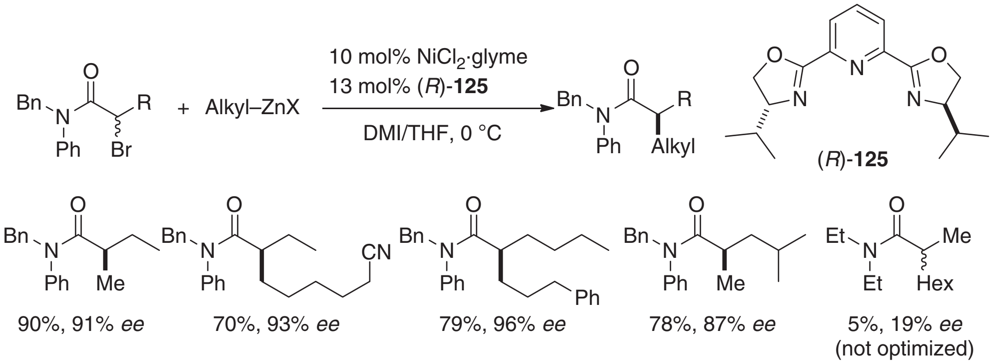
X	$t_{1/2}$[h]
I	0.35
Br	0.40
Cl	1.5

Scheme 50



Initial relative rates of consumption of RX	
k_I/k_{Br}	>15
k_{Br}/k_{Cl}	>15

Scheme 51



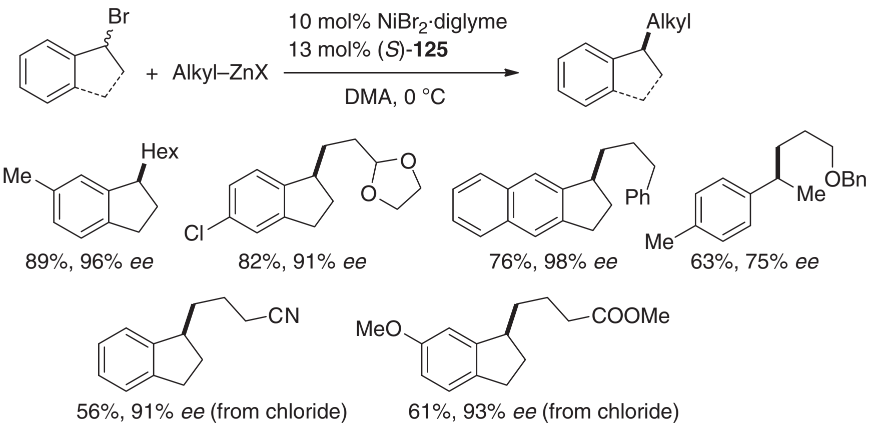
Scheme 52

α-bromoamide moieties without affecting unactivated primary or secondary alkyl bromide groups. The amide could be converted into the corresponding alcohol by $LiAlH_4$ without loss of *ee*. When an excess amount of racemic amide was used, racemic starting material was recovered, suggesting that no kinetic resolution occurred. This could be explained by a catalytic cycle shown in Scheme 45 of Section 3.07.4.2.2, where recombination of alkyl radical from alkyl halides with chiral Ni complexes may proceed stereoselectively.

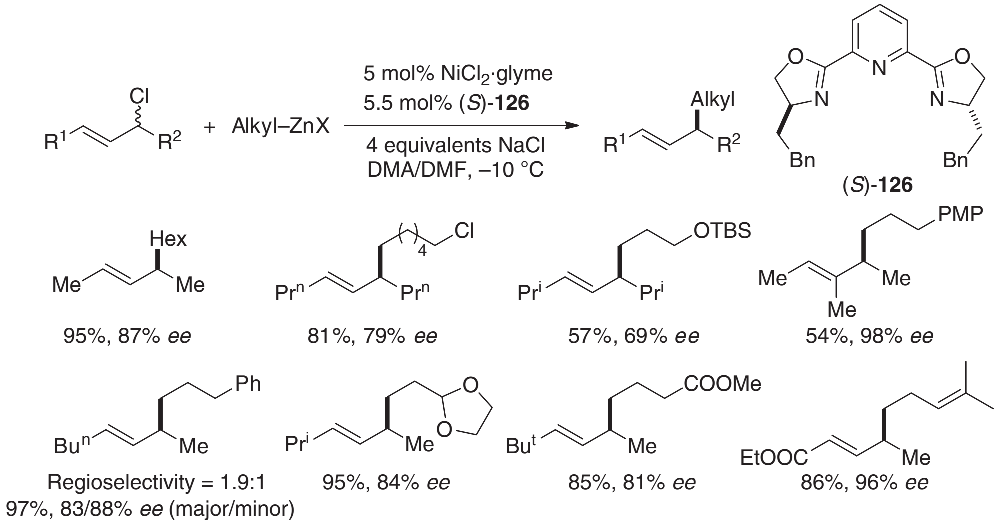
Activated benzylic and allylic secondary alkyl chlorides and bromides are also suitable substrates for the enantioselective Negishi coupling. For example, bromoindanes coupled with alkylzinc reagents in the presence of an Ni salt and chiral Pybox ligand **125** resulted in a high enantiomeric excess in the range of 91–99% though enantioselectivity decreased in the case of acyclic benzyl bromide. Chloroindanes also participated in the asymmetric coupling resulting in moderate yields (Scheme 53).[218]

Allylic chlorides coupled with alkylzinc halides in the presence of Ni and **126**. The addition of an excess amount of NaCl accelerated the coupling, exerting little influence on the *ee*, probably by increasing the ionic strength of the reaction media to activate the organozinc reagents.[219] Racemic symmetrical allylic chlorides gave coupling products in good yields with high enantiomeric excesses. The reaction of unsymmetrical allylic chlorides possibly gives two regioisomers. When the difference between the two substituents is small, such as ^{n}Bu versus Me, only modest regioselectivity (1.9:1) was observed. Substrates having larger steric difference, for example, ^{i}Pr/Me, ^{t}Bu/Me, and carbonyl group/Me led to excellent regioselectivities being coupled with alkylzinc halides at less hindered sites (Scheme 54).

The asymmetric Negishi coupling of allylic chlorides has been applied to a formal total synthesis of a 14-membered macrocycle, fluvirucinine A_1, where two tertiary stereocenters are generated by these asymmetric Negishi reactions of racemic secondary



Scheme 53



Scheme 54

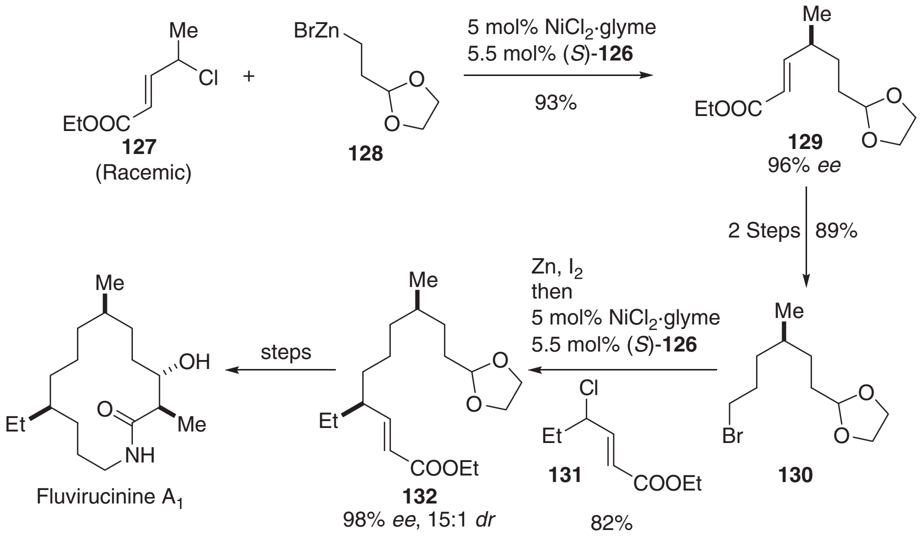
allylic chlorides (Scheme 55).[219] Owing to the difficulty of constructing isolated chiral centers by diastereoselective reactions, this methodology would be useful for the asymmetric total synthesis of a wide variety of natural products.

As described in Section 3.07.4.2.3, diamine ligands are effective for the Suzuki–Miyaura coupling and a variety of chiral diamines are commercially available. For the reaction of homobenzylic bromide with alkyl-9-BBN, the electron-deficient diamine **133** provided a good yield with high enantiomeric excess.[220] In contrast, both yield and *ee* decreased when the sterically congested diamine ligand **136** was used (Scheme 56). The chiral ligand **133** afforded high enantioselectivities for various homobenzylic secondary alkyl bromides though the reaction of cyclic homobenzylic substrate and γ-phenyl analog resulted in poor *ee*'s (Scheme 57). These results suggest that the interaction of β-aryl group with Ni center plays an important role in the stereoselective step of the catalytic cycle.

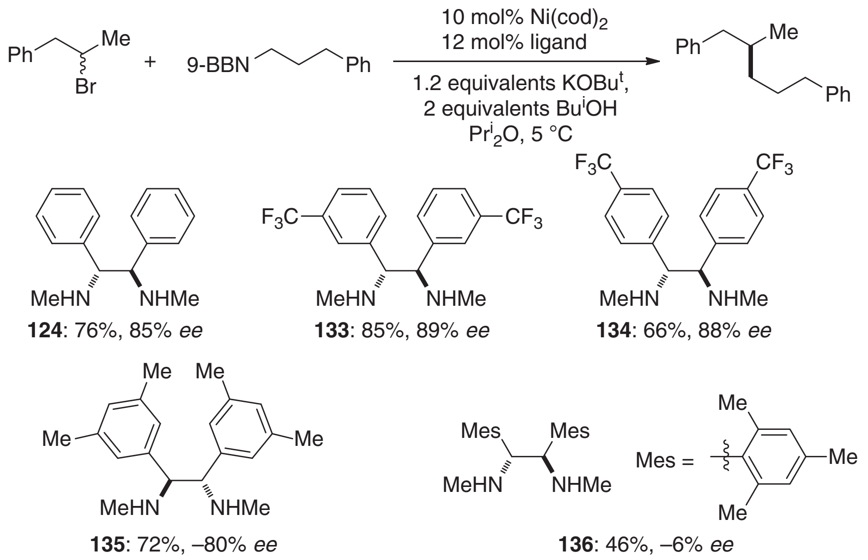
The importance of such an interaction to achieve a high *ee* was also evidenced by the reaction of other families of substrates bearing coordinating heteroatom functionalities. For example, acylated halohydrines coupled with alkylboranes under similar conditions resulted in good to excellent yields with excellent enantiomeric excesses. Similarly, γ-haloamides afforded the corresponding coupling products in good yields with high enantioselectivities (Scheme 58).[221,222] These asymmetric reactions can provide useful chiral building blocks possessing alcohol, carboxylic acid, and ketone eligible for further transformations.

Carbamate, sulfonamide, and sulfone groups also act as appropriate directing groups in the asymmetric Suzuki–Miyaura coupling reactions as shown in Scheme 59.[223] These results suggest that C=O or S=O double bond at δ-position is effective to attain a high enantioselectivity. When one more methylene was inserted between the reaction site and the directing functionality, the enantioselectivity dropped appreciably although the yields of products were not affected.[223]

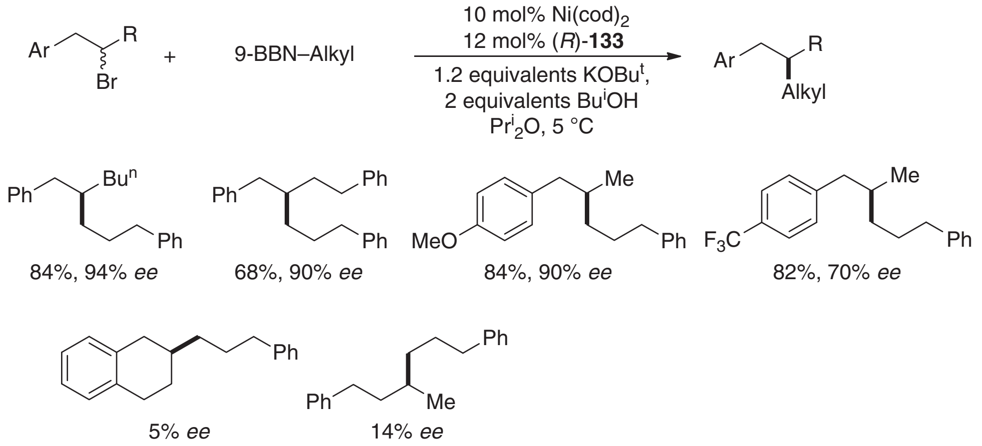
β-*N*-Alkyl-*N*-arylamino group is also useful for enantioselective cross-coupling, where the position of the amino group is important to achieve a high enantioselectivity as shown in Scheme 60.[224] Secondary alkyl chlorides without (**138**) or with (**139**) the amino group at the γ-position coupled with 3-anisylpropyl-9-BBN resulted in poor enantioselectivities in contrast to the



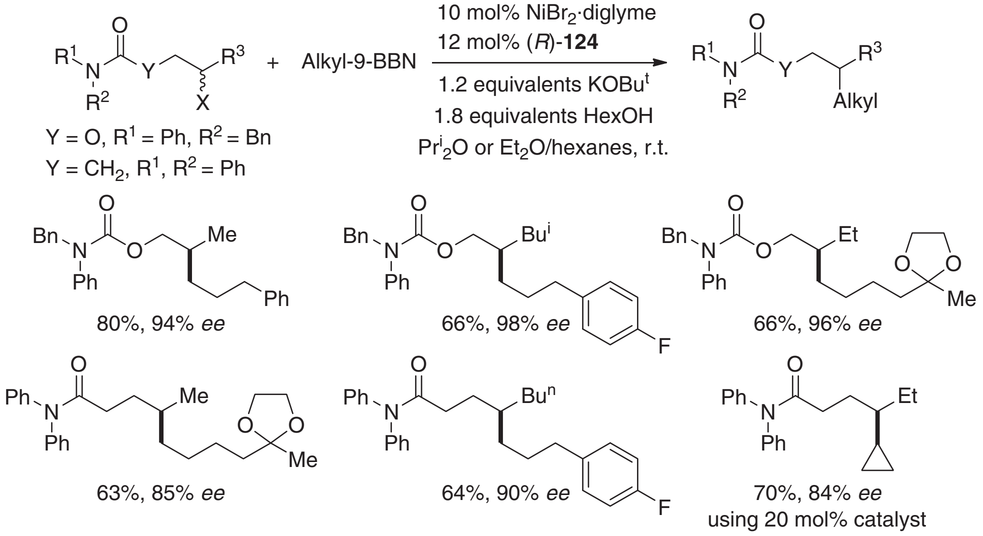
Scheme 55



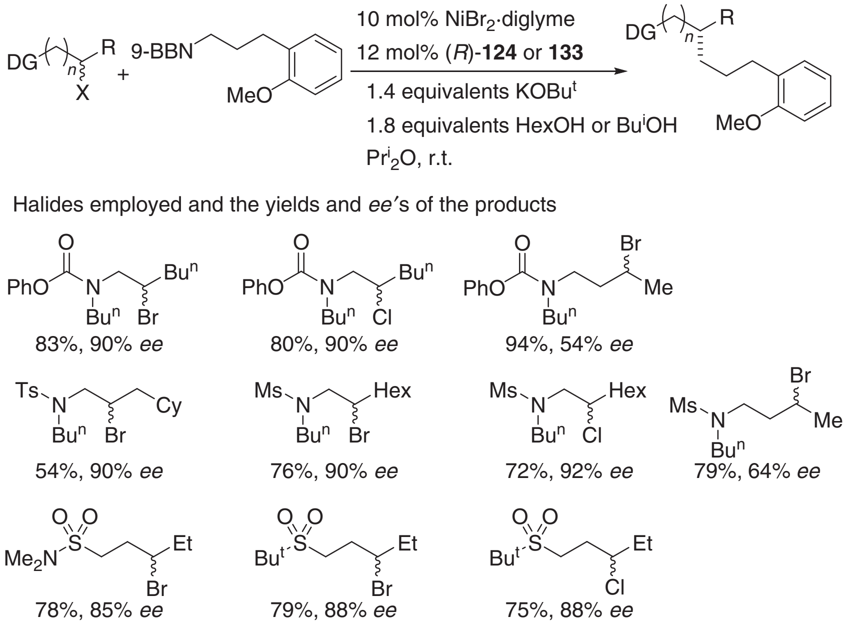
Scheme 56



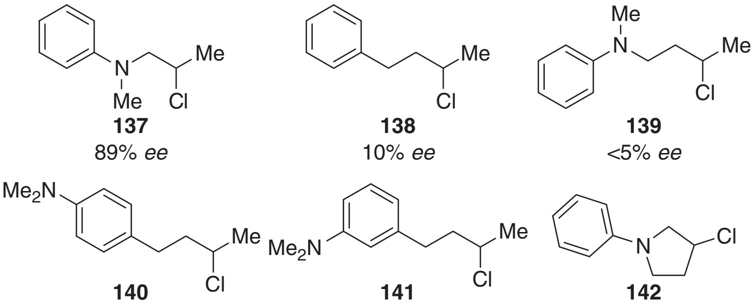
Scheme 57



Scheme 58



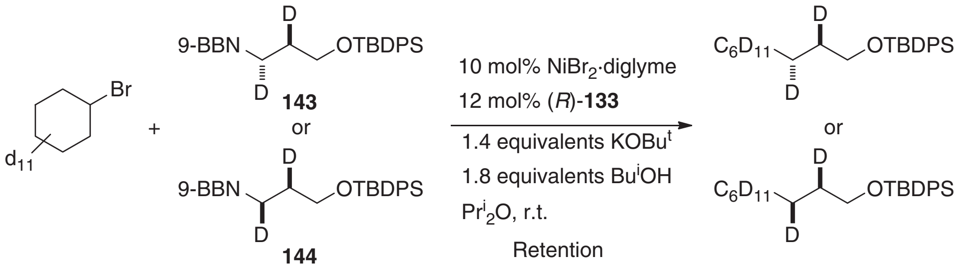
Scheme 59



Scheme 60

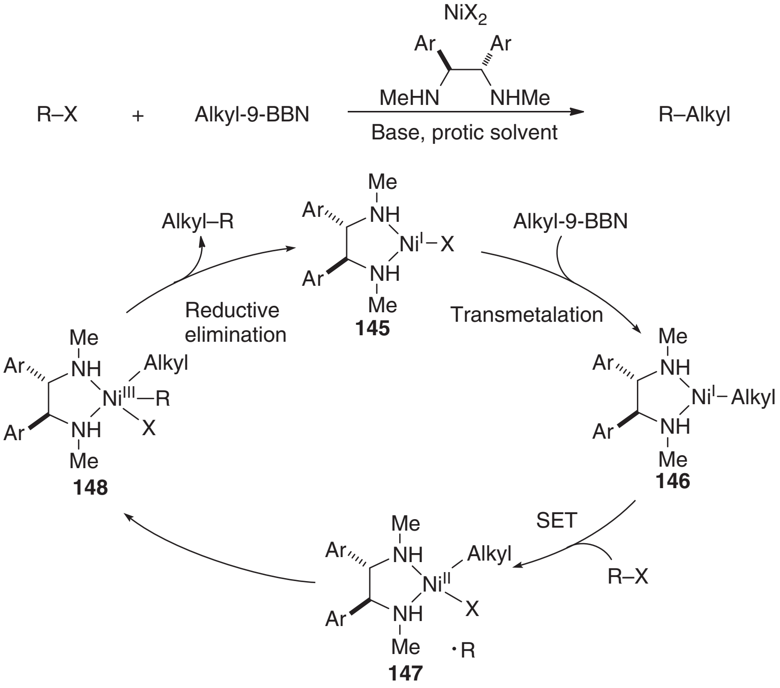
satisfactory level of *ee*'s obtained in the case of *β*-aminoalkyl chloride **137**. Likewise, the dimethylamino group on the phenyl ring of substrates **140** and **141** had no effect on the *ee*. Cyclic analog **142** was not a suitable substrate for the asymmetric coupling probably due to the difficulty of coordination. These data suggest that the amino group did not affect the relative reactivity of the Suzuki–Miyaura coupling.

As mentioned above, chiral information of the carbon carrying a leaving group is lost during oxidative addition involving alkyl radical intermediates. However, alkyl group of the alkylborane is transferred to the coupling products with retention of configuration at the reacting site as shown in Scheme 61, where a complete stereoretention was observed in both deuterated alkylboranes **143** and **144**.[223,225] This result indicates that transmetalation from the alkylborane as well as the alkylmagnesium halides[226] and the dialkylzinc[204] to nickel proceeds with retention of configuration and that alkylnickel intermediates are configurationally stable under reaction conditions, which is consistent with Pd-catalyzed coupling reactions.[227,228]



Scheme 61

An outline of a possible reaction pathway is shown in Scheme 62. Nickel(I) complex **145** is assumed to be catalytic active species, which undergoes transmetalation with alkyl-9-BBNs to form Ni–alkyl complex **146**. This transmetalation process appears to be a rate-determining step. Oxidative addition of alkyl halides to Ni(I) center includes two steps. First, SET from Ni(I) to R–X forms Ni(II) complex **147** and alkyl radical. Second, recombination of alkyl radical with complex **147** affords dialkyl Ni(III) **148**, determining the stereochemistry of the chiral centers. Subsequent reductive elimination gives coupling products and regenerates complex **145**. No epimerization of starting material was observed when enantiomeric pure α-chloroamides were employed to the reaction with Ph-(9-BBN),[229] suggesting that the carbon–halogen bond cleavage process is irreversible.



Scheme 62

3.07.4.3 Palladium Catalysts

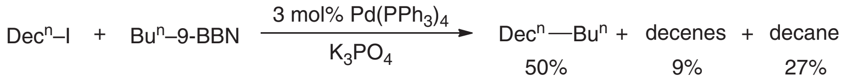
As Pd was found to be an excellent catalyst for cross-coupling reactions using various carbon nucleophiles such as organolithiums,[171] -boranes,[230] -zincs,[231] -stannanes,[232,233] and -silanes[234], numerous examples of useful catalytic reactions have been developed for use in laboratories[235,236] and industrial productions.[129–132,237] Remarkable progress in the development of catalytic systems for Pd-catalyzed cross-coupling employing alkyl halides has been made since the early 2000s.[238]

3.07.4.3.1 Using alkylborane and alkylzinc reagents

Alkyl–alkyl Suzuki–Miyaura coupling and Negishi coupling catalyzed by Pd has been extensively studied during the past decade by use of phosphine or *N*-heterocyclic carbene (NHC) ligand systems.

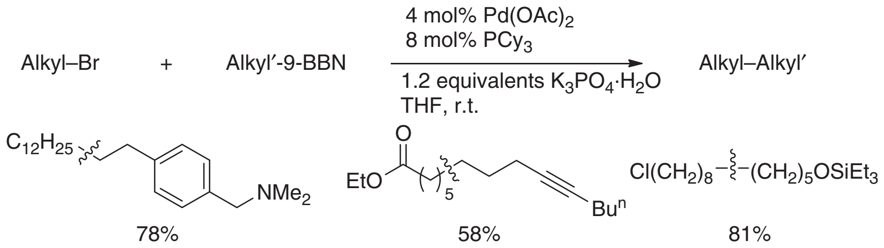
3.07.4.3.1.1 Phosphine ligands

In 1992, it was reported that the reaction of alkyl iodides with alkylboranes using Pd(PPh_3)$_4$ gave cross-coupling products in moderate yields accompanied by significant amounts of β-H elimination products as well as hydrodehalogenated (reduction) products of alkyl iodides (equation 33).[239]



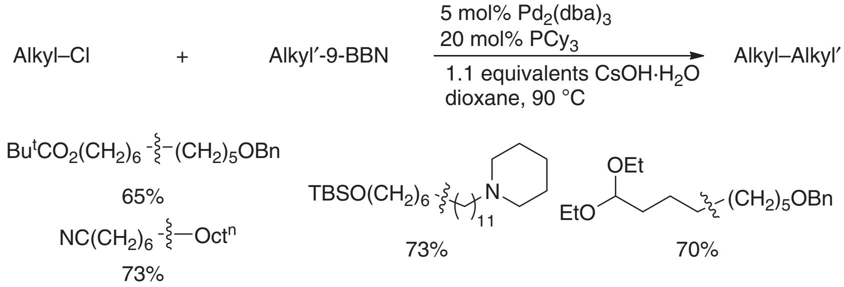
$$\text{Dec}^n\text{–I} + \text{Bu}^n\text{–9-BBN} \xrightarrow[\text{K}_3\text{PO}_4]{3\text{ mol\% Pd(PPh}_3)_4} \underset{50\%}{\text{Dec}^n\text{—Bu}^n} + \underset{9\%}{\text{decenes}} + \underset{27\%}{\text{decane}} \tag{33}$$

A decade later, Fu found that this alkyl–alkyl cross-coupling proceeded efficiently under mild conditions when bulky tricyclohexylphosphine was employed as the ligand (Scheme 63).[240]



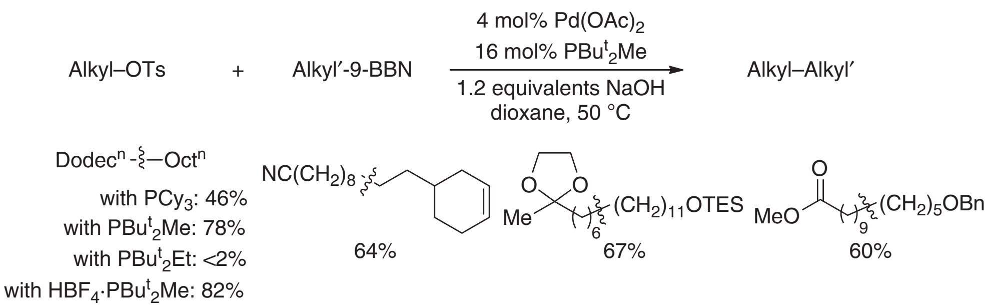
Scheme 63

Alkyl chlorides (Scheme 64)[241] and tosylates (Scheme 65)[242] underwent cross-coupling on heating. P^tBu_2Me showed better results than PCy_3 in the reaction of tosylates. When P^tBu_2Et was used instead of P^tBu_2Me, yield largely dropped indicating that this reaction is sensitive to the steric effect. An air-stable phosphonium salt, $HBF_4{\cdot}P^tBu_2Me$,[243] is a good alternative and showed a comparable ligand effect (Scheme 65).[242]

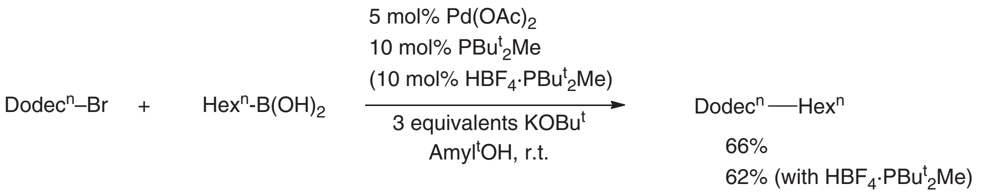


Scheme 64

As alkyl-9-BBN derivatives are not commercially available and not stable in air, they are generally prepared by hydroboration of the corresponding olefins before use. Corresponding boronic acids are more stable and many are available from commercial sources. Cross-coupling of alkyl bromides and alkyl boronic acids proceeded efficiently by use of P^tBu_2Me in *tert*-amyl alcohol as shown in equation 34.[244] When air- and moisture-stable $HBF_4{\cdot}P^tBu_2Me$ is used as a ligand precursor, the reaction can be run with no special techniques or apparatus.

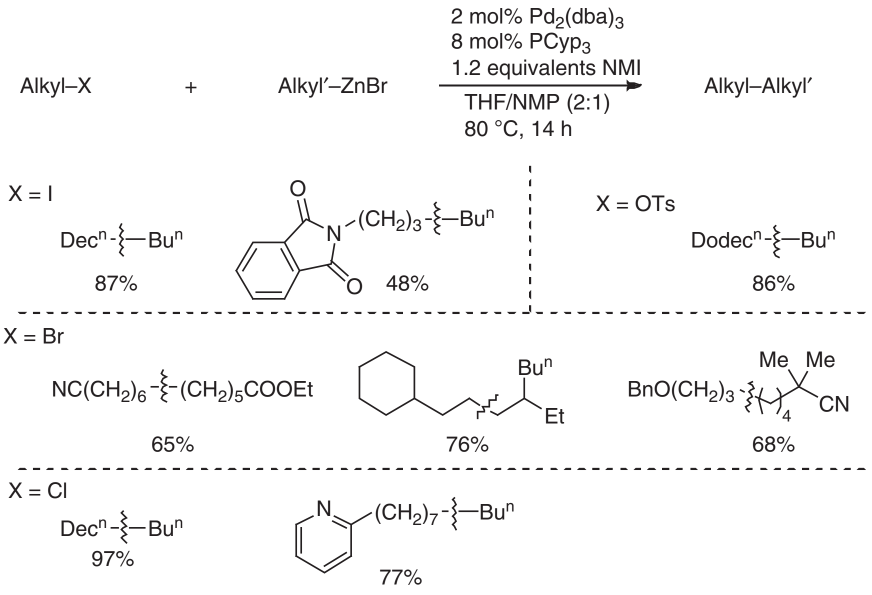


Scheme 65



(34)

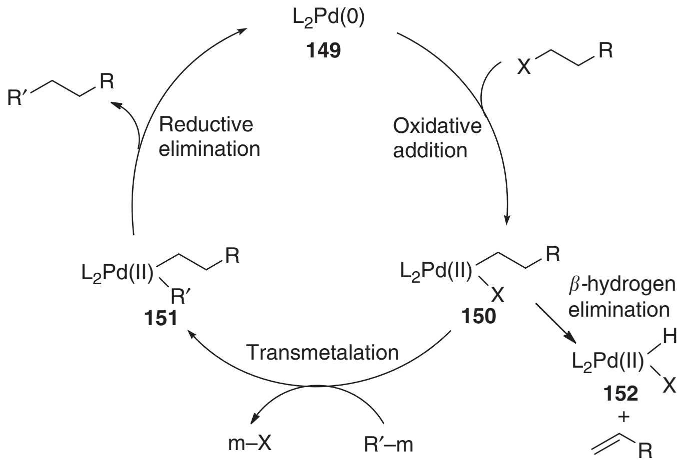
This protocol using sterically hindered trialkylphosphine can furnish efficient coupling of alkyl halides with alkylzinc reagents, where tricyclopentylphosphine gave better yields.[245] As shown in Scheme 66, a wide range of functionalized alkyl iodides, bromides, tosylates, and chlorides coupled with alkylzinc reagents in good yields.



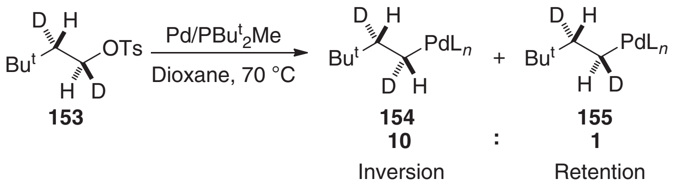
Scheme 66

Fu et al. have shown that Pd-catalyzed Suzuki–Miyaura coupling of alkyl halides using bulky trialkylphosphines proceeds via the conventional mechanism comprising oxidative addition, transmetalation, and reductive elimination as shown in Scheme 67. Trialkylphosphines play an important role in both steps of the oxidative addition (**149** to **150**) and reductive elimination (**151** to **149**). The high electron-donating ability of the trialkylphosphines accelerates the oxidative addition step and bulkiness of the ligand suppresses β-hydrogen elimination (**150** to **152**) to facilitate reductive elimination in the catalytic cycle.[245]

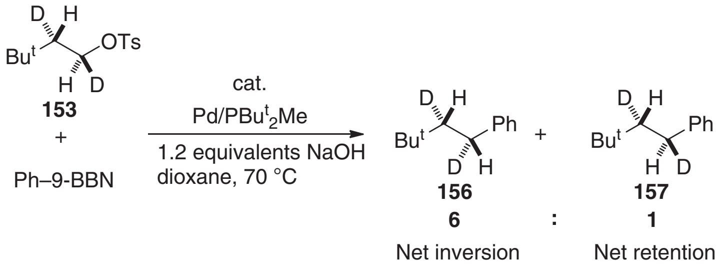
The stereochemistry of these processes was examined using the diastereomeric pure deuterated tosylate **153** and the findings indicate that oxidative addition proceeded with inversion of the stereochemistry at the reacting carbon to give **154** as the major product (equation 35), and the stereochemistry was retained during the following reductive elimination as shown in equation 36.[242] This result indicates that oxidative addition of alkyl tosylates to such a Pd–phosphine complex proceeds in an ionic mechanism in sharp contrast with Ni–amine catalytic systems using alkyl halides as described in Section 3.07.4.2.



Scheme 67

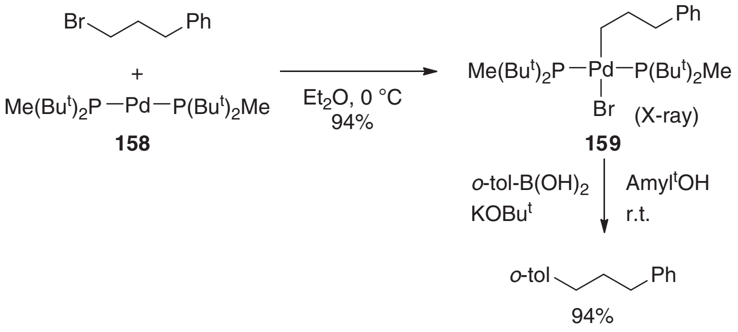


(35)



(36)

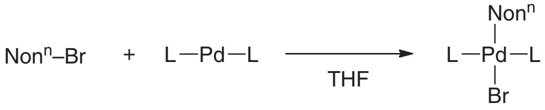
An alkylpalladium intermediate **159**, as the product of oxidative addition process, was successfully isolated and its structure was determined by X-ray analysis. In addition, when **159** was treated with a boronic acid and a base, the complex underwent successive transmetalation and reductive elimination to give the coupling product in 94% yield (Scheme 68).[244]



Scheme 68

Kinetic studies on the oxidative addition step in the catalytic cycle showed that the activation parameters for the oxidative addition of ^{n}non-Br to Pd(P^{t}Bu$_2$Me)$_2$ were $\Delta G^{\ddagger}=87.1$ kJ mol^{-1} at 20 °C, $\Delta H^{\ddagger}=10$ kJ mol^{-1}, and $\Delta S^{\ddagger}=-2.6\times10^2$ J kmol^{-1}. The large negative $\Delta S^{\ddagger}$ values are in accordance with the associative S$_N$2-type pathway. The addition of excess P^{t}Bu$_2$Me to this reaction does not affect the rate, indicating that the active species of the oxidative addition toward alkyl bromide should be PdL$_2$, and not PdL or PdL$_3$ · $\Delta G^{\ddagger}$ of the oxidative addition of ^{n}non-Br to PdL$_2$ was estimated for a series of trialkylphosphines as shown in Table 5. The activation barrier decreases with increasing solvent polarity.[246]

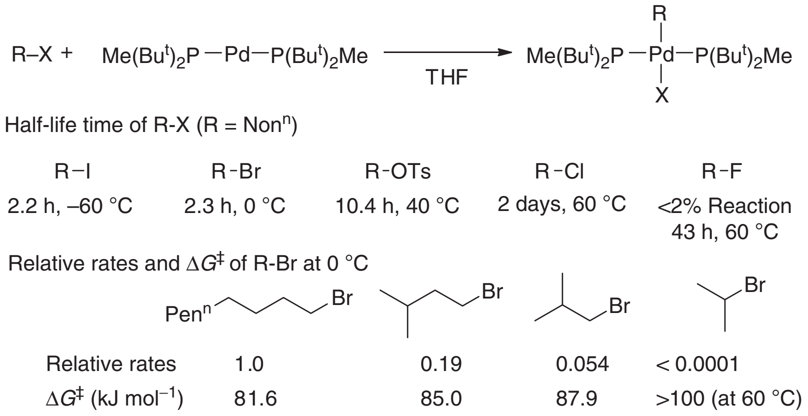
Table 5 $\Delta G^‡$s of oxidative addition of alkyl bromide to Pd complexes having trialkylphosphine ligands



L	$\Delta G^‡$ *(KJ mol^{-1})*
$P(Bu^t)_2Me$	81.6 (0 °C)
PCy_3	83.7 (0 °C)
$P(Bu^t)_2Et$	106 (60 °C)
$P(Bu^t)_3$	>119 (60 °C)

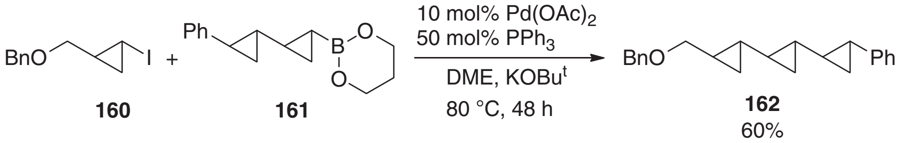
Source: Reproduced from Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749–5752, with permission from Wiley.

Relationship between structure and reactivity of alkyl halides was also examined using $Pd(P^tBu_2Me)_2$.[246] Results in Scheme 69 show that oxidative addition of ^{n}non-X to $Pd(P^tBu_2Me)_2$ becomes slower in the order of X=I>Br>OTs>Cl>F in THF. Secondary alkyl halides are much less reactive than primary halides. Branched structures at *β*- and *γ*-positions also affected reactivity of alkyl halides, indicating that this reaction is sensitive to steric factors.



Scheme 69

A major unwanted side reaction of this Pd-catalyzed reaction is *β*-hydrogen elimination from alkylpalladium intermediates. Accordingly, when substrates containing no *β*-hydrogen are employed or when *β*-hydrogen elimination is relatively slow, the coupling reaction takes place exclusively. For instance, cyclopropyl halides worked as good coupling partners for Pd-catalyzed coupling reactions. When cyclopropyl iodide **160** and cyclopropylboronic ester **161** were treated with $Pd(OAc)_2$ in the presence of PPh_3 and ^tBuOK, the cross-coupling proceeded smoothly to give the unique carbon framework **162** in a good yield (equation 37).[247]

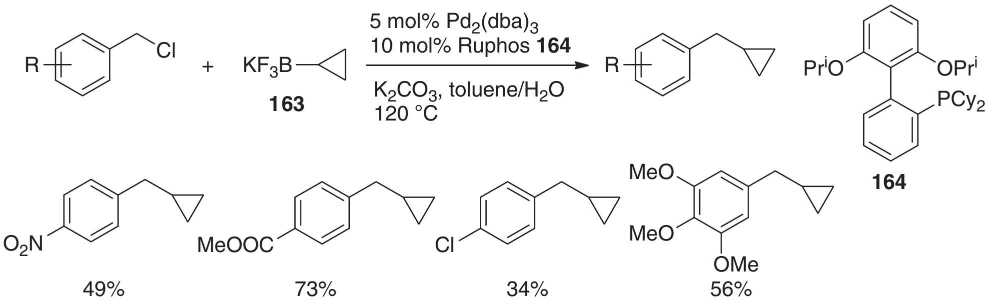


(37)

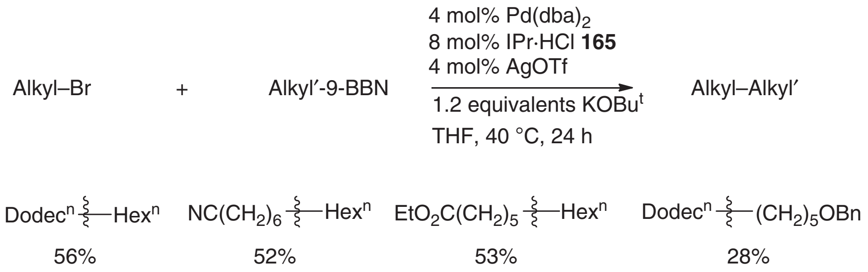
Efficient C(sp^3)–C(sp^3) coupling of benzyl chlorides with cyclopropyltrifluoroborate (**163**) was furnished by Pd in the presence of a sterically hindered biarylphosphine **164** (Scheme 70).[248]

3.07.4.3.1.2 NHC ligands

NHCs have attracted a great deal of attention as a promising alternative to phosphine ligands due to their large *σ*-electron-donating abilities and strong metal-binding characteristics. Thus NHCs have been utilized for various transition metal-catalyzed transformations including cross-coupling reactions at *sp*- and sp^2-hybridized carbons.[249] As for the sp^3–sp^3 coupling reactions, Caddick and Clock et al. for the first time employed NHC ligands in Suzuki–Miyaura coupling though yields were moderate (Scheme 71).[250]

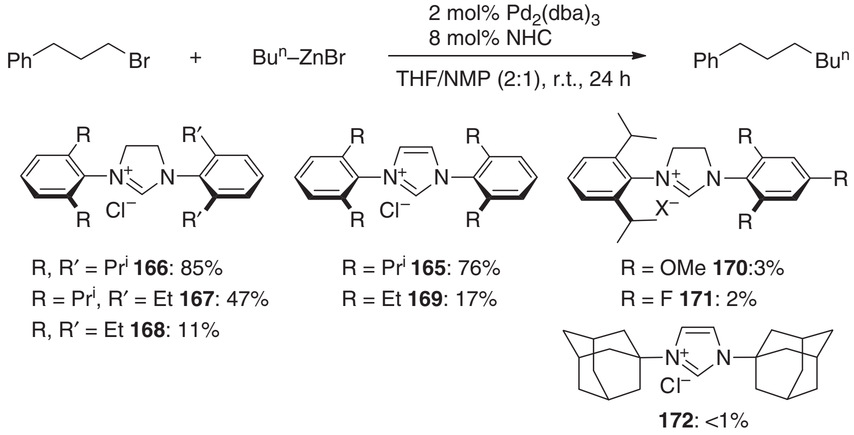


Scheme 70



Scheme 71

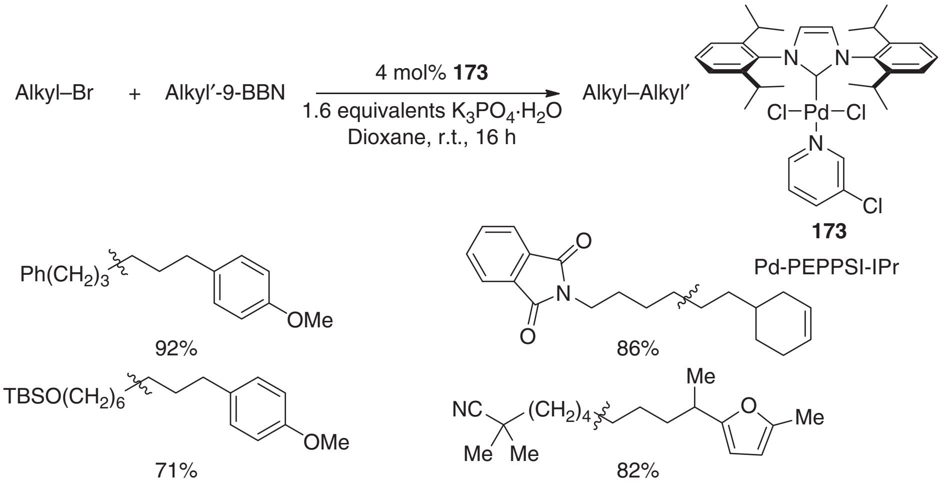
Organ also applied a series of imidazolium and imidazolinium salts to the Pd-catalyzed alkyl–alkyl Negishi coupling and demonstrated that the yields largely depend on both steric and electronic factors of the substituents on the nitrogen atoms of the NHC ligands as shown in Scheme 72.[251–253] SIPr (**166**) and IPr (**165**) gave similar results. The introduction of electron donating and withdrawing groups on the aryl group led to a decrease in the yield of the coupling reaction (**170** and **171**).



Scheme 72

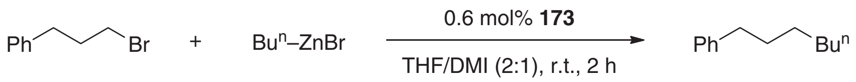
Owing to the susceptibility of isolated NHCs to moisture and oxygen, Pd–NHC complexes are often prepared *in situ* by reacting a Pd source with an imidazolium salt in the presence of a base. Organ developed a new class of air- and moisture-stable Pd–NHC complexes, Pd–PEPPSIs, which could be easily prepared by the reaction of imidazolium salts, $PdCl_2$, K_2CO_3, and 3-chloropyridine, in air in good yields.[254–256] Pd–PEPPSIs have a large advantage for Negishi coupling over the corresponding *in situ* generated NHC-based catalyst, with a 10 times higher catalytic activity (turnover frequency 300/h vs. 30/h) and giving better yields under milder conditions.[254] Selected examples of alkyl–alkyl Suzuki–Miyaura coupling using Pd–PEPPSI–IPr (**173**) are shown in Scheme 73.[254,257,258]

It is known that bases accelerate Suzuki–Miyaura coupling by forming borate complexes that facilitate transmetalation.[228,259] In Negishi coupling, the presence of an Li salt improved the reactivity of organozincs in some cases.[260,261] Alkyl–alkyl Negishi coupling using Pd–PEPPSI catalyst was found to be sensitive to coexisting salts and solvents.[262,263] When salt-free alkylzinc bromide was used, no coupling product was formed. On the contrary, when 2 equivalents of Li salts was added to the reaction mixture, the coupling product was formed in quantitative yield. The results of other salts are shown in Table 6. This suggests that



Scheme 73

Table 6 Effects of Li and Mg salts on Pd-catalyzed Negishi coupling

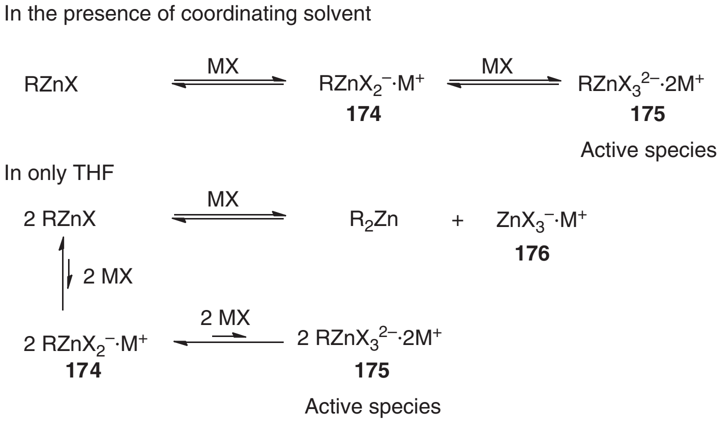


Additive (2.0 equivalents)	*Conversion (%)*
–	0
LiBr or LiCl	>95
$MgBr_2$	92
TBAB	79
LiBr+12-crown-4	61
LiOAc	0

Source: Reproduced from Hunter, H. N.; Hadei, N.; Blagojevic, V.; *et al. Chem. Eur. J.* **2011**, *17*, 7845–7851, with permission from Wiley.

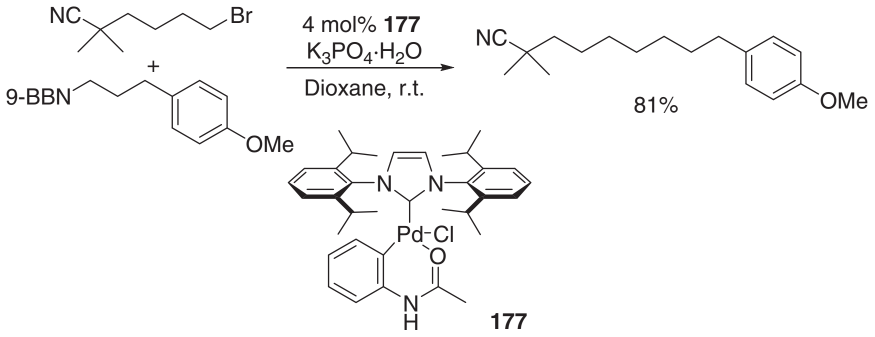
the addition of Li or Mg salts to alkylzinc halides forms higher-order zincates by coordination of halogen anions leading to the acceleration of transmetalation. Indeed, no additive effects were observed with LiOAc.[259]

On the contrary, the addition of $ZnBr_2$ to the reaction mixture prevented the cross-coupling reaction.[262] ^{1}H NMR spectra of Et_2Zn showed a characteristic upfield shift of its methylene protons by the addition of $^nBu_4N \cdot Br$, suggesting that the electron density on the zinc center was increased. On the basis of these results, Organ proposed that M_2RZnX_3 (**175**) generated by complexation of RZnX with 2 equivalents of MX, not the lower-order zincate $MRZnX_2$ (**176**) or other members of the Schlenk equilibrium, participate in transmetalation with Pd catalysts.[262,263] Cosolvents such as NMP, *N*-methylimidazole (NMI), and 3-dimethyl-2-imidazolidinone (DMI) coordinate to the metal cation of **175** and **176** and stabilize the charged species to shift the equilibrium toward reactive zincate **175** (Scheme 74).



Scheme 74

A new stable NHC–Pd complex **177** containing a palladacycle framework was synthesized in air on a large scale and was employed as a catalyst for Suzuki–Miyaura cross-coupling between alkyl groups as well as for all combinations of sp^2- and sp^3-hybridized substrates (equation 38).[264]

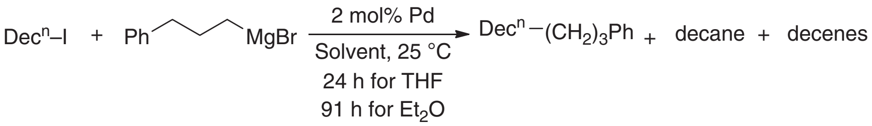


(38)

3.07.4.3.2 Using Grignard reagents

Pd-catalyzed alkyl–alkyl cross-coupling using Grignard reagents is rarely discussed unlike the reactions at *sp*- or sp^2-carbons.[265] It was reported in 1986 that when a mixture prepared by the reduction of (dppf)PdCl$_2$ with 2 equivalents of DIBAL in THF was used as a catalyst, cross-coupling of alkyl iodides with alkyl Grignard reagents proceeded in moderate yields.[266] Soon after, however, contradictory results were reported claiming that the reduction and elimination of alkyl halides to give a mixture of saturated and unsaturated hydrocarbons took place under similar conditions or in the absence of catalysts as shown in Table 7.[267,268]

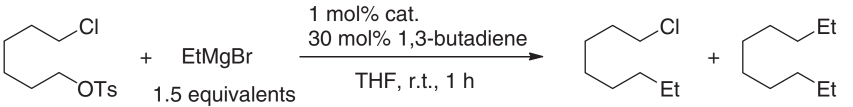
Table 7 Pd-catalyzed cross-coupling of alkyl iodides with alkyl Grignard reagents



Solvent	*Cat.*	*Yield (%)*	*Distribution of products*
			Dec^n(CH$_2$)$_3$Ph:decane:decenes
THF	None	100	1:88:11
THF	(dppf)Pd(0)	100	0:84:16
THF	(dppf)PdCl$_2$	100	1:88:11
Et$_2$O	None	10	0:99:1
Et$_2$O	(dppf)Pd(0)	83	0:85:15
Et$_2$O	(dppf)PdCl$_2$	66	0:96:4

As shown in Section 3.07.4.2.1, 1,3-butadiene shows significant additive effects on Ni-catalyzed alkyl–alkyl cross-coupling reactions. Similar additive effects are also observed on the palladium-catalyzed cross-coupling reaction of alkyl tosylates and bromides with Grignard reagents. The formation of anionic alkylpalladium intermediates was proposed as the key active species for achieving cross-coupling by suppressing undesirable side reactions. Palladium catalyst afforded better yields than nickel in the reaction of *sec*-alkyl Grignard reagents and reacted site selectively on the C(sp^3) over C(sp^2) (Scheme 75).[269]

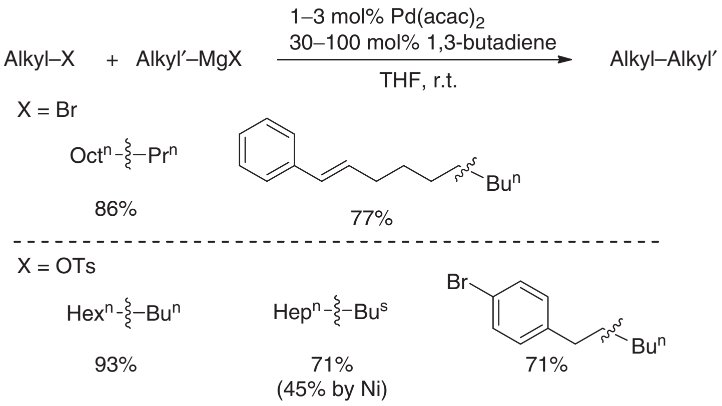
In addition, Pd catalyst showed higher chemoselectivity in the competitive reactions between chloride and tosylate than Ni catalyst as shown in equation 39.



178 **179** **180**

(39)

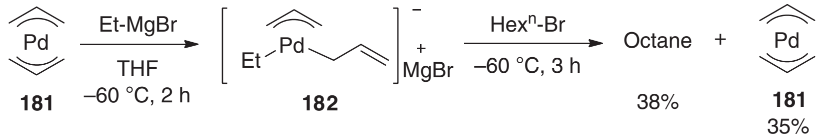
Cat.	Yield of **179**	Yield of **180**
Pd(acac)$_2$	86%	0%
NiCl$_2$	87%	13%



Scheme 75

When palladium containing perovskite $LaFe_{0.95}Pd_{0.05}O_3$ (LFPO) was employed as the palladium source instead of palladium salts, a trace amount of palladium leached from the LFPO-catalyzed cross-coupling of alkyl iodides, bromides, and tosylates with alkyl Grignard reagents in the presence of butadiene or isoprene and the recovered LFPO could be reused.[184]

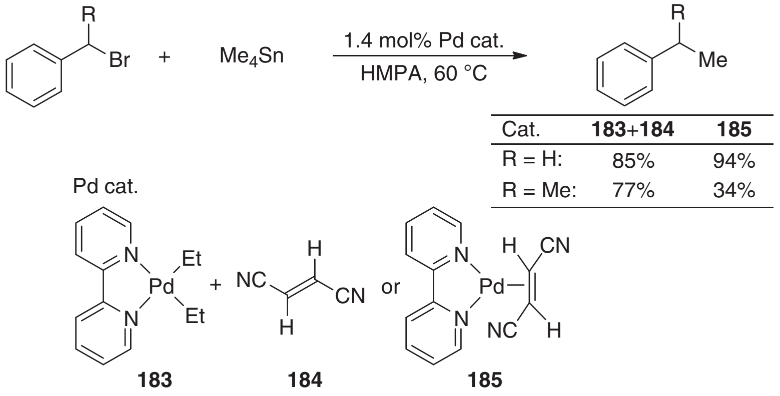
This cross-coupling proceeded in the presence of a catalytic amount of bis(η^3-allyl)palladium (**181**) without using butadiene. Bis(η^3-allyl)palladium (**181**) reacted with EtMgBr at −60 °C to give bis(η^1,η^3-allyl)palladate complex **182**, which showed one set of η^1- and η^3-allyl signals on its ^{1}H NMR analysis. The coupling product, octane, and bis(η^3-allyl)palladium (**181**) were formed by the addition of n-hexyl bromide to the solution of the ate complex (equation 40).[187] It should be noted that no evidence for the formation of coupling products involving an allyl group, such as 1-pentene or 1-nonene, was observed, suggesting that alkyl–alkyl coupling proceeds exclusively in the reaction with alkyl halides rather than alkyl–allyl or allyl–allyl coupling.



(40)

3.07.4.3.3 Using alkylstannane reagents

In the case of the Pd-catalyzed Migita–Kosugi–Stille coupling of alkyl halides with alkylstannanes, only one report is available with a narrow substrate variation. The reaction proceeded either by using (bpy)$PdEt_2$ (**183**) in the presence of fumaronitrile (**184**) as the ligand or with a complex **185** (Scheme 76).[270]



Cat.	183+184	185
R = H:	85%	94%
R = Me:	77%	34%

Scheme 76

3.07.4.4 Silver Catalysts

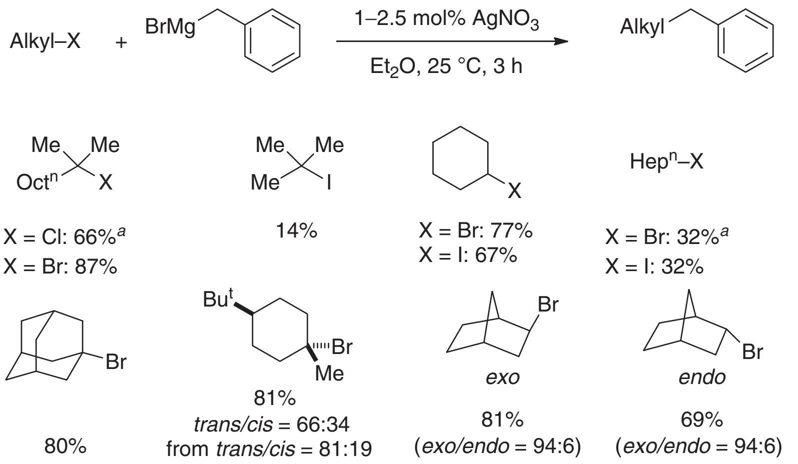
In the early 1970s, Kochi found that the reaction of EtBr with EtMgBr in the presence of a catalytic amount of AgBr in THF gave a high yield of butane. However, a study of the reaction of EtMgBr with various alkyl bromides revealed that this catalyst promotes not only cross-coupling but also the homocoupling of alkyl bromides and alkyl Grignard reagents giving mixtures of coupling products as shown in Table 8. The relative reaction rate for each alkyl bromide in the overall reactions decreased in the order of ^{t}Bu > ^{i}Pr > ^{n}Pr with a ratio of approximately 20:3:1, suggesting the formation of alkyl radical intermediates.[271] This is in agreement with evidence showing that alkyl silver(I) complexes readily undergo thermal decomposition even at −50 °C to give the dimer of alkyl group and Ag(0) through homolytic cleavage of Ag–C bond.[272] Under these catalytic conditions, alkyl halides may play a role not only as a coupling partner but also as a reoxidizing reagent of Ag(0).

Table 8 Products distribution of Ag-catalyzed coupling reaction of alkyl bromides with EtMgBr

$$\text{Alkyl–Br} + \text{Et–MgBr} \xrightarrow[\text{THF, 2 °C}]{\text{0.25 mol\% AgBr}} \text{Alkyl–Et} + \text{Alkyl–Alkyl} + \text{Et–Et}$$

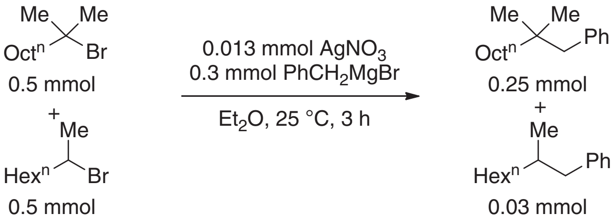
Alkyl	*Distribution of products*			*Relative rate*
	Et–alkyl	*Alkyl–alkyl*	*Et–Et*	
Et	–	–	–	1.0
Pr^n	13	3	84	0.9
Pr^i	46	14	40	2.9
Bu^t	52	4	44	18.9

Recently, it was found that benzyl Grignard reagents can be coupled with secondary and tertiary alkyl halides in the presence of a catalytic amount of silver salt as shown in Scheme 77.[273] Reaction of primary alkyl halides gave the corresponding coupling products in poor yields. A competitive reaction revealed that the tertiary bromide reacted with benzyl Grignard reagent much faster than the secondary derivatives (equation 41). These results also support a radical mechanism (*vide infra*).



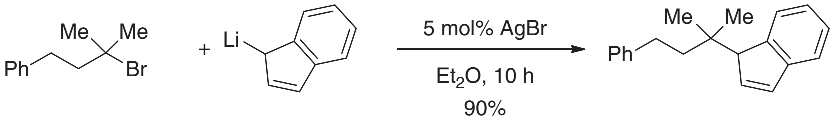
^{a}Under refluxing Et$_2$O

Scheme 77

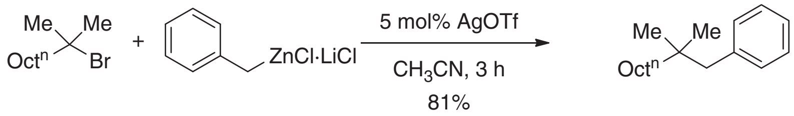


(41)

Benzylic lithium reagents[274] and zinc reagents[275] were alkylated in the presence of silver salts as shown in equations 42 and 43. Allylic Grignard reagents and zinc reagents also worked as coupling partners.

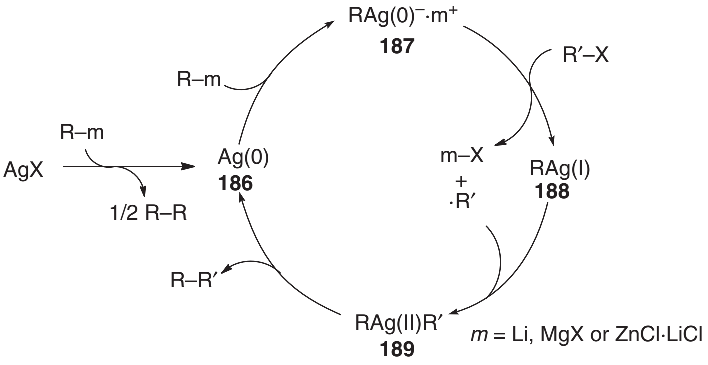


(42)



(43)

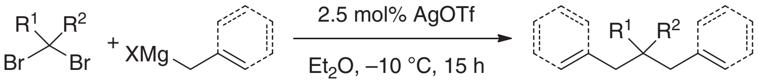
A proposed mechanism is shown in Scheme 78.[275] The first step is reduction of the Ag(I) salt to Ag(0) **186** with an organometallic reagent. The Ag(0) then reacts with 1 equivalent of the organometallic reagents to form the anionic ate complexes **187**. SET from Ag(0) to alkyl halides gives alkyl radicals and **188** and subsequent recombination forms dialkylsilver complexes **189**, which undergo reductive elimination to give coupling products and Ag(0) (**186**).



Scheme 78

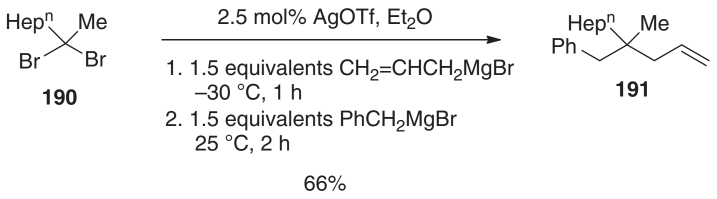
As shown in Table 9, *gem*-dibromoalkanes are suitable substrates to construct tertiary and quaternary carbon centers via Ag-catalyzed diallylation and dibenzylation. Various *gem*-dibromoalkanes coupled with allyl and benzyl Grignard reagents in good yields though the corresponding chlorides and iodides resulted in moderate yields.[276]

Table 9 Diallylation and dibenzylation of dibromoalkanes by Ag catalyst



R¹	*R²*	*Grignard*	*Yield (%)*
Hep^n	H	Allyl	70
$PhCH_2CH_2$	Me	Allyl	83
Hep^n	Me	Allyl	79
$-CH_2CH_2CH(Bu^t)CH_2CH_2-$		Allyl	81
$TBSO(CH_2)_8$	Me	Allyl	90
$PhCH_2CH_2$	H	Benzyl	83
$PhCH_2CH_2$	Me	Benzyl	77
Hep^n	Me	Benzyl	61

The fact that the monoallylated product was obtained when 1 equivalent of allyl Grignard reagent was employed indicates that this Ag-catalyzed disubstitution proceeds through sequential substitution. Therefore, stepwise introduction of two different Grignard reagents into *gem*-dibromoalkane **190** could successfully be achieved (equation 44).

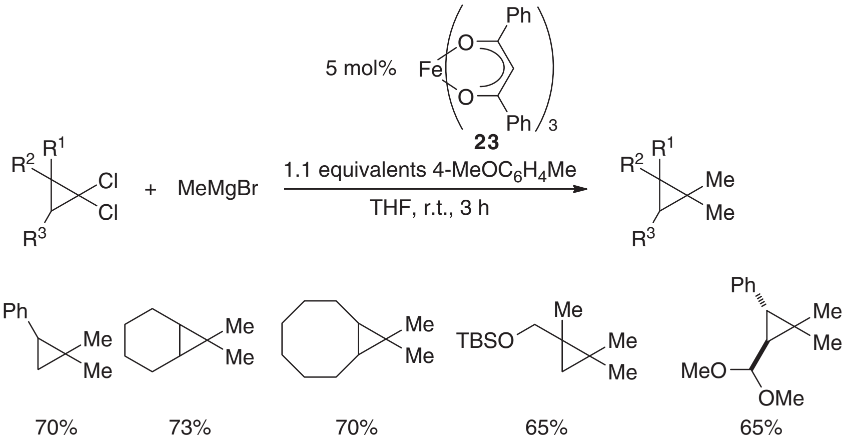


(44)

3.07.4.5 Iron Catalysts

The use of iron instead of noble metals is an important theme with respect to not only economical aspects but also resource problems and has received much attention.[277–283] Although iron-catalyzed cross-coupling reactions between unsaturated sp^2- or sp-hybridized carbons and saturated sp^3 carbons have been developed using various ligands,[280–283] examples of alkyl–alkyl cross-coupling catalyzed by Fe remain limited and are less efficient.

Double methylation of *gem*-dichlorocyclopropanes by MeMgBr proceeded in the presence of iron catalyst **23** to afford poly-substituted cyclopropanes in moderate to good yields. *gem*-Dichlorocyclopropanes fused with a cyclohexane or cyclooctane ring also underwent dimethylation efficiently (Scheme 79).[282]



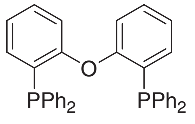
Scheme 79

Only one report is available regarding the Fe-catalyzed cross-coupling of simple alkyl halides with alkyl Grignard reagents.[283] As shown in Table 10, the reduction of ^{n}DecBr predominated in the absence of a ligand to give decane in 58% yield accompanied by significant amounts of decenes and icosane, which might be formed by β-hydrogen elimination and homocoupling,

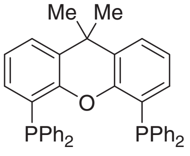
Table 10 Iron-catalyzed cross-coupling of alkyl bromides with alkyl Grignard reagents

$$\mathrm{Dec^n{-}Br + Bu^n{-}MgBr} \xrightarrow[\mathrm{Et_2O,\ r.t.,\ 15\ h}]{\mathrm{1\ mol\%\ Fe(OAc)_2}\atop \mathrm{1\ mol\%\ ligand}} \mathrm{Dec^n{-}Bu^n + decane + decenes + icosane}$$

Ligand	*Tetradecane (%)*	*Decane (%)*	*Decenes (%)*	*Icosane*
None	3	58	15	16
PPh$_3$	15	50	7	7
DPEphos **192**	5	62	10	13
Xantphos **193**	51	31	2	10



DPEphos **192**

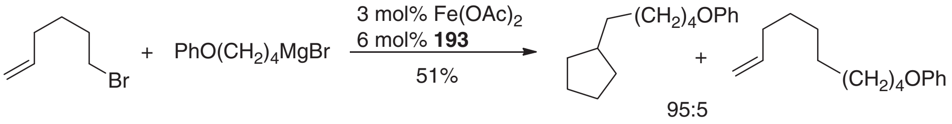


Xantphos **193**

Source: Reproduced from Dongol, K. G.; Koh, H.; Sau, M.; Chai, C. L. L. *Adv. Synth. Catal.* **2007**, *349*, 1015–1018, with permission from Wiley.

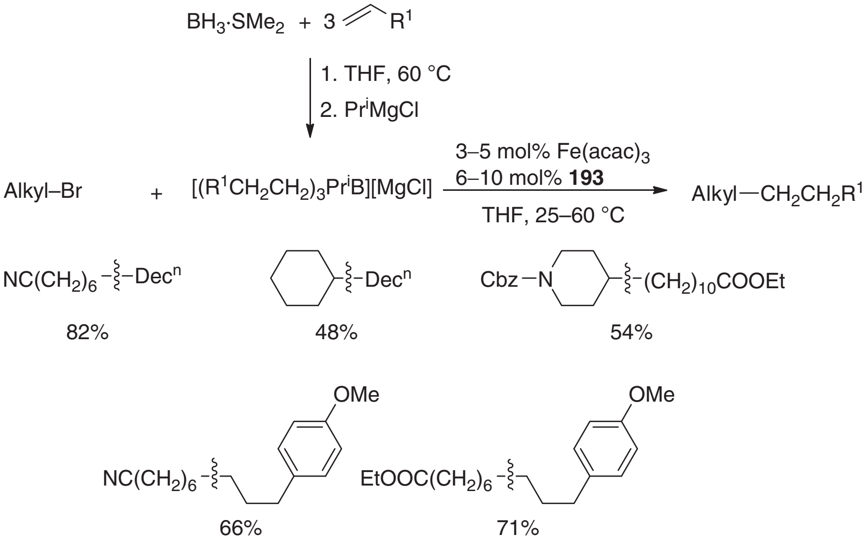
respectively, and only a 3% yield of the cross-coupling product was produced. Among the phosphine ligands examined, xantphos (**193**) gave the best result though the yield was still moderate (51%).

When 6-bromo-1-hexene was used as a substrate, cyclized coupling predominated over direct coupling in a ratio of 95:5, suggesting the formation of alkyl radical intermediates (equation 45).



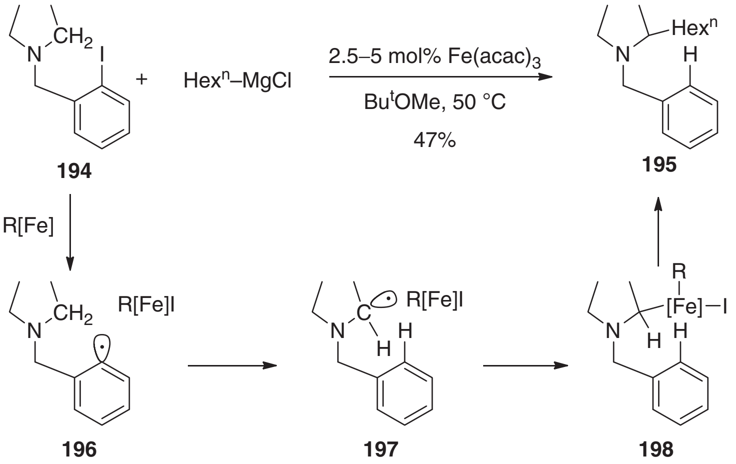
(45)

Iron–xantphos catalyst is also effective for alkyl–alkyl cross-coupling with trialkylboranes, when activated by a stoichiometric amount of ^{i}PrMgX as tetraalkylborates, which can be prepared by hydroboration of olefins followed by treatment with ^{i}PrMgCl (Scheme 80).[284]



Scheme 80

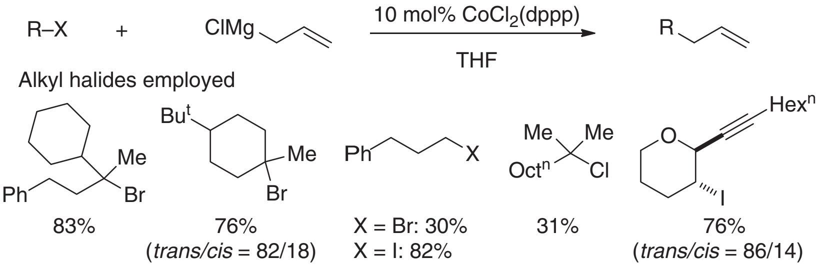
When an aryl halide **194** having a tertiary amine group at an appropriate position was subjected to Fe-catalyzed cross-coupling with an alkyl Grignar reagent, alkylation at a methylene carbon with C(sp^3)–H bond cleavage proceeded. This reaction would be triggered by SET from Fe catalyst to **194** giving rise to aryl radical **196**. Subsequent 1,5-hydrogen shift followed by recombination with Fe and reductive elimination forms **195** (Scheme 81).[285]



Scheme 81

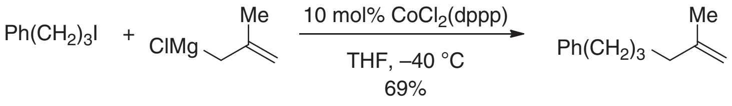
3.07.4.6 Cobalt Catalysts

Cobalt-catalyzed coupling reaction has a long history[286] since Kharasch utilized a Co salt as a catalyst for cross- and homocoupling reactions.[136,287] However, the utilization of a Co catalyst for the sp^3–sp^3 cross-coupling is rare, presumably due, in part, to the fact that it is a good electron transfer reagent.[288] Oshima et al. found that Co complexes having a bidentate phosphine ligand, 1,3-bis (diphenylphosphino)propane (DPPP), were effective for the allylation and benzylation of secondary and tertiary alkyl halides. As shown in Scheme 82, various sterically hindered alkyl halides worked successfully though primary bromides and tertiary chlorides gave lower yields.[288–290]

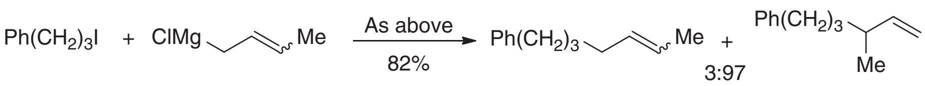


Scheme 82

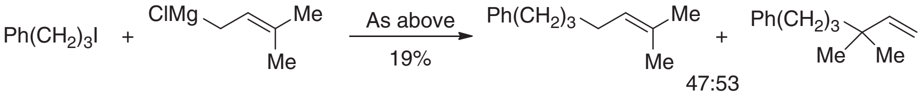
Methallyl Grignard reagent also produced the cross-coupling product in 69% yield (equation 46). The introduction of a methyl group at the terminal carbon exerted little effect on the reactivity, although 3% of the regioisomer was formed (equation 47). When two methyl groups were introduced at the terminal carbon, the yield decreased drastically to 19% giving a mixture of regioisomers in nearly a 1:1 ratio (equation 48).



(46)

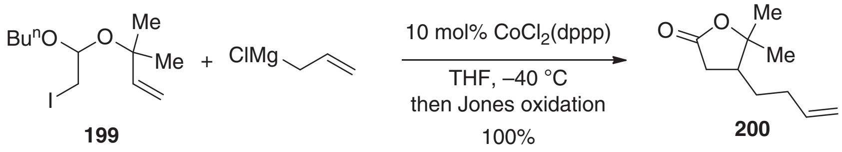


(47)



(48)

As this catalytic allylation includes alkyl radical intermediacies, radical cyclization/cross-coupling sequence is possible. Thus, the allylation of alkyl iodide **199** having terminal olefin group afforded 5-*exo* cyclized product **200** in an excellent yield (equation 49).



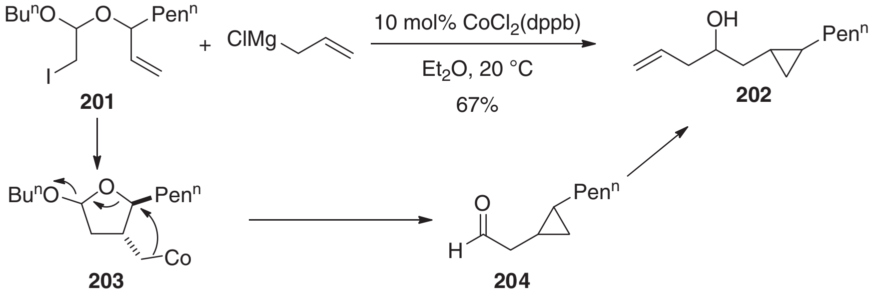
(49)

Interestingly, when a similar reaction was carried out in Et_2O, cyclopropane derivative **202** was formed instead of a five-membered ring. This product may arise along a reaction pathway as depicted in Scheme 83.[290]

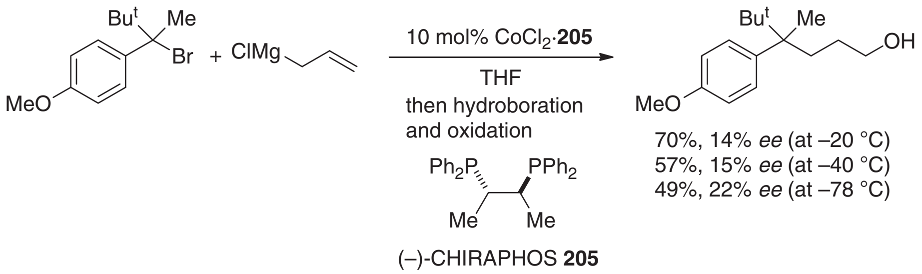
When chiral diphosphine, (−)-chiraphos (**205**), was used instead of DPPP, chiral induction was observed, albeit with low enantioselectivities (Scheme 84).[290]

Cobalt-catalyzed sequential cyclization/cross-coupling reaction of 6-halo-1-hexenes with silylmethylmagnesium halides was furnished by the use of *N*-heterocyclic carbene ligand **168**. As shown in Scheme 85, this reaction proceeds efficiently under mild conditions to provide various cyclic systems having silyl group, which can be transferred into hydroxyl group by oxidation.[291,292]

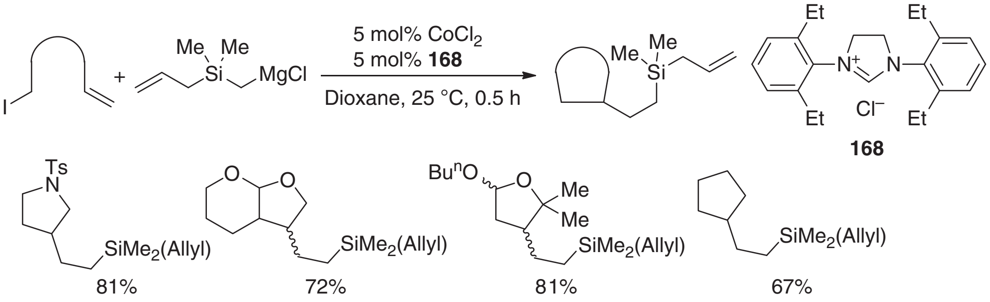
This catalytic system could be applied to simple alkyl iodides giving rise to the corresponding organosilanes in good yields (equation 50).[292]



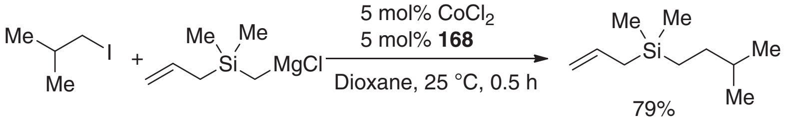
Scheme 83



Scheme 84



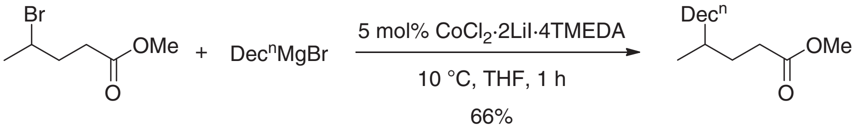
Scheme 85



(50)

Cahiez reported that a Co-catalyzed system can be successfully applied to the cross-coupling of alkyl Grignard reagents having a β-hydrogen(s) by the combined use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and LiI or MgI_2 salt. Under mild conditions, secondary alkyl bromides and iodides coupled with primary alkyl Grignard reagents efficiently, although the use of tertiary alkyl bromides and/or secondary and tertiary alkyl Grignard reagents resulted in low yields. In the latter case, reduction and β-hydrogen elimination of alkyl bromides predominated (Table 11).[293]

As the Co-catalyzed reaction is rapid under mild conditions, functional groups such as ketone, ester, and nitrile can survive in this catalytic system (equation 51).



(51)

Table 11 Co-catalyzed Kumada–Tamao–Corriu cross-coupling

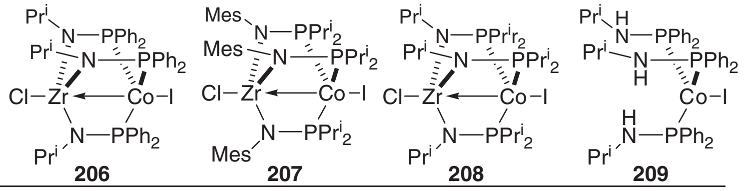
$$\text{R–X} \quad + \quad \text{R'MgBr} \xrightarrow[10\ ^\circ\text{C, THF, 1 h}]{5\ \text{mol\% CoCl}_2\cdot 2\text{LiI}\cdot 4\text{TMEDA}} \text{R–R'}$$

R–X	*R′MgBr*	*Yield (%)*
Bu^sCl	Dec^nMgBr	<1
Bu^sBr	Dec^nMgBr	79
Bu^sI	Dec^nMgBr	75
Pen^nBr	Oct^nMgBr	96
Pen^tBr	Oct^nMgBr	0
Dec^nBr	Bu^sMgBr	20
Dec^nBr	Bu^tMgBr	0

Source: Reproduced from Cahiez, G.; Chaboche, C.; Duplais, C.; Giulliani, A.; Moyeux, A. *Adv. Synth. Catal.* **2008**, *350*, 1484–1488, with permission from Wiley.

Zr–Co heterobimetallic complexes (**206–208**) were found to be effective for the cross-coupling of unactivated primary and secondary alkyl chlorides with alkyl Grignard reagents. As the monometallic Co complex, $ICo(Ph_2PNH^iPr)_3$ (**209**), showed no catalytic activity toward the coupling of alkyl chlorides, Zr was proposed to participate in the catalysis via Zr–Co interactions (Scheme 86).[294]

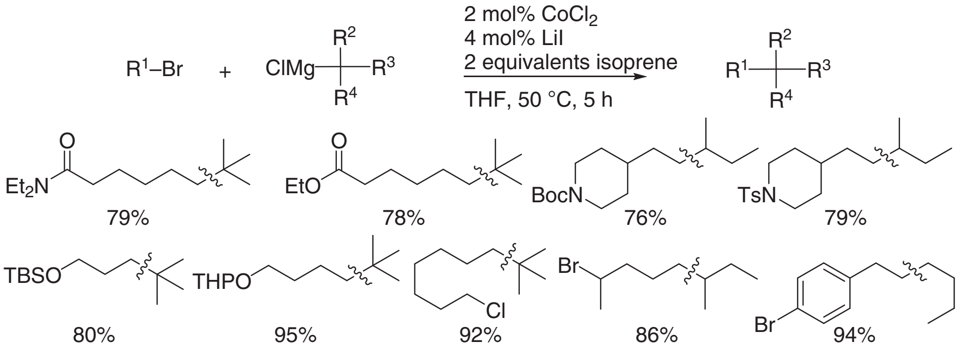
$$\text{R–Cl} \quad + \quad \text{Oct}^n\text{–MgBr} \xrightarrow[\text{THF, r.t.}]{\substack{5\ \text{mol\% cat.} \\ 30\ \text{mol\% TMEDA}}} \text{R—Oct}^n$$



R–Cl	Yield (%)	Yield (%)	Yield (%)	Yield (%)
Bu^nCl	28	46	77	Trace
CyCl	38	56	78	Trace

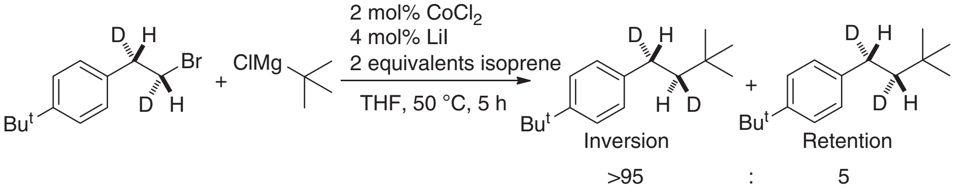
Scheme 86

Recently, a new catalytic system consisting of $CoCl_2$, LiI, and a conjugated diene like 1,3-butadiene or isoprene was reported to efficiently catalyze cross-coupling of alkyl halides with alkyl Grignard reagents.[295] It was demonstrated that not only primary and secondary alkyl Grignard reagents but also tertiary alkyl Grignard reagents can be employed as the coupling partner creating quaternary carbon centers and that various functionalities such as acetal, silyl ether, amide, and ester were well tolerated. Chemoselective cross-coupling of primary alkyl bromide over alkyl chloride, secondary alkyl bromide, and aryl bromide was achieved (Scheme 87).



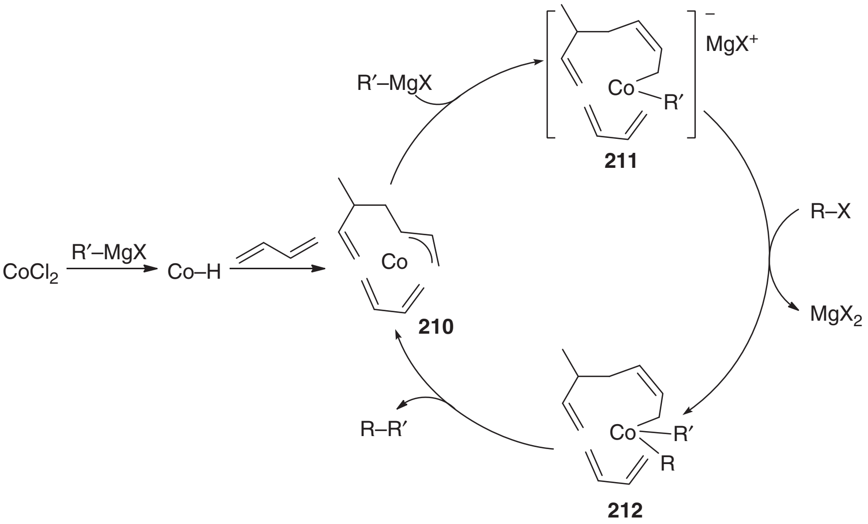
Scheme 87

Control experiments suggested that this reaction proceeds by an ionic mechanism with net inversion of stereochemistry at the reaction site of alkyl halides (equation 52). This feature is in large contrast to the radical mechanisms of the aforementioned Co catalysts.



(52)

A catalytic cycle shown in Scheme 88 was proposed, in which CoCl$_2$ is initially reduced to Co(I) by alkyl Grignard reagents and gives a complex **210** by the reaction with 1,3-diene.[296–298] Complex **210** readily reacts with Grignard reagents to form an anionic complex **211**, which attacks alkyl halides to give a coupling product directly or through complex **212** via an S$_N$2 mechanism.



Scheme 88

For related chapters in this Comprehensive, you can refer to – Chapter 3.04.

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3.08 Coupling Reactions Between sp^3 and sp^2 Carbon Centers

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3.08.1	**Introduction**	393
3.08.2	**Copper-Catalyzed or -Mediated Coupling Reactions**	393
3.08.2.1	Coupling Reactions with Alkyl Halides and Related Electrophiles	394
3.08.2.1.1	Copper-mediated coupling reactions	394
3.08.2.1.2	Copper-catalyzed coupling reactions	395
3.08.2.2	Coupling with Allyl Halides and Related Electrophiles	399
3.08.2.3	Coupling with Aryl and Alkenyl Halides	403
3.08.2.4	Coupling with Acyl Halides and Related Electrophiles	405
3.08.3	**Palladium-Catalyzed Coupling Reactions**	405
3.08.3.1	Coupling Reaction with Nonactivated Alkyl Halides and Related Electrophiles	406
3.08.3.1.1	Cross-coupling reactions with Grignard reagents	406
3.08.3.1.2	Cross-coupling reactions with organozinc and -zirconium reagents	410
3.08.3.1.3	Cross-coupling reactions with organotin reagents	410
3.08.3.1.4	Cross-coupling reactions with organoboron reagents	412
3.08.3.1.5	Cross-coupling with organosilicon reagents	412
3.08.3.2	Coupling with Activated Alkyl Halides and Related Electrophiles	412
3.08.3.2.1	Coupling with benzyl halides and related electrophiles	412
3.08.3.2.2	Coupling with α-halosulfoxides	414
3.08.3.2.3	Coupling with allyl halides and related electrophiles	414
3.08.3.3	Coupling with Aryl and Alkenyl Halides	416
3.08.3.3.1	Cross-coupling reactions with Grignard reagents	417
3.08.3.3.2	Cross-coupling with organozinc reagents	418
3.08.3.3.3	Cross-coupling with organoboron reagents	420
3.08.3.3.4	Cross-coupling with organotin reagents.	426
3.08.3.3.5	Cross-coupling with organosilicon reagents	426
3.08.3.3.6	Cross-coupling with organoindium reagents	429
3.08.3.4	Coupling with Acyl Halides and Related Electrophiles	430
3.08.4	**Nickel-Catalyzed Coupling Reactions**	430
3.08.4.1	Coupling Reaction with Nonactivated Alkyl Halides and Related Electrophiles	431
3.08.4.1.1	Cross-coupling reactions with Grignard reagents	432
3.08.4.1.2	Cross-coupling reactions with organozinc reagents	432
3.08.4.1.3	Cross-coupling reactions with organotin reagents	432
3.08.4.1.4	Cross-coupling with organoboron reagents	432
3.08.4.1.5	Cross-coupling with organosilicon reagents	433
3.08.4.2	Coupling Reactions with Activated Alkyl Halides and Related Electrophiles	433
3.08.4.2.1	Coupling with benzyl halides and related electrophiles	433
3.08.4.2.2	Coupling with allyl halides and related electrophiles	434
3.08.4.2.3	Cross-coupling with α-halocarbonyl compounds	434
3.08.4.2.4	Cross-coupling with other activated electrophiles	436
3.08.4.3	Coupling with Aryl and Alkenyl Halides	438
3.08.4.3.1	Cross-coupling with organomagnesium reagents	438
3.08.4.3.2	Cross-coupling with organozinc reagents	440
3.08.4.4	Coupling Reactions with Acyl Halides and Related Electrophiles	442
3.08.5	**Cobalt-Catalyzed Coupling Reactions**	442
3.08.5.1	Coupling Reactions with Nonactivated Alkyl Halides	443
3.08.5.1.1	Cross-coupling with alkenylmagnesium reagents	444
3.08.5.1.2	Cross-coupling with arylmagnesium reagents	445
3.08.5.2	Coupling Reactions with Activated Alkyl Halides and Related Electrophiles	445
3.08.5.3	Coupling Reactions with Aryl and Alkenyl Halides	447
3.08.5.3.1	Cross-coupling with alkenyl halides	447
3.08.5.3.2	Coupling with aryl halides	448
3.08.5.4	Coupling Reactions with Acyl Halides	450
3.08.6	**Iron-Catalyzed Coupling Reactions**	451
3.08.6.1	Coupling Reactions with Nonactivated Alkyl Halides	453

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3.08.6.1.1 Cross-coupling with organomagnesium reagents 453
3.08.6.1.2 Cross-coupling with organoaluminum and -zinc reagents 454
3.08.6.2 Coupling with Activated Alkyl Halides. 456
3.08.6.3 Coupling with Aryl and Alkenyl Halides 456
3.08.6.3.1 Cross-coupling reactions with alkenyl halides and related electrophiles 456
3.08.6.3.2 Cross-coupling reactions with aryl halides and related electrophiles 458
3.08.6.4 Coupling with Acyl Halides 459
References 460

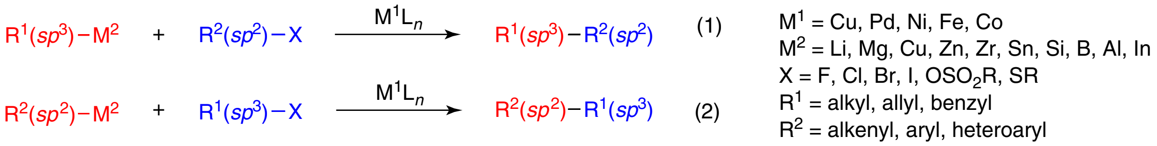
Glossary

Cross-coupling	A carbon–carbon bond-forming reaction between an organic electrophile and nucleophile.
***β*-Hydride elimination**	Elimination of a hydride from an adjacent carbon of a metal alkyl complex to form an alkene and a metal hydride complex.
Organometallic reagent	A chemical compound containing bonds between a metal and carbon.
Oxidative addition	The insertion of a metal or metal complex into a covalent bond, increasing the oxidation state of the metal center.
Reductive elimination	Reverse of oxidative addition. Dissociation of two ligands from the metal center, thereby forming a new covalent bond between those ligands and decreasing the oxidation state of the metal.

3.08.1 Introduction

The selective cross-coupling of two carbon centers is one of the most straightforward and efficient methods for carbon–carbon bond formation. In the last few decades transition metal-catalyzed cross-coupling reactions of organometallic reagents and organic electrophiles have emerged as a powerful synthetic tool for this purpose, allowing the construction of complex structures from simple building blocks.[1–4] These methods have profoundly changed the protocols for the small- and large-scale synthesis of natural products, pharmaceuticals, agrochemicals, organic materials, and polymers.

This chapter describes cross-coupling reactions between organometallic reagents and organic electrophiles catalyzed or mediated by a transition metal complex or salt for the selective formation of a $C(sp^2)$–$C(sp^3)$ bond. The following two types of reactions will be covered: coupling reactions of $C(sp^3)$ organometallics with $C(sp^2)$ electrophiles (Scheme 1, equation 1) and coupling reactions of $C(sp^2)$ organometallics with $C(sp^3)$ electrophiles (Scheme 1, equation 2). A variety of transition metals such as copper, palladium, nickel, iron, cobalt, or others can be used for these cross-coupling reactions.[5–8]



Scheme 1 $C(sp^2)$–$C(sp^3)$ cross-coupling reactions.

Compared to straightforward $C(sp^2)$–$C(sp^2)$ and $C(sp^2)$–$C(sp)$ cross-couplings, reactions with $C(sp^3)$ organometallics or electrophiles have suffered from several serious problems. While coupling reactions of primary $C(sp^3)$ organometallics (equation 1) or coupling reactions with primary alkyl halides (equation 2) can be achieved efficiently, the use of secondary and tertiary alkyl halides or organometallics is still problematic, mainly due to *β*-hydride elimination. However, these problems can be circumvented by careful choice and (sometimes complex) combination of transition metal, ligand, organometallic reagent, and reaction conditions. Even catalytic asymmetric cross-coupling reactions with different organometallic reagents are now available.[9]

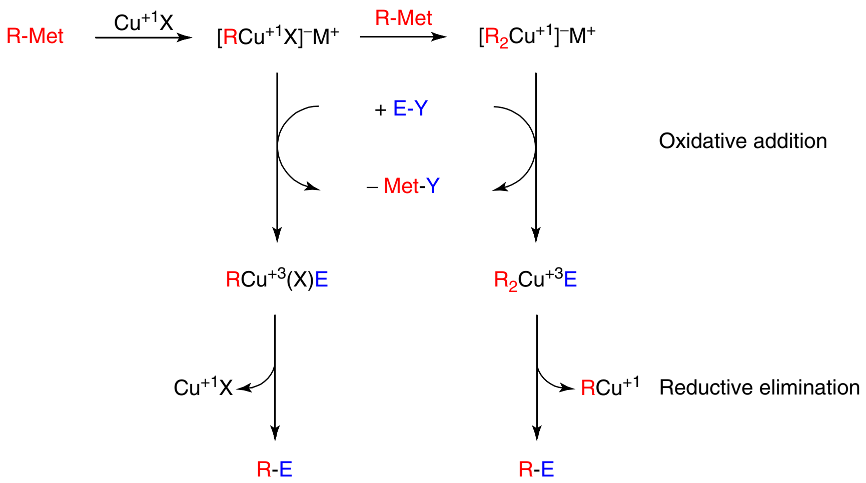
The field of transition metal-catalyzed cross-coupling reactions for the construction of $C(sp^2)$–$C(sp^3)$ bonds has grown tremendously in the last 20 years. A complete survey of this area would contain enough material for a book on its own. Therefore, this chapter focuses on the five transitions metals (Cu, Pd, Ni, Fe, and Co) mostly used for this task, with emphasis on synthetically useful procedures and their scope and limitations.

Furthermore, this section will focus on coupling reactions of preformed organometallic reagents with organic electrophiles bearing a suitable leaving group. Nucleophilic addition reactions to epoxides or aziridines, oxidative and reductive coupling reactions, and coupling reactions based on C–H activation are not covered.

3.08.2 Copper-Catalyzed or -Mediated Coupling Reactions

Organocopper(I) compounds and organocuprates are versatile reagents and are frequently used in organic synthesis.[10–12] These nucleophilic reagents are either used stoichiometrically (copper-mediated) or generated *in situ* from a catalytic amount of a suitable copper complex and a stoichiometric amount of an organometallic reagent. Depending on the exact structure of the organocopper compound, one can distinguish between simple organocopper reagents RCu and organocuprates such as R_2CuM (homocuprate), RCu(X)M (heterocuprate) ,or $R_nCu(X_m)M_y$ (higher-order cuprate), where R stands for an organic moiety (e.g., aryl, alkenyl, and alkyl), X for a nontransferable ligand (e.g., halide, cyanide, and thiocyanate), and M for a metal cation (e.g., Li^+, Mg^{2+}, and Zn^{2+}). The chemistry of nucleophilic organocopper compounds has been reviewed many times.[13–19] It is worth mentioning that the solvent and the nature of the ligands and the counterion have a huge effect on the reactivity of organocopper(I) compounds.

The general mechanism for C–C coupling reactions with nucleophilic organocopper(I) compounds is shown in **Scheme 2** and proceeds through a Cu(I)/Cu(III) redox sequence.[20,21] Reactions with stoichiometric organocopper reagents and catalytic processes proceed through the same three elementary steps. The first step is the transmetalation of an organometallic reagent with a copper(I) salt. For stoichiometric reactions, this step is typically transformed in a separate operation prior to the addition of the electrophile. Depending on the nature of the organometallic compound, the amount of copper(I) salt, and the presence of additives or additional ligands, either a mono- or a diorganocopper complex is formed. Regardless of the exact nature of the organocopper(I) compound, the next step, nucleophilic attack of a *d*-orbital of the copper(I)-complex on an electrophile, gives a copper(III) intermediate (oxidative addition). Decomposition (reductive elimination) of the copper(III) complex furnishes the product and a copper(I) species. In catalytic processes, this copper(I) species can enter the next catalytic cycle.



Scheme 2 General mechanism for C–C-coupling reactions with organocopper(I) compounds.

Copper-catalyzed or -mediated reactions are mostly limited to more reactive organometallic reagents, such as organolithium, -magnesium, or -zinc compounds.

3.08.2.1 Coupling Reactions with Alkyl Halides and Related Electrophiles

Today the copper-mediated or -catalyzed coupling of organolithium or Grignard reagents with alkyl halides is one of the most important reaction for C–C bond formation with $C(sp^3)$ electrophiles and is extensively used in synthesis. Especially for coupling reactions with primary alkyl halides, copper-mediated (stoichiometric amount of the copper reagent or salt) or -catalyzed (typically less than of a 20% copper salt) procedures are often the methods of choice.

3.08.2.1.1 Copper-mediated coupling reactions

The coupling between primary alkyl halides (**Table 1**, entries 1, 4, and 6–8) or tosylates (entries 2, 3, and 5) and aryl- (entries 1–5) or alkenylcopper (entries 6–8) reagents affords the $C(sp^2)–C(sp^3)$ coupling product, usually in good to excellent yields. In some cases, the right choice of the organocopper(I) reagent is crucial for obtaining good yields (entries 7 and 8).

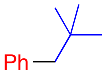
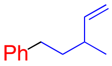
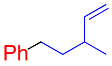
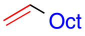
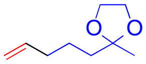
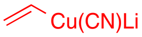
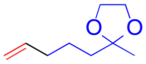
Functionalized arylcopper compounds also react with primary alkyl iodides (**Scheme 3**).[25] The aromatic copper reagent is prepared from corresponding aryl Grignard by transmetalation with $CuCN \cdot 2LiCl$. The addition of trimethyl phosphite is essential for obtaining high yields, as it leads to organocuprates, which are stable at 20 °C. This reaction shows a high chemoselectivity, and the polyfunctional products, bearing sensitive ester, amide, nitrile, or even keto groups, are isolated in very good yields.

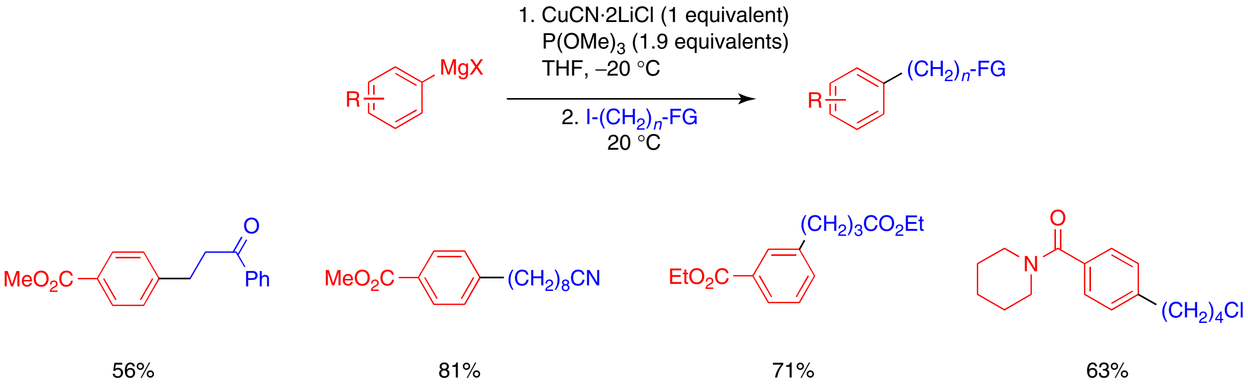
The coupling with nonactivated secondary alkyl halides is usually more challenging. Still aryl- (**Table 2**, entries 1–3) or alkenylcopper reagents (entries 4 and 5) react with secondary alkyl halides (entries 2–5) or tosylates (entry 1). The yield of the coupling product strongly depends on the combination of the leaving group of the alkyl halide and the nature of the copper(I) reagent (compare entries 1 and 2 or entries 4 and 5).

An important aspect of the coupling of organocopper(I) compounds with secondary alkyl halides is the stereochemistry of this reaction. The alkylation of Ph_2CuLi with secondary alkyl bromides[22] or tosylates[23] takes place with inversion of configuration (**Scheme 4**, equations 1 and 2) in agreement with a typical S_N2 reaction, while the reaction of a secondary alkyl iodide[27] leads to a racemic product (**Scheme 4**, equation 3).

Table 1 Cross-coupling between aryl- and alkenylcopper(I) compounds and primary alkyl halides and tosylates

$$\text{Alk-X} + \text{R-[Cu]} \longrightarrow \text{Alk-R}$$

Entry	*X*	*R-(Cu)*	*Product*	*Yield (%)*	*References*
1	I	Ph_2CuLi	Ph–Oct	99	22
2	OTs	Ph_2CuLi	Ph–Oct	81	23
3	OTs	Ph_2CuLi		80	23
4	Br	$Ph_2Cu(CN)Li$		91	24
5	OTs	$Ph_2Cu(CN)Li$		95	24
6	I			95	22
7	Cl			7	24
8	Cl			58	24



Scheme 3 Copper-mediated alkylation of functionalized aryl Grignard reagents.

3.08.2.1.2 Copper-catalyzed coupling reactions

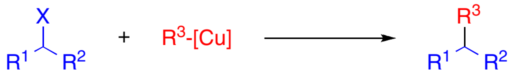
Drawbacks of the above-described copper-mediated coupling reactions are the use of excess amounts of the copper(I) salts and organometallic reagents and the thermal instability of organocopper(I) compounds. Therefore, copper-catalyzed methods offer an attractive and more economical alternative. Especially for the coupling with primary alkyl halides, copper-catalyzed procedures lead to similar (Scheme 5)[22,28] or even better yields (Scheme 6),[28] while the amount of organometallic reagent can be reduced drastically (from 4 to 1.2–1.4 equivalents).

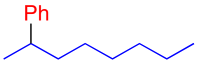
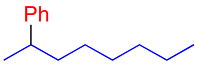
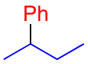
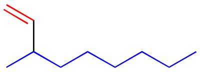
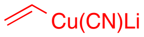
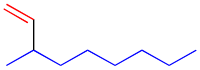
The coupling between arylmagnesium or -lithium reagents and primary alkyl halides can be achieved efficiently with different readily available copper salts, such as CuCl, CuBr, CuI, CuCN, CuCN · LiCl, $CuCl_2$, or Li_2CuCl_4 (Kochi catalyst), typically with less than 5 mol% of the catalyst. Several representative examples are shown in Table 3. Aryl Grignard can be coupled with primary alkyl halides (entries 2–5) or tosylates (entry 1). These reactions show some chemoselectivity. Chloro substituent (entry 4) or cyano group (entry 5) are tolerated. Secondary alkyl halide gives, in general, poor results (entry 6). In the presence of suitable copper catalyst, aryllithium compounds react with primary alkyl bromide (entry 7) or even chloride (entry 8), furnishing the coupling products in high yields.

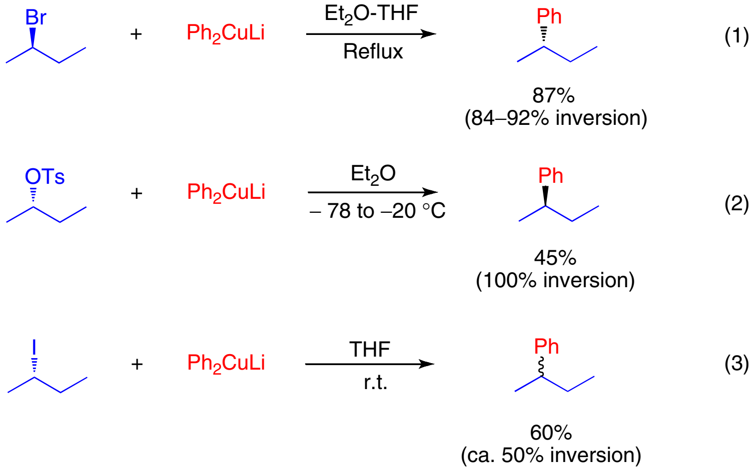
For the alkylation of Grignard reagents bearing sensitive functionalities, higher catalyst loadings are necessary (Scheme 7).[25] In the presence of 20 mol% CuCN · 2LiCl, the alkylation products are obtained in good yields. Ester or cyano groups are tolerated under these conditions. However, better yields are obtained with stoichoimetric amounts of CuCN · 2LiCl (Scheme 3).

Alkenylmetal compounds react in a similar manner (Table 4). Alkenyl Grignard reagents can be alkylated with primary alkyl halides (entries 1–2 and 4) or tosylates (entries 3 and 5). In some cases, a slight isomerization of the double bond is observed

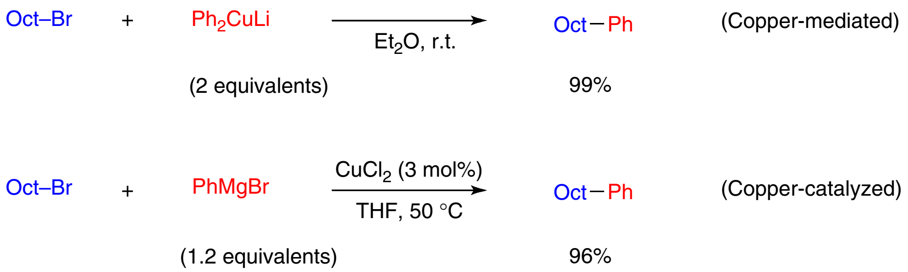
Table 2 Cross-coupling between aryl- and alkenylcopper(I) compounds and secondary alkyl halides and tosylates



Entry	*X*	*R^3-(Cu)*	*Product*	*Yield (%)*	*References*
1	OTs	Ph_2CuLi		60	23
2	I	$Ph_2Cu(CN)Li$		7	26
3	Br	Ph_2CuLi		87	22
4	I			23	26
5	I			90	26



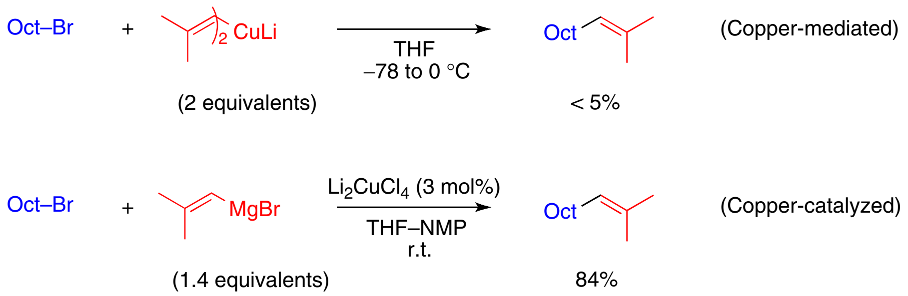
Scheme 4 Stereoselectivity for the alkylation of Ph_2CuLi with secondary alkyl halides.



Scheme 5 Copper-mediated or -catalyzed phenylation of octyl bromide.

(entry 4). Alkenyllithium reagents couple efficiently with primary alkyl bromides (entries 6 and 7), and a chloro substituent is tolerated under these conditions (entry 7).

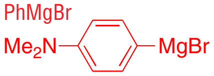
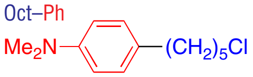
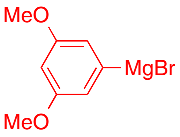
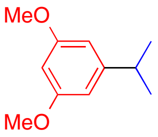
Copper-catalyzed cross-coupling reactions are usually limited to the more reactive alkyl bromides, iodides, or tosylates as electrophilic coupling partner. However, in the presence of 1-phenylpropyne as additive, phenylmagnesium bromide reacts with less reactive alkyl chlorides or even alkyl fluorides (Scheme 8).[34]

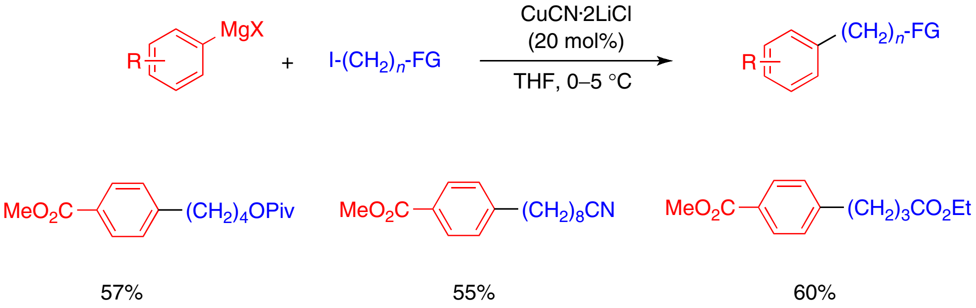


Scheme 6 Copper-mediated or -catalyzed alkenylation of octyl bromide.

Table 3 Copper-catalyzed coupling between alkyl halides and aromatic organometallic reagents

$$\text{Alk-X} + \text{Ar-Met} \xrightarrow{\text{Cu-catalyst}} \text{Alk-Ar}$$

Entry	*Alk–X*	*Ar–Met*	*Catalyst (mol%)*	*Product*	*Yield (%)*	*References*
1	Et–OTs	PhMgBr	Li_2CuCl_4 (0.5)	Et–Ph	90	29
2	Oct–Br	PhMgBr	Li_2CuCl_4 (3)	Oct–Ph	70	28
3	Oct–Br	PhMgBr	$CuCl_2$ (3)	Oct–Ph	96	30
4	$Cl(CH_2)_5$–Br		$CuCl_2$ (3)		93	30
5		PhMgBr	$CuCl_2$ (3)		83	30
6	*i*-PrI		Li_2CuCl_4 (3)		16	31
7	Oct–Br	PhLi	$CuCl_2$ (3)	Oct–Ph	95	30
8	Oct–Cl	PhLi	$CuCl_2$ (3)	Oct–Ph	70	30



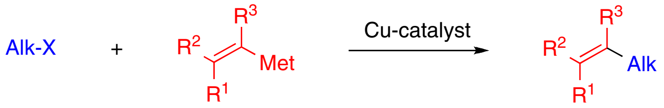
Scheme 7 Copper-catalyzed alkylation of functionalized arylmagnesium reagents.

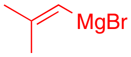
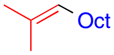
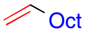
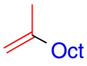
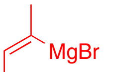
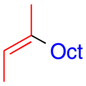
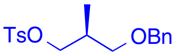
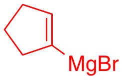
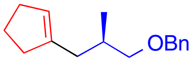
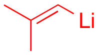
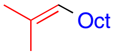
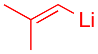
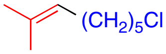
More reactive benzyl halides are excellent coupling partners, and the copper-catalyzed benzylation of aryl Grignard is a useful method for the construction of the diarylmethane framework. Thus, functionalized organomagnesium reagents react with aryl bromides in the presence of CuCN · 2LiCl, providing the diarylmethanes in good yields (Scheme 9).[25]

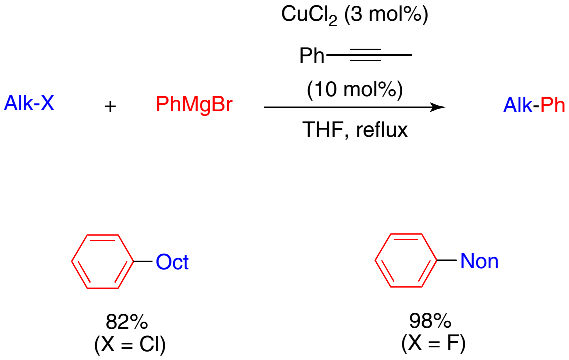
The copper-catalyzed cross-coupling reaction of arylmagnesium reagents with benzylic phosphates leads to diarylmethanes or heterocyclic analogs in good to excellent yields (Scheme 10).[35]

Copper-catalyzed coupling reactions with nonactivated alkyl halides are usually restricted to reactive organometallic compounds, such as organolithium or Grignard reagents. However, there is one example of a copper-catalyzed reaction of arylboron reagents with primary alkyl halides or tosylates (Scheme 11).[36] Aryl or heteroaryl boronate esters can be alkylated in good yields with different primary alkyl electrophiles. This method complements palladium- and nickel-catalyzed procedures (see below).

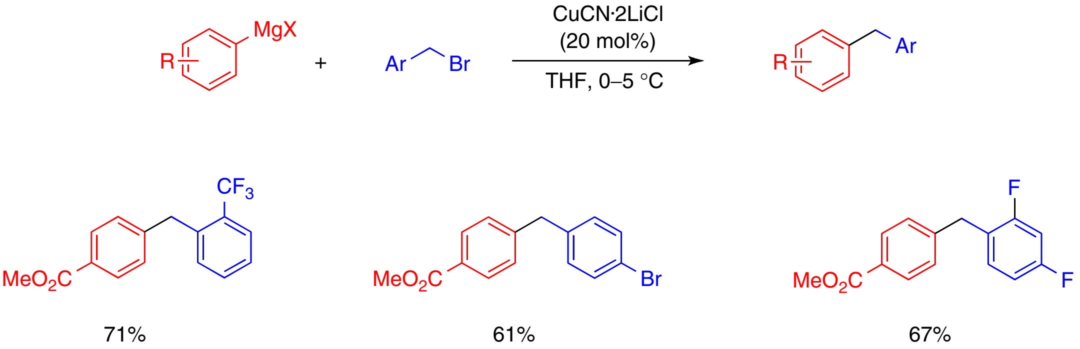
Table 4 Copper-catalyzed coupling between alkyl halides and alkenymetal reagents



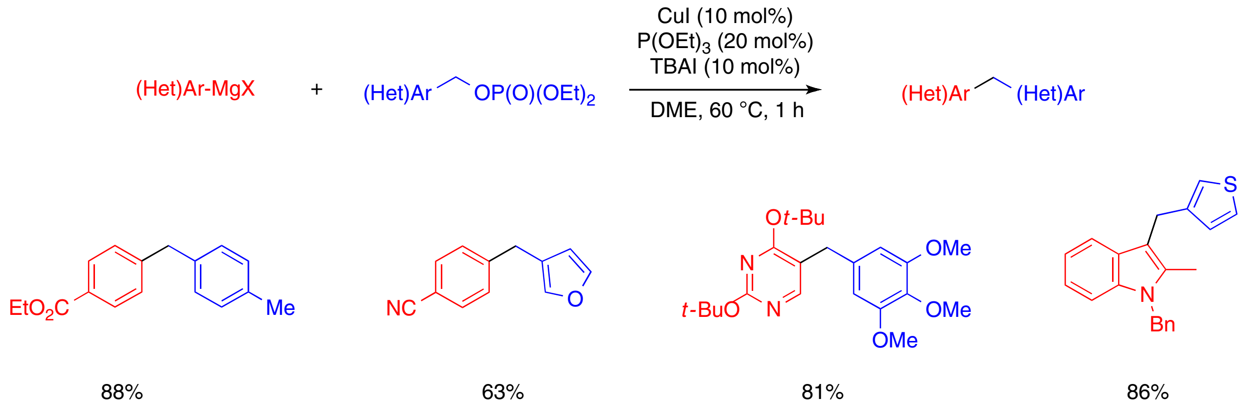
Entry	*Alk–X*	*R–Met*	*Catalyst (mol%)*	*Product*	*Yield (%)*	*References*
1	Oct–Br		Li_2CuCl_4 (3)		84	28
2	Oct–I		CuI (10)		82	32
3	Oct–OTs		CuI (10)		80	32
4	Oct–I	 (*E*/*Z*=10/90)	CuI (10)		96 (*E*/*Z*=12/88)	32
5			Li_2CuCl_4 (10)		90	33
6	Oct–Br		$CuCl_2$ (3)		97	30
7	$Cl(CH_2)_5$–Br		$CuCl_2$ (3)		95	30



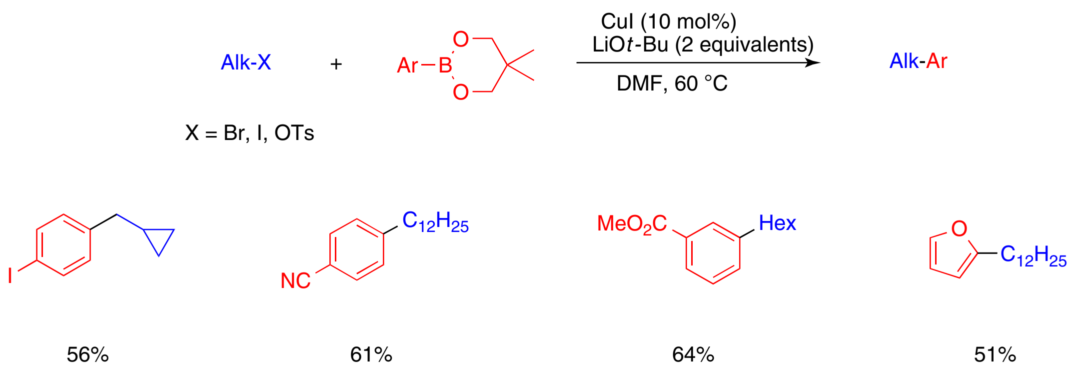
Scheme 8 Copper-catalyzed coupling of phenylmagnesium bromide with alkyl chlorides or fluorides.



Scheme 9 Copper-catalyzed benzylation of aryl Grignard reagents.



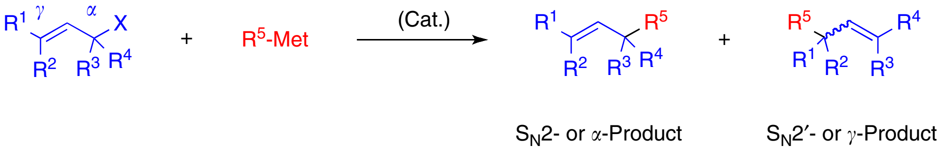
Scheme 10 Copper-catalyzed cross-coupling between arylmagnesium reagents and benzylic phosphates.



Scheme 11 Copper-catalyzed coupling of arylboron reagents with alkyl electrophiles.

3.08.2.2 Coupling with Allyl Halides and Related Electrophiles

Allylic alkylation is a valuable tool for organic synthesis. The most fundamental and important problem in the reaction between allylic electrophiles and organometallic reagents is the regio- and stereocontrol (Scheme 12). Copper-mediated or -catalyzed procedures are among the most important protocols for highly regio- and stereoselective allylic alkylation reactions.[10–12,37–39]

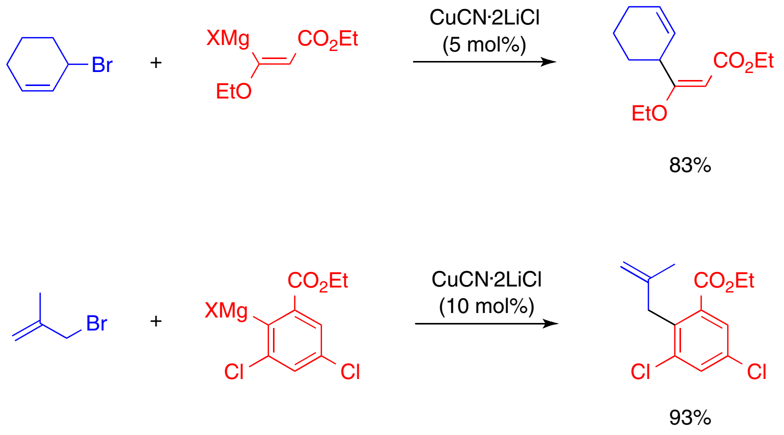


Scheme 12 Regio- and stereochemistry for reactions between allylic electrophiles and organometallic reagents.

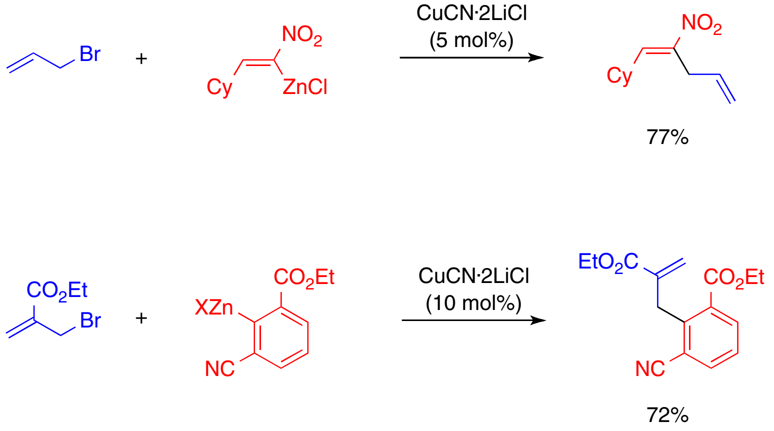
Copper-catalyzed allylation reactions between simple, symmetric allyl halides and various organometallic reagents are not affected by these selectivity problems and proceed very efficiently. Various alkenyl- or aryl organometallics, such as organomagnesium (Scheme 13) or organozinc reagents (Scheme 14) react with allyl bromides.[4,10–12,40,41] The yields are in general good to excellent and catalyst loadings as low as 5 mol% are sufficient.

Reactions with unsymmetrical allylic electrophiles are much more complicated. In general, copper-mediated or -catalyzed reactions proceed with high *anti*-selectivity, leading to the S_N2 or *anti* S_N2'-products, often with excellent transfer of chirality. *Syn*-selective S_N2' reactions can be achieved with copper-coordinating leaving groups.[42] Because several efficient asymmetric synthesis for allylic alcohols are available,[43] copper-mediated coupling reactions with enantioenriched allylic electrophiles are an important method for the construction of asymmetric tertiary or quaternary carbon centers (Scheme 15).

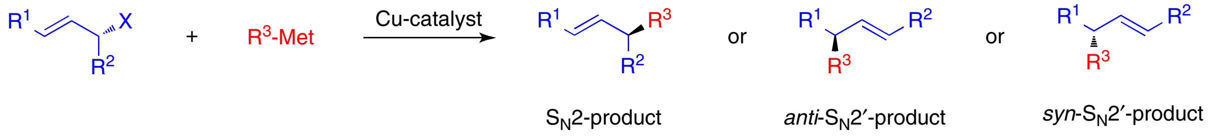
Monoorganocopper reagents react preferentially via the S_N2'-mechanism (Scheme 16, equation 1).[44,45] The regioselectivity of diorganocuprates depends on the choice of reagents, reaction conditions, and particularly on the substrate and leaving group



Scheme 13 Copper-catalyzed allylation of organomagnesium reagents.



Scheme 14 Copper-catalyzed allylation of organozinc reagents.



Scheme 15 Regio- and stereocontrol in the allylation of copper reagents.

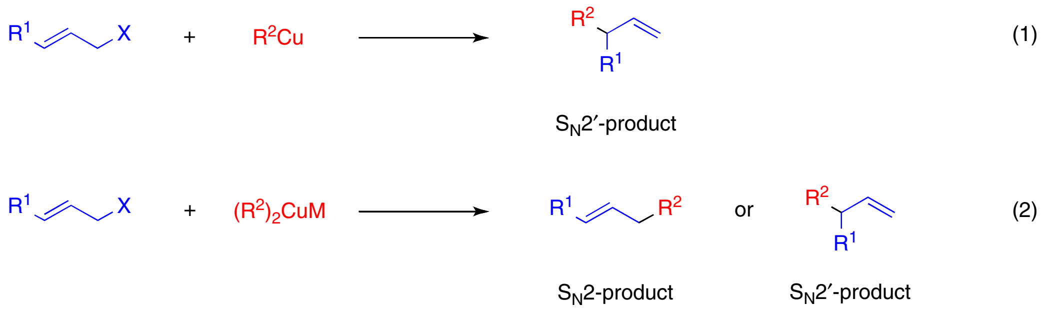
(Scheme 16, equation 2). Based on these facts, several highly regio- and stereoselective copper-mediated or -catalyzed allylation reactions have been developed. In some cases even complementary procedures or enantioselective variants exist.

Polyfunctional mixed lithium arylcuprates react with cyclic 2-iodoallylic acetates with high S_N2 selectivity (>98:2, Scheme 17).[46] The bulky neophyl group plays the role of a nontransferable ligand. The allylated products are obtained in high yields and with excellent enantioselectivities (>90% chirality transfer).

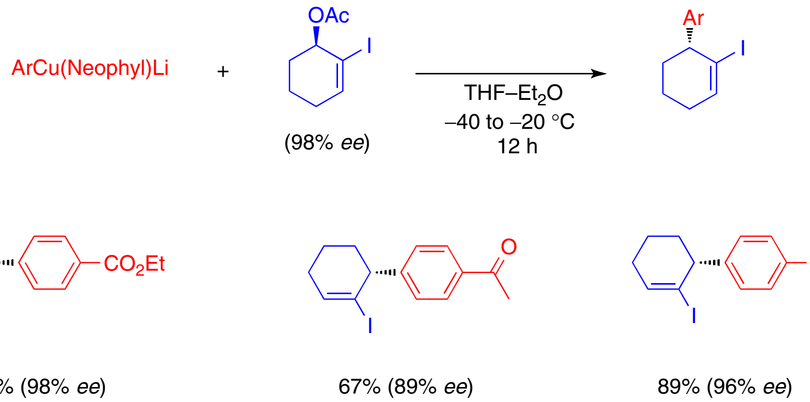
In the presence of zinc salts, the same diorganocuprates react with electrophiles bearing a pentafluorobenzoate leaving group via the *anti* S_N2' pathway.[46] Thus, the addition of 1 equivalent zinc bromide to the lithium arylcuprate leads to a highly stereoselective *anti* S_N2' substitution (Scheme 18). The high *anti* S_N2' selectivity is general for copper-mediated reaction of organozinc compounds with similar electrophiles.[47,48]

Two complementary methods exist for allylation with 4-cyclopenten-1,3-diol derivatives. Reaction between aryl or alkenyl Grignard and cyclic monoacetates in the presence of CuCN (0.3 equivalent) yields the S_N2 products in good yields and high regioselectivity (>90:10, Scheme 19).[49,50] The presence of stoichiometric amounts of chloride salts ($MgCl_2$ or LiCl) is crucial for obtaining high regioselectivities.

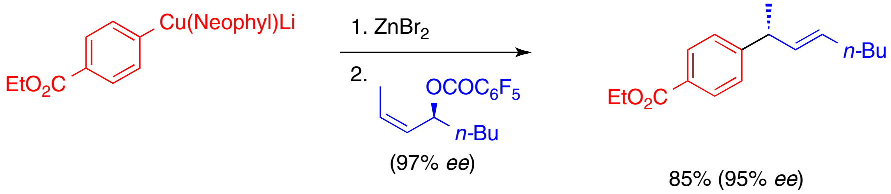
Using CuCl (30 mol%) as catalyst, 4-cyclopenten-1,3-diol derivatives bearing a methoxymonoacetate leaving group react with aryl- or alkenylzinc reagents with high *anti* S_N2' selectivity (>99:1, Scheme 20).[51]



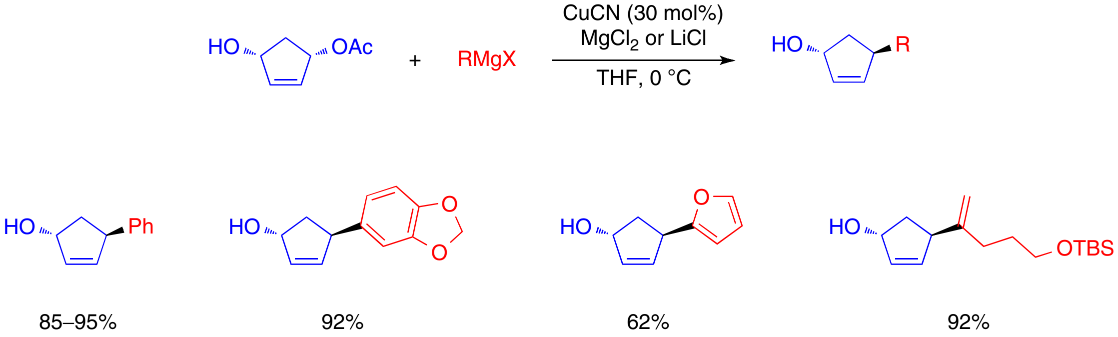
Scheme 16 Regiocontrol in the allylation of copper reagents.



Scheme 17 Stereoselective S$_N$2 substitution of cyclic 2-iodoallylic acetates with lithium diorganocuprates.

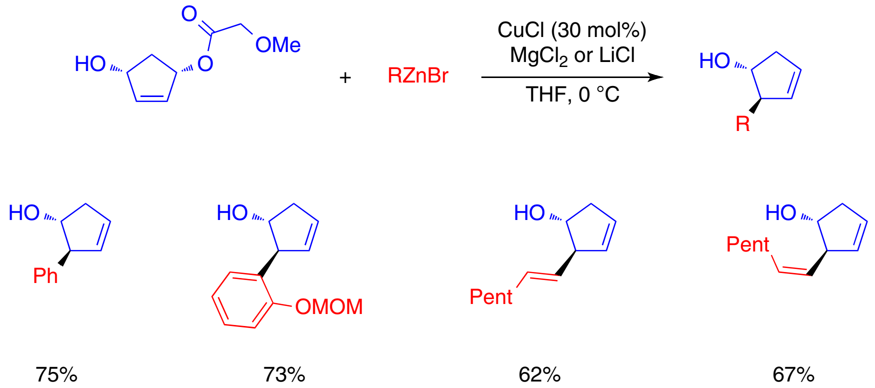


Scheme 18 Stereoselective anti S$_N$2′ Substitution of lithium diorganocuprates with chiral pentafluorobenzoate.



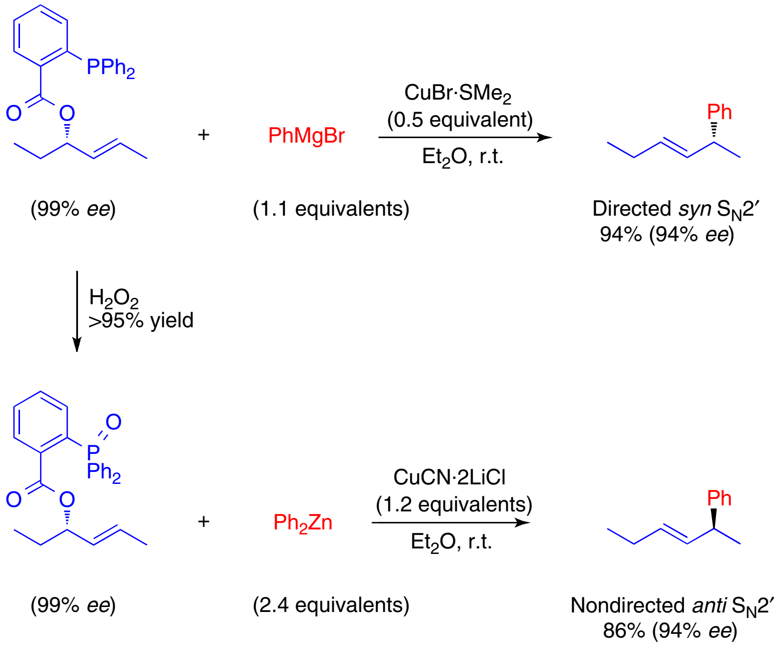
Scheme 19 Copper-catalyzed S$_N$2 substitution of 4-cyclopentene-1,3-diol monoacetate with Grignard reagents.

As mentioned before, *syn* S$_N$2′ substitution can be achieved in some cases with copper-coordinating leaving groups. Thus, the copper-coordinating *ortho*-diphenylphosphanylbenzoate (*o*-DPPB) leaving group leads to a highly selective directed *syn* S$_N$2′ substitution with phenylmagnesium bromide in the presence of CuBr · SMe$_2$ (Scheme 21). The reaction proceeds with excellent stereoselectivity (98:2) and chirality transfer.[52] Oxidation of phsophine to phosphine oxide (*o*-DPPB oxide) furnishes a



Scheme 20 Copper-catalyzed anti-S_N2' substitution with organozinc reagents.

nondirecting leaving group. Copper-mediated reaction of diphenylzinc with the *o*-DPPB oxide system gives the *anti* S_N2' product with high stereoselectivity and chirality transfer. This methodology enables the synthesis of both enantiomers starting from one substrate.



Scheme 21 Copper-mediated stereoselective and stereodivergent allylation reactions with the *o*-DPPB/*o*-DPPB-oxide system.

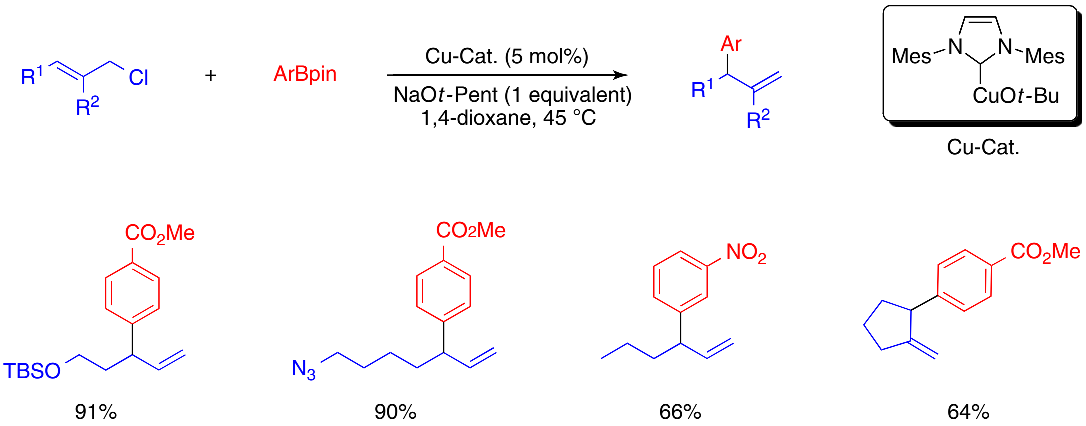
The copper-catalyzed allylic substitution is not limited to reactive organometallic reagents. Arylboronic esters react with allyl chlorides with high S_N2' selectivity using only 5 mol% of the *N*-heterocyclic carbene (NHC)–copper(I) catalyst (Scheme 22).[53] The reaction has a broad substrate scope, and a variety of sensitive functional groups are tolerated.

A similar copper-catalyzed coupling between allylic phosphates and arylboronic esters is also known (Table 5).[54] The reaction proceeds with high γ-*E*-selectivity and excellent *anti*-chirality transfer (Table 5, entry 4). Cyclic allylic phosphates also undergo efficient stereo- and regioselective coupling (Table 5, entry 5).

The copper-catalyzed asymmetric allylic alkylation is an important method for the synthesis of optically active molecules.[37–39] With alkyl nucleophiles, typically organomagnesium or -zinc reagents, excellent regio- and enantioselectivities can be obtained. In contrast, there are only a few reports on reactions with aryl- or vinyl nucleophiles with comparable selectivities.

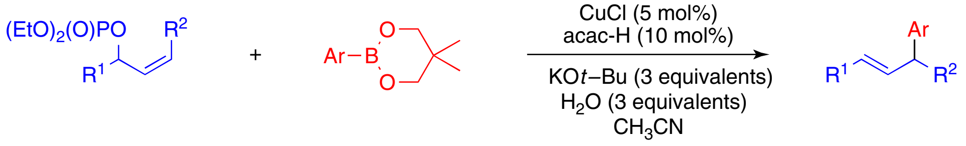
A highly regio- and enantioselective allylation of aryl Grignard reagents can be achieved with a monodentate chiral NHC–copper complex (Scheme 23).[55] The reaction gives the S_N2' product in high yields and enantioselectivities but is limited to cinnamyl bromides as coupling partners.

In the presence of copper(II) chloride and an NHC silver(I) complex (NHC–Ag), easily accessible vinylaluminum reagents couple with allylic phosphates (Table 6).[56,57] The reaction proceeds with high site- (>98% S_N2') and enantioselectivity. No

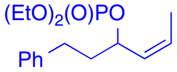
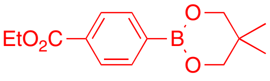
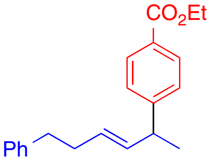
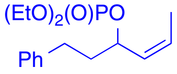
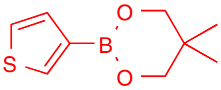
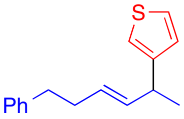
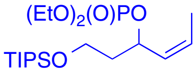
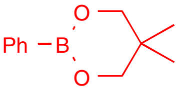
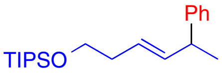
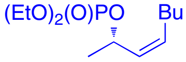
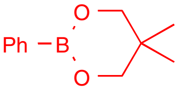
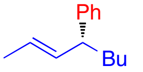
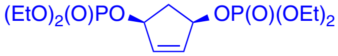
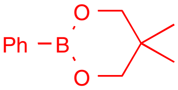
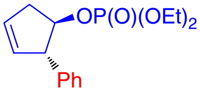


Scheme 22 Copper-catalyzed coupling between arylboronates and allyl chlorides.

Table 5 Copper-catalyzed coupling between allylic phosphates and arylboronates



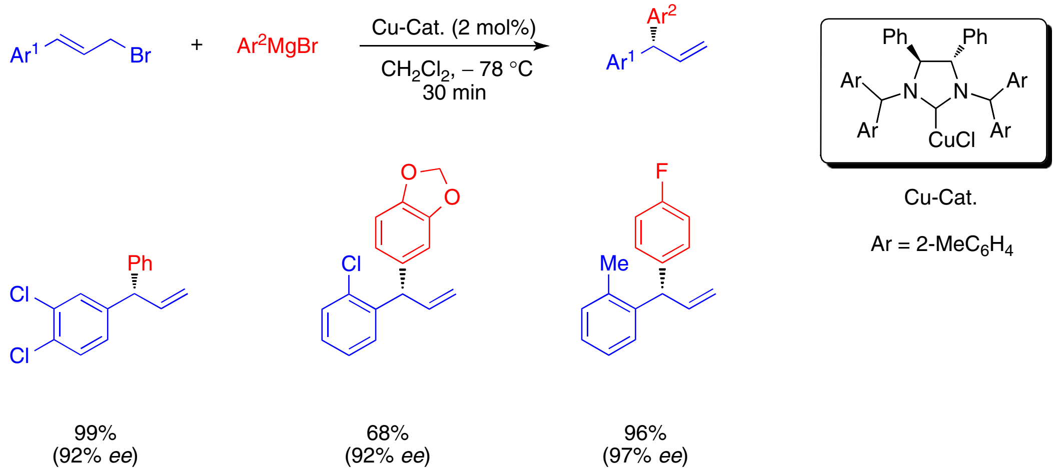
Acac-H = acetylacetone

Entry	*Phosphate*	*Boronate*	*Product*	*Yield (%)*
1				61
2				60
3				59
4	 (94% *ee*)		 (94% *ee*)	70
5				61

isomerization of the double bond from vinylaluminum reagent occurs. This method can be applied to the asymmetric synthesis of quaternary carbon centers bearing a vinyl moiety (Table 6, entries 4–6).

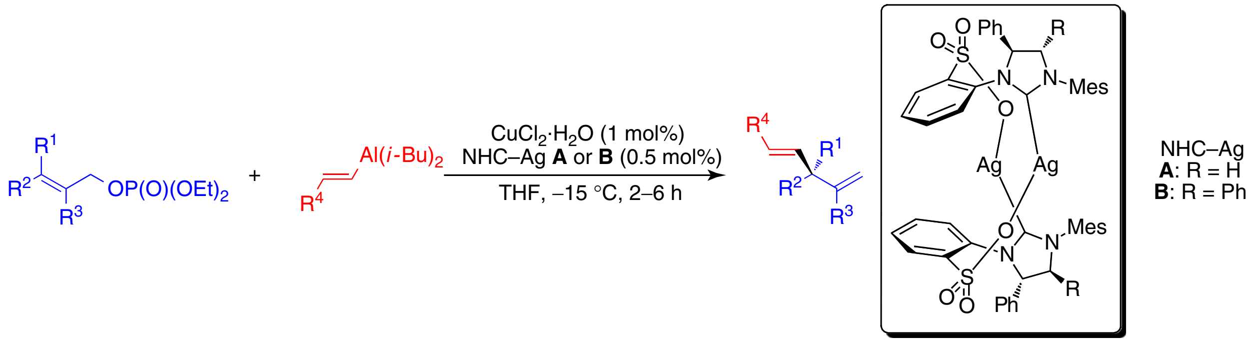
3.08.2.3 Coupling with Aryl and Alkenyl Halides

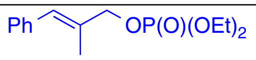
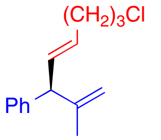
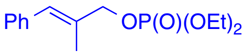
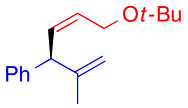
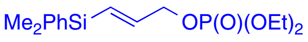
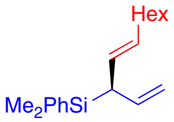
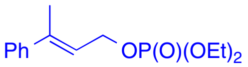
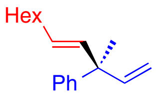
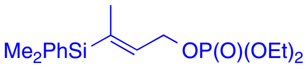
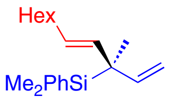
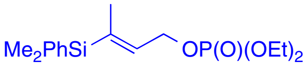
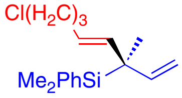
The copper-mediated nucleophilic substitution of alkenyl or aryl halides is of great historical value because it completely changed the approach to construct carbon–carbon bonds with nonactivated C(sp^2) centers. The first reports of substitution reactions on



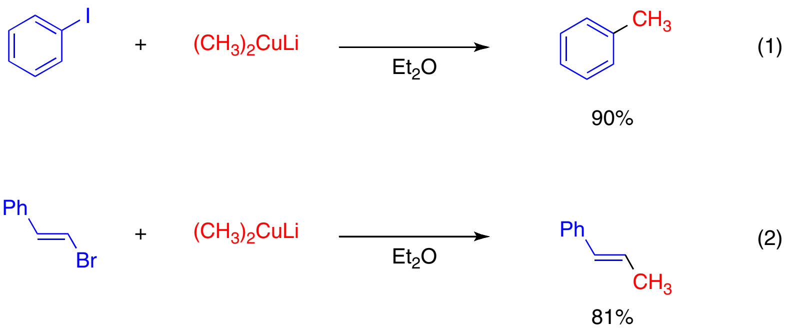
Scheme 23 Enantioselective allylation of aryl Grignard reagents.

Table 6 Regio- and enantioselective copper-catalyzed allylation of vinylaluminum reagents



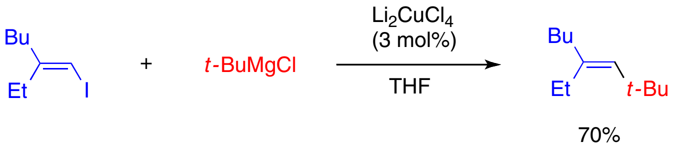
Entry	*Phosphate*	*Product*	*NHC–Ag*	*Yield (%)*	*ee (%)*	*References*
1			B	86	92	56
2			A	91	80	56
3			A	94	92	56
4			B	82	87	57
5			B	85	91	57
6			A	91	92	57

aryl iodides (Scheme 24, equation 1) and alkenyl bromides (Scheme 24, equation 2)[58,59] paved the way for the development of modern cross-coupling chemistry.[1–3] Nowadays, these 'modern' palladium-, nickel-, iron-, or cobalt-catalyzed cross-coupling reactions with nonactivated C(sp^2) electrophiles (e.g., aryl or alkenyl halides) are used, due to a higher efficiency and practicability, greater scope, and/or reduced costs and waste compared to copper-mediated or -catalyzed reactions.



Scheme 24 Reaction of Me$_2$CuLi with iodobenzene and bromostyrene.

Exceptions are cross-coupling reactions with sterically hindered tertiary alkyl nucleophiles, considered to be particularly difficult. In some cases, these couplings can be achieved efficiently with different copper catalysts. Thus, alkenyl iodides undergo coupling with *t*-BuMgCl in the presence of Kochi's catalyst Li_2CuCl_4, affording the trisubstituted olefin with retention of configuration (Scheme 25).[60]



Scheme 25 Copper-catalyzed cross-coupling of an alkenyl iodide.

Copper(I) iodide (3–10 mol%) catalyzes the cross-coupling of chloroazaheterocycles with tertiary alkyl Grignard reagents (Table 7).[61] Dichloroazaheterocycles are converted to the monoalkylated chloroazaheterocycles (Table 7, entries 1–3), whereas trichloroazaheterocycles can be selectively converted to either the mono-, di-, or trisubstituted product (entries 4–6).

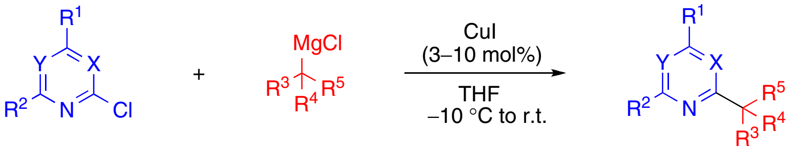
3.08.2.4 Coupling with Acyl Halides and Related Electrophiles

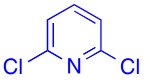
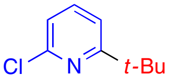
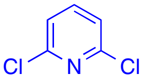
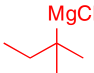
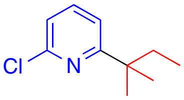
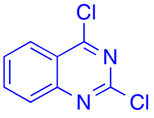
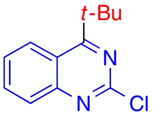
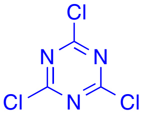
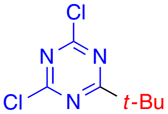
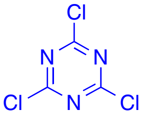
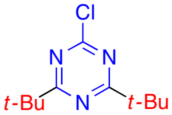
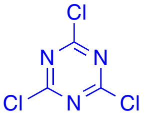
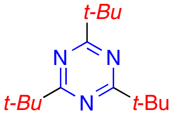
The cross-coupling of organocopper(I) reagents with acid chlorides is an important method for the synthesis of ketones, due to its broad applicability and functional group compatibility.[10–13,62] Since the first reported reaction between lithium diorganocuprates and acid chlorides,[63,64] a variety of copper-mediated acylations with various organometallic reagents and different copper(I) salts have been developed (Table 8).[65–70] Typically preformed organocuprates, prepared by transmetalation from different organometallic reagents, are used. Organolithium (entry 1), organomagnesium (entry 2), and mono- or diorganozinc (entries 3 and 4) reagents in combination with different copper(I) salts are suitable nucleophiles. In addition, thioesters (entry 5), acid anhydrides (entry 6), or ethyl cyanoformate (Mander's reagent, entry 7)[71] can be used as acyl electrophiles. Copper-catalyzed cross-coupling reactions are possible (typically 20–30 mol% copper; see entry 6). However, acylation reactions with preformed organocuprates are usually more reliable and afford better yields.

3.08.3 Palladium-Catalyzed Coupling Reactions

Palladium-catalyzed cross-coupling reactions have become one of the most important tools for synthetic organic chemistry.[1–4] Their relevance was recently acknowledged by the bestowal of the 2010 Chemistry Nobel prize 'for palladium-catalyzed cross-coupling in organic synthesis.' The Suzuki–Miyaura (with organoboron nucleophiles), Stille (organotin reagents), Negishi (organozinc, -zirconium, or -aluminum compounds), Kumada–Corriu (organomagnesium nucleophiles), or Hiyama–Denmark (silicon reagents) reactions, just to mention the most prominent coupling reactions, have found widespread applications in the synthesis of pharmaceuticals, agrochemicals, natural products, and materials.[72,73] Historically, the use of C(sp^3)-nucleophiles and/or nonactivated C(sp^3) electrophiles in palladium-catalyzed coupling reactions has suffered from several severe problems.[74–77] A closer examination of the general proposed mechanism for palladium-catalyzed cross-coupling reactions reveals

Table 7 Copper-catalyzed cross-coupling of tertiary Grignard reagents with chloroazaheterocycles



Entry	*Azacycle*	*Grignard*	*Product*	*Yield (%)*
1		*t*-BuMgCl (1.05 equivalents)		85
2		 (1.05 equivalents)		74
3		*t*-BuMgCl (1.05 equivalents)		92
4		*t*-BuMgCl (1.0 equivalent)		98
5		*t*-BuMgCl (2.5 equivalents)		83
6		*t*-BuMgCl (4.5 equivalents)		51

several possible side reactions, which have complicated the use of alkyl coupling partners, especially those bearing *β*-hydrogens (Schemes 26 and 27). The general catalytic cycle for metal-catalyzed cross-coupling reactions consists of three critical steps: (1) oxidative addition of a carbon–heteroatom bond into the transition metal, (2) transmetalation or ligand exchange of the leaving group by the organometallic reagent, and (3) reductive elimination from the diorgano-metal complex to form the new C–C bond and regenerate the active catalyst. The oxidative addition, which is proposed to be a nucleophilic substitution for palladium, is generally slow with C(sp^3) electrophiles, compared to the analogous addition to C(sp^2) or C(sp) electrophiles, which normally proceeds in a concerted manner. As shown in Schemes 2 and 3, slow oxidative addition leads to the formation of various side products. A slow transmetalation rate leads to competing *β*-hydride elimination and by-product formation. Additionally, slow reductive elimination also leads to competing *β*-hydride elimination and the formation of side products. In the case of strongly basic organometallic reagents, direct *β*-hydride elimination can also become an issue.

Despite all these issues, powerful palladium-catalyzed methods for the selective C(sp^2)–C(sp^3) bond formation are available.

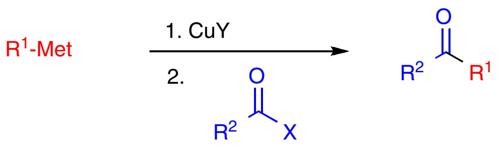
3.08.3.1 Coupling Reaction with Nonactivated Alkyl Halides and Related Electrophiles

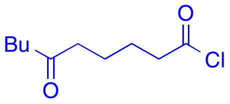
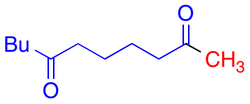
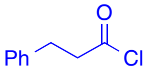
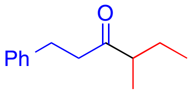
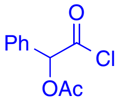
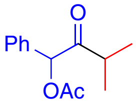
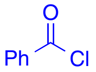
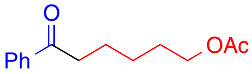
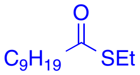
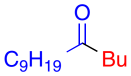
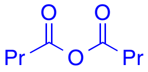
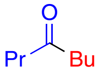
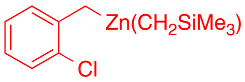
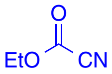
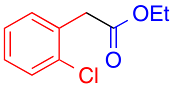
Originally, nonactivated alkyl halides containing *β*-hydrogens were regarded as unsuitable electrophiles for palladium-catalyzed coupling reactions. Since the pioneering report of a palladium-catalyzed cross-coupling between primary alkyl iodides and organoboranes, a variety of versatile methods based on palladium catalysis have been developed.[78] One major drawback of all palladium-catalyzed cross-coupling reaction with C(sp^2) electrophiles is the fact that nonactivated secondary alkyl halides or sulfonates are not suitable coupling partners.

3.08.3.1.1 Cross-coupling reactions with Grignard reagents

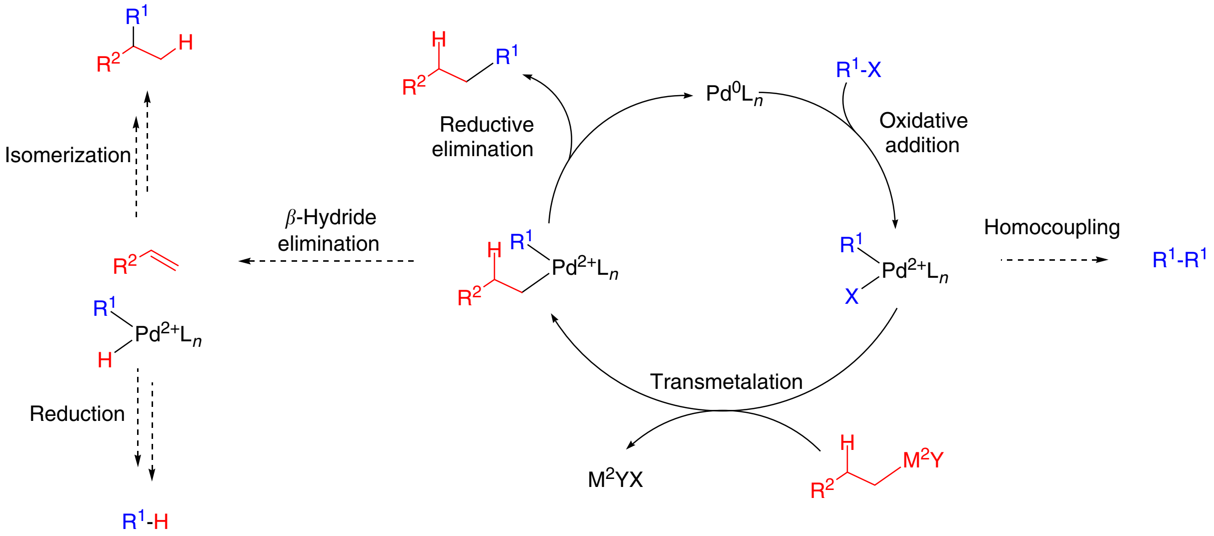
Aryl Grignard reagents react with alkyl chlorides in the presence of a palladium acetate and tricyclohexylphosphine (Scheme 28).[79] The cross-coupling products are obtained in good to excellent yields and sensitive functional groups, such as esters, nitriles, or acetals are tolerated.

Table 8 Copper-mediated or catalyzed acylation of organometallic reagents



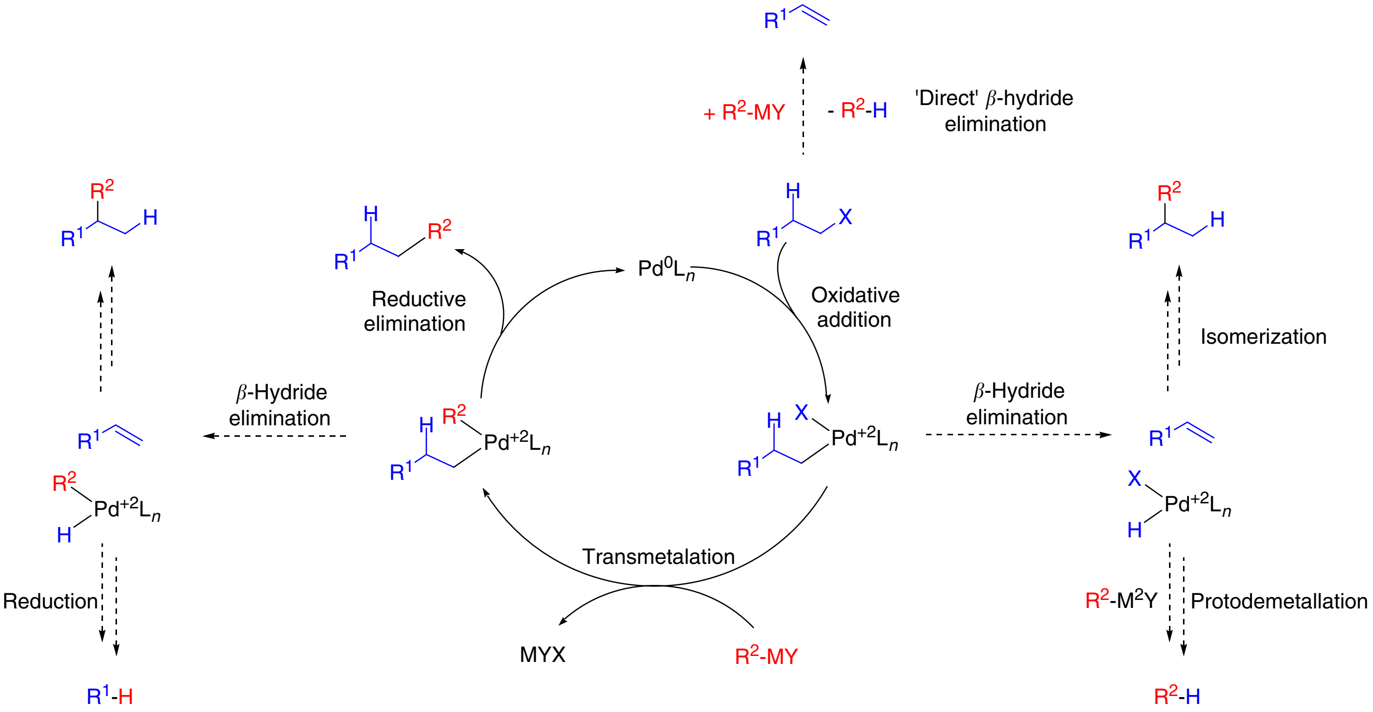
Entry	R^1–Met	CuX (equivalent)[a]	RCOX	Product	Yield (%)	References
1	MeLi	CuI (0.5)			95	64
2	s-BuMgX	Li_2CuCl_4 (1.0)			89	65
3	i-PrZnI	CuCN · 2LiCl (1.0)			82	66
4	$(AcO(CH_2)_5)_2Zn$	CuCN · 2LiCl (1.0)			87	67
5	BuMgBr	CuI (1.5)			83	68
6	$LiAl(Bu)_4$	CuCl (0.25)			76	69
7		CuCN · 2LiCl (1.0)			77	70

[a] In relation to R^1–Met.

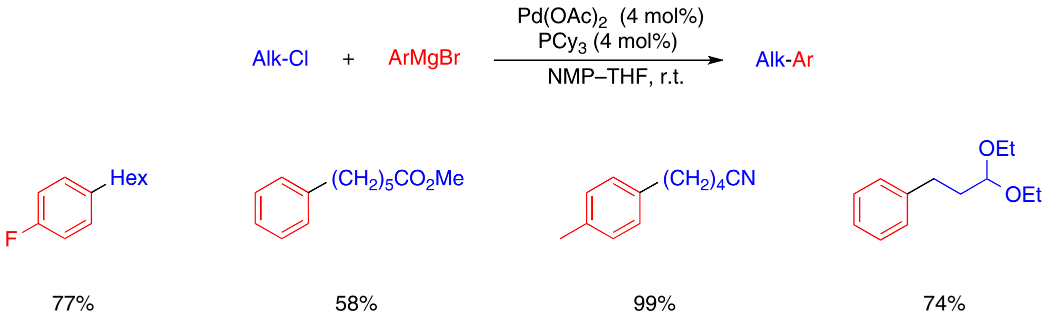


Scheme 26 Palladium-catalyzed cross-coupling of alkyl nucleophiles and possible side reactions.

Improved procedures use dimeric palladium/NHC complexes or air-stable secondary phosphine chlorides as preligands (Table 9).[80,81] Similar yields can be obtained, but in shorter reaction times. In addition, the functional group compatibility is broader. For example, ketone moieties are tolerated (Table 9, entry 6).

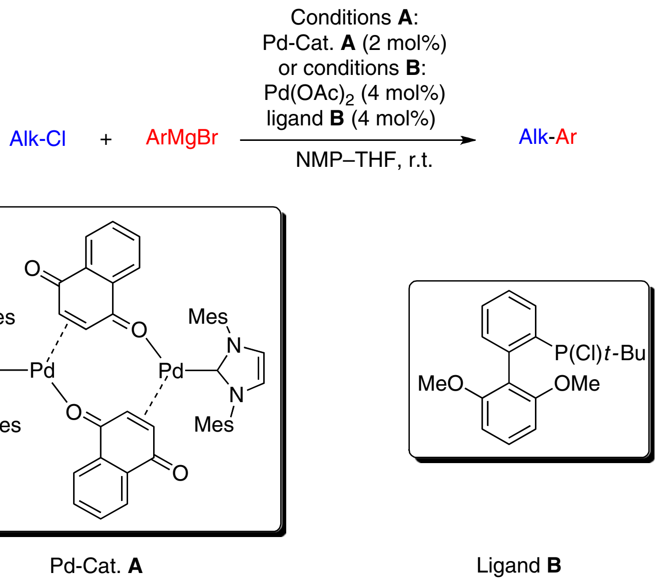


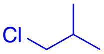
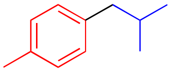
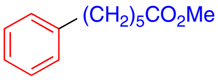
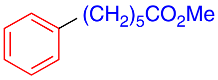
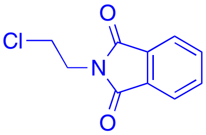
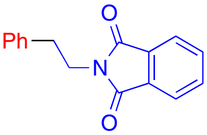
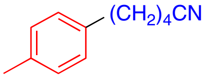
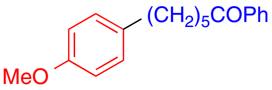
Scheme 27 Palladium-catalyzed cross-coupling with alkyl electrophiles and possible side reactions.



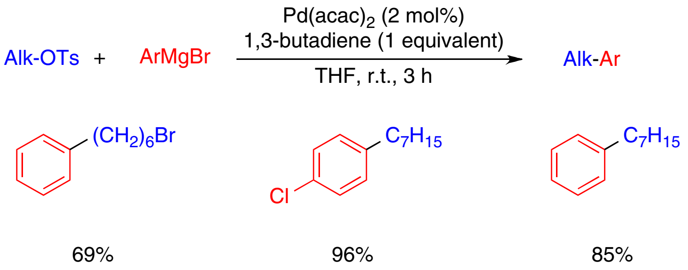
Scheme 28 Palladium-catalyzed cross-coupling of aryl Grignard reagents with alkyl chlorides.

Table 9 Palladium-catalyzed alkylation of aryl Grignard reagents



Entry	*Alk-Cl*	*Conditions*	*Product*	*Yield (%)*	*References*
1		A		99	79
2	$Cl(CH_2)_5CO_2Me$	A		92	79
3	$Cl(CH_2)_5CO_2Me$	B		51	80
4		A		45	79
5	$Cl(CH_2)_4CN$	A		93	79
6	$Cl(CH_2)_5COPh$	B		71	80

A different catalyst system based on Pd(acac)$_2$/butadiene facilitates the cross-coupling of aryl Grignard reagents with primary alkyl tosylates in the presence of aryl or alkyl halides (Scheme 29).[82]

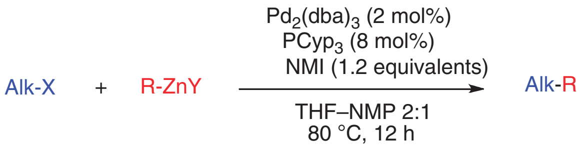


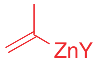
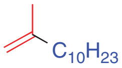
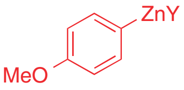
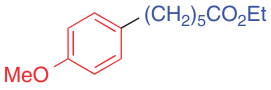
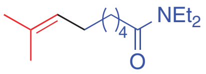
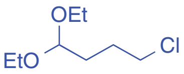
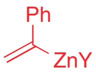
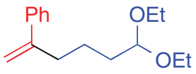
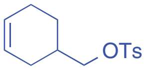
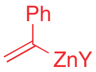
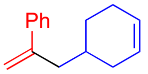
Scheme 29 Palladium-catalyzed cross-coupling of alkyl tosylates with aryl Grignard reagents.

3.08.3.1.2 Cross-coupling reactions with organozinc and -zirconium reagents

Alkenyl- or arylzinc reagents couple efficiently with primary alkyl halides using a Pd$_2$(dba)$_3$/tricyclopentylphosphine (PCyp$_3$)-based catalyst and *N*-methylimidazole (NMI) as additive (Table 10).[83] Alkyl iodides (entry 1), bromides (entries 2 and 3), chlorides (entry 4), or even tosylates (entry 5) are suitable coupling partners and sensitive functionalities, such as an ester (entry 2), amide (entry 3), or acetal (entry 4), are tolerated. This method is quite robust and can be included into a one-pot hydrozincation/cross-coupling protocol.

Table 10 Palladium-catalyzed cross-coupling of alkyl halides with alkenyl- or arylzinc reagents



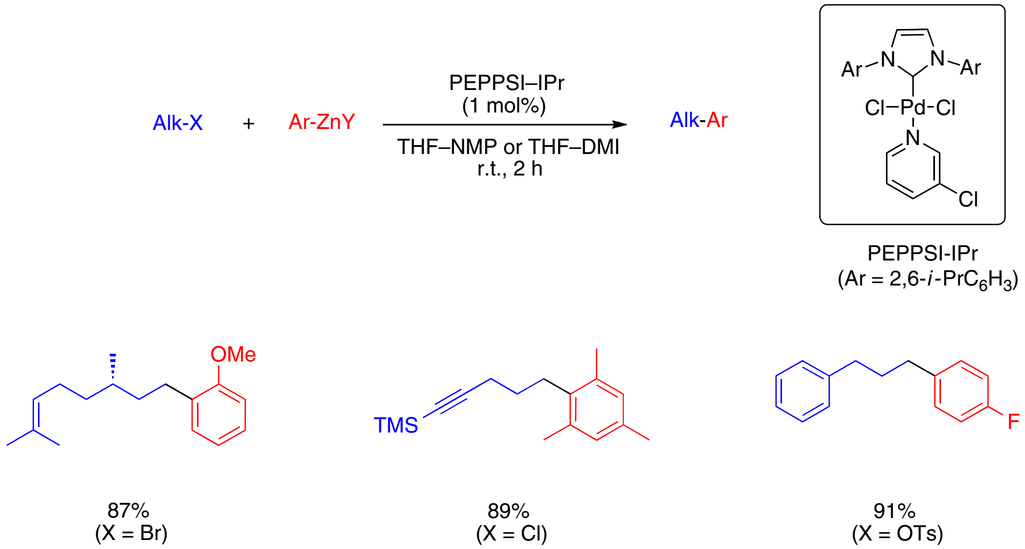
Entry	*Alk–X*	*R–ZnY*	*Product*	*Yield (%)*
1	*n*-Dec–I			98
2	EtO$_2$C(CH$_2$)$_5$ – Br			74
3	Et$_2$N(O)C(CH$_2$)$_5$ – Br			81
4				73
5				58

The use of an air- and moisture-stable palladium–NHC precatalyst leads to similar scope and yields (Scheme 30), and no stoichiometric additive is needed.[84] Additionally, this reaction is generally performed at ambient temperature.

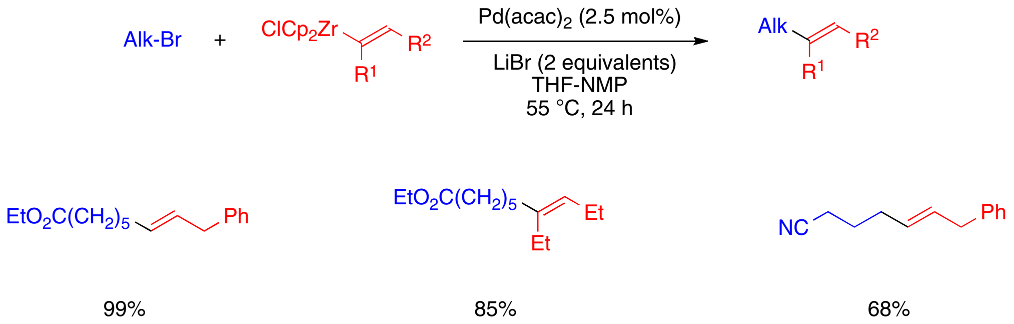
Readily available alkenylzirconium reagents react with primary alkyl bromides in the presence of a catalytic amount of Pd(acac)$_2$ and LiBr as stoichiometric additive (Scheme 31).[85] No ligand is needed, and the di- or trisubstituted olefins are obtained in high yields.

3.08.3.1.3 Cross-coupling reactions with organotin reagents

The palladium-catalyzed cross-coupling of alkenyl- or aryltin reagents proceeds smoothly in the presence of a hindered trialkylphosphine or a diaminoalkylphosphine ligand and Me$_4$NF as base (Table 11).[86,87] Similar yields are obtained for the

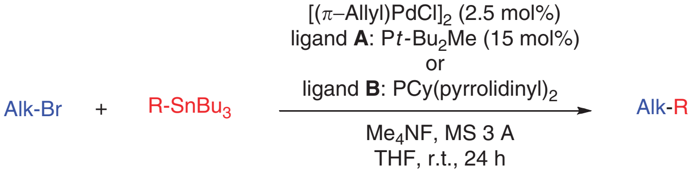


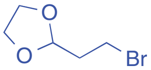
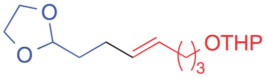
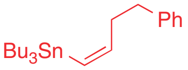
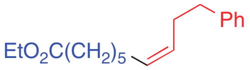
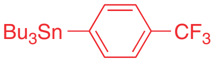
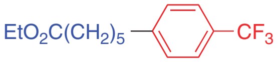
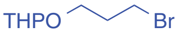
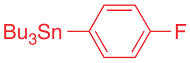
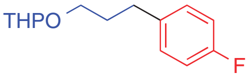
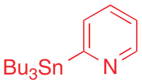
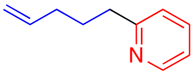
Scheme 30 Palladium-catalyzed cross-coupling of alkyl halides with arylzinc reagents.



Scheme 31 Palladium-catalyzed cross-coupling of alkenylzirconium reagents with primary alkyl halides.

Table 11 Palladium-catalyzed cross-coupling of primary alkyl bromides with alkenyl- or aryltin reagents

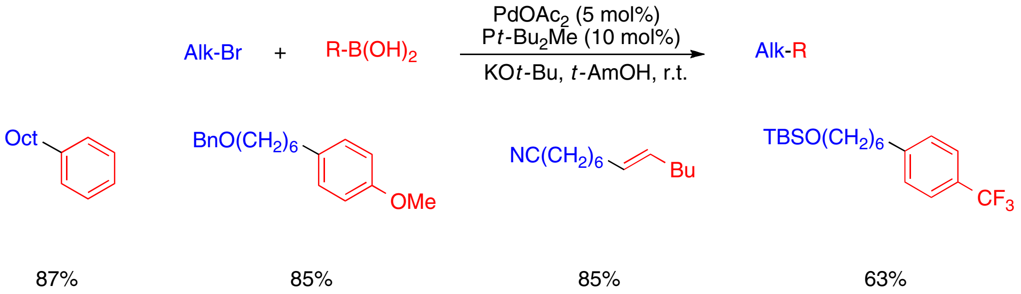


Entry	*Alk–Br*	*R–SnBu$_3$*	*Product*	*Ligand*	*Yield (%)*
1 2				**A** **B**	71 60
3 4	$EtO_2C(CH_2)_5$–Br			**A** **B**	74 89
5	$EtO_2C(CH_2)_5$–Br			**B**	57
6				**B**	64
7				**B**	53

cross-coupling of alkenyltin reagents with both ligands (entries 1–4). However, the diaminoalkylphoshine ligand is essential for obtaining high yields in the cross-coupling of aryltin reagents (entries 5–7). Various functional groups are tolerated under these conditions, and heteroaryltin reagents are suitable nucleophlic coupling partners (entry 7).

3.08.3.1.4 Cross-coupling reactions with organoboron reagents

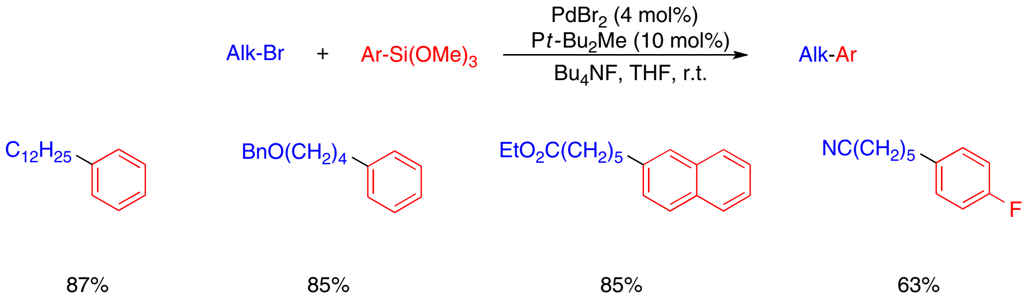
Aryl- or alkenylboronic acids react with primary alkyl halides in the presence of catalytic amounts of palladium acetate and a hindered trialkylphosphine (Scheme 32).[88] The catalyst system tolerates a variety of functional groups and the obtained yields are high. The correct combination of ligand (P*t*Bu_2Me), base (KO*t*Bu), and solvent (*tert*-amyl alcohol) is important, and variation of the reaction parameters leads to markedly decreased yields. Mechanistic studies have shown an exceptionally high reactivity of the generated palladium complex. In fact, oxidative addition in primary alkyl bromides occurs already at 0 °C.



Scheme 32 Palladium-catalyzed cross-coupling of aryl- and alkenylboronic acids with alkyl bromides.

3.08.3.1.5 Cross-coupling with organosilicon reagents

The palladium-catalyzed cross-coupling reaction of arylsilanes with primary alkyl bromides proceeds efficiently in the presence of the same trialkylphosphine ligand and Bu_4NF as base (Scheme 33).[89]



Scheme 33 Palladium-catalyzed cross-coupling reactions of arylsilanes with alkyl bromides.

3.08.3.2 Coupling with Activated Alkyl Halides and Related Electrophiles

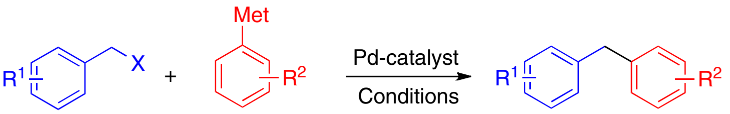
Palladium-catalyzed cross-coupling with activated alkyl halides (allyl, benzyl, etc.) is in general more straightforward. Faster oxidative addition and in most cases the absence of β-hydrogens lead to fewer side reactions.[74–77] Contrary to nonactivated alkyl halides, palladium-catalyzed cross-coupling with activated secondary halides is possible. Several stereoselective coupling reactions have been developed.

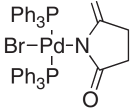
3.08.3.2.1 Coupling with benzyl halides and related electrophiles

Several methods exist for the cross-coupling of benzylic electrophiles with different organometallic reagents (Table 12).[90–99] Organoborane reagents are employed most frequently (entries 1–5), but methods for the coupling of organosilane (entry 6), organotin (entry 7), organozinc (entry 8), or organoindium reagents (entry 9) have also been developed. Benzylic halides (entries 1 and 5–9) as well as benzyl acetates, carbonates, phosphates, or tosylates (entries 2–4 and 6) can be coupled.

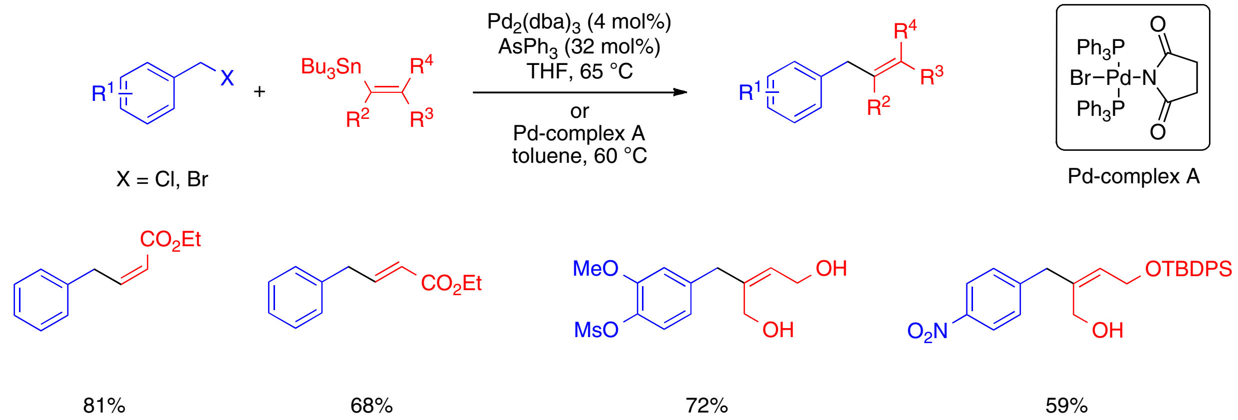
Palladium-catalyzed cross-coupling of alkenyl stannanes with benzylic bromides give the di- or trisubstituted olefins with complete retention of the double bond configuration (Scheme 34).[100,101]

Table 12 Palladium-catalyzed cross-coupling between benzylic electrophiles and aryl organometallics



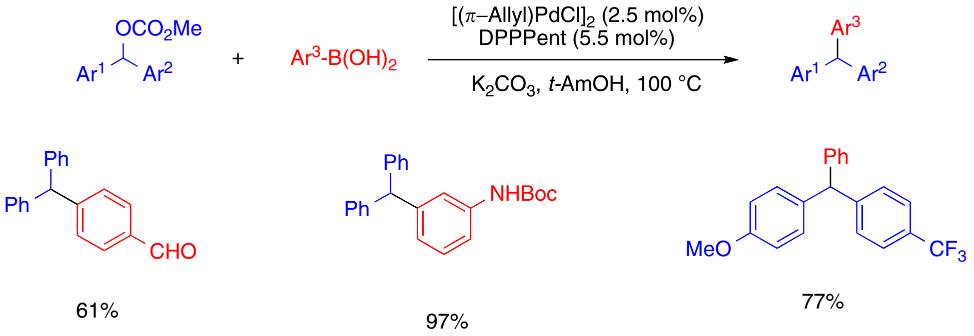
Entry	*X*	*Met*	*Pd–catalyst*	*References*
1	Cl, Br	$B(OH)_2$	$Pd(OAc)_2$, PPh_3	91
2	OAc	$B(OH)_2$	$[(\pi\text{-allyl})PdCl]_2$, DPEPhos[a]	92
3	$OP(O)(OEt)_2$	$B(OH)_2$	$Pd(OAc)_2$, PPh_3	93
4	OCO_2Me	$B(OH)_2$	$[(\pi\text{-allyl})PdCl]_2$, DPPPent[b]	94
5	Cl, Br	BF_3K	$PdCl_2(dppf)$[c]	95
6	Cl, Br, OTs	$Si(OMe)_3$	K_2PdCl_4, PEG-600	96
7	Br	$SnBu_3$		97
8	Cl	ZnX	$PdCl_2(PPh_3)_2$	98
9	Br	In	$PdCl_2(dppf)$	99

[a] DPEPhos = (Oxydi-2,1-phenylene)bis(diphenylphosphine).
[b] DPPpent = 1,5-*Bis*-(diphenylphosphino)-pentane.
[c] dppf = 1,1'-*Bis*-(diphenylphosphino)-ferrocene.



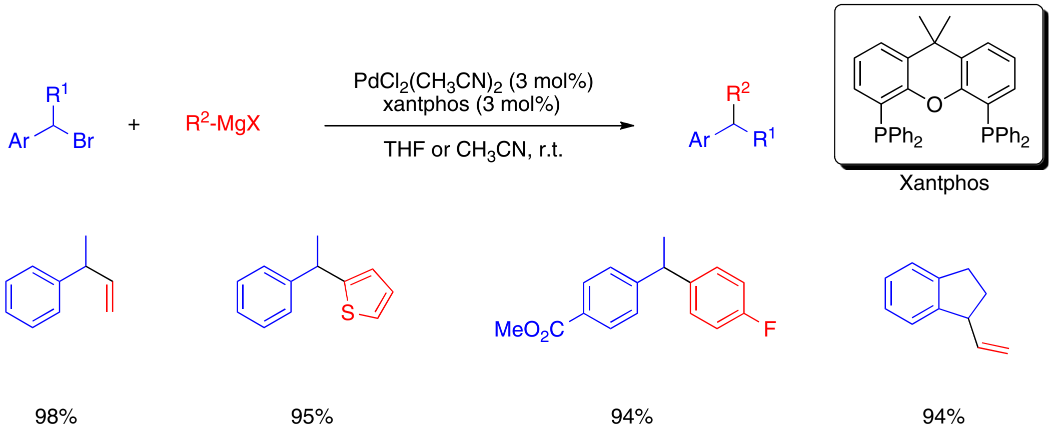
Scheme 34 Palladium-catalyzed cross-coupling of benzyl bromides with alkenyl stannanes.

As mentioned before, activated secondary alkyl halides are suitable substrates for palladium-catalyzed cross-coupling reactions. Thus, the reaction of arylboronic acids with diarylmethane carbonates in the presence of a palladium catalyst leads to the desired triarylmethanes (Scheme 35).[102]



Scheme 35 Palladium-catalyzed cross-coupling between diarylmethane carbonates and arylboronic acids.

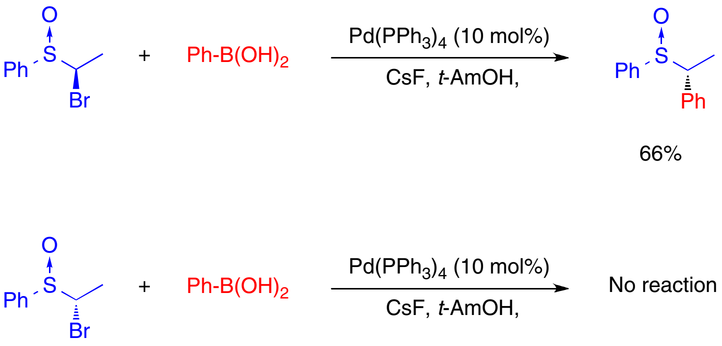
Similarly, the palladium-catalyzed reaction of aryl- or vinyl Grignard reagents with secondary benzylic bromides gives the coupling products in good yields (Scheme 36).[103] The reaction proceeds with inversion of configuration.



Scheme 36 Palladium-catalyzed cross-coupling between secondary benzylic bromides and Grignard reagents.

3.08.3.2.2 Coupling with α-halosulfoxides

Secondary α-bromo sulfoxides can be coupled with arylboronic acids (Scheme 37).[104,105] The reaction is stereospecific and proceeds with inversion of configuration. The two diastereomers of the sulfoxide show a remarkable difference in reactivity. While the *syn*-diastereomer reacts with phenylboronic acid, the *anti*-diastereomer remains unchanged.



Scheme 37 Diastereoselective cross-coupling between α-bromosulfoxides and arylboronic acids.

3.08.3.2.3 Coupling with allyl halides and related electrophiles

The palladium-catalyzed allylation of nucleophiles (Tsuji–Trost reaction) is an important method for the formation of carbon–carbon or carbon–heteroatom bonds, due to the broad scope of these reactions and the existence of powerful enantioselective variants.[106–108] Although the palladium-catalyzed allylic substitution with aryl or alkenyl organometallics is another powerful approach for the construction of $C(sp^2)$–$C(sp^3)$ bonds, it is worth mentioning that these reactions are not as well explored as the corresponding copper-catalyzed variants, especially with regard to stereoselective reactions.

A variety of methods exist for the cross-coupling of aryl organometallic reagents with linear, primary allylic electrophiles (Table 13).[96,100, 109–111] The linear S_N2-product is formed in all cases. Procedures exist for the coupling between organoboron (entries 1–5), -silicon (entry 6), or -tin reagents (entry 7) with allyl halides, acetates, or ethers.

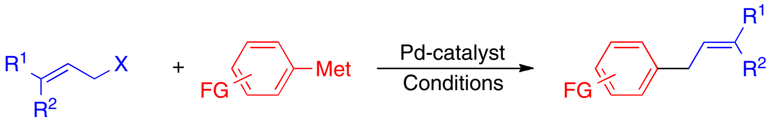
The palladium-catalyzed coupling of arylboronic acids with peracetylated glycols provides a stereoselective synthesis of *C*-arylglycosides (Scheme 38).[113] The carbon-Ferrier type products are obtained in good yields as a single stereoisomer.

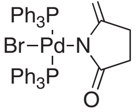
Cinnamyl alcohols can be used directly for palladium-catalyzed coupling with arylboronic acids (Scheme 39).[114] Interestingly, branched isomers lead to the same product, implying a (π-allyl)–palladium complex as intermediate.

In the case of unsymmetrical 1,3-disubstituted allylic electrophiles, two complementary procedures exist.

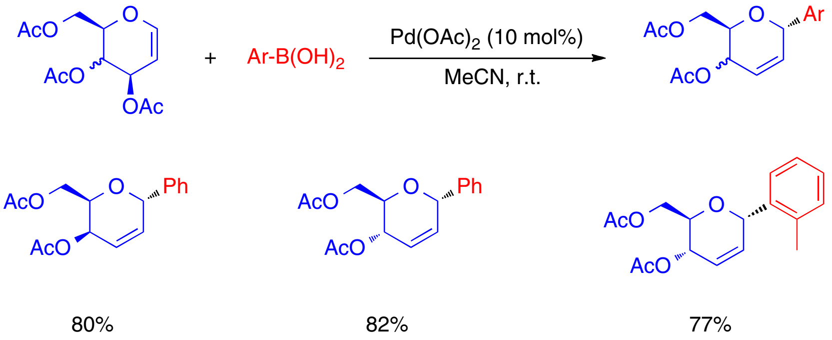
The palladium-catalyzed reaction of arylboronic acids with (*E*)-allylic acetate affords the allyl–aryl coupling product with excellent S_N2' and *E*-selectivity (Scheme 40).[115] The reaction is stereospecific and the *syn*-S_N2' products are obtained with almost complete transfer of chirality.

Table 13 Palladium-catalyzed cross-coupling between allylic electrophiles and aryl organometallics

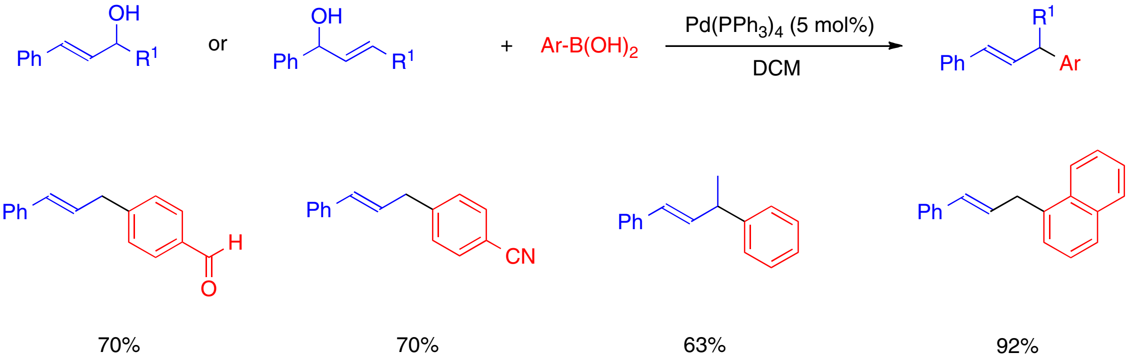


Entry	*R¹, R²*	*X*	*Met*	*Pd-catalyst*	*References*
1	Ar, H	Br	$B(OH)_2$	$Pd(dba)_2$	109
2	Ph, H	OAc	$B(OH)_2$	$PdCl_2$[tri-(2-furyl)phosphine]$_2$	110
3	H, Me	Br	BF_3K	$Pd(OAc)_2$	111
4	H, Me	Br	$B(OH)_2$	$Pd_2(dba)_3$	111
5	Ar, H	OPh	$B(OH)_2$	$PdCl_2$, DPEPhos	112
6	Ar, H	Br, Cl	$Si(OMe)_3$	K_2PdCl_4, PEG[a]	96
7	Ph, Alk, H	Br	$SnBu_3$		100

[a] PEG = Polyethylenglycol.



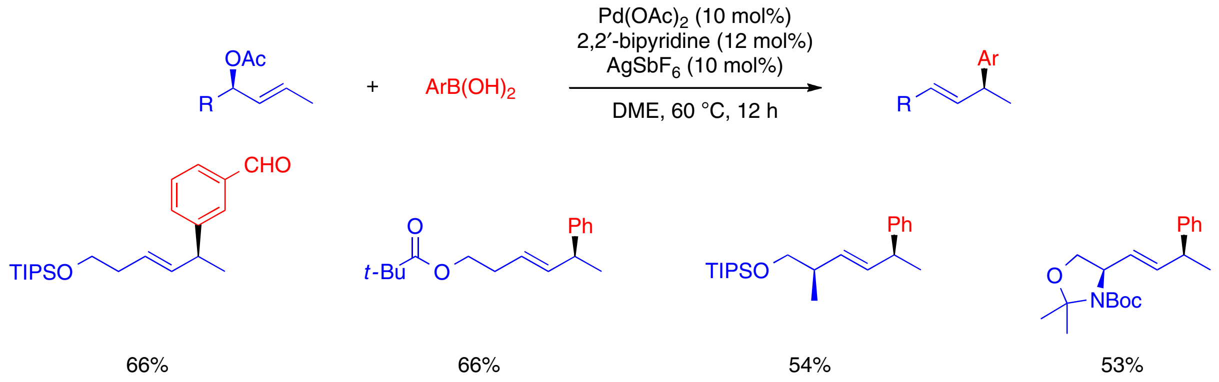
Scheme 38 Palladium-catalyzed c-glycosylation of peracetylated glycals with arylboronic acids.



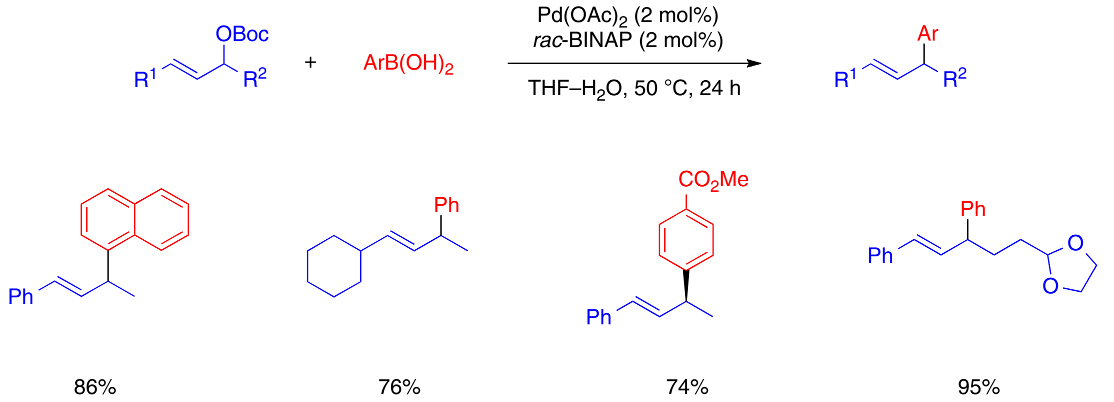
Scheme 39 Palladium-catalyzed cross-coupling between cinnamyl alcohols and arylboronic acids.

With allylic carbonates and a different palladium catalyst, the S_N2 products are obtained with complete regio- and (*E*)-selectivity (Scheme 41).[116] The coupling of enantioenriched carbonates gives the allyl–aryl coupling product with inversion of configuration.

Palladium-catalyzed cross-coupling of alkenylstannanes or -boron derivatives with allylic electrophiles leads to synthetically useful skipped dienes (Table 14).[97,100,114,117] Allylic bromides (entry 1), acetates (entry 2), or cinnamyl alcohols (entry 3) are suitable electrophiles. In all cases, the linear coupling product is formed.

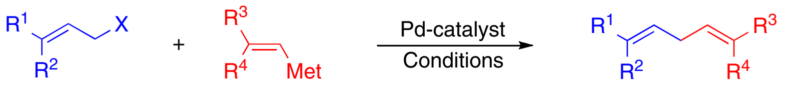


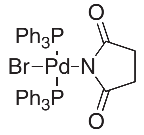
Scheme 40 Stereoselective palladium-catalyzed coupling between allylic acetates and arylboronic acids.



Scheme 41 Palladium-catalyzed regioselective coupling between arylboronic acids and allylic carbonates.

Table 14 Palladium-catalyzed cross-coupling of alkenyl stannanes and boranes with allylic electrophiles



Entry	*R^1, R^2*	*X*	*Met*	*Pd-catalyst*	*References*
1	Ph, Alk, H	Br	SnBu$_3$		97, 100
2	Ar, Alk, H	OAc	BF$_3$K	PdCl$_2$(dppf)	117
3	Ph	OH	B(OH)$_2$	Pd(PPh$_3$)$_4$	114

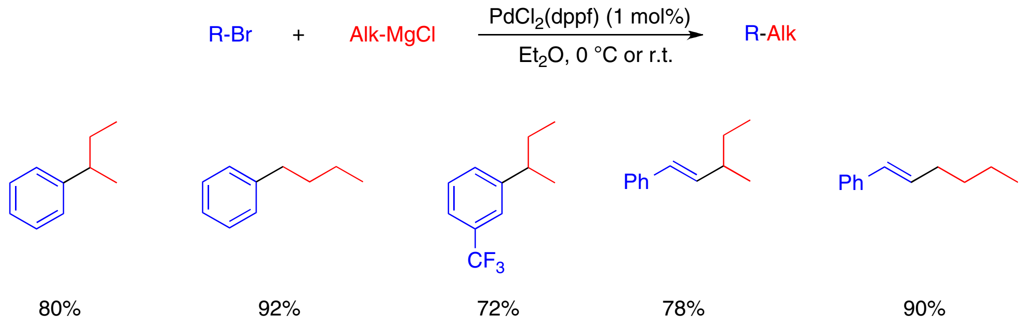
3.08.3.3 Coupling with Aryl and Alkenyl Halides

The palladium-catalyzed coupling of alkyl organometallics with aryl or alkenyl electrophiles provides a powerful method for the construction of C(sp^2)–C(sp^3) bonds. Cross-coupling reactions of C(sp^2) halides and primary alkyl organometallic reagents are straightforward and generally high yielding. The palladium-catalyzed cross-coupling of secondary alkyl reagents has been found to be more difficult and is frequently accompanied by the formation of side products from isomerization or reduction (Scheme 26).[74,75] However, these side reactions can be suppressed with the appropriate choice of ligand and conditions. No useful, general procedure exists for the palladium-catalyzed cross-coupling of tertiary alkyl organometallics.

3.08.3.3.1 Cross-coupling reactions with Grignard reagents

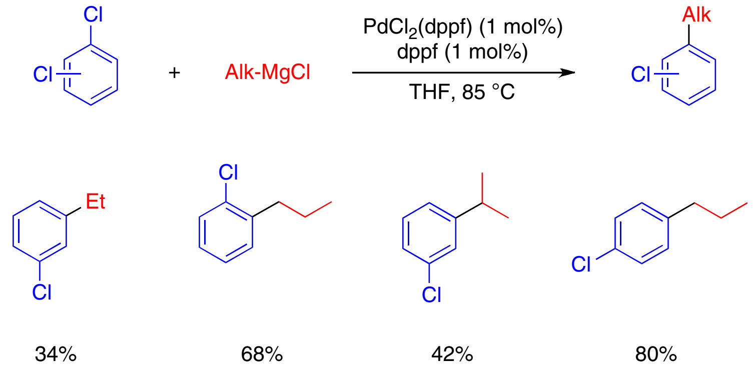
Due to the high reactivity of organomagnesium reagents, palladium-catalyzed Kumada cross-couplings are limited compared to cross-coupling reactions with less reactive nucleophiles (see below).

An early study showed that selective cross-coupling of primary or secondary organomagnesium (as well as organozinc reagents; see below) reagents with aryl or alkenyl bromides can be achieved with $PdCl_2$(dppf) as catalyst (Scheme 42).[118] The bidentate phosphine ligand with a large bite angle forces the coupling partners into a *cis* geometry, thereby facilitating the reductive elimination to the desired product (compare Scheme 26). Since this report, dppf has become a common ligand for palladium-catalyzed cross-coupling reactions with alkyl Grignard reagents (and alkylzinc reagents).



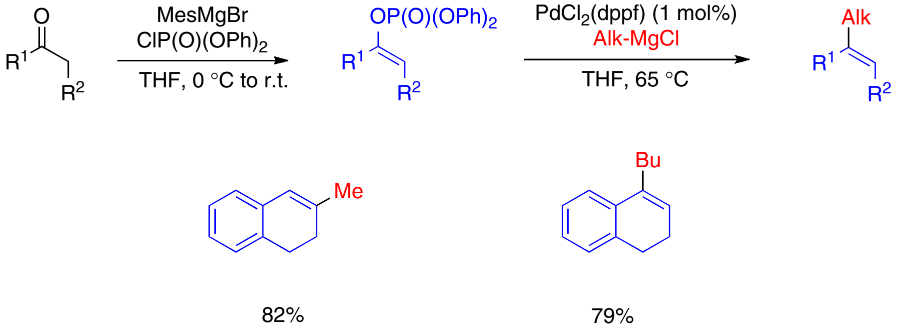
Scheme 42 Palladium-catalyzed cross-coupling of primary and secondary alkyl Grignard.

$PdCl_2$(dppf) can be used as catalyst for the selective monoalkylation of dichlorobenzene derivatives (Scheme 43).[119] The monoalkylation products are obtained in good to excellent yields for coupling reactions with primary or secondary alkyl Grignards.



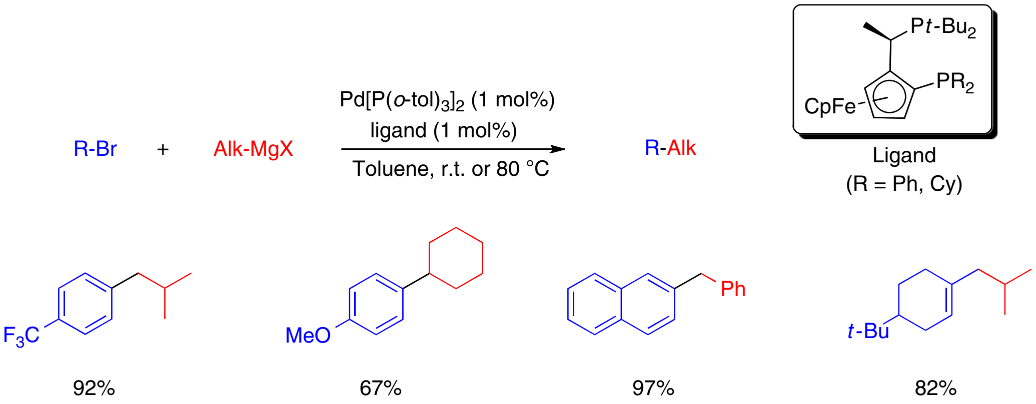
Scheme 43 Palladium-catalyzed monoalkylation of dichlorobenzenes.

Enol phosphates, prepared *in situ* from the corresponding ketones with the sterically hindered mesityl magnesium bromide and $ClP(O)(OPh)_2$, react with alkyl Grignard in the presence of $PdCl_2$(dppf) (Scheme 44).[120]



Scheme 44 Palladium-catalyzed cross-coupling of enol phosphates.

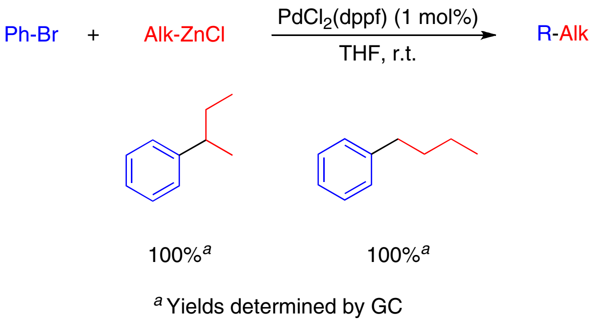
Aryl or vinyl tosylates can be coupled with primary or cyclic secondary alkyl Grignard if an electron-rich bidentate phosphine ligand is used (**Scheme 45**).[121] The cross-coupling of acylic secondary organomagnesium reagents is low yielding, and the dehalogenated arene is obtained as a major side product.



Scheme 45 Palladium-catalyzed cross-coupling between aryl- or alkenyl tosylates and alkyl Grignard.

3.08.3.3.2 Cross-coupling with organozinc reagents

$PdCl_2$(dppf) was found to be a highly active catalyst for the coupling of alkylzinc reagents (**Scheme 46**).[117] Cross-coupling of *n*- or *sec*-butylzinc chloride with bromobenzene leads to desired coupling products without isomerization. However, this study is limited to these two reactions.



Scheme 46 Palladium-catalyzed cross-coupling of alkylzinc reagents with bromobenzene.

Since this early report, several catalytic systems have been developed for the cross-coupling of primary alkylzinc reagents with aryl electrophiles (**Table 15**).[84,122–127] Aryl iodides, bromides, chlorides, or triflates can be coupled efficiently using a variety of different catalysts.

Unsaturated halides bearing acidic protons can be coupled with alkylzinc reagents using a $Pd(OAc)_2$/SPhos catalytic system (**Scheme 47**).[128–130] Thus, a variety of bromo- or iodoanilines, alcohols, amides, or even phenols react with primary alkyl or benzylic zinc reagents. Depending on the acidity of the NH or OH group and the nature of the organozinc reagent, slow addition of the organozinc reagent is necessary to obtain good yields.

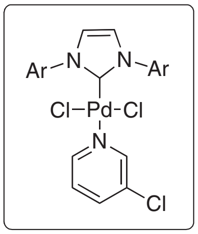
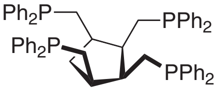
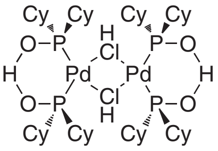
Dibromothiazoles undergo a regioselective palladium-catalyzed cross-coupling with primary or secondary alkylzinc reagents (**Scheme 48**).[131] The C2 position is more electron deficient and therefore more susceptible to oxidative addition of a nucleophilic Pd(0) species. This method allows the preparation of C2-functionalized thiazoles with a second C–Br bond for further functionalization.

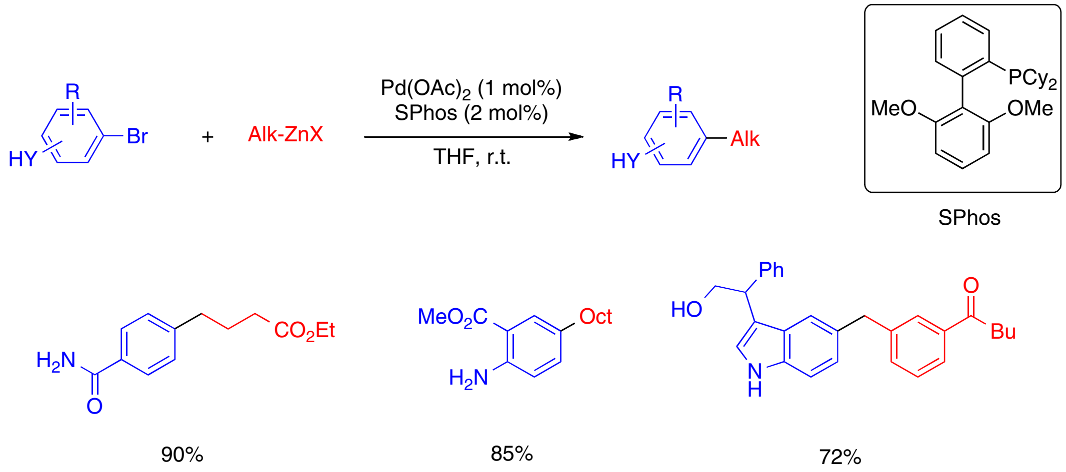
The cross-coupling of heterocycles is not limited to halides or sulfonates as leaving group. The palladium-catalyzed cross-coupling of thiomethyl-substituted heterocycles with functionalized alkyl or benzylic zinc reagents gives the corresponding heterocycles in good yields (**Scheme 49**).[132]

The coupling of secondary or tertiary alkyl zinc reagents often leads to a certain degree of isomerization, depending on the nature of the catalyst and the catalytic system. The following example of a palladium-catalyzed cross-coupling using a chelating ligand containing a phosphine and an electron-deficient olefin illustrates the problems and limitations of secondary and tertiary

Table 15 Palladium-catalyzed cross-coupling reactions between aryl halides and primary alkylzinc reagents

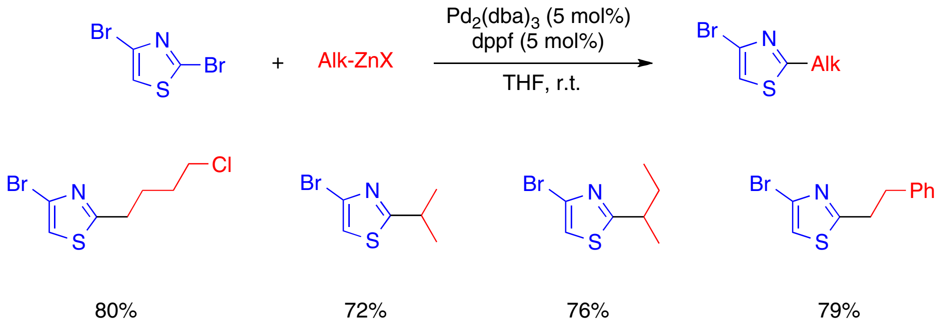
$$\text{Ar-X} \quad + \quad \text{Alk-ZnCl} \xrightarrow[\text{Conditions}]{\text{Pd-catalyst}} \text{Ar-Alk}$$

Entry	*X*	*Pd-catalyst*	*References*
1	Br	Pd(PPh$_3$)$_2$Cl$_2$	122
2	Cl, Br, OTf	 PEPPSI-IPr (Ar = 2,6-*i*-PrC$_6$H$_3$)	84
3	Br, Cl		123
4	Br	[(π-Allyl)PdCl]$_2$ 	124
5	Cl, Br, I	 POPd7	125
6	OTf	Pd(dba)$_2$, dppf, Bu$_4$NI	126
7	I	Pd(OAc)$_2$, Bu$_4$NBr	127

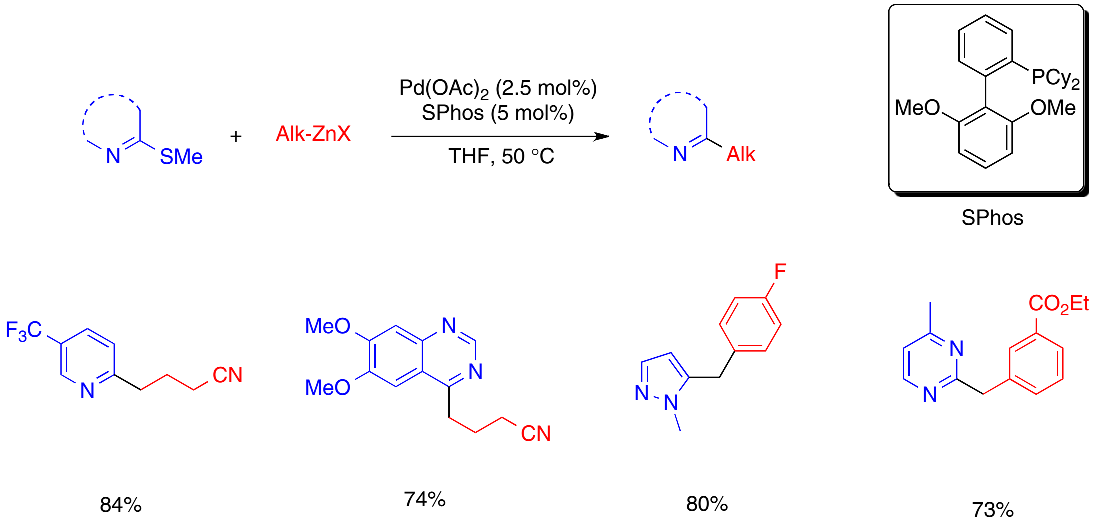


Scheme 47 Palladium-catalyzed cross-coupling of alkylzinc halides with aryl halides bearing acidic protons.

alkylzinc reagents (Scheme 50).[133] Reaction of cyclic secondary alkylzinc reagents, such as cyclopentylzinc chloride, gives the coupling products in good yields (equation 1). Acyclic secondary zinc reagents give the isomerized linear product in substantial amounts (ratio linear/branched = 45/55 in this example with *sec*-butylzinc chloride; see equation 2). The reaction with a tertiary alkylzinc reagent, such as *tert*-butylzinc chloride, furnishes the isomerized product exclusively (equation 3).



Scheme 48 Palladium-catalyzed regioselective cross-couplings with 2,4-dibromothiazole.



Scheme 49 Palladium-catalyzed thiomethyl-substituted heterocycles.

A significant improvement for the coupling of secondary acyclic zinc reagent was achieved with a bulky dialkylbiarylphosphine ligand (**Scheme 51**).[134] The branched products are obtained in good to excellent yields with high selectivity (branched/linear >23:1).

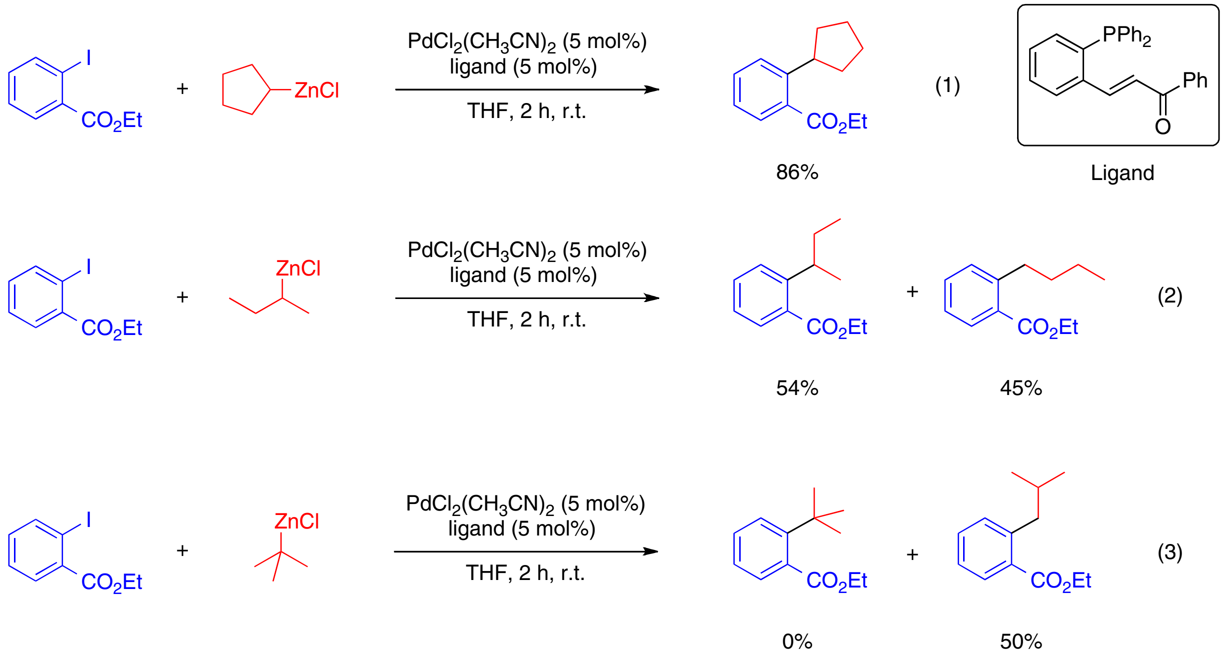
Alkenyl halides, triflates, or phosphates react with primary or secondary alkylzinc halides in the presence of different palladium catalysts (**Table 16**).[126,135–139] The reactions are in most cases highly stereospecific, and the configuration of the double bond is retained. This method can be expanded to the stereoselective synthesis of 1,3-dienes (entry 6). In some cases, the stereochemical outcome of the reaction can be controlled by the ligand (entry 7).

Enantioenriched zinc reagents, prepared via an enantioselective deprotonation with *s*BuLi and (–)sparteine followed by transmetalation with $ZnCl_2$, undergo a palladium-catalyzed cross-coupling reaction with aryl bromides (**Scheme 52**).[141,142] The α-arylated pyrrolidines are obtained in good yields and with high enantioselectivity. The high degree of stereoselectivity shows that the secondary zinc reagents are configurationally stable under the reaction conditions.

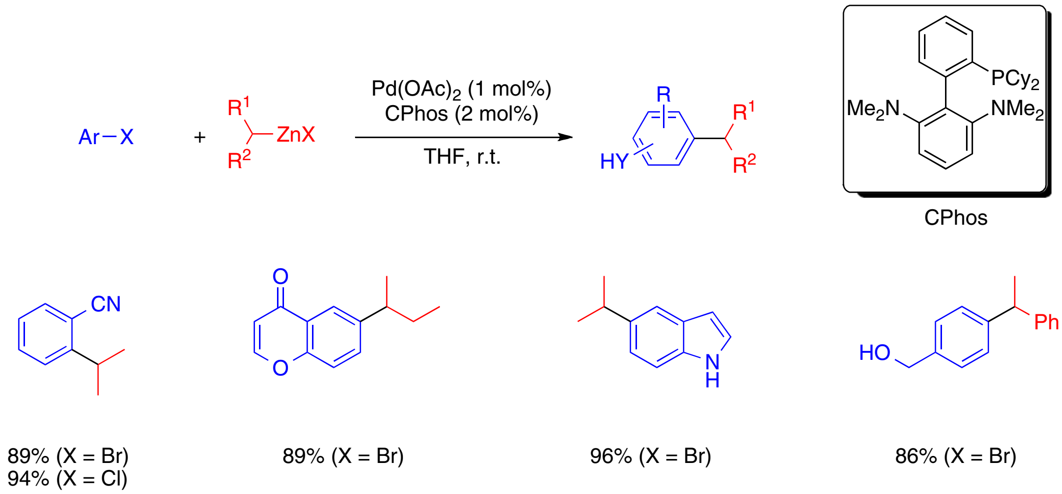
Palladium-catalyzed coupling reactions of substituted five- or six-membered cycloalkylzinc reagents with aryl iodides proceed with high diastereoselectivity (**Scheme 53**).[143] In all cases the thermodynamically most stable stereoisomer is formed, independent from the stereochemistry of the organozinc reagent. This method was extended to the diastereoselective synthesis of substituted piperidines.[144]

3.08.3.3.3 Cross-coupling with organoboron reagents

Since the seminal report of a palladium-catalyzed coupling reaction between alkyl boranes and aryl or alkenyl halides,[145] the B-*alkyl*-Suzuki–Miyaura coupling has become one of the most popular tools for the construction of C(sp^2)–C(sp^3) bonds. Numerous methods have been developed for palladium-catalyzed C(sp^2)–C(sp^3) bond formation starting from alkylboron reagents and aryl or alkenyl halides (**Table 17**).[145–154] Alkylboranes, easily obtained via hydroboration of alkenes (entries 1–4), alkyl boronic acids (entries 5–9), or esters (entry 10), or alkyl potassium trifluoroborates (entry 11) can be coupled with all kinds of aryl halides and triflates. Alkenyl halides or triflates are also suitable coupling partners. These couplings are generally limited to primary alkyl boron reagents. The choice of bases is crucial for coupling reactions with organoboron reagents.[145,146] Depending

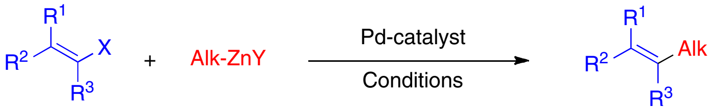


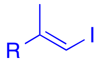
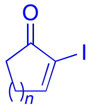
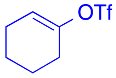
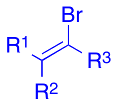
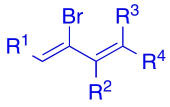
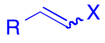
Scheme 50 Palladium-catalyzed cross-coupling with secondary and tertiary alkylzinc halides.



Scheme 51 Palladium-catalyzed cross-coupling of secondary alkylzinc halides.

Table 16 Palladium-catalyzed cross-coupling of alkenyl electrophiles with alkylzinc reagents

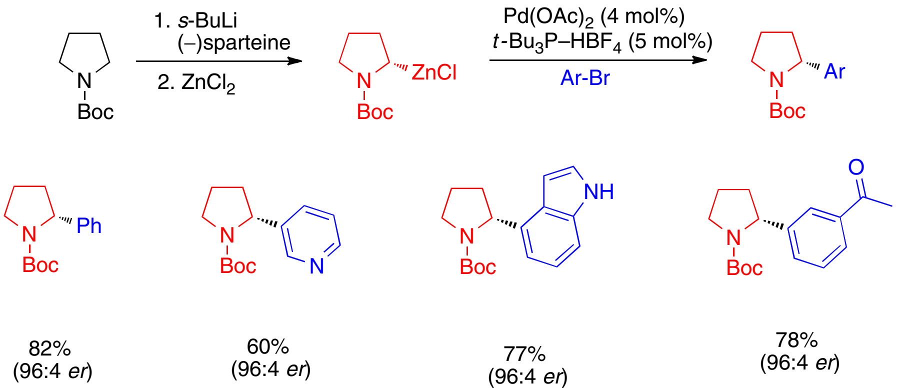


Entry	*Alkenyl halide*	*Alk–ZnX*	*Pd-catalyst*	*References*
1		1° alkyl	$Pd(PPh_3)_4$	135
2		1° alkyl	$Pd(PPh_3)_2Cl_2$	136
3		1° alkyl	$Pd(dba)_2$, dppf, Bu_4NI	126
4		1° alkyl	$Pd_2(dba)_3$, dppf	137
5		1° or 2° alkyl	$PdCl_2$(Amphos), *N*-MeI[a]	138
6		1° alkyl	Pd(*t*-$Bu_3P)_2$	139
7		1° alkyl	$Pd(PPh_3)_2Cl_2$, TMEDA or $PdCl_2$(Amphos)	140

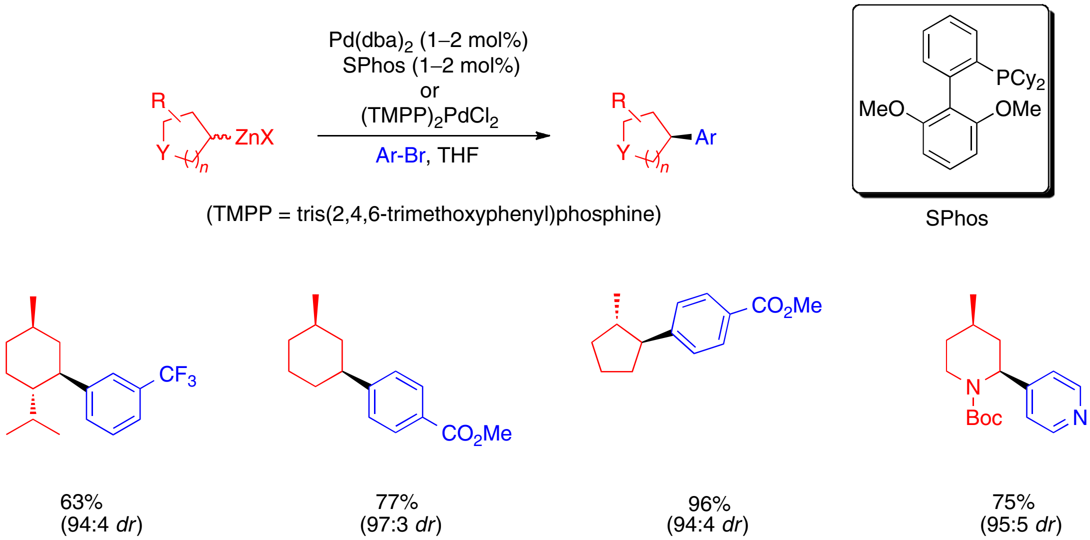
[a] Amphos, *p*-dimethylaminophenyl-di-*tert*-butylphosphine; *N*-MeI, *N*-methylimidazole.

on the exact nature of the boron reagent, different bases can be used. Often thallium salts show a rate-enhancing effect in $C(sp^2)$–$C(sp^3)$–Suzuki reactions.[147,148] However, one has to consider the high toxicity of these salts. Silver(I) salts can lead to a similar rate acceleration.[151,155] Generally no reaction is observed in the absence of base.

The cross-coupling of secondary alkylboron reagents is limited, due to the extremely slow transmetalation of these hindered substrates. Exceptions are cyclopropylboron reagents.[157–161] The exocyclic C–B bond possesses a substantial amount of *s*-character, which leads to faster transmetalation, and the geometry of cyclopropane prevents β-hydride elimination. The cross-coupling is in



Scheme 52 Palladium-catalyzed cross-coupling of chiral zinc reagents.



Scheme 53 Diastereoselective cross-coupling of cycloalkylzinc halides.

general stereospecific, with retention of configuration at the cyclopropane ring. Thus, cyclopropyl boronates react with aryl bromides in the presence of catalytic amounts of Pd(PPh$_3$)$_4$ to yield the *trans*-susbtituted cyclopropanes (**Scheme 54**).[158]

Similarly, disubstituted cyclopropyl potassium trifluoroborates react stereospecifically with aryl bromides, furnishing trisubstituted cyclopropanes in high yields (**Scheme 55**).[161]

A rare example of the palladium-catalyzed cross-coupling with secondary alkylboron reagents is the reaction between alkyl potassium trifluoroborates and aryl halides (**Scheme 56**).[162] Cylic secondary potassium trifluoroborates give the coupling products in high yields, while the coupling of acylic secondary alkyl reagents leads to isomerization and a mixture of linear and branched products.

Coupling of secondary benzylic pinacol boronates is also possible (**Scheme 57**).[163] The reaction is stereospecific, and cross-coupling of chiral boronates proceeds with almost complete retention of configuration ($>$90%).

A major advantage of the *B*-alkyl Suzuki–Miyaura coupling is the easy access to functionalized alkylboron reagents.

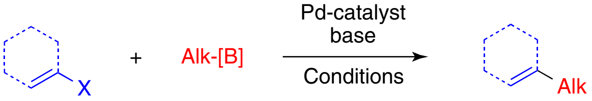
Functionalized primary alkylboranes can be easily obtained by hydroboration from the corresponding alkenes and directly used for palladium-catalyzed cross-coupling reactions. This procedure has been applied to the synthesis of various complex molecules.

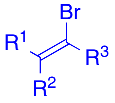
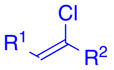
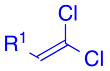
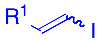
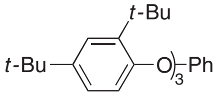
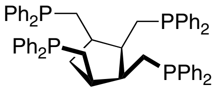
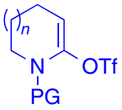
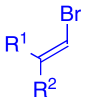
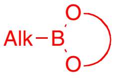
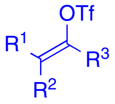
Nonnatural α-amino acids have be synthesized via this approach (**Scheme 58**).[164,165] The starting alkene was prepared by a Wittig reaction from Garner's aldehyde.

C1-Iodoglycals react with a variety of *in situ*-generated alkylboranes in the presence of catalytic amount of a palladium catalyst (**Scheme 59**).[166] This method allows the flexible preparation of complex C1-substituted glycols.

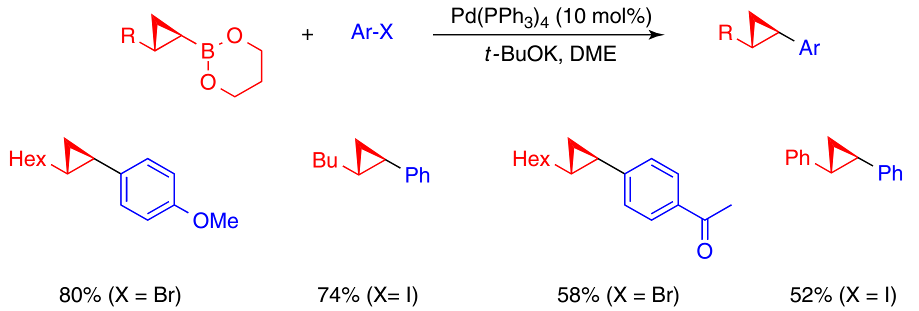
Alkyl boronic acids, esters, or trifluoroborates are less reactive compared to alkylboranes. However, they show an excellent compatibility with a wide range of functional groups, a high stability to air and moisture, and generally a long shelf life. In addition, a variety of functionalized alkylboronic acid derivatives, especially potassium trifluoroborates,[167] are readily available.

Table 17 Palladium-catalyzed cross-coupling of primary alkylboron reagents with aryl or alkenyl electrophiles

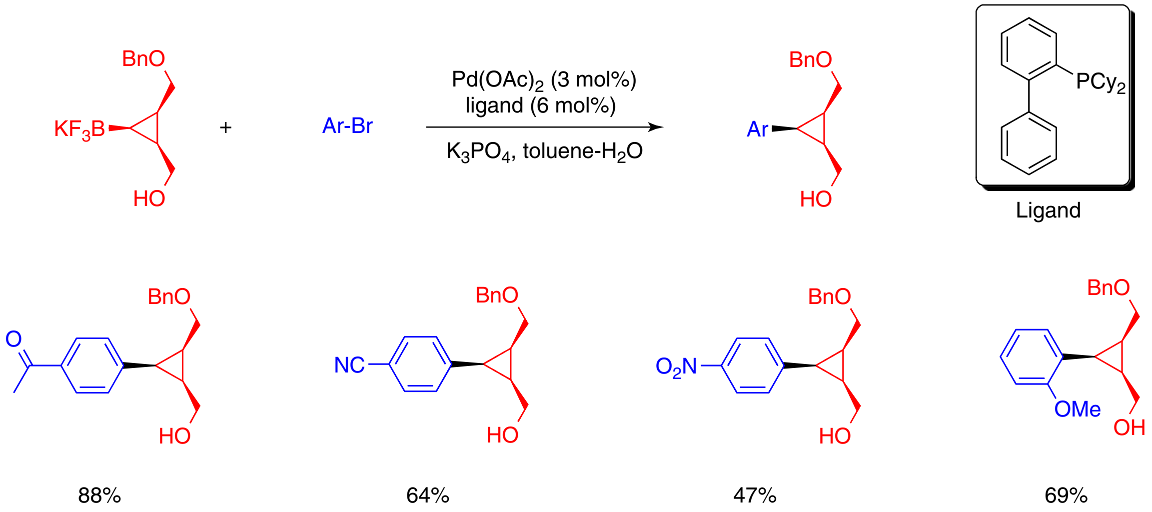


Entry	*R–X*	*Alkylboron reagent*	*Pd-catalyst, base*	*References*
1	Ar–I, Ar–Br, 	Alk-9-BBN	$PdCl_2(dppf)$ NaOH	145
2	Ar–Br	Alk-9-BBN	$Pd(OAc)_2$, SPhos $K_3PO_4 \cdot H_2O$	149
3		Alk-9-BBN	$PdCl_2(dppp)$[a] $KF\text{-}K_3PO_4$	150
4		Alk-9-BBN	$Pd_2(dba)_3$, XanthPhos $CsF\text{-}Cs_2CO_3$	150
5	Ar–I, Ar–Br, Ar–OTf 	$Alk\text{-}B(OH)_2$	$PdCl_2(dppf)$ K_2CO_3, Ag_2O	151
6	Ar–Br, Ar–OTf	$Alk\text{-}B(OH)_2$	$PdCl_2(dppf)$	152
7	Ar–Br	$Alk\text{-}B(OH)_2$	$Pd(OAc)_2$  K_3PO_4	153
8	Ar–Br, Ar–Cl	$Alk\text{-}B(OH)_2$	$[(\pi\text{-allyl})PdCl]_2$  K_2CO_3	154
9		$Alk\text{-}B(OH)_2$	$PdCl_2(dppf)$ K_2CO_3, Ag_2O	155
10	Ar–I, Ar–Br, 		$PdCl_2(dppf)$ Tl_2CO_3	146
11	Ar–OTf, 	$Alk\text{-}BF_3K$	$PdCl_2(dppf)$ Cs_2CO_3	156

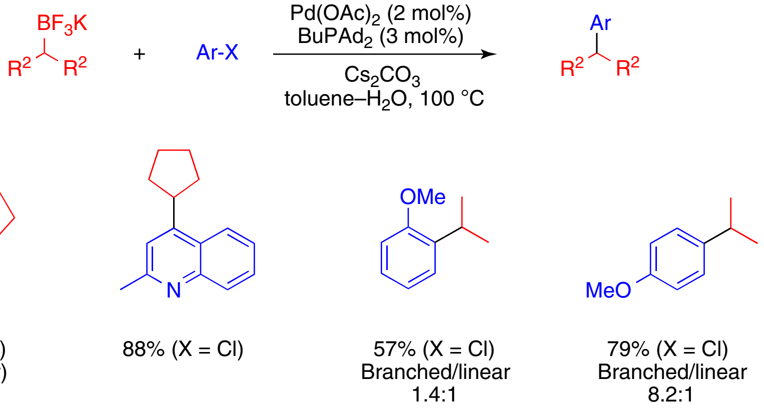
[a] 1,3-Bis-(diphenylphosphino)propane.



Scheme 54 Palladium-catalyzed cross-coupling of cyclopropyl boronic esters.

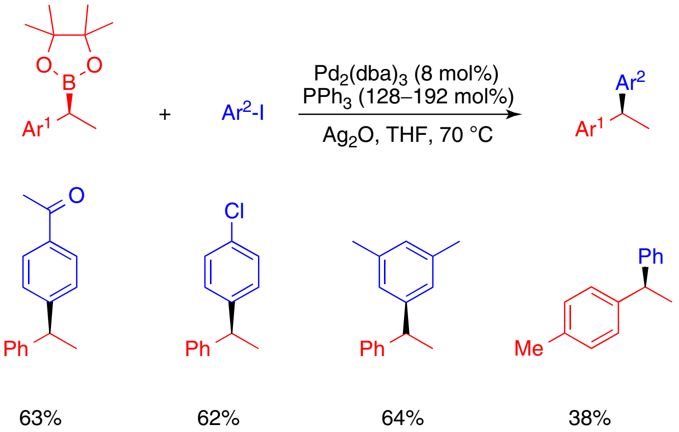


Scheme 55 Palladium-catalyzed coupling of cyclopropyl potassium trifluoroborates.

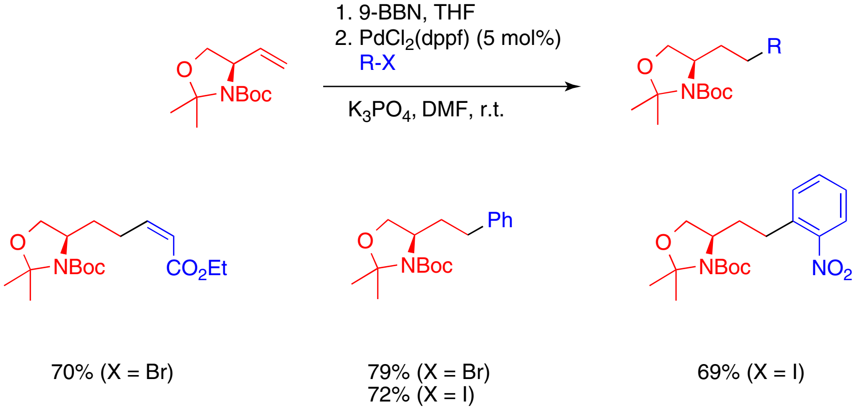


Scheme 56 Palladium-catalyzed cross-coupling of secondary alkyl potassium trifluoroborates.

Palladium-catalyzed cross-couplings with these reagents allow the introduction of various functional groups (Table 18).[168–174] Coupling with potassium trifluoroboronato homoenolate leads to ketones, esters, or amides (entries 1 and 2). Cross-coupling with amino- or amidomethyltrifluoroborates allows for the introduction of the biological important aminomethyl moiety (entries 3–5). Similar reactions have been developed for the synthesis of hydroxy- or alkoxymethylated aromatics (entries 6 and 7).



Scheme 57 Palladium-catalyzed cross-coupling of secondary pinacol boronates with stereoretention.



Scheme 58 Palladium-catalyzed cross-coupling of amino acid synthons.

Secondary alkyl β-trifluoroborato amides undergo a stereospecific cross-coupling with aryl chlorides (**Scheme 60**).[175] The coupling products are obtained with a complete inversion of configuration. Isomerization or β-hydride elimination is not an issue in this reaction.

Enantioenriched α-(acylamino)benzylboronic esters undergo a similar stereospecific cross-coupling with aryl bromides (**Scheme 61**).[176,177] Interestingly, the stereochemical course of this reaction can be switched by the choice of additives. In the presence of phenol, the coupling product is obtained with almost complete inversion of configuration (>90%). Retention of configuration can be achieved by the addition of $Zr(O\textit{i}Pr)_4$-*i*PrOH with excellent enantiospecificity (>80%).

3.08.3.3.4 Cross-coupling with organotin reagents.

Aryl- or alkenyltin reagents are frequently used nucleophiles in palladium-catalyzed coupling reactions.[1–4] In contrast, examples of the coupling of alkyltin reagents are extremely rare.[180–181] With the exception of Me_4Sn, which produces the methylated coupling products in good yields, coupling reactions with tetraalkyltin compounds often lead to low yields or fail altogether.[178,179]

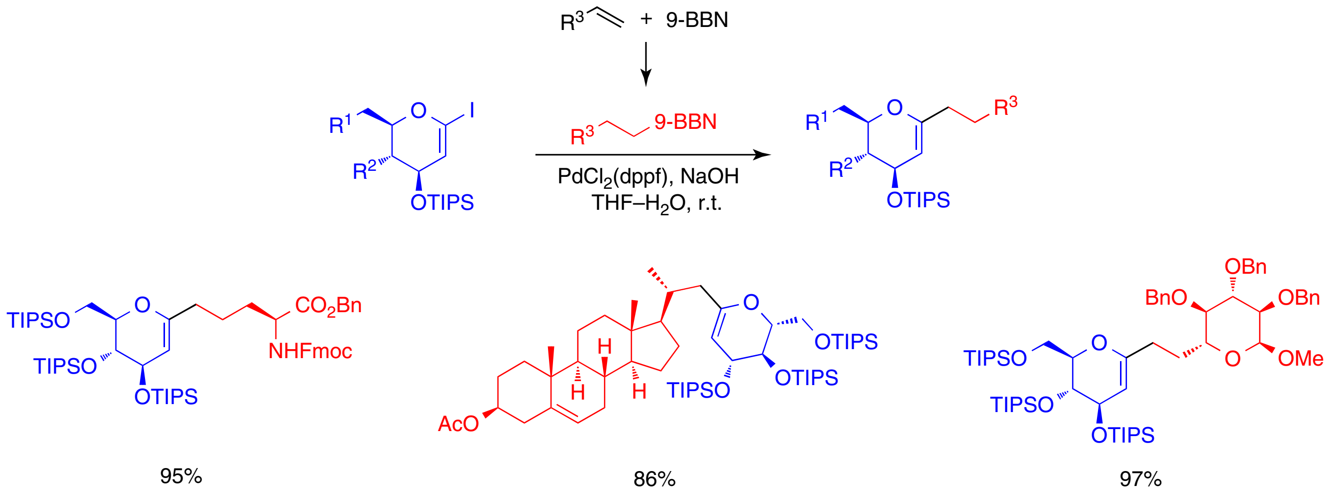
A major improvement was achieved with activated alkyltin compounds (**Scheme 62**).[182] These activated tin reagents, prepared *in situ* from the corresponding alkyl halides, react with aryl iodides, generating the coupling products in good yields and with no toxic by-products. Unfortunately, the method is limited to primary alkyl halides.

3.08.3.3.5 Cross-coupling with organosilicon reagents

Compared to coupling reactions with aryl- or alkynylsilicon reagents, the use of alkylsilicon compounds is still limited.[183,184]

Alkylsilicon reagents undergo palladium-catalyzed cross-coupling with aryl halides or triflates (**Scheme 63**).[185,186] The presence of a fluoride source, such as tetra-*n*-butylammonium fluoride (TBAF), is essential for a successful reaction. It is proposed that fluoride reacts with the alkylsilicon reagent to form a more reactive pentavalent silicon intermediate, which can undergo transmetalation.

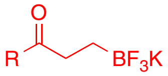
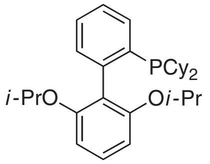
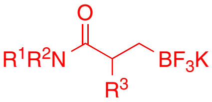
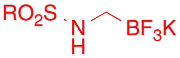
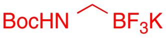
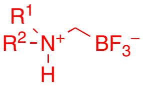
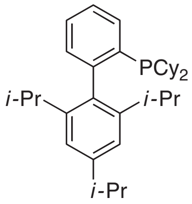
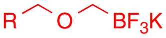
An improved procedure uses 2-(2-hydroxyprop-2-yl)phenyl-substituted alkylsilanes (**Scheme 64**).[187] These reagents are more stable than the widely used polyfluorinated alkylsilanes, and intramolecular activation allows cross-coupling under fluoride-free

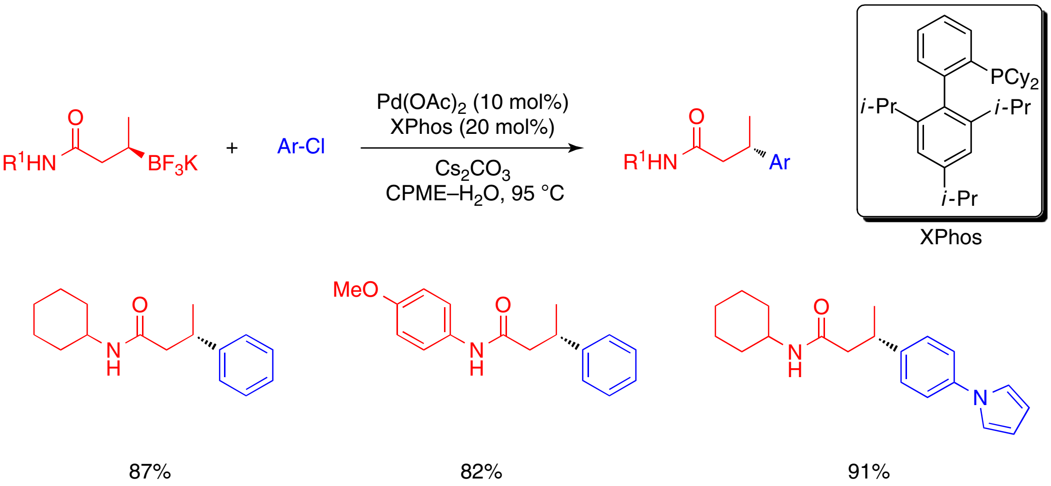


Scheme 59 Palladium-catalyzed cross-coupling of C1-iodoglycals.

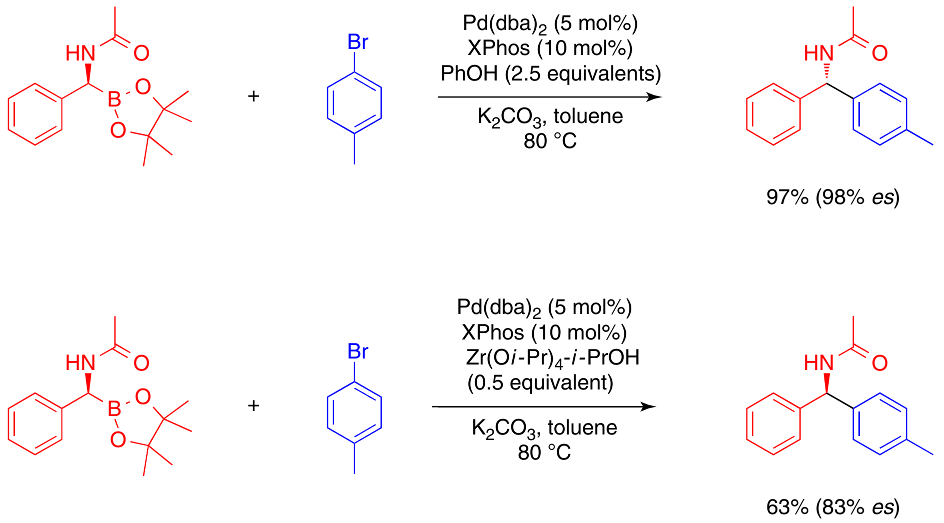
Table 18 Palladium-catalyzed cross-coupling with functionalized alkylboron reagents

$$\mathrm{FG\text{-}(CH_2)_{\mathit{n}}\text{-}BX_2} \;+\; \mathrm{Ar\text{-}X} \xrightarrow[\text{Conditions}]{\text{Pd-catalyst, base}} \mathrm{FG\text{-}(CH_2)_{\mathit{n}}\text{-}Ar}$$

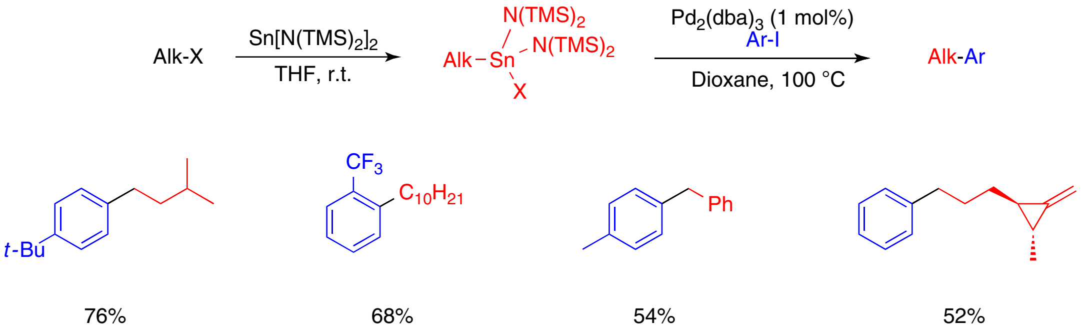
Entry	*Boron reagent*	*X*	*Pd-catalyst*	*References*
1	 R = alkyl, OR, NR$_2$	Br, Cl	Pd(OAc)$_2$  RuPhos	168
2		Cl	Pd(OAc)$_2$, RuPhos	169
3		Cl	PdCl$_2$(MeCN)$_2$, RuPhos	170
4		Cl	Pd(OAc)$_2$, SPhos	171
5		Cl	Pd(OAc)$_2$,  XPhos	172
6		Cl	Pd(dba)$_2$, RuPhos	173
7		Cl	Pd(OAc)$_2$, RuPhos	174



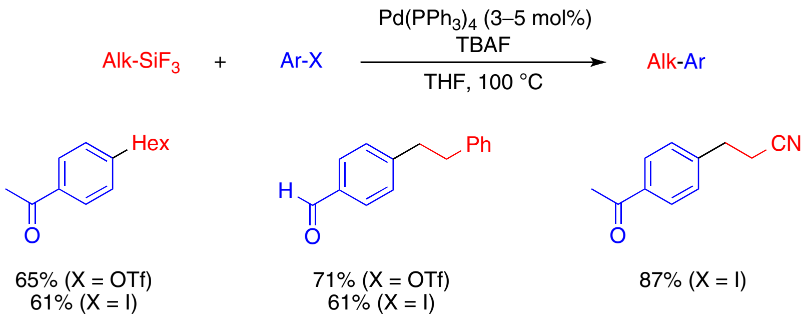
Scheme 60 Stereospecific cross-coupling of secondary alkyl β-trifluoroborato amides.



Scheme 61 Stereospecific cross-coupling of α-(acylamino)benzylboronic esters.



Scheme 62 Palladium-catalyzed cross-coupling of activated alkyltin reagents.

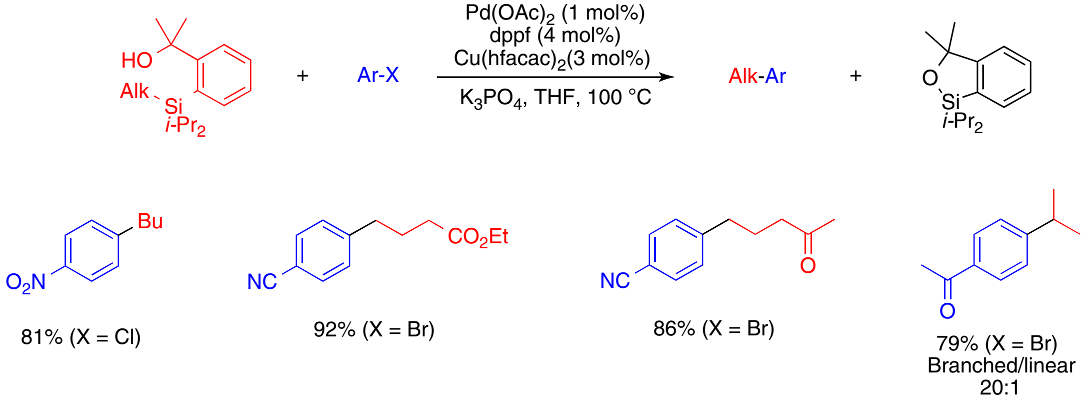


Scheme 63 Palladium-catalyzed cross-coupling of alkylsilicon reagents.

conditions. A copper cocatalyst was found to be crucial for improved yields. Various functionalized alkylsilicon species give the coupling products in good yields; in addition, secondary alkylsilicon reagents also furnished the desired products.

3.08.3.3.6 Cross-coupling with organoindium reagents

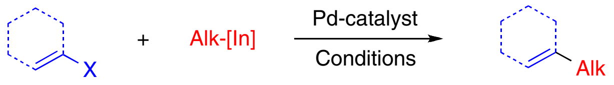
Organoindium reagents are an attractive alternative as nucleophilic coupling partners for cross-coupling reactions. They are substantially less reactive then organomagnesium or zinc reagents, and therefore tolerate a variety of functional groups.[188] However, they undergo transmetalation with palladium more readily than organoboron or -silicon compounds. Additionally, trialkylindium reagents can transfer all three alkyl groups, which results in only substoichiometric amounts of metal waste.

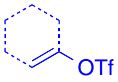
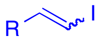
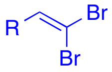


Scheme 64 Palladium-catalyzed cross-coupling of 2-(2-hydroxyprop-2-yl)phenyl-substituted alkylsilanes.

Several procedures have been developed for the palladium-catalyzed cross-coupling of alkylindium reagents with aryl or alkenyl electrophiles (Table 19).[189–190] Alkenyl iodides undergo a stereospecific cross-coupling with retention of configuration (entry 3). Reaction of trialkylindium reagents with dibromoalkenes gives the double-substitution products in high yields (entry 4).

Table 19 Palladium-catalyzed cross-coupling of alkylindium reagents with aryl or alkenyl halides



Entry	*R–X*	*Alkylindium reagent*	*Pd-catalyst*	*References*
1	Ar–I, Ar–Br, Ar–OTf	Alk_3In	$PdCl_2(dppf)$	189
2		Alk_3In	$PdCl_2(PPh_3)_2$	189
3		Alk_3In	$PdCl_2(dppf)$	190
4		Alk_3In	$Pd(t\text{-}Bu_3P)_2$	190

3.08.3.4 Coupling with Acyl Halides and Related Electrophiles

The palladium-catalyzed reaction of alkyl organometallics with carboxylic acid chlorides or related electrophiles is one of the most important methods for the preparation of ketones, and it is widely used in organic synthesis. This methodology has been extensively reviewed.[62] Table 20 shows some representative examples. Organozinc reagents[191] and organotin compounds are used frequently in this methodology (entries 1 and 2). Reactions with organoindium reagents are also possible, although not as well studied (entry 3). The coupling of alkylboron compounds is limited to reactive cyclopropyl boronic acids (entry 4).

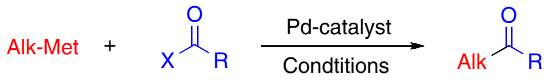
The palladium-catalyzed coupling of alkylorganometallics with less reactive thioesters is an attractive alternative to the moisture-sensitive acid chlorides.

Coupling of *B*-alkyl-9-BBN derivatives with thioesters can be achieved in the presence of catalytic amounts of $Pd(PPh_3)_4$ and a stoichiometric amount of copper(I)-thiophene-2-carboxylate (CuTC). Additional base is required to activate the borane, and the desired ketones are obtained in high yields (Scheme 65).[195]

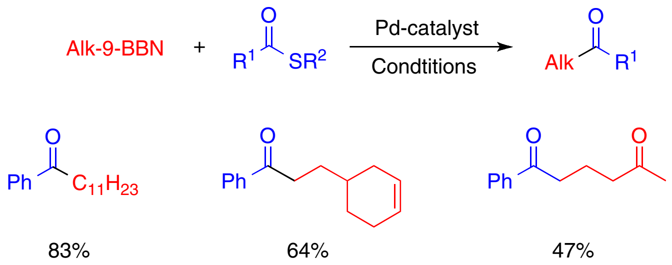
3.08.4 Nickel-Catalyzed Coupling Reactions

From the beginning of the development of cross-coupling reactions, nickel has been identified as one of the most useful and catalytically active transition metals.[1–4,195] The seminal reports of a nickel-catalyzed reaction between Grignard reagents and aryl or alkenyl halides paved way for the development of modern cross-coupling chemistry.[196,197] Today, nickel-catalyzed cross-coupling reactions offer a powerful alternative to the more frequently employed palladium-catalyzed processes.

Table 20 Palladium-catalyzed acylation of alkyl organometallics

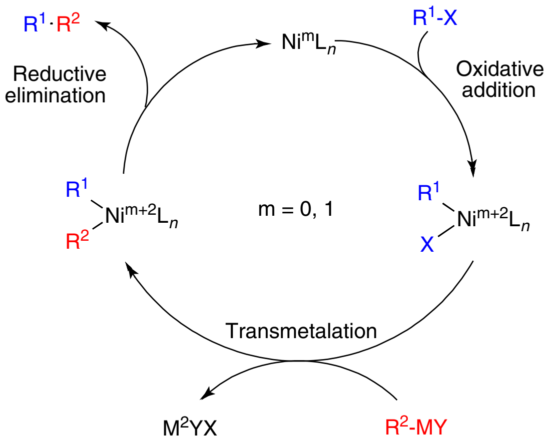


Entry	*Met*	*X*	*Pd-catalyst*	*References*
1	AlkZnY	Cl	$Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$	192
2	Alk_4Sn	Cl	$BnPdCl(PPh_3)_2$	193
3	Me_3In	Cl	$Pd(PPh_3)_4$	189
4		Cl	$PdCl_2(dppf)$	194



Scheme 65 Palladium-catalyzed cross-coupling of thioesters.

The mechanisms of nickel-catalyzed reactions can be different from the usual pathway of palladium-catalyzed cross-couplings, due to the ability of nickel to form radical intermediates and to switch more readily between four oxidation states (0, I, II, and III). The usual catalytic cycle, consisting of oxidative addition, transmetalation, and reductive elimination, is considered to be operative in most cases, although two alternative cycles, either Ni(0)/Ni(II) or Ni(I)/Ni(III), are proposed (Scheme 66).[195,198] The formation of side products from *β*-hydride elimination or protodemetalation (see Schemes 26 and 27) is a frequently encountered issue in the nickel-catalyzed cross-coupling of C(sp^3) nucleophiles or electrophiles. However, the development of new ligands and catalysts allows the efficient nickel-catalyzed construction of C(sp^2)–C(sp^3) bonds.



Scheme 66 General mechanism for the nickel-catalyzed cross-coupling reactions.

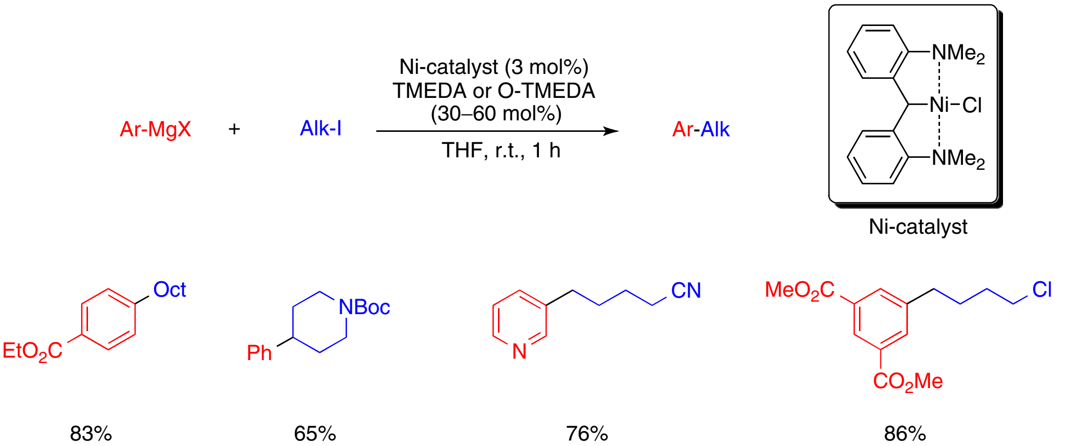
Also, from an economical standpoint, nickel, with a cost of roughly \$1 mol^{-1}, is an attractive alternative to the significantly more expensive palladium (ca. \$2350 mol^{-1}) (Prices as of 09 Mar 2012).

3.08.4.1 Coupling Reaction with Nonactivated Alkyl Halides and Related Electrophiles

For the cross-coupling of nonactivated alkyl halides, nickel is one of the most versatile metals. Compared to similar palladium-catalyzed coupling reactions, nickel is able to couple not only primary but also secondary alkyl halides with different organometallic reagents.[6,199]

3.08.4.1.1 Cross-coupling reactions with Grignard reagents

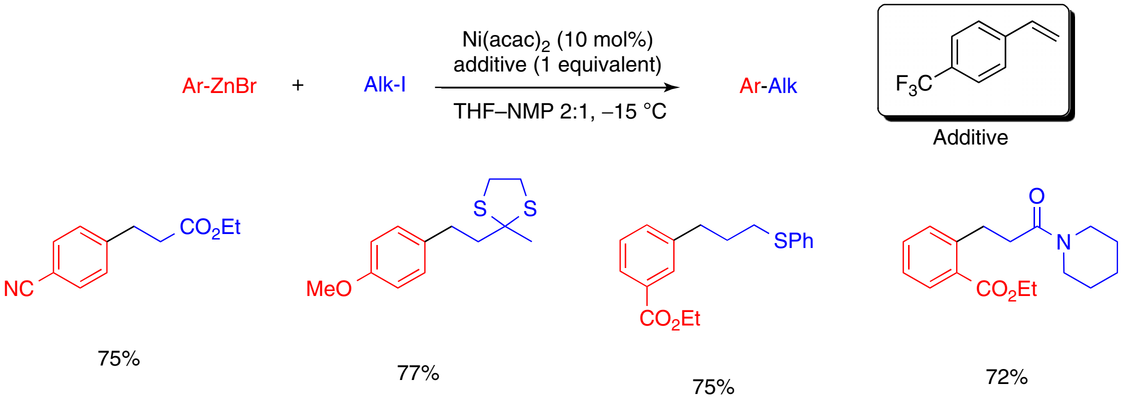
The nickel-catalyzed cross-coupling of alkyl halides and Grignard reagents is mostly limited to alkyl–alkyl couplings.[200,201] Examples of the cross-coupling between alkyl halides and aryl- or alkenylmagnesium reagents are rare and in most cases restricted to phenylmagnesium bromide.[201–203] A useful exception is the cross-coupling of primary alkyl halides with functionalized aryl- or heteroaryl Grignard reagents catalyzed by a nickel pincer complex (Scheme 67).[204] The addition of *N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA, or O-TMEDA (bis-[2-(*N*,*N*-dimethylamino)ethyl] ether)[205] for functionalized Grignard reagents) leads to much improved yields. Secondary alkyl halides furnish the coupling products in very low yields.



Scheme 67 Nickel-catalyzed cross-coupling of alkyl halides with aryl Grignard reagents.

3.08.4.1.2 Cross-coupling reactions with organozinc reagents

Arylzinc bromides undergo a nickel-catalyzed cross-coupling with various polyfunctional alkyl iodides in the presence of 4-(trifluoromethyl)styrene (Scheme 68).[206]



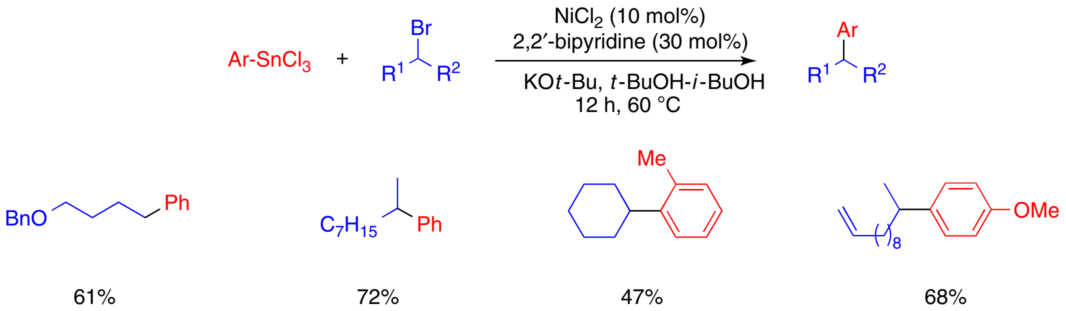
Scheme 68 Nickel-catalyzed cross-coupling between arylzinc reagents and alkyl iodides.

3.08.4.1.3 Cross-coupling reactions with organotin reagents

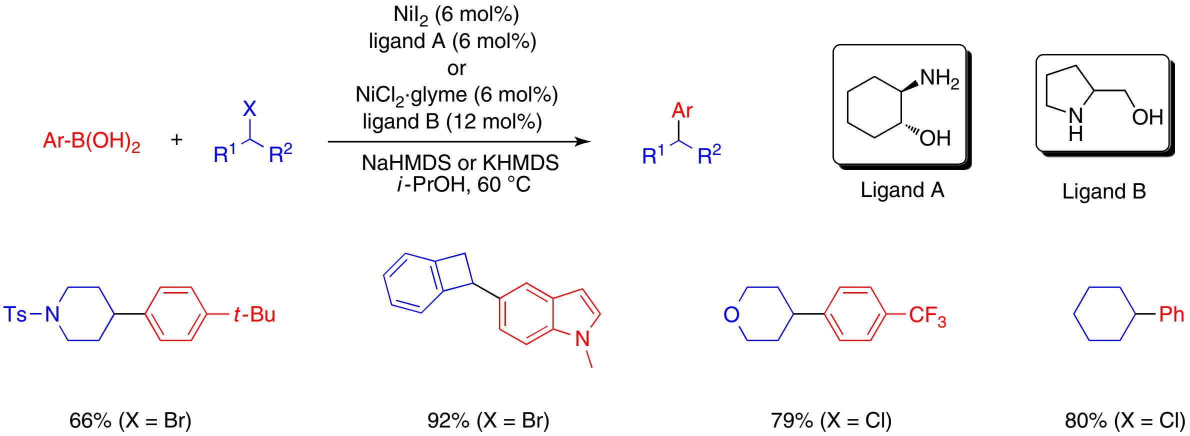
The cross-coupling of organotin reagents with alkyl halides can be catalyzed efficiently by nickel. Trichloroaryl- or alkenyltin reagents react with primary or even secondary alkyl bromides in the presence of the inexpensive $NiCl_2$/2,2′-bipyridine catalyst system (Scheme 69).[207]

3.08.4.1.4 Cross-coupling with organoboron reagents

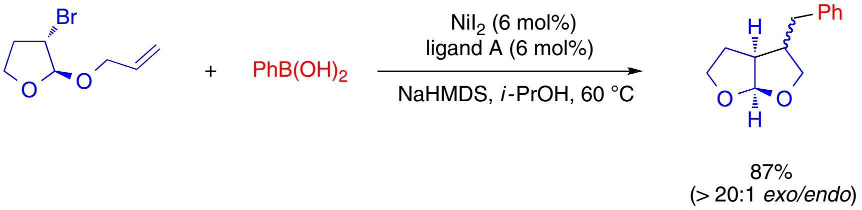
Nickel-catalyzed cross-coupling of arylboronic acids with primary or secondary alkyl halides is also possible (Scheme 70).[208,209] With different aminoalcohols as ligands, functionalized aryl- or heteroarylboronic acids react with primary or secondary alkyl bromides and even less reactive chlorides. Alkyl bromides, bearing a tethered olefin, undergo a cyclization/cross-coupling reaction, indicating a radical species involved in the oxidative addition step (Scheme 71).



Scheme 69 Nickel-catalyzed cross-coupling of trichloroaryltin reagents with primary and secondary alkyl bromides.



Scheme 70 Nickel-catalyzed cross-coupling of secondary alkyl halides with arylboronic acids.



Scheme 71 Nickel-catalyzed cyclization/cross-coupling sequence.

3.08.4.1.5 Cross-coupling with organosilicon reagents

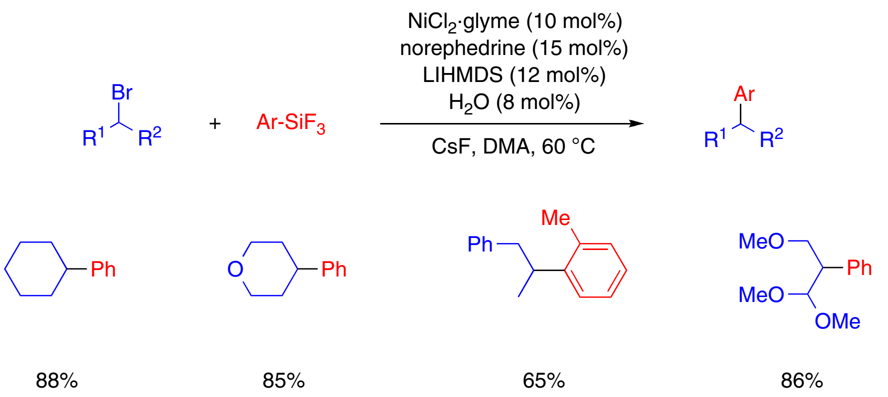
Aminoalcohols are useful ligands for the nickel-catalyzed cross-coupling of secondary alkyl halides with arylsilicon reagents (Scheme 72).[210,211] A nickel/norephedrine complex provides is an efficient catalyst for the coupling of nonactivated secondary alkyl bromides. Interestingly, trace amounts of water increase the yield of the reaction.

3.08.4.2 Coupling Reactions with Activated Alkyl Halides and Related Electrophiles

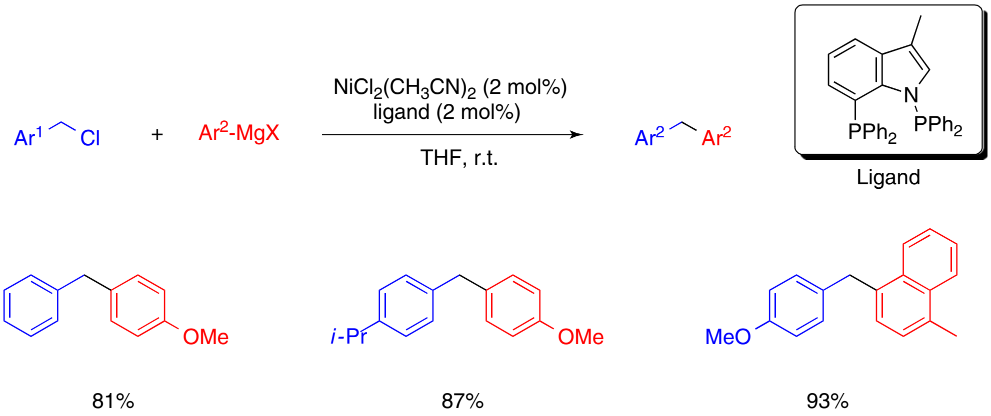
Nickel-catalyzed cross-coupling reactions with activated alkyl electrophiles are not as widespread as their copper- or palladium-catalyzed counterparts. However, in the recent years powerful asymmetric coupling reactions have been developed that allow the transformation of racemic starting materials into enantioenriched products.[9]

3.08.4.2.1 Coupling with benzyl halides and related electrophiles

The nickel-catalyzed coupling of C(sp^2) nucleophiles with benzylic electrophiles is not well established, probably due to the existence of versatile palladium- or copper-catalyzed methods. A rare example is the cross-coupling of aryl Grignard reagents with benzylic chlorides employing a bidentate phosphine ligand (Scheme 73).[212]



Scheme 72 Nickel-catalyzed cross-coupling between arylsilanes and secondary alkyl bromides.



Scheme 73 Nickel-catalyzed cross-coupling of aryl Grignard with benzylic chlorides.

3.08.4.2.2 Coupling with allyl halides and related electrophiles

Nickel complexes are able to facilitate allylic substitution reactions. As for copper- or palladium-catalyzed reactions, regio- and stereoselectivity is influenced by substrate and the leaving group, ligand, and reaction conditions. In some cases palladium and nickel lead to opposite regioisomers.[213] The high catalytic activity of nickel permits substitution of unusual leaving groups.

Aryl or alkenyl Grignard reagents couple with a range of different allylic electrophiles, such as silyl ethers, selenides, or sulfides in the presence of a suitable nickel catalyst (Table 21).[213–216] The regioselectivity of this reaction is in general lower than with copper or palladium catalysis.

Allylic carbonates react with aryl or alkenyl boronates in the presence of catalytic amounts of $NiCl_2$(dppf) (Scheme 74).[217] The reaction proceed with complete S_N2-selectivity.

Amines can serve as leaving group in the nickel-catalyzed allylation of boronic acids.[218] Thus, reaction of aryl- or alkenylboronic acids with allylic amines leads to the alkylated products with modest regioselectivity (Scheme 75).

Asymmetric nickel-catalyzed cross-coupling reactions with allylic electrophiles are also known.[219,220] The reaction of phenylmagesium bromide with a cyclic unsaturated acetal in the presence of a chiral nickel complex gives, after acidic workup, the ketone with high enantioselectivity (Scheme 76).[221]

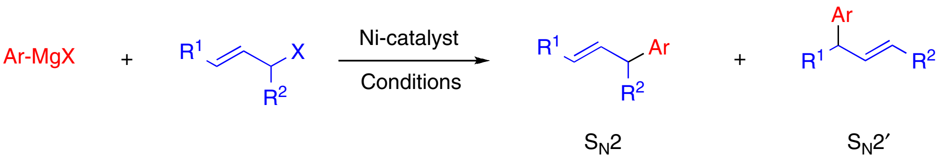
In the presence of a nickel/pybox catalyst, racemic propargylic halides or carbonates react with arylzinc reagents in a stereoconvergent manner. The coupling products are obtained in good yields and high enantioselectivities (Scheme 77).[222,223]

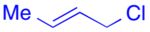
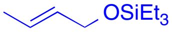
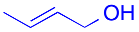
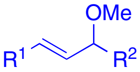
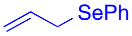
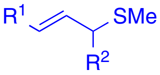
3.08.4.2.3 Cross-coupling with α-halocarbonyl compounds

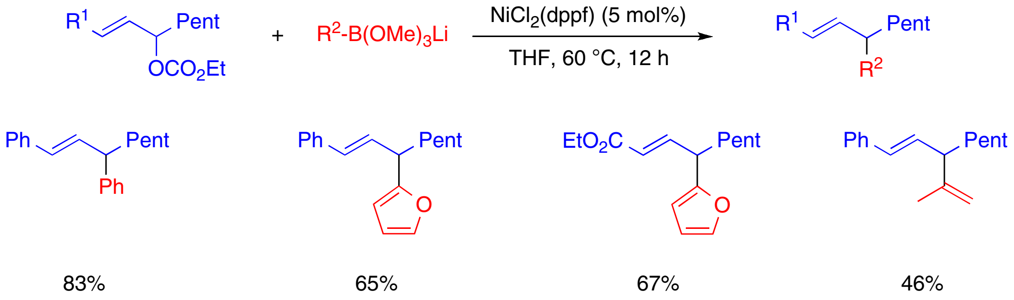
α-Halocarbonyl compounds are versatile substrates for nickel-catalyzed cross-coupling reactions. Several asymmetric coupling reactions have been developed.

Aryl Grignard reagents react with racemic α-bromoketones in the presence of a nickel/bisoxazoline catalyst to give the coupling product in high enantioselectivities (Scheme 78).[224]

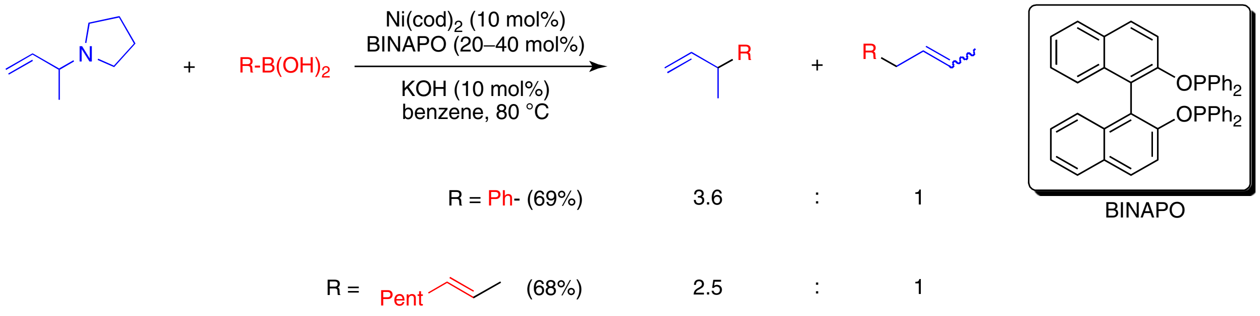
Table 21 Nickel-catalyzed allylation of aryl Grignard reagents



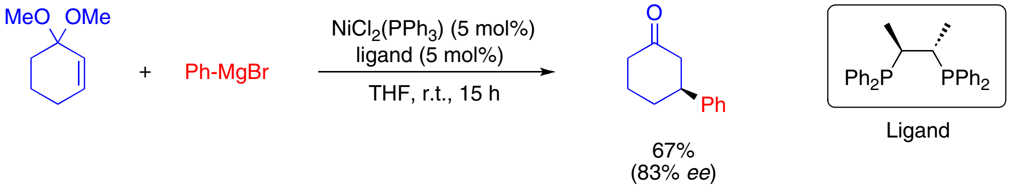
Entry	*Allylic electrophile*	*Ni-catalyst*	*S_N2/S_N2'*	*References*
1		$NiCl_2(dppf)$	25:75	213
2		$NiCl_2(dppf)$	12:88	213
3		$NiCl_2(dppf)$	20:80	213
4		$NiCl_2(PPh_3)_2$	1:1–99:1	214
5		$NiCl_2(PPh_3)_2$	–	215
6		$NiCl_2(dppp)$ or $NiCl_2(PPh_3)_2$	1:1–2:1	216



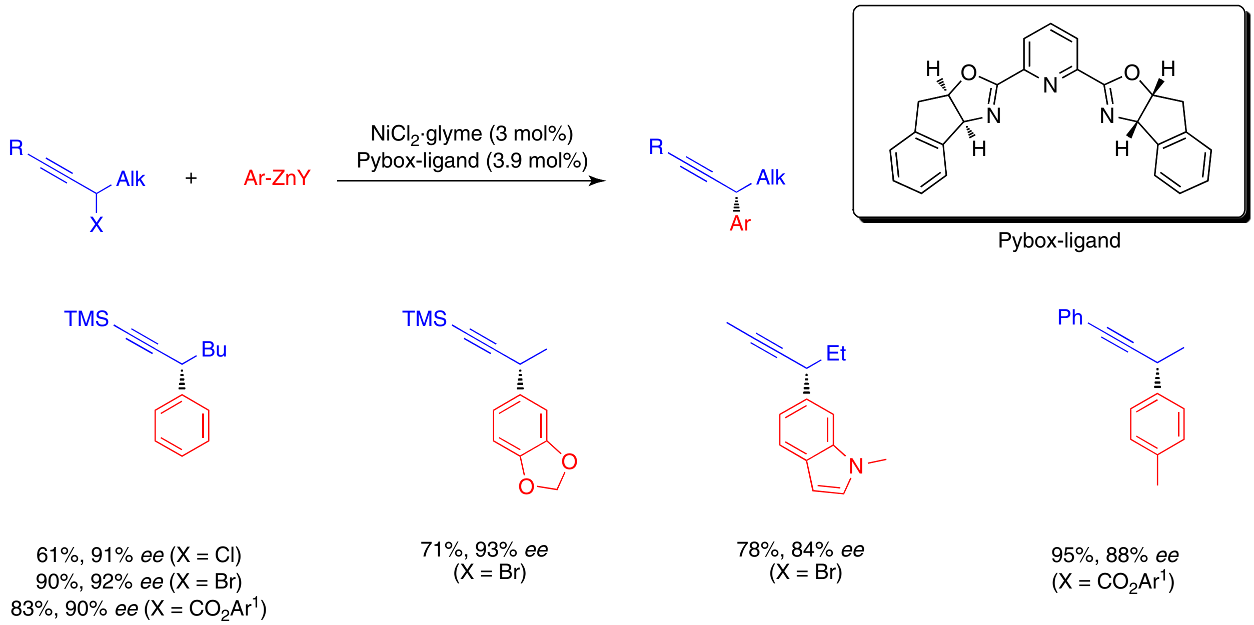
Scheme 74 Nickel-catalyzed allylation of aryl- or alkenylborates.



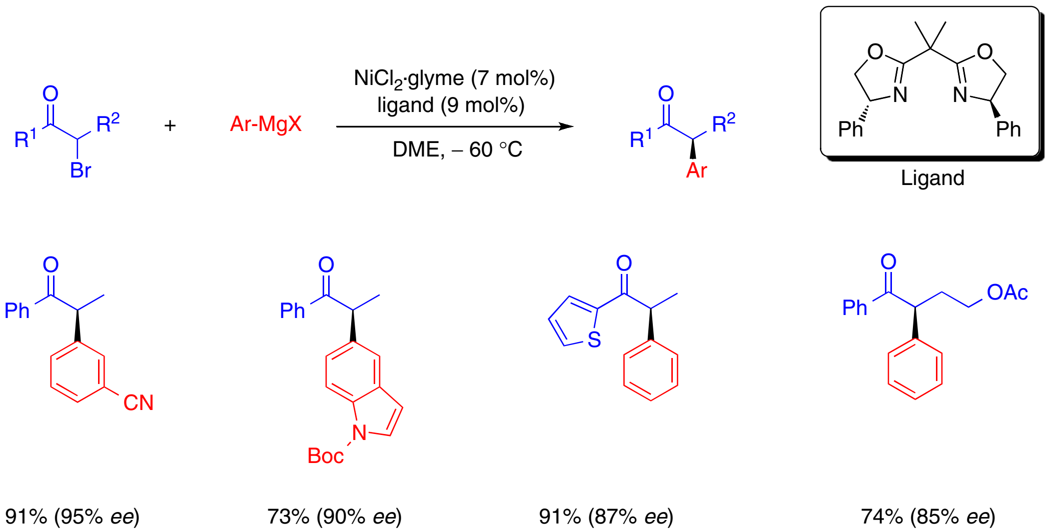
Scheme 75 Nickel-catalyzed coupling reaction between organoboronic acids and allylic amines.



Scheme 76 Nickel-catalyzed enantioselective allylation of phenylmagnesium bromide.



Scheme 77 Nickel-catalyzed enantioselective cross-coupling of propargylic electrophiles with arylzinc reagents.



Scheme 78 Nickel-catalyzed asymmetric cross-coupling between aryl Grignard reagents and α-bromoketones.

Alkenylzirconocene reagents undergo a similar enantioselective cross-coupling reaction (Scheme 79).[225] The β,γ-unsaturated ketones are obtained in high yields and good enantioselectivities.

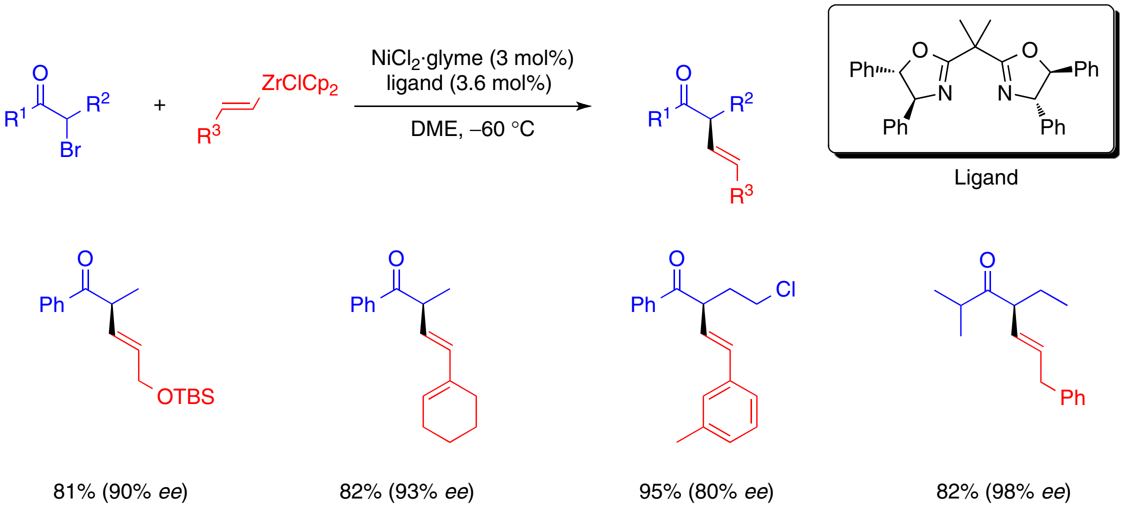
Arylboron compounds can be coupled with α-chloroamides in a stereoconvergent manner in the presence of a chiral nickel/diamine catalyst (Scheme 80).[226] Indolinylamides lead to the best yields and highest enantioselectivities.

Arylsilanes undergo a nickel-catalyzed cross-coupling with different α-halocarbonyl compounds (Scheme 81).[211] α-Haloketones, -esters, -amides, or -nitriles are suitable coupling partners.

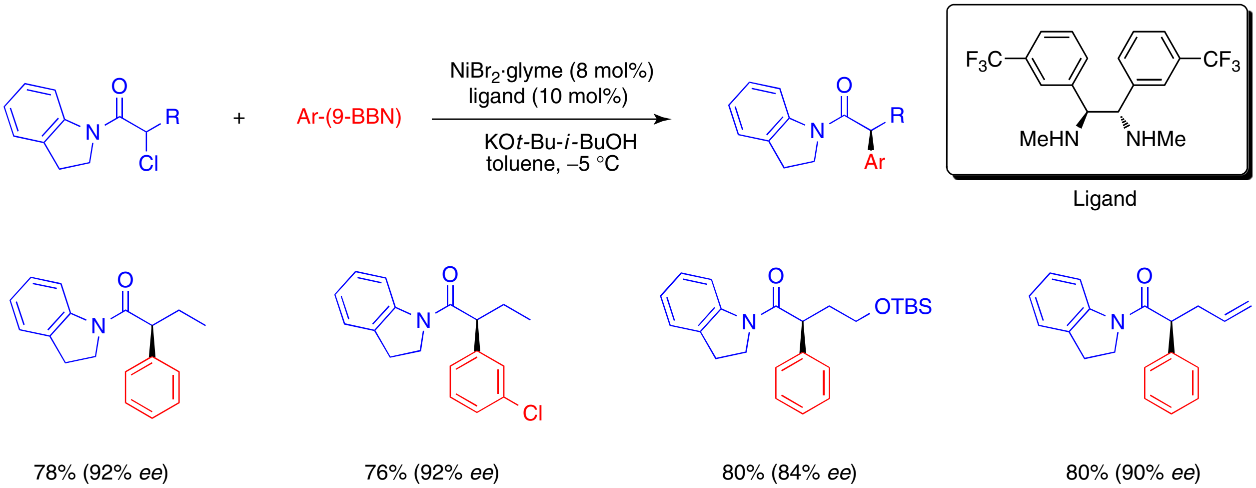
Using a chiral nickel/diamine catalyst, an asymmetric coupling between α-bromo esters and aryl- or alkenylsilanols can be achieved (Scheme 82).[227] Best results are obtained with sterically demanding esters, such as 2,6-di-*tert*-butyl-4-methylphenol (BHT).

3.08.4.2.4 Cross-coupling with other activated electrophiles

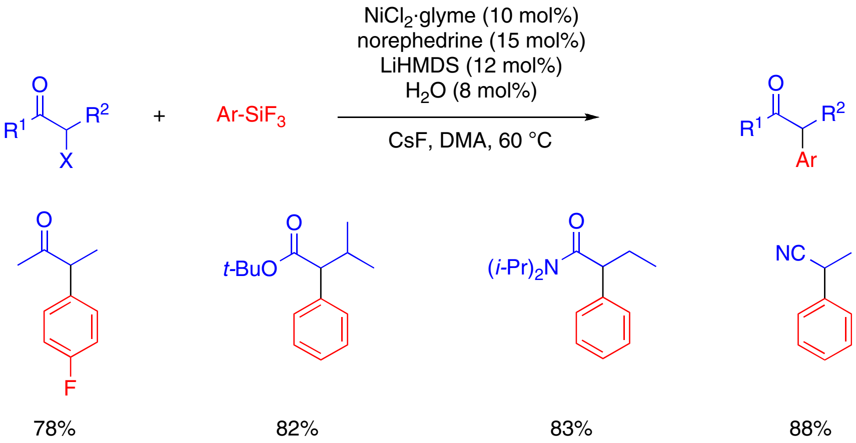
Several nickel-catalyzed cross-coupling reactions between organometallic reagents and various other activated electrophiles have been reported.



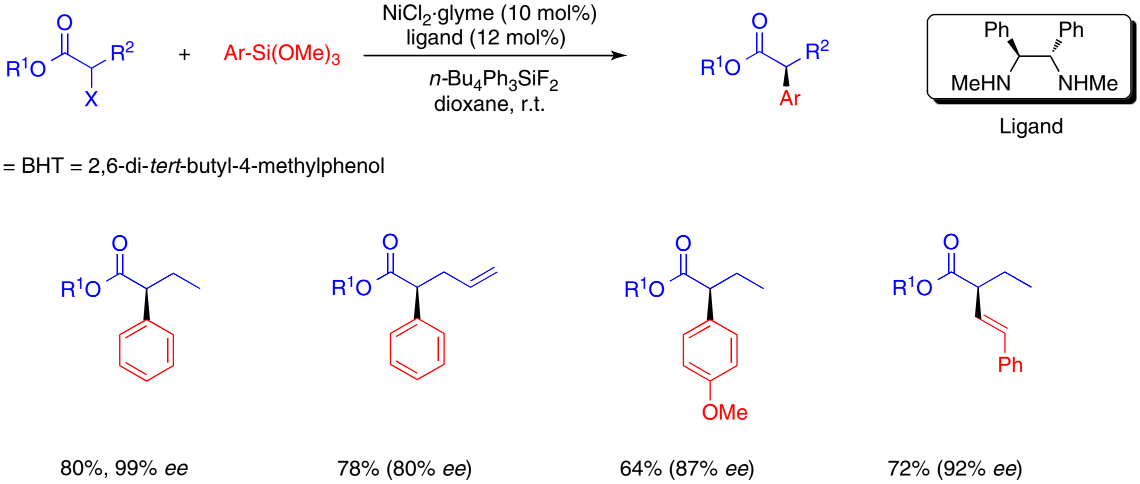
Scheme 79 Nickel-catalyzed enantioselective cross-coupling of alkenylzirconocene reagents.



Scheme 80 Nickel-catalyzed asymmetric cross-coupling of arylboron reagents.

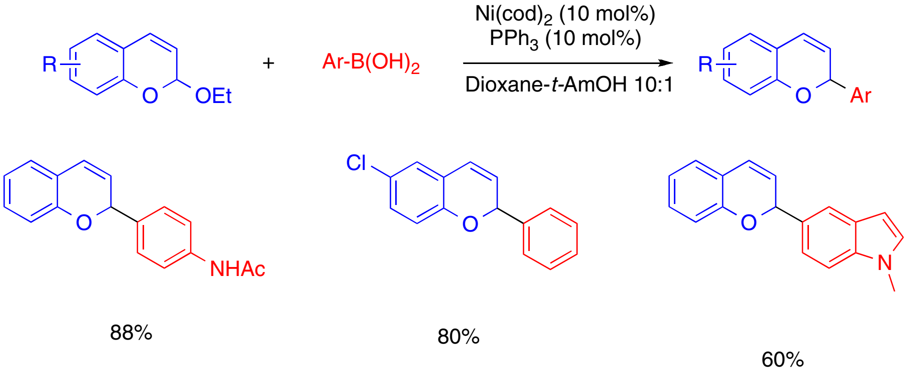


Scheme 81 Nickel-catalyzed cross-coupling between arylsilicon reagents and α-halocarbonyl compounds.



Scheme 82 Nickel-catalyzed asymmetric cross-coupling of α-bromo esters.

Chromene acetals undergo a nickel-catalyzed cross-coupling with aryl- or heteroarylboronic acids (Scheme 83).[228]



Scheme 83 Nickel-catalyzed cross-coupling of chromene acetals.

The nickel-catalyzed coupling between arylzinc reagents and different glycosyl halides furnishes the *C*-aryl glycosides (Scheme 84).[229,230] The reaction with acetobromo-α-D-glucose gives the coupling products in high yields and excellent *β*-selectivity (1: > 10 *α*:*β*). However, yield and stereoselectivity strongly depend on the glycosyl donor, and reaction conditions have to be optimized for each substrate.

3.08.4.3 Coupling with Aryl and Alkenyl Halides

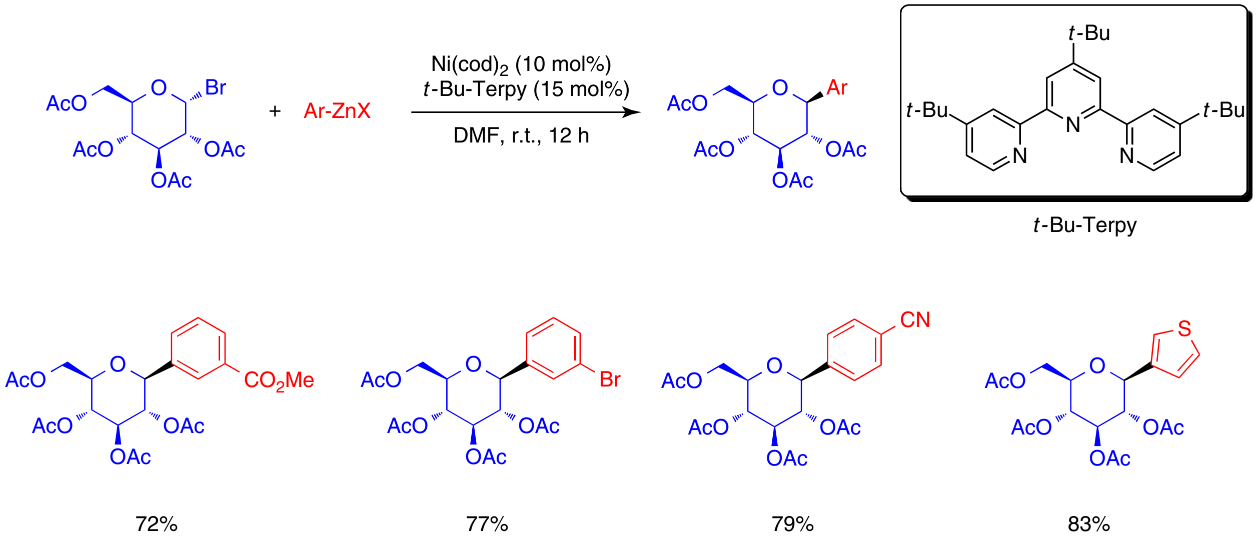
The nickel–catalyzed cross-coupling of alkyl organometallics provides a useful alternative to palladium-catalyzed reactions. Reactive nickel catalysts allow the cross-coupling of tertiary alkyl nucleophiles, which is not possible with palladium. However, the nickel-catalyzed cross-coupling is mostly limited to more reactive alkylzinc or Grignard reagents.

3.08.4.3.1 Cross-coupling with organomagnesium reagents

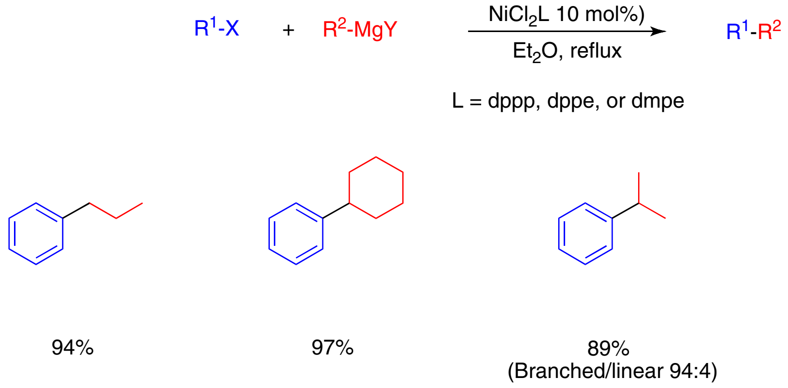
Nickel–phosphine complexes can catalyze the coupling reaction between alkyl Grignard reagents and aryl or alkenyl chlorides.[195,231–234] Primary or secondary alkyl Grignard reagents can be used (Scheme 85).[231] The coupling of secondary acyclic Grignard lead to the desired branched products with excellent selectivities.[235]

Dihalophenols undergo a regioselective nickel-catalyzed cross-coupling with alkylmagnesium reagents (Scheme 86).[236] High *ortho* preference is observed.

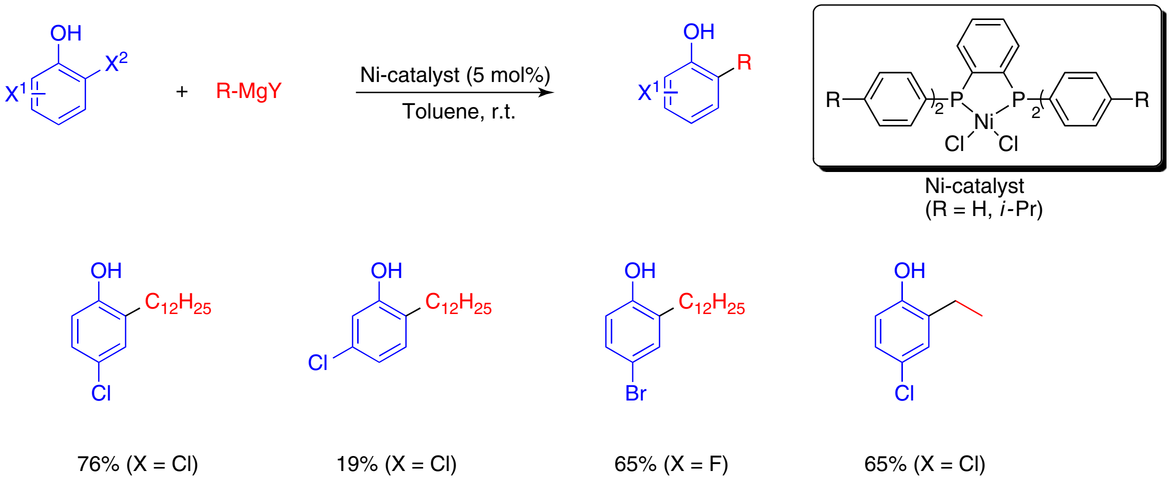
In contrast to palladium-catalyzed reactions, tertiary alkyl organometallic reagents can be used as nucleophiles in nickel-catalyzed reactions.[237–239] The reaction of tertiary alkyl Grignard with aryl or vinyl bromides or aryl triflates lead to the coupling products in high yields without isomerization (> 30:1) (Scheme 87).[239]



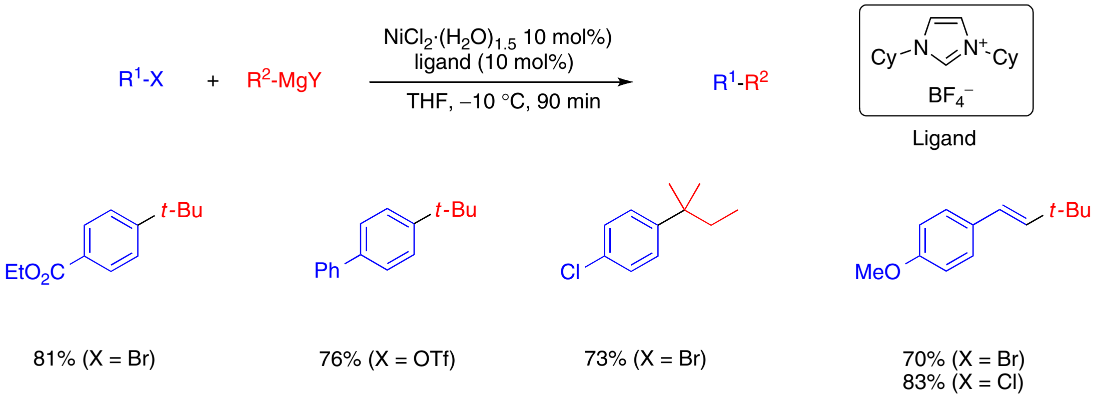
Scheme 84 Nickel-catalyzed cross-coupling of glycosyl bromides.



Scheme 85 Nickel-catalyzed cross-coupling of primary or secondary alkyl Grignard reagents.



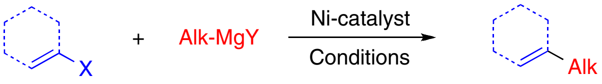
Scheme 86 Nickel-catalyzed *ortho*-selective cross-coupling of dihalophenols.

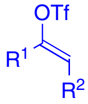
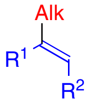
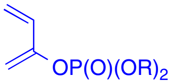
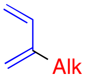
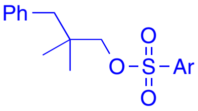
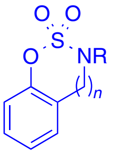
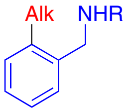


Scheme 87 Nickel-catalyzed cross-coupling of tertiary alkyl Grignard.

Nickel-catalyzed cross-coupling reactions have been reported between alkyl Grignard reagents and several different electrophiles (Table 22).[240–243] These include vinyl triflates (entry 1), dienyl phosphates (entry 2), or neopentyl arenesulfonates (entry 3). Cross-coupling with cyclic sulfamates leads to alkylation and ring cleavage (entry 4).

Table 22 Nickel-catalyzed cross-coupling reactions with C–O-electrophiles



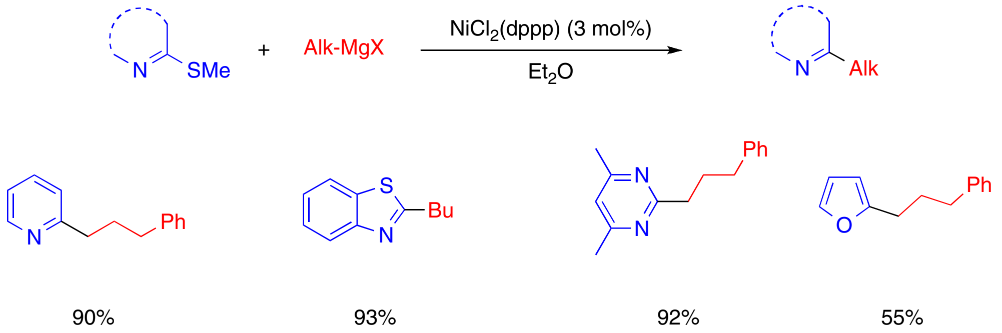
Entry	*R–X*	*Product*	*Ni-catalyst*	*References*
1			$NiCl_2$(dppe)	240
2			$NiCl_2$(dppe) or $NiCl_2$(dppp)	241
3		Ar–Alk	$NiCl_2$dppe	242
4			$NiCl_2$(dppf)	243

Aryl or alkenyl sulfides can be used as substrates in nickel-catalyzed coupling reactions. Heterocyclic sulfides undergo an efficient coupling with alkylmagnesium reagents in the presence of nickel catalyst (Scheme 88).[244,245]

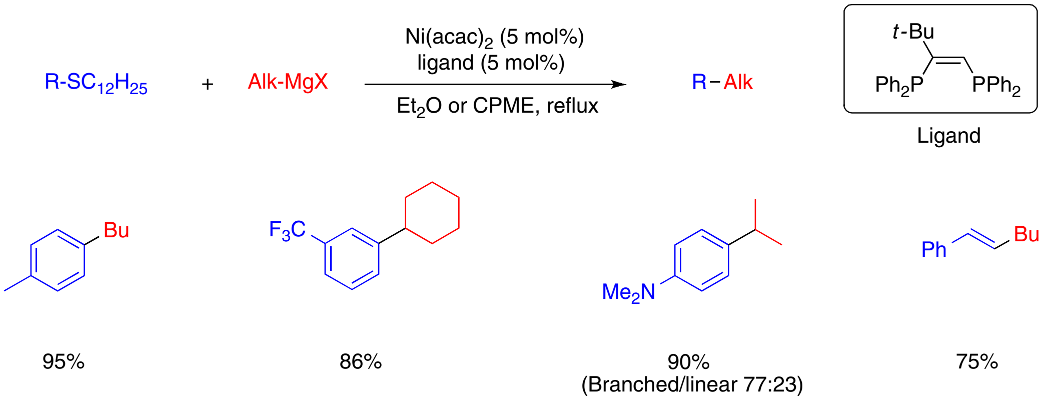
In contrast to palladium, the higher catalytic activity of nickel allows the coupling of nonactivated aryl or alkenyl sulfides (Scheme 89).[246,247] Reaction of secondary alkymagnesium reagents leads to a certain degree of isomerization.

3.08.4.3.2 Cross-coupling with organozinc reagents

Organozinc compounds undergo nickel-catalyzed cross-coupling reactions with a variety of aryl or alkenyl electrophiles (Table 23).[248–253] A heterogeneous nickel catalyst can be used for the coupling between functionalized alkylzinc reagents and aryl chlorides (entry 1). Benzylic zinc reagents undergo nickel-catalyzed cross-coupling reactions with aryl halides (entry 2). Other suitable electrophiles include aminoheteroaryl chlorides (entry 3) or 4-diethylphosphonooxocoumarins (entry 4) or thiomethylated *N*-heterocycles (entry 5). *S*-Aryl-thioglycolates represent an uncommon coupling partner, used in nickel-catalyzed C(sp^3)–C(sp^2)-bond-forming reactions (entry 6).

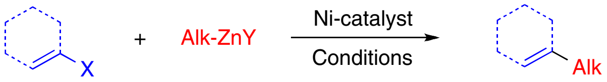


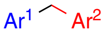
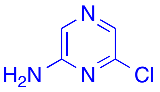
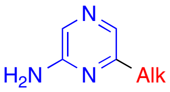
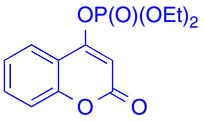
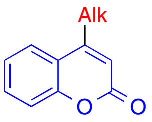
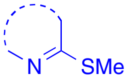
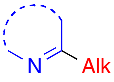
Scheme 88 Nickel-catalyzed cross-coupling of thiomethyl substituted heterocycles.



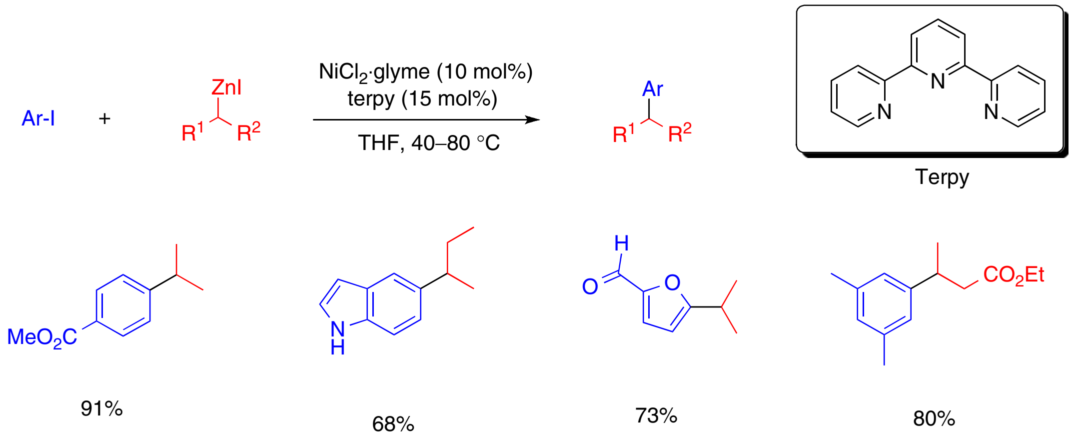
Scheme 89 Nickel-catalyzed cross-coupling of aryl- and alkenylsulfides.

Table 23 Nickel-catalyzed cross-coupling of alkylzinc reagents



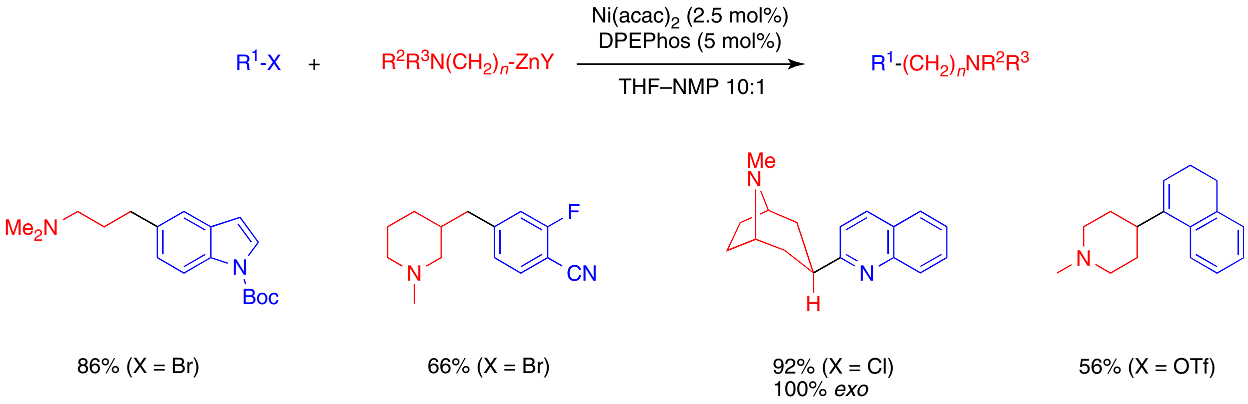
Entry	*R–X*	*Alk–ZnY*	*Product*	*Ni-catalyst*	*References*
1	Ar–Cl	FG-$(CH_2)_n$–ZnY	Ar–$(CH_2)_n$-FG	Ni/C, PPh_3	248
2	Ar^1–Cl, Ar^1–Br, Ar^1–OTs			$Ni(acac)_2$, PPh_3	249,250
3		Alk–ZnY		$NiCl_2(dppp)$	251
4		Alk–ZnY		$NiCl_2(dppe)$	252
5		Alk–ZnY		$Ni(acac)_2$, DPEPhos	253
6	Ar-SCH_2CO_2H	Alk–ZnY	Ar–Alk	$(MePh_2P)_2NiCl_2$	254

The nickel-catalyzed coupling of secondary alkylzinc halides lead to isomerization, just as in palladium-catalyzed reactions. The use of tridentate nitrogen-based ligands can prevent this side reaction. Thus, the reaction of secondary alkylzinc reagents with aryl iodides in the presence of a nickel/terpyridine catalyst gives the coupling products in high yield and no traces of isomerization (> 100:1) (Scheme 90).[255] Exogenous salts can have a dramatic effect on the yield and isomerization.



Scheme 90 Nickel-catalyzed cross-coupling of secondary alkylzinc halides.

Nickel-catalyzed cross-couplings of aminoalkyl zinc reagents with aryl or alkenyl halides or triflates furnish the biologically interesting aminoalkylated products (Scheme 91).[256,257] Secondary alkylzinc reagents perform equally well in this coupling and undergo a stereoselective reaction in certain cases.



Scheme 91 Nickel-catalyzed cross-coupling of aminoalkylzinc reagents.

3.08.4.4 Coupling Reactions with Acyl Halides and Related Electrophiles

Nickel-catalyzed cross-coupling of alkylorganometallics with acyl halides is not as common as the copper- and palladium-mediated procedures. However, it provides a useful alternative for the synthesis of ketones.

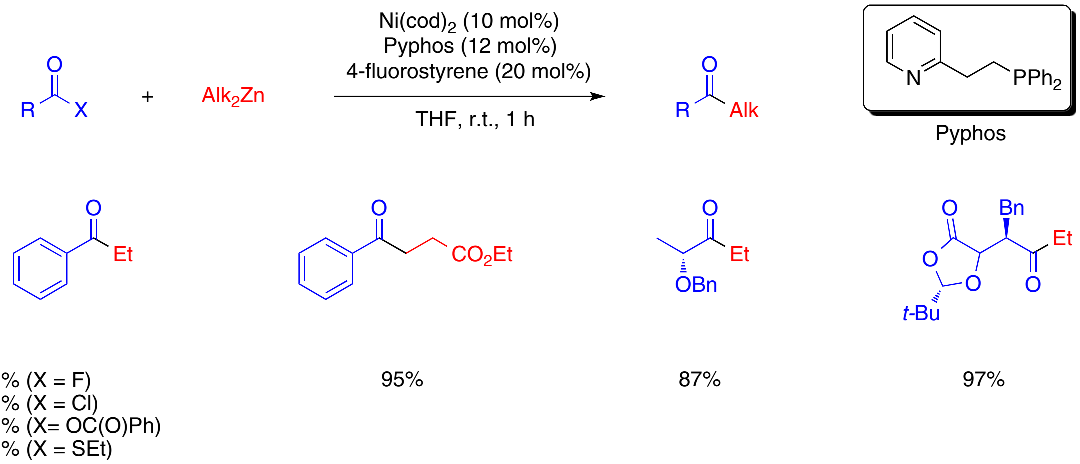
The nickel-catalyzed reaction of dialkylzinc reagents with carboxylic acid fluorides, chlorides, anhydrides, or thioesters is an especially mild method for the preparation of ketones (Scheme 92).[258] Sensitive functionalized acyl fluorides can participate in the reaction without the epimerization of stereocenters, a shortcoming of palladium- or copper-catalyzed procedures.

The nickel-catalyzed opening of cyclic anhydrides with alkylzinc reagents leads to the formation of γ- or δ-keto acids (Scheme 93).[259,260]

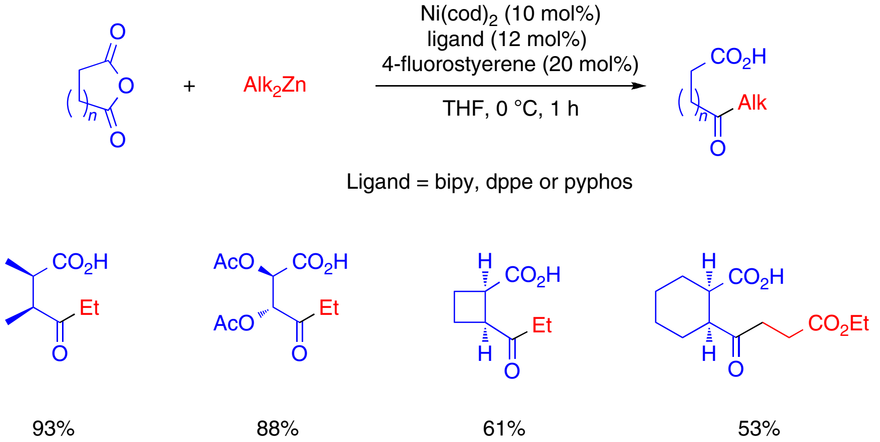
An enantioselective ring opening can be achieved with chiral ligands (Scheme 94).

3.08.5 Cobalt-Catalyzed Coupling Reactions

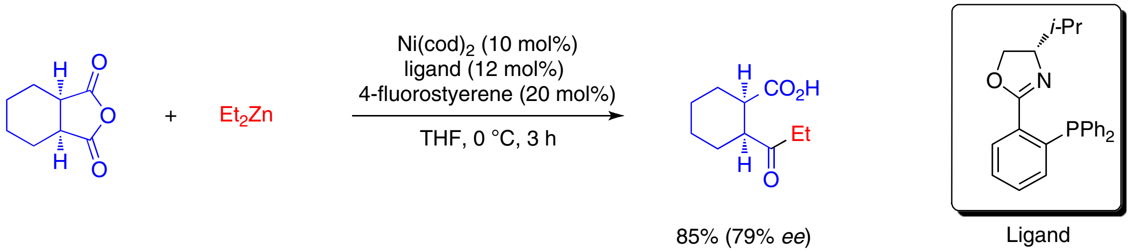
Since the first reports of cobalt-mediated reactions with organometallic compounds,[261,262] cobalt-catalyzed carbon–carbon bond-forming reactions have received special attention.[263,264] The scope of these cobalt-catalyzed coupling reactions is different from typical palladium- or nickel-catalyzed reactions, but similar to the scope of iron-catalyzed cross-couplings. β-Hydride elimination from alkylcobalt intermediate is not an issue. Therefore, cobalt-catalyzed cross-coupling reactions are especially interesting for couplings involving C(sp^3) organometallics or C(sp^3) electrophiles. Not much is known about the mechanism of cobalt-catalyzed coupling reactions.



Scheme 92 Nickel-catalyzed acylation of alkylzinc reagents.



Scheme 93 Nickel-catalyzed ring-opening of cyclic anhydrides.



Scheme 94 Nickel-catalyzed enantioselective ring-opening of cylic anhydrides.

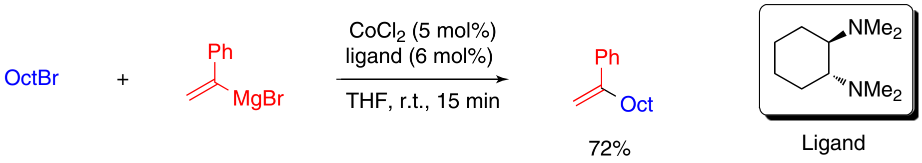
The general proposed catalytic cycle proceeds either through a Co(0)/Co(II) or a Co(I)/Co(III) cycle, involving single electron transfer (SET) processes or radical intermediates. This has been employed in several tandem radical cyclization and cross-coupling procedures. Since the active catalyst, a low-valent cobalt intermediate, is formed via reduction of a stable Co(II) precursor, cobalt-catalyzed coupling reactions are limited to strongly reducing organometallic compounds, mostly Grignard reagents.

3.08.5.1 Coupling Reactions with Nonactivated Alkyl Halides

The cobalt-catalyzed alkylation of alkenyl or aryl organometallic reagent is a useful extension to palladium- and nickel-catalyzed cross-coupling reactions. The scope is comparable to iron-catalyzed reactions, although sometimes better results and a higher chemoselectivity are observed with cobalt. These couplings are limited to organomagnesium reagents as nucleophiles.

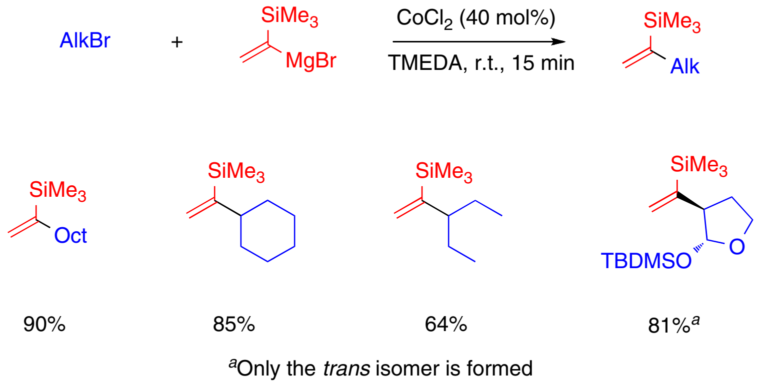
3.08.5.1.1 Cross-coupling with alkenylmagnesium reagents

In the presence of 5 mol% cobalt(II)chloride and *N*,*N*,*N*′,*N*′-tetramethyl-1,2-cyclohexyldiamine as ligand, styrylmagnesium bromide reacts with octylbromide, furnishing the coupling product in 72% yield (Scheme 95).[265]



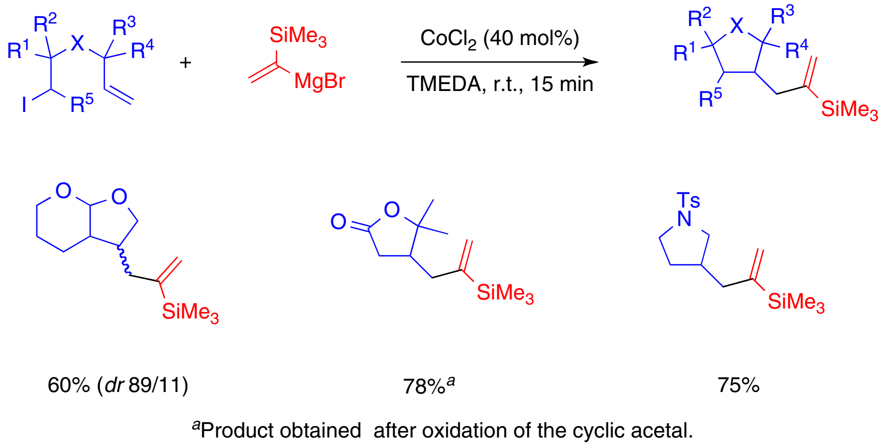
Scheme 95 Cobalt-catalyzed coupling between styrylmagnesium bromide and octyl bromide.

The cobalt-catalyzed cross-coupling of various primary and secondary alkyl bromides and 1-(trimethylsilyl)ethenylmagnesium bromide using TMEDA as solvent gives the alkylated products in good to excellent yields.[5] However, the reaction needs a large excess of the Grignard reagent (4 equivalents) and is limited to this specific organomagnesium compound (Scheme 96).[266]



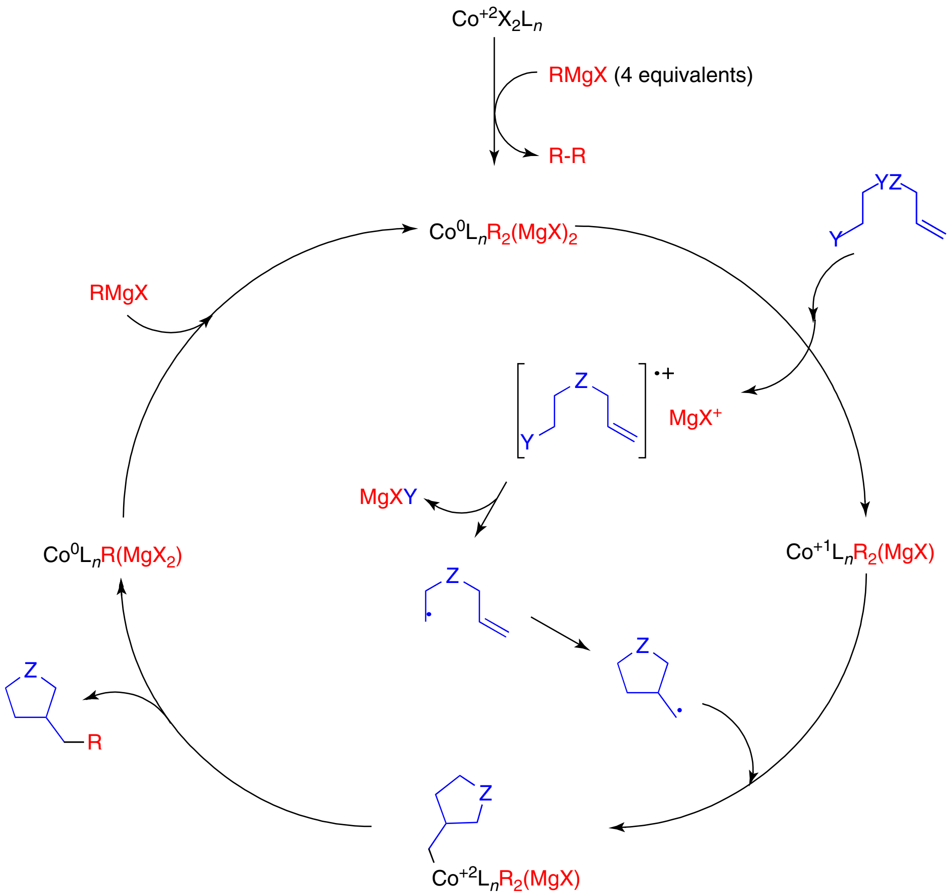
Scheme 96 Cobalt-catalyzed coupling of 1-(trimethylsilyl)ethenylmagnesium bromide and alkyl bromides.

When ε-alkenyl iodides are employed as coupling partners, a cyclic product is obtained via a tandem radical-cyclization/cross-coupling reaction. Various heterocycles can be synthesized in good to excellent yields (Scheme 97).[266]



Scheme 97 Tandem cobalt-catalyzed radical cyclization and cross-coupling of 1-(trimethylsilyl)ethenylmagnesium bromide.

The proposed mechanism for this and similar reactions involves a SET from a cobalt(0) species to the alkyl halide, followed by formation of an alkyl radical and subsequent radical cyclization. Recombination of the radical with a cobalt(I) complex and reductive elimination provides the product and a cobalt(0) complex, which is reconverted to the active catalyst by reaction with the Grignard reagent (Scheme 98).[267]



Scheme 98 Mechanism for the tandem radical cyclization and cross-coupling reactions.

3.08.5.1.2 *Cross-coupling with arylmagnesium reagents*

Several methods exist for the cobalt-catalyzed alkylation of aryl Grignard reagents. In general, best yields are obtained with diamine ligands, such as *N*,*N*,*N'*,*N'*-tetramethyl-1,2-cyclohexyldiamine[265] or TMEDA[268] (Table 24). Primary and secondary alkyl bromides or iodides can be used successfully (Table 24, entries 1–3, 5, 6, and 8), whereas alkyl chlorides or tosylates lead to low yields (entries 4 and 7). Tertiary alkyl bromides cannot be used. The reaction is highly chemoselective, and various sensitive groups such as an ester (entry 9), amide (entry 10), or even a keto function (entry 11) are tolerated. Coupling with 1-bromo-5-chloropentane gives selectively the corresponding alkyl chloride (entry 12). High chemoselectivity is also observed with secondary alkyl bromides (entry 13). In general, the use of a $Co(acac)_3$/TMEDA system leads to higher yields and improved tolerance of functional groups. Noteworthy is the chemoselectivity of cobalt-catalyzed alkylations compared to similar iron-catalyzed reactions. Secondary functionalized alkyl halides are especially problematic substrates for iron-catalyzed couplings.

The cobalt-catalyzed coupling with cyclic haloacetals bearing a stereogenic center in the α-position gives the β-arylated furans or pyrans in good yields (Scheme 99).[265] The stereoselectivity of this reaction is highly dependent on the size of the ring. Good selectivities are only obtained with the furan.

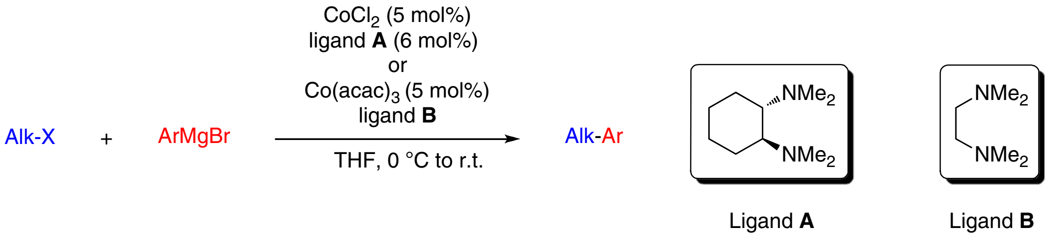
The mechanism of these reactions is similar to the one previously described (Scheme 98), and this fact has been employed in the development of several tandem radical cyclization and arylation procedures. Thus, the reaction between ε-alkenyl halides and phenylmagnesium bromide in the presence of a cobalt catalyst leads to the cyclized coupling products (Table 25).[267] Various heterocyclic (Table 25, entries 1–4) or carbocyclic compounds (entry 5) can be synthesized with this procedure. The yield and the stereoselectivity of this reaction depend strongly on the number and the position of the substituents on the starting material. The reaction is limited to substrates bearing a terminal olefin. Otherwise, no coupling is observed and the reaction leads to a Heck-type product (entry 6).

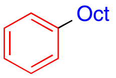
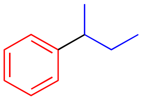
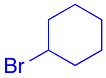
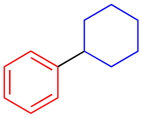
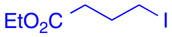
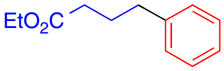
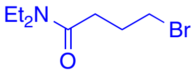
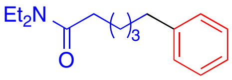
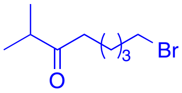
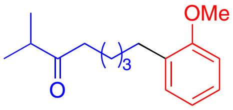
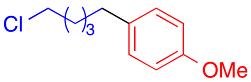
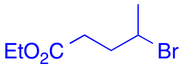
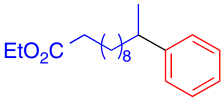
This reaction can be also applied to the synthesis of oxasilacyclopentanes (Scheme 100).[269] These products can be converted to synthetically useful 1,3-diols by a Tamao–Fleming oxidation.

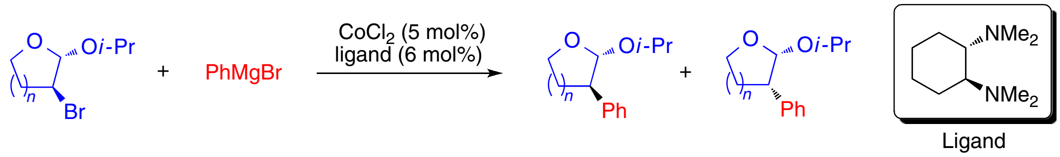
3.08.5.2 Coupling Reactions with Activated Alkyl Halides and Related Electrophiles

Copper-, palladium-, or nickel-catalyzed cross-couplings of allylic substrates with aromatic organometallic compounds are useful methods for the construction of $C(sp^2)–C(sp^3)$ bonds. Less is known about cobalt-catalyzed allylation reactions. The reaction of

Table 24 Cobalt-catalyzed coupling between alkyl halides and arylmagnesium reagents



Entry	*Alk–X*	*Product*	*Ligand*	*Yield (%)*
1	Oct–I		A	99
2	Oct–Br		A	80
3	Oct–Br		B	95
4	Oct–Cl		A	10
5	*s*-Bu–I		B	94
6	*s*-Bu–Br		B	92
7	*s*-Bu–OTs		B	10
8			A	95
9			A	91
10			B	84
11			B	88
12			B	89
13			B	92



n = 2: 83%, *trans/cis* = 60/40
n = 1: 80%, *trans/cis* = 96/4

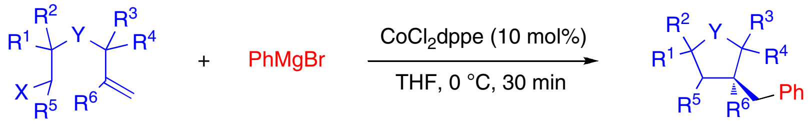
Scheme 99 Cobalt-catalyzed stereoselective cross-coupling with cyclic haloacetals.

phenylmagnesium bromide with allylic ethers in the presence of cobalt salts furnishes the coupling products in good yields. But the reaction is not regioselective, except for 1- and 3-phenyl-2-propenyl ethers (Scheme 101).[270]

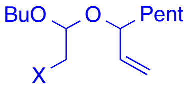
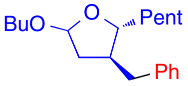
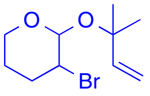
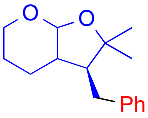
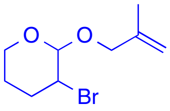
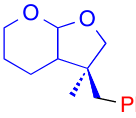
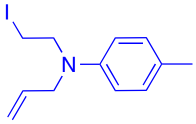
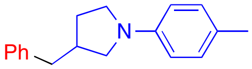
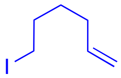
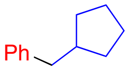
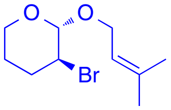
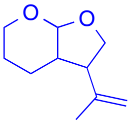
Under similar conditions, coupling with allylic acetate gives selectively the monosubstituted products (Scheme 102).[270]

A useful extension is the cobalt-catalyzed allylation of diarylzinc compounds. The cross-coupling is highly stereoselective and stereospecific and leads to the S_N2 products with complete retention of the configuration of the double bond (Table 26).[271] Sensitive functional groups (Table 26, entries 1–6) or heteroaromatic zinc reagents (entry 3) are well tolerated, and readily available allylic phosphates can be employed as coupling partners (entries 5 and 6).

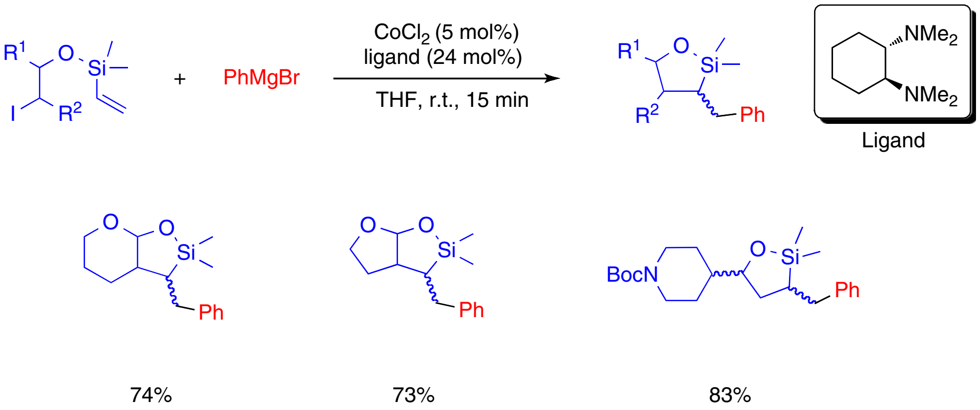
Table 25 Cobalt-catalyzed tandem radical cyclization and arylation



Dppe = Bis(diphenylphosphino)ethan

Entry	*Alkenyl halide*	*Product*	*Yield (%)*[a]
1			X=I: 78 (55/45) X=Br: 80 (55/45)
2			84 (62/38)
3			51 (single)
4			81
5			59
6			89

[a]The diastereometric ratio is given in parentheses.

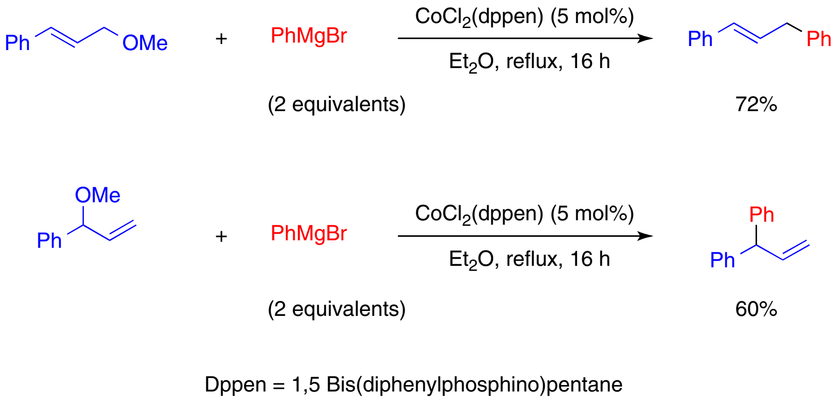


Scheme 100 Cobalt-catalyzed synthesis of oxasilacyclopentanes.

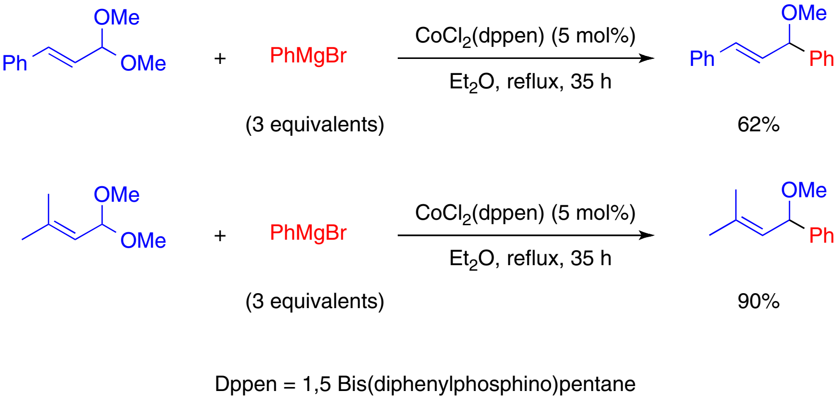
3.08.5.3 Coupling Reactions with Aryl and Alkenyl Halides

3.08.5.3.1 Cross-coupling with alkenyl halides

The first cobalt-catalyzed cross-couplings between alkenyl halides and alkyl Grignard reagents were limited to very reactive bromostyrenes, and an excess of the organomagnesium reagent was needed.[272] However, the use of *N*-methylpyrrolidinone



Scheme 101 Cobalt-catalyzed cross-coupling of phenylmagnesium bromide with allylic ethers.



Scheme 102 Cobalt-catalyzed arylation of allylic acetals.

(NMP) as additive (4–9 equivalents) dramatically improves the yield and hence the utility of these reactions (Scheme 103).[273] Only a slight excess of the Grignard reagent (1.1 equivalents) is needed, and the reaction is highly stereospecific.

Good yields are obtained by coupling alkenyl iodides, bromides, or chlorides (Table 27, entry 1) with primary (entries 1 and 2) or secondary aliphatic organomagnesium reagents (entries 3 and 4).[273] The reaction is highly chemoselective, tolerating, for example, a sensitive ester or keto functionality (entries 5 and 6). Only tertiary alkyl Grignard reagents give poor results (entry 7).

The coupling of trimethylsilylmethylmagnesium chloride with alkenyl halides is also possible. Good yields are obtained in the presence of 5 mol% cobalt(II)chloride as catalyst and without any additive. Only α,β-disubstituted alkenyl halides give poor yields (Scheme 104).[274]

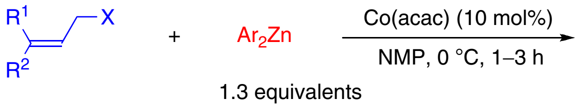
With 1,2-dihaloethylenes as electrophilic coupling partners, only the monosubstituted alkenyl halides are obtained (Table 28).[273,275] This reaction is complementary to the iron-catalyzed reaction, where the double-substituted product is formed exclusively. Primary Grignard reagents (Table 28, entry 1), trimethylsilylmethylmagnesium chloride (Table 28, entries 2 and 4), or dimethylphenylsilylmagnesium chloride (Table 28, entry 3) are suitable nucleophiles for this reaction. It is noteworthy that (*E*)-1,2-dihaloethylenes react faster than the corresponding (*Z*)-isomers, and a stereodifferentiation between (*E*)- and (*Z*)-dihaloethylenes is possible. Thus the reaction of trimethylsilylmagnesium chloride with a mixture of (*Z*)- and (*E*)-1,2-dibromoethylene (5 equivalents) furnishes only the (*E*)-1-bromoalkene (Table 28, entry 4).

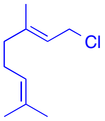
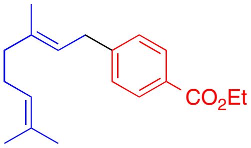
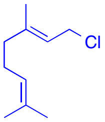
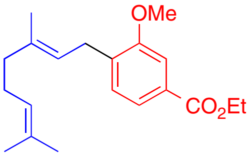
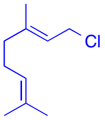
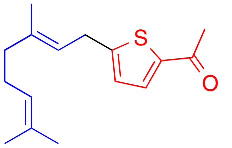
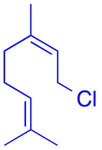
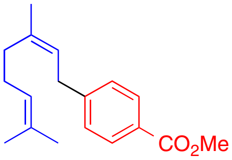
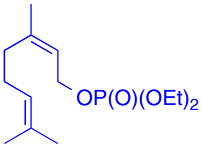
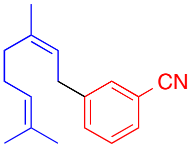
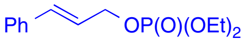
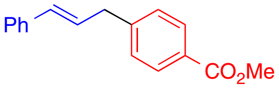
The cobalt-catalyzed alkenylation can be extended to alkylzinc halides.[276] The coupling of the less reactive organozinc compounds is slower, higher temperatures are needed, and the reaction is limited to alkenyl iodides. In addition, higher loading of the catalyst (20–30 mol%) and a large excess of the zinc reagents (3–8 equivalents) are needed (Table 29). However, the coupling is stereospecific (Table 29, entries 1, 2, and 4) and chemoselective. Alkylzinc reagents bearing functional groups, such as an ester (entries 5 and 6) or cyano group (entry 4) or benzylic zinc halide (entry 3), are tolerated.

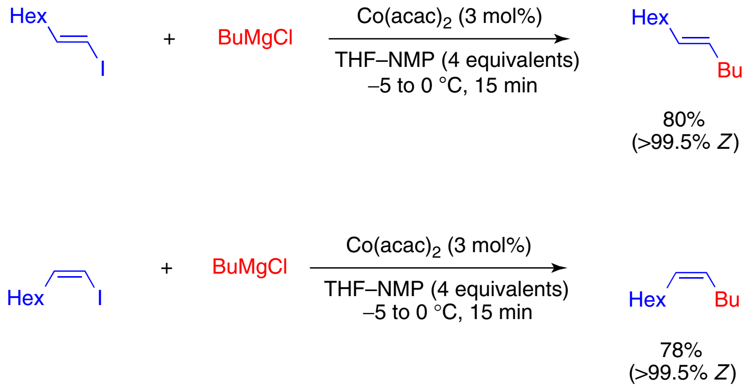
3.08.5.3.2 Coupling with aryl halides

The cobalt-catalyzed coupling of aryl halides with alkyl organometallics could represent an interesting alternative to the related palladium- or nickel-catalyzed methods. However, there is only one report in this field. The cobalt-catalyzed coupling between

Table 26 Cobalt-catalyzed allylation of diarylzinc reagents

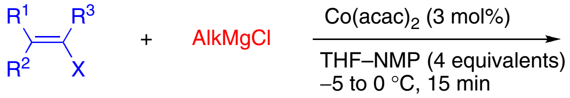


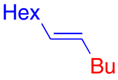
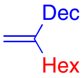
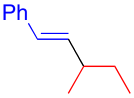
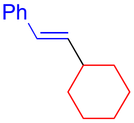
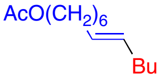
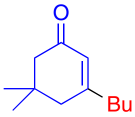
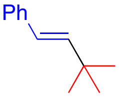
Entry	Allyl chloride or phosphate	Product	Yield (%)
1			72
2		 Nocarasin C	78
3			78
4			76
5			70
6			67

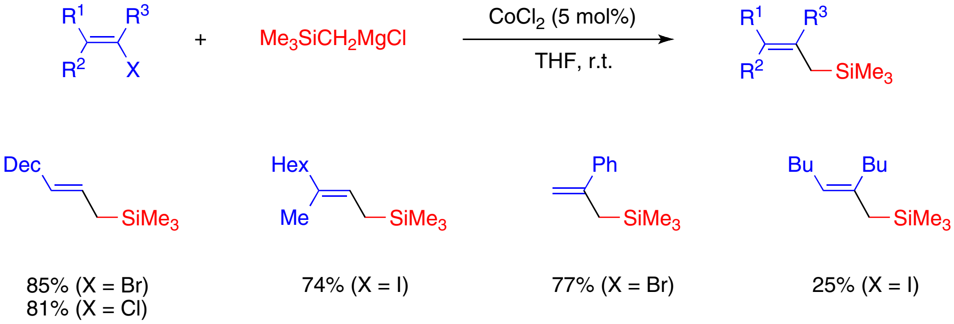


Scheme 103 Stereospecific cobalt-catalyzed coupling reactions.

Table 27 Cobalt-Catalyzed Cross-Coupling between Alkenyl Halides and Alkyl organomagnesium reagents



Entry	*Product*	*Yield (%)*
1		80 (X=I) 80 (X=Br) 73 (X=Cl)
2		73 (X=Br)
3		71 (X=Br)
4		87 (X=Br)
5		65 (X=Br)
6		63 (X=Cl)
7		36 (X=Br)



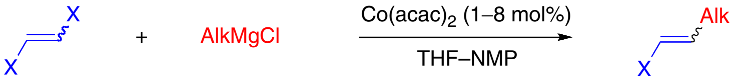
Scheme 104 Cobalt-catalyzed coupling of alkenyl halides with trimethylsilylmagnesium chloride.

aryl bromides and alkylmagnesium reagents generally gives the coupling products in good to excellent yields in short reaction times (Scheme 105).[277] However, the method is limited to primary alkyl Grignard reagents.

3.08.5.4 Coupling Reactions with Acyl Halides

Dialkylzinc reagents react with carboxylic acid chlorides in the presence of a catalytic amount of cobalt(II)bromide in a THF–NMP solvent mixture (Scheme 106).[278] Good to excellent yields are obtained with various aliphatic and aromatic acid chlorides or trifluoroacetic anhydride. However, an excess of the diorganozinc reagent (3 equivalents) is needed.

Table 28 Cobalt-catalyzed selective coupling between 1,2-dihaloethylenes and alkyl Grignard reagents



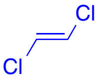
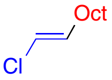
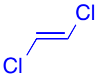
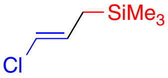
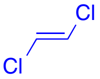
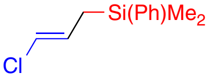
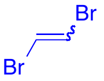
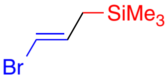
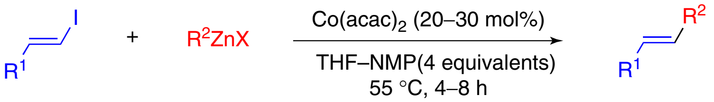
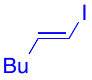
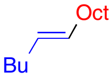
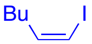
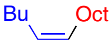
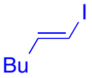
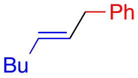
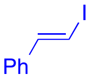
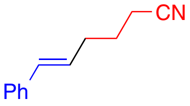
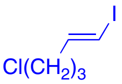
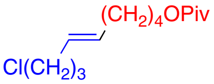
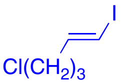
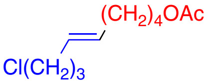
Entry	*XCH=CHX*	*Product*	*Yield (%)*	*References*
1			57	273
2			88	275
3			78	275
4	 (*E*/*Z*=65/35)		74 (100% *E*)	275

Table 29 Cobalt-catalyzed coupling of organozinc halides with alkenyl iodides

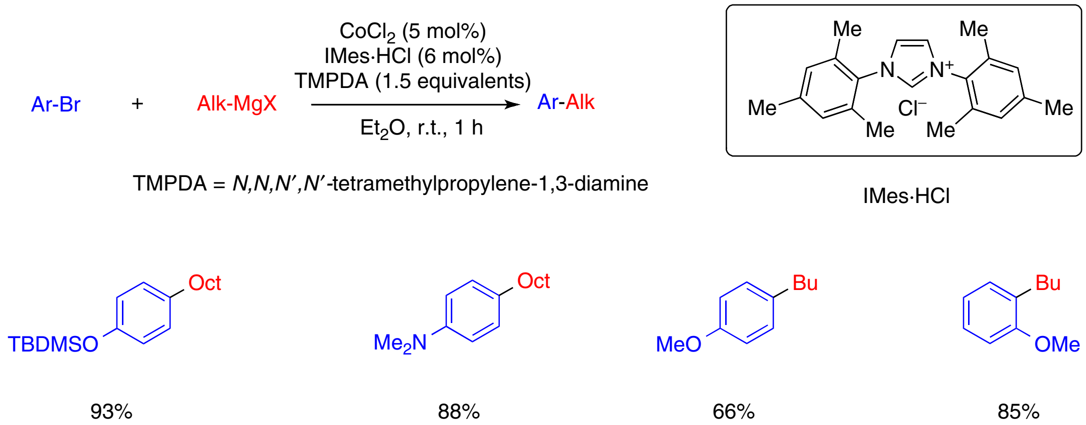


Entry	*Alkenyl halide*	*Product*	*Yield (%)*
1			81
2			71
3			54
4	 (*E*/*Z*=91/9)		50 (*E*/*Z*=91/9)
5			65
6			77

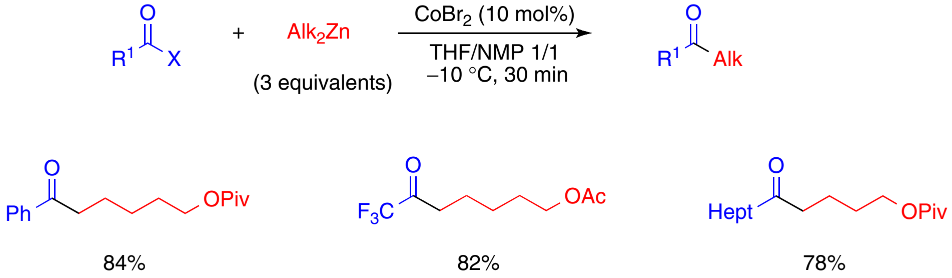
3.08.6 Iron-Catalyzed Coupling Reactions

Iron is one of the most abundant and consequently one of the cheapest metals on earth. Iron salts and complexes are in general nontoxic and environmentally safe. Thus, iron-catalyzed cross-couplings are an attractive alternative to nickel- or palladium-catalyzed processes.[279–281]. Since the first reports of an iron-catalyzed cross-coupling reaction,[282,283] several useful iron-catalyzed procedures have been developed, which are in certain cases superior to other methods.

As for cobalt-catalyzed reactions, β-hydride elimination from alkyl-iron intermediates is not a issue, making iron an ideal catalyst for the cross-coupling of alkyl electrophiles or nucleophiles. The mechanism of iron-catalyzed cross-coupling reactions is not well understood. Various catalytic cycles have been proposed, with iron shuttling between Fe(-II)/Fe(0),[284–288] Fe(0)/Fe(II),[289]

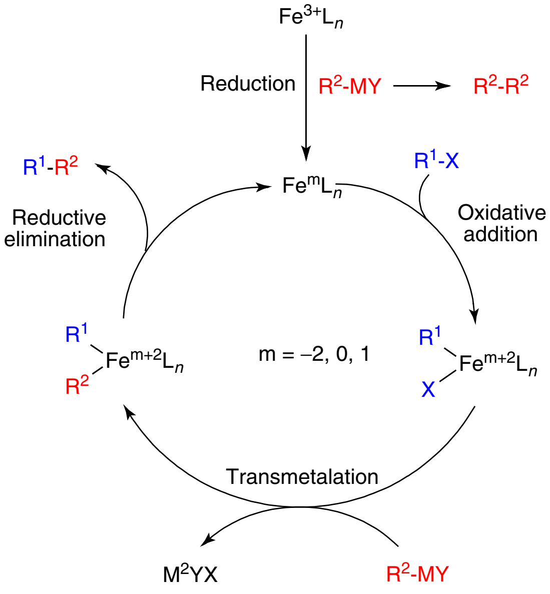


Scheme 105 Cobalt-catalyzed cross-coupling between aryl bromides and alkyl Grignard reagents.



Scheme 106 Cobalt-catalyzed acylation of diorganozinc reagents.

Fe(I)/Fe(III),[290–293] or Fe(II)/Fe(III)[294] have been proposed (Scheme 107). These studies also indicate that different Fe species are formed depending on the nature of the organometallic reagent.[295] A common feature of all proposed mechanisms is the reduction of the Fe(III) precursor to the catalytic active species through action of the organometallic reagent. Because only strongly reducing organometallic reagents are capable of effecting this reduction, iron-catalyzed coupling reactions are mostly limited to Grignard reagents.



Scheme 107 General mechanism of iron-catalyzed cross-coupling reactions.

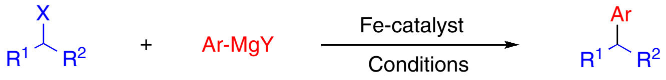
3.08.6.1 Coupling Reactions with Nonactivated Alkyl Halides

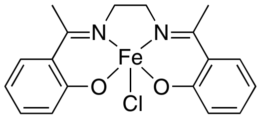
Several iron-catalyzed cross-coupling reactions between organometallic reagents and alkyl halides have been developed. Primary or secondary alkyl halides can be coupled efficiently with aryl- or alkenyl nucleophiles.

3.08.6.1.1 Cross-coupling with organomagnesium reagents

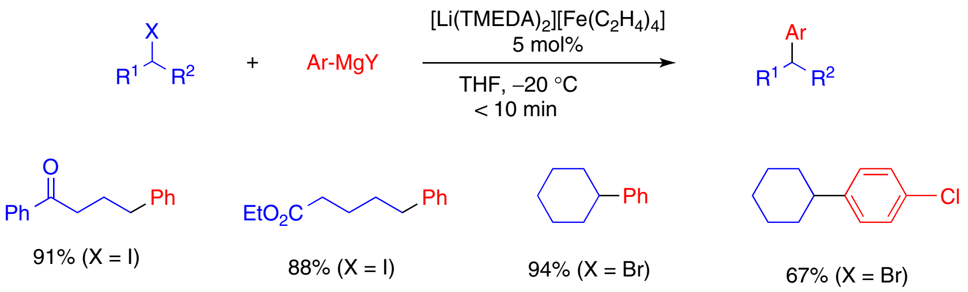
Arylmagnesium reagents undergo efficient cross-coupling with primary or secondary alkyl halides in the presence of an iron catalyst (Table 30).[289,296–301] The reaction with alkyl iodides, bromides, or chlorides leads to the desired coupling product, often in comparable yields, although in some cases more active catalysts or special conditions have to be used for less reactive alkyl chlorides (entry 5). The coupling of an alkyl tosylate has been reported (entry 1). However, *in situ* formation of the corresponding alkyl halide might be possible in this case (see Scheme 114). Amines or diamines are often used as additive or ligand and can increase the yield significantly (entries 2, 4, and 5).

Table 30 Iron-catalyzed cross-coupling between aryl Grignard reagents and alkyl halides



Entry	*X*	*Fe-catalyst*	*References*
1	I, Br, Cl, OTs	$Fe(acac)_3$	296
2	I, Br, Cl	$FeCl_3 \cdot$ TMEDA (1.2 equivalents)	297
3	I, Br, Cl		298
4	I, Br, Cl	$FeCl_3$ Et_3N, TMEDA or DABCO (20 mol%)	299
5	Cl	$FeCl_3$ IPr · HCl	300
6	I, Br	$FeCl_3 \cdot$ TMEDA/HMTA	289
7	Br, I	$[Li(TMEDA)]_2[Fe(C_2H_4)_4]$	301

A low-valent iron(II) complex shows an exceptional catalytic activity. The complex catalyzes the rapid reaction of arylmagnesium reagents with alkyl bromides or iodides (Scheme 108).[301] Due to the mild conditions, several sensitive functional groups, such as an ester or ketone, are tolerated.

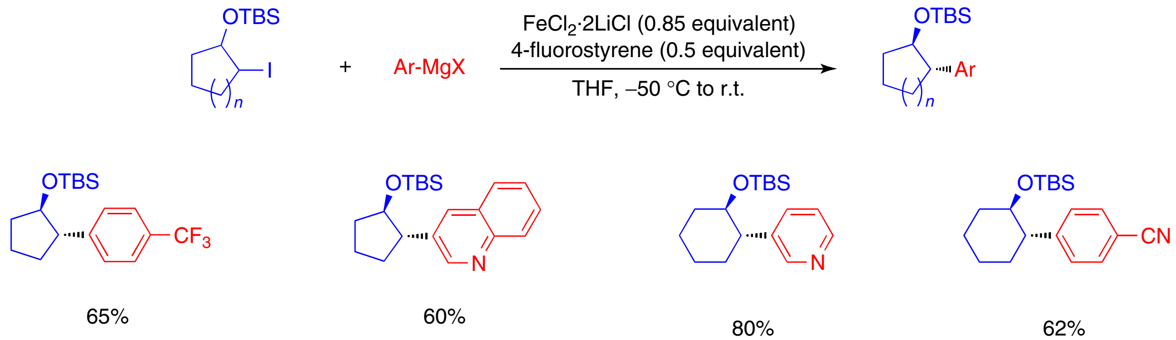


Scheme 108 Iron-catalyzed coupling between alkyl halides and aryl Grignard reagents.

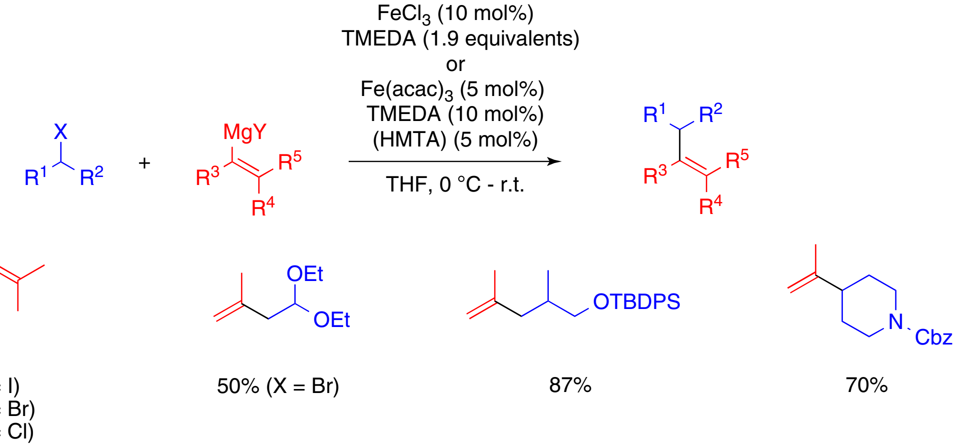
Cyclic iodohydrine derivatives undergo diastereoselective iron-mediated cross-coupling with aryl Grignards (Scheme 109).[302] The reaction is highly stereoconvergent and the thermodynamically favored *trans*-products are formed.

Alkenylmagnesium halides also react with alkyl electrophiles in the presence of iron catalysts (Scheme 110).[303,304] The reaction tolerates functional groups such as acetals or amides, and is in general stereoselective.

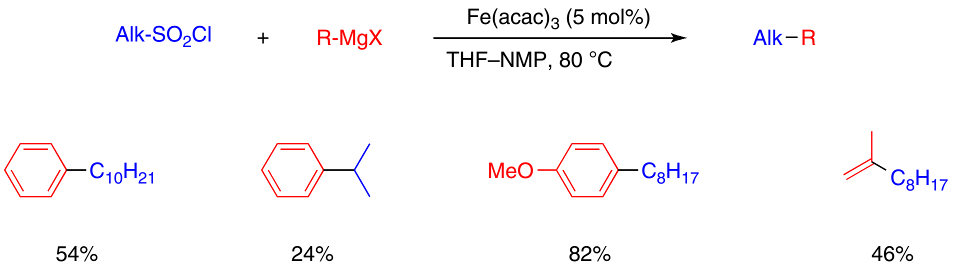
Sulfonyl chlorides react with aryl- or alkenylmagnesium halides in the presence of $Fe(acac)_3$ under extrusion of sulfur dioxide to give the C–C coupling product (Scheme 111).[305]



Scheme 109 Iron-mediated diastereoselctive cross-coupling with 2-iodocyclo alcanol derivatives.



Scheme 110 Iron-catalyzed cross-coupling between alkyl halides and alkenyl Grignard.



Scheme 111 Iron-catalyzed desulfinylative cross-coupling of alkylsulfonyl chlorides.

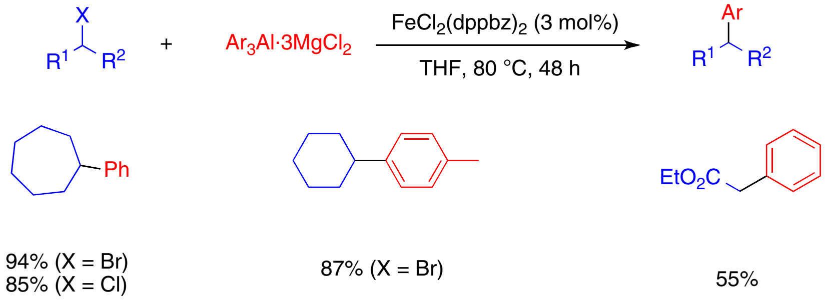
3.08.6.1.2 Cross-coupling with organoaluminum and -zinc reagents

An iron-catalyzed cross-coupling between triarylaluminum reagents and alkyl bromides or chlorides has been reported (Scheme 112).[306] Magnesium salts have a critical effect on the yield and selectivity of the reaction.

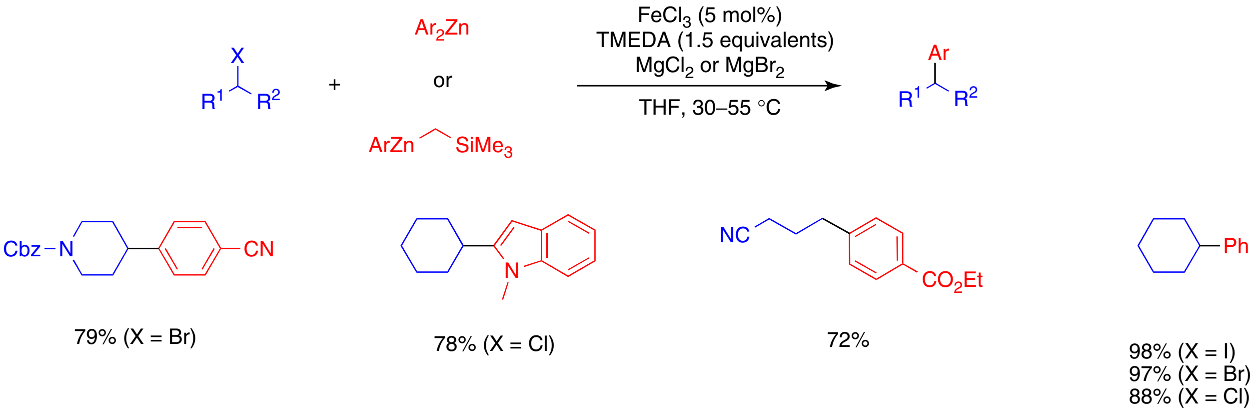
Diarylzinc reagents undergo an iron-catalyzed cross-coupling with primary or secondary alkyl halides (Scheme 113).[307] However, only one aryl group is transferred during the reaction. This drawback can be resolved by the use of a mixed diorganozinc reagent with one nontransferable group. Magnesium salts have a pronounced effect on the yield of the reaction.

This method was extended to the cross-coupling of alkyl sulfonates (Scheme 114).[308] The presence of magnesium salts is necessary for the reaction to proceed. The *in situ* formation of alkyl iodides as reactive coupling partners is postulated.

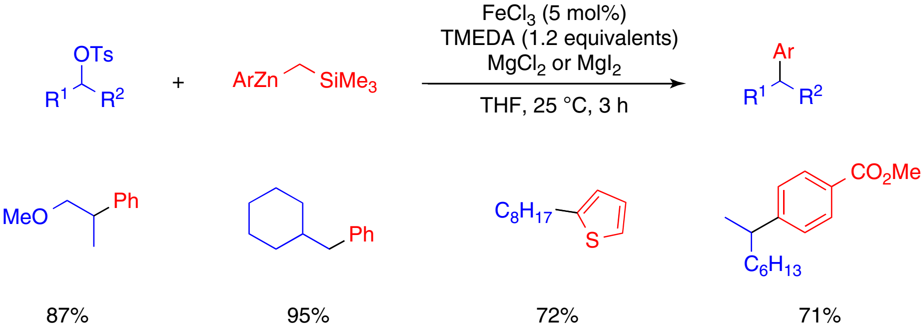
In a similar manner, mixed alkenylzinc reagents, bearing one nontransferable group, react with alkyl halides in the presence of $FeCl_3$ to give the olefins in high yields in a stereospecific manner (Scheme 115).[309]



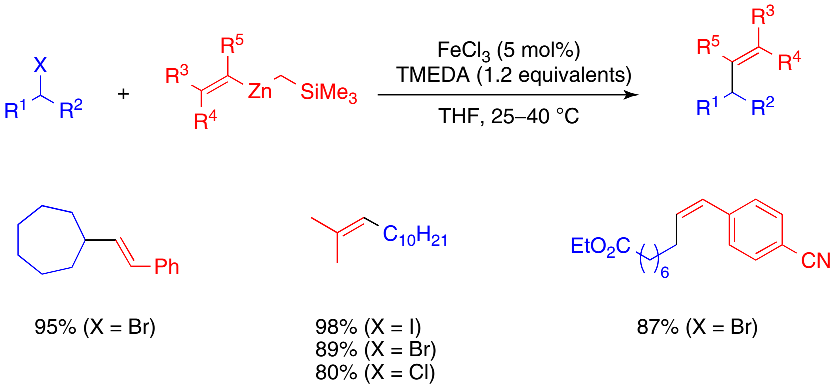
Scheme 112 Iron-catalyzed alkylation of arylaluminum reagents.



Scheme 113 Iron-catalyzed cross-coupling between diorganozinc reagents and alkyl halides.



Scheme 114 Iron-catalyzed cross-coupling of alkyl tosylates.

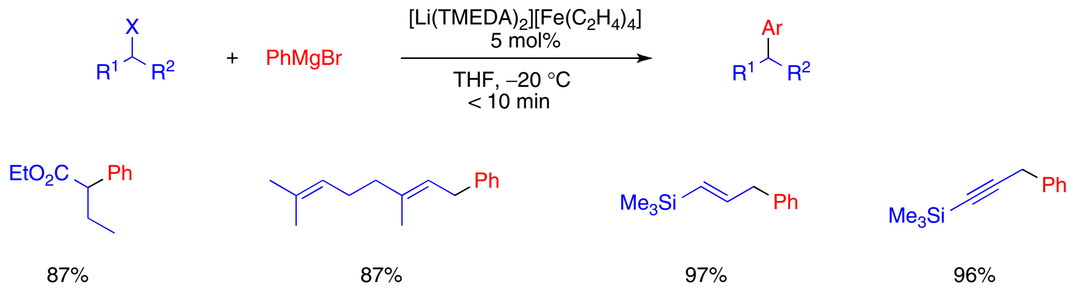


Scheme 115 Iron-catalyzed cross-coupling between alkenylzinc reagents and alkyl halides.

3.08.6.2 Coupling with Activated Alkyl Halides.

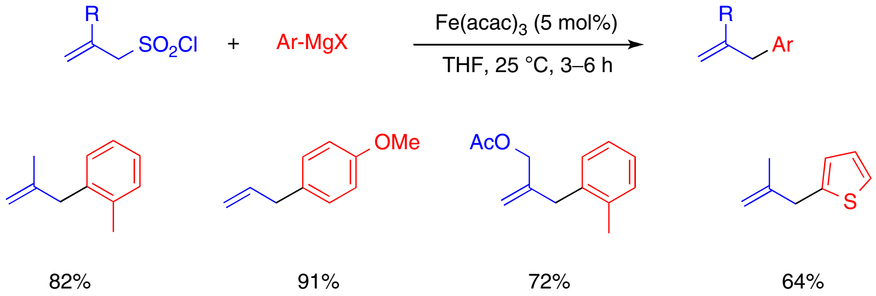
Iron-catalyzed cross-coupling reactions between activated alkyl halides and organometallic reagents are possible but are rare and not well explored.

The low-valent iron complex [Li(TMEDA)$_2$][Fe(C$_2$H$_4$)$_4$] can catalyze the coupling of phenylmagnesium bromide with various activated alkyl halides (Scheme 116).[301]



Scheme 116 Iron-catalyzed cross-coupling of phenylmagnesium bromide with activated alkyl halides.

Alk-2-enesulfonyl chlorides have been used as coupling partners in an iron-catalyzed desulfinylative coupling reaction with alkyl Grignard reagents (Scheme 117).[310]



Scheme 117 Iron-catalyzed cross-coupling of allylsulfonyl chlorides.

3.08.6.3 Coupling with Aryl and Alkenyl Halides

The iron-catalyzed cross-coupling between C(sp^2) electrophiles and alkyl nucleophiles is an attractive and environmentally more benign alternative to palladium- and nickel-catalyzed procedures. However, this method is in general limited to coupling reactions with organomagnesium reagents.

3.08.6.3.1 Cross-coupling reactions with alkenyl halides and related electrophiles

Since the seminal report of an iron-catalyzed coupling of vinyl bromides with alkyl Grignards,[282] procedures for the cross-coupling of various alkenyl electrophiles have been reported.

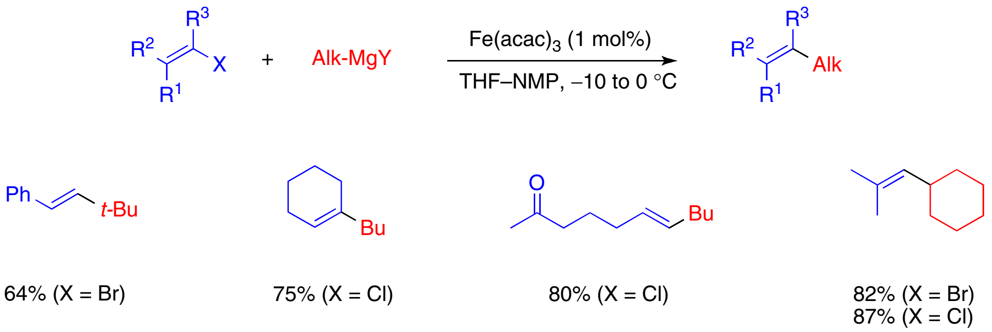
NMP as cosolvent has a dramatic effect on the iron-catalyzed cross-coupling of alkenyl halides (Scheme 118).[311] Primary, secondary, or even tertiary alkylmagnesium reagents can be coupled efficiently with alkenyl bromides or chlorides. The products are obtained with complete retention of the double bond geometry, and even sensitive keto functionalities are tolerated.

Enol triflates couple with alkylmagnesium reagents in the presence of catalytic amounts of Fe(acac)$_3$ (Scheme 119).[287] The cross-coupling proceeds rapidly under very mild conditions and is compatible with sensitive functional groups.

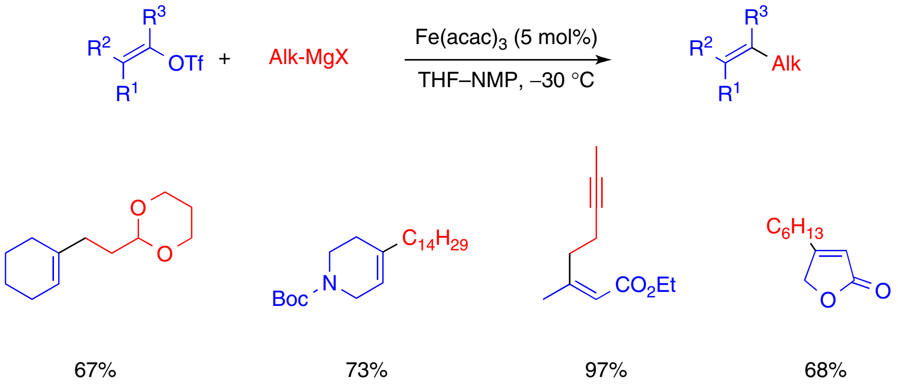
An iron-catalyzed cross-coupling of enol phosphates has also been developed (Scheme 120).[312] An important feature of the method is the preferred reaction of the (*E*)-isomer, allowing a kinetic differentiation from a mixture of isomers.

The iron-catalyzed cross-coupling of (*E*)- or (*Z*)-enol tosylates provides a stereocomplementray method for the construction of trisubstituted α,β-unsaturated methyl esters (Scheme 121).[313] The (*E*)- or (*Z*)-enol tosylates are easily obtained from the corresponding β-keto esters.

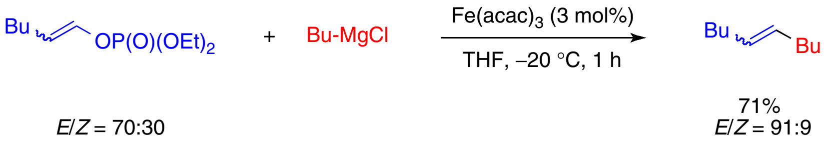
Alkenyl pivalates undergo an iron-catalyzed cross-coupling with alkyl Grignard reagents in the presence of stoichiometric amounts of LiCl (Scheme 122).[314] The reaction is limited to primary alkylmagnesium halides. Secondary Grignard reagents as well as methylmagnesium chloride are unreactive under the reported conditions.



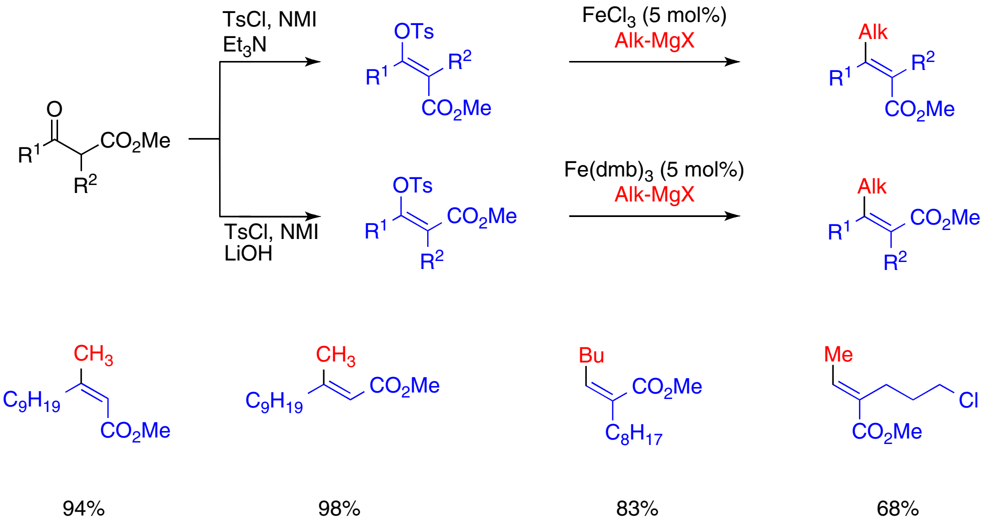
Scheme 118 Iron-catalyzed alkenylation of organomagnesium reagents.



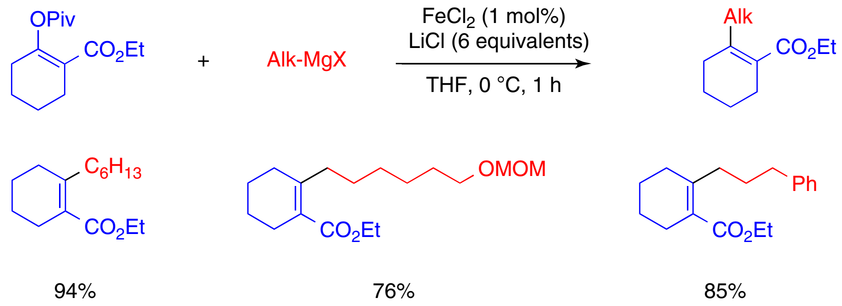
Scheme 119 Iron-catalyzed cross-coupling of enol triflates.



Scheme 120 Iron-catalyzed cross-coupling of an enol phosphate.



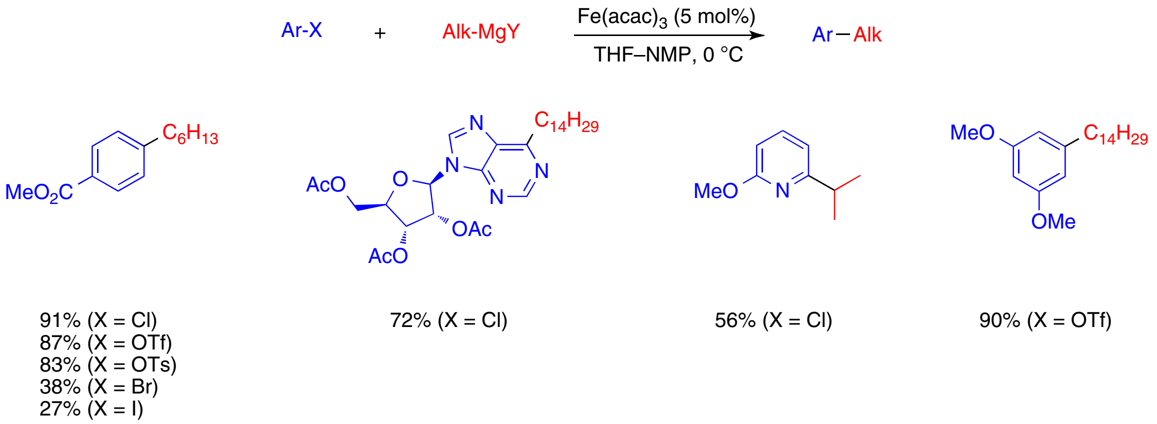
Scheme 121 Iron-catalyzed cross-coupling of enol tosylates.



Scheme 122 Iron-catalyzed cross-coupling between alkenyl pivalates and alkyl Grignard.

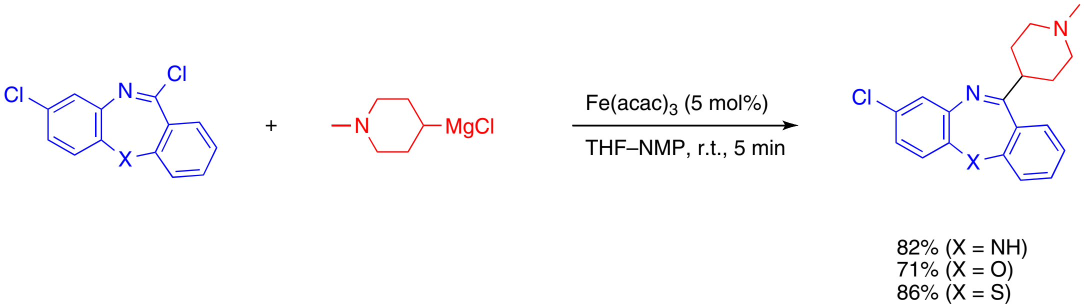
3.08.6.3.2 Cross-coupling reactions with aryl halides and related electrophiles

Iron salts are able to catalyze the cross-coupling between alkylmagnesium reagents and aryl chlorides, triflates, or tosylates (Scheme 123).[285,286] The scope of this reaction is quite broad, and both primary and secondary alkyl Grignard couple efficiently. Interestingly, the reaction of the corresponding aryl bromide or iodide furnishes the coupling product in considerable lower yields.



Scheme 123 Iron-catalyzed cross-coupling of aryl chlorides, triflates, and tosylates.

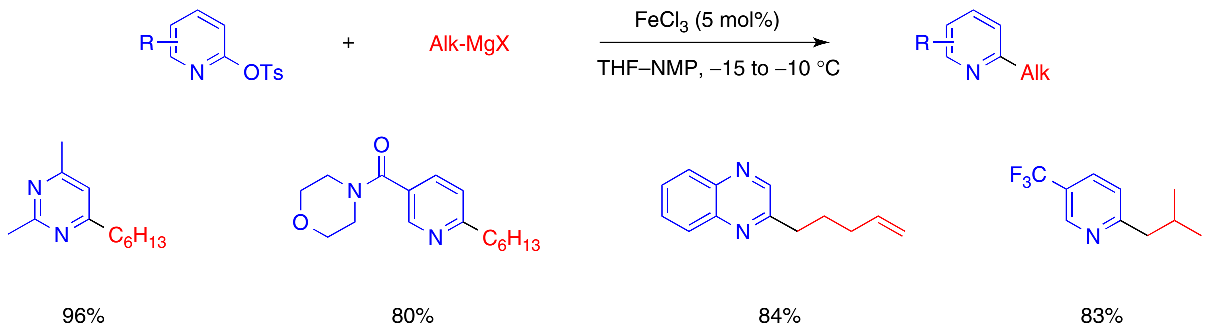
Iron-catalyzed cross-coupling between imidoyl chlorides furnishes the alkylated imines in good yields (Scheme 124).[315] This method was applied to the synthesis of clozapine analogs.



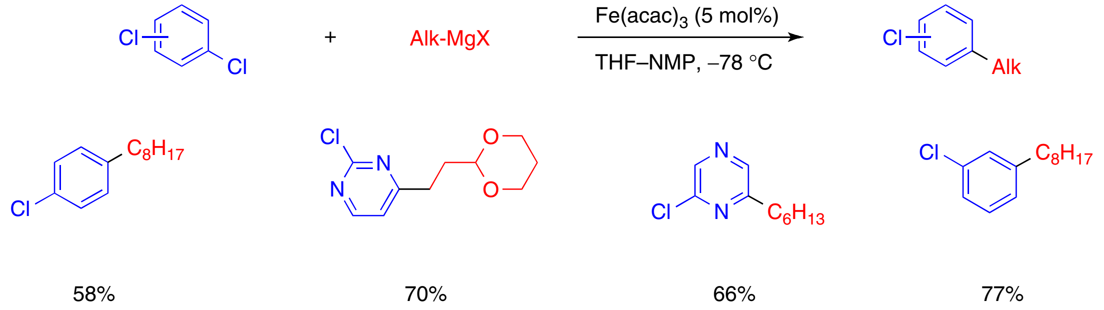
Scheme 124 Iron-catalyzed cross-coupling of imidoyl chlorides with Grignard reagents.

Heteroaromatic sulfonates or phosphates are suitable coupling partners in iron-catalyzed reactions (Scheme 125).[316] The reactions proceed rapidly (<15 min) at low temperatures, allowing good functional group tolerance.

Dichloroarenes can be selectively monoalkylated with alkyl Grignard in the presence of a catalytic amount of Fe(acac)$_3$ (Schemes 125 and 126).[287]



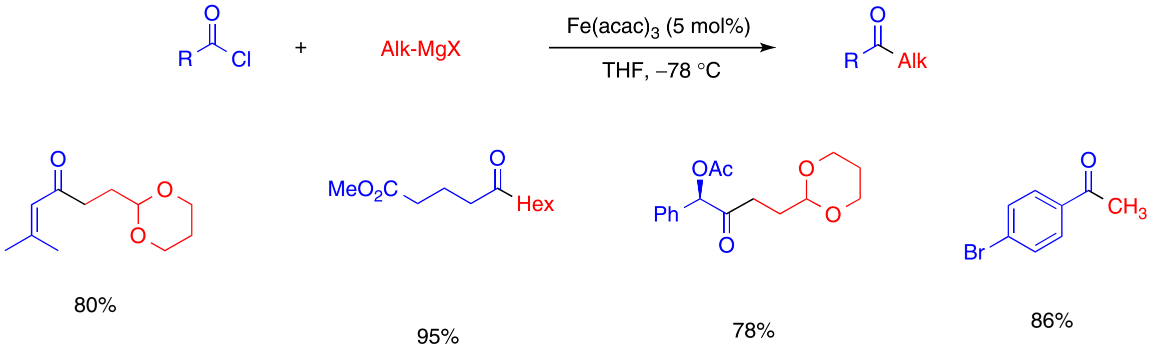
Scheme 125 Iron-catalyzed alkylation of heteroaromatic sulfonates.



Scheme 126 Iron-catalyzed monoalkylation of dichloroarenes.

3.08.6.4 Coupling with Acyl Halides

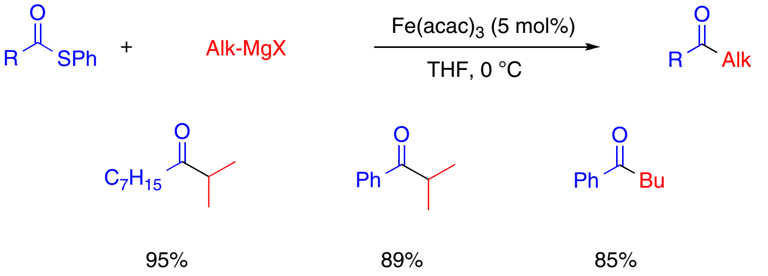
Iron salts are an effective catalyst for the coupling of alkylmagnesium reagents with acyl chlorides.[63,317] This reaction proceeds rapidly at low temperatures and shows an excellent functional group tolerance (Scheme 127).[287]



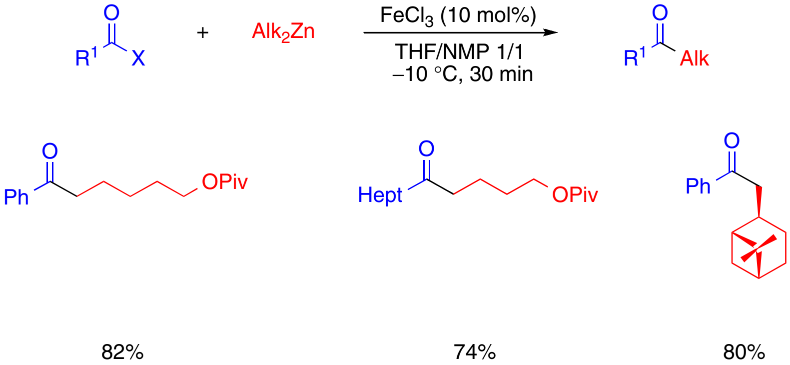
Scheme 127 Iron-catalyzed cross-coupling between acid chlorides and alkyl Grignard.

Thioesters also undergo an iron-catalyzed cross-coupling with Grignard reagents (Scheme 128).[318,319]

Unlike the above-described coupling reactions, iron-catalyzed cross-coupling of acid chlorides is not limited to organomagnesium reagents. Organozinc reagents are also suitable nucleophiles for this transformation (Scheme 129).[278] Thus, dialkyzinc compounds undergo a smooth coupling reaction with acid chlorides.



Scheme 128 Iron-catalyzed cross-coupling of thioesters.



Scheme 129 Iron-catalyzed acylation of dialkylzinc reagents.

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3.09 Coupling Reactions Between C(sp^2) and C(sp) Carbon Centers

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3.09.1 General Introduction 465
3.09.1.1 General Mechanistic Considerations of the Sonogashira–Cassar–Heck Cross-Coupling 466
3.09.2 Transition Metal-Catalyzed Coupling of Terminal and Masked Alkynes with C(sp^2)-Halides 467
3.09.2.1 Pd-Catalyzed/Cu-Cocatalyzed and Cu-Free Coupling 467
3.09.2.1.1 Coupling of aryl iodides 467
3.09.2.1.2 Coupling of aryl bromides 471
3.09.2.1.3 Coupling of aryl chlorides 481
3.09.2.1.4 Coupling of aryl pseudohalides (perfluoroalkyl sulfonates and alkyl/aryl sulfonates) 485
3.09.2.1.5 Coupling of vinyl halides and pseudohalides 488
3.09.2.1.6 Synthesis of ynones 492
3.09.2.1.7 Heterogeneous and supported catalytic systems 496
3.09.2.2 Nickel-Catalyzed Coupling 499
3.09.2.3 Copper- and Gold-Catalyzed Coupling 499
3.09.3 Transition Metal-Catalyzed Coupling of C(sp)-Metal Reagents with C(sp^2)-Halides and Pseudohalides 504
3.09.3.1 Alkynylmagnesium Reagents 504
3.09.3.2 Alkynylzinc Reagents 506
3.09.3.3 Alkynyltin Reagents 508
3.09.3.4 Alkynylboron Reagents 510
3.09.3.5 Alkynylaluminum and Indium Reagents 512
3.09.4 Transition Metal-Catalyzed Coupling of C(sp^2)-Metal Reagents with C(sp)-Halides and Pseudohalides 513
3.09.5 Domino Reactions Involving C(sp^2)–C(sp) Coupling as the Key Step 517
References 524

Glossary

Cascade reaction or domino reaction A process of two or more bond-forming reactions under identical conditions, in which the subsequent transformation takes place at the functionalities obtained in the former transformations.

Castro–Stephens coupling A cross-coupling reaction between a copper(I) acetylide and an electron-poor aryl halide forming a disubstituted alkyne.

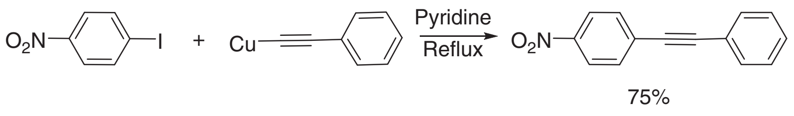
Cross-coupling reaction In organic chemistry it is a catch-all term for a variety of reactions analogous to the aromatic nucleophilic substitution with the aid of a transition metal catalyst.

Inversed Sonogashira reaction A cross-coupling reaction used in organic synthesis to form C(sp^2)–C(sp) bonds from halogenated alkyne and heteroarenes with the aid of a transition metal catalyst.

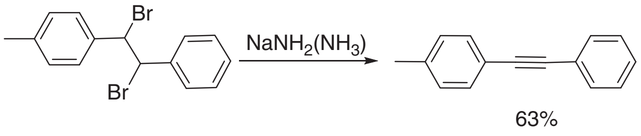
Sonogashira–Cassar–Heck reaction A cross-coupling reaction used in organic synthesis to form C(sp^2)–C(sp) bonds from terminal alkyne and an aryl or vinyl halide with the aid of a transition metal catalyst.

3.09.1 General Introduction

Conjugated aryl and vinyl acetylenes have been known for a long time as valuable intermediates and targets in the synthesis of pharmaceuticals,[1] natural products,[2] molecular electronics,[3] and machinery.[4] During the 'precross-coupling' era, Stephens–Castro substitution (1963)[5,6] and addition–elimination[7,8] reactions remained the main tools for the construction of acetylene-containing compounds (equations 1 and 2).



(1)



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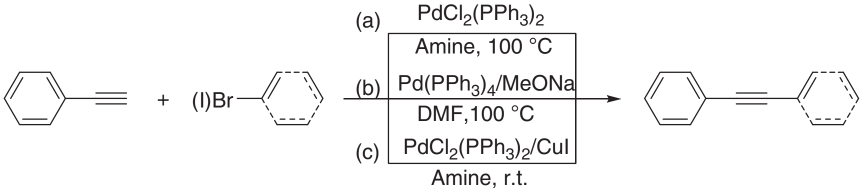
However, in the mid 1970s, these rather harsh and synthetically limited transformations were replaced with a more universal transition metal-catalyzed cross-coupling of C(sp^2)-halides and pseudohalides with C(sp)-metal reagents, and later on with terminal acetylenes (Sonogashira–Cassar–Heck reactions), which became a leading methodology toward the synthesis of substituted alkynes.

Several excellent review articles have been published on the topic in recent years discussing a variety of catalytic methods for the construction of C(sp^2)–C(sp) bonds.[9,10] The main goal of this overview is to spot the most user-friendly and practical catalytic systems and their recent manifold applications in organic synthesis.

3.09.1.1 General Mechanistic Considerations of the Sonogashira–Cassar–Heck Cross-Coupling

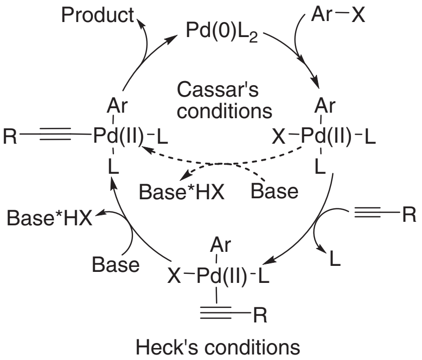
The straightforward transition metal-catalyzed coupling of aryl and vinyl halides and pseudohalides with terminal alkynes originates from seminal studies of Dieck and Heck,[11] Cassar,[12] and Sonogashira et al.[13] who independently suggested different sets of reaction conditions for this transformation (Scheme 1).



Scheme 1 (a) Dieck–Heck conditions; (b) Cassar conditions; and (c) Sonogashira–Tohda–Hagihara conditions.

The original protocol developed by Heck was conceptually similar to the previously known Mizoroki–Heck olefination of aryl halides and employed a palladium/phosphine catalyst in alkylamine medium, whereas Cassar's conditions suggested the use of alkali metal alkoxides in dimethylformamide (DMF). Both methods were limited to activated substrates such as aryl iodides, heteroaryl, and aryl bromides bearing electron-withdrawing substituents or vinyl halides, and required moderate heating to achieve reasonable turnover numbers (TONs).

Mechanistically, these reactions must follow the typical cross-coupling catalytic cycle proceeding via the (i) oxidative addition of Pd(0) species across C(sp^2)–X bond of the aryl halide, (ii) transmetalation step, and, eventually, (iii) reductive elimination of the product with regeneration of Pd (0) species (Scheme 2), although with some nuances. For example, the displacement of one ligand L by weakly coordinating alkyne to form ArPd (II)(η^2-alkyne) complex, in which the terminal proton is, apparently, more acidic than in a free alkyne,[14,15] before deprotonation/transmetalation is reasonable under Dieck–Heck conditions.

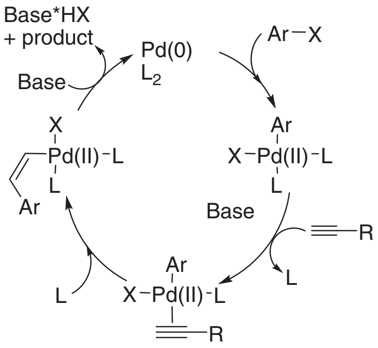


Scheme 2 Plausible mechanism for the Dieck–Heck–Cassar reaction.

However, the role of amine is not limited to the abstraction of the acidic proton. For example, it was shown that employment of the amine solvent under Dieck–Heck conditions accelerates the usually rate-limiting oxidative addition step due to the formation of a more reactive Pd(0)L(amine) complex by substitution of a strongly coordinating L (usually, phosphine) in the parent Pd(0)L$_2$.[16] In the same way, they can facilitate the formation of the Pd(II)(η^2-alkyne) complex.

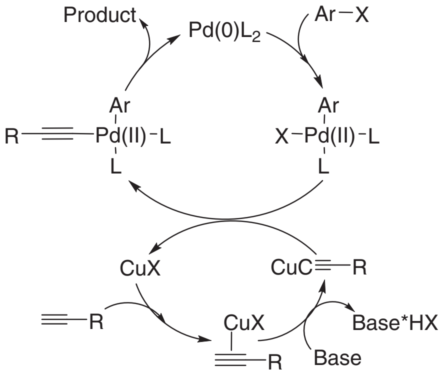
The terminal and internal alkynes involved in the reactions can also affect the reaction rate. For example, coordination of the alkynes to Pd(0)L$_2$ species may significantly retard the oxidative addition step, at least under amine-free (Cassar's) conditions.[17]

An alternative mechanism, that was originally suggested by Dieck and Heck,[11] may also be considered (Scheme 3). The two catalytic cycles have two common mechanistic steps: the oxidative addition and the formation of the ArPd(II)(η^2-alkyne) intermediate, but carbopalladation of the coordinated alkyne resembling the classical Mizoroki–Heck reaction takes place along the alternative pathway. The cross-coupling product is then expelled via a *trans*-β-H elimination and base-assisted reductive elimination of HX to regenerate active Pd(0). However, this mechanism is unlikely as neither a stereochemically unreasonable *trans*-β-H elimination nor carbopalladation byproducts has ever been observed in palladium-catalyzed C(sp)–C(sp^2) bond-forming reaction.[18] Theoretical studies also predict a very high energy barrier for the carbopalladation mechanism, which indicates that this mechanism is not operative under the reaction conditions.[19]



Scheme 3 Carbopalladation mechanism of the Dieck–Heck–Cassar reaction.

Addition of CuI as a cocatalyst distinguishes the protocol suggested by Sonogashira from the Dieck–Heck–Cassar reaction. It is assumed that the role of copper additive is to form a more nucleophilic 'Stephens–Castro' copper acetylide via a complementary catalytic cycle as can be seen in Scheme 4.



Scheme 4 Plausible mechanism of the Sonogashira–Tohda–Hagihara coupling.

Although the copper acetylide species have never been observed directly over the course of the Sonogashira coupling, their formation is assumed via the π-complexation to the terminal alkyne followed by deprotonation by the amine base.[20] Moreover, transmetalation step using preformed copper acetylides was studied stoichiometrically to reveal expected products formation.[21]

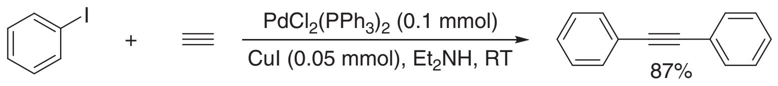
Of course, involvement of the copper acetylides greatly facilitates the transmetalation step. Thus, the reactions of the activated substrates such as aryl iodides or electron-poor aryl bromides, for which oxidative addition does not limit the reaction rate, proceed under remarkably mild reaction conditions. However, along with this beneficial effect the presence of copper cocatalyst brings some disadvantages. For example, oxidative homocoupling of alkynes to form diyne byproducts (Glaser reaction)[22,23] as well as copper-promoted oligomerization of the terminal alkynes[24,25] often takes place under Pd/Cu-catalyzed conditions.

3.09.2 Transition Metal-Catalyzed Coupling of Terminal and Masked Alkynes with C(sp^2)-Halides

3.09.2.1 Pd-Catalyzed/Cu-Cocatalyzed and Cu-Free Coupling

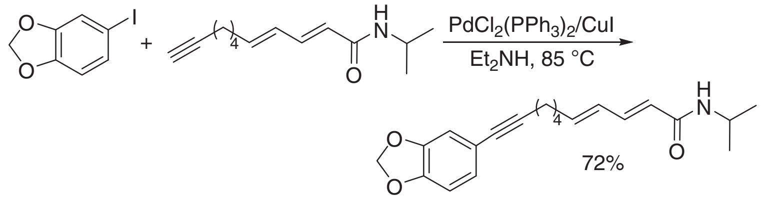
3.09.2.1.1 Coupling of aryl iodides

In a typical example, described in the original paper by Sonogashira et al., 0.05 mmol of CuI and 0.1 mmol of $PdCl_2(PPh_3)_2$ in diethylamine were able to catalyze coupling of 10 mmol of iodobenzene with gaseous acetylene to form diphenylacetylene in 87% chemical yield at r.t. (equation 3).[13]



(3)

The mild reaction conditions were applied to the synthesis of not only functionalized alkynes bearing different sensitive functional groups (equation 4)[26] but also to the synthesis of extended π-conjugated systems and biologically active molecules that could not be synthesized using other synthetic methods known at that time. For example, coupling of diiodoarenes with di- or monoethynylbenzenes (equations 5 and 6) takes place in the presence of $Pd(PPh_3)_4$/CuI in diethylamine under very mild heating.[27,28] Another example represents the synthesis of a series of alkynyl-modified uracil nucleosides that was accomplished efficiently using the standard Sonogashira protocol (equation 7).[29] Remarkably, trimethylsilyl (TMS)-protected acetylenes couple efficiently under these reaction conditions, which opens a facile access to uracil nucleosides with an acetylenic terminus after tetrabutylammonium fluoride (TBAF)-promoted deprotection.



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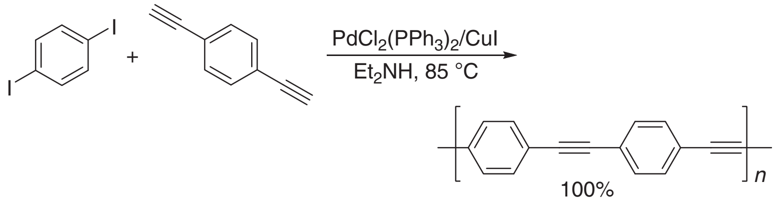

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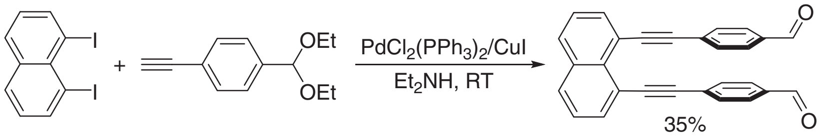

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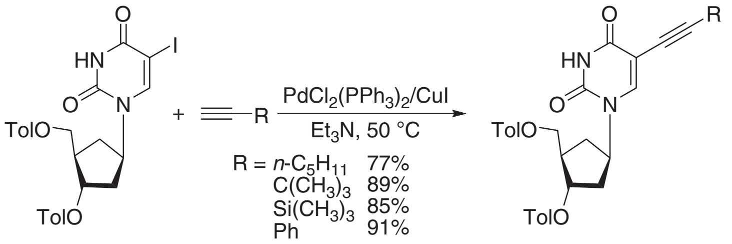
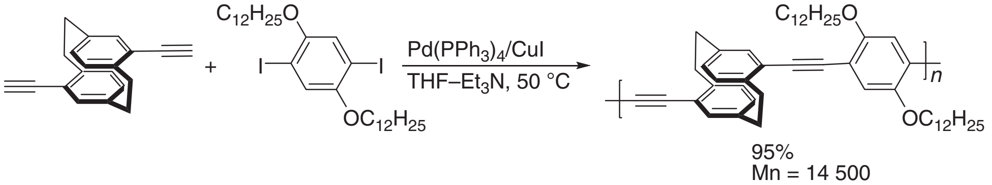


(7)

It was found later that utilization of the secondary amine as a solvent is not necessary and its amount can be reduced to cosolvent[30] or even to nearly stoichiometric quantities which, of course, greatly simplifies the workup and isolation of the product. For example, a series of unprotected alkynylamino nucleosides was synthesized using 10 mol% of $Pd(PPh_3)_4$, 5 mol% of CuI in DMF in the presence of only 4 equivalents of triethylamine as a base (Scheme 5).[31] Remarkably, the reactions reached complete conversion at room temperature after only 4 h, indicating that large excess of amine is not necessarily the primary cause to mild reaction conditions under the classical Sonogashira protocol.

More complex polymerization of pseudo-*p*-diethynyl[2.2]paracyclophane with diiodobenzene (equation 8) in tetrahydrofuran (THF)–Et_3N mixture proceeded smoothly in the presence of a catalytic amount of $Pd(PPh_3)_4$ and CuI to afford the corresponding polymer in 95% isolated yield with number average molecular weight (Mn) of 14 500.[32]



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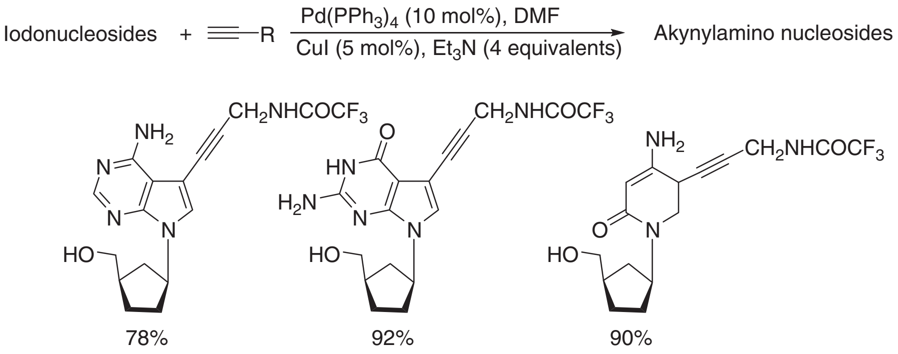
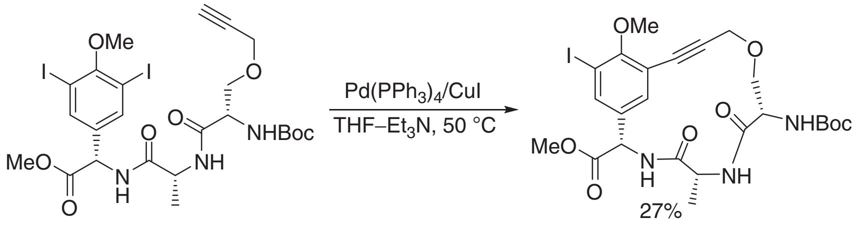


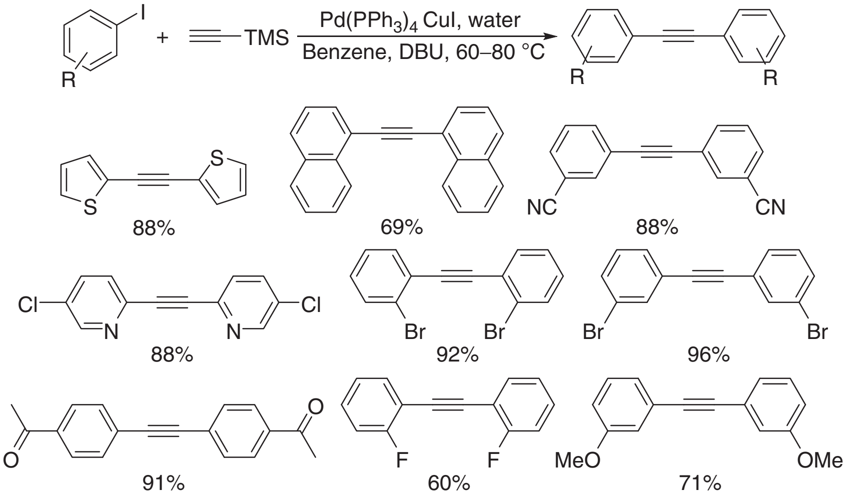
Scheme 5 Pd/Cu-catalyzed coupling of unprotected iodonucleosides with terminal alkynes.

The synthesis of a range of highly constrained cyclic tripeptides has been performed using an intramolecular Sonogashira coupling (equation 9).[33] To achieve this goal, $Pd(PPh_3)_4$/CuI in Et_2NH/THF was employed. The desired cyclization product was obtained in 27% isolated yield.



(9)

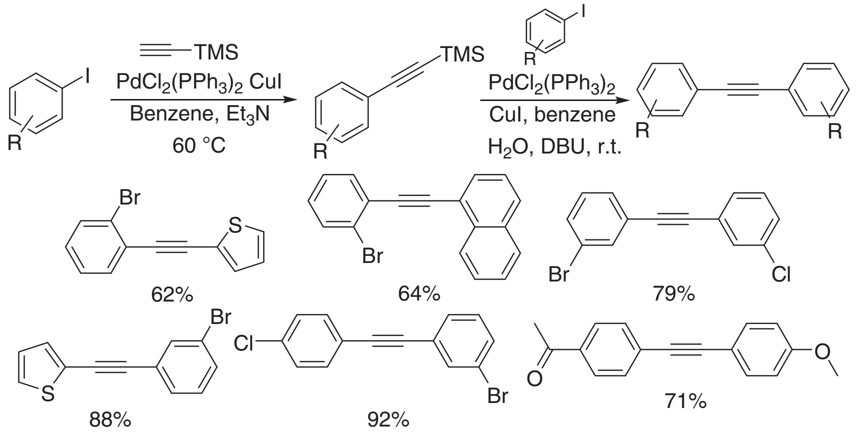
A modification of the Sonogoshira coupling reaction employing an amidine base (e.g., 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) and a substoichiometric amount of water generates symmetrical and unsymmetrical bisarylethynylenes in one pot through the *in situ* deprotection of trimethylsilylethynylene intermediates.[34] As outlined in Scheme 6, symmetrical bisarylethynylenes are produced in excellent yield in benzene when 6.0 equivalents of DBU and 30 mol% of water along with 6 mol% of $PdCl_2(PPh_3)_2$ and 10 mol% of CuI are used. The *in situ* silane deprotection step is, apparently, amidine base-dependent, but it is also copper(I)-dependent. Reactions executed with no CuI resulted in a complete recovery of the starting material. This indicates that CuI association is necessary and rules out a possibility of nucleophilic activation involving only silicon and the amidine base. In addition, yields are depressed when no water was intentionally added, suggesting the involvement of adventitious moisture.



Scheme 6 Pd/Cu-catalyzed coupling of iodoarenes with terminal alkynes in the presence of amidine bases.

Unsymmetrical bisarylethynylenes were also prepared using a one-pot protocol (Scheme 7). Addition of benzene to a flask containing 6 mol% $PdCl_2(PPh_3)_2$, 10 mol% CuI, and a first aryl iodide followed by addition of 6.0 equivalents of Et_3N and trimethylsilylethynylene provided a standard Sonogashira product *in situ*, after vigorous stirring for 18 h. Sequential addition of

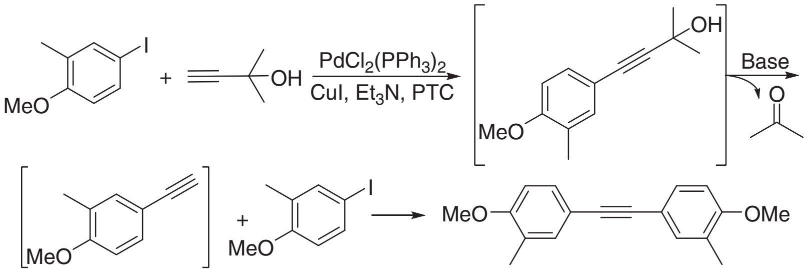
1.0 equivalent of a second aryl iodide, 12.0 equivalents of DBU, and 40 mol% water gave rise to unsymmetrical bisarylethynylene after 18 h at room temperature (Scheme 7).



Scheme 7 Synthesis of unsymmetrical bisarylethynylenes via one-pot coupling of aryl iodides with masked (TMS-protected) terminal acetylenes.

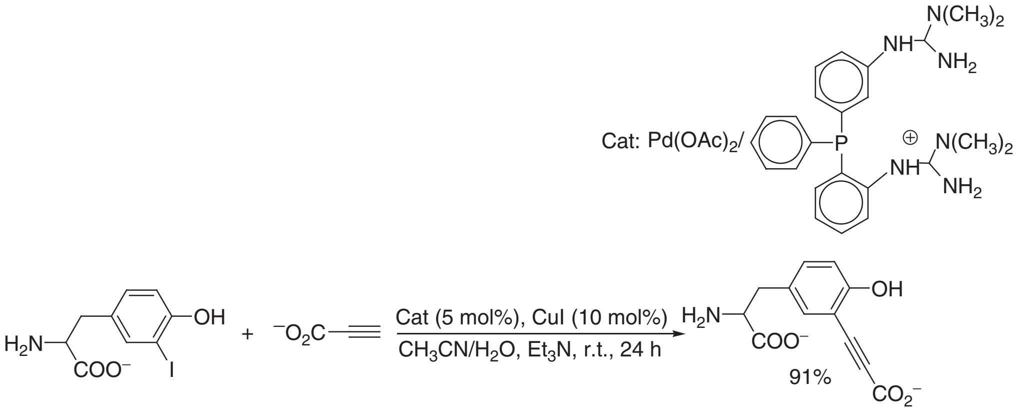
Both methods demonstrate a very good functional group compatibility and moderate sensitivity to steric and electronic properties of the starting aryl iodides.

A similar *in situ* elimination of acetone from 2-methylbut-3-yn-2-ol under basic conditions followed by one-pot stepwise cross-coupling with aryl iodides is another strategy toward the synthesis of symmetrical and nonsymmetrical diarylacetylenes (equation 10).[35] This transformation was realized under phase-transfer conditions using aryl iodide and 2-methyl-3-butyn-2-ol (in 1:1 ratio) in degased benzene in the presence of benzyltriethylammonium chloride PTC, cuprous iodide, triphenylphosphine, and $PdCl_2(PPh_3)_2$. After the full conversion of the aryl iodide was detected, the second coupling partner was added and the reaction was resumed.



(10)

Water-soluble palladium complexes bearing sulfonated[36,37] or cationic guanidine-modified triphenylphosphine ligands afforded efficient coupling of water-soluble substrates in acetonitrile/water or even pure water buffered with 3-[tris(hydroxymethyl)methylamino]-1-propanesulfonic acid (TAPS, pH 8.3).[38] For example, 3-iodotyrosine reacted with propiolic acid (equation 11) in 25 h to give the C–C coupled product in 86% yield. Moreover, regioselective Sonogashira coupling of a multifunctional and unprotected peptide, Pro(*p*-I-Phe)-bradykinin, as well as conjugated bradykinin derivatives with propiolic acid, was accomplished in 75–91% yield after 3 h at 35 °C (equation 12).



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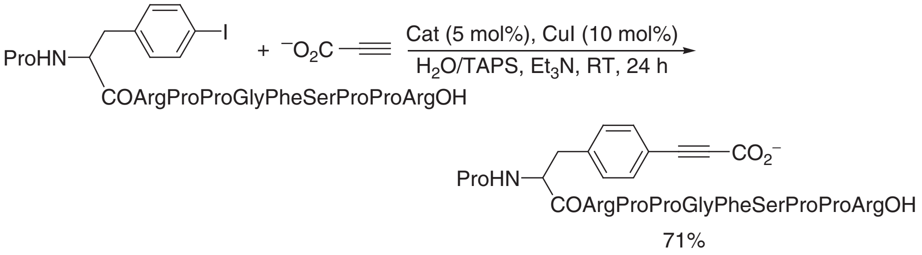


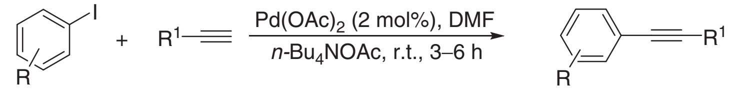
(12)

In general, the Sonogashira coupling of aryl iodides proceeds relatively easily under more or less standard reaction conditions using catalytic copper iodide and not too sophisticated palladium–phosphane ligand complexes, such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, or catalysts derived *in situ* from the corresponding palladium precursors and triphenylphosphine ligand.[39] Moreover, several groups reported that coupling of aryl iodides and terminal acetylenes can be catalyzed by palladium salts or palladium metal under ligand-less conditions. For example, Sonogashira coupling between iodobenzenes and alkyl and aryl alkynes in the presence of palladium nanoclusters (5 mol% in Pd) prepared in 1:1 MeCN/MeOH mixture as a catalyst and K_2CO_3 as a base under ambient conditions.[40] The desired products were isolated in high yields. The catalyst obtained at the end of the reaction was washed with hexane and methanol, and redispersed in the solvent mixture and could be reused for Sonogashira coupling without loss of the activity. Another example suggests stable, crystalline, and polydispersed Pd(0) nanoparticles as catalysts in a Sonogashira reaction that proceeds in acetone or room-temperature ionic liquid, 1,3-di-*n*-butylimidazolium tetrafluoroborate ([bbim]BF4), as solvent under ultrasound irradiation to give enhanced reaction rates, excellent chemoselectivity, and high yields in the absence of a copper cocatalyst and a phosphine ligand.[41] As was demonstrated, aryl iodides bearing electron-releasing (alkyl or MeO) or electron-withdrawing (NO_2, COR, CO_2R, etc.) groups couple successfully at ambient temperature (30 °C) with aliphatic or aromatic acetylenes leading to the formation of the corresponding products in excellent yield.

An oil-in-water microemulsion stabilized by nonionic surfactants such as Triton X100 (polyoxyethylene(10) isooctylphenyl ether) containing $PdCl_2$ and NaOH can be used as an effective catalyst system for rapid copper- and ligand-free Sonogashira reaction of aryl iodides and phenylacetylene. Excellent yield of the Sonogashira reaction catalyzed by 0.5 mol% palladium could be achieved within minutes.[42]

Development of ligand-free protocols is important from the economical point of view; however, very complicated experimental procedures are associated with the preparation of the described microemulsions or nanosized catalysts, as well as the dependence of the reproducibility on a specific size of the nanocatalysts are the obvious drawbacks of the suggested methods.

More operationally simple ligand-free protocols include homogenously catalyzed by $Pd_2(dba)_3$ or $Pd(OAc)_2$ alkynylation of aryl iodides with aliphatic terminal alkynes bearing a variety of functional groups in the presence of *n*-Bu_4NOAc as a base in DMF.[43] As was reported by the authors, the reaction reaches full conversion at room temperature over 3–6 h even with no copper additive (**Scheme 8**).



R	R^1	
R = 4-CO_2Me	R^1 = Ph	97%
4-CO_2Me	1-Cy	90%
4-NO_2	Ph	97%
4-NO_2	$(CH_2)_4OH$	98%
2-OMe	Ph	68%
2-OMe	$(CH_2)_4OH$	77%
4-OMe	$(CH_2)_4Cl$	80%
4-OMe	$(CH_2)_4OH$	93%

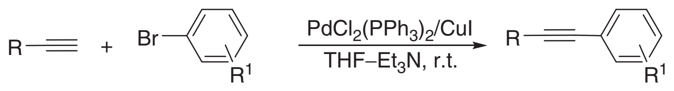
Scheme 8 Palladium-catalyzed coupling of iodoarenes with terminal alkynes under ligandless and copper-free conditions.

Comparative yields can be obtained in acetonitrile using 3 equivalents of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base[44] or even in water using 5 equivalents of pyrrolidine as a base.[45] The reactions proceed under air and have been shown to tolerate a variety of functional groups such as NO_2, COR, CO_2R, CN, MeO, etc.

3.09.2.1.2 Coupling of aryl bromides

Aryl bromides are significantly less reactive in cross-coupling reactions, in general, and in Sonogashira–Cassar–Heck cross-coupling, in particular. For example, only activated (electron-poor) heteroaryl bromides (e.g., 2-bromopyridine) react with reasonable efficiency under the original Sonogashira–Heck mild conditions, whereas electron-poor to electron-rich aryl bromides, normally demonstrate diminished conversions or require significantly higher reaction temperature (>80 °C) to achieve higher conversions,[11–13] although on account of the enhanced formation of the diyne byproduct.[46]

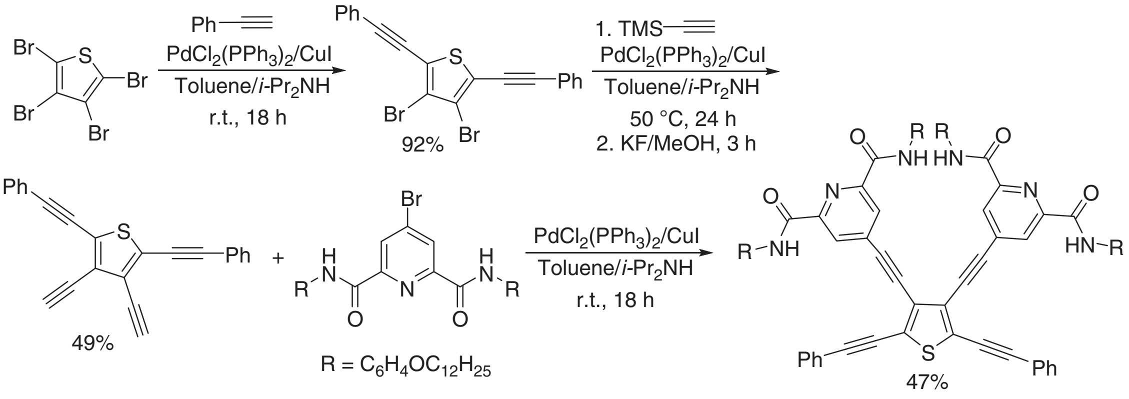
Initially, the quest for a more efficient protocol for the palladium-catalyzed alkyne coupling of the more challenging substrates revolved around the modification of the different reaction parameters such as the nature of the bases, solvents, and additives. Thus, Krause and coworkers demonstrated that activated bromoarenes bearing electron-withdrawing groups such as esters or carbonyls deliver the desired products in high yield even at room temperature if allowed to react in THF in the presence of 2 mol% of $PdCl_2(PPh_3)_2$, 4 mol% of CuI, and 1.5 equivalents of Et_3N as a base (Scheme 9).[47] Slow addition of the starting alkyne over the course of the reaction almost prevented the formation of Glaser coupling byproduct.



R	R^1	Yield (%)
Ph	4-CHO	82
$SiMe_3$	2-CO_2Me	88
$SiMe_3$	4-COMe	92

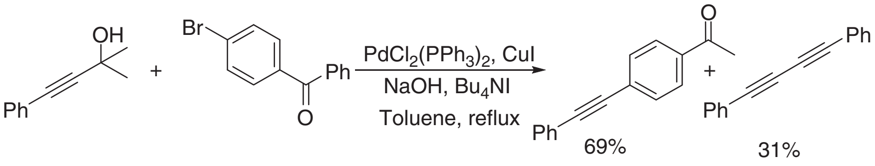
Scheme 9 Pd/Cu-catalyzed coupling of bromoarenes with terminal alkynes.

The amide-functionalized phenylethynylthiophenes were prepared in four steps starting from 2,3,4,5-tetrabromothiophene according to Scheme 10.[48] Chemical yields of the coupling products were good to excellent using the standard Sonogashira conditions owing to the electron-deficient character of the starting bromides.



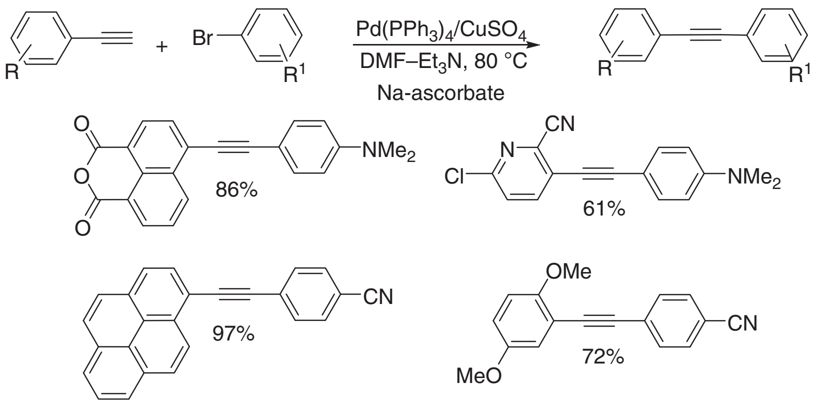
Scheme 10 Application of the Pd/Cu-catalyzed coupling of bromoarenes with terminal alkynes for the synthesis of amide-functionalized phenylethynylthiophenes.

Unsymmetrical bisarylethynylenes can be also prepared via cross-coupling aryl bromides with 2-methyl-4-arylbut-3-yn-2-ol that eliminates acetone slowly releasing terminal alkyne. This transformation takes place using this simple catalytic system under phase-transfer conditions (equation 13).[49] The reaction is not very chemoselective and is often accompanied by a significant amount of Glaser homocoupled byproduct.



(13)

Another modification of the Sonogashira protocol that allowed coupling aryl bromides in an efficient way using the structurally simple $Pd(PPh_3)_4$ catalyst was suggested by Bag et al. They exploited the reducing ability of sodium ascorbate to generate Cu(I) from $CuSO_4$ over the course of the reaction.[50] This allowed carrying out cross-coupling of aryl bromides with terminal acetylenes under higher temperatures while reducing the undesired oxidative homocoupling of the starting alkyne (Scheme 11). Thus, the Sonogashira reaction was best performed using a $CuSO_4$/Na-ascorbate couple in a 1:6 mol% ratio as a source of active Cu(I) (1 mol%), $Pd(PPh_3)_4$ (3 mol%) in a 1:1 DMF/Et_3N at 80 °C. The synthesis of several donor–acceptor containing conjugated alkynes was undertaken to demonstrate the generality of the method. The products were isolated to purity in good to excellent yields along with negligible amounts of the homocoupled alkynes. Most importantly, in all cases throughout the investigation, the reducing agent, sodium ascorbate, was observed to not adversely impact vulnerable functional groups, such as NO_2, CN, or anhydride.

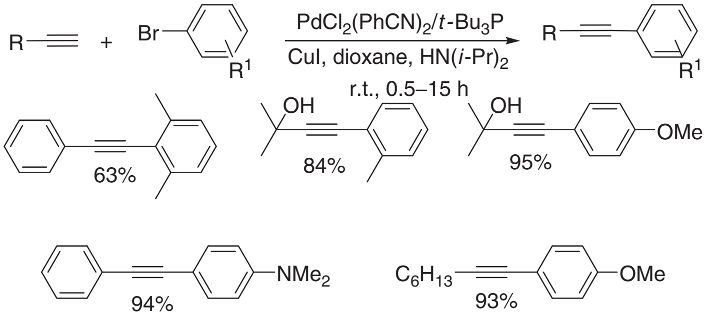


Scheme 11 Palladium-catalyzed coupling of bromoarenes with terminal alkynes in the presence of the *in situ* generated copper cocatalyst.

$PdCl_2(PPh_3)_2$ combined with 3 equivalents of TBAF under copper-, amine-, and solvent-free conditions provided general and fast Sonogashira cross-coupling reactions of aryl bromides with terminal alkynes. The results indicated that the palladium-catalyzed Sonogashira reaction tolerated a variety of functional groups (NO_2, MeO, COMe, etc.), and couplings of representative aryl bromides with functionalized and unfuctionalyzed alkynes occurred efficiently to produce excellent yields of the corresponding products in 1–6 h. Moreover, the coupling of the activated bromides could be conducted smoothly at room temperature after 6 h to give a yield identical with that at 80 °C.[51]

However, only the understanding that modification of catalytic species by means of the process-oriented ligand design may eventually lead to the development of highly active catalytic systems, initiated the major breakthrough in the field. In particular, it was recognized that the steric bulk of phosphine ligands coordinated to palladium promote the formation of a formally monoligated complex PdL_1, which turns out to be highly active for oxidative addition. This, in combination with electron-rich character of the ligands that also favors the usually rate-limiting step, solved multiple problems of the cross-coupling, in general, and of the alkynes synthesis, in particular.[52–54]

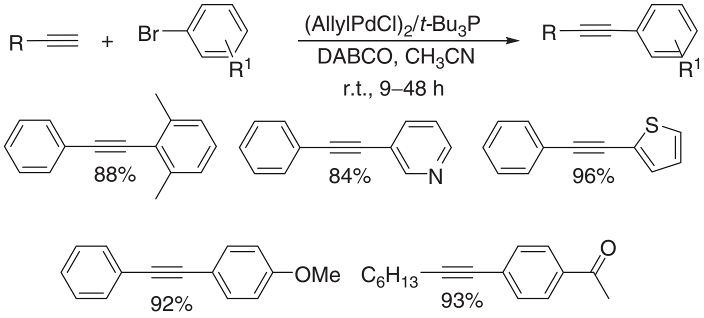
Thus, in 2000, Fu and coworkers employed a new catalyst derived from $PdCl_2(PhCN)_2$/t-Bu_3P for the room-temperature coupling of aryl bromides with a variety of terminal alkynes. This first, truly general protocol, comprised stirring of the starting materials in 1/1.2 ratio with 3 mol% of the palladium source, 6 mol% of the ligand, 2 mol% of CuI in dioxane in the presence of 1.2 equivalents of bulky HN(i-Pr)$_2$ for 0.5–15 h depending on the steric/electronic properties of the starting bromides (Scheme 12).[55]



Scheme 12 CuI/$PdCl_2(PhCN)_2$/t-Bu_3P-catalyzed room-temperature coupling of aryl bromides with terminal alkynes.

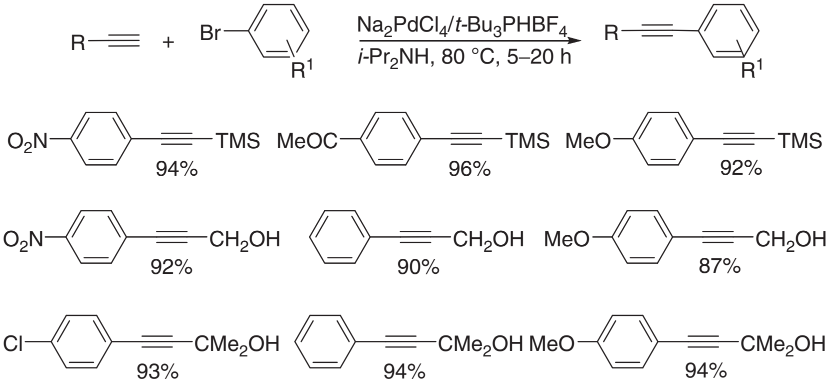
Using this catalyst, even very electron-rich 4-bromo-*N*,*N*-dimethylaniline and hindered 2,6-bromoxylene react cleanly at room temperature. It was also demonstrated that a lower catalyst loading may be employed, and 4-bromoanisole couples with phenylacetylene in the presence of just 0.5 mol% of $PdCl_2(PhCN)_2$, 1.0 mol% of t-Bu_3P (reaction time: 22 h; 99% isolated yield) which corresponds to approximately 200 turnovers.

Following this study, it was demonstrated that $Pd_2(dba)_3$/t-Bu_3P[56] or $(AllylPdCl)_2$/t-Bu_3P[25] operate successfully even without copper additives. The first system promotes the Sonogashira reaction of aryl bromides at room temperature in high yield. The catalyst formed under reaction conditions is highly active, even allowing the use of only 0.5 mol% palladium and ligand. Both Et_3N and THF can be used as the solvent in combination with Et_3N as the base. The $(AllylPdCl)_2$/t-Bu_3P combination was shown to operate essentially in any organic solvent (e.g., nonpolar toluene, polar aprotic DMF, acetonitrile or THF, protic alcohols, etc.) and in the presence of different bases (e.g., Cs_2CO_3, Et_3N, HMDS, DBU, *n*- or *t*-$BuNH_2$, (*i*-Pr)$_2$NEt, (*i*-Pr)$_2$NH, etc.), however, best results were obtained in acetonitrile in the presence of DABCO or piperidine bases. Under these conditions, electron-deficient, -neutral, and -rich aryl bromides couple with both aryl and alkyl acetylenes delivering products in good to excellent yields and chemoselectivity. Even sterically demanding 2-bromoxylene reacts with phenylacetylene in excellent yield, demonstrating the generality of the suggested method. In addition, heterocyclic compounds, such as 3-bromopyridine and 3-bromothiophene, coupled with phenylacetylene in good yield (Scheme 13).



Scheme 13 Pd/*t*-Bu$_3$P-catalyzed room-temperature coupling of aryl bromides with terminal alkynes under copper-free conditions.

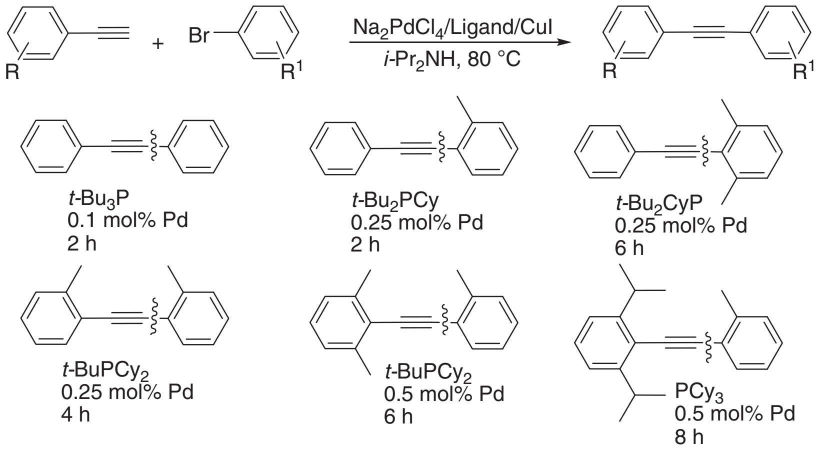
The extreme sensitivity of some trialkylphosphines to air could become an obstacle to their wide application in synthesis not only because of the complicated manipulation but also because of poor reproducibility of results due to the presence of the oxide contaminants. However, it was found that air-stable protonated trialkylphosphines can successfully replace readily oxidazable free ligands used in these protocols. For example, the pK_a values of the conjugate acids of *t*-Bu$_3$P is 11.4, thus it can be quantitatively protonated with a variety of acids. For example, [(*t*-Bu)$_3$PH]BF_4 can be synthesized in near-quantitative yield simply by mixing a solution of the phosphine in CH_2Cl_2 with a solution of aqueous HBF_4 (48 wt%). Separation of the phases and concentration of the organic layer provide analytically pure phosphonium salt that shows a sign of oxidation after exposure to air for several months (^{31}P, ^{13}C, and ^{1}H NMR; elemental analysis).[57] Thus, a mixture of Na_2PdCl_4, CuI, and (*t*-Bu)$_3$PHBF$_4$ (molar ratio 4:3:8) dispersed in $H_2N(i\text{-Pr})_2{}^+Br^-$ can be used as a 'single source' precatalyst for the Sonogashira coupling of aryl bromides with various aryl- and alkylacetylenes in HN(*i*-Pr)$_2$ solvent. Arylacetylenes require just 0.005 mol% of Pd catalyst at 80 °C, with TOFs ranging between 3200 and 10 000 h^{-1}.[58] Under these reaction conditions, activated aryl bromides react within a few hours, whereas deactivated, electron-rich, or sterically hindered aryl bromides couple within less than 20 h at 80 °C. Coupling of various aryl bromides with trialkylsilylacetylene, propargylic alcohol, and alkylacetylenes proceeded smoothly at catalyst concentrations of 0.01–0.1 mol%. Moreover, the catalyst was used for 1 mol scale synthesis (Scheme 14). Comparable results may be achieved using another bulky phosphine, diadamantyl-*n*-butylphosphine.[59] Both phosphines are commercially available now in both protected and unprotected forms.



Scheme 14 Utilization of the air-stable protonated trialkylphosphines as ligands for the coupling of aryl bromides with aryl- and alkylacetylenes.

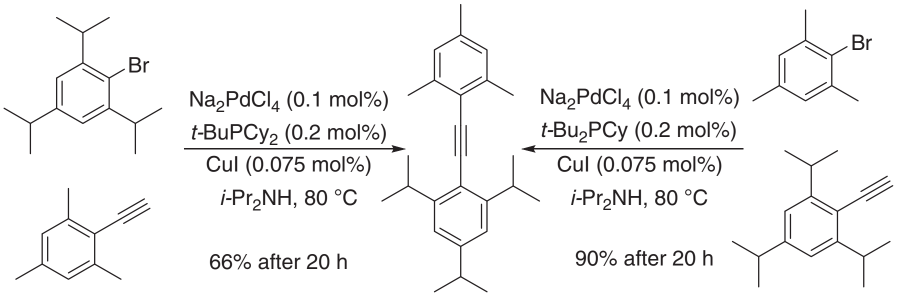
A very useful study on substrates– and catalyst–activity relationships in Sonogashira coupling of aryl bromides was performed by Plenio and coworkers.[60,61] Hundred and sixty-eight different Pd/Cu-catalyzed Sonogashira cross-coupling reactions of six acetylenes with seven aryl bromides possessing different steric and electronic properties in the presence of four differently bulky electron-rich phosphines *t*-Bu$_3$P, *t*-Bu$_2$PCy, *t*-BuPCy$_2$, and Cy$_3$P were analyzed. Stereoelectronic properties of the substrates and ligands were correlated with their performance in Sonogashira coupling.

The detailed analysis of the experimental data revealed several rules for the target-directed catalyst choice: (a) reactions of sterically less-demanding substrates such as arylacetylenes with no *ortho*-substituents and aryl bromides with no *ortho*-substituents are best done with the bulkiest catalyst derived from Na$_2$PdCl$_4$/*t*-Bu$_3$P catalyst; (b) reactions of sterically less-demanding arylacetylenes (no *ortho*-substituents) with sterically congested aryl bromides (bulky *ortho*-substituents) are best done with either *t*-Bu$_2$PCy or *t*-BuPCy$_2$; (c) reactions of bulky 2- or 2,6-substituted arylacetylenes and aryl bromides are best done in the presence of *t*-BuPCy$_2$; and (d) reactions of 2,6-disubstituted arylacetylenes (very bulky *ortho*-substituents) and aryl bromides are best done in the presence of the least crowded Pd/PCy$_3$ (Scheme 15).



Scheme 15 Substrates- and catalyst structure–activity relationships in Sonogashira coupling of aryl bromides.

As for substrates scope, expectedly the steric bulk around the aryl bromide is more influential than that of the acetylenes even if the catalysts' guidelines described above are followed. For example, the alternative routes toward the sterically crowned tolanes show only 66% after 20 h when 2-bromo-1,3,5-triisopropylbenzene couple with 2-ethynyl-1,3,5-trimethylbenzene, whereas 90% conversion was observed over the same time period for opposite substrates, when using different, but the 'best,' phosphines for the respective transformations (Scheme 16). However, the presence of electron-withdrawing groups at the aryl bromides compensates for a moderate steric bulk at the aryl bromide.



Scheme 16 Alternative routes toward the sterically crowded tolanes.

Other bulky electron-rich phosphines such as phosphorinanes (prepared via hydrophosphination of diisopropylidene acetone with a corresponding primary phosphine),[62] neopentylphosphines,[63] and phenylphosphatrioxaadamantanes (prepared via the condensation of PH$_3$ with 2,4-pentanedione under acidic conditions)[64] (Figure 1) show comparable reactivity in the Sonogashira coupling of aryl bromides with terminal acetylenes.

Palladium complexes bearing biaryl-based bulky monophosphine ligands such as X-Phos and S-Phos developed by Gelman and Buchwald[24] and cataCXium PIntb developed by Beller and coworkers[65] represent a very powerful family of catalysts for the described transformation (Figure 2).

CataCXium PIntb allows for the efficient coupling of both activated and deactivated (hetero)aryl bromides in the presence of sodium tetrachloropalladate in tetramethylethylenediamine (TMEDA) at 80 °C. The role of TMEDA as a solvent and a base is crucial for the success of this reaction. When other amines such as triethylamine, DABCO, and diisopropylamine were applied,

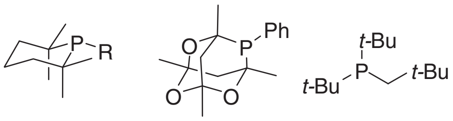


Figure 1 Representative bulky electron-rich monophosphine ligands.

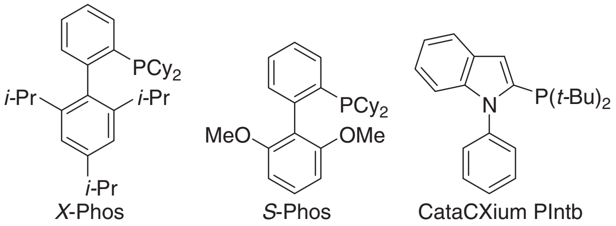
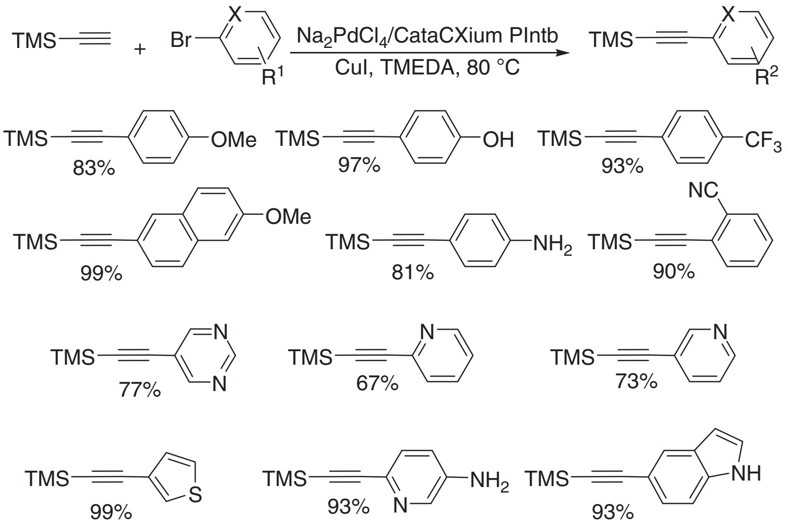


Figure 2 Representative biaryl-based bulky monophosphine ligands.

only low yields were obtained. The use of Na_2CO_3 and Cs_2CO_3 in different solvents gave no conversion at all. The reaction proceeds only slowly at room temperature.

The catalyst system gives high TONs (up to 14 100) and shows a broad tolerance toward functional groups such as OH and NH_2, as well as heterocycles (Scheme 17).



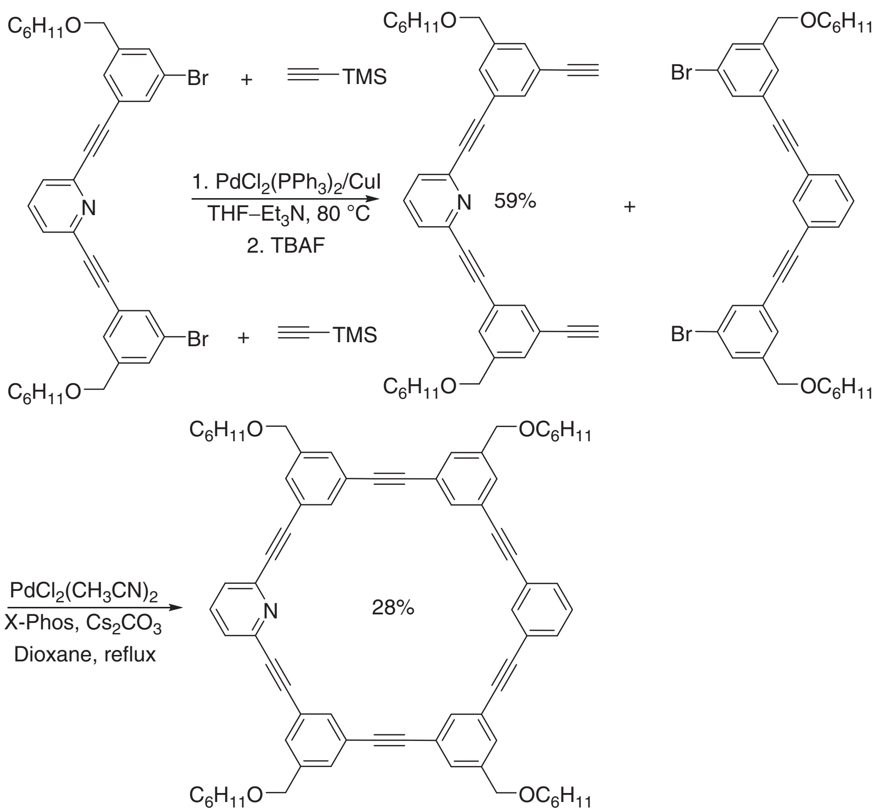
Scheme 17 Cu/Pd/CataCXium PIntb-catalyzed coupling of (hetero)aryl bromides with TMS-protected acetylenes.

For example, no competitive palladium-catalyzed amination or aryl ether formation was observed with bromophenols, anilines, or aminopyridines. With respect to biologically active compounds, it is important that heterocycles afford the desired products in high yield. Six-membered nitrogen heterocycles such as pyridines (67–93%) were as easily coupled as five-membered sulfur and oxygen heterocycles (86–99%).

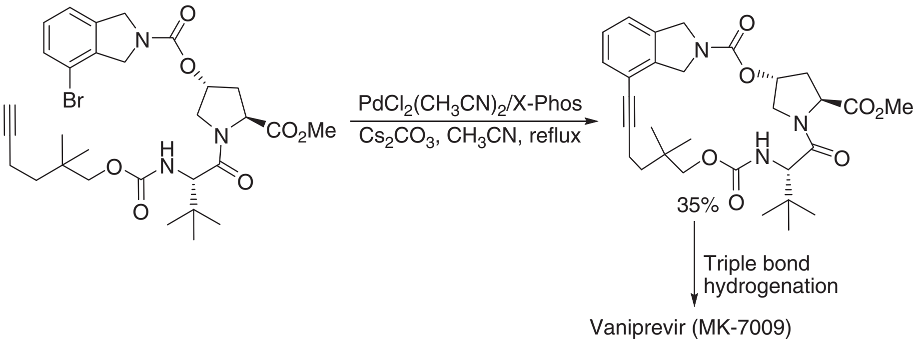
X- and S-Phos ligands were initially designed for activation of less-reactive aryl chlorides (*vide infra*); however, they also proved themselves as extremely versatile catalysts for the coupling of aryl bromides under very mild reaction conditions. In general, under the optimized reaction conditions, efficient coupling of aryl bromides with terminal alkynes takes place in acetonitrile or dioxane in the presence of 1–2 mol% $PdCl_2(CH_3CN)_2$ in combination with X- or S-Phos and Cs_2CO_3, K_2CO_3, or K_3PO_4 as a base at r.t. to 60 °C. For example, a nontrivial synthesis of alkyne-based macrocycles was accomplished using this catalyst at the key step (Scheme 18).[66] To prevent intermolecular oligomerization, the coupling reaction was carried out under slow addition conditions (full scope and limitations of the method will be discussed in Section 3.09.2.1.3).

The following example stresses an excellent functional group compatibility of the Buchwald's catalyst. The $PdCl_2(CH_3CN)_2$/X-Phos systems was used in multistep synthesis Vaniprevir (MK-7009) (Scheme 19).[67]

Lipshutz et al. developed conditions for efficient cross-coupling between lipophilic terminal alkynes and aryl bromides catalyzed by lipophilic $PdCl_2$/X-Phos in the absence of copper in pure water at ambient temperatures. To this end, micellar



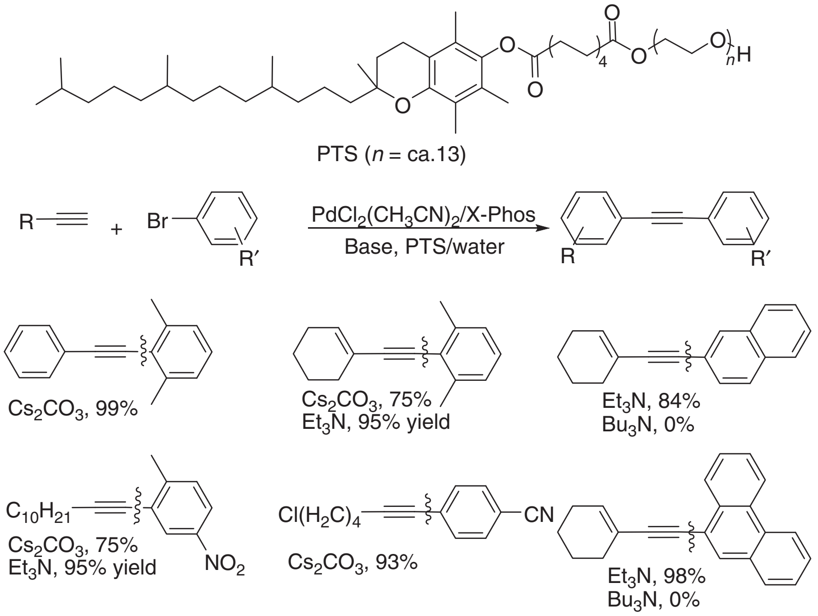
Scheme 18 Application of the CuI/PdCl$_2$(CH$_3$CN)$_2$/X-Phos catalyst for the synthesis of macrocyclic acetylenes.



Scheme 19 Application of the PdCl$_2$(CH$_3$CN)$_2$/X-Phos catalyst for the synthesis of macrocyclic acetylenes under copper-free conditions.

catalysis using the vitamin E core of the nanomicelle-forming amphiphile phase transfer surfactant (3% by weight in pure water) was employed.[68] Internal acetylenes could be constructed from aryl bromides and 1-alkynes at room temperature using a 3% (by weight) PTS/H_2O solution, excess Cs_2CO_3 as a base, and X-Phos as a ligand in the presence of catalytic $PdCl_2(CH_3CN)_2$. The H_2O used as a solvent is briefly degassed before mixing with PTS to prevent ligand oxidation. Reactions are best performed under inert atmosphere, although without rigorous exclusion of air. Significant sensitivity to base was also noted. Among heterogeneous bases, Cs_2CO_3 and K_3PO_4 gave excellent results. Otherwise, NEt_3 or pyrrolidine can be bases of choice. However, in some cases further variations of bases can lead to considerable difference conversion and isolated yields under essentially identical conditions. For example, both 2-bromonaphthalene and 9-bromophenanthrene gave the corresponding unsymmetrical internal alkynes using Et_3N as a base, however, neither *n*-Bu_3N nor (*n*-octyl)$_3$N led to any products, although the acetylenic partner was consumed by formation of polymeric materials (Scheme 20). Although cross-coupling of hindered bromides such as 2-bromoxylene with aromatic acetylene works perfect in the presence of Cs_2CO_3, their coupling with 1-ethynylcyclohex-1-ene was quantitatively achieved only using Et_3N or pyrrolidine as a base.

In principle, other ligands can be employed under the micellar catalysis as well.[68]



Scheme 20 Coupling of aryl bromides with terminal acetylenes under micellar catalysis.

Slight chemical modification of the monodentate ligands allowed developing water-soluble catalysts for the Sonogashira coupling of aryl bromides (Figure 3).[69,70]

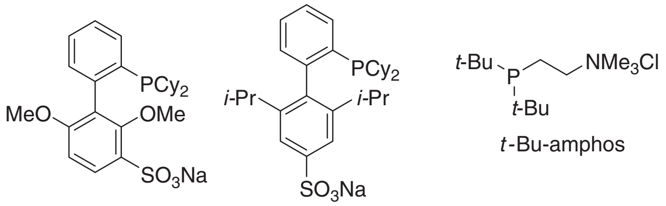
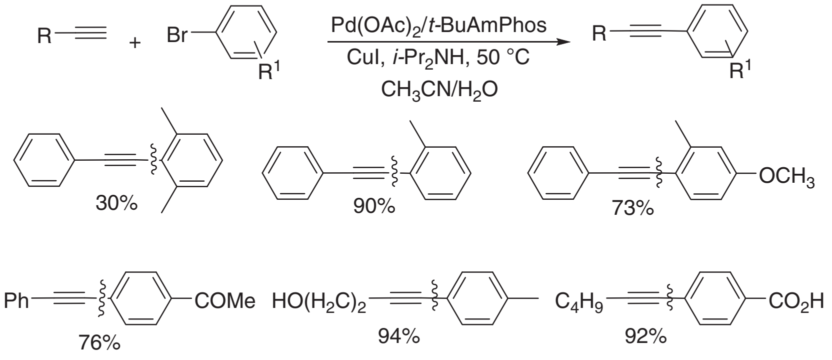


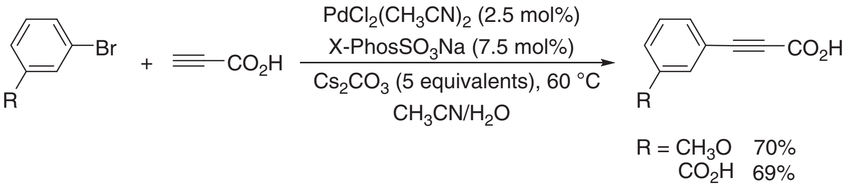
Figure 3 Representative examples of water-soluble monophosphine ligands.

Coupling reactions in water/acetonitrile media can be carried out with 3 mol% of *t*-Bu-Amphos, 3 mol% of $Pd(OAc)_2$, and 1 mol% of CuI in the presence of 1.2 equivalents of diisopropylamine. The lower 1% CuI loading was found to give better results in preparative scale couplings. Good to excellent isolated yields of alkyne products were obtained under the optimized conditions (Scheme 21).[70] The reaction was found to tolerate a variety of vulnerable functional groups (e.g., cyano, unprotected acids, and carbonyls) and to be moderately sensitive to the steric and electronic properties of the aryl bromides. For example, in comparison with the electron-neutral and -deficient substrates, slightly lower yield of the product (73%) was obtained when 4-bromoanisole was allowed to react with phenylacetylene. However, introduction of a single *o*-methyl group had no effect on the yield of coupled product, whereas an attempted alkynylation of 2-bromo-*m*-xylene with phenyl acetylene gave only 30% of the internal alkyne.



Scheme 21 Application of the water-soluble monophosphine ligands for the Cu/Pd-catalyzed coupling of aryl bromides with terminal acetylenes.

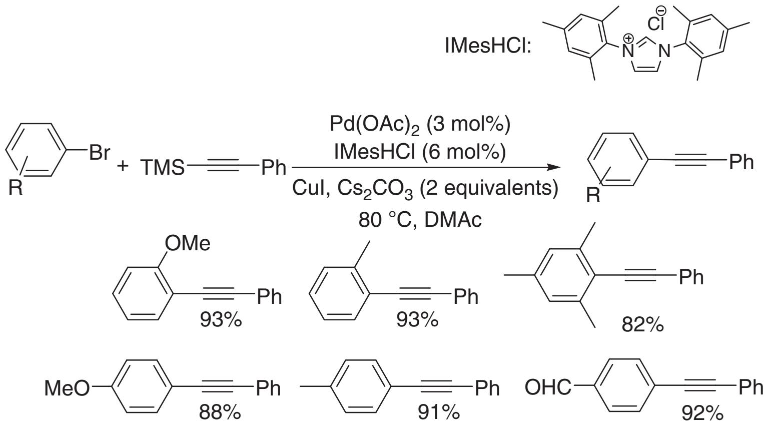
Using a catalyst based on [PdCl$_2$(CH$_3$CN)$_2$]/sulfonated X-Phos in a water/acetonitrile biphasic solvent system, propiolic acid was successfully coupled with 3-bromoanisole and 3-bromobenzoic acid to provide aryl alkynoic acids in yields of 70% and 69%, respectively (Scheme 22). This result represents a significant advancement in Sonogashira coupling reactions, as electron-deficient propiolate esters have been problematic coupling partners due to their increased reactivity toward nucleophilic attack and their propensity to polymerize in the presence of Pd catalysts.



Scheme 22 Application of the water-soluble monophosphine ligands for the Pd-catalyzed coupling of aryl bromides with propiolic acid.

This catalytic system is able to catalyze the coupling of aryl chlorides; however, the scope and limitations will be discussed in Section 3.09.2.1.3.

Bulky monodentate cyclic and acyclic carbene-based systems have been also reported as efficient catalysts for the coupling of aryl bromides. For example, Yang and Nolan established that Pd-carbene species are formed *in situ* from a palladium precursor with imidazolium salts under basic conditions. The combination of 3 mol% Pd(OAc)$_2$ and 6 mol% IMesHCl in the presence of Cs$_2$CO$_3$ as base proves to be a highly efficient system in assisting coupling of aryl bromides with alkynylsilanes.[71] Under optimized conditions, excellent product yields could be obtained from a wide array of arylbromides with 1-phenyl-2 (trimethylsilyl)acetylene in a very short time (Scheme 23). For example, the electron-deficient 4-bromobenzaldehyde was completely converted to the product in less than 15 min whereas for electron-neutral and electron-rich aryl bromides, complete or near-complete conversions could be reached in 30 min.

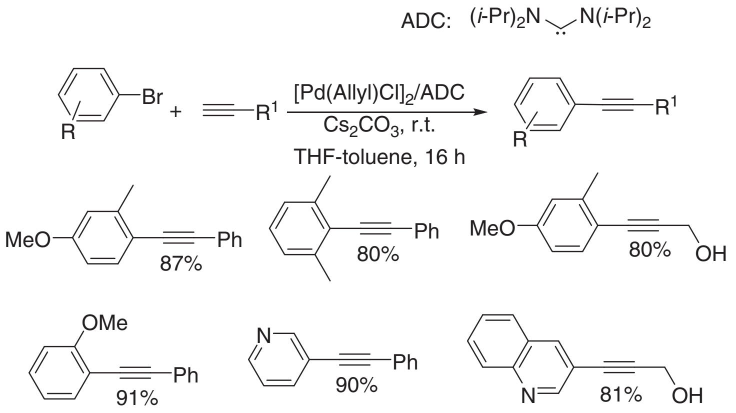


Scheme 23 Pd/bulky monodentate cyclic carbene-based systems as catalysts in Sonogashira coupling.

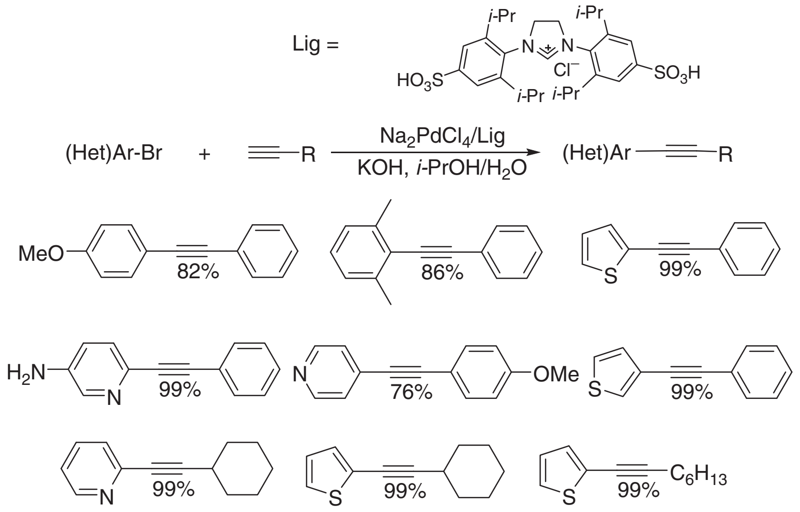
More exotic cyclic diaminocarbenes in combination with [Pd(allyl)Cl]$_2$ show comparable reactivity.[72] The optimized copper-free protocol comprises mixing of aryl bromide alkyne (1:1.1), [Pd(allyl)Cl]$_2$ (1.5 mol%), ligand (4 mol%), Cs$_2$CO$_3$ in toluene–THF, at room temperature for 16 h. The room- temperature Sonogashira reaction worked well with both aromatic and aliphatic alkynes. A range of sterically hindered, electron-rich, and heterocyclic aryl bromides were employed as coupling partners. The resulting products were consistently obtained in good isolated yields (Scheme 24).

Sulfonated monodentate N-heterocyclic carbene (NHC) ligands, readily accessible either by direct sulfonation of the NHC precursors or by the synthesis of the desired NHCs from the corresponding sulfonated anilines, were employed for Sonogashira coupling of aryl bromides in aqueous medium.[73] Thus, bulky sulfonated, diisopropyl-substituted NHC *in situ* generated from the corresponding NHC precursor in the presence of Na$_2$PdCl$_4$ (0.25 mol%) in water/*i*-PrOH mixture was found to catalyze efficient coupling of a variety of sterically hindered and electron-rich to electron-deficient (hetero)aryl bromides with aromatic and aliphatic acetylenes in good to excellent yield in the presence of 3 equivalents of KOH at reflux temperature (Scheme 25).

Reactions promoted by the catalysts derived from tetradentate ligands (bi-[74] and tri-[75] and tetradenate[76] phosphines (Figure 4)) generally proceed under harsher reaction conditions; however, often show very impressive TONs. The Tedicyp/[(allyl)PdCl]$_2$ system with K$_2$CO$_3$ as a base, CuI as cocatalyst in DMF catalyzes the coupling of aryl bromides with alkynes using



Scheme 24 Pd/monodentate acyclic carbene-based systems as catalysts in Sonogashira coupling.



Scheme 25 Water-soluble bulky monodentate cyclic carbenes systems as ligands in Sonogashira coupling.

very high substrates/catalyst ratios in good yields. In the presence of activating groups 0.0001 mol% Tedicyp–palladium complex (ratio substrate/catalyst: 1 000 000) led to the coupling products in 70–100% yields. A TON of 2 800 000 has been obtained for the coupling of 1-bromo-3,5-di(trifluoromethyl)benzene with phenylacetylene (equation 14). Bi- and tridentate ferrocene-based ligands allow aryl alkynylation at 10^{-1}–10^{-4} mol% catalyst loadings with TONs up to 950 000 under essentially identical reaction conditions. However, the best results were obtained at 130 °C which, of course, may be a limitation for the synthesis of thermally less-stable functionalized targets.

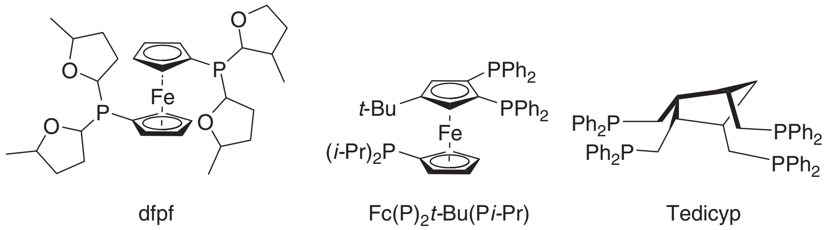
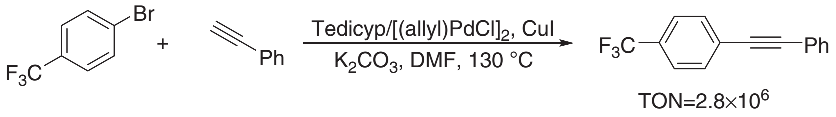


Figure 4 Representative polydentate ligands for the Sonogashira reaction.



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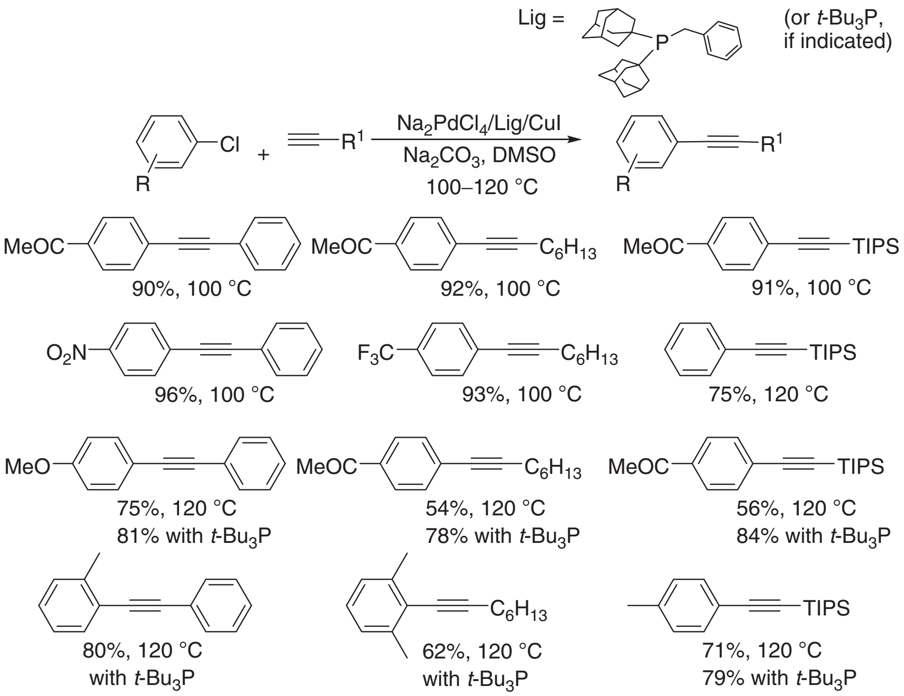
3.09.2.1.3 Coupling of aryl chlorides

Despite some occasional reports, the least reactive aryl chlorides have remained poor coupling partners in Sonogashira reaction until 2003 when Plenio and coworkers[77] and Gelman and Buchwald[24] independently reported the development of different catalysts for the general and efficient coupling of aryl chlorides.

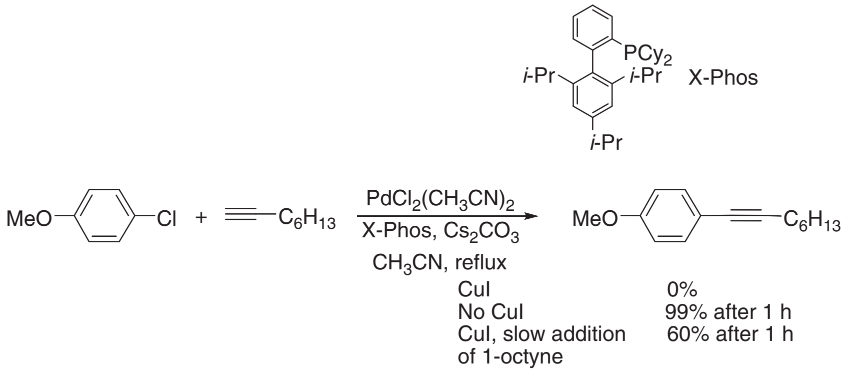
Koellhofer and Plenio suggested a high-yielding catalyst based on Na_2PdCl_4 and a sterically demanding and electron-rich phosphine ligands such as bis-adamantylbenzyl phosphine 1-Ad_2PBn or *t*-Bu_3P cocatalyzed by CuI in dimethyl sulfoxide (DMSO) at 100–120 °C in the presence of Na_2CO_3 as a base (the respective phosphonium salts 1-$Ad_2PBn \cdot HBr$ and *t*-$Bu_3P \cdot HBF_4$ were used as ligand precursors to avoid oxidation of the air-sensitive phosphine moieties). The choice of the base is decisive for the success of the reactions. Although amines work well for the coupling of alkynes and aryl bromides,[58] they are inefficient in corresponding reactions with aryl chlorides and Na_2CO_3 appeared to be the best choice. Furthermore, the nature of the palladium source is critical for the success of the coupling reaction. The best results were achieved with Na_2PdCl_4, whereas $PdCl_2(PhCN)_2$ or $Pd(OAc)_2$ showed no conversion at all. Temperatures of 100 °C are sufficient for the coupling of activated substrates, whereas heating up to 120 °C is needed to drive deactivated substrates to complete conversion. The method allows at least coupling of NO_2 and carbonyl-functionalized aryl chlorides with aromatic, aliphatic, and TMS-acetylenes and appears to be moderately sensitive to the steric bulk of the starting materials. For example, although 2-chlorotoluene reacts efficiently, yield drops significantly when an additional methyl group is installed in the 2′-position (Scheme 26).



Scheme 26 Pd/Cu-catalyzed coupling of aryl chlorides in the presence of bulky and electron-rich phosphine ligands.

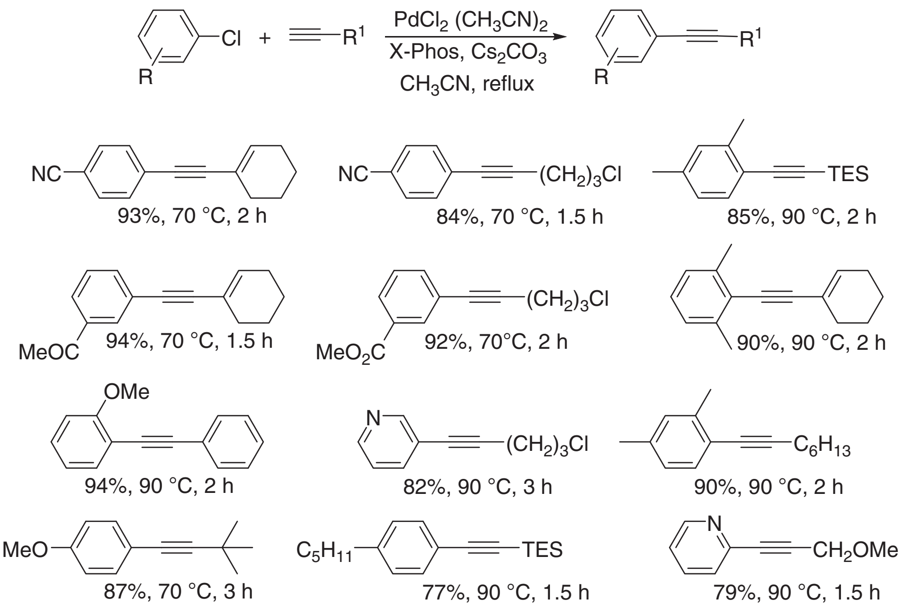
Gelman and Buchwald discovered that employment of biphenyl-based bulky electron-rich ligands (Figure 2) under the standard copper-cocatalyzed Sonogashira conditions lead to rapid oligomerization of the starting alkyne with negligible conversion of the starting aryl chloride.[24] However, exclusion of the copper co-catalyst or, alternatively, slow addition of the alkyne into the reaction mixture, suppresses the side reaction and leads to the clean formation of the coupled product from the corresponding aryl chloride at only acetonitrile reflux temperature using a catalyst derived from $PdCl_2(CH_3CN)_2$, and X-Phos, and Cs_2CO_3 as a base (Scheme 27).

These findings led to the discovery of a new protocol for the palladium-catalyzed coupling of alkynes with aryl chlorides. The reaction conditions employed (1 mol% of $[PdCl_2(CH_3CN)_2]$, 3 mol% of X-Phos, 1.3 equivalents of the terminal alkyne, and 2.6 equivalents of Cs_2CO_3 in acetonitrile at 70–90 °C) typically provided very fast and selective transformation of aryl chlorides to the desired product. The choice of the solvent, as well as of the base, was important for the success of the reaction described here: only moderately polar aprotic solvents (acetonitrile and dioxane), in combination with inorganic bases (e.g., Cs_2CO_3 or K_3PO_4) proved to be useful. In contrast to these observations, no critical role of the precatalyst was detected, although the best results were obtained with $PdCl_2(CH_3CN)_2$ or $PdCl_2$. As illustrated in Scheme 28, the reactions of electron-deficient aryl chlorides could be carried out at 70 °C. The transformation with electron-neutral and electron-rich aryl chlorides necessitated a reaction temperature of 90 °C. The coupling of more polymerizable aryl acetylenes required that the alkyne be added over 2 h, otherwise incomplete



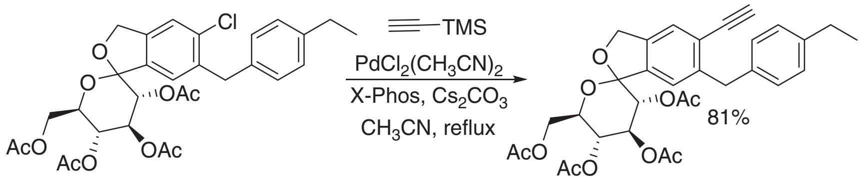
Scheme 27 Possible deleterious effect of the copper-catalyst in reactions catalyzed by PdCl$_2$/X-Phos.

conversion of the aryl chlorides and nonproductive consumption of the alkynes again takes place. The present method was found to be relatively insensitive to the steric hindrance of the starting aryl chloride. For example, 2-chloro-*m*-xylene was converted to the corresponding acetylene in excellent yield. Good functional group compatibility and wide scope of alkynes highlight the new method. Functionalized, as well as unfunctionalized alkynes, can be successfully coupled with a variety of aryl and heteroaryl chlorides to yield the corresponding disubstituted acetylenes. Although it was found that the use of TMS-protected acetylenes was inefficient due to the significant desilylation of the product that takes place under our reaction conditions, the use of triethylsilylacetylene was a suitable surrogate.



Scheme 28 Pd-catalyzed coupling of aryl chlorides in the presence of bulky and electron-rich phosphine ligands under copper-free conditions.

A new building block for the synthesis of C-arylglucoside with an O-spiroketal ring system[78] and new acetylated O-hydroxyacetamide carbamate derivatives (highly potent endocannabinoid hydrolase inhibitors)[79] were synthesized in 81% and 34% isolated yield, respectively, using unmodified Buchwald conditions manifesting excellent functional group compatibility of the catalyst (equations 15 and 16).



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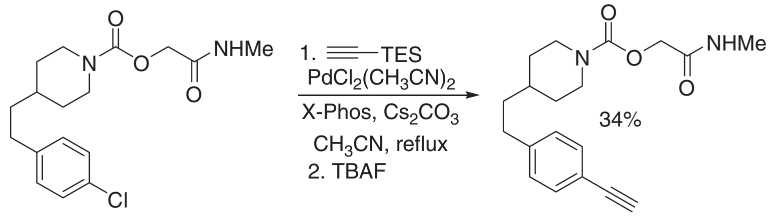

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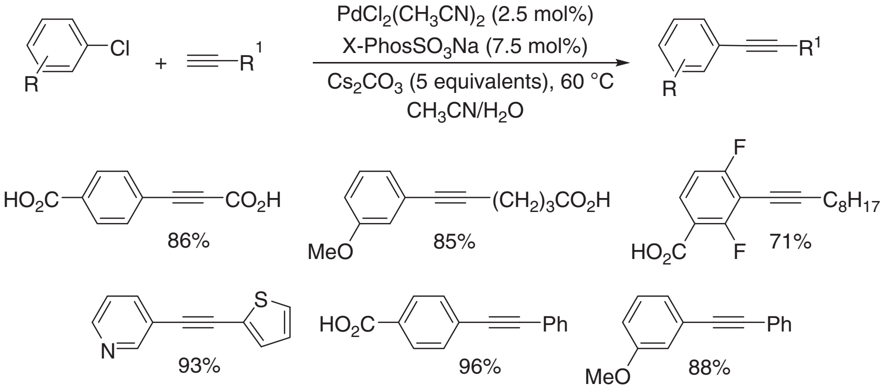
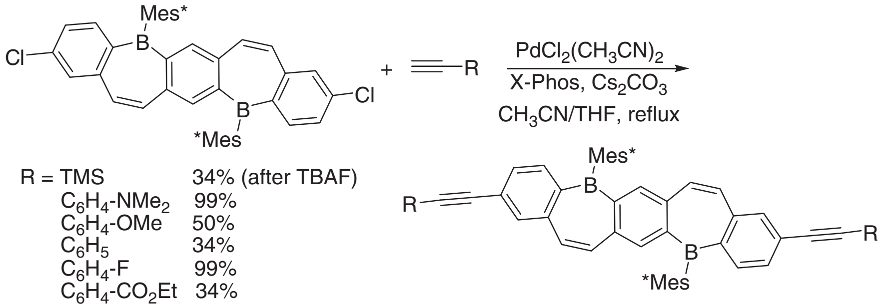
Water-soluble sulfonated X-Phos (**Figure 3**) shows unprecedented reactivity in acetonitrile–water system. Good yields were obtained for the coupling of hydrophilic aryl chlorides bearing carboxyl groups and an alkyne derived from an aliphatic carboxylic acid. Interestingly, by using this ligand and a water/acetonitrile solvent system, the coupling of aryl chlorides and aryl alkynes proceeds and obviates the need to employ slow addition of the aryl alkyne. This result may be attributed to the lower effective concentration of the alkyne in proximity to the catalyst, which resides at the water/organic interface (**Scheme 29**).



Scheme 29 Application of the water-soluble monophosphine ligands for the Pd-catalyzed coupling of aryl chlorides with terminal acetylenes.

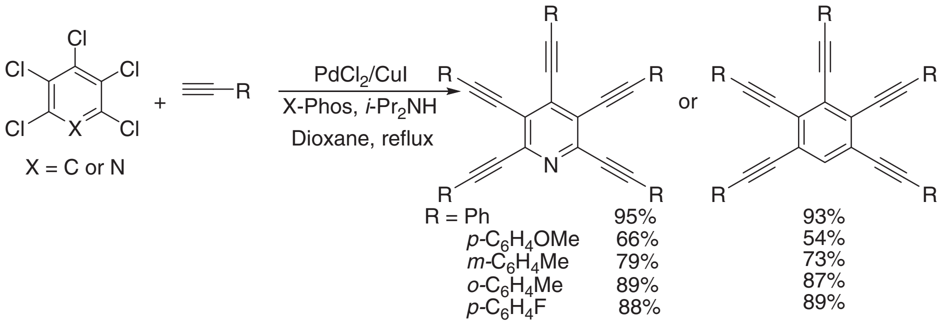
This protocol with almost no modification was used to synthesize functionalized bora-acenes possessing interesting photoelectronic properties (**Scheme 30**).[80]



Scheme 30 Application of the PdCl^2/X-Phos catalyst for the synthesis of functionalized bora-acenes.

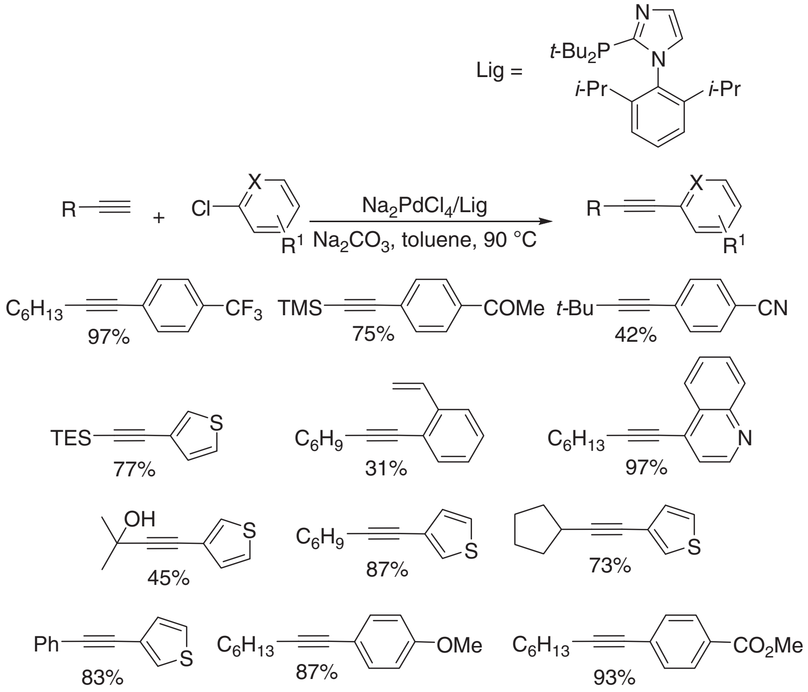
Despite the observed deleterious effect of the copper additives, Langer and coworkers employed this catalytic system for the synthesis of the multialkynyl arenes.[81] They demonstrated that 5 mol% of $PdCl_2(CH_3CN)_2$, 10 mol% X-Phos, 3 mol% of CuI, 3 equivalents of *i*-Pr_2NH in 1,4-dioxane promote polyalkynylation of penta- and hexachloroarenes with terminal acetylenes in excellent yield (**Scheme 31**). Addition of alkyne moieties to the pyridine leads to an activating effect due to the withdrawing nature of the alkyne giving the pentaethynylpyridine as a major product (**Scheme 31**). The reaction of hexachlorobenzene with 8 equivalents of phenylacetylene, using the procedure developed for the synthesis of pentasubstituted arenes proceeded sluggishly and gave the fully substituted product in only 36% yield. Nevertheless, the yield of the product could be increased to 93% by increasing the temperature (100 °C), extending the reaction time (20 h), and using a slightly increased catalyst loading.

Beller and coworkers developed a very useful catalytic system based on [N-(2,6-diisopropylphenyl)-2-imidazolyl]-di-tert-butylphosphine.[82] This ligand is formed straightforwardly from easily available substrates (2,6-diisopropylamine, glyoxal, formaldehyde, and chloro-di-tert-butylphosphine) in two steps. It was found that 8 mol% of this phosphine ligand in



Scheme 31 Application of the $PdCl_2$/X-Phos catalyst for the polyalkynylation of penta- and hexachloroarenes.

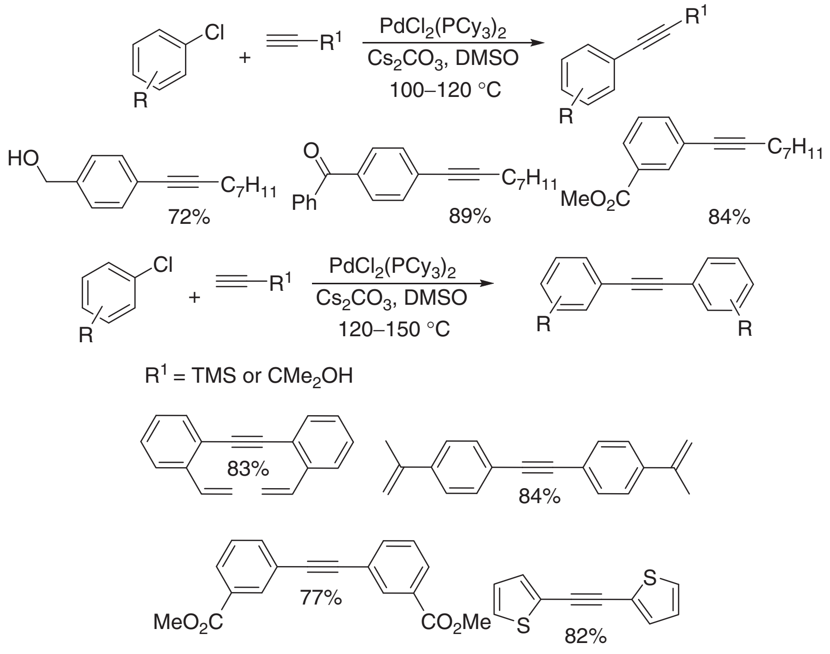
combination with 1 mol% $PdCl_2(CH_3CN)_2$ and Na_2CO_3 as a base promotes alkynylation of functionalized aryl and heteroaryl chlorides at 90 °C in toluene with no copper additive. In general, good to excellent coupling results with a variety of aryl and heteroaryl chlorides – including challenging substrates – have been obtained at low catalyst loading. Various functional groups including amino, silyl, and vinyl groups are tolerated under these conditions (Scheme 32).



Scheme 32 $PdCl_2(CH_3CN)_2$/[N-(2,6-diisopropylphenyl)-2-imidazolyl]-di-tert-butylphosphine-catalyzed coupling of aryl chlorides.

Advantageously, the reaction can also be performed in propylene carbonate as a solvent that offers a possibility of catalyst recycling via extraction of the nonpolar product with nonpolar solvents from the reaction mixture. However, a large excess of a ligand (8 mol%) is needed to drive reactions to completion.

Yia and Hua reported that structurally defined $PdCl_2(PCy_3)_2$ shows high catalytic activity in cross-coupling of electron-rich, electron-neutral, and electron-deficient aryl chlorides with a variety of terminal alkynes under copper-free conditions and with Cs_2CO_3 as a base in DMSO at 100–150 °C affording internal alkynes in good to excellent yields.[83] Although the complete conversion requires somewhat harsh reaction conditions, a variety of important functional groups such as alcohol, ester, and ketone were tolerated under the present conditions (Scheme 33). Diaryl acetylenes can be prepared in one-pot using TMS[83] or acetone-protected[84] alkynes as starting materials as TMS and acetone extrusion starts spontaneously under the reaction conditions. Interestingly, in the cases of highly electron-deficient chlorobenzene derivatives such as 1-chloro-4-nitrobenzene and chloropentafluorobenzene, the desired diarylacetylene could not be obtained in satisfactory yields, because the formation of some unidentified compounds with molecular weights higher than that of the corresponding diarylated acetylene were found.

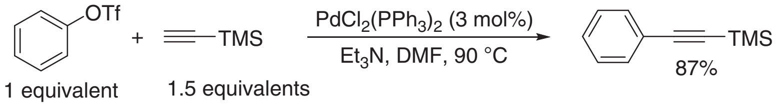


Scheme 33 PdCl$_2$(PCy$_3$)$_2$-catalyzed coupling of aryl chlorides.

3.09.2.1.4 Coupling of aryl pseudohalides (perfluoroalkyl sulfonates and alkyl/aryl sulfonates)

Aryl trifluoromethanesulfonates (triflates) are reactive partners in many cross-coupling processes that are synthetically useful and readily accessible from the corresponding phenols. Usually, their reactivity may be considered somewhere in between the reactivity of aryl bromides and aryl iodides. Thus, no specially designed catalytic systems are required in order to induce coupling of these convenient substrates.

In 1986, Chen and Yang reported that aryl fluoroalkanesulfonates successfully couple with terminal alkynes in the presence of 2–3 mol% PdCl$_2$(PPh$_3$)$_2$ catalyst and Et$_3$N as a base in DMF at 90 °C over 3–17 h leading to the formation of internal alkynes in good to excellent yield (equation 17).[85]



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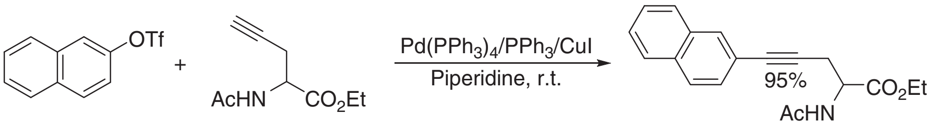
Addition of copper iodide as a cocatalyst allowed carrying out these reactions under milder reaction conditions and, therefore, employing functionalized potentially thermally unstable substrates (equation 18).[86]



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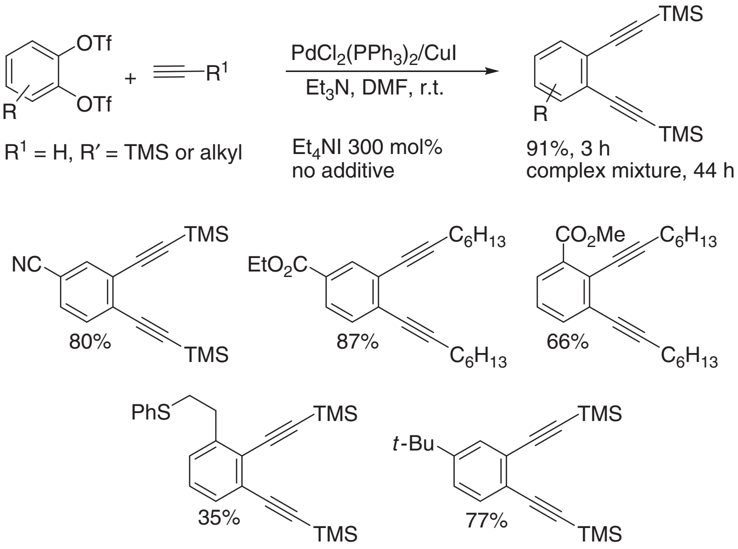
Another interesting modification was suggested by Rychnovsky who has attempted synthesis of bislkynylated benzene starting from aryl 1,2-bistriflates (Scheme 34).[87] He found that addition of 300 mol% of Et$_4$NI to the reaction mixture under Chen's conditions significantly enhances the reaction rate and 91% of the desired product forms after only 3 h, whereas the same reaction with no additives results in the formation of complex mixture of products after 44 h. Excellent results have been obtained for functionalized substrates as well.

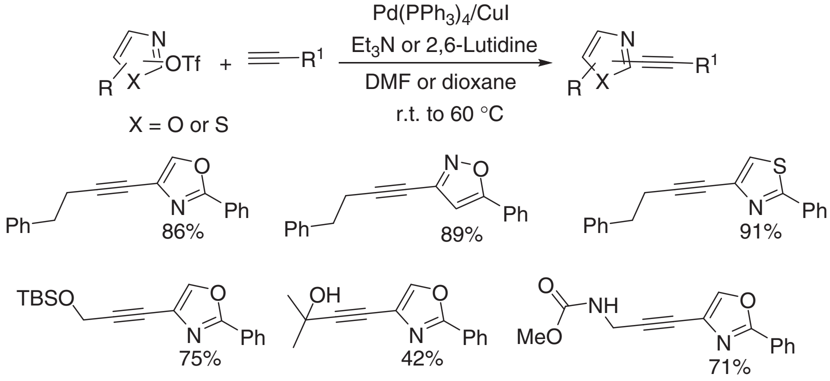
Although no reasonable explanation was given to this activity, the beneficial effect was attributed to the presence of the iodide ion. It is interesting to note that the paper describing these findings was published almost concurrently to Jeffery who discovered a very similar acceleration of Heck coupling in the presence of tetraalkylammonium salts.[88]

Since then, the protocols have not been much modified but became a very useful tool for the construction of internal alkynes from aryl triflates. For example, Dai et al. employed Rychnovsky's conditions for the synthesis of a series of alkynylated 2-carboxamidearenes in good to excellent yield.[89]



Scheme 34 Pd/Cu-catalyzed coupling of aryl triflates with terminal alkynes.

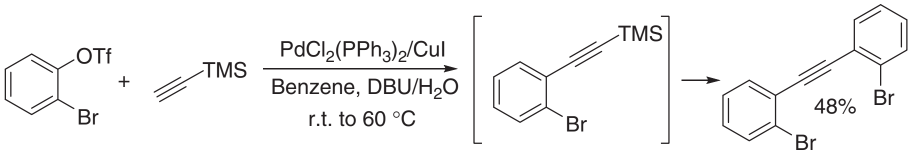
Functionalized trifloyl oxazoles and triazoles were successfully coupled with functionalized terminal alkynes under very mild reaction conditions in good to excellent yield.[90] As outlined in **Scheme 35**, Sonogashira coupling can be readily achieved using catalytic Pd(PPh$_3$)$_4$ and CuI, with full conversion achieved in DMF or 1,4-dioxane at r.t. to 65 °C after 24 h. The coupling process is clean and devoid of side reactions such as alkyne homocoupling. Good reactivity was observed with a wide variety of functional groups, including ethers, alcohols, and silanes. Additionally, the use of an unprotected carbamate group illustrates alkyne compatibility with basic heteroatoms.



Scheme 35 Pd/Cu-catalyzed coupling of heteroaryl triflates with terminal alkynes.

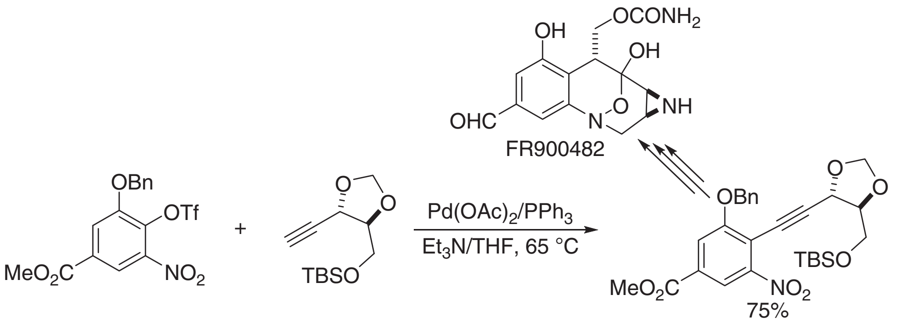
The following example highlights the excellent functional group compatibility of the palladium-catalyzed coupling of aryl-triflates with terminal alkynes. Fukuyama and coworkers employed this transformation as a C–C bond-forming step in the total synthesis of the antitumor antibiotic FR900482 (**Scheme 36**).[91]

One-pot synthesis of symmetrical and unsymmetrical bisarylethynes starting from TMS-protected acetylenes and aryltriflates can be realized using slightly modified conditions.[34] It was demonstrated that addition of amidine base such as DBU and water causes *in situ* deprotection of the masked acetylene and coupling with an additional equivalent of aryl triflates (equation 19).



(19)

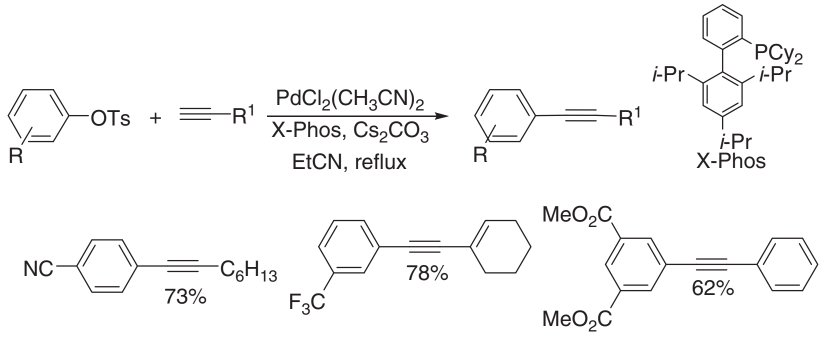
Aryl sulfonates are relatively nonreactive coupling partners in Sonogashira reaction, although development of catalysts capable of activating these substrates is important from the economical point of view as sulfonates are much less expensive and more



Scheme 36 Application of the Pd/Cu-catalyzed coupling of aryl triflates for the synthesis of functionalized targets.

readily available than the corresponding aryl fluoroalkanesulfonates. In addition, aryl sulfonates are more stable under hydrolytic conditions compared to the fluorinated sulfonates, which makes them more attractive from the synthetic point of view.

The first coupling of aryl toluenesulfonates with terminal alkynes was reported by Gelman and Buchwald.[24] To this end they employed the earlier described $PdCl_2(CH_3CN)_2$/X-Phos catalyst. Unfortunately, the reaction conditions were not quite specific (only three examples have been reported, Scheme 37) and required somewhat elevated temperature (100 °C) and higher catalyst loading (5 mol%) in order to achieve complete conversion.



Scheme 37 $PdCl_2(CH_3CN)_2$/X-Phos-catalyzed coupling of aryl tosylates.

Later, two groups independently reported more general and efficient catalytic systems for the coupling of (hetero)aryl tosylates and mesylates. The first catalyst reported by Kwong and coworkers is based on a bulky monophosphine ligand CM-Phos (Figure 5) that showed satisfactory performance during attempted coupling of 4-*t*-butylphenyl tosylates with 1-heptyne.[92] It was found that a combination of $Pd(OAc)_2$ with CM-Phos in 1:3 ratio is the best catalyst system for this tosylate coupling. A survey of often used inorganic bases revealed that K_3PO_4 and $K_3PO_4 \cdot H_2O$ were equally efficient in *t*-BuOH as a solvent at 100 °C (Scheme 38). Copper additives were not necessary for this reaction.

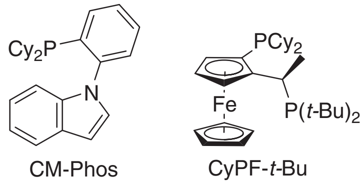
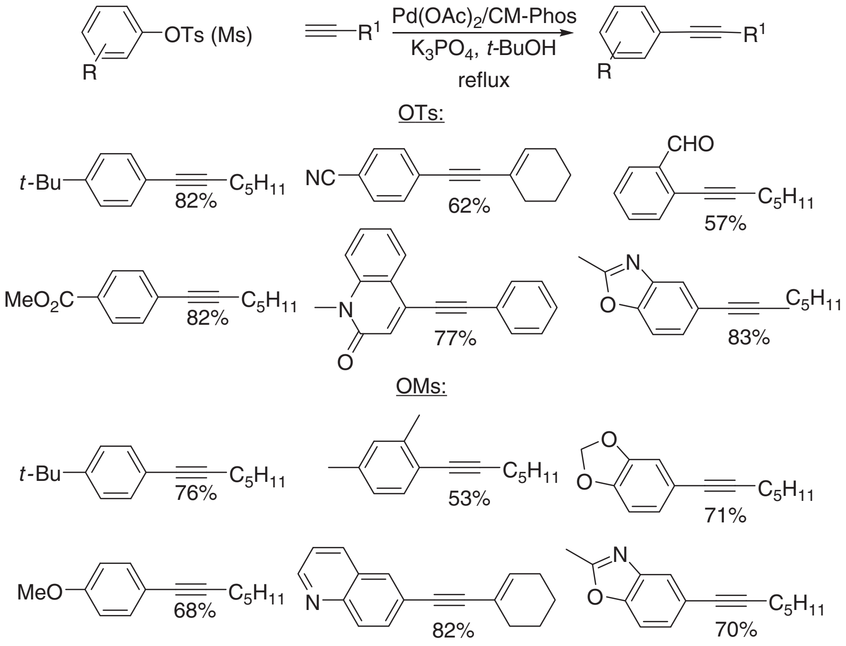


Figure 5 Bulky monophosphine ligands designed for the coupling of aryl tosylates.

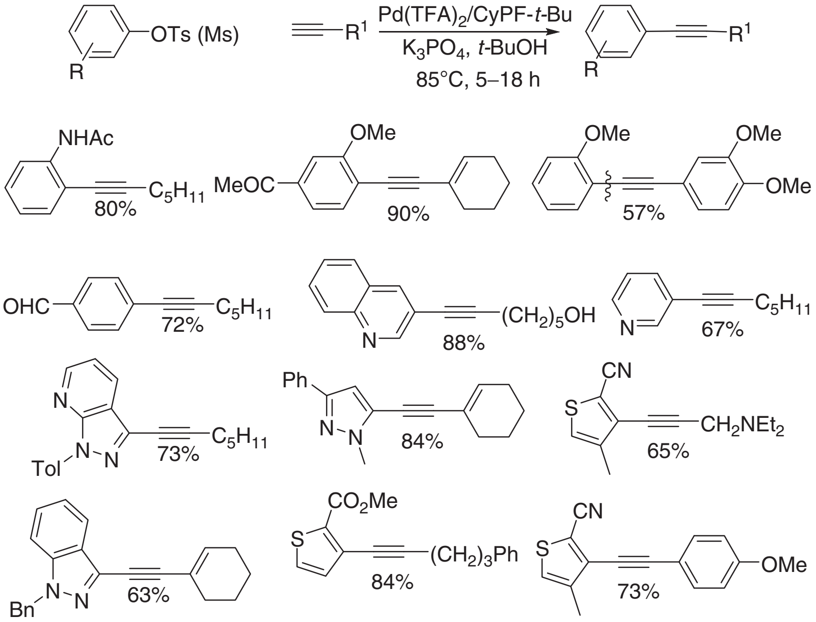
Common functional groups such as methoxy, cyano, keto, ester, and aldehyde were compatible under the stated reaction conditions. Heterocyclic benzothiazolyl and quinolinyl tosylates furnished the corresponding coupling products smoothly. In view of commonly used sulfonate leaving groups, the mesylate can be regarded as the most inert group, since the pK_a of the corresponding conjugate acid is higher in comparison to tosylates. However, the $Pd(OAc)_2$/CM-Phos combination was found to be effective in promoting the Sonogashira coupling of aryl mesylates. An array of aryl mesylates were examined in this coupling reaction using 1-hexyne as the nucleophile. Heteroaryl mesylates were also compatible in this system. Aryl alkyne and conjugated alkyne were found to be capable coupling partners.

Lindenschmidt and coworkers discovered that 1-dicyclohexylphosphino-2-(di-*t*-butylphosphinoethyl)ferrocene (CyPF-*t*-Bu, Figure 5) in combination with $Pd(TFA)_2$ and K_3PO_4 effectively catalyzes coupling of aryl tosylates with terminal alkynes



Scheme 38 Pd(OAc)$_2$/CM-Phos-catalyzed coupling of aryl tosylates and mesylates.

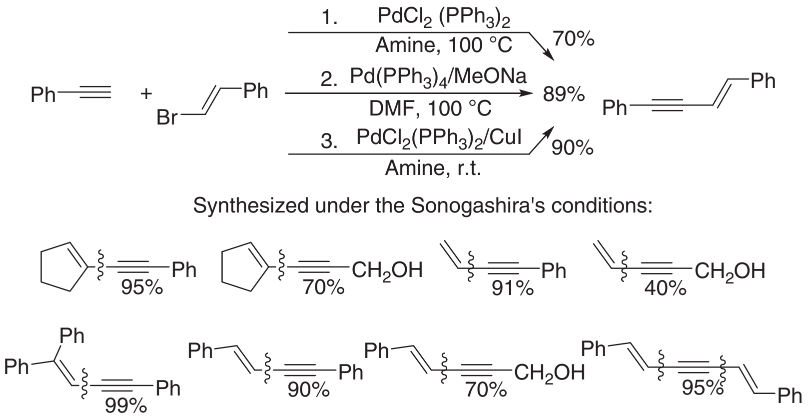
reaction in *t*-BuOH at 85 °C to form alkyne with no copper additives.[93] The optimized reaction conditions accept a broad substrate scope in both aryl tosylate and alkyne coupling partners (Scheme 39). Diversely and, in particular, *ortho*-substituted aryl tosylates are tolerated and react with comparable efficiency. Importantly, nonactivated substrates, such as phenyl tosylate, or even deactivated aryl tosylates, such as *p*-tolyl- or *o*-methoxyphenyl tosylates, were found to be reactive under these conditions. A number of potentially reactive functionalities, such as heterocycles, ketones, aldehydes, hydroxy groups, nitriles, methyl esters, and even a free primary amine, are compatible and remain unaffected, which illustrates the robustness of the catalyst system.



Scheme 39 Pd(TFA)$_2$/CyPF-*t*-Bu-catalyzed coupling of aryl tosylates and mesylates.

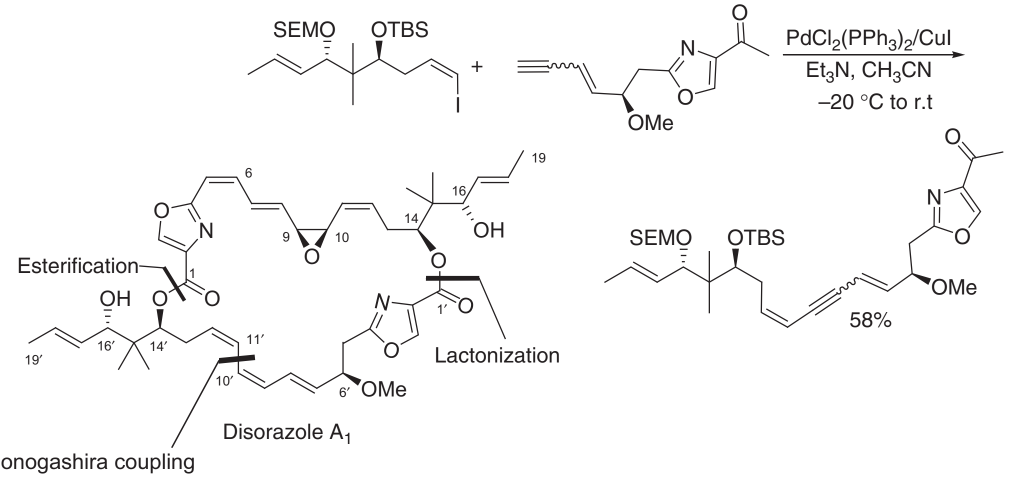
3.09.2.1.5 Coupling of vinyl halides and pseudohalides

Employment of vinyl halides as coupling partners in the palladium-catalyzed alkyne synthesis was described in the seminal reports by Dieck and Heck,[11] Cassar,[12] and Sonogashira et al. (Scheme 40).[13] Although all protocols led to the formation of the products in good to excellent yield, the mild Sonogashira's conditions became the most popular in this type of coupling. All enynes described in the original paper were synthesized at room temperature with absolute stereospecificity.



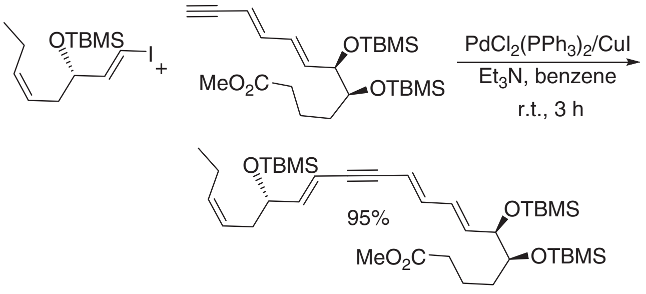
Scheme 40 Coupling of vinyl bromides under the standard Sonogashira–Cassar–Heck conditions.

Typically, vinyl iodides are very reactive under the standard Sonogashira conditions. For instance, ynediene moiety over the course of the asymmetric total synthesis of Disorazole A1 and C1 (Scheme 41) was performed at low temperature (– 20 °C to r.t.) in order to avoid decomposition of a thermally unstable target molecule.[94] The described coupling was accomplished in 58% yield (97% based on the recovered enantiopure *Z*-vinyl iodide) in the presence of 10 mol% of PdCl$_2$(PPh$_3$)$_2$, 30 mol% of CuI, and Et$_3$N in CH$_3$CN with no racemization.



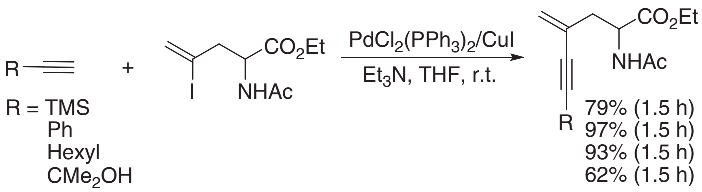
Scheme 41 Coupling of vinyl iodides toward the synthesis of highly functionalized enediynes.

Another example of stereospecific C–C bond formation, which also highlights the perfect functional group compatibility, is the Sonogashira coupling of enantiopure *E*-vinyl iodide with a terminal ynediene as a route toward Lipoxine A$_5$ (equation 20).[95] The desired precursor was synthesized in excellent yield after only 3 h at room temperature.



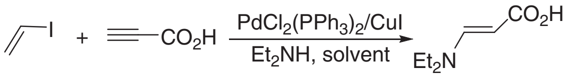
(20)

A variety of functionalized alkynes can be coupled with vinyl halides. For example, a series of alkyne-functionalized N-acetyl-allylglycinates was prepared from the corresponding iodo derivatives using the standard Sonogashira conditions (**Scheme 42**).[96]



Scheme 42 Modification of N-Acetyl-allylglycinates via Pd/Cu-catalyzed Sonogashira coupling.

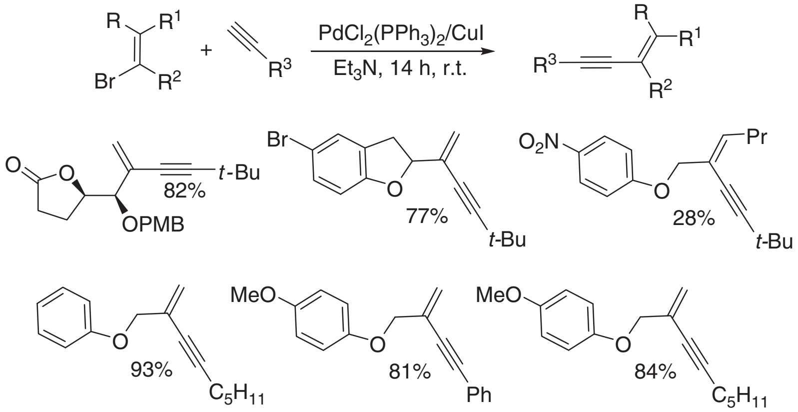
It must be noticed that coupling of electron-deficient alkynes such as propionic acid and its derivatives is problematic due to the nucleophilic character of the alkyne (equation 21).

 (21)

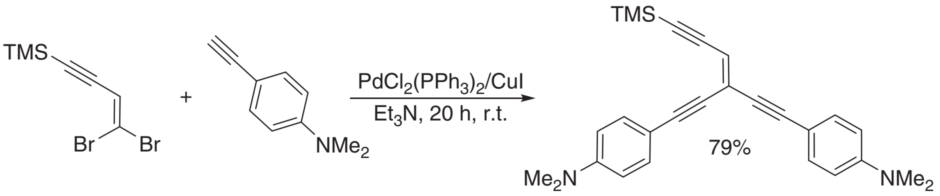
Many very efficient methods for the stereoselective synthesis of vinyl iodides are available.[97]

Vinyl bromides can also be prepared stereoselectively[98,99] and, therefore, appear as very attractive coupling partners for the synthesis of enynes. Coupling of these substrates takes place using essentially similar catalytic systems and is highlighted by very mild reaction conditions and excellent functional group compatibility.

Synthesis of differently substituted enynes (**Scheme 43**)[100] and highly π-extended macromolecules with a conjugated enyne core (equation 22) has been performed using the standard Sonogashira conditions employing a $PdCl_2(PPh_3)_2/CuI$ catalyst in Et_3N at room temperature.[101,102]

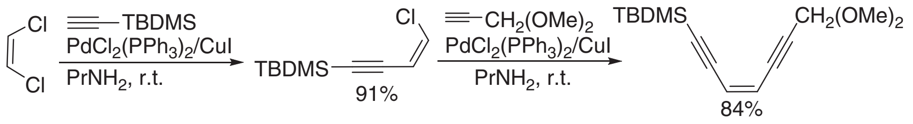


Scheme 43 Synthesis of differently substituted enynes via Pd/Cu-catalyzed Sonogashira coupling of vinyl bromides.

 (22)

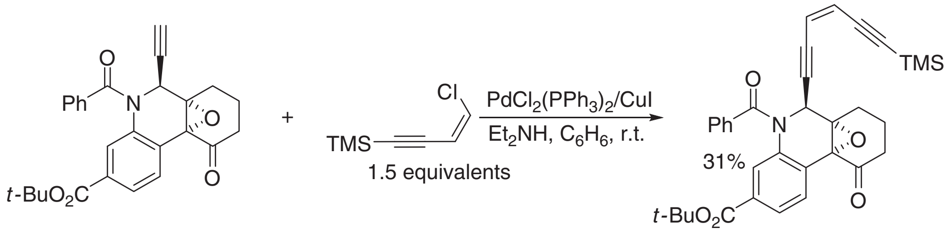
Unlike aryl chlorides, reactivity of alkenyl chlorides is sufficient and they can be activated using a very simple catalytic system.

Monocoupling of dichloroethylene with *t*-butyldiphenylsilylacetylene in the presence of $PdCl_2(PPh_3)_2/CuI$ catalyst in propylamine proceeded smoothly at only 0 °C to provide the tert-butyldiphenylsilyl (TBDPS)-protected *Z*-enyne. A second coupling (performed at room temperature) with dimethoxy propargyl acetal delivered the *Z*-enediyne in 81% yield (equation 23).[103]



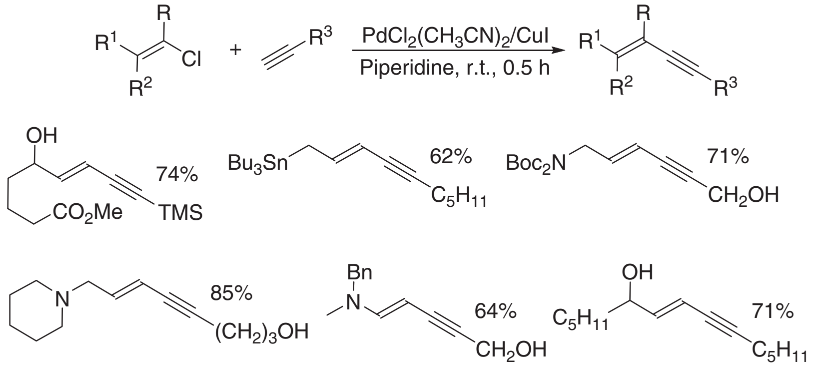
(23)

Again, perfect chemoselectivity of the method allows application of the Sonogashira coupling to the synthesis of much functionalized targets. For example, synthesis of the Dynemicin precursor (equation 24) was accomplished in 31% yield with no racemization or isomerization.[104]



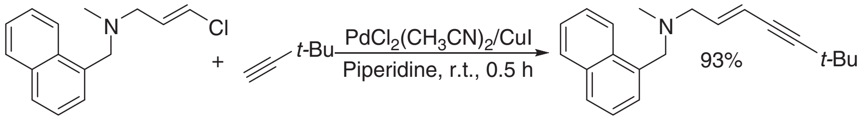
(24)

In principle, it was demonstrated that coupling of vinyl chlorides with terminal alkynes obviates the use of phosphine ligands.[105] Thus, attempted coupling of (*E*)-5-(chloromethylene)decane with heptyne in piperidine in the presence of palladium catalysts coordinated with nitrile ligands such as $PdCl_2(PhCN)_2$ or $PdCl_2(MeCN)_2$ led to the formation of the desired coupling product in 93% after only 30 min at room temperature. The demonstrated scope of the method is excellent and the reaction conditions tolerate a wide spectrum of sensitive functional groups on either coupling partner including organotin derivatives (Scheme 44).



Scheme 44 Synthesis of differently substituted enynes via Pd/Cu-catalyzed Sonogashira coupling of vinyl chlorides.

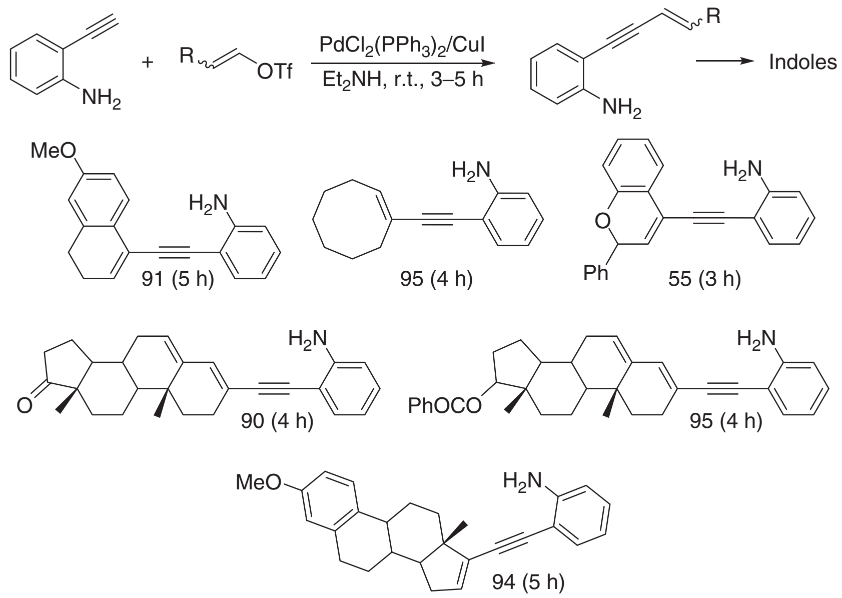
An illustration of the efficiency of this procedure is the high yielding synthesis of terbinafine, a strong antimycotic agent (equation 25).



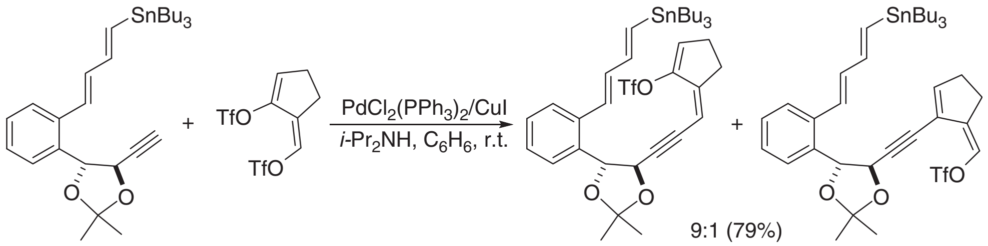
(25)

Vinyl triflates and tosylates are versatile coupling partners as they are readily prepared from the corresponding enolizable carbonyl compounds. In 1989, Cacchi and coworkers demonstrated that employment of standard Sonogashira conditions ($PdCl_2(PPh_3)_2$, CuI in Et_2NH at room temperature for 3–5 h to the coupling of vinyl triflates and *o*-substituted arylalkynes affords functionalized enynes in high yield (Scheme 45).[106] The suggested transformation led to the discovery of a mild and general synthesis of 2-substituted indoles after a subsequent cyclization.

Steric hindrance around the triflate leaving group may have a decisive influence on their reactivity, which can be used in synthesis of complex molecules. Thus, coupling of functionalized alkyne with (*Z*)-(2-(trifluoromethylsulfonyloxy)cyclopent-2-enylidene)methyl trifluoromethane-sulfonate[107] leads to the formation of 9:1 mixture of regioisomers, although coupling of a less-substituted triflates site is preferred (equation 26). The coupling takes place under essentially Cacchi's conditions.[106]



Scheme 45 Synthesis of differently substituted enynes via Pd/Cu-catalyzed Sonogashira coupling of vinyl triflates.



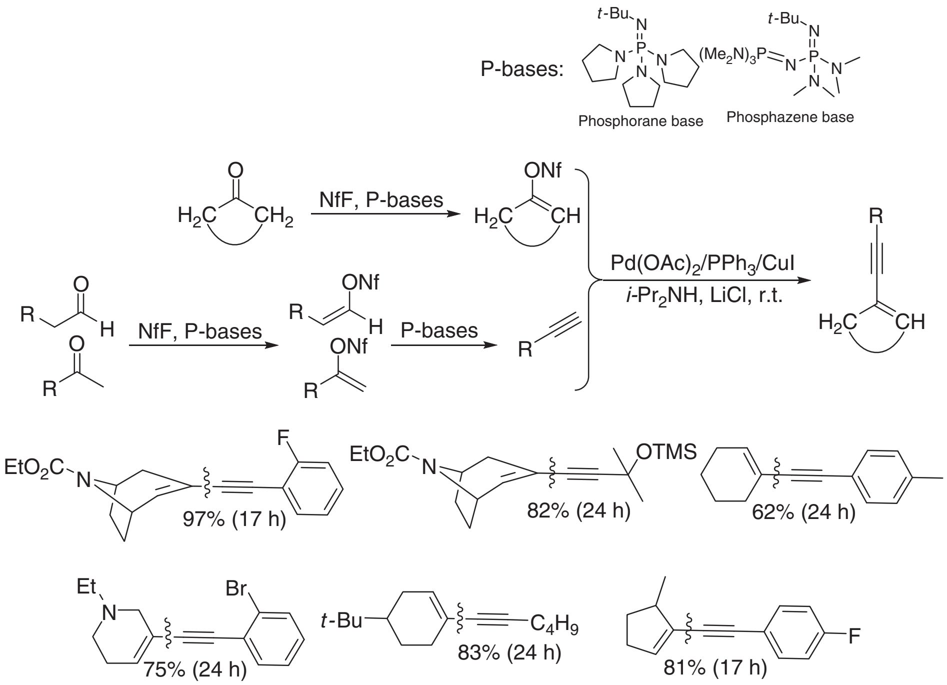
(26)

A general and versatile method for C–C cross-coupling synthesis of conjugated enynes in one-pot sequence starting from readily available carbonyl compounds was developed by Lyapkalo and Vogel.[108] Although routinely, the coupling protocols consist of two steps that include O-sulfonylation of the starting carbonyl compounds, followed by Pd-catalyzed cross-coupling of the isolated alkenyl perfluoroalkanesulfonate with terminal alkyne leading to the desired products. The suggested method comprises one-pot conversion of cyclic ketones into nonafluorosulfonate esters (electrophile) and of methyl alkyl ketones or aldehydes into terminal alkynes by interaction with 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonylfluoride (NfF) promoted by non-nucleophilic bases such as (tert-butylimino)-tris(1-pyrrolidinyl)phosphorane or 1-(tert-butylimino)-1,1,3,3,3-pentakis(dimethylamino)-1-diphosphazene (Scheme 46). The *in situ* formed coupling partners react under the standard Sonogashira conditions (5 mol% of $Pd(OAc)_2$/10 mol% of PPh_3/10 mol% of CuI/LiCl in *i*-Pr_2NH). The operational simplicity of the one-pot protocol and high yields of products afford a flexible, convergent approach toward a variety of conjugated enynes.

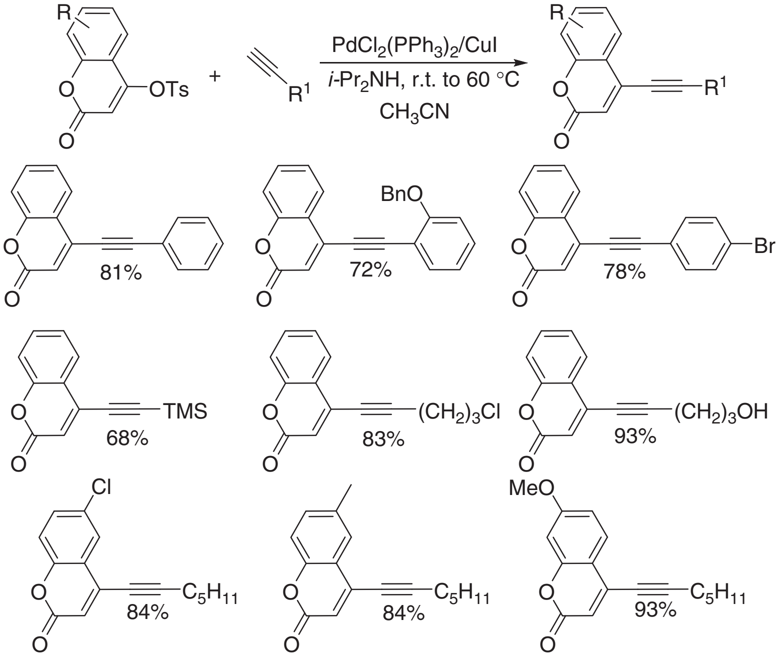
Hydrolytic instability of alkenyl triflates sometimes limits their utilization in Sonogashira coupling, especially, during multistep synthesis. In such cases, more robust alkenyl tosylates may be employed. Unlike relatively inert aryl tosylates, vinyl tosylates demonstrate sufficient reactivity in cross-coupling.[109–111] For example, an efficient protocol was developed by Yang and coworkers when they searched for a way to synthesize 4-alkynylcoumarines from the corresponding benzopyrones.[112] Thus, reaction tosylcoumarines with a variety of terminal acetylenes in the presence of diisopropylethylamine and catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI in acetonitrile resulted in the formation of a series of enynes in good to excellent yields as shown in Scheme 47. As can be seen from the scheme, all the selected terminal acetylenes (except trimethylsilylacetylene) reacted smoothly with the starting tosylates under the Sonogashira conditions between 50 and 60 °C in less than 12 h. Due to the low boiling point of trimethylsilylacetylene (bp 53 °C), the coupling was carried out at 25 °C and needed 48 h to complete. Since many functional groups (such as bromo, chloro, hydroxy, and cyano) can tolerate the reaction conditions, the expected enynes were obtained in good to excellent yields (72–92%). Substituents (such as methyl, methoxy, and chloro) on the coumarin scaffolds do not change the coupling efficiency, and all the reactions were completed in less than 12 h.

3.09.2.1.6 Synthesis of ynones

Synthesis of ynones can be accomplished via Sonogashira coupling of acyl chlorides with terminal alkynes under standard Sonogashira conditions[113] but using stoichiometric base.[114,115] For example, coupling of *p*-methoxybenzoyl chloride and TMS-acetylene takes place in the presence of 1.0 equivalent of triethylamine as the HCl-scavenging base, 2 mol% of $PdCl_2(PPh_3)_2$,



Scheme 46 A versatile one-pot synthesis of conjugated enynes starting from carbonyl compounds.

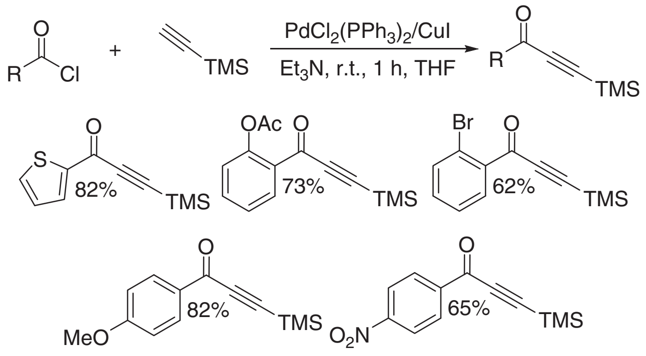


Scheme 47 Synthesis of differently substituted enynes via Pd/Cu-catalyzed Sonogashira coupling of vinyl tosylates.

4 mol% of CuI in THF. In accordance with Sonogashira couplings, the absence of the copper cocatalyst causes the reaction time to be prolonged considerably.

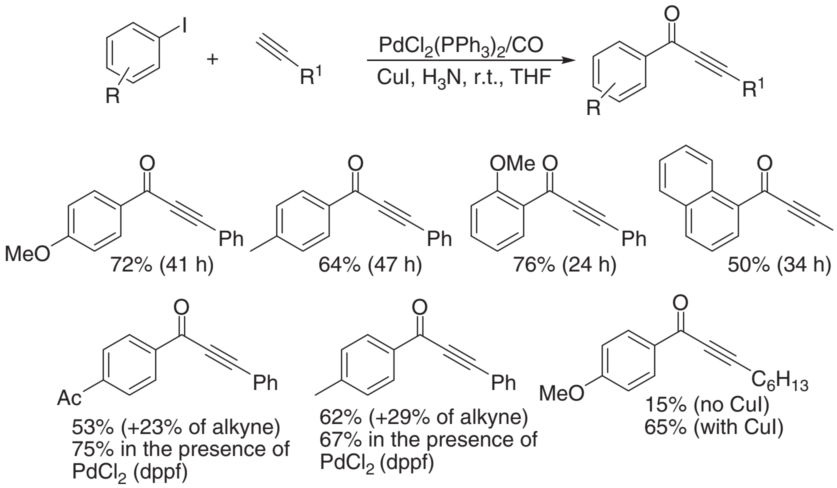
Applying these peculiar conditions to a variety of (hetero)-aroyl chlorides, the corresponding (TMS)-alkynones were obtained in moderate to good yield (Scheme 48).

However, carbonylative Sonogashira coupling of aryl halides and pseudohalides appears as a more straightforward approach to the synthesis of this class of compounds. For example, carbonylative coupling of phenylethyne with 4-methoxy-1-iodobenzene in the presence of 1 mol% $PdCl_2(PPh_3)_2$, 2 equivalents of 0.5 M aqueous ammonia as a base, under CO (1 atm) in THF leads to the



Scheme 48 Pd/Cu-catalyzed Sonogashira coupling of (hetero)aroyl chlorides.

formation of the corresponding alkynyl ketone in 72% isolated yield after 41 h at room temperature.[116] Interestingly, no alkyne coupling byproduct is obtained under these conditions, although substitution of ammonia with Et_3N led to the classical coupling product on account of the desired ynone even under higher pressure of the carbon monoxide. Moreover, addition of a catalytic amount of CuI to the reaction system was found to be less effective in affording noncarbonylated coupling product as a major product (Scheme 49).



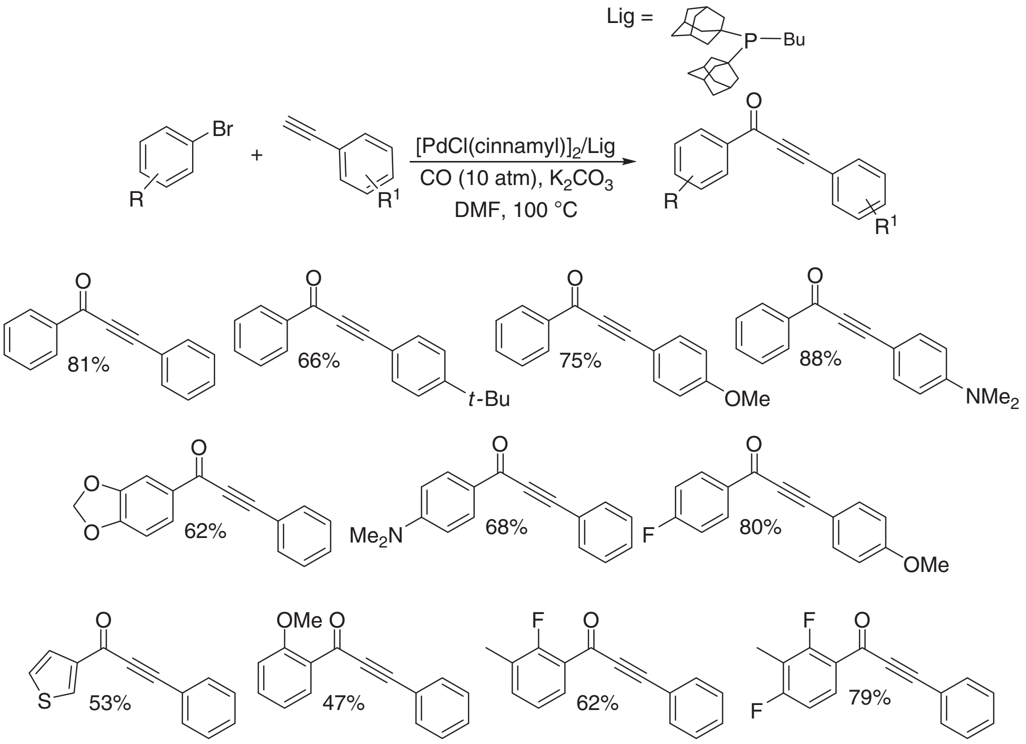
Scheme 49 Pd/Cu-catalyzed carbonylative Sonogashira coupling of aryl iodides with terminal alkynes.

Coupling of electron-neutral aryl iodides resulted in the formation of the desired products in good yields. Although the reaction with electron-deficient 4-iodoacetophenone or 4-iodo-1-chlorobenzene afforded the mixture of carbonylative and noncarbonylative coupling products, the selectivity to ynone was remarkably improved when $PdCl_2$(dppf) (5 mol%) was employed as a catalyst. Coupling of aliphatic alkynes proceeded more slowly. For example, reaction of 1-octyne took place with 4-methoxy-1-iodobenzene to afford product in 15% yield after stirring for 86 h under these conditions. Although in this case, addition of copper was reported as positive (Scheme 50).

A general and convenient copper-free palladium-catalyzed carbonylative Sonogashira coupling of aryl bromides[117] and triflates[118] was discovered recently by Beller and coworkers. Carbonylative (10 atm of CO) Sonogashira reaction of bromobenzene and phenyl acetylene with a catalyst system consisting of [(cinnamyl)PdCl]$_2$ (1 mol%) and BuPAd$_2$ (di-1-adamantyl-*n*-butylphosphine, cataCXium A) employing simple K_2CO_3 led to a 71% yield with 100% selectivity obtained. Remarkably, the reaction temperature has a pronounced influence on this model reaction: increasing the temperature to 120 °C led to the selective formation of 1,2-diphenylethyne. However, decreasing the Pd/L ratio from 1:3 to 1:1.5 produced the ynone in 83% yield.

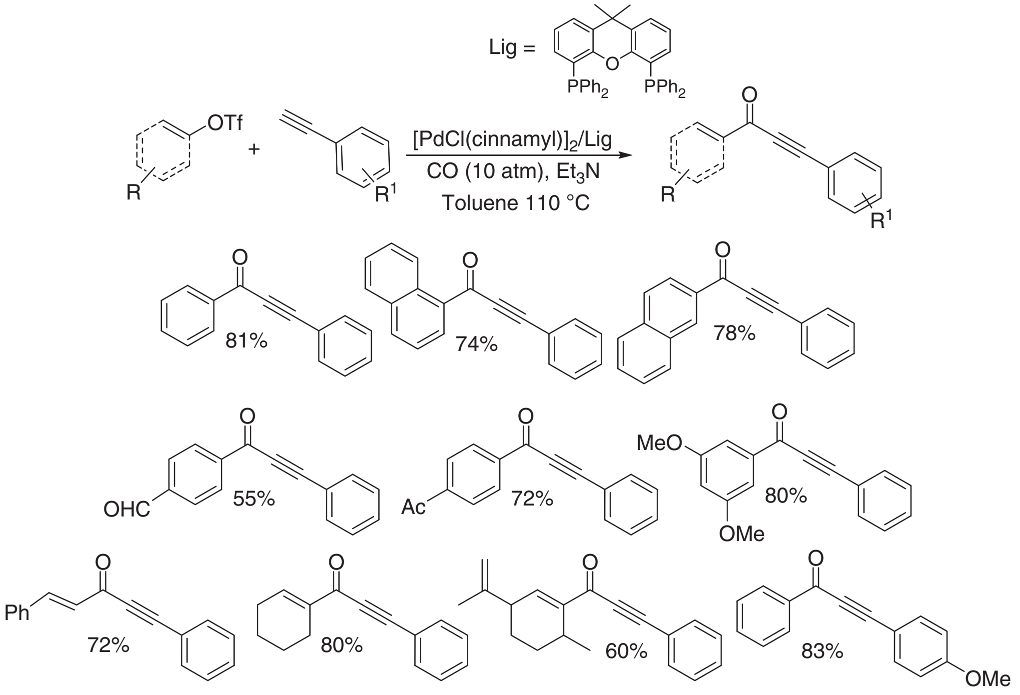
As shown in Scheme 50, in general, good to very good yields (47%–88%) were achieved. With respect to functional group tolerance, ether, amino, alkyl, and fluoride substituents were tolerated without problems both in the alkyne and aryl part. *Ortho*-substituted aryl bromides also resulted in the corresponding alkynones with moderate to good yields (47–79%). However, electron-deficient *p*-CF_3-, *p*-CHO-, and *p*-CN-substituted bromoarenes were not successfully carbonylated under these conditions. Here, apart from traces of the alkynones, a large amount of the respective Sonogashira coupling product was formed.

Aryl and vinyl triflates couple efficiently using [(cinnamyl)PdCl]$_2$ (1 mol%), Xanthphos (2 mol%) at 10 atm of carbon monoxide with NEt_3 as a base in toluene at 110 °C (Scheme 51). Unlike aryl bromides, the new palladium-catalyzed carbonylative



Scheme 50 Pd/Cu-catalyzed carbonylative Sonogashira coupling of aryl bromides with terminal alkynes.

Sonogashira reaction took place in the presence of both electron-donating and electron-withdrawing substituents in moderate to good isolated yields (50–81%).

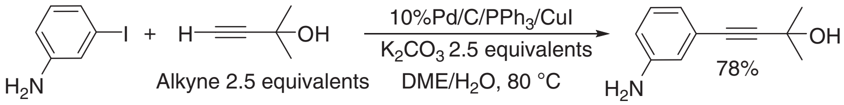


Scheme 51 Pd/Cu-catalyzed carbonylative Sonogashira coupling of aryl and vinyl iodides with terminal alkynes.

Vinyl triflates reacted also well under these conditions and gave the corresponding products in 60–80% yield. Furthermore, different aryl acetylenes were tested and the corresponding 1,3-diarylalkynones were isolated in good yields. However, applying more reactive alkynes with *p*-CN, *p*-NO_2, *p*-CHO, and *p*-CH_3CO substituents mainly resulted in the noncarbonylative Sonogashira reaction.

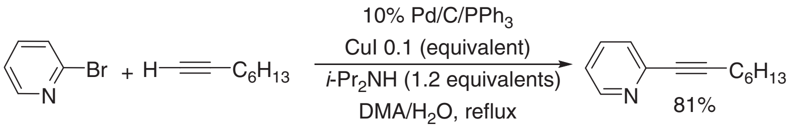
3.09.2.1.7 Heterogeneous and supported catalytic systems

Facile catalyst separation and recovery is an important issue from the environmental and economical point of view and, therefore, motivated the development of heterogeneous or heterogenized catalysts. For example, it was found that efficient Sonogashira coupling can be carried out in the presence of palladium on charcoal (Pd/C) in the presence of PPh_3, CuI cocatalyst, and K_2CO_3 as a base and in DME/H_2O (equation 27). Reactions led to the formation of the corresponding alkynes in high yields starting from substituted aryl iodides, bromides, as well as heterocyclic halides.[119,120]



(27)

Utilization of organic bases such as *i*-Pr_2NH,[121] Et_3N,[122] (*S*)-prolinol,[123] or 2-aminoethanol[124] was found beneficial and showed satisfactory performance in the reactions of aryl bromides and even of activated aryl chlorides[121] (equations 28–30). Various functional groups such as hydroxy, alkyl, cyano, chloro, aryl, etc., on the acetylene were well tolerated. No significant dimerization of terminal alkynes was observed.



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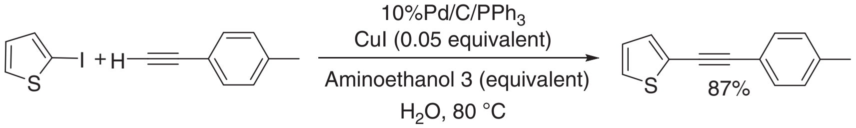

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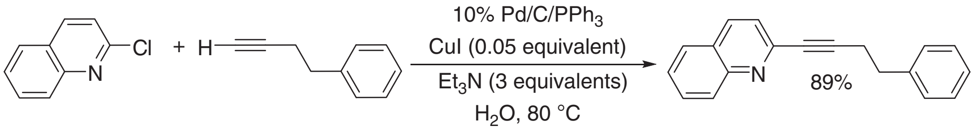


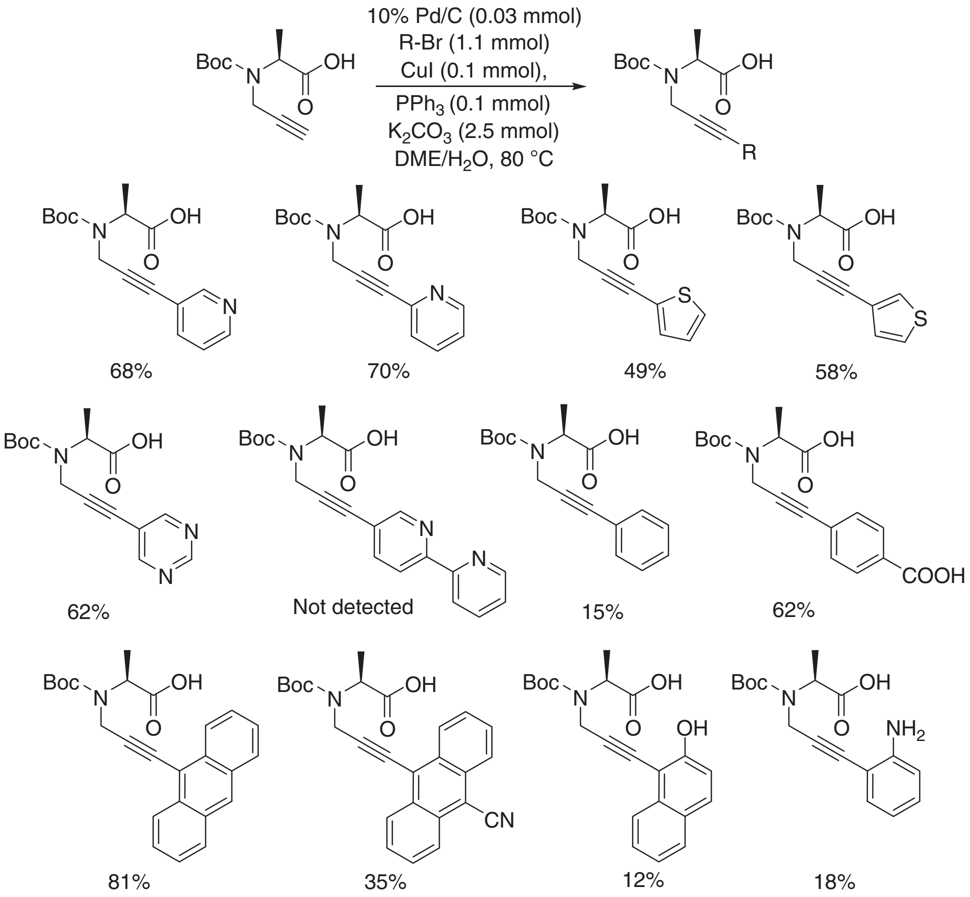
(30)

Modification of polypeptide with nonnatural functional groups is highly important due to the tendency of peptides to form β-turns motifs in the region of *N*-alkyl amino acid residues. Thus, *N*-(3-arylpropyl)-amino acid precursors were successfully modified by means of Sonogashira coupling with appropriate halides.[125] Effective coupling was achieved using palladium on carbon (Pd/C) as a catalyst and DME/H_2O as a solvent. For example, heating a mixture of 3-bromopyridine and *N*-propargylalanine in the presence of 10% Pd/C, PPh_3, CuI, and K_2CO_3 in DME-water (1:1) afforded coupling product in 68% yield. Other cosolvents such as ethanol, ethylene, glycol, or *N*,*N*-dimethylacetamide (DMA) can also be used as the organic components of the solvent mixture. Triphenylphospine and *p*-diphenylphosphinobenzoic acid (4-DPPBA) showed some superiority over other tested ligands, whereas Cs_2CO_3 and K_2CO_3 were selected as the most efficient bases. *N*-Propargylalanine coupled in good yields with electron-deficient aryl bromides, although electron-rich aryl bromides showed lower reactivity (**Scheme 52**).

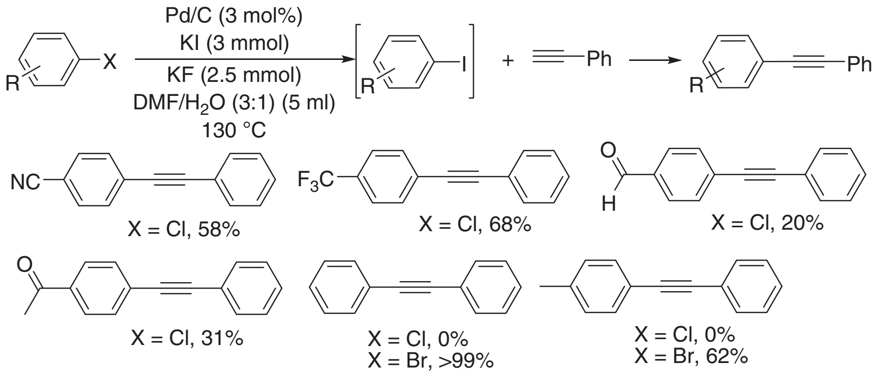
The efficient 'Pd/C only'-based catalytic system for the coupling of aryl bromides and chlorides is of major interest for both industrial and academic applications. Activation of less-reactive aryl chlorides and bromides using the simple Pd/C under ligand- and copper-free conditions was achieved via halogen exchange (HALEX)–Sonogashira coupling sequence (**Scheme 53**).[126]

Reactions were carried out in DMF/H_2O (3:1) under the nitrogen atmosphere, using Pd/C as catalyst, KF as base, and KI as iodide source. Under these conditions, aryl chlorides couple with phenylacetylene in moderate to good yields, although bromides show significantly better reactivity. In the case of aryl chlorides, strong electron-withdrawing groups accelerate the reaction. Attempts to couple electron-neutral and electron-rich aryl chlorides failed even with 5 mol% Pd/C. For aryl bromides, good to excellent yield was obtained for the electron-neutral and moderately electron-rich substrates. Little or no conversion was observed using aryl bromides bearing strongly electron-donating substituents.

The recovery of the Pd/C catalyst was also examined under the same reaction conditions. After the first run, the catalyst was separated by simple vacuum filtration, washed, dried, and then reused without any further activation. Although the catalyst showed a slight decrease in the activity after the first cycle, it remained constant over the course of five additional cycles.



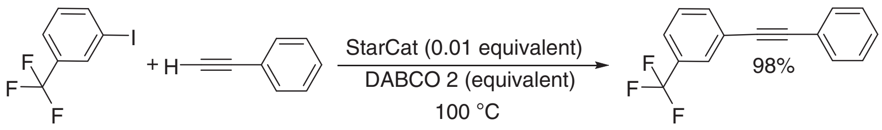
Scheme 52 Modification of propargyl amino acids with nonnatural functional groups via Pd/C-catalyzed Sonogashira coupling.



Scheme 53 Pd/C-catalyzed coupling of aryl chlorides and bromides under ligand- and copper-free conditions via HALEX–Sonogashira coupling sequence.

Palladium nanoparticles on different polymeric supports can also catalyze C–C cross-coupling reactions. One example is palladium on starch ('StarCat').[127] Palladium loading on the supporting material ranges between 0.5 and 5 wt.%; however, the active surface areas and pore diameters were not constant and depend on the Pd loading and solvent used in the process (up to 177 m^2 g^{-1} and 6.3–13.0 nm, respectively).

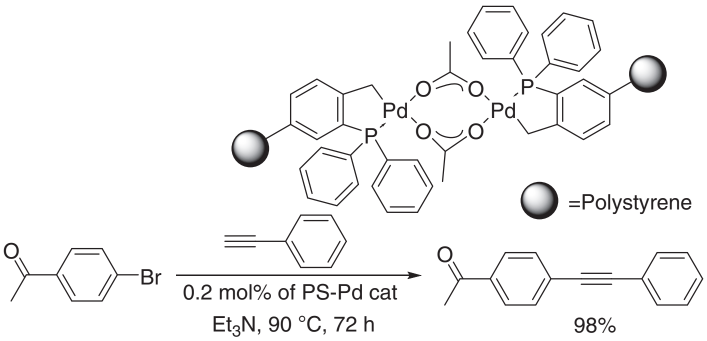
The catalyst operates under copper- and phosphine-free conditions in the presence of DABCO as a base. The coupling of aryl iodides takes place within an hour and conversion levels are typically higher than 90% (equation 31). Only insignificant amount of the homocoupling products was found.



(31)

The reactions can be carried out using microwave heating under solvent-free conditions.[128] Conversions were high in all cases but significant amounts of homocoupling were observed. The selectivity to the desired cross-coupled product was not significantly improved with an increase in the Pd loading. Starch-supported catalysts were reusable and remained active, selective after four repetitive runs.

Polystyrene (PS) was used as a support for palladacycle-based precatalyst for the coupling of aryl bromides with terminal alkynes.[129] For example, reaction of 4-bromoacetophenone with phenylacetylene was carried out in Et_3N with 0.2 mol% of the supported catalyst at 90 °C. After 72 h, only the cross-coupled product was obtained with over 98% yield (equation 32). The PS-supported catalysts of this type were soluble in THF, DMA, DMF, chloroform, and CH_2Cl_2. After the reaction, the catalyst can be easily isolated by simple precipitation with ether or acetonitrile without removal of the salts generated in the reaction.



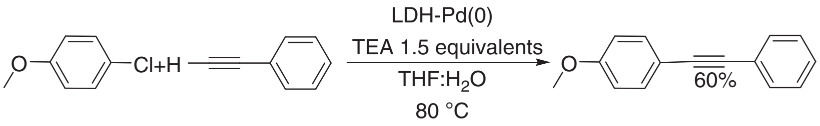
(32)

Similar polymer-supported catalyst can also be used in biphasic systems.[130] For example, monomethyl polyethylene glycol (MeOPEG)-linked phosphines operate under biphasic conditions in DMSO/heptane mixture with *i*-Pr_2NH as a base and Na_2PdCl_4 as the palladium source (0.5–2 mol%). Results are summarized in **Scheme 54**. The catalytic system was reused for five cycles, although no significant deactivation of the catalyst occurs. Activation of aryl chlorides was not possible using MeOPEG-supported phosphine ligands.

Magnetite Fe_3O_4 nanoparticles have emerged as promising support due to its easy separation from reaction medium using an external magnet. In the work of Jin and Lee, the commercially available Fe_3O_4 nanoparticles were coated with a thin layer of silica using a well-known sol–gel process to give silica-coated Fe_3O_4. Triethoxysilane-functionalized palladium complex was anchored onto the surface of silica (**Scheme 55**).[131] Palladium loading of 0.21 mmol per gram of the support was confirmed by ICP-AES.

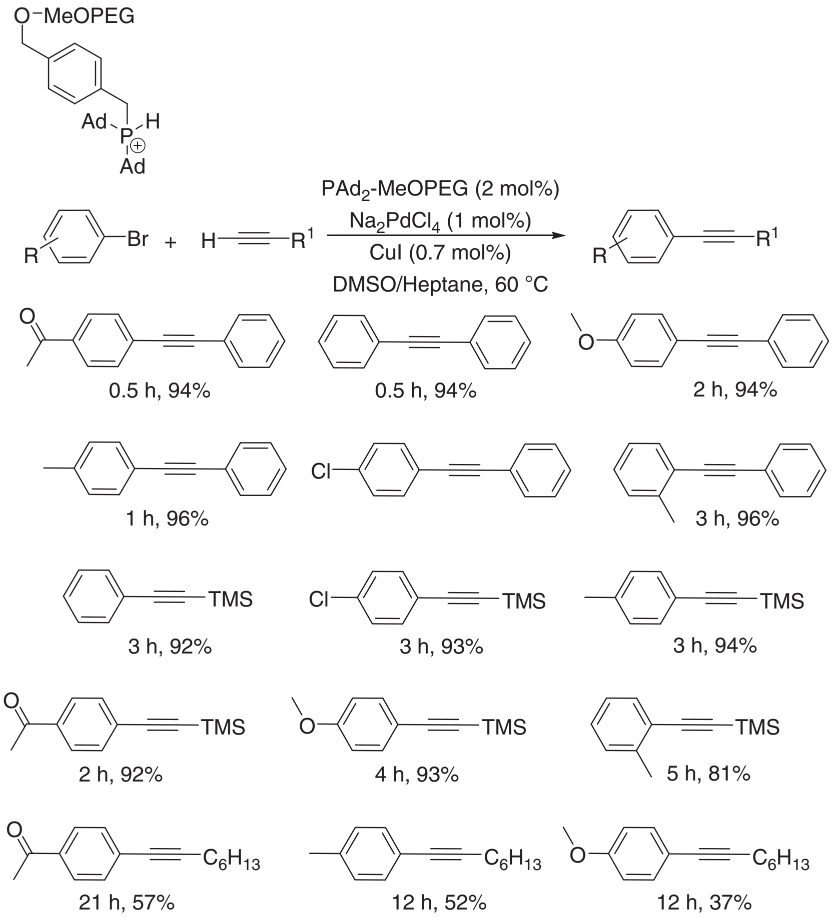
Magnetite-anchored catalyst (Pd-SiO_2/Fe_3O_4) performed efficiently in copper-free Sonogashira coupling at only 60 °C in aqueous solvent with piperidine as base and TBAB as a phase-transfer agent (**Scheme 55**). It was observed that the coupling of chlorobenzene, 1-chloronaphthalene, and activated aryl chlorides with phenylacetylene proceeded in excellent yields. This catalytic system was also effective for the couplings of deactivated aryl chlorides under mild conditions. Furthermore, sterically hindered and deactivated 2-chloro-1,3-dimethylbenzene underwent smooth coupling. The scope of the alkynes included substrates such as propargyl alcohol, 1-octyne, and (triisopropylsilyl)acetylene.

Layered double hydroxide-supported nanopalladium (LDH-Pd) was reported as a very efficient heterogeneous catalysis, allowing reactions of nonreactive aryl chlorides and bromides.[132] Thus, 0.01 equivalent of LDH-Pd catalyst afforded diphenylacetylenes in good yield with TEA base in THF/H_2O mixture. TOF of the catalyst remained almost constant over five reaction cycles – 103 h^{-1} at the first cycle and 96 h^{-1} in the fifth in the reaction between 4-bromoacetophenone and phenyl acetylene. However, more obvious decrease in TOF was observed for the reactions of electron-rich aryl chlorides. For instance, the reaction between 4-chloroacetophenone with phenylacetylene showed TOF of 60 h^{-1} in the first cycle and 48 h^{-1} in the fifth (equation 33).



(33)

Palladium complexes based on dendritic phosphine ligands as copper-free recoverable catalysts for the Sonogashira reaction were introduced by Astruc et al. (**Figure 6**).[133,134] In these reactions, Et_3N was used as solvent and the amount of the catalyst was correlated to 1 mol% depending on the dendrimer generation at 25–120 °C. Good conversions were obtained with the first and second generation dendrimers at 80 °C in the coupling of iodobenzene with phenyl acetylene. A negative dendritic effect was



Scheme 54 Sonogashira coupling of aryl bromides with terminal alkynes catalyzed by the polymer-supported catalyst.

clearly observed for the metallodendrimer of third generation. This effect is best taken into account by the increased steric effect as the generation number increases. Raising the reaction temperature on replacing Et_3N by amines with higher boiling points (e.g., Bu_2NH or Bu_3N) did not improve the conversion rates. The dendritic catalysts showed very weak reactivity with the aryl chloride substrates, only traces of expected product were observed.

Recovery of the metallodendritic catalysts was achieved by its simple precipitation in pentane for the cyclohexyl complexes. Second generation metallodendrimer was recovered at least six times and third generation dendrimer was recovered at least seven times, both without any loss of activity.

3.09.2.2 Nickel-Catalyzed Coupling

In recent decades, nickel-based complexes started attracting attention as catalysts for cross-coupling reactions.[135] However, not much is known about nickel-catalyzed Sonogashira–Hagihara reaction.

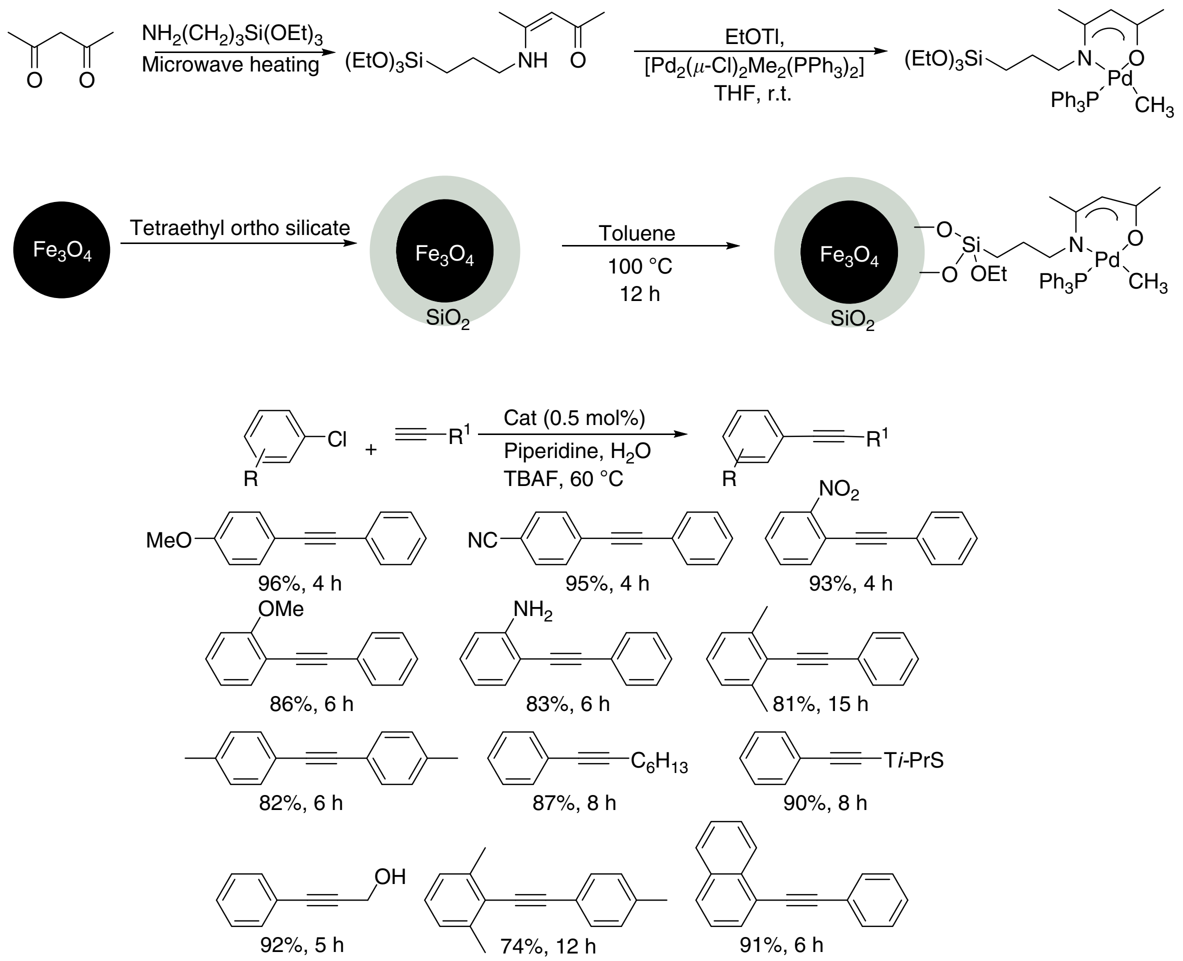
First, nickel-catalyzed Sonogashira reaction was presented by Beletskaya et al.[136] As was demonstrated, reaction of 4-iodoanisole with phenylacetylene in the presence of commercially available $NiCl_2(PPh_3)_2$/CuI and K_2CO_3 as a base proceeds smoothly in aqueous dioxane. The yields of the coupled products strongly depend on the nickel catalyst used. Various Ni complexes with both mono- and bidentate ligands, as well as simple Ni salts have been studied. Ni complexes with bidentate ligands (dppf, dppb, and dppe), electron-rich monodentate ligand such as Ph_2PMe, or the phosphine-free Ni derivatives failed to give the desired coupled product.

The catalytic system gave high yields of the coupled products between arylacetylenes and aryl iodides possessing both donor and acceptor substituents (Scheme 56). The reactions were highly selective as no alkyne homocoupling byproduct has been observed.

Several catalytic systems based on nanosized nickel metal have been reported to activate aryl iodides under microwave and conventional heating.[137,138]

3.09.2.3 Copper- and Gold-Catalyzed Coupling

Recent studies demonstrated that Sonogashira–Hagihara coupling can be performed using only copper catalysts. For example, CuI/PPh_3 combination was found capable of promoting coupling of terminal acetylenes and vinyl or aryl iodides in



Scheme 55 Sonogashira coupling of aryl bromides with terminal alkynes catalyzed by the magnetite-supported catalyst.

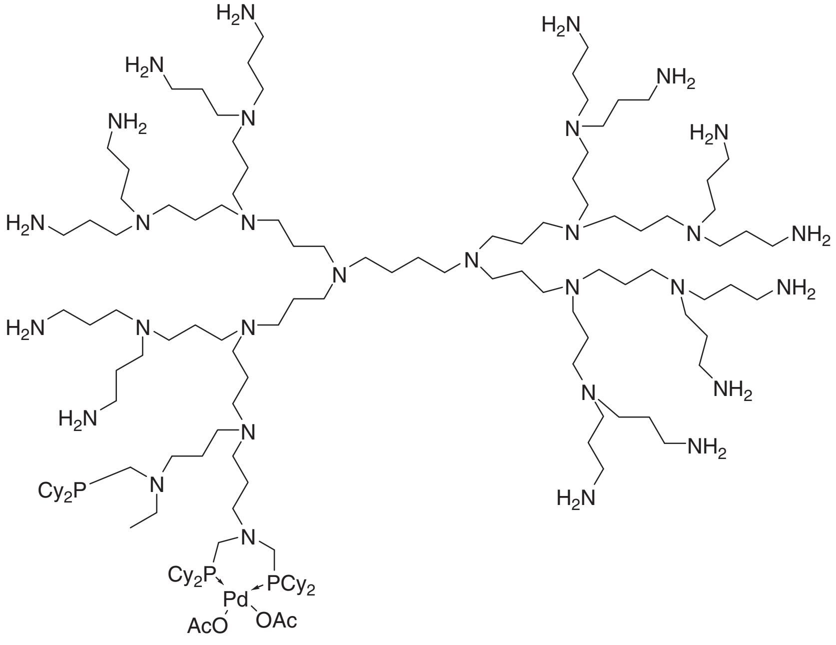
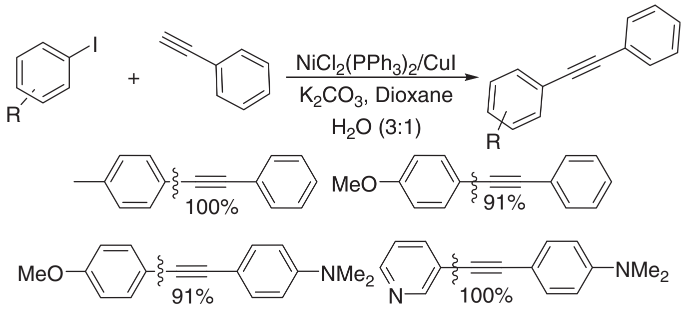
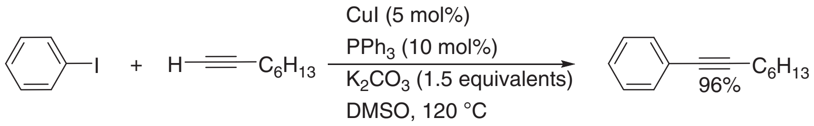


Figure 6 Metallodendritic catalysts.



Scheme 56 The nickel-catalyzed Sonogashira reaction.

intermolecular[139,140] (equation 34) and intramolecular (equation 35) fashion[141] in the presence of K_2CO_3 in DMF or DMSO at 80–120 °C. Interestingly, unlike Pd-catalyzed protocols, employment of organic amine bases, such as NBu_3, deleteriously affected the reaction.The reaction of 4-substituted iodobenzenes bearing different functional groups (e.g., CO_2H, COR, CO_2R, OR, etc.) with phenylacetylene gave the corresponding diphenylacetylene derivatives in excellent yields. *E*/*Z*-bromostyrenes also reacted smoothly, whereas the *E*/*Z* ratio of the enyne product was the same as in the starting material.



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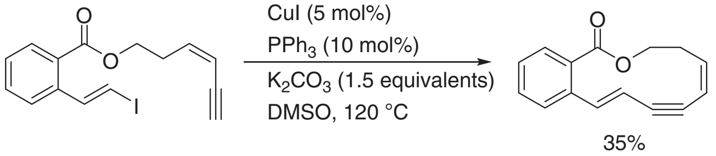
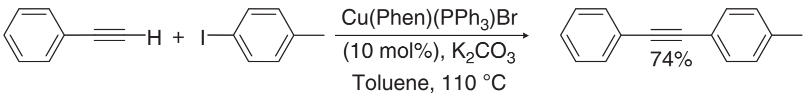


(35)

Some ligandless protocols have been also suggested. For example, Rothenberg and coworkers demonstrated that non-noble metallic copper catalyst alone catalyzes conversion of activated aryl iodides into internal alkynes in DMF in the presence of tetrabutylammonium acetate as the base.[126] Similar reactions may be performed using either copper nanoclusters or alumina silica-supported copper.[142] Although these reactions were found sensitive to a correct choice of the solvent/base combination, a simpler product recovery and purification is a clear advantage of the phosphine-free protocols.

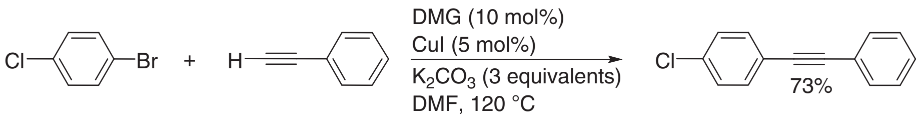
Generally, the scope of these ligandless protocols is similar to that of most soluble copper-based catalysts reported, whose application is generally limited to aryl iodides and arylacetylenes as substrates. Remarkably in silica/alumina-supported reactions no evidence for the formation of the Hay coupling product was obtained in significant quantities.

The real improvement in the scope of the transformation came together with the progress made in the field of carbon–heteroatom bond-forming chemistry. For example, the use of Venkataraman's catalyst (Cu(phen)(PPh_3)Br or Cu(phen)(PPh_3)$_2NO_3$) allowed the synthesis of substituted alkynes from aryl iodides in less polar medium (toluene) under relatively mild conditions (equation 36).[143]



(36)

Coupling of less-reactive aryl bromides became possible in the presence of CuI/*N*,*N*-dimethylglycine (equation 37) or CuI/DABCO catalysts (equation 38). The catalysts operate in DMF in the presence of K_2CO_3 or Cs_2CO_3 at 80–140 °C and show clean reactions even in the presence of vulnerable functional groups such as carboxyl, methoxy, nitro, cyano, heteroaryl, and other groups. The same conditions can be employed for coupling of stereodefined vinyl halides. No double isomerization takes place.



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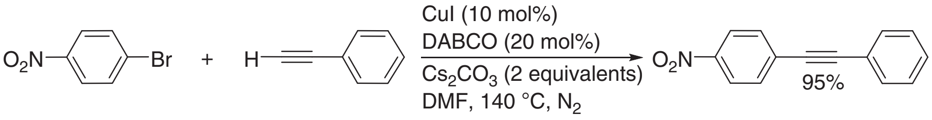
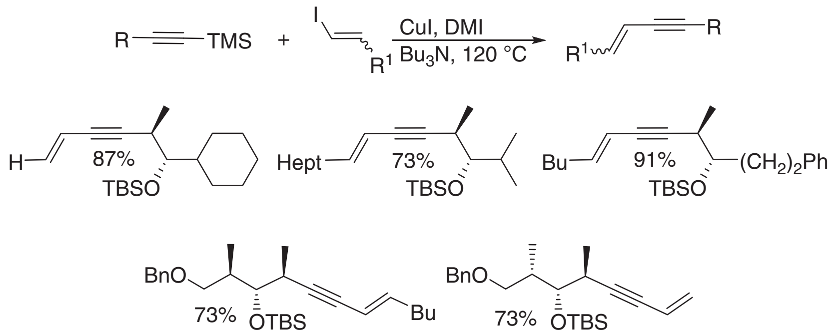


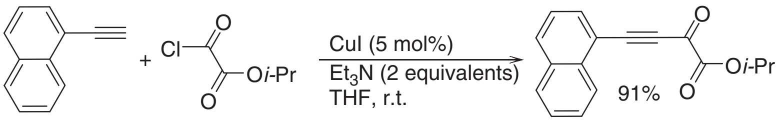
(38)

A slight modification of the protocol introduced by Marshall et al. allows *in situ* desilylation cross-coupling of TMS-protected alkynes with vinyl iodides.[144] When CuCl in 1,3-dimethylimidazolidin-2-one was added to the masked terminal acetylene, a yellow precipitate gradually formed. This precipitate is presumed to be the copper acetylide complex. Treatment of the mixture with Et_3N and the vinyl iodide afforded the coupled product in 10% yield after 3.5 h at 85 °C. After a reaction time of 40 h, the enyne could be isolated in 83% yield. Increasing the reaction temperature to 100 or 130 °C significantly shortened the reaction time with no decrease in yield. When less than 2 equivalents of CuCl were employed, the coupling reactions were markedly slower and decomposition of the products occurred. Insignificant TMS-acetylene homocoupling products may be coproduced under the suggested conditions. No racemization or isomerization of the enantio- or diastereomerically pure starting materials takes place as well (Scheme 57).



Scheme 57 Copper-catalyzed Sonogashira reaction of vinyl iodides.

An approach toward aromatic or aliphatic alkynones is the copper-catalyzed reaction of terminal alkynes with acyl chlorides which proceeds in the presence of approximately 5 mol% of CuI under ligandless conditions in the presence of triethylamine in polar solvents such as THF at room temperature (equation 39).[145,146] However, the cross-coupling nature of these reactions has not been proven.



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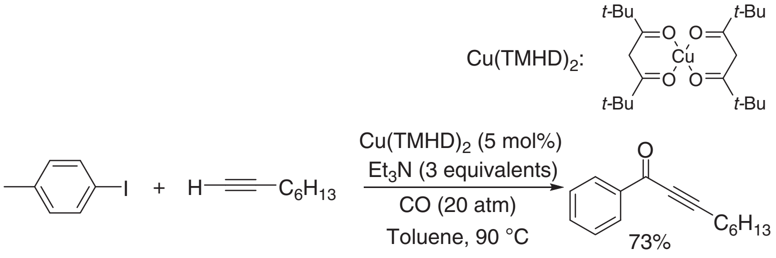
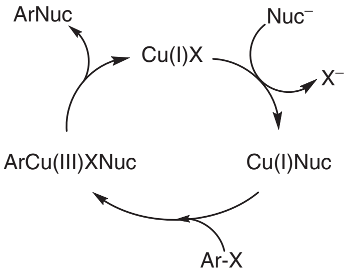
If performed under the atmosphere of carbon monoxide, the transformation leads to the formation of aryl alkynones in good yield and selectivity (equation 40).[147]



(40)

Although no detailed mechanistic studies have been performed, this transformation indicates that copper-catalyzed Sonogashira-like reactions proceed via the Cu(I)–Cu(III) catalytic cycle (Scheme 58) since formation of the carbonylated products via nucleophilic substitution pathway is unlikely.

Gold complexes have been overlooked for many years as a potential catalyst in organic reactions, due to the belief that gold is chemically inert. The use of gold as a catalyst has gained attention in recent years after catalytic activity of gold complexes and gold



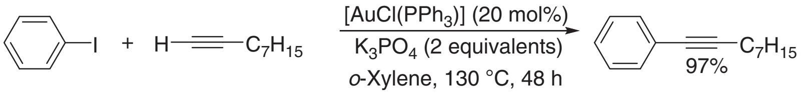
Scheme 58 Plausible mechanism of the Cu-catalyzed Sonogashira reaction.

nanoparticles was observed in reactions like oxidation of CO,[148] selective oxidation of alcohols,[149] direct arene functionalization,[150] and C–C bond formation.[151]

Au^I is isoelectronic to Cu^I and, therefore, can interact with acetylenic group. These attributes made gold a perfect candidate for Sonogashira cross-coupling.

First example for gold-catalyzed Sonogashira cross-coupling was presented by Corma and coworkers.[152] They explored gold supported on CeO_2. The catalyst contained Au^0, Au^I, and Au^{III} species, and was found to be active in copper-free Sonogashira reactions.

Homogeneous experiments with gold complexes were also conducted. The homogeneous complexes were studied with the Sonogashira cross-coupling of aryl iodides with a series of alkynes containing electron-donating and electron-withdrawing substituents in the alkyne. Catalytic loads were high (20 mol%) and reactions were carried out in xylene at 130 °C (equation 41). K_3PO_4 was used as a base and reaction times were 24–48 h.

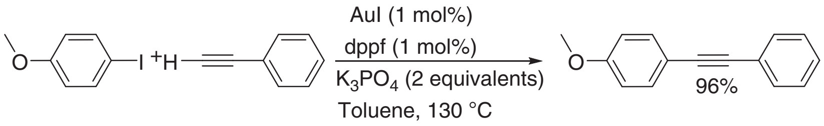


(41)

Much lower catalyst loading were reported by Wang and coworkers.[153] A catalyst derived from AuI/dppf was found to catalyze coupling of terminal alkynes with aryl iodides and bromides which generated the corresponding cross-coupling products in good to excellent yields. Good yields were obtained in toluene and xylene, and K_3PO_4 was found to act as an excellent base (equation 41).

Electron-neutral, -rich, and -poor aryl iodides react with phenylacetylene well to generate the corresponding cross-coupling products in excellent yields, whereas *ortho*-substituted aryl iodides were inert under these reaction conditions. Both aromatic and aliphatic terminal alkynes couple with iodobenzene smoothly to produce the desired product in excellent yields. Activated aryl bromides also reacted with phenylacetylene in excellent yields, but electron-rich aryl bromides afforded the product in poor yield.

Experimental results showed that Au°, Au^I, and Au^{III} were all effective catalysts for Sonogashira reactions in the presence of dppf, but Au^I was the best of choice, which is in agreement with the literature data.[152,154] Homocoupling of terminal alkynes did not occur.



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Supported gold catalysis (**Figure 7**) was also examined by Corma et al.[155] Gold–NHC complexes were chemically attached to a polymer support. Reaction conditions were similar to previously described leading to the formation of products in modest yields.

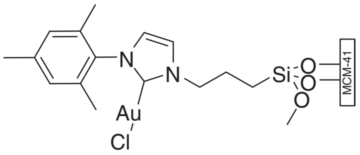


Figure 7 Supported gold catalyst.

Another supported gold catalysis was performed by Antunes under microwave irradiation.[154] Au/silica gave best results among other supports. Reactions were conducted in DMF in the presence of K_2CO_3 as a base. Reaction times were reduced to several hours and less active bromides as well as aliphatic alkynes were also able to react under these conditions. It is claimed that DMF being a good microwave absorber, contributes to the formation of soluble species, Au^{III} on oxidative addition and Au^{I} after reductive elimination, and perhaps also Au^{I}-acetylides.

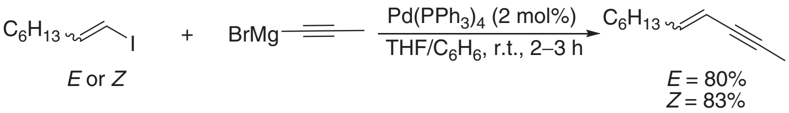
Although gold seems like a promising catalyst for cross-coupling reactions, its true role in the catalytic cycle appeared controversial. It was argued that isoelectronic metal centers do not necessarily behave similarly, and a mechanistic investigation was conducted to validate gold as a catalyst. According to experimental data, Au^{I} is not able to oxidatively add across carbon–halogen bonds.[156] Therefore, palladium contamination was claimed to be the true catalysts in the gold-catalyzed Sonogashira reactions. Later publication showed, by the combined kinetic and theoretical studies, that gold is intrinsically active enough to perform the Sonogashira coupling reaction between phenylacetylene and iodobenzene.[157]

This way or another, currently, gold-catalyzed Sonogashira-type reactions are only of fundamental interest and have no practical value as they require very harsh reaction conditions and demonstrate a poor scope and many limitations compared to palladium-catalyzed versions.

3.09.3 Transition Metal-Catalyzed Coupling of C(sp)-Metal Reagents with C(sp^2)-Halides and Pseudohalides

3.09.3.1 Alkynylmagnesium Reagents

Stereospecific base-free coupling of alkenyl[158] and aryl iodides[159] with alkynyl Grignard reagents proceeds under very mild conditions in high yield with catalytic amounts of $Pd(PPh_3)_4$ in THF/benzene mixtures (equations 43 and 44).



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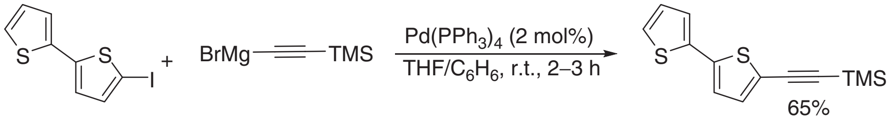
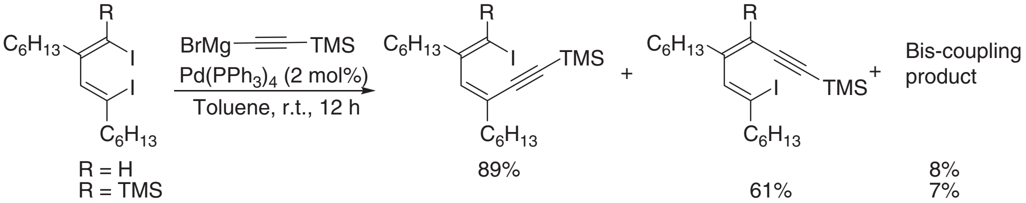


(44)

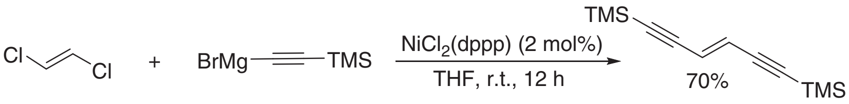
Although Sonogashira–Cassar–Heck cross-coupling is more straightforward as it obviates the use of organometallic reagents, these coupling reactions have their own advantages, such as good chemoselectivity. For example, almost no Glaser homocoupling byproducts are observed under these reaction conditions.

The coupling reaction of 1,4-diiodo-1,3-alkadienes with the Grignard reagents in the presence of a catalytic amount of $Pd(PPh_3)_4$ proceeded with excellent site-selectivity. The general trend of the site-selectivity of the reaction can be summarized as follows: the coupling reaction occurs at the sterically less-hindered vinyl carbon preferentially; therefore, the reaction proceeded more readily at the vinyliodo moiety having no or an alkyl substituent rather than that having a more congested TMS group at the α-position (**Scheme 59**).[160] The present finding opens a new entry to a variety of 1-iodo-1,3-alkadienes that can be utilized as starting compounds for preparation of polysubstituted conjugated dienes and cyclopentenones using the reactivity of the vinyliodo moiety present in them.



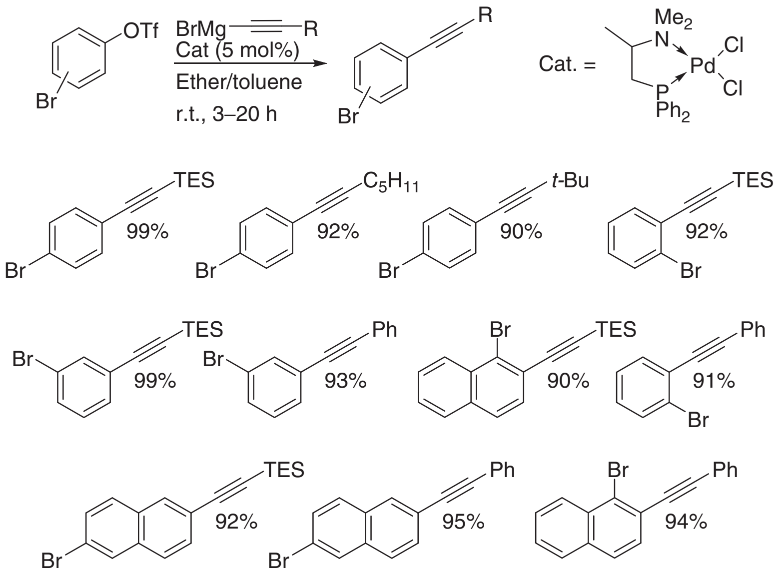
Scheme 59 Regioselective Pd-catalyzed coupling of vinyl iodides with alkynyl Grignard reagents.

$NiCl_2$(dppp) was found to catalyze a similar coupling of vinyl chlorides with alkynylmagnesium bromide in good yield at room temperature and 50 mmol scale (equation 45).[161]



(45)

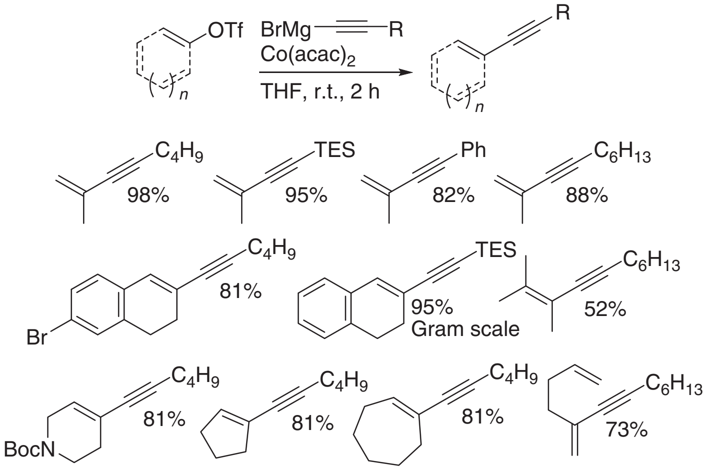
Dichloro[(2-dimethylamino)propyldiphenylphosphine]palladium was found to be much more effective catalyst than other palladium complexes for cross-coupling of aryl triflates with alkynyl Grignard reagents. Moreover, reaction of aromatic compounds bearing both bromide and triflate with alkynyl Grignard reagents in the presence of this catalyst gave high yields of alkynyl arene bromides, which were formed by selective replacement of triflate by alkynyl group. The reaction proceeds well with 2 equivalents of alkynylmagnesium bromide in the presence of 1 equivalent of lithium bromide and 5 mol% of the palladium catalyst at 20 °C in ether/toluene mixture (Scheme 60).[162]



Scheme 60 Pd-catalyzed and base-free coupling of aryl triflates with alkynyl Grignard reagents.

Alkenyl triflates, in combination with Co(acac)$_3$ catalyst, were found to be excellent coupling partners for alkynyl Grignard reagents, where no special additives, including a phosphine ligand, are needed.[163]

Co(acac)$_3$ was found to be applicable to various combinations of alkynylmagnesium bromides and alkenyl triflates. Both α- and β-substituted vinyl triflates couple with alkynyl Grignard reagents to give the corresponding enynes in a good yield (Scheme 61). Less-reactive cyclic alkenyl triflates with a five- to seven-membered ring also underwent the coupling within 2 h by raising the temperature to 40 °C. Even sterically demanding trisubstituted vinyl triflates participated in the coupling, albeit with a moderate yield. Carbamate and alkene functionalities are compatible with the coupling conditions. If needed, less volatile nonaflates can be used instead. The present method is also highlighted by a wide scope on alkynyl Grignard reagents. The reaction of nonsubstituted reagents was as efficient as of those possessing a reactive acetylenic methyne proton or bulky aliphatic, silyl, or aromatic groups. The simplicity of the catalyst system, which does not even require ligands, allows conducting the coupling reactions on a gram-scale.



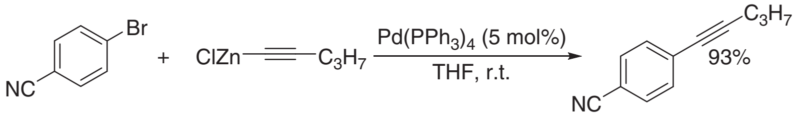
Scheme 61 Cocatalyzed coupling of vinyl triflates with alkynyl Grignard reagents.

A marked preference of the catalyst system for alkenyl triflates revealed that reaction of substrates bearing both bromide and triflate groups react with 1 equivalent of alkynyl Grignard reagent resulting in the formation of predominantly the triflate-derived coupling product.

3.09.3.2 Alkynylzinc Reagents

Alkynylzinc reagents can be conveniently prepared by a simple reaction between alkynyllithiums or alkynylmagnesiums with anhydrous zinc chloride. These reagents are more convenient from the synthetic point of view rather than the corresponding alkynyl Grignard reagents as they are less basic and less nucleophilic and, consequently, tolerate a wide range of functional groups that are normally incompatible with Grignard conditions.

It was demonstrated that these reagents (even prepared *in situ*) are capable of coupling with a variety of functionalized aryl, vinyl, and even allenyl iodides and bromides, using catalytic Pd(PPh$_3$)$_4$.[164–168] Standard reaction conditions comprise the *in situ* preparation of the zinc reagent by reacting the corresponding ethynyllithium with ZnCl$_2$ at -78 °C and subsequent exposure of the reagent to 0.5–5 mol% of Pd(PPh$_3$)$_4$ and nucleophile in THF. Reactions of aryl iodides and vinyl halides take place readily at room temperature, whereas aryl bromides require moderate heating to achieve complete conversions. Noteworthy, stereodefined vinyl halides react in a highly stereospecific fashion (equations 46–49).



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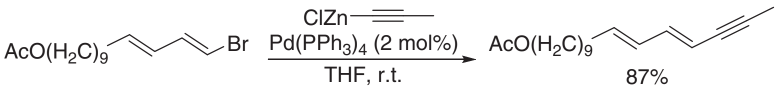

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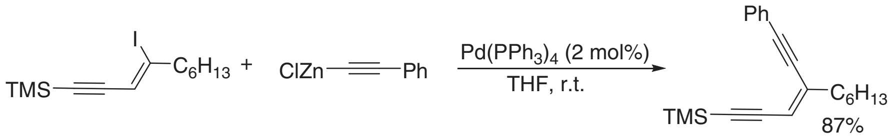

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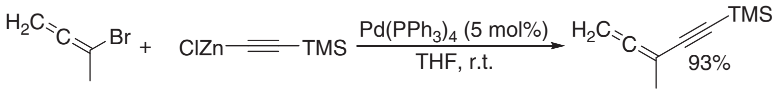
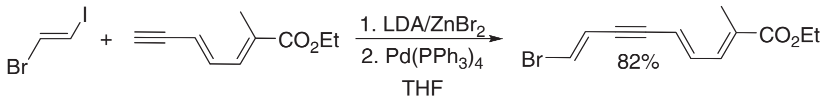


(49)

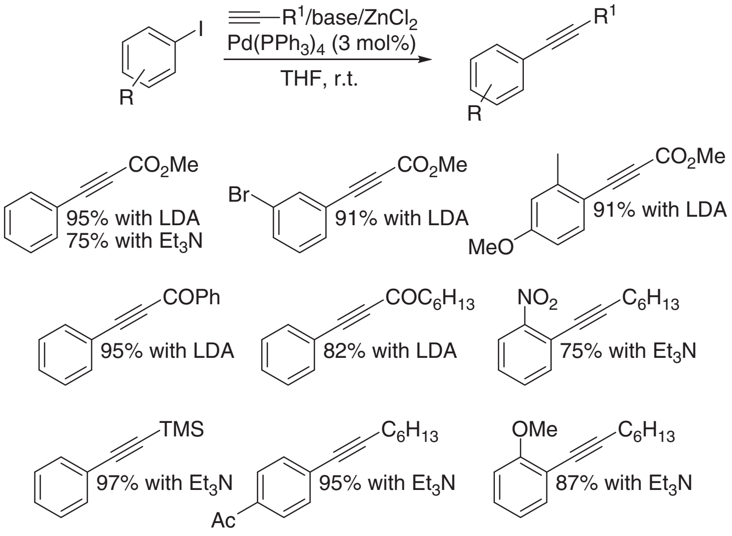
Nucleophile-sensitive alkynylzinc reagents can be *in situ* prepared using nonnucleophilic bases such as lithium diisopropylamide (LDA).[169] For example, it was demonstrated that the yields obtained with LDA/ZnCl$_2$-treated methyl propyonate are uniformly excellent, whereas the use of *n*-BuLi in place of LDA led only to traces of the desired cross-coupling products. Furthermore, LDA also permits the use of intrinsically more sensitive 1-propyn-3-ones without noticeable difficulties (**Scheme 62**). Moreover, the use of amines as bases for the Pd-catalyzed alkynylation is also possible. For example, to premixed ZnBr$_2$ and Et$_3$N (1:4 ratio) in THF were added an organic halide, a terminal alkyne, and a suitable Pd catalyst. Some other bases, solvents, and reagent ratios were examined for this reaction, but the procedure mentioned above was found to be superior to the other combinations. The reaction did not proceed without ZnBr$_2$ ruling out the possibility of the Sonogashira mechanism.

This improved protocol is especially useful for the synthesis of functionalized extended enyne systems (equation 50).[170]

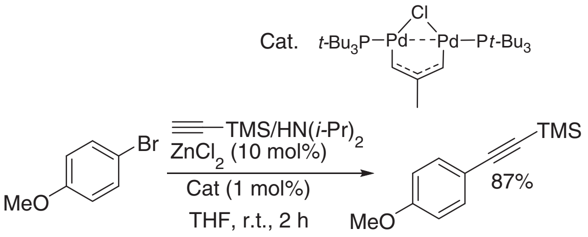


(50)

Moreover, it was demonstrated that, in principle, ZnCl$_2$ may be used at substoichiometric quantities although in the presence of Pd(I) dimer-based precatalysts (equation 51).[171]

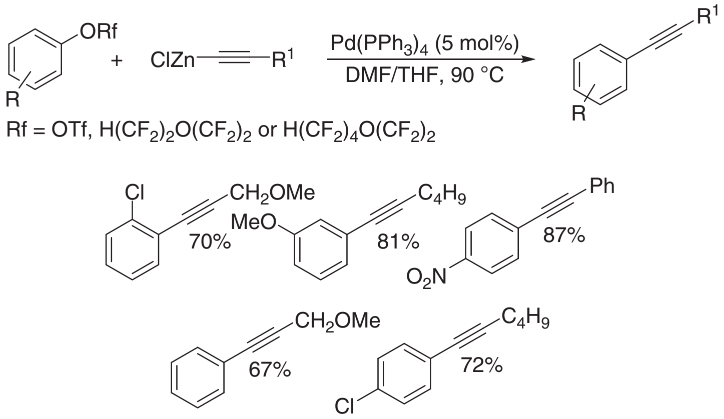


Scheme 62 Pd-catalyzed and base-free coupling of aryl iodides with alkynylzinc reagents.



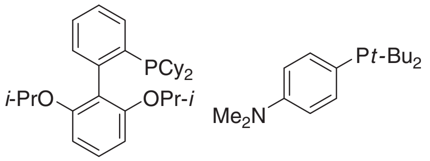
(51)

Also aryl and vinyl triflates have been demonstrated to couple under the same catalyst, although in the presence of LiCl as a stoichiometric additive and in THF–DMF mixture at elevated temperature (90 °C).[172] The method is applicable to phenyl fluoroalkanesulfonates with either electron-withdrawing or electron-donating substituents on the benzene ring. The functional groups, such as chloro, methoxy, or nitro groups on the benzene ring are tolerated in this reaction (Scheme 63). $Pd_2(dba)_3$/dppf system was reported to catalyze similar coupling in THF alone at lower temperature (65 °C).[173]



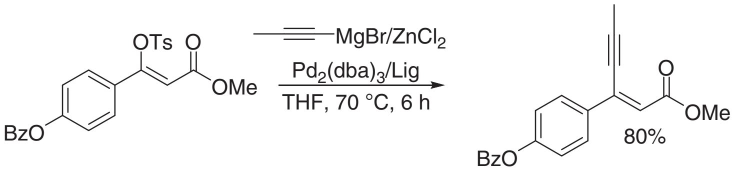
Scheme 63 Pd-catalyzed and base-free coupling of aryl fluoroalkanesulfonates with alkynylzinc reagents.

Crystalline enol tosylates have been reported to participate in this type of coupling leading to the formation of enynes in good to excellent yield in the presence of the same catalyst.[174] But employment of bulky monodentate phosphines such as RuPhos or A-^{ta}Phos was proven beneficial (Figure 8) (equation 52).[175]



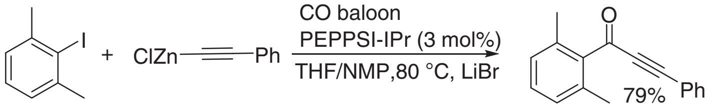
RuPhos A-^{ta}Phos

Figure 8 Ligands employed for the Pd-catalyzed coupling of alkenyl toluene sulfonates with alkynylzinc reagents.



(52)

Utility of alkynylzinc reagents in carbonylative cross-couplings was demonstrated recently.[176] Thus, heating aryl iodides with the alkynylzinc reagents in the presence of phosphine-free commercially available PEPPSI-IPr catalyst and 3 equivalents of lithium bromide under a balloon of CO leads to the formation of the ynone in good to excellent yields (equation 53). Experiments with no LiBr added returned mostly the direct coupling product and large amounts of alkyne dimer. Less satisfactory results on account CO-free biphenyl byproduct may be obtained when electron-rich aryl iodides are employed. However, addition of PPh$_3$ and increasing CO pressure improve the yield of the ynone.



(53)

3.09.3.3 Alkynyltin Reagents

In 1987, Echavarren and Stille established the general method for synthesis of internal acetylenes via coupling of alkynyltin reagents with aryl triflates[177] and vinyl iodides.[178]

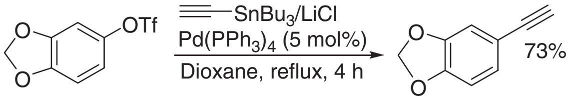
The synthesis of alkynylstannanes is straightforward. They are prepared by the reaction of the lithium acetylide with trimethyl or tributyltin chloride and by the reaction of the terminal acetylene with (diethy1amino)trimethylstannane (equations 54 and 55). Tributyl or trimethyltin reagents can be employed. The trimethyl tin reagents have the advantage that they are more reactive, and the byproduct of the coupling, trimethyltin iodide, is water soluble and, therefore, can be removed easily from the coupled product. They are, however, unstable relative to the tributyl analog and cannot be stored for longer periods or readily purified by silica chromatography.

$$\mathrm{R{-}{\equiv}{-}Li} \;+\; \mathrm{ClSnR_3} \longrightarrow \mathrm{R{-}{\equiv}{-}SnR_3} \qquad (54)$$

$$\mathrm{R{-}{\equiv}{-}H} \;+\; \mathrm{Me_2NSnR_3} \longrightarrow \mathrm{R{-}{\equiv}{-}SnR_3} \qquad (55)$$

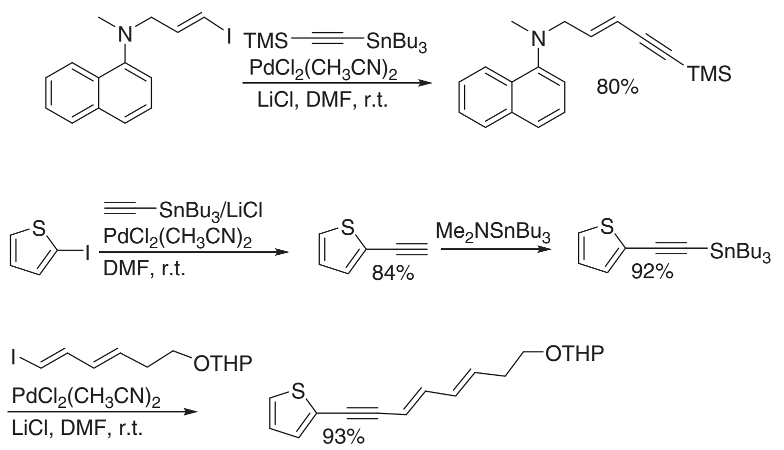
R′ = Me or Bu

The resulting alkynylstannanes readily couple with aryl triflates or vinyl iodides under very mild reaction conditions. For example, the coupling reaction works well with Pd(PPh$_3$)$_4$ as catalyst, in the presence of 3 equivalents of lithium chloride in refluxing dioxane or DMF (equation 56).



(56)

In many cases, however, DMF is a beneficial solvent as it efficiently solubilizes LiCl as well as acts as a ligand often obviating the need in phosphine ligands, at least when coupling of vinyl iodides is carried out (equation 57 and Scheme 64). The coupling reaction proceeds at room temperature or slightly above and in a very stereospecific fashion with retention of the double bond geometry of the vinyl iodide in the coupled product.

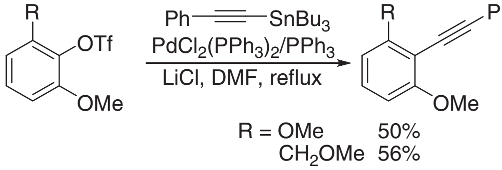


(57)

Scheme 64 Pd-catalyzed and base-free coupling of aryl and vinyl iodides with alkynyltin reagents.

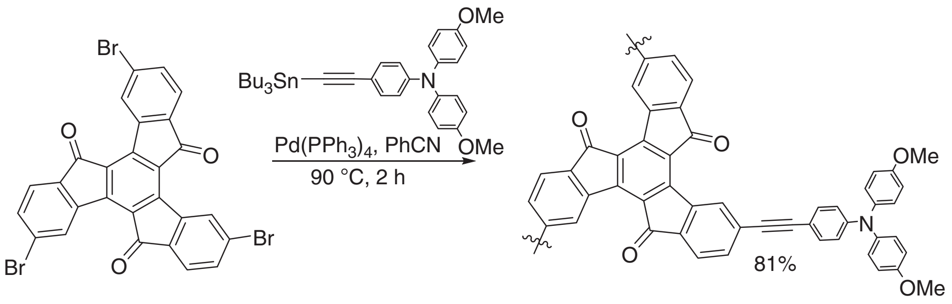
Even highly substituted aryl triflates couple under these reaction conditions, although they require higher reaction temperature to achieve reasonable conversions (equation 58).[179] It was established that the best catalytic system for the reactions of 2,2′-substituted triflates involves the use of $PdC1_2(PPh_3)_2$ (3–15 mol%)/PPh_3/LiC in refluxing DMF.

Unlike more activated substrates, sterically congested triflates require the presence of (even excessive) triphenylphosphines. In its absence, palladium black precipitates after a few minutes, especially with electron-rich substrates. Second, higher catalyst loading is needed for reactions of electron-rich sterically hindered substrates to work efficiently. Thus, as a rule, reactions with electron-rich triflates work best with 10–15 mol% palladium whereas aryl triflates having electron-withdrawing groups react efficiently with a reduced amount of palladium (3–6 mol%).[179,180]



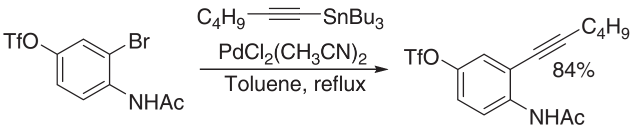
(58)

Unlike aryl triflates, coupling of aryl iodides and bromides with alkystannanes obviates the use of LiCl (equation 59).[173,181–184]



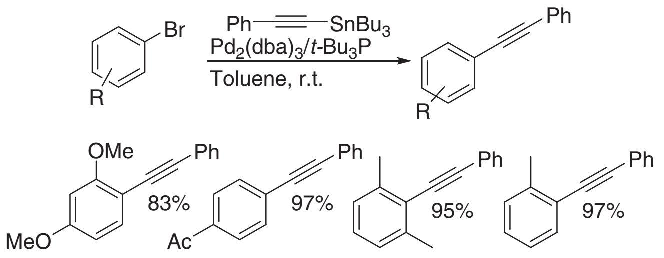
(59)

Moreover, coupling at the bromo position can be carried out selectively in the presence of the aryl triflate by the exclusion of lithium chloride (equation 60).[185]



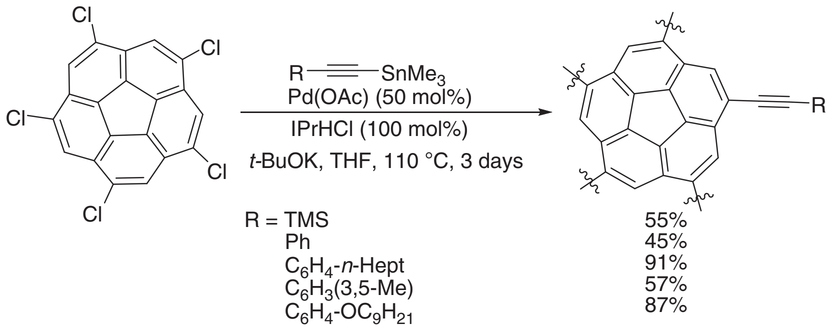
(60)

Room temperature coupling of aryl bromides can be realized through the employment of bulky monophosphine ligands such as t-Bu_3P. For example, Fu and coworkers demonstrated that $Pd_2(dba)_3$/t-Bu_3P effects the room temperature cross-coupling of activated, *ortho*-substituted, *ortho*-substituted and deactivated, and di-*o*-substituted bromides aryl bromides with a broad range of organotin reagents in excellent yield (Scheme 65).[186]



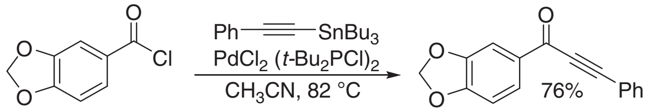
Scheme 65 Pd-catalyzed and base-free coupling of aryl bromides with alkynyltin reagents.

Even aryl chlorides can be coupled with alkynyltin reagents.[187,188] For this purpose, NHC carbene-based ligands may be employed.[172,173] For example, synthesis of pentaalkynylated corannulenes from the corresponding pentachlorinated starting materials (**Scheme 66**).



Scheme 66 Pd-catalyzed coupling of aryl chlorides with alkynyltin reagents.

Chemoselective cross-coupling of aliphatic and aromatic acyl chlorides with alkynylstannanes proceeds in up to 98% yield using 2.5 mol% of bis(di-*t*-butylchlorophosphine)palladium(II) dichloride as the precatalyst. Various functional groups including aryl chlorides and bromides, which usually undergo oxidative addition to palladium complexes ligands, are tolerated. This procedure allows convenient ynone formation (equation 61).[189] Alternatively, this class of compounds can be targeted using carbonylative version of alkynylstannanes with aryl halides.[176]



(61)

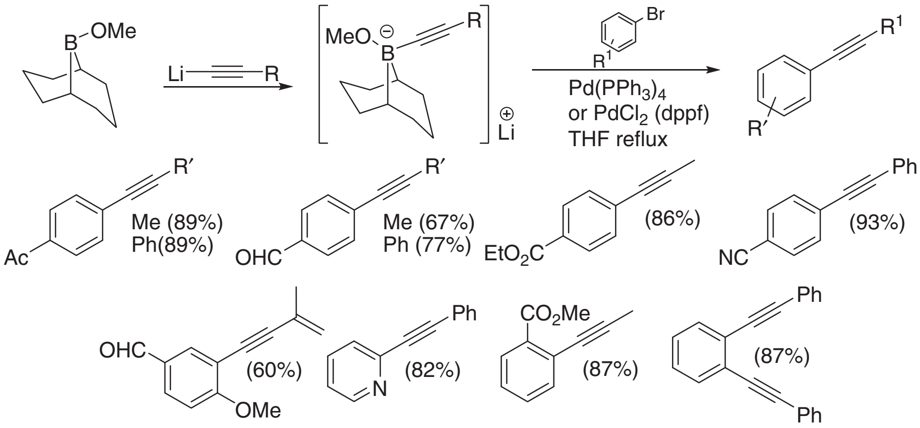
3.09.3.4 Alkynylboron Reagents

Organoboron compounds are less toxic than organostannane reagents, and unlike alkynylzinc and magnesium, many organoboron compounds possess remarkable oxidative and thermal stabilities.

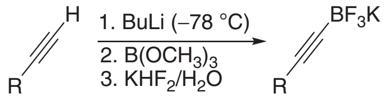
In 1995, two different catalytic systems for palladium-catalyzed coupling of alkynylboron reagents with aryl and alkenyl halides were independently reported. Both methods employed a nucleophilic 'ate' complexes 9-alkynyl-9-borabicyclo[3.3.1]nonane (9-alkynyl-9-BBN) that can be generated *in situ* from 9-methoxy-9-BBN and the corresponding alkali metal acetylides (**Scheme 67**) and either $PdCl_2(dppf)$[190] or $Pd(PPh_3)_4$[191] as the catalysts. Alkynyl potassium, sodium, and lithium reagents are equally suitable as starting materials and can be chosen based on the criteria of availability. However, magnesium-based reagents were found inefficient in this type of reaction. More importantly, the reaction turned out to be compatible with a variety of sensitive functionalities including aldehyde, ketone, ester, and nitrile groups. Moreover, basic heteroatoms in the starting materials do not compete with the organometallic reagent for the Lewis-acidic boron center of 9-OMe–9-BBN and, therefore, do not pose any chemoselectivity problems.

1-Alkynyl(triisopropoxy)boronates, readily prepared in a similar fashion from triisopropoxyborane, successfully couple with aryl iodides or vinyl bromides in DMF at 60 °C heating but require the presence of the copper cocatalyst.[192]

Potassium alkynyltrifluoroborates are very robust, insensitive to air and moisture, and storable reagents. These reagents are readily prepared by reaction of a deprotonated terminal alkyne $B(OMe)_3$ followed by interaction with aqueous KHF_2.[193] Unlike 9-BBN and trialkyborate derivatives, this method allows for the synthesis of functionalized alkynyltrifluoroborates (**Scheme 68**).



Scheme 67 Pd-catalyzed and base-free coupling of aryl bromides with 9-alkynyl-9-BBN.



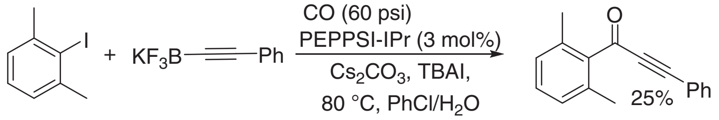
R =	
n-Bu	78%
n-Oct	74%
Ph	78%
$(CH_2)_2Ph$	70%
$(CH_2)_3Cl$	80%
$(CH)_2OTBDMS$	66%
TMS	77%

Scheme 68 Synthesis of alkynyltrifluoroborates.

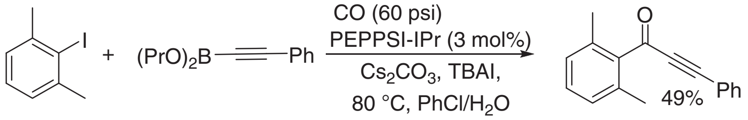
Under the optimized reaction conditions, potassium alkynyltrifluoroborates couple efficiently with aryl bromides in refluxing THF in the presence of 9 mol% of $PdCl_2$(dppf) and 3 equivalents of Cs_2CO_3 leading to the formation of the desired coupling products in good to excellent yield (Scheme 69). Most importantly, the coupling turned out to be general with respect to a diverse array of functionalized aryl bromides. Compatibility was demonstrated with cyano, aldehyde, ketone, and hydroxy groups as well as carboxylic acids.[194] Activated bromides, for instance, *p*-bromobenzonitrile, *p*-bromobenzoic acid, and *o*-bromobenzaldehyde, offer high yields of the corresponding cross-coupled product, as did the unprotected 7-bromoindole. In some cases, the use of anhydrous THF is crucial due to the competitive Pd-assisted hydration of the triple bonds. Some activated heteroaryl chlorides can also be coupled with potassium alkynyltrifluoroborates using this catalyst.

Aryl and alkenyl triflates were also suitable coupling partners under the described reaction conditions.[193,195] Unlike the aryl bromide case, however, 2 mol% of the catalyst produced yields comparable to those obtained with 9 mol% for aryl bromides, although it required a reaction time of 12 h. Thus, activated aryl triflates, as well as an electron-rich triflate, led to the corresponding coupled product in good to excellent yield. Heteroaryl triflates gave modest alkynylation. Enhanced reactivity was reported using the same catalyst under microwave heating.[196]

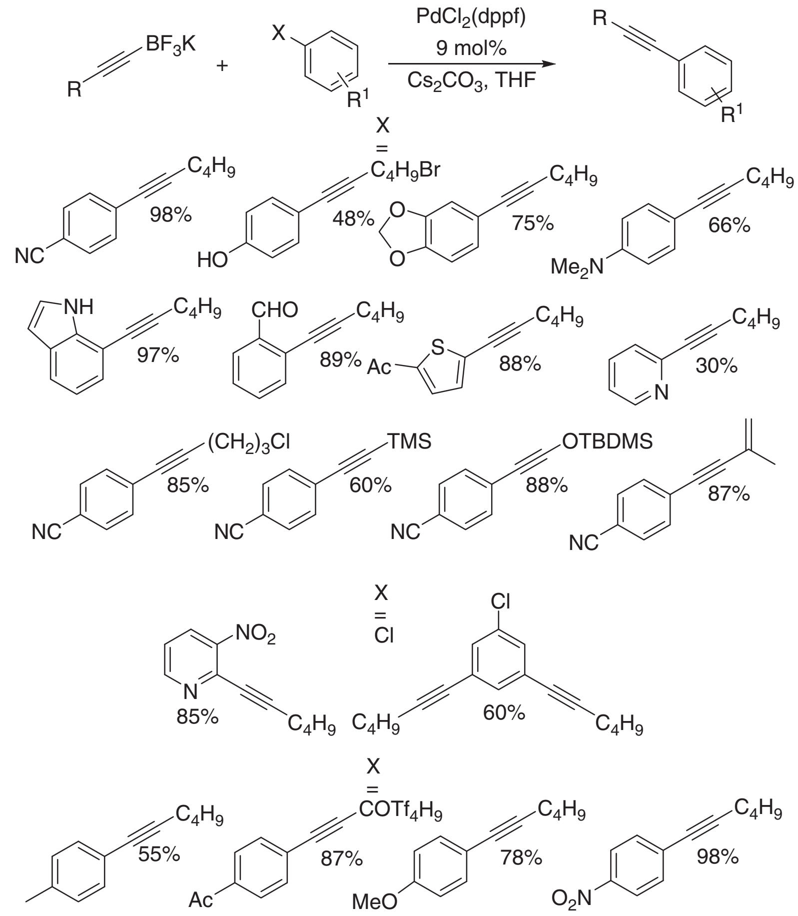
Synthesis of alkynyl aryl ketones from aryl iodides using potassium alkynyltrifluoroborates or alkynyl boronates under the CO atmosphere using PEPPSI-IPr catalyst and Cs_2CO_3 as a base was reported (equations 62 and 63).[176]



(62)



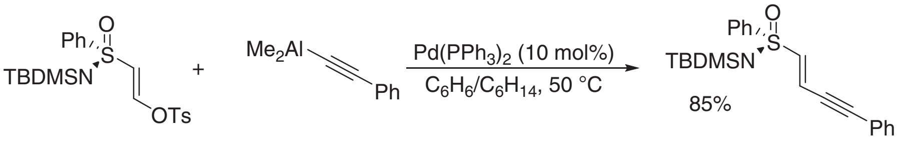
(63)



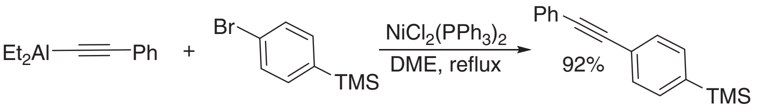
Scheme 69 Pd-catalyzed coupling of aryl halides and pseudohalides with potassium alkynyltrifluoroborates.

3.09.3.5 Alkynylaluminum and Indium Reagents

The first palladium-catalyzed alkynylation of alkenyl tosylates with dimethylalkynyl aluminum reagent was reported in 1990 (equation 64).[197] Thus, when the β-tosylvinylsulfoximine was treated with dimethylphenylethynylalane in hexane/toluene mixture at 50 °C for 45 min in the presence of $Pd(PPh_3)_4$ (10 mol%), the desired coupling product was produced in 85% yield.

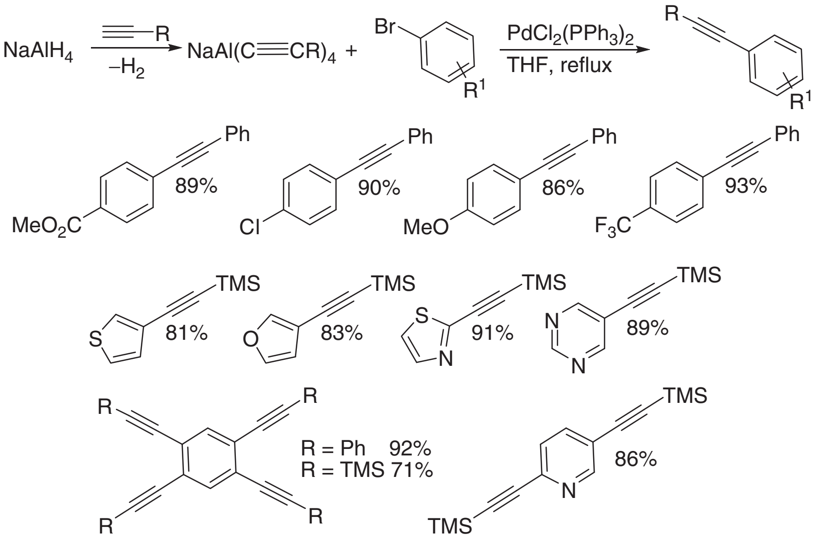
 (64)

Nickel-catalyzed coupling of aryl bromides with dialkylphenylethynylalane was also recently described.[198] It was found that the reactions take place effectively at 80 °C in the presence of 4 mol% of $NiCl_2(PPh_3)_2$ in 4 h and afford the coupling products in excellent yield starting from substituted aryl bromides either having the electron-donating or electron-withdrawing substituents on it (equation 65).

 (65)

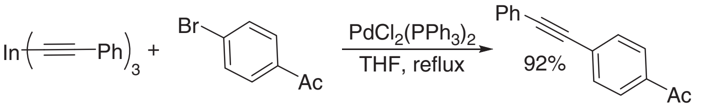
However, due to their pyrophoric nature, trialkylalanes have never received much attention as alkynylating agents. In order to overcome this problem, Blum and coworkers suggested the use of very stable sodium or lithium tetraalkynylaluminate in combination with simple $PdCl_2(PPh_3)_2$ catalyst as convenient coupling partners for alkynylation of aryl bromides.[199] These reagents can be readily prepared in excellent yields from $NaAlH_4$ or $LiAlH_4$ and the respective terminal alkynes in THF

(**Scheme 70**). They are usually moderately air- and moisture-stable solids, readily soluble in THF and DME, and withstand prolonged heating even above 150 °C. Typically, 2–4 equivalents of an appropriate organic bromide is reacted with 1 equivalent of the sodium tetraalknylaluminate in the presence of 2.5 mol% of $PdCl_2(PPh_3)_2$ to deliver the desired product in good to excellent yield and selectivity. **Scheme 69** indicates that the cross-coupling of tetraalkynylaluminates with a variety of aryl bromides proceeds well, regardless of the nature of the substituents on the substrates. Some electron-attracting groups seem, however, to enhance the reaction rate. The processes take place in a selective manner. Vulnerable functions, such as chloro, triflate, cyano, and ester groups, as well as C–C double bonds, are not affected. The sodium tetraalkynylaluminates were also shown to cross-couple with a variety of heteroaryl bromides and polybromoarenes. Analogous tetraalkynylindates were reported later.[200]



Scheme 70 Synthesis and cross-coupling of lithium tetraalkynylaluminates.

In general, alkynylindium derivatives are also less pyrophoric and, therefore, very convenient coupling partners in this type of reactions. It was found that the reaction of vinyl triflates, aryl iodides, bromides, and triflates with alkynylindiums (100 mol%) in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ (3 mol%) afford after refluxing in the cross-coupling products in a quantitative yield (equations 66 and 67).[201–204] Finally, a carbonylative version of this reaction was recently reported.[204]



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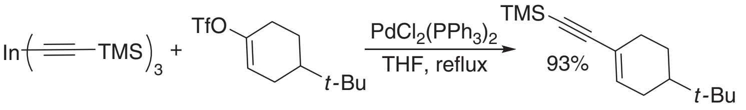
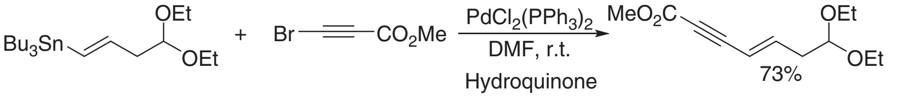


(67)

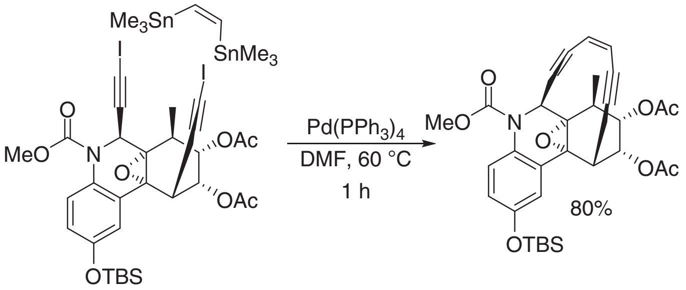
3.09.4 Transition Metal-Catalyzed Coupling of C(sp^2)-Metal Reagents with C(sp)-Halides and Pseudohalides

Oxidative addition of zero-valent palladium across the C(sp)–halogen bond is well known,[205] therefore, construction of C(sp^2)–C(sp) bonds can be realized through the conventional transition metal-catalyzed cross-coupling of alkynyl halides with C(sp^2)-based organometallics. Indeed, in 1990, a series of protected *E*-enynals via cross-coupling of stereochemically well-defined vinyltin acetals with bromoalkynes was reported (equation 68).[206] Using $PdCl_2(MeCN)_2$ as catalyst at room temperature, conversion rates above 70% were obtained whatever the nature of the solvent (DMF, THF, NMP, chloroform, or benzene). Catalysts of the type $PdCl_2(PhCN)_2$, $PdCl_2(PPh_3)_2$, or $PdC1_2[P\text{-}(o\text{-Tolyl})_3]_2$ have also good efficiency but tetrakis(triphenylphosphine)palladium appears to be much less efficient and must be used in the presence of lithium chloride in order to obtain the desired products in reasonable yields. Due to the ability of the target enyne to polymerize, the reaction was conducted in the presence of hydroquinone (5%).

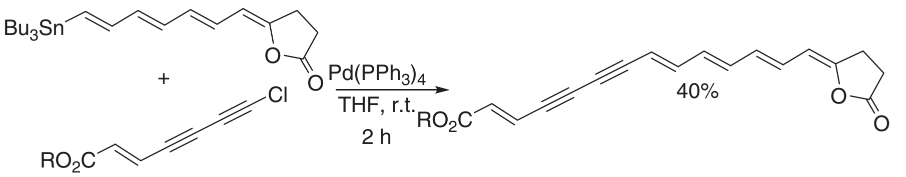


(68)

Excellent stereospecificity and functional group compatibility highlight the method and it was successfully applied to the synthesis of enediynes[207–211] and enyne[212,213] motifs in good to excellent yield (equations 69 and 70).

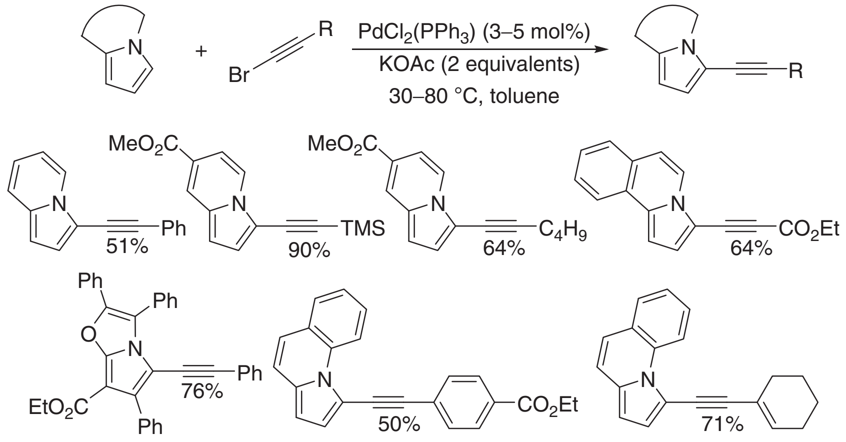


(69)



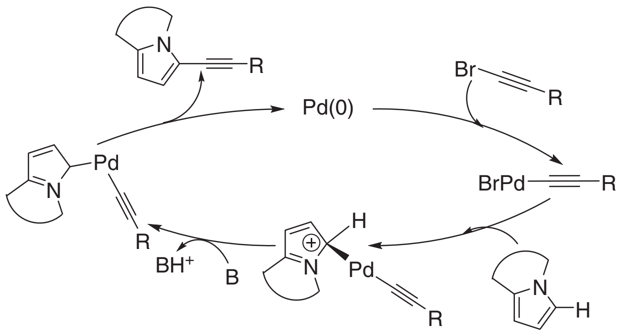
(70)

In 2007, Gevorgyan and coworkers reported the first example of straightforward transition metal-catalyzed direct alkynylation of electron-rich *N*-fused heterocycles with halogenated acetylenes.[214] As was demonstrated, a number of electron-rich *N*-fused heterocycles undergo smooth and regioselective coupling reaction with bromoalkynes in the presence of 3 mol% of $PdCl_2(PPh_3)_2$ and 2 equivalents of KOAc in toluene (Scheme 71). This direct alkynylation reaction appeared to be quite general with respect to the electron-rich *N*-fused heterocyclic core. Thus, unsubstituted- and ester-containing indolizines, pyrrolo-isoquinoline, substituted pyrroloxazole, and pyrroloquinoline were smoothly alkynylated to give the corresponding products in good to very high yields. This alkynylation reaction also demonstrated a remarkable tolerance toward functional groups at the bromoalkyne. Indeed, bromoalkynes possessing alkyl, aryl, alkenyl, TMS, and ester groups were nearly equally efficient in direct alkynylation. It should be mentioned that, in contrast to bromoalkynes, their chloro and iodo counterparts were much less efficient.



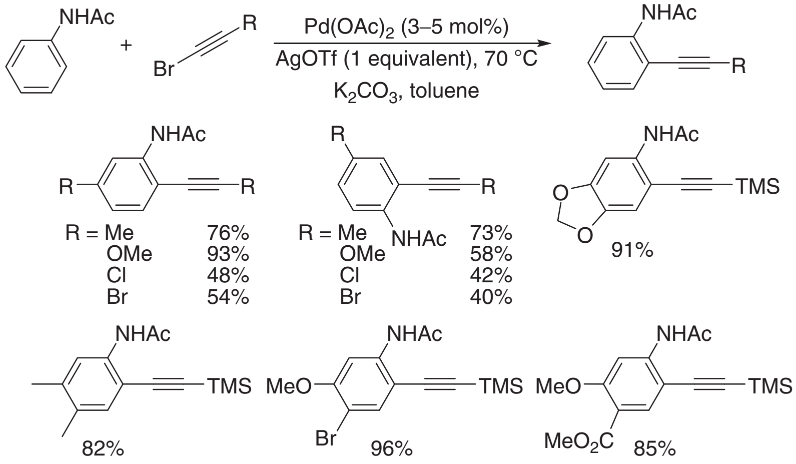
Scheme 71 Pd-catalyzed direct alkynylation of electron-rich *N*-fused heterocycles with halogenated acetylenes.

The proposed mechanism apparently operates via a nucleophilic attack of the most electron-rich C-3 position of the heterocycle at alkynylpalladium intermediate (formed by the oxidative addition of zero-valent palladium across the C(sp)–halogen bond of the bromoacetylene) to form iminium intermediate that on deprotonation furnishes the Pd(II) intermediate ready for the conventional reductive elimination to produce alkynylated heterocycle (Scheme 72).



Scheme 72 Plausible mechanism of the direct alkynylation of electron-rich *N*-fused heterocycles with halogenated acetylenes.

Subsequently, direct palladium-catalyzed regioselective C-3 alkynylation of indoles with various aryl- and alkenyl-substituted alkynyl bromides[215] and anilides were reported.[216] For example, it was found that *N*-acetylated anilines undergo smooth alkynylation with bromoacetylenes in the presence of $Pd(OAc)_2$, K_2CO_3, and AgOTf in toluene at 70 °C. Electron-rich substrates bearing alkyl or methoxy groups furnished the corresponding alkynylarenes in good yields and formed no dialkynylated products. However, diminished but still synthetically acceptable yields were obtained with anilides bearing electron-withdrawing groups (Scheme 73). These results agree with the general reactivity trend observed in C–H functionalization reactions involving electrophilic palladation.

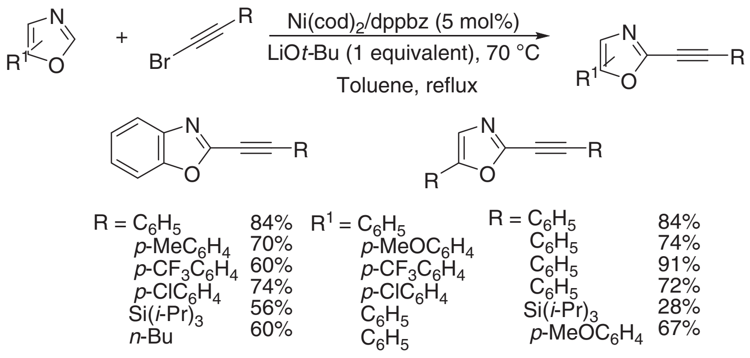


Scheme 73 Direct palladium-catalyzed regioselective alkynylation of anilides.

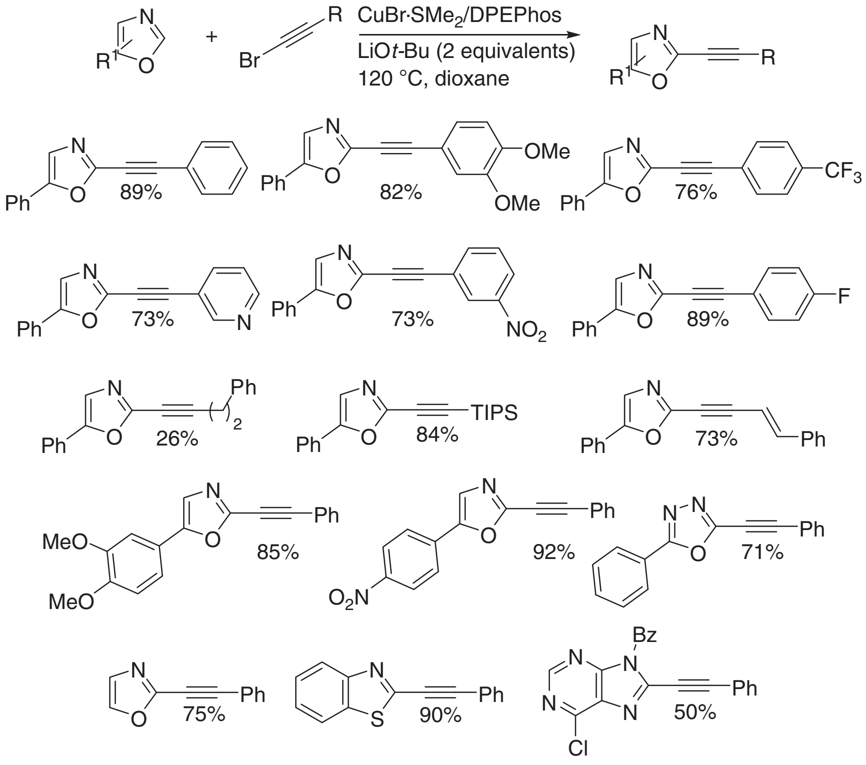
Nickel-catalyzed direct alkynylation of azoles with alkynyl bromides was also reported. The nickel-based catalyst enables various alkynyl bromides to serve as promising alkynyl sources to azoles. Additionally, in some cases, addition of a catalytic amount of CuI is observed to enhance the reaction dramatically.[217] Thus, $Ni(cod)_2$/1,2-bis(diphenylphosphino)benzene (dppbz) catalyst system in refluxing toluene was shown to promote the reaction. Notably, the combination of bench-stable $Ni(acac)_2$ and Zn instead of air-sensitive $Ni(cod)_2$ was also available for use, providing the desired products in an acceptable yield. A variety of alkynyl bromides (e.g., *p*-methyl-, *p*-chloro-, and *p*-trifluoromethyl-substituted (bromoethynyl)benzenes) reacted smoothly to give the corresponding alkynylazoles in good yields. The sterically demanding substrates did not interfere with the reaction (Scheme 74).

Finally, the similar transformation was reported to be efficiently promoted by a 15 mol% of $CuBr•SMe_2$/DPEPhos (bis[(2-diphenylphosphino)phenyl] ether) in the presence of *t*-BuOLi in dioxane at 120 °C.[218] Interestingly, the use of uncomplexed CuBr led to less satisfactory results. Both electron-rich and electron-deficient alkynyl bromides reacted regioselectively at the C-2 position of oxazoles in good yields, with substitution being tolerated at each of the *ortho*, *meta*, and *para* positions. The reaction proceeds equally well with heteroaryl- and alkenyl-substituted alkynes, although alkyl-substituted substrates gave only a low yield. The scope of oxazoles also included electron-rich and electron-poor molecules. Remarkably, unsubstituted oxazole itself was regioselectively alkynylated at the C-2 position, albeit in moderate yield. Other heterocycles such as benzoxazole, benzothiazole, 1,3,4-oxadiazole, and 1,2,4-triazole were also found to be suitable substrates (Scheme 75).

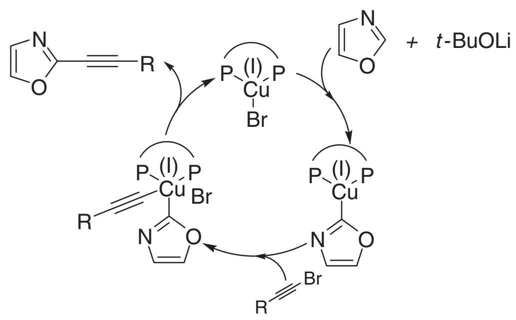
The reaction probably proceeds through the formation of a copper(III) intermediate via oxidative addition of Cu(I)-oxazolate complex across the C(sp)–Br bond, as illustrated in Scheme 76.



Scheme 74 Nickel-catalyzed direct alkynylation of azoles with alkynyl bromides.



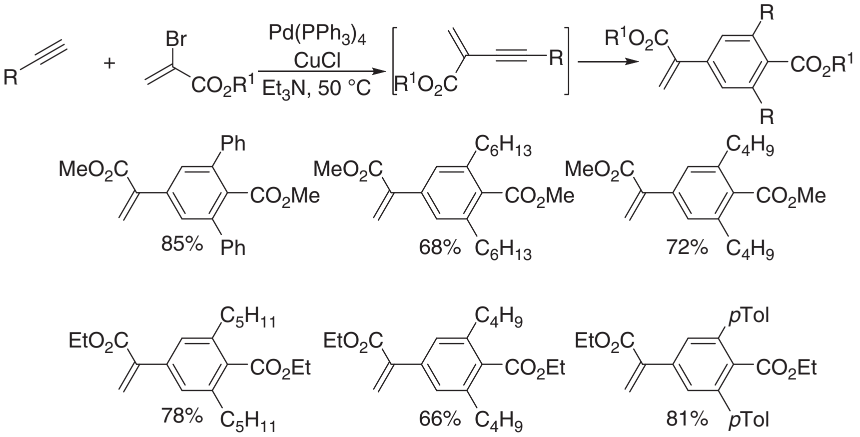
Scheme 75 Copper-catalyzed direct alkynylation of azoles with alkynyl bromides.



Scheme 76 Plausible mechanism of the direct copper-catalyzed alkynylation of electron-rich heterocycles with halogenated acetylenes.

3.09.5 Domino Reactions Involving C(sp^2)–C(sp) Coupling as the Key Step

Terminal and internal triple bonds are versatile functional groups that can participate in various palladium-promoted chemical transformations.[219–223] Based on this, numerous cascade reactions that include C(sp^2)–C(sp) coupling as the key step have been developed. For example, sequential Sonogashira coupling/benzannulation reactions take place under the standard Sonogashira –Hagihara conditions represent a regioselective and straightforward approach to the synthesis of polysubstituted benzenes.[224] Thus, the reaction of methyl bromoacrylate and ethynyl-benzene in the presence of catalytic amounts of $Pd(PPh_3)_4$ and copper(I) chloride in THF in the presence of triethylamine as a base leads to the formation of 2′-(1-methoxycarbonyl-vinyl)-[1,1′;3′,1″]terphenyl-5′-carboxylic acid methyl ester in 85% isolated yield and excellent stereoselectivity. Alkynes bearing alkyl- and aryl-substituted groups were found to react in a similar fashion. In all cases, the corresponding products were formed in high to excellent yields (Scheme 77).

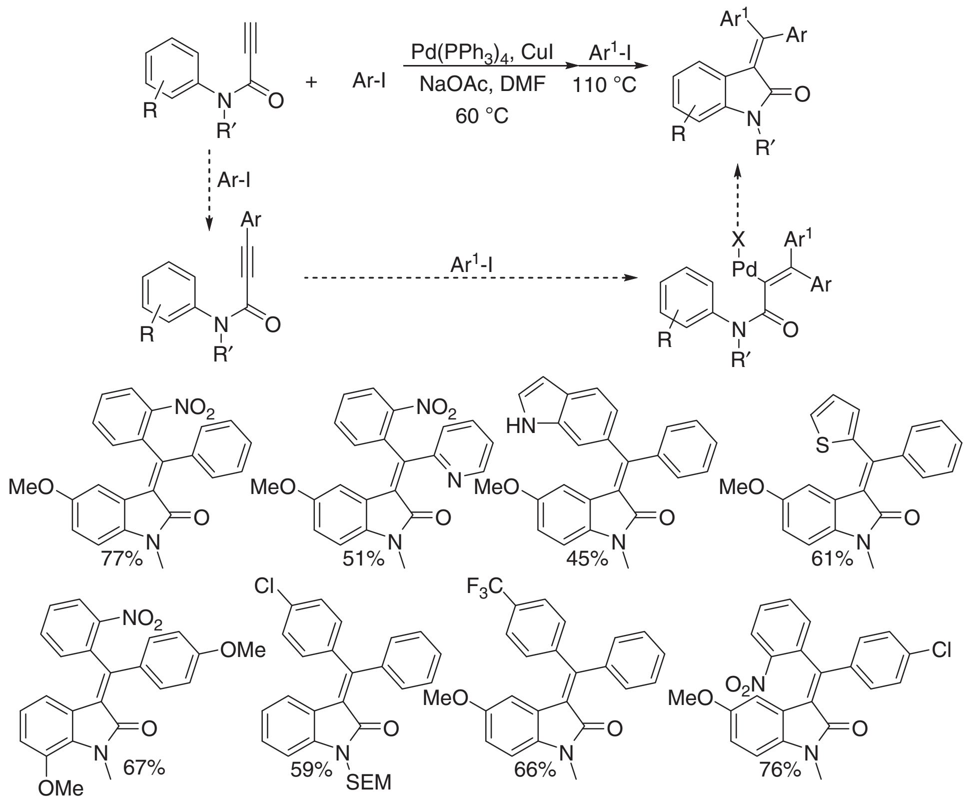


Scheme 77 Sequential Sonogashira coupling/benzannulation reactions toward the synthesis of polysubstituted benzenes.

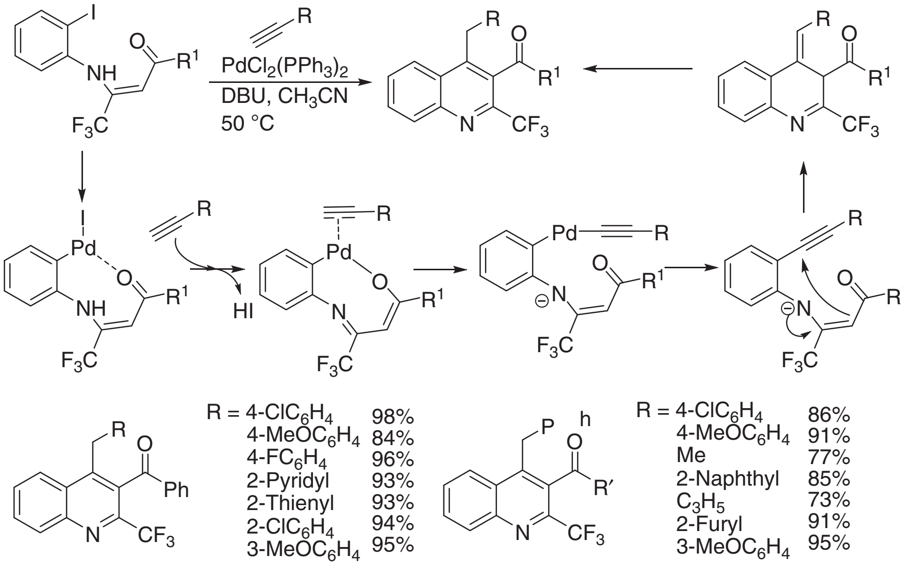
A flexible and stereocontrolled three-component synthesis of unsymmetrically substituted 3-(diarylmethylene)indolinones from *N*-aryl-*N*-alkyl propiolamides and two different aryl iodides was reported.[225] The underlying principle of our approach is shown in Scheme 77. The Sonogashira coupling of *N*-aryl-*N*-alkyl propiolamides with an aryl iodide should give the phenyl propiolamide, which would then react with a second aryl halide, in the presence of the same catalyst, to afford the target compound through a sequence of intermolecular carbopalladation, C–H activation, and a C–C bond-forming process.

The scope of this new three-component reaction included a range of substituted aryl iodides and propiolamides (Scheme 78). The outcome of this reaction was found to be only weakly influenced by the electronic properties of the aryl halides, and a variety of oxindoles substituted by an electron-donating or electron-withdrawing group were readily synthesized in good to excellent yields. However, *ortho*-, *meta*-, and *para*-substituted aryl iodides can be used as the second aryl iodide, only *para*- and *meta*-substituted aryl halides were well tolerated when used added as the first aryl iodide. The chlorine atom is compatible with this reaction sequence by providing a handle for further functionalization. The *N*-(2-trimethylsilylethoxymethoxy) anilides participated in this reaction providing a route to *N*-unsubstituted oxindoles. Both the *E*- and the *Z*-oxindole can be prepared from the same starting materials by simply changing the order of addition of the two aryl halides. 3-Iodopyridine, 5-iodoindole, and 2-iodothiophene were appropriate starting materials for this transformation.

Palladium-catalyzed synthesis of 2-trifluoromethylquinolines from *β*-trifluoromethyl *β*-enaminoketones and terminal alkynes through a domino Sonogashira–alkyne carbocyclization process proceeds in the presence of 10 mol% of $PdCl_2(PPh_3)_2$ as the catalyst and 2.2 equivalents of DBU in acetonitrile at 60 °C.[226] A possible mechanism of this transformation is proposed in Scheme 79. The first step is the oxidative addition of Pd(0) across the aryl halide bond. The presence of the *ortho*-*β*-acyl-enamine group apparently facilitates this step. Coordination of the alkyne to the ArPdOR complex then followed. The terminal alkyne C–H bond activation is accomplished by the coordination of the alkyne to the ArPdOR complex. On coordination, the C–H bond is weakened, and HOR is removed from Pd(II) in the presence of a base to form an arylalkynylpalladium species, which undergoes reductive elimination to afford the C(sp^2)–C(sp) bond regenerating the catalyst. The product then undergoes a base-catalyzed alkyne carbocyclization/isomerization to the target compound. Arylacetylenes bearing electron-withdrawing substituents gave higher yields and required shorter times than those bearing electron-donating substituents. All *para*-, *meta*-, and *ortho*-substituted phenylacetylenes and 2-ethynylnaphthalene were smoothly transformed into the desired products, which indicated that steric bulk did not significantly affect the reactivity. The cascade processes all occurred with good yields, even the terminal alkyne possessing a heterocyclic ring. However, aliphatic terminal alkynes, such as 1-hexyne, did not give the desired product under the standard conditions (Scheme 79).

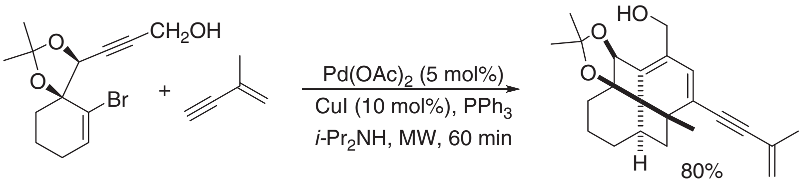


Scheme 78 Stereocontrolled three-component synthesis of unsymmetrically substituted 3-(diarylmethylene)indolinones from *N*-aryl-*N*-alkyl propiolamides and two different aryl iodides.



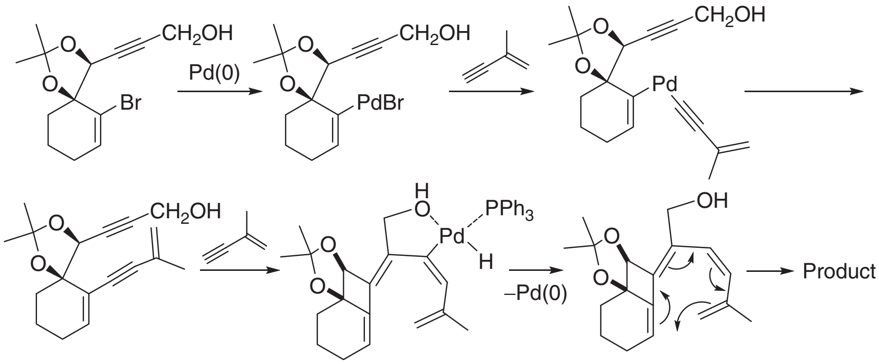
Scheme 79 Palladium-catalyzed synthesis of 2-trifluoromethylquinolines from β-trifluoromethyl β-enaminoketones and terminal alkynes through a domino Sonogashira–alkyne carbocyclization process.

A cascade reaction that involves a 4-*exo-dig* cyclocarbopalladation, a Sonogashira-type coupling, a regioselective alkynylation of a disubstituted triple bond, and $8\pi/6\pi$ electrocyclization is another spectacular example of an efficient one-pot synthesis of the complex carbocyclic molecules such as [4.5.4.6]-fenestradienes directly from alkenyl bromides using $Pd(OAc)_2/PPh_3/CuI$ catalyst in *i*-Pr_2NH under microwave heating (equation 71).[227] Differently substituted [4.5.4.6]-fenestradienes can be prepared this way in diastereopure form.



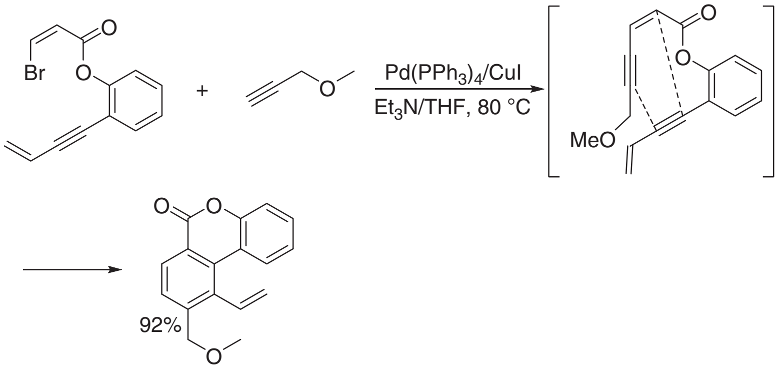
(71)

The mechanistic pathway is depicted in Scheme 80. After an initial 4-*exo-dig* cyclocarbopalladation of the alkenyl bromide, a Sonogashira-type reaction leads to the formation of the C(sp^2)–C(sp) bond. The resulting highly unsaturated trienyne could then react with a second equivalent of the enyne to afford the hydrido palladium intermediate, which, in due time, undergoes rapid reductive elimination to regenerate Pd(0).



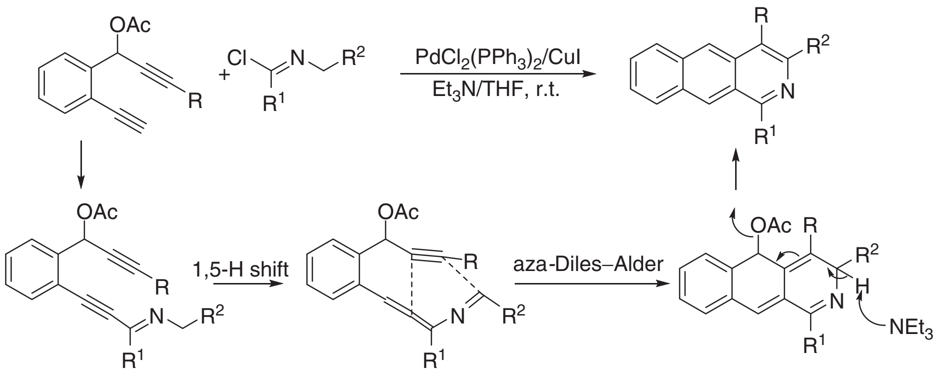
Scheme 80 Cascade reaction involving 4-*exo-dig* cyclocarbopalladation, a Sonogashira-type coupling, a regioselective alkynylation of a disubstituted triple bond, and 8π/6π electrocyclization.

Various kinds of 6*H*-dibenzo[*b*,*d*]pyran-6-ones were synthesized via a sequential one-pot procedure using the Sonogashira coupling-benzannulation reaction of aryl 3-bromopropenoates, in which the *ortho*-position of aryl group is substituted with enynes, with acetylenes in the presence of palladium and copper catalysts.[228] The Sonogashira coupling between the aryl 3-bromopropenoates, bearing enynes at the *ortho*-position of aryl group, and alkynes gave *in situ* the enyne intermediates, which subsequently underwent the palladium-catalyzed benzannulation reaction to afford the 6*H*-dibenzo[*b*,*d*]pyran-6-ones (equation 72). The cascade is efficiently catalyzed by 5 mol% of Pd(PPh$_3$)$_4$ and 10 mol% of CuI in Et$_3$N/THF at 80 °C. A variety of alkynes can be employed under these reaction conditions to synthesize functionalized 6*H*-dibenzo[*b*,*d*]pyran-6-ones.



(72)

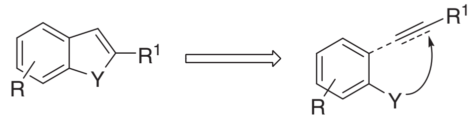
Cascade reactions involving Sonogashira-type chemistry are now routinely used for the synthesis of heterocyclic motifs. An interesting example demonstrating this approach is a sequential Sonogashira coupling/alkynyl imine–allenyl imine isomerization/*aza*-Diels–Alder/elimination–aromatization reaction, providing a facile synthesis of substituted 2-azaanthracenes from 1,6-diynes and imidoyl chlorides (Scheme 80).[229] This sequence takes place in the presence of 5 mol% of PdCl$_2$(PPh$_3$)$_2$/CuI as the catalysts in Et$_3$N/acetonitrile (1:3) at r.t. The reactions proceeded smoothly to afford the corresponding 2-azaanthracenes in moderate to good yields when the diynes were substituted with an alkyl or aryl group. Substituents at the imidoyl chlorides coupling partner can bear either electron-donating or electron-withdrawing groups. It should be noted that the presence of a substituent on the *ortho* position negatively affected the reaction. The following plausible mechanism for this reaction is proposed. Sonogashira coupling reaction of 1,6-diyne and imidoyl chloride affords the intermediate alkynyl imine, which undergoes a base-assisted 1,5-hydride shift to form allene intermediate. This reaction is followed by an aza-Diels–Alder reaction to form tricyclic intermediate which, subsequently, eliminates a molecule of AcOH giving the final product (Scheme 81).



R	R^1	R^2	
Ph	Ph	Ph	74%
4-$MeOC_6H_4$	Ph	Ph	77%
n-Hex	Ph	4-MeC_6H_4	81%
C_3H_5	Ph	4-MeC_6H_4	79%
C_3H_5	4-$MeOC_6H_4$	Ph	75%
C_3H_5	2-ClC_6H_4	Ph	52%
n-Hex	Ph	Vinyl	69%

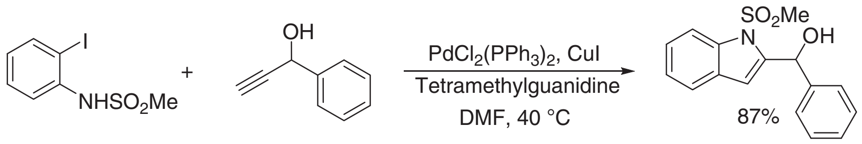
Scheme 81 Sequential Sonogashira coupling/alkynyl imine–allenyl imine isomerization/*aza*-Diels–Alder/elimination–aromatization reaction toward the synthesis of substituted 2-azaanthracenes.

Indoles and benzofuranes can be prepared using domino alkyne coupling/cyclization approach (Scheme 82).[220,222]



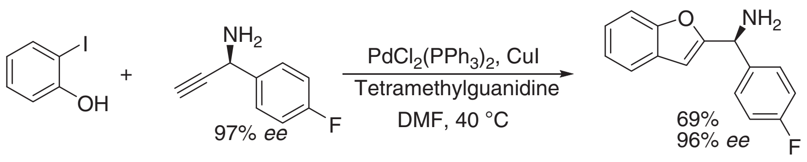
Scheme 82 Domino alkyne coupling/cyclization approach toward substituted indoles.

Treatment of 1-alkynes with *o*-iodo-*N*-mesylanilides under Sonogashira conditions directly produces indole products in a single operative step through a domino coupling/cyclization sequence with palladium and copper catalysts involved both in the coupling and in the cyclization reaction (equation 73).[230] It was later found that in some cases this reaction can be catalyzed by CuI in the presence of ppb levels of palladium.[231]



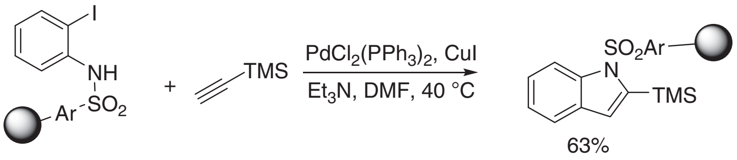
(73)

When racemic and enantiopure propargylic alcohols and propargylic amines[232] have been subjected to the same hetero-annulation reaction with 2-iodophenol (equation 74), the corresponding benzofuran derivatives were obtained in good yield and with minor racemization.



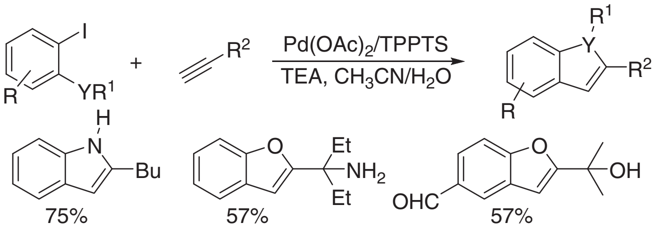
(74)

Given the importance of the indole nucleus in medicinal chemistry, a facile solid-phase construction of 2-substituted indole derivatives via palladium-mediated coupling/intramolecular indole cyclization of terminal alkynes based on a traceless, activating sulfonyl linker was described (equation 75).[233] The cyclization step is, apparently, copper-promoted.



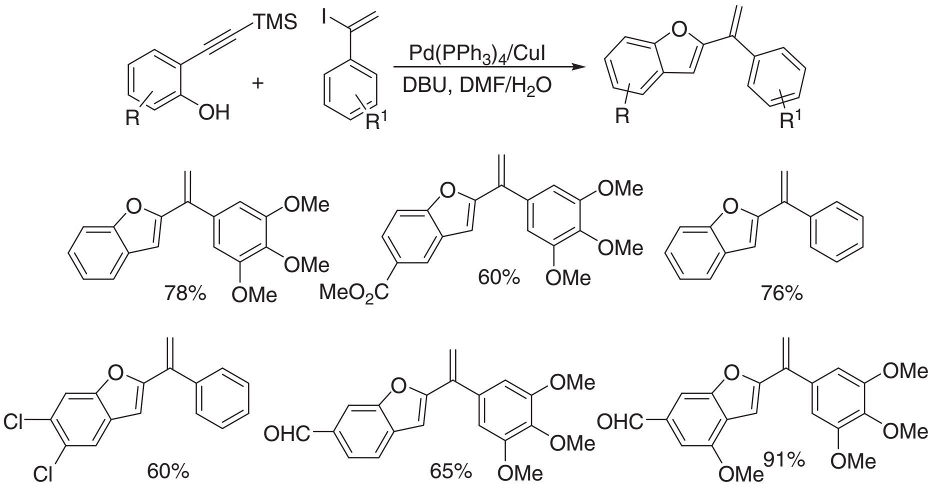
(75)

Synthesis of 2-substituted indoles from *o*-iodoaniline or *o*-iodotrifluoroacetanilide and terminal alkynes in the presence of Pd(OAc)$_2$, water-soluble triphenylphosphinetrisulfonate sodium salt (TPPTS), and Et$_3$N in MeCN and H$_2$O without any copper promoter was reported by Genet et al.[234] Also, substituted benzofuranes are accessible via this domino reaction (**Scheme 83**). In this case, the indole ring was suggested to arise from the intramolecular cyclization of an organopalladate intermediate.



Scheme 83 One-pot synthesis of 2-substituted indoles from *o*-iodoaniline or *o*-iodotrifluoroacetanilide and terminal alkynes.

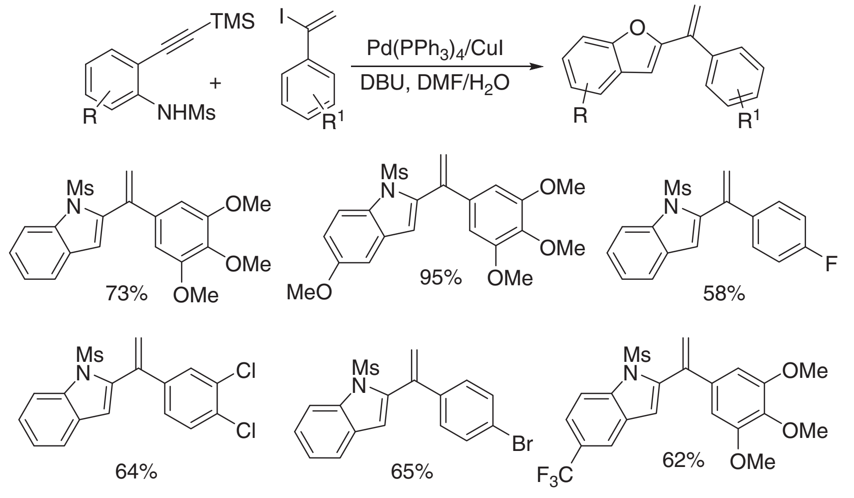
A convergent synthetic strategy toward 2-(1-phenylvinyl)benzofurans from readily accessible vinyl iodides based on a sequential C–Si bond cleavage of TMS-protected alkynes followed by a Pd-catalyzed Sonogashira coupling and subsequent 5-*endo-dig* cyclization of the intermediate enyne was suggested.[235] Under the optimized reaction conditions, 1:1.6 mixture of the alkenyl iodides and silylated alkyne 5 mol% Pd(PPh$_3$)$_4$, 10 mol% CuI, 12 equivalents of DBU, and 0.8 equivalent of H$_2$O in DMF at room temperature leads to the formation of the desired products in excellent overall yield for the three steps. Both electron-donating and electron-withdrawing groups such as OMe, CO$_2$Me, and CHO on the silylated arylalkynes were well tolerated. Variations with respect to the 1-phenylvinyl iodide partners also included electron-rich and electron-deficient substrates (**Scheme 84**).



Scheme 84 A convergent synthetic strategy toward 2-(1-phenylvinyl)benzofurans via a sequential C–Si bond cleavage of TMS-protected alkynes followed by a Pd-catalyzed Sonogashira coupling and subsequent 5-*endo-dig* cyclization.

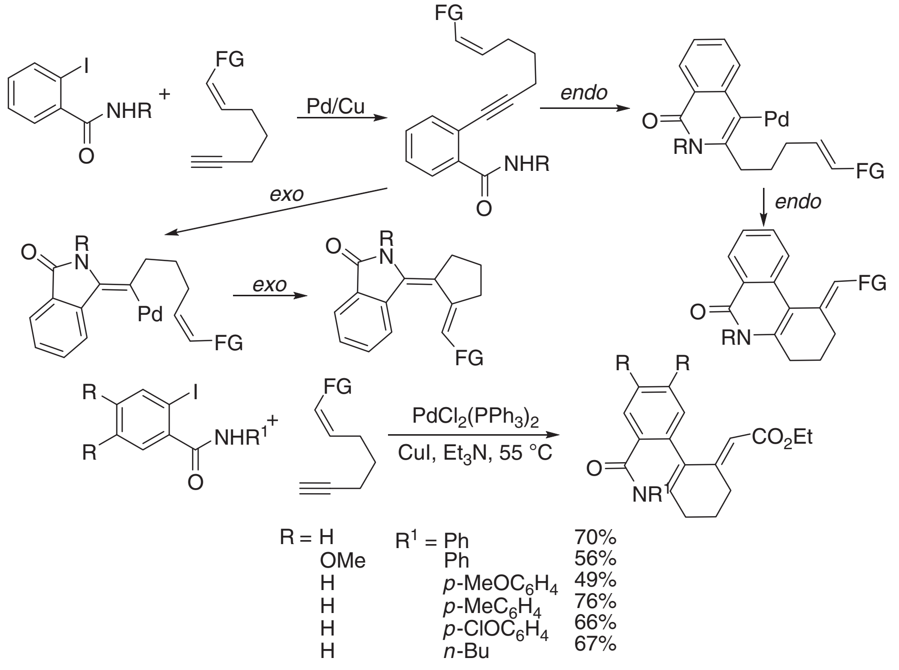
A similar strategy was applied to the synthesis of 2-(1-phenylvinyl)indoles from alkenyl iodides and *o*-(trimethylsilylethynyl)-*N*-mesylanilides (**Scheme 85**). Unfortunately, *N*-tosylanilides, trifluoromethyl acetanilides, acetamides, and *N*-Boc carbamates showed little reactivity, if any.

Functionalized alkylidene-1,2,3,4-tetrahydrodibenzo[*b*,*d*]phenanthridin-6(5*H*)-ones have been synthesized regio- and stereoselectively from either *o*-iodobenzamides and alkynes by consecutive Pd-catalyzed Sonogashira coupling and nucleophilic addition/oxidative Heck-type coupling cascade reactions without the isolation of intermediates.[236] The underlying general synthetic idea is outlined in **Scheme 86**. After Sonogashira coupling between *o*-iodobenzamides and enynes, the resulting 2-alkynylamide is expected to undergo a palladium-catalyzed nucleopalladation/Heck-type coupling cascade to afford the



Scheme 85 One-pot synthesis of 2-(1-phenylvinyl)indoles from alkenyl iodides and *o*-(trimethylsilylethynyl)-*N*-mesylanilides.

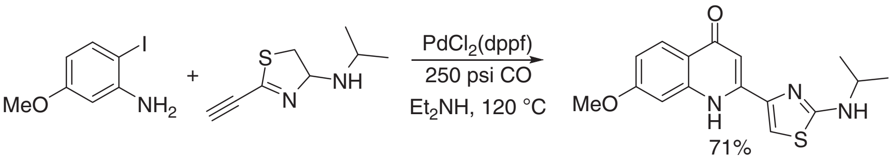
corresponding polycyclic products stereoselectively. The oxidation of the Pd(0) released in the final step is needed to regenerate the catalytic PdX$_2$ species. Regiochemical variants are possible: two modes of nucleopalladation, *exo* and *endo*, would lead to the corresponding isoindolones or phenanthridinone-type structures, respectively. Similarly, depending on the size of the tether, *exo* and *endo* pathways could also compete in the Heck-coupling reaction.



Scheme 86 Consecutive Pd-catalyzed Sonogashira coupling and nucleophilic addition/oxidative Heck-type coupling cascade.

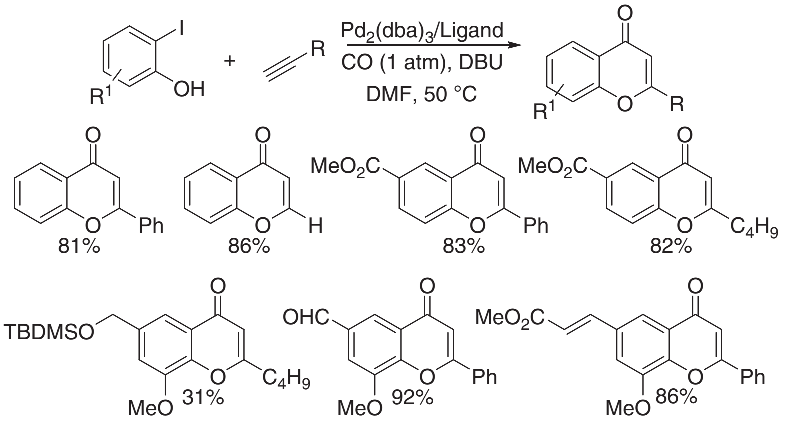
The results show that substitution on the benzamide ring is well tolerated. In addition, the benzamides offer the possibility of substitution at the nitrogen as a means of structure diversification. For example, substrates derived from anilines with substituents of different electronic character all participate effectively. In terms of regiochemical control, it was observed that in intermolecular cases, benzamides display a remarkable preference for the 6-*endo* mode in the initial intramolecular addition of the amide nitrogen onto the triple bond, and this leads to the predominant formation of tetrahydrophenanthridin-6(5*H*)-ones rather than the alternative regioisomeric isoindolones.

Carbonylative cyclization is another approach to the synthesis of carbonyl-containing heterocycles.[223,237] For example, a convergent synthesis of quinolone motif toward the synthesis of the protease inhibitor BILN 2061 was developed via palladium-catalyzed carbonylative coupling of 2-iodo-5-methoxyaniline with thiazolylacetylene using PdCl$_2$(dppf) as catalyst in Et$_2$NH at 120 °C under 250 psi of CO, and obtained the desired quinolone in 70% isolated yield (equation 76).[238]



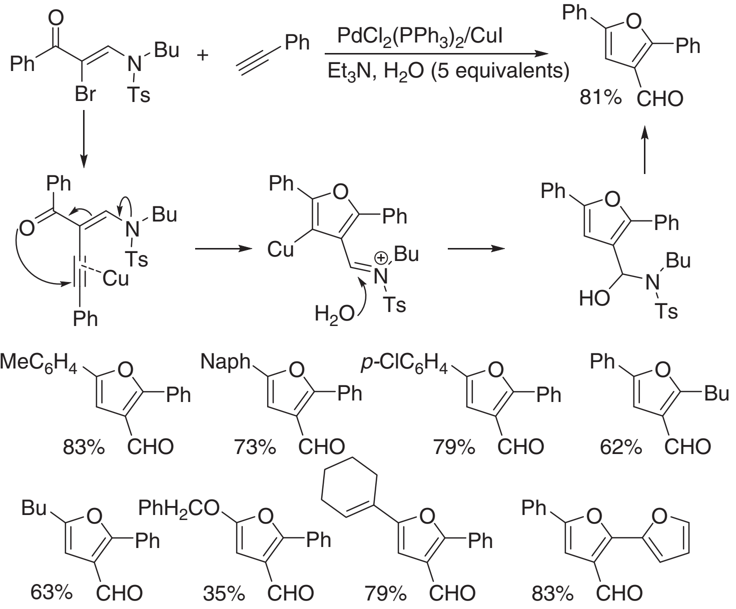
(76)

Coupling of *o*-iodophenol with terminal acetylenes under 1 atm of carbon monoxide is catalyzed by $Pd_2(dba)_3$/1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane (**Figure 1**) in DMF as a solvent with Cs_2CO_3 or DBU as a base at 50 °C.[239] Overall, the method works well and tolerates a variety of functional groups (**Scheme 87**).



Scheme 87 Palladium-catalyzed carbonylative coupling of *o*-iodophenols with terminal acetylenes.

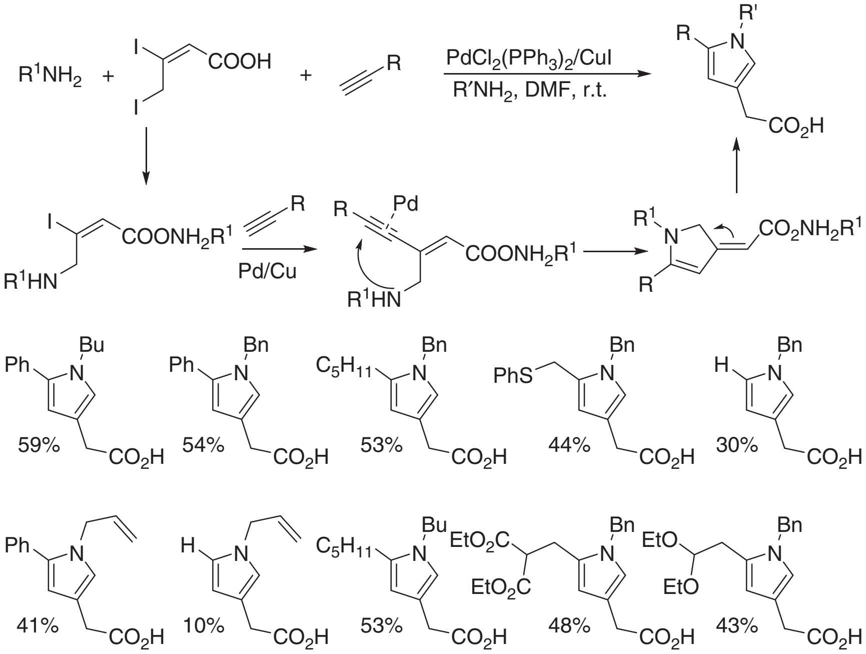
Palladium-catalyzed cascade transformations give facile access to pyrroles[240] and furans.[241] For example, the reaction of (*Z*)-*N*-(2-bromo-3-oxo-3-phenylprop-1-enyl)-*N*-butyl-4-methylbenzene-sulfonamide with phenylacetylene in the presence of $PdCl_2(PPh_3)_2$ (5 mol%) and CuI (10 mol%) as catalysts in aqueous Et_3N leads to the formation of 2,5-diphenylfuran-3-carbaldehyde in 67% yield. The cyclization is, apparently, copper-promoted, and the cascade proceeds via Sonogashira coupling of α-bromoenaminone and terminal acetylene to give the alkynylated enaminone, which on coordination of its alkynyl moiety to the Cu(I) facilitates an intramolecular cyclization to afford the iminium cation. Hydrolysis of the latter with regeneration of the Cu(I) catalyst leads to the desired 3-formyl furan (**Scheme 88**).



Scheme 88 Palladium-catalyzed cascade synthesis of furans.

The method is functional group-compatible and differently substituted 3-formyl furans can be prepared in practical yield and selectivity.

Interesting one-pot allylic amination/palladium-catalyzed Sonogashira cross-coupling and heterocyclization cascade allows the direct synthesis of 1,2,4-trisubstituted and 1,3-disubstituted pyrroles starting from readily available diiodobutenoic acid. A plausible mechanism accounting for this three-component domino process is depicted in Scheme 89 and includes initial C–N-allylic amination leading to the ammonium salt, followed by a Sonogashira cross-coupling reaction and subsequent intramolecular hydroamidation, providing dihydroexoalkylidene pyrrole, which rearranges into pyrrole.



Scheme 89 One-pot allylic amination/palladium-catalyzed Sonogashira cross-coupling and heterocyclization cascade.

All the alkyne precursors gave good yields of the corresponding coupling products. A number of functional groups on alkyne were tolerated, including esters, ethers, acetals, and sulfide groups. The scope of the process was found to be less broad with respect to the N fragment only and allowed good yields of pyrroles for a variety of α-unsubstituted alkylamines. For example, α-methylbenzylamine did not provide the expected heterocycle when coupled with phenylacetylene. Aryl, alkyl, allyl, and benzyl amines all performed well, although the basicity on the nitrogen atom was found to be essential.

Attempts with tosylamine of benzylcarbamate used in place of a primary amine failed.

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3.10 Coupling Reactions Between *sp* Carbon Centers

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3.10.1	**Introduction**	528
3.10.2	**Oxidative Coupling Reactions of Terminal Alkynes**	530
3.10.2.1	Homocoupling of Terminal Alkynes	530
3.10.2.1.1	Copper catalysis	530
3.10.2.1.2	Palladium–copper catalysis	539
3.10.2.2	Coupling of Two Different Terminal Alkynes	547
3.10.3	**Coupling Reactions of Terminal Alkynes and 1-Haloalkynes**	550
3.10.3.1	Copper Catalysis	550
3.10.3.2	Palladium Catalysis	553
3.10.4	**Oxidative Homocoupling of Organometallic Alkynides**	556
3.10.4.1	Homocoupling Reactions of Alkynyl Grignard Reagents	556
3.10.4.2	Homocoupling Reactions of Alkynylboron Reagents	558
3.10.4.3	Homocoupling Reactions of Alkynylstannane Reagents	560
3.10.4.4	Homocoupling Reactions of Alkynylsilane Reagents	561
3.10.5	**Coupling of Organometallic Alkynides and 1-Haloalkynes**	563
3.10.5.1	Heterocoupling Reactions of Alkynyl Grignard Reagents	563
3.10.5.2	Heterocoupling Reactions of Alkynylcopper Reagents	563
3.10.5.3	Heterocoupling Reactions of Alkynylstannane Reagents	563
3.10.5.4	Heterocoupling Reactions of Alkynylsilane Reagents	564
3.10.6	**Decarboxylative Coupling of Propiolic Acids**	564
3.10.7	**Elimination Reactions of Haloolefins**	566
3.10.7.1	Synthesis of Conjugated Diynes from Haloenynes	566
3.10.7.2	Synthesis of Conjugated Diynes from 1,1-Dihaloalkenes	569
3.10.8	**Applications**	571
3.10.8.1	Natural Product Synthesis	571
3.10.8.2	Linear Polyalkynes	572
3.10.8.3	Cyclic Alkynes	575
3.10.8.4	Polymer Synthesis	577
References		577

Glossary

SBA-15 Mesoporous silica sieve based on uniform hexagonal pores with a narrow pore size distribution and a tunable pore diameter of between 5 and 15 nm.

Solkanes 365mfc ($CF_3CH_2CF_2CH_3$) It is a hydrofluorocarbon commercially available developed as an environmentally friendly solvent.

Turnover number (TON) The TON specifies the maximum use that can be made of a catalyst for a special reaction under defined conditions by a number of molecular reactions or reaction cycles occurring at the reactive center up to the decay of activity.

3.10.1 Introduction

1,4-Disubstituted-1,3-diynes are an important class of natural and synthetic compounds that exhibit a broad range of pharmacological activities, such as antibacterial, antimicrobial, antifungal, antitumor, anticancer, antihuman immunodeficiency virus, and pesticidal properties. Examples of naturally occurring acetylenes containing a butadiyne or polyyne framework are depicted in Figure 1.[1] They have been isolated from fungi, bacteria, marine sponges, corals, and a wide variety of plant species. Dihydromatricaria acid is the only example of a conjugated 1,3-diyne that has been isolated from an insect (the soldier beetle). Besides their remarkable interest in organic synthesis, conjugated 1,3-diynes have also been employed for a number of applications, particularly in the construction of linearly π-conjugated acetylenic oligomers and polymers, supramolecular materials, as well as macrocyclic annulenes and substituted heterocyclic compounds (cf. Section 3.10.8).

The coupling reactions between *sp*-carbon centers of alkynyl substrates provide synthetically useful and straightforward routes to 1,4-disubstituted-1,3-diynes. Following the pioneering work by Glaser,[2] much attention has been paid to the development of

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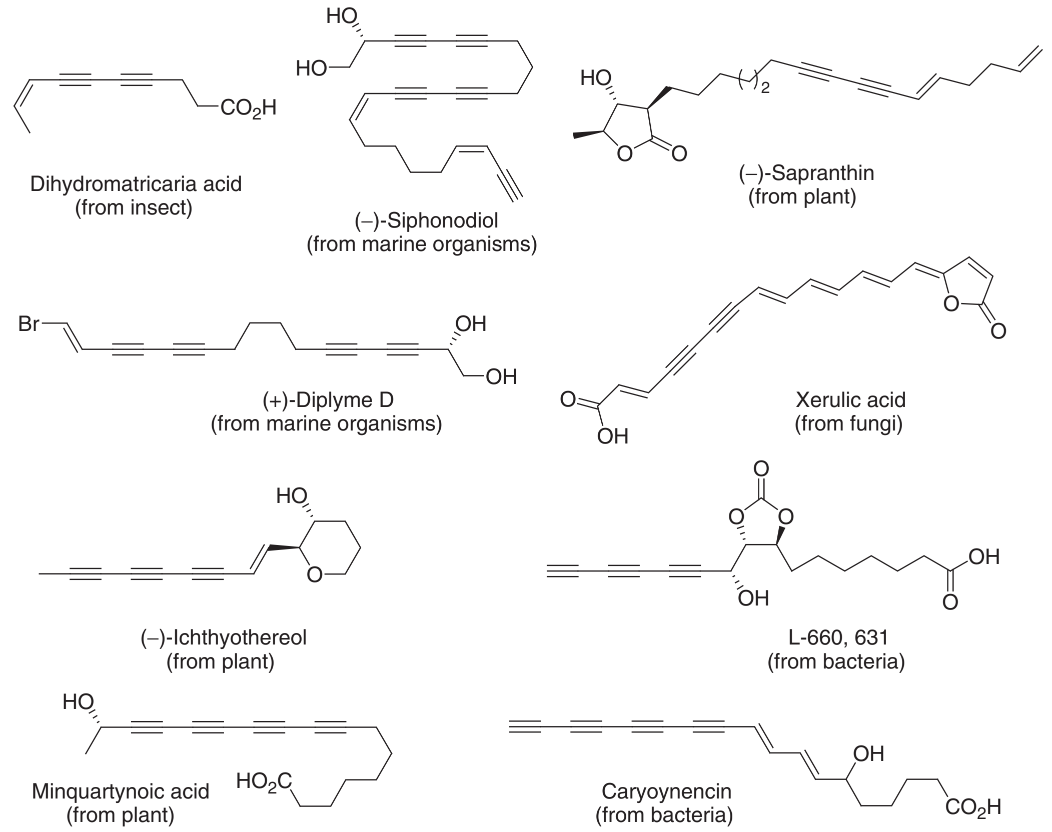

Dihydromatricaria acid (from insect)
(–)-Siphonodiol (from marine organisms)
(–)-Sapranthin (from plant)
(+)-Diplyme D (from marine organisms)
Xerulic acid (from fungi)
(–)-Ichthyothereol (from plant)
L-660, 631 (from bacteria)
Minquartynoic acid (from plant)
Caryoynencin (from bacteria)

Figure 1 Examples of conjugated diyne and polyyne natural products.

efficient procedures for the synthesis of this type of compounds. By far, the most extensively documented procedure to symmetrically 1,3-diynes is the oxidative homocoupling of terminal acetylenes, reported by Glaser and Eglinton. Parallel to the evolution of homocoupling reactions, Cadiot and Chodkiewicz described in 1957 practical processes to provide unsymmetrical 1,4-disubstituted-1,3-diynes based on the heterocoupling of terminal alkynes with 1-bromoalkynes. Till date, these two methods constitute the most widely used procedures in the field of butadiyne and polyyne natural product synthesis and several reviews collate this vast array of chemistry[3–7] (**Figure 2**).

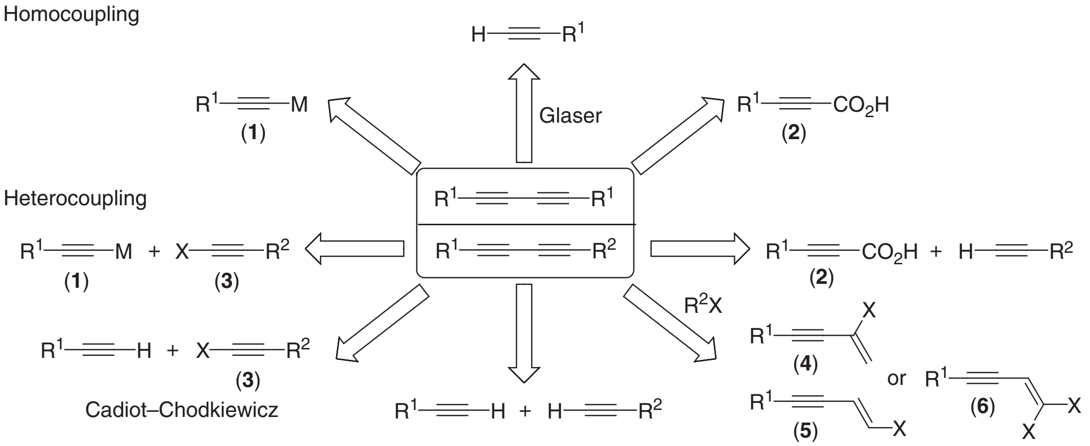


Figure 2 Strategies for the synthesis of symmetrical and unsymmetrical 1,3-diynes.

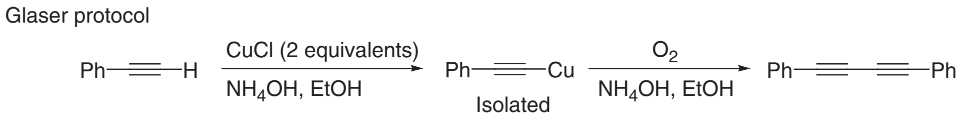
In the past 20 years, a broad range of research efforts has been conducted for constructing symmetrically and unsymmetrically 1,4-disubstituted-1,3-diyne derivatives.[4,5] These strategies include (1) oxidative homocoupling reactions of organometallic acetylides (**1**) or propiolic acid (**2**), (2) heterocoupling of organometallic acetylide derivatives (**1**) with a 1-haloalkyne (**3**), (3) decarboxylative heterocoupling of propiolic acid derivatives (**2**) with terminal alkynes, and (4) oxidative heterocoupling of two different terminal alkynes with a high loading of one alkyne partner. These protocols are less widely used than the classical processes (i.e., Glaser or Eglinton and Cadiot–Chodkiewicz), but nevertheless they have led to some significant applications. Alternative protocols to homo- and cross-coupling reactions between *sp*-carbon centers of alkyne derivatives are elimination reactions of haloenynes (4) and (5), or *gem*-dihaloenynes (6).

3.10.2 Oxidative Coupling Reactions of Terminal Alkynes

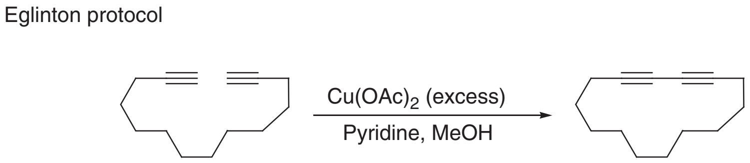
3.10.2.1 Homocoupling of Terminal Alkynes

3.10.2.1.1 Copper catalysis

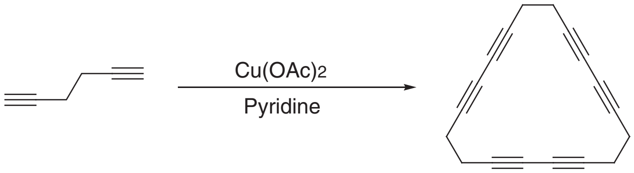
The oxidative dimerization of terminal alkynes, known as the Glaser coupling,[2] was discovered in 1869. It is involved in the original procedure the oxidative formation of 1,4-diphenyl-1,3-butadiyne from copper(I) phenylacetylide under air in an ethanolic ammonia solution (**Scheme 1**). Later, extensive modifications to improve the disadvantage of the original protocol have been made with respect to the amount and type of oxidizing agent (e.g., hydrogen peroxide, potassium permanganate, potassium ferrocyanide, iodine, or cupric salts).[7] However, this reaction failed to see broad application because of the apparent need to isolate the potentially explosive copper(I) acetylide before oxidation. Subsequent to Glaser's discovery of the homocoupling of copper(I) phenylacetylide, in 1957 Eglinton and Galbraith[8] successfully improved the acetylenic coupling reaction by using stoichiometric amounts (or excess) of copper(II) acetate in methanolic pyridine instead of ammoniacal cuprous salts (equation 1). In contrast to Glaser's protocol, the conditions developed by Eglinton made the process homogeneous and faster, although both methods were, however, not fully catalytic. Pure pyridine can be used as the coordinating solvent, or in the presence of methanol as the cosolvent to prevent precipitation of the copper(I) derivatives formed in the course of the reaction. Given that it is easily adapted to high-dilution conditions, the Eglinton's protocol ($Cu(OAc)_2$ and pyridine) proved to be an effective procedure in intramolecular oxidative dimerization processes and was the method of choice for the construction of a variety of macrocyclic diynes (C_{12}–C_{50}) (equations 1 and 2).[5,7,9,10]



Scheme 1

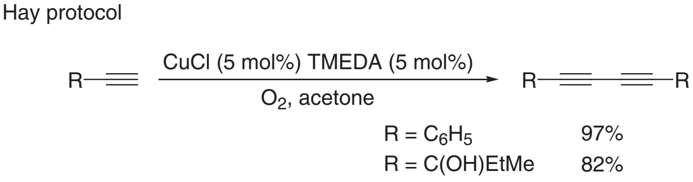


(1)



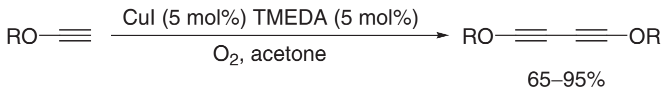
(2)

In 1960, an important modification was reported by Hay,[11] who achieved oxidative acetylenic homocouplings with O_2 in the presence of catalytic amounts of CuCl in pyridine as the coordinating solvent. Further works with respect to the nature of the amine demonstrated that the tetramethylethylenediamine (TMEDA)–CuCl complex[11] (equation 3) is by far the most effective catalyst for the oxidative coupling of 1-alkynes, allowing the reaction to occur considerably fast with high yields in virtually any organic solvent.



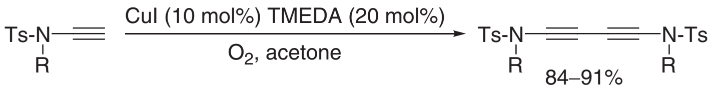
(3)

In the case of alkoxyalkyne (equation 4)[12] or tosyl ynamide homocouplings (equation 5),[13] the TMEDA–CuI complex proved to be a more effective catalyst than TMEDA–CuCl due to its improved solubility in acetone. Since then, the Glaser reaction and its modifications have widely been used to synthesize various symmetrical diacetylenes and diacetylene-containing polymers, as well as macrocycles.[7] Comprehensive reviews of the Glaser reaction scope, techniques, and limitations have been published.[4–7]



(4)

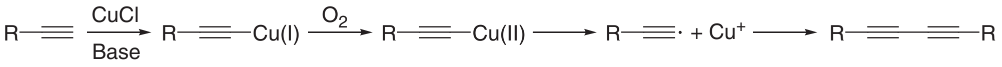
R = n-$C_{10}H_{21}$ (78%), c-C_6H_{11} (95%), t-Bu (77%), 2,6-dimethylphenyl (65%), L-menthyl (76%), 1-adamantyl (85%)



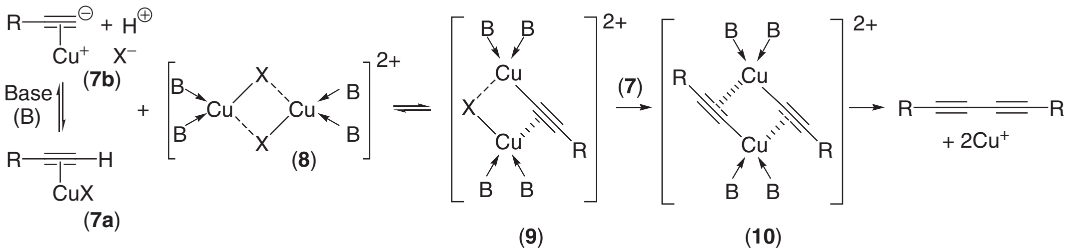
(5)

R = n-C_3H_7 (100%), allyl (86%), Bn (91%), 4-MeC_6H_4 (84%)

The basic mechanism of the Glaser's coupling invoked the formation of a copper phenylacetylide as the species that undergoes subsequent oxidative dimerization to give diphenylacetylene and Cu_2O.[7] Subsequent studies postulated the formation of acetylenic radicals that would then recombine to provide the corresponding 1,3-diynes (Scheme 2).[7] This radical mechanism was further discarded, and Bohlmann[14] proposed acetylene activation by π-complex (**7a**) formation, which would activate the alkyne toward deprotonation to form **7b**. Copper–acetylene π-complex (**7a**) or (**7b**) and copper(II) complex (**8**) are in equilibrium with dinuclear copper(II)–acetylide complex (**9**). Subsequent dimerization to **10** is followed by collapse to 1,3-diynes (Scheme 3). A review summarizing mechanistic investigations of the oxidative couplings has been published by Diederich,[4] who concluded that Bohlmann's mechanism is still most reasonable and most consistent with the experimental data.

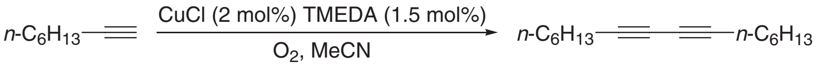


Scheme 2



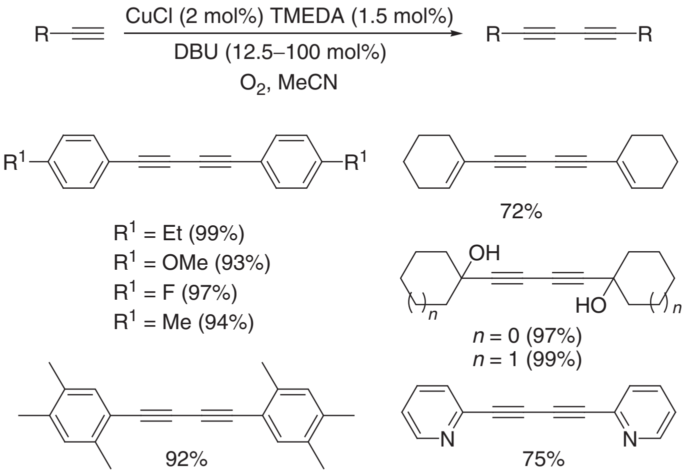
Scheme 3

Although the Cu-catalyzed oxidative coupling of arylacetylenes has wide scope, it is less successful for less acidic terminal alkynes, such as alkyl- or silyl-alkynes. In the last decade, a number of improvements of the Glaser, Eglinton, and Hay coupling reactions have emerged. It has been shown that the homocoupling reaction rate can be accelerated by adding 1,8-diazabicyclo[5.4.0]undec-7ene (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base.[5,15] Accordingly, it was possible to couple efficiently (hetero)aromatic acetylenes (Scheme 4) as well as weakly acidic aliphatic terminal alkynes (equation 6). Coupling was also achieved using Et_3N as the base and air as an oxidant at ambient temperature (equation 7).[16] Under these conditions, 1-hexyne, 1-decyne, and ethynylcyclopropane were converted into the corresponding 1,4-dialkyl-1,3-diynes in good to excellent yields. The catalytic system based on CuCl and piperidine has also been shown to display high catalytic activity for the oxidative homocoupling reactions of terminal alkynes in toluene leading to 1,3-diynes in high yields (equation 8).[17]



(6)

DBU (100 mol%)	55%
DABCO (100 mol%)	71%



Scheme 4

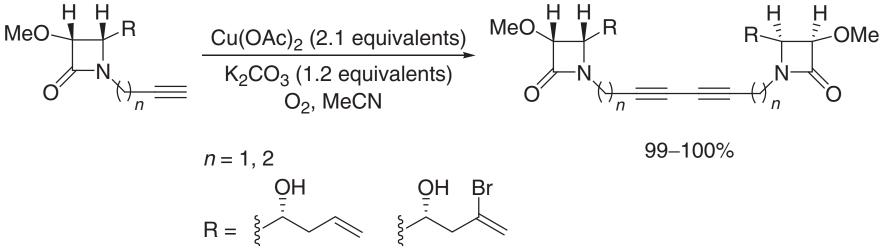
$$\mathrm{R{-}{\equiv}} \xrightarrow[\text{Et}_3\text{N (3 equivalents), acetone, air, 20 °C}]{\text{CuCl (5 mol\%) TMEDA (10 mol\%)}} \underset{\text{78–98\%}}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{7}$$

R = n-C_6H_{13} (80%), n-C_8H_{17} (92%), cyclopropyl (78%), $HO(Me)_2C$ (91%),
4-MeC_6H_4 (95%), 4-FC_6H_4 (98%), 2-thienyl (89%), 2-pyridyl (91%)

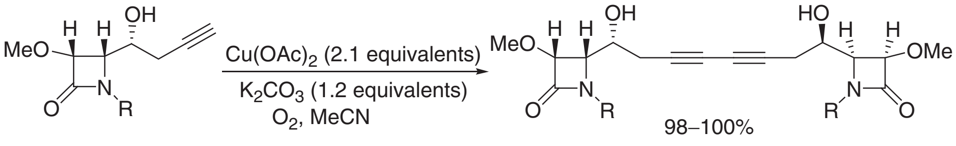
$$\mathrm{R{-}{\equiv}} \xrightarrow[\text{Toluene, air, 60 °C}]{\text{CuCl (2 mol\%) piperidine (10 mol\%)}} \underset{\text{77–96\%}}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{8}$$

R = n-C_6H_{13} (94%), $Cl(CH_2)_3$ (90%), $CN(CH_2)_3$ (87%), $HO(Me)_2C$ (77%),
4-MeC_6H_4 (89%), 2-MeC_6H_4 (88%), 2-$CF_3C_6H_4$ (94%), 2-thienyl (92%)

Copper(II) acetate in combination with a mineral base such as K_2CO_3 (instead of amine reagents as base) in acetonitrile was proven to be an extremely effective system for promoting the homocoupling of various (β-lactam)acetylenes in high yields (equations 9 and 10).[18] This protocol requires the use of stoichiometric amounts in copper(II), whereas the Hay-type coupling reactions (equations 3–5) are catalytic with copper(I).



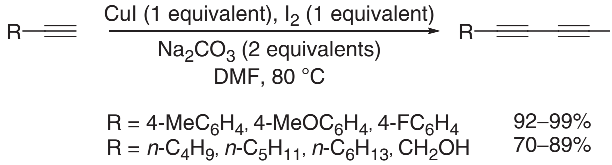
(9)



(10)

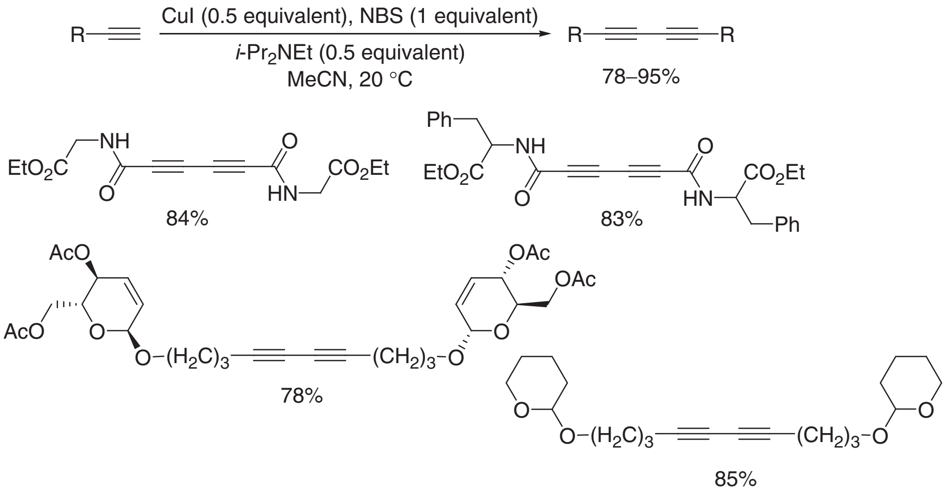
R = PMP, 2-bromoallyl, 2-bromobenzyl

In their investigations of the oxidative dimerization of aliphatic and aromatic alkynes, Jia and coworkers[19] found that the use of stoichiometric amounts of CuI in combination with iodine as the oxidant at 80 °C leads to the homocoupling product in good to excellent yields in the absence of O_2 (equation 11).



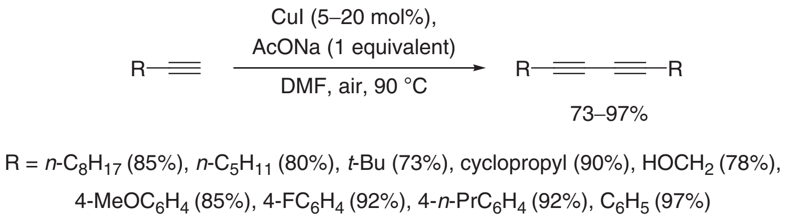
(11)

Glaser-type coupling reaction under CuI/*N*-bromosuccinimide (NBS)/*i*-Pr_2NEt system is also a useful procedure for aromatic and aliphatic terminal alkynes, including those having a sugar and amino acid building blocks. The characteristic feature of this reaction is its high tolerance for various functional groups (e.g., amides, esters, ethers, and hydroxyl groups), in addition to protecting groups such as acid-sensitive tetrahydropyranyl (THP), alkali-sensitive acetyl, and TBDMS (Scheme 5).[20] In this protocol, NBS does not act as an oxidizing agent and the authors proposed a plausible route involving the formation of 1-haloalkyne intermediate that could then react with copper acetylide species formed in the course of the reaction (Cadiot–Chodkiewicz-type reaction; cf. Section 3.10.3).

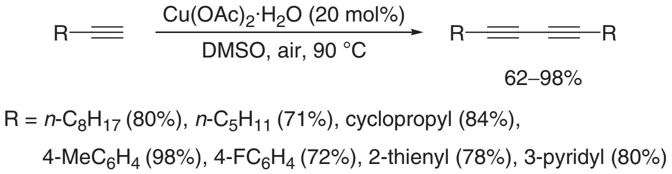


Scheme 5

Recently, variations in which homocoupling of terminal alkynes can be carried out using catalytic amounts of CuI in the presence of AcONa (equation 12)[21] and CuCl[22] or $Cu(OAc)_2$[23] (equation 13) as the catalyst without any other additives were reported. In all cases, the yields were good to excellent.



(12)

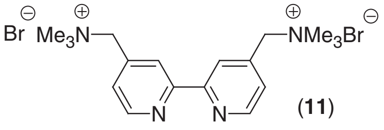


(13)

Homocoupling of terminal alkynes is usually achieved in organic solvents, such as MeCN, *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), and toluene. In recent years, with the development of environmentally benign synthesis methods and sustainable technologies, there have been an increasing number of attempts by chemists to search for an environmentally friendly alternative reaction medium. It was shown that Glaser coupling reactions can be carried out in water in the presence of I_2 as the oxidant and $CuSO_4 \cdot 5H_2O$/cationic 2,2′-bipyridyl (**11**) as the catalyst system at 120 °C (equation 14).[24] The reaction of aromatic alkynes with both electron-donating and electron-withdrawing groups gave their corresponding 1,3-diynes in good yields. To achieve successfully homocoupling of aliphatic acetylenes, it was necessary to add tetra-*n*-butylammonium bromide as the additive (equation 14).

Cu-catalyzed Glaser-type coupling reaction with Solkane® 365mfc ($CF_3CH_2CF_2CH_3$) as the medium was also reported to proceed successfully with both aliphatic and aromatic alkynes (equation 15).[25] Solkane® 365 is a hydrofluorocarbon commercially available developed as an environmentally friendly solvent.

Reaction in supercritical carbon dioxide ($scCO_2$) has been examined using AcONa as the base and $CuCl_2$.[26] Control experiments revealed that the presence of MeOH increased the AcONa and $CuCl_2$ solubilities in $scCO_2$, thereby leading to large reaction rate enhancements (equation 16). Conjugated 1,3-diynes were obtained in high yields starting from various acetylenes, including less acidic terminal alkynes, such as alkyl- or silyl-alkynes (Table 1).



(**11**)

$$\mathrm{R{-}{\equiv}} \xrightarrow[\mathrm{I_2\ (25\ mol\%),\ H_2O,\ 120\ °C}]{\mathrm{CuSO_4{\cdot}5H_2O/(\mathbf{11})\ (5\ mol\%),\ AcOK}} \mathrm{R{-}{\equiv}{-}{\equiv}{-}R} \tag{14}$$

R = Aromatic 63–93%

R = Aliphatic (+ $n\text{-}Bu_4NBr$) 50–73%

$$\mathrm{R{-}{\equiv}} \xrightarrow[\mathrm{CF_3CH_2CF_2CH_3,\ O_2,\ 20\ °C}]{\mathrm{CuCl\ (10\ mol\%),\ TMEDA\ (10\ mol\%)}} \underset{82\text{–}96\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{15}$$

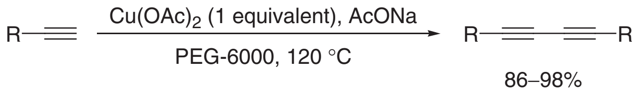
R = Aromatic, aliphatic, heteroaryl, fluoroaryl, phthalocyanine

$$\mathrm{R{-}{\equiv}} \xrightarrow[\mathrm{MeOH,\ scCO_2}]{\mathrm{CuCl_2\ (2\ equivalents),\ AcONa\ (2\ equivalents)}} \underset{71\text{–}100\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{16}$$

Table 1 Homocoupling of terminal alkynes in $scCO_2$ (equation 16)

R	*Yield (%)*
$n\text{-}C_4H_9$	92
$n\text{-}C_5H_{11}$	95
$n\text{-}C_6H_{13}$	92
t-Bu	97
Me_3Si	80
$ClCH_2$	90
$HOCH_2$	71
$AcOCH_2$	93
EtO_2C	90
$4\text{-}MeC_6H_4$	90
$4\text{-}MeOC_6H_4$	72
$4\text{-}FC_6H_4$	100

Polyethylene glycol (PEG) was also shown to be an environmentally benign reaction medium for the copper(II)-mediated Glaser homocoupling of terminal alkynes. Reactions were promoted by stoichiometric amounts of $Cu(OAc)_2$[27] in the presence of AcONa as the base at high temperature (equation 17). 1,4-Diaryl-1,3-diynes were easily separated by extraction, and the Cu–PEG system could be reused 5 times without significant loss of activity (R=Ph, yields=97–81%). Aliphatic alkynes also underwent homocoupling in greater than 95% yield (equation 17, Table 2).



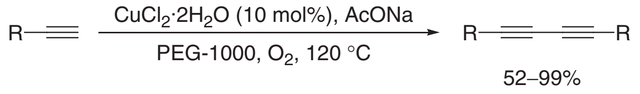
(17)

Table 2 Homocoupling of terminal alkynes in PEG (equations 17 and 18)

R	*Isolated yield (%)*	*Gas chromatographic yield (%)*
	Condition A	*Condition B*
C_6H_5	99	99
4-FC_6H_4	87	97
n-C_4H_9	96	52
n-C_6H_{13}	98	95

Condition A: $Cu(OAc)_2$ (1 equivalent), AcONa (1.5 equivalents), PEG-6000, 120 °C.
Condition B: $CuCl_2 \cdot 2H_2O$ (10 mol%), AcONa (1 equivalent), PEG-1000, O_2, 120 °C.

Recently with respect to copper(II) salt, a catalytic version was developed using $CuCl_2 \cdot 2H_2O$ in the presence of dioxygen (equation 18).[28] For alkyl-substituted alkynes, in comparison with the aryl counterparts, generally longer reaction times were required to obtain satisfactory results. All yields in this case were determined by gas chromatography (GC) (Table 2); isolated yields are preferable to GC yields to assess the practical utility of a given methodology.



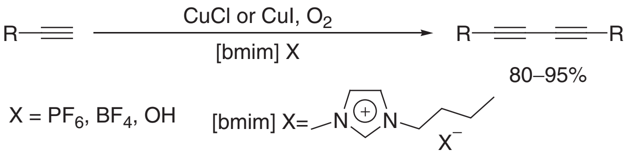
(18)

Among other variations on the Glaser homocoupling reactions is the use of ionic liquids that have shown enhanced reaction rates, improved yields, higher solubilities, and higher functional group compatibility. In addition, the use of this hydrophobic medium facilitated the copper catalyst recovery and can be recycled in subsequent runs. Several ionic liquids were successfully used including [bmim]PF_6, [bmim]BF_4, and [bmim]OH (Table 3).[5,29] In the latter case, [bmim]OH acts as both the solvent and the base providing 1,3-diynes in good to excellent yields (equation 19).

Table 3 Homocoupling of terminal alkynes in ionic liquids (equation 19)

R	*Yield (%)*	
	Condition A	*Condition B*
Ph	95	98
n-C_4H_9	95	85
CH_2OH	89	80
CH_2OMe	89	80

Condition A: CuCl (0.2 mol%), TMEDA (0.2 mol%) [bmim]PF_6, O_2.
Condition B: CuI, [bmim]OH, O_2.



(19)

In 2010, an environmentally friendly and solvent-free procedure that allows the homocoupling reactions of 1-alkynes was reported.[30] It involves the use of catalytic amounts of $CuCl_2$ and triethylamine at 60 °C in air (equation 20). The $CuCl_2$ catalyst can be recovered and reused 5 times with only a moderate reduction in catalytic activity (R=Ph, yields=96–85%) simply by filtration, acidification, and drying. This solvent-free homocoupling reaction worked well with (hetero)aromatic acetylenes, but the yields were lower with aliphatic substrates, including alkynes based on propargylic alcohols (Table 4).

$$\mathrm{R{-}{\equiv}} \xrightarrow[\text{Neat, 60 °C, air}]{\mathrm{CuCl_2}\text{ (3 mol\%), }\mathrm{Et_3N}\text{ (3 mol\%)}} \underset{40\text{–}99\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{20}$$

Table 4 Homocoupling of terminal alkynes under solvent-free procedure (equation 20)

R	*Yield (%)*
4-$MeOC_6H_4$	99
4-FC_6H_4	80
2-ClC_6H_4	85
3-$NH_2C_6H_4$	50
3-Thienyl	90
2-Pyridyl	70
Ferrocenyl	99
$BrCH_2$	60
n-C_4H_9	75
$HOCH_2$	45

In spite of the wide array of existing Glaser coupling methods under homogeneous solutions, efforts to completely eliminate the need for organic solvents by carrying out the reaction on the surface of solid supports have been investigated. Recently, a review summarizing this field of chemistry has been published.[31] Solvent-free procedure under microwave irradiation was developed using KF/Al_2O_3 and excess of $CuCl_2$ (3.7 equivalents).[31] Later, this methodology was notably improved by grinding in a mortar a mixture of the terminal acetylene with KF/Al_2O_3 in the presence of catalytic amounts of $Cu(OAc)_2$ (20 mol%) and morpholine at room temperature (equation 21).[32] Alkynes based on propargylic ethers and amines gave the corresponding diynes in moderate to excellent yields. A Cu-catalyzed homocoupling of terminal alkynes under solvent-free conditions employing a vibration ball mill technology has been developed.[33] The use of CuI (5 mol%) in combination with 60 wt.% KF and Al_2O_3 (γ, neutral) as the base effectively catalyzed homocoupling of various terminal alkynes with (hetero)aromatic, as well as aliphatic substituents, whereas lower loadings of these reagents (32 wt.% KF) required the presence of DABCO as an additional base (equation 22).

$$\mathrm{R{-}{\equiv}} \xrightarrow[\substack{\text{Morpholine (1.2 equivalents)}\\ \mathrm{KF/Al_2O_3}\text{, neat, r.t.}}]{\mathrm{Cu(OAc)_2}\text{ (20 mol\%)}} \underset{60\text{–}96\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{21}$$

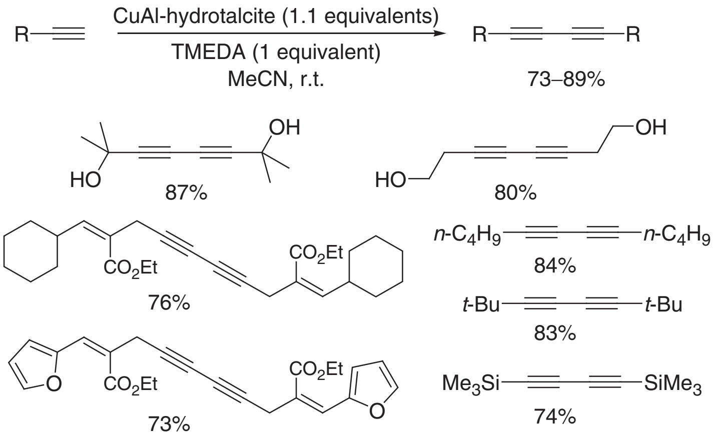
R = C_6H_5 (96%), Bn (90%), $PhOCH_2$ (65%), 1-naphthyl-OCH_2 (60%),
Bn_2NCH_2 (90%), $PhEtNCH_2$ (93%)

$$\mathrm{R{-}{\equiv}} \xrightarrow[\substack{\text{(with or without DABCO)}\\ \text{ball mill zirconia}\\ \text{10 min, 30 Hz}}]{\text{CuI (5 mol\%), }\mathrm{KF\text{-}Al_2O_3}} \underset{68\text{–}99\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{22}$$

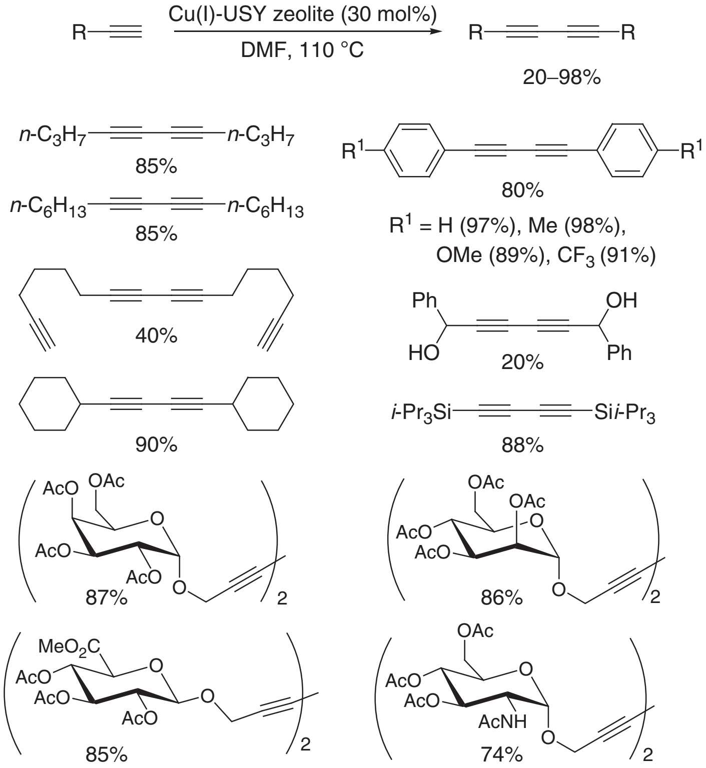
R = C_6H_5, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$,
4-FC_6H_4, 3-pyridyl, *n*-C_8H_{17}, *n*-$C_{10}H_{21}$

In recent years, several other copper-based heterogeneous catalytic systems for the homocoupling of terminal alkynes have been reported. CuAl–hydrotalcite[34] exhibited excellent recyclability (up to nine cycle) in acetonitrile and air at 25 °C, although stoichiometric amounts of TMEDA and catalyst were required. Good yields of 1,3-diynes were obtained in all cases, including substrates containing hydroxyl, silane, or conjugate ester functionalities (**Scheme 6**). Glaser coupling studies in the presence of copper(I)-modified zeolites[35] revealed that Cu(I)–ultrastable zeolite Y (USY) (30 mol%) was the most efficient catalyst, and the reaction efficiency is directly correlated with the pore size of the zeolite as well as with the Si/Al ratio. The characteristic feature of this reaction is its ability to occur in the absence of base and was successfully achieved, not only for common substrates but also for some carbohydrates having a propargyl moiety (**Scheme 7**).

In the reported heterogeneous system with supported copper hydroxide on titanium oxide, which showed good catalytic activity ($Cu(OH)_x/TiO_2$, 5 mol% Cu)[36] in toluene at 100 °C, the presence of a base is not necessary. Although various hydrocarbon-based acetylenes, including less acidic terminal alkynes (e.g., alkyl- or silyl-alkynes), could be converted into the corresponding diynes (equation 23), the $Cu(OH)_x/TiO_2$-catalyzed system possessed a serious problem; inactive copper(I) acetylide species were formed during the homocoupling, probably as a result of the slow reoxidation of copper(I) species. To overcome the



Scheme 6



Scheme 7

problem, a much more efficient catalyst was developed by changing TiO_2 by KMn_8O_{16}.[37] This manganese oxide-based octahedral molecular sieve acts as not only a support, but also an electron-transfer mediator (cocatalyst) for the reoxidation of the copper (I) species. As a result, $Cu(OH)_x/KMn_8O_{16}$ showed high catalytic activity (turn over number (TON)) = 666 and selectivity >99%) and could be reused at least 13 times without an appreciable loss of its high catalytic performance (R═Ph, yields = 98–90%); the oxidation state of copper species in $Cu(OH)_x/KMn_8O_{16}$ was 2^+, even after the thirteenth reuse. The scope of the reaction was very wide; various kinds of alkynes including aromatic, aliphatic, heteroaromatic, double-bond containing, and silylacetylene derivatives could be converted rapidly (10 min, toluene 100 °C) into the corresponding diynes in high yields (73–94%, equation 24).

Supported ionic liquid phase (SILP) technology has been established in the past 5 years as an innovative method to immobilize homogeneous transition metal complexes in catalysis. Recently, the SILP technology was applied for the synthesis of several catalysts by immobilization of (Cu(TMEDA)(OH))Cl in a nanometric film of an ionic liquid on various support materials.[38] The catalytic systems based on silica and 1-butyl-2,3-dimethylimidazolium triflate (bmmim(OTf)) successfully accomplished the homocoupling of several terminal alkynes at room temperature and could be reused at least 4 times with no significant loss of catalytic activity (equation 25).

$$\mathrm{R}{-}{\equiv} \xrightarrow[\mathrm{O_2,\ toluene,\ 100\ ^\circ C}]{\mathrm{Cu(OH)}_x/\mathrm{TiO_2\ (5\ mol\%)}} \underset{\text{80–99\%}}{\mathrm{R}{-}{\equiv}{-}{\equiv}{-}\mathrm{R}} \tag{23}$$

R = 4-MeC_6H_4 (86%), 2-MeC_6H_4 (99%), 4-FC_6H_4 (80%), 3-ClC_6H_4 (94%), *n*-C_4H_9 (95%), *n*-C_6H_{13} (88%), *n*-C_8H_{17} (99%), *n*-$C_{14}H_{29}$ (96%), *i*-Pr_3Si (95%)

$$\mathrm{R}{-}{\equiv} \xrightarrow[\mathrm{O_2,\ toluene,\ 100\ ^\circ C}]{\mathrm{Cu(OH)}_x/\mathrm{KMn_8O_{16}\ (2–10\ mol\%)}} \underset{\text{73–94\%}}{\mathrm{R}{-}{\equiv}{-}{\equiv}{-}\mathrm{R}} \tag{24}$$

R = 4-$MeOC_6H_4$ (94%), 4-$CF_3C_6H_4$ (73%), 4-FC_6H_4 (90%), 4-ClC_6H_4 (83%), 2-thienyl (80%), 1-naphthyl (92%), *n*-C_8H_{17} (75%), $Cl(CH_2)_4$ (83%), *i*-Pr_3Si (90%)

$$\mathrm{R}{-}{\equiv} \xrightarrow[\mathrm{Air,\ hexane\ or\ Et_2O,\ r.t.}]{\mathrm{Cu/silica/bmmim(OTf)\ (5\ mol\%)}} \underset{\text{75–94\%}}{\mathrm{R}{-}{\equiv}{-}{\equiv}{-}\mathrm{R}} \tag{25}$$

R = C_6H_5 (93%), 4-EtC_6H_4 (73%), 4-$CF_3C_6H_4$ (80%), *n*-C_6H_{13} (86%), Me_3Si (94%)

Copper(0) nanoparticles (CuNPs; 3.0±1.5 nm) were also found to promote homocoupling of terminal alkynes in refluxing tetrahydrofuran (THF), under a nitrogen atmosphere, in either the absence (400 mol% Cu) or the presence of Na_2CO_3 (50 mol% Cu), providing a wide range of diaryl- and dialkyl-substituted 1,3-diynes in moderate to high yields (65–90%, equation 26).[39] The enhanced reaction rate in the presence of the base allowing the use of only 0.5 equivalent of CuNPs was attributed to the deprotonation of the alkyne before the formation of alkynyl-CuNP species. Later, this CuNP-based methodology was upgraded using supported CuNPs.[40] Among various supported catalysts prepared, CuNPs/TiO_2 (~1.0±0.4 nm), which exhibited the best catalytic activity, was found to be much more efficient than other commercially available catalysts (e.g., Cu, Cu_2O, CuO, CuCl, and $CuCl_2$). Low catalyst loading (1 mol% Cu) effectively catalyzed the oxidative homocoupling of terminal alkynes in the presence of piperidine as the base in THF at 65 °C (equation 27). The process was equally effective but faster under solvent-free conditions (Table 5).

$$\mathrm{R}{-}{\equiv} \xrightarrow[\substack{\mathrm{CuNPs\ (50\ mol\%)\ +\ Na_2CO_3\ (1\ equivalent)} \\ \mathrm{THF,\ 65\ ^\circ C}}]{\substack{\mathrm{CuNPs\ (400\ mol\%)^*} \\ \mathrm{or}}} \underset{\text{65–90\%}}{\mathrm{R}{-}{\equiv}{-}{\equiv}{-}\mathrm{R}} \tag{26}$$

*R = C_6H_5 (90%), 4-$Me_2NC_6H_4$ (75%), 3,5-$(CF_3)_2C_6H_3$ (65%), $(CH_2)_2Ph$ (71%), *n*-C_4H_9 (74%), *n*-$C_{10}H_{21}$ (66%), $(CH_2)_2$*i*-Pr (65%), CH_2OTHP (85%), CH_2OH (68%)

$$\mathrm{R}{-}{\equiv} \xrightarrow[\substack{\mathrm{Piperidine\ (30\ mol\%)} \\ \mathrm{THF\ or\ neat,\ 65\ ^\circ C}}]{\mathrm{CuNPs/TiO_2\ (1\ mol\%)}} \underset{\text{60–96\% or 51–97\%}}{\mathrm{R}{-}{\equiv}{-}{\equiv}{-}\mathrm{R}} \tag{27}$$

Table 5 Homocoupling of terminal alkynes under CuNPS/TiO_2 (equation 27)

R	*Yield (%)*	
	THF	*Neat*
4-$MeOC_6H_4$	60	51
4-$CF_3C_6H_4$	75	93
2-$NH_2C_6H_4$	93	-
4-MeC_6H_4	90	94
2-Pyridyl	91	70
Cyclohexyl	92	93
$Cl(CH_2)_4$	70	78
$CN(CH_2)_4$	91	90
n-C_6H_{13}	92	93
$THPOCH_2$	90	68

Recently, it was shown that using a 3-(2-aminoethylamino)propyl-functionalized MCM-41-immobilized copper(I) complex (MCM-41–2 N-CuI, 1 mol%) as the catalyst and piperidine (10 mol%) as the base in air, the homocoupling of a variety of terminal alkynes proceeded in good to excellent yields.[41] This catalyst exhibited higher catalytic activity than CuI and can be recovered by simple filtration and reused at least 10 times without any decrease in activity (equation 28).

$$\mathrm{R{-}{\equiv}} \xrightarrow[\substack{\text{Piperidine (10 mol\%)} \\ \mathrm{CH_2Cl_2},\ \text{air, r.t.}}]{\text{MCM-41-2N-CuI (1 mol\%)}} \underset{78\text{–}98\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{28}$$

R = 4-MeC_6H_4 (91%), 3-MeC_6H_4 (93%), 4-FC_6H_4 (96%), 3-FC_6H_4 (98%), 2-thienyl (87%), *n*-C_4H_9 (83%), *n*-C_6H_{13} (81%), 1-hydroxycyclohexyl (78%), Me_3Si (85%), MeO_2CCH_2 (89%)

Based on the mechanism proposed by Bohlmann involving the formation of the alkynyldicopper(II) intermediate ($Cu_2(\mu\text{-}C{\equiv}CR)_2$), Mizuno[42] developed a catalyst with a dicopper(II) core (equation 29). The monomeric dicopper-substituted silicotungstate ($TBA_4(\gamma\text{-}H_2SiW_{10}O_{36}Cu_2(\mu\text{-}1,1\text{-}N_3)_2)$ (**12**)) was found to be an effective homogeneous catalyst for the oxidative homocoupling of various kinds of structurally diverse terminal alkynes, including aliphatic, aromatic, and heteroaromatic derivatives (Table 6). The coupling reaction required only 2.2 mol% of the copper complex (**12**) in benzonitrile and dioxygen at 100 °C. The catalyst (**12**) reached a high value (TON = 468 in a 20-mmol-scale reaction of $PhC{\equiv}CH$) in comparison with other catalysts, and could be recovered (precipitation method) and recycled at least 4 times without significant loss of catalytic activity. Kinetic studies conducted to gain an insight into the reaction mechanism allowed the authors to find that the dicopper core in complex (**12**) plays an important role in the present oxidative alkyne homocoupling and suggested that the reaction possibly proceeds by initial ligand exchange between the azido groups in **12** and the alkynyl groups to form the alkynylcopper(II) species ($Cu_2(\mu\text{-}C{\equiv}CR)_2$).

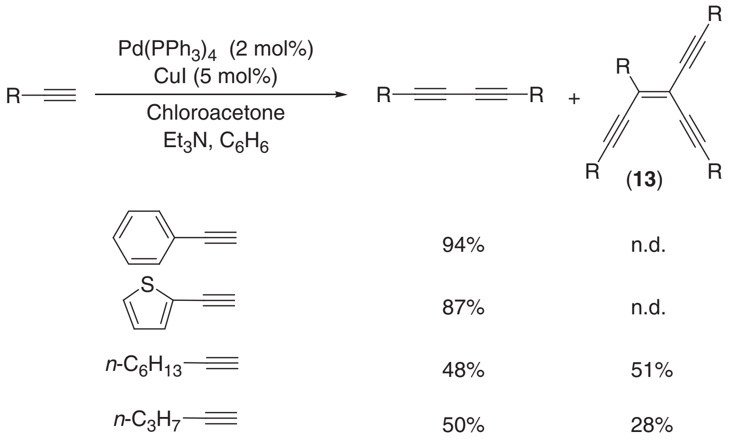
$$\mathrm{R{-}{\equiv}} \xrightarrow[\mathrm{PhCN,\ O_2,\ 100\ ^\circ C}]{\mathrm{TBA_4(\gamma\text{-}H_2SiW_{10}O_{36}Cu_2(\mu\text{-}1,1\text{-}N_3)_2)}\ (\mathbf{12})\ \text{(2.2 mol\%)}} \underset{82\text{–}99\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{29}$$

Table 6 Homocoupling of 1-alkynes using silicotungstate complex (**12**) (equation 29)

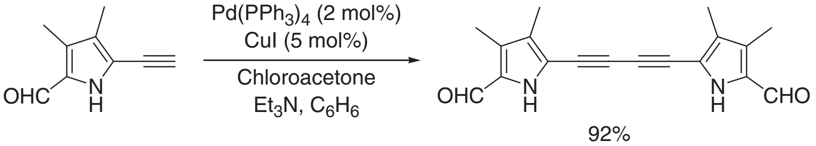
R	*Yield (%)*
4-$MeOC_6H_4$	82
4-FC_6H_4	89
3-ClC_6H_4	93
3-MeC_6H_4	93
4-MeC_6H_4	97
3-Pyridyl	82
n-C_6H_{13}	86
n-C_8H_{17}	89
$C(OH)Me_2$	99
1-Hydroxycyclohexyl	82

3.10.2.1.2 Palladium–copper catalysis

In recent years, the combination of mixed catalysts of copper salts with palladium species and phosphine ligands has also been utilized for the homocoupling of terminal alkynes. A relevant suggestion in the pioneering works of Sonogashira[43] in 1975 was the formation of symmetrical 1,3-diynes via dialkynylpalladium species, in the catalytic cycle of couplings of terminal alkynes with aryl- or vinyl halides. Since then, this Pd/Cu-catalyzed oxidative homocoupling reaction has been proved to be one of the extremely powerful tools to construct symmetrical 1,3-diynes from terminal alkynes because of its efficiency and wide range of substrate applicability under mild conditions. Rossi et al.[44a] developed a protocol for the synthesis of 1,4-disubstituted-1,3-diynes from 1-alkynes using $Pd(PPh_3)_4$/CuI as the catalyst system and triethylamine in the presence of chloroacetone as an oxidant (Scheme 8). The reaction was effective for coupling of aromatic alkynes, but aliphatic alkynes furnished the corresponding 1,3-diynes together with oligomers (**13**) (Scheme 8). An elegant application of this protocol is the synthesis of diacetylenic dipyrroledialdehyde reported by Kim et al.[44b] (equation 30). Although the reaction required the use of both the palladium complex and the copper salts as catalysts, this method may represent a good alternative, in nonpolar organic solution, to the Glaser reaction.

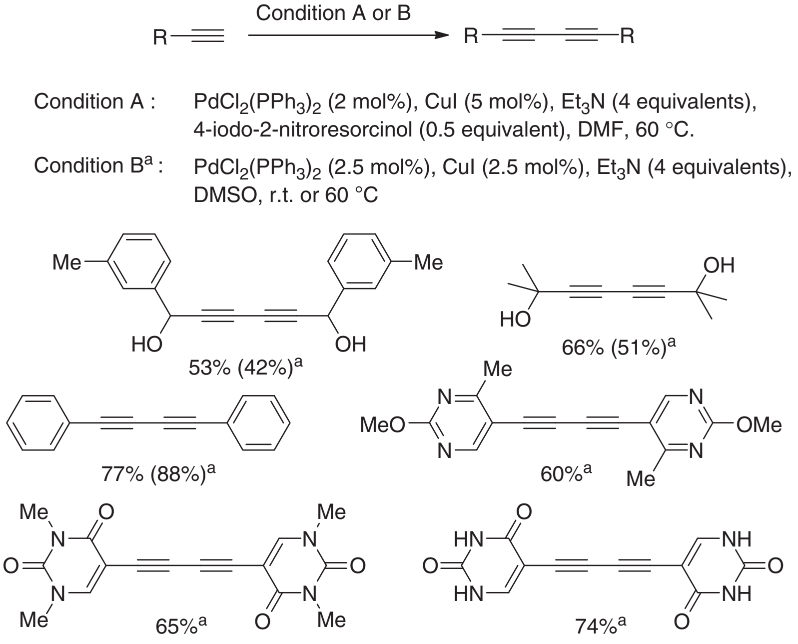


Scheme 8



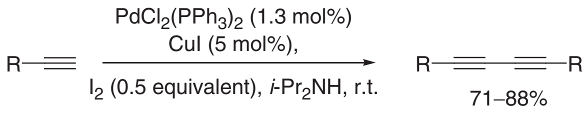
(30)

Focused research to improve this Pd/Cu-catalyzed procedure has led to interesting variations of the original method by using different oxidizing agents. Kundu et al. described the dimerization of alkynes for the synthesis of 1,3-diynes using Sonogashira's catalysts ($PdCl_2(PPh_3)_2$/CuI) in the presence of 4-iodo-2-nitroresorcinol (condition A) or DMSO (condition B) as oxidants (Scheme 9).[45a] Studies with respect to the roles of the catalysts revealed that palladium is the active catalytic species, because its absence suppressed the formation of 1,3-diynes, whereas in the absence of CuI the reaction proceeds, albeit in lower yield (32% instead of 77%, R=Ph). Of the two conditions developed by the authors, condition A was more effective for coupling of alkynes based on propargylic alcohols, whereas condition B has the advantage to be suitable for pyrimidine or uracil-substituted acetylenic, owing to the excellent solubility of these compounds in DMSO (Scheme 9).



Scheme 9 *Note*: a, in Scheme 9 refers to yield isolated when the reaction was performed under condition B.

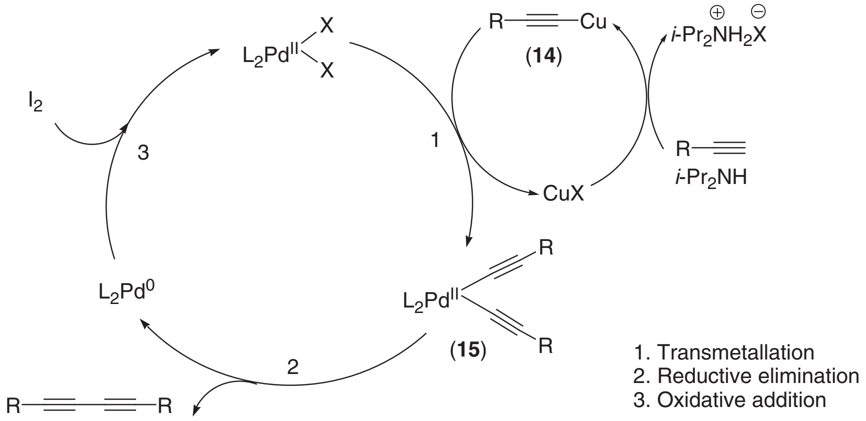
Later, Liu and Burton[45b] have demonstrated that using I_2 as the oxidant in the presence of the same catalyst system proved superior, and the homocoupling reaction successfully proceeds particularly with aliphatic alkynes (equation 31), which are well known to be sluggish in undergoing dimerization due to the weaker acidity of the acetylenic proton.



(31)

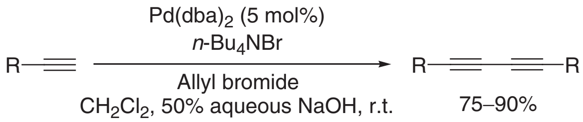
R = C_6H_5 (88%), n-C_4H_9 (86%), n-C_6H_{13} (84%), n-C_7H_{15} (84%), n-C_8H_{17} (88%), n-C_9H_{19} (71%), n-$C_{10}H_{21}$ (77%)

The proposed mechanism for this reaction is shown in Scheme 10. The alkynylcopper intermediate (**14**) formed from the reaction of a terminal alkyne and CuI in the presence of diisopropylamine undergoes double transmetalation with $L_2Pd(II)X_2$ to furnish dialkynylpalladium species (**15**). Further reductive elimination leads to the homocoupling product and Pd(0) species, precursor to Pd(II) complex through an oxidative addition step in the presence of I_2.



Scheme 10

Besides iodine or chloroacetone as oxidizing reagents, several other oxidizing reagents[46] were used to efficiently achieve the oxidative addition step to complete the catalytic cycle (Scheme 10). *p*-Chloranil was found to allow exclusively oxidative dimerization of aromatic alkynes,[5] whereas in the presence of allyl bromide the reaction was useful for the synthesis of 1,4-dialkyl-1,3-diynes under phase-transfer catalysis. Of note that, in the latter case, homocoupling occurred in the absence of copper salts (equation 32).[47]

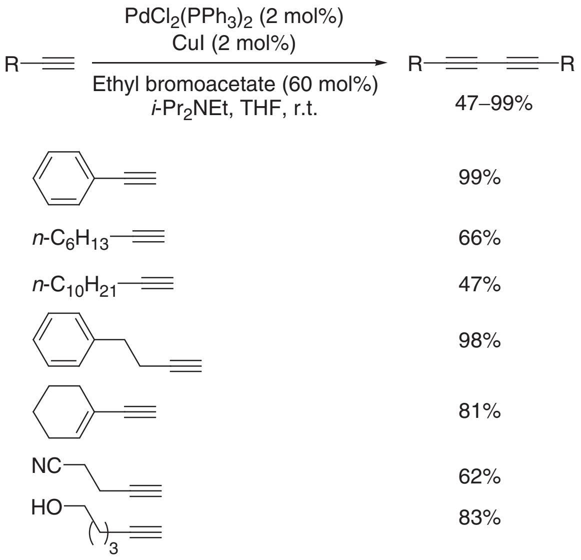


(32)

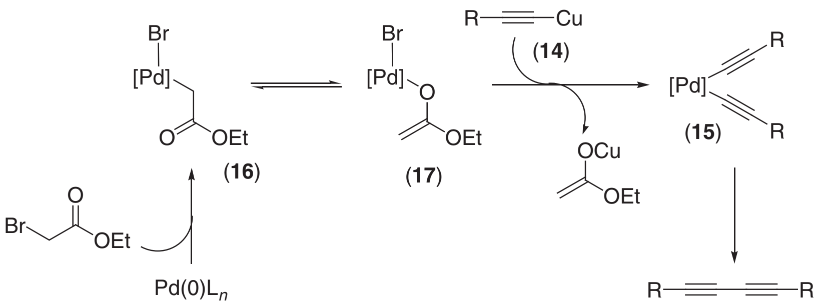
R = C_2H_5, n-C_3H_7, n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}

Zhang and coworkers performed the homocoupling of terminal alkynes in THF at room temperature using ethyl bromoacetate (Scheme 11), which initiates the reaction through the oxidative addition of Pd(0) species, forming PdBr(enolate) intermediate (**16**). Isomerization of **16** generates the oxygen-bound palladium enolate bromide (**17**), which undergoes a double transmetalation with alkynyl copper reagent (**14**) to generate **15**, precursor of 1,3-diynes via a reductive elimination step (Scheme 12).[48] This method represents an attractive route to synthesize symmetrical 1,3-diynes because of its mildness and efficiency. Many aromatic and aliphatic alkynes were coupled, including those containing alkenyl, hydroxy, or nitrile functionalities (Scheme 11).

As a general and useful oxidizing reagent, (diacetoxyiodo)benzene (DIB) was also found to achieve homocoupling of terminal alkynes when carrying out the reaction in the presence of $PdCl_2$ and CuI as catalysts (equation 33).[49] In this protocols no phosphine ligands were required and the authors suggested that DIB regenerates the Pd(II) catalyst by oxidizing Pd(0) species as outlined in Scheme 13. A variant of this procedure was reported in the absence of a palladium catalyst (equation 34),[50] but the reaction required stoichiometric amounts of copper iodide.



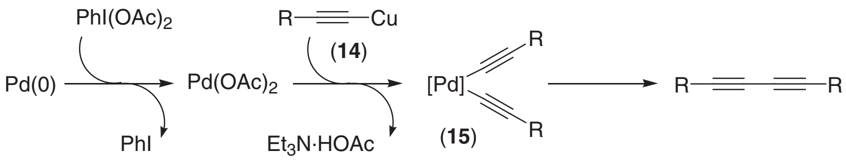
Scheme 11



Scheme 12

$$\mathrm{R{-}{\equiv}} \xrightarrow[\substack{\mathrm{PhI(OAc)_2}\ (60\ \mathrm{mol\%}) \\ \mathrm{Et_3N,\ THF,\ r.t.}}]{\substack{\mathrm{PdCl_2}\ (2\ \mathrm{mol\%}) \\ \mathrm{CuI}\ (2\ \mathrm{mol\%})}} \underset{62\text{–}90\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{33}$$

R = C_6H_5, 4-MeC_6H_4, *n*-C_4H_9, *n*-C_6H_{13}, $Me_2C(OH)$

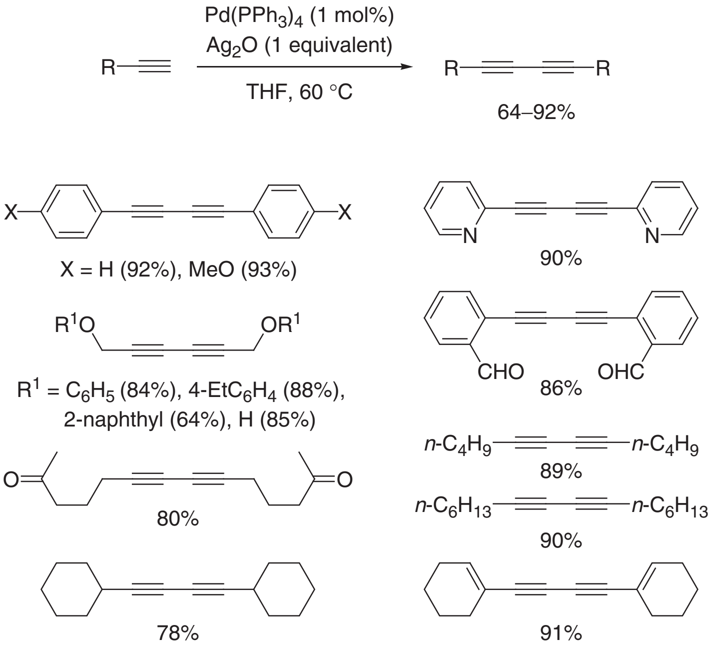


Scheme 13

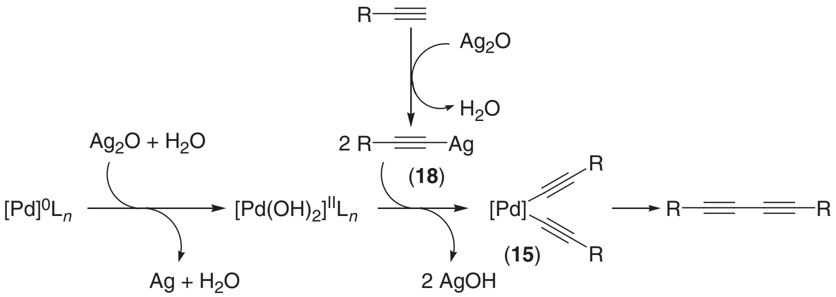
$$\mathrm{R{-}{\equiv}} \xrightarrow[\substack{\mathrm{PhI(OAc)_2}\ (60\ \mathrm{mol\%}) \\ \mathrm{Et_3N,\ MeCN,\ r.t.}}]{\mathrm{CuI}\ (1\ \text{equivalent})} \underset{70\text{–}90\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{34}$$

R = C_6H_5, 4-MeC_6H_4, 2-$CF_3C_6H_4$, *n*-C_4H_9, *n*-C_8H_{17}

Recently, on the basis of literature works, Zhao and coworkers[51] described an amine and copper salt-free protocol for terminal alkyne homocoupling. The reaction was carried out with only 1 mol% of palladium complex in the presence of silver(I) oxide in THF at 60 °C and was successfully accomplished with a variety of terminal aromatic and aliphatic alkynes containing hydroxy, ketone, and aldehyde functionalities (**Scheme 14**). In this simple and practical protocol, Ag_2O was suggested to act both as an activator, in the generation of silver acetylide (**18**), and as a reoxidizing agent for the Pd(0) species to Pd(II), as was demonstrated by means of X-ray photoelectron spectroscopy analysis (**Scheme 15**).



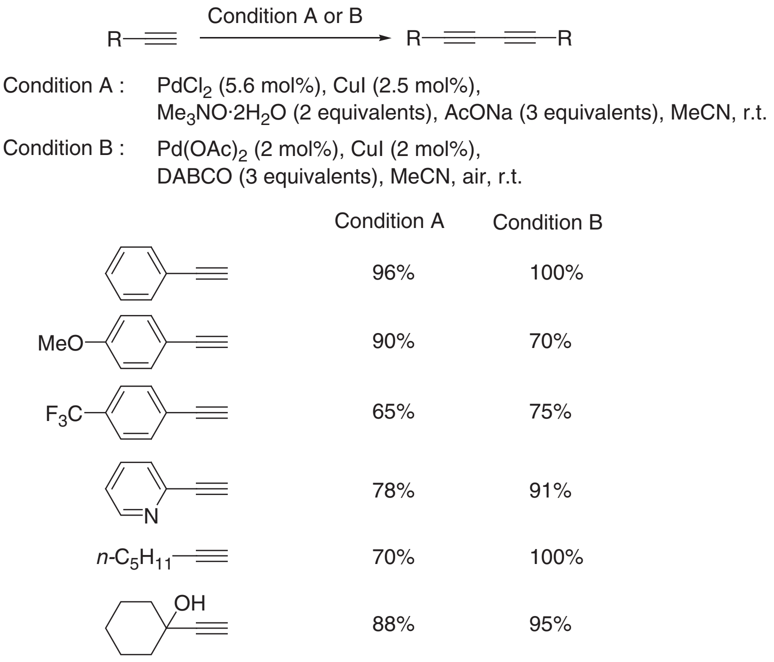
Scheme 14



Scheme 15

In the presence of Me_3NO as the oxidant, Li et al. reported an amine- and phosphine-free protocol for the homocoupling of terminal alkynes using $PdCl_2$/CuI as the catalyst system and AcONa as the base.[52a] The condition (condition A, **Scheme 16**), which tolerates the presence of several different functional groups, afforded the corresponding 1,3-diynes in moderate to good yields (**Scheme 16**). Molecular oxygen or air has also been used as an oxidant for the Pd/Cu mixed systems according to the concept of green chemistry. The same research group has developed a second protocol (condition B) for the homocoupling reaction where the trimethylamine oxide (Me_3NO) was substituted by air as an oxidizing agent. In the presence $Pd(OAc)_2$/CuI as catalysts and DABCO under aerobic conditions, several 1,3 diynes were obtained in moderate to excellent yields (**Scheme 16**), whereas low yields were obtained without either $Pd(OAc)_2$ or CuI. The catalyst loadings could be decreased to 0.0001 mol%, and for phenylacetylene an excellent yield could still be obtained (94%, TON = 940 000).

In contrast to their early work,[53a] Fairlamb et al. have shown that the presence of stoichiometric quantity of air (or added oxidant such as I_2) is essential for alkyne dimerization[53b] when using Sonogashira's catalysts ($PdCl_2(PPh_3)_2$/CuI) in a MeCN/Et_3N solvent mixture, with additional Ph_3P at room temperature (equation 35). The role of phosphine excess is to thwart the enyne



Condition A : $PdCl_2$ (5.6 mol%), CuI (2.5 mol%), $Me_3NO{\cdot}2H_2O$ (2 equivalents), AcONa (3 equivalents), MeCN, r.t.

Condition B : $Pd(OAc)_2$ (2 mol%), CuI (2 mol%), DABCO (3 equivalents), MeCN, air, r.t.

Condition A	Condition B
96%	100%
90%	70%
65%	75%
78%	91%
70%	100%
88%	95%

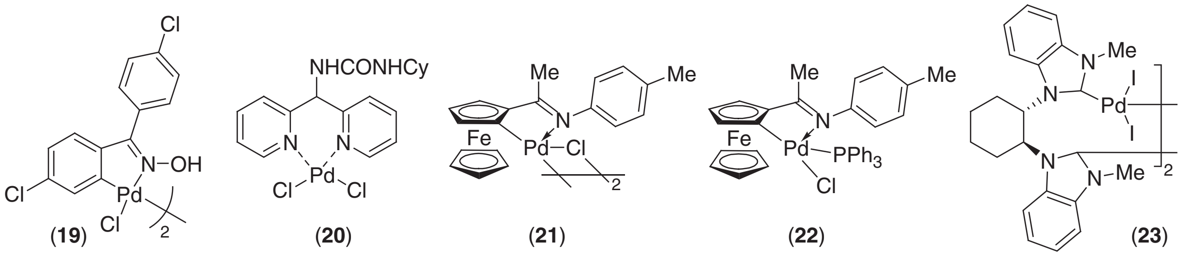
Scheme 16

(**13**) generation (cf. Scheme 8) and increase the yield of 1,3-diynes. A comparison between O_2 and I_2 by the authors concluded that the employment of iodine as the stoichiometric oxidant appears to be the method of choice.

$$\mathrm{R{-}{\equiv}} \xrightarrow[\substack{\mathrm{PPh_3\ (9\ mol\%)} \\ \mathrm{CH_3CN/Et_3N,\ O_2,\ 60\ ^\circ C}}]{\substack{\mathrm{PdCl_2(PPh_3)_2\ (3\ mol\%)} \\ \mathrm{CuI\ (3\ mol\%)}}} \underset{22\text{–}85\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{35}$$

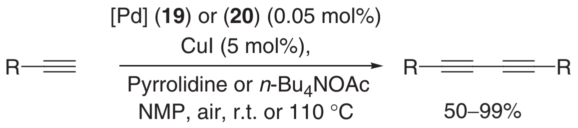
R = C_6H_5 (80%), 4-NCC_6H_4 (22%), 4-$MeSC_6H_4$ (85%), 4-$Me_2NC_6H_4$ (80%)

Studies with respect to the palladium complexes (Scheme 17) lead Nájera and coworkers to show that the phosphine-free palladium complexes (**19**) and (**20**) are efficient precatalysts (TONs up to 1000 for complex (**19**)) for the synthesis of conjugated diynes using copper iodide as a cocatalyst under air (equation 36).[54] The reactions were carried out with a low catalyst loading of palladium, and for substrates studied, the catalytic activity of **20** was higher than that of **19**. Cyclopalladated ferrocenylimine complexes (**21**) and (**22**)[55] proved to be useful catalysts for homocoupling of (hetero)aromatic alkynes giving rise to similar results (equation 37), although complex (**22**) exhibited higher catalytic activity than **21** with respect to homocoupling of aliphatic terminal alkynes. *N*-Heterocyclic carbene (NHC) palladium complex (**23**) was also an effective catalyst in the Glaser-type coupling reaction of terminal alkynes in the presence of CuI and aerobic conditions to give the corresponding symmetrical 1,4-disubstituted-1,3-diynes under mild conditions. Electron-rich arylacetylenes were coupled in good yields; however, electron-poor aryl acetylenes and aliphatic substrates afforded the corresponding coupling products in moderate yields (equation 38).[56]



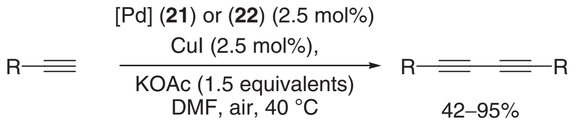
(**19**) (**20**) (**21**) (**22**) (**23**)

Scheme 17



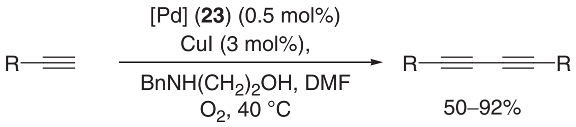
(36)

[Pd] (**19**), R = *n*-C_6H_{13} (60%), *n*-C_7H_{15} (50%), C_6H_5 (82%), *i*-Pr_3Si (75%)
[Pd] (**20**), R = *n*-C_6H_{13} (92%), *c*-C_6H_{11} (90%), C_6H_5 (99%), *i*-Pr_3Si (92%)



(37)

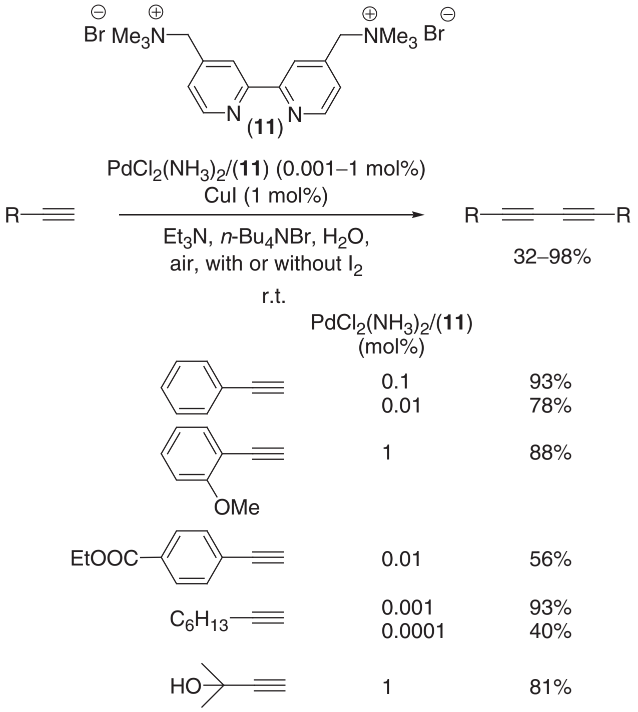
[Pd] (**21**), R = *n*-C_5H_{11} (50%), *n*-C_8H_{17} (61%), $Me_2(OH)C$ (42%), 1-hydroxycyclohexyl (61%)
[Pd] (**22**), R = *n*-C_5H_{11} (88%), *n*-C_8H_{17} (82%), $Me_2(OH)C$ (92%), 1-hydroxycyclohexyl (89%)



(38)

R = C_6H_5 (86%), 4-MeC_6H_4 (90%), 4-$MeOC_6H_4$ (92%),
3-$NH_2C_6H_4$ (82%), 2-$CF_3C_6H_4$ (50%), $BnOCH_2$ (60%)

Most of the Pd/Cu-catalyzed terminal alkyne homocoupling reactions have been carried out in organic solvents. Tsai and coworkers[57] developed a catalyst system based on $PdCl_2(NH_3)_2$ together with a cationic 2,2-bipyridyl ligand (**11**) and CuI allowing reaction in water (Scheme 18). For aromatic terminal alkynes, the reaction could be performed in either the presence or the absence of iodine. The addition of I_2 was required in the case of aliphatic acetylene homocoupling. The main feature of this reaction is the fact that homocoupling proceeds at room temperature using extremely low catalysts loading of palladium



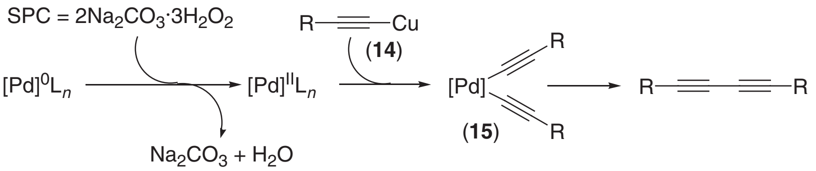
Scheme 18

(0.001–1 mol%) and CuI (1 mol%). In addition, by a simple process of extraction, the residual aqueous solution exhibited activity for reuse for four cycles without a significant decrease in activity (R=Ph, yields = 94–77%; R = *n*-C_6H_{13}, yields = 93–78%).

In the context to find environmentally friendly, solvents and catalysts for the Pd/Cu-catalyzed homocoupling reaction of terminal alkynes, Jiang and coworkers[58] reported the use of a polymer-supported palladium complex with phosphines as the solid carrier (equation 39). The reaction was carried out in aqueous acetonitrile in the presence of sodium percarbonate (SPC), which was suggested to act both as a base, in the generation of copper acetylide, and as a reoxidazing agent for the Pd(0) species to Pd(II) (**Scheme 19**). Although the process required relatively high catalyst loading (Pd: 10 mol% and CuI: 6 mol%), the palladium complex immobilized on a synthetic PS-PEG_{400}-PPh_2 resin was recovered by simple filtration and reused for several times, with partial loss of catalytic activity being observed in the fifth cycle (R=C(OH)Me_2, yields = 99–58%). A variety of aromatic and aliphatic alkynes were transformed into the expected 1,3-diynes, including substrates containing hydroxy, chloro, trimethylsilyl, and ester functionalities.

$$\mathrm{R{-}{\equiv}} \xrightarrow[\text{2 Na}_2\text{CO}_3\cdot 3\text{H}_2\text{O}_2\text{ (3 equivalents)},\ \text{H}_2\text{O-CH}_3\text{CN, r.t.}]{\text{PdCl}_2/\text{PS-PEG}_{400}\text{-PPh}_2\text{ (10 mol\%)},\ \text{CuI (6 mol\%)}} \underset{58\text{–}99\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{39}$$

R = C_6H_5 (96%), 3-FC_6H_4 (96%), 4-MeC_6H_4 (95%), $HOCH_2$ (82%),
C_2H_5OOC (58%), *n*-C_6H_{13} (93%), *t*-Bu (81%), $SiMe_3$ (71%), $ClCH_2$ (67%)



Scheme 19

Recently, a mesoporous silica SBA-15-supported palladium complex with nitrogen-containing ligands as the solid carrier was reported.[59] Reactions were performed at room temperature, and a variety of aromatic and aliphatic alkynes were transformed into the expected 1,3-diynes in moderate to good yields using 1 mol% of the SBA-15@DABCO–Pd-complex together with CuI and DABCO in acetonitrile (equation 40). In addition, the catalyst could be reused over four cycles with negligible loss of activity. Although heterogeneous supported palladium catalysts outlined in equations 39 and 40 proved to be effective, they required multistep and rather complex procedures to obtain the definitive catalysts.

$$\mathrm{R{-}{\equiv}} \xrightarrow[\text{DABCO (1 equivalent), CH}_3\text{CN, r.t.}]{\text{SBA-15@DABCO-Pd (1 mol\%)},\ \text{CuI (1 mol\%)}} \underset{62\text{–}94\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{40}$$

R = 4-FC_6H_4 (94%), 4-MeC_6H_4 (81%), MeCH(OH) (62%), $Me_2C(OH)$ (88%),
$HO(CH_2)_4$ (74%), $HO(CH_2)_2$ (84%), *n*-C_8H_{17} (92%), *n*-C_4H_9 (70%), *t*-Bu (65%)

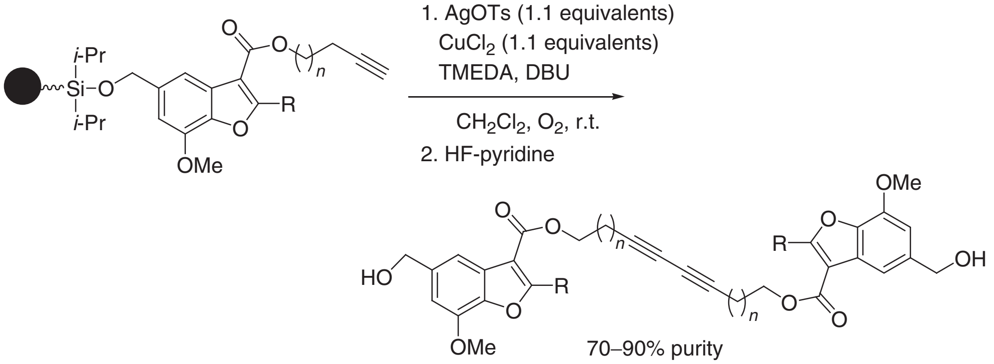
In 2007, an environmentally friendly phosphine- and base-free synthetic method for a variety of symmetrical 1,3-diynes was described by Sajiki and coworkers.[60] The reaction was achieved in DMSO using extremely low catalyst loading of heterogeneous and commercially available Pd/C (0.01–0.03 mol%) together with CuI (equation 41). This high yielding reaction could be performed in the presence of either molecular oxygen (O_2) or atmospheric conditions (air) giving rise to similar results. In the latter case, higher amounts of palladium catalyst (0.05–0.3 mol%) were required. From a practical point of view and effectiveness, this methodology is advantageous in the sense that reactions can be carried out at room temperature under neutral conditions without any base. It seems much simpler to implement than those, mentioned previously, requiring synthetic heterogeneous supported palladium catalysts. Therefore, it appears to be promising for future applications in modern acetylenic chemistry.

$$\mathrm{R{-}{\equiv}} \xrightarrow[\text{DMSO, O}_2\text{ or air, r.t.}]{\text{Pd/C (0.01–0.03 mol\%)},\ \text{CuI (3 mol\%)}} \underset{81\text{–}99\%}{\mathrm{R{-}{\equiv}{-}{\equiv}{-}R}} \tag{41}$$

R = C_6H_5 (98%), 4-MeC_6H_4 (96%), 3-ClC_6H_4 (91%), 2-$CF_3C_6H_4$ (96%), 3,5-$CF_3C_6H_3$ (94%),
n-C_3H_7 (99%), $CN(CH_2)_3$ (94%), $PhSCH_2$ (81%), $AcOCH_2$ (87%), MePhC(OH) (96%)

Apart from the palladium catalysts employed in combination with copper salts to achieve the alkyne homocoupling reactions, other combinations based on transition metals such as Ag/Cu and Fe/Cu have been developed for the same task. Liao and Fathi[61] reported a novel protocol of AgOTs–$CuCl_2$–TMEDA allowing efficiently homocoupling of aliphatic alkyne-containing benzofuran nucleus on solid support (equation 42). In this case, the protocol was shown to be more efficient than the Pd-catalyzed methods and the Glaser–Eglinton–Hay couplings as well as their many variants, and provided an efficient way to synthesize a diversified symmetrical bis-benzofuran-linked 1,3-diynes library on solid support. The authors suggested that the silver activates the C–C triple bond, thereby facilitating Cu(II)-mediated oxidative alkyne homocoupling.

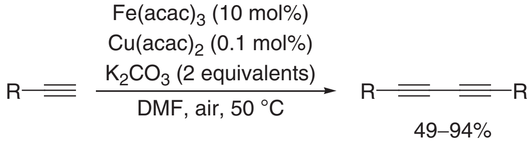
Recently, an economically competitive protocol for homocoupling reaction of terminal alkynes has also been reported using catalytic amounts of $Fe(acac)_3$ (acac, acetylacetonate) in combination of a low catalyst loading of copper salt (0.1 mol%) and air as the oxidant (equation 43).[62] Both aromatic and aliphatic terminal alkynes undergo homocoupling successfully furnishing the corresponding 1,3-diyne in moderate to excellent yields.



(42)

$n = 1, 2$

R = C_6H_5, 4-MeC_6H_4, 4-*t*-BuC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$CF_3C_6H_4$, 4-*n*-BuC_6H_4, 2-thienyl



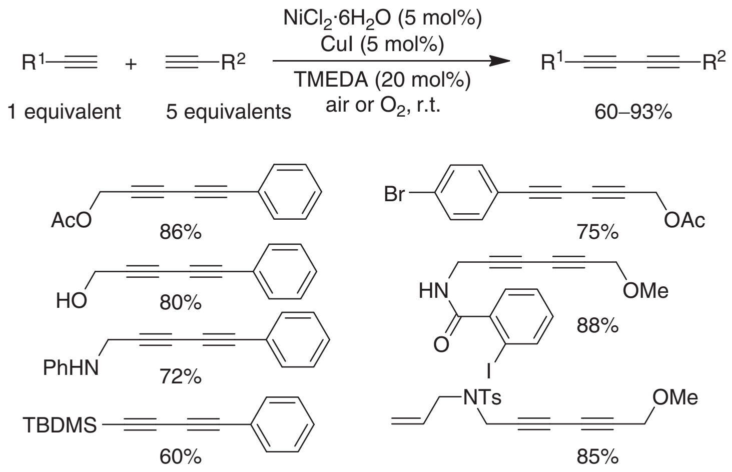
$$\mathrm{R{-}{\equiv}} \xrightarrow[\text{DMF, air, 50 °C}]{\substack{\mathrm{Fe(acac)_3}\ (10\ \text{mol\%}) \\ \mathrm{Cu(acac)_2}\ (0.1\ \text{mol\%}) \\ \mathrm{K_2CO_3}\ (2\ \text{equivalents})}} \mathrm{R{-}{\equiv}{-}{\equiv}{-}R}\quad 49\text{–}94\% \tag{43}$$

R = C_6H_5 (94%), 4-MeC_6H_4 (86%), 4-$MeOC_6H_4$ (88%), 3-$NH_2C_6H_4$ (87%),
2-ClC_6H_4 (62%), 1-naphthyl (90%), *n*-C_4H_9 (86%), *n*-C_5H_{11} (89%),
$HO(CH_2)_3$ (91%), $ClCH_2$ (49%), 3-thienyl (87%), ferrocenyl (64%)

In the past two decades, catalytic systems based on other transition metals have been developed for the homocoupling reaction of terminal alkynes, which include, nickel, cobalt, gold, and titane.[4,5,31] Although these reactions may open up new routes to form homocoupling products in acceptable yields, their scope are limited, as they exhibit low tolerance to functional groups and are less widely used than the classical methods, and thus remain largely of theoretical interest. Nevertheless, some of these techniques have led to some significant results in specialized applications, in particular, the Ni/Cu-mediated alkyne homocoupling reaction for the active-template synthesis of [2]rotaxanes[63a] or the cobalt-catalyzed oxidative homocoupling of terminal alkynes using nitrobenzene as an oxidizing agent under reductive conditions (Zn powder).[63b]

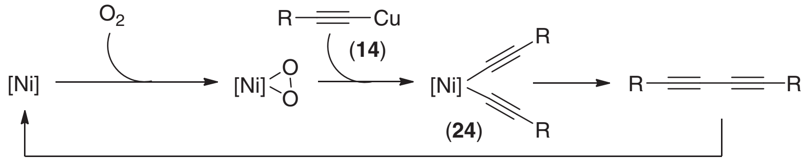
3.10.2.2 Coupling of Two Different Terminal Alkynes

After the pioneering work by Glaser, in the past 5 years many efforts have been devoted toward the development of catalytic protocols for heterocoupling of two different terminal alkynes. In this regard, a useful and convenient synthesis of unsymmetrical conjugated diynes has been reported by Lei and coworkers[64] (**Scheme 20**). This method employed bimetallic $CuI/NiCl_2 \cdot 6H_2O$ as the catalytic system, together with TMEDA as the ligand and O_2 or air as the oxidant at room temperature. This protocol requires a high loading of one alkyne partner (5:1 ratio) for the efficiency of the heterocoupling reaction. By utilizing the different polarity between alkyne substrates, the authors could overcome the problem of separation of heterocoupling products from homocoupling side products. When the ratio of the two different terminal alkynes was 1:1, yields of cross-coupled 1,3-diyne decreased significantly (<50%). The method developed was efficient with a variety of alkynes based on propargylic alcohols and amines, and functional groups such as OR, OH, NHR, and TBDMS as well as iodo- or bromo-atoms on the aromatic ring of aryl acetylene substrates were well tolerated. Unfortunately, no example was reported with aliphatic alkynes, and therefore, it is difficult to estimate if these substrates would behave similarly. On the basis that Cu(I) was more reactive toward terminal alkynes than the

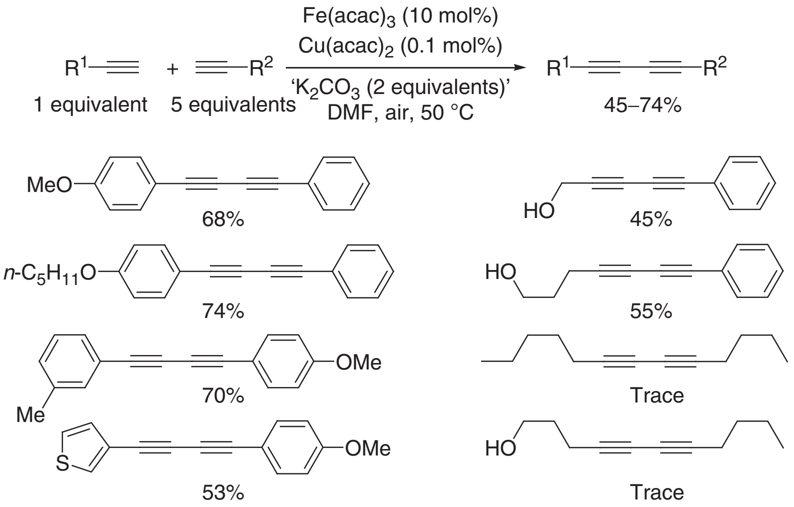


Scheme 20

Ni(0) species, the authors suggested a mechanism involving oxidation of the Ni complex by O_2 to generate a $Ni(O_2)$ species, which is transmetallated stepwise with the copper acetylide (**14**) to form the dialkynyl–Ni intermediate (**24**). The final reductive elimination would release the coupling product and regenerate the Ni(0) complex (Scheme 21). However, this mechanism does not permit distinction between possible formations of heterocoupling versus homocoupling products, unless the coupling might be under statistical control. $Fe(acac)_3$ in combination with a trace quantity of $Cu(acac)_2$ has also been found to catalyze homocoupling of two different terminal alkynes including (hetero)aromatic and alkynes based on propargylic alcohols.[62] Unfortunately, when using two different aliphatic terminal alkynes as the substrates, the outcomes were disappointing (Scheme 22).

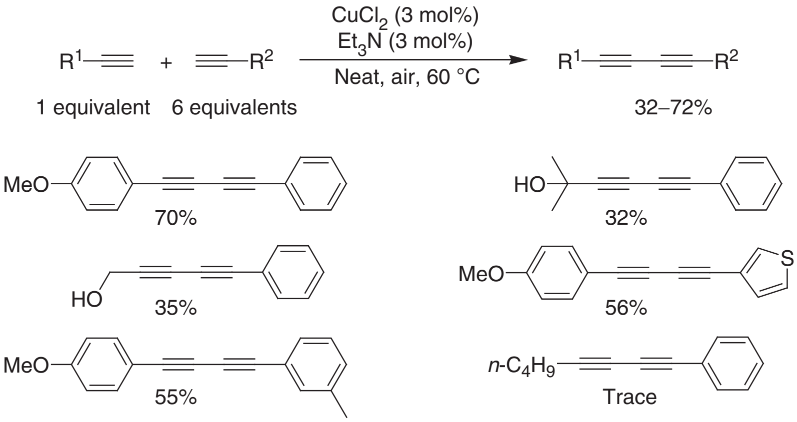


Scheme 21



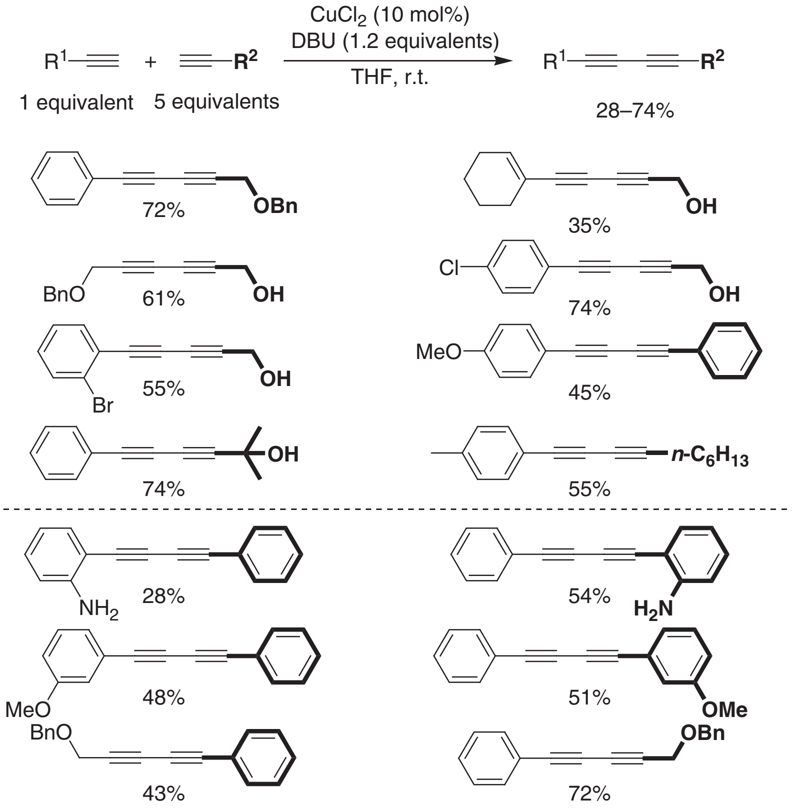
Scheme 22

The previously reported environmentally friendly methodology by Chen[30] under solvent-free conditions was extended to the cross-coupling of two different terminal alkynes by using again a sixfold excess of one of the terminal alkyne substrates. The reaction conducted in the presence of catalytic amounts of $CuCl_2$ and Et_3N furnished unsymmetrical 1,3-diynes, including thiophene-substituted acetylenic substrate in acceptable yields ranging from 32% to 72% (Scheme 23). Nevertheless, again in the case of aliphatic alkynes as the second coupling partner, only traces of unsymmetrical 1,3-diynes were observed.



Scheme 23

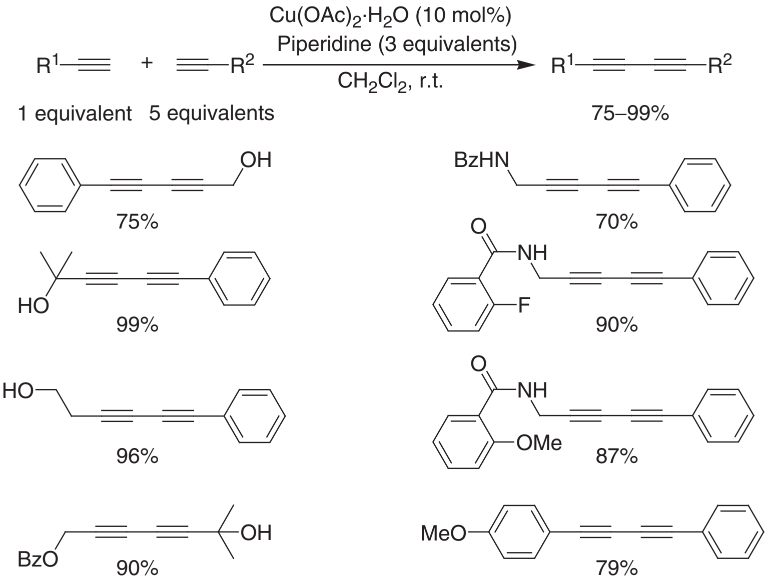
Recently, a similar reaction was developed by Balamurugan et al.[65] employing a catalytic amount of $CuCl_2$ (10 mol%) and stoichiometric amounts of DBU in THF at room temperature. This procedure, which proved to be effective for homocoupling of terminal alkynes, was successfully extended to the heterocoupling of different pairs of terminal alkynes. Aromatic alkynes and propargylic alcohol derivatives underwent oxidative heterocoupling reactions under these conditions to give the expected 1,3-diynes in moderate to good yields (Scheme 24). Even two different aryl alkynes could also be coupled in moderate efficiencies.



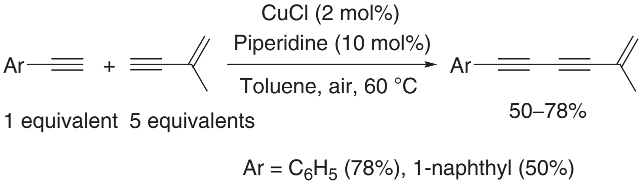
Scheme 24

The reaction was tolerant to various functionalities on the aromatic ring of aryl alkyne substrate, such as amino groups or bromo- and chloro-atoms. It is worth noting that in contrast to the Chen's conditions, the reaction between an aryl and an aliphatic alkyne underwent smooth coupling to furnish the expected unsymmetrically substituted 1,3-diyne in an acceptable 55% yield. Results from some experiments, in which the reactions were conducted by taking the coupling partners in exactly opposite molar ratios, showed that the strategic choice of alkyne in excess is essential for efficiency of the coupling, yield being higher when electron-rich alkyne is used in fivefold excess (**Scheme 24**).

A variant of this procedure was described by Kesavan,[66] who used catalytic amounts of $Cu(OAc)_2$ and piperidine as the base in CH_2Cl_2 at room temperature (**Scheme 25**). It was found that this heterocoupling reaction of two different terminal alkynes proceeds with no need for any other additives or an oxygen atmosphere, and does not suffer from poor yields as in the case of copper(II)chloride.[30,65] Unsymmetrical 1,3-diynes were synthesized in 70–99% yield when an excess of one of the terminal alkyne substrate was used. These yields are among the best reported yields for the heterocoupling of terminal alkynes. The reaction tolerates a wide range of functional groups such as amide, ester, and alcohol. In addition, electron-withdrawing as well as electron-donating groups in phenylacetylenes did not influence progress of the reaction to form heterodiynes in very good yields. The only unfavorable criticism to this work is apparently the heterocoupling that was not attempted when one of the alkyne partners is an aliphatic alkyne. It would be recommended to study this possibility in order to enlarge the scope of the reaction. The catalytic system based on CuCl and piperidine has also been shown to achieve the oxidative heterocoupling reactions of terminal aryl alkynes with conjugated enyne in toluene leading to unsymmetrical 1,3-diynes in acceptable yields (equation 44).[17]



Scheme 25

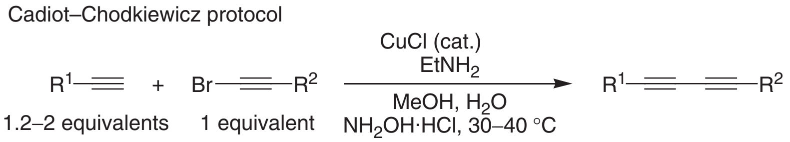


(44)

3.10.3 Coupling Reactions of Terminal Alkynes and 1-Haloalkynes

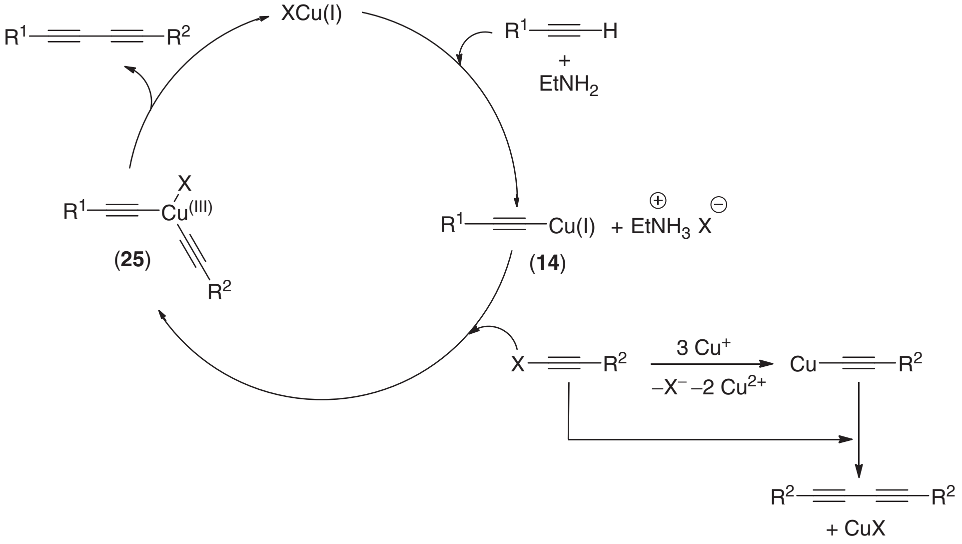
3.10.3.1 Copper Catalysis

The aforementioned heterocoupling methods between two different alkynes suffers from some limitations such as the simultaneous formation of the symmetrical side products and the use of excess (e.g., fivefold) of one of the alkyne partners. A solution to circumvent this problem consists of the coupling reaction between terminal alkynes and a haloalkyne, catalyzed by a copper(I) salt in the presence of an amine as the base. This useful reaction, discovered by Chodkiewicz and Cadiot in 1955,[67] affords unsymmetrically 1,4-disubstituted-1,3-diynes (equation 45).



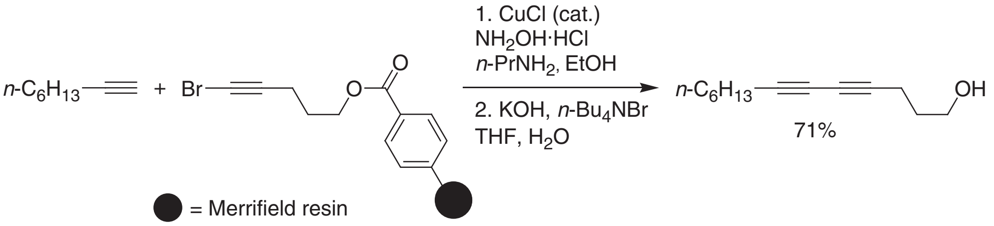
(45)

Although this reaction was discovered for over five decades, there have been few mechanistic studies on the process of C–C triple bond formation due to the high reactivity of commonly used bromoacetylenes, which make kinetic studies difficult. As outlined in **Scheme 26**, it has been assumed that the Cadiot–Chodkiewicz coupling mechanism involves deprotonation by an amine base of the acetylenic proton followed by formation of the copper(I) acetylide (**14**) (cf. Section 3.10.2, **Schemes 2** and **3**). An oxidative addition of bromoalkyne to an *in situ* formed copper acetylide is envisioned to take place as a second step leading to the Cu(III) species (**25**),[7] which subsequently evolves through reductive elimination to produce 1,4-disubstituted-1,3-diyne and regenerate Cu(I) species (**Scheme 26**). The role of the base is essential for the outcome of the coupling; it is not only necessary to neutralize the hydrobromic acid resulting from the reaction, but also facilitates the formation of the copper(I) acetylide and influences considerably the copper(I) ion oxidability. Besides the use of amine, hydroxylamine hydrochloride, a reducing agent, is often added to reduce the level of Cu(II) formed, and therefore replenish Cu(I) lost during this process. Under the Cadiot–Chodkiewicz conditions, 1-bromoalkynes can undergo a selfcoupling to the corresponding symmetrical 1,3-diyne, particularly in the case of less acidic alkynes, such as aliphatic acetylenes. However, this homocoupled product, generated from 1-bromoalkyne by halogen–metal exchange, can be suppressed by amines or by the use of low concentrations of the copper(I) ion and the haloacetylene[7] (**Scheme 26**).



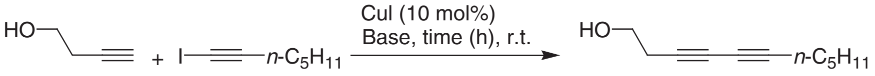
Scheme 26

Since its discovery, the Cadiot–Chodkiewicz coupling was applied extensively to the synthesis of a wide range of diacetylenic and polyyne compounds (cf. Section 3.10.8).[7] Besides the original coupling protocol, several complementary variations have been reported. The influence of various factors, such as the catalyst, the nature of base, the solvent, and the temperature of the reaction, have been investigated with the aim to inhibit the selfcoupling of 1-haloalkynes, and thus favor the heterocoupling. In this context, a polymer-supported technique was developed by Kurth and coworkers.[68] It consists to attach appropriately ω-functionalized 1-haloalkynes to a suitable polymer support, which inhibit their mutual interactions, thereby favoring the heterocoupling with the terminal alkyne partner in solution (equation 46). With the solution-phase results for comparison, the coupling of immobilized bromoalkyne with 1-octyne under Cadiot–Chodkiewicz conditions proceeded in 71% yield and completely suppressed the formation of homocoupling product arising from haloalkyne, whereas the corresponding reaction in solution gave up to 34% homocoupled side product. Although this procedure seems to be interesting, however, it requires the preparation of polymer-containing 1-haloalkynes through multistep synthesis.



(46)

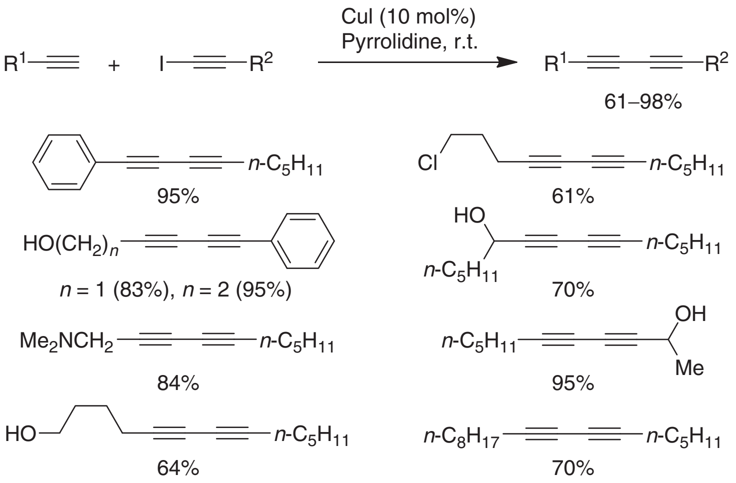
A significant contribution to the original Cadiot–Chodkiewicz coupling was made by the group of Alami,[69] who reported a simple and convenient CuI-catalyzed cross-coupling reaction of 1-iodo- and 1-bromoalkynes with terminal alkynes in pyrrolidine. It is worth noting that the amines play a critical role in the outcome of this transformation. A gradual increase in reaction rate and yield of the coupled product was shown with an increase in the basicity of the amine and a decrease in its steric hindrance. The use of pyrrolidine as the amine solvent gave best results, whereas other aliphatic amines gave poor yields (equation 47, Table 7). Under these conditions, 1-iodoalkynes that are well known to be less successful coupling partners under Cadiot–Chodkiewicz protocol[7] gave excellent yields of unsymmetrical 1,3-diynes without any formation of the side homocoupled product. This simple protocol was successful even with less acidic terminal alkynes. A variety of aliphatic alkynes were transformed into the expected 1,3-diynes, including substrates containing hydroxy, chloro, amine, and ester functionalities (Scheme 27). This methodology that substantially upgraded the original Cadiot–Chodkiewisz coupling is advantageous in the sense that reactions proceed at room temperature and the aliphatic substrate scope covered is large.



(47)

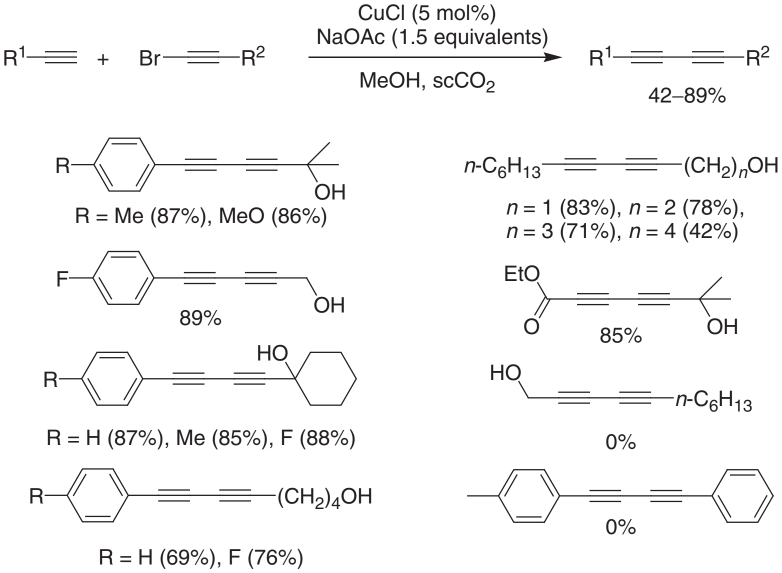
Table 7 Influence of the amine on Cu-catalyzed heterocoupling (equation 47)

Amine	*pKa*	*Time (h)*	*Yield (%)*
Et_3N	10.75	24	20
n-$BuNH_2$	10.77	6	54
Et_2NH	11.02	7	35
i-Pr_2NH	11.05	3	25
Piperidine	11.12	2	79
Pyrrolidine	11.27	0.25	95



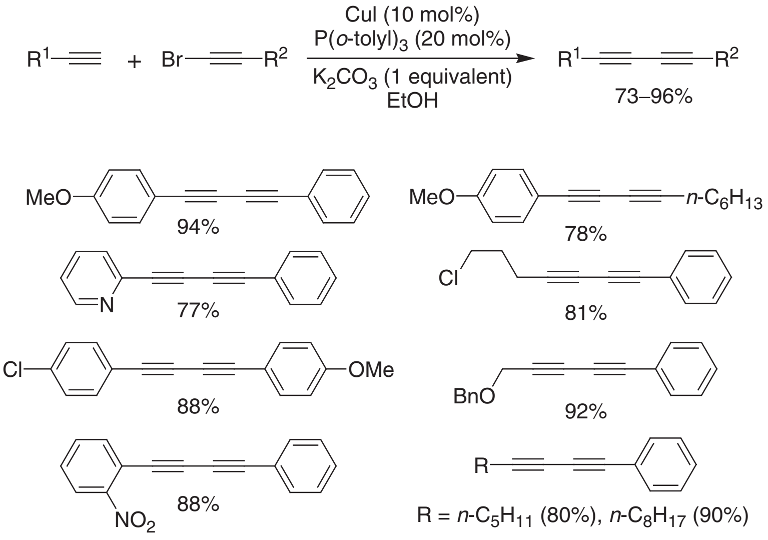
Scheme 27

Another protocol for the coupling of 1-bromoalkynes with terminal alkynes was described by Jiang and Wang.[70] It involves the use of supercritical carbon dioxide as an environmentally benign reaction medium, which has the advantages of greater selectivity and the ease with which the reaction rate can be controlled. The conditions developed used sodium acetate as the base rather than an amine, but are limited to only 1-bromoalkynol substrates. The reactions failed with 1-bromoalkynes having no hydroxyl group, even though the terminal alkyne partner contains a hydroxyl functionality (Scheme 28). Although these results suggest that the hydroxyl group within 1-bromoalkynols has an important effect on the effectiveness of the reaction, no comment was made about its role in the context of using $scCO_2$ as the reaction medium.



Scheme 28

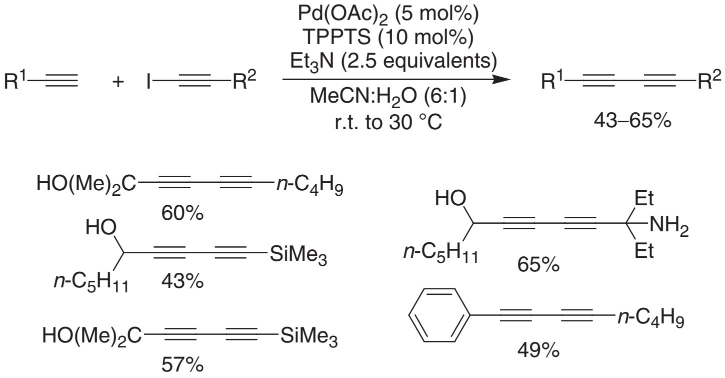
Because the ligands play an important role in transition metal-catalyzed reactions, recently Wang's research group[71] investigated the Cu-catalyzed Cadiot–Chodkiewicz couplings of 1-bromoacetylenes with terminal alkynes in the presence of several phosphine and nitrogen ligands. The use of CuI as the catalyst and tris(*o*-tolyl)phosphine as the ligand in the presence of a mineral base K_2CO_3 in refluxing EtOH allows coupling to proceed successfully with both (hetero)aromatic and aliphatic substrates (Scheme 29). Nitrogen ligands such as 1,10-phenanthroline, pyridine, quinoline, DABCO, or 2-acetylcyclohexanone gave poor yields.



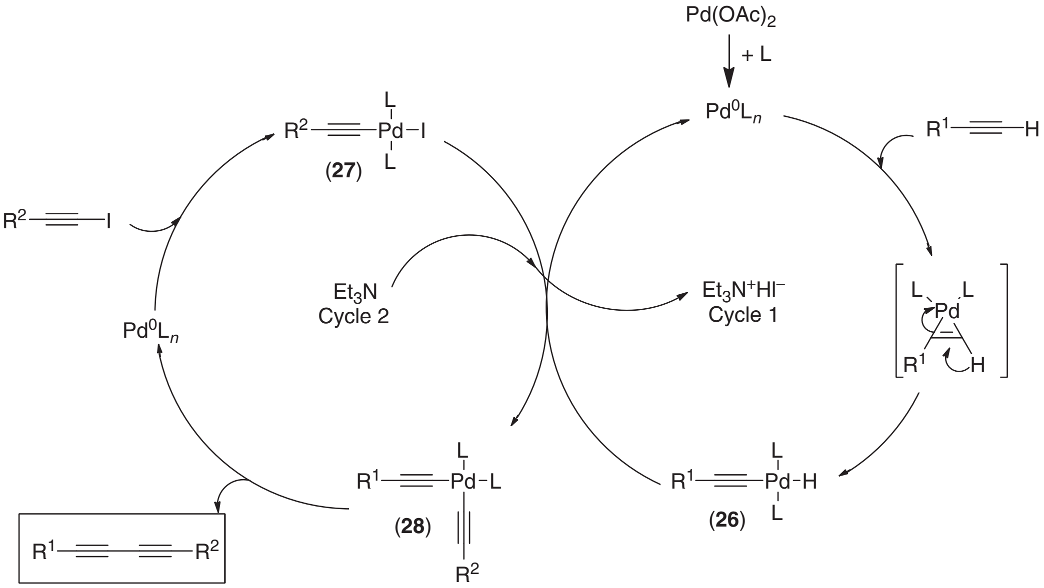
Scheme 29

3.10.3.2 Palladium Catalysis

Currently, the Cadiot–Chodkiewicz reaction of terminal alkynes with 1-haloalkynes in the presence of a Cu catalyst without the use of a Pd complex is the most widely used method for coupling between *sp* carbon centers. In view of the facile oxidative addition of Pd to 1-haloalkynes, the Pd-catalyzed reaction of terminal alkynes with 1-haloalkynes might be expected to proceed readily to provide a satisfactory alternative to the Cadiot–Chodkiewicz reaction. The pioneering work on this transformation was first reported in 1995 by Amatore and coworkers.[72] The authors demonstrated that heterocoupling reaction of terminal alkynes with 1-iodoalkynes could be achieved by using a palladium water-soluble catalyst, prepared *in situ* from $Pd(OAc)_2$ and sulfonated triphenylphosphine $P(C_6H_4\text{-}m\text{-}SO_3Na)_3$ (TPPTS), without any copper(I) promoter (Scheme 30). The reaction takes place in the presence of Et_3N in a homogeneous acetonitrile–water system, providing unsymmetrical 1,3-diynes with different functions on the carbon skeleton such as trimethylsilyl group, primary, secondary, and tertiary alcohols. Although moderate yields were obtained (45–65%), homocoupling side products were not observed except when phenylacetylene was used as the terminal alkyne coupling partner. In this case, 14% of 1,4-diphenyl-1,4-diyne were formed. Preliminary mechanistic investigations of this heterocoupling process by the authors suggested the involvement of two linked catalytic cycles, as outlined in Scheme 31. In the first cycle, hydridoalkynylpalladium complex (**26**) would be formed through oxidative addition of Pd(0) in the carbon–hydrogen bond of the terminal alkyne, whereas in the second cycle, the Pd(0) species would react with 1-iodoalkyne through oxidative addition, leading to the iodoalkynylpalladium complex (**27**). Transmetalation of two alkynylpalladium species (**26**) and (**27**), under triethylamine would result in dialkynylpalladium complex (**28**), which evolves through reductive elimination to give the unsymmetrical 1,3-diyne derivative with regeneration of the Pd(0) catalyst.

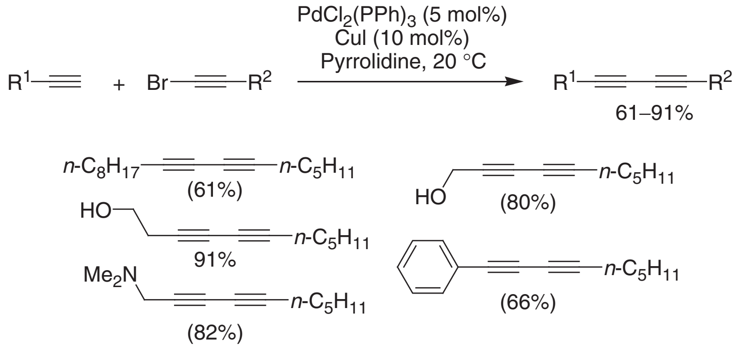


Scheme 30

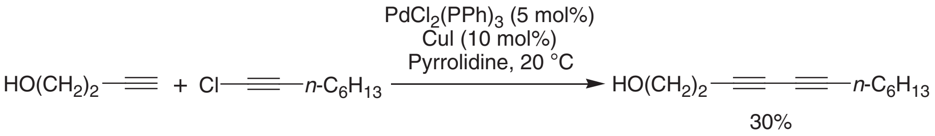


Scheme 31

One year later, the group of Alami[69] showed that employment of a combination of palladium complex and copper catalyst in pyrrolidine is also a useful protocol for the synthesis of unsymmetrical 1,3-diynes at room temperature. In contrast to heterocoupling of 1-iodoalkynes with terminal alkynes in the presence of only CuI as the catalyst (Scheme 27), the reactivity of 1-bromoalkyne derivatives could be enhanced by the addition of $PdCl_2(PPh_3)_2$ as the cocatalyst, leading to 1,3-diynes in better yields (Scheme 32). In addition to the coupling of 1-bromo- and 1-iodoalkyne derivatives, the authors described one example of heterocoupling of 1-chlorooctyne with butyn-1-ol giving rise to the expected unsymmetrical 1,3-diyne in a moderate 30% yield (equation 48).

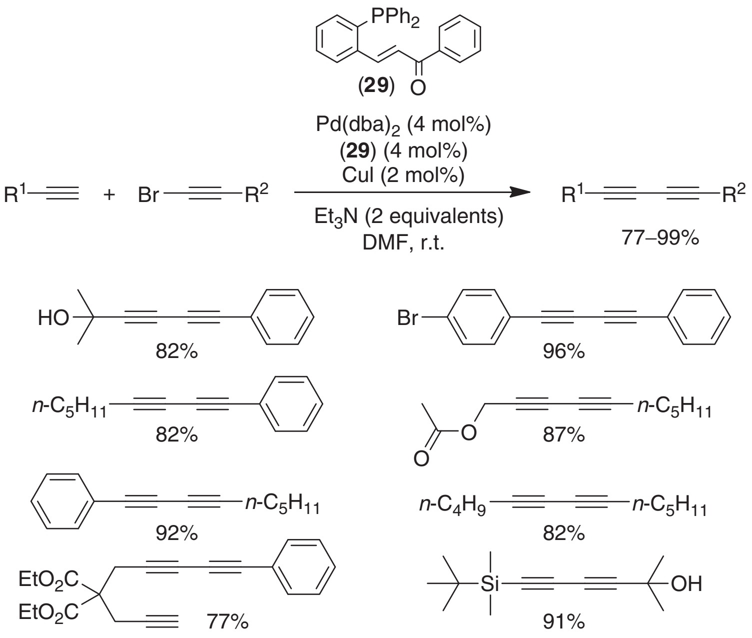


Scheme 32



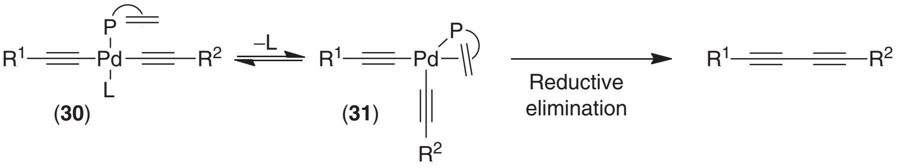
(48)

Based on the general comprehension of palladium-catalyzed coupling reactions, and that the performance of homogeneous catalysts is highly dependent on the ancillary ligand coordinated to the metal center, Lei and coworkers[73] investigated the effects of steric ligands and π-acid ligands to facilitate the reductive elimination of dialkynylpalladium species (**28**) outlined in Scheme 31. This study showed that π-acceptor phosphine electron-deficient olefin ligands (**29**) combined with $Pd(dba)_2$ are effective catalytic system in promoting C*sp*–C*sp* cross-couplings (Scheme 33). Reactions were conducted in DMF in the presence of Et_3N, and a catalytic amount of CuI is essential in this coupling as well. Homocoupling is clearly suppressed under these conditions and occurs only to a minor extent (<10%). The cross-coupling worked well for aliphatic and aromatic terminal alkynes as well as 1-bromoalkynes, and had a high tolerance for various functional groups such as esters, ethers, hydroxyl groups, TBDMS, and bromine atom on the aromatic alkyne partner. In addition, the C*sp*–C*sp* coupling of two different alkynes in which the electronic properties are similar such as n-$C_5H_{11}C\equiv CBr$ and n-$C_4H_9C\equiv CH$ gave the corresponding unsymmetrically



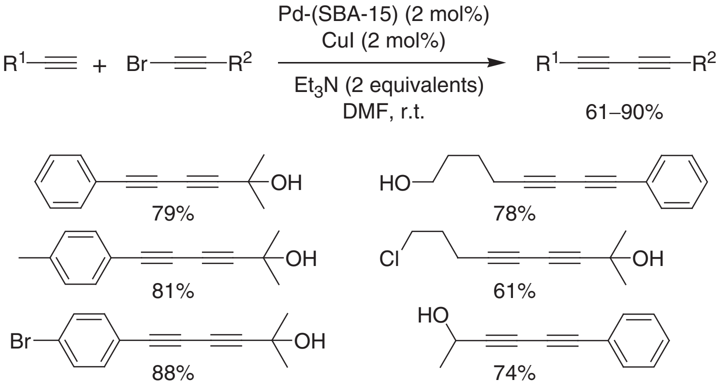
Scheme 33

1,3-diynes in a high selective manner (82%). In contrast, both Cadiot–Chodkiewicz reactions and other Pd-catalyzed processes typically gave low yields of cross-coupled products along with homocoupled side products. More interestingly, the catalytic system is not sensitive to the choices of the electrophile and the nucleophile with regard to their electronic properties. A mechanism was postulated by the authors, in which the formation of the dialkynylpalladium complex (**30**), common to all proposed mechanisms,[74] could proceed through transmetallation of a copper(I) acetylide (Scheme 34). More deep kinetics investigations of this coupling has established that reductive elimination was the rate-determining step, and in the reaction system with 1 equivalent of ligand, two species (**30** and **31**) could exist in equilibrium after transmetalation. The bidentate feature of ligand (**29**) would facilitate the shift from **30** to **31**, and the π-acceptor ability of the olefin part of ligand would accelerate the reductive elimination of **31** to produce the cross-coupled diynes (Scheme 34). A review summarizing mechanistic investigations of the Pd/Cu-catalyzed non-oxidative heterocoupling reaction has been published by Diederich.[4]



Scheme 34

Recently, an amine-functionalized mesoporous silica SBA-15-supported palladium has been utilized as a highly efficient phosphine-free and reusable catalyst for the C*sp*–C*sp* cross-coupling of 1-haloalkynes with terminal alkynes (Scheme 35).[75] The catalyst, designed as Pd-(SBA-15), was fully characterized and consisted of both Pd(II) and Pd(0) species in the ratio of 3.5:1. Several 1-bromoalkynes and aromatic/aliphatic terminal alkynes were selectively coupled to afford unsymmetrical 1,4-disubstituted-1,3-diynes in moderate to good yields. The Pd-(SBA-15) catalyst could be easily separated by simple filtration and reused 3 times, with partial loss of catalytic activity being observed in the third run (R^1=Ph, R^2=C(OH)Me_2, yields=99–65%).



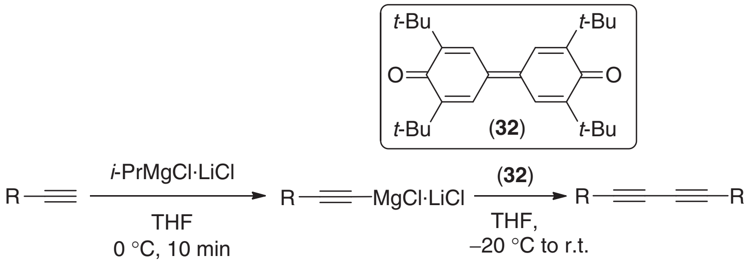
Scheme 35

3.10.4 Oxidative Homocoupling of Organometallic Alkynides

3.10.4.1 Homocoupling Reactions of Alkynyl Grignard Reagents

Analogous to the copper-catalyzed oxidative homocoupling of terminal alkynes, the addition of oxidants (e.g., iodine, copper(II) and cobalt(II) salts, oxovanadium(V), or nitrobenzene)[4–6] to alkynylmagnesium halides can undergo a dimerization process leading to symmetrical 1,3-diynes. When iodine is employed as an oxidizing agent, a 1-iodoalkyne is postulated as an intermediate.[7] In this context, three recent reports[76] demonstrated that both aliphatic and (hetero)aromatic 1-iodoalkynes underwent homocoupling reactions to furnish symmetrical 1,3-diynes in good to excellent yields. Although the 1-haloalkynes are usually prepared from terminal alkynes by halogenation, the absence of any transition metal and base can make the method described by Jiang more valuable.[76c]

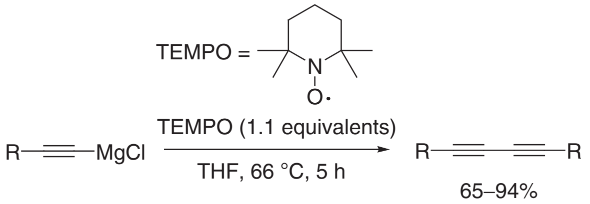
Besides the oxidizing agents mentioned above, Knochel and coworkers[77] employed a stoichiometric amount of the readily available 3,3′,5,5′-tetra-*tert*-butyl-4,4′-diphenoquinone (**32**), which acts as a two-electron acceptor. Reactions of alkynylmagnesium chloride with **32** proceed cleanly with the formation of the expected 1,3-diynes in 80–90% yield (Scheme 36). Similarly to the aforementioned protocol, Studer and coworkers[78] showed that the use of a stoichiometric amount of 2,2,6,6-tertramethylpiperidine-*N*-oxyl



$R = C_6H_5$ (80%), n-C_6H_{13} (81%), $SiMe_3$ (90%), 1-cyclohexenyl (88%)

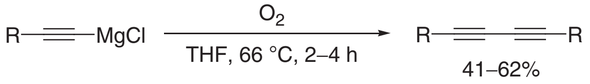
Scheme 36

radical (TEMPO) as the oxidizing agent, alkynyl Grignard reagents underwent homocoupling to give the corresponding products in 86–94% yield (equation 49). Achieving the homocoupling reaction with O_2 without the addition of TEMPO revealed also successful (equation 50). Although homocoupled products were obtained in moderate yields (41–62%), this transformation with dioxygen in the absence of a transition metal catalyst is unprecedented and is of theoretical high interest. As transition metals are known to mediate homocoupling of Grignard reagents (cf. *vide infra* equations 51–53), trace analysis of metals on reaction mixtures for an alkynyl Grignard coupling was examined and revealed the presence of trace amounts of Mn (22 ppm), Fe (11 ppm), and Cu (2 ppm). The Pd was also detected, but could not be quantified (Pd < 0.01 ppm). These data lead the authors to conclude that 'it is unlikely that the trace amounts of transition metals present are able to catalyze homocoupling of alkynyl Grignard reagents efficiently.'



(49)

$R = C_6H_5$ (90%), 4-$CF_3C_6H_4$ (94%), 4-$MeOC_6H_4$ (86%), n-C_6H_{13} (94%),
c-C_6H_{11} (76%), Me_3Si (65%), 1-cyclohexenyl (72%)



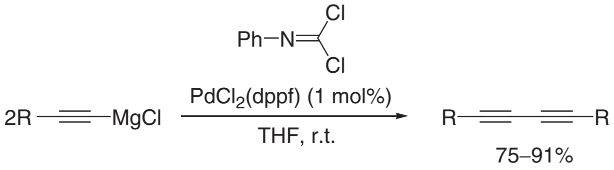
(50)

$R = C_6H_5$ (60%), 4-$CF_3C_6H_4$ (52%), 4-$MeOC_6H_4$ (62%), n-C_6H_{13} (46%),
c-C_6H_{11} (41%)

The transition metal-catalyzed oxidative homocoupling of acetylenic Grignard derivatives has opened up this concept to a larger number of alkynes derivatives. Ito et al.[79] described that the use of Grignard reagents in the presence of N-substituted isocyanide dichlorides and $PdCl_2$(1,1′-bis(diphenylphosphino)ferrocene (dppf)) as the catalyst gave oxidative coupling products in good yields (equation 51). A variant using $Pd(acac)_2$ in the presence of iodine instead of N-substituted isocyanide dichlorides has also been described.[4]

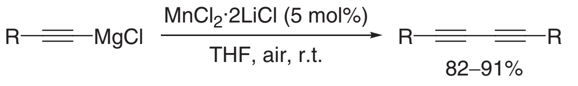
In terms of economic and environmental considerations, development of cheaper metals as catalysts in place of Pd is an attractive route. In 2007, an efficient and environmentally friendly protocol was developed by Cahiez[80] to form symmetrical 1,3-diynes by using a catalytic amount of $MnCl_2$ under an atmospheric oxygen as an oxidant (equation 52). This contribution constitutes the pioneering work in that air might be used as an oxidant to achieve homocoupling of Grignard reagents.

Recently, Itoh[81] reported the $FeCl_3$-catalyzed homocoupling reaction of alkynyl Grignard reagents using 1,2-diiodoethane as the oxidant in a mixed solvent of THF and ionic liquids, $[P_{444Me}][NTf_2]$. Under these conditions, the desired diacetylenes were obtained in moderate yields (equation 53). Ionic liquids were essential to realize the reaction because in pure THF the homocoupling failed.



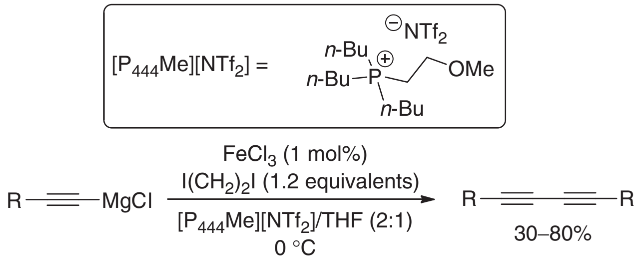
(51)

$R = C_6H_5$ (91%), $Me_2(MeO)C$ (75%)



(52)

R = n-C_4H_9 (91%), C_6H_5 (89%), t-$BuCOO(CH_2)_2$ (82%), morpholin-4-yl-$(CH_2)_2$ 85%



(53)

R = C_6H_5 (55%), 4-$MeOC_6H_4$ (52%), 4-$CF_3C_6H_4$ (80%), Me_3Si (35%)

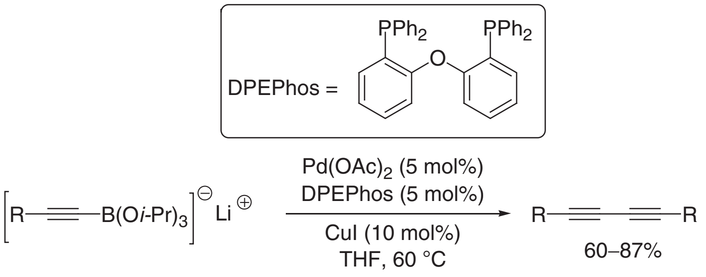
Among other alkali acetylides, lithium acetylides were also shown to participate in homocoupling reactions to provide the corresponding diacetylenes. Reactions can be achieved using transition metal catalysts (e.g., Pd and Ni) or in the presence of oxovanadium(V) or thionyl chloride.[4,5] In the latter case, the homocoupling product diphenylbuta-1,3-diyne (yield = 96%) was explained by the formation of a hypervalent trigonal–bipyramidal sulfurane intermediate. Lithium acetylides are often used as precursors for generating other organometallic acetylides with interesting coupling properties. Except for the homocoupling of alkynyl metalloids (boron, tin, and silicon) that will be presented later, other alkynyl complexes (e.g., Ti, Zr, Ni, Hg, Al, Pb, and Te)[4,5,7] have also been shown to undergo homocoupling reactions, but with moderate generality.

Although the methodologies discussed in this section (cf. Section 3.10.4) proved to be suitable for the synthesis of non-functionalized symmetrical 1,3-diynes, however, they require the presence of stoichiometric amounts of oxidizing agents and the previous preparation of alkali acetylide reagents by deprotonation of the corresponding terminal alkynes with *i*-PrMgCl or *n*-BuLi. Therefore, given their limited scope and low tolerance to functional groups, none of these methods has seen applications to date in modern acetylenic chemistry.

3.10.4.2 Homocoupling Reactions of Alkynylboron Reagents

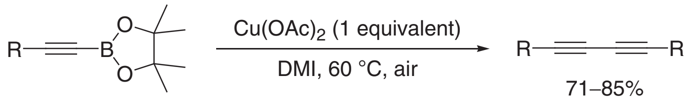
In 2004, Oh et al.[82] realized the synthesis of 1,3-diynes by coupling lithium alkynyltriisopropoxyborates using palladium acetate and DPEPhos as the catalytic system in the presence of CuI, which was shown to be necessary for the smooth transformation (equation 54). It is worth noting that the reaction does not need any base or oxidant. Electron-rich and electron-deficient groups in the arylalkynylborates caused no changes in the yields. Given that lithium acetylides are used as precursors for alkynylborates, substrates containing an ester, cyano, and pyridyl substituent could not be prepared by this method.

To avoid the use of expensive metals in combination of sophisticated phosphine ligands, Nishihara et al.[83] reported in 2005 the homocoupling of alkynylboronates using stoichiometric amounts of copper(II) acetate under air in a polar aprotic solvent, *N*,*N*′-dimethyl-2-imidazolidinone (DMI). The homocoupling products were obtained in good yields and the reaction does not require any added base, which is normally required for activation of organoboron compounds (equation 55).



(54)

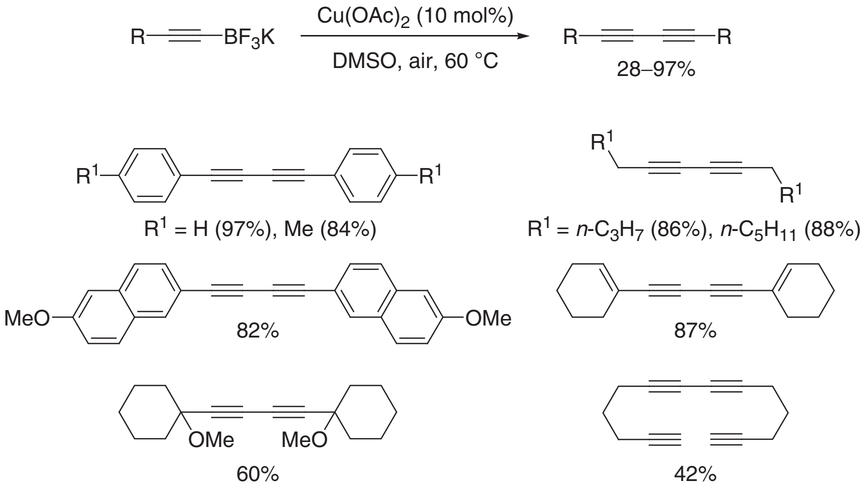
R = 4-$MeOC_6H_4$ (76%), 4-$NO_2C_6H_4$ (72%), n-C_4H_9 (87%), $TBDMSOCH_2$ (76%),
$TBDMSO(CH_2)_2$ (81%), $TBDMSO(CH_2)_3$ (78%), $BnO(CH_2)_4$ (82%), 1-cyclohexenyl (73%)



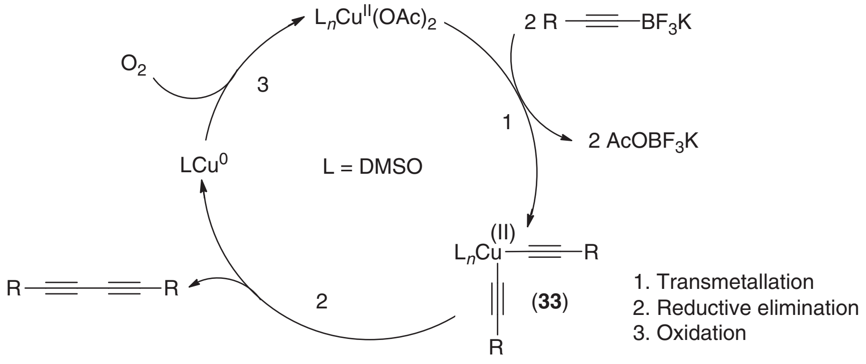
(55)

R = C_6H_5 (78%), 4-$MeOC_6H_4$ (74%), 3-$CF_3C_6H_4$ (78%), 2-thienyl (85%),
n-C_6H_{13} (79%), TBDMSO$(CH_2)_4$ (71%), $(EtO)_2CH$ (78%), $MeOCH_2$ (71%)

In 2008, Stefani and coworkers[84] reported that the use of moisture- and air-stable potassium alkynyltrifluoroborates as substrates, the oxidative homocoupling reaction efficiently occurred in the presence of only catalytic amounts of copper(II) acetate under air atmosphere in DMSO. Various potassium alkynyltrifluoroborates were found to undergo homocoupling reactions efficiently, including aromatic and aliphatic substrates with an oxy-functionality (Scheme 37). The authors proposed a mechanism based on the Cu(II)/Cu(0) couple (Scheme 38). It involves the formation of dialkynylcopper(II) species (**33**) through reaction of alkynyltrifluoroborate with copper(II) acetate. Reductive elimination of **33** would lead to 1,3-diyne and Cu(0), which was oxidized by O_2 and DMSO to generate the active Cu(II) species.

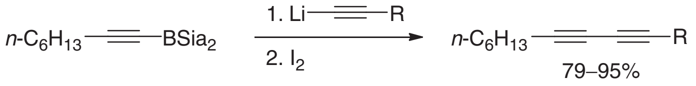


Scheme 37



Scheme 38

The reaction of alkynylborates can provide an efficient and selective method of coupling two unlike boron-bound groups. Oxidation of lithium dialkynyldialkylborates with iodine gave symmetrical 1,3-diynes.[4] Furthermore, this methodology was extended to the synthesis of unsymmetrical 1,3-diynes via iodination of unsymmetrical lithium dialkynyldialkylborates, formed by the stepwise addition of two different lithium acetylides to dicyclohexyl(methylthio)borane.[4] These intramolecular coupling reactions of organoborons, which are particularly effective in the case of aliphatic alkynes, gave good yields of the corresponding 1,3-diynes and provide interesting alternatives to the more conventional procedures (equation 56).



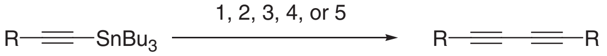
$$n\text{-}C_6H_{13}\text{—}\equiv\text{—}BSia_2 \xrightarrow[\text{2. } I_2]{\text{1. Li—}\equiv\text{—R}} n\text{-}C_6H_{13}\text{—}\equiv\text{—}\equiv\text{—R} \quad \text{79–95\%} \qquad (56)$$

R = C_2H_5 (95%), *c*-C_6H_{11} (80%), *n*-C_4H_9 (79%), C_6H_5 (79%)

3.10.4.3 Homocoupling Reactions of Alkynylstannane Reagents

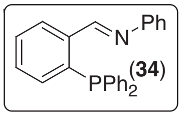
Alkynylstannane regents may also participate in homocoupling reactions to provide the corresponding 1,3-diynes. Several protocols were described which might constitute alternatives to the more established methods. The use of stoichiometric amounts of oxidizing reagents, $Cu(NO_3)_2$ or $AgNO_3$, in THF allows homocoupling of alkynyltributylstannanes in moderate yields (Scheme 39).[85a] The 85% yield obtained using this procedure contrast sharply with the 34% yield obtained for the homocoupling of 3-(tetrahydro-2*H*-pyran-2-yloxy)-1-propyne under standard Glaser conditions.

Transition metal-catalyzed process was described by Kang et al.,[85b] who employed copper(II) or Mn(II) salts in DMF or *N*-methylpyrrolidinone (NMP), respectively, in the presence of iodine as the oxidizing agent at 100 °C. Protocols achieving the homocoupling in the presence of palladium complex alone,[85d] or in combination with a copper(II) salt[85c] as the oxidant, were also reported. Hiyama and coworkers[85e] described a procedure that consists in the use of palladium–iminophosphine complex (**34**) and allyl acetate as an oxidant in DMF. Under these conditions, both aromatic and aliphatic ethynyltributylstannanes undergo homocoupling reaction to give the corresponding 1,3-diynes in good yields (Scheme 39). The use of atmosphere air as the oxidant gave poor yields (R=Ph (34%) and R=*n*-Bu (34%)). Similar to the mechanism discussed previously (cf. Section 3.10.2.1, Scheme 10), in these palladium-catalyzed processes, dialkynylpalladium(II) species was proposed to account for the formation of 1,3-diyne through a reductive elimination step.[85c] The role of oxidizing reagents (e.g., Cu(II), I_2, allyl acetate, O_2) is to regenerate the Pd(II) from Pd(0) species.



$$R\text{—}\equiv\text{—}SnBu_3 \xrightarrow{\text{1, 2, 3, 4, or 5}} R\text{—}\equiv\text{—}\equiv\text{—}R$$

1. $Cu(NO_3)_2{\cdot}3H_2O$ (1 equivalents), THF, r.t. (Ref. 85a)
   R = C_6H_5 (50%), 4-MeC_6H_4 (67%), *n*-C_4H_9 (60%), $THPOCH_2$ (85%)
2. $CuCl_2$ (10 mol %), or $MnBr_2$ (10 mol%), I_2 (0.5 equivalent), DMF or NMP, 100 °C (Ref. 85b)
   R = C_6H_5 (Cu: 95%, Mn: 81%)
3. $Pd(OAc)_2$ (5 mol %), $CuCl_2$ (2 equivalents), THF, r.t. (Ref. 85c)
   R = C_6H_5 (94%)
4. $Pd(OAc)_2$ (5 mol %), O_2, DMSO, r.t. (Ref. 85d)
   R = C_6H_5 (89%)
5. $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (3 mol %), (**34**) (6 mol%), allyl acetate, DMF, 40 °C (Ref. 85e)
   R = C_6H_5 (86%), 4-$CF_3C_6H_4$ (92%), 2-$CF_3C_6H_4$ (90%), 4-$MeOC_6H_4$ (93%), *n*-C_4H_9 (84%)

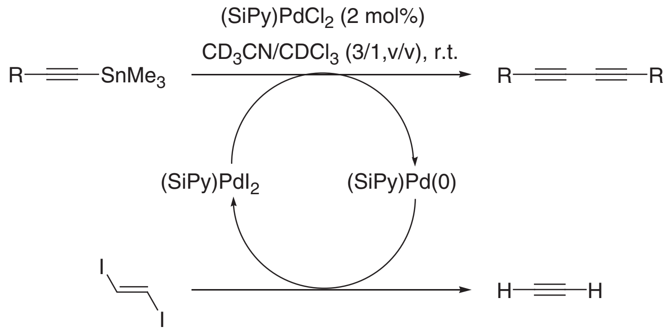


(**34**)

Scheme 39

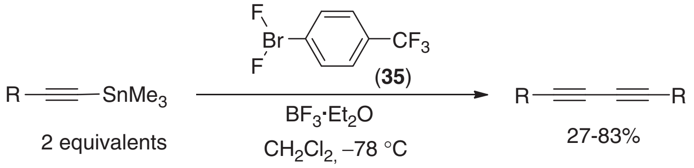
More reactive ethynyl(trimethyl)stannane substrates were also employed by Wright et al.[86] to generate their corresponding 1,3-diynes. Reactions were achieved using catalytic amounts of $(SiPy)PdCl_2$ complex $((Me_2Si(2\text{-pyridyl})_2)PdCl_2)$ along with (*E*)-1,2-diiodoethene as the oxidant (Scheme 40). The (*E*)-1,2-diiodoethene shows a remarkable selectivity for oxidation of the palladium(0) species, leaving the easily oxidized alkynylstannane bond intact. Use of $PdCl_2(PPh_3)_2$ as the catalyst instead of $(SiPy)PdCl_2$ showed no significant catalytic homocoupling of the alkynylstannane derivatives.

Homocoupling of ethynyl(trimethyl)stannanes were also found to occur in the presence of aryldifluoro-λ^3-bromane (**35**) and $BF_3 \cdot Et_2O$ at low temperature.[87] To be successful, the reaction required an excess of 1-alkynyltrimethylstannane (>2 equivalents) relative to hypervalent bromane (**35**) and worked only for aliphatic-substituted alkynes. Homocoupling products were formed in 27–83% yields (equation 57). The authors proposed a mechanism, which initially involves Lewis acid that promote the formation of 1-alkynyl(aryl)fluoro-λ^3-bromane (**36**) through a ligand exchange and its reaction with a second equivalent of ethynylstannane (Michael addition) to afford intermediate (**37**). The latter would evolve into the carbene (**38**) by a reductive elimination, and subsequently, a 1,2-shift of the alkynyl group in **38** would furnish the homocoupled product (Scheme 41).



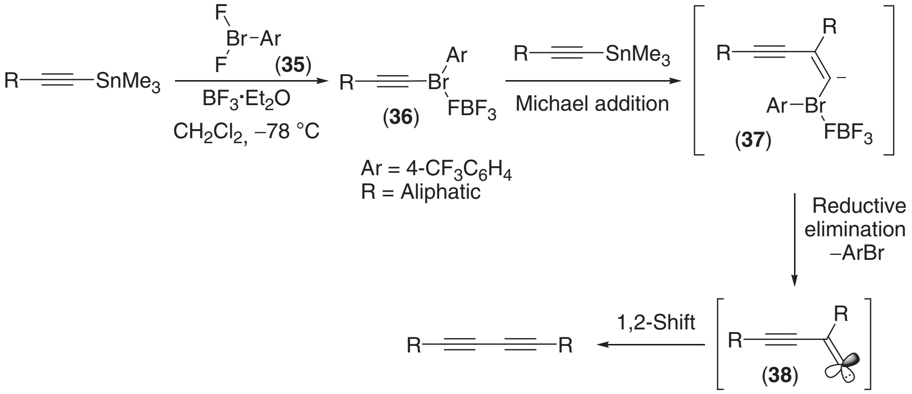
R (NMR yields) = C_6H_5 (93%), 4-MeOC_6H_4 (90%), Me_3Si (95%), 4-*t*-BuC_6H_4 (85%)

Scheme 40



(57)

R = *n*-C_4H_9 (74%), *n*-C_8H_{17} (78%), *c*-C_6H_{11} (80%), Cl$(CH_2)_3$ (69%)
t-Bu (83%), HC≡C$(CH_2)_3$ (45%), Me_3Si (27%), C_6H_5 (33%)

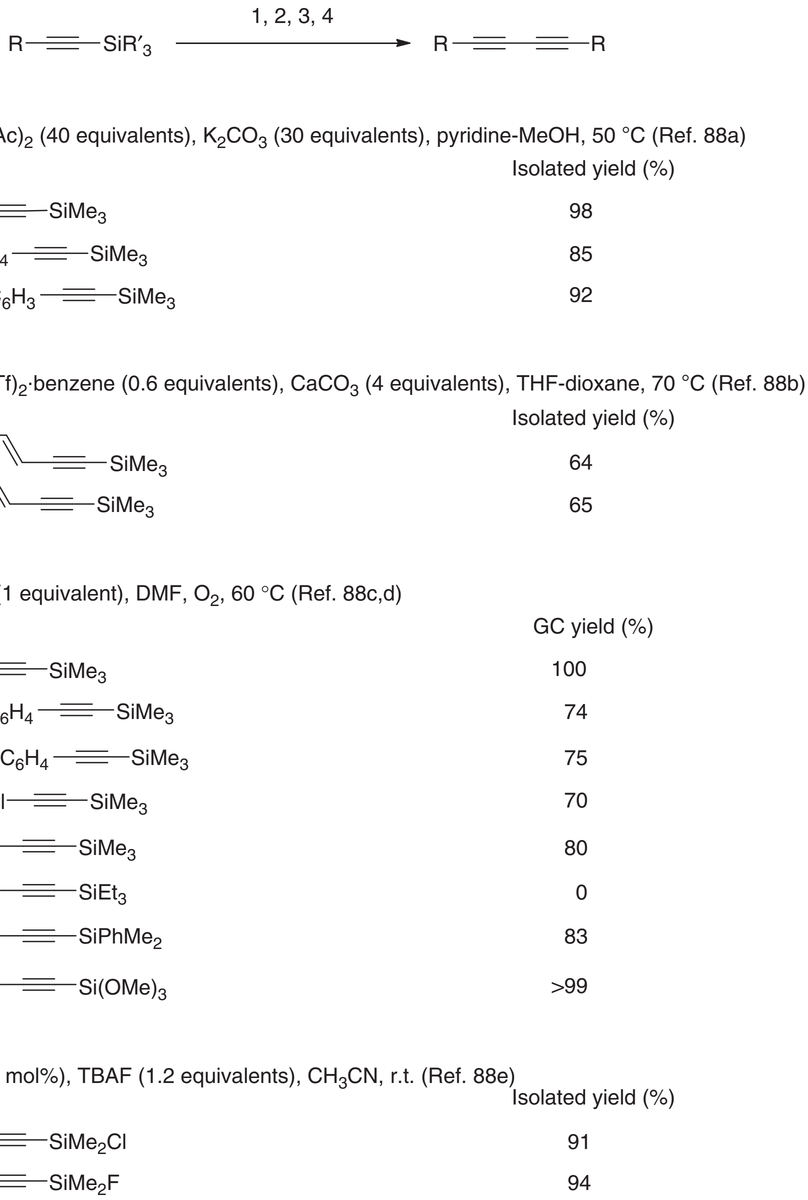


Scheme 41

3.10.4.4 Homocoupling Reactions of Alkynylsilane Reagents

Much attention has been focused on homocoupling of alkynyltrimethylsilanes since these reagents, especially functionalized substrates, are more widely available[43] than their counterpart boron and tin derivatives. Haley et al. developed a one-pot desilylation/dimerization sequence of alkynyltrimethylsilane derivatives;[88a] however, the protocol required large excess of both $Cu(OAc)_2$ and K_2CO_3 in a pyridine-methanol solution (Scheme 42). A catalytic version of this transformation was reported by Fiandanese and coworkers[88b] for the synthesis of diendiynes from silylated enynes employing copper(I) triflate complex and $CaCO_3$ as the base. Although this protocol furnished lower yields of diendiynes (33–65%) than the above-mentioned one ($Cu(OAc)_2/K_2CO_3$, 67–98%), it involves in the dimerization process the use of only catalytic amounts of copper salts (0.6 instead of 40 equivalents).

An interesting procedure reported by Mori and coworkers[88c,d] allows the dimerization of alkynylsilanes to give 1,3-conjugated diynes using CuCl in a polar solvent, such as DMF. Under these conditions, no base was needed to remove the trimethylsilyl protecting group. Studies with respect to substituent effects on silicon revealed that oxygen-substituted alkynylsilanes (e.g., $Si(OMe)_3$, $SiMe_2OSiMe_3$, and $SiMe_2(OH)$) underwent efficiently the homocoupling reactions, whereas with alkyl-substituted derivatives having a long alkyl chain (e.g., $SiEt_3$, Si(*i*-Pr)$_3$), no reaction occurred presumably for steric considerations as was suggested by the authors (Scheme 42).



$$R-\equiv-SiR'_3 \xrightarrow{1,\ 2,\ 3,\ 4} R-\equiv-\equiv-R$$

1. $Cu(OAc)_2$ (40 equivalents), K_2CO_3 (30 equivalents), pyridine-MeOH, 50 °C (Ref. 88a)

	Isolated yield (%)
$C_6H_5-\equiv-SiMe_3$	98
$2\text{-}BrC_6H_4-\equiv-SiMe_3$	85
$2,6\text{-}Br_2C_6H_3-\equiv-SiMe_3$	92

2. $(CuOTf)_2$·benzene (0.6 equivalents), $CaCO_3$ (4 equivalents), THF-dioxane, 70 °C (Ref. 88b)

	Isolated yield (%)
$Me_3Si-CH=CH-\equiv-SiMe_3$	64
$C_6H_5-CH=CH-\equiv-SiMe_3$	65

3. CuCl (1 equivalent), DMF, O_2, 60 °C (Ref. 88c,d)

	GC yield (%)
$C_6H_5-\equiv-SiMe_3$	100
$4\text{-}MeOC_6H_4-\equiv-SiMe_3$	74
$4\text{-}MeCOC_6H_4-\equiv-SiMe_3$	75
2-Thienyl$-\equiv-SiMe_3$	70
$n\text{-}C_6H_{13}-\equiv-SiMe_3$	80
$n\text{-}C_6H_{13}-\equiv-SiEt_3$	0
$n\text{-}C_6H_{13}-\equiv-SiPhMe_2$	83
$n\text{-}C_6H_{13}-\equiv-Si(OMe)_3$	>99

4. CuI (5 mol%), TBAF (1.2 equivalents), CH_3CN, r.t. (Ref. 88e)

	Isolated yield (%)
$C_6H_5-\equiv-SiMe_2Cl$	91
$C_6H_5-\equiv-SiMe_2F$	94

Scheme 42

Kang et al.[88e] reported the homocoupling of alkynyl halodimethylsilanes in the presence of tetrabutylammonium fluoride (TBAF). The methodology is advantageous in the sense that reactions proceed at room temperature in the presence of TBAF, and only catalytic amounts of CuCl are required to provide excellent yields of 1,4-diphenyl-1,3-butadiyne (Scheme 42). Unfortunately, only this example was reported, and therefore, it is difficult to estimate if other alkynyl halodimethylsilanes (especially aliphatic derivatives) would behave similarly.

Dimethoxy(methyl)ethynylsilanes may also be used as reagents in the synthesis of 1,3-diynes. Homocoupling reactions were performed in the presence of $Pd(OAc)_2$/dppp as the catalytic system without any added activators. For this Pd-catalyzed dimerization, the 1,3-diynes were obtained in modest yields (equation 58).[89]

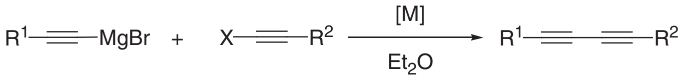
$$R-\equiv-SiMe(OMe)_2 \xrightarrow[\text{DMSO, } O_2,\ 70\ °C]{Pd(OAc)_2\ (5\ mol\%),\ dppp\ (7.5\ mol\%)} \underset{50\text{–}69\%}{R-\equiv-\equiv-R} \qquad (58)$$

R = C_6H_5 (69%), 1-naphthyl (57%), 1-cyclohexenyl (50%)

3.10.5 Coupling of Organometallic Alkynides and 1-Haloalkynes

3.10.5.1 Heterocoupling Reactions of Alkynyl Grignard Reagents

Similarly to the Cadiot–Chodkiewicz protocol, several groups attempted coupling of preformed organometallic acetylides with 1-haloalkynes to provide unsymmetrical 1,3-diynes. In the presence of catalytic amounts of cobalt(II) or copper(I) salts, nonfunctionalized aliphatic and aromatic alkynyl Grignard reagents underwent heterocoupling with 1-haloalkynes, but yields were low (**Scheme 43**).[4] Homocoupling arising from halogen/magnesium exchange, which generally takes place predominantly, and the lack of selectivity inherent in the use of Grignard reagent are the major drawbacks of these methods.

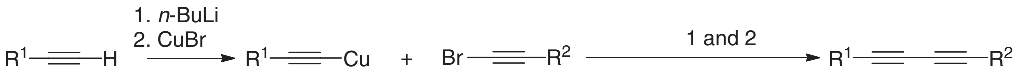


R^1	X	R^2	[M]	Yield (%)
n-C_4H_9	Br	C_6H_5	$CoCl_2$	31
C_6H_5	I	n-C_4H_9	CuCl	35

Scheme 43

3.10.5.2 Heterocoupling Reactions of Alkynylcopper Reagents

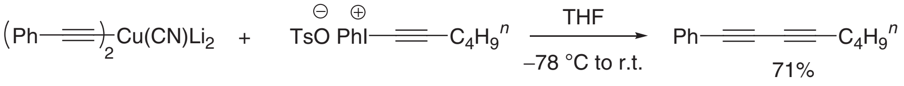
Curtis et al.[90a] reported a procedure allowing the heterocoupling between preformed copper(I) acetylides and 1-bromoalkynes (**Scheme 44**), but the coupling products were obtained in modest yields (26–66%). A similar methodology was developed by Zweifel and coworkers,[90b] who generated *in situ* the copper (I) acetylides and then subjected it to 1-bromoethynyltrimethylsilane to produce in good yields (70–93%) the silylated 1,3-diynes of wide interest in organic synthesis (**Scheme 44**).



1. Pyridine, 35–50 °C	Yield[90a]
$R^1 = CH_3, C_6H_5$, 2-thienyl $R^2 = CH_2OH$	26–66%
2. Pyridine, r.t. (*in situ* formation of Cu acetylide)	Yield[90b]
$R^1 = n$-C_6H_{13}, c-C_6H_{11}, 1-c-hexenyl, t-C_4H_9, $THPO(CH_2)_9$ $R^2 = SiMe_3$	70–93%

Scheme 44

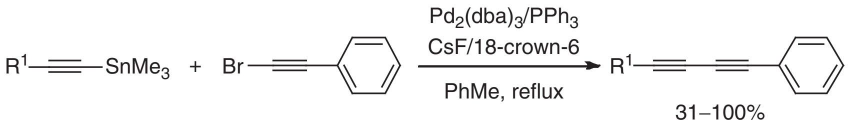
Heterocoupling with more reactive reagents was investigated by Stang and coworkers,[91] who subjected lithium dialkynylcuprates with alkynyl(phenyl)iodonium tosylates at low temperature providing unsymmetrical 1,3-diynes in a 71% yield with reasonable selectivity with respect to homocoupling (equation 59).



(59)

3.10.5.3 Heterocoupling Reactions of Alkynylstannane Reagents

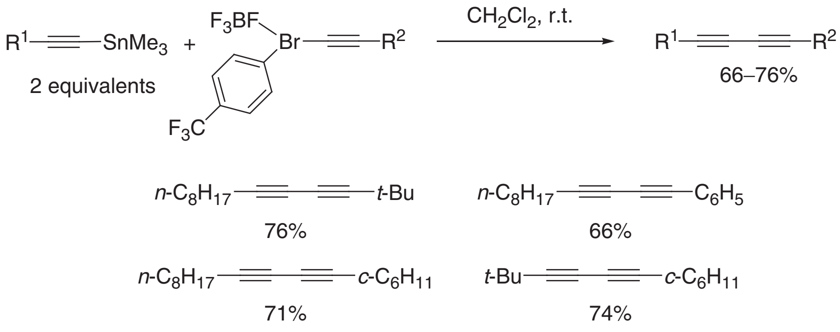
The Stille reaction of alkynylstannanes with 1-bromoalkynes using $Pd_2(dba)_3/PPh_3$ as the catalytic system in the presence of CsF was studied by Lukevics and coworkers (equation 60).[92] The presence of a fluoride ion source was found to be important for the outcome of this transformation, and unsymmetrical 1,3-diyne products were obtained in yields ranging from 31% to 100% (equation 60).



(60)

R^1 = 4-$MeOC_6H_4$ (39%), 4-FC_6H_4 (52%), C_6H_5 (100%),
2-Me-5-pyridyl (31%), 1-cyclohexenyl (45%)

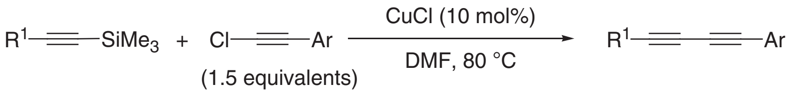
The previously reported methodology by Ochiai[87] was extended to produce unsymmetrical 1,3-diynes by cross-coupling of alkynyl(trimethyl)stannanes with alkynyl(aryl)difluoro-λ^3-bromane (equation 61).



(61)

3.10.5.4 Heterocoupling Reactions of Alkynylsilane Reagents

The reaction of alkynylsilanes with 1-chloroalkynes was studied in 1998 by Mori and coworkers[93] and deserves special attention. Heterocoupling was achieved using only catalytic amounts of CuCl under neutral conditions without any base in DMF at 80 °C (**Scheme 45**). Under these conditions, homocoupling arising from 1-chloroalkynes is clearly suppressed and occurs to a minor extent. Although yields of isolated unsymmetrical 1,3-diynes were moderate (32–69%), these results are quite remarkable considering that reactions of 1-chloroalkynes with terminal alkynes often furnish cross-coupled products in low yields[7,69] (cf. equation 48). Due its simplicity, this procedure seems to be promising for the synthesis of polyynes and cyclic alkynes.

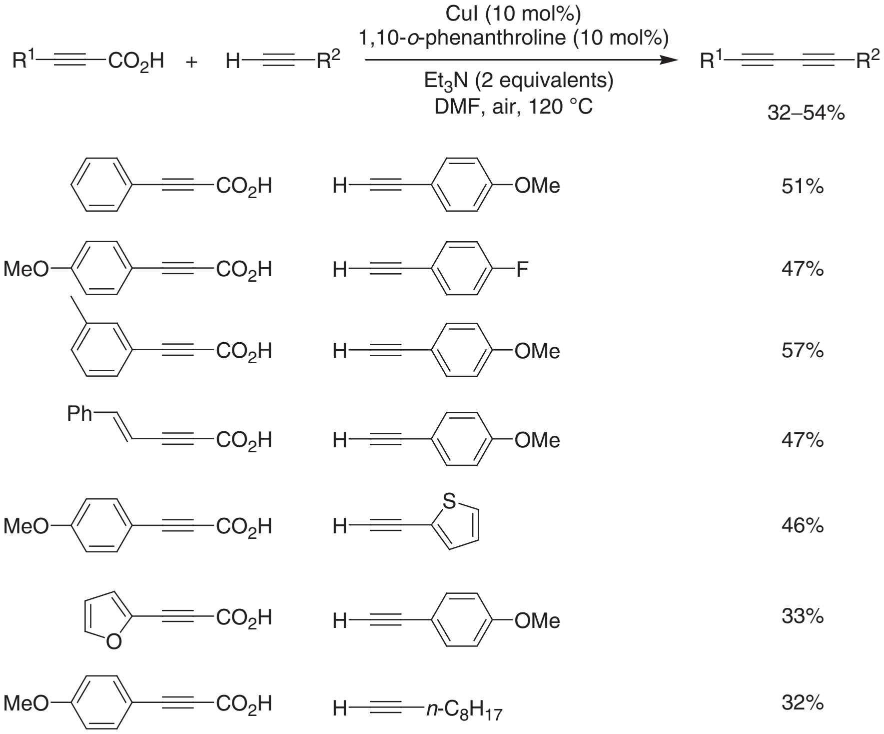


R^1	Ar	Yield (%)
4-$MeOC_6H_4$	C_6H_5	65
4-$MeOC_6H_4$	4-ClC_6H_4	54
4-$MeCOC_6H_4$	C_6H_5	69
4-$MeCOC_6H_4$	4-ClC_6H_4	42
4-NCC_6H_4	4-$MeCOC_6H_4$	61
4-$Bu^tMe_2SiOC_6H_4$	4-ClC_6H_4	32

Scheme 45

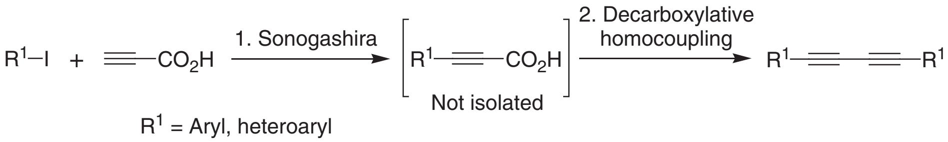
3.10.6 Decarboxylative Coupling of Propiolic Acids

In recent years, alkynyl carboxylic acids have shown a great potential in catalytic transformations. They can also be considered to be valid candidates for the replacement of organometallic acetylides in metal-catalyzed decarboxylative cross-coupling reactions.[94] The possibility for *in situ* generating alkynyl acetylides through a CO_2-release process in the presence of transition metals has attracted the interest of several groups. In this context, Yu et al.[95] reported that propiolic acid may be used as the coupling partner with terminal alkyne in the construction of unsymmetrical conjugated diynes (Scheme 46). The coupling was carried out using CuI/1,10-*o*-phenanthroline as the catalytic system and Et_3N as a base under air. Both aliphatic and (hetero)aromatic terminal alkynes bearing various substituents on the benzene nucleus (e.g., MeO, Cl, F, and vinyl groups) are good substrates for the decarboxylative coupling with styryl and (hetero)aryl propiolic acid partners. Although the corresponding 1,3-diynes were isolated in low to modest yields (32–54%, Scheme 46), this protocol avoids the use of 1-haloalkyne and alkynyl metal reagents (Cadiot–Chodkiewicz type reaction), and only carbon dioxide is produced as by-products. Given that this protocol employs copper as the catalyst and a base (Glaser-type reaction), it is surprising to note that no comment was made about side dimerization reactions that can occur from both coupling reaction partners, the terminal alkyne and alkynyl carboxylic acid.

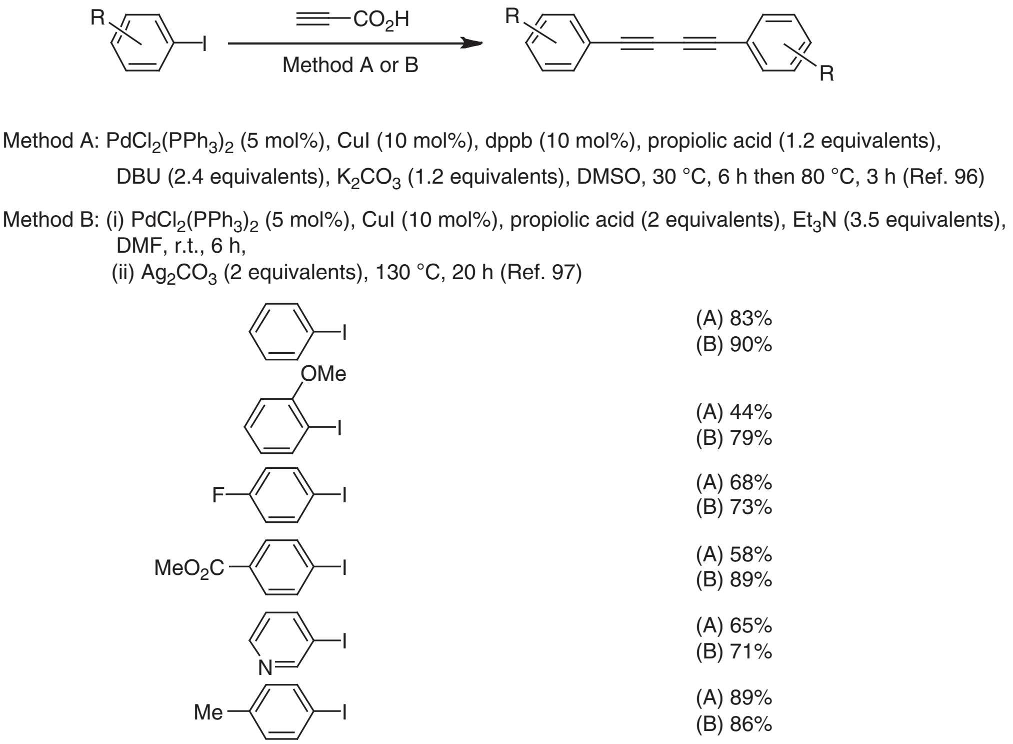


Scheme 46

In 2011, Lee et al.[96] and Kim et al.[97] reported seemingly independent, if not simultaneous, studies of a one-pot synthesis of symmetrical 1,3-diynes using a sequence of Sonogashira reaction and decarboxylative homocoupling of arylpropiolic acid (Scheme 47). In both methods, the synthesis of symmetrical 1,3-diynes was achieved through the reaction of an aryl iodide with propiolic acid in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI; diarylalkyne by-products formed during this one-pot sequence are clearly suppressed under these conditions and occur only to a minor extent. On the use of Lee's protocol,[96] the addition of 1,1′-bis(diphenylphosphino)butane (dppb) was found to be necessary for the reaction efficiency; the reagents and catalyst are mixed together and experimental conditions are set up in such a way to promote the reaction cascade. Under Kim's conditions,[97] no ligand has been required and the transformation was achieved in a sequential way by introducing Ag_2CO_3 in a second step to promote the decarboxylative homocoupling reaction. Generally, both procedures worked well with aryl iodides independent of the type of the substituent on the aromatic ring; however, in some cases (e.g., 2-iodoanisole or methyl 4-iodobenzoate), Kim's protocol seems to be more efficient than that reported by Lee (Scheme 48). In contrast with the aforementioned report,[95] the substrate scope was limited only to the synthesis of 1,4-diarylsubstituted 1,3-diynes (Scheme 48).



Scheme 47

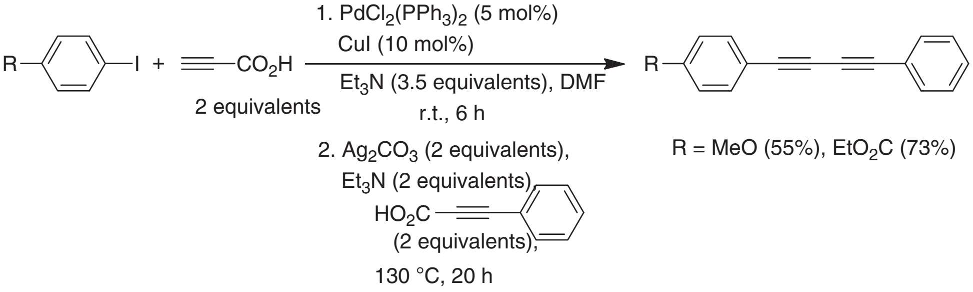


Method A: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), dppb (10 mol%), propiolic acid (1.2 equivalents), DBU (2.4 equivalents), K_2CO_3 (1.2 equivalents), DMSO, 30 °C, 6 h then 80 °C, 3 h (Ref. 96)

Method B: (i) $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), propiolic acid (2 equivalents), Et_3N (3.5 equivalents), DMF, r.t., 6 h,
(ii) Ag_2CO_3 (2 equivalents), 130 °C, 20 h (Ref. 97)

Scheme 48

In addition to the homocoupling of alkynyl carboxylic acids, Kim and coworkers[97] described an analogous heterocoupling of two different 3-substituted propiolic acids (equation 62). Besides the expected heterocoupled product, the reaction furnished symmetrical 1,3-diynes arising from homocoupling of both alkynyl propiolic acids employed. It was found that the amount of the second alkynyl propiolic acid added and base controls the reaction outcome. Therefore, using 2 equivalents of either phenylpropiolic acid or Et_3N, under otherwise standard conditions, afforded the desired unsymmetrical 1,3-diynes in 55–73% yields (equation 62).



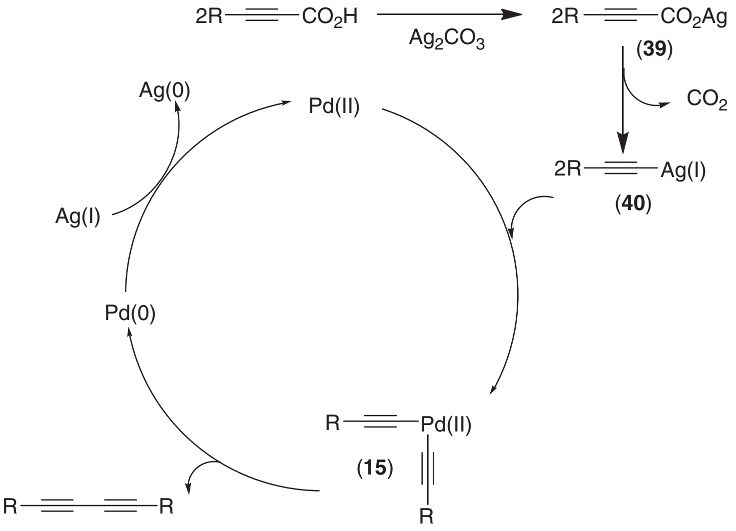
(62)

A proposed reaction mechanism for the formation of 1,4-disubstituted-1,3-diynes is shown in Scheme 49. Initially, the palladium(0) species, formed after the Sonogashira process, is oxidized by silver carbonate to palladium(II) catalyst. Also, 3-arylpropiolic acid, generated from the corresponding iodoarene, can be converted into Ag(I)-acetylide intermediate (**40**) through the decarboxylation of Ag(I)-carboxylate intermediate (**39**). Transmetalation of two Ag(I)-acetylides (**40**) to Pd(II) would directly give dialkynylpalladium species (**15**), which would evolve via reductive elimination to form the 1,3-diyne product and regenerate Pd(0) catalyst.

3.10.7 Elimination Reactions of Haloolefins

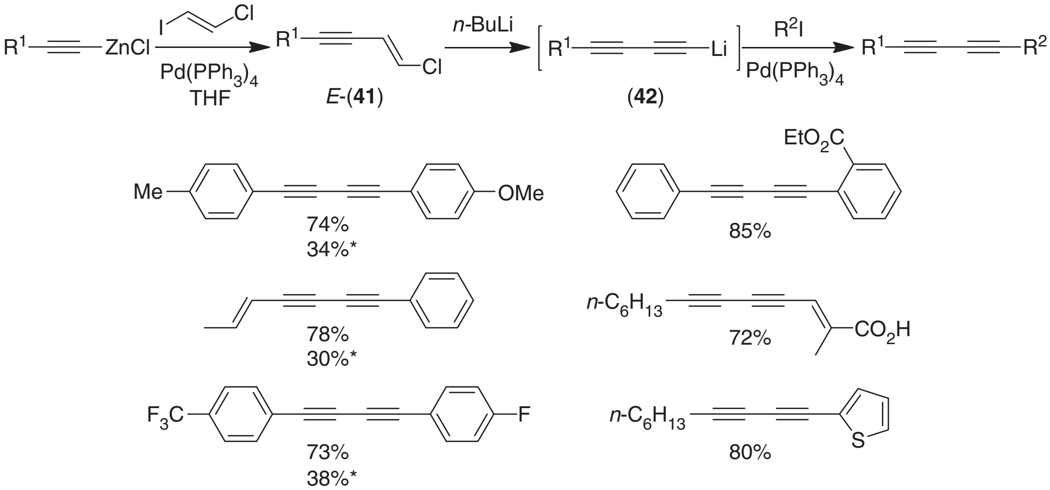
3.10.7.1 Synthesis of Conjugated Diynes from Haloenynes

Besides Cadiot–Chodkiewicz cross-coupling, unsymmetrical 1,3-diynes can also be prepared by a two-step sequence involving (1) the Pd-catalyzed coupling reaction of alkynylzinc derivatives with 1,2-dihaloalkenes and (2) the conversion of the resulting haloenynes *E*-(**41**) by a strong base into the corresponding 1,3-diynyl lithium (**42**), which can undergo further functionalization processes to provide unsymmetrically disubstituted 1,3-diynes. Pioneering work by Negishi et al.[98] showed that the scope of this



Scheme 49

selective method was very wide and constitutes a superior alternative to Cadiot–Chodkiewicz reaction in many cases (Scheme 50). The reaction worked well for aliphatic and aromatic alkyne derivatives and had a high tolerance of various functional groups in haloenynes (R^1 group) and in the unsaturated organic R^2 groups incorporated such as esters, ethers, nitro, fluoro, and carboxylic acid groups. Although the conversion of terminal alkynes into 1,3 diynes by this method requires two steps, it avoids the preparation of 1-bromoalkynes required in the Cadiot–Chodkiewicz cross-coupling.



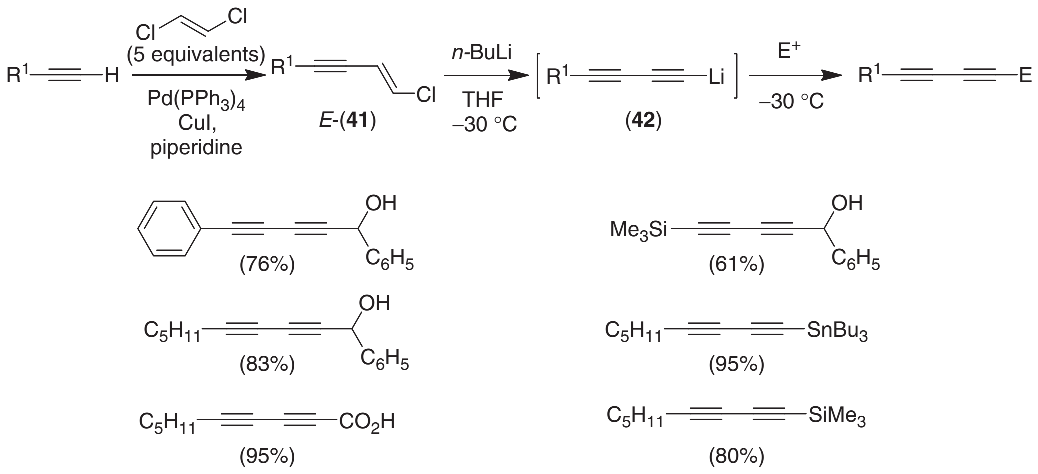
*Yield under Cadiot–Chodkiewicz conditions: CuCl, $NH_2OH{\cdot}HCl$, n-$PrNH_2$, EtOH

Scheme 50

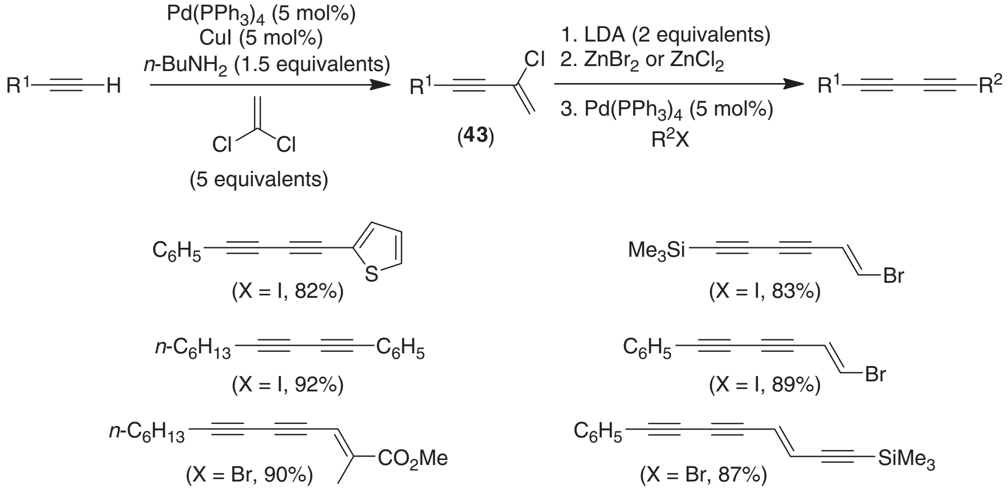
A similar reaction was developed by the Alami et al.[99a] involving the coupling of 1,2-(*E*)-dichloroethylene with terminal alkyne to generate chloroenyne derivatives *E*-(**41**).[99b] Accordingly, the intermediate 1,3-diynyl lithium (**42**), formed through Fritsch–Buttenberg–Wiechell (FBW) rearrangement, can be trapped with various electrophiles (e.g., RCHO, CO_2, I_2, Bu_3SnCl, Me_3SiCl, H_2O, etc.) leading to terminal or internal diynes in good yields (Scheme 51).

1,1-Dichloroethylene was also used as coupling partner in this sequence to provide chloroenynes (**43**), which was then successfully converted into unsymmetrical diynes in good to excellent yields.[100] Various terminal alkynes were employed in the C*sp*–C*sp*^{2} coupling of the first step and a wide range of electrophile partner (R^2X) were tolerated on the second C*sp*–C*sp*^{2} coupling, such as aryl and alkenyl halides including 1,2-iodobromoethylene (Scheme 52).

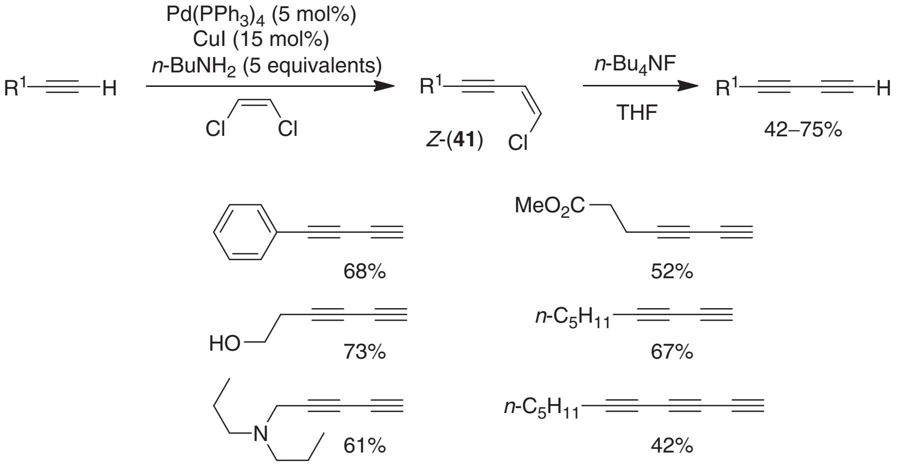
Rather than using a very strong base (e.g., *n*-BuLi, LDA) for conversion of chloroenynes *E*-(**41**) or (**43**) into 1,3-diynyl lithium (**42**), Kende and coworkers[101] demonstrated that starting from *Z*-(**41**), the elimination reaction could be achieved successfully using n-Bu_4NF as the base at room temperature. Accordingly, this strategy furnished in moderate to good yields exclusively terminal 1,3-diynes (Scheme 53).



Scheme 51

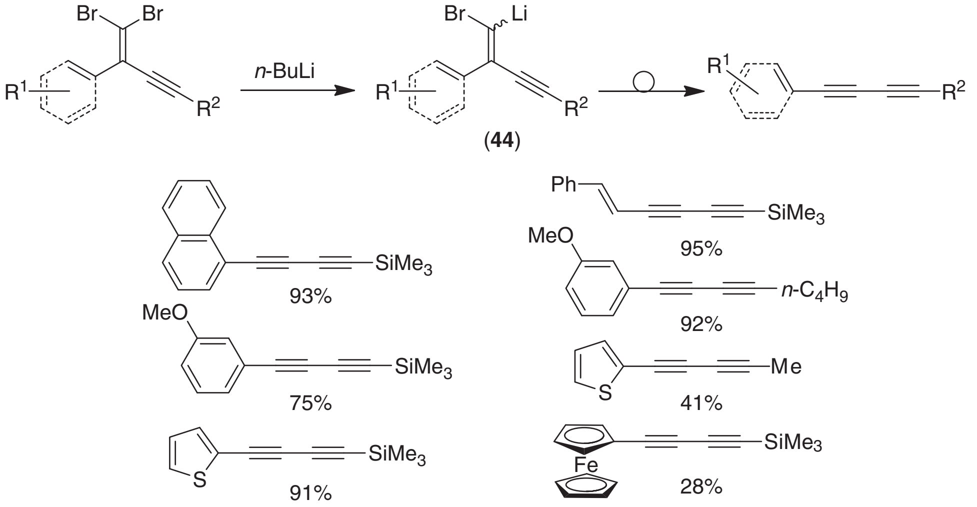


Scheme 52

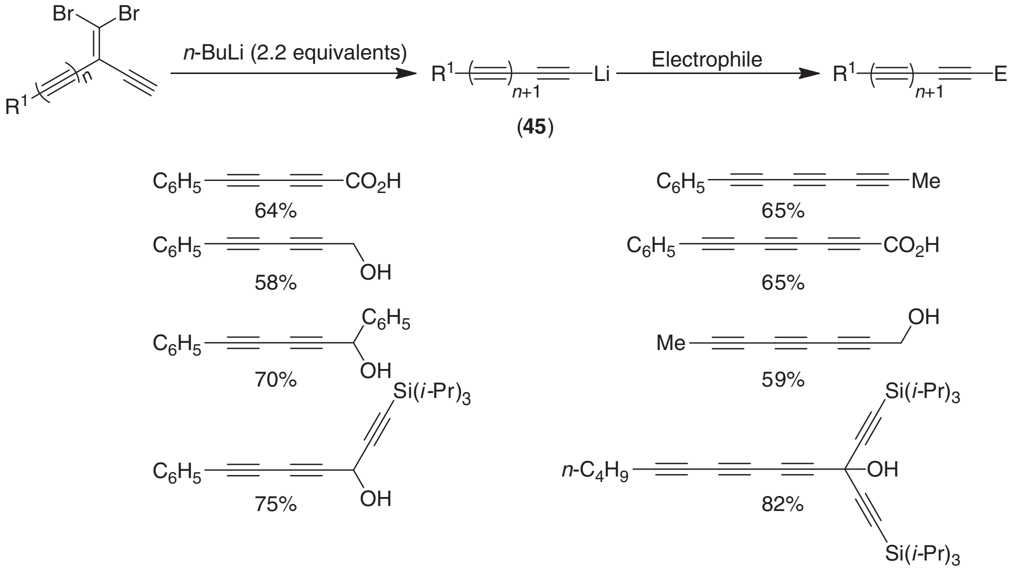


Scheme 53

Dependent on reaction conditions and substrates, carbenoid species (**44**), formed from 1,1-dibromoolefin through a lithium halogen exchange reaction, can undergo 1,2-alkyne migration according to FBW rearrangement to afford 1,3-diynes (Scheme 54).[102] Recently, Tykwinski and coworkers[102c] exploited this carbenoid rearrangement and reported a new route to unsymmetrical 1,3-butadiynes and 1,3,5-hexatriynes (Scheme 55). This rearrangement allows a range of pendant groups to be appended to the diyne skeleton, including aromatic hydrocarbon, electron-rich and electron-poor aryl, heteroaryl, alkyl, and vinyl functionalities. The lithium acetylide (**45**) formed from FBW reaction can also undergo transmetallation to furnish the corresponding zinc, copper, tin, or platinum acetylides, leading to the divergent formation of symmetrical and unsymmetrical conjugated acetylenes.



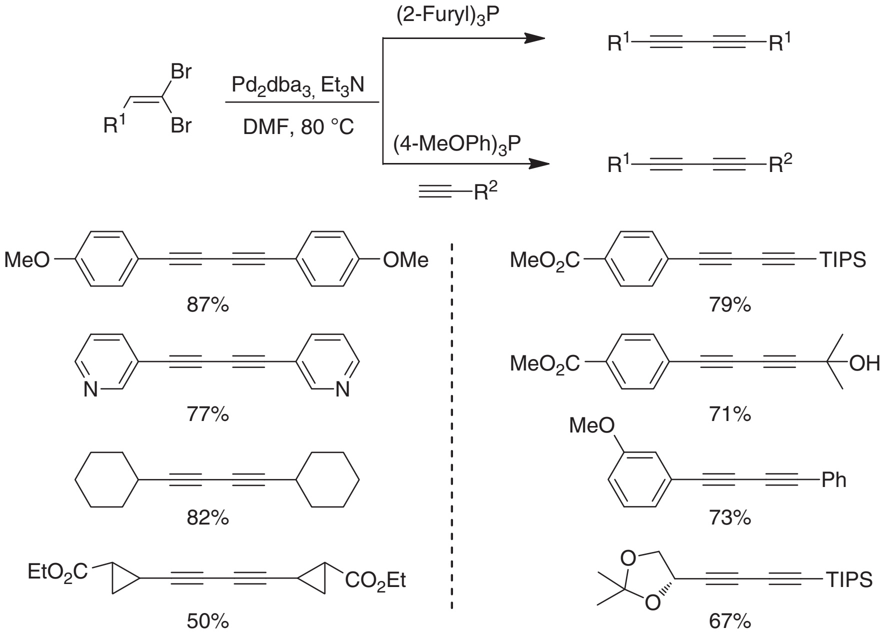
Scheme 54



Scheme 55

3.10.7.2 Synthesis of Conjugated Diynes from 1,1-Dihaloalkenes

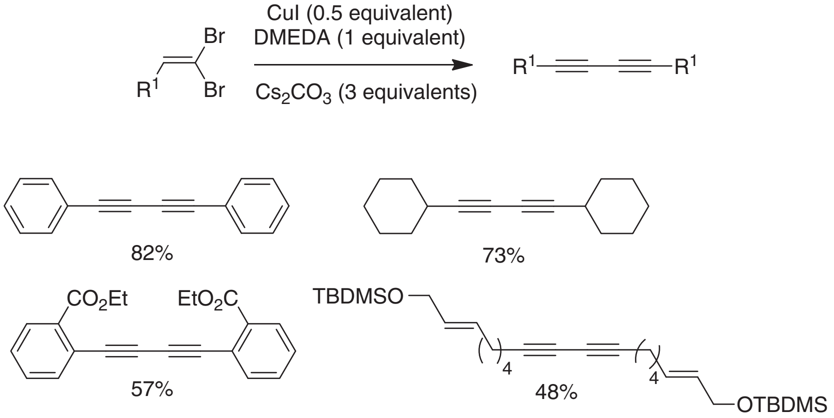
An elegant palladium-catalyzed synthesis of both symmetrical and unsymmetrical 1,3-diynes from 1,1-dibromoalk-1-enes was described by Shen,[103] who showed that the nature of phosphine ligand plays a critical role in the outcome of this transformation (Scheme 56). Symmetrical 1,3-diynes were obtained in excellent yields when 1,1-dibromoalk-1-enes were treated under Pd/Cu-cocatalysis in the presence of tris(2-furyl)phosphine, whereas unsymmetrical diynes were formed when conducting the reaction



Scheme 56

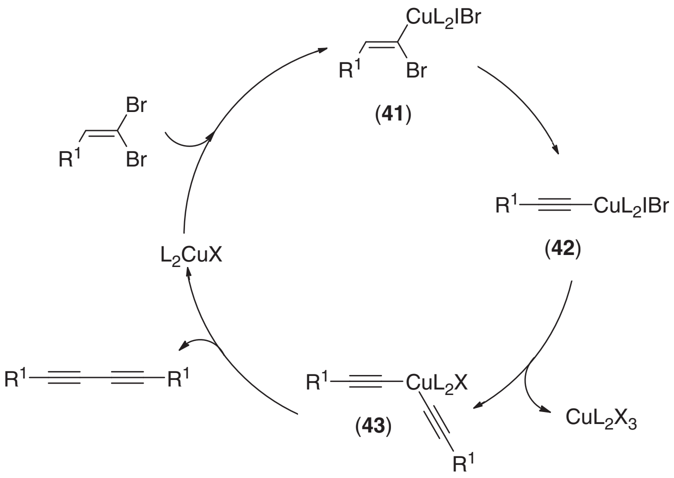
with terminal alkyne in the presence of tris(4-methoxyphenyl)phosphine as the ligand without addition of CuI (Scheme 56). These reactions demonstrate the importance of ligands and additives in palladium-catalyzed reactions. The electronic characteristics and substitution patterns of 1,1-dibromoalkens do not affect the formation of both symmetric and unsymmetric 1,3-diynes.

Based on the reactivity of *gem*-dibromoolefins, recently Evano and coworkers[104] demonstrated that these derivatives can undergo smooth dimerization to symmetrical 1,3-diynes in the presence of a substoichiometric amount of copper iodide (0.5 equivalent), a diamine ligand *N,N*′-dimethylethylenediamine (DMEDA), and cesium carbonate. Accordingly, a variety of 1,3-diynes could be obtained in moderate to good yields, and the reaction is compatible with a variety of aromatic and aliphatic groups (Scheme 57).



Scheme 57

A plausible mechanism for the reaction is outlined in Scheme 58. 1,1-Dibromoalk-1-ene would first undergo copper insertion into the more reactive *trans* C–Br bond to give species (**41**). The latter would evolve into the alkynylcopper (**42**) in the highly dipolar DMF solvent and in the presence of cesium carbonate. Ligand exchange between two alkynylcopper would then give dialkynylcopper (**43**) together with the formation of copper trihalide as one of the final products, which accounts for the stoichiometry (0.5 equivalent of copper salt/dibromide) of the reaction. Finally, reductive elimination from **43** would give the expected symmetric 1,3-diyne.



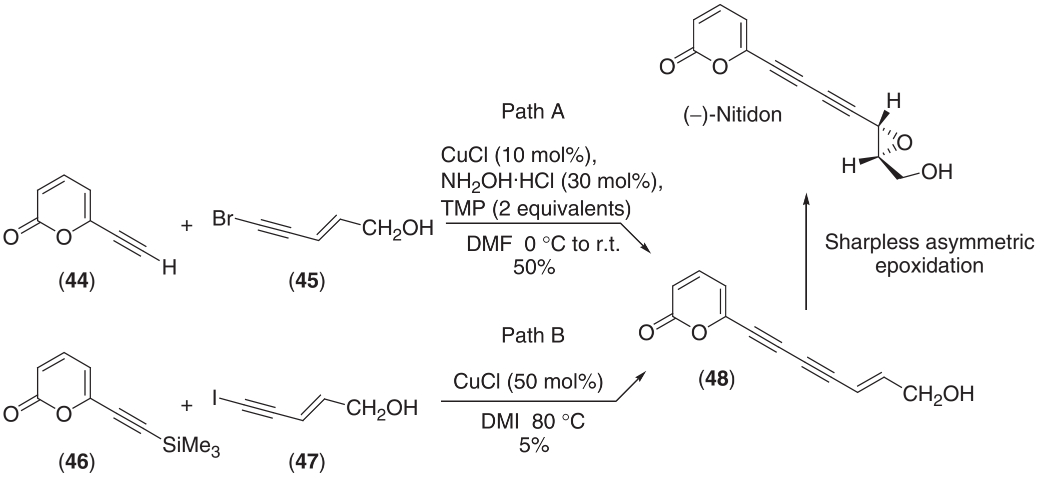
Scheme 58

3.10.8 Applications

3.10.8.1 Natural Product Synthesis

Many metabolites found in nature contain diynes moieties, and therefore, the coupling reactions between two *sp* carbon centers have found frequent uses in their syntheses, with some selected examples being mentioned in more general reviews on cross-coupling reactions.[1,4] This section covers recent applications of this coupling methodology toward the total synthesis of natural products. For aspects related to biosynthesis and biological activity of polyacetylenic natural products, the reader is referred to the review by Hansen and Boll.[105]

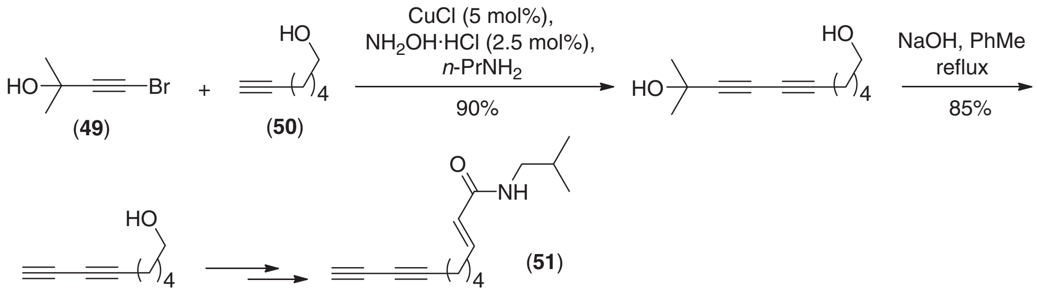
Up to date, the Cadiot–Chodkiewicz coupling reaction remains a method of choice for assembling natural acetylenic compounds. Rossi and coworkers[106] prepared the naturally antibacterial, antifungal, and cytotoxic basidiomycete metabolite (–)-nitidon by Sharpless asymmetric epoxidation of conjugated diyne (**48**) (Scheme 59). The authors found that the best route for the preparation of (*E*)-enediynol (**48**) involves a modification of the Cadiot–Chodkiewicz reaction (path A), whereas reaction between alkynyltrimethylsilanes (**46**) and 1-iodoalkyne (**47**) gave unsatisfactory result (Scheme 59).



Scheme 59

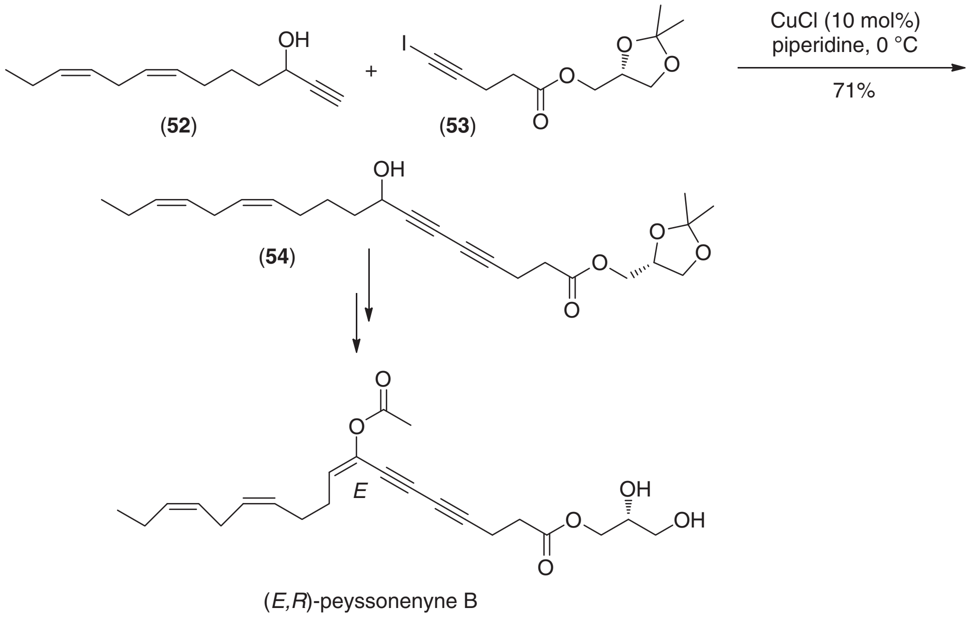
Echinacea extracts contain naturally polyunsaturated alkyl amides, which may have interests in the treatment of bacterial and viral infections. De Voss and coworkers[107] achieved the synthesis of many polyunsaturated alkyl amides; among them, compound **51** containing a terminal 1,3-diyne moiety was prepared via a Cadiot–Chodkiewicz coupling of an appropriate alkyn-1-ol (**50**) with a common bromoacetylene precursor (**49**), followed by a retro Favorski reaction to furnish terminal bisacetylene product (Scheme 60).

Peyssonenynes were isolated in 2004 from the Fijian red marine alga *Peyssonnelia caulifera*. *In vitro* assays showed that these compounds inhibited deoxyribonucleic acid (DNA) methyl transferase 1 with IC_{50} value ranging from 9 to 16 μM. In their



Scheme 60

synthesis, Lera and coworkers[108] constructed the diyne moiety of peyssonenyne B by selecting conditions reported by Alami (CuI and piperdine)[69] given their experimental simplicity in comparison with standard Cadiot–Chodkiewicz protocol (CuCl, $HONH_2$. HCl, Et_2NH, and MeOH). Condensation of propargylic alcohol (**52**) and 1-iodoalkyne (**53**) provided diynol (**54**), which was further converted into (*E*,*R*)-peyssonenyne B (**Scheme 61**).



Scheme 61

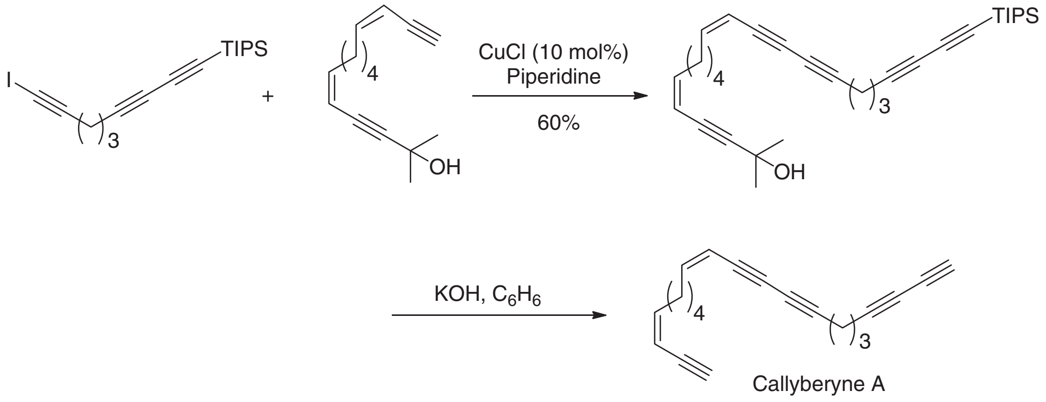
By using the same protocol, López and coworkers[109] described the synthesis of callyberyne A, a sponge-derived hydrocarbon polyacetylene that exhibited potent metamorphosis-inducing activity in the ascidian *Halocynthia roretzi* (**Scheme 62**).

Trocheliophorolide D containing a conjugated triynes system and a (*Z*)-double bond is a member of butenolide lipids isolated from the soft corals *Sarcophyton trocheliophorum*. This marine natural product collected in the Red Sea exhibits antibacterial activity against only Gram-positive bacteria and is toxic to brine shrimp. Kim and coworkers[110] constructed the triyne unit of trocheliophorolide D during the final stage of the synthesis using a mild palladium coupling protocol between bromodiyne (**55**) and 2-propynol (**Scheme 63**).

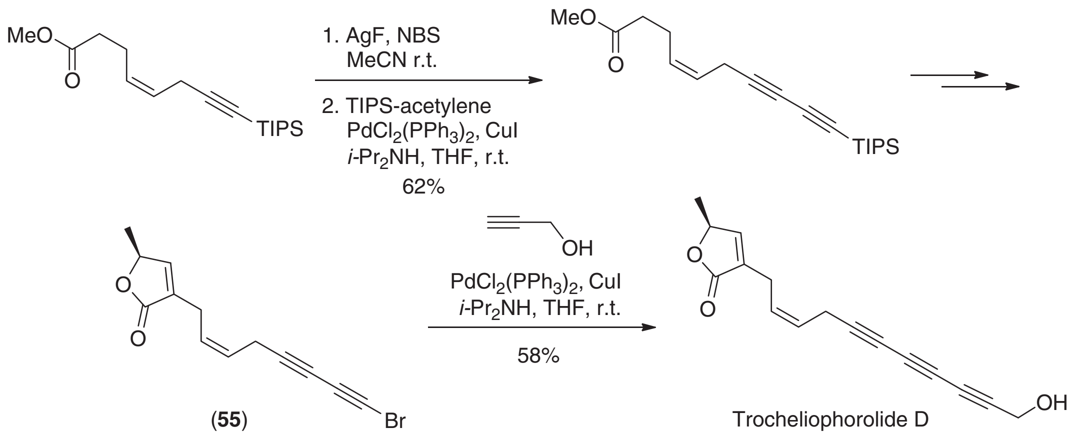
Recently, Bandichhor and coworkers[111] reported the total synthesis of polyacetylene panaxjapyne C. The key step of this synthesis includes a Cadiot–Chodkiewicz cross-coupling between terminal alkyne (**57**) and alkynyl bromide (**56**). Further deprotection of the *p*-methoxybenzyl group in intermediate (**58**) with TFA afforded the target molecule panaxjapyne C (**Scheme 64**).

3.10.8.2 Linear Polyalkynes

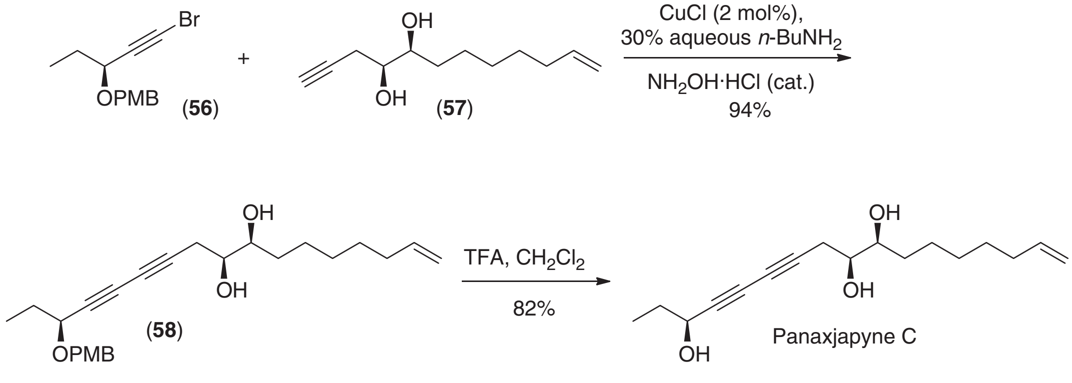
The unique properties of polyynes continue to garner attention and increased research interest. In addition to their unusual electrical and optical properties, they display a wide range of potential applications in material sciences. In this section, the authors present a number of recent studies illustrating the synthetic advances reported over the past decade. The most common synthetic method for the assembly of polyynes involves bond formation between two acetylenes via oxidative coupling using the classic protocols developed by Glaser, Hay, and Eglinton. The instability of simple and higher polyynes is a major challenge in



Scheme 62



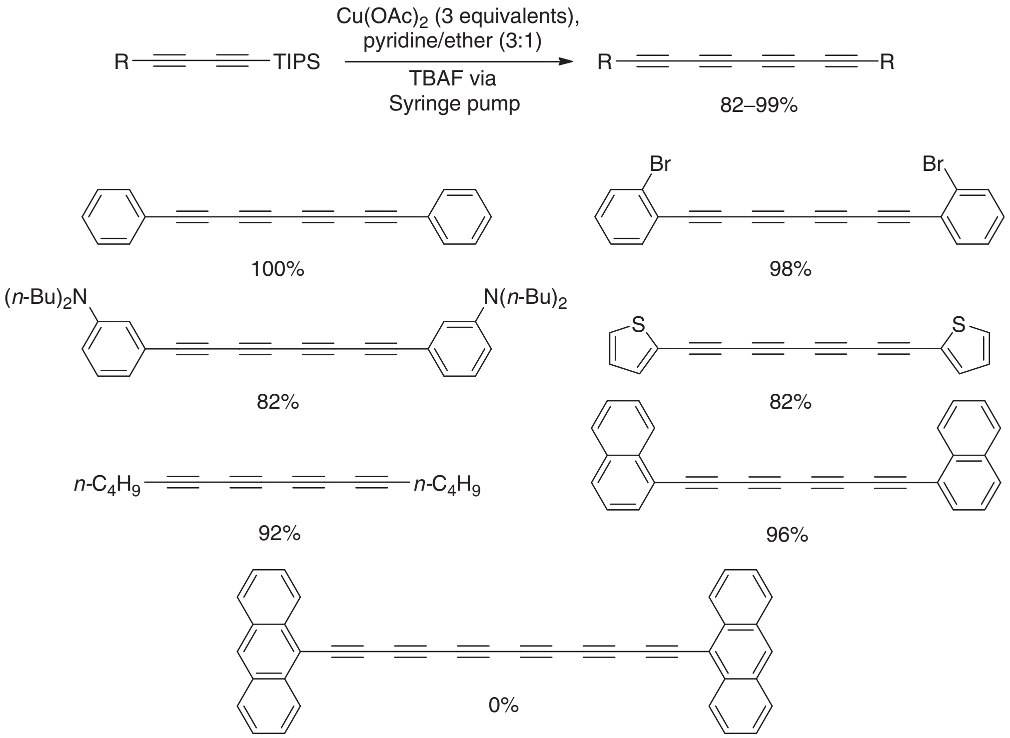
Scheme 63



Scheme 64

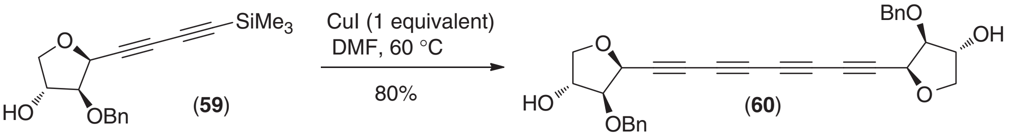
their synthesis. They are highly sensitive to polymerization and prone to rapid decomposition. Newer combinations and modifications have been developed involving the *in situ* one-pot desilylation/dimerization of acetylenes.

In 2001, Fallis and coworkers[112] described an efficient method for the *in situ* desilylation/oxidative dimerization of (triisopropylsilyl)acetylenes. This protocol is based on the addition of a fluoride source to a solution of the substrate and a copper salt; in this manner, this method avoids the complications encountered with sensitive diynes by eliminating the deprotection and isolation steps. This method afforded yields of tetraynes in the range of 82–99% for various substituted aromatic and alkyl systems, but revealed to be unsuccessful to form a hexayne product (Scheme 65).

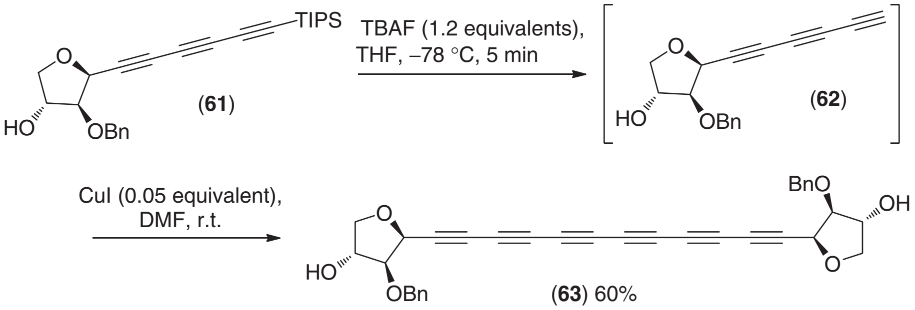


Scheme 65

A good example of the synthetic possibilities opened up by this method was provided by Shaw and coworkers,[113] who achieved the synthesis of tetrahydrofuranyl-tetrayne (**60**) from TMS-diyne derivative (**59**) in the presence of CuI under neutral conditions without base (equation 63). For more challenging hexayne (**63**), its synthesis was achieved by desilylation of **61** followed by the treatment of the terminal triyne intermediate (**62**) with CuI in dry DMF (Scheme 66).

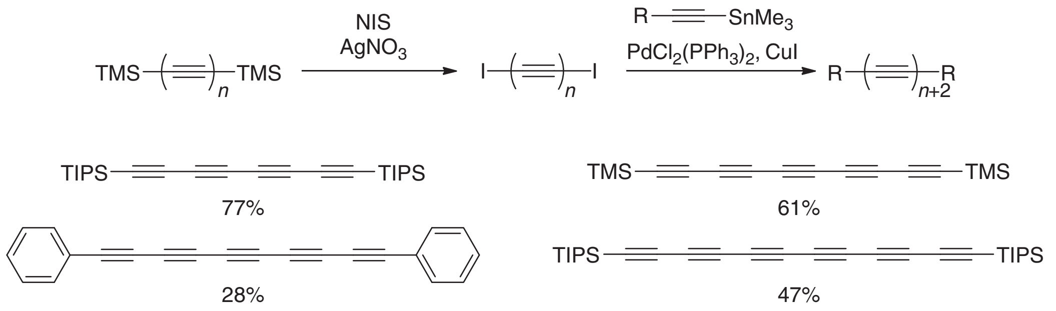


(63)



Scheme 66

Recently, Goroff and coworkers[114] developed an iterative synthetic method for obtaining symmetrical polyynes. This route encompasses a series of iodination and Stille coupling reactions, in which each cycle symmetrically increases the length of the resulting polyyne by four carbon atoms. The silyl end groups are iodinated by using $AgNO_3$ and *N*-iodosuccinimide, resulting in relatively stable diiodopolyyne intermediates. A variety of tin acetylides are mixed with the diiodoalkyne in a symmetric double cross-coupling reaction to produce a polyyne that is increased by two C≡C bonds in length. With this method, tetraynes, pentaynes, and hexaynes have been prepared (Scheme 67).

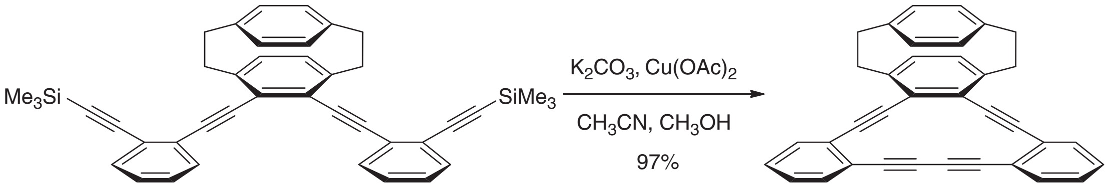


Scheme 67

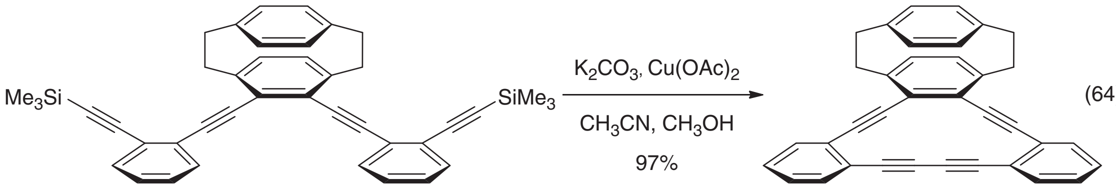
3.10.8.3 Cyclic Alkynes

Macrocycles consisting of benzene cores linked by acetylenic units have attracted considerable recent attention in supramolecular chemistry and materials sciences. The oxidative coupling of α,ω-diethynyl derivatives by the Eglington method, which can be performed under homogenous high-dilution conditions, is suitable to obtain cyclic diynes. For aspects related to studies illustrating the synthetic advances of cyclic polyacetylenes, the reader is referred to the excellent review by Diederich[4] and Haley,[115] and the recent report by Stefani.[5] A wide variety of annulenes[115] and catenanes have been synthesized by Glaser-type oxidative homocoupling reactions. A limited selection of these molecules is illustrated here.

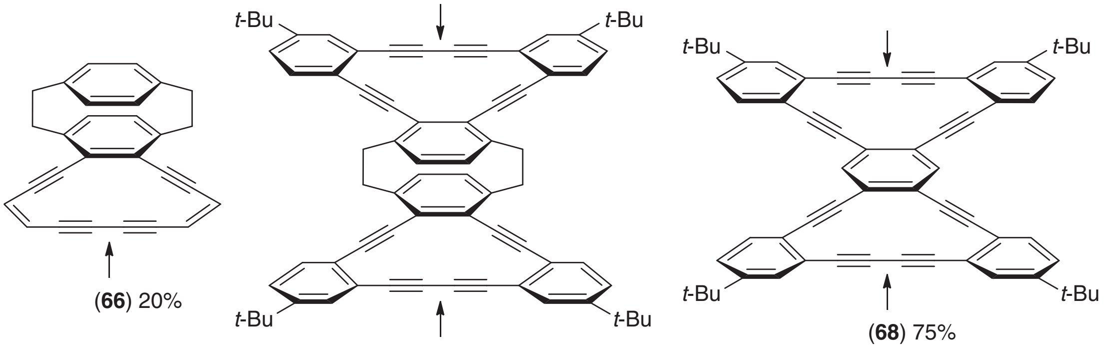
Haley and coworkers[116] described the synthesis of a series of [2.2]paracyclophane/dehydrobenzo[14]annulene (PC/DBA) hybrids with potential applications in materials science. Tetrayne (**64**) was desilylated and cyclized using a one-pot procedure to give *ortho* PC/DBA (**65**) in 97% yield (equation 64). To study the tropicity of the annulene ring, alkene hybrids (**66**) and (**67**) were prepared in the same manner starting from their corresponding TMS derivatives (Scheme 68). For annulene (**68**), the 1,3-diyne framework was built up starting from the corresponding terminal alkyne using a palladium copper catalysis protocol ($PdCl_2(dppe)$, CuI, I_2, i-Pr_2NH, and THF), which proved to be more efficient than oxidative homocoupling under Eglinton conditions.



(**64**) (**65**) (64)

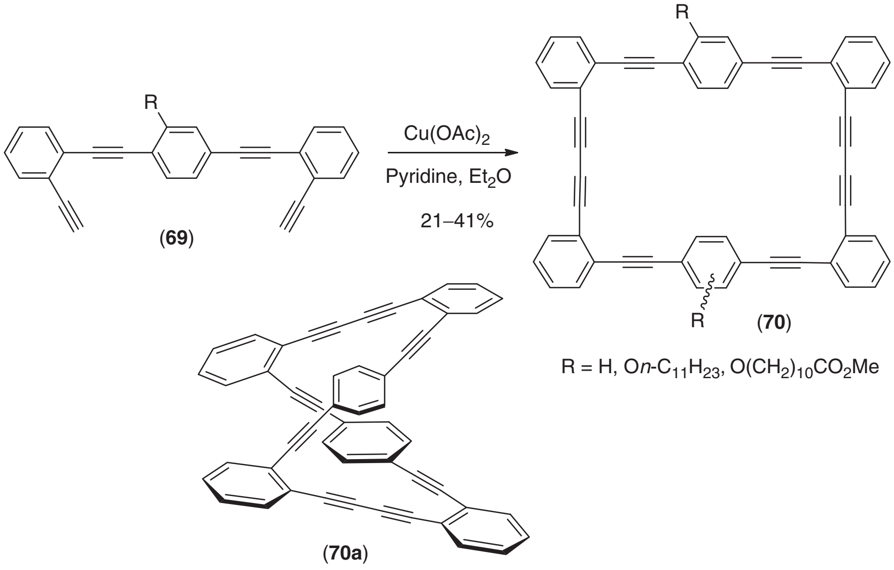


(**64**) (**65**) (64)

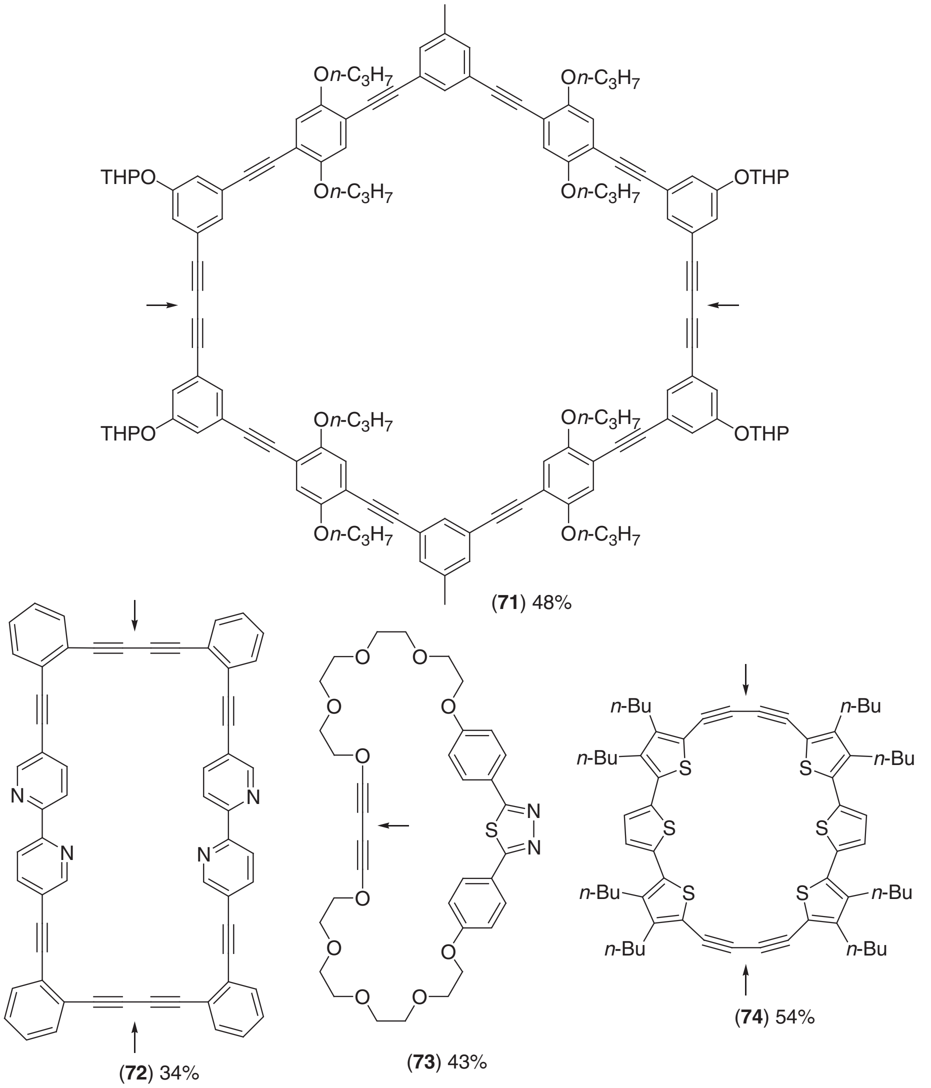


(**66**) 20% (**67**) 65% (**68**) 75%

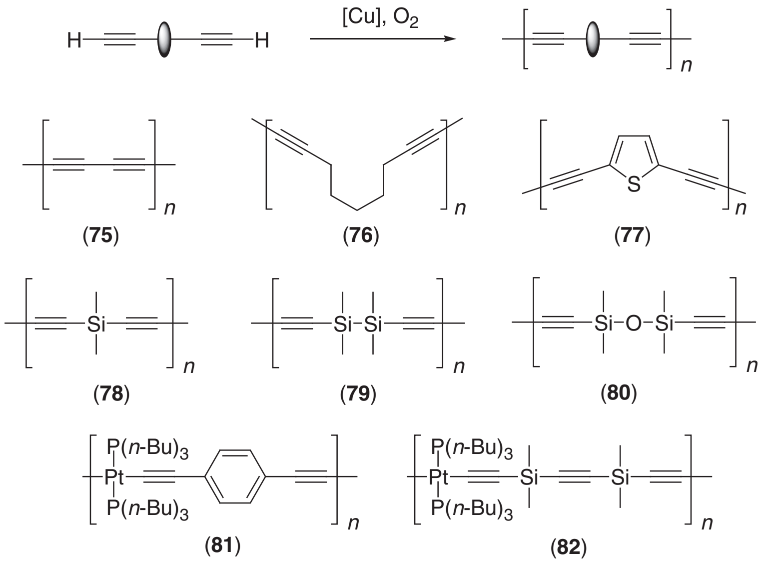
Scheme 68



Scheme 69



Scheme 70



Scheme 71

Fallis and coworkers[117] were able to synthesize a series of acetylenic cyclophanes that have the potential to act as unique liquid crystalline materials. In this study, the intramolecular oxidative homocoupling of **69** under Eglinton conditions with Cu(OAc)$_2$ in pyridine gave cyclophanes (**70**) in 21–41% yields (**Scheme 69**). X-ray crystallographic analysis of the parent hydrocarbon core cyclophane (**70a**) confirmed the twisted helical geometry of this molecule (**Scheme 69**).

Oxidative Glaser homocoupling reactions have also been used in the synthesis of several (hetero)aromatic macrocyclic polyacetylenes[5] including macrocycle (**71**), cyclophane (**72**) containing a 2,2′-bipyridine moiety, the 1,3,4-thiadiazole polyether (**73**),[118] and macrocycle (**74**) with thiophene rings (**Scheme 70**).

3.10.8.4 Polymer Synthesis

Another major application of Glaser-type coupling reaction is the oxidative polymerization of α,ω-diethynyl monomers which would be expected to yield high-molecular-weight, linear polymers (**Scheme 71**).[4,6] Accordingly, a wide variety of linear acetylenic polymers have been synthesized from terminal *bis*-alkynes (**75–81**).

A platinum–polyyne polymer (**82**),[6] containing diethynylsilane groups in the main chain, can be synthesized by the Hay reaction conditions after appropriate modification to protect the cleavage of Si–C bonds. The characteristics of the synthesis are as follows: (1) since the Si–C≡C bond may be cleaved by uncomplexed copper(II) chloride, a large excess of TMEDA, which is added to catch free copper(II) ion, may retard the formation of the oxygen complex; (2) a homogeneous catalyst solution is prepared by oxygen bubbling for many hours to complete the formation of the oxygen complex in methylene chloride in the presence of molecular sieves; (3) polymerization is carried out in methylene chloride over the molecular sieves using 3.5 equivalents of the above reagent; and (4) to optimize the molecular weight of the polymer, the coupling is monitored by gel permeation chromatography, and it requires 7 h. Under the above conditions, a white polymer film (**82**; $M = 77\,000$) can be obtained.

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3.11 Pinacol Coupling Reactions

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3.11.1 **Introduction** 581
3.11.2 **Reagents for the Pinacol Coupling Reaction** 582
3.11.2.1 Alkali and Alkaline Earth Metals 582
3.11.2.1.1 Alkali metals 582
3.11.2.1.2 Alkaline earth metals 583
3.11.2.2 Transition Metals 585
3.11.2.2.1 Stoichiometric protocols 585
3.11.2.2.1.1 Titanium 585
3.11.2.2.1.2 Titanium(II)-species 585
3.11.2.2.1.3 Titanium(III)-species 586
3.11.2.2.1.4 Titanium-induced enantioselective pinacol coupling 590
3.11.2.2.1.5 Vanadium 591
3.11.2.2.1.6 Chromium 592
3.11.2.2.1.7 Manganese 592
3.11.2.2.1.8 Iron 592
3.11.2.2.1.9 Nickel 593
3.11.2.2.1.10 Zinc 593
3.11.2.2.1.11 Zirconium 593
3.11.2.2.1.12 Niobium 593
3.11.2.2.1.13 Tantalum and cadmium 594
3.11.2.2.2 Catalytic protocols 594
3.11.2.2.2.1 Titanium 595
3.11.2.2.2.2 Vanadium 597
3.11.2.2.2.3 Chromium 599
3.11.2.2.2.4 Molybdenum 600
3.11.2.2.2.5 Ruthenium 601
3.11.2.2.2.6 Nickel and zirconium 601
3.11.2.3 Lanthanides 601
3.11.2.3.1 Stoichiometric protocols 601
3.11.2.3.1.1 Samarium 601
3.11.2.3.1.2 Cerium 606
3.11.2.3.1.3 Ytterbium 607
3.11.2.3.1.4 Uranium 608
3.11.2.3.1.5 Neodymium and gadolinium 608
3.11.2.3.1.6 Other lanthanides 608
3.11.2.3.2 Catalytic protocols 608
3.11.2.3.2.1 Samarium 608
3.11.2.3.2.2 Cerium 610
3.11.2.4 p-Block elements 610
3.11.2.4.1 Aluminum 610
3.11.2.4.2 Silicon 610
3.11.2.4.3 Indium 611
3.11.2.4.4 Tin 612
3.11.2.4.5 Tellurium 612
3.11.2.4.6 Bismuth 612
3.11.3 **Pinacol Coupling Reactions in Natural Product Synthesis** 613
3.11.3.1 Titanium 613
3.11.3.2 Samarium 615
References 618

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Glossary

anti Used to denote the relative configuration of any two stereogenic centers in a chain: If the chain is written in a planar zigzag conformation and the corresponding ligands at the stereogenic center are on opposite sides of the plane, the relative configuration is called *anti*.

dl For explanation of *like (lk)* versus *unlike (ul)* relative topicity and *like (l)* versus *unlike (u)* relative configuration.

meso Stereodescriptor for an achiral member of a set of diastereomers that also includes at least one chiral member.

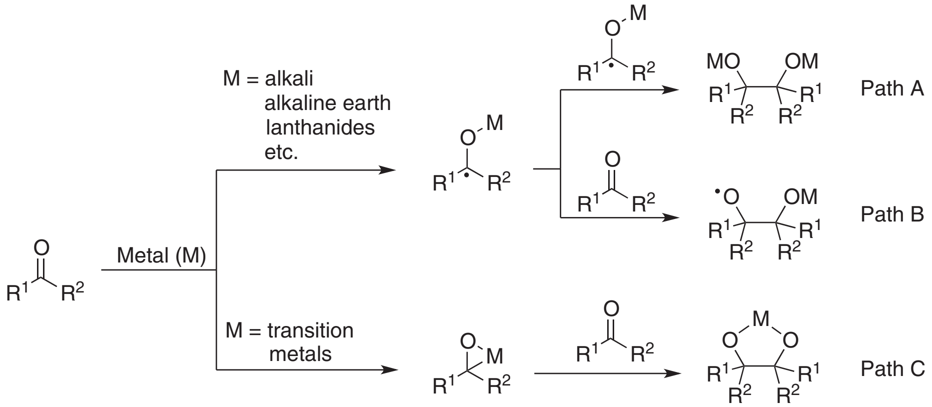
Mischmetall An alloy of the light lanthanides in various naturally occurring proportions. The usual mischmetall contains 48–50% cerium, 32–34% lanthanum, 13–14% neodymium, 4–5% praseodymium, and 1.5% other rare earth metals.

syn Used to describe the configuration of any two stereogenic centers in a chain: If the chain is written in a planar zigzag conformation and the corresponding ligands at the stereogenic center are on the same sides of the plane, the configuration is *syn*.

3.11.1 Introduction

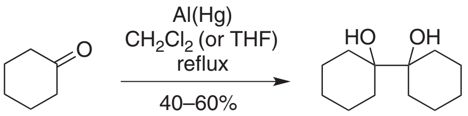
Since Fittig first reported the reductive coupling of ketones and aldehydes to give 1,2-diol in 1859,[1] the pinacol coupling reaction has been used for constructing vicinally functionalized C–C bonds.[2] Versatility of this reaction resides in its intrinsic ability to give 1,2-diols, that is significant structure motifs in natural products, as well as in the functional molecules including chiral auxiliaries or chiral ligands.

The reaction can be initiated with a range of low-valent metallic derivatives and p-block elements. Scheme 1 shows typical reaction mechanisms. The first step is generation of a ketyl radical, generally achieved through homolytic cleavage of the carbonyl π-bond by low-valent metallic species. Simultaneous electron transfer from the low-valent metal derivatives atom gives the metal-bound ketyl radical, which may dimerize (path A) or may add to a second carbonyl group (path B), forming a C–C bond. In path B, the second one-electron transfer must follow. For pinacol couplings mediated by transition metals, insertion of a carbonyl group into the metal–carbon bond of the initially formed metal oxiranes has been proposed (path C).



Scheme 1 Three proposed mechanisms for the pinacol coupling.

Traditionally used reducing agents include such alkali, alkaline earth metals, or metal amalgams, which suffered from sluggish reaction leading only to low to modest yields. Early improvement was the use of aluminum amalgam (equation 1).[3] Use of dichloromethane or tetrahydrofuran (THF) as a solvent greatly facilitated the yield up to 40–60%.



(1)

The reaction can lead to either *syn*- or *anti*-diol. Stereochemical course of the reaction depends on many factors, including reducing agents used and, of course, structure of the carbonyl substrates. For example, earlier examples using alkali or alkaline earth metals provided poor diastereoselection. However, the later methods utilizing several transition metals, lanthanides, or p-block elements gave higher selectivities. Recently, high levels of diastereoselection and even enantioselection have been achieved using specifically designed metal complexes.

3.11.2 Reagents for the Pinacol Coupling Reaction

Reducing agents for the pinacol couplings are widespread in the periodic table (**Figure 1**). For example, lithium,[4] sodium,[5] magnesium,[6] cerium,[7] samarium,[8,9] ytterbium,[10] titanium,[11] vanadium,[12] chromium,[13] zinc,[14] and aluminium[3] proved effective and commonly used for the pinacol coupling reaction. Recently, various other elements (silicon,[15] calcium,[16] manganese,[17] iron,[18] nickel,[19] gadolinium,[20] zirconium,[21] niobium,[22] molybdenum,[23] ruthenium,[24] cadmium,[25] indium,[26] tin,[27] tantalum,[22c] tellurium,[28] bismuth,[29] praseodymium,[30] dysprosium,[30] thulium,[30] lutetium,[30] neodymium,[20] and uranium[31]) have started to be used.[32]

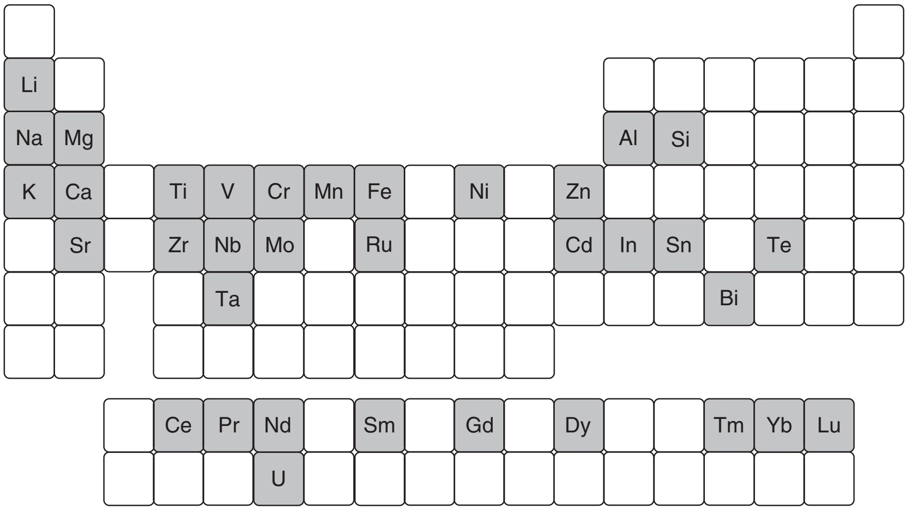
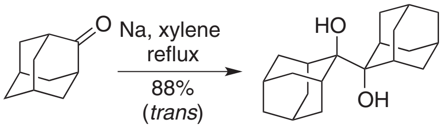


Figure 1 Elements for pinacol coupling.

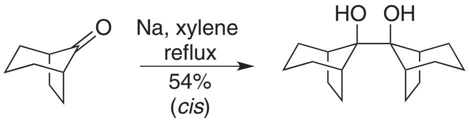
3.11.2.1 Alkali and Alkaline Earth Metals

3.11.2.1.1 Alkali metals

Although alkali metals were first used for the pinacol coupling reactions, few examples were reported compared to other metals because of the reactivity, chemoselectivity, and drastic conditions. Among the alkali metals, sodium is the oldest metal ever used,[5] frequently resulting in unsatisfactory yields and selectivity. In few cases, high diastereoselectivity was reported (equations 2 and 3).[33]



(2)

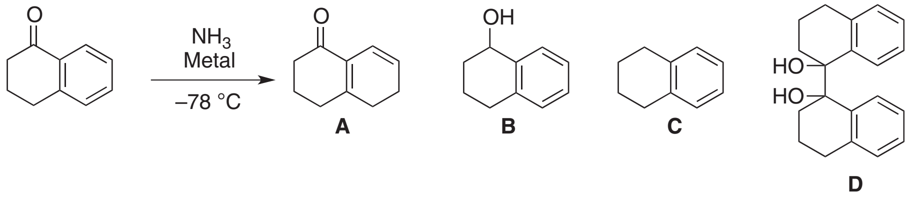


(3)

Alkali metals in combination with a stoichiometric amount of liquid NH_3 or Me_3SiCl were sometimes used for the pinacol coupling.[4a,5b] Although lithium is the suitable alkali metal for the formation of pinacol products in these protocols, the yield, and diastereoselectivity were low (**Tables 1** and **2**).[34]

A mild solvent-free pinacol coupling was also developed by using alkali metals such as Na, K, and Li, when a catalytic amount of bromobenzene was used.[35] A single electron-transfer mechanism was proposed for the coupling (**Scheme 2**). Thus, bromobenzene accepts one electron from the alkali metal, giving the corresponding radical anion species, which transmits the electron to the carbonyl compounds to induce the coupling. The required reaction time decreases in the order of Li > Na > K. Nevertheless, because of the high reactivity, use of K usually leads to lower yield of the desired products. Similar yields are attainable by using Li and Na (**Table 3**). The diastereoselectivity of the catalytic reductive coupling is mostly high, when Li was used. It was noted that magnesium was not effective for this purpose.

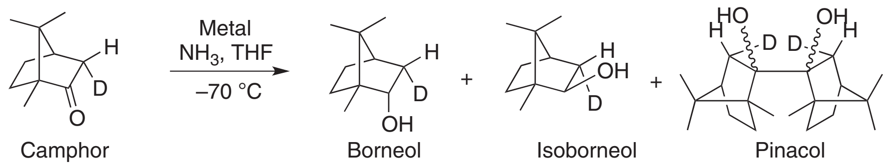
Table 1 Pinacol coupling by using alkali metals in combination with liquid NH_3



Entry	*Metal*	*Product (%)*			
		A	***B***	***C***	***D***
1	Li	21	10	7	42
2	Na	30	56	4	~2

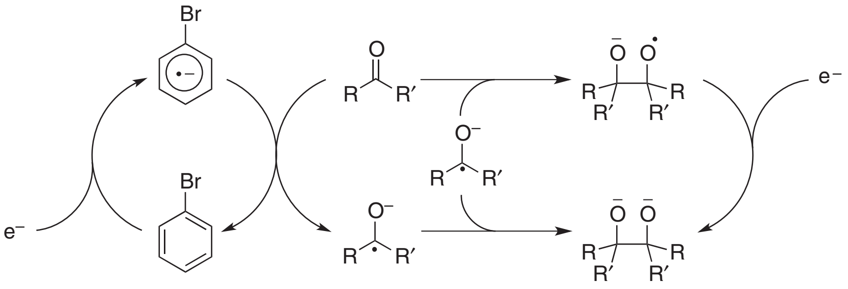
Source: Reproduced from Marcinow, Z.; Rabideau, P. W. *J. Org. Chem.* **1988**, *53*, 2117–2119, with permission from ACS.

Table 2 Other examples using alkali metals in combination with liquid NH_3



Entry	*Metal*	*Product (%)*			
		Camphor	*Borneol*	*Isoborneol*	*Pinacol*
1	Li	59	15	5	21
2	Na	57	22	15	6
3	K	64	14	22	<1

Source: Reproduced from Huffman, J. W.; Wallace, R. H. *J. Am. Chem. Soc.* **1989**, *111*, 8691–8698, with permission from ACS.

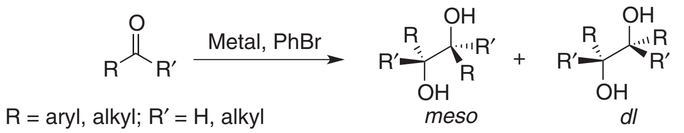


Scheme 2 A single electron-transfer mechanism. Reproduced with permission from Zhao, H.; Li, D.-J.; Deng, L.; Liu, L.; Guo, Q.-X. *Chem. Commun.* **2003**, 506–507.

3.11.2.1.2 Alkaline earth metals

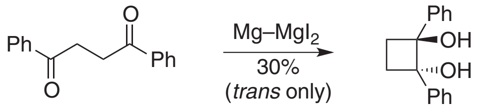
Magnesium has been used to mediate pinacol coupling because of its ready availability. The classical pinacol coupling using magnesium amalgam gave unsatisfactory yields (e.g., magnesium amalgam cannot reduce aryl ketones).[2b] Combination of Mg/MgI_2 (equation 4),[36,37] Mg/Me_3SiCl,[38] and Mg–NH_4Cl in water[39] turned out to be most useful for the reduction of aryl ketones, and ultrasonic irradiation accelerates the reaction.[40] After substantial studies, Mg–graphite was found to be a simple, widely applicable, and mercury-free reagents for the pinacol reactions, enabling coupling of aldehydes/ketones with moderate selectivity (equation 5).[41] Although efficient methods have been developed, the selectivity mostly remained low so long as magnesium reagents were used.

Table 3 Alkali metal mediated pinacol coupling in the presence of bromobenzene

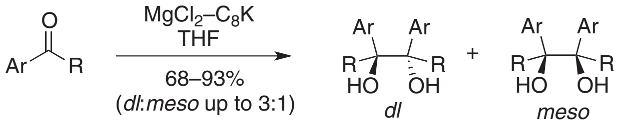


Entry	*Substrate*	*Metal*	*Yield (%)*	dl/meso
1	$PhCOCH_3$	Li	87	74/26
2	$PhCOCH_3$	Na	93	77/23
3	$PhCOCH_3$	K	47	84/16
4	2,4-$Cl_2C_6H_3CHO$	Li	90	*dl* only
5	*o*-ClC_4H_4CHO	Li	81	*dl* only
6	$PhCH{=}CHCOCH_3$	Li	75	*dl* only

Source: Reproduced with permission from Zhao, H.; Li, D.-J.; Deng, L.; Liu, L.; Guo, Q.-X. *Chem. Commun.* **2003**, 506–507.

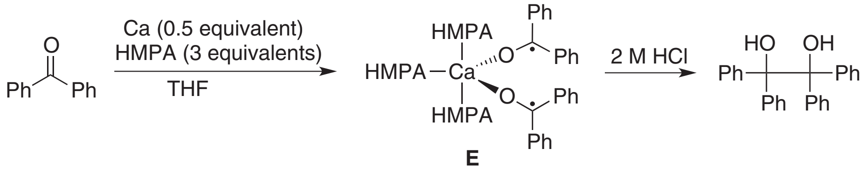


(4)



(5)

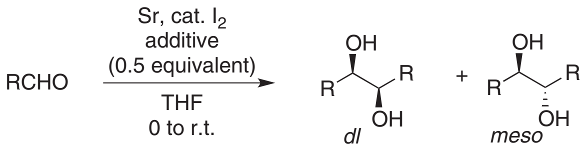
Wakatsuki and coworkers first showed the structurally characterized calcium–benzophenone ketyl complex **E** by using fresh calcium chips and hexamethylphosphoric triamide (HMPA). Hydrolysis of **E** gave the coupling product, benzopinacol, almost quantitatively (Scheme 3).[16]



Scheme 3 Structurally characterized calcium–benzophenone ketyl complex. Reproduced from Hou, Z.; Jia, X.; Hoshino, M.; Wakatsuki, Y. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1292–1293.

Recent studies showed that strontium in the presence of a catalytic amount of iodine and Lewis acid also promote the pinacol coupling of aromatic and aliphatic aldehydes with moderate selectivity (Table 4).[42]

Table 4 Pinacol coupling induced by strontium metal



Entry	*R*	*Additive*	*Yield (%)*	dl/meso
1	Ph	TMSOTf	11	91/9
2	Ph	$Al(OEt)_3$	63	75/25
3	4-ClC_6H_4	$Al(OEt)_3$	61	60/40
4	4-$MeOC_6H_4$	$Al(OEt)_3$	23	91/9
5	4-MeC_6H_4	$Al(OEt)_3$	57	73/27
6	Cy	$Al(OEt)_3$	87	62/38
7	$PhCH_2CH_2$	$Al(OEt)_3$	53	76/24

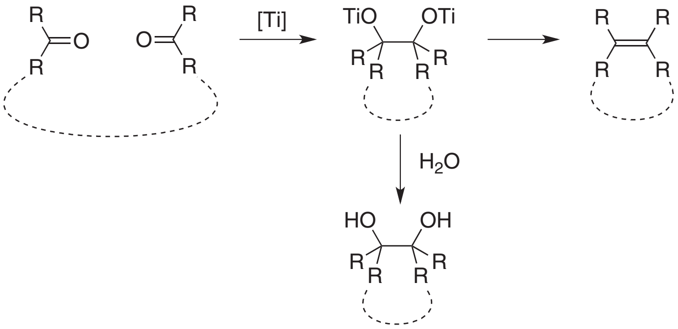
Source: Reproduced with permission from Miyoshi, N.; Kohno, T.; Wada, M.; *et al. Chem. Lett.* **2009**, *38*, 984–985.

3.11.2.2 Transition Metals

3.11.2.2.1 Stoichiometric protocols

3.11.2.2.1.1 Titanium

Titanium is the most popular element for the pinacol coupling reaction. In the early 1970s, Mukaiyama et al.,[43] Tyrlik and Wolochowicz[44] and McMurry and Fleming,[45] independently developed the low-valent titanium species, which were used for the reductive coupling of ketones and aldehydes to give alkenes (**Scheme 4**). By lowering the reaction temperature, it is possible to stop the reaction at the stage of the intermediate pinacols. Although readily reducible functional groups such as nitro, epoxide, and sulfoxide are not compatible with low-valent titanium reactions, less readily reducible groups such as nitrile, ester, and amide often survive under the mild conditions.[46]

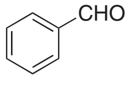
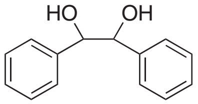
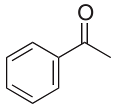
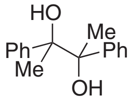
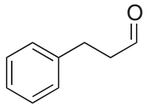
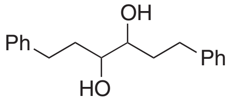
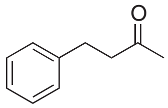
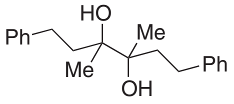


Scheme 4 Principle of the pinacol coupling and McMurry reaction. Reproduced from Fürstner, A.; Bogdanovic, B. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2442–2469.

3.11.2.2.1.2 Titanium(II)-species

The first example of the pinacol coupling mediated by Ti(II) was the use of as a reductant developed by Mukaiyama et al.[43] By using the low-valent titanium species generated *in situ* by combining $TiCl_4$ and Zn, aldehydes and ketones, such as benzophenone, acetophenone, benzaldehyde, 3-phenylpropanal, and 4-phenyl-2-butanone, were reduced and coupled (**Table 5**). The products were the corresponding pinacols, or olefins by deoxygenation, where the distribution depended on the reaction temperature. Although the Mukaiyama's reagent successfully coupled aromatic ketones and aldehydes, it was less effective for aliphatic substrates.

Table 5 Pinacol coupling by using Mukaiyama's $TiCl_4$–Zn reagents

Entry	*Aldehydes and ketones*	*Products*	*Yield (%)*
1			98
2			91
3			78[a]
4			86[b]

[a]The reaction was performed at reflux.

[b]The reaction was performed at 0 °C in THF.

The reaction was performed at 85 °C in 1,4-dioxane.

Source: Reproduced with permission from Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, *2*, 1041–1044.

However, Corey et al. used low-valent titanium species, Ti(II)–hexamethylbenzene π-complex (**Figure 2**), or the combination of $TiCl_4$ and Mg–amalgam, which were effective in the pinacol coupling of aliphatic ketones/aldehydes (**Table 6**).[47]

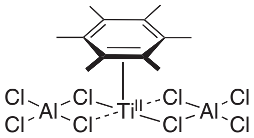
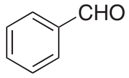
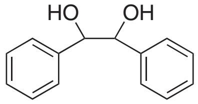
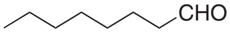
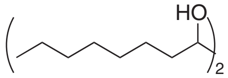
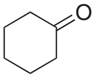
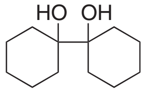
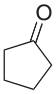
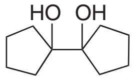


Figure 2 Ti(II)–hexamethylbenzene π-complex. Reproduced from Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. J. *Org. Chem.* **1976**, *41*, 260–265, with permission from ACS.

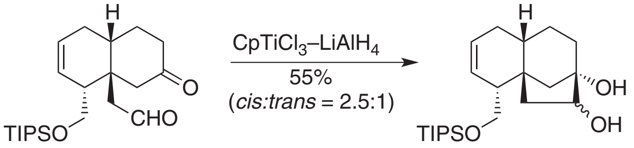
Table 6 $TiCl_4$ and Mg–amalgam-induced pinacol coupling

Entry	*Aldehydes and ketones*	*Products*	*Yield (%)*
1			84
2			80
3			93
4			95

Note: The reaction was performed at 0 °C.

Source: Reproduced from Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260–265, with permission from ACS.

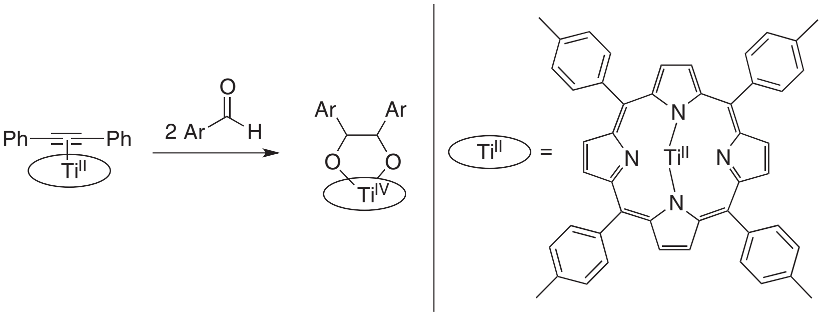
Corey et al. also found other low-valent titanium reagents ($CpTiCl_3$–$LiAlH_4$), which were favorable for the pinacol coupling of the ketone–aldehyde systems (equation 6).



(6)

The intramolecular coupling of various aldehydes using $TiCl_3$/Zn–Cu were established by McMurry and Rico.[48] Under these conditions, *cis*-diols are predominant when smaller rings are formed, whereas *trans*-diols become predominant when the ring sizes are larger than 10 (Table 7).

Reactions of a low-valent titanium(II) tetratolylporphyrin (TTP) complex, (TTP)Ti(η^2-PhC≡CPh), with various aromatic aldehydes/ketones also afforded the reductively coupled products (equation 7).[49]

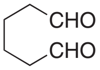
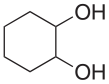
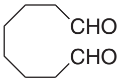
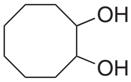
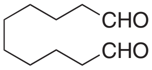
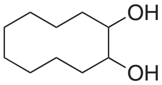
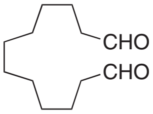
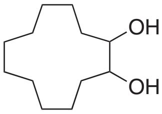
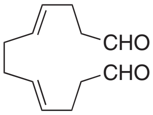
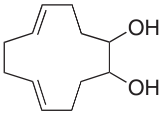
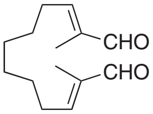
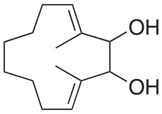
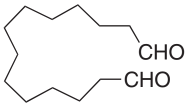
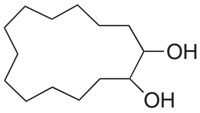


(7)

3.11.2.2.1.3 *Titanium(III)-species*

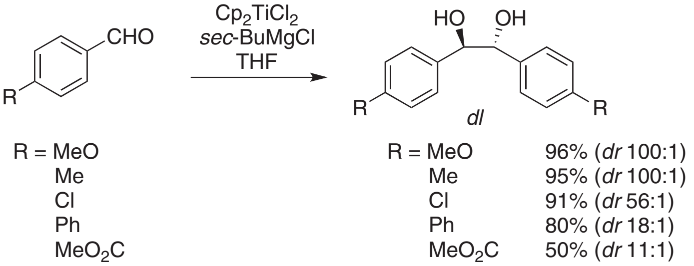
Seebach exploited Ti(III) species for the pinacol coupling. Treatment of aromatic aldehydes with $TiCl_3$, generated from $TiCl_4$ and *n*-BuLi, gave *dl*-diol in moderate yields.[50] Under these conditions, aliphatic and aromatic ketones were unreactive. Subsequently,

Table 7 $TiCl_3$/Zn–Cu-induced intermolecular pinacol coupling

Entry	*Dialdehyde*	*Pinacol*	cis/trans	*Yield (%)*
1			100/1	85
2			70/30	82
3			25/75	80
4			25/75	75
5			5/95	83
6			5/95	84
7			30/70	89

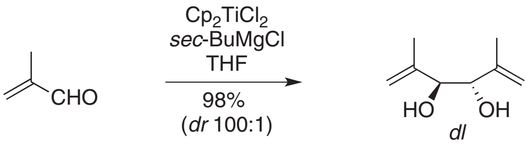
Source: Reproduced from McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169–1172.

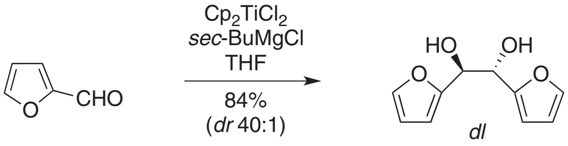
Inanaga reported that the Ti(III) reagent, formulated as $(Cp_2TiCl)_2MgCl_2$, generated from Cp_2TiCl_2 with Grignard reagents, was an effective reagent for diastereoselective pinacol coupling of aromatic and α,β-unsaturated aldehydes (equations 8–11).[51] Aromatic aldehydes having electron-withdrawing groups showed lower reactivity and selectivity. Aliphatic aldehydes hardly reacted under the conditions. The stereoselectivity was attributed to the trimetallic structure of Ti(IV)–Mg(II)–Ti(IV) intermediate **F** (**Figure 3**), in which R groups are arranged *anti* to each other to minimize the steric repulsion, thus affording the *dl*-diol. Cp_2TiCl_2/SmI_2, Cp_2TiCl_2/Zn, or Cp_2TiCl_2/*i*-PrMgI were also used successfully. Other combinations Ti(O*i*-Pr)$_4$/EtMgBr,[52] $TiCl_4$/(*i*-Bu)$_2$Te,[53] or $TiCl_4$/Zn[54] also gave *dl*-diol with high selectivity.

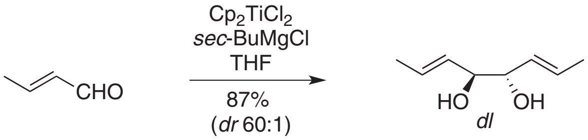
 (8)

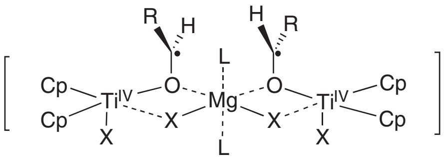
R = MeO, Me, Cl, Ph, MeO_2C

R =	
MeO	96% (*dr* 100:1)
Me	95% (*dr* 100:1)
Cl	91% (*dr* 56:1)
Ph	80% (*dr* 18:1)
MeO_2C	50% (*dr* 11:1)

 (9)

 (10)

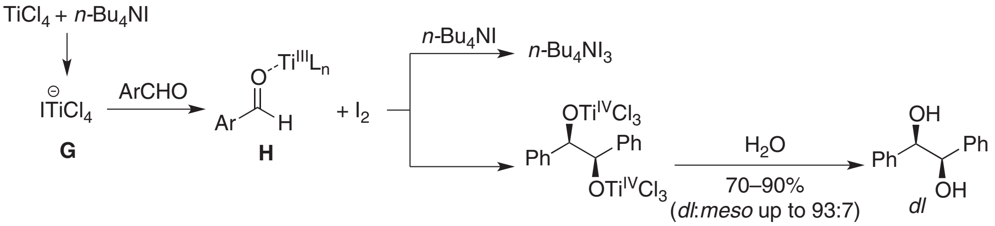
 (11)



F

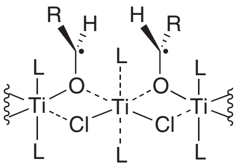
Figure 3 The trimetallic structure of Ti(IV)–Mg(II)–Ti(IV) intermediate. Reproduced from Hamada, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717–5718.

The metal or metallic hydride for the generation of Ti(III) species results in the concomitant formation of the metal salts, which may cause the side reactions, decrease of the selectivities, or sacrificing the functionalities by their Lewis acidity. Oshima and coworkers reported that the combination of $TiCl_4$ and n-Bu_4NI (tetrabutylammonium iodide (TBAI)), promotes the pinacol reaction of aromatic aldehydes to afford *dl*-diol with high selectivity.[55] $MePh_3PI$ or $MeEt_3NI$ proved equally effective. The following mechanism was proposed (Scheme 5): 1. Reaction of $TiCl_4$ with TBAI forms the pentacoordinate titanium ate-complex **G**, 2. coordination of a carbonyl oxygen to the titanium center in **G** facilitates reduction to Ti(III) species **H**, 3. finally, **H** forms the corresponding ketyl radical, dimerizing to afford the pinacol product.



Scheme 5 $TiCl_4$–TBAI-induced pinacol coupling. Reproduced with permission from Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, *65*, 5066–5068.

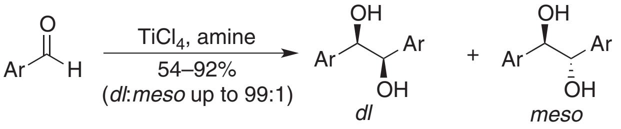
In all of the reactions mentioned above, the Ti(III) species are generated *in situ*. Porta et al., found a convenient method to give *dl*-diols, in which a commercially available Ti(III) solution in THF/CH_2Cl_2 (1:2) is used in the presence of excess CH_2Cl_2.[56] For maintaining the Lewis acidity and coordination power of Ti(III), use of excess amount of CH_2Cl_2 was essential for decreasing the effect of coordinating solvent, as THF, otherwise the yield and *dl*-selectivity would become lower. High preference for the *dl*-diol formation was explained by a Ti(IV)-bridging control[57] through a Ti(IV)-ketyl aggregate **I** (Figure 4) or the similar intermediates, in which the aromatic groups are arranged *anti* to each other to minimize the steric interaction, and the stable octahedral Ti(IV) complex was formed with bridging ligands.[58]



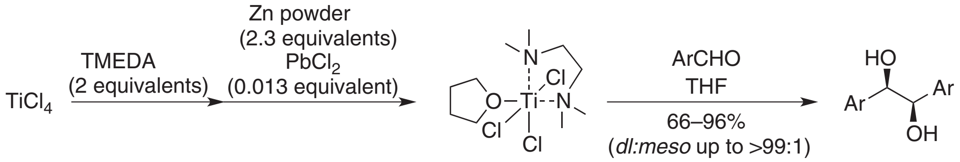
I

Figure 4 Structure of Ti(IV)-ketyl aggregate. Reproduced from Clerici, A.; Clerici, L.; Porta, O. *Tetrahedron Lett.* **1996**, *37*, 3035–3038.

Addition of nonchelating amines, e.g., Et_3N[59] or i-Pr_2NEt,[60] to $TiCl_4$ is equally effective in generating a Ti(III) species (equation 12).

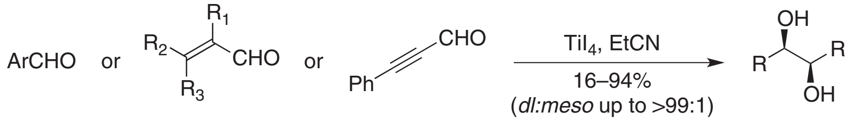
 (12)

$TiCl_3$(tmeda)(thf), a monomeric titanium(III) complex prepared by a reaction of $TiCl_4$ with *N*,*N*,*N′*,*N′*-tetramethylethylenediamine (TMEDA), Zn, and a catalytic amount of $PbCl_2$ (Scheme 6), promoted the reductive coupling of aromatic aldehydes under mild conditions to give 1,2-diols in good to excellent yields with high *dl*-selectivity.[61]



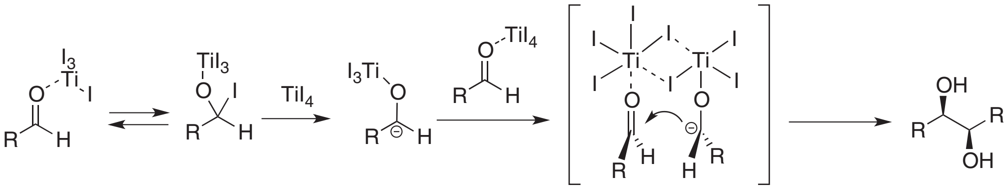
Scheme 6 $TiCl_3$(tmeda)(thf)-induced pinacol coupling. Reproduced with permission from Oshiki, T.; Kiriyama, T.; Tsuchida, K.; Takai, K. *Chem. Lett.* **2000**, *29*, 334–335.

Hayakawa and Shimizu reported that TiI_4 in EtCN without the use of low-valentmetal species promotes pinacol coupling of aldehydes to give the corresponding *dl*-diols.[62] Aliphatic aldehydes were inert to this reagent (equation 13).



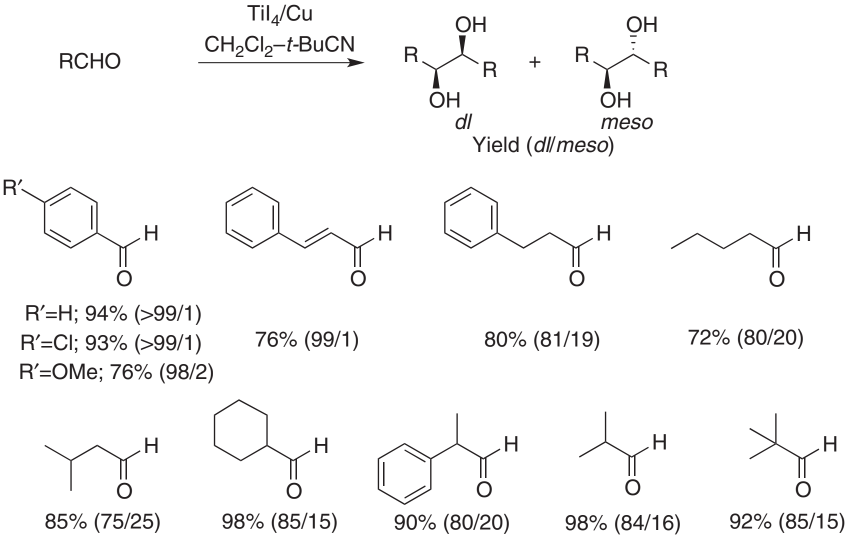
(13)

The plausible mechanism involves the carbonyl addition of an iodide followed by reductive dehalogenation by TiI_4 to form an anionic species, which undergoes addition to another aldehyde to afford the pinacol (Scheme 7).



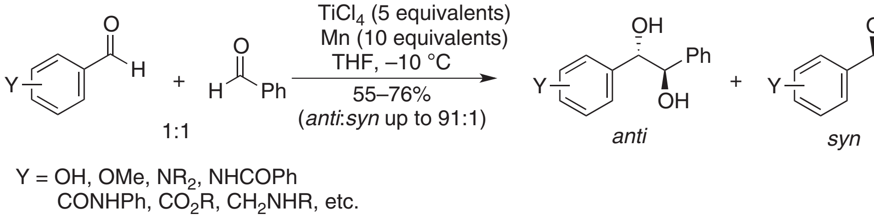
Scheme 7 Plausible mechanism for the TiI_4-induced pinacol coupling. Reproduced with permission from Hayakawa, R.; Shimizu, M. *Chem. Lett.* **2000**, *29*, 724–725.

Later, Mukaiyama et al., found that either $TiBr_2$/Cu or TiI_4/Cu in a mixed solvent of CH_2Cl_2 and *t*-BuCN promotes the reductive coupling of aromatic and aliphatic aldehydes to give the corresponding pinacols in moderate to high yields and *dl*-diastereoselectivity (Scheme 8).[63]



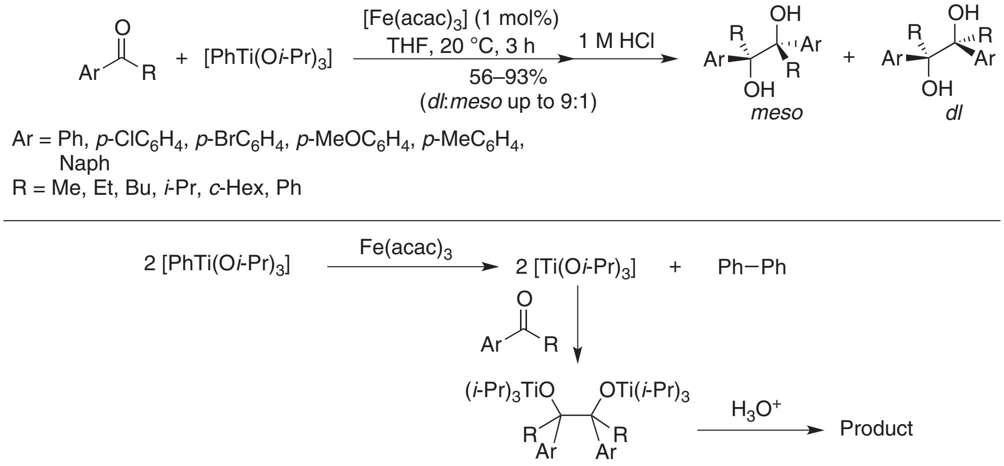
Scheme 8 Pinacol coupling by using TiI_4/Cu. Reproduced with permission from Mukaiyama, T.; Yoshimura, N.; Igarashi, K. *Chem. Lett.* **2000**, *29*, 838–839.

Duan et al., developed crossed pinacol coupling between two structurally similar aromatic aldehydes in the presence of low-valent titanium (equation 14).[64] The desired unsymmetrical pinacols were obtained in good yields and diastereoselectivities.



(14)

Hayashi and Sasaki described the reaction of aromatic ketones with phenyltitanium triisopropoxide ($[PhTi(O\textit{i}\text{-}Pr)_3]$) in the presence of $[Fe(acac)_3]$ as a catalyst (1 mol%), giving the corresponding pinacols in high yield (**Scheme 9**).[65] The catalytic cycle involves an iron-catalyzed disproportionation of $[PhTi(O\textit{i}\text{-}Pr)_3]$ into biphenyl and a low-valent titanium species.

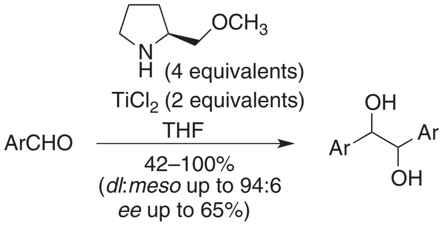


Scheme 9 Hayashi's method for the generation of low-valent Ti(III). Reproduced with permission from Hayashi, T.; Sasaki, K. *Chem. Lett.* **2011**, *40*, 492–494.

Various other low-valent titanium species, e.g., $TiCl_3$–K/I_2,[66] $TiCl_3$–Li/naphthalene,[67] or $TiCl_2$–Zn,[68] have also been employed for the pinacol coupling.

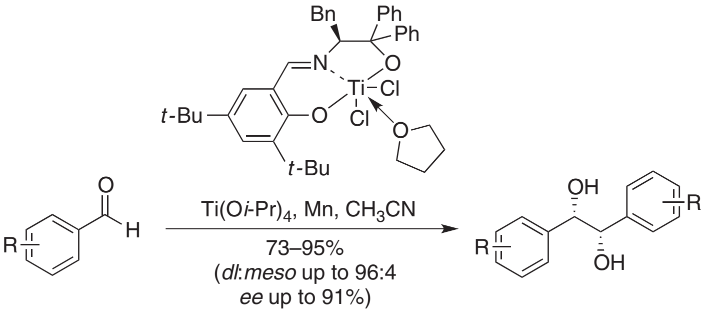
3.11.2.2.1.4 Titanium-induced enantioselective pinacol coupling

Concerning the enantioselective version of the reaction, a chiral titanium complex or titanium in combination with a chiral ligand was used as the most reliable tool. Matsubara et al., first described the stoichiometric enantioselective pinacol coupling by using titanium (II) chloride and enantiopure tertiary amines or vicinal diamines as additives.[69] In the case of aromatic aldehydes, the enantiomeric excess ranged 0–41%. Enders and Ullrich also reported the enantioselective pinacol coupling of aromatic aldehydes with titanium (II) chloride in the presence of 2 equivalents of (*S*)-2-methoxymethylpyrrolidine, giving moderate to excellent yields, good *dl*-diastereoselectivities, and enantiomeric excesses of up to 65% (equation 15).[70]



(15)

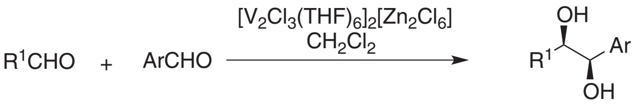
Riant and coworkers reported the enantioselective pinacol coupling reaction of aromatic aldehydes by using a titanium hemi-SALEN complex (equation 16).[71] The *ee* decreased when electron-withdrawing substituents were present at the *para* position.



(16)

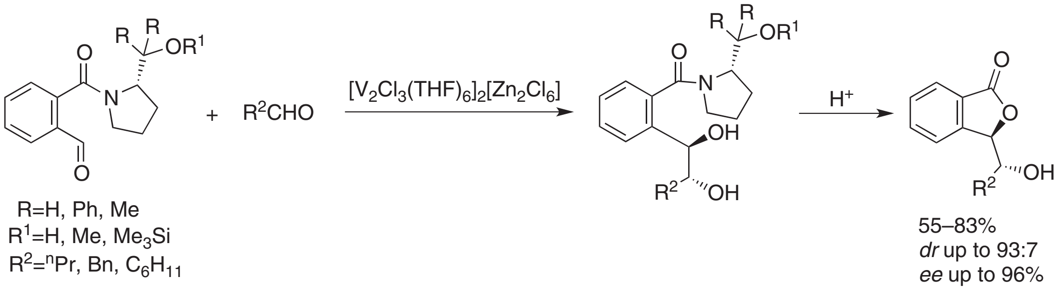
3.11.2.2.1.5 Vanadium

A low-valent vanadium species, generated from vanadium pentoxide, Zn/Hg, and concentrated hydrochloric acid, was capable of coupling aromatic aldehydes, α,β-unsaturated aldehydes, and benzxylideneacetophenone.[13] In 1989, Pedersen and coworkers described that a well-characterized vanadium(II) complex $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ enables the intermolecular cross-pinacol coupling of nonaryl aldehydes and aryl aldehydes in stereoselective manner (equation 17).[72] Slow addition of an aryl aldehyde to a CH_2Cl_2 solution of $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ and a nonaryl aldehyde is necessary to obtain good yields of the cross coupled products.



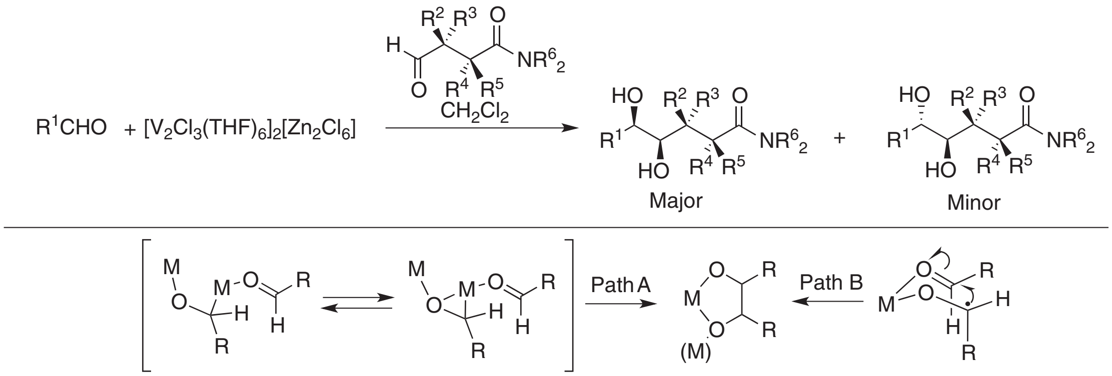
(17)

The crossed pinacol couplings between aliphatic and aromatic aldehydes containing chiral auxiliary proceeded with high enantioselectivities by using $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (Scheme 10).[73]



Scheme 10 Enantioselective pinacol coupling by using $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$. Reproduced from Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Giaroni, P. *J. Org. Chem.* **1992**, *57*, 782–784, with permission from ACS.

In general, nonaryl aldehydes do not undergo reductive coupling at an appreciable rate. However, if the aldehyde can chelate to the vanadium center, the susceptibility to reductive coupling is significantly enhanced (Scheme 11).[72b] The reaction was believed to proceed via either path A or B, furnishing a cross-coupled product with two aldehydes of different reactivities.

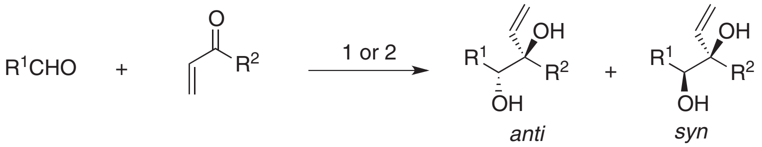


Scheme 11 Cross-coupling reaction of two aldehydes of different reactivities. Reproduced from Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014–8016, with permission from ACS.

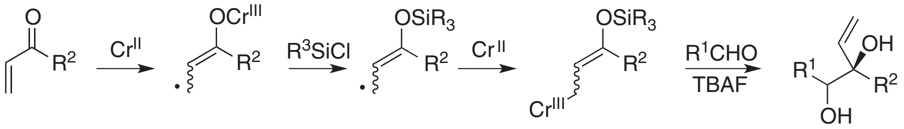
3.11.2.2.1.6 Chromium

Early investigations reported the mechanism and kinetics of the reductive coupling of aldehydes by Cr(II) salts.[13,74] Recently, it was found that a low-valent chromium reagent, formed from $CrCl_3$ and 2 equivalents of *n*-BuLi, served as an efficient reagent for the pinacol coupling.[75]

Takai et al. reported a chromium-mediated cross-coupling of α,β-unsaturated ketone and aldehyde by using an excess of $CrCl_2$ and organosilyl chlorides, e.g., Me_3SiCl, Et_3SiCl, Me_2SiCl_2, or $PhMe_2SiCl$ (equation 18).[76] *t*-$BuMe_2SiCl$ or *i*-Pr_3SiCl was not effective. The key factor that leads to the crossed reaction is the trapping of an enolate with R_3SiCl leading to a γ-siloxy-substituted allylic radical. Such allyl radical can be easily reduced with Cr(II) to generate the corresponding allyl chromium species, which reacts with aldehydes to afford the diol. The diastereoselectivity depends on the substituents R of R_3SiCl and the reaction temperature. When the reaction is performed at low temperature, *anti*-diol is generally obtained, whereas high temperature gives *syn*-diol (**Scheme 12**). However, a drawback is that a large amount of toxic chromium waste is produced.



(18)



1. $CrCl_2$, R_3SiCl, 0 °C then *n*-Bu_4NF, 44–99%, *anti*:*syn* up to 99:1; 2. $CrCl_2$, R_3SiCl, 75 °C, then *n*-Bu_4NF, 42–85% (*anti*:*syn* up to 99:1).

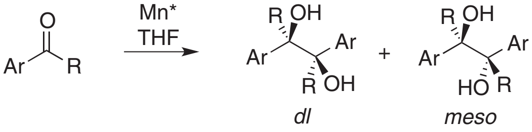
Scheme 12 Plausible mechanism for the $CrCl_2$-induced pinacol coupling. Reproduced with permission from Takai, K.; Morita, R.; Toratsu, C. *Chirality* **2003**, *15*, 17–23.

3.11.2.2.1.7 Manganese

Rieke and Kim found a useful method for pinacol coupling. Activated manganese (Mn*) is prepared by reducing manganese halides with Li in the presence of naphthalene as an electron carrier (equation 19).[77]

$$MnCl_2 + Li/Np \longrightarrow Mn^* \qquad (19)$$

Mn* was used for the reductive dimerization of aryl aldehydes/ketones to give the corresponding 1,2-diol in good yields. Diastereoselectivity was generally poor except for aryl ketones (equation 20).

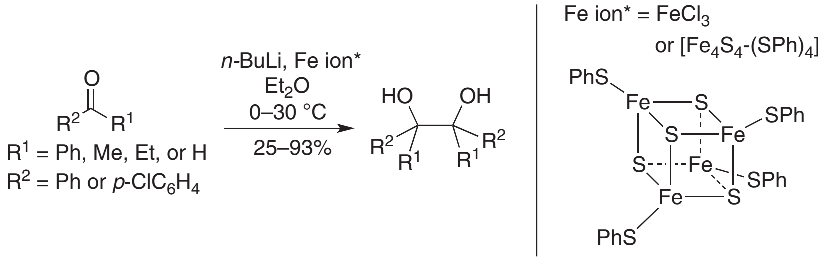


(20)

Manganese in aqueous solution in the presence of a catalytic amount of acetic acid or in aqueous ammonium chloride enables the pinacol coupling of aromatic aldehydes or ketones. Although the yields are good, the selectivities are poor.[78]

3.11.2.2.1.8 Iron

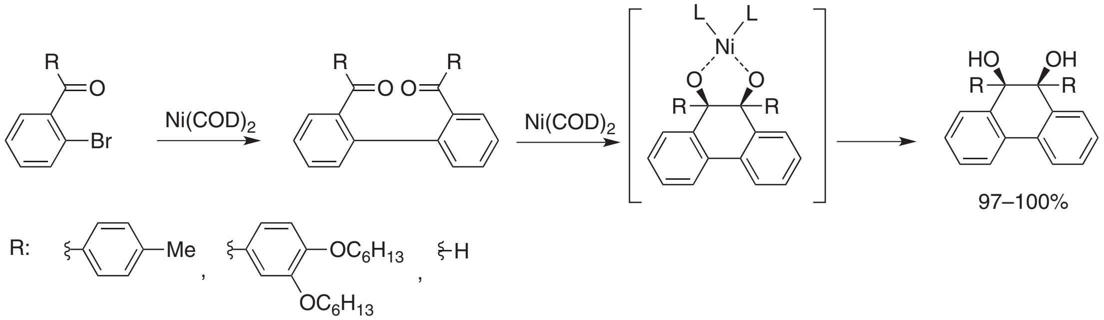
Inoue used a combination of *n*-BuLi and $FeCl_3$ or $[Fe_4S_4\text{-}(SPh)_4]$ for the pinacol coupling of aromatic aldehydes and ketones (equation 21).[18] The yields and stereoselectivity remained moderate.



(21)

3.11.2.2.1.9 Nickel

2-Bromobenzophenone and 2-bromobenzaldehyde can be transformed to the pinacols in excellent yields in one pot by Ni(0)-mediated cascade reaction (**Scheme 13**).[19] The reaction proceeded stereoselectively to afford *cis*-diol. The reaction sequence starts from the formation of 2,2′-substituted biphenyl intermediates via the aryl–aryl coupling followed by the intramolecular pinacol coupling reaction.

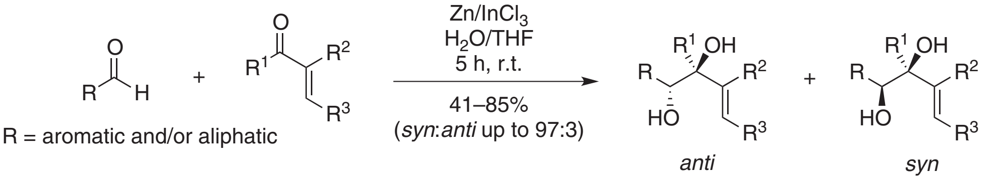


Scheme 13 Ni(0)-mediated cascade reaction. Reproduced from Reisch, H. A.; Enkelmann, V.; Scherf, U. *J. Org. Chem.* **1999**, *64*, 655–658, with permission from ACS.

3.11.2.2.1.10 Zinc

Various aromatic ketones, α,β-unsaturated aldehydes, and aromatic aldehydes are reductively dimerized to give the protected pinacols in the presence of zinc dust and Me_3SiCl with the ratio of 1.5:1 in good yields.[79] Yields are improved by sonication, instead of simple stirring, although the selectivities are poor, unfortunately.

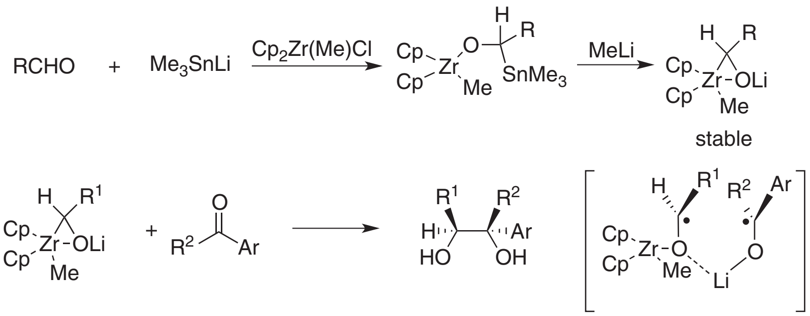
Zn/$InCl_3$-mediated cross-coupling reaction between aldehyde and α,β-unsaturated ketone in aqueous media was also developed which, unfortunately, gave poor selectivities (equation 22).[80]



(22)

3.11.2.2.1.11 Zirconium

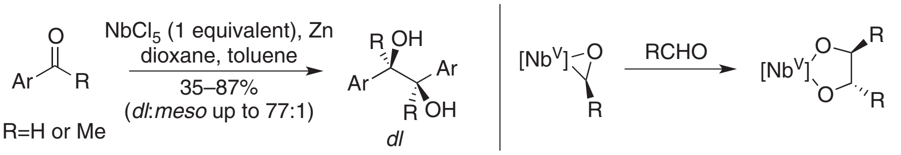
Crossed pinacol coupling between aromatic ketones/aldehydes was described by employing a stoichiometric amount of anionic zirconocene complex derived from aldehydes through a route involving transmetalation of zirconocene (α-stannyl alkoxide) complex with methyllithium (**Scheme 14**).[21] The cross-coupled products are produced with high stereoselectivity, that is ascribed to the lithium-bound intermediate as shown in **Scheme 14**.



Scheme 14 Crossed pinacol coupling mediated by anionic zirconocene complex. Reproduced with permission from Askham, F.; Carroll, K. M. *J. Org. Chem.* **1993**, *58*, 7328–7329.

3.11.2.2.1.12 Niobium

A niobium(III) complex, $NbCl_3$(1,2-dimethoxyethane (DME)), promoted the highly stereoselective pinacol coupling reaction of not only aromatic aldehydes and ketones, but also aliphatic aldehydes at −10 °C. The Nb(III) species, generated *in situ* by reducing $NbCl_5$ with Zn[81] or Bu_4NI,[55] has also been used for the coupling reactions (equation 23). The predominant formation of the *dl* (*anti*) isomer is explained by the mechanism involving the niobiooxirane intermediate. In contrast, intramolecular pinacol couplings mediated by $NbCl_3$ proceeded in lower yield and with essentially no diastereoselectivity (equation 24).[22]



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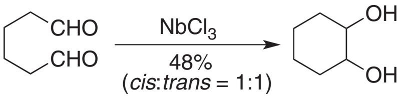
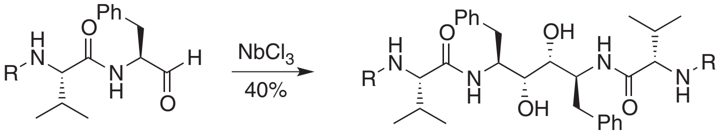


(24)

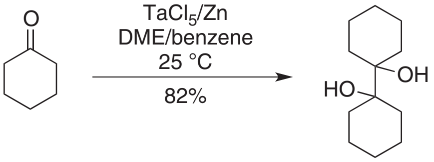
Kammermeier, Jendralla and coworkers employed $NbCl_3$ in a gram-scale synthesis of a C_2-symmetric HIV-protease inhibitor (equation 25). Homocoupling of the illustrated dipeptidic aldehyde proceeded in modest yield and with good diastereoselectivity ($>$9:1).[82]



(25)

3.11.2.2.1.13 Tantalum and cadmium

Tantalum and cadmium metal also affect the pinacol coupling of ketones and aldehydes. Pinacol coupling of aliphatic aldehydes and aliphatic ketones was established by using $TaCl_5$/Zn (equations 26 and 27).[22c] *In situ* generation of cadmium from $CdCl_2 \cdot H_2O$ in *N*,*N*-dimethylformamide (DMF)/H_2O by reduction with samarium metal enabled the coupling of aromatic aldehydes in good yields and selectivity (equation 28).[25]



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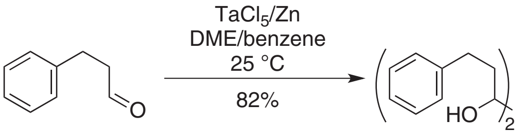
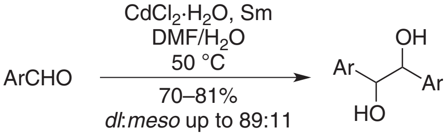


(27)



(28)

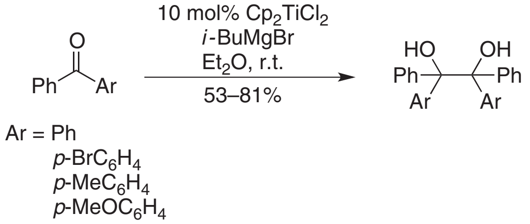
3.11.2.2.2 Catalytic protocols

One of the significant goals of pinacol coupling reactions has been to establish a catalytic system of low-valent metals to avoid the use of expensive and toxic reagents. However, the catalytic protocol only appeared in 1970s.[83] In addition to the practical significance, these advances lay the necessary basis for the development of catalytic, asymmetric pinacol coupling reactions.

The breakthrough came after the development of catalytic cycles of the McMurry coupling reaction by Fürstner and Hupperts in 1995.[84] Soon after, it was found that the use of Me_3SiCl, acetic anhydride, or acetyl chloride[85] facilitates reduction of the metal–oxygen bonds in combination with catalytic amounts of transition metal salt, such as titanium and vanadium, and a stoichiometric reducing agent affect the catalytic pinacol coupling.

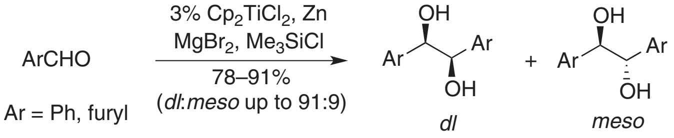
3.11.2.2.2.1 Titanium

In 1988, Zhang and Liu first reported the catalytic protocol by using titanium. Treatment of aromatic ketones with catalytic Cp_2TiCl_2 and stoichiometric *i*-BuMgBr gives the corresponding 1,2-diol in 53–81% yields (equation 29).[86]



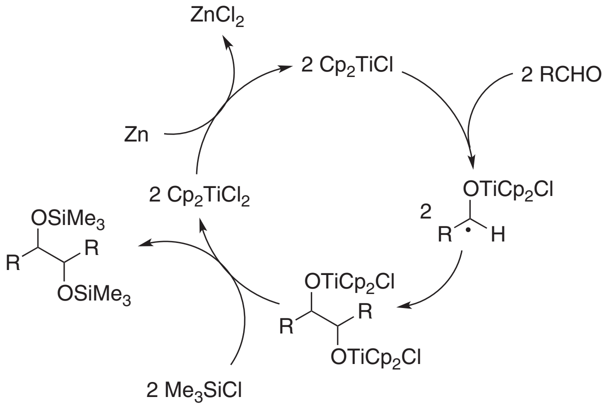
(29)

The catalytic pinacol coupling of aromatic aldehydes was described by Gansäuer by using a trinuclear complex derived from titanocene chloride (3 mol%) and magnesium bromide (1 equivalent) in the presence of Zn powder and Me_3SiCl (equation 30).[87] It was argued that 1 equivalent of $MgBr_2$ contributes to a tighter trimeric species for the better steric tuning. Under the optimized conditions, a variety of symmetrical 1,2-diols were synthesized in good yields and selectivities. The *dl*-selectivity was attributed to a similar dimeric structure **A**, as proposed by Hamada and Inanaga (**Figure 3**, vide supra).[51] Hirao et al., also applied the same protocol to aliphatic aldehydes and ketones.[88] High diastereoselectivity was attained when cyclohexanecarboxaldehyde is used, but the selectivities remained low for other acyclic aldehydes and ketones.



(30)

Scheme 15 illustrates the proposed mechanism. Cp_2TiCl_2 is reduced by zinc to Cp_2TiCl, which in turn reduces aldehydes to the ketyl species followed by the dimerization to give a titanium pinacolate. Slow addition of the mixture of Me_3SiCl and aldehydes is the key to higher selectivity and provided evidence for the silylation to be the rate-determining step.



Scheme 15 Possible pathway for the titanium-catalyzed, zinc-mediated pinacol coupling. Reproduced with permission from Otera, J. Ed.; *Modern Carbonyl Chemistry* **2000**; pp 69–91.

A slightly higher selectivity (>20:1) for aromatic aldehydes was achieved using *rac*-ethylenebis(η^5-tetrahydroindenyl)titanium dichloride ($EBTHITiCl_2$, **Figure 5**) as a catalyst in place of Cp_2TiCl_2.[89]

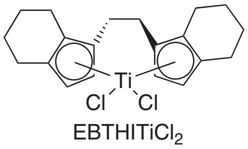
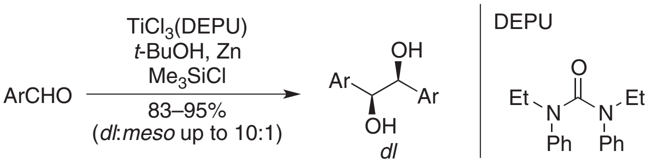


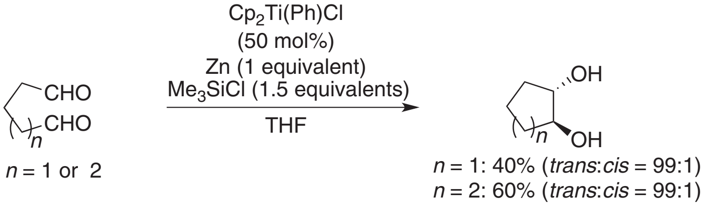
Figure 5 Structure of $EBTHITiCl_2$.

In 1997, Nelson and coworkers reported $TiCl_3(THF)_3$ as a highly efficient catalyst (1 mol%) for the pinacol coupling in the presence of stoichiometric amount of Zn and Me_3SiCl.[90] Certain additive including 5–30 mol% of proton source (*t*-BuOH, catechol, or 2,2′-biphenol) or Lewis basic reagents (*N*,*N*′-dimethylpropyleneurea, DMF, or *N*,*N*-dimethylacetamide) dramatically enhanced the reaction rates, *c.* 5–10 times faster relative to the parent $TiCl_3(THF)_3$ catalyst. The $TiCl_3(THF)_3$–*t*-BuOH catalytic system emerged as the optimal catalyst in terms of the turnover rates and the operational simplicity. The most successful catalyst system was derived from 5 mol% $TiCl_3(THF)_3$–*t*-BuOH and 30 mol% 1,3-diethyl-1,3-diphenylurea (DEPU), delivering the pinacol in substantially enhanced levels of stereoselectivity in comparison with the results by the parent $TiCl_3(THF)_3$–*t*-BuOH catalyst (equation 31).

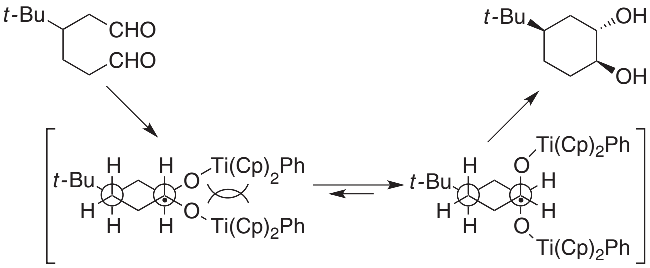


(31)

In 1999, Itoh and coworkers found that a catalytic amount (3 or 10 mol%) of $Cp_2Ti(Ph)Cl$ and a stoichiometric amount (1 equivalent) of Zn in the presence of Me_3SiCl (1.5 equivalents) promote both inter- and intramolecular pinacol coupling of benzaldehyde derivatives as well as aliphatic aldehydes to afford the corresponding 1,2-diols in high yields with moderate to good *dl*-selectivity (equation 32).[91] However, the intramolecular $Cp_2Ti(Ph)Cl$-catalyzed pinacol gave cyclic *trans*-1,2-diols with excellent diastereoselectivity. These results clearly indicated that the bulky Ti(IV) complex surrounded by the cyclopentadienyl and one phenyl ligands cannot coordinate to the other carbonyl terminus, and cyclization must proceed via diradical intermediates in which two bulky $Cp_2(Ph)TiO$-moieties occupy the axial positions to each other in order to minimize the steric repulsion (Scheme 16).

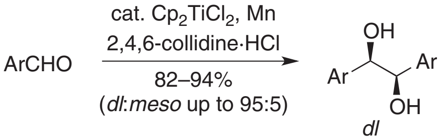


(32)



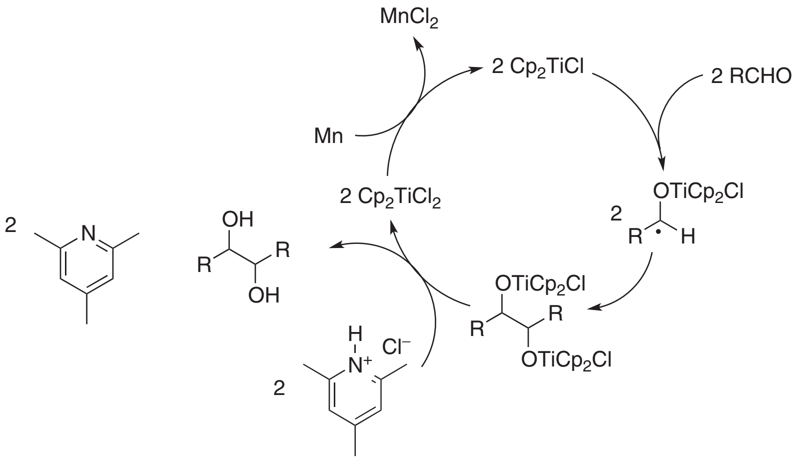
Scheme 16 Origin of selectivity. Reproduced with permission from Yamamoto, Y.; Hattori, R.; Miwa, T.; *et al. J. Org. Chem.* **2001**, *66*, 3865–3870.

In 1998, Gansäuer and Bauer demonstrated that combination of 2,4,6-collidine hydrochloride and Mn(0) achieves a catalytic turnover through protonolysis of the metal–oxygen bond instead of Me_3SiCl (equation 33).[92] Through the addition of a weakly acidic proton source, the diol product is released from the catalyst system through a rapid proton-transfer step, propagating the catalytic cycle (Scheme 17). This protocol was applied to various aromatic aldehydes to afford the corresponding diols in excellent yields and diastereoselectivity.

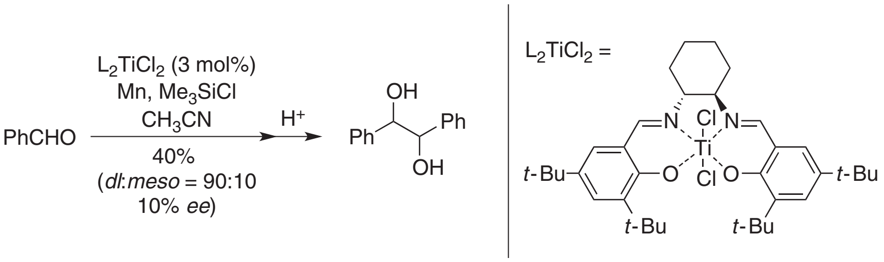


(33)

The catalytic, enantioselective pinacol coupling by using titanium was first reported by Umani-Ronchi and coworkers in 1999.[93] Treatment of benzaldehyde with a catalytic amount of a chiral Ti–Schiff base complex in the presence of stoichiometric amount of Mn powder and Me_3SiCl afforded 1,2-diphenyl-1,2-ethanediol in 40% yield (*dl*:*meso* = 90:10) with 10% *ee* (equation 34).



Scheme 17 Possible pathway for the titanium-catalyzed, manganese-mediated pinacol coupling. Reproduced with permission from Otera, J. Ed.; *Modern Carbonyl Chemistry* **2000**; pp 69–91.



(34)

Dunlap and Nicholas tried to apply the chiral Brintzinger's catalyst, (*R*,*R*)-ethylenebis(tetrahydroindenyl) (**J**) titanium dichloride, for the catalytic pinacol coupling reactions (Figure 6).[94] A moderate selectivity (60% *ee*) was recorded for the resulting pinacol under unoptimized conditions. Although similar ligands, the *ansa*-bis(indenyl) (**K**) and *ansa*-bis(tetrahydroindenyl) (**L**) metal complex, were used for the enantioselective pinacol coupling reaction, the racemate was obtained by using **K** and a low *ee* resulted with **L**.[95] Riant and coworkers found the hemi-SALEN (**M**) complex induced a moderate selectivity (66% *ee*) through a catalytic path.[71] The first successful results were obtained by using SALEN (**N**) complex in the presence of Zn and Me_3SiCl by Chatterjee et al.[96] It was also found that the *in situ* generated Ti–Schiff base complex by using **O** showed a good enantioselectivity for a wide range of substrate.[97]

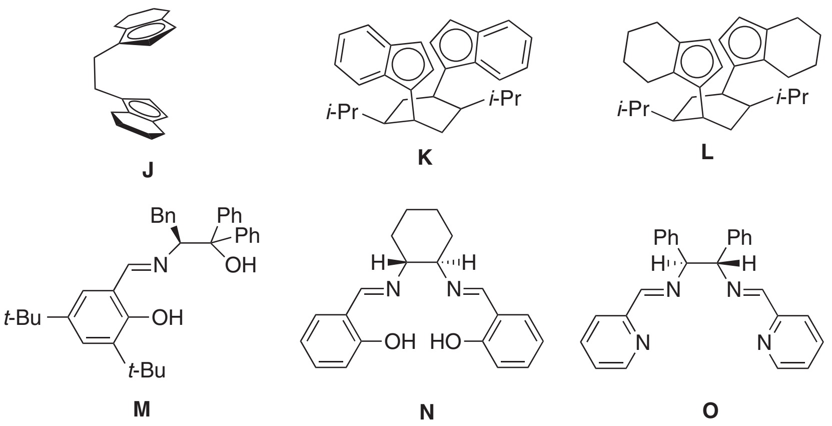
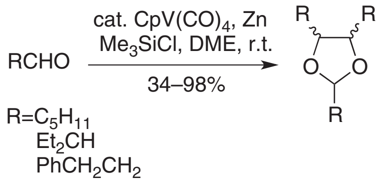


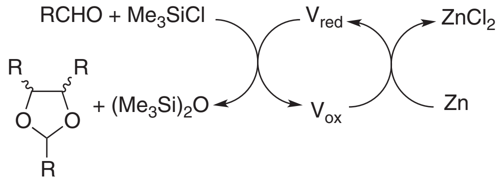
Figure 6 Chiral ligands for the enantioslective pinacol coupling.

3.11.2.2.2.2 Vanadium

Treatment of aliphatic aldehydes with a catalytic amount of $CpV(CO)_4$ (3 mol%) in the presence of the stoichiometric amount of Me_3SiCl (1.0 equivalent) and Zn powder (1.5 equivalents) furnished the pinacol derivatives (equation 35).[98] The low-valent vanadium species were regenerated *in situ* by Zn as a stoichiometric reductant (Scheme 18). The diastereoselectivity of the dioxolanes obtained was generally very low.



(35)



Scheme 18 Vanadium catalyzed, zinc-mediated pinacol coupling. Reproduced with permission from Hirao, T.; Hasegawa, T.; Muguruma, Y.; Ikeda, I. *J. Org. Chem.* **1996**, *61*, 366–367.

Based on the similar reagents, diastereoselective catalytic protocols were also developed e.g., $Cp_2VCl_2/Me_3SiCl/Zn$,[99] $VOCl_3/Me_3SiCl/Al$,[100] etc. (Table 8).

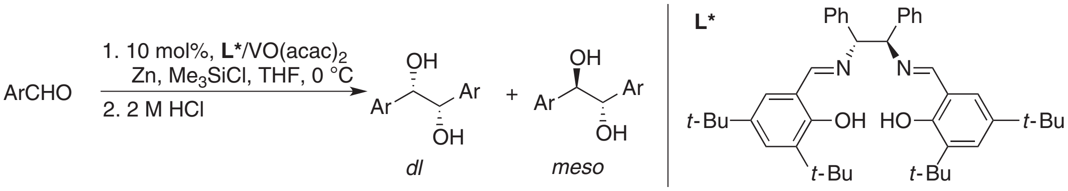
Table 8 Scope of the vanadium-catalyzed pinacol coupling

Entry	*Ar*	*Yield (%)*	dl/meso
1	Ph	68	>95/5
2	*p*-MeC_6H_4	62	>95/5
3	*p*-ClC_6H_4	89	>95/5
4	*p*-$MeOC_6H_4$	49	90/10
5	*m*-ClC_6H_4	77	>95/5

Source: Reproduced from Hirao, T.; Hatano, B.; Imamoto, Y.; Ogawa, A. *J. Org. Chem.* **1999**, *64*, 7665–7667, with permission from ACS.

Dai and coworkers first developed the catalytic enantioselective pinacol coupling of aromatic aldehydes by using chiral SALEN–vanadium complex in the presence of Zn powder and Me_3SiCl in 2009 (Table 9).[101] The corresponding 1,2-diols were obtained in high diastereoselectivities (up to *dl*:*meso*=90:10) and moderate to high enantioselectivities (up to 82% *ee*).

Table 9 SALEN–vanadium complex-induced enantioselective pinacol coupling

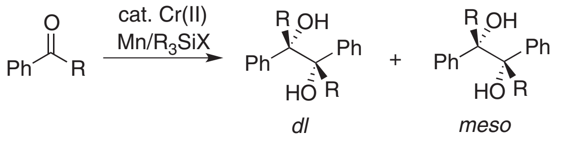


Entry	*Aldehyde*	*Yield (%)*	dl/meso	*ee (%)*
1	Ph	88	89/11	72
2	*p*-$CH_3C_6H_4$	82	86/14	78
3	*o*-$CH_3C_6H_4$	84	81/19	82
4	*p*-ClC_6H_4	83	79/21	68
5	*p*-BrC_6H_4	77	82/18	70
6	*p*-FC_6H_4	66	77/23	52
7	*p*-$CH_3OC_6H_4$	84	90/10	81
8	2-Furyl	76	84/16	37

Source: Reproduced from Sun, J.; Dai, Z.; Li, C.; Pan, X.; Zhu, C. *J. Organomet. Chem.* **2009**, *694*, 3219–3221.

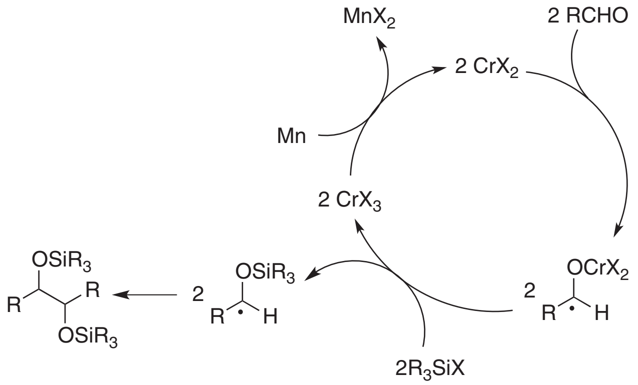
3.11.2.2.2.3 Chromium

After Fürstner and Shi established the catalytic system of Nozaki–Hiyama–Kishi reaction,[102] many groups developed the catalytic pinacol coupling reaction of aldehydes or ketones using chromium. Svatoš and Boland first reported a chromium(II)-catalyzed pinacol coupling of aromatic ketones and aldehydes in 1998, whereas aliphatic aldehydes are inert to these conditions (equation 36).[103] Scheme 19 illustrates the proposed mechanism. The turnover step relies on a combination of manganese and Me_3SiCl to regenerate CrX_2 from an intermediary chromium(III) species. After the reaction of the CrX_2 catalyst with carbonyl compounds, the generated chromium ketyl is silylated by Me_3SiCl to give the silylated ketyl species and CrX_3. Dimerization of the silylated ketyl affords the pinacol product, and the reaction of CrX_3 by Mn metal regenerates the CrX_2 species.



R = H (88%): *dl*:*meso* = 52:48
R = Me (57%): *dl*:*meso* = 48:52

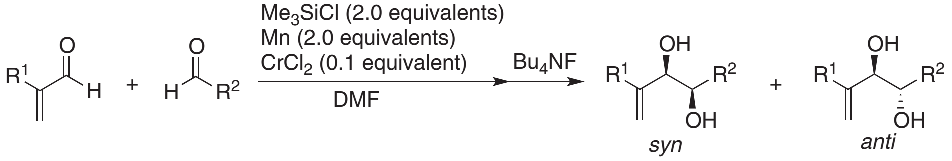
(36)



Scheme 19 Possible pathway for the chromium-catalyzed, manganese-mediated pinacol coupling. Reproduced with permission from Otera, J. Ed.; *Modern Carbonyl Chemistry* **2000**; pp 69–91.

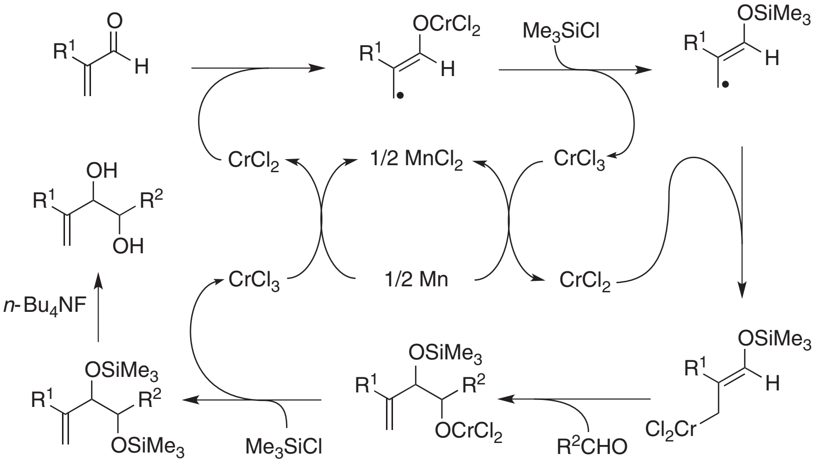
A chromium-catalyzed pinacol "cross-coupling" was also developed.[104] Combination of cat. $CrCl_2$ and Mn/Me_3SiCl promotes the cross-coupling of α,β-unsaturated carbonyl compounds and aldehydes. The amount of the chromium salt can be reduced to 10 mol% (Table 10). Various vinyl ketones were coupled with aldehydes in good yields and with high diastereoselectivity. The reaction did not proceed through a conventional dimerization mechanism of two ketyl radicals, but an attack of the chromium–allyl species to another aldehyde as shown in Scheme 20. With decrease in the steric demand, the selectivity decreased.[105]

Table 10 Chromium-catalyzed coupling reaction of acroleins with aliphatic aldehydes



Entry	*R¹*	*R²*	*Yield (%)*	syn/anti
1	*t*-Bu	*t*-Bu	61	97.5/2.5
2	*t*-Bu	Et	69	93/7
3	*t*-Bu	$Ph(CH_2)_2$	73	86/14
4	*i*-Pr	*t*-Bu	68	92/8
5	Et	*t*-Bu	75	52.5/47.5
6	Me	*t*-Bu	54	28/72
7	Et	Et	58	24/76
8	*i*-Pr	*i*-Pr	81	65/35

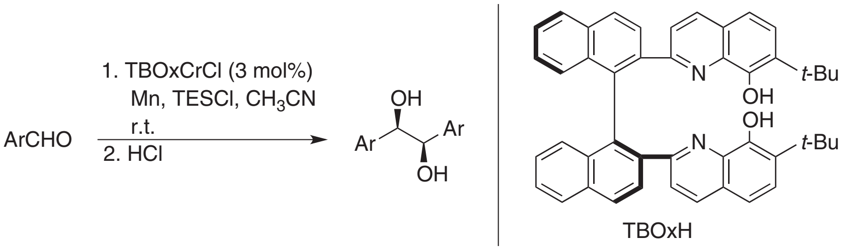
Source: Reproduced with permission from Groth, U.; Jung, M.; Vogel, T. *Chem. Eur. J.* **2005**, *11*, 3127–3135.



Scheme 20 Possible mechanism for the chromium-catalyzed, manganese-mediated pinacol coupling. Reproduced with permission from Groth, U.; Jung, M.; Vogel, T. *Chem. Eur. J.* **2005**, *11*, 3127–3135.

Through the study on Nozaki–Hiyama–Kishi reaction, Fürstner found that the reducing ability of Cp_2Cr toward aromatic aldehydes is higher than that of $CrCl_2$, because Cp is a more electron-donating ligand than the chloro ligand.[106] An electron-rich Cr(II) complex was suggested as an attractive catalyst for the pinacol coupling. In 2004, Yamamoto and coworkers developed the efficient catalytic enantioselective pinacol coupling of aromatic aldehydes by using a Cr complex of a tethered bis(8-quinolinolato) ligand, instead of the Cp-based chiral Cr complex as a catalyst (Table 11).[107] This method proved to be also applicable to aliphatic aldehydes.

Table 11 Asymmetric pinacol coupling of aromatic aldehydes

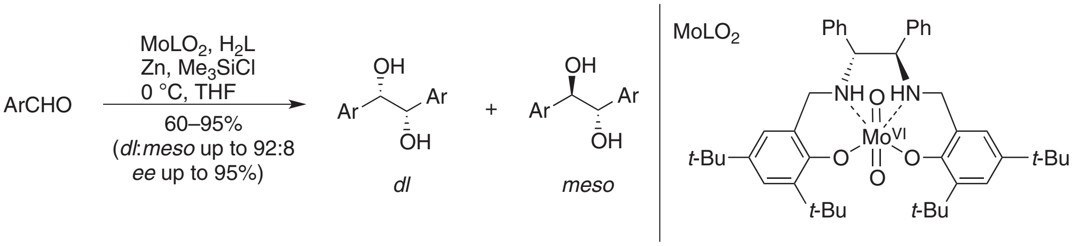


Entry	*Ar*	*Time (h)*	*Yield (%)*	dl/meso	ee *(%)*
1	Ph	10	94	98/2	97
2	*o*-MePh	18	93	98/2	98
3	*p*-MePh	12	93	97/3	97
4	*m*-MePh	12	92	98/2	97
5	*p*-BrPh	10	91	97/3	98
6	*p*-ClPh	9	94	97/3	98
7	*p*-CF_3Ph	20	89	92/8	95
8	1-Naph	14	92	96/4	98
9	2-Naph	14	88	97/3	95

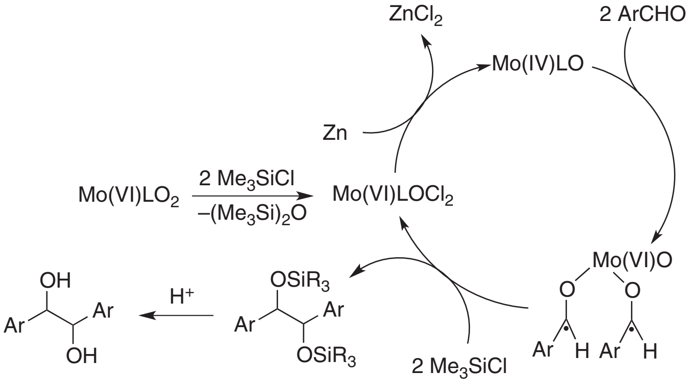
Source: Reproduced with permission from Xia, G.; Yamamoto, H. *Chem. Lett.* **2007**, *36*, 1082–1087.

3.11.2.2.2.4 Molybdenum

Zhu and coworkers found that the chiral SALAN–Mo(VI) dioxo-complex (10 mol%) catalyzed the asymmetric pinacol coupling of aromatic aldehydes in the presence of 2 equivalents of Me_3SiCl and 4 equivalents of Zn powder as coreductants (equation 37).[23] Chiral diols were obtained with high diastereo- and enantioselectivity up to 92/8 and 95%, respectively. Scheme 21 illustrates the plausible mechanism.



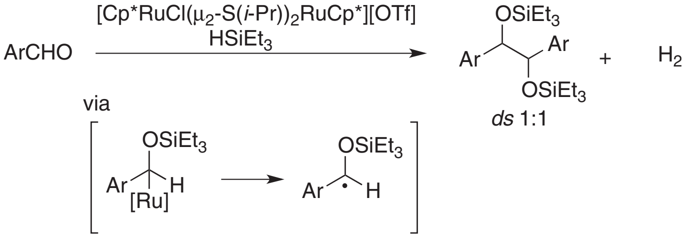
(37)



Scheme 21 Possible mechanism for molybdenum-catalyzed, zinc-mediated pinacol coupling. Reproduced with permission from Yang, H.; Wang, H.; Zhu, C. *J. Org. Chem.* **2007**, *72*, 10029–10034.

3.11.2.2.2.5 Ruthenium

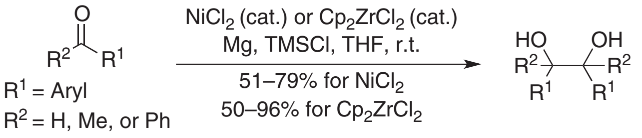
In 1995, Hidai and coworkers reported that a cationic thiolate-bridged diruthenium complex [Cp*RuCl-(μ$_2$-S(*i*-Pr))$_2$RuCp*][OTf] catalyzed the pinacol coupling of aromatic aldehydes in the presence of triethylsilane (equation 38).[108] It was postulated that the reaction proceeds through coupling of the silylated ketyls, generated through homolysis of the Ru–C bonds.



(38)

3.11.2.2.2.6 Nickel and zirconium

NiCl$_2$(cat.)/Mg/Me$_3$SiCl-[109] and Cp$_2$ZrCl$_2$(cat.)/Mg/Me$_3$SiCl[110]-mediated pinacol couplings were also described (equation 39). The proposed catalytic cycle is similar to that of titanium. Although these systems were applicable to various aromatic aldehydes/ketones, the diastereoselectivity remained low.



(39)

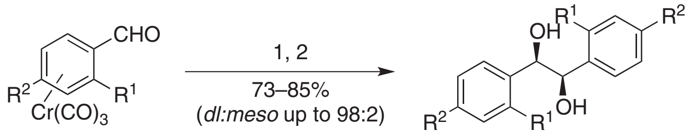
3.11.2.3 Lanthanides

3.11.2.3.1 Stoichiometric protocols

3.11.2.3.1.1 Samarium

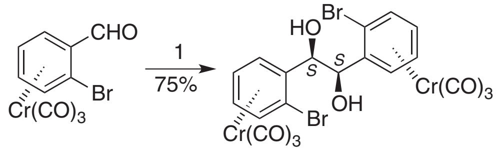
In 1983, Kagan and coworkers first described the use of SmI$_2$, generated from Sm powder and ICH$_2$CH$_2$I in THF, for intermolecular pinacol coupling of both aliphatic and aromatic aldehydes.[8] This publication fueled the explosive research on the wide use of this samarium reagent, among the lanthanides, for both intra- and intermolecular pinacol coupling. Although many samarium reagents have been developed, e.g., Sm/Me_3SiCl/NaI,[111] $SmBr_2$,[112] Sm/Et_2AlI,[113] $Sm(OTf)_2$,[114] SmI_2/Me_3SiCl,[115] or $SmCl_3$/Sm,[116] the diastereoselectivities of intermolecular reaction remain poor.

Uemura and coworkers developed the stereoselective intermolecular pinacol coupling by using SmI_2. The reaction of tricarbonyl(benzaldehyde)chromium complex with SmI_2 gave *dl*-diol in good yield (equation 40).[117] Reversed selectivity was observed by adding HMPA. Use of enantiomerically pure tricarbonyl(benzaldehyde)chromium complex gave the enantiomerically pure *dl*-pinacol complexes in good yield (equations 41 and 42).

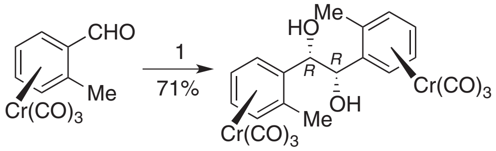


(40)

R^1 = H, Me, OMe, O*i*-Pr, NMe_2
R^2 = H, Br, Me, OMe



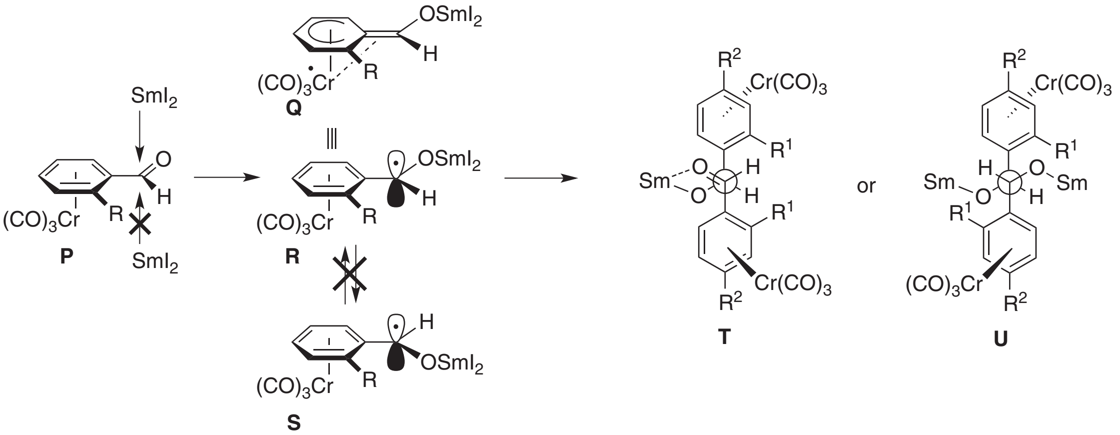
(41)



(42)

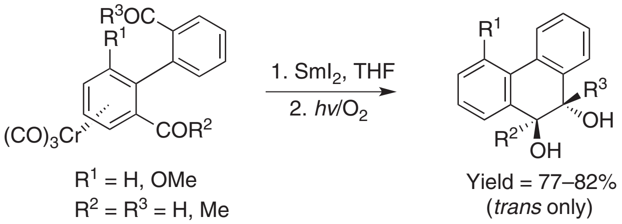
1. SmI_2, THF, –78 °C; 2. I_2, CH_2Cl_2, 73–85% (*dl:meso* up to 98:2)

The proposed mechanism is illustrated in Scheme 22. By the stereoelectronic effect, a carbonyl oxygen of the Cr-complexed *ortho* substituted benzaldehydes possessing an electron-donating substituents tends to be *anti* to the *ortho*-substituents **P**. *Exo*-attack of samarium iodide onto the carbonyl would give the chromium-stabilized ketyl **Q**, which incorporates a substantial character **R** of the exocyclic double bond by the interaction of d-orbital on the chromium with the p-orbital of the benzylic carbon. With restricted rotation around C_{α}–C_{ipso} bond, ketyl **T** undergoes coupling with another aldehyde from the opposite side of the tricarbonylchromium fragment. Stereochemical rationale is that the two arenes couple via an intramolecular coordination **T** of the samarium with the carbonyl oxygen (Scheme 22). However, HMPA precludes such coordination, leading to *meso*-diols via the transition state **U**.



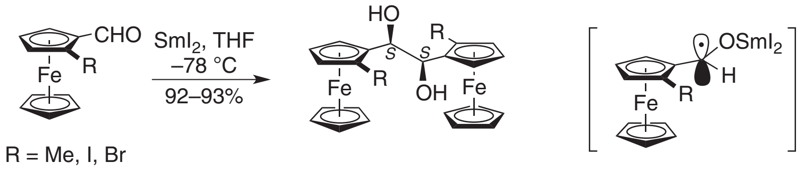
Scheme 22 Proposed reaction mechanism of tricarbonyl(benzaldehyde)chromium complex with SmI_2. Reproduced with permission from Taniguchi, N.; Uemura, M. *Tetrahedron* **1998**, *54*, 12775–12788.

Similarly, chiral 1,2-diols were prepared from mono $Cr(CO)_3$-complexed biphenyl derivatives (equation 43).[118]

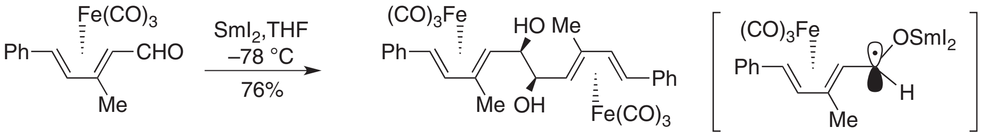


(43)

The intermolecular pinacol couplings of planar chiral α-substituted ferrocenecarboxyaldehydes and tricarbonyl(dienal)iron complex were also demonstrated (equations 44 and 45). Reductive coupling at low temperature (–78 °C) produced enantiomerically pure *dl*-diol in good yields.

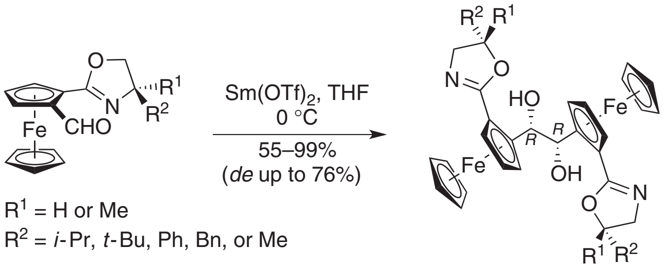


(44)



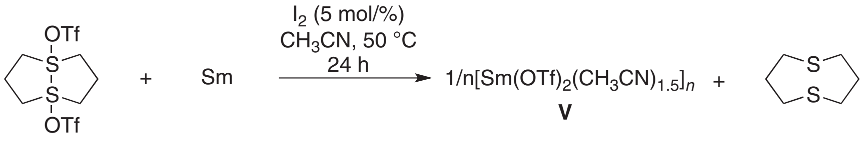
(45)

Fukuzawa and coworkers reported the pinacol coupling of planar-chiral *ortho*-substituted formylferrocene by using SmI_2 or $Sm(OTf)_2$ prepared from $Sm(OTf)_3$[114] (equation 46).[119] The (*R*,*R*) isomers were selectively obtained (up to 76% *de*).



(46)

In 1998, Mashima and Tani et al., prepared a *salt-free* $Sm(OTf)_2$-complex by the oxidative reaction of metallic Sm with the hypervalent sulfur reagent and it was effective for the diastereoselective intermolecular pinacol coupling of aromatic ketones (equation 47).[120]



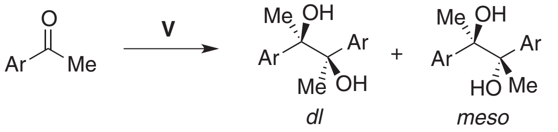
(47)

Choice of the solvent was crucial: THF decreased both the diastereoselectivity and the yield compared to acetonitrile (**Table 12**). Mechanistically, two adjacent Sm(II) centers binding a ketyl radical were assumed to dimerize to give a bimetallopinacolate intermediate, in which two samarium atoms are connected by chelating triflato ligands and that minimization of steric interference through *anti*-orientation of the aryl groups, explaining the observed diastereoselectivity (**Figure 7**).

Various polyethylene glycols (PEG) promote the stereoselective pinacol coupling of aromatic and aliphatic aldehydes (**Table 13**).[121] In the case of benzaldehyde, *meso*-diols is selectively obtained, whereas aliphatic aldehydes leads to *dl*-diols as major products.

Apart from the samarium-mediated *intermolecular* coupling reaction, a number of publications have appeared on the stereocontrolled *intramolecular* reaction by the aid of neighboring coordinating groups. Hanessian and coworkers investigated the

Table 12 Pinacol coupling by using *salt-free* Sm(OTf)$_2$-complex



Entry	Ar	Solvent	Temperature (°C)	Yield (%)	dl/meso
1	Ph	CH_3CN	r.t.	99	90/10
2	Ph	CH_3CN	–40	99	94/6
3	Ph	EtCN	–78	60	94/6
4	Ph	THF	r.t.	59	82/18
5	Ph	THF	–78	20	88/12
6	Ph	THF/HMPA	r.t.	0	–
7	Ph	CH_3CN	–40	92	95/5
8	*p*-MeC_6H_4	CH_3CN	–40	92	93/7
9	*p*-$MeOC_6H_4$	CH_3CN	r.t.	74	78/22
10	*p*-$MeOOCC_6H_4$	CH_3CN	–40	73	88/12
11	*p*-FC_6H_4	CH_3CN	–40	73	84/16

Source: Reproduced from Mashima, K.; Oshiki, T.; Tani, K. *J. Org. Chem.* **1998**, *63*, 7114–7116, with permission from ACS.

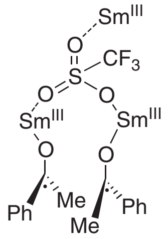
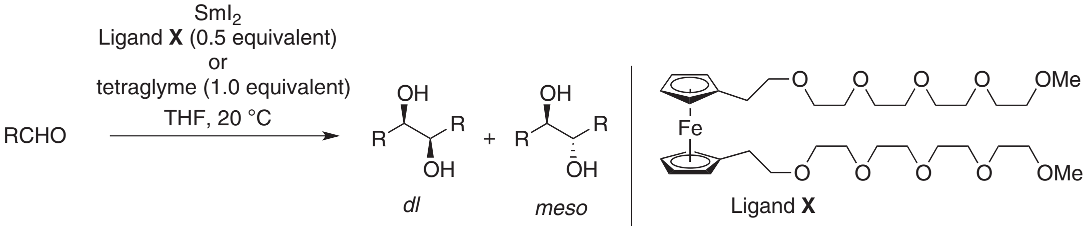
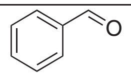
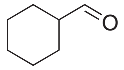
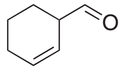
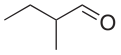
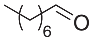


Figure 7 Origin of diastereoselectivity.

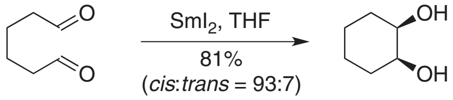
Table 13 Polyethylene glycols promoted stereoselective pinacol coupling



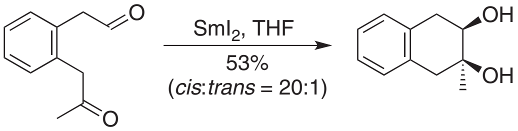
Entry	Aldehydes	PEG	Yield (%)	dl/meso
1		**X**	89	1/5
2		Tetraglyme	83	1/5.9
3		**X**	81	10/1
4		Tetraglyme	29	10/1
5		**X**	77	11/1
6		Tetraglyme	53	14/1
7		**X**	44	10/1
8		Tetraglyme	24	10/1
9		**X**	45	2.2/1
10		Tetraglyme	68	3/1

Source: Reproduced with permission from Christensen, B. T.; Riber, D.; Daasbjerg, K.; Skrydstrup, T. *Chem. Commun.* **1999**, 2051–2052.

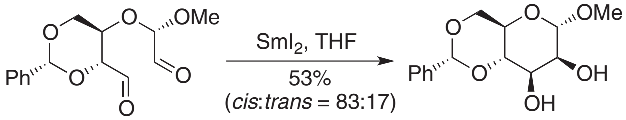
intramolecular pinacol coupling of aliphatic 1,5- and 1,6-dialdehydes by using SmI_2 (equations 48–55),[122] where *cis*-diols were selectively obtained. An inherent geometric preference for the coordination of a ketyl radical with the distal aldehyde carbonyl and the samarium species implies the formation of an 8- or 9-membered ring (**Scheme 23**). Presence of an alkoxy,[122] ester,[123] amide,[123] or siloxy[124] group at the neighboring carbon on either or one of the carbonyl groups forces *anti*-orientation of the resulting hydroxy groups with respect to the substituent.



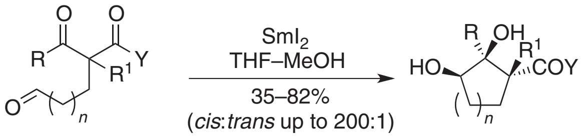
(48)



(49)



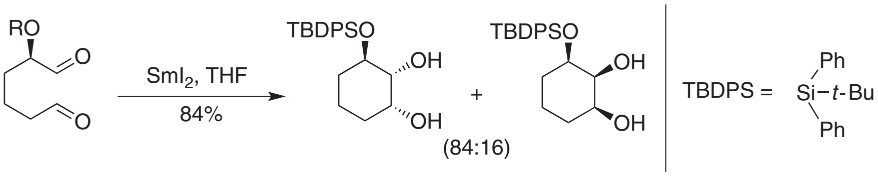
(50)



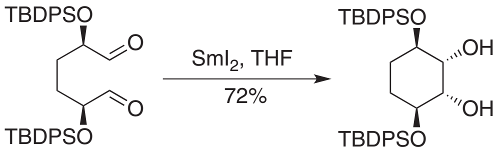
Y = OR, NR_2

R = aryl or alkyl; R^1 = H or alkyl

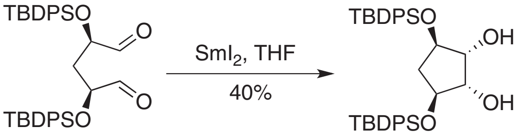
(51)



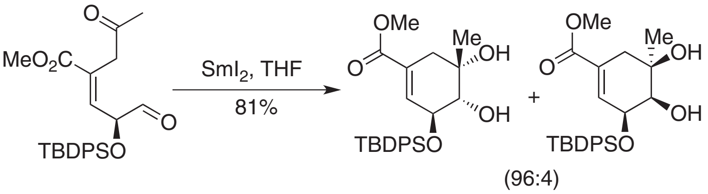
(52)



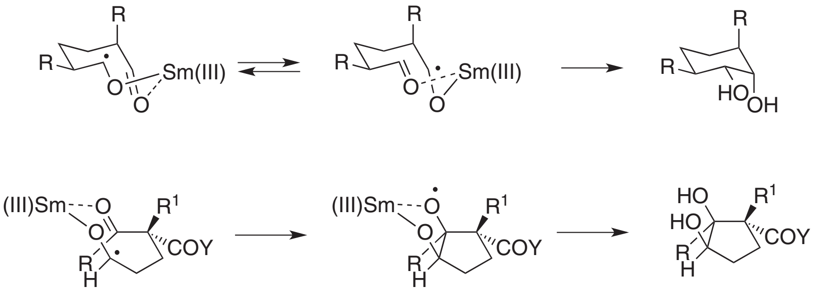
(53)



(54)

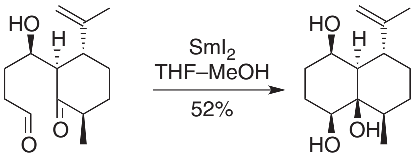


(55)



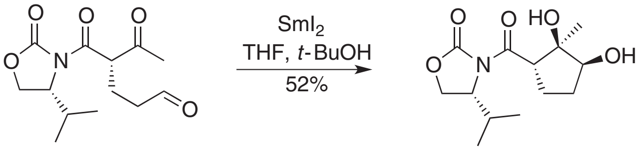
Scheme 23 Samarium-mediated intermolecular coupling reaction. Reproduced with permission from Chatterjee, A.; Joshi, N. N. *Tetrahedron* **2006**, *62*, 12137–12158.

However, the hydroxy group was effective for the stereocontrolled pinacol couplings promoted by SmI_2 (equation 56).



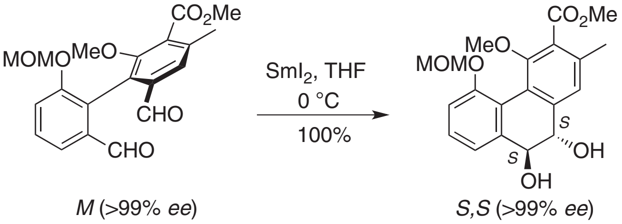
(56)

Because the neighboring substituents to the carbonyl groups affect on stereochemistry of the resulting 1,2-diol, many optically pure aldehydes were treated with SmI_2 to form the enantiomerically pure diol. Molander and Kenny provided the first example of intramolecular cross-coupling reaction (equation 57).[123]

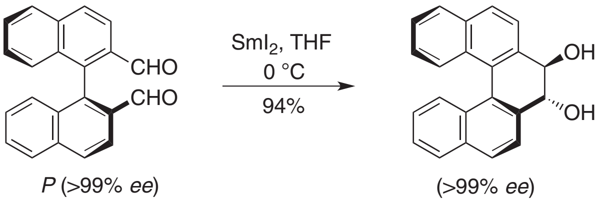


(57)

Suzuki and coworkers described two salient features of the pinacol coupling of 2,2′-biaryldicarbaldehydes: 1. the stereoselectivity to give only the *trans*-diol, and 2. the stereospecificity to transmit the axial chirality on to stereogenic centers of the product (equations 58 and 59).[125] The stereospecificity was attributed to the mode of reaction with respect to the mutual relation of two aldehyde faces. Taking the (*M*)-isomer as an example, the results showed that the reaction of two aldehydes proceed from *Re* face respectively to give (*S*,*S*)-diol (Scheme 24).



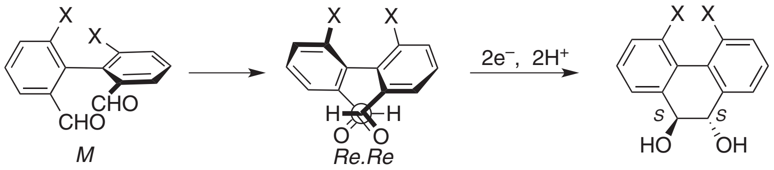
(58)



(59)

3.11.2.3.1.2 Cerium

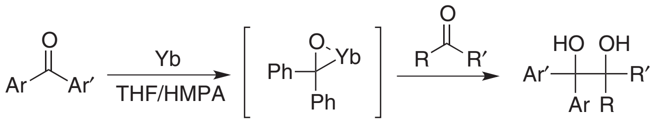
Imamoto et al., first developed the pinacol coupling of both aromatic and aliphatic aldehydes and ketones by using low-valent cerium reagents.[7] Carboxyl, cyano, and vinyl halide groups stayed intact.



Scheme 24 Possible mode of the pinacol cyclization. Reproduced with permission from Ohmori, K.; Kitamura, M.; Suzuki, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 1226–1229.

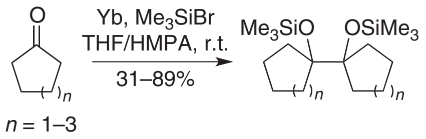
3.11.2.3.1.3 Ytterbium

Deacon et al., first found the pinacol coupling of benzophenone by using diorgano-ytterbium R_2Yb (R=PhCC or C_6F_5), in 1981.[10a] Fujiwara et al., described the Yb metal-mediated pinacol coupling reaction in 1987.[10b] The reaction of aromatic ketones and aldehyde gave the pinacol products in good yields with poor selectivity, whereas an aliphatic ketone, 2-octanone, did not undergo the reaction. Under these conditions, the reaction was proposed to proceed through the ytterbium oxirane intermediate (equation 60). Cross-coupling of benzophenone with various ketones was reported.[10b,126]

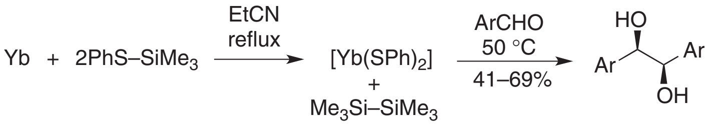


(60)

Metallic ytterbium was found to promote pinacol coupling effectively in the presence of Me_3SiBr[127] or phenylthiotrimethylsilane (equations 61 and 62).[128] The former method was applied for cyclic aliphatic ketones, whereas the latter was effective for aromatic systems.

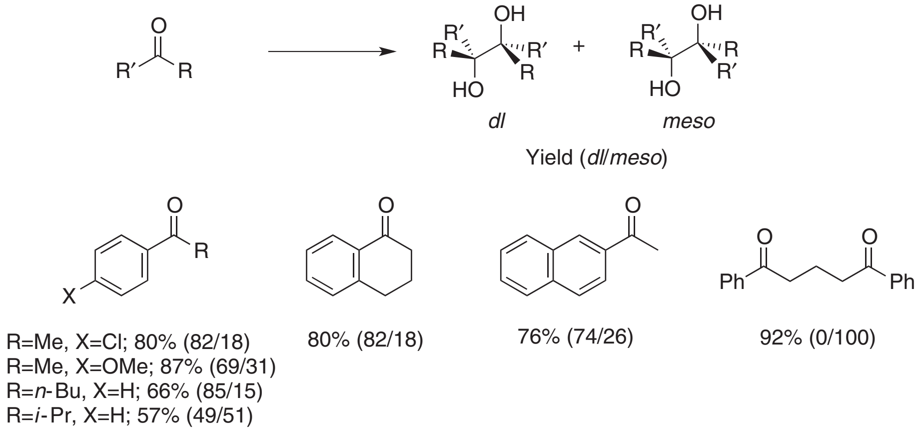


(61)



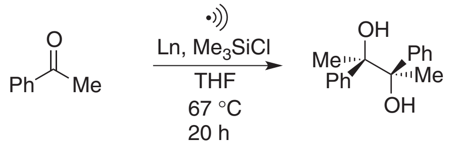
(62)

Hirao and coworkers also reported that the pinacol coupling of aromatic and aliphatic ketones in diastereoselective manner by the combination of Yb metal and Me_3SiCl (Scheme 25, see also Table 14).[30] *dl*-Diols were selectively obtained by the intermolecular coupling, whereas the intramolecular reaction provided the *meso*-diol.



Scheme 25 Ytterbium-induced pinacol coupling. Reproduced with permission from Ogawa, A.; Takeuch, H.; Hirao, T. *Tetrahedron Lett.* **1999**, *40*, 7113–7114.

Table 14 Pinacol coupling of acetophenone by using various lanthanides

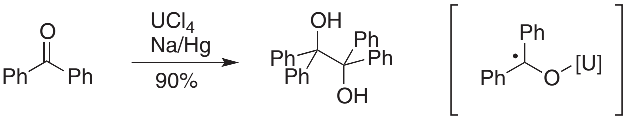


Entry	*Ln*	*Yield (%)*	dl/meso
1	Pr	78	74/26
2	Nd	77	76/24
3	Gd	85	74/26
4	Dy	87	75/25
5	Tm	85	70/30
6	Yb	80	89/11
7	Lu	47	63/37

Source: Reproduced from Ogawa, A.; Takeuch, H.; Hirao, T. *Tetrahedron Lett.* **1999**, *40*, 7113–7114.

3.11.2.3.1.4 Uranium

Ephrtikhine and coworkers reported that treatment of either cyclohexanone or benzophenone with UCl_4 and Na/Hg affords the corresponding 1,2-diol in good yield (equation 63).[31] The uranium benzopinacolates $U(Ph_4C_2O_2)Cl_2$ and $U(Ph_4C_2O_2)_2(thf)_2$ were isolated and characterized by X-ray crystallography. The reaction proceeded via dimerization of the ketyl radical intermediate.



(63)

3.11.2.3.1.5 Neodymium and gadolinium

Sussine and coworkers reported that neodymium affected the pinacol coupling of benzophenone and of fluorenone, whereas gadolinium only affects the pinacol coupling of benzophenone.[20]

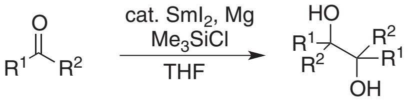
3.11.2.3.1.6 Other lanthanides

Other lanthanides were also proved useful as reducing agents for the pinacol coupling in the presence of Me_3SiCl under sonication conditions.[30] Table 14 summarizes the pinacol coupling of acetophenone by using rare earth metals. Most of the reactions proceeded with modest yields and diastereoselectivities.

3.11.2.3.2 Catalytic protocols

3.11.2.3.2.1 Samarium

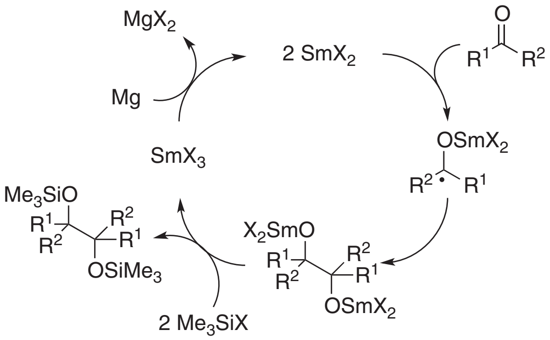
SmI_2-catalyzed pinacol coupling was established by Endo and coworkers in the presence of stoichiometric amount of Mg/Me_3SiCl (equation 64),[129] which enabled the coupling of aromatic and aliphatic aldehydes and ketones. The proposed mechanism was similar to that of the catalytic cycle of transition metal (see also Scheme 15). Me_3SiCl was used to facilitate cleavage of the metal–oxygen bonds, and Mg was used as a stoichiometric reducing agent (Scheme 26).



R^1 = Ph, R^2 = H (66%)
R^1 = $BnCH_2$, R^2 = H (57%)
R^1 = Ph, R^2 = Me (68%)
R^1 = $BnCH_2$, R^2 = Me (58%)

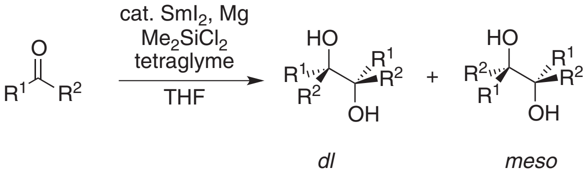
(64)

SmI_2–tetraglyme complex (10 mol%) catalyzed the intermolecular pinacol coupling of aromatic/aliphatic aldehydes in the presence of stoichiometric amount of Me_2SiCl_2 and Mg.[130] The stereoselectivities were as high as 95:5 for the *dl/meso* for pivalaldehyde (Table 15). Reversal of the diastereoselectivity was observed between aromatic and aliphatic substrate, indicating that the different mechanisms are operative. In the case of aromatic carbonyl compounds, formation of the Sm(III)-bound ketyl radicals are relatively facile than the cases of aliphatic counterparts, as the LUMO's of aromatic carbonyls have lower energy than those of the aliphatic counterparts. Concentration of these radical species would be sufficiently high to allow the dimerization between two such species, resulting in the *meso* products. However, aliphatic ketyl radicals have lower concentration, and the



Scheme 26 Possible mechanism for samarium-catalyzed, magnesium-mediated pinacol coupling. Reproduced with permission from Nomura, R.; Matsuno, T.; Endo, T. *J. Am. Chem. Soc.* **1996**, *118*, 11666–11667.

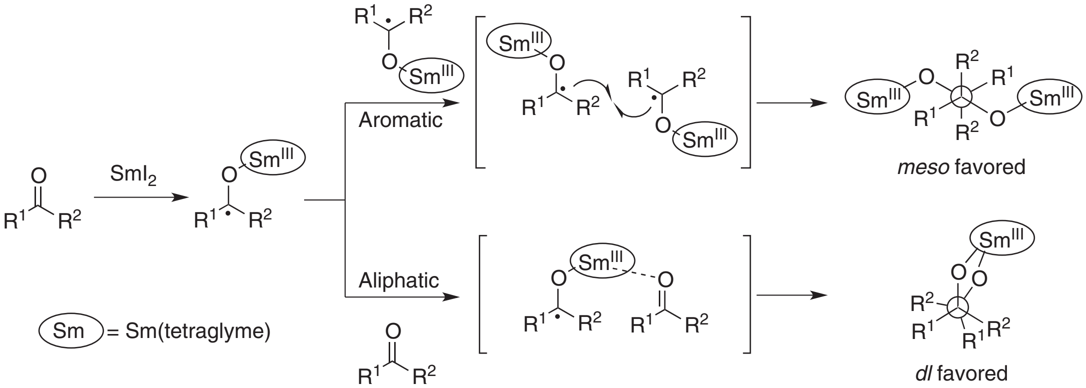
Table 15 SmI_2–tetraglyme complex catalyzed intermolecular pinacol coupling



Entry	*R¹*	*R²*	*Yield (%)*	dl/meso
1	Ph	H	83	20:80
2	Ph	Me	62	19:81
3	C_6H_{11}	H	63	81:19
4	*t*-Bu	H	76	95:5
5	C_6H_{11}	Me	74	94:6

Source: Reproduced with permission from Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *7*, 1919–1922.

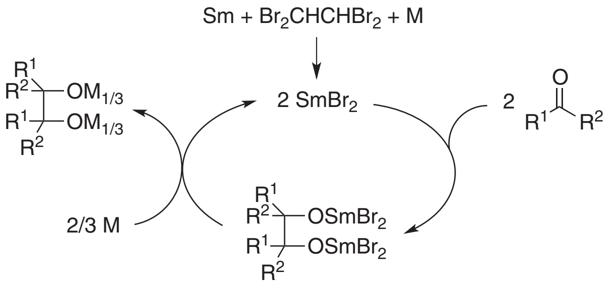
Lewis acidic Sm center of the Sm(III)-bound ketyl radical prefers to attack another aldehyde, conforming a *pseudo*-bridged arrangement (Scheme 27).



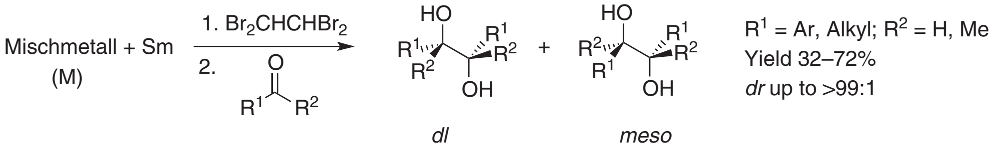
Scheme 27 Proposed mechanism for the diastereoselective pinacol coupling. Reproduced with permission from Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *7*, 1919–1922.

A catalytic cycle by using $SmBr_2$ was also proposed.[131] Reduction of Sm(III) as well as cleavage of the Sm–O bond were achieved by using *Mischmetall* (mixed-metal), a cheap alloy of light lanthanides for industrial applications, instead of Mg/Me_3SiCl (Scheme 28). The *dl*-selectivity went up to 100% for the reaction of aldehyde with high steric demand.

In some cases, slow addition of the carbonyl compound was necessary for effecting the regeneration of the Sm(II) species. These conditions allowed the coupling of various aldehydes and ketones (equation 65).



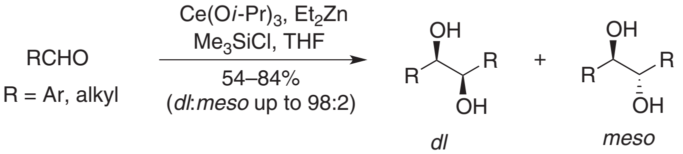
Scheme 28 Proposed catalytic mechanism. Reproduced with permission from Lannou, M.-I.; Hélion, F.; Namy, J.-L. *Tetrahedron* **2003**, *59*, 10551–10565.



(65)

3.11.2.3.2.2 Cerium

Groth and Jeske first developed the Ce(III)-catalyzed pinacol coupling in the presence of a stoichiometric amount of Me_3SiCl and Et_2Zn for the catalyst regeneration.[132] The protocol proved to be effective even at 3 mol% loading of the catalyst. The reactions of both aromatic and aliphatic aldehydes afforded *dl*-diol in high yields and excellent selectivities (equation 66). Further studies showed that Ce(O*t*-Bu)$_3$ was superior to other cerium(III) catalysts precursors.[133] Remarkably, the pinacol coupling of simple (not sterically demanding) aldehydes, such as hexanal, proceed in high diastereoselectivies.



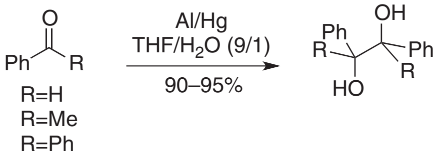
(66)

3.11.2.4 p-Block elements

Although rather rare, the p-block elements-mediated pinacol couplings are covered in this section.

3.11.2.4.1 Aluminum

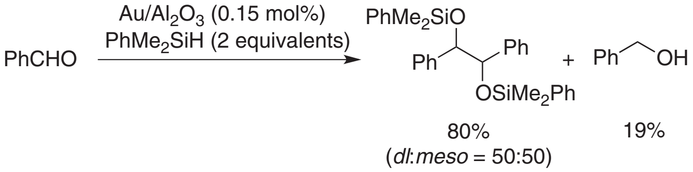
Schreibmann reported pioneering work of the aluminum-mediated pinacol coupling, using aluminum amalgam for the coupling of acetophenone (cf. equation 1).[3] Later, aluminum power also proved to promote the reaction in aqueous solution (equation 67 and Table 16).[134,135] In the case of aluminum amalgam, presence of metal fluoride sometimes enables the stereoselective reaction (Table 16).[136]



(67)

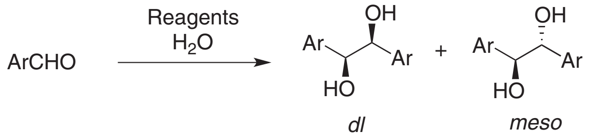
3.11.2.4.2 Silicon

Treatment of aromatic aldehydes with hexamethyldisilane in combination with a catalytic amount of CsF or TBAF afforded diols in moderate yields without pronounced selectivities.[15] Au/Al_2O_3, prepared by metal vapor deposition,[137] catalyzed the silylative pinacol coupling of carbonyl compounds (equation 68).[138] Au(0) may act as a radical initiator, giving the pinacol products with a *meso*/*dl* ratio of 50:50 (Scheme 29).



(68)

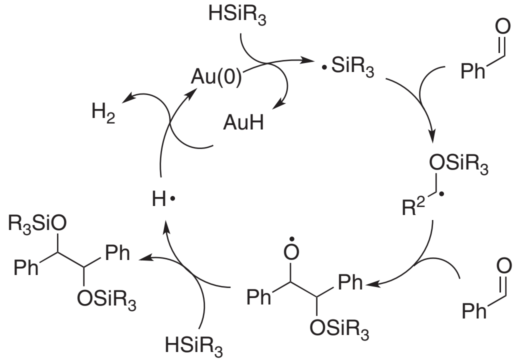
Table 16 Aluminium-mediated pinacol coupling of aromatic aldehydes



Entry	Aldehydes	Reagents	Yield (%)	Yield (%)	dl/meso
1	PhCHO	Al[a]	91	91	51:49
2		Al/CuF	96	96	97:31
3	*p*-ClPhCHO	Al[a]	98	98	71:29
4		Al/CuF	57	57	96:4
5	*p*-MePhCHO	Al[a]	88	88	71:29
6		Al/CuF	82	82	95:5

[a] Aqueous NaOH–MeOH under ultrasound.

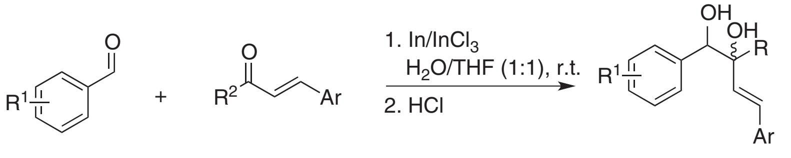
Source: Reproduced with permission from Bian, Y.-J.; Liu, S.-M.; Li, J.-T.; Li, T.-S. *Synthetic Commun.* **2002**, *32*, 1169–1173 and Li, L.-H.; Chan, T. H. *Org. Lett.* **2000**, *2*, 1129–1132.



Scheme 29 Plausible mechanism for the silicon-catalyzed pinacol coupling. Reproduced with permission from Raffa, P.; Evangelisti, C.; Vitulli, G.; Salvadori, P. *Tetrahedron Lett.* **2008**, *49*, 3221–3224.

3.11.2.4.3 Indium

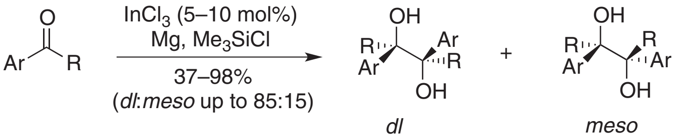
The indium-mediated pinacol coupling of aromatic aldehydes was also developed.[26] The reaction proceeded in water or in water/*t*-BuOH under sonication to give diols in good yields and moderate selectivities. In/$InCl_3$ was found to promote the pinacol cross-coupling of aromatic aldehydes with α,β-unsaturated ketones (equation 69).[139]



Yield 42–61%
anti:*syn* up to 99:1

(69)

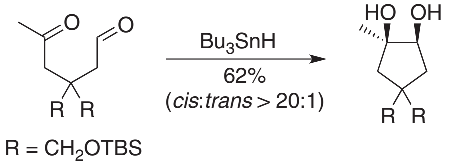
A catalytic protocol was also achieved by using $InCl_3$ in the presence of a stoichiometric amount of both Me_3SiCl and Mg metal, giving diols in good to moderate yields in high diastereoselectivity (equation 70).[140]



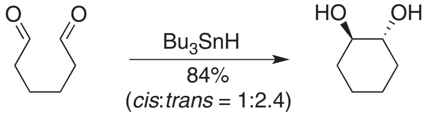
(70)

3.11.2.4.4 Tin

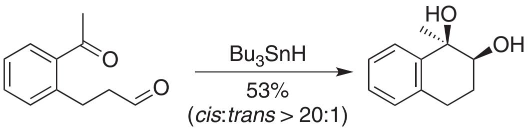
Bu_3SnH effected intramolecular pinacol couplings of 1,5- and 1,6-dialdehydes and ketoaldehydes in the presence of 2,2′-azobisisobutyronitrile (AIBN) (equations 71–73).[27] 1,5-Dicarbonyl compounds undergo cyclization in excellent *cis* selectivities, whereas 1,6-dicarbonyl compounds provided variable stereoselectivities. Isotope-labeling experiments revealed an interesting new reaction pathway, involving homolytic substitution as a key step (**Scheme 30**). Other metal hydrides [Ph_3SnH, $(Me_3Si)_3SiH$, and Bu_3GeH] effected intramolecular pinacol couplings.



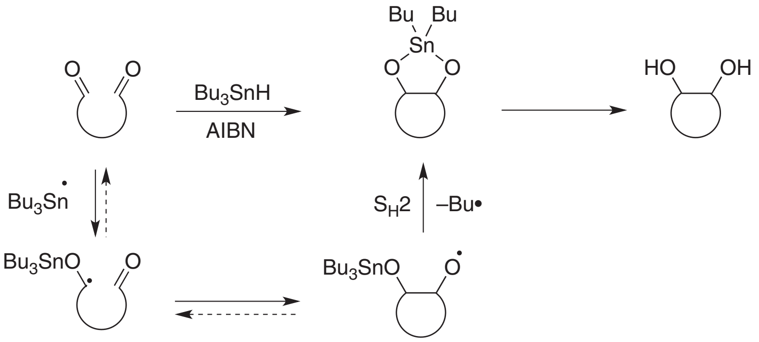
(71)



(72)



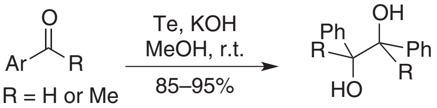
(73)



Scheme 30 Mechanism for the Bu_3SnH-madiated pinacol coupling. Reproduced with permission from Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1995**, *117*, 7283–7284.

3.11.2.4.5 Tellurium

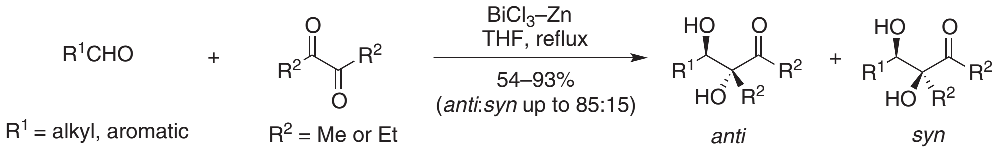
Te/KOH effected the pinacol coupling of aromatic carbonyl compounds (equation 74).[28] The reaction of acetophenone gave exclusively the *meso*-diol, whereas the reactions of aromatic aldehydes were not diastereoselective.



(74)

3.11.2.4.6 Bismuth

Miyoshi et al., found that diketones and aldehydes were coupled in the presence of $BiCl_3$ and Zn to afford the corresponding α,β-dihydroxylketones with diastereoselectivities ranging from 2:1 to 6:1 in favor of the *anti*-diols (equation 75).[29] The reaction proceeded smoothly by using a catalytic amount of $BiCl_3$.



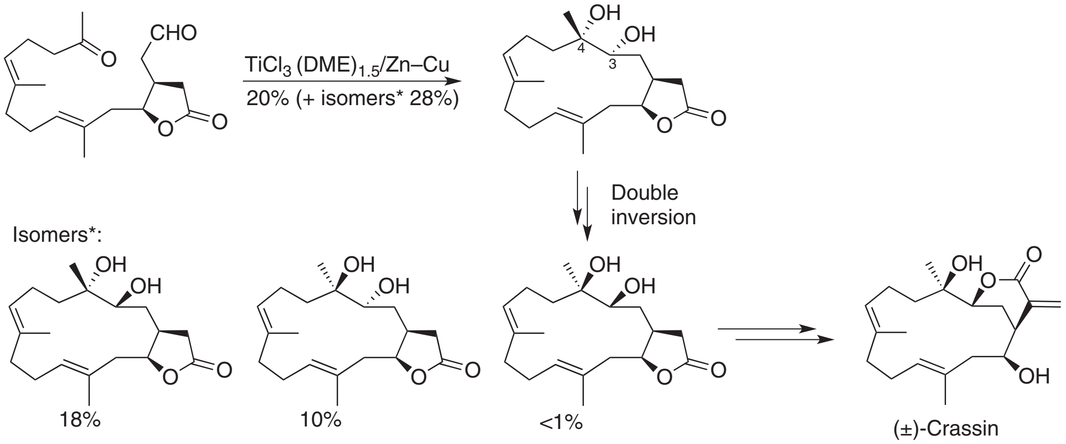
(75)

3.11.3 Pinacol Coupling Reactions in Natural Product Synthesis

These new methods and/or reagents for the pinacol coupling have been used in natural product synthesis, where the functional-group compatibility was tested. Especially, the mild and selective nature of the Sm- and Ti-mediated pinacol coupling have enjoyed wide application.

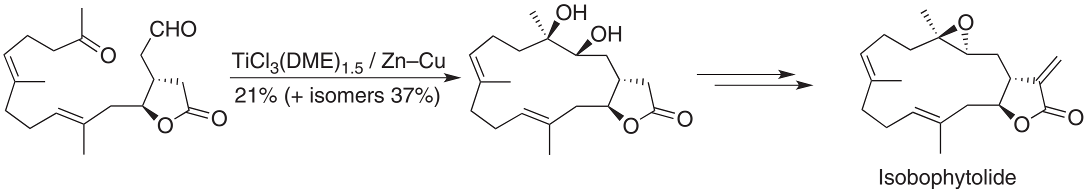
3.11.3.1 Titanium

McMurry and Dushin synthesized crassin by using $TiCl_3$/Zn–Cu for constructing the 14-membered ring in diterpenoid.[141] The internal pinacol coupling of a ketoaldehyde gave 48% yield of an isomeric mixture of the cyclic diols. Because of the low yield (<1%) of the desired isomer, the major isomer was epimerized at the C3, C4 centers by double inversion (**Scheme 31**).



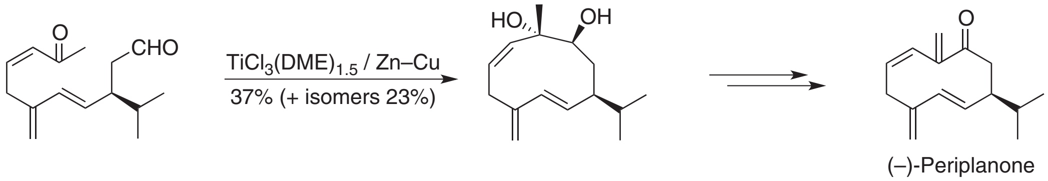
Scheme 31 Synthesis of (±)-crassin. Reproduced with permission from McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8928–8929.

Recognizing the close relationship of crassin and isobophytolide,[142] McMurry prepared a ketoaldehyde with *trans*-annulated butyrolactone, which was subjected to an intramolecular pinacol reaction to give an advanced intermediate (**Scheme 32**). Again, all four stereoisomers were produced.



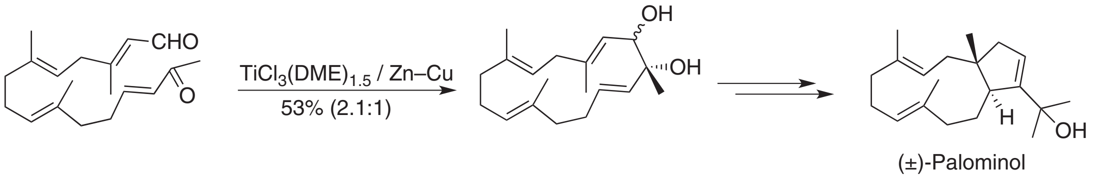
Scheme 32 Synthesis of isobophytolide. Reproduced with permission from McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6942–6949.

In another example, McMurry and Siemers reported the synthesis of (–)-periplanone C, a sesquiterpene isolated as an insect sex pheromone.[143] The 10-membered ring was constructed by the pinacol coupling using $TiCl_3(DME)_{1.5}$ and Zn–Cu (**Scheme 33**), giving a separable mixture of two diastereomers in a ratio of 2.1:1.



Scheme 33 Synthesis of (–)-periplanone. Reproduced with permission from McMurry, J. E. Siemers, N. O. *Tetrahedron Lett.* **1994**, *35*, 4505–4508.

Corey applied a Ti-mediated intramolecular pinacol coupling for constructing a 15-membered ring of palominol, a marine cytotoxic diterpenoid (**Scheme 34**).[144] Slow addition of ketoaldehyde (32 h) to the titanium reagent furnished the product in 53% yield as a mixture of diastereomers (2.1:1).



Scheme 34 Synthesis of (±)-palominol. Reproduced with permission from Corey, E. J.; Kania, R. S. *Tetrahedron Lett.* **1998**, *39*, 741–744.

Taxol® is a clinically used anticancer agent (**Figure 8**), for which many different synthetic approaches have been addressed. Among others, intramolecular pinacol coupling has been used as the reliable tool for the construction of the ring systems.

Nicolaou et al., achieved the total synthesis of Taxol® via pinacol cyclization to form the B-ring (**Scheme 35**).[145] The reaction proceeded in moderate yield (23%), producing two major side products, a lactol and an olefin.

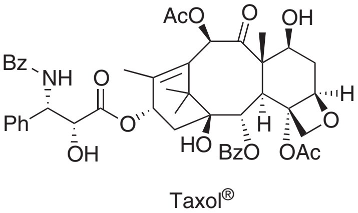
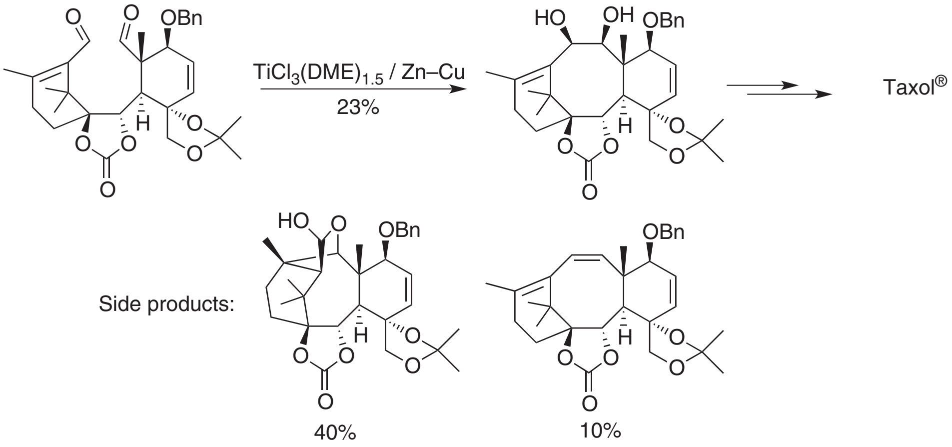
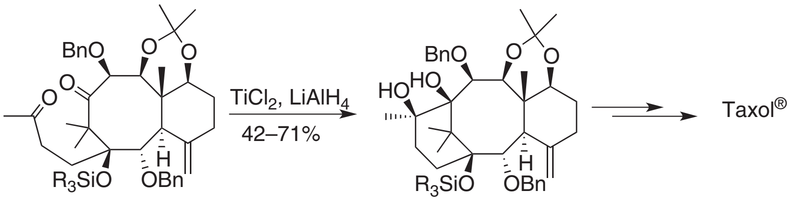


Figure 8 Structure of Taxol®.



Scheme 35 Nicolaou's synthesis of Taxol®. Reproduced with permission from Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; *et al. Nature* **1994**, *367*, 630–634.

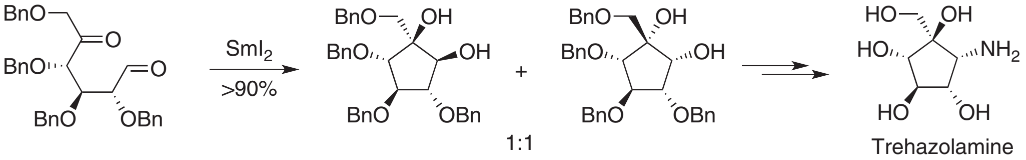
Mukaiyama and coworkers constructed the A-ring using $TiCl_2/LiAlH_4$ (**Scheme 36**).[146] Low-valent titanium reagent, prepared from $TiCl_2$ and $LiAlH_4$, was more reactive than the one prepared from $TiCl_3$ or $TiCl_4$ and $LiAlH_4$. Partially reduced alcohols and rearranged compounds were the major side products.



Scheme 36 Mukaiyama's synthesis of Taxol®. Reproduced with permission from Shiina, I.; Iwadare, H.; Hasegawa, M.; Tani, Y.; Mukaiyama, T. *Chem. Lett.* **1998**, *27*, 1–2.

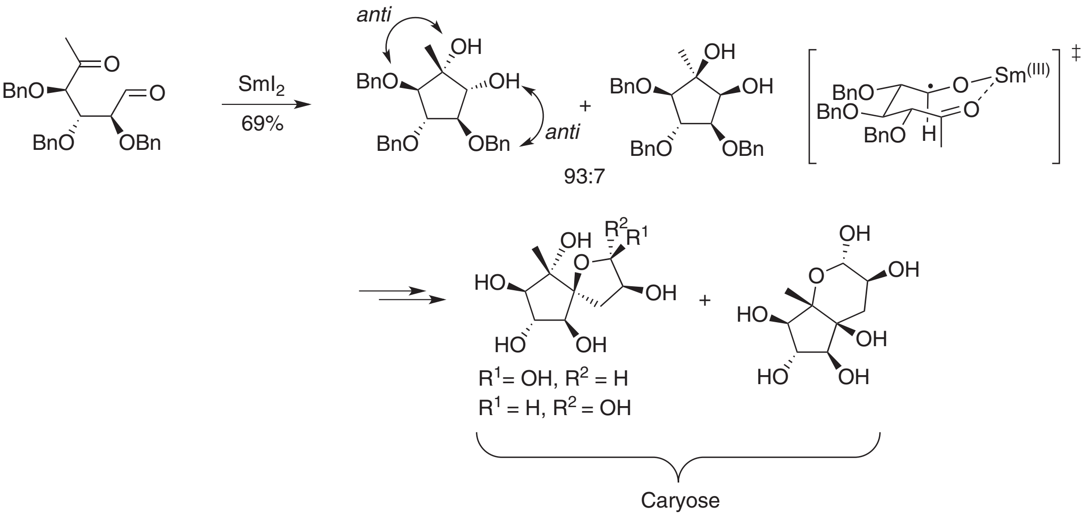
3.11.3.2 Samarium

Chiara described synthesis of the aglycon of the potent trehalase inhibitor, trehazolamine, from D-glucose.[147] Pinacol cyclization provided the necessary cyclopentane framework (Scheme 37). Treatment of protected ketoaldehyde with SmI_2 furnished two *cis*-diols exclusively as a 1:1 mixture of isomers in 90% yield.[148]



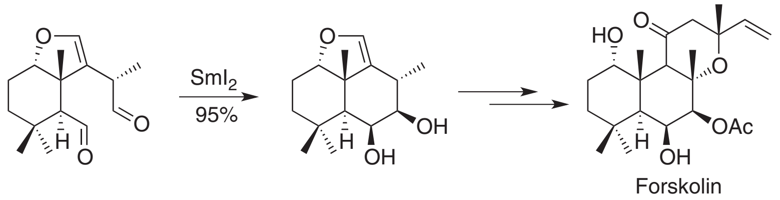
Scheme 37 Synthesis of trehazolamine. Reproduced with permission from De Gracia, I. S.; Dietrich, H.; Bobo, S.; Chiara, J. L. *J. Org. Chem.* **1998**, *63*, 5883–5889.

Ladonisi et al. utilized a SmI_2-mediated stereoselective intramolecular pinacol coupling of ketoaldehyde for the synthesis of caryose, a component of the cell wall lipopolysaccharides (Scheme 38).[149] The major *cis*-diol contains the newly formed diol *anti* to the directing α-benzyloxy substituents.



Scheme 38 Synthesis of caryose. Reproduced with permission from Adinolfi, M.; Barone, G.; Ladonisi, A.; Mangoni, L.; Manna, R. *Tetrahedron* **1997**, *53*, 11767–11780.

For approaching forskolin, a diterpenoid with adenylate cycle activating activity, Pancrazi and coworkers employed a SmI_2-mediated pinacol coupling of dialdehyde to give *cis*-diol (Scheme 39).[150]

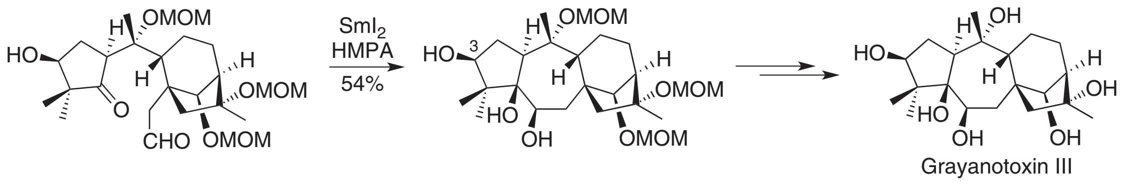


Scheme 39 Synthesis of forskolin. Reproduced with permission from Anies, C.; Pancrazi, A.; Lallemand, J.-Y.; Prange, T. *Bull. Soc. Chem. Fr.* **1997**, *134*, 203–222.

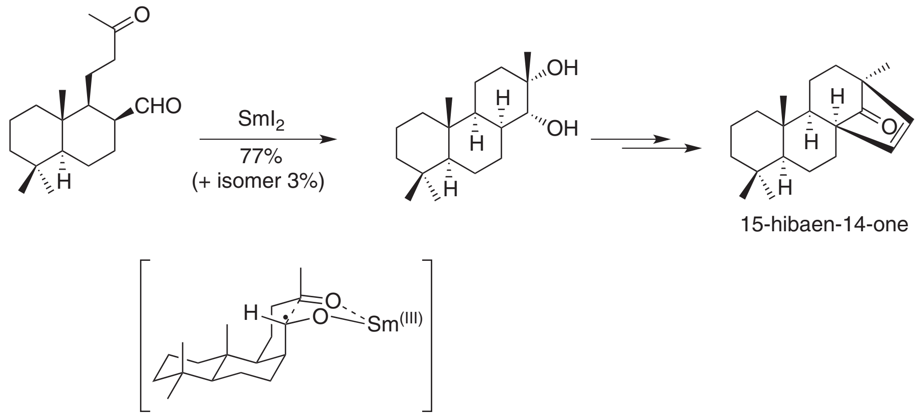
Shirahama, Matsuda and coworkers achieved the total synthesis grayanotoxin III, a diterpene isolated from the leaves of carious plants of the family *Ericaceae*, by exploiting SmI_2-mediated intramolecular pinacol coupling (Scheme 40).[151] Cyclization of ketoaldehyde with SmI_2 in the presence of HMPA exclusively gave the *cis*-diol in good yield. Interestingly, the C3 hydroxy group plays an important role. No cyclization took place when the hydroxy group was protected as a methoxymethyl (MOM) ether.

Marcos et al., used the SmI_2-mediated pinacol coupling of ketoaldehyde, prepared from the natural diterpene zamoranic acid, for the synthesis of the 15-hibaen-14-one (Scheme 41).[152] The desired *cis*-diol was obtained with high diastereoselectivity (25:1), arising from the chair-like transition state.

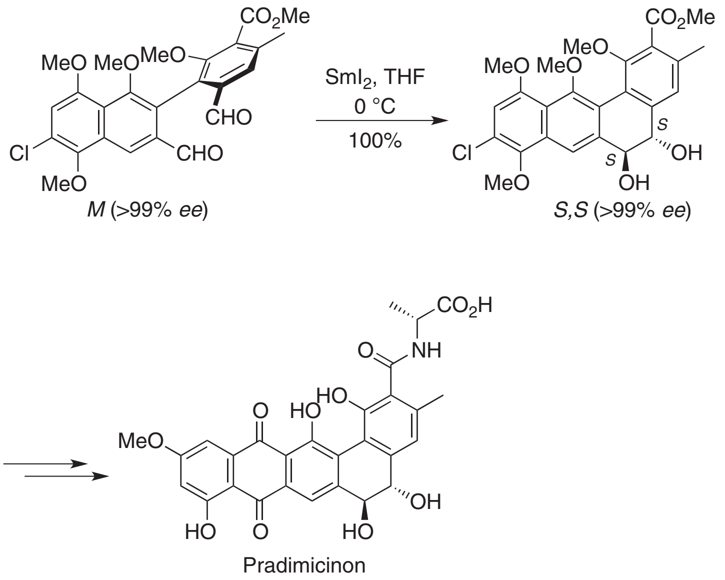
Suzuki and coworkers achieved the total synthesis of pradimicinone, the common aglycon of the benanomicin–pradimicin antibiotics (BpAs), by using SmI_2-mediated pinacol coupling of axially chiral biaryldialdehyde (Scheme 42).[153] The cyclization



Scheme 40 Synthesis of grayanotoxin III. Reproduced with permission from Kan, T.; Matsuda, F.; Yanagiya, M.; Shirahama, H. *Synlett* **1991**, 391–392.



Scheme 41 Synthesis of 15-hibaen-14-one. Reproduced with permission from Marcos, I. S.; MMoro, R. F.; Carballares, S.; Urones, J. G. *Synlett* **2002**, 458–462.

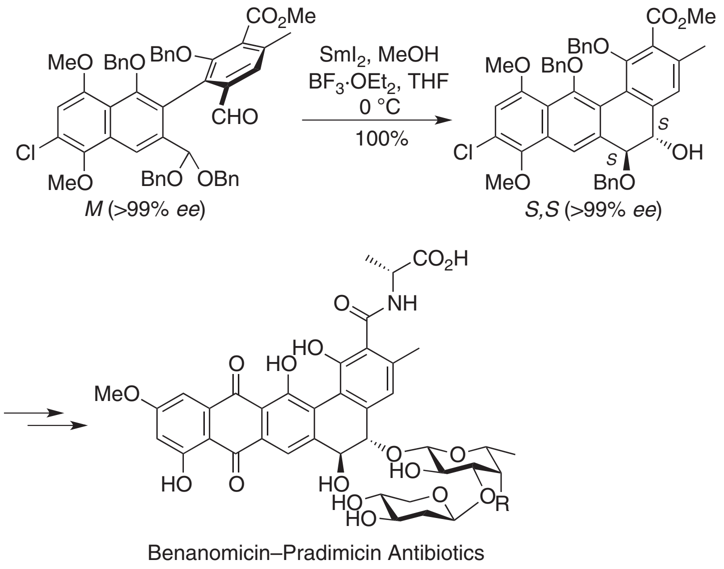


Scheme 42 Synthesis of pradimicinon. Reproduced with permission from Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 1229–1232.

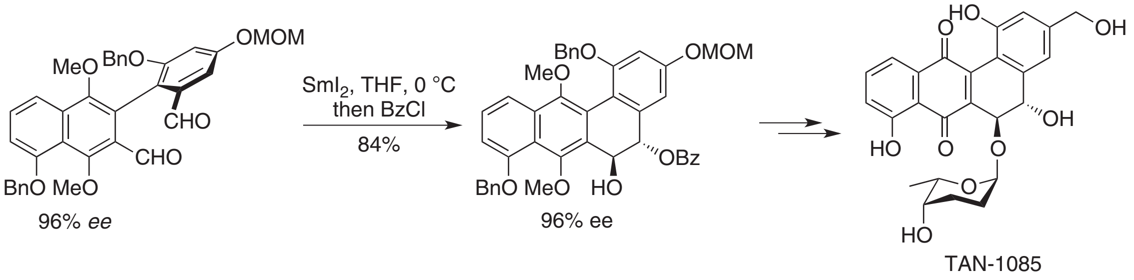
proceeded to give *trans*-1,2-diol in quantitative yield with complete transfer of the axial chirality (*M*) to the stereogenic center of the diol moiety (*S*,*S*) of product.[125]

For the total synthesis of BpAs, the discrimination of the *pseudo*-C_2-symmetric 1,2-diol generated by the pinacol coupling is necessary. For this purpose, the semipinacol coupling was devised.[154] The reductive coupling of acetal–aldehyde by using SmI_2 in the presence of $BF_3 \cdot OEt_2$ and one equivalent of MeOH gave the mono-protected 1,2-*trans*-diol in good yield. Again, the axial chirality was completely transferred to the stereogenic centers (Scheme 43).[155]

The same strategy was applied to the synthesis of other natural products.[156,157] In the synthesis of TAN-1085, the pinacol coupling was directly quenched with benzoyl chloride, giving the C5-benzoate of *trans*-diol in 84% yield (Scheme 44).

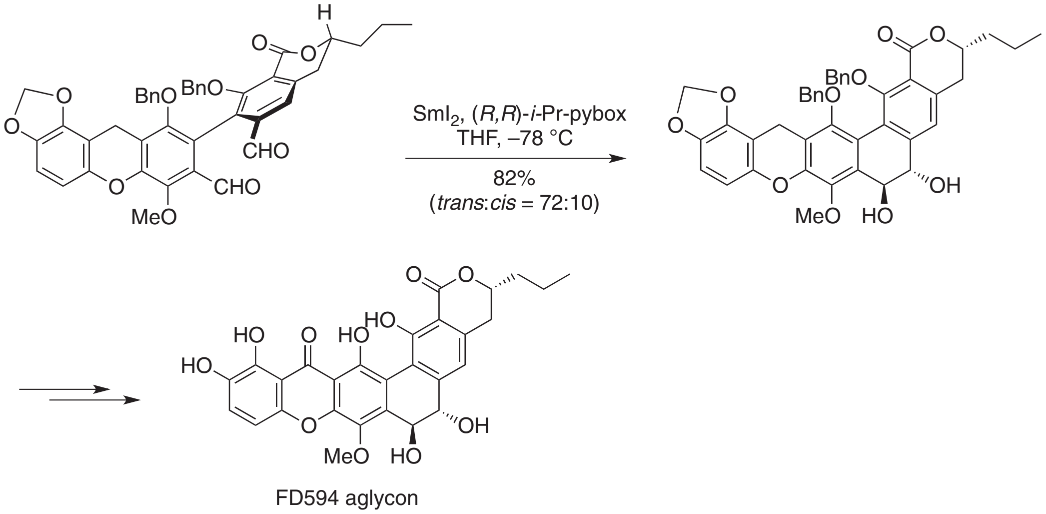


Scheme 43 Synthesis of benanomicin–pradimicin antibiotics. Reproduced with permission from Ohmori, K.; Tamiya, M.; Kitamura, M.; Kato, H.; Oorui, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 3871–3874.



Scheme 44 Synthesis of TAN-1085. Reproduced with permission from Ohmori, K.; Mori, K.; Ishikawa, Y.; *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 3167–3171.

For the synthesis of FD-594 aglycon, judicious choice of the additive and low temperature were necessary for the high yield and *trans*/*cis* selectivity (Scheme 45). Pybox ligands proved effective as additive for improving the yield and stereoselectivity.



Scheme 45 Synthesis of FD594 agalycon. Reproduced with permission from Masuo, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 3462–3465.

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3.12 Acyloin Coupling Reactions

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3.12.1 **Introduction** 621
3.12.2 **Traditional Acyloin Coupling Reactions** 621
3.12.2.1 Mechanism 622
3.12.2.2 Heterogeneous Conditions 622
3.12.2.3 Homogeneous Conditions 624
3.12.2.4 Cross-Acyloin Condensation 624
3.12.2.5 Miscellaneous Reductive Methods 626
3.12.2.6 Recent Synthetic Applications 627
3.12.3 ***N*-heterocyclic Carbene (NHC) Catalyzed Acyloin Coupling Reactions** 628
3.12.3.1 Synthesis of Symmetrical Acyloins 628
3.12.3.2 Cross-acyloin Condensations 629
3.12.3.2.1 Asymmetric intermolecular acyloin couplings 635
3.12.3.3 Intramolecular Aldehyde–Ketone Cross-acyloin Couplings 636
3.12.3.3.1 Enantioselective intramolecular aldehyde–ketone coupling reactions 637
3.12.3.3.2 Synthetic applications 639
3.12.3.4 Asymmetric Dual Secondary Amine/NHC Catalysis 642
3.12.4 **Indirect Approaches to Unsymmetrical Acyloins** 646
3.12.4.1 Acylzirconocene Chlorides 646
3.12.4.2 Acylsilanes 647
3.12.4.3 Acylphosphonates 648
3.12.4.4 O-Silyl Thiazolium Carbinols 650
3.12.4.5 α-Ketoesters 650
3.12.4.6 *N*-Silyloxyketene Imines 652
3.12.5 **Summary** 653
References 653

Glossary

Acyloin An α-hydroxy ketone.

Benzoin A specific class of acyloins in which the substituents on the α-hydroxy ketone are aromatic.

Cross-acyloin An unsymmetrical acyloin in which at least one of the substituents is alkyl.

Cross-benzoin An unsymmetrical acyloin in which both substituents are aromatic.

Traditional acyloin condensation The reductive coupling of two esters in a inter- or intramolecular fashion.

3.12.1 Introduction

The α-hydroxy ketone group, or acyloin, is prevalent in natural products and pharmaceuticals, and the development of efficient methods to install this functional group remains an important synthetic challenge. As a result, several distinct methods for the synthesis of α-hydroxy ketones have been developed. This chapter presents a review of approaches toward this structural motif in which the acyloin is derived from the coupling of two carbonyl units to form a new carbon–carbon σ-bond (**Figure 1**). This definition encompasses the traditional acyloin condensation, involving the reductive coupling of two aliphatic esters, and recent catalytic approaches that invoke acyl anion intermediates (umpolung reactivity). Both enzymes and small molecules have been employed as catalysts in acyloin coupling reactions, but the use of enzymes will not be discussed in this chapter since this topic has been recently reviewed.[1]

3.12.2 Traditional Acyloin Coupling Reactions

The traditional acyloin condensation involves the reductive coupling of two esters in either an inter- or intramolecular fashion to generate α-hydroxy ketone products (equation 1). This process is one of the oldest known carbon–carbon bond-forming reactions,[2] but

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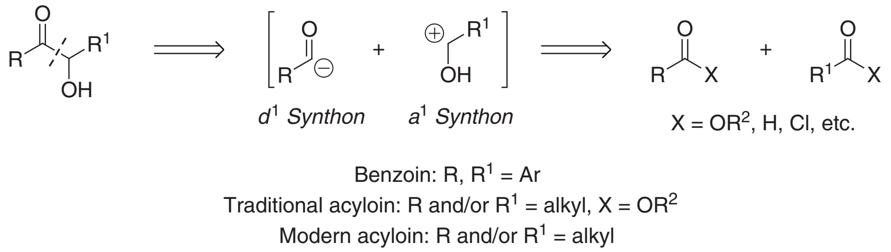
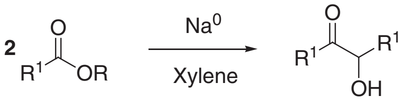


Figure 1 Acyloin coupling reactions.

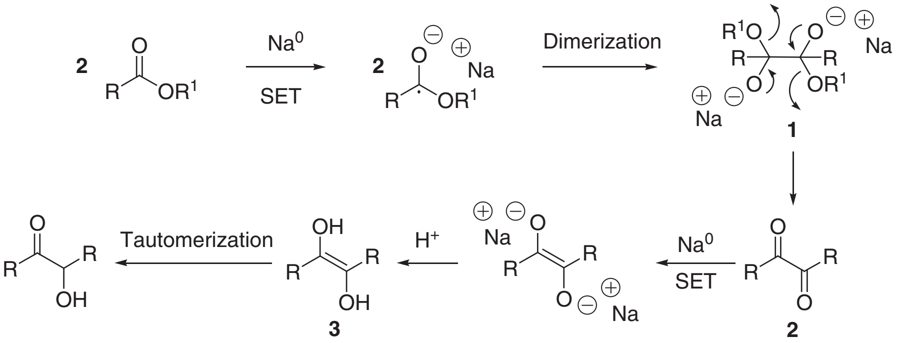
its synthetic utility is curtailed by harsh reaction conditions, limited functional group tolerance, and difficulties with preparing unsymmetrical acyloins. Despite these limitations, the acyloin condensation remains an important reaction in the synthetic chemist's toolbox since the intramolecular variant is a reliable method for carbocycle formation, including medium and large rings (8–34).[2–4]



(1)

3.12.2.1 Mechanism

There are currently two postulated mechanisms for the acyloin condensation, both involving single electron transfer (SET) processes to generate radical anion intermediates. The originally proposed mechanism involves dimerization of the radical anion derived from SET to the ester to give rise to dialkoxy anion **1** (Scheme 1).[2] The expulsion of the alkoxy leaving groups generates diketone **2**. Further reduction through SET from the metal to the diketone produces a dienolate intermediate, which on acidic workup affords enediol **3** that readily tautomerizes to the α-hydroxy ketone product.



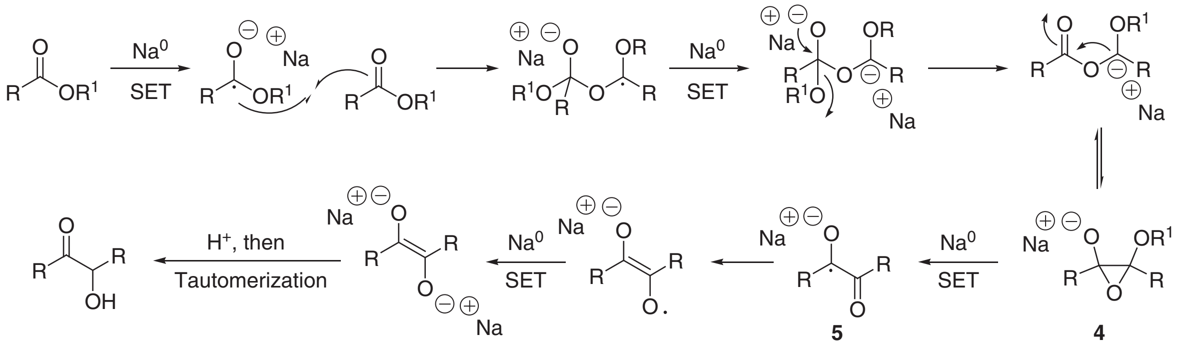
Scheme 1

In 1975, Bloomfield proposed an alternative mechanism due to several examples in the literature that did not conform to the original mechanism.[4,5] The revised mechanism involves the addition of the initially formed radical anion to an equivalent of unreacted ester (Scheme 2). On expulsion of an alkoxide, the intermediate carbanion undergoes nucleophilic addition to the adjacent ketone to generate epoxide **4**. SET to epoxide **4**, and subsequent expulsion of a second alkoxy group delivers semidione **5**. The semidione is reduced to the dienolate, which on acidic workup and tautomerization affords the α-hydroxy ketone product. This mechanism explains some of the anomalies in the literature, but due to the lack of kinetic and mechanistic data regarding this process, the proper mechanism of the acyloin condensation remains a topic of debate.[5]

The acyloin condensation can be performed under either hetero- or homogeneous conditions.[2–4] The exclusion of air and moisture from the reaction is imperative since the acyloin products, as well as the radical anions formed during the reaction, are readily oxidized. The heterogeneous conditions are generally higher yielding and applicable to a broader range of substrates; however, recent developments have broadened the scope of the homogeneous conditions, which may make them a more attractive option for synthetic applications.

3.12.2.2 Heterogeneous Conditions

Under heterogeneous conditions, the esters are exposed to an excess of an alkali metal in refluxing toluene or xylenes. Sodium is the most commonly used alkali metal, although sodium/potassium alloys have also been employed. Since the reaction occurs at

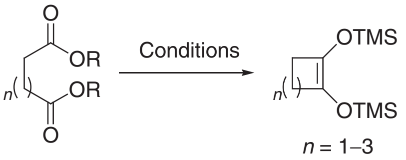


Scheme 2

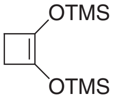
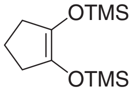
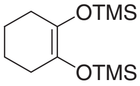
the metal surface, finely dispersed sodium and vigorous stirring of the reaction mixture are necessary. The alkali metal is molten at elevated reaction temperatures, thus the use of toluene (bp 111 °C) or xylene (bp 138 °C) is advantageous, although other solvents have been used in certain cases.[3] In 1964, Schräpler and Rühlmann reported the addition of trimethylsilyl chloride (TMSCl) as an alkoxide scavenger.[6,7] The introduction of TMSCl to the reaction resulted in improved yields due to the suppression of base-mediated byproduct formation, such as β-elimination, Claisen, and Dieckmann condensation products.[8] With TMSCl present in the reaction mixture, the resultant acyloin products can be isolated as the bis-silylenol ethers or converted to α-hydroxy ketones *in situ* on treatment with acid. This modification is the most widely used procedure in the literature for synthetic applications of the acyloin condensation.

In the past twenty years, two other modifications to the standard heterogeneous conditions have been reported. In 1990, Salaün reported the use of ultrasound in conjunction with TMSCl to promote the intramolecular acyloin condensation of 1,4-, 1,5-, and 1,6-diesters.[9] As described above, the typical heterogeneous conditions require the reaction to be run at reflux in a high boiling solvent with finely dispersed sodium. With sonication, the reactions were complete in just a few hours at 0 °C or room temperature. Another significant advantage to the use of ultrasound is that finely dispersed sodium is no longer necessary to facilitate the reaction. Instead the use of small, diced pieces of sodium (~5 mm) delivers the acyloin products in yields comparable with TMSCl at elevated temperature (Table 1).

Table 1 Comparison of conditions for the intramolecular acyloin condensation



Conditions:
A- Na, TMSCl, xylenes, reflux
B- Na, TMSCl, THF, 0–23 °C
C- Na-solid support TMSCl, THF, 60 °C

n	*Product*	***A***[6,7]	***B***[9]	***C***[10] *(support-wt.%)*
1		81	82	70 (Glass 100 mesh – 5%) 62 (PE – 10%) 58 (NaCl – 10%)
2		93	85	–
3		89	83	60 (PE – 16%)

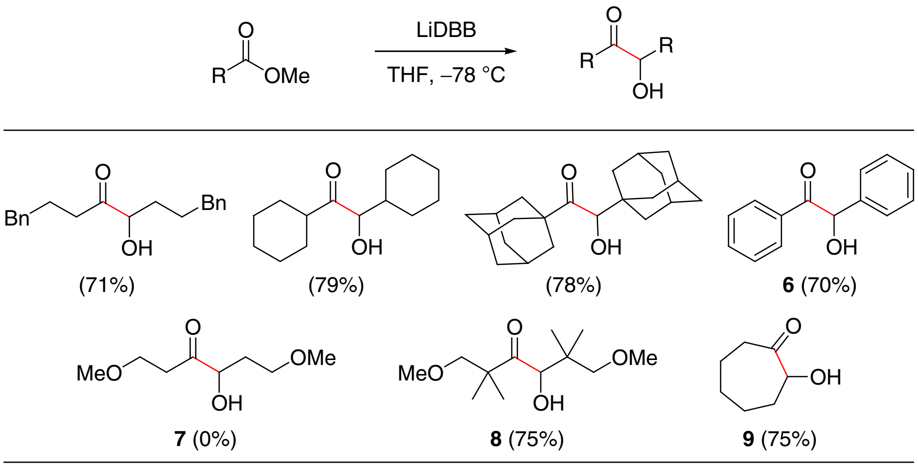
In 1997, Makosza and Grela disclosed another alternative to the standard heterogeneous conditions involving the use of sodium adsorbed on solid support.[10,11] Reagents adsorbed on solid supports (i.e. alumina, titanium dioxide, sodium chloride) have shown improved selectivity and are often easier to handle than the stand-alone reagents.[11] The main drawbacks associated with sodium deposited on solid support are the vigorous and unsafe conditions required for their preparation. In the report by Makosza and Grela, a more practical procedure was developed for the deposition of sodium onto a variety of solid supports from its solution in ammonia. On evaporation of the ammonia, nonpyrophoric powders containing 5–20 wt.% sodium were obtained and subsequently used in the acyloin condensation (**Table 1**).

Data compiled from the lead reference for each of the above-mentioned advances[7,9,10] allows for side-by-side comparison of the intramolecular acyloin condensation to form 4–6 membered rings (**Table 1**). The ultrasound-promoted acyloin condensation afforded the bis-silylenol ethers in $>80\%$ yield, which is comparable to the standard conditions with TMSCl. Alternatively, the use of solid-supported sodium delivered the acyloin products in just a few hours, but in slightly lower yields compared to the other methods (58–70% yield). Based on these results, it is evident that the scope of the ultrasound-promoted acyloin should be further explored due to the advantages of reduced reaction times, lower temperatures, and that finely dispersed sodium is no longer necessary.

3.12.2.3 Homogeneous Conditions

Under homogeneous conditions, the reactions are performed with sodium in liquid ammonia.[2,3] These conditions have not been widely utilized in the literature,[12,13] however, a recent report by Donohoe advances the homogeneous conditions as a more attractive option for synthetic applications.[14] Donohoe and coworkers explored the use of lithium di-*tert*-butylbiphenyl (LiDBB) to promote the acyloin condensation. By exposing a selection of methyl esters to LiDBB in tetrahydrofuran (THF) at –78 °C, symmetrical acyloin products bearing primary, secondary, tertiary, and aromatic substituents were obtained in good yield (**Table 2**). The synthesis of benzoin **6** is noteworthy as there are only a few isolated examples in which benzoin products are prepared through reductive coupling due to the potential for overreduction to the diol. The exposure of benzoin to LiDBB at room temperature is known to generate bibenzyl, highlighting the importance of maintaining a low reaction temperature.[15] The conditions developed by Donohoe are not applicable to the coupling of α- or β-alkoxy esters, presumably due to reductive cleavage or elimination of the alkoxy group, respectively. Substitution at the α-position of the β-alkoxy ester renders these competent substrates, affording acyloin **8** in 75% yield, compared to 0% yield for acyloin **7**. The use of LiDBB to effect intramolecular acyloin condensation was also explored by the synthesis of 2-hydroxycycloheptanone **9** in 75% yield.

Table 2 Substrate scope of LiDBB-promoted acyloin coupling



3.12.2.4 Cross-Acyloin Condensation

Due to the nature of the mechanism, the inherent problem with the synthesis of unsymmetrical acyloins is the inability to control the chemoselectivity and the consequential formation of a statistical mixture of four acyloin products (**Figure 2**). In order to achieve a selective cross-acyloin condensation, preferential formation of the mixed diketone must occur, followed by a selective protonation to generate a single regioisomer of the unsymmetrical α-hydroxy ketone.

Given the challenges associated with this process, only a few isolated examples exist in the literature where this transformation has been explored. For example, in 1993 Hutchinson and coworkers reported a cross-acyloin reaction in which the alkoxides were tethered by an 8- or 14-carbon chain to promote an intramolecular reaction.[16] Through crossover experiments, it was determined that the reaction was actually intermolecular, and as expected, a statistical mixture of products was obtained. In 2011, Donohoe demonstrated that high levels of selectivity could be obtained through use of rigid alkyl tether instead of a long alkyl chain tether.[14] Toward this end, the sequential acylation of *exo*,*exo*-norbonyl-diol **10** gave rise to a variety of differentially substituted

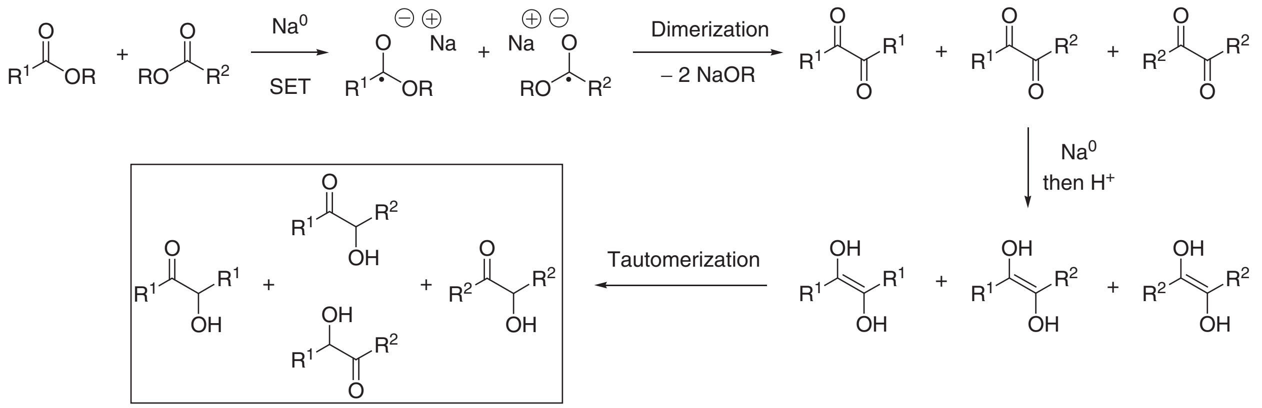
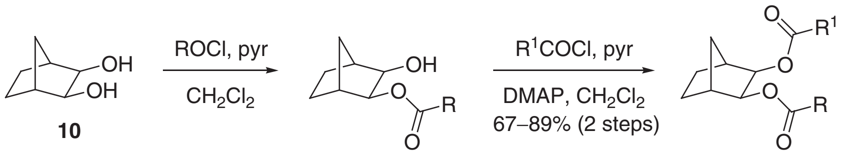


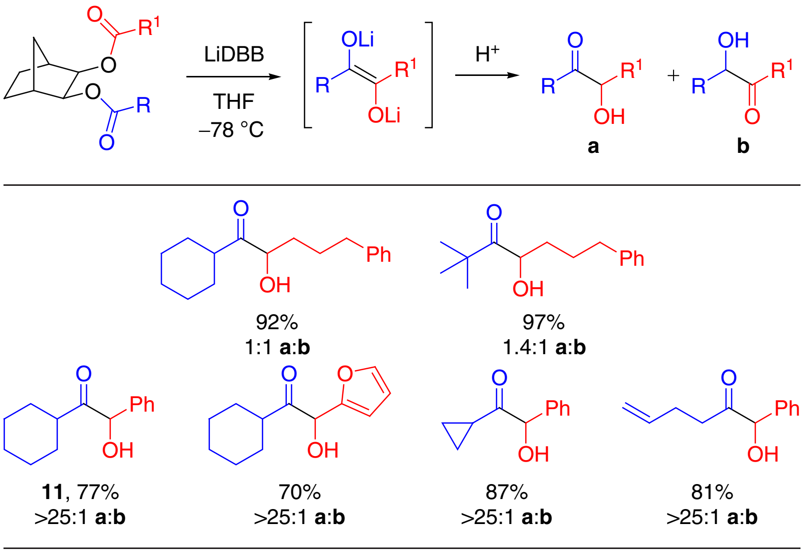
Figure 2 Traditional cross-acyloin condensation.

diesters in 67–89% yield for the two steps (equation 2). The ability to prepare a range of unsymmetrical diesters provided the opportunity to explore intramolecular cross-acyloin reactions. With tethered diesters bearing two different alkyl substituents, the cross-acyloin product was obtained exclusively, unfortunately as a ∼1:1 mixture of regioisomers (Table 3). The absence of the symmetrical acyloin products suggests that the rigid norbornenyl-tether promotes an intramolecular reaction, whereas the poor regioselectivity is indicative of a nonselective protonation on acidic workup. Attempts to improve the regioselectivity by replacing the cyclohexyl with a more sterically encumbering *tert*-butyl group resulted in only a modest increase in regioselectivity. Conversely, with the diester bearing a cyclohexyl and a phenyl group, acyloin **11a** was obtained as the only detectable regioisomer in 77% yield. The generality of the reaction was explored with a variety of diesters, each bearing an alkyl and an aryl substituent. In each case, the cross-acyloin product with the carbonyl adjacent to the alkyl component was obtained in good yield (70–87%) and with excellent regioselectivity (>25:1).

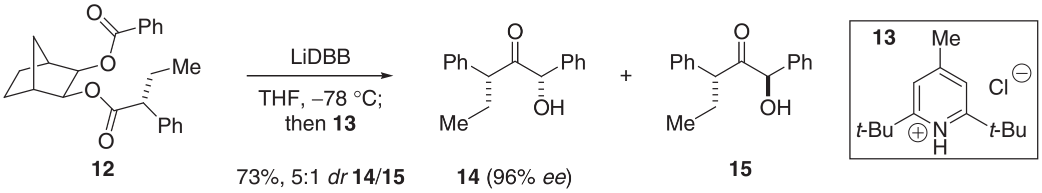


(2)

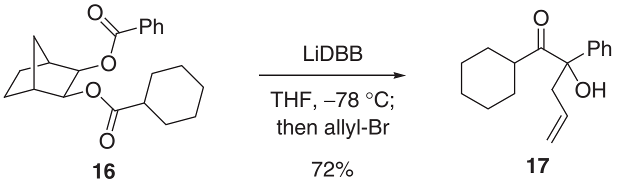
Table 3 Substrate scope of cross-acyloin reaction promoted by LiDBB



This novel cross-acyloin methodology shows potential for application to more complex systems due to the improved functional group tolerance and milder reaction conditions as compared to standard heterogeneous conditions. The ability to control the stereochemical outcome would further enhance the synthetic potential of this reaction. Toward this end, diester **12**, prepared from (*R*)-2-phenylbutanoic acid, was treated with LiDBB to effect the cross-acyloin condensation. On quenching with hydrochloride salt **13**, a bulky proton source, a separable 5:1 mixture of acyloins **14** and **15** was obtained (equation 3). Isolation of the major diastereomer **14** revealed that the reaction proceeded with minimal loss in enantiopurity (96% *ee*). Donohoe also demonstrated that the dienolate intermediate could undergo addition to a carbon-based electrophile. The subjection of diester **16** to the standard reaction conditions followed by addition of allyl bromide afforded tertiary alcohol **17** in 72% yield (equation 4).



(3)



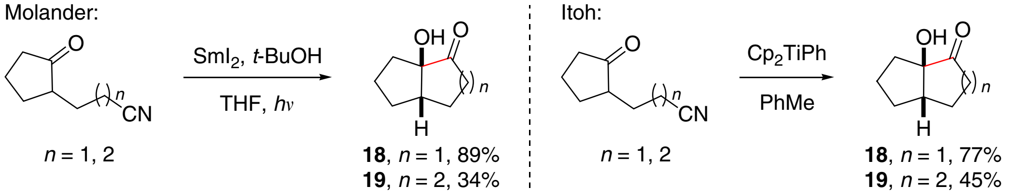
(4)

The LiDBB-promoted cross-acyloin reaction developed by Donohoe is a substantial contribution and represents the first regioselective cross-acyloin condensation under reductive conditions. The control of the selectivity of the protonation or formation of two C–C bonds in one-pot through appropriate choice of electrophile provides the foundation for further developments and applications.

3.12.2.5 Miscellaneous Reductive Methods

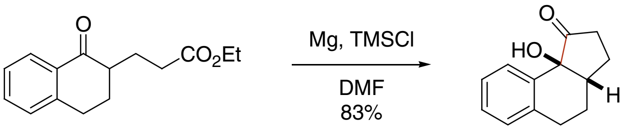
Molander,[17,18] Itoh,[19,20] Nishiguchi,[21,22] and others[23–25] have explored the use of alternative metal sources for the synthesis of tertiary α-hydroxy ketones by the cyclization of ketoesters and ketonitriles. Initial attempts to prepare these products from ketoesters under traditional heterogeneous conditions were met with limited success.[26,27] However, recent examples employing samarium iodide, Cp_2TiPh, and magnesium enable efficient access to these cyclic acyloin products.

Corey originally reported the intramolecular addition of ketyl radicals to tethered nitriles to afford five-membered acyloin products.[28] This transformation was further explored in the late 1990s by Molander[18] and Itoh.[20] Molander's conditions involve treatment of the ketonitrile with samarium iodide and *tert*-butanol under photochemical irradiation to afford the cyclized products.[18] With Molander's conditions, 5- and 6-membered tertiary α-hydroxy ketones were formed in moderate to good yield (equation 5). Molander found that photochemical irradiation was necessary for the reaction to reach full conversion. Kakiuchi later reported that similar yields could be obtained through use of an excess of hexamethylphosphoramide instead of photochemical irradiation.[29]



(5)

Itoh has developed a titanium-mediated method for preparing α-hydroxy ketones by the cyclization of ketonitriles. The exposure of the cyclization precursor to Cp_2TiPh in toluene, followed by acidic hydrolysis affords the α-hydroxy ketones in moderate to good yield (equation 5).[20] In comparison to Molander's methodology, a slightly lower yield was obtained for the synthesis of five-membered acyloin **18**, whereas a marginal improvement in yield was observed with six-membered acyloin **19**. In both Molander and Itoh's work, the yields were significantly higher for acyloins in which a five-membered ring was formed during the course of the reaction, compared to a six-membered ring. Nishiguchi recently developed a related Mg-promoted cyclization,[22] which employs ketoesters instead of ketonitriles as the cyclization precursors. In this study, several tricyclic α-hydroxy cyclopentanones were prepared from the requisite ketoester precursors. For example, in the presence of Mg and TMSCl, acyloin **20** was obtained in 83% yield (equation 6). This substrate was also prepared by Molander[18] and Itoh[19] in 71% and 58% yield, respectively, from the corresponding ketonitrile.



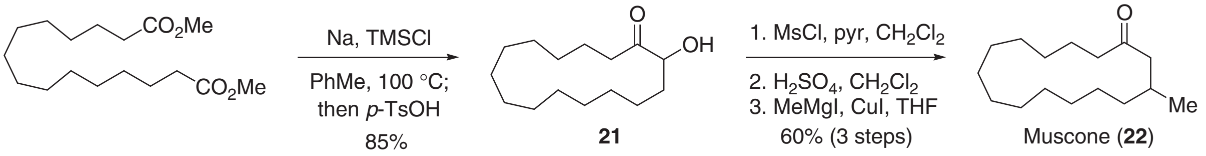
20

(6)

The above approach toward cyclic acyloins are proposed to proceed through a SET mechanism, similar to that described in Scheme 1. A number of other metal-mediated methods have been described, but involve acyl anion intermediates. These approaches present a unique opportunity to prepare cross-acyloins in a predictable and selective manner, and are discussed in Section 3.12.4.

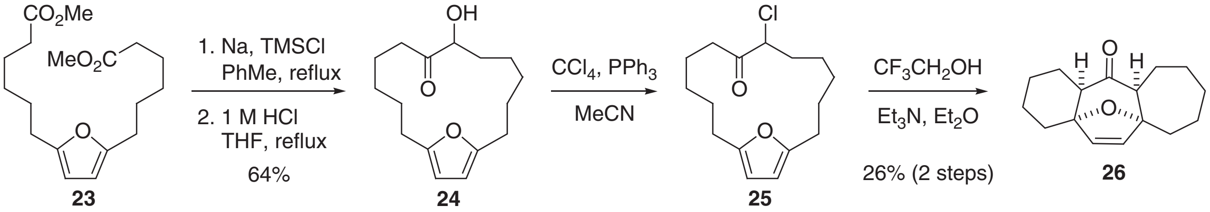
3.12.2.6 Recent Synthetic Applications

There have been a limited number of synthetic applications of the acyloin condensation due to the harsh reaction conditions and limited functional group tolerance. However, the intramolecular acyloin condensation remains a reliable method for the synthesis of large carbocycles.[3] The use of the intramolecular acyloin condensation for the synthesis of macrocyclic ketones, prevalent in the perfume industry, has been explored extensively. A recent application by Takabe toward the synthesis of a precursor to muscone (**22**), the primary contributor to the odor of natural musk, is described as a representative example.[30] In their synthesis, an intramolecular acyloin condensation was employed to prepare 15-membered macrocycle **21** from pentadecanoic acid methyl ester. Under heterogeneous conditions with sodium and TMSCl, α-hydroxy ketone **21** was generated in 85% yield (Scheme 3). A subsequent elimination, conjugate addition sequence afforded racemic muscone (**22**) in 60% yield.



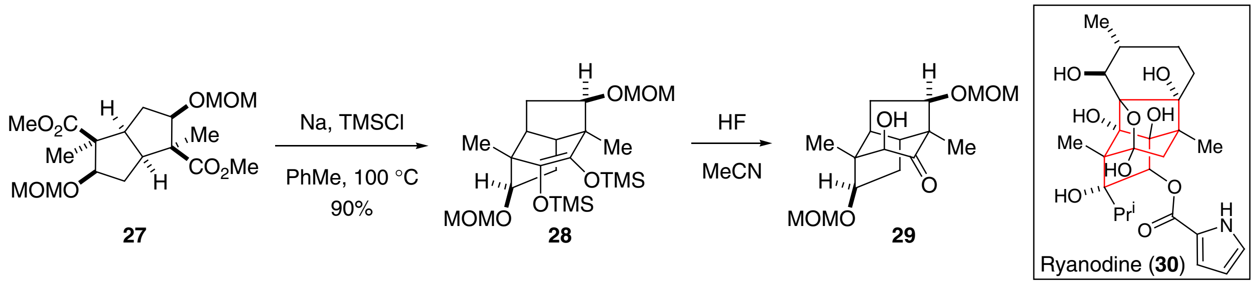
Scheme 3

Another recent synthetic application of the intramolecular acyloin condensation involves the synthesis of tetracyclic systems that map onto the core of the biologically active cortistatins. In this report by Gung and Conyers,[31] macrocylic α-hydroxy ketones were generated by intramolecular acyloin condensation and after subsequent steps, converted to a range of tetracyclic ethers. Toward this end, the exposure of diester **23** to sodium and TMSCl afforded 16-membered α-hydroxy ketone **24** in good yield (Scheme 4). The conversion of α-hydroxy ketone **24** to α-chloroketone **25** followed by acid-catalyzed cyclization afforded tetracyclic ketone **26**. A related 14-membered macrocycle was also prepared by this method, which on cycloaddition gave rise to a tetracycle with five- and six-membered carbocycles flanking the central cycloheptanone ring. Interestingly, alternative approaches toward the cyclization precursor, α-chloroketone **25**, met with failure.



Scheme 4

In addition to these examples that demonstrate the utility of the acyloin condensation for the synthesis of large rings, other reports by the Sieburth[32] and Nakata[33] groups highlight the use of the intramolecular acyloin condensation for the formation of small rings (4–6). In 1994, Sieburth applied the acyloin condensation toward the synthesis of a tricyclo[3.3.2.0]decane ring system, which maps onto the core of the bioactive *Anopterus* alkaloids such as ryanodine (**30**).[32] An acyloin condensation of diester **27** was employed to construct the six-membered ring of the compact tricyclic core. The exposure of diester **27** to heterogeneous conditions in the presence of sodium and TMSCl afforded bis-silylenol ether **28** in 90% yield (Scheme 5). Careful handling of these silyl intermediates is typically necessary to prevent hydrolysis, but bis-silyl enol ether **28** was stable to mild acid and chromatography, presumably due to the crowded steric environment. Instead, bis-silylenol ether **28** was treated with HF to cleave the silyl groups, furnishing α-hydroxy ketone **29**.



Scheme 5

In 2006, Nakata and coworkers disclosed an extension of the intramolecular acyloin condensation to prepare α-hydroxy acetals from γ-alkoxy esters (**Figure 3**).[33] Toward this end, the treatment of γ-alkoxy ester **31** under heterogeneous conditions with TMSCl generated an intermediate tri-silyl ether (**Scheme 6**). Subsequent addition of camphorsulfonic acid (CSA) gave α-hydroxy acetal **32** in 40% yield and 4:1 *dr*. α-Hydroxy acetal **32** was converted to *trans*-fused bicyclic ether **33** by a three-step sequence, involving a silane reduction to cleave the methoxy group. This strategy could potentially be applied toward the synthesis of polycyclic targets, as *trans*-fused tetrahydropyrans are a common structural motif in natural products.[34] Given the harsh conditions of the acyloin condensation, these operations would have to be performed at an early stage or on a substrate with limited functionalization.

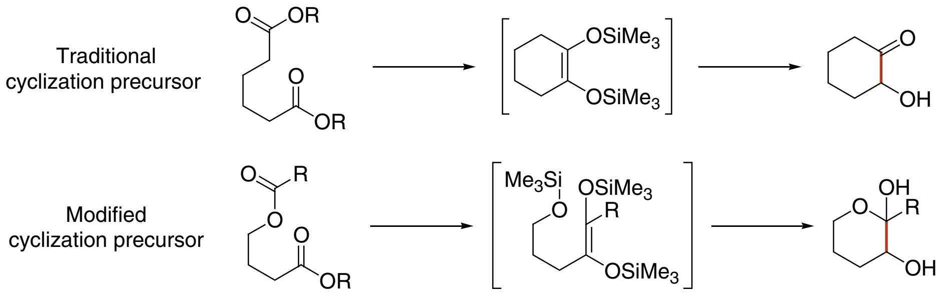
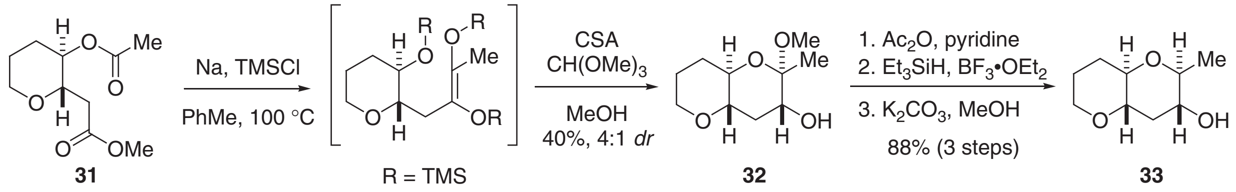


Figure 3 Acyloin condensation with γ-alkoxy esters.



Scheme 6

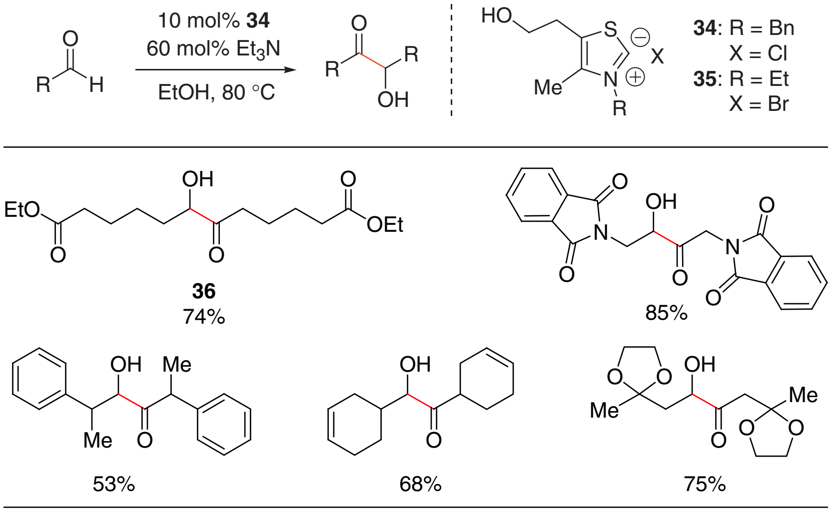
3.12.3 *N*-heterocyclic Carbene (NHC) Catalyzed Acyloin Coupling Reactions

3.12.3.1 Synthesis of Symmetrical Acyloins

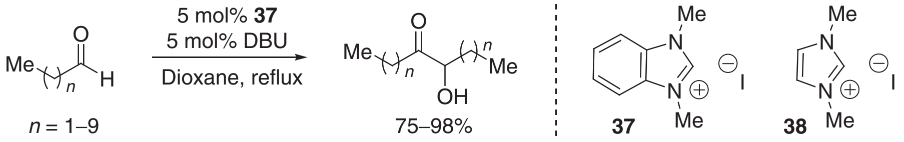
The inherent limitations of the traditional acyloin condensation have driven the development of new, catalytic approaches for accessing acyloins. The NHC-catalyzed benzoin reaction has been extensively studied,[35] whereas reports of the related acyloin condensation are far less prevalent.[36–39] The seminal report by Stetter in 1976 described the coupling of linear aliphatic aldehydes in the presence of thiazolium salt **34** and triethylamine to afford symmetrical acyloin products in good yield (67–83%).[36] In a subsequent report, the substrate scope was extended to include branched and functionalized aliphatic aldehydes (**Table 4**).[37] The broadened substrate scope demonstrates the improved functional group tolerance of the NHC-catalyzed method compared to the traditional reductive conditions. For example, acyloin **36** could not be accessed by traditional acyloin conditions since the ester would be reduced in the presence of sodium metal (see Section 3.12.2). However, under the mild NHC-catalyzed conditions, acyloin **36** is prepared in 74% yield.

In Stetter's work, thiazolium salt **34** proved to be the optimal catalyst under the reaction conditions. Miyashita later demonstrated that benzimidazolium catalyst **37** could also facilitate the acyloin coupling of linear, aliphatic aldehydes.[39] In the

Table 4 Substrate scope of Stetter's NHC-catalyzed acyloin coupling reaction



presence of 5 mol % benzimidazolium catalyst **37** and 5 mol % 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the acyloin adducts were prepared in 75–98% yield (equation 7). The selection of catalyst **37** was critical as the related imidazolium catalyst **38** gave rise to aldol condensation products exclusively. The extension of this methodology to branched aldehydes was not reported, thus these conditions are currently limited to the synthesis of symmetrical, unbranched acyloins. Notably, this system represents the only NHC-catalyzed acyloin condensation that utilizes a benzimidazolium catalyst; all other reports employ thiazolium or triazolium salts.



(7)

3.12.3.2 Cross-acyloin Condensations

In recent years there has been renewed interest in the development of NHC-catalyzed cross-acyloin reactions. This approach toward unsymmetrical acyloins is accompanied by a new set of challenges compared to the traditional reductive conditions (see Section 3.12.2.4). In the NHC-catalyzed cross-acyloin coupling, the catalyst must undergo preferential addition to one aldehyde over the other to produce any appreciable levels of selectivity (Figure 4). Following addition of the NHC to the aldehyde and formation of the Breslow intermediate,[40] the subsequent addition to the other aldehyde must be favored over addition to itself. Additionally, the potential reversibility of the cross-acyloin reaction can complicate the regiochemical outcome through formation of a thermodynamic mixture of products. One approach taken by Stetter,[41,42] Zeitler and Connon,[43,44] Yang,[45] and others[46–48] is the use of aldehydes that are notably different in size or reactivity to favor formation of one cross-acyloin regioisomer over the other three possible products.

In 1977, Stetter and Dämbkes reported the first nonenzyme catalyzed cross-acyloin reaction between a range of aryl and aliphatic aldehydes.[41] The conditions developed by Stetter involve treatment of an aromatic aldehyde with a threefold excess of an aliphatic aldehyde in the presence of thiazolium catalyst **39** and triethylamine (Table 5). The cross-acyloin products were obtained in up to 90% yield, however the regioselectivity varied drastically depending on the substitution of the aldehyde. For example, in the reaction of benzaldehyde or 4-chlorobenzaldehyde with *iso*-butyraldehyde, modest levels of regioselectivity were observed. In contrast, the reaction between acetaldehyde and 2-chlorobenzaldehyde delivered acyloin **41a** exclusively in 52% yield. In the reaction between 2-chlorobenzaldehyde and *iso*-butyraldehyde, Stetter reported the isolation of acyloin **42b** as the sole product in 81% yield. Due to the dramatic difference in selectivity between the two reactions with 2-chlorobenzaldehyde, Zeitler and Connon recently repeated these experiments and obtained contradictory results.[43] Under identical conditions to Stetter, acyloin **42** was obtained in 64% yield as a 97:3 ratio of **42a** to **42b** (shown in parentheses in Table 5). Given their results and the related experiment with acetaldehyde, they suggest that Stetter incorrectly assigned the product from the reaction between 2-chlorobenzaldehyde and *iso*-butyraldehyde as **42b**.

In this report by Stetter there is an isolated example of a cross-acyloin reaction between two aliphatic aldehydes. The reaction between *iso*-butyraldehyde and octanal with catalyst **34** afforded unsymmetrical bis-alkyl substituted acyloin **43** in 56% yield as a 70:30 ratio of **43a** to **43b**. Catalyst **34** was employed since it has been shown to provide better yields with aliphatic aldehydes as

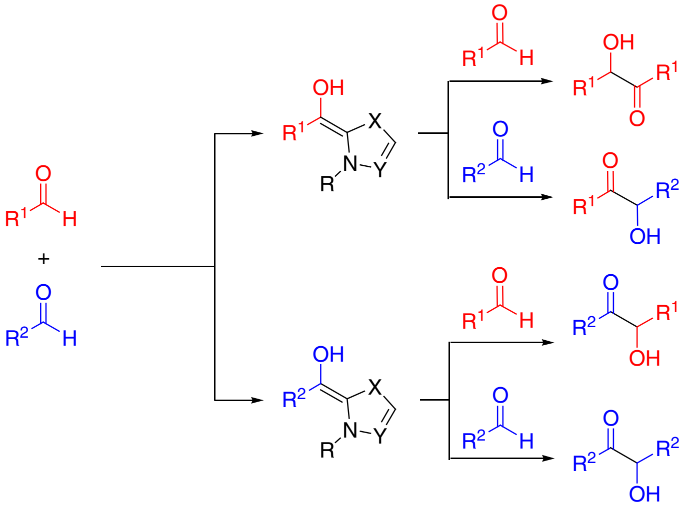
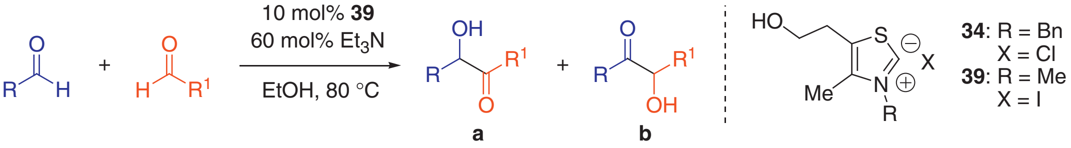
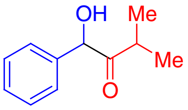
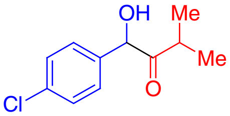
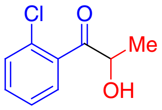
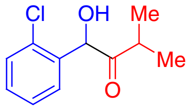
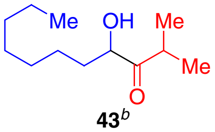


Figure 4 NHC-catalyzed cross-acyloin reaction.

Table 5 Scope of Stetter's NHC-catalyzed cross-acyloin condensation



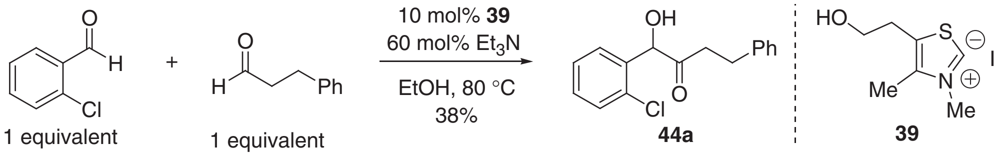
 56% Yield 65:35 **a**:**b**	 **40** 75% Yield 55:45 **a**:**b**	 **41** 52% Yield >99:1 **a**:**b**	 **42**[a] 81% Yield (64%) 1:99 **a**:**b** (97:3 **a**:**b**)	 **43**[b] 56% Yield 70:30 **a**:**b**

[a]Result from Zeitler and Connon are shown in parenthesis (Ref. 43).

[b]Reaction performed with catalyst **34**.

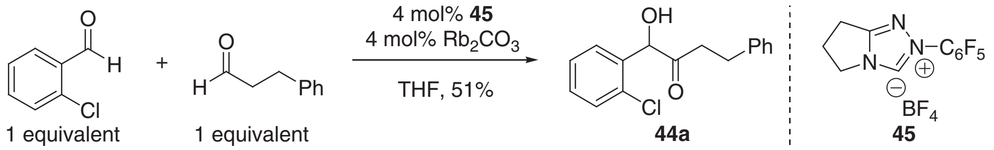
compared to catalysts **35** and **39**. The moderate selectivity for acyloin **43a** is presumably due to the difference in reactivity between the branched and linear aldehyde. Despite renewed interest in NHC-catalyzed cross-acyloin reactions, the synthesis of acyloin **43** remains one of the few examples of a bis-alkyl substituted cross-acyloin coupling.[42,46,49]

Recently, Zeitler and Connon explored the influence of the structure of the aldehyde and catalyst on the cross-acyloin reaction. They were also interested in using equimolar amounts of each aldehyde, as compared to Stetter's conditions, which require a threefold excess of the aliphatic aldehyde. Under otherwise identical conditions to Stetter, equimolar amounts of 2-chlorobenzaldehyde and hydrocinnamaldehyde were employed in a cross-acyloin reaction. From this reaction, the major cross-acyloin product **44a** was obtained in 38% yield (equation 8). The success of *N*-pentafluorophenyl substituted triazolium catalyst **45** in their benzoin condensation studies prompted them to evaluate this catalyst in the cross-acyloin reaction. In the presence of 4 mol% catalyst **45** and 4 mol % Rb_2CO_3, acyloin **44a** was generated in 51% yield (equation 9).



44a **39**

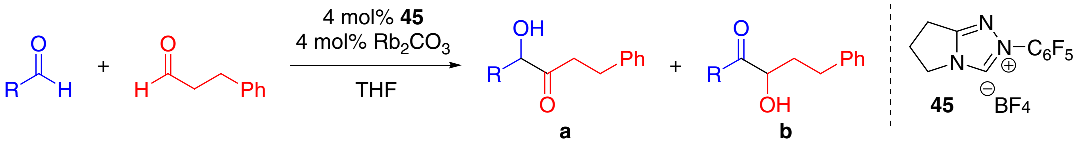
(8)

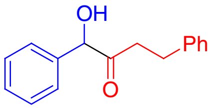


(9)

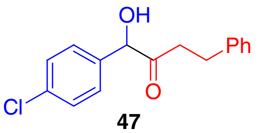
Due to the increased yield and lower catalyst loading, triazolium **45** was established as the optimal catalyst for their cross-acyloin studies. The role of *ortho*-substitution was explored in the reaction between hydrocinnamaldehyde and a variety of benzaldehyde derivatives. In the reaction between hydrocinnamaldehyde and *para*-, *meta*-, or *ortho*-chlorobenzaldehyde with triazolium catalyst **45**, moderate to good selectivity for the cross-acyloin regioisomer with the alcohol adjacent to the aryl group (**a**) was observed (Table 6). However, the ratio of symmetrical to cross-acyloin products varied significantly based on the substitution around the aromatic ring. For example, acyloin **47** was obtained with excellent regioselectivity (96:4), but the yield for the cross-acyloin products (45%) compared to the combined symmetrical acyloin products (49%) was unsatisfactory. Alternatively, with 2-chlorobenzaldehyde the selectivity for **44a** over **44b** was slightly diminished, but formation of the cross-acyloin products was significantly favored over the symmetrical acyloins.

Table 6 Zeitler and Connon's NHC-catalyzed cross-acyloin reaction

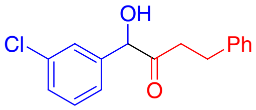




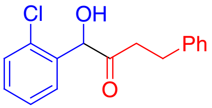
46
59%, 81:19 **a**:**b**
(23% Homoacyloin)



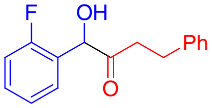
47
45%, 96:4 **a**:**b**
(49% Homoacyloin)



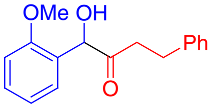
56%, 89:11 **a**:**b**
(39% Homoacyloin)



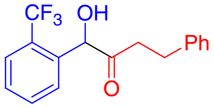
44
60%, 85:15 **a**:**b**
(23% Homoacyloin)



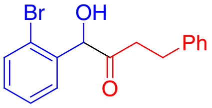
48
48%, 71:29 **a**:**b**
(49% Homoacyloin)



49
80%, 74:26 **a**:**b**
(18% Homoacyloin)



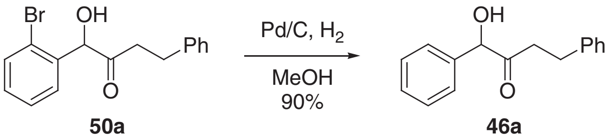
91%, 89:11 **a**:**b**
(7% Homoacyloin)



50
78%, 94:6 **a**:**b**[a]
(7% Homoacyloin)

[a] Reaction performed with 8 mol% 45 and 8 mol% Rb_2CO_3.

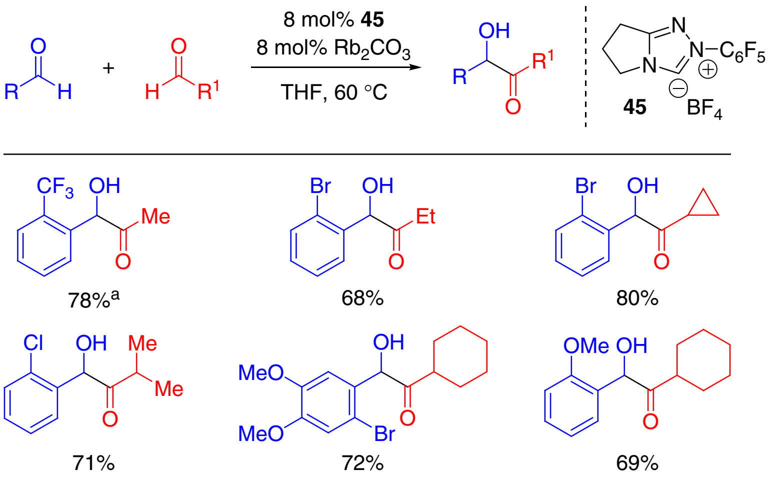
Variation of the substituent at the 2-position revealed that both the size and electronic nature of the *ortho*-substituent are important to obtain the cross-acyloin products in good yield and selectivity. With 2-fluorobenzaldehyde the cross-acyloin products were obtained in only 48% yield and 71:29 ratio of **48a** to **48b**, similar to unsubstituted aryl aldehydes. However, a bromide or trifluoromethyl group at the 2-position afforded the cross-acyloin products in excellent yield and selectivity. With the electron-donating methoxy group at the 2-position, cross-acyloin **49** was obtained in good yield but with diminished selectivity compared with electron-withdrawing substituents at this position. Zeitler and Connon were particularly interested in 2-bromo-substituted acyloin **50** since the bromide could serve as a removable directing group or functional handle for further elaboration. Toward this end, acyloin **50a** was converted to acyloin **46a** by reductive removal of the bromide under hydrogenation conditions in 90% yield (equation 10).



(10)

Since 2-trifluoromethyl- and 2-bromobenzaldehyde provided the best yields and selectivities for the cross-acyloin reaction with hydrocinnamaldehyde, both were employed to evaluate the scope of the aliphatic aldehyde (Table 7, yields are of the major regioisomer). With acetaldehyde and propanal, the cross-acyloin reaction proceeded under the previously optimized conditions, but branched aldehydes required elevated temperatures to reach full conversion. In all cases, the major regioisomer was obtained

Table 7 Substrate scope of the cross-acyloin reaction with 2-substituted benzaldehydes



[a]Reaction performed with 10 equivalents acetaldehyde at 23 °C.

in >65% yield, demonstrating the preference for addition of the NHC catalyst to the aliphatic aldehyde over the *ortho*-substituted benzaldehyde.

In a subsequent report, Zeitler and Connon applied their optimized conditions to the synthesis of unsymmetrical acyloins derived from branched aliphatic aldehydes and 4-substituted benzaldehydes. 4-Chlorobenzaldehyde had previously been shown to deliver the cross-acyloin product with excellent regioselectivity, but in unsatisfactory yield due to competing symmetrical acyloin formation. When the reaction with 4-chlorobenzaldehyde was performed with *iso*-butyraldehyde, the formation of symmetrical acyloin products was suppressed, and the major regioisomer **40a** was obtained in 63% yield (Figure 5). Similar results were obtained using 4-bromobenzaldehyde and *iso*-butyraldehyde or cyclohexanecarbaldehyde. Interestingly, the reaction between 4-chlorobenzaldehyde and *iso*-butyraldehyde afforded similar yields of acyloin **40** in ethanol, chloroform, and toluene compared to the standard conditions in THF.

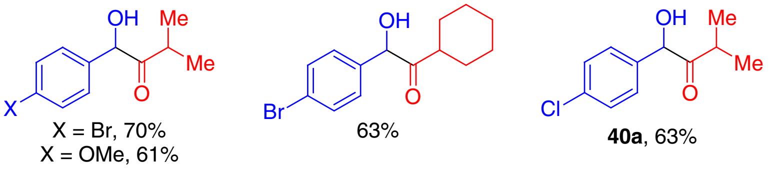


Figure 5 NHC-catalyzed cross-acyloin coupling with 4-substituted benzaldehyde derivatives.

In 2011, Yang reported the cross-acyloin reaction of aromatic aldehydes with acetaldehyde. Yang discovered that the regioselectivity of the cross-acyloin reaction between 4-substituted benzaldehydes and acetaldehyde was dependent on the identity of the catalyst. A catalyst screen revealed that *N*-pentafluorophenyl substituted triazolium catalyst **45** provided the best selectivity for the acyloin derived from initial addition of the NHC to the aliphatic aldehyde (Table 8). Alternatively, thiazolium catalyst **35** resulted in excellent selectivity for the acyloin derived from initial addition of the NHC to the aromatic aldehyde. The conditions developed by Yang employed cesium carbonate as the base in either *m*-xylenes or THF depending on the catalyst. With conditions in hand to obtain each regioisomer selectively through appropriate choice of catalyst, a variety of 4-substituted benzaldehydes were employed in the reaction with acetaldehyde. The regioselectivity with thiazolium catalyst **35** was superior to triazolium catalyst **45**, with the major regioisomer **b** formed in a >90:10 ratio in all cases. The yields for the coupling reactions were excellent with the exception of 4-methoxybenzaldehyde, in which the diminished yields were attributed to low conversion.

Also in 2011, Glorius reported an NHC-catalyzed hydroxymethylation in which formaldehyde was coupled with a diverse set of aromatic aldehydes in a highly selective manner.[47] This transformation was originally reported by Inoue in 1985, but was plagued by low yields and limited substrate scope.[46] A catalyst screen of several common NHCs revealed that the use of thiazolium **52** was essential to obtain good yields of the hydroxymethylated products (Table 9). Under their optimized reaction conditions, α-hydroxyacetophenone (**53**) was generated in 70% yield. In contrast, thiazolium **34**, previously employed by Stetter, resulted in only a 26% yield of acyloin **53** under otherwise identical conditions. The formation of the other cross-acyloin regioisomer with the hydroxy adjacent to the aromatic ring was not observed. A variety of aldehydes were employed in the NHC-catalyzed hydroxymethylation reaction under the optimized conditions with catalyst **52**. The synthesis of α-hydroxy ketone **54** is

Table 8 Scope of Yang's regioselective cross-acyloin reaction with acetaldehyde

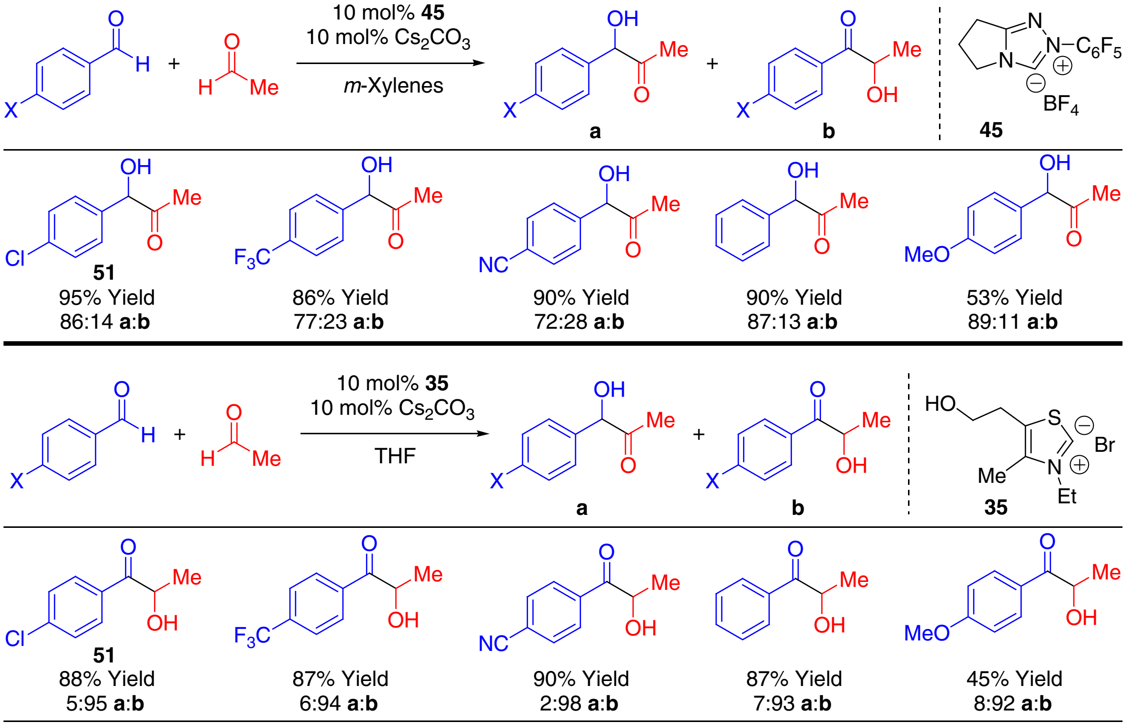
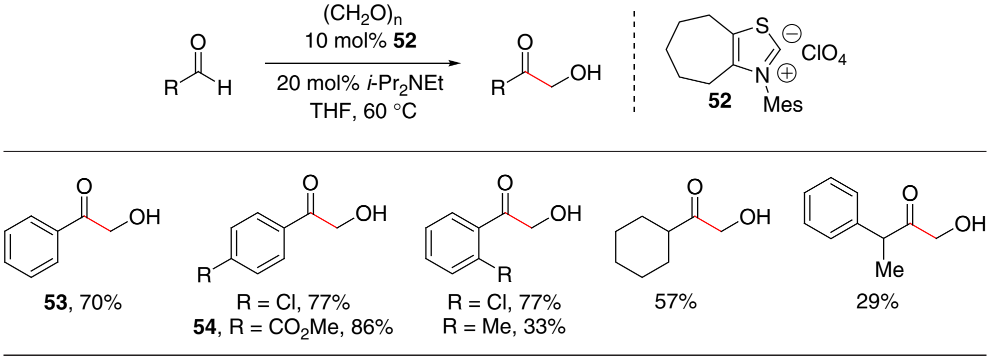


Table 9 Substrate scope of NHC-catalyzed α-hydroxylation

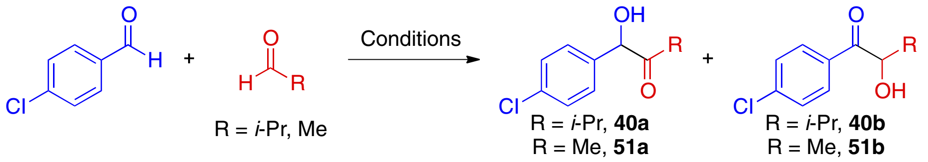


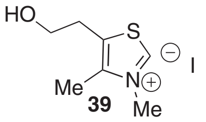
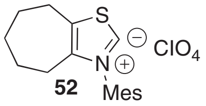
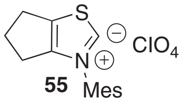
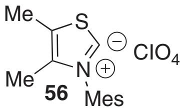
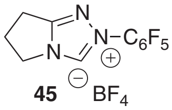
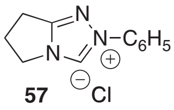
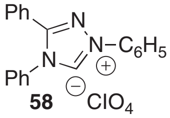
noteworthy as this is another example of an acyloin that would be inaccessible by traditional reductive approaches due to the methyl ester on the aromatic ring, but with NHC catalysis is prepared in 86% yield. Aliphatic aldehydes were also successfully employed in the hydroxymethylation reaction, albeit in slightly lower yield.

Glorius also explored the use of catalyst **52** in the reaction between 4-chlorobenzaldehyde and *iso*-butyraldehyde.[48] The cross-acyloin products were obtained in excellent yield, but with only minimal selectivity in favor of regioisomer **40b** (Table 10, entry 2). In this report, Glorius screened a number of NHC catalysts to promote the cross-acyloin reaction between 4-chlorobenzaldehyde and *iso*-butyraldehyde. Several of these catalysts failed to promote the cross-acyloin reaction or provided unsatisfactory levels of selectivity. Details regarding which NHC catalysts are unsuccessful in this reaction can aid in the design of more general cross-acyloin methods. Toward this end, Table 10 was assembled with selected data from the recent cross-acyloin publications to allow for easy comparison between the catalysts, conditions, and selectivity.

On side-by-side comparison of the thiazolium (entry 1–4) and triazolium catalysts (entry 5–7) it is apparent that the thiazolium salts have a slight preference for regioisomer **b**, derived from initial addition of the NHC to the aromatic aldehyde, whereas triazolium salts are generally more selective for acyloin regioisomer **a**. In the reaction between 4-chlorobenzaldehyde and *iso*-butyraldehyde, none of the thiazolium catalysts afforded the cross-acyloin products with acceptable levels of selectivity and

Table 10 Comparison of NHC catalysts in cross-acyloin reaction with 4-chlorobenzaldehyde



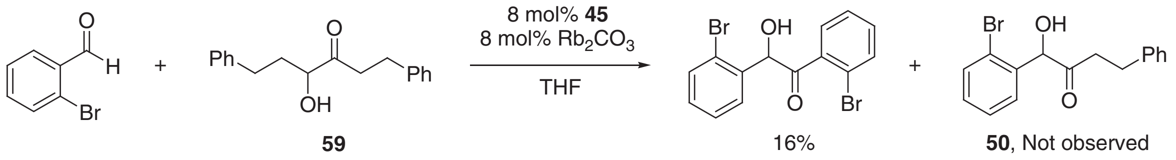
Entry	*NHC*	*R*	*Conditions*	***a:b***	*% Yield*
1	 **39**	*i*-Pr	**A**	45:55	75
2	 **52**	*i*-Pr	**A**	45:55	87
3	 **55**	*i*-Pr	**A**	20:80	20
4	 **56**	*i*-Pr *i*-Pr	**A** **B**	44:56 nd	>99 0
5	 **45**	*i*-Pr *i*-Pr Me	**A** **B** **C**	83:17 84:16 83:17	>99 75 91
6	 **57**	*i*-Pr Me	**B** **C**	48:52 90:10	84 71
7	 **58**	*i*-Pr	**A**	90:10	7

Conditions:

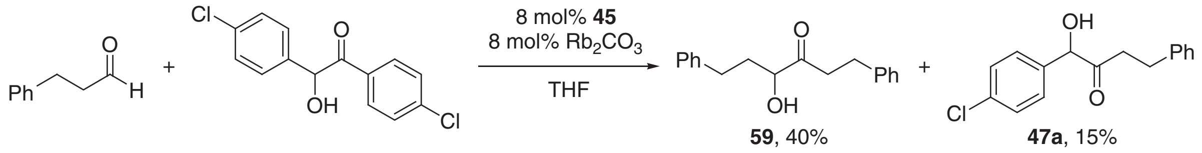
A[47]: 10 mol% NHC, 60 mol% Et_3N
B[42]: 10 mol% NHC, 10 mol% Rb_2CO_3
C[44]: 10 mol% NHC, 10 mol% Cs_2CO_3

yield. Thiazolium **55** resulted in the best selectivity for this reaction, but unsatisfactory yield (20%). The other thiazolium salts all provided acyloin **40** in excellent yield, but with minimal levels of selectivity. Interestingly, with thiazolium **56**, depending on the conditions, the reaction proceeded in nearly quantitative yield (**A**), or afforded none of the desired product (**B**). With respect to the triazolium salts, catalyst **45** appears to be the most general for cross-acyloin reactions in which regioisomer **a** is the desired product. Under the conditions developed by Stetter, Zeitler and Connon, and Yang, similar yields and levels of selectivity were obtained in each case. The same is not true for triazolium **57**, bearing an *N*-phenyl substituent instead of pentafluorophenyl. In the reaction between 4-chlorobenzaldehyde and *iso*-butyraldehyde, the cross-acyloin products were obtained in 84% yield, but as a 1:1 mixture of regioisomers, however, with acetaldehyde excellent levels of selectivity for **51a** to **b** were observed. Triazolium **58** was also employed in the standard reaction and although excellent selectivity for **40a** was observed, the poor yield (7%) makes this catalyst unsuitable for the cross-acyloin reaction.

It is evident that despite these recent advances, a general, chemoselective, NHC-catalyzed cross-acyloin reaction remains elusive. To facilitate the development of more broadly applicable cross-acyloin reactions, a fundamental understanding of the factors governing the regioselectivity is necessary. Zeitler and Connon have initiated crossover studies to probe whether the cross-acyloin reactions are under kinetic or thermodynamic control. In these crossover studies, a symmetrical acyloin product was treated with an aldehyde under their standard conditions. The formation of cross-acyloin products would indicate that the reaction is reversible to a certain extent. The first crossover experiment paired 2-bromobenzaldehyde with acyloin **59**, derived from hydrocinnamaldehyde. Under the standard conditions, the formation of cross-acyloin **50** was not observed, with only a 16% yield of the benzoin product (equation 11). The opposite scenario, in which hydrocinnamaldehyde was exposed to the benzoin derived from 4-chlorobenzaldehyde, produced a significant amount of acyloin **59**. In addition, a 15% yield of cross-acyloin product **47a** was observed, along with a minimal amount of 4-chlorobenzaldehyde (equation 12).

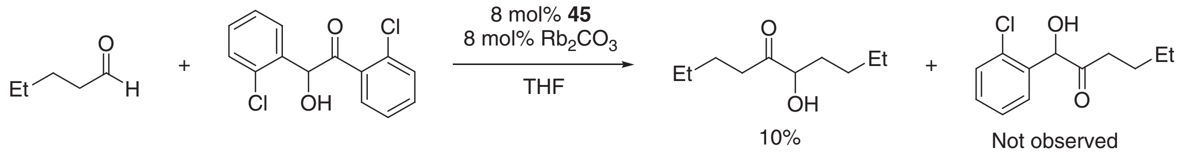


(11)

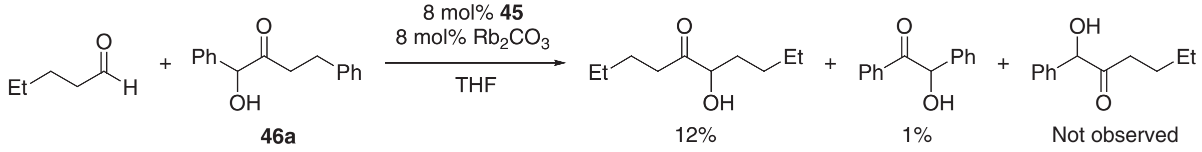


(12)

A series of experiments with pentanal were also carried out. Subjecting pentanal and the benzoin derived from 2-chlorobenzaldehyde to the standard conditions did not afford any of the cross-acyloin products and produced only 10% dimerized pentanal (equation 13). Finally, to determine if the cross-acyloin products could undergo retroacyloin, acyloin **46a** was exposed to pentanal in the presence of catalyst **45**. A minimal amount of benzoin formation was observed in this reaction, along with 12% dimerized pentanal, but none of the cross-acyloin product (equation 14).



(13)

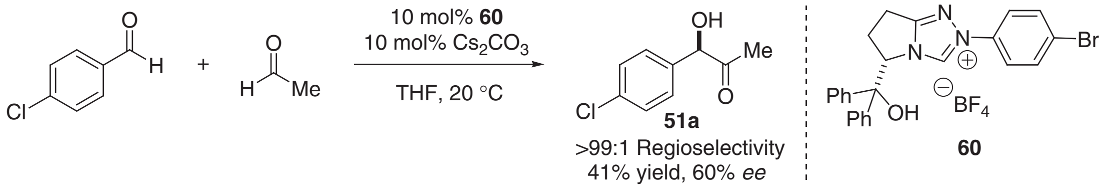


(14)

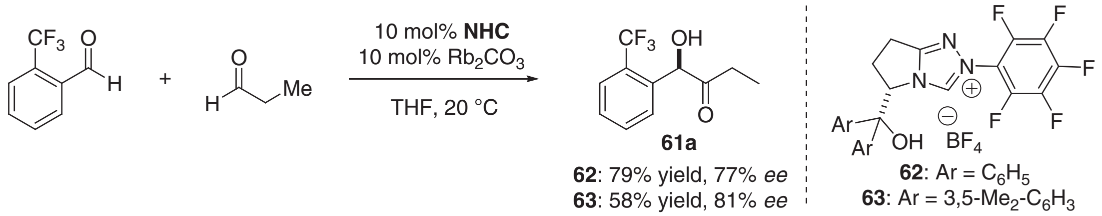
Several conclusions were drawn from these crossover experiments. First, *ortho*-substituted aromatic and aliphatic aldehydes dimerize to the symmetrical acyloins very slowly under the reaction conditions. As a result, *ortho*-substituted benzoins are more stable than the related *para*-substituted benzoins, which undergo more facile retrobenzoin reaction. Aliphatic aldehydes also fail to undergo retroacyloin. The results of this study suggest that the product distribution of alkyl-aryl substituted acyloins derived from unhindered aromatic and aliphatic aldehydes are under thermodynamic control to a certain extent. In contrast, alkyl-aryl substituted acyloins prepared from hindered, *ortho*-substituted aldehydes are under kinetic control, resulting in a highly selective reaction. These efforts by Zeitler and Connon provide insight into the reversibility of these reactions, and serve as a starting point for future mechanistic studies. Future investigations into (1) the preference for addition of the NHC catalyst to the aromatic or aliphatic aldehyde and (2) the reversal in regioselectivity observed with thiazolium and triazolium catalysts will facilitate the development of more general methods for the synthesis of unsymmetrical acyloins.

3.12.3.2.1 Asymmetric intermolecular acyloin couplings

Due to the prevalence of acyloins in natural products and pharmaceuticals, the ability to install this functional group in an asymmetric manner is an important goal. Toward this end, both Yang and Zeitler and Connon performed the cross-acyloin reaction between an aromatic and an aliphatic aldehyde in the presence of different chiral, bifunctional, L-pyroglutamic acid-derived triazolium catalysts. Yang demonstrated that with catalyst **60** in the reaction between 4-chlorobenzaldehyde and acetaldehyde, α-hydroxy ketone **51a** could be obtained with excellent regioselectivity (>99:1) in 41% yield and 60% *ee* (equation 15).[45] Alternatively, in the reaction between 2-trifluoromethylbenzaldehyde and propanal, Zeitler and Connon obtained acyloin **61a** in 79% yield and 77% *ee* with catalyst **62** (equation 16).[44] Modification of the aryl substituent to the more sterically encumbering 3,5-dimethylphenyl group (catalyst **63**) resulted in a minimal increase in enantioselectivity (81%), but a significant decrease in yield (58%). To render these transformations synthetically useful, the levels of enantioselectivity would have to improve. Nonetheless, these isolated examples demonstrate the feasibility of an enantioselective, intermolecular cross-acyloin reaction.



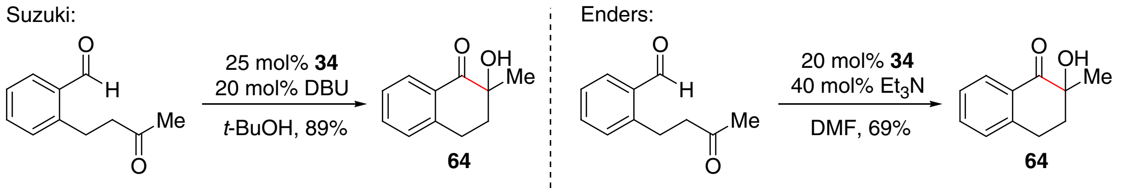
(15)



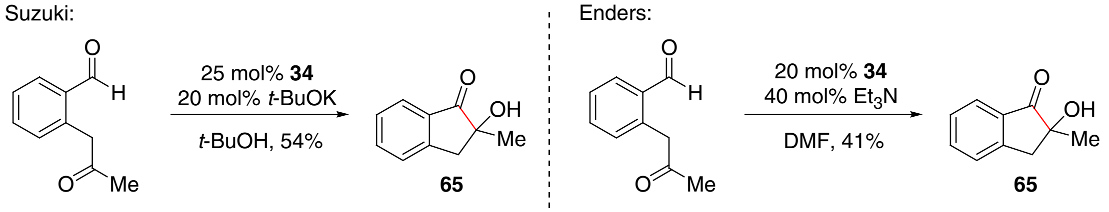
(16)

3.12.3.3 Intramolecular Aldehyde–Ketone Cross-acyloin Couplings

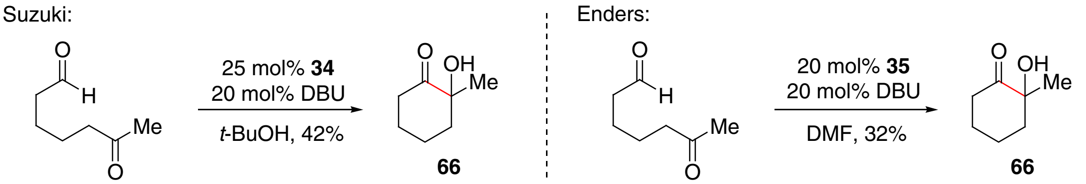
The traditional acyloin condensation is most commonly employed for the intramolecular coupling of tethered diesters (See Section 3.12.3.3.2). In contrast, the intramolecular NHC-catalyzed acyloin has not been explored, presumably due to the potential for inter- over intramolecular aldehyde coupling. However, there have been several reports detailing intramolecular aldehyde–ketone cross-acyloin couplings to generate tertiary α-hydroxy ketones. Suzuki and coworkers first reported the application of this novel NHC-catalyzed transformation for the synthesis of preanthraquinones in 2003 (see Section 3.12.3.2).[50] Shortly thereafter, Suzuki[51] and Enders[52] independently reported more general protocols for the synthesis of five- and six-membered α-hydroxy ketones from tethered ketoaldehyde precursors. In their original reports, Suzuki and Enders employed the same thiazolium catalyst (**34**) and reported the synthesis of several of the same substrates, allowing for easy comparison of their methods. The conditions developed by Suzuki were higher yielding, but required a higher catalyst loading compared to Enders' protocol. For example, the synthesis of substituted α-tetralone **64** was achieved in 69% and 89% yield with Enders and Suzuki's conditions, respectively (equation 17). The main difference between their conditions is the use of a slight excess of catalyst relative to base by Suzuki, whereas Enders employs an excess of base relative to the catalyst. In both Suzuki and Enders' work, the yields were higher for acyloins in which a six-membered ring was formed during the course of the reaction, compared to a five-membered ring (equation 18). The synthesis of α-hydroxy cyclohexanone **66** was also achieved, albeit in significantly lower yield due to competing intermolecular acyloin coupling (equation 19).



(17)

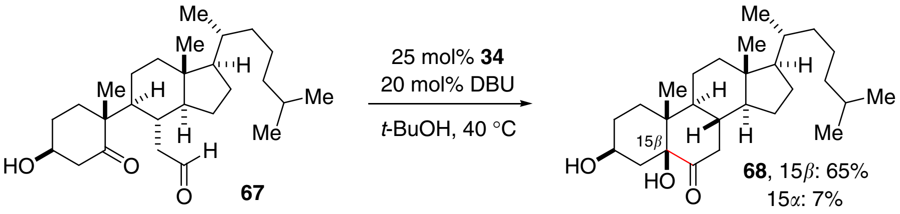


(18)



(19)

The substrate scope for this intramolecular cross-acyloin reaction is limited. Each of these substrates required a significant amount of optimization, as evidenced by the different conditions employed by Enders for the synthesis of acyloin **64** compared to **66**. Suzuki also varied the conditions slightly, for example changing the base to potassium *tert*-butoxide for the synthesis of five-membered acyloin **65**. Attempts to form seven-membered rings or vary the ketone substituent were unsuccessful, instead generating the acyloin products derived from the intermolecular coupling of the two aldehydes. Suzuki and coworkers were able to effect the cyclization of the more complex, cholesterol-derived ketoaldehyde **67** to arrive at α-hydroxy ketone **68** in 65% yield, with only 7% of the minor α-stereoisomer isolated (equation 20).[51]



(20)

3.12.3.3.1 Enantioselective intramolecular aldehyde–ketone coupling reactions

In 2006, Enders and Suzuki independently reported an enantioselective variant of the intramolecular aldehyde–ketone coupling reaction. As in the original 2004 reports, Suzuki and Enders prepared several of the same enantioenriched cyclic acyloins, allowing for a direct comparison between the chiral catalysts employed for the cyclization. Enders reported that both triazolium catalysts **69** and **70**, derived from α-tetralone and L-pyroglutamic acid, respectively, effected the intramolecular aldehyde–ketone coupling with high enantiomeric excess (**Figure 6**).[53] Likewise, Suzuki discovered that the amino-indanol derived triazolium catalyst **71** afforded the enantioenriched cyclic acyloins in good yield and enantioselectivity.[54]

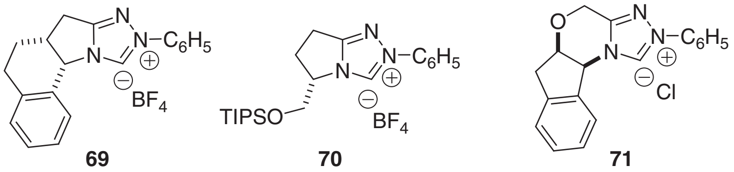
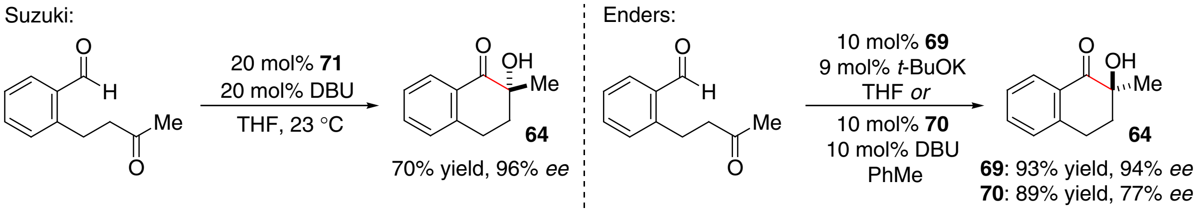
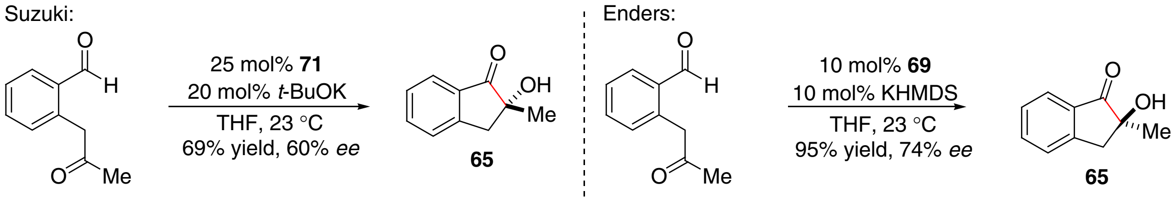


Figure 6 Chiral triazolium catalysts **69**–**71**.

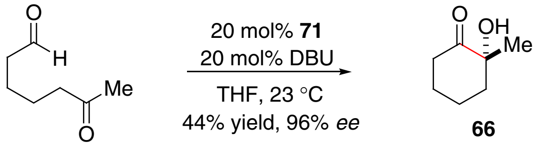
For the synthesis of six-membered acyloin **64**, triazolium **69** was the best catalyst, generating the cyclic acyloin in excellent yield and enantioselectivity (equation 21). The marginal increase in enantioselectivity with catalyst **71** is discounted due to the lower yield and higher catalyst loading. Enders explored several ketoaldehyde precursors with differentially substituted ketones bearing a methyl, ethyl, *n*-butyl, *iso*-butyl, and benzyl group and found that they underwent cyclization to the six-membered acyloins in moderate to good yield and excellent enantioselectivity. In general, higher levels of enantioselectivity were obtained with catalyst **69** compared to catalyst **70**. For the synthesis of five-membered acyloin **65**, Enders only reported results with catalyst **69**. Toward this end, acyloin **65** was obtained in 95% yield and 74% *ee* with catalyst **69** and 69% yield and 60% *ee* with catalyst **71** (equation 22). In both cases, five-membered acyloin **65** was obtained with diminished levels of enantiomeric excess compared to related six-membered acyloin **64**. Suzuki also reported the synthesis of enantioenriched α-hydroxy cyclohexanone **66**. With chiral catalyst **71**, a modest yield of the cyclized product was obtained, but with exquisite levels of enantioselectivity (96%). The low yield was attributed to formation of the symmetrical acyloin product, which was isolated in 28% yield (equation 23).



(21)

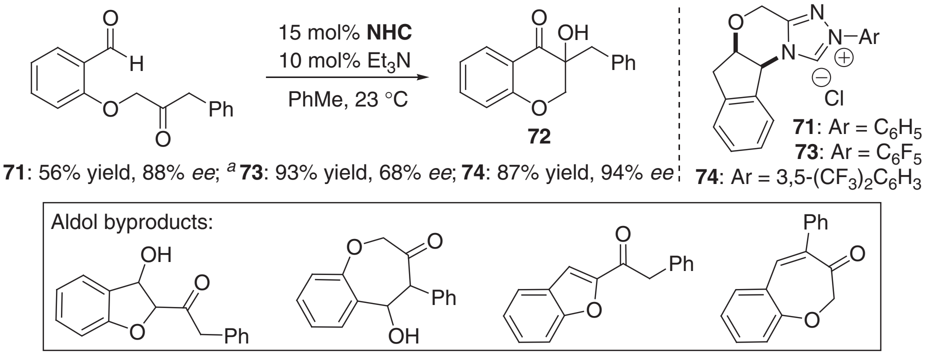


(22)



(23)

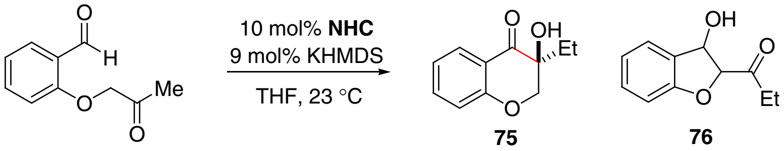
Along with the preparation of tertiary α-hydroxy ketones, Suzuki reported a single example of the synthesis of an enantioenriched 4-chromanone. Chromanones are a common structural motif in bioactive natural products and there remains a need for efficient and selective methods for accessing these privileged structures. Subsequent reports by Suzuki[55] and Enders[56] explored the challenges associated with the synthesis of 4-chromanones by this NHC-catalyzed methodology. In the study by Suzuki, initial efforts toward the synthesis of chromanone **72** with catalyst **71** were met with some success (equation 24).[54] Due to a competing aldol pathway, reexamination of the reaction conditions was necessary. Suzuki found that the introduction of electron-withdrawing groups to the *N*-aryl substituent of the catalyst increased the acidity of the NHC and suppressed the undesired aldol pathway, but led to diminished levels of enantioselectivity in certain cases.[55] For example, *N*-pentafluorophenyl substituted triazolium **73** afforded chromanone **72** in excellent yield (93%), but only 68% *ee*. Fine-tuning of the *N*-aryl substituent led to the identification of 3,5-trifluoromethylphenyl substituted triazolium **74** as the optimal catalyst, furnishing 4-chromanone **72** in 87% yield and 94% *ee*.



(24)

[a]Reaction performed in THF at 23 °C.

Enders also developed an approach toward enantioenriched 4-chromanones.[56] Of the triazolium catalysts that were successful in the synthesis of tertiary α-hydroxy ketones, only catalyst **69** afforded desired chromanone product **75**, along with variable amounts of aldol product **76**. On optimization, they discovered a slight excess of NHC catalyst relative to base was necessary to suppress the aldol pathway. Under their optimized conditions, acyloin **75** was obtained in 90% yield and 91% *ee* with catalyst **69** (equation 25). With optimized conditions in hand, variation of the ketone and substitution around the aromatic ring was explored. Ketone substituents with increased steric demand, such as *iso*-butyl and cyclohexyl, afforded the requisite chromanones with exquisite levels of selectivity and in good yield. Substitution around the aromatic ring was not as well tolerated. In most cases, significantly lower yields and a slight decrease in enantioselectivity were observed.

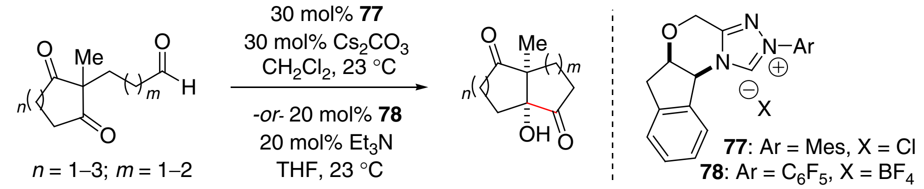


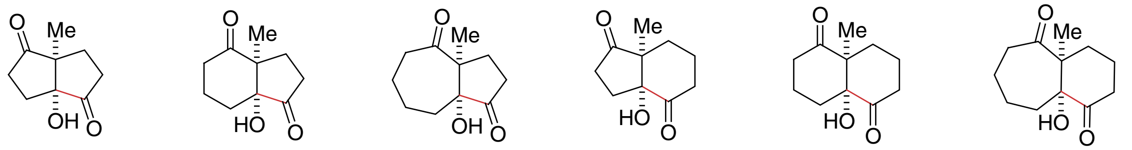
with **69**: 90% yield **75**, 91% *ee*
with **70**: 90% yield **76**

(25)

Sakai and coworkers have also developed an NHC-catalyzed aldehyde–ketone cyclization to generate functionalized bicyclic carbocycles in an asymmetric fashion.[57] Starting with a five-, six-, or seven-membered 1,3-diketone, the formation of five- and six-membered tertiary α-hydroxy ketones was achieved. In addition to providing efficient access to the synthetically useful acyloin moiety, this process introduces two contiguous stereocenters, one of which is quaternary. The yield and enantioselectivity varied drastically depending on both the 1,3-diketone precursor and the size of the ring formed during the reaction. In the presence of amino-indanol derived catalyst **77** and cesium carbonate, the five- and six-membered acyloins were prepared in moderate to good yield but the levels of enantioselectivity were erratic, especially for 5-membered acyloins **79**–**81** (Table 11). For example, acyloin **79** was obtained in only 32% yield and 26% *ee*, whereas acyloin **81** was generated in 78% yield, but with no enantioinduction. The use of catalyst **78** with triethylamine increased the yield of acyloin **79** to 90%, but decreased the enantioselectivity. A more drastic impact was observed with acyloin **81**, which could be produced in 83% yield and 69% *ee* under the modified conditions. The related six-membered systems provided more consistent results, with acyloins **82**–**84** formed in greater than 85% *ee* under the standard conditions with catalyst **77**. The bicyclic products obtained from these reactions have the potential for synthetic applications, especially the 6,6-system which resembles a precursor to the Wieland–Miescher ketone.

Table 11 Substrate scope of Sakai's asymmetric aldehyde–ketone cyclization





	79	**80**	**81**	**82**[a]	**83**[a]	**84**[a]
77:	32% yield, 26% *ee*	50% yield, 78% *ee*	78% yield, 0% *ee*	43% yield, 95% *ee*	67% yield, >99% *ee*	47% yield, 86% *ee*
78:	90% yield, 13% *ee*		83% yield, 69% *ee*			

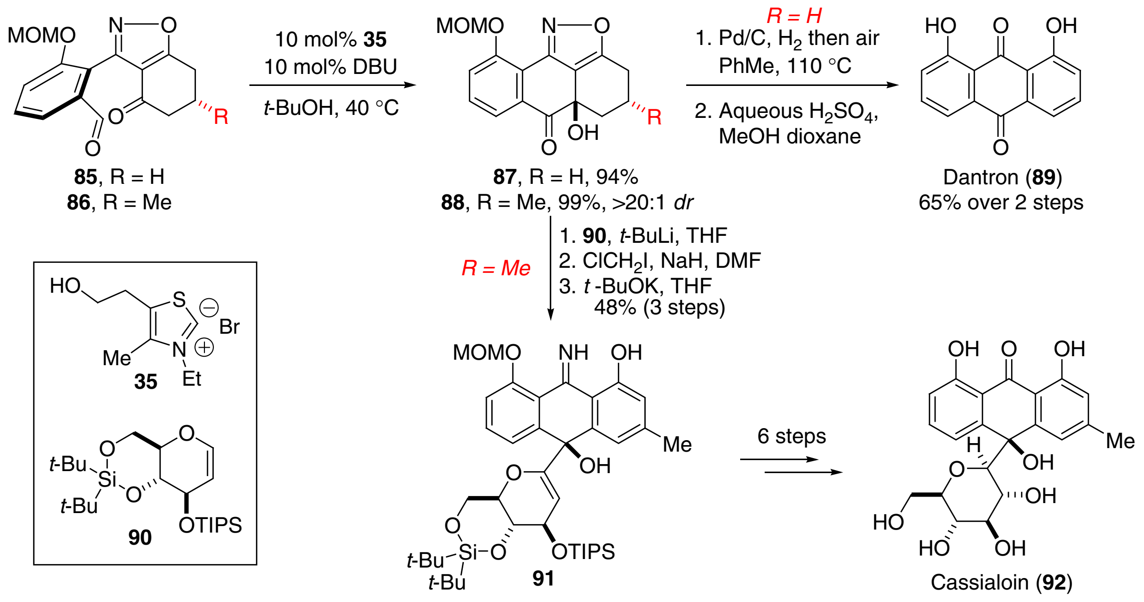
[a]Reaction performed at reflux.

3.12.3.3.2 Synthetic applications

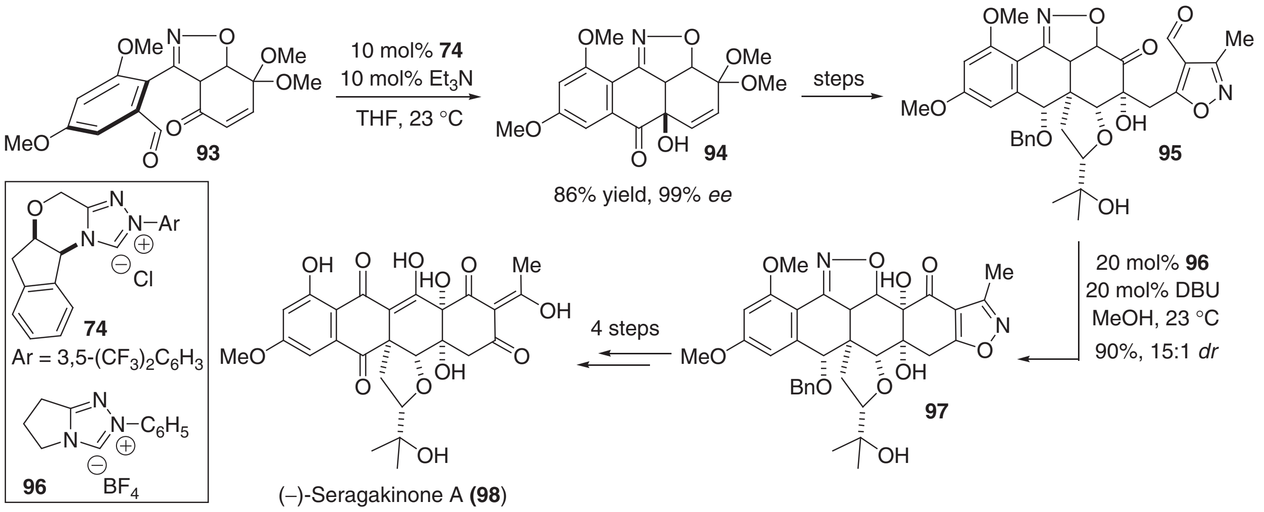
The Suzuki and Nicolaou groups have applied the intramolecular NHC-catalyzed aldehyde–ketone cyclization as a key step in several recent total syntheses. Suzuki first reported this transformation for the synthesis of preanthraquinones from functionalized isoxazoles.[50] In the same report, this cyclization reaction was applied toward the synthesis of dantron (**89**), which is used to counteract certain side effects of opioids in terminally ill patients.[58] The synthesis begins with the treatment of ketoaldehyde **85** with thiazolium catalyst **35** and DBU to afford cyclic acyloin **87** in 94% yield (Scheme 7). Palladium-catalyzed cleavage of the N–O bond and subsequent oxidation generated an intermediate imine, which upon hydrolysis furnished dantron (**105**) in 65% yield. This approach was also applied toward the first total synthesis of the anthrone C-glycoside natural product cassialoin (**92**).[59] In their synthesis of cassialoin, a β-substituted cyclohexanone was employed to control the stereoselectivity of the resultant tertiary alcohol. Toward this end, the exposure of β-substituted ketoaldehyde **86** to catalyst **35** gave rise to acyloin **88** in excellent yield and as a single diastereomer. Subsequent 1,2-addition of glycal **90** and cleavage of the isoxazole furnished imino-anthraquinone **91**, which was converted to the natural product in six additional steps.

An alternative strategy to control the stereoselectivity of the resultant tertiary α-hydroxy ketone is the use of a chiral catalyst. Suzuki applied the enantioselective variant of the intramolecular aldehyde–ketone coupling reaction toward the total synthesis of (−)-seragakinone A and (+)-sappanone B. The total synthesis of (−)-seragakinone A (**98**) employs an isoxazole-containing ketoaldehyde and features two NHC-catalyzed cyclizations to construct the pentacyclic core of the natural product (Scheme 8). The first cyclization employs chiral triazolium catalyst **74** in the presence of triethylamine to effect formation of acyloin **94** in 86% yield and 99% *ee*. α-Hydroxy ketone **94** is converted to ketoaldehyde **95** over several steps, setting up a second aldehyde–ketone cyclization to assemble the remaining cyclohexanone ring. Toward this end, ketoaldehyde **95** was treated with triazolium salt **96** and DBU to generate acyloin **97** in 90% yield and excellent diastereoselectivity. From diol **97**, four additional steps were required to complete the first total synthesis of (−)-seragakinone A (**98**).

Suzuki employed the same catalyst toward the enantioselective total synthesis of the 4-chromanone containing natural product (+)-sappanone B (**101**). On synthesis of ketoaldehyde **99** in five steps from commercially available starting materials, exposure to catalyst **74** and triethylamine afforded 4-chromanone **100** in 92% yield and 95% *ee* (Scheme 9). The subsequent deprotection of the methoxy groups in two steps afforded (+)-sappanone B (**101**) in eight steps and 60% overall yield.



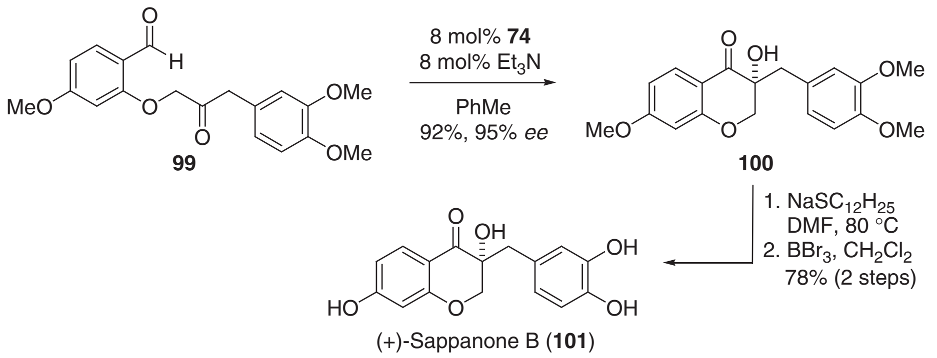
Scheme 7



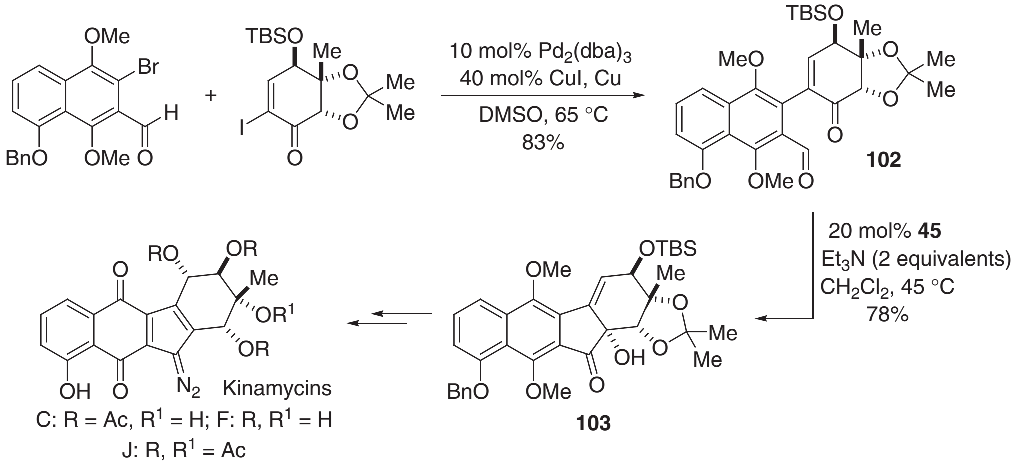
Scheme 8

Nicolaou has also employed the aldehyde–ketone cyclization strategy to assemble polycyclic natural products.[60,61] In 2007, they reported the total synthesis of the diazofluorenone-containing kinamycin natural products, which possess potent antibiotic and antitumor activity.[60] Their approach involved construction of the fluorenone core by an NHC-catalyzed cyclization of ketoaldehyde **102**, prepared by a modified Ullmann coupling (Scheme 10). Ketoaldehyde **102** was exposed to *N*-pentafluorophenyl substituted triazolium **45** and triethylamine to generate α-hydroxy cyclopentanone **103** in 78% yield as a single diastereomer. The high yield of the NHC-catalyzed aldehyde–ketone cyclization is noteworthy given the complexity of the cyclization precursor and the previously reported poor yields for the formation of five-membered cyclic acyloins.[53,54] The synthesis of kinamycin C was accomplished in 10 additional steps from acyloin **103**. Kinamycin C was readily converted to kinamycins F and J by base-mediated hydrolysis or acetate formation, respectively. The Nicolaou group also applied the NHC-catalyzed cyclization toward the synthesis of the monomeric unit of the structurally related lomaiviticins, which are dimeric diazofluorenone-containing natural products.[61]

In addition to these syntheses by the Suzuki and Nicolaou groups, the Miller group has also reported the use of the NHC-catalyzed intramolecular coupling to achieve the formal synthesis of *trans*-resorcylide (**109**).[62] In contrast to the previously discussed aldehyde–ketone coupling reactions, their synthesis involves a dialdehyde cyclization precursor. The synthesis of the

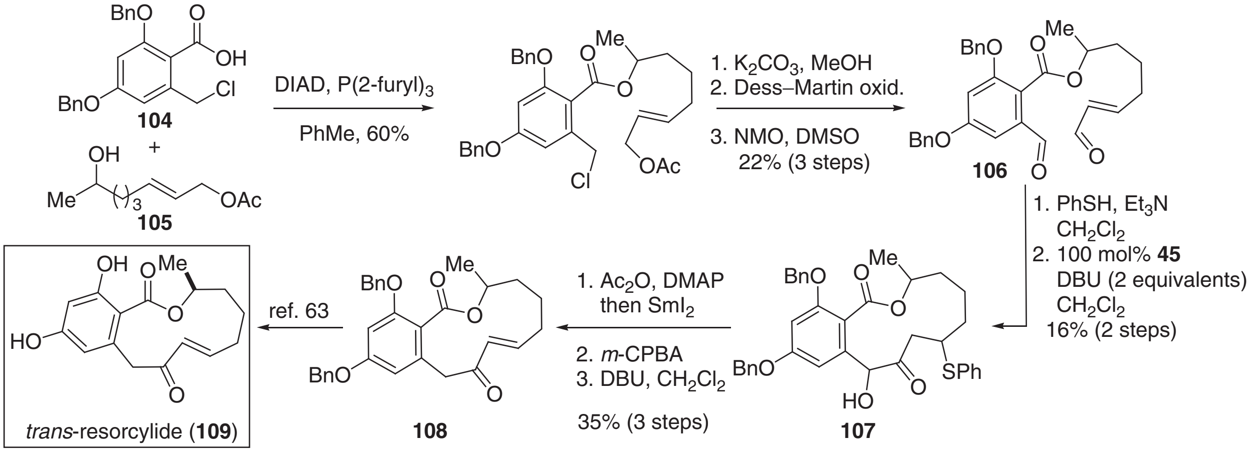


Scheme 9



Scheme 10

requisite dialdehyde was achieved in four steps from substituted benzoic acid **104** and secondary alcohol **105** (Scheme 11). α,β-Unsaturated aldehyde **106** was converted to an intermediate β-thioether, which upon subsequent exposure to a stoichiometric amount of triazolium salt **45** and DBU afforded α-hydroxy ketone **107** in 21% yield. Despite the poor yield for the cyclization, this is a noteworthy contribution to the field in that it represents the first intramolecular cross-acyloin coupling between two aldehydes. Completion of the formal synthesis of *trans*-resorcylide (**109**) was achieved by cleavage of the β-hydroxy group and a two-step elimination of the thioether to furnish enone **108**.[63] The NHC-catalyzed cyclization was applied toward the macrocyclization of several differentially substituted dialdehydes, in which up to 47% yield of the acyloin products was obtained.[62]

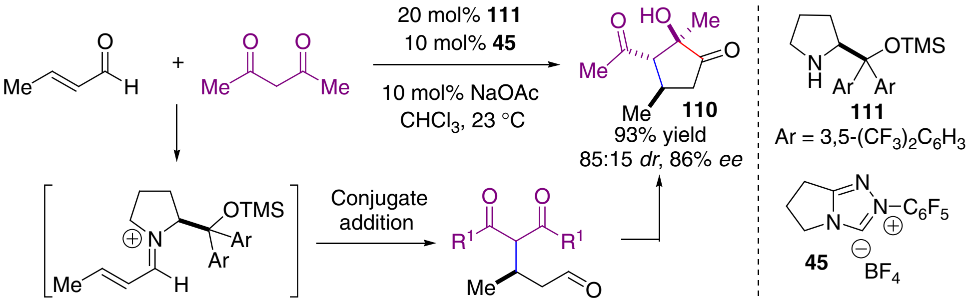


Scheme 11

3.12.3.4 Asymmetric Dual Secondary Amine/NHC Catalysis

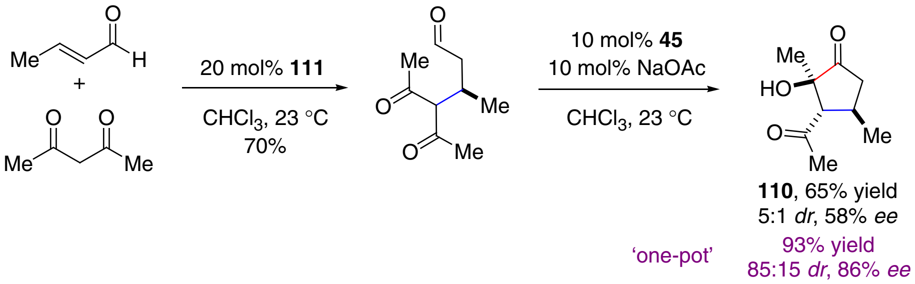
The use of NHCs in cascade reactions and dual catalysis has only recently been explored.[64] Cascade and dual catalytic processes offer the advantage of forming several carbon–carbon bonds in a single operation to rapidly generate molecular complexity from simple starting materials. In 2009, Rovis reported a dual catalytic system with an NHC and proline-derived secondary amine catalyst to form highly functionalized cyclopentanones.[65] Since this report, Enders,[66] Rovis,[67] and Melchiorre[68] have reported further advances involving the combination of NHCs and proline-based organocatalysts.

The original report by Rovis employs secondary amine **111** with triazolium **45** to facilitate an iminium-catalyzed conjugate addition/benzoin cascade, affording acyloin products in high yield and enantioselectivity (equation 26).[65] This cascade process involves the formation of two carbon–carbon bonds and three contiguous stereocenters. The initial bond-forming event is catalyzed by amine **111** and serves as the stereodefining step. As a result, an achiral NHC catalyst could be used to effect the benzoin reaction and deliver the α-hydroxy ketone products. Under the optimized conditions, the reaction between crotonaldehyde and acetylacetone afforded cyclopentanone **110** in 93% yield and 86% *ee*, with only two of the four possible diastereomers formed (85:15 *dr*).



(26)

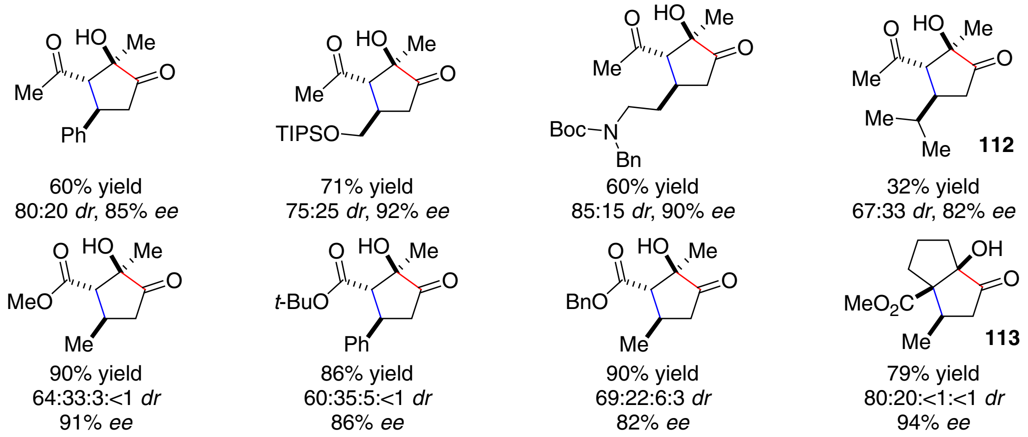
Interestingly, when the reaction with crotonaldehyde and acetylacetone was performed as a two-step sequence, acyloin **110** was obtained in only 65% yield and 58% *ee* compared to 93% yield and 86% *ee* under the dual catalytic conditions (Scheme 12). They discovered that the intermediate aldehyde undergoes a retro-Michael in the presence of secondary amine **111**, resulting in decreased enantioselectivity. In the presence of triazolium **45**, the aldehyde is rapidly funneled toward the acyloin product, minimizing the loss of enantioselectivity.



Scheme 12

A number of β-alkyl and aryl substituted enals were employed in the cascade reaction with acetylacetone. In each case, the formation of only two diastereomers was observed with the acyloin products formed in >80% *ee* (Figure 7). A number of functional groups on the aldehyde were tolerated, including protected alcohols and amines. With the more sterically encumbering *iso*-propyl group at the β-position, cyclopentanone **112** was obtained in diminished yield and diastereoselectivity, but with good levels of enantioselectivity. The use of unsymmetrical 1,3-dicarbonyls in the cascade reaction was also explored. The acyloins derived from methyl, *tert*-butyl, and benzyl acetoacetate were obtained in high enantiomeric excess but moderate diastereoselectivity, and as a mixture of all four possible diastereomers. Cyclic 1,3-dicarbonyls also performed well in the reaction, as in the synthesis of bicyclic acyloin **113** in 79% yield, 80:20 *dr*, and 94% *ee*.

In 2011, Enders[66] reported a related conjugate addition/benzoin cascade involving the addition of β-oxosulfones to α,β-unsaturated aldehydes. Since the reaction proceeds through an iminium intermediate, the resultant cyclopentanone products possess a similar substitution pattern to those prepared by Rovis. In the presence of 20 mol% amine **111** and 10 mol% NHC **45**, the reaction between (phenylsulfonyl)acetone and crotonaldehyde proceeded in 86% yield and 86% *ee*, but modest diastereoselectivity (66:34) (equation 27). As in the previous cascade reaction, only two of the four possible diastereomers were observed. In an effort to improve the diastereoselectivity, other amine catalysts were explored. They determined that secondary amine **115** had a marginal effect on the diastereoselectivity, but significantly diminished the yield and enantioselectivity.



60% yield
80:20 *dr*, 85% *ee*

71% yield
75:25 *dr*, 92% *ee*

60% yield
85:15 *dr*, 90% *ee*

32% yield
67:33 *dr*, 82% *ee*

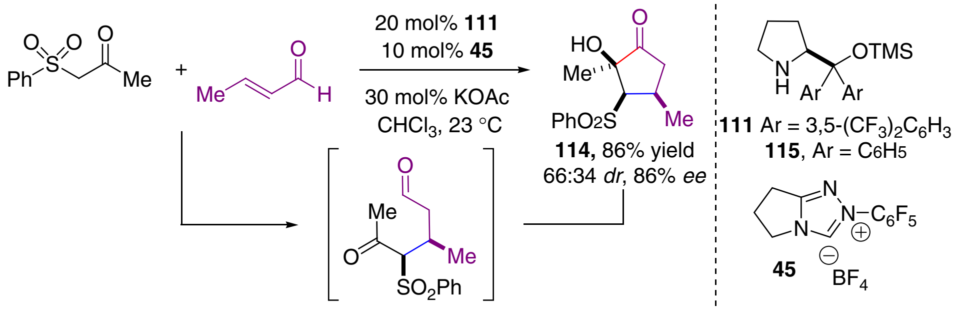
90% yield
64:33:3:<1 *dr*
91% *ee*

86% yield
60:35:5:<1 *dr*
86% *ee*

90% yield
69:22:6:3 *dr*
82% *ee*

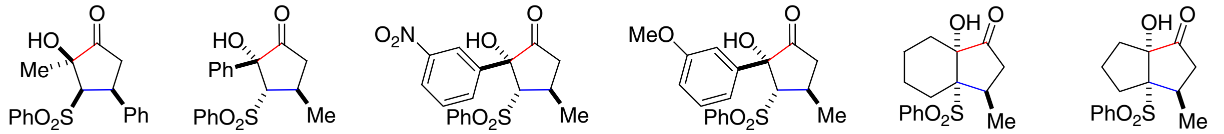
79% yield
80:20:<1:<1 *dr*
94% *ee*

Figure 7 Substrate scope of the iminium-catalyzed conjugate addition/benzoin cascade.



(27)

Variation of the sulfone and *α*,*β*-unsaturated aldehyde was explored to evaluate the scope of the reaction. Interestingly, with cinnamaldehyde instead of crotonaldehyde, a single diastereomer of acyloin **116** was obtained, but in unsatisfactory yield (Figure 8). Alternatively, the use of an aryl-substituted sulfone with crotonaldehyde afforded cyclopentanone **117** with exquisite diastereoselectivity, and in significantly higher yield compared to acyloin **116**. The use of aromatic ketones not only improved the yield, but also completely reversed the stereoselectivity of the resultant cyclopentanones (**116** vs. **117**). A number of substituents around the aromatic ring were tolerated, affording the products in good yield and enantiomeric excess. The formation of a single acyloin diastereomer was observed in most cases, with the exception of the 3-NO_2-substituted cyclopentanone. Cyclic *β*-oxo-sulfones were also employed in the cascade reaction to form bicyclic systems. With the 6-membered sulfone, cyclopentanone **118** was obtained with excellent diastereo- and enantioselectivity, but poor yield. In contrast, the five-membered sulfone delivered sulfone **119** in higher yield, but diminished diastereo- and enantioselectivity.



116
33% yield
99:1 *dr*, 94% *ee*

117
72% yield
99:1 *dr*, 92% *ee*

80% yield
74:26 *dr*, 83% *ee*

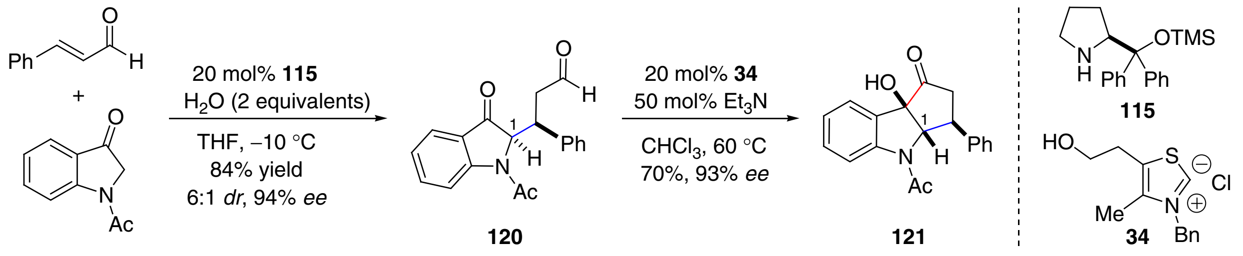
81% yield
99:1 *dr*, 83% *ee*

118
20% yield
99:1 *dr*, 91% *ee*

119
53% yield
67:33 *dr*, 41% *ee*

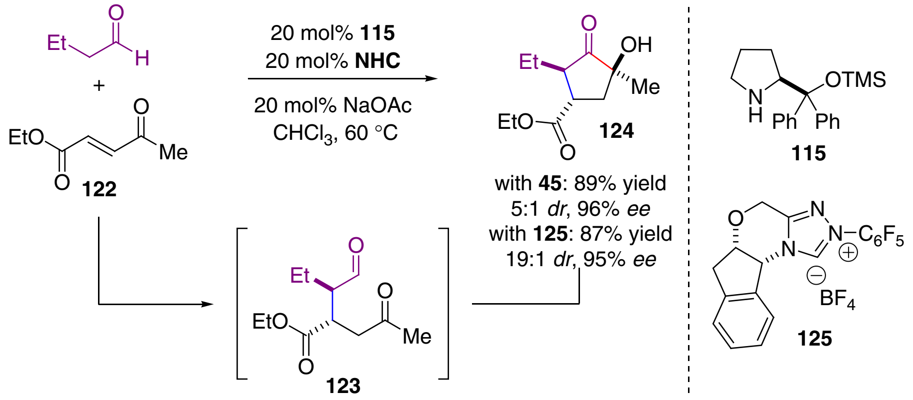
Figure 8 Substrate scope the conjugate addition/benzoin cascade with *β*-oxosulfones.

Also in 2011, Xu reported a two-step Michael addition/benzoin reaction with amine **115** and thiazolium **34** to prepare enantioenriched tricyclic indolin-3-ones (Scheme 13).[69] A significant amount of optimization was necessary for the organocatalytic Michael addition of 1-acetylindolin-3-one to cinnamaldehyde. The screening of a number of catalysts, solvents, and additives revealed that amine **115** provided the highest levels of enantioselectivity and that water was necessary to increase the rate of the reaction. A number of ketoaldehydes were prepared by this methodology with good levels of diastereoselectivity and excellent enantioselectivity. Xu reported an isolated example of the tandem reaction in which ketoaldehyde **120** was employed in an NHC-catalyzed cross-acyloin reaction. In the presence of thiazolium catalyst **34** and triethylamine, ketoaldehyde **120** underwent an intramolecular aldehyde–ketone cyclization to afford cyclopentanone **121** in good yield and with no loss in enantioselectivity. Interestingly, the conditions for the acyloin reaction resulted in complete inversion of the C-1 stereocenter.



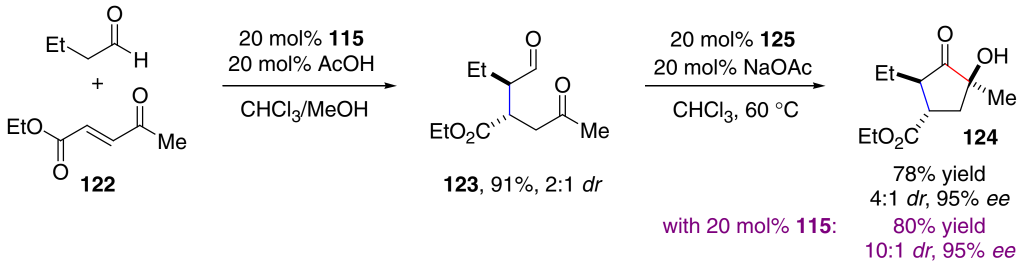
Scheme 13

In addition to iminium activation, proline derivatives are known to catalyze reactions invoking enamine intermediates. The combination of enamine catalysis with NHC catalysis was recently explored by Rovis to prepare functionalized cyclopentanones by a Michael addition/benzoin cascade.[67] The resultant cyclopentanones possess a unique substitution pattern compared to those obtained through the iminium-catalyzed process. In the presence of amine **115** and triazolium **45**, the reaction between butanal and enone **122** proceeded in 89% yield and 96% *ee*, but an unsatisfactory 5:1 *dr* (major: Σ minor) (equation 28). They discovered that use of a chiral NHC catalyst drastically improved the diastereoselectivity. When the same reaction was performed with triazolium catalyst **125** instead of catalyst **45**, acyloin **124** was obtained in 87% yield, 19:1 *dr* (major: Σ minor), and 95% *ee*. However, with the antipode of catalyst **125**, cyclopentanone **124** was produced with similar levels of enantioselectivity, but decreased yield and diastereoselectivity (4:1).



(28)

The increased diastereomeric ratio with NHC **125** suggests that the high levels of enantioselectivity are a result of the initial Michael addition, whereas the NHC plays a critical role in the diastereoselectivity. To determine if the amine catalyst was also influencing the diastereomeric outcome, the cascade reaction was performed as a two-step sequence. Toward this end, ketoaldehyde **123** was prepared in 91% yield and as a 2:1 mixture of diastereomers. The subsequent exposure of aldehyde **123** to catalyst **125** and sodium acetate afforded cyclopentanone **124** in 78% yield and 95% *ee*, but a 4:1 diastereomeric ratio (Scheme 14). Interestingly, the introduction of 20 mol% catalyst **115** afforded acyloin **124** in an improved 10:1 ratio of diastereomers. They suggest the moderate increase in diastereoselectivity from 2:1 to 4:1 during the acyloin reaction is due to preferential cyclization of one diastereomer of ketoaldehyde **123** over the other in the presence of chiral NHC **125**. The addition of amine **115** is thought to promote epimerization of the α-stereocenter of aldehyde **123**. This epimerization funnels the less reactive diastereomer toward its epimer, which undergoes facile cyclization to acyloin **124**, resulting in increased diastereoselectivity. This mechanism explains how acyloin **124** is obtained with high diastereoselectivity, despite the 2:1 *dr* of the ketoaldehyde starting material.



Scheme 14

To investigate the scope of the cascade reaction, Rovis and coworkers varied the enone and aldehyde coupling partners (Figure 9). The replacement of the ester with an amide afforded α-hydroxy cyclopentanone **126** in good yield and enantioselectivity. However, the use of diketones afforded the cyclized products in poor yield. Variation of the aldehyde was well tolerated under the reaction conditions. For example, cyclopentanones **127** and **128** were obtained in excellent yield and 96:4 and 90:10 *dr*, respectively.

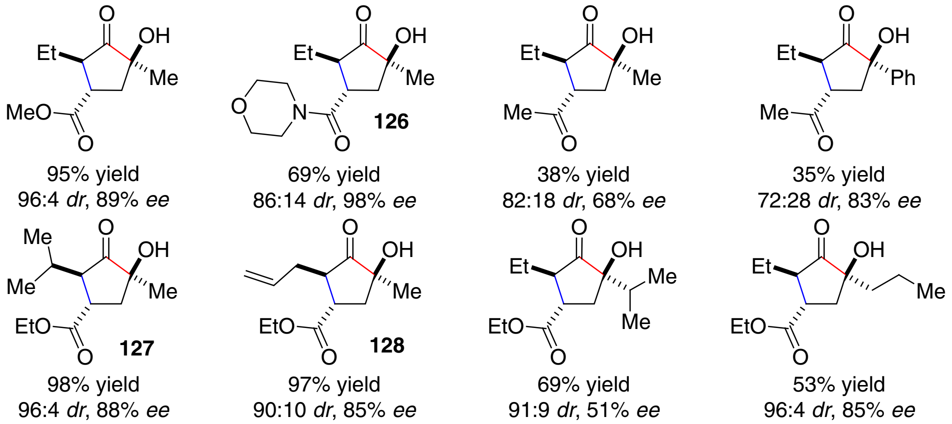
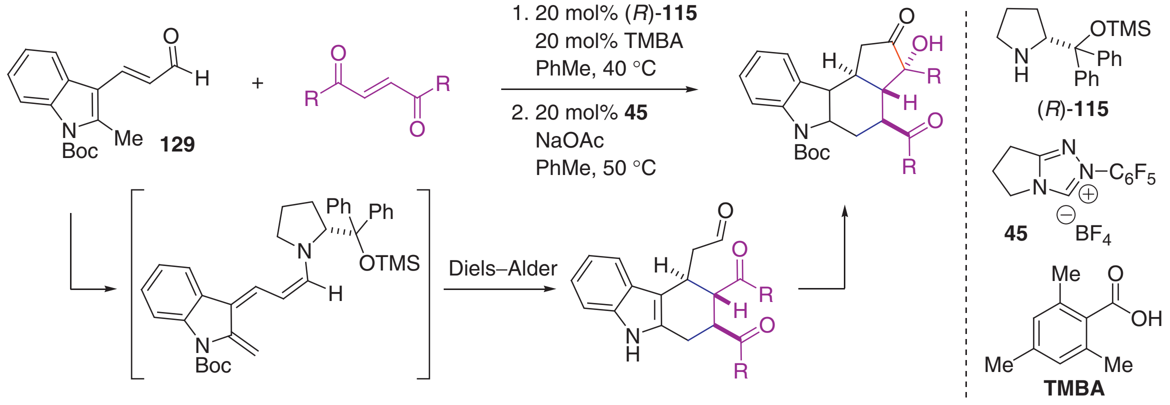
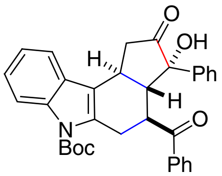
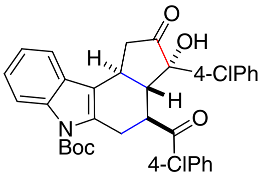
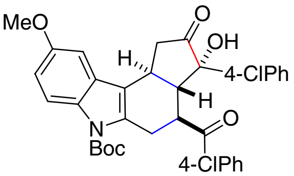
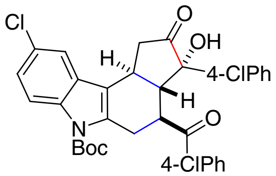


Figure 9 Substrate scope of the enamine-catalyzed Michael addition/benzoin cascade.

Most recently, Melchiorre and coworkers employed enamine catalysis to achieve a Diels–Alder/benzoin cascade between indoles and enones. This cascade process involves the formation of three carbon–carbon bonds and four contiguous stereocenters to generate tetracyclic acyloin products.[68] The optimized conditions involve exposure of diene **129** and an enone to amine **115** and 2,4,6-trimethylbenzoic acid (TMBA) to initiate the Diels–Alder reaction and generate an intermediate aldehyde. The subsequent addition of triazolium catalyst **45** and sodium acetate affords the acyloin products. In this report, Melchiorre employed the amine-catalyzed Diels–Alder reaction to prepare a number of ketoaldehydes and also demonstrated the potential of the dual catalytic Diels–Alder/benzoin cascade. Four examples of the dual catalytic process were reported in which variation of the 4-substitutent on the indole and enone was explored (Table 12). The resultant acyloin products were obtained in moderate to good yield, and excellent enantioselectivity.

Table 12 Substrate scope of Melchiorre's dual catalytic Diels–Alder/benzoin cascade



			
40% Yield 8:1 *dr*, 99% *ee*	53% Yield 6:1 *dr*, 99% *ee*	66% Yield 6:1 *dr*, 99% *ee*	61% Yield 6:1 *dr*, 97% *ee*

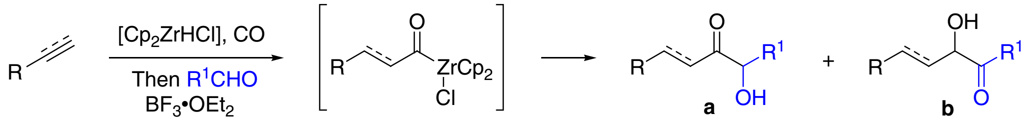
3.12.4 Indirect Approaches to Unsymmetrical Acyloins

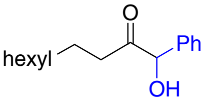
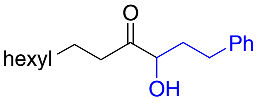
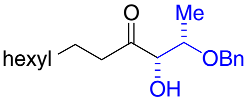
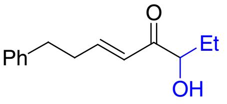
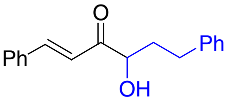
The mild conditions required for the synthesis of acyloins with NHC catalysis compared to the traditional reductive conditions have significantly enhanced the substrate scope of these coupling reactions. However, the current methods are limited with respect to the synthesis of unsymmetrical acyloins. As a result, several indirect approaches toward these synthetically useful building blocks have been developed. These methods present the unique opportunity to prepare cross-acyloins in a predictable and selective manner through use of acyl anion equivalents.

3.12.4.1 Acylzirconocene Chlorides

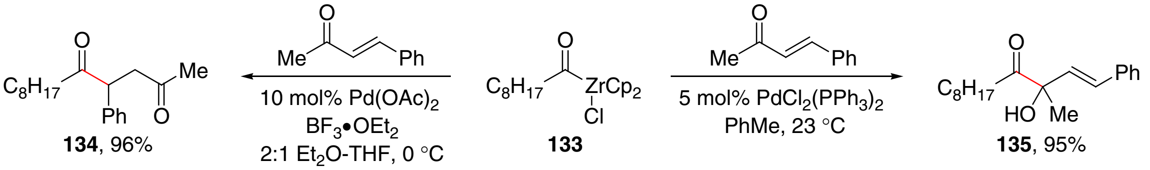
The use of acyl metal species for the synthesis of acyloins was initially reported in the 1980s. These efforts described the use of *in situ* generated acyl anion intermediates, such as acyl lithium[70] and samarium species.[71–73] The synthetic utility of these reactions was limited due to the need for low temperatures for acyl lithium intermediates (– 110 °C) and the unpredictable reactivity of the acyl samarium species. In 1998, Taguchi and Hanzawa reported a Lewis acid-mediated addition of acylzirconocene chlorides to aldehydes to afford cross-acyloin products.[74] This methodology was employed for the synthesis of unsymmetrical alkyl-aryl and alkyl-alkyl substituted α-hydroxy ketones. The acylzirconocene chlorides are prepared in situ from an alkene or alkyne by sequential addition of Schwartz reagent ([Cp_2ZrHCl]) and carbon monoxide. The subsequent treatment of the stable acyl anion intermediate with an aldehyde and BF_3•OEt_2 delivered the acyloin products in high yield and regioselectivity. Acylzirconocene chlorides derived from alkynes gave rise to a single regioisomer of the acyloin product; however, those prepared from alkenes afforded a mixture of regioisomers in certain cases (Table 13). For example, acyloin **130** was obtained in 79% yield as a single regioisomer, whereas acyloin **131** was obtained in similar yield, but as a 67:33 mixture of α-hydroxy ketones **131a** and **131b**. Aldehydes bearing α-stereocenters performed well in the reaction, as acyloin **132** was obtained as a single regioisomer in favor of the *syn* product (5.4:1 *syn*/*anti*).

Table 13 Substrate scope of acylzirconocene chloride addition to aldehydes



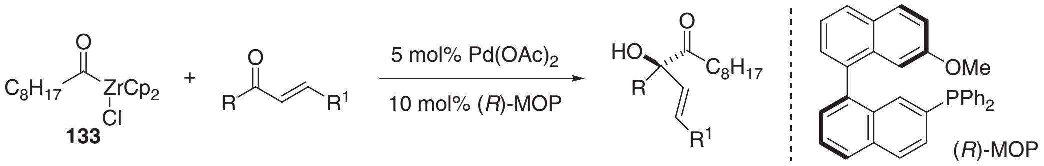
 **130**, 79%	 **131**, 78% 63:37 **a**:**b**	 **132**, 53% 5.4:1 *syn*/*anti*	 48%	 60%

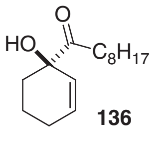
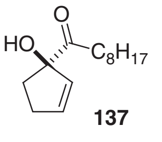
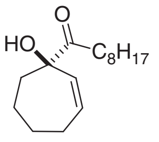
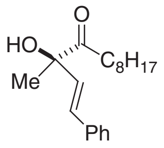
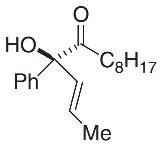
Attempts to form acyloins bearing a tertiary alcohol by addition of acylzirconocene chlorides to ketones were unsuccessful under the Lewis acid-mediated conditions. Taguchi and Hanzawa later reported a palladium-catalyzed acylation of enones with acylzirconocene chlorides in which the 1,2- or 1,4-addition products were obtained selectively through an appropriate choice of catalyst (Scheme 15).[75] In the presence of palladium acetate and BF_3•OEt_2, acylzirconocene chloride **133** underwent 1,4-addition to benzylideneacetone to afford diketone **134** in 96% yield. Alternatively, tertiary α-hydroxy ketone **135** was obtained with $PdCl_2(PPh_3)_2$ in 95% yield. The use of 5 mol% $Pd(OAc)_2$ and 10 mol% triphenylphosphine also gave rise to the 1,2-addition product selectively, thus the synthesis of enantioenriched tertiary α-hydroxy ketones with chiral phosphanes was explored. After screening a number of palladium catalysts and phosphane ligands, they determined that (*R*)-2-(diphenylphosphanyl)-2′-methoxy-1,1′-binaphthyl ((*R*)-MOP) afforded the products with the highest levels of enantioselectivity. The optimized conditions with palladium acetate and (*R*)-MOP produced acyloin **136** in 88% yield and 66% *ee* (Table 14).[76] Unfortunately, the yields and



Scheme 15

Table 14 Enantioselective Pd-catalyzed 1,2-addition of acylzirconocene chlorides



 **136**	 **137**			
88% Yield 66% *ee*	36% Yield 67% *ee*	92% Yield 38% *ee*	91% Yield 17% *ee*	84% Yield 6% *ee*

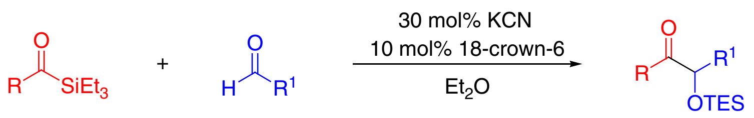
enantioselectivity were highly substrate dependent. For example, the 1,2-addition of acylzirconocene **133** to cyclopentenone afforded acyloin **137** in poor yield, but good enantioselectivity, whereas the acyloin derived from cycloheptenone was obtained in excellent yield, but only 38% *ee*. Likewise, the use of acyclic unsaturated ketones with (*R*)-MOP produced the acylated products in good yield, but with poor levels of enantioselectivity.

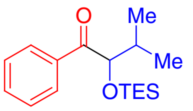
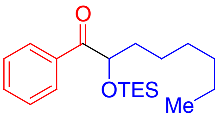
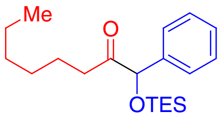
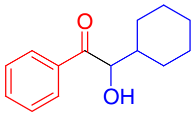
3.12.4.2 Acylsilanes

In the early 1980s, Degl'Innocenti[77,78] and Heathcock[79] independently reported the protodesilylation of acylsilanes on exposure to fluoride ion and water to generate the corresponding aldehydes. The introduction of other electrophiles, such as alkyl halides or aldehydes, enabled the synthesis of ketones and acyloins, respectively. Degl'Innocenti reported an isolated example of a cross-acyloin reaction between 2-furoyl trimethylsilane and butanal promoted by cesium fluoride.[78] Likewise, Heathcock reported the synthesis of α-hydroxy ketones by the reaction of benzoyl trimethylsilane with cyclohexanone and acetone in the presence of tetra-*n*-butylammonium fluoride (TBAF).[79] These pioneering efforts by Degl'Innocenti and Heathcock demonstrated the ability to prepare acyloins from acylsilanes and aldehydes through fluoride activation, but at the time, the generality and practicality were lacking.

Based on these Lewis base and acylsilane studies, Johnson and coworkers have extensively explored the scope and mechanism of cyanide-catalyzed benzoin-type reactions between acylsilanes and aldehydes or ketones.[80] The original report by Johnson involved the addition of acylsilanes to aldehydes in the presence of 18-crown-6 and a substoichiometric amount of potassium cyanide (KCN) to generate α-siloxy ketone products.[81] When both the acylsilane and aldehyde were aromatic, the cross-benzoin products were obtained in up to 95% yield. Alkyl-aryl substituted cross-acyloin products could also be prepared under these conditions, albeit in slightly lower yields (51–75%) (Table 15). Through appropriate choice of the acylsilane and aldehyde, either α-siloxy ketone regioisomer could be prepared (Table 15, **138** and **139**). With aliphatic aldehydes, it was necessary to use an excess of the aldehyde to obtain the cross-acyloin products in good yield. The use of [18-crown-6•K]CN as the catalyst also produced the cross-acyloin products in good yield, as in the synthesis of acyloin **140** from benzoyl triethylsilane and cyclohexanecarboxyaldehyde. The coupled products were generally isolated as the triethylsilyl (TES) ether, which is readily cleaved under mildly acidic conditions. Unfortunately, all attempts to form bis-alkyl substituted acyloins under these conditions were unsuccessful.

Table 15 Substrate scope of cyanide-catalyzed acyloin reaction of acylsilanes



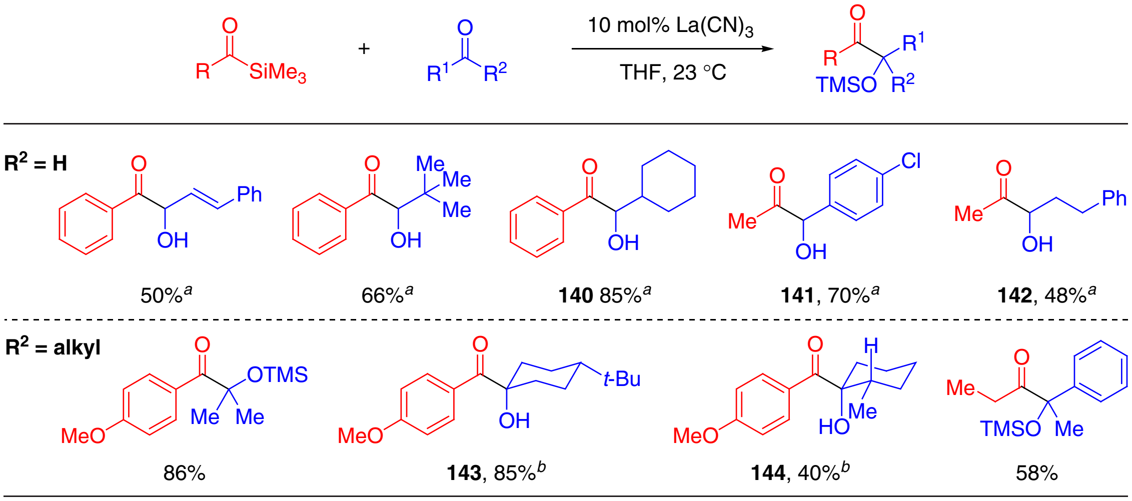
			
66%	**138**, 70%	**139**, 51%[a]	**140**, 94%[a]

[a] Reaction performed with 50 mol% KCN and 30 mol% 18-crown-6.

[b] 20 mol% [18-crown-6•K]CN complex; deprotection of the α-siloxyketone with 1 M HCl in MeOH.

A subsequent report by Bausch and Johnson in 2004 discussed the use of lanthanum cyanide to catalyze the cross-acyloin reaction between acylsilanes and aldehydes.[82] Changing the catalyst from KCN to lanthanum cyanide decreased the reaction times, improved the yields, and expanded the substrate scope of the coupling reaction. With 10 mol% $La(CN)_3$ only a mild excess of aldehyde (1.5 equivalents) was necessary for the reaction to reach complete conversion within 15 min (**Table 16**, $R^2 = H$). The modified conditions resulted in a broader substrate scope and enabled the use of α,β-unsaturated, secondary, and tertiary substituted aliphatic aldehydes in the cross-acyloin reaction. Coupling reactions with acetyl trimethylsilane were unsuccessful with KCN, but were readily accomplished with lanthanum cyanide as the catalyst. For example, the reaction of acetyl trimethylsilane with 4-chlorobenzaldehyde and hydrocinnamaldehyde delivered acyloins **141** and **142** in 70% and 48% yield, respectively. The synthesis of acyloin **142** is noteworthy as this is the first example of an unsymmetrical bis-alkyl substituted acyloin prepared from the coupling of an acylsilane and aldehyde.

Table 16 Acylsilane addition to aldehydes and ketones



[a] Trimethylsilyl ether was deprotected with 1 M HCl in MeOH.

[b] Trimethylsilyl ether was cleaved with n-Bu_4F to simplify purification, yield is over two steps.

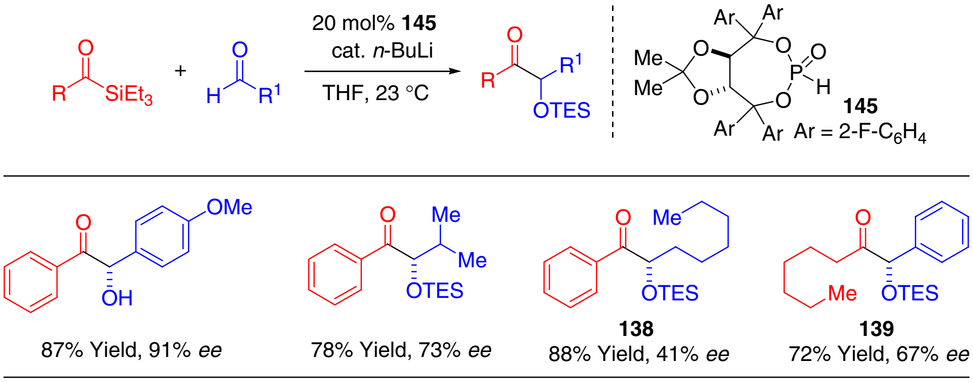
The scope of this method was recently expanded to include the reaction between acylsilanes and ketones.[83] Several tertiary α-hydroxy ketones were prepared in good yield using the previously optimized conditions with lanthanum cyanide as the catalyst. Acyloins **143** and **144** were obtained as a single diastereomer, demonstrating the potential for a substrate-controlled diastereoselective addition. The yield for acyloin **144** was considerably lower than with other substrates, presumably due to steric congestion caused by the α-stereocenter in the ketone starting material. The use of acyclic aldehydes and ketones bearing α- or β-stereocenters in this reaction was not reported. However, the use of chiral carbonyl coupling partners would be an interesting extension if a selective addition could be achieved, similar to Hanzawa's work with α-hydroxy aldehydes (see Section 3.12.4.1).

With conditions to engage a wide range of aldehydes and ketones in the cross-acyloin reaction with acylsilanes, the development of an asymmetric variant was explored. Since the cyanide-catalyzed approach could not be rendered enantioselective, Johnson and coworkers explored the use of chiral metallophosphites as a novel class of acyl anion catalysts.[84] A number of α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOL)-derived phosphites were prepared and evaluated in the addition of benzoyl triethylsilane to *p*-anisaldehyde. On identification of phosphite **145** as the optimal catalyst, the scope of the reaction was investigated. The acyloin coupling reactions between aryl aldehydes and acylsilanes afforded the mixed benzoin products in up to 87% yield and 91% enantiomeric excess. Enantioenriched α-hydroxy ketones derived from aliphatic acylsilanes or aldehydes were obtained in good yield (72–88%), but with diminished levels of enantioselectivity (**Table 17**). Despite the moderate levels of enantioselectivity, these results are significant as this is one of the first examples of a nonenzymatic, enantioselective cross-acyloin reaction. More importantly, Johnson and coworkers have developed a new class of catalysts for umpolung reactions based on the chiral TADDOL scaffold.

3.12.4.3 Acylphosphonates

In 2005, Johnson[85] and Demir[86] independently reported the use of acylphosphonates as coupling partners in the cyanide-catalyzed cross-benzoin reaction. Whereas the Johnson group only reported the use of aromatic acylphosphonates, Demir and coworkers demonstrated that aliphatic acylphosphonates and aldehydes could also be employed to generate cross-acyloin products. In Demir's work, high yields were obtained with 20 mol% CsF and 30 mol% trimethylsilyl cyanide (TMSCN) in

Table 17 Metallophosphite-catalyzed acylsilane additions to aldehydes



87% Yield, 91% *ee*

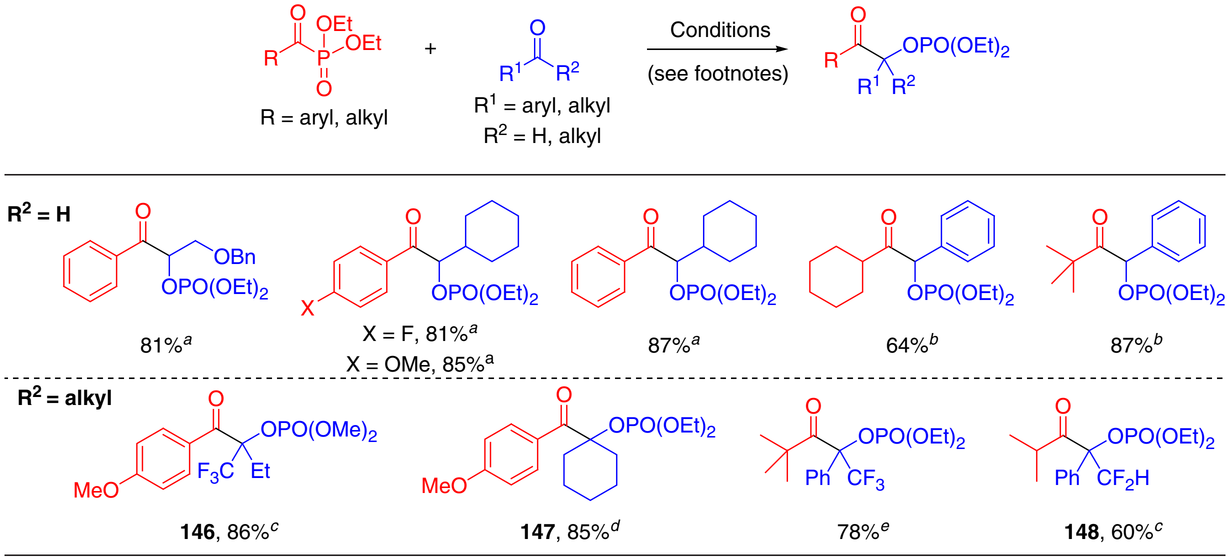
78% Yield, 73% *ee*

138
88% Yield, 41% *ee*

139
72% Yield, 67% *ee*

reactions with benzoylphosphonate (Table 18). The introduction of electron donating and withdrawing groups at the 4-position of the aryl acylphosphonate was well tolerated, producing the coupled products in comparable yields with benzoylphosphonate. Interestingly, when aliphatic acylphosphonates were employed in the reaction, the previously optimized conditions failed to provide the acyloin products in satisfactory yield. Instead, catalytic KCN and 18-crown-6 were employed to effect the coupling reaction. All attempts to prepare bis-alkyl substituted acyloins were unsuccessful due to low conversion and poor yields of the desired product.

Table 18 Acylphosphonate additions to aldehydes and ketones



R^2 = H: 81%[a]; X = F, 81%[a]; X = OMe, 85%[a]; 87%[a]; 64%[b]; 87%[b]

R^2 = alkyl: **146**, 86%[c]; **147**, 85%[d]; 78%[e]; **148**, 60%[c]

[a] 20 mol% CsF, 30 mol% TMSCN in DMF.

[b] 30 mol% KCN, 30 mol% 18-crown-6 in PhMe.

[c] 20 mol% KCN, 10 mol% Cu(OTf)$_2$ in DMF at 50 °C.

[d] 20 mol % (3,5-bistrifluoromethylphenyl) thiouera in THF.

[e] 20 mol% KCN in PhMe at 80 °C.

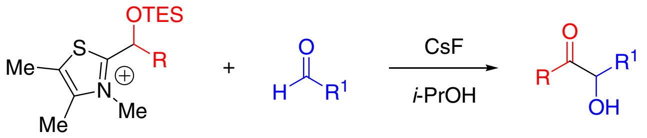
The extension of this methodology to the cyanide-catalyzed addition of acylphosphonates to ketones required further optimization of the reaction conditions.[87] Demir investigated different additives, solvents, and reaction temperatures to improve the yield of the α-hydroxy ketone products (Table 18, R^2=alkyl). For example, the synthesis of acyloins **146** and **148** required the addition of 10 mol% copper triflate, whereas the introduction of (3,5-bistrifluoromethylphenyl)thiourea was necessary to obtain acyloin **147** in 85% yield. In addition to the need for individual optimization of each substrate, the scope is limited to trifluoro- and difluoromethyl ketones, with the exception of cyclohexanone.

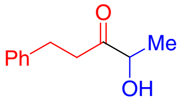
3.12.4.4 O-Silyl Thiazolium Carbinols

Given the limited number of examples involving the preparation of alkyl-alkyl cross-acyloins, more general methods to introduce this structural motif are still needed. In 2009, the Scheidt group reported the reaction of aliphatic *O*-silyl thiazolium carbinols with aldehydes to generate unsymmetrical bis-alkyl cross-acyloins in good yield.[88] *O*-Silyl thiazolium carbinols represent a novel class of acyl anion equivalents that have been employed by the Scheidt group in a number of umpolung processes.[89,90] These acyl anion equivalents are bench-top stable and easily prepared on large scale by a three-step sequence. In contrast to the cyanide-catalyzed reactions with acylsilanes and acylphosphonates, the acyl anion is generated through fluoride activation with *O*-silyl thiazolium carbinols. This coupling strategy represents the first indirect cross-acyloin reaction involving NHCs, but a stoichiometric amount of NHC is required since the thiazolium salt is incorporated into the starting material.

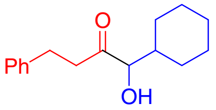
To effect the cross-acyloin reaction, the desired *O*-silyl thiazolium carbinol is exposed to cesium fluoride and an aliphatic aldehyde in *iso*-propanol. Under the optimized conditions, a range of α-hydroxy ketone products were generated in moderate to good yield (41–80%) (Table 19). Either of the acyloin regioisomers is accessible by the appropriate choice of the *O*-silyl thiazolium carbinol and aldehyde coupling partners (**149** and **142**). Both aldehydes and thiazolium carbinols with terminal protected alcohols performed well in the reaction, affording acyloins **150** and **151** in 67% and 49% yield, respectively. This methodology is distinct in that the focus is the synthesis of unsymmetrical bis-alkyl acyloins, a current limitation of several of the indirect methods.

Table 19 O-Silyl thiazolium carbinol additions to aldehydes

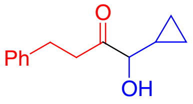




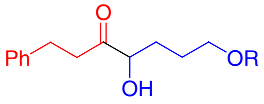
149, 80%



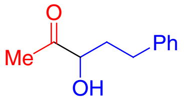
41%



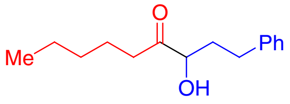
71%



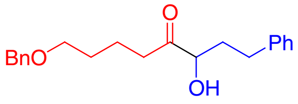
150, R = Bn, 67%
R = TIPS, 72%



142, 56%



62%



151, 49%

3.12.4.5 α-Ketoesters

In 2012, Zeitler and Connon reported the NHC-catalyzed cross-acyloin reaction between aldehydes and α-ketoesters to deliver α-hydroxy-*β*-ketoacid products.[91] The substitution pattern of the ketoacid products is analogous to those obtained from the thiamine pyrophosphate dependent synthesis of acetolactate from two molecules of pyrophosphate. This methodology represents the first NHC-catalyzed indirect approach to unsymmetrical acyloins, wherein the α-ketoester serves as a masked aldehyde. Decarboxylation of the ketoacid products would afford the acyloin formally derived from the coupling of two different aldehydes (Figure 10).

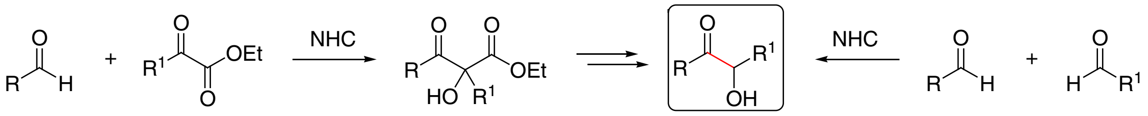
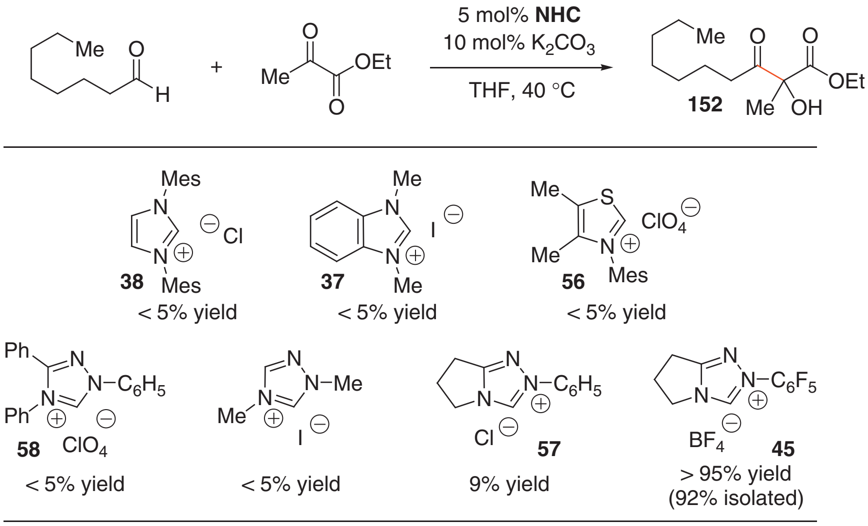


Figure 10 NHC-catalyzed coupling of aldehydes and α-ketoesters.

α-Ketoesters are known to undergo NHC-catalyzed hydroacylation,[92] therefore, it was necessary to identify a catalyst that disfavored the hydride transfer pathway and favored the cross-acyloin reaction. The screening of a diverse set of catalysts revealed that only catalyst **60** produced the cross-acyloin products in an appreciable yield (Table 20). This catalyst was also employed in

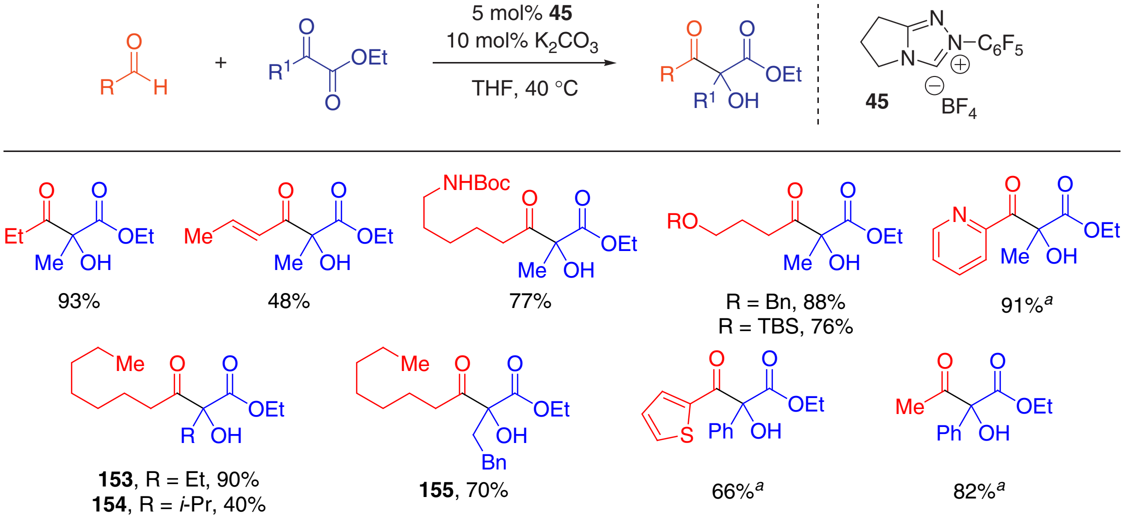
Table 20 Optimization of NHC catalyst



several NHC-catalyzed cross-acyloin methods (see Section 3.12.3.2). In the presence of 5 mol% catalyst **45** and 10 mol% potassium carbonate, α-hydroxy-*β*-ketoacid **152** was obtained in 92% yield. They determined that potassium phosphate and Hünig's base in combination with triazolium **45** also afforded the coupled product in high yield (>90%).

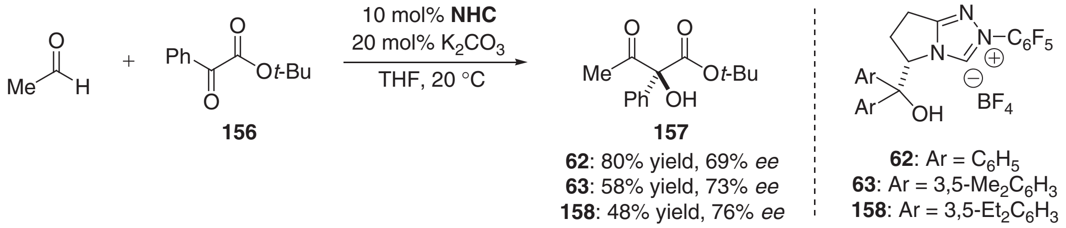
With optimized conditions in hand, a range of aldehydes were employed in the cross-acyloin reaction with ethyl pyruvate. Aldehydes bearing a number of functional groups, including protected alcohols, amines, and aromatic and heteroaromatic substituents, performed well in the reaction (Table 21). Aromatic aldehydes were problematic coupling partners, but on changing the solvent to chloroform, the aryl-substituted α-hydroxy-*β*-ketoacids were obtained in good to excellent yield. Variation of the α-ketoester at R^1 was also explored. Ketoesters bearing an ethyl, *iso*-propyl, and hydrocinnamyl group were employed in the reaction with octanal. α-Hydroxy-*β*-ketoacids **153**, **154**, and **155** were obtained in 90%, 40%, and 70% yield, respectively. The diminished yields for ketoacids **154** and **155**, bearing an *iso*-propyl and hydrocinnamyl substituent at R^1, are likely due to unfavorable steric interactions caused by the larger ketone substituents. The phenyl-substituted ketoester also delivered the coupled products in good to excellent yield on changing the solvent from THF to chloroform.

Table 21 Substrate scope of NHC-catalyzed coupling of α-ketoesters and aldehydes



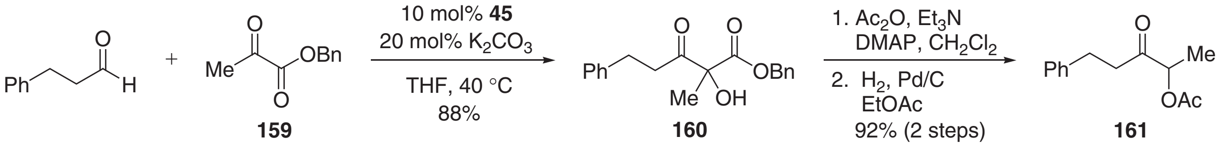
[a]Reaction conducted in $CHCl_3$ at 40 °C.

Zeitler and Connon also demonstrated the potential to carry out this coupling reaction in an enantioselective fashion. On treatment of *tert*-butyl α-ketoster **156** and acetaldehyde with 10 mol % catalyst **62** and potassium carbonate, α-hydroxy-*β*-ketoacid **157** was obtained in 80% yield and 69% *ee* (equation 29). They observed diminished levels of enantioinduction with ethyl pyruvate compared to the more sterically encumbering *tert*-butyl ketoester. Variation of the aryl groups on the catalyst was investigated in an effort to improve the enantioselectivity. The use of 3,5-$Me_2C_6H_3$ and 3,5-$Et_2C_6H_3$ substituted triazoliums **63** and **158** resulted in diminished yields, but a marginal increase in enantioselectivity.



(29)

It was envisioned that the α-hydroxy-*β*-ketoacid products could be converted to the acyloins formally derived from the regioselective coupling of two different aldehydes. Toward this end, benzyl α-ketoesters were identified as ideal substrates from which the cross-acyloin products could be obtained. The reaction between benzyl α-ketoester **159** and hydrocinnamaldehyde worked well under the standard conditions, providing α-hydroxy-*β*-ketoacid **160** in 88% yield (Scheme 16). An acetylation and hydrogenolysis sequence delivered α-acetoxy ketone **161**, the acyloin formally derived from the coupling of hydrocinnamaldehyde and formaldehyde. The formation of the acetate before decarboxylation was necessary to prevent keto-enol tautomerization, which would generate a mixture of regioisomers.



Scheme 16

3.12.4.6 *N*-Silyloxyketene Imines

In 2010, Denmark and coworkers reported a novel bis-phosphoramide-catalyzed cross-acyloin reaction between *N*-siloxyketene imines and benzaldehyde derivatives.[93] *N*-Siloxyketene imines are another unique class of acyl anion equivalents, which on reaction with an aldehyde afford versatile *β*-hydroxy cyanohydrin intermediates (Figure 11). From the in situ generated cyanohydrins, acidic workup followed by base-mediated retrocyanation delivers the cross-acyloin products. Alternatively, reduction (R^2=H) or nucleophilic addition to the cyanohydrin gives rise to glycolate aldol products.

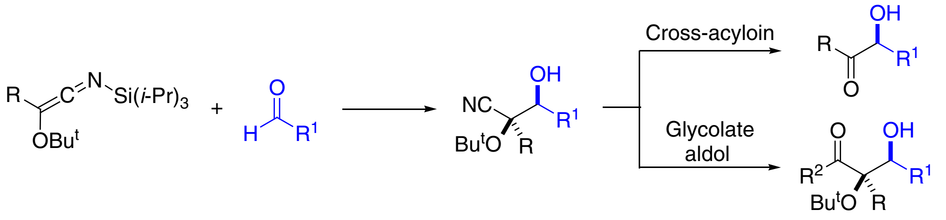
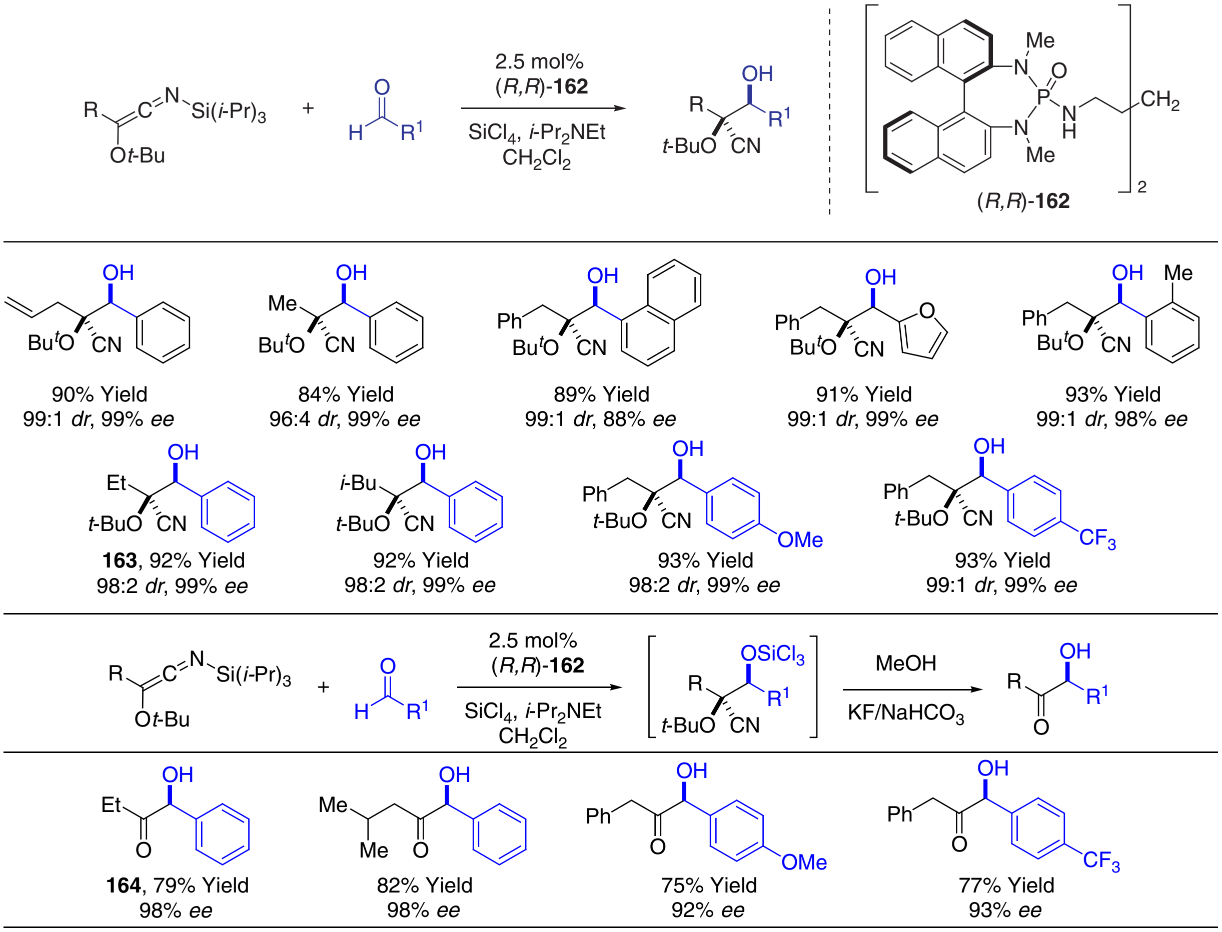


Figure 11 Synthesis of cross-acyloin and glycolate aldol products from *N*-siloxyketene imines.

N-Siloxyketene imines bearing a methyl, ethyl, *iso*-butyl, benzyl, and allyl group were prepared by a two-step sequence from the corresponding cyanohydrins. The treatment of an *N*-siloxyketene imine and benzaldehyde with silicon tetrachloride and 2.5 mol % bis-phosphoramide catalyst (*R*,*R*)-**162** furnished the corresponding *β*-hydroxy cyanohydrins in good yield and with excellent diastereo- and enantioselectivity (Table 22). A wide range of aromatic aldehydes and *N*-siloxyketene imines were employed in the aldol reaction with catalyst **162**, demonstrating the broad functional group tolerance of this method. The *β*-hydroxy cyanohydrin products could be isolated or converted directly to α-hydroxy ketones. The intermediate silyl ether was deprotected under mildly acidic conditions with methanol, which following basic workup afforded the cross-acyloin products in good yield and >90% *ee*. Comparison of the corresponding *β*-hydroxy cyanohydrins and acyloin products reveals that the deprotection, retrocyanation sequence proceeds with minimal loss in enantioselectivity. For example, cyanohydrin **163** was

Table 22 Substrate scope of *N*-siloxyketene imine addition to aldehydes



obtained in 92% yield and 99% *ee*, whereas acyloin **164** was generated in 79% yield and 98% *ee*. The use of aliphatic aldehydes in this coupling reaction was not reported, but would be a useful extension of this methodology.

3.12.5 Summary

There have recently been tremendous advances in the development of approaches toward unsymmetrical acyloins. Several NHC catalysts and acyl anion equivalents have been identified that enable the preparation of differentially substituted α-hydroxy ketones in a regioselective manner. Given the prevalence of this structural motif in natural products and pharmaceuticals, more general cross-acyloin methods are still needed. A fundamental understanding of the mechanism and factors governing regioselectivity will facilitate the development of broadly applicable approaches for the synthesis of unsymmetrical acyloins and significantly enhance the potential of these coupling reactions in synthetic applications.

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3.13 Oxidative Coupling of Phenols and Phenol Ethers

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3.13.1 Introduction 656
3.13.1.1 General 656
3.13.1.2 Mechanistic Considerations 657
3.13.1.3 How to Control Oxidative Phenolic Coupling Processes 660
3.13.2 Synthesis of Oxygenated Biaryls 665
3.13.2.1 Via Oxidative Coupling of Phenols 665
3.13.2.1.1 Regioselective phenolic biaryl coupling 665
3.13.2.1.2 Stereoselective phenolic biaryl coupling 672
3.13.2.1.2.1 Diastereoselective phenolic biaryl coupling 672
3.13.2.1.2.2 Enantioselective phenolic biaryl coupling 678
3.13.2.2 Via Oxidative Coupling of Phenol Ethers 685
3.13.2.2.1 Intramolecular biaryl coupling 685
3.13.2.2.2 Intermolecular biaryl coupling 694
3.13.3 Synthesis of Diaryl Ethers 699
3.13.3.1 Via Chemoselective Oxidative Coupling of Phenols 699
3.13.3.2 Via Coupling Reactions Involving Quinonoids 706
3.13.4 Synthesis of Spirodienones 708
3.13.5 Oxidative Phenolic Coupling Involving Conjugated Double Bonds 711
3.13.5.1 Chemo- and Regioselectivity in Hydroxyphenylpropenoid Coupling Reactions 712
3.13.5.2 Stereoselectivity in Hydroxyphenylpropenoid Coupling Reactions 717
3.13.5.3 Chemo- and Regioselectivity in Hydroxystilbenoid Coupling Reactions 720
3.13.6 Oxidative Phenolic C–C Coupling Involving Quinonoids 725
3.13.7 Conclusion 736
References 736

Glossary

Asymmetric induction Influence of the chirality of a substrate, reagent, or catalyst in a chemical reaction leading the preferential formation of one enantiomer or diastereoisomer over another.

Atropoisomers Isolable conformational stereoisomers resulting from a sterically hindered rotation around a sigma bond.

Biaryl Molecule featuring two aromatic rings linked together by a carbon–carbon bond.

Diaryl ether Molecule featuring two aromatic rings linked together by an ether (carbon–oxygen–carbon) bond.

Hypervalent molecule Molecule containing one or more main group elements formally bearing more than eight electrons in their valence shells.

Single-electron transfer The transfer of an electron from a metal or a molecule to a substrate to form radical species.

Umpolung German for polarity inversion in a chemical transformation of a functional group leading to the reversal of polarity of that group.

3.13.1 Introduction

3.13.1.1 General

The oxidative coupling of phenols belongs to the category of those venerable organic reaction processes that do not cease to sustain the interest of chemists even after more than a century of investigations and applications. The reasons for which this oxidative transformation of phenolic materials maintains a privileged place in the organic reaction toolbox are (1) the possibilities it offers for rapidly accessing C–C coupled biaryl units, which are featured in numerous naturally occurring and bioactive molecules and often utilized when devising ligands for use in the design of chiral reagents and catalysts and (2) its reliance on the chemistry at play in the biosynthesis of natural products of different classes, including *inter alia* plant polyphenols, alkaloids, terpenoids, polyketides, and glycopeptides, which continue to incite synthetic organic chemists to elaborate biomimetic routes to these compounds by oxidative coupling of phenolic precursors. Since the earliest reports in 1871 on the conversion of gallic acid (3,4,5-trihydroxybenzoic acid) or its ethyl ester into the naturally occurring biaryl bislactone ellagic acid using molecular iodine or

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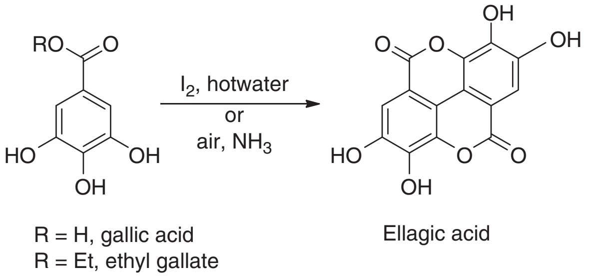
air as oxidants (Scheme 1),[1] numerous halogen-based, oxygen-based, metal-based inorganic, organic, and enzymatic oxidants, as well as anodic oxidation, have been utilized through the years to promote the formation of not only C–C but also, albeit to a lesser extent, C–O coupled products from various phenols or their simple ethers.



Scheme 1

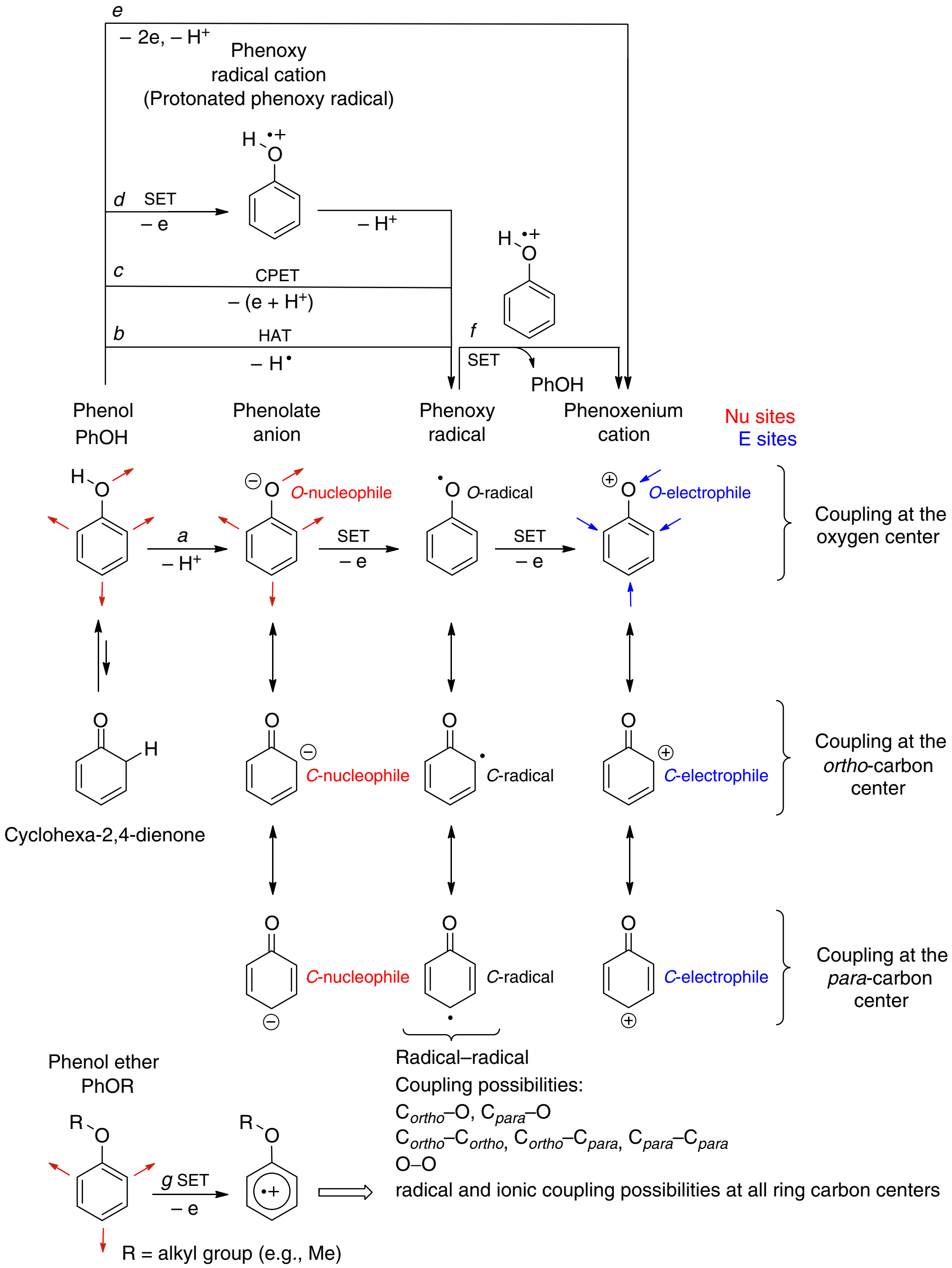
Several excellent review articles and book chapters punctuate this relentless century and a half of research work.[2–14] This considerable amount of literature on the subject constitutes an invaluable resource to trace the history of the development of the oxidative coupling of phenols as a major and biosynthetically relevant organic reaction and yet to still find sources of inspiration for novel applications in organic synthesis. In this sequel of the chapter that was written by Donald A Whiting[14] for the 1991 and first edition of *Comprehensive Organic Synthesis*, the authors restate the mechanistic diversity of the reaction, which to this day continues to elude chemists, and mainly focus the discussion on applications of the reaction in synthesis methodology development and natural product synthesis work by highlighting a selection of reports that have appeared in the literature from the mid-1990s to 2012. For the most part, with the exception of a few seminal works, reports that have already been highlighted in review and book chapter articles published during this period are not discussed again herein.

3.13.1.2 Mechanistic Considerations

The understanding of the reaction mechanisms that underpin the various aspects of the oxidative coupling of phenols has unsurprisingly fueled numerous investigations over the years and it is still today a topic of active research. Since the seminal work of Pummerer and coworkers[15] that first pointed out the role of phenoxy radicals as intermediates in phenol oxidation processes, and the influential suggestions of Barton and Cohen, and Erdtman and Wachtmeister on phenoxy radicals pairing in the biogenesis of phenol-derived natural products,[16] the dehydrogenative one-electron oxidation of phenols has first and often been put forward to rationalize the formation of their oxidation products by coupling the resulting delocalized phenoxy radicals ($PhO^{\bullet}$). However, the versatile (oxidation) chemistry of phenols allows several other alternatives, including ionic and pericyclic processes, which can also lead to the formation of diverse C–C and C–O coupled products. All of these different mechanistic options have already been presented and discussed several times in the literature over the years. The few references the authors recommend reading to rapidly get versed in the mechanistic intricacies of the oxidative coupling of phenols are those by Musso,[4,17] Scott,[5] McDonald and Hamilton,[8] Waters,[18] Whiting,[14] Rieker,[19] Lessene and Feldman,[11] Yamamura and Nishiyama,[12] and authors.[13] In this section, the authors attempt to provide a comprehensive summary of the different and most experimentally feasible mechanistic pathways open to phenols for coupling under oxidative conditions.

According to some of the basic chemical reactivity criteria of phenols (Scheme 2)[20]: The electron richness of phenols that renders them susceptible to oxidation also makes them decent nucleophiles. Phenols can be considered as aromatic (stable) enol tautomers of cyclohexadienones with a nucleophilic character that can express itself both at the oxygen atom of the hydroxyl group and, by virtue of the conjugation of the nonbinding electronic doublets of the oxygen atom with the phenyl ring, at the *ortho*- or *para*-carbon centers. This conjugation effect also confers to the polarized phenolic O–H bond a mild but quite exploitable Brønsted acidity with pK_a values globally ranging from approximately 7 to 12 ($pK_a = 9.9$ for phenol itself), the presence of electron-withdrawing *ortho*- and/or *para*-substituents on the phenolic ring lowering the pK_a. Phenols can thus be relatively easily deprotonated into resonance-stabilized phenolate anions, which are harder but still ambident nucleophiles and which can readily be one-electron oxidized into phenoxy radicals via single-electron transfer (SET) (Scheme 2, path *a*). Oxidation potentials of phenolate anions are typically lower than those of their phenol parents. For phenol itself (PhOH), the oxidation potential globally ranges from approximately 1.0 to 1.4 V, whereas that of its phenolate anion (PhO^-) is much lower and comprises between approximately −0.6 and +0.3 V (vs. Ag/AgCl).[13,19]

Phenols can also be directly converted into phenoxy radicals via hydrogen atom transfer (HAT) (Scheme 2, path *b*) when reacting with another free radical species or an appropriate oxidant. Such a hydrogen abstraction from phenols is made possible by the relatively low energy of their O–H bond with bond dissociation energy (BDE) values globally ranging from approximately 73 to 95 $\mathrm{Kcal\,mol^{-1}}$ (gas-phase BDE≈87 $\mathrm{Kcal\,mol^{-1}}$ for phenol itself), the presence of electron-releasing *ortho*- and/or *para*-substituents on the phenolic ring stabilizing the phenoxy radical and hence lowering the O–H BDE.[21] Phenols, as well as phenol

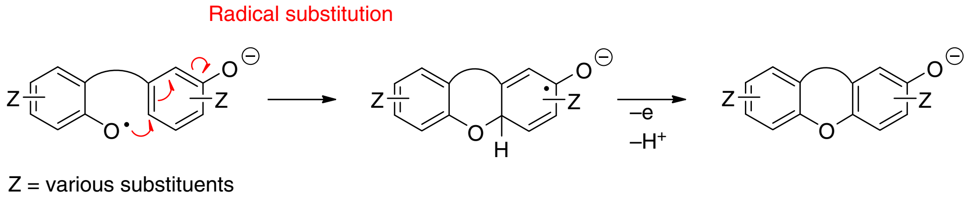


Scheme 2

ethers, can also be directly one-electron oxidized via SET to furnish phenoxy or phenol ether-derived radical cations ($PhOH^{\bullet+}$ or $PhOR^{\bullet+}$) (**Scheme 2**, path *d* and *g*). In this case, the ionization potential (IP) constitutes another determining energetic factor; the lower the IP (calculated), the easier the electron abstraction should be.[21d,e,22] In the case of phenols, deprotonation rapidly ensues to generate phenoxy radicals (**Scheme 2**, path *d*). In addition to this sequential transfer of an electron, then a proton, a concerted proton–electron transfer (CPET), which is reminiscent of, but mechanistically different from the HAT process, is also possible (**Scheme 2**, path *c*).[23] Furthermore, phenoxy radicals are characterized by oxidation potentials that are lower than those of their phenol parents (*ca.* 0.7–0.8 V vs. 1.0–1.4 V (vs. Ag/AgCl) for the phenoxy radical ($PhO^{\bullet}$) and its phenol parent (PhOH)),[13,19] and can thus also readily be one-electron oxidized to furnish resonance-stabilized phenoxenium cations (**Scheme 2**, path *a*). Phenoxenium ions can also be produced directly from phenols via two-electron oxidation using appropriate oxidizing systems, including anodic oxidation[12,24] (**Scheme 2**, path *e*).[13,19] They can even also result from SET between a phenoxy radical and its protonated form, a phenoxy radical cation, in sufficiently acidic media ($PhO^{\bullet}+PhOH^{\bullet+}\rightarrow PhO^{+}+PhOH$, **Scheme 2**, path *f*), as recently demonstrated by Omura[25] in agreement with Waters' earlier proposal on the rapid disproportionation of phenoxy radicals into phenoxenium cations and phenols under acidic conditions ($2\times PhO^{\bullet}+H^{+}\rightarrow PhO^{+}+PhOH$).[18]

The aforementioned intermediate species produced from the oxidation of phenols or their simple ethers, viz phenoxy radicals ($PhO^{\bullet}$), protonated phenoxy radicals ($PhOH^{\bullet+}$), phenoxenium cations (PhO^{+}), and phenol ether-derived radical cations ($PhOR^{\bullet+}$), as well as the starting phenols (PhOH), phenolate anions (PhO^{-}), and phenol ethers (PhOR), can all potentially be involved in coupling processes.

Electron-delocalized phenoxy radicals ($PhO^{\bullet}$) can pair up together in different ways to produce C–C, C–O and even, albeit to a much lesser extent, weakly bonded O–O coupled products (**Scheme 2**).[2–5,8,12–19] If circumstances permit, such as in intramolecular cases with phenolic moieties of different oxidation potentials, a phenoxy radical may be driven to react with an unoxidized phenol, a phenolate anion or a phenol ether via a radical aromatic substitution pathway. Once the new bond-forming radical insertion is thus accomplished, a second one-electron oxidation would lead to a final coupled product (**Scheme 3**).[8,14]



Scheme 3

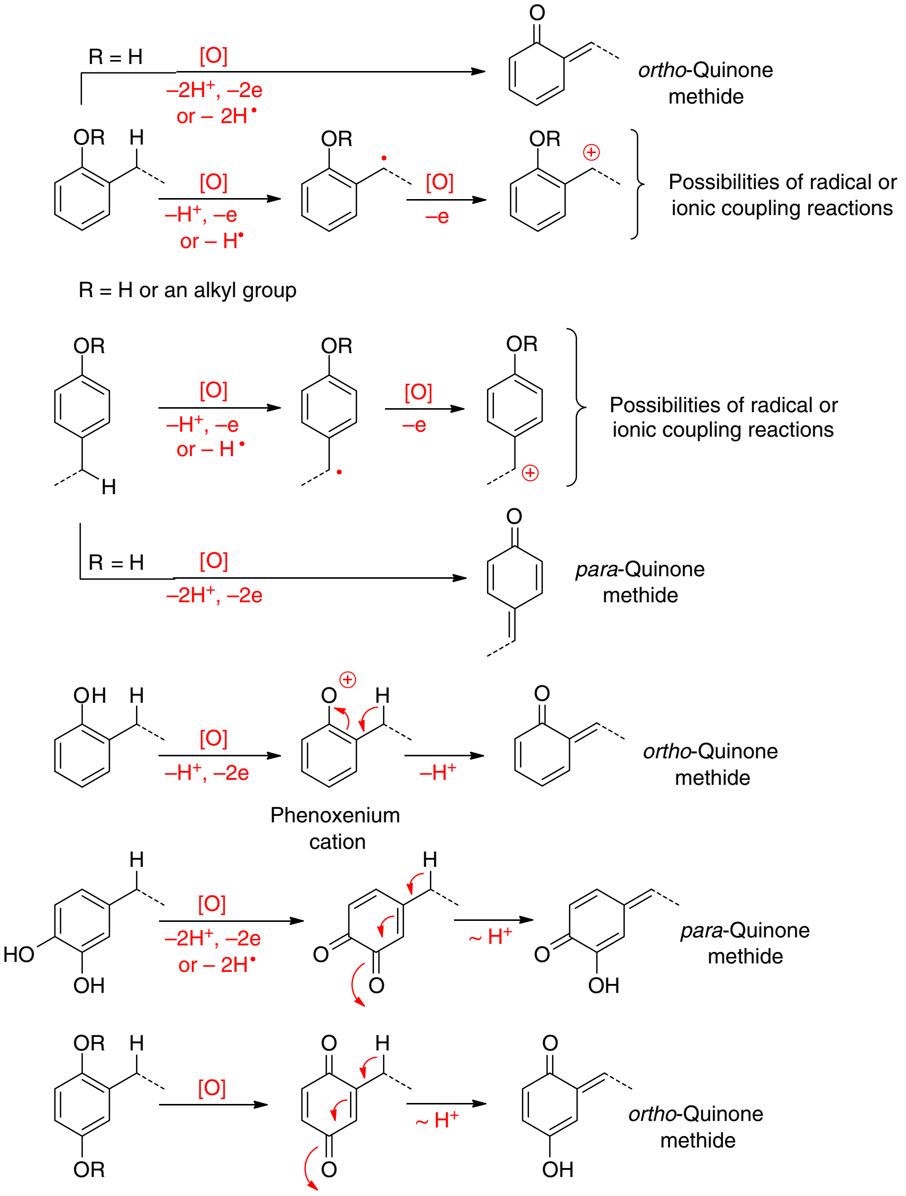
Charge-delocalized phenoxenium cations (PhO^{+}) are potent electrophiles that can suffer nucleophilic attacks from phenols, phenolate anions, or phenol ethers to conceivably produce a similar range of C–C and C–O coupled products in view of the ambident character of the electrophilic phenoxenium cations (**Scheme 2**) and of the nucleophilic phenols or phenolate anions that can be set up to react together.[26]

Phenol ethers (PhOR) essentially act as carbon-based nucleophiles (**Scheme 2**). Phenol ether-derived radical cations ($PhOR^{\bullet+}$) can engage, usually most efficiently in intramolecular settings, in either radical (substitution) or ionic reactions with intact phenol ethers or pair up in radical coupling reactions to notably furnish, after one-electron oxidation and/or rearomatizing deprotonation, C–C coupled biaryl products (see Section 3.13.1.3, **Scheme 7**, and Section 3.13.2.2).[9,27,28] Phenols or phenolate anions could in principle also be used to trap phenol ether-derived radical cations, in which case C–O coupled products, including diaryl ethers, could conceivably also be generated.

Moreover, phenols, phenol ethers, and their derivatives bearing an additional hydroxy or alkoxy group in *ortho*- or *para*-positions can be easily oxidized into quinonoid species such as *ortho*- or *para*-quinones, -quinone monoketals and -quinols, which can act as Michael-type electrophiles in coupling reactions with phenols (or phenolate anions) or phenol ethers, or as diene/(hetero)dienophile systems in Diels–Alder-type cyclodimerizations, to generate various types of C–C and C–O coupled products (see Sections 3.13.3.2 and 3.13.6).[4,29]

This apparent mishmash of reacting species that can combine in different ways according to different mechanisms along different reaction pathways does not bode well for the synthetic utility of the oxidative coupling of phenols in general. Early applications were indeed often characterized by the production of complex mixtures from which targeted compounds could only be separated in low yields. Difficulties in mastering the ambident reactivity of a particular phenol and of the reaction (oxidation) intermediates derived therefrom are causes of lack of chemoselectivity in C–C versus C–O bond formation. Furthermore, electron- and charge-delocalizations through the phenyl ring allow for different coupling connections (i.e., *ortho*–*ortho*, *ortho*–*para*, *para*–*para*), which are causes of lack of regioselectivity in C–C bond formation. Moreover, products of an initial coupling event are often themselves phenolic species that can be as, or even sometimes more, easily oxidized than the starting phenols. Over-oxidation is thus another major concern in oxidative phenolic coupling reactions, because it can notably engender oligo/polymerization events.

Additional levels of mechanistic diversity can even be reached with phenols or phenol ethers bearing certain types of substituents, such as alkyl groups that are also susceptible to oxidation at the benzylic position. Benzylic C–H bonds are intrinsically activated by the adjacent phenolic ring, through which the unpaired electron of a benzylic radical or the positive charge of a benzylic carbocation is delocalized and stabilized. Hence, coupling reactions can also occur at benzylic sites (**Scheme 4**). This type of chemistry was, for example, recently used by van der Westhuizen and coworkers in their synthesis of flavanoid procyanidin analogs.[30] The tetramethylated 3-oxocatechin **1** was oxidized with an excess of the one-electron oxidant $AgBF_4$ to furnish the transient benzylic carbocation **2**, which was then trapped by the nucleophilic tetramethylated catechin **3** to afford the procyanidin analog **4** in a relatively decent yield of 44% (**Scheme 5**).[30] This is a rare example of an efficient procyanidin-type direct oxidative coupling of flavanoid species.[20] With phenols bearing alkyl groups at their *ortho*- or *para*-positions, concomitant phenolic and benzylic oxidation leads to the production of the corresponding quinone methides (**Scheme 4**), which can also act as potent (softer) electrophiles or as cycloaddition π-components (see Section 3.13.6). Moreover, phenoxenium cations and *ortho*/*para*-quinones derived from the oxidation of alkylated phenols can suffer the loss of a benzylic proton or tautomerize to furnish reactive quinone methides as well (Scheme 4).[31]



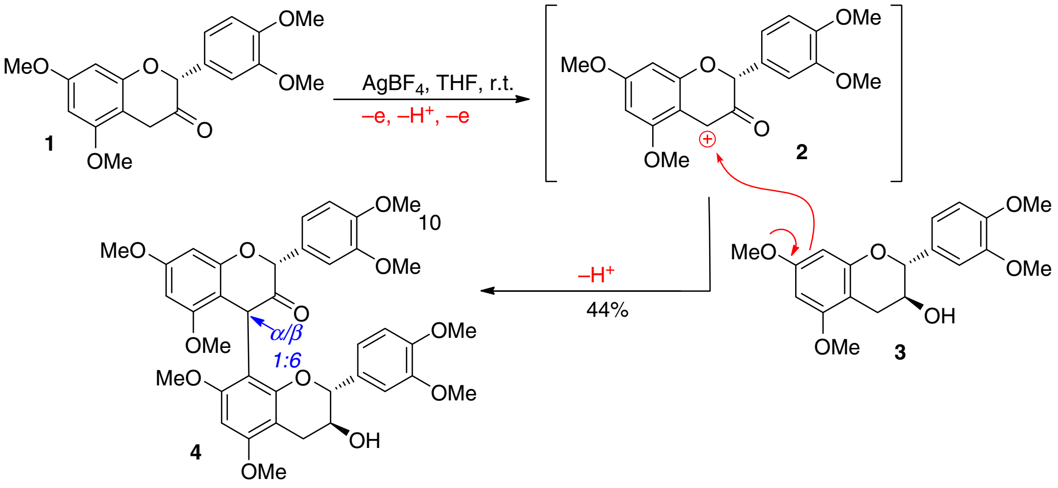
Scheme 4

Finally, phenols bearing substituents with conjugated double bonds oxidatively couple by engaging their side-chain double bonds in additional C–C and C–O coupling modes. Typical examples of such coupling reactions are those occurring with natural stilbenoids (e.g., resveratrol)[32] and *para*-hydroxyphenylpropenoid precursors of lignans and lignin dimers and higher oligo/polymers[33] (see Section 3.13.5).

3.13.1.3 How to Control Oxidative Phenolic Coupling Processes

It is obviously not easy to make general predictions about the outcome of oxidative phenolic coupling reactions. Numerous factors can influence the reaction course that a given phenol will prefer to follow and the manner(s) through which it will be brought to couple along this reaction pathway:

1. The choice of the oxidizing reagent or system is of course primordial, because its capacity to mediate either one- or two-electron transfers can be exploited to control the oxidation of a phenol (PhOH) into either a phenoxy radical ($PhO^•$) or a phenoxenium



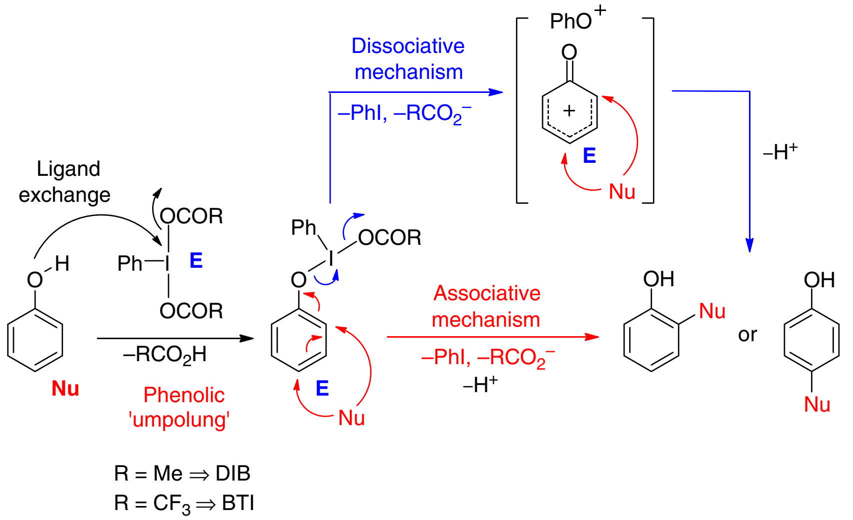
Scheme 5

ion (PhO^+).[13] Typical one-electron oxidants that have regularly met with some success in phenoxy radical coupling reactions are iron(III), silver(I), and copper(II) species such as alkaline $K_3Fe(CN)_6$, $FeCl_3$, Ag_2O, and various Cu(II)-amine complexes.[13,34] Oxidase enzymes such as laccases, tyrosinases and peroxidases,[35,36a] and even cytochrome P-450 enzymes,[36b–d] which all rely on the one-electron transfer capability of transition metals such as iron, copper, or manganese, also belong to this class of oxidants. Typical metal-based oxidants that are capable of converting a phenol into a phenoxenium ion or a metal-bound equivalent thereof are thallium(III) and lead(IV) species, such as $Tl(NO_3)_3$, $Tl(OCOCF_3)_3$, and $Pb(OAc)_4$, Cu(I/II)-amine complexes, notably under autoxidation conditions (i.e., in the presence of oxygen), and perhaps also manganese(III) and vanadium(V) species, such as $Mn(acac)_3$ and VOX_3 (X=Cl, F).[8,11,13,19,37,38] However, the question of whether these metallic oxidants induce a concerted two-electron transfer from phenols or generate phenoxenium ions via two successive one-electron transfers remains open in most cases. Because phenoxy radicals have oxidation potentials generally lower than those of phenols (see Section 3.13.1.2),[13,19] there is no reason for overlooking the possibility left to typical one-electron oxidants, including anodic oxidation,[12] to oxidize initially formed phenoxy radicals into phenoxenium ions. Among the reagents that are today most frequently used to generate phenoxenium ions or equivalents thereof from phenols are hypervalent iodine(III) compounds, such as (diacetoxyiodo)benzene (DIB) and [bis(trifluoroacetoxy)iodo]benzene (BTI).[39] Like a metallic center of a typical metal-based two-electron oxidant, the iodine(III) atom of these reagents act as an electrophilic center in a ligand exchange step with the nucleophilic phenolic substrate. The resulting transient phenoxyiodanyl species can dissociate and release a phenoxenium ion as a consequence of the two-electron reduction of the iodine(III) center (i.e., dissociative mechanism).[40] This two-electron transfer, which is indeed strongly driven by the facile I(III)→I(I) reduction, can nevertheless also occur concomitantly with the concerted attack of a nucleophile (i.e., associative mechanism),[41] such as another phenol or a phenol ether (**Scheme 6**, see Section 3.13.4). The question of whether such a hypervalent iodine-mediated phenolic 'umpolung' process follows a dissociative or an associative mechanism has fueled several investigations and discussions that globally reached as often the conclusion that it depends on the reaction conditions, the polarity of the solvent, the nature of the iodine(III) ligands as well as that of the starting phenol.[41]

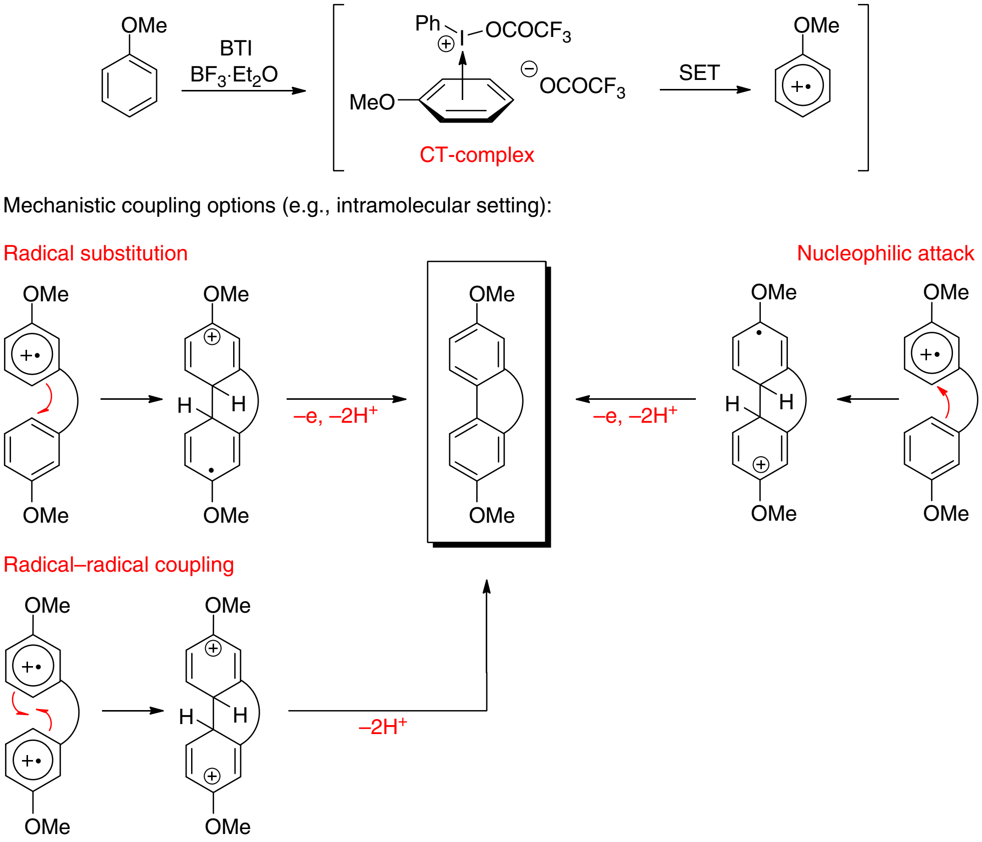
Hypervalent iodine(III) reagents, such as in particular BTI, were also found to be particularly efficient at inducing the oxidative coupling of phenol ethers. Simple alkyl aryl ethers such as phenyl methyl ethers have oxidation potentials generally higher than those of phenols (*ca.* 1.2–1.6 V vs. 1.0–1.4 V).[9,13,19] BTI, usually activated by a Lewis acid such as BF_3 etherate, reacts with a phenol ether by first forming a charge-transfer (CT) complex within which SET occurs from the electron-rich phenol ether moiety to the BTI-derived iodonium center (**Scheme 7**). A radical cation ($PhOR^{\bullet+}$) is thus generated. Kita and coworkers were the first, in the mid-1990s, to utilize BTI in this manner for inducing the coupling of phenol ethers in intramolecular settings.[28,42]

Several other oxidizing systems, such as anodic oxidation, MnO_2, $Mn(acac)_3$, $Pb(OAc)_4$, VOX_3 (X=Cl, F), and $Tl(OCOCF_3)_3$, had been used earlier, often in the presence of Lewis or Brønsted acids, to promote SET from simple phenol ethers.[9,27,37a,43] VOF_3, $Pb(OAc)_4$, and $Tl(OCOCF_3)_3$, notably in the presence of BF_3 etherate or trifluoroacetic acid (TFA), are the metal-based reagents that usually give the best results in phenol ether coupling reactions.[9,43]

2. The protonation state of the starting phenol is also of the highest importance. In the absence of a base, the one-electron oxidation of a phenol (PhOH) first gives a highly acidic radical cation ($PhOH^{\bullet+}$) that rapidly deprotonates into a neutral phenoxy radical ($PhO^\bullet$). Because phenoxy radicals have oxidation potentials lower than those of phenols (see Section 3.13.1.2),[13,19] the system used to oxidize the starting phenol should also be capable of subsequently promoting a second SET to convert $PhO^\bullet$ into a phenoxenium cation (PhO^+). In the presence of an appropriate base, the starting PhOH is first converted into a phenolate anion (PhO^-). Because phenolate anions have oxidation potentials significantly lower than those of



Scheme 6

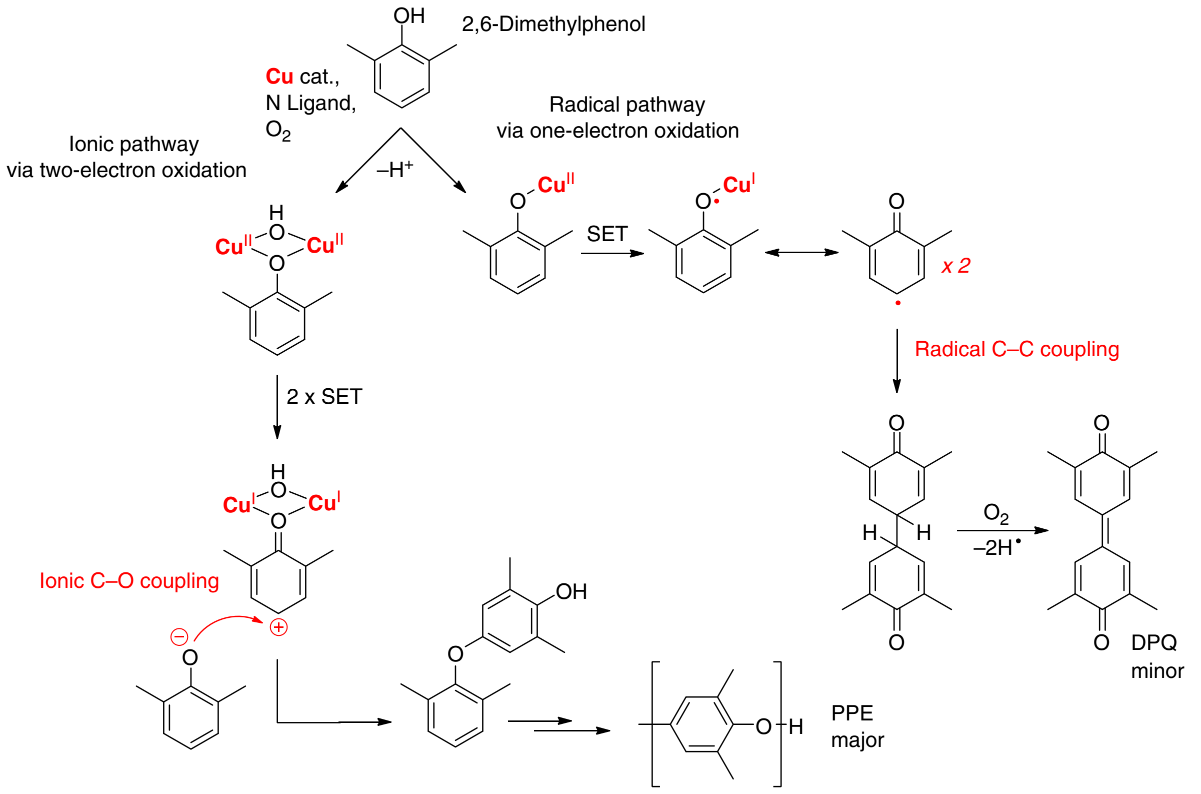


Scheme 7

phenoxy radicals (approximately from −0.6 V to +0.3 V for PhO^- vs. 0.7–0.8 V for $\mathrm{PhO}^{\bullet}$),[13,19] their oxidation could be stopped at the $\mathrm{PhO}^{\bullet}$ stage using an oxidant with the appropriate reduction potential. In this context, the electrochemical anodic oxidation offers an undeniable advantage, because the electrode potential can be tuned at will.[9,13,19] Nevertheless, an adequate choice of a chemical oxidant used under appropriate reaction conditions should, in principle, favor the selective oxidation of a phenol (PhOH) into either PhO^+ (using a stronger oxidant in a neutral to weakly acidic medium) or $\mathrm{PhO}^{\bullet}$ (using a weaker oxidant in a sufficiently basic medium).[13,19]

3. All physicochemical parameters of oxidative coupling reactions of phenols or phenol ethers, besides the aforementioned addition (or not) of a base in the reaction medium, can influence the mechanistic pathway(s) followed by the reaction, and hence affect the product distribution. In this respect, the oxidative coupling of phenols or phenol ethers is no different from any other sort of chemical reaction. The type of solvent used, whether it is more or less polar and coordinating, protic or aprotic, more or less basic or acidic, can have a significant impact on the reactivity of the starting phenol or its phenolate anion and/or on the stability of oxidized phenolic intermediates, especially those with a pronounced ionic character such as phenoxenium cations (PhO^+) and radical cations ($PhOR^{\bullet+}$). The concentrations of the reacting phenolic species in a given solvent constitute another useful leverage to control the reaction outcome. A higher dilution of a starting phenol can be applied to limit the extent of oligomerization events, even though it generally slows down the reaction rate. A higher concentration may instead be preferred to facilitate contact between reacting phenolic species, and furthermore, to help the formation of π-complex intermediates that can adopt configurations (i.e., orientation of the two reacting phenolic species with respect to one another within the complex) spatially favoring a mode of coupling over another in terms of both chemoselectivity (C–C vs. C–O) and regioselectivity.[29h,44] The order and rate of addition of the starting phenols and the oxidizing reagent are experimental factors that can be varied to modulate the relative concentration and respective stoichiometry of the reacting species as the reaction progresses. The application of such experimental techniques can be helpful when cross-coupling (as opposed to dimerization) of different phenols with different oxidation potentials is desired, in which case solutions of the phenol with the lower potential (i.e., the more reactive one) and of an appropriate oxidant capable of oxidizing both phenols should be slowly added to a solution of the less reactive phenol, hence present in large excess at the onset of the reaction.[29h,44a] Finally, the temperature at which the reaction is run is another influencing factor that can notably also impact the chemo- and regioselectivities of a coupling reaction. At a lower temperature under kinetically controlled conditions, the distribution of C–C and C–O coupled products should tend to reflect the ease of formation of reaction intermediates, whereas the same reaction run at a higher temperature might differently lead to thermodynamically preferred coupled products.[45]
4. The structure of the starting phenols or phenol ethers, however and unarguably, remains the factor that should be first analyzed before planning their oxidative coupling. The general chemical reactivity criteria that are inherent in the phenol function should be borne in mind. The acidity of the phenolic O–H bond, the ambident nucleophilicity of phenols and their phenolate anions,[46] the oxidation potential of phenols, phenolate anions, and phenol ethers, together with the phenolic O–H BDE and/or their IP, the resonance stabilization of phenolate anions and oxidized intermediates (PhO^-, $PhO^\bullet$, PhO^+, $PhOR^{\bullet+}$), the relative contribution of each canonical form of these charge- and/or electron-delocalized resonance hybrids are criteria that are all relevant to the manner(s) through which phenols or phenol ethers behave under oxidative coupling conditions. All of these chemical properties can be drastically modulated, often even out of the typical modulation range of the simplest phenols and phenol ethers, by the presence of substituents according to their electronic effects, steric demand, and positioning on the phenolic ring.[20–22]

It is thus, for example, difficult to ascertain that a delocalized dipolar phenoxy radical $PhO^\bullet$, which is typically characterized by a higher electron density on its oxygen atom, is more inclined to participate in C–O bond-forming radical coupling reactions, as proposed early on by Waters.[18] This is in fact rarely the case, as most phenolic radical coupling reactions lead to C–C coupled products. The steric demand of substituents such as alkyl groups at different key positions on the phenolic ring is sufficient to force phenoxy radicals to pair up in either C–C or C–O modes, quasi-independently from the influence of the electron-density distribution in $PhO^\bullet$.[13,44b] The presence of electronegative *ortho*-positioned halogen atoms (F or Cl) has been besides shown to significantly favor the formation of C–O coupled products (see Section 3.13.3.1).[47] However, phenoxenium ions (PhO^+) are commonly viewed as carbon-based electrophiles, because their positive charge is expected to reside mainly on ring carbon centers rather than on the electronegative oxygen atom. They would constitute the most likely and appropriate intermediates toward a preferred formation of C–C coupled products by reacting with phenols (acting as carbon-based nucleophiles) in an electrophilic aromatic substitution fashion under acidic conditions.[18,26a,b] However, the presence of a strongly electron-withdrawing group, such as a *para*-positioned nitro group, on PhO^+ significantly destabilizes the delocalization of the positive charge within the phenyl ring to the extent that the formation of C–O coupled products becomes major on reaction with a carbon-based nucleophile, such as the methyl phenyl ether anisole.[26a] Moreover, the quasi-exclusive formation of C–O coupled products on copper-catalyzed aerobic oxidation of 2,6-dimethylphenol has been shown by calculations to result from the attack of 2,6-dimethylphenol (acting as an oxygen-based nucleophile) onto the PhO^+ derived from it via a double SET within a PhO^--bridged dinuclear Cu(II) species (thus formally acting as a two-electron oxidant).[26c] This copper-catalyzed oxidation of 2,6-dimethylphenol, in the presence of a nitrogen-based copper ligand (amine) and molecular oxygen (O_2), is the mode of production of the C–O coupled poly(2,6-dimethylphenylene ether) (PPE) polymer, a valuable industrial thermoplastic. The question of whether this polymerization reaction follows an ionic or a radical coupling pathway has been and still is a source of opposing opinions in the literature. Gamez and coworkers recently summarized the last five decades of mechanistic studies on this polymerization reaction and concluded from the available experimental and theoretical data mostly in favor of the ionic pathway implying a passage via a PhO^+-generating dinuclear Cu(II) species (Scheme 8).[26d] The intervention of a PhO^--coordinated mononuclear copper alternative would instead produce a phenoxy radical ($PhO^\bullet$) that would lead via radical pairing to the corresponding C–C coupled diphenoquinone (DPQ), which is usually observed as a minor by-product in this oxidative phenolic polymerization process (Scheme 8). The presence of *ortho*-substituents larger than methyl groups on the starting phenol is known to favor the formation of DPQ products, probably because the added steric bulk around the phenolate oxygen center diminishes its nucleophilic character and blocks the assembly of any PhO^--bridged dinuclear copper species (see Section 3.13.2.1.1, Scheme 11).



Scheme 8

Wherever the mechanistic truth lies, the above case exemplifies the fact that the structure of a given phenol and the capacity of a given oxidant to act as a one- and/or two-electron transfer agent can constitute interdependent factors affecting the type of oxidized phenolic species that can be generated and their mode of coupling. Furthermore, whichever type of (oxidized) phenolic intermediate is involved, whichever mode of coupling may be preferred in intermolecular settings, molecular constraints, and relative spatial orientations of reacting centers in intramolecular settings can force coupling reactions to adopt different preferences.

The take-home message at this point is that oxidative phenolic coupling can occur between two unsubstituted ring carbons, leading to biaryl compounds, or between an unsubstituted ring carbon and a phenolic oxygen atom, leading to diaryl ethers, but that it can also occur at substituted ring carbons, leading to both C–C and C–O coupled cyclohexadienone compounds, or involve conjugated side-chain carbon centers that can either couple together or with ring carbons or the phenolic oxygen of another phenol, leading to various possible C–C and C–O coupled products. Moreover, under oxidative conditions, phenols can also be oxidized into *ortho*- or *para*-quinones, quinols, quinone ketals, quinone methides that can react either together or with unoxidized phenolic species, again leading to various possible C–C and C–O coupled products. So, there is a fortiori no unique answer to the question of how to control such mechanistically versatile and capricious coupling processes.

These introductory sections can be concluded only by stating that all options are conceivable and possible. Each envisaged oxidative coupling of phenols and/or phenol ethers should be carefully designed, even though the trial-and-error method still today remains a valid initial approach and may yet constitute a source of new fundamental insights into the mechanistic complexity of this reaction class. Optimization of yields and selectivities is largely still accomplished on a case-by-case basis. Nevertheless, considerable progress has been made toward the mastering of this close to a century-and-a-half-old reaction, especially over the past 30 years or so, both in terms of the understanding of the mechanisms at play and of applications in synthetic organic chemistry. If the oxidative coupling of phenols was for a long time viewed only as a nonselective and low-yielding reaction worthy of being studied only because of its connections with the biosynthesis of many natural products, this is not the case anymore. Numerous methods have been either revisited or devised *de novo* to solve issues of chemo- and regio-selectivities, as well as those of stereoselectivity that notably concern the construction of C–C coupled biaryl compounds. The content of the following sections, far from being exhaustive, highlights, to the authors' opinion, some of the most enlightening and successful achievements in the field over the past 20 years or so, and should attest to the continued relevance of this reaction and its adaptations in modern organic synthesis.

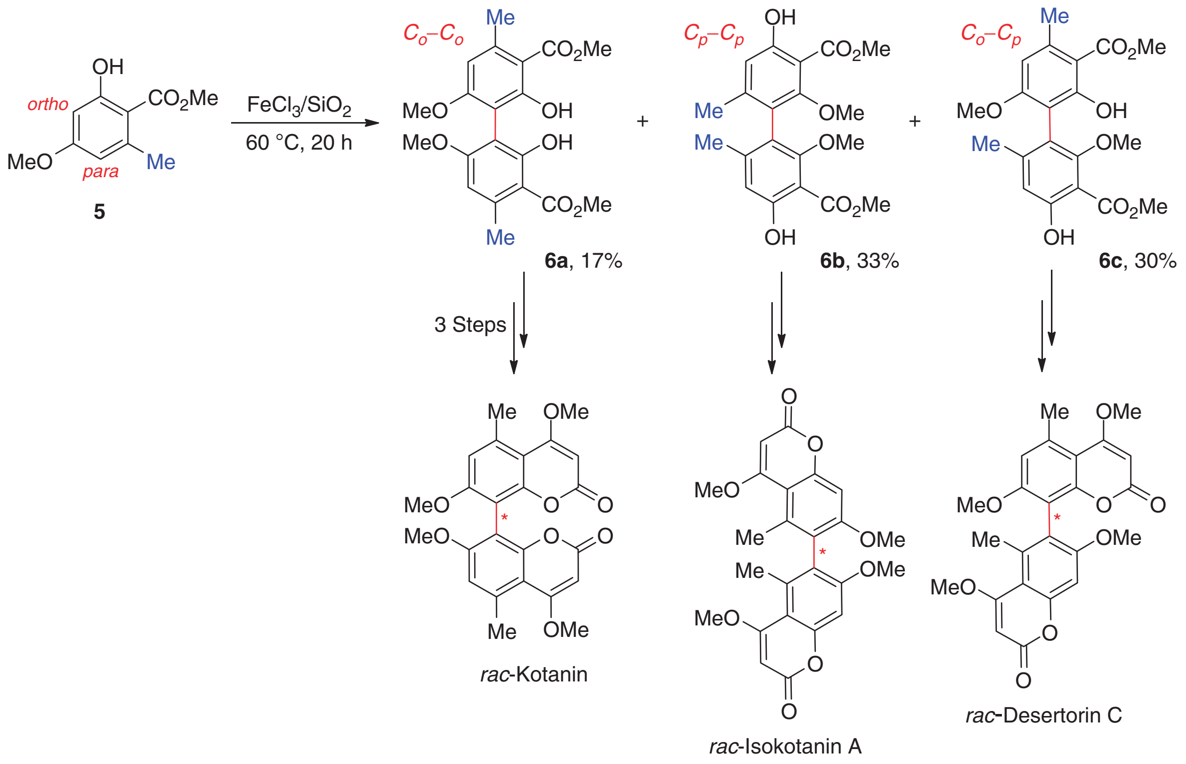
3.13.2 Synthesis of Oxygenated Biaryls

3.13.2.1 Via Oxidative Coupling of Phenols

The oxidative coupling of phenols offers, in many cases, an efficient means to access hydroxylated biaryl frameworks, and it is particularly well suited to the synthesis of natural biaryls that are biosynthetically elaborated by such a coupling reaction.[6,13,48] However, as discussed in the introduction, this process is highly sensitive to both the nature of the phenolic substrate and reaction conditions. Except in the cases of intramolecular coupling or intermolecular coupling of phenols having one or two of their *ortho*/*para*-positions substituted, the coupling process often suffers from moderate chemo- and regioselectivities and usually gives mixtures of various dimers, oligomers, as well as quinones. Numerous coupling methods relying on a large palette of classical metallic or enzymatic oxidizing systems, as well as more unusual reagents such as, recently, sodium hypochlorite (NaOCl),[49] have been described to successfully produce biaryl compounds from phenols (including naphthols). Most of these methods that generally employ an excess of the oxidizing reagent in solution have evolved over the last few years to greener catalytic processes using heterogeneous catalytic systems with molecular oxygen as the sole oxidant.[50] In many cases, these catalytic processes have been found to be faster and more efficient than those relying on the use of classical oxidizing reagents. A survey of the literature shows that all possible C–O and C–C coupled species can be obtained with a reasonable level of chemo- and regioselectivities, which are generally highly dependent on the steric and electronic effects of the substituent(s) of the starting phenols. The reports that are highlighted below constitute a selection of examples of inter- and intramolecular oxidative coupling and cross-coupling of phenols leading to C–C coupled biaryl products.

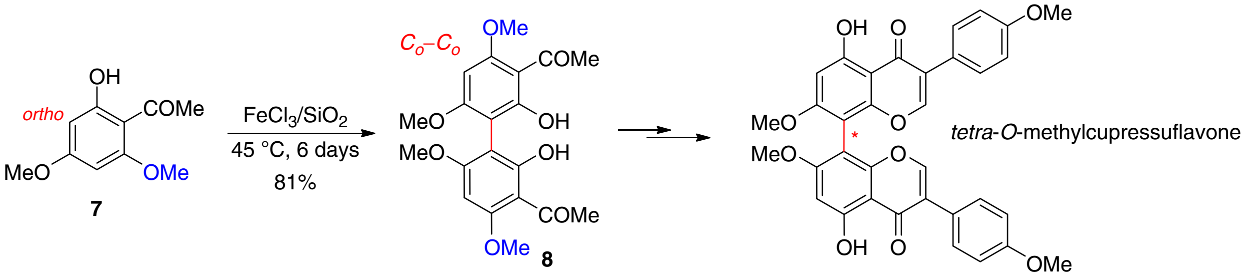
3.13.2.1.1 Regioselective phenolic biaryl coupling

Controlling the regioselectivity of C–C coupling of oxidized phenols is not a trivial challenge, because it is highly substrate-dependent and notably influenced by the presence of substituents that can fortunately sometimes favor or block but unfortunately also often differentiate available reacting centers with consequent formation of product mixtures. Certain phenolic substrates are just not appropriately substituted to engender coupling in a regioselective manner. A recent illustration of this issue can be found in the work of Müller and coworkers, who reported the oxidative coupling of methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**5**) using ferric chloride adsorbed on silica gel (SiO_2).[51] Three regioisomeric dimeric orsellinates **6a–c**, respectively resulting from C_{ortho}–C_{ortho}, C_{para}–C_{para}, and C_{ortho}–C_{para} coupling of the phenoxy radical derived from **5**, were obtained in 17, 33, and 30% yields (Scheme 9).[51] This lack of selectivity was nevertheless advantageously exploited by the authors, because each dimeric orsellinate was then further elaborated via the same three-step procedure to complete the synthesis of the fungal atropoisomeric dimeric coumarins (±)-kotanin, (±)-isokotanin A, and (±)-desertorin C (Scheme 9).[51a]



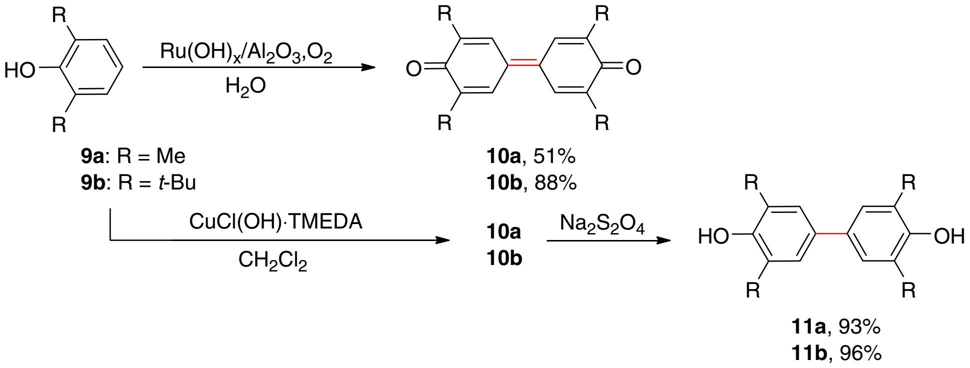
Scheme 9

The lack of selectivity observed in the phenolic oxidation of **5** can be attributed to the poor electron-donating capacity of its *meta*-methyl group. A stronger electron-donating substituent such as a methoxy group at the same position induces a fully regioselective C_{ortho}–C_{ortho} coupling (Scheme 10), as described by Harada and coworkers who converted the phenolic ketone **7** into the biaryl **8** in 81% yield using the same solid-state iron(III)-mediated coupling procedure in the context of their synthesis of the naturally occurring tetramethylated biflavone cupressuflavone.[52]



Scheme 10

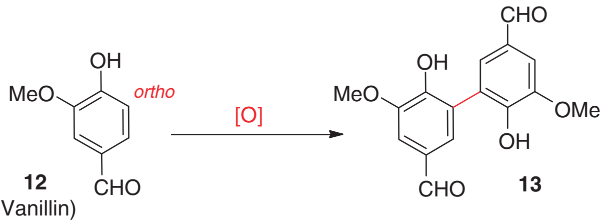
Both the efficiency and the regioselectivity of the coupling process can of course be greatly improved when the two *ortho*-positions of a phenol unit are substituted. Thus, 2,6-dialkylated phenols can be forced to preferentially couple at their *para*-positions. As discussed above (see Section 3.13.1.3, Scheme 8), the copper-catalyzed autoxidation of such phenols usually leads preferentially to C–O coupled products. Using a supported ruthenium catalyst Ru(OH)x/Al_2O_3 and O_2 in water, 2,6-dimethylphenol (**9a**) was, however, converted into the C–C coupled DPQ **10a** in 51% yield. As expected, the higher steric demand of *t*-butyl groups imposes even stronger chemo- and regioselective preferences in favor of the formation of the C_{para}–C_{para} coupled DPQ **10b** (Scheme 11).[50f] Besides, catalysis of the oxidative coupling of both **9a** and **9b** with Koga's copper–amine complex CuCl(OH)·TMEDA (tetramethylethylenediamine), followed by a reductive workup using sodium dithionite ($Na_2S_2O_4$), has been reported to furnish the biphenols **11a** and **11b**, respectively, in high yields.[53a,c,d] The λ^3-iodane DIB reagent has also recently been shown to selectively produce the C_{para}–C_{para} coupled products **10a** and **11a** via a proposed radical pairing pathway, the use of a large excess of **9a** enabling the complete conversion of **10a** into **11a** through comproportionation.[53b]



Scheme 11

Numerous *para*-substituted phenols can be efficiently converted into their biarylic dimers via oxidative C_{ortho}–C_{ortho} coupling (see also Section 3.13.3.1). For example, vanillin (**12**) has often been used as a phenol model to evaluate the performances of various oxidizing systems. Some representative examples of the oxidative coupling of vanillin (**12**) into the C_{ortho}–C_{ortho} coupled biaryl **13** are shown in Table 1. Thus, vanillin (**12**) can be enzymatically converted into dehydrodivanillin (**13**) in quantitative yield using horseradish peroxidase (HRP) in the presence of hydrogen peroxide (H_2O_2).[54] This biocatalytic one-electron oxidizing system also turned out to be the best system for the preparation of biarylic dityrosines from tyrosine derivatives in good to very high yields.[19] The chemo and regiochemical preferences thus observed in these radical pairing reactions in favor of the C_{ortho}–C_{ortho} coupling over the C_{ortho}–O coupling alternative, which would have led to isodityrosine diaryl ethers, was tentatively attributed to some directing complex associations of tyrosyl monomers with each other and/or with the HRP enzyme.[19] The fact that these HRP-mediated coupling selectivities are also highly pH-dependent and can be modulated by the introduction of halogen *ortho*-substituents are discussed later on (see Section 3.13.3.1). Peroxidase-catalyzed C_{ortho}–C_{ortho} coupling of 2-methoxyphenols can also be performed on solid-supported phenols.[55a] Laccases have also been used recently to catalyze the formation of biaryls in yields of approximately 80% from *para*-substituted phenolic salicylic esters in the presence of air (O_2).[55b]

Table 1



[O]	Yield of **13** (%)	References
HRP–H_2O_2	100	54
$FeSO_4$, $Na_2S_2O_8$, H_2O	95	56
Anodic oxidation, CH_3CN, $NaClO_4$, Et_4NOH	65	57
DIB, CH_3CN	52	58

The one-electron oxidation of vanillin can also be efficiently mediated by more conventional oxidants such as iron sulfate in the presence of aqueous sodium peroxydisulfate, which was recently reported to afford **13** in high yield as well (Table 1).[56] Anodic oxidation is another classical option to dehydrodimerize vanillin into **13**. The anodic dimerization of vanillin at constant potential (0.25 V/SCE) using platinum electrodes in acetonitrile gave **13** in 65% yield (Table 1).[57] Two-electron oxidation approaches can also be relied on to generate **13** from vanillin. For example, Stevens and coworkers used the λ^3-iodane DIB reagent (0.5 equivalent) in acetonitrile to convert vanillin into **13** in 52% yield (Table 1).[58] The authors mentioned that this oxidative coupling is limited to *para*-substituted 2-alkoxyphenols, although the reaction fails with 2-methoxy-4-nitrophenol, probably as a consequence of the strong electron-withdrawing effect of the nitro group that prevents the phenol to attack DIB for the initial ligand exchange step (see Section 3.13.1.3, Scheme 6). Also interestingly, all observed coupled products exclusively resulted from the C_{ortho}–C_{ortho} coupling mode, and no *para*-coupling occurred when *ortho*-vanillin (i.e., 2-hydroxy-3-methoxybenzaldehyde) was similarly treated with DIB.[58]

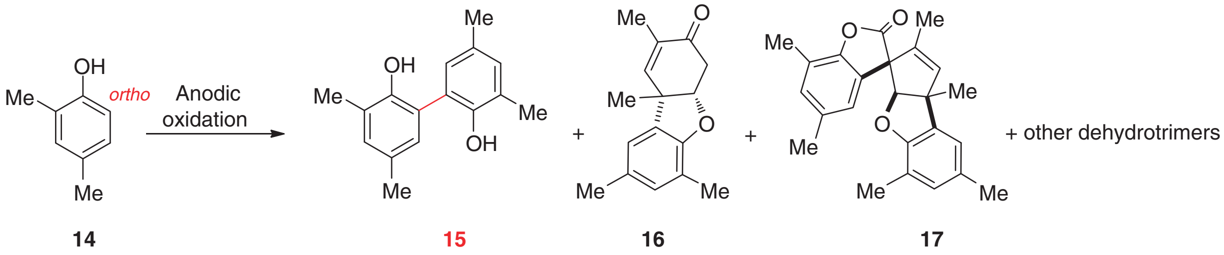
Para-methylated phenols such as *para*-cresol or 2,4-dimethylphenol (**14**) are usually poor substrates for regioselective C_{ortho}–C_{ortho} coupling. In general, biphenols such as **15** are obtained but together with Pummerer's ketones, such as **16**, which result from preferential C_{ortho}–C_{para} coupling with subsequent conjugate addition, and dehydrotrimeric derivatives such as the pentacyclic compound **17** (Scheme 12). Waldvogel and coworkers recently found a solution to this problem by relying on anodic oxidation using boron-doped diamond (BDD) electrodes under solvent-free conditions.[59a] In contrast to the use of other electrode materials such as platinum, these BDD electrodes resulted in an unusual highly selective formation of the C_{ortho}–C_{ortho} coupled biphenol **15** in 56% yield.[59a] However, other phenols gave either no detectable product or ended up in decomposition, but the scope of this electrolytic method relying on the use of BDD anodes was later on significantly improved notably by using fluorinated alcohol mediators. The combination of the use of hexafluoroisopropanol (HFIP) as mediator in the presence of tetraalkylammonium or imidazolium salts as supporting electrolytes allows anodic selective coupling of various phenolic substrates to the corresponding C_{ortho}–C_{ortho} coupled biphenols (**18a–f**) in moderate to good yields (Scheme 12).[59b]

In the same vein, the same authors also developed yet another protocol to overcome the lack of regioselectivity of the oxidative coupling of phenols, this time by relying on a template-directed anodic oxidation based on the use of tetraphenoxyborate intermediates.[59c] Various phenols, including 2,4-dimethylphenol (**14**), were thus anodically coupled to the corresponding C_{ortho}–C_{ortho} coupled biphenols after their elaboration into tetraphenoxyborates. For example, electrolysis of **19**, which was performed in a nondivided standard electrolysis cell equipped with two platinum sheets as anode and cathode, furnished the biphenol **15** in 85% yield after hydrolytic workup (Scheme 13).[59c]

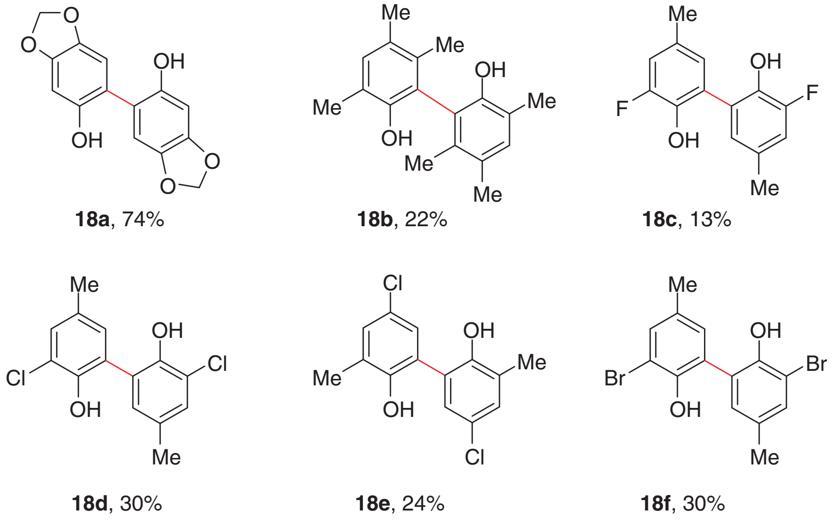
A similar template-directed strategy using a bioinspired dicopper complex was developed by Meyer and coworkers to force the oxidative coupling of *para*-ethylphenol in a C_{ortho}–C_{ortho} mode.[60] The authors suggested that the C_{ortho}–C_{ortho} coupling occurs via a ligand-to-metal charge-transfer excited copper(I) phenoxide state when two *para*-ethylphenol molecules are bound in close proximity within the bimetallic pocket of a highly preorganized dicopper complex **(PhO)$_2$-A′** derived from the starting complex **A** (Scheme 14).[60]

Waldvogel and coworkers also took up the challenge of affecting anodic coupling of phenols at their *meta*-position by using 2-methoxyphenols.[59d] This is of course quite feasible with such phenolic phenol ether hybrid substrates, but such a coupling mode has rarely, if ever, been described. They again relied on the use of BDD anodes to oxidize a series of guaiacol (i.e., 2-methoxyphenols) derivatives, such as **20a–d**, and managed to construct the C_{ortho}–C_{meta} coupled products **21a–c** in rather low but, in some cases, satisfying yields (Scheme 15). The steric demand of the substituent at the *para*-position seems to affect the extent of this atypical regioselectivity, because an increasing bulk at that locus appeared to diminish the capacity of the tested phenols to couple at the adjacent *meta*-position (Scheme 15).[59d]

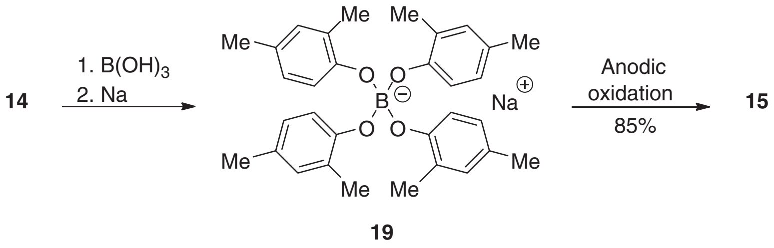
The mode of coupling of guaiacol derivatives was also affected by the presence of additional electron-releasing groups. For example, electrolysis of 2,5-dimethoxyphenol (**23a**) performed with the same BDD anodic protocol produced only the C_{para}–C_{para}



Anode material/conditions	Product ratio: **15** : **16** : **17**
Platinum/MeOH	1 : 11 : 6
BDD/solvent free	18 : 1 : 0



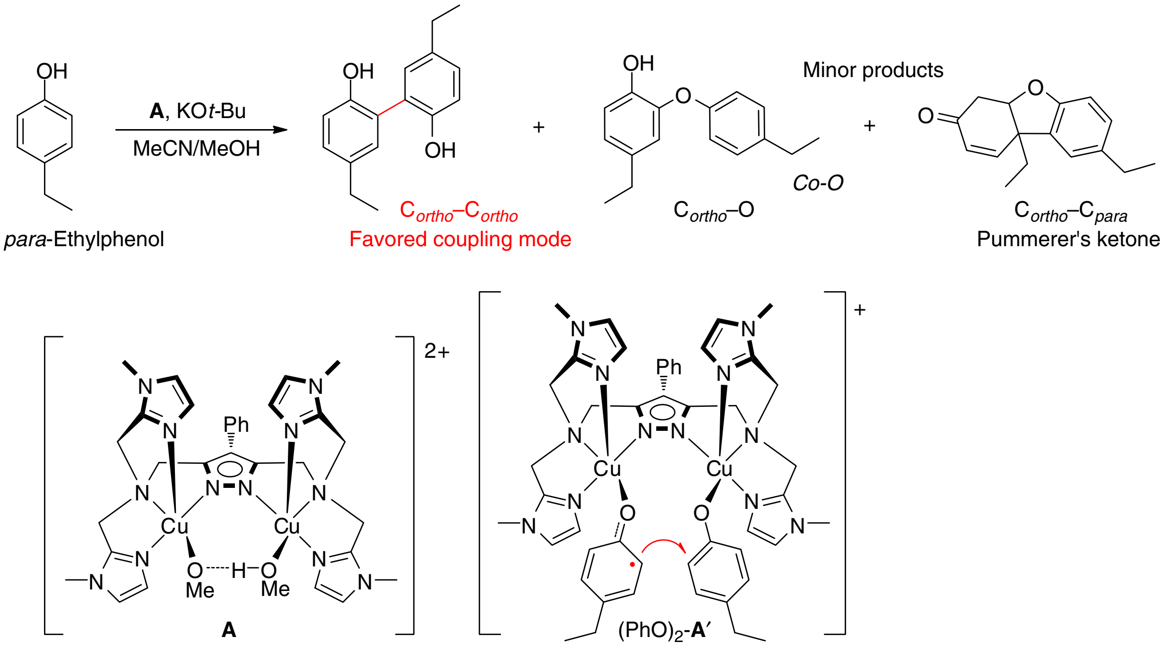
Scheme 12



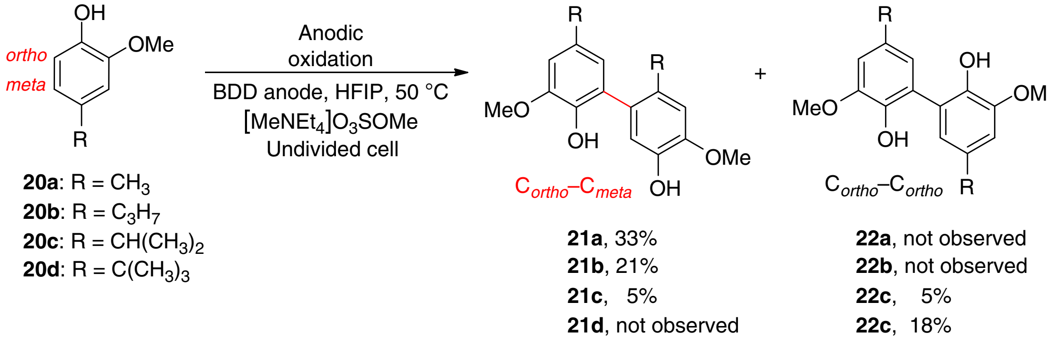
Scheme 13

coupled biphenol **24a** in 83%, and this without overoxidation to the DPQ structure, whereas 2,6-dimethoxyphenol (**23b**) surprisingly and exclusively led to the C_{para}–C_{meta} coupled biphenol **24b** in 44%. Besides, and even more surprisingly, anodic oxidation of 2,4-dimethoxyphenol (**23c**) exclusively generated the previously unknown C_{meta}–C_{meta} coupled biphenol **24c** in 45% (Scheme 16).[59d]

The observation of the C_{para}–C_{meta} coupled biphenol **24b** led Waldvogel and coworkers to suggest that the formation of these dehydrodimers of guaiacol derivatives is not due, at least not exclusively, to radical–radical coupling of electrochemically generated phenoxy radicals ($PhO^{\bullet}$),[59d] for the oxidative coupling of 2,6-disubstituted phenols using metallic oxidants is known to form C_{para}–C_{para} coupled dehydrodimers in high yields under conditions presumably favorable to phenoxy radical pairing (*vide supra*, Scheme 11, and see Section 3.13.1.3, Scheme 8). Waldvogel and coworkers thus proposed that, under the electrochemical conditions they used, a 2-methoxyphenolic substrate is first one-electron oxidized into a phenoxy radical cation ($PhOH^{\bullet+}$), which can easily loose a proton to afford a phenoxy radical ($PhO^{\bullet}$).[59d] This $PhO^{\bullet}$ at the BDD anode would then combine at its *ortho* or *para*-position with another but intact phenol in a radical substitution manner via an attack at the carbon center *para* to the



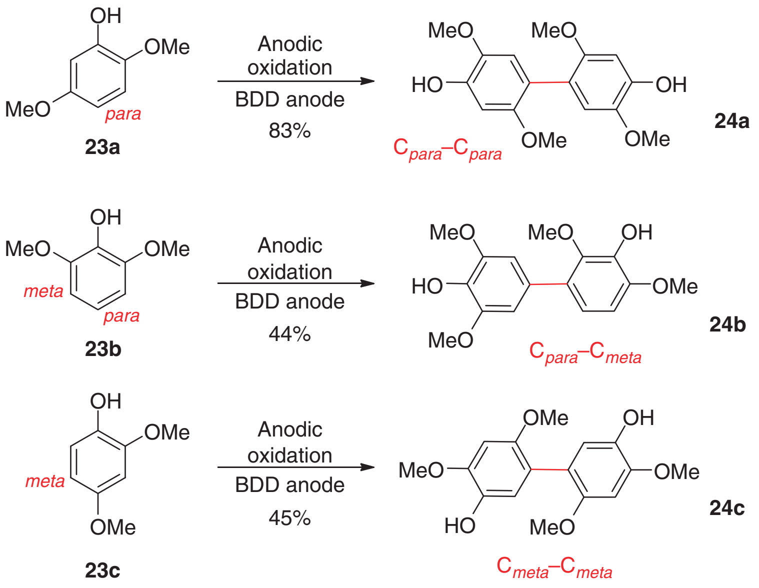
Scheme 14



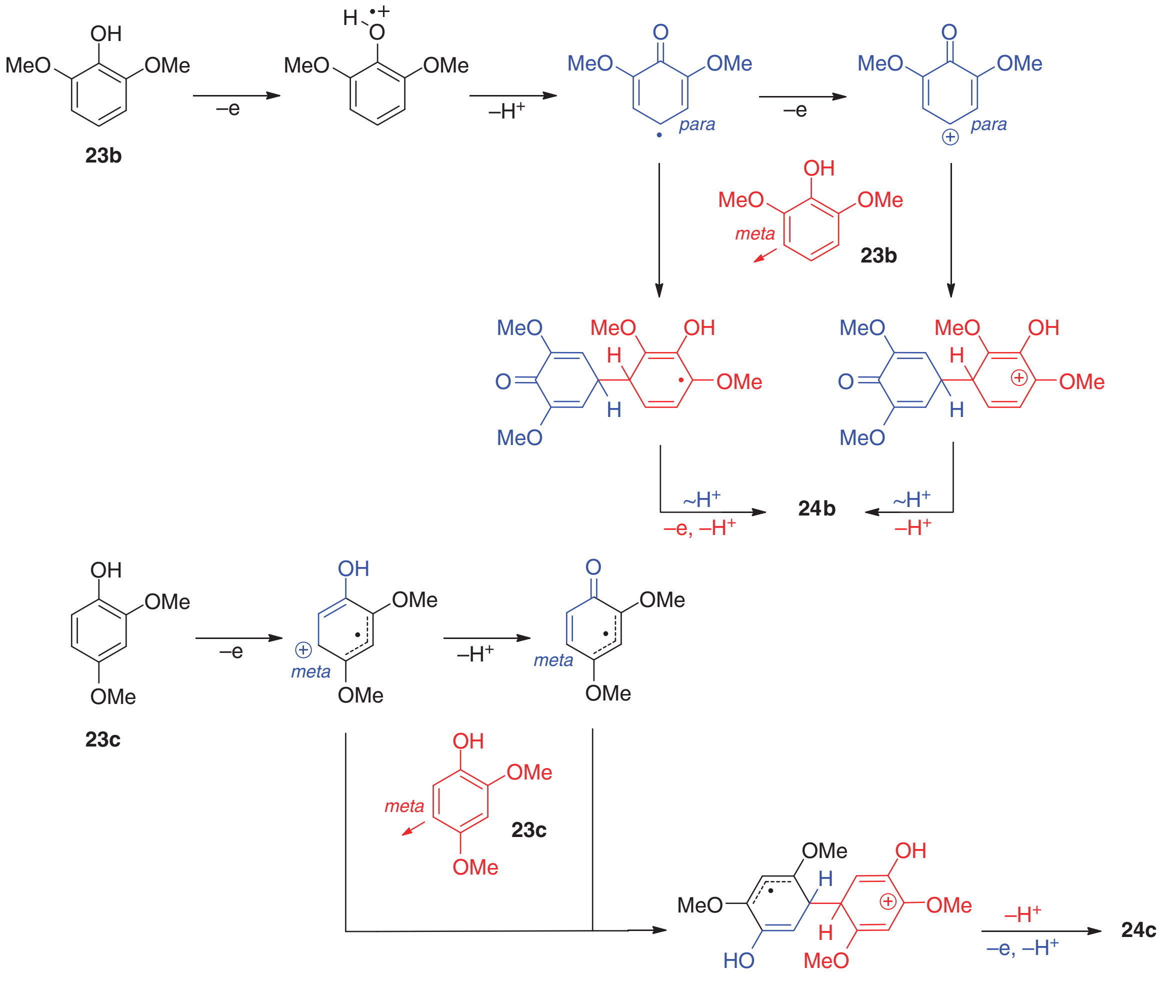
Scheme 15

2-methoxy substituent (and *meta* to the phenolic hydroxy group). A second one-electron oxidation (of the coupled radical intermediate) and a rearomatizing deprotonation would finally lead to some of the observed products. This mechanism can indeed explain the formation of the $C_{ortho/para}$–C_{meta} coupled products **21a–c** and **24b**.[59d] Alternatively, one can also suggest that a second one-electron oxidation of a 2-methoxyphenolic substrate at the BDD anode could generate a phenoxenium cation (PhO^+), which can then be trapped at its *ortho* or *para*-position in an electrophilic substitution manner by an intact phenol expressing, as expected, its nucleophilic character at the carbon center *para* to the 2-methoxy substituent. With substrates **20a–c** and **23b**, this carbon position *meta* to the phenolic hydroxy group is doubly activated by the *ortho*/*para*-directing effect of their alkyl/methoxy substituents. The exclusive formation of the C_{meta}–C_{meta} coupled biphenol **24c** is more intriguing in terms of regioselectivity, although the initially formed $PhOH^{\bullet+}$ derived from **23c** and its corresponding $PhO^{\bullet}$, for which the spin density distribution could be under the influence of the 1,3-dimethoxyallylic unit, should be able to express some electrophilic character at their *meta*-position and thus combined with some intact nucleophilic **23c** at the same more accessible *meta*-position to furnish, after a second one-electron oxidation and rearomatizing deprotonations, the biphenol **24c** (Scheme 17).

In the case of certain naphthols, efficient and regioselective oxidative coupling is known to occur just in the presence of air as oxidant without the need for any special directing device. Wulff and coworkers took advantage of this particularity of the reactivity of naphthols to couple various naphthols, as well as phenanthrols, in their continuous work on the synthesis of vaulted biaryls as chiral ligands for asymmetric synthesis.[61] Interestingly, the oxidative dimerization of 3-phenyl-1-naphthol (**25**) simply induced by melting this naphthol at 190 °C in the presence of air afforded the C_{ortho}–C_{ortho} coupled binaphthol **26a** in 87% yield, whereas the action of ferric chloride on the same naphthol mainly produced the C_{para}–C_{para} coupled binaphthol **26b** without any observation of the C_{ortho}–C_{ortho} coupled regioisomer **26a** (Scheme 18).[61a] No clear-cut rationale was established for this change of

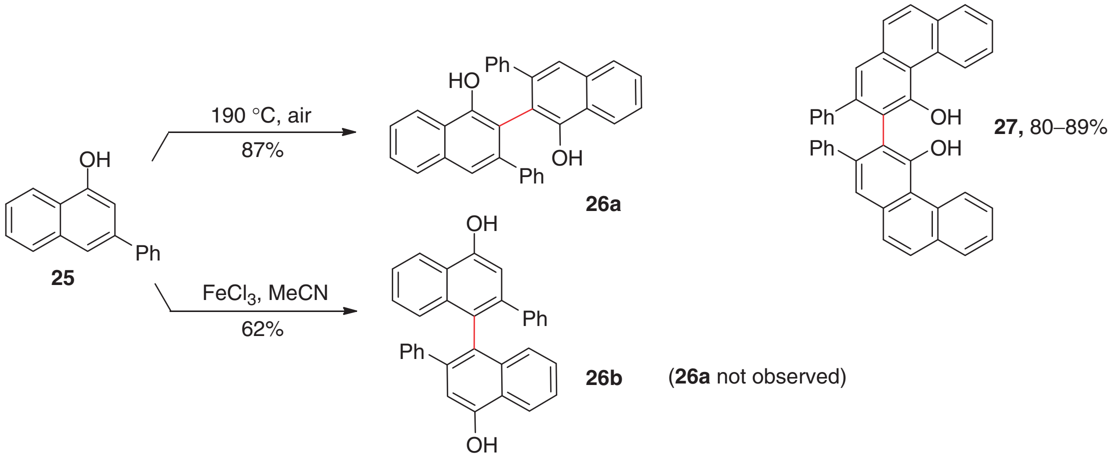


Scheme 16



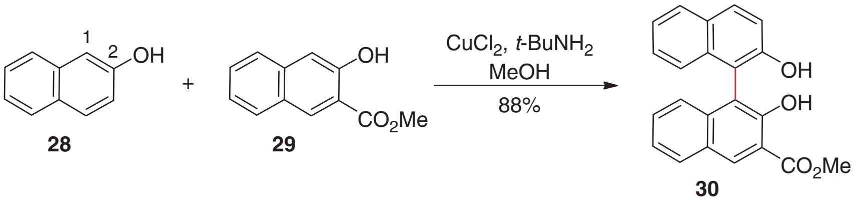
Scheme 17

regioselectivity. Similarly, the air oxidation of the phenanthrol homolog of **25** also gave the C_{ortho}–C_{ortho} coupled product **27** in high yields (Scheme 18), but the use of ferric chloride was in this case found rather inefficient and only led to product mixtures.[61a]



Scheme 18

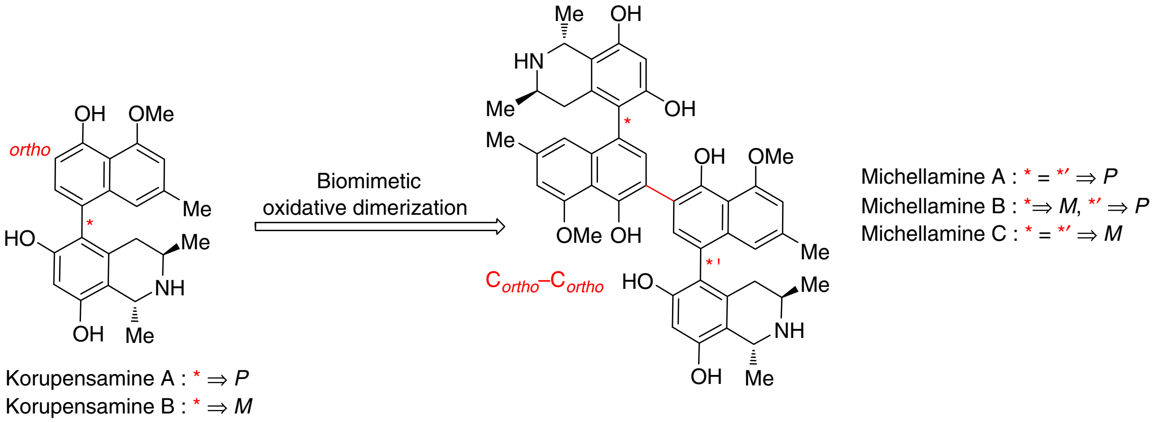
Hovorka and coworkers had earlier reported the Cu(II)-mediated oxidative cross-coupling of two differently substituted 2-naphthols.[62a] For example, 2-naphthols **28** and **29** were cross-coupled using $CuCl_2$ in the presence of a primary amine such as *t*-$BuNH_2$ or $EtNH_2$ in degassed methanol to furnish the binaphthol **30** in 88% yield (Scheme 19).[62a] It was suggested that this process goes through a one-electron oxidation of the more electron-rich naphthol (i.e., **28**) and that the resulting (nucleophilic) naphthoxy radical then attacks, in a radical substitution manner, the naphtholate anion derived from the more electron-deficient naphthol (i.e., **29**), both species being presumably coordinated to Cu. This mechanism was later on refined on the basis of *ab initio* calculations by Kocovsky and coworkers,[62b] who proposed that the high yield of cross-coupling results from a privileged interaction between the low-energy SOMO of the thus-electrophilic naphthoxy radical and the close-in-energy HOMO of the naphtholate anion counterpart, the regiochemical exclusivity observed under such an orbital controlled reaction being in agreement with the fact that the C1 center exhibits the highest orbital coefficient value in both reacting species.[62b]



Scheme 19

Numerous biomimetic syntheses of phenolic natural products have relied on regioselective oxidative coupling reactions. For example, dimerization of korupensamines A and B has been reported by Bringmann and coworkers for the synthesis of michellamines A, B, and C, which are naturally occurring *M*/*P* axially chiral quateraryl compounds known for their antiviral activities against HIV-1 and HIV-2 (Scheme 20).[63]

Direct one-electron oxidations of the unprotected trihydroxylated korupensamines using either Ag_2O, $FeCl_3$, $K_3Fe(CN)_6$, or the organic di-*tert*-butylperoxide (DTBP) oxidant were found inefficient and exclusively led to complex product mixtures. A tactic relying on a preliminary partial protection of the phenolic groups of korupensamines was then implemented to direct the reaction toward the requisite biaryl construction. The tribenzylated korupensamine B derivative *M*-**31** was then oxidized using Ag_2O in the presence of a catalytic amount of triethylamine. The resulting C_{ortho}–C_{ortho} coupled DPQ **32** was then submitted to standard catalytic hydrogenation/hydrogenolysis conditions to furnish michellamine C in 94% yield (Scheme 21). This highly efficient coupling reaction, which presumably involved an aryloxy radical ($ArO^{\bullet}$) intermediate, was also successfully implemented for the synthesis of michellamine A from the corresponding korupensamine A derivative.[63] Hoye and coworkers have also described similar biomimetic approaches to the total syntheses of these dimeric naphthylisoquinoline alkaloids.[64] Bringmann and coworkers also succeeded in controlling the direct oxidative coupling of unprotected korupensamines A and B into michellamines A, B, and C by using a korupensamine-dimerizing enzyme that they isolated from *Ancistrocladus korupensis*.[63a,65] Furthermore, the same authors also developed an alternative biomimetic and preparatively useful version of this direct intermolecular C_{ortho}–C_{ortho}



Scheme 20

coupling using a two-electron oxidant, such as $Pb(OAc)_4$ (LTA) or the λ^3-iodane BTI reagent in the presence of BF_3 etherate, to produce michellamines (**Scheme 21**).[63a,66] Both one- and two-electron oxidative reaction conditions were also successfully applied to the preparation of a variety of dimers of natural and unnatural monomeric naphthylisoquinolines. These studies notably led to the total synthesis of jozimine C, jozipeltine A, pindikamine A, and the C_{para}–C_{para} coupled jozimine D (**Scheme 21**).[63a]

Besides these examples of intermolecular oxidative coupling, intramolecular cases of phenolic coupling reactions have also recently been described as key steps in syntheses of natural products. For example, Tatsuta and coworkers achieved the total synthesis of TMC-66, an endothelin converting enzyme inhibitor, via a challenging intramolecular C_{ortho}–C_{ortho} coupling reaction between two phenolic moieties, each *ortho*-substituted with two different electron-withdrawing groups, to elaborate the benzo[*a*]naphthacenequinone skeleton of TMC-66 from precursor **34**. After testing a variety of known oxidants, only Koga's reagent [CuCl(OH)·TMEDA][53c] was found to be effective, but the desired biaryl product **35** was only obtained in a relatively low yield of approximately 20%.[67] A much higher yield (89%) was obtained by using a variant of Koga's reagent, CuCl (OH)·(*N*-methylimidazole)$_2$ in refluxing DMF (**Scheme 22**).[67]

An interesting example of an intramolecular C_{para}–C_{para} coupling reaction was recently reported by Ley and coworkers,[68] who evidenced the dual oxygenation/dehydrogenation functionality of tyrosinase enzymes in a synthetically valuable transformation by showing that simple *N*-isovanillyltyramine derivatives such as **36** can thus be converted to good yields into the corresponding hydroxylated dibenzoazocanes such as **38** (**Scheme 23**). The tyrosinase is thus capable of first inducing a very specific chemo- and regioselective *ortho*-oxygenation of the monophenolic ring of **36**, which is then followed by an intramolecular oxidative coupling step to deliver **38** in 50% yield.[68] The authors suggested that this second biotransformation presumably operates via an *ortho*-quinone intermediate **37b** (see Section 3.13.6), which would result from enzymatic dehydrogenation of the initially produced catechol **37a** and which would then suffer a rapid nucleophilic 1,4-attack by the 2-methoxyphenol ring (**Scheme 23**).

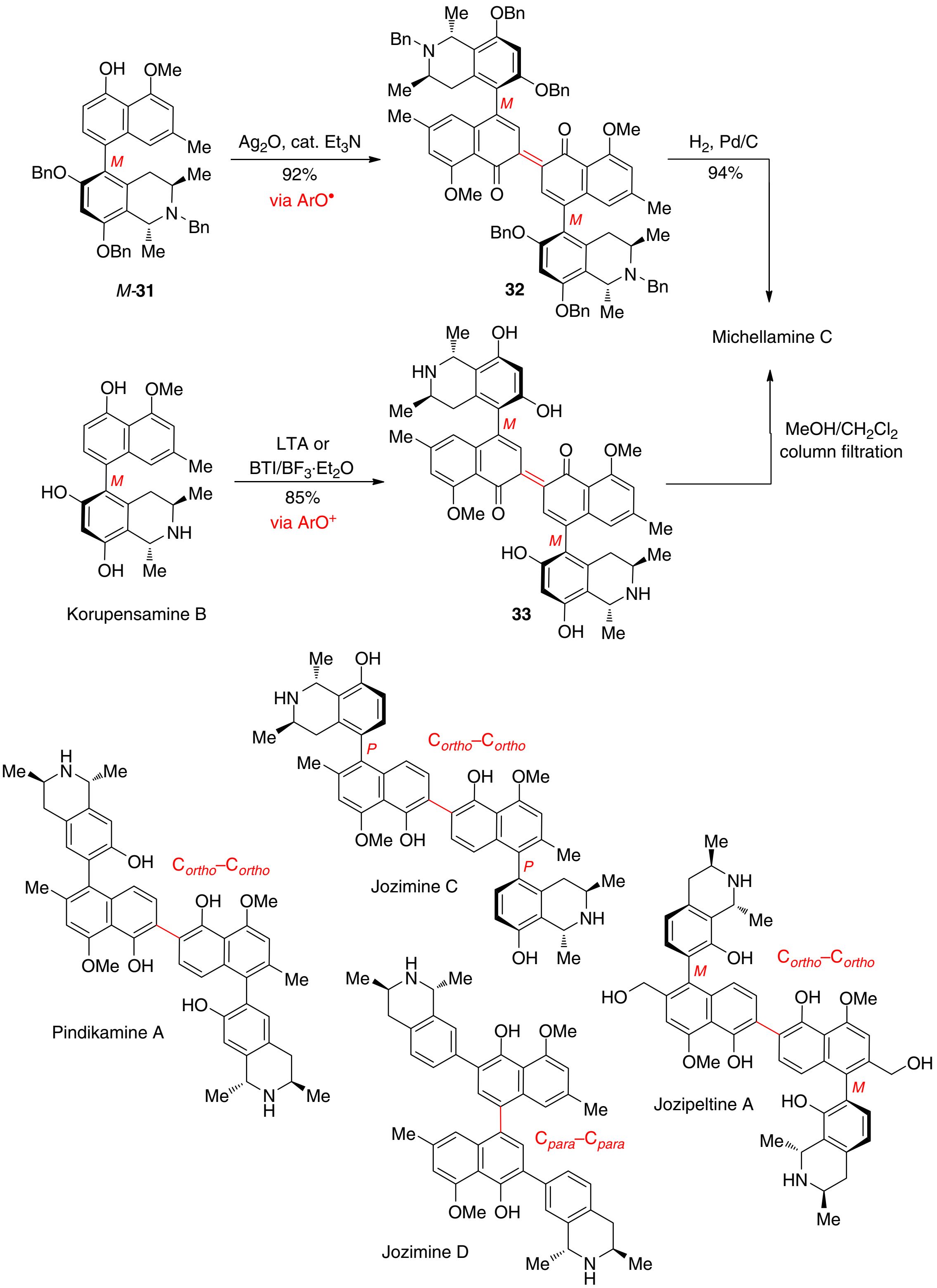
3.13.2.1.2 Stereoselective phenolic biaryl coupling

Significant progress has been made in recent years in efforts to perform phenolic biaryl coupling in a stereocontrolled manner. The two strategies that have been considered to achieve this goal are classically either based on atropodiastereoselective coupling reactions stereocontrolled by either intrinsic chiral moieties or by added artificial chiral auxiliaries, or based on atropoenantioselective coupling reactions using stereocontrolling chiral oxidizing reagents.

3.13.2.1.2.1 Diastereoselective phenolic biaryl coupling

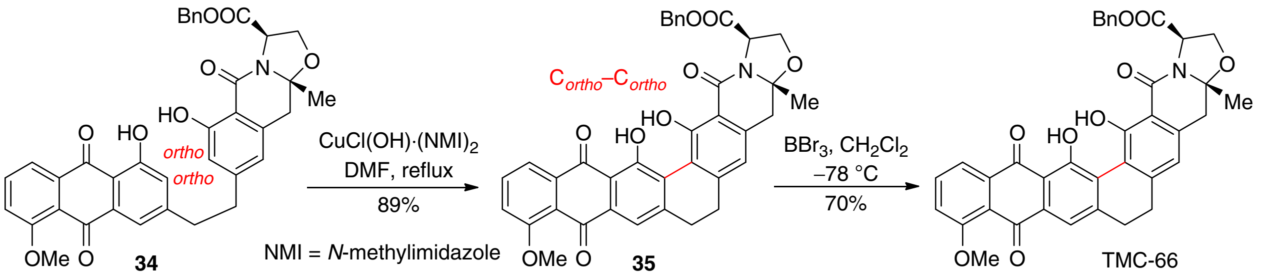
In the case of atropodiastereoselective biaryl coupling reactions of phenols, the first substrate-controlled option based on internal induction of asymmetry concerns phenolic substrates that bear additional stereogenic centers in the proximity of the carbon center(s) to be engaged in the formation of the chiral biaryl axis. For example, Bringmann and coworkers played this option early on in their total synthesis of the mastigophorenes, plant (liverwort) biaryls known for their neurotrophic activities.[69] The herbertenediol monomethyl ether **39** was oxidized with the peroxide DTBP in refluxing chlorobenzene to furnish the C_{ortho}–C_{ortho} coupled biaryl precursors of *P*-mastigophorene A and *M*-mastigophorene B. Unfortunately, after demethylation, the mastigophorenes were obtained in a moderate yield of 28% and with a diastereomeric ratio of only 60:40 (**Scheme 24**).[69] The chiral herbertenediol cyclopentyl moiety, *para*-positioned relatively to the biaryl axis, is most likely too far away to induce any higher control of asymmetry during such an intermolecular oxidative coupling reaction.

Higher diastereomeric excesses are usually obtained when atropodiastereoselective phenolic coupling reactions are intramolecularly performed after having added an artificial chiral unit bridging two molecules of phenolic substrates. Numerous examples of this second substrate-controlled option have been reported. Thus, for example, the asymmetric synthesis of 1,1′-binaphthol derivatives, such as **42**, using a chiral bridge such as the inexpensive 7-deoxycholic acid turned out to be remarkably efficient.[70a] Among the coupling reagents tested, $Mn(acac)_3$ in acetonitrile was found to be the most effective, yielding from **40** the desired

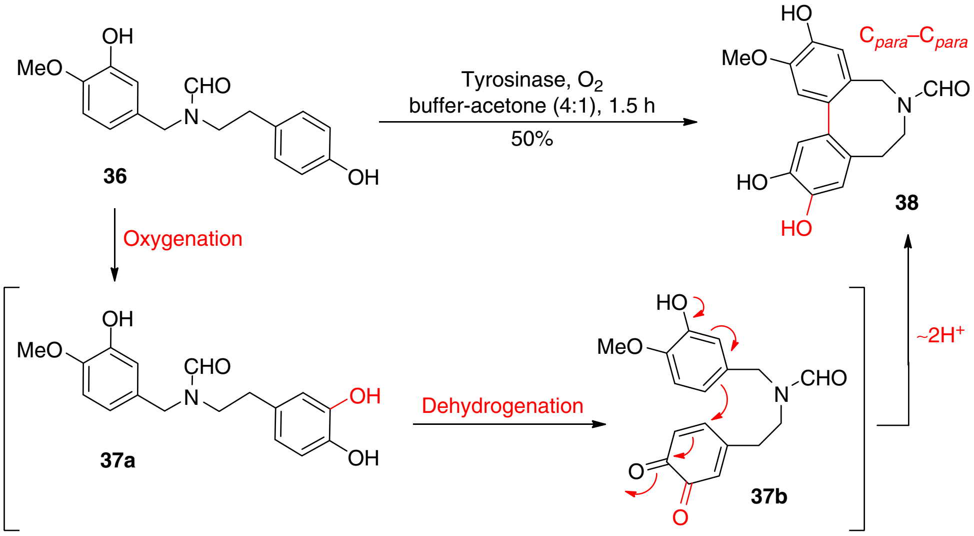


Scheme 21

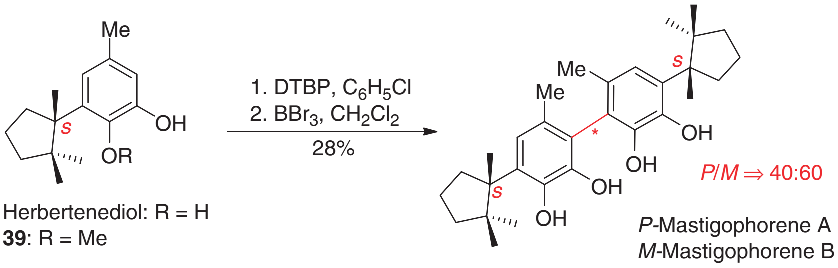
coupled product **41** in 65% yield with a diastereoisomeric excess (*de*) of 65% (Scheme 25), whereas the use of copper–amine complexes such as $CuCl_2$/*t*-$BuNH_2$ or $CuSO_4$/pyridine in MeOH gave poorer *de*s of only 33% and 45%, respectively.[70a] Reductive cleavage of the cholic acid-derived bridging auxiliary with LAH, followed *in situ* by acetylation afforded the enantiomerically enriched *P*-**42** (Scheme 25).[70a]



Scheme 22



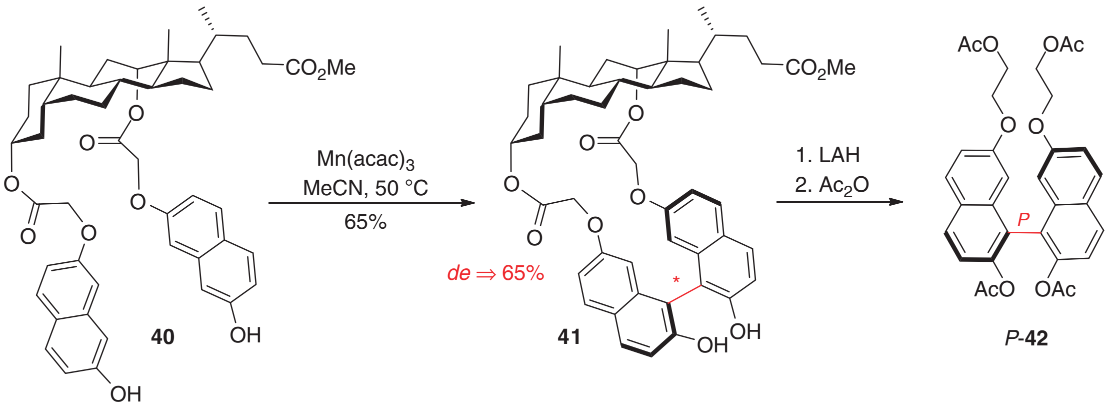
Scheme 23



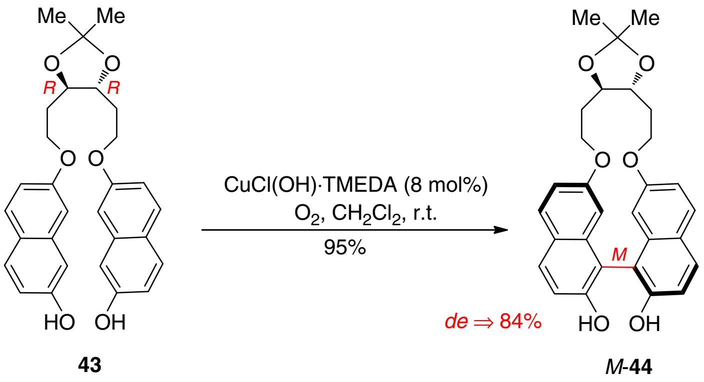
Scheme 24

Relying on the same strategy, Lipshutz and collaborators accomplished a catalytic oxidative intramolecular biaryl coupling of the tethered mono-protected 2,7-dihydroxynaphthalene **43**. In contrast to the case reported by Maitra and Bandyopadhyay,[70a] a copper–amine complex system (Koga's reagent) used here in catalytic amounts in the presence of molecular oxygen was found operational and delivered the desired binaphthol *M*-**44** in 95% yield as a separable 12:1 mixture of diastereomers (Scheme 26).[70b] The use of other oxidizing metallic salts (e.g., Mn(II), Fe(III) salts) required stoichiometric amounts and gave inferior yields of the desired biaryl.[70b]

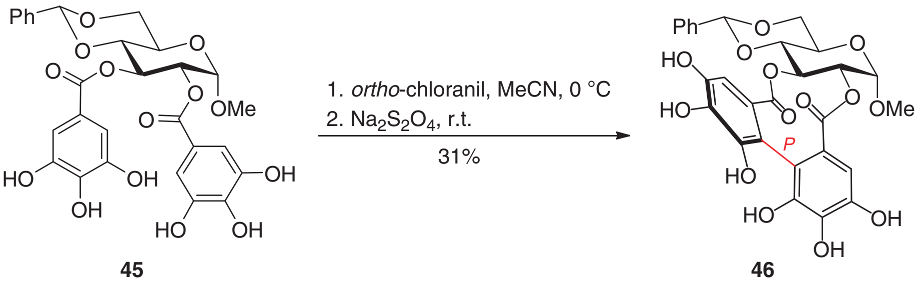
A cyclic glucose derivative can also serve as a chiral bridging template to atroposelectively forge phenolic biaryl bond from two gallic acid ester units.[71a] Feldman and coworkers[71b] had earlier shown that the organic oxidant *ortho*-chloranil is capable of mediating the intermolecular coupling of methyl gallate in Et_2O into a dehydrogenated hexahydroxydiphenoate (HHDP) unit via dimerization of the α-hydroxy *ortho*-quinone initially produced by the action of *ortho*-chloranil on methyl gallate (see Section 3.13.6, Scheme 92). Reduction of this dehydrogenated HHDP species with $Na_2S_2O_4$ afforded dimethyl HHDP in 79% yield.[71b] A similar but intramolecular oxidative coupling reaction performed on the 2,3-*O*-bis-galloylated glucopyranoside **45** furnished the biaryl product *P*-**46** in 31% yield as a sole atropoisomer (Scheme 27).[71a]



Scheme 25



Scheme 26



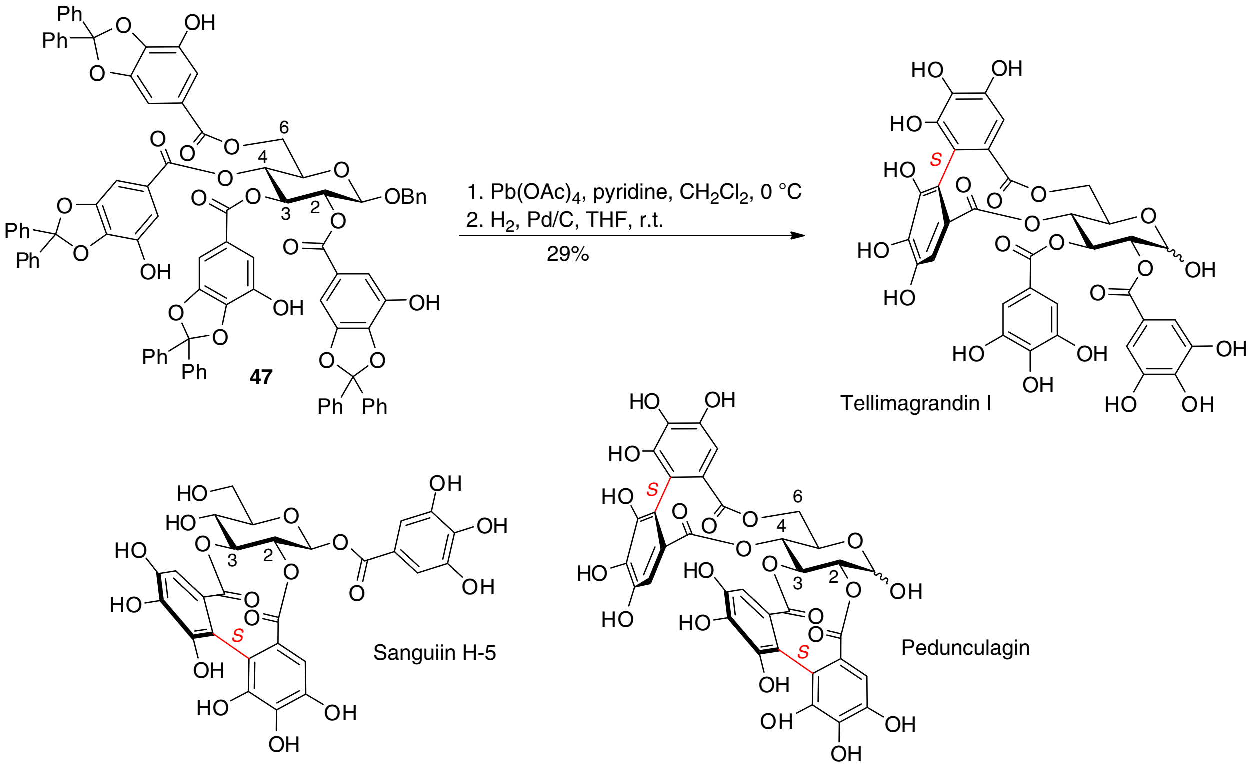
Scheme 27

This example constitutes the first example of intramolecular atroposelective oxidative coupling of galloyl units successfully achieved in a protecting-group-free manner. This is quite remarkable because the high susceptibility of pyrogallolic (i.e., 3,4,5-trihydroxyphenyl) systems toward oxidative transformations often led to complex oligomerized materials. It is worth noting that the use of other oxidants such as Fe(III) salts, copper–amine complexes, and λ^3-iodanes (DIB, BTI) were totally inoperative, leading to either complete recovery of the starting material or cleavage of its 4,6-*O*-benzylidene acetal group without observation of any biaryl product.[71a]

Such a stereoselective strategy based on the use of a glucose derivative as a stereo-directing template for oxidative phenolic coupling reactions has been widely applied to the synthesis of natural occurring ellagitannins.[72] These plant polyphenols feature one or more axially chiral HHDP units connected to a D-glucopyranosic scaffold. The desired stereoselectivity of the intramolecular coupling reaction of two glucose-attached galloyl residues is correctly induced by the chirality of the glucopyranose core in agreement with the Haslam–Schmidt ellagitannin biosynthesis hypothesis that states that stereocontrol in the coupling reactions of galloyl units is induced by the chirality of the sugar core rather than owing to the action of some stereo-dirigent oxidase enzymes.[72] Atropisomerically pure *P*- (or *S*-) HHDP units are thus, for example, obtained when 2,3- or 4,6-galloyl unit pairs on a

$^4C_1$-glucopyranose are coupled together. This biomimetic strategy is economic and efficient, because no introduction of additional chiral information (from a chiral auxiliary) is needed and only one atropodiastereomer is formed.[72] Such a substrate-controlled asymmetric strategy for the synthesis of ellagitannins corresponds to the aforementioned first option for intrinsically chiral phenolic substrates, and owes its high performances to its intramolecular setting and to a close proximity between the glucose stereogenic centers and the carbon centers engaged in the formation of the biaryl axis.

The first total chemical synthesis of an ellagitannin natural product was reported in 1994 by Feldman and coworkers[73a] The 4,6-(*S*)-HHDP-bearing tellimagrandin I was synthesized via an oxidative coupling reaction between the diphenylmethylene-protected 4- and 6-galloyl units of the glucopyranosic precursor **47**. After having screened a large number of phenolic oxidants, Feldman and coworkers identified a variant of the Wessely oxidation using the two-electron oxidant $Pb(OAc)_4$, plus a base, as the best procedure to deliver the desired glucose-bound HHDP moiety. This oxidative coupling methodology afforded a mixture of diphenyl ketal regioisomers in good yield and with a full stereocontrol exclusively leading to the *S*-diastereoisomers. Hydrogenolysis of the crude reaction mixture released all diphenylmethylene and the anomeric benzyl protections to furnish tellimagrandin I in 29% yield over the two steps (Scheme 28).[73a]

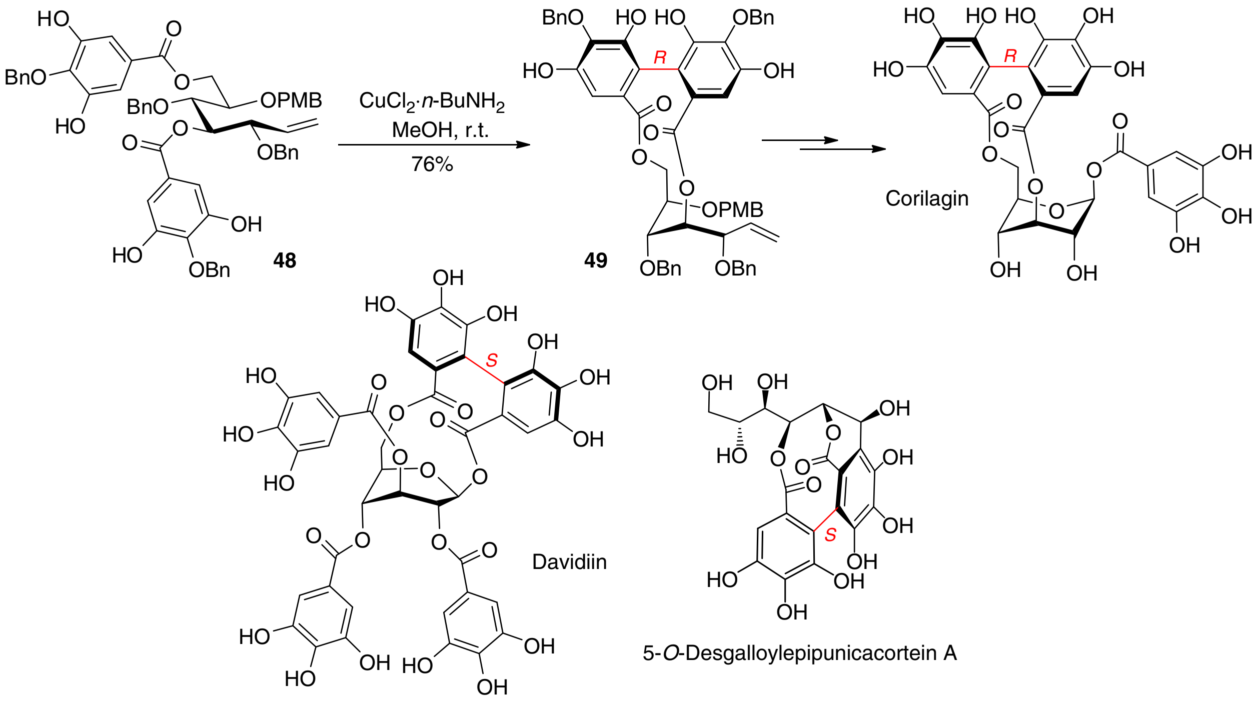


Scheme 28

No evidence for any formation of 2,3-HHDP-containing material, even on increasing the quantity of oxidant, was obtained. However, starting from a related glucopyranose precursor but protected by a benzylidene acetal group at the 4- and 6-positions, galloyl coupling at the 2- and 3-positions was effective, suggesting that the two free galloyl moieties at these positions must reach a special conformational status that is propitious for the intramolecular coupling reaction. Feldman group then extended the application of their $Pb(OAc)_4$-mediated oxidative phenolic coupling methodology to the total syntheses of the monomeric ellagitannin sanguiin H-5 and pedunculagin (Scheme 28).[73b,c]

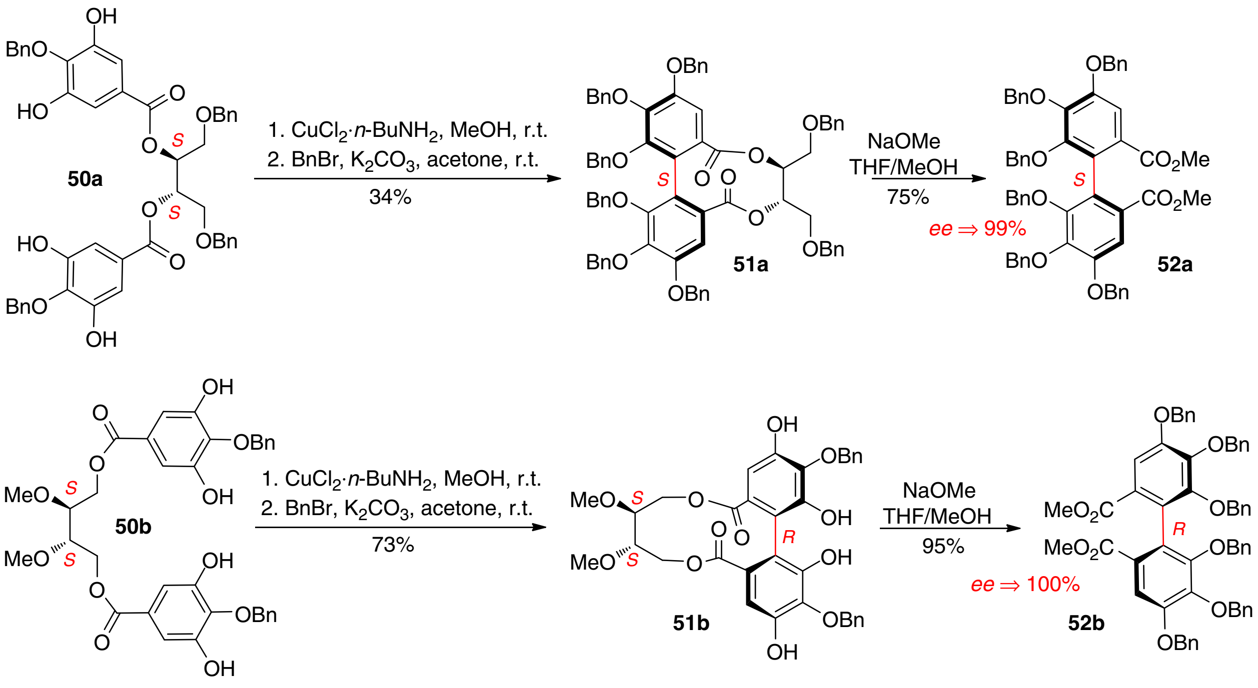
Yamada and coworkers developed a successful alternative to the Feldman procedure to build atroposelectively HHDP moieties linked to a glucose core. In the course of the total synthesis of a representative of the subclass of ellagitannins based on a $^1C_4$-glucopyranose core, these authors relied on a $CuCl_2$-amine complex-mediated oxidative coupling of symmetrically protected 4-*O*-benzylgalloyl esters. Unlike the Feldman procedure, this method provides only a single regioisomer.[74a] The implementation of this oxidative coupling reaction on a temporarily ring-opened sugar analog **48** led Yamada and coworkers to achieve the total synthesis of the 3,6-(*R*)-HHDP-containing ellagitannin corilagin via the axially oriented bisbenzylated (*R*)-HHDP-bearing coupled product **49** (Scheme 29).[74a]

Yamada and coworkers recently extended the application of their efficient atroposelective coupling methodology to the synthesis of the 1,6-(*S*)-HHDP-containing ellagitannin (+)-davidiin (Scheme 29).[74b] This methodology was also implemented



Scheme 29

with success by the same authors in the total chemical synthesis of a first member of the *C*-glucosidic ellagitannins subclass, the 2,3-(*S*)-HHDP-containing 5-*O*-desgalloylepipunicacortein A (Scheme 29).[71a] In the same vein of investigation, Yamada and workers also recently described a protocol for independently accessing each atropoisomer of the HHDP construct.[74c] In this case, they went back to the second substrate-controlled atropodiastereoselective coupling option based on the use of chiral template auxiliaries. Two molecules of 4-*O*-benzylgallic acid were mounted onto chiral bridges derived from L-(+)-tartaric acid to give access to the two 1,2-bis-4-*O*-benzylgalloyl esters **50a**/**b** (Scheme 30). Phenolic coupling was again induced using the $CuCl_2$-*n*-butylamine complex and afforded with full atroposelective control, and after perbenzylation, the (*S*)- and (*R*)-HHDP products



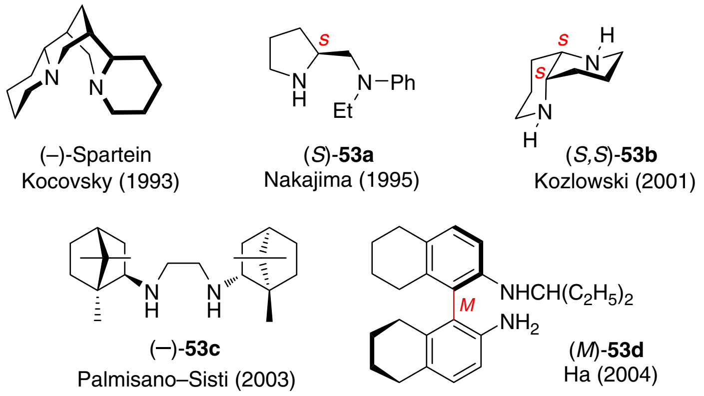
Scheme 30

51a/**b** were obtained in moderate to good yields. Methanolysis of **51a**/**b** under refluxing conditions efficiently released the tartaric acid-derived auxiliaries and furnished the (*S*)- and (*R*)-HHDP products **52a**/**b** in good to high yields with excellent enantiomeric excesses (Scheme 30).[74c]

3.13.2.1.2.2 Enantioselective phenolic biaryl coupling

Practical applications of stereoselective oxidative coupling of phenols with chiral catalysts have been so far essentially limited to coupling of 2-naphthol and its derivatives. The resulting enantiomerically pure binaphthol (BINOL) derivatives can be used as chiral auxiliaries and are popular ligands for both stoichiometric and catalytic asymmetric synthesis. Symmetrical and unsymmetrical BINOLs can be prepared by enantioselective oxidative coupling of naphthols using chiral metal complexes such as those derived from copper, vanadium, iron, and ruthenium. The authors refer the reader to a selection of the numerous review articles that have appeared in the literature on the topic and related ones.[75]

During the last two decades, extensive efforts have been dedicated to the development of catalytic systems susceptible to achieve the same high level of selectivity generally obtained by employing stoichiometric amounts of chiral reagents. Among the catalytic systems explored to tackle this challenge, copper–diamine complexes have been largely investigated. Several chiral diamine ligands in association with copper sources have provided efficient catalytic enantioselective access to chiral BINOL derivatives (Scheme 31).[50b,e,76]



(–)-Spartein
Kocovsky (1993)

(*S*)-**53a**
Nakajima (1995)

(*S*,*S*)-**53b**
Kozlowski (2001)

(–)-**53c**
Palmisano–Sisti (2003)

(*M*)-**53d**
Ha (2004)

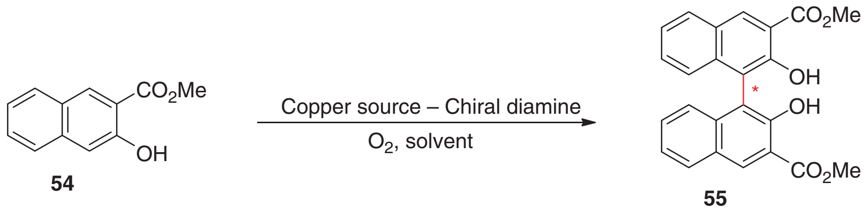
Scheme 31

In 1993, Kocovsky and coworkers were the first to propose a catalytic system composed of 10 mol% of CuCl$_2$, 20 mol% of (–)-sparteine as chiral ligand (Scheme 31), and 1 equivalent of AgCl as terminal oxidant to accomplish the oxidative self-coupling of 2-naphthol (**28**) in 70% yield.[76a] In sharp contrast to the excellent enantioselectivity obtained under stoichiometric conditions (up to 100% *ee*),[76a] this catalytic system failed to offer an enantiomeric excess of synthetic value (only approximately 3% *ee*). Unable to withstand this failure, the seminal attempt validated the feasibility of the catalytic process and opened up the door to the development of better catalytic systems. In 1995, Nakajima and coworkers drastically improved the enantioselectivity of the copper–diamine catalytic system up to 70% *ee* under aerobic conditions, using the L-proline derivative **53a** as a diamine copper ligand. However, they performed coupling on methyl 3-hydroxy-2-naphthoate (**54**) and noted that no asymmetric induction was observed with unsubstituted 2-naphthol.[76b] Later, the same research group also reported the use of (–)-sparteine as chiral ligand and managed to significantly improve the coupling enantioselectivity up to 78% *ee* using the prolyldiamine **53a** (Table 2, entries 1 and 2).[76c]

In 2001, on the basis of results from computer-aided identification of novel ligands, Kozlowski and coworkers reported that (*S*,*S*)-1,5-diaza-*cis*-decalin (*S*,*S*)-**53b** and its (*R*,*R*)-antipode used as ligands in the presence of CuI lead, respectively, to dimers *M*-**55** and *P*-**55** in very good yields (82–85%) with impressive enantiomeric excesses up to 92–93% (Table 2, entries 3 and 4).[50b,76d] In 2003, Palmisano, Sisti, and coworkers conceived a new C$_2$-symmetrical 1,2-diamine ligand **53c** (Scheme 31), which was prepared from commercial (1 *R*)-(+)-camphor.[76e] Under optimal conditions employing a copper triflate source with air (O$_2$) as oxidant, the self-coupling of naphthol **54** into **55** could be achieved in 90% yield with 65% *ee* (Table 2, entry 5).[76e] In 2004, mono-*N*-alkylated octahydrobinaphthyl-2,2′-diamine (H$_8$-BINAM) chiral ligands were employed by Ha and coworkers for the asymmetric catalytic oxidative coupling of **54**.[50e] The diamine ligand *M*-**53d** performed the best and enabled the production of **54** in 95% yield with a highest enantiomeric excess of 94% *ee* (Table 2, entry 6).[50e]

In contrast to related transformations utilizing stoichiometric copper oxidants for which a radical-anion-type coupling mechanism was proposed (see Section 3.13.2.1.1, Scheme 19), Kozlowski and coworkers suggested a radical–radical pairing mechanism for these catalytic copper–diamine complex-mediated process (see Section 3.13.1.3, Scheme 8).[76d] The high enantioselectivities obtained with these copper–diamine complexes have been rationalized in terms of an initial bidentate coordination of the substrate, involving both its naphtholic oxygen and the carbonyl oxygen of its ester function, to a liganded Cu(II) form of the catalyst. SET in the resulting liganded Cu(II)·naphthol complex would yield an *ortho*-carbon-centered radical with a

Table 2



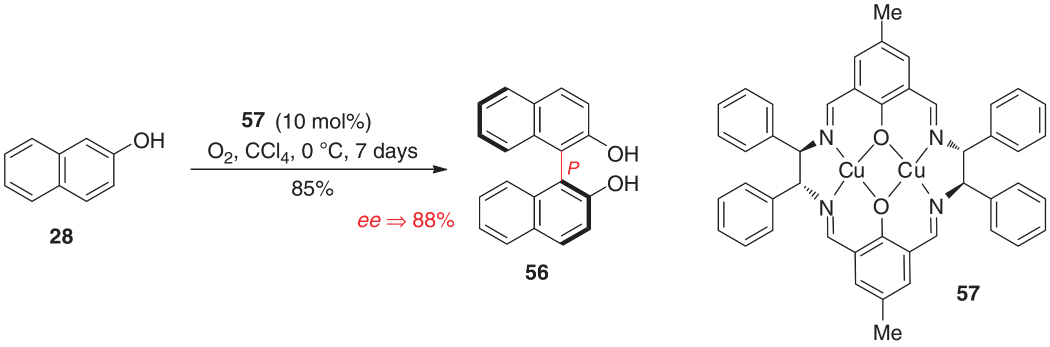
54

55

Entry	*Copper source (mol%)*	*Chiral diamine (mol%)*	*Solvent, (°C), time*	*Yield (%)*	ee *(%)*
1	CuCl (10)	(−)- **sparteine** (11)	CH_2Cl_2, reflux, 24 h	38	47 (*P*)
2	CuCl (10)	(*S*)-**53a** (11)	CH_2Cl_2, r.t., 24 h	85	78 (*P*)
3	CuI (10)	(*S*,*S*)-**53b** (10)	MeCN, 40 °C, 48 h	85	93 (*M*)
4	CuI (10)	(*R*,*R*)-**53b** (10)	MeCN, 40 °C, 48 h	82	92 (*P*)
5	$Cu(OTf)_2{\cdot}C_6H_6$ (10)	(−)-**53c** (10)	CH_2Cl_2/MeCN (2:1) 40 °C, 5–48 h	90	65 (*M*)
6	CuCl (9)	(*M*)-**53d** (10)	CH_2Cl_2, 0 °C, 48 h	95	94 (*M*)

tetrahedral Cu(I) center. The approach of the second (one-electron oxidized) substrate molecule would then occur from the less-hindered face of this radical complex to give the biaryl product with the observed full stereoselectivity.[50b,76d]

The success of Jacobsen's salen-based chiral catalysts in a broad range of asymmetric catalytic reactions led Gao and coworkers to investigate a family of dicopper catalysts for the asymmetric oxidative coupling of 2-naphthol (**28**).[77] In the presence of 10 mol % of the Schiff base dicopper(II) complex catalyst **57** in CCl_4, the (*P*)-BINOL **56** was generated in 85% yield with 88% *ee* after 7 days (Scheme 32). The good level of coupling enantioselectivity observed with this unsubstituted 2-naphthol (**28**) was in this case tentatively attributed to self-coupling of two naphthyl radicals simultaneously formed on a planar rigid dicopper platform.[77]



28

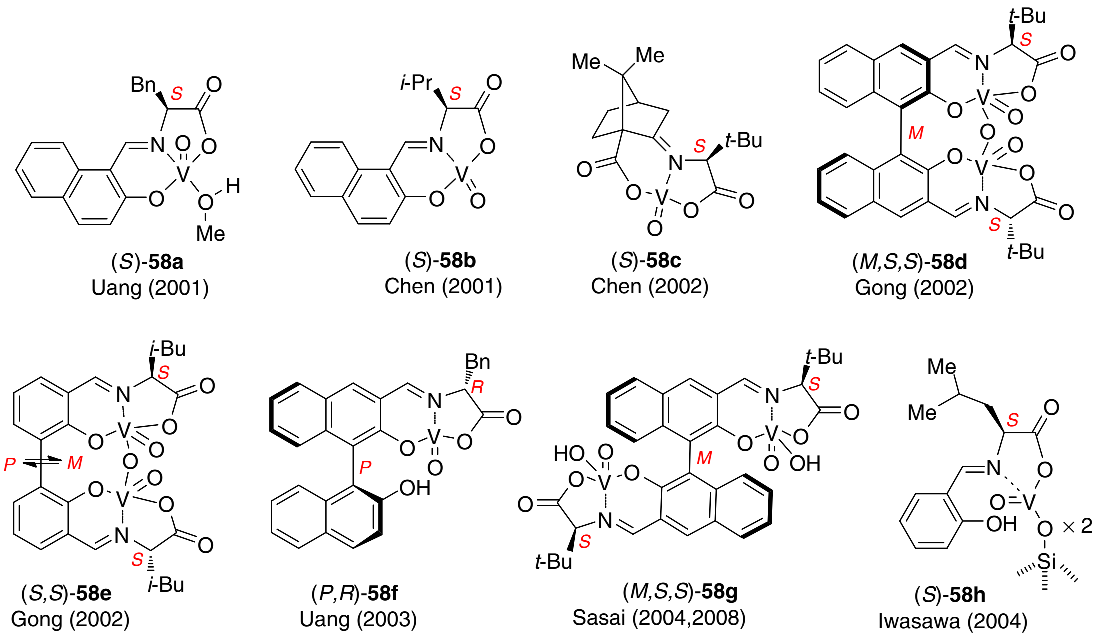
56

57

Scheme 32

Thus, the use of copper salts together with chiral diamines and a terminal oxidant provides a valuable means for catalytic enantioselective access to chiral BINOL derivatives. A large variety of mono- and dinuclear oxovanadium-based catalysts harboring chiral Schiff base-type ligands have also been studied during the same period for their application in asymmetric oxidative coupling of 2-naphthol and derivatives (Scheme 33).[50c,78]

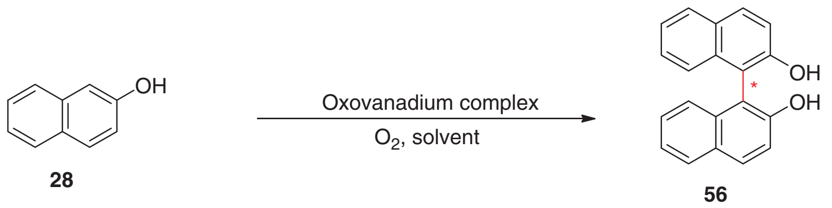
In 2001, the groups of Uang and Chen independently reported the use of chiral tridentate Schiff base ligands on oxovanadium complexes for the enantioselective catalytic oxidative coupling of 2-naphthol derivatives.[78a,b] Uang and coworkers reported that 2 mol% of complex **58a** (Scheme 33) with 2 mol% of TMSCl as promoter in the presence of molecular oxygen exhibited the highest reactivity and enantioselectivity in chloroform at room temperature for 24 h. A yield of 82% with 51% *ee* was obtained for the self-coupling of 2-naphthol (**28**) (Table 3, entry 1).[78a] Similar enantioselectivities were obtained with various substituted 2-naphthol derivatives. However, this catalytic system failed to engender the enantioselective coupling of methyl 3-hydroxy-2-naphthoate (**54**), in sharp contrast to the good to excellent results obtained by using copper–diamine complexes (see Table 2). Chen and coworkers used a similar oxovanadium(IV) complex catalyst **58b** and obtained slightly better results by performing the reaction in CCl_4 at room temperature for 6 days (Table 3, entry 2).[78b] The same group next investigated the reactivity and enantiocontrol capacity of novel chiral oxovanadyl(IV) dicarboxylates, such as **58c**, derived from (+)-ketopinic acid and α-amino acids.[50c] Under optimized reaction conditions, the self-coupling of **28** in CCl_4 at 45 °C for 7 days proceeded in almost quantitative yield and with a good enantiomeric excess of 84% (Table 2, entry 3).[50c] Gong and coworkers envisioned that the enantioselectivity should be improved if the catalyst contains two chiral centers. In 2002, they reported on the rational design of novel oxovanadium



Scheme 33

complexes (*M*,*S*,*S*)-**58d** and (*S*,*S*)-**58e**.[78c,d] In the presence of 5–10 mol% of their catalysts, the self-coupling of **28** in CCl_4 at 0 °C for several days afforded the (*M*)-BINOL **56** in high yields and good enantioselectivities (Table 3, entries 4 and 5). It is worth noting that the conformationally flexible biphenyl catalyst **58e** exhibits a level of enantioselective control similar to that observed with its atropoisomerically pure 1,1′-binaphthyl analog **58d**.[78d] In 2003, Uang and Chu also reported the use of binaphthyl but mononuclear oxovanadium complexes with a free hydroxyl group derived from (*S*)-3-formyl-1,1′-bi-2-naphthol and *α*-amino acids, such as **58f**, which were found to accelerate the catalytic asymmetric coupling of 2-naphthols, but only moderate to good enantioselectivities were observed (Table 3, entry 6).[78e] In 2004 and 2008, Sasai and coworkers reported on their version of Gong's dinuclear complex catalyst, (*M*,*S*,*S*)-**58g**, which promoted the asymmetric coupling of **28** in higher yield and enantioselectivity than Gong's (*M*,*S*,*S*)-**58d** (Table 3, entry 7).[78f,g] The structural and kinetic analyses of mono- and dinuclear oxovanadium complexes realized later by Sasai and coworkers revealed that two vanadium metals in one chiral complex activate two molecules of 2-naphthol simultaneously in a homogenic coupling reaction, and enable a high reaction rate with high enantiocontrol.[79] To the best of the authors' knowledge, only one example of heterogeneous oxovanadium complex catalysis has been so far reported for the asymmetric oxidative coupling of **28**.[78f,g] Iwasawa and coworkers have shown that the self-dimerized chiral assembly of the vanadium–Schiff-base complex (*S*)-**58h** occurs on a SiO_2 surface and enables the asymmetric oxidative coupling of **28** in toluene

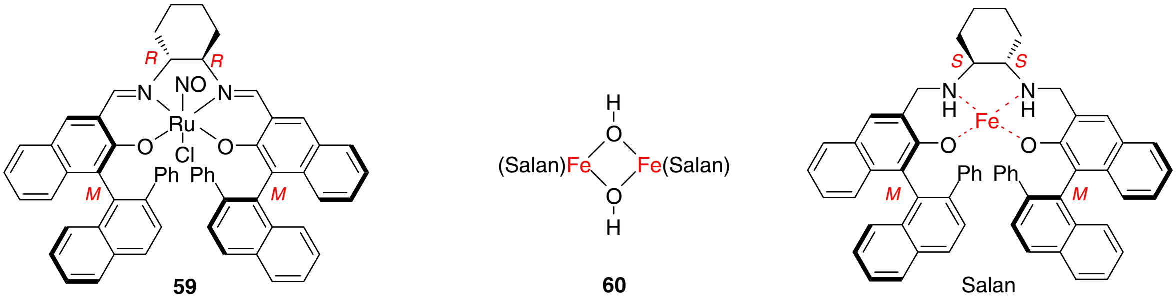
Table 3



Entry	Oxovanadium complex (mol%)	Solvent, °C, time	Yield (%)	ee (%)
1	(*S*)-**58a** (2)+TMSCl (2)	$CHCl_3$, r.t., 24 h	82	51 (*M*)
2	(*S*)-**58b** (10)	CCl_4, r.t., 6 days	94	62 (*M*)
3	(*S*)-**58c** (3)	CCl_4, 45 °C, 7 days	99	84 (*P*)
4	(*M*,*S*,*S*)-**58d** (10)	CCl_4, 0 °C, 6 days	93	83 (*M*)
5	(*S*,*S*)-**58e** (5)	CCl_4, 0 °C, 7 days	89	89 (*M*)
6	(*P*,*R*)-**58f** (5)	$CHCl_3$, r.t., 16 h	93	90 (*M*)
7	(*M*,*S*,*S*)-**58g** (5)	CH_2Cl_2,0 °C, 72 h	100	90 (*P*)
8	(*S*)-**58h** (3)	Toluene, –10 °C, 11 days	93	90 (*M*)

at −10 °C for several days into (*M*)-**56** in 93% yield with an enantiomeric excess of 90% (Table 3, entry 8).[78h] All together, oxovanadium complex catalysts thus offer an efficient and complementary alternative to the use of chiral copper–diamine complexes for the asymmetric oxidative coupling of simple 2-naphthols into BINOLs.

Katsuki and coworkers accomplished the asymmetric oxidative coupling of 2-naphthols by using the chiral NO-ruthenium(II)-salen complex **59** (Scheme 34) in the presence of molecular oxygen under visible light irradiation.[80] Optically active BINOL derivatives were synthesized in toluene at ambient temperature with moderate to good enantioselectivity using only 2–5 mol% of **59**. For example, the oxidative coupling of 2-naphthol (**28**) with this catalyst afforded (*M*)-**56** as the sole product in 72% yield and 65% *ee*. More electron-deficient 2-naphthols, such as 6-bromo-2-naphthol, led to much lower yields but slightly higher *ee*s, whereas an electron-releasing methoxy group at the 6-position caused a drastic decrease in the enantioselectivity down to the 30% *ee* range.[80] Later on, Katsuki and coworkers reported on the utilization of chiral iron–salan complexes of type **60**.[81] These di-μ-hydroxy dimeric iron complexes containing a chiral salan ligand such as the one depicted in Scheme 34 were found particularly valuable for the asymmetric synthesis of 3,3′-disubstituted BINOLs. The aerobic oxidative self-coupling of 2-naphthol (**28**) carried out in toluene at 60 °C for 72 h with 4 mol% of **60** furnished (*M*)-**56** in 84–87% yield with 64% *ee*, whereas various 3-substituted naphthols were converted into the corresponding *M*-BINOLs in yields ranging from 64 to 94% with *ee*s ranging from 16 to 96%.[81a] However, the Fe–salan complex **60** could not catalyze the coupling of the 3-methyl ester-substituted naphthol **54**, which thus seems to be a special naphtholic substrate mainly reserved for the catalytic performances of copper–diamine complexes (see Table 2). The same authors recently reported results of a mechanistic study on the manner through which Fe–salan complexes catalyze such oxidative coupling reactions. They proposed an SET from a naphthol-bearing Fe(III)–monosalan complex intermediate species to molecular oxygen that leads, via a Fe(IV) species, to a Fe(III)-bound naphthoxy radical cation (ArO$^{\bullet+}$-Fe), which then accommodates a second naphthol molecule on the iron center for enabling asymmetric coupling via nucleophilic attack of the second naphthoxy unit onto the ArO$^{\bullet+}$ moiety, followed by one-electron oxidation and rearomatizing deprotonations to the BINOL product.[81c]



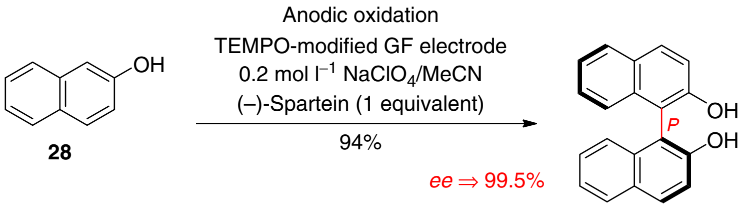
59
Katsuki (2000)

60
Katsuki (2009)

Salan
ligand

Scheme 34

Besides the extensive and relatively recent use of copper-, vanadium-, ruthenium- and iron-based catalysts for enantioselective coupling of naphthols, one must herein also mention an earlier and remarkable case for which anodic oxidation was successfully applied. Such an electrochemical method is usually not so appropriate for the oxidative coupling of naphthols, because their electrolysis causes a deposit of a naphthol-derived polymer film on electrodes, which prevents continuation of the reaction. Osa and coworkers found a solution to this problem by using a TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl)-modified graphite felt electrode in the presence of a deprotonation reagent such as 2,6-lutidine. Replacing 2,6-lutidine by a chiral alkaloid such as (−)-sparteine, they were then able to convert, for example, 2-naphthol (**28**) into (*P*)-**56** in 94% isolated yield with an enantiomeric excess of 99.5% (Scheme 35).[82]

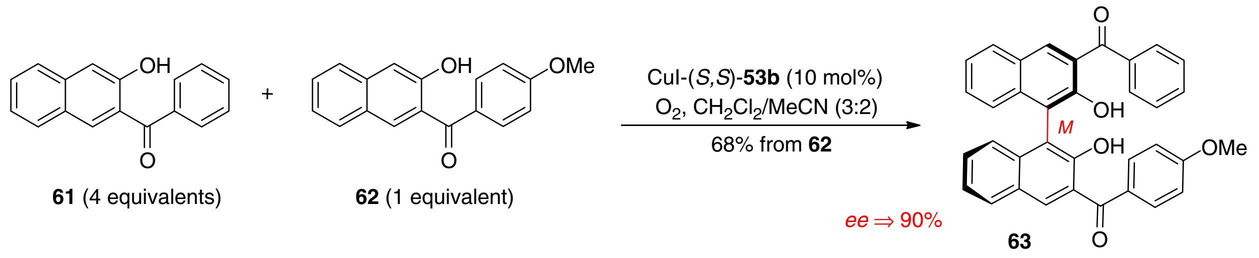


28

56

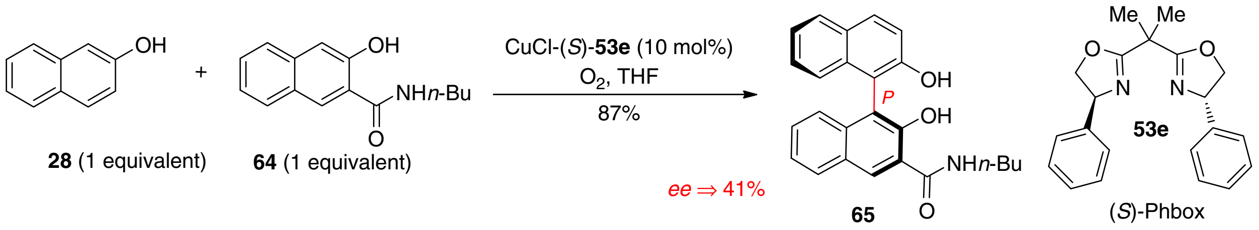
Scheme 35

Examples of enantioselective cross-coupling of differently substituted naphthols are less numerous, but quite successful cases have nevertheless been reported.[62b,76d,83,84] For example, Kozlowski and coworkers have reported that the asymmetric oxidative cross-coupling reaction between an excess of naphthol **61** and naphthol **62** using their chiral copper–diamine (**53b**, Scheme 31)[50b] complex yields the cross-coupled binaphthyl **63** in 68% yield (from **62**) with 90% *ee* (Scheme 36).[76d] The observation of a statistical distribution of self- and cross-coupled products led these authors to conclude that the reaction operates via an aryloxy radical–radical pairing process.[62b,76d]



Scheme 36

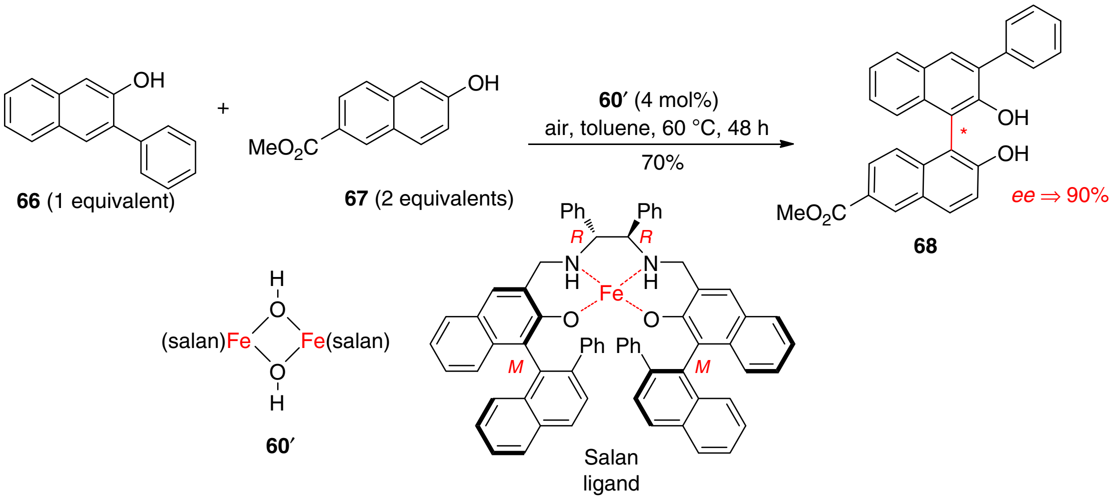
Habaue and coworkers reported that the copper(I)-(*S*)-(−)-isopropylidene bis(4-phenyl-2-oxazoline) catalyst [CuCl-(*S*)-Phbox, **53e**] is effective for the oxidative cross-coupling reaction between equimolar amounts of 2-naphthol (**28**) and the 3-hydroxy-2-naphthamide derivative **64** and gives the C1-symmetric BINOL **65** (Scheme 37). The reaction proceeded in a highly cross-coupling selective manner to generate the binaphthyl **65** in a very good yield of 87%, but with only a moderate enantioselectivity of 41% (Scheme 37).[83b] This low stereoselectivity could be because of the lack of a carbonyl group at the 3-position of one of the naphthol partner, because the presence of such a coordinating group of functions such as esters or ketones (*vide supra*, and thus perhaps also amides) at the 3-position of both naphthol partners has appeared as a determining factor of the coupling enantioselectivity performances of chiral copper–amine catalysts. As already discussed (see Section 3.13.2.1.1, Scheme 19), the authors proposed that the observed cross-coupling efficacy would be because of a privileged one-electron oxidation of the more electron-rich naphthol (i.e., **28**, Scheme 37) into an aryloxy radical that could then concertedly and selectively reacts with the less electron-rich naphthol **64** in a radical substitution manner (see Section 3.13.1.2).[83a,b]



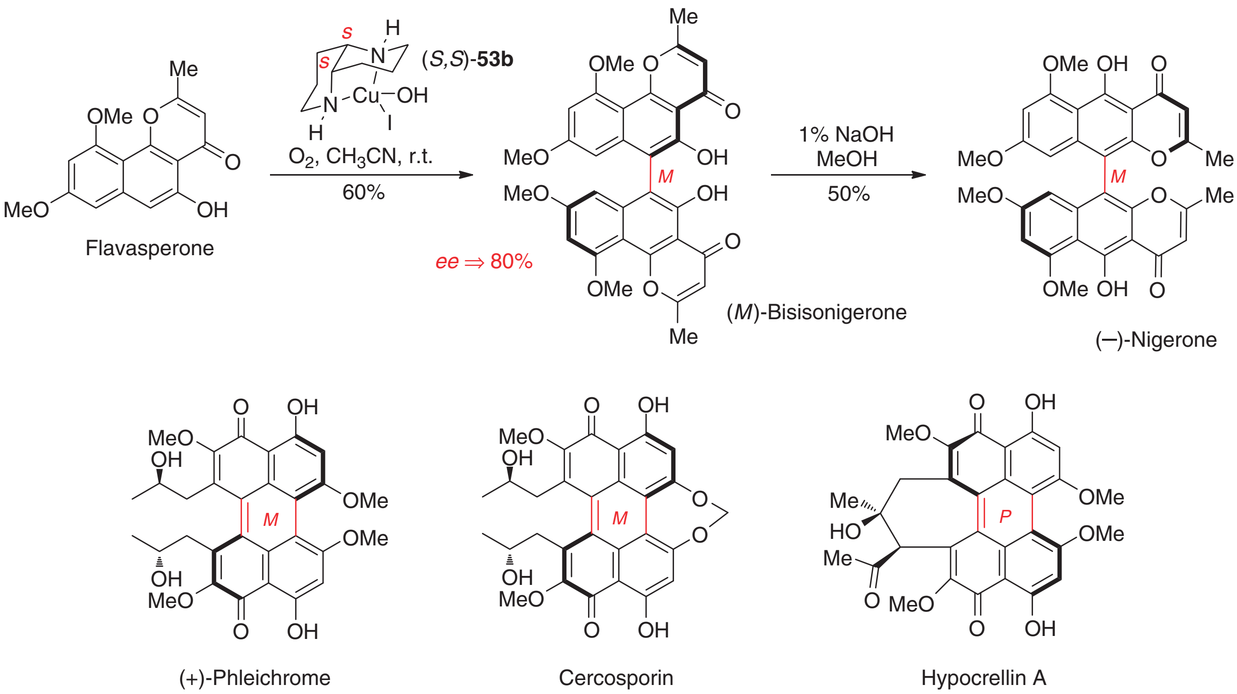
Scheme 37

A highly enantioselective aerobic oxidative cross-coupling of 2-naphthols with a broad substrate scope was described by Katsuki and coworkers, who relied on their chiral iron–salan complex system of type **60** (Scheme 34).[84] Enantiomeric excesses of 87–95% were obtained, although chemical yields only ranged from 44 to 70%. The best results were obtained with naphthols **66** and **67** that were induced to cross-couple into **68** in 70% yield with 90% *ee* (Scheme 38). The presence of carbonyl-containing electron-withdrawing substituents at the 3-position of the naphthols did not appear essential for reaching high enantioselectivity with this iron–salan catalyst system, but still the presence of a substituent at C3 of the more electron-rich naphthol partner (i.e., **66**, Scheme 38) seemed advantageous to the efficacy of such an asymmetric cross-coupling reaction.[84] Generally, the success of such cross-coupling reactions is highly substrate- and catalyst-dependent.

Several oxidative methods have thus been developed over the past 20 years to access binaphthols in a stereoselective manner. Their applications in the synthesis of natural binaphthyls have been so far rather limited, but the few examples highlighted below should illustrate their value and potential in asymmetric synthesis of complex natural products. The catalytic copper–diamine complex based on the chiral diamine **53b**, which was developed by Kozlowski and coworkers (Scheme 31),[50b] has recently found an application in the enantioselective preparation of the bisnaphthopyrone natural product (−)-nigerone.[85a,b] This copper–diazadecaline complex catalyst induced the atroposelective dimerization of the precursor flavasperone to furnish (*M*)-bisisonigerone in 60% yield with 80% *ee*. This key oxidative coupling step was followed by an isomerization step that afforded (−)-nigerone in 50% yield (Scheme 39).[85a,b] Kozlowski and coworkers also relied on their copper-diazadecaline



Scheme 38

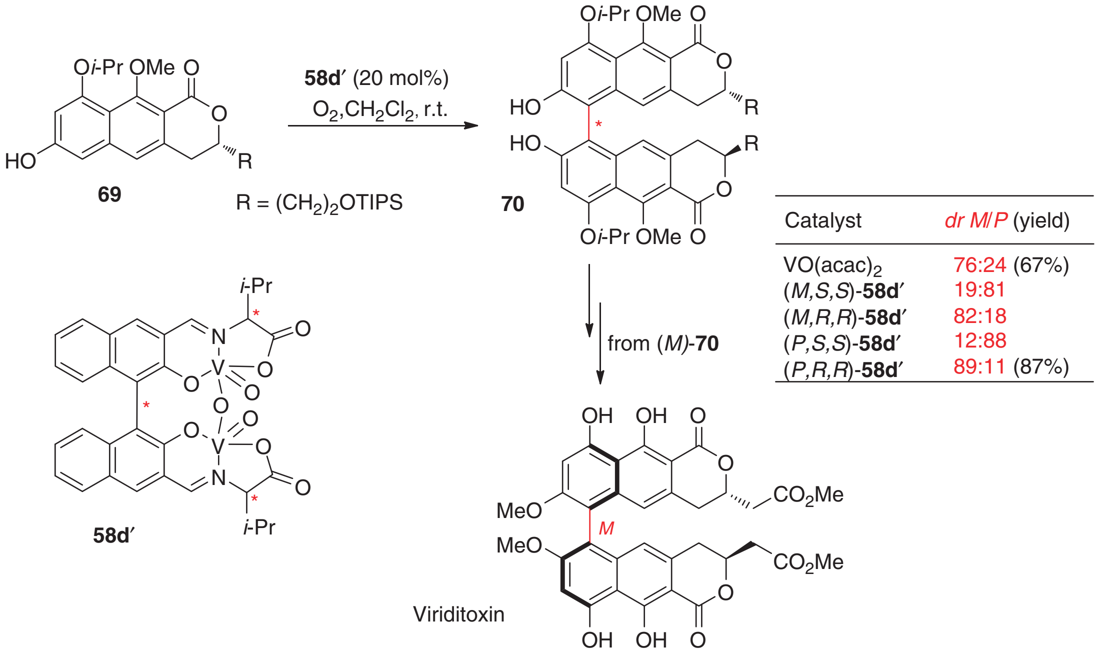


Scheme 39

(Cu-**53b**) catalyst-based tactic to achieve the total synthesis of several perylenequinone natural products such as (+)-phleichrome,[85c] cercosporin,[85d,e] and hypocrellin A[85f] (Scheme 39).

Oxovanadium catalysts have also found applications in enantioselective syntheses of biaryl natural products. For example, Shaw and coworkers have recently reported the first total synthesis of the 6,6′-binaphthopyran-2-one (−)-viriditoxin (Scheme 40).[86] To control the chirality of the 6,6′-biaryl bond, they first relied on a substrate-controlled approach using Uang's VO(acac)$_2$-catalyzed process.[87] A single C$_{ortho}$–C$_{ortho}$ coupled regioisomer, the desired product (*M*)-**70**, was obtained in 67% yield in a 76:24 diastereomeric ratio, a quite respectable diastereoselectivity when considering asymmetric induction from the rather distal stereogenic center of the substrate **69** (Scheme 40). In order to enhance the atroposelectivity of the biaryl bond formation, they then explored the stereocontrol capacity of a series of four stereoisomers of the oxovanadium catalyst **58d′**, a variant of the aforementioned Gong's catalyst **58d** (Scheme 33).[50h,78c]

The naphthopyranone **69** was treated with these four isomers of **58d′**. The desired (*M*)-**70** coupled product was obtained in 87% yield with an enhanced atroposelectivity of 89:11 by using (*P*,*R*,*R*)-**58d′** (Scheme 40). In all cases, these chiral dinuclear



69

70

58d′

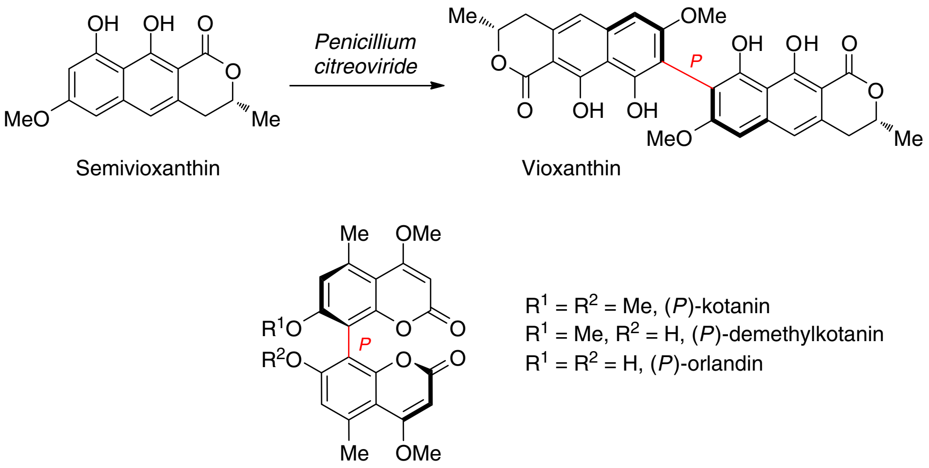
Viriditoxin

Catalyst	*dr M*/*P* (yield)
VO(acac)$_2$	76:24 (67%)
(*M*,*S*,*S*)-**58d′**	19:81
(*M*,*R*,*R*)-**58d′**	82:18
(*P*,*S*,*S*)-**58d′**	12:88
(*P*,*R*,*R*)-**58d′**	89:11 (87%)

Scheme 40

vanadium catalysts exhibited superior diastereoselectivity and reactivity than VO(acac)$_2$. The synthesis of viriditoxin was completed after five additional steps.[87]

Numerous other phenolic natural products do display biaryl axial homochirality in their structure, and their biosyntheses are commonly thought to imply regio- and stereoselective action of phenoxy radical-producing one-electron oxidases, such as laccases and peroxidases. However, as discussed in Section 3.13.5.2, *in vitro* phenolic coupling experiments with these enzymes only lead to racemic products. In this vein of investigation on biosynthetic oxidative coupling of phenols, Müller and coworkers have recently tried to identify a biocatalyst system responsible for the regio- and stereoselective genesis of some fungal biaryl.[88] They could notably show that vioxanthin is biosynthesized in *Penicillium citreoviride* through a regio- and stereoselective dehydrodimerization of monomeric semivioxanthin (Scheme 41).[88a] Similar observations were made in *Aspergillus niger* with the exclusive formation of (*P*)-atropoisomers of the 8,8′-bicoumarins, kotanin, demethylkotanin, and orlandin (Scheme 41).[88b] The biocatalysts responsible for the regio- and stereoselective control of these oxidative biraryl coupling of natural phenolics were not identified.[88] Could some specific fungal oxidases be alone capable of such exclusive controls or would they need the implication of additional helper regio/stereocontrolling proteins such as the so-called 'dirigent' proteins that have been evidenced in plant lignan biosynthesis (see Section 3.13.5.2)? The questions remain, investigation goes on…



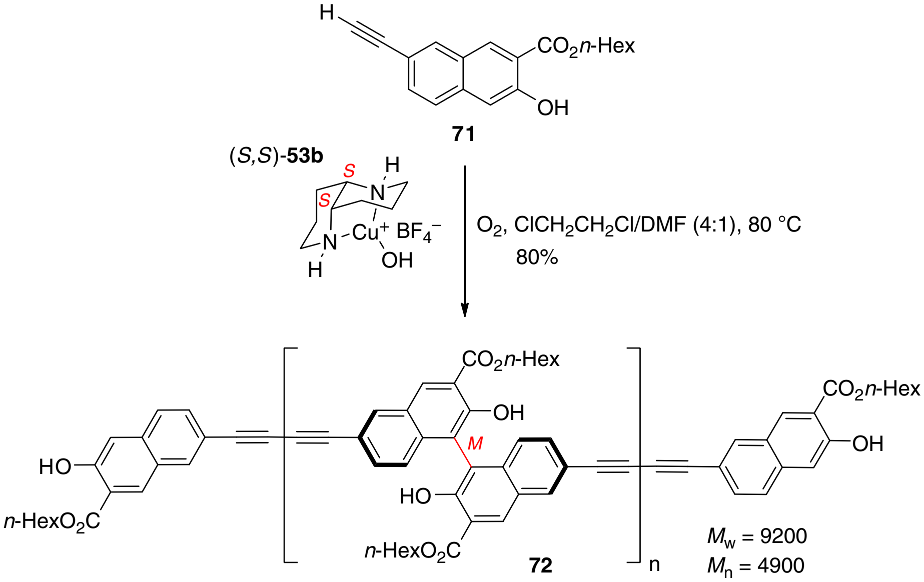
Semivioxanthin

Vioxanthin

$R^1 = R^2$ = Me, (*P*)-kotanin
R^1 = Me, R^2 = H, (*P*)-demethylkotanin
$R^1 = R^2$ = H, (*P*)-orlandin

Scheme 41

The authors end this section by an example of an application of oxidative phenolic biaryl coupling in the preparation of optically active binaphthyl-based polymers, which are extensively utilized in organic materials. This example is again taken from the work of Kozlowski and coworkers, who have used their chiral copper–amine catalyst based on the diamine (*S*,*S*)-**53b** (Scheme 31) to perform enantioselective oxidative biaryl coupling of 2-naphthols, such as **71**. The biaryl coupling of this naphthylalkyne occurred in tandem with the Glaser–Hay alkyne coupling to furnish the polybinaphthyl **72** in good yield and atroposelectivity (Scheme 42).[89]



Scheme 42

3.13.2.2 Via Oxidative Coupling of Phenol Ethers

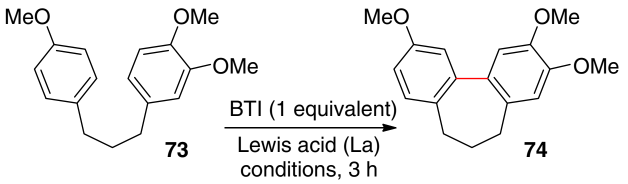
3.13.2.2.1 Intramolecular biaryl coupling

Kita and coworkers have extensively studied the use of λ^3-iodane reagents, in particular BTI, in the oxidative activation of simple alkyl phenol ethers, and they were the first to demonstrate that these reactions go through a SET mechanism, wherein the aromatic ring reacts with the hypervalent iodine reagent to generate a radical cation intermediate ($PhOR^{\bullet+}$), which likely results from an initial formation of a CT complex (see Section 3.13.1.3, Scheme 7).[42c] Such a reactive radical cation can then be trapped with various nucleophilic entities.[90] Most of these BTI-induced oxidative nucleophilic substitution reactions were best performed in the fluoroalcohol solvents 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) or 2,2,2,-trifluoroethanol (TFE), which exhibit high ionizing power together with low nucleophilicity and effectively stabilize reactive aromatic radical cation species.[91] Alternatively, the addition of an appropriate Lewis acid, such as the classically used $BF_3 \cdot Et_2O$ and TMSOTf, as well as that of soft solid Brönsted acids (e.g., heteropolyacids (HPAs) and other series of solid clay catalysts), have been shown to enhance the SET oxidizing ability of the λ^3-iodane reagent by coordinating the ligand of the iodine atom.[90a,92] In the context of their investigation on nonphenolic oxidative coupling of simple alkyl phenol ethers via a SET mechanism (see Section 3.13.1.2, Scheme 2), Kita and coworkers used electron-rich aromatic rings as carbon-based nucleophiles to carry out the synthesis of several biaryls. One of their first achievements in this arena concerned the intramolecular oxidative biaryl coupling of phenol ether derivatives, such as the 1,3-diarylpropane **73**, a reaction that was shown to proceed smoothly using BTI in the presence of $BF_3 \cdot Et_2O$ (Table 4).[28,42b,93] It is worth noting that the absence of the Lewis acid caused a coupling rate decrease and undesirable overoxidation of the biaryl product **74**. Best results were obtained at low temperature (i.e., −40 °C) in TFE or dichloromethane, in the presence of 2 equivalents of $BF_3 \cdot Et_2O$ (Table 4).

A selection of several other examples of this metal-free intramolecular oxidative biaryl coupling is given in Table 5. Under the aforementioned optimized experimental conditions (i.e., 1 equivalent of BTI and 2 equivalents of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at −40 °C), several electron-rich phenyl ether derivatives of type **75** were successfully converted into the corresponding biaryls **76** in good to excellent yields.[28,42b,93] It is interesting to note that oxidation of the benzylic position of the dibenzyl ether derivatives did not take place to any significant extent and that the silylated moiety of silaketal derivatives was also shown to be stable under the BTI conditions used.[42b] Subsequent removal of these silicon- or oxygen-tethered intramolecular-coupling templates was performed using either a standard tetrabutylammonium fluoride (TBAF) desilylating treatment or a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidizing protocol to furnish the 2,2′-dihydroxy or 2,2′-diformyl biphenyls **77** (Table 5).[42b,93] This practical two-step sequence thus gives access to both symmetrical and unsymmetrical biaryls.

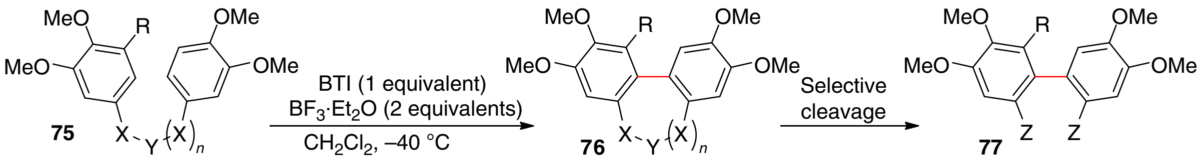
This Kita's methodology was also used with success by Domínguez and coworkers for the synthesis of several phenanthro-fused heterocycles, such as thiazoles, isoxazoles, pyrazoles, pyrimidines, and furans.[94a] Selected examples of these nonphenolic

Table 4



Solvent	*Temperature (°C)*	*Isolated yield of **74** (%)*	
		No La	*$BF_3 \cdot Et_2O$*
HFIP	0	63	63
TFE	−40	65	84
CH_3CN	−40	46	73
CH_2Cl_2	−40	25	91

Table 5

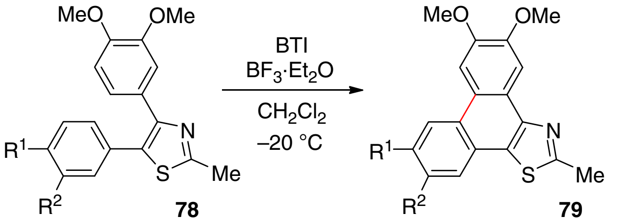


X	*Y*	*R*	n	***76** (%)*	*Conditions*	*Z*	***77** (%)*
CH_2	CH_2	OMe	1	99	/	/	/
CH_2	CH_2	OTBS	1	75	/	/	/
CH_2	$NCOCF_3$	OMe	1	85	/	/	/
CH_2	$NCOCF_3$	OMe	2	68	/	/	/
CH_2	$NCOCF_3$	OTBS	1	64	/	/	/
O	$SiBu^t_2$	OMe	1	81	TBAF, THF, r.t., 2 h	OH	98
CH_2	O	OMe	1	85	DDQ, CH_2Cl_2/H_2O (18:1) reflux, 24 h	CHO	66

intramolecular oxidative biaryl couplings are given in Table 6. 4,5-Diarylthiazoles **78** were cleanly converted into the corresponding phenanthro-fused thiazoles **79** in good yields (i.e., 72–81%); it is interesting to note that activation with electron-donating groups is needed for at least one of the aromatic rings. These yields constitute a net improvement in comparison with those obtained using oxidizing reagents based on transition metals such as Ru(IV), Fe(III), and V(V).[94b,c] Similar observations were made when bisphenol ethers of type **80**, such as 4,5-diarylisoxazoles (X=O, *n*=0), 5,6-diarylpyrimidines (X=N, *n*=1), and 4,5-diarylpyrazoles (X=NPh, *n*=0), were treated under the same BTI conditions, hence providing a simple and efficient access to the corresponding phenanthro[9,10-*d*]heterocyclic systems **81** (Table 6).[94d–f] Domínguez and coworkers also used a BTI-mediated intramolecular coupling tactic to synthesize tetrahydrobenzo[*c*]phenanthridines **83** and benzo[*c*]phenanthridinones **85** (Table 6).[94g] They showed that tetracycles **83** could be isolated in good yields, a spontaneous aromatization process accompanying the formation of the biaryl bond, that substitution *ortho* to the coupling position (i.e., R^4=OMe) did not affect the yield, and that at least two methoxy groups were needed for a radical cation $PhOR^{\bullet +}$ to be formed (Table 6).

As far as benzo[*c*]phenanthridinone derivatives **85** are concerned, a higher temperature (i.e., 40 °C, refluxing dichloromethane) was required to ensure intramolecular coupling in good yields from the proper *cis*-conformation of the starting amide rotamers **84** (Table 6).[94g] Dibenzo[*a*,*c*]phenanthridine precursors **86** also succumbed to the BTI-mediated intramolecular oxidative biaryl coupling to afford the pentacyclic systems **87** in moderate to very good yields (Table 6).[94h] Again, better yields were obtained when compared with those resulting from oxidizing reagents based on transition metals such as Ru(IV), Fe(III), and V(V) (i.e., yield values ranging between 4 and 55%). The only exception was a thallium(III)-based system (i.e., $Tl(OCOCF_3)_3$–$BF_3 \cdot Et_2O$ in CCl_4/CH_3CN, −40 °C→r.t., 65 h) that led to isolation of **87** (R^1=R^2=R^5=H, R^3=R^4=OMe) in a high yield of 93% (vs. 75% using BTI–$BF_3 \cdot Et_2O$).[94h] However, this intramolecular oxidative coupling of phenol ethers did find some limitations in recent work on the synthesis of pyrazolo[1,5-*f*]phenanthridines (data not shown), as no cyclization could be promoted, even when

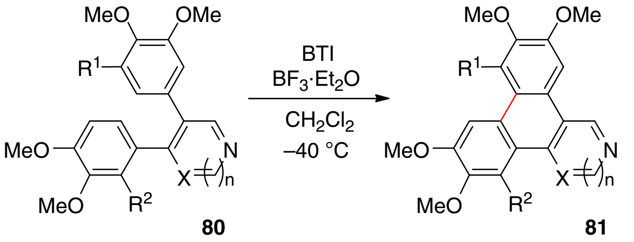
Table 6



78 **79**

R^1	R^2	**79** (%)
OMe	OMe	81[a]
OMe	H	77
H	H	74
H	NO_2	72

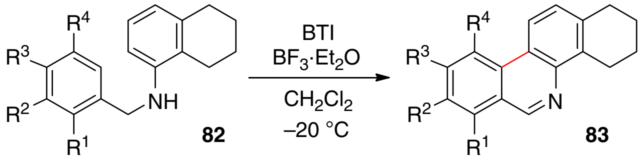
[a] Lower yields (approximately 20–45%) using transition metal-based oxidants.



80 **81**

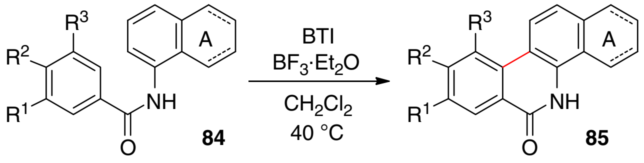
R^1	R^2	X	*n*	**81** (%)
H	H	O	0	85[a]
H	OMe	O	0	61
H	H	N	1	74
H	OMe	N	1	51
OMe	H	N	1	88
H	H	NPh	0	86
H	OMe	NPh	0	55

[a] Lower yields (approximately 42–80%) using transition metal-based oxidants.



82 **83**

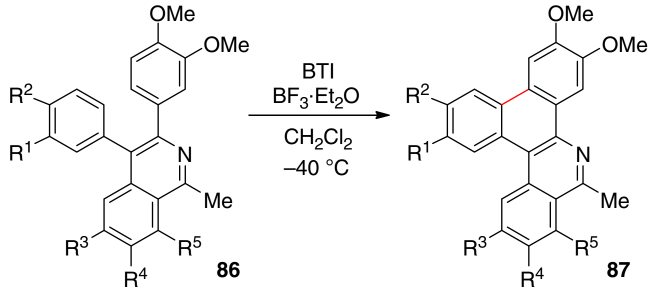
R^1	R^2	R^3	R^4	**83** (%)
H	OMe	OMe	H	77
H	OCH_2O		H	60
OMe	OMe	OMe	H	74
H	OMe	OMe	OMe	73



84 **85**

R^1	R^2	R^3	A	**85** (%)
OMe	OMe	H	*a*	69
OMe	OMe	OMe	*a*	63
OMe	OMe	H	*b*	42

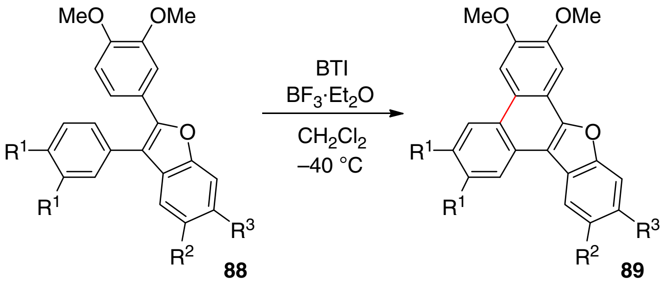
[a] Cyclohexane. [b] Benzene.



86 **87**

R^1	R^2	R^3	R^4	R^5	**87** (%)
H	H	OMe	OMe	H	75[a]
OMe	H	OMe	OMe	H	86
H	NO_2	OMe	OMe	H	42[b]
OMe	H	OMe	H	H	61
OMe	H	OMe	H	OMe	80
H	F	H	F	H	75
H	H	H	H	H	72

[a,b] Better yield (93 and 73%, respectively) using $Tl(OCOCF_3)_3$–$BF_3 \cdot Et_2O$.



88 **89**

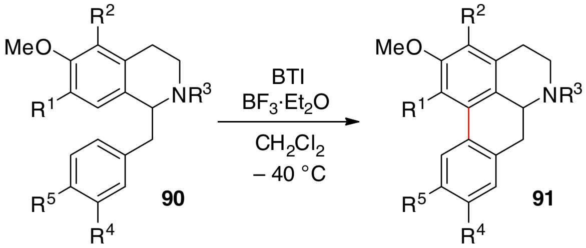
R^1	R^2	R^3	**89** (%)
OMe	H	H	80
H	H	H	40[a]
OMe	Me	Me	84
OMe	F	F	79
OMe	OMe	OMe	73
OMe	OCH_2O		83

[a] Increased to 79% when reaction was run at –20 °C.

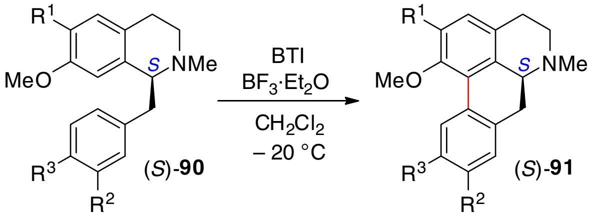
employing different oxidizing agents such as $FeCl_3$, VOF_3, $MoCl_5$, or BTI, all attempts resulting in the recovery of the starting material.[94i] Finally, the pentacyclic benzo[*b*]phenanthro[9,10-*d*]furans **89** are other examples of compounds prepared by the Domínguez team using this metal-free BTI-mediated intramolecular oxidative coupling, starting in this case from 2,3-diarylbenzo[*b*]furans **88** as phenol ether substrates (Table 6).[94j]

This intramolecular biaryl coupling methodology also found successful applications in the synthesis of aporphine alkaloids **91**. The cyclization of racemic *N*-substituted 1-benzyltetrahydroisoquinolines **90** was achieved in moderate to good yields (Table 7). These yields are nevertheless quite satisfactory when considering that this aporphine biaryl bond creation is in competition with the oxidative formation of neospirinedienone structures (see Section 3.13.4).[95] Several tetra- and pentasubstituted racemic aporphine alkaloids, including (±)-glaucine ($R^1{=}R^4{=}R^5{=}OMe$, $R^2{=}H$, $R^3{=}Me$), (±)-thalicsimidine ($R^1{=}R^2{=}R^4{=}R^5{=}OMe$, $R^3{=}Me$), (±)-phoebine ($R^1{=}R^2{=}OMe$, $R^3{=}Me$, R^4–$R^5{=}OCH_2O$), and (±)-romucosine G ($R^1{=}R^2{=}R^4{=}R^5{=}OMe$, $R^3{=}CO_2Me$) were thus synthesized (Table 7).[95]

Table 7



R^1	R^2	R^3	R^4	R^5	**91** (%)
OMe	H	Me	OMe	OMe	58
OMe	H	Me	OCH_2O		36
H	OMe	Me	OMe	OMe	34
H	OMe	CHO	OMe	OMe	42
OMe	OMe	Me	OMe	OMe	31
OMe	OMe	Me	OCH_2O		29
OMe	OMe	CHO	OMe	OMe	72
OMe	OMe	CHO	OCH_2O		67
OMe	OMe	CO_2Me	OMe	OMe	52

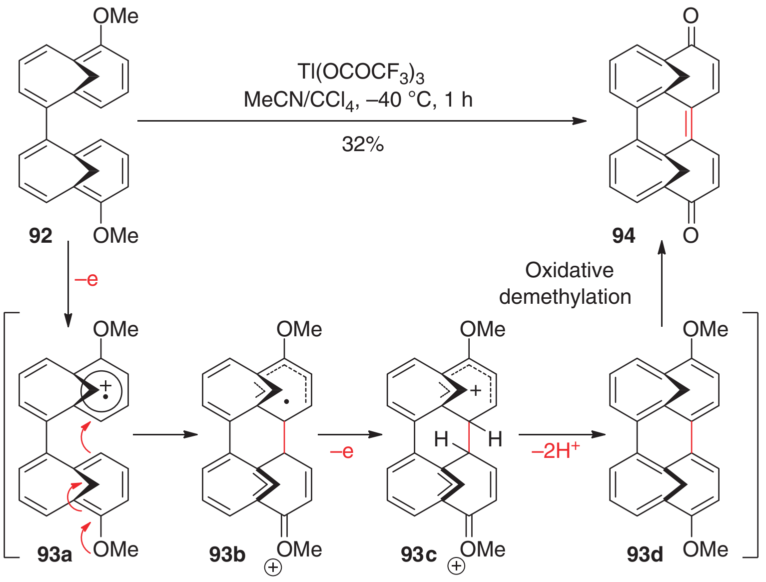


R^1	R^2	R^3	(*S*)-**91** (%)[a]	ee (%)[b]
OMe	OMe	OMe	75	94
H	OCH_2O		75	91
H	OMe	OMe	78	93

[a] Isolated yield. [b] Determined by HPLC.

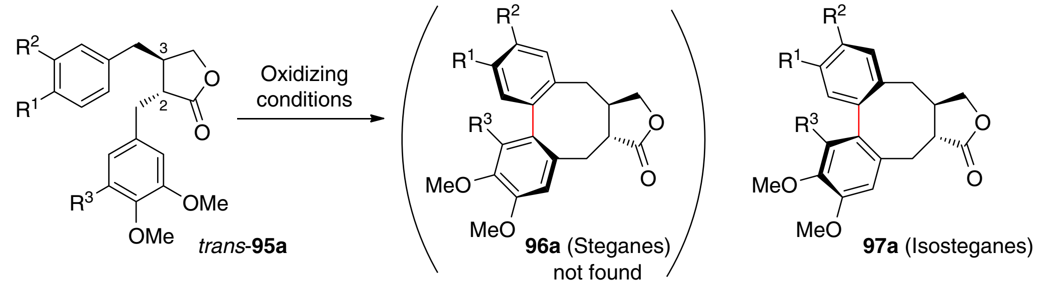
Badía and coworkers utilized enantiopure precursors (*S*)-**90** to generate aporphines (*S*)-**91** in good yields with no noticeable racemization at the stereogenic center present in the starting compound (Table 7).[95c] For example, the (*S*)-(+)-glaucine (**91**, $R^1{=}R^2{=}R^3{=}OMe$) was obtained with an enantiomeric excess of 94% from the (*S*)-laudanosine **90** in a yield of 75% (Table 7). In comparison, the best metal-based oxidizing system identified by the authors was a combination of RuO_2–TFAA–TFA–$BF_3{\cdot}Et_2O$, at low temperature (−10 °C), which allowed the isolation of the (+)-glaucine **91** in a similar yield, but with a slight racemization of the stereogenic center (91% *ee*).[95c] As previously mentioned for the synthesis of dibenzo[*a*,*c*]phenanthridines by the Domínguez group, thallium(III) trifluoroacetate (i.e., $Tl(OCOCF_3)_3$, also referred to as TTFA) was shown to be able to promote intramolecular biaryl coupling of phenol ethers and, in some cases, in an even more efficient manner in comparison with the hypervalent iodine (III)-based system (e.g., see transformation **86**→**87** in Table 6).[94h] Miller and coworkers performed the oxidation of the *meso*-7,7′-dimethoxy-2,2′-bi(1,6-methano[10]-annulenyl) **92** with TTFA in anhydrous acetonitrile/carbon tetrachloride at − 40 °C, and isolated 32% of the *syn*-3a(12c),9a(9b)-dihomoperylene-3,10-dione **94**, the polycyclic structure of which was confirmed by X-ray crystallographic analysis (Scheme 43).[96] Although the authors did not comment the mechanism of this transformation, it may involve the initial formation of a radical cation of type **93a**, which results from a SET from the electron-rich aromatic substrate to thallium(III), as suggested earlier by McKillop, Taylor, and coworkers.[43c] This electrophilic species could next combine intramolecularly with the second but unoxidized anisole-type motif acting as a nucleophile to give a radical cation species of type **93b**, which would then suffer an additional one-electron transfer to reach the dication **93c**, followed successively by rearomatizing deprotonations and oxidative demethylation into **94**, as shown in Scheme 43. The other two mechanistic options that are depicted in Scheme 7 (see Section 3.13.1.3) for intramolecular coupling of phenol ethers via radical substitution or radical pairing are also conceivable for this thallium(III)-mediated coupling reaction. One can also mention that the authors reported a lower yield of 18% of **94** when **92** was treated with vanadium(V) oxytrifluoride (VOF_3) in anhydrous CH_2Cl_2.[96]

Intramolecular oxidative biaryl coupling of phenol ether units has also found many applications in the synthesis of lignans, in particular those of the dibenzocyclooctadiene class. Some examples taken from Ward's work are summarized in Table 8.[75i,97a] Oxidation of *trans*-2,3-dibenzylbutyrolactones **95a** was reported to furnish the corresponding isostegane-type compounds **97a** as single diastereomers; none of the steganes **96a** was obtained. This diastereoselective formation of the isostegane eight-membered ring proceeded in moderate to good yields with different types of one-electron oxidants (i.e., DDQ, VFO_3, or *in situ*-generated Ru

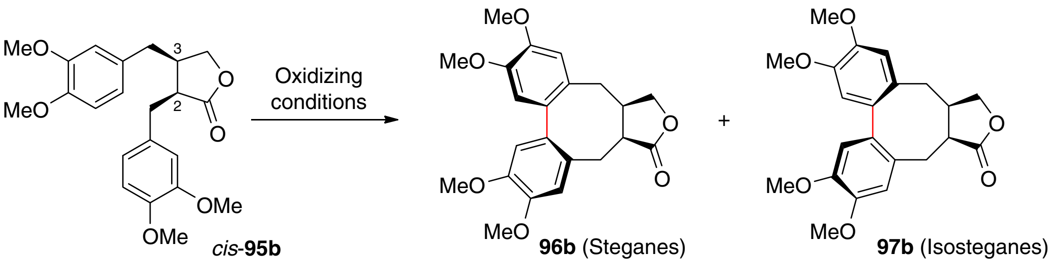


Scheme 43

Table 8



R^1	R^2	R^3	Oxidizing conditions	**97a** (%)
OMe	OMe	H	$RuO_2{\cdot}2H_2O$, TFA –TFAA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –10 °C to r.t.	89
OMe	OMe	H	DDQ, TFA, r.t.	52
OCH_2O		OMe	$RuO_2{\cdot}2H_2O$, TFA–TFAA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, r.t.	59
OCH_2O		OMe	VFO_3, TFA, CH_2Cl_2, –45 °C	65

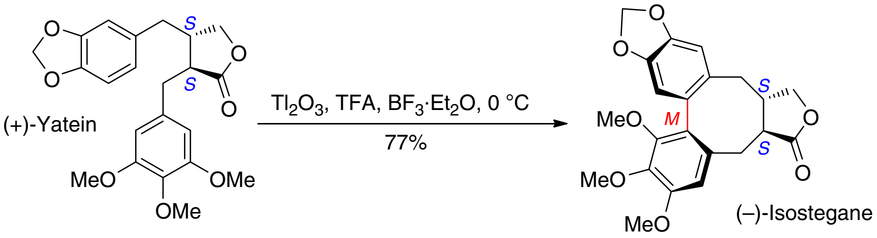


Oxidizing conditions	**96b:97b** (Combined yield%)[a]
$RuO_2{\cdot}2H_2O$, TFA –TFAA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –10 °C to r.t.	1:1.6 (91%)
DDQ, TFA, r.t.	1:1.5 (51%)

[a] Inseparable mixture.

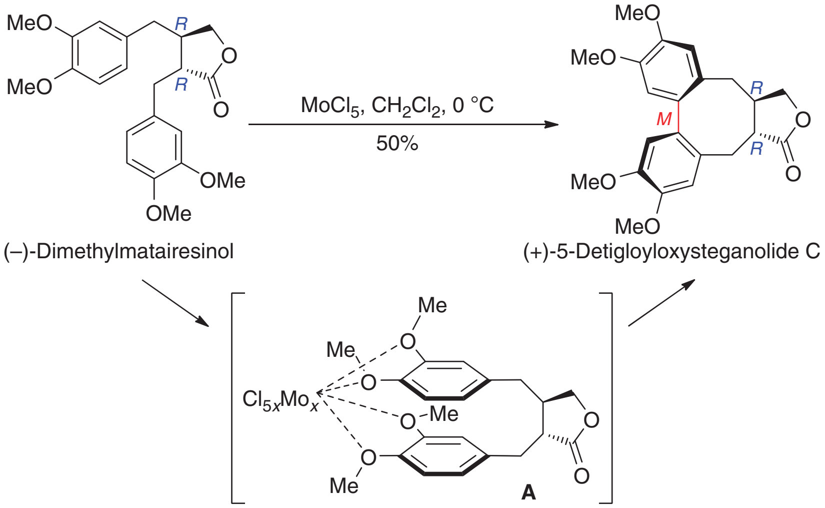
$(OCOCF_3)_3$) (Table 8).[97b,c] In contrast, oxidation of *cis*-2,3-dibenzylbutyrolactones **95b** afforded inseparable mixtures of steganes **96b** and isosteganes **97b**, with diastereomeric ratios slightly in favor of the isostegane skeleton (Table 8). In this case, the biaryl bond formation was best performed with the ruthenium(III)-based oxidizing system.[97b,c]

In a similar approach, Enders and coworkers reported a short synthesis (i.e., seven steps from piperonal) of (−)-isostegane that includes, at the last stage, the treatment of the (*S*,*S*)-dibenzylbutyrolactone (+)-yatein with thallium(III) trifluoroacetate, generated *in situ* from thallium(III) oxide and TFA, in the presence of $BF_3{\cdot}Et_2O$ at 0 °C, to forge the key biaryl bond in an atroposelective manner and in a good yield of 77% (Scheme 44).[98]



Scheme 44

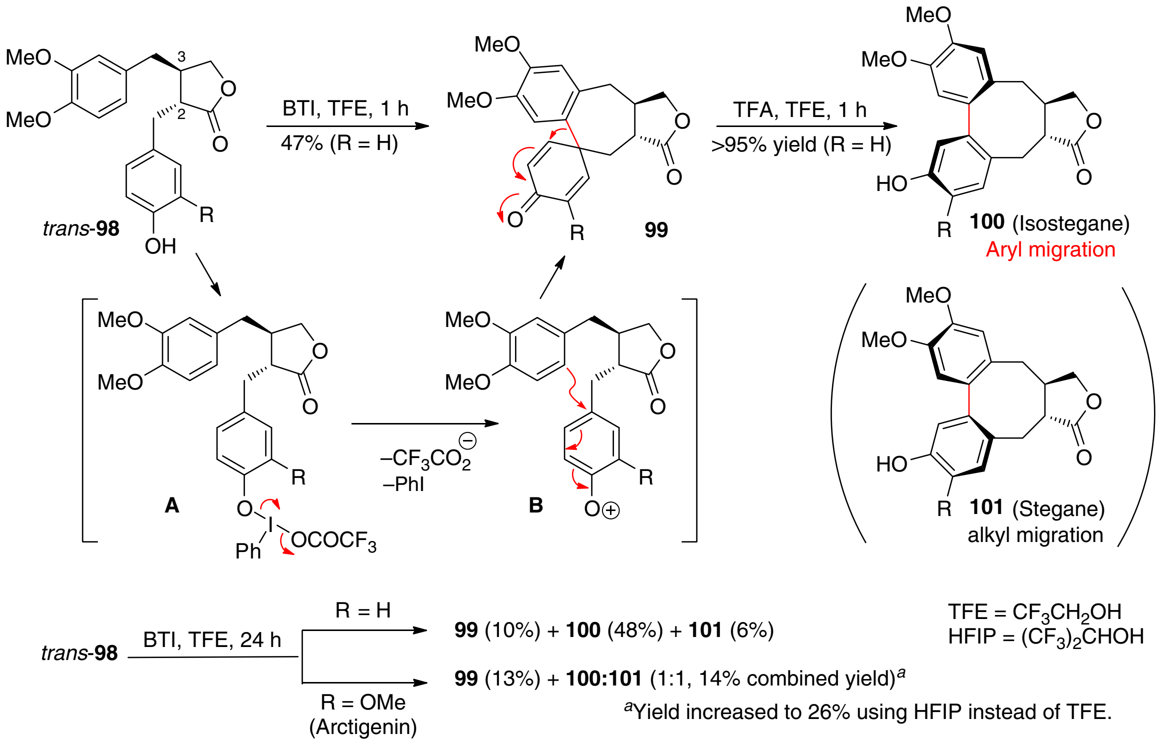
In parallel investigations, Waldvogel and coworkers successfully applied their molybdenum(V)-based oxidative procedure (*vide infra*) to the synthesis of the (+)-5-detigloyloxysteganolide C lignan from its natural precursor (−)-dimethylmatairesinol (Scheme 45).[99] In CH_2Cl_2 at 0 °C, the use of $MoCl_5$ as the sole reagent allowed a clean oxidative cyclization to form the desired eight-membered ring in an atroposelective manner and in a decent yield of 50%. The authors explained the high selectivity for the eight-membered ring formation and the absence of benzylic coupling by the passage via a directing intermediate complex of type **A**, the formation of which is the consequence of the oxophilic Lewis acid character of the molybdenum reagent (Scheme 45).[99]



Scheme 45

Alternatively, the biarylic bond of the dibenzocyclooctadiene-type lignans could also be achieved through oxidative coupling of 2,3-dibenzylbutyrolactone precursors bearing both phenolic and phenol ether units.[97a] For example, *trans*-2,3-dibenzylbutyrolactones **98** having a hydroxyl group at the *para* position of the 2-benzyl moiety were shown to react with the λ^3-iodane BTI reagent to afford, probably through a mechanism involving species such as the λ^3-iodanyl **A** and/or the phenoxenium (PhO^+) **B**, the corresponding spirodienone **99** (e.g., with R=H, 47% after 1 h in TFE). This spirodienone could then undergo an acid-induced (i. e., TFA in TFE, 1 h) dienone-phenol rearrangement to give, through an aryl rather than an alkyl migration, the isostegane derivative **100** in a nearly quantitative yield (Scheme 46).[100] Surprisingly, when the same BTI-mediated reaction was run over 24 h, the isostegane **100** was still isolated as the major compound, but in only 48% yield. Some of the corresponding stegane isomer **101** (6%) and the spirodienone 4 (10%) were also isolated (Scheme 46). In the case of arctigenin (i.e., *trans*-**98** with R=OMe), rather disappointing results were obtained, because the stegane isomers **100** and **101** were formed in equal amounts and isolated as a 1:1 mixture in a combined yield of 14% (Scheme 46). The replacement of TFE by HFIP allowed a slight gain in yield up to 26%.[100]

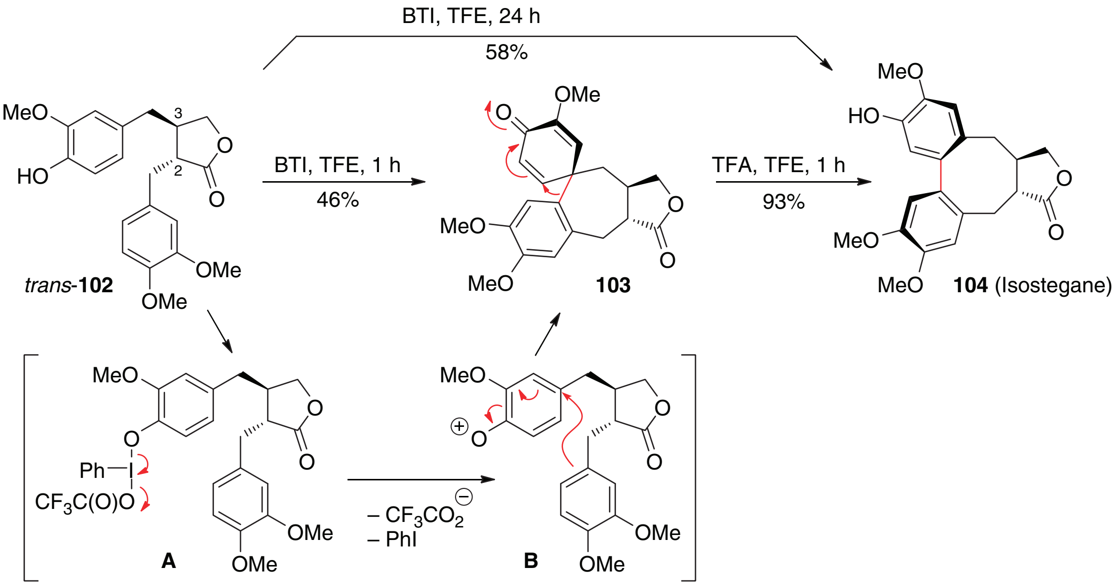
Thus, besides this minor solvent effect, the dienone-phenol rearrangement of **99** into **100** and **101** is strongly and directly influenced by the substitution pattern of the phenolic ring. Ward and coworkers also investigated oxidative cyclization of *cis*-2,3-dibenzylbutyrolactones **98** (data not shown), and they reported that phenolic oxidative coupling reactions of such substrates performed using either BTI in TFE, DDQ-TFA or a ruthenium-based oxidizing system all furnished 1:1 mixtures of the stegane isomers in yields ranging from 60 to 80%.[97b,c]



Scheme 46

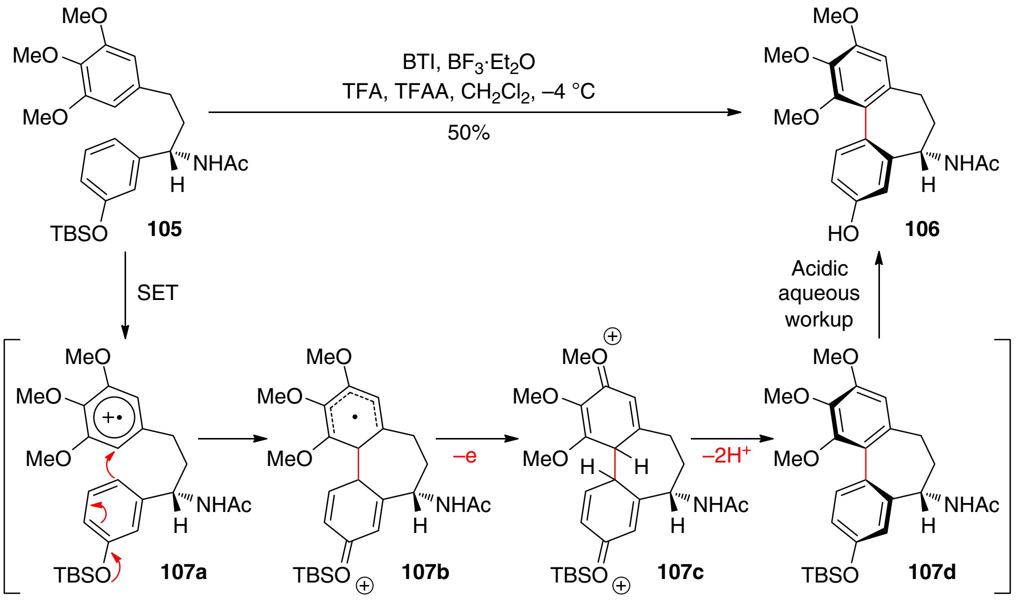
Furthermore, on treatment with BTI in TFE, the *trans*-2,3-dibenzylbutyrolactone **102**, in which the phenolic OH group is located at the *para*-position of the 3-benzyl moiety, was fully converted after 1 h to afford a major product, which was isolated in a yield of 46% and characterized as the spirodienone **103**. Its formation was again explained through the intermediacy of a phenoxenium species (PhO^+) **B** (Scheme 47). When the reaction was allowed to continue for a longer time, no sign of **103** was observed, and the isostegane **104** was isolated in 58% yield.[97b] The passage by the spirodienone **103** and its dienone-phenol rearrangement into the isostegane **104** was confirmed by treating **103** with TFA in TFE, which furnished **104** in 93% yield (Scheme 47). It is interesting to note that when similar oxidizing conditions were applied to a *trans*-2,3-dibenzylbutyrolactone having a phenolic OH group at the *meta*-position of the 3-benzyl moiety, the formation of the corresponding spirodienone was not observed and only the isostegane final product was isolated in a yield of 61% (data not shown).[97b] Moreover, treatment of this *trans*-2,3-dibenzylbutyrolactone **102** with ruthenium tetra(trifluoroacetate) cleanly afforded the isostegane derivative **104** in a good yield of 85%.[97c]

Another recent example of intramolecular oxidative biaryl coupling performed on phenol ethers using a modified version of the BTI-based Kita's protocol is the synthesis of the *N*-acetylcolchinol **106** described by Kocienski and coworkers.[101] On treatment with BTI (1.2 equivalents) and $BF_3{\cdot}Et_2O$ (2.4 equivalents) in a mixture of TFA, TFAA and CH_2Cl_2 at –4 °C, the 1,3-diarylpropylacetamide **105** was found to cleanly cyclize into the targeted colchicine derivative **106**, which was isolated in 50% yield (Scheme 48). The use of TBSOTf as a BTI activator in replacement of $BF_3{\cdot}Et_2O$ also furnished **106** in approximately 50% yield, but with several minor by-products that were difficult to separate. The classical Kita's BTI conditions (i.e., BTI–$BF_3{\cdot}Et_2O$ in CH_2Cl_2 at –40 °C) were found much less appropriate, giving rise to **106** in only 12% yield. However, Kocienski and coworkers also used McKillop's thallium(III)-based conditions by adding a solution of **105** in CH_2Cl_2 to TTFA–$BF_3{\cdot}Et_2O$ in a 20:1 TFA–TFAA mixture at –4 °C. The *N*-acetylcolchinol **106** was obtained in this case in 47% yield.[101] Further optimization studies of this **105** to **106** conversion revealed that replacement of the TBS group in **105** by a TIPS or an acetyl group also gave **106** in 47% yields, whereas none of the desired product was obtained using a MOM group. Moreover, submission of the unprotected phenolic analog of **105** to their oxidative conditions furnished **106** in 25% yield, thus suggesting that the reaction could take place, at least in part, through a phenolic coupling pathway. LCMS monitoring of the cyclization of **105** did not, however, show any evidence of removal of the TBS group during the reaction. Kocienski and coworkers thus concluded that its loss must occur during the aqueous workup.



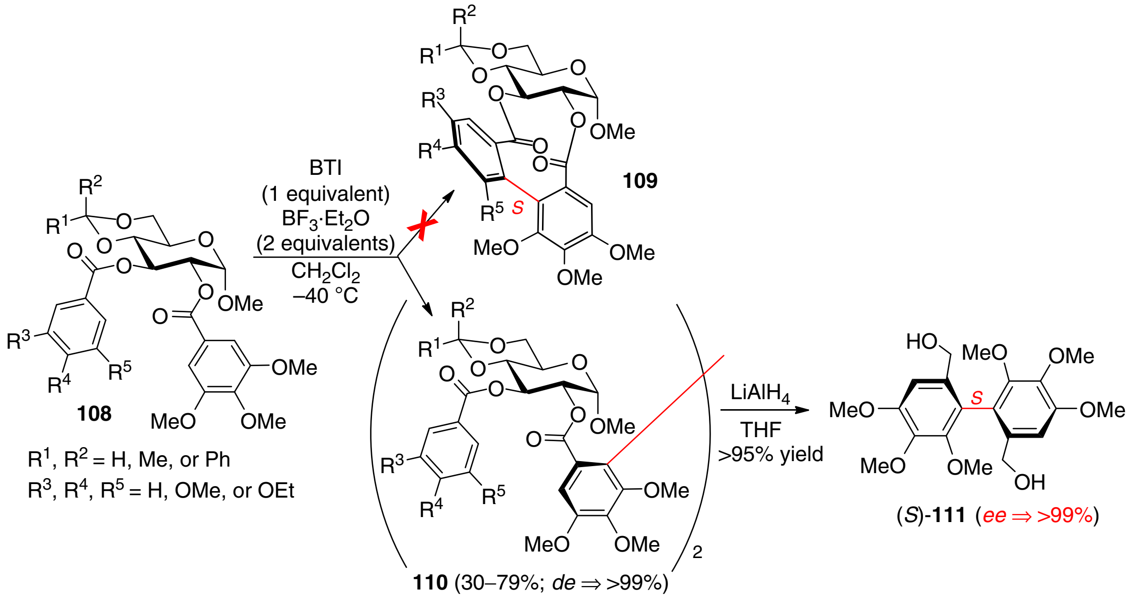
Scheme 47

Consequently, this **105** to **106** conversion is likely to follow a nonphenolic pathway in which a radical cation **107a** is initially formed through a SET mechanism from the more electron-rich trimethoxylated phenyl ring (Scheme 48). This species would next combine intramolecularly with the silylated phenyl ring, acting as a nucleophile, to give the radical cation **107b** en route to *N*-acetylcolchinol **106**, as depicted in Scheme 48.[101]



Scheme 48

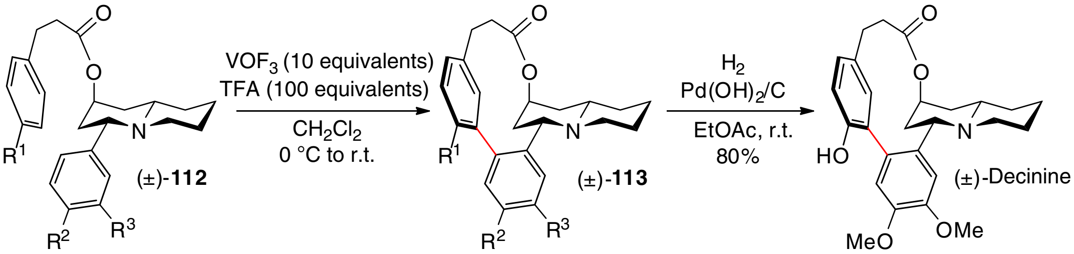
Kita and coworkers also tested their BTI–BF$_3$·Et$_2$O-mediated oxidative biaryl coupling reaction in the context of the synthesis of ellagitannin natural products.[42a,72] A series of 1,2-digalloylated derivatives of protected methyl α-D-glucopyranosides **108** were thus coupled in the aim of benefiting from an induction of asymmetry from the chiral glucopyranoside core during the intramolecular formation of the ellagitannin biaryl HHDP motif. However, instead of giving the initially targeted biaryl-containing compounds **109**, the coupling reactions unexpectedly occurred in an intermolecular fashion to afford the dimers **110**, yet still with high diastereoselectivity and in moderate to good yields (Scheme 49).[42a,90a,93] Only the aromatic ring attached to the 2-position of the sugar moiety participated in these intermolecular coupling reactions, and only the methyl α-D-glucopyranoside derivative was effective in bringing about this reaction, in contrast to its *β*-anomer or other sugar substrates based on D-galactose or D-mannose that were found totally inefficient.[42a] The reduction of these dimers with $LiAlH_4$ quantitatively released the sugar units and afforded the biaryl (*S*)-**111** with an enantiomeric excess value superior to 99% (Scheme 49).[42a,90a,93]



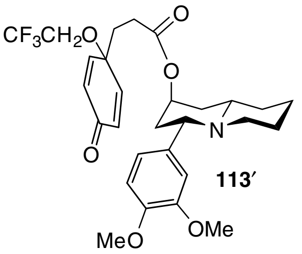
Scheme 49

To complete their recent synthesis of (±)-decinine, a quinolizidine alkaloid of the *Lythraceae* family featuring a strained 12-membered ring, Yang and coworkers also relied on an oxidative biaryl coupling step.[102] They submitted various phenolic and nonphenolic advanced intermediates of type **112** to various oxidation conditions (Table 9). Attempts to oxidatively couple the bisphenolic racemate **112** (i.e., $R^1=R^2=R^3=OH$) were all unsuccessful using different oxidants (e.g., DIB, BTI, cerium ammonium nitrate (CAN), $K_3Fe(CN)_6$) in different solvents conditions (e.g., CH_2Cl_2, TFE, HFIP, CH_3CN, MeOH). Decomposition was reported in the majority of cases. With the mixed phenolic/nonphenolic variant of **112** (i.e., $R^1=OH$, $R^2=R^3=OMe$), Kita's BTI–$BF_3·Et_2O$ system, used either in CH_2Cl_2, TFE, or HFIP at low temperatures, also mainly led to decomposition or, at best, to the

Table 9



R^1	R^2	R^3	**113** (%)
OH	OH	OH	Decomposition
OH	OMe	OMe	Decomposition
OMOM	OMe	OMe	Decomposition
OBn	OMe	OMe	Decomposition
OAc	OMe	OMe	Side-chain oxidation
OMe	OMe	OMe	7
OPNB	OMe	OMe	32



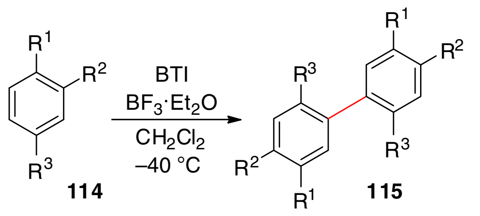
113′

formation of the cyclohexa-2,5-dienone **113′** (Table 9).[102] Yang and coworkers then explored the utilization of nonphenolic variants of **112**. Again, most of the attempts led to decomposition or undesired chemical transformations, until treatment of the per-methylated **112** (i.e., $R^1=R^2=R^3=OMe$) with vanadium(V) oxytrifluoride (VOF_3) in the presence of TFA in CH_2Cl_2 at 0 °C afforded the desired product (±)-**113** in a modest yield of 7%, but with the desired axial chirality (Table 9). Application of these conditions to a *para*-nitrobenzylated (PNB) version of **112** (i.e., $R^1=OPNB$, $R^2=R^3=OMe$) furnished the corresponding biaryl (±)-**113** in 32% yield, again with the desired axial chirality (Table 9). The authors noted that the large excess of TFA (100 equivalents) played a crucial role in the success of the reaction by maintaining the oxidation-sensitive tertiary amine of the substrate under the form of an ammonium salt. The PNB-protected biaryl (±)-**113** was finally released by hydrogenolysis using Pearlman's catalyst (i.e., $Pd(OH)_2/C$), hence completing the first total synthesis of (±)-decinine (Table 9).[102]

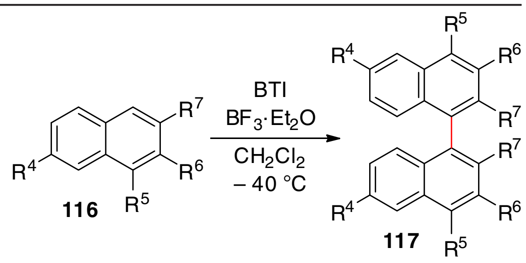
3.13.2.2.2 Intermolecular biaryl coupling

Kita and coworkers have also shown that their method of oxidative biaryl coupling of phenol ethers can also be used to engender self- or cross-coupling reactions in an intermolecular fashion. For example, self-coupling of substituted methoxybenzenes **114** into biaryls **115** was successfully performed, in most cases, using BTI–$BF_3{\cdot}Et_2O$ (Table 10). A notable exception was the complete lack of reaction when **114** is equipped with a strong electron-withdrawing NO_2 group.[90b] Polymer-supported (PS) versions of hypervalent iodine(III) reagents, such as PS-DIB or PS-BTI,[103] were also tested by Kita and coworkers to achieve these self-coupling reactions. Although reaction times were longer (15–17 h vs. 1.5 h) with PS-DIB, likely because of sparse solubility in CH_2Cl_2 at −40 °C, conversions of **114** proceeded smoothly to furnish biaryls **115** in good isolated yields (75–77%). PS-BTI showed higher solubility and gave compounds **115** in shorter reaction times (typically 3 h) and in better yields (82–89%).[90b] Binaphthyl compounds **117** were also synthesized in good yields under the same conditions (Table 10), but the use of an excess of BTI or higher reaction temperature (typically > 0 °C) gave oligomers or quinone derivatives as overoxidation by-products.[90b]

Table 10



R^1	R^2	R^3	**115** (yield %)
OMe	OMe	OMe	92
OMe	OMe	Me	93
OMe	OMe	Br	97
OMe	OMe	NO_2	No reaction
OMe	Me	OMe	92
OMe	Br	OMe	91
Br	OMe	H	72

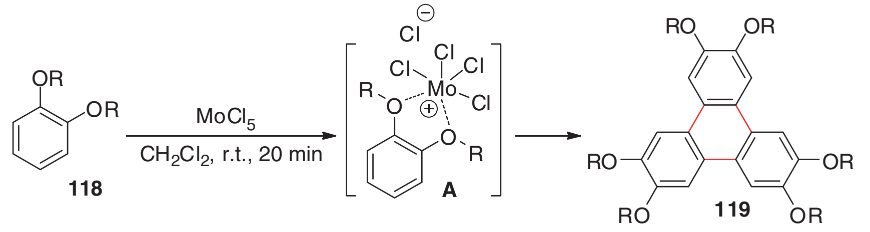


R^4	R^5	R^6	R^7	**117** (yield %)
H	H	H	OMe	91
H	H	OMe	OMe	61
Br	H	H	OMe	98
H	OMe	H	H	94
OMe	H	H	OMe	82

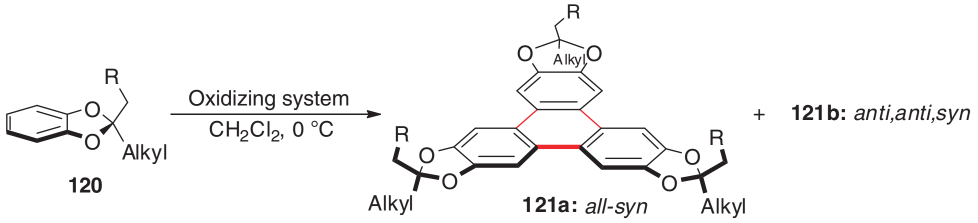
The performances of molybdenum(V) chloride ($MoCl_5$) in oxidative coupling of phenol ethers have also been evaluated in intermolecular scenarios.[104] For example, Kumar and coworkers discovered that $MoCl_5$ could mediate the oxidative trimerization of 1,2-dialkoxybenzenes **118** into hexaalkoxytriphenylenes **119** in high yields (Table 11).[105] This $MoCl_5$-based method constitutes a rapid and better alternative to methods based on the use of other oxidants such as chloranil or $FeCl_3$ to prepare discotic mesogens and potential candidates for opto-electronic devices.[105] Although $MoCl_5$ was considered as a two-electron oxidant by these authors and others, Waldvogel and coworkers proposed that it can act as a one-electron oxidant by first forming a coordinated species of type **A** within which a SET from the π-system to the molybdenum center would occur to form a radical cation species ($PhOR^{\bullet+}$). Such a species would then evolve to react with another electron-rich arene to create C–C bond, and so on.[106a] Moreover, $MoCl_5$ is known to cleave ketals. Waldvogel and coworkers showed that catechol ketals were very quickly oxidatively converted into the corresponding triphenylene ketals. A noteworthy series of examples is the oxidative trimerization of catechol ketals **120** that, on treatment with $MoCl_5$ or $MoCl_5$–$TiCl_4$ mixtures, led to the corresponding triphenylene ketals with a marked preference for the all-*syn* stereoisomers **121a** (Table 11).[106b] Waldvogel and coworkers also demonstrated that the oxidative transformation itself initially provides a statistical distribution of isomers, in which the *anti,anti,syn* isomers **121b** in fact dominate.

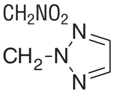
An *in situ* isomerization ensues and would be induced by some partially reduced molybdenum chloride species, or by the $TiCl_4$ Lewis acid additive. Selectivity for the all-*syn*- versus the *anti,anti,syn*-isomers could thus be obtained in a ratio up to 17:1 (**Table 11**). The isomerization of the *anti,anti,syn*-isomers **121b** to the desired C_3-symmetric all-*syn*-derivatives **121a** could be achieved in yields up to 96%.[106b,c]

Table 11



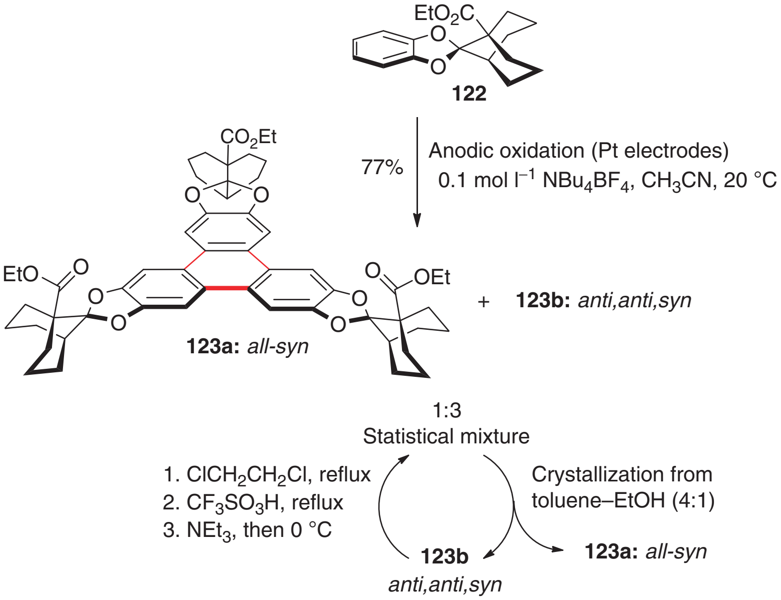
R	**119** (%)
Bu	95
C_6H_{13}	94
$C_{10}H_{21}$	80
Me	74



R	*Alkyl*	*Oxidizing system*	***121a*** *(%)*	***121b*** *(%)*
CO_2Me	Bu^t	$MoCl_5$ (2 equivalents), 2 h	12	37
CO_2Me	Bu^t	$MoCl_5$ (2 equivalents), $TiCl_4$ (2 equivalents), 2 h	50	22
CO_2Me	Bu^t	$MoCl_5$ (3 equivalents), $TiCl_4$ (3 equivalents), 2 h	52	25
CO_2Me	Bu^t	$MoCl_5$ (3 equivalents), $TiCl_4$ (3 equivalents), 2 h	68	4
CO_2Me	Pr^i	$MoCl_5$ (3 equivalents), $TiCl_4$ (3 equivalents), 8 h	41	6
CO_2Me	Cyclohexyl	$MoCl_5$ (3 equivalents), $TiCl_4$ (3 equivalents), 10 h	48	–
CN	Bu^t	$MoCl_5$ (3 equivalents), 15 min	52	22
CN	Bu^t	$MoCl_5$ (3 equivalents), $TiCl_4$ (3 equivalents), 5 h	48	20
CH_2CN	Bu^t	$MoCl_5$ (3 equivalents), $TiCl_4$ (3 equivalents), 5 h	41	21
CH_2CN_2CN	Bu^t	$MoCl_5$ (3 equivalents), $TiCl_4$ (3 equivalents), 4 h	38	42
CH_2NO_2	Bu^t	$MoCl_5$ (3 equivalents), $TiCl_4$ (3 equivalents), 5 h	47	28
 CH_2-N	Bu^t	$MoCl_5$ (3 equivalents), $TiCl_4$ (3 equivalents), 4 h	41	22
	Bu^t	$MoCl_5$ (3 equivalents), 1 h	45	35

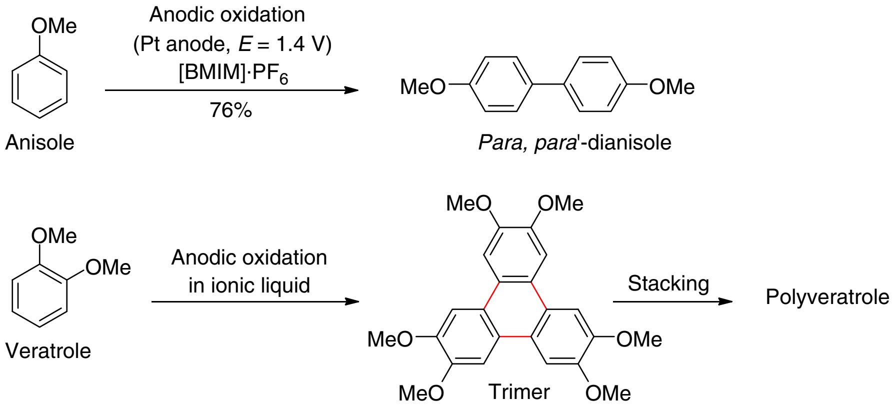
However, this molybdenum(V)-mediated procedure found some limitations when rigid catechol ketals such as **122** were submitted to oxidative trimerization. Waldvogel and coworkers then turned to rely on an electrochemical protocol and found very simple galvanostic conditions (i.e., 0.45 A cm^{-2}, 3.1 F) using platinum sheets as electrode material to convert **122** into a 1:3 statistical mixture of trimers **123a** and **123b** (**Scheme 50**).[107] Best results were obtained under an inert atmosphere using acetonitrile and tetrabutylammonium tetrafluoroborate (NBu_4BF_4) as solvent and electrolyte, respectively. Of particular note is that the desired triphenylene ketals precipitated out in acetonitrile shortly after starting the reaction, thus allowing a continual removal of the products from the reaction medium to prevent any further oxidation or subsequent side reaction. The all-*syn* and *anti,anti,syn*-isomers **123a** and **123b** were then separated by crystallization, and the undesired trimer **123b** could be equilibrated back to the statistical mixture under strongly acidic reaction conditions (**Scheme 50**). Repetition of this sequence gave access to large amounts of the all-*syn* isomer **123a**, because this electrochemically induced trimerization could be performed easily on a 20 g scale.[107]

Another recent example of the use of an electrooxidative procedure for the conversion of phenol ethers into biaryls was described by Jouikov and coworkers. They notably showed that ionic liquids (IL), which combine both solvent and electrolyte in one system, are convenient media for anodic oxidation of aromatic compounds in a simple undivided cell.[108] In contrast to alkylated arenes, methoxylated arenes such as anisole and veratrole are highly soluble in IL, in particular in [BMIM]·PF_6 (i.e., 1-butyl-3-methylimidazolium hexafluorophosphate). When an anodic oxidative self-coupling of anisole was performed in [BMIM]·PF_6, using a platinum electrode and a potential value of 1.4 V, *para,para'*-dianisole was isolated as the sole coupled product in a good yield of 76% (**Scheme 51**). In the case of veratrole, the expected hexamethoxytriphenylene is easier to oxidize than the starting molecule, so this product is usually obtained as the corresponding radical cation, which forms stacks of trimeric



Scheme 50

fragments. The resulting pseudo polymeric tubular systems are interesting as liquid crystal precursors. Jouikov and coworkers did observe the characteristic intense blue color attributed to this polyveratrole formation when they applied their anodic oxidation conditions to veratrole. Several IL, either of the imidazolium family (e.g., [BMIM]·BF$_4$, [BMIM]·PF$_6$, and [BMIM]·NTf$_2$) or phosphonium- and ammonium-based ones (e.g., [(C$_6$H$_{13}$)$_3$PC$_{14}$H$_{29}$]·NTf$_2$ and [Me$_3$BuN]·NTf$_2$) were used with success for this oxidative transformation.[108]



Scheme 51

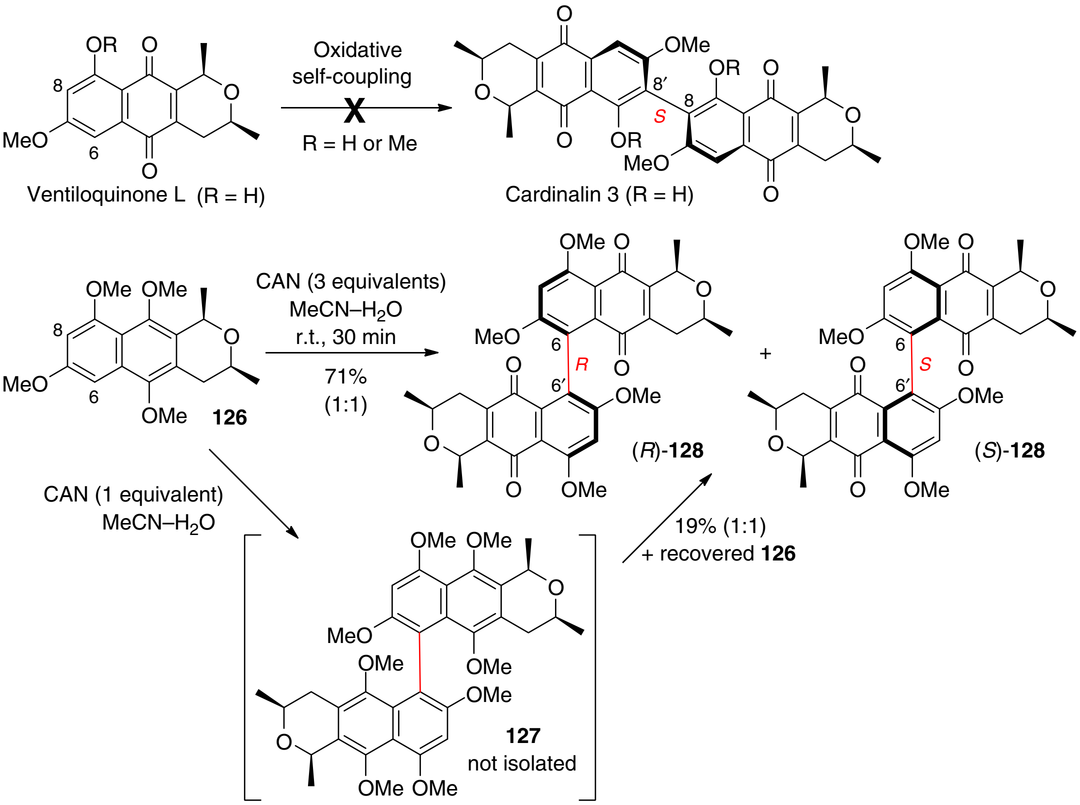
Back to MoCl$_5$-mediated biaryl formation, Waldvogel and coworkers showed that such a coupling reaction can also be performed with phenol ethers bearing sensitive substituents, such as iodo-substituents.[104,109a] Electron-rich iodobenzenes **124** were indeed successfully converted into biaryls **125** in good yields, without significant loss of the iodo-substituent(s) (Table 12). The authors specified that addition of MoCl$_5$ in small portions was advantageous to keep the deiodinated by-product to $<$ 5%. This molybdenum-based procedure, which was presented as an environmentally friendly alternative to the use of thallium(III)- and lead(IV)-based reagents, allowed direct access to **125** (i.e., R=I) with four iodo-substituents adjacent to the biaryl axis, and this in a fair yield of 47%, despite the steric demand of the iodo substituents (Table 12).[109a] The other oxidants tested in this study on diiodobenzene **124** (R=I) led to either no conversion (using VCl$_4$ or VOCl$_3$), decomposition (using FeCl$_3$–H$_2$SO$_4$), or the expected biaryl **125**, but in lower yields (18 and 20% using 2 equivalents of FeCl$_3$–HOAc or 15 equivalents of VOF$_3$, respectively). Two years later, the same authors reported major yield improvements, up to 75% for the tetraiodinated biaryl **125** (R=I), using Kita's λ^3-iodane-based BTI–BF$_3$·Et$_2$O oxidizing system (Table 12).[109b] This clean coupling reaction usually occurred *para* to an alkoxy substituent in spite of the steric demand of the iodine atom(s), likely through a SET mechanism, and was applied successfully to substrates with benzodioxole moieties (data not shown), thus offering direct access to multiply iodinated biaryls, which are notably potential candidates as novel contrast media for X-ray diagnostics.[109b]

Table 12

R	*Oxidant (equivalent)*	*Conditions*	***125** (%)*
H	$MoCl_5$ (1.2)	CH_2Cl_2, 0 °C, 40 min	81
Me	$MoCl_5$ (1.2)	CH_2Cl_2, 0 °C, 40 min	58
I	$MoCl_5$ (0.7)	CH_2Cl_2, 0 °C, 40 min	47
H	BTI (0.5)–BF_3•Et_2O (1.0)	CH_2Cl_2, 0 °C to r.t., 1–2.5 h	66[a]
I	BTI (0.5)–BF_3•Et_2O (1.0)	CH_2Cl_2, 0 °C to r.t., 1–2.5 h	75[b]

[a] 23% of recovered 124.
[b] 13% of recovered 124.

A recent example of an intermolecular oxidative biaryl self-coupling applied to the synthesis of natural products can be found in the work reported by Brimble and coworkers on their biomimetic studies toward the cytotoxic cardinalin 3, a member of a family of dimeric pyranonaphthoquinones.[110] After having set up an efficient enantioselective synthesis of ventiloquinone L, a wide range of known phenolic oxidative dimerization conditions, including basic ferricyanide, $FeCl_3$, lead(IV) salts, copper(I)/O_2, hν/O_2, and CAN, were tested, but no cardinalin 3 was ever isolated (Scheme 52). Similarly, attempted coupling of the ventiloquinone L methyl ether failed to deliver the corresponding dimer. The authors thus decided to consider an advanced aromatic

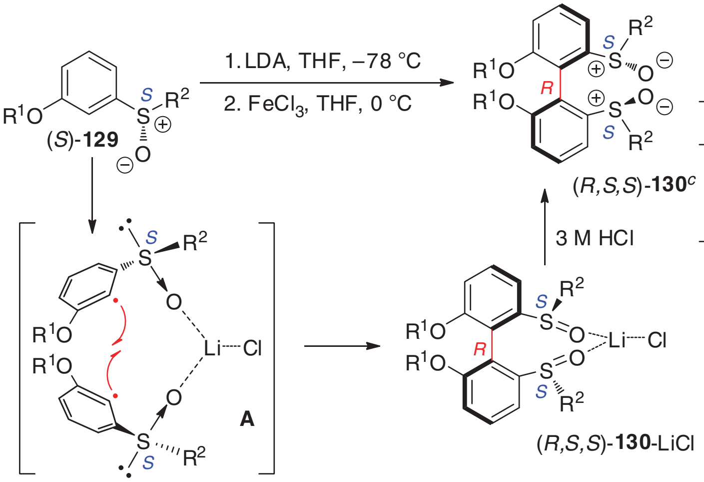


Scheme 52

intermediate instead of a pyranonaphthoquinone as candidate to the key dimerization step, and they selected the naphthopyran **126**. A quick screening of oxidative conditions led them to identify the one-electron oxidant CAN as the most promising reagent. Indeed, on treatment with 3 equivalents of CAN in acetonitrile and water, at room temperature, compound **126** cleanly dimerized to afford, in a good yield of 71%, a 1:1 mixture of the two C6–C6′ coupled atropoisomers (*R*)-**128** and (*S*)-**128** (Scheme 52). So, the desired C8–C8′ biaryl coupling did not operate, and the chirality of the pyran ring of **126** did not exert any asymmetric induction in the biaryl-forming step. Nevertheless, such a CAN-mediated C6–C6′ dimerization of a naphthopyran is extremely rare, and this tandem oxidative biaryl coupling-demethylation sequence was further investigated to determine which event occurs first. Treatment of **126** with 1 equivalent of CAN only allowed isolation of dimers (*R*)-**128** and (*S*)-**128**, in 19% yield and again as a 1:1 mixture, along with a substantial amount of unreacted **126**. Submission of ventiloquinone L methyl ether to varying amounts of CAN did not afford any of the dimers, thus suggesting that the biaryl bond formation is the first event, even if the dimeric naphthopyran **127** was not observed (Scheme 52). Final selective deprotection by treatment with boron trichloride furnished the corresponding atropoisomeric mixture of the C6 regioisomer of cardinalin 3.[110]

A highly efficient diastereoselective self-coupling of phenol ethers was recently reported by Zhou, Li, and coworkers, who used chiral sulfoxide auxiliaries to control the axial chirality of biaryl products.[111a] The *tert*-butyl- and *para*-tolylsulfinyl groups were both shown to be very good inducers of asymmetry when enantiopure sulfoxides such as **129** were deprotonated on treatment with LDA to generate the corresponding *ortho*-lithiated intermediates, and subsequently oxidized using $FeCl_3$ to promote coupling[111b] into bis-sulfoxides **130** by radical pairing. These biarylic bis-sulfoxides were thus obtained in good yields with high diastereoselectivity (Table 13).[111a] A computational study was carried out at the B3LYP/6−311+G** level to delineate the origin of such an impressive diastereoselectivity, and it was found that the major diastereomers (*R*,*S*,*S*)-**130** were more stable than (*S*,*S*,*S*)-**130**, owing to the absence of repulsion between the two R^2 groups (i.e., *tert*-butyl or *para*-tolyl). The authors hence proposed that the chiral induction could originate from this repulsive effect between these R^2 groups and, in addition, from the coordination of the lithium cation with the sulfinyl groups, keeping the two S=O bonds on the same side (see the coordinated bisradical intermediate **A** in Table 13). The resulting (*R*,*S*,*S*)-**130**-LiCl species were then smoothly hydrolyzed under acidic conditions to afford the bis-sulfoxides (*R*,*S*,*S*)-**130** (Table 13).[111a]

Table 13



R^1	R^2	**130** (yield %)[a]	*dr*[b]
Me	Bu^t	76	> 95:5
Me	Tol^p	73	92:8

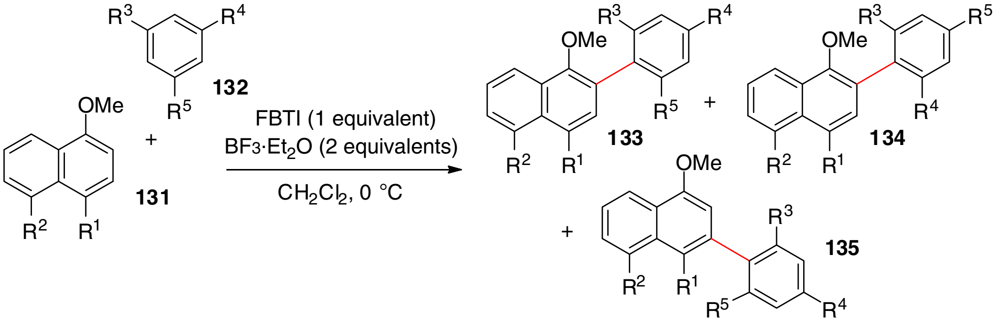
[a] Mixtures of both diastereomers.

[b] Determined by ^1H NMR on the crude mixture.

[c] The absolute configuration of major diastereomer was determined by X-ray analysis.

As far as cross-coupling reactions are concerned, Kita and coworkers recently reported an efficient access to oxygenated naphthalene–benzene biaryls.[112] This intermolecular C–H cross-coupling between aromatic ethers was performed without the use of prefunctionalized substrates, again relying on an activated λ^3-iodane-induced SET process. Initial attempts carried out by using the BTI–$BF_3{\cdot}Et_2O$ system (*vide supra*) afforded the mixed biaryl **133** (i.e., R^2=H, R^1=R^3=R^4=OMe, R^5=Me) in a decent yield of 63%, but also led to the formation of the undesired self-coupled product from **132** (i.e., R^3=R^4=OMe, R^5=Me) in approximately 10% yield. A change in the nature of the oxidant significantly affected the ratio of the coupled products, as well as the reaction yield. Other BTI-like λ^3-iodanes were investigated, varying the substitution pattern of the phenyl ligand with either electron-donating groups (e.g., 2,4,6-MeC_6H_2, 4-Me, or 4-$MeOC_6H_4$) or electron-withdrawing groups (e.g., 4-CF_3, C_6F_5, or 4-$CF_3C_6F_4$). Best results were obtained with commercially available per-fluorinated BTI (i.e., $C_6F_5I(OCOCF_3)_2$, also referred to as FBTI). No self-coupling was observed using this per-fluorinated λ^3-iodane, and the yield could be raised up to > 99% (Table 14).[112] It is worth noting that none of the other typical chemical SET oxidants (e.g., $FeCl_3$, $MoCl_5$, $Mn(OAc)_3$, CAN, DDQ) or anodic oxidations produced the cross-coupled biaryl as the major product. The FBTI–$BF_3{\cdot}Et_2O$ system was thus found to be highly selective with respect to the oxidation of methoxynaphthalene **131** (i.e., R^1=OMe, R^2=H), producing the corresponding radical cation ($PhOR^{\bullet+}$) as the sole reactive species, which is then trapped by the benzene derivatives **132** (i.e., $R^3{=}R^4{=}OMe$, $R^5{=}Me$ or OMe) to give the mixed biaryls **133** in quasiquantitative yields (Table 14). This very efficient methodology was next applied to a series of substituted benzenes of type **132** to produce the desired oxygenated mixed biaryls, without any formation of self-coupled dimers (Table 14). Several protecting groups (e.g., benzyl, acetyl) and functionalities (e.g., alkyne, phenol, amine) were shown acceptable on coupling partners of type **132**, and led to the isolation of mixed biaryls **133** and **134** in good yields (Table 14).[112] Similarly, a series of differently substituted methoxynaphthalenes of type **131** was successfully cross-coupled with 1,3,5-trimethoxybenzene to give mixed biaryls **133** and/or **135** in good to excellent combined yields and ratios dependent on the substitution pattern of the starting methoxynaphthalenes **131** (Table 14). The compatibility of Kita's FBTI-based cross-coupling conditions with the presence of a bromine atom is particularly worth noting, because such a halogen substituent is usually sacrificed in most classical biaryl cross-coupling methods.

Table 14



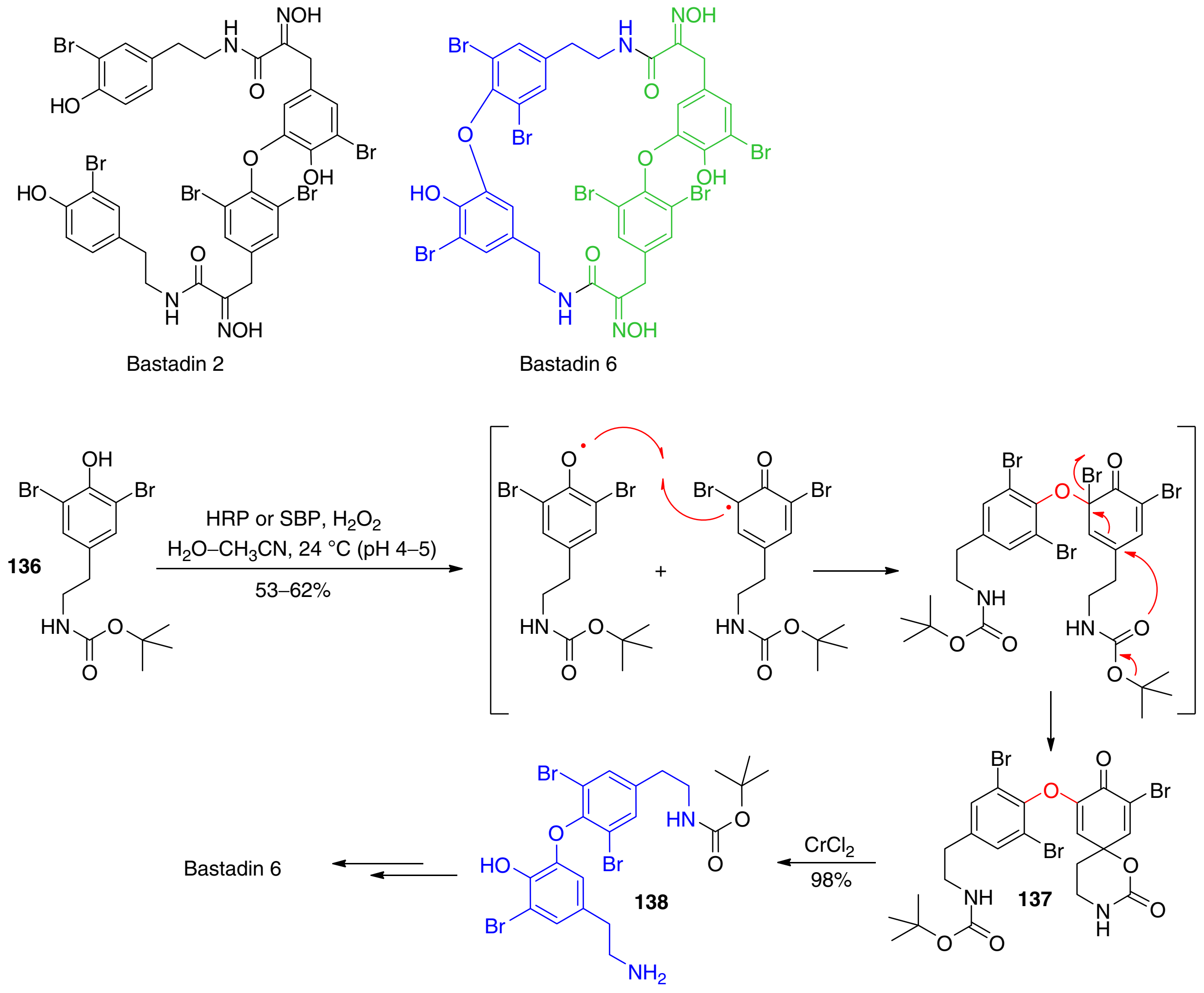
R^1	R^2	R^3	R^4	R^5	*Regioisomeric mixed biaryls (isolated yields)*
OMe	H	OMe	OMe	Me	**133** (>99%)
OMe	H	OMe	OMe	OMe	**133** (>99%)
OMe	H	OBn	OBn	OBn	**133** (87%)
OMe	H	OMe	OMe	CH_2OAc	**133** (80%)
OMe	H	OMe	OMe	C≡C–Bu	**133** (60%)
OMe	H	OMe	OMe	H	**133** (65%)
OMe	H	OMe	OMe	OBn	**133** (58%) and **134** (41%)
OMe	H	OMe	OMe	OH	**133** (nd) and **134** (68%)
OMe	H	OMe	OMe	NHTs	**133** (4%) and **134** (88%)
OBu^t	H	OMe	OMe	OMe	**133** (49%) and **135** (49%)
OBn	H	OMe	OMe	OMe	**133** (53%) and **135** (32%)
Me	H	OMe	OMe	OMe	**133** (nd) and **135** (60%)
OMe	OAc	OMe	OMe	OMe	**133**:**135** (72:28; combined yield: 99%)
OMe	OTBDPS	OMe	OMe	OMe	**133**:**135** (0:100; combined yield: 77%)
OMe	Br	OMe	OMe	OMe	**133**:**135** (10:90; combined yield: 96%)
OBu^t	OTBDPS	OMe	OMe	OMe	**133**:**135** (0:100; combined yield: 80%)

Abbreviation: nd, not determined.

3.13.3 Synthesis of Diaryl Ethers

3.13.3.1 Via Chemoselective Oxidative Coupling of Phenols

Diaryl ether motifs are featured in numerous synthetic and natural compounds that are used as *inter alia* pharmaceutical drugs, agrochemical agents, polymeric materials, and various material additives.[113] Most natural diaryl ethers have phenolic precursors, and their biosynthesis is thus viewed to rely on oxidative coupling processes. However, the methods that have usually been utilized to generate diaryl ethers are the classical copper-promoted Ullmann coupling reaction between aryl halides and phenols, or more modern palladium-catalyzed variants thereof, and the nucleophilic aromatic substitution (S_NAr) of activated aryl halides with phenols.[113,114] Applications of oxidative coupling of phenols in the synthesis of diaryl ethers are rare. Nevertheless, a few relatively recent examples are worth mentioning such as the use of HRP and soybean peroxidases (SBP) by Sih and coworkers to generate *ortho*-brominated diaryl ethers from dibromotyramine/tyrosine derivatives that then serve in the total synthesis of two members of the family of tyrosine-derived marine sponge bastadin metabolites, bastadins 2 and 6 (Scheme 53).[115]

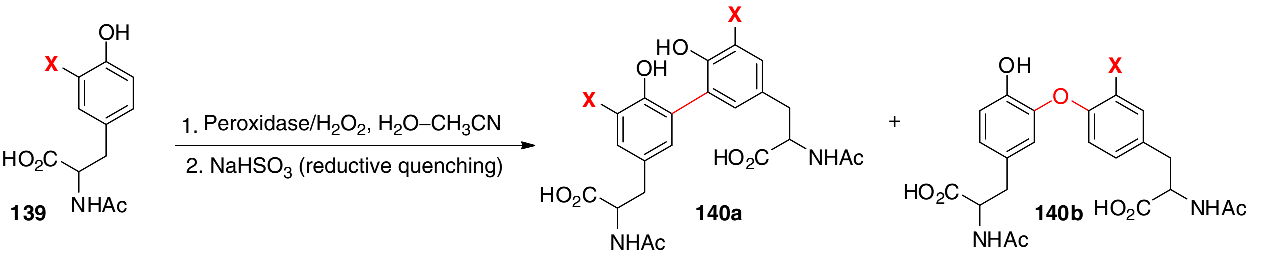


Scheme 53

The *N*-Boc-3,5-dibromotyramine (**136**) was found to be a particularly good substrate for these enzymatic one-electron oxidants. C–O coupling of two canonical forms of the resulting phenoxy radical ($PhO^\bullet$), followed by a nucleophilic *ipso*-attack of the Boc carbonyl oxygen with displacement of the bromine atom at the site of the initial radical coupling, gave rise to the spirodienone **137**, as shown in Scheme 53, in remarkably high yields of 53–62% at pH 4–5. Reduction of **137** using $CrCl_2$ led to the diaryl ether **138**, which was then utilized in the successful synthesis of the 28-membered macrocyclic bastadin 6.[115a] The choice of reaction conditions (i.e., amount of H_2O_2 and organic cosolvent, enzyme/substrate ratio, pH, reaction time) and the halogenation pattern of the substrates were found to be highly important for the success of the reaction and selection of the mode of coupling.[115] The reaction rate, using **136** as a substrate, was slower at more acidic pH, and more by-products were formed at neutral to alkaline pH.[115a] In general, unhalogenated and monohalogenated substrates preferentially lead to C–C coupled products in a pH range of 8–10,[19,115b] and less enzyme is needed to promote C–C than C–O coupling reactions.[115] The case of *ortho*-monohalogenated substrates is particularly interesting, because phenoxy radical C–C coupling occurs between unhalogenated *ortho*-positions, whereas C–O coupling, which can become predominant at slightly acidic pH and/or at higher enzyme/substrate ratio, systematically involves the halogenated carbon position, as exemplified by the case of peroxidase-mediated oxidative couplings of *N*-acetyl-3-halogenotyrosines **139** (Table 15).[115b] It appears from these results that the more electronegative the halogen atom is, the more favored the C–O coupling mode is. The influence of the enzyme/substrate ratio on the coupling mode selection remains more difficult to rationalize.[115b] Nevertheless, clear options were made available to direct the chemoselectivity of these peroxidase-mediated oxidative coupling reactions of phenols one way or another (C–C or C–O) by selecting the appropriate halogen substituent and reaction conditions.

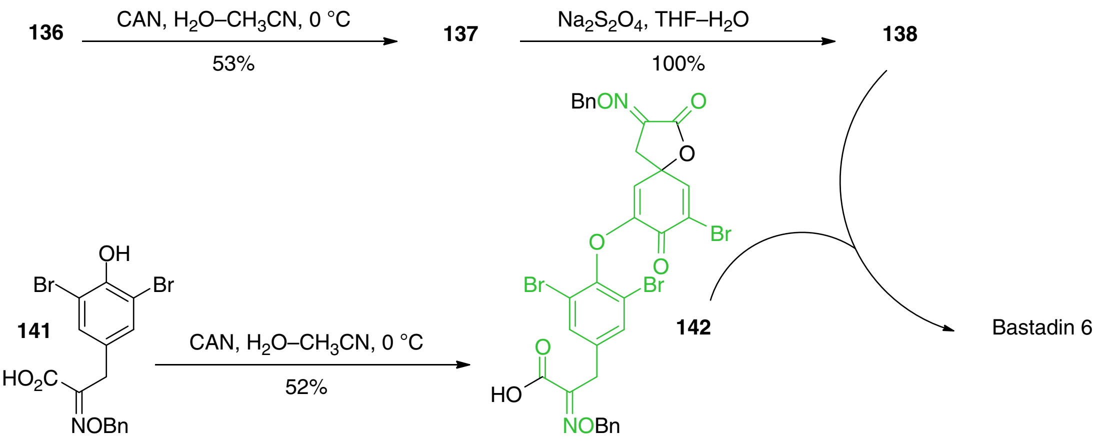
Kobayashi and coworkers recently reported an improved yet very similar synthesis of bastadin 6 by relying on the use of cerium (IV) ammonium nitrate (CAN) to generate the two C–O coupled moieties.[116] Sodium dithionite was used as the reducing agent. The diaryl ether **138** was obtained in 53% yield, and treatment of the oxime-protected *ortho*-dibromophenol **141** with CAN

Table 15



X	Peroxidase	pH	Enzyme/substrate	Isolated yields (%) 140a	140b
F	HRP	6	6 units per μmol	0	56
Cl	SBP	9	1 unit per μmol	0	43
Cl	SBP	9	0.1 unit per μmol	30	0
Br	HRP	9	6 units per μmol	40	0
I	HRP	9	6 units per μmol	75	0

afforded in 52% yield the second C–O coupled moiety **142**, which was then used to acylate **138** and reduced en route to bastadin 6 (Schemes 53 and 54).[116]

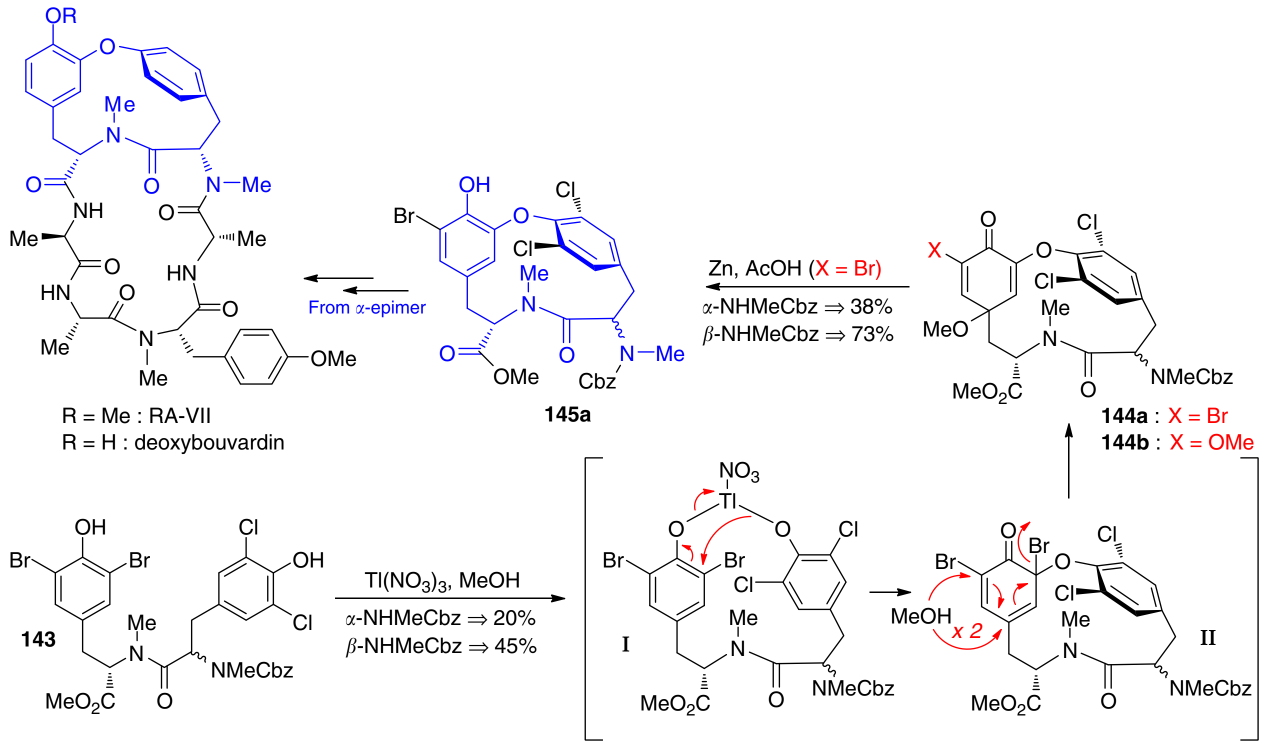


Scheme 54

The use of the oxidant $Tl(NO_3)_3$[37b,117] in MeOH has found numerous interesting applications in the preparation of *ortho*-halogenated diaryl ethers that were first introduced by Yamamura and coworkers for the synthesis of structurally complex molecules such as *inter alia* some marine sponge bastadin metabolites, including the first total synthesis of the aforementioned bastadins 2 and 6, the isodityrosine-containing tripeptide K-13, and some analogs of the glycopeptide antibiotic vancomycin.[118] Inoue and coworkers relied on Yamamura's methodology in their synthesis of the antitumoral Rubiaceae plant-derived bicyclic hexapeptides RA-VII and deoxybouvardin, which both feature a 14-membered cycloisodityrosine moiety.[119] Each of the diastereomeric tetrahalogeno bisphenolic amides **143** was treated with $Tl(NO_3)_3$ in MeOH to generate a 1:3 mixture of the macrocyclized products **144a** and **144b** (Scheme 55). Yamamura and coworkers early proposed that $Tl(NO_3)_3$ behaves as a two-electron oxidant in similar intramolecular cyclization processes, forming a cyclic chelate [**I**] with the two phenolic functions before the oxidative formation of the desired C–O bond (Scheme 55).[118c,120] The resulting cyclohexa-2,4-dienone [**II**] then suffers nucleophilic attacks from methanol to displace either one or both bromide atoms to deliver the mixture of 4-methoxy-cyclohexa-2,5-dienones **144a** and **144b**. The brominated compound **144a** is then reduced using Zn in AcOH to afford the 14-membered cyclodiaryl ether **145a**. Its α-epimer was then further transformed to complete the synthesis of RA-VII and deoxybouvardin (Scheme 55).[119]

Yamamura and coworkers completed the synthesis of vancomycin analogs SAV-1 and SAV-2 using this methodology, although the first coupling reaction (**146**→**147**, Scheme 56) apparently did not require any reduction step. In any event, both diaryl ether bond-forming 16-membered macrocylizations occurred in relatively good yields of approximately 40% (Scheme 56).[121]

Evans and coworkers also relied on Yamamura's thallium(III) method to synthesize the orienticin C aglycone, a bis-dechloro analog of the vancomycin aglycone that features the vancomycin phenolic biaryl moiety.[122] The tetrahalogeno bisphenolic

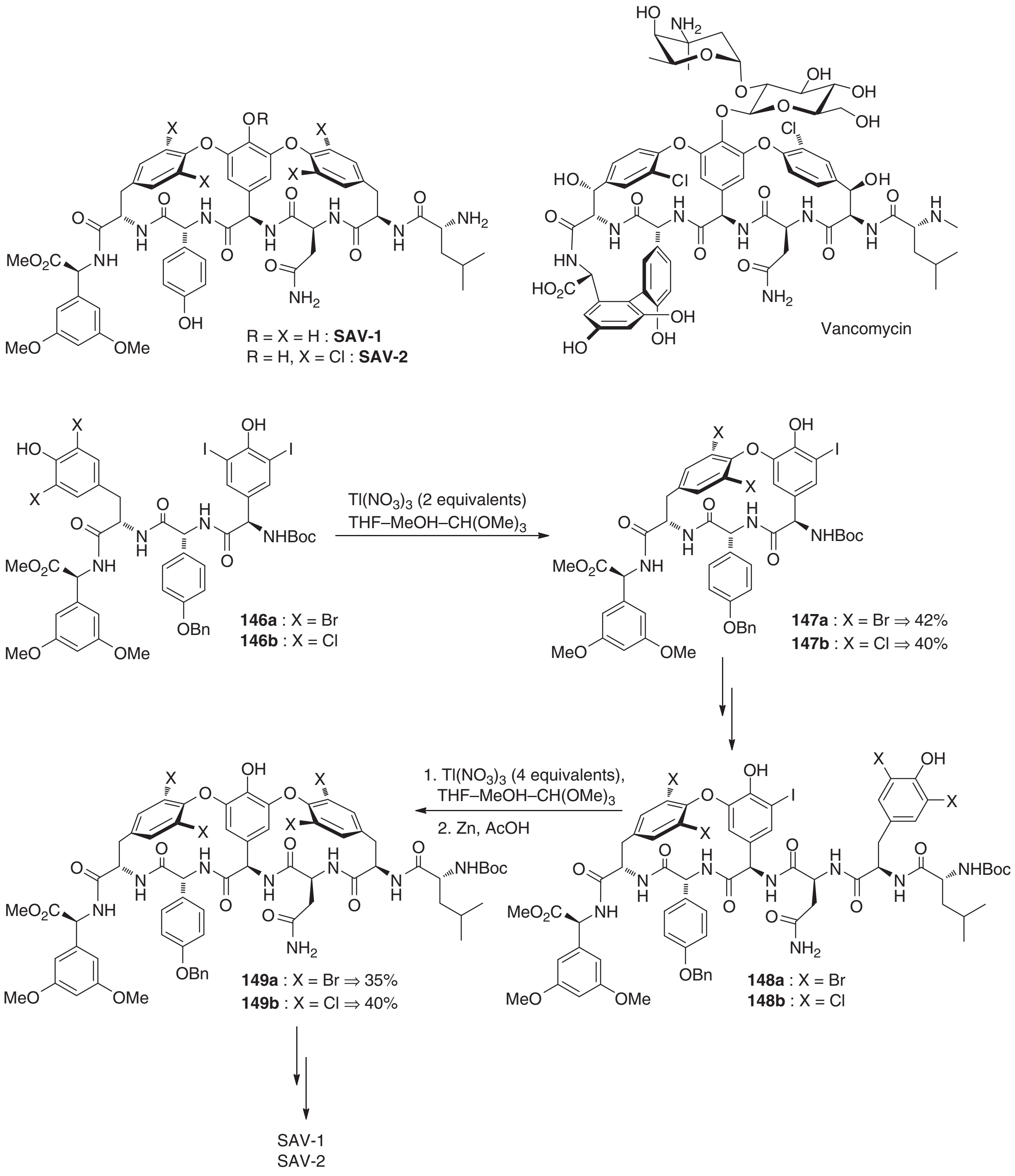


Scheme 55

tetrapeptide **150** was treated with $Tl(NO_3)_3$, then with $CrCl_2$ (reduction step) to afford the macrocylic diaryl ether **151** in yields ranging from 54 to 70% (Scheme 57). The remaining phenolic function was protected as a mesylate. The choice of this electron-withdrawing group was notably and judiciously made to raise the oxidation potential of this aromatic ring in order to favor the oxidative C–C coupling of the two phenol ether units at the next step. This coupling was induced by the oxidant VOF_3 on the mesylate **152** and predominantly afforded the highly strained *R*-atropisomer of the bicylic biaryl **153**.[122a] Further transformations, including the atropisomerization of the biaryl unit into the required *S*-isomer, led to the bisphenolic heptapeptide **154**, which was then also submitted to $Tl(NO_3)_3$-mediated oxidative coupling conditions. The desired tricyclic bis(diaryl ether) **155** was generated, but in a low yield of 20% as a material contaminated with some by-products. Evans and coworkers hence decided to revisit their diaryl ether-forming macrocyclization tactic and relied on the S_NAr approach to complete their synthesis of the orienticin C aglycone,[122b] as well as that of the vancomycin aglycone.[122c]

Nishiyama and coworkers followed in Yamamura's footsteps and recently reported the total synthesis of the marine 17-membered cycloisodityrosines, eurypamides A, B, and D, by relying on the $Tl(NO_3)_3$-mediated oxidative coupling of tetrahalogeno bisphenolic intermediates to seal the target macrocycles, as illustrated in Scheme 58, with the conversion of **156** into **157** in a good yield of 72%.[123] In these syntheses, as well as in the other $Tl(NO_3)_3$-induced macrocyclizations for which the two phenols also bear different halogen atoms (Schemes 55–58), the C–O bond is always established at a carbon center bearing a less electronegative halogen atom. This preference could be linked to an oxidation mechanism perhaps involving a more facile (two-electron) oxidation of the phenol bearing the less electronegative *ortho*-positioned halogen atoms, followed by or concerted with the nucleophilic *ortho*-attack of the phenolic oxygen of the other phenol, as depicted in Scheme 55. Alternatively, two SET from both phenoxy functions to the thallium(III) center would lead to a bisphenoxy biradical species. The relative distribution of electron density either at a phenoxy oxygen or at an halogenated *ortho*-carbon atoms would then direct the sense of the intramolecular coupling mode, in which case it would thus be the phenoxy radical bearing the less electronegative halogen atoms that better accommodates the unpaired electron at its halogenated carbon atoms (Schemes 55–58).

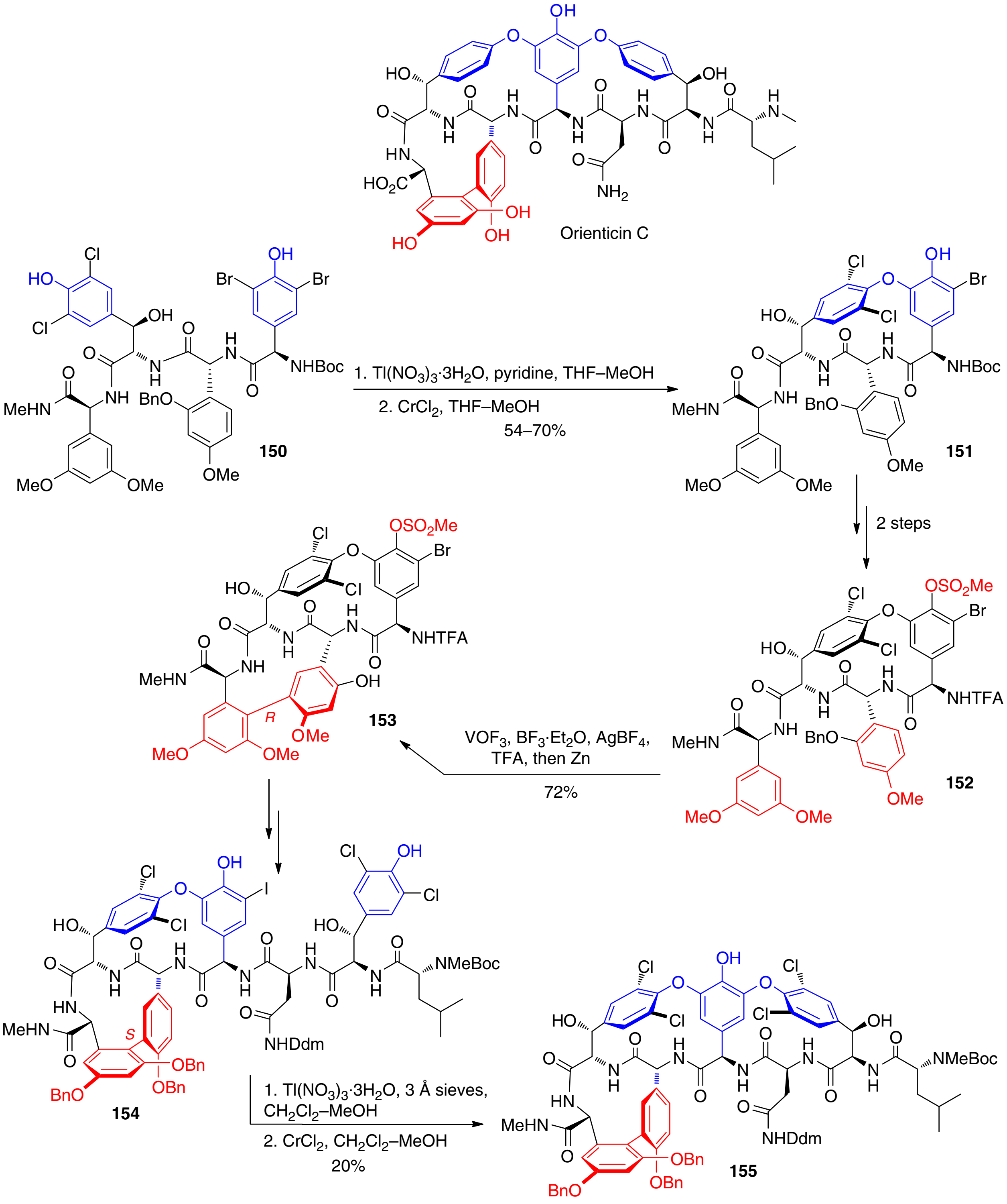
Further evidence for this chemoselective influence of halogen atoms in intramolecular C–O coupling reactions also emerged from cases of intermolecular reaction. One of the most illustrating examples is the anodic oxidation of *N*-protected 3,5-dibromo- and -diiodotyrosine methyl esters **158a**/**b** that has been thoroughly investigated by Yamamura, Nishiyama, and coworkers (Scheme 59).[124a] The dibromo derivative **158a** led to the formation of the diaryl ether isodityrosine derivative **159a** in 45% yield, whereas the diiodo derivative **158b** led to the biaryl dityrosine derivative **159b** as the sole dimeric product in 28% yield (Scheme 59).[124a] The diaryl ether **159a** was also obtained in 38% using the $Tl(NO_3)_3$ oxidant.[124a] The same trends were also observed by Sih and coworkers, although they relied on HRP to mediate, generally in even higher yields, similar coupling reactions using, for example, *N*-acetyl-3,5-dichloro- and -dibromotyrosines to generate the corresponding diaryl ether products in 76% and 42%, respectively, and using *N*-acetyl-3,5-diiodityrosine to generate the corresponding biaryl product in 45% yield under the same



Scheme 56

reaction conditions (pH, enzyme/substrate ratio, amount of H_2O_2, solvent, etc.).[125a] The higher yield (76%) of the C–O coupled product derived from the *ortho*-dichlorophenolic substrate further denotes the importance of having starting phenols flanked by more electronegative halogen atoms to better promote the C–O coupling mode.

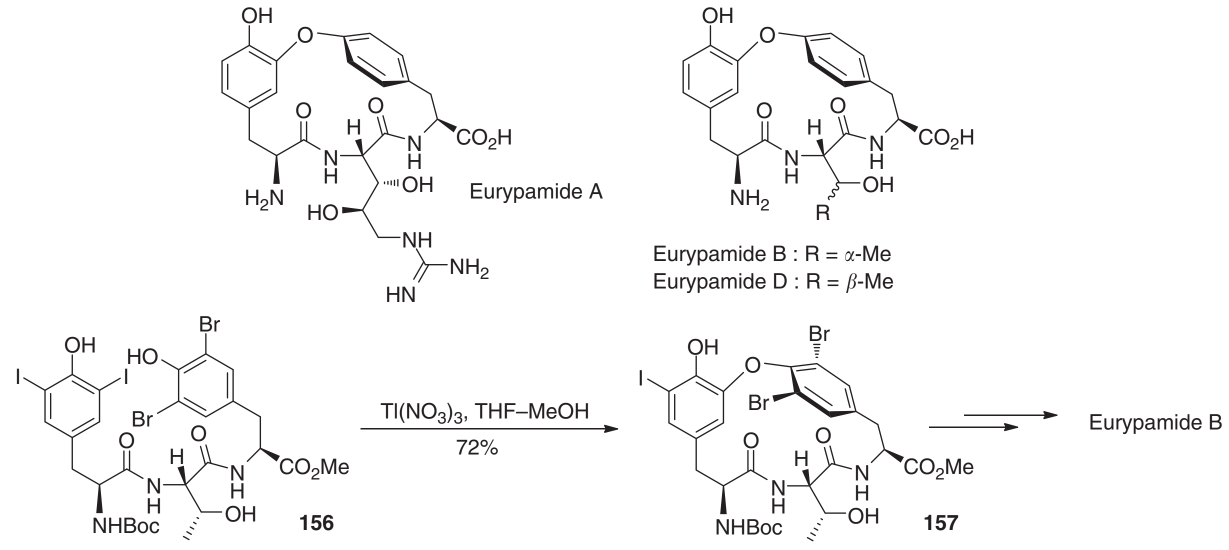
Yamamura and Nishiyama attempted to rationalize this halogen effect by performing calculations on *ortho*-dibromo- and diiodophenoxy radicals and concluded that the energetic preference for the O-radical over the C-radical is significantly larger for the dibromo- than for the diiodophenoxy radical.[124b,c] Hence, it would seem that the more electronegative the halogen atoms are, the more stable the phenoxy O-radical is, and the more favored the C–O coupling mode is. The corollary conclusion would be that



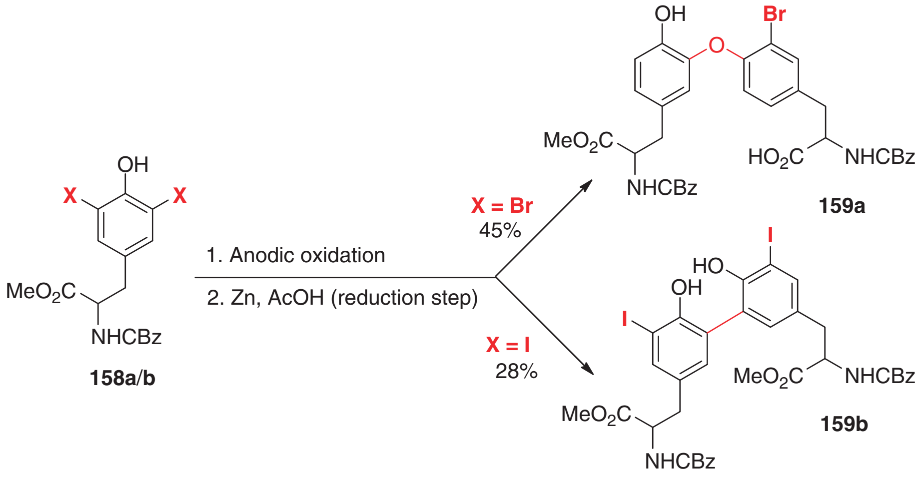
Scheme 57

ortho-positioned less electronegative halogen atoms are more inclined to accommodate the unpaired electron at their carbon atom bearer and to consequently direct phenolic coupling at this locus. This trend is also corroborated by the aforementioned results on the enzymatic coupling of monohalogenated phenols (Table 15).

A remarkable demonstration of the validity of these 'halogen-effect guidelines' is notably found in a recent report of Nishiyama and coworkers on the total synthesis of verbenachalcone and some congeners.[126] To access the diaryl ether core bond of



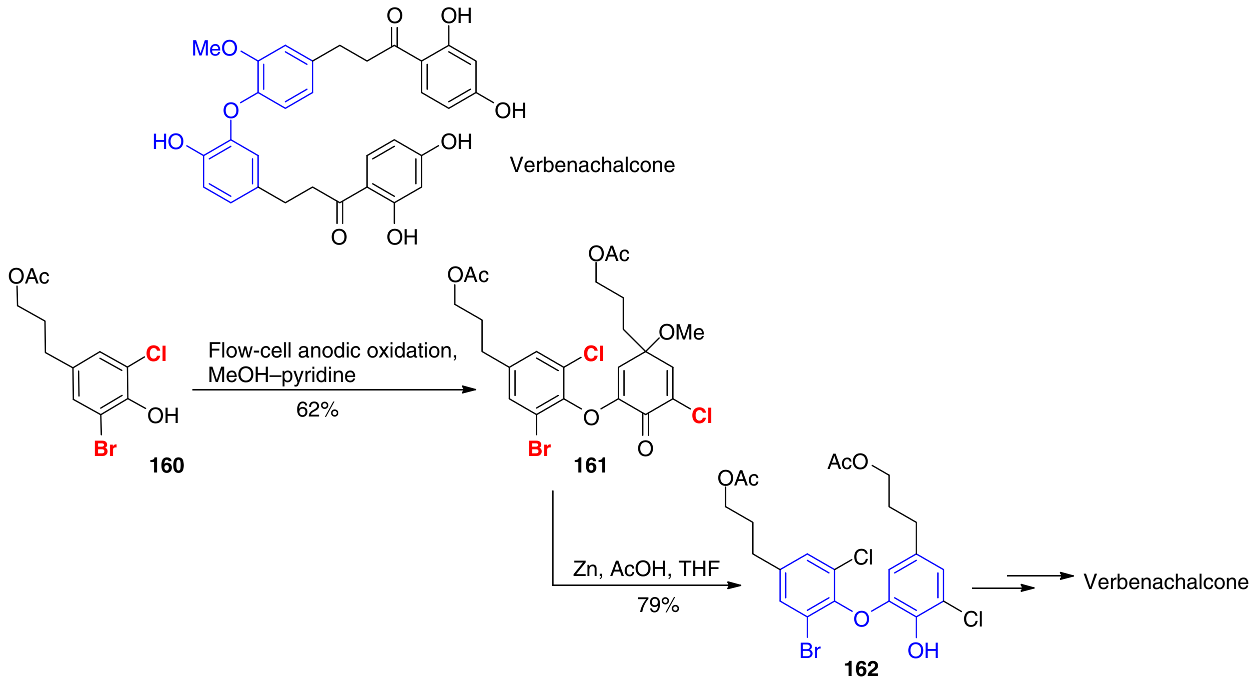
Scheme 58



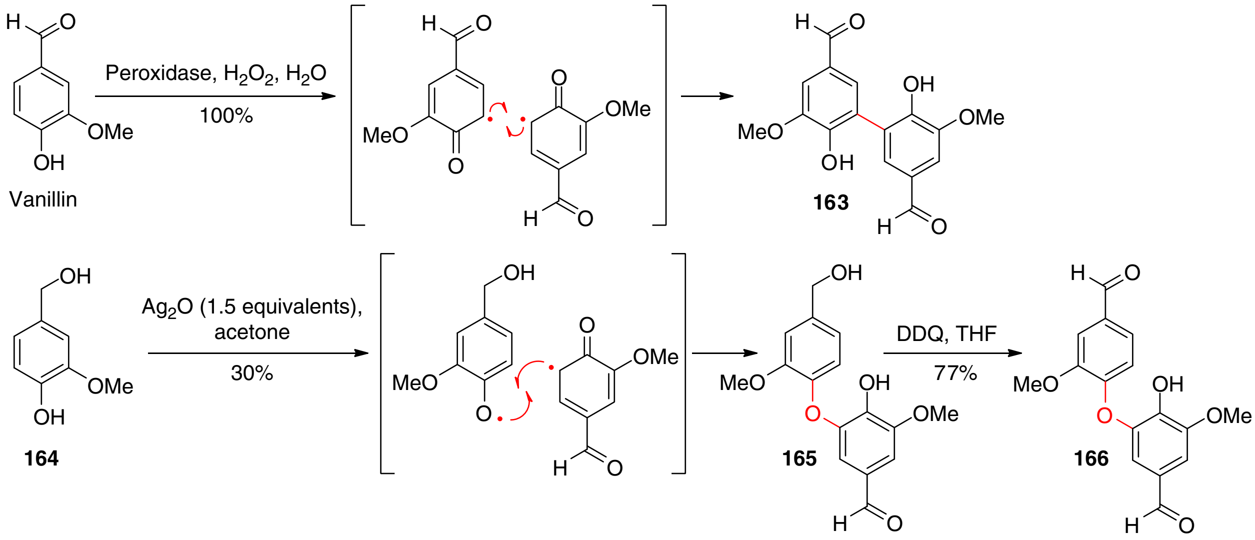
Scheme 59

verbenachalcone, they judiciously used the mixed-chlori/brominated phenol **160** and optimized anodic one-electron oxidation conditions to convert it into the C–O coupled product **161** in 62% yield at a multigram scale (Scheme 60).[126a] The more electronegative chlorine atom imposes its control on coupling via the phenoxy O-radical and the less electronegative bromine atom contributes to promote the participation of the C-radical. The resulting C–O coupled intermediate, thermodynamically favored over the alternative O–O coupled intermediate, then suffers the nucleophilic *ipso*-attack of MeOH (with displacement of the bromine atom) to generate **161**, which is then reduced into the diaryl ether **162** en route to verbenachalcone (Scheme 60).

The discussion above stresses the importance of the structure of the phenolic substrates in a manner through which they will preferentially couple, regardless of the oxidation process to which they are subjected. Another case that illustrates this point is Ralph's synthesis of the diaryl ether isodivanillin (**166**),[127] for which vanillin itself was not an appropriate starting phenol under one-electron oxidation conditions. The vanillin-derived phenoxy radical predominantly leads to C–C coupled products. Using the peroxidase-H_2O_2 oxidizing system, it is even possible to convert vanillin into the biaryl divanillin (**163**) in quantitative yield.[54] Because the electron-withdrawing resonance effect of the vanillin aldehyde certainly contributes to augment the electron density at the phenoxy C-radical,[54b] vanillyl alcohol (**164**) was instead used as starting phenol. Using the strong one-electron oxidant Ag_2O, the diaryl ether (**165**) was obtained in 30% yield as a result of a cross-coupling between the vanillyl alcohol-derived phenoxy O-radical and the C-radical derived from some vanillin generated *in situ* by oxidation of **164** with Ag_2O (Scheme 61).[127]



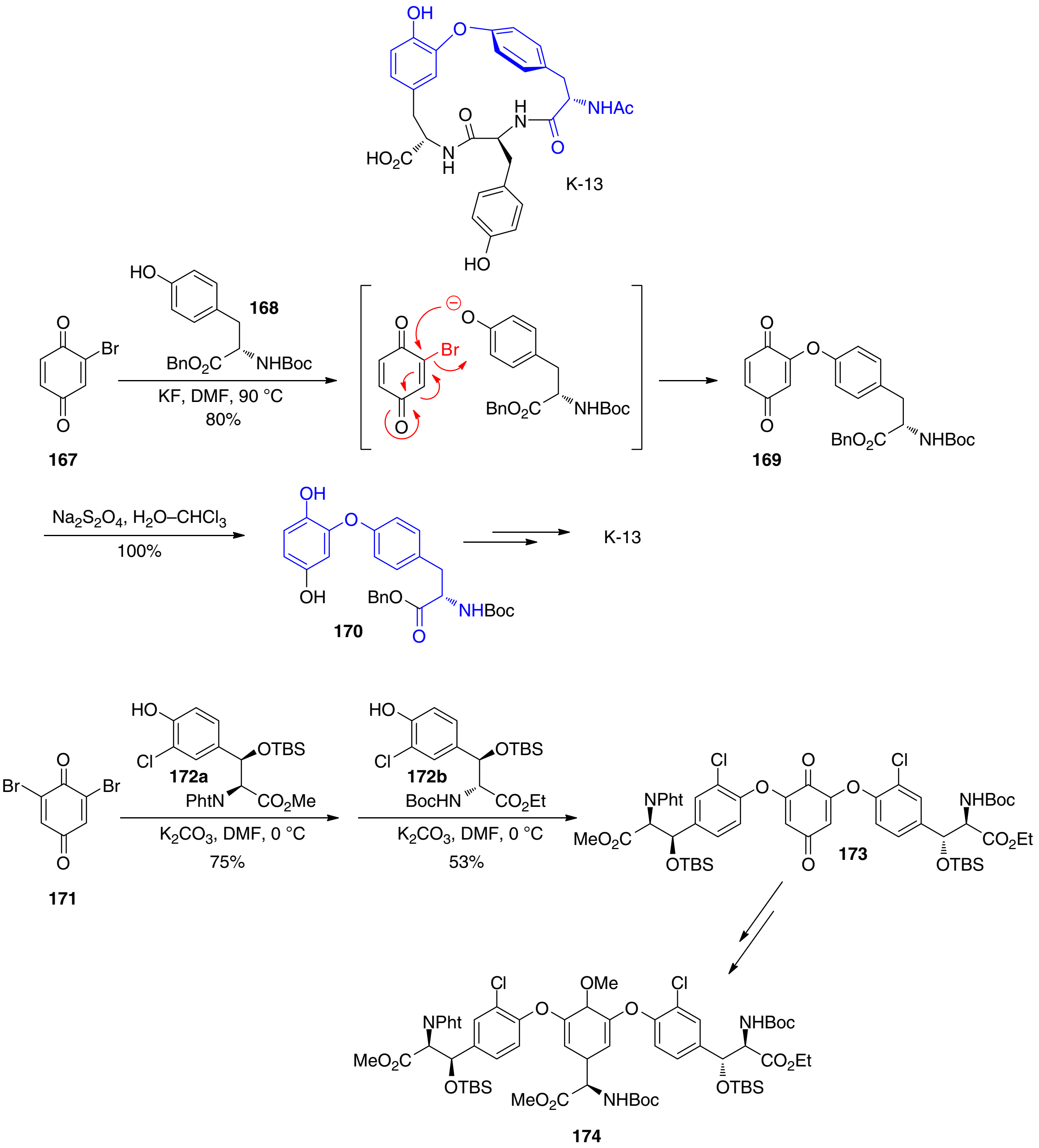
Scheme 60



Scheme 61

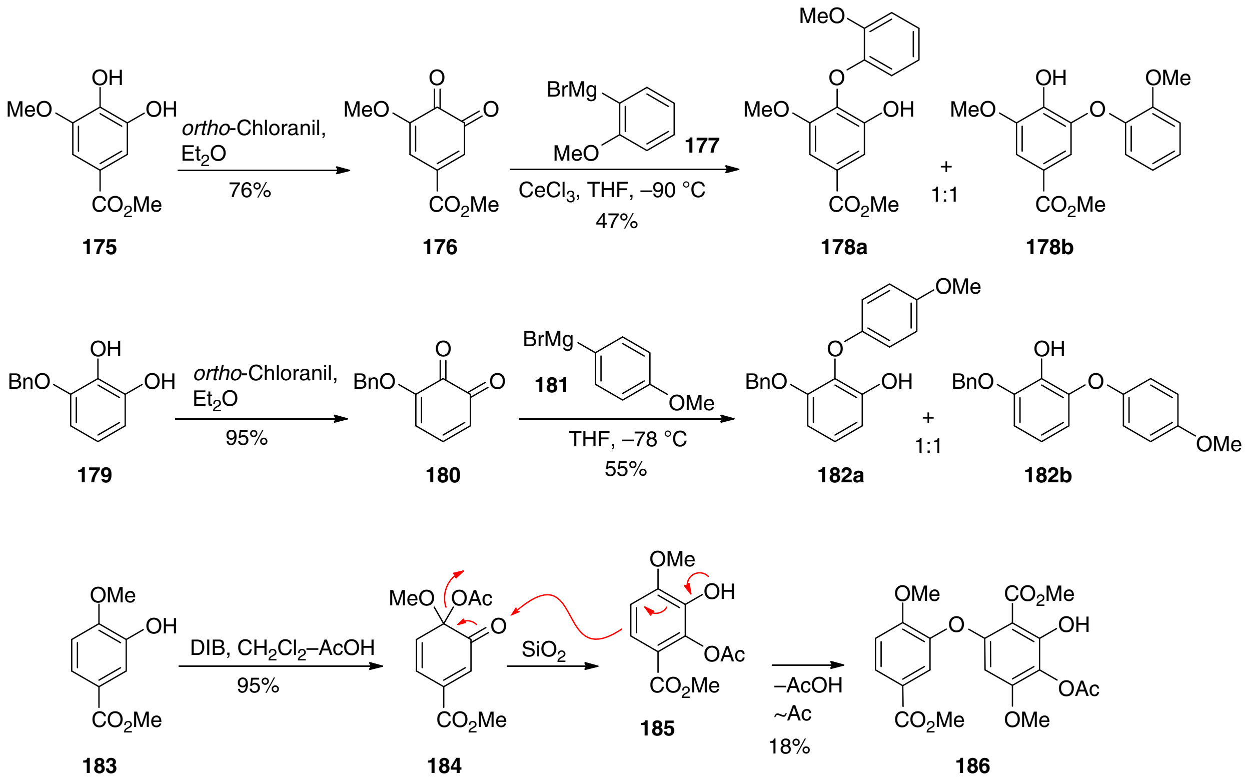
3.13.3.2 Via Coupling Reactions Involving Quinonoids

Different strategies have been implemented to forge diaryl ether bonds by instead relying on the use of a 'preoxidized' phenolic reaction partner, that is a quinonoid compound, and a second phenolic (ether) partner. For example, in their formal synthesis of the isodityrosine-containing macrocyclic tripeptide K-13 and their preparation of an advanced intermediate for the synthesis of vancomycin, Rao and coworkers utilized brominated *para*-quinones as electrophilic aryl donors in addition–elimination reactions with phenolate anions.[128] For example, 2-bromobenzoquinone (**167**) reacted with the tyrosine derivative **168** in the presence of KF in DMF at 90 °C to afford the 2-aryloxybenzoquinone **169** in 80% yield (Scheme 62). Reduction of this quinone with sodium dithionite furnished the diaryl ether **170**.[128c] An extension of this strategy using 2,6-dibromobenzoquinone (**171**) and, sequentially, the β-hydroxytyrosines derivatives **172a** and **172b** led to a first synthesis of the vancomycinic acid moiety **174** of vancomycin (Scheme 62).[128d]



Scheme 62

Other types of quinonoid compounds have been used in concert with phenolic derivatives in reactions leading to the synthesis of diaryl ethers. For example, Feldman and coworkers reported that the *ortho*-quinone **176**, which they prepared by oxidizing the catecholic methyl 3-*O*-methylgallate **175** with the organic oxidant *ortho*-chloranil in Et_2O, reacts with the 2-bromoanisole-derived Grignard reagent **177** in the presence of $CeCl_3$ to furnish a 1:1 mixture of the diaryl ether regioisomers **178a** and **178b** in 47% yield (Scheme 63).[129] The mechanism of such oxophilic combinations of Grignard reagents with *ortho*-quinones has not been fully elucidated, but it could involve a SET from the organometallic species to the quinone, followed by a radical coupling with the resulting semiquinone radical anion.[129b,130] The same methodology was also recently reported by Pettus and coworkers, who described the preparation of the 1:1 mixture of the diaryl ethers **182a** and **182b** by reacting 3-benzyloxy-1,2-quinone (**180**) with *p*-methoxyphenylmagesium bromide (**181**) (Scheme 63).[131] Moreover, and this time without any organometallic artifice, the *ortho*-quinol acetate **184**, which was prepared by acetoxylative dearomatization of the 2-methoxyphenol **183** using the λ^3-iodane DIB reagent, partially rearranges on exposure to SiO_2 into the phenol **185**, which then attacks **184** in an oxophilic manner to furnish, after migration of the acetyl group, the diaryl ether **186** in yields up to 18% (Scheme 63).[132] Notwithstanding this low yield, this unusual and intriguing reaction opens new doors for the synthesis of diaryl ethers from phenols and their quinonoid oxidation transforms.

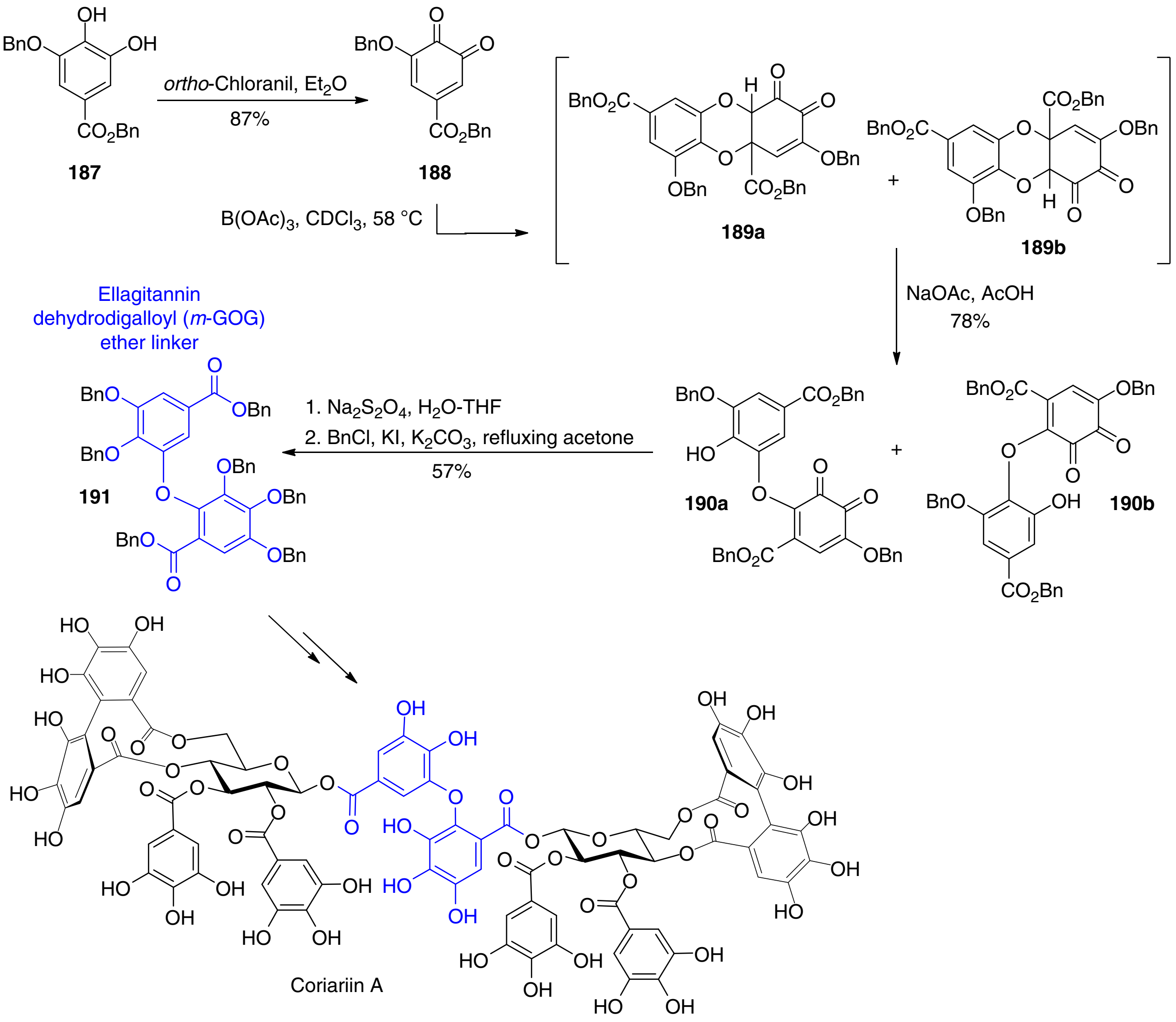


Scheme 63

Another option to access (indirectly) diaryl ethers is to rely only on *ortho*-quinonoid species as 'preoxidized' phenolic reaction partners and to exploit their capacity to cyclodimerize in a hetero-Diels–Alder fashion. This is illustrated by the case of the *ortho*-quinone **188**, which was converted into a mixture of benzodioxanes **189a** and **189b** on heating and mediation with the Lewis acid $B(OAc)_3$ (Scheme 64).[133] Treatment of this mixture with NaOAc in AcOH promoted the opening of the benzodioxane ring via β-elimination, and the resulting *ortho*-quinones **190a** and **190b** were then reduced and perbenzylated to afford the diaryl ether **191** as the sole regioisomer in 44% yield from the *ortho*-quinone **188**.[133a] This diaryl ether **191** corresponds to the dehydrodigalloyl (*m*-GOG) ether linker of oligomeric ellagitannins,[72] and served in the first successful total synthesis of the dimer coriariin A.[134]

3.13.4 Synthesis of Spirodienones

Spirodienone motifs are featured in numerous key synthetic intermediates and natural bioactive compounds that mainly belong to the alkaloid family. Most of these structures can be accessed through oxidative activation of either a phenol or a phenol ether moiety, and subsequent trapping of the resulting reactive species (e.g., PhO^+, $PhO^\bullet$, $PhOR^{\bullet+}$) by an electron-rich arene. In this context, Kita and coworkers reported in the mid-to-late 1990s the synthesis of several *Amaryllidaceae* alkaloids, during which strategic C–C connections were established between phenolic and phenyl alkyl ether moieties within the same molecular entity.[135] Several *N*-protected norbelladine derivatives **192** were submitted to BTI-mediated phenolic activation, thus forming most probably the corresponding phenoxy-λ^3-iodane species **A**, which may then suffer a carbon-based nucleophilic addition from the electron-rich aromatic ring, following an associative mechanism according to the authors (Table 16).[135a] Direct formation of C–C bonds predominantly occurred according to either a C_{para}–C_{para} or a C_{ortho}–C_{para} coupling mode, and again, reactions proceeded more satisfactorily in nonnucleophilic polar protic solvents such as the fluoroalcohols TFE and HFIP. No coupling reaction was observed in either benzene or dichloromethane. The oxidative C_{para}–C_{para} coupling gave access to spirodienones **193**, which



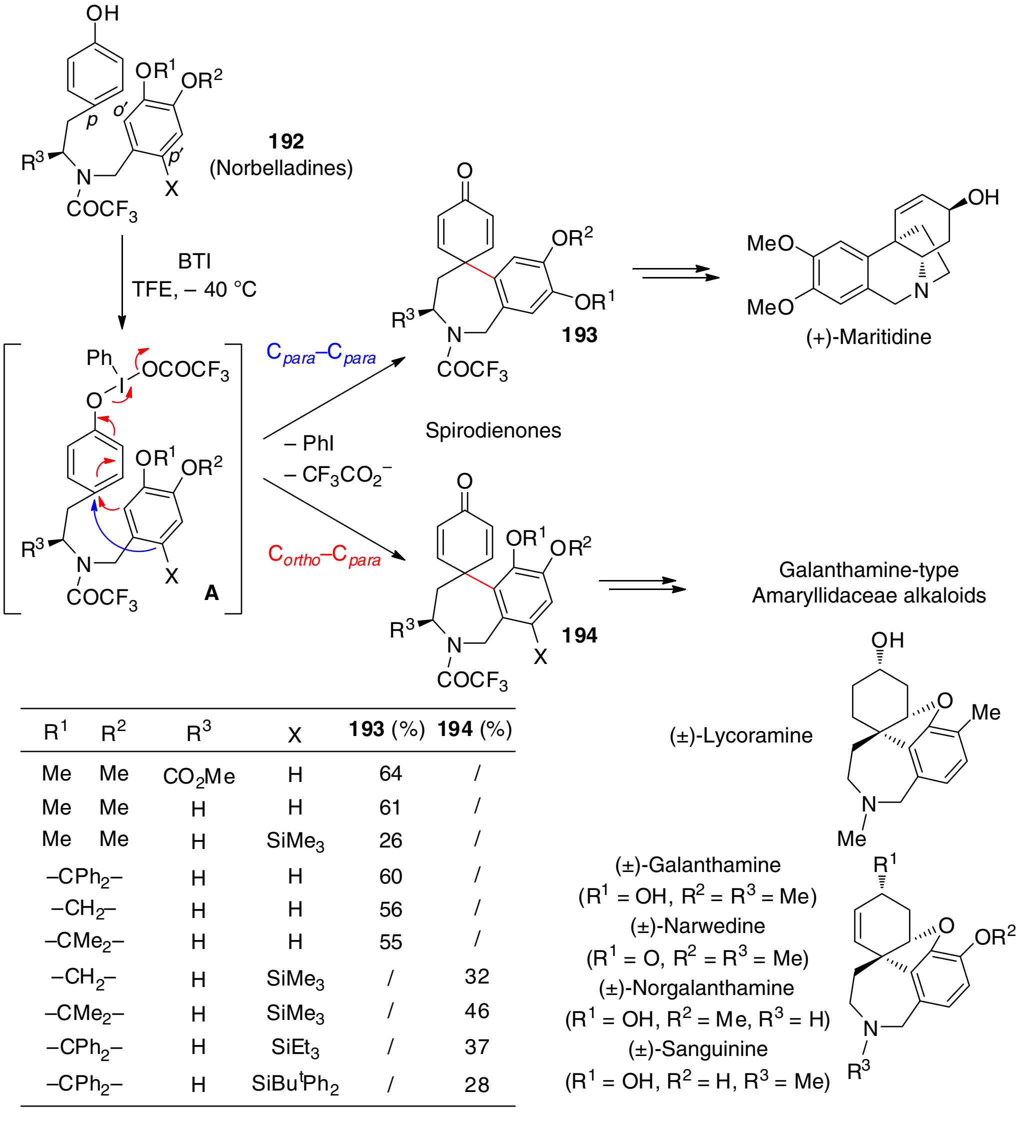
Scheme 64

constitute valuable intermediates for the synthesis of maritidine-type analogs, whereas the C_{ortho}–C_{para} coupling afforded spirodienones **194** en route to a series of galanthamine-type *Amaryllidaceae* alkaloids. It is interesting to note that this C_{ortho}–C_{para} coupling could be favored when starting from norbelladines **192** with both the *para*-site and the catechol unit protected with a trialkylsilyl and a methylenedioxy group, respectively (Table 16).[135b] The authors also indicated that these substrates did not react at all with K_3FeCN_6 or Mn(acac)$_3$.

Just a few years ago, Kita and coworkers revisited this intramolecular phenolic oxidative coupling by developing a catalytic version based on an *in situ* reoxidation of the iodoarene at low temperature. Screening of several oxidizing conditions (e.g., *m*-CPBA in CH_2Cl_2, urea·H_2O_2 in TFE, urea·H_2O_2–CF_3CO_2H in TFE) led to the identification of urea·H_2O_2–TFAA in TFE as the best system, which allowed the formation of an alternative oxidant, the bis(trifluoroacetyl) peroxide **195** (Scheme 65).[135c] In addition, 4-fluoro(iodobenzene) **196** showed the best catalytic activities in comparison with other iodoarenes, such as iodobenzene or 4-methyl(iodobenzene). The performances of this first iodoarene-catalyzed C–C bond forming system were validated with the desired conversion of a series of *N*-protected norbelladine derivatives, such as **192a** that was converted into the C_{para}–C_{para} coupled spirodienone **193a**, in yields ranging from 55 to 80% (Scheme 65).[135c]

Ley and coworkers followed a similar approach for their own work on *Amaryllidaceae* alkaloid synthesis, but they chose to use recyclable PS versions of hypervalent iodine(III) reagents (i.e., PS-DIB and PS-BTI)[103] as two-electron oxidants to perform the oxidative activation of the phenolic unit.[136] In their work on maritidine-type alkaloids, Ley and coworkers reported the first examples of total syntheses of natural products solely relying on a sequence of PS reagents, in which the intramolecular phenolic oxidative cyclization of the *N*-trifluoroacetylated norbelladine derivative **197** into the *spiro*-cyclohexa-2,5-dienone **200** was used as the key step (Scheme 66).[137a] It is interesting to note that either PS-DIB or PS-BTI gave a clean **197**→**200** conversion, and furnished the desired C_{para}–C_{para} coupled product as the only observed compound by LC-MS in a 70% yield, whereas the corresponding

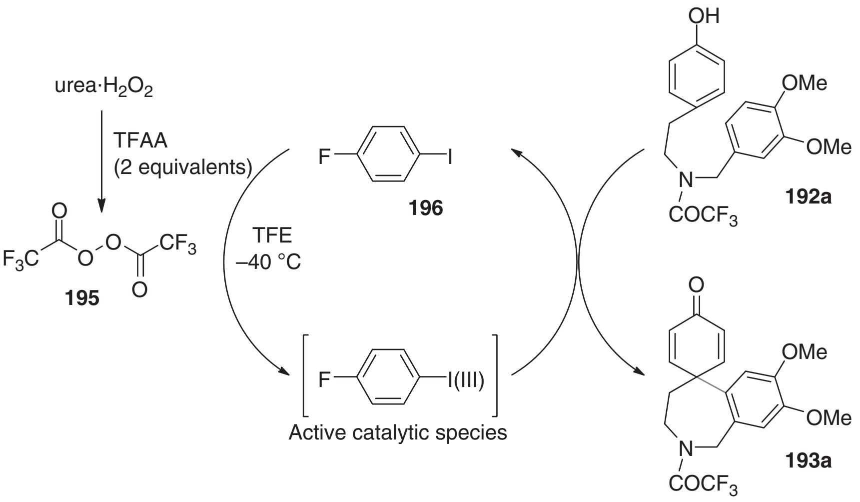
Table 16



R^1	R^2	R^3	X	**193** (%)	**194** (%)
Me	Me	CO_2Me	H	64	/
Me	Me	H	H	61	/
Me	Me	H	$SiMe_3$	26	/
$–CPh_2–$		H	H	60	/
$–CH_2–$		H	H	56	/
$–CMe_2–$		H	H	55	/
$–CH_2–$		H	$SiMe_3$	/	32
$–CMe_2–$		H	$SiMe_3$	/	46
$–CPh_2–$		H	$SiEt_3$	/	37
$–CPh_2–$		H	$SiBu^tPh_2$	/	28

solution-phase variant afforded **200** in yields no >55%.[136c] The authors also indicated that it was essential to use TFE as the solvent in order to guarantee good conversion in this intramolecular process.[136b] This observation could be related to the nature of the reaction intermediates involved in this oxidative coupling, especially if one considers a dissociative mechanism during which, after a ligand-exchange step between the phenolic substrate and the PS-λ^3-iodane that gives rise to the formation of **198**, departure of both the second oxygenated ligand and the iodo-PS would lead to the phenoxenium ion **199**. Such a cationic species could be stabilized by a polar solvent such as TFE (Scheme 66). Nevertheless, an associative mechanism cannot be totally discarded. In addition, the poor nucleophilicity of TFE may be seen as an advantage as it avoids any nucleophilic competition with the dimethoxybenzene ring in the intramolecular *spiro*-cyclization reaction. Recently, Ley and coworkers successfully adapted their multistep syntheses of maritidine-type alkaloids, including their PS-λ^3-iodane-mediated phenolic oxidative coupling, to flow chemistry.[137b,c]

In the same vein of investigation, Ley's group achieved the first synthesis of (+)-plicamine, and related alkaloids, through the key spirodienone intermediate **204**, which was prepared by PS-DIB-induced intramolecular oxidative phenolic coupling of **201** (Scheme 66).[138] This C–C bond-forming reaction was again performed in TFE, and furnished the *spiro*-compound **204** as the only isolated compound in 82% yield. The authors speculated on a mechanism involving radical intermediates to explain that the nonquantitative yield of the reaction could be possibly because of some radical coupling side reactions between the starting material and the resin polymer.[138a,b] A more classic iodane chemistry-based depiction of the **201**→**204** conversion is proposed in Scheme 66, and it again illustrates either the associative pathway via **202** or the dissociative pathway with a passage through the phenoxenium ion **203**.



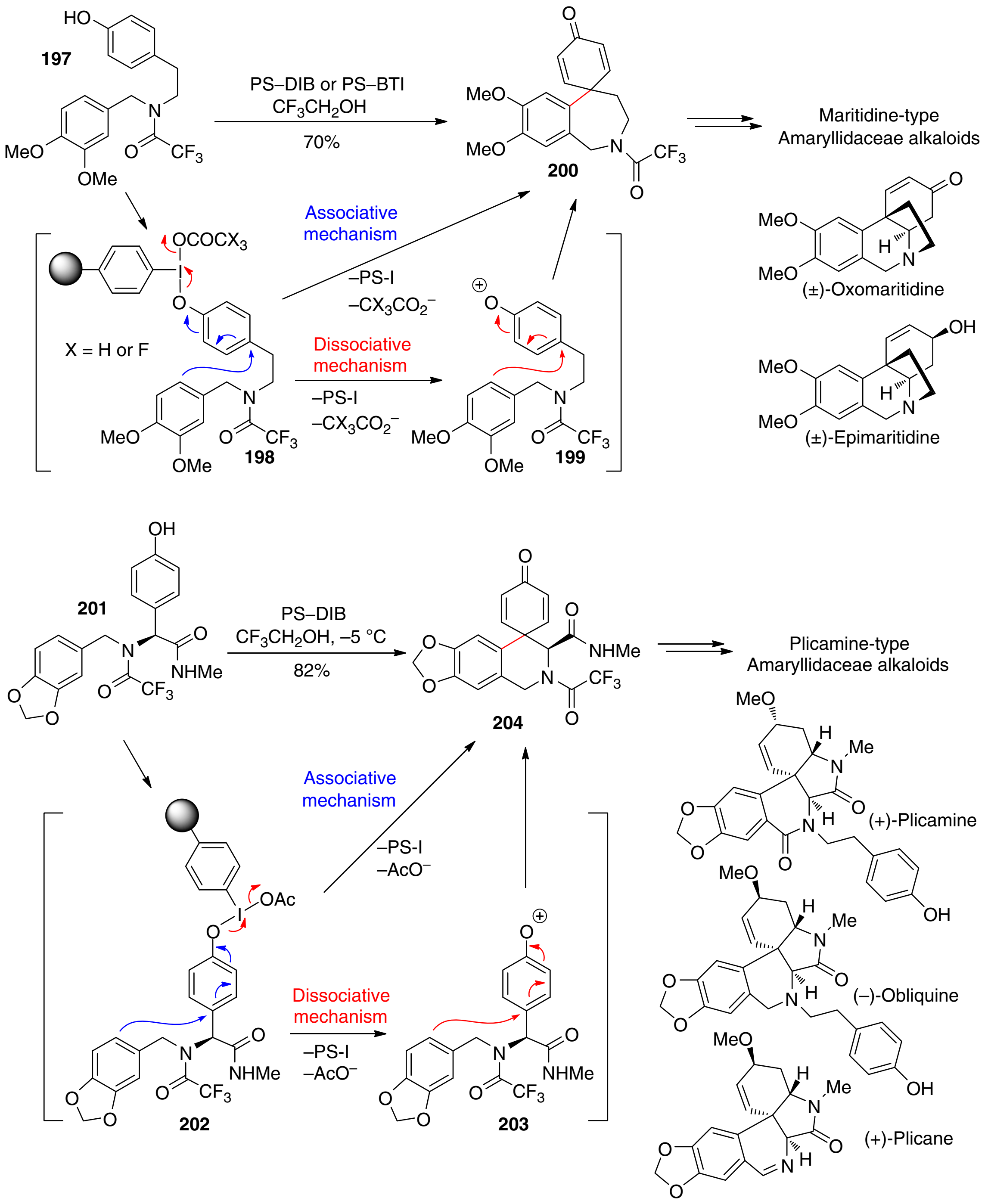
Scheme 65

Neospirinedienone and morphinandienone alkaloids (i.e., compounds **206a** and **206b**, respectively, in Table 17) can be accessed through oxidative coupling of phenol ethers. Several parallel investigations, carried out by different research teams, have shown that intramolecular oxidative coupling of *N*-protected benzyltetrahydroisoquinoline derivatives **205** can be preferentially directed toward the formation of these spirodienone-type structures instead of the related aporphine skeleta (see Section 3.13.2.2.1, Table 7).[95a,b,c,139] Indeed, the use of the λ^3-iodane BTI in combination with an acid additive at low temperature allowed smooth conversion of tricyclic substrates **205** into tetracycles **206a** and/or **206b**, depending on the experimental conditions. Screening of acid additives included $BF_3{\cdot}Et_2O$, FSO_3H, TfOH, TMSOTf, H_2SO_4 (98%), HBF_4 (42%), CF_3CO_2H, Nafion-H, and Montmorillonite K-10 enabled the authors to identify $BF_3{\cdot}Et_2O$ as the most efficient additive for this reaction.[95a] Treatment of *N*-deactivated benzyltetrahydroisoquinolines **205** with the BTI–$BF_3{\cdot}Et_2O$–CH_2Cl_2 system furnished, in good to excellent yields, neospirinedienones **206a** as the sole product (Table 17).[95a,b,d]

In contrast, the use of HPA, such as tungsto(VI) phosphoric acid (i.e., $H_3[PW_{12}O_{40}]$) in acetonitrile, afforded mixtures of **206a** and **206b** (Table 17). More interestingly, when some water (approximately 2.5%) was added to the acetonitrile reaction mixture, formation of the morphinandienones **206b** was significantly favored (Table 17).[95a,139] Kita and coworkers explained these results by invoking a SET mechanism and the formation of the radical cation ($PhOR^{\bullet +}$) **A**, which could then be trapped in an intramolecular fashion to give **B**. Under anhydrous conditions, rearrangement of the latter (see path *a*) gave structure **206a**, whereas the presence of water led to the isolation of **206b**, as depicted in Table 17. Further exploitation by Kita and coworkers of these observations can be found in the synthesis of a series of morphinandienone derivatives **206b**, such as flavinantine, amurine, and pallidine, by treatment of *N*-methylated benzyltetrahydroisoquinolines with a BTI–HPA–$BF_3{\cdot}Et_2O$ oxidizing system, in acetonitrile at –20 °C, in this case taking advantage of the hydration water of HPA.[95a,139]

3.13.5 Oxidative Phenolic Coupling Involving Conjugated Double Bonds

Numerous naturally occurring phenolics bear side chains with olefinic functions that are conjugated with the phenol ring. Many of these phenols (e.g., resveratrol (3,5,4′-trihydroxystilbene) and natural analogs, *para*-hydroxycinnam(yl/al/ic/oyl) derivatives) serve as precursors in anabolic processes leading to various types of dimeric and oligomeric plant polyphenols (e.g., lignins, lignans, oligostilbenoids, certain classes of tannins).[20] These processes are commonly thought to result from one-electron oxidation-mediated C–C and C–O radical coupling reactions involving, thanks to the phenoxy radical delocalization (Scheme 67), participation of the conjugated olefinic *β*-carbon center. Since the seminal and first major efforts by Karl Freudenberg in the 1950s and 1960s toward the understanding of plant cell wall lignification from *para*-hydroxycinnamyl alcohols,[140] this classical chemistry of the oxidative coupling of phenols never ceased to interest chemists and biochemists.[33] The recent literature on the topic is still quite abundant, notably because several issues related to the controls of the regio- and stereochemistry of the process still resist full understanding, and because metabolic engineering of plant phenolics (essentially lignins) might offer today solutions for a more efficient utilization of cellulosic biomass in industrial processing (bioenergy, pulp and paper, feed, and food crop industries).[33a,b] This latter and more biochemically oriented topic is somewhat out of the scope of this chapter, so below are highlighted only some of the most pertinent results that, to the authors' opinion, best illustrate the advances made toward the understanding of the oxidative dimerization of the aforementioned conjugated olefinic phenols.

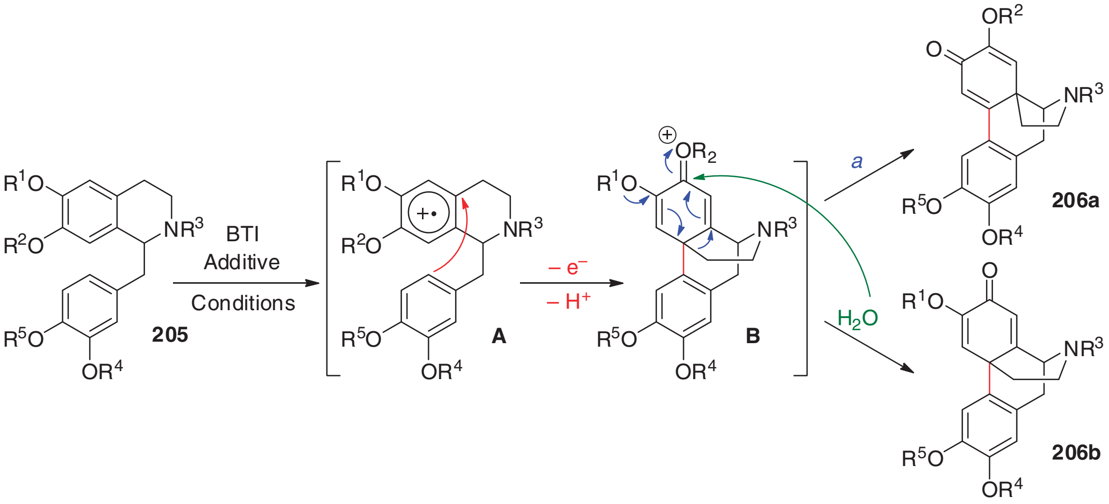


Scheme 66

3.13.5.1 Chemo- and Regioselectivity in Hydroxyphenylpropenoid Coupling Reactions

The oxidative dimerization of these phenols does not lead to biaryls or diaryl ethers as major products, for the participation of their conjugated olefinic *β*-carbon center usually predominates in coupling reactions. In the case of *para*-hydroxyphenylpropenoid precursors of lignins and lignans, numerous experimental and theoretical investigations that have been conducted over the years have indicated this regiochemical preference. Smith and coworkers recently reported results of a DFT study on the radical self- and cross-coupling reactions involved in the dimerization of the main monolignols (i.e., *p*-coumaryl, coniferyl, and sinapyl alcohols). Both spin densities and reaction enthalpies were taken into account, and the results confirmed that the most favorable self- or cross-coupling modes all involve the *β*- (or 8-) carbon center of the corresponding phenoxy radicals and that the formation of

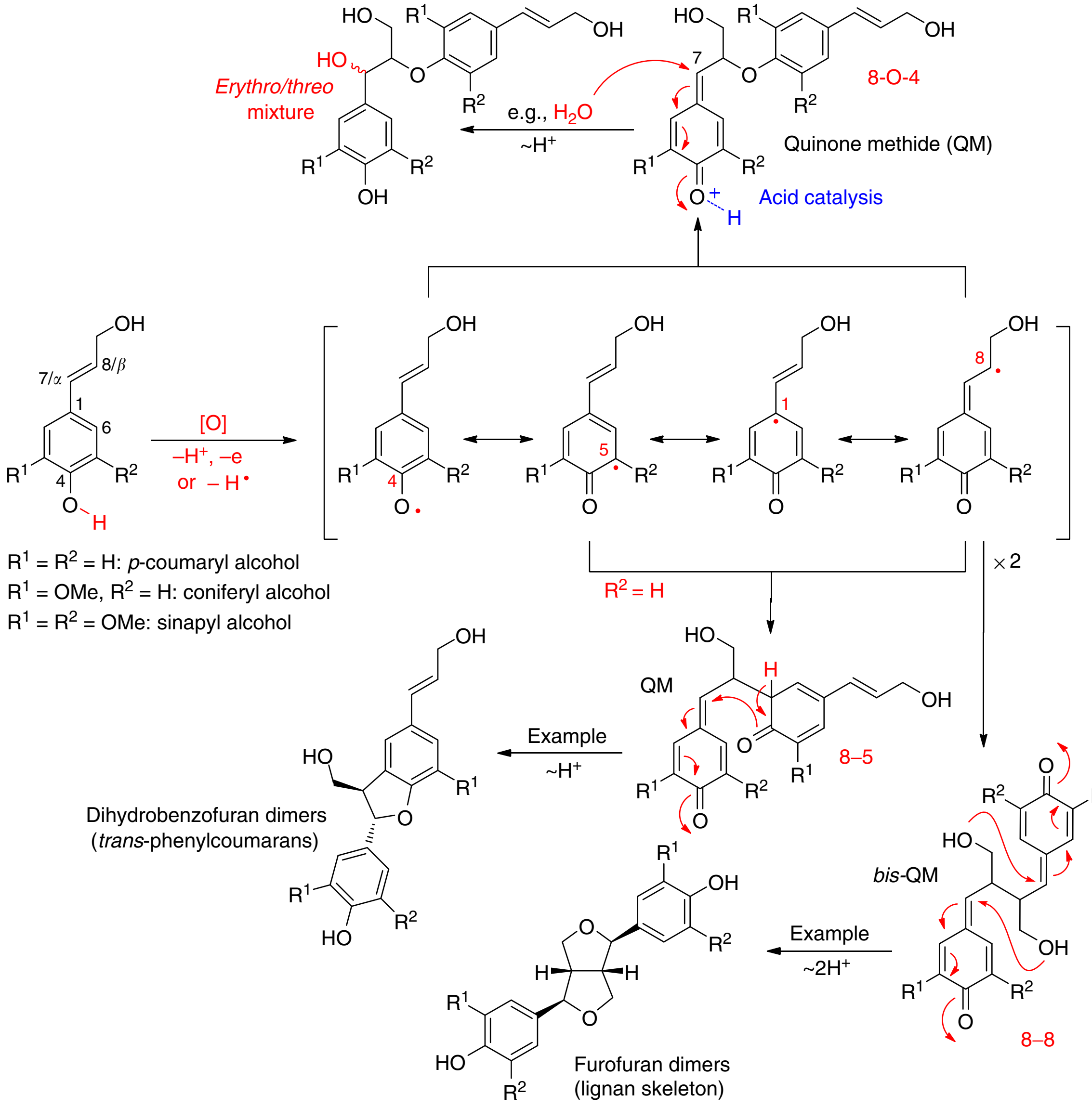
Table 17



R^1	R^2	R^3	R^4	R^5	*Additive*	*Conditions*	**206a** *(%)*	**206b** *(%)*
Me	Me	CHO	Me	Me	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −40 °C	91	
Me	Me	CHO	$–CH_2–$		$BF_3{\cdot}Et_2O$	CH_2Cl_2, −40 °C	94	
Me	Me	$COCH_3$	Me	Me	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −40 °C	70	
Me	Me	$COCF_3$	Me	Me	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −40 °C	42	
Me	Me	$COCF_3$	Me	Me	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −40 °C	90	
Me	Me	COC_6F_5	Me	Me	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −40 °C	53	
Bn	Me	$COCF_3$	Me	Me	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −40 °C	73	
Me	Bn	$COCF_3$	Me	Me	$BF_3{\cdot}Et_2O$	CH_2Cl_2, −40 °C	98	
Me	Me	$COCF_3$	Me	Me	$H_3[PW_{12}O_{40}]$	CH_2Cl_2, −20 °C	32	63
Me	Me	$COCF_3$	Me	Me	$H_3[PW_{12}O_{40}]$	CH_2Cl_2, −20 °C	28	34
Me	Me	$COCF_3$	Me	Me	$H_3[PW_{12}O_{40}]$	CH_3CN, 2.5% H_2O, −20 °C	9	84
Me	Me	$COCF_3$	Me	Me	$H_4[SiW_{12}O_{40}]$	CH_3CN, 2.5% H_2O, −20 °C	8	87
Me	Me	$COCF_3$	Me	Me	$H_3[PW_{12}O_{40}]$, TFAA	CH_3CN, −20 °C	90	
Me	Me	COC_6F_5	Me	Me	$H_3[PW_{12}O_{40}]$	CH_3CN, 2.5% H_2O, −20 °C	Trace	67
Bn	Me	$COCF_3$	Me	Me	$H_3[PW_{12}O_{40}]$	CH_3CN, 2.5% H_2O, −20 °C	10	62
Me	Bn	$COCF_3$	Me	Me	$H_3[PW_{12}O_{40}]$	CH_3CN, 2.5% H_2O, −20 °C	Trace	72
Me	Me	Me	Me	Me	$H_3[PW_{12}O_{40}]$, $BF_3{\cdot}Et_2O$	CH_3CN, −20 °C		90
Me	Me	Me	$–CH_2–$		$H_3[PW_{12}O_{40}]$, $BF_3{\cdot}Et_2O$	CH_3CN, −20 °C		90
Bn	Me	Me	Me	Me	$H_3[PW_{12}O_{40}]$, $BF_3{\cdot}Et_2O$	CH_3CN, −20 °C		76
Me	Bn	Me	Me	Me	$H_3[PW_{12}O_{40}]$, $BF_3{\cdot}Et_2O$	CH_3CN, −20 °C		85
Me	Me	Me	Bn	Me	$H_3[PW_{12}O_{40}]$, $BF_3{\cdot}Et_2O$	CH_3CN, −20 °C		79
Me	Me	Me	Me	Bn	$H_3[PW_{12}O_{40}]$, $BF_3{\cdot}Et_2O$	CH_3CN, −20 °C		82

8-O-4, 8–8, and 8–5 linked dimers (Scheme 67) is preferred by approximately 5–20 kcal mol^{-1} over that of 5-O-4 (diaryl ether), 5–5 (biaryl) and 8–1 linked dimers.[141] The *p*-coumaryl radical self- and cross-coupling reactions were computed to be the most thermodynamically favorable, but *p*-coumaryl alcohol is typically a minor monolignol. For cross-coupling reactions via a particular coupling mode, it was calculated that the more reactive radical preferentially couples at its site with the highest spin density. For example, in the case of a 8-O-4 linkage between *p*-coumaryl and coniferyl radicals, it is the more reactive *p*-coumaryl radical that should couple at its O4 site, because the spin density at this site is higher than that at C8.[141] The same type of coupling between coniferyl and sinapyl radicals should lead to connection between the O4 site of highest spin density in the more reactive coniferyl radical and the sinapyl C8 site.

This is what was, at least in part, observed experimentally by reacting an equimolar mixture of coniferyl and sinapyl alcohols in the presence of $Cu(OAc)_2$ in a pH 9 borate solution at 100 °C.[142a] However, the yields of each dimer from such a cross-coupling reaction are low to moderate ($<10\%$), and the reaction outcome significantly varies when using other types of oxidants in similar or different media, such as for example $Mn(OAc)_3$ in pyridine, which turned out to be the best oxidizing system to favor the production of all possible 8-O-4 cross-coupled dimers from coniferyl and sinapyl alcohols as major products in a global yield of approximately 50%.[142a,c] Using copper(II), iron(III), or manganese(III) salts in (aqueous) basic media, all of the resulting (di)lignols derived from coniferyl or sinapyl alcohols, or a mixture therefrom, are 8-O-4, 8–5 or 8–8 linked species.[142] No 5-O-4

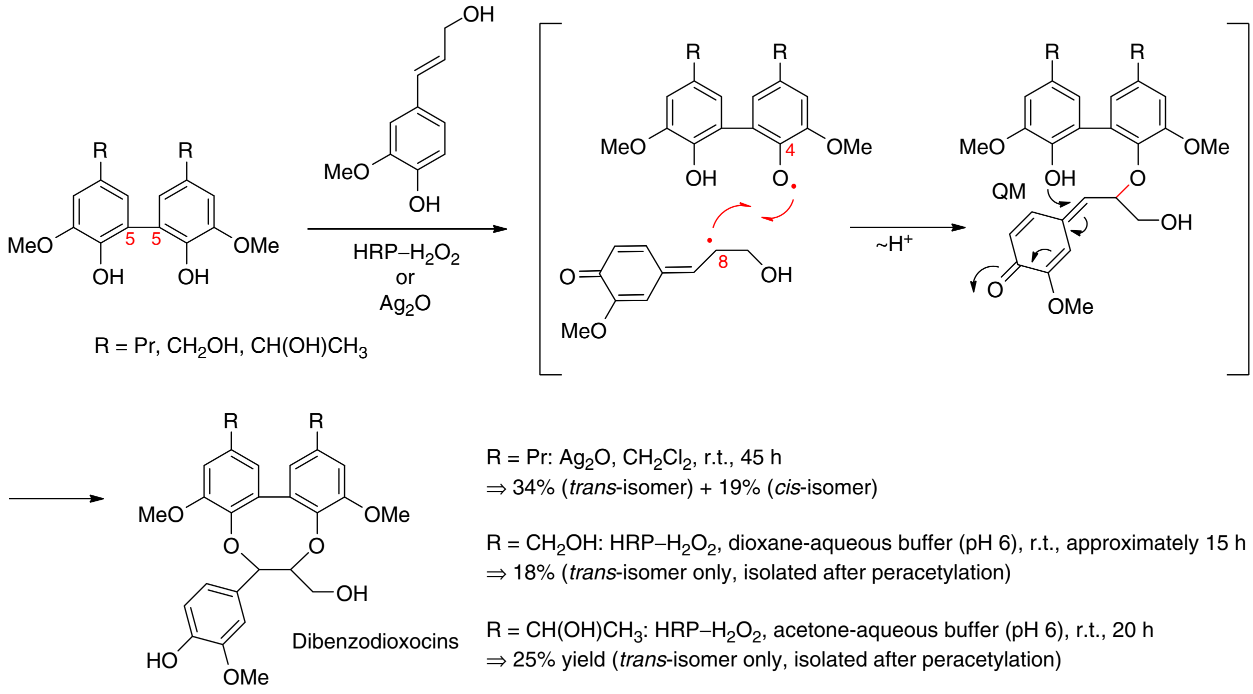


Scheme 67

(diaryl ether), 5–5 (biaryl) or 8–1 linked dehydrodimer was observed, as expected from Smith's recent DFT calculations.[141] Moreover, the one-electron oxidant Ag_2O was successfully used to convert coniferyl alcohol in anhydrous CH_2Cl_2 (24 h at room temperature) into the corresponding racemic *trans*-phenylcoumaran 8–5 linked dehydrodimer (see Scheme 67), which was isolated in a relatively high yield of 50%.[143] In a 1:1 CH_2Cl_2–H_2O mixture using the same oxidant, the reaction was much faster (1 h) and led to the racemic furofuran 8–8 linked dehydrodimer (referred to as pinoresinol) as the main isolated product in 25% yield. In these later cases of 8–5 and 8–8 coupling reactions, the quinone methide intermediates are intramolecularly trapped to lead to the observed dehydrodimer products (Scheme 67). In the case of the 8-O-4 coupling mode, the quinone methide intermediate needs to be trapped by an external nucleophile. Mono- or already formed di/oligolignols can play this role via phenol addition at the electrophilic quinone methide C7 center.[142,143] The formation of 8-O-4 linked dehydrodimeric benzylic alcohols, as shown in Scheme 67, obviously necessitates the presence of water. Its addition to the quinone methide C7 center can efficiently compete with that of phenolic nucleophiles under acidic catalysis. Thus, for example, quenching the Ag_2O-mediated dehydrodimerization of coniferyl alcohol in acetone with an acidic aqueous solution (1 mol l^{-1} HCl) enabled the isolation of the corresponding 8-O-4 linked benzylic alcohol (see Scheme 67) in 32% as a 40:60 *erythro*/*threo* mixture.[143]

The dehydrogenation of *para*-hydroxyphenylpropenoids using typical dehydrogenases such as HRP with H_2O_2 or laccases with O_2 followed the same regioselectivity trends. These enzymatic oxidizing systems are also highly sensitive to reaction conditions (e.g., pH, amount of water, nature, and amount of cosolvents) and to the nature of the starting phenylpropenoids.[144,145] For example, the yields of 8-O-4 and 8–5 linked dehydrodimers derived from isoeugenol, methyl ferulate, and coniferyl alcohol are generally higher (from approximately 20 up to 65% for the 8–5 linked dehydrodiisoeugenol) when using HRP-H_2O_2 under acidic conditions (pH 3) in the presence of 70–90 vol% methanol.[144] No significant formation of 8–8 linked dehydrodimers was observed under these conditions. Enzyme-independent formation of head-to-tail π-complexes was invoked to explain such a regioselectivity. At pH values close to neutrality, more oligomeric products are generated.[144]

It is during lignin oligomerization that biaryl (5–5) and diaryl ether (5-O-4) linked structures are formed, as a result of oxidative cross-coupling between preformed oligomers or between a preformed oligomer and a monolignol such as coniferyl alcohol.[146] Of particular note is the fact that the lignin biaryl unit is quasi exclusively featured in eight-membered dibenzodioxocin ring structures that result from the oxidative cross-coupling of a preformed 5–5 linked oligomer at the C8 center of a monolignol, followed by an intramolecular phenol addition to the quinone methide intermediate, as depicted in Scheme 68.[33h,147] Model compounds of this important (and relatively recently discovered)[147a] lignin structure have been synthesized via one-step oxidative coupling procedures in moderate but satisfactory yields using either HRP-H_2O_2 at pH 6 or Ag_2O as oxidizing reagents (Scheme 68).[44a,147b]



R = Pr: Ag_2O, CH_2Cl_2, r.t., 45 h
⇒ 34% (*trans*-isomer) + 19% (*cis*-isomer)

R = CH_2OH: HRP–H_2O_2, dioxane-aqueous buffer (pH 6), r.t., approximately 15 h
⇒ 18% (*trans*-isomer only, isolated after peracetylation)

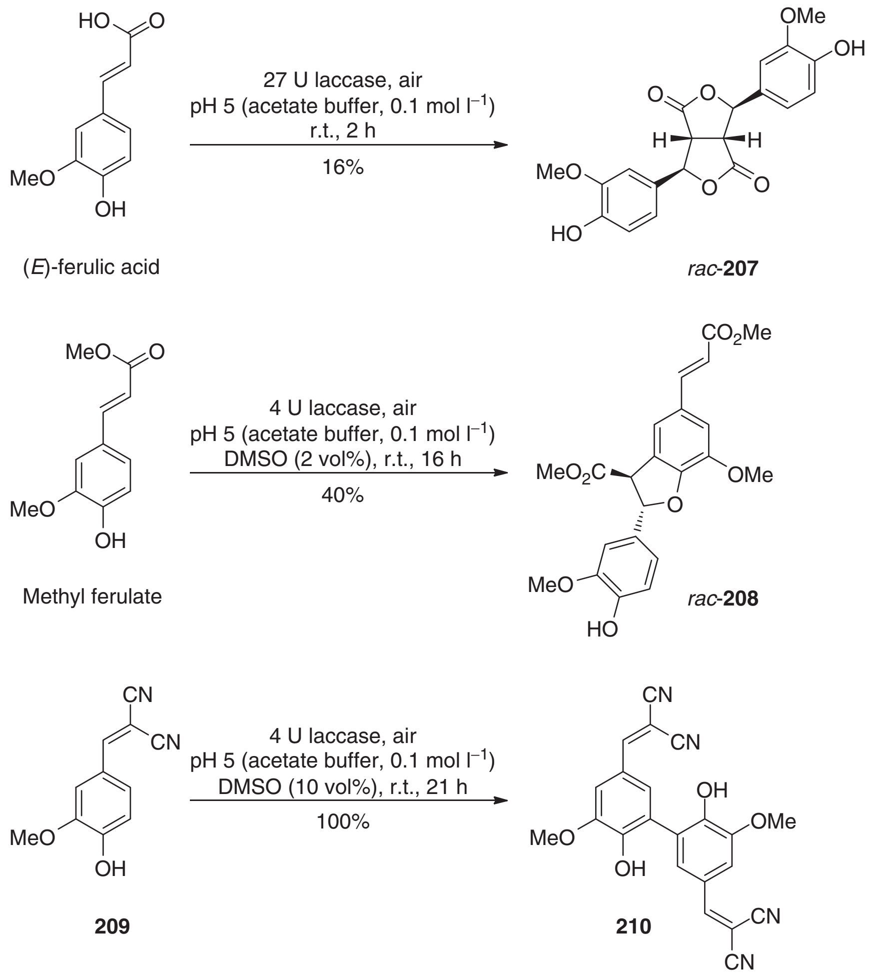
R = $CH(OH)CH_3$: HRP–H_2O_2, acetone-aqueous buffer (pH 6), r.t., 20 h
⇒ 25% yield (*trans*-isomer only, isolated after peracetylation)

Scheme 68

Beifuss and coworkers recently revisited the use of laccases plus air (O_2) to generate dehydrodimers derived from various natural and nonnatural *para*-hydroxyphenylpropenoids.[145] The oxidation of (*E*)-ferulic acid with 27 U of a laccase from *Trametes versicolor* in a pH 5 acetate buffer afforded the racemic furofuran 8–8 linked dilactone **207** in 16% as the sole isolated product (Scheme 69).

This dilactone can also be obtained using the classical Cartwright and Haworth's procedure,[148c] which makes use of $FeCl_3$ in the presence of O_2, in isolated yields from more than 20% up to 56%.[148] Methyl (*E*)-ferulate was converted into the 8–5 linked *trans*-phenylcoumaran **208** in an isolated yield of 40% using only 4 U of the same laccase in the same acetate buffer in the presence of 2 vol% dimethylsulfoxide (DMSO) (Scheme 69).[145] This result compares well with those of previous oxidations of other (*E*)-ferulates using Ag_2O in acetone. For example, the Ag_2O-mediated dehydrodimerization of ethyl (*E*)-ferulate led to the corresponding *trans*phenylcoumaran in 28% after crystallization.[127] Also, an arabinofuranosidyl (*E*)-ferulate was similarly oxidized with Ag_2O to the desired phenylcoumaran in 55%, but as an unexpected 1:1 *trans-cis* mixture.[149] However, the most interesting result of Beifuss' work is perhaps the laccase-catalyzed oxidation of *para*-hydroxyphenylpropenoids bearing an additional electron-withdrawing carbon-based function (ethyl ester, methyl ketone, carbonitrile) at the olefinic C8 center. With such substrates, no 8–5 coupled product was formed. Instead, only 5–5 coupled biphenyls were formed in yields between 80 and 100%. For example, the dicarbonitrile **209** was converted into the corresponding biphenyl **210** in a quantitative yield (Scheme 69).[145] Similar observations had previously been made by Stevens and coworkers, who generated **210** in 59% yield by using the λ^3-iodane DIB reagent to oxidatively couple the phenol **209**.[58]

The preparation of dehydrodimers from ferulates has been the topic of several investigations, notably because of the presence of feruloylated hemicellulosic chains in grass cell walls and the negative impact of their cross-linking by oxidative coupling on the



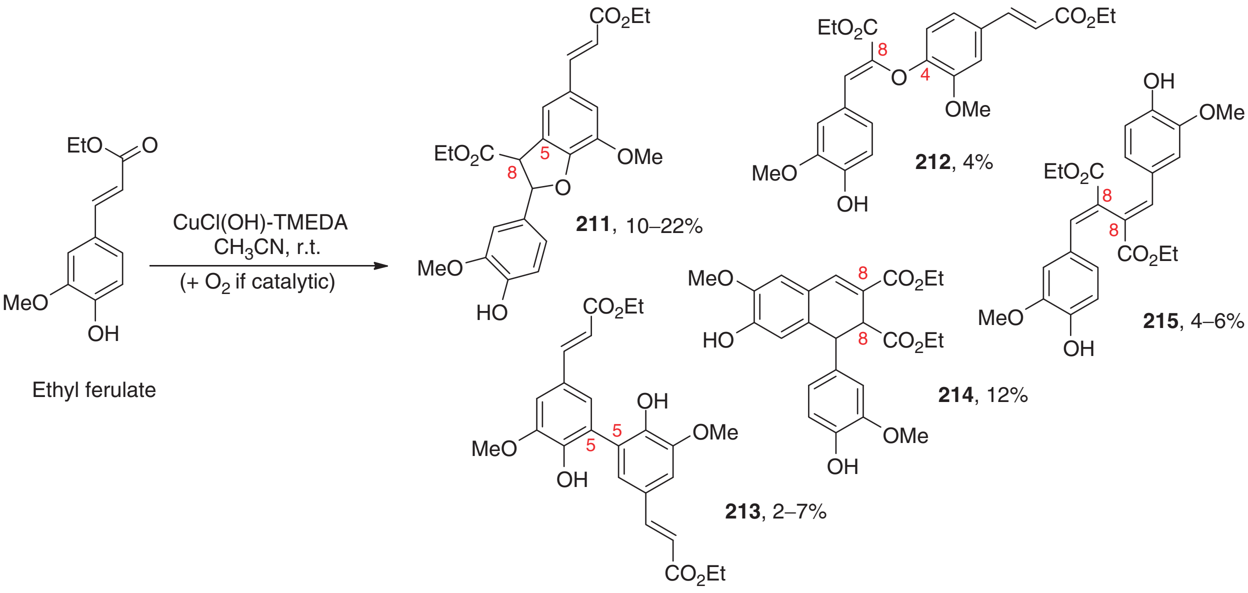
Scheme 69

utilization of these grass carbohydrates as forage feed for ruminants and, more generally, as renewable bioresources.[127,150,151] Like monolignols, ferulates can oxidatively be converted into not only 8–5 linked dehydrodimers such as the phenylcoumaran **208** (Scheme 69) but also 8-O-4 and 8–8 linked variants. The occurrence of 5–5 and 4-O-5 linked dehydrodiferulates has also been evidenced in plants. Besides the independent synthesis of each possible dehydrodiferulate by various synthetic methodologies,[127] oxidative coupling procedures have been implemented to access, in one chemical operation, separable mixtures of these dimers that can then serve as reference compounds for quality analysis of grasses.[151,152]

In this vein, Lu and coworkers have recently reported the use of a copper(II)-amine complex system (CuCl(OH)-tetramethylethylenediamine (TMEDA)) to generate in a single step and at a preparative scale a separable mixture of five dehydrodiferulates **211**–**215** from ethyl ferulate (Scheme 70).[151] The added value of this reaction protocol is the production of the 5–5 linked dimer **213** in low but preparatively exploitable yield. As discussed above in this section, the formation of such a biaryl species is usually not observed on oxidative coupling of *para*-hydroxyphenylpropenoids. Here, a copper(II) chelation of two molecules of ethyl ferulate might contribute to maintain them long enough in a relative spatial orientation that enables the 5–5 coupling mode.

The catecholic caffeic acid and its esters are other examples of *para*-hydroxyphenylpropenoids that can be transformed through oxidative phenolic coupling reactions into oligomeric plant polyphenols, including dimeric lignans and neolignans.[20] For example, Tringali and coworkers recently submitted the naturally occurring caffeic acid phenethyl ester (CAPE) to oxidative coupling conditions. Using an excess of MnO_2 in CH_2Cl_2 at room temperature, the 8–8 coupled benzo[*kl*]xanthene lignan **216** and the racemic aryldihydronaphthalene lignan **217** were generated and isolated in 43% and 12% yields, respectively (Scheme 71).[153]

However, when CAPE was oxidized with Ag_2O, the main dehydrodimer was instead the 8–5 coupled neoligan-type racemic *trans*-phenylcoumaran **218**, isolated in approximately 18% yield. The authors speculated that the preference for the 8–8 coupling in the case of the MnO_2-mediated reaction could be because of the formation of a stable complex between Mn(II) ions and the bidentate *ortho*-hydroxyquinone methide radical **219**. Interestingly, when CAPE was oxidized with Ag_2O in the presence of Mn(II) ions [Mn(acac)$_2$], the main dehydrodimer was the 8–8 coupled benzoxanthene **216** (51%), together with traces of **217**, but the 8–5 coupled phenylcoumaran **218** was not detected (Scheme 71). These observations are thus in agreement with the authors'



Scheme 70

initial speculations, which were further corroborated by DFT calculations that notably indicated that the chelation of a Mn(II) ion by the radical **219** drastically affects the spin density repartition of the latter (i.e., decrease at C5 and increase at C8) in favor of the 8–8 coupling mode.[153] A significant increase in the yield of **216** and **217** was gained by using $Mn(OAc)_3$ in $CHCl_3$ in place of MnO_2 in CH_2Cl_2, and this methodology was then applied to the synthesis of the natural benzoxanthene lignans mongolicumin A and rufescidride.[153]

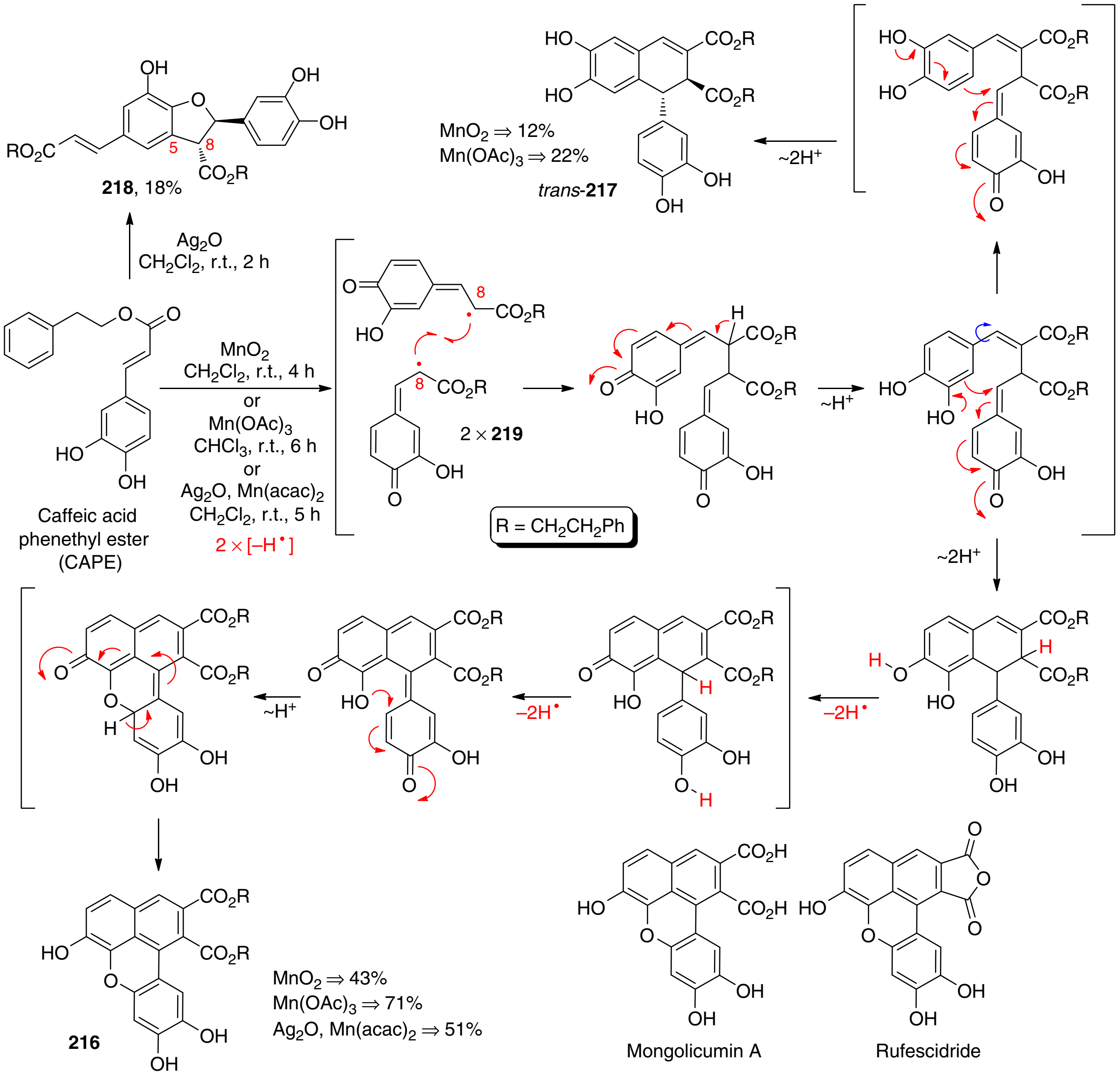
The λ^3-iodane DIB reagent has been used to promote nonradical oxidative coupling of *para*-hydroxyphenylpropenoids. For example, Antus and coworkers reported simple syntheses of phenylcoumaran neolignans by relying on a DIB-mediated oxidative activation of isoeugenol (Scheme 72).[154a]

These authors proposed a dissociative-type mechanism leading to a partial formation of the phenoxenium ion intermediate **220**, which would then be trapped by some intact isoeugenol, as depicted in Scheme 72. The resulting *para*-quinone methide intermediate **221** (or its protonated cationic form) would then undergo a rearomatizing C–O bond-forming intramolecular nucleophilic addition with the remaining phenolic function to furnish (±)-dehydrodiisoeugenol in 35–40% yield. This 8–5 coupled compound then served as a common intermediate in the synthesis of fragnasols A–C (Scheme 72).[154a] Kuo and coworkers also applied the same hypervalent iodine-based tactic in their total synthesis of the neolignan salvinal.[154b]

The authors finish this section by a related example that concerns the oxidative coupling of *ortho*-hydroxyphenylpropenoids into benzoxanthenone natural products, such as carpanone (Scheme 73). Lindsey and coworkers recently revisited this known oxidative coupling transformation in the context of their own work on the synthesis of carpanone and unnatural analogs.[155a] They used a copper(II)-amine catalyst system to induce the transformation of the *ortho*-hydroxyphenylpropenoid **222** into the 8–8 coupled intermediate **223**, which undergoes a rapid *endo*-selective inverse-electron demand Diels–Alder reaction to furnish carpanone in 91% yield as a single diastereomer. The bidentate (−)-sparteine was found to be more efficient than the monodentate *tert*-butyl amine in directing the 8–8 phenolic coupling step, but this chiral amine failed to induce any enantiocontrol. The λ^3-iodane DIB reagent was also tested, but it only worked with less electron-rich substrates that were converted into numerous analogs of carpanone.[155b,c] Ley and coworkers also reported a synthesis of carpanone using solid-supported reagents, notably including a supported-cobalt salen complex that was used in concert with O_2 to convert **222** into carpanone in 78% yield.[155d]

3.13.5.2 Stereoselectivity in Hydroxyphenylpropenoid Coupling Reactions

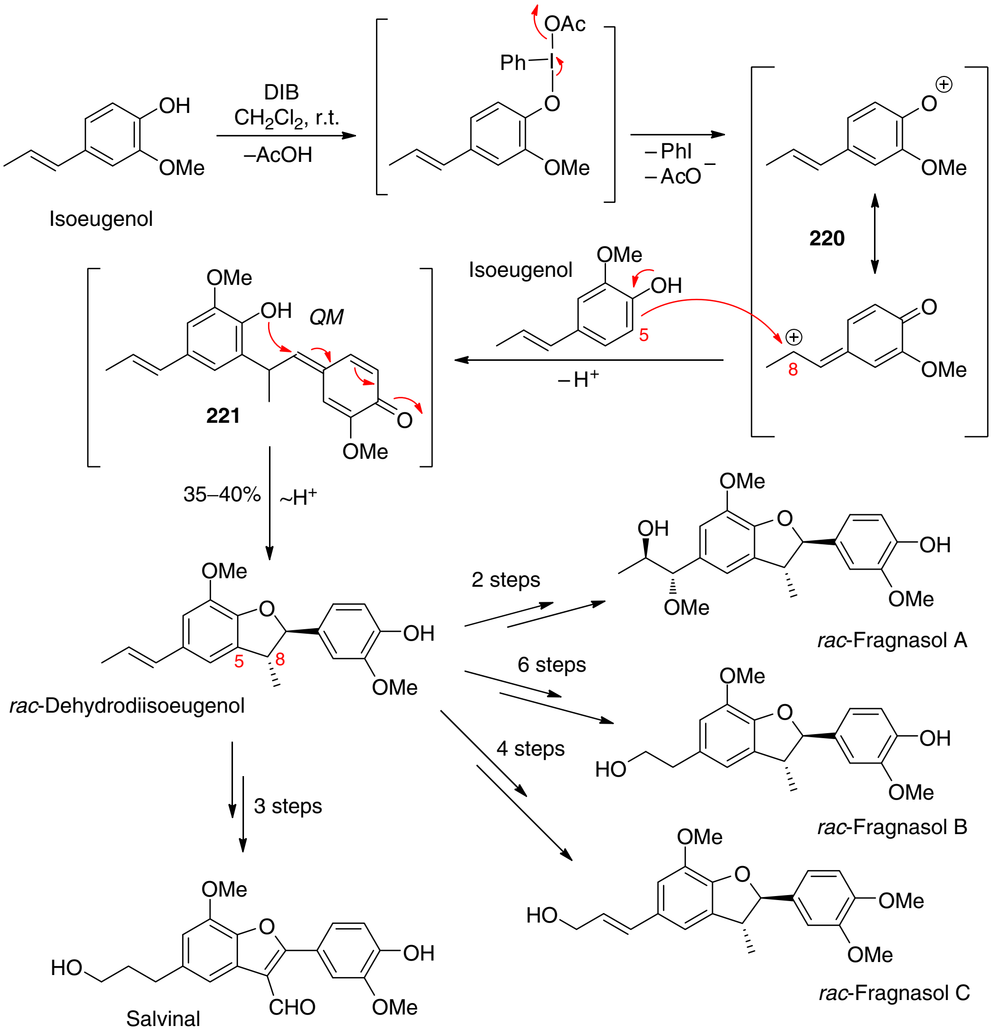
Besides issues of chemo- and regioselectivities, the oxidative coupling of achiral *para*-hydroxyphenylpropenoids creates stereogenic centers in several 8-O-4, 8–5, and 8–8 linked dehydrodimers. As seen above (see Section 3.13.5.1), excellent levels of diastereoselectivity can notably be observed in the formation of 8–5 and 8–8 dimers, irrespective of the type of oxidizing reagent used. However, only racemates are produced, even when using enzymatic (homochiral) oxidants such as HRP or laccases. The natural lignin polymer itself has no detectable optical activity, and would essentially result from ‘combinatorial’ combinations of phenoxy radicals derived from monolignols and growing oligolignols that are influenced by the inherent chemical reactivity of these radicals, the reactivity and energetic preferences of the structures of their coupling intermediates and products, and the physicochemical parameters of the medium (i.e., the plant cell wall), in which lignification takes place *a priori* without any specific protein intervention (*vide infra*).[33d] However, the situation is clearly different in the case of naturally occurring lignans and neolignans, which are usually (not always) isolated as optically active compounds.



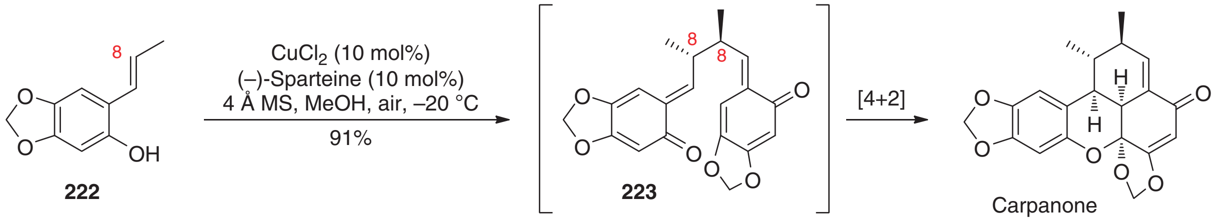
Scheme 71

Substrate-controlled approaches relying on the use of chiral auxiliaries have been developed to perform oxidative coupling of *para*-hydroxyphenylpropenoid derivatives in a diastereoselective fashion.[156] Although the diastereomeric excesses rarely exceeded 80%, these asymmetric syntheses permitted to access some lignans and neolignans in enantiomeric pure forms. For example, the HRP-catalyzed oxidation (pH 3) of the ferulic acid ethyl (*S*)-alaninate amide derivative **224a** afforded the corresponding phenylcoumaran 8–5 linked dimer **225a** in 70% yield with a diastereoisomeric excess of 65%. After purification by preparative RP-HPLC, the major diastereoisomer was converted into optically pure dehydrodiconiferyl alcohol **226** (Scheme 74).[156a] Better diastereomeric excesses (81–84%) were obtained by relying on the use of an Oppolzer's sultam auxiliary, but the chemical yields of the oxidation of the chiral feruloyl amide **224b** into the phenylcoumaran diastereomers **225b**, using either HRP-H_2O_2 in buffered aqueous acetone (pH 3.5) at 0 °C or Ag_2O in CH_2Cl_2 at r.t., were much lower (Scheme 74).[156b,c]

The most remarkable discovery in this domain of the oxidative coupling of phenols is unarguably that made by Norman Lewis' group in 1997.[157a] They found and isolated a 78-KDa protein from *Forsythia* species that works in concert with *Forsythia* oxidases (laccases), as well as with an inorganic one-electron oxidant (ammonium peroxydisulfate), to generate enantioselectively the 8–8 linked dehydrodimer (+)-pinoresinol from the achiral coniferyl alcohol. This protein (*Fi*DIR1), which does not possess any catalytic oxidase activity, is capable of controlling both the regio- and stereochemistry of the oxidative coupling of the coniferyl radical into (+)-pinoresinol with enantiomeric excesses above 99%, whereas oxidases alone furnished racemic mixtures of

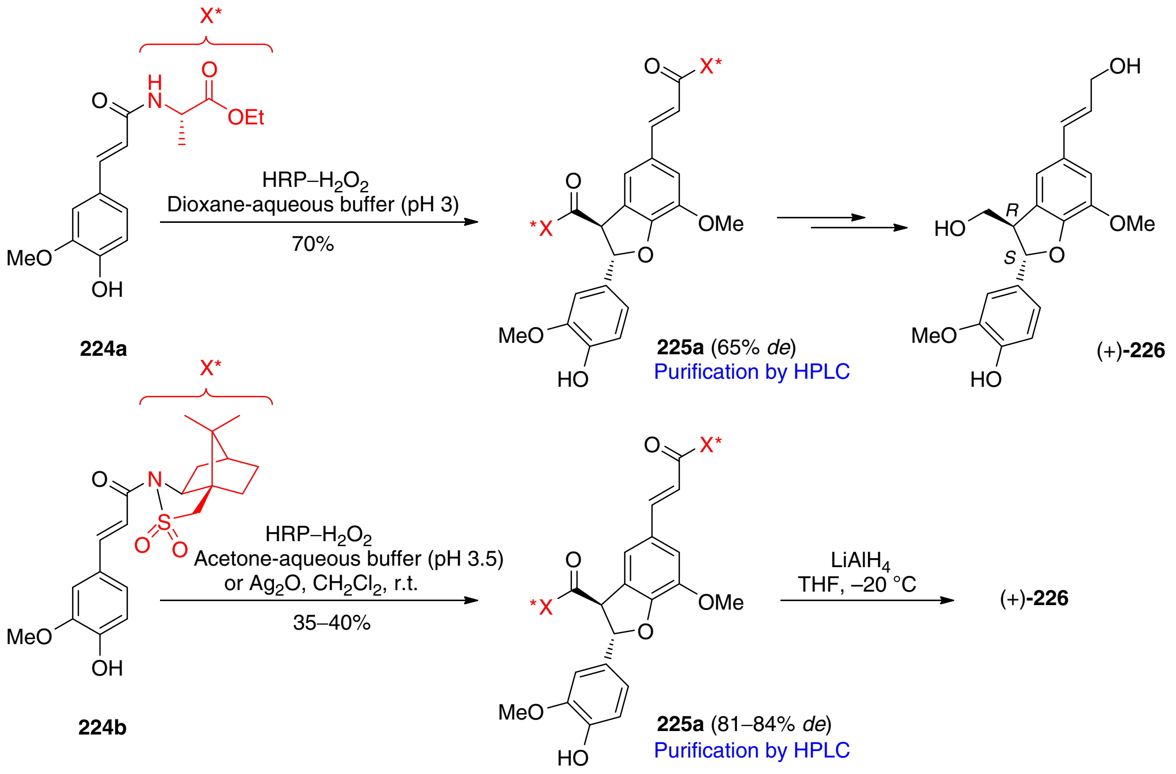


Scheme 72



Scheme 73

different coupling products. This so-called ‘dirigent’ protein would act by specifically recognizing and mutually aligning two coniferyl radicals in such a way that the 8–8 coupling exclusively occurs from the *si* faces of those radicals (Schemes 67 and 75).[157a,b] Related ‘dirigent’ proteins were then also found in other lignan-producing plants.[157c,d] A dirigent protein from *Arabidopsis thaliana* (*At*DIR6) was recently found by Shaller and Beifuss’ groups to control *in vitro* the oxidative coupling of coniferyl alcohol into (–)-pinoresinol with a best enantiomeric excess of 78% using a commercial laccase from *T. versicolor* (Scheme 75).[158] The unusual regio- and stereoselective phenolic 8–2 coupling of the catecholic caffeic acid into (–)-*cis/trans*-blechnic acids in the fern *Blechnum spicant* would also be similarly controlled by some dirigent proteins (Scheme 75).[157e] Whether or not some ‘dirigent’ proteins could also be involved in chemo- and regioselectivity controls during the oxidative assembly of monolignols into lignin primary structures remains a subject of fierce debate and intensive investigations.[33d,f]



Scheme 74

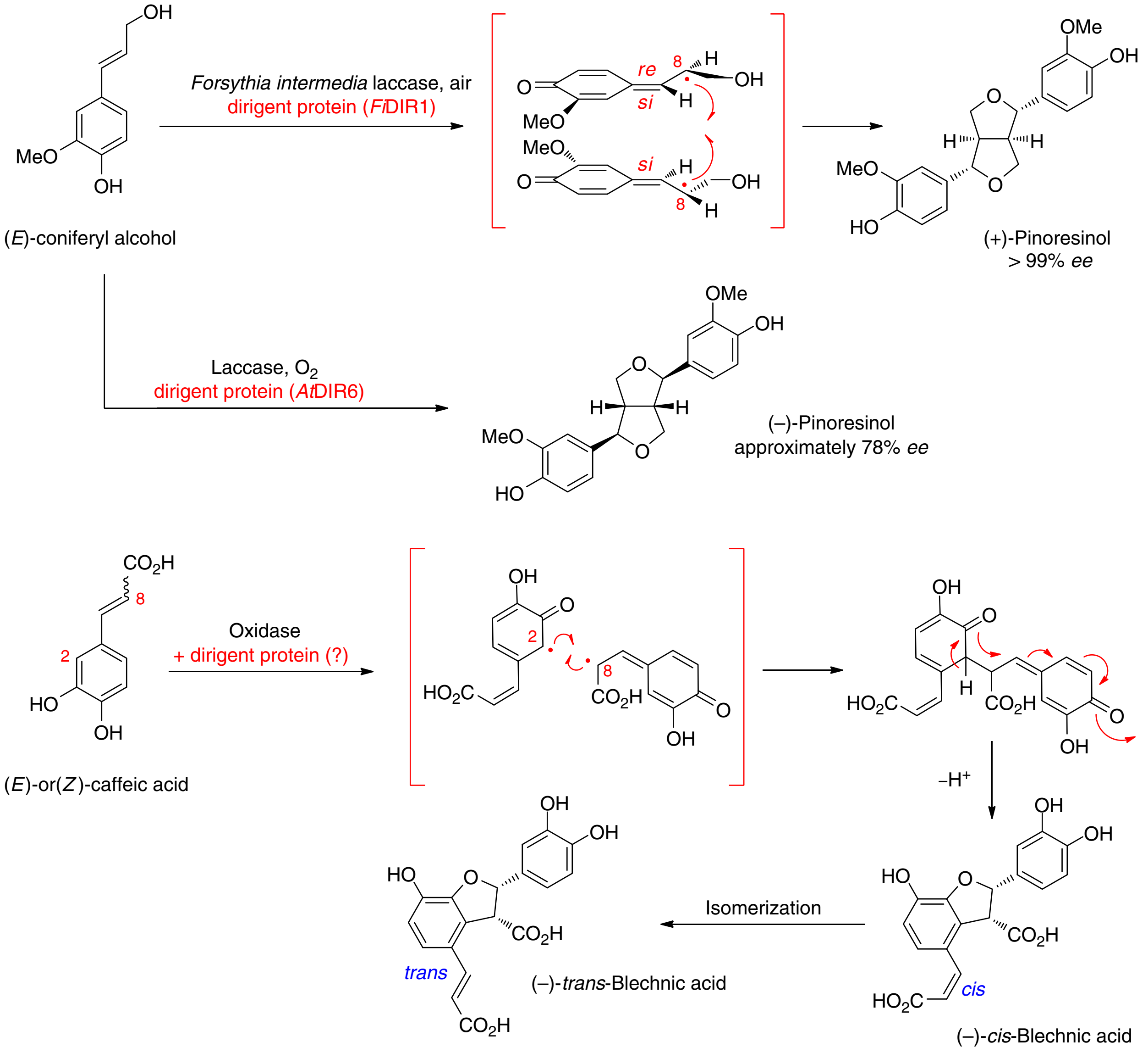
3.13.5.3 Chemo- and Regioselectivity in Hydroxystilbenoid Coupling Reactions

The anabolism of naturally occurring hydroxylated stilbenes, such as the phytoalexin *trans*-resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) and analogs, does also rely, although not exclusively, on oxidative phenolic coupling reactions. The central carbon–carbon double bond that is conjugated with the two phenolic rings and *para*-positioned to one of the phenolic hydroxyl groups renders this phenolic compound prone to undergo oligomerization via radical coupling events similar to those leading to lignan and lignin oligomers, with frequent participation of the conjugated olefinic β-carbon center of the starting 4-hydroxystyrene moiety at the oxidative dimerization stage (Scheme 76, see radical form **C**).

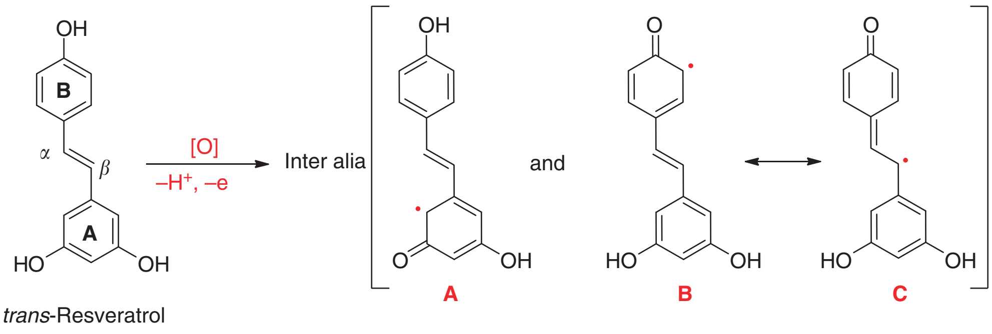
Again, oxidases such as laccases and peroxidases are thought to be involved in the biosynthesis of the resulting so-called oligostilbenes,[32] and have of course been used in biomimetic syntheses, as well as typical metallic phenol oxidants such as those based on iron(III), silver(I), copper(I/II), as well as thallium(III) or manganese(III/IV) ions.[159] The state-of-the-art of oxidative resveratrol coupling reactions has recently been reviewed by Weber and coworkers;[159a] below are discussed only a few examples that the authors found most pertinent for highlighting both the progress made and the questions remaining to be solved in this avenue of the oxidative coupling of phenols. Most of the aforementioned biomimetic approaches to oligostilbenoids suffer from the usual lack of regio- and stereocontrols observed in such (random) radical coupling processes, hence rarely affording products in high yields. However, a worth noting exception is the regio- and diastereoselective **B**+**C** dimerization of resveratrol into its racemic *trans*-dehydrodimer (δ-viniferin) in high yields on treatment with the one-electron oxidants $FeCl_3$ or AgOAc,[160a,b] whereas a fast **A**+**C** dimerization into the racemic ε-viniferin is additionally or exclusively observed, albeit in moderate yields, by using instead $K_3[Fe(CN)_6]$ or $Tl(NO_3)_3$ (Scheme 77).[160a] Lin and coworkers also claimed to generate ε-viniferin in 30% yield from resveratrol using $FeCl_3$ in aqueous MeOH at room temperature.[161a–c] The same research group also described the synthesis of bisisorhapontigenin A, an **A**+**C** type dehydrodimer and ε-viniferin analog, in approximately 20% yield, and shegansu B, a **B**+**C** type dehydrodimer and δ-viniferin analog, in 4% yield, by treating isorhapontigenin (3,5,4′-trihydroxy-3′-methoxy-*trans*-stilbene) with $FeCl_3$ in acetone–water at room temperature.[161d] Other minor products apparently derived from one-electron oxidation of the resorcinol ring of isorhapontigenin, including C–O coupled products, were also obtained.[161d]

The reasons for the change of regiochemistry in the resveratrol coupling reactions shown in Scheme 77, and involving or not an oxidation of the resorcinol A-ring, remain obscure. According to recent voltammetric analyses, the oxidation of the resorcinol A-ring occurs at pH-dependent potentials higher than those for the oxidation of the phenol B-ring (*ca.* <0.9 V vs. <0.7 V, respectively (vs. Ag/AgCl)),[162a] and calculations indicate that the resorcinol-derived phenoxy radical is less stable than the phenol-derived one by approximately 7 kcal mol^{-1}.[162b] However, calculations also indicate that the free energy (ΔG) of formation of the quinone methide intermediate resulting from the **A**+**C** coupling is much higher (by *ca.* 10 kcal mol^{-1}) than that resulting from the

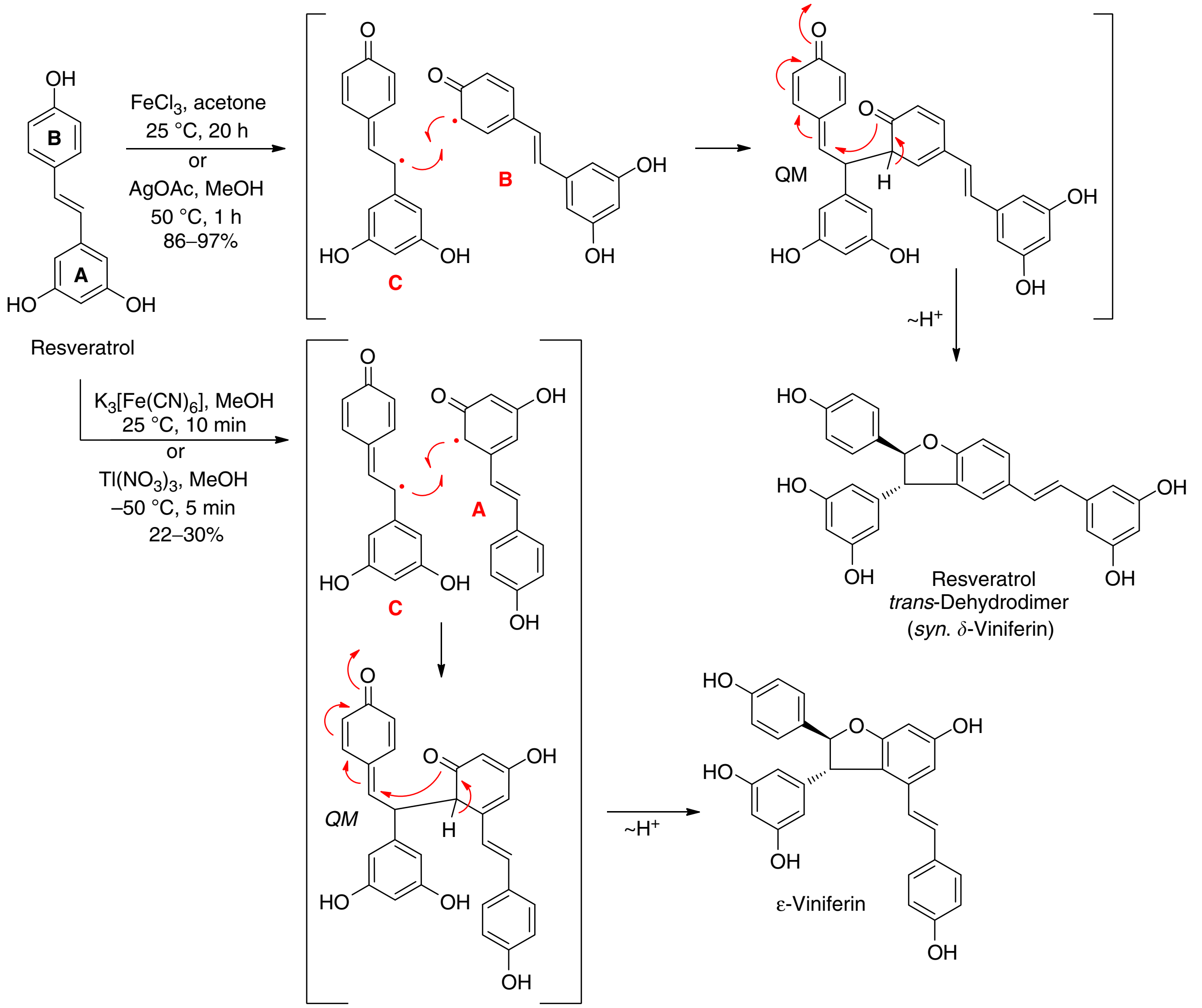
B+C coupling.[162b] The low temperature and/or very short times of the reaction conditions used by Niwa and coworkers to forge the ε-viniferin dehydrodimer (Scheme 77)[160a] suggest a kinetic preference for an enhanced participation of a highly energetic short-lived radical form **A** in a thermodynamically favored coupling mode.



Scheme 75



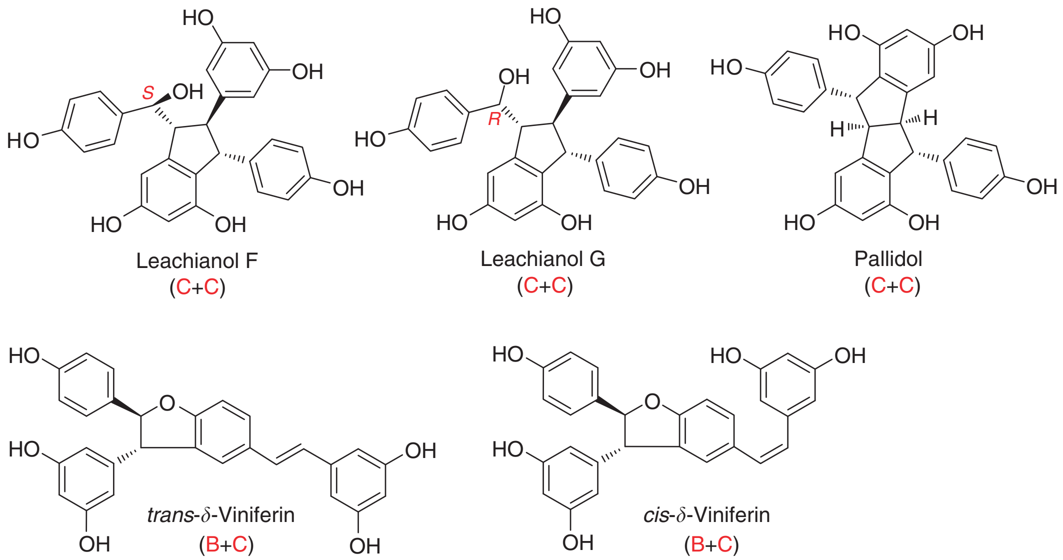
Scheme 76



Scheme 77

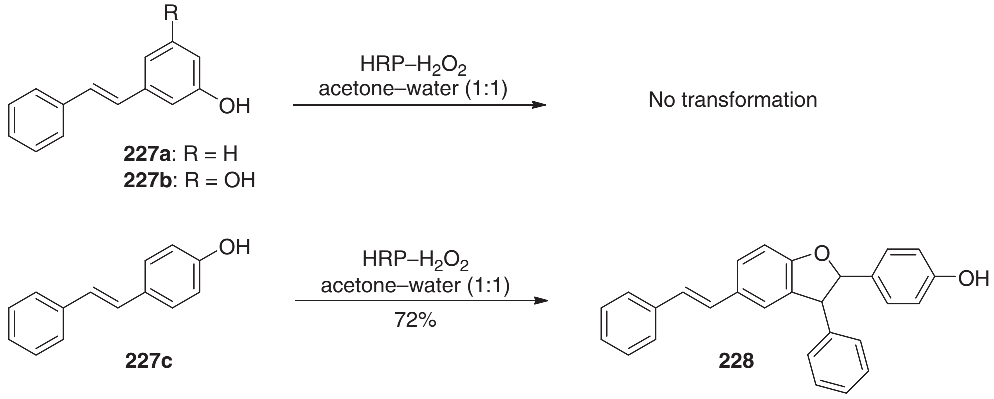
However, the nature and specific reactivity features of the metallic oxidants used, the type of complexes they may form with resveratrol and its oxidized forms,[162b] as well as the possibility of alternative ionic or mixed radical ionic coupling pathways through either phenolic two-electron oxidation or direct oxidation of the resveratrol central olefin unit into a radical cation intermediate should be further considered in future attempts to fully rationalize changes in resveratrol coupling regiochemistry. Along these lines, in their recent review article on the synthesis of oligostilbenoids,[159a] Weber and coworkers underlined the possible influence of the Lewis acidity and hard/soft character of the metallic oxidants, and of the polarity, solvation, and metal coordination properties of the solvents on the mechanistic pathways that resveratrol and analogs thereof could follow during their oxidation, while suggesting some regio- and stereocontrolling π-stacking preferences at the stage of their coupling, and more provocative mechanistic depictions invoking radical addition pathways.[159a,c] Although these interesting yet speculative suggestions freshen up older commonly accepted concepts on resveratrol oxidative (radical–radical) coupling, they are still far from providing a clear all-embracing rationale of what controls the participation of the phenol B-ring and/or resorcinol A-ring of resveratrol during its oxidative dehydrodimerization. More designed experimentations and sounder mechanistic proofs that could perhaps be backed up by theoretical calculations are in demand before general rules can be drawn.

Niwa and coworkers also used peroxidases of various origins to oxidize resveratrol in pH 6 buffer acetone solutions. Only complex mixtures of coupled products were obtained, all products resulting from oxidation of the phenol B-ring, so no trace of ε-viniferin.[160a] These results were recently confirmed by Pan and coworkers, who investigated the use of HRP at different pHs.[163] At pH values between 3 and 6, the HRP–H_2O_2 system afforded similar mixtures of coupled products containing, in varying amounts, leachianols F and G, pallidol, and *trans*/*cis*-δ-viniferins, all exclusively resulting from the oxidation of the phenol B-ring of resveratrol (Scheme 78). The formation of the diastereoisomeric leachianols was predominant at pH values between 4 and 6, with a best combined yield of approximately 55% (HPLC estimated) at pH 6. The best yield of pallidol was of approximately 20% at pH 5. At pH 3, only traces of leachianols and δ-viniferins were observed, and no oxidative transformation of resveratrol occurs below pH 3. Most remarkably, a privileged formation of *trans*-*δ*-viniferin with an HPLC yield of 93% (89% isolated yield) was observed at pH 8. Pan and coworkers disclosed glimpses of a possible rationale of this pH-dependent HRP-catalyzed dehydrodimerization of resveratrol, which would be because of pH-induced changes of the HRP conformation that could perhaps modulate the manner and affinity through/with which the enzyme accommodates the resveratrol-derived phenoxy radical mesomers during dimerization.[163]



Scheme 78

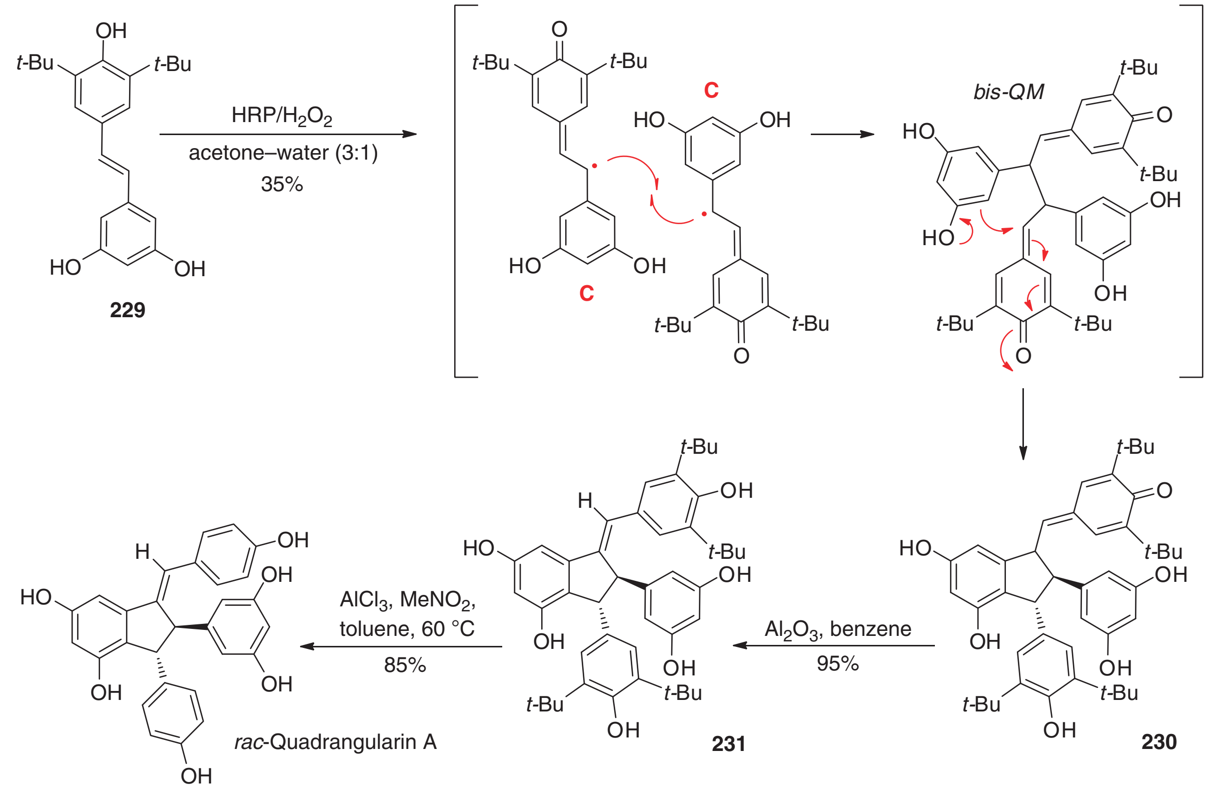
Moreover, no product derived from the oxidation of the resorcinol A-ring, such as *ε*-viniferin, was observed under any of those conditions. Interestingly, resveratrol analogs **227a** and **227b** resisted the HRP-H_2O_2 oxidation, whereas **227c** was converted into the *δ*-viniferin analog **228** in 72% yield (Scheme 79), hence demonstrating that neither the resorcinol A-ring nor the central olefin is involved in the oxidative dimerization of resveratrol; the phenol B-ring being solely oxidized by HRP.[163] Obviously, some other oxidizing systems must be involved in the biogenesis of *ε*-viniferin, and generally, in the one-electron oxidation of the resveratrol resorcinol A-ring.



Scheme 79

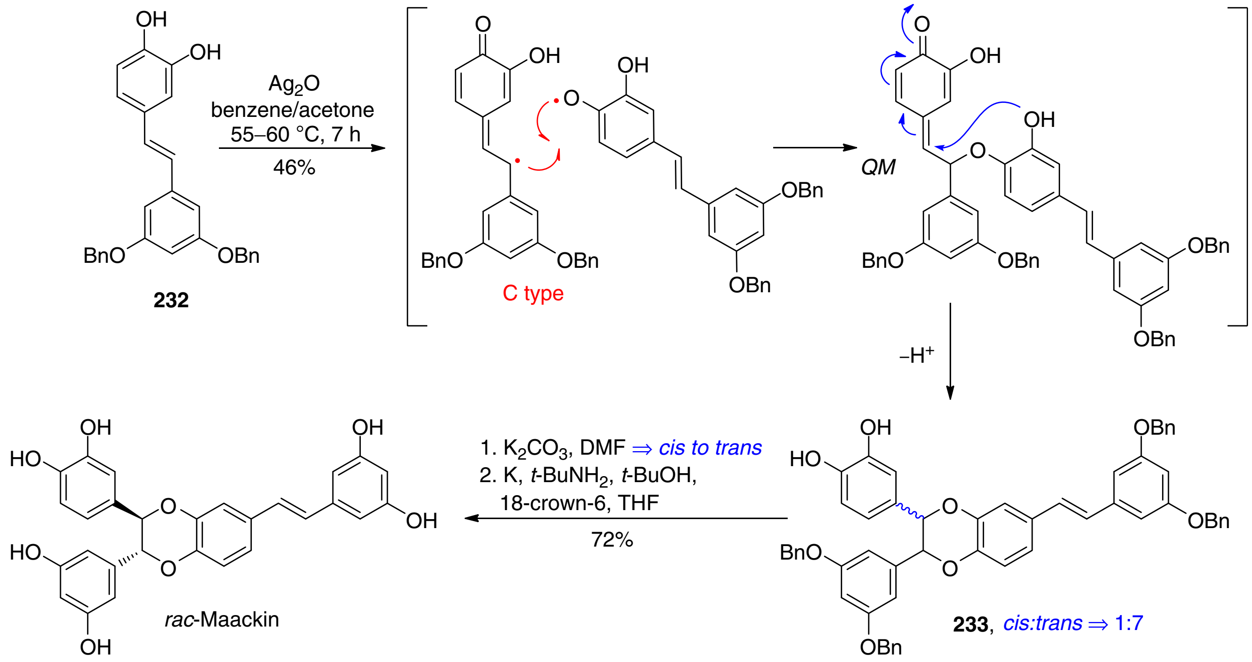
Instead of tweeking the HRP conformation by adjusting the pH of the reaction medium, Hou and coworkers modified the resveratrol structure to direct its HRP-mediated dimerization.[164] The presence of two *ortho*-positioned *tert*-butyl substituents on the phenol B-ring of **229** blocked participation of the radical form **B**, and the **C+C** indane-type dimer **230** was generated in 35% yield (Scheme 80). This quinone methide was aromatized by a Al_2O_3-promoted prototropic rearrangement to afford **231**, from which the two *tert*-butyl groups were conveniently removed using $AlCl_3$ to furnish *rac*-quadrangularin A (Scheme 80). This is the first total synthesis of this resveratrol indane dehydrodimer.[164]

Maackin is another example of a naturally occurring dehydrodistilbenoid that is derived from the catecholic resveratrol analog, piceatannol (3,5,3′,4′-tetrahydroxy-*trans*-stilbene). Pan and coworkers[165] accomplished a first racemic total synthesis of this



Scheme 80

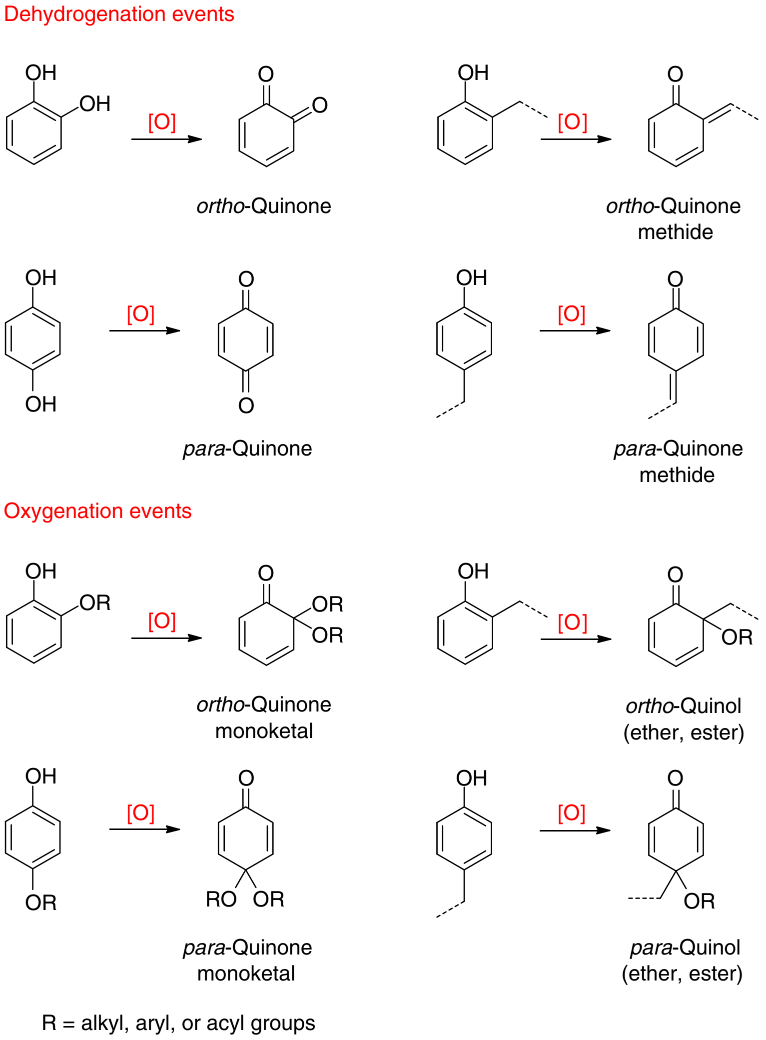
benzodioxane compound by using Ag_2O to oxidatively couple a piceatannol derivative (**232**), on which the resorcinol ring hydroxyl groups were protected to avoid any incidental oxidation of that phenolic unit. The benzodioxane **233** was thus generated in a relatively good yield of 46% as a 1:7 *cis*:*trans* mixture, presumably via radical coupling as depicted in Scheme 81. After *cis*-to-*trans* isomerization and cleavage of the benzyl protecting groups, (±)-maackin was obtained in 72% yield.[165]



Scheme 81

3.13.6 Oxidative Phenolic C–C Coupling Involving Quinonoids

Another facet of the oxidative coupling of phenols and phenol ethers involves their oxidative dearomatization into electrophilic quinonoid species (i.e., *ortho-* or *para-*quinones, -quinone methides, -quinone monoketals, -quinols, Scheme 82) that can either react together in cycloaddition (e.g., (hetero)-Diels–Alder reactions), as well as, in some cases, in nucleophilic addition processes, or react with phenols (or phenolate anions) or phenol ethers in nucleophilic addition or substitution processes. This type of oxidative phenolic coupling has been exploited to forge biaryl systems and to elaborate structurally more complex and non-aromatic architectures via C–C bond formation(s). A few rare examples of the use of quinonoids in the synthesis of diaryl ether systems via C–O bond formation have also been described (see Section 3.13.3.2, Schemes 62–64).

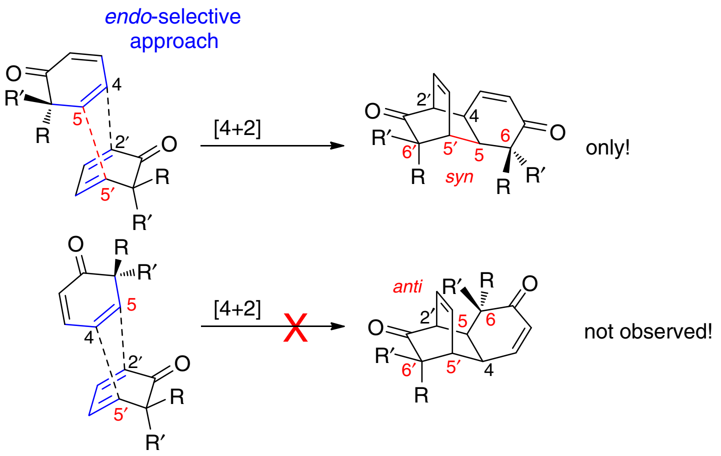


Scheme 82

The various options offered by the reactivity of such quinonoid species in phenolic coupling scenarios, and the various methods of their preparation, have been the topic or a subtopic of several review and book chapter articles since the mid-1990s.[12,29,31,166] Below is highlighted only a short selection of examples chosen to illustrate some of the most significant utilizations of phenol-derived quinonoids in phenolic coupling reactions.

One of the most remarkable and productive coupling reactions involving quinonoid species is the [4+2] cycloaddition of *ortho*-quinone monoketals or *ortho*-quinols into bicyclo[2.2.2]octenone systems. Indeed, these cyclohexa-2,4-dienone derivatives express a strong propensity to engage in Diels–Alder cyclodimerization processes, which is evidently because of the capacity of their dienone unit to behave both as a diene and as a dienophile. This dimerization often occurs spontaneously at ambient temperature, and can only be blocked, or at least retarded, if the cyclohexa-2,4-dienone core bears some specific substituents at some specific positions.[166e,167] Furthermore, this dimerization occurs in a strictly regio-, site-, and stereoselective manner (Scheme 83).[166e]

Moreover, such bicyclo[2.2.2]octenone systems are featured in the structure of several natural products, the biogenesis of which presumably results from the Diels–Alder cyclodimerization of some *ortho*-quinols, themselves naturally derived from an oxygenative dearomatization of some 2-alkylphenol precursors. This sequence of events has been put to the test with success in the synthesis of natural products such as, *inter alia*, (±)-**234**, (±)-grandifloracin, (±)-biscarvacrol, and (+)-aquaticol, which were all generated in one chemical step from their presumed 2-alkylphenol precursors by using the λ^5-iodane oxidizing reagent 2-iodoxybenzoic acid (IBX) or its stabilized (nonexplosive) formulation SIBX to mediate their dearomatizing *ortho*-selective oxygenation (hydroxylation) into spontaneously dimerizing *ortho*-quinol intermediates (Schemes 84 and 85).[168]



R, R′= alkoxy groups ⇒ *ortho*-Quinone monoketals
R = OH, R′ = alkyl group ⇒ *ortho*-Quinols

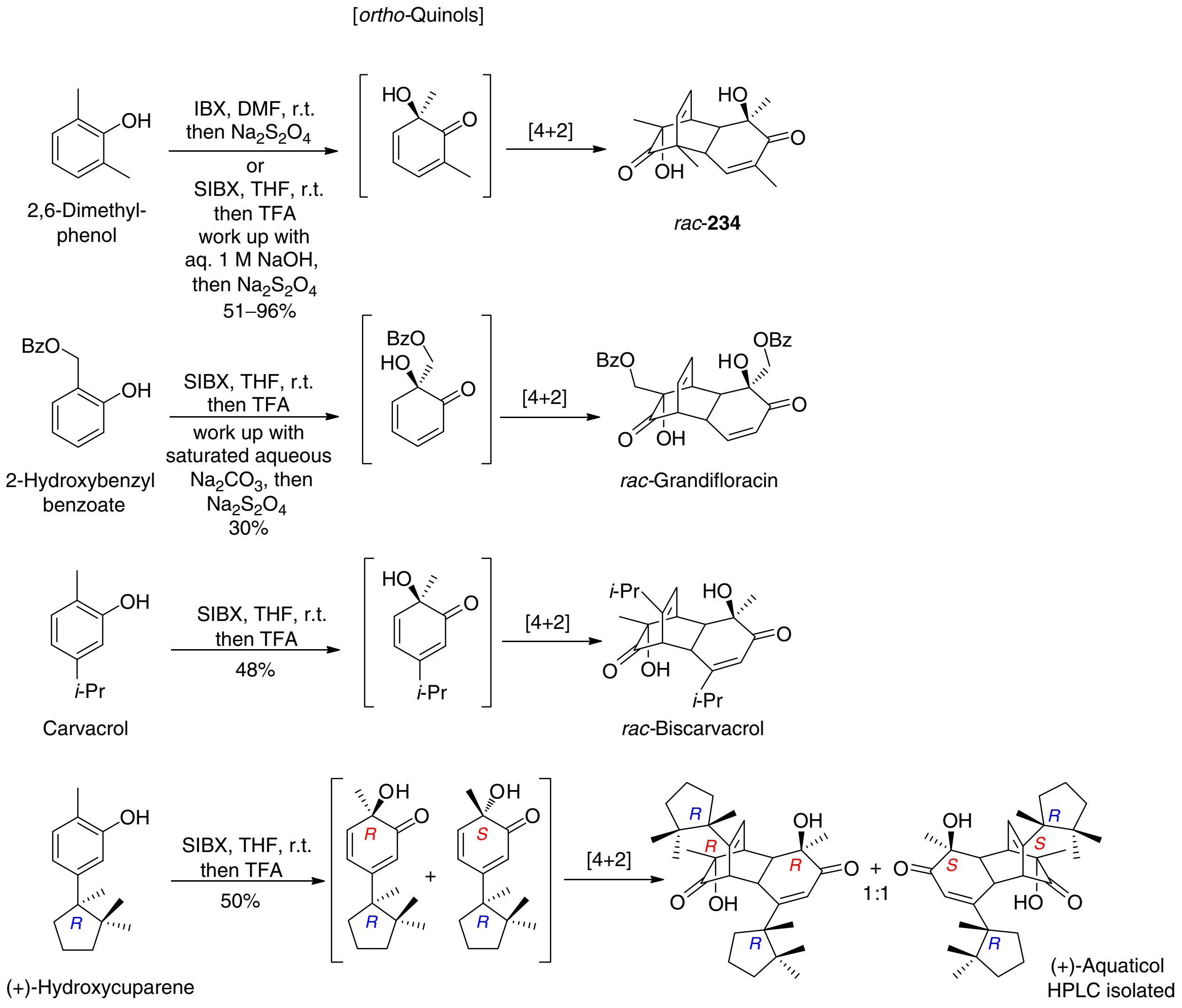
Scheme 83

Boppisetti and Birman reported an asymmetric version of this hydroxylative phenol dearomatization-Diels–Alder domino reaction by using a chiral λ^5-iodane to convert 2,6-dimethylphenol into the corresponding dimer **234** in 65% yield and 63% *ee* (Scheme 86).[169] Porco and coworkers developed an outstandingly enantioselective variant of this dimerization by relying on a chiral (−)-sparteine-based Cu(II)-amine–O_2 complex that notably enabled them to access (+)-aquaticol as a single diastereomer in 72% yield (Scheme 86).[170]

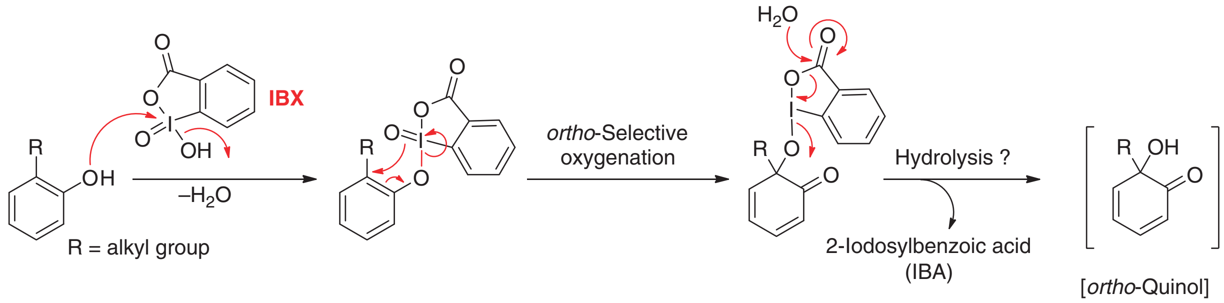
A recent example of the exploitation of the facility with which *ortho*-quinone monoketals also undergo Diels–Alder cycloadditions was recently reported by Snyder and Kontes in their total syntheses of complex neolignans, such as helisterculin A.[171] The 2-methoxy phenolic rosmarinic acid derivative **235** was dearomatized using DIB in the presence of methanol to give the corresponding *ortho*-quinone moketal **236**, which spontaneously cyclodimerized to afford **237** in nearly quantitative yield (Scheme 87). A tandem retro-Diels–Alder/Diels–Alder sequence using an excess of the protected methyl caffeoate **238** as a competing dienophile was then implemented in refluxing mesitylene to furnish the cycloadduct **239** en route to helisterculin A (Scheme 87).[171]

Everything there is to know about the use of *ortho*-quinone methides in organic synthesis, including their utilization in phenolic coupling reactions, has been recently discussed in detail in an excellent review article by Pettus and coworkers.[31a] The capacity of *ortho*-quinone methides to engage in cycloaddition reactions has also long been exploited in oxidative phenolic coupling transformations. Of note is the recent syntheses of the naturally occurring trimeric *spiro*-chroman products schefflone and tocopherol trimers by Lei and coworkers.[172] These researchers relied on the use of Ag_2O to oxidize 2-methylphenols, such as espintanol, into the corresponding *ortho*-quinone methides. Several organic (CAN and DDQ) and metallic (MnO_2, $K_3Fe(CN)_6$, and Ag(I) salts) oxidizing agents were tried, but Ag_2O in benzene at room temperature turned out to be the best agent to selectively promote the required oxidation of both the benzylic methyl and phenolic hydroxy groups. Thus, espintanol was converted into the *ortho*-quinone methide **240** that rapidly undergoes a (reversible) hetero-Diels–Alder dimerization into the *spiro*-chromanic *ortho*-quinol ether **241**, which then reacts as a dienophile with the oxo-diene **240** to furnish in a single operation (±)-schefflone in 72% yield (Scheme 88).[172]

Para-quinone methides have been cited above several times as electrophilic intermediates in oxidative coupling of *para*-hydroxyphenylpropenoids and stilbenoids (see Section 3.13.5). They can also be generated in other types of coupling approaches such as that recently developed by Pettus and coworkers in their racemic total synthesis of the natural pigment and telomerase inhibitor, brazilin.[173] Phenol **242** was subjected to an *ortho*-selective oxygenation using the λ^5-iodane IBX, which first leads to the formation of an *ortho*-quinone **243**, and $Na_2S_2O_4$ to reduce this quinone. The resulting catechol **244** was back oxidized with the λ^3-iodane BTI into the *ortho*-quinone **245** that was then tautomerized by the action of some Hunig's base into the *para*-quinone methide **246**. The addition of LiI promoted its C–C bond-forming cyclization into the *cis*-fused **247**, the debenzylation of which affording (±)-brazilin in a good overall yield (Scheme 89).[173]

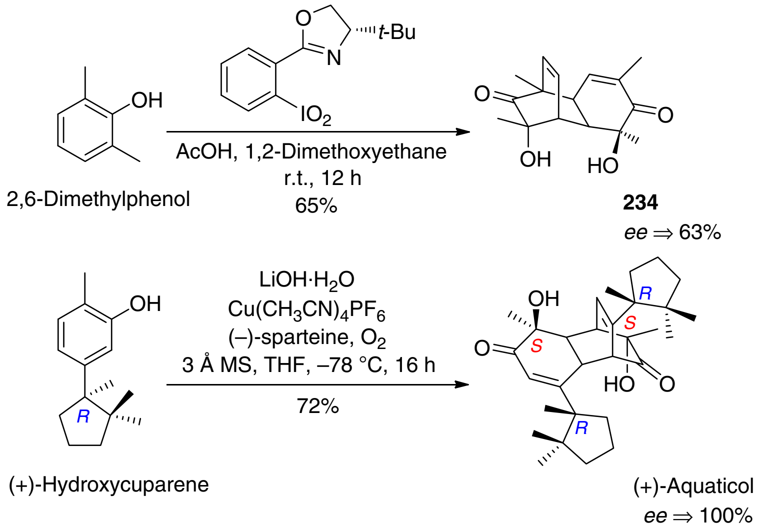


Scheme 84

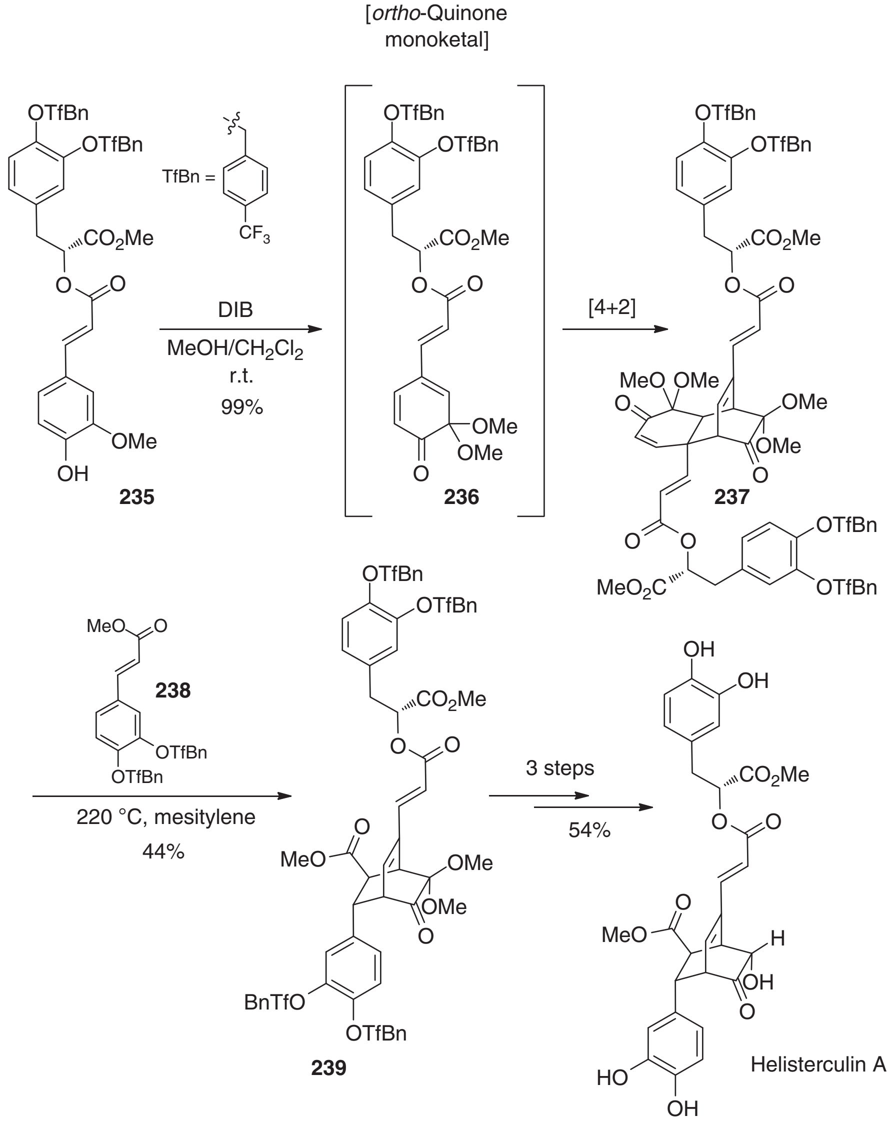


Scheme 85

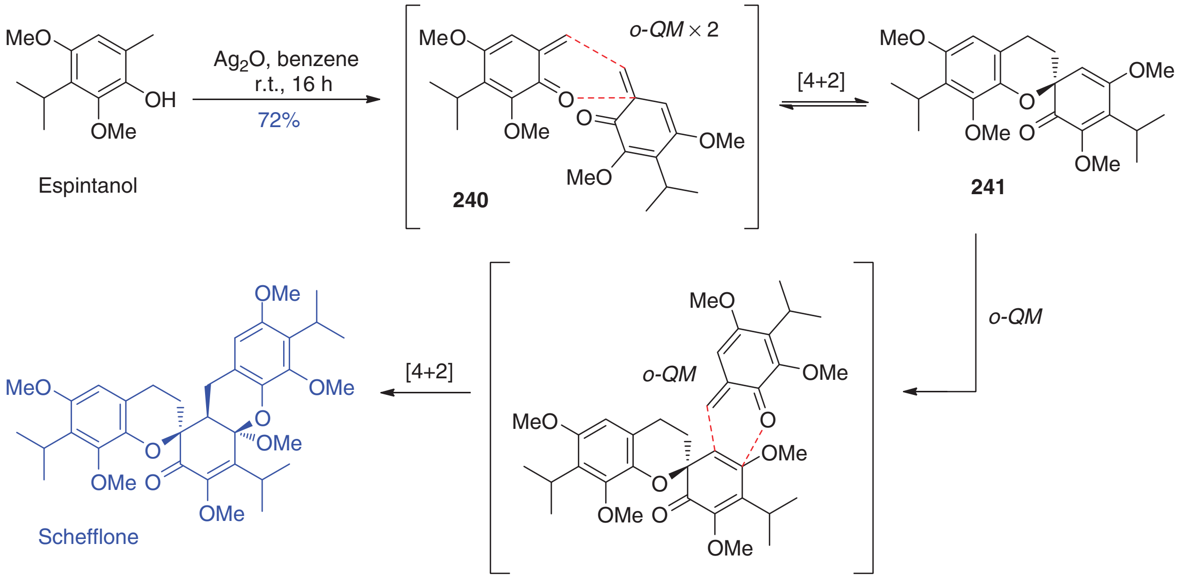
One of the key transformations in Pettus' synthesis of brazilin was the IBX-mediated *ortho*-selective oxygenation of a phenol into an *ortho*-quinone.[168a] This method of preparation of *ortho*-quinones, as well as the related SIBX-mediated hydroxylative demethoxylation of phenolic methyl phenyl ethers,[174] were used by Kuboki, Ohira, and coworkers in their syntheses of 1,4-benzodioxanic neolignans.[175] *Ortho*-quinones also offer indisputable value as intermediates in oxidative phenolic coupling reactions by virtue of their electrophilic character, like all other aforementioned quinonoids. They can also act as carbodienophiles and/or carbodienes in [4+2] cycloaddition processes, and their 1,2-diketonic unit can even act as a heterodiene in hetero-Diels–Alder cyclodimerizations to forge benzodioxanic motifs, as illustrated above in the case of the synthesis of coriariin A



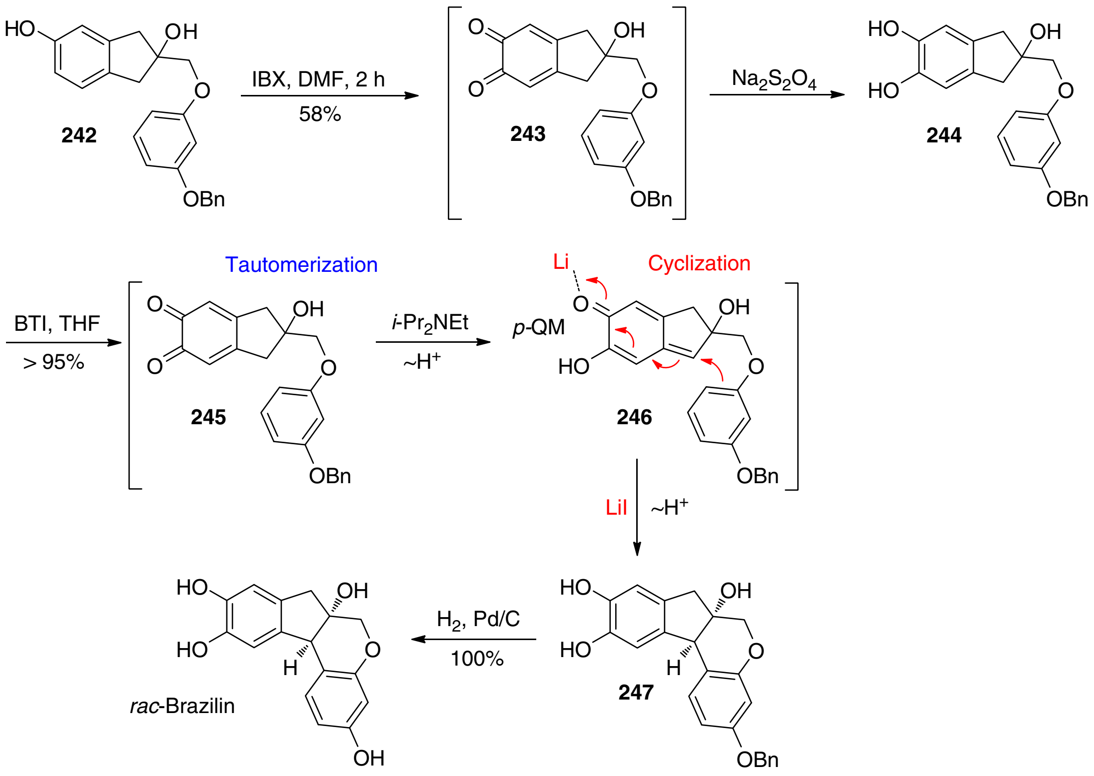
Scheme 86



Scheme 87



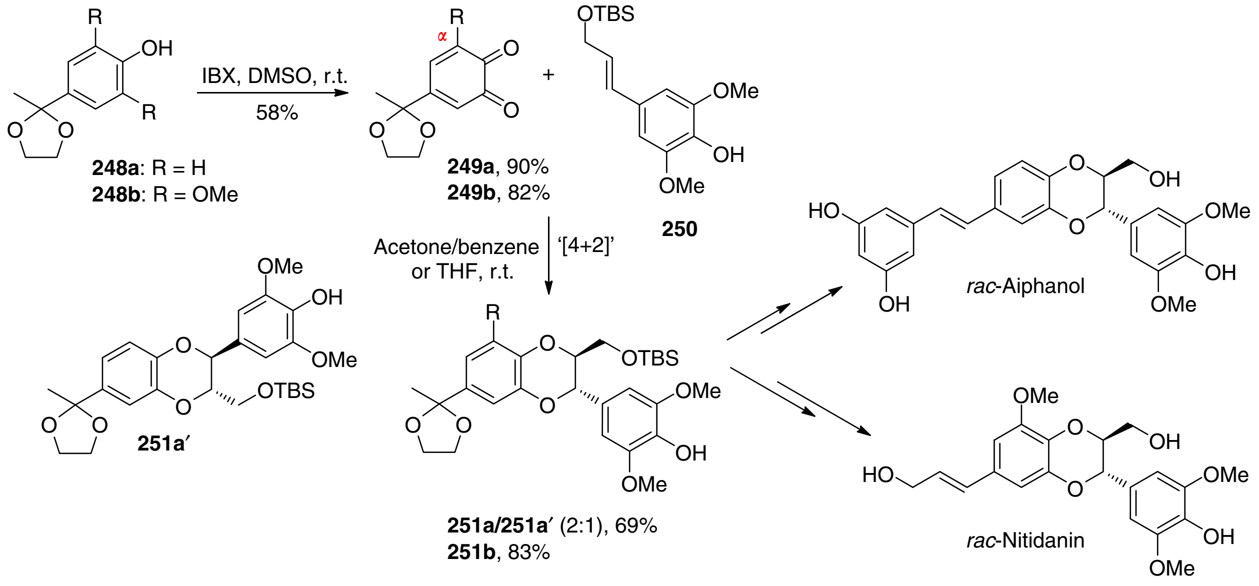
Scheme 88



Scheme 89

(see Section 3.13.3.2, Scheme 64). Kuboki and coworkers utilized the *ortho*-quinones **249a**/**b** in coupling reactions with the silylated *para*-hydroxycinnamyl alcohol **250** to elaborate, in a formal [4+2] cycloaddition fashion, the *trans*-benzodioxanes **251a**/**b** en route to the synthesis of the neolignans (±)-aiphanol and (±)-nitidanin (Scheme 90).[175a,b]

Further investigations by the same authors disclosed the fact that the α-methoxylated quinone **249b** does indeed lead to a single regioisomer **251b**, but that the quinone **249a**, in fact, gives rise to a 2:1 regioisomeric mixture of **251a** and **251a′** (Scheme 90). Using the β-methoxylated quinone **253**, a complete reversal of regioselectivity was observed, and the *trans*-benzodioxanes **254**/**254′** were obtained as a 1:15 mixture (Scheme 91).[175c] Only traces of *cis*-isomers were observed in all cases. These syntheses



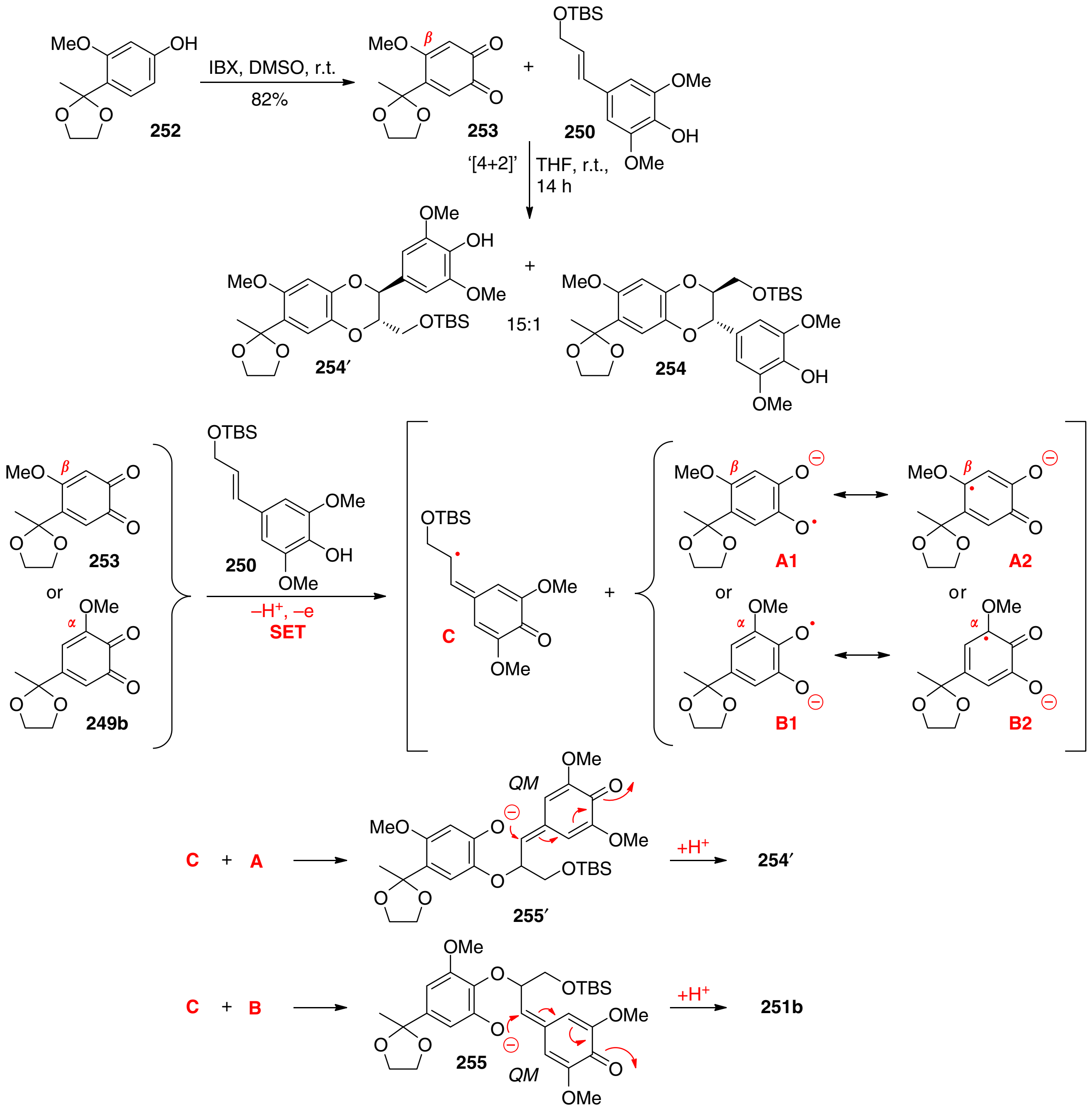
Scheme 90

of regioisomeric *trans*-benzodioxanes are reminiscent of several others that were accomplished by oxidizing, for example, catecholic *para*-hydroxyphenylpropenoids, flavonoids, or stilbenoids using one-electron oxidants (e.g., Ag_2O, Ag_2CO_3, $K_3Fe(CN)_6$, HRP-H_2O_2), such as in the course of the syntheses of americanol A and its regioisomer isoamericanol A from caffeic acid,[176a] those of the flavanolignans sinaiticin,[176b] (iso)silibins and analogs thereof,[176c] or that of maackin from 3,5-dibenzylated piceatannol,[165] which is depicted therein in Scheme 81. Although such oxidations of catechols can convert them into *ortho*-quinones, no mention of such intermediates was made in these works; only phenoxy radicals were invoked or suspected. The predominance of *trans*-products constitutes an argument against the participation of *ortho*-quinones as heterodienes in Diels–Alder scenarios. Kuboki, Ohira, and coworkers proposed an interesting mechanistic alternative to rationalize both the regiochemistry and relative stereochemistry of their *trans*-benzodioxane products. This alternative is based on the oxidizing power of *ortho*-quinones that are indeed capable of accommodating SET (Scheme 91).[175c] The positioning of the methoxy group in quinones **253** or **249b** would influence the electronic repartition on the resulting one-electron reduced quinones (i.e., semi-quinone **A** or **B**), the methoxy group stabilizing the adjacent carbon-centered radical (see semi-quinone form **A2** vs. **B2** in Scheme 91). Preferential regioselective radical coupling would then occur between the semi-quinone **A** or **B** and the phenoxy radical **C** derived from the one-electron oxidation of **250**, classically followed by an intramolecular nucleophilic addition within the quinone methide intermediate **255′** or **255** to deliver the thermodynamically more stable *trans*-benzodioxane **254′** or **251b**, respectively (Scheme 91). This proposal would certainly demand to be put to the test of further experimental and theoretical examinations, but it nevertheless has the merit of offering a clear and simple depiction of the different reaction outcomes.[175c]

Next to catechols, pyrogallol motifs (3,4,5-trihydroxyphenyls) are also often encountered in natural products, notably in plant polyphenols. Their oxidation is one of the founding chemical events of the elaboration of the structures of these natural products.[20] Their dehydrogenative oxidation can easily lead to α-hydroxy-*ortho*-quinones, which can participate in (hetero)-Diels–Alder cycloadditions, including cyclodimerizations, as well as in dimerizing nucleophilic addition reactions. This dichotomy in the reactivity of such *ortho*-quinones is because of the electron-releasing effect of their α-hydroxy group, which is part of a (di)enol unit and can engage in conjugate additions with the dienedione unit of the *ortho*-quinone ring. This is, for example, illustrated in the synthesis of the ellagitannin dehydrohexahydroxydiphenoyl (DHHDP) unit that was reported by Feldman and Quideau.[71b,72] Treating methyl gallate (**256**) with the organic oxidant *ortho*-chloranil in anhydrous Et_2O at −40 °C gave rise to a reddish solution of the α-hydroxy-*ortho*-quinone **257**, which when allowed to warm up to room temperature afforded a pale yellow precipitate of **259** in a good and reproducible yield of 64% (Scheme 92). This dimethyl dehydrodigallate **259** (i.e., a DHHDP-type system) [71b] can be viewed as resulting from a C–C bond-forming 2′→5 (or 5′→2) ring closure from the C–C linked intermediate **258**, itself resulting from a dimerizing nucleophilic 1,6-addition of **257**. This newly formed bond could be cleaved on reduction of **259** using sodium dithionite, which afforded the biaryl compound **260** in a good yield (Scheme 92). This HHDP **260** corresponds to the biarylic HHDP unit also featured in ellagitannins.[71b,177]

In the same vein, Kawabata and coworkers recently reported the conversion of methyl 2,3,4-trihydroxybenzoate **261** into a novel benzocoumarin-type dimer **264** by using *ortho*-chloranil in acetonitrile. The initially formed α-hydroxy-*ortho*-quinone **262** would react with some unoxidized **261** in a 1,4-addition fashion to deliver **264** in 18% yield, after rearomatizing prototropies and intramolecular transesterification of intermediate **263** (Scheme 93).[177]

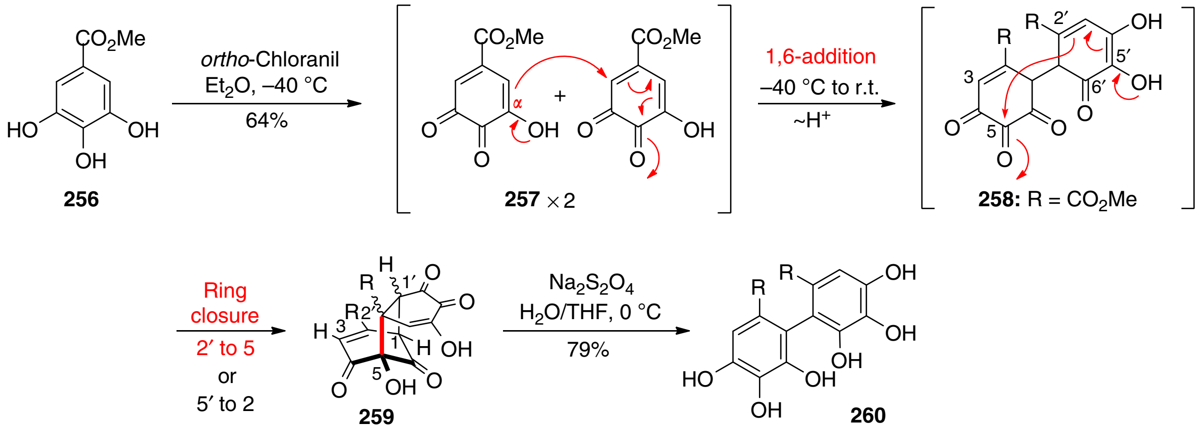
The oxidative coupling chemistry of pyrogallol and its derivatives also leads to the formation of seven-membered benzotropolone motifs featured in numerous natural products, the simplest of this being purpurogallin whose formation from



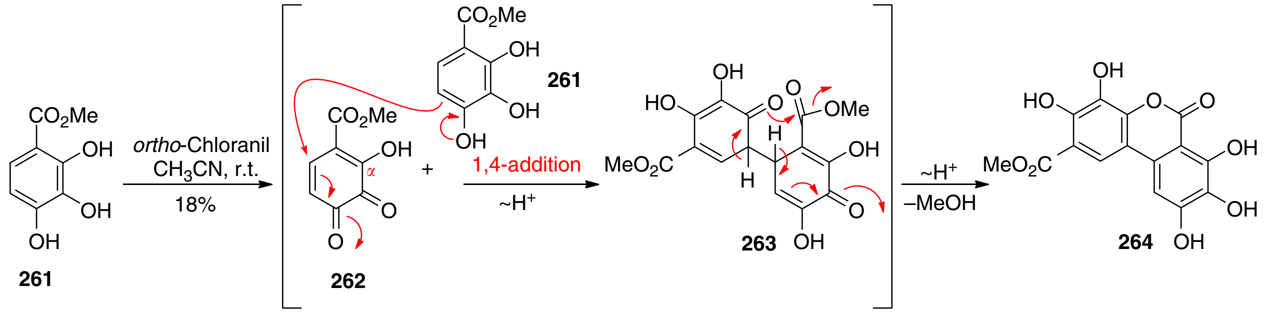
Scheme 91

pyrogallol has been investigated since the late 1950s.[178] Mechanisms with a passage by the bicyclo[3.2.1]octenedione **265** were proposed in those early days (Scheme 94), but it is only recently that experimental evidence of such a mechanism has been gathered,[179] notably as a result of the growing interest in the chemistry of tea compounds that comprise *inter alia* benzotropolone-containing theaflavins.[180] These polyphenolic black tea pigments are derived from the oxidative coupling of catecholic and pyrogallolic catechins, in particular, epicatechin, epigallocatechin, and their gallates.[180]

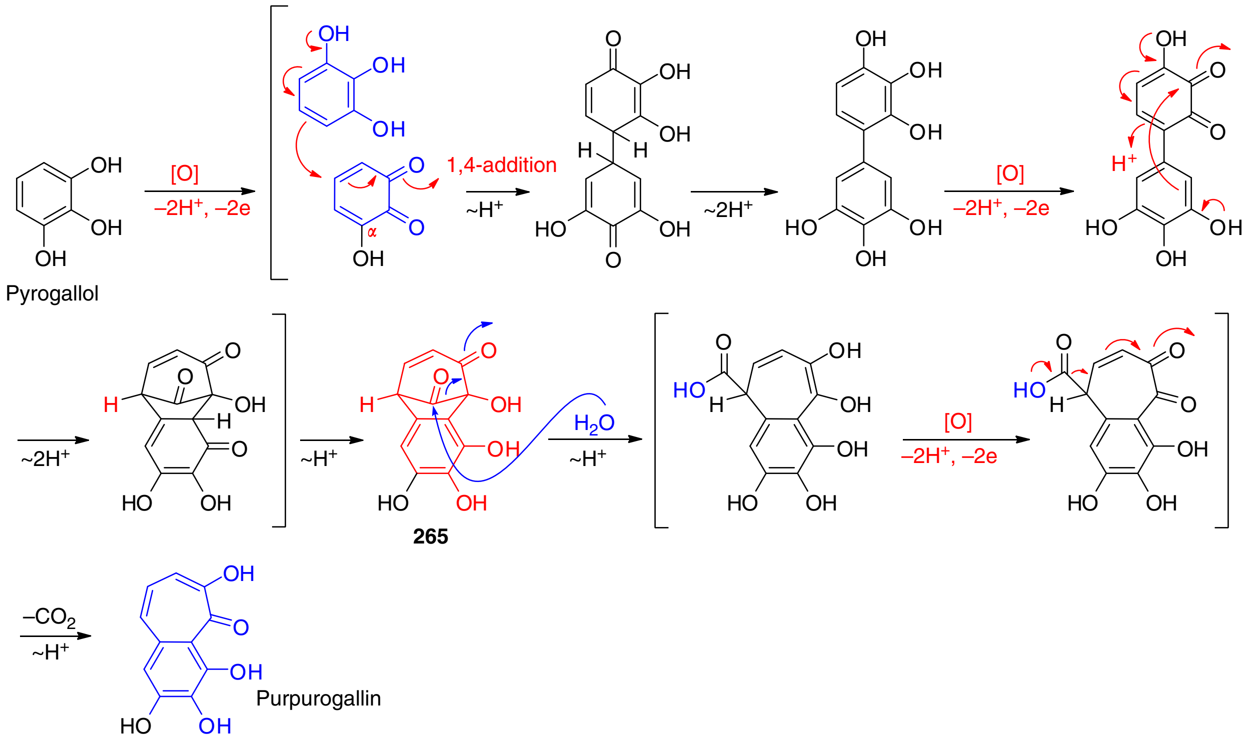
Free theaflavin would be accordingly derived from an intial nucleophilic addition of the unoxidized pyrogallolic motif of epigallocatechin onto the *ortho*-quinone derived from the oxidation of the catecholic motif of epicatechin (Scheme 95). Nakatsuba and coworkers used 5-methylpyrogallol (**266**) and the *ortho*-quinone **267** derived from 4-methylcatechol as catechin model compounds.[179] Using 2 equivalents of **267** in anhydrous CH_2Cl_2, they managed to isolate in 68% yield colorless crystals of the bicyclo[3.2.1]octenedione **265′**, the analog of **265** that was proposed by Salfeld in 1957[178c] as an intermediate in the formation of purpurogallin (Schemes 94 and 95). Using a third equivalent of **267** as a terminal oxidant in anhydrous CH_2Cl_2 at 0 °C, and treating the reaction mixture with water, they obtained the benzotropolone theaflavin model compound **268** in a yield of 94% (Scheme 95), hence demonstrating the experimental feasibility of a more than 50-year-old mechanistic proposal (Scheme 94).[179]



Scheme 92

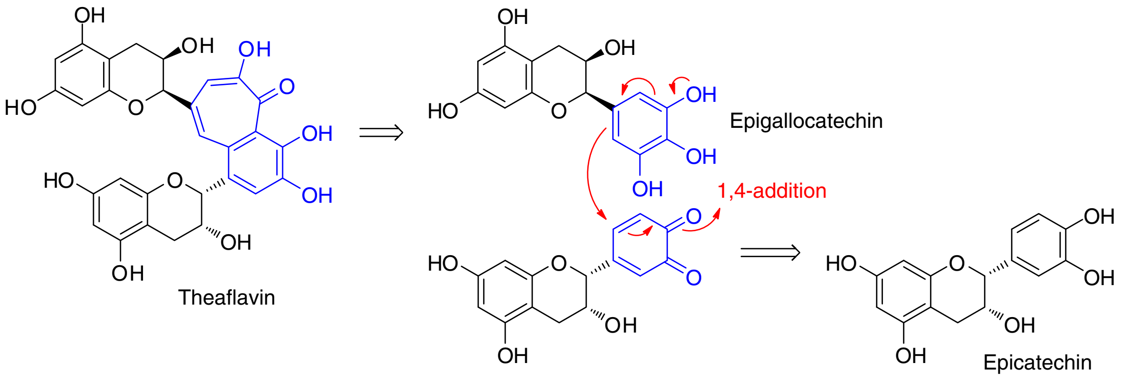


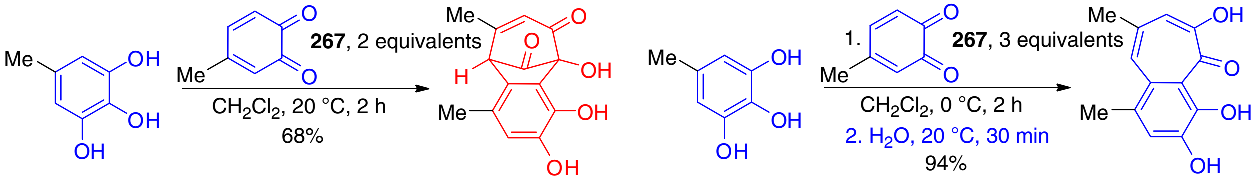
Scheme 93



Scheme 94

Moreover, coupling of two α-hydroxy-*ortho*-quinones derived from some polyphenoloxidase-mediated oxidation of tea pyrogallolic epigallocatechin has been proposed to lead to the formation of mixtures of various theatannins, including benzotropolone-containing compounds such as hydroxytheaflavin (Scheme 96),[181] via chemical transformations analogous to those taking place during the oxidation of simpler gallates.[71b] The formation of hydroxytheaflavin would follow a mechanistic path similar to that leading to purpurogallin and theaflavin (see Schemes 94 and 95), but would require a 1,2-shift of the chroman unit of one epigallocatechin component, as depicted in Scheme 96.[181]





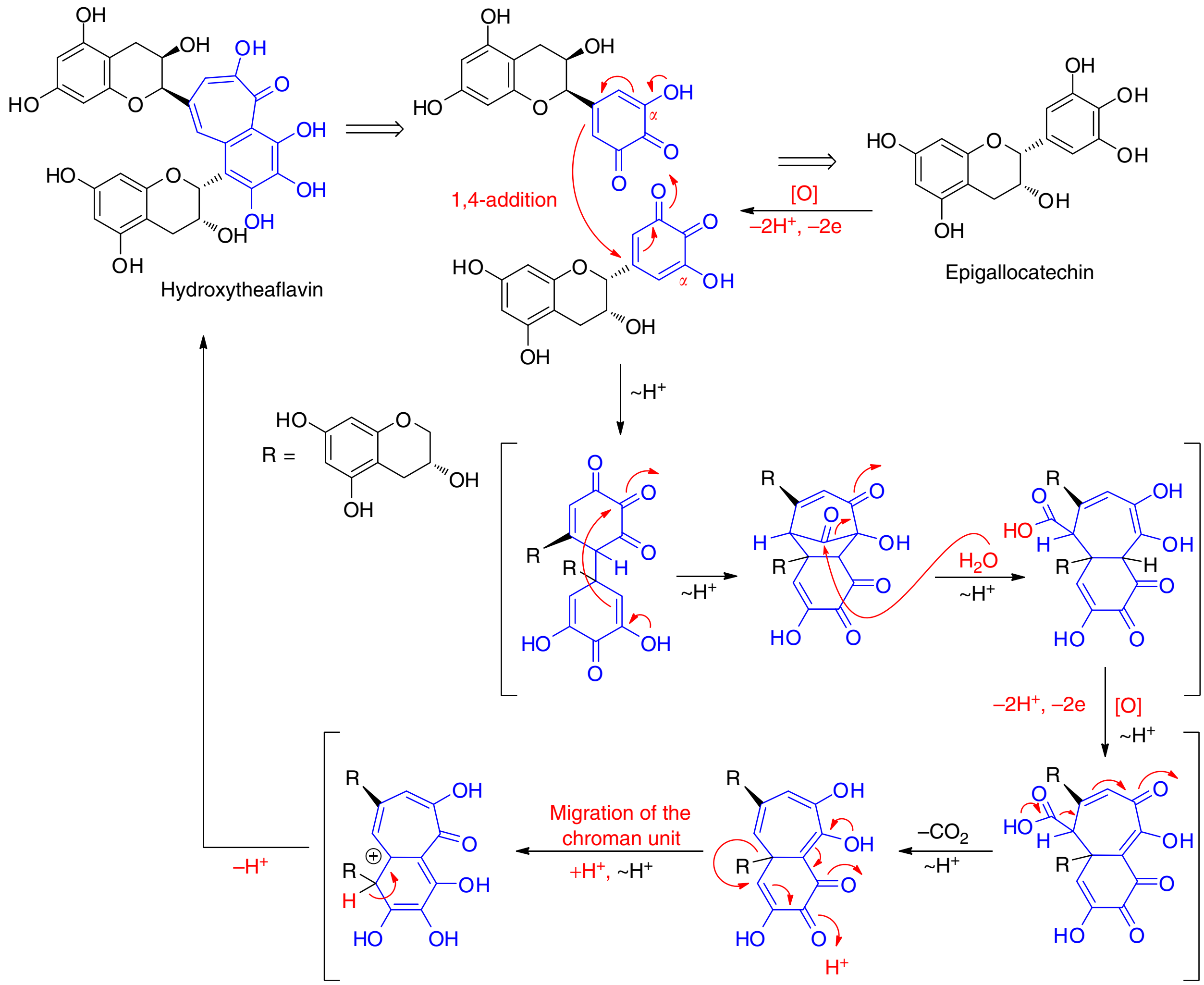
266 **265′** **266** **268**

Scheme 95

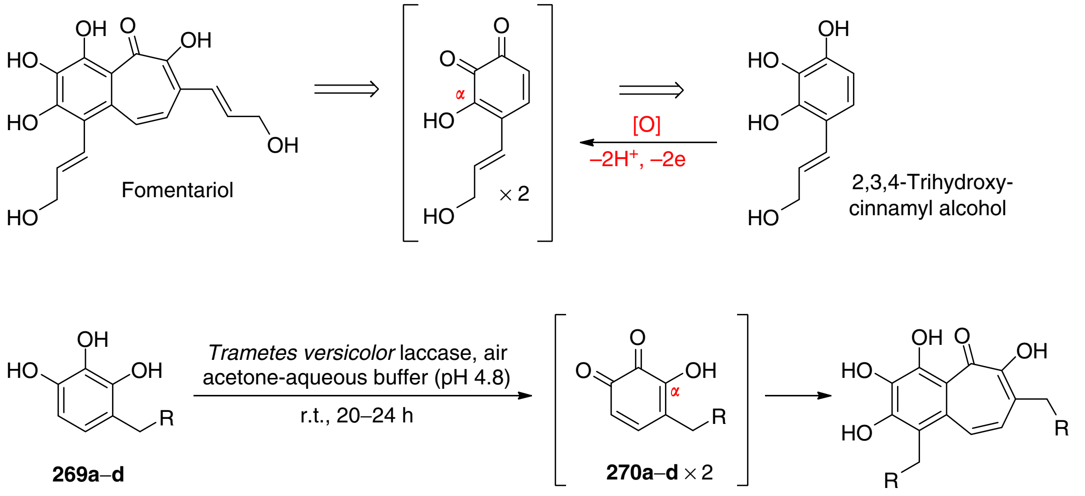
Similar couplings between α-hydroxy-*ortho*-quinones have also been proposed to rationalize the formation of benzotropolones related to the fungal fomentariol, which is naturally derived from the oxidative coupling of the pyrogallolic 2,3,4-trihydroxycinnamyl alcohol (Scheme 97). Öhrlein and coworkers recently reported the synthesis of a series of fomentariol analogs by treating different 2,3,4-trihydroxyphenyl derivatives, such as **269a–d**, with a commercial fungal laccase in the presence of O_2 at slightly acidic pH (Scheme 97).[182] Besides demonstrating once again the propensity of pyrogallols to cyclodimerize into benzotropolones under oxidative conditions, these results also underline the usefulness of commercial laccases as general bioorganic oxidizing reagents for preparative synthesis.

The penultimate example of this final section dedicated to the involvement of quinonoids in oxidative coupling of phenols and their ethers is taken from some recent works reported by Kita and cowokers.[183] They relied on *para*-quinone monoketals, such as **272** that can easily be made by treating 4-methoxyphenol with DIB in methanol, to forge various oxygenated biaryls. Such a masked *para*-quinone expresses a quite versatile electrophilic character, because direct and conjugate additions of nucleophiles, as well as direct nucleophilic substitutions can be performed. However, conjugate substitutions with nucleophiles attacking the α-carbon of the conjugated enone unit are much more difficult to mediate (Scheme 98). Using Montmorillonites as proton sources instead of conventional Brønsted or Lewis acid activators, Kita and coworkers managed to tune the electrophilicity of **272** in favor of the conjugate substitution mode. Using 1,3-dimethoxybenzene (**273**) as the nucleophile, biaryl compounds such as **274a–e** were obtained in good to excellent yields (Scheme 98).[183a] This methodology was applied in the synthesis of the gilvocarcin core structure by coupling the naphthoquinone monoketal **275** with the 3,5-dihydroxy benzoate **276** (Scheme 98).[183a] Later on, Kita and coworkers exploited the same methodology to construct teraryl compounds by resubmitting initially formed phenolic biaryls to a second oxidative dearomatization–conjugate substitution sequence using various nucleophilic aryls.[183b] They even went on to develop their protocol to the point of being able to elaborate at will higher oligoaryl systems, such as **277** and **278**, in highly decent yields (Scheme 99).[183b]

The ultimate example, which is taken from some earlier work reported by Heathcock and Chi in the context of their racemic total synthesis of the fungal *spiro*-dienone preussomerin G,[184] concerns the reactivity of *para*-quinones and their capacity to engage in oxophilic additions with phenols (or phenolates) in a manner similar to that described above for the synthesis of diaryl ethers from *ortho*-quinones and *ortho*-quinols (see Section 3.13.3.2, Scheme 63). In Heathcock's case, the 1,4-dimethoxyphenyl moiety of *spiro*-ketal **279** was oxidized with CAN to generate the *para*-quinone **280**. On hydrolytic

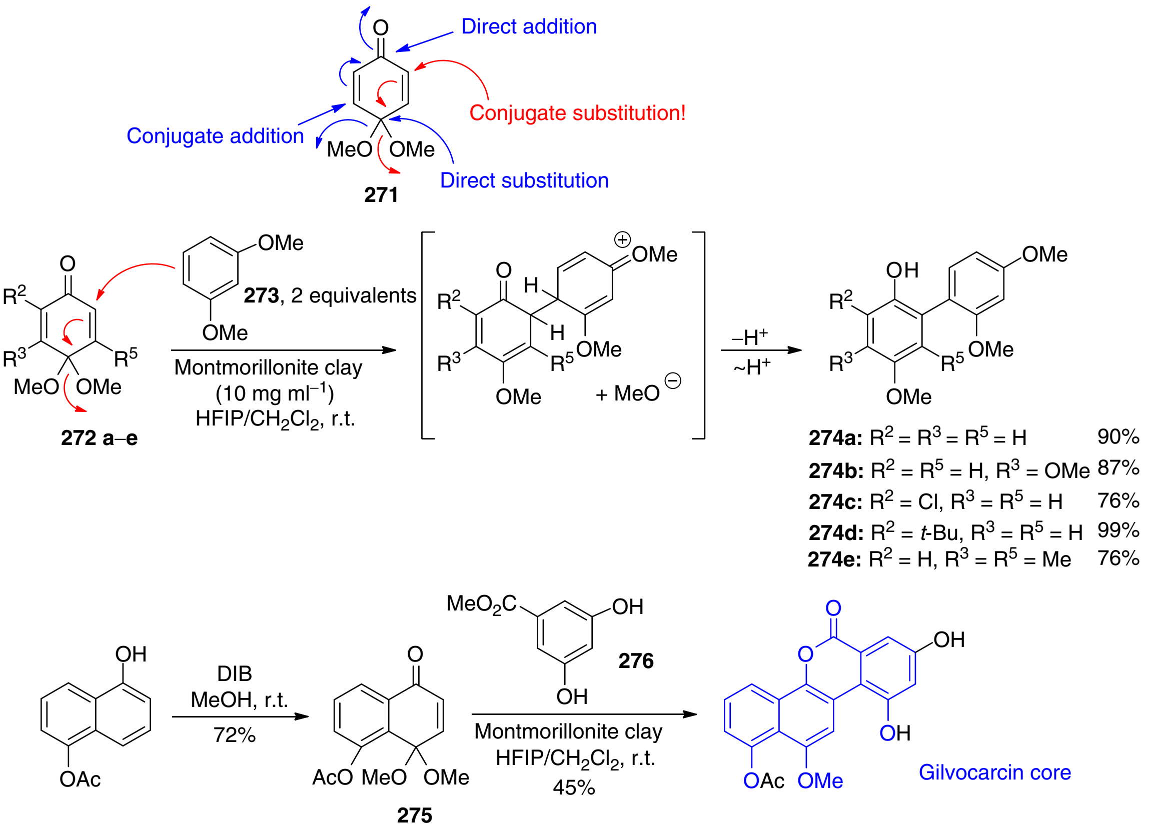


Scheme 96

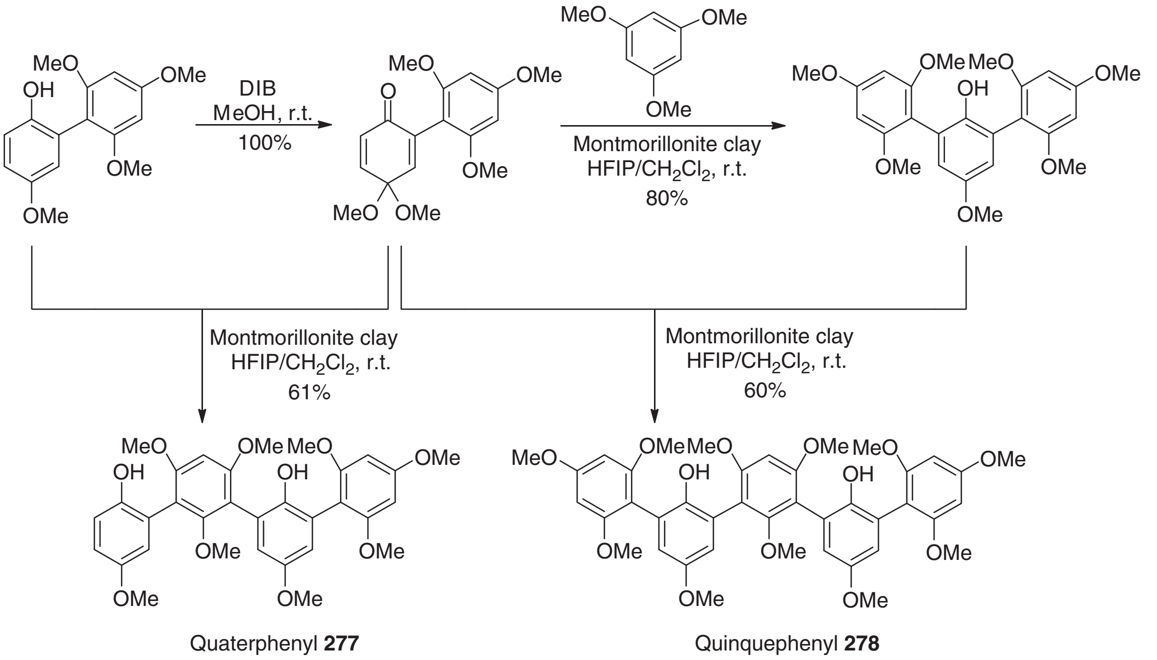


271a: R = CH_3 66%
271b: R = C_3H_7 88%
271c: R = $C_2H_4CO_2H$ 51%
271d: R = $C_2H_4CH_2OH$ 56%

Scheme 97

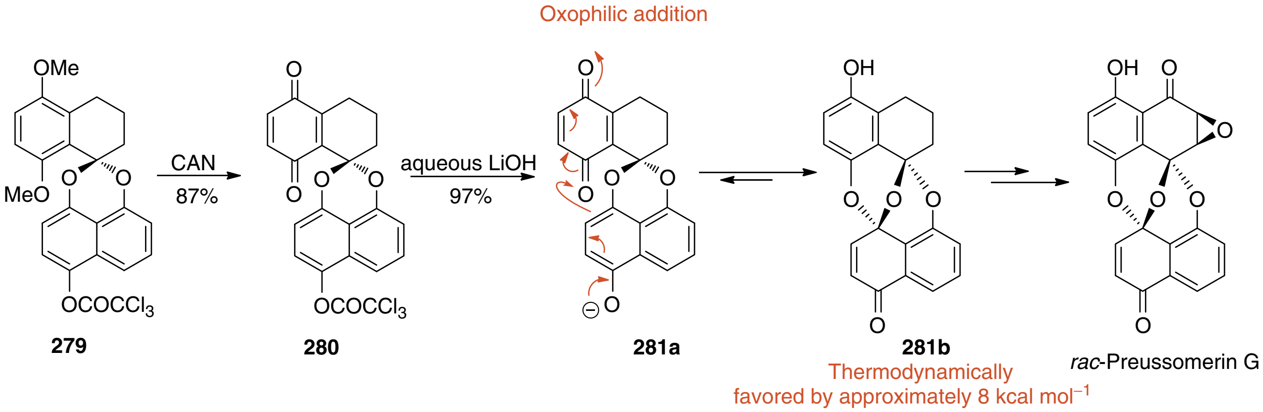


Scheme 98



Scheme 99

cleavage of the trichloroacetate protecting group, the released phenolate anion intramolecularly trapped the *para*-quinone by its oxygen end in a 1,6-addition fashion to furnish the thermodynamically more stable *para*-quinone *spiro*-ketal **281b**, en route to preussomerin G (Scheme 100).[184]



Scheme 100

3.13.7 Conclusion

Many more examples from several other talented organic chemists could or should have been discussed in this chapter, so numerous the applications and novel developments of the oxidative coupling chemistry of phenols and phenol ethers have been over the past 20 years. The selection of research reports highlighted therein was made in an attempt to approach such a broad and rich topic by providing the reader with essential information and comprehensive illustrations on the many mechanistic options available to phenols and phenol ethers during oxidative coupling transformations, on the utility and implications of this versatile class of organic reactions in the synthesis and biosynthesis of natural products, on the exploitation of phenols and phenol ethers as starting materials for the preparation of diverse chemicals (e.g., reagents, catalysts, pharmaceuticals, polymers, and materials). Major progress has been made in the understanding of the mechanisms and in the control of the chemo-, regio-, and stereoselectivity of these oxidative transformations of phenols and phenol ethers. Efficient catalytic versions have been developed, certain relying on the use of enzymes, in an effort to better comply with current guidelines on the development of greener chemical methodologies. Many questions remain, speculation continues notably on some mechanistic and control aspects of the oxidative coupling of phenols in natural product biosynthesis, and further progress is awaited to still increase the preparative value of this class of chemical transformations in organic synthesis. There is no doubt that chemists of various disciplines will continue to join forces to meet these challenges with success in the future.

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3.14 The Pinacol Rearrangement

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3.14.1 **Introduction** 741
3.14.2 **Historic Context** 741
3.14.3 **General Reactivity** 741
3.14.3.1 Glossary: Wagner–Meerwein Shift 742
3.14.4 **Aza-Pinacol Rearrangements** 743
3.14.5 **Asymmetric Pinacol Rearrangements** 746
3.14.6 **Catalytic Enantioselective Pinacol Rearrangements** 751
3.14.7 **Natural Product Synthesis** 754
References 755

3.14.1 Introduction

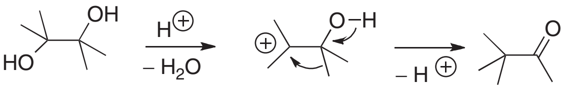
Diols represent readily accessible building blocks in organic chemistry. Several important reactions have been developed for their construction, among which the reductive dimerization of aldehydes and ketones and the dihydroxylation of alkenes stand out. In its enantioselective variant, the Sharpless AD process, the latter process provides an almost general entry into 1,2-diols with defined absolute configuration. This particular reaction is discussed in Chapter 7.16. Subsequent derivatization of these ubiquitous diol functionalities offers significant potential for organic synthesis. Probably the oldest of these reactions is the pinacol rearrangement, which is the topic of the current chapter.

3.14.2 Historic Context

The pinacol rearrangement reaction goes back to the seminal observation by Fittig in 1859 that 2,3-dimethyl-2,3-butane diol reacts within an acid-promoted rearrangement,[1,2] although the exact product constitution remained unclear by the time. It was Butlerov in 1874, who uncovered the structure of the product as 3,3-dimethyl-2-butanone and characterized it as the consequence of a carbon skeleton rearrangement.[3] Its mechanistic context was elucidated in connection with extensive studies by Meerwein and by the postulation of carbocations as intermediates. The full historic context of the observation, description, and development of the pinacol rearrangement was discussed authoritatively by Berson.[4]

3.14.3 General Reactivity

Vicinal diols undergo a rearrangement to aldehydes or ketones, respectively, on treatment with Brønstedt or Lewis acids. Under these conditions competing reactions such as dehydration to allylic alcohols or 1,3-dienes are usually not observed, which underlines the chemoselectivity of the overall reaction. As shown in Scheme 1, for the initial conversion of 2,3-dimethyl-2,3-butane diol into 3,3-dimethyl-2-butanone, the mechanism of the pinacol rearrangement comprises a protonation of one of the alcohols, which on loss of water generates an intermediary carbocation. The following 1,2-migration of one of the neighboring methyl substituents occurs in an anionotropic manner and is aided by the concomitant thermodynamically favored formation of a carbonyl group on loss of a proton. Formally, this constitutes a catalytic role of the proton, although Brønstedt and Lewis acids are often employed in stoichiometric amounts.



Scheme 1 Pinacol rearrangement of 2,3-dimethyl-2,3-butane diol into 3,3-dimethyl-2-butanone.

The decisive step of the overall molecular transformation consists in the rearrangement of the carbon framework. Within this context, the pinacol rearrangement can be characterized as a special case of the broader class of Wagner–Meerwein rearrangements. It is important to note that the reaction allows for the selective installation of quaternary carbon atoms. For reactions

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which involve different substituents at this position, the rearrangement can provide a convenient access to quaternary stereogenic centers. Although the pinacol rearrangement is not reversible, retro-rearrangements concerning the carbon framework, where alkyl groups migrate from quaternary centers, have been observed for a series of cases under special conditions. These reactions are commonly known as Nametkin rearrangements.[5]

3.14.3.1 Glossary: Wagner–Meerwein Shift

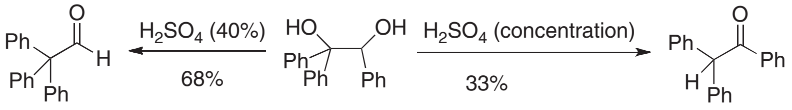
The molecular course of the rearrangement of the carbon framework represents the classical 1,2-migration known as the Wagner–Meerwein shift. Such a process proceeds essentially in an intramolecular manner and comprises a C–C bond cleavage followed by a different C–C bond formation. In principle, such a migration can occur with stereochemical fidelity; retention of configuration should be expected for the migration of stereogenic groups.

Within the general sequence, the reaction is often divided into pinacol rearrangements and semipinacol rearrangements. Strictly, the pinacol rearrangement refers only to reactions with vicinal diols as starting materials, whereas all other reactions of 1,2-disubstituted alcohols, epoxides or related substrates are considered as semipinacol rearrangements. There still remains some confusion on this term. As pointed out in a former review, the term semipinacol rearrangement was initially defined as those pinacol rearrangements displaying the migration of a group from a tertiary center toward a secondary center.[6] It is nowadays used more widely in the context of any pinacol rearrangement that includes 1,2-difunctionalized molecules, where one of the two groups is displaying leaving group character under the reaction conditions and the second one capable of forming a carbonyl group (*see* Chapter 3.16).

The general reaction features of the pinacol and the semipinacol rearrangement were reviewed previously.[6–8] In the following, the term pinacol rearrangement will be employed for all examples, regardless of the nature of the leaving group in the activation step.

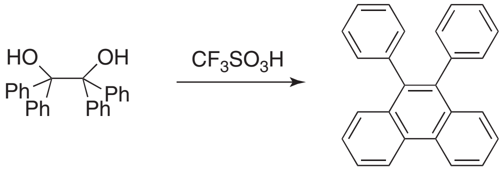
Usually, for unsymmetrically substituted diols, the reaction proceeds through the most stable carbocation and hence proceeds through protonation of the more reactive hydroxyl group of the substrate. Selective reactions often make use of stabilized benzylic cations as intermediates.

The subsequent migration step often involves the group that is the most capable to stabilize positive charge. As commonly observed in Wagner–Meerwein rearrangements, it is sometimes difficult to provide general rules in order to predict this step. Conformational, steric, and stereochemical aspects may play an important role as do the exact reaction conditions. An illustrative example is given for the rearrangement of 1,1,2,-triphenyl ethane diol, which in acid media forms the expected diphenyl carbocation (**Scheme 2**).[7] However, depending on the acid strength, entirely different migration scenarios are observed. Although phenyl migration and aldehyde formation occur in 40% sulfuric acid, concentrated sulfuric acid leads to formal hydride migration and ketone formation. The scenario might still be more complicated as a hydride to ketone isomerization cannot be ruled out in strong acidic medium.



Scheme 2 Dependence of the pinacol rearrangement on acid strength.

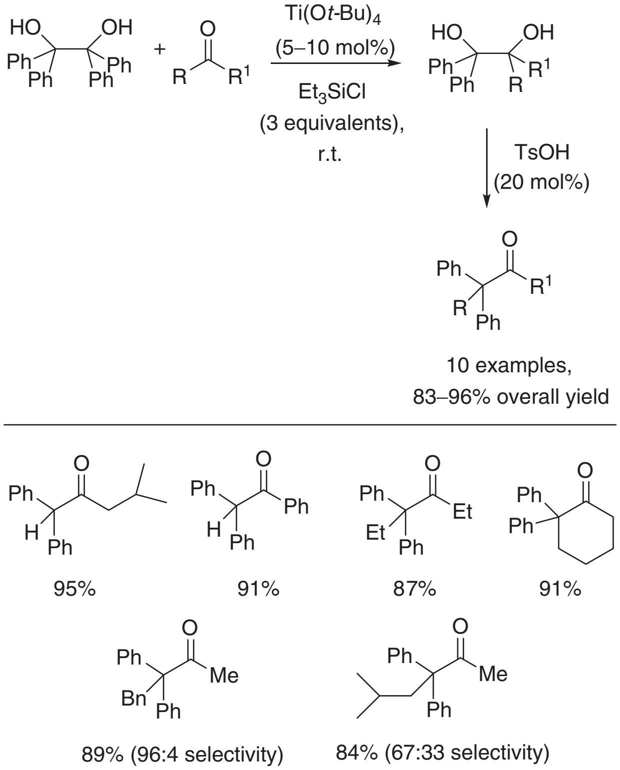
As to a noteworthy exception, benzopinacol does not undergo phenyl migration, but generates 9,10-diphenylphenanthrene in the presence of triflic acid as promoter. A total of 7 different examples with yields in the range of 87–99% were reported (**Scheme 3**).[9]



Scheme 3 Acid-promoted rearrangement of benzopinacol.

In general, aryl groups and hydrogen are the two kinetically preferred classes of migrating groups. The *t*-butyl group and related tertiary carbon atoms show a higher migration tendency than do simple alkyl groups, such as ethyl or methyl. The cyclopropyl group undergoes faster migration than simpler secondary and primary alkyl groups and does not suffer from ring opening. These tendencies should be of general consideration when planning a pinacol rearrangement for unsymmetrical diols or derivatives.[7]

A significant improvement on the selective Wagner–Meerwein shift in unsymmetrically substituted diols was recently reported by Mahrwald and Scheffler (**Scheme 4**).[10] These authors found that treatment of benzopinacol with a catalytic amount of titanium tetrakis-*t*-butoxide in the presence of a ketone or an aldehyde results in an efficient *retro*-pinacol/pinacol coupling yielding the mixed diols in excellent selectivity. On completion of the process, a catalytic amount of toluene sulfonic acid is added to the reaction mixture resulting in the promotion of the pinacol rearrangement. The latter proceeds with the expected complete regioselectivity and excellent chemoselectivity regarding the migration.



Scheme 4 Sequential *retro*-pinacol/pinacol coupling/pinacol rearrangement.

Apart from diols, pinacol rearrangements can proceed starting from a series of different 1,2-difunctionalization pattern. As already discussed, these reactions are usually summarized under the category of semipinacol rearrangement. They include epoxides, 2-hydroxy epoxides, 2-hydroxy sulfides, 2-hydroxy selenides, halohydrins, 2-halo acetals, amino alcohols, and 2-hydroxy and 2-amino ketones. The general features of these reactions were summarized previously.[6,11]

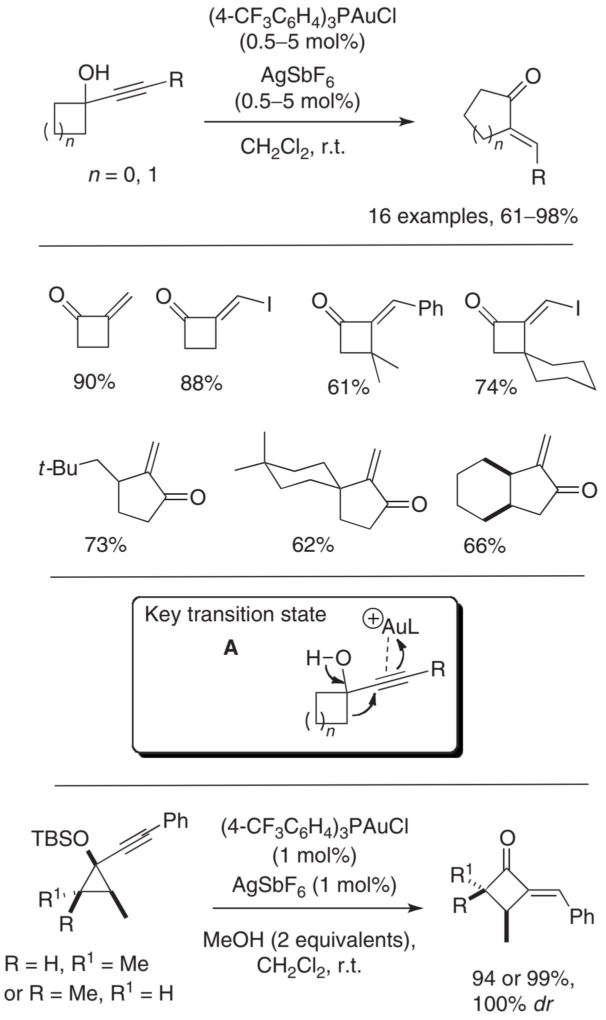
In addition to its importance as an isolated transformation itself, the pinacol rearrangement has also received significant attention as the termination step of cascade reactions. In this context, the major number of examples still refers to a combination with Prins cyclizations, a sequence that is particularly valuable in the course of natural product synthesis.[12] Another recent topic has been the use of pinacol rearrangements for the termination of metal-mediated cascade reactions, in particular for platinum and gold catalysis.[13] These reactions are characterized by an initial activation of a π-system involving a subsequent carbocyclization. This original concept was introduced by Toste, who reported the gold-catalyzed ring expansion of alkynylcyclopropanols and alkynylcyclobutanols to the corresponding cyclobutanons and cyclopentanons, respectively (Scheme 5).[14] The reaction is suggested to proceed through a key step **A** of a gold-mediated activation of the alkyne moiety, which triggers the subsequent pinacol rearrangement. The migratory ring expansion is stereospecific as demonstrated for two diastereomeric cyclopropyl substrates, which undergo cyclobutanone formation with retention of configuration at the migrating carbon.

An example for a pinacol rearrangement as termination of a C–C bond-forming event between unsaturated bonds is given in Scheme 6. Kirsch and coworkers developed a sequence of gold-catalyzed enyne cyclization followed by pinacol rearrangement.[15] The reaction initiates with an *endo*-selective carbocyclization followed by the corresponding Wagner–Meerwein shift.

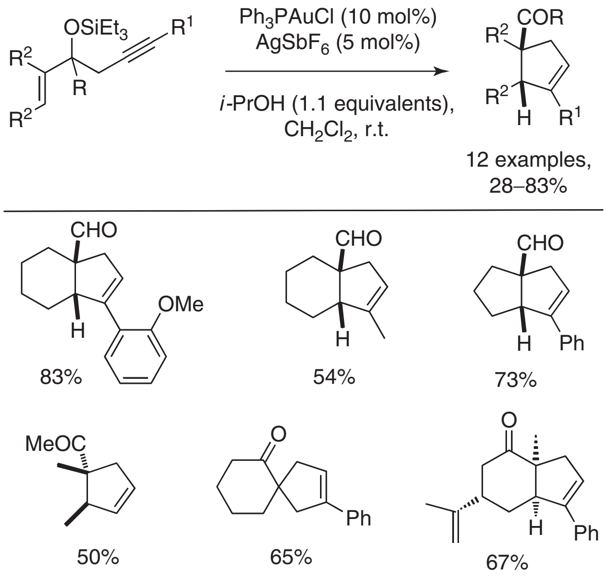
3.14.4 Aza-Pinacol Rearrangements

In the following, some progress in the general area of the pinacol rearrangement involving nitrogen groups will be discussed. It is followed by two sections on chiral pinacol rearrangements. In the final section, selected examples of the pinacol rearrangement in the synthesis of natural products are given.

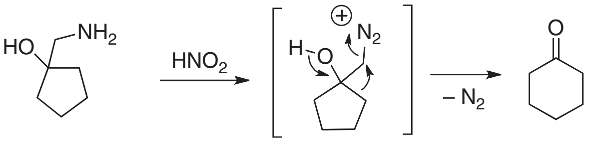
The classic case of a pinacol-type rearrangement of an amino alcohol is known as the Tiffeneau–Demjanow reaction (Scheme 7). It is usually started from an amino alcohol with a primary amino group that undergoes diazotization followed by rearrangement of the intermediary primary carbocation. It has been used most prominently for ring enlargement and received extensive reviewing.[16,17]



Scheme 5 Gold-catalyzed ring expansion on pinacol rearrangement.

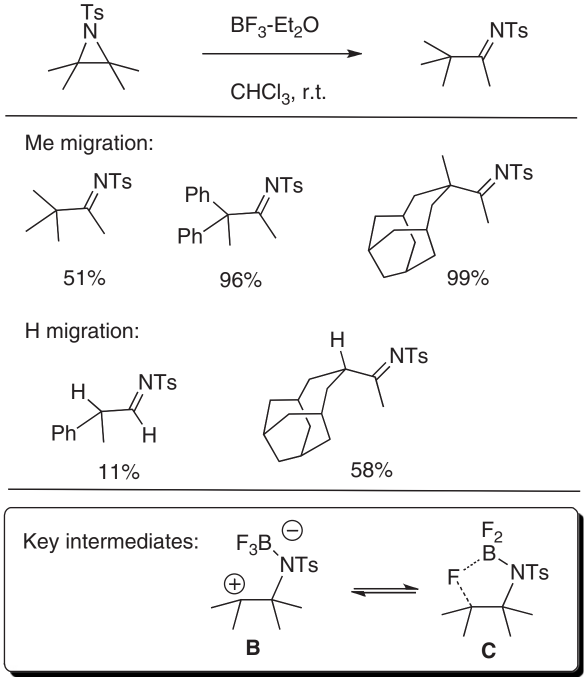


Scheme 6 Gold-catalyzed carbocyclization/pinacol rearrangement.



Scheme 7 Tiffeneau–Demjanow reaction.

Other nitrogen-containing variants of the pinacol rearrangement appeared more recently as alternative pathways. For example, Nakayama showed that in the presence of catalytic amounts of borontrifluoride etherate, *N*-tosyl aziridines rearrange cleanly into the corresponding imines (Scheme 8).[18] The reaction proceeds through a BF_3-mediated activation of the aziridine generating a carbocationic intermediate **B**. The latter can be stabilized temporarily through the reversible chelation with one of the fluorine atoms of the Lewis acid (**C**). Ultimately, the carbocation will engage in a Wagner–Meerwein rearrangement under concomitant formation of an imine functionality. Given the acidic conditions of the transformation, hydrolysis to the corresponding ketone was observed as a side reaction in some cases.

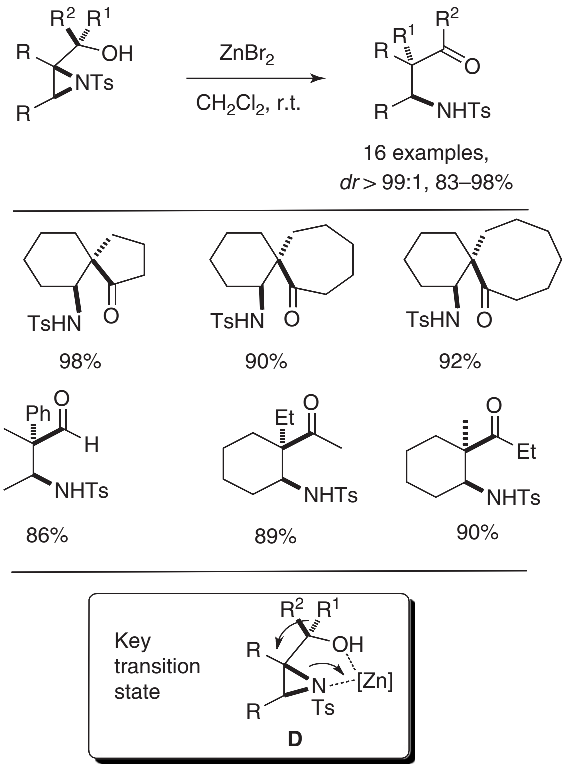


Scheme 8 Pinacol rearrangement of aziridines.

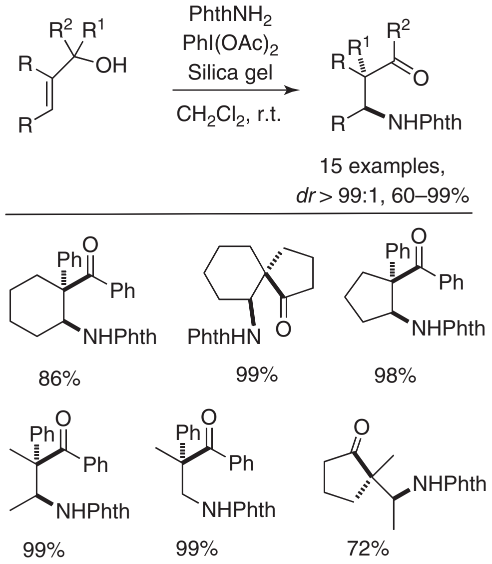
Tu developed a diastereoselective pinacol rearrangement starting from the *N*-tosylated aziridines of allylic alcohols.[19] These reactions proceed readily with zinc bromide as Lewis acidic promoter and provide convenient access to *β*-aminated *α*-quaternary ketones through a chelate transition state **D**. The reaction is very efficient for aziridines derived from cycloalkenes, but also proceeds for those from acyclic ones. The migration is proposed to proceed in an antiperiplanar Wagner–Meerwein shift, which ensures that the migrating substituent is already predetermined from the relative stereochemistry of the starting material as can be observed from the last two examples of the product selection in Scheme 9.

The reaction was further advanced by the development of a tandem aziridination/pinacol rearrangement sequence.[20] Starting from allylic alcohols, the aziridination was accomplished using the established protocol consisting of a combination of *N*-amino phthalimide and iodosobenzene diacetate in the presence of silica gel. Under such conditions, the corresponding *β*-aminated *α*-quaternary ketones could be readily generated in diastereoselective manner (Scheme 10).

An unprecedented aza-pinacol rearrangement was discovered during studies toward the synthesis of isomers of swainsonine.[21] Here, treatment of the aldehyde with tributyl allyltin in the presence of magnesium bromide as Lewis acid did not result in the expected production of the corresponding homoallylic alcohol. Instead, the magnesium chelate activates the carbonyl and promotes an aza-pinacol rearrangement on hydride migration. The resulting intermediary iminium is then allylated diastereoselectively by the tin reagent to provide the primary alcohol as the final product (Scheme 11). A related rearrangement has further found application in the combination of an aza-Prins-pinacol reaction.[22,23]



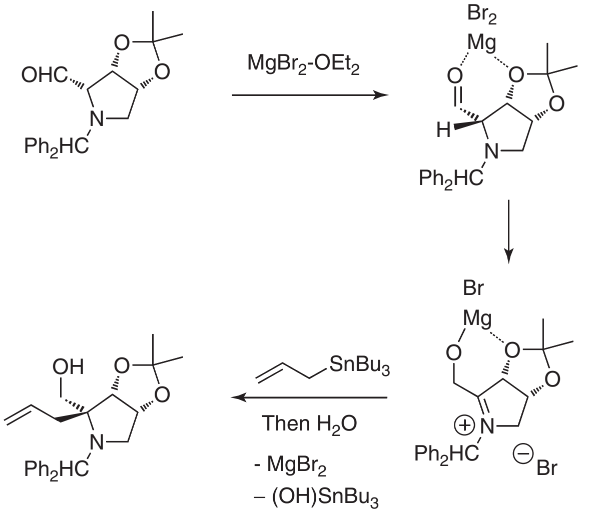
Scheme 9 Diastereoselective pinacol rearrangement of 2,3-aziridine alcohols.



Scheme 10 Sequential aziridination/pinacol rearrangement of allylic alcohols.

3.14.5 Asymmetric Pinacol Rearrangements

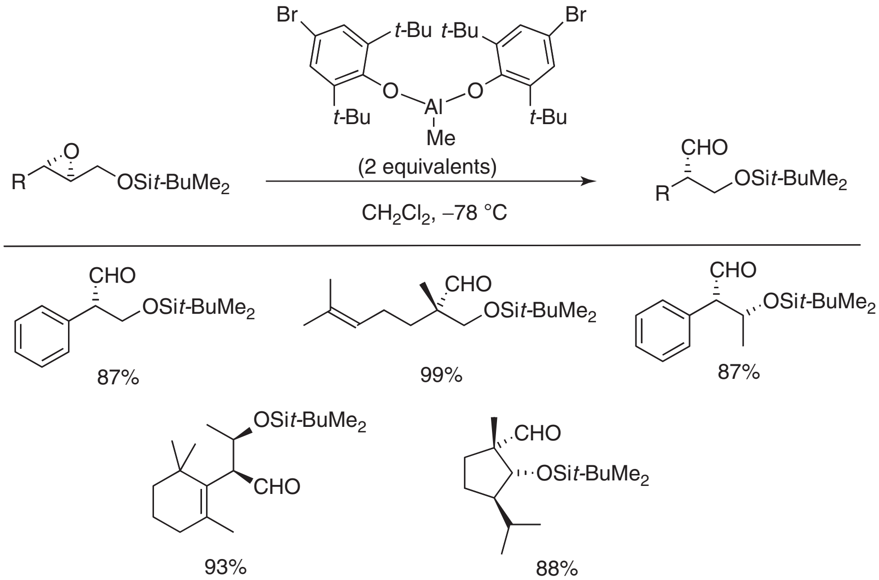
Asymmetric pinacol rearrangements have proven particularly valuable in the construction of tertiary and quaternary stereogenic centers with defined configuration. Major synthetic tools in the field of diastereoselective pinacol rearrangements for the construction of quaternary stereocenters were developed by the group of Tu.[24]



Scheme 11 An example of an aza-pinacol rearrangement.

Generally, the use of chiral diols and their derivatives give rise to α-stereogenic ketones within the pinacol rearrangement. This approach is usually based on efficient substrate control because of a suitable chiral environment embedded within the substrate. It is the most common application of the stereoselective pinacol rearrangement in natural product synthesis (see Section 3.14.7).

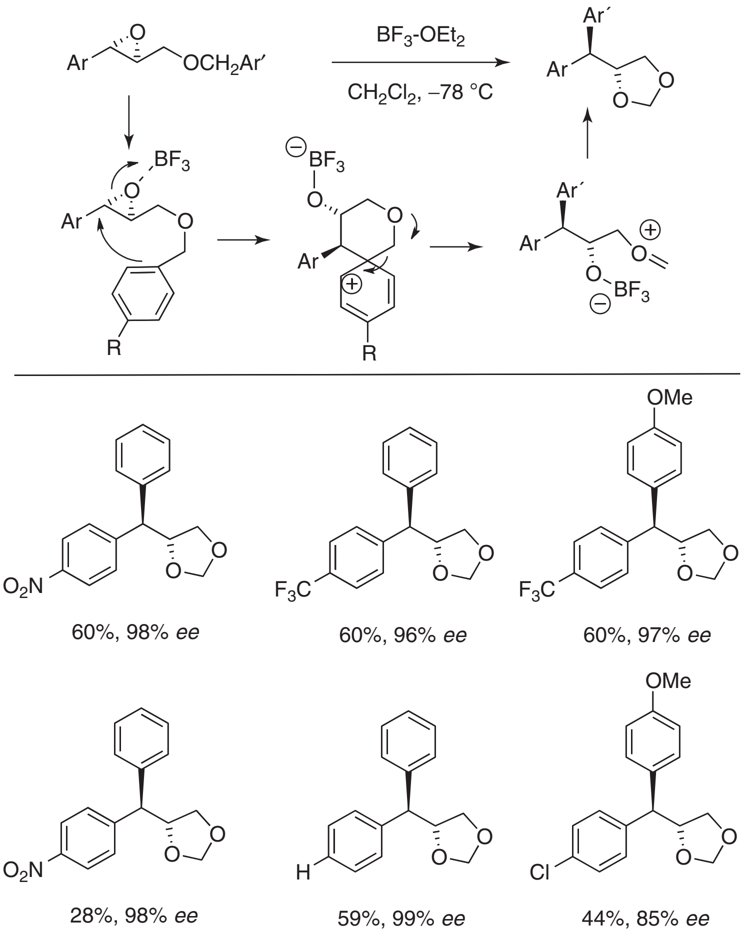
Various studies have been carried out in order to develop a broad applicability of this transformation. The proof of principle demonstration was accomplished by Yamamoto, who within his development of designer Lewis acids[25] employed one of his seminal bulky aluminum reagents to promote the stereoselective pinacol rearrangement of various glycidols (Scheme 12).[26] This substrate class is conveniently accessible in enantiomerically pure form through the Sharpless asymmetric epoxidation reaction. The pincacol rearrangement proceeds with full stereospecificity for a series of open chain glycidols. Glycidols with a cyclohexene oxide functional group undergo the corresponding stereoselective ring contraction.



Scheme 12 Stereoselective pinacol rearrangement mediated by an aluminum designer Lewis acid.

In a related transformation, Suda accomplished an asymmetric pinacol rearrangement of glycidol derivatives using a chromium-porphyrine complex.[27]

More recently, Pericás reported that borontrifluoride induced an alternative stereospecific rearrangement of benzylated glycidols (Scheme 13).[28] It proceeds through an attack of the aryl group of the ether on epoxide activation by the Lewis acid. The subsequent fragmentation installs the chiral diarylated center in a stereospecific fashion. This clean rearrangement process is favored by electron-withdrawing substituents on the skeletal aryl group, and by electron-donating ones at the aryl of the benzyl ether. However, electron-donation must be fine-tuned as a 3,5-dimethoxybenzyl ether only leads to formation of a benzannelation product.



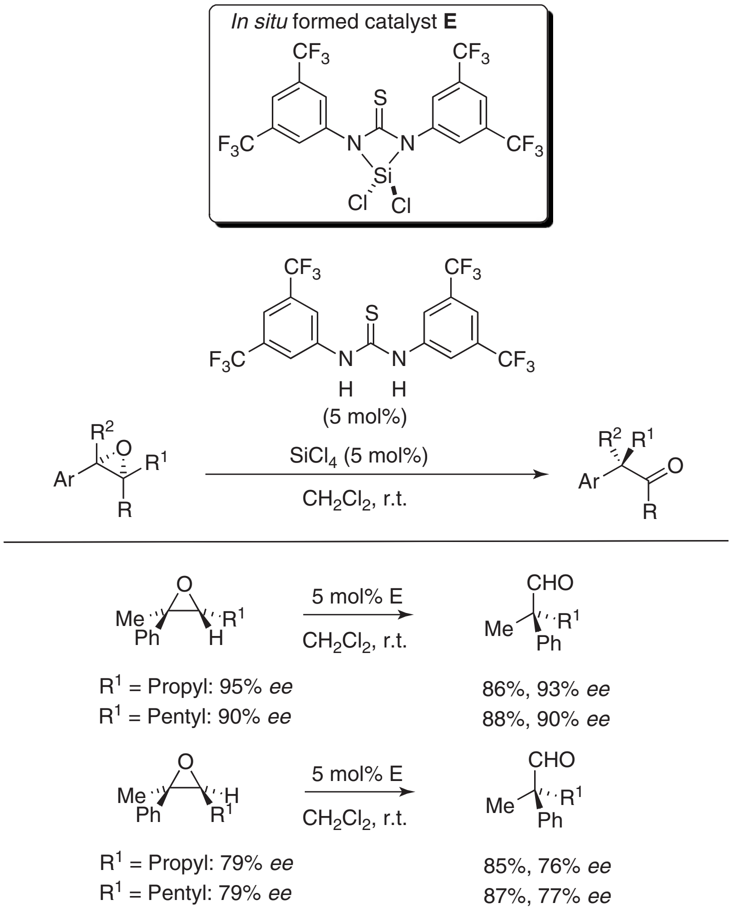
Scheme 13 Stereospecific pinacol rearrangement of benzylated glycidols.

Within an elegant conceptual alternative, Schreiner reported the combination of tetrachlorosilane and a thiourea as an *in situ* generated efficient Lewis acid catalyst for the rearrangement of chiral epoxides derived from styrene derivatives (Scheme 14).[29] The latter are excellent substrates for a Shi asymmetric epoxidation giving rise to enantiomerically enriched starting materials. Extensive studies suggest that the active catalyst is a tetrahedrally coordinated silicon **E** within a planar four-membered ring arrangement of the thiourea. Natural bond orbital charge analysis suggests a dominating situation of a doubly charged thioureate and a silicon dication. In the presence of this silicon Lewis acid catalyst **E**, clean rearrangements proceeded with only neglectable loss of enantiopurity. Importantly, the catalyst features the rearrangement of both the *cis*- and *trans*-isomeric epoxides with identical rates and fidelity regarding enantiomeric excess. As to another important feature of this system, for reactions with R or $R^1=H$, hydride migration is effectively suppressed in favor of the other substituent. Hence, the present reactions lead to exclusive or widely preferential formation of aldehydes. This is different for other Lewis acids, as for example diethylaluminum chloride forms nearly equimolar mixtures.

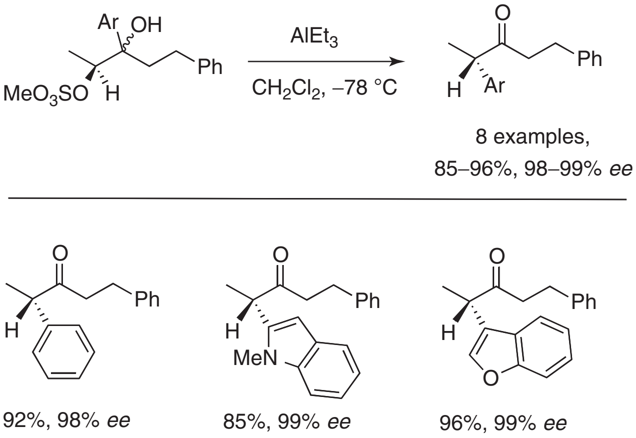
It is of importance to note that the center that bears the alcohol that is to be converted into the ketone does not require being of defined stereochemistry. It can be sufficient to rely on a memory effect regarding the stereochemistry of the neighboring position.

For example, Suzuki demonstrated that an efficient aryl migration is possible for mono-mesylated diols when submitted to reaction with triethylaluminum (Scheme 15).[30] Lewis acid assisted removal of the mesylate generates the corresponding cation, which can be considered a dynamic chiral intermediate. The subsequent 1,2-migration of the aryl groups proceeds with complete stereospecificity to generate the corresponding ketones in higher than 98% enantiomeric excess. The reaction can also be performed as a one-pot sequence starting from mesylation of the free diol followed by the aluminum-mediated pinacol rearrangement. Although enantiomeric excesses remain unchanged, the chemical yields are significantly decreased in some cases.

This approach was further expanded to the synthesis of angular stereogenic centers (Scheme 16).[31] Starting from the corresponding enantiopure *cis*-diol, that can also be generated *in situ* by 1,2-addition to the corresponding ketone, treatment with

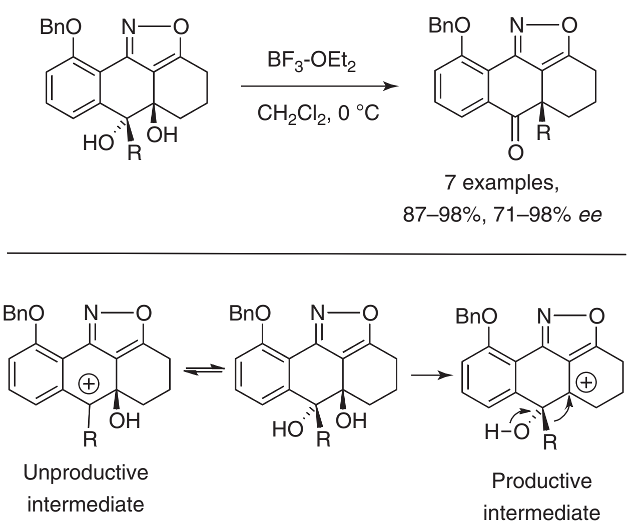


Scheme 14 Silane-catalyzed stereoselective pinacol rearrangement.



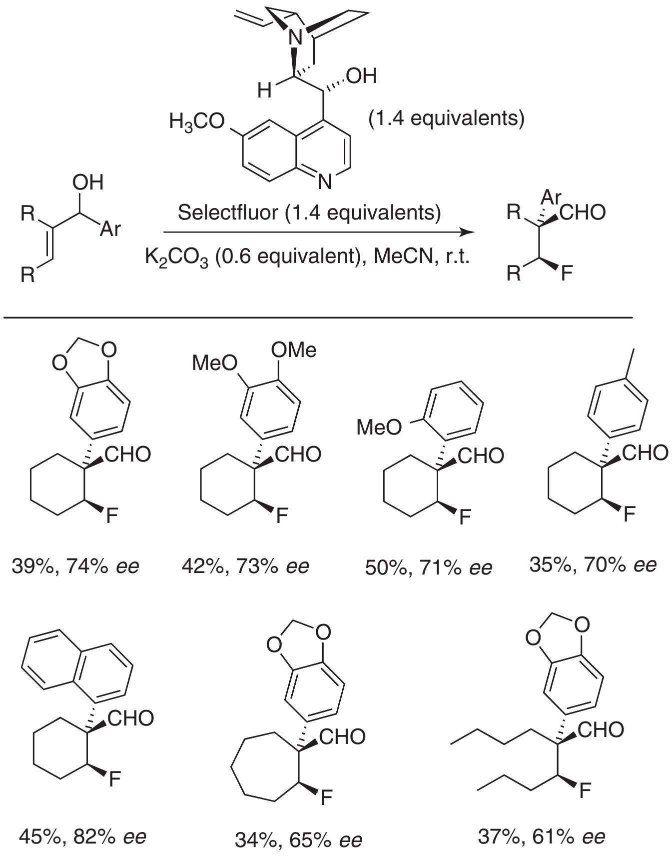
Scheme 15 Stereospecific pinacol rearrangement preserving enantiopurity.

borontrifluoride etherate led to the initiation of the pinacol rearrangement. In this case, an isoxazole group ensured that only a single productive carbocation could serve as the desired precursor for the pinacol rearrangement, whereas the other one reverts to the initial diol. The following suprafacial Wagner–Meerwein rearrangement then ensures preservation of the initial enantiomeric excess. It is important that this shift proceeds with significant rate in order to avoid racemization. This was observed partly in case of an acetylene (R=CC*n*Bu, 71% *ee*), which exercises low-migration tendency and stabilizes the neighboring cation. Other substituents such as vinyl, tolyl, furanyl, indolyl, or allyl all guarantee fast migration and thus generate the corresponding products with 98% *ee*.



Scheme 16 Stereospecific pinacol rearrangement using an isoxazole anker.

In the area of chiral reagent control, Tu reported the combination of selectfluor and a chiral alkaloid for the generation of intermediary cations from alkene fluorination to force enantioselective pinacol rearrangements (Scheme 17).[32] Since a strong acid is released on consumption of selectfluor, neutralization through addition of potassium carbonate base was found to guarantee high enantioselectivity. A 1/1-combination of quinine and selectfluor proved to generate a powerful chiral reagent for the enantioselective pinacol rearrangement of allylic alcohols. A fluorinated quinuclidinium group within quinine was postulated as the active reagent, differentiating the prochiral alkene of the allylic alcohol on fluorination. The products are formed as



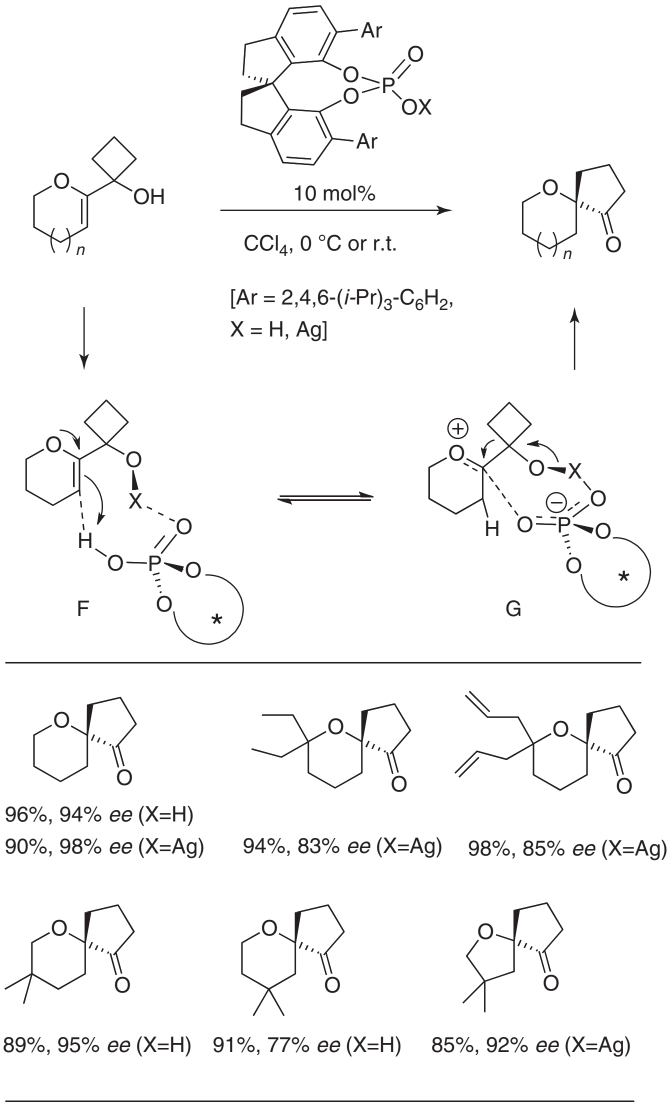
Scheme 17 Enantioselective pinacol rearrangements through fluorination of allylic alcohols.

α-quaternary β-fluoro carbaldehydes, which are obtained as single diastereoisomers in enantiomeric excesses in the range of 54–82% *ee*.

3.14.6 Catalytic Enantioselective Pinacol Rearrangements

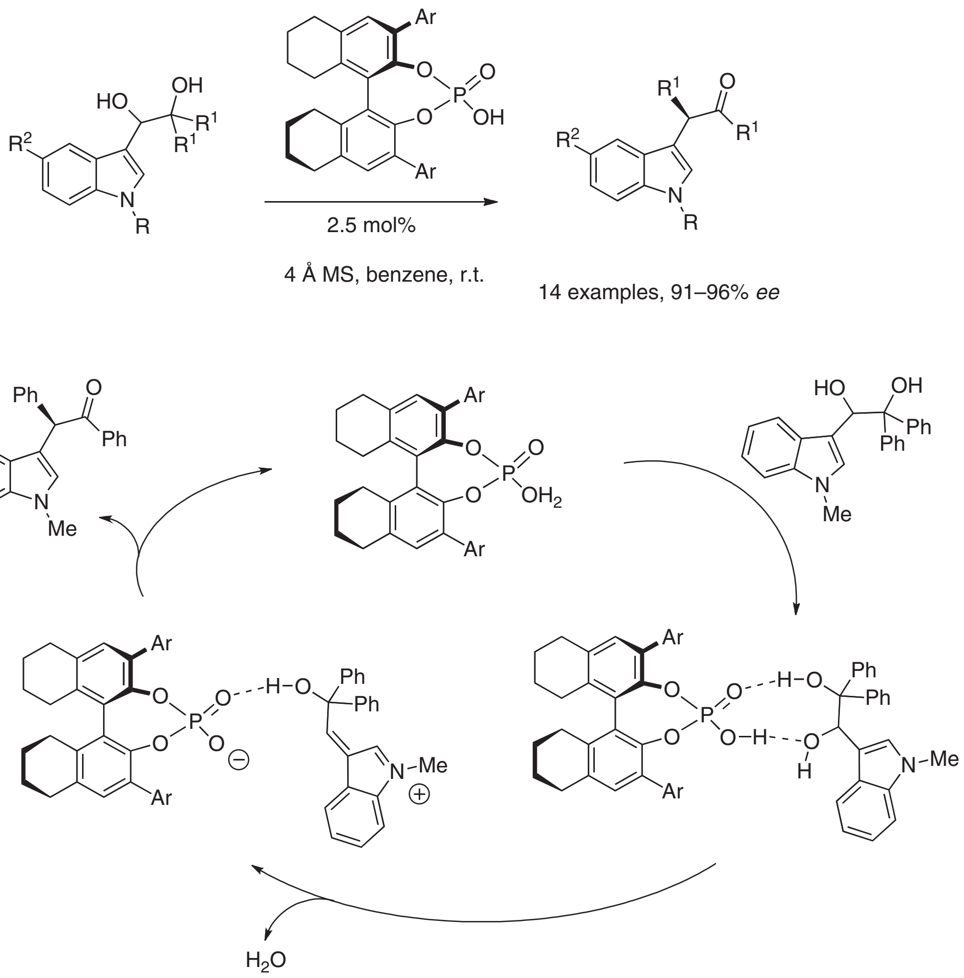
The use of chiral acid promoters is of particular interest to the development of enantioselective pinacol rearrangements as such an approach allows for an enantioselective synthesis under reagent control. Significant advance has been obtained recently through the concept of chiral Brønstedt acid catalysts.[33,34]

An initial approach in this direction was reported by Tu and coworkers (Scheme 18).[35] This reaction employs a chiral phosphoric acid catalyst derived from a sterically congested BINOL backbone or its corresponding silver salt. In the presence of this catalyst chiral allylic alcohols are converted into the corresponding spiro derivatives on pinacol rearrangement. The reaction requires the presence of an enolether functionality within the allylic alcohol. The former entity is crucial in the initial step of the generation of the cationic intermediate next to the alcohol group. The overall cycle is believed to initiate with intermediate A, which contains two hydrogen bonds between the catalyst and the substrate (or, alternatively, silver-assisted chelation in the case of the silver posphonate; in this case **F** is accessed after proton/silver exchange between catalyst and allylic alcohol). Protonation of the enolether furnishes intermediate **G**, in which the carbocation is formally masked by the phosphonate group. The subsequent pinacol rearrangement proceeds in the proximity of the chiral catalyst and thus results with excellent enantioselectivity. A total of nine examples with 51–98% yield and enantioselectivities in the range of 77–98% *ee* were reported.



Scheme 18 Brønstedt acid-catalyzed pinacol rearrangement.

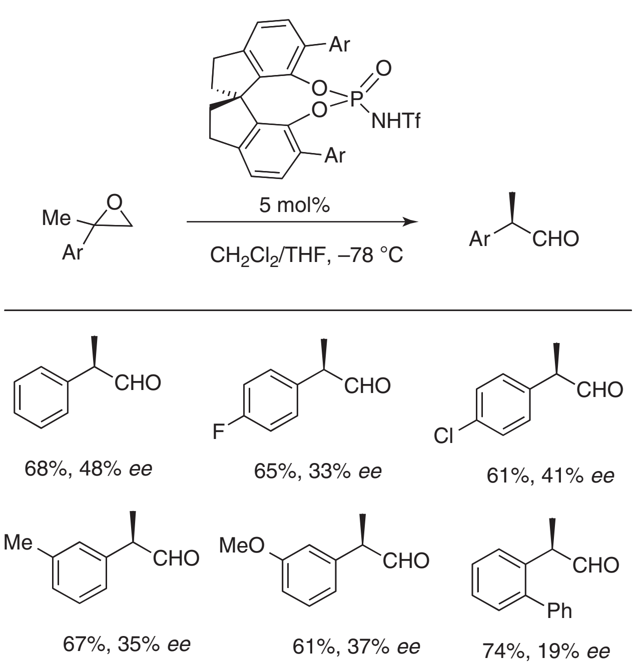
Antilla contributed another important advance by introducing the use of chiral Brønstedt acids as catalysts for an enantioselective pinacol rearrangement on diols (Scheme 19).[36] By using 2.5 mol% of a chiral phosphate, a series of racemic indolyl diols could be cleanly converted into the corresponding α-indolyl ketones. The reaction is of broad scope for a series of aryl groups that undergo migration, and the respective products were obtained in over 90% *ee* in all cases. The reaction is suggested to proceed through an initial two-point binding between the chiral phosphate catalyst and the diol. Subsequent protonation of the internal alcohol leads to loss of water. This step is favored by the stabilization of the resulting formal cation through resonance of the indenyl substituent. This iminium intermediate still binds to the chiral phosphate through a hydrogen bridge, such that the following aryl migration proceeds within the chiral environment of the catalyst. Formal proton transfer from the remaining alcohol to the catalyst regenerates the original phosphate and provides the pinacol rearrangement product.



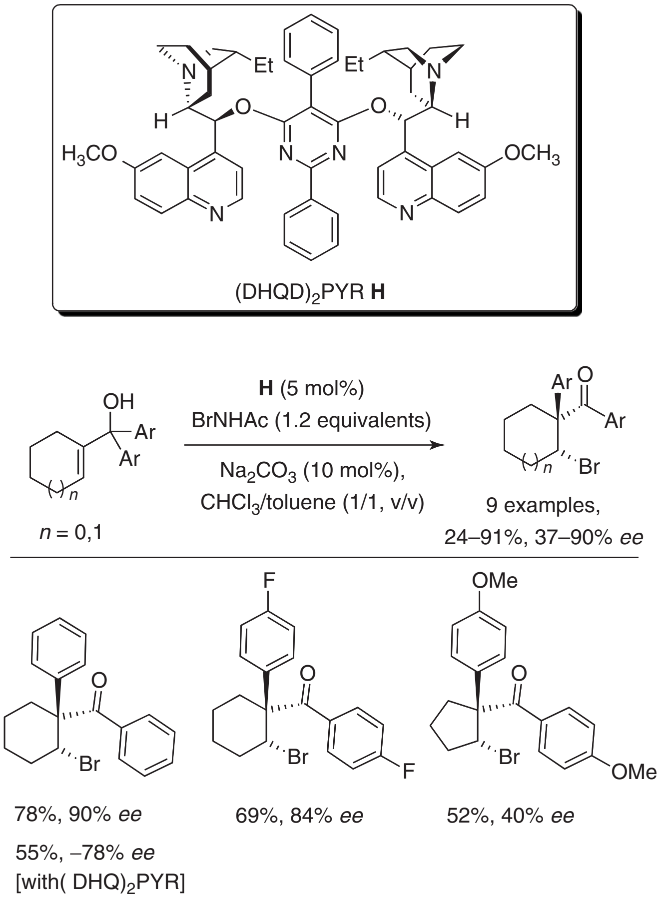
Scheme 19 Enantioselective pinacol rearrangement using a chiral Brønstedt acid catalyst. Ar=1-naphthyl.

A complementary approach was developed by Zhuang and Du, who reported the use of a chiral phosphorimide Brønstedt acid for the pinacol rearrangement of racemic 1,1-disubstituted epoxides (Scheme 20).[37] This reaction generates chiral nonracemic aldehydes within a typical pinacol rearrangement. A series of 14 examples was reported with yields between 48 and 74% and 19–48% *ee* for the corresponding alcohol products obtained from direct reduction of the aldehydes. The reaction is currently limited to gem-disubstituted epoxides, as trisubstitued ones underwent the allylic alcohol formation. Although the *ee* values are not perfect, the work is an important contribution to the development of enantioselective pinacol rearrangement using chiral Brønstedt catalysts.

Alternative approaches make use of recent progress in the important field of organocatalysis. Henecke could demonstrate that unlike the case of the quinine/selectfluor combination (Scheme 7), a Sharpless ligand such as $(DHQD)_2PYR$ **H** can be employed in catalytic amounts when *N*-bromo acetamide is used as the halide source (Scheme 21).[38] Under such modified conditions, the pinacol rearrangement of allylic alcohols proceeds with up to 90% *ee*. It is interesting to note that the corresponding $(DHQ)_2PYR$ ligand derived from quinine shows the expected pseudoenantiomeric behavior resulting in the formation of the opposite enantiomer, although the *ee* value is significantly lower.



Scheme 20 Enantioselective catalytic pinacol rearrangement of epoxides. Products were isolated and *ee* was determined after reduction to the corresponding alcohols.

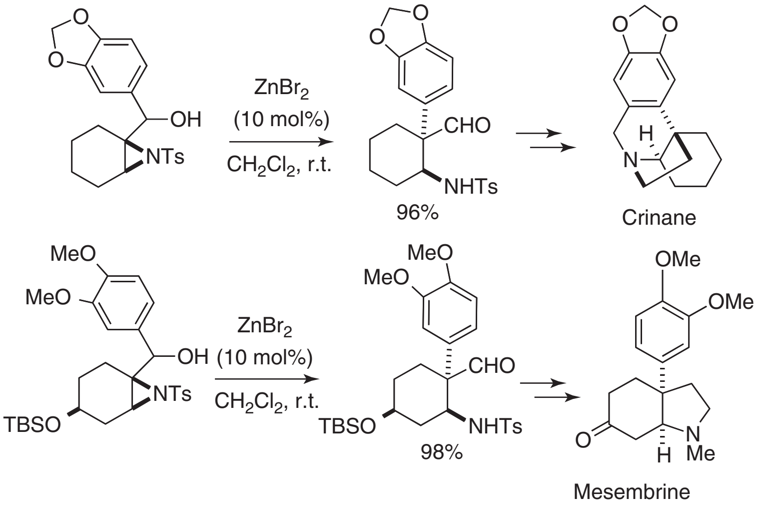


Scheme 21 Organocatalytic pinacol rearrangement of allylic alcohols using $(DHQ)_2PYR$ as chiral catalyst.

3.14.7 Natural Product Synthesis

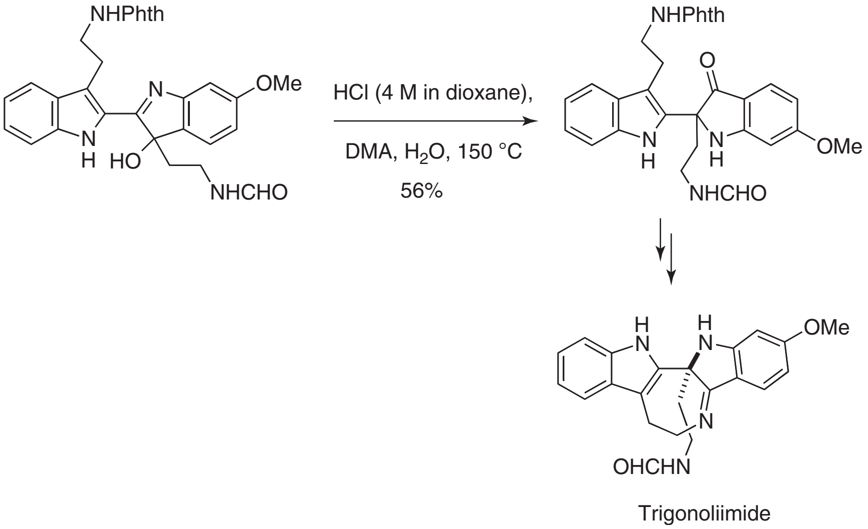
Owing to the characteristic that the pinacol rearrangement can generate complex structures, which are otherwise difficult to access, significant application of the pinacol rearrangement has been made in the field of natural products synthesis. Several advances are covered in recent review articles.[11,12,39] In combination with the work discussed so far, three selected examples are noteworthy.

With respect to the discussed zinc bromide-catalyzed pinacol rearrangement of 2,3-aziridino alcohols (Scheme 9), Tu followed this work with a concise synthesis of some alkaloids. Based on the established rearrangements several β-amino aldehydes bearing correct α-quaternary stereocenters could be generated, which served as versatile building blocks in the syntheses of crinane and mesembrine (Scheme 22).[40]



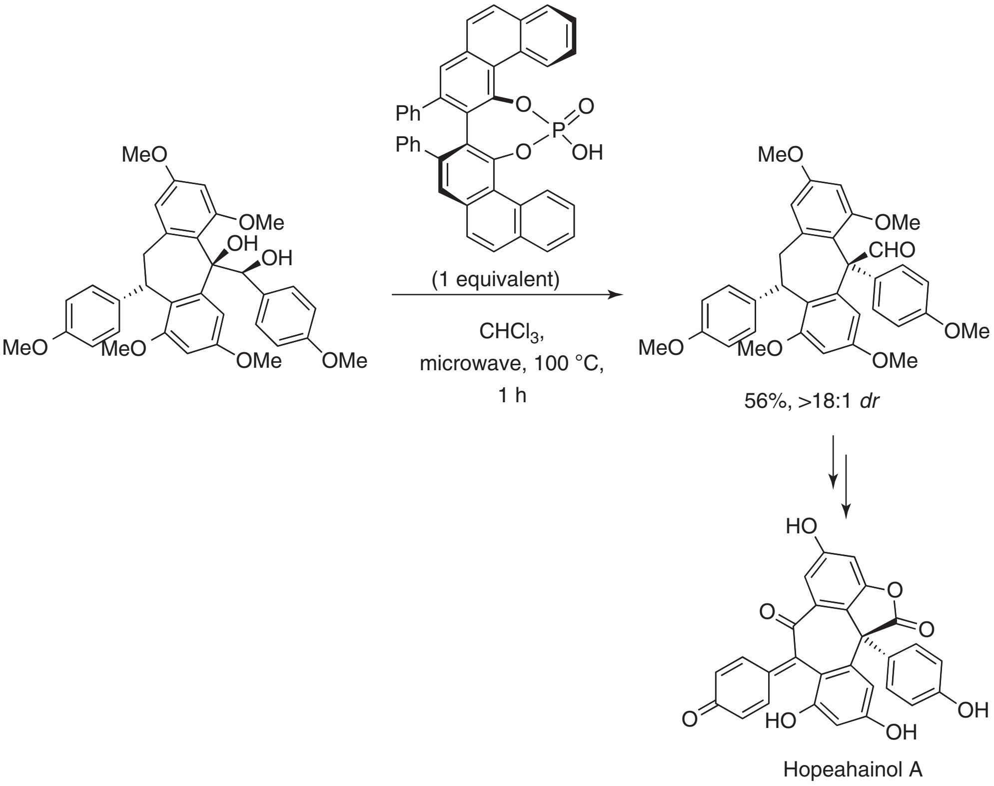
Scheme 22 Application of aza-pinacol rearrangements in alkaloid synthesis.

Tambar reported an interesting aza-pinacol rearrangement within the total synthesis of trigonoliimide (Scheme 23).[41] Employing hydrochloric acid as promoter, protonation of the imine moiety triggered the desired pinacol rearrangement as an entirely selective transformation leading to the desired oxindol derivative bearing the required quaternary center.



Scheme 23 Aza-pinacol rearrangement in the synthesis of trigonoliimide.

Finally, Snyder employed the use of a chiral phosphoric acid based on 2,2′-diphenyl-(4-biphenanthrol) as backbone in a pinacol rearrangement as one of the key steps in the total synthesis of hopeanol and hopeahainol A (Scheme 24).[42] As shown in Scheme 21, the (R)-configured reagent gave the correct stereoisomer in 56% yield and 18.4:1 diastereomeric ratio. The corresponding (S)-configured reagent gave rise to the same product in almost identical reaction outcome, whereas the racemic acid resulted in a slightly decreased *dr* value of 13.6:1. In addition, a substrate with a diastereomeric diol configuration underwent a significantly less selective rearrangement. Although the exact effects of the phosphoric acids are not yet fully understood, their use as efficient Brønstedt acid reagents for chiral rearrangement reactions natural product synthesis has now been demonstrated. Significant advances can be expected for the future.



Scheme 24 Brønstedt acid-mediated enantioselective pinacol rearrangement as key step in the synthesis of hopeahainol A.

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3.15 Acid-Catalyzed Rearrangement of Epoxides

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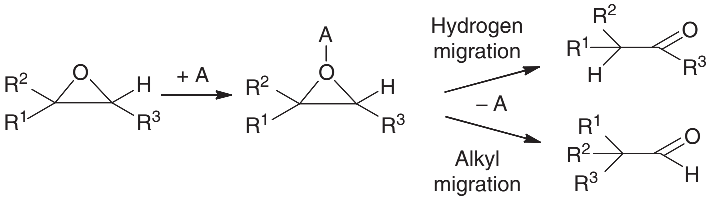
3.15.1 Introduction 757
3.15.2 Brønsted Acid-Catalyzed Rearrangements 758
3.15.2.1 Brønsted Organic Acids 758
3.15.2.2 Brønsted Inorganic Acids 760
3.15.3 Lewis Acids Derived from Main Group Elements 762
3.15.3.1 BF_3-Induced Rearrangements 762
3.15.3.2 Aluminum-Induced Epoxide Opening 769
3.15.3.3 Other Lewis Acid-Induced Epoxide Opening 772
3.15.4 Transition Metal-Based Lewis Acids 775
3.15.4.1 Titanium/Zirconium/Hafnium 775
3.15.4.2 Vanadium 781
3.15.4.3 Chromium 781
3.15.4.4 Iron 781
3.15.4.5 Cobalt/Iridium 783
3.15.4.6 Copper/Gold 784
3.15.5 Other Metals 785
3.15.5.1 Zinc 785
3.15.5.2 Rare Earths 785
3.15.6 Solid Catalysts 787
3.15.6.1 Metal Oxides 787
3.15.6.2 Metal Sulfates and Precipitated Phosphates 788
3.15.6.3 Clays 789
3.15.6.4 Zeolites 789
3.15.6.5 Mesoporous Materials 791
3.15.6.6 Resins 791
3.15.7 Conclusion 792
References 792

3.15.1 Introduction

Epoxides, strained three-membered ring heterocycles, belong to one of the most versatile classes of organic compounds available to synthetic chemists due to their strained ring structure, which makes them prone to react with a large number of nucleophiles, electrophiles, acids, bases, and reducing and oxidizing reagents.[1] At present, the epoxide ring-opening reaction is one of the most important procedures to deliver potential intermediates for the synthesis of oxygen-containing natural products and biologically active compounds. In particular, the skeletal rearrangement reaction of epoxides under acidic conditions to produce carbonyl compounds has attracted considerable interest in recent years, in view of the efficiency of the rearrangement and the synthetic and industrial utility of this process.

More commonly, epoxides react with acids to form aldehydes or ketones, generally via hydride, alkyl, or aryl 1,2-migration pathways (the Meinwald rearrangement, Scheme 1).[2]

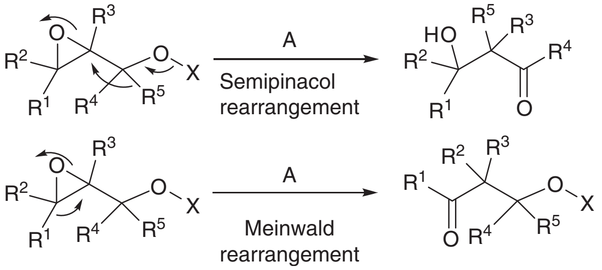


Scheme 1

doi:10.1016/B978-0-08-097742-3.00320-7

Epoxide isomerization can also occur when a functional group is vicinal to the epoxide, giving rise to a rich chemistry, especially if there is participation by the functional group. This methodology has been applied in the multistep synthesis of complex structures and has been particularly useful to achieve clean ring expansions or ring contractions.

In the case of α-hydroxy and α-silyloxy epoxides, two alternative pathways are known – the semipinacol rearrangement or the Meinwald rearrangement (Scheme 2).



Scheme 2

Moreover, the semipinacol rearrangement of epoxy alcohol,[3] that results in ring-expanded products, enables the rapid formation of relatively complex molecules in high yield.

A number of factors have been identified as critical in determining the product distribution of this reaction, such as the migratory aptitude of the epoxide substituents, the Lewis acid catalyst utilized, and the solvent employed. Typically, if there is no structural bias, a mixture of products is produced due to the lack of regioselectivity in the ring-opening process. Hence, there has been considerable interest in the development of Lewis acids that display enhanced selectivity and are efficient in catalytic quantities.

A relatively large number of catalyst types have been used in the literature for epoxide rearrangements, including both homogeneous and heterogeneous systems.

The originally reported procedures utilized Brønsted acids or Lewis acids in stoichiometric quantities. More recent protocols employing catalytic quantities of acids have all proved to be efficient. Various Brønsted acids and Lewis acids derived from the main group elements and transition metal have been used, including lanthanide-based Lewis acids.

This chapter covers the progress made in the field of acid-catalyzed rearrangements of epoxides since 1990, following the work of Bruce Rickborn[4] in the first version of Comprehensive Organic Syntheses. It attempts to summarize those acid-mediated rearrangement reactions successfully used in organic synthesis. The chapter is subdivided into several sections, each in turn dedicated to Brønsted acids, Lewis acids derived from the main group, transition metals, and other metals including lanthanides and also heterogenous acids.

Works reported in patent literatures are not discussed, and the extensive use of intermolecular rearrangement is beyond the scope of this chapter.

3.15.2 Brønsted Acid-Catalyzed Rearrangements

Brønsted acids are known to induce rearrangements in the reactions involving epoxide openings, but in the last 20 years these acids have been relatively less used for this type of reaction. However, more recent works are directed toward heterogeneous catalysis with the development of many solid acid catalysts (see Section 3.15.6).

3.15.2.1 Brønsted Organic Acids

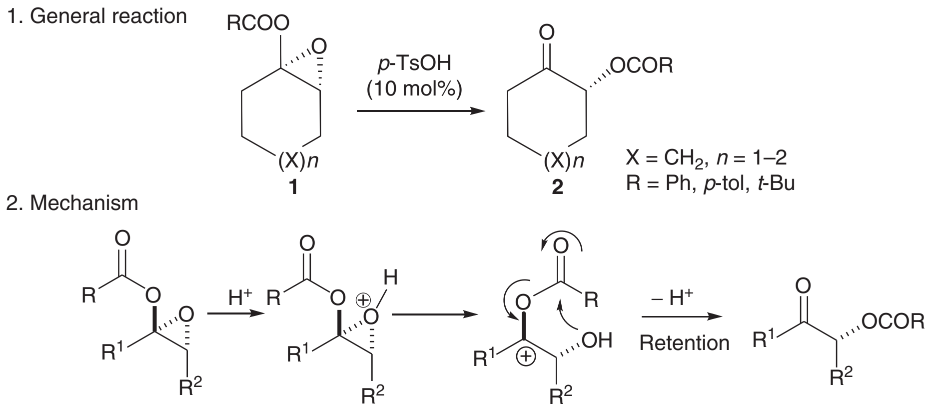
Some works using organic Brønsted acids such as methanesulfonic acid (CH_3SO_3H), trifluoromethanesulfonic acid (CF_3SO_3H) or *p*-toluenesulfonic acid (*p*-TsOH), camphor sulfonic acid (CSA), and trifluoroacetic acid (CF_3CO_2H) for ring-opening reactions/rearrangement of epoxides have been described.

p-TsOH has proved to be an efficient catalyst for the rearrangement of a variety of chiral enol ester epoxides, **1**, via alcyloxy 1,2-migration pathways, giving enantiomerically enriched α-acyloxy ketones, **2**, in high stereospecificity (Scheme 3).[5] For example, starting from (*R*,*R*)-1-benzoyloxyl-1,2-epoxycycloheptane in 97% *ee*, **2** is obtained in 97% *ee*.

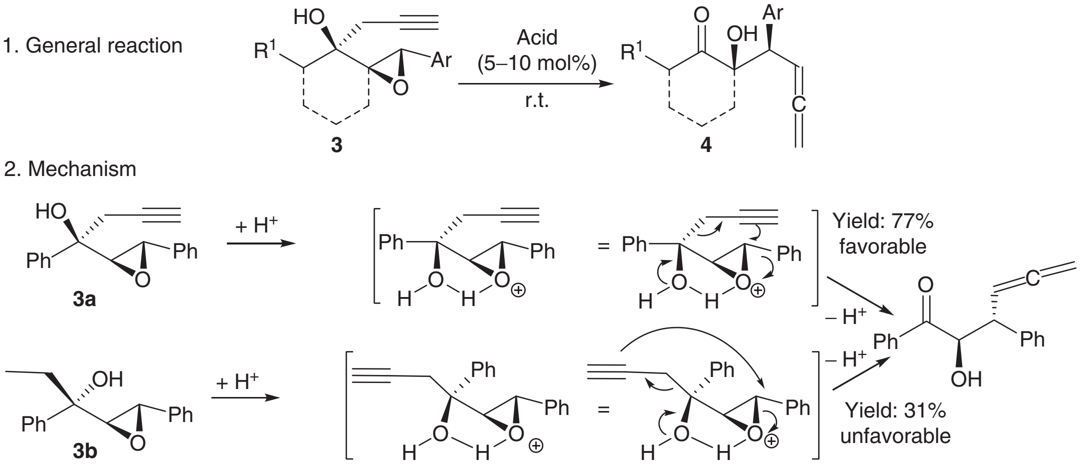
Detailed mechanistic studies led Shi et al. to conclude that with a strong acid, such as *p*-TSOH, the rearrangement can proceed through complexation to the epoxide oxygen, thus leading to the cleavage of the C1–O bond to form a carbocation intermediate, and subsequent alcyloxy migration occurs with the retention of configuration (Scheme 3).

TsOH, CF_3CO_2H, and CH_3SO_3H catalyze the skeletal rearrangement of various hydroxyl-epoxy-alkynes, **3**, leading to the formation of synthetically useful keto-hydroxy-allenes, **4** (Scheme 4).[6]

A possible sequential mechanism of this rearrangement reaction is proposed as depicted in Scheme 4. Activated by protic acid, the epoxide ring opening leads to the formation of a five-membered ring intermediate that rearranges into an allene through a



Scheme 3



Scheme 4

C–C 3,3-migration acting as a nucleophilic reagent. Owing to the configurational orientation of the alkyne away from the epoxide, only one attack process is favored. This mechanism is supported by experimental results, as demonstrated by the fact that the *syn*-diastereoisomer, **3a**, affords a better yield (77%) of keto-hydroxy-allene when compared to the *anti*-diastereoisomer, **3b** (31%).

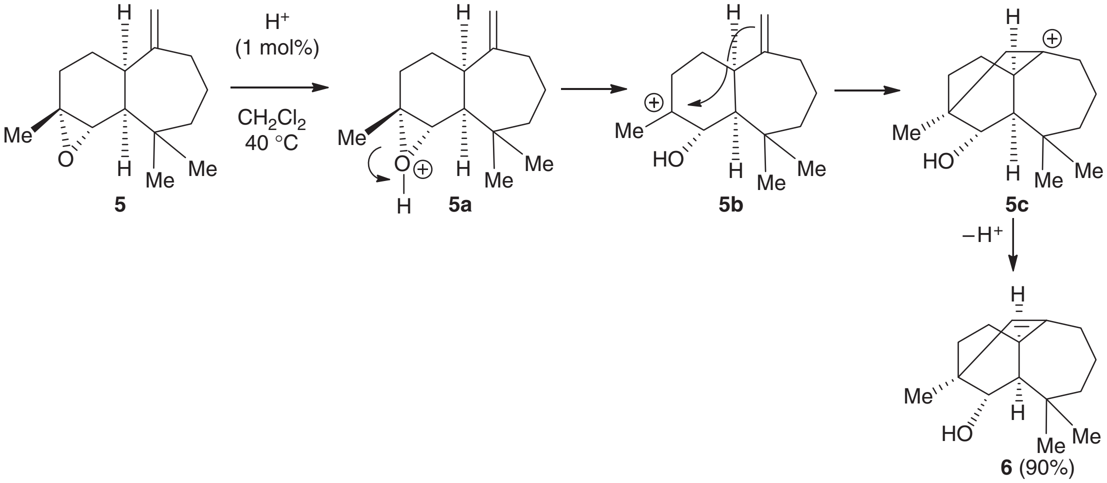
CH_3SO_3H and *p*-TsOH have been shown to be efficient catalysts for the stereoselective domino rearrangement involving the sequential ring opening of epoxides derived from sesquiterpernic himachalenes.[7] The (2*S*, 3*R*)-2,3-epoxy-*cis*-himachal-7,13-ene, **5**, is converted into the enantiomerically pure tricyclic alcohol **6** in the presence of catalytic amounts of CH_3SO_3H and *p*-TsOH (Scheme 5). Selectivity reached 80% at room temperature with CH_3SO_3H and 90% at 40 °C with *p*-TsOH in dichloromethane. The proposed mechanism for the formation of alcohol involves the epoxide ring opening followed by two successive rearrangements of the carbocation intermediates, **5b** and **5c**.

Under similar catalytic conditions, CH_3SO_3H- and *p*-TsOH-catalyzed reaction of (1*S*, 6*S*, 7*R*)-6,7-epoxy-*cis*-himachal-2,3-ene, **7**, provides the enantiomerically pure bicyclic ketone **8** (50%) and the bicyclic aryl compound **9** (25%) at room temperature in dichloromethane.

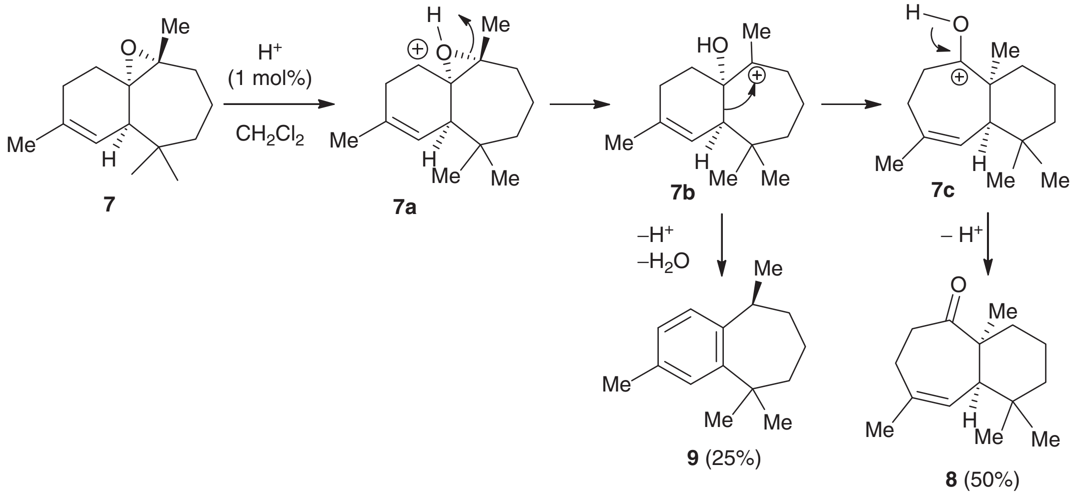
The formation of compound **8** occurs probably via (1) the formation of the carbocation (**7b**) by ring opening of the epoxide, (2) rearrangement of the carbocation (**7b**) into the carbocation (**7c**), and (3) elimination of H^+. Compound **9** can be obtained from carbocation-like **7b** by double formal elimination of H^+ and H_2O with the aromatization of the six-membered ring as the driving force (Scheme 6).

Another versatile domino rearrangement has been reported by Oshima and coworkers[8] for diphenylhomobenzoquinine epoxides.[8] CH_3SO_3H-catalyzed reaction of diphenyl-substituted homobenzoquinone epoxide proceeds cleanly to give the tricyclic diketo alcohol **11** (Scheme 7).

In contrast, CF_3CO_2H catalysis brought about further rearrangement to form new products, and the product distribution is dependent upon the amount of acid. The formation of **11** can be explained by regioselective epoxide ring opening followed by a *trans*-annular cyclization of the endo-phenyl group. Compounds **12** and **13** are obtained from the transformation of **11** by several processes. For **12**, the rearrangement seems to proceed through a sequence of reactions: acid-induced cyclopropane ring opening,



Scheme 5



Scheme 6

dehydration followed by double bond migration, and *trans*-annular ipso S_E2-Ar electrophilic aromatic substitution. Compounds **14** and **15** arise from the decarbonylation of epoxide **10** induced by the acid.

Giner et al. reported examples of intramolecular formation of bicyclic orthoesters from epoxy esters derived from natural products promoted by CF_3CO_2H in catalytic amounts (2 mol%) (Scheme 10).[9]

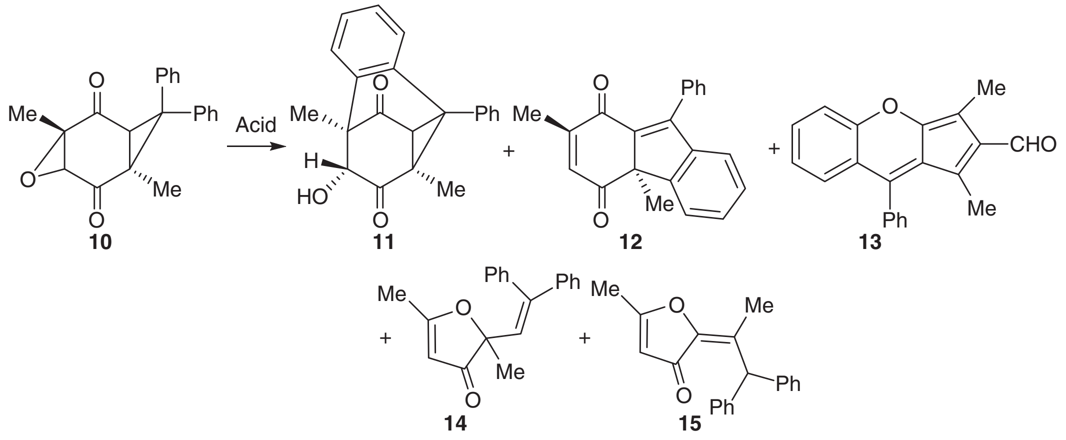
This epoxy ester–orthoester rearrangement provides an efficient approach in the biomimetic syntheses of natural orthoester such as ortho sterol B (an antiviral marine steroidal orthoester) and petuniasterone D (a natural insecticide) (Scheme 8).[10]

An efficient route to chiral 2,2-disubstituted chromenes and tetrahydroquinolines through intramolecular cyclization of chiral 3,4-epoxy alcohols has been described by Zammattio and coworkers.[11] For example, 1,2,3,4-tetrahydroquinoline-4-ol **19** is obtained as the exclusive product of the cyclization reaction by treatment of **18** with trifluoroacetic acid (Scheme 9). However, a loss of stereoselectivity is observed when the reaction is carried out on enantioenriched epoxyalcohols.

Similarly, for oxygen analogs, ring closure occurs in refluxing toluene with a catalytic amount of camphor sulfonic acid (4 mol%) affording chromenes, but in this case the intramolecular cyclization is not stereoselective.

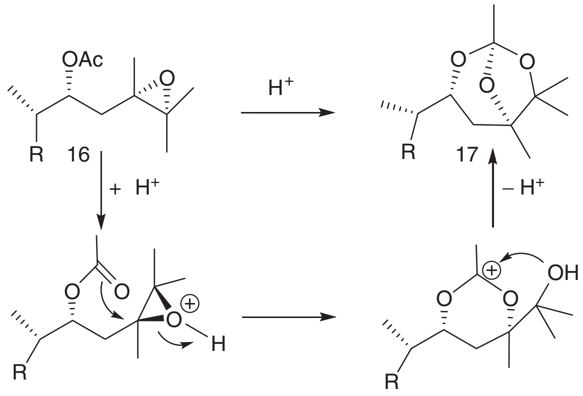
3.15.2.2 Brønsted Inorganic Acids

Brønsted inorganic acids, such as H_2SO_4 and HCl, are also sometimes used to promote opening and rearrangement of epoxides. Only a few examples have been described in recent years. However, the example of the rearrangement of epoxides derived from

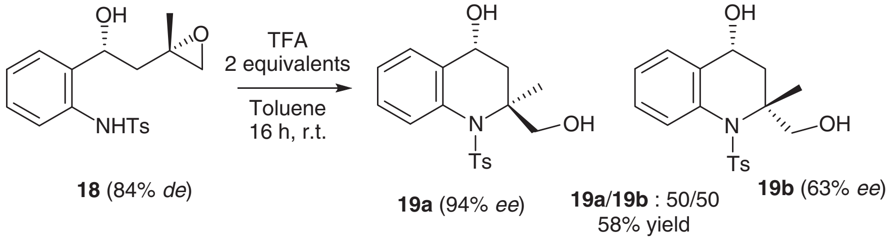


Acid (equivalent)	Time (h)	Yield (%)				
		11	**12**	**13**	**14**	**15**
CH_3SO_3H (3)	2	99	0	0	0	0
CF_3CO_2H (1)	1.5	90	2	0	7	0
CF_3CO_2H (3)	1.5	10	52	3	23	11
CF_3CO_2H (10)	1.5	0	53	0	0	46

Scheme 7



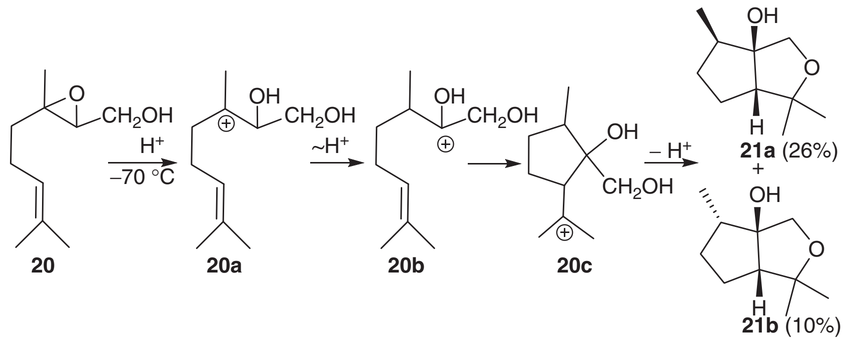
Scheme 8



Scheme 9

2-naphthylcycloalkene into 2-naphthylcycloalkanone catalyzed by H_2SO_4, a method useful in the large-scale synthesis of naphthylcycloalkanone with different substituents on the naphthalene moiety, can be mentioned.[12]

Interesting examples are described for the terpene and sesquiterpene series. Rearrangement/cyclization of acyclic terpenoid epoxides is induced by the use of a super acid at low temperature.[13,14] In the case of 2,3-epoxygeraniol, **20**, the HSO_3F–SO_2FCl system promotes the ring opening of epoxide followed by H migration and a double cyclization to yield epimer hydroxyoxides **21a** (main product) and **21b** (Scheme 10).



Scheme 10

More recently, Bruno et al. reported the acid-induced rearrangement of monoepoxides of artemisiifolin, a natural germacrane-8–12-olide isolated from *Ambrosia artemisiifolia*.[15] Under HCl/$CHCl_3$ catalysis, 1,10-epoxygermacronolides cyclize into eudesmanolides, whereas 4,5-epoxygermacronildes yield guaianolides.

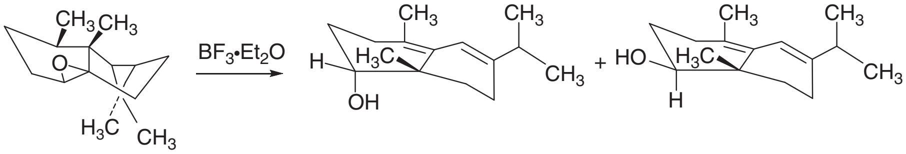
3.15.3 Lewis Acids Derived from Main Group Elements

3.15.3.1 BF_3-Induced Rearrangements

Epoxides are often treated with boron trifluoride (mostly as the diethyl-etherate complex), which is the most used Lewis acid for rearrangements. It is known that the treatment of epoxides with this Lewis acid can give, besides ketones by the epoxide-opening cascade, other rearrangement products, especially in natural product chemistry.[16]

Terpene feedstocks represent an important source of intermediates and ingredients for flavors and fragrances. They are also a natural and sustainable supply of building blocks for the fine chemical industry.[17] Rearrangement of their epoxide derivatives has often been investigated in order to produce new and industrially interesting compounds.

Two dienols epimers (**23a** and **23b**) from the calarene epoxide (**22**) were obtained in the presence of 0.16 equivalent of $BF_3 \bullet Et_2O$-catalyzed reaction in 33% and 66% yield, respectively (Scheme 11).[18]



22 **23a** **23b**

Scheme 11

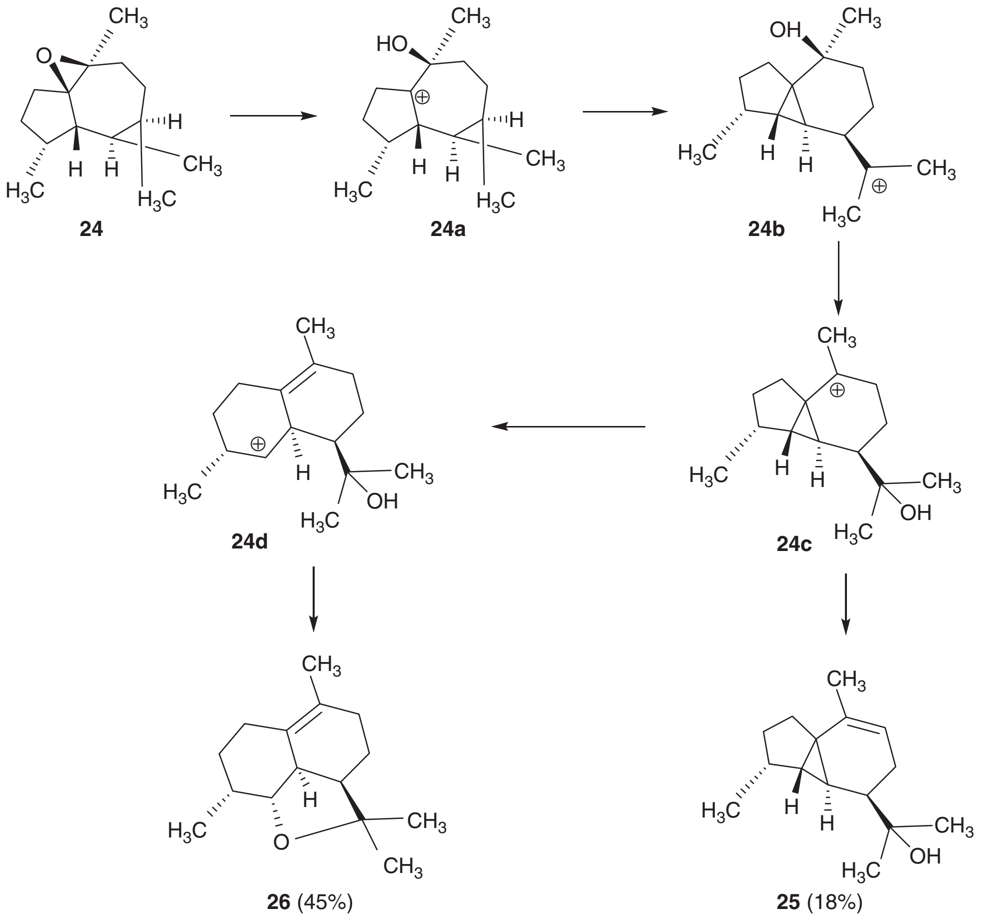
Increasing the quantity to 0.5 equivalent of the catalyst leads to a higher yield (85%) of compound **23b**. The dienol **23a** can only be synthesized with a longer time reaction. The calarene epoxide (**22**) did not allow isolation of these alcohols in a reduction reaction using $LiAlH_4$ or $LiEt_3BH$. These reagents are more susceptible to stearic hindrance due to the closeness of the two cyclohexanes of the calarene.

The stereochemistry of each dienol was established by analysis of ^{1}H-NMR and NOESY correlation peaks between protons. The authors explain the formation of the two alcohols by supposing that two allylic alcohol epimers are first formed, leading then to the most stable carbocation transformed by a Wagner–Merwein rearrangement with cyclopropane ring opening to form **23a** and **23b**. Olfactory evaluation of these new compounds suggested that they have useful fruity woody odors.

In the synthesis of the four stereoisomers of the fragrance magnolione, a compound with structure and odor characteristics similar to jasmonic acid or methyl jasmonate,[19] epoxide rearrangement to introduce a second carbonyl group in the structure of isomers represents a key step. After a number of experimental trials, the Lewis acid $(Ph_3C)BF_4$ was preferred to $BF_3 \bullet Et_2O$ to obtain higher yields.[20]

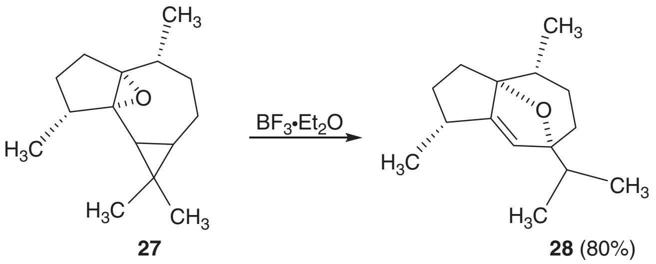
Rearrangement reaction of the epoxide of (+)-ledene leads to products with a guaiane skeleton.[21] Guaiane sesquiterpenes have aroused much interest on account of their wide spectrum of biological properties.[22]

The natural sesquiterpene (+)-ledene is extracted from the essential oils of *Melaleuca alternifolia* or *Melaleuca leucadendron*, and its epoxidation with dimethyldioxirane selectively gives the epoxide **24** as the sole product. When the latter is treated with $BF_3 \bullet Et_2O$ under mild conditions (Scheme 12), a clean reaction takes place to give products **25** and **26**.[23]



Scheme 12

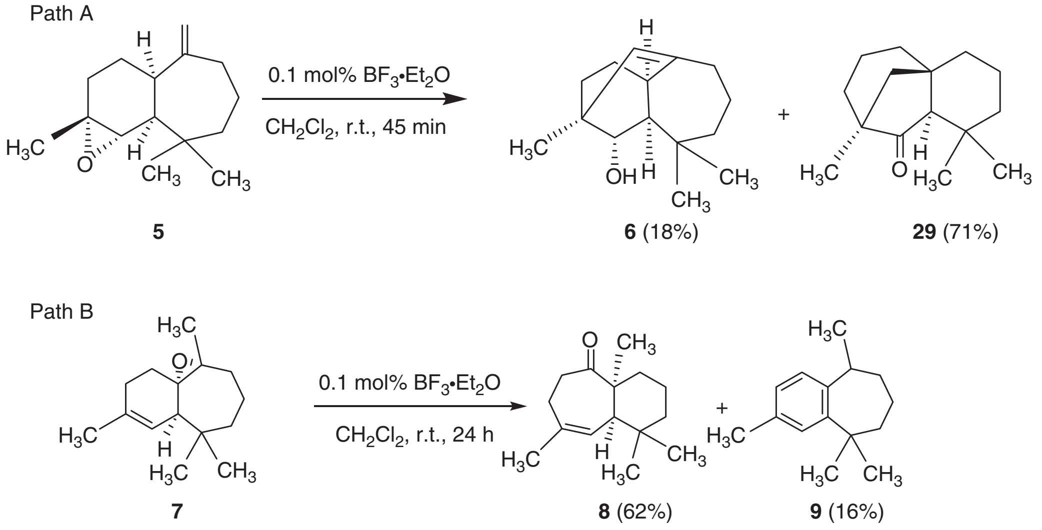
The formation of the C8-bridgehead carbocation occurred in the first step. Subsequently, after the opening of the cyclopropane ring to give another carbocation intermediate, this latter was converted to the more stable corresponding cyclopropylcarbinyl carbocation by hydration–dehydration. Following this step, the elimination of a proton gave the cubebene product **25** and the cadinene product **26** via a further rearrangement of carbocation. Similarly, the treatment of the isoledene-epoxide (**27**) led to an 80% yield of the α-ether bridge compound **28** (Scheme 13).



Scheme 13

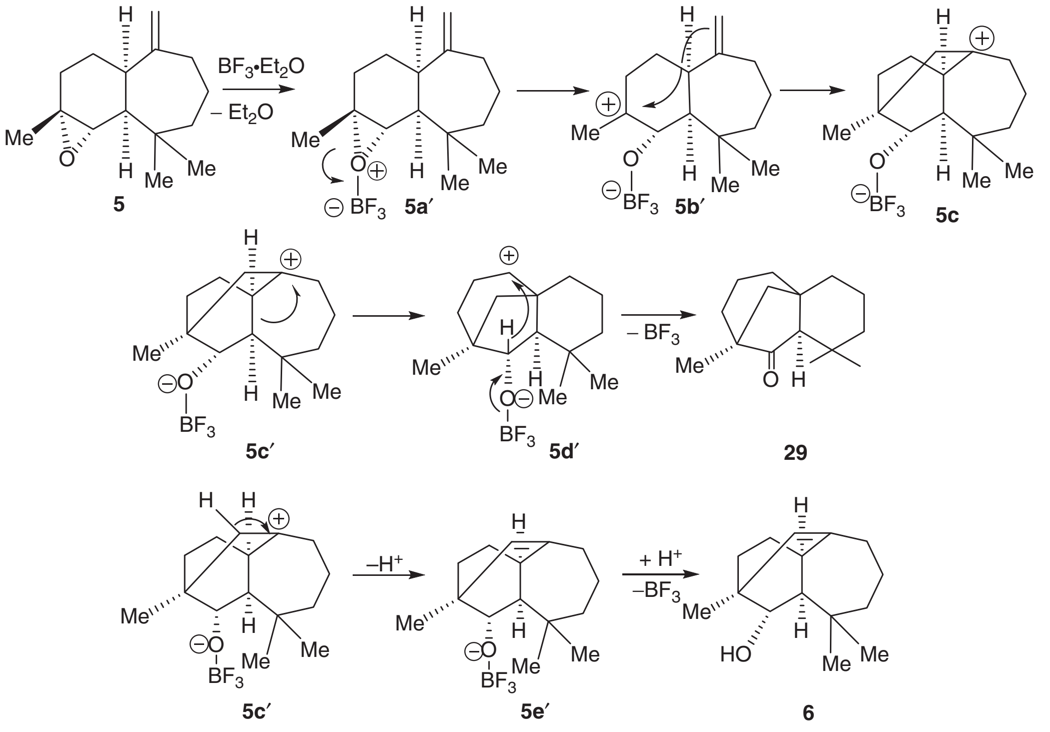
In the synthesis of the oxo-bridged guaiane core of the englerins a $BF_3 \cdot Et_2O$ *trans*-annular bis-epoxidation rearrangement is necessary to provide the substituted furanyl ring of the englerin skeleton.[24] The hydroazulene ring, or bicyclo[5.3.0]decane, system present in the guaiane-type sesquiterpene family is an important structure in the bioactive molecules with anti-inflammatory, antitumor, or cytotoxic properties.[25] A series of Lewis and Brønsted acids were also tested, and it was the $HClO_4$ Brønsted acid that provided the best yield of the desired oxo-bridged englerin configuration.

The reaction of epoxyhimachalenes, himachalene being a sesquiterpene from the essential oil of the Atlas cedar (*Cedrus atlantica*), with 0.1 mol% $BF_3 \cdot Et_2O$ gives the new tricyclic ketone **29** and the alcohol **6** in 71% and 18% isolated yield (Scheme 14, path A) for the 2α,3α-epoxy-cis-himachal-7,13-ene **5** and two main products, the bicyclic ketone **8** and the aryle compound **9** from 6*β*,7*β*-epoxy-cis-himachal-2-ene **7** (62% and 16% isolated yield, Scheme 14, path B).[7–26] All the compounds have been fully characterized by spectroscopic methods. Compounds **8** and **9** have also been obtained after treatment of the epoxide with Brønsted acids (cf. Part 2.1).



Scheme 14

Among the various Lewis acids studied, $BF_3 \bullet Et_2O$ and $BF_3 \bullet MeOH$ are the catalysts that give a rapid and complete transformation of the epoxides and promote the rearrangement into enantiomerically pure ketones (**8** and **29**) in good yields and with high selectivity. The mechanism of this rearrangement is displayed in Scheme 15. Once 2*α*,3*α*-epoxy-*cis*-himachal-7,13-ene **5** is open, with the assistance of BF_3 (**5b′**), the nucleophilic C=C double bond attacks the carbocation intermediate, leading to the formation of another carbocation (**5c′**), which rearranges to form the seven-membered cycle (**5d′**) and then, via a hydride shift,

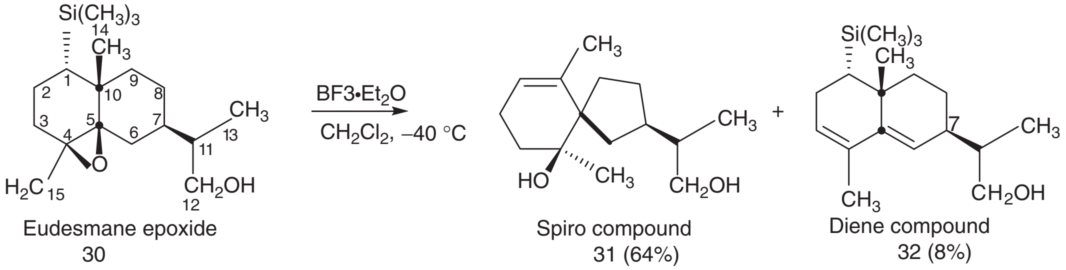


Scheme 15

the resulting ketone **29**. From the carbocation **5c′**, another rearrangement arises via proton elimination yielding compound **6**. Surprisingly, products from other elimination reactions were not observed. To obtain compounds **8** and **9** from 6α,7α-epoxy-cis-himachal-2-ene, the mechanism appears to be the same as the one described in Part 2.1.

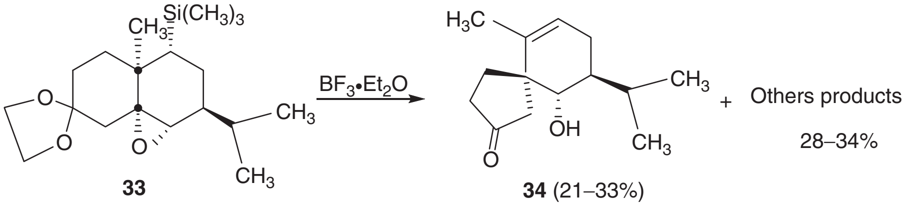
This reaction represents an easy and efficient access to complex chiral ketones that could have interesting chemical and biological properties due to their core substructures found in some natural products.[27]

Spirovetivane sesquiterpenes are fragrant compounds extracted from essential oils. Recently, a research group reported the first synthesis of these molecules starting from santonin, a commercial natural product.[28] The synthetic strategy is based on a regio- and stereoselective silicon-guided rearrangement of a bicyclic trimethylsilyl eudesmane epoxide skeleton. Treatment of the epoxide **30** with $BF_3 \bullet Et_2O$ in CH_2Cl_2 at − 40 °C allows the migration of C9-methylene to the carbocation at C5 with concomitant contraction of the ring to give the spiro compound **31** and the diene **32** from the epoxide opening and dehydration in 64% and 8% yield (Scheme 16). During the rearrangement, the methyl group C14 remains bonded to the former bridgehead carbon, so the double bond is formed by the elimination of the $Si(CH_3)_3$ trimethylsilyl group toward a carbocation produced upon migration of the C9-methylene. A complete assignment of the ^1H and ^{13}C-NMR spectra for all the compounds was done with the help of ^1H–^{13}C bidimensional correlation and decoupling experiments.



Scheme 16

A similar strategy was used in the synthesis of solavetione, another spirocyclic natural product, from carvone.[29] Based on experimental results, it was envisaged that a similar rearrangement directed by $Si(CH_3)_3$ bonded in C9 in the eudesmane moiety should favor the migration of methylene C1, allowing the synthesis of spiroaxane-type sesquiterpenes, which can be used as synthetic intermediates for the synthesis of gleenol and axenol (Scheme 17).[30]

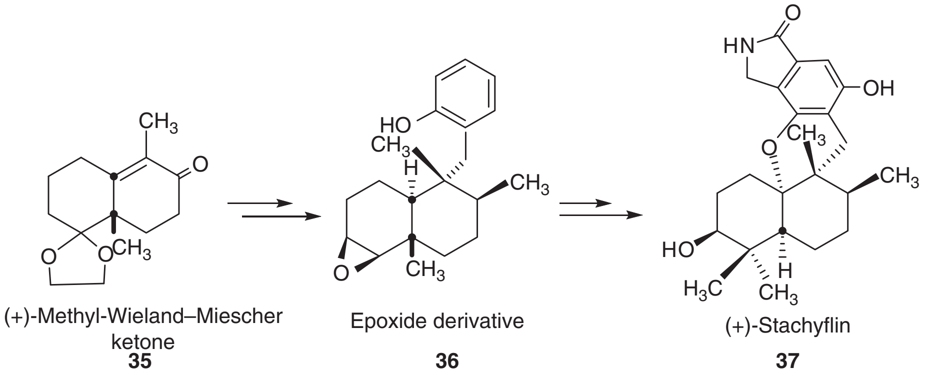


Scheme 17

Treatment of compound **33** with $BF_3 \bullet Et_2O$ in different solvents gives a product mixture with the expected spiroaxane-type sesquiterpene (**34**). The presence of the $Si(CH_3)_3$ group on the same ring of the epoxide favors the migration of methylene C1 to give the spiro compound. The reaction is not selective. Indeed, other products are also obtained due to either the cleavage of the oxirane ring providing a 3,6-diketone, or the cleavage of the acetyl moiety affording the opening of the second cycle and migration of the methyl group. But the synthetic utility of this spiro rearrangement is an important step in the total synthesis of the two spiroaxanes, (–)-gleenol and (–)-axenol (the enantiomer of natural (+)-axenol), which have been prepared from carvone in approximately 0.5% overall yield.

Different synthesis of biological molecules, starting from other substrates according to the nature of the targeted compounds, are also described, often with a key step involving Lewis acids, in particular BF_3.

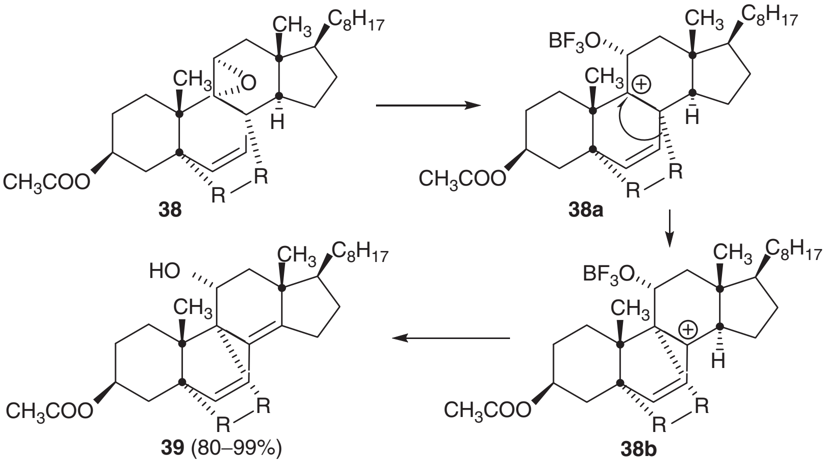
In the enantioselective total synthesis of (+)-stachyflin (**37**), a potent antiviral inhibitor of influenza virus activity,[31] the key step is the $BF_3 \bullet Et_2O$-induced cascade epoxide-opening/rearrangement/cyclization reaction to stereoselectively build the required pentacyclic ring system.[32] This cascade reaction proceeds in a stepwise manner through the agency of different carbocation intermediates. DFT calculations support the rationalization of the observed reaction. Initially the synthesis of the epoxide precursors (**36**) of the key cascade reaction starts from the known enantiomerically pure enone, the (+)-5-methyl-Wieland–Miescher ketone (**35**) (Scheme 18).



Scheme 18

The preparation of new steroid structures with useful biological activities is also of interest,[33] notably steroids with small carbon bridges that are potential therapeutic agents.

A simple and efficient synthesis of a new class of uncommon 5α–9α-bridged steroid derivatives has been developed, implying $BF_3 \bullet Et_2O$ also as an important step.[34] Starting from the corresponding bridged epoxide **38**, after the epoxide opening in the presence of Lewis acid and formation of the C9 carbocation intermediate **38a**, there is migration of the bridge from position C8 to C9 to produce C9 carbocation intermediate **38b**; then, after a base abstraction of the proton of C14, the 5α–9α-bridged steroid **39** was obtained in high yield (Scheme 19).



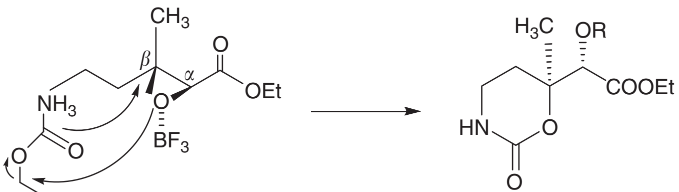
R–R represents the dienophile used in the Diels–Alder reaction of the 5,7,9(11)-cholestatriene to give the product leading **38** after epoxydation

Scheme 19

This pathway is favored by an electron-rich double bond on the migrating bridge and is stereocontrolled without further diene migration, giving a single product. Various Lewis acids have been investigated, and it has been found that $BF_3 \bullet Et_2O$ in benzene or dichloromethane gives the best result. This reaction was applied with success to other accessible steroidal epoxy adducts. Further cyclization and lactonization reactions lead to several new stereoidal lactones.

A new, inexpensive, and scalable synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline is described involving the intramolecular opening of an epoxide by a carbamate promoted by Lewis acids. An unexpected rearrangement is also observed based on a C2–N disconnection protocol.[35] The scientific community has made great efforts to prepare unusual amino acids, including (2*S*,3*R*)-3-hydroxy-3-methylproline, because these amino acids represent important building blocks in the synthesis of the anticancer polyoxypeptin drugs.[36]

Synthesis starts from inexpensive commercially available 3-amino-1-propanol; after different steps, the racemic epoxide **40** is obtained. Treatment of the latter with 1.2 equivalents of $BF_3 \bullet Et_2O$ in CH_2Cl_2 at −78 °C affords the cyclic compound **41** in 80% isolated yield. In the presence of $BF_3 \bullet Et_2O$ there is an attack on the *β*-carbon atom of the activated epoxide by the carbamate carbonyl group to form an oxazinanone ring with the reversion of the carbon-*β* center and the alkoxide anion resulting from the ring opening that immediately catches the leaving group cation to form an ether (Scheme 20).



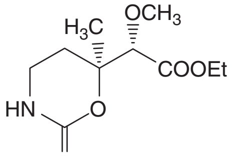
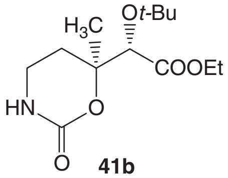
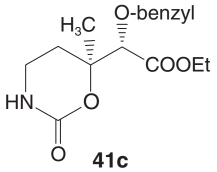
40

41

Scheme 20

To explore the generality and stereochemistry of benzyl or alkyl migration, the reaction was studied with different epoxides, and the results are shown in Table 1.

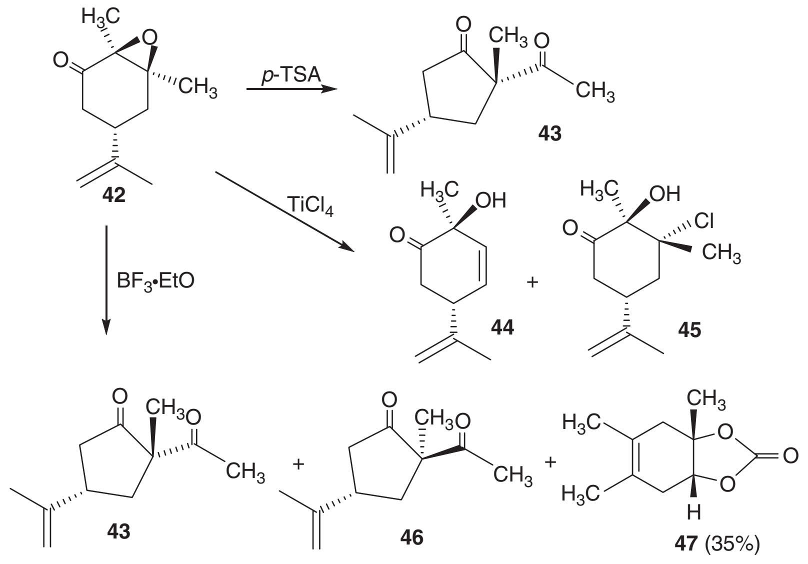
Table 1 Results of rearrangement of various epoxides

R	*Product*	*Isolated yield (%)*
$-CH_3$	 **41a**	73
–*t*-Bu	 **41b**	34
–Benzyl	 **41c**	80

Satisfactory yields are obtained up to 80%. In the case of the –O–*t*-Bu alkyl group, the yield is lower due to a partial transformation of the ether function into the corresponding alcohol under the acidic reaction conditions.

Among the variety of functionalized epoxides, *α*,*β*-epoxy ketones have proved to be interesting and useful substrates in organic synthesis. Owing to the presence of a carbonyl function on the epoxide carbon atom, regio- and stereoselective transformations can occur.[37] To develop a convenient reaction for the enantioselective 2-acetylcyclopentanones, investigations have been carried out on epoxide **42**, derived from carvone. Results show some unexpected rearrangement depending on the acid used and the temperature of the reaction.[38] Indeed, when using an excess of *p*-toluenesulfonic acid (*p*-TSA) in methylene chloride at room temperature, the *anti*-epoxide derived from carvone gives the corresponding *β*-ketone **43**, with the ring contracted (pentane ring) in good yield and in a highly stereoselective manner (Scheme 21). Reaction with the *syn*-epoxide gives the other *β*-ketone diastereomer with the same result in yield and stereoselectivity.

When the *anti*-epoxide is exposed to a Lewis acid such as titanium tetrachloride ($TiCl_4$), a 1:1 mixture of chlorohydrins **45** and allyl alcohol **44** is obtained in 70% yield. However, only chlorohydrins are formed from the *syn*-epoxide (78% yield). In contrast, the reaction of the *anti*-epoxide with 30 mol% of BF_3 Et_2O is found to be nonstereoselective and temperature dependent. In fact, treatment of the epoxide with 1 equivalent of acid at -70 °C in methylene chloride for 4 h gives a 2:1 mixture of the diketones **43** and **46**. If the reaction mixture is treated at -70 °C and then at room temperature for 14 h, an unusual lactone **47** is obtained in 35% yield along with 30% yield of a 2:1 mixture of the diketones **43** and **46**. Similarly, the reaction with the *syn*-epoxide furnishes diketones in 94% yield in a 1:3 ratio. The formation of the diketones **43** and **46** from the epoxides with $BF_3 \bullet Et_2O$ reveals that the reaction proceeds through a carbonium ion, and the anchimeric assistance of the isopropenyl substituent plays an important role in product distribution. The formation of lactone from the *anti*-epoxide involves a deep-seated rearrangement.[31] A plausible mechanism is the intermolecular nucleophilic attack of the isopropenyl double bond on the boron trifluoride-coordinated epoxide from the *anti*-face leading to the bicyclo[2.2.2]octylcarbonium ion. Intramolecular addition of oxygen to ketone followed



Scheme 21

by ring cleavage and trapping of the carbonium ion by the resultant carboxylate produces the lactone. This proposed mechanism is supported by the fact that no lactone is obtained with the *syn*-epoxide containing the epoxy function and the isopropenyl group on the same side.

Another interesting structural motif in medicinal chemistry is the enantiopure diarylmethane derivatives. A large number of therapeutic agents possess this structure.[39] Pure benzyl-type ethers of arylglycidols containing electron-withdrawing substituents on the aryl moiety and electron-donating groups on the benzyl ring treated by $BF_3 \bullet Et_2O$ afford either enantiopure diarylmethanes or enantiopure *trans*-4,5-disubstituted tetrahydrobenzo[c]oxepin-4-ols.[40] Although epoxy-ene or epoxy-arene cyclizations are known,[41] there is an unprecedented intramolecular stereospecific process during this reaction. An ipso substitution occurs in the benzyl ether moiety by the activated epoxide **48**, followed by fragmentation, which releases a phenyl group to a benzylic position **48a**, ultimately leading to the formation of an enantiopure diarylmethane derivative **49** (Scheme 22). Starting from several enantiopure epoxy-ethers (*ee* 95–99%), enantiopure 4-(diaryl-methyl)1,3-dioxolanes are obtained in good yield as the sole reaction products (Scheme 22).

Interestingly, another structural motif such as tetrabenzoxepinol can be obtained by the modification of the electronic properties of the benzyl ring using 3,5-dimethylbenzyl for the R^1 substituent. Thus, the electrophilic attack of the epoxide on the benzyl ether moiety can be fine-tuned to shift the ipso substitution to the ortho/ortho′ positions.[40]

Another example of this useful rearrangement for constructing polycyclic diketo alcohols is reported.[42] The BF_3-catalyzed rearrangement of diphenyl-substituted and *endo*-monophenyl-substituted homobenzoquinone epoxides **50** proceeds through a regioselective oxirane opening and a crucial *trans*-annular cyclization of the endo aromatic ring to afford the tricyclic diketo alcohol **51**. The latter plays a crucial role in the epoxide opening through its Π-electron nucleophilic character.

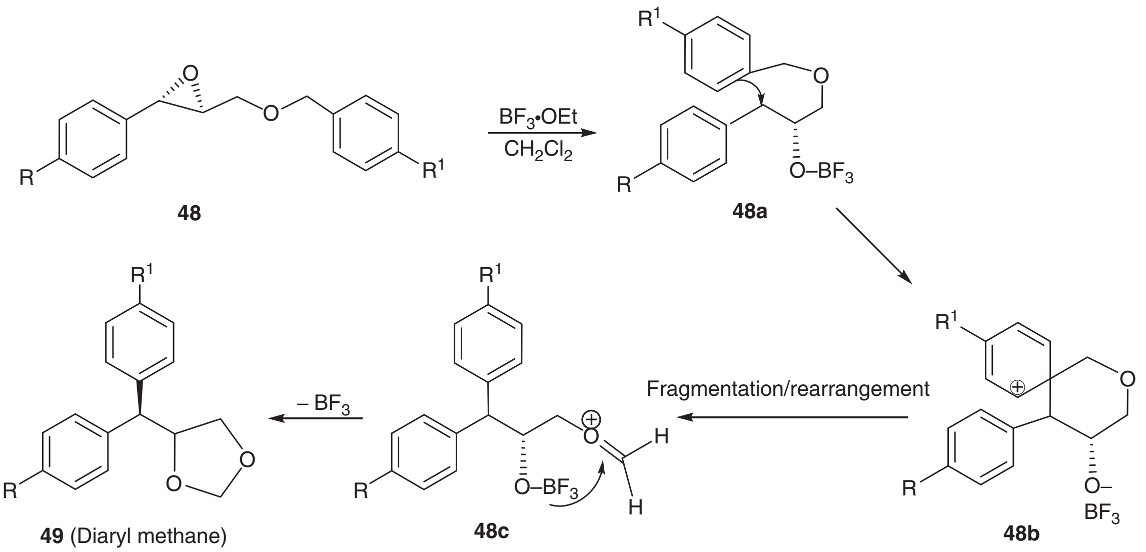
The conformationally semirigid dibenzocycloheptene spiro-linked epoxides **52** were likely to produce the corresponding diketo alcohol **53** and the bicyclo-[4.2.1]nonaene diketo alcohol **54** with an 1,2-acyl migration combined with cyclopropane ring cleavage (Scheme 23(b)).

The formation of chiral benzilic quaternary carbon centers present in many natural products is described. The cyclic 2-aryl-2,3-epoxy acylates rearrange via the C2-cleavage of epoxide. Subsequently, the treatment of the epoxy *para*-nitrobenzoate **55** with $BF_3 \bullet Et_2O$ gives the optically active product **56** with the same enantiomeric excess as the starting epoxy alcohol (Scheme 24).[43] The epoxide **55** was prepared by treatment with *t*-BuOOH/VO(acac)2 and then with *p*-nitrobenzoic acid in the Mitsonubu reaction.

This rearrangement of epoxy acylate systems proceeds stereospecifically and leads to the optically active benzylic quaternary carbons.

In the enantioselective total synthesis of lyngbyatoxin A, a potent activator of protein kinase C,[44] the crucial step involves an enantiospecific $BF_3 \bullet Et_2O$-mediated rearrangement of chiral vinyl epoxides carrying a seven-substituent indole moiety.[45] The reaction proved to be rapid and highly efficient, requiring only short reaction times. *N*-allyl or *N*-benzoyl indole substrates give exclusively the products of vinyl migration, including when the secondary indole stabilized carbocation is preferred over the tertiary allylic species. In contrast, in the presence of the *N*-tosyl derivative, the tertiary and allylic carbocation is favored, but hydride migration is faster than the migration of the indole moiety. This surprising result can be explained by the proposition of the mechanism invoked in earlier works.[46]

Organosilicon compounds are useful reagents in the preparation of natural products and have become a powerful tool in organic synthesis[47] due to the control of the stereochemistry of reactions taking place in their vicinity. In this strategy, the



R	R^1	T (°C)	Time (min)	BF_3•OEt (equivalent)	Yield (%)	*ee* product (%)
NO_2	Phenyl	r.t.	30	1.0	60	98 (**49a**)
CF_3	Phenyl	r.t.	180	0.5	60	96 (**49b**)
CF_3	*p*-Methoxy-phenyl	–35	30	1.0	60	97 (**49c**)
H	*p*-Methoxy-phenyl	–35	5	0.5	59	>99 (**49d**)

Scheme 22

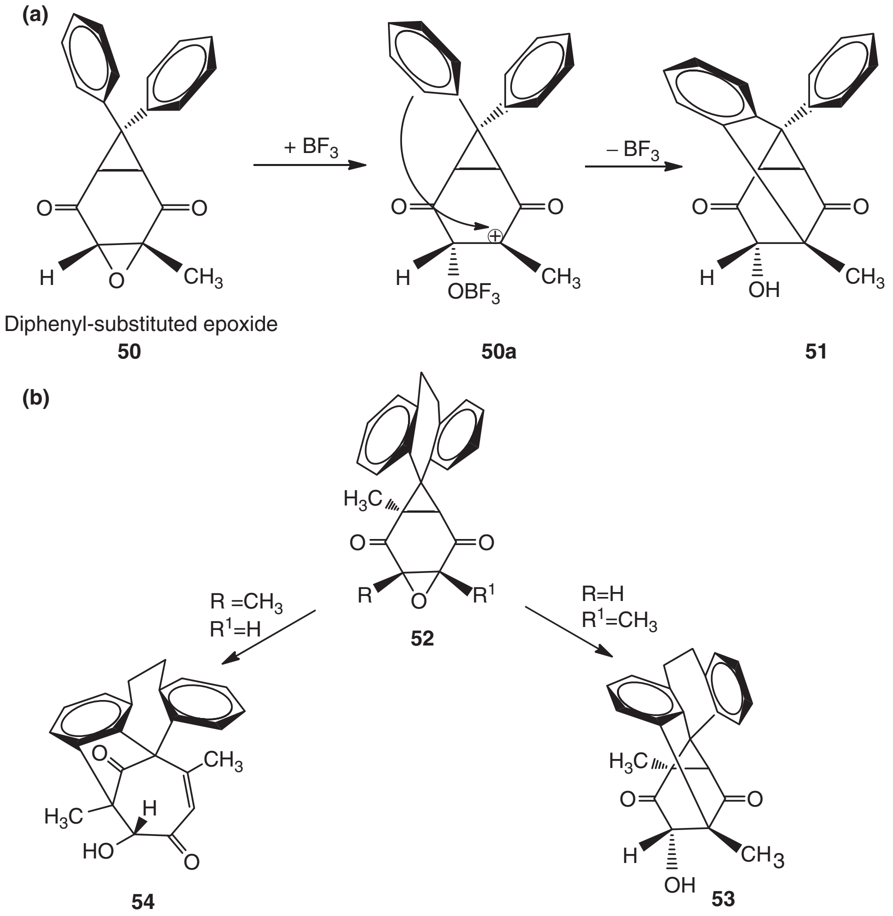
cyclization of epoxy-allylsilanes has been explored under Lewis acid conditions. 3-Methylenecyclohexanol derivatives were selectively obtained in good yields from a rearrangement/cyclization process.[48] The nature of the silyl group plays a crucial role in these reactions since structurally similar epoxy-allylsilanes bearing either a trimethylsilyl or the phenyldimethylsilyl group gives, in the first case, the expected product resulting from 5-exo or 6-endo attack[49] and, unexpectedly, the 3-methylenecyclohexanol derivatives for the second (Scheme 25). Good yields of methylenecyclohexanols are obtained in the presence of 1 equivalent of boron trifluoride etherate. In contrast, aluminum-based Lewis acids give low yields of the cyclized products. A plausible mechanism has been proposed to explain the formation of 3-methylenecyclohexanol derivatives (Scheme 25).[50] The opening reaction of the epoxide **57** results in the formation of the most stable carbocation **57a** to give the corresponding aldehyde **57b**, followed by reaction with the allyl silane unit to give an intermediate carbocation **57c**, stabilized by hyperconjugation from the adjacent C–Si bond, and finally losing its silyl group to afford **58**. It is also likely that both steric and electronic effects play an important role in governing the stereochemical outcome of the reaction.

Similarly, synthesis of 5-methylenecycloheptanols is successfully carried out by treating epoxycyclopropylsilanes in the presence of boron trifluoride etherate in good yields and with a high degree of stereocontrol favoring the *trans* isomer. The product, which has an *anti* relationship between the hydroxy group and the C-2 substituent, must result from an antiperiplanar transition state in which the bulky Lewis acid complexed to the carbonyl group shows a steric preference to be equatorial and *anti* to the pseudoequatorial substituent on C-2.

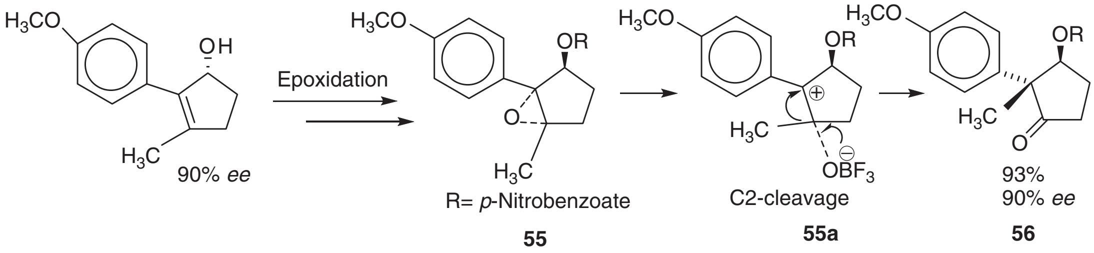
The substituted 5-methylenecycloheptanols might be excellent building blocks for the total synthesis of cycloheptane-containing naturally occurring terpenes such as karahaenone and perforenone.[51]

3.15.3.2 Aluminum-Induced Epoxide Opening

Aluminum-Lewis acids are used to facilitate manifold organic transformations, and $Al(OTf)_3$ has been found to be a highly effective Lewis acid and catalyst (in low quantities) for the ring opening of a variety of epoxides by a range of alcohols[52] or for efficient acetal formation using an orthoester[53] or aminoalcohol in the presence of various alkyl- and arylamines.[54] Very little work has been done using only organoaluminum reagents in Lewis acid-activated reactions. Generally, organoaluminum reagents lead to the stereoselective creation of carbon–halogen or carbon–carbon bonds.[55] Skeletal rearrangement of 2,3-diazonorbornene oxide in the presence of diethyl aluminum chloride (Et_2AlCl) leads to *syn*-chlorohydroxy-disubstituted diazonorbornane in a regio- and stereoselective manner.[56] The same Lewis acid is involved in the synthesis of the monosubstituted 2-aryl



Scheme 23

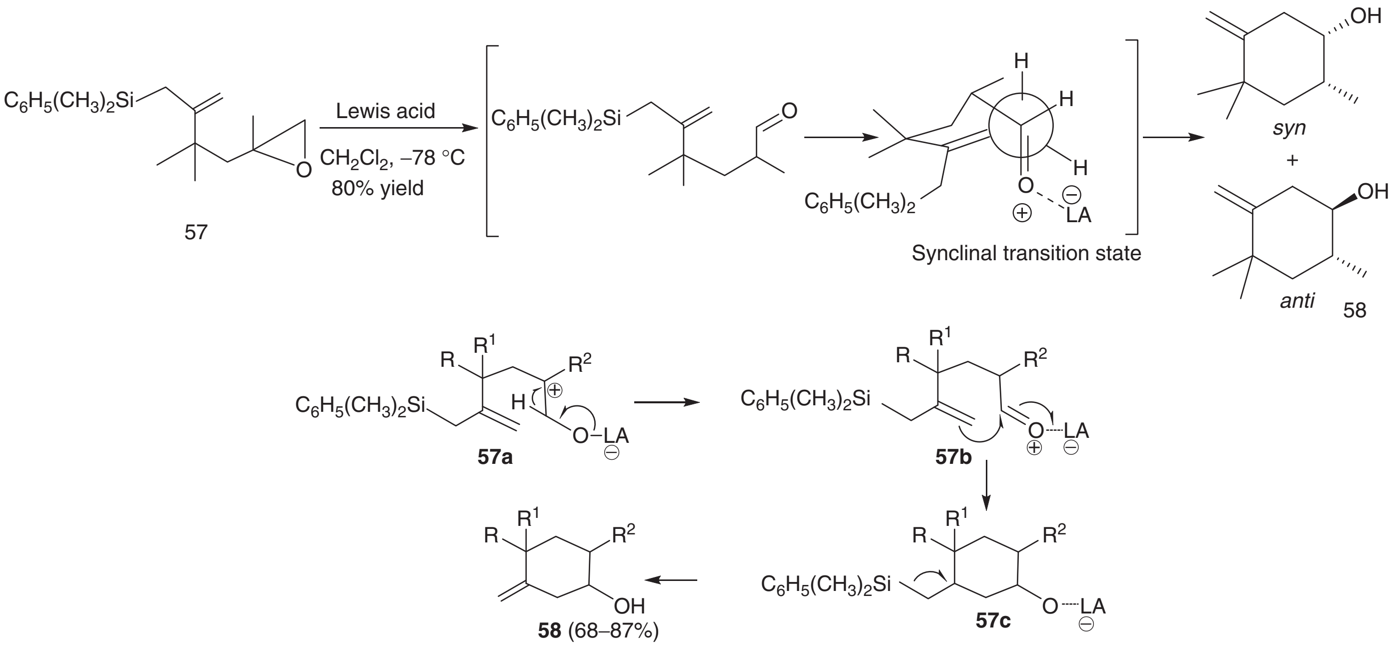


Scheme 24

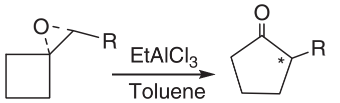
cyclopentanones **60** from optically active benzylidene cyclobutane epoxide **59** (Scheme 26).[57] The stereoselectivity of the rearrangement was found to be highly sensitive to the Lewis acid and solvent. The reaction is effectively achieved with Et_2AlCl in toluene at −78 °C. The cyclopentanone is cleanly obtained and high *ee* values are maintained. The rearrangement is likely to follow a concerted process with inversion of the configuration. This process provides a viable pathway to obtain optically active cyclopentanones, which still represent a challenge to obtain.

Quaternary carbon stereocenters are present in a wide variety of organic compounds, and their construction in a stereoselective manner remains a significant interest in organic synthesis. The optically active α-hydroxy epoxide **61** treated by 2 equivalents of aluminium isoproxide ($Al(i\text{-}PrO)_3$) in refluxing temperature of isopropanol leads to the 1,3-diol (**62**) derivative containing a quaternary stereocenter at C2 as a major by-product and the expected allylic diol **63** (Scheme 27).

This by-product results from a tandem reaction sequence involving an initial semipinacol rearrangement of the hydroxyl epoxide and a Meerwein–Ponndorf–Verley reduction.[58] This strategy has been extended to the stereoselective construction of quaternary centers via semipinacol rearrangement from a range of racemic cyclohexenyl or cyclopentenyl alcohol derivatives. The corresponding cyclohexane-epoxides **64** in the same conditions described above undergo a reductive rearrangement to produce 1,3-diols **65a** as the major product and **65b** as the minor product in good yield (Scheme 28). This methodology permits the


$C_6H_5(CH_3)_2Si$
57
Lewis acid
CH_2Cl_2, –78 °C
80% yield
Synclinal transition state
syn
anti
58
57a
57b
57c
58 (68–87%)
R
R^1
R^2
LA
OH

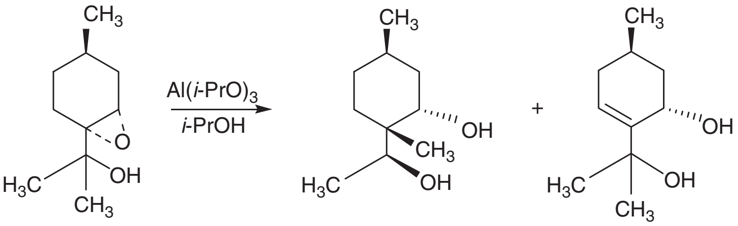
Scheme 25



59 **60**

R	Epoxide *ee* (%)	Yield of **60** (%); *ee* (%)
Ph	90 (**59a**)	90; 90 (*S*) (**60a**)
p-MeO–Ph	91 (**59b**)	98; 82 (*S*) (**60b**)
p-Me–Ph	93 (**59c**)	82; 88 (*S*) (**60c**)
p-Et–Ph	94 (**59d**)	99; 91 (*S*) (**60d**)
p-Br–Ph	96 (**59e**)	94; 93 (*S*) (**60e**)
m-Me–Ph	95 (**59f**)	82; 92 (*S*) (**60f**)

Scheme 26



61 **62** (25%) **63** (45%)

Scheme 27

construction of three carbon stereocenters, with one being quaternary, in only one simple reaction. In this transformation, the Al(*i*-PrO)$_3$ Lewis acid plays a dual role to promote the semipinacol rearrangement and as a reducing agent for hydride transfer, following the more favorable pathway in terms of steric hindrance, which affords the C1–C2 *syn* diastereomer as the major product. The main limitation of this reaction is the requirement of 2 equivalents of Al(*i*-PrO)$_3$.

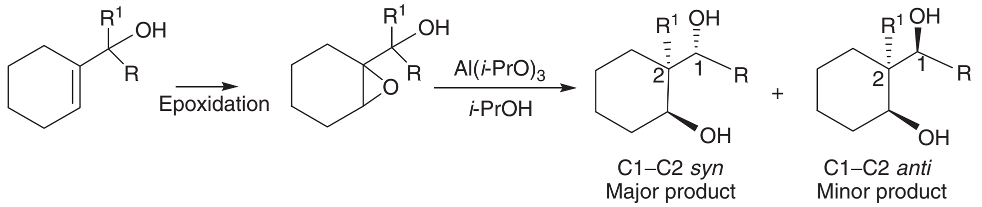
Methylaluminum bis(4-bromo-2,6-di-tert-butyl)-phenoxide (MABR), a bulky Lewis acid reported by Maruoka and Yamamoto,[59] is generally effective for the rearrangement of epoxy-silyl ether. For example, the treatment of epoxy-silyl ether derivatives by MABR affords stereoselectively the corresponding β-siloxy aldehydes, which are intermediates in the synthesis of α,α-disubstituted α-amino acids, an important class of nonproteinogenic amino acids.[60] Similarly, threo- and erythro β-siloxy aldehydes have been obtained from erythro epoxy allyl in the presence of MABR with a stereoselectivity depending on the electronic effect of the silyl substituents rather than on their steric effect.[61]

3.15.3.3 Other Lewis Acid-Induced Epoxide Opening

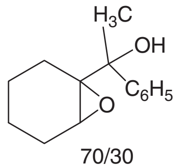
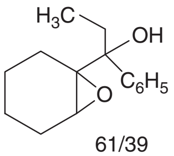
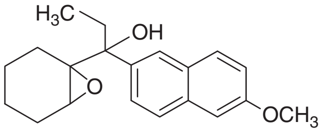
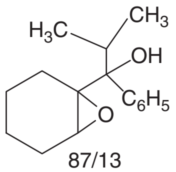
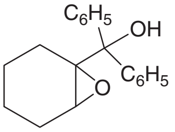
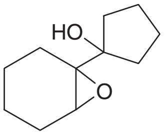
A variety of bismuth compounds have been used in organic transformations over the last 10–15 years because of their low toxicities, a wide range of reactivities, and low cost.[62] Catalytic quantities of bismuth(III) compounds are effective in promoting the rearrangement of epoxides to carbonyl compounds. Rearrangement of *cis*- or *trans*-stilbene oxides (**66**, **68**, **70**, **72**) in the presence of 20 mol% of $BiOClO_4.xH_2O$, a commercially available bismuth compound requiring no special handling, gives diphenylacetaldehydes (**67**,**71**,**73**) as the only clean product, necessitating no further purification (Scheme 29).[63]

In all cases, the phenyl group was found to migrate in preference to hydrogen. In contrast, using other Lewis acids such as $BF_3 \bullet Et_2O$ or $MgBr_2$, the reaction is not regioselective and gives a mixture of both diphenylacetaldehyde and deoxybenzoin (hydrogen migration). The rearrangement of α-pinene oxide **74** with bismuth(III) oxide perchlorate occurs quite readily at room temperature to give the expected aldehyde **75** in 88% yield (Scheme 29). Similarly, bismuth triflate, $Bi(OTf)_3.xH_2O$, also represents a highly efficient catalyst for rearrangement of stilbene epoxides to carbonyl compounds.[64] 0.1 mol% is sufficient to promote a smooth reaction and in the case of styrene oxide, rearrangement occurs even with as little as 0.01% of the catalyst. This fact makes the procedure attractive for large-scale synthesis. The rearrangement of epoxides bearing electron-withdrawing groups such as acyl-substituted epoxides involves the formation of the corresponding carbonyl product with the exclusive migration of the acyl group, providing an easy access to β-oxoaldehydes.

Rearrangement of 2,2,3,3-tetrasubstituted 2,3-epoxy alcohol derivatives having only a slight difference in the stability of carbocation at C2 and C3 positions proceeds through the C3 carbocation to afford two types of carbonyl compounds, α-hydroxy ketone or β-hydroxy ketone, in a regio- and stereoselective manner in the presence of $SnCl_4$, which has been found to be the best Lewis acid for selective rearrangement.[65] The control of the stereochemistry of the products obtained is achieved via the chelation or nonchelation transition state with $SnCl_4$ only by changing the type of protecting group on

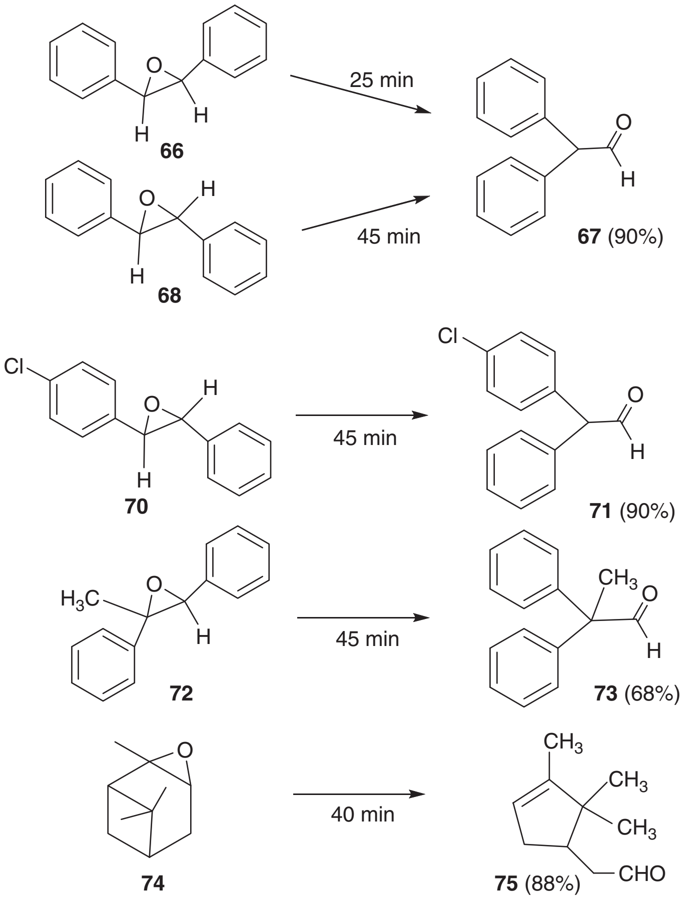


64 **65a** **65b**

Epoxides (*syn*/*anti*)	Yield of products (%)	**65a**/**65b** Ratio
 70/30	85	80/20
 61/39	98	72/28
 75/25	73	65/35
 87/13	95	73/27
	91	80/20
	98	>98/<1

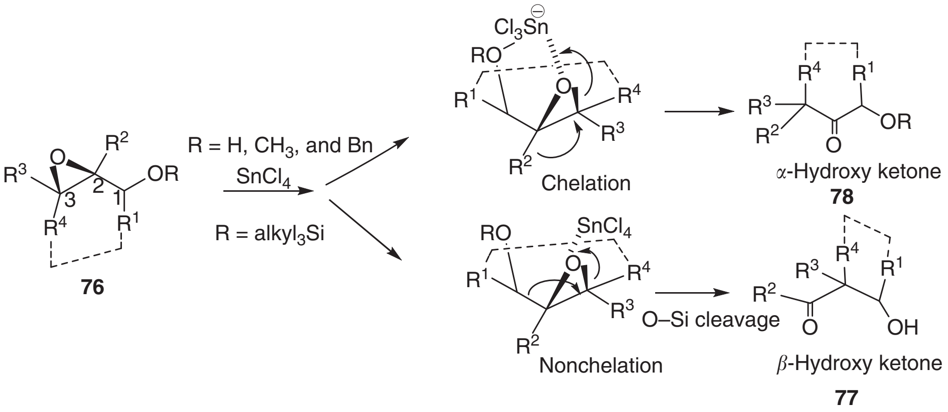
Scheme 28

the alcohol. The epoxy-silyl ethers **76**, which form nonchelated intermediates, afford the *β*-hydroxy ketones **77** as major products. In the case of epoxy alcohols and epoxy alkyl ethers, the *α*-hydroxy ketones **78** are the major products following the Meinwald rearrangement. The hydroxyl or alkyl ether derivatives can form the bidentate chelation state between the two oxygen



Scheme 29

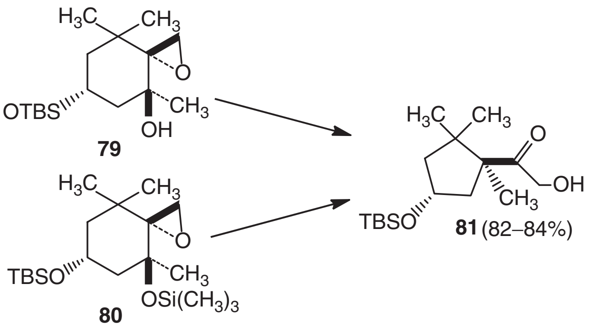
atoms and tin metal, and consequently it is the C2 alkyl group which selectively migrates to produce the α-hydroxy ketones **78** (Scheme 30).



Scheme 30

This method has been applied to the asymmetric synthesis of carbonyl compounds bearing chiral quaternary carbon centers, a structural subunit present in many biologically active natural products.[66]

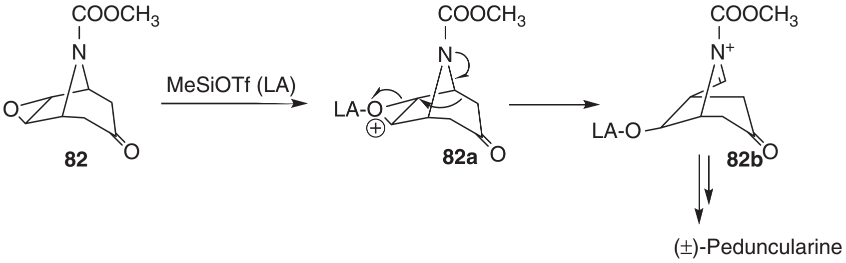
This tin chelation-controlled conversion of 2,3-epoxy alcohol to the stereoselective formation of a cyclopropane ring is also described using $SnBr_4$.[67] Under $SnCl_4$ activation, new α-hydroxy- (**79**) and α-trimethylsilyloxy-spiro epoxides (**80**) are transformed into the corresponding cyclopentyl hydroxymethylketone **81** in a stereospecific way (82–84% yield) following an original tandem Payne/Meinwald rearrangement (Scheme 31).[68] Surprisingly, the reaction of the trimethylsilyloxy-spiro epoxide with



Scheme 31

MABR allows an interesting divergence of the mechanism. A stereoselective Meinwald rearrangement gives the cyclohexane carbaldehyde in 98% yield.

Indium complexes have received increasing attention in the last few years as catalysts for various organic reactions due to their fast coordination–dissociation equilibrium. In the field of Lewis acid catalysis, Indium(III) halides and Indium(III) triflate have emerged as mild Lewis acids for chemo-, regio-, and stereoselective chemical transformation.[69] $InCl_3$ has been used in the catalyzed rearrangement of aryl-substituted epoxides[70] to form carbonyl compounds with high regioselectivity via the cleavage of the benzylic C–O bond. The synthesis of benzylic aldehydes and ketones can be done in high yield, up to 95%. This procedure occurs under mild conditions, and is a fast reaction. Moreover, the compatibility of $InCl_3$ with sensitive functionalities such as methoxy or ester groups or alkene and alkyne bonds represents an interesting factor in using this type of Lewis acid. Recently, in the synthesis of (–)-peduncularine, an indole alkaloid, the key step is an efficient MeSiOTf Lewis acid-induced nitrogen-driven rearrangement iminium-trapping cascade (**82a**, **82b**) from an easily accessible epoxytropinone **82** (Scheme 32).[71]



Scheme 32

3.15.4 Transition Metal-Based Lewis Acids

In the last decade, a number of transition metal-based catalysts have been developed for this important process, largely addressing the issues associated with traditional epoxide-opening reactions. In particular, the emergence of mild and highly efficient chiral catalysts has rendered the asymmetric ring-opening reaction a powerful tool for the synthesis of stereogenic quaternary carbon.[72]

A wide variety of transition-metal catalysts have been developed for the rearrangement of epoxides, and they often exhibit both higher reactivities than classical Lewis acids as well as improved functional group tolerance (Figure 1).

The low-valence electron-rich transition-metal complexes, such as Ir, Rh, and Pd complexes, acting more like Lewis bases in epoxide isomerization, are beyond the scope of this chapter.

3.15.4.1 Titanium/Zirconium/Hafnium

Titanium (IV) compounds, TiX_4 (X = halide, alkoxide, etc.), are the most important Lewis acids in organic chemistry. The Lewis acidity of TiX_4 is controlled by the nature of the anionic groups, X. Among them, the tetrahalides show stronger Lewis acidity, whereas the tetraalkoxides are milder Lewis acids.

$TiCl_4$ is well known for epoxide rearrangement, in particular for the construction of quaternary carbon stereocenters. In an early work, Yamamoto and colleagues demonstrated its versatility and practical utility in the site-specific 1,2-rearrangement of epoxy-silyl ether, giving the β-hydroxy carbonyl compound.[73]

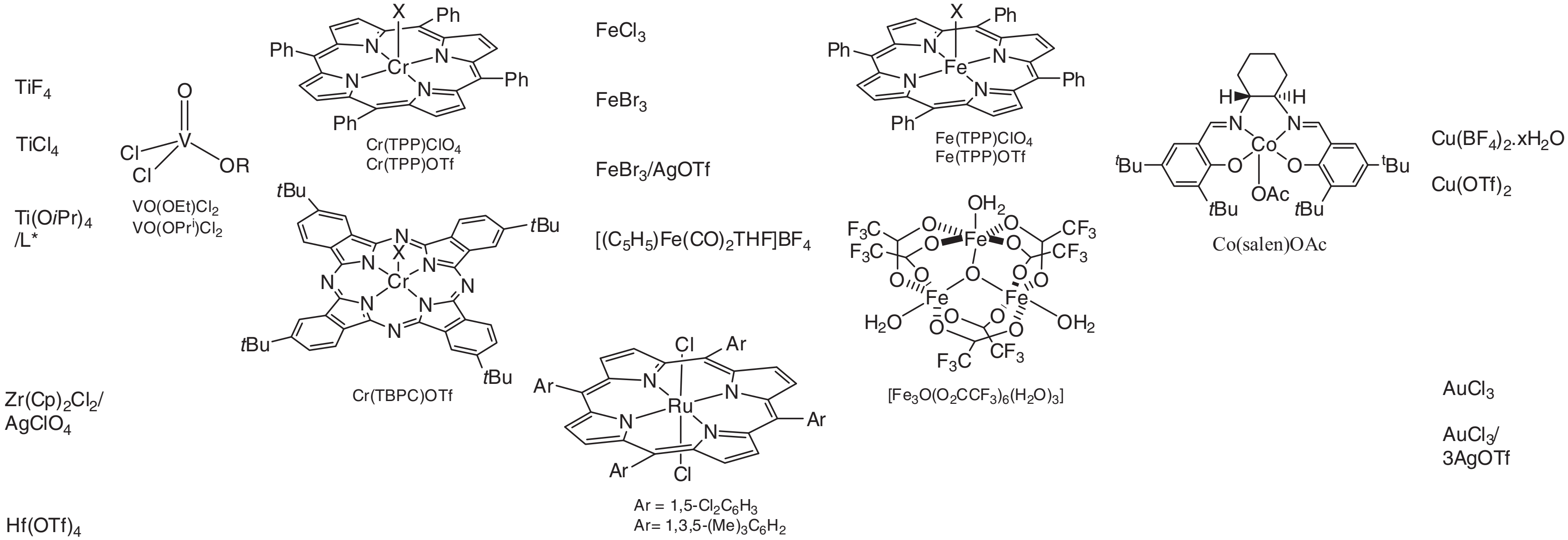
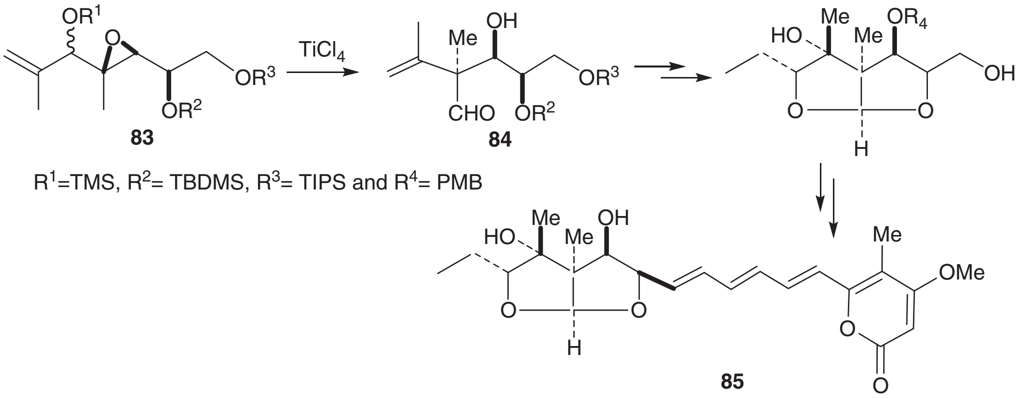


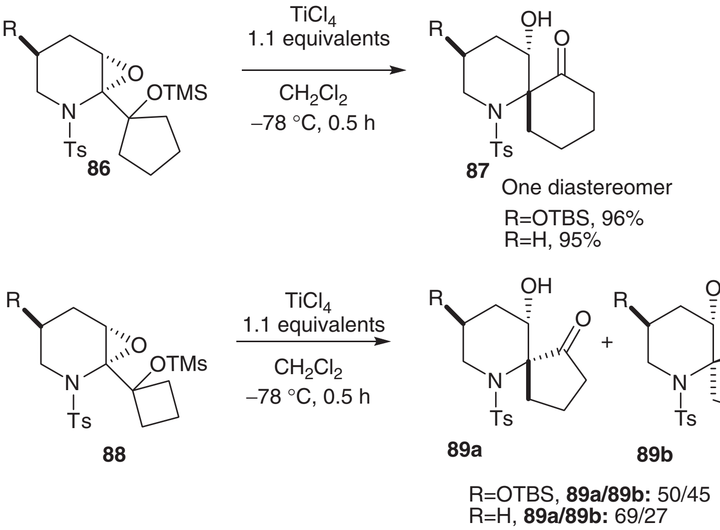
Figure 1 Transition metal-based Lewis acid used in epoxide rearrangement.

This stereoselective 1,2-rearrangement reaction of epoxy-silyl ether **83** catalyzed by $TiCl_4$ is applied in the key step of the total synthesis of (+)-asteltoxin **85** (Scheme 33).[74]



Scheme 33

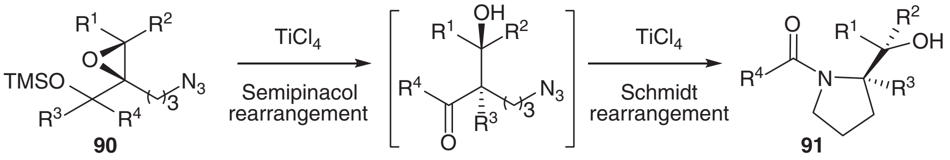
Diastereoselective construction of quaternary stereocenters in the case of 1-azaspirocyclic cycloalkanones can be achieved using a siloxy-epoxide semipinacol ring expansion process (Scheme 34).[75]



Scheme 34

Cyclopentanolsilyl ethers **86** expand to form cyclohexanones **87** in high yield with complete diastereoselectivity via a 1,2-*anti* alkyl shift. In contrast, for cyclobutanol silyl ethers **88**, the expansion occurs via either a 1,2-*anti*- or 1,2-*syn* alkyl shift.

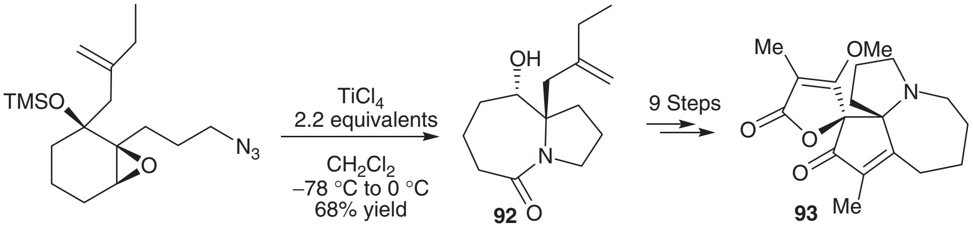
Tandem semipinacol/Aubé's-type Schmidt intramolecular rearrangement of azido α-siloxy epoxides **90** catalyzed by $TiCl_4$ allow also the diastereoselective construction of quaternary stereocenters, leading to various monocyclic amides **91** (Scheme 35) and bi- and tricyclic lactams bearing aza-quaternary carbon units.[76]



Scheme 35

In Scheme 35, the α-siloxy-epoxy-azide substrate **90** undergoes a Lewis acid-promoted semipinacol rearrangement to generate a keto-azide intermediate through a carbon–carbon 1,2-migration, which successively undergoes a Schmidt rearrangement through a carbon–nitrogen migration to give the monocyclic amide **91**.

As an applicable example, a bicyclic lactam **92** is obtained in a key strategy level step for the total synthesis of stemonamine **93** (Scheme 36).[77]



Scheme 36

In addition, some key tricyclic aza-quaternary skeletons incorporated in many important alkaloids, such as cephalotaxine, erythrinan, and homoerythrinan are constructed by this methodology.[76]

Finally, it is important to mention that $TiCl_4$ can sometimes be more effective than conventional acids (TsOH, BF_3) or certain reactions. In the case of epoxy allylsilanes (cf. part 3.1, Scheme 25), the stereoselectivity of the tandem rearrangement-cyclization process leading to methylenecyclohexanol compounds depends on the nature of the catalyst. $TiCl_4$, a bulkier Lewis acid than $BF_3.\bullet Et_2O$, leads to a better diastereoselectivity in favor of the 1,2-trans isomer, as shown in the example reported in Scheme 2.[78]

For the rearrangement of epoxy alkynes into functionalized allenes (cf. part 2.1, Scheme 25, Scheme 4), $TiCl_4$ affords results similar to those of protic acids such as TsOH (10 mol%) but using lower catalyst loading (5 mol%).

Chiral titanium(IV) complexes can be also used for the enantioselective formation of quaternary carbon stereocenters.

A titanium isopropoxide/tartrate system is applied for tandem Katsuki–Sharpless asymmetric epoxidation and 1,2-rearrangement of cyclopropylidene alcohols **94** (Scheme 37).[79]

This tandem asymmetric epoxidation and ring expansion proceeds with the complete transfer of the chirality of the *in situ*-generated epoxy alcohol, and the observed stereoselectivity can be interpreted from a concerted *anti*-1,2-migration of the C–C bond of the cyclopropane ring to the epoxide moiety. This concise and highly efficient enantioselective approach to cyclobutanones **95** was applied by Fukumoto and coworkers for the total synthesis of both (+) and (–)-α-cuprarenones **96**, (+)debromoaplysin **97**, and (–)-aplysin **98** (Scheme 37).

The enantiomeric Ti-complex based on (*R*)-1,1′-bi-2-naphtol (BINOL), generated *in situ* from $Ti(O^iPr)_4$ and the chiral ligand, is applied to the kinetic resolution of a range of tertiary α-hydroxyl epoxides **99** via the asymmetric semipinacol rearrangement, affording α-quaternary *β*-hydroxy ketones **100** in 24–61% *ee* and tertiary α-hydroxy epoxides in 51–94% *ee*[80] (Scheme 38).

A chiral $Ti(O^iPr)_4$ catalyst is also used for the resolution of racemic enol ester **101**. High-resolution efficiency was observed with the BINOL–Ti catalyst for a number of cyclic systems, leading to both enantiomers of enriched α-acyloxy ketones **102** and enol ester epoxides (Scheme 39).[81]

Corey[82] used a cationic cyclization in the synthesis of neotripterifordine, a powerful anti-HIV drug (Scheme 40). In the presence of $TiCl_4$ as catalyst, the optically pure precursor **103** undergoes a cationic cyclization following the opening of the epoxide. It follows the stereoselective creation of tricycle **104** with a *trans*-decalin substructure.

TiF_4 has been shown to be a viable catalyst for epoxide rearrangement. Pedro and colleagues[83] reported the skeletal rearrangement of 4,5-epoxy-9-trimethylsilyldecaline **104** as the key step in the total synthesis of (–)-aristolochene **106**, an eremophilane sesquiterpene that is a component of the defensive secretion of some termites (Scheme 41).

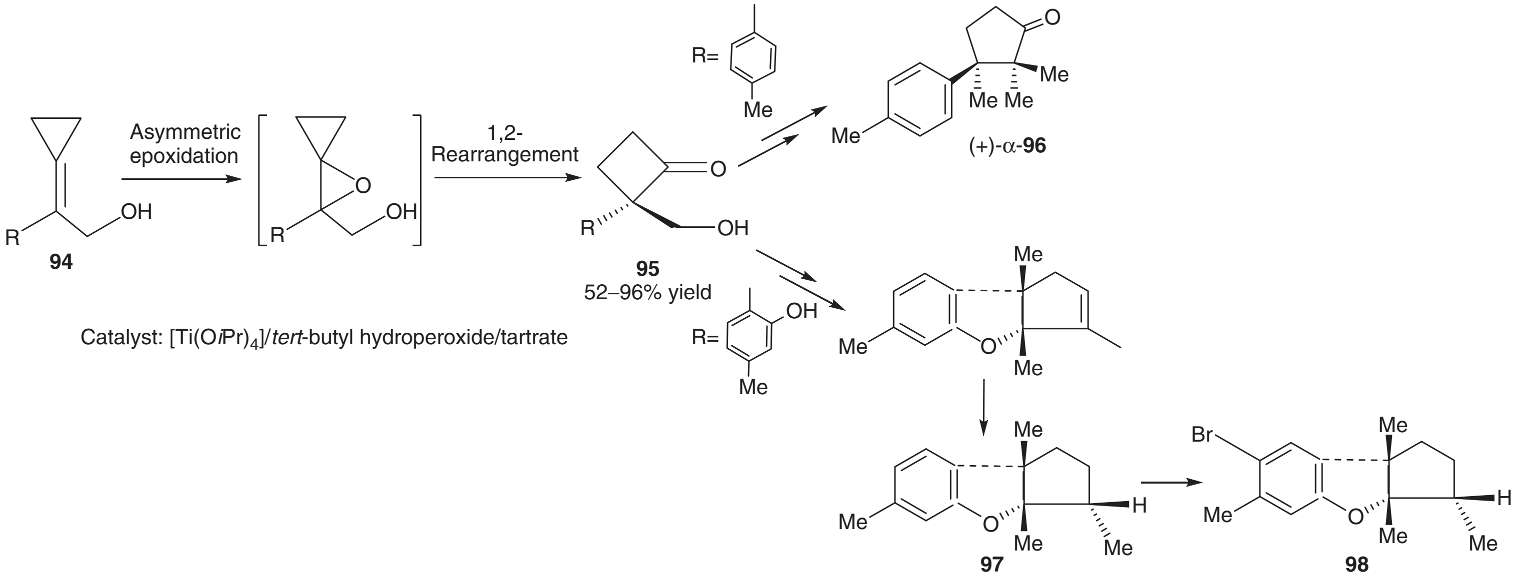
In this case, TiF_4 is preferred to $BF_3\bullet Et_2O$ to avoid the migration of the isopropylidene double bond.

Zr-based Lewis acids such as cationic zirconocene are efficient in the rearrangement of various epoxy esters into 2,7,8-trioxabicyclo[3.2.1]octanes (ABO-esters) (Scheme 42). The cationic catalyst is prepared *in situ* from Cp_2ZrCl_2 and catalytic amounts of $AgClO_4$.[84]

Acid-sensitive α-amino and α-hydroxy acid derivatives are converted in high yield using this protocol. In addition, a convenient and general asymmetric synthesis of bicyclic orthoesters is achieved starting from chiral epoxy alcohol derivatives.[85]

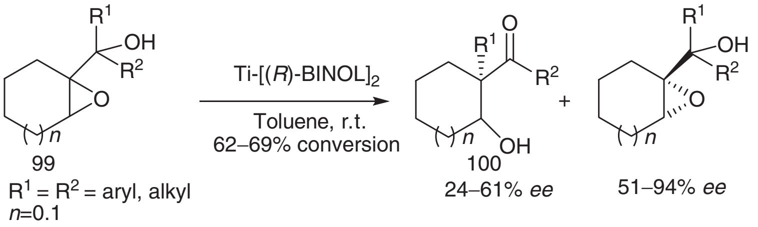
Product formation can be explained by the irreversible formation of the cationic zirconocene, followed by neighboring group-assisted Lewis acid-induced opening of the epoxide to give the dialkoxycarbenium ion. Irreversible S_N2 attack of the zirconocene-complexed alkoxide at C_2 leads to the 2,7,8-trioxabicyclo[3.2.1]octane skeleton (Scheme 43).

This epoxy ester-orthoester rearrangement provides an efficient strategy for the synthesis of the mushroom components (*S*)-γ-hydroxyleucine lactone and (*S*)-α-vinylglycine.[85]

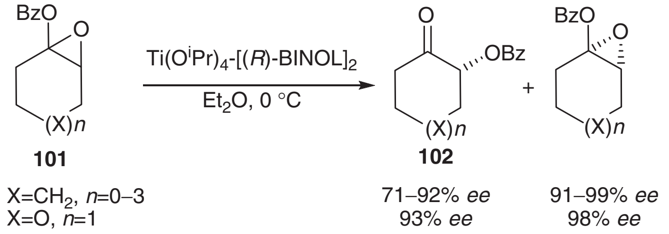


Catalyst: [Ti(O*i*Pr)$_4$]/*tert*-butyl hydroperoxide/tartrate

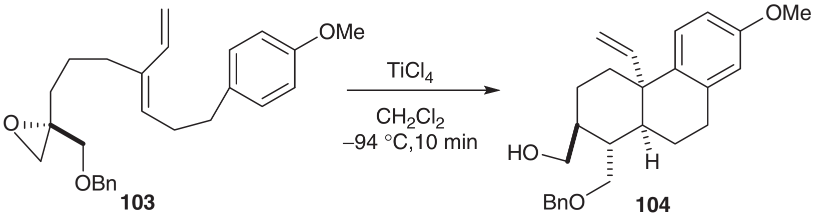
Scheme 37



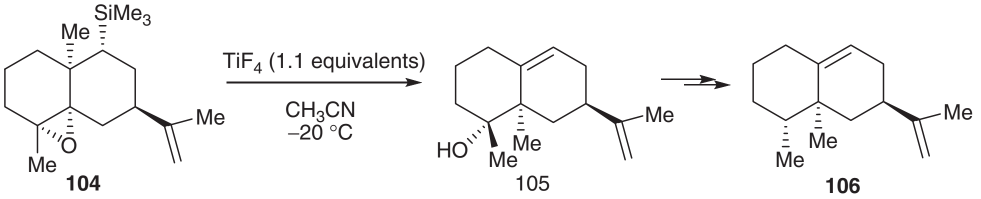
Scheme 38



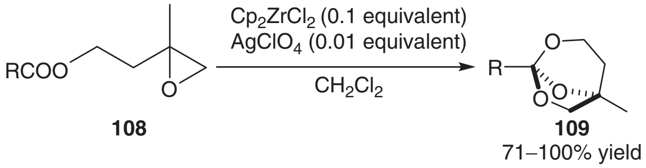
Scheme 39



Scheme 40

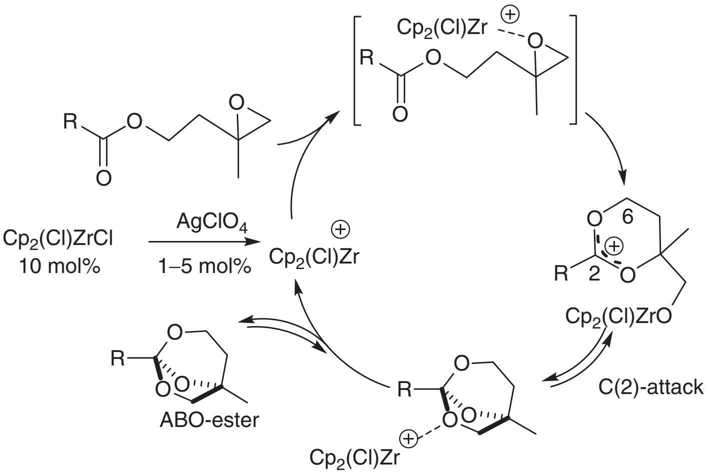


Scheme 41



Scheme 42

Hafnium(IV)-centered Lewis acid usage is limited in organic chemistry because of its lower availability and its similarity to zirconium, but we can mention the classical epoxide rearrangement, catalyzed by $Hf(OTf)_4$ via the hydride 1,2-migration pathway, reported for the synthesis of 1,2-hydroxy-dibenzochrysene.[86]



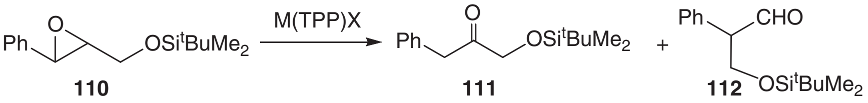
Scheme 43

3.15.4.2 Vanadium

Very few works report the use of vanadium for rearrangement of epoxides. Llama[87] studied the rearrangement of various model epoxides with high-valence vanadium complexes, such as $VO(OEt)Cl_2$ and $VO(OPr^i)Cl_2$. Monosubstituted and 1,1′-disubstituted epoxides were isomerized by ring opening and hydrogen migration to selectively produce the corresponding aldehydes. In addition, high regioselectivity of the ring opening is obtained for 4,4′-disubstituted and 1,1,2-trisubstituted epoxides, leading to corresponding ketones via a hydrogen shift.

3.15.4.3 Chromium

Cr(III)-based Lewis acids such as metalloporphyrin complexes,[88] $Cr(TPP)ClO_4$, and Cr(TPP)OTf, as well as the metallophthalocyanine complex,[89] Cr(TBPC)OTf, have been studied by Suda for the catalytic rearrangement of 2,3-epoxy-silyl ethers **110** into aldehydes via alkyl migration (Scheme 44).



Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	**111**	**112**
$Cr(TPP)ClO_4$ (2)	$Cl(CH_2)_2Cl$	83	2	11	87
Cr(TPP)OTf (1)	$Cl(CH_2)_2Cl$	83	1	0	97
$Fe(TPP)ClO_4$ (0.5)	$Cl(CH_2)_2Cl$	83	0.5	65	32
$Fe(TPP)ClO_4$ (0.5)	Dioxane	100	0.5	>99	0

Scheme 44

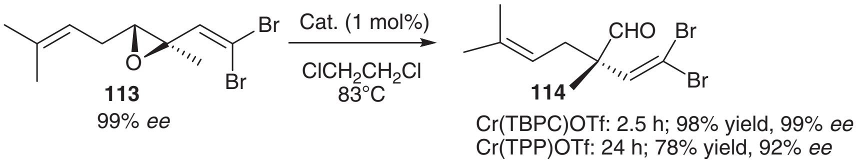
Cr(TPP)OTf in low catalyst loading proved to be more efficient than $Cr(TPP)ClO_4$ in terms of activity and selectivity (Scheme 44) and was successfully applied to a variety of epoxides such as trialkyl-substituted epoxides, spiroepoxides, and bicyclic epoxides, furnishing the corresponding aldehydes in good to high yields (56–99%).

In addition, stereoselective rearrangements of various optically active epoxide silyl ethers or vinyl epoxides could be achieved in high enantioselectivities (93–99% *ee*), leading to the corresponding aldehydes. One example is reported in Scheme 45.

Again, Cr(TBPC)OTf proved to be a more regio- and stereoselective catalyst for the rearrangement of epoxides to aldehydes than Cr(TPP)OTf (Scheme 45). Moreover, its facile recovery and reusability (five times without loss of *ee* and yield) as well as its faster reaction rate make it an ideal catalyst.

3.15.4.4 Iron

Iron is an attractive and often advantageous alternative to other transition metals in the field of catalysis, given its ready availability, low price, and environment-friendly character. Fe(III)-based Lewis acids have been known for a long time to be



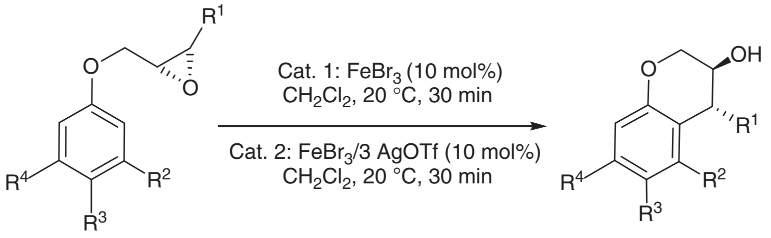
113
99% *ee*

114
Cr(TBPC)OTf: 2.5 h; 98% yield, 99% *ee*
Cr(TPP)OTf: 24 h; 78% yield, 92% *ee*

Scheme 45

efficient catalysts in the rearrangement of epoxides activated by adjacent aryl, vinyl, silyl, or carbonyl substituents.[90] In extension of this work, Liang studied the rearrangement of epoxy alkynes into functionalized allenes (cf. part 2.1, Scheme 4) by $FeCl_3$ and observed similar results than with protic acids such as TsOH (10 mol%), but with lower catalyst loading (5 mol%).[6]

In addition, Pericas's research group reported in 2008 the rearrangement/cyclization of arenes with tethered epoxide cycloalkylation efficiently catalyzed by $FeBr_3$, or a $FeBr_3$–3AgOTf system.[91] Examples of rearrangement/cyclization of aryl and benzyl glycidyl ethers **115** into 3-chromanols **116** are reported in Scheme 46.

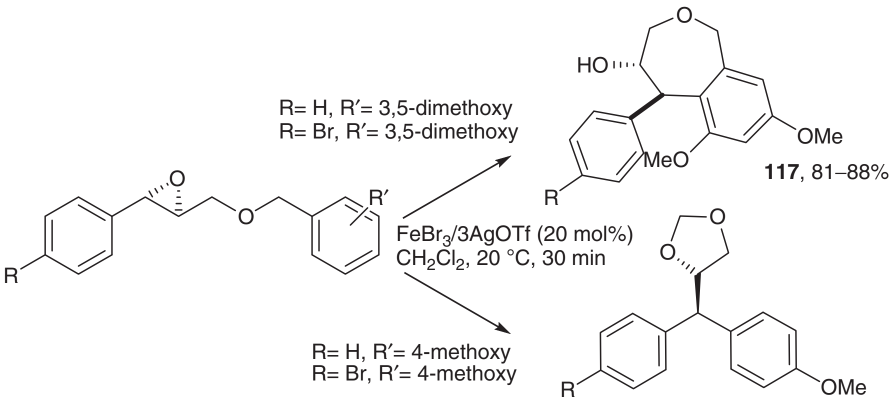


115 **116**

R^1	R^2	R^3	R^4	Cat.	Yield
Ph	OMe	H	OMe	1	92
Ph	Me	H	Me	1	88
Ph	Me	H	Me	2	97
Ph	H	*t*-Bu	H	1	95
Ph	H	*t*-Bu	H	2	99

Scheme 46

The $FeBr_3$–3AgOTf system appears to be the catalyst of choice for this set of stereospecific processes, leading to higher yields than $FeBr_3$ and the more conventional BF_3 Lewis acid (cf. part 3.1). Intramolecular cycloalkylation has been applied to the synthesis of tetrahydrobenzooxepin **117** and dioxolane **118** derivatives (Scheme 47).



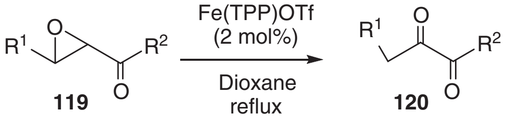
117, 81–88%

118, 82–96%

Scheme 47

Fe(III)–porphyrin complexes, such as Fe(TPP)ClO_4 and Fe(TPP)OTf, have been reported by Suda et al. as useful Lewis acid catalysts for the ring-opening rearrangement reaction of monoalkyl-substituted epoxides into aldehydes[92] and for the rearrangement of 2,3-epoxy-silyl ethers into ketone.[93] But, contrary to the Cr(III)–porphyrin complex, Fe(III)–porphyrin complexes preferentially promote epoxide rearrangement via hydrogen migration. In the case of 2,3-epoxy-silyl ethers, best results are obtained with a Fe(TPP)OTf-dioxane system, leading to higher yields and almost complete regioselectivity (Scheme 44).

For α,β-epoxy ketones **119**, which are known to rearrange into 1,2- and/or 1,3-diketones with acids, Fe(TPP)OTf at a low catalyst loading (2%)[94] also induces regioselective hydrogen migration, leading to 1,2-diketones **120** in high isolated yield (85–95%). This catalytic version of Lewis acid-mediated rearrangement of α,β-epoxy ketones into 1,2-diketones is applicable to a variety of epoxy ketones (Scheme 48).



R^1	R^2	Time (h)	Yield (%)
$CH_3(CH_2)_5$	CH_3	1·5	95
$CH_3(CH_2)_8$	CH_3	1·5	88
$CH_2{=}CH(CH_2)_8$	CH_3	2	92
$Ph(CH_2)_2$	CH_3	1·5	87
Ph	CH_3	0·25	85

Scheme 48

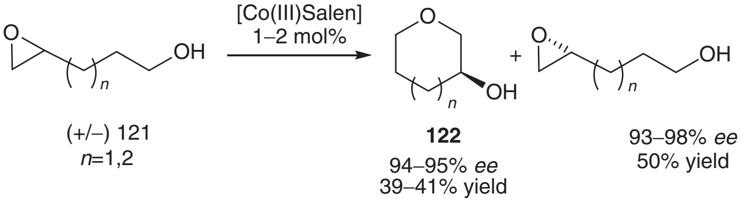
For these reactions, conventional Lewis acids such as $BF_3{\bullet}Et_2O$, $TiCl_4$, and $MgBr_2{\bullet}OEt_2$ are unsuccessful.

It is worth mentioning that Ru(IV)–porphyrin complexes catalyzed the selective conversion of terminal alkenes and dienes into aldehydes through epoxidation rearrangement, probably via hydrogen migration.[95]

Other iron-based Lewis acids based, such as $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(THF)]BF_4$[96] and $[Fe_3O(O_2CCF_3)_6(H_2O)_3]$,[97] a mixed-valent triiron (III, III, II) complex, selectively catalyze the isomerization of aryl-substituted epoxides to aldehydes in excellent yield. $[Fe_3O(O_2CCF_3)_6(H_2O)_3]$ is more active, working with only 2 mol% of catalyst at room temperature for 3 h, compared to $[(\eta^5\text{-}C_5H_5)Fe(CO)_2(THF)]BF_4$, for which 10 mol% of catalyst and a longer time reaction is required to reach a complete reaction.

3.15.4.5 Cobalt/Iridium

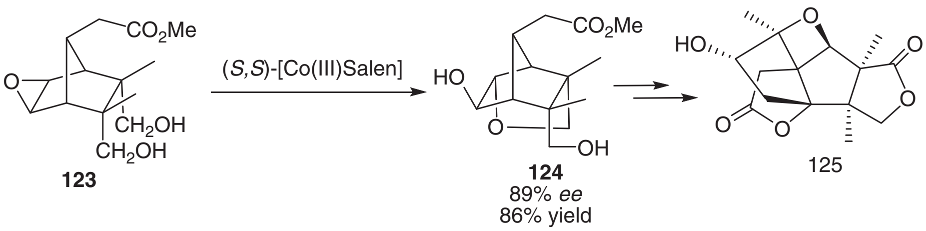
Jacobsen reported that chiral [Co(salen)OAc] works as a useful Lewis acid catalyst for intramolecular asymmetric epoxide ring-opening/cyclization reactions.[98] This methodology can be effectively applied with exceptional regio- and enantiocontrol to the kinetic resolution of racemic terminal epoxy alcohols **121** (Scheme 49) as well as to the intramolecular desymmetrization of meso-epoxy substrates, leading to the synthesis of novel cyclic and bicyclic ethers, ranging from three- to seven-membered rings in good yields and high enantiopurity.[98]



Scheme 49

An elegant application of this protocol has recently been reported, which relied on the desymmetrization of a meso-epoxide to produce a key intermediate for the synthesis of merrilactone A (Scheme 50).[99]

$IrCl_3$ is also an effective and regioselective catalyst for the Meinwald rearrangement of epoxides. Rearrangement of model epoxides such as styrene oxide, methylstyrene oxide, or stilbene oxide selectively and quantitatively yield the corresponding aldehyde.[100] This alternative Lewis acid for the Meinwald rearrangement is interesting because the hydrated iridium complex is very stable and active, as the reaction can be run with 1% molar ratio of catalyst under mild conditions (no inert atmosphere or high temperature is required).

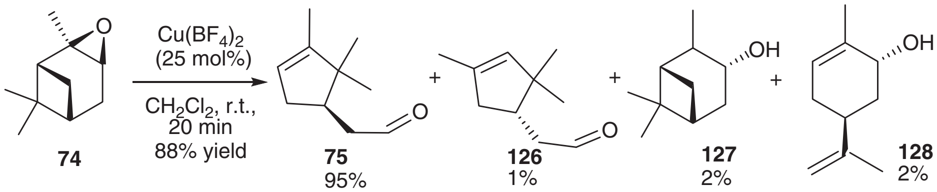


Scheme 50

3.15.4.6 Copper/Gold

Cu-based Lewis acids have been widely used in organic syntheses. Among the Cu(II) salts commercially available, [Cu(BF$_4$)$_2$] nH$_2$O[101–103] and Cu(OTf)$_2$[102] are the most popular reagents for epoxide rearrangement. They efficiently catalyze the rearrangement of a range of epoxides to carbonyl compounds, aldehydes, or ketones depending on the starting epoxides, in high yields under mild reaction conditions. The low toxicity and ease of handling of this reagent make it an attractive alternative to the more corrosive or costly Lewis acids frequently employed.

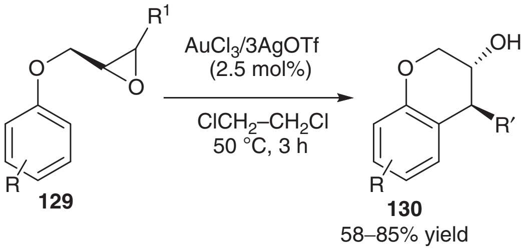
For example, α-pinene epoxide **74** undergoes a highly efficient Meinwald rearrangement in the presence of catalytic quantities of [Cu(BF$_4$)$_2$] nH$_2$O to give campholenic aldehyde **75** in high yield and excellent selectivity (Scheme 51).[102]



Scheme 51

Au(III) salts promote the rearrangement of epoxides. AuCl$_3$ Lewis acid has been reported to promote the skeletal rearrangement of epoxy alkynes into functionalized allenes via a semipinacol-type rearrangement (cf. part 2.1, Scheme 4). The reaction required 5 mol% of catalyst, as with the other transition metal-based Lewis acids such as FeCl$_3$ or TiCl$_4$.[6]

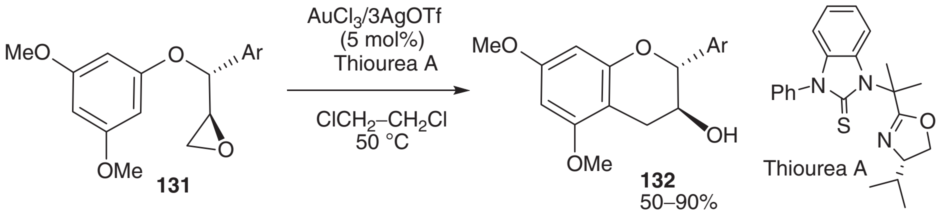
In 2004, He's research group reported that AuCl$_3$–3AgOTf can catalyze the cycloalkylation of electron-rich arenes with tethered epoxides **129** to give 3-chromanol-type structures **130** in moderate to good yields via an endo cycloaddition reaction (Scheme 52).[104] The reaction shows high diastereoselectivity in *trans* products.



Scheme 52

In addition, the stereospecific cycloalkylation of enantiopure substrates with an inversion of configuration of the carbon chiral atom linked to the aryl ring has been reported. The presence of silver salts (AgOTf) as cocatalyst is required to achieve good yields and to lower catalyst loading.

Using a thiourea ligand to moderate the Lewis acidity of AuCl$_3$–AgOTf, Chen and Yang applied the Au-catalyzed cycloalkylation of aryl epoxides **131** to generate a library of catachin-derived natural products[105] (Scheme 53).



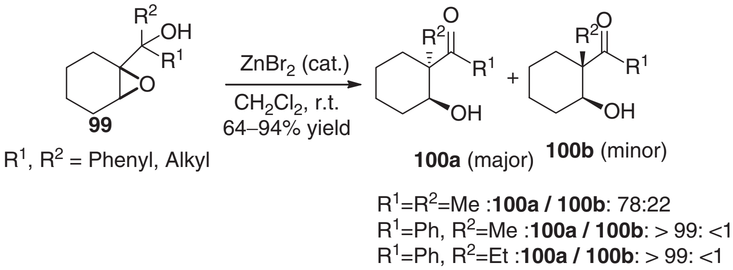
Scheme 53

3.15.5 Other Metals

3.15.5.1 Zinc

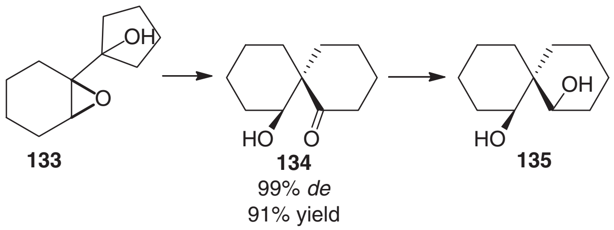
The mild Lewis acidity of zinc-based Lewis acid promotes several synthetic reactions such as the rearrangement of unprotected α-hydroxy epoxides.

Zn(II) salts such as $ZnCl_2$[106] and $ZnBr_2$[107,108] prove to be facile and efficient catalysts (2–8 mol%) for the construction of chiral quaternary carbon through a stereoselective semipinacol rearrangement of α-hydroxy epoxides **99** (Scheme 54).



Scheme 54

Compared to other Lewis acids used for this type of rearrangement, Zn(II) Lewis acid has a double advantage: (1) the direct use of α-hydroxy epoxides and (2) the smaller amount of catalyst needed. As an example of its application, important diastereomerically enriched spirocyclic diol ligands **135**, which are useful intermediates for the preparation of effective chiral ligands for hydrogenation reactions, have been synthesized via this rearrangement, followed by reduction of the spirocyclic β-hydroxy ketones **134** obtained with appropriate hydride reagents (Scheme 55).[107]



Scheme 55

On the other hand, Chapuis described the preparation of analogs of campholenal **75**, an important building block for sandalwood-like odorants, by catalytic $ZnBr_2$ isomerization of α-pinene epoxide derivatives.[108]

3.15.5.2 Rare Earths

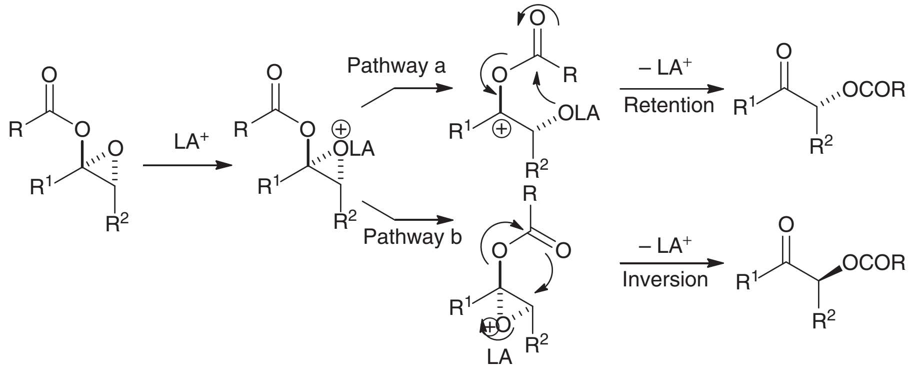
Rare earth salts have been shown to be viable alternatives to more conventional Lewis acids for a number of transformations, including a variety of epoxide-opening reactions. Different rare earth salts have been used as Lewis acids in epoxide rearrangement (Figure 2). The practical advantages of such salts are their stability to moisture, low toxicity, ease of handling, recyclable nature, and ability to function as catalysts.

$Sc(OTf)_3$	SmI_2	$ErCl_3$	$YbCl_3$
$La(OTf)_3$	$SmIO$	$Er(OTf)_3$	$Yb(OTf)_3$
	t-$BuOSmI_2$		

Figure 2 Rare earth Lewis acids used in epoxide rearrangement.

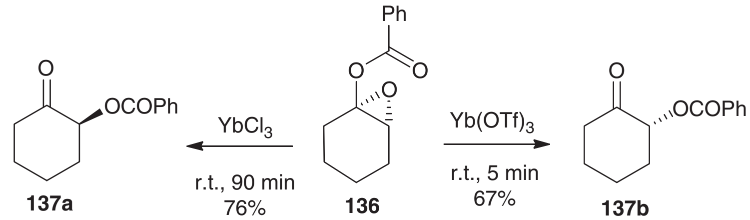
The first report by Kagan et al., in 1985, described the isomerization of terminal epoxides into ketones catalyzed by samarium salts.[109]

Later, Shi studied different rare earth salts such as $La(OTf)_3$, $ErCl_3$, $YbCl_3$, and $Yb(OTf)_3$ for the acid-catalyzed rearrangement of a series of enol ester epoxides, and the obtained results underscore the important role of the catalyst acidity.[5] Indeed, rearrangement occurs through two distinct pathways depending on the acidity of the catalyst: strong acids such as $Yb(OTf)_3$ favor retention of configuration, whereas weak acids like $YbCl_3$ favor inversion of configuration (Scheme 56).



Scheme 56

This dual pathway provides a flexible route to both enantiomers of α-acyloxy ketone from one enantiomer of an enol ester epoxide by a judicious choice of Lewis acid (Scheme 57).



137a
82% *ee*

136
92% *ee*

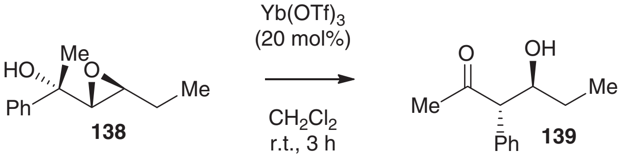
137b
66% *ee*

Scheme 57

However, better results in terms of activity and enantioselectivity have been reported using *p*-TsOH instead of $Yb(OTf)_3$.[5]

More recently, the use of $Yb(OTf)_3$ has been described to induce a tandem Payne/Meinwald rearrangement of a α-hydroxyspiro epoxide, leading to a cyclopentyl hydroxyketone as a single diastereoisomer in 60% yield (cf. part 2, Scheme 31).[110]

$Sc(OTf)_3$, $La(OTf)_3$, and $Yb(OTf)_3$ can also be used to catalyze the semipinacol rearrangement of homochiral epoxyalcohols with inversion of stereoselectivity at the site of the epoxide opening.[111] If all these Lewis acids induce the migration of the aryl group to afford the corresponding aryl-β-hydroxy ketone, the rates of the reaction decrease in the order $Yb(OTf)_3 > Sc(OTf)_3 > La(OTf)_3$. One example is reported in Scheme 58.



138

139

99% *de*
99% yield

Scheme 58

This efficient stereoselective methodology has been extended by the same authors to other epoxyalcohols.[112]

The use of $Er(OTf)_3$ can also be mentioned for the rearrangement of aromatic and aliphatic epoxides into aldehydes and ketones[113] and the application of $Sc(OTf)_3$ for the regio- and stereoselective synthesis of α-D-gluco-, α-L-ido-, and α-L-altropyranosiduronic acids from Δ^4-uronates through an acid-catalyzed rearrangement step via a hydrogen shift to afford α-L-C4 keto-pyranosides as key intermediates.[114]

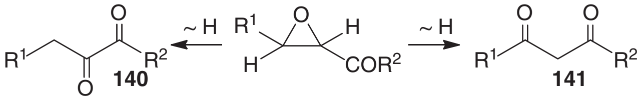
3.15.6 Solid Catalysts

The development of heterogeneous catalysts provides an alternative and highly promising strategy to overcome many limitations associated with the use of Brønsted or Lewis acid catalysts in solution such as ease of work-up, facile catalyst recovery, and recycling. In the context of sustainable development ('green chemistry'), the design of heterogeneous catalyts is an important issue for the development of environmentally friendly epoxide-rearrangement processes. Different types of solid Brønsted and Lewis acids have been studied for these catalyzed reactions, such as metal oxides (e.g., silica and alumina), metal sulfates and precipitated phosphates, protonated resin, zeolites, clay, and mesoporous materials. These heterogeneous catalysts have been studied mainly for the rearrangement of model epoxides such as aliphatic and cyclic oxides. Some interesting examples involve the rearrangement of terpenes. The regioselectivities observed for these rearrangements are strongly dependent on the type of catalyst, the distribution of catalytic sites (Lewis and/or Brønsted acids), and the pore structure, due to the occurrence of several consecutive reactions of the chemisorbed epoxide.

3.15.6.1 Metal Oxides

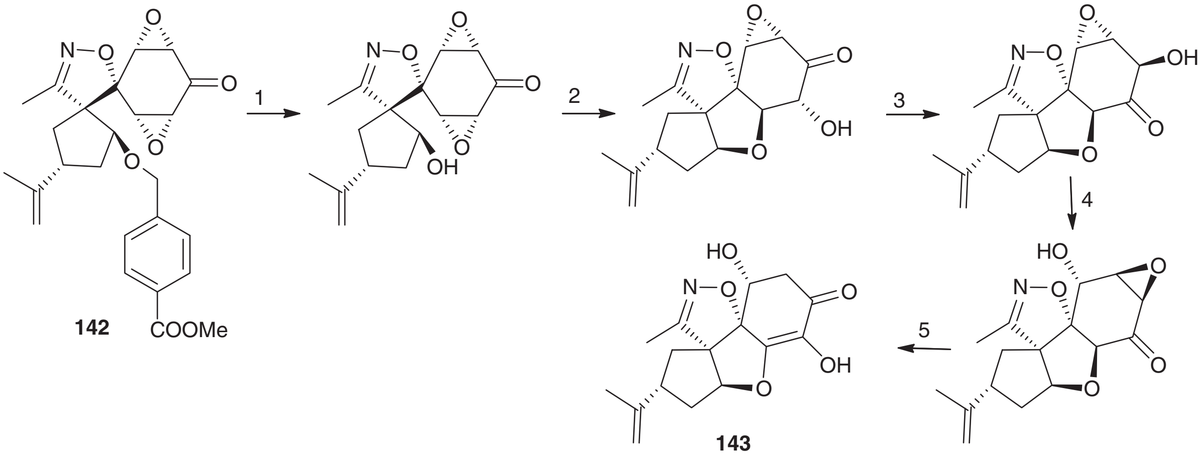
Metal oxides (silica and alumina) are well known to promote the rearrangement of epoxides. Their use has been extended to α-epoxyketones[115] and cyclic α,β-epoxy ketones (i.e., isophorone epoxide, 2,3-epoxy-3-methylcyclohexan-1-one, and pulegone epoxide).[116] The rearrangement of cyclic α,β-epoxy ketones toward α-ketoaldehydes and diketones has been used for the preparation of pharmaceuticals, synthetic food flavorings, and perfumes.

For α-epoxyketones such as chalcone epoxides, the course of the rearrangement is governed by two main factors: the direction of the ring opening and the relative migratory aptitudes of the substituents (Scheme 59). With silica as the catalyst, the rearrangement involves the migration of the proton to selectively form 1,3-diphenylpropane-1,2-diones **140** in high yield (95–98%), whereas acid induces migration of the benzoyl group to lead 1,3-diketones **141**.



Scheme 59

Neef[117] described an unusual rearrangement of the quinol bis-epoxide **142** by microwave-assisted thermolysis on silica gel (Scheme 60).



Scheme 60

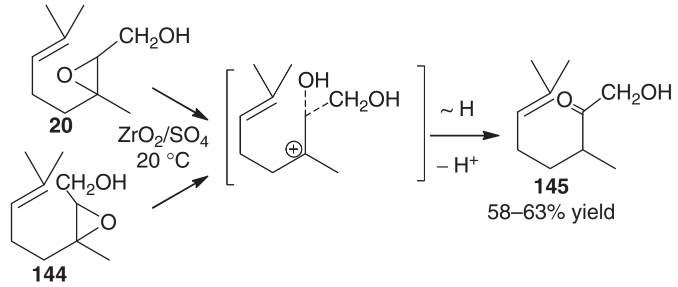
The reaction occurs by a cascade of reactions: (1) benzylic ether cleavage, (2) S_N2 epoxide opening, (3) ene–diol tautomerization, (4) Payne-rearrangement, and (5) 1,2-H shift to lead to the formation of the spirocyclohexenone isoxazoline **143**, which is a pharmacophoric group of considerable interest.

Modified silica, such as SiO_2–Al_2O_3 or SiO_2–TiO_2, is known to have strong acid sites on the surface. These systems promote the epoxide rearrangement of cyclic epoxides such as epoxycyclooctane and epoxycyclododecane, but in all cases, a mixture of compounds including ring-opening products has been obtained.[118]

3.15.6.2 Metal Sulfates and Precipitated Phosphates

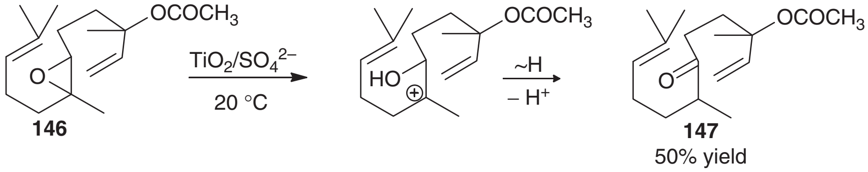
The use of different metal sulfates, $FeSO_4$, $NiSO_4$, and solid H_3PO_4, was also reported to promote rearrangement of epoxides. The rearrangement leads to a mixture of products in the case of epoxycyclooctane and epoxycyclododecane,[118] as described with SiO_2–Al_2O_3 and SiO_2–TiO_2, as well as in the case of 1,2-epoxyoctane.[119]

Sulphated zirconia, ZrO_2–SO_4, was used as a solid Brønsted acid catalyst for the rearrangement of acyclic terpenoid.[119,120] In the case of 2,3-epoxygeraniol **20** and 2,3-epoxynerol **144**, the rearrangement mainly affords the corresponding ketone **145** at room temperature via epoxy ring opening followed by 1,2-hydride shift (Scheme 61).[120]



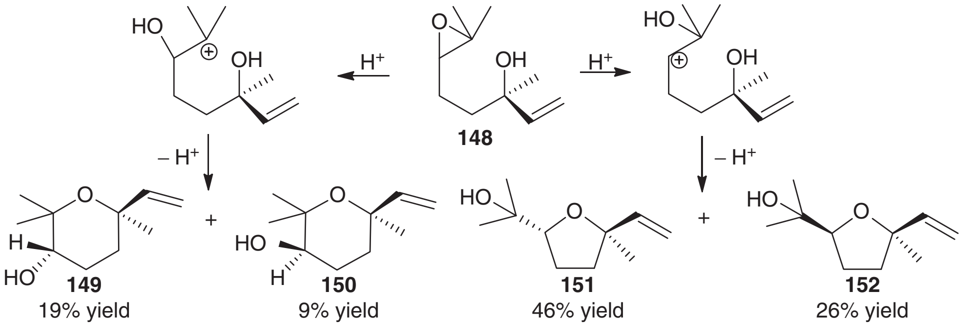
Scheme 61

A similar rearrangement is observed for 6,7-epoxide of cis-nerolidyl acetate **146** with the TiO_2/SO_4 catalyst (Scheme 62).[121]



Scheme 62

In contrast, 6,7-epoxylinalool **148** undergoes epoxy ring opening and heterocyclization over the ZrO_2/SO_4 catalyst, affording a mixture of compounds, **149–152** (Scheme 63).[121]

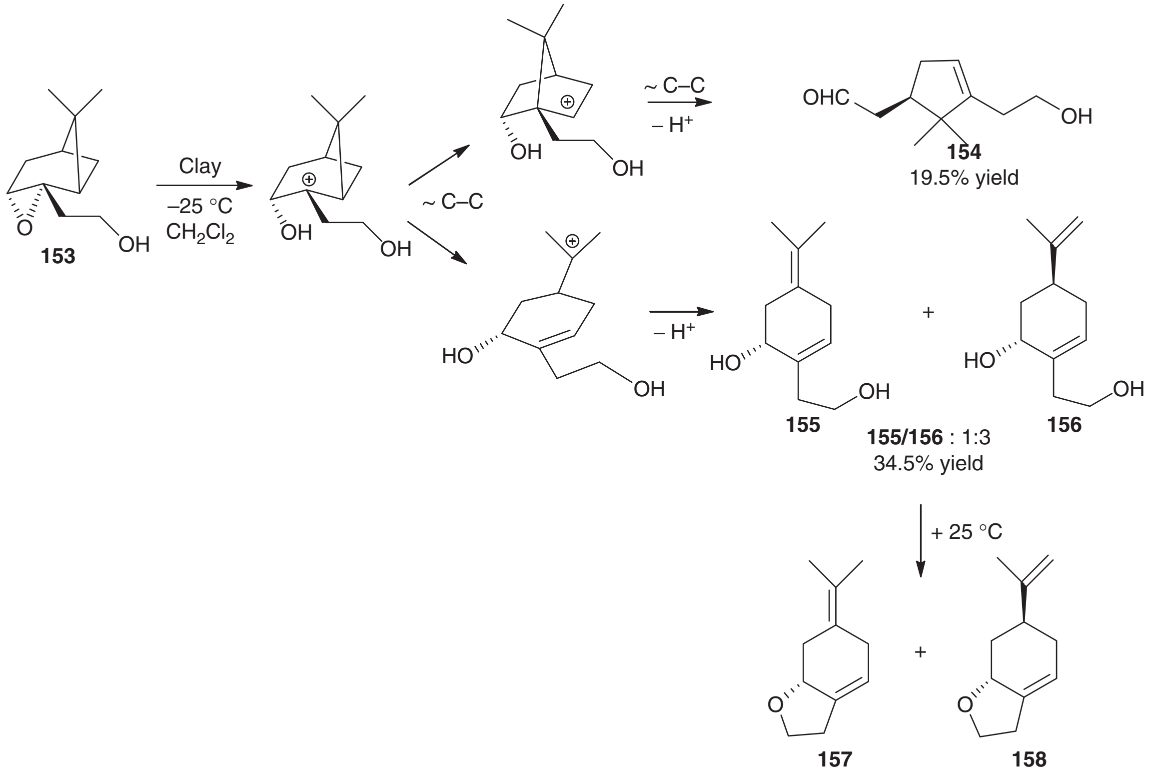


Scheme 63

3.15.6.3 Clays

There are many varieties of clay. Some of them have been successfully used for the rearrangement of epoxides.

Askanite–bentonite clay, a natural montmorillonite clay, catalyzes the skeletal rearrangement of cyclic terpenoids such as (*R*)-nopol oxide[122] and (–)-myrtenal epoxide.[123] (*R*)-nopol oxide **153** is converted into a variety of products whose composition and ratio depend on the temperature (Scheme 64). At -25 °C, the major isomerization products are hydroxyl aldehyde **154**, analogous to campholenic aldehyde, and diols possessing a *p*-menthane skeleton **155**, **156**; the last two are transformed at room temperature into bicyclic ethers **157**, **158**.



Scheme 64

The transformation of (–)-myrtenal epoxide **159** over askanite–bentonite clay involves the rearrangement of the pinane skeleton, leading to optically active dialdehyde **160** (an analog of campholenic aldehyde), aldehydes having a *p*-menthane skeleton **161–162**, and an unusual optically active bicyclic aldehyde **163–164** (Scheme 65).

Montmorillonite K10, the synthetic analog of askanite–bentonite clay, catalyzes the rearrangement of cyclic α,β-epoxy ketones, such as isophorone epoxide and pulegone epoxide.[124] Rearrangement of pulegone epoxide **165** leads to 1,3-dione **166** as a major product by preferential epoxide ring opening at the β-carbon atom with subsequent 1,2-acyl migration.

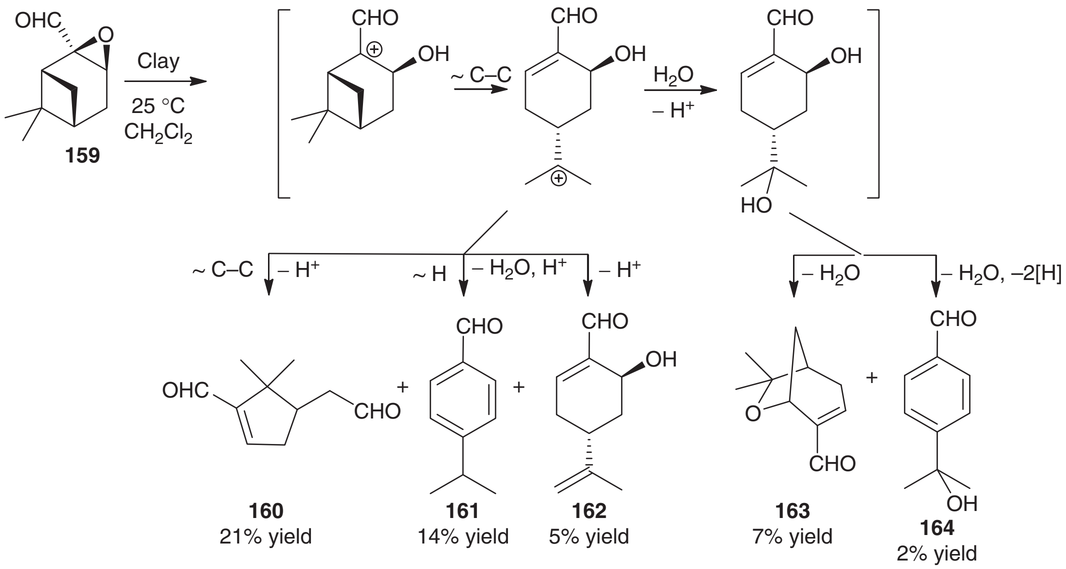
In the case of isophorone epoxide **168**, a mixture of 1,2-dione **169** and keto aldehyde **170** resulting from a hydrogen migration and an acyl migration, respectively, is obtained. From an industrial standpoint, the desired compound is the 2-formyl-2,4,4-trimethylcyclopentanone **170** because it is a useful intermediate in perfumes and synthetic flavor production.

Finally, it is interesting to note that a natural palygorskite acid-activated clay has been identified as an excellent catalytic material for promoting a facile 1,2 proton migration of chalcone epoxide to yield 1,3-diphenyl-1,3-propanedione **141**, in contrast to silica, which forms 1,2-diketone (Scheme 59).[125]

3.15.6.4 Zeolites

Zeolites are microporous materials with a well-defined pore system that makes possible the control of product distribution according to shape-selectivity effects. Likewise, depending on the type of zeolite, the acidic properties of the catalyst can be adjusted and varied according to the requirements needed in each reaction.

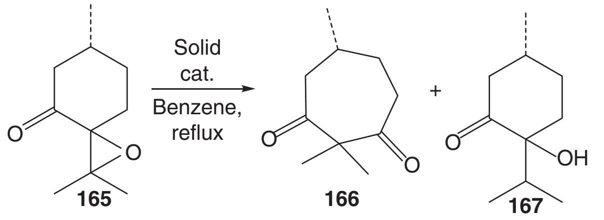
Mordenite, one of the zeolites catalogued as a strong acid zeolite, has been used for the isomerization of styrene epoxide to phenylacetaldehyde.[126] High selectivities toward aldehydes have been obtained in the isomerization of styrene epoxide and



Scheme 65

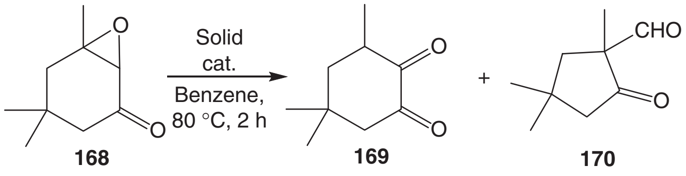
derivatives over various Brønsted acidic zeolites such as HY (Si/Al), H-beta(Si/Al), and H-offretite.[127] Over these various zeolites, the rearrangement 1,2-epoxyoctane, a molecule representative of aliphatic bulky epoxides, gave octanal as the main product along with other condensation products. ZSM-5 zeolite was also reported as an efficient catalyst in terms of activity and selectivity for 1,2-epoxyoctane rearrangement.[119]

H-mordenite, H-beta, and HM Brønsted zeolites catalyze the rearrangement of various cyclic α,β-epoxy ketones: pulegone epoxide (Scheme 66) and isophorone epoxide (Scheme 67), as well as piperitone epoxide and 2,3-epoxy-3-methylcyclohexan-1-one.[124] All these compounds except pulegone epoxide lead to α-formyl ketones as major products (Scheme 66).[124] The rearrangement of isophorone epoxide **168** to keto aldehyde **170** can be carried out in a discontinuous liquid-phase batch reactor as well as in a continuous vapor-phase fixed-bed reactor over various Brønsted zeolitic materials (H-ZSM-5, H-BEA, H-US-Y, H-Fer, etc.) (Scheme 67).[128]



Catalyst	Time (h)	Conv. (%)	Selectivity (%)	
			166	**167**
Mont. K10	2	100	62	22
NaHY	20	97	67	29
HM	4	98	70	22
H-beta	2	100	78	6

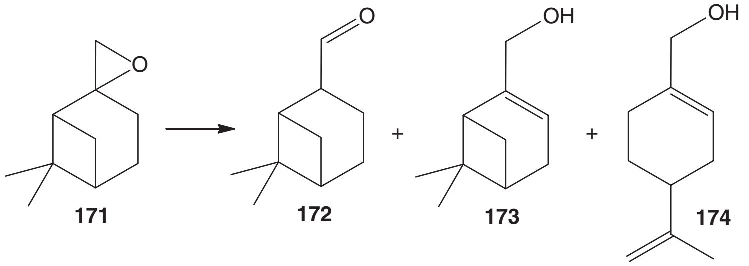
Scheme 66



Catalyst	Conv. (%)	Selectivity (%)	
		169	**170**
Mont. K10	100	14	78
H-Mor	100	8	81
H-Beta	100	15	56
NaHY	63	18	67

Scheme 67

Beta zeolites, such as Zr-beta, Sn-beta, Ti-beta, Ta-beta, Nb-beta, Al-beta, and Ga-beta, have been identified as active and selective for epoxide rearrangement of β-pinene epoxide **171** to myrtanal **172** (Scheme 68).[129] Brønsted acidic zeolites Al-beta and Ga-beta were found to be less effective than Lewis acidic zeolites for this reaction. Zr-beta catalyst, which gives the best selectivity in myrtanal **172** (94%), can be reused several times in batch mode (nine cycles) and in a fixed-bed reactor (six cycles) without any leaching of the metal or crystal degradation.



	Catalyst	Time (h)	Conv. (%)	Product selectivity (%)		
				172	**173**	**174**
Beta zeolite	Zr-beta	2	98	94	0	1
	Sn-beta	2	98	89	2	2
	Ti-beta	2	74	86	2	2
	Nb-beta	2	38	70	7	7
	Ta-beta	2	36	72	7	5
	Al-beta	2	46	74	8	5
	Ga-beta	2	37	63	9	6
Mesoporous MCM-14	Sn-MCM-41	6	98	82	4	5
	Ti-MCM-41	6	98	49	13	7
	Zr-MCM-41	6	45	35	7	20
	Al-MCM-41	3	98	49	4	16
	Si-MCM-41	6	31	35	18	16

Scheme 68

As zeolites are microporous materials with small pore size, strong diffusional and steric hindrances usually occur when processing bulky molecules, and as a result, the activity of zeolites is mainly due to the active sites located on the external surface.

The external surface is a property of high relevance when the zeolite is intended to be used as a catalyst in reactions involving bulky compounds. A superior catalytic activity is found over nanoscale zeolites such as nanocrystalline ZSM-5 (~20–50 nm) for the rearrangement of 1,2-epoxyoctane, 2-methyl-2,3-epoxybutane, and isophorone epoxide due to facile accessibility of the epoxide molecules to the active sites in this catalyst.[130]

3.15.6.5 Mesoporous Materials

In contrast to zeolites, mesoporous materials have high surface areas and large mesopores that circumvent the diffusional problems present in zeolites. The possibility of incorporating metal into the silica walls means that these materials turn into solids with acid sites of medium strength, with potential applications as acid catalysts in the rearrangement of epoxides of bulky molecules.

Diverse Lewis acidic mesoporous molecular sieves, with pore diameter of approximately 3.5 nm (Sn-MCM-41, Ti-MCM-41, Zr-MCM-41, Al-MCM-41, Si-MCM-41, Sn-MCM-41), have been identified as active and selective catalysts for epoxide rearrangement of β-pinene epoxide **171** to myrtanal **172**. Sn-MCM-41 proved to be the best catalyst, which could be recycled (four cycles) almost without loss of activity or selectivity (80%).[131]

Aluminum-containing mesostructured materials which present both Brønsted and Lewis acid sites also prove to be efficient catalysts for epoxide rearrangement, generally superior to the zeolites in terms of both activity and aldehyde selectivity. Al-MCM-41 (pore diameter 2.1–2.3 nm) effectively catalyzed the rearrangement of long straight-chain epoxides (of 1,2-epoxyoctane)[132] and the isomerization of isophorone epoxide **168** toward keto aldehyde **170**.[133]

Mesoporous aluminosilicates, with a pore width between 1.37 and 1.48 nm, efficiently catalyzed the Meinwald rearrangement of a range of epoxides (epoxides of styrene, methylstyrene, trans-stilbene, and α-pinene) to produce the corresponding aldehydes.[134] For example, the reaction of α-pinene epoxide **74** proceeds with high conversion (85%), giving the campholenic aldehyde **75** as the main product (75%) in addition to small quantities of fencholenal **126** and *trans*-carveol **128** (see Scheme 51). In all these cases, it has been found that the presence of low amounts of aluminum in the material exhibited high selectivity and consequently higher yield of the aldehyde product.

3.15.6.6 Resins

Different types of ion-exchange resins in H^+ form have been used for the rearrangement of epoxides such as Dowex, Reillex, and Amberlyst. Few results have been reported in recent years. However, we can mention the work done in the field of biomass product transformation (rearrangement of epoxidized terpenes[131] and vegetable oils[135]).

3.15.7 Conclusion

The challenges associated with the synthesis of products containing oxygen together with their interesting biological properties have prompted chemists to develop a plethora of elegant, efficient, and innovative epoxide rearrangement methods. Acid-catalyzed ring-opening intramolecular cascade rearrangements provide efficient atom economy and selective approaches to a variety of structurally diverse multifunctional architectures.

A wide range of acids are currently available to perform epoxide rearrangements: Brønsted acids and Lewis acids derived from the main group elements, and transition metals, including lanthanides. Although some progress has been made for epoxide rearrangements catalyzed by Brønsted acids and main group Lewis acids with the emergence of highly effective bismuth, tin, or indium-promoting agents, the most impressive results have been achieved with Lewis acids derived from transition metal and heterogeneous acid catalysts. Transition-metal Lewis acid catalysts, thanks to the wide variety of choice of metals in the periodic table, modulate the functional tolerance groups, and achieve both higher activities and selectivities than conventional Lewis acids using reduced catalyst loading. The development of immobilized Brønsted and Lewis acid catalysts provides an alternative and highly promising environmental and economical strategy due to the ease of work-up, facile catalyst recovery, and recycling.

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3.16 The Semipinacol Rearrangements

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3.16.1	**Introduction**	795
3.16.2	**Rearrangement of 2-Heterosubstituted Alcohols**	798
3.16.2.1	Sulfonates as Leaving Group	798
3.16.2.2	Halides as Leaving Group	799
3.16.2.3	N_2 as Leaving Group	801
3.16.2.4	Thiolates or Selenolates as Leaving Group	802
3.16.3	**Rearrangement of Allylic Alcohols**	804
3.16.3.1	Induced by Halogenium Ions	804
3.16.3.2	Induced by Selenium Ion	807
3.16.3.3	Induced by Brønsted Acids	807
3.16.3.4	Induced by Lewis Acids	809
3.16.3.5	Prins-Pinacol Rearrangement	811
3.16.3.6	Other Tandem Version	812
3.16.3.7	Enantioselective Version	814
3.16.4	**Rearrangement of Propargylic Alcohols**	817
3.16.5	**Rearrangement of Epoxides**	819
3.16.5.1	Epoxy Alcohols and Their Derivatives	819
3.16.5.1.1	Promoters of the rearrangement	819
3.16.5.1.2	Patterns of the rearrangement	820
3.16.5.1.3	Side reaction	824
3.16.5.1.4	Substrate scope of the rearrangement	825
3.16.5.1.5	Tandem processes	829
3.16.5.1.6	Application of the rearrangement	831
3.16.5.2	Analogs of 2,3-Epoxy Alcohols	839
3.16.5.3	Simple Epoxides and 2,3-Epoxy Ketones	840
3.16.6	**Rearrangement of α-Hydroxy Ketones and α-Hydroxy Imines**	843
3.16.7	**Miscellaneous Type**	848
3.16.8	**Summary and Outlook**	848
References		849

Glossary

Aromatic ring umploung A chemical process that converts the nucleophilic aromatic ring into an electrophilic one by oxidative activation or other transformations.

Brønsted acid Any compound that is capable of donating a proton to a base such as HCl, H_2SO_4, and H_3PO_4.

Homologation Any chemical reaction that transforms the reactant into the next member of the corresponding homologous series.

Kinetic resolution A chemical process for the syntheses of chiral molecules from a pair of enantiomers through the reaction-rate difference between the two isomers. Normally, chiral starting material, product or both could be obtained selectively.

Lewis acid Any electrophilic compound that can accept a pair of electrons to form a Lewis adduct through a coordinate covalent bond such as H^+, $AlCl_3$, and BF_3.

Quaternary carbon Any carbon center directly connected to four other carbon atoms through a single bond.

3.16.1 Introduction

The term 'semipinacol rearrangement' was first used by Tiffeneau in 1923 to define a special case of pinacol rearrangement (Scheme 1).[1] During this transformation, the migration occurred toward the secondary center, instead of the tertiary one, which was observed in the normal pinacol rearrangement (Scheme 2).[2] However, like the normal pinacol rearrangement, the formation of more stable oxonium ion intermediate with complete octet configuration at all centers from corresponding carbocation intermediate is believed to be the driving force for the 1,2-rearrangement. Several variations on this type of transformation have emerged till date. Subsequently, the concept has been further extended to describe *all such rearrangements that are either related to, or*

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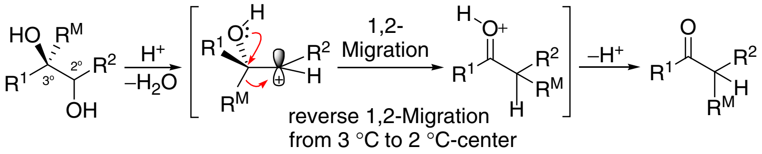
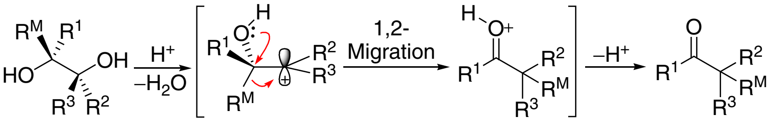
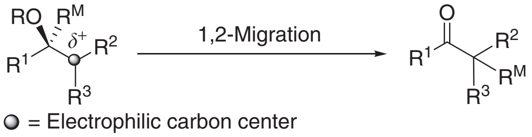
reminiscent of, the pinacol rearrangement.[3] Accordingly, a general depiction shown in Scheme 3 was more appropriate for better recognizing and understanding the semipinacol rearrangement. *Mechanistically, all such processes share a common reactive species in which an electrophilic carbon center, including but not limited to carbocations, is vicinal to an oxygen-containing carbon and can drive the 1,2-migration of a C–C or C–H bond to terminate the process, generating a carbonyl group.*[4] In light of this attractive feature, organic chemists have created many ingenious versions of the semipinacol rearrangement.



Scheme 1 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.



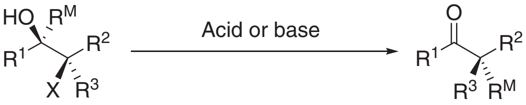
Scheme 2 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.



Scheme 3 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

According to the type of electrophilic carbon center involved in the reaction, the semipinacol rearrangement can basically be categorized into following five types:

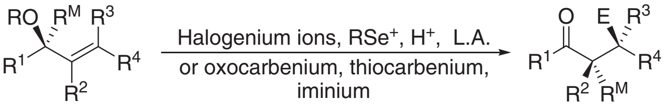
In type I, the substrates relate to 2-heterosubstituted alcohols and their derivatives (Scheme 4). Among them, the electrophilic carbon centers are generally connected with good leaving groups like chlorine (Cl), bromine (Br), iodine (I), nitrogen (N_2), mesylate (OMs), tosylate (OTs), S-R (SR), Se-R (SeR) (R=substituent) and the carbon–carbon migration is facilitated by the loss of the leaving group under either acidic or basic conditions.



X = OMs, OTs, Cl, Br, I, N_2^+, SR, SeR, etc.

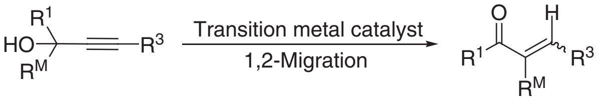
Scheme 4 Type I rearrangement. Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Type II relates to the rearrangements of allylic alcohols and their derivatives (Scheme 5). Different from type I, the electrophilic carbon center in type II is a carbocation generated by the addition of an electrophile to the C=C bond of the allylic alcohol. Generally, electrophiles such as halogeniums, selenium cations, and Brønsted and Lewis acids give the carbocation through intermolecular additions. However, the use of oxocarbeniums, thiocarbeniums, and iminiums mainly go through intramolecular ones. The latter case is now widely known as the Prins-pinacol rearrangement after the systematic studies carried out in Overman's group.[5]



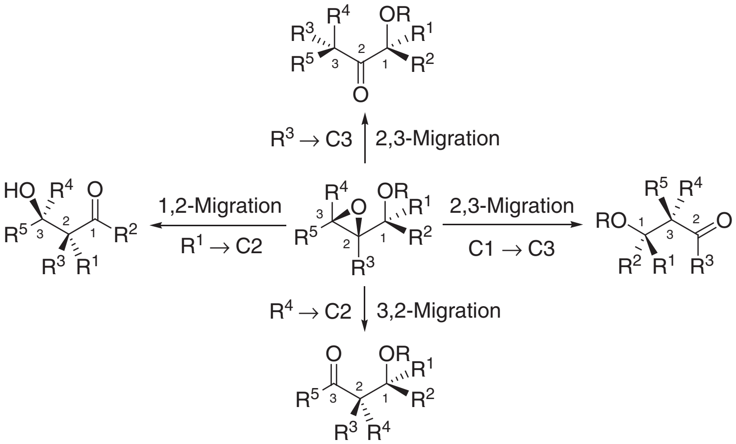
Scheme 5 Type II rearrangement. Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Type III refers to the rearrangements of propargylic alcohols. Similar to the type II rearrangements, the electrophilic carbon center is a putative carbocation which is generated through the coordination of triple bond with π-acid and subsequently terminated by a 1,2-migration (**Scheme 6**).



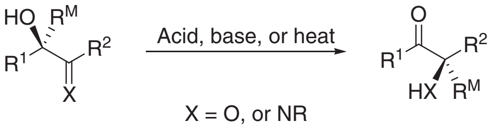
Scheme 6 Type III rearrangement.

Type IV involves the rearrangements of epoxides,[6] among which the rearrangement of 2,3-epoxy alcohols and their derivatives have been extensively investigated (**Scheme 7**).[7] In this case, the electrophilic carbon center can be either carbon of the oxirane moiety, and the migration is generally initiated by acid-promoted epoxide ring opening. Based on the structural features of the substrates and reaction conditions, the rearrangement can undergo 1,2-, 2,3-, or 3,2-migration fashion (according to the numbering in 2,3-epoxy alcohols).



Scheme 7 Type IV rearrangement. Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Type V refers to the rearrangements of tertiary α-hydroxy ketones and imines (**Scheme 8**). This reaction is also known as the 'acyloin rearrangement' or 'α-ketol rearrangement',[8] wherein the electrophilic carbon center becomes the carbonyl or imine carbon. Because of the presence of tertiary α-hydroxy ketone or imine moieties, the isomerization involving an enolization/protonation procedure is unavailable. Thus, the 1,2-migration of the C–C bond toward the carbonyl or imine group becomes the only path to effect the isomerization.



Scheme 8 Type V rearrangement. Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

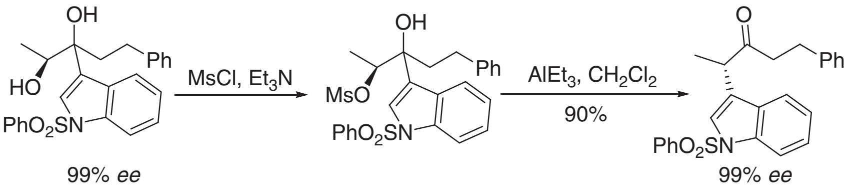
Broadly speaking, compared with the classic pinacol rearrangement, the semipinacol rearrangement has the following distinctive advantages: (1) It has a much larger substrate scope. Except 1,2-diols, substrates such as epoxides and allylic alcohols can be applied into the rearrangement and afford structurally diverse products. (2) According to the substrates used, the rearrangement can be carried out under a variety of reaction conditions, for example, the rearrangements of tertiary α-hydroxy ketones can proceed under acidic, basic, or thermal conditions. (3) Different from the pinacol rearrangement, the semipinacol rearrangement generally has much better regioselectivity, because the required electrophilic center can be generated in a site-specific way. (4) Except following the usual migrating trends in pinacol rearrangement, the migratory aptitude of substituents is also often controlled by the stereoelectronic effect, namely the migratory group must be antiperiplanar to the leaving one. Therefore, stereospecific rearrangements with inversion of stereochemistry at the migration terminus are generally observed. Based on this feature, a series of structural units with quaternary carbon-containing continuous stereocenters have been diastereoselective constructed.[9] (5) As the key step, the semipinacol rearrangement can be involved in many tandem reactions, which are generally achieved by combining the rearrangement with the transformations that will either form the required electrophilic carbon center or functionalize the resulting carbonyl group.[10]

3.16.2 Rearrangement of 2-Heterosubstituted Alcohols

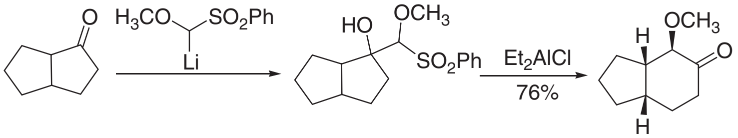
The rearrangement of 2-heterosubstituted alcohols and their derivatives represents the largest class of semipinacol rearrangement. Because a series of good leaving groups such as OMs, OTs, Cl, Br, I, N_2, SR, and SeR can be used in the reaction, this will result in a large number of substrates that can be subjected to the rearrangement (**Scheme 4**). However, the presence of these groups will lead to the formation of epoxides as a main side reaction. Normally, the migrating groups are *anti* to the leaving ones, which will give good stereoselectivities and regioselectivities in most of the corresponding rearrangements. In the following, these types of reactions will be introduced according to the leaving group attached to the electrophilic carbon center.

3.16.2.1 Sulfonates as Leaving Group

The semipinacol rearrangement of α-hydroxy sulfonates and their analogs are reproducibly efficient in both acyclic and cyclic systems. Both Lewis acids and bases can promote the 1,2-migration with loss of leaving group such as OMs or OTs (**Scheme 9**).[11] Compared with the simple sulfur-based rearrangement, this type of reaction is more regioselective and possesses broader substrate scope in ring expansions. For example, the adducts derived from the anion of methoxymethyl phenyl sulfone and cyclic ketones rearrange on addition of Lewis acid (**Scheme 10**). The rearrangement is stereospecific, namely a single diastereoisomer is formed. During this transformation, the carbon that is more capable of stabilizing an electron deficiency at the transition state migrates preferably. Furthermore, substrates with five- or six-membered ring are also applicable for the related ring expansion procedure.[12]

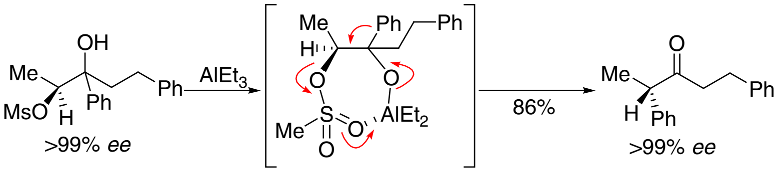


Scheme 9



Scheme 10

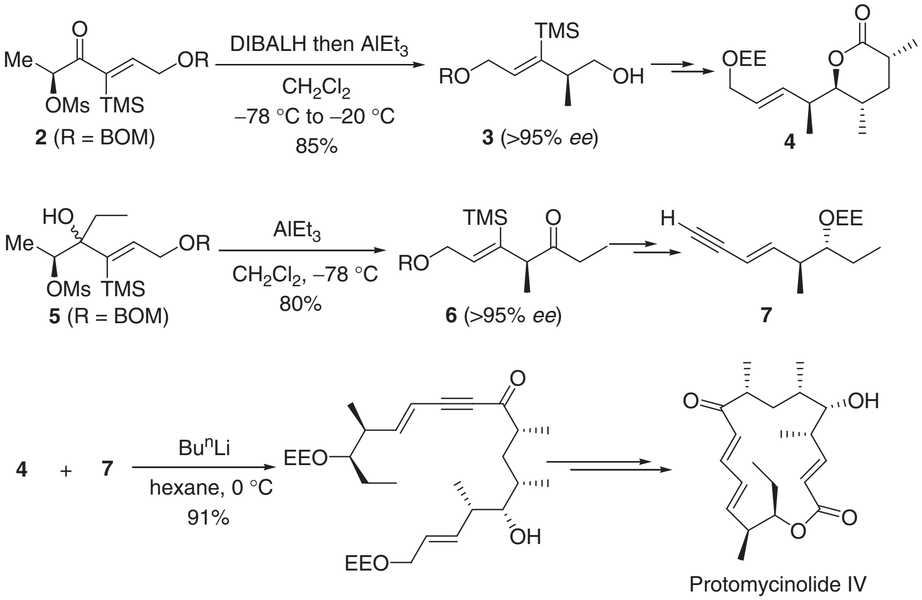
Tsuchihashi et al. developed an efficient organoaluminum-promoted semipinacol rearrangement of lactate-derived 1,2-hydroxy mesylate.[13] The reaction proceeded through a proposed Al-chelated intermediate **1** as depicted in **Scheme 11** where the hard-hard interaction between Al-MsO groups and the pushing effect of the aluminum alkoxide ensure the concerted nature of the process to effect the complete chirality transfer to give enantiomerically pure α-chiral ketones with full inversion at the C–OMs stereocenter.



1

Scheme 11

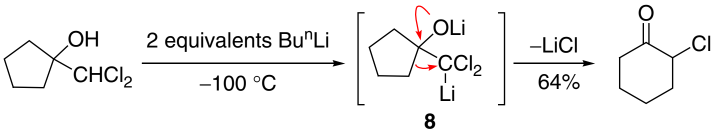
This methodology was successfully applied in the convergent total synthesis of protomycinolide IV (Scheme 12).[14] An $AlEt_3$-promoted, stereospecific 1,2-alkenyl migration was used twice to afford the intermediates **3** and **6**. During these two reactions, no *E*/*Z* isomerization of the alkenyl geometry was observed. Subsequently, **3** and **6** were further converted to the key coupling precursors **4** and **7** by means of chemical transformations.



Scheme 12 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

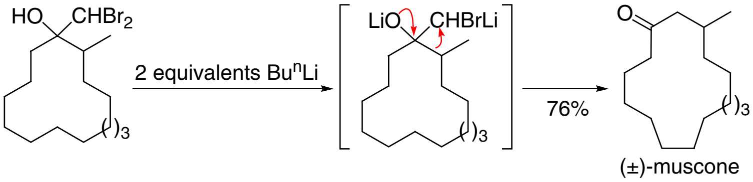
3.16.2.2 Halides as Leaving Group

Halohydrins or 2-haloketones can undergo semipinacol rearrangement either under basic conditions or in the presence of various silver salts. In general, this kind of transformation is initiated by the loss of halogen, and subsequent 1,2-migration of a C–C bond results in the formation of a carbonyl group along with skeletal rearrangement. Based on the structural feature, there are mainly three types of substrates involved in this rearrangement. The first one worth rising is dihalomethylcycloalkanol compound. For dichloromethylcycloalkanol substrate, treatment with 2 equivalents of *n*-butyllithium generates a dilithiated species **8**, which then rearranges to give a homologated 2-chloro ketone (Scheme 13).[15]



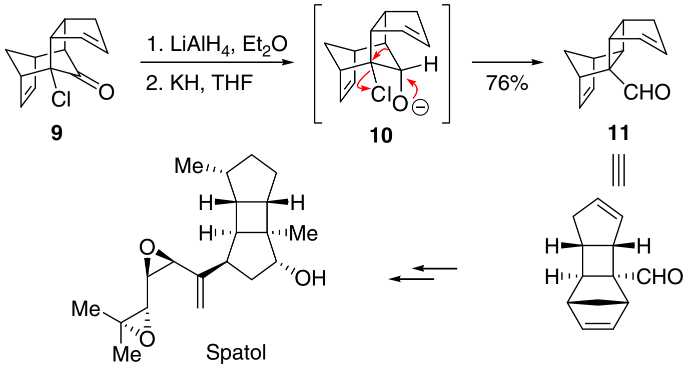
Scheme 13

Dibromomethylcycloalkanol also could go through a similar fashion rearrangment, however, with a different dilithio intermediate which is formed via halogen–metal exchange rather than deprotonation. As shown in Scheme 14 toward the synthesis of (±)-muscone,[15] the more substituted group usually tends to migrate in the reaction of unsymmetrical ketones.



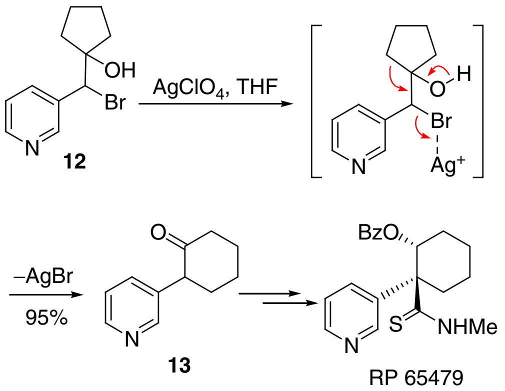
Scheme 14

The second type of substrate refers to the 2-monohalo alcohols, which also could go through semipinacol rearrangement under basic conditions. In the formal synthesis of spatol by Harmata et al.,[16] successive reduction and deprotonation of the compound **9** afforded the chlorohydrin anion **10**, which went through a semipinacol rearrangement to give a ring-contracted product **11** directly in 76% yield (Scheme 15).



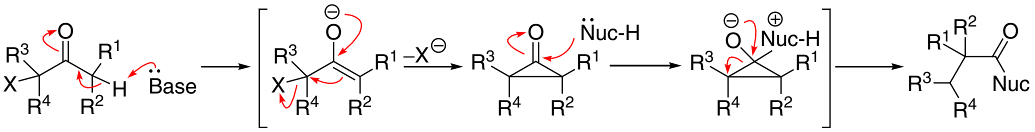
Scheme 15 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Additionally, the halogen atom also could be removed using silver salt. Accompanied by the precipitation of silver halide, the corresponding carbocation is formed and further promotes the rearrangement. In the synthesis of potent potassium channel opener RP 65479 (Scheme 16),[17] Hart et al. obtained ketone **13** in 95% yield by a AgClO$_4$-mediated semipinacol rearrangement of bromohydrin **12**.



Scheme 16 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

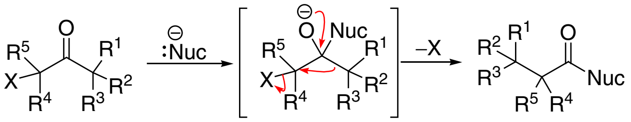
The third one refers to the Favorskii rearrangement and its variation, the *quasi*-Favorskii rearrangement.[18] As a valuable synthetic procedure, the Favorskii rearrangement converts 2-halo ketones and their derivatives to carboxylic acids or carboxylic acid derivatives through a cyclopropanone intermediate, which normally gives the thermodynamically more stable carbanion following the cleavage of the three-membered ring (Scheme 17).



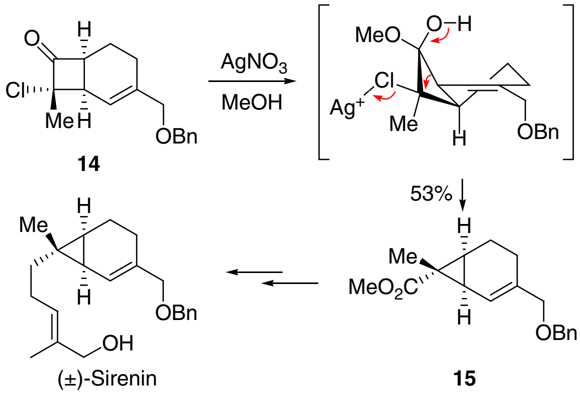
Scheme 17

Although the cyclopropanone intermediate sometimes cannot be formed because of the lack of enolizable hydrogen or special configuration of the substrates, the *quasi*-Favorskii rearrangement is operational. During this procedure, the carbon without halogen atom migrates toward the one with halogen (Scheme 18).

For example, in Harding's synthesis of the female sexual pheromone (±)-sirenin (Scheme 19),[19] the ring-contracted product **15** was obtained diastereoselectively through the AgNO$_3$-mediated semipinacol rearrangement of α-chlorocyclobutanone **14** in 53% yield.

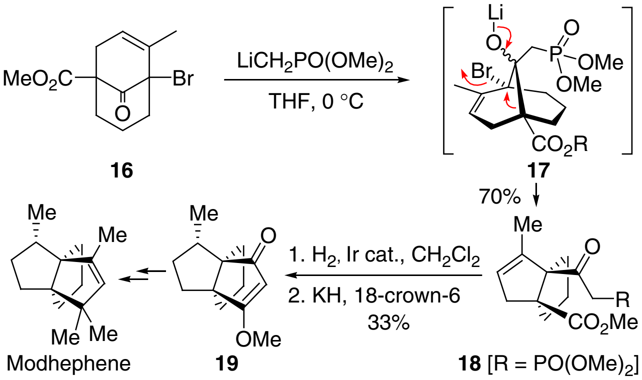


Scheme 18



Scheme 19 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

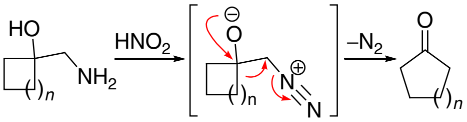
Besides the normal nucleophile (alcohol, amine or H_2O), other nucleophilic reagents such as alkyl phosphonate anion or vinyllithium have also been applied into the *quasi*-Favorskii rearrangement. In this case, ketone will be formed as the product. Kraus and Shi successfully used such a semipinacol rearrangement of compound **16** to construct the main skeleton of modhephene (Scheme 20).[20] During this procedure, the nucleophilic addition of methyl phosphonate anion to **16** gives the intermediate **17**, which undergoes a ring contraction to afford keto ester **18** in 70% yield. Next, vinylogous ester **19** is obtained with subsequent hydrogenation and intramolecular nucleophilic addition, and eventually converted into modhephene.



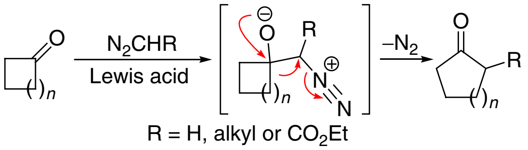
Scheme 20 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

3.16.2.3 N_2 as Leaving Group

Diazotization of 1,2-amino alcohols by nitrous acid or direct addition of diazoalkane to ketones can lead to efficient ketone homologations.[21] These processes are widely known as Tiffeneau–Demjanov rearrangement, which occur with a mechanism similar to that of semipinacol rearrangement. The reaction generally involves a 1,2-diazo hydroxyl zwitterion intermediate, which can undergo 1,2-migration with loss of N_2 to give the homologated ketone (Schemes 21 and 22).

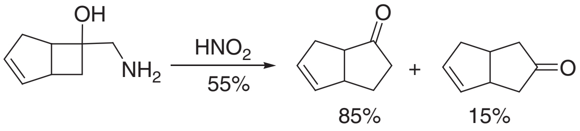


Scheme 21



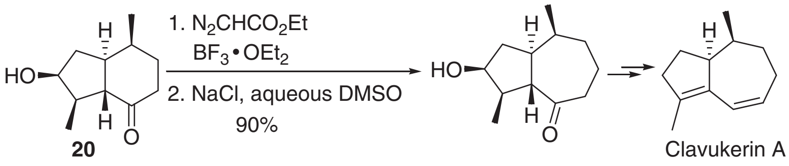
Scheme 22

Although the degree of substitution of migrating group appears to be of little importance for unsymmetrical ketones, migration of the less substituted group is usually preferred in cyclic systems (equation 1),[22] resulting in various ring-expanded products.

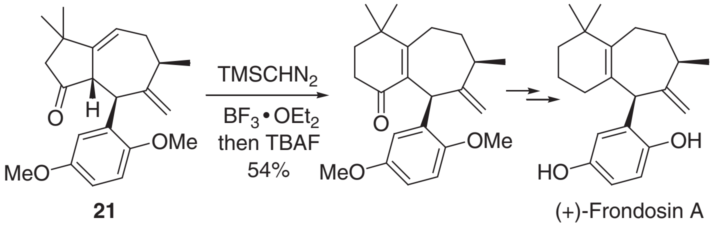


(1)

Based on this feature, Honda et al. applied this selective rearrangement in the total synthesis of clavukerin A (Scheme 23).[23] A similar approach was used in the synthesis of (+)-frondosin A by Trost et al. (Scheme 24).[24] Within these two approaches, the rearrangements of **20** and **21** proceeded via exclusive 1,2-migration of the less substituted methylene group.



Scheme 23 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.



Scheme 24 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

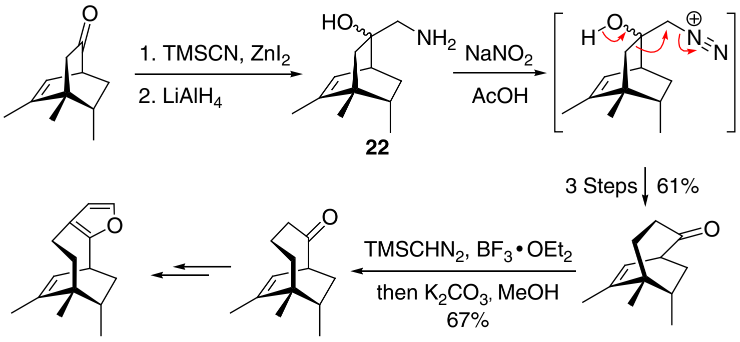
Except the normal ring system, the rearrangement proceeds readily and goes through the expected mechanism even in bridged or highly strained polycyclic systems. For example, two such rearrangements were used to establish the key bicyclo-[4.2.2]-decane skeleton **22** of (±)-nakafuran-8.[25] The first ring expansion of **22** was carried out with AcOH and $NaNO_2$ to give ketone **23** in 61% yield. The second ring expansion was performed by treating **23** with $TMSCHN_2$ and $BF_3 \cdot OEt_2$ to afford **24** in 67% yield. In both steps, the predominant 1,2-migration of the methylene group gave 12:1 and 2:1 regioselectivity for **23** and **24**, respectively (Scheme 25).

Although the sequence has been usually applied to the formation of five- to eight-membered rings, expansion from a 12- to 13-membered ring is also possible and has been used in the synthesis of (±)-muscone by Nagel's group (Scheme 26).[26] In the presence of H_2O and AcOH, treatment of 1,2-amino alcohol **25** with sodium nitrite smoothly afforded the 13-membered cycloketone **26** in 50–60% yield.

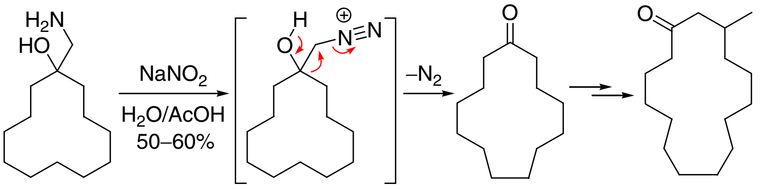
3.16.2.4 Thiolates or Selenolates as Leaving Group

2-Hydroxy thiolates can go through semipinacol rearrangement to give ketones under a variety of conditions. The resulting carbonyl group could be formed at either the hydroxy-bearing carbon or the carbon bearing the sulfur group.

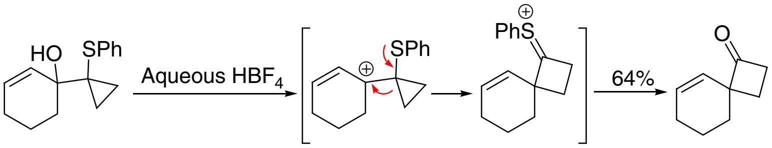
In the presence of protic acid such as *p*-TsOH and HBF_4, it is the carbon bearing the sulfur group which ultimately becomes the carbonyl carbon. The reaction initiates via protonation of the hydroxy group, and the migrating group connected to the carbon bearing the sulfur will shift along with the loss of H_2O. Hydrolysis of the sulfonium intermediate will give the ketone product. This C–C bond formation appears to be restricted to the expansion of small rings, particularly cyclopropanes (equation 2).[27]



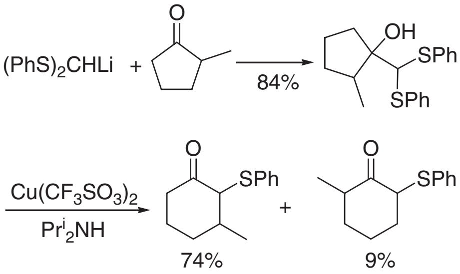
Scheme 25 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.



Scheme 26 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

 (2)

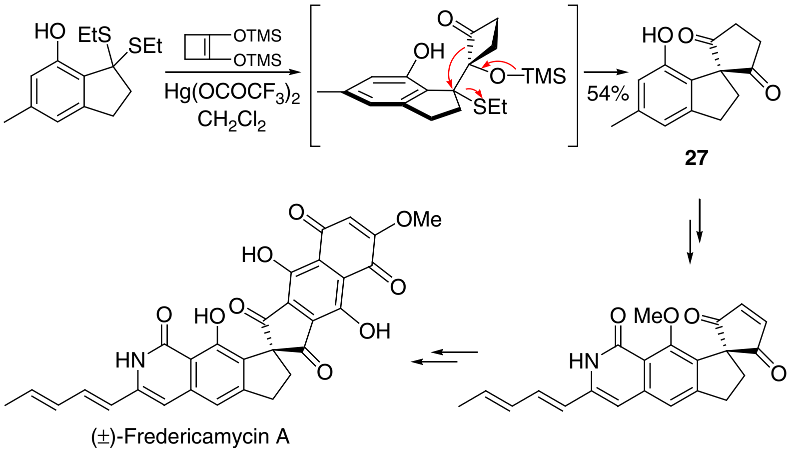
Although the use of Lewis acid favors loss of the sulfur group, the preferred conditions involve the use of soft thiophilic reagents like copper(II) (Scheme 27) and mercury(II) salts, dichlorocarbene generated *in situ* from TlOEt in $CHCl_3$, or electrogenerated chloronium ion.[28] During this procedure, the carbon bearing the sulfur group becomes the migration terminus, and carbonyl forms at the hydroxy-bearing carbon. This procedure provides a method for producing the homologous α-thiophenoxy ketones, and it results in ring expansion in the case of cyclic ketones. In general, hydrogen migrates faster than alkyl groups, among which the most substituted one migrates preferentially.



Scheme 27

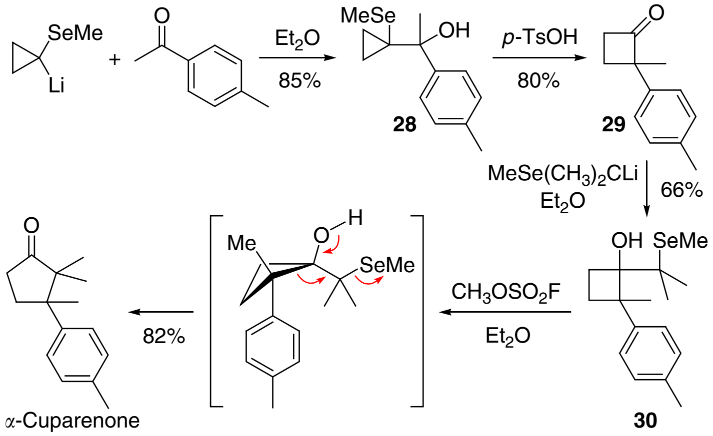
Such rearrangement was used to construct the spirocyclic compound **27**, a key intermediate in synthesis of (±)-fredericamycin A (Scheme 28).[29]

The semipinacol rearrangements of 2-hydroxy selenolates are very similar to those of 2-hydroxy thiolates, but most of the rearrangements occur only if the selenyl moiety is attached to a fully substituted carbon. Till now, the rearrangement has been applied mainly to the ring expansion of cyclic ketones.



Scheme 28 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Using semipinacol rearrangement of 1,2-hydroxy seleno compounds, Krief developed a concise synthesis of α-cuparenone through a sequential ring expansion (Scheme 29).[30] Promoted by *p*-TsOH, the first expansion from a three- to four-membered ring in 1,2-hydroxy selenocyclopropane **28** gave cyclobutanone **29** in 80% yield. The second ring expansion of **30** was promoted by CH_3OSO_2F and provided α-cuparenone in 82% yield.



Scheme 29 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

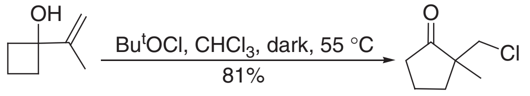
3.16.3 Rearrangement of Allylic Alcohols

The semipinacol rearrangement of allylic alcohols and their derivatives represents another broad class of transformations, which result in the efficient construction of many useful structures (Scheme 5). Among them, not only a large variety of promoters can be used, but also some enantioselective rearrangements have been achieved by using chiral catalysts. However, the intermolecular carbocation-promoted semipinacol rearrangement of allylic alcohols, which could build more than one C–C bond within a single step, still remains a challenge for organic chemists. Below, these rearrangements will be introduced according to the different types of electrophiles that can be used in the reaction as well as related tandem[31] or enantioselective version.

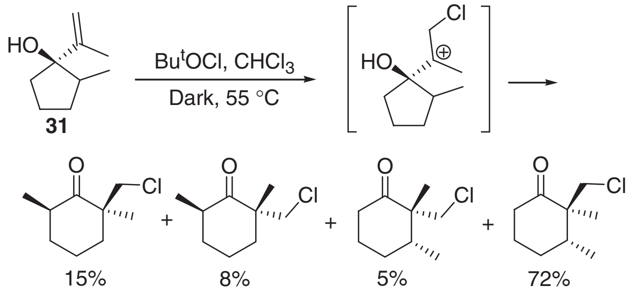
3.16.3.1 Induced by Halogenium Ions

Halogenium ions are highly electrophilic species that can induce semipinacol rearrangement of various allylic alcohols and their derivatives. The rearrangement is usually initiated by addition of halogenium ion to C=C bond, which will give the plausible halonium ion intermediate. The resulting intermediate will then undergo a 1,2-migration to afford synthetically useful *β*-halo carbonyl compounds. Till date, fluoronium, chloronium, bromonium, and iodonium generated by different reagents have all been successfully applied into this type of rearrangement.

Johnson and coworkers have reported the chlorinative ring homologation of simple cyclobutanes (equation 3), cyclopentanes, cyclohexanes, and isopropenyl [2.2.1]-heptanol. As described, treatment of a warm, dark solution of **31** with Bu^tOCl gave four isomers in the ratio 15:8:5:72 (equation 4). The result was rationalized in terms of a nonconcerted mechanism with some carbonium-ion character in the transition state. Tertiary carbon migration was shown to predominate over secondary carbon migration. An additional requirement for obtaining the observed *trans:cis* ratio (72:5) is that the alkyl shift occurs before rotational equilibration of the carbonium ion can take place.[32]

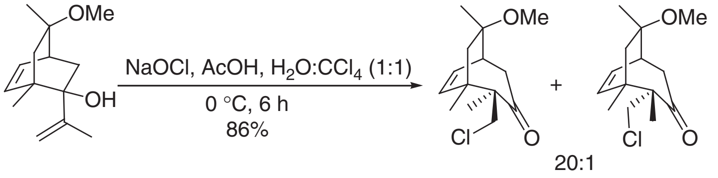


(3)

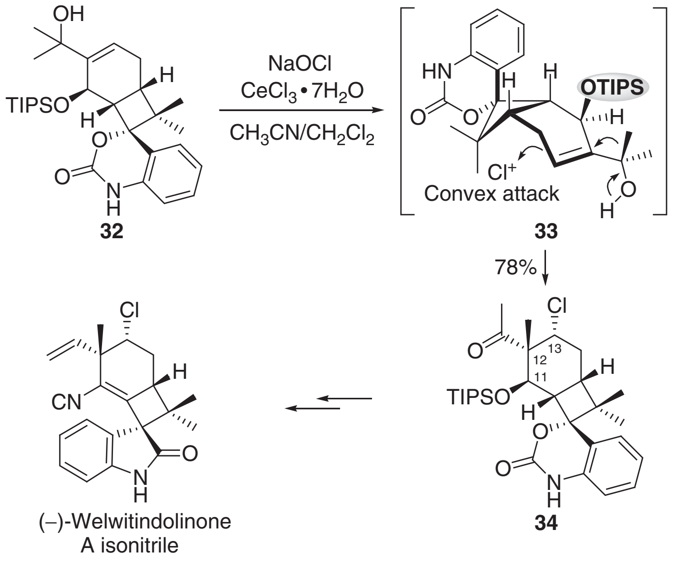


(4)

Under acidic conditions, NaOCl was used instead of potentially explosive Bu^tOCl, and the selectivity of the reaction was improved (equation 5).[33] In Wood's report of the total synthesis of (–)-welwitindolinone A isonitrile (Scheme 30),[34] such a rearrangement was used to install both a C12 quaternary center and the adjacent neopentyl chlorine diastereoselectively. In the presence of NaOCl and $CeCl_3 \cdot 7H_2O$, the 1,2-methyl migration *anti* to the chloronium ion derived from tertiary allylic alcohol **32** provided chloro ketone **34** as a single diastereomer in 78% yield. As shown in **33**, the presence of a sufficiently large protecting group like TIPS on the C11 secondary hydroxyl is crucial to override the potentially favorable formation of possible chlorogenium ion from the least hindered convex face in the rigid structure.

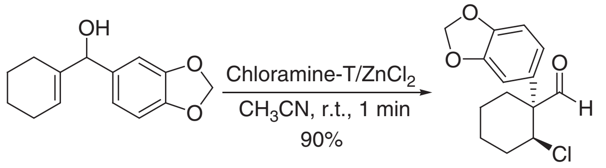


(5)

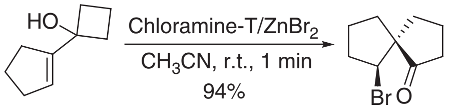


Scheme 30 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

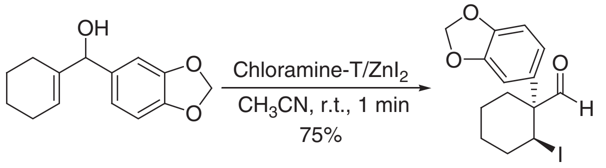
Halogenium ions generated from the chloramine-T/ZnX_2 combination are also capable of inducing the semipinacol rearrangement of allylic alcohols, which afforded the α-quaternary β-haloketo compounds in a highly efficient and stereoselective manner. The products with different halogen atoms could be obtained readily by altering the anion of ZnX_2 (X=Cl, Br, or I) (equations 6, 7, 8).[35]



(6)

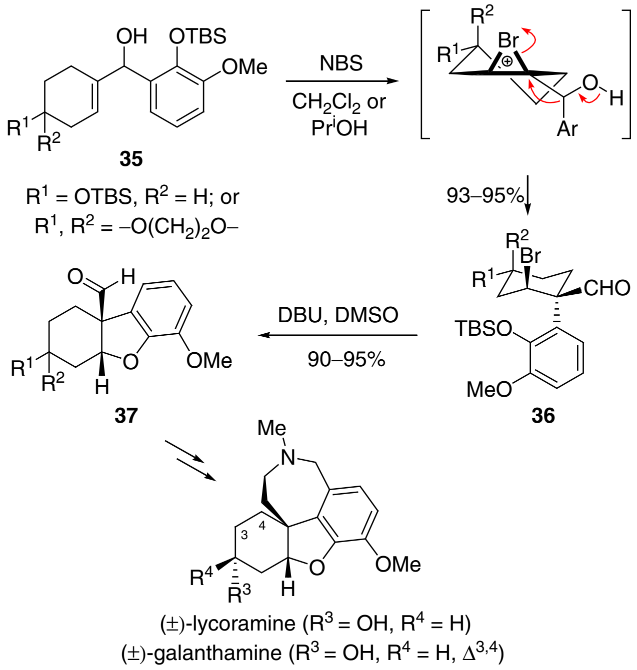


(7)



(8)

Based on above mentioned rearrangements, Tu et al. developed a sequential, NBS-induced semipinacol rearrangement/desilylation/cyclization process to construct the tricyclic benzofuran core **37** of galanthamine-type *Amaryllidaceae* alkaloids (Scheme 31).[36] When the allylic alcohol mixture **35** (R′=OTBS, d.r.=3:2) was treated with NBS in CH_2Cl_2, the key β-bromo aldehyde **36** was obtained in 95% yield through a 1,2-aryl migration. Because of the existence of a diastereoselective amplification effect, only one diastereomer of **36** was obtained. Next, with the use of the DBU-mediated desilylation/cyclization protocol, **37** was generated and eventually converted into (±)-lycoramine and (±)-galanthamine.

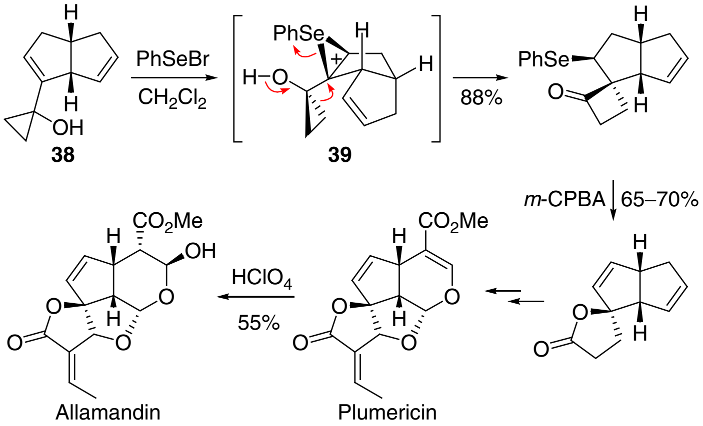


Scheme 31 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

3.16.3.2 Induced by Selenium Ion

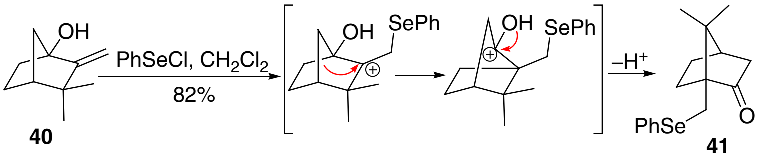
Selenium ion has similar electrophilicity as halogenium ions. Accordingly, it also can induce the semipinacol rearrangement of allylic alcohols through the same pattern.

A selenium-initiated substitutive spiro annulation approach was developed and further used in the total syntheses of plumericin and allamandin by Trost et al. (Scheme 32).[37] The stereoselectivity exhibited in the reaction can be rationalized as follows. The electrophilic selenium species approaches as expected from the convex face of **38** to generate an episelenonium ion **39**. This allows only one rotamer to rearrange, namely the one with a *trans* periplanar arrangement of C–C (cyclopropane) and C–Se bonds.



Scheme 32 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Selenium-initiated rearrangement of allylic alcohols sometimes refers to 'the tandem electrophilic carbon–carbon double-bond addition–Wagner–Meerwein rearrangement,'[38] in which a carbonium ion rather than an episelenonium ion has been proposed. Treatment of (1*R*)-3,3-dimethyl-2-methylenenorbornan-1-ol **40** with the electrophilic selanylating reagent phenylselenyl chloride, enantiospecifically yields (1*S*)-10-(phenylselanyl) camphor **41** as the only product (equation 9).[38]

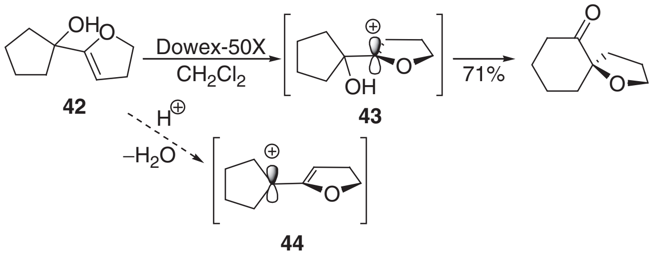


(9)

3.16.3.3 Induced by Brønsted Acids

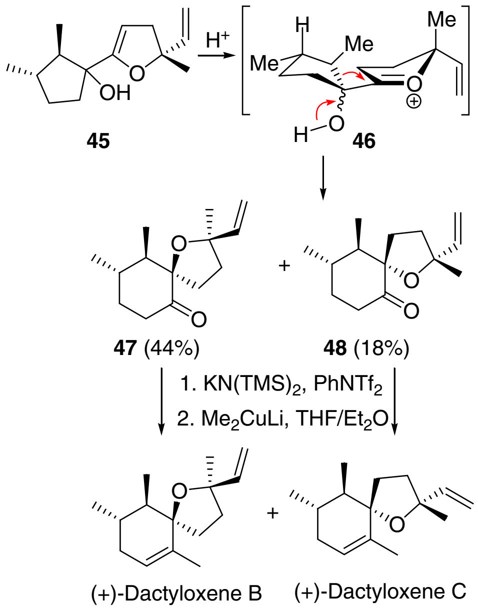
Like those of halogenium ions and selenium ions, the hydrogen of strong Brønsted acids also can be rapidly added to the C=C functional group of the allylic alcohols to give carbocations, which may be terminated by a 1,2-rearrangement under proper reaction conditions.

Paquette et al. developed a series of Brønsted acid-induced semipinacol rearrangements of vinyl ether-derived tertiary allylic alcohols (Scheme 33).[39] Although allylic alcohol like **42** is capable of direct protonation at the tertiary hydroxyl group with subsequent loss of water to give allylic cation **44**, such alcohol prefers to undergo a rapid rearrangement through the ring expansion of the oxonium ion **43**.



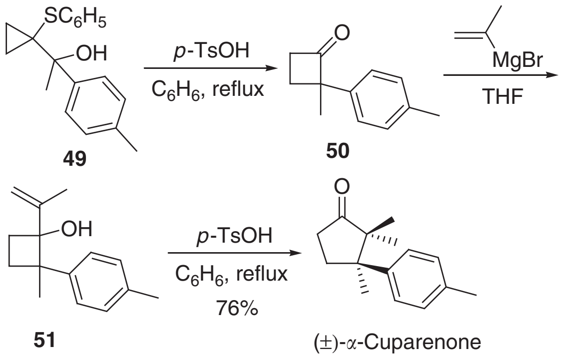
Scheme 33

Using this reaction as a key step, Paquette et al. finished the syntheses of several terpenoids containing an oxa-spirocyclic ring. For instance, in the syntheses of (+)-dactyloxene B and C (Scheme 34),[40] rearrangement of **45** through the oxonium intermediate **46** afforded two diastereofacial isomers **47** and **48** in 44% and 18% yield, respectively. Close to other semipinacol procedures, 1,2-migration of the more substituted alkyl group was preferred. The method has also been used to synthesize (−)-grindelic acid and theaspirones.



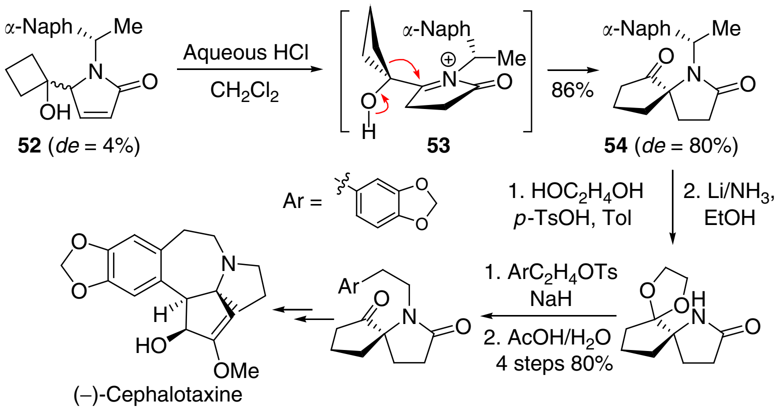
Scheme 34 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

The Brønsted acid-induced semipinacol rearrangement of a range of isopropenyl cyclobutanols was investigated by Piras et al. In their report on the synthesis of (±)-α-cuparenone, two semipinacol rearrangements were successfully applied in the presence of *p*-TsOH. The first one was a *p*-TsOH promoted ring expansion of **49,** which gave the product cyclopentanone **50**. The cyclobutanone **50** was then reacted with isopropenyl magnesium bromide to give the cyclobutanol **51** as a mixture of geometric isomers. Finally, treatment of allylic alcohol **51** with *p*-TsOH in benzene led to the selective 1,2-migration of the more substituted alkyl group, giving the ring expansion product (±)-α-cuparenone in 76% yield (Scheme 35).[41] This strategy, which gives cyclopentanones possessing two adjacent quaternary carbon centers, has also been used in the syntheses of cuparene-type sesquiterpenes.



Scheme 35

Royer and coworkers also applied such transformation in their synthesis of (−)-cephalotaxine, during which a semipinacol rearrangement of the α,β-unsaturated γ-lactam-derived homoallylic alcohol **52** provided enantiomerically pure 1-aza-spiro ketone **54**, the high *de* value of which was controlled by the chiral auxiliary attached to the nitrogen (Scheme 36).[42] In the presence of HCl, **52** was transformed into the expected α-hydroxy iminium ion **53**, which then went through ring expansion to give **54** in 86% yield with notable diastereoselective amplification.

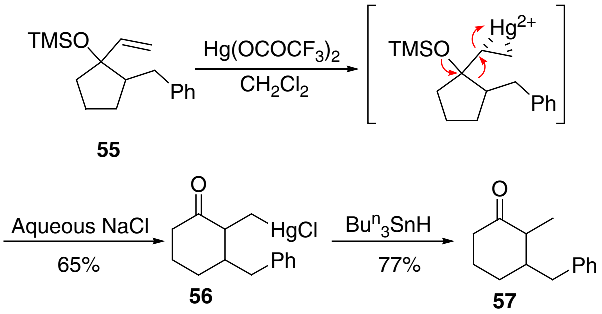


Scheme 36 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

3.16.3.4 Induced by Lewis Acids

Lewis acids such as $BF_3 \cdot OEt_2$,[43] $Hg(OCOCF_3)_2$,[44] $Pd(OAc)_2$[45–47] and CuCl[48] also have been used to induce the semipinacol rearrangement of allylic alcohols by activating the C=C bond. Similarly, it is also the more-substituted carbon which migrates preferentially.

Kim et al. developed a mercuric trifluoroacetate promoted ring expansion reaction of 1-vinyl-1-cycloalkanol silyl ethers. As described, in the presence of 1.2 equivalents of mercuric trifluoroacetate, compound **55** could go through a semipinacol rearrangement, which was quenched by aqueous sodium chloride to give **56**. Demercuration of **56** with tri-*n*-butyltin hydride afforded **57**. As mentioned above, if the substrates are dissymmetric ones, the more substituted alkyl group tends to migrate first. As expected, the rearrangement of **55** gave a 98:2 regioisomeric mixture, of which **56** was the major product (Scheme 37).[44]

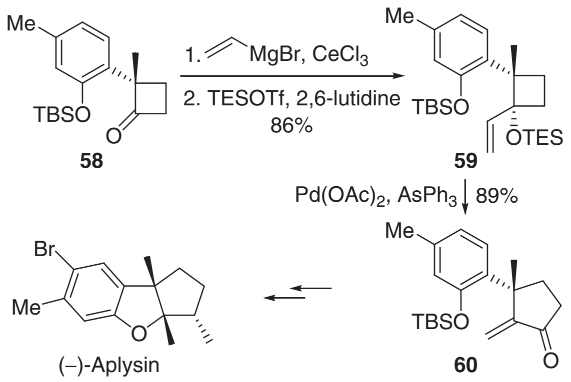


Scheme 37

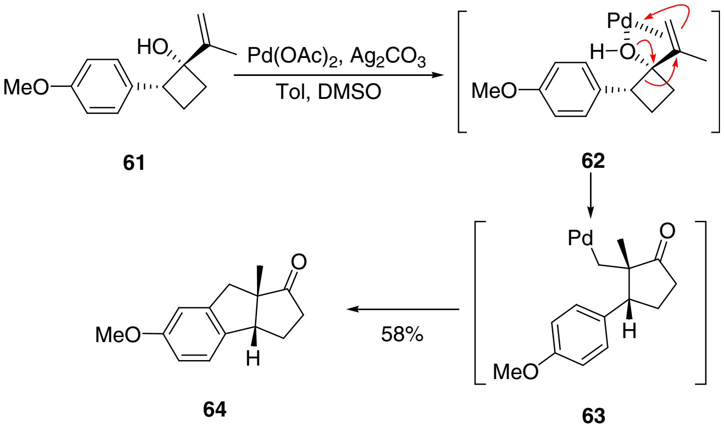
Using $Pd(OAc)_2$ as promoter, Nemoto and Fukumoto developed an useful ring expansion of various chiral vinylcyclobutanols to generate cyclopentanones containing a chiral quaternary carbon center.[45] In combination with a strategy for preparing chiral cyclobutanones, this method has been applied in the syntheses of several terpenes. For instance, in the synthesis of (–)-aplysin (Scheme 38),[45g] vinylcyclobutanol **59**, obtained from **58** by addition of Grignard reagent and subsequent hydroxyl protection, underwent $Pd(OAc)_2$-promoted ring expansion to give the key intermediate **60** in 89% yield.

Orellana et al. described a tandem semipinacol rearrangement and direct arylation process under the catalysis of $Pd(OAc)_2$. This method provides a useful strategy for the synthesis of benzodiquinanes. As drawn in **62**, the reaction was initiated by coordination of the Pd (II) catalyst with the C=C bond and the hydroxy group of **61** simultaneously. Next, the intermediate **62** went through an 1,2-alkyl shift to give the palladium homoenolate **63**, which then afforded the benzodiquinane **64** via a direct arylation reaction (Scheme 39).[46]

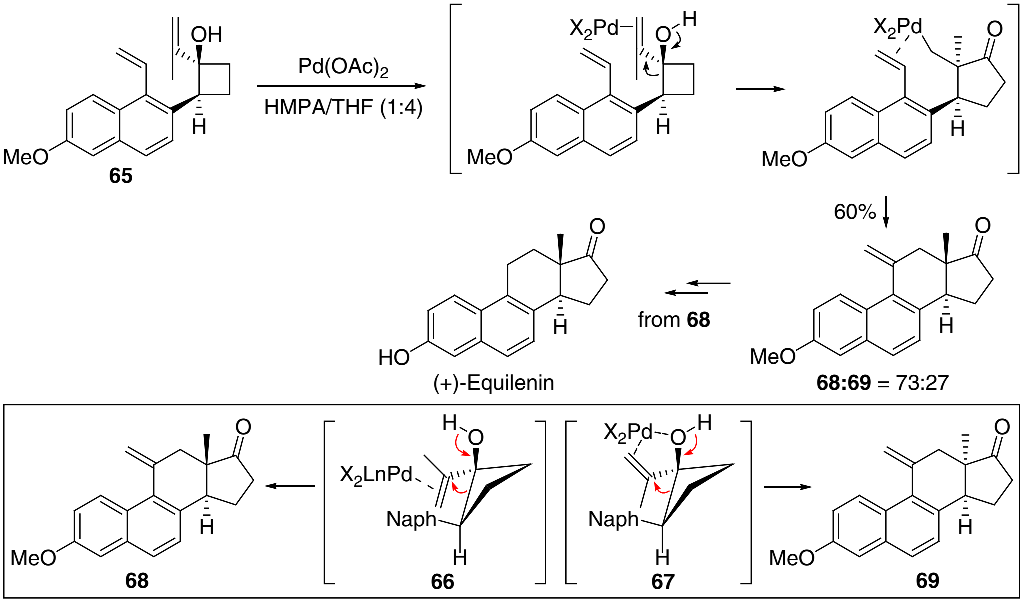
Another tandem Pd(II)-promoted ring expansion/intramolecular insertion process was reported by Nemoto and Ihara, and has been applied to the synthesis of (+)-equilenin (Scheme 40).[47] Initiated by the coordination of the Pd(II) complex to the isopropenyl group in **65**, the reaction went through a cascade cyclobutane ring expansion/olefin insertion/elimination of palladium procedure to give **68** with the desired steroidal framework in 60% yield. During this reaction, solvents proved to be a key factor in the stereochemical control, since the *cis*-product **69** became the main product by the use of a nonpolar solvent such as toluene. The authors attributed the selectivity to the different conformation of the isopropenyl group during the reaction. In the presence of HMPA and THF, the ring expansion probably proceeded via the intermediate **66**, in which the palladium was associated only with the olefin since the hydroxyl group had already coordinated with HMPA, giving the *trans*-diastereomer **68** as



Scheme 38 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.



Scheme 39



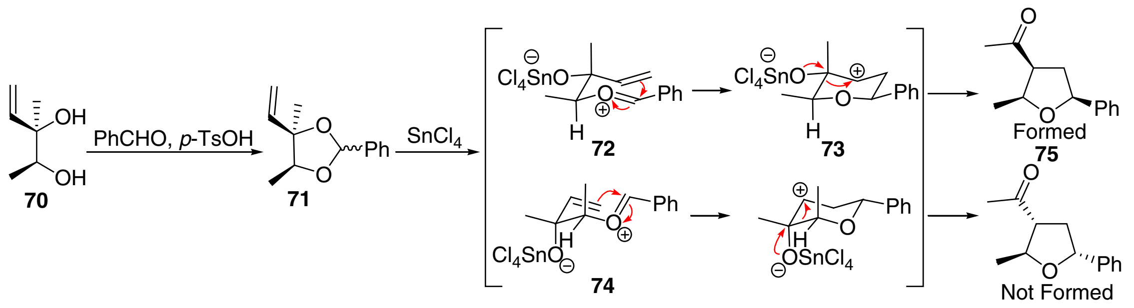
Scheme 40 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

the product. In contrast, the use of nonpolar solvent would give **67** as the predominant intermediate, in which the palladium was proposed to be associated with both the olefin and the hydroxyl group.

3.16.3.5 Prins-Pinacol Rearrangement

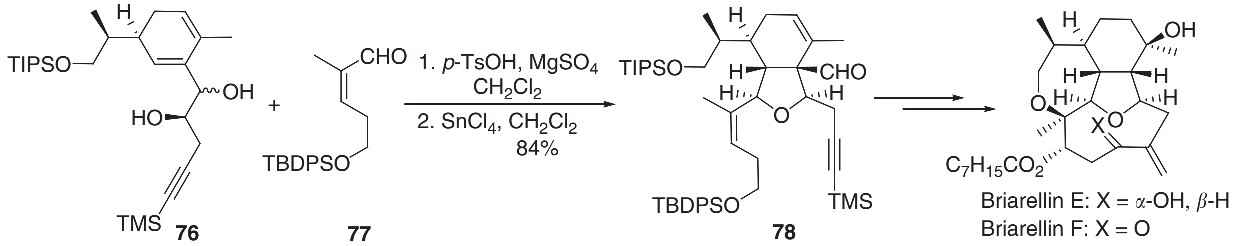
The Prins-pinacol rearrangement involves a Prins reaction followed in tandem by a pinacol-like (or semipinacol) rearrangement. It proceeds via electrophilic addition of various carbeniums to the C=C bond of allylic alcohols, resulting in the formation of a cationic center, which then induces successive 1,2-migrations to generate carbonyl groups sequentially. Within these type of reactions, intramolecular ones find broader utilities. In sharp contrast, there is only one example with the intermolecular version.[49]

As one of the outstanding reactions developed by Overman's group, intramolecular Prins-pinacol rearrangement has shown its power through rapid construction of substituted oxacyclic ring systems in a stereo- and enantioselective fashion. In 1978, Overman and coworkers first developed a useful method for the synthesis of 3-acyltetrahydrofurans (Scheme 41). The allylic acetal **71** is easily prepared by protic acid-catalyzed condensation of allylic diol **70** with benzaldehyde. Rearrangement of allylic acetal **71** with $SnC1_4$ occurred readily at temperatures between −70 and −20 °C and only *cis*-2,5-disubstituted-3-acyltetrahydrofuran stereoisomer **75** was observed. Due to the small inversion and rotation barriers (~10–14 kcal/mol) of oxonium ions, the more stable *E* oxonium ion stereoisomer is most likely involved in the cyclization. Between the two possible chair conformations of this intermediate (**72** and **74**), **72** should be more favorable since the methyl group at the secondary carbon is at an equatorial position. Semipinacol rearrangement of the tetrahydropyranyl cation **73**, resulting from the cyclization of **72**, would lead to the rearrangement product **75**. During this procedure, because of the similar size of CH_3 and the Lewis acid coordinated oxygen substituents, the relative stereochemistry at the allylic stereogenic center is of little significance to the reaction.[50]



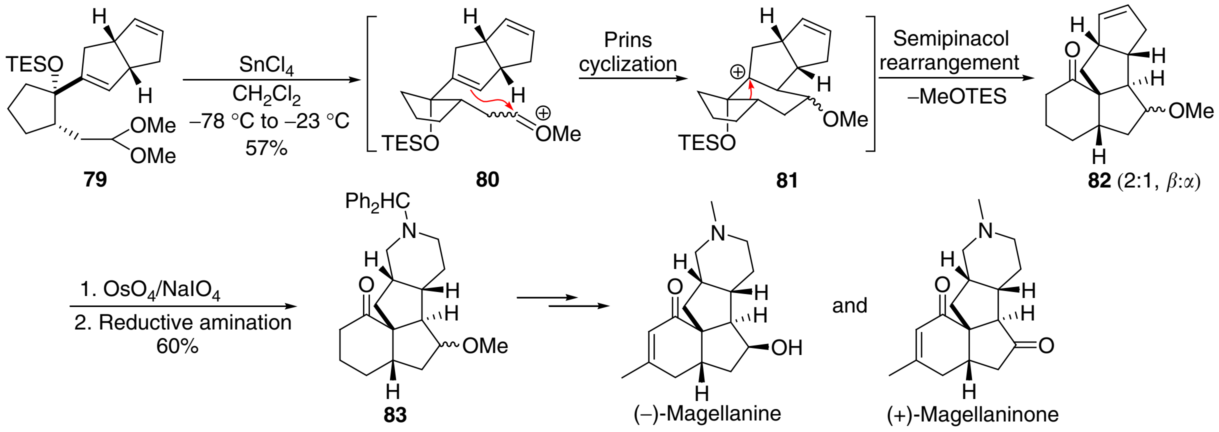
Scheme 41

Such rearrangement has been used in the enantioselective total syntheses of Briarellins E and F. As shown in Scheme 42, following the *p*-TsOH-promoted condensation of a (*Z*)-*α*,*β*-unsaturated aldehyde **77** and an (*S*)-carvone-derived alkynyl dienyl diol **76**, a $SnCl_4$-catalyzed intramolecular Prins-pinacol reaction of the resulting acetyl intermediate stereoselectively afforded the key intermediate **78**, a formyl tetrahydroisobenzofuran compound (Scheme 42).[51]



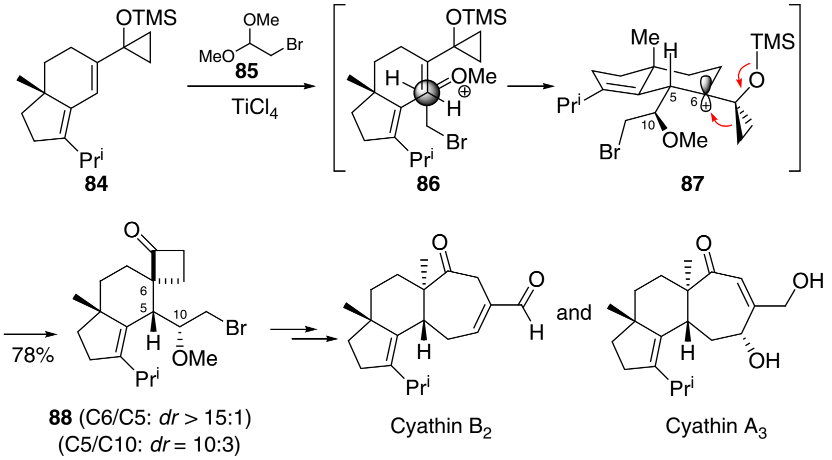
Scheme 42

Except oxacyclic ring systems, carbocyclic ring systems also can be assembled through Prins-pinacol rearrangement, wherein the oxygen atom of the oxocarbenium ion moiety is external to the ring formed by Prins cyclization. Accordingly, a variety of carbocyclic ring systems have been constructed. One typical example is the total syntheses of (−)-magellanine and (+)-magellaninone achieved by Overman's group (Scheme 43).[52] The key carbotetracycle intermediate **82** was obtained through a Prins-pinacol rearrangement of compound **79**. During this procedure, Prins cyclization of the oxocarbenium ion **80** from the less hindered convex face gave the *β*-siloxy carbenium ion **81**, which underwent a semipinacol rearrangement to successfully install the crucial quaternary carbon stereocenter and construct the tetracyclic skeleton of the magellanane alkaloids. Subsequent oxidative cleavage of the double bond of **82** and double reductive amination of the resulting dialdehyde furnishes the advanced intermediate **83**, which is eventually converted to (−)-magellanine and (+)-magellaninone.



Scheme 43

For intermolecular Prins-pinacol rearrangement, there is only one such transformation developed by Cha's group.[49] Using this rearrangement as a key step, they finished the total syntheses of cyathin A$_3$ and cyathin B$_2$ (Scheme 44).[53] In the presence of TiCl$_4$, cyclopropanol silyl ether **84** reacted with acetal **85** to afford spiro cyclobutanone **88** as the major product in 78% yield. As expected, the two newly formed C–C bonds in **86** and **87** were at the opposite side of the angular methyl group, which was a result of a preferential *cis*-1,2-migration procedure. The authors attributed the selectivity of the ring expansion to the minimization of torsional strain, since *trans*-addition would proceed via a transition state in which the newly introduced side chain and the C–C═O bond were fully eclipsed. By means of additional chemical conversions, compound **88**, as a key quaternary carbon scaffold, was then transformed into the target molecules.

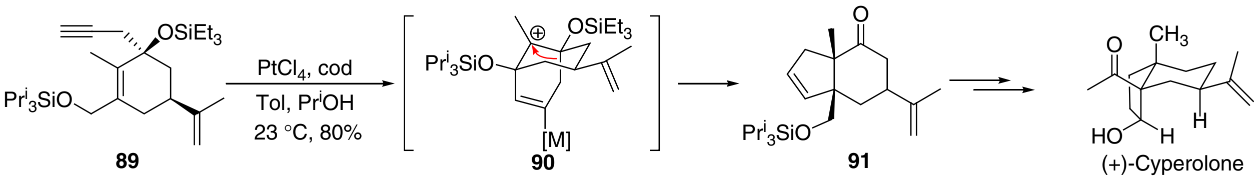


Scheme 44 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

3.16.3.6 Other Tandem Version

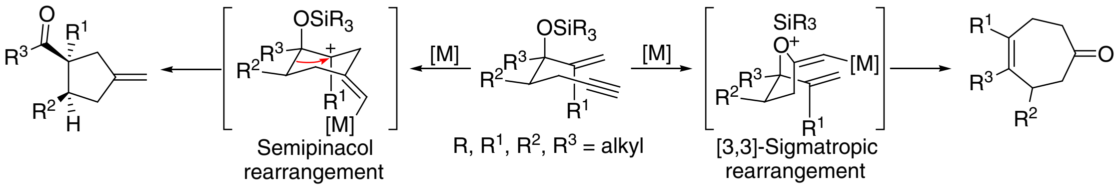
In the case of the allylic alcohols with additional unsaturated carbon–carbon bond, such as alkynyl, allenyl, or alkenyl moiety, interesting cascade reactions involving the semipinacol rearrangement have been developed by employment of π-acids.[54] Among these transformations, transition-metal induced cyclizations are generally applied to give cationic intermediates, which are terminated by subsequent semipinacol rearrangements. This type of reaction possesses the following features: (1) The hydroxyl group is always protected as silyl ether to prevent competitive heterocyclization. (2) The presence of a substituent at C-2 position is essential for better stabilizing the cationic intermediate. (3) The use of external proton source sometimes is necessary for regenerating the catalyst.

For allylic alcohol with additional alkynyl functionality, coordination of 3-silyloxy-1,5-enyne compound **89** with the noble metal catalysts like $PtCl_4$ will initiate a 6-*endo-dig* carbocyclization to afford the cationic intermediate **90**, which goes through a semipinacol rearrangement to produce the ketone **91**.[55] Using this method as the key step, Kirsch and coworkers finished the total synthesis of (+)-cyperolone (Scheme 45).[56]

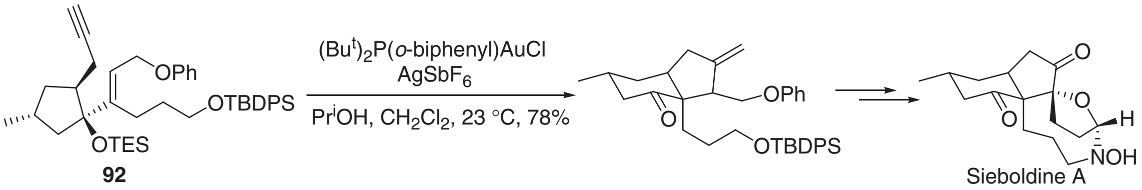


Scheme 45

For 3-silyloxy-1,6-enyne compound, the corresponding tandem process will start with a 6-*exo-dig* cyclization of the alkene moiety with gold(I) catalyst.[57] It has been found that the electronic property of the phosphine ligand affects the selectivity of this transformation significantly.[57a] The use of less electron-rich gold (I) complex like $(C_6F_5)_3PAuCl$ will lead to the heterocyclization-Claisen product. By contrast, the cyclization-semipinacol product will be obtained with a more electron-rich gold (I) complex such as $(Bu^t)_2P$(*o*-biphenyl)AuCl (Scheme 46). Based on the related rearrangement of compound **92**, Overman and coworkers reported the first total synthesis of (+)-sieboldine A (Scheme 47).[58]

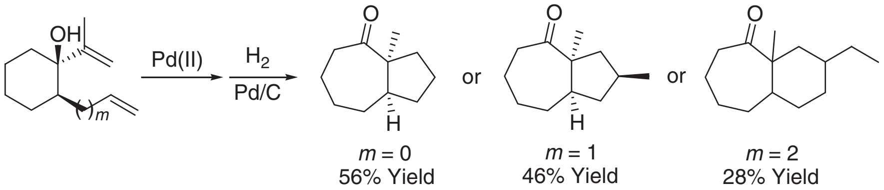


Scheme 46



Scheme 47

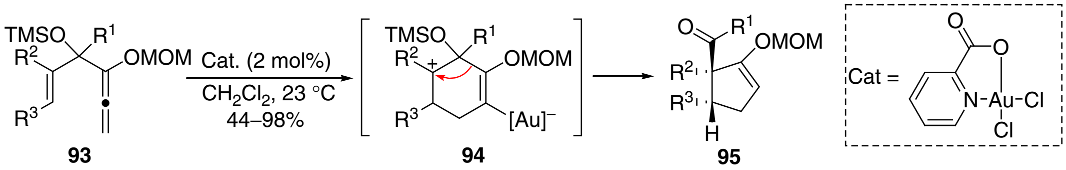
In addition, a substrate with 1,*n*-diene-3-ol (n=5, 6, 8) moiety could also give a similar type of products in the presence of palladium catalyst, but with a much lower selectivity compared with the 3-silyloxy-1,6-enyne compound (Scheme 48).[59]



Scheme 48

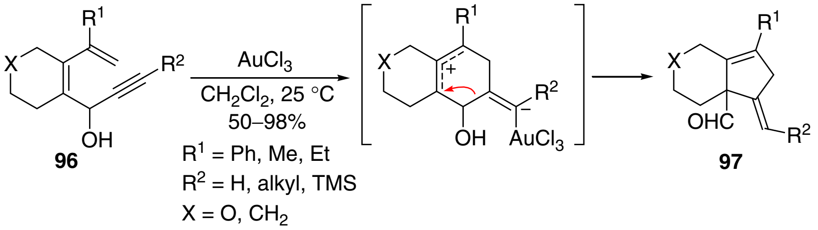
Furthermore, a substrate with 3-silyloxy-1,4,5-trienes motif is also applicable for this kind of tandem protocol, which is initiated by the activation of the allene moiety. Zhang et al. have described the conversion from compound **93** to

3-acylcyclopentene **95** with gold(I) as the catalyst. In this case, a semipinacol rearrangement of cationic intermediate **94** might be involved (Scheme 49).[60]



Scheme 49

Additionally, Liu and coworkers have tried the noble metal-catalyzed reaction of *cis*-4,6-dien-1-yn-3-ols, which contain three π-electron moieties. Cyclization of the substrate **96** via a 6-*exo-dig* pathway gives the allyl cation intermediate, subsequent semipinacol rearrangement of which would afford the product **97**. It is worth mentioning that this skeletal rearrangement proceeds with reasonable chirality transfer (Scheme 50).[61]

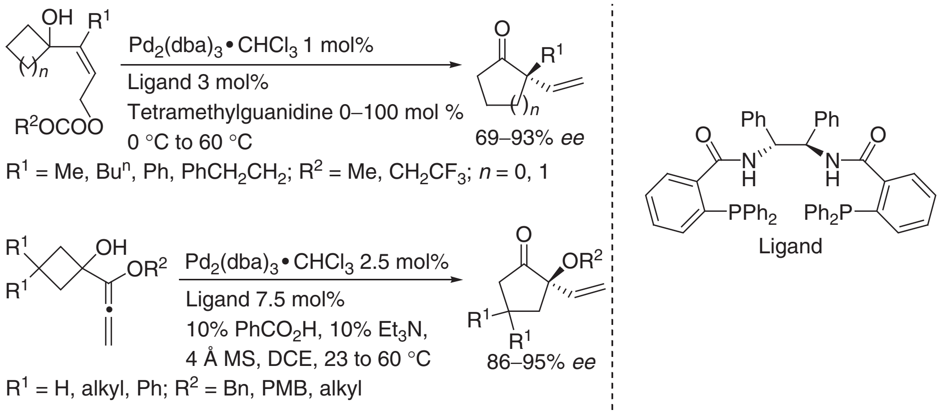


Scheme 50

3.16.3.7 Enantioselective Version

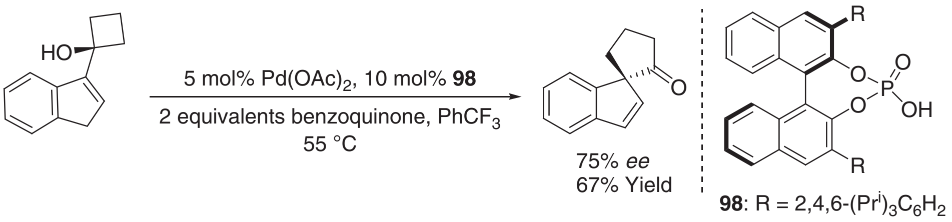
Since the newly formed stereocenter of the rearrangement product is commonly formed through a concerted transition state, the related enantioselectivity control is feasible by the employment of appropriate chiral catalyst, which possesses excellent enantioface selectivity on interacting with the substrate. Therefore, in the presence of a proper catalyst, even the racemic substrate in theory could afford a single chiral product by introducing two substituents with very different migrating aptitude. Up to now, chiral Lewis acid, cinchona alkaloids, and chiral Brønsted acids have been successfully applied into this type of rearrangement, in which the substrates usually have no chiral center.

Trost et al. first developed such a catalytic asymmetric semipinacol rearrangement of allylic alcohol using Pd(0) and their ligands.[62] Subsequently, they further expanded the substrate scope to allenylcyclobutanols (Scheme 51).[63]



Scheme 51

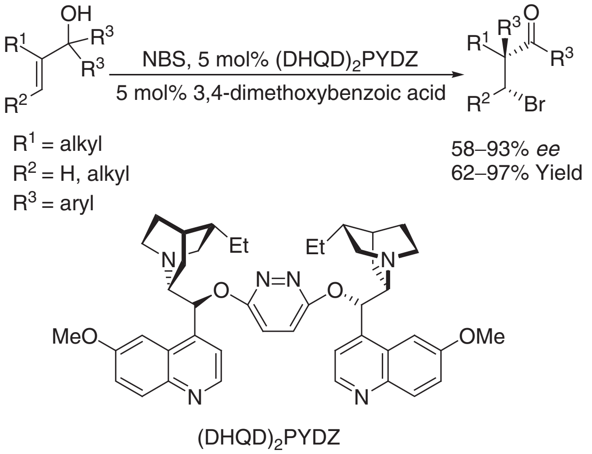
Using Pd(II) and the BINOL-derived phosphoric acid **98** as catalyst, Rainey et al. also reported a similar type of migratory ring expansion for the synthesis of indene derivatives. The transformation is proposed through an enantioselective allylic C – H activation with concomitant semipinacol ring expansion to the nascent π-allylpalladium species procedure (equation 10).[64]



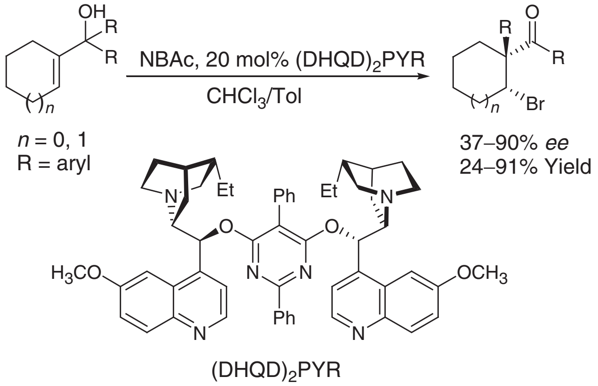
(10)

Because of the similar stereocontrol fashion with the Sharpless asymmetric dihydroxylation, halogenation/semipinacol rearrangement reaction catalyzed by cinchona alkaloid derivatives has been attempted by several research groups driven by this inspiration.

Tu and coworkers first developed an asymmetric bromination/semipinacol rearrangement of allylic alcohols under the catalysis of $(DHQD)_2PYDZ$. As a result, *β*-bromoketones containing a quaternary carbon center were obtained with up to 97% yield and 93% *ee* (Scheme 52).[65] Using the $(DHQD)_2PYR$ catalyst and NBAc, Hennecke et al. also described a similar enantioselective semipinacol rearrangement of cyclic allylic alcohols (Scheme 53).[66]

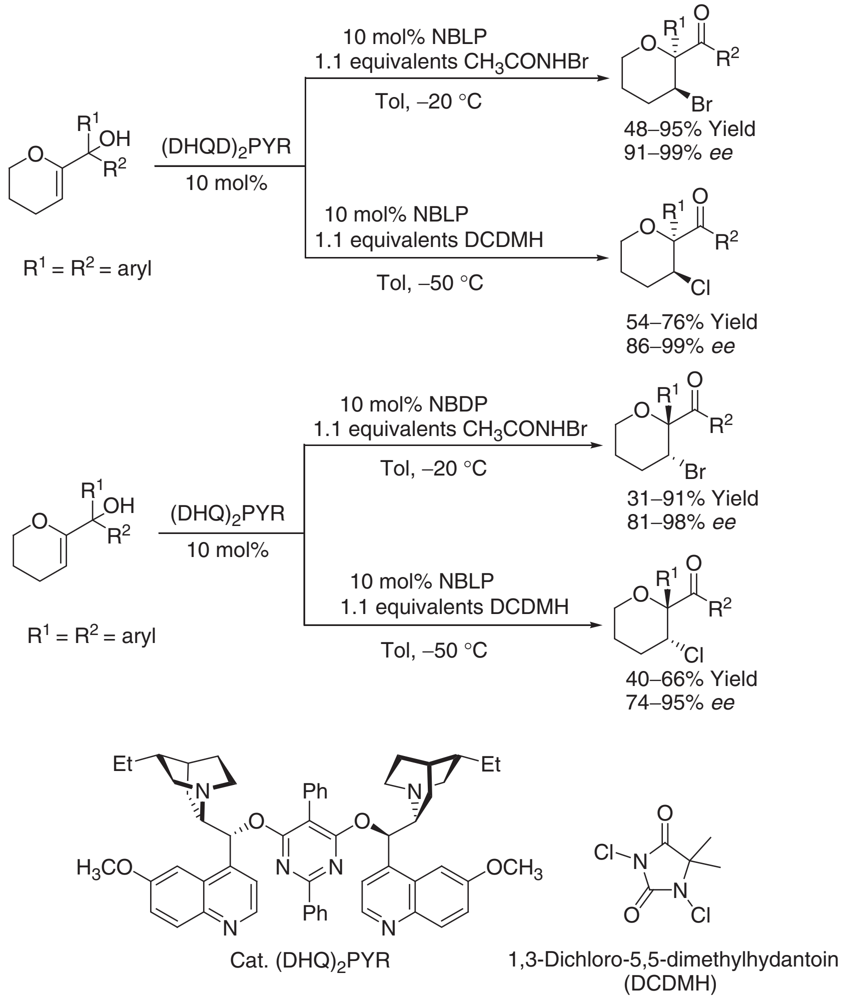


Scheme 52



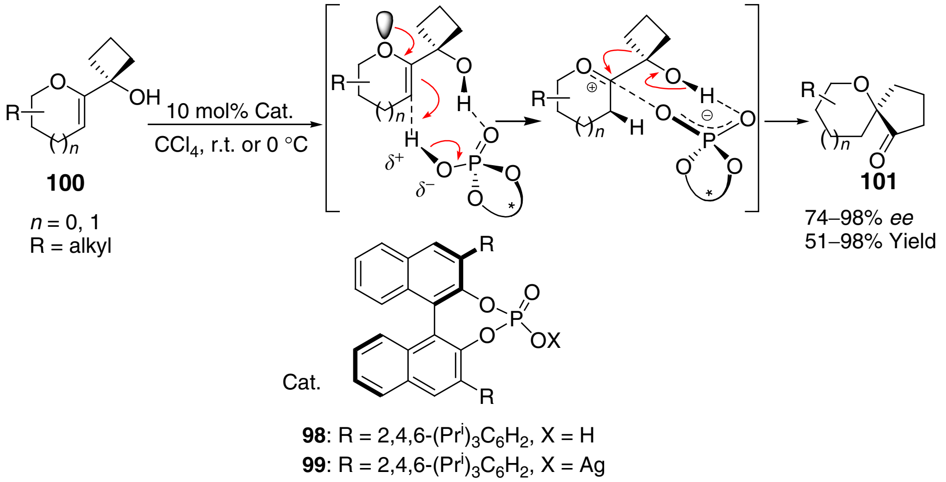
Scheme 53

2-Oxa allylic alcohols are also applicable in the similar conditions. In this case, N-Boc-L-phenylglycine (NBLP) or N-Boc-D-phenylglycine (NBDP) was used as an additive to improve the enantioselectivity. The reaction is valuable and versatile since two adjacent stereocenters, one of which is chiral oxa-quaternary carbon, were constructed effectively and two types of *β*-haloketo compounds (X=Br, Cl) were readily obtained. Moreover, both (+) and (−) enantiomers of the products could be obtained respectively with moderate to good yields and high *ee* (Scheme 54).[67]



Scheme 54

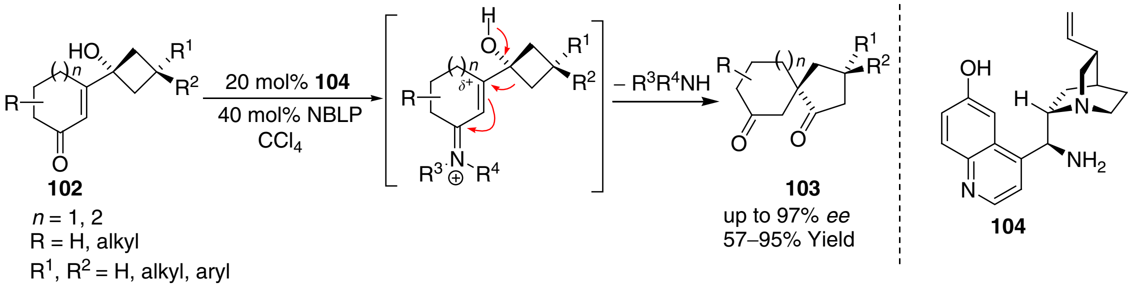
In addition, the electron-rich nature of the carbon–carbon double bond in the allylic alcohols could be further harnessed by using chiral Brønsted acid to enable a semipinacol-type rearrangement in an asymmetric way. Under the catalysis of the phosphoric acid **98** or its silver salt **99** in CCl_4, the 2-oxo allylic alcohols **100** rearranged smoothly to the chiral spiroethers **101**, presumably through protonation of the enol ether and a subsequent 1,2-carbon migration involving hydrogen bonding (Scheme 55).[68]



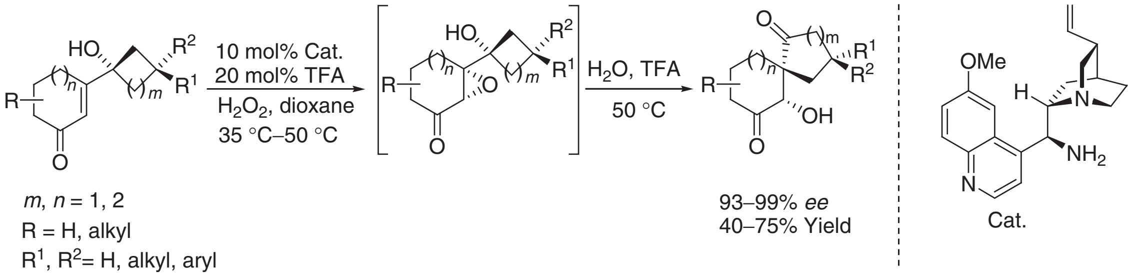
98: R = 2,4,6-$(Pr^i)_3C_6H_2$, X = H
99: R = 2,4,6-$(Pr^i)_3C_6H_2$, X = Ag

Scheme 55

Very recently, the asymmetric semipinacol rearrangement of allylic alcohols was further advanced by incorporating organocatalysis. Designed enone substrates **102** possessing an allylic alcohol motif undergo the semipinacol-type rearrangement under the promotion of a cinchona-derived catalyst **104** to form the 1,4-diketone products **103** bearing a quaternary carbon enantioselectively. The combination of the cinchona-derived amine **104** and N-Boc-L-phenylglycine (NBLP) in CCl_4 could effectively catalyze the rearrangement (Scheme 56).[69] Using the cinchona-derived amine as catalyst, an asymmetric epoxidation/semipinacol rearrangement of vinylogous α-ketol was carried out in a one-pot reaction (Scheme 57),[70] tri-oxygenated spirocycloalkanediones were obtained in up to 75% yield and 99% *ee*.

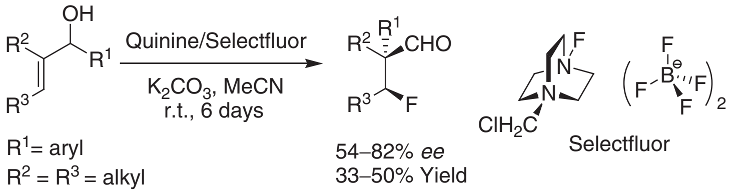


Scheme 56



Scheme 57

In contrast, asymmetric semipinacol rearrangement of racemic allylic alcohols induced by chiral electrophiles is very rare. To date, there is only one report on this kind of transformation. In this work, the enantioselective synthesis of α-quaternary *β*-fluoro aldehydes through the asymmetric semipinacol rearrangement of a range of secondary aryl allylic alcohols mediated by a quinine/Selectfluor combination was achieved. The reaction exhibited an excellent level of enantioconvergence, as no kinetic resolution of the racemic substrates was observed (Scheme 58).[71]



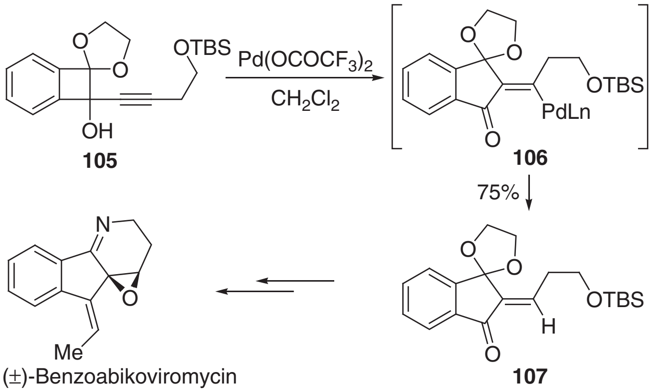
Scheme 58

3.16.4 Rearrangement of Propargylic Alcohols

Propargylic alcohols also could go through semipinacol rearrangements in the presence of transition metal catalyst.[54] This type of 1,2-migration is usually induced by the positive charge, which is generated by the coordination of metal catalyst with the alkyne moiety. Corresponding substrate scope is the main focus on the following two categories.

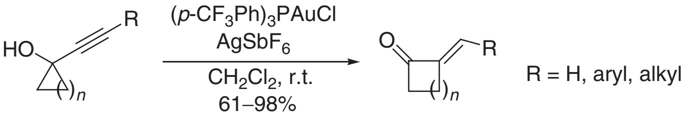
The first one involves the substrate containing ring strain, which acts as the main driving force for the rearrangement process. Therefore, compounds with three- or four-membered ring motif are generally applied. Similar to the normal semipinacol rearrangements, the cycloalkanol carbon that stabilizes positive charge better migrates preferentially.

Liebeskind's group has done the pioneering study under this topic.[72] They discovered that alkynyl cyclobutanol could efficiently undergo a semipinacol rearrangement in the presence of Pd (II) catalyst. Such a reaction has been applied in the synthesis of (±)-benzoabikoviromycin (Scheme 59). Under the catalysis of $Pd(OCOCF_3)_2$, **105** went through a stereospecific ring expansion via selective 1,2-migration of the ketal group to give the vinyl-palladium intermediate **106**, which was then protonated to afford the monoketal **107** in 75% yield with the desired geometry for subsequent chemical transformations. The formation of the more stable benzylic cationic intermediate was the key factor for the selectivity of the migration.

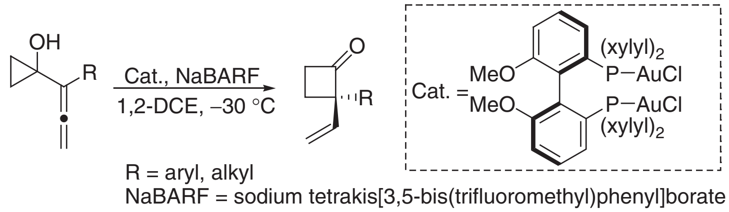


Scheme 59 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

A similar type of transformation could also be achieved using gold(I) catalyst. Toste and coworkers have reported the ring expansion of cyclopropanols and cyclobutanols through the activation of the triple bond (Scheme 60).[73] Based on these results, they have also successfully developed an enantioselective ring expansion of allenylcyclopropanols using gold(I) catalyst (Scheme 61).[74]

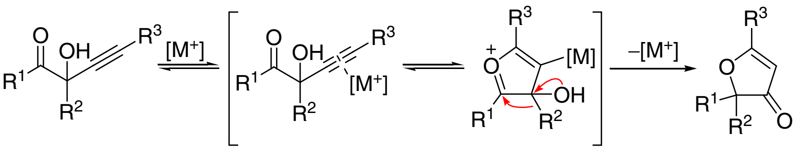


Scheme 60



Scheme 61

The second category of the propargylic alcohol substrate features an additional carbonyl or imine functionality at the β-position of the hydroxyl group.[75] After the activation of the triple bond, the substrate will form a cyclic oxonium intermediate, which is capable of going through a semipinacol rearrangement to give 3(2*H*)-furanone compound. Because the contraction of five-membered intermediate is not favorable, migration of the group R^2 is usually observed (Scheme 62).



Scheme 62

3.16.5 Rearrangement of Epoxides

Oxirane, as the simplest cyclic ether, consists of three ring atoms. Since this structure represents a typical three-membered ring, this makes it highly strained. Due to this structural feature, epoxides are more reactive than other ethers. As a result, a number of acid-promoted semipinacol rearrangement of epoxides via different migration patterns induced by an oxirane ring-opening have been developed, and have shown wide utilities in natural product syntheses. This section will focus on the rearrangement of epoxides and their derivatives (analogs) as well as some applications of these rearrangements.

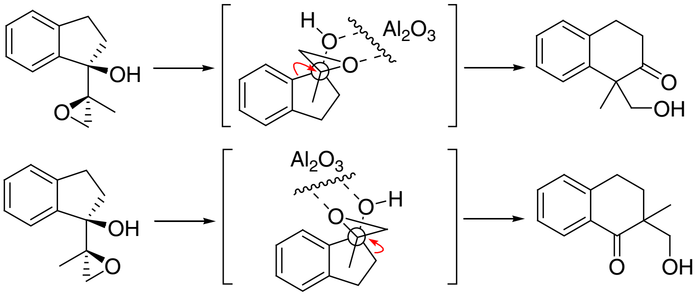
3.16.5.1 Epoxy Alcohols and Their Derivatives

Since the first report in 1968,[76] the semipinacol rearrangement of 2,3-epoxy alcohols and their derivatives has been extensively investigated in both cyclic and acyclic systems.[4,7] Generally speaking, this type of rearrangement has the following features. First, it can be promoted by a variety of reagents either in a stoichiometric or a catalytic manner. Second, because the migrating group usually attacks the *anti* side of the epoxy moiety, the rearrangement procedure can proceed with excellent stereoselectivity and regioselectivity. Particularly, the stereochemistry of the migrating carbon center can be rigorously retained in most cases. Third, the rearrangement can produce a large number of aldol-type products diastereoselectively, and even enantioselectively with the use of enantiopure 2,3-epoxy alcohols, which are readily available through sharpless asymmetric epoxidation (SAE), as well as Jacobsen and Shi epoxidations. Especially, it is very effective for the products containing a stereogenic quaternary carbon center at the migration terminus, which are difficult or impossible to synthesize by the classical aldol reaction. Fourth, the carbonyl group resulting from the rearrangement can further be functionalized *in situ* to effect corresponding tandem processes. All these make this process extremely useful in organic synthesis.

3.16.5.1.1 Promoters of the rearrangement

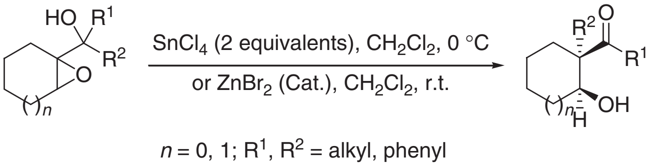
Due to the existence of the oxygen atom in the strained three-membered ring, oxygenophilic reagents suitable for initiating the epoxide-cleavage will likely promote the corresponding semipinacol rearrangement. Accordingly, a wide range of Lewis acids, Brønsted acids and acidic reagents have been applied in the rearrangement of 2,3-epoxy alcohols in the last 40 years. These not only provide different choices for further use of related methodologies, but also give the possibilities toward new tandem protocols.

As the first example of this kind of reaction, Cheer and Johnson reported the rearrangement of epoxy alcohols catalyzed by boron trifluoride or acidic alumina. Based on the different results by the two catalysts, a 'surface-adsorbed' transition state was proposed (Scheme 63).[76]



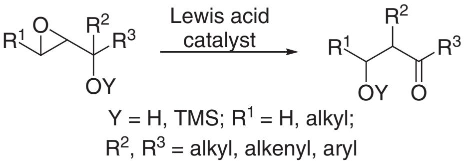
Scheme 63

In general, a stoichiometric amount of Lewis acid is the most common reagent for the rearrangement. However, by variation of the metal reagents, a number of transformations have been improved by using a catalytic amount of Lewis acid, which might offer potential industrial and commercial benefits. For example, Marson et al. have developed a stereoselective semipinacol rearrangement of 2,3-epxoy alcohols mediated by 2 equivalents of $SnCl_4$,[77] which more or less affects its further application (Scheme 64). Fortunately, a catalytic amount of $ZnBr_2$ was found to be effective for this reaction through catalyst screening.[78]

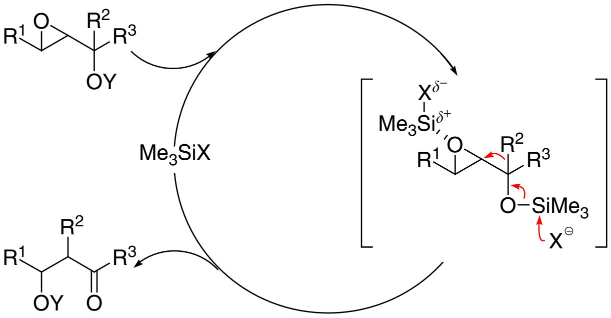


Scheme 64

Another type of Lewis acid which could effectively promote (catalyze) the semipinacol rearrangement is silyl reagent. Right after their report of the epoxy silyl ether rearrangements under the Lewis acidic conditions (Scheme 65),[79] Suzuki et al. developed a catalytic version by using TMSX (X=OTf, I), which generally gave better results than the stoichiometric conditions.[80] Because of the special reaction mechanism and chemical property of TMSX, the catalyst could be regenerated during the course of the rearrangement (Scheme 66). Till date, the scope of silyl reagents has been further expanded, for example, the use of TBSOTf, and TESOTf.

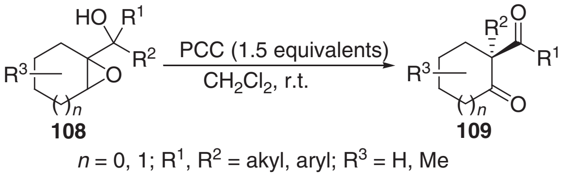


Scheme 65



Scheme 66

Additionally, intrinsic acidic character of some reagents could also initiate the rearrangement procedure. It was found that PCC (pyridinium chlorochromate) type reagents could promote the 1,2-migration reaction of epoxy alcohol **108** and further oxidize the resulting hydroxyl group to give product **109** in a one-pot manner (Scheme 67).[81] Further study proved that some epoxides like **110a** and **110b** (**111a** and **111b**) could undergo an interesting diastereoselective oxidation with PCC type reagents.[82] On treatment with PCC, one of the diastereoisomers could react selectively to form the corresponding 1,3-dicarbonyl compounds, and the other was recovered with up to 96% *de* in good yield (Table 1). This method has been successfully applied in the synthesis of the spiroketal moiety of the HIV-1 protease inhibitive didemnaketals.[83]



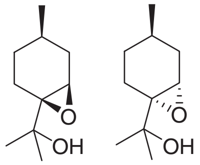
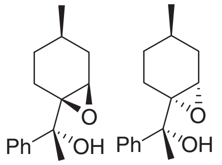
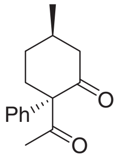
Scheme 67

Sometimes, the substrates containing special structural units, such as three- or four-membered rings, possess high ring strain energy and are prone to undergo further transformation. In this case, very mild acidic reagents are sufficient to promote the rearrangement. Fukumoto et al. successfully finished the enantioselective total synthesis of (−)-frontalin with a semipinacol rearrangement as the key step, during which ketone **113** could be easily obtained by the treatment of substrate **112** with silica gel (Scheme 68).[84]

3.16.5.1.2 Patterns of the rearrangement

Depending on the structural features of the substrate and reaction conditions, the semipinacol rearrangement of 2,3-epoxy alchols and their derivatives can proceed mainly via 1,2-, 2,3-, or 3,2-migration fashion.[4] Basically, the migration is induced by the position of epoxy opening, which forms the most stable carbocation intermediate. As a result, epoxy ring-opening at C2-position will lead to 1,2- or 3,2-migration, and the opening at C3-position will give 2,3-migration (Scheme 69).

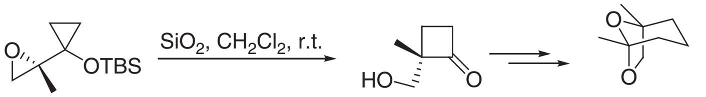
Table 1 Diastereo-recognizable reaction between Cr(VI) reagents and tertiary α-hydroxy epoxide

No.	*Substrate a/b, ratio*	*Reaction time*	*Recovered a/b, ratio, yield (%)*[a]	*Product, yield (%)*[b]
1	 **110a/110b** 61/39	5 h	96/4, 53	not detected
2	 **111a/111b** 63/37	4.5 h	92/8, 42	 84

[a]The yield refers to the ratios of recovered a + b to starting a + b.

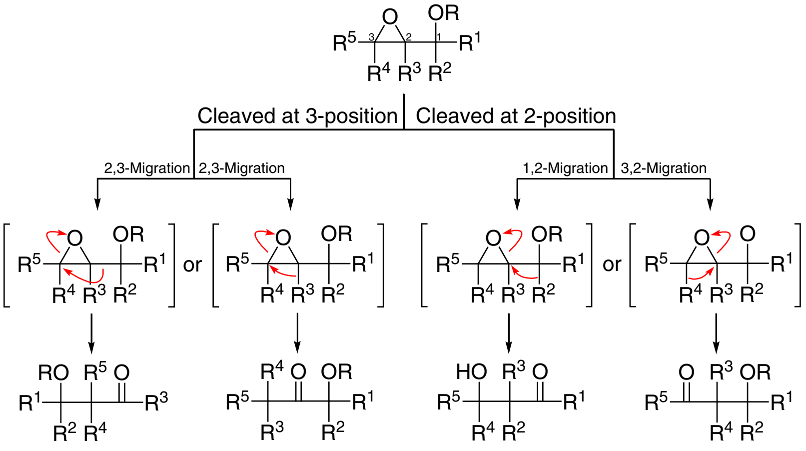
[b]The yield refers to the ratios to the corresponding starting isomer.

Source: Reprinted from Tu, Y. Q.; Ren, S. K.; Jia, Y. X.; *et al. Tetrahedron Lett.* **2001**, *42*, 2141.



112 **113**

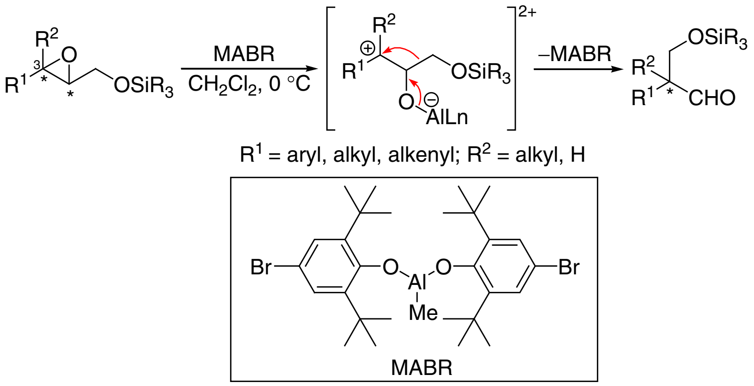
Scheme 68



Scheme 69

One representative work is Yamamoto et al.'s report on the semipinacol rearrangement of epoxy silyl ethers promoted by a hindered Al-based Lewis acid such as methylaluminum bis(4-bromo-2,6-di-*tert*-butyl phenoxide) (MABR) (Scheme 70).[85] Because the substrates with two substituents or a cation-stabilizing group at C-3 were used, selective ring-opening at C-3 tends to give a site-specific 2,3-migration, affording various chiral 2-quaternary aldeyhyde aldols. It should be noted that the use of bulky ligand on the catalyst is crucial for this rearrangement. Firstly, the repulsion between the catalyst and the siloxy methyl moiety is expected to facilitate the alkyl transfer. Secondly, the bulky ligand would probably prevent it from interacting with the cation intermediate as either a base or a nucleophile.

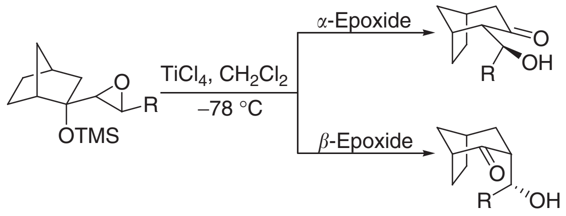
In general, semipinacol rearrangements of 2,3-epoxy alcohols and their derivatives are stereoselective. The migrating group is usually antiperiplanar to the C–O bond that breaks, and the inversion of the configuration at carbon receiving the migrating group is always observed. Therefore, these kind of reactions is very useful in chiral synthesis, especially after the achievement of SAE and other enantioselective epoxidation reactions. There are a number of factors that affect the course of migration, such as the



Scheme 70

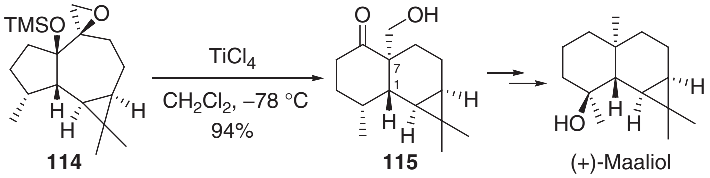
stereochemistry of the substrates, migratory aptitude of the substituents, electronic factors, ring strain energy, and reaction promoters.

Normally, the stereoelectronic requirement for the semipinacol rearrangement is the dominant factor. In Cha's report on 1,2-migration of 2,3-epoxy silyl ethers derived from norcamphor, the rearrangement reactions are stereospecific. The relative configuration of the epoxy group induces the selectivity of the migrating carbon, and the common migrating aptitude for norbornane derivatives was not observed (**Scheme 71**).[86]



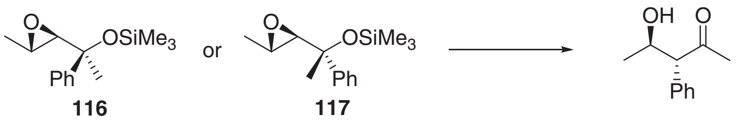
Scheme 71

In the case of the epoxy alcohol with a rigid structure skeleton, only a specific migrating group meets the stereoelectronic requirement for the rearrangement. Consequently, the related reaction is highly regioselective. During this transformation, the stereochemistry of the substrates plays an important role in the related semipinacol rearrangements. In the synthesis of (+)-maaliol (**Scheme 72**), Wijnberg and de Groot used a semipinacol rearrangement of *cis*-2,3-epoxy silyl ether **114** to transform a 5,7-membered ring system to a 6,6-membered one.[87] Treatment of **114** with $TiCl_4$ in CH_2C1_2 at -78 °C generated *β*-hydroxy ketone **115** in 94% yield. Ketone **115** has a *trans*-fused 6,6-membered ring skeleton and the desired angular hydroxymethyl group at the C7 quaternary center.



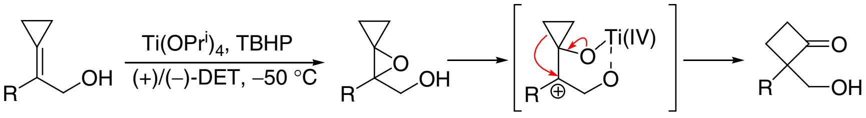
Scheme 72

However, if the carbon–carbon bond between the epoxy and hydroxyl is rotatable, migratory aptitude of the substituents is most likely to kick in. Since a carbocation is formed following the epoxide cleavage during the semipinacol rearrangement, the adjacent substituent which is capable of stabilizing the carbocation better tends to migrate preferentially.[5c] Normally, the relative migration aptitude is close to that of pinacol rearrangement, i.e., aryl ~ H ~ alkenyl > Bu^t ≫ cyclopropyl > 2°alkyl > 1°alkyl. Because of this feature, the reaction can be regioselective by introduction of two substituents with very different migration aptitude. Especially, if the carbon bond between C1 and C2 during the transition state is freely rotatable, the configuration of the alkoxy *α*-carbon sometimes will not affect the rearrangement results. For example, in the report on the semipinacol rearrangement of epoxy silyl ethers, Tsuchihashi et al. observed that both the *erythro-trans* isomer **116** and the *threo-trans* isomer **117** afforded the same *threo* aldol as the only isolable product (equation 11). Conversely, a mixture of two isomers will most likely be formed if substrates with two substituents having similar migration aptitude are used.[79]



(11)

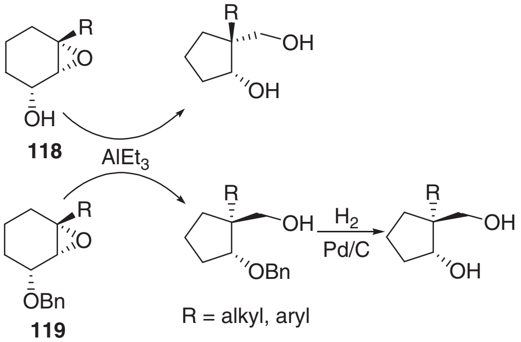
Ring strain energy also can be the dominant factor for migration fashion. Nemoto and Fukumoto investigated the domino asymmetric epoxidation and enantiospecific ring expansion of cyclopropylidene alcohols.[88] Due to the ring strain energy of cyclopropyl moiety, 3,2-migration became the preferred way of the rearrangement process, which gave the chiral cyclobutanone as the sole product on the epoxy opening at C2-position (Scheme 73).



TBHP = *tert*-butyl hydroperoxide; DET = diethyl tartrate; R = alkyl, aryl

Scheme 73

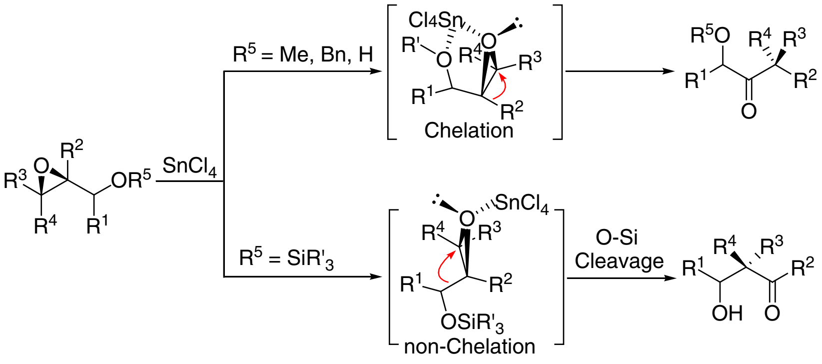
Additionally, the protecting group on the hydroxyl also affects the migration pattern. Substrate **118** could go through an $AlEt_3$-promoted tandem reduction rearrangement reaction to give 2-quaternary C1-C3 *syn* 1,3-diol products.[89] Interestingly, *trans* 1,3-diol compounds were obtained with Bn-protected substrates **119** under the same conditions.[90–91] Even though the mechanism of the second transformation remaines unclear, the relative configuration of the product can be controlled optionally by this strategy (Scheme 74).



R = alkyl, aryl

Scheme 74

Besides the relative configuration, the protecting group also can affect the regioselectivity of the rearrangement. Kita et al. have found that the semipinacol rearrangement of epoxy substrates will result in two different types of products with bidentate Lewis acid by varying the protecting group of the hydroxyl (Scheme 75).[92] They attribute the experimental results to the alteration of the corresponding chelation transition state. Because the bidentate chelation between the two oxygen atoms and Sn metal will be



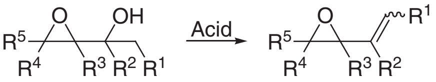
Scheme 75

formed in the corresponding transition state with the use of alkyl ether substrate, the migration aptitude of the alkyloxy methyl group will be reduced. Consequently, the alkyl group on the other side of the epoxy will shift selectively to form the α-alkyloxy ketones. On the contrary, *β*-hydroxyl ketones will be the final products by using of bulky trialkylsilyl group, which prevents the formation of bidentate chelation.

3.16.5.1.3 Side reaction

Like most reactions in organic chemistry, the appearance of side reactions can be a problem of the related rearrangement procedure and will affect the reaction results.

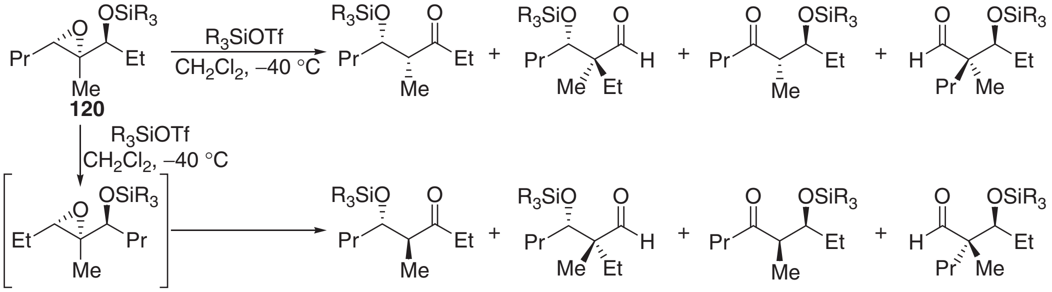
Generally, elimination of the hydroxyl group is one of the common side reactions of the semipinacol rearrangement of 2,3-epoxy alcohol, which is mainly due to the use of acidic reagents and the existence of hydroxyl group in the substrates. Especially those with tertiary hydroxyl group should be handled with caution (Scheme 76). Fortunately, this kind of reaction could normally be minimized by lowering the reaction temperature, changing the promoter, or employment of hydroxyl protecting group.



Scheme 76

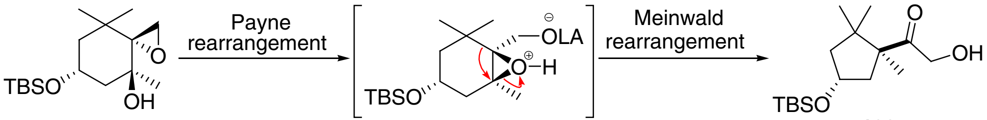
Because 2,3-epoxy alcohol compounds and their derivatives contain adjacent nucleophilic and electrophilic groups, this makes Payne rearrangement another major side reaction.[93] Since the Payne rearrangement will result in a new 2,3-epoxy alcohol compound, which also can go through semipinacol rearrangement, the involvement of this side reaction will usually give a mixture of different products.

During Jung and Heuvel's study on the silyl triflate-promoted rearrangement of optically active tertiary epoxide primary alcohols and sily ethers, they found that the rearrangement of epoxy silyl ether **120** afforded four more products because of the existence of the Payne rearrangement (Scheme 77).[94]



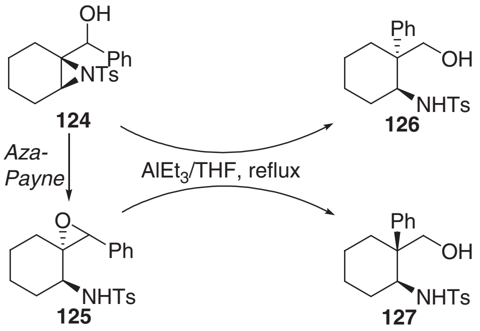
Scheme 77

At another extreme, if the substrate goes through related Payne rearrangement exclusively, reaction with high stereoselectivity and regioselectivity could also be achieved by the semipinacol rearrangement of the Payne rearrangement product. In 2012, Gosselin et al. reported the Lewis acid-induced tandem Payne/Meinwald rearrangement of α-hydroxyl-spiro epoxide **121**, which gave ketone **123** as the single product in the presence of $Yb(OTf)_3$, $BF_3•OEt_2$, or $SnCl_4$ (equation 12).[95] This tandem procedure began with the acid-induced Payne rearrangement of substrate **121**, followed by a ring contraction of the resulting intermediate **122** to furnish stereospecifically the ketone **123**.



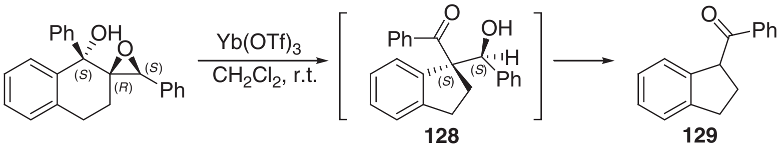
121 **122** **123** (12)

Moreover, as the Payne rearrangement of 2,3-epoxy alcohol is always accompanied by an inversion of configuration at the C2-position, this side reaction can be very useful if the original expoxy alcohol has the same ring opening position and migrating group as the one resulting from Payne rearrangement, which will lead to a pair of diastereoisomers. One example is the reaction of compound **124** and its Payne rearrangement product **125** (Scheme 78).[90] These two compounds afforded products **126** and **127** with opposite relative configuration on the treatment of $AlEt_3$, and this provides a strategy to stereoselectively get a pair of C2-epimers from the same starting material.



Scheme 78

In addition to the side reaction of the substrates, the side reaction can also occur after the rearrangement. Sometimes, the semipinacol rearrangement of 2,3-epoxy alcohols is mentioned as a 'nonaldol aldol' process, because aldol products are obtained through a nonaldol procedure. Therefore, retroaldol fragmentation will be found in some cases with less stable product. Roberts et al. have published a research paper related to the semipinacol rearrangement of some spirocyclic epoxyalcohols (Scheme 79). Because of the unstability of the rearrangement product **128**, the retroaldol product **129** became the final product.[96] Similar results were also observed by Liang et al.[97]

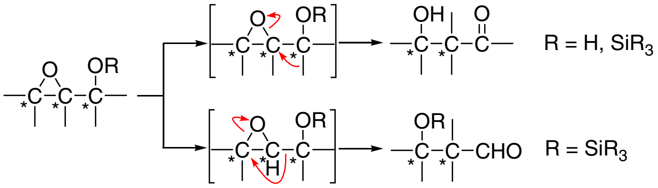


Scheme 79

3.16.5.1.4 Substrate scope of the rearrangement

In the past several decades, a large variety of 2,3-epoxy alcohols and their derivatives have been successfully applied into the semipinacol rearrangement. Accordingly, lots of synthetic important intermediates have been obtained, such as α-quaternary β-hydroxy carbonyl compounds, α-quaternary β–amino carbonyl compounds, and acyclic or cyclic aldols. Based on their structures, they can be divided into acyclic or cyclic type.

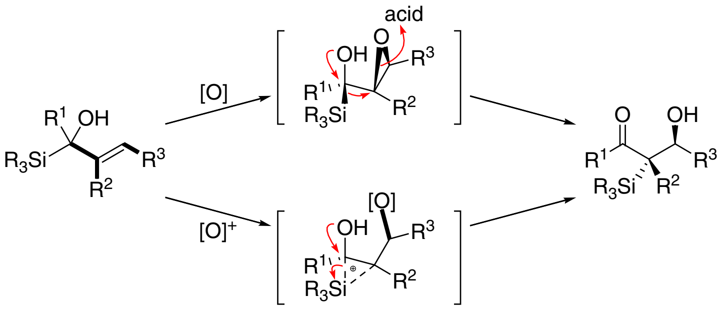
In acyclic systems, Tsuchihashi and Yamamoto have done a lot of pioneering work. They first developed the 1,2-rearrangement of epoxy silyl ether compounds, which gave a new method toward the synthesis of β-hydroxy carbonyl compounds.[79] Subsequently, a different rearrangement pattern was achieved by varying the structure of the substrate and the catalyst (Scheme 80).[80] These transformations are highly stereoselective and site-specific. Especially, in combination with SAE, a number of enantiopure aldol-type products can be accessed through these nonaldol processes, most of which have focused on phenyl, vinyl, alkyl, or hydrogen migration.



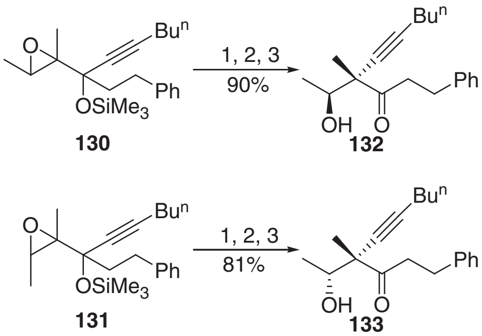
Scheme 80

Except the groups mentioned above, the silyl group also can be the one to migrate during the course of the semipinacol rearrangement. Bienz et al. reported a stereoselective tandem reaction which converted α-silylated allylic alcohols to aldol-type products by using epoxidizing reagents (Scheme 81).[98] They proposed that the reaction proceeded either by a cascade process involving epoxidation of the allylic-alcohol moiety followed by an acid-promoted semipinacol rearrangement, or through a rearrangement of the silanium ion intermediate to give the final products.

Generally, the alkynyl group has poor migratory aptitude because of the deficiency of its π-electrons to participate in the adjacent cationic species in terms of electronic and/or spatial factors. This is also supported by computational studies, which shows a larger activation energy of the ethynyl shift than that of the vinyl migration.[99] However, the migration aptitude improves significantly by conversion of alkynyl group into its corresponding Co complex, because an alkyne-Co complex strongly stabilizes a cationic charge at its α-position,[100] which makes it a better migrating group than *p*-methoxyphenyl group. Suzuki and coworkers successfully developed a stereospecific semipinacol rearrangement of alkyne-Co complex substrates.[101] Among them, substrate **130** and **131** were subjected to this protocol to give α-quaternary β-hydroxy carbonyl compounds **132** and **133**, respectively (Scheme 82).



Scheme 81

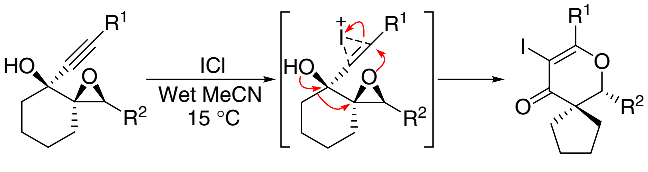


130 **132** **131** **133**

1. $Co_2(CO)_8$, hexane; 2. TMSOTf (5 mol%), CH_2Cl_2, –78 °C, 1 h; 3. CAN, MeOH

Scheme 82

Without the assistance of Co complex, an interesting rearrangement pattern can also be observed by varying the reaction promoter, which is capable of activating the triple bond. For instance, 2,3-dihydro-5-iodopyran-4-one compound was constructed through a tandem cyclization/migration reaction of 1-alkynyl-2,3-epoxy alcohol in the presence of ICl (Scheme 83). A wet solvent is crucial for this transformation.[102]



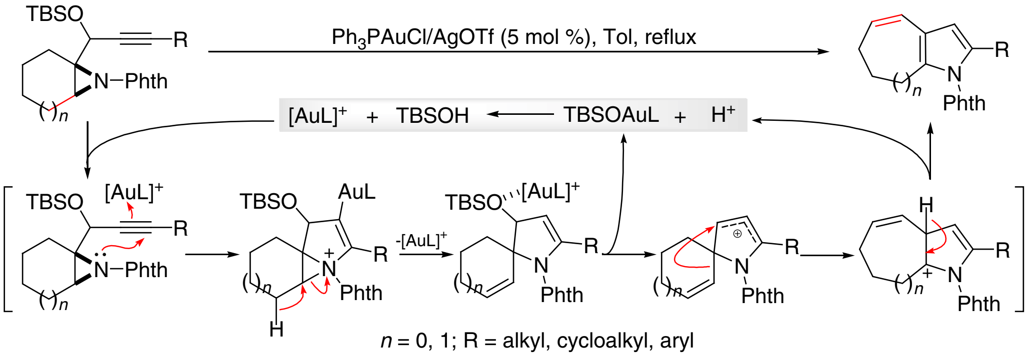
R^1, R^2 = aryl, alkyl

Scheme 83

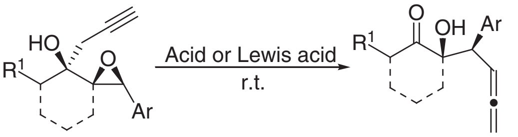
In a similar activation mode, the propargylic aziridine can go through an unusual tandem rearrangement process to give substituted pyrroles under the catalysis of Au (I) (Scheme 84).[103]

If there is a methylene group between the alkynyl and hydroxyl group, a semipinacol rearrangement involving a 3,3-migration might occur. Both cyclic and acyclic substrates can give the desired products, and the presence of an aryl group at 3-position is essential for this reaction (Scheme 85).[104]

In cyclic systems, the semipinacol rearrangement provides a viable solution to the cyclic aldol problem. A large number of α-quaternary β-hydroxy carbonyl compounds have been synthesized through this strategy; especially those that cannot be



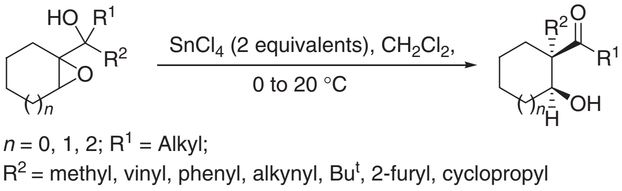
Scheme 84



Scheme 85

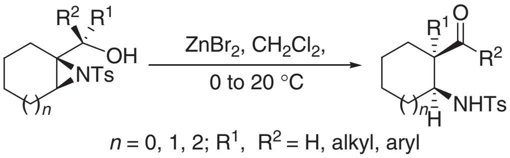
obtained through simple aldol condensations have been achieved with excellent stereoselectivities. Usually the migrating group can shift within the ring system or either from exocyclic to endocyclic position, or in the reverse way.

Early work on this type of transformation was reported by Marson et al. His group first developed a highly diastereoselective semipinacol rearrangement of 2,3-epoxy alcohols promoted by tin(IV) chloride at ambient temperatures (Scheme 86).[77] A number of migrating groups are applicable to this reaction, such as methyl, *tert*-butyl, cyclopropyl, vinyl, alkynyl, phenyl, and 2-furyl. It is noteworthy that both *syn* and *anti* epoxy alcohols give the same diastereoisomerically pure *β*-hydroxy ketone.



Scheme 86

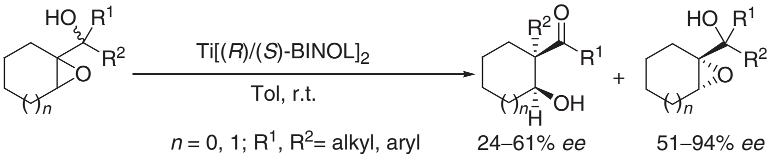
If 2,3-aziridino alcohols are applied to this reaction, then the corresponding *β*-amino carbonyl compounds, which are synthetically versatile intermediates, are produced in high yield (Scheme 87).[105] Like the previous one, this reaction is also stereoselective.



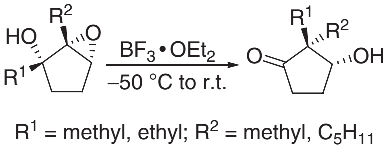
Scheme 87

An enantioselective version of this type transformation has been attempted by Tu's group.[106] Because the classic SAE is not efficient in the epoxidation of the related allylic tertiary alcohols, a kinetic resolution was carried out by employment of the chiral catalyst Ti[(*R*)/(*S*)-BINOL]$_2$, which gave moderate to excellent *ee* for the unreacted starting material (Scheme 88).

Also, the migration could happen within the ring system without changing the ring size. A select example is Walsh's report on the semipinacol rearrangement of enantiopure 2,3-epoxy alcohols with a five-membered ring. This procedure offered a quaternary-center containing aldols in good yield and excellent *ee* (Scheme 89).[107]

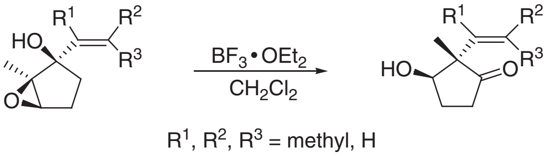


Scheme 88



Scheme 89

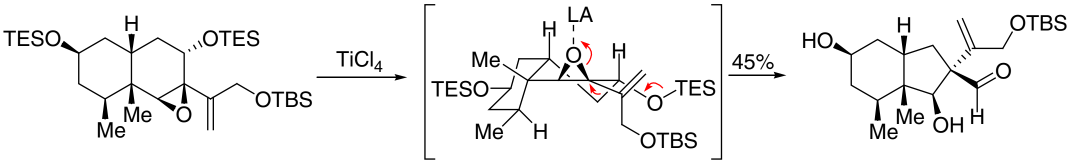
Snape further extended this transformation by introducing a more synthetically divergent alkenyl substituent (Scheme 90).[108] Unfortunately, application of six-membered ring substrate to this reaction condition was not successful.



Scheme 90

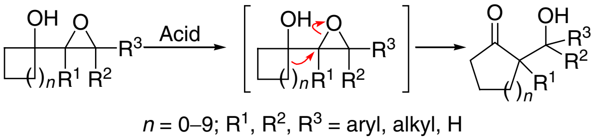
Moreover, the rearrangements of cyclic substrates are always accompanied with ring contraction or expansion processes, which provide a general strategy for constructing the key skeletons of some bioactive molecules.

Due to the existence of a high ring strain energy with three- or four-membered rings, the most popular semipinacol ring contraction are transformations from six-membered ring to five-membered ones. Among them, the migration patterns mainly depend on the position where epoxy opens. Only a few examples involve the participation of the hydroxyl group (related moiety), for instance, the key step of Danishefsky's total synthesis of peribysin E (Scheme 91).[109]



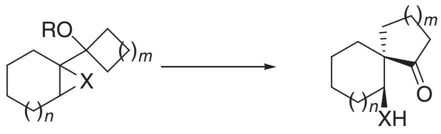
Scheme 91

In sharp contrast, ring expansion has much better applicability. Usually, thermally favorable expansions from three- to four-membered ring or from four- to five-membered are well studied. However, much bigger ring sizes such as a 12-membered one is also applicable in this type of transformation (Scheme 92).[77]



Scheme 92

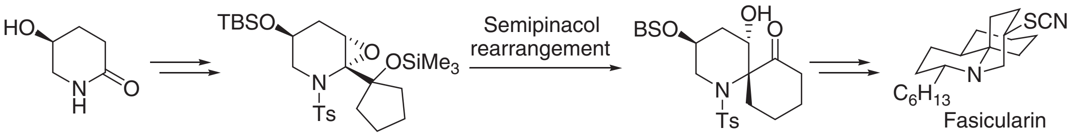
One important application of ring expansion rearrangement is the synthesis of spirocyclic β-hydroxyl (amino) ketones, which are widely used as chiral catalysts or ligands in organic synthesis upon reduction of the carbonyl group (Scheme 93).



n = 0, 1; m = 1–9; R = H, SiR^1_3; X = O, NTs

Scheme 93

Importantly, this type of transformation becomes even more practical by introduction of a nitrogen atom on the ring system. One good example is Dake's formal synthesis of fasicularin, which involves an α-siloxy-epoxide ring expansion to form 1-azaspirocyclic ketone **134** (Scheme 94).[110]



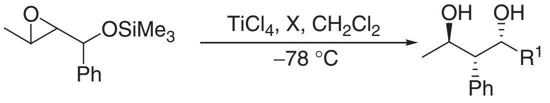
134

Scheme 94

3.16.5.1.5 Tandem processes

Tandem reactions are of great importance to organic chemists, because of their high efficiency and selectivity by combining multiple reactions in one step.[111–112] Definitely, there is no exception to the semipinacol rearrangement of 2,3-epoxy alcohols and their derivatives. Since the products of the rearrangement normally contain a carbonyl group, the tandem protocols are always focused on this functional group. To date, different types of reactions have been employed into related cascade procedures, such as Meerwein–Pondorf–Verley reaction, Evans–Tishchenko reaction, Mukaiyama aldol reaction and Schmidt reaction.

In 1986, when Yamamoto and Tsuchihashi first reported the rearrangement reaction of epoxy silyl ether compounds, they already attempted the related cascade procedures such as *in situ* reduction by Et_3SiH or alkylation with allyltrimethylsilane of the rearrangement product (Scheme 95).[79]

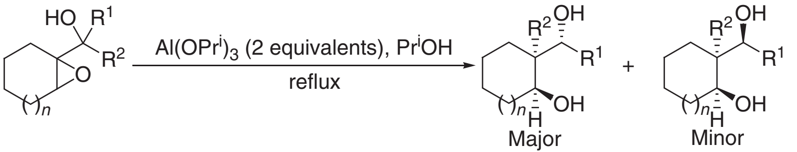


X = Et_3SiH, R^1 = H, 58% yield

X = $CH_2{=}CHCH_2SiMe_3$, R^1 = $CH_2CH{=}CH_2$, 80% yield

Scheme 95

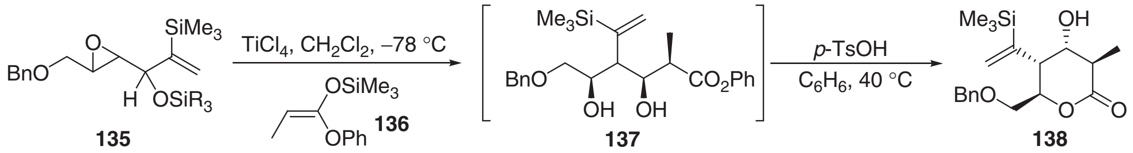
The reduction process also can be achieved using Meerwein–Pondorf-Verley reaction. Tu et al. successfully converted epoxy alcohols into 1,3-diols using $Al(OPr^i)_3$ and Pr^iOH (Scheme 96).[113]



n = 0, 1, 2; R^1, R^2 = alkyl, aryl

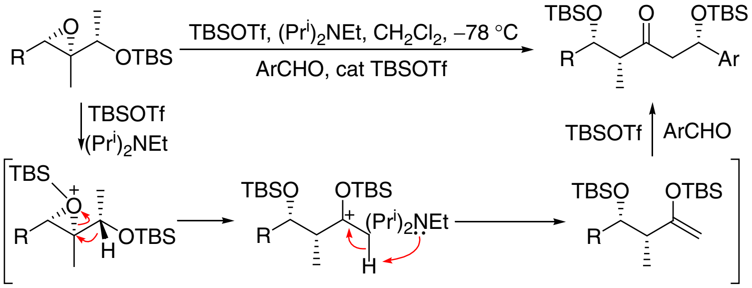
Scheme 96

In combination with Mukaiyama aldol reaction, the aldehyde generated by semipinacol rearrangement of epoxy secondary silyl alcohols can be captured by enol silane. Stereoselective synthesis of more than three-contiguous asymmetric centers with this strategy has been realized by Suzuki and coworkers.[114] Premixing of $TiCl_4$ and epoxy silyl ether **135** at −78 °C followed by the addition of silyl ketene acetal **136** gave **137**, which afforded **138** as the sole product after acid treatment. A similar type of reaction was also observed by Rahn and Kalesse (Scheme 97).[115]



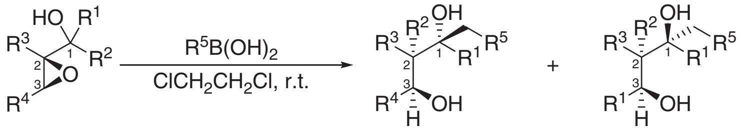
Scheme 97

It is worth mentioning that the semipinacol rearrangement/Mukaiyama aldol reaction could also follow a different way from the one described above, i.e., the rearrangement product in the reaction becomes the nucleophilic part. Jung has applied this method in the synthesis of 1,5-bis-silyloxy-3-alkanone by introduction of a hindered amine base and silyl triflates, which gives a silyl enol ether intermediate for the following aldol reaction (Scheme 98).[116]



Scheme 98

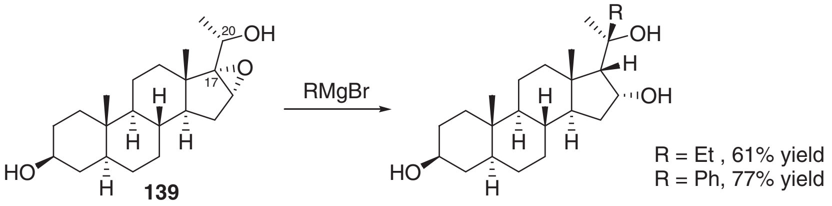
Additionally, semipinacol rearrangement/alkylation reactions can be effected by using reagents with dual roles. For example, Tu's group has developed a boron-mediated tandem process of 2,3-epoxy alcohols, which gave multifunctional 1,3-diols in good to excellent yields and stereoselectivities (Scheme 99).[117] During this procedure, instead of the relative configuration of C1 in the substrates, it is the substituent R^4 that affects the relative configuration of C1 in the product.



R^1, R^2 = alkyl, aryl; R^3 = alkyl; R^4 = alkyl, H; R^5 = ethynyl, vinyl

Scheme 99

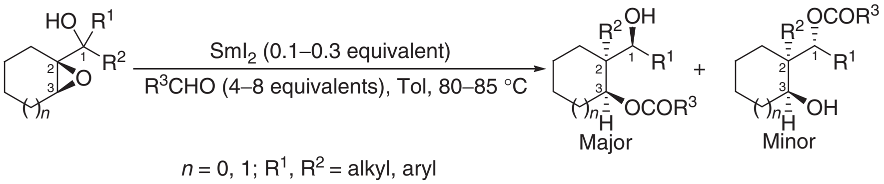
In addition to boronic acid, Grignard reagents, the most common alkylation reagent sometimes are capable of inducing a similar tandem process. Tian and coworkers reported an interesting cascade reaction of 20(*S*)-hydroxy-5α-prognane-16(17)-epoxide **139** to give related steroids analogs with an unusual C17α side chain (Scheme 100).[118] The *S* stereochemistry of C20 was crucial for this procedure.



Scheme 100

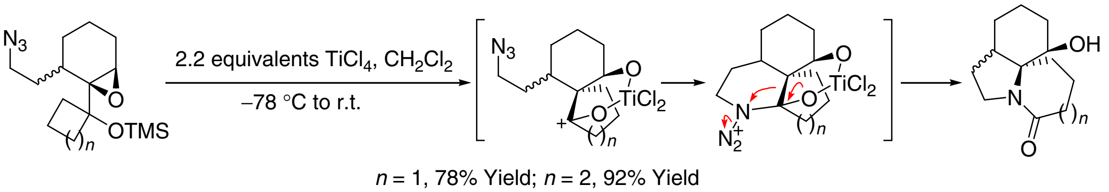
Further extension of the tandem protocol can be achieved by making use of the *β*-hydroxy carbonyl moiety, which can be generated by most of the semipinacol rearrangements of 2,3-epoxy alcohols. One excellent example is the involvement of Evan–Tishchenko reaction (Scheme 101). This transformation process has the following features: (1) three contiguous stereocenters are constructed in one step; (2) only one diastereoisomer product can be obtained from a mixed two C1 epimers;

(3) a catalytic amount of SmI_2 is effective for this reaction; (4) it is different from the results by the same group, the C1–OH of the major product has a *β*-configuration.[119]



Scheme 101

In a similar way, the carbonyl group also can undergo an intramolecular Schmidt rearrangement by properly adding an azide group into the substrate. As expected, azaquaternary carbon units will be constructed in one step. Considering the diverse and important bioactivities of alkaloids, this kind of tandem reaction is of great interest to organic chemists. Based on this assumption, Tu's group has designed and developed a tandem semipinacol/Aubé type intramolecular Schmidt reaction of α-silanol-epoxy-azide using $TiCl_4$ (Scheme 102).[120] Based on this method, total syntheses of some bioactive alkaloids incorporating the key tricyclic azaquaternary skeletons have been accomplished.

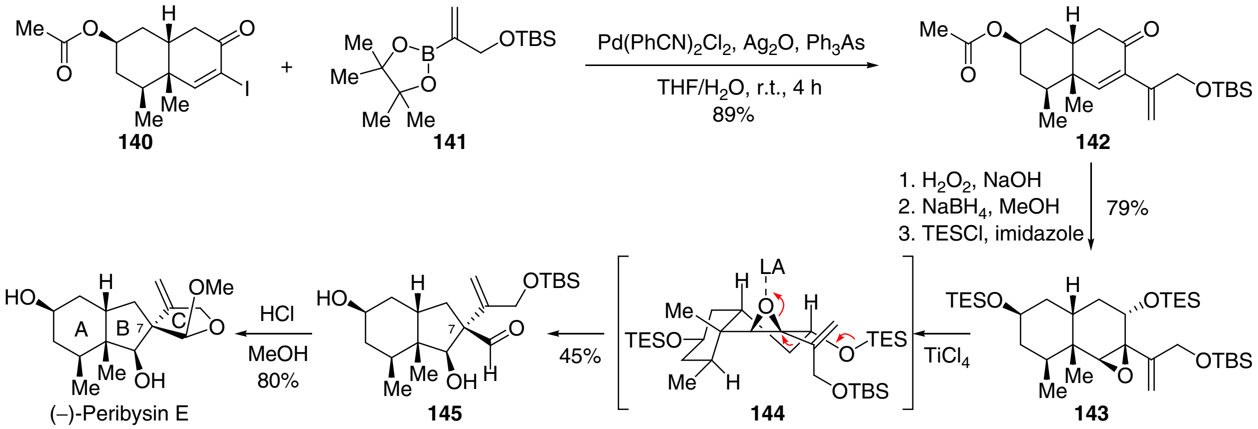


Scheme 102

3.16.5.1.6 Application of the rearrangement

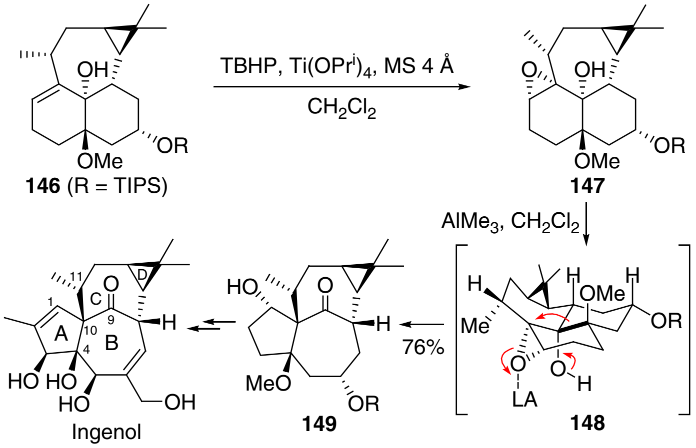
Because of the versatility and high efficiency of the semipinacol rearrangement of 2,3-epoxy alcohols and their derivatives, it has been widely used in the syntheses of natural products and bioactive molecules. Among the three types of rearrangements, 1,2-migration has been well studied and finds the most diverse synthetic utilities.

A semipinacol ring contraction of TES-protected 2,3-epoxy alcohol **143** was used to construct B-ring of peribysin E by Danishefsky and coworkers. In the presence of $TiCl_4$, the expected aldehyde **145** was generated in 45% yield with the requisite stereochemistry at the C7 quaternary carbon center (Scheme 103).[121] Interestingly, the absence of a TES protecting group only led to the recovery of the starting material along with the decomposed products, which was attributed to the incompatibility between the hydroxyl group and the Lewis acid. Next, the C-ring was constructed through a HCl-mediated cyclization of **145** to provide (−)-peribysin E. Similarly, the total synthesis of naturally occurring (+)-peribysin E has also been accomplished by the same route starting from (*R*)-carvone.[109]



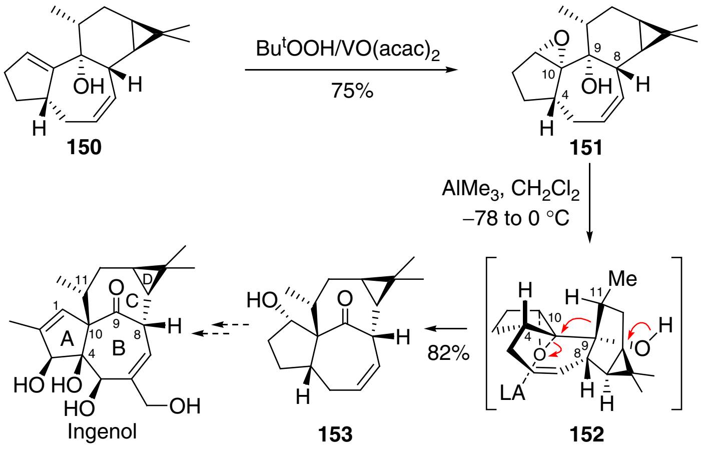
Scheme 103 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Ingenol has attracted the attention of organic chemists, because of its special structural skeleton featuring a highly strained 'inside–outside' *trans*-intrabridgehead stereochemistry in the BC ring system. Tanino and Kuwajima achieved the total synthesis of this natural product using an elegant strategy based on the semipinacol rearrangement of 2,3-epoxy alcohol (Scheme 104).[122] Treatment of **147** with $AlMe_3$ resulted in a facile, stereospecific 1,2-migration to give *β*-hydroxy ketone **149**, which has the complete ABCD ring system of ingenol and the requisite stereochemistry at the C10 quaternary center.



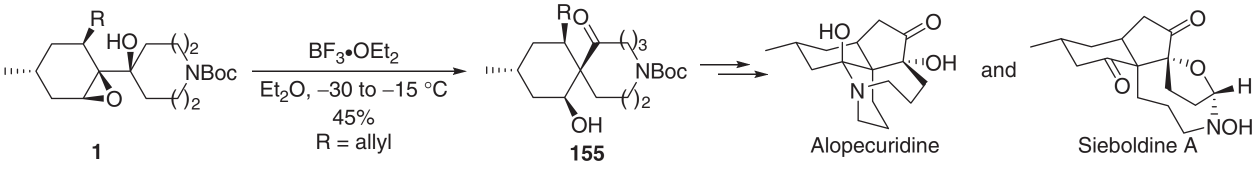
Scheme 104 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Cha also finished the synthesis of ingenol by a similar strategy (Scheme 105).[123] In this case, the semipinacol rearrangement of 2,3-epoxy alcohol **151** with a different ring system efficiently assembled the carbocyclic core **153** in 82% yield. During this procedure, the stereochemistry of C4 in **151** was suggested to be crucial for the desired 1,2-migration of the C9–C11 bond. As shown in **152**, this conformation satisfies the stereoelectronic requirements perfectly, wherein C10–O bond is antiperiplanar to the C9–C11 bond.



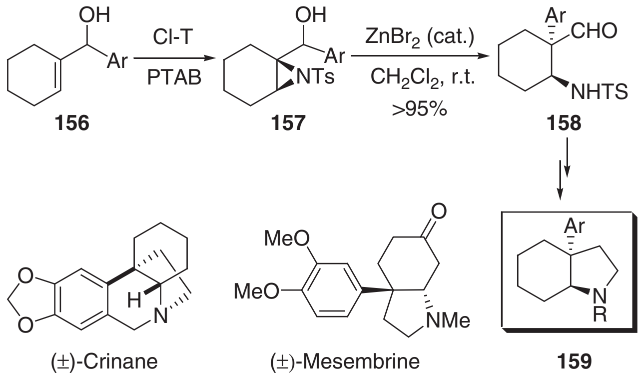
Scheme 105 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Over the past decade, Tu's group has developed a range of semipinacol rearrangements of 2,3-epoxy alcohols and further applied these methods into total syntheses of natural products.[124] For example, a semipinacol rearrangement of epoxy alcohol **154** with functionalized medium-sized ring system has been successfully used in the first total synthesis of (±)-alopecuridine and biomimetic synthesis of (±)-sieboldine A (Scheme 106).[125]



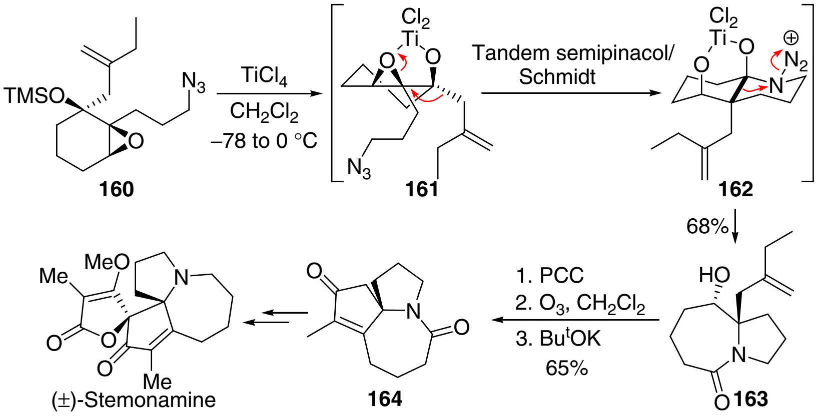
Scheme 106

Similarly, a general approach to the *cis*-3a-aryloctahydroindole alkaloids was realized by employment of Lewis acid-catalyzed semipinacol rearrangement of 2,3-aziridino alcohols (Scheme 107).[126] Amino aldehyde **158**, as a single stereoisomer, was obtained in more than 95% yield by rearrangement of 2,3-aziridino alcohol **157** with $ZnBr_2$ in CH_2Cl_2. Next, further transformation of the core structure **159**, which was obtained through aldehyde homologation and cyclization of **157**, gave the final products (±)-crinane and (±)-mesembrine.



Scheme 107 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Furthermore, Tu et al. have applied the tandem semipinacol/Schmidt reaction of 1-siloxy 2,3-epoxy azides into the construction of aza-quaternary alkaloids like steonamine (Scheme 108).[127] The key intermediate **163** with the desired ring skeleton was formed by the cascade procedure of **160** with $TiCl_4$ in CH_2Cl_2 at − 78 °C to 0 °C. Subsequent PCC oxidation, ozonolysis, and aldol reaction produced the tricyclic lactam **164** in 65% yield, and this compound was then converted into (±)-stemonamine. In the similar way, (±)-cephalotaxine, (±)-maistemonine, (±)-stemonamide, and (±)-isomaistemonine were also synthesized.[128]

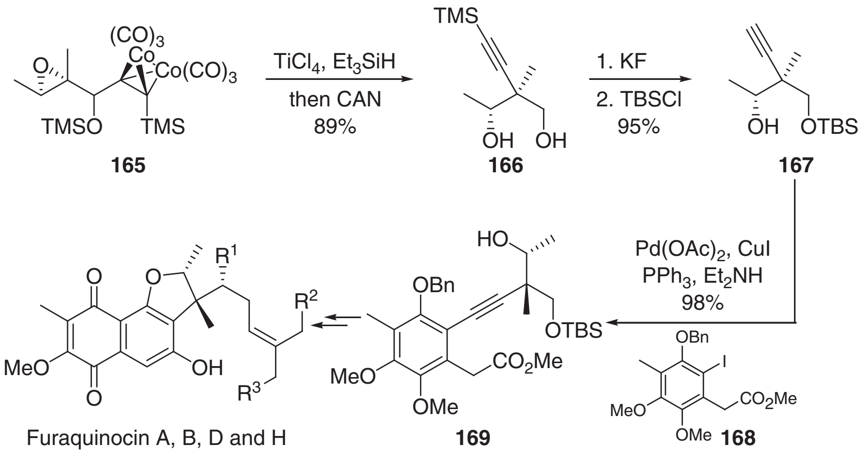


Scheme 108 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

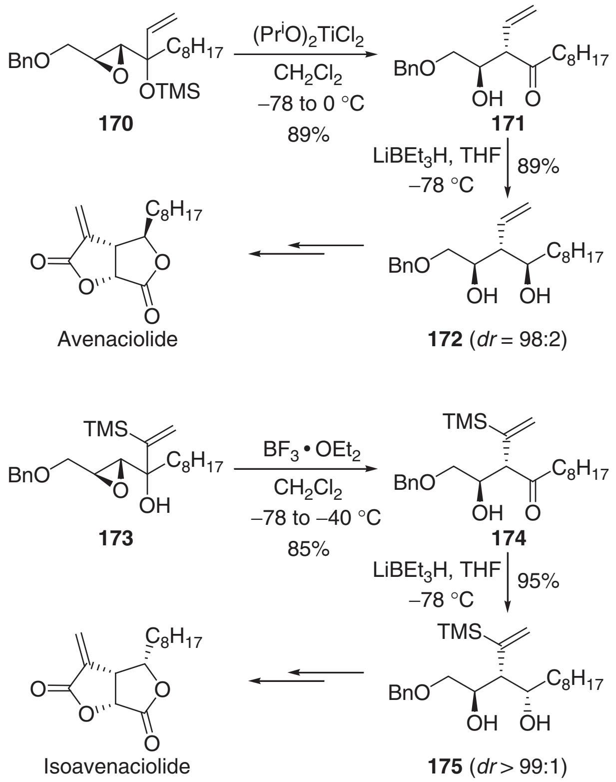
Based on the systematic studies of 1,2-shift reactions, Suzuki and coworkers has achieved the syntheses of furaquinocin-type antibiotics.[129,130] As shown in Scheme 109, tandem reaction of **165** with $TiCl_4$ and Et_3SiH led to a facile 1,2-migration of the Co-complexed alkynyl group, followed by *in situ* reduction of the formed aldehyde, giving the 1,3-diol **166** in 89% yield after oxidative decomplexation. As mentioned before, the Co-complexed substrate clearly showed much higher migration aptitude in this reaction than that of the normal alkynyl group. After the Sonogashira reaction with aryl iodide **168**, TBS-protected diol **167** was eventually converted into furaquinocins A, B, D, and H through further chemical transformations.

Tsuchihashi, Suzuki, and coworkers have applied a semipinacol rearrangement/reduction sequence toward the total synthesis of avenaciolide and isoavenaciolide (Scheme 110).[114,131–133] The introduction of TMS not only showed a rate enhancement effect relative to a simple vinyl group, but also exerted a strong 1,2-stereodirecting effect. Consequently, compounds **172** and **175** bearing different relative configuration could be obtained selectively.

Jung's group has done outstanding work on the semipinacol rearrangement of acyclic 2,3-epoxy silyl ethers, which is called a 'nonaldol aldol' process.[134–138] The transformation features an unusual 1,2-migration of a C–H bond and provides the synthetically useful aldehyde aldol products with excellent diastereoselectivity in good yields. As shown in the transformations from **176** to **177** and from **178** to **179** (Scheme 111), the research group prepared the C1–C11 subunit of tedanolides by successively using



Scheme 109 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.



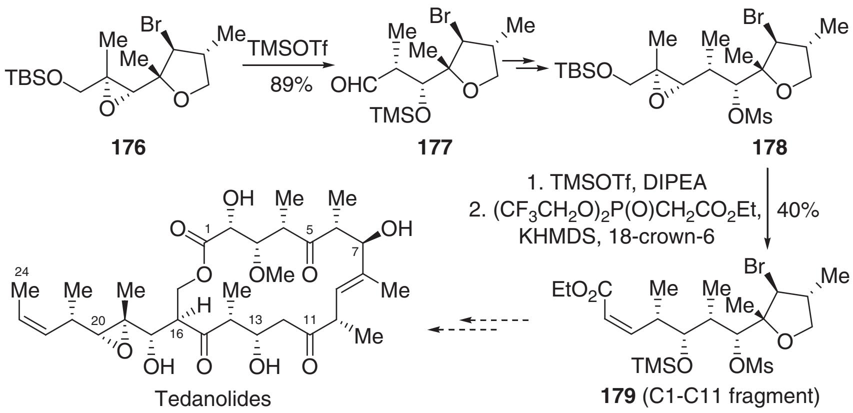
Scheme 110 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

this method.[139] Applying such rearrangement at an early stage, Jung et al. completed the total synthesis of auripyrone A (Scheme 112).[140] During this process, the crucial aldehyde **181** containing the requisite *syn*, *anti*-stereochemistry from C10 to C12, was obtained from the 2,3-epoxy silyl ether **180** in excellent yield and diastereoselectivity.

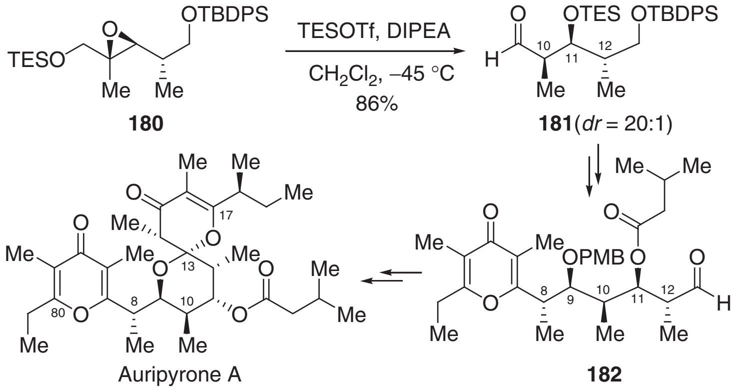
Similarly, Sammakia's group achieved the total synthesis of the oxopolyene macrolide RK-397 using this process as one of the key steps (Scheme 113).[141] As described, the aldehyde **184** possessing the desired C30 and C31 stereocenters in the target was obtained in 95% yield with 24:1 diastereoselectivity by the rearrangement of **183**.

Although only a few examples have been reported compared to 1,2-migration pattern, the 3,2- and 2,3-migration still have some remarkable applications in natural product syntheses.

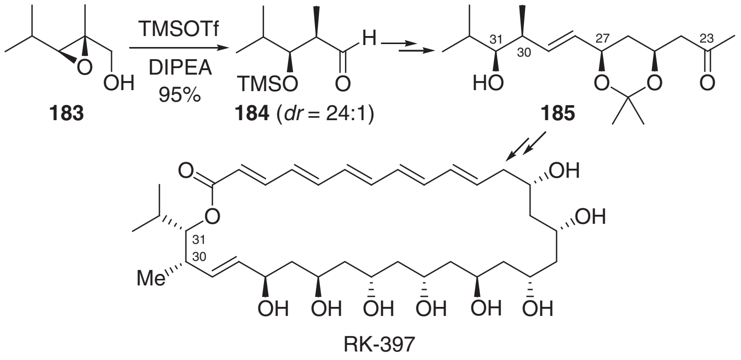
For instance, in Kimura et al. asymmetric synthesis of (*S*)-noremopamil (Scheme 114),[142] chiral 2,3-epoxy silyl ether **186** successfully was converted into aldehyde **187** in 99% yield with diastereoselective generation of the quaternary carbon center in the presence of **189** (MAD, methyl aluminum bis(4-methyl-2,6-di-tert-butylphenoxide)) through the expected 3,2-migration of the isopropyl group.



Scheme 111 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

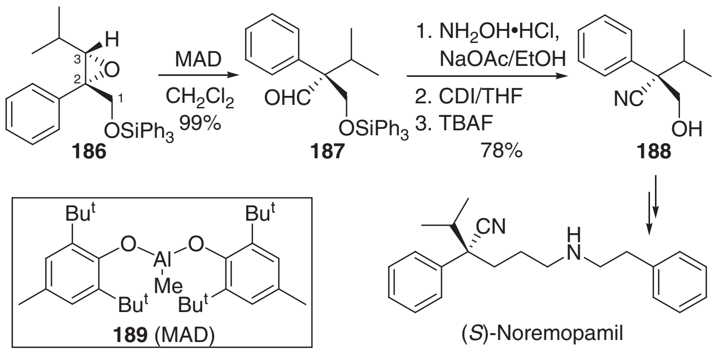


Scheme 112 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.



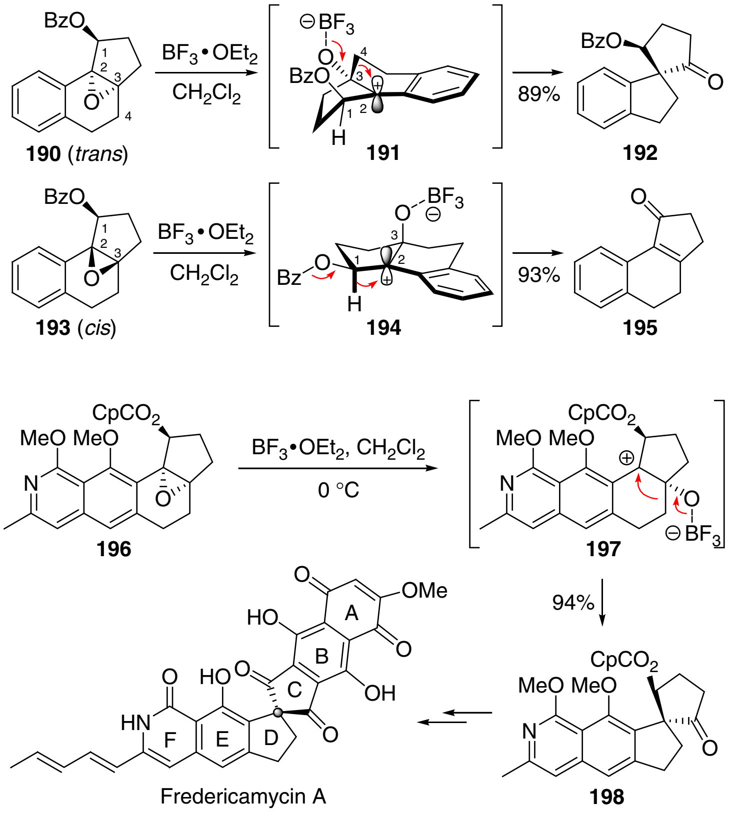
Scheme 113 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Another good example is the total synthesis of fredericamycin A finished by Kita et al. During the model study of the related semipinacol rearrangement, an interesting migration selectivity of *trans* and *cis*-benzofused epoxyacylate **190** and **193** was revealed (Scheme 115).[143,144] Under the same reaction conditions, *trans*-isomer **190** afforded the desired spirocyclic product **192** via a 3,2-migration of the C3–C4 bond, whereas the *cis*-isomer **193** went through a 1,2-migration of the C–H bond adjacent to the benzoyl group, giving enone **195** as a single product. The authors explained this by suggesting the configuration difference between benzylic carbocations **191** and **194** generated by regioselective epoxide opening of **190** and **193**, respectively. In **191**, migration of the C–C bond in the six-membered ring, which is oriented antiperiplanar to the empty vicinyl p orbital, led to 3,2-migration to give the desired spirocyclic **192**. Since such a situation does not exist in **194**, the alternative 1,2-migration of the C–H bond adjacent to the benzoyl group afforded the enone **195** as the product. Additionally, the benzoyl group was found to be necessary



Scheme 114 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

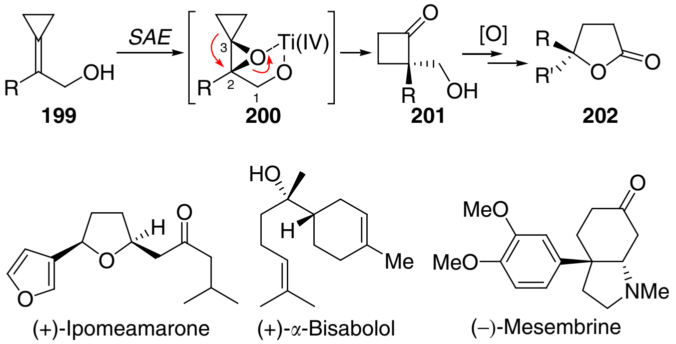
for migration selectivity, since other *trans*-substrates (-OSiMe$_2$Bu^t and -OMe) led only to enone **195** under the same reaction conditions. The authors suggested that the electron-donating effect of -OSiMe$_2$Bu^t or -OMe might accelerate the hydride shift rather than the skeletal rearrangement. Based on these results, the authors successfully constructed the optically pure spiro CDEF-ring core **198** through the rearrangement of the epoxy camphanoate **196**, and achieved the total synthesis of fredericamycin A.



Scheme 115 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

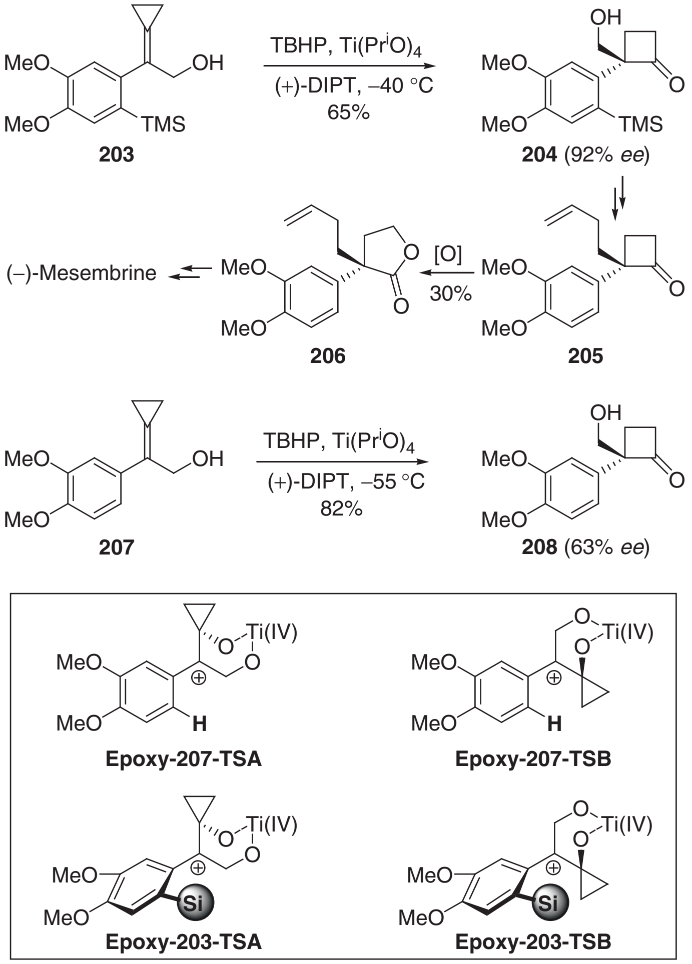
Based on their methodology toward the construction of cyclobutanones **201** containing a chiral quaternary carbon (Scheme 116),[88] Nemoto, Fukumoto, and coworkers applied this tandem, asymmetric epoxidation/ring expansion process of cyclopropylidene ethenals **199** into the syntheses of (+)-ipomeamarone,[145] (+)-α-bisabolol[146] and (−)-mesembrine.[147,148]

In the synthesis of (−)-mesembrine (Scheme 117) under classical SAE conditions, it was found that the presence of a bulky silyl group at the *ortho*-position of the phenyl ring could induce a dramatic increase in enantioselectivity. Substrate **203** containing an *ortho*-TMS group on the phenyl ring was directly converted into cyclobutanone **204** with 92% *ee* in 65% yield. However, the use of **207** afforded **208** with a much lower stereoselectivity of 63% *ee* despite a higher yield of 82%. The following explanation was provided to account for this remarkable substituent effect. For substrate **207**, the preferred transition states are epoxy-**207**-TSA and epoxy-**207**-TSB, in which the corresponding benzylic carbocation can be stabilized by overlap with the phenyl group. Thus, in



Scheme 116 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

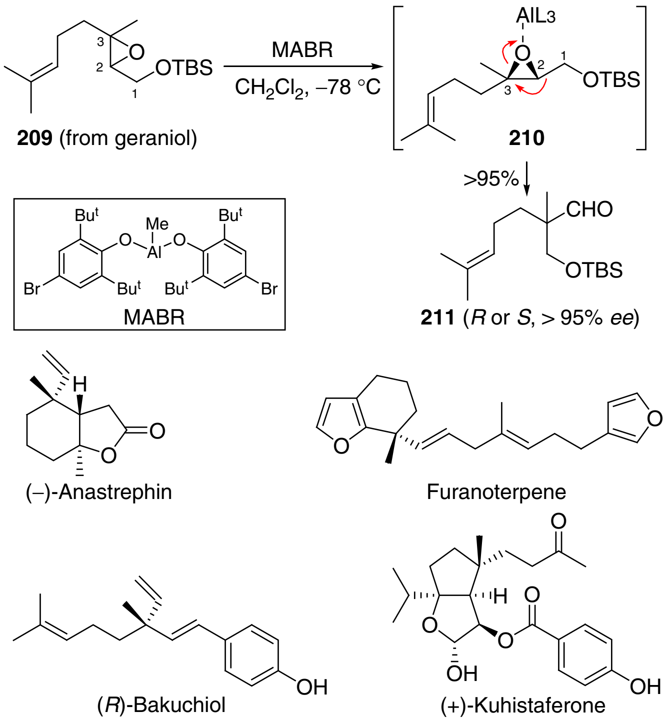
spite of the high reactivity of **207**, epimerization is possible. In sharp contrast, in the case of **203**, due to the steric hindrance between TMS and the hydroxyl methyl and cyclopropyl groups, epoxy-**203**-TSA and epoxy-**203**-TSB became the preferred transition states, in which the phenyl group is apparently no longer coplanar with the potential carbocation center. Thus, the lack of such stabilization should reduce reactivity, preventing the epimerization from taking place.



Scheme 117 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

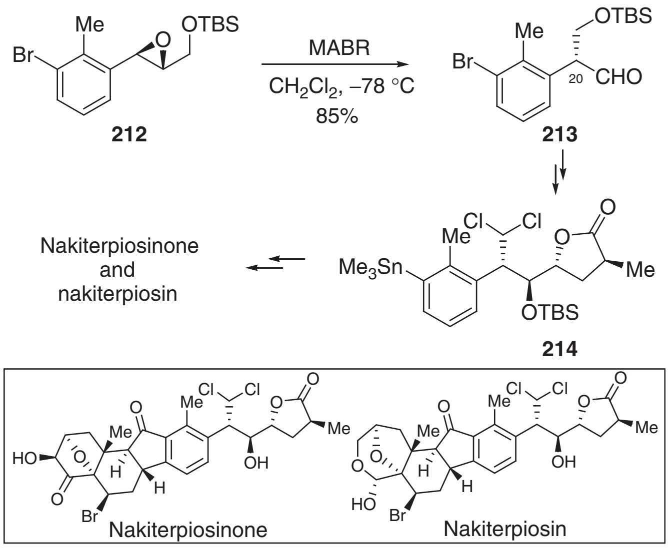
In the case of 2,3-migration, semipinacol rearrangements of 2,3-epoxy silyl ethers developed by Yamamoto and coworkers finds the widest utility,[85,149,150] especially during the early stage while preparing the key chiral building blocks on a large scale.

For example, both enantiomers of the 2-quaternary aldehyde **211** could be obtained from an MABR-promoted semipinacol rearrangement of chiral **209**, which is readily available from geraniol via SAE (Scheme 118). Using **211** as the key precursor, Shishido and Li have synthesized a set of natural products, including (−)-anastrephin,[151] furanoterpene,[152] (+)-kuhistaferone,[153] and (*R*)-bakuchiol.[154]



Scheme 118 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

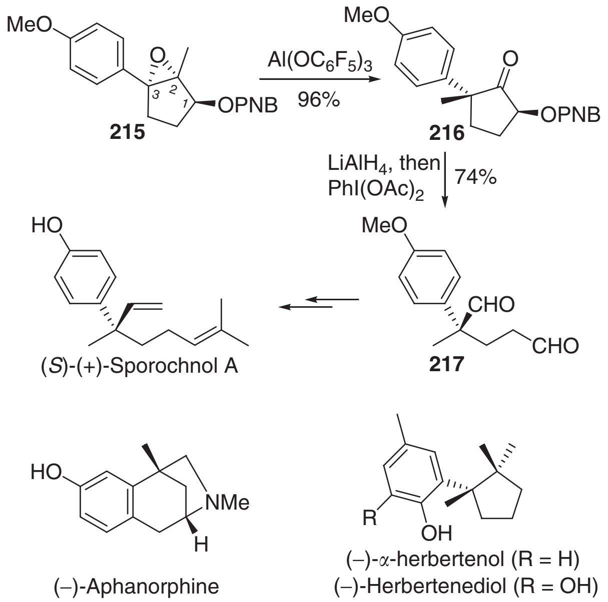
In Chen's total syntheses of nakiterpiosin and nakiterpiosinone (Scheme 119),[155] chiral aldehyde **213** was produced from the 2,3-epoxy silyl ether **212** in 85% yield using Yamamoto's protocol. Subsequently, induced by the C20 stereocenter in **213**, the key intermediate **214** featuring the right side of the target molecules was obtained with three other desired stereocenters.



Scheme 119 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Kita and coworkers used a semipinacol rearrangement of 3-aryl-2,3-epoxy acylate **215** to construct the benzylic quaternary carbon center of (+)-sporochnol A (Scheme 120).[157] Because of the electron-withdrawing nature of the acyloxy alkyl group and the carbocation-stabilizing ability of the electron-rich aryl group, treatment of **215** with $Al(OC_6F_5)_3$ led to a regioselective

C3-cleavage of the oxirane ring, and the subsequent 2,3-migration of the methyl group provided cyclopentanone **216** in 96% yield. As a key step, the reaction has also been applied in the syntheses of (−)-aphanorphine, (−)-α-herbertenol, and (−)-herbertenediol.[158]

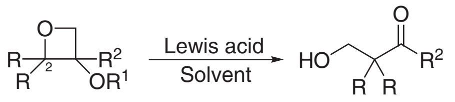


Scheme 120 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

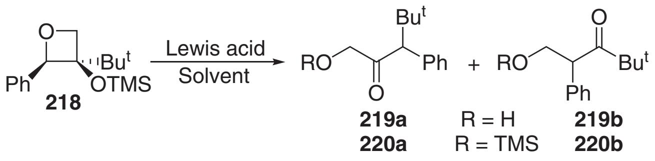
3.16.5.2 Analogs of 2,3-Epoxy Alcohols

Because four- or five-membered oxygen containing rings also could be opened under Lewis acid conditions, oxetane and tetrahydrofuran compounds, as epoxide's analogs, are also able to go through related semipinacol rearrangements. Generally, the C–O bond that gives the most stable carbocation tends to break. Although this kind of study is very limited, it is helpful to be presented.

Oxetanols with two substituents at the 2-position normally undergo acid-promoted rearrangement reactions to give hydroxymethyl group migrating products, which was observed by Kagan and Donnelly (Scheme 121).[159,160] The reaction becomes a little more complicated with only one substituent presenting at the same position, since both the hydroxymethyl group and the substituent at 3-position are involved in the 1,2-shift process. Fortunately, Bach and Eilers found that the regioselectivity sometimes could be tuned by different Lewis acid, for example the use of $TiCl_4$ and $AlMeCl_2$ gave totally different results (Scheme 122).[161]



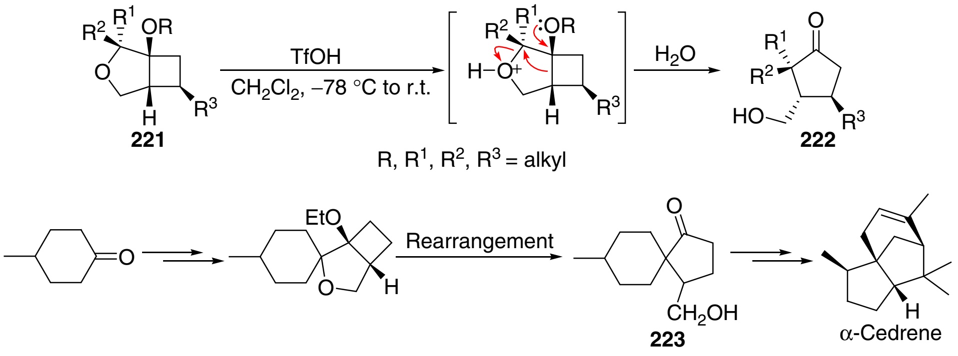
Scheme 121



Lewis acid = $TiCl_4$, Solvent = ether, product: **219a** 100% yield
Lewis acid = $AlMeCl_2$, Solvent = Tol, product: **219a** 9% yield, **219b** 17%, **220b** 74%

Scheme 122

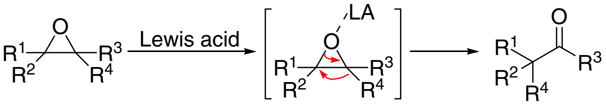
Cleaving the C–O bond of a tetrahydrofuran moiety by employment of acid also can initiate the rearrangement reaction. Ghosh's group did elegant work in this topic.[162–165] They reported that oxabicyclo[3,2,0]hepatanes **221** could afford multi-substituted cyclopentanones **222** on the treatment of acid. During this transformation, an exclusive migration of the stereo-electronically disfavored cyclobutane bond was observed. Based on this protocol, a series of spiro cyclopentanones can be easily obtained, such as **223**, which has been successfully applied in the formal synthesis of α-cedrene (Scheme 123).[163]



Scheme 123

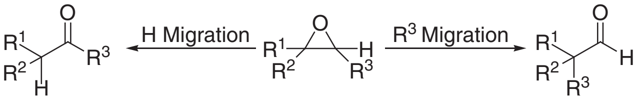
3.16.5.3 Simple Epoxides and 2,3-Epoxy Ketones

Because of the lack of hydroxyl group, simple epoxides and 2,3-epoxy ketones generally give much simpler rearrangement results compared with 2,3-epoxy alcohols. Like those of 2,3-epoxy alcohols, the first step of semipinacol rearrangements of simple epoxides and 2,3-epoxy ketones is the cleavage of epoxy moiety. Normally, this will result in the most stable carbocation, and then the group, which is capable of stabilizing the carbocation better, is most likely to migrate to afford the carbonyl compound (Scheme 124). It should be noted that the migrating group may include those which are not directly connected to the epoxy carbon, which is actually a typical Wagner–Meerwein rearrangement process.[166–168]



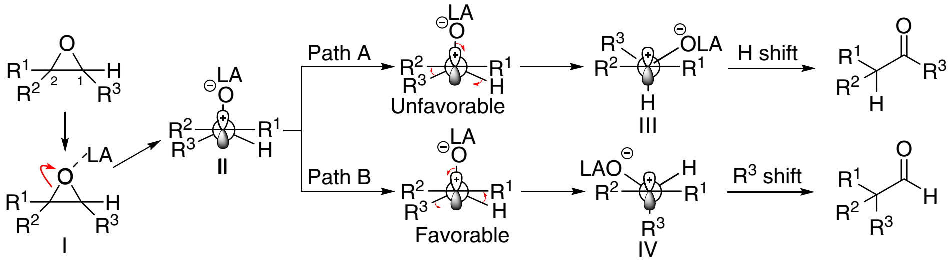
Scheme 124

These above-mentioned features explain not only most of the rearrangement procedures, but also the design of related substrates, which usually have different numbers or types of substituents at each side of the epoxy moiety. Therefore, these semipinacol rearrangements, in principle, go through H migration or alkyl (acyl) migration, leading to the corresponding ketones or aldehydes (Scheme 125).



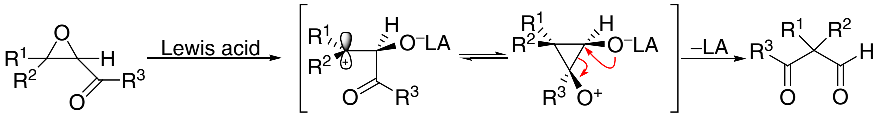
Scheme 125

In most of the simple epoxy substrates, migration of alkyl group is usually more preferred than that of hydrogen. This can be attributed to the mechanistic rationale introduced by Jung and Coxon.[169,170] First, coordination of the Lewis acid with epoxy oxygen would give complex **I**, which would form the relatively stable carbocation **II** by rupture of the C–O bond to relieve the ring strain of the epoxy moiety. Next, the H or R^3 will be placed at proper position, i.e., overlapping with vacant p orbital on the carbocation, for the subsequent 1,2-migration that could be finished through the bond rotation between C1 and C2. Clearly, path A with a clockwise rotation to align the hydrogen with the *p* orbital giving **III** requires more serious eclipsing interaction than that of path B, which is caused by the size difference between H and R^3 group. Therefore, this larger steric eclipsing interaction of path A causes **IV** to be formed predominantly, especially when the migration is favored (Scheme 126).



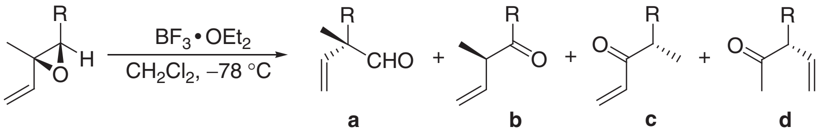
Scheme 126

In the case of 2,3-epoxy ketones, the rearrangements also show the similar migrating tendency. Besides the analysis above, this procedure could also be explained as following. Firstly, because the existence of partial positive charges on adjacent carbon atom of the carbonyl group is energetically unstable, the epoxy will normally be ruptured at β-position under the treatment of Lewis acid. Secondly, since the carbonyl group could probably stabilize the developing positive charge through a reverse polarization of the carbonyl π-bond and formation of a cyclopropyloxenium ion, the migration of acyl group is usually favored over the hydrogen shift (Scheme 127).[171]



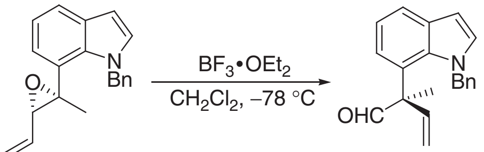
Scheme 127

One good example of the rearrangement of simple epoxides is Tanner's report about the total synthesis of lyngbyatoxin A.[172] They used an enantiospecific Lewis acid mediated rearrangement reaction to introduce the quaternary stereogenic center. During the investigation of the reaction conditions toward the compound **229**, they found that the rearrangement was affected by several factors, such as the absolute configuration of the epoxy, the position of the epoxy substituent, and electron property of the substituents (Scheme 128). Firstly, the reaction is highly stereospecific. The configuration of the products mainly depends on that of the substrates. Secondly, the cation-stabilizing effect of the substituent controls the opening position of the epoxy, which further influences the migration pattern. Consequently, the use of substrate **227** exclusively resulted in a phenyl migration product. While subjection of the *N*-allyl or *N*-benzyl indole substrates resulted in solely vinyl migration due to the carbocation-stabilizing effect of the indole nitrogen, which was confirmed by the introduction of tosyl on the nitrogen. Eventually, the desired compound **229** was obtained using substrates **228** (equation 13).



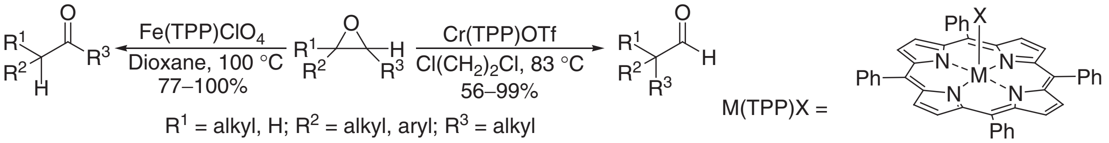
Compound	R	a	b	c	d
224	All-indole	0	0	0	>99%
225	Bn-indole	0	0	0	>99%
226	Tos-indole	40%	60%	0	0
227	Ph	>99%	0	0	0

Scheme 128



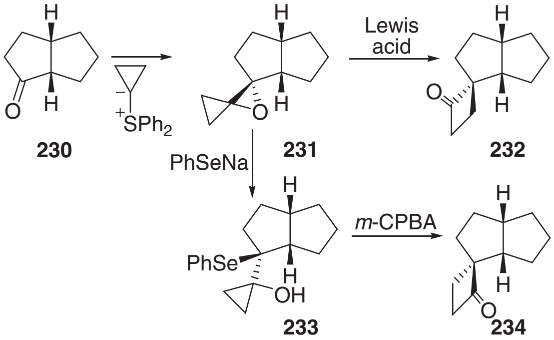
228 **229** (13)

Despite the factors above, the migration patterns also could be adjusted by use of different catalysts. Suda et al. have reported regioselective isomerization of epoxides catalyzed by metalloporphyrin. Depending on the catalyst, a ketone or aldehyde type of product could be selectively obtained. When Fe(TPP)ClO_4 was used, the reaction gave almost quantitative yield of hydrogen migration product.[173] On the contrary, the use of Cr(TPP)OTf lead to exclusively alkyl migration products (Scheme 129).[174]



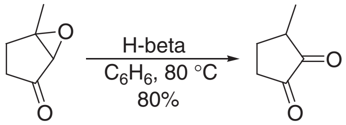
Scheme 129

Like those of 2,3-epoxy alcohols, ring expansion and contraction will be observed in the presence of cyclic substrates. A classic example is the rearrangement of oxaspiropentanes, which give synthetically important and challenging cyclobutanones.[175] Additionally, the relative configuration of the product can be reversed by an alternative procedure. For instance, the epoxide compound **231** derived from ketone **230** could undergo a Lewis acid-catalyzed rearrangement to give cyclobutanone **232** as the major isomer. Alternatively, the epoxy also could be cleaved with sodium phenylselenide to afford **233**, which could be converted predominantly to **234** through a *m*-CPBA oxidation/ring enlargement process (Scheme 130).[176]



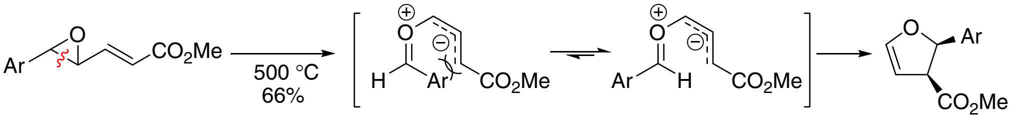
Scheme 130

For ring contraction, transformation from six-membered rings to five-membered ones has been used broadly. Instead of ring contraction process, the epoxy embedded in five-membered ring usually goes through other rearrangement way. For example, compound **235** afforded 1,2-dione **236** as the major product in acidic conditions, and no acyl migration product was observed (equation 14).[177]



235 **236** (14)

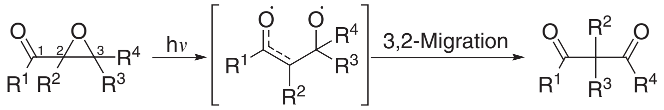
Besides regular acidic conditions, the epoxide also could be isomerized thermally under simple heating conditions. Sometimes, the thermolysis of the substrate will give a different product compared to those from the normal rearrangement fashion. In Steel's report on the short synthesis of Epiasarinin, they used a epoxide-dihydrofuran rearrangement to successfully get the key intermediate **238** (Scheme 131).[178] Interestingly, this reaction is initiated by the cleavage of the C–C bond of the epoxide followed by intramolecular cyclization to give the expected product.



237 **238**

Scheme 131

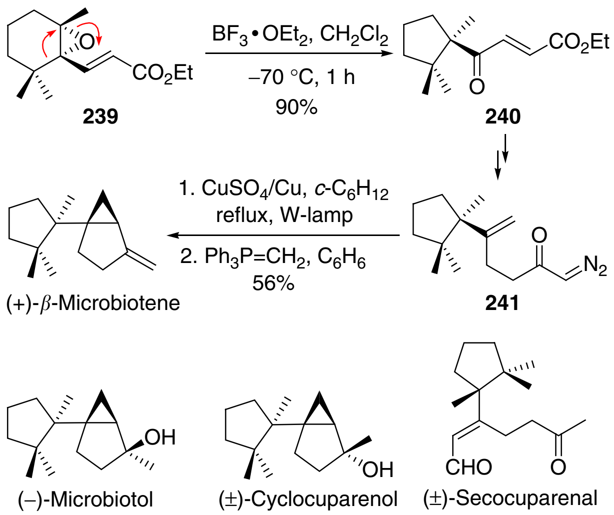
Photochemical rearrangement of 2,3-epoxy ketones has also been attempted, which usually gives 3,2-migration products on special epoxy opening at 2-position (**Scheme 132**).[179] These type of reactions also feature an unusual order for the migration aptitude of substituents at 3-position, namely benzhydryl and benzyl > hydrogen > methylene > methyl ≫ phenyl.



Scheme 132

Although compared with the rearrangement of 2,3-epoxy alcohols and their derivatives, the applications of the corresponding reaction with simple epoxides or 2,3-epoxy ketones are limited. There are still some elegant ones worth mentioning.

Srikrishna et al. have investigated the semipinacol rearrangement of tetrasubstituted cyclic epoxides. Because of the existence of one electron-withdrawing substituent, these substrates undergo reliable and regioselective epoxide opening to afford the ring-contracted products in good yields. As shown in the syntheses of microbiotol-type sesquiterpenes (**Scheme 133**), such synthetic route involves a rearrangement of **239**, which contains an *α*,*β*-unsaturated ester group bonded to the oxirane. Through this conversion, the cyclopentyl ketone **240** was formed in 90% yield.[180] Further chemical transformations of **240** led to the diazo ketone **241**, which went through intramolecular cyclopropanation and Wittig olefination to give (+)-*β*-microbiotene in 56% yield. Additionally, they also applied this method into the syntheses of other terpenes featuring a cyclopentane ring with multiple quaternary carbon centers.[181,182]



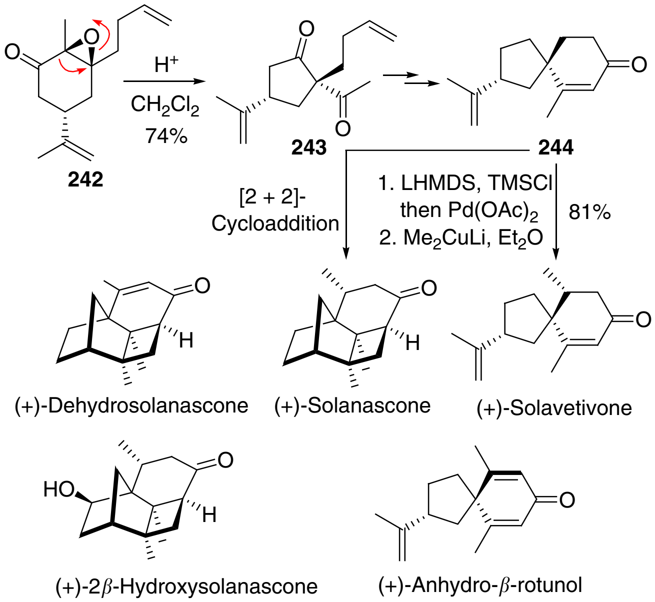
Scheme 133 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

In a similar way, tetrasubstituted 2,3-epoxy cyclohexenone **242** underwent a ring contraction via regioselective epoxide opening to afford the 1,3-diketone **243** in the presence of acid (**Scheme 134**). With the key intermediate **243** in hand, Srikrishna et al. finished the syntheses of several phytoalexins, including the spirocyclic (+)-solavetivone and its [2 + 2]-cycloadduct (+)-solanascone.[183,184]

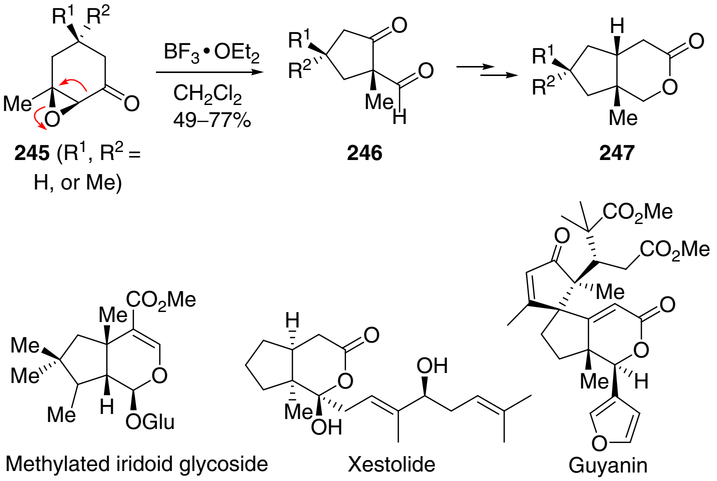
Trisubstituted 2,3-epoxy cyclohexenones **245** also could go through a semipinacol rearrangement to form the 1,3-keto aldehydes **246** in medium to good yields (**Scheme 135**). Based on this result, Cazes and coworkers obtained pseudoiridolactones **247**, which exist in several terpene natural products, for example, guyanin, xestolide, and methylated iridoid glycoside.[185,186]

3.16.6 Rearrangement of α-Hydroxy Ketones and α-Hydroxy Imines

Rearrangement of α-hydroxy ketones and imines is also called ‘α-ketol rearrangement’ or ‘acyloin rearrangement,’ which has been well documented (**Scheme 8**).[8] This rearrangement is an isomeric process of α-hydroxy ketone or imine through 1,2-migration of alkyl or aryl group. It can be promoted by acid, base, or heat. Different from other kinds of semipinacol rearrangements, acyloin rearrangement is a reversible procedure, which means more stable α-hydroxy or α-amino ketone will be formed at the end of the reaction. Therefore, this type of transformation is very useful if the desired product is much more stable than the corresponding substrate. Additionally, because of the existence of two contiguously coordinative functional groups, it could also exhibit



Scheme 134 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Society.



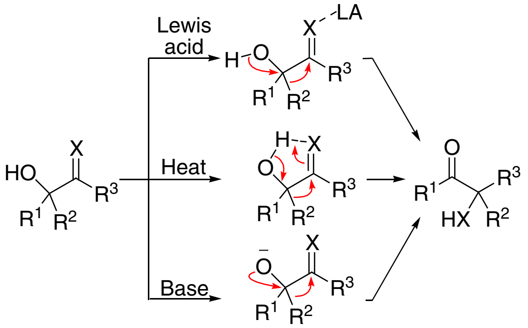
Scheme 135 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

asymmetric induction. However, the synthesis of unstable α-hydroxy or α-amino ketone is not practical by this method. Another drawback of this transformation is that the optimistic reaction conditions often require extensive screening.

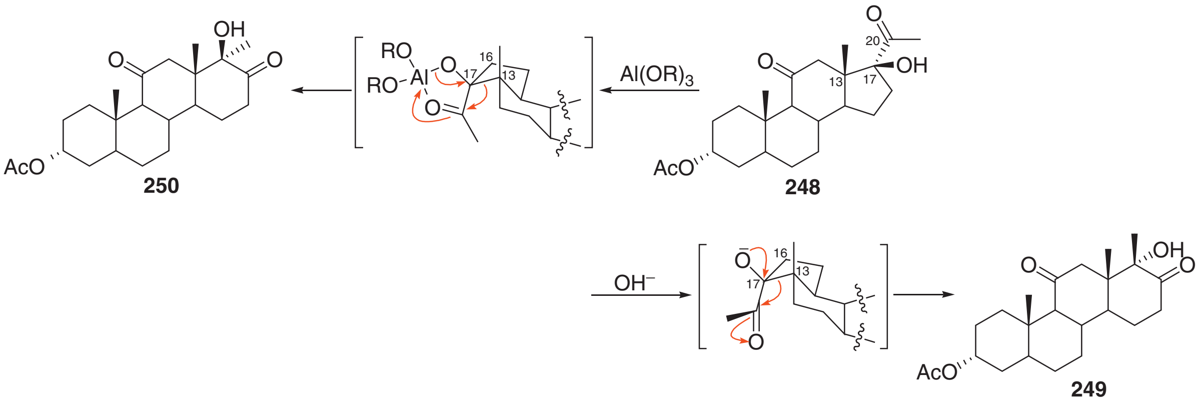
Normally, in the presence of Lewis acid or Brønsted acid, the rearrangement will be initiated by the activation of the carbonyl or imine group. Under thermal conditions, an intramolecular hydrogen transfer will first occur, whereas under basic conditions, the deprotonation of the hydroxyl group is the first step of the reaction. Next, the rearrangement procedure will proceed to give a thermodynamically more stable product (Scheme 136).

Among α-ketol rearrangement reactions, the D-homoannulations with steroidal α-ketols have been intensively studied.[8] First, the structure of product in this type of transformation depends on the promoter used. For example, with 17β-hydroxy-20-keto derivatives of type **248**, the use of base gives the stereospecifically D-homo ketol **249**, whereas Lewis acid $Al(OR)_3$ results in ketone **250** due to the coordination effect (Scheme 137). Secondly, selective bond migration could be achieved using promoters through different conformation control. With 17α-hydroxy-20-ketosteroids, the more substituted C13 tends to migrate under basic conditions, and the less substituted C16 tends to migrate under the treatment of Lewis acid (Scheme 138).

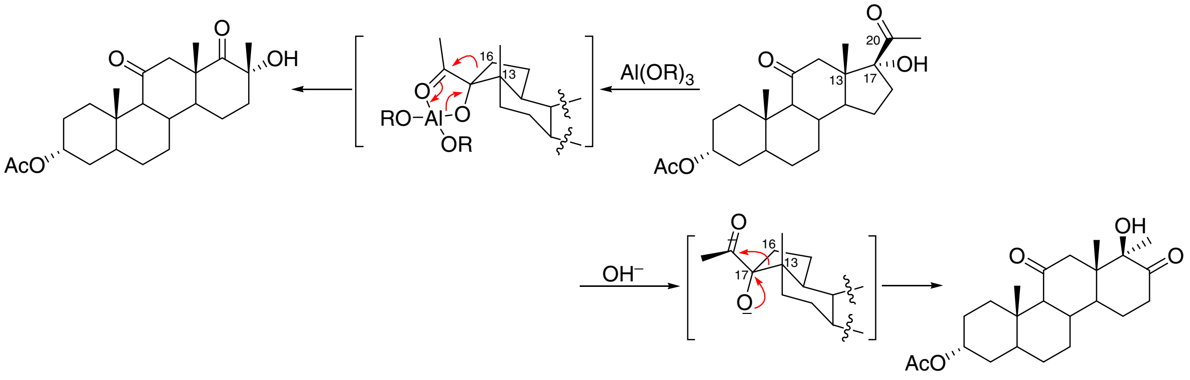
Compared with the one with α-hydroxy ketone, the rearrangement of α-hydroxy imine is a simpler process and generally goes through a concerted intramolecular transition state regardless of the catalysts used (Scheme 139).[8] Therefore, subtle conformation



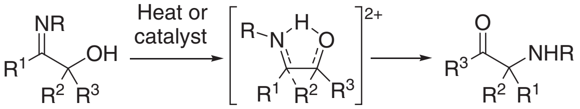
Scheme 136



Scheme 137



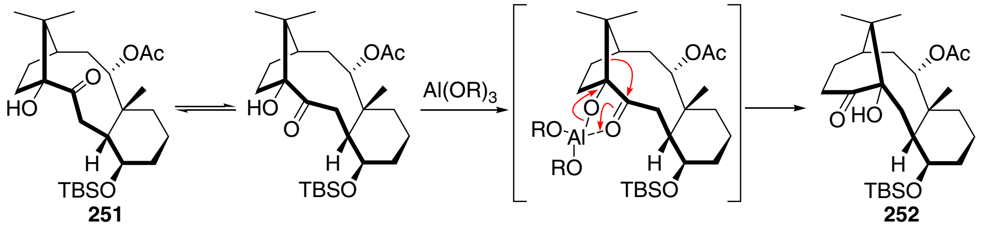
Scheme 138



Scheme 139

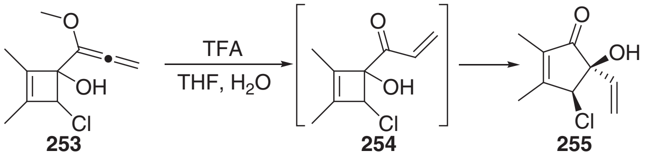
and steric factors clearly affect the speed and extent of this type of rearrangement. Because of the involvement of the nitrogen atom in this procedure, the use of protic acid as a catalyst will effectively minimize the reversibility of this reaction.

Due to the coordinative property of the α-hydroxy ketone moiety, the use of metal catalysts, in some cases, will orient the migrating group to favor its rearrangement by coordination with the substrates. For example, the transformation from **251** to **252** is facilitated by the coordination between the aluminum reagent and the α-hydroxy ketone unit, which is aligned at a conformation to accelerate the rearrangement process (Scheme 140).[187] It should be noted that the acceleration is independent of the stability of the corresponding α-hydroxy ketones. However, the 1,2-migration will be significantly facilitated with a kinetically and thermodynamically favorable product.

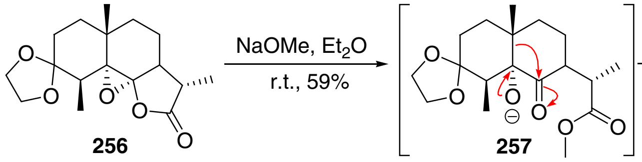


Scheme 140

Substrates with potential α-ketol moiety are also capable of undergoing the rearrangement from the *in situ* generated α-hydroxy ketone intermediates. For instance, with the employment of TFA, compound **253** will give allylic alcohol **255** through the 1,2-migration rearrangement of the intermediate **254** which is produced *in situ* by the hydrolysis of the exocyclic enol ether moiety (equation 15).[188] Similarly, compound **256** affords **258** as the major product involving the rearrangement of intermediate **257** (equation 16).[189]

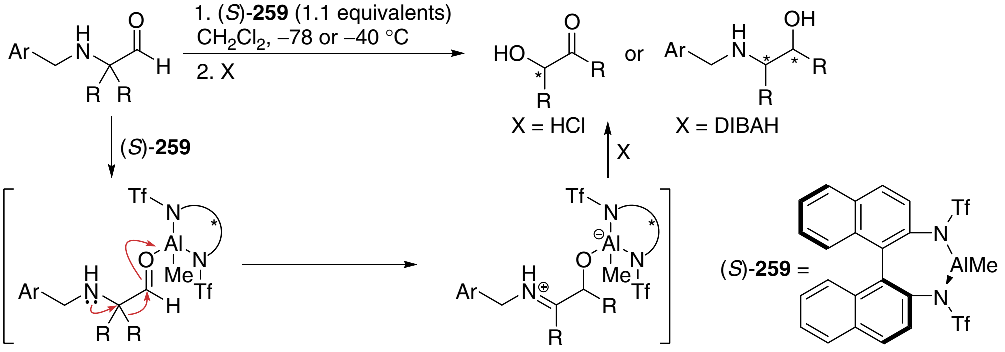


(15)



(16)

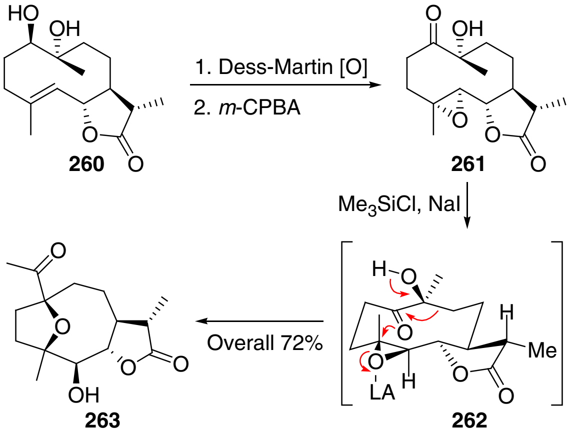
Additionally, since the substrates contain the prochiral functional group, the enantioselective control of the rearrangement achiral α-hydroxy ketone or imine as well as its reverse version are possible through appropriate asymmetric induction. Maruoka has reported an asymmetric skeletal rearrangement of symmetrically α-amino aldehydes (Scheme 141). Under the activation of (*S*)-**259**, the substrates go through an asymmetric rearrangement to afford the zwitterionic iminium intermediates, which produce optically active α-hydroxy ketones and *anti* amino alcohols on hydrolysis and reduction respectively.[190]



Scheme 141

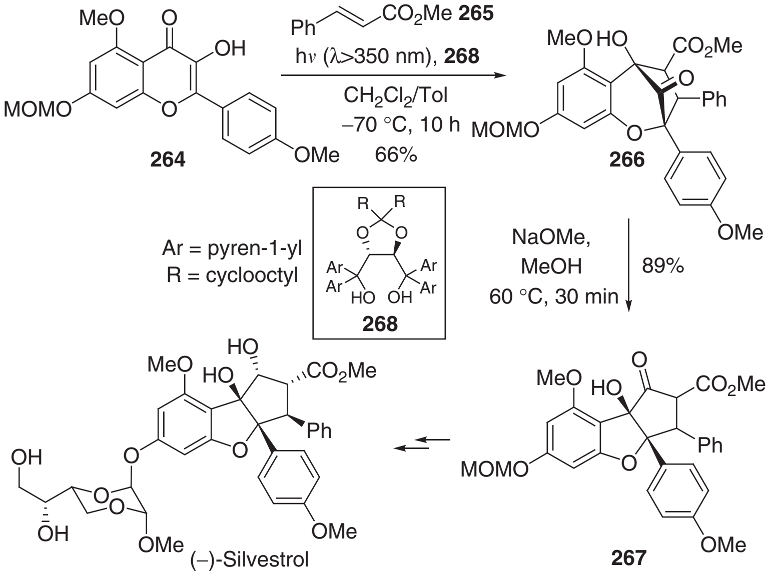
As can be expected, α-ketol rearrangement has also found its application in the syntheses of natural products.

1,4-epoxy cyclononane, as a core skeleton, commonly exists in bioactive terpenoids such as dihydroparthenolide diol, erementholide A, and eleutherobin. One such structure (**263**) has been constructed by Oltra's group through a tandem *trans*-annular cyclization and ring contraction process (Scheme 142).[191] As shown in intermediate **262**, the whole process was started by a Lewis acid-promoted epoxide ring opening of **261** and terminated by the semipinacol rearrangement of the α-tertiary hydroxy ketone moiety. As a result, **263** with a rigid and complex skeleton was achieved efficiently in a stereoselective manner.



Scheme 142 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

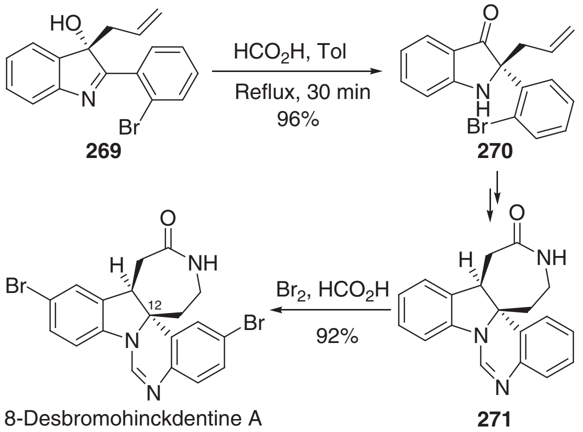
Another example is Porco and coworkers' state-of-the-art approach to the complex rocaglate silverstrol isolated from the plant *Aglaia foveolata*.[192–195] In their synthetic route (Scheme 143), the α-tertiary hydroxy ketone **266**, which was prepared from an asymmetric [3 + 2]-photocycloaddition of **264** and **265**, underwent a base-mediated rearrangement to give the rocaglamide core **267** in 89% yield. The authors proposed that the formation of the enolate of β-keto ester **267** under basic conditions was probably the driving force for the transformation from the ketol toward the rocaglamide core.



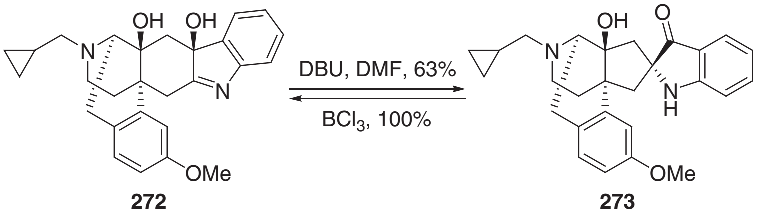
Scheme 143 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

Similarly, the rearrangement of α-hydroxy imines has been used in the syntheses of alkaloids. McWhorter and coworkers applied an HCO_2H-promoted rearrangement of the α-tertiary hydroxy imine **269** in the synthesis of 8-desbromohinckdentine A (Scheme 144).[196,197] The stereospecific 1,2-migration of the allyl group afforded indolone **270** with required key C12 quaternary carbon center. After transformation from **270** to the hinckdentine A core **271**, the target molecule was obtained by a bromination reaction.

Moreover, the rearrangement of α-hydroxy imine can be applied into the synthesis of the spirocyclic alkaloids, such as Nagase and coworkers' report on the syntheses of indolomorphinan alkaloids (Scheme 145),[198] treatment of indoleninomorphinan **272** with DBU resulted in the spiro indolone **273** in 63% yield. Interestingly, **273** can be converted back into **272** in the presence of BCl_3.



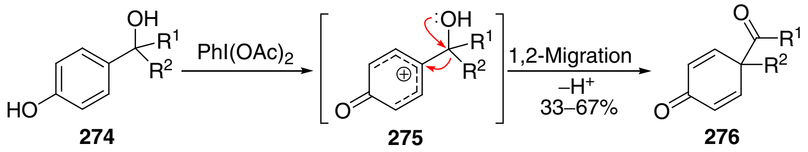
Scheme 144 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.



Scheme 145 Reproduced from Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556, with permission from American Chemical Society.

3.16.7 Miscellaneous Type

Besides the five types of semipinacol rearrangements described above, the prerequisite electrophilic carbon center could also be derived from an aromatic one through an 'aromatic ring umploung' procedure.[199] Generally, in the presence of oxidation reagents, the nucleophilic aromatic rings, like phenols and their derivatives, can be converted into highly reactive electrophilic moieties, which are able to induce subsequent transformations. In light of this hypothesis, an oxidative semipinacol rearrangement of tertiary alcohols **274** has been realized by Canesi and coworkers (Scheme 146).[200] This reaction was initiated by the oxidative dearomatization of the tertiary alcohol **274** with iodobenzene diacetate to give the intermediate **275**. Next, the delocalized positive charge in **275** induced a semipinacol rearrangement affording the synthetically useful product **276** in moderate to good yields.



R^1 = Me, Et, Bu^n, $CH_2CH{=}CH_2$, CH_2OTBS
R^2 = $CH_2CH{=}CH_2$, $CH{=}CH_2$, Ph, Bu^n

Scheme 146

3.16.8 Summary and Outlook

In the past several decades, with the persistence of the researchers, semipinacol rearrangement has displayed its fascination in the field of organic chemistry. It not only has broad substrate scope toward the construction of various carbonyl-containing systems, especially the cyclic ones, but also has demonstrated high efficiencies once involved in the corresponding tandem protocols. Moreover, semipinacol rearrangement is quite effective in the formation of quaternary carbon centers, which are generally impossible, or extremely challenging to be constructed by other methods. Along with continuous methodological breakthroughs in the development of asymmetric catalytic reactions and new cascade protocols, semipinacol rearrangement will remain an active topic in the syntheses of natural products and the discovery of unnatural bioactive molecules.

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3.17 The Favorskii Rearrangement (Extend to Rings)

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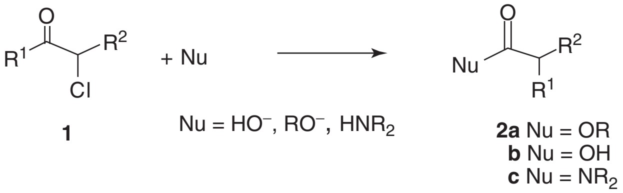
3.17.1 **Introduction** 853
3.17.2 **Mechanism of the Favorskii Rearrangement** 853
3.17.2.1 The Cyclopropanone Mechanism 854
3.17.2.2 The Semibenzilic Mechanism 857
3.17.3 **The Favorskii Rearrangement in Acyclic Structures** 858
3.17.3.1 α-Halo Ketones 858
3.17.3.2 Di- and Tri-halo Ketones 860
3.17.4 **The Favorskii Rearrangement in Alicyclic Structures** 861
3.17.4.1 Monocyclic α-Halo Ketones 861
3.17.4.2 α,α′-Dihalo and α,α,α′-Trihalo Cyclic Ketones 868
3.17.4.3 Rearrangement in Polycyclic Halo Ketones 868
3.17.5 **Homo- and Quasi-Favorskii Rearrangements** 872
3.17.5.1 Homo-Favorskii Rearrangement 872
3.17.5.2 Quasi-Favorskii Rearrangement 873
3.17.6 **Favorskii-Like Reactions** 877
3.17.6.1 Epoxides 877
3.17.6.2 Ring Transformations Under Favorskii Reaction Conditions 880
3.17.7 **Oxy-Favorskii Rearrangement** 882
3.17.8 **Favorskii Rearrangement in Biosynthetic Transformations** 883
References 885

3.17.1 Introduction

The reaction of α-halo (chloro, bromo, or iodo) ketones under the treatment with a base such as hydroxide, alkoxide, or N- or O-nucleophiles is called the Favorskii rearrangement. The reaction was originally described over 100 years ago by Favorskii,[1,2] though related transformations have been published even earlier.[3] This reaction has developed into a powerful synthetic tool and proceeds with a rearrangement of the molecular skeleton to give acid salts, esters, and amides dependent on the nucleophilic base.

The use of alkoxide in the reaction of α-halo ketones **1** under the treatment with a base leads to esters **2a** and employing hydroxide ions or ammonia and amines as bases leads to the free acid (salt) **2b** or amide **2c**, respectively (Scheme 1).



Scheme 1

The Favorskii rearrangement has found application in synthesis of acyclic and alicyclic molecules, most useful from a synthetic point of view being rearrangements with the predictable stereochemical outcome. Interestingly, some biosynthetic transformations were suggested to proceed involving the Favorskii rearrangement step.

The Favorskii rearrangement and its application in synthesis have been reviewed earlier.[4–7] During past years a number of successful syntheses of various organic compounds including complex natural molecules have been reported using this reaction. The Favorskii rearrangement in acyclic and alicyclic systems that enforce sufficient structural rigidity or conformational bias, and factors controlling the course of the rearrangement is of practical and theoretical importance. In addition, we are still far from the detailed understanding of the reaction mechanism and reaction results are discussed in a view of the proposed mechanisms.

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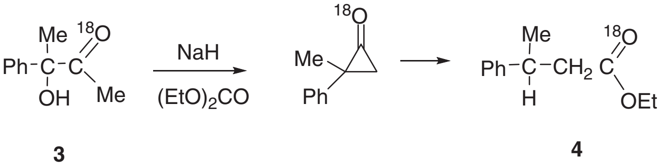
3.17.2 Mechanism of the Favorskii Rearrangement

The Favorskii rearrangement mechanism has been the subject of many studies, and yet, controversy over the mechanism of this reaction persists. Several mechanisms for the Favorskii rearrangement have been proposed, two of them received much evidence both by experimental and theoretical studies. The understanding of the mechanism of the rearrangement permits greater control over the course of the reaction to yield the desired product and avoid competing pathways.

Enolizable α-haloketones undergo skeletal rearrangement to esters, carboxylic acids, or amides via alkoxide-, hydroxide-, or amine-catalyzed reaction. Reaction of cyclic α-halo ketones proceeds with the ring contraction.

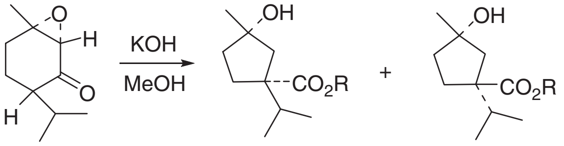
The reaction has also been carried out on α-hydroxyketones **3**[8] and on α,β-epoxy ketones **5**.[9] The intermediate cyclopropanone in the former case was proved by isotopic labeling ^{18}O of the carbonyl group and retention of the isotope in **4** (Scheme 2).



3 **4**

Scheme 2

The rearrangement of 2,3-epoxycyclohexanone (piperitone oxide) **5** with hydroxide and methoxide ions gave two major products, *cis*- and *trans*-hydroxy acid derivatives **6** and **7**, respectively. In the reaction of **5** with sodium methoxide in methanol-*d*, which had been stopped before completion, the recovered oxide **5** was composed of approximately equal amounts of mono-deuterated and nondeuterated material. Each of the hydroxyl esters **6** and **7** produced from deuterated **5** contained essentially one deuterium atom bound to carbon. These results are clearly compatible with the Favorskii rearrangement mechanism and are analogous to the reaction when halide is present in **5** and indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step (Scheme 3).[10]



5 **6** **7**

R = H, Me

Scheme 3

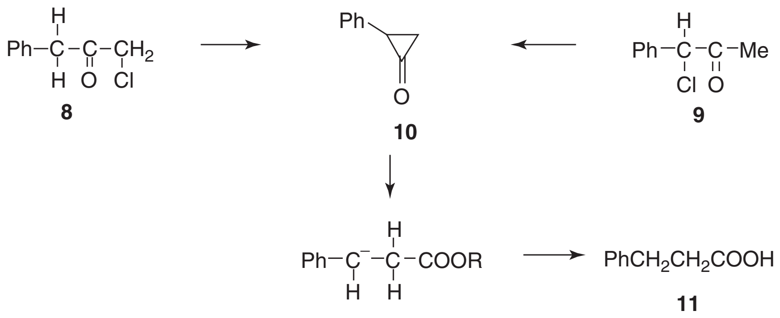
Two generally accepted mechanisms of this rearrangement are discussed further in detail.

3.17.2.1 The Cyclopropanone Mechanism

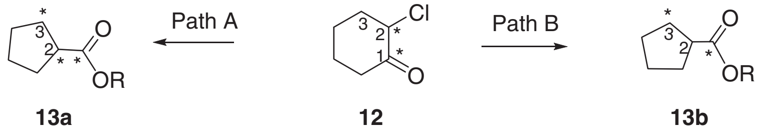
Several mechanisms have been proposed for the Favorskii rearrangement, two of them are widely accepted. In general, the finding that **8** and **9** both give **11** (this behavior is typical) shows that any mechanism where halogen leaves and R takes its place is invalid, since in such case **8** would be expected to give **11** (with $PhCH_2$ migrating), but **9** should give PhCHMeCOOH (with CH_3 migrating). That is, in the case of **9**, it was PhCH that migrated, but not the methyl group (Scheme 4). The intermediate in both cases is **10**, which opens to give the carbanion stabilized by resonance. This path accounts for the fact that **8** and **9** give the same product (Scheme 4).[11]

Another important proof of this pathway was determined by a radioactive labeling of 2-chlorocyclohexanone **12** which affords cyclopentanecarboxylic acid ester **13** under treatment of base. Atoms C-1 and C-2 were equally labeled with ^{14}C in **12**, and it was converted into **13**.[12] The product **13a** was found to contain 50% of the label on the carbonyl carbon, 25% on C-2, and 25% on C-3 (Scheme 5, path A). The carbonyl carbon, which originally carried half of the radioactivity, still had this much, so that the rearrangement did not directly affect it. However, if the C-2 carbon had migrated to C-6, then this half of the radioactivity would be found exclusively on C-3 of the cyclopentane ester product **13b** (Scheme 5, path B).

It was found that the atoms C-2 and C-3 were equally labeled and this showed that both migrations occurred, and with equal probability. C-2 and C-6 of **12** are not equivalent, and this means, that a symmetric intermediate should be involved. The type of intermediate that best fits the observations is a cyclopropanone, and the mechanism (for the general case) was formulated. Initial removal of the α-hydrogen led to formation of an enolate ion which rearranged to the cyclopropanone intermediate, subjected to



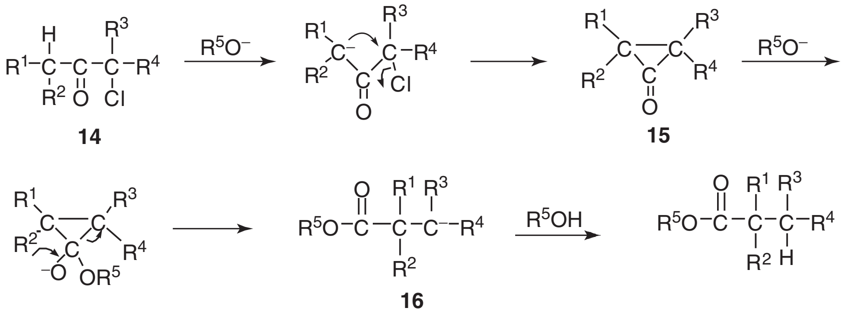
Scheme 4



Scheme 5

attack by a nucleophile giving ring-opened product. The intermediate in the case of **12** is a symmetrical compound, and the three-membered ring can be opened with equal probability on either side of the carbonyl, accounting for the results with ^{14}C.[13]

It is obvious, that for this mechanism an α-hydrogen is required on the nonhalogenated side of the carbonyl in starting compound **14** (Scheme 6). In the general case, **15** is not symmetrical and should open on the side that gives the more stable carbanion **16**.

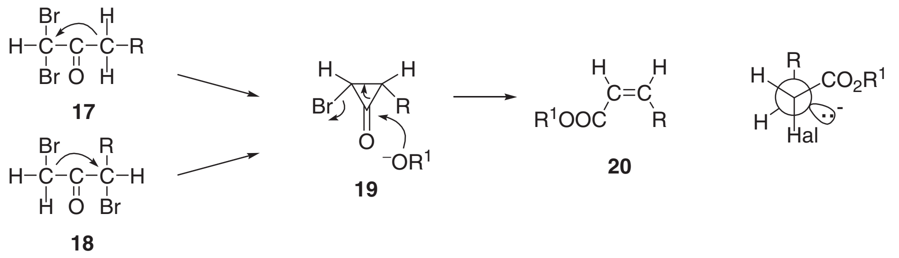


Scheme 6

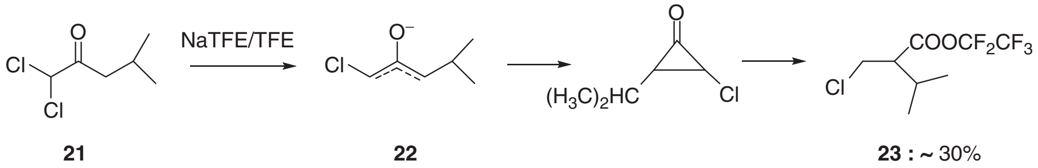
The cyclopropanone intermediate *trans*-**15** has been isolated in the reaction of 2,2,6,6-tetramethylheptan-4-one (dineopentyl ketone) with *t*-BuOK in *t*-BuOH (**15**, $R_1=R_3=t$-Bu and $R_2=R_4=H$), which was converted into the respective rearranged ester **16** ($R_1=R_3=R_5=$ *t*-Bu, $R_2=R_4=H$) (Scheme 6). Cyclopropanone **15** has been resolved to enantiomers to prove the *trans*-stereochemistry of substituents.[14] In addition, cyclopropanones synthesized by other methods have been shown to give Favorskii products on treatment with NaOMe or other bases.[15]

When the Favorskii rearrangement is applied to the α,α-dihalogeno ketones **17** containing an α′-hydrogen or to α,α′-dihalogeno ketones **18** containing an α-hydrogen, the product is an α,β-unsaturated ester **20**. In either case the same cyclopropanone intermediate **19** is formed. Ring opening is different, involving simultaneous elimination of halide ion to give α,β-unsaturated ester **20** (Scheme 7).[16] These rearrangements are usually stereospecific though subsequent *cis* to *trans* isomerization under the base often complicates this feature. The most plausible explanation of the stereochemistry of the reaction product is used employing the Newman projection to explain the loss of halogen (Scheme 7).

Favorskii rearrangement via oxalyl intermediate **22** is the preferred reaction path in reactions of dichloromethyl isobutyl ketone **21** with sodium 2,2,2-trifluoroethoxide in 2,2,2-trifluoroethanol in low temperature (−28 °C) to afford **23**, which undergoes dehydrochlorination at higher temperature (Scheme 8). The analogous oxalyl intermediate was postulated to form in reaction of 1,3-dibromobutan-2-one and some other halo ketones, and [4 + 3] cycloaducts were obtained in the presence of furan with a minor formation of the Favorskii rearranged product as it easily dehydrohalogenated.[17]

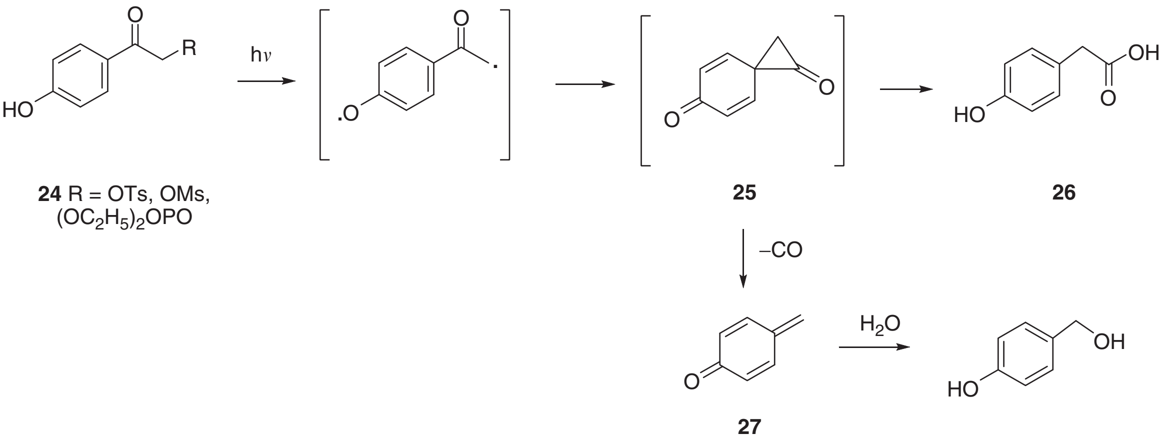


Scheme 7



Scheme 8

The spirodione intermediate **25** (Scheme 9) was proposed and proved by spectroscopic methods and theoretical computations in the Favorskii rearrangement of *p*-hydroxyphenacyl **24** reaction under photo reaction conditions.[18] The lifetime of spirodione **25** is short, however, it was trapped at high water concentrations yielding *p*-hydroxyphenyl acetic acid **26** (Scheme 9).

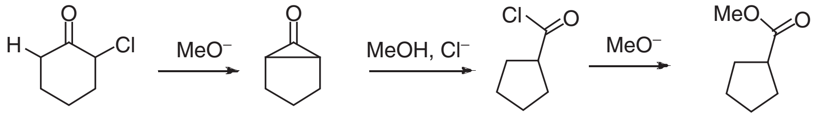


Scheme 9

Alternative pathway at moderate water content included decarbonylation of **25** to give p-quinone methide **27** and, consequently, *p*-hydroxybenzyl alcohol. The reaction course depends on the water content.[19] Analogous reaction mechanism was observed in the photo-Favorskii rearrangement of 3-trifluoromethyl (or methoxy)-4-hydroxyphenacyl γ-aminobutyric acid (**24**, $R{=}O_2CH_2CH_2CH_2NH_3{}^+$)[20] and other leaving groups[21] containing substrates. Under irradiation at $\lambda > 300$ nm the Favorskii rearrangement products were obtained. The singlet–triplet intersystem crossing (ISC) results in a rise of the strong triplet–triplet excited state, which undergoes the photo-Favorskii rearrangement, concomitantly releasing the substrate. This reaction could be used for photoremoval of protecting groups found applications in chemistry and biology.

Recently evidence in favor of the 'normal' cyclopropanone reaction mechanism was obtained by theoretical studies. High-level *ab initio* calculations gave new insights into the cyclopropanone formation providing detailed pictures of the transition state structures and a concerted profile for C–C bond formation versus C–Cl bond length increase.[22]

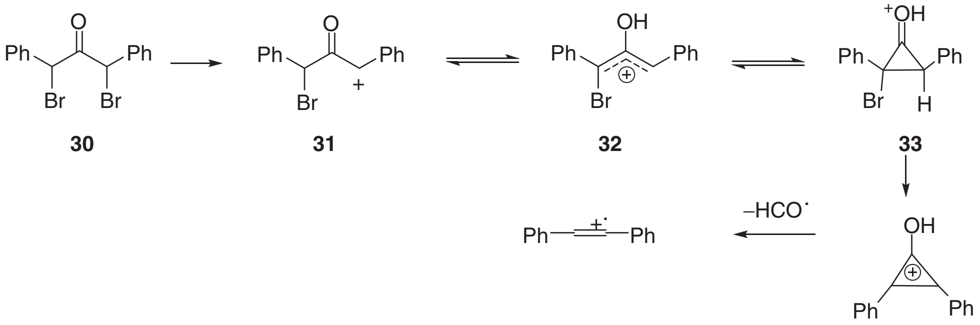
A new elementary step with a small activation energy in cyclopropanone mechanism which involves an acyl chloride intermediate **28** was proposed based on the theoretical computations (Scheme 10).[23] The rearrangement of α-chlorocyclohexanone in the presence of MeO^-/MeOH was investigated by ONIOM-RB3LYP computations including eight solvent molecules giving the transition state energy of -9.57 kcal mol^{-1}. In the cyclopropanone route the chloride ion reacts as a nucleophile toward the intermediate to give an acyl chloride intermediate **28** being susceptible to subsequent MeO^- attack to give rearrangement product **29**. The chloride ion is a leaving group and at the same time a nucleophile. The semibenzilic mechanism was found to be energetically unfavorable.



28 **29**

Scheme 10

An interesting example of the Favorskii rearrangement by the collision-induced dissociation (CID) conditions was reported.[24] The gas-phase synthesis of hydroxydiphenylpropenylium **34**·H^+ from α,α-dibromodibenzyl ketone **30** by soft electrospray ionization was reported (Scheme 11). The initial carbocation **31** was enolized and further delocalized to more stable **32**. Under CID conditions the ring-closure reaction proceeded to give the protonated cyclopropanone **33**. Once the unstable **33** was formed, the transformation to **34** through a Favorskii rearrangement could be achieved. Owing to the large ring strain in cyclopropenone, decarbonylation occurred when heated to above 150 °C or excited with the UV light to give **35**.

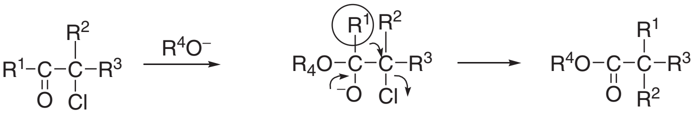


30 **31** **32** **33** **35** **34·H⁺**

Scheme 11

3.17.2.2 The Semibenzilic Mechanism

The semibenzilic mechanism involves initial nucleophilic attack of the base on the carbon atom of the carbonyl group of initial ketone **36** to give intermediate addition product **37**. The following concerted displacement of the halide and a migration of group R^1 afford the rearranged product **38** (Scheme 12).

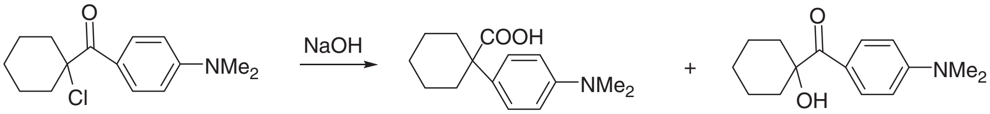


36 **37** **38**

Scheme 12

This process is usually called quasi-Favorskii rearrangement.

A model compound, 1-chlorocyclohexyl 4-dimethylaminophenylketone **39** was selected to study the mechanism. On treatment with dry, powdered sodium hydroxide in refluxing xylene **39** yielded 1-(4-dimethylaminophenyl)cyclohexanecarboxylic acid **40**, and 1-hydroxycyclohexyl 4-dimethylaminophenylketone **41** in 68 and 18% yields, respectively (Scheme 13).[25]

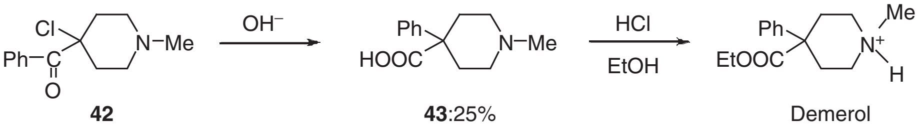


39 **40:**68% **41**:18%

Scheme 13

This mechanism operates in the absence of the acidic α-hydrogen in acyclic and monocyclic halo ketones. Monocyclic and bicyclic substrates undergo ring contraction to give the corresponding cyclic or bicyclic homolog. The reaction is stereospecific, inversion at the carbon to which the halogen is attached.

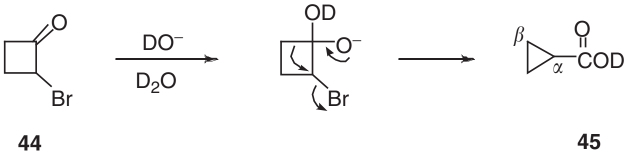
Ketones that do not have α-hydrogen rearrange to give the same type of product. An example could be the preparation of **43, a** precursor of Demerol, when subjected 1-methy-4-chloro-4-benzoylpiperidine **42** to alkaline treatment (Scheme 14).[26]



Scheme 14

It has been shown that even when there is an appropriate α-hydrogen, the semibenzilic mechanism may still operate. The quasi-Favorskii rearrangement obviously cannot take place by the cyclopropanone mechanism. The semibenzilic mechanism is a base-catalyzed pinacol rearrangement-type mechanism, requiring inversion at the migration terminus, and this has been confirmed. The mechanism discussed is in accord with the facts when the halo ketone contains hydrogen on the other side of the carbonyl group.

One such example is the ring contraction of α-halo cyclobutanones. The semibenzilic mechanism has been shown for 2-bromocyclobutanone **44** by experiments involving deuterium labeling, as well as by other experiments (Scheme 15).[27] In order to distinguish between a cyclopropanone and semibenzilic mechanism, the ring contraction was studied is deuterium oxide using sodium carbonate as a base. The ratio β-H/α-H=4 in **45** was consistent with the semibenzylic mechanism.



Scheme 15

This pathway was supported by theoretical studies using quantum mechanical/molecular mechanical study.[28] The comparison of both mechanisms for four- and six-membered rings revealed the ring size effect, that is, smaller rings prefer the semibenzilic mechanism.

The mechanism involves the following steps: attack of the nucleophile on the carbonyl carbon atom to form tetrahedral intermediate, the anionic intermediate undergoes a facile 1,2-alkyl shift, similar to the benzilic rearrangement, and as a result the halogen attached to the α-carbon is displaced with the inversion of configuration. When the substrate is bicyclic and there is no hydrogen α-position, enolization is not possible because the double bond of the enol would be incorporated in the bridgehead and this reaction would violate Bredt's rule (for rings smaller than 8 carbon atoms). The cyclopropanone intermediate would be highly strained and its formation is disfavored.

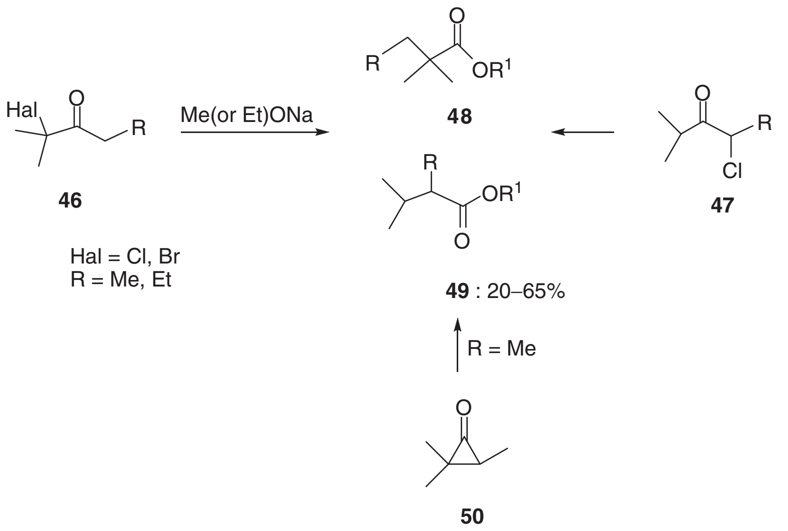
3.17.3 The Favorskii Rearrangement in Acyclic Structures

3.17.3.1 α-Halo Ketones

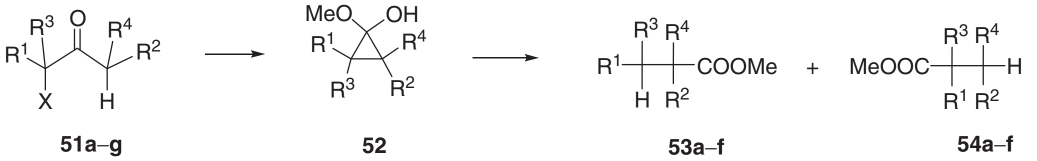
α-Halo ketones are very reactive compounds and the Favorskii rearrangement is competing side reactions – dehydrohalogenation, nucleophilic substitution, or epoxidation. Consequently, different types of products have been observed under reaction conditions. The substituents present in starting acyclic α-chloro and α-bromo ketones have major influence on the course of the reaction.

Four 2- and 4-halo-2-methyl-3-pentanones **46** and **47** and related halo ketones were found to yield the same ratio of esters **48** and **49** using the same bases (Scheme 16).[29] The evidence that **50** is an intermediate in the Favorskii rearrangement was obtained by almost the same ratio of products **48** and **49** from treatment of trimethylcyclopropanone **50** with alkoxides. In the reaction with potassium *tert*-butoxide almost exclusively ester **48** was formed.

A detailed investigation of the basic methanolysis of acyclic halo ketones was performed.[30] Favorskii rearrangement products **53** and **54** were obtained from α-halo ketones **51a-f** with an excess of methanolic methoxide solution (Scheme 17). Using one equivalent of methanolic methoxide solution intermediate methyl hemiacetals of the alkyl-substituted cyclopropanones **52** were



Scheme 16

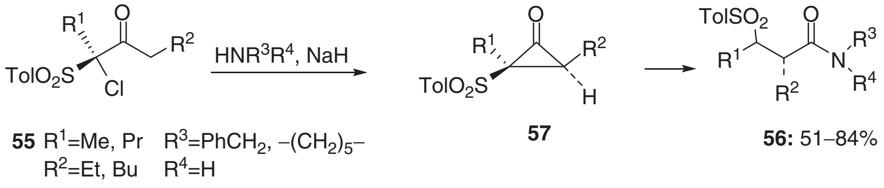


	R^1	R^2	R^3	R^4	X	yield (%)
a	Me	Me	H	H	Cl	40
b	Me	Me	H	H	Br	n.a.
c	Et	Me	H	H	Cl	57
d	Et	Et	H	H	Cl	73
e	Et	Et	H	H	Br	n.a.
f	*i*-Pr	*i*-Pr	H	H	Cl	67

Scheme 17

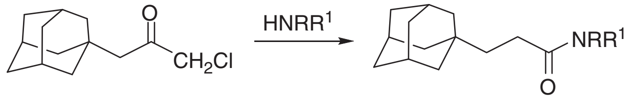
formed and characterized by nuclear magnetic resonance (NMR) spectroscopy. With an excess of the methoxide solution the acetals were cleaved to afford the rearranged products **53** and **54**.

The Favorskii rearrangement could be employed in the asymmetric synthesis. The first asymmetric Favorskii rearrangement of α-chloro α-sulfonyl ketones to afford enantiomerically pure α-alkyl amides in enantiomeric excess up to 94% was reported.[31] Chiral α-chloro ketones **55** were synthesized in enantiomerically enriched form (*ee* 75–99%) and were treated with NaH in dry tetrahydrofurane (THF) with benzylamine or piperidine to afford chiral sulfonyl amides **56** as the rearrangement products in high *ee* (Scheme 18). Subsequently enantiomerically pure *R*-amides and other derivatives were prepared from the rearrangement products.[32] The mechanism of the rearrangement was presumed to involve cyclopropanone intermediate **57** via six-membered conformation in the transition state for cyclization by coordination of the sulfone oxygen with sodium. However, there are only a few reports on the asymmetric rearrangement because of easy racemization of α-halo ketones under the strong basic conditions.



Scheme 18

The Favorskii reaction in the presence of amines was used for the synthesis of amides which could further be employed to obtain α-aminoketones. Reaction of 3-(1-adamantyl)-1-chloro-2-propanone **58** with amines in diethyl ether in the absence of base gave the corresponding N,N-disubstituted amides **59** in moderate yield (Scheme 19).[33]

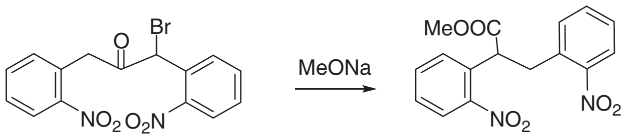


58

59:32–74% R = H, Et,
R^1 = Et, 1-adamantyl, p-$C_6H_4CH_3$

Scheme 19

The Favorskii rearrangement of bisaryl bromoketone **60** gave methyl ester **61**, a key intermediate in the elaboration of synthesis of alkaloid cryptolepine and related alkaloids of diverse therapeutic value and used in medicine for treatment of various diseases (Scheme 20).[34]



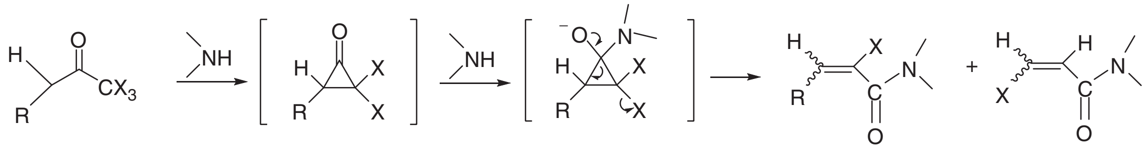
60

61:57%

Scheme 20

3.17.3.2 Di- and Tri-halo Ketones

α,α,α-Trichloromethyl ketones are potential substrates for the Favorskii rearrangement. Such ketones **62** under basic conditions (ratio ketones/amines was 1:4) were found almost in all cases to react by a Favorskii rearrangement path (Scheme 21) via the corresponding cyclopropanones **63** to give halo propenamides **64** and **65**.[35] The major products of the reaction are the α,β-unsaturated amides **64** and **65**. Formation of unsaturated 2-halo propenamides may be explained by the nucleophilic attack of an amine on the carbonyl carbon of the cyclic intermediate **63** following by the ring opening to give **64**. The formation of unsaturated 3-halopropenamides **65** is explained by elimination of HHal yielding acetylenic compound which undergoes nucleophilic addition of HHal next and a formation of **65**. The *Z*/*E* stereochemistry of **64** and **65** was determined based on NMR data. The *Z* stereoisomer was the main in 2-halopropenamides **64**, and a mixture of *Z*/*E* stereoisomers was observed in **65** (Table 1).



62 **63** **64** **65**

Scheme 21

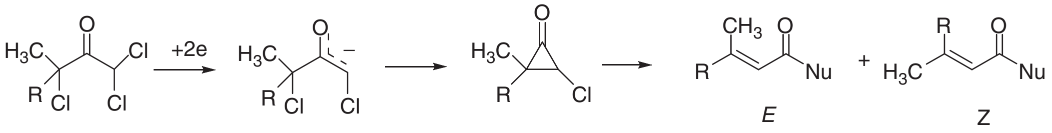
However, in the halo ketones **62** where electronic and steric effects were present, nucleophilic substitution reaction became dominant.

Electrochemical reduction of α,α′-trihaloketones **66** afforded the *Z*/*E* mixture of α,β-unsaturated amides **67** via a chloro-cyclopropanone as intermediate in a moderate to high yields, after the process was carried out in aprotic solvents in the presence of primary and secondary amines (Scheme 22).[36] The *Z*/*E* ratio was found to be independent of the nature of the halogen atom and the nucleophile used.

The same approach using electrochemically activated polyhaloketones which undergo Favorskii rearrangement was used to generate precursors for the *N*-acryloylation of chiral oxazolidin-2-ones.[37]

Table 1 Rearrangement product ratio in reaction of α,α,α-trihalomethyl ketones **62** with pyrrolidine, *t*-$BuNH_2$, and *n*-$BuNH_2$

	R	*X*	*Amine*	***64***	***Z-65/E-65***
1	Ph	Cl	Pyrrolidine	30	56/14
2	Ph	Cl	*t*-$BuNH_2$	56	44
3	Ph	Cl	*n*-$BuNH_2$	58	40/2
4	Ph	Br	Pyrrolidine	49	5/71
5	Ph	Br	*t*-$BuNH_2$	–	71
6	Ph	Br	*n*-$BuNH_2$	31	69
7	CH_3	Cl	Pyrrolidine		39
8	CH_3	Cl	*t*-$BuNH_2$	–	93



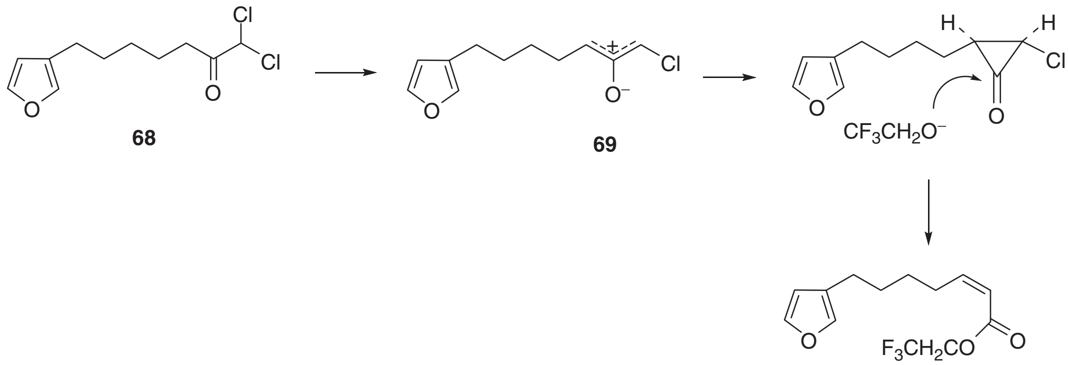
66

67 : 29–74%

Nu: primary or secondary amines

Scheme 22

α,α-Dichloroketones **68** when treated with triethylamine in trifluoroethanol were found to undergo the Favorskii rearrangement in preference to an intramolecular [4 + 3] cycloaddition. The α,β-unsaturated trifluoroethyl esters **70** were obtained with good *cis* selectivity via generated oxyallyl cation **69** and subsequently formed *cis*-cyclopropane, followed by a stereospecific nucleophilic ring opening (Scheme 23).[38]



68

69

70 : 57–66%
E:*Z* = 4:1

Scheme 23

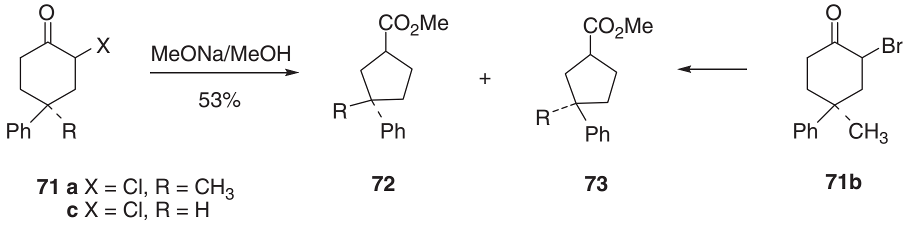
3.17.4 The Favorskii Rearrangement in Alicyclic Structures

3.17.4.1 Monocyclic α-Halo Ketones

Cyclic α-halo ketones have been widely used in Favorskii rearrangement for the synthesis of ring-contraction products. However, no examples exist in the literature on rearrangement of monocyclic five-membered rings. In this case only products of aldol condensation, substitution, or other reactions are formed.

There are many natural or nonnatural molecules with remarkable biological activity possessing a cyclopentyl unit in their structure. Such a moiety can be found in alkaloids, steroids, prostaglandins, triquinanes, indans, etc.

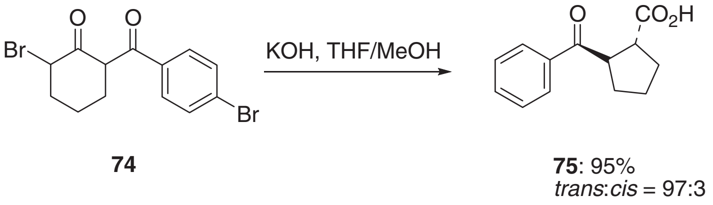
The ring contraction of a carbocyclic compound is a good route to assemble cyclopentyl units, Favorskii rearrangement is a well-established strategy.[39] The Favorskii reactions of α-halo cyclohexanones are well studied, and usually the chloro compounds provide higher yields compared to other halo derivatives. The rearrangement of α-halo cyclohexanones is dependent on the concentration of the base. The reaction of chloro cyclohexanone **71** with 0.2 M MeONa in MeOH gave a mixture of two isomeric esters **72** and **73** in a 3:1 ratio (Scheme 24). The esters were not isomerized under the reaction conditions, but prolonged (163 h) reflux with 1 M MeONa changed the ratio to 55: 45. When the reaction of **71b** was carried out at low methoxide concentrations, the same two esters **72** and **73** were obtained, but in an inverse ratio (1:3).[40] Reaction of either *cis*- or *trans*-2-bromo-5-methyl-5-phenylcyclohexanone **71b** with MeONa in MeOH gave a mixture of two esters, **72** and **73**, plus two new esters. The formation of high yields of ester product even at low methoxide ion concentrations indicates the importance of the 1,3-diaxial effect in curbing side reactions, particularly in preventing the halogen atom from assuming the axial position, as such 1,3-diaxial effects are absent in **71c**.



Scheme 24

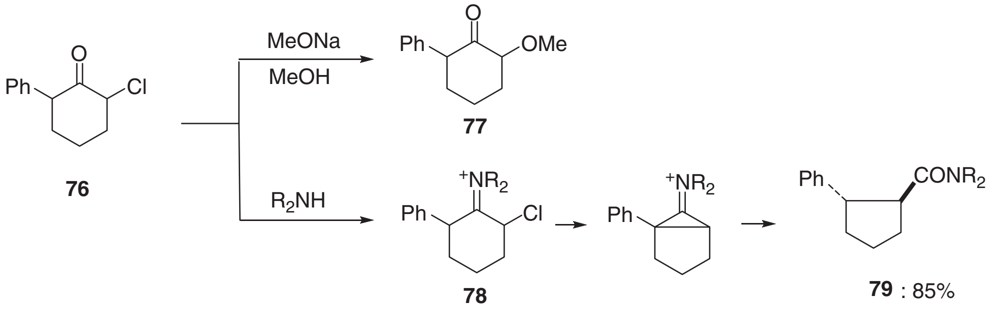
A Favorskii rearrangement on *trans*-4-phenyl-2-chlorocyclohexanone **71c** with sodium methoxide led to *cis*-methyl 3-phenylcyclopentanecarboxylate (Schemes 24, 73 R=H).[41]

Treatment of bromo diketone **74** with methanolic aqueous hydroxide resulted in the efficient conversion to ketoacid **75** as a 97:3 mixture of *trans*- and *cis*-isomers. Racemic *trans*-ketoacid **75** was resolved to *R*,*R*-enantiomer which was used for a synthesis of a selective diacyl glycerolacyltransferase-1 (DGAT-1) inhibitor (Scheme 25).[42]



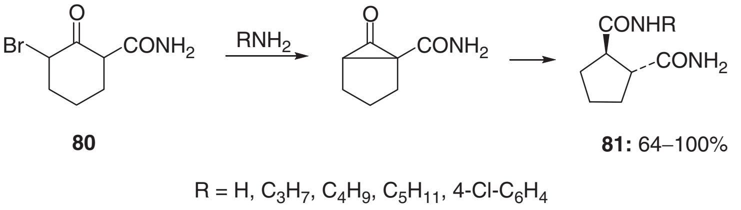
Scheme 25

Reaction of *cis*-2-chloro-6-phenylcyclohexanone **76** with 0.05 M MeONa in MeOH did not yield the ring-contraction product and gave a nearly quantitative conversion into a mixture of *cis*- and *trans*-2-methoxy-6-phenylcyclohexanones **77**. Reaction of **76** with excess of piperidine at 0 °C for 1 h gave conversion into amide, *trans*-2-phenylcyclopentanecarboxypiperidide **79** (Scheme 26) in high yield.[43] On adding MeONa increase in amide relative to methoxy ketones was observed. Comparison of the behavior of **76** and 2-chlorocyclohexanone toward piperidine showed that the presence of the phenyl group promotes enamine **78** and cyclopropane intermediate formations to yield the Favorskii amide *trans*-**79**.



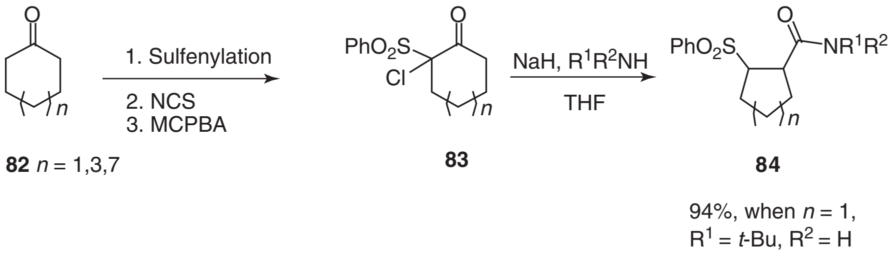
Scheme 26

6-Bromocyclohexanone-2-carboxyamide **80** in the presence of ammonia and amines afforded *trans*-cyclopentane dicarboxamides **81** via cyclopropanone intermediate in high yield (Scheme 27), except in the case when R=*p*-chlorophenyl (23%).[44]



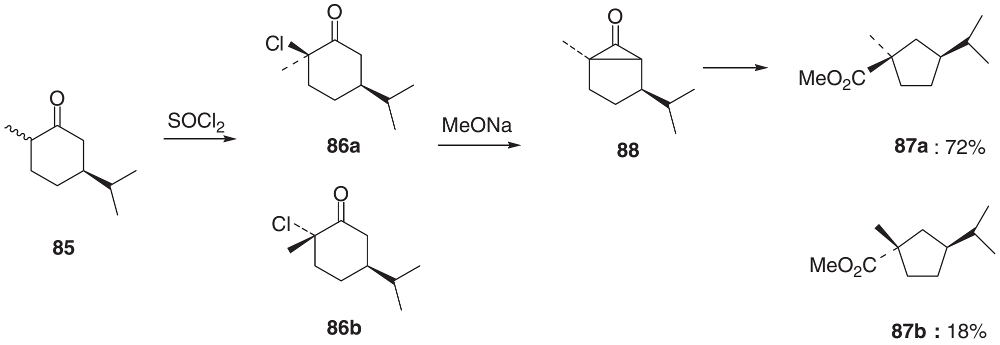
Scheme 27

Some Favorskii rearrangements of α-halo ketones with amines afford amides in low to moderate yield. The Favorskii reaction of cyclic α-chloro-α-sulfonyl ketones **83** with sodium hydride in the presence of amine afforded *β*-sulfonyl amides **84** with skeletal rearrangement in good to excellent yield (Scheme 28).[45] Cyclic α-chloro-α-sulfonyl ketones **83** may be synthesized from cyclic ketones **82** in three steps in high overall yields. Treatment of the cyclic α-chloro-α-sulfonyl ketones with alkoxides and hydroxide gave carboxylic esters and acids with cleavage of the ring in good to excellent yields.[46]



Scheme 28

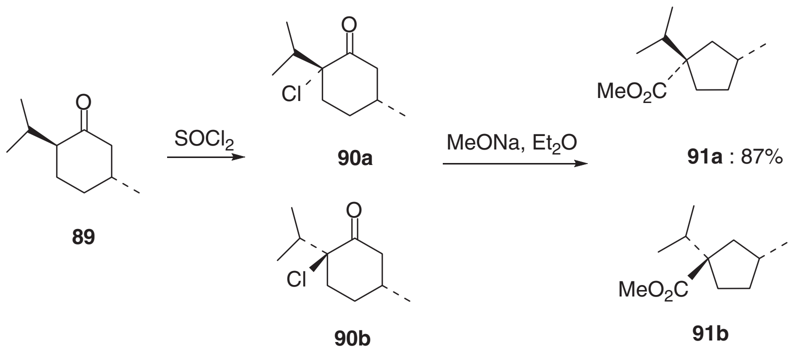
Natural terpenoid (+)-(*S*)-carvone was exploited in the synthesis of chiral alkyl cyclopentanols. (+)-(*S*)-carvone was hydrogenated to give (5*S*)-carvomenthone **85** as a C-2 epimeric mixture. The reaction with sulfuryl chloride afforded epimeric **86a,b** in 4:1 ratio.[47] Treatment of the mixture with MeONa in ether smoothly led to a Favorskii rearrangement yielding a mixture of diastereomeric cyclopentanecarboxylic acid esters **87a and b** in the same ratio. The enantiomerically pure major diastereomer **87a** was obtained by column chromatographical purification. The stereospecificity of the rearrangement is explained by a formation of cyclopropanone **88** which underwent a regioselective ring opening to give **87a** (Scheme 29).



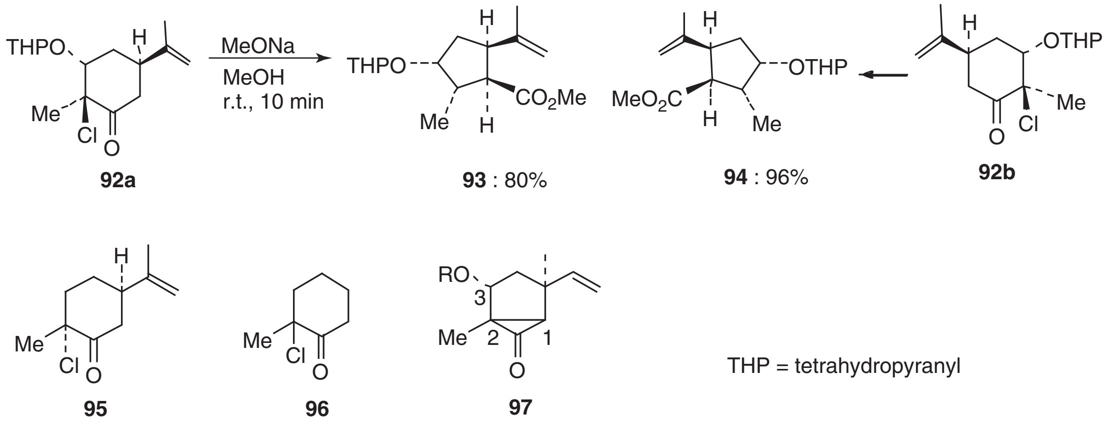
Scheme 29

This approach was extended for the synthesis of diastereomeric cyclopentanecarboxylic acid esters **91a and b** from (2*S*,5*R*)-(−)-menthone **89** (Scheme 30). In this case diastereomeric chloro ketones **90a/90b** were obtained in ratio 2:1, then were separated and treated under the same conditions to afford in high yield diastereomers (1*S*,3*R*)-**91a** and (1*R*,3*R*)-**91b**, respectively (Scheme 30).[47]

The Favorskii rearrangement of chiral α-chloro ketone **92a**, which was derived from (−)-(5*R*)-carvone, is efficient and highly stereoselective generating two new stereocenters in **93**.[48] The obtained functionalized cyclopentanecarboxylate **93** was transformed into natural monoterpene (+)-iridomyrmecin. The enantiomeric (+)-(5*S*)-carvone derivative **92b** gave the respective five-membered enantiomer **94** which was used as the steroid ring D precursor (Scheme 31). A similar α-chloro ketone **95** and simplest chloro ketone **96** did not yield any Favorskii reaction products under the analogous conditions. It is clear that the 3-oxy substituents play a critical role in this rearrangement via intermediate cyclopropanone derivative **97**. The presence of the 3-OTPH group in **97** induces selective cleavage of the adjacent bond between C-1 and C-2, and remarkably protonation of C-2 occurs with



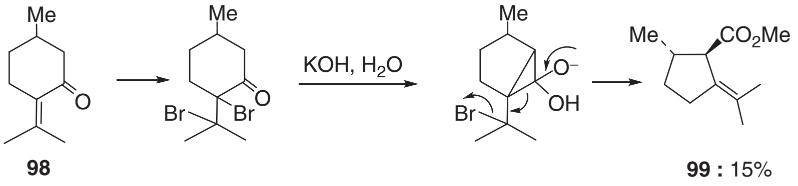
Scheme 30



Scheme 31

complete retention of stereochemistry. Coordination of the oxygen in the tetrahydropyranyl (THP) ring with the alcohol that donates its proton during the rearrangement could be a possible explanation for the desired regioselective opening of the cyclopropane ring.[49]

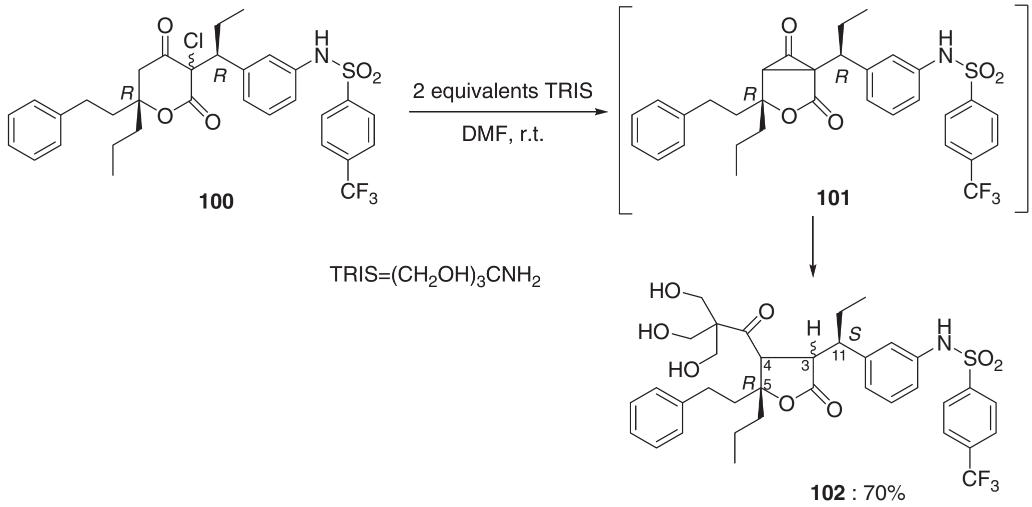
A related example of the stereoselective synthesis is transformation of (*S*)-pulegone **98** via bromination and the Favorskii rearrangement to *trans*-pulegenic acid **99** on a route to *trans*-fused dihydronepetalactones (Scheme 32), compounds isolated from the leaves and also the defensive secretions of some ant species.[50]



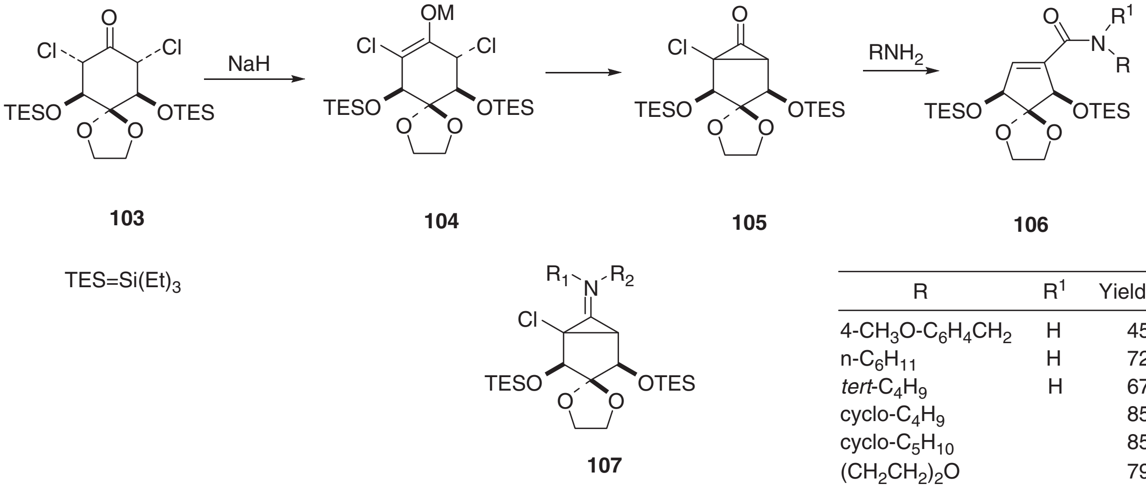
Scheme 32

A novel Favorskii rearrangement of α-chloro keto lactones yielding butyrolactones was reported.[51] Chiral chloro derivative **100** of HIV drug Tipranavir was obtained with N-chlorosuccinimide and the diastereomeric chloro derivatives (ratio 70:30) were treated with tris(hydroxymethyl)aminomethane (TRIS) in dimethylformamide (DMF) (Scheme 33). The diastereomers of butyrolactones **102** were isolated with the formation of a new sterocenter at C-3 and C-4, configuration at C-5 and C-11 remaining the same (at the latter atom the substituent priority is changed). The reaction proceeded through the intermediate cyclopropanone **101**.

An attempt to obtain chiral cyclopentene derivatives by performing asymmetric Favorskii rearrangement of *meso*-dichloro cyclohexanone **103** was unsuccessful.[52] However, some diastereoselectivity in **106** was obtained by employing chiral amines, (*S*)-α-methylbenzylamine and L-proline derivatives. Formation of enolate **104** was directly observed by ^{1}H NMR spectroscopy and this process was found to be fast compared to Favorskii rearrangement. The differences in reactivity between the metal and amine-mediated Favorskii rearrangements led to the proposed alternative formation of cyclopropyliminium species **107** instead of cyclopropanone intermediate **105** (Scheme 34).



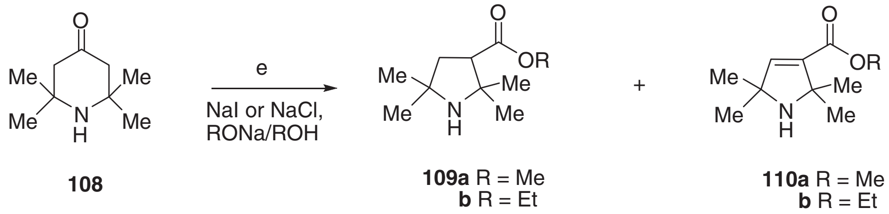
Scheme 33



R	R^1	Yield (%)
4-CH_3O-$C_6H_4CH_2$	H	45
n-C_6H_{11}	H	72
tert-C_4H_9	H	67
cyclo-C_4H_9		85
cyclo-C_5H_{10}		85
$(CH_2CH_2)_2O$		79
CH_3OCH_3		71
$(CH_2CH_2)_2NCH_3$		75

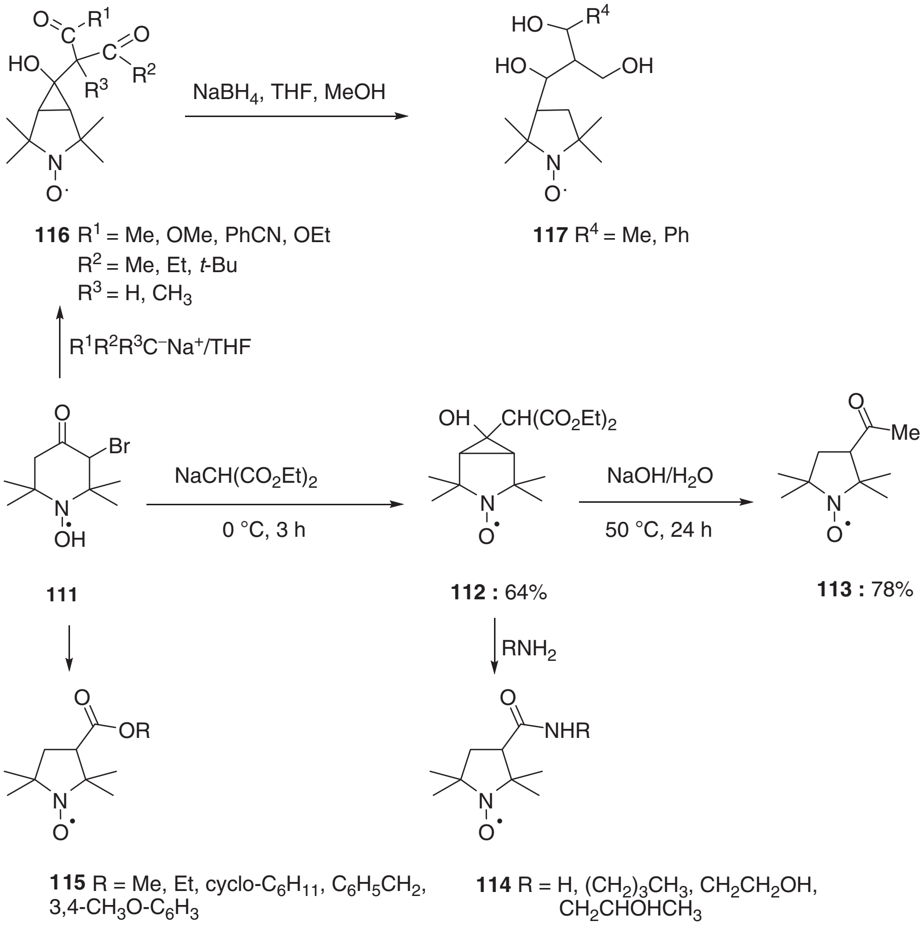
Scheme 34

Electrochemically induced Favorskii rearrangement of piperidin-4-ones **108** in the presence of sodium halides formed a mixture of pyrrolidine carboxylate **109** and dihydro-1*H*-pyrrole carboxylate **110** (Scheme 35).[53] Products were isolated by vacuum distillation in 70% yield. The ratio **109**:**110** changes from 2:1 to 1:2 with the increase of MeONa quantity from 0.5 to 3.0 equivalents. The reaction in the presence of NaI was found to be rather selective process, whereas using NaCl no selectivity was observed and yields were very low.



Scheme 35

Using ethyl sodium malonate as nucleophile in the reaction with 3-bromo-4-oxo-2,2,6,6-tetramethylpiperidin-1-oxyl radical **111** led to an interesting result which could be a direct proof of cyclopropanone intermediate in the Favorskii rearrangement. Cyclopropane ring closure and nucleophile addition to the carbonyl group gives the isolable intermediate cyclopropane derivative **112**, which can be readily degraded by aqueous sodium hydroxide at 50 °C to the rearrangement product **113**.[54] In the presence of ammonia or amines amides **114** were obtained. Treatment of **111** with solid sodium alkoxide of primary or secondary alcohol in ether led directly to the rearrangement products **115** (Scheme 36).[55] The reaction of **111** with C-nucleophiles under the Favorskii reaction conditions gave novel bicyclic nitroxides **116** through partial Favorskii rearrangement.[56] The reaction was carried out by slowly adding appropriate C-nucleophile as sodium salt $R_1R_2R_3C^-Na^+$ to a solution of **111** in THF. The rearrangement proceeded only in part, however the cyclopropane ring opened under harsh reduction conditions with $NaBH_4$ followed by the addition of methanol producing sodium methylate *in situ*, and final Favorskii product **117** was formed as a mixture of diastereomers (Scheme 36).

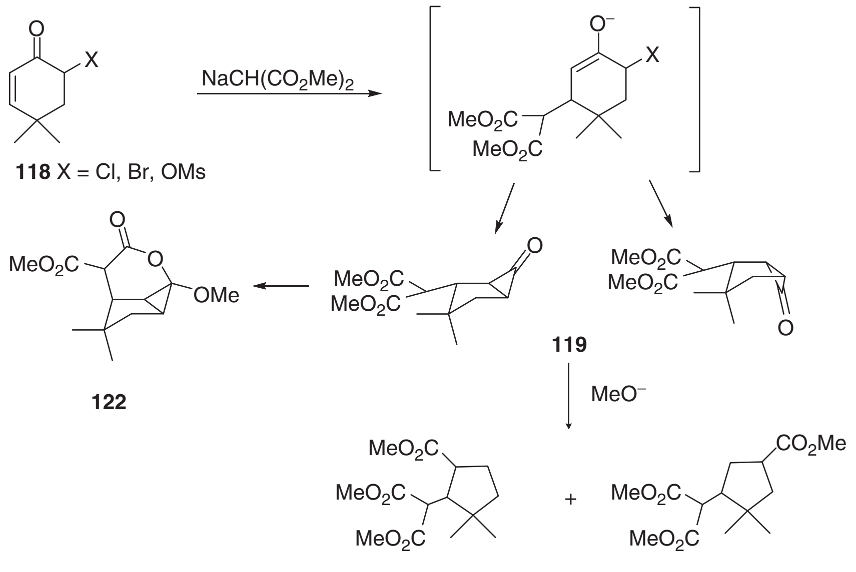


Scheme 36

The described Favorskii reactions of **111** represent, in certain cases, a viable alternative method for the direct synthesis of pyrrolidine type of spin labels and related derivatives.

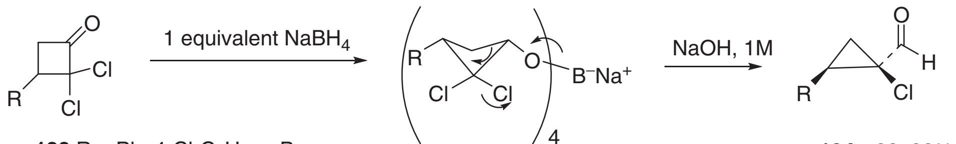
The anion of dimethyl malonate was generated with sodium methoxide in methanol followed by the addition of a solution of the α,β-unsaturated bromo or chloro ketones **118** in furan to afford the Favorskii rearrangement products *cis*- and *trans*-esters **120** and **121**, and tricyclic acetal **122** via intermediate cyclopropanones **119** up on reaction with methoxide ion (Scheme 37).[57] The reactions involving bromoketone **118** did not produce products of conjugate addition without loss of the nucleofuge.

Cyclopropanecarboxaldehydes **124** were stereoselectively obtained from 3-aryl- and alkyl-substituted 2,2-dichlorocyclobutanones **123**.[58] The ring contraction of cyclobutanones **123** was accomplished in one step without isolation of intermediate products by first adding $NaBH_4$ to cyclobutanone and the following basic workup. The reaction proceeds in the stereoselective way because of steric hindrance of the substituent in the 3-position yielding *cis*-substituted 1-chlorocyclopropanecarboxyaldehydes (Scheme 38). The mechanism of this reaction involves semibenzilic pathway where the leaving group should be in the pseudoequatorial position.[59]



120 : 8–18% **121** : 7–17%

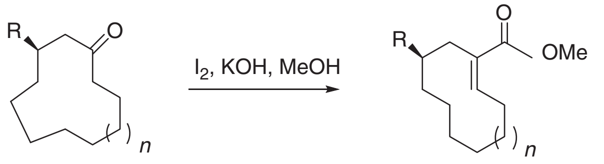
Scheme 37



123 R = Ph, 4-Cl-C$_6$H$_5$, *n*-Bu **124 :** 92–99%

Scheme 38

The synthesis of macrocyclic musks was achieved by the ring-contraction methodology. Cyclopentadecanone Exaltone® **125a** was submitted to the Favorskii conditions (a solution of macrocyclic ketone was added to a solution of I$_2$ in CH$_3$OH, followed by an addition of a solution of KOH in CH$_3$OH) and **126a** was isolated in 83% yield.[60] Treatment of isomuscone **125b** furnished the unsaturated ester **126b** in 83% yield. Cycloheptadecanone **125c** gave **126c** in 50% yield. Rearrangement with the nonsymmetric macrocyclic ketone (–)-(*R*)-muscone **125d** (Scheme 39) proceeded with a complete regioselectivity in favor of **126d**. Similarly, (–)-(R)-homomuscone **125e** afforded only **126e**.

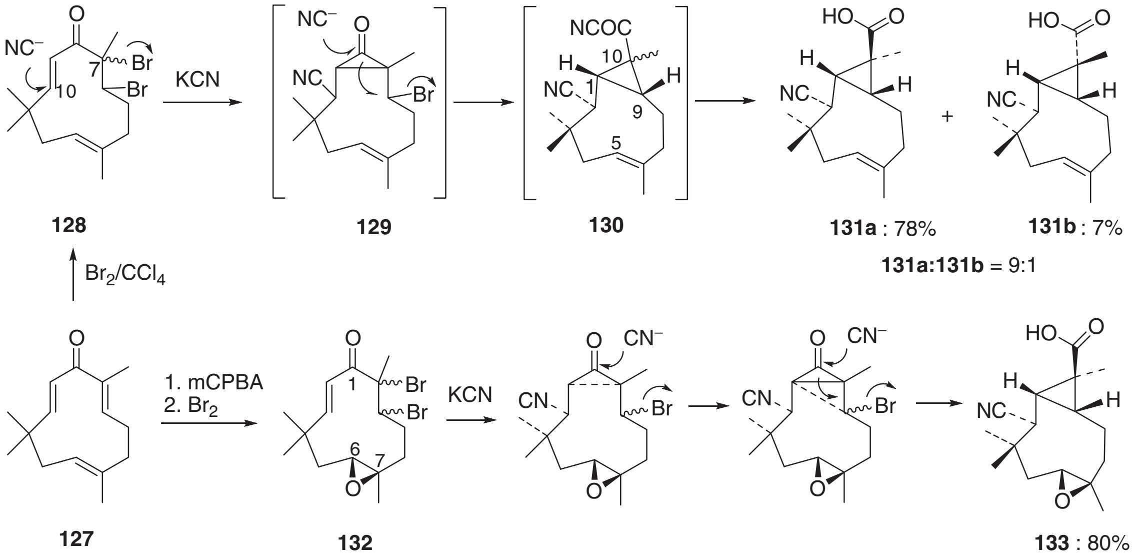


125a *n*=5, R=H
b *n*=6, R=H
c *n*=7, R=H
d *n*=5, R=CH$_3$
e *n*=6, R=CH$_3$

	Yield (%)
126a *n*=5, R=H	83
b *n*=6, R=H	83
c *n*=7, R=H	50
d *n*=5, R=CH$_3$	56
e *n*=6, R=CH$_3$	48

Scheme 39

An interesting ring-contracting transannular Favorskii rearrangement reaction was observed when the stereoisomeric mixture of macrocyclic dibromo ketone zerumbone **128** was treated with aqueous KCN at room temperature in the presence of *α*- or *β*-cyclodextrin.[61] The carbon skeleton of zerumbone **127**, a monocyclic sesquiterpene, can be imagined as a synthetic precursor of the B/C ring system of paclitaxel. Therefore synthesis of zerumbone derivatives attracted attention of synthetic chemists. This unique ring-contracting transannular reaction involving the successive generation of two cyclopropane rings is initiated by conjugate addition of cyanide ion to C10. The resulting carbanion at C9 displaces the bromine at C7, forming the cyclopropanone intermediate **129** (Scheme 40). Nucleophilic addition of a second cyanide ion to the carbonyl group opens the strained cyclopropanone to generate another carbanion at C9, which now displaces the remaining bromine, creating the final cyclopropane ring **130**. The acyl cyanide **130** is rapidly hydrolyzed to afford the acids **131a** and **131b** in ratio 9:1 (Scheme 39). Oxidation of the 6,7-double bond and addition of one equivalent of bromine gave a stereoisomeric mixture of 10,11-dibromo-6,7-epoxy-4,4,7,11-tetramethyl-2-cycloundecenone **132**. Treatment of the latter mixture with aqueous KCN at room temperature initiated a Favorskii rearrangement paralleling the reaction of zerumbone dibromide **128** with cyanide afford ring-contracted acid **133**.[62] The structures of **131a** and **133** were confirmed by the X-ray analysis.



Scheme 40

Several zerumbone derivatives were found to be selective inhibitors to the growth of Gram-positive bacteria.

3.17.4.2 α,α′-Dihalo and α,α,α′-Trihalo Cyclic Ketones

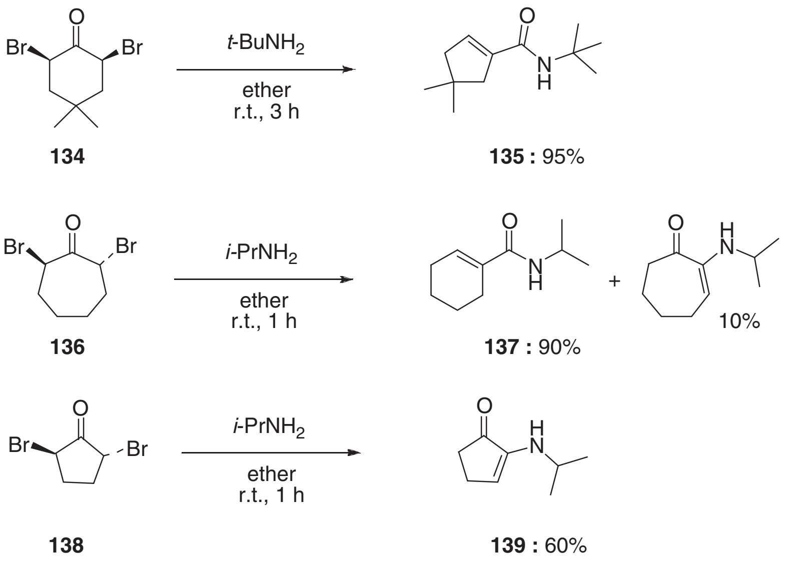
Cyclic α,α′-dibromo ketones react with primary amines in ether in different ways depending up on the ring size. *Cis*-2,6-dibromo-4,4-dimethyl-2-cyclohexanone **134** reacted smoothly with primary amines to afford ring-contracted Favorskii rearrangement product **135** in high yield. The reaction of *trans*-2,7-dibromocycloheptanone **136** at room temperature for 2 days is more complicated. However, the main product is the Favorskii carboxylic amide **137**. However, no ring contraction has been observed in the case of *trans*-2,5-dibromocyclopentanone **138** because of the impossibility to generate a very strained bicyclic cyclopropanone, that is, a bicyclo[2.1.0]pentane-5-one. The main product is ‘α-imino ketone’ **139**, which occurs entirely under the enamine form (Scheme 41).[63]

α,α,α′-Dibromochlorocycloalkanones **140** and α,α′,α-dibromochlorocycloalkanones **141** reacted under Favorskii conditions to afford methyl 2-chlorocycloalkenecarboxylate **142** as the main product, whereas **143** occurred always in a low yield (Scheme 42). The influence of ring size does not alter the yield by more than ±3%. The solvent polarity facilitates this selectivity by *ca.* 2%. The yields of compounds formed by preferred loss of bromide over chloride are *ca.* 2% higher in methanol than in benzene. However, ring size and the relative position of bromine atoms do exert a remarkable influence on the formation of (*Z*)- and (*E*)-isomers of **142**. The yields of (*Z*)-**142** are remarkably higher with α,α-dibromo-α′-chlorocycloalkanones. No significant differences were observed in the *Z*:*E* ratio on changing the polarity of solvent.[64]

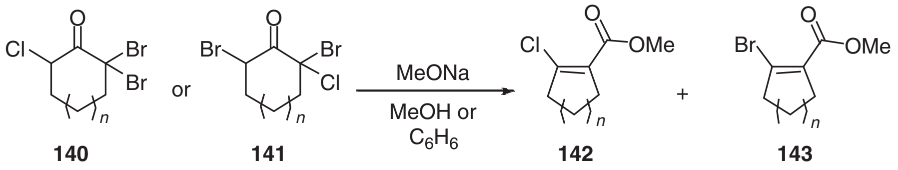
3.17.4.3 Rearrangement in Polycyclic Halo Ketones

A strategy for the construction of hexahydronaphthalenecarboxylates **145** was developed via the Favorskii rearrangement of 1,1-dichloro bicyclo[5.4.0]undec-5-en-2-ones **144** (Scheme 43) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol or ethanol in good yield.[65] Methyl groups could be appended in positions 2, 3, and 4 in cyclohexadiene ring and in the 7-position ($R = CH_3$).

Favorskii rearrangement of several various ring size α-bromo cyclic ketones fused to benzene ring **146** was promoted using $NiCl_2$ and $CuCl_2$, and a comparison was made with the typical rearrangement conditions by using MeONa in MeOH (Scheme 44).[66] Rearrangement products, including benzofurane and chromane carboxylates **147** ($n = 1$, and $n = 2$, respectively) were obtained in good yields, higher yields with $NiCl_2$, however, the reaction using $NiCl_2$ required longer time and excess of the

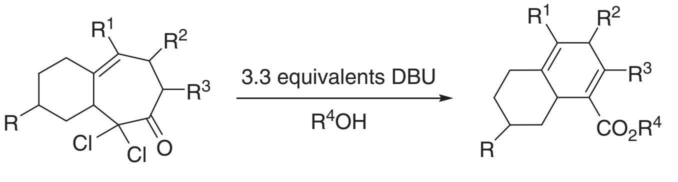


Scheme 41



yield	**142**	**143**
n = 1	94.5	2.0
2	95.5	3.0
4	95.0	4.0
6	97.0	0.5

Scheme 42

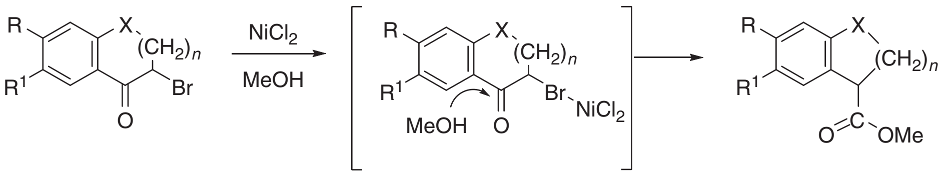


144

R,R^1,R^2,R^3 = H or Me
R^4 = Me or Et

145 : 57–84%

Scheme 43



146

147a-h

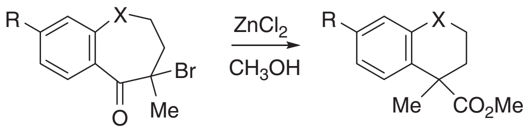
Scheme 44

promoter was required to facilitate the reaction (Table 2). The reaction presumably includes complexation of bromine atom with $NiCl_2$, followed by the simultaneous attack of methoxy group and the elimination of bromide.

Table 2 Rearrangement products in reaction of indanone, benzoxepinones, and chromanones with $NiCl_2$ and $CuCl_2$, and NaOMe in MeOH

Compound	*R*	*R¹*	*X*	*n*	*Yield (%)*		
147					*$NiCl_2$*	*$CuCl_2$*	*NaOMe*
a	H	H	CH_2	0	95	90	83
b	H	H	O	1	97	84	79
c	H	H	O	2	86	70	73
d	H	Me	O	1	91	90	81
e	H	Me	O	2	96	90	88
f	Me	Me	O	1	95	89	85
g	Me	Me	O	2	90	89	76
h	H	OMe	O	2	92	86	85

The similar α-bromo cycloalkyl aryl ketones **148** without α-hydrogen after prolonged heating in the presence of Lewis acid, that is, anhydrous $ZnCl_2$ in methanol, afforded ring-contracted product **149** (Scheme 45).[67] Tetralone, the six-membered analog of ketone **148**, did not react under these conditions.



148

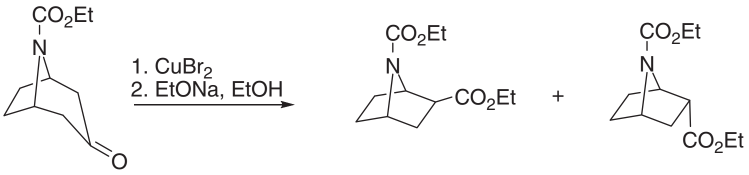
149

	Yield (%)
a R=OMe, X=CH_2	61
b R=H, X=CH_2	91
c R=OMe, X=O	44
d R=H, X=O	22

Scheme 45

The Favorskii rearrangement using sodium ethoxide in ethanol of the bromo derivative of N-carbethoxy-7-azabicyclo[3.2.1]heptane **150** without isolation of it afforded in a moderate yield a mixture of the *exo-* and *endo-* esters of 7-azabicyclo[2.2.1]heptane **151** in a ratio 4:1, which are useful synthetic intermediates for the synthesis of natural products (Scheme 46).[68]

Fused carbocyclic α,*β*-unsaturated cyclic ketone 4,8-dibromodiisophor-2(7)-en-3-one-l-carboxylic acid **152**, derivative of natural compound, under treatment of base afforded ring-contracted product **153** via semibenzilic pathway because of the absence of α-hydrogen (Scheme 47).[69]



150

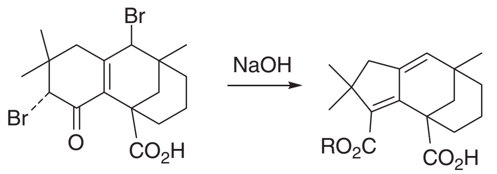
151 *exo* : 30%

151 *endo* : 7%

Scheme 46

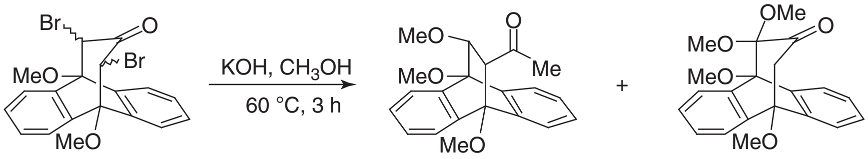
Submitting *cis-* and *trans-*isomers of polycyclic compound **154** to Favorskii conditions (KOH/MeOH, 60 °C) afforded the single isomer of Favorskii ester **155** and the α-ketoacetal **156** (Scheme 48).[70]

Both 2-*exo*-bromobicyclo[3.3.1]nonan-3-one **157** and its 2-*endo-* epimer **158** afforded methyl *endo*-bicyclo[3.2.1]octane-6-carboxylate **159** stereoselectively in the Favorskii reaction using sodium methoxide in methanol. The stereoselectivity of the reaction decreases using sodium methoxide in dimethoxyethane (DME) at room temperature, and the product contains some 6-*exo*-epimer **159**. However, the reaction in DME at 0 °C gave the only rearranged product **159** (Scheme 49).[71]



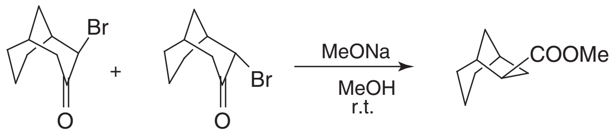
152 R=H, Me, Et **153** : 90%

Scheme 47



154 **155 :** 35% **156 :** 11%

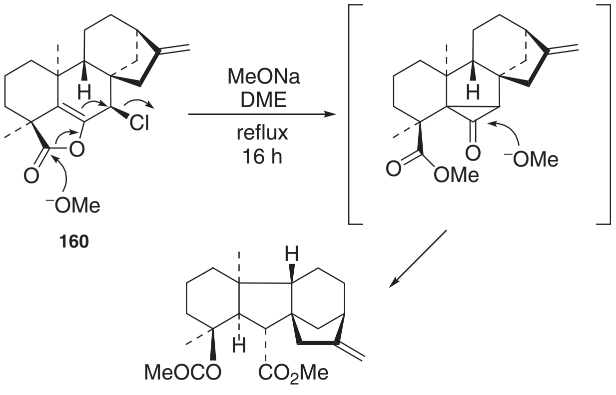
Scheme 48



157 **158** **159 :** 94%

Scheme 49

Since the enol form of ketones is necessary for Favorskii rearrangement, halo-enol-lactones behave similarly to halo ketones. The polycyclic chloro-enol-lactone **160** up on treatment with sodium methoxide in DME yields the only stereoisomer of **161**, analog of diterpene gibberellin A_{12}. The reaction proceeded via a cyclopropanone mechanism (Scheme 50) and only the α-CO_2Me at C-7 is formed stereospecifically.[72]

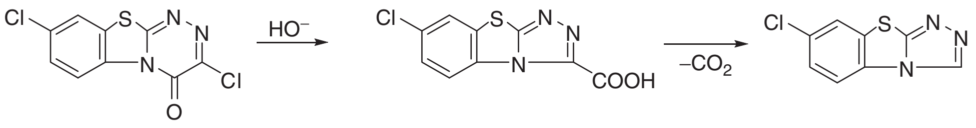


160

161 : 75%

Scheme 50

Favorskii rearrangement of triazino[3,4-b][1,3]benzothiazole-4-one **162** with 10% NaOH solution for 1 h afforded an unexpected product **164** in 65% yield. It was proved that compound **163** on boiling with NaOH solution underwent decarboxylation with ring contraction to form a new fused heterocycle, 7-chloro[1,2,4]triazolo[3,4-*b*][1,3]benzothiazole **164** (Scheme 51).[73]

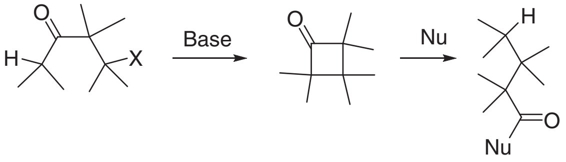


162 **163** **164** : 65%

Scheme 51

3.17.5 Homo- and Quasi-Favorskii Rearrangements

There are two major variations of the Favorskii rearrangement: the homo-Favorskii when β-halo or tosyl ketones **165** are treated with base in the presence of a nucleophile, going through the corresponding cyclobutanone (Scheme 52) to afford rearranged product **166**, and the quasi-Favorskii, when the α-halo-ketone does not have any enolizable hydrogen.

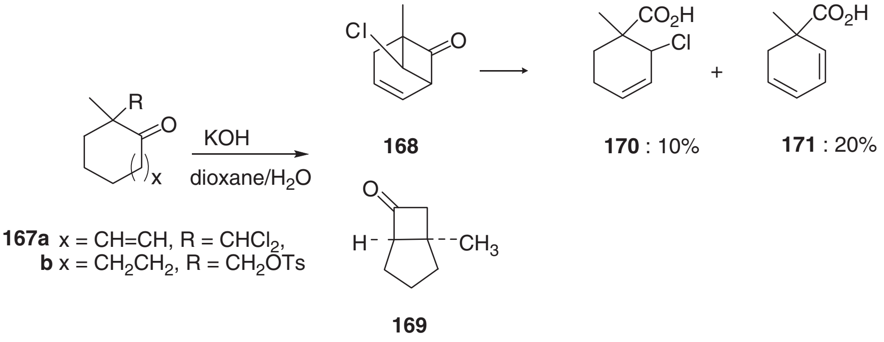


165 X = Cl, Br, I, OTs **166**

Scheme 52

3.17.5.1 Homo-Favorskii Rearrangement

Reaction of dichloromethyl-2-cyclohexenone **167a** in the alkaline media led to a chloroolefinic acid **170** and dienoic acid **171**.[74] The first step of the homo-Favorskii rearrangement, the cyclobutanone **168** formation, can take place along two paths, such that, bicycloheptanones of both the [3.1.1] and [3.2.0] types, **168** and **169**, respectively, had been intermediates in the base-induced reaction of ketone **167a** (Scheme 53). This was evidenced as the reaction of the saturated methylcyclohexyl p-toluenesulfonate **167b** afforded both **169** and **170** skeletons.



168 **170** : 10% **171** : 20%

167a x = CH=CH, R = CHCl$_2$,
b x = CH$_2$CH$_2$, R = CH$_2$OTs

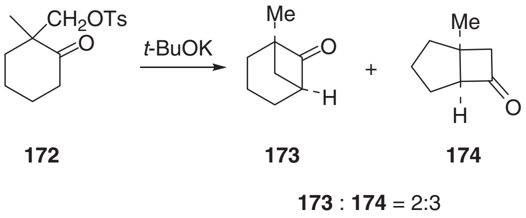
169

Scheme 53

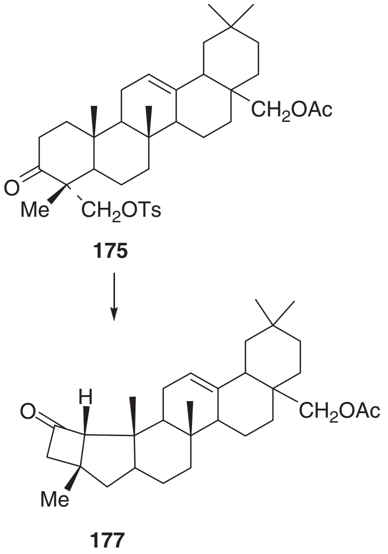
Analogously, this behavior was observed in the case of **172** leading to a mixture of the bicyclo[3.1.1]heptanone **173** and bicyclo[3.2.0]heptanone **174** in the ratio 2:3 in homo-Favorskii rearrangement by reaction of *tert*-BuOK in *tert*-BuOH (Scheme 54).[75] The same result was obtained from the reaction of **172** with NaOH in MeOH.

The homo-Favorskii rearrangement proceeds in a stereospecific manner as it was demonstrated using triterpenoids. Two epimeric keto tosylates **175** and **176** at C$_4$ on treatment with *tert*-butoxide under the same conditions furnished single bicyclo[3.2.0]heptane fragment containing compounds **177** and **178** in the stereospecific way. The compounds showed opposite Cotton effect in the circular dichroism spectra indicating opposite configuration of bicyclo[3.2.0]heptane system containing carbonyl chromophore (Scheme 55).[76]

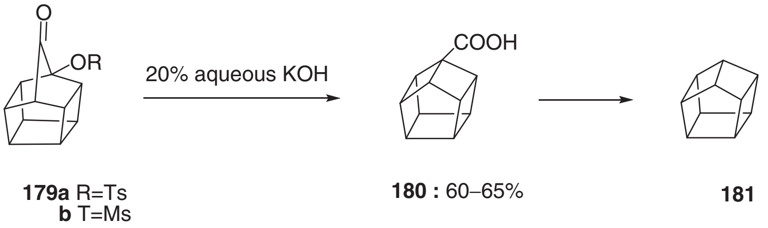
The final steps in the preparation of highly symmetric the cubane and pentaprismane skeletons were achieved utilizing Favorskii ring contraction. Treatment of homopentaprismanone tosylate **179a**[77] or mesylate **179b**[78] afforded pentaprismane **180** skeleton which easily decarboxylated to **181** (Scheme 56).



Scheme 54



Scheme 55



Scheme 56

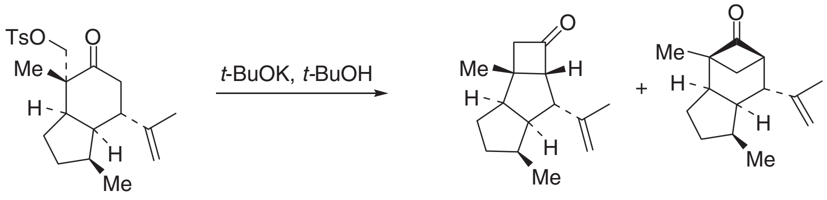
However, attempts to synthesize other highly symmetric polyhedranes, [3]-prismane using this approach failed.[79]

The homo-Favorskii rearrangement was used in the stereocontrolled synthesis of sesquiterpene kelsoene. The key step involved a base-catalyzed rearrangement of keto tosylate **182** to a mixture of two cyclobutanone rings containing tricyclic compounds **183** and **184** in a ratio 4:5 (Scheme 57).[80] The **183** corresponds to the product of the homo-Favorskii rearrangement. Interestingly, the acidic conditions induced the bicyclo[3.1.1]heptane skeleton **184** isomerization into less strained bicyclo[3.2.0]heptane framework. The enantioselective synthesis of (+)-kelsoene was realized starting from enantiomerically pure precursors.[81]

3.17.5.2 Quasi-Favorskii Rearrangement

Favorskii skeletal rearrangement developed into a useful synthetic tool as the bridgehead halo ketones are a key step in the synthesis of natural compounds. Some cyclic α-halo alcohols and their derivatives under basic conditions also follow the semibenzylic Favorskii rearrangement pathway.

A series of bicyclic bridgehead halo derivatives were used for the synthesis of bicyclo[3.3.0]octanes, important moieties in natural polyquinanes, after the report of the first such reaction.[82] Substituted bicyclo[3.3.1]nonanes **185** under treatment of BuLi

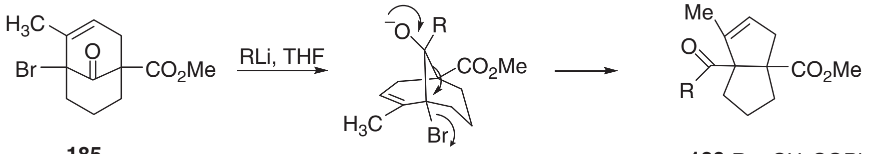


182 **183** **184**

183+184 : 95%, ratio 4:5

Scheme 57

and in the presence of acetophenone or lithio dimethylphosphonate were converted to precursors **186** of sesquiterpene modhephene (Scheme 58).[83] An electron-withdrawing group is adjacent to the carbonyl group.

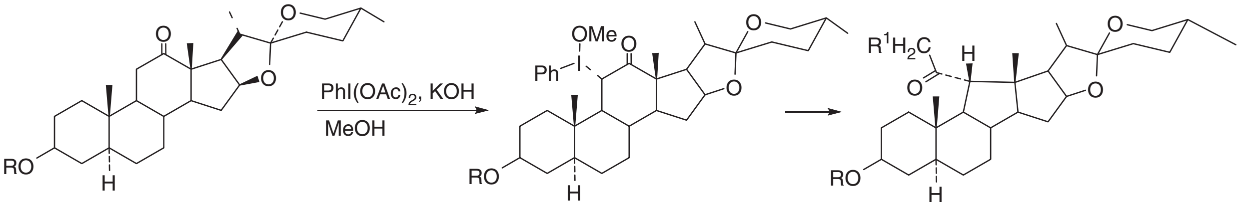


185

186 R = CH_2COPh : 41%,
$CH_2OP(OMe)_2$: 70%

Scheme 58

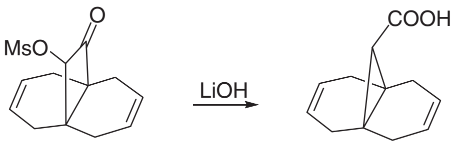
Hypervalent-iodine-induced Favorskii quasi rearrangement by treatment of stereoidal ketones **187** with $PhI(OAc)_2$ and KOH in MeOH proceeded to yield C ring-contraction product **189**. The ring contraction can be explained by axial approach of $PhI(OAc)_2$ to produce the diaxial adduct in which the considerable 1,3-diaxial strain between the iodine containing moiety and the angular 18 and 19 methyl groups is released by epimerization leading to the equatorial iodine containing **188** to fulfill the stereoelectronic requirements for the Favorskii rearrangement (Scheme 59).[84]



187 R = Me, Ac **189** **188** R^1 = H, Me : 12–57%

Scheme 59

A new synthetic route to the 1,6-methano[10]annulene skeleton has been developed. The key step in this route is the semibenzylic Favorskii rearrangement of a [4.4.2]propellane keto mesylate **190** to a [4.4.1lpropellane carboxylic acid **191** in 50% aqueous THF solution of LiOH (Scheme 60).[85]

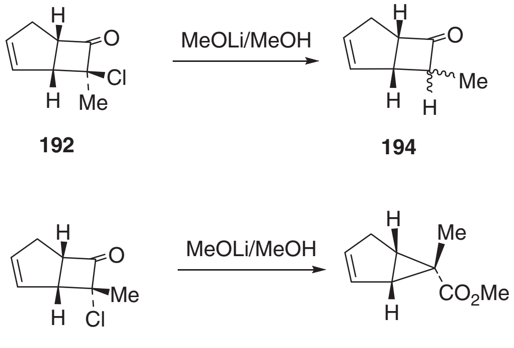


190 **191** : 96%

Scheme 60

The rearrangement is stereospecific as treatment of the isomers **192** and **193** with lithium methoxide in methanol gave two distinct reactions. At room temperature, *exo*-**192** rapidly and quantitatively gave a C-7 epimeric mixture of

5-methoxy-7-methylbicyclo-[3,2,0]but-2-en-6-ones **194** (Scheme 61).[86] **193** rearranges stereospecifically to methyl *exo*-6-methylbicyclo[3.1.0]hex-2-ene-*endo*-6-carboxylate **195**. These results can be rationalized by different mechanisms as substitution occurred rapidly with the 7-*exo*-chloro compound. The 7-*endo*-chloro isomer **193** undergoes a comparatively slow semibenzilic acid rearrangement. This is in accord with the known stereochemistry of this reaction where the attacking nucleophile is *syn* to the leaving group. However, up on treatment with aqueous lithium hydroxide *exo*-**192** produced the respective *exo*-carboxylic acid, thus it appears that aqueous hydroxide ion does not promote enolization at a rate competitive with the semibenzilic rearrangement.



192

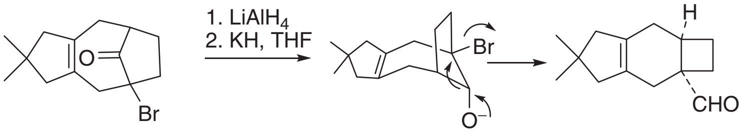
194

193 : 100%

195 : 83%

Scheme 61

The quasi-Favorskii rearrangement as a synthetic tool was used for the synthesis of skeletons of various natural products. The synthesis of the sesquiterpene sterpurene is an example of this methodology.[87] The rearrangement of **196** involved careful reduction with $LiAlH_4$ at 0 °C, making sure not to reduce the bridgehead bromide and subsequent rearrangement in the presence of strong base KH to give aldehyde **197** at lower concentrations, although a mixture contained the corresponding acid, ester, and alcohol (Scheme 62).

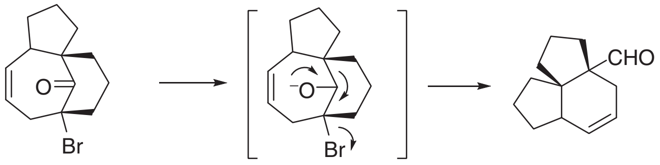


196

197 : 91%

Scheme 62

The example of quasi-Favorskii rearrangement is presented in Scheme 63. Treatment of bromoketone **198** with $LiAlH_4$ afforded not a simple reduction product, but a quasi-Favorskii rearranged product **200** in nearly quantitative yield via the intermediate structure **199**.[88]



198

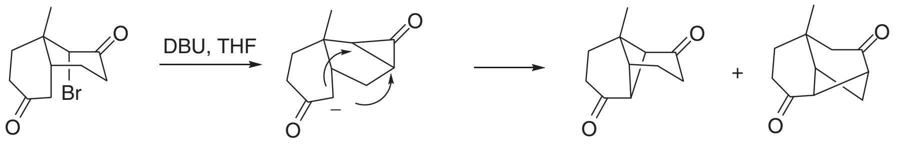
199

200 : 98%

Scheme 63

A key step in synthesis of natural sesquiterpenoid tetracyclic compounds copaene and ylangene involved the quasi-Favorskii rearrangement of **201** under the nonnucleophilic base DBU in THF.[89] The reaction proceeds through Favorskii intermediate **202** to yield the copaene or ylangene skeleton **203** and product **204** (Scheme 64).

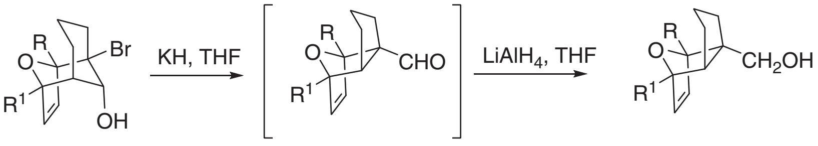
Treatment of tricyclic halo alcohols **205** with potassium hydride resulted in a quasi-Favorskii rearrangement to produce aldehydes **206a–c**, which were reduced *in situ* with $LiAH_4$ to give the corresponding alcohols **207a–e** (Scheme 65). The *in situ* reduction was carried out because of the apparent instability of the aldehydes resulting from the quasi-Favorskii rearrangement.[90]



201 **202** **203** **204**

203+**204** : 46%; ratio 0.8:1

Scheme 64

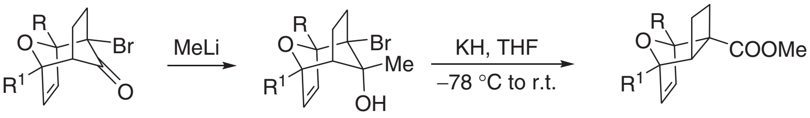


205 **206**

	Yield (%)
207 a R = R^1 = H	61
b R = Me, R^1 = H	68
c R = R^1 = Me	73
d R = CH$_2$OH, R^1 = H	54
e R = (CH$_2$)$_3$OTBS, R^1 = H	83

Scheme 65

The addition of methyllithium to the five-membered ring **208** could be conducted without Favorskii rearrangement to give alcohols **209**. Separate treatment of these alcohols with potassium hydride in THF smoothly afforded quasi-Favorskii rearrangement products **210** in very good yields (Scheme 66).[91]

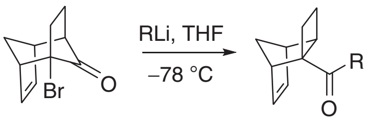


208 **209**

	Yield (%)
210 a R = R^1 = H	72
b R = Me, R^1 = H	62
c R = R^1 = Me	68

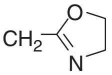
Scheme 66

The reaction was explored with the carbocyclic analog of **208**. The bromoketone **211** using a slight excess of various lithium organic reagents at raising the temperature over the course of the reaction resulted in a quasi-Favorskii rearrangement products **212** in good yield (Scheme 67).[92] The reaction of **211** with isobutenyllithium LiCH=CMe$_2$ afforded the respective butenyl ketone, a key intermediate in the synthesis of carbocyclic core of tricycloclavunone.[93]



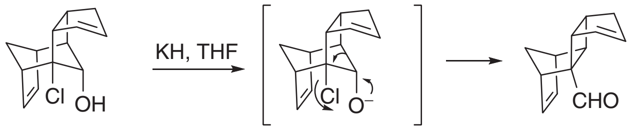
211 **212 :** 60–88%

R=CH$_2$CN, CH$_2$PO(OMe)$_2$, CH$_2$POPh$_2$, CH$_2$COO-*t*Bu,
CH$_2$CO-NMe$_2$, CH$_2$-SO$_2$-N(CH$_2$CHCH$_2$)$_2$, CH$_2$SO$_2$Ph,



Scheme 67

The synthesis of the diterpene spatol from brown algae *Spatoglossum howleii* involved quasi-Favorskii rearrangement of chloro alcohol **213** in the presence of potassium hydride in THF presumably via intermediate **214** to yield aldehyde **215** (Scheme 68).[94]



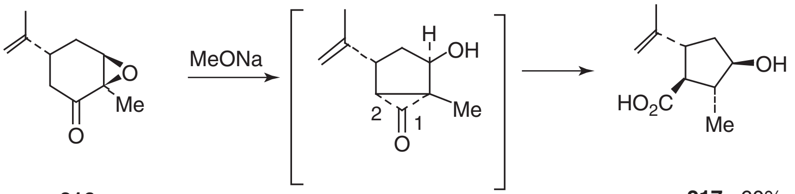
213 **214** **215** : 76%

Scheme 68

3.17.6 Favorskii-Like Reactions

3.17.6.1 Epoxides

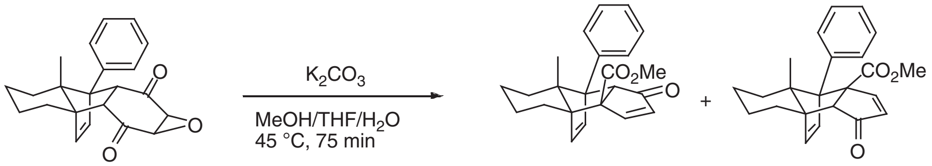
Favorskii rearrangement of (+)-carvone monoepoxide **216** afforded a highly functionalized cyclopentanecarboxylic acid **217** in good yield. The stereochemical array in **217** requires cyclopropanone derivative **218** as an intermediate (presumably formed by the S_N2-type displacement of the epoxide moiety) in which the selective cleavage of the bond between C-1 and C-2 is coupled with the stereoselective protonation at C-2 resulting in retention of the stereochemistry (Scheme 69).[95]



216 **218** **217** : 60%

Scheme 69

Favorskii rearrangement of the polycyclic epoxide **219** regioselectively afforded a 95:5 ratio of stereoisomers **220** and **221** in 81% yield, the ring contraction being preponderant opposite to the phenyl substituent (Scheme 70).[96]



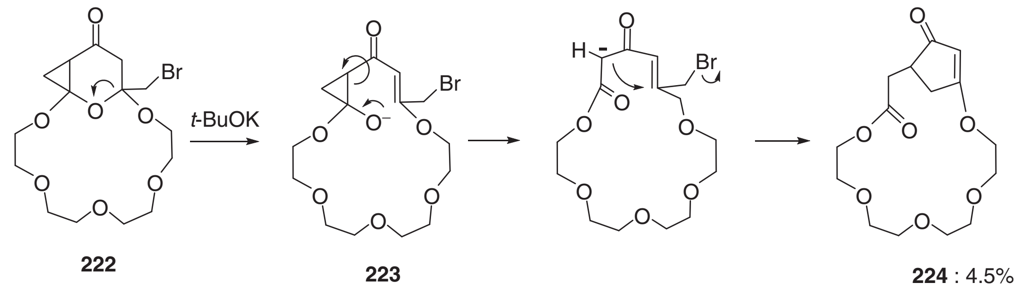
219 **220** **221**

220 : 221 = 95 : 5
81% yield overall

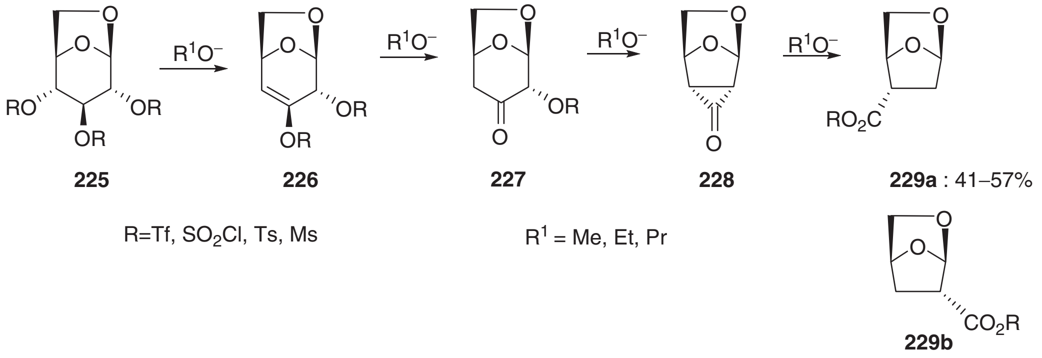
Scheme 70

2,6-Bis(bromomethyl)-4-pyrone and tetraethylene glycol in the presence of potassium *tert*-butoxide in *tert*-butanol unexpectedly afforded macrocycle **224**, which is related to antibiotic Kjellmanianone. The reaction was proposed to proceed via the crown-type compound **222** which gives an alkoxide ion **223** undergoing a ring opening reaction comparable to Favorskii rearrangement (Scheme 71) and eventual transformation to macrocycle **224**.[97]

The reaction of various 2,3,4-trisulfonated 1,6-anhydro-β-D-glucopyranoses **225** up on treatment with alkoxides gave Favorskii rearrangement 1,5-anhydro-2,3-dideoxy-3-methoxycarbonyl-β-D-*erythro*-pentofuranose **229** in 41–57% yield (Scheme 72).[98] The yield increased with the improved leaving group ability, that is tris(trifluoromethanesulfonate) > tris(chlorosulfate) > tritosylate > trimesylate. A study of different bases showed that the yield of the Favorskii product was increased 10–20% by using ethoxide as base. Reaction of the corresponding chlorosulfonated 1,6-anhydrogalactopyranose or anhydromannopyranose gave the same product though in lower yield. The following mechanism was proposed: 1. *syn*-elimination leads to **226**, 2. base catalyzed *trans*-esterification of the enol tosylates of **226** gives ketone **227**, 3. base-induced formation of the Favorskii intermediate **228**, and 4. opening of the cyclopropanone with alkoxide to give **229a**. There is much evidence for **228** being an intermediate in the Favorskii reaction. It is curious, however, that the regioisomeric ester **229b** is not formed in the reaction. This must be because of the electron-withdrawing power of the acetal functionality which makes negative charge accumulation on C-2 more favorable than C-3.

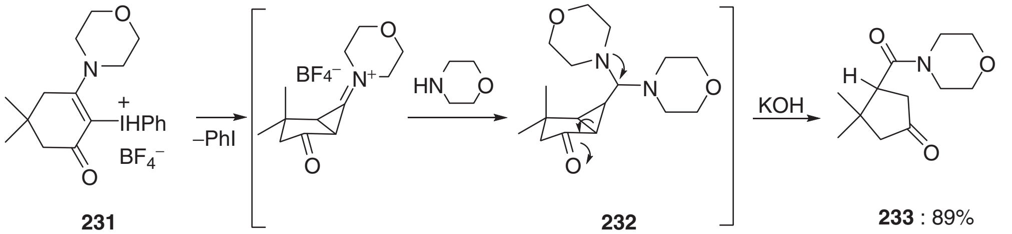


Scheme 71



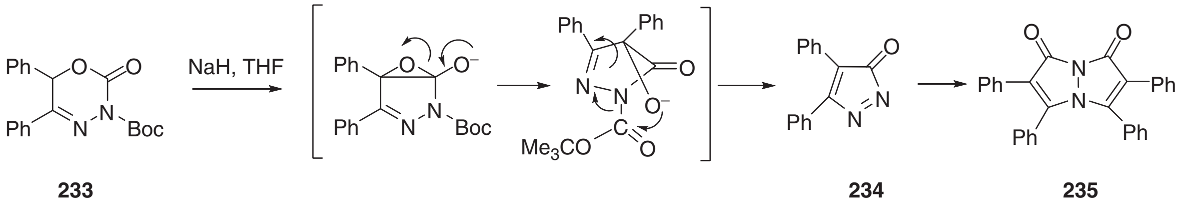
Scheme 72

A Favorskii-like regioselective ring contraction was observed during aminolysis with equimolar amount of morpholine of the iodonium salt **231**. The latter via intermediate tetrafluoro borate salt **232** with sodium hydroxide yielded rearrangement product **233** in very good yield (89%). This unexpected reaction was confirmed by separate experiments (Scheme 73).[99]



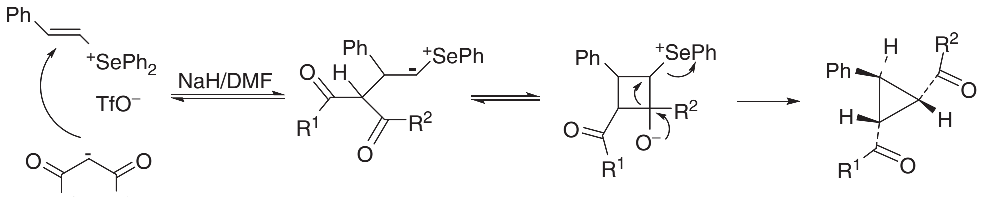
Scheme 73

A Favorskii-like ring contraction of 1,3,4-oxadiazinone **233** with sodium hydride in THF produced the diazacyclopentadienone **234**, which then dimerized with loss of one molecule of nitrogen to give bimane **235** (Scheme 74).[100]



Scheme 74

A novel tandem Michael–Favorskii-type reaction involving alkenylselenonium salt with active methylene carbanions was reported. Selenonium ylides **236** formed from the Michael addition of the carbanion to the alkenylselenonium salt attack the more active carbonyl group to form a cyclobutane ring which is followed by the 1,2-migration of the *endo* carbon–carbon bond with the elimination of diphenyl selenide to form a cyclopropane derivative **237**. The ring-contraction reaction is similar to the semibenzylic pathway for the Favorskii rearrangement (Scheme 75).[101]

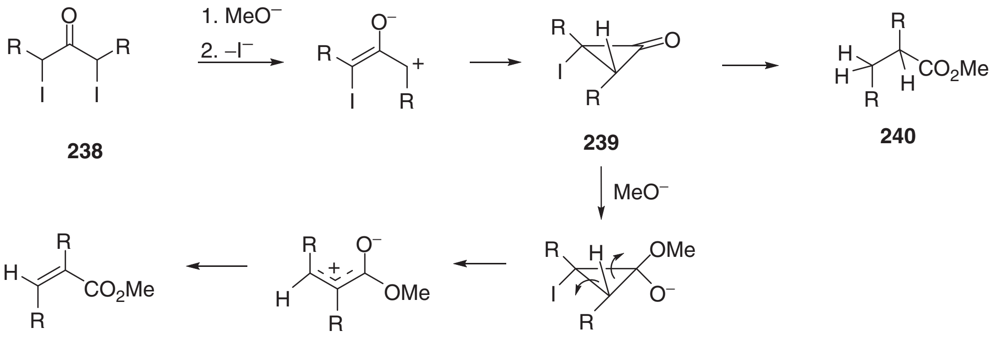


236

	Yield (%)
237a R^1 = Me, R^2 = Me	63
b R^1 = Ph, R^2 = Ph	58
c R^1 = Ph, R^2 = CN	56
d R^1 = Me, R^2 = OBn	44

Scheme 75

Symmetrical α,α′-diiodo ketones **238** were reported to undergo alkoxide-promoted conversion to α,β-unsaturated esters **242** via an intermediate α-iodocyclopropanone **239** (Scheme 75).[102] The reaction did not follow the classical Favorskii rearrangement, a conclusion based on the deuterium labeling experiments as saturated iodo esters **240** were not likely intermediates. An electrocyclic reaction via the disrotatory electrocyclic ring opening of halocyclopropanone **241** accounted for the *Z* stereochemistry of the formed α,β-unsaturated esters **242** (Scheme 76).

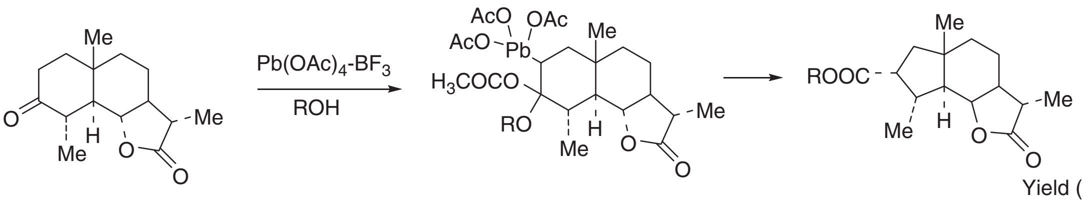


238 **239** **240**

242 : 60–83% **241**

Scheme 76

A novel Favorskii-type rearrangements were observed in the oxidation of cycloalkanones. Lead (IV) tetraacetate promoted Favorskii-type rearrangement in α-santonin **243**. The latter underwent ring contraction when treated with lead (IV) tetraacetate in the of boron trifluoride and alcohol via intermediate **244** to yield ring-contracted carboxylates **245** (Scheme 77).[103]

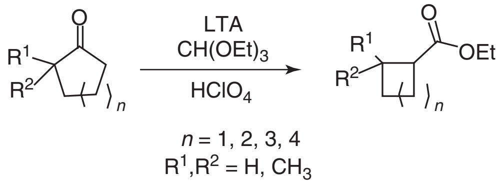


243 **244**

	Yield (%)
245a R = Me	67
b R = Et	59
c R = Bn	54

Scheme 77

Aliphatic cycloalkanones **246** reacted with the suspension of lead (IV)ethanoate in triethyl orthoformate in the presence of perchloric acid to give the ring-contracted ethyl carboxylates **247** in good yields.[104] The presence of perchloric acid is essential, cyclohexanones did not react with lead (IV) ethanoate at all, however, in the presence of perchloric acid and triethyl orthoformate, smoothly converts to the ethyl cyclopentane carboxylate in 70% yield (Scheme 78).



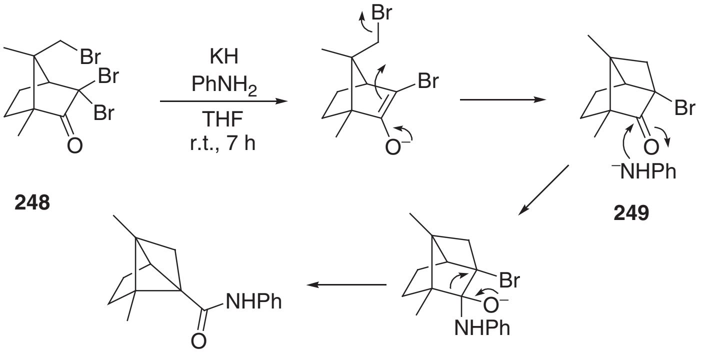
246

247 : 55–70%

Scheme 78

3.17.6.2 Ring Transformations Under Favorskii Reaction Conditions

Treatment of 3,3,8-tribromocamphor **248** with potassium anilide (generated *in situ* from potassium hydride and aniline) in THF at room temperature for 7 h lead to an interesting tricyclic compound **250** in 85%. The reaction proceeded through an intermediate ring-closure product **249** that further underwent Favorskii rearrangement. Monitoring of the reaction by NMR showed that the compound **249** predominates in the reaction mixture after 30 min. The compound **249** can be separately obtained by reaction of **248** with aqueous potassium hydroxide in refluxing DMF (82% yield), or with potassium hydride in THF at room temperature (88%), and then eventually converted into **250** in the reaction with potassium anilide (85% yield) (Scheme 79).[105]



248

249

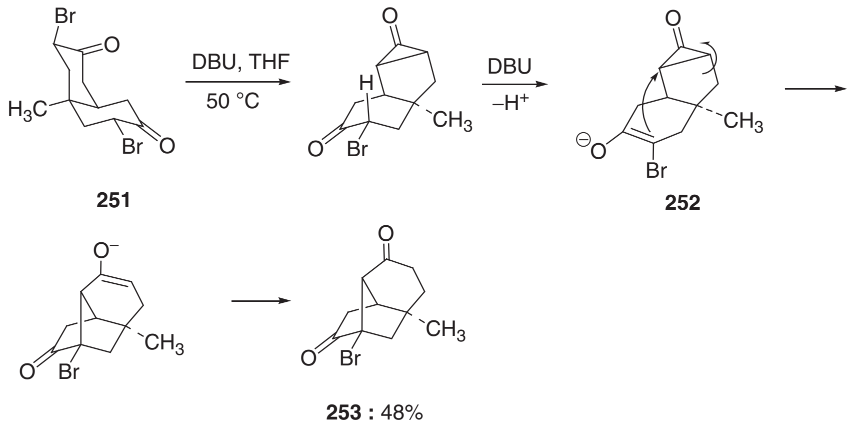
250 : 85%

Scheme 79

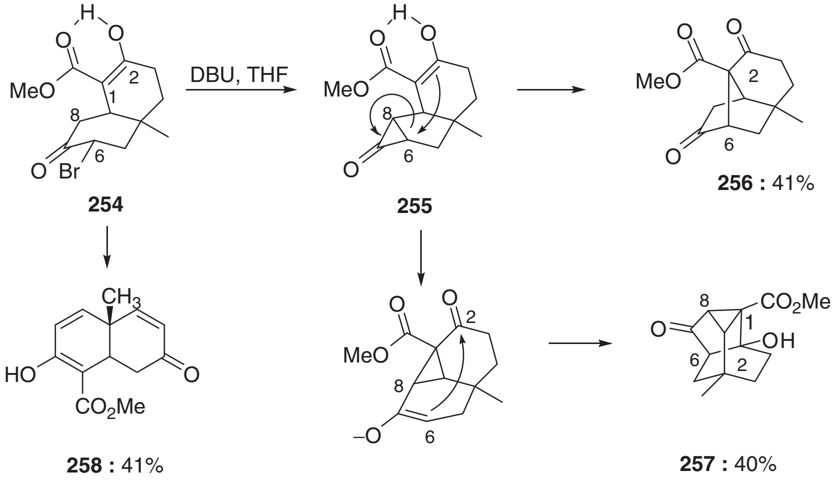
The novel intramolecular nucleophilic ring openings of Favorskii intermediates cyclopropanones intermediated by enolate ions to yield policyclic skeletons was described.[106] Treatment of diequatorial *cis*-3,6-dibromo-4a-methyldecalin-2,7-dione **251** with DBU in THF gave only 1-bromo-5-methyltricyclo[4.4.0.0^{1,7}]decane-2,8-dione **253**. Several mechanistic pathways can account for the formation of **253**, but a Favorskii-like route involving an intermediate cyclopropanone **252**, followed by an intramolecular nucleophilic attack by a bromo enolate anion on a cyclopropanone carbon with subsequent protonation, most reasonably fits the experimental results. However, an alternative S_N2' reaction of the bromo enolate anion cannot be ruled out (Scheme 80).

Dehydrobromination of monobromo ester **254** with DBU in THF afforded a surprising mixture of the tetracyclic keto alcohol **257**, tricyclic keto ester **256**, and a simple dehydrobromination product unsaturated ester **258**. Both **256** and **257** can be rationalized as the result of competitive intramolecular nucleophilic attack onto C-6 and C-8 of a common Favorskii intermediate **255** formed in a first step. Intramolecular nucleophilic ring opening at C-6 followed by protonation provides **256**, whereas nucleophilic attack at C-8 followed by an intramolecular aldol-addition to the keto group leads to the tetracyclic ketol **257** (Scheme 81).[106]

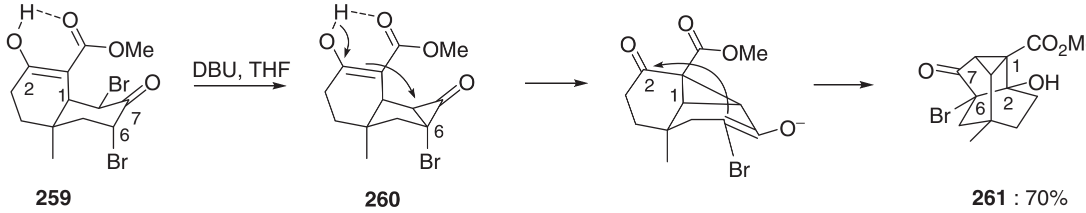
The dehydrobromination of similar dibromo ester **259** with either DBU in THF or with LiBr/Li_2CO_3 in DMF gave tetracyclic **261** as the sole product in 70% isolated yield. The formation of **261** can be rationalized mechanistically through an intramolecular nucleophilic ring opening of the bromocyclopropanone intermediate **260** by the keto ester enolate anion. The formation of the bromocyclopropanone **260** appeared to be the result of a preferential loss of equatorial bromide as opposed to the loss of an axial bromide (position 6 in **259**). It is well documented that rigid polycyclic axial α-bromo ketones do not undergo Favorskii rearrangement (Scheme 82).[106]



Scheme 80

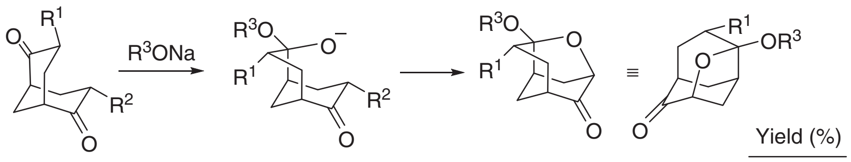


Scheme 81



Scheme 82

The reaction of α,α-dihalogeno bicyclo[3.3.1]nonanediones **262** under Favorskii raction conditions in the presence of sodium methoxide, ethoxide, propoxide, and potassium cyanide led to the intramolecular ring closure via C–O bond formation giving the highly functionalized chiral 2-oxatricyclo[4.3.1.0^{3,8}]decanes (2-oxaprotoadamantane) **264**. The process leading to the intramolecular ring closure can be explained by a pathway implying intermediate alkoxy bicyclo[3.3.1]nonanolate species **263** (Scheme 83).[107] The anion **263** is the key intermediate in the process and halogen is released during an intramolecular process at C-7 and not at C-3 as in a usual Favorskii process. The ring with the charged oxygen atom at C-2 should adopt the twist-boat conformation to undergo transannular ring closure. Evidently the cyclopropanone mechanism of the Favorskii rearrangement involving a highly strained symmetrical intermediate makes this path much less favorable even though an α-hydrogen is present in the initial halo ketones. Therefore the semibenzylic mechanism at the initial stage is operative in this structure and it is viable stereoelectronically in this system. The subsequent intramolecular nucleophilic attack of the bromine atom by the anionic oxygen led to the cyclic ether formation.



262a $R^1 = R^2 = Br$
b $R^1 = R^2 = Cl$

263

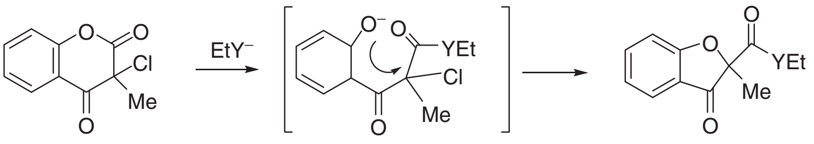
	Yield (%)
264a R^1 = Br, R^3 = Me	57
b R^1 = Cl, R^3 = Me	65
c R^1 = Br, R^3 = Et	16
d R^1 = Cl, R^3 = Et	10

Scheme 83

3.17.7 Oxy-Favorskii Rearrangement

Base-induced ring contraction of α-halolactones is the oxy-Favorskii rearrangement. It is a promising method for constructing various oxacyclic systems.

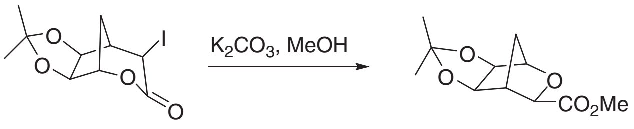
Treatment of **265** in dry dioxane/ethanol (ratio) 2:1with 1 equivalent of sodium ethoxide gave an immediate reaction producing compound **267** (Y=0) in 88% yield via intermediate **266**. This reaction was a chemical support for a molecular mechanistic hypothesis that the anticoagulant activity of 3-substituted 4-hydroxycoumarin drugs is a result of mechanism-based inactivation of vitamin K epoxide reductase since the analogous reaction of **265** with ethanethiol (a model for the reaction of **265** with a cysteine residue) and triethylamine gave the thioester **267** (Y=S) in 82% yield (Scheme 84).[108]



265 **266** **267** : 88% (Y=O), 82% (Y=S)

Scheme 84

When **268** was treated with K_2CO_3 in methanol it was converted smoothly into the key intermediate **269** in 80% yield. The *exo* configuration of the methyl ester functionality of **269** was readily established based on the NMR studies (Scheme 85).[109]

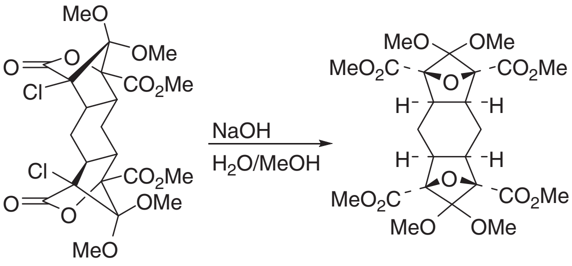


268 **269** : 80%

Scheme 85

The synthesis of four highly strained pentacyclic bis-oxa-bridged derivatives in which the bridge is part of an oxa-bicyclo[2.1.1]hexane framework with interesting structural variations was presented.[110] One example is presented further. C2-symmetric pentacyclic bis-lactone **270** up on treatment with NaOH in aqueous MeOH afforded **271** in which the two oxa bridges are *syn* to each other, separated by central cyclohexane and cycloheptane rings (Scheme 86).

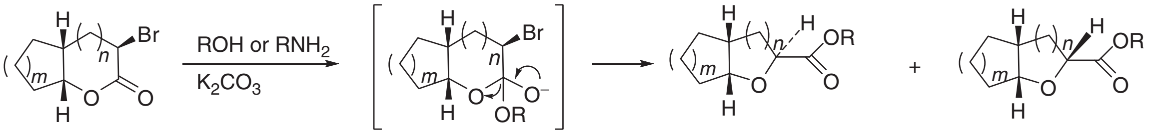
A systematic study with sterically rigid bicyclic molecules to evaluate the potential of the oxy-Favorskii rearrangement was conducted to provide a new synthetic method for the construction of substituted oxabicyclic skeletons in the natural products and bioactive molecules, communiol E, laurenenyne A, and dysiherbaine. The entire synthetic process might be stereospecific and applicable to a variety of bicyclic lactones. The stereochemically pure *β*-bromolactones **272a-c** were treated with K_2CO_3 in MeOH at room temperature. The expected ring ring-contracted esters **274a-c** were obtained as the major products.[111] It is thought that oxy-Favorskii rearrangement takes place through the intermediate **273** and intramolecular S_N2-type displacement delivers the *trans*-ester **274** (Scheme 87). Remarkably, formation of the five-membered ring was quite efficient, whereas the oxetane ring ($n=0$) was inaccessible (yield 15%), probably because of ring strain. The generality of the oxy-Favorskii rearrangement was explored by varying the nucleophiles. Interestingly, neither a secondary alcohol (*i*-PrOH) nor a tertiary alcohol (*t*-BuOH) induced rearrangement, whereas primary amines such as $MeNH_2$ and *i*-$PrNH_2$ resulted in good yields and selectivities.



270

271 : 52%

Scheme 86



272 a *m* = 2, *n* = 1 R = Me, *i*-Pr
b *m* = 1, *n* = 1
c *m* = 1, *n* = 0

273

274a-c : 15–100%

275a-c

Scheme 87

Epimeric esters **275a-c** were detected, which suggested that epimerization at the α-position took place. A comparative study with bromolactone **272** of the opposite configuration of the bromo atom revealed that the reaction was stereospecific and there was no equilibrium between **274** and **275**. Thus partial racemization occurred before rearrangement, not after formation of the product. The racemization was minimized when the reaction temperature was first cooled to 78 °C and then warmed to room temperature (the ratio **274a**/**275a** changed from 2:1 to 10:1).

3.17.8 Favorskii Rearrangement in Biosynthetic Transformations

Biosynthetic carbon skeleton rearrangements involving Favorskii-like process have been proposed in a few secondary metabolite pathways.

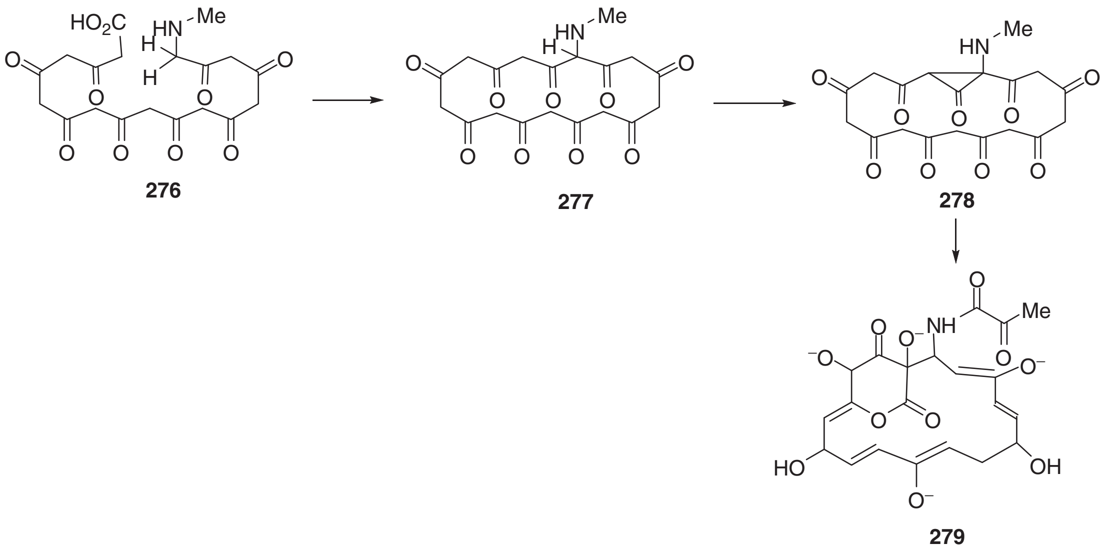
The biosynthesis of lankacidin antibiotics implied Favorskii-type rearrangement of the 18-membered polyketide ring **278** with extrusion of a carbonyl group to afford **279**, precursor of antibiotics (Scheme 88). To study the mechanism of the formation of lankacidin ring, the labeled glycine was administered to the fermentation of lankacidin producing organism *Streptomyces sp*. The deuterium incorporation was not observed at the C-3 methine group from glycine, and it seems less likely that the deuterium is lost by chemical exchange at the stage of either a linear polyketide **276** or a 17-membered product **277** because of the reactivity of the corresponding position. The deuterium loss can be rationalized instead by assuming involvement of a Favorskii-type rearrangement in the biosynthesis, since the Favorskii mechanism requires removal of the corresponding hydrogen from a plausible 18-membered cyclic polyketide intermediate (**277** → **278** → **279**) *vide supra*.[112]

Several studies involved analysis of the enterocin Favorskii biosynthetic rearrangement. Enterocin is an atypical type II polyketide synthase (PKS) product from the marine actinomycete '*Streptomyces maritimus*'. The enterocin biosynthesis gene cluster (enc) codes for proteins involved in the assembly and attachment of the rare benzoate primer that initiates polyketide assembly with the addition of seven malonate molecules and culminates in a Favorskii-like rearrangement (via favorskiiase flavoprotein) of the linear poly-*β*-ketone to give its distinctive nonaromatic, caged core structure.[113]

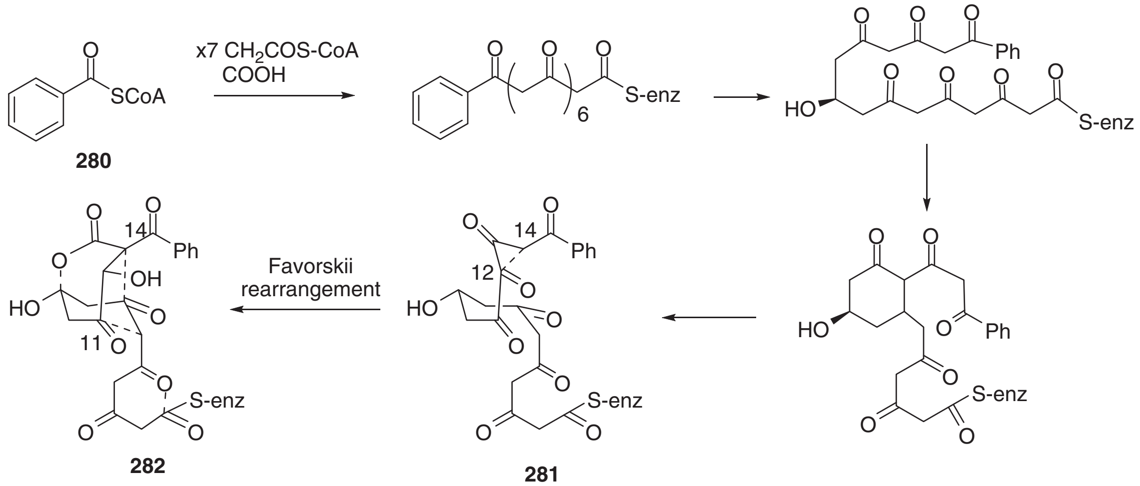
Bacteriostatic polyketides enterocin and wailupemycins A-C are PKS-derived products which originate from an intermediate assembled from an uncommon benzoyl-coenzyme A starter unit **280** and seven malonate molecules[114] that gave **281** has underwent a Favorskii-like rearrangement to yield **282** (Scheme 89).[115]

The ambrucitins and jerangolids are antifungal polyketides produced by *Sorangium cellulosum* strains. Comparative analysis of gene clusters suggested schemes for the biosynthesis of these compounds probably involving a Favorskii rearrangement.[116]

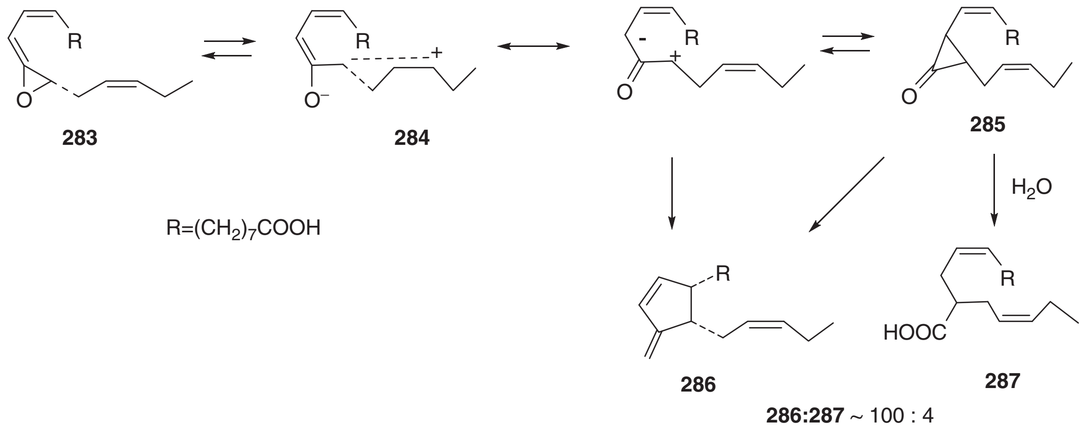
Biosynthesis of cyclopentenone 12-oxo-10,15-phytodienoic acid (12-oxo-PDA) 287 and related jasmonates in plants is controlled by three enzymes, among which the allene oxide synthase (AOS) is the most intriguing enzymes of the plant lipoxygenase pathway widespread in plants. Its products play important biological roles. The AOS conversions of the 12,13-EOT, (9Z, 11E,



Scheme 88



Scheme 89



Scheme 90

15Z)-12,13-epoxy-9,11,15-octadecatrienoic acid **283** (allene oxide formed from 13-HPOT α-linolenic acid (9Z,11E,13 S,15Z)-13-hydroperoxy-9,11,15-octadecatrienoic acid (13(S)-HPOT)) afforded cyclopentenone acid **286** and a minor byproduct of 12-oxo-PDA biosynthesis oxylipin **287** as estimated by GC–MS.[117]

Compounds **286** and likely **287** are the products of backbone rearrangement with a cyclopropanone intermediate **285** (the Favorskii-type rearrangement). The detection of Favorskii products indicated the presence of the cyclopropanone intermediate **285** along with allene oxides in the AOS conversion of 13-HPOT (Scheme 90) and also γ-9-HPOT. This pathway, from oxyallyl **284** to cyclopropanone **285** followed by ring cleavage to form the carboxylic acid **287** (Scheme 90), fully reflects the mechanism of a Favorskii rearrangement (except its initial stage).

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3.18 The Ramberg–Bäcklund Rearrangement and the Eschenmoser Coupling Reaction

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3.18.1 **The Ramberg–Bäcklund Rearrangement** 888
3.18.1.1 Introduction 888
3.18.1.2 Mechanism and Stereochemistry 888
3.18.1.3 Preparation of α-Halosulfone Precursors 890
3.18.1.4 The Ramberg–Bäcklund Rearrangement of α-Halosulfones: Reaction Conditions, Scope, Limitations, and Functional Group Compatibility 890
3.18.1.5 The Ramberg–Bäcklund Rearrangement of Sulfones with Other than Halide Leaving Groups 892
3.18.1.5.1 The Ramberg–Bäcklund rearrangement with sulfinate leaving group 892
3.18.1.5.2 The epoxy-Ramberg–Bäcklund rearrangement 894
3.18.1.6 Synthetic Modifications of the Ramberg–Bäcklund Rearrangement 895
3.18.1.6.1 The Meyers' modification (one-pot or *in situ* halogenation) of the Ramberg–Bäcklund rearrangement 895
3.18.1.6.2 The Ramberg–Bäcklund rearrangement of sulfonyl carboxylic esters (decarboxylative Ramberg–Bäcklund rearrangement) 897
3.18.1.6.3 The Michael-induced Ramberg–Bäcklund rearrangement 899
3.18.1.7 Synthetic Applications of the Ramberg–Bäcklund Rearrangement 899
3.18.1.7.1 Synthesis of acyclic alkenes 900
3.18.1.7.2 Synthesis of cycloalkenes via ring contraction 902
3.18.1.7.2.1 Synthesis of carbocyclic alkenes via ring contraction 903
3.18.1.7.2.2 Synthesis of heterocyclic alkenes via ring contraction 907
3.18.1.7.2.3 Synthesis of macrocycles, paracyclophanes, and related systems via the Ramberg–Bäcklund ring contraction 910
3.18.1.7.3 Synthesis of conjugated dienes, polyenes, enynes, and diynes 911
3.18.1.7.4 Application of the Ramberg–Bäcklund rearrangement in natural products and bioactive molecules synthesis 915
3.18.1.7.4.1 Application of the Ramberg–Bäcklund rearrangement in carbohydrate chemistry 915
3.18.1.7.4.2 Application of the Ramberg–Bäcklund rearrangement in the synthesis of carotenoids and related polyenes 920
3.18.1.7.4.3 Application of the Ramberg–Bäcklund rearrangement in amino acid synthesis 922
3.18.1.7.4.4 Application of the Ramberg–Bäcklund rearrangement for the synthesis of alkaloids 922
3.18.1.7.4.5 Application of the Ramberg–Bäcklund rearrangement for the synthesis of polyphenols 923
3.18.1.7.4.6 Application of the Ramberg–Bäcklund rearrangement for the macrocyclic construction 923
3.18.1.7.4.7 Application of the Ramberg–Bäcklund rearrangement for the synthesis of steroids 924
3.18.1.7.4.8 Application of the Ramberg–Bäcklund Rearrangement for the synthesis of stilbenoid systems 925
3.18.2 **The Eschenmoser Coupling Reaction (Eschenmoser Sulfide Contraction)** 926
3.18.2.1 Introduction 926
3.18.2.2 Mechanism 927
3.18.2.3 Synthetic Modification of the Eschenmoser Coupling Reaction 930
3.18.2.3.1 Selenoamides as substrates for the Eschenmoser coupling reaction 930
3.18.2.3.2 The Eschenmoser coupling reaction under continuous-flow conditions 931
3.18.2.3.3 α-Methyl-β-ketoesters through the Eschenmoser coupling reaction 931
3.18.2.4 Application of the Eschenmoser Coupling Reaction in the Synthesis of exo-Cyclic Enamines 932
3.18.2.4.1 Indole and pyrrolidine systems 932
3.18.2.4.2 Piperidine systems 933
3.18.2.4.3 Pyridine systems 935
3.18.2.4.4 Quinoline systems 935
3.18.2.5 Application of the Eschenmoser Coupling Reaction in Natural Product and Bioactive Molecule Synthesis 936
3.18.2.5.1 In total synthesis of alkaloids 936
3.18.2.5.2 In macrocycle synthesis 939
3.18.2.5.3 In the synthesis of antibiotics 939
References 940

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Glossary

A rearrangement reaction It is a broad class of organic reactions where the carbon skeleton of a molecule is rearranged to give a structural isomer of the original molecule. Often, migrations are from one atom to an adjacent one but some are over longer distances.

Olefination reactions They are general strategies that allow the synthesis of alkenes via formation of new carbon –carbon double bond.

Ring contractions They are chemical reactions that decrease the number of atoms in a ring of a cyclic compounds. In some cases ring contraction can be accompanied by sulfur extrusion reaction.

Sulfur extrusion reaction It is a chemical reaction where one of the products is elemental sulfur or its derivative.

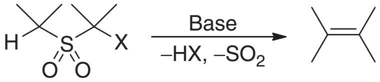
Thiirane It is also known as episulfide; it is a three-membered cyclic chemical compound with the formula C_2H_4S. It is the smallest sulfur-containing heterocycle. Its oxidized form is 1,1-thiirane dioxide, also known as episulfone. Both episulfide and episulfone are very unstable reaction intermediates.

Thiophile It is a chemical compound which has an affinity to sulfur-containing compounds, can react with them, produces new sulfur-containing compounds and, thus, can assist to Sulfur extrusion reactions.

3.18.1 The Ramberg–Bäcklund Rearrangement

3.18.1.1 Introduction

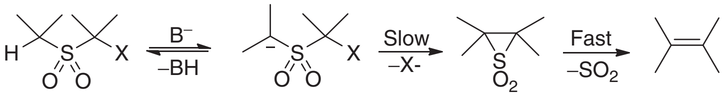
The Ramberg–Bäcklund rearrangement (RBR)[1] of α-halo sulfones in the presence of base, leading to regio-defined olefins with accompanying loss of hydrogen halide and sulfur dioxide is one of the most important reactions of sulfones in general and is of both synthetic and mechanistic interest (Scheme 1) (for chemistry of sulfones, *see* Chapter 1.12 and for synthesis of sulfones, *see* Chapter 7.28). A salient feature of the reaction is its general applicability. The RBR is general for molecules containing the structural elements of a sulfonyl group, a α-halogen, and at least one α′-hydrogen atom. The double bond in the product regiospecifically replaces the sulfonyl group in the starting material. The isolation of previously postulated episulfone intermediate, as well as its various important synthetic modifications including Meyers' *in situ* halogenation of sulfones has triggered the renewed interest in this type of rearrangement. The accessibility of the precursor sulfides and sulfones make this reaction especially valuable in the synthetic terms. RBR can be applied to the preparation of a broad variety of alkenes, including tetra-substituted patterns, strained alkenes such as cyclobutenes and polyenes. Due to these novel developments, a number of synthetic applications have been described, including preparation of various natural products, novel electrically conducting materials, and enediynes. A number of excellent reviews have been published on this topic[2–5] including the seminal contribution of Paquette.[6] Consequently, the authors shall concentrate on the latest developments in this area.



Scheme 1

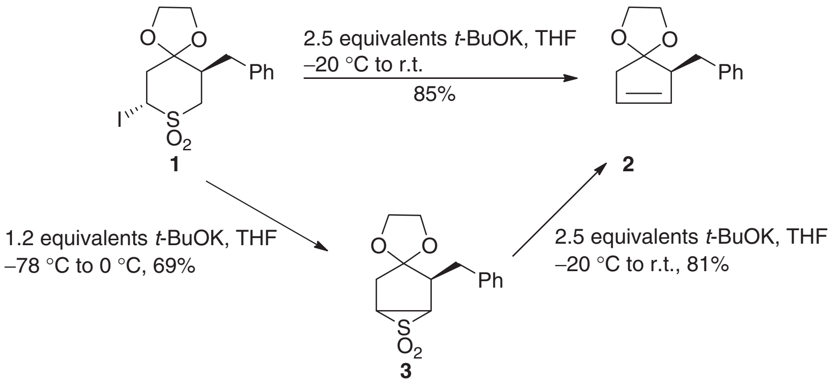
3.18.1.2 Mechanism and Stereochemistry

The generally accepted anionic mechanism of the RBR is shown in Scheme 2. It has been established[6,7] that the first step is fast and reversible formation of the α-sulfonyl anion and that the second step, involving 1,3-displacement of the halide ion by the carbanion and formation of an episulfone, is rate determining, and the stereochemistry of the resulting olefin is established during this step (Scheme 2).



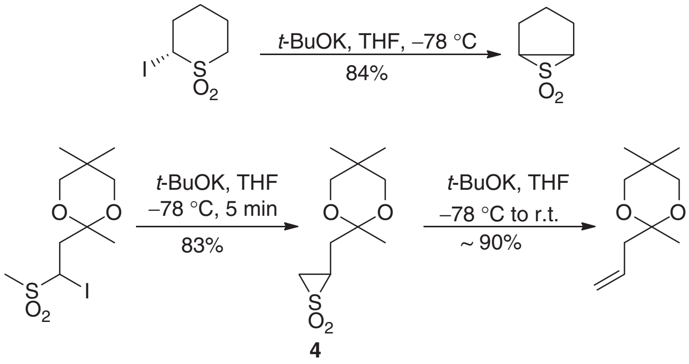
Scheme 2

The postulated episulfone intermediate could not be isolated under usual rearrangement conditions. Only in the year 1989, Taylor and coworker[8] reported the first example of an isolable episulfone obtained by low-temperature treatment of a α-halo sulfone with base. This was made possible by the facile low-temperature RBR of a 2-iodothiane dioxide **1** (Scheme 3). Treatment of **1** with 2.5 equivalents of potassium *t*-butoxide in tetrahydrofuran (THF) at −20 °C, followed by warming to room temperature, produced the expected cyclopentene **2** in 85% yield. When the reaction was carried out at −78 to 0 °C with 1.2 equivalents of potassium *t*-butoxide, however, **2** was the minor product, the episulfone **3** being obtained as a white crystalline solid in 69% yield. Treatment of **3** with excess potassium *t*-butoxide at −20 °C to room temperature gave **2** as the only observable product in 81% yield.



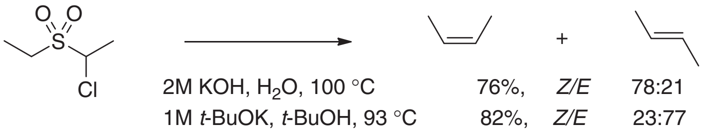
Scheme 3

Later, it has been shown[9] that the presence of iodine as the leaving group is not strictly necessary; the α-chloro and α-bromo sulfones also gave the corresponding episulfones in high yield on treatment with potassium *t*-butoxide at low temperature. Similarly, the alkyl substitution in the *β*-position to the sulfonyl group does not preclude episulfone formation. However, all attempts to isolate α-alkylated derivatives, that is, compounds bearing substituents at the episulfone bridgehead position, were unsuccessful, although their RBR to the corresponding cyclopentenes occurred efficiently. This suggested that the rate of loss of sulfur dioxide (either thermally or in a base-promoted process) from a trisubstituted episulfone is fast compared with the disubstituted examples, allowing isolation of the latter compounds from the basic reaction media.[9] The presence of an acetal group at C-4 of the thian ring was not essential for episulfone stability (Scheme 4).[10] The importance of the ring size has also been investigated and it has been established that the 6-thiabicyclo[3.1.0]hexane 6,6-dioxide system is particularly favored. No trace of the expected episulfones was observed when seven-, five-, or four-membered α-iodo sulfones were treated under the standard conditions for episulfone isolation.[10] The scope of the procedure described above was extended and the first acyclic episulfone 4 was prepared by the RBR (Scheme 4).[10]



Scheme 4

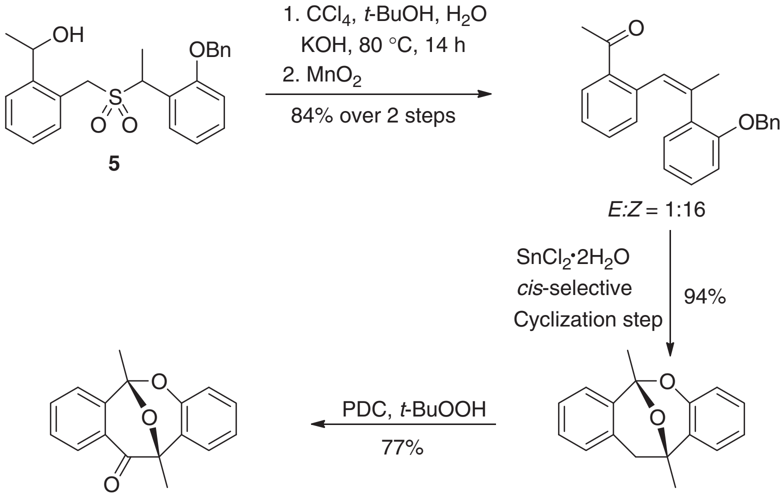
One of the remarkable mechanistic features of the RBR is the stereochemistry of the olefinic products produced from acyclic α-halo sulfones. The earlier publications claim the predominant formation of *Z*-alkenes with the *E*:*Z* ratio insensitive to the nature of solvents and, over a wide range, to the nature of base. However, later it was shown that the use of stronger hindered bases, such as potassium *t*-butoxide in either protic or aprotic solvents favors *E*-alkenes (Scheme 5).[11]



Scheme 5

It is widely accepted,[11–16] that on either thermal treatment or under normal Ramberg–Bäcklund reaction conditions (2 mol l^{-1} potassium hydroxide) the elimination of sulfur dioxide from the corresponding episulfone is a *cis*-stereospecific process. The final ratio of *cis*- and *trans*-isomers in the reaction products reflects the ratio of *cis*- and *trans*-disubstituted thiirane dioxide defined in the intramolecular cyclization step. However, when a stronger base such as potassium *t*-butoxide is employed, epimerization can occur to favor the thermodynamically more stable *trans*-disubstituted thiirane dioxide and ultimately the *E*-alkene. It should be noted that the question, why the *cis*-disubstituted thiirane dioxides are predominant in the cyclization step, still remains open.

Unlike aliphatic systems, benzylic sulfone systems were reported to undergo the RBR with the formation of *trans*-stilbene products as major isomers.[11,13–15] Deuterium-labeling experiments[16] have shown that phenyl substituents are sufficiently anion stabilizing to ensure a fast epimerization of the episulfone thus affording exclusively the *trans*-stilbene product. However, with electron rich aromatic substituents, benzylic sulfone systems (e.g., **5**) have been found to give unexpectedly high *Z*-stereoselectivity (up to E:Z = 1:16) in the Meyers variant of the RBR.[17] This remarkable *cis*-selectivity leading to disubstituted and particularly trisubstituted stilbenes (up to a 95% of the *cis*-isomer) has been achieved through manipulation of aryl groups remote from the central sulfone system. The authors explained the observed *cis*-selectivity by an intramolecular base promoted extrusion of SO_2, which is taking place before full epimerization of the intermediate episulfone has occurs, and therefore retain the *cis*-configuration in the product. This high level of double-bond stereocontrol has been utilized in the synthesis of integrastatin nucleus, the core of two highly bioactive anti-human immunodeficiency virus compounds (Scheme 6).[17]



Scheme 6

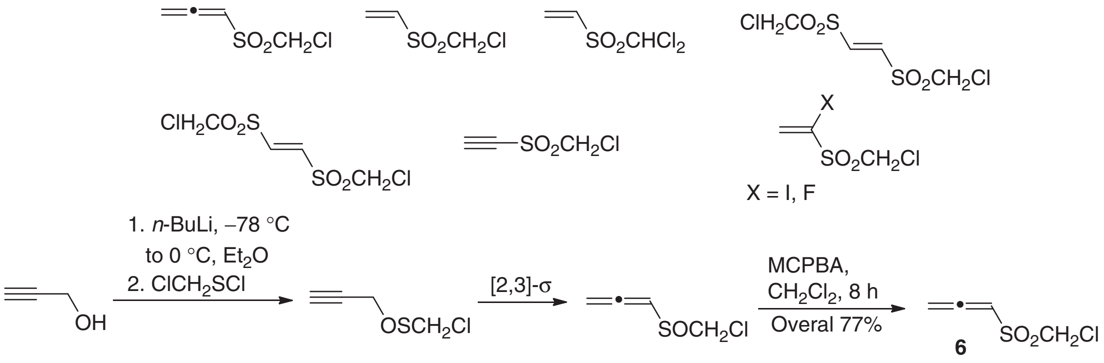
3.18.1.3 Preparation of α-Halosulfone Precursors

The original version of RBR involved base induced reaction of preformed α-halosulfones, became less popular in past years due to the intensive use of Meyers and similar one-pot modifications. Preparative routes to α-halosulfones are well reviewed.[4–6,18] Mainly, they include chlorination of the corresponding sulfides followed by the oxidation of the α-halosulfides,[18] and halogenation of α-sulfonyl carbanions. Other approaches based on the utilization of α-halosulfoxides, sulfonyl halides, and α,β-unsaturated sulfones are also reported.

An interesting approach involving α,β-unsaturated α′-halomethyl sulfones as 'prepackaged' Ramberg–Bäcklund reagents for tandem synthetic processes has been reported.[19–21] In this case the necessary reaction components, sulfonyl group and α-halogen, are already present in the same reagent. Such 'prepackaged' Ramberg–Bäcklund reagents, following an appropriate first step, such as Diels–Alder addition, react with a base, giving olefinic end products with an increase in total number of carbon atoms and thus can be utilized in a iterative ring-growing procedure for construction of linear fused carbocycles (see Section 3.18.1.7.2.1). Examples of this class of reagents are shown in Scheme 7. The parent compound, chloromethyl 1,2-propadienyl sulfone **6**, can be simply prepared via coupling of chloromethylsulfenyl chloride with propargylic alcohol followed by the [2,3]-sigmatropic rearrangement of the sulfenate ester to chloromethyl 1,2-alkadienyl sulfoxide and its oxidation to the corresponding sulfone.[21]

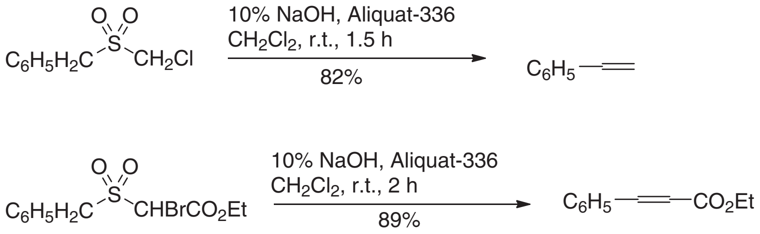
3.18.1.4 The Ramberg–Bäcklund Rearrangement of α-Halosulfones: Reaction Conditions, Scope, Limitations, and Functional Group Compatibility

The original RBR procedure involves heating the α-halosulfones in aqueous potassium hydroxide at 100 °C. However, this procedure is suitable for water-soluble substrates only. To avoid the solubility problems arising from aqueous conditions dioxane can be used as cosolvent.[22] The Ramberg–Bäcklund reaction using hydroxide as base can also be performed under phase-transfer conditions.[23–25] One advantage of using these conditions involving halocarbon solvents such as dichloromethane is that it allows



Scheme 7

a wide range of nonpolar α-halosulfones to react and permit simple isolation of olefinic products. Next, the reaction could be performed under very mild conditions. Important to note, that certain base-sensitive functionality, for example, esters, within the α-halosulfones are stable at the reaction conditions (Scheme 8).[24] The RBR occurred readily, however, the rate of reaction varying markedly from one substrate to another.

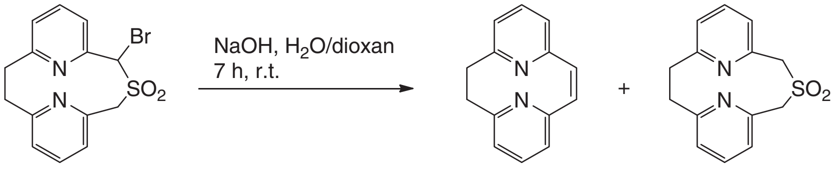


Scheme 8

Generally, the RBR takes place in a wide variety of base–solvent systems with the yield and stereochemical output being often strongly dependent on the conditions chosen. If polar solvent are required, solutions of alkoxide in the corresponding alcohol are usually applied.[26] Since hydrogen atoms α to the sulfonyl group undergo exchange with the alkaline medium much faster than the olefinic product is formed, incorporation of deuterium at the vinylic positions of alkenes can be carried out very efficiently by performing the RBR in a mixture THF–D_2O.[27] Aternatively, initial hydrogen–deuterium exchange could be accomplished in a α-chloro sulfone precursor with NaOD in a dioxane–D_2O mixture followed by the RBR with potassium *tert*-butoxide in anhydrous THF.[28] The combination of potassium *tert*-butoxide in THF is widely used now. This combination allows performing the transformations at room temperature and even at −78 °C and thus minimizing side reactions.[29] Other solvents, such as dimethyl sulfoxide (DMSO),[30,31] have also been employed. In some case when standard potassium *tert*-butoxide/THF system was unsuccessful, stronger bases such as methyllitium,[29] *n*-butyllithium,[32] or lithium diisopropylamide (LDA)[33] can be applied.

Since RBR are always performed under basic conditions, sulfones containing incompatible functional groups must obviously be protected. Carbonyl groups, for example, may be protected as acetals, and alcohols are usually protected as ethers or silyl ethers.[34] In one example, the vicinal amino and hydroxy groups in sulfides were first converted into the corresponding dimethyloxazolidines and next to the sulfones followed by the one-pot-RBR.[35] However, a number of structurally diverse α-halosulfones are compatible with these conditions. They include alkenes, alkynes, aromatics and heteroaromatics, acids, esters, lactones, amides, carbamates, enones, and in some cases unprotected ketones and alcohols.

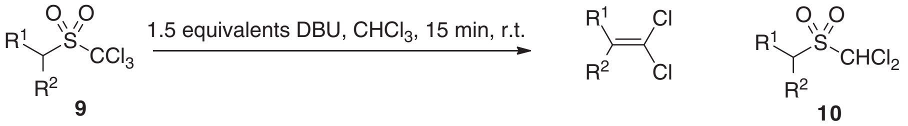
One of the common competing to RBR reactions is a loss of α-sulfonyl halogen.[22,26] Thus, the olefinic cyclophane [2.2]-(2,6)pyridinophan-l-ene **7** was obtained in 43% yield along with a modest amount of the debrominated sulfone **8** which presumably arises by displacement of the rather stable anion of **8** on attack of hydroxide anion on bromine (Scheme 9).[22]



7 (43%) **8**

Scheme 9

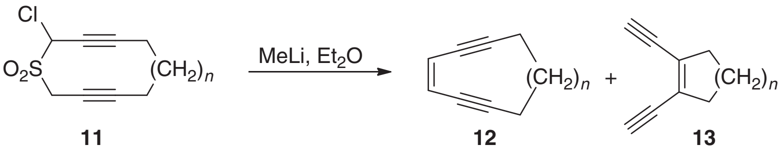
Similarly, the competing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) reduction of trichloromethylsulfones **9** to dichloromethylsulfones **10** was also reported (Scheme 10).[30] Interesting, that the use of DMSO as a solvent reduces the amount of the side product to minimum (e.g., 2% vs. 26% in $CHCl_3$, for $R^1 = R^2 = 4\text{-}ClC_6H_4$).



$R^1 = R^2 = Ph$	63%	37%
$R^1 = R^2 = 4\text{-}ClC_6H_4$	74%	26%
$R^1 = Ph, R^2 = Me$	73%	27%

Scheme 10

Application of the RBR under standard conditions (*t*-BuOK, THF, − 78 °C) for the preparation of a series of cyclic conjugated enediynes **12** ($n = 1–8$) related to the natural anticancer antibiotics calicheamicin and esperamicin, was successful for the less strained systems ($n = 3–8$), whereas more strained 11-membered ring sulfone **11** ($n = 2$) only on exposure to methyllithium, leads to the desired cyclic enediyne **12** ($n = 2$) along with the corresponding acyclic enediyne **13** ($n = 2$) (Scheme 11).[29] Similarly, 10-membered ring sulfone **11** ($n = 1$) with methyllithium gives exclusively the acyclic enediyne **13** ($n = 1$). This unexpected formation of the acyclic enediyne by-products **13** was explained by the involvement of Cope-type rearrangement of the intermediate episulfone followed by spontaneous rearrangement with loss of sulfur dioxide.



$n = 1$,	0%	24%
$n = 2$,	12%	12%

Scheme 11

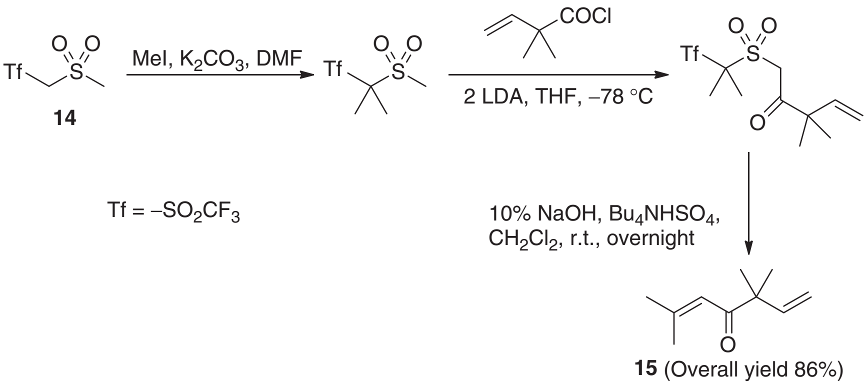
3.18.1.5 The Ramberg–Bäcklund Rearrangement of Sulfones with Other than Halide Leaving Groups

The RBR can also be performed with sulfones in which the usual halide ion is replaced by other leaving groups including sulfinates, epoxides, and sulfonates. Application of sulfonates, particularly, tosylates as leaving group in the RBR was investigated by Meyers, however, it was shown to be of limited synthetic utility.[36]

3.18.1.5.1 The Ramberg–Bäcklund rearrangement with sulfinate leaving group

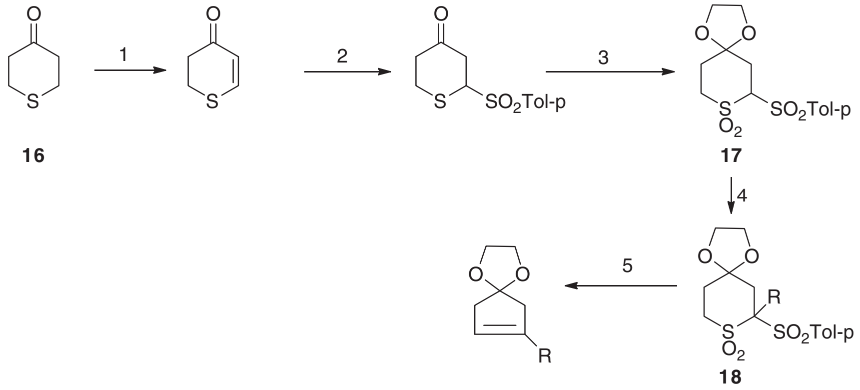
The utility of sulfinate as leaving group in the RBR was first demonstrated by Hendrickson in his general approach to olefin synthesis via multiple (up to four) alkylations of mesyltriflone.[37,38] Mesyltriflone **14** was developed as an olefin polyanion equivalent capable first of multiple constructions such as alkylations and acylations, then of Ramberg–Bäcklund elimination to a polysubstituted olefin. Triflyl group $–SO_2CF_3$ was ideal due to both powerful electron-withdrawing and leaving group properties. Also the alkylations and the RBR are base-induced processes; the latter can proceed only when the α-position is dialkylated, since the triflinate group cannot be displaced when an α-carbanion species can be formed. The use of carbon electrophiles other than alkylating agents is also viable. Acylation proved to be even more facile, and acid chlorides, anhydrides, esters, and chloroformates all reacted in good yield. Aldehydes and ketones reacted similarly to give the *β*-hydroxy sulfones, and carboxylation gave the *β*-sulfo acid, all expected reactions of α-sulfone carbanions. With the lower-energy carbanions of the α′-acylated or carboxylated compounds the reaction proceeds smoothly in high yield with phase-transfer alkali or on heating with potassium carbonate. With simple α′-alkylated compounds stronger bases were required such as potassium *tert*-butoxide. Application of this synthetic concept to the synthesis of artemisia ketone **15** is outlined in Scheme 12. It illustrates the effectiveness of the concept in quickly assembling olefinic compounds from much simpler and available starting materials.[37] Obviously, that this approach is applicable only to the synthesis of 1,1-di-, tri-, and tetra-substituted alkenes.

It was also shown that *p*-toluenesulfinate ion acts as a good leaving group and may be used instead of a halogen under Ramberg–Bäcklund-type reaction conditions.[32,39,40] Thus, alkyl-substituted 3-cyclopentenones were prepared in moderate to good yields starting from 4-thianone **16** by the selective alkylation and Ramberg–Bäcklund-type reactions. Sulfone **17** can stabilize a carbanion at the α-position of the sulfone and undergoes regioselective alkylation. *p*-Toluenesulfinate ion also acts as a good leaving group in the presence of base such as sodium hydride in DMSO, and **18** can be transformed into the required



Scheme 12

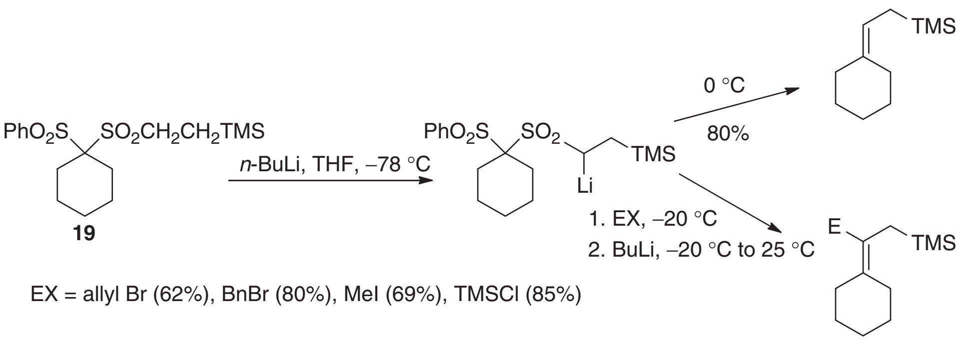
cyclopentenes in good yields (Scheme 13).[39] It should be pointed out, that whereas RBR of sulfones substituted with simple alkyl groups proceeds smoothly with high yields, benzyl- and allylsubstituted sulfones give rise to the isomerized products (as minor by-product for benzyl derivative and the only isolable product for allylic one).[39]



1. NCS, pyridine, 83%; 2. 4-TolSO$_2$Na, HCl, EtOH, 94%; 3. OHCH$_2$CH$_2$OH, 4-TsOH, C$_6$H$_6$; MCPBA, CH$_2$Cl$_2$, 92%; 4. for R=Me:MeI, K$_2$CO$_3$, acetone, r.t., 6–10 h; for R=C$_6$H$_5$CH$_2$CH$_2$, *n*-C$_5$H$_{11}$: RHal, NaH, DMF, 70 °C, 20–24 h; 5. NaH-KH, Me$_2$SO, 20–30 °C, 24–48 h, N$_2$; R=Me, 60%; C$_6$H$_5$CH$_2$CH$_2$, 70%, *n*-C$_5$H$_{11}$, 87%.

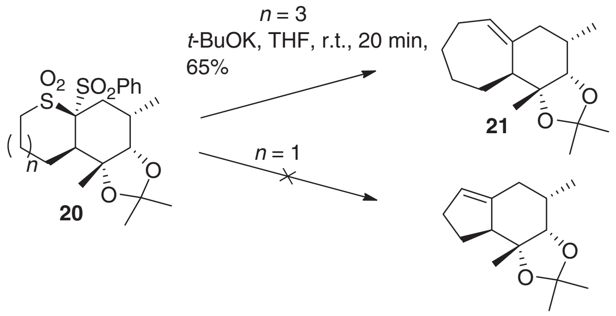
Scheme 13 Reproduced from Matsuyama, H.; Miyazawa, Y.; Takei, Y.; Kobayashi, M. *J. Org. Chem.* **1987**, *52*, 1703–1710, with permission from American Chemical Society.

α-Sulfonyl sulfones also have been applied for the conversion of the *β*-silylethyl α-sulfonyl sulfones to the exocyclic allylsilanes (Scheme 14).[32] *β*-Silylethyl bis-sulfone **19** underwent metalation to provide the corresponding sulfonyl anion which could be converted to allylsilanes. Otherwise, the intermediate anion can be intercepted by addition of an electrophile in the presence of 4% hexamethylphosphoric acid triamide, followed by warming to −20 °C for 1 h. These alkylated intermediates need not be isolated; standard protocol simply involves following the functionalization step with a second equivalent of *n*-butyllithium to produce new α-sulfonyl anions, which decompose on warming to the corresponding allylsilanes (Scheme 14).[32]



Scheme 14

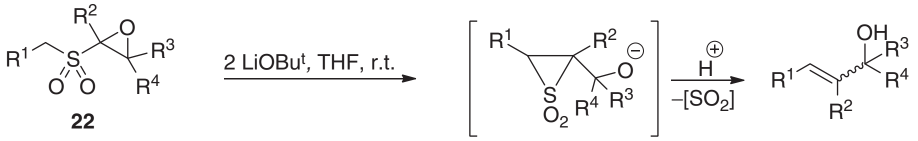
A similar approach involving the fluoride-induced intramolecular sulfenylation of α-silyl sulfones has been employed in the preparation of cyclic and bicyclic alkene (Scheme 15).[40] Interesting, the more flexible disulfone **20** ($n=3$) underwent the desired ring contraction with potassium *tert*-butoxide in THF within 20 min at reflux to give the 7,6-ring fused tricyclic olefin **21** in 65% yield. However, the smaller ring homolog **20** ($n=1$) resists the ring contraction. This was explained by the strain required to form the requisite fused episulfone intermediate.



Scheme 15

3.18.1.5.2 The epoxy-Ramberg–Bäcklund rearrangement

One further variant of the RBR, namely, the epoxy-RBR (ERBR), has been developed by Taylor.[41,42] In this reaction α,β-epoxy sulfones **22**, on treatment with base, are converted into a range of mono-, di-, and trisubstituted allylic alcohols. In this modification the leaving group is incorporated into a three-membered ring (Scheme 16, Table 1). The key step involves a favored 3-*exo-tet* ring opening, but proceeds via a strained 1-hetera-4-thiaspiro[2.2]pentane transition state. A major advantage of this new reaction is that the alkene formation is accompanied by the introduction of valuable allylic functionality in the adjacent position. In terms of stereoselectivity, most systems gave *E*/*Z* mixtures of products, but the stronger bases lithium bis(trimethylsilyl)amide (LHMDS) and *t*-BuOK/LDA gave mainly the E-alkenes. The optimized ERBR conditions were found to be 2 equivalents of lithium *tert*-butoxide in THF at 25 °C, the use of 2 equivalents of base was optimal, possibly because of the formation of the anion, necessary to form the episulfone, in equilibrium amounts.[41] It was shown, that the ERBR is sensitive to the substitution patterns around the central α,β-epoxy sulfonyl moiety. For example, 1,2-di- and 1,1,2-trisubstituted α,β-epoxy sulfones (entry 7, Table 1) generate the corresponding alcohols in higher yield than their 1-monosubstituted counterparts (entry 1). Additionally substitution of the α′-position diminishes the yields of ERBR products. These examples clearly demonstrate that the particular mechanistic features of the Ramberg–Bäcklund reaction facilitate what is formally an S_N2-type process at a tertiary carbon atom to



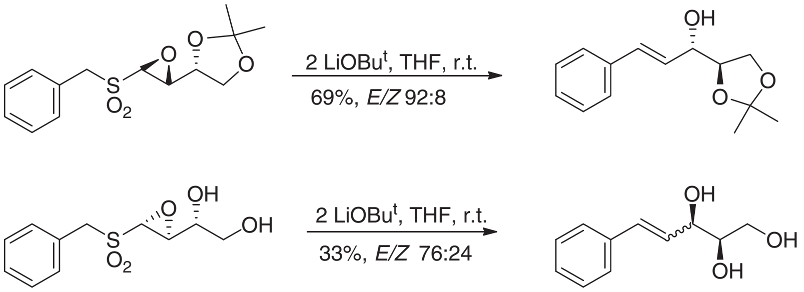
Scheme 16

Table 1 ERBR of α,β-epoxy sulfones (Scheme 16)

No.	*R¹*	*R²*	*R³*	*R⁴*	*E/Z ratio*	*Yield (%)*
1	Ph	H	Ph	H	65:35	35
2	Ph	H	3-$O_2NC_6H_4$	H	>95:5	69
3	Ph	H	4-FC_6H_4	H	>95:5	68
4	Ph	H	2-Naphthyl	H	>95:5	78
5	Ph	H	4-Biphenylyl	H	>95:5	71
6	Ph	H	Et	H	9:1	75
7	Ph	Me	Me	H	>95:5	92
8	Ph	Ph	H	H	>95:5	48
9	Ph	H	CH_2OH	H	75:25	50
10	Ph	H	CH_2OTBS	H	93:7	79
11	Ph	H	H	H	65:35	35
12	*E*-PhCH=CH	H	H	H	*E*,*E*:*E*,*Z* 60:40	79

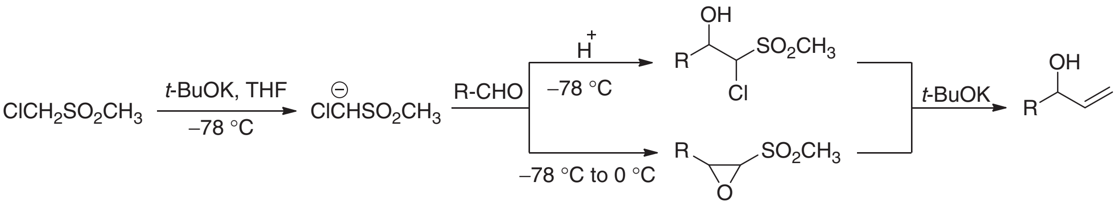
occur during the episulfone formation. It should be noted, that additional structural functionality would need to be compatible with the basic reaction conditions (Table 1, entries 9 and 10). The ERBR protocol was also applied for the preparation of primary allylic alcohols from terminal epoxides (entries 11 and 12).

Modification of ERBR enabled the preparation of enantioenriched allylic alcohols following the diastereoselective epoxidation of enantioenriched vinyl sulfones that were accessed efficiently from the chiral pool (Scheme 17).[41]



Scheme 17

The close variation of the ERBR involves the reaction of the carbanions of chloromethyl sulfones with an aldehyde to afford the corresponding chlorohydrin and/or oxirane.[43] These can be isolated and then subjected to base-induced rearrangement to give the corresponding allylic alcohols. Alternatively, the same alcohol was obtained on direct treatment of a mixture of benzaldehyde and chloromethyl methyl sulfone with 3 equivalents of potassium *tert*-butoxide at −78 °C and subsequent warming the mixture to 0 °C. Other aromatic and aliphatic aldehydes react with chloromethyl methyl sulfone in a similar way (Scheme 18). The oxiranes produced from aliphatic ketones do not enter the RBR under the above conditions as do the oxiranes produced from aldehydes. When these oxiranes were treated with an excess of potassium *tert*-butoxide even at room temperature, the formation of allylic alcohols was never observed.



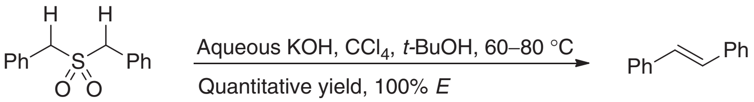
R = Ph, 63%; 4-ClC_6H_4, 68%; 4-$MeOC_6H_4$, 35%; Pr^i, 66%

Scheme 18

3.18.1.6 Synthetic Modifications of the Ramberg–Bäcklund Rearrangement

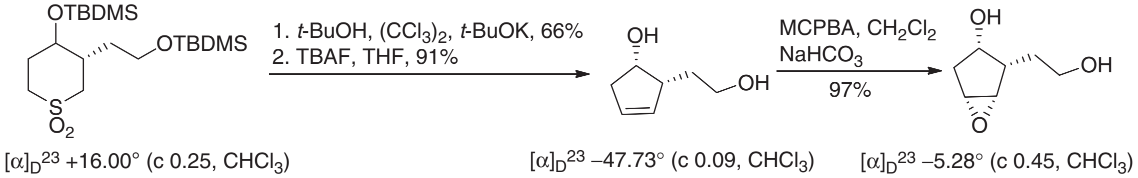
3.18.1.6.1 The Meyers' modification (one-pot or in situ *halogenation) of the Ramberg–Bäcklund rearrangement*

A number of modifications and extensions of the original RBR have been developed. Since, usually, the preparation of α-halo sulfones is the most problematic stage in the Ramberg–Bäcklund strategy, the well-known Meyers procedure[14] represents a very attractive approach and had been used with considerable frequency in organic synthesis. It involves treatment of a sulfone possessing both α- and α′-hydrogens with potassium hydroxide suspended in a mixture of *t*-BuOH and carbon tetrachloride, which serves as the halogen source for *in situ* sulfone chlorination and, thus, allows to avoid the preparation of the α-halo sulfone in a separate step. In this way dibenzyl sulfones are rapidly converted into the stilbenes with high yields. Reaction is highly stereospecific, *dl* sulfones being converted mainly into *trans*-stilbenes, and *meso*-sulfones into *cis*-stilbenes, in accordance with the stereochemistry usually observed in the RBR (Scheme 19).



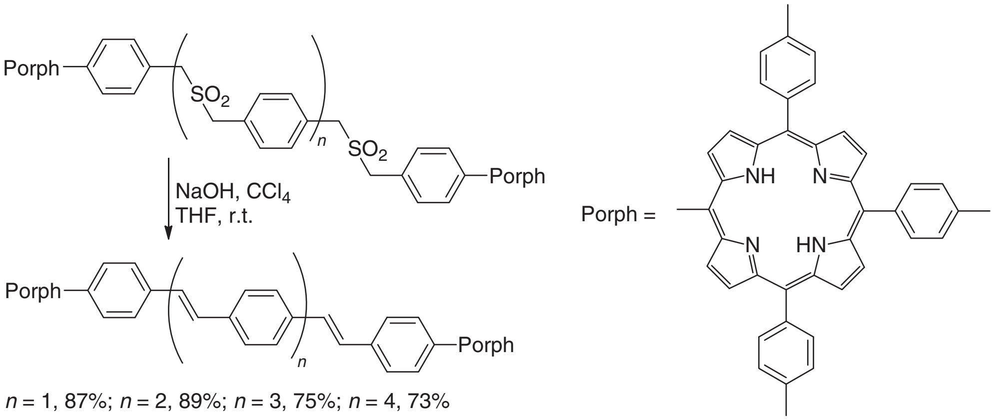
Scheme 19

The same protocol was used as a key step in the synthesis of prostaglandin synthons in optically pure form (Scheme 20).[44] Hexachloroethane, instead of carbon tetrachloride, was used as the chlorine source in this case.



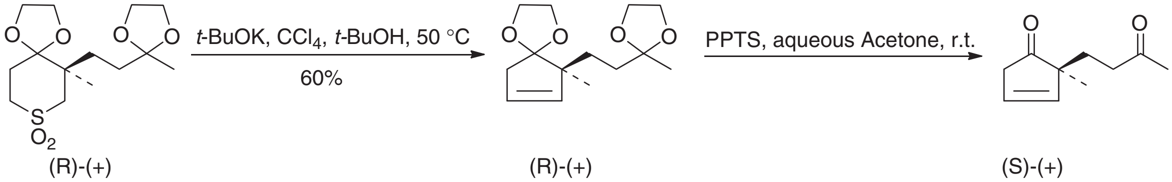
Scheme 20 Reproduced from Fujisawa, T.; Mobele, B. I.; Shimizu, M. *Tetrahedron Lett.* **1991**, *32*, 7055–7058.

In another application, the Meyers modification of the RBR was the key step in the preparation of oligo[phenylenevinylenes] terminated with porphyrins, novel electrically conducting materials (Scheme 21).[45] RBR allows a control of the conjugation length of phenylenevinylene oligomers, which is very important for organic semiconductors. Five double bonds were formed in one step, and they were all *trans*.

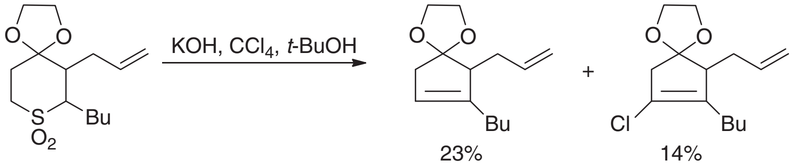


Scheme 21

A ring-contraction approach through the Meyers modification of the RBR was successfully employed to the synthesis of some optically active cyclopentenones (Scheme 22).[46,47] It is interesting to note that the same strategy was rather disappointing when applied to the synthesis of 2,3-disubstituted cyclopentenones because of the formation of the chlorinated by-product together with the desired cyclopentene (Scheme 23).[48]



Scheme 22



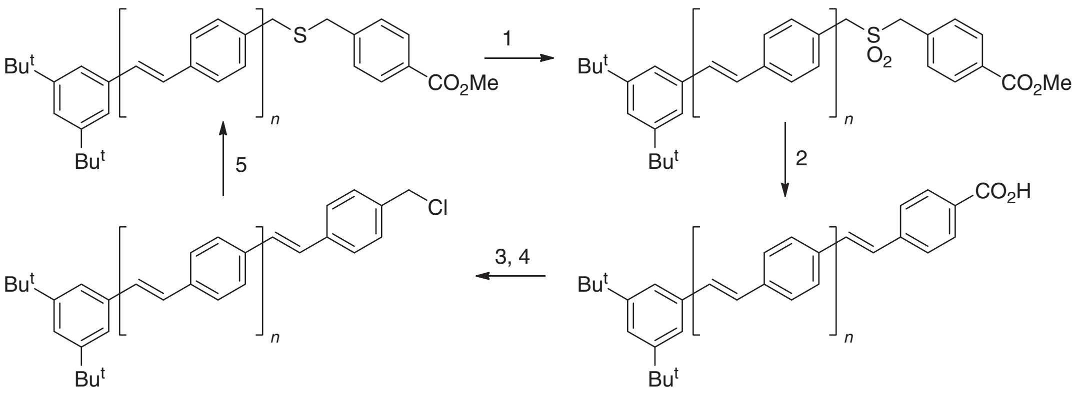
Scheme 23 Reproduced from Casy, G.; Taylor, R. J. K. *Tetrahedron* **1989**, *45*, 455–466.

However, one should note some limitations in the applicability of the Meyers protocol to the synthesis of alkenes. This procedure works well with dibenzyl and benzhydryl alkyl type sulfones or diallyl sulfones, whereas sulfones of other structural types may behave differently and yield complex mixtures of products. The major side-reaction of the Meyers protocol is the formation of dichlorocarbene from carbon tetrachloride under the basic reaction conditions and its addition to the alkene product to give the corresponding *gem*-dichlorocyclopropane derivatives.[49] A further disadvantage is the dihalogenation of diprimary alkylsulfones before base-induced 1,3-elimination to afford almost exclusively the potassium salts of alkenesulfonates. Benzyl-primary alkyl sulfones usually give mixtures of β-alkylstyrenes, α-chloro-β-alkylstyrenes, and potassium alkenesulfonates. Whatever type of sulfone is used as substrate, carbonyl and primary or secondary hydroxy groups must be protected since they are reactive under Meyers chlorinating conditions.

N-chlorosuccinimide (NCS) can also serve as the halogen source for *in situ* sulfone chlorination. One useful one-pot modification of the RBR involves treatment of a sulfone with potassium *tert*-butoxide in THF at − 105 °C followed by trapping of the intermediate carbanion with NCS and exposure of the resultant mixture to a second equivalent of potassium *t*-butoxide.[50] It was also shown that replacing NCS with *N*-iodosuccinimide (NIS) during the Ramberg–Bäcklund step can facilitate the ring contraction and formation of the corresponding cycloalkenes.[50]

Chan et al.[13] have suggested an improved version of the standard Meyers procedure, which involves replacement of carbon tetrachloride by dibromodifluoromethane and of powdered potassium hydroxide by alumina-supported potassium hydroxide. With this reagent, $KOH/A1_2O_3$-CBr_2F_2-*t*-BuOH, the one-pot RBR proceeds smoothly with good yields and gives alkenes as the only product. Substitution of carbon tetrachloride by CBr_2F_2 as halogen source suppress the formation of dichlorocarbene adducts since only relatively unreactive difluorocarbene, if any at all, could evolve. The problem of dihalogenation of diprimary alkyl sulfones was solved by the use of alumina-supported potassium hydroxide instead of pulverized potassium hydroxide. The efficacy of this reagent is believed to be a consequence of a large increase in the surface area of the catalyst and perhaps also the activating effect produced by the alumina surface.

The above version of the RBR has been used for the iterative stereoselective synthesis of oligo[*p*-phenylene-(*E*)-vinylene]-*p*-benzoic acid derivatives, the basic building block for novel electrically conducting materials, the oligo[*p*-phenylene-(*E*)-vinylene]s (Scheme 24),[51] as well as for the synthesis of various optically active (m)(n)paracyclophanes (Scheme 25).[52]



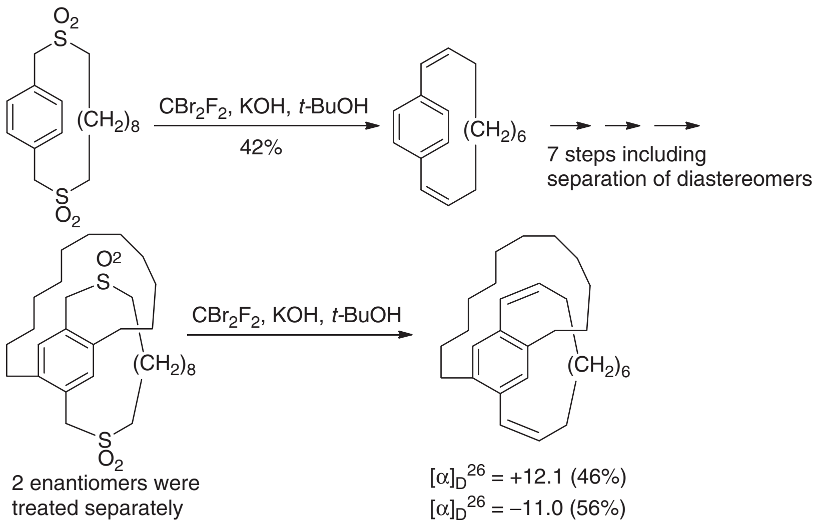
1. $n = 0$; oxone, MeOH; 2. $n = 0$; KOH/Al$_2$O$_3$, CBr$_2$F$_2$, *t*-BuOH; 3. $n = 0$; LiAlH$_4$, THF; 4. SO$_2$Cl$_2$, CCl$_4$; 5. $n = 1$; NaOMe, MeOH, 4-MeO$_2$C-C$_6$H$_4$-CH$_2$S(C=S)OMe... $n = 0, 1, 2$.

Scheme 24

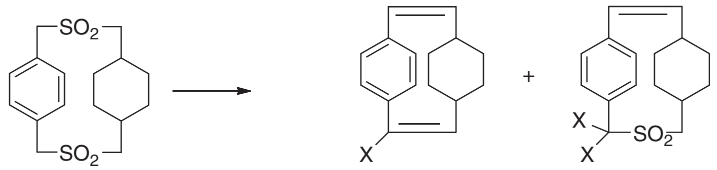
However, the same double RBR strategy was not successful in the preparation of hexahydro[2.2]paracyclophane.[53] Under the variety of conditions for halogenative RBR (Scheme 26), only the first double bond was obtained as desired. The second sulfur dioxide extrusion in this highly strained system proceeds with low yield because of the formation of vinyl halide products due to the dihalogenation at the remaining benzylic carbon before the rearrangement.

3.18.1.6.2 The Ramberg–Bäcklund rearrangement of sulfonyl carboxylic esters (decarboxylative Ramberg–Bäcklund rearrangement)

It was reported that some α-isopropylsulfonyl carboxylic esters can undergo the RBR under Meyers conditions (Scheme 27).[54] In the case of the dialkyl substituted derivatives, chlorination at the isopropyl group should occur initially and then the intermediate chlorinated carboxylate **23** due to the electron-withdrawing effect of the chloro substituted isopropyl group, would undergo decarboxylation to give a carbanion **24**. The latter reacts by 1,3-displacement of chloride ion to give the corresponding episulfone precursor of the alkene. For the monoaryl derivatives, the resulting alkenes were in admixture with chloroalkenes, and in the case of the monobenzyl derivatives the chloroalkene was the only reaction product. The formation of chloroalkenes may be explained by the initial chlorination adjacent to the ester group instead of the isopropyl group. The resulting α-chloro carboxylate undergoes decarboxylative chlorination, followed by 1,3-elimination of chloride ion from the intermediate dichloro derivative **25**.

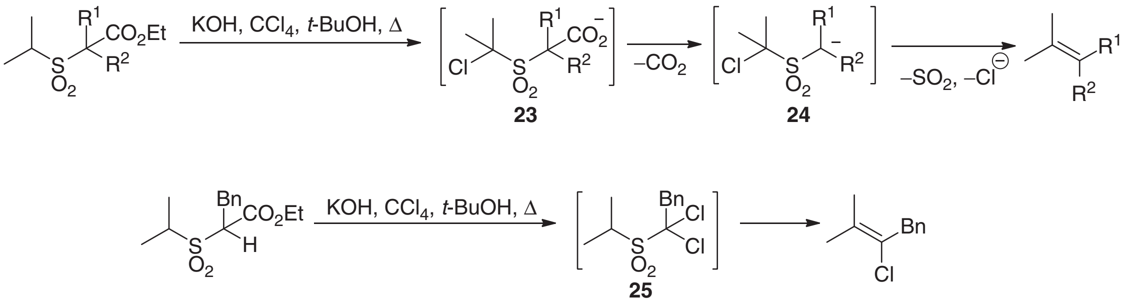


Scheme 25



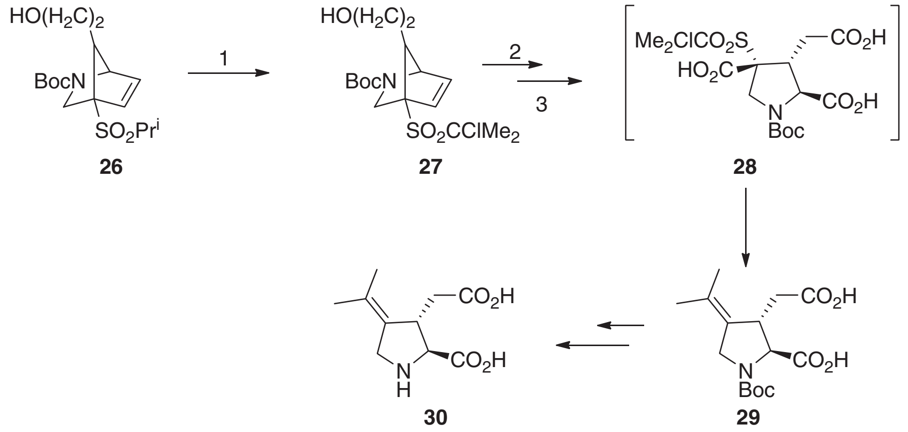
1. KOH, CCl_4, *t*-BuOH, 27 °C, 13 h	X = Cl, 8.4%	X = Cl, 22.3%
2. KOH, CCl_4, *t*-BuOH, 80 °C, 5 h	X = Cl, 10.5%	–
3. KOH/Al_2O_3, CCl_4, *t*-BuOH, 27 °C, 24 h	X = Cl, 16.8%	–
4. KOH/Al_2O_3, CBr_2F_2, *t*-BuOH, 27 °C, 24 h	X = Br, 6.2%	–

Scheme 26



Scheme 27

Total syntheses of (±)-α-isokainic acid **30** and (±)-α-dihydroallokainic acid have been achieved via tandem radical addition-homoallylic rearrangement and a decarboxylative Ramberg–Bäcklund reaction.[55] This tandem intermolecular C–C bond forming radical addition-homoallylic rearrangement sequence was facilitated by the multifaceted use of the sulfone moiety, which was then constructively removed in a decarboxylative RBR to install the isopropylidene unit (Scheme 28). First, it was established that the introduction of the chloro substituent for the RBR was better achieved before oxidative cleavage of the double bond in azabicycle **26**. Chlorination of **26** was carried out by deprotonation α to the sulfone with *n*-butyllithium followed by trapping of lithiated species using hexachloroethane. Thus obtained chlorinated product **27** then underwent oxidative cleavage of the double bond and converted to the transient sulfonyl triacid **28**, which after heating cleanly led to unsaturated diacid **29** via the desired decarboxylative RBR. The latter was deprotected to give the α-isokainic acid **30** (Scheme 28).

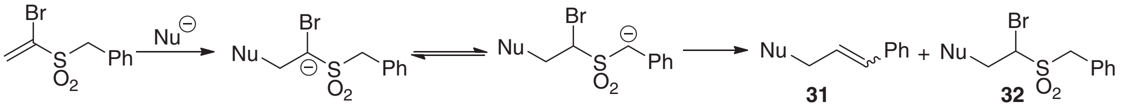


1. BuLi (2.2 equivalents), C_2Cl_6 (3 equivalents), THF, –78 °C to 20 °C, 150 min, 86%; 2. O_3/O_2, then Me_2S, CH_2Cl_2, –78 °C to 20 °C, 1 h; 3. 4-AcNH/TEMPO (0.1 equivalent), Br_2 (6 equivalents), KOH (added to maintain pH 11.5), $Na_2S_2O_5$ (10 equivalents), $MeCN/H_2O$ (1:1), 0 °C to 95 °C, 4.5 h.

Scheme 28

3.18.1.6.3 *The Michael-induced Ramberg–Bäcklund rearrangement*

A Michael-induced Ramberg–Bäcklund reaction (MIRBR) in which the intermediate α-sulfonyl carbanions can be generated indirectly has also been developed.[56] MIRBR circumvents the use of strong base for the formation of α-sulfonyl carbanions, involves addition of a suitable nucleophile to α-haloalkyl sulfones carrying a Michael acceptor system attached to the α′-position and allows introduction of a functionality (e.g., arylsulfonyl, alkoxides, or phenoxide) during the reaction. In practice, however, the process is apparently limited to dienyl sulfone substrates and thus, leads to a diene synthesis. Another disadvantage of the MIRBR is the absence of any useful stereocontrol. Usually, all possible isomeric products are formed. Later, a new variant of the MIRBR has been suggested.[57] This version of MIRBR allows producing allylic alcohols, sulfides, and amines (Scheme 29).



Nu = MeO, BnS, ^{i}PrS, BnNH, ^{t}BuNH, (S)-PhCHMeNH, NH_2, $MeC(CO_2Me)_2$

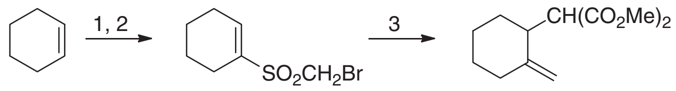
Scheme 29

This new variant of MIRBR has several interesting features, most notably the use of α-halovinyl sulfones as substrates. With an appropriate choice of substituents in the α-halo sulfones and of the reaction conditions, a one-pot tandem conjugated addition-proton exchange-RBR is possible (Scheme 29). In some cases the formation of the functionalized alkenes **31** was accompanied by the formation of the corresponding conjugated adducts **32**. However, further treatment of the latter with Nu under the conditions of one-pot transformation produced the corresponding alkene **31** with the same *E*:*Z* ratio. The stereochemical output of this MIRBR is a mixture of *E*/*Z*-isomers and the *E*:*Z* ratios, as expected from the literature,[3,5] reflect the basicity of the reagent.[57] With the weak amine bases, *cis*-isomers predominate, whereas methoxide and *t*-butoxide favor the formation of the *trans*-alkenes. In terms of mechanism of allylic amine forming reactions, there is the possibility that they proceed via intermediary sulfonyl aziridines,[42] rather than as shown in Scheme 29.

α-Haloalkyl vinyl sulfones can react with CH-acids enolates in several possible routes depending on the position and number of halogen atoms. These include vinylogic RBR leading to the formation of conjugated dienes,[58] cyclization initiated by Michael addition giving tetrahydrothiophene *S*,*S*-dioxide derivative,[59] or MIRBR.[60,61] A recent example of the latter, afforded preparation of the functionalized derivatives of methylenecyclohexane, is presented on Scheme 30.[61]

3.18.1.7 Synthetic Applications of the Ramberg–Bäcklund Rearrangement

The Ramberg–Bäcklund reaction can be used to synthesize mono-, 1,1- or 1,2-di-, tri-, and tetra-substituted alkenes, including alkenes substituted with a variety of functional groups. Since high stereocontrol is not a general feature of the original RBR of acyclic α-halo sulfones, the reaction is most useful when stereoisomeric alkenes are not needed, or otherwise, the newly generated double-bond should undergo reduction to the final products. Nevertheless, very high (*E*)-stereoselectivity can be achieved in



1. $BrCH_2SO_2Br$, CH_2Cl_2, 10 °C, 24 h; 2. Na_2CO_3, H_2O/Dioxane, 50 °C, 30 h, 54%
(total yield for two steps; 3. $CH_2(CO_2Me)_2$, NaH, THF, 20 °C, 17 h, 26%.

Scheme 30 Reproduced from Vasin, V. A.; Bolusheva, I. Y.; Razin, V. V. *Russ. J. Org. Chem.* **2010**, *46*, 758–759, with permission from Springer.

favorable circumstances, especially with functionalized alkenes. In synthetic terms, the most prominent feature of the RBR reaction is the regiospecific formation of alkenes. The position of the newly generated double bond is fixed by the position of the sulfone group in the precursor, and never migrates under the reaction conditions.

3.18.1.7.1 Synthesis of acyclic alkenes

The RBR was applied to a synthesis of [G1] and [G2]-oligo-(phenylenevinylene) dendrimers via multiple dendrimer backbone rearrangements of oligo(dibenzyl sulfone) dendrimers.[62] Both [G1]-tri(phenylenevinylene) **34** and [G2]-nona-(phenylenevinylene) **36** dendrimers were readily prepared from the corresponding [G1]-tri(sulfone) **33** and [G2]-nona-(sulfone) **35** derivatives, respectively, via dendrimer metamorphosis multiple RBR on a single molecule involving up to nine transformations (**Scheme 31**). However, it was impossible to extend this dendrimer metamorphosis strategy to the [G3]-series due to steric shielding and heterogeneous nature of the RB reaction conditions. The [G1]–[G3]-oligo(sulfone) dendrimers, in turn, were readily prepared by the hydrogen peroxide oxidation under homogeneous reaction conditions from the corresponding [G1] to [G3]-oligo-(sulfide) dendrimers via functional group conversions occurred in the interior domain. Under standard Chan's conditions (KOH/Al_2O_3, CBr_2F_2) in *t*-BuOH the reaction was too slow and sluggish, however a mixture of THF and *t*-BuOH was a better solvent system for the reaction as the oligo(sulfone) dendrimers were found to have slightly better solubility and the rearrangements of all three sulfones proceeded smoothly even at -45 °C. The all (*E*)-[G1]-tri(phenylenevinylene) dendrimer **34** was isolated in 91% yield from the corresponding sulfone. In the case of dendrimer **35**, the (*E*)-stereoselectivity of the RBR decreased and the newly generated double bonds were of both (*E*)- and (*Z*)-configurations. Nonetheless, the all (*E*)-[G2]-nona-(phenylenevinylene) isomer **36** could be isolated as the major product in 48% yield after careful silica gel chromatography. Both the pure all (*E*)-isomer **36** and the geometrical mixtures could be separately converted to the same saturated [G2]-nona(phenyleneethylene) dendrimer in 78% and 82% yield, respectively, by catalytic hydrogenation with 10% Pd/C.

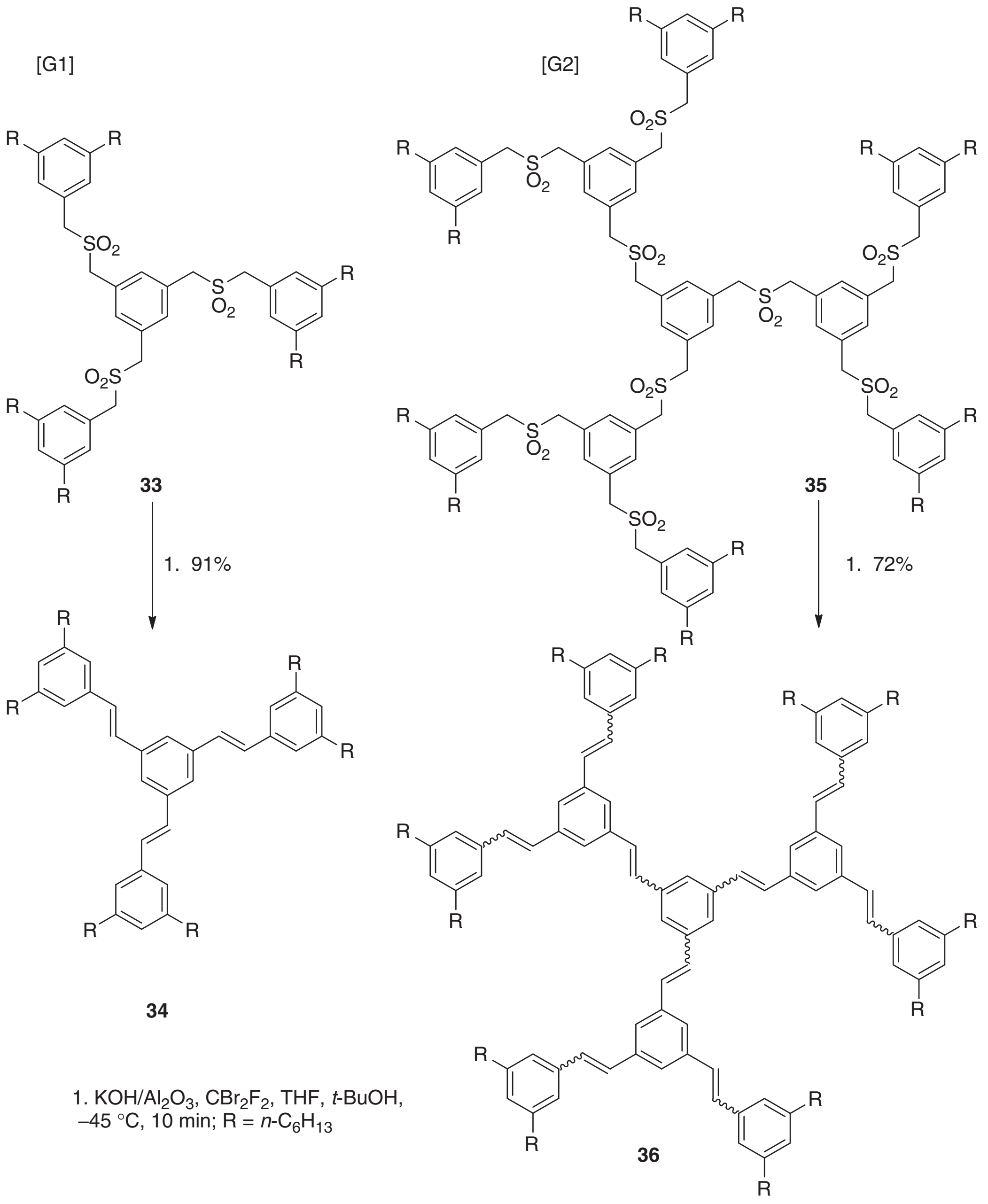
The Ramberg–Bäcklund reaction has been utilised as part of a short and flexible route to the anticancer stilbenes derivatives including combretastatin A-4 as well as its several novel analogs.[63] The tandem halogenation–RBR proceeded efficiently with the stereoselectivity depending on the applied conditions. Thus, using the Chan's conditions[13] (**Scheme 32**), resulted in the formation the O-silylated stilbene **37** as a 90:10 mixture of (*E*)- and (*Z*)-isomers in 81% yield. Desilylation of **37** with tetrabutylammonium fluoride on silica provided the corresponding phenols in 72% yield. Conducting the reaction with dibromotetrafluoroethane as a bromine source[64] (**Scheme 32**), similarly provided **37** as an 85:15 mixture of (*E*)- and (*Z*)-isomers in 72% yield. However, the original Meyers conditions[14] (**Scheme 32**), produced two types of change in the output of the reaction. Under these conditions, *in situ* deprotection of the *t*-butyldimethylsilyl ether occurred but, more importantly, the required stilbene was produced in 69% yield as a 47:53 mixture of inseparable (*E*)- and (*Z*)-isomers **37** (**Scheme 32**).

It is important to note, that although it is generally accepted that the use of benzylic sulfones in the Ramberg–Bäcklund reaction would always produce the (*E*)-stilbene as the major isomeric product, some more recent examples, all proceed with electron-rich aromatic systems under Meyers' conditions, lead to an unexpected high ratio in favor of the (*Z*)-isomer.[17,65]

The RBR has been successfully utilized to convert readily available α- and α'-hydrogen bearing substituted dibenzyl sulfones into corresponding stilbene derivatives, which is conveniently followed by hydrogenation in the presence of 10% Pd/C to afford the natural bibenzyls.[66]

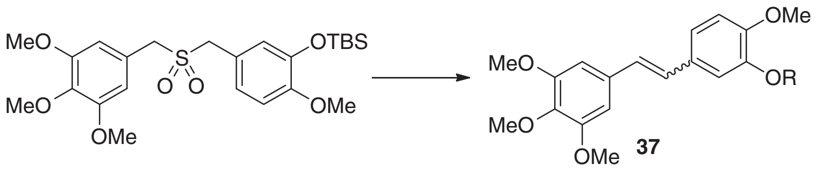
The RBR has been employed as the key step in an enantioselective synthesis of C2-symmetrical and pseudosymmetrical acyclic 1,6-diamino-2,5-diols.[35] This synthetic protocol allowed to achieve the assembly of two enantiopure β-amino alcohol moieties in a totally regio- and stereocontrolled way. First, the vicinal amino and hydroxy groups in sulfides **38** were converted into the corresponding dimethyloxazolidines derivatives in order to avoid interferences with the strongly basic conditions required for the RBR. The protected compounds **39** were then oxidized with *m*-chloroperoxybenzoic acid in dichloromethane to afford the sulfones **40** in nearly quantitative yields. The optimal reaction conditions for the RBR of **40** involved the use of potassium hydroxide on alumina as a base and dibromodifluoromethane as the brominating agent, in *t*-butyl alcohol at room temperature. The resulting olefins **41** were obtained as approximately 70:30 mixtures of the *E* and *Z* isomers and then underwent hydrogenation and deprotection to afford the required 1,6-diamino-2,5-diols (**Scheme 33**) which were most conveniently purified and characterized after their conversion to the corresponding bis(*N*-Boc) derivatives. The above methodology can also be applied to the synthesis of pseudosymmetrical 1,6-diamino-2,5-diols.

The RBR was successfully applied to the synthesis of alkylidenecyclopropanes **43**.[33] The best results were obtained using LDA as a base at -15 °C, whereas the use of MeLi or *n*-BuLi gave the expected alkylidenecyclopropane **43** (R^1=Ph, R^2=Me) accompanied by the corresponding dechlorinated cyclopropyl sulfone **42** (in the ratio 70:30), probably coming from a lithium–halogen exchange (**Scheme 34**).



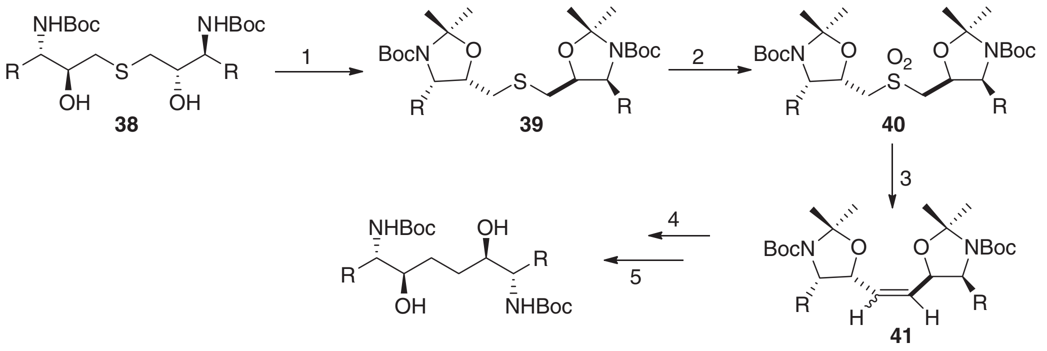
1. KOH/Al_2O_3, CBr_2F_2, THF, *t*-BuOH, –45 °C, 10 min; R = *n*-C_6H_{13}

Scheme 31



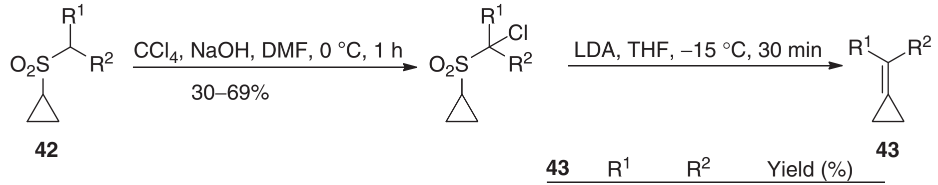
(a) R = TBS; CF_2Br_2, *t*-BuOH, KOH/Al_2O_3, 0 °C to r.t., 12 h, 81%, *E*:*Z* = 90:10
(b) R = TBS; $C_2F_4Br_2$, *t*-BuOH, KOH/Al_2O_3, Δ, 12 h, 72%, *E*:*Z* = 85:15
(c) R = H; CCl_4, *t*-BuOH, KOH, H_2O, Δ, 12 h, 69%, *E*:*Z* = 47:53

Scheme 32



1. $Me_2C(OMe)_2$, cat.TosOH, C_6H_6, r.t., R = Me (84%), Bn (72%); 2. MCPBA, DCM, r.t., R = Me (97%), Bn (100%); 3. CF_2Br_2, *t*-BuOH, KOH/Al_2O_3, r.t., 4 h, R = Me (63%), Bn (59%); 4. H_2, 10% Pd/C, MeOH, R = Me (81%), Bn (78%); 5. (1) HCl, EtOH/H_2O; (2) Boc_2O, Et_3N, $CHCl_3$, R = Me (54%), Bn (61%).

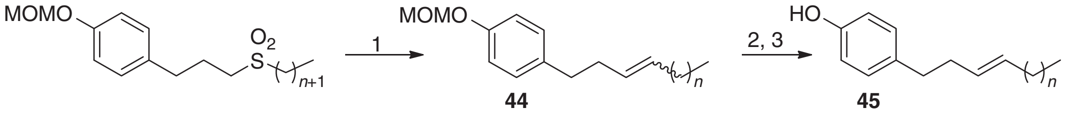
Scheme 33 Reproduced from Aguilar, N.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron Lett.* **1999**, *40*, 3917–3920.



43	R^1	R^2	Yield (%)
	Ph	Me	90
	Ph	Et	66
	Ph	Bn	35
	Me	Bn	45

Scheme 34

The one-pot version of the RBR was applied to the synthesis of natural alkenylphenols, gibbilimbols B and D **45**.[67] The required sulfones were easily obtained from the corresponding sulfides by oxone oxidation in CH_2Cl_2/MeOH in excellent yields. Subjecting these sulfones to the modified RBR (KOH/Al_2O_3, CBr_2F_2, CH_2Cl_2)[68] invariably gave alkenes **44** (Scheme 35). Although the conversion was low (10%) for each of the Ramberg–Bäcklund transformations, the starting sulfones can be recycled completely and after repeating the reaction several times, the products **44** were prepared in satisfactory yields as inseparable 1:1 mixture of *E* and *Z* isomers. The latters were subjected to deprotection and isomerization to give gibbilimbols B (*n*=5) and D (*n*=3) **45**, respectively, with an *E*-configuration of the double bond.



n = 5, gibbilimbol B; *n* = 3, gibbilimbol D

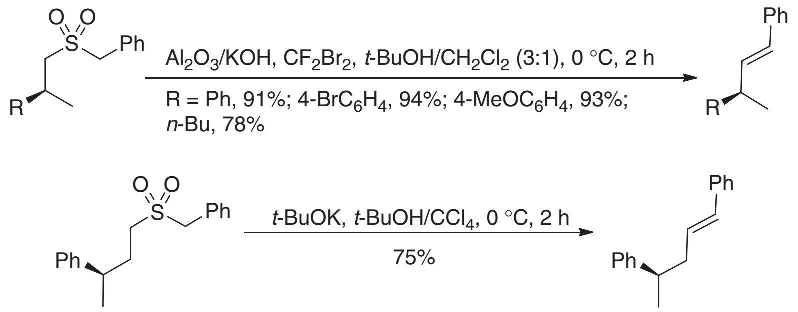
1. KOH/Al_2O_3, CBr_2F_2, CH_2Cl_2, r.t.; 2. conc. HCl, MeOH, reflux; 3. PhSH, AIBN, C_6H_6, reflux.

Scheme 35

Chiral allylic and homoallylic compounds with varying substitution patterns were prepared with high yields (up to 94%) and excellent enantioselectivities (up to 97%) by a novel route, which involved enantioselective Ir-catalyzed hydrogenation of unsaturated sulfones followed by the one-pot RBR.[69] The chiral acyclic sulfones underwent rearrangement with complete *trans*-selectivity and no erosion of enantiometric excess was observed during the RBR of the substrates tested (Scheme 36).

3.18.1.7.2 Synthesis of cycloalkenes via ring contraction

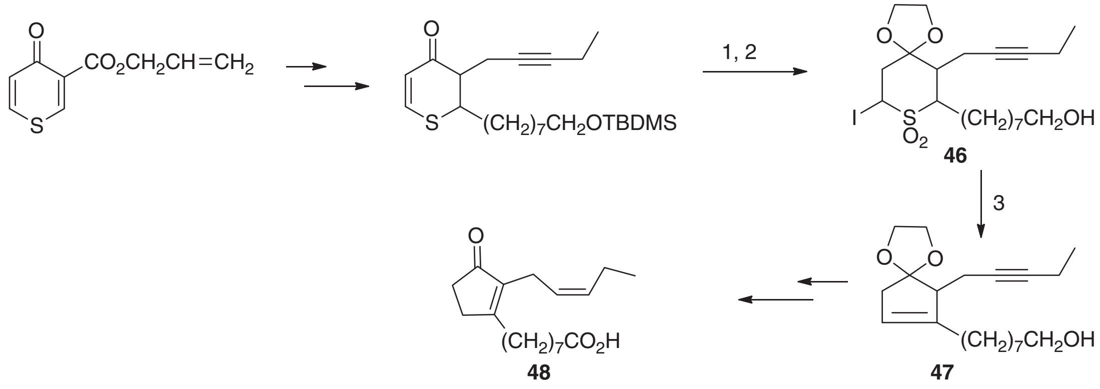
One of the significant areas of application of the RBR is the preparation of cycloalkenes and heterocycles of various ring sizes and different substitution patterns and, particularly, the synthesis of strained cycloalkenes by ring contraction. Some examples cited below demonstrate this strategy (see Sections 3.18.1.7.2.1, 3.18.1.7.2.2 and 3.18.1.7.2.3).



Scheme 36

3.18.1.7.2.1 Synthesis of carbocyclic alkenes via ring contraction

The RBR has been employed to prepare protected 2,3-disubstituted cyclopent-3-enones which have been converted into cyclopent-3- and 2-enones. This methodology was then applied to a formal total synthesis of the antimicrobial natural product tetrahydrodicranenone B **48** via the facile (− 78 °C, < 1 h) RBR as the key step (Scheme 37).[48,70] Important, that the most straightforward approach involving the formation of the corresponding cyclic six-membered sulfone and treatment of the latter under Meyers' conditions with carbon tetrachloride/t-BuOH with a large excess of potassium hydroxide at 50 °C to effect α-chlorination and *in situ* Ramberg–Bäcklund ring contraction was rather disappointing. Under these conditions the desired cyclopentene derivative was isolated in 23% yield only along with the corresponding vinyl chloride (yield of 14%) (see Scheme 23). The Ramberg–Bäcklund leaving group was introduced by a Michael-type process. Halosilanes have been employed for halide conjugate addition to simple enones. Thus, the Ramberg–Bäcklund precursor, α-iodoacetal **46**, was obtained from the corresponding sulfone via clean iodide addition-acetalisation-desilylation by the treatment with ethylene glycol and preformed iodotrimethylsilane in 65% yield. Ramberg–Bäcklund ring contraction of α-iodosulphone **46** was achieved using potassium *t*-butoxide (2.05 equivalents) and cyclopentene **47** being produced in 65% yield as the sole observable product (Scheme 37).

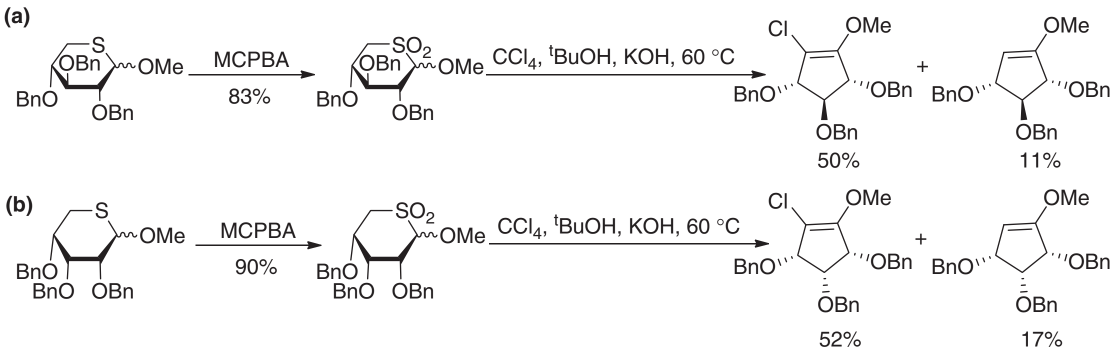


1. MCPBA, CH_2Cl_2, Na_2CO_3, 83%; 2. Me_3SiI (iodotrimethylsilane), $HOCH_2CH_2OH$, CH_3CN, r.t., 65%;
3. t-BuOK, THF, –78 °C, 30 min, 65%.

Scheme 37 Reproduced from Casy, G.; Taylor, R. J. K. *Tetrahedron* **1989**, *45*, 455–466.

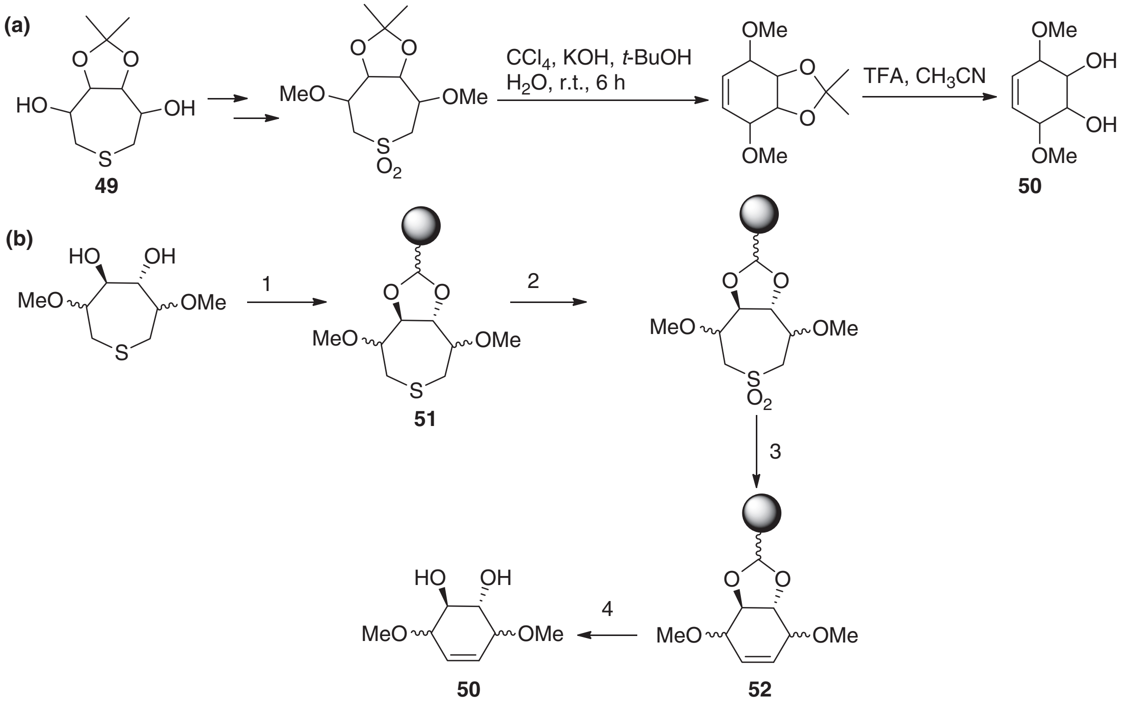
A novel approach to polyoxygenated enantiopure cyclopentenes, α-chlorocyclopentenones, and cyclopentenones which utilizes the RBR of thiosugar-derived sulfones was described.[71] First, benzyl-protected methyl 5-thio-D-xylopyranoside and methyl 5-thio-D-ribopyranoside were prepared from D-xylose, and D-ribose, respectively. Oxidation of these cyclic sulfides by *m*-chloroperbenzoic acid gave the corresponding sulfones in a reasonable overall yield. The RBR of D-xylose derived sulfone under Meyers' conditions (KOH/CCl_4/^{t}BuOH), gave a 5:1 chromatographically separated mixture of the enol ethers (Scheme 38a). The major product results from double chlorination followed by episulfone formation and loss of sulfur dioxide. Similarly (Scheme 38b), RBR of ribose-derived sulfone gave the corresponding cyclopentenes (approximately 3:1) in 69% overall yield.

Likewise, the optically pure polyoxygenated cyclopentenes and cyclohexenes were obtained through the Ramberg–Bäcklund reaction in moderate to good overall yield starting from the polyoxygenated tetrahydrothiopyrans and thiepanes, respectively.[72] The thiosugars were converted to the anomeric chlorides by treatment with NCS, followed by *in situ* MCPBA oxidation to yield the corresponding chlorosulfones. Conversion of these compounds to the polyoxygenated cycloalkenes proceeded very well under the reaction with potassium *tert*-butoxide in THF at − 15 °C. The procedures can be applied to the preparation of polyoxygenated cycloalkenes on a relatively large scale (up to 30 mmol).



Scheme 38

The Meyers' modification of the RBR was much more successful for the preparation of cyclohexene derivatives conduritol **50**.[73] Thus, a library consisting of all the 10 thiepanes stereoisomers was generated and the individual library members were obtained in high yield by high-performance liquid chromatography (HPLC) separation. The hydroxy groups of the thiepane derivatives **49** were protected as methyl ethers. Oxidation of the latter to the corresponding sulfones and extrusion of the SO_2 group by the RBR afforded conduritol derivatives **50** (Scheme 39a).

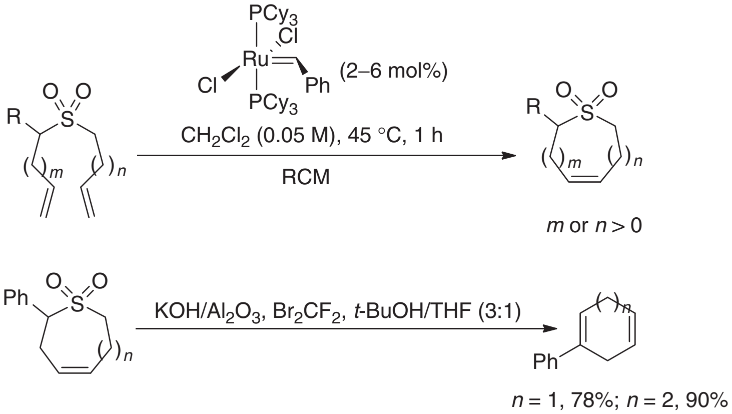


1. polystyrene-CHO, *p*-TSA, C_6H_6, 20 h, reflux, 95%; 2. MCPBA, CH_2Cl_2, r.t., 3 h; 3. CCl_4, KOH, *t*-BuOH H_2O, r.t., 6 h; 4. TFA, CH_2Cl_2, reflux, 30 min.

Scheme 39

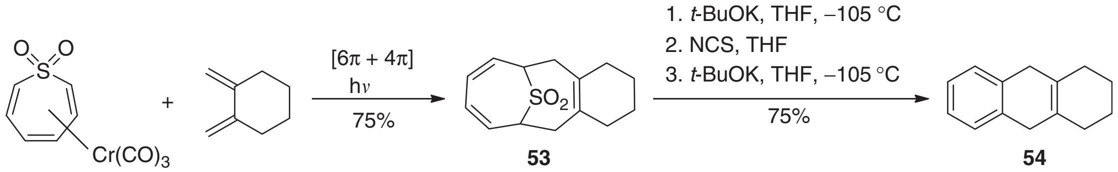
Using polystyrene-CHO resin as solid support for thiepane diols **49**, this flexible and efficient solution-phase preparation of conduritols was adapted to the solid phase.[73] First, the diol-loaded polystyrene-CHO resin **51** was prepared. The subsequent oxidation of the sulfur atom, performed with *m*-chloroperoxybenzoic acid, leads to the sulfone derivatives. Submitting of the polymer-supported sulfones to the RBR under the modified Meyers conditions resulted in the resin-supported cyclohexene derivatives **52** being obtained. Finally, trifluoroacetic acid (TFA) treatment led to removal of the immobilized organic molecule, and no memory of the immobilization (traceless cleavage) remained on the target (Scheme 39b). Highly pure conduritol derivatives **50** were obtained in slightly higher yields with respect to those using solution phase reactions. The polystyrene-CHO resin support acts as a very efficient protecting group of the two vicinal alcoholic groups of the substrate. Moreover, supporting thiepanes on resin greatly simplifies the isolation and makes purification of the final products unnecessary. The synthetic utility of the above RBR on resin-supported substrates has emerged for the first time as a general potential route for the preparation, in addition to conduritols, also olefins, which are difficult to synthesize with other methods.

Chan's version of the standard Meyers procedure[13] worked well for the preparation of cyclic dienes.[74] In turn, a versatile strategy for the synthesis of the corresponding cyclic sulfones was proposed. This strategy was based on the ring-closing metathesis (RCM) of acyclic sulfones which can be readily prepared from alkenyl alcohols and alkenyl halides through standard functional group transformations.[74] This method can be applied to the synthesis of a number of structurally diverse cyclic sulfonyl alkenes. Six-membered sulfones were produced uneventfully, whereas the formation of seven-, eight-, and nine-membered cyclic sulfones required a higher loading of the catalyst and the metathesis reaction to be performed under dilute conditions and for a longer reaction time. In all cases, however, the cyclized products were isolated in good to excellent yields (Scheme 40). Thus obtained sulfones underwent clean and high-yielding one-pot RBR on treatment with Br_2CF_2 in the presence of potassium hydroxide supported on alumina to the corresponding cyclic dienes (Scheme 40).



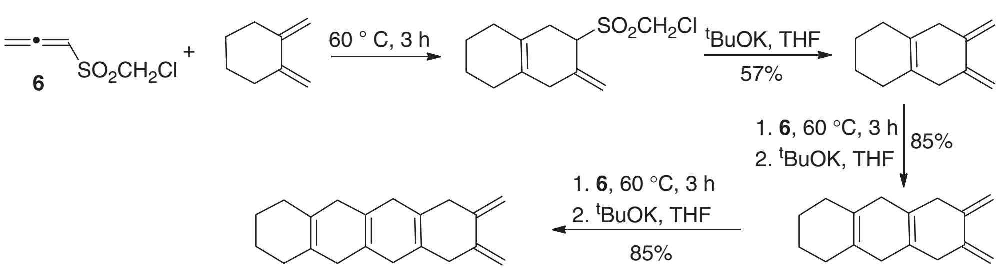
Scheme 40

The RBR has been shown to be a powerful method for the rapid construction of stereochemically rich and structurally elaborate polycyclic systems. For example, this ring-contraction approach was used in a benzannulation sequence based on a chromium(0)-promoted $[6\pi + 4\pi]$ cycloaddition of thiepin 1,1-dioxide with various diene partners, followed by a one-pot RBR.[50] Noteworthy features of this protocol include the simultaneous formation of two rings, rather than the usual one, and that all six of the carbon atoms comprising the incipient benzo ring are delivered by the thiepin dioxide triene moiety. Scheme 41 presents a typical benzannulation sequence. Treatment of the cycloadduct **53** in one-pot manner with potassium *tert*-butoxide in THF at −105 °C, followed by trapping of the intermediate carbanion with NCS and exposure of the resultant mixture to a second equivalent of potassium *tert*-butoxide, afforded the hexahydroanthracene **54** in quite good yield (Scheme 41). It has been shown that in some cases the efficiency of the ring-contraction step is dramatically improved by employing *N*-iodosuccinimide instead of NCS as positive halogen source.[50]



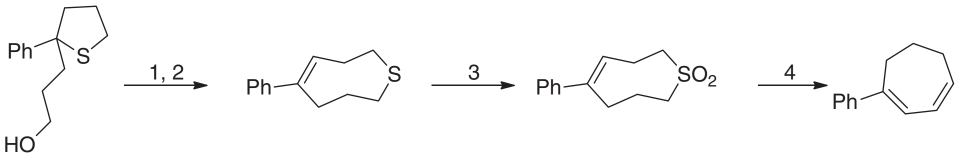
Scheme 41 Reproduced from Rigby, J. H.; Warshakoon, N. C. *J. Org. Chem.* **1996**, *61*, 7644–7645, with permission from American Chemical Society.

A series of linear fused carbocycles was constructed through an iterative ring growing procedure using so called 'prepackaged' Ramberg–Bäcklund reagents.[19,21] These α,β-unsaturated chloromethyl sulfones, may be defined as compounds having sulfonyl and α-halogen groups which, following an appropriate first step, require only base to give, by the Ramberg–Bäcklund reaction, olefinic end products with an increase in total number of carbon atoms. An illustrative example of such reaction sequence is presented on Scheme 42.[21] Chloromethyl 1,2-propadienyl sulfone **6** undergoes Diels–Alder cycloaddition with 1,2-bis(methylene)cyclohexane to give the intermediate adduct which under Ramberg–Bäcklund conditions (THF/*t*-BuOK) can be converted to the corresponding conjugated diene ready for further reaction with sulfone **6**. Repetition of the process gave the corresponding tetraene and then the pentaene. The above protocol was expanded with Diels–Alder adducts obtained from reaction of sulfone **6** and its homologs with cyclopentadiene, furan, furfural diethyl acetal, 1,3-cyclohexadiene, 1,2-bis(methylene)cyclohexane, and 2,3-dimethyl-1,3-butadiene.[19]



Scheme 42

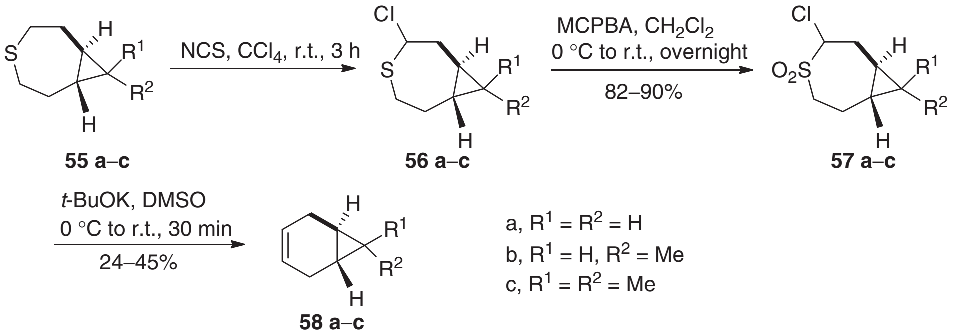
Medium-sized cycloalkenes can be prepared as well via the Meyers' modification of the RBR (Scheme 43).[75] This is especially important due to the fact that traditional ring-closure strategies which are effective for five- or six-membered systems are more problematic for medium or larger ring systems owing to the high transannular interactions and an unfavorable entropy factor. A more easily synthesized bicyclic intermediate system can overcome many of the enthalpic and entropic barriers associated with direct formation of the medium-sized ring. This approach employs the ring expansion of thioacetals, *O,S*-acetals, or its carbon analog under mild conditions. The reaction is believed to proceed via intramolecular alkylation of the nucleophilic heteroatom, to form a bicyclic sulfonium ion intermediate followed by Et_3N-induced E_2 process. The products, ring-expanded dithia-, thia-, or oxathia-derivatives, could be converted to the corresponding cycloalkenes by the Ramberg–Bäcklund reaction. A similar approach has been used for the preparation of useful medium-ring ether structures (see Section 3.18.1.7.2.2).[76]



1. Tf_2O, Py/CH_2Cl_2 (1:20), –78 °C, 15 min; 2. Et_3N, 35 °C, 48 h, 93%; 3. MCPBA, CH_2Cl_2, 0 °C; 4. KOH, *t*-BuOH, CCl_4, 80 °C, 58%.

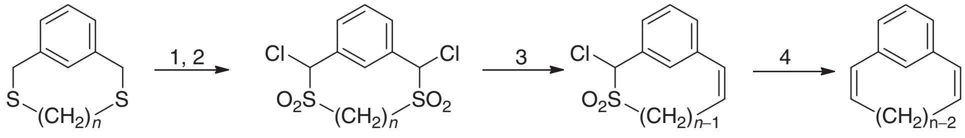
Scheme 43

The RBR was successfully applied to the synthesis of highly strained polycyclic hydrocarbons, *trans*-bicyclo[4.1.0] hept-3-ene derivatives **58**.[31] Treatment of the bicyclic sulfides **55** with NCS gave a quantitative yield of crude α-chloro sulfides **56** as very labile intermediates. Because of the instability of **56**, they were not purified but were immediately oxidized with *m*-chloroperbenzoic acid in methylene chloride to give the corresponding α-chloro sulfones **57** in 82–90% yields. In the case of sulfone **57b**, a mixture of diastereomers due to the presence of both epimers of the chloride was obtained and subjected to the Ramberg–Bäcklund ring contraction without separation of diastereomers. Treatment of the sulfones **57** with 5 equivalents of potassium *tert*-butoxide in DMSO gave 24–45% of distilled *trans*-bicyclo[4.1.0]-hept-3-enes **58** (Scheme 44).



Scheme 44

The application of the RBR for the conversion of several 3,*n*-dithiabicyclo[n.3.1]-alkatrienes to the corresponding bicyclo[n.3.1]-alkapentaenes was reported (Scheme 45).[77] The chlorination of 3,n-dithiabicyclo[n.3.1]-alkatrienes has been examined carefully in terms of the significance of this step in the synthesis of bridged system via RBR. It has been shown that chlorination had occurred, as expected, at the benzylic position with highly purified NCS. Unlike the data of Paquette[6] and Tuleen,[78] i.e., that geminal dihalogenation is enhanced by the introduction of the first halogen atom, since the α-hydrogen becomes more acidic, the same product, the bis-(α-chloroalkyl) sulfide, was obtained by the use of 2 or 4 equivalents of NCS. This may reflect the crowded nature of this cyclic system.



$n = 6, 7$

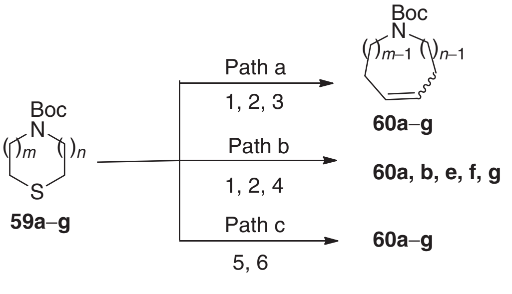
1. NCS, CCl_4, r.t., 2 h; 2. MCPBA, CH_2Cl_2, r.t., 48 h; 3. *t*-BuOK, DME, r.t.; 4. *t*-BuOK, THF, r.t., 21 h.

Scheme 45 Reproduced from Doomes, E.; McKnight, A. A. *J. Heterocycl. Chem.* **1995**, *32*, 1467–1471.

3.18.1.7.2.2 Synthesis of heterocyclic alkenes via ring contraction

The RBR is particularly attractive in terms of heterocyclic ring formation due to its general applicability, high yields, and mild reaction conditions. It has found broad application in the synthesis of medium-sized heterocycles and was extended to large flexible systems as well.

For example, a series of azacycles **60a–h** of varying sizes, ranging from 6 to 12 carbon atoms, were synthesized in this approach (Scheme 46).[79] The starting sulfides **59** were synthesized from their corresponding amino-alcohols and lactones following routine functional group manipulations and then were treated in several alternative ways. First, sulfides **59a–h** were converted to the α-chlorosulfides followed by oxidation by standard procedures[31] and each chlorosulfone was then treated with potassium *tert*-butoxide (path a) or aqueous KOH (path b) to generate alkenes **60**. Alternatively (path c), sulfides **59** were oxidized to the corresponding sulfones and then treated with alumina-supported KOH and dibromodifluoromethane according to the procedure developed by Chan.[13] The results of these transformations are presented in Table 2. The most striking feature is the dependence of the alkenes stereochemistry on both the nature of the base, and the ring size. When the Ramberg–Bäcklund reaction is done with *t*-BuOK, the *trans*-olefin is produced with high stereoselectivity for ring sizes 9–13 (olefins **60c–g**). Only the *cis*-olefins were formed for seven- and eight-membered rings (olefins **60a–b**), regardless of the conditions used. This is especially interesting since the *trans*-olefins are known to predominate on using *t*-BuOK (see Section 3.18.1.2). The yields for the formation of these smaller rings were consistently lower than those for the larger rings. The possible explanation involves severe transannular interactions encountered within the smaller rings when trying to adopt the required conformation for episulfone formation, thus facilitating side reactions. The larger ring sizes (compunds **60c–g**) showed a marked decrease in the stereoselectivity of the olefin formation when the base was changed to aqueous potassium hydroxide and give the *trans–cis* mixtures. In addition, the yields were also significantly decreased when compared to the potassium *tert*-butoxide values. The Chan modification of the RBR proved successful for synthesizing all ring sizes; however, it was not very useful in terms of stereoselectivity for larger rings. In conclusion, the use of *t*-BuOK in the RBR has been shown to be useful in introducing double bonds stereoselectively into azamacrocyclic systems.[79]



1. NCS, CCl_4, reflux, 3 h; 2. MCPBA, CH_2Cl_2, 0 °C to r.t., 18 h; 3. *t*-BuOK (4 equivalents)/THF, DMSO, r.t., 10 min; 4. 2 M aqueous KOH, reflux, 1–3 h; 5. MCPBA, CH_2Cl_2, 0 °C to r.t., 1 h; 6. KOH/Al_2O_3, CBr_2F_2, *t*-BuOH, 60–80 °C, 1 h.

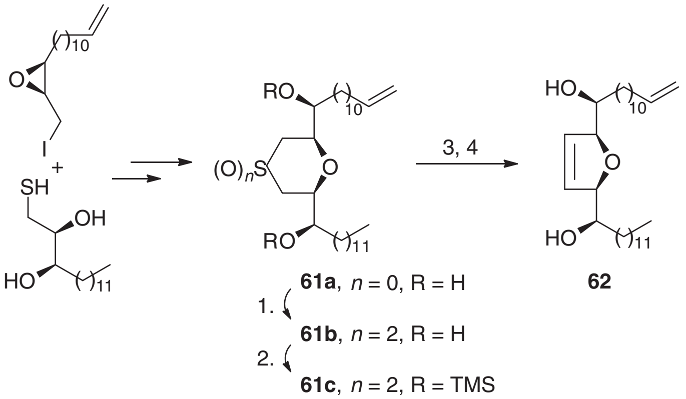
Scheme 46

The Ramberg–Bäcklund olefination protocol offers a very simple convergent strategy to the monotetrahydrofuranoid acetogenins when coupled to a ruthenium-catalyzed butenolide annulation.[34] In this convergent approach two approximately equal halves were joined via a RBR to form a 1,4-oxathiane **61a**. Under proper conditions, the latter does undergo the RBR to form a 2,5-dihydrofuran **62** (Scheme 47). It is important to note that chlorination of either **61a** or its corresponding sulfoxide have failed. Furthermore, the bis-TBDMS ether of **61** also fails to undergo α-chlorination. Chlorination of the bis-acetate of **61** with NCS

Table 2 Synthesis of medium and large azacycles via the RBR (Scheme 46)

Azacycle ***60***	*m*	*n*	*Base*	*Trans:cis ratio*	*Yield (%)*
a	2	2	*t*-BuOK	0:100	66
			aq KOH	0:100	43
			KOH/Al_2O_3	0:100	63
b	3	2	*t*-BuOK	0:100	41
			aq KOH	0:100	33
			KOH/Al_2O_3	0:100	33
c	3	3	*t*-BuOK	94:6	100
			KOH/Al_2O_3	65:35	59
d	3	4	*t*-BuOK	95:5	54
			KOH/Al_2O_3	60:40	67
e	4	4	*t*-BuOK	98: 2	97
			aq KOH	61:39	57
			KOH/Al_2O_3	73:27	68
f	4	5	*t*-BuOK	99:1	76
			aq KOH	62:38	70
			KOH/Al_2O_3	85:15	62
g	5	5	*t*-BuOK	94:6	93
			aq KOH	44:56	79
			KOH/Al_2O_3	61:39	53

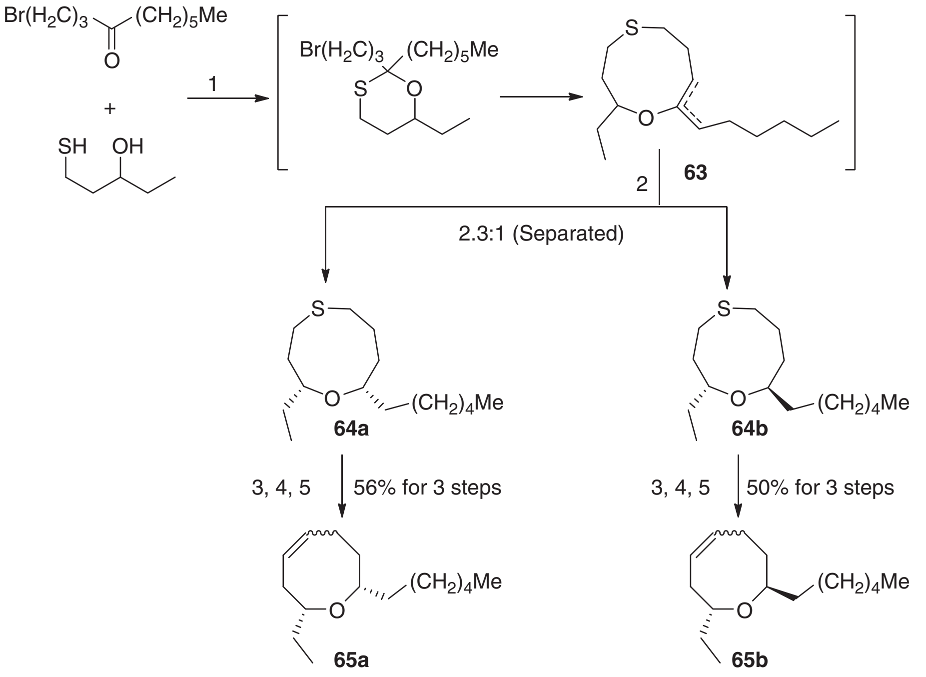
succeeded only in 2:1 benzene–hexane mixture. The best protocol invokes *in situ* chlorination-rearrangement of the corresponding sulfone **61c**, which required protection of the hydroxy groups as their silyl ethers, under standard Meyers conditions (Scheme 47).[34]



1. MCPBA, C_6H_6/hexane, 0 °C, 95%; 2. TMSCl, Py, CH_2Cl_2, 0 °C to r.t., 94%; 3. *t*-BuOK, *t*-BuOH, CCl_4, r.t., 65%; 4. TsOH, H_2O, EtOH, r.t., 95%.

Scheme 47

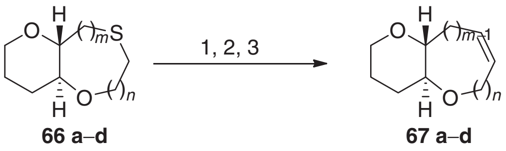
A reaction sequence which involves the ring expansion of halo-*O*,*S*-acetals followed by the Ramberg–Bäcklund ring contraction represents a concise strategy for the synthesis of medium-ring ethers.[76] Medium-ring ethers are widespread in nature, occurring in red algal metabolites such as laurencin and laurenyne and as substructures of various toxins, such as the brevetoxins and ciguatoxins. This methodology has been utilized for the synthesis of racemic *cis*- and *trans*-lauthisan. Medium rings are generally difficult to synthesize via standard cyclization methodologies due to many of the enthalpic and entropic barriers associated with direct formation of the medium-sized ring. More easily synthesized intermediate bicyclic system can overcome such difficulties. This approach employs the ring expansion of halo-*O*,*S*-acetals under mild conditions. The reaction is believed to proceed via intramolecular alkylation of the nucleophilic heteroatom, to form a bicyclic sulfonium ion intermediate. Removal of the α-proton by Et_3N initiates fragmentation to afford the corresponding ring-expanded thioenol ether **63** *in situ*. Reduction of **63** led smoothly to the corresponding saturated ethers **64a** and **64b**. The product oxathia-cycloalkanes **64** could be converted to useful medium-ring ether structures **65** by Ramberg–Bäcklund reaction widely used in the synthesis of strained cyclic systems. A number of methods for the production of the desired α-chloro sulfone from the sulfides **64** were successful, however, reaction of **64a** or **64b** with NCS followed by sulfur oxidation with *m*-CPBA to yield a mixture of all four possible α-chloro sulfones was found to be the most efficient and convenient. The RBR of the α-chloro sulfone proceeded smoothly with *t*-BuOK to yield the desired alkenes **65a** or **65b**, respectively, as approximately 9:1 mixtures of (*Z*)- and (*E*)-double-bond isomers (56%, three steps) (Scheme 48). The predominance of the (*Z*)-isomer is in line with the selectivity normally seen for this rearrangement, but production of the (*E*)-isomer is not surprising, as the reaction has been well utilized in the synthesis of strained systems. The (*E*)-isomer was found to isomerize rapidly to the (*Z*)-form in $CDCl_3$ which had not been pretreated with basic alumina to remove acid. Hydrogenation of alkenes **65a** and **65b** provided *cis*- and *trans*-lauthisan, respectively. The described ring expansion–ring-contraction sequence should be amenable to the generation of 7- to 10-membered cyclic ethers, by adjusting the length of the halo-alkyl chain and suitable choice of either oxathiane or oxathiolane systems. Additionally, the use of enantiomerically enriched mercapto-alcohols, would lead to enantioselective syntheses of medium-ring ether compounds.[76]



1. $BF_3 \cdot Et_2O$, CH_2Cl_2, 3 Å molecular sieves, 2 h; then Et_3N, 1 h; 2. $NaBH_3CN$, TFA, THF,15 min, 49%; 3. NCS, CCl_4, 0 °C, 4–6 h; 4. MCPBA, CH_2Cl_2, 0–2 °C, 16 h; 5. *t*-BuOK, THF, 0 °C, 4–16 h.

Scheme 48

The RBR provided a good approach to the synthesis of a number of *trans*-fused unsaturated oxabicycles **67**.[80] According to this strategy, cycloalkenes **67** were generated by standard thioannulation procedures[80] from the *O*-linked acyclic precursor via sulfur connection to form the 1,*n*-oxathianes **66** followed by successive α-halogenation, oxidation at sulfur, and SO_2-extrusion (Scheme 49). Oxathiacycles **66a–c** were obtained as single isomers in good yields, whereas the formation of compound **66d** (40% yield) was accompanied by the formation of the corresponding dimer (40%) and trimer (12%). Since the intermediate α-chloro sulfides and α-chloro sulfones were formed as mixtures of regio- and stereoisomers, it was convenient to use them in a crude form, and to withhold purification until the RBR itself has been completed. In the case of compound **67d**, where the size of the unsaturated ring allows the possibility of *cis*- and *trans*-geometry of the double bond, a *cis:trans* mixture was obtained.



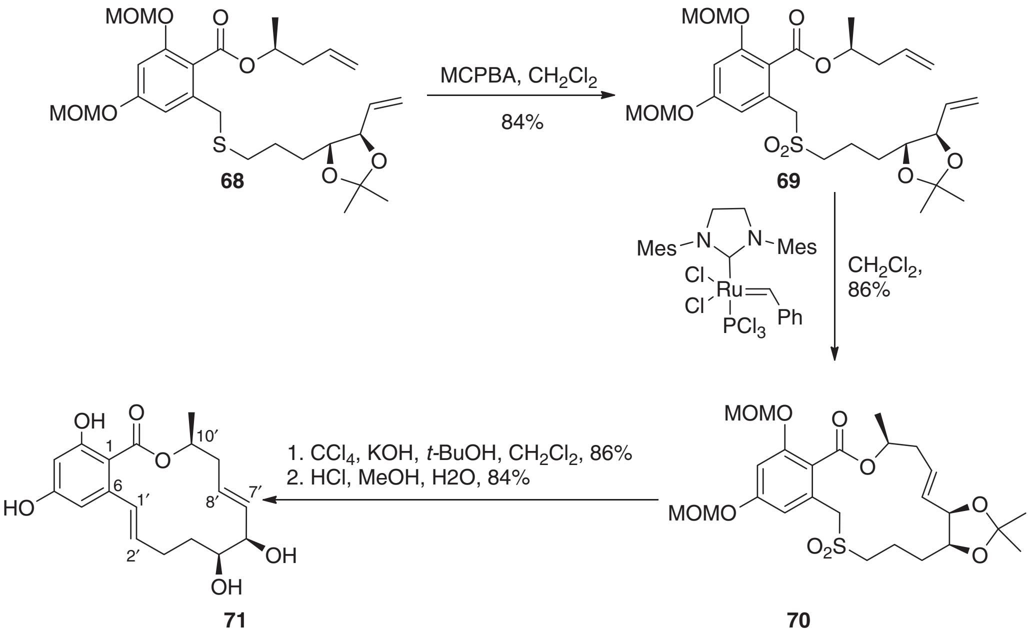
66, 67 a; $m = n = 1$, 40%
66, 67 b; $m = n = 2$, 41%
66, 67 c; $m = 1$, $n = 2$, 37%
66, 67 d; $m = 1$, $n = 3$, 48%

1. NCS (1.5 equivalents), CCl_4, 0 °C, 4–5 h; 2. MCPBA (1.5 equivalents), CH_2Cl_2, 0–2 °C, 8–10 h; 3. *t*-BuOK (1.2 equivalents), THF, 0 °C, 4–5 h.

Scheme 49

3.18.1.7.2.3 Synthesis of macrocycles, paracyclophanes, and related systems via the Ramberg–Bäcklund ring contraction

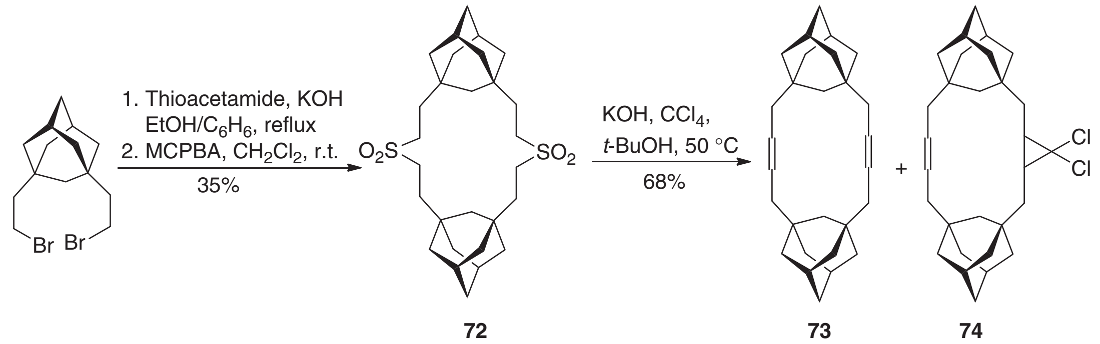
A combination of RCM and the RBR has been applied to the synthesis of the macrocyclic bioactive resorcylic acid lactone aigialomycin D **71**.[81] The same synthetic protocol, a combination of RBR with ring-closing metathesis, has previously been applied to the synthesis of cyclohexadienes and cycloheptadienes.[74] This synthetic strategy enables the C1′–C2′ alkene to be masked as a sulfone during formation of the macrocycle by ring-closing metathesis at the C7′–C8′ olefin, thus avoiding competing formation of a cyclohexene. A subsequent RBR efficiently produces the C1′–C2′ *E*-alkene. The sulfone substrate for the Meyers-modified RBR represents a masked alkene, a property that can be exploited in an RCM-based synthesis of macrocyclic dienes. The key steps of this reaction sequence are presented on the Scheme 50.[81] Oxidation of the thioether **68** to the corresponding sulfone **69** was performed using *m*-CPBA (Scheme 50). The desired sulfone was isolated in 84% yield, and only traces of alkene epoxidation products were observed during this process. Macrocycle formation by RCM proceeded smoothly and rapidly under microwave irradiation, the reaction being completed in 30 min with heating up to 75 °C. The 15-membered sulfone **70** was isolated in 86% yield, with only the *E*-alkene isomer being observed. The macrocyclic sulfone **70** was subjected to a RBR using Meyers' conditions, which proceeded efficiently with no discernible side products. The corresponding 14-membered *E*-alkene was isolated in 84% yield, with no indication of *Z*-isomer formation. The stereoselectivity observed here is of particular interest because high stereocontrol is not a guaranteed feature of the RBR in nonconstrained systems. Final deprotection of this macrocycle gave aigialomycin D **71** in 86% yield.



Scheme 50

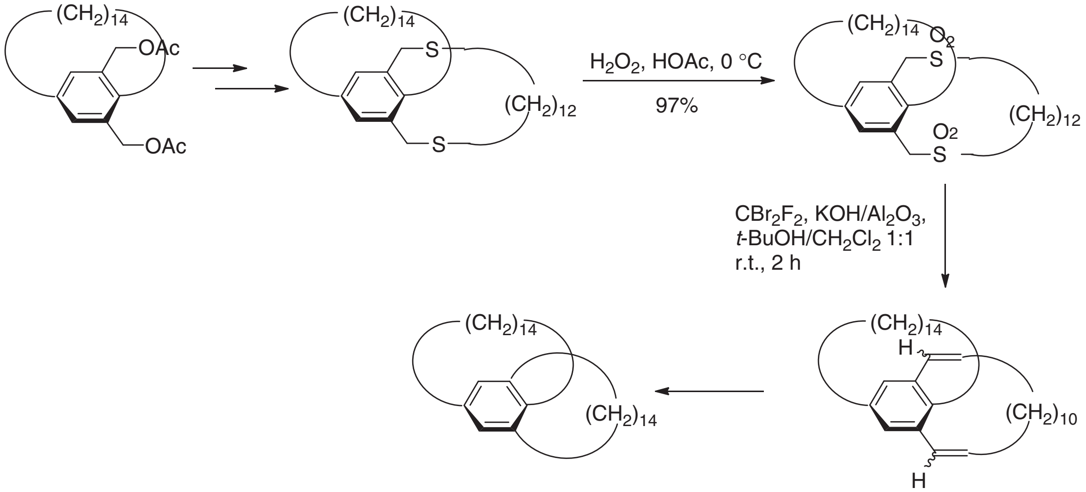
One of the first synthetic methodologies leading to completely aliphatic adamantane-containing phane molecules involves the use of intermolecular sulfur-based cyclocoupling in conjunction with the Meyer's modification of the RBR.[49] This synthetic approach provides a straightforward entry to various [m.n.]adamantanophanes, as it was demonstrated by the synthesis of [4.4](1,3)adamantanophandienes **73** (Scheme 51). Intermolecular cyclization of readily available 1,3-bis(2-bromoethyl)-adamantane with thioacetamide gave a macrocyclic thioether which was subsequently oxidized with *m*-CPBA to give disulfone **72** in 95% yield. The Ramberg–Bäcklund ring contraction of disulfone **72** afforded a mixture of stereoisomeric adamantanophanes **73** and the corresponding *gem*-dichlorocyclopropane derivative **74**. The major product 4,6:11,13-di(1,3-adamantano)cyclotetradeca-*trans*, *trans*-1,8-diene was isolated from the mixture by column chromatography and unambigously identified by X-ray crystallography.

Unlike the other members of cyclophane family, the synthesis of [m][n]metaparacyclophanes presented considerable synthetic challenges on account of the difficulties anticipated in the assembly of the respective contiguous three- and four-point bridgehead attachments in them. The Chan's modification of the Ramberg–Bäcklund reaction, which was previously applied for the synthesis of various optically active [m][n]paracyclophanes (see Scheme 25, Section 3.18.1.6.1),[52] was also successful in the first synthesis of [m][n]metaparacyclophane.[82] The reaction sequence began with the bis-chloromethylation of [14]paracyclophane in refluxing CS_2, which yielded a nonseparable mixture of 16,19- and 16,20-bis(chloromethyl)-[14]paracyclophane in an 8:1 ratio. Acetolysis of these dichlorides gave the corresponding diacetate mixture from which the minor component 16,20-bis(acetoxymethyl)[14]-paracyclophane was isolated and elaborated into the desired cyclophane via cyclocoupling with 1,12-dodecanedithiol, oxidation to the disulfone of 2,15-dithia[16][14]metaparacyclophane and subsequent sulfur dioxide extrusion



Scheme 51 Reproduced from Mlinaric-Majerski, K.; Pavlovic, D.; Marinic, Z. *Tetrahedron Lett.* **1996**, *37*, 4829–4832.

by a one-flask Ramberg–Bäcklund procedure[13] followed by hydrogenation (Scheme 52). It should be noted that though Vögtle's one-step pyrolytic sulfur dioxide extrusion methodology[83] continues to be a powerful synthetic tool for the synthesis of small and medium-sized cyclophanes, for the assembly of a long cyclophane bridge, above two-step sequence for the removal of the sulfone functionalities by the combination of a one-flask Ramberg–Bäcklund reaction and hydrogenation offers a convenient alternative, that allows one to avoid the use of a rather sophisticated pyrolysis apparatus.



Scheme 52

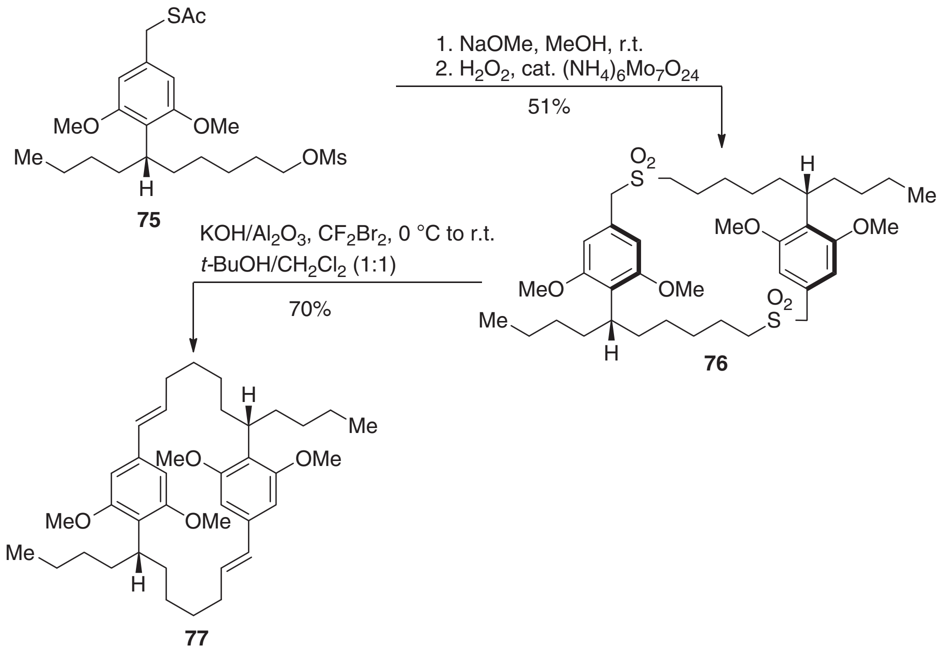
Chan's modification of the Ramberg–Bäcklund reaction provided an effective approach for the preparation of one more member of cyclophane family, naturally occurring cylindrocyclophanes.[84] This approach involves head-to-tail dimerization followed by the Ramberg–Bäcklund reaction to generate [7.7]paracyclophane intermediate **77**. Thus, the crucial cyclodimerization of **75** was brought about by treatment with NaOMe in MeOH at ambient temperature and afforded the corresponding macrocyclic bis(thioether), whose oxidation with H_2O_2 in the presence of $(NH_4)_6Mo_7O_{24} \cdot 4\,H_2O$ furnished macrocyclic bis(sulfone) **76** in 51% overall yield. Treatment of sulfone **76** with alumina-impregnated KOH (KOH/Al_2O_3) in the presence of CF_2Br_2 in CH_2Cl_2/*t*-BuOH (1:1) at 0–23 °C led to the expected bis(olefin) **77** in 70% yield (approximately *E,E*/*E,Z*=12:1 before complete isomerization to *E,E*-**77** with $[Pd(CH_3CN)_2Cl_2]$) (Scheme 53). The latter was then converted into cylindrocyclophanes A and F.

An application of the Ramberg–Bäcklund reaction to the synthesis of the numerous cyclophane systems that have one or more double bonds in their bridges was reviewed just recently.[85]

3.18.1.7.3 Synthesis of conjugated dienes, polyenes, enynes, and diynes

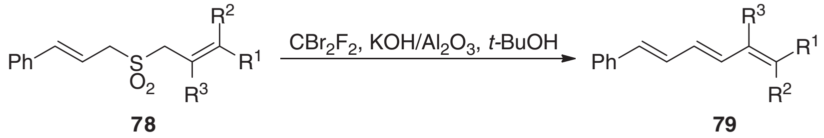
Diallyl sulfones can undergo facile transformation into conjugated trienes under Meyers or Chan modification of the RBR.[86] Usually, the reactions proceed with retention of the geometry of preexisting double bonds and prevailing *E*-geometry of the newly generated double bond. However, certain exceptions are known.

Thus, starting from geometrically pure diallyl sulfones **78**, various conjugated 1,3,5-hexatrienes **79**, an important structural unit in a variety of natural products such as phytoene, vitamins D_2 and D_3, leukotrienes B_4 and C_4, asukamicin and mocimycin, have been prepared by the Chan modification of the RBR (Scheme 54).[87] It is important to note that the stereoselectivity of this



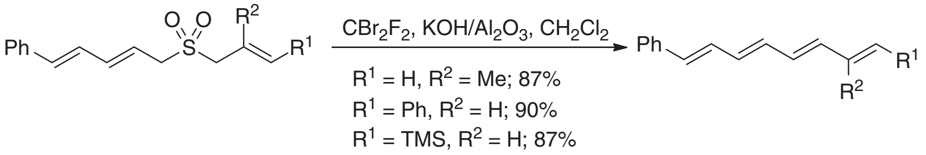
Scheme 53 Reproduced from Nicolaou, K. C.; Sun, Y.-P.; Korman, H.; Sarlah, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 5875–5878.

reaction is dependent on the reaction conditions, and that it is possible to maintain a high level of stereocontrol in the formation of 1,3,5-trienes by appropriate choice of solvent and temperature. Thus, the (*Z*,*E*,*Z*)-triene isomer could be isolated in a 91:9 ratio in favor of the (*Z*,*Z*,*Z*)-isomer when the reaction was conducted at -78 °C in *t*-BuOH-CBr_2F_2 (1:1) solution, starting from the di-(*Z*)-cinnamyl sulfone. However, when methanol was employed as the solvent, only the corresponding (*1E*,*3E*,*5E*)-triene was obtained, indicating a substantial loss of the stereointegrity of the terminal double bonds.



Scheme 54

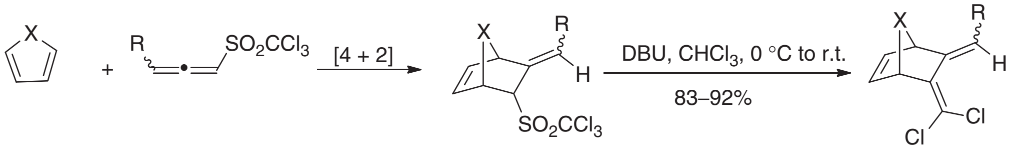
This methodology can be extended for the preparation of all-*trans* 1,3,5,7-octatetraenes in excellent yields from allylic dienylic sulfones (Scheme 55).[88] Here, again, the double bonds of stereochemically defined allylic dienylic sulfones retain their stereochemistry and the newly formed double bond has an (*E*)-configuration.



Scheme 55

Exo-cyclic double bond was introduced into bi- and monocyclic cyclohexene systems to prepare cisoid dienes by a facile amine-catalyzed RBR of allylic trichloromethyl sulfones (Scheme 56).[89] This method involves the conversion of the trichloromethyl sulfonyl group to 1,1-dichloroalkene. The [4 + 2] cycloaddition reaction of trichloromethane sulfonyl allene with conjugated dienes gives Diels–Alder adducts which then were subjected to the RBR in dry chloroform in the presence of DBU as a base. Interesting to note, exposure of trichloromethyl sulfones to an aqueous alkali condition invariably leads to a mixture of products and the yield of the expected 1,1-dichloroalkene is often low.[90]

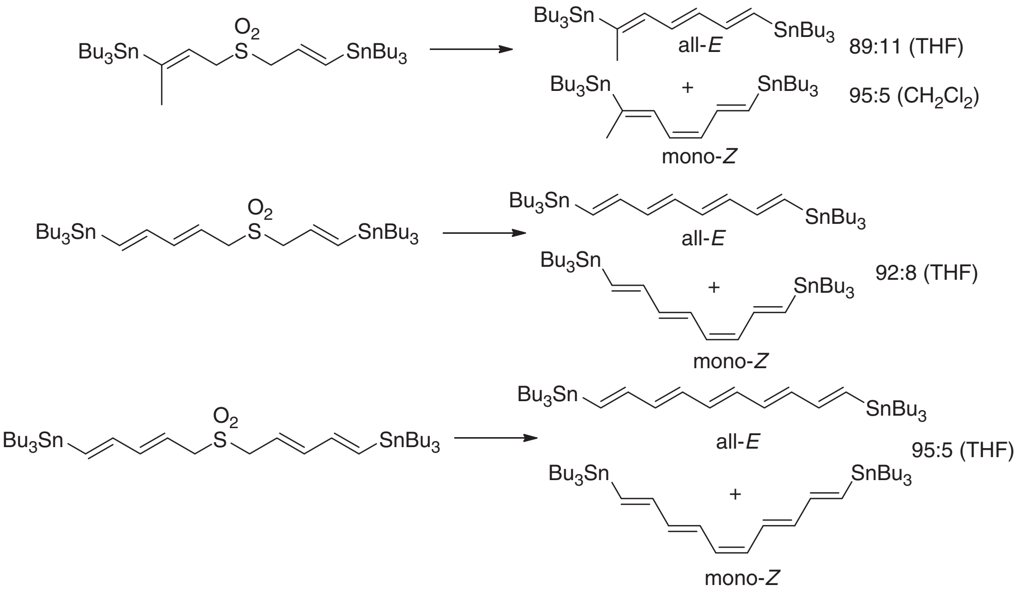
Interesting applications of the RBR in the stereoselective synthesis of functionalized extended polyenes are reported. Thus, a family of 1,ω-bis(tributylstannylated) conjugated trienes, tetraenes, and pentaenes has been prepared by this approach and merits interest as bifunctional reagents for three-component Stille coupling reactions.[91] The all-*E*- or mono-*Z*-configured



X = CH_2, R = H; X = CH_2, R = Ph; X = O, R = H; X = CH_2CH_2, R = H.

Scheme 56

1,6-bis(tributylstannyl)hexa-1,3,5-trienes, 1,6-bis(tributylstannyl)octa-1,3,5,7-tetraenes, and 1,10-bis(tributylstannyl)deca-1,3,5,7,9-pentaene, were accessible through using the RBR as a key step. Their central C=C bond was established by RBRs in THF with moderate to good *E* selectivities, whereas Julia olefinations resulted in very good *Z* selectivities. The *E* selectivities were improved by up to all-*E*/mono-*Z* ratio=94:6–100:0 by conducting the Ramberg–Bäcklund reaction in CH_2Cl_2 rather than in THF, albeit at the cost of up to 5% protonolysis of the less-hindered C–$SnBu_3$ bond (Scheme 57).

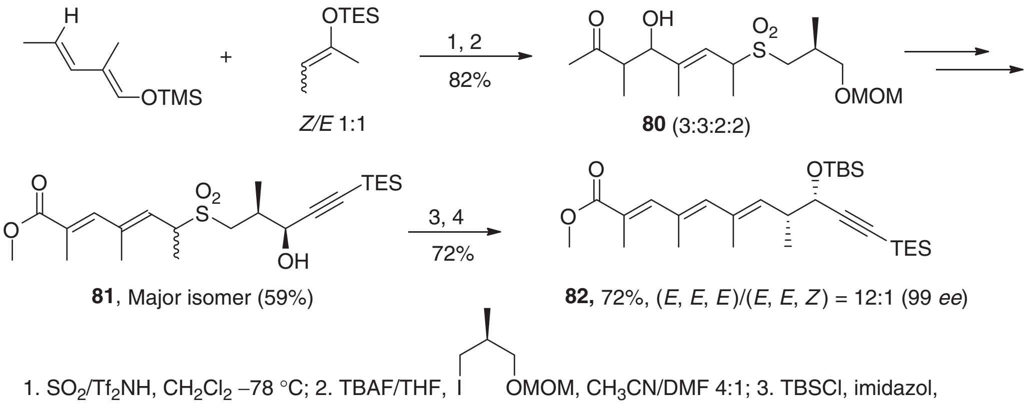


Reaction conditions: CBr_2F_2 (4 equivalents), KOH (33% on Al_2O_3, 10 equivalents), THF or CH_2Cl_2, 0 °C for 15 min, r.t. for 30 min.

Scheme 57

The Ramberg–Bäcklund reaction was the key step for the preparation of the conjugated (*E*,*E*,*E*)-triene unit of apoptolidin,[92] one of the most selective cytotoxic agents. The quick construction of its enantiomerically enriched C(1)–C(11) fragment has been performed in only seven steps and with an overall yield of 22%.[92] The reaction sequence has been started from the addition of SO_2 to trimethylsilyloxy-1,3-pentadiene in the presence of a catalytic amount of bistrifluoromethanesulfonimide as an acid promoter, and a 3:2 mixture of (*Z*/*E*-triethylsilyloxy-2-butene followed by the reaction of thus obtained silyl sulfinate intermediate with the iodo derivative to give a 3:3:2:2 mixture of the corresponding (*3RS*,*4RS*,*5E*,*7RS*,*2S*)-sulfones in 82% yield. The introduction of alkyne moiety before the Ramberg–Bäcklund reaction afforded free alcohol **80** as a 3:3:1:1 mixture of four diastereoisomers, from which 2 major *syn*-diastereoisomers **81**: *2E*,*4E*,*6RS*,*2′R*,*3′S* were isolated with the yield of 59%. Protection of the free alcohol of **81** provided the corresponding TBS ethers which were directly added to a suspension of KOH/Al_2O_3 in CH_2Cl_2, at − 10 °C. Subsequent heating to 40 °C for 12 h induced the Ramberg–Bäcklund reaction (Scheme 58). After purification by flash chromatography on silica gel, a 12:1 mixture of the desired (*E*,*E*,*E*)-triene (+)-**82** and its (*E*,*E*,*Z*)-isomer was isolated in 72% yield (99% *ee*).[92]

The Ramberg–Bäcklund reaction was used as the key process for the construction of monocyclic conjugated enediynes related to the natural anticancer antibiotics calicheamicin and esperamicin.[29] The reaction sequence applied for the synthesis of the 10-membered ring enediyne and its homologs is presented on Scheme 59. Treatment of the corresponding cyclic dipropargylic chlorosulfones with potassium *tert*-butoxide gave the desired enediynes in 32–52% isolated yields. Attempts to construct these ring systems via the palladium-catalyzed coupling of terminal acetylenes with vinyl halides have failed.



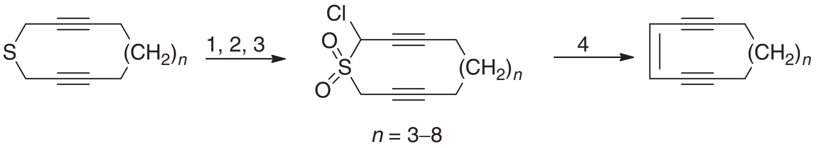
80 (3:3:2:2)

81, Major isomer (59%)

82, 72%, (*E*, *E*, *E*)/(*E*, *E*, *Z*) = 12:1 (99 *ee*)

1. SO_2/Tf_2NH, CH_2Cl_2 –78 °C; 2. TBAF/THF, I OMOM, CH_3CN/DMF 4:1; 3. TBSCl, imidazol, DMF, 20 °C, overnight; 4. KOH/Al_2O_3, CBr_2F_2, CH_2Cl_2, 0 °C to 40 °C for 14 h.

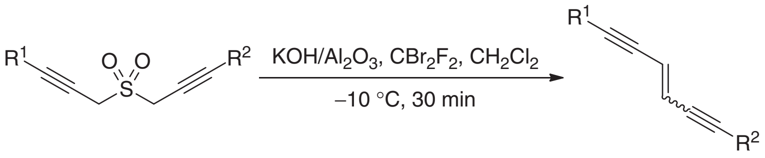
Scheme 58



1. MCPBA, CH_2Cl_2, –78 °C; 2. SO_2Cl_2, pyrydine, CH_2Cl_2, –78 °C; 3. MCPBA, CH_2Cl_2, –78 °C; 4. *t*-BuOK (1.2 equivalents), THF, –78 °C.

Scheme 59

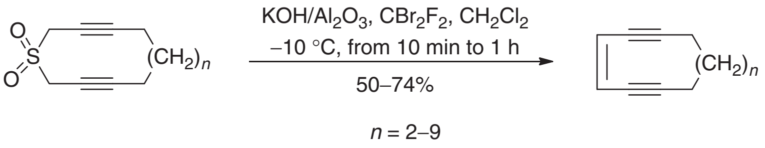
Dipropargylic sulfones has also been converted to the corresponding enediyne unit without the necessity to prepare an α-halo dipropargyl sulfone precursor in a separate step under Chan's modification of the RBR and thus provided an easy entry to readily separable (*E*)- and (*Z*)-hex-3-ene-1,5-diynes in good yields (Scheme 60).[93] It is noteworthy that the previously described protocol, CBr_2F_2, KOH/Al_2O_3, *t*-BuOH, invariably led to intractable reaction mixtures, indicating the unsuitability of a protic solvent for these sulfone substrates. However, when CH_2Cl_2 was used in place of *t*-BuOH, the reaction proceeded smoothly at -10 °C to give a readily separable mixture (~1:1) of the (*E*)- and (*Z*)-enediynes.



R^1	R^2	Yield (%)	
		E	*Z*
H	*t*-Bu	33	27
H	*n*-C_5H_{11}	43	37
Ph	H	49	45
n-C_5H_{11}	Ph	33	27
t-Bu	Ph	43	47
n-C_5H_{11}	*n*-C_5H_{11}	41	40
Ph	Ph	40	40

Scheme 60

The above one-pot methodology was extended to the synthesis of conjugated cyclic enediynes (Scheme 61).[68] The latter were prepared with the yields somewhat higher than those obtained via preformed α-halosulfones.[29]



Scheme 61

3.18.1.7.4 Application of the Ramberg–Bäcklund rearrangement in natural products and bioactive molecules synthesis

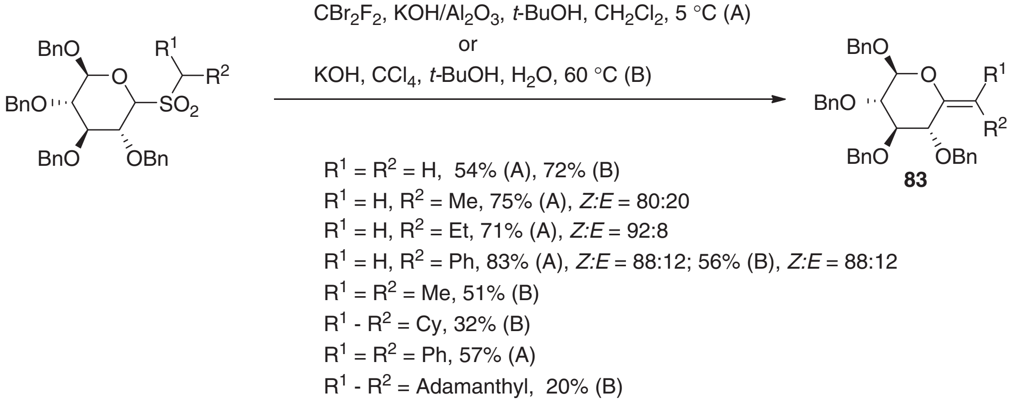
The utility of the RBR in the preparation of complex polyfunctional natural products has received wide recognition by scientific community especially due to the wide scope of the RBR in terms of substrates and complete regiocontrol regarding to alkene construction as well. A number of applications of the reaction in natural product synthesis and related areas, mainly published recently, are discussed here. Obviously, attention is concentrated on the RBR as the key process and the complete synthetic information can be found in the original literature.

3.18.1.7.4.1 Application of the Ramberg–Bäcklund rearrangement in carbohydrate chemistry

Application of the RBR for the preparation of *exo*-glycals from easily available *S*-glycoside dioxides was simultaneously developed by the groups of Franck[94] and Taylor.[95] *exo*-Glycals are unsaturated sugars that have a double bond attached to the anomeric center outside the sugar ring. These carbohydrate molecules are useful precursors for the synthesis of *C*-glycosides and compounds containing quaternary carbons, provided that the olefins can be properly reduced or functionalized. The method was successful with a number of sugar derivatives including glucose, galactose, mannose, xylose, fucose, ribose, altrose, and daunosamine derivatives.

The subject was thoroughly reviewed.[96–98]

In general, this approach involves the conversion of readily available furanose and pyranose systems into the corresponding protected aryl or alkyl thioglycosides and then to *S*-glycoside dioxides. The Meyers or Chan variant of the Ramberg–Bäcklund reaction using these sulfones would be expected to produce the corresponding *exo*-glycals. A range of *exo*-glycals **83** (all with the *Z*-alkene predominating) were prepared using this RBR methodology (Scheme 62).[95,99] The conversion of sulfones derived from glucose, galactose, mannose, cellobiose, and ribose into di-, tri-, and tetra-substituted alkenes under Meyers variant of the RBR was reported.[99] The availability of highly hindered glycals, particularly adamantene derivative is noteworthy. The compatibility of other than benzyloxy protecting groups with the Ramberg–Bäcklund conditions was explored as well as the ability to remove the hydroxyl protecting groups without reducing or hydrolysing the enol ether moiety.[100] The RBR of *S*-glycosides dioxides, protected by *t*-butyldimethylsilyl (TBDMS) groups proceeded smoothly; desilylation was accomplished using tetrabutylammonium fluoride (TBAF).[99]



CBr_2F_2, KOH/Al_2O_3, *t*-BuOH, CH_2Cl_2, 5 °C (A)
or
KOH, CCl_4, *t*-BuOH, H_2O, 60 °C (B)

$R^1 = R^2$ = H, 54% (A), 72% (B)
R^1 = H, R^2 = Me, 75% (A), *Z:E* = 80:20
R^1 = H, R^2 = Et, 71% (A), *Z:E* = 92:8
R^1 = H, R^2 = Ph, 83% (A), *Z:E* = 88:12; 56% (B), *Z:E* = 88:12
$R^1 = R^2$ = Me, 51% (B)
R^1 - R^2 = Cy, 32% (B)
$R^1 = R^2$ = Ph, 57% (A)
R^1 - R^2 = Adamanthyl, 20% (B)

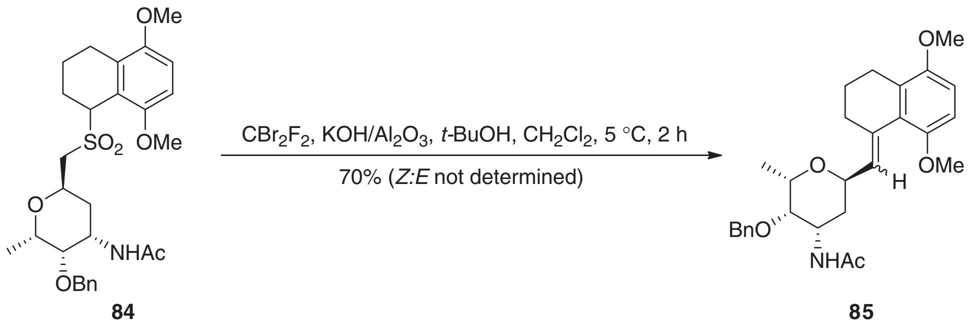
Scheme 62

Good illustration of the RBR approach in the sugar chemistry is the preparation of the *C*-glycoside of daunomycin **85**.[94] In this example, the *S*-glycoside of daunosamine is not used; the daunosamine was instead functionalized as the axial-1-hydroxymethyl compound. Then the hydroxymethyl derivative was converted via the 1-iodomethyl *C*-glycoside to the required thioether in 85% yield before the Ramberg–Bäcklund chemistry. The daunomycin *C*-glycoside analog **85**, was obtained after oxidation of thioether with monoperoxyphthalic acid (MMPP) to the sulfone **84** followed by RBR under the standard Chan conditions (Scheme 63).

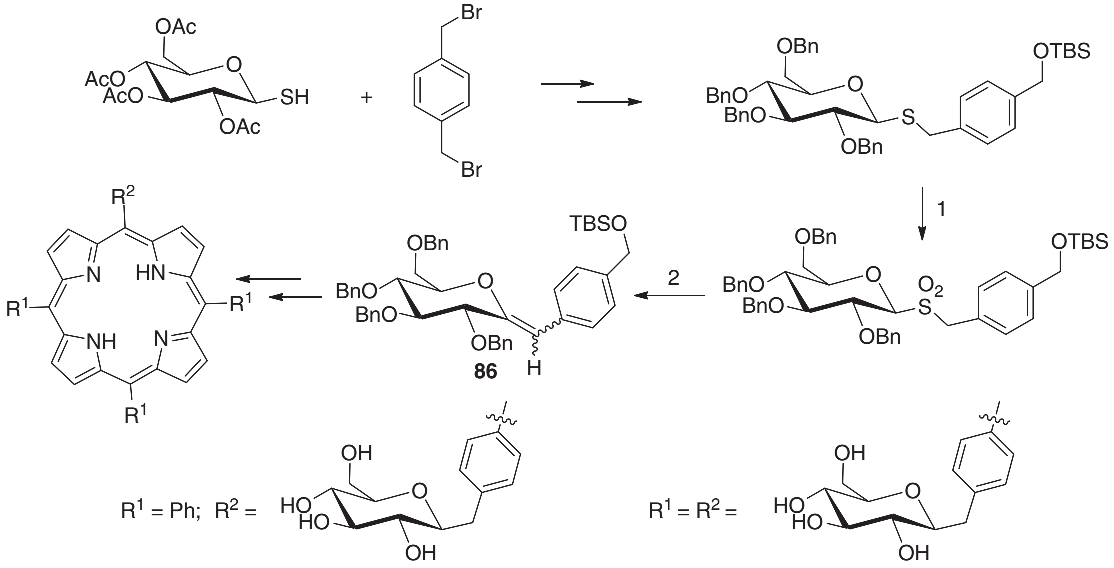
The RBR under Chan's conditions has been applied to the synthesis of *exo*-glycal **86**, which in turn was used as a key intermediate in the preparation of hydrolytically stable porphyrin systems (Scheme 64).[101]

Ramberg–Bäcklund methodology was also used to prepare the spirocyclic sugars, which are simplified analogs of natural products such as papulacandin D.[100,102] The benzylated thioglucose derivative **87** was alkylated giving the corresponding sulfide, which was oxidized to sulfone, both steps proceeding in good yield. The Ramberg–Bäcklund reaction proceeded smoothly on the unprotected alcohol using Chan's CBr_2F_2 conditions giving *exo*-glycal **88** in 74% yield. Cyclization of the latter by treatment with camphorsulfonic acid in methanol produced a separable mixture of spiroacetals (30:70) in 75% yield (Scheme 65).

The *exo*-glycal approach has been applied for the preparation of the C-10 *exo*-olefinated deoxoartemisinin derivatives, synthetic analogs of natural sesquiterpene endoperoxide artemisinin.[103,104] Since the C-10 position of the dihydroartemisinin, cyclic hemiacetal, can be regarded as a sugar-anomeric center, an effective method for target compounds by using the RBR of *S*-glycoside dioxides to 1-*exo*-alkylidene glycals was developed. The reaction of dihydroartemisinin with the corresponding thiol in the presence of $BF_3 \cdot Et_2O$ gave a separable mixture of stereoisomeric thioacetal dihydroartemisinins with a C-10α (major isomers),

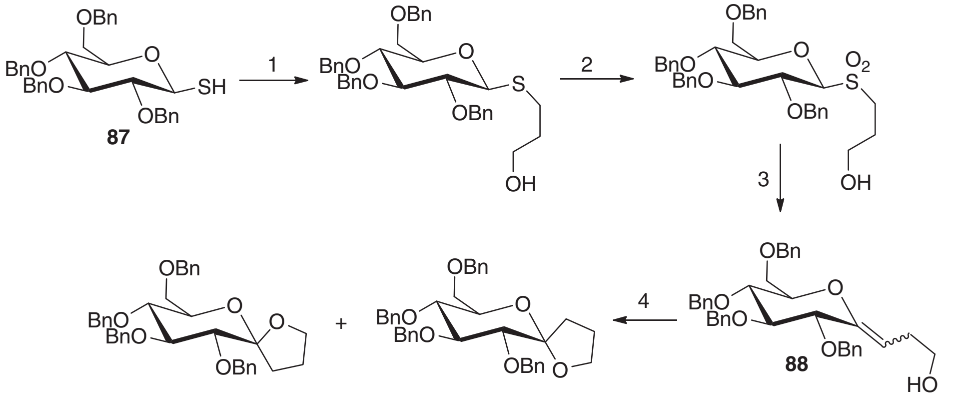


Scheme 63



1. MMPA, THF-EtOH-H_2O, 60 °C, 2 h, 87%; 2. CBr_2F_2, KOH/Al_2O_3, *t*-BuOH, CH_2Cl_2, 0 °C to r.t., 88%.

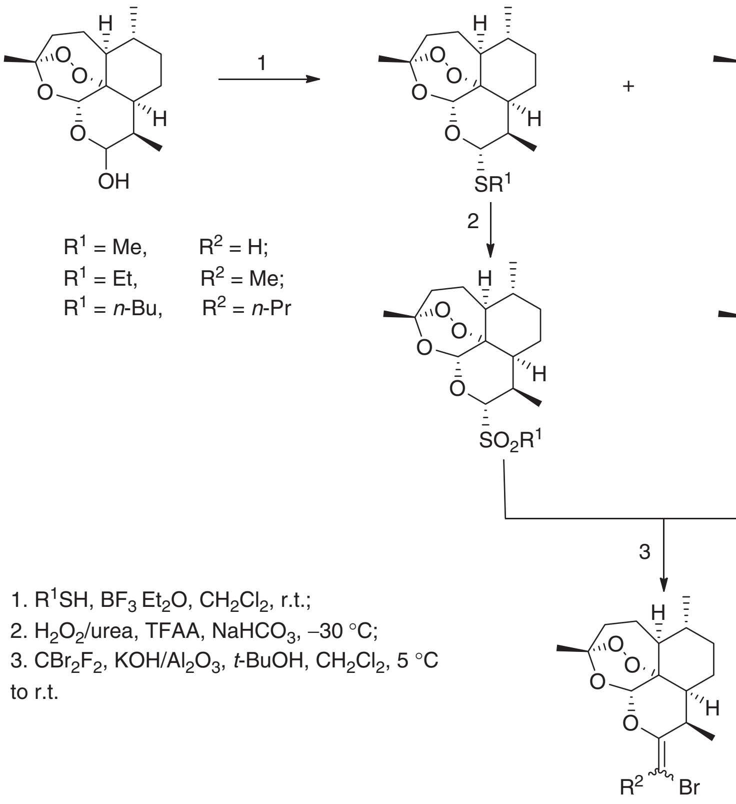
Scheme 64



1. $Cl(CH_2)_3OH$, K_2CO_3, acetone, 75%; 2. MCPBA, CH_2Cl_2, Na_2HPO_4, 82%; 3. CBr_2F_2, KOH/Al_2O_3, *t*-BuOH, CH_2Cl_2, 74% (*Z*:*E* = 80 : 20); 4. CSA, MeOH, 75%.

Scheme 65 Reproduced from Nicolaou, K. C.; Sun, Y.-P.; Korman, H.; Sarlah, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 5875–5878.

and C-10β (minor isomers) stereochemistry. Continuous oxidation reaction of each purified thioacetal compounds with H_2O_2/urea (UHP), trifluoroacetic anhydride (TFAA), and $NaHCO_3$ produced 10α- and 10β-substituted sulfonyl dihydroartemisinins, respectively. *exo*-Olefination of these deoxoartemisinin derivatives under the modified RBR conditions gave a *E* and *Z* mixture of 10-bromo-alkenylidene deoxoartemisinins (**Scheme 66**).[103,104] The streoselectivity of *exo*-olefination was greatly improved when longer alkyl chains were used. 10-(1-Bromobutylidene)deoxoartemisinin ($R^1=n$-Bu, $R^2=n$-Pr) was formed with a high stereoselectivity (*E*/*Z*) 92:8) and yield (84%) from 10α-*n*-butanesulfonyl dihydroartemisinin.

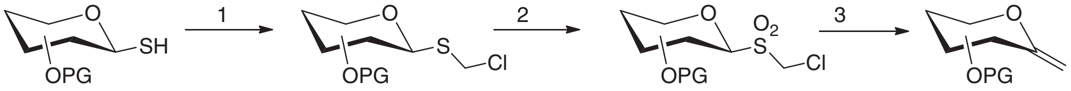


R^1 = Me, R^2 = H;
R^1 = Et, R^2 = Me;
R^1 = *n*-Bu, R^2 = *n*-Pr

1. R^1SH, $BF_3\,Et_2O$, CH_2Cl_2, r.t.;
2. H_2O_2/urea, TFAA, $NaHCO_3$, –30 °C;
3. CBr_2F_2, KOH/Al_2O_3, *t*-BuOH, CH_2Cl_2, 5 °C to r.t.

Scheme 66

An alternative approach to the synthesis of methylene *exo*-glycals (the simplest version of *exo*-glycals) using the classical RBR was described.[105] This efficient procedure was based on glycosylthiomethyl chlorides, which could be readily prepared from the corresponding glycosyl thiol by the reaction with dichloromethane under the action of DBU. Obviously, nonbase-labile protecting groups were used to protect these sugar thiols. Methyl-, benzyl-, isopropylidene-, or benzylidene-protected glycosyl thiols were all efficiently converted into the corresponding glycosylthiomethyl chlorides in good to high yields (70–86%). Oxidation with *m*-chloroperoxybenzoic acid followed by treatment of these glycosylchloromethyl sulfones with excessive $KOBu^t$ in DMSO gave rise to the desired *exo*-methylenic sugars in high yields (**Scheme 67**). The reaction proceeded very cleanly without any by-product formation observed.



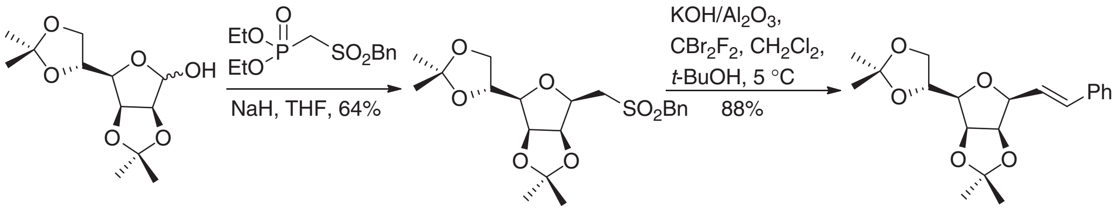
PG = Protecting group

1. DBU, CH_2Cl_2, r.t., overnight, 70–86%; 2. MCPBA, CH_2Cl_2, 92–99%; 3. *t*-BuOK, DMSO, r.t., 4 h, 81–94%.

Scheme 67

The use of $C_2Br_2F_4$ in the Ramberg–Bäcklund reaction in place of Chan's original CBr_2F_2 should be noted. The higher boiling point ($C_2Br_2F_4$, bp 47 °C, cf. CBr_2F_2, bp 23 °C) allows many RBR that would otherwise be difficult at lower temperatures.[64,106,107]

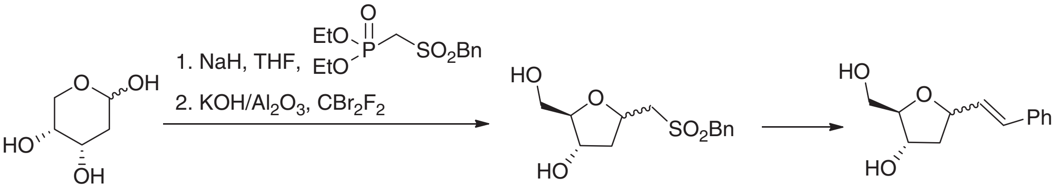
A stream-lined Ramberg–Bäcklund approach to *C*-glycosides, which involves the synthesis of glycosyl sulfones by a tandem Horner–Wadsworth–Emmons (HWE)/conjugate-addition *C*-glycosidation followed by a tandem halogenation–RBR sequence, utilizing one-pot variant of the Ramberg–Bäcklund was developed.[108] Proof-of-principle studies were carried out using the benzylsulfonylphosphonate and diisopropylidene mannofuranose (**Scheme 68**). It was found, that the HWE/conjugate-addition process proceeded in a reasonable 64% yield using sodium hydride in THF giving the corresponding sulfonyl *C*-glycoside stereoselectively as the *β*-isomer. This sulfone was next subjected to the halogenation-RBR sequence. The standard Meyers conditions gave only a 48% yield of the olefin **89**, but use of the supported KOH/Al_2O_3-CBr_2F_2 conditions produced alkene **89** in 88% yield, exclusively as the 1,2-*cis*-diastereomer with the *β*-anomeric configuration, and the *E*-geometry. The above reaction sequence was extended to ribose derivatives and the compatibility of a range of protecting groups was investigated as well. Benzyl, acetonide, and *tert*-butyldimethylsilyl protecting groups were all accommodated within this methodology.[108]



89

Scheme 68

It was also shown[108] that this reaction sequence could be carried out in one-pot manner by adding KOH/Al_2O_3 and CBr_2F_2 to the reaction mixture after 18 h. *C*-Glycoside **89** was isolated in an excellent 78% yield. Later, a protecting group-free approach to *C*-glycoside synthesis based on the above one-pot sequence was disclosed.[109] Thus, 2-deoxy-D-erythro-pentose (2-deoxyribose) and benzylsulfonylphosphonate gave the corresponding styrenyl *C*-glycoside **90** in good yield as a mixture of diastereomers under the one-pot procedure (**Scheme 69**).This sequence is not limited to a single monosaccharide. D-Arabinose and D-lyxose were both converted into the corresponding styrenyl *C*-glycosides by this method as well.

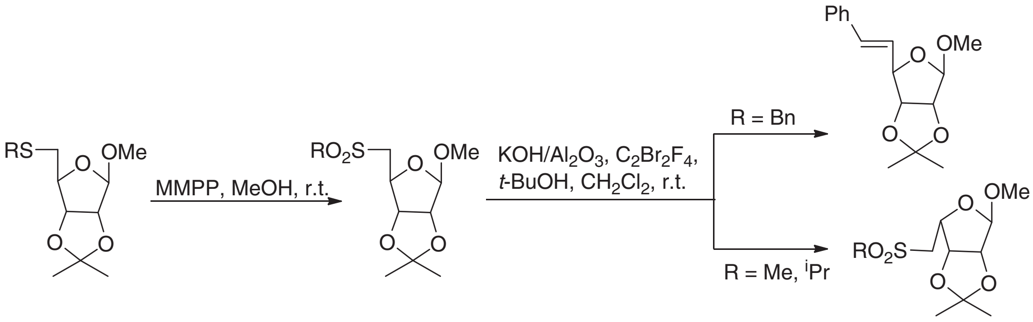


90

58%, *α*:*β* = 1:1

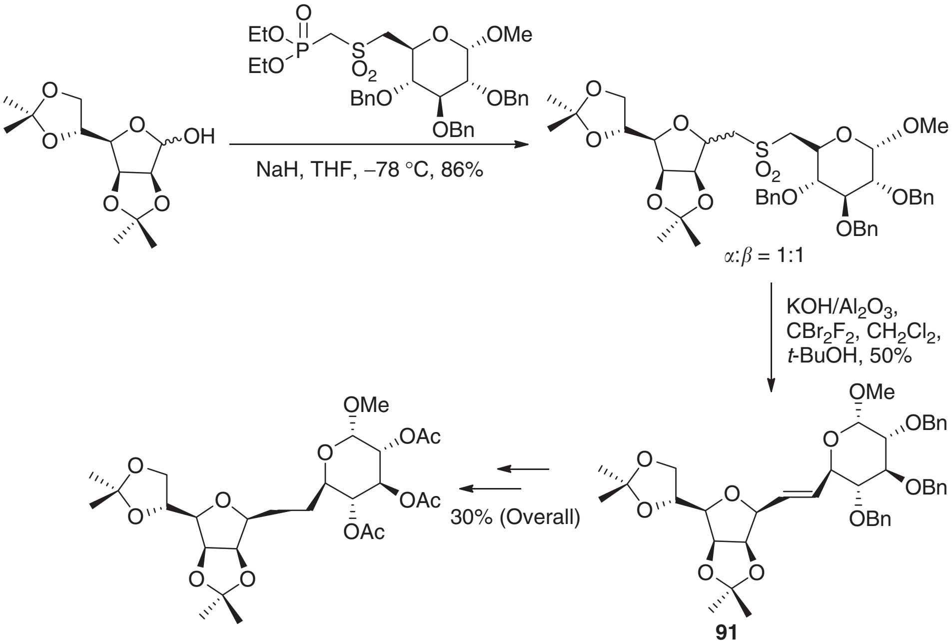
Scheme 69

The effect of sulfonyl substitution on the outcome of the RBR was reported.[110] Thus, when several 5-deoxy-2,3-*O*-isopropylidene-5-(alkylsulfonyl)-*β*-D-ribofuranosides were treated under modified Ramberg–Bäcklund conditions, benzylsulfonyl derivative afforded the corresponding olefinic sugar in good yield (73%) of the *trans*-isomer in high selectivity. In contrast, the methyl- and the isopropyl-analogs under the same reaction conditions underwent only epimerization at C-4 to generate the α-L-*lyxo* derivatives (**Scheme 70**).



Scheme 70

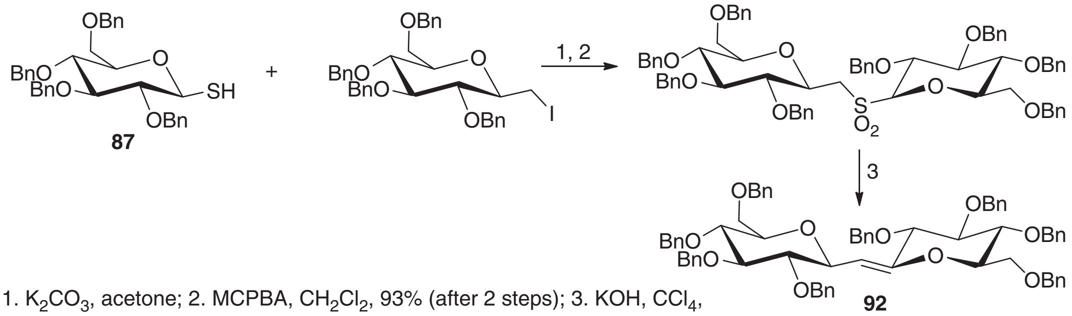
C-Linked disaccharides are also available via the stream-lined RBR methodology. Thus, the HWE/conjugate-addition sequence of a carbohydrate-derived phosphonate reagent with diisopropylidene mannofuranose proceeded in high yield (86%) and produced the adduct sulfone as a mixture of diastereomers. The key halogenation-RBR was again carried out using the conditions devised by Chan et al. giving *E*-alkene **91** as the only isolable product (Scheme 71).[108] Finally, the novel disaccharide was obtained after reduction and debenzylation–acetylation sequence with the overall yield of 30% for 11 transformations.



91

Scheme 71 Reproduced from McAllister, G. D.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem. Int. Ed.* **2003**, *42*, 1387–1391.

The Ramberg–Bäcklund approach to *exo*-glycals was extended to the construction of a range of *C*-linked disaccharides from readily prepared *S*-linked precursors.[102,111] Alkylation of benzylated thioglucose derivative **87** (see Scheme 65) with the sugar iodide prepared from the hydroboration/iodination of *exo*-glycal **83** (see Scheme 62, $R^1=R^2=H$)[95] gave the corresponding sulfide, which was immediately oxidised giving the corresponding sulfone. The Ramberg–Bäcklund reaction using Meyers' conditions gave enol ether **92**, predominantly as the *Z*-isomer (*Z*:*E*=91:9) (Scheme 72). Reduction with concomitant debenzylation, followed by acetylation gave *C*-isotrehalose (not shown on Scheme 72). Similarly, higher homolog of *C*-trehalose, and methyl *C*-gentiobioside can be obtained. This methodology offers a rapid, convergent, and practically simple route to *β*,*β*-(1,1′)-carba-disaccharides.



87

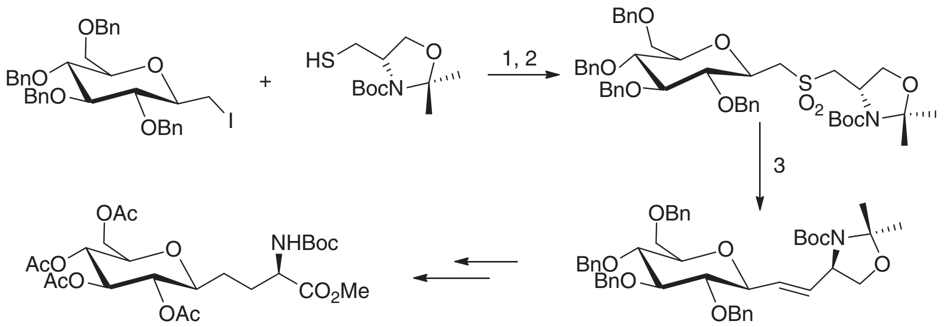
92

1. K$_2$CO$_3$, acetone; 2. MCPBA, CH$_2$Cl$_2$, 93% (after 2 steps); 3. KOH, CCl$_4$, *t*-BuOH, H$_2$O, 60 °C, 48% (*Z*:*E* = 91:9).

Scheme 72

It proved possible to use the RBR in the synthesis of novel *C*-glycosyl amino acids.[99,112] This was achieved either via glycosylsulfone approach giving, for example, a carba-analog of glucosyl serine (Scheme 73),[102] or by a hydroboration/Suzuki sequence from Ramberg–Bäcklund derived *exo*-glycal **83** ($R^1=R^2=H$)[95] (for the preparation of glycal **83** see Scheme 62).

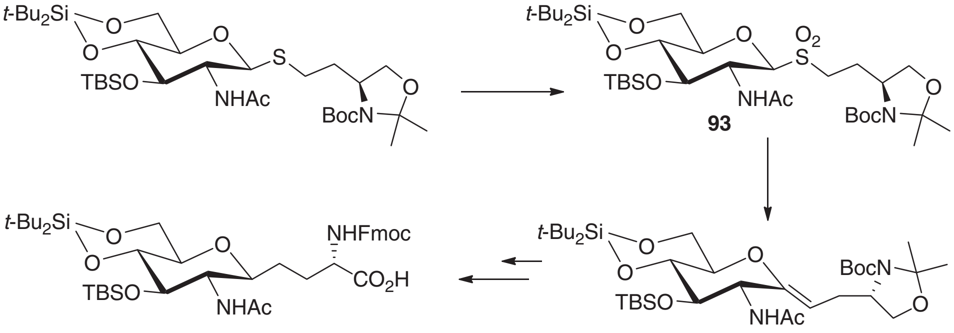
An *exo*-glycal approach was subsequently used in the stereoselective synthesis of the *C*-glycoside analog of *N*-Fmoc-serine *β*-*N*-acetylglucosaminide from a sulfone derivative of serinol thio-*N*-acetylglucosamide (Scheme 74).[106] Important to note, that



1. K_2CO_3, acetone, reflux, 71%; 2. MCPBA, Na_2HPO_4, CH_2Cl_2, 95%; 3. KOH/Al_2O_3, CBr_2F_2, *t*-BuOH, 60 °C, 37% (all *E*).

Scheme 73

the base-sensitive *O*-acetyl groups in a starting thioglycoside were replaced by stable di-*tert*-butylsilylene group for protecting the 4-and 6-hydroxyls and a *tert*-butyl-dimethylsilyl group for the 3-OH group for the upcoming Ramberg–Bäcklund reaction. Sulfone **93** underwent RBR using Chan's conditions to give the corresponding *exo*-deoxyglycal in 38% yield solely as the *Z*-isomer. Subsequent transformations gave the protected *C*-glycosyl amino acid (Scheme 74).



1. MCPBA, Na_2HPO_4, CH_2Cl_2, 77%; 2. KOH/Al_2O_3, $C_2Br_2F_4$, *t*-BuOH, 50 °C, 38%.

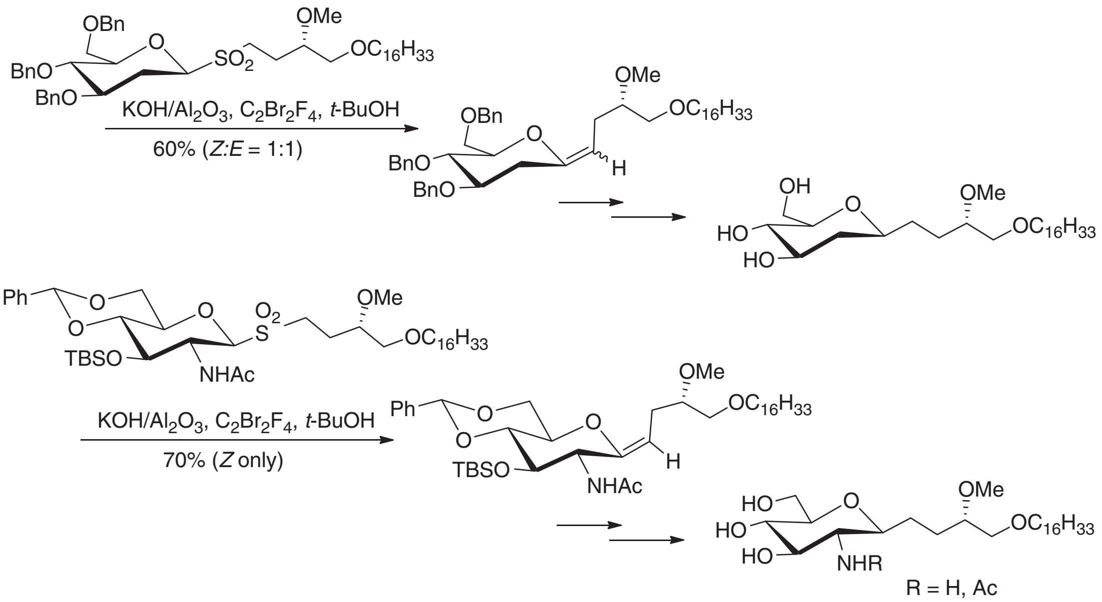
Scheme 74

The synthesis of novel *C*-glycosyl glycerolipids was published.[64,107] Scheme 75 outlines their syntheses from glucosamine- and 2-deoxyglucose-derived sulfones, respectively. It was thus found, that the RB conditions using CF_2Br_2 (bp 23 °C) failed to afford good yields of the alkene, if the sulfones did not have one benzylic group. The simple expedient of using CF_2BrCF_2Br (bp 47 °C) at reflux solved this problem.

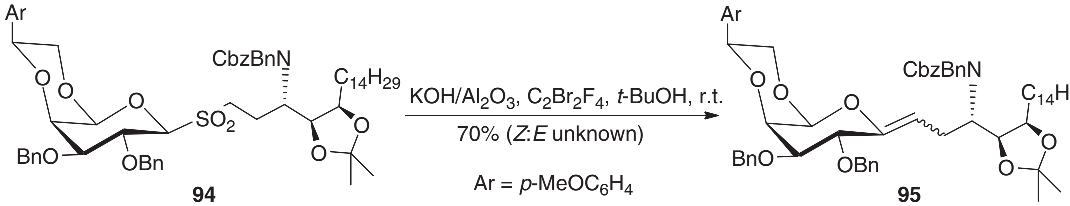
Here again, the synthesis of the *C*-glycoside analog of immunostimulant α-galactoceramide KRN7000 was achieved through RBR of sulfone **94**, giving *exo*-glycal **95** as an undetermined mixture of isomers (Scheme 76).[113]

3.18.1.7.4.2 Application of the Ramberg–Bäcklund rearrangement in the synthesis of carotenoids and related polyenes

The Ramberg–Bäcklund reaction was applied as the key step for the stereoselective quick construction of the conjugated (*E*,*E*,*E*)-triene unit in formal total synthesis of apoptolidin and its analogs.[92] Several applications of the RBR in the synthesis of carotenoid systems are reported.[86,114,115] Thus, the Ramberg–Bäcklund reaction played a key role to build up the central conjugated triene moiety of the keto-carotenoids canthaxanthin, astaxanthin, and astacene.[116] The major advantage of carotenoid synthesis utilizing sulfone chemistry is that the intermediate sulfone compounds are stable and easily purified by recrystallization. Furthermore, base-promoted SO_2 elimination followed by dehydrosulfonation produces the conjugated double bonds with *E*-configuration. The synthesis of canthaxanthin depicted in Scheme 77. To accomplish the preparation of canthaxanthin, the RBR of the oxidized C_{40} trisulfone was efficiently effected by the use of a mild base, NaOMe, in the presence of CCl_4 as a halogenating agent to give the C_{40} disulfone. Base-promoted dehydrosulfonation reaction of this disulfone compounds produced the fully conjugated polyene of canthaxanthin. It should be noted, that the RBR of the oxidized trisulfone under Meyer's condition utilizing KOH/*t*-BuOH in CCl_4 produced the desired disulfone only in approximately 40% yields. The yield was extremely low when a strong base, *t*-BuOK, was used in large excess and marginal under slowly generated *t*-BuOK (KOH/*t*-BuOH), which indicated that the α-polychlorination of the ketone in the presence of excess strong base complicated the Ramberg–Bäcklund reaction. Unfavorable

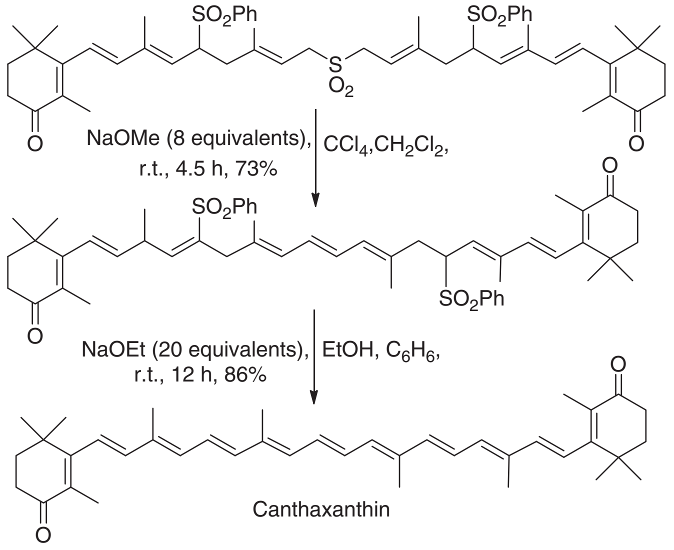


Scheme 75



Scheme 76

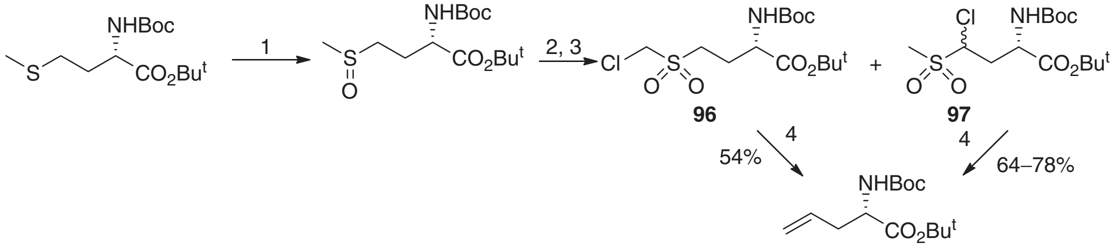
pKa of NaOMe for the deprotonation at the α-carbon of the ketone, however, was in favor of the Ramberg–Bäcklund reaction of the trisulfone. The effect of the halogenating agent was also elucidated by changing CCl_4 to C_2Cl_6. No evidence of the carbene adduct was obtained in the RBR of the trisulfone using CCl_4. Hexachloroethane was, however, less effective for the reaction using NaOMe as a base.



Scheme 77

3.18.1.7.4.3 Application of the Ramberg–Bäcklund rearrangement in amino acid synthesis

Unsaturated α-amino acids in homochiral form were obtained using the Ramberg–Bäcklund reaction as the key step.[117] The method is illustrated by the conversion of methionine into allylglycine (as its Boc, *tert*-butyl ester derivative) in optically enriched form (Scheme 78). The protected derivative of L-methionine was efficiently converted into the required sulfone, but all attempts to generate and chlorinate the corresponding α-sulfonyl anion were unsuccessful. A reliable method was eventually developed by preparing the sulfoxide and carrying out the chlorination with SO_2Cl_2.The resulting α-chlorosulfoxides were oxidized and gave the chromatographically separated mixture of the sulfones **96** and **97** (approximately 1:15). Efficient rearrangement to the protected allylglycine (64–78%) could be achieved by carrying out the reaction under homogeneous conditions adding a THF solution of sulfone **97** to a solution of KOBu^t in THF at − 78 °C and using 5 equivalents of base. A low temperature was critical to minimize racemization. Essentially optically pure product was obtained when the reaction temperature was kept at less than − 30 °C.

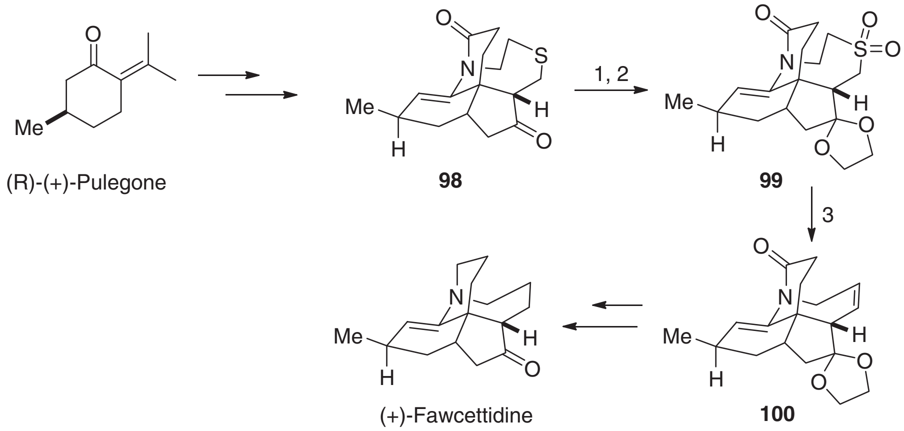


1., MCPBA, CH_2Cl_2, 94%; 2. SO_2Cl_2, CaO; 3. MCPBA, CH_2Cl_2, **97**, 45%; **96**, 3%; 4. KOBu-*t*, THF, –78 °C.

Scheme 78

3.18.1.7.4.4 Application of the Ramberg–Bäcklund rearrangement for the synthesis of alkaloids

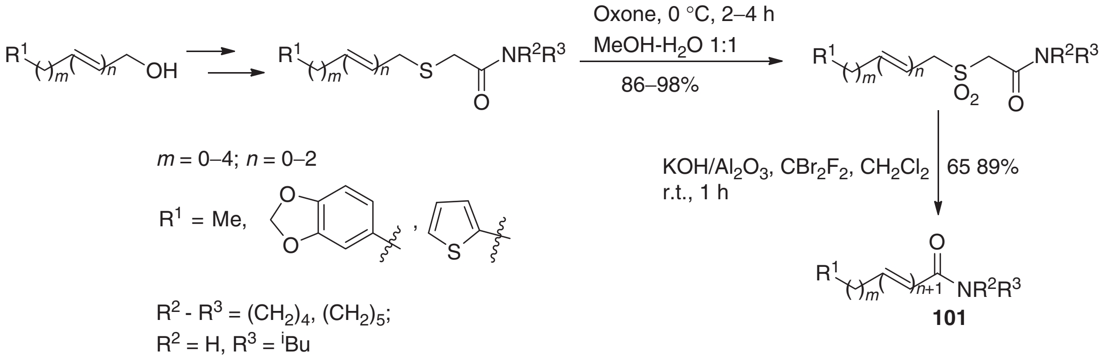
A total synthesis of the *Lycopodium* alkaloid (+)-fawcettidine was developed which requires 16 steps from the chiral starting material (R)-(+)-pulegone. Key steps included a platinum(II)-catalyzed annulation reaction of a functionalized enamide and a one-pot Ramberg–Bäcklund process to form a seven-membered ring.[118] The exocyclic alkene **100** that was thus formed provides functionalization necessary to facilitate formation of the final ring of (+)-fawcettidine (Scheme 79). According the synthetic protocol the protection of the carbonyl group of **98** followed by sulfide oxidation with mCPBA to give sulfone **99** proceeded uneventfully. All attempts to carry out the Ramberg–Bäcklund process using two-step procedure failed. However, the one-step procedure disclosed by Chan et al. turned out to be successful and provided the isolation of alkene **100** in 46% yield. The conversion of **100** into (+)-fawcettidine was subsequently carried out by standard procedures.



1. Ethylene glycol, PPTS, C_6H_6, 87%; 2. MCPBA, CH_2Cl_2, 98%; 3. CBr_2F_2, KOH/Al_2O_3, *t*-BuOH, CH_2Cl_2, 46%.

Scheme 79

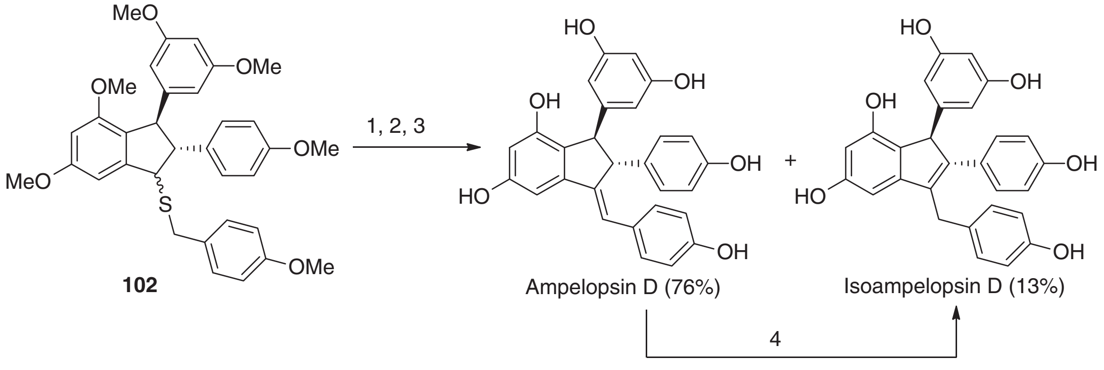
A one-flask Ramberg–Bäcklund reaction provided a convenient and rapid approach for the stereoselective synthesis of naturally occurring unsaturated amide alkaloids bearing pyrrolidine, isobutyl, and piperidine moieties.[119,120] The preparation of 13 natural products and one related analog are reported in detail (Scheme 80).[119] The approach was based on the previously published procedure for the formation of conjugated trienes from diallyl sulfones,[87] conjugated tetraenes from allylic dienylic sulfones,[88] and linear and cyclic enediynes from dipropargylic disulfones,[68] respectively. The reaction sequence started from the preparation of the unsaturated alcohols, which were then transformed to the corresponding sulfides by standard procedures. Oxidation of these sulfides with oxone in methanol/water gave high yield (with one exception of thienyl substituent) of the sulfones. The low yields (32–35%) of the thienyl derivatives were explained by the side reaction of heteroaromatics sulfides. Subject of the sulfones to the modified Ramberg–Bäcklund reaction invariably gave geometrically defined unsaturated amide alkaloids **101** with *E*-configuration of the newly formed double bond in good yields. The stereochemistry of the preexisting double bonds was retained during these transformations. According to nuclear magnetic resonance (NMR) spectroscopy, the stereoselectivity of the reaction was more than 95%.



Scheme 80

3.18.1.7.4.5 *Application of the Ramberg–Bäcklund rearrangement for the synthesis of polyphenols*

The Ramberg–Bäcklund reaction has been explored in the total synthesis of polyphenol-based bicyclic natural products from resveratrol family.[121–123] One of the illustrative and highly efficient examples involves the preparation of ampelopsin D and its isomer isoampelopsin D using stilbene derivatives as the common building blocks (Scheme 81).[122,123] Thus, the tetraaryl sulfide intermediate **102** was converted into the natural product ampelopsin D through a highly stereoselective RBR using Meyers' modified conditions that afforded permethylated ampelopsin D (*E*-isomer) along with its chromatographically separable *Z*-olefin isomer in a 5:1 ratio (40% and 7% yield over two steps, respectively). No other procedure affords such favorable and/or controlled ratio of alkene products. If the natural product ampelopsin D was then exposed to the action of HCl in methanol at 80 °C for 2 h, its central olefin could be isomerized smoothly in near quantitative yield (95%) to the more thermodynamically stable tetra-substituted olefin of isoampelopsin D.

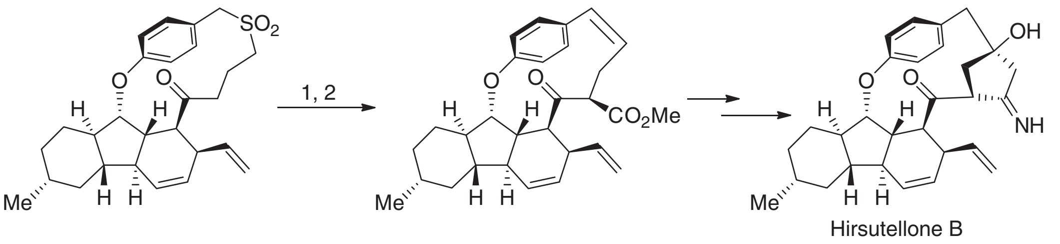


1. MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to 25 °C, 3 h, 78%; 2. ${}^{t}BuOH/H_2O/CCl_4$ 4:1:4, KOH (20 equivalents), 80 °C,12 h, 52%; 3. BBr_3 (1.0 M in CH_2Cl_2, 12 equivalents), CH_2Cl_2, 25 °C, 6 h; 4. HCl, MeOH, 80 °C, 95%.

Scheme 81

3.18.1.7.4.6 *Application of the Ramberg–Bäcklund rearrangement for the macrocyclic construction*

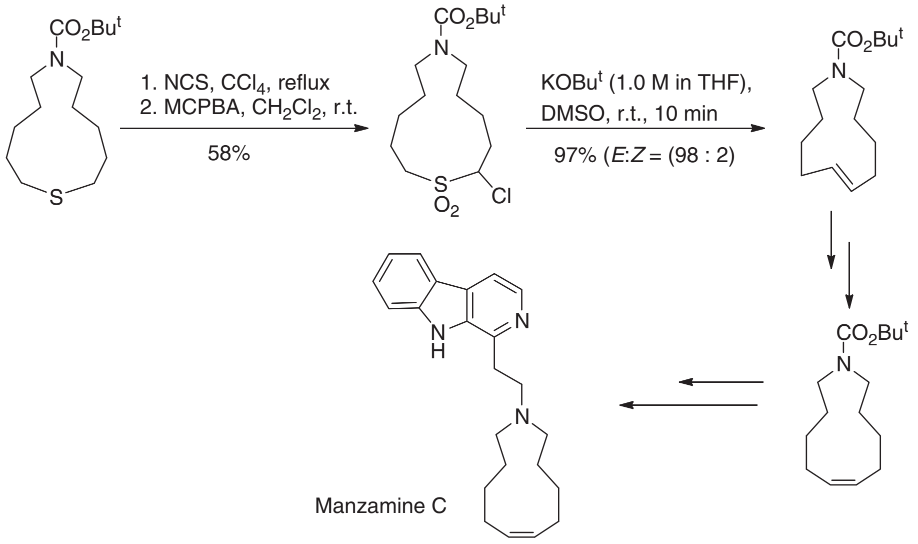
A ring-contraction approach via the Ramberg–Bäcklund reaction was explored in the total synthesis of macrocyclic natural product hirsutellone B in its enantiomerically pure form.[124] The hirsutellones share a number of unique structural features, including a 6,5,6-fused tricyclic core, a γ-lactam- or succinimide-containing moiety, a 12- or 13-membered paracyclophane structural motif which encompasses an aryl ether linkage, and 10 stereogenic centers. From the five rings within the hirsutellone B molecule, the most synthetically challenging is the 13-membered paracyclophane, whose strain is exacerbated by the presence of the other structural motifs associated with it. Therefore, its design can proceed through a sequence involving formation of a larger less strained 14-membered sulfone ring and subsequent ring contraction through a Ramberg–Bäcklund reaction (Scheme 82). Thus, treatment of macrocyclic sulfone with alumina-impregnated KOH (KOH/Al_2O_3) in the presence of CF_2Br_2 in CH_2Cl_2/*t*-BuOH (1:1) at 0 to 25 °C led to the corresponding olefin (exclusively *Z* and in high yield) through a Ramberg–Bäcklund reaction. Diastereoselective carboxymethylation of this product then furnished the keto ester (61% overall yield for two steps), which after additional functionalization gave hirsutellone B.



1. KOH/Al_2O_3 (15% w/w, 2 g per mmol), CBr_2F_2 (5 equivalents), CH_2Cl_2/^{t}BuOH (1:1), 0 to 25 °C, 2 h;
2. LHMDS (3.3 equivalents), $NCCO_2Me$ (8.3 equivalents), THF, –78 to –50 °C, 0.5 h, 61% for two steps.

Scheme 82

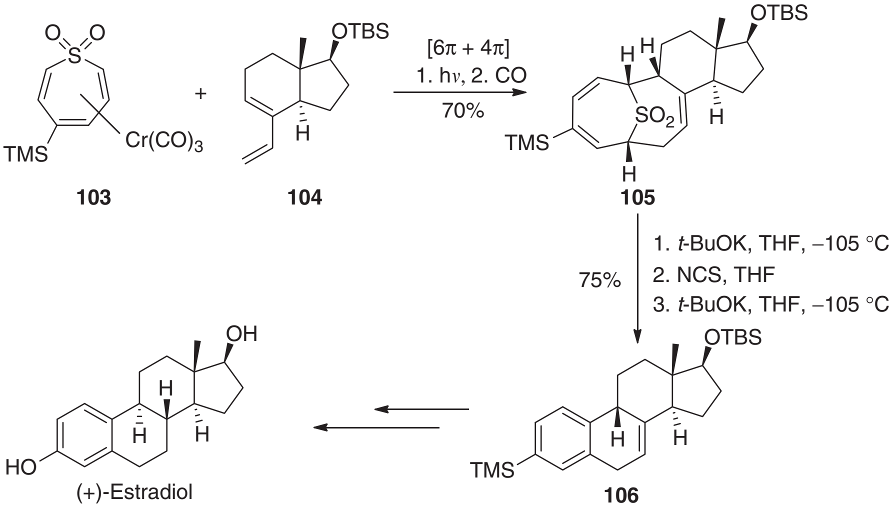
A total synthesis of the marine alkaloid manzamine C has also been accomplished using a Ramberg–Bäcklund reaction as a key step to construct the required azacycloundecene ring.[125] A general aza-macrocyclization strategy via the RBR ring contraction[79] was applied for the preparation of azacycloundec-6-ene unit. 12-Membered sulfide was converted to the corresponding α-chlorosulfone in 58% overall yield. Treatment of this α-chlorosulfone with potassium *t*-butoxide produced *trans*-olefin with high stereospecifity (*trans*/*cis* = 98:2) and in a 97% yield. The formation of almost exclusive *trans*-alkene in this cyclic system is worthy of notice. Although several milder, less bulky bases (2 mol l^{-1} KOH, DBU, triethylamine, and urea) were used in an attempt to predominantly form the *cis*-olefin, the conditions that would generate stereochemically pure *Z*-alkene directly by RBR were not found. However, a simple olefin inversion furnished the required *Z*-azacycloundecane, and finally, the synthesis of manzamine C was accomplished (Scheme 83).[125]



Scheme 83

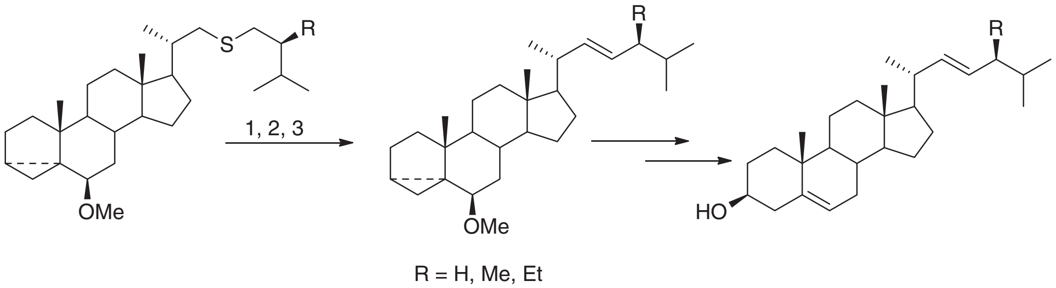
3.18.1.7.4.7 Application of the Ramberg–Bäcklund rearrangement for the synthesis of steroids

The RBR can be used as a key step in construction of the tetracyclic steroid nucleus. Thus, a benzannulation sequence featuring $[6\pi + 4\pi]$ cycloaddition of (η^6-thiepin 1,1-dioxide)-tricarbonylchromium(0) complexes with highly substituted dienes followed by the RBR was applied to the total synthesis of enantiomerically pure (+)-estradiol (**Scheme 84**).[126] The higher-order cycloaddition-Ramberg–Bäcklund reaction protocol serves as the key strategy-level transformation. First, a mixture of thiepin 1,1-dioxide complex **103** and excess diene **104** were irradiated and afforded sulfone **105** as a single regio- and stereoisomer in a quite good yield. This sulfone **105** was subject to the one-pot RB sequence. It was treated sequentially with *t*-BuOK/THF at −105 °C, then excess NIS, and, finally, a second equivalent of *t*-BuOK/THF at − 105 °C. The use of NIS in excess afforded a 65% yield of a mixture of the desired tetracycle **106** and an overoxidized, equilenin-type byproduct. It was reasoned, that the presence of excess NIS was responsible for the oxidation. Employing only 1 equivalent of NIS did indeed suppress the formation of the overoxidized byproduct, but it also had the undesired effect of depressing the yield of **106** to only 30%. It was found that the cleanest conversion to **106** could be achieved using 1 equivalent of NCS as the halogen source (**Scheme 84**).



Scheme 84

The use of the RBR allowed a convenient preparation of the side chain of a wide range of branched steroids.[127,128] A useful strategy for preparing Δ^{22}-unsaturated steroids bearing a side-chain is based on the use of stigmasterol, a readily available sterol of vegetal origin.[127] Addition of sulfides, prepared from stigmasterol, to a preheated (90 °C; bath) solution of NCS (1 equivalent) in CCl_4, followed by filtration of the formed succinimide after a few minutes and treatment of the filtrate with MCPBA (1 equivalent) in the presence of $NaHCO_3$ (1.5 equivalents) resulted in the clean formation of the Ramberg–Bäcklund precursors in good yields. Treatment of these α-chlorosulfones with excess *t*-BuOK afforded selectively and in high yields the corresponding Δ^{22}-unsaturated steroids with high *trans*-stereoselectivity (**Scheme 85**).



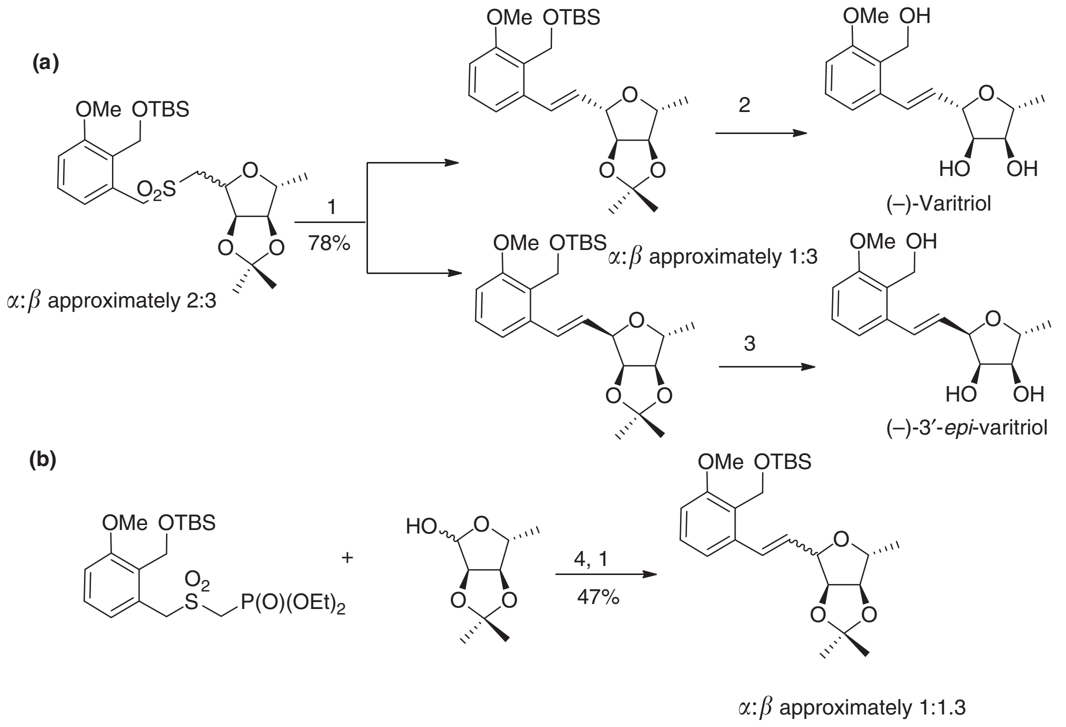
1. NCS (1 equivalent), CCl_4, 90 °C, 15 min; 2. MCPBA, $NaHCO_3$, r.t., 3 h; 3. *t*-BuOK (3.5 equivalents), THF, r.t., 3–4 h, 70–73%.

Scheme 85

3.18.1.7.4.8 Application of the Ramberg–Bäcklund Rearrangement for the synthesis of stilbenoid systems

The RBR has been widely used for the preparation of a wide range of stilbenoid systems, including anticancer agents such as combretastatin[63] and varitriol.[129] For example, a reaction sequence HWE/conjugate addition/RBR was involved as the cornerstone in a concise route to the antitumor natural product (–)-varitriol, together with its novel isomer (–)-3′-*epi*-varitriol.[129] Thus, the

Ramberg–Bäcklund reaction of the inseparable mixture of isomeric sulfones (α:$\beta \sim 2{:}3$), prepared from silylated phosphonate and D-(–)-ribose derived lactol under standard HWE/conjugate addition, gave an excellent yield of *trans*-alkene products (α:$\beta \sim 1{:}3$) (**Scheme 86a**).[129] Fortunately, the two epimers could be separated by careful chromatography on silica. Global deprotection of each isomer gave (–)-varitriol and its 3′-epimer in excellent yield. The HWE/conjugate addition/Ramberg–Bäcklund sequence could be carried out as a one-pot operation with the protected phosphonate and lactol (**Scheme 86b**). However, despite producing the corresponding alkenes directly in reasonable overall yield, the stereocontrol was even more disappointing (α:β approximately 1:1.3).



1. KOH/Al_2O_3, CH_2Cl_2-^tBuOH, CB_2F_2; 1 M HCl, THF, 18 h, 72%; 3. 1 M HCl, THF, 7 days, 83%;
4. NaH, THF, 0 °C to r.t.

Scheme 86

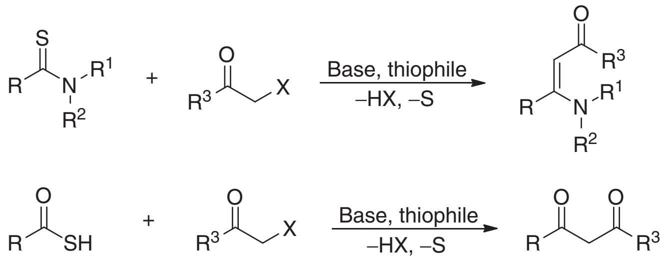
3.18.2 The Eschenmoser Coupling Reaction (Eschenmoser Sulfide Contraction)

3.18.2.1 Introduction

The Eschenmoser coupling reaction (ECR) or the Eschenmoser sulfide contraction is an efficient and convergent method for the synthesis of vinylogous amides and carbamates (3-aminoalk-2-enoic esters and ketones) from secondary and tertiary thioamides and electrophilic agents, usually enolizable α-halocarbonyl compounds (for synthesis of thioamides and thiolactams, *see* Chapter 6.10). The reaction proceeds via alkylation of the thioamide at sulfur atom with subsequent ring closure to form an episulfide. The latter undergo sulfur elimination with a corresponding thiophilic reagent such as phosphine or phosphite resulting in formation of the new carbon–carbon double bond (**Scheme 87**). A variety of secondary and tertiary thioamides works well in the reaction and provides its broad synthetic application. However, primary thioamides are not suitable substrates because they can easily transform to nitriles under the reaction conditions. Since alkylation proceeds under mild conditions, a wide range of functional groups are compatible with the ECR. Vinylogous amides and carbamates are versatile reagents whose ambident electrophilicity and nucleophilicity, and therefore their ability to participate in pericyclic and radical processes, make them valuable intermediates for natural product synthesis.[130]

The method of carbon–carbon bond formation via alkylative coupling followed by episulfide contraction was described for the first time by Knott in 1955,[131] but has emerged as an important carbon–carbon bond forming process later when it was applied to the total synthesis of vitamin B12 by Eschenmoser and his group.[132–136] In a modification of this reaction alkylation of thiocarboxylic acids leads to the direct synthesis of 1,3-dicarbonyl compounds[134] (**Scheme 87**).

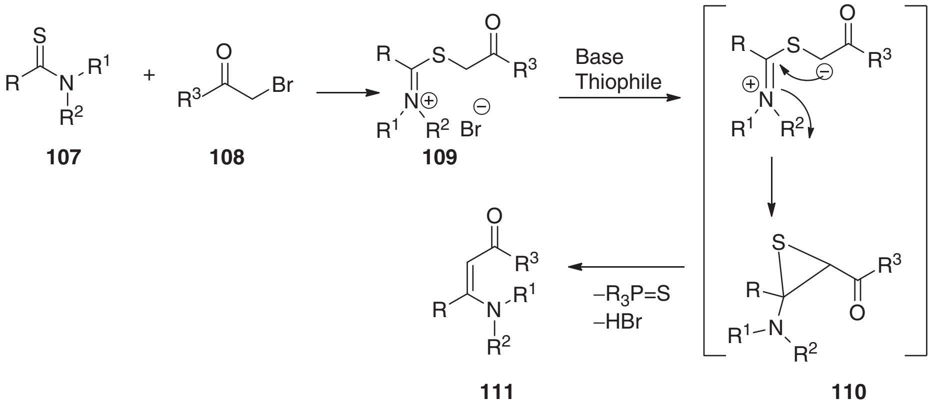
The subject was thoroughly reviewed by Shiosaky[137] in the first edition of Comprehensive Organic Synthesis.



Scheme 87

3.18.2.2 Mechanism

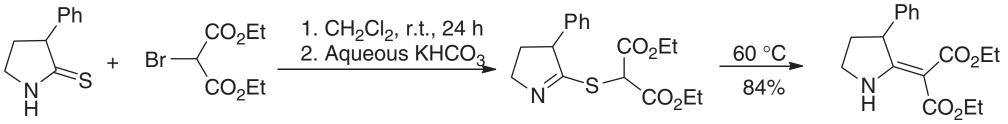
During the extensive model studies relevant to the synthesis of vitamin B12 Eschenmoser et al. developed a general method for the synthesis of vinylogous amidine, the characteristic unit of corrin chromophore.[134,135] Now, this method is known as the Eschenmoser sulfide contraction reaction.[132,133,136] Actually, the ECR consists of two stages, the coupling one and the sulfide contraction. Depending on the nature of the coupling stage, there are two version of the reaction. The first one involves the alkylative coupling and the second version based on the oxidative coupling. In both versions the coupling substrate is thioamide or thiolactam. In the well-accepted alkylative version, thioamides or thiolactams **107** are treated with enolizable α-halocarbonyl compounds **108** to form α-thioiminium salts **109**. The carbon atom presented in the α-position to both the sulfur atom and the carbonyl group attacks the proximal electrophilic thioiminoester carbon resulting in the formation of transient episulfide **110** from which sulfur is lost in the presence of a suitable sulfur scavenger (usually a phosphine or a phosphite) to give vinylogous amide **111** (Scheme 88). Although, the formation of the episulfides **110** is widely accepted, these intermediates have never been isolated and the detailed reaction mechanism for the sulfide contraction step has not yet been fully proven. The α-thioiminium salts **109** can be isolated, but usually they are directly treated by the combination of the base and thiophile to promote the second step of the reaction and to carry out the process in a one-pot manner.



Scheme 88

The conditions for the reaction depend on the nature of the reactants. Thioiminium salts formed from tertiary thioamides undergo sulfide contraction under mild conditions (e.g., at ambient temperature with triethylamine as base), whereas those from secondary thioamides are first deprotonated to thioimidates, which subsequently lose sulfur only in the presence of powerful bases such as potassium *tert*-butoxide, and frequently at elevated temperatures and for prolonged reaction times.[138] Furthermore, tertiary thioamides usually produce the corresponding vinylogous amides with the higher yields than their secondary analogous ones do.[139,140] The use of an additive, NaI, can consistently reduce the required time for thioiminium formation.[141]

The applied electrophile must possess a sufficiently acidic α-proton for abstraction in the following step to initiate sulfur extrusion. Common electrophiles include α-activated carbonyl compounds. If the active methylene species such as dialkyl bromomalonates are used, the extrusion of elemental sulfur from the thioimidate intermediate may take place spontaneously with gentle warming in the absence of thiophile. Thus, the reaction of the 3-phenylpyrrolidine-2-thione with diethyl bromomalonate followed by the deprotonation with aqueous potassium carbonate or potassium hydrogen carbonate solution afforded the corresponding putative thioimidate. Warming of the latter at 60 °C resulted in deposition of elemental sulfur and the formation of the desired vinylogous urethane diethyl 2-(3-phenylpyrrolidin-2-ylidene)malonate in 84% overall yield (Scheme 89).[142] In much the same way, the Eschenmoser sulfide contraction of pyrrolidinethiolactams with ethyl 2-bromoacetoacetate gave the corresponding alkylidenepyrrolidines.[143] Similarly, the ECRs of 17-oxo-2-thionosparteine with alkyl or phenyl bromoacetates in the presence of triethylamine and under reflux in $CHCl_3$ yielded the new vinylogous carbamates of sparteine in moderate yields (see Scheme 108 in Section 3.18.2.4.3)[144]



Scheme 89

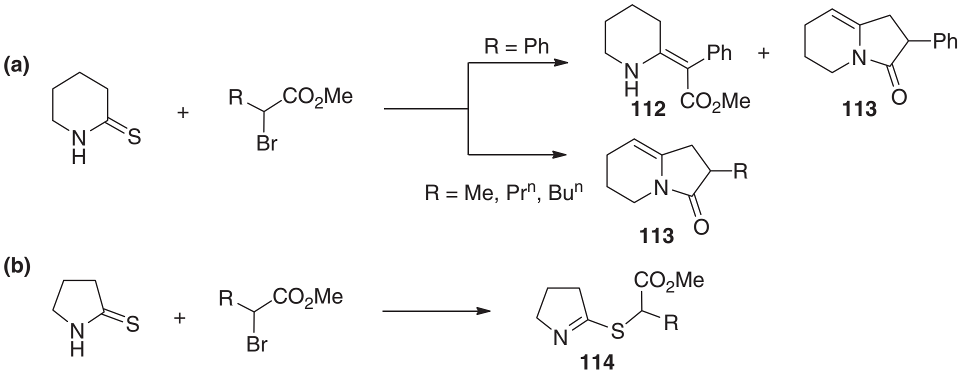
The role of the thiophile is to assist extrusion of the sulfur atom from the episulfide intermediate to produce the alkene. A number of compounds can serve as an acceptable thiophile, including triarylphosphines, trialkylphosphines, and trialkyl phosphites. Eschenmoser developed a bi-functional reagent, bis(*N*,*N*-dimethyl-3-aminopropyl)phenyl phosphine $PhP[(CH_2)_3NMe_2]_2$, which contains both base and thiophile units.[132] The main advantage of this dual reagent is its efficient removal from the product through aqueous washings, thereby overcoming the difficulties in the separation of the desired product from phosphine sulfide by-products. This reagent have been successfully applied to the synthesis of macrocyclic β-keto lactones from ω-hydroxy thioamides and chloroacetyl chloride.[138]

Some examples of the Eschenmoser episulfide contraction, which proceeded well without thiophile assistance, are reported.[143,145–147]

The second step of the ECR requires the presence of a base to generate an anion in the α-thioiminium intermediate **109** that leads to episulfide formation. Inorganic bases such as carbonate and bicarbonate, hydroxide, alkoxides, and hydrides have been employed successfully, as well as various organic bases such as triethylamine, *N*-methylmorpholine, *N*-methylpiperidine, and diisopropylethylamine. Since a mild organic base is sufficient for deprotonation in most cases, the reaction is compatible with numerous functional groups and base-sensitive asymmetric centers.

The most frequent complication of the alkylative Eschenmoser sulfide contraction is the reversibility of the thioamide alkylation,[138,144,148] which occurs when electrophile bears a nucleophilic leaving group and resulting in lower yields.[144] Thus, in the crossover experiments, reaction of preformed α-thioiminium salt with a second distinguishable electrophile give rise to the exchange of alkyl appendage and to the formation of a mixture of two α-thioiminium salts.[138] However, this problem can be overcome by using an electrophile bearing a nonnucleophilic leaving group, such as triflates.[149,150,151] The use of chloroform as a solvent can give an advantage in that the formed salt precipitates in the media avoiding the reversibility of its formation.[141]

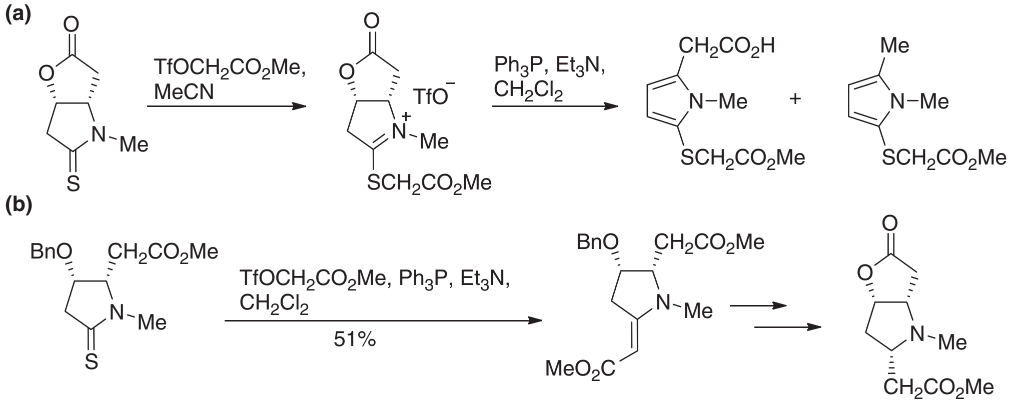
The structures of a thioamide substrate as well as an active α-halide have a pronounce effect on the products of the Eschenmoser sulfide contraction reaction. It was shown, that the formation of *N*-secondary tetrasubstituted β-enaminocarbonyl compounds or bicyclic thiazolidinones promoted by DBU from piperidine-thiones or pyrrolidine-thiones, respectively, depends on the size of the thiolactam ring, the nature of the substitution in the α-bromoester, and the strength and/or the bulkiness of the employed tertiary amine.[147,152] Thus, the reaction of the piperidin-2-thione with methyl α-bromophenylacetate in the presence of Et_3N or DBU and Ph_3P afforded a mixture of the corresponding enamino compound **112** and the unexpected thiazolidinone **113** (R=Ph, Scheme 90a).[147] The enamino compound was obtained as a sole product when the reaction was carried using DBU (2 equivalents) as base and in the absence of Ph_3P as a thiophile. The reactions of the piperidin-2-thione with other α-bromoesters (R=alkyl) at any set of conditions did not resulted in the extrusion of the sulfur atom to give the corresponding β-enaminoesters but gave the thiazolidinones **113** (R=Me, Pr^n, Bu^n) in good yields. However, the different behavior was observed for the pyrrolidine-derived thiolactam under the same reaction conditions. In all cases, the formation of either β-enaminocarbonyls or the thiazolidinones was not observed, but rather the respective thioimines **114** were obtained in high yields, independent of the nature of the R-group (Scheme 90b).[152] The unexpected formation of thiazolidinones in the ECR was reported previously.[142]



Scheme 90

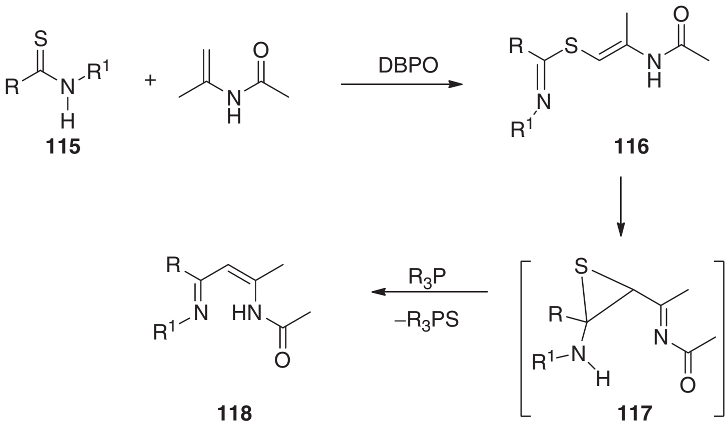
for analogous compounds. Although the factors controlling thiazolidinones formation are not fully clear yet, it can be explained in terms of the relative acidity of the hydrogen atoms in the intermediate thioimine salts.[141]

One of the possible complications of the Eschenmoser alkylation sulfide contraction is the deprotonation of thioalkyliminium salts adjacent to the azomethine carbon under the reaction conditions. Thus, when the Eschenmoser sulfide contraction was applied to a thiolactam bearing a *β*-acyloxy group, a mixture of pyrroles instead of pyrrolidine derivatives was obtained (**Scheme 91a**).[153] It was presumed, that these pyrroles were the result of such a deprotonation, followed by *β*-elimination and aromatization. Thus problem was overcome, changing the *β*-substituent to a worse leaving alkoxy group, which retarded the rate of elimination such that sulfide contraction products could be achieved. Although this did not completely eliminate the aromatization problem, desired vinylogous urethanes were obtained in a reasonable yield (**Scheme 91b**).



Scheme 91

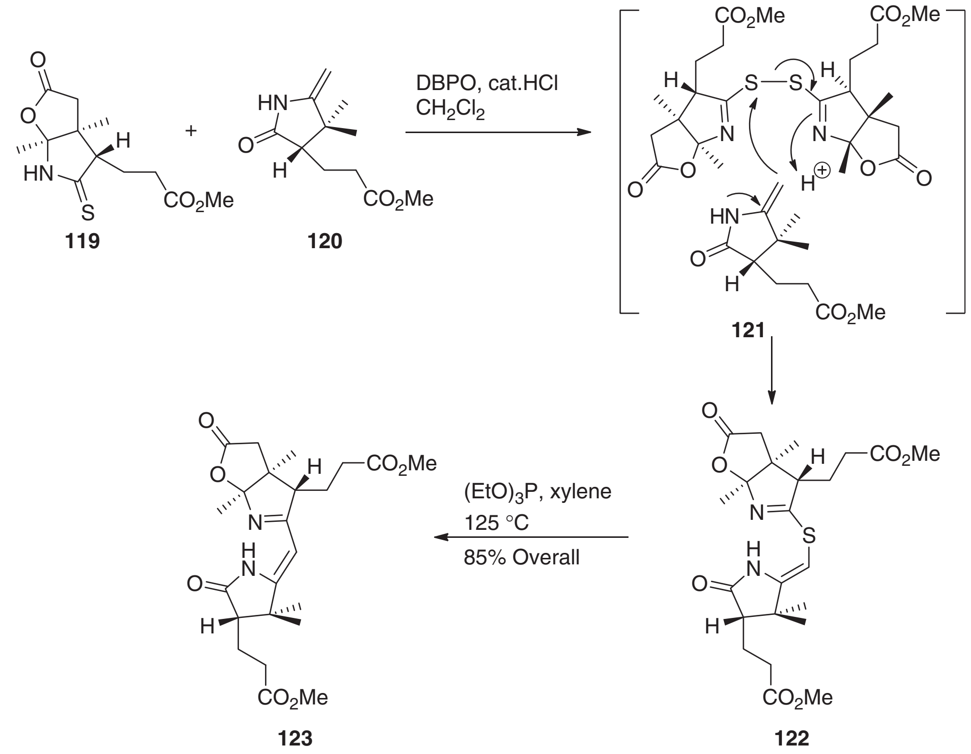
In the oxidative mode of the Eschenmoser sulfide contraction[134,136,154] (**Scheme 92**), thioamide **115** is first oxidized by benzoyl peroxide to give most likely a symmetrical disulfide which undergoes the nucleophile attack of the enamine and produces the sulfur-bridged intermediate **116**. The latter under the action of a phosphine or phosphite thiophile gives rise to the vinylogous amidine **118** via putative episulfide **117**.



Scheme 92

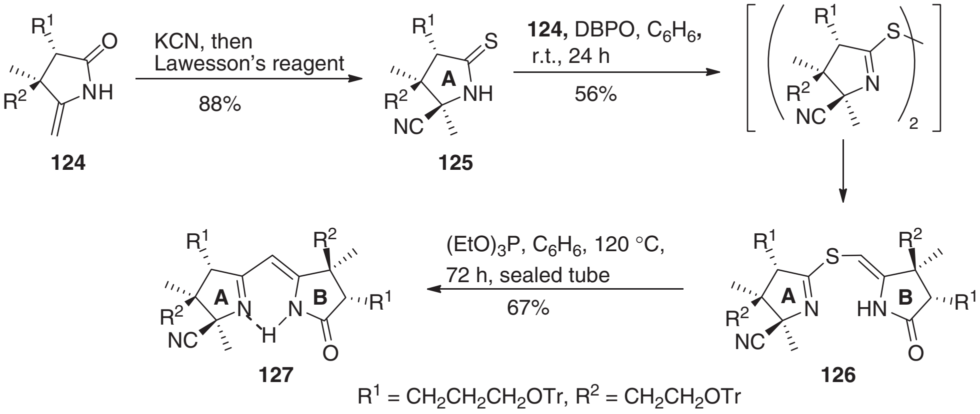
This approach can be exemplified by the Eschenmoser's synthesis of thiodextroline, one of the key intermediates in the total synthesis of vitamin B12 (**Scheme 93**).[155] When a solution of the thiolactam **119** and the enamine **120** in CH$_2$Cl$_2$ was treated with benzoyl peroxide and a catalytic amount of HCl, the thiolactam moiety in **119** underwent oxidation to the transient bisimidoyl disulfide **121** which reacted with enamine **120** with formation of a new carbon–sulfur bond and gave the sulfur-bridged compound **122**. Heating of the latter in xylene in the presence of thiophile triethyl phosphite gave rise to an intramolecular reaction and produced the olefinic product **123**, which was then converted to the required thiodextroline.

Later, this oxidative approach has been applied to a stereocontrolled nonracemic synthesis of a vitamin B12 A-B-semicorrin **127**.[156] Both A and B rings of **127** were prepared from the same precursor, enamide **124** and their coupling has been achieved via Eschenmoser sulfide contraction. For the synthesis of ring A precursor **125**, the exocyclic double bond in enamide **124** was first



Scheme 93

protected as cyano lactam, which was *in situ* treated with Lawesson's reagent, to furnish thiolactam **125** in 88% yield. This thiolactam was produced as a mixture of diastereomers (6:1, NMR) in favor of the (2*R*)-isomer. According to the protocol developed by Eschenmoser et al.[134] treatment of a mixture of enamide **124** and thio lactam **125** with benzoyl peroxide gave the stable sulfide **126** which was isolated in 56% yield. On being heated in benzene, sulfide **126** was converted into A–B-semicorrin **127** in 90% yield, as a mixture of four diastereomers (approximately 36:6:6:1) probably arising from an epimerization (6:1) at C-3, during the sulfide contraction. Diastereomerically pure **127** was obtained in 67% yield after HPLC separation (Scheme 94).



Scheme 94

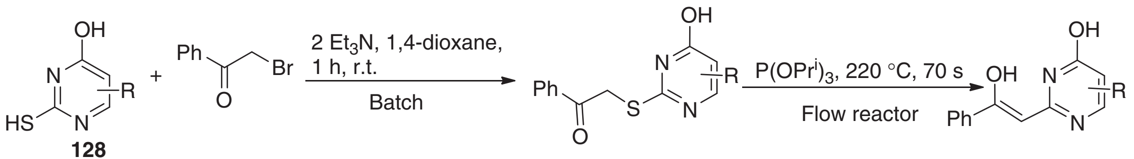
3.18.2.3 Synthetic Modification of the Eschenmoser Coupling Reaction

3.18.2.3.1 Selenoamides as substrates for the Eschenmoser coupling reaction

The use of proline derived selenoamides instead of thioamides as substrates for the ECR was reported.[157] Although the reaction provided access to cyclic enaminoesters under mild conditions (sodium bicarbonate, dichloromethane, room temperature), it was applicable for selected cases and the yields were rather low (17–35%). It was suggested, that the change of sulfur with selenium, in the two-step mechanism of the ECR could have a positive effect on the first alkylation step. However, the second step of the reaction was slowed down, possibly due to the larger size of the selenium atom, which might disfavor the formation of the epi-selenide intermediate, and hence the production of the final enamino ester. Furthermore, taking into account selenamide preparation problems, the use of selenoamides in the Eschenmoser reaction seems to be of limited practical value.

3.18.2.3.2 The Eschenmoser coupling reaction under continuous-flow conditions

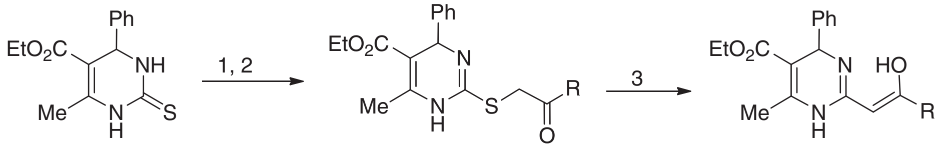
Ternary thioamides usually undergo the episulfide formation and subsequent sulfide contraction smoothly due to the strong electron accepting nature of the thioiminium intermediate. However, prolonged reaction time and increased reaction temperature are necessary in most cases for the sufficient conversion of secondary thioamide derivatives. A flow chemistry system was used to promote the Eschenmoser coupling of mercaptopyrimidinol derivatives **128** and improve the long reaction times under enhanced reaction conditions.[158] Reaction temperatures far beyond the solvent boiling point were applied under pressurized flow conditions for a minimum residence time. The transformation was carried out in a one-pot manner, without isolation of the *S*-alkylated intermediates. The anhydrous 1,4-dioxane solutions containing pyrimidine derivative **128**, triethylamine and the corresponding α-bromoketone were sonicated for approximately 1/2 h, and then triisopropylphosphite (TIP) was added as thiophilic agent before the reaction solutions were fed through the flow chemistry setup. It was found that under pressurized reaction conditions at approximately 220 °C with a flow rate of 250 μl min^{-1}, the desired Eschenmoser coupling products were obtained within 70 s residence and the maximum conversion of approximately 98%. The ECR of a number of secondary thiolactame building blocks, including 2-mercaptopyrimidin-4-ol derivatives, dihydropyrimidine substrates, and *N*-phenylthioacetamide proceeded smoothly with high yields (Scheme 95). Various aromatic and heterocyclic α-bromoketone building blocks worked well under those pressurized flow conditions. For small-scale synthesis flow chemistry is of great advantage to realize these conditions on the laboratory bench in safely time mode.[158]



R = 6-Me (48%), 5,6-di-Me (55%), C_6H_4 (78%)

Scheme 95

To avoid an excessive chromatographic work-up, which is usually necessary to separate the desired products from the phosphine and phosphine sulfide by-products, commercially available polymer-supported triphenylphosphine, which acts as thiophilic agent as well as scavenger for unreacted α-bromoketones was applied.[159] In this way a one-pot, two-step conversion of 3,4-dihydropyrimidin-2(1H)-thiones to 2-(2-hydroxy-2-arylvinyl) dihydropyrimidine derivatives via Eschenmoser sulfide contraction was achieved (Scheme 96).[159]



R = Ph, 4-BrC_6H_4, 4-PhC_6H_4, 4-CNC_6H_4, 4-$NO_2C_6H_4$, 3-BrC_6H_4, β-$C_{10}H_7$, 4-ClC_6H_4, 2,5-$(MeO)_2C_6H_3$, 4-MeOC_6H_4

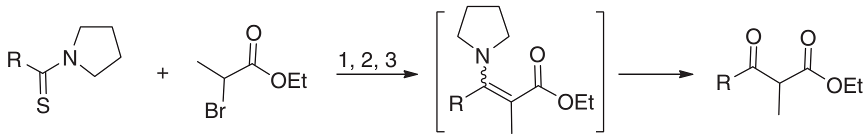
1. K_2CO_3 (1.5 equivalents), Me_2CO_2; 2. $RCOCH_2Br$ (1.2 equivalents), r.t., 30 min;

3. ●— PPh_3, 80 °C, 10 h, 77–91%.

Scheme 96

3.18.2.3.3 α-Methyl-β-ketoesters through the Eschenmoser coupling reaction

Several α-substituted *β*-ketoesters were easily obtained by an efficient direct condensation of bromoesters with thiolactams through the Eschenmoser sulfur extrusion reaction in one-pot manner.[160] This strategy represents a quick and convenient route that can take its place among the available methodologies that provide access to these compounds. The title compounds were produced by hydrolysis of the corresponding enaminoesters without isolation of the latter (Scheme 97). The ECR was modified to minimize the formation of byproducts in the condensation–extrusion process and to facilitate the elimination of these byproducts in the experimental work-up. In this way, a mixture of the corresponding thioamide and 2-bromopropionic acid ethyl ester was briefly heated at 80 °C without solvent, followed by dilution with acetonitrile, treatment with triethylamine and a thiophile, and finally *in situ* hydrolysis by HCl. The yields of the reaction and purity of the β-ketoester products were substantially improved using tris(dimethylamino)phosphine or tris(diethylamino)phosphine as the thiophilic reagent. Under these conditions α-alkylated β-ketoesters were synthesized via an Eschenmoser reaction in moderate to good yields.



R = ^{n}Pr, 60%; ^{i}Bu, 70%; ^{n}Pent, 72%; Ph, 67%

1. 80 °C, 30–45 min; 2. Et_3N, $(Me_2N)_3P$, MeCN, r.t.; 3. HCl, MeCN, r.t., 30 min.

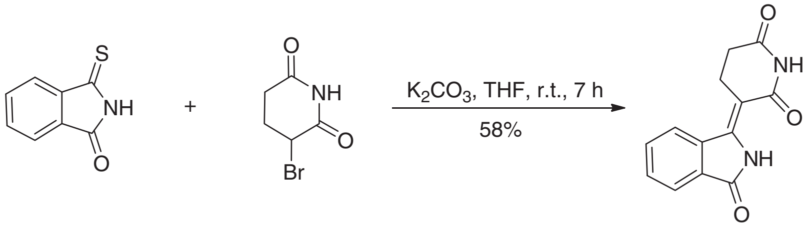
Scheme 97

3.18.2.4 Application of the Eschenmoser Coupling Reaction in the Synthesis of exo-Cyclic Enamines

3.18.2.4.1 Indole and pyrrolidine systems

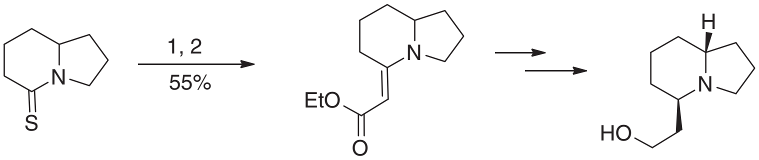
The ECR was widely applied for development of stereoselective approaches to functionalized pyrrolidines and related systems. Synthesis of such systems is a topic of considerable interest in the context of natural product and small molecule synthesis, and medicinal chemistry. For example, 2,2,5-trisubstituted pyrrolidine moieties were found in a range of natural products, including brevianamide C, fusarin, azaspirene, lepadiformine, and kaitocephalin.

The ECR was applied to the synthesis of 3-alkylidene-isoindolinones, simple models, and precursors of several naturally occurring products, including, for example, isoindolobenzazocine alkaloid magallanesine. Thus, alkylation of monothiophthalimide with various α-bromoketone derivatives in the presence of potassium carbonate followed by elimination of sulfur generated the corresponding (*Z*)-3-alkylidene-isoindolinones as single isomers.[146] The entire process was carried out in one-pot manner and without adding any thiophile. This methodology was successfully used for the synthesis of thalidomide analogous (Scheme 98).



Scheme 98

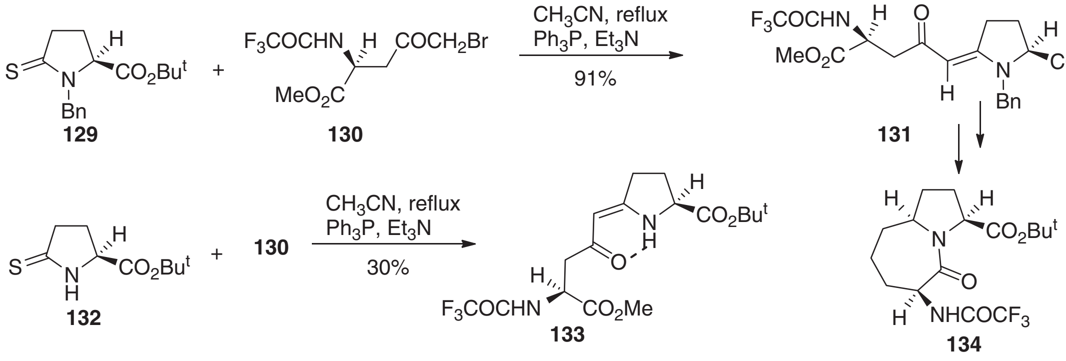
The Eschenmoser sulfide contraction was the key step in an efficient and concise synthetic strategy to prepare 5-substituted indolizidines of a natural origin (e.g., 167B toxin) or new synthetic products with diverse functionalities on the C-5 side chain via 5-thioindolizidinone.[161] This strategy was applied to the total synthesis of 5-(20-hydroxyethyl)indolizidine. To attach C-5 side-chain 5-thioindolizidinone was reacted with bromoacetone, however, the resulting enamino ketone proved to be unstable. The more stable enamino ester was prepared in a moderate yield from thioindolizidinone by the reaction with ethyl bromoacetate (Scheme 99). It was obtained as a mixture of *E* and *Z* isomers in the ratio 1:3.1 (according to NMR spectra). The subsequent transformations resulted in the racemic mixture of 5*R*,9*R*- and 5*S*,9*S*-5-(20-hydroxyethyl)indolizidine in 17% overall yield for seven steps.



1. $BrCH_2CO_2Et$, MeCN, r.t., 18 h; 2. Ph_3P, $^iPr_2NEt$, MeCN, r.t., 18 h.

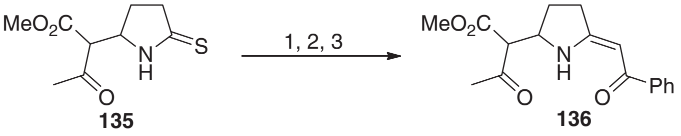
Scheme 99

Bicyclic pyrrolidine lactam **134**, designed as an external turn constraint, was synthesized by a stereoselective route involving ECR as a key step.[139,140] Thus, Eschenmoser olefination using the trisubstituted *N*-benzyl thiolactam **129** and bromide **130** and Ph_3P/Et_3N in acetonitrile gave the vinylogous amide **131** with *E*-stereochemistry in 91% yield (Scheme 100). Interestingly, when bromoketone **130** was heated under the same reaction conditions with the disubstituted thiolactam **132**, the desired product **133** was obtained in 30% yield only and was shown to be the *Z*-isomer. The hydrogen bond between the N–H of the vinylogous amide and its carbonyl group presumably accounts for this specificity.



Scheme 100

An ECR of pyroglutamic acid derived thiolactams with α-bromoketone was applied for the preparation of a 2,5-disubstituted pyrrolidine **136** from a C-5 substituted lactam. Reaction of thiolactam **135** with 2-bromoacetophenone in diethyl ether, followed by treatment with triethylamine in dichloromethane and triphenylphosphine in chloroform at 60 °C produced the desired vinylogous amide **136** in 68% yield as a single geometric isomer about the double bond, probably the *Z*-isomer (Scheme 101).[162] This vinylogous amide **136** was a plausible precursor of a tricyclic guanidine used, in turn, as a model compound in the total synthesis of alkaloid ptilomycalin A.



1. 2-Bromoacetophenone (1.2 equivalents), Et_2O, r.t., 18 h; 2. Et_3N (2.05 equivalents), CH_2Cl_2, r.t., 2 h, 83%; 3. PPh_3 (4 equivalents), $CHCl_3$, 60 °C, 18 h, 82%.

Scheme 101

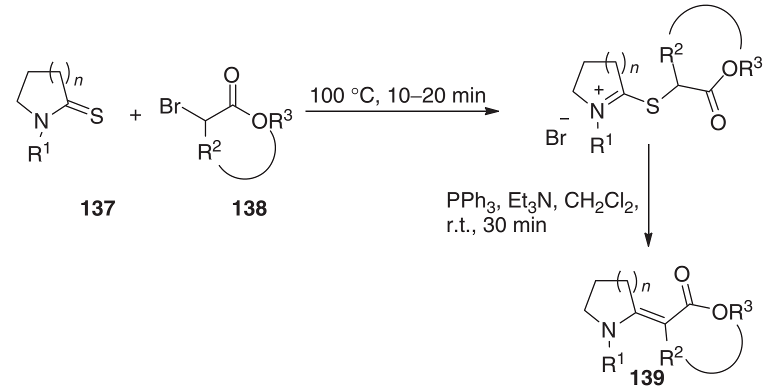
The ECR was applied to the synthesis of *β*-enamino lactones **139**.[163] Since alkylative coupling with α-bromo lactones **138** under standard conditions (dichloromethane or acetonitrile as solvents, room temperature) took 500 h, possibly due to steric hindrance, the first step of this transformation was carried out under solvent free conditions. Thus, heating of thiolactams **137** and α-bromo lactones **138** for a few minutes without solvent gave the intermediate thioiminium salts. Treatment of these salts with dichloromethane solution of triphenyl phosphine and triethyl amine afforded the expected *β*-enaminolactones **139** in good yields (Scheme 102 and Table 3). According to ^{1}H-NMR spectra assignments, *N*-benzyl *β*-enamino lactones **139** (R^1=Bn) were formed as *E*-isomers only, although *N*-methyl *β*-enamino lactones **139** (R^1=Me) were produced as mixtures of *E*- and *Z*-isomers. The above conditions were extended to the reaction with ethyl α-bromoacetate and the alkylation required only 3 min.

The ECR in combination with Ireland–Claisen ester rearrangement and subsequent reduction provided a rapid access to 2,2,5-trisubstituted pyrrolidine derivatives from allylic pyroglutamates in a highly diastereoselective and efficient manner.[164] The Eschenmoser sulfide contraction was effected by the reaction of thiolactams **140** with diethyl bromomalonate–sodium bicarbonate and gave the corresponding enamines in excellent yields (Scheme 103). The latter could be reduced to the 2,2,5-trisubstituted pyrrolidine system using sodium cyanoborohydride or sodium borohydride–ruthenium trichloride.

Similarly, conversion of 5-(*tert*-butyldiphenylsiloxymethyl)pyrrolidin-2-thione to pyrrolidin-2-ylidene malonates was achieved on treatment with diethyl or dibenzyl bromomalonate in dichloromethane at room temperature followed by the addition of aqueous potassium hydrogen carbonate.[165] These pyrrolidine derivatives were used in the synthesis of 2-methylidene-1-azabicyclo[3.1.0]hexane systems related to the natural product antitumor antibiotic carzinophilin.

3.18.2.4.2 Piperidine systems

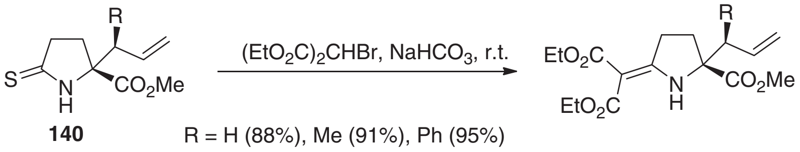
The ECR was employed in the construction of 2,6-disubstituted 3-piperidinol chiral building blocks needed for the synthesis of the 3-piperidinol alkaloids in enantiomerically pure form (Scheme 104).[166]



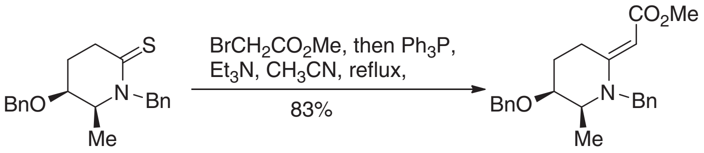
Scheme 102

Table 3 Preparation of β-enamino lactones via Eschenmoser sulfide contraction (Scheme 102)

No.	*R¹*	*$-R^2-R^3-$*	*Yield (%)*
1	Bn	$-(CH_2)_2-$	82
2	Bn	$-(CH_2)_2-$	84
3	Bn	$-(CH_2)_2-$	39
1	Bn	$-CH_2CH(CH_3)-$	89
2	Bn	$-CH_2CH(CH_3)-$	79
1	Me	$-(CH_2)_2-$	78
1	Me	$-(CH_2)_2-$	86

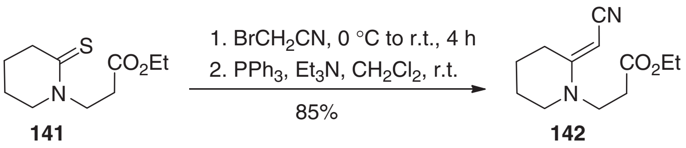


Scheme 103



Scheme 104

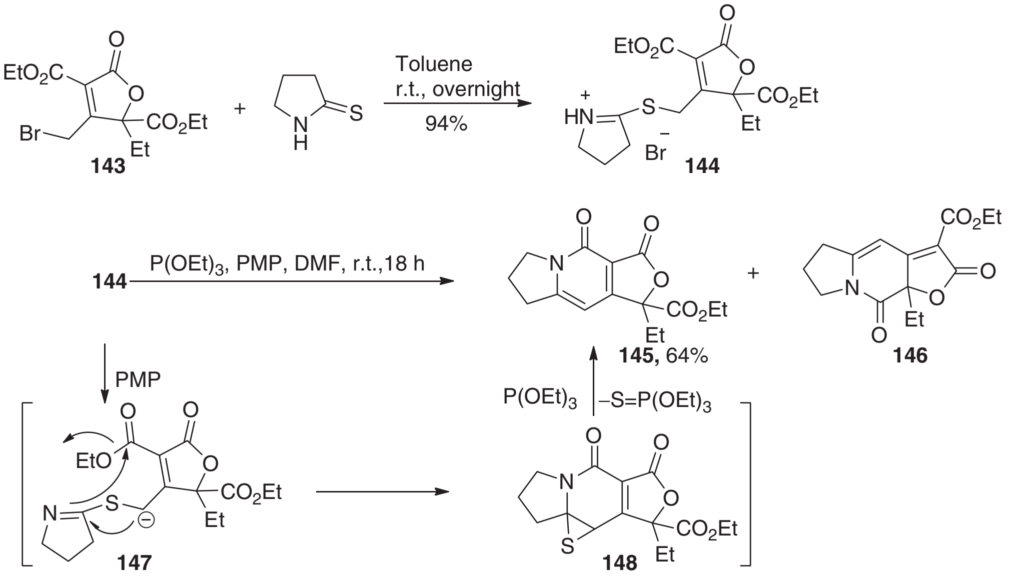
In line with the general sulfide contraction approach to alkaloid synthesis, (±)-lamprolobine and (±)-epilamprolobine, having the saturated quinolizidine core, were prepared by a route featuring reaction of thiolactam **141** with bromoacetonitrile to give vinylogous cyanamide **142** followed by controlled manipulation of this pivotal enamine intermediate.[167] Cyanamide **142** was formed as a single geometrical isomer (presumably the *E*-isomer, although it was not confirmed unambiguously) and served as the precursor for both diastereomeric target alkaloids via intramolecular nucleophilic displacement and formation of quinolizidine ring system (Scheme 105).



Scheme 105

3.18.2.4.3 Pyridine systems

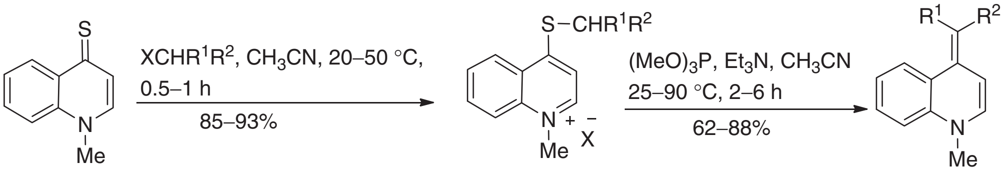
An interesting pyridone forming reaction via a tandem vinylogous sulfide contraction reaction/δ-lactam formation was reported.[168] This pyridon ring system can be used as a building block in formal total synthesis of (*rac*)- and (*S*)-camptothecin alkaloids. The reaction sequence involved nucleophilic displacement of α,*β*-unsaturated *γ*-lactone **143** by thioamide to give the crystalline thioiminium hydrobromide salt **144,** which served as starting material for a tandem vinylogous sulfide contraction reaction/δ-lactam formation. The combination pentamethylpiperidine, triethylphosphite, and *N*,*N*-dimethylformamide (DMF) was found to work very efficiently and afforded the crude reaction product as a mixture of regioisomers **145**/**146** in the ratio 6.7:1. The required isomer **145** can be easily purified by product precipitation from EtOAc/hexane. The mechanism of this reaction was assumed as follows. The reaction was initiated by deprotonation of the CH_2S-carbon atom in the thioiminium salt, which is triply activated by the ester, the lactone and the iminothioether moieties (Scheme 106). The carbanion **147** thus formed apparently attacks the imino group resulting in a subsequent δ-lactam formation. The generated elusive tetracyclic episulfide **148** is desulfurized by the phosphite reagent giving rise to pyridone **145**. The undesired regioisomer **146** is formed by intramolecular attack of the carbanion **147** at the imino group and a subsequent nucleophilic attack of the negatively charged N atom at the sterically more hindered ester group.



Scheme 106

3.18.2.4.4 Quinoline systems

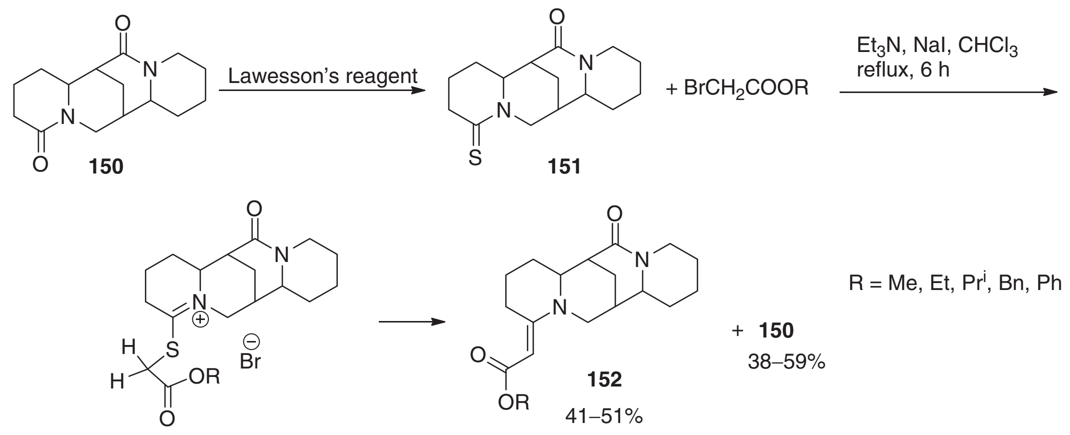
Mono- and bifunctional *N*-substituted 4-alkylidenequinolines **149** were synthesized by the sulfide contraction process in two steps.[169] The first step involved *S*-alkylation of *N*-methyl quinolinethiones with commercially available α-activated halides in dry acetonitrile at room temperature. The resulting quinolinium salts were isolated and then subject to the sulfide contraction in the presence of triethylamine as a base and trimethyl phosphite as a thiophilic reagent (Scheme 107). The most notable feature of this transformation is the stereoselective production of monofunctional 4-alkylidenequinolines. The reaction was extended to various *N*-substituted derivatives. To accomplish this, the readily available 4(1*H*)-quinolinethione was first *S*-alkylated with α-activated halides in ethanol followed by potassium carbonate treatment of the resulting protonated quinolinium salts. Next, these salts underwent quaternization with allyl bromide, ethyl bromoacetate, or benzyl bromide, respectively. Finally, the Eschenmoser episulfide contraction produced the corresponding *N*-substituted quinolinethiones.[169]



$XCHR^1R^2 = BrCH(CO_2Et)_2, BrCH_2CO_2Et, ClCH_2CN, ClCH_2COMe, BrCH_2COPh$

Scheme 107

The ECR was applied for the modification of bis-quinolizidine alkaloids toward improvement of their biological activity. Thus, new vinylogous carbamates of sparteine **152** have been prepared by the reaction of (+)-17-oxo-2-thionosparteine **151** with alkyl and phenyl bromoacetates.[144] The condensation of (+)17-oxo-2-thionosparteine with the corresponding bromoacetate gave the intermediate *α*-thioiminium salts. These salts were not isolated and the entire coupling process was conducted as a one-pot procedure. However, the reaction yielded a mixture of products in a ~1:1 ratio, one of which proved to be dilactam **150** and the second one is the single diastereoisomer of compound **152** with *E* configuration of the newly generated carbon–carbon double bond in the side chain. The formation of dilactam **150** indicated that the alkylation of thioamide was a reversible process leading to the initial dilactam on hydrolytic work-up. Changes in the reaction conditions, including solvents ($CHCl_3$, THF), base (1,4-diazabicyclo[2.2.2]octane (DABCO), imidazole, and triethylamine), and temperature, did not improve the results (Scheme 108).



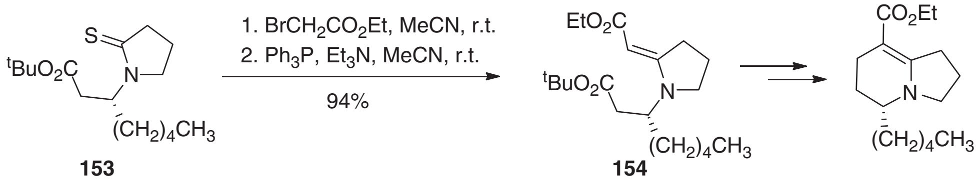
Scheme 108

3.18.2.5 Application of the Eschenmoser Coupling Reaction in Natural Product and Bioactive Molecule Synthesis

3.18.2.5.1 In total synthesis of alkaloids

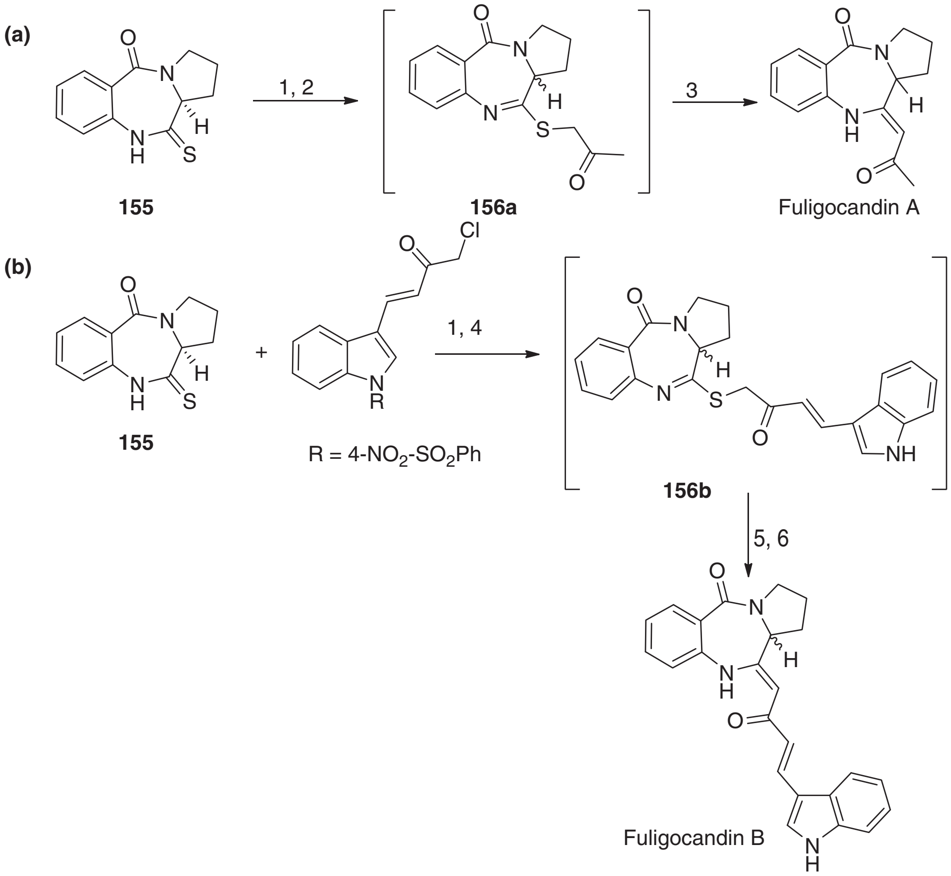
The Eschenmoser sulfide contraction reaction has been successfully applied as a key pathway in many synthetic strategies addressed to the synthesis of natural products. It provides an easy access to *β*-acylated enamines and related compounds, which can act as both nucleophiles and as electrophiles, and thus are versatile intermediates in alkaloid synthesis.

Synthesis of racemic indolizidine alkaloid 209B and its (–)-enantiomer represents one of the nice examples of such approach.[170] Construction of the indolizidine nucleus of this alkaloid was based on the pivotal cycloalkylation process of the intermediate **154**, derived from pyrrolidine thione **153** by the Eschenmoser sulfide contraction, and depends on the enamine-like nucleophilicity of this cyclic vinylogous urethane (Scheme 109). Similarly, exploring of piperridine thiones made possible to extend this route to the synthesis of quinolizidine analogs.[171]



Scheme 109

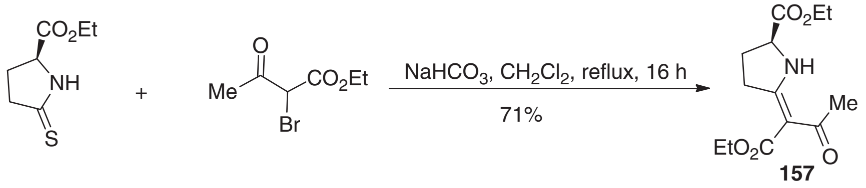
Practical total syntheses of the natural products fuligocandin A and fuligocandin B have been achieved through a convergent strategy depending on the Eschenmoser episulfide contraction as a key step.[145] A considerably improved procedure for the Eschenmoser coupling has been invented. Conducting the reaction in DMSO proved to be an efficient and general method for the synthesis of a variety of vinylogous amides, such as azepan-2-ylidenepropan-2-one. First, selective monothionation of cycloanthralinoproline with the P_2S_5–Py_2 complex afforded the monothione **155** in 85% yield. Next, a one-pot alkylation of the monothione **155** and subsequent sulfur extrusion gave fuligocandin *A* as the required *Z* isomer. It is important to note that under standard Eschenmoser episulfide contraction conditions such as potassium *tert*-butoxide or triethylamine and triphenylphosphine in benzene or xylene at high temperatures, the desired vinylogous amide was not formed. To overcome this problem the reaction was carried out using DMSO as a solvent. DMSO has facilitated not only the initial S_N2 alkylation but also the carbon–carbon double bond formation by exposing the carbanion toward the electrophilic sp^2 carbon. Fuligocandin A was obtained in an excellent yield (98%) when DABCO was used as a base and trimethyl phosphite as sulfur scavenger. The unstable intermediate thioimidate **156a** could be isolated, but the best results were obtained when it was used immediately *in situ* (Scheme 110a). The use of the relatively volatile trimethyl phosphite instead of more commonly used triethyl phosphite simplified the workup. Under the conditions that successfully gave fuligocandin A, the racemic fuligocandin B was isolated in 20% yield only and the indole *N*-protecting group was also removed. However, the episulfide contraction of the alkylated intermediate **156b** proceeded very rapidly in hot DMSO in the absence of both base and thiophile to give the *N*-protected fuligocandin B in 57% isolated yield (Scheme 110b).



1. NaH, DMSO, r.t., 30 min; 2. MeC(=O)Cl, r.t., 40 min; 3. $P(OMe)_3$, Dabco, 90 °C, 14 h, 98%; 4. r.t., 40 °C; 5. 90 °C, 2 h, 57%; 6. Cs_2O_3, MeOH, r.t., 91%.

Scheme 110

The Eschenmoser sulfide contraction based on the elaboration of glutamic acid was employed in the studies toward the total synthesis of batzelladine A.[143] This approach began with ethyl (*S*)-pyroglutamate. Thionation of the latter with Lawesson's reagent followed by Eschenmoser sulfide contraction with ethyl 2-bromoacetoacetate gave the corresponding alkylidenepyrrolidine precursor **157** in good overall yield (Scheme 111). The compound **157** was formed as a single double bond isomer, and was then subject to the further transformations to the target product. Although, a more direct route to the required alkylidenepyrrolidine



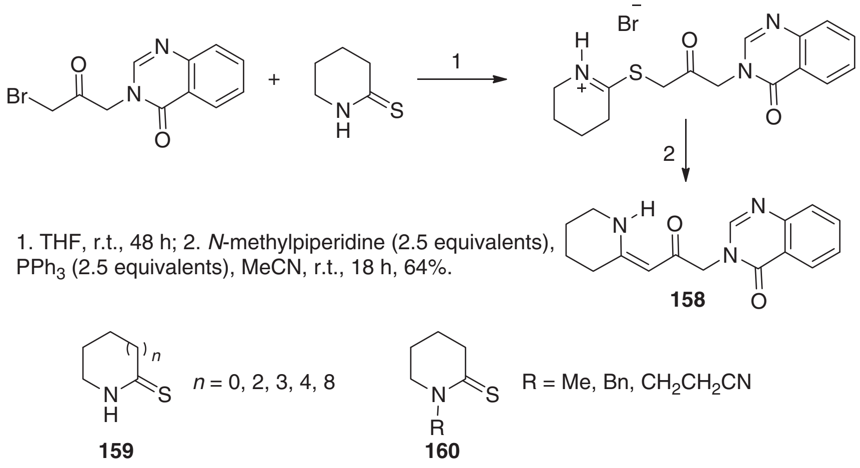
Scheme 111

precursor would involve Eschenmoser sulfide contraction with ethyl 2-bromoacetate, it was found to be low yielding and capricious, such that the present route was the most efficient. This finding is consistent with the previous observations, that the *N*-secondary tetrasubstituted *exo*-cyclic *β*-enaminocarbonyl compounds from piperidine thiolactams are better prepared using a *α*-bromocarbonyl reagent with a second electron-withdrawing substituent group (CN, COR, or CO_2R) attached to the *α*-carbonyl carbon, and phosphines as thiophile reagents need not be employed.[172,173]

Preparation of (Z)-enaminone precursor by the coupling of thiolactam, derived from ethyl (*S*)-(–)-pyroglutamate, with bromoacetone and subsequent desulfurization of the corresponding thioether by treatment with triphenyl phosphine and *N*-methylpiperidine in boiling benzene, was the starting point in an enantiospecific synthesis of a coccinellied alkaloid (–)-adalinine.[174]

Similarly, the reaction sequence involving a two-carbon homologation of *N*-benzylthiopyroglutamate via a sulfide contraction was employed in an enantiospecific synthetic route to (–)-natural and (+)-unnatural cocaines,[150] in a chirospecific route to conformationally constrained 1-carboxy-7-azabicyclo[2.2.1]heptane amino acids,[175] in the preparation of the optically pure 2,5-difunctionalized homotropane, serves as the common intermediate for the synthesis of either natural (+)- or unnatural (–)-anatoxins,[151] and of *s-trans* conformationally constrained anatoxin analogs.[176]

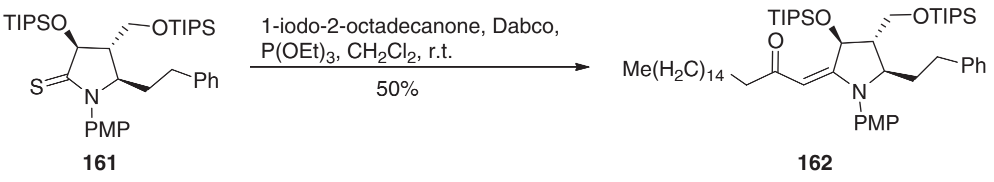
The Eschenmoser sulfide contraction was involved as a key step in the synthesis of antimalarial alkaloid (±)-deoxyfebrifugine.[177] Thus, the reaction between 3-(3-bromo-2-oxopropyl)quinazolin-4(3*H*)-one and piperidine-2-thione in dry THF resulted in precipitation of the corresponding *S*-alkylated product. Then the solvent was removed and replaced by acetonitrile. Treatment of this solution with triphenyl phosphine and *N*-methylpiperidine effected the sulfide contraction to give enaminone **158** with *Z*-geometry of the double bond due to hydrogen bonding (Scheme 112). The latter was converted into deoxyfebrifugine by a chemoselective reduction of the carbon–carbon double bond. This methodology was extended and permitted access to related systems with significant variation in both heterocyclic portions. The reaction was accomplished with a range of thiolactams **159** of varying ring size and *N*-substituted piperidine-2-thiones **160** as well. With piperidine-2-thiones **160** bearing alkyl substituents on nitrogen, triethylamine was used as the base instead of *N*-methylpiperidine. The Eschenmoser reaction proceeded more easily, and the yields of enaminone products were generally better. In these cases the products were found to have *E*-configuration of the double bond, presumably for steric reasons and because hydrogen bonding to the carbonyl group was not possible.



1. THF, r.t., 48 h; 2. *N*-methylpiperidine (2.5 equivalents), PPh_3 (2.5 equivalents), MeCN, r.t., 18 h, 64%.

Scheme 112

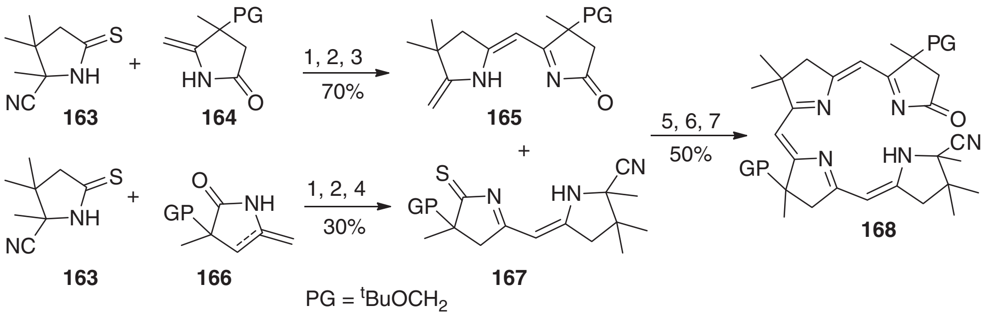
The Eschenmoser coupling reaction provided an expedient approach to an analog of a new class of pyrrolidine alkaloids, Plakoridine A and B, having vinylogous amide structure.[178,179] To construct the key 2-pyrrolidinone intermediate the conversion of thioamide **161** to the vinylogous amide **162**, a model compound for Plakoridine A, was successfully carried out employing 1-iodo-2-octadecanone, prepared by oxidation of 1-octadecene with silver chromate-iodine, followed by sequential treatments with DABCO and triethylphosphite in dichloromethane at ambient temperature. The desired **162** was produced in 50% yield (Scheme 113).[178]



Scheme 113

3.18.2.5.2 In macrocycle synthesis

The Eschenmoser's methodology for constructing pyrrolic hydroporphinoid systems[180] was applied to the synthesis of an octahydroporphyrin precursor of tolyporphin chromophore.[181] The sulfide contraction and iminoester cyclization has allowed to assemble the octahydroporphyrin from the four monocyclic precursors. Thus, base mediated coupling of the thiolactam **163** with the enamide **164** in the presence of NIS, followed by sulfide contraction with triethyl phosphite, furnished a bicyclic intermediate **165** in 70% overall yield. Similarly, the coupling of **166** with **164** followed by thionation gave the corresponding bicyclic intermediate **167** in 30% overall yield. The eneamide **166** exists as a mixture of *exo* and *endo* enamide forms, which apparently results in the lower coupling yield. The sulfide contraction method was once again used to couple **165** with **167** to yield the tetracyclic lactam **168**, which was then converted to octahydroporphyrin (Scheme 114).

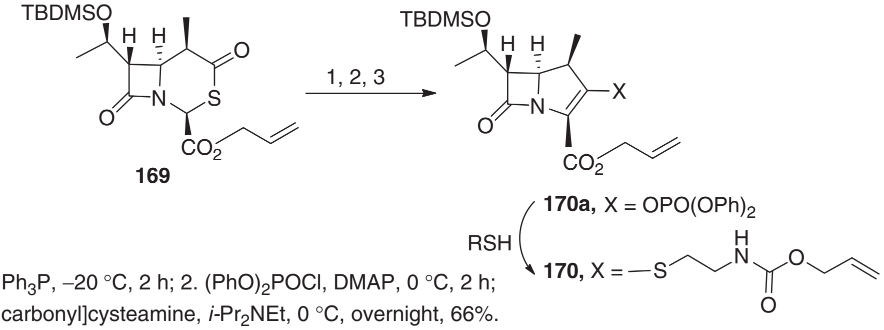


1. NIS, DBU (2 equivalents), MeCN, 3 h, r.t.; 2. $(EtO)_3P$, xylenes, 23 h, 125 °C; 3. *t*-BuOK/*t*-BuOH, 3 h, 85 °C; 4. Lawesson's reagent, toluene, 3 h, 80 °C; 5. NIS, DBU (4 equivalents), MeCN, 3 h, r.t.; 6. $CdCl_2$, $NaHCO_3$, PPh_3, MeCN, 4 h, r.t.; 7. KCN, MeOH, 10 min, r.t.

Scheme 114

3.18.2.5.3 In the synthesis of antibiotics

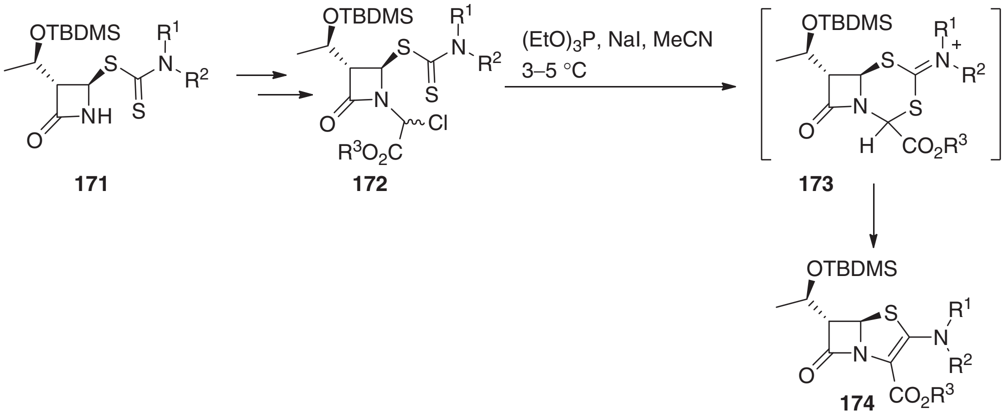
A synthesis of the 1β-alkylcarbapenems **170** was achieved on the basis of Eschenmoser sulfide contraction via the bicyclic 1,3-thiazinone intermediates **169**.[182] This was the first example of applying Eschenmoser sulfur extrusion reaction to the ring-contraction reaction. The sulfide contraction of bicyclic thiazinone is probably initiated by abstraction of H-4 in **169** by base (sodium hydride or potassium *tert*-butoxide). The resulting carbanion should intramolecularly attack on the carbonyl group in the thiazinone moiety to form thiirane. Subsequently, the thiirane was subjected to the sulfur extrusion with the aid of triphenyl phosphine, could be converted to the corresponding carbapenem enolate, which is effectively trapped *in situ* by $(PhO)_2POCl$ to give enolphosphate **170a** ($X{=}OPO(OPh)_2$). Without isolation of **170a**, addition of the mercaptans to the reaction mixture afforded carbapenems **170** in good yields in one-pot procedure from **169**. An illustrative example of these transformations is shown in Scheme 115.



1. NaH, DMF, Ph_3P, −20 °C, 2 h; 2. $(PhO)_2POCl$, DMAP, 0 °C, 2 h;
3. *N*-[(allyloxy)carbonyl]cysteamine, *i*-Pr_2NEt, 0 °C, overnight, 66%.

Scheme 115

The ECR was involved in a simple synthesis of C2-dialkylaminopenems.[183] The reaction sequence was accomplished in one-pot manner starting from dithiocarbamates **171**, which were converted to the corresponding glyoxylates followed by treatment with methansulfonyl chloride and *N*,*N*-diisopropylethylamine in acetonitrile to give crude chlorides **172**. Addition of triethyl phosphite and sodium iodide to this acetonitrile solution provided the penem nucleous **174** (Scheme 116, Table 4). The conversion of chlorides **172** to aminopenems **174** most likely proceeded via an intramolecular cyclization of **172** to yield thiazinone intermediates **173**, transannular cyclization of the latter to the corresponding episulfides and sulfur exclusion by phosphite to give C2-alkylaminopenems.



Scheme 116

Table 4 Synthesis of C2-alkylaminopenems via sulfide contraction approach (Scheme 116)

NR^1R^2	*R^3*	*Yield (%)*
Morpholinyl	Bn	16
Morpholinyl	Allyl	23
Thiomorpholinyl	Bn	35
Thiomorpholinyl	Allyl	33
Pyrrolidinyl	Bn	38[a]
Dimethylamino	2-Chloroallyl	43[a]
Dimethylamino	2-Trimethylsilyletyl	30
Dimethylamino	Bn	57[a]
Benzylmethylamino	Bn	42[a]

[a] Sulfosalicylate salt was used for isolation.

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3.19 The Wolff Rearrangement

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3.19.1 Introduction 945
3.19.1.1 Historical 945
3.19.1.2 Initiation Methods 945
3.19.1.2.1 Thermolysis 945
3.19.1.2.2 Photolysis 946
3.19.1.2.3 Catalysis 947
3.19.1.2.4 Other methods 947
3.19.2 Mechanistic Considerations 948
3.19.2.1 Stereochemistry of α-Diazocarbonyl Compounds 948
3.19.2.2 Concerted and Stepwise Pathways 949
3.19.2.3 Oxirene Participation 951
3.19.2.4 Migratory Aptitude 952
3.19.3 Applications 954
3.19.3.1 Reactions of Ketenes Derived from the Wolff Rearrangement with Nucleophiles 954
3.19.3.2 Cycloaddition Reactions of Ketenes Derived from the Wolff Rearrangement 958
3.19.3.3 Pericyclic Reactions of Ketenes Derived from the Wolff Rearrangement 960
3.19.3.4 Decarbonylation 962
3.19.3.5 Oxidation 963
3.19.3.6 Ring Contraction 963
3.19.3.6.1 Reaction scope 963
3.19.3.6.2 Synthesis of strained frameworks 968
3.19.3.6.3 Diazodiketones 970
3.19.3.6.4 Resists 972
3.19.3.6.5 Ring contractions in total synthesis 974
3.19.3.7 Homologation of Carboxylic Acids 974
3.19.3.7.1 Reaction scope 974
3.19.3.7.2 Homologation of α-amino acids 978
3.19.3.7.3 Application in total synthesis 981
3.19.3.8 Vinylogous Wolff Rearrangement 982
3.19.3.8.1 Reaction scope 982
3.19.3.8.2 Applications in total synthesis 982
3.19.3.9 Hetero Wolff Rearrangements 983
3.19.3.9.1 1,2,3-Thiadiazoles and 1,2,3-selenadiazoles 983
3.19.3.9.2 1,2,3-Triazoles and related substrates 984
3.19.3.9.3 Wolff rearrangement involving phosphorous atoms 984
3.19.3.9.4 α-Diazosulfones and -sulfoxides 985
3.19.4 Final Remarks 986
References 986

Glossary

Carbene Electrically neutral species H_2C, and its derivatives, in which the carbon is covalently bonded to two substituents of any kind and bears an electron pair of nonbonding electrons, which may be spin-paired (singlet state) or spin-nonpaired (triplet state).

Excited state State of a system with energy higher than that of the ground state. The term can refer to an electronically excited state, but also to vibrational and/or rotational excitations of the electronic ground state.

Homologation Chemical reaction or sequence of chemical processes that transforms the starting material into the next member of a homologous series, typically by the introduction of a $-CH_2-$ unit.

Laser flash photolysis Spectroscopic technique used for the formation and detection of transient species of a given compound or mixtures, by single wavelength irradiation with a pulsed light. The sample irradiation can be performed by a nanosecond, picosecond, or femtosecond pulse width, interacting with the sample and therefore starting a chemical reaction or exciting the sample. The

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absorption of light by the sample is recorded within short time intervals to detect relaxation or reaction processes.

Matrix isolation Isolation of a reactant or an unstable species by dilution in an inert matrix, typically nitrogen or noble gases. After solidification, the structure can be identified by spectroscopic or other means.

Resist Material sensitive to light used in photolithography process, as part of microfabrication, to form a patterned coating on a surface.

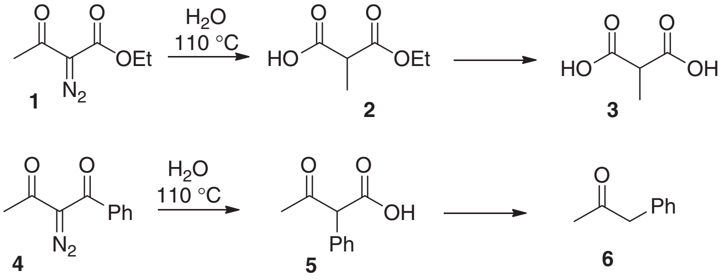
Ring contraction Chemical reaction that decreases the number of atoms in a ring of a cyclic compound.

Vinylogy Transmission of electronic effects of a functional group through a double bond or a conjugated organic bonding system.

3.19.1 Introduction

3.19.1.1 Historical

The Wolff rearrangement was named after the findings of Ludwig Wolff when he heated α-diazo ketone **1** in water (which was assumed at that time to have a cyclic structure) and obtained carboxylic acid **3**, after hydrolysis of ester **2**, instead of the expected α-hydroxy ketone (Scheme 1). In some cases, like **4**, the carboxylic acid **5** could not be detected due to the decarboxylation reaction and only **6** was observed. Right after these preliminary results, indicating a 1,2-shift, the migratory aptitudes of the substituents in the order Ph > Me > OMe was stated.[1] Despite these valuable findings at the beginning of the 20th century, the way water was incorporated in the reaction was unclear. At the time, Wolff proposed that the α-hydroxy ketone was formed in the reaction media and that the formation of the carboxylic acid-derived from a double-migration reaction in analogy with the pinacol and benzilic acid rearrangements. Only some years later, Schröter[2] proposed the presence of ketenes as possible intermediates, and Wolff accepted this proposal in a comprehensive paper dealing with silver-ion-catalyzed rearrangements of α-diazo ketones.[3] More than 20 years after, the formation of carboxylic acids from α-diazo ketones was adapted as the Arndt–Eistert homologation reaction[4] and a carbene was proposed as intermediate and further developed for photochemical ketene generation by Horner.[5]



Scheme 1

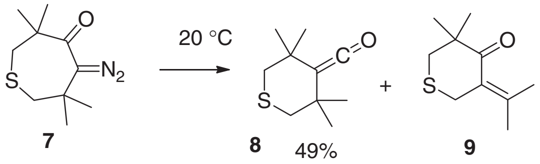
Due to the lack of methods for the preparation of α-diazo ketones, the synthetic utility of such rearrangement was kept buried for more than 20 years. With the advances in the acylation of diazoalkanes[6] and diazo transfer reactions,[7] Wolff rearrangement started to be used as a tool for the preparation of organic molecules and the first review in the Arndt–Eistert homologation reaction was published in 1942.[8] Later on, several reviews focusing on the Wolff rearrangement have been published.[4,9] On the occasion of the 100th anniversary of this reaction, Kirmse authored a comprehensive and very complete review on this topic,[10] whereas Tidwell reviewed the history of ketene discovery.[11]

3.19.1.2 Initiation Methods

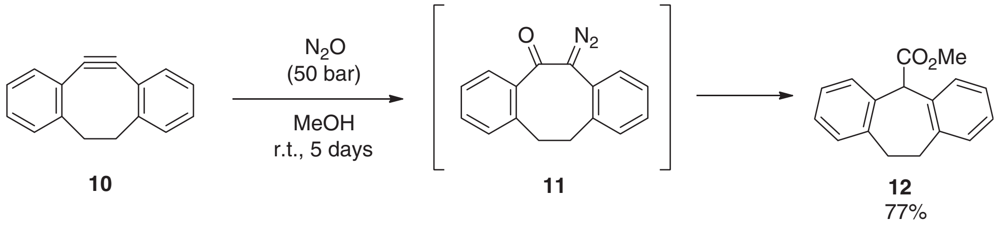
Besides the use of silver salts, the Wolff rearrangement can also be promoted by other methods such as thermolysis, photolysis, metal catalysts, or using microwave irradiation.[12]

3.19.1.2.1 Thermolysis

Thermolysis is usually avoided since temperatures as high as 180 °C are commonly needed, which can be even higher as reported for the gas phase pyrolysis of carbomethoxybenzocyclobutenone at 750 °C.[13] Although the thermal stability of α-diazocarbonyl compounds can be lowered by the presence of bulky substituents or by electronic means, the diazo group can be displaced by nucleophiles,[14] circumventing the rearrangement. Furthermore, the high temperatures employed can decompose the desired product. Nevertheless, the ketene formed in the rearrangement can be efficiently trapped using a high boiling point amine or alcohol as solvent, as reported for aniline and benzyl alcohol toward formation of anilide[4] and benzyl ester.[15] If the steric effects in the starting diazo carbonyl compound are so strong that the thermal stability is greatly reduced, as observed for twisted diazo ketone **7** due to ring strain (equation 1),[16] the decomposition is possible at room temperature and the ketene can be obtained and further reacted with a nucleophile such as methanol (Scheme 2).[17]



(1)



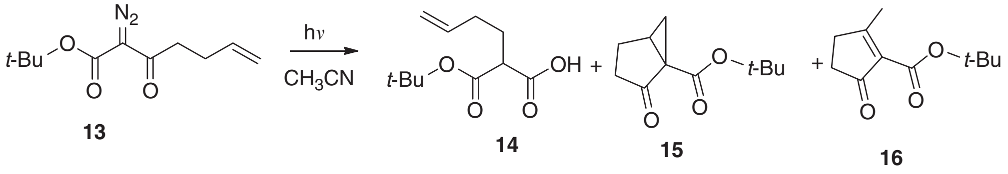
Scheme 2

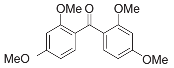
3.19.1.2.2 Photolysis

Irradiation of α-diazocarbonyl compounds, typically with a medium-pressure mercury arc lamp, as a tool to promote the nitrogen extrusion and formation of the ketene, has been first reported by Horner in 1951.[5a,18] Despite the excellent selectivities obtained with this method, which in several cases have been reported to be better than thermolytic or catalytic conditions, several issues should be considered. First, the photostability of the product formed should be taken into account, since the prolonged irradiation of photolabile compounds can easily result in the formation of byproducts. Second, depending on the irradiation wavelength used, different active species can be formed in solution, which on reaction lead to the formation of more than one product due to competing reactions.

The UV spectra of diazocarbonyl compounds show two absorption bands: 240–270 nm (stronger) and 270–310 nm. The use of protic solvents decreases the intensity of the first band relative to the second.[19] The excitation of the second band generates the lowest energy excited state (^1S) of the diazo ketone due to a $\pi \rightarrow \sigma$ overlap-forbidden transition. The use of higher energies can promote a second transition, relative to the 240–270 nm band, corresponding to a $\pi \rightarrow \pi$ excitation which may lead to byproduct formation.[20]

When photolysis is used as a method to induce the diazo moiety extrusion, additives to the reaction media can change the ratio of the species formed. The use of triplet sensitizers, such as benzophenone or derivatives, induce the formation of a carbene in the triplet state which in most cases leads to the formation of side-products such as **15** and **16** at the cost of the Wolff rearrangement product **14** (Scheme 3).[21] Notwithstanding the lower yields obtained for the Wolff rearrangement products, such experiments are very useful in mechanistic studies allowing one to discard or confirm the presence of triplet carbenes as intermediates in the Wolff rearrangement.



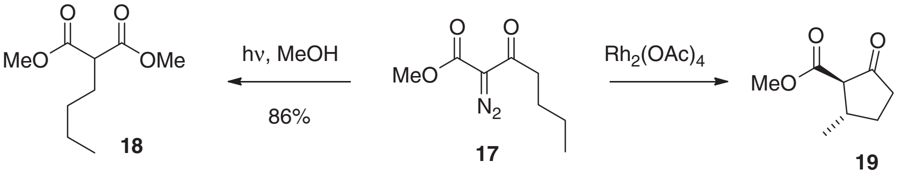
Entry	Additive	Ratio (%)		
		14	**15**	**16**
i.	None	83	17	
ii.		4	90	6

Scheme 3

In order to have a better control in the product distribution, a careful choice of the solvent should be made. The solvent can play a determinant role in the intermediaries' stabilization, as well as being responsible for the formation of unwanted side products. For instance, the use of *iso*-propanol or other nucleophilic solvents can lead to the formation of unwanted products derived from O–H or C–H insertion reactions.[22] Nevertheless, alcohols can be used to efficiently trap the ketene, allowing the formation of carboxylic esters, instead of the carbene that would lead to O–H insertion products.[23] Analogously, ammonium salts[24] and amines[25] can be used to prepare amides under photolytic conditions.

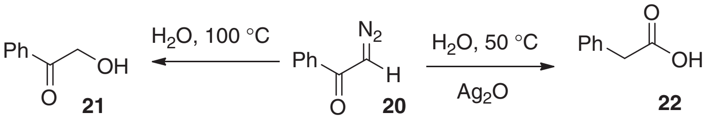
3.19.1.2.3 Catalysis

Silver salts have been the most widely used catalysts to promote the Wolff rearrangement. They were first reported by Wolff himself, but along the years other metals besides silver have demonstrated the ability to perform this rearrangement. The use of metal catalysts allows the reaction to proceed at lower temperatures (at room temperature in several cases), nevertheless the success of the reaction will strongly depend on the type of interaction with the metal. Metal complexes such as dirhodium(II) and copper(I) have the ability to form a somewhat stable metallocarbene after the nitrogen extrusion. In such cases, the stability of the metallocarbene is such that the Wolff rearrangement can be surpassed and typical reactions of metalocarbenes arise.[26] For instance, although the photolysis of 2-diazo-3-oxoheptanoate **17** leads to the formation of the Wolff rearrangement product **18** in 86% yield when the reaction was conducted in methanol, the presence of $Rh_2(OAc)_4$ promotes the C–H insertion reaction and cyclopentanone derivative **19** is exclusively obtained (**Scheme 4**).[21a]



Scheme 4

Besides dirhodium,[27] and copper,[28] platinum[3] and mercury[29] complexes and silver salts[4,30] have also been observed to promote the rearrangement. In the case of silver salts, the use of basic conditions by the addition of tertiary amines or carbonates is needed. The addition of base allows the reaction to proceed in a reproducible way, once the reaction using silver oxide alone usually proceed through a heterogeneous system and nonreproducible yields were commonly obtained.[30a] The use of ultrasound proved to be advantageous for the reaction rates, allowing the reaction to be performed at room temperature with silver salts.[31] Perhaps the best example about the influence of the reaction conditions on the products' distribution is the one reported by Wolff.[1b,1d,3] Although diazoacetophenone **20** yielded the expected alcohol in boiling water, phenyl acetic acid **22** was obtained when silver oxide was used (**Scheme 5**).

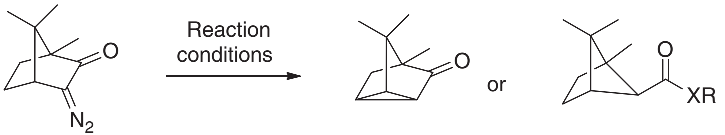


Scheme 5

In situ-generated silver nanoclusters have been recently reported to be efficient promoters for the Wolff rearrangement of several α-diazoketones. The redox process was accomplished by the reduction of silver(I) oxide (Ag_2O) resulting in the *in situ* formation of Ag_n responsible for the nitrogen extrusion and concomitant Wolff rearrangement. The controlled potential coulometry coupled with cyclic voltammetric studies suggested a reaction mechanism comprising an electron transfer followed by a chemical reaction in an electrocatalytic manner. The presence of pyridine in the reaction medium gave rise to the formation of a UV–vis band indicative of the presence of a ketene or carbene in the reaction medium. The reaction could be successfully employed to several α-diazoketones in excellent yields, being dependent on the α-substituents of the diazo compound.[30d,32]

3.19.1.2.4 Other methods

Besides the methods described so far, other approaches have been developed to achieve the ketene formation starting from α-diazo carbonyl compounds. Microwave irradiation[33] of diazo compounds has been employed as a way to induce the ketene formation which was trapped by benzyl amine. A combination of the microwave effect and the dielectric constant of the solvent was claimed to be on the basis for the success of the Wolff rearrangement of ring strained 3-diazocamphor **23** (**Scheme 6**). The irradiation of 3-diazocamphor substrate **23** with microwaves in benzylamine exhibited nonthermal effects and yielded exclusively the Wolff rearranged product **25** in a way similar to that observed under photochemical conditions. The microwave irradiation was also employed in the Wolff rearrangement of cyclic 2-diazo-1,3-diketones leading to the formation of ring-contracted products and further used in the preparation of cycloalkanones[34] and α-spiro-δ-lactones.[35]



23 **24** **25**

Entry	Reaction conditions	**24** (C–H insertion)	**25** (Wolff Rearrangement)
1	Microwave, $PhCH_2NH_2$	–	73% (XR = $HNCH_2Ph$)
2	Δ, 180 °C, $PhCH_2NH_2$	43%	–
3	Microwave, H_2O	70%	–
4	h*v*, Dioxane: H_2O	–	40% (XR = OH)

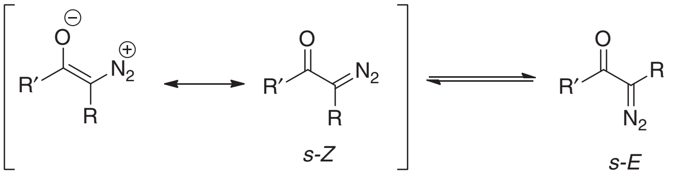
Scheme 6

3.19.2 Mechanistic Considerations

The Wolff rearrangement can occur in a stepwise or concerted fashion, meaning that the nitrogen extrusion can occur with a carbene formation followed by the 1,2-shift or bypassing the formation of this intermediate. The conformation of the starting diazo compound has been pointed as a crucial topic for the pathway of the reaction, as well as dictating which of the substituents suffer the 1,2-shift. Additionally, considering the method used for the Wolff rearrangement initiation, other species can be relevant for the reaction mechanism. For instance, when dealing with photolytic methods, excited states of the starting diazo compound can be on the basis of a concerted pathway, which can happen only if both leaving group (N_2) and the migrating group are oriented in an antiperiplanar manner. Regarding the protonation of α-diazocarbonyl compounds in acidic media, the carbonyl moiety is more basic in equilibrium conditions however the *C*-protonation of the reactant is also expected as observed in hydrolysis studies.[36]

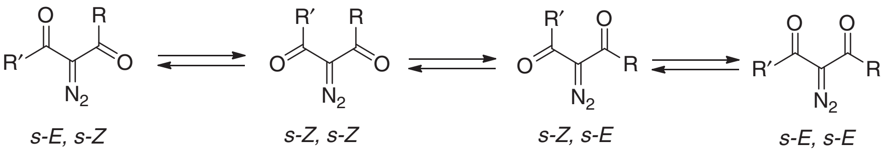
3.19.2.1 Stereochemistry of α-Diazocarbonyl Compounds

Unless bulky substituents are present, α-diazoketones tend to adopt a conformation in which the C=O and C=N_2 are in the same plane. In the case of acyclic structures, such planar geometry can exist in two interconvertible forms, as demonstrated by the partial double-bond character of the C–C bond observed by spectroscopic studies.[30d,37] Therefore, α-diazoketones can exist in the *s-Z* and *s-E* conformations (**Scheme 7**), and the population level will depend on the substituents of the diazoketone. In the absence of bulky substituents, the *s-Z* conformation will be the most populated. A NMR conformational study demonstrated a 7:3 *s-Z*/*s-E* ratio for the aldehyde (R′=H), corresponding to a 1.33 kcal mol^{-1} energy difference between both conformations.[38] When changing R′ to methyl, ethyl, or benzyl groups the same ratio increases to 9:1, with an energy barrier between both conformations ranging from 15.5 kcal mol^{-1} (R=Et) to 18.2 kcal mol^{-1} (R=Bn), whereas the presence of *tert*-butyl group completely suppress the *s-E* conformation.[37] The presence of one or more chlorine atoms in the alkyl group of diazoacetone, also leads to a marked preference toward the *s-Z* conformer, which can be elucidated by the dipole moment values of the molecules.[39] The presence of an aryl in diazoacetone derivative (R′=aryl; R= H) can also change the distribution of population toward the *s-Z* conformation. In this case, although the presence of *para*-substituents, such as methyl, or halogens increases such preference, the introduction of substituents at the *ortho*- or *meta*-position increased the population in the *s-E* conformation and both conformers can exist in solution.[40] The preference for such conformation is attributed not only to stereochemical constrains, i.e., the molecule adopting a conformation such as the repulsion interaction between R′ and N_2 are diminished, but also due to electronic effects. Likewise, the sterically hindrance between R and R′ substituents can be compensated by additional electrostatic interactions.[36c] The attraction effect between the charge of the oxygen carbonyl to the central nitrogen of the diazoketone is also responsible for the preference toward *s-Z* conformation.[36c,38] In the case of diazo acetic esters (R′=alkoxy), the energy of activation is considerably smaller (9–12 kcal mol^{-1}) than for the diazo ketones, due to the presence of a cross-conjugated system that reduces the double-bond character of the central C–C bond.[37b]

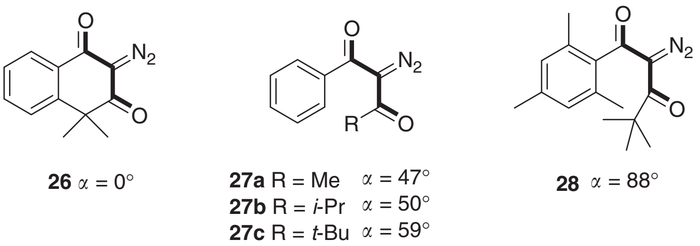


Scheme 7

If an extra carbonyl is present in the molecule, like in the case of 2-diazo-1,3-diketones or diazo malonate derivatives, there are four (R′≠ R) or three possible (R′=R) planar stable conformations (Scheme 8). Considering R′≠R, both carbonyls can be oriented to the same side of the N_2 moiety (*s-Z,s-Z*), one of the carbonyls can be to the opposite side of the other carbonyl and the N_2 group (*s-E, s-Z* and *s-Z, s-E*) or both carbonyls can be on the opposite side of the N_2 group (*s-E, s-E*). Analogously to the diazoketones case, the population of both conformations will be strongly dictated by the bulkiness of the substituents. The planarity of the CO–CN_2–CO fragment (α in Scheme 9) is strongly influenced by the presence of alkyl substituents as observed for acylaroyldiazomethanes **27** and **28**. Hence, the bulkiness of the substituents, which deviates the CO–CN_2–CO angle from planarity, linearly influences the thermal decomposition rates of acyclic diazo dicarbonyl compounds.[41] Regarding the diazo compound derived from ethyl malonate (R=R′=OEt), three completely flat conformations were determined by density functional theory means, demonstrating the absence of substantial steric interactions, in which the *s-E, s-E* was predicted to be the least stable whereas the *s-Z, s-Z* and the *s-E, s-Z* conformations had similar energies. Once again, the preference for the *s-Z* arrangement is explained by the electronic attraction of the positively charged nitrogen to the oxygen of the carbonyl group and the barrier for the interconversion between conformations was calculated to be in the 7.6–9.8 kcal mol^{-1} range.[42]



Scheme 8



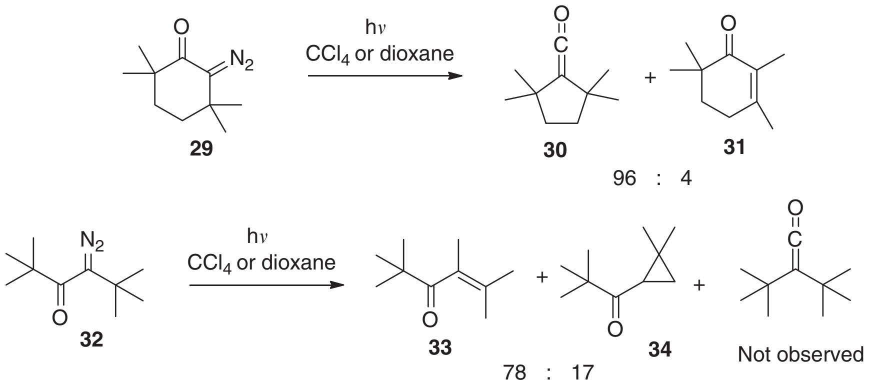
Scheme 9

3.19.2.2 Concerted and Stepwise Pathways

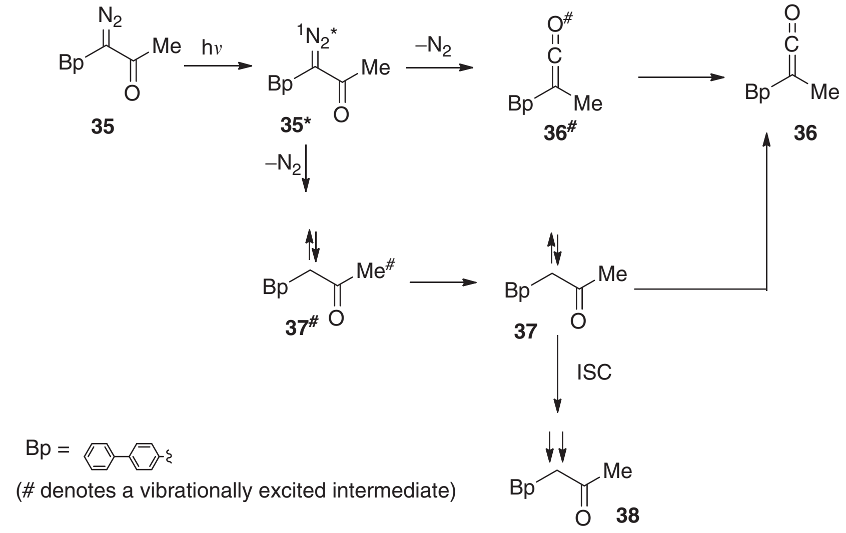
Despite the extensive studies on the clarification of the Wolff rearrangement mechanism, a general mechanism for this transformation has not been postulated. Nevertheless, the conformation of the starting diazo compound and the ketone substituents has been pointed as key factors in the carbene formation.

In 1966, Kaplan and Meloy suggested that the direct ketene formation arises only from the *s-Z* conformation of the diazo carbonyl compound, and that the use of heat or light activation of *s-E* conformers promoted the stepwise mechanism.[37b] This rule has been verified for acyclic diazo carbonyl compounds in which the *s-Z* conformation was determined to be 9 kcal mol^{-1} less stable than the *s-E* conformer. In this case, the ketene formation or products derived thereof were not observed under photochemical of thermolytical conditions which was attributed to the presumed *s-E* configuration preference of the substrate **32** (Scheme 10).[43] The formation of ketene derived from *tert*-butyl disubstituted diazo compound was later observed in the gas phase and excited vibrational states of the starting diazo compound or the carbene were suggested as being responsible for the ketene formation.[44]

The corroboration of this aspect has been done along the years, mainly based on the chemical analyses of stable photoproducts. However with the development of ultrafast flash photolysis, new evidences pointing in other directions have been brought to light.[45] The time-resolved UV–vis and IR spectroscopic studies of $BpCN_2COMe$[46] **35** and $BpCOCN_2Me$[47] confirmed that the concerted and stepwise pathways contributed with similar quantum yields to the ketene formation. If a carbene is formed, it can exist in the triplet or singlet state and its population will depend on the energies of each level. The differences in energy, known as the singlet-triplet gap, will be responsible for the ability of its intersystem crossing (ISC) and consequently dictate the product distribution. Conformational factors and the nature of the solvent influence the singlet-triplet energy difference and smaller differences in energy lead to faster ISC.[9a,45] Additionally, other species such as a singlet diazo excited state have been suggested to be in the basis for the formation of a hot carbene (Scheme 11). Two pathways with different rates for the ketene formation have been identified. Hence, the excitation of the diazo compound leads to the concerted ketene formation whereas the stepwise pathway is a slower process and the ketene formation arises from the relaxed singlet state of the carbene.



Scheme 10



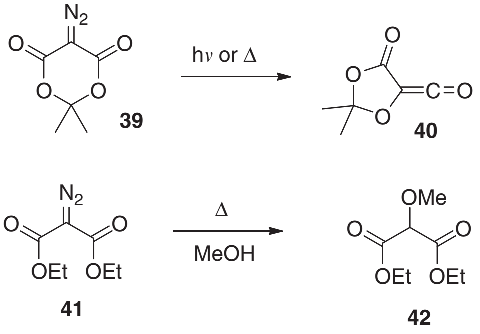
Scheme 11

In the case of simpler diazo acetone, similar conclusions regarding the origin of the ketene have been withdrawn. In this case, due to the molecule preference in adopting an *s*-*Z* conformation, the carbene contribution was determined to be the minor one (which is in strong agreement with the Kaplan's and Meloy's first proposal). According to this rule, the rearrangement of cyclic diazo ketones should in principle occur through a concerted process, once the compound is locked in an *s*-*Z* conformation. However, recent investigations on the photolysis of diazonaphthoquinone suggest that the indirect ketene formation through a carbene pathway might also be involved.[48] Summarizing, to the light of these new findings, ketene formation from diazo ketones can happen through a concerted or a stepwise process (via carbene), although the substituents of the ketone play a determinant role in the conformation of the substrate.

Regarding the nature of the intervenient species for the ketene formation, at the current time, there is not a complete agreement on the presence of a carbene. Although Tomioka pointed the excited state of the methyl diazo acetate as the species to suffer a concerted rearrangement toward ketene formation,[49] Toscano[50] and coworkers demonstrated that the ketene was formed almost exclusively from the carbene derived from methyl-2-diazo-(2-naphthyl)acetate which was later supported by laser flash photolysis investigations.[51] In any case, a lower ketene formation ability of diazo excited states of diazo esters or carbene esters when compared with corresponding ketones was speculated due to the loss of the ester resonance.[45a,46a]

Different hypothesis have been advanced for malonate derivatives. When comparing the thermal and photolytic reactions of acyclic ethyl diazomalonate and cyclic Meldrum's acid, two different dediazotization pathways were advanced.[42,52] Acyclic carbene malonates can adopt a conformation in which the carbonyl group is orthogonal to the carbene plane, reducing the energy of the singlet carbene by conjugative stabilization of its unshared pair. However, carbonyl carbenes incorporated in a small to medium-sized cyclic systems cannot achieve the same stabilization. For this reason, a concerted pathway is more likely to occur in cyclic systems (through diazo excited state in photolytic conditions),[53] whereas a stepwise mechanism through carbene formation is preferential in acyclic systems such as malonic ester derivatives. The marked difference in the cyclic versus acyclic compounds reactivity is demonstrated by the product distribution under thermal and photolytic conditions. Although the decomposition of

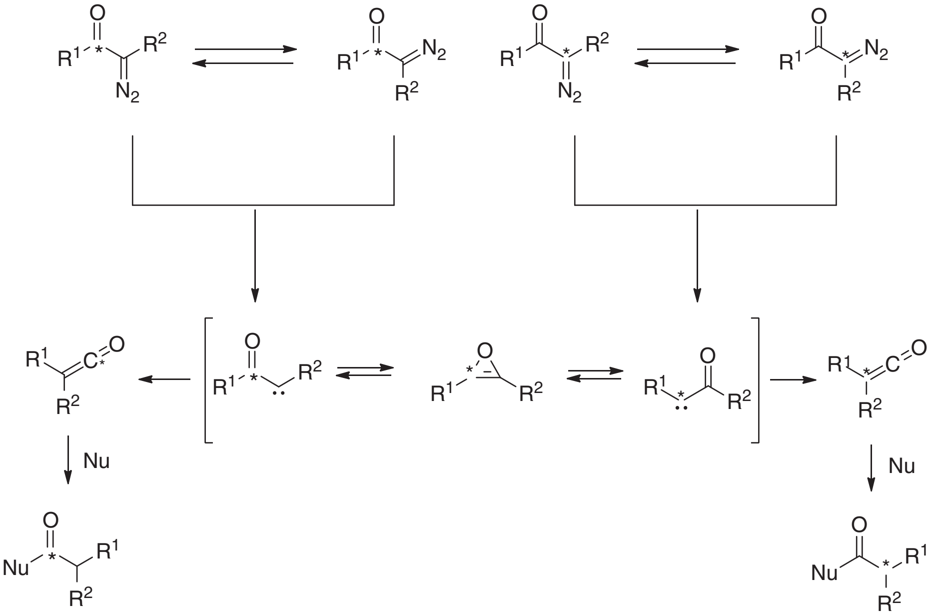
Meldrum's acid **39** leads preferentially to Wolff rearrangement product **40**, the dediazotization of the acyclic homolog **41** leads to the exclusive formation of carbene derived product **42** (Scheme 12).[54] Diazirine isomer of diazo Meldrum's acid isomerizes to the diazo compound under thermal conditions, whereas under UV irradiation a dicarbonylcarbene intermediate was advanced to be on the basis of the Wolff rearrangement mechanism[52] although a pathway surpassing the formation of the carbene was also advanced.[55] The isomerization of the diazo Meldrum's acid to the aziridine is also feasible through a different excited state, resulting in the ylide formation after carbene trapping by the alcoholic solvent.[53,56]



Scheme 12

3.19.2.3 Oxirene Participation

The presence of an oxirene as an intermediary in the Wolff rearrangement has been first pointed in 1935.[57] Such species have been suggested to be on the basis of the oxocarbene isomerism. Along the years, several studies on Wolff rearrangement have been made in an attempt to isolate and/or characterize oxirenes.[58] Several experiments in the photochemical decomposition of labeled α-diazo ketones which have resulted in a label scrambling in the product have been reported.[59–62] If a carbon of the carbonyl α-diazo compound is isotopically labeled, the interconversion of the carbene formed into the isomerized oxocarbene will be reflected in the labeled-carbon position of the final product. In such case, the presence of a transient oxirene can explain the oxocarbene isomerization (Scheme 13). Despite the scarce experimental evidences on the existence of oxirenes, alternative mechanisms for the oxocarbene interconversion have not been completely established. However, their presence is still puzzling and seems to be dependent on several constrains. Despite its challenging nature, the search and characterization of oxirenes as intermediates or transition states in the oxocarbene isomerism resulted in few experimental evidences in the latest years. However,

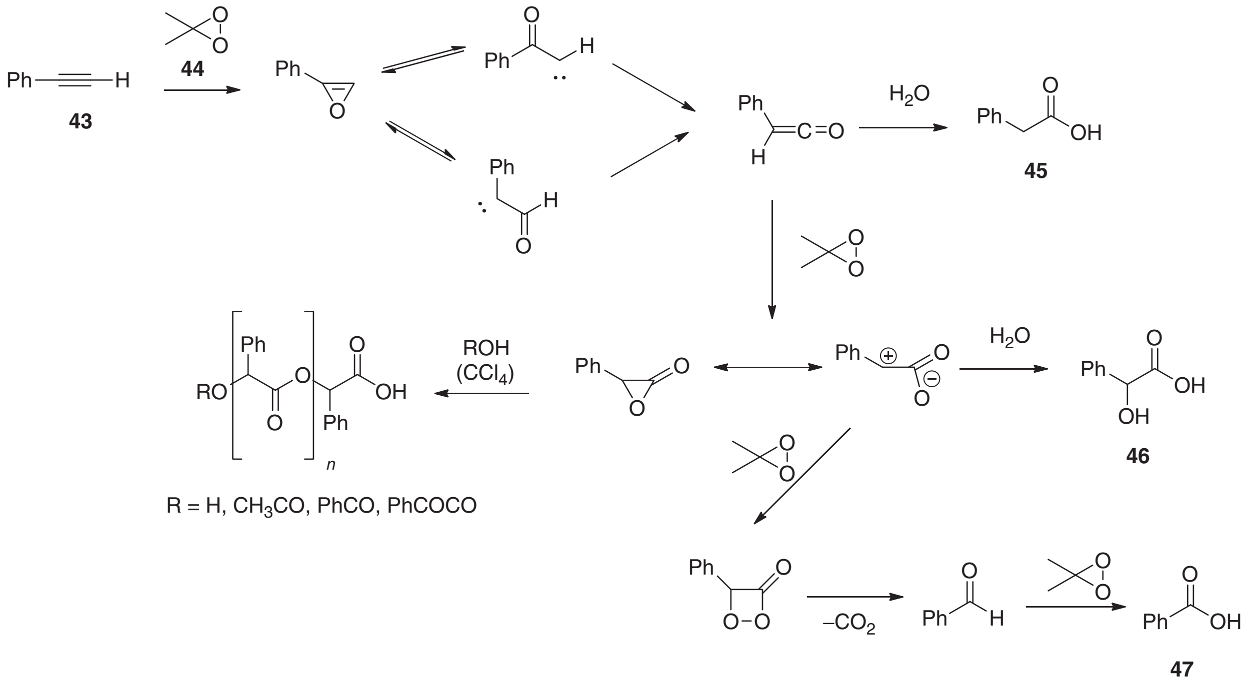


Scheme 13

several computational and theoretical studies on the nature of oxirenes have been performed[63] and the topic has been extensively reviewed.[10,58a,b]

The interconversion of oxocarbenes is dependent on the carbene stability, conformational effects, and/or migratory aptitudes. For instance, if the energy gap between the singlet and the triplet state are close enough so that the carbene can populate both states, the isotopic scrambling can be surpassed due to triplet state quenching by the solvent, as observed for low migratory trifluoromethyl substituent containing substrates.[64] Substituents with weaker migratory aptitudes tend to increase the isotopic scrambling whereas six- and seven-membered ring-derived carbenes in a locked *s-Z* conformation do not perform the oxocarbene equilibrium.[54a] However, when considering larger rings such as 12-membered ones, the *s-Z* locked constrain is lost and the isotopic scrambling can be observed.[65] The isotopic scrambling is also dependent on the solvent nucleophilicity. Increasing the nucleophilic ability of the solvent usually leads to decreased isotopic scrambling, probably due to the fastest quenching of the ketene. The method used to initiate the rearrangement also influences the isotopic scrambling, since higher scramble levels have been observed for the photolytic methods than for the thermal ones. This evidence have been supported by extended-Hückel molecular orbital calculations that indicated that rearrangement of the oxocarbene to oxirene require excess vibrational energy, meaning that only the 'hot' carbene can achieve the upper vibrational level of its ground electronic state.[66]

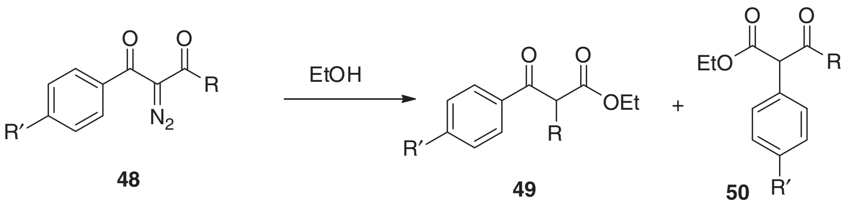
In an attempt to demonstrate the possible involvement of an oxirene in oxocarbene isomerism and consequently in the Wolff rearrangement, Zeller and coworkers[67] adopted a different strategy than the isotopic scrambling mentioned. The oxidation of phenylethyne **43**, with isolated or *in situ*-generated dimethyldioxirane **44** yields mandelic acid **46** and/or phenylacetic acid **45** as main products. Despite the importance of the water content on the reaction conditions, the authors claimed that the formation of both acids is prevenient from phenyloxirene, in which phenylacetic acid **45** is formed by direct quenching of the carbene by water and mandelic acid **46** by further oxidation with dimethyldioxirane **44** (Scheme 14). Additionally, benzoic acid **47** is formed after decarboxylation and a sequence of oxidations.



Scheme 14

3.19.2.4 Migratory Aptitude

A wide variety of substituents of the α-diazo carbonyl compound are able to migrate. Hydrogen,[68] alkyl,[18,21a,69] aryl,[15,30a,68,70] amines,[71] alkoxy,[22,72] and thioalkyl[73] are known to migrate under rearrangement conditions. The relative migratory aptitude of a substituent is increased if the migrating center has a high electronegativity and an electron-poor $R{-}C{=}O$ bond.[12a] Nevertheless, the migratory aptitude of the substituents does not solely depend on the electronic nature of the substituent, but also and mainly on the reactant conformation and the duality concerted and nonconcerted mechanisms. Therefore, the ranking of migratory aptitudes is not fully disclosed, although hydrogen comes as the first in the migratory ability ranking. Previous studies have demonstrated that under thermolytic conditions, phenyl migrates more readily than methyl substituent (Scheme 15). If photolytic conditions are used, this tendency is opposite and methyl is able to migrate faster than phenyl. The substituents of the

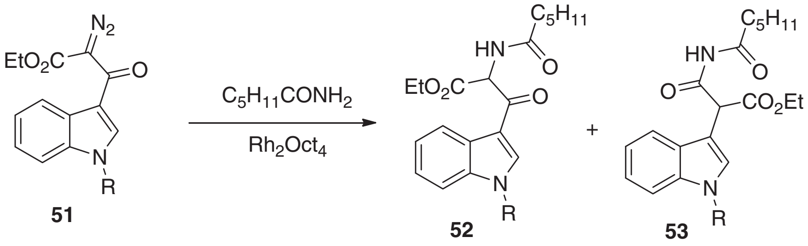


Entry	R	R′	Conditions	Yield (%)	
				49	**50**
i	H	H	Δ	>90	
ii			hν	>90	
iii	Me	H	Δ	28	46
iv			hν	61	3
v	Me	OMe	Δ	18	56
vi			hν	40	13
vii	Me	NO_2	Δ	21	–
viii			hν	15	–

Scheme 15

aromatic ring moderately affect the migration ability, and the presence of 4-nitro in the phenyl ring can suppress the aryl migration in favor of the methyl migration.[68]

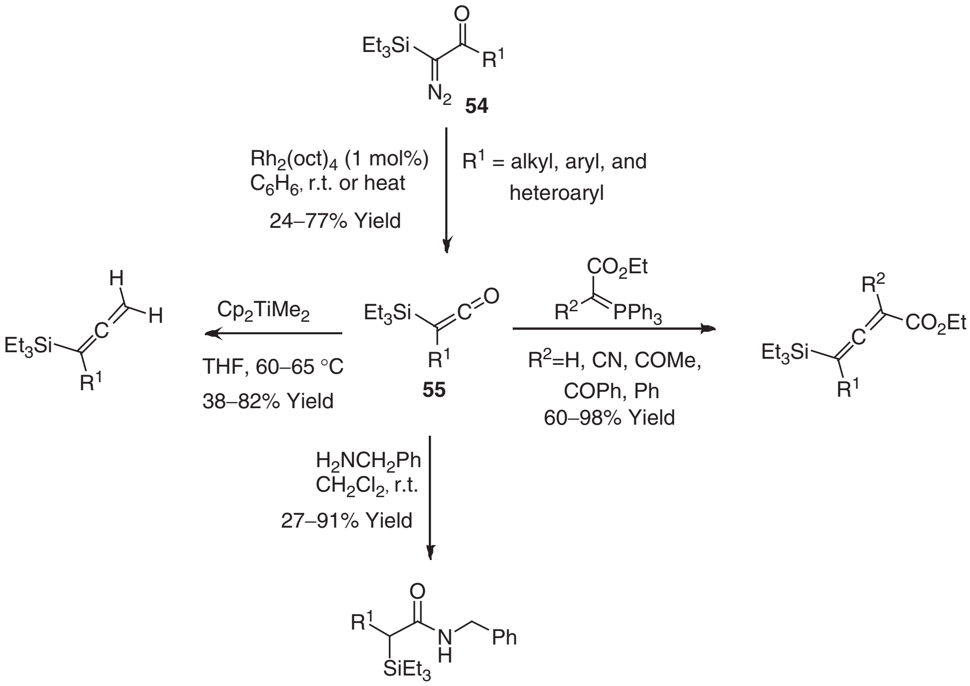
The indole moiety was observed to own a good migratory aptitude toward Wolff rearrangement. The use of dirhodium compounds for the decomposition of α-diazo ketones rarely leads to the formation of ketenes. However, the dirhodium-catalyzed decomposition of 3-indolyl diazoketoesters **51** results in the ketene formation followed by interception with an amide to form **52** (Scheme 16). The migratory aptitude of the indole moiety is extremely dependent on the electronic character of its substituents, and the presence of electron-withdrawing substituents in the nitrogen of the indole suppresses the formation of the rearrangement product **53**.[27d] Dirhodium complexes are also good promoters in the Wolff rearrangement of α-silyl-α-diazo ketones **54**. Persistent $R_3SiR'C{=}C{=}O$ ketenes **55** are formed in the presence of dirhodium complexes[74] or under photolytic irradiation[75] starting from $R'COCN_2SiR_3$ **54**. Contrarily, their thermal decomposition results in the silyl shift from carbon to oxygen.[76] These persistent ketenes have been trapped with amines and modified by Wittig-type alkylidenation with carboethoxy-stabilized phosphoranes and methylenation with the Lombardo or Petasis reagent (Scheme 17).[74]



Entry	R	Yield (%)	
		52	**53**
		(N-H insertion)	(Wolff Rearrangement)
i	Boc	39	55
ii	$BrC_6H_4SO_2$	52	23
iii	$NO_2C_6H_4SO_2$	52	0
iv	Me	0	81

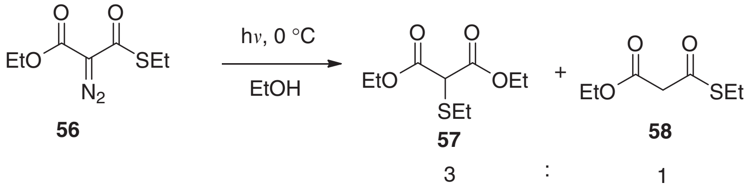
Scheme 16

Alkoxy substituents can also migrate, although usually in low yields due to side reactions such as O–H or C–H insertions and hydrogen abstraction reactions. Additionally, the presence of agents able to stabilize the carbene through electronic delocalization decreases the alkoxy migratory aptitude.[22,72] Thioalkyl substituents are better migrants than alkoxy ones, as observed in the photolysis of malonyl monothioester derivative **56** (equation 2).[73d] However, amines were observed to lack a suitable reactivity toward Wolff rearrangement, and the photolysis of diethyldiazoacetamide leads to the formation of the rearranged product in low yield contrasting to the preferential reactivity toward C–H and O–H insertion reactions.[71a,b] Such preference toward C–H insertion can be explained based on the low migratory aptitudes of the amine in conjugation with conformational factors of the



Scheme 17

diazo acetamide. The presence of the nitrogen atom allows the substrate to adopt a conformation that puts a C–H bond close to the carbene center, making the intramolecular C–H insertion a preferential pathway.[71a,b,77]



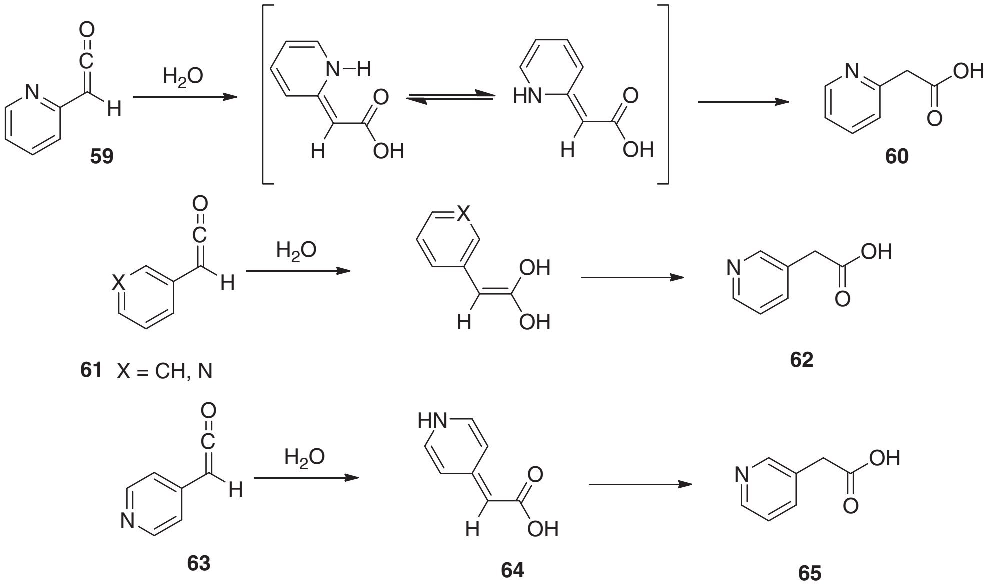
(2)

In summary, the general ranking of migratory ability in photochemically induced Wolff rearrangement is $H > alkyl \geq aryl > SR > OR \geq NR_2$. For thermally induced reactions, alkyl and aryl exchange places, whereas heteroatoms do not migrate, hence the series is $H > aryl \geq alkyl$.

3.19.3 Applications

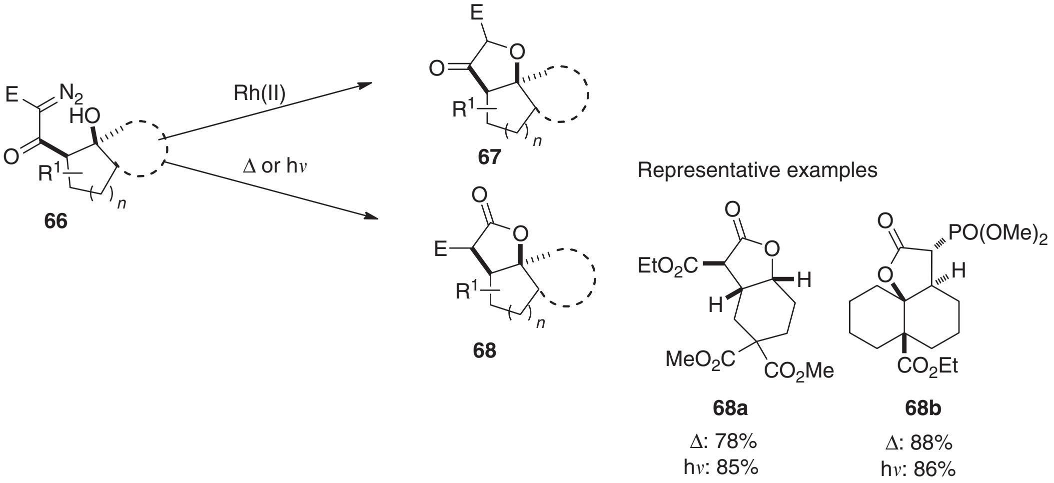
3.19.3.1 Reactions of Ketenes Derived from the Wolff Rearrangement with Nucleophiles

Ketenes derived from the Wolff rearrangement can be efficiently trapped by a wide variety of nucleophiles, in which water, alcohols, and amines are the most common ones to furnish carboxylic acids, esters, and amides, respectively.[78] Additionally, they can also be trapped by radicals like nitroxyl radical tetramethylpiperidinyloxyl (TEMPO) to yield a 1,2-diaddition product[79] or dimethyl sulfide to provide the sulfur ylide in low yields though.[80] The hydration of ketenes to form carboxylic acids can be uncatalyzed, hydroxide catalyzed, and hydronium catalyzed. The hydroxide-ion catalyzed and the uncatalyzed hydration reactions happen through direct nucleophilic attack on the carbonyl carbon of the ketene, in which the presence of bulky substituent groups on the ketene slows the reaction kinetics.[81] The hydration of ketenes, along with hydration of other carbonyl compounds, involves multiple water molecules creating a water cluster around the ketene. Several structures with different amounts of water molecules around the ketene have been considered in computational studies. Phenylketene **61** (X=CH) and 3-pyridylketene **61** (X=CN) hydration involves formation of a transient acid enol that is converted to the product **62** in a subsequent rapid step. However the position of nitrogen atom of the pyridyl moiety plays a determinant role in the reaction rate. For instance, 2-pyridyl ketene **59** undergoes hydration through the formation of two isomeric dihydropyridines, and 4-pyridyl ketene **63** leads to a 1,4-dihydropyridine **64** which is converted to pyridylacetic acid **65** in a 10^3 times slower process (Scheme 18).[82] Similar hydration rate constants for ketenes bearing a 2- or 3-thiophenyl or furyl substituent as for 2-, 3-, and 4-pyridylketenes were observed.[83]



Scheme 18

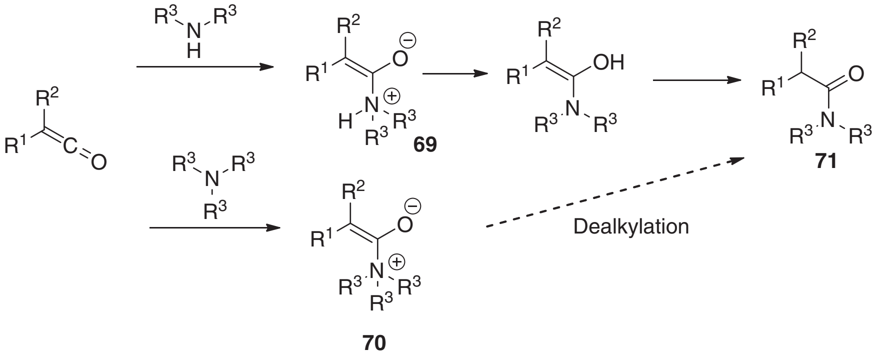
Due to the possibility to perform the ketene generation without introducing any other reactants in the reaction mixture, this has been used to perform photolithographic attachments of functional organic molecules via ester or amide linkages[84] or to pattern cells and biomolecules by diazoketo-functionalized photoresists after entrapment of the ketene with water.[85] Ketenes derived from the Wolff rearrangement can be intramolecularly trapped by the presence of a hydroxyl group. Depending on the type of reactions conditions used to initiate the nitrogen extrusion reaction of α-diazo-β-ketoesters **66**, furanones **67** or lactones **68** can be obtained (Scheme 19). Although the presence of a metalocarbene mediated by the dirhodium complexes leads to the formation of furanones **67** through an intramolecular O–H insertion reaction, the thermal or photochemical decomposition of the same compound leads to the formation of the ketene. The nucleophilic attack of the neighboring OH group to the ketene results in the formation of lactones **68** in good yields, in which O–H insertion is a minor path (5–18%) in the thermal process and absent in the photolytic one.[86]



Scheme 19

The treatment of trialkylsilyloxy substituted α-diazo-α-ketophosphonates with $Rh_2(OAc)_4$ results in ketene formation followed by intramolecular nucleophilic attack of the silyl ether and migration of the silyl group to provide a α-phosphono-δ-lactone.[27a] In the absence of the silyl ether group, C–H insertion products are provided whereas the Wolff rearrangement is a minor process.[87]

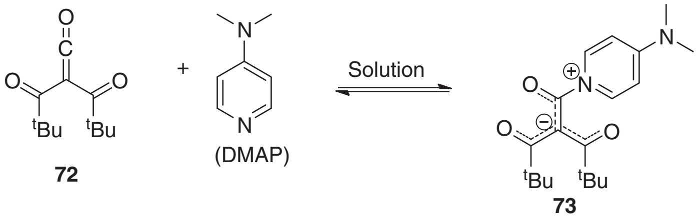
The addition of amines to ketenes has been widely studied in acetonitrile solutions.[82b,88] The direct addition of an amine to a ketene leads to the formation of a zwitterionics species that tautomerizes to the final amide **71** if a primary or secondary amine is used, or dealkylates by alkene loss[89] to yield the amide **71** if a tertiary amine is the nucleophile (Scheme 20). The nucleophilic



Scheme 20

strength of several amines toward addition to ketenes has been studied by laser flash photolysis. Secondary amines are stronger nucleophiles than tertiary ones suggesting that the base acts as a nucleophile by direct attack to the ketene carbon atom. Tertiary amines (triethylamine) react more slowly than secondary ones (diethylamine) by approximately 1000 and the reaction rates are also dependent on steric effects of both the ketene and the amine. This last effect seems to be responsible for the similar reactivity between secondary and primary amines.[88b] The use of water as the reaction solvent lowers the reactivity by two orders of magnitude when compared with acetonitrile.[90]

The first α-oxoketene-pyridine zwitterion **73** was isolated after reaction of dipivaloylketene **72** with 4-(dimethylamino)pyridine (DMAP). The zwitterion is stable at −60 °C, although in solution at room temperature it quickly cleaves into the reactants (Scheme 21). Ketene dimers derived from dipivaloylketene also react with DMAP to furnish the zwitterion. If 4-aminopyridine is used instead of DMAP, the amide derived from the NH_2 nucleophilic attack is obtained. In the presence of amines or alcohols, the zwitterion is converted into the corresponding amides or alcohols in moderate to good yields.[91] The quenching of ketenes can also be performed by 2H-azirines whereas the resulting zwitterion proceeds to the formation of (4 + 2) monoadducts through a stepwise nonpericyclic mechanism.[92]

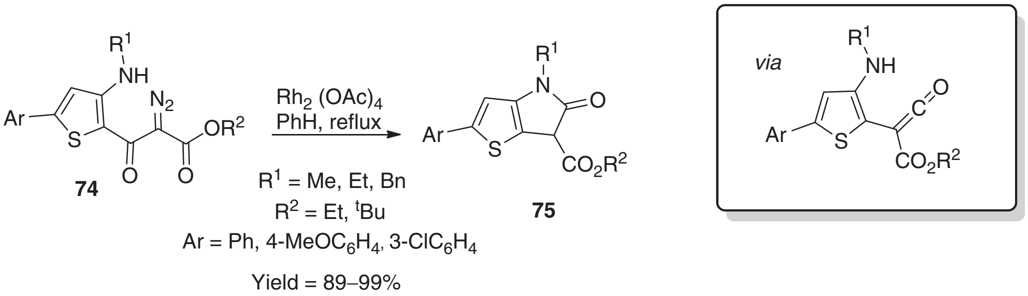


Scheme 21

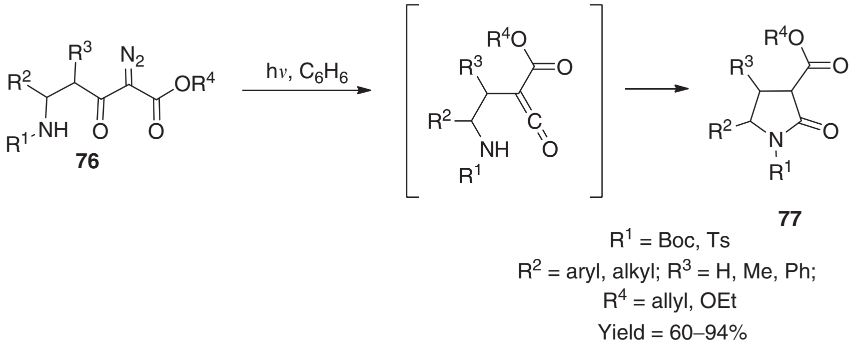
In the context of organic synthesis, the entrapment of ketenes derived from the Wolff rearrangement with amines has been explored in the preparation of amides in good yields (68–92%) using microwaves to promote the ketene formation,[33] as well as amide formation of a ketose derivative employing silver salts as rearrangement promoter,[93] or in the modification of ferrocene derivatives.[94] A photolabile end functionalized monomethyl poly(ethylene glycol) containing a terminal α-diazo ketone moiety was used to monofunctionalize lysozyme and ribonuclease. The reaction was achieved by ketene formation triggered by UV light irradiation of the modified PEG derivative and subsequent quenching of the ketene with the respective protein.[95]

Intramolecular ketene quench with amines has been reported even in the presence of dirhodium catalysts. In an attempt to isolate the N–H insertion product onto the metallocarbene derived from the reaction of a α-diazo-β-ketoester **74** bearing a secondary amine, an alternative way to prepare thienopyrrolones **75** was developed. An hydrogen bond formed between the secondary amine and the carbonyl of the ketone forcing a *cis* conformation of rhodium carbenoid and the keto carbonyl group was advanced to be a promoter for the Wolff rearrangement toward ketene formation (Scheme 22).[27b] Other examples of intramolecular quench of ketenes through tertiary amine intramolecular nucleophilic attack have been reported, as for α-diazo-β-ketophosphonates resulting in a consequent [1,5]-H shift-ring closure sequence.[96] Protected amines with a trityl group can also react intramolecularly with ketenes. This strategy has resulted in the formation of β-lactams under photolysis conditions,[97] as well as by using dirhodium complexes.[98]

Boc- and tosyl-protected amines **76** are also efficient ketene quenchers under photolytic conditions, although sulfinyl protected ones failed in the same reaction (Scheme 23).[99] For the tosyl protected amines, the presence of an alkyl group at the β-position of the starting diazo compound (R^2) led to the product **77** formation in lower yields due to the existence of competitive migration of the two substituents of the carbonyl groups. Such methodology was applied to the preparation of γ-lactams in excellent yields



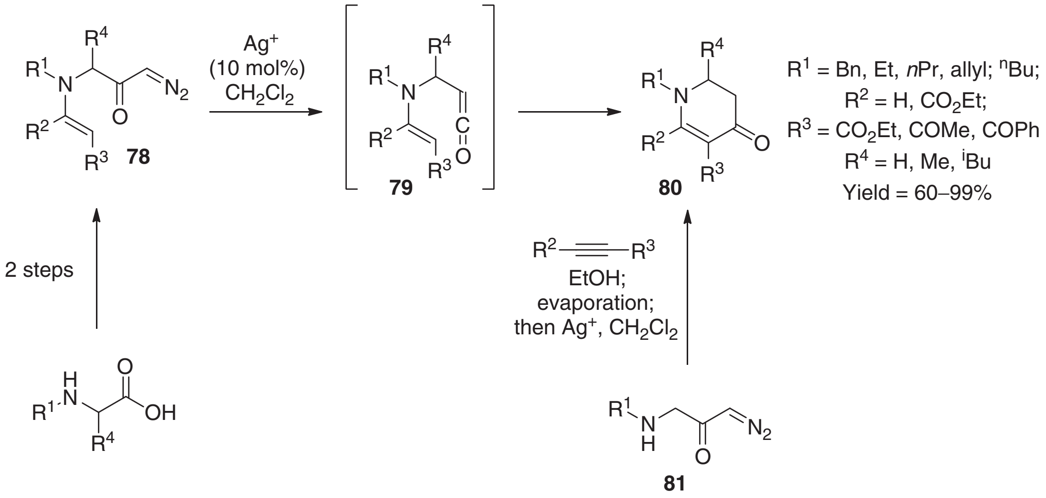
Scheme 22



Scheme 23

although in moderate diastereoselectivities when tosyl was used as the amine protecting group. The use of dirhodium complexes as reaction promoters resulted in the intramolecular N–H insertion reaction of the metallocarbene, evidencing once more the difficulty of these catalysts to promote the Wolff rearrangement and subsequent ketene delivery.

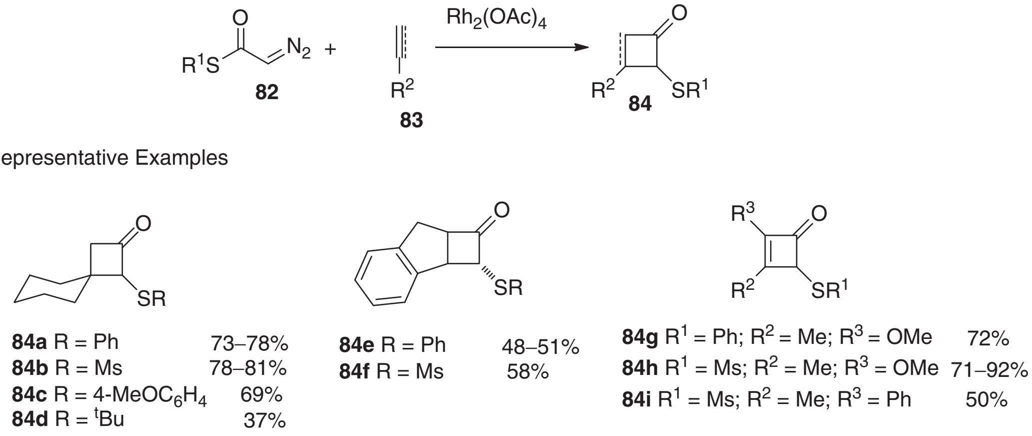
Reports on the use of carbon nucleophiles to trap the ketene derived from the Wolff rearrangement are scarce. An expeditious way to prepare enaminones **80** from diazoketones **78** carrying a pendant enamine moiety has been developed (Scheme 24).[100] Silver salts such as $PhCO_2Ag$ or Ag_2O were used as sources for the ketene **79** formation and the subsequently carbon nucleophilic attack of the vinylogous amide through a rare *6-exo-dig* cyclization provided the desired enaminone. Starting from α-amino-α-diazoketones **81**, a sequential procedure for the formation of the enaminone **78** through an aza-Michael addition, Wolff rearrangement, and ketene cyclization was further optimized.[100b]



Scheme 24

3.19.3.2 Cycloaddition Reactions of Ketenes Derived from the Wolff Rearrangement

Due to the high reactivity of ketenes, they can react through a [2 + 2] cycloaddition reaction with alkenes in order to prepare cyclobutanones. Diazo compound **39** derived from Meldrum's acid was reported to react with cycloalkene derivatives forming a 2-spirocyclobutanone under photolytic irradiation.[54c,101] $Rh_2(OAc)_4$ is an efficient promoter for the Wolff rearrangement of aryl α-diazo thiol esters **82** and the ketenes formed react in a [2 + 2] cycloaddition with unactivated ketenophiles such as methylenecyclohexane to yield **84** (Scheme 25). The reaction can be performed with a variety of alkenes, including cyclic ones, which in this case result in the formation of the product with an *endo* orientation, whereas *trans* adducts are obtained for acyclic alkenes. Alkynes are also good partners in this method and cyclobutenones can be obtained in the same way.[102] Intramolecular [2 + 2] cycloaddition of ketenes with alkenes can be performed employing photolytic irradiation of the diazo compound for ketene generation in order to prepare fused cyclobutanones in good yields.[103]



Scheme 25

Ketenes derived from the Wolff rearrangement can also react intramolecularly with conjugated cycloalkenones after irradiation of the starting diazo compound with UV light. Despite the rational study which demonstrated that a three carbon distance between the reactive sites of cyclohexenone and the ketene is needed, the correspondent 1,4-diketone are obtained in modest yields (up to 40%).[104]

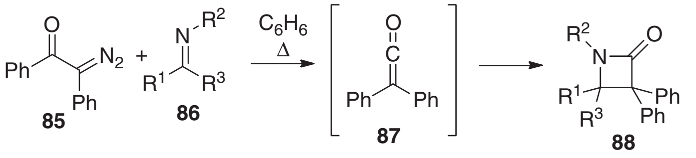
The [2 + 2] cycloaddition reaction between a ketene and an imine to generate β-lactams **88**, developed by Staudinger[105] and named after him, has been widely explored.[106] The Wolff rearrangement as a tool to provide ketenes that further react with C=N bonds can be performed under photolytic, thermal or metal-catalyzed conditions. Diphenylketene **87**, thermally generated from 2-diazo-1,2-diphenylethanone **85**, react efficiently with a wide variety of imines **86** (Scheme 26).[107] The same reaction was also applied to the modification of amino acid-derived diazo ketones through UV irradiation[108] and microwave pyrolysis[109] and further extended to the modification of peptide derived imines.[110] The dirhodium-catalyzed ketenes formation from aryl α-diazo thiol esters can also be used for the β-lactams formation after reaction with imines.[102] Di(2-azulenyl)ketene generated by thermal decomposition of the diazo precursor react in the same fashion with azulene imines to yield β-lactams in 32–61% yields. This same ketene reacts with azobenzene providing the 1,2-diazetidin-3-one in 57% yield.[111]

Benzoyl(phenyl)ketene **90** derived from the corresponding α-diazo-β-diketone **89** can be used as a partner for the [2 + 4] cycloaddition with α,β-unsaturated aldehydes or ketones **97**, keto-imines **91**, and thiones **93** (Scheme 27). The cycloadducts can be obtained in good to excellent yields and in a chemospecific manner after reaction of the thermal generated ketene with the carbonyl, imine group, or thiocarbonyl of the dienophile. If α,β-unsaturated imines **95** are used in the presence of this ketene, β-lactams **96** are obtained through a [2 + 2] cycloaddition instead.[112]

A three-component reaction microwave-assisted protocol was developed based on the reaction between an acylketene generated by Wolff rearrangement and *in situ* formed imines derived from reaction of aldehydes with primary amines (Scheme 28). The microwave irradiation of cyclic 2-diazo-1,3-diketones **39** is a suitable process for the ring contraction and ketene formation,[34a] which then reacts with imines in a hetero Diels–Alder reaction providing the correspondent oxazinones **99** in modest yields.[113]

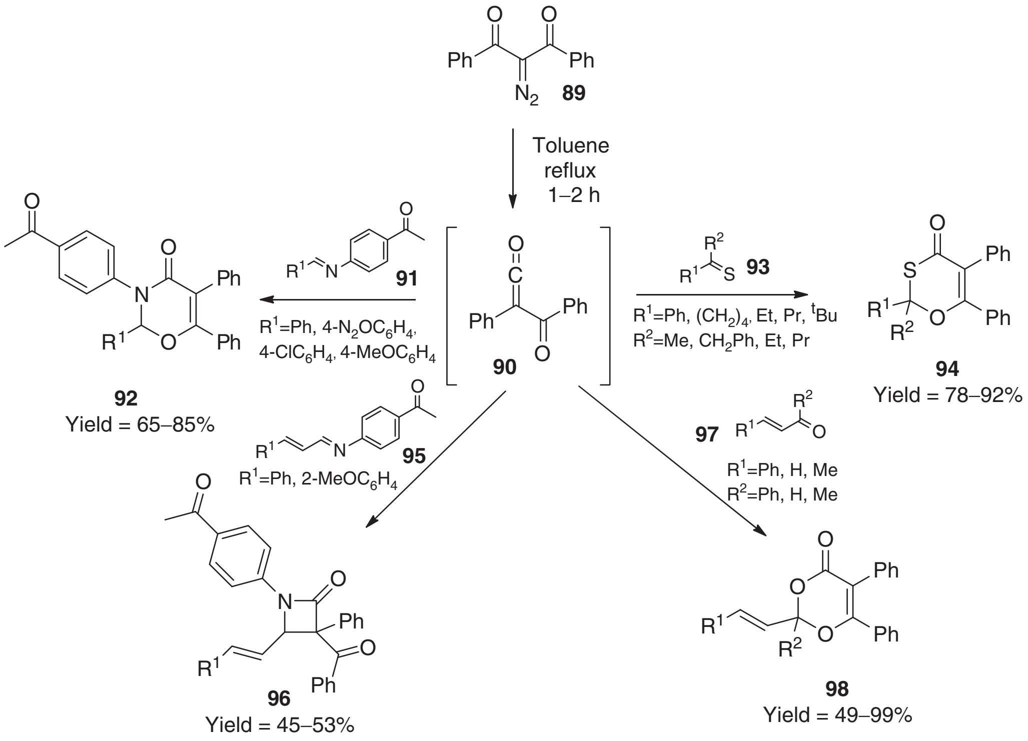
Vinylketenes derived from the Wolff rearrangement can react with alkynes in a [2 + 2] cycloaddition which ultimately leads to the formation of substituted arenes,[114] or they can react in a [4 + 2] cycloaddition with alkenes,[75c] imines,[115] ketoesters,[115] or enamines.[116] Starting from α-silyl-α-diazo-α,β-unsaturated ketones **100** as vinylketene precursors **101**, conjugated cyclohexenones can be obtained after reaction with ethyl cyanoacrylate whereas phenols are obtained when dienophile dimethylacetylene dicarboxylate (DMAD) is used.[75c] If ketomalonate **104** or *N*-(trimethylsilyl)imines **102** are used, the correspondent lactones **105** and lactams **103** are obtained in excellent yields (Scheme 29).[115]

Trialkylsilylketenes can react through a [4 + 1] cycloaddition process for the formation of five-membered rings. Using sulfur ylides or (trimethylsilyl)diazomethane with the vinylketene it is possible to obtain 2-silyl cyclopentenones in good yields.[75b] If the vinyl group is embedded within the framework of an aromatic ring, 2-indanones are obtained instead.[75a]

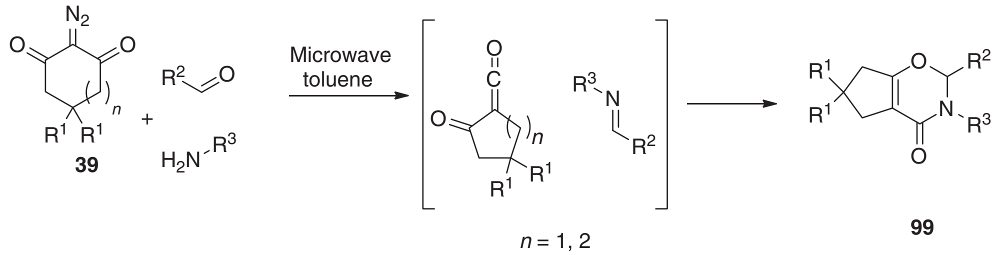


Entry	R^1	R^2	R^3	Yield (%)	Reference
i	Ph	^{i}Pr	H	85	107a
ii	Ph	$CHPh_2$	H	78	107a
iii	$4\text{-}MeOC_6H_4$	$CHPh_2$	H	61	107a
iv	$4\text{-}ClC_6H_4$	$CHPh_2$	H	59	107a
v	$4\text{-}NO_2C_6H_4$	$CHPh_2$	H	61	107a
vi	$4\text{-}Me_2NC_6H_4$	$CHPh_2$	H	62	107a
vii	Ph	CHMePh	H	81	107a
viii	2-Pyrryl	Ph	H	72	107b
ix	2-Pyrryl	$4\text{-}MeC_6H_6$	H	54	107b
x	2-Pyrryl	$4\text{-}ClC_6H_4$	H	56	107b
xi	2-Thienyl	$CHPh_2$	H	90	107b
xii	2-Thienyl	$4\text{-}MeC_6H_4$	H	82	107b
xiii	2-Thienyl	$4\text{-}ClC_6H_4$	H	86	107b
xiv	2-Furyl	$CHPh_2$	H	91	107b
xv	1-Naphthyl	Ph	H	90	107b
xvi	2-Naphthyl	Ph	H	92	107b
xvii	Ph	*i*Pr	PhCO	52	107c
xviii	Ph	$CH(4\text{-}MeC_6H_4)Me$	PhCO	31	107c
xix	Ph	CHPhMe	PhCO	44	107c
xx	Ph	$CHPh_2$	PhCO	11	107c
xxi	Ph	Ph	PhCO	47	107c

Scheme 26

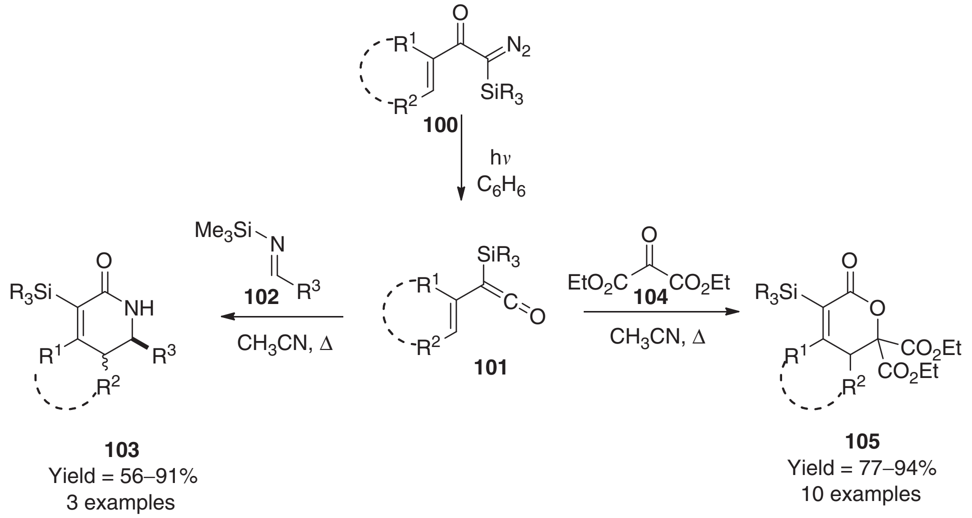


Scheme 27



$n = 1, 2$
R^1 = H, Me
R^2 = Ph, 2-Pyridyl, 2-furanyl, C_5H_{11}
R^3 = ^{i}Pr, CH_2Ph, allyl, propargyl,
yield = 34–56%

Scheme 28

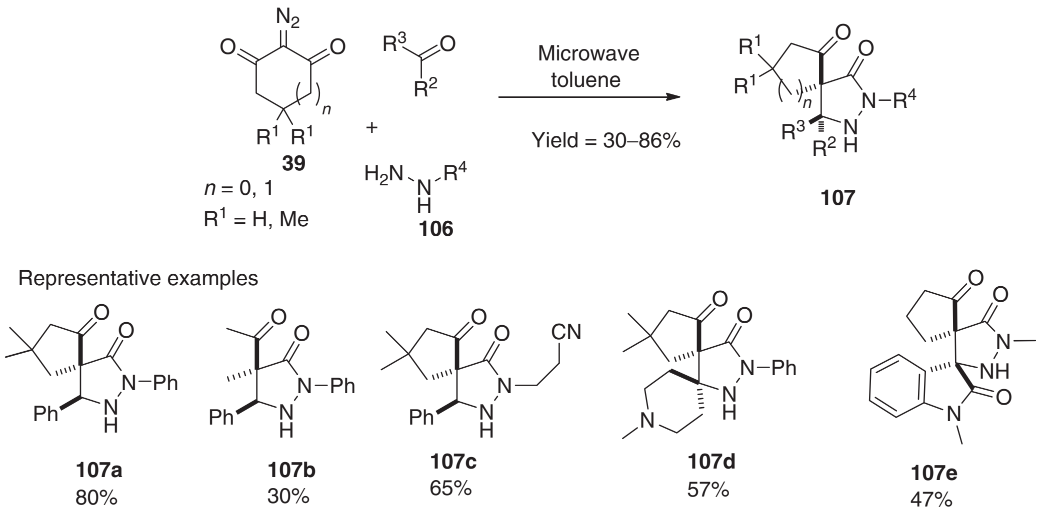


Scheme 29

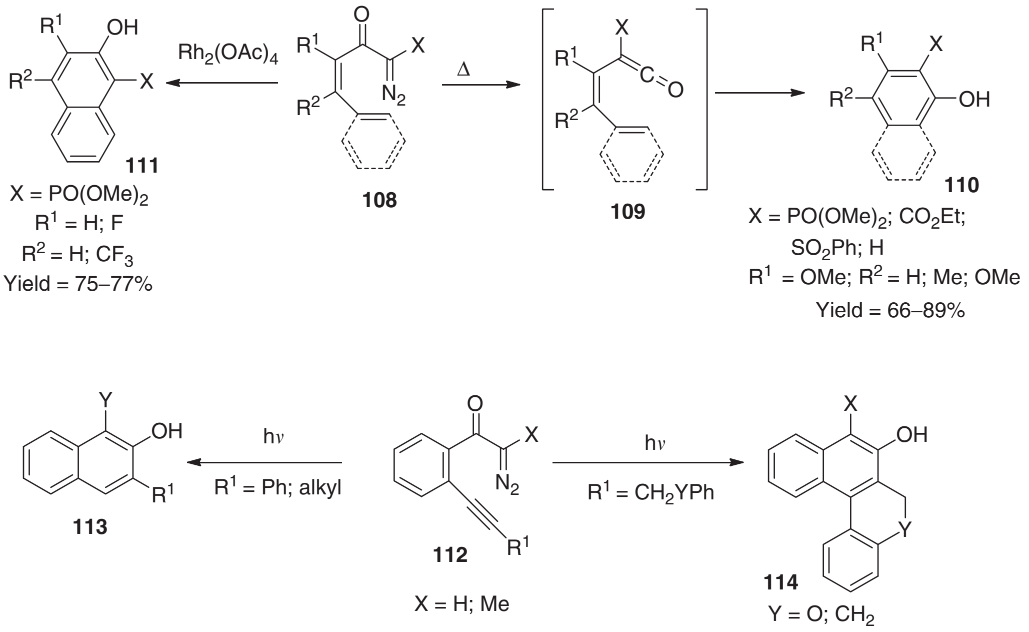
A 1,3-dipolar cycloaddition of hydrazines **106** with ketenes derived from the microwave irradiation of α-diazo diketones, as a tool to prepare pyrazolidin-3-ones **107** was developed and further expanded to the preparation of spirooxindoles. α-Oxo-ketenes were used as dipolarophiles in a reaction where the previous formation of the hydrazine, before the diazo addition to the reaction medium, provided the product in better yields. Aliphatic and aromatic ketones and aldehydes, as well as α,β-unsaturated carbonyl compounds were successfully tested, along with alkyl and aryl hydrazines. Concerning the α-diazo diketones component, cyclic ones provided the desired product in good yields, whereas lower yields were observed for reactions derived from acyclic ketenes (Scheme 30).[117]

3.19.3.3 Pericyclic Reactions of Ketenes Derived from the Wolff Rearrangement

Highly substituted phenols **110** and **111** can be prepared starting from β,γ-unsaturated diazo ketones **108**. Pericyclic reactions were observed after UV irradiation of the starting diazo compound and subsequent formation of the ketene **109** (Scheme 31). The success of the reaction is independent from the ketene substituent since the fenolic compounds were obtained when hydrogen, phosphoryl, ethoxycarbonyl, and sulfonyl substituents were present. Regardless the nature of the double bond, the reaction proceeds whether the double bond is part of an aromatic system, heterocyclic, or simple alkenyl.[118] However, if dirhodium complexes are used to initiate the nitrogen extrusion reaction, a competitive formal intramolecular C–H insertion of the metalocarbenes is usually observed and regioisomeric phenols **111** are obtained instead.[118b,119] Regarding the substituents of the double bond, whereas electron-rich ones favor the rearrangement, electronegative moieties favor the metalocarbenes formation and the C–H insertion competitive process. If a triple bond is present in the starting diazo compound **112**, related phenolic compounds **113** and **114** can be obtained by thermolysis or photolysis. A radical-based mechanism was proposed to be on the basis of this transformation in which the ketene substituent plays a crucial role in the ketene reactivity. If a terminal diazo is used, the thermolytic process leads to a dimer formation instead of the expected phenol.[120]



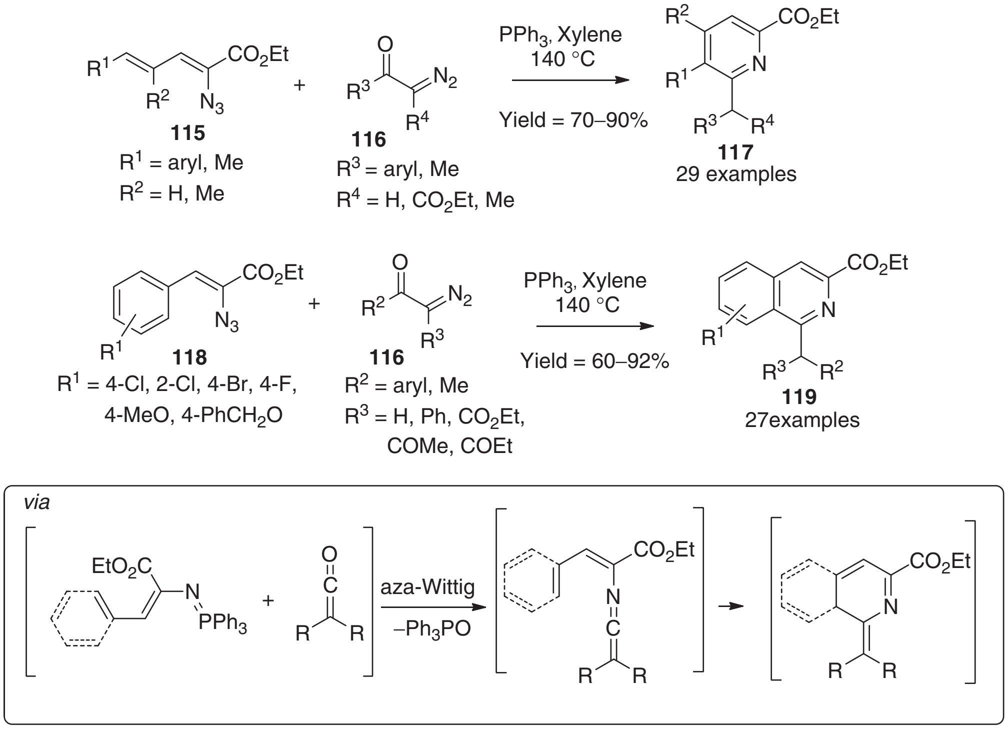
Scheme 30



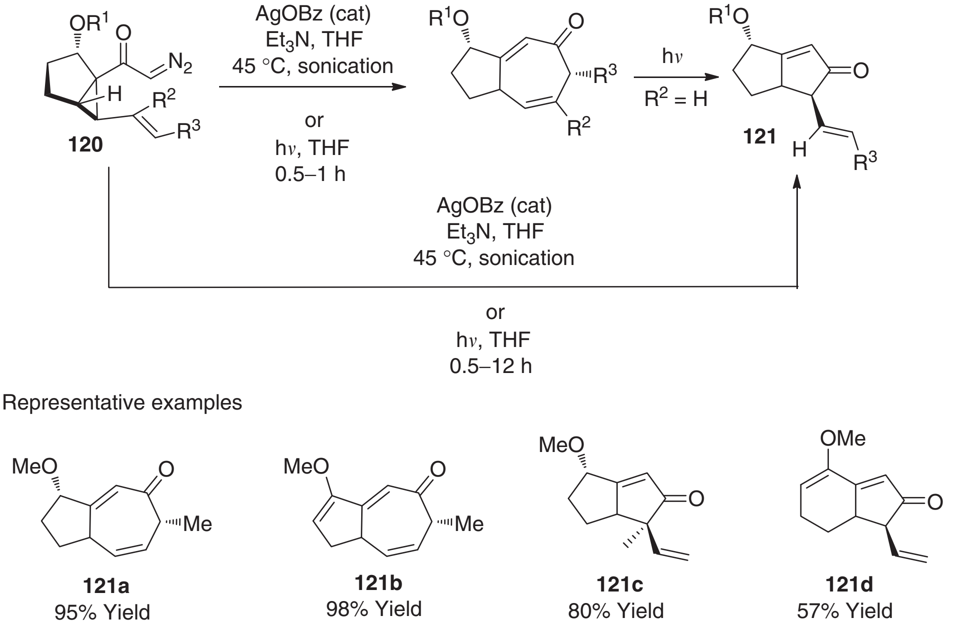
Scheme 31

Pyridines[121] **117** and isoquinolines[122] **119** can be prepared through a Staudinger–Meyer reaction coupled with a Wolff rearrangement and subsequent aza-Wittig reaction of the ketene and the phosphazene, starting from 2-azido-2,4-dienoates **115** and 2-azido-3-arylacrylates **118**, respectively (Scheme 32). Despite the harsh reaction conditions (xylene at 140 °C) the products can be obtained in good to excellent yields with a wide substrate scope in what concerns the substituents of both the azide and the diazo component. In the preparation of isoquinolines **119**, the use of nonsymmetrical α-diazo diketones can lead to the formation of two possible isomers depending on the migrating substituent in the ketene formation.

Fused carbocyclic skeletons can be obtained by a Wolff/Cope rearrangement sequence of diazoketones **120** bearing a fused [5–3] carbocyclic system (Scheme 33). The rather complex products obtained by using a catalytic amount of AgOBz and triethylamine, aided by sonication or under photolytic irradiation can be further modified toward vinyl cyclopentanones **121** after a net 1,3-acyl migration. This last transformation can be also performed under both conditions, whereas a substrate dependence on the reaction conditions was observed. The reaction is tolerant to several substituents in the olefin and totally diastereoselective.[123]



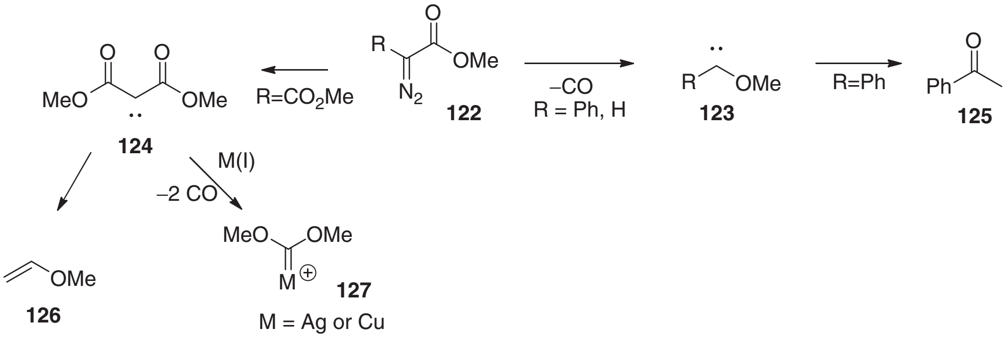
Scheme 32



Scheme 33

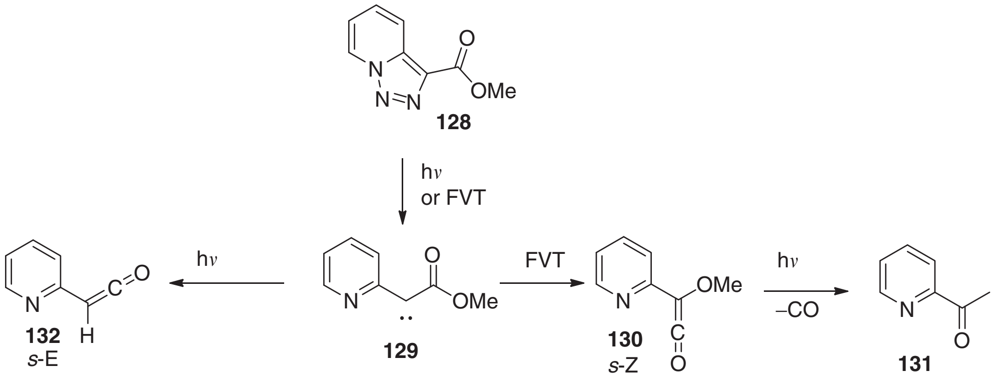
3.19.3.4 Decarbonylation

Carbenes can be produced by decarbonylation of Wolff rearrangement derived ketenes. The carbene formed can then react in several ways, which have been studied by the use of matrix isolation techniques. The gas phase decomposition of simple diazo esters leads to the formation of ketones **125** derived from alkoxy carbenes **123**.[124] However, if the diazo compound is derived from malonate, having an additional ester functional group, the products formed will be an olefin[125] **126** or a Fischer carbene **127** if copper(I) or silver(I) are present whereas divalent metals do not promote the carbene formation (Scheme 34).[126] The vacuum pyrolysis[127] or matrix photolysis[128] of cyclic diazo compounds was observed to provide the decarbonylated product after ring contraction reaction.



Scheme 34

The flash vacuum thermolysis of a 1,2,3-triazole **128**, diazo precursor, leads to the formation of methoxy(2-pyridyl)ketene **129** largely in the *s*-Z form, which under photolysis results in the formation of the 2-acetylpyridine **131** after decarbonylation. However, the photolysis of the same triazole results in the formation of formaldehyde and 2-pyridylketene **132** predominantly in the *s*-E form (Scheme 35).[129] This same compound can be obtained by the photolysis of the matrix isolated 2-diazoacetylpyridine or interconverted to the *s*-Z form under photochemical irradiation.[130]



Scheme 35

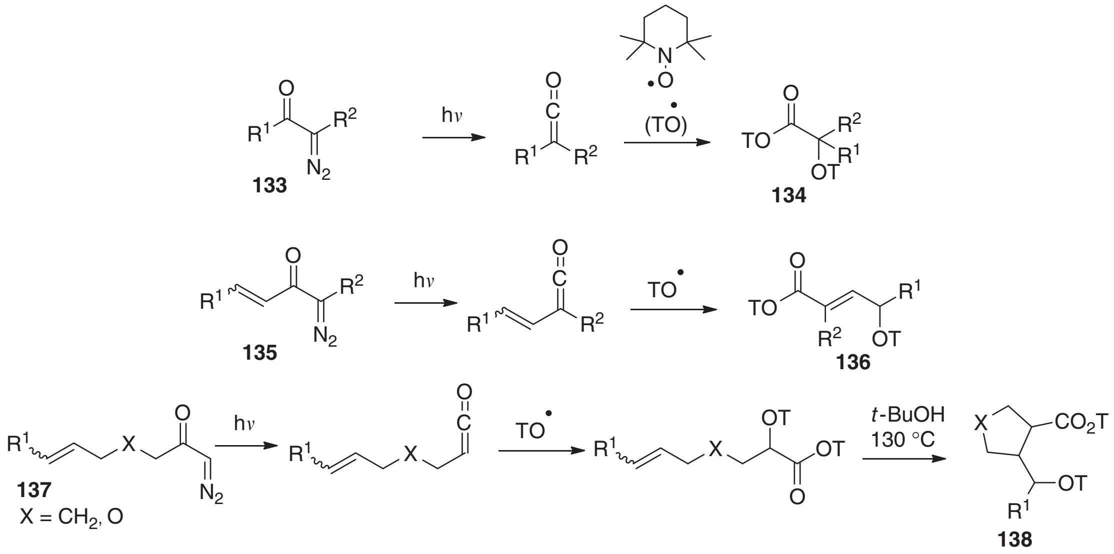
3.19.3.5 Oxidation

Ketenes generated by Wolff rearrangement can be trapped by tetramethylpiperidinyloxy radical (TEMPO) with a subsequent reaction of the radical formed with an additional TEMPO radical, yielding the corresponding 1,2-adducts **134**. If α,β-unsaturated ketones **135** are used, the 1,4-addition product **136** is obtained instead. The reaction can be applied to a variety of ketenes, and if a 4-pentenyl moiety is present in the substrate **137**, longer reaction times allow the product cyclization toward formation of cyclopentane rings or derivatives **138** (Scheme 36).[79] Epoxidation of methyl alkynes with dimethyldioxirane results in the formation of carbonyl carbenes that can further rearrange and provide the α-hydroxy carboxylic acids after hydrolysis.[131] The photooxygenation of cyclic diazo ketones with molecular oxygen leads to the formation of the ring contracted in moderate yields, in which CO_2 is loss after the formation of the 3-oxo-1,2-dioxetanes.[132]

3.19.3.6 Ring Contraction

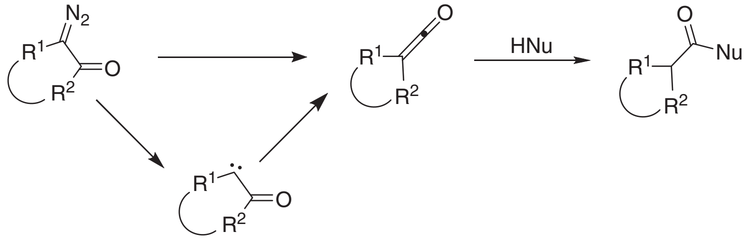
3.19.3.6.1 Reaction scope

In general, ring contraction reactions are accompanied with an increase in the ring strain energy, which would render it thermodynamically unfavorable. As a result, highly energetic cyclic molecules, like cyclic α-diazo ketones, offer the possibility to perform ring contraction reactions by compensation of the increase in strain energy with the exothermic nitrogen extrusion and migration steps. The application of the Wolff rearrangement to cyclic α-diazocarbonylic compounds induces one-membered ring



Scheme 36

contractions (Scheme 37), with formation of a highly reactive exocyclic ketene intermediates. A nucleophilic attack at this stage in the intermediate will be exothermic, releasing additional strain energy (due to the presence of exocyclic double bond) and by furnishing stable carboxylic acid derivatives.[10,133]



Scheme 37

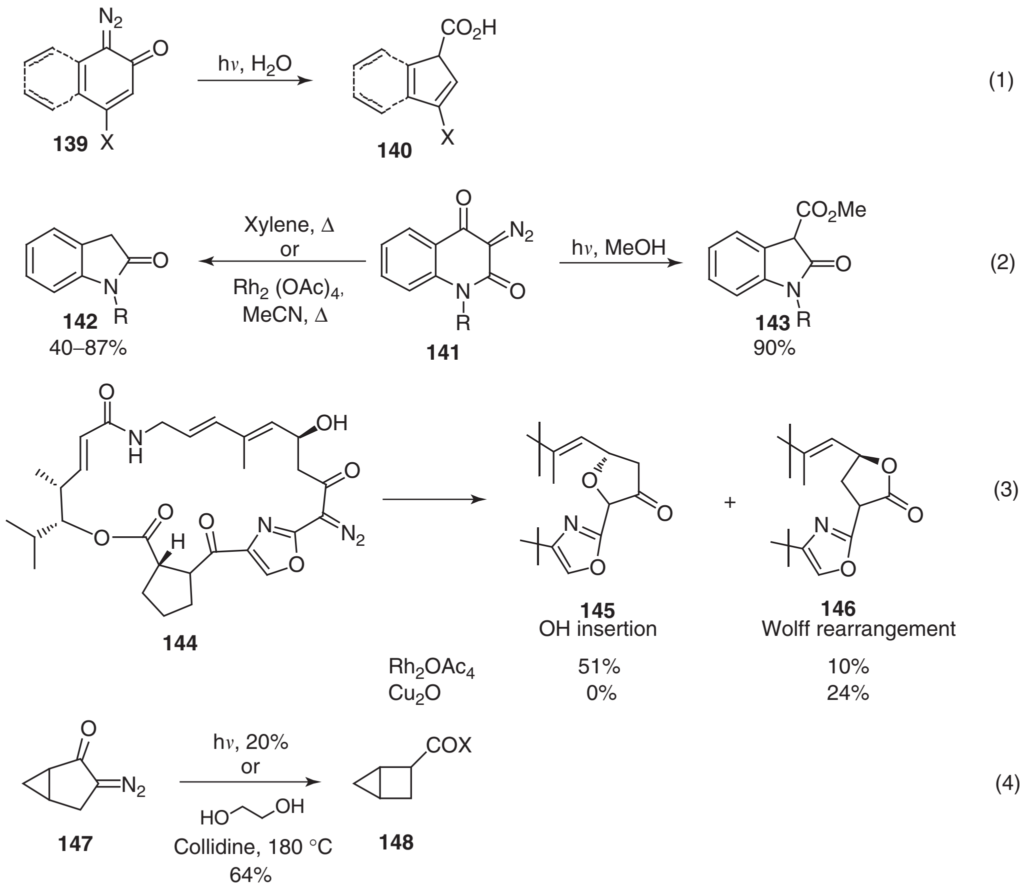
Recently, ring contractions have been detected in photochemical studies of 6- and 7-hydroxyquinolines[134] and 2-halophenols.[135] On irradiation occurs an extrusion of small molecules (hydrogen and HX) leading to α-carbene ketones, that suffer ring contractions. However, these transformations have limited synthetic interest due to their low efficiency, being exclusively dedicated to understand the photochemistry and the environmental impact of such compounds.

One of the first examples of ring-contracting Wolff rearrangements were observed in the light-induced degradation of 2-diazocyclohexa-3,5-dienones **139**. In the presence of water the respective cyclopentadienecarboxylic acids **140** were obtained (Scheme 38, equation 1).[136]

Since then, considerable development has been achieved in this transformation, and nowadays ring-contracting Wolff rearrangements are essentially performed with UV irradiation. Although they can also be performed by thermal and metal catalysis these methods generally display lower selectivity than photochemical reactions.[10] More recently, microwave irradiation was also applied to promote ring contractions.[137] As an example, the ring contraction in 3-diazo-1-methylquinoline-2,3-dione **141** in the presence of dirhodium (II) carboxylate catalysts or under thermolysis conditions, due to the harsher conditions required tend to suffer decarboxylation after the Wolff rearrangement.[138] Meanwhile, the photolysis in methanol afforded the ring-contracted methyl esters **143** in 90% yield (Scheme 38, equation 2).[139] From studies in 17-diazo pristinamycin II$_B$ **144**, the diazo decomposition in presence of dirhodium(II) tetraacetate gave a mixture of OH insertion **145** and Wolff rearrangement **146** products. Copper catalysis provided exclusively, although in low yields, the Wolff ring-contracted product **146** (Scheme 38, equation 3).[27c]

However, the photolysis of 3-diazobicyclo[3.1.0]hexan-2-one **147** produces the ring-contracted product **148** in 20% which is considerably lower than 64% that can be achieved in the thermolysis in glycol-collidine (Scheme 38).[140]

Regarding the substrate scope, these transformations are exclusively applied to α-diazo carbonyl compounds since they can be easily prepared by diazo transfer reactions to the respective carbonyl compounds.[10] For instance, cyclic α-diazo ketones can be prepared by reaction of sulfonyl azides with enolates, whereas 2-diazo-1,3-diketones can be prepared from sulfonyl azides in presence of a weak base. The synthesis of diazo compounds has been thoroughly reviewed in the literature and it is suggested the reading of excellent reviews in the field.[7]



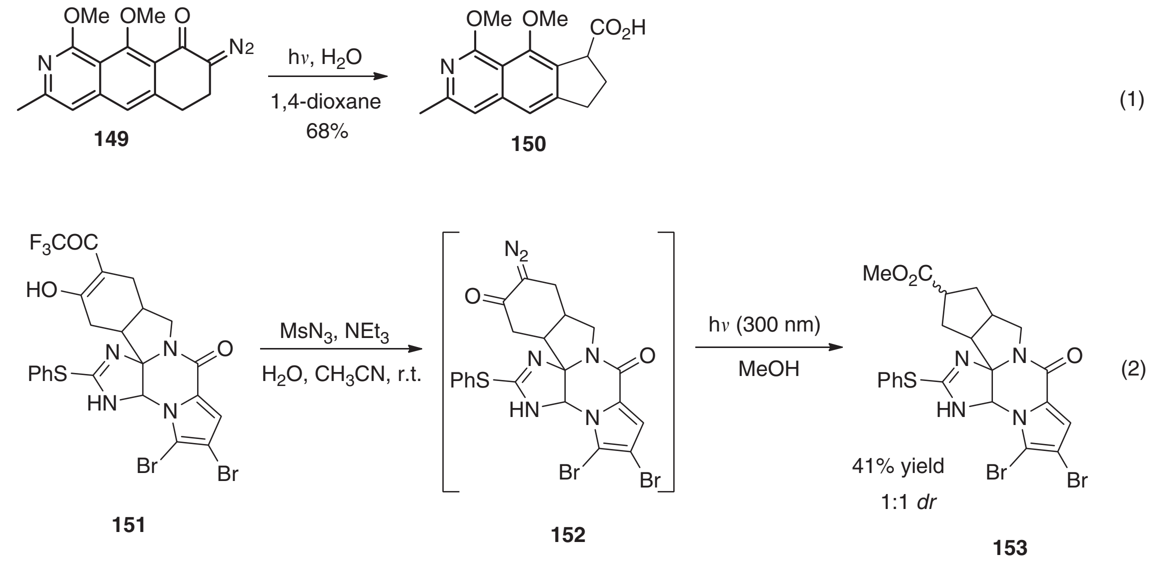
Scheme 38

In terms of the substrates ring size, the majority of the Wolff rearrangements described takes place in five- and six-membered cyclic α-diazocarbonyl compounds.[10] One illustrative example of ring contraction of six-membered rings is the preparation of a building block for the fredericamycin synthesis. The synthesis was completed by a ring-contracting Wolff rearrangement of a six-membered cylic diazo ketone. This transformation provided the respective cyclopentane carboxylic acid **150** in 68% yield after irradiation in aqueous dioxane (Scheme 39, equation 1).[141] The construction of the pentacyclic core of dibromopalau'amine prepared by an oxidative-type Pummerer reaction, also relied in a Wolff ring contraction of a diazo cyclohexanone. This substrate was found to be highly reactive and was photolysed in methanol without any isolation and purification (Scheme 39, equation 2).[142] However, the ring contraction of α-diazocyclohexanones competes directly with Favorskii rearrangement. The latter method is in general preferable because α-chloro ketones are more readily prepared than diazo compounds.[143]

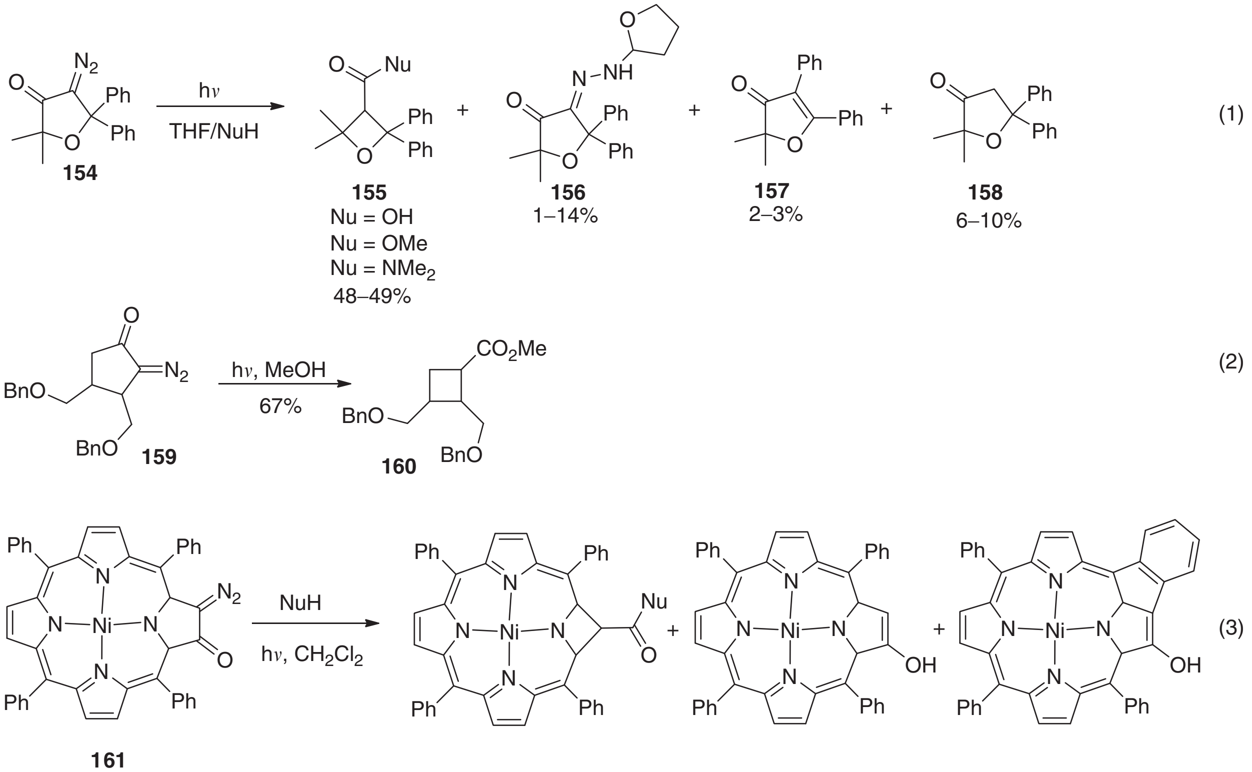
The photolysis of five-membered 2,2-dimethyl-5,5-diphenyl-4-diazodihydrofuran-3(2*H*)-ones **154** provided as the major product the respective oxetane carboxylic acid derivative **155** (up to 49% yield). Other products resulting from C–H insertion **156**, 1,2-phenyl-shift **157**, or proton abstraction **158** were also found in the end of the reaction (Scheme 40, equation 1).[144] The α-diazo cyclopentanones **159** are also suitable substrates furnishing the cyclobutane methyl carboxylates **160** in good yields 67% (Scheme 40, equation 2).[145] Recently, the unprecedented preparation of pyrrole ring-contracted azeteoporphyrins **162** was achieved, though in low yields (11–34%), by irradiation of 2-diazo-3-oxochlorins **161** (Scheme 40, equation 3). Despite the utilization of several nucleophiles, the main product in these experiments was always the formation of hydroxyporphyrins (up to 55% yield, obtained with Cu as central metal).[146]

The ring contraction from cyclobutyl to cyclopropyl is considerably less explored.[10] It is known that 2-diazo-3,4-bis(diphenylmethylene) cyclobutanone **165** can undergo photolysis in presence of water providing 13% yield of the respective carboxylic acid **166**, however this procedure is less efficient than thermolysis in aqueous dioxane which furnishes the same product in 53% yield (Scheme 41, equation 1).[147]

Rearrangements in larger[148] sized rings are also known. The synthesis of benzocyclohexane core of occidol **168** can be done by ring contraction of the respective diazo benzocycloheptanone **167** in 60% yield (Scheme 41, equation 2).[149] Meanwhile, the bicyclo[4.3.1]decane core present in CP-225 917 and CP-263 114 was synthesized by a ring contraction Wolff rearrangement in the four-membered bridge (Scheme 41, equation 3).[148c] Due to the installed stereochemistry in the carbon skeleton, the hydrolysis of the ketene produced a mixture of diastereomers of **170** and **171**.



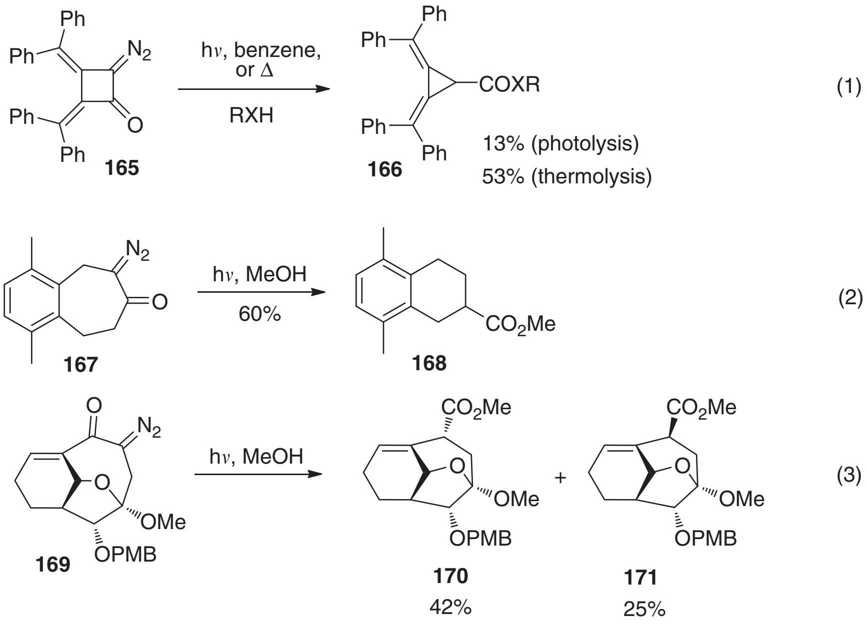
Scheme 39



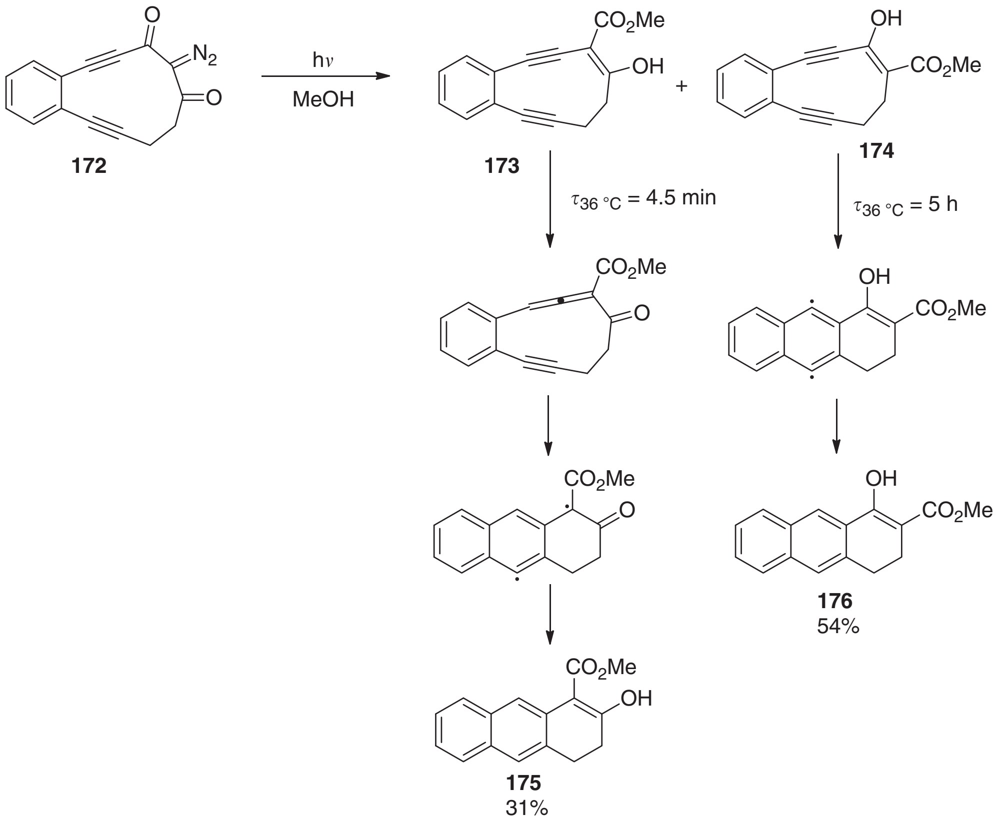
	162	163	164
Nu=OBn	16%	29%	12%
Nu=NHNHTs	11%	6%	76%
Nu=Ofurfuryl	28%	35%	12%
Nu=no Nu	–	trace	76%

Scheme 40

Popik's group demonstrated that ring contractions can be used to generate cyclic enediynes *in situ*, suitable to Bergman cyclization. The ene diyne diazo diketone **172** is an 11-membered cycle and undergo Wolff rearrangement in methanol with migration of both the alkyl and alkynyl fragments providing two regioisomeric ketoesters **176** and **175** (7:4 ratio, toward the migration of the alkyl group, Scheme 42). The minor isomer **173** can isomerize to an enyne–allene that undergoes facile Bergman



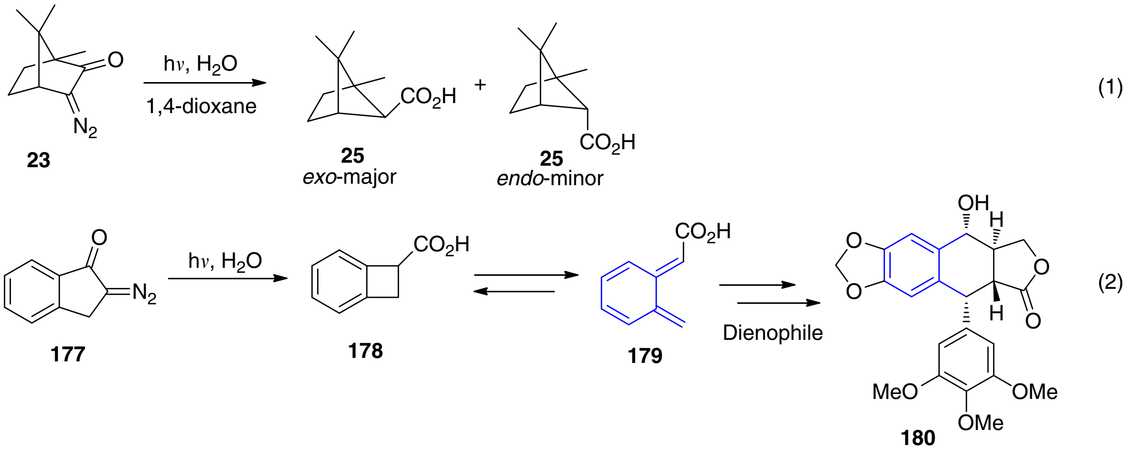
Scheme 41



Scheme 42

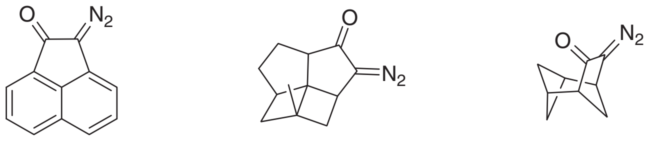
cyclization (half-life up to 5 min at 36 °C vs. 5 h for the major isomer). Ene diynes are natural antibiotics that on Bergman cyclization create diradical species capable of inducing DNA damage. High concentrations (> 500 μM) of ene diyne diazo diketone discussed in this work was able to cleave DNA on UV irradiation demonstrating a biological application for photo-triggered Bergman cyclizations.[148a,b,150]

From all the examples described so far it is clear that there are restrictions to prepare almost any type of strained rings. Already in the earlier works it was demonstrated that was possible to prepare highly strained fused ring systems. In 1955, the photolysis of diazocamphor **23** yields *exo*-1,5,5-trimethyl-bicyclo[2.1.1]hexane-6-carboxylic acid **25** as the major product due to a kinetically controlled hydration of the ketene intermediate in the least hindered *endo* side (Scheme 43, equation 1).[151] Three years later, benzocyclobutene-2-carboxylic acid **178** was prepared by Wolff rearrangement from 2-diazo-indenone **177**.[152] The access of benzocyclobutenes by Wolff rearrangement can be used to generate *in situ ortho*-quinodimethanes **179** by thermal cycloreversion reaction, which can be intercepted with dienophiles (Scheme 43, equation 2). This feature was exemplified in the synthetic route for the preparation of the tricyclic core of podophyllotoxin analogs **180**.[153]



Scheme 43

In fact, it was suggested that the extent of this reaction has some degree of correlation with the variation of strain energy between the starting material and the product, ΔE_{strain}, rather than with the strain energy of the products. Experimentally, it has been observed that ring-contracted product yields are poor to negligible for $\Delta E_{\text{strain}} > 120$ KJ mol^{-1}, moderate for $120 > \Delta E_{\text{strain}} > 100$ KJ mol^{-1} and fair for $\Delta E_{\text{strain}} < 100$ KJ mol^{-1} (Scheme 44).[10]



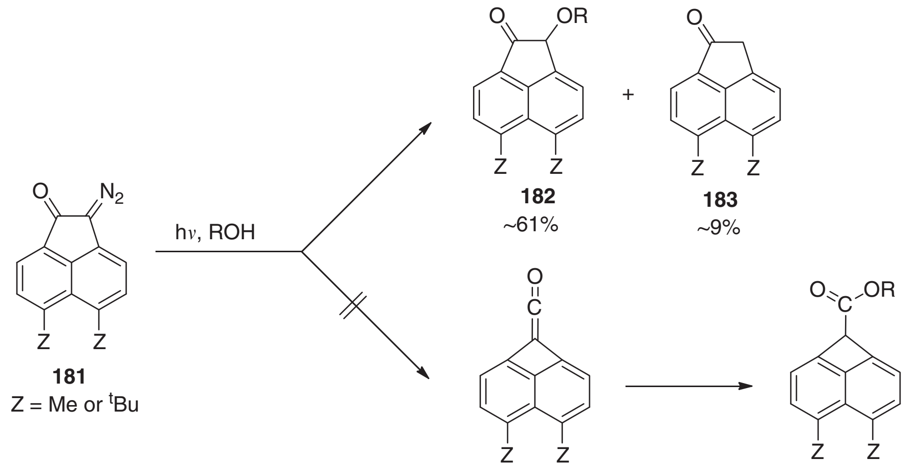
% Wolff product (hν, ROH)	0	20	45
ΔE_{strain} (KJ mol^{-1}) MM2	187	110	99

Scheme 44

Taking the example of 2-diazo-1-oxonaphthenes **181**, its ring contraction does not occur due to the large increase in the in-plane strain. Chapman and coworkers found that the photochemical nitrogen extrusion in an argon matrix leads to the formation of α-keto carbenes which can undergo ring contraction on adequate excitation (T_0–T_1).[154] The lack of Wolff rearrangement in solution points to the high reactivity of the α-keto carbene formed that reacts with solvent furnishing O–H insertion **182** and hydrogen abstraction products **183** (Scheme 45). The kinetic barrier toward ring contraction should be considerably higher than these alternative pathways.[155]

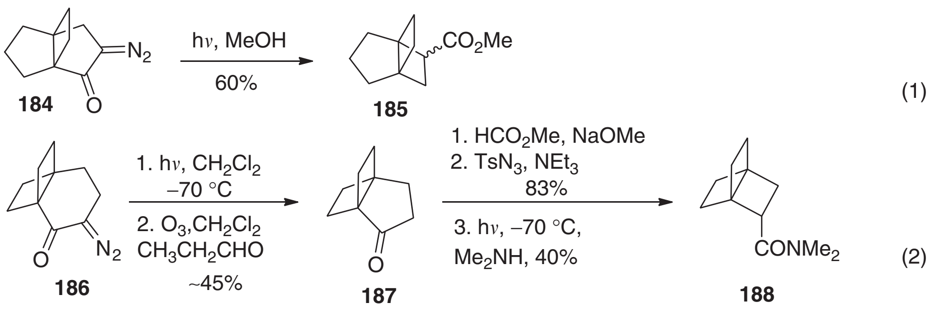
3.19.3.6.2 Synthesis of strained frameworks

The ability to prepare and/or modify highly strained molecules was explored in challenging substrates like propellanes, fenestranes, pagodanes, and cyclophanes. The ability to increase the ring strain energy by contraction has been explored to modify propellanes to test the boundaries of tetrahedral carbon atoms. A propellane is a class of organic compounds whose carbon skeleton consists of three rings of carbon atoms sharing a common carbon–carbon covalent bond. The synthesis of [3.2.2]propellane skeleton **185** can be obtained from the respective [3.3.2]propellan-2-one **184** by photolysis in methanol (60% yield, Scheme 46, equation 1).[156] A simple [2.2.2]propellane **188**, with a short-life at 25 °C of 28 min, was prepared in two sequential



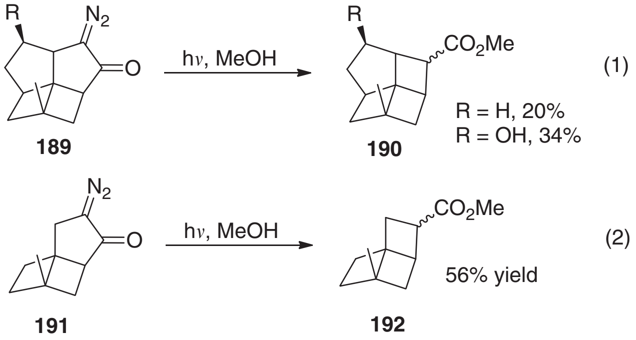
Scheme 45

Wolff rearrangements starting from a [4.2.2]propellane skeleton **186**. The first rearrangement was conducted in dichloromethane in order to undergo ozonolysis of the ketene intermediary. The intermediate [3.2.2]propellan-2-one **187** was converted in the respective α-diazoketone and rearranged once again (Scheme 46, equation 2).[157]



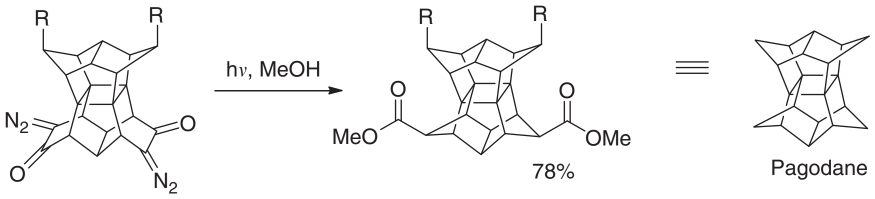
Scheme 46

Fenestranes bears a central quaternary carbon atom which serves as a common vertex for four fused carbocycles. The Wolff rearrangement of [4.4.5.5]fenestranes **189** to yield [4.4.4.5]fenestranes **190** were conducted in low yields due to high ring strain inherent to its fused framework. Interestingly, the presence of a hydroxyl group in the five-membered ring improved the reaction yield from 20%[23b,158] to 34%[159] compared with the respective alkane (Scheme 47, equation 1). Meanwhile, a less strained fenestrane model bearing only three fused rings **191** underwent the same synthetic sequence presenting a yield of 56% of **192** for the ring contraction step (Scheme 47, equation 2).[160]



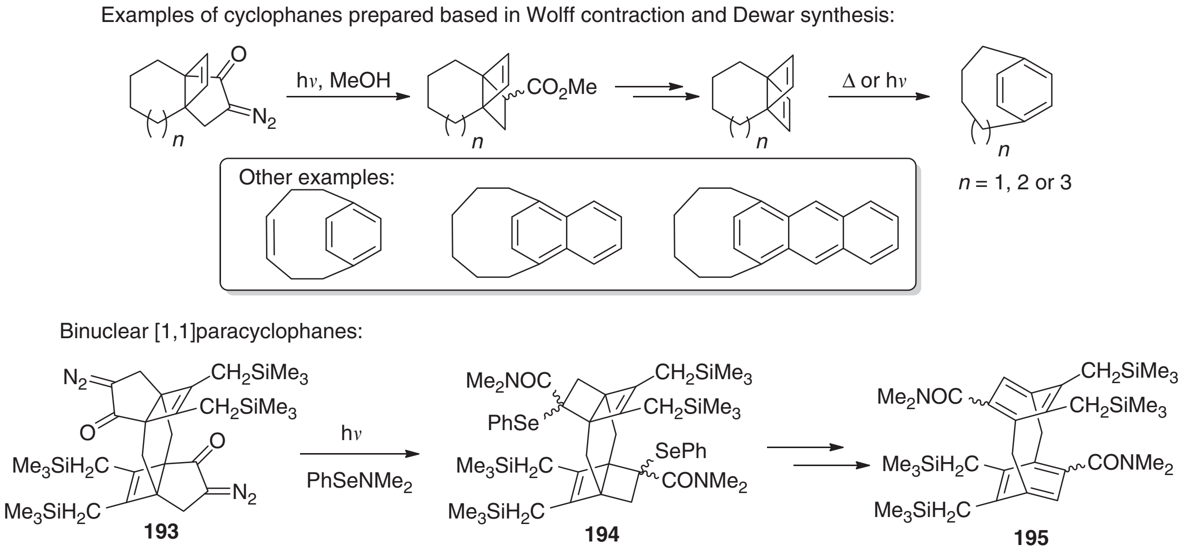
Scheme 47

Pagodane, possesses 20 carbons resembling an oriental pagoda, due to the existence of a central cyclobutane ring that forms part of several propellanes where each of the four carbon atoms is the center of a [5.5.5.5]fenestrane. Its synthesis is highly challenging and was accomplished taking advantage of ring contraction of cyclic diazoketones (equation 3).[23a,161]



(3)

The cyclophanes are ideal candidates to test and study benzene ring deformations. In this field the Wolff ring contractions have been useful to prepare Dewar benzene precursors from suitable $[n+3,3,2]$propellenes.[162] The latter can be converted into the respective paracyclophane on heating at 60 °C as observed in the synthesis of [6]paracyclophane,[162e] (Z)-[6]paracycloph-3-ene,[162f] [6]-1,4-naphthalenophane and anthracenophane.[162g] [5]Paracyclophane[163] and [4]paracyclophane[164] are unstable being generated photochemically. Although [5]paracyclophane showed to have a short life time up to hours, [4]paracyclophane was only isolated in a matrix at 77 K (Scheme 48, below). The synthesis of challenging binuclear [1.1]paracyclophane **195** was also accomplished taking advantage of a double ring contraction binuclear propellanes. The nature of the substituents in the benzene ring were crucial to enhance the kinetic stability of the binuclear [1.1]paracyclophanes synthesized.[165] When each paracyclophane was doubly substituted with bulky CH_2SiMe_3 and $CONMe_2$, it was stable in solution up to 50 °C (Scheme 48, below).[165b]



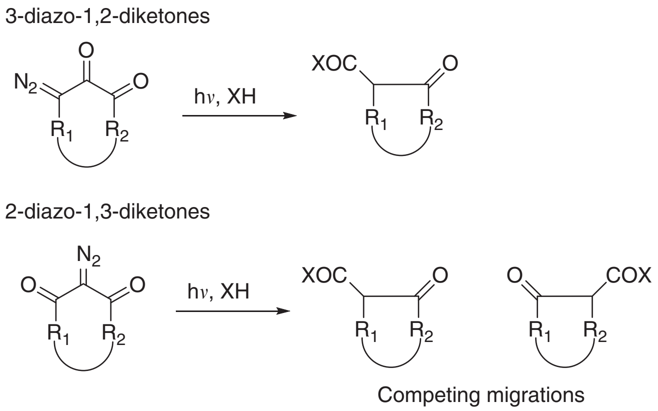
Scheme 48

3.19.3.6.3 Diazodiketones

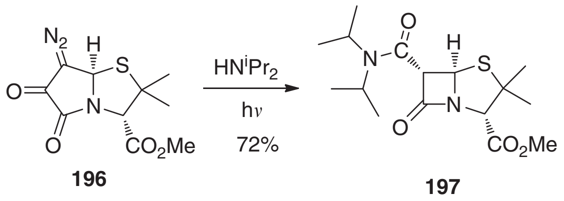
So far, the authors have not discussed the ring contraction of cyclic diazodiketones. In case of 3-diazo-1,2-diketones the migrating group will be the acyl substituent whereas for 2-diazo-1,3-diketones there will be two migrating groups in competition (Scheme 49).

In the ring contractions in cyclic 3-diazo-1,2-diketones the acyl substituent is described to be an efficient migrating group. This behavior was demonstrated for the synthesis of C_3O_2 and C_4O_2 from 3,6-bisdiazocyclohexane-1,2,4,5-tetraone[166] and 3,5-bisdiazocyclopentane-1,2,4-trione,[167] respectively, in argon matrix at 17 K. Although, the synthetic value of Wolff rearrangements in 3-diazo-1,2-diketones is better demonstrated for the synthesis of azetidin-2-one-3-carboxylic acids (β-lactams) from 4-diazopyrrolidine-2,3-diones. The ring contraction reactions provide the desired β-lactams in good yields and this synthetic methodology was particularly useful in the preparation of bicylic β-lactams **197**[168] (Scheme 50).

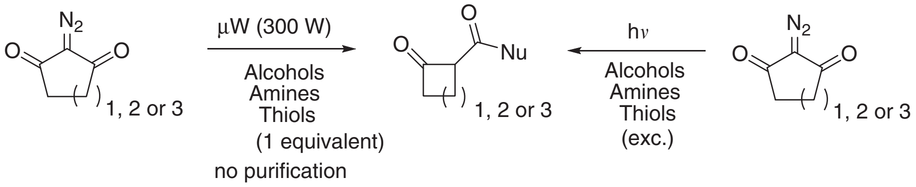
Ring contraction of cyclic 2-diazo-1,3-diketones proceed smoothly with the formation of β-keto acids, esters and amides.[10] The Wolff rearrangement of nonsubstituted or C_2-symmetrical cyclic 2-diazo-1,3-diketones like, 5,5-dimethyl-2-diazo-1,3-cyclohexanedione **39** proceeds in near quantitative yields under UV irradiation. In 2009, it was demonstrated that microwave irradiation can be used to activate 2-diazo-1,3-cyclohexanedione toward ring contraction reactions (Scheme 51).[137a,169] The utilization of a 1:1 mol ratio of diazo and nucleophile led to the formation of β-keto esters, thioesters and amides with high purity discarding any purification. For this type of substrates the ring contracting Wolff rearrangements are highly competitive with the Dieckman condensation (acylation of enolates).



Scheme 49



Scheme 50



Scheme 51

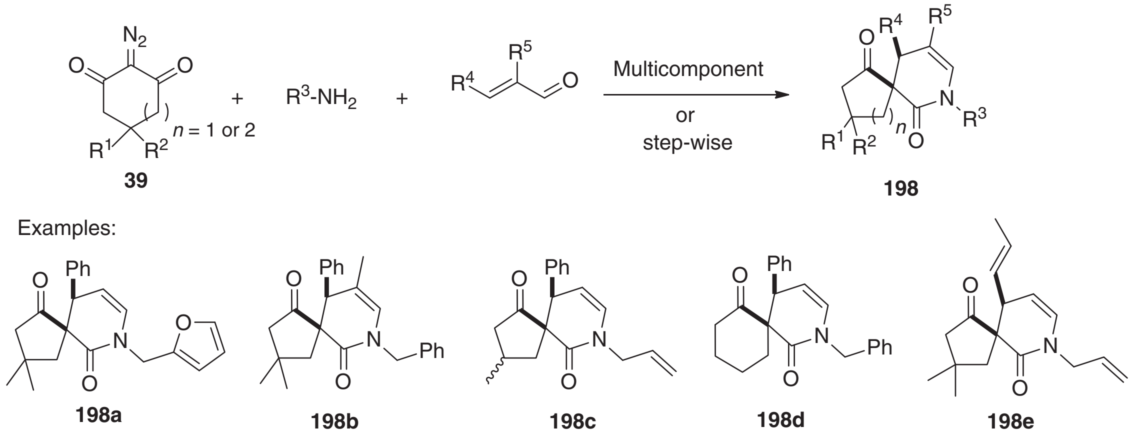
When the nucleophile that intercepts the exocyclic intermediate is an conjugated aldimine a highly reactive diene/dienophile is formed creating the perfect conditions for [2 + 4]cycloaddition. A multicomponent protocol can be applied when the water formed does not attack the ketene in the presence of the imine. For those cases where this actually takes place, the one-pot protocol must be followed. After the formation of the imine at 140 °C in toluene under microwave irradiation, all the volatiles are removed before addition of the diazo compound. The imination/Wolff rearrangement/[2 + 4]cycloaddition domino sequence provides in moderate to good yields (24–95%, Scheme 52) highly complex α-spiro-δ-lactams **198**.[137(c)]

When the ring contraction of cyclic 2-diazo-1,3-diketones is applied in substrates without C_2 symmetry, the preparation of β-keto esters and amides faces several selectivity issues. Besides inherent diastereoselectivity control, the methodology provides a mixture of regioisomers due to distinct migration aptitudes of the alkyl substituents in the diazo starting compound. Taking 4-methyl-2-diazo-1,3-cyclohexanedione **199** as an example, migration of C-4 produced *trans*-2-methyl-5-oxocyclopentanecarboxylic acid **200** whereas migration of C-6 gave 3-methyl-2-oxocyclopentanecarboxylic acid **201** as a mixture of diastereomers (Scheme 53).[170]

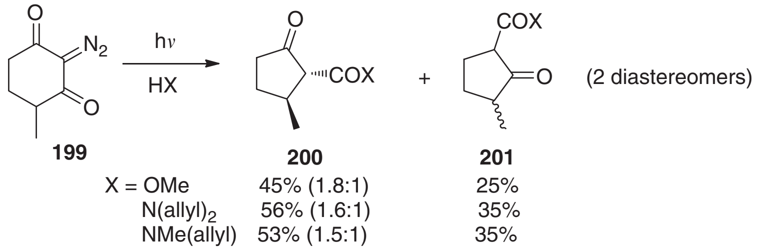
The 2-diazo-β-keto esters and amides are also suitable substrates for ring contraction Wolff rearrangements. However, in this case, the migration of the heteroatom does not take place in favor of the migration of alkyl[137b] or aryl groups.[171]

An interesting example is the preparation of β-lactams **203** on contraction of 3-diazopyrrolidine-2,4-diones **202**, which can be prepared straightforwardly from α-amino esters (Scheme 54). However, in order for this reaction to occur, the α-amino esters must have a secondary amino group and the α position completely alkylated. The migration occurs almost exclusively from the alkyl group and depending on the alkyl substituents in the migrating center the *cis:trans* selectivity of the reaction can reach 75:25.

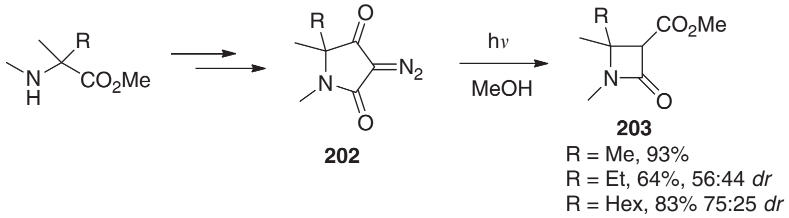
Even though aryl and alkyl groups display higher migration aptitude than heteroatoms of amides and esters, in their absence 1,2-shifts heteroatoms are known (Scheme 55).[10]



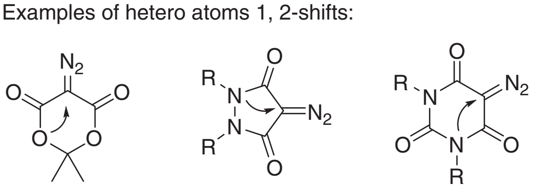
Scheme 52



Scheme 53



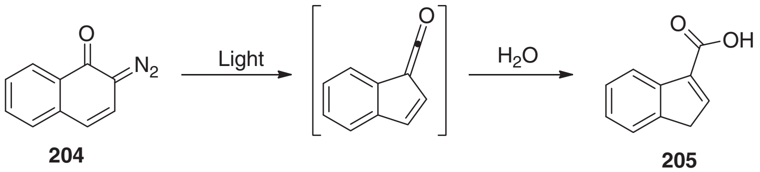
Scheme 54



Scheme 55

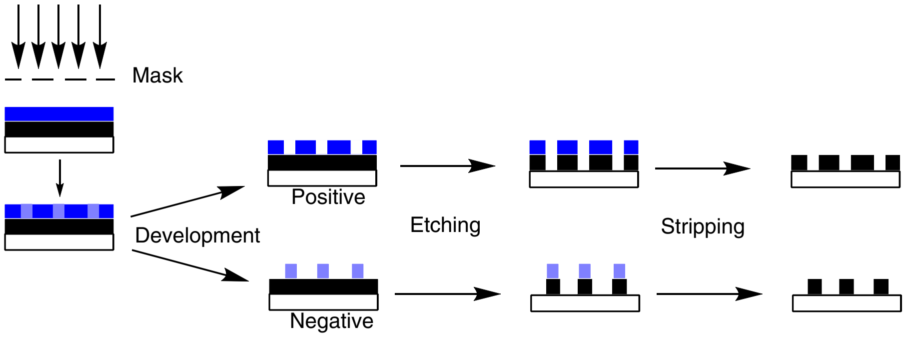
3.19.3.6.4 Resists

The photochemical decomposition of *o*-quinone diazides (diazo quinones) is a quite remarkable process that leads to the ring contraction of the benzene ring.[79d,172] The efficiency of this transformation is limited by loss of aromaticity, rendering the process much more efficient in naphthalene or higher aromatic ring systems. The ring contraction and ketene hydrolysis provides 1*H*-indene-3-carboxylic acids **205**, which displays a very distinct solubility in aqueous basic solutions compared with the parent diazo quinone **204** (Scheme 56).[173] The change in solubility in diazo quinones on irradiation allowed the exploration of these compounds as photoresists in the field of photolitography.[10,174]



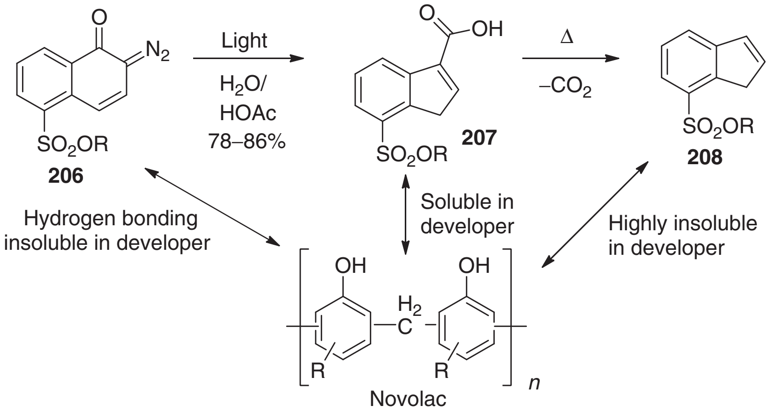
Scheme 56

The photoresist technique is used to produce printing plates, printed circuit boards, and integrated circuits. In the first step in photolithography an uniform layer of photoresist is placed on a substrate. Afterwards with help of a mask a certain pattern is irradiated in the resist. If the solubility of a photoresist increases during irradiation, it is termed a positive resist, whereas if the solubility decreases, is negative. In the third step, is removed the more soluble portions of the photoresist and the unprotected areas are etched (ablation) to imprint the pattern of the mask in the substrate (**Scheme 57**).



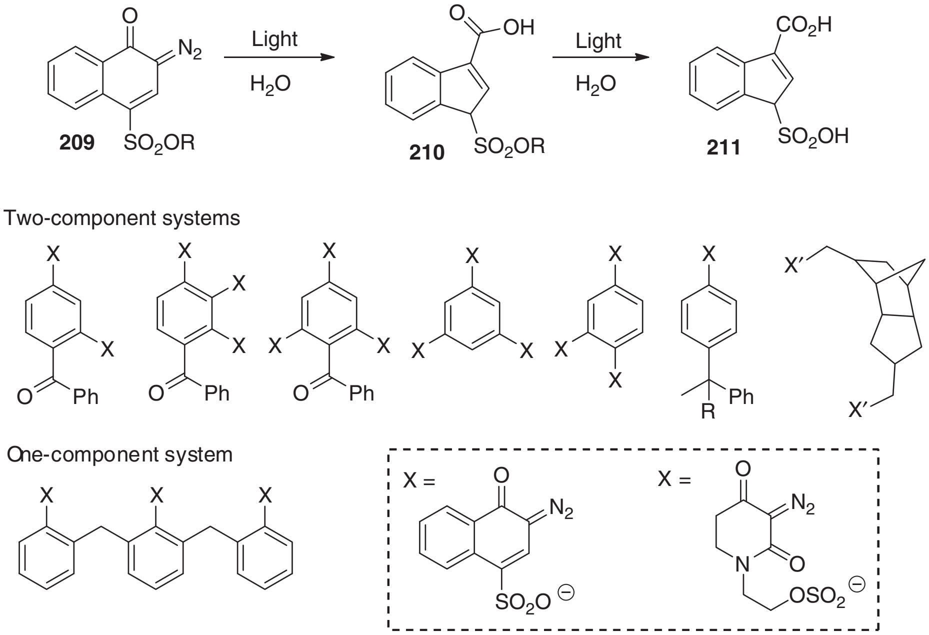
Scheme 57

Nowadays in industrial resists, 2-diazonaphthalen-1-one-5-sulfonates **206** are used in combination with a Novolac binder (a phenolic resin) (**Scheme 58**).[174a,175] The solubility of resin is substantially reduced by interactions, presumably hydrogen bonds, with the diazo compound. However, on photolysis, the indenecarboxylic acids **207** become soluble along with the resin (positive photoresist). It is necessary to have a sufficient concentration of water in the resist to avoid ketene interception by the phenolic groups of novolac. Decarboxylation of indene carboxylic acids at elevated temperatures,[176] with formation of mixtures of isomeric indenes **208**, strongly reduces the solubility of the exposed areas of the resist (negative resist).



Scheme 58

In contrast, the ring contraction of aryl 2-diazonaphthalen-1-one-4-sulfonates **209** is followed by light-induced hydrolysis of **210** to give sulfonic acids **211**. In combination with an acid-dependent crosslinking agent, aryl 2-diazonaphthalen-1-one-4-sulfonates provide negative photoresists (**Scheme 59**, top).[173,175] Other resists are available like, two-component resists bearing up to three diazo quinones linked in the same core[177] and a one-component system where the diazo quinone is directly linked to fragments of Novolac[178] (**Scheme 59**, below).



Scheme 59

The 2-diazo-1(2*H*)-naphthalenone has been recently explored as potential UV-phototriggered releasing agents. The incorporation of this compound in polyethylene glycol chains forms a micellar structure that can incorporate in its interior hydrophobic molecules.[179] Due to switch of solubility on UV irradiation, the micellar structure is destroyed and its payload released. The discovery that two-photon absorption of near infrared radiation of 2-diazo-1(2*H*)-naphthalenone[180] can induce the same Wolff rearrangement opens perspectives to the preparation of polyethylene glycol-dendritic polyesters copolymers as infrared-sensitive delivery vectors.[181]

3.19.3.6.5 Ring contractions in total synthesis

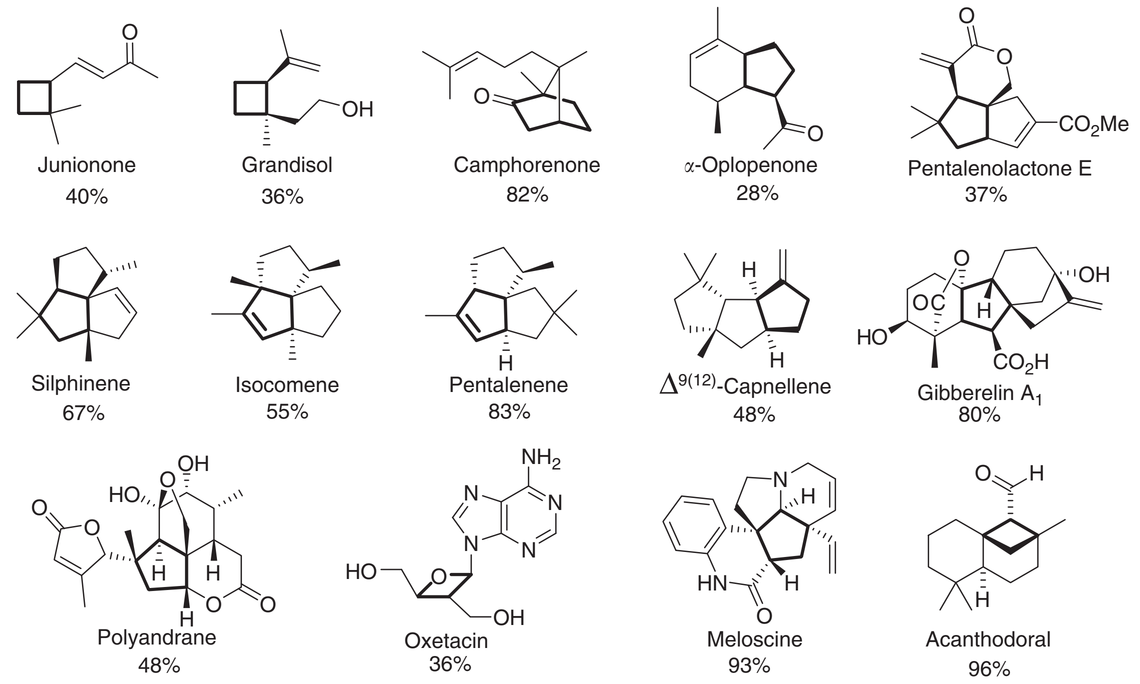
The ring-contracting Wolff rearrangement has been applied in the total synthesis of many natural products and related targets. The construction of fused polycyclic systems, present in many terpenes and alkaloids skeletons, took advantage of this unique methodology. In **Scheme 60** is exemplified the structure of several natural products that were synthesized with aid of this methodology. The cycle that was prepared by contraction is highlighted in bold and the yields given correspond to the ring-contracting step. Junione,[182] grandisol,[183] acanthodoral,[184] and oxetacin[23c] bear a four-membered ring that were obtained by ring contraction of cyclopentanones. Although, α-oplopenone,[185] pentalenolactone E methyl ester,[186] silphinene,[187] isocomene,[188] pentalenene,[189] $\Delta^{9(12)}$capnellene,[190] gibberellin A_1,[191] polyandrane,[192] and Meloscine[193] relied in the contraction of diazo cyclohexanones. An isolated example of Wolff rearrangement in a diazo cycloheptanone was explored for the synthesis of camphorenone.[194]

3.19.3.7 Homologation of Carboxylic Acids

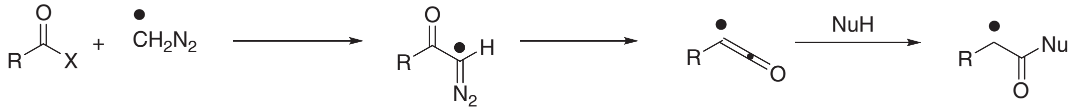
3.19.3.7.1 Reaction scope

The preparation of homologated carboxylic acids is known as the Arndt–Eistert synthesis, which is a series of chemical reactions designed to convert a carboxylic acid to a higher carboxylic acid homolog (**Scheme 61**).[10,195] The first part of the synthesis aims at the preparation of α-diazomethyl ketones from the respective carboxylic acid by a formal acylation with diazomethane. In the second part, the Wolff rearrangement in α-diazomethyl ketones in presence of nucleophiles results in the incorporation of a methylene fragment between the R-migrating group and the carboxylic acid derivative, accomplishing the homologation.

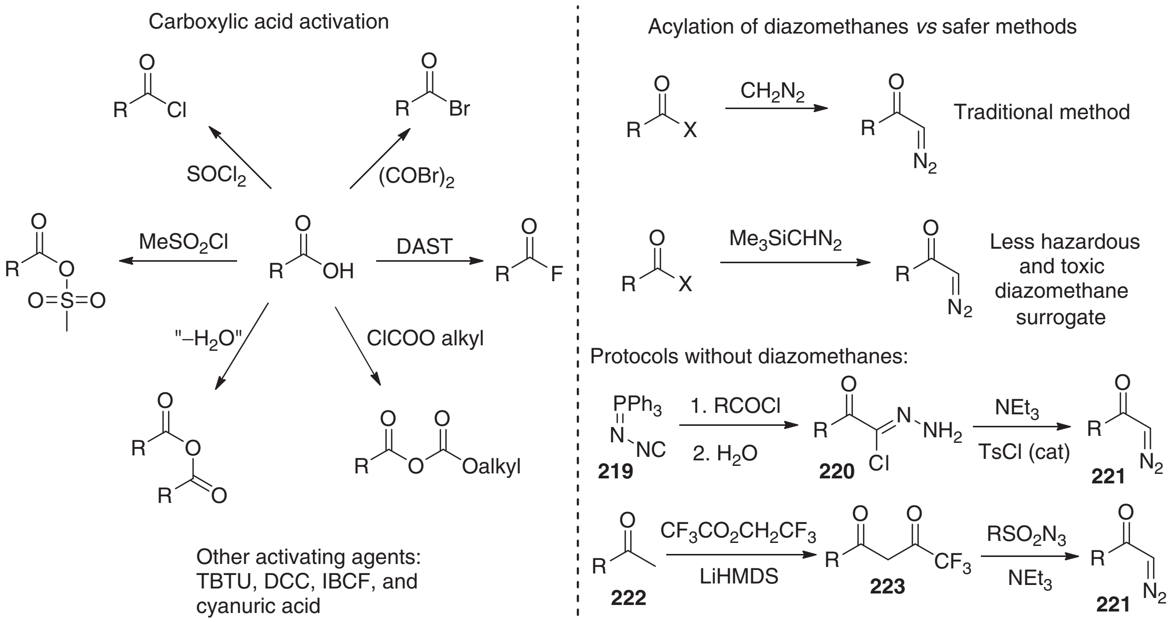
The activation of the carboxylic acid (**Scheme 62**, left) toward acylation reaction with diazomethane can be accomplished by the preparation of the respective acyl chloride,[7a,7c,d,7f,196] bromide,[197] fluoride,[196a] or anhydride.[7a,7c,d,7f] Mixed carboxylic-carbonic anhydrides can be generated *in situ* from the carboxylic acid and alkyl chloroformates, which are also suitable for acylation since the attack in the more electrophilic carbonyl provides the desirable α-diazomethyl ketone.[198] The methods described so far for activation of carboxylic acids are not adequate to prepare hindered α-diazomethyl ketones. For this type of substrates a method based in the formation of highly reactive acyl mesylates was developed. Simpler unhindered carboxylic acids are converted to the respective symmetrical anhydride.[199] Dicyclohexyl carbodiimides,[200] cyanuric acid,[201] IBCF,[202] and TBTU[203] can also be applied as activating agents, however the results obtained in general do not justify their application (**Scheme 62**, left).



Scheme 60

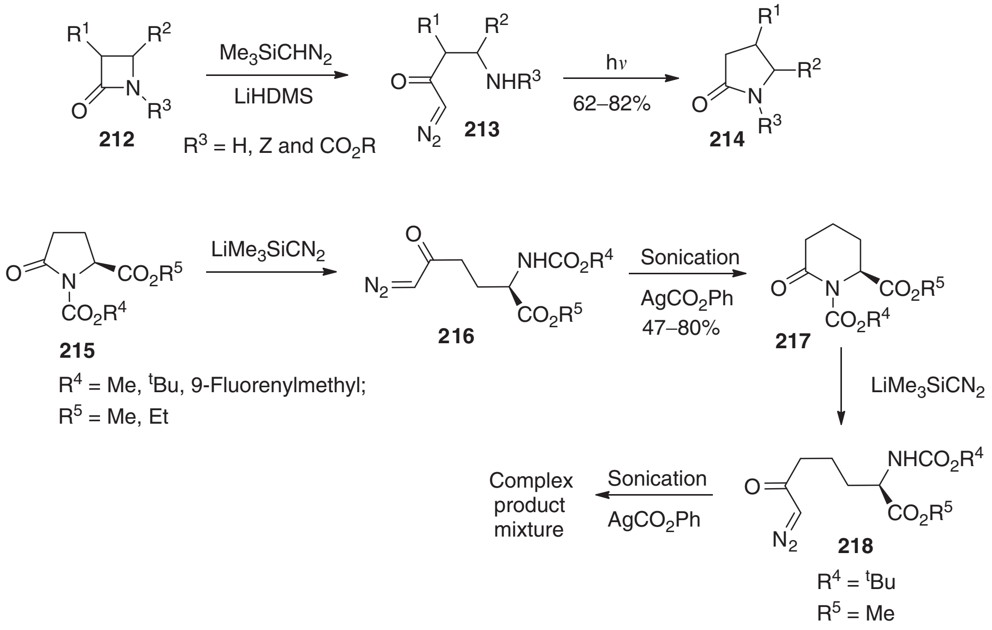


Scheme 61



Scheme 62

The traditional procedure involves the acylation of highly explosive and carcinogenic diazomethane (**Scheme 62**, right). Nowadays, it is possible to perform the Arndt–Eistert synthesis under safer conditions, relying on the application of less hazardous trimethylsilyl diazomethane ($TMSCHN_2$, **Scheme 62**, right).[196c,204] Another feature of $TMSCHN_2$ relates with its facile deprotonation providing a highly nucleophilic carbanion. Its nucleophilic character allows the ring opening of β-lactams **212** to furnish the respective β'-amino-α-diazomethyl ketone **213**, which on irradiation provides the homologated γ-lactam **214** in good yields (62–82%, **Scheme 63**, top).[204c] The same synthetic strategy was also applied to γ-lactam **215** to prepare 6-oxopipecolates **217** (**Scheme 63**, below).[205] Meanwhile, the prepared 6-oxopipecolates were also ring opened with $TMSCHN_2$ but the respective diazo ketone **218** provided a complex mixture after irradiation.



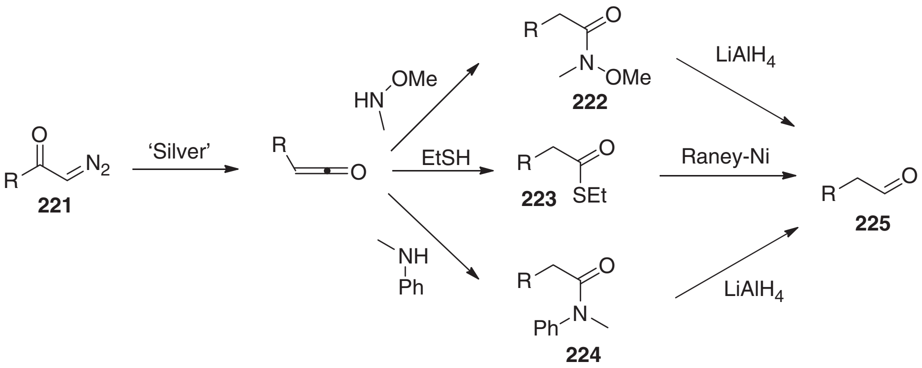
Scheme 63

The preparation of α-diazomethyl ketones without using diazo compounds is available by other alternative methodologies. The first is based in the reaction of *N*-isocyanotriphenyliminophosphorane **219** with acyl chlorides to yield α-ketohydrazidoyl chlorides **220** after hydrolysis. The final diazomethyl ketone **221** is obtained after dehydrochlorination mediated by tosylation of the terminal nitrogen atom (**Scheme 62**, right).[206] In alternative, it is possible to use diazo transfer reactions to prepare the desired α-diazomethyl ketones.[207] The diazo transfer to methyl ketones is achieved in a two-step synthesis, starting with the activation of the methyl ketone **221** by trifluoroacetylation, followed by diacylative diazo transfer from sulfonazides (**Scheme 62**, right). Despite this strategy not being always feasible, it proved to be highly fruitful in the preparation of α-β-unsaturated diazo ketones.

Nowadays, the decomposition of α-diazomethyl ketones is preferably done with homogeneous silver ion catalysis (heterogeneous silver oxide[30d,32b] catalysts tend to provide erratic results[10]). Although, the traditional catalyst to perform this transformation is silver benzoate/triethyl amine,[30a] the silver trifluoroacetate/triethyl amine[208] system allows easier product purification. Utilization of sonication in combination with silver catalysts can considerably enhance the reaction rate[31b,198a] and also eliminate the need of basic triethyl amine (which is ideal for base sensitive substrates).[198c,d,209] However, the silver catalysis struggles to provide adequate decomposition of hindered α-diazomethyl ketones, leaving photolysis as the method of choice.[10] In addition, substrates containing sulfur atoms can poison silver catalysts. For these cases, dirhodium(II) tetraacetate has proven to be a competent catalyst.[102]

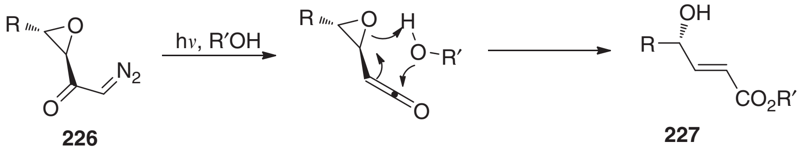
This methodology can be applied to a considerably large scope of carboxylic acids, from alkyl, aryl, vinyl, heteroaryl to enantioenriched, furnishing the corresponding homologated carboxylic acids, esters, and amides. It is also possible to undergo homologations in α-diazoesters, amides and thioesters, with migration of the heteroatom however, these transformations have limited synthetic interest. Despite there being a few examples of side reactions along with the Wolff rearrangement, the functional group tolerance is high. Regarding the preparation of homologated carboxylic acids, due to solubility issues of some starting materials in aqueous solvents, it is preferable to run the homologation in presence of alcoholic solvents and submit the homologated esters to saponification, instead of using water as the nucleophile.[10]

Besides the preparation of homologated carboxylic acids and its derivatives, it is also possible to synthesize homologated aldehydes **225** from the α-diazomethyl ketones **221** (**Scheme 64**). This can be achieved by simply intercepting the ketene intermediary with *O*,*N*-dimethylhydroxylamine,[210] methyl phenyl amine,[211] or thioethanol.[211] The respective aldehydes can be furnished from the respective amides **222** and **224** by reduction with lithium aluminum hydride whereas the thioesters **223** are reduced with Raney-Ni.



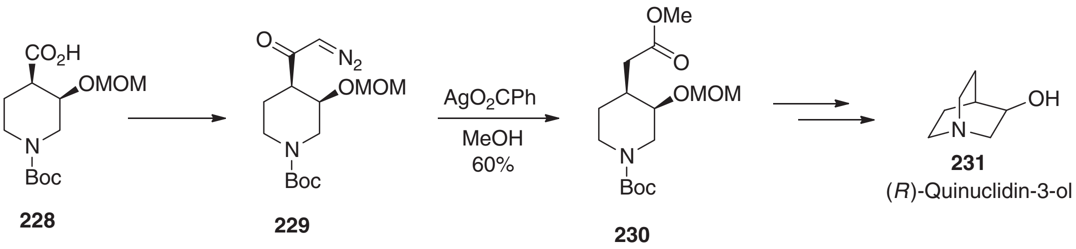
Scheme 64

Another particular example of Wolff homologation is the preparation of *γ*-hydroxy-*α*,*β*-unsaturated esters **227** from the *α*,*β*-epoxy diazomethyl ketones **226**.[212] On photolysis, the ketene suffers a nucleophilic attack followed by the ring opening of the epoxide. Retention of configuration at C4 is observed if an enantiopure diazomethyl ketone is used in this transformation (Scheme 65).[213]



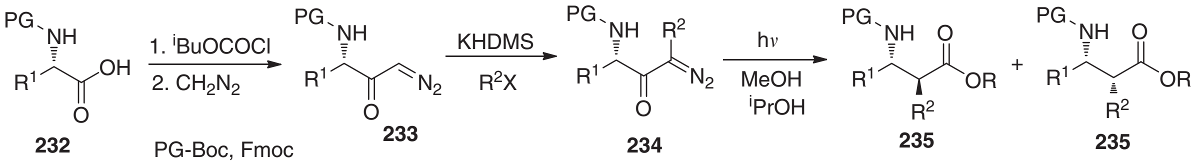
Scheme 65

If the carboxylic acid α-position is chiral it has been demonstrated that the respective α′-diazomethyl ketone can be prepared without racemization and the rearrangement proceeds with retention of configuration.[198b] This feature can be exemplified in the synthesis of (*R*)-quinuclidin-3-ol **231** from (3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-3-(methoxymethoxy)piperidine-4-carboxylic acid **228**.[214] It starts with the preparation of the respective α-diazomethyl ketone **229**, followed by the Wolff rearrangement with retention of configuration. The synthesized homologated methyl ester **230** is reduced and tosylated, suitable for N-alkylation on BOC deprotection. To prepare the desired enantiomer, the N-alkylation should take place in the upper face of the piperidine ring, which is possible due to the homologation with retention of configuration (Scheme 66).



Scheme 66

The homologation can also be performed in fully substituted diazoketones **234** leading to α-substituted carboxylic acids **235**. These compounds were obtained after alkylation in the presence of KHDMS into methyldiazoketone **234**. The addition of the nucleophile to the ketene generates a chiral center. It was observed that if there is a chiral center in the starting material, as it happens in diazomethanes **233** obtained from protected α-amino acids, interesting levels of diastereoselectivity can be obtained (Scheme 67).[215]



PG-Boc, Fmoc

R^1-Me, ^{i}Pr, Bz, 1-Naphthylmethyl, Ph_2CH

R^2-Me

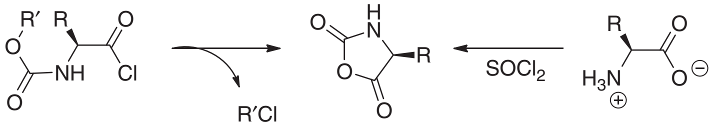
anti/*syn* up to >10:1

25–49% yields

Scheme 67

3.19.3.7.2 Homologation of α-amino acids

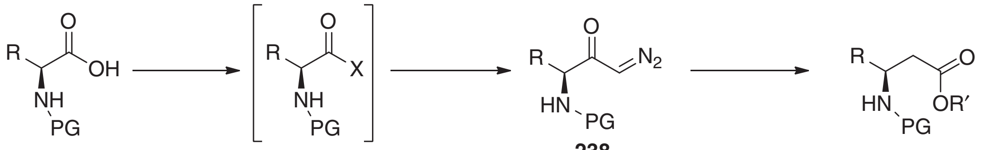
The Arndt–Eistert synthesis is particularly useful for the preparation of *β*-amino acids from α-amino acids. Since it is required to undergo the activation of the carboxylic acid group for diazomethanes acylations, the amino functionality must not interfere with the activated carboxylic derivative and, in this way must have a protecting group. However, the choice of protecting group is not straightforward. Initial experiments in the field demonstrated that disubstituted amino glycyl chloride, *N*-phthaloylglycyl chloride can be acylated in diazomethane furnishing the desired diazoketone.[216] Meanwhile, the utilization of Boc- and Z-protected amino acids chlorides led to partial racemization and decomposition toward Leuchs anhydrides **236**.[216,217] The formation of HCl during the preparation of acyl chloride can potentiate the loss of the amino protecting groups, providing the Leuchs anhydrides **236** on reaction with the activating reagents (Scheme 68). In addition, the basic conditions used to scavenge HCl promote racemization.[218]



236

Scheme 68

The racemization can be avoided if the mixed carboxylic-carbonic anhydrides are prepared.[58c–e,80b] However, their higher reactivity sometimes allows inadvertent hydrolysis leading to the erosion of the yields in this methodology (Scheme 69).[31a,208,219] However, Fmoc-protected amino acid chlorides were found to be stable coupling compounds that can sustain the undesired racemization (Scheme 69).[220] Another viable alternative involves the preparation of α-amino acids pentafluoro esters[221] and acyl



238

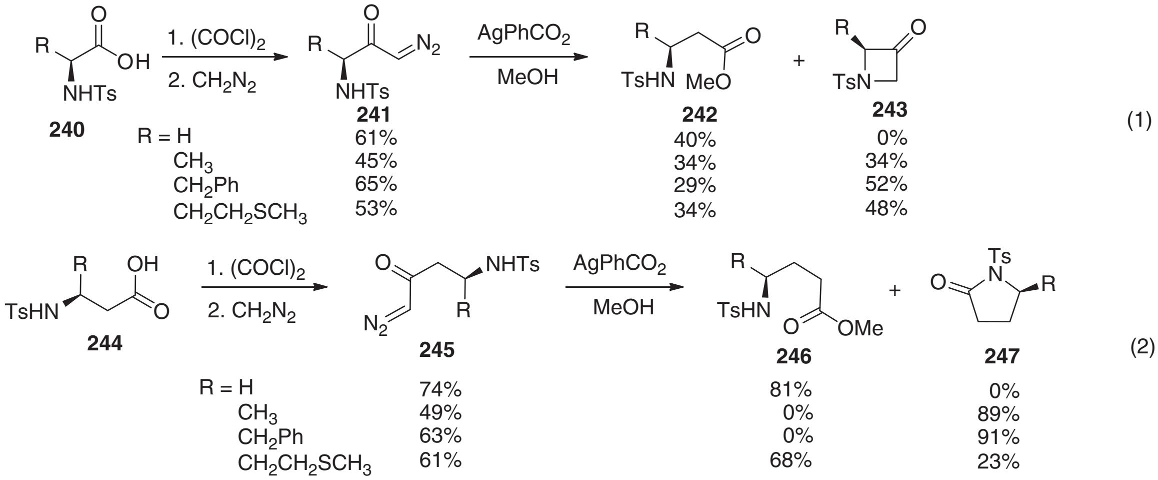
239

Entry	Amino acid	First step		Second step		
		X	Yield (%)	Catalyst	R′	Yield (%)
i	Z-Ala	OCOEt	80	$PhCO_2Ag/NEt_3$	Me	95
ii	Z-Ala	OC_6F_5	96	$PhCO_2Ag/Na_2CO_3$	H	86
iii	Fmoc-Ala	Cl	93	$PhCO_2Ag$	H	90
iv	Fmoc-Ala	OCO^iBu	68	CF_3CO_2Ag/NEt_3	H	72
v	Fmoc-Ala	OC_6F_5	93	$PhCO_2Ag$	H	84
vi	Fmoc-Leu	Cl	96	$PhCO_2Ag$	H	82
vii	Fmoc-Leu	OCO^iBu	87	CF_3CO_2Ag/NEt_3	H	66
viii	Fmoc-Leu	OC_6F_5	96	$PhCO_2Ag$	H	79
ix	Boc-Val	F	94	$PhCO_2Ag$	H	90
x	Fmoc-Phg	F	90	$PhCO_2Ag$	H	85

Scheme 69

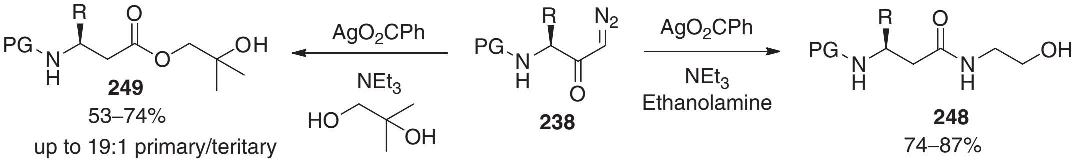
fluorides.[222] Due to the higher tolerance of the former toward hydrolysis, it is possible to obtain the respective diazomethyl ketones **238** in excellent yields (Scheme 69).

N-protected tosyl α-amino acids **240** can also be acylated with diazomethane without any signs of racemization.[223] The Wolff rearrangement step revealed that for this type of substrates there is a competition between the homologation and N–H insertions (Scheme 70, equation 1). The formation of products **243** from direct N–H insertion suggests the possibility of the involvement of free carbene as a discrete reaction intermediate in the diazo decomposition. The different product ratios of direct N–H insertion versus Wolff rearrangement can be explained by the different degrees of steric hindrance of the side chain of the amino acid derivatives. In case of homologated tosyl-protected *β*-amino acids **244** (R=H) only Wolff rearrangement is observed (Scheme 70, equation 2). Depending on the side chain, there is a preference for the ketene to undergo methanolysis or to be intercepted in an intramolecular fashion by tosylamine. The homologation of nitrotoluenesulfonic-protected α-amino acids furnishes exclusively the homologated *N*-methyl *β*-amino acids. The methylation of the α-amino acids occurs during the acylation of acyl chloride with diazomethane.[224] The *N*-methylation with diazomethane was not observed with the tosyl protecting group.



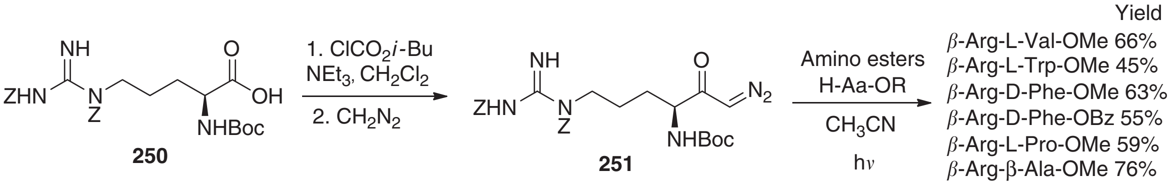
Scheme 70

Although the homologation of α-diazomethyl compounds **238** derived from α-amino acids is performed in methanol or aqueous mixtures, it is also possible to use other nucleophiles to scavenge the ketene intermediary. Ethanol amine can be used as nucleophile affording only **248** due to selective scavenging by the amine. Diols bearing two distinct alcohols can be acylated with high selectivity in the primary over secondary or tertiary alcohols (Scheme 71).[225] This feature has been used to selectively link *β*-aminoacids to pentoses,[225] hexoses,[219a] 2′-deoxynucleosides,[225] or amino-modified oligonucleotides.[226]



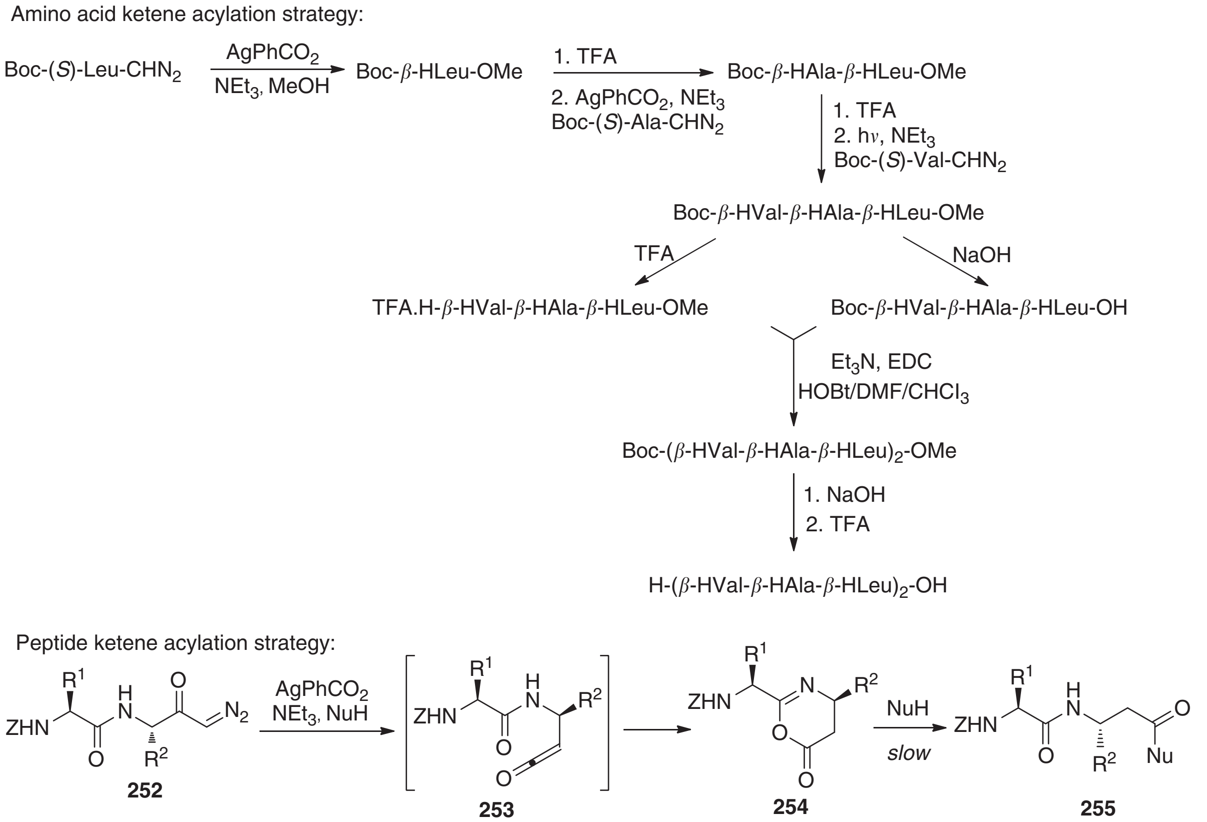
Scheme 71

If the nucleophile is the amino group of an amino acid it is possible to prepare a dipeptide containing one protected *β*-amino acid. As example, several protected *β*-homoarginine dipeptides were prepared by photolysis of N$^{\alpha}$-Boc-N$^{\gamma}$-Z,Z-Arg-CHN$_2$ **251** (Scheme 72).[227]



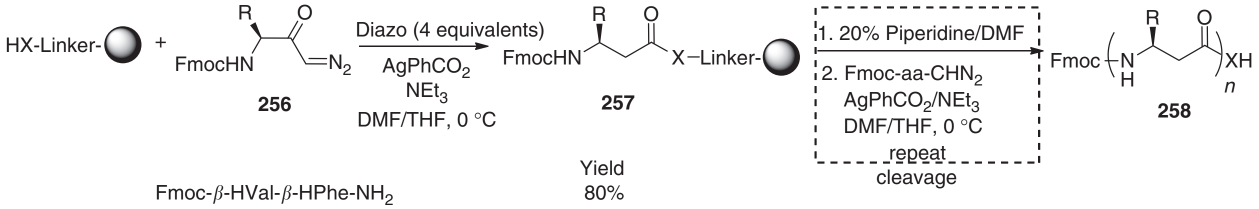
Scheme 72

The introduction of another *β*-amino acid in the peptide can be accomplished by two strategies. In the first, the deprotection of the N-terminus in the dipeptide allows the coupling with the adequate diazomethyl derivative of the amino acid that is selected to be introduced (Scheme 73, amino acid ketene acylation strategy). This methodology allowed the preparation of *β*-peptides with up to six *β*-amino acids.[208] These short chains of *β*-amino acids have attracted considerable attention mainly because of their high tendency to form helices. In the second strategy, the diazo ketone can be prepared in the peptide. However, the ketene **253** obtained on irradiation or silver catalysis is intramolecularly intercepted by the peptidic ligation furnishing 4,5-dihydro-2,3-oxazin-6-ones **254**, which react very slowly with nucleophiles (Scheme 73, peptide ketene acylation strategy).[228] Thus, the first methodology is the most widely applied.[10]



Scheme 73

The solid phase synthesis of *β*-peptides and *β*-amino acid containing peptides via Arndt–Eistert homologation of Fmoc-protected amino acid diazoketones **256** were carried out on Wang, Rink, and 2-chlorotrityl resins. This procedure is highly versatile and an easy execute relying in quantitative coupling reactions which furnished highly pure peptides **258** (Scheme 74).[229]



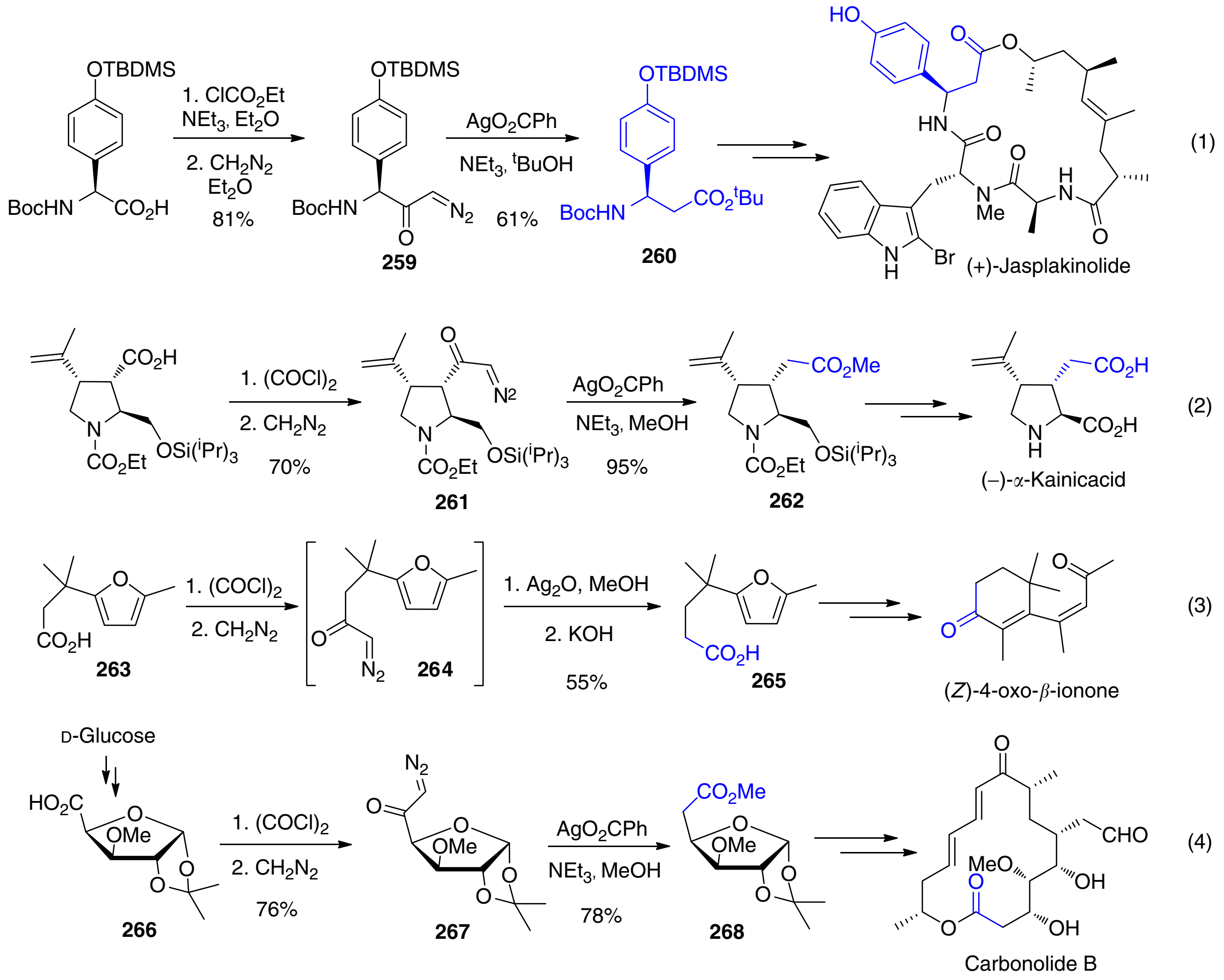
	Yield
Fmoc-β-HVal-β-HPhe-NH_2	80%
Fmoc-β-HTyr-β-HPhe-OH	65%
TFA.H-β-HTyr-β-HVal-β-HPhe-NH_2	75%
Acetyl-β-HLys-β-HTyr-β-HPhe-OH	65%
Fmoc-β-HTyr-β-HTyr-β-HVal-β-HPhe-NH_2	60%
Acetyl-Ser-Asp-β-**HLys**-Pro-OH	80%
Acetyl-Val-β-**HGlu**-Phe-Ile-OH	95%

Scheme 74

3.19.3.7.3 Application in total synthesis

The Arndt–Eistert homologation of carboxylic acids has been considerably applied in the total synthesis, not only in the preparation of small β-peptides or cyclic peptides, but to synthetize alkaloids, terpenoids, steroids, and macrolides.[10]

The cyclodepsipeptide (+)-jasplakinolide has a homoserine fragment in its structure, which was synthesized by homologation of the protected Boc-serine-OTBDMS **259**. The methyldiazo ketone **259** was prepared by applying the mixed carboxylic-carbonic anhydride methodology to avoid racemization of the α-position. The rearrangement is promoted by silver benzoate/triethyl amine in the presence of *tert*-butyl alcohol (three steps yield 49%, Scheme 75, equation 1).[230] Despite (–)-α-kainic acid being prepared from an enantiopure proline derivative **262**, the respective α-diazomethyl ketone **261** can be introduced after the activation of the carboxylic acid with oxalyl chloride without racemization. The Wolff rearrangement step takes place with high efficiency providing the methyl ester **262** in 95% (Scheme 75, equation 2).[231]



Scheme 75

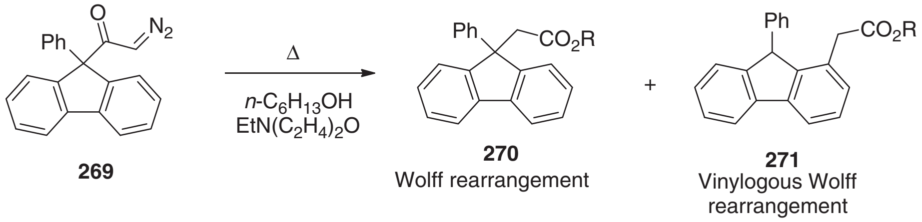
An example of application of Arndt–Eistert homologation in the total synthesis of terpenes is the preparation of (*Z*)-4-oxo-β-ionone. It starts by the conversion of 3-methyl-3-(5-methylfuran-2-yl)butanoic acid **263** in the respective diazoketone **264** applying the same conditions as described in the previous synthesis, followed by the rearrangement, this time in presence of silver oxide (I). The homologated acid **265** is obtained after saponification in a total four-step yield of 55% (Scheme 75, equation 3). This synthesis illustrates well the preference in the literature to prepare homologated carboxylic acids from the respective homologated methyl esters rather than undergo the rearrangement itself in the presence of water.[232]

The macrolide Carbonolide B bears in its core 1,2,3-trihydroxyde fragment with specific stereochemistry that can be obtained from carbohydrates. Hence, the total synthesis starts from modification of D-glucose, which undergoes a homologation step. The carboxylic acid **266** was activated with oxalyl chloride without racemization of the carbohydrate and the homologated methyl ester **268** was obtained in a combined total yield of 59%. The secondary hydroxyl groups in the carbohydrate were protected as ketal and methyl ether during the procedure.[233]

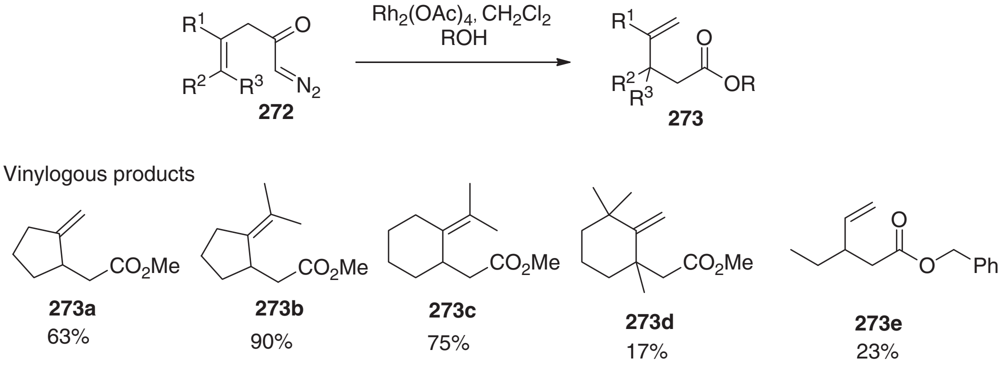
3.19.3.8 Vinylogous Wolff Rearrangement

3.19.3.8.1 Reaction scope

Besides the regular products derived from the Wolff rearrangement, *β*,*γ*-unsaturated diazo ketones can lead to products derived from an additional 1,3-shift of the CH_2CO_2R group. Such reaction is termed 'vinylogous Wolff rearrangement' and was first reported for the formation of **271** after reaction of phenylfluorene derivatives **269**, in which the vinyl system integrates the aryl system of the molecule (Scheme 76).[234] The inclusion of an aryl system in such rearrangement was later reported for the benzofuranyl moiety, whereas benzothienyl proceeded through regular Wolff rearrangement without inclusion of the double bond.[235] Besides the usual thermal conditions, catalytic methods with Cu(II)[236] and Rh(II)[237] complexes favors the formation of vinylogous Wolff rearrangement products **273** (Scheme 77). Dirhodium complexes afford the vinylogous Wolff rearranged products in better yields than copper complexes, although the enantioselectivity of the transformation is very low, and the products were obtained in only up to 31% *ee* when chiral dirhodium complexes were used.[237a] If the α-CH_2 is replaced by an oxygen atom, the formation of the vinylogous product is highly suppressed and O–H insertion products are exclusively formed. In the absence of alcohol in the reaction media, competitive intramolecular C–H insertion happens and the vinylogous Wolff rearranged product could not be detected. *β*,*γ*-Unsaturated α-diazo-*β*-ketoesters analogously afford the vinylogous rearranged products under dirhodium catalysis conditions.[238]



Scheme 76

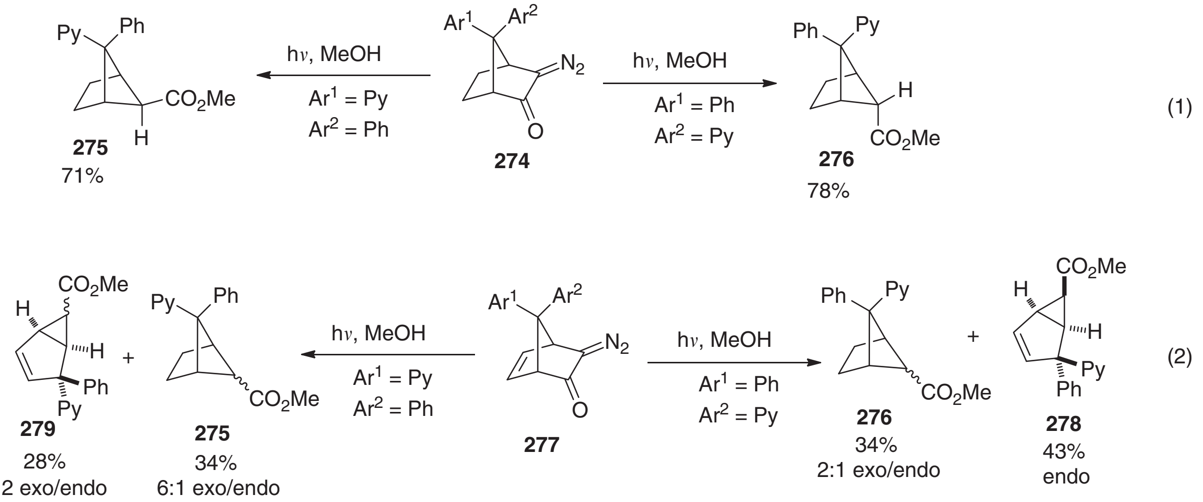


Scheme 77

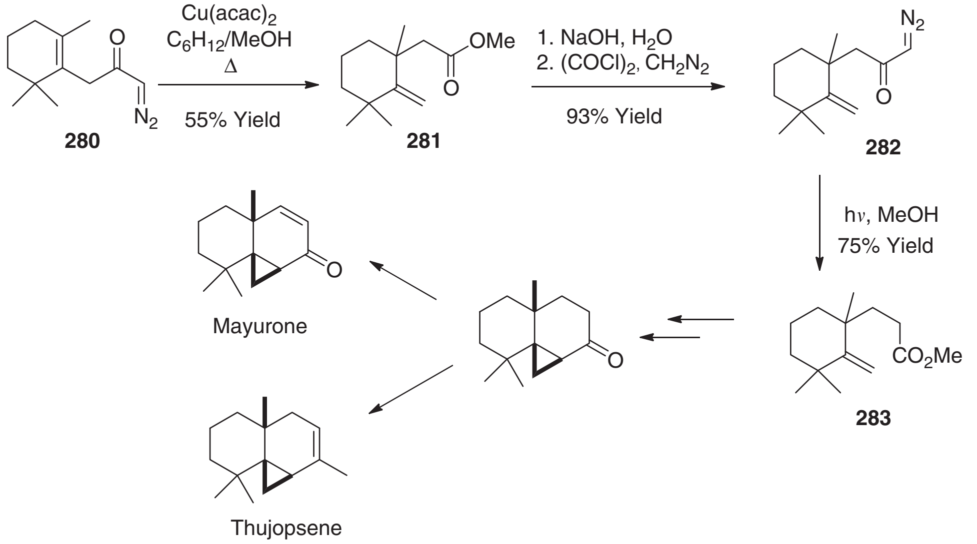
A similar reactivity is observed for bicyclic compounds. Norbornyl systems **277** bearing a diazoketone moiety and a double bond at the *β*,*γ*-positions leads to the formation of the ring-contracted product **278** and **279** fused with a cyclopropane ring (Scheme 78). In contrast, in the absence of the double bond, only ring-contracted products **275** and **276** are obtained. The mechanism proposed for the former transformation, points the diastereoselective protonation of the enolic precursor through a *π*-bond of the methanol molecule to the face of a phenyl group.[239]

3.19.3.8.2 Applications in total synthesis

A sequential use of diazo compounds and Wolff rearrangement based reaction were used in the preparation of mayurone and thujopsene sesquiterpenes from the thujopsene class. A vinylogous Wolff rearrangement of **280** followed by a photochemical Wolff rearrangement of **282** and an intramolecular copper-catalyzed cyclopropanation reaction were explored in this synthesis using the diazo ketones in three consecutive steps (Scheme 79).[240]



Scheme 78



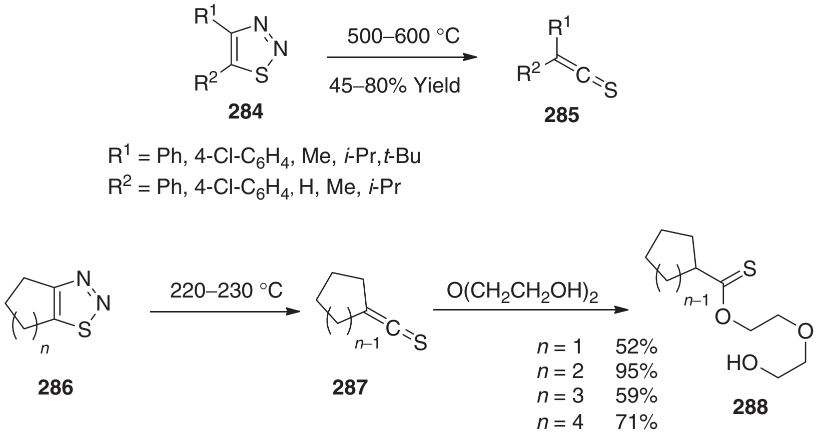
Scheme 79

3.19.3.9 Hetero Wolff Rearrangements

3.19.3.9.1 1,2,3-Thiadiazoles and 1,2,3-selenadiazoles

The flash thermolysis of 1,2,3-thiadiazoles **284** leads to the formation of thioketenes **285** in good yields (Scheme 80), which can then be transformed into the corresponding thioesters after reaction with alcohols.[241] Despite the simplicity of the transformation, harsh reaction conditions are needed with temperatures in the 500–600 °C range. The reaction is tolerant to the presence of several alkyl and aryl substituents, and lower temperature can be used for bicyclic thiadiazole derivatives **286** (220–230 °C).[242] Additionally, the presence of CS_2 in the reaction media leads to the formation of benzotrithiocarbonate.[243] Under photolytic conditions, a mixture of compounds is obtained mostly due to dimerization processes with reduced synthetic usefulness.[244] The synthetic utility of the Wolff rearrangement as a tool for the preparation of thioketenes is rather limited and better procedures are available.[245]

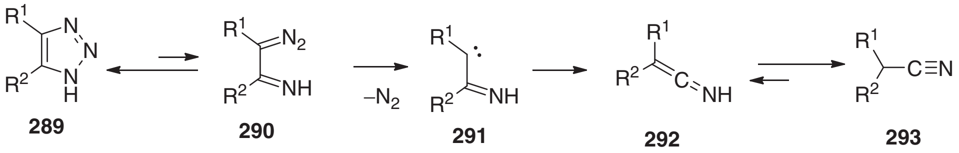
Analogously to 1,2,3-thiadiazoles, 1,2,3-selenadiazoles can be converted to selenoketenes through a Wolff rearrangement in which the alkyne formation is a competitive process. The use of low temperatures (150 K) allows the preparation of the ketene in reasonable yields on irradiation of 1,2,3-selenadiazol[246] or through pyrolysis at the vapor phase.[247] In solution the same ketenes are not obtained and products derived thereof, like dimers, prevail.[248]



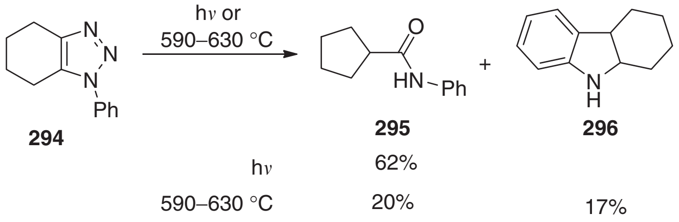
Scheme 80

3.19.3.9.2 1,2,3-Triazoles and related substrates

1,2,3-Triazoles **289** can suffer Wolff rearrangement after molecular nitrogen extrusion through plausible formation of diazoimine **290**,[249] which can latter isomerize to acetonitriles **293** (Scheme 81). The decomposition of 4-phenyl-1,2,3-triazole results in the formation of phenylacetonitrile through a phenylketenimine pathway, together with other side products such as ethers and esters. Pyrolytic (290 °C) processes are better than photolytic ones, providing the acetonitrile in 60% yield instead of 32% observed under photolytic irradiation.[250] A different scenario is observed for 1-phenyl-1,2,3-triazoles **294**, in which photolysis increased the formation of the ring-contracted product **295** in detriment of the cyclized product **296** (Scheme 82).[251] Keteneimines can be obtained in good yields (up to 80%) by irradiation of 1-substituted-1,2,3-triazoles.[252] Pyrolysis of 1*H*-benzotriazoles affords the ring-contracted cyanocyclopentadiene also through a ketenimine pathway,[253] whereas the photolysis of 1-substituted benzotriazoles resulted in the formation of reduced or substituted products due to the reaction of the carbene with the solvent before Wolff rearrangement.[254]



Scheme 81

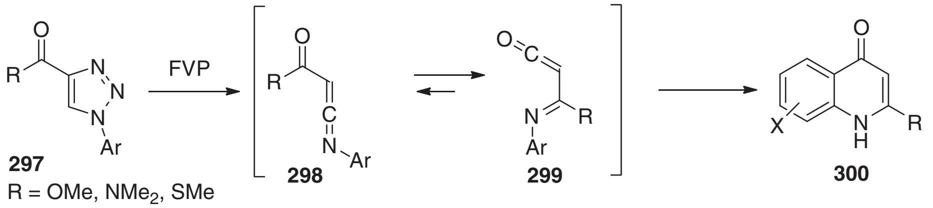


Scheme 82

The Wolff rearrangement of 1,2,3-triazoles **297** bearing an ester or amide at the 4-position is an expeditious way for the preparation of quinolones **300**.[255] The carbene formed proceeds to the formation of the ketenimine **298** and further interconversion to imidoylketene **299** through a 1,3-shift of the alkoxy or amide group. The flash vacuum pyrolysis of the triazole furnishes the 4-quinolones **300** after a last cyclization step (Scheme 83).

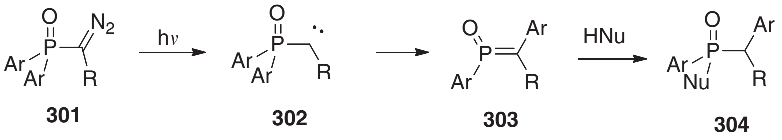
3.19.3.9.3 Wolff rearrangement involving phosphorous atoms

α-Diazophosphane oxides **301** can suffer Wolff rearrangement with migration of an aryl group to give phosphenes **303** that can be further trapped by water, alcohols and amines to provide **304**. The presence of an additional electron-withdrawing group such as ester or amide (R=CO_2Et or $CONH_2$) decreases other competitive reactions whereas the electronic nature of the migrating group has a pivotal influence on the reaction outcome. If a ketone is present (**301**, R=COR′), both groups compete for the ketene



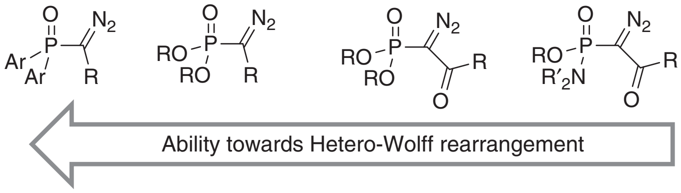
Scheme 83

formation and the selectivity is dictated taking into account the electronic nature and the bulkiness of the ketone substituent[256] (Scheme 84).



Scheme 84

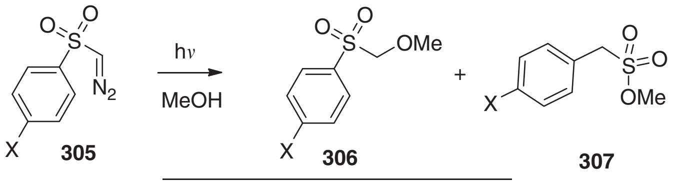
A similar trend is observed for other phosphorous derivatives (Scheme 85). The attachment of electron-rich substituents to the phosphorous atom decreases its ability to participate in the Wolff rearrangement whereas the presence of ketones induces the normal Wolff rearrangement through a ketene pathway, with R migration.[10]



Scheme 85

3.19.3.9.4 α-Diazosulfones and -sulfoxides

The photolysis of α-diazosulfones generates sulfonyl carbenes as demonstrated by the sulfene-pyridine ylide detection under laser flash photolysis.[257] However, the extent of the rearrangement depends on the nature of the substituents. Although arylsulfonyldiazomethanes participate in a hetero Wolff rearrangement although in a small extent, the normal Wolff rearrangement through involvement of a ketone, if present, is preferred.[258] The presence of a sulfonyl group lowers the migratory aptitude of the aryl substituent to provide **307** and the photolysis of α-diazosulfones **305** leads mainly to the formation of O–H insertion products **306** when the photolysis is performed in methanol (Scheme 86).[259] Additionally, the pyrolysis of (*p*-tolylsulfonyl)phenyldiazomethane leads to the formation of a diarylcarbene after SO_2 extrusion.[260] Depending on the nature of the solvent, the photolysis of disulfonyldiazomethanes can lead to the formation of sulfenes in low yields through a hetero-Wolff rearrangement.

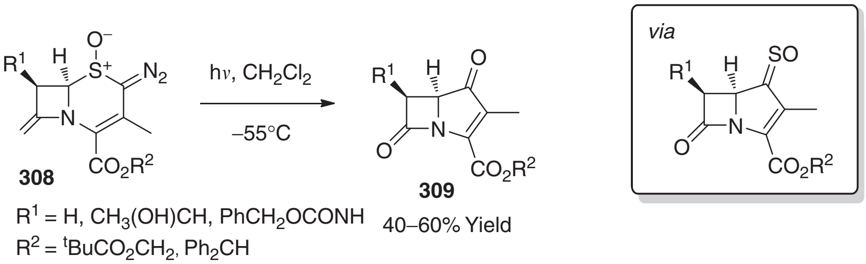


Entry	R	Yield 306 (%)	Yield 307 (%)
i	CH_3O	78	12
ii	CH_3	76	10
iii	H	79	8
iv	NO_2	32	7

Scheme 86

The process is accompanied by the formation of competitive products such as C–H insertion, hydrogen abstraction, or sulfonic acid thioester after a series of rearrangements and decarboxylation processes.[261]

Contrarily to α-diazosulfones, α-diazosulfoxides can easily rearrange through a hetero-Wolff process comprising the sulfine intermediary. The ring contraction of cephalosporins derivatives **308** leads to the formation of carbapenems **309** in reasonable yields under photolytic conditions at low temperatures (**Scheme 87**).[262] The $Rh_2(OAc)_4$-catalyzed decomposition of α-diazosulfoxides also leads to the formation of sulfines which can be trapped by dienes to provide cycloaddition adducts. In the absence of a diene, dimeric alkene species are formed instead.[263] Microwave irradiation can also be used to promote the reaction in a thermal process.[137b] Irradiation of similar compounds in argon matrices at 10 K provided evidences for the formation of α-oxosulfines as intervenient in the process together with oxathiirane that can either decompose to CO_2, COS, and alkenes or rearranging into oxathiane-diones.[264] The photolysis of 3-sulfinyl-3*H*-pyrazoles leads to the formation of sulfinylcarbenes that can either be isolated after Wolff rearrangement to the sulfine or trapped with 2-diazopropane and converted into the corresponding ketone.[265]



308

309

R^1 = H, $CH_3(OH)CH$, $PhCH_2OCONH$

R^2 = $^tBuCO_2CH_2$, Ph_2CH

40–60% Yield

Scheme 87

3.19.4 Final Remarks

The Wolff rearrangement is a valuable methodology for the synthesis of a range of molecules namely by ring contraction and homologation of carboxylic acids. There are still some open issues such as more comprehensive knowledge of the reaction mechanism involved, replacement of the diazo precursor group and the reach for conditions that minimize the competitive reaction pathways characteristic of the carbenes formed such as C–H, O–H, N–H insertion, and cycloadditions (The authors would like to acknowledge Fundação para a Ciência e Tecnologia for the fellowships of NRC and AFT).

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3.20 Nitrogen- and Sulfur-Based Stevens and Related Rearrangements

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3.20.1 Introduction 993
3.20.1.1 Definitions 993
3.20.1.2 Mechanisms 993
3.20.2 Procedures for Ylide Generation 995
3.20.2.1 Deprotonation of Onium Salts 995
3.20.2.2 Fluoride-Mediated Desilylation Reactions 997
3.20.2.3 Tin–Lithium Exchange Reactions 997
3.20.2.4 Additions of Amines and Sulfides to Carbenes and Carbenoids 998
3.20.2.4.1 Thermal and photochemical decompositions of diazo precursors 998
3.20.2.4.2 Metal-catalyzed decomposition of diazo compounds 999
3.20.2.5 Miscellaneous 1000
3.20.2.5.1 Addition of tertiary amines to π-activated/Fischer carbene 1001
3.20.2.5.2 Addition of sulfides to (2-furyl)carbenoids 1001
3.20.2.5.3 Addition of tertiary amines to *in situ* formed π-allyl complexes 1002
3.20.2.5.4 Prototropy within zwitterionic species 1002
3.20.3 [1,2]-Stevens Rearrangements 1003
3.20.3.1 Base-promoted Deprotonations of Onium Salts 1003
3.20.3.2 Intramolecular Additions of Amines and Sulfides to Carbenes and Carbenoids 1006
3.20.3.2.1 Spiro ammonium ylide intermediates 1006
3.20.3.2.2 Fused ylide intermediates 1009
3.20.3.3 Intermolecular Coupling of Amines/Sulfides and Carbenoids 1009
3.20.4 [2,3]-Stevens Rearrangements 1012
3.20.4.1 By Deprotonations of Onium Salts 1012
3.20.4.1.1 Allylic substrates 1012
3.20.4.1.2 Propargylic substrates 1014
3.20.4.2 Intramolecular Additions of Allylic Amines to Carbenes and Carbenoids 1016
3.20.4.3 Intermolecular Coupling of Amines and Carbenoids 1019
3.20.4.4 Intermolecular Coupling of Sulfides with Carbenes/Carbenoids and the Doyle-Kirmse Reaction 1019
3.20.5 Competition between [1,2] and [2,3] Rearrangements 1021
3.20.6 Enantioselective and Enantiospecific Rearrangements 1022
3.20.7 Stevens Rearrangements of Aminals, Hemiaminals, and Oxathiolanes 1026
3.20.8 Sommelet–Hauser Rearrangements 1030
3.20.9 Lewis-Acid Promoted Stevens Rearrangements of Tertiary Amines 1032
3.20.10 Conclusion 1034
References 1034

Glossary

Chemically induced dynamic nuclear polarization It is a non-Boltzmann nuclear spin state distribution detected by nuclear magnetic resonance spectroscopy.

Circular dichroism Electronic or vibrational spectroscopies that are associated to the differential absorption of left and right circularly polarized light. They are most often used to investigate the configuration of chiral (nonracemic) molecules.

Hofmann elimination A process in which a quaternary ammonium ion reacts with a base to afford an alkene and a tertiary amine by an elimination reaction.

Pfeiffer effect An unbalance in the enantiomeric composition of chiral configurationally labile molecules in the presence of other nonracemic molecules and substances.

Radical An atom, molecule, or ion that has unpaired valence electrons or an open electron shell.

Woodward–Hoffmann rules Set of rules that predict the reactivity based on the conservation of orbital symmetry.

Ylides Compounds in which an anionic site Y^- (usually on carbon atoms) is attached directly to a heteroatom X^+ (usually nitrogen, phosphorus, or sulfur) carrying a formal positive charge.

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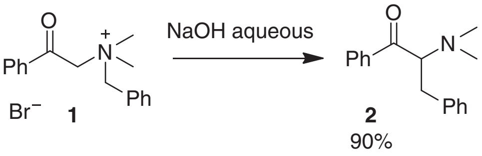
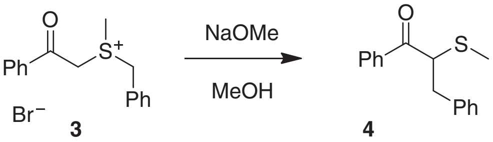
3.20.1 Introduction

3.20.1.1 Definitions

Stevens and related rearrangements are reactions that involve the formation of ammonium, sulfonium, and oxonium ylide intermediates and then migrations of activated alkyl groups from the onium heteroatoms to the nucleophilic ylide carbons. For the purpose of this review and in continuation with the previous Comprehensive Organic Synthesis report,[1] only reactions involving ammonium and sulfonium intermediates will be detailed. This choice is dictated by the abundant synthetic and mechanistic similarities occurring between the nitrogen- and sulfur-based rearrangements. In fact, these transformations have been studied in parallel since the reports in 1928 and 1932 by Stevens of the treatment of phenacylbenzyl dimethylammonium **1** and methylsulfonium **3** bromides with sodium hydroxide or methoxide to form amine **2** and sulfide **4** in good yields (equations 1 and 2).[2,3] These migrations of benzyl groups from the N and S atoms to the adjacent carbon centers are typical examples of so-called [1,2]-Stevens rearrangements. Transformations of this type are often synthetically useful and they will be strongly detailed in this review.

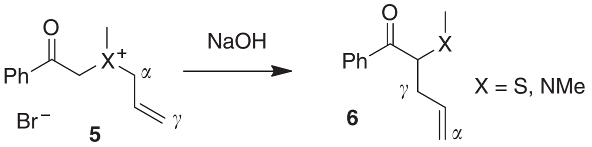


(1)



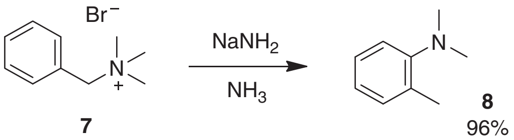
(2)

[2,3]-Stevens rearrangements in which substrates carry allyl or propargyl substituents on the onium atoms were historically reported later (**5** to **6**, equation 3).[4,5] They are also the focus of many studies which will be covered extensively. In these reactions, on migration of the unsaturated side-chains to the nucleophilic ylide carbon, the C–C bond is usually formed at the γ-carbon of the migrating side chains and important mechanistic differences occur that will be described.



(3)

If the onium ion carries a benzylic substituent, a related rearrangement often occurs that involves, in one elemental step, an attack by the nucleophilic ylide carbon of the aromatic nucleus of the benzyl group (**7** to **8**, equation 4). This reactivity, which will be also detailed, was first reported by Sommelet and its mechanism investigated by Hauser and hence its Sommelet–Hauser denomination.[6,7]



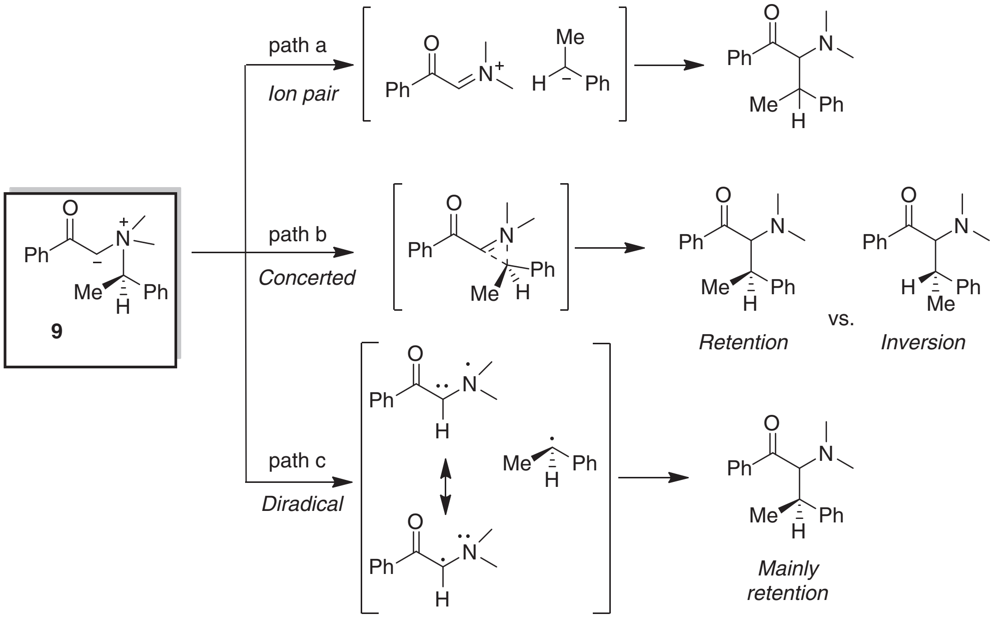
(4)

The fields of [1,2]-Stevens, [2,3]-Stevens, and Sommelet–Hauser rearrangements of ammonium and sulfonium ylides were reviewed previously; the previous Comprehensive Organic Synthesis report dated from 1991.[1,8–13] After a section detailing the mechanisms that are considered for these reactions, this chapter will survey the recent advances that have occurred in the last 20 years or so and demonstrate how broad and active the field is (over 200 references).

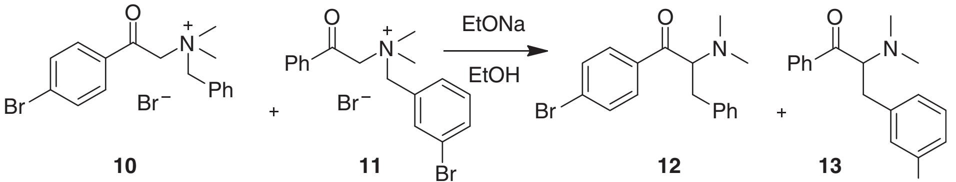
3.20.1.2 Mechanisms

The mechanisms of Stevens rearrangements, and of the [1,2]-shift in particular, have been a source of study and debate since the discovery of the reactions.[1]

In the nitrogen series, Stevens proposed an ion-pair mechanism in the early 1930s. It is detailed in Scheme 1 (path a) using chiral ylide **9** as an illustrative example. The ammonium ylide undergoes a heterolytic cleavage forming a benzylic anion and a cationic iminium species, which recombine in a second elemental step to give a tertiary amine.[14] This rationale was based on the absence of cross-over products during the reaction of a 1:1 mixture of tagged starting materials, such as compounds **10** and **11** (equation 5).[14] Such a cross-over experiment was later reinvestigated using C^{14}-labelled starting material leading to the same conclusion.[15] This mechanism was also justified by the fact that electron-withdrawing substituents on migrating benzyl groups favor the migration.[16,17]

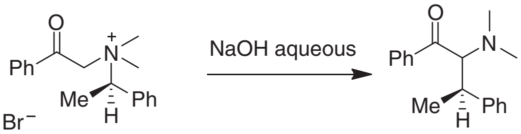


Scheme 1



10 **11** **12** 20% **13** 26% (5)

Then, based on the 1947 report by Kenyon of the first example of stereoselective Stevens rearrangement using enantioenriched substrate **9** (equation 6), a transfer of chirality was observed and a net retention of configuration was determined in the formation of **14** on [1,2]-migration.[18] This result was confirmed by later studies [19–21] and deemed incompatible with the detailed ion-pair mechanism for which a loss of chiral information is expected due to the formation of achiral sp^2-hybridized iminium and configurationally labile benzylic anionic intermediates. Wittig[22] and Hauser[23] then postulated that the mechanism should pass by an intramolecularly concerted pathway (Scheme 1, path b).

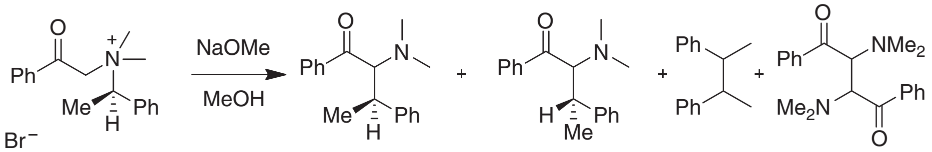


(*R*)-**9** **14** (6)

However, this affirmation was not so simple. According to the Woodward–Hoffmann rules,[24] the [1,2]-Stevens rearrangement is symmetry forbidden due to its four active electron nature. Using thermal conditions, it should involve a suprafacial–antarafacial mode of action rather than a suprafacial–suprafacial mechanism. As such, an inversion of the configuration of the migrating stereocenter would be expected, giving **15** instead of **14** (equation 7), which is contradicted by the experimental results of Kenyon and others.

A careful study of byproducts and an *in situ* analysis by chemically induced dynamic nuclear polarization (CIDNP) nuclear magnetic resonance experiment pushed Baldwin[25] and other researchers[26] to postulate a nonconcerted mechanism via radical intermediates. At the ylide stage, a homolytic cleavage of the most reactive carbon–nitrogen bond leads to a tight radical pair in which the two fragments are closely positioned within a solvent caging. A fast recombination provides the desired rearranged product with the observed retention of configuration (Scheme 1, path c).

Investigations on the impact of solvent viscosity have showed that the intramolecularity and stereoselectivity of the reaction are dependent on an intimate solvent cage structure and on the fast recombination of the separated entities[27–29]; radicals escaping the solvent cage losing their stereochemical information faster and being able to give compounds **16** and **17** in both meso and racemic forms (equation 7).



(*R*)-**9** **14** 75% ratio 3.5:1 **15** **16** 6% **17** 6% (7)

These three main pathways were probed by computational means. Extensive studies were performed by Heard and Yates in the 1990s.[30–32] It was found that the diradical pair mechanism (Scheme 1, path c) is favored over the concerted and the ion pair propositions. Recently, a full investigation of the diradical pathway was done considering both closed-shell and diradicaloid species. This diradical mechanism was shown to be again preferred in most instances. Some exceptions in favor of concerted processes were however noticed, and in the case of Sommelet–Hauser reactions in particular.[33]

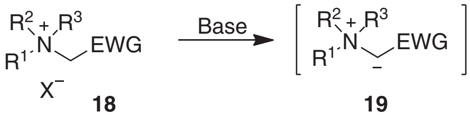
For [2,3]-Stevens rearrangements, the processes can, in principle, involve radical intermediates as well. However, experimental evidences (including regio and stereoselectivity) suggest concerted mechanisms in most cases, in line with the six active electron nature of the reactions.

Finally, most of the observations and mechanistic propositions detailed above for ammonium ylide intermediates are valid for processes involving sulfonium moieties. The differences in reactivity and selectivity are not so much explained by the higher stability of the sulfonium ylides in comparison with the ammonium than by the leaving group ability of the onium group which decreases in the order S > N.[34]

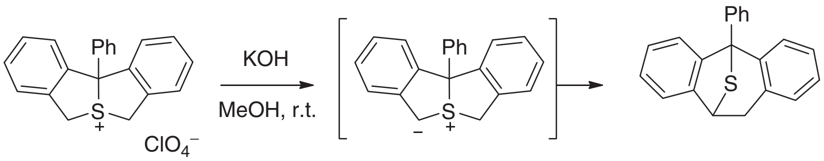
3.20.2 Procedures for Ylide Generation

3.20.2.1 Deprotonation of Onium Salts

As shown earlier in equation 1, in the nitrogen series, the treatment of a quaternary ammonium salt with a strong base is usually sufficient to lead to a deprotonation and generate the ammonium ylide intermediate (**18** to **19**, equation 8). This acid–base approach is general. Nevertheless, to be performed readily and selectively, the presence of a relatively strong electron-withdrawing group (EWG) is required on one of the four arms of the ammonium precursor. It enhances the acidity of the neighboring set of hydrogen atom(s) and activates this α-position for the ylide formation. The presence of the EWG is less of a necessity in the case of sulfonium salts due to the more acidic nature of the α-hydrogen atoms (**20** to **21**, Scheme 2).[35]



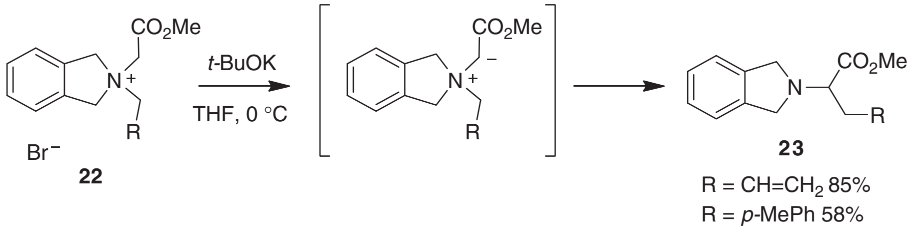
18 **19** (8)



20 **21**

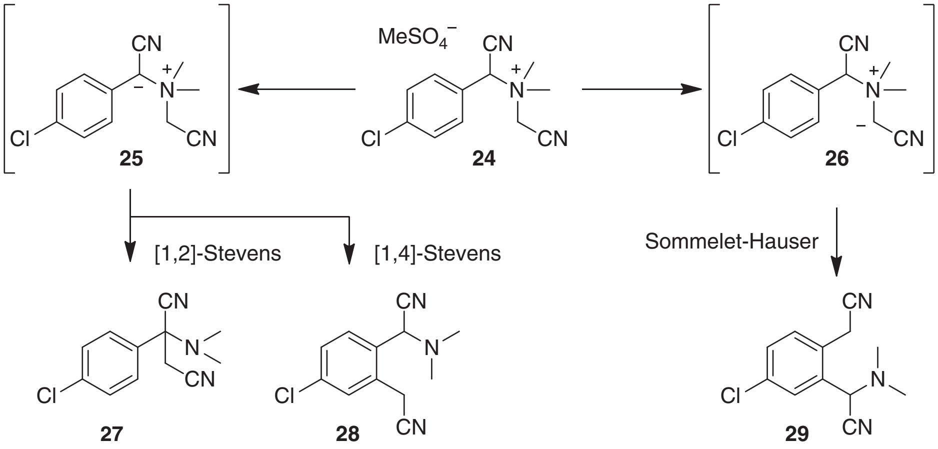
Scheme 2

In the historical example of Stevens (equation 1), it was a ketone moiety that allowed the deprotonation and then the rearrangement.[2] Ester or cyano groups are also routinely used. When NaOH or NaOEt do not promote the reaction,[36] stronger bases such as *t*-BuOK can be used instead with a good chance of success.[37] For instance, in the case with ammonium salts **22**, deprotonation occurs on the ester chain leading to the exocyclic ylide and amines **23** are obtained by migration of the activated allylic and exocyclic benzylic side chain (Scheme 3).



Scheme 3

When two or more activating groups are present in positions adjacent to the charged nitrogen atom, competitive pathways occur that lead often to (complex) mixtures of products. This is exemplified by the study of Jonczyk using two cyano as directing groups.[38–40] In this particular case, a competition between Sommelet–Hauser, [1,2] and [1,4]-Stevens rearrangements was noticed (Scheme 4). Deprotonation of ammonium **24** afforded most stable ylides **25** and **26**. Ylide **25** proceeded then through [1,2] or [1,4]-rearrangements to obtain products **27** and **28**, respectively, whereas **26** formed the Sommelet–Hauser product **29**. Ratios between the different molecules can be addressed by the choice of base and solvent used (Table 1). For instance, the reaction with solid $NaHCO_3$ in dimethylformamide (DMF) at −30 °C afforded only the [1,2] product (entry i), whereas the treatment with 25% aqueous NH_3 in CH_2Cl_2 led to the Sommelet–Hauser rearrangement (Table 1, entry iv). Mixtures of Sommelet–Hauser and [1,4] products were obtained with solid K_2CO_3 in DMF or dimethyl sulfoxide (DMSO) (entries ii and iii).



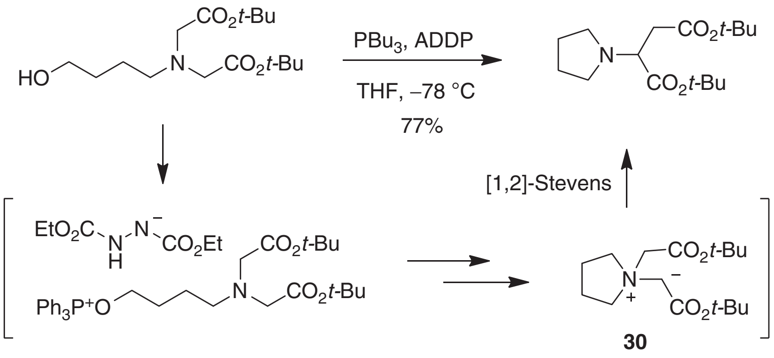
Scheme 4

Table 1 Screening of reaction conditions for the rearrangement of 24

Entry	*Conditions*	**27**	**28**	**29**
i	$NaHCO_3$, DMF, −30 °C	100	0	0
ii	Solid K_2CO_3, DMF, −30 °C	0	46	54
iii	Solid K_2CO_3, DMSO, 20 °C	0	67	33
iv	25% aqueous NH_3, CH_2Cl_2, −30 °C	0	0	100

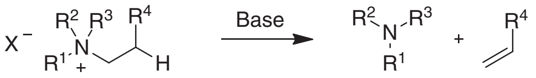
Interestingly, depending on the substrate and the reaction used to form the quaternary ammonium salt precursor, tandem reactions can occur. For instance, in the quaternary ammonium synthesis using standard Mitsunobu conditions, there is not always a need to add an extra base to form the ylide (Scheme 5).[41] In this case, the anionic counterion is basic enough to promote the deprotonation and form ylide **30**; the product of [1,2]-Stevens is then obtained.

To conclude, the deprotonation of an onium salt is an efficient method to generate ammonium and sulfonium ylides. When more than one activating EWG is present, the chemo- and regioselectivity of the formation can be an issue even if experimental



Scheme 5

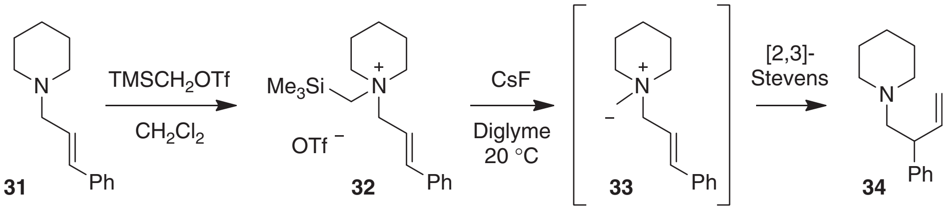
conditions can sometimes be found to address the problem. Also, as strong bases such as *t*-BuOK are used, unwanted Hofmann elimination reactions can compete with the ylide formation (equation 9).



(9)

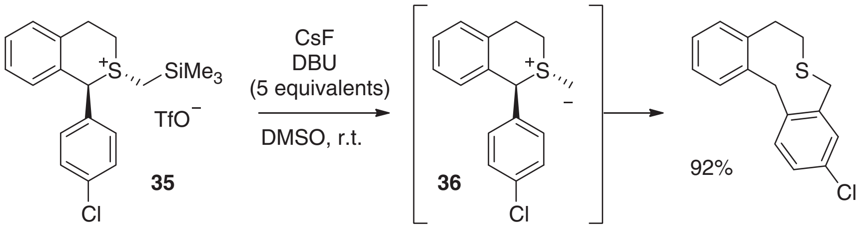
3.20.2.2 Fluoride-Mediated Desilylation Reactions

As just shown, the deprotonation method is particularly efficient when it comes to form ylides at positions adjacent to EWG. As it is not always desired, care was thus taken to find alternative methods to generate highly reactive unstabilized ylide intermediates, even in the presence of acidic benzylic or allylic side chains. The ylides are obtained by fluoride-mediated desilylations of trimethylsilyl substituted onium salts.[42,43] For instance, ammonium salt **32**, made by the reaction of amine **31** with (trimethylsilyl)methyl triflate, reacts with CsF at 20 °C to give ylide **33** (Scheme 6); product **34** of [2,3]-Stevens rearrangement being obtained.[44,45]



Scheme 6

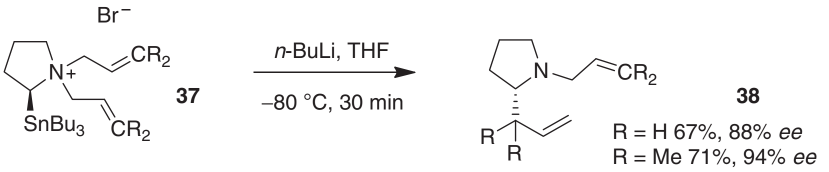
This desilylation method has been used extensively by Sato and coworkers in the context of Sommelet–Hauser reactions. For instance, in the sulfur series, it was shown that **35** reacted with cesium fluoride to generate the corresponding ylide **36** and afford the product of Sommelet–Hauser reactivity (Scheme 7). In the absence of the chlorine atom, a small amount of [1,2]-Stevens product is isolated.[46] Further results and examples are detailed later in this review (Section 3.20.8).



Scheme 7

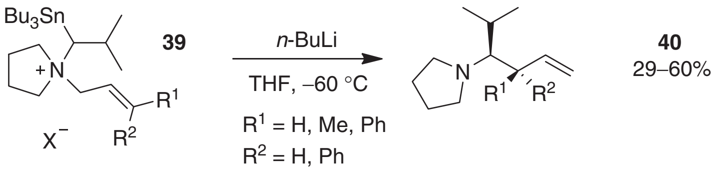
3.20.2.3 Tin–Lithium Exchange Reactions

Another alternative procedure for the regioselective formation of ylide intermediates is a C–Sn to C–Li exchange reaction that proceeds rapidly at positions adjacent to onium atoms, even at low temperature.[47] For instance, treatment with *n*-BuLi of ammonium salts **37** led to the corresponding ylide (equation 10). After its formation, the [2,3]-Stevens rearrangement proceeded through a clear concerted mechanism. Yet, in this case, an interesting inversion of configuration of the original stereocenter was observed.



(10)

This method can be applied to substrates carrying exocyclic C–Sn bonds. The rearrangement also proceeds with possibly high regio- and stereoselectivity (equation 11).[48]



(11)

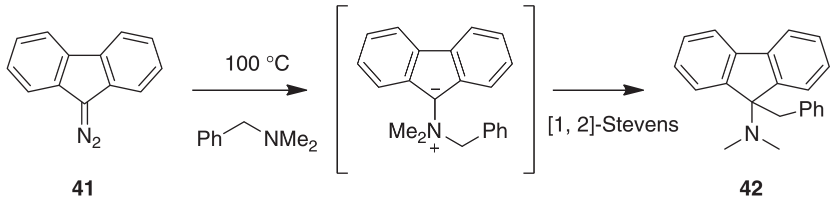
Nevertheless, to date, the most common method to generate an ylide regioselectively remains the addition of a carbene equivalent to an amine or a sulfide. This is detailed in the following section.

3.20.2.4 Additions of Amines and Sulfides to Carbenes and Carbenoids

The use of carbene or carbene-like moieties for the direct formation of ylide intermediates by reactions with amines or sulfides has been known for some time.[1] The carbenes or carbenoids can be generated photochemically, thermally, or by metal-catalyzed processes.

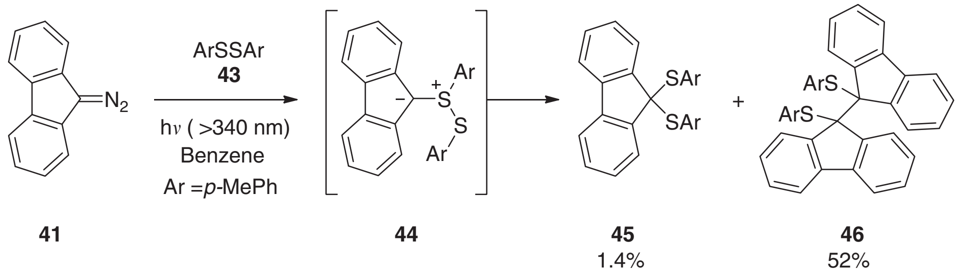
3.20.2.4.1 Thermal and photochemical decompositions of diazo precursors

The formation of ylide intermediates by thermal decomposition of diazo precursors in the presence of tertiary amines was shown to be a possibility as early as 1952 by the reaction at high temperature of benzyldimethylamine with diazofluorene **41** to obtain the [1,2]-Stevens rearranged product **42** (Scheme 8).[49]



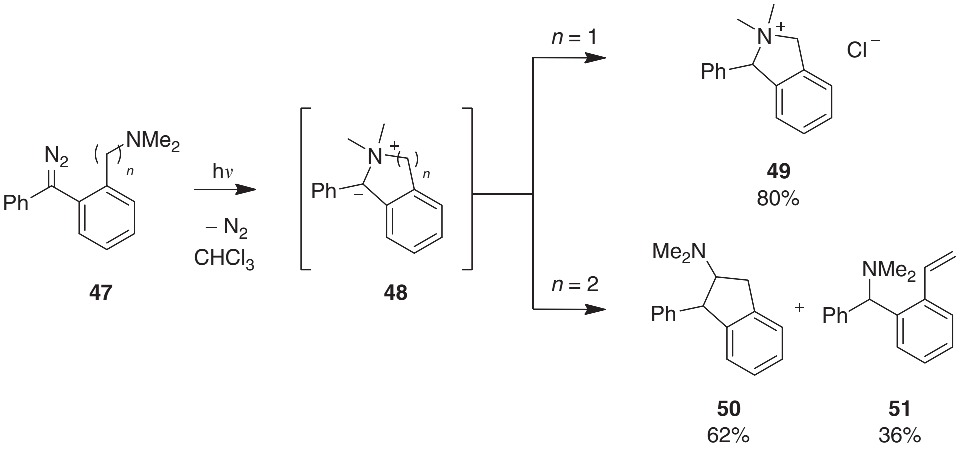
Scheme 8

Diazo derivative **41** was also treated with di-*p*-tolyl disulfide **43** to obtain, under photochemical irradiation this time (> 340 nm), compounds **45** and 9′-bis(*p*-tolylmercapto)bifluorenyl **46** as minor and major products, respectively (Scheme 9).[50] Three different pathways were proposed by the authors to rationalize the results, all of them involving the same first ylide intermediate 44.



Scheme 9

Recently, the photochemical decomposition of diazo compound **47** to generate intramolecular ylides **48** has been reported (Scheme 10). Interestingly, a rearrangement was not observed in the dihydroisoindole series ($n=1$), as only the ammonium salt **49** was afforded at the end of the reaction. In this case, the ylide intermediate acted as a base which was able to react with $CHCl_3$. In the homologous series, indane **50** was obtained along with product **51** of Hofmann elimination.[51]

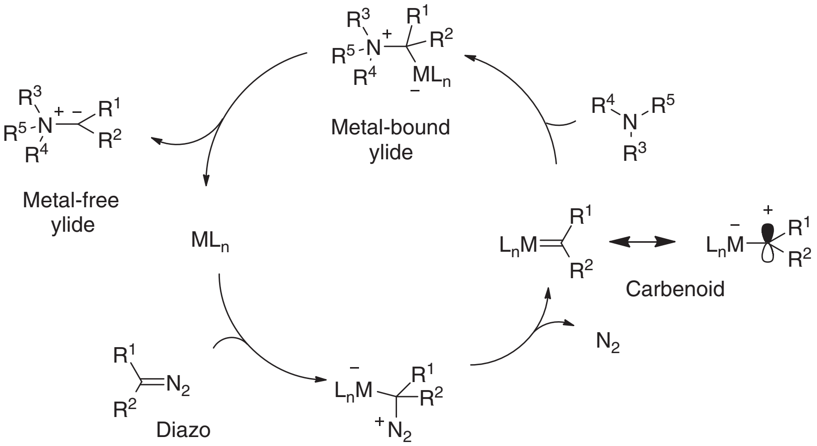


Scheme 10

This series of experiments showed that thermal and photochemical decompositions of diazo compounds are effective methods for generating ylide intermediates which, however, do not always undergo Stevens-like rearrangements.

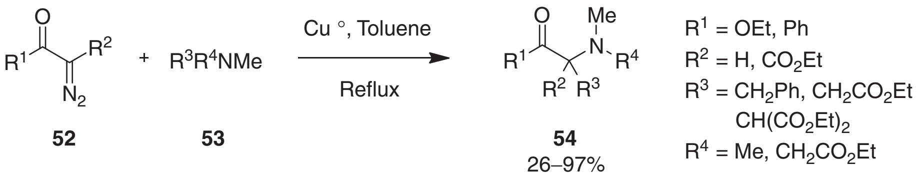
3.20.2.4.2 Metal-catalyzed decomposition of diazo compounds

In view of the tremendous developments in metal catalyzed diazo decomposition methods for the generation of carbene equivalents, straight photochemical and thermal processes have become somewhat old-fashioned as better yields and cleaner crude reaction mixtures are often being observed with metal-mediated reactions. In fact, under these conditions, diazo compounds decompose to form electrophilic metal carbenoids. These species react in nucleophilic addition reactions with amines and sulfides to obtain metal-bounded ylides. These intermediates can undergo the rearrangements directly or dissociate to form the free ylides that often have a similar reactivity to the metal associated species, but not always. This is detailed in Scheme 11 for the formation of ammonium ylides. An analogous mechanism occurs in the sulfonium series.



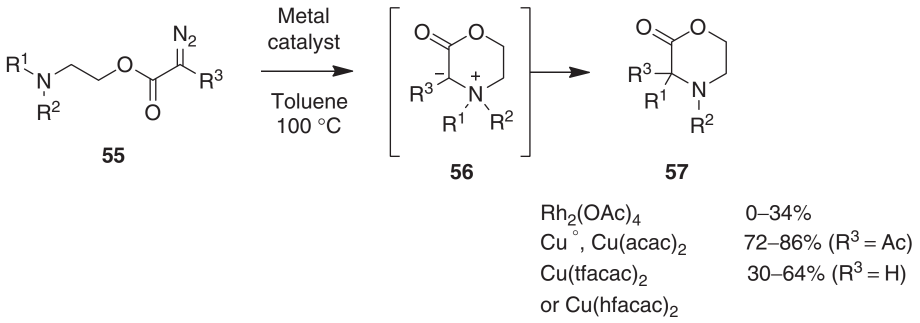
Scheme 11

Dimeric Rh(II) complexes such as $Rh_2(OAc)_4$ are classical catalysts for this transformation. It was found that high temperatures are usually necessary due to the high affinity of amine and sulfide substrates for the vacant coordination sites of the metal complexes; the Lewis acid–base reaction inhibiting the catalysts.[52] To avoid the dimerization of the carbenoids, high dilution conditions and slow addition of the diazo reagents are often used.[52] It was also found that C–H insertion and cyclopropanation reactions can compete with the desired Stevens rearrangement.[53] Copper catalysts that are less acidic are popular in this field due to its good reactivity and selectivity. For instance, in 1993, the intermolecular coupling reaction of ethyldiazoacetate **52** with different tertiary amines **53** using copper powder was characterized. A large variety of α-amino esters/α-amino ketones **54** were afforded (equation 12).[54] It was observed that excess of amines (up to 5 equivalents) and copper (1.5 equivalents) was necessary. After this report, intramolecular processes of ylide formation were essentially studied.[55–57]



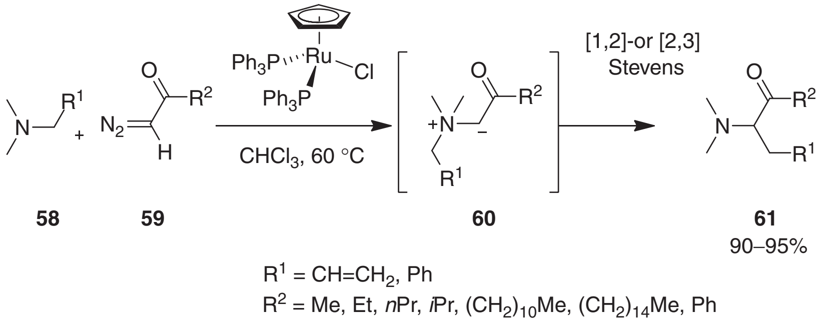
(12)

For instance, compound **55** containing both an amine and a diazo moiety was reacted with either dirhodium or copper sources to yield cyclic ylides of type **56** which rearranged to afford products **57** (Scheme 12). This strategy is general and has been applied in numerous examples that are detailed in Sections 3.20.3.2 and 3.20.3.3.



Scheme 12

Although copper and dirhodium salts and complexes remain the standards in diazo decomposition reactions, ruthenium species have been reported as potential alternatives for ylide synthesis.[58] The reaction of N-benzyl or N-allyldimethyl amines **58** with α-diazo ketones **59** in presence of 1 mol% of half-sandwich complex [RuCl(η^5-C_5H_5)(PPh_3)$_2$] led to the formation of ylides **60** which underwent the classical rearrangements and gave tertiary amines **61** in excellent yield for this intermolecular reaction (Scheme 13).

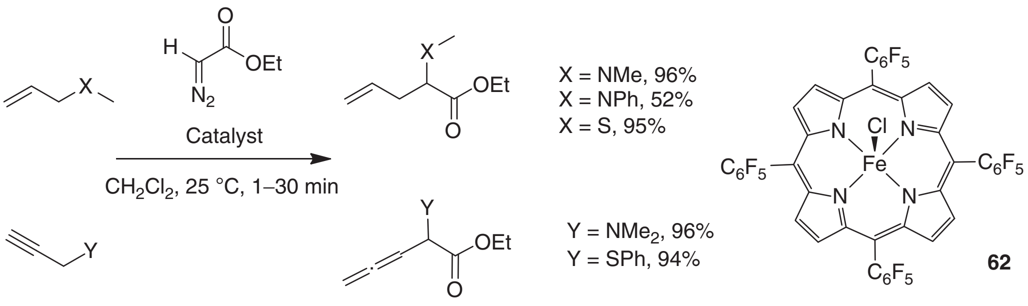


Scheme 13

Another alternative is the use of corrole- and porphyrin-based metal complexes. In 2008, it was shown that electron-deficient iron porphyrins (e.g. **62**) are very effective catalysts for the decomposition of ethyl diazoacetate and for the promotion of the [2,3]-Stevens rearrangement (Scheme 14).[59] A rapid and full conversion occurred (1–30 min, 25 °C, one-pot, 52–96% yield). Moreover, nucleophilic amines or thiols are less poisonous with the iron porphyrin than with the rhodium or ruthenium analogs.

3.20.2.5 Miscellaneous

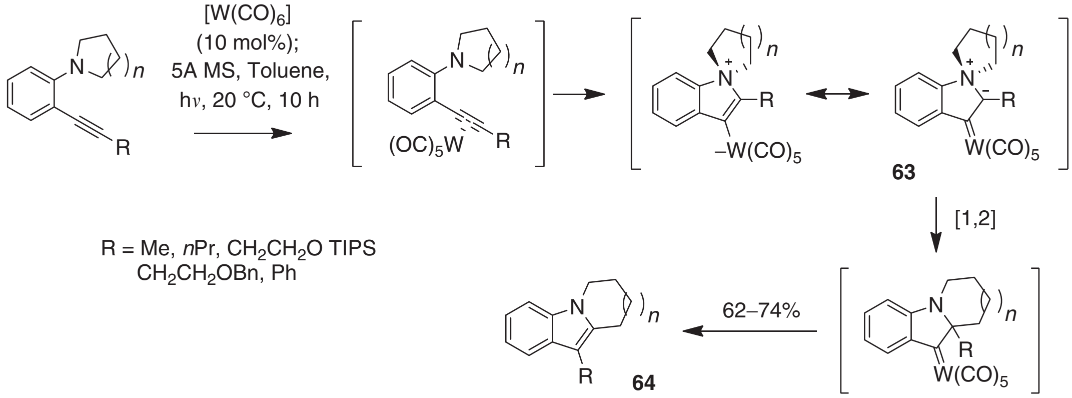
In addition to these general methods of ammonium and sulfonium ylide preparation, other processes yielding these intermediates have been reported. They are detailed in this section.



Scheme 14

3.20.2.5.1 Addition of tertiary amines to π-activated/Fischer carbene

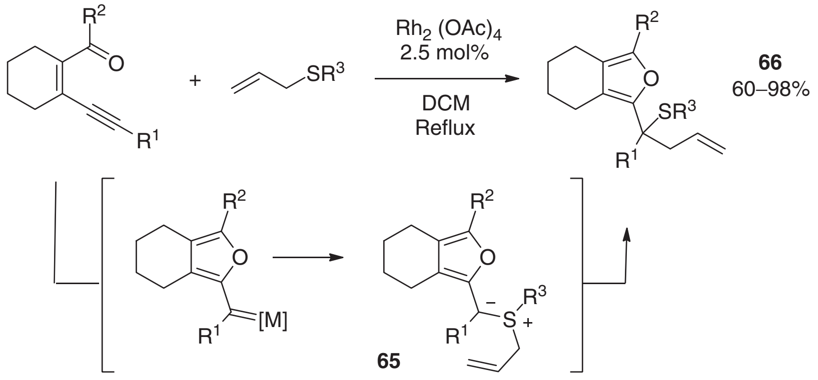
It was shown by Iwasawa that ammonium ylides can be generated using α-acetylenic anilines as substrates and $W(CO)_6$ or $ReBr(CO)_5$ as catalysts.[60] Nucleophilic attack of the nitrogen atom on the activated alkynes formed ylides of type **63**, which underwent ring expansion reaction via a [1,2]-shift mechanism (Scheme 15). Further migration of the group R and release of the metal complexes afforded N-fused tricyclic products **64**.



Scheme 15

3.20.2.5.2 Addition of sulfides to (2-furyl)carbenoids

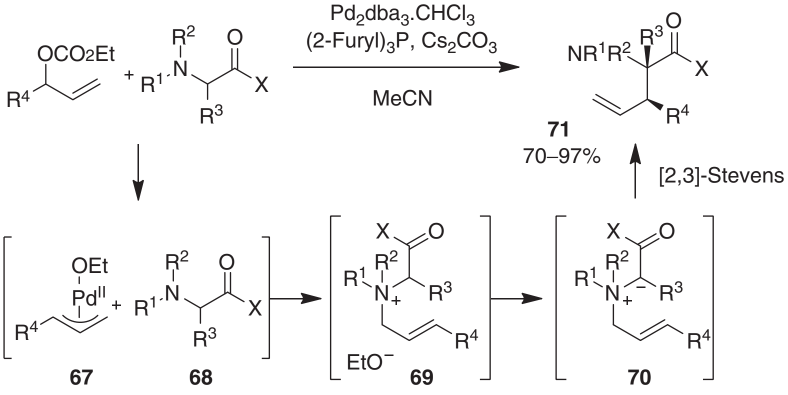
Conjugated ene–yne-carbonyl compounds were shown to react in presence of a variety of transition metal complexes, and $Rh_2(OAc)_4$ in particular, to generate (2-furyl)carbenoids that can be transferred to allyl sulfide moieties (Scheme 16). The resulting sulfur ylides **65** then undergo [2,3]-sigmatropic rearrangements to give furan-containing sulfides **66** in good yields.[61]



Scheme 16

3.20.2.5.3 Addition of tertiary amines to *in situ* formed π-allyl complexes

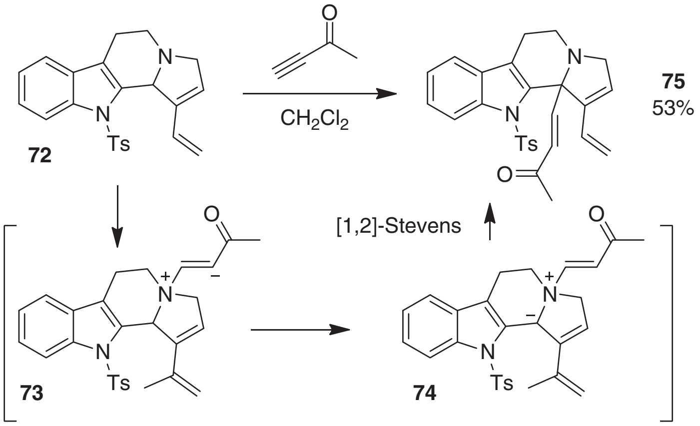
Recently, a palladium-catalyzed Stevens rearrangement was also reported.[62] The reaction made use of classical Trost–Tsuji chemistry to form the π-allyl-Pd(II) complexes **67** from allyl carbonates. Then nucleophilic attack of aminoesters **68** led to ammonium intermediates **69** which, after deprotonation by the *in situ* generated alkoxide bases, formed ylides **70**. The intermediates rearranged to give final products **71** (Scheme 17). Using camphorsultam auxiliaries, high levels of diastereoselectivity were obtained.



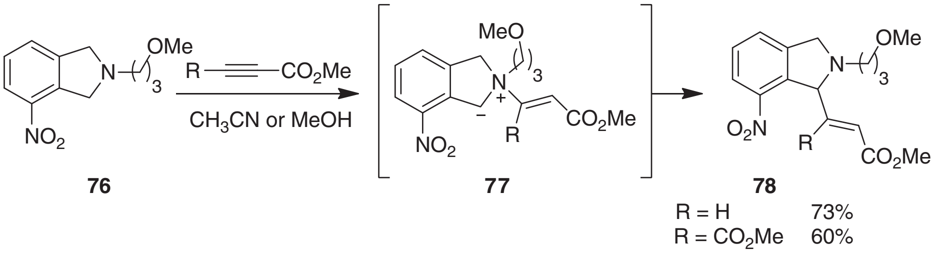
Scheme 17

3.20.2.5.4 Prototropy within zwitterionic species

Finally, ylides can be formed by reactions of tertiary amines of type **72** with electron-poor alkynes. After a first addition reaction to give intermediates **73**, a prototropy occurs and forms a more stable ylide **74**. It then reacts through a [1,2]-shift to give product **75** with 53% yield (Scheme 18).[63,64] In a similar process, it was possible to generate ylides **77** from **76** and afford amines **78** in moderate yield (60–73% yield). A very high regioselectivity was obtained which can be explained by the formation of the most stable ylide **77** (Scheme 19).[65] Of note in both of these examples is the double-bond nature of the migrating group, which is rather unusual.



Scheme 18



Scheme 19

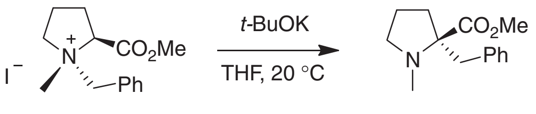
In conclusion, with a better mechanistic knowledge and improved synthetic procedures to generate the ylides selectively, many research groups decided to study and utilize Stevens rearrangements in the past two decades for synthetic and other purposes. Their results are detailed in the following sections. First, examples of [1,2]-Stevens reactions will be presented, followed by the [2,3]-Stevens and Sommelet–Hauser rearrangements.

3.20.3 [1,2]-Stevens Rearrangements

3.20.3.1 Base-promoted Deprotonations of Onium Salts

This section includes concentrated examples that use onium salts as substrates and acid–base reactions to generate ylide intermediates. In most of the selected reactions, as it is either clear or obvious which acidic protons are involved, the ylides will not be usually detailed; only the structure of the products will be presented.

In 1999, West reported the rearrangement of the enantio- and diastereomerically pure ammonium salt (1*S*,2*S*)-**79** (equation 13).[66] Treatment of this compound derived from proline with *t*-BuOK in THF afforded the rearranged product (*R*)-**80** in a good yield. A strong loss of stereochemical information was observed (**80**: 54% *ee*), which was interpreted as the result of a diradical mechanistic pathway (see Section 3.20.1.2). Recently, it was shown by Palombi that electrolytic conditions transformed (1*R*,2*R*)-**79** into (*S*)-**80** in good yield (92%) with a smaller decrease of the enantiomeric purity (84% *ee*).[67]

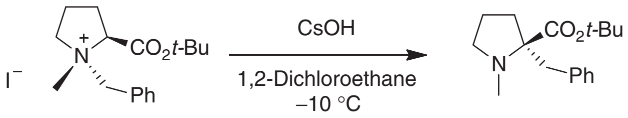


(1*S*, 2*S*)-**79**

(*R*)-**80**
73%, 54% *ee*

(13)

These losses of enantiopurity enticed researchers to look for solutions. Using bulky *t*-butyl instead of methyl esters, Tayama observed, in fact, a more efficient transfer of chirality to form **82** (80%, 72% *ee*) from ammonium (1*S*,2*S*)-**81** (equation 14).[68] The use of biphasic conditions further improved the situation as treatment with CsOH (solid) in 1,2-dichloroethane provided the rearranged product (*R*)-**82** in 73% yield and 92% *ee*. The authors have proposed that the biphasic conditions increase the solvent cage effect and hence the stronger retention of configuration during the Stevens rearrangement (Scheme 1, path c).

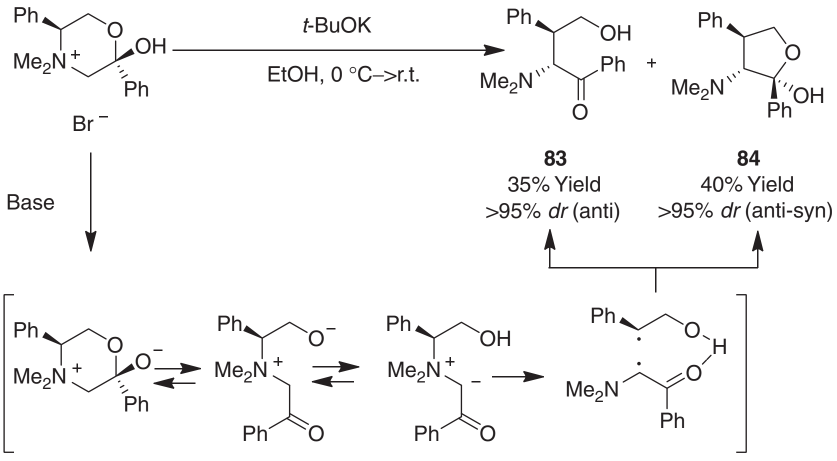


(1*S*,2*S*)-**81**
dr >99%

(*R*)-**82**
73%, >92% *ee*

(14)

Using a different class of substrate, Tomooka was able to generate amine **83** (35%) and hemiacetal **84** (40%) in a single step using *t*-BuOK as base (Scheme 20). An original and interesting H-bonded structure of the diradical intermediate **85** was proposed to rationalize the excellent diastereoselectivity (*dr* > 20:1) for both **83** and **84**.[69]



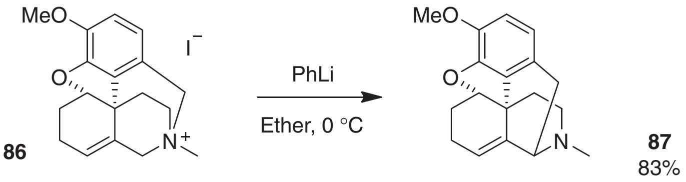
83
35% Yield
>95% *dr* (anti)

84
40% Yield
>95% *dr* (anti-syn)

85

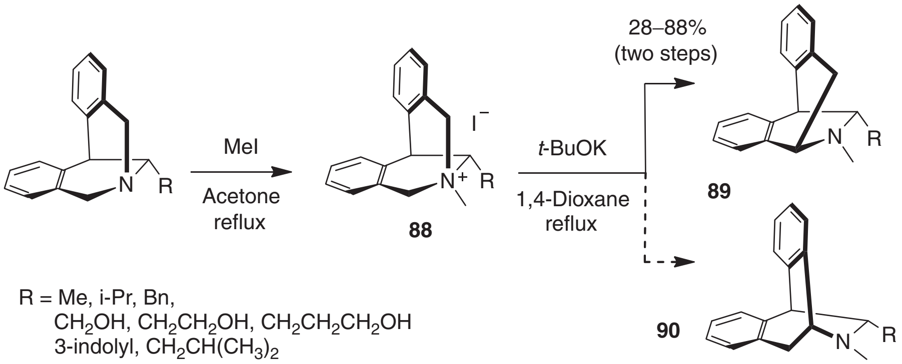
Scheme 20

Also, in an attempt to synthesize morphine analogs, Cheng reported in 2000 the rearrangement of ammonium salt **86** to access the pentacyclic motif **87** in good yield 83%, (equation 15).[70] Deprotonation occurs on the allylic position and the benzylic group migrated; no other reactive combination was observed.



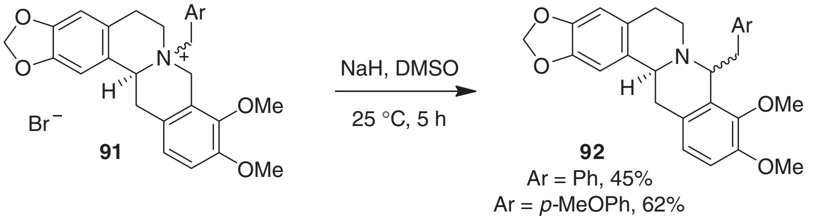
(15)

A similar reactivity was reported, a year after by Hannessian and Mauduit in the synthesis of isopavine analogs (28–88%, Scheme 21).[71] In this series, the presence of two activated benzylic positions could have formally led to a mixture of products. However, only amine **89** was observed; its formation being the result of a lower strain pathway. This chemistry was extended later to other isopavine derivatives.[72]



Scheme 21

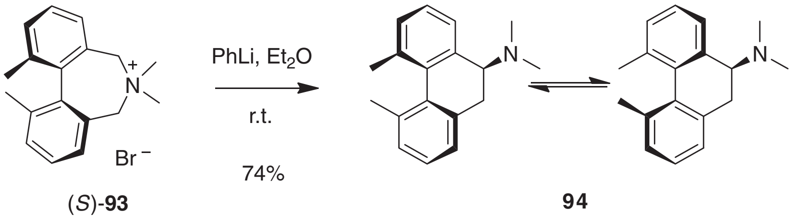
In a somewhat related study, a regio- and enantioselective [1,2]-Stevens rearrangement was reported by Valpuesta in the synthesis of isoquinoline alkaloids.[73,74] Racemic canadine was alkylated with benzyl bromides to obtain mixtures of *cis* and *trans* ammonium salts of type **91** (ratio *cis*:*trans*, 8:1 for Ar=Ph and 4:1 for Ar=*p*-MeOPh). The major diastereoisomers were separated by fractional crystallization and reacted with the sodium hydride in DMSO to give amines **92** in moderate yields (45–62%, equation 16). Interestingly, deprotonation occurs only at the endocyclic, electron-rich, benzylic position and the process is totally stereospecific as *cis* and *trans* diastereoisomers of **91** afford *cis* and *trans*-**92** exclusively.



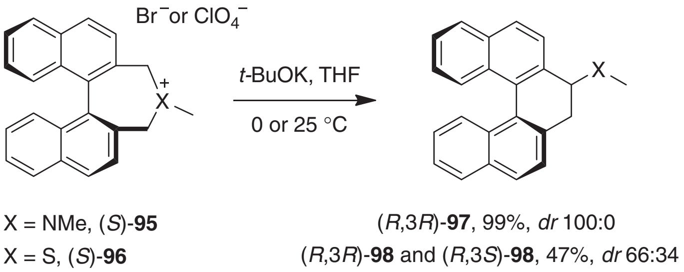
(16)

In these previous examples, the quaternary nitrogen atoms were stereogenic in all instances and the transformations resulted in efficient 'transfer of chirality' to the adjacent carbons. Other approaches were investigated to create and control stereochemistry during the Stevens rearrangement. In 1968, Mislow reported the total transfer of the axial chirality of the C_2-symmetric diphenylazepinium cation **93** to the stereogenic center of amine **94** (Scheme 22).[75] The reaction, induced by a deprotonation with PhLi, occurred with a ring contraction to form a single enantiomer. Compound **94** was, however, conformationally labile as free rotation occurred around the biphenyl axis at room temperature but no racemization happened at the newly created sp^3-stereocenter.

Zavada and collaborators have described a similar reactivity starting from binaphthyl ammonium iodide (*S*)-**95** (equation 17).[76] Treatment of this salt with *t*-BuOK in THF yielded rearranged product (*R*,3*R*)-**97** with a full transfer of chirality as well. Due to the higher barrier of interconversion around the binaphthyl axis, atropisomers were not observed this time. Interestingly, in this example, the configuration of the sp^3-stereocenter is opposite to that generated for **94**, the configuration of **97** being ascertained by circular dichroism. Also, when the sulfur analog **96** was treated under the similar reaction conditions, a moderate level of diastereoselectivity was obtained (*dr* 66:34, 0 °C), which could be improved by lowering the temperature (*dr* 83:17, −78 °C).

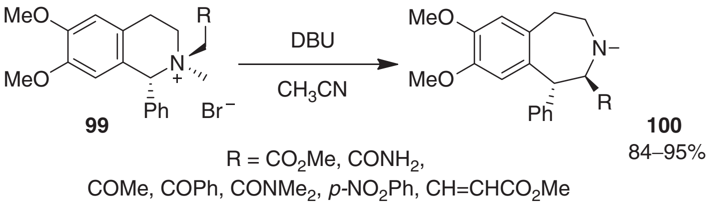


Scheme 22



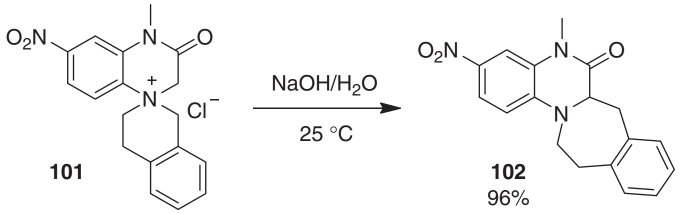
(17)

In these previous two examples, the Stevens rearrangement has proceeded through a ring contraction; this reactivity being the result of endocyclic deprotonation and migration steps. However, nothing prevents ring expansion reactions if an exocyclic deprotonation is promoted and if a group with effective migratory aptitude is included within the ring system. For instance, ammonium salts **99** reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to yield exclusively the corresponding *trans*-benzazepine derivatives **100** (equation 18).[77,78] Not surprisingly, deprotonation occurred α to the EWG R and the secondary benzylic position displayed a higher migratory aptitude than the nonactivated methylene and CH_3 groups.



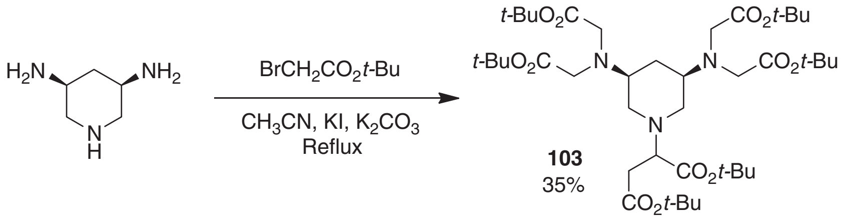
(18)

Spiro ammonium salt **101** was also treated with NaOH to afford ring expanded product **102** (96%, equation 19).[79,80] This example presents a clear indication of the better migrating aptitude of benzylic moieties versus homobenzylic ones.

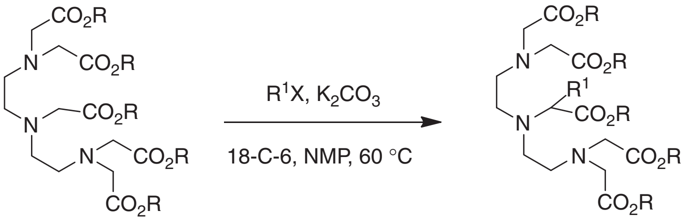


(19)

Finally, several instances of Stevens rearrangements have been reported in the context of alkylation reactions of amines with *t*-butyl bromoacetate (equations 20 and 21).[81,82] In these transformations, compounds of type **103** and **104** were isolated as by-products, the formation of which can be rationalized through an *in situ* ammonium formation and base-induced Stevens rearrangements.



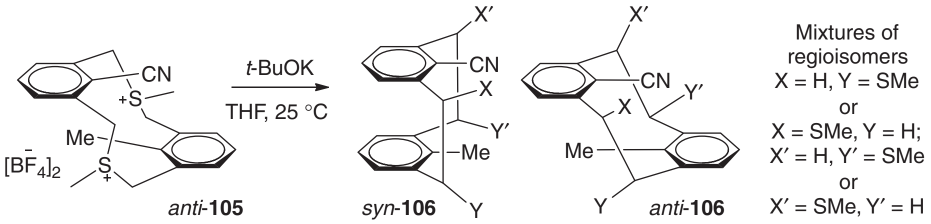
(20)



104
57–62%

(21)

In the sulfur series, an interesting stereochemical observation was made by Lai et al. while performing a double Stevens rearrangement on *anti*-**105**, a rigid precursor to dithiacyclophane **106** (equation 22).[83] Upon the reaction, a predominant formation of *syn*-**106** over *anti*-**106** was noticed – this isomerization being at first glance surprising. Compounds **106** are, however, complex mixtures of regioisomers.

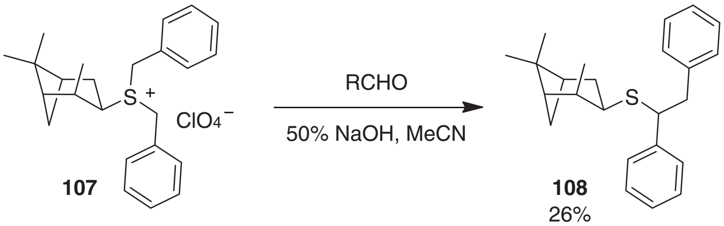


anti-**105** *syn*-**106** *anti*-**106**

Mixtures of regioisomers
X = H, Y = SMe
or
X = SMe, Y = H;
X′ = H, Y′ = SMe
or
X′ = SMe, Y′ = H

(22)

Also, while studying the asymmetric epoxidation using chiral sulfur ylides, Aggarwal observed that the basic treatment (NaOH in MeCN) of sulfonium salt **107** afforded only the rearranged product **108** in moderate yield with a complete lack of reaction with the aldehyde present in the solution (equation 23).[84]



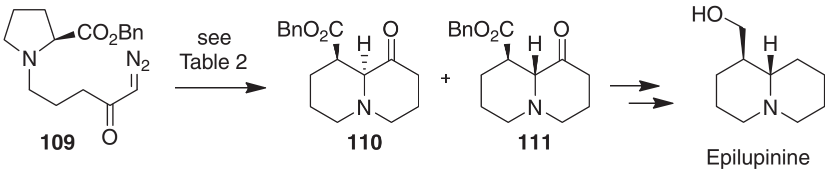
107 **108** 26%

(23)

3.20.3.2 Intramolecular Additions of Amines and Sulfides to Carbenes and Carbenoids

3.20.3.2.1 Spiro ammonium ylide intermediates

In parallel to these base-induced reactions, many processes occurring through metal-catalyzed diazo decompositions were developed, those forming spiro ylide intermediates in particular. Interesting structures of ring expansion were isolated; many of them being pertinent to classes of natural products. For instance, in 1994, West and Naidu completed the synthesis of epilupinine starting from diazoketone **109** derived from proline (Scheme 23).[85,86]



109 **110** **111**

Scheme 23

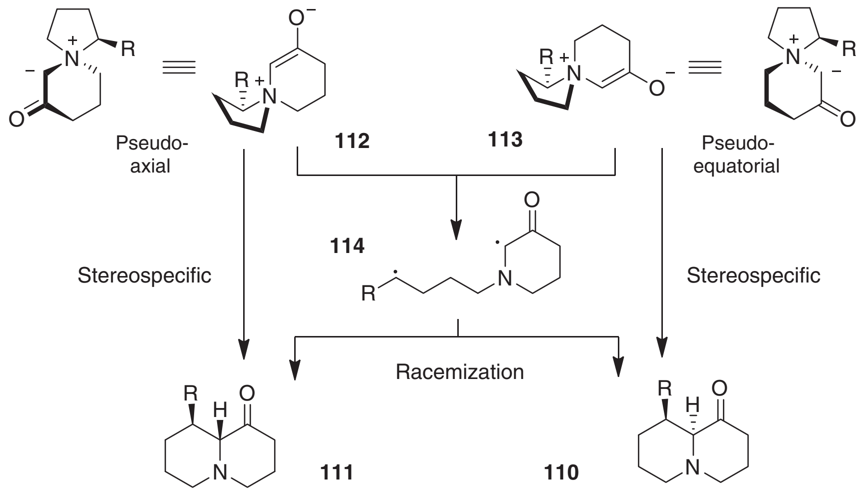
It was observed that both the diastereoselectivity (ratio **110**:**111**) and the enantioselectivity of the reaction depended on the reaction conditions and the nature of the metal catalyst (see Table 2). In our view, this is an indication of metal-bound rather than metal-free ylide intermediates.

A variation in the diastereoselectivity was also observed on using methyl instead of benzyl esters. An increase in *dr* values in the case of $Rh_2(OAc)_4$ as catalyst and a decrease for $Cu(acac)_2$ were noticed showing that steric effects are also influent. Presumably, the stereocontrol occurs at the formation stage of the diastereomeric ylides (Scheme 24). In fact, ammonium ylides **112** and **113** can be generated with either a pseudo-equatorial or pseudo-axial orientation of the newly created N^+–C bond. Considering that the migration of the adjacent secondary stereocenter occurs with full regio- and stereoselectivity when the process is heterolytic,

Table 2 Screening of conditions for the synthesis of an epilupinine precursor (see Scheme 23)

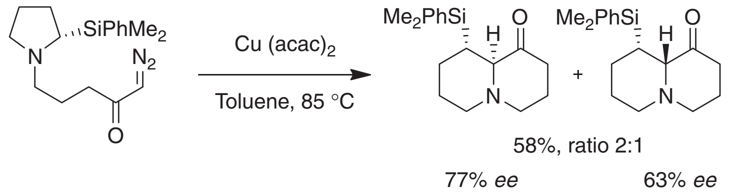
Entry	*Conditions*	*Yield (%)*	**110:111**	*ee of* **111**
i	$Rh_2(OAc)_4$ (3 mol%), CH_2Cl_2, r.t.	74	25:75	440–55%
ii	$Cu(acac)_2$ (5 mol%), toluene, reflux	84	5:95	665–75%
iii	Cu powder (50 mol%), toluene, reflux	87	6:94	nd
iv	Cu powder (15 mol%), toluene, reflux	87	7:93	nd

then the ratio among the diastereomeric products is a reflection of the proportion between the stable ylides. Racemization is, however, due to the formation of diradical intermediates (e.g., **114**).



Scheme 24

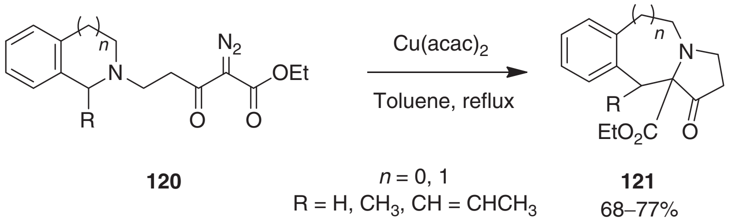
It was later shown that silyl groups can replace ester moieties in this reaction. If slightly better enantioselectivity levels were obtained, a lower diastereoselectivity was, however, noticed (equation 24).[87]



(24)

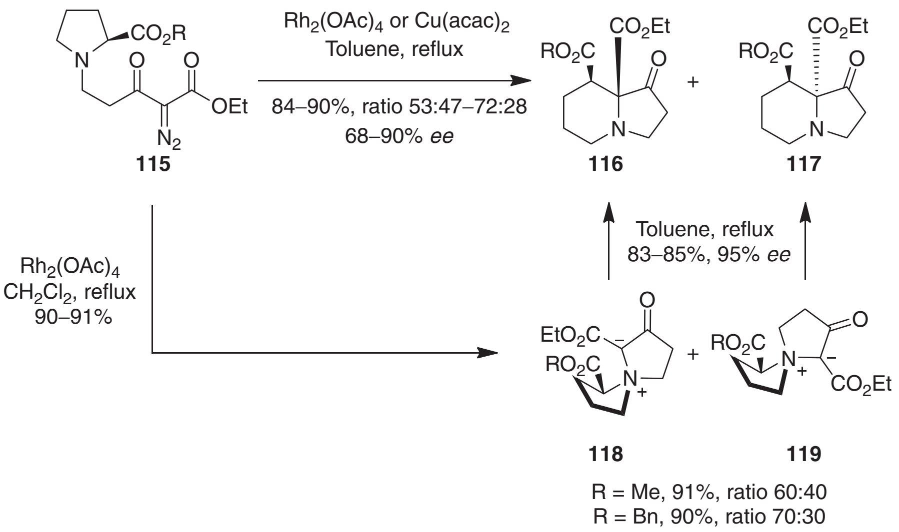
In a related study, intramolecular coupling reactions with more stable diazo precursors were studied by Saba.[88] In the case of α-diazo-β-ketoester **115**, the reaction proceeded in toluene, at high temperature, to the rearranged products **116** and **117** with moderate diastereo- and enantioselectivity levels (Scheme 25). Interestingly, using dichloromethane as solvent, it was possible to isolate ylides **118** and **119**. Heating these single components in toluene at reflux afforded this time amines **116** and **117** as single diastereoisomers, respectively, in good yields and excellent enantiomeric excess. The Stevens rearrangement is, therefore, completely stereospecific after the ylide formation.

The use of more stable diazo precursors had actually been studied previously by Padwa and coworkers for the synthesis of benzazepine alkaloids. Treatment of diazoacetoacetates **120** with $Cu(acac)_2$ provided the rearranged products **121** in good yields (68–77%, equation 25).[89]



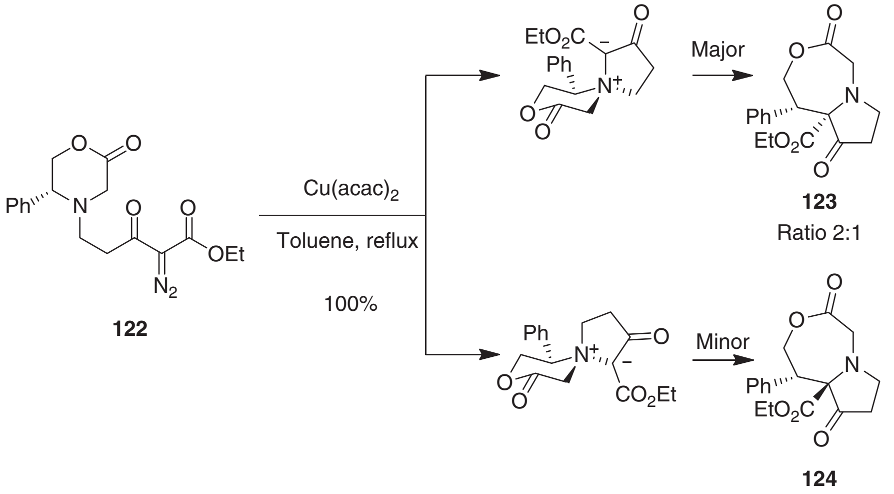
120 $n = 0, 1$
$R = H, CH_3, CH = CHCH_3$ **121**
68–77%

(25)



Scheme 25

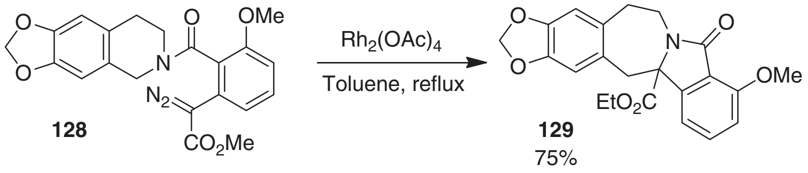
In 2000, Saba used conditions similar to morpholinone-derived **122**. Spiro [5,6]-ammonium ylide intermediates were generated, which rearranged to afford a mixture of products of types **123** and **124**. The 2:1 ratio was explained by the moderately preferred pseudo-equatorial conformation of the exocyclic side chain before the ylide formation (Scheme 26).[90,91]



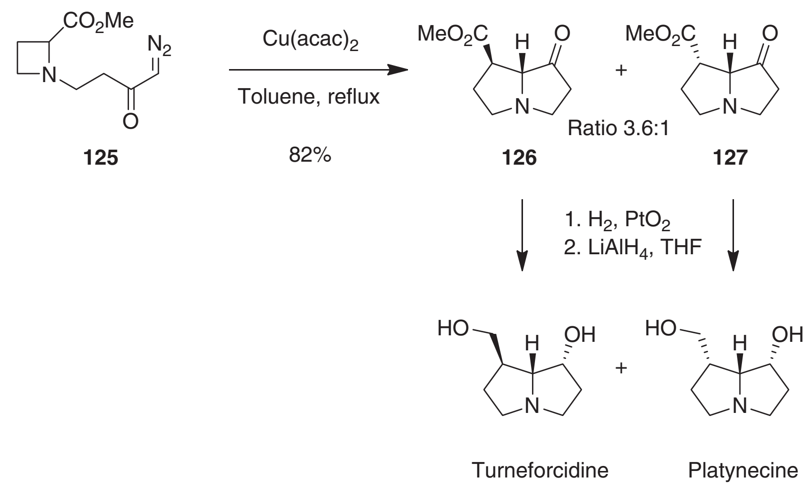
Scheme 26

The reactivity of azetidines was also studied in the context of this ‘spiro-to-fused’ strategy (Scheme 27).[92] In this case, amines **126** and **127** were isolated starting from **125**; these compounds being precursors to natural products turneforcidine and platynecine, respectively.

Finally, the reactivity of amides rather than tertiary amines was investigated (equation 26).[93] Very interestingly, ring expanded product **129** was obtained from the diazo derivative **128**. Clearly, this reactivity advocates for an acyl ammonium ylide intermediate.



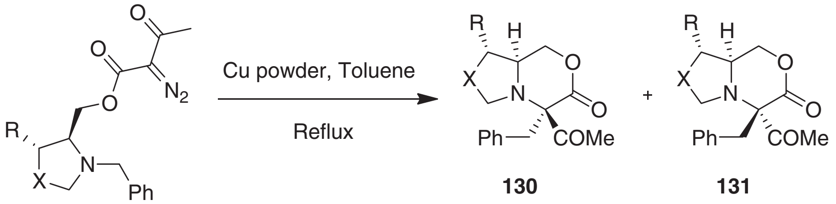
(26)



Scheme 27

3.20.3.2.2 Fused ylide intermediates

In the previous examples, the diazo moieties were carried by exocyclic side chains attached to the reactive cyclic nitrogen atom leading to spiro quaternary ammonium ylides. In 2003, West and coworkers showed that it was possible to link the reactive diazo to a carbon adjacent to the nitrogen atom and not the heteroatom itself.[94] The intermediate formed is then a fused bicyclic ylide and not a spiro derivative. In this case, the rearrangement also occurs, but products of ring-expansion are not formed as the exocyclic benzyl group migrates from the nitrogen to the α-carbon to form **130** and **131** (equation 27).



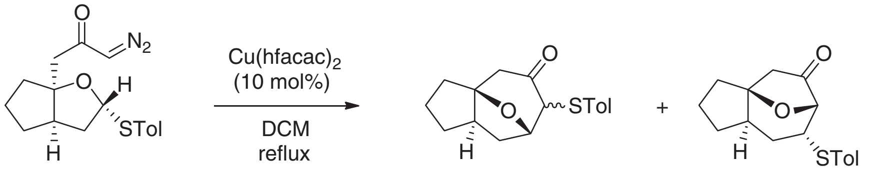
130 **131**

$R = CH_3, X = O$ 57% Yield; 2.8:1 ratio

$R = H, X = CH_2$ 67% Yield; 4.5:1 ratio

(27)

Finally, while studying the synthesis of ether-bridged cycloheptanes, the formation of **133** (13%) was noticed by West and collaborators (equation 28). This minor compound is provided by a [1,2]-Stevens rearrangement of the sulfonium ylide; the major product **134** resulting from [1,2]-reaction of the competitive oxonium ylide moiety.[95]

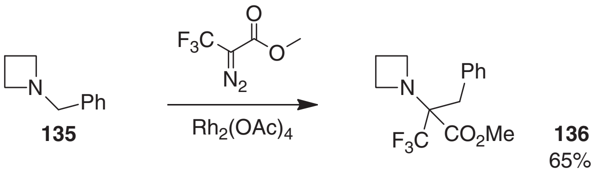


132 **133**, 13%, *dr* 1.9:1 **134**, 68%, *dr* 1.6:1

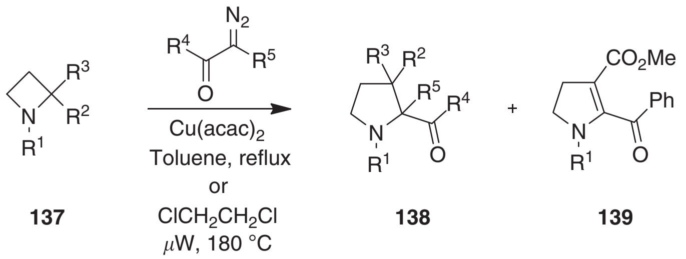
(28)

3.20.3.3 Intermolecular Coupling of Amines/Sulfides and Carbenoids

As mentioned, in the nitrogen series, a relatively small number of examples of intermolecular reactivity were reported and these studies have often involved the rearrangements of azetidines (equation 29). For instance, the treatment of **135** with trifluoromethyl diazopropionate was investigated. Interestingly, a novel azetidine product **136** was formed by migration of the exocyclic benzyl group, and this despite the ring strain.[96] A pyrrolidine product, which could have been expected, was not observed. This situation was upset by the enhancement of the migratory aptitude of the N-adjacent endocyclic carbon (substrates **137**: equation 30, Table 3, entries i–iv) or the use of a more reactive diazo reagent (entries v–vii). Using diazoacetophenone, an oxidation occurred on the rearranged product **138** leading to **139** (Table 3, entry iv).[97]



(29)

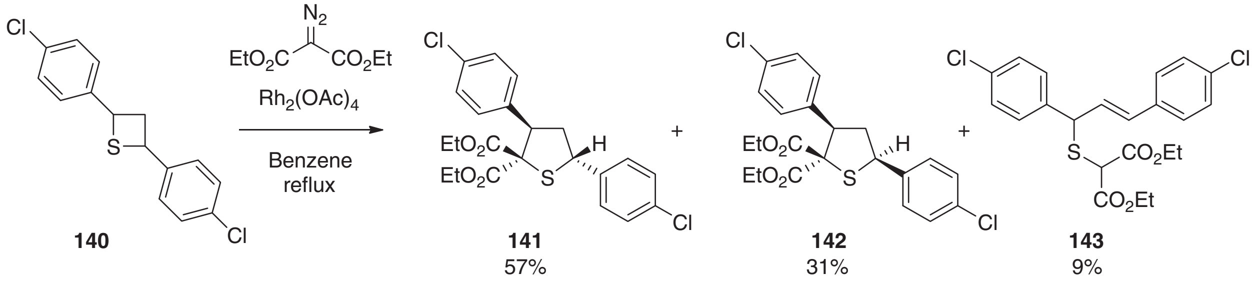


(30)

Table 3 Examples of compounds used in equations 29 and 30

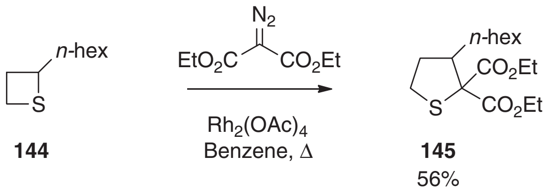
Entry	*R¹*	*R²*	*R³*	*R⁴*	*R⁵*	*Product*	*Yield (%)*
i	Bn	CO_2Me	H	OEt	CO_2Et	138	81
ii	C_5H_{11}	CO_2Me	H	OEt	H	138	62
iii	Allyl	CO_2Me	H	OEt	COPh	138	32
iv	C_5H_{11}	CO_2Me	H	Ph	H	139	65
v	Bn	Me	Me	OEt	H	138	62
vi	Bn	H	H	OEt	H	138	67
vii	Bn	H	H	Ph	H	138	39

In the sulfur series, examples of intermolecular [1,2]-Stevens rearrangements are more numerous. For instance, four-membered ring thietanes reacted readily with diazo compounds.[98] Exposing a solution of a diastereomeric mixture of 2,4-bis(4-chlorophenyl)thietane **140** (*cis*:*trans* 1:2.2) to diethyl 2-diazomalonate in presence of $Rh_2(OAc)_4$ (2 mol%) afforded a diastereomeric mixture of tetrahydrothiophenes **141** and **142** along with the allyl thioether **143** (equation 31).



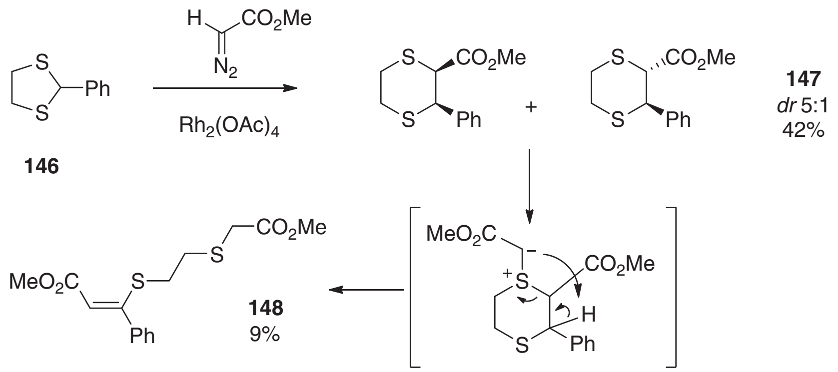
(31)

Substituting the chlorines by different atoms or groups (H, Me, NO_2) did not modify the reactivity; *trans*-**141** still remaining the major diastereoisomer. A similar reactivity was observed with alkyl-2-substituted thietanes (**144** to **145**, equation 32).



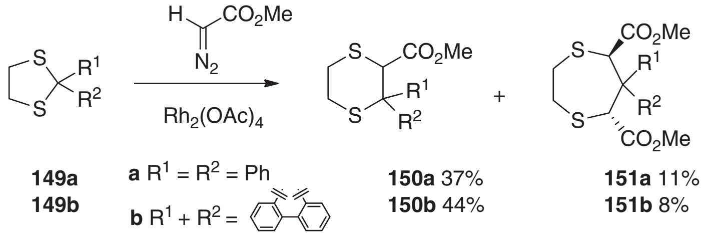
(32)

Dithiolanes were also considered as substrates.[99] For instance, treatment of 2-phenyl-1,3-dithiolane **146** with methyl diazoacetate in presence of $Rh_2(OAc)_4$ led to diastereomeric products of [1,2]-Stevens rearrangement **147** obtained with moderate selectivity and yield (*dr* 5:1, 42%). The relatively low yield is explained in part by the *in situ* consumption of products **147** that react themselves with the carbenoid reagent leading, after the second insertion, to compound **148** of Hofman elimination (Scheme 28).



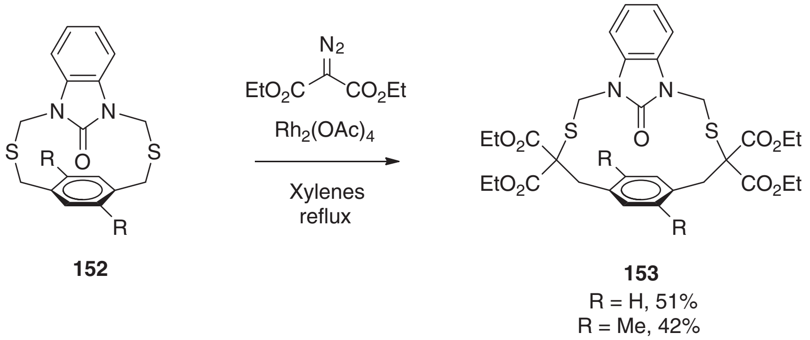
Scheme 28

This double insertion behavior was also observed with disubstituted dithiolanes **149** leading, along with classical product **150**, to 1,4-dithiepanes **151**. This derivative was generated only in its *trans* isomeric form (equation 33).



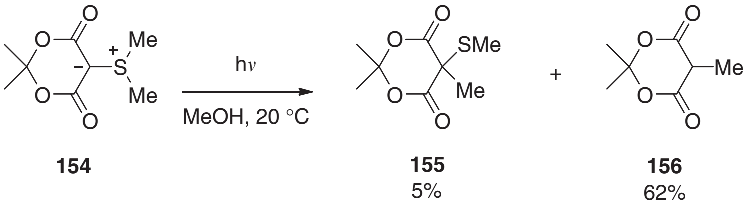
(33)

This tendency of disulfides to react twice with carbenoid intermediates was made use by Diver and coworkers for the synthesis of novel benzimidazolidinone cyclophanes (equation 34).[100] Precursors **152** were treated a slight excess of diethyl 2-diazomalonate in presence of $Rh_2(OAc)_4$ (2 mol%) to afford compounds **153** with moderate yields (42–51%). The double insertion was highly regioselective; the [1,2]-shifts occurring only at the benzylic positions due to the better stability of corresponding diradical intermediates.



(34)

Finally, stable dioxosulfonium ylides of type **154** were studied by Nicolaev trying to perform photochemically the reverse reaction than usual – that is the generation of a carbene and a sulfide by C–S bond cleavage (equation 35). The main process was a Stevens-like 1,2-migration of a methyl group to yield **155** (5% at the end) that underwent apparently a subsequent Norrish type II photocleavage and afforded desulfurized compound **156** (62%).[101]



(35)

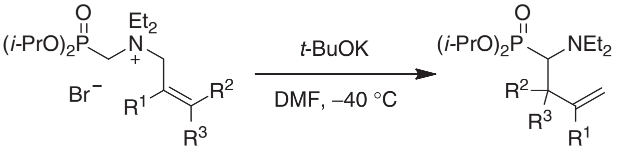
3.20.4 [2,3]-Stevens Rearrangements

As the [1,2]-variant, the [2,3]-Stevens rearrangement has received a lot of interest in the past two decades; the higher reactivity and usually concerted nature of the mechanism being beneficial factors in addition.

3.20.4.1 By Deprotonations of Onium Salts

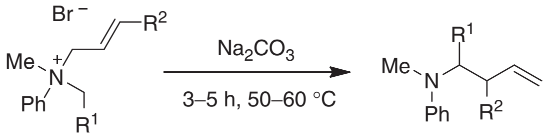
3.20.4.1.1 Allylic substrates

In the nitrogen series, quite a few examples have made use of acid–base reactions for the generation of the ylide intermediates; the reactivity and regioselectivity being modulated by phosphonates (**157**),[102] esters or ketones (**158**),[103] or hydrazones (**159**)[104] as electron-withdrawing groups (equations 36–38).



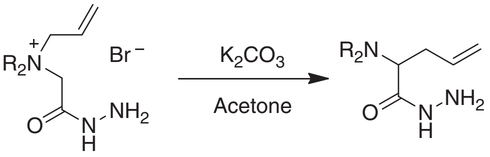
157 51–77% $R^1, R^2 = H, Me$

$R^3 = H, Me, Ph$ (36)



158 18–68% $R^1 = CO_2Me$, COMe, COPh, *p*-ClPh

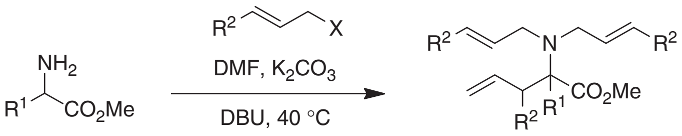
$R^2 = H, Me$ (37)



159 30–40% $R_2 = Me_2, Et_2, (CH_2)_5, (CH_2CH_2)_2O$ (38)

One-pot protocols were also developed for the preparation of products of [2,3]-rearrangement without the necessity to isolate quaternary ammonium salt precursors. Examples are, for instance, the direct reactions of secondary allylic amines (**160**) with methyl iodide[105] or primary amines (**161**) and allyl iodide/bromide in basic media (equation 39 and equation 40).[106]

160 58–62% R = H, Me, Ph (39)

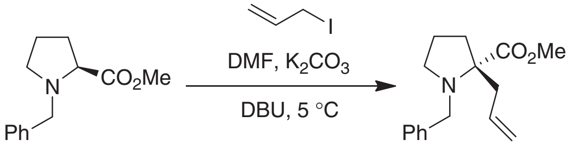


161 16–80% $R^1 = H, Me, Ph$

$R^2 = H, Me$

X = Br, Cl, I (40)

Another example is the asymmetric synthesis of proline derivative **162** obtained in moderate yield but good enantiomeric excess (equation 41).[106] Interestingly, an inversion of configuration was observed. It is probably due to the preferred *trans* arrangement of the benzyl and ester groups on alkylation with the allylic reactant. Then, suprafacial migration of the three carbons fragment occurs on deprotonation leading to the observed selectivity.

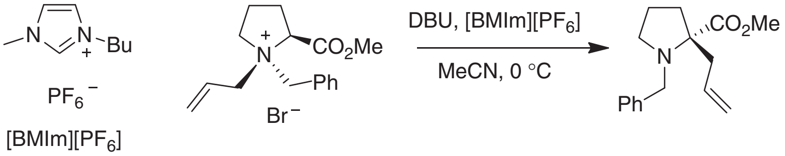


162

48%, 86% *ee*

(41)

The possibility of using an ionic liquid medium to activate and stabilize the ylide intermediate was studied by Santos for the synthesis of the product **162** (equation 42). Using [BMIm][PF$_6$], the stereoselective [2,3]-Stevens rearrangement of ammonium salt **163** was performed with a better yield but lower enantiomeric purity.[107] Of note, in those examples in which the quaternary nitrogen atom carried both allylic and benzylic substituents, only the [2,3]-Stevens rearrangement was noticed.

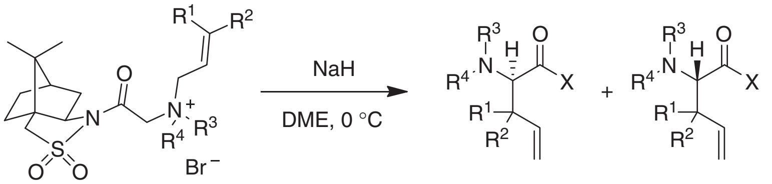


163

162 65%, 80% *ee*

(42)

An asymmetric variant was developed using a chiral auxiliary approach, and a camphorsultam auxiliary in particular (**164,** equation 43).[108] High levels of diastereo- and enantioselectivity were obtained.



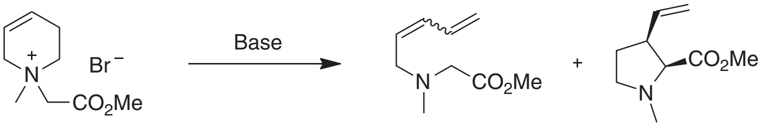
164

70–99%
dr 97:3 to 99:1

R^1 = H, Me, CO_2Me
R^2 = H, Me
R^3 = Me, Bn, allyl
R^4 = Me, allyl

(43)

On substrates of type **165**, early attempts to promote a [2,3]-rearrangement were unsuccessful. Using NaOMe as a base, only diene **166** of Hofmann elimination was isolated.[109,110] Recently, under a different set of conditions (NaH in DME at reflux), it was possible to obtain compounds **167** as single diastereoisomers of *cis* configuration (**Scheme 29**).[111]

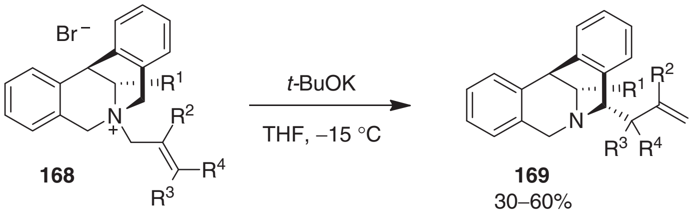


165 **166** **167**

	166	167
NaOMe/MeOH	63%	0%
NaH/DME	5%	58%

Scheme 29

Related to the already discussed synthesis of isopavine, Hannessian and collaborators reported the rearrangement of N-allyl-azociniums **168** (equation 44).[112] Treatments with *t*-BuOK in THF afforded expected products **169** in moderate yields as single diastereoisomers.



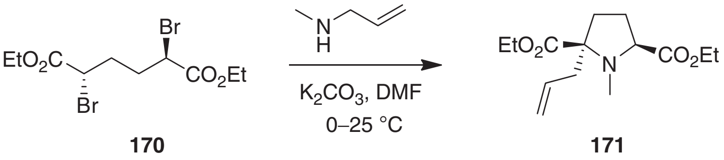
168

169
30–60%

R^1 = Me, *i*Pr, *i*Bu, Bn
R^2, R^3, R^4 = H, Me

(44)

Finally, as in the case of the [1,2]-Stevens reactions, one-pot nitrogen alkylation, deprotonation, and subsequent [2,3]-sigmatropic rearrangements are feasible. For instance, from dibromo **170** and N-methylallylamine, *in situ* formation of a quaternary ammonium salt occurs which affords after the rearrangement 2-substituted proline **171** in moderate yield but excellent *cis*/*trans* ratio (equation 45).[113]

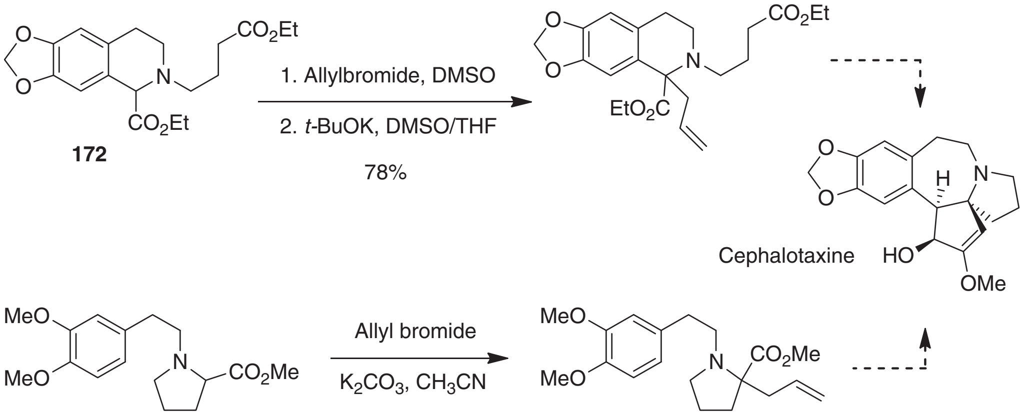


170 **171**

58%, *dr* 13:5 *cis*:*trans*

(45)

A one-pot strategy was also used in the synthesis of cephalotaxine, starting from two very different substrates **172** and **173** (Scheme 30).[114,115]



172 **173**

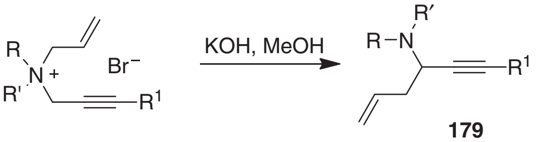
Scheme 30

However, this method tended to produce complex mixtures of products when more than one nitrogen atom was present in the starting substrate (Scheme 31, path a). To upset the situation, Nemoto found that an evaporation of the excess of allyl bromide before an addition of the base is favorable; product **173** being isolated in decent yield on this modification (Scheme 31, path b).[116]

3.20.4.1.2 Propargylic substrates

[2,3]-Stevens rearrangements also happened with propargylic chains to afford allenes as intermediates or products. In the presence of strong electron-withdrawing groups that ensure a regioselective deprotonation in adjacent position, the nucleophilic ylide carbons reacted with the propargyl moiety in S_N2-like manner. From substrates **175** and **176**, original compounds of type **177** and **178** were isolated in moderate yields (Scheme 32).[117–121]

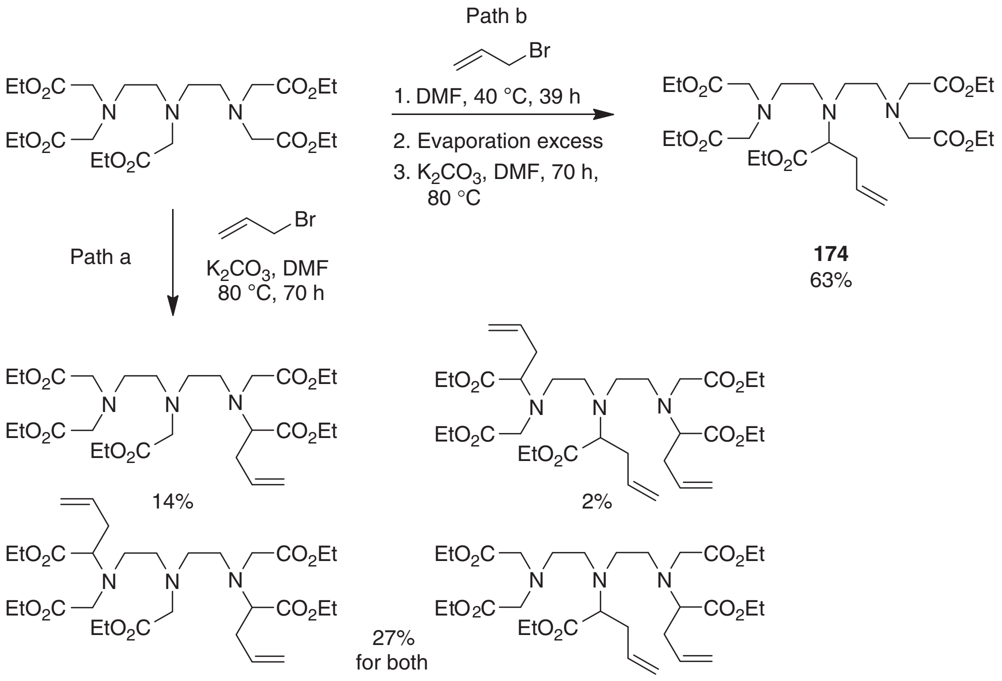
In mixed allylic/propargylic substrates, the deprotonation happened α to the alkyne moiety (rather than the alkene) and afforded products of [2,3]-Stevens such as **179** (equation 46).[122] Such a regioselective deprotonation of the propargylic residue occurred also with substrates **180**. The resulting ylides reacted with the allylic fragment in a S_E2' fashion forming intermediates **181**, which underwent ring closing reactions to generate dihydrofuranes **182** (equation 47).



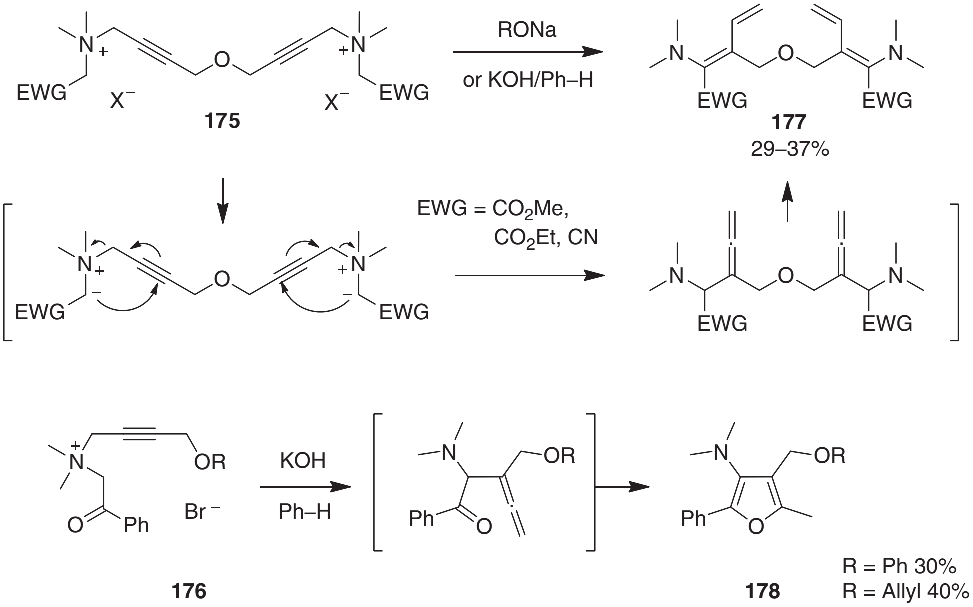
179
52–74%

R, R′ = Me_2, Et_2, $(CH_2)_5$, $O(CH_2CH_2)_2$
R^1 = Ph, *m*-Tol, *p*-Tol

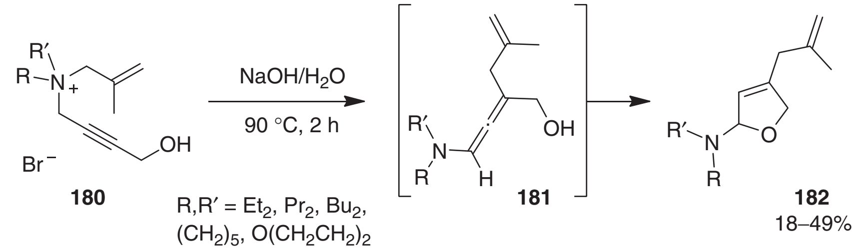
(46)



Scheme 31



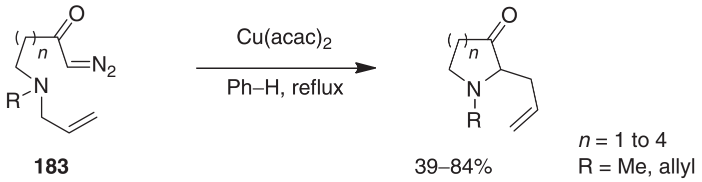
Scheme 32



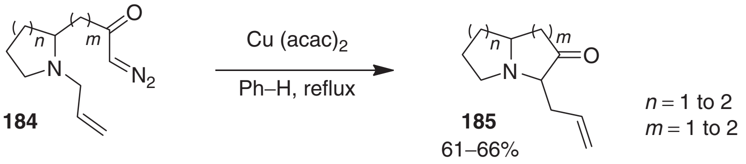
(47)

3.20.4.2 Intramolecular Additions of Allylic Amines to Carbenes and Carbenoids

As early as 1994, tandem intramolecular formations of allylic ammonium ylides followed by [2,3]-Stevens rearrangements were studied for the synthesis of cyclic amines. Clark and coworkers investigated first the formation of five- to eight-membered ring molecules starting from diazo compounds of type **183** (equation 48).[123,124] Further examples with substrates **184** afforded fused nitrogen ylide intermediates and, as a consequence, bicyclic products of type **185** (equation 49).[125] In both instances, $Cu(acac)_2$ was used as catalyst.

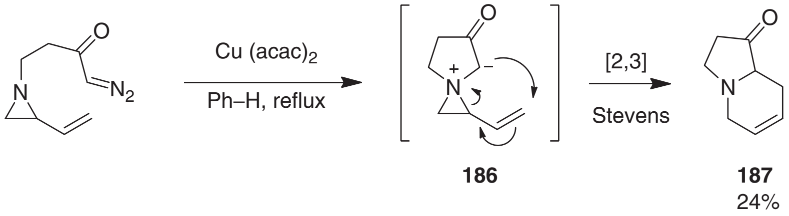


(48)

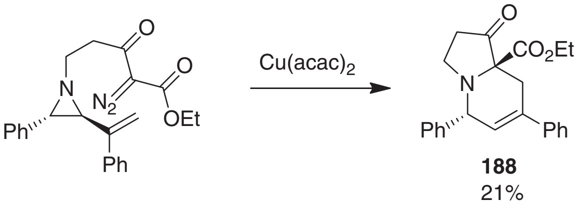


(49)

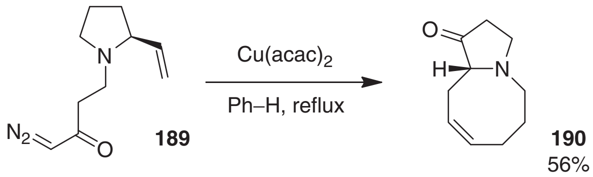
As observed in the [1,2]-Stevens rearrangement, the intermediate can be a spiro ammonium ylide such as intermediate **186**.[125] The low yield (24%) of this particular transformation was attributed to the instability of product **187** (equation 50). This reactivity was later extended to the formation of amine **188** (equation 51).[126] Using substrate **189** (equation 52), this type of process affords an eight-membered ring product **190** in a very decent yield of 56%, as shown by Clark and coworkers.[127]



(50)



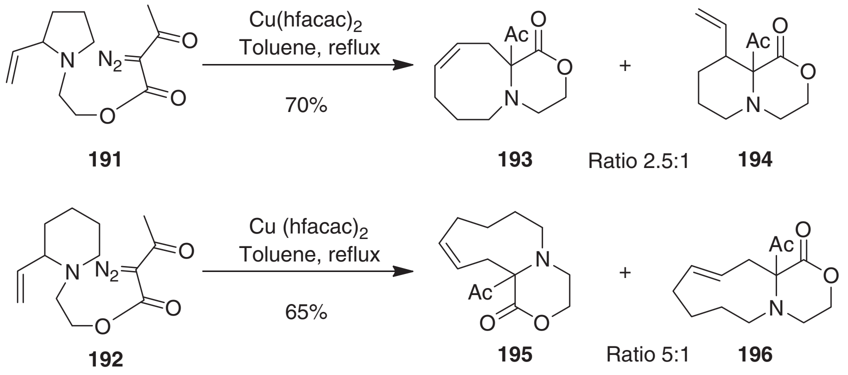
(51)



(52)

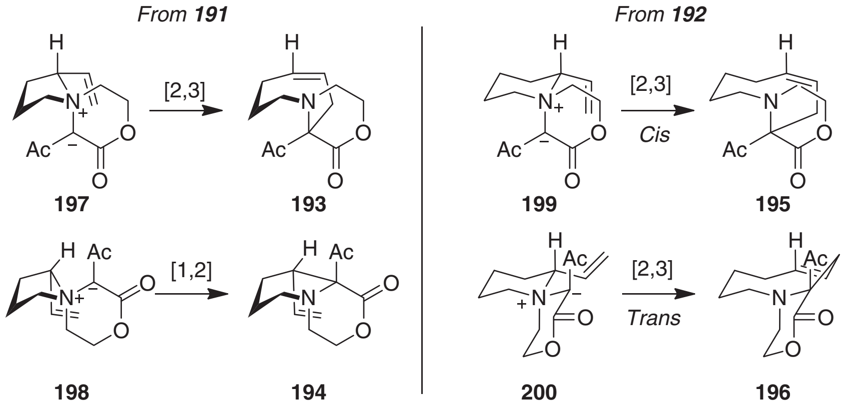
The analogous reaction with less-reactive carbenoid precursors **191** and **192** afforded a competition between the [2,3]- and [1,2]-rearrangement to form **193**/**194** and **195**/**196**, respectively (Scheme 33).[128]

Starting from pyrrolidine **191**, a rather large proportion (20%) of product **194** of [1,2]-Stevens was obtained whereas only adducts of [2,3]-Stevens were isolated from piperidine **192** (Scheme 33). This relatively high proportion of [1,2]-adduct **194** was interpreted as the result of the preferred conformation assumed by one of the diastereomeric *spiro* ammonium ylide intermediate, namely **198** (Scheme 34). In this case, due to the orientation of the double bond in pseudo-axial position, the enolate reached only with difficulty the γ carbon of the allyl moiety and hence the competing [1,2]-pathway. Such a geometrical limitation did not



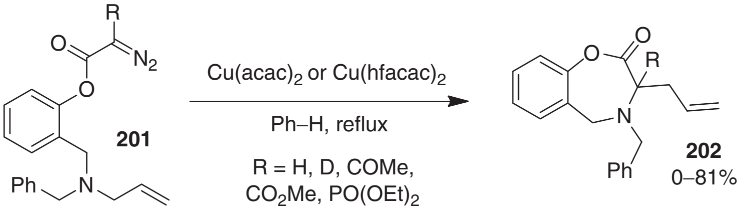
Scheme 33

occur with **197** (pseudo-equatorial allyl moiety). In the piperidine series, the situation is more favorable as both ylides **199** and **200** can lead to products of [2,3]-Stevens rearrangement, **195** and **196**.



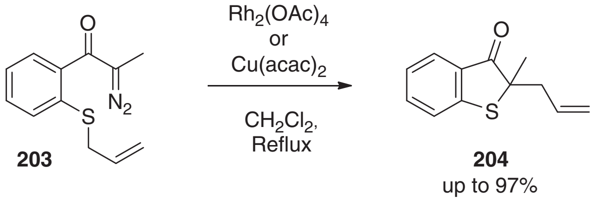
Scheme 34

Finally, diazo compounds of type **201** also afforded products of [2,3]-Stevens rearrangement (equation 53).[129,130] Whereas poor to moderate reactivity was observed using rhodium acetate as catalyst, $Cu(acac)_2$ or $Cu(hfacac)_2$ gave products **202** in better yields. As usual, the presence of two benzyl migrating groups did not perturb the [2,3]-reactivity.



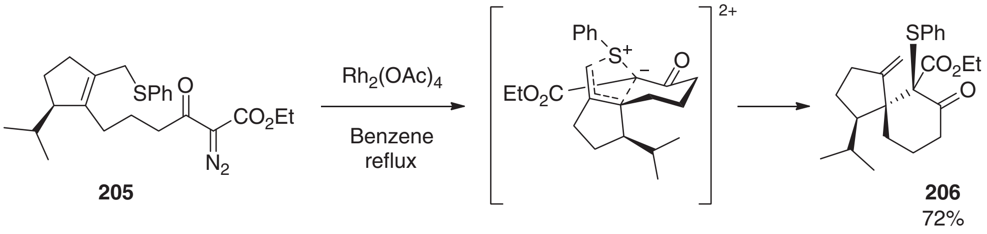
(53)

Examples of tandem intramolecular formation of allylic ylides followed by [2,3]-sigmatropic shift can also be found in the sulfur series. For instance, compound **203** afforded benzothiophenone **204** with excellent yield on treatment with decomposition catalysts (equation 54).[131]



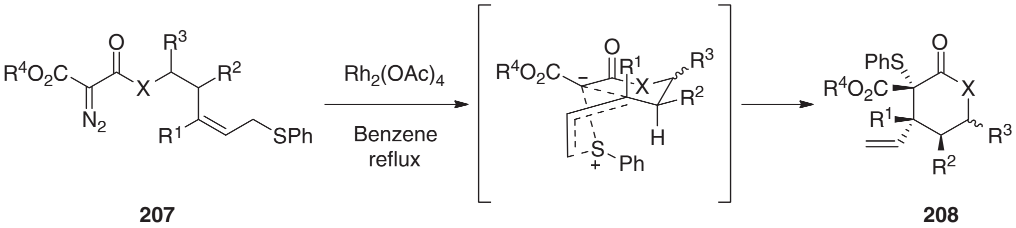
(54)

In a key step toward (+)-acorenone B, it was shown that **205** reacted in the presence of $Rh_2(OAc)_4$ to form **206** via a cyclic allylsulfonium ylide (Scheme 35).[132] In one step, the spirocyclic carbon skeleton was formed as a single stereoisomer. The stereochemistry was explained by the favorable conformation of the transition state depicted below in Scheme 35.



Scheme 35

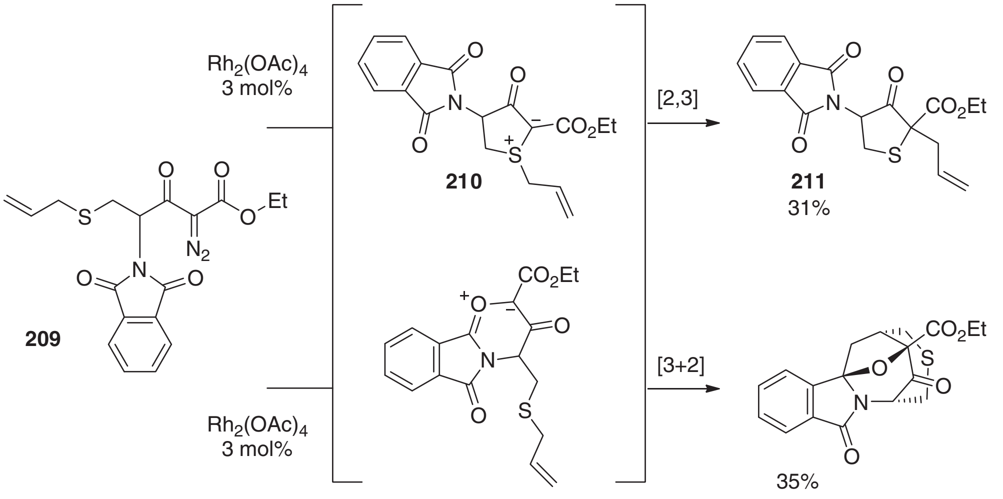
This approach was used by the same authors to form highly functionalized δ-lactone or cyclohexanone derivatives **207** to **208**, (Scheme 36).[133,134] A *trans*-stereochemistry was observed in all instances between the R^2 and vinyl groups whereas a *cis*-arrangement occurred between the thiophenyl and the olefin.



X = O, $R^1 = R^2$ = Me, R^3 = H, R^4 = Et 80%
X = CH_2, $R^1 = R^2 = R^4$ = Me, R^3 = H 78%
X = CH_2, $R^1 = R^4$ = Me, R^2 = C(Me)CH_2, R^3 = H 61%

Scheme 36

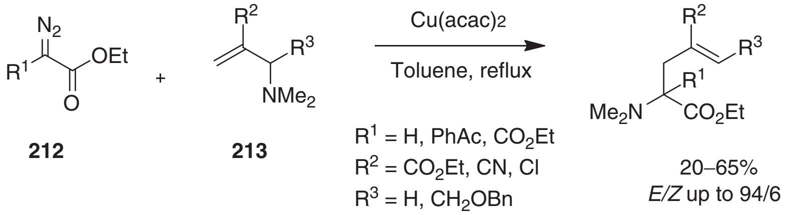
Finally, recently, it was shown that 2-diazo-3-keto-phtalimidocarboxylic ester **209** derived from methionine reacted in the presence of $Rh_2(OAc)_4$ to afford the corresponding cyclic sulfonium ylide **210** and its expected product of [2,3]-Stevens rearrangement **211** (Scheme 37).[135] The modest yield of **211** (31%) is due to the occurrence of a competitive pathway that sees the involvement of the carbonyl of the phthalimide and an intramolecular cycloaddition on carbonyl ylide formation.



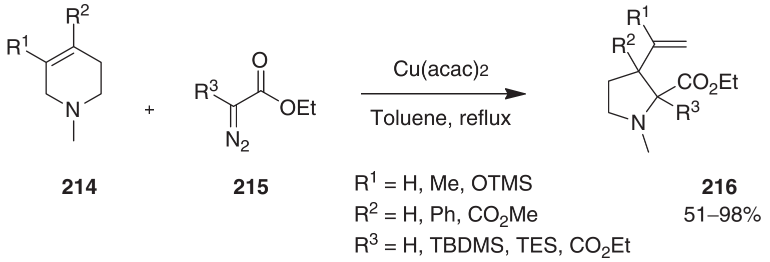
Scheme 37

3.20.4.3 Intermolecular Coupling of Amines and Carbenoids

The [2,3]-Stevens rearrangement has also been less studied in its intermolecular variant. It was, nevertheless, shown that diazo derivatives **212** and allylic amines **213** reacted, in presence of usually Cu(acac)$_2$, to form the expected products (equation 55).[136] Under very analogous conditions, N-methyltetrahydropyridine **214** and diazo **215** formed the corresponding pyrrolidines **216** in moderate to excellent yields (equation 56).[137,138]

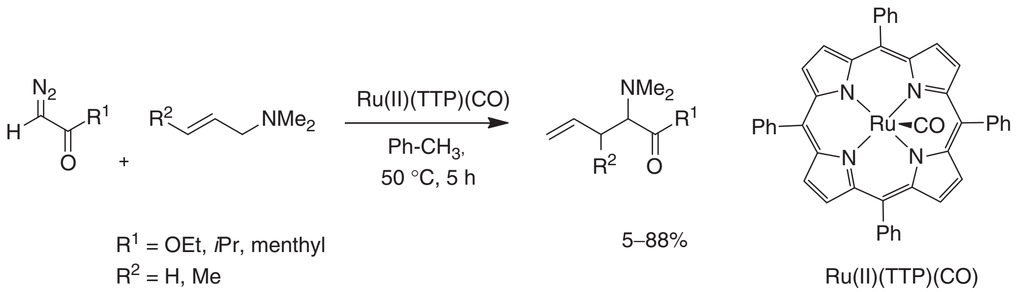


(55)



(56)

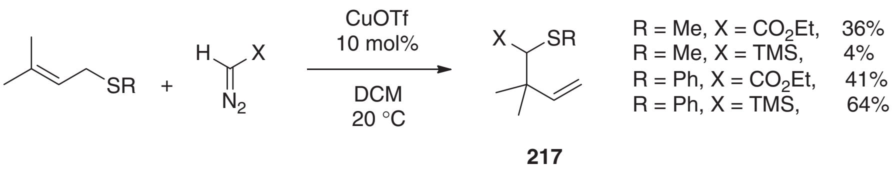
Other catalysts that copper sources can be used as shown by the recent investigations on ruthenium (Scheme 38) and iron (Scheme 14) porphyrin complexes.[59,139,140]



Scheme 38

3.20.4.4 Intermolecular Coupling of Sulfides with Carbenes/Carbenoids and the Doyle-Kirmse Reaction

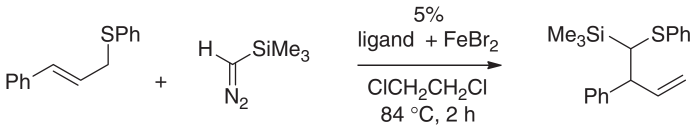
In the past two decades, quite a few examples of intermolecular reactions of allyl, propargyl, or allenyl sulfides with metal carbene complexes have been reported. These reactions follow a concerted [2,3]-sigmatropic pathway and are called Doyle–Kirmse rearrangements when trimethylsilyldiazomethane (TMSD) is used as diazo reactant. It was shown that different catalysts can be used to activate and modulate the reactions of allyl sulfides with ethyl diazoacetate or TMSD (equation 57).[141]



(57)

With CuOTf, yields of the [2,3]-adduct remained modest. An improvement of 10% yield was achieved on addition of 10 mol% of 4-methyl-2,6-di-*tert*-butylpyridine. In comparison, Rh$_2$(OAc)$_4$ afforded **217** (R=Ph, X=TMS) in 86% yield instead of 64%.

Several combinations of iron(II) chloride/bromide and monophosphine/diphoshine were tested at high temperature (equation 58) and dppeFeCl_2 in particular. The results are summarized in **Table 4**. dppe and BINAP ensured higher yields than dppp. The diastereoselectivity was essentially unaffected by the ligands and no enantioselectivity was detected using (*R*)-BINAP.[142] This methodology was applied for the synthesis of racemic 3-hydroxybakuchiol and corylifolin.[143] Palladium dichloride complexes with phosphine and bisoxazoline ligands were also tested to afford products of [2,3]-Stevens in good yields.[144]

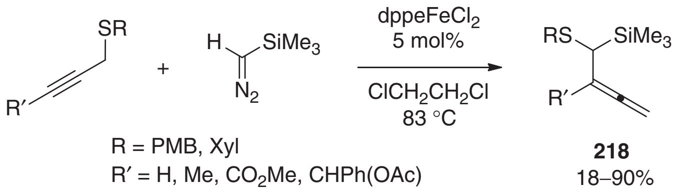


(58)

Table 4 Ligands used to promote the Doyle-Kirmse reaction (equation 58)

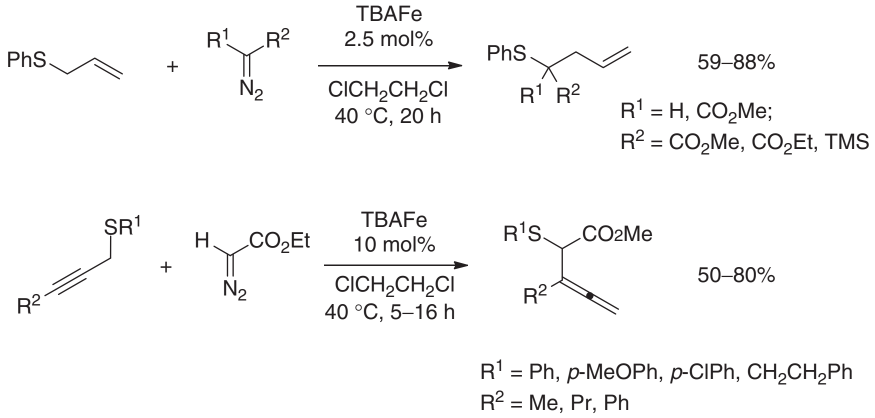
Entry	*Ligand*	*Product (%)*	*Diastereoselectivity*
i	dppe	93	80:20
ii	Ph_3P	88	85:15
iii	(*R*)-BINAP	92	83:17
iv	dppp	37	80:20
v	none	87	80:20

With propargyl sulfides, a similar reactivity was noticed as these compounds reacted with TMSD to afford allenylsilanes **218** in moderate to good yields (equation 59).[145]



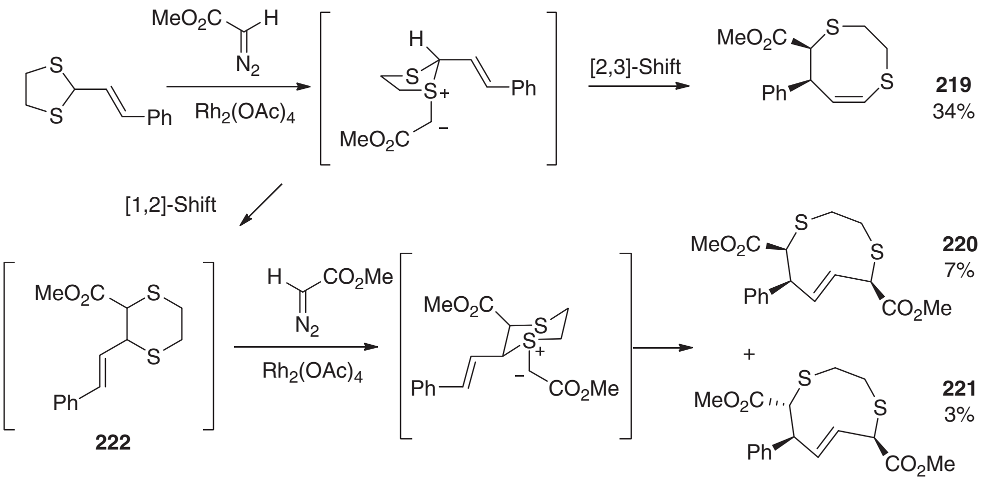
(59)

A variety of catalysts and conditions can be used. Ruthenium and iron porphyrin complexes are effective.[59,140] Dimeric Rh(II) complexes allow reactions in aqueous media or with trifluoroacetyl diazo reagents.[146,147] Rh(II) complexes can also be used to mediate the preparation of neoglycoconjugates.[148] Gold and silver catalysts were utilized under mild conditions with much success.[149,150] Recently, Plietker and coworkers developed the use of $Bu_4N[Fe(CO)_3(NO)]$ (TBAFe) for carbene-transfer reactions.[151] This salt is effective for the dediazoniation of a large variety of precursors and for the efficient transfer of the carbenoids to allyl and propargyl sulfide moieties (**Scheme 39**).



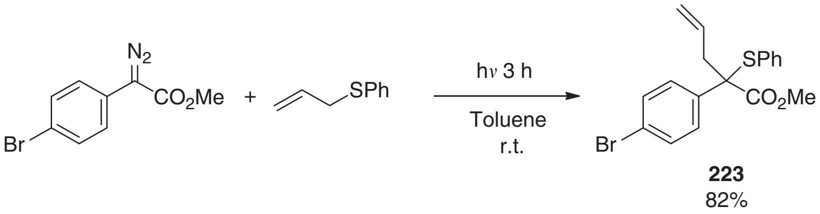
Scheme 39

The interaction of 2-styryl-1,3-dithiolane with methyl diazoacetate in presence of $Rh_2(OAc)_4$ was also studied (**Scheme 40**).[99] Several products were identified; adduct **219** being the expected adduct of [2,3]-Stevens rearrangement. However, as a small proportion of [1,2]-shift occurred on the initial ylide, adducts **220** and **221** were also observed albeit in quite lower yields due to a second new insertion of methoxycarbonylcarbene onto **222**.



Scheme 40

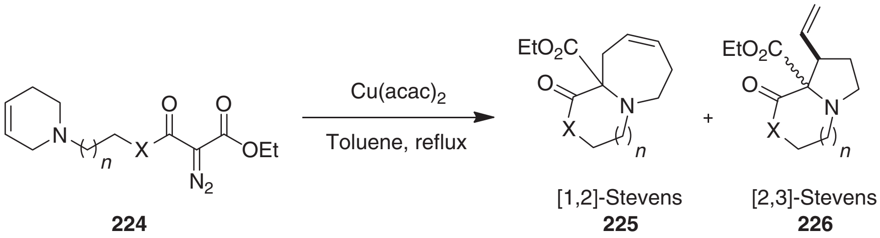
Finally, as detailed in Section 3.20.2.4.1, photochemical conditions are often sufficient to generate carbene and ylide intermediates. A photo-irradiation for 3 h of ethyl diazoarylacetate and allyl sulfide was sufficient in this particular case to generate product **223** in good yield (equation 60).[152]



(60)

3.20.5 Competition between [1,2] and [2,3] Rearrangements

Examples have so far shown that allyl substituents tend to migrate faster than other groups on ylide formation to promote, in situations devoid of geometrical constraints, the [2,3]-pathway quasi exclusively. However, it is not always the case as illustrated in some already reported examples and in a series of studies highlighted below. For instance, amines of type **224** afforded products **225** and **226** of [1,2] and [2,3]-Stevens rearrangements, respectively (equation 61, Table 5).[153]

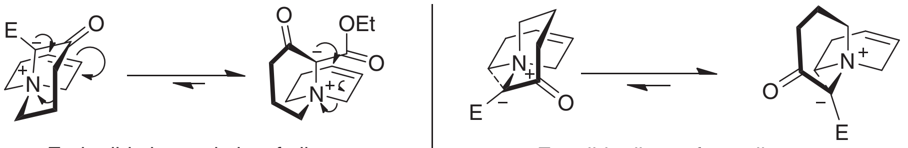


(61)

Table 5 Yields and stereoselectivity observed (equation 61)

Entry	*X*	*n*	**225** *(%)*	**226** *(%)*	cis/trans *Ratio in* **226**
i	CH_2	1	43	43	60:40
ii	O	1	42	42	50:50
iii	CH_2	2	23	54	57:43
iv	O	2	8	60	70:30

The presence of both products was explained by the conformation of the diastereomeric ylide intermediates as previously detailed for compound **191** (Scheme 33). The so-called *endo*- or *exo*-ylides led to [2,3] and [1,2]-rearrangements, respectively. The presence of a 1:1 ratio of products in the case of the smaller ring system (n = 1) can be explained by a slow exchange between the two conformations and a similar energy for the two. The difference in ratio observed when n = 2 was explained by a faster reactivity of the *endo* form and a rapid interconversion between the two intermediates, which favored the predominant formation of the [2,3]-product **226** (Scheme 41).

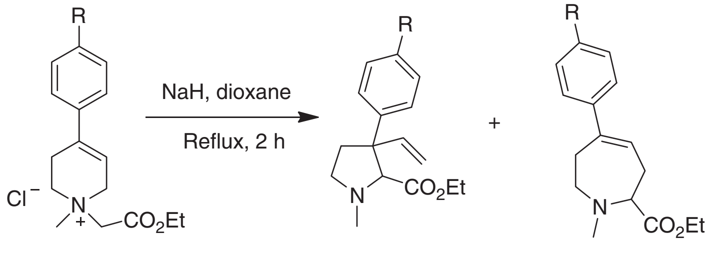


Endo ylide in proximity of alkene
[2,3]-Stevens

Exo ylide distant from alkene
[1,2]-Stevens

Scheme 41

The investigation of Sweeney on the reaction of **165** to form, on basic treatment, the [2,3]-rearranged product **166** was previously highlighted (Scheme 29). In a related study, Soldatova and coworkers observed that substitution on the double bond of an aryl group (substrate **227**) modified the reactivity in favor of the [1,2]-shift azepine products **229** in addition to the expected proline derivatives **228** (equation 62).[154,155] Interestingly, the ratio between these products depends on the substitution on the aryl moiety; electron-donating groups (e.g., Me, Table 6, entry ii) favoring the [2,3]-mechanism whereas electron-withdrawing moieties favor the [1,2] (e.g., Br, Table 6, entry iii).



[2,3]-Stevens
[1,2]-Stevens

227 **228** **229**

(62)

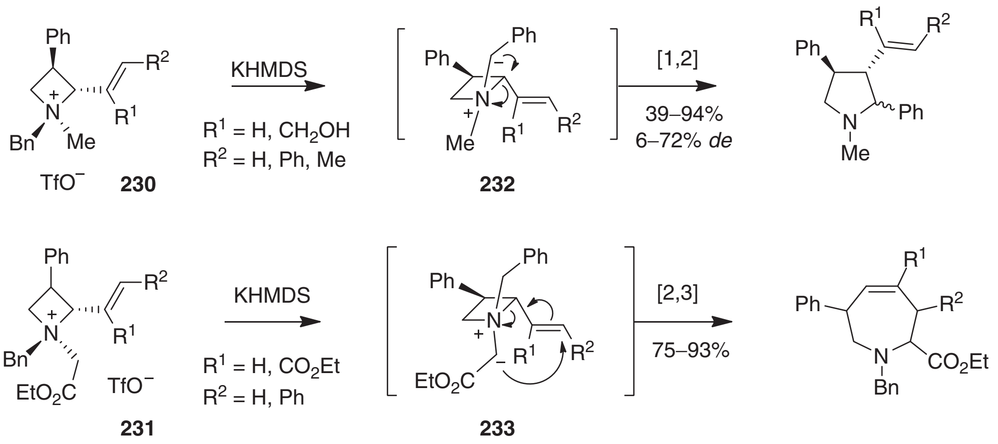
Table 6 Competion between [1,2] and [2,3]-Stevens Rearrangements (equation 62)

Entry	*R*	**228** *(%)*	**229** *(%)*
i	H	39	25
ii	Me	58	5
iii	Br	Trace	60

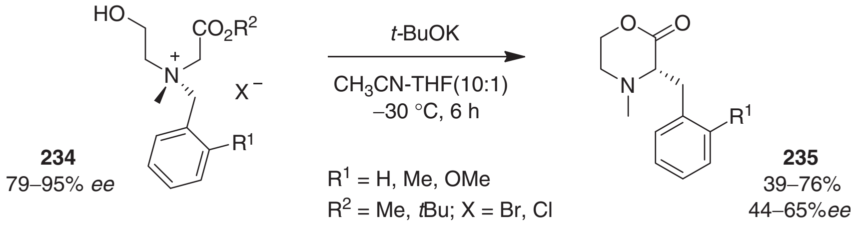
The synthesis of the alkenyl azetidines **230** was reported (Scheme 42).[156] Products resulting from a [2,3]-rearrangement were not observed in this case whereas this reactivity was present for the ammonium derivatives **231**.[157] In the first case, ylide **232** was formed on the benzylic chain, resulting in a *trans* arrangement of the moiety with the exocyclic double bond which was incompatible for geometrical reason with a reactivity at the terminal allylic carbon. In the second case, ylide **233** was generated α to the ester, in a position *cis* to the alkene, which allowed then easily the [2,3]-rearrangement pathway.

3.20.6 Enantioselective and Enantiospecific Rearrangements

In the previous paragraphs, many examples of highly stereoselective Stevens rearrangements have been detailed, all of them involving substrates carrying at least two stereogenic elements in their backbone before the transformation. In the nitrogen series, a few studies have dealt recently with enantiospecific and enantioselective rearrangements. For instance, enantioenriched ammonium salts **234** were treated with *t*-BuOK in CH_3CN/THF to afford lactones **235** (39–76%). In this study involving a [1,2]-Stevens rearrangement, moderate enantiomeric excesses were reported which were linked to the probable diradical nature of the mechanism (equation 63).[158]

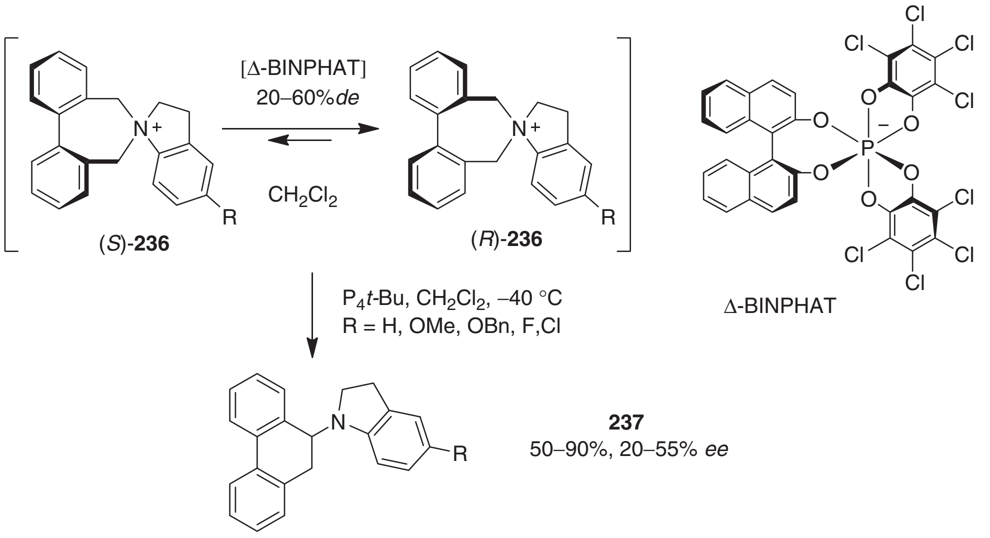


Scheme 42



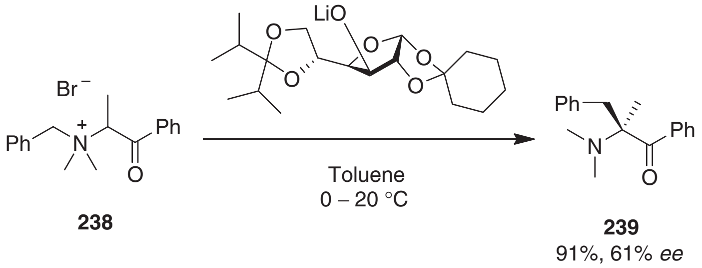
(63)

A different approach was recently proposed. It involved the association of a configurationally labile diphenylazepinium cation **236** (axial chirality, (*S*) and (*R*) conformers) with an enantiopure counterion (BINPHAT, Δ or Λ enantiomers, Scheme 43).[159] In a relatively low polarity solvent such as CH_2Cl_2, a supramolecular stereoselective interaction occurred (*Pfeiffer* effect) and a preferred diastereomeric ion pair was formed. Reaction with the strongly basic P_4*t*-Bu led to the ring-contracted product **237** of [1,2]-Stevens in moderate to good yields and decent levels of enantiomeric excesses (20–55%, Scheme 43).[160] Interestingly, a strong correlation was found between the level of diastereocontrol in the starting ion pairs (20–60% *de*) and the enantiomeric purity of the products (20–55% *ee*), indicating an efficient transfer of chirality in this particular process.



Scheme 43

The use of chiral bases was also investigated (equation 64).[161] Moderate enantiomeric excesses were observed in the reaction of racemic quaternary ammonium salt **238** with a sugar-derived enantiopure alkoxide base to yield nonracemic adduct **239**.



(64)

With chalcogen substrates, in an important development and unlike the nitrogen series, it was shown that enantiopure catalysts can be used to control the enantioselectivity of the rearrangement. First, Uemura and collaborators reported that aryl cinnamyl sulfide of type **240** reacted with ethyl diazoacetate in presence of $Rh_2(5S\text{-MEPY})_4$ **242** or combinations of bisoxazoline **243** and CuOTf to afford products **241** of [2,3]-Stevens in nonracemic form (equation 65, *ee* up to 20%).[162] Yields, diastereo- and enantioselectivity levels were modest (see Table 7) but this work initiated a flurry of further studies. Structures of catalysts and ligands are indicated in Figure 1.

Table 7 Examples of catalysts (equation 64)

Entry	*Catalyst*	*Condition*	*Yield (%)*	*dr (ee %)*
i	**242**	DCM, 40 °C	49	60 (18):40 (17)
ii	CuOTf + **243**	Toluene, 0 °C	41	65 (20):35 (14)

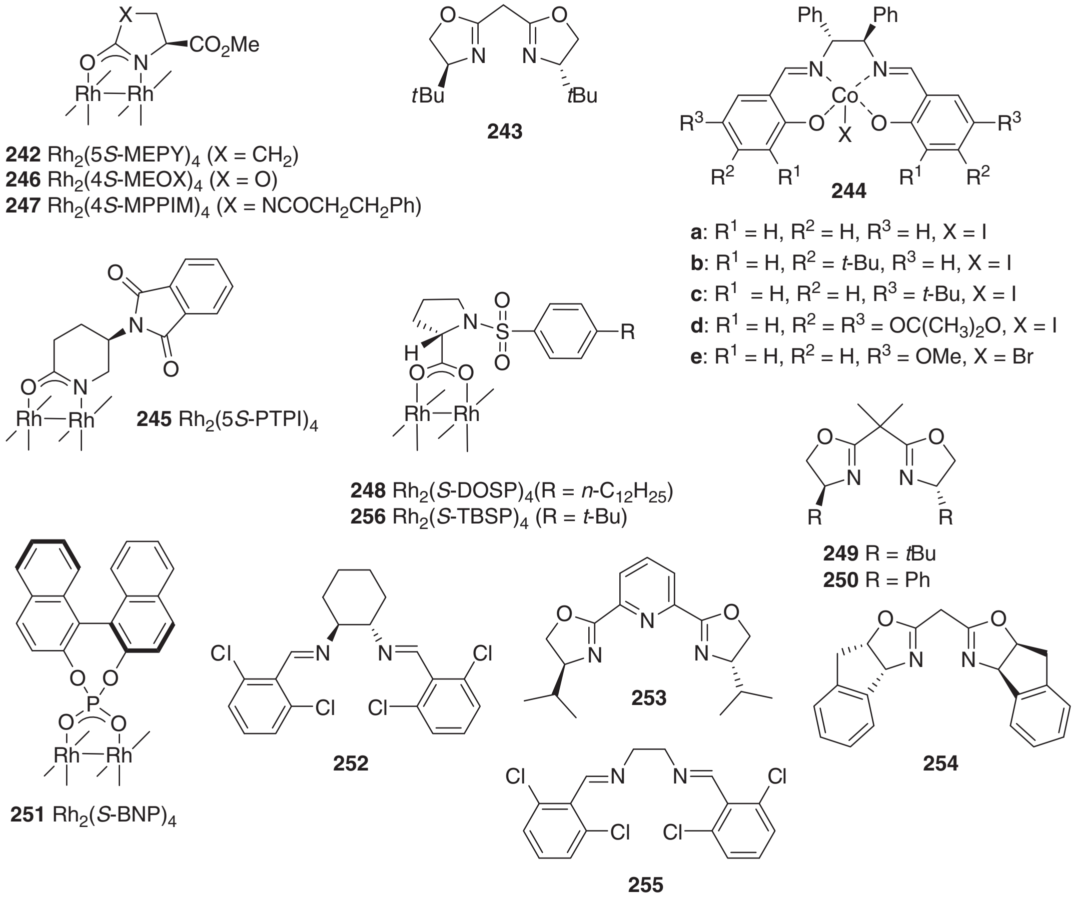
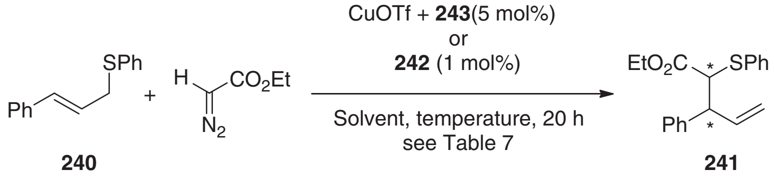
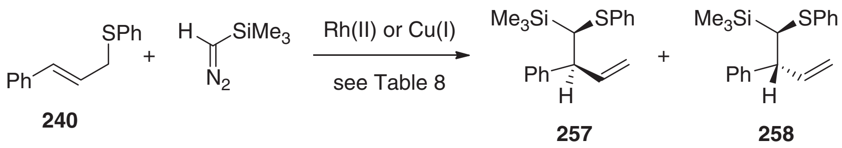


Figure 1 Enantioselective Stevens rearrangements: catalysts and ligands.



(65)

For instance, Fukuda and Katsuki performed the analogous reaction with the *t*-Butyl ester as substrate and Co(III)-salen complexes **244** as catalysts. The corresponding thioether products were obtained with better enantiomeric excesses (up to 64% *ee*).[163,164] It was proposed that the Co-salen complexes dictated only the discrimination of the enantiotopic lone pairs on the sulfur atom of sulfides **240** and that the reaction occurred through a metal-free ylide mechanism as no effect was noticed on the diastereoselectivity. This proposition, substantiated by Hashimoto using $Rh_2(S\text{-}PTPI)_4$ **245** as catalyst (*ee* up to 58%),[165] was, however, challenged by Aggarwal in its study of the Doyle–Kirmse reaction between the (*E*)-cinnamyl methyl sulfide **240** and TMSD (equation 66) using various achiral and chiral Rh(II) or Cu(I) catalysts (see Table 8 and Figure 1). The diastereoselectivity was found to fluctuate (*dr* up to 90:10) and only a low enantioselectivity was observed with the range of catalysts used.[166]

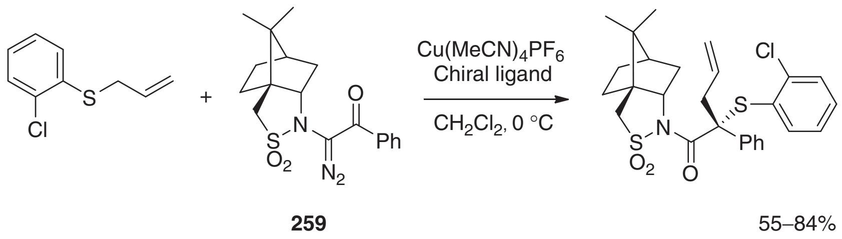


(66)

Table 8 Enantioselectivities observed with different catalysts (equation 66)

Entry	*Catalyst*	*Yield (%)*	**257:258** *(ee %)*
i	$Rh_2(OAc)_4$	90	90:10
ii	**242**	94	43 (13):51 (15)
iii	**246**	74	53 (10):47 (<5)
iv	**247**	73	68 (<5):32 (<5)
v	**248**	82	80 (<5):20 (<5)
vi	$Cu(CH_3CN)_4PF_6 +$ **249**	96	88 (<5):12 (18)

It was then shown that the asymmetric efficiency of the copper-catalyzed decomposition of ethyl diazoacetate (CuOTf, ligands **243** and **250**) and subsequent [2,3]-sigmatropic rearrangement depended strongly on the structure of the starting allyl sulfide (*ee* up to 52%).[167] Wang and coworkers also reported the use of aryldiazoacetates in conjunction with a host of catalysts (**242**, **251**, $Cu(CH_3CN)_4PF_6$ with ligands **249**, **250**, **252**, **253**, and **254**).[168] The ratio among the diastereomeric products was found to be essentially constant militating again for a metal-free ylide mechanism. Moderate to good enantioselectivity was achieved (*ee* up to 78% with ligand **249**). To improve the stereoselectivity, a double asymmetric induction was pursued by the same authors.[169] Diazo derivatives **259** containing Oppolzer's camphorsultam auxiliary reacted with allyl 2-chlorophenyl sulfide in presence of a chiral Cu(I) catalyst (equation 67 and Table 9). Stereoinduction was found to be predominated by the configuration of the diazo compound rather than the ligand. Interestingly, the highest level of stereoinduction was achieved with achiral ligand **255**.

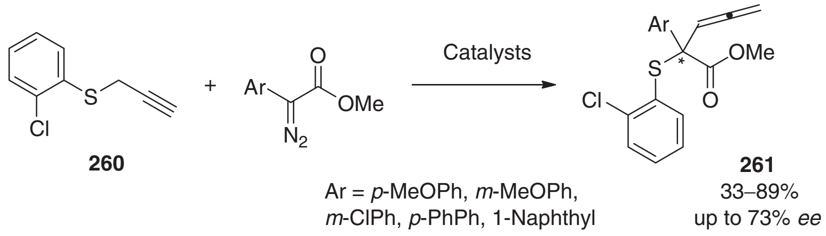


(67)

The reaction was also tested with propargylic sulfide **260** and an excellent diastereoselectivity was obtained (up to 96% *de*). With more traditional aryldiazoacetates (equation 68), the above-mentioned catalysts afforded moderately high enantioselectivities (up to 73% *ee* with $Cu(CH_3CN)_4PF_6 +$ **249** or **256**).[170]

Table 9 Chiral ligands and selectivity observed (equation 67)

Entry	*Chiral ligand*	*Yield (%)*	*de (%)*
i	no ligand	55	30
ii	(*S*,*S*)-**252**	70	90
iii	**254**	82	23
iv	**249**	79	87
v	**250**	84	86
vi	(*R*,*R*)-**252**	70	80
vii	**255**	72	92

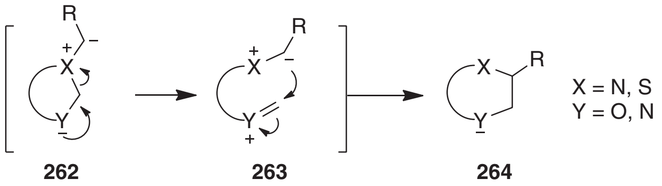


Ar = *p*-MeOPh, *m*-MeOPh, *m*-ClPh, *p*-PhPh, 1-Naphthyl

(68)

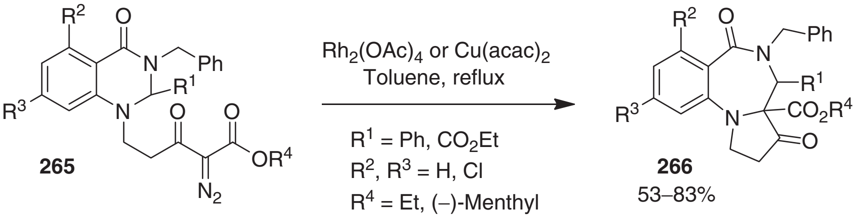
3.20.7 Stevens Rearrangements of Aminals, Hemiaminals, and Oxathiolanes

Stevens-like rearrangements of aminals, hemiaminals, and oxathiolanes have also been studied. The difference is the presence of a second heteroatom (O, N) that allows a facile ring opening reaction of the ylide intermediates (e.g., **262**) and the formation of subsequent zwitterionic intermediates of type **263**. These moieties then collapse to form the ethano-bridged compounds **264** in place of starting methano adducts (Scheme 44). (This type of transformation could be considered as an ion-pair mechanism Scheme 3, path a.)



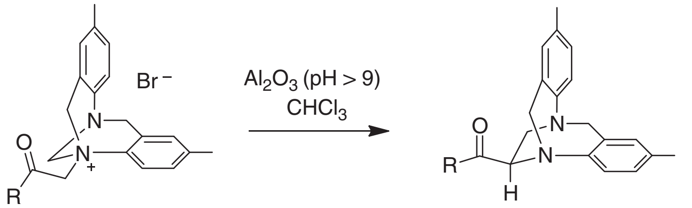
Scheme 44

For instance, Saba and coworkers were able to prepare pyrrolobenzodiazepinone derivatives of type **266** by intramolecular carbenoid trapping of acyl aminals **265** (equation 69).[171]



(69)

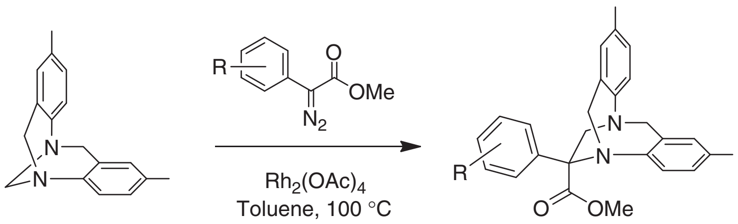
Recently, the synthesis of ethano-Tröger bases **268** was reported using a base-promoted rearrangement of quaternary ammonium salts of type **267** (equation 70). The reaction proceeded with moderate to good yields (34–85%) and an excellent diastereoselectivity for the new stereogenic center.[172]



267 R = Ph, *p*-MeOPh, *p*-MePh, *p*-FPh, *o*-BrPh **268** 34–85%, *dr* >98:2

(70)

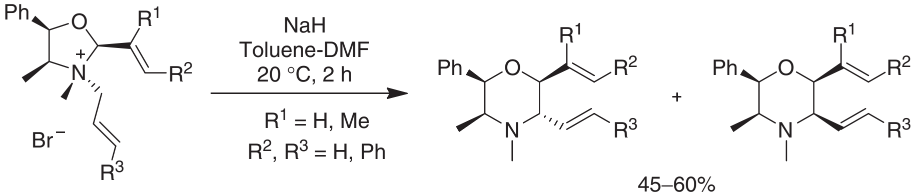
It was later shown that the formation of ammonium salts **267** is actually not necessary as regular methano-Tröger **269** reacted with aryldiazoesters under $Rh_2(OAc)_4$ catalysis to form in a single step compounds **270** (equation 71).[173] The protocol was found to be diastereoselective (up to 20:1, quaternary center introduction), regioselective with unsymmetrical substrates but also highly enantiospecific as most products were obtained with enantiomeric excesses higher than 97% *ee*. Extension of this asymmetric process to aryldiazoketones required the use of CuTC as catalyst instead.[174]



269 R = H, Me, OMe, Cl, Br, CF_3, NO_2 **270** 50–89%, 64–99% *ee*

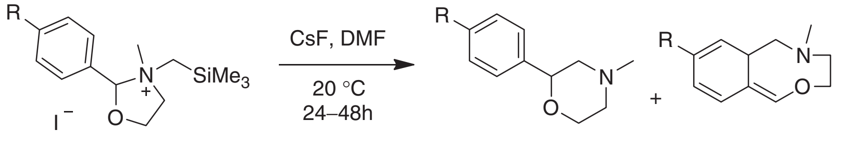
(71)

As mentioned, hemiaminal derivatives also reacted. For instance, Pedrosa reported the synthesis of enantiopure morpholine derivatives **272** and **273** using the base-promoted ring expansion of the oxazolidinium salts **271**; the diastereoselectivity being unfortunately moderate (*dr* up to 2:1, equation 72).[175] Treatment of quaternary ammonium salts **274** with CsF in DMF afforded morpholine derivatives **275** as well. A small amount of Sommelet–Hauser adduct **276** was observed in the case of the methoxy-substituted substrate (equation 73).[176]



271 **272** 45–60% Ratio upto 68/32 **273**

(72)

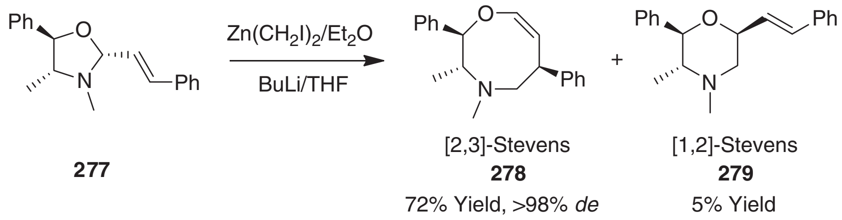


274 [1,2]-Stevens **275** Sommelet-Hauser **276**

	275	276
R = H	71%	0%
R = OMe	49%	17%

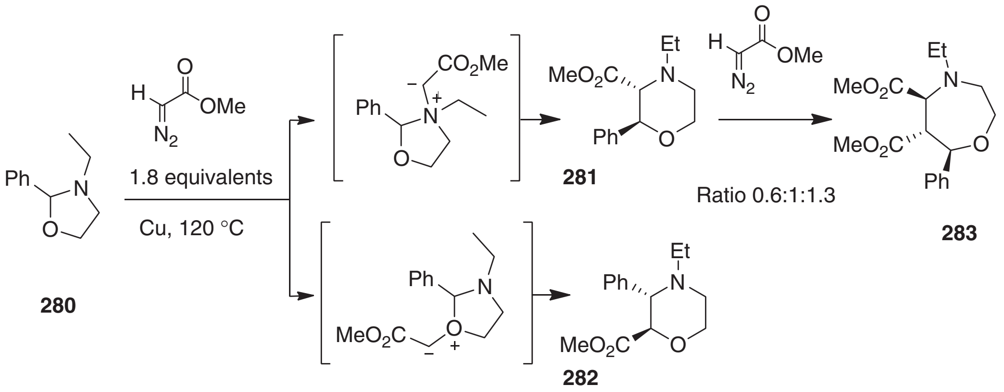
(73)

In 2003, Aggarwal and coworkers reported the rearrangement of oxazolidines **277** using Simmons–Smith reagent $Zn(CH_2I)_2$ (equation 74). An addition of *n*-BuLi was necessary to generate a zinc-free ylide and induce the rearrangement.[177] Whereas [2,3]-product **278** was mainly obtained, 5% of [1,2]-shift adduct **278** was observed. Both compounds were obtained in excellent diastereomeric ratio.



277 **278** **279** (74)

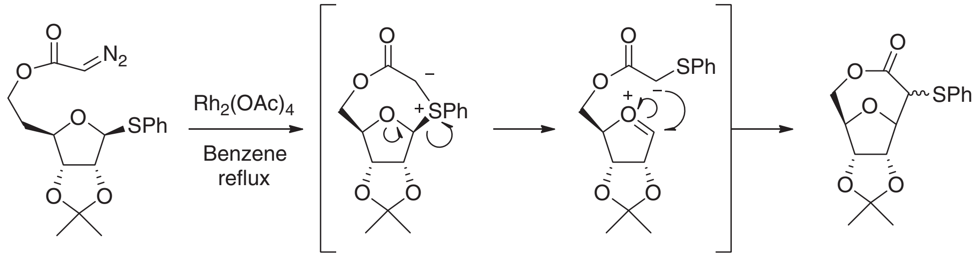
Reaction of oxazoline **280** with methyldiazoacetate under copper catalysis revealed yet another twist to the Stevens rearrangement as a competition between ammonium and oxonium processes was revealed. In fact, a mixture of regioisomeric **281** (N-Stevens) and **282** (O-Stevens) was obtained with a preference for **281**. Interestingly, this adduct is able to react *in situ* with the excess of diazo reagent and form oxazepane **283** (Scheme 45).[178]



280 **281** **282** **283**

Scheme 45

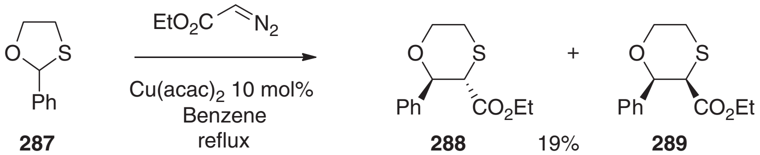
Stevens rearrangements on hemithioacetals were also reported. It was the case in the study by Kim and collaborators of the synthesis of (+)-showdomycin.[179] Treatment of diazo-substituted 1-β-phenylthiofuranoside **284** in presence of $Rh_2(OAc)_4$ afforded product **286** of intramolecular ring-closure (equation 75). The proposed mechanism detailed the formation of oxonium **285** as intermediate which explained the connectivity observed and the loss of stereocontrol, i.e. the formation of a 3:2 mixture of separable epimers.



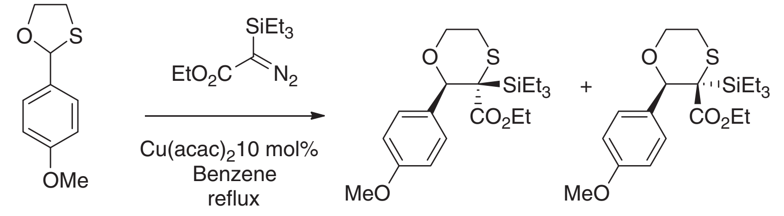
284 **285** **286** (75)

48%, *dr* 3:2

1,3-Oxathiolanes were then shown to react.[180,181] Initial investigations into the reaction of 2-phenyl-1,3-oxathiolane **287** and ethyl diazoacetate in presence of $Cu(acac)_2$ or $Cu(CH_3CN)_4PF_6$ afforded both *trans* and *cis* 1,4-oxathiolanes **288** and **289** in a low 2:1 ratio and yield (equation 76). The use of triethylsilyl diazoacetate and electron-rich aryl-substituted oxathiolane (**290**; *p*-MeO) improved the situation to give **291** and **292** in better yield and in a 20:1 ratio (equation 77).



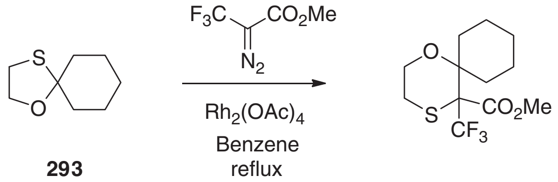
287 **288** 19% *dr* 2:1 **289** (76)



290 **291** 62% *dr* 20:1 **292**

(77)

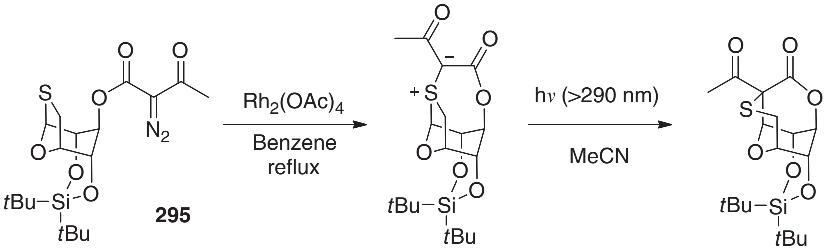
The reactivity of 1,3-oxathiolanes with trifluoromethyl diazoacetate was also studied.[182] $Rh_2(OAc)_4$ was shown to be an effective catalyst and trifluoromethyl 1,4-oxathiolanes were obtained in excellent yields (up to 95%) and diastereoselectivity (up to 99:1). For instance, the [1,2]-Stevens rearrangement was feasible on **293** to give spiro-1,4-oxathiolane **294** in moderate yield (equation 78).



293 **294** 59%

(78)

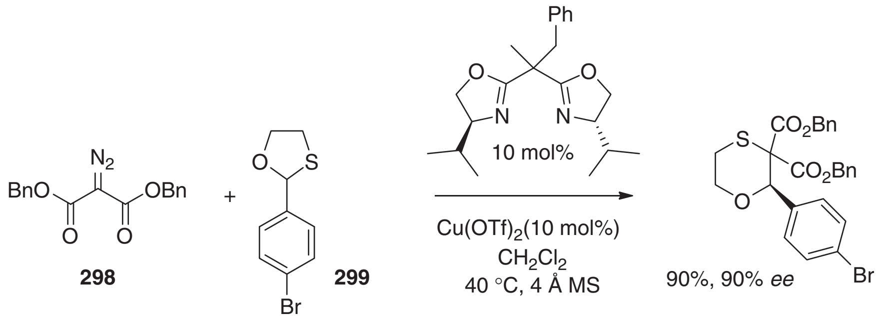
Another interesting intramolecular variant was proposed by Porter for the synthesis of a tagetitoxin precursor (Scheme 46).[183] Exposure of the tricyclic compound **295** to 1 mol% of $Rh_2(OAc)_4$ afforded the tetracyclic sulfonium ylide **296** in good yield (88%). This compound was remarkably stable at high temperature in a variety of solvents (xylenes, methanol, DMSO); only a photolysis in acetonitrile afforded tetracycle **297** in 69% yield.



295 **296** 88% **297** 69%

Scheme 46

Finally, the enantioselective [1,2]-Stevens rearrangement of 1,3-oxathiolane **299** was reported by a treatment with diazomalonate **298** in presence of combinations of bisoxazoline ligands and $Cu(OTf)_2$ as catalysts (equation 79).[184] Enantiomeric excesses (up to 90% *ee*) were obtained using 1,3-oxathiolanes with an aryl group bearing electron-withdrawing groups such as a halogen atom or a trifluoromethyl group.

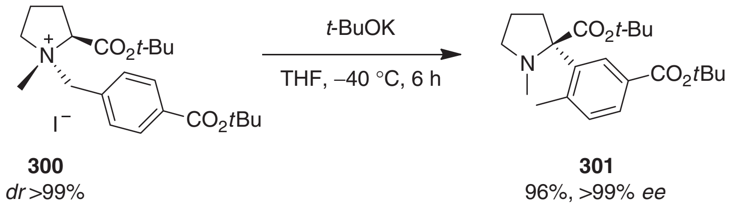


298 **299**

(79)

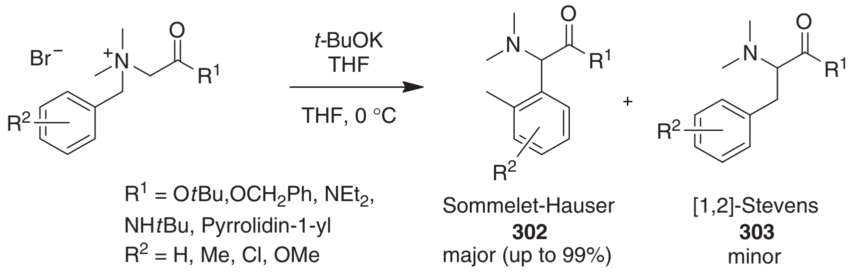
3.20.8 Sommelet–Hauser Rearrangements

As already discussed, when the quaternary ammonium ion carries a benzyl substituent, a Sommelet–Hauser rearrangement frequently occur in competition with [1,2]-Stevens processes. Often, the latter reactions are favored over the Sommelet–Hauser rearrangement, but it is not always the case. For example, Tayama and Kimura observed the exclusive formation of the Sommelet–Hauser product **301** when ammonium salt **300** was treated with *t*-BuOK on THF at −40 °C (equation 80).[68] Interestingly, a full transfer of chirality was obtained.



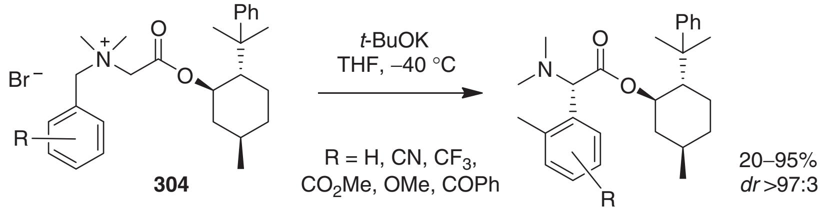
(80)

With another class of substrates, the authors noticed that the presence of electron-withdrawing groups on the aromatic residue improved the ratio of Sommelet–Hauser over [1,2]-products. The use of *t*-BuOK in THF seemed also particularly favorable for the formation of compounds **302** (equation 81).[185] It was finally observed that products of [1,2]-Stevens **303** were not observed when amides were used instead of esters; adducts **304** being obtained in excellent yields (up to 99%).



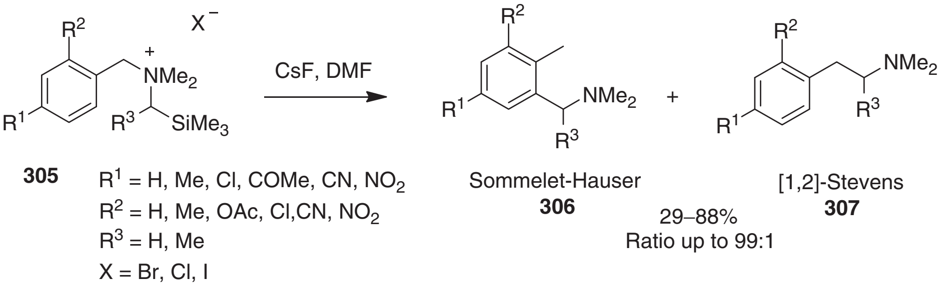
(81)

To control the absolute configuration of the amino-acid products, various chiral auxiliaries were introduced. It was shown that a 8-phenylmethyl ester group is particularly efficient as the rearrangement of ammoniums **304** occurred with excellent diastereoselectivity (*dr* >97:3) and with moderate to good yields (20–95%, equation 82).[186] This methodology can be extended to the synthesis of α-quaternary α-aryl amino acid derivatives.[187]

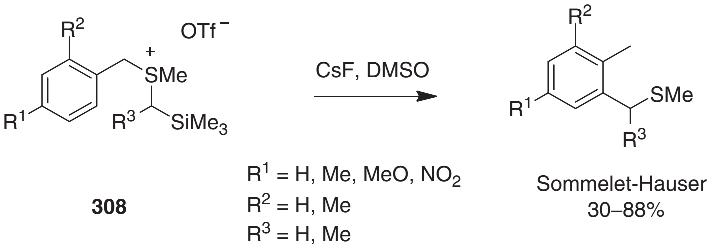


(82)

In the context of ylide formations induced by fluorine-mediated desilylation reactions, many Sommelet–Hauser processes were studied. Care was taken by Sato and coworkers to isolate and characterize these adducts along with products of [1,2]- and possibly [2,3]-Stevens rearrangements. For example, treatment of ammonium salts **305** with CsF in DMF afforded the Sommelet–Hauser products **306**; adduct **307** resulting of a [1,2]-shift (equation 83).[188,189] Results showed that the Sommelet–Hauser adduct was favored by the presence of electron-donating or weak electron-withdrawing groups on the aromatic residue whereas strong electron-withdrawing groups favored the [1,2]-shift.[190,191] The analogous reaction in the sulfur series was reported (equation 84).[192] Interestingly, sulfonium salts **308** rearranged exclusively to Sommelet–Hauser products without contamination from Stevens adducts.

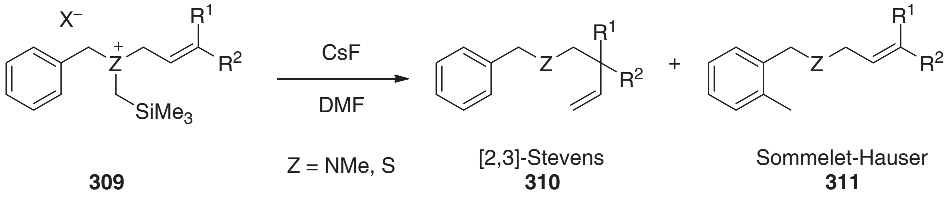


(83)



(84)

A comparative study of the reactivity of nitrogen and sulfur ylides containing allylic and nonsymmetrical benzylic side-chains was reported (equation 85 and Table 10). With substrates of type **309**, a mixture of products of [2,3]-Stevens **310** and Sommelet–Hauser **311** was obtained in the nitrogen series; compounds with two methyl groups on the γ carbon reacting exclusively to form adducts **311**. With sulfonium substrates, products **310** of [2,3]-Stevens were only observed and isolated.

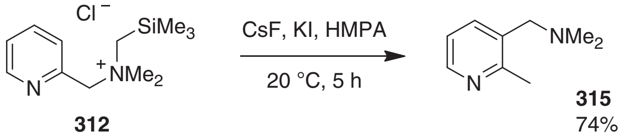


(85)

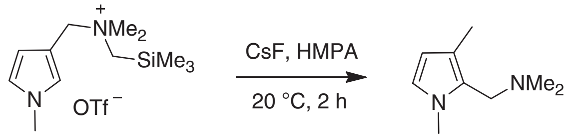
Table 10 Competition between [2,3]-Stevens and Sommelet–Hauser rearrangements (equation 85)

Entry	*Z*	*R¹*	*R²*	*X⁻*	*Total yield (%)*	*Ratio 310:311*
i	N–Me	H	H	Br	61	50:50
ii	N–Me	Me	H	Cl	50	34:66
iii	N–Me	Me	Me	Br	74	0:100
v	S	H	H	OTf	60	100:0
vi	S	Me	H	OTf	93	100:0
vii	S	Me	Me	OTf	98	100:0

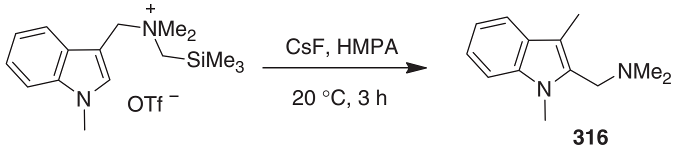
The Sommelet–Hauser rearrangement was extended to nitrogen-containing heteroaromatic rings like pyridines **312** (equation 86), pyrroles **313** (equation 87), or indoles **314** (equation 88), in some instances with quite a bit of success (e.g., **315** (74%) and **316** (81%)).[193]



(86)

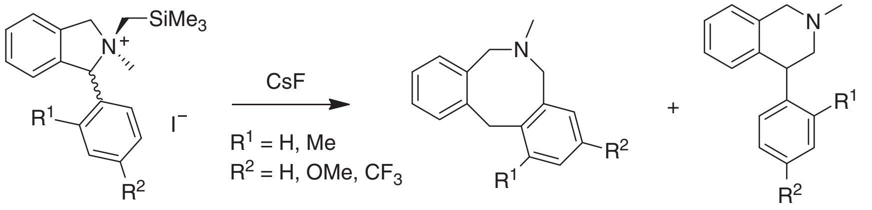


313 9% (87)



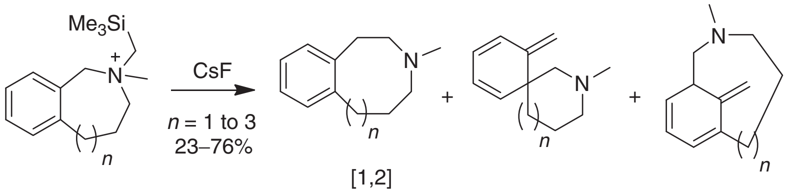
314 **316** 81% (88)

The reactivity of isoindolinium derivatives **317** was also investigated (equation 89).[194] Relations between the ratio of *cis*/*trans* isomers and the proportion of Sommelet–Hauser **318** and [1,2]-Stevens **319** products was investigated. It was observed that *trans*-isomers formed exclusively the [1,2]-**319** whereas the *cis*-precursors led to mixtures of **318** and **319**. A related study was performed on tetrahydroisoquinolinium precursors; the occurrence of concurrent Hofmann-elimination pathways somewhat complicating the analysis.[195]



317 Sommelet-Hauser **318** 89–95% Ratio up to 85:15 [1,2]-Stevens **319** (89)

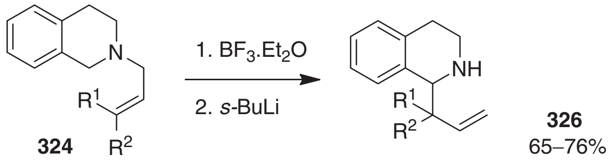
The reactivity of benzocycloammonium salts of type **320** was also reported (equation 90).[196] A competition between [1,2]-Stevens and Sommelet–Hauser pathways was again noticed with a predominance for the [1,2]-adduct **321**. Interestingly, the Sommelet–Hauser reaction led to two isomeric derivatives **322** and **323**, the latter compound being unable to aromatize in view of the strained bicyclic structure.



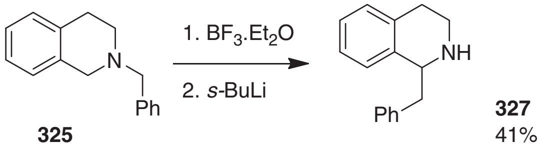
320 [1,2] **321** **322** **323** (90)

3.20.9 Lewis-Acid Promoted Stevens Rearrangements of Tertiary Amines

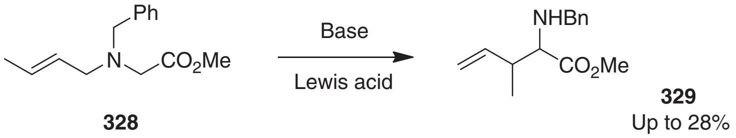
Finally and interestingly, it was recently noticed in the nitrogen series that an all-carbon quaternary ammonium salts or ylides are not necessary to induce a Stevens-rearrangement. One of the C–N bonds can be substituted by a nitrogen–boron bond for instance; boron being possibly replaced by another *Lewis* acidic atoms. The advantage of this approach is an increased diversity and the formation of secondary and not tertiary amines at the end of the reaction. For instance, allylic and benzylic amines **324** and **325** were shown to react by Kessar with $BF_3 \cdot Et_2O$ and treatment of the adduct with a strong base (*s*-BuLi) yielded products **326** and **327** of [2,3] and [1,2]-Stevens like character (equation 91 and equation 92).[197] This Lewis-acid activation approach was confirmed by Coldham using substrate **328**, $BF_3 \cdot Et_2O$ and a series of other *Lewis* acids. The reaction afforded products **329** although in moderate yields (up to 28%, equation 93).[198]



(91)

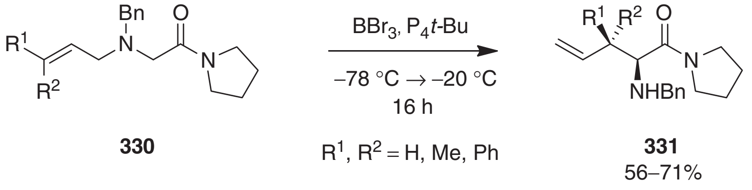


(92)



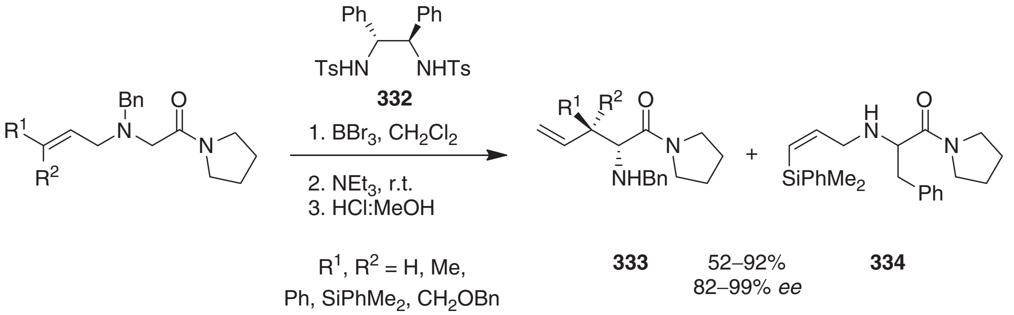
(93)

Somfai improved the reactivity moving from α-amino esters to more reactive α-amino amides of type **330** (equation 94).[199] Using BBr_3 as a Lewis acid and nonionic Schwesinger's phosphazene base P_4t-Bu, products **331** were obtained in 56 to 71% yield.[200,201] With substrates carrying bisubstituted (*E*)-olefins (R^1=Me or Ph, R^2=H) a good *syn*-selectivity was observed in addition (up to 20:1 ratio).



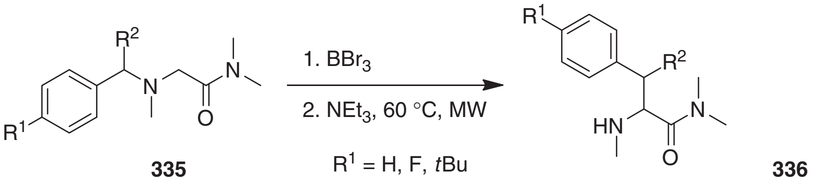
(94)

An effective asymmetric version of this *Lewis*-acid mediated rearrangement was later reported using chiral diamine **332** as chiral auxiliary in addition to BBr_3 (equation 95).[202,203] A replacement of P_4t-Bu by triethylamine was also possible. Rearrangement product **333** was then afforded with an excellent enantioselectivity (82–99% *ee*). Only when a bulky (*Z*)-substituent was present on the allyl moiety (R^1=H, R^2=$SiPhMe_2$) was the product of the [1,2]-Stevens rearrangement **334** obtained in 71% yield and a lower enantiomeric purity of 61%.



(95)

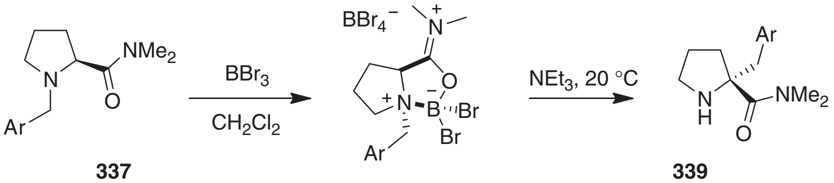
This excellent result probably prompted the authors to study the [1,2]-Stevens process more closely. Using tertiary amines **335**, secondary amines **336** were obtained in moderate yields (46–60%, equation 96).[204]



335 **336** 46–60%

(96)

Finally, an analogous reaction was performed on proline derivatives **337** (Scheme 47).[205] The secondary chiral amine **339** was obtained in good yield (62–85%) and excellent enantiomeric ratio (>98:2). This high level of chirality transfer can be explained by the formation of the rigid bicyclic intermediate **338** before the deprotonation.



337 *er* >98:2 **338** **339** 62–85%, *er* >98:2

Scheme 47

3.20.10 Conclusion

Helped by a better mechanistic knowledge and improved synthetic procedures to generate the ylide intermediates selectively, and metal-catalyzed decompositions of diazo compounds in particular, many research groups have decided over the past two decades to study and utilize nitrogen- and sulfur-based Stevens rearrangements. More than 200 references, excluding oxygen-based transformations, were accounted for this review. Whereas an emphasis had been given to the [2,3]-Stevens rearrangement in the previous comprehensive report,[1] herein it has not been the case as a balanced distribution of [1,2]- and [2,3]-Stevens processes has been highlighted.

Applications from mechanistic studies to methodology development and natural product synthesis were investigated. Regio- and stereoselective processes were often achieved with high levels of control although, in many instances, this has required an extensive survey of reaction conditions and a need to isolate pure onium moieties or ylide intermediates before the migration step. If progress has been made in the enantioselective Stevens rearrangements of sulfides, this has not been the case for the nitrogen series. Only one transformation has been reported so far using a chiral tertiary amine as substrate and a stoichiometric amount of chiral *Lewis* acid. Realizing an enantioselective N-Stevens rearrangement with only a catalytic amount of chiral selector is thus one of the many directions of research that will most probably be studied in the next two decades.

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3.21 The Wittig Rearrangement

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3.21.1 **Overview** 1038
3.21.2 **1,2-Rearrangements** 1039
3.21.2.1 Introduction and Historical Background 1039
3.21.2.2 Mechanism and Stereochemistry 1039
3.21.2.3 Rearrangements of Acetals and Glycosides 1041
3.21.2.4 Rearrangements of Aryl Ethers and Enol Ethers 1041
3.21.2.5 Rearrangements of α-Alkoxy Ketones, Esters, and Amides 1043
3.21.2.6 Rearrangements of Hydroximates, Carbamates, and Alkoxypyridines 1045
3.21.3 **1,4-Rearrangements** 1046
3.21.4 **2,3-Rearrangements** 1047
3.21.4.1 Introduction and Historical Background 1047
3.21.4.2 Mechanism and Stereochemistry 1048
3.21.4.3 Rearrangements of Allyl Lithiomethyl Ethers 1049
3.21.4.4 Rearrangement of Allyl Benzyl Ethers 1050
3.21.4.5 Rearrangement of Diallyl Ethers 1051
3.21.4.6 Rearrangement of Propargyl Ethers 1052
3.21.4.7 Rearrangement of Enolates 1056
3.21.4.8 Rearrangement of Dienolates 1058
3.21.4.9 Rearrangements of Enol Ethers and Enamines 1060
3.21.4.10 Cascade 2,3-Wittig/3,3-Oxy-Cope Rearrangements 1062
3.21.4.11 Enantioselective 2,3-Wittig Rearrangements 1063
3.21.4.11.1 Strategies that utilize chiral auxiliaries 1063
3.21.4.11.2 Strategies that utilize chiral bases 1065
3.21.4.12 Catalytic 2,3-Wittig Rearrangements 1066
3.21.4.13 Aza-2,3-Wittig Rearrangements 1068
3.21.4.14 Sila-2,3-Wittig Rearrangements 1069
References 1071

Glossary

Chiral auxiliary A chiral subunit that is incorporated into a molecule before a chemical reaction for the purpose of controlling product stereochemistry. This unit is then removed after the stereoselective reaction.

Chirality transfer A process in which a stereocenter present in a starting material controls the configuration of a stereocenter formed in a chemical reaction.

Sigmatropic rearrangement An intramolecular reaction in which one sigma bond is exchanged for another. This is frequently, but not always, accompanied by rearrangement of one or more pi-bonds.

Tandem reaction A chemical transformation that results from two or more chemical reactions that occur sequentially. These transformations are also referred to as 'cascade reactions' or 'domino reactions.'

3.21.1 Overview

The Wittig rearrangement is a sigmatropic rearrangement of metallated allyl- or benzyl ether derivatives that leads to cleavage of the ether C–O bond and formation of a new C–C bond.[1] There are several different types of Wittig rearrangements, and they are classified using numeric prefixes that describe the position of the bond that is formed relative to the position of the atoms in the starting material. The ether oxygen atom is numbered '1', and the carbon atom in the C–O bond that is cleaved is also numbered '1'. Numbering follows down the chain in each direction, and the name of the rearrangement reflects the numbered atoms that are attached in the new sigma bond (Scheme 1). For example, the 1,2-Wittig rearrangement involves cleavage of the C1–O1 bond and formation of a new bond between the C1 atom that was cleaved and the C2 atom that was the site of initial metallation. In some instances starting materials are converted to mixtures of products that result from competition between the various Wittig rearrangement pathways.

The 1,4-Wittig rearrangement and the 3,4-Wittig rearrangement are relatively rare processes, and in most cases are observed as minor competing pathways in other Wittig rearrangements. In contrast, the 2,3-Wittig rearrangement and the 1,2-Wittig rearrangement are widely documented and are of considerable utility for the preparation of substituted alcohols. As such, this

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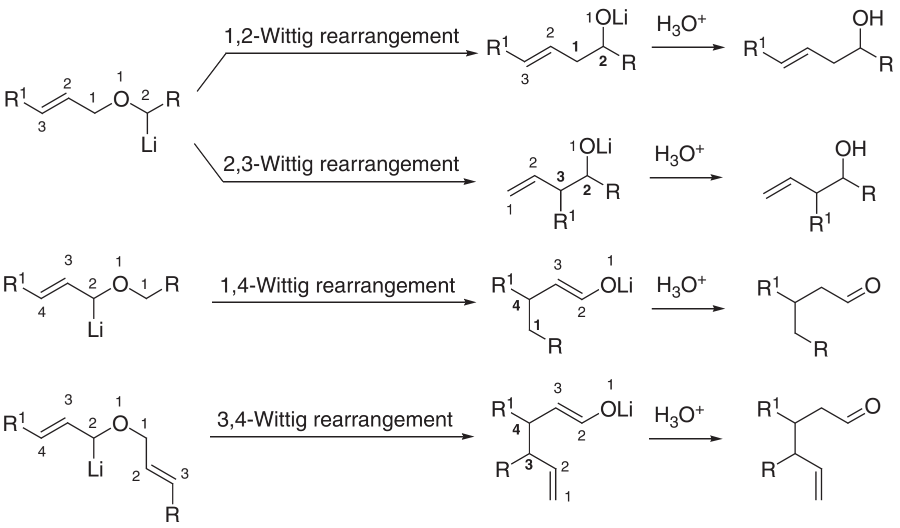


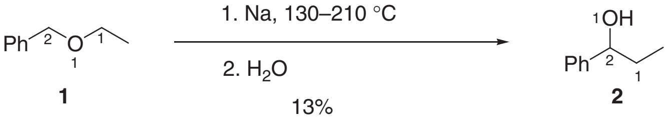
Scheme 1 Wittig rearrangement nomenclature.

chapter is primarily focused on developments in the areas of 1,2-Wittig rearrangement and 2,3-Wittig rearrangement chemistry that have occurred since publication of the First Edition of Comprehensive Organic Synthesis. However, a brief description of synthetically useful 1,4-rearrangements is also provided.

3.21.2 1,2-Rearrangements

3.21.2.1 Introduction and Historical Background

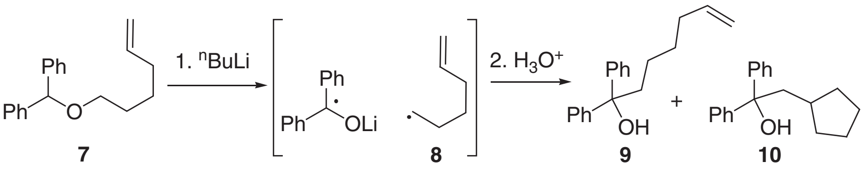
The 1,2-rearrangement of a dialkyl ether to a secondary alcohol (the 1,2-Wittig rearrangement) was first observed in 1924 by Schorigin, who was exploring reactions between sodium and ethyl benzyl ether.[2] As shown in equation 1, treatment of benzyl ethyl ether **1** with sodium at high temperature led to the formation of 1-phenylpropan-1-ol **2** in 13% yield via 1,2-migration of the ethyl group to the benzylic carbon. Subsequent studies by Wittig in 1942 led to the recognition that the transformations proceed via α-alkoxy carbanion intermediates, and resulted in the development of improved reaction conditions.[1,3,4] The synthetic utility of the 1,2-Wittig rearrangement is frequently limited by the requirement for strongly basic reaction conditions. In addition, low chemical yields are obtained even with simple substrates due to competing intramolecular elimination processes. However, in recent years 1,2-Wittig rearrangements of certain classes of ethers have proven useful for the stereoselective construction of relatively complex molecules. These reactions have also been employed as key steps in the synthesis of several natural products.



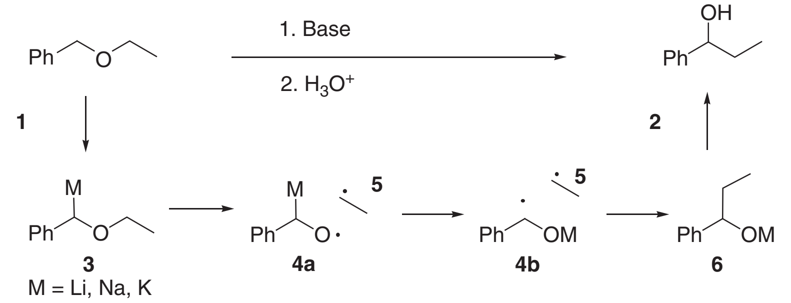
(1)

3.21.2.2 Mechanism and Stereochemistry

The mechanism of the 1,2-Wittig rearrangement proceeds via initial metallation (deprotonation) of the ether **1** with a strongly basic reagent, such as ^{n}BuLi, to yield **3** (Scheme 2).[4] This intermediate undergoes homolysis to two radicals **4a** and **5**, the former of which undergoes 1,2-metal migration to give **4b**. The recombination of **4b** and **5** then affords alkoxide **6**. Considerable evidence has been gathered that supports this mechanism.[4] One particularly compelling piece of data is the observation that small amounts of **10** are formed in the rearrangement of **7**, as **10** is most likely generated via 5-*endo*-cyclization of intermediate radical **8** (equation 2).[5]

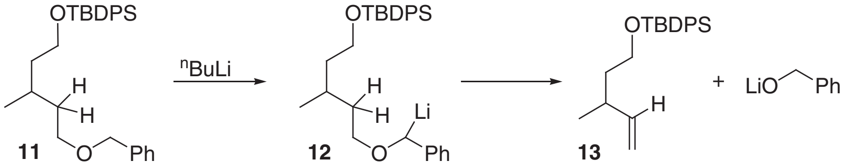


(2)



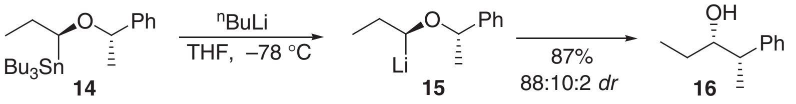
Scheme 2 Mechanism of 1,2-Wittig rearrangement of dialkyl ethers.

The 1,2-Wittig rearrangement of many simple alkyl ethers proceeds in modest yield due to competing intramolecular E2 elimination. For example, attempts to effect 1,2-Wittig rearrangement of **11** led to the formation of alkene **13** as the major product (equation 3).[6] This type of intramolecular E2 elimination is the most common side reaction that is observed in many 1,2-Wittig rearrangements.

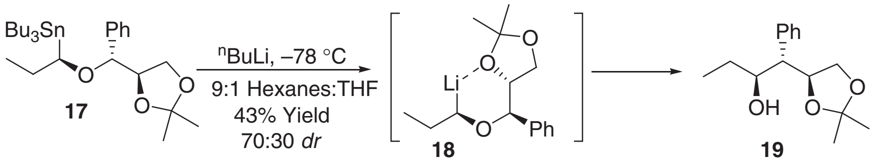


(3)

The stereochemical outcome of 1,2-Wittig rearrangements has been investigated using ether substrates bearing stereocenters adjacent to the oxygen atom. In most cases, such as the conversion of **14** to **16** (equation 4), the transformations proceed with retention of configuration at the migrating carbon stereocenter and inversion of configuration at the metallated carbon stereocenter.[7] However, in some instances, such as the conversion of **17** to **19** (equation 5), lithium ion chelation with a neighboring heteroatom (such as in intermediate **18**) can lead to rearrangement with retention of configuration at the metallated carbon stereocenter.[8] Due to the nature of the radical intermediates, partial scrambling of stereochemistry is frequently observed in 1,2-Wittig rearrangements of stereodefined organolithium reagents.

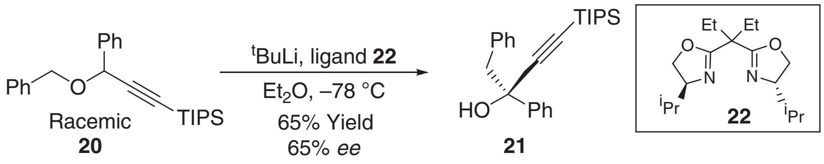


(4)



(5)

Although control of relative stereochemistry is reasonably efficient in many 1,2-Wittig rearrangement reactions, the control of absolute stereochemistry through enantioselective transformations remains a significant challenge. The one reported approach to asymmetric 1,2-Wittig rearrangements utilizes chiral bis-oxazoline ligand **22** to control asymmetric induction. This strategy provides products such as **21** with up to 65% *ee* (equation 6).[9]

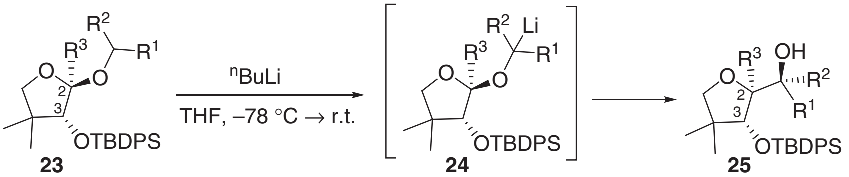


(6)

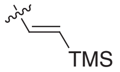
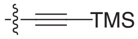
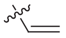
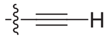
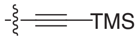
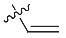
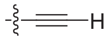
3.21.2.3 Rearrangements of Acetals and Glycosides

The 1,2-Wittig rearrangement of 2-alkoxyfuran acetals **23** provides a stereoselective method for the preparation of functionalized C-glycoside derivatives **25** (Table 1).[10] The products are obtained with high diastereoselectivity, and the stereochemistry of the migrating carbon stereocenter (the site of metallation) in the substrate does not influence the stereochemistry of the product (entries 3–4). The yields obtained in these transformations are higher than those typically obtained in Wittig rearrangements of ethers. This may be due to the relatively high stability of the two α-alkoxy radicals that are generated on homolysis of the lithiated acetal **24**.[11] Thus, bond homolysis and Wittig rearrangement of **24** occurs more rapidly than competing side reactions such as intramolecular E2 elimination. However, substrate structure and reaction conditions also influence the relative rates of rearrangement and elimination; hence the presence of an alkoxy group at the 3-position of the tetrahydrofuran ring is essential to minimize competing E2 processes. Despite this limitation, these transformations have demonstrated utility in the synthesis of complex molecules and natural products. For example, the 1,2-Wittig rearrangement of relatively complex acetal substrate **26** was used as a key step in a stereoselective total synthesis of zaragozic acid A, and provided **27** in moderate yield with good diastereoselectivity (equation 7).[12] The Wittig rearrangement of glucose derived acetals such as **28** is an effective method for the preparation of C-glycosides (e.g., **29**) (equation 8).[10a]

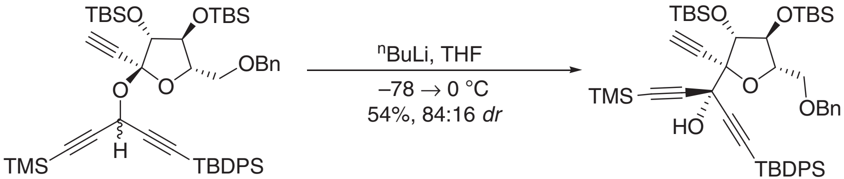
Table 1 1,2-Wittig rearrangement of 2-alkoxyfuran acetals



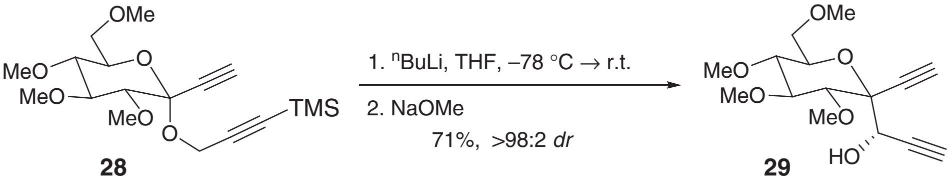
23 **24** **25**

Entry	*R*^{1}	*R*^{2}	*R*^{3}	*Yield (%)*	*dr*	*Reference*
1	Ph	H	H	77	>98:2	10a
2		H	H	60	>98:2	10a
3^{a,b}				78	>98:2	10b
4^{a,c}				65	>98:2	10b

[a] Partial desilylation of the alkyne occurred under the reaction conditions.
[b] The (*R*)-stereoisomer of 23 was used as the starting material.
[c] The (*S*)-stereoisomer of 23 was used as the starting material.



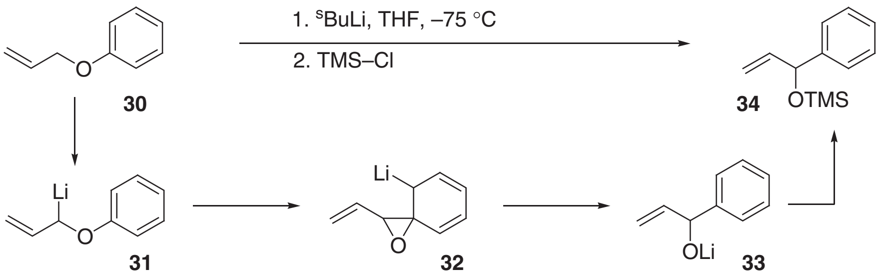
26 **27** (7)



28 **29** (8)

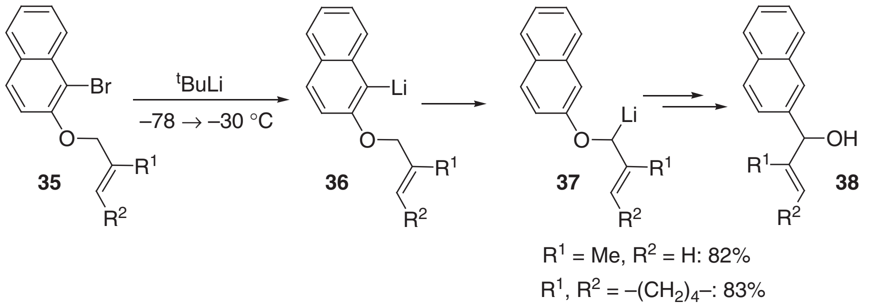
3.21.2.4 Rearrangements of Aryl Ethers and Enol Ethers

Although most studies on 1,2-Wittig rearrangements have focused on dialkyl ether substrates, a number of 1,2-rearrangements of aryl alkyl ethers and alkyl enol ethers have also been demonstrated. The rearrangements of metallated alkyl enol ethers proceed via a homolysis/radical recombination mechanism analogous to that shown above in Scheme 1.[13] However, Schlosser has illustrated that the 1,2-Wittig rearrangement of allyl aryl ethers such as **30** proceeds via a nucleophilic aromatic substitution mechanism (Scheme 3).[14] The carbanion **31** generated by metallation of **30** can undergo nucleophilic addition to the arene to generate **32**, which is transformed to alkoxide **33** by elimination. Trapping of **33** with TMS-Cl then yields **34**; quenching of **33** with water would provide the corresponding alcohol.



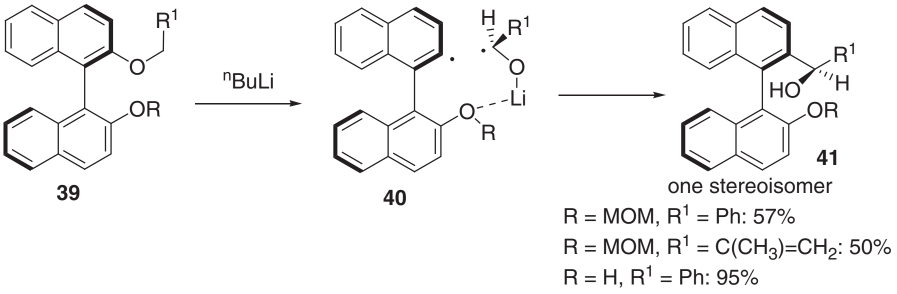
Scheme 3 Mechanism of 1,2-Wittig rearrangement of allyl aryl ethers.

In most Wittig rearrangements of aryl ether derivatives the generation of the α-alkoxy carbanion is effected by deprotonation of the substrate with an alkyllithium reagent. However, reactions of 2-bromoaryl ethers **35** proceed via a different pathway involving metal–halogen exchange to give **36** followed by anion translocation to provide **37** (equation 9).[15] The 1,2-Wittig rearrangement of **37** then proceeds by a mechanism analogous to that shown in Scheme 3 to afford alcohols **38**.



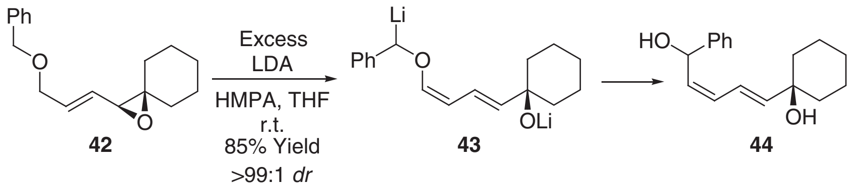
(9)

The 1,2-Wittig rearrangement of binaphthol-derived allyl and benzyl ethers **39** has been used for the stereoselective construction of 2-naphthylmethyl alcohols **41** (equation 10).[16] The 1,2-rearrangements proceed in good yield and high stereocontrol, and the products of these reactions have shown some utility as ligands for asymmetric catalysis. Both monoprotected binaphthol ethers (**39**, R=MOM) and unprotected binaphthol ethers (**39**, R=H) are suitable substrates for these reactions. The double rearrangement of bis (benzyl) ether derivatives (**39**, R=Bn, R_1=Ph) proceeds in low yield, although double rearrangement of bis (allyl ether derivatives (**39**, R=allyl, R^1=CH=CH_2) is quite efficient.[16c] The high asymmetric induction in these transformations is believed to result from stereoselective recombination of the two lithium-chelated radical fragments in intermediate **40**.

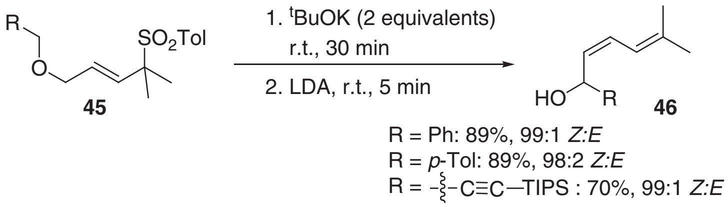


(10)

The stereoselective synthesis of *Z*-dienols has been accomplished through a one-pot 1,4-elimination of an allylic ether derivative followed by 1,2-Wittig rearrangement of the resulting enol ether. This transformation was first observed when epoxide **42** was treated with excess LDA. Ring-opening elimination followed by metallation of the benzylic carbon occurred to generate **43**. The dianion **43** then underwent 1,2-Wittig rearrangement, and 1,6-diol **44** was obtained on aqueous workup (equation 11).[17] Related reactions of allylic sulfones **45** also proceed with good stereoselectivity and chemical yield to afford dienols **46** (equation 10).[18] The best results in these latter transformations are obtained when the 1,4-elimination is conducted using ^{t}BuOK as base, and then LDA is added to effect the 1,2-rearrangement.



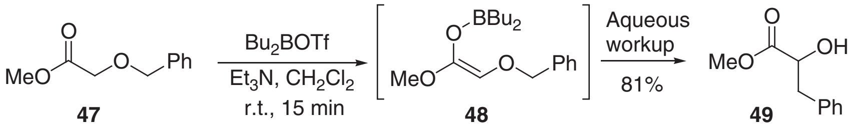
(11)



(12)

3.21.2.5 Rearrangements of α-Alkoxy Ketones, Esters, and Amides

The 1,2-Wittig rearrangement of α-alkoxy ketones can be effected under fairly mild reaction conditions due to the relatively high acidity of protons adjacent to carbonyl functional groups. For example, treatment of methyl-*O*-benzyl glycolate **47** with Bu_2BOTf and Et_3N provided **49** in 81% yield (equation 13).[19a] These transformations proceed by way of intermediate enolates (e.g., **48**), although the precise mechanism of the 1,2-rearrangement is currently unknown.



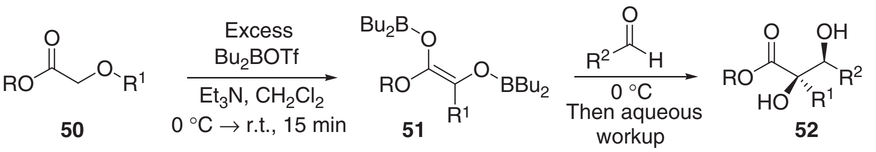
(13)

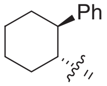
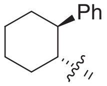
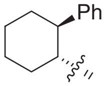
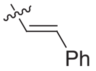
Tandem 1,2-Wittig rearrangement/aldol reactions (*see* Chapter 2.08) of ethers **50** derived from glycolate esters have been used for the highly stereoselective construction of substituted *syn*-1,2-diols **52** bearing ester functional groups (**Table 2**).[19a,b] The reactions are effective with a broad array of aldehyde electrophiles, although the scope is currently limited to *O*-benzyl or *O*-allyl glycolate esters. Transformations of the *O*-allyl glycolate ester substrates may proceed via 2,3-Wittig rearrangement pathways rather than 1,2-rearrangements. The use of esters bearing a 2-phenylcyclohexyl chiral auxiliary provides enantiomerically enriched products with up to 95% *ee* after reductive cleavage of the auxiliary (entries 2–4).[19b] The tandem Wittig rearrangement/aldol reactions have been shown to proceed by way of enedioldiboronate intermediates **51**, which are generated by 1,2-Wittig rearrangement of **50** followed by a second enolization event. The products of these transformations (**52**) are difficult to obtain through traditional aldol methods, and the presence of both boron groups on **51** may be of importance for reactivity and stereocontrol in the aldol step.

A related tandem sequence involving a 1,2-Wittig rearrangement of **53** followed by a Mannich reaction between **54** and an imine electrophile provides stereocontrolled access to enantiomerically enriched α-hydroxy-*β*-amino esters **55**–**56** (Scheme 4).[19c] *Syn*-amino alcohol products **55** are obtained when *N*-benzyl or *N*-boc imines are employed as electrophiles. However, use of α-phenylsulfonyl amines affords *anti*-amino alcohol derivatives **56** with high selectivity. These transformations are also effective with allyl ether derivatives of **53**, and a number of different imine electrophiles can be used in these reactions.

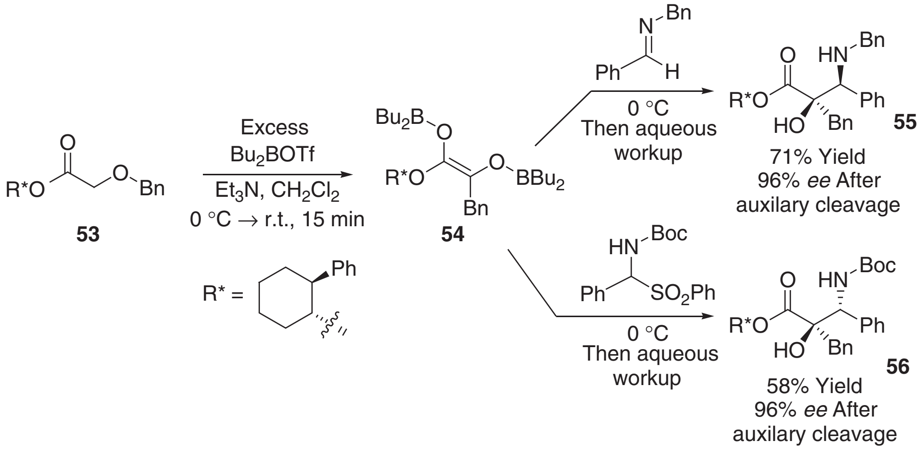
Ketone enolates have also been demonstrated to undergo very efficient 1,2-Wittig rearrangement reactions. The most interesting examples of these transformations have been used in cascade anionic oxy-Cope rearrangement/1,2-Wittig rearrangement sequences that afford relatively complex bridged- or fused-bicyclic ring systems.[20] For example, treatment of **57** with KH and 18-crown-6 effects 3,3-sigmatropic rearrangement (*see* Chapters 5.20 and 5.21) to yield enolate **58** (equation 14).[20a] Isomerization of enolate **58** to enolate **59** followed by 1,2-Wittig rearrangement then provides **60** as a single stereoisomer. The analogous tandem reaction sequence of **61** provided highly substituted *cis*-decalin **63** in moderate yield but with excellent (>20:1) stereocontrol (equation 15).[20b]

Table 2 Tandem 1,2-Wittig rearrangement/aldol reactions

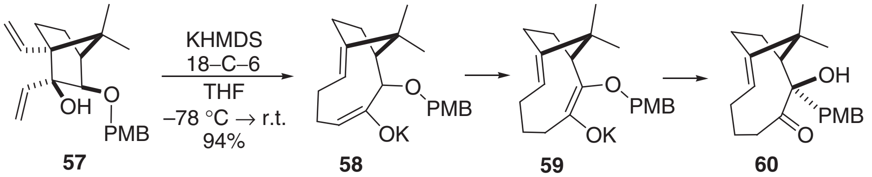


Entry	*R*	*R¹*	*R²*	*Yield (%)*	*syn:anti*	*ee (%)*[a]	*Reference*
1	Me	Bn	Ph	72	>20:1	–	19a
2		Bn	$^{n}C_9H_{19}$	88	>20:1	95	19b
3		Allyl	^{i}Pr	68	>20:1	89	19b
4		Allyl		59	>20:1	95	19b

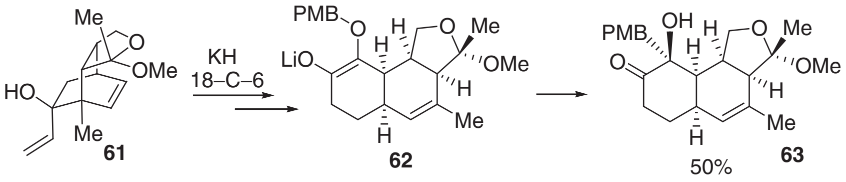
[a]Determined after reduction to the corresponding triol.



Scheme 4 Tandem enolate 1,2-Wittig rearrangement/Mannich reactions.

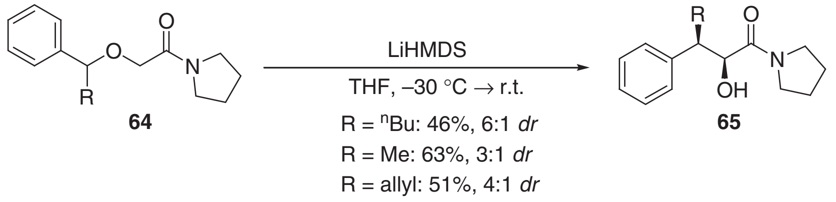


(14)

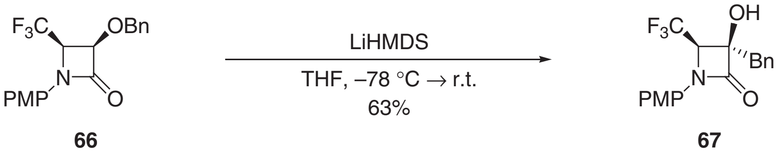


(15)

The 1,2-Wittig rearrangement of enolates obtained via deprotonation of α-alkoxy amides **64** has been used for the construction of substituted α-hydroxy amide derivatives 65. These reactions proceed with moderate to good diastereoselectivity (2–6:1) favoring the *syn*-stereoisomer (equation 16).[21a] The related 1,2-Wittig rearrangement of α-benzyloxy lactam **66** afforded highly substituted α-hydroxy-*β*-lactam **67** with excellent stereocontrol (equation 17).[21b]

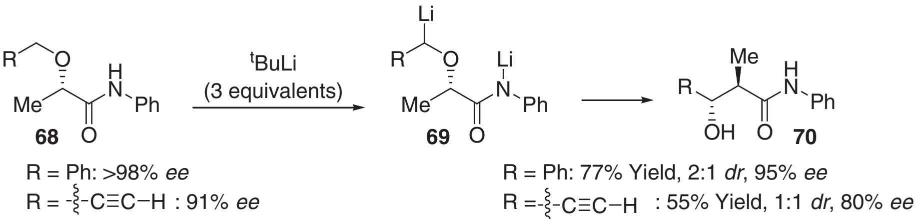


(16)



(17)

The 1,2-Wittig rearrangement of enantiomerically enriched α-alkoxy-NH-amides **68** provides *β*-hydroxy amide products **70** in good yield with only modest erosion of optical purity (equation 18).[22] In contrast to the reactions described above, these rearrangements do not proceed via intermediate enolates, but instead involve dilithiated species **69**. In most transformations chemical yields are good, but diastereoselectivities are modest.

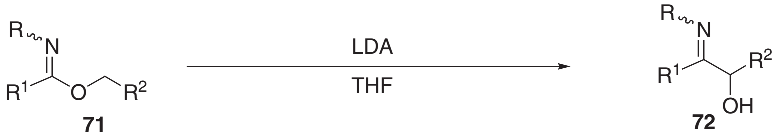


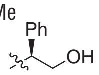
(18)

3.21.2.6 Rearrangements of Hydroximates, Carbamates, and Alkoxypyridines

The imino-Wittig rearrangement was first reported in 1981,[23] and involves the 1,2-migration of an imino functional group in substrates such as **71** to provide **72** (Table 3). The stereochemistry of hydroximate substrates has a significant influence on the outcome of these transformations.[24] Rearrangement of *Z*-hydroximates produces *Z*-oxime derivatives in good yields, but the analogous *E*-hydroximate substrates typically afford mixtures of *E*- and *Z*-oxime stereoisomers in moderate yield. Substrates bearing chiral oxime ether groups are converted to rearranged products with moderate to good asymmetric induction (3–9:1 *dr*; entry 5).[25] The rearrangement of ester derivatives by way of enolate intermediates proceeds smoothly (entry 6).[26] The products **72** generated in the imino 1,2-Wittig rearrangement reactions can be reduced to synthetically valuable amino alcohols, which have been used in the synthesis of natural products such as cytoxazone[24b] and dysiherbaine.[27]

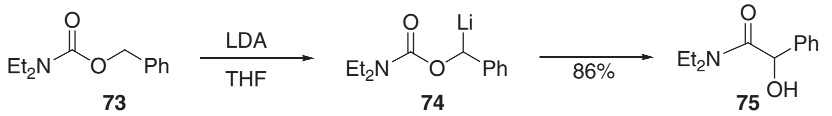
Table 3 Imino 1,2-Wittig rearrangement reactions



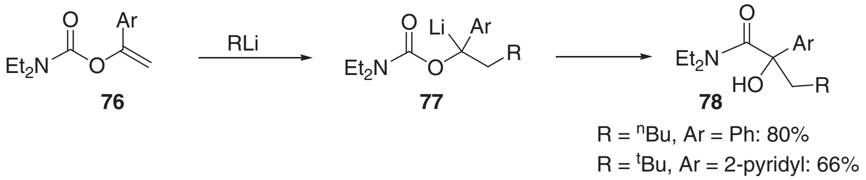
Entry	*R*	*R¹*	*R²*	*Yield (%)*	*E:Z*	*Reference*
1	*Z*-OMe	Ph	Ph	89	*Z*-only	24a
2	*E*-OMe	Ph	Ph	41	3:1	24a
3	*Z*-OMe	Et	Ph	64	Z-only	24a
4	OMe	2-furyl	$CH=CH_2$	95	–	27
5	*Z*- 	*p*-$MeOC_6H_4$	$CH=CH_2$	63[a]	*Z*-only	25
6	*p*-$MeOC_6H_4$	CF_3	CO_2Me	81	–	26

[a] The *R*-stereoismer was formed with 9:1 *dr*.

Carbamates **73** and **76** and 2-pyridyl ethers **79** and **82** undergo mechanistically related 1,2-Wittig rearrangements to generate α-hydroxy amides **75** and **78** (equations 19–20)[28a] and hydroxymethylpyridines **81** and **84** (equations 21–22).[29a] The reactive organolithium intermediates in these transformations can be generated through one of two methods. Deprotonation of benzyl ethers **73** and **79**, afford intermediates **74**, and **80**, which then rearrange to yield secondary alcohols. Alternatively, carbolithiation of enol ether derivatives **76** and **82** afford more highly substituted organolithium intermediates **77** and **83** that are converted to tertiary alcohol products.[28b,29b] The carbolithiation method is quite attractive, as two carbon–carbon bonds are generated in a one-flask operation.



(19)



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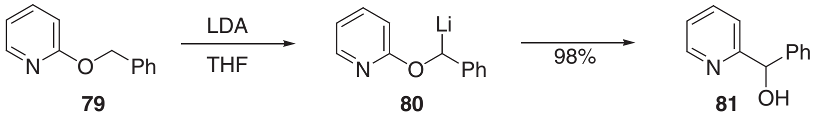

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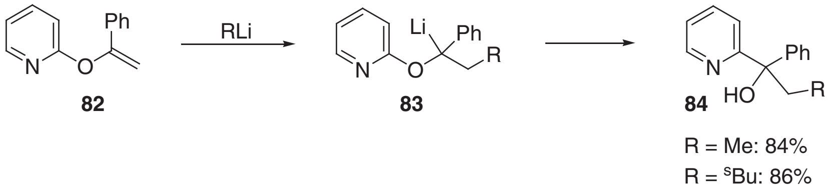
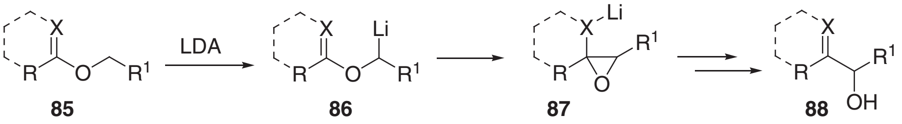


(22)

The 1,2-Wittig rearrangement reactions of hydroximates, carbamates, and hydroxypyridines proceed via a mechanism similar to that described above in Scheme 3 for reactions of allyl (aryl) ethers.[28,29] Lithiation of **85** generates intermediate **86**, which undergoes intramolecular addition to the $C{=}X$ π bond to yield **87** (Scheme 5). Elimination of **87** followed by aqueous workup then provides the observed alcohol products.



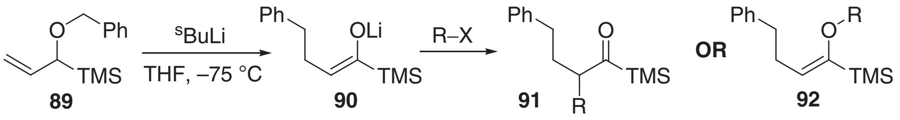
Scheme 5 Mechanism of hydroximate, carbamate, or hydroxypyridine 1,2-Wittig rearrangement.

3.21.3 1,4-Rearrangements

The 1,4-Wittig rearrangement is a relatively uncommon transformation, and has only occasionally proven to be synthetically useful. Maleczka has developed a highly selective 1,4-Wittig rearrangement of allylsilanes **89**.[30] Treatment of these substrates with ^{s}BuLi leads to lithiation followed by 1,4-rearrangement to give enolate **90**. Trapping of **90** with various electrophiles then provides acyl silanes **91** or vinyl silanes **92** in good yield (Table 4). The mechanism of the 1,4-rearrangement of **89** has not been fully elucidated, but appears to involve concerted rearrangement (similar to the 2,3-Wittig rearrangements described in Section 3.21.4) rather than bond homolysis followed by radical recombination that is typical for the 1,2-Wittig rearrangements described above.

The conversion of 3-iodopropyl enol ethers **93** to 4-penten-1-ol derivatives **97** has been accomplished by an unusual 1,4-Wittig rearrangement process (Table 5).[31] In contrast to typical Wittig rearrangement reactions, these transformations most likely occur through metal halogen exchange of **93** followed by intramolecular carbolithiation of the alkene in intermediate **94**. This process

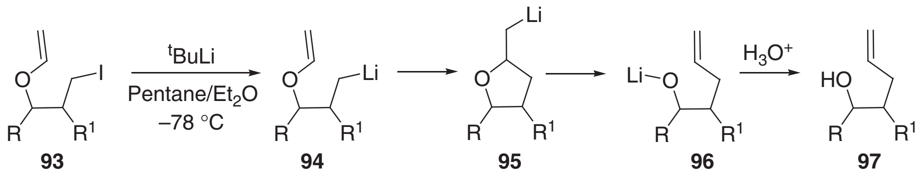
Table 4 Allylsilane 1,4-Wittig rearrangement



Entry	*R–X*	*Product*	*Yield (%)*
1	Allyl–Br	91	55
2	Me–I	91	73
3	Ac–Cl	92	69

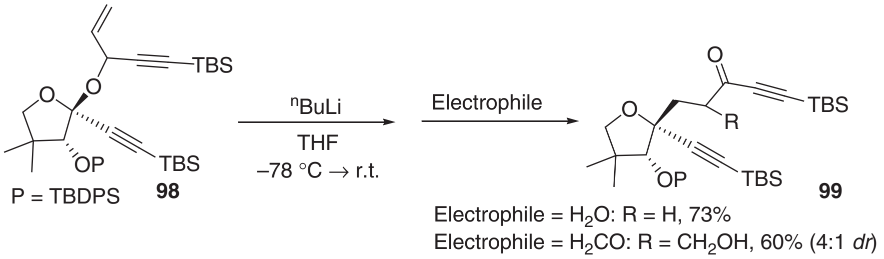
yields lithiated tetrahydrofuran **95**, which undergoes ring-opening β-alkoxide elimination to generate **96**. Aqueous workup then provides **97** in excellent chemical yield.

Table 5 1,4-Wittig rearrangement of 3-iodopropyl enol ethers



Entry	*R*	*R¹*	*Yield (%)*
1	H	H	93
2	Me	H	94
3	H	Et	96

The 1,4-Wittig rearrangement of *O*-glycoside **98** followed by trapping with an electrophile afforded **99** in good yield (equation 23).[10b] Interestingly, a nearly identical substrate that lacks the TBS-substituent on the C2 alkynyl group undergoes clean 1,2-Wittig rearrangement rather than 1,4-rearrangement. The reason for this change in mechanism is unclear.

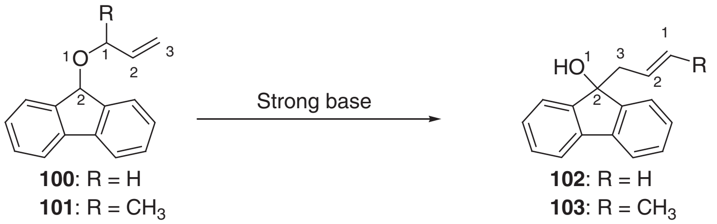


(23)

3.21.4 2,3-Rearrangements

3.21.4.1 Introduction and Historical Background

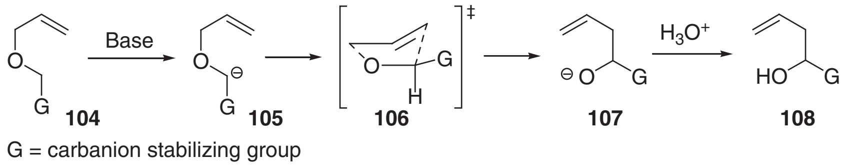
The base-induced rearrangement of allyl fluorenyl ether (**100**) to homoallylic alcohol **102** was first described in 1949 by Wittig (equation 24).[32] However, the mechanism of this reaction was unclear, as the alcohol product **102** could be formed by either a 1,2- or 2,3-rearrangement pathway. The first unambiguous case of 2,3-Wittig rearrangement that could be differentiated from a 1,2-rearrangement was reported in 1960 by Cast and Stevens in the conversion of **101** to **103**.[33] The 2,3-Wittig rearrangement has been widely utilized as a tool for organic synthesis, and is among the best methods available for the stereoselective generation of substituted homoallylic alcohols.[1,34]



(24)

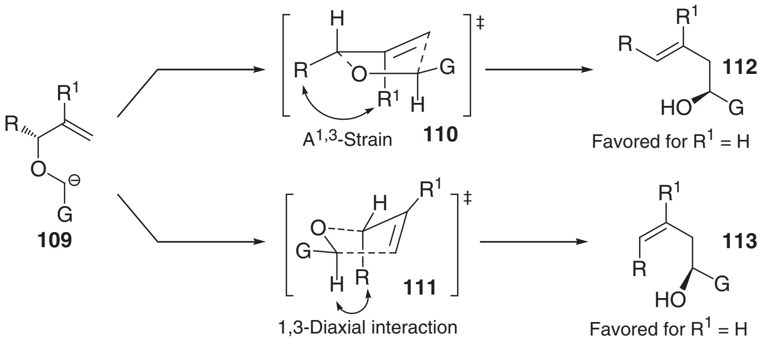
3.21.4.2 Mechanism and Stereochemistry

Most 2,3-Wittig rearrangements employ allylic ether substrates **104** bearing carbanion stabilizing groups, such as arenes, alkenes, alkynes, or strong electron-withdrawing groups like esters or amides. The mechanism of the 2,3-Wittig rearrangement involves initial metallation of the ether **104** to generate an intermediate stabilized carbanion **105** (Scheme 6). Intermediate **105** then undergoes a concerted sigmatropic rearrangement through a five-membered envelope-like transition state **106** to provide the homoallylic alkoxide **107**. Protonation of the alkoxide during an aqueous workup affords the homoallylic alcohol product **108**.



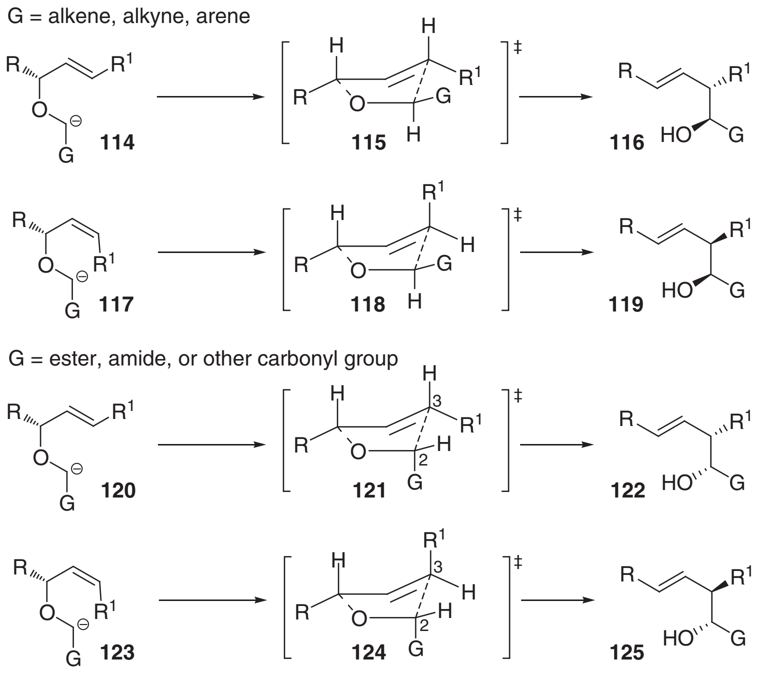
Scheme 6 Mechanism of the 2,3-Wittig rearrangement.

Due to the concerted reaction mechanism and the highly organized transition state, many 2,3-Wittig rearrangements proceed with selective formation of one alkene stereoisomer.[1] In most instances *E*-alkene products are generated via transition state **110** in which 1,3-diaxial interactions are minimized. However, selectivities are substrate dependent, and in some cases *Z*-selective transformations are observed in situations where transition state **110** suffers from significant allylic strain ($A^{1,3}$) interactions between R and R^1. The low energy pathway in these instances provides *Z*-alkene products **113** by way of transition state **111** (Scheme 7). Chirality transfer is typically quite efficient due to preferential equatorial orientation of the G-group in transition states **110** and **111**. Thus, enantiomerically enriched substrates such as **109** are converted to products with little or no erosion of optical purity.



Scheme 7 Chirality transfer and alkene stereochemistry.

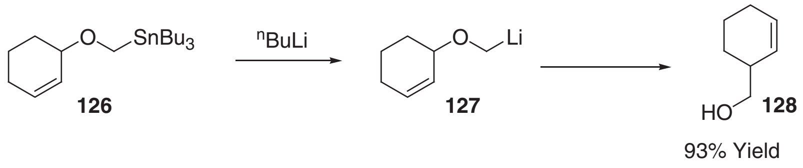
Allyl ether substrates **114** and **117** bearing internal alkenes undergo diastereoselective conversion to **116** and **119** via envelope-like transitions states **115** and **118** when G=alkenyl, alkynyl, or aryl (Scheme 8).[35] In these cases equatorial orientation of the both the R-group and the G-group is preferred. However, the stereoselectivity is reversed if the anion stabilizing group G is a carbonyl-containing functional group such as an ester or amide (**120** or **123**, G=CO_2R or $CONR_2$). Rearrangements of these substrates proceed through transition states **121** or **124** where the electron-withdrawing group is in a pseudoaxial orientation. This axial positioning of the carbonyl leads to stabilization of developing negative charge at C3 (the alkene carbon bearing the R^1 group) in the transition state.[35]



Scheme 8 Transition state models for reactions of internal alkene substrates.

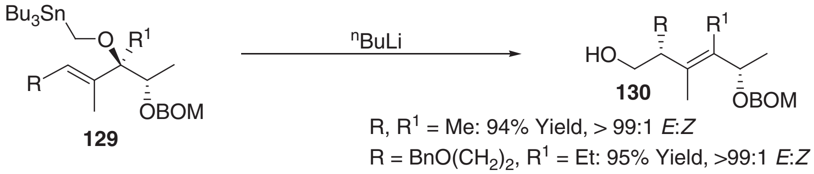
3.21.4.3 Rearrangements of Allyl Lithiomethyl Ethers

The 2,3-Wittig rearrangement of allyl lithiomethyl ethers (the Still-Wittig rearrangement) was first reported by Still in 1978, and featured a transmetallation strategy for the generation of the lithiated ether.[1,36] Treatment of a stannylmethyl ether such as **126** with ^{n}BuLi leads to formation of **127**, which undergoes rapid sigmatropic rearrangement to afford homoallylic alcohol **128** after aqueous workup (equation 25).



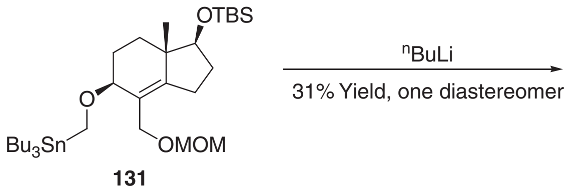
(25)

Over the past three decades, 2,3-Wittig rearrangements of allyl lithiomethyl ethers have found numerous applications in organic synthesis.[1,34] For example, the stereoselective construction of highly functionalized tetrasubstituted alkenes **130** was accomplished by 2,3-Wittig rearrangement of **129** (equation 26).[37] The 2,3-Still–Wittig rearrangement has also been used for the formation of quaternary carbon stereocenters in quite sterically hindered systems such as the conversion of **131** to **132** (equation 27),[38] or the conversion of **133** to **134** (equation 28).[39] However, in some cases yields in these transformations are modest due to competing side reactions such as 1,2-Wittig rearrangement or protodestannylation of the substrate to afford the corresponding methyl ether.

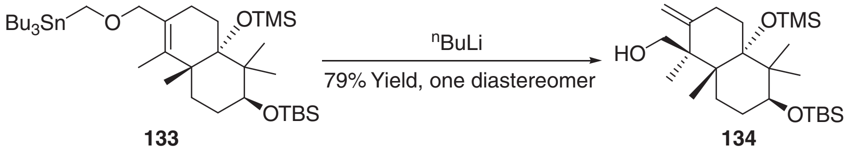


R, R^1 = Me: 94% Yield, > 99:1 *E*:*Z*
R = $BnO(CH_2)_2$, R^1 = Et: 95% Yield, >99:1 *E*:*Z*

(26)

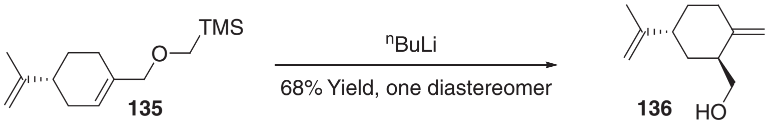


(27)

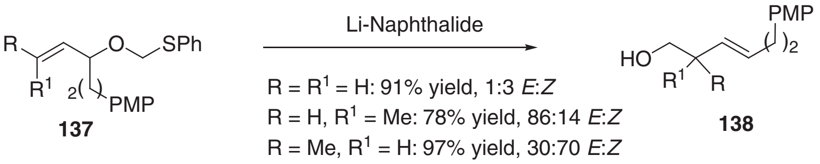


(28)

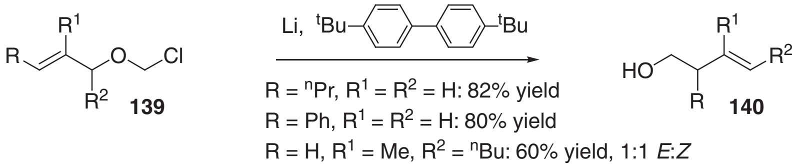
One significant limitation of the Still–Wittig rearrangement is the need for a stoichiometric amount of an organotin species, as tributyltin regents are rather toxic, and removal of tin-containing byproducts can be problematic in some cases. To address these limitations, the generation of the requisite alkoxymethyllithium reagent from more innocuous precursors has been explored. Mulzer has illustrated that (trimethylsilyl)methyl ethers such as **135** are suitable substrates for 2,3-Wittig rearrangements. Treatment of **135** with ^{n}BuLi leads to formation of the intermediate lithiated ether, and rearrangement occurs to provide **136** in 68% yield as a single diastereomer (equation 29).[40] In general, this approach provides yields and stereoselectivities comparable to those obtained with the analogous organostannanes. The reduction of (alkoxymethyl)phenylsulfides **137** is also an effective means for generation of lithiomethyl ethers in 2,3-Wittig rearrangements (equation 30).[41] Substrates such as **137** are straightforward to prepare, and are less toxic than organotin reagents. Chlorine–lithium exchange reactions of **139** have also been used to access alkoxymethyllithium reagents in 2,3-Wittig rearrangements to afford products **140** (equation 31).[42] Although this strategy alleviates the need for organotin compounds, chloromethyl ethers such as **139** are quite reactive alkylating agents with considerable toxicity.



(29)



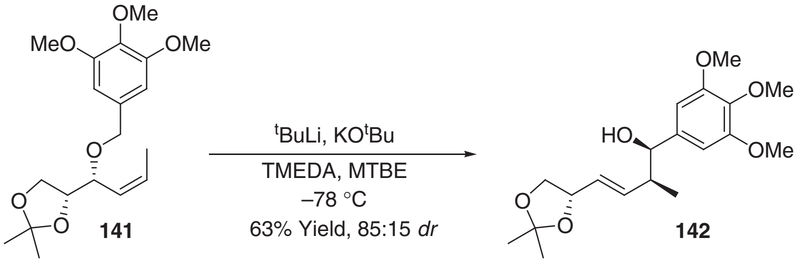
(30)



(31)

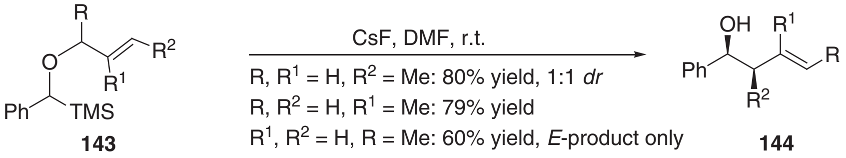
3.21.4.4 Rearrangement of Allyl Benzyl Ethers

Allyl benzyl ether derivatives were among the first substrates examined in 2,3-Wittig rearrangements, and have been used to probe the mechanism and the stereochemical outcomes of these transformations.[1,34] Selective metallation of the benzylic carbon atom can usually be accomplished under appropriate conditions. For example, treatment of **141** with ^{t}BuLi/KO^{t}Bu leads to benzylic metallation and subsequent 2,3-Wittig rearrangement then affords benzyl alcohol derivative **142** (equation 32).[43]



(32)

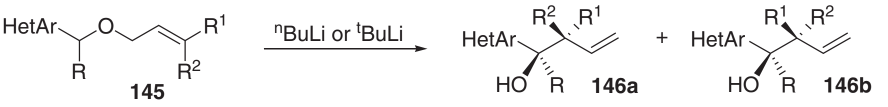
One significant limitation of most 2,3-Wittig rearrangement reactions is the requirement for a strong base, such as an alkyllithium reagent or LDA, which limits functional group tolerance. However, studies by Reetz[44] and Maleczka[45] have shown that 2,3-Wittig rearrangements of allyl benzyl ethers bearing trimethylsilyl groups at the benzylic position can be effected under very mild conditions. Treatment of silylated substrates **143** with a fluoride anion source such as CsF affords products **144** in good yield (equation 33). These reactions are quite effective for substrates substituted at the allylic position ($R \neq H$) or the internal alkene carbon atom ($R^1 \neq H$). However, diastereoselectivities are poor for *E*-alkenes ($R^2 \neq H$), and are much lower than those typically obtained in traditional 2,3-Wittig rearrangements of lithiated allyl benzyl ethers. This low stereoselectivity suggests the rearrangements of substrates such as **143** may not proceed via organoalkali metal intermediates, but instead could involve pentavalent organosilicate intermediates.

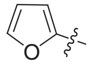
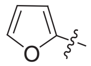
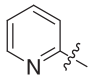
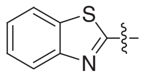


(33)

Heteroaryl allyl ethers **145** have also been shown to undergo 2,3-Wittig rearrangement reactions to yield **146a,b** (Table 6).[46] However, competing 1,2-Wittig rearrangements are also observed in these transformations, and the rearrangement pathway is greatly influenced by substrate structure. For example, substrate **147** undergoes benzylic metallation followed by 2,3-rearrangement of **148** to afford **149**, whereas substrate **150** undergoes allylic deprotonation followed by 1,2-rearrangement of **151** to yield **152** (Scheme 9).[46b] These changes in migratory pathway often result from differences in the relative ease of deprotonating the benzylic carbon in the substrate. For example, the 2-methoxyphenyl substituent at the benzylic position of **147** increases the acidity of the benzylic proton and facilitates deprotonation at the benzylic position.

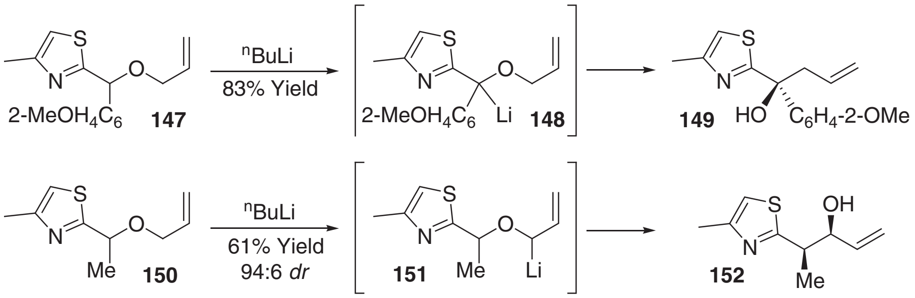
Table 6 2,3-Wittig rearrangement of heteroaryl allyl ethers



Entry	*HetAr*	*R*	*R¹*	*R²*	*dr*	*Yield (%)*	*Reference*
1		H	H	Me	3:1	73	46a
2		H	Me	H	9:1	64	46a
3		H	Ph	H	40:60	76	46b
4		Me	Ph	H	2:98	67	46b

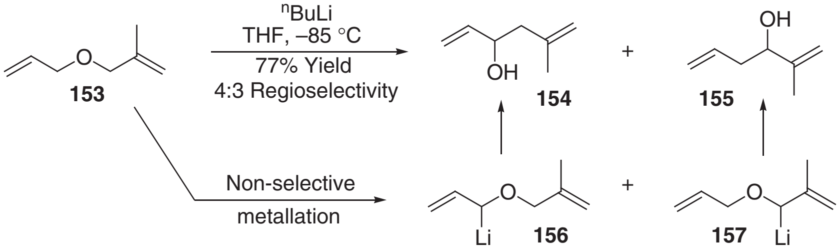
3.21.4.5 Rearrangement of Diallyl Ethers

The 2,3-Wittig rearrangement of diallyl ethers is a useful method for the construction of 1,5-diene-3-ols, which are valuable intermediates in organic synthesis.[1] These products can also be induced to undergo a 3,3-sigmatropic rearrangement to provide



Scheme 9 1,2- vs. 2,3-Wittig rearrangement.

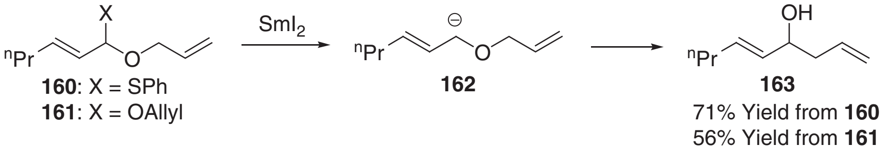
substituted aldehydes as described in Section 3.21.4.10. The synthetic utility of 2,3-Wittig rearrangements of diallyl ethers is limited by the difficulty of achieving selective deprotonation of one allylic position in preference to the other. If selective deprotonation is not achieved, mixtures of regioisomeric products are generated. For example, treatment of **153** with ^{n}BuLi leads to a roughly 1:1 mixture of lithiated ethers **156** and **157**, which undergo 2,3-Wittig rearrangement to afford a mixture of homoallylic alcohols **154** and **155** on workup (Scheme 10).[47]



Scheme 10 Nonselective 2,3-Wittig rearrangement of diallyl ether **153.**

Despite this limitation, selective metallation can be achieved with certain types of substrates **158**, and selective 2,3-rearrangement then occurs to yield a single product **159** (Table 7).[1,47,48] For example, the presence of a bulky alkyl substituent on an allylic carbon atom can inhibit deprotonation at that site (entries 1, 3, and 4). Alternatively, the presence of an appropriately positioned anion stabilizing group at an allylic position or on one of the alkenes may favor deprotonation of one allylic site over the other (entry 2).

In order to further expand the scope of 2,3-Wittig rearrangements of diallyl ethers, several approaches have been examined to achieve selective generation of one allylic anion from a sterically and electronically unbiased diallyl ether. One strategy involves use of samarium diiodide to effect reduction of thioacetals **160** or diallyl ethers **161** to the corresponding carbanions **162**. These compounds then undergo 2,3-Wittig rearrangement to afford **163** (equation 34).[49]



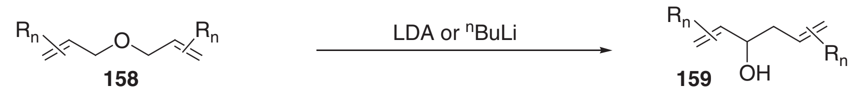
(34)

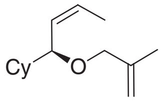
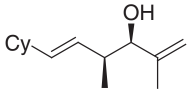
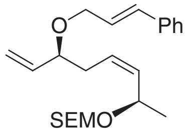
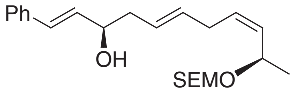
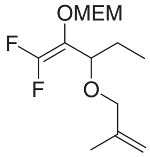
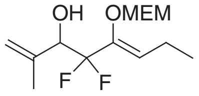
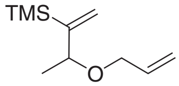
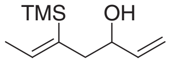
An alternative method for selective anion generation involves reduction of alkenyl halides **164** with excess SmI$_2$. Treatment of **164** with SmI$_2$ leads to formation of vinyl radical **165**, which undergoes 1,5-hydrogen atom transfer to provide radical **166**. The reduction of **166** with SmI$_2$ then yields carbanion **167**, which undergoes 2,3-Wittig rearrangement to **168**. Aqueous workup then affords the alcohol **169** (Scheme 11). These conditions allow for selective 2,3-Wittig rearrangements of molecules **170** bearing two quite similar allylic groups to provide products **171** in good yield (Table 8).[50]

3.21.4.6 Rearrangement of Propargyl Ethers

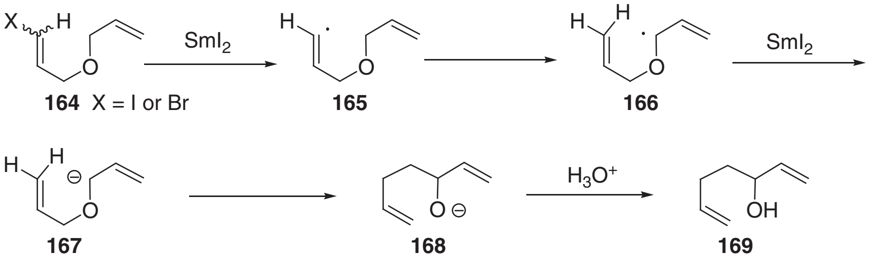
The 2,3-Wittig rearrangement of allyl propargyl ethers is a highly valuable method for generating substituted propargylic alcohols, and is of considerable synthetic utility.[1] These substrates (**172**) generally undergo chemoselective deprotonation at the propargylic position, and rearrangement of the resulting intermediate **173** then affords alkoxide **174**, which gives propargylic alcohol derivatives **175** on aqueous workup (equation 35). Transformations of acyclic alkene derivatives proceed with good to excellent

Table 7 2,3-Wittig rearrangement of diallyl ethers



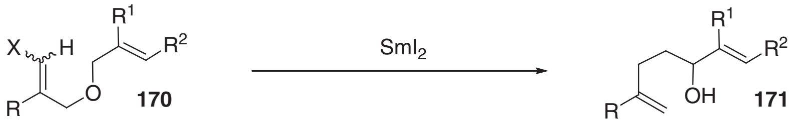
Entry	Substrate	Product	dr	Yield (%)	Reference
1			97:3	90	48a
2			–	74	48b
3			–	84	48c
4			64:36[a]	62	48d

[a] Selectivity for *E*-stereoismer.



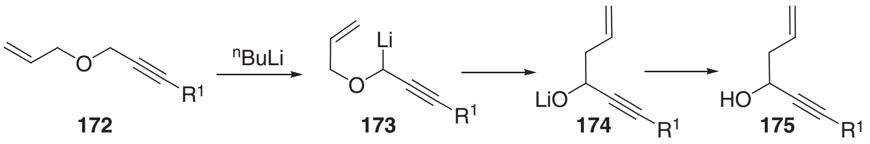
Scheme 11 Anion generation via reduction and 1,5-hydrogen atom transfer.

Table 8 Reductive 2,3-Wittig rearrangement of halogenated diallyl ethers



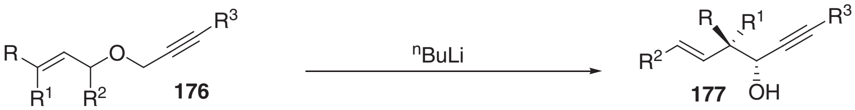
Entry	X	R	R^1	R^2	Yield (%)
1	I	Me	H	^{n}Hept	64
2	Br	Me	H	H	55
3	I	Me	^{n}Hex	H	81
4	Br	^{n}Hex	Me	H	86

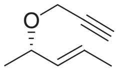
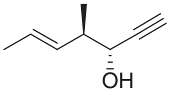
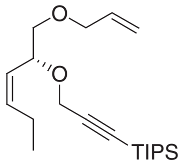
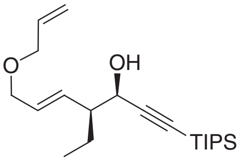
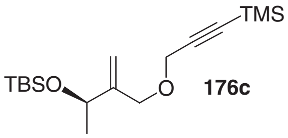
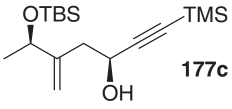
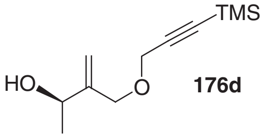
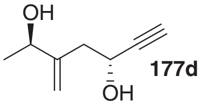
levels of diastereoselectivity, and with efficient transfer of chirality (Table 9). The reactions are stereospecific, with conversion of *E*-alkene derivatives to *anti*-disubstituted products (entry 1), and of *Z*-alkene substrates to *syn*-product stereoisomers (entry 2).[51]



(35)

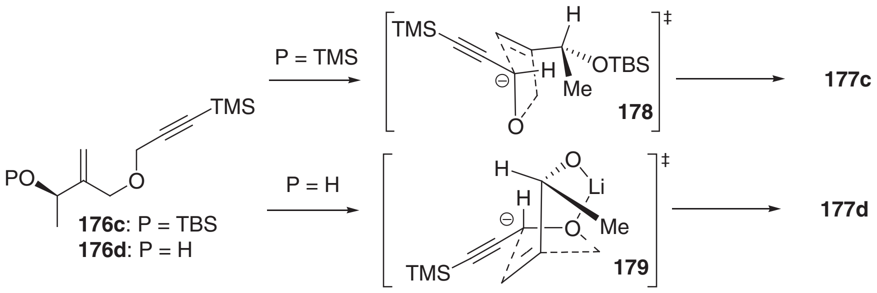
Table 9 2,3-Wittig rearrangement of acyclic allyl propargyl ethers



Entry	*Substrate*	*Product*	*dr*	*Yield (%)*	*Reference*
1			9:1	71	51a
2			>98:2	99	51b
3	 176c	 177c	81:19	92	52
4[a]	 176d	 177d	89:11	86	52

[a] Alkyne desilylation occurred during the course of the reaction.

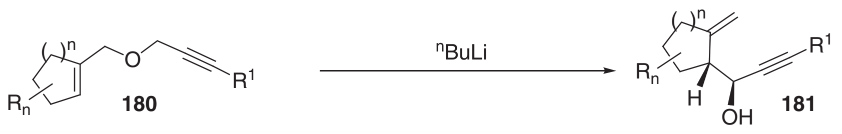
Remote 1,4-asymmetric induction has been achieved in 2,3-Wittig rearrangements of certain acyclic allyl propargyl ethers such as **176c** and **176d** (Table 9, entries 3–4).[52] The stereochemical outcome of these transformations can be controlled by use or omission of a protecting group for the allylic alcohol moiety. Substrate **176c** bearing a silyl protecting group is converted to *syn*-disubstituted product **177c**, whereas the unprotected alcohol substrate **176d** is transformed to the *anti*-stereoisomer **177d**. The reaction of the protected alcohol **176c** proceeds via transition state **178**, in which steric repulsion is minimized. In contrast, the unprotected substrate **176d** is converted to the *anti*-stereoisomer **177d** via transition state **179**, which may be stabilized by chelation of a lithium cation between the two oxygen atoms (Scheme 12).

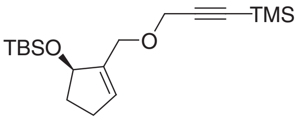
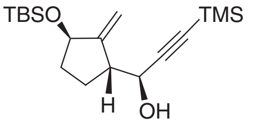
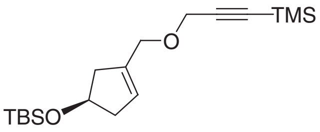
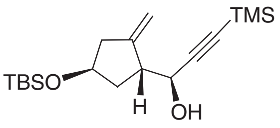
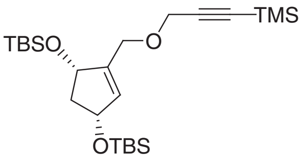
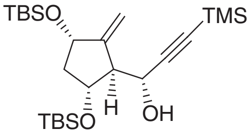
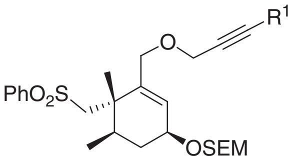
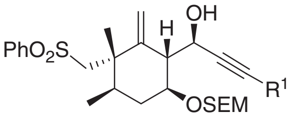


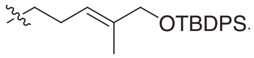
Scheme 12 Stereochemical model for 1,4-asymmetric induction.

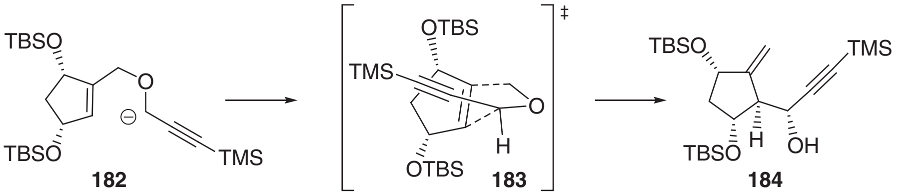
The stereoselective generation of molecules with two contiguous stereocenters where one stereocenter is located on a ring and the other is adjacent to the ring is quite challenging, particularly for carbocyclic systems. The 2,3-Wittig rearrangement of allyl propargyl ethers bearing cycloalkenyl groups has shown considerable utility for the construction of these types of molecules. The transformations are effective with both carbocyclic and heterocyclic alkenes, and can be broadly divided into two categories depending on whether or not the ether linkage is appended to a stereocenter. Allyl propargyl ether starting materials **180** that lack a stereocenter adjacent to the ether oxygen atom are converted to products **181** in good yield with moderate to good diastereoselectivity (Table 10).[53] The reactions are effective with both five- and six-membered cycloalkene derivatives, and can be applied to relatively complex substrates (entry 4). The stereoselectivity in these transformations is controlled by a preference for rearrangement of the propargyl anion (**182**) through transition state **183** (Scheme 13). The major stereoisomer **184** results from approach of the carbanion to the less hindered face of the ring with the alkyne in a pseudoequatorial position. In most instances the presence of a TMS-substituent on the alkyne is required to obtain good stereocontrol.

Table 10 2,3-Wittig rearrangement of cyclic allyl propargyl ethers



Entry	*Substrate*	*Product*	*dr*	*Yield (%)*	*Reference*
1			>20:1	98	53a
2			6:1	77	53b
3			>20:1	90	53c
4[a]			5:1	72	53d

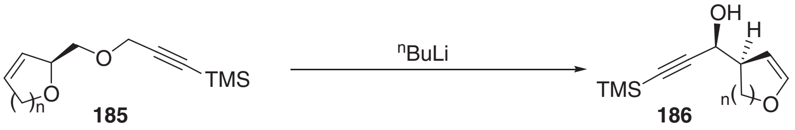
[a] R^1 =


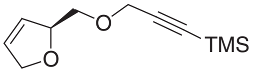
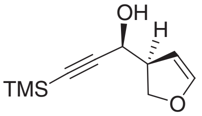
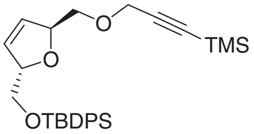
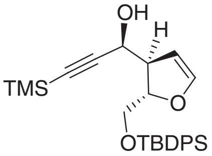
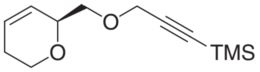
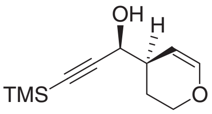


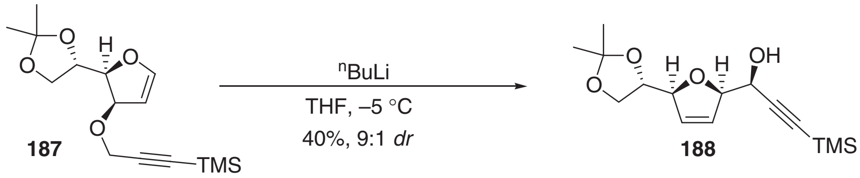
Scheme 13 Stereochemical model for rearrangement of **182**.

The 2,3-Wittig rearrangement of propargyl acetals **185** derived from 2,5-dihydrofuran provides access to substituted 2,3-dihydrofuran derivatives **186** in good yield with good to excellent stereocontrol (Table 11).[54] In these reactions the propargylic anion is delivered with transfer of chirality similar to that observed in the acyclic systems described above. These reactions have also been employed for the stereoselective construction of dihydropyran derivatives (entry 3). The 2,3-Wittig rearrangements of 2,3-dihydrofurans such as **187** have been used for the formation of 2,5-dihydrofuran products (e.g., **188**), although yields and selectivities for these systems are lower than for the 2,3-dihydrofurans (equation 36).[55]

Table 11 2,3-Wittig rearrangement of propargylic dihydrofuranyl and dihydropyranyl ethers



Entry	*Substrate*	*Product*	*dr*	*Yield (%)*
1			>20:1	64
2			>20:1	73
3			>20:1	67



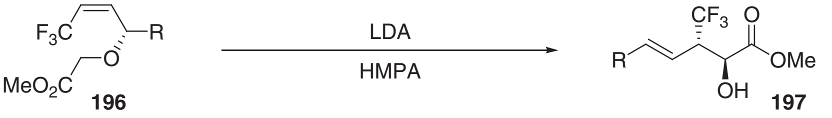
(36)

In contrast to the reactions of allyl propargyl ethers described above, 2,3-Wittig rearrangements of benzyl propargyl ethers are relatively rare. In many instances these substrates undergo preferential deprotonation at the propargylic carbon, which leads to 1,2-Wittig rearrangement. In some cases selective benzylic deprotonation can be achieved, and a few examples of selective 2,3-Wittig rearrangement of thiazole and benzothiazole derivatives **189** have been described. However, the reaction pathway is highly substrate dependent, and competing 1,2-Wittig rearrangement is the major pathway with some derivatives (entry 4). These transformations afford allenic alcohols **191** in moderate to good yield (Table 12).[56]

3.21.4.7 Rearrangement of Enolates

Enolates derived from α-allyloxy acids, esters, and amides undergo 2,3-Wittig rearrangements to yield α-hydroxy carbonyl compounds.[1] For example, treatment of ester **192** with excess LDA leads to the generation of dianion **193**, which is stereoselectively converted to **195** by 2,3-Wittig rearrangement and aqueous workup (Scheme 14).[57] This reaction proceeds via transition state **194**, in which the enolate is in an *endo*-relationship with the alkene π-system (which is commonly observed in enolate 2,3-Wittig rearrangements).

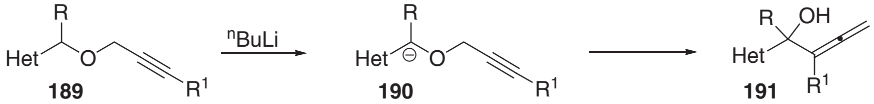
The 2,3-Wittig rearrangement of lithium enolates has been thoroughly explored,[1] and these transformations have found recent applications in the synthesis of α-hydroxy-β-trifluoromethyl esters **197**.[58] When *Z*-allyl ethers **196** are employed as substrates the transformations proceed in high yield, high diastereoselectivity, and essentially complete transfer of chirality (equation 37). However, yields and diastereoselectivities are lower for *E*-allyl ethers.

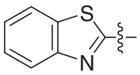
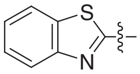
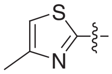
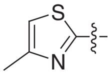


R = CH_2OBn: 73% Yield, >99:1 *dr*, > 98% *ee*
R = C_5H_{11}: 64% Yield, >99:1 *dr*, >98% *ee*

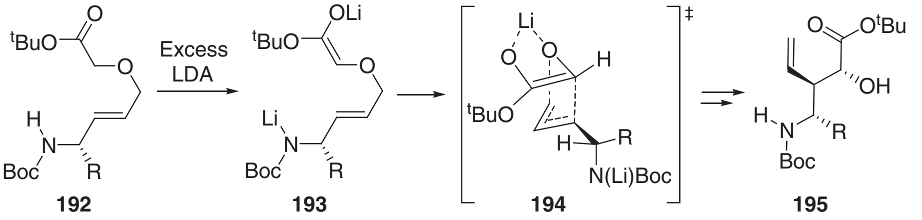
(37)

Table 12 2,3-Wittig rearrangement of heteroaryl propargyl ethers



Entry	*Het*	*R*	*R¹*	*Yield (%)*
1		Me	Ph	54
2		Me	Me	78
3		Ph	Me	79
4		Me	Me	20[a]

[a] 1,2-Witting rearrangement was observed as the major product.

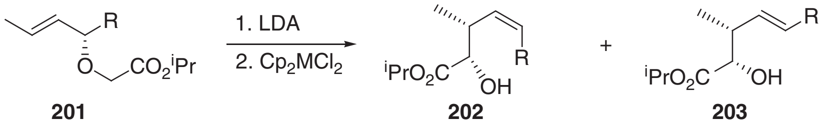


R = Me: 78% Yield, 90:9:1 *dr*
R = ^{i}Pr: 55% Yield, 92:4:4 *dr*

Scheme 14 Stereochemical model for rearrangement of ester enolate **193.**

Early studies on 2,3-Wittig rearrangements were focused on the reactivity of lithium enolates. However, more recent studies have illustrated that titanium, tin, and boron enolates **199** also undergo stereoselective 2,3-Wittig rearrangements (Table 13).[59] In some instances tin, boron, or titanium enolates are much more reactive in 2,3-Wittig rearrangements than the corresponding lithium enolates, and relatively high yields of products **200** are obtained with these derivatives. In many cases diastereoselectivities are also much higher when these other metals are used in place of lithium (entries 1–2).

Zirconium enolates derived from **201** also undergo stereoselective 2,3-Wittig rearrangements. However, the stereochemical outcome of these transformations is opposite of that typically observed for other metal enolates. Treatment of **201** with LDA and Cp_2ZrCl_2 provides *Z*-alkene products **202** with high diastereoselectivities.[59a,60] In contrast, use of LDA and Cp_2TiCl_2 affords *E*-alkenes **203** with modest stereocontrol (equation 38).

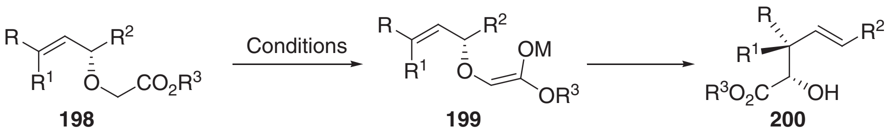


(38)

M = Zr, R = $(CH_2)_2OBn$: 62% yield, 55:1 *dr* (**202**)
M = Ti, R = $(CH_2)_2OBn$: 31% yield, 1:4 *dr* (**203**)
M = Zr, R = CH_3: 91% yield, **202** only

Esters and carboxylic acids bearing α-propargyloxy groups **204** undergo 2,3-Wittig rearrangements via the corresponding enolates to yield substituted allenes **205** or **206** (Table 14).[61] Substrates bearing alkyl groups at the propargylic position rearrange in good yield and with high diastereoselectivity. In contrast derivatives of **204** with $R^1{=}CH_2OBn$ are transformed to 1–2:1 mixtures of diastereomers **205** and **206** with relatively low yield. Isomer **205** is favored in rearrangements of lithium or zirconium enolates (entries 1, 2, and 4), but isomer **206** is the major product in rearrangements of enolsilanes (entries 3 and 5). These latter

Table 13 2,3-Wittig rearrangement of tin, boron, and titanium, enolates



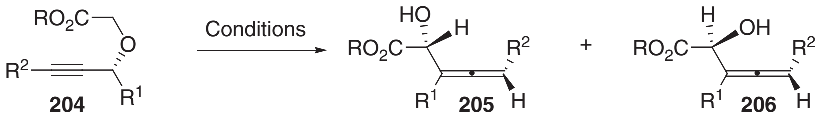
Entry	*R*	*R*^{1}	*R*^{2}	*R*^{3}	*Conditions*	*M*	*dr*[a]	*Yield (%)*	*Reference*
1	Me	H	CH_2OBn	^{i}Pr	LDA	Li	10:10:1	37	59a
2	Me	H	CH_2OBn	^{i}Pr	(a) LDA (b) Cp_2TiCl_2	Cp_2TiCl	58:1:1	72	59a
3	Me	H	H	Me	(a) LDA (b) TMSCl (c) $SnCl_4$[b]	$SnCl_3$	92:8	73	59b
4	Me	H	H	Me	$SnOTf_2$, ^{i}Pr$_2$Net	Sn(OTf)	>99:1	40	59c
5	Me	H	H	Me	Bu_2BOTf, ^{i}Pr$_2$Net	BBu_2	92:8	50	59c
6	H	Me	H	Me	Bu_2BOTf, ^{i}Pr$_2$Net	BBu_2	69:31	66	59c

[a] Diastereomeric ratio refers to ratio of all observed stereoisomers (*syn vs. anti* and *E vs. Z*).

[b] The reaction was conducted using the isolated, purified enolsilane generated in step b.

transformations of enolsilanes are not true anionic 2,3-Wittig rearrangements, but instead involve cationic oxonium ylide intermediates, which are described in more detail in Chapter 3.20.

Table 14 2,3-Wittig rearrangement of a-propargyloxy esters and acids



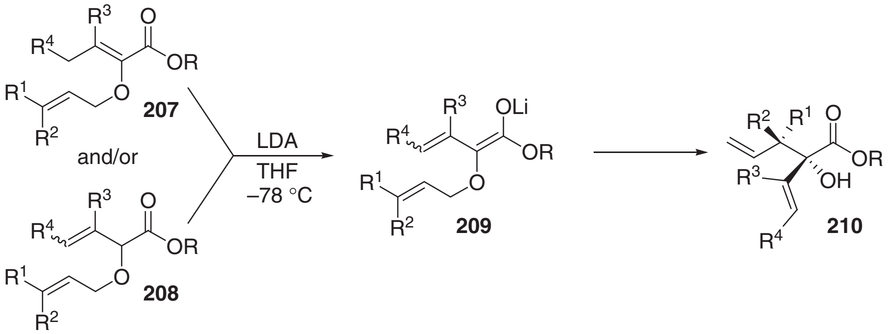
Entry	*R*	*R*^{1}	*R*^{2}	*Conditions*	***205:206***	*Yield (%)*
1	H	Me	C_7H_{15}	2.5 equivalents LDA	93:7	80
2	Me	Me	C_7H_{15}	(a) LDA (b) Cp_2TiCl_2	100:0	57
3	Me	Me	C_7H_{15}	TESOTf, Et_3N	10:90	96
4	H	CH_2OBn	C_7H_{15}	2.5 equivalents LDA	60:40	21
5	Me	CH_2OBn	C_7H_{15}	TESOTf, Et_3N	33:67	67

Many other recent studies on the 2,3-Wittig rearrangement of enolates and related stabilized carbanions have been focused on substrates bearing chiral auxiliaries or enol ether derived alkenes. These transformations are described below in Sections 3.21.4.9 and 3.21.4.11.

3.21.4.8 Rearrangement of Dienolates

The ester dienolate 2,3-Wittig rearrangement was developed by Hiersemann and was initially reported in 1999.[62,63] These transformations involve either γ-deprotonation of α,β-unsaturated ester **207** or α-deprotonation of γ,δ-unsaturated ester **208** to form dienolate **209**. Although substrates **207** and **208** are frequently prepared as mixtures, the mixture of **207**/**208** may be employed directly in the generation of **209**. On formation, dienolate **209** undergoes 2,3-Wittig rearrangement, and subsequent aqueous workup then affords product **210** (Scheme 15).

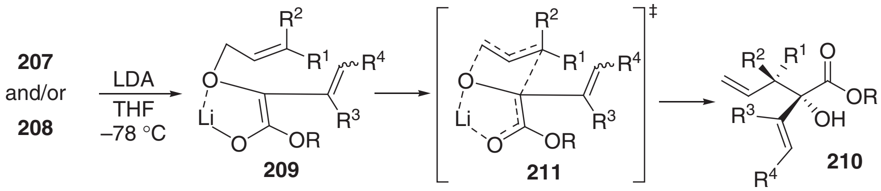
The dienolate 2,3-Wittig rearrangement reactions proceed with good to excellent *syn*:*anti* diastereoselectivity, with the major stereoisomer dependent on the *E*/*Z* configuration of the allylic ether (Table 15). The stereochemical outcome of these reactions is believed to result from rearrangement via the cyclic transition state **211** in which the lithium atom is chelated between the enolate oxygen atom and the neighboring ether oxygen atom. Endo orientation of the enolate with respect to the alkene π-system is favored in this transition state, which leads to generation of the observed product stereoisomer **210**. The dienolate 2,3-Wittig rearrangements generally limited to substrates **207**/**208** where $R^4 = H$ or R^3 and R^4 are linked together in a ring. Most substrates in which $R^4 \neq H$ are converted to mixtures of *E*/*Z* alkene stereoisomers. However, a substrate with $R^4 = OBn$ represents a

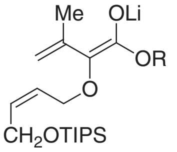
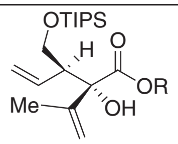
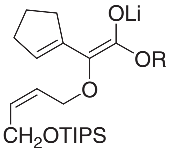
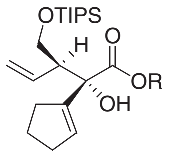
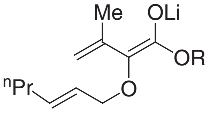
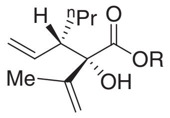
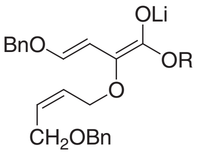
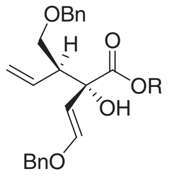


Scheme 15 Ester dienolate 2,3-Wittig rearrangement.

notable exception, as rearrangement occurred with high selectivity for the *E*-alkene product (entry 4). This latter reaction was used for the preparation of a key intermediate in a total synthesis of the natural product viridiofungin A.[64]

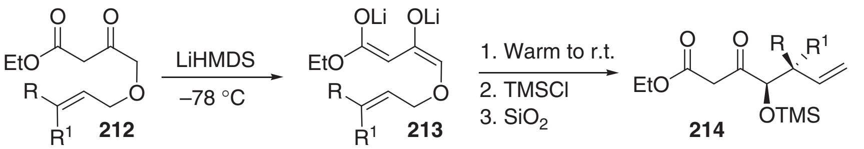
Table 15 Ester dienolate 2,3-Wittig rearrangement



Entry	*Dienolate*[a]	*Product*	*dr*	*Yield (%)*	*Reference*
1[a]			>95:5	92	63a
2[b]			>95:5	90	63a
3[b]			93:7	90	63b
4[c]			95:5	55	64

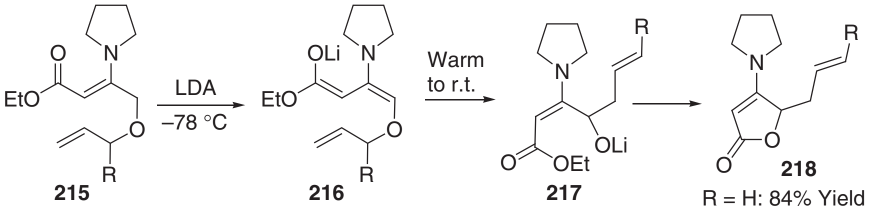
[a] Generated via deprotonation of **207** or **208** with **LDA.**
[b] R = (-)-menthyl.
[c] R = ^{i}Pr.

The generation of dianionic dienolates **213** has been accomplished by deprotonation of *γ*-allyloxy-*β*-ketoesters **212** with excess LiHMDS. These dienolates undergo 2,3-Wittig rearrangement to provide products **214** with moderate to good diastereoselectivity (equation 39).[65] Substrates **212** bearing *E*-disubstituted alkenes are converted to **214** with considerably higher stereocontrol than the analogous *Z*-alkene substrates. Related dieneolates **216** prepared by deprotonation of enamines derived from *β*-ketoesters (**215**) undergo 2,3-Wittig rearrangement to generate intermediate alkoxides **217**. These alkoxide products then undergo intramolecular esterification to yield lactones **218** (equation 40).[66]



R = Me, R^1 = H: 64% yield, 87:13 *dr*
R = CH_2OPMB, R^1 = H: 89% yield, 94:6 *dr*
R = H, R^1 = CH_2OPMB: 79% yield, 4:1 *dr*

(39)

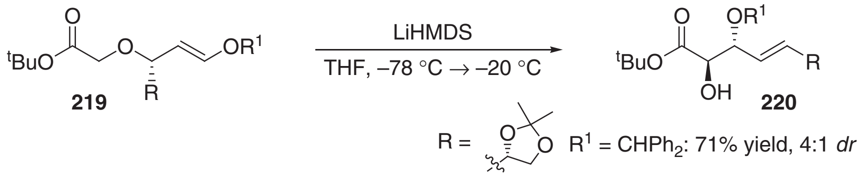


R = H: 84% Yield
R = Me: 72% Yield

(40)

3.21.4.9 Rearrangements of Enol Ethers and Enamines

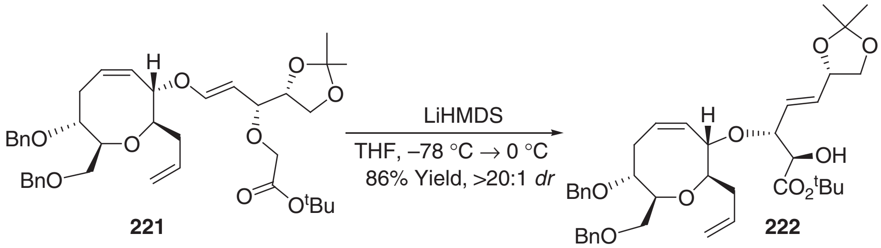
2,3-Wittig rearrangements of allylic ethers bearing alkoxy or amino groups on the alkene moiety are relatively rare. However, these transformations provide an interesting and stereoselective route to 1,2-alkoxy alcohols and 1,2-amino alcohols. For example, the 2,3-Wittig rearrangement of simple enol ethers bearing pendant α-alkoxy esters (**219**) provides α-hydroxy-*β*-alkoxy esters **220** in good chemical yields but with moderate diastereoselectivity (equation 41).[67] However, the more complex substrate **221** underwent 2,3-Wittig rearrangement to afford **222** with excellent stereoselectivity. The rearranged product **222** was subsequently used in a recent approach to the EF-ring system of ciguatoxin 3C (equation 42).[67] The 2,3-Wittig rearrangement of *β*-ketoester-derived enamine **223** (via the corresponding dienolate as shown above in equation 40) provided lactone **224** in good yield and 95:5 *dr* (equation 43).[66] Importantly, this transformation leads to the stereocontrolled formation of two rings attached by a sigma bond with stereocenters at both points of attachment. This structural feature is common in many biologically active natural products, but the stereocontrolled generation of these ring systems is often quite challenging.



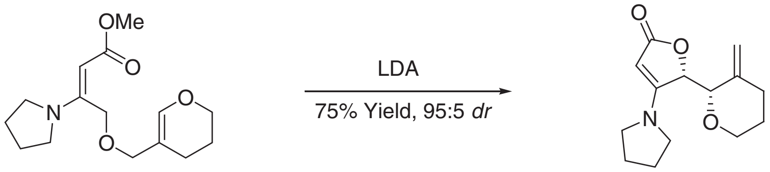
R^1 = $CHPh_2$: 71% yield, 4:1 *dr*

R = ^{i}Pr, R^1 = Bn: 86% yield, 1:1 *dr*

(41)

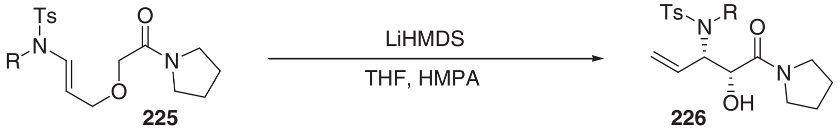


(42)



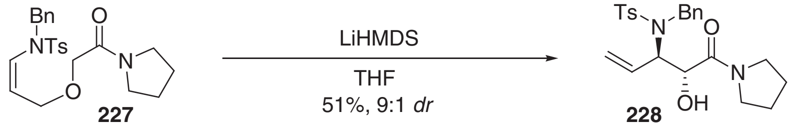
(43)

N-Tosyl enamines derived from α-alkoxy amides undergo stereoselective 2,3-Wittig rearrangement to provide 1,2-amino alcohol derivatives.[68] The rearrangement of substrates **225** bearing *E*-enamines affords *syn*-disubstituted products **226** (equation 44). The use of HMPA or DMPU as cosolvent is required to obtain high diastereoselectivity in transformations of *E*-enamine derivatives. The analogous *Z*-enamine derivative **227** was transformed to *anti*-amino alcohol **228** in moderate yield with synthetically useful diastereoselectivity (equation 45). Use of HMPA in reactions of the *Z*-enamines led to complex mixtures of products, but acceptable results were obtained without this cosolvent.



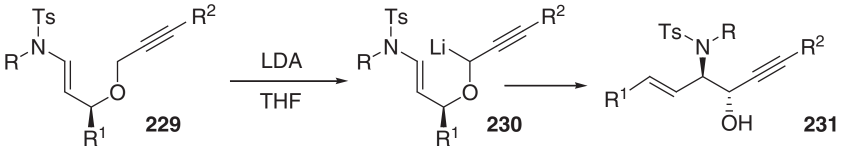
R = Bn: 77% yield, >24:1 *dr*
R = Allyl: 75% yield, >24:1 *dr*

(44)



(45)

Propargyl ethers **229** that are derived from *N*-tosyl-3-aminoallyl alcohols undergo selective lithiation at the propargylic position to generate **230**. The 2,3-Wittig rearrangement of **230** then affords *anti*-amino alcohols **231** (equation 46).[68b] The reactions proceed in good chemical yields with high diastereoselectivities, and chirality transfer is nearly complete for enantiomerically enriched substrates.

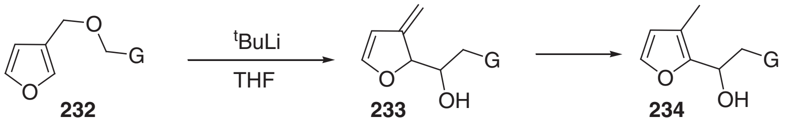


97% *ee* for R^1 = H

R = Bn, R^1 = H, R^2 = TMS: 92% yield, 13:1 *dr*
R = Allyl, R^1 = H, R^2 = TIPS: 89% yield, >24:1 *dr*
R = Bn, R^1 = CH_2OPMB, R^3 = TMS: 76% yield, 9:1 *dr*, >90% *ee*

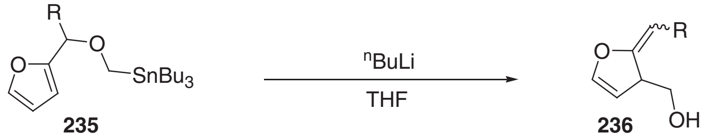
(46)

Furans, although aromatic, exhibit some reactivities that are similar to those of enol ethers (e.g., hydrolysis to aldehydes/ketones on treatment with strong aqueous acid). Furans have also been shown to undergo 2,3-Wittig rearrangement reactions, although many of these transformations also produce side products resulting from competing 1,2-Wittig rearrangement. Some 3-furylmethyl ethers **232** undergo 2,3-Wittig rearrangement to initially generate **233**. However, rearomatization occurs after rearrangement to afford hydroxymethyl furan derivatives **234** (equation 47).[69] In contrast, 2-furylmethyl ethers **235** undergo 2,3-Wittig rearrangement to afford products **236** that usually do not undergo rearomatization (equation 48).[70] However, substitution at the carbon adjacent to the furan ring (R≠H) is necessary to obtain useful yields of products.



G = $CH{=}CH_2$: 95%
G = Ph: 64%

(47)



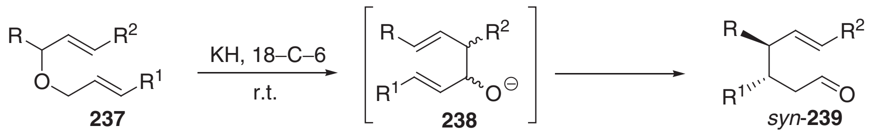
R = Me: 50%
R = Cy: 66%
R = H: 20%

(48)

3.21.4.10 Cascade 2,3-Wittig/3,3-Oxy-Cope Rearrangements

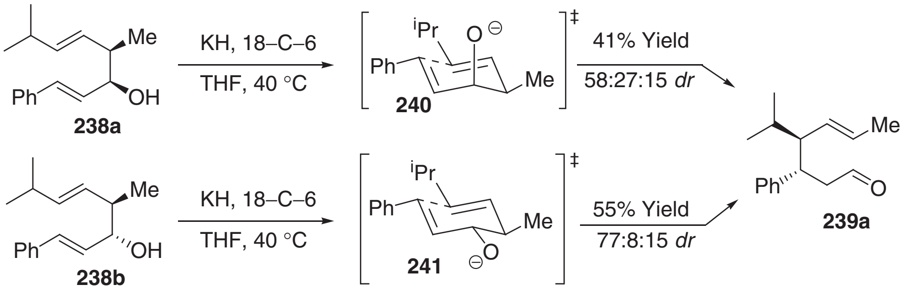
The 2,3-Wittig rearrangement of diallyl ether derivatives leads to the formation of 1,5-dienes, which can undergo subsequent 3,3-sigmatropic rearrangement (*see* Chapters 5.20 and 5.21).[1] The most common cascade sequence of this type involves oxy-Cope rearrangement of intermediates **238** that are formed on 2,3-Wittig rearrangement of **237** (Table 16).[71] These transformations lead to the generation of substituted aldehydes **239** with moderate to good stereocontrol. The stereoselectivity of the Wittig rearrangement step has only a modest effect on the overall outcome of the cascade reaction (Scheme 16).[71b] For example, the anionic oxy-Cope rearrangement of *syn*-disubstituted alcohol **238a** and *anti*-disubstituted alcohol **238b**, which would be generated as intermediates in the cascade Wittig rearrangement/anionic oxy-Cope rearrangement of **237** (Table 1, entry 4) both provided **239a** as the major product, although there were slight differences in product distributions. The slightly lower stereoselectivities observed in the reaction of **238a** may result from axial orientation of the alkoxide in the transition state **240** for oxy-Cope rearrangement. This destabilizes the transition state **240**, and decreases the difference in energies between this transition state and transition states leading to other stereoisomers.

Table 16 Cascade 2,3 Wittig rearrangement/anionic oxy-Cope rearrangement



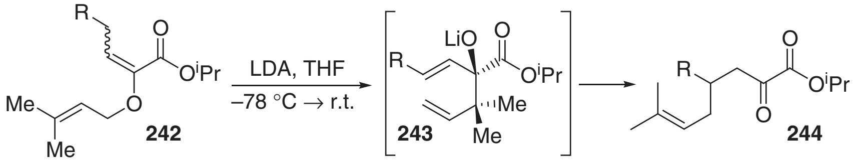
Entry	*R*	*R¹*	*R²*	*Yield (%)*	*Product Ratio (E-Syn : Z-Syn : E-anti)*	*Reference*
1	H	Ph	Me	76	3:1 (*E*:*Z*)	71a
2[a]	H	TMS	Me	50	62:38 (*E*:*Z*)	71a
3	H	Ph	^{i}Pr	67	100:0 (*E*:*Z*)	71a
4	^{i}Pr	Ph	Me	52	71:18:11	71b
5	^{i}Pr	Ph	^{n}Bu	55	78:17:5	71b
6	^{i}Pr	Ph	H	50	6:1 (*syn*:*anti*)	71c

[a] The substrate was used as a 78:22 mixture of *E*:*Z* stereoisomers.



Scheme 16 Stereocontrol in anionic oxy-Cope rearrangement.

Deprotonation of *O*-allyl esters **242** leads to the formation of the corresponding dienolates (as described in Section 3.21.4.8), which then undergo 2,3-Wittig rearrangement to yield **243**. This intermediate then is transformed to α-keto esters **244** by anionic oxy-Cope rearrangement (equation 49).[72] However, the presence of the *gem*-dimethyl group on the allyl moiety in substrates **242** is essential for high reactivity in the oxy-Cope rearrangement. Substrates bearing only one alkene substituent undergo 2,3-Wittig rearrangement in high yield, but the resulting products must be heated to 150 °C to induce the oxy-Cope rearrangement.



R = H: 84%
R = Ph: 88%
R = Me: 40%

(49)

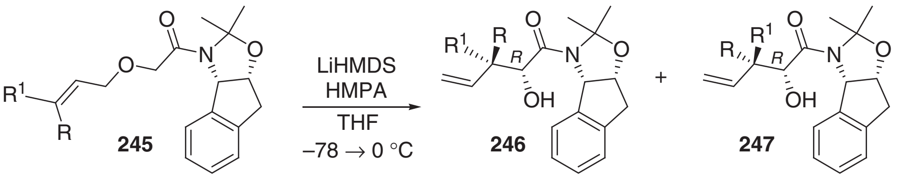
3.21.4.11 Enantioselective 2,3-Wittig Rearrangements

3.21.4.11.1 Strategies that utilize chiral auxiliaries

The 2,3-Wittig rearrangement of many allylic ether derivatives leads to the formation of chiral homoallylic alcohol products with 1–2 stereocenters. As noted above, the diastereoselectivities in these reactions are frequently high. However, under typical reaction conditions racemic products are generated. Given the significance of the products formed in these reactions there has been considerable effort dedicated to the development of enantioselective variants of the 2,3-Wittig rearrangement.[1,73] Initial work in this area was focused on the use of chiral auxiliaries to control asymmetric induction, and a number of chiral esters, amides, and oxazolines were examined as outlined in the first edition of Comprehensive Organic Synthesis.[1] Many approaches provided either modest asymmetric induction or led to mixtures of *syn*/*anti* stereoisomers. However, more recent studies in this area have led to significant improvements.

Lithium enolates derived from (1*S*,2*R*)-1-amino-2-indanol amide **245** undergo 2,3-Wittig rearrangement to provide disubstituted α-hydroxy amides **246** or **247** with good control of stereoselectivity (Table 17).[74] In all instances high selectivity was observed for the formation of products **246** and **247**, which possess the 2*R* configuration. The selectivity was determined to be >98:2 favoring the 2*R* configuration for a terminal alkene substrate (entry 1). Substrates bearing *E*-alkenes were converted to **246** with high *syn*:*anti* diastereoselectivity (entries 2–4). However, transformations of analogous *Z*-alkenes proceed with low selectivity (entry 5). Rearrangements of enamines (R^1 = NTs) occur with selectivities comparable to those obtained with other alkene substrates (entry 6).[68b]

Table 17 Asymmetric Wittig rearrangement of aminoindanol-derived amides



Entry	*R*	*R¹*	*Yield (%)*	***246:247***	*Reference*
1	H	H	95	>98% 2*R*	74
2	H	Me	97	90:10	74
3	H	Et	96	87:13	74
4	H	Ph	87	91:9	74
5	Et	H	93	32:68	74
6[a]	H	TsN(allyl)	80	94:6	68b

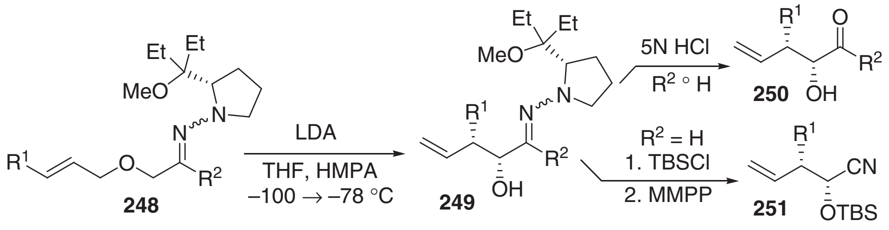
[a] The 1*R*,2*S* substrate stereoisomer (*ent*-**245**) was converted to *ent*-**246.**

Hydrazones **248**, which are referred to as SAEP hydrazones [SAEP = (*S*)-1-amino-2-(1-ethyl-1-methoxypyropyl)pyrrolidine] have been shown to undergo highly stereoselective 2,3-Wittig rearrangement reactions to afford α-1-amino-2-(1-ethyl-**249** (Table 18).[75] In transformations that employ ketone-derived hydrazones, intermediates **249** are hydrolyzed with aqueous acid to yield enantiomerically enriched α-hydroxy ketones **250** in good yield. The *syn*-disubstituted products are generated with high diastereoselectivity and with high *ee* (entries 1–3). Hydrazones **252** obtained from cyclic ketones also undergo stereoselective 2,3-Wittig rearrangement, and treatment of the resulting products **253** with aqueous acid provides **254** in good yield and with high *ee* (equation 50).[76] However, diastereoselectivities are slightly lower than in analogous reactions of acyclic ketones.

When aldehyde-derived hydrazones are used as starting materials the intermediates **249** generated in the 2,3-Wittig rearrangements of **248** (R = H) can be converted to enantiomerically enriched α-hydroxy nitriles **251** (Table 18, entries 4–6). This is advantageous over simple hydrolysis to the corresponding aldehydes, as α-hydroxy nitriles are easier to handle and are less prone to epimerization than α-hydroxy aldehydes. If desired, the nitrile products can subsequently be reduced to aldehydes under mild conditions that prevent epimerization.

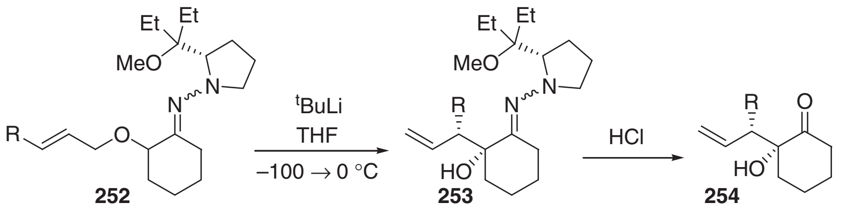
The 2,3-Wittig rearrangements of anions **255** generated by deprotonation of SAEP hydrazones **248** are believed to proceed via transition state **256** (Scheme 17).[75a] In this transition state the alkene approaches the carbanion away from the bulky substituent on the pyrrolidine ring, and the R^1 group is positioned in an endo orientation respect to the anion π-system. In addition, there is a favorable interaction between the lithium cation and the alkoxy substituent on the pyrrolidine. The 2,3-rearrangement of **255** by this pathway leads to formation of the observed major stereoisomers **249**.

Table 18 Asymmetric Wittig rearrangement of SAEP hydrazones



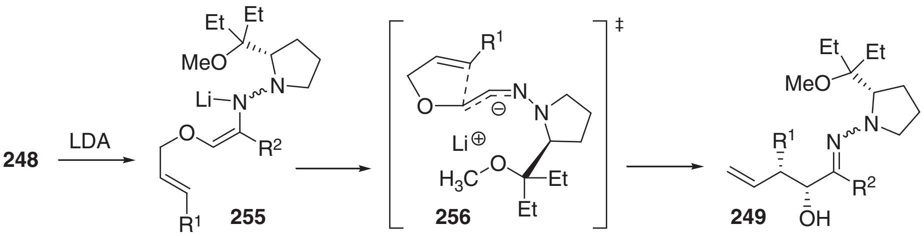
Entry	*R¹*	*R²*	*dr*[a]	*Yield (%)* ***250*** *or* ***251***	*ee (%)*	*Reference*
1	Me	Et	97:3	76 (**250**)	81	75a
2	Me	Ph	90:10	97 (**250**)	90	75a
3	^{n}Pr	Ph	94:6	99 (**250**)	90	75a
4	Me	H	$>$98:2	77 (**251**)	96	75b
5	Et	H	93:7	68 (**251**)	97	75b
6	^{i}Pr	H	88:12	83 (**251**)	95	75b

[a]Ratio of *syn* vs. *anti* product stereoisomers of **250** or **251**.



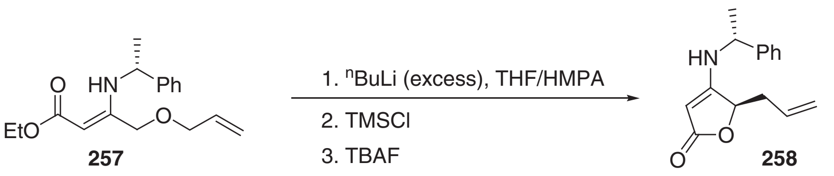
R = Me: 65% Yield, 88:12 *dr*, 96% *ee*
R = ^{i}Pr: 61% Yield, 88:12 *dr*, 96% *ee*

(50)



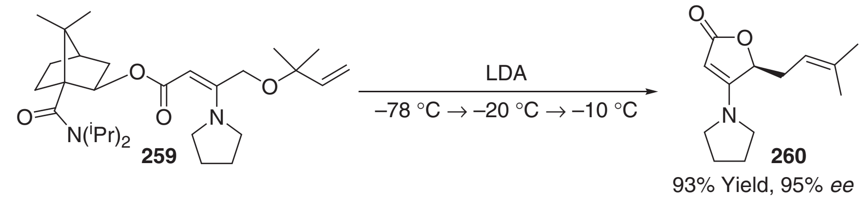
Scheme 17 Stereochemical model.

Two different approaches have been used to control asymmetric induction in 2,3-Wittig rearrangements of dienolates derived from γ-allyloxy-β-enaminoesters. The first approach employed enamine substrate **257** derived from a chiral amine. However, this strategy resulted in the formation of **258** with only modest stereoselectivity (equation 51).[77] A second strategy, which led to much better asymmetric induction, involved use of the chiral ester **259**. The 2,3-Wittig rearrangement of **259** resulted in the formation of **260** in excellent yield with high enantioselectivity (equation 52). In addition, the chiral auxiliary was spontaneously cleaved during the lactonization step, thus alleviating the need to remove the auxiliary in a subsequent manipulation.[78]



64% Yield, 88:12 *dr*

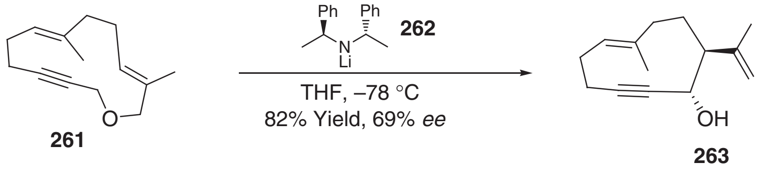
(51)



(52)

3.21.4.11.2 Strategies that utilize chiral bases

Although chiral auxiliaries have proven useful in 2,3-Wittig rearrangement reactions, this strategy is inherently limited in scope. Installation of a chiral auxiliary on a carbonyl-containing substrate is fairly straightforward. Simple acyl-transfer chemistry can be used to generate a chiral ester or amide, and ketones and aldehydes can easily be transformed to chiral hydrazones. However, for allyl ether derivatives that lack carbonyl functionality it is neither easy nor practical to insert a chiral auxiliary into the starting material. To circumvent this limitation, a different approach has been developed to effect enantioselective 2,3-Wittig rearrangement reactions. This strategy involves the use of a chiral base to achieve the stereoselective lithiation of an allylic ether. Early studies in this area employed chiral lithium dialkylamide reagents such as **262** for the stereoselective metallation of substrates such as **261**, **264**, or **266**. (equations 53–55).[1,79] In many instances, such as the formation of **263** or **265**, levels of asymmetric induction and/or chemical yields were modest. However, good results were obtained in some systems (e.g., **267**).



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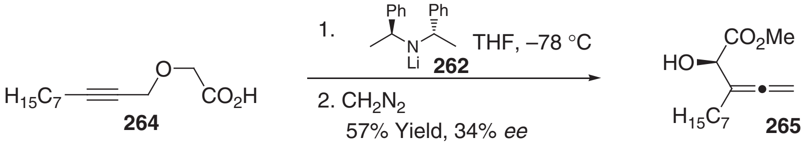

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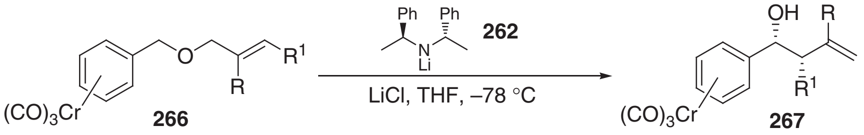
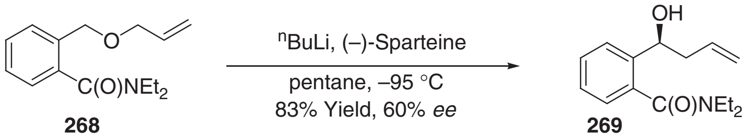


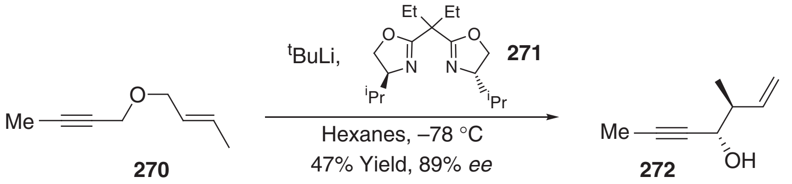
(55)

R, R^1 = H: 80% yield, 96% *ee*
R = Me, R^1 = H: 33% yield, 91% *ee*
R = H, R^1 = Me: 82% yield, 96% *ee*, 19:1 *dr*

In more recent years several groups have developed asymmetric 2,3-Wittig rearrangements in which mixtures of organolithium reagents and chiral ligands are used to effect the stereoselective lithiation of an allylic ether. The naturally occurring alkaloid (–)-sparteine has been employed as a chiral ligand in these transformations, and has provided modest stereocontrol in some systems such as the conversion of **268** to **269** (equation 56).[80] However, the best yields and selectivities in these transformations have been obtained using chiral bis(oxazolines) such as **271** and **274** as ligands. These bis(oxazoline) ligands have been shown to promote highly selective 2,3-Wittig rearrangements of allyl(propargyl) ethers such as **270** (equation 57)[81a] and allyl(benzyl) ethers **273** (equation 58).[81b,82] Although stereocontrol is not perfect, enantioselectivities of up to 98% ee have been achieved in the best cases.[82b] In some instances use of a catalytic amount of the chiral ligand **274** is feasible, although chemical yields are diminished under these conditions (equation 58).[82a]



(56)



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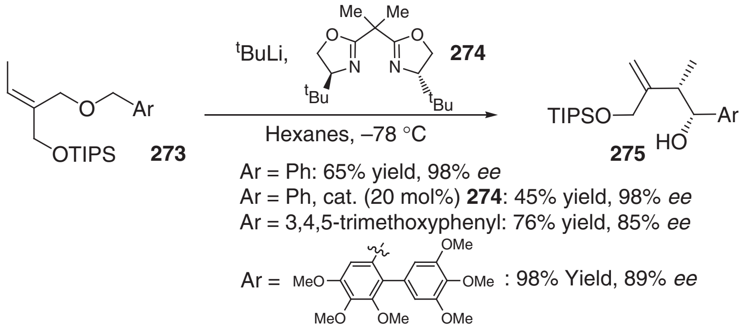


Ar = Ph: 65% yield, 98% *ee*
Ar = Ph, cat. (20 mol%) **274**: 45% yield, 98% *ee*
Ar = 3,4,5-trimethoxyphenyl: 76% yield, 85% *ee*

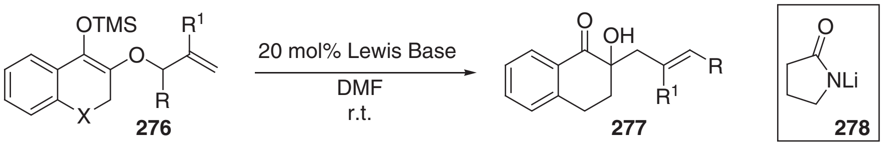
(58)

3.21.4.12 Catalytic 2,3-Wittig Rearrangements

Nearly all 2,3-Wittig rearrangements require the use of a stoichiometric amount of a base, and the enantioselective transformations described above usually also require stoichiometric amounts of chiral reagents or ligands. Catalytic 2,3-Wittig rearrangements are quite rare, but future studies in this area could be of great significance. For example, a catalytic asymmetric 2,3-Wittig rearrangement would require only a small amount of chiral material to effect asymmetric induction, and a Wittig rearrangement induced by a catalyst rather than a strong base may exhibit improved functional group tolerance.

Thus far, two strategies have been examined to effect catalytic 2,3-Wittig rearrangements. The first employs Lewis bases as catalysts for rearrangements of enolsilanes **276** (Table 19)[83] or silyl ketene acetals **279** (Table 20).[83b,84] In the absence of a catalyst, substrates **276** and **279** undergo 3,3-sigmatropic rearrangements (*see* Chapters 5.20 and 5.21). However, use of either LiHMDS, sodium 2-pyrrolidone **278**, metal alkoxides, or tetrabutylammonium carboxylates as catalysts leads to high selectivity for formation of the 2,3-rearrangement products **277** and **280**. In most instances the reactions proceed in good chemical yields. However, the diastereoselectivity of these transformations has not yet been explored. The identity of the true catalyst for these rearrangements is not entirely clear, as the alkoxide products initially formed in these reactions are also competent catalysts, and these species may be responsible for propagation of the catalytic cycle.[83a]

Table 19 Lewis base catalyzed Wittig rearrangement of enolsilanes

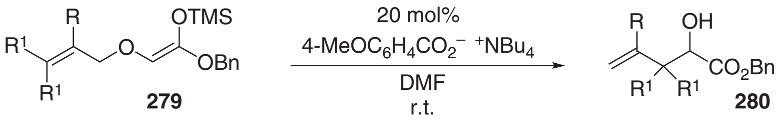


Entry	*R*	*R¹*	*X*	*Lewis Base*	*Yield (%)*	*Reference*
1	H	Me	CH_2	LiHMDS	84	83b
2	Me	H	CH_2	**278**	76	83b
3	H	H	CH_2	**278**	93	83b
4[a]	H	H	O	LiOBn	79	83a

[a] The substrate contained a TES ether rather than a TMS ether, and 10 mol% catalyst loading was employed.

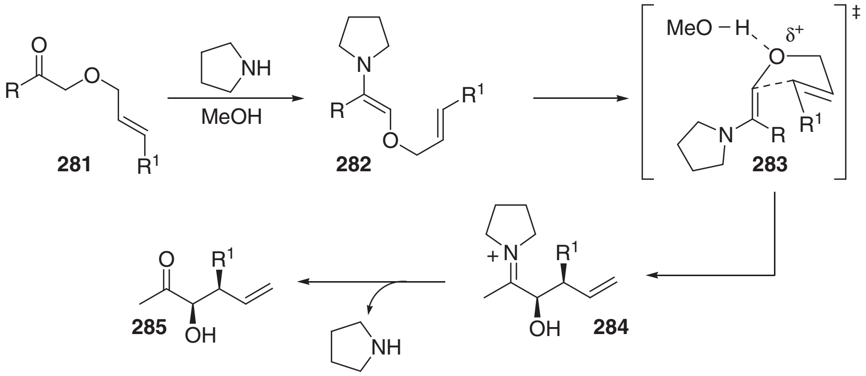
A second recent and intriguing strategy used to achieve catalytic 2,3-Wittig rearrangements involves the use of pyrrolidine as an organocatalyst in reactions of *O*-allyl-α-alkoxy ketone derivatives **281**.[85] The ketone first reacts with the amine catalyst to generate intermediate enamine **282**, which contains the thermodynamically favored *E*-enamine geometry. Intermediate **282** undergoes facile 2,3-Wittig rearrangement at or below room temperature to yield *syn*-disubstituted imininium ion **284**. Hydrolysis of iminium ion **284** then affords the α-hydroxy ketone product with regeneration of the pyrrolidine catalyst Scheme 18).

Table 20 Lewis base catalyzed Wittig rearrangement of silyl ketene acetals



Entry	*R*	*R¹*	*Yield (%)*	*Reference*
1	H	H	83	84
2	Me	H	40	83b
3	Cl	H	80	83b
4	Me	Me	17	83b

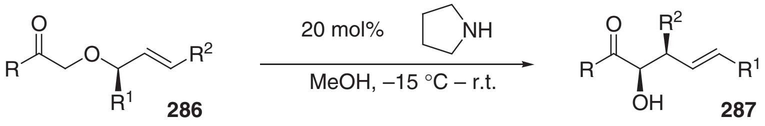
The rearrangement of 282 is believed to proceed via transition state 283, in which the enamine is in an *endo* position with respect to the alkene π-system. Hydrogen bonding between the methanol solvent and the substrate is believed to accelerate the rearrangement through stabilization of the developing charge in the transition state.

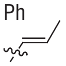


Scheme 18 Mechanism of pyrrolidine-catalyzed 2,3- Wittig rearrangement.

The pyrrolidine-catalyzed 2,3-Wittig rearrangements of 286 to 287 proceed in good yield for a variety of different substrates, although diastereoselectivities are modest (Table 21). However, chirality transfer is highly efficient; only slight loss of optical purity is observed with an enantiopure substrate (entry 1).

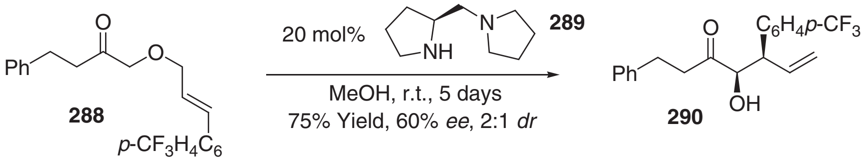
Table 21 Pyrrolidine-catalyzed 2,3-Wittig rearrangement



Entry	*R*	*R¹*	*R²*	*dr*	*Yield (%)*
1[a]	Me	Me	C_6H_4-*p*CF_3	4:1	86
2	Et	H	Ph	6:1	92
3	Me	H		3.5:1	82
4	Me	H	-§≡TIPS	1:1	84

[a] Substrate **286** = 94% *ee*; product **287** = 92% *ee*.

Preliminary studies on the use of chiral pyrrolidine 289 as a catalyst for the asymmetric 2,3-Wittig rearrangement of 288 have provided promising initial results, and illustrate the feasibility of the enantioselective reaction. However, reaction rates are slow and product **290** was generated with modest enantioselectivity (equation 59). Thus, further improvement of the catalyst will be necessary to achieve a practical and useful transformation.

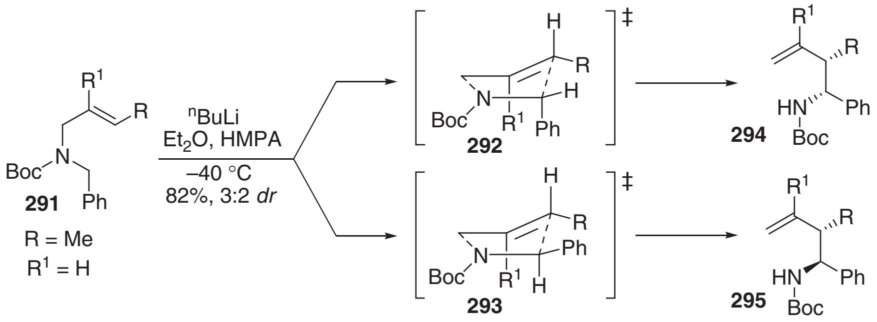


(59)

3.21.4.13 Aza-2,3-Wittig Rearrangements

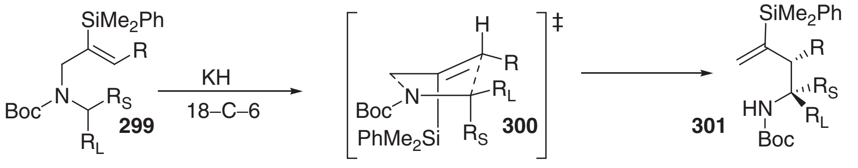
The aza-2,3-Wittig rearrangement is the amino analog of the classical 2,3-Wittig rearrangement, and involves conversion of a tertiary allylic amine to a secondary homoallylic amine.[86] These transformations are less common than 2,3-Wittig rearrangements of allylic ethers, but nonetheless provide a synthetically useful entry into substituted acyclic and cyclic secondary amines.

The first example of aza-2,3-Wittig rearrangement of an acyclic allylamine derivative was reported in 1995 by Anderson (Scheme 19). The rearrangement of **291** proceeded in good yield, but diastereoselectivity was poor and a 3:2 mixture of **294** and **295** was obtained.[87] The low stereocontrol in this reaction was attributed to the small difference in energies between transition states **292** and **293**. In principle transition state **292** should be destabilized by a 1,3-diaxial interaction between R^1 and the phenyl group. However, when R^1 is a small group such as a hydrogen atom, this diaxial interaction has relatively little effect on the relative transition state energies of **292** vs. **293**.



Scheme 19 The aza-2,3-Wittig rearrangement.

Subsequent studies indicated that substrates **296** bearing sterically bulky silyl groups as R^1 undergo aza-2,3-Wittig rearrangement to provide *anti*-disubstituted products **298** with considerably higher stereoselectivity than for substrates where $R^1=H$ (Table 22).[88] In transformations of **296** the transition state analogous to **292** is destabilized due to steric interactions between R^1 and G (the anion-stabilizing group). Substrates bearing ester, amide, or alkyne anion stabilizing groups undergo rearrangement in good yield with good to excellent diastereoselectivity (entries 4–6). However, the reactions are less effective with other stabilizing groups such as nitriles (3:1 *dr*) or ketones (no reaction). Substitution of α to the anion-stabilizing group is tolerated, as substrates **299** are converted to trisubstituted products **301** with good yields and diastereoselectivities (equation 60). In these transformations the major product results from pseudoequatorial orientation of the larger group (R_L) in transition state **300**.[89]

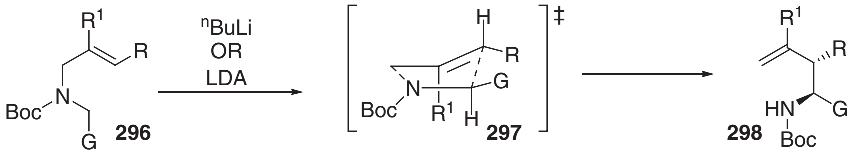


(60)

$R_L = CONEt_2$, $R_S = Me$: 77% yield, >20:1 *dr*
$R_L = Me$, $R_S = CO_2Me$: 77% yield, 7:1 *dr*
$R_L = {}^iPr$, $R_S = CO_2Me$: 72% yield, >20:1 *dr*

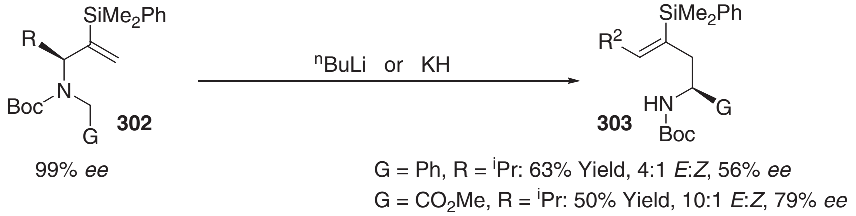
The aza-2,3-Wittig rearrangement proceeds with transfer of chirality, albeit much less efficiently than the analogous rearrangements of allylic ethers. For example, treatment of enantiomerically pure (99% *ee*) substrate **302** with a strong base leads to

Table 22 Aza-2,3-Wittig rearrangements of acyclic amines



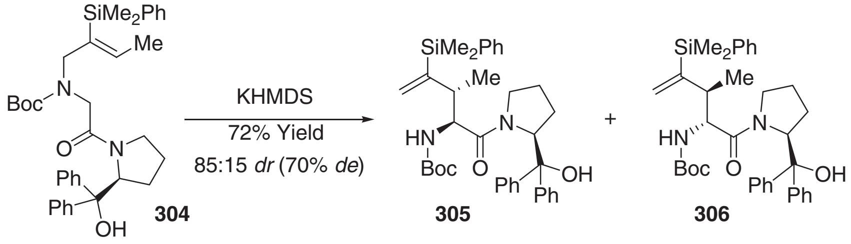
Entry	G	R	R^1	dr	Yield (%)	Reference
1	Ph	Me	TMS	> 20:1	88	88a
2	Ph	^{i}Pr	TMS	11:1	94	88a
3	Ph	Et	TMS	18:1	92	88a
4	CN	Me	Me_2PhSi	3:1	67	88b
5	CO_2Me	Me	Me_2PhSi	> 20:1	70	88b
6	$CONMe_2$	Me	Me_2PhSi	> 20:1	71	88b
7	$-\equiv-$TMS	Me	Me_2PhSi	10:1	77	88b

formation of **303** with significantly diminished optical purity (equation 61).[90] The presence of a bulky silyl substituent at the internal alkene carbon is required to avoid the formation of mixtures of alkene stereoisomers. Use of a 2-substituted pyrrolidine derivative as a chiral auxiliary in the aza-2,3-Wittig rearrangement of **304** resulted in the formation of **305** and **306** with modest asymmetric induction (equation 62).[91]



G = Ph, R = ^{i}Pr: 63% Yield, 4:1 *E*:*Z*, 56% *ee*
G = CO_2Me, R = ^{i}Pr: 50% Yield, 10:1 *E*:*Z*, 79% *ee*

(61)



(62)

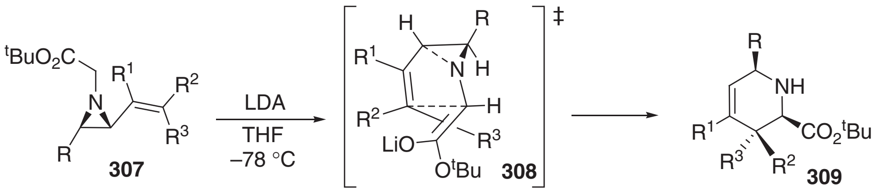
Treatment of *N*-carboalkoxymethyl-2-vinylaziridines **307** leads to deprotonation followed by ring-expanding 2,3-Wittig rearrangement to yield *cis*-2,6-disubstituted piperidines **309** (Table 23).[92] The ester group is essential for optimal results, as other anion stabilizing groups such as nitriles or arenes lead to lower diastereoselectivity or poor reactivity. Substrates bearing either *E*- or *Z*-disubstituted alkenes are transformed to trisubstituted piperidines with complete stereocontrol (entries 4–6). The stereochemical outcome of these reactions has been explained using transition state model **308**. However, some evidence suggests the mechanism of these reactions may involve ring-opened anionic or radical intermediates rather than a concerted sigmatropic rearrangement.

3.21.4.14 Sila-2,3-Wittig Rearrangements

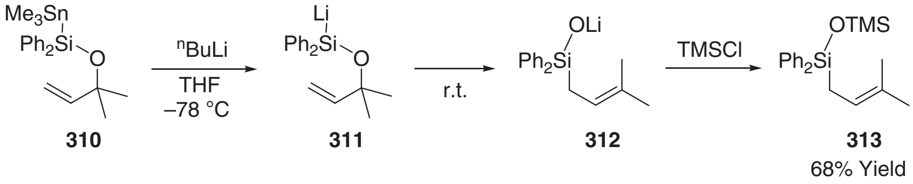
The sila-2,3-Wittig rearrangement is a synthetically useful method for the preparation of substituted allylsilane derivatives from allylic alcohols or allylic amines.[93] These transformations proceed through intermediate (allyloxy)silyllithium reagents **311** (Scheme 20), which are usually generated via transmetallation of silylstannanes **310** with ⁿBuLi. The 2,3-Wittig rearrangement of **311** affords **312**, which is then treated with TMSCl to yield **313.**

The sila-2,3-Wittig rearrangement is effective with silylstannane substrates derived from a range of tertiary alcohols (Table 24). The *E*:*Z* selectivities are modest, with a slight preference for formation of the *Z*-stereoisomer in most cases (entries 1 and 3). A silylstannane prepared from 1-vinylcyclohex-2-enol underwent selective 2,3-Wittig rearrangement with migration to the exocyclic

Table 23 Aza-2,3-Wittig rearrangements of vinylaziridines

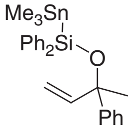
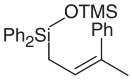
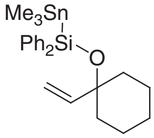
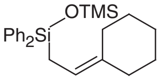
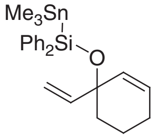
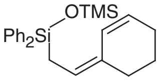
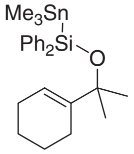
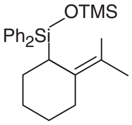
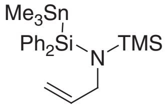
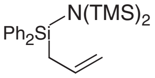


Entry	*R*	*R^1*	*R^2*	*R^3*	*Yield (%)*	*Reference*
1	^{t}Bu	H	H	H	95	92a
2	Me	Ph	H	H	57	92b
3	^{i}Pr	Ph	H	H	66	92b
4	BnOCH$_2$	H	H	Me	95	92c
5	^{t}Bu	H	Me	H	94	92c
6	C_5H_{11}	H	H	Me	97	92c



Scheme 20 The sila-2,3-Wittig rearrangement.

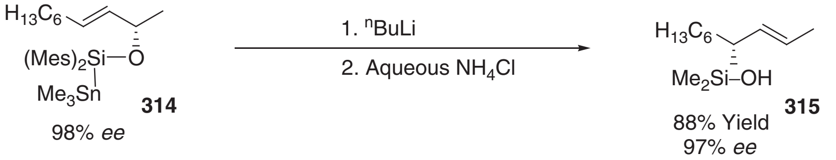
Table 24 Sila-2,3-Wittig rearrangements

Entry	*Substrate*[a]	*Product*	*E:Z*	*Yield (%)*
1			29:71	77
2			–	80
3			35:65	65
4			–	79
5			–	86

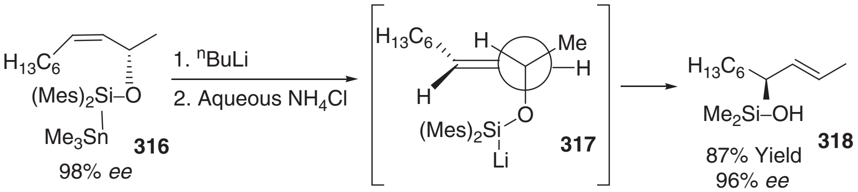
[a] Reaction Conditions: 2.0 equivalents ^{n}BuLi, −78 °C→r.t., then TMSCl.

alkene in preference to the endocyclic alkene (entry 3). Silylstannanes prepared from allylic amines also have been shown to undergo aza-sila-2,3-Wittig rearrangements to generate allylsilane products (entry 5). However, silylated amines are quite hydrolytically labile, and in most cases uses of alcohol-derived silylstannanes as precursors to allylsilanes (via 2,3-Wittig rearrangements) may be more straightforward.

The sila-2,3-Wittig rearrangements proceed with near perfect chirality transfer; substrates such as **314** and **316** are transformed to allylic silanes **315** and **318** with little or no erosion of enantiomeric purity (equations 63–64).[94] However, product stereochemistry is dependent on alkene geometry. The rearrangement of **316** to **318** likely proceeds via conformation **317** in which allylic strain is minimized. This transition state gives rise to the observed (*S*)-(*E*) product stereoisomer.



(63)



(64)

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3.22 Carbonylation and Decarbonylation Reactions

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3.22.1	Introduction	1073
3.22.2	Carbonylation of C–X Bonds	1073
3.22.3	Carbonylation of C–C Unsaturated Bonds	1079
3.22.4	Carbonylation of C–H Bonds	1083
3.22.5	Carbonylative Cyclization	1085
3.22.6	Carbonylative Ring-Expansion	1089
3.22.7	Carbonylation Without CO Gas	1091
3.22.8	Decarbonylation	1093
References		1097

Glossary

Atom transfer carbonylation It is a method to obtain aliphatic carboxylic acid derivatives from alkyl iodides and CO, which utilizes an atom transfer reaction from alkyl iodides to acyl radicals leading to acyl iodides.

Cativa process It is an industrial process for the production of acetic acid by iridium-catalyzed carbonylation of methanol, which was recently developed by BP Chemicals.

Microreactor It is a reaction device in which chemical reactions take place in a very narrow space (microchannels), typically tens to hundreds of micrometer wide and deep. The tiny microchannels allow not only the efficient mixing of substrates and reagents, but also very rapid heat, light, and mass transfer through the walls.

Monsanto process It is an industrial process for the production of acetic acid by rhodium-catalyzed carbonylation of methanol. Since HI is used as a cocatalyst, Rh-catalyzed carbonylation of iodomethane is involved as the key step.

Natural bite angle The natural bite angle of chelating ligand is defined as the selective chelation angle (L–M–L bond angle) that is determined by the chelating ligand backbone.

3.22.1 Introduction

Carbon monoxide is a potentially abundant feedstock which is produced from naphtha and coal as the resources in industry. The mission of carbonylation chemistry is to realize the introduction of carbon monoxide into organic molecules as a starting material for the preparation of carbonyl compounds. Such naturally affecting transformations require ready access to a variety of C–C bond forming processes.[1–5] Due to its strong σ-donating and π-accepting ability, carbon monoxide can form complexes with a wide range of transition metals, a fact that has been exploited in the development of transition metal-catalyzed carbonylation reactions.[6–9] Currently, a wide variety of transition metal-catalyzed carbonylation reactions are available, some of which have already found industrial applications, including the Roelen reaction (hydroformylation), the Reppe reaction, and acetic acid synthesis (Monsanto[10] and Cativa[11] processes). Due to its variable isoelectronic nature, CO can also react with carbocations, carbanions, and carbon radicals, resulting in the formation of acyl cations,[12] acyl anions,[13,14] and acyl radicals[15–18] as reactive species, respectively. Although all of these reactive species are also available for the synthesis of carbonyl compounds, the significant potential of radical species for carbonylation has just been recognized in the past two decades.[15] In this chapter, the authors will discuss important advances in carbonylation chemistry, which the past two decades have witnessed. Because of space limitations, the carbonylation chemistry of cations and anions will not be covered, instead, the chapter will focus on carbonylation and decarbonylation reactions involving organotransition metal and radical intermediates.

3.22.2 Carbonylation of C–X Bonds

Pd-catalyzed cross-coupling reactions of aryl halides or vinyl halides (or its equivalents such as triflates) with alkenes, alkynes, and organometallic reagents constitute a powerful tool for the construction of C–C bonds, known as name reactions like Mizoroki–Heck reaction, Sonogashira coupling reaction, Suzuki–Miyaura coupling reaction, Kosugi–Migita–Stille coupling reaction, and Negishi coupling reaction.[19] These reactions exploit oxidative addition of R–X to Pd(0) to form R–Pd–X as the first intermediates. Keeping up with the development of such cross-coupling reactions, Pd-catalyzed carbonylative cross-coupling reactions have also been developed.[20–22] Pd-catalyzed alkoxycarbonylation or aminocarbonylation of aryl, vinyl, and heteroaryl halides, known as

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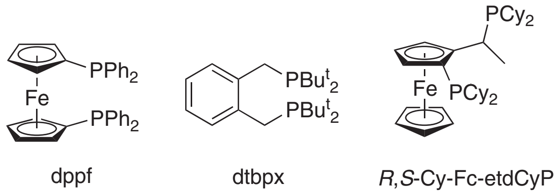
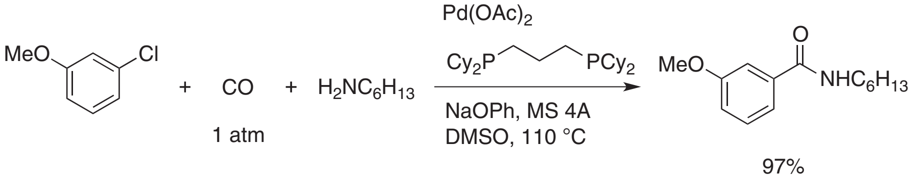
the Heck carbonylation,[23] readily leads to the production of carboxylic acid esters and amides, respectively. The reaction proceeds via oxidative addition of C–X bonds to Pd metal center, carbonyl insertion, and alcoholysis or aminolysis of the resulting acyl Pd complexes to lead to products. Inherent to a relatively strong C–Cl bonds, aryl chlorides are more reluctant to oxidative addition than aryl bromides and iodides and therefore several ligands, which include dppf (1,1′-bis(diphenylphosphino)ferrocene), dtbpx (1,2-bis(di-*tert*-butylphosphanyl)-*o*-xylene), and R,S-Cy-Fc-etdCyP ((R)-1-{(1S)-2-(dicyclohexylphosphanyl)ferrocenyl}-ethyldicyclohexylphosphane), are designed to affect the carbonylation of aryl chlorides (Scheme 1).[20] Recent work demonstrates that Pd catalyst having 1,3-bis(dicyclohexylphosphino)propane as a ligand works well for carbonylation of chlroarenes (equation 1).[24]

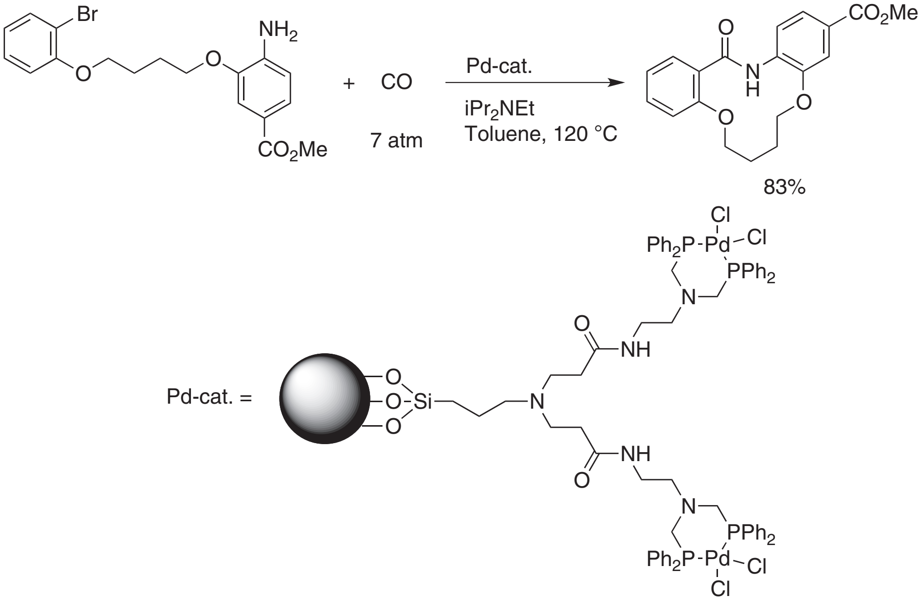


Scheme 1



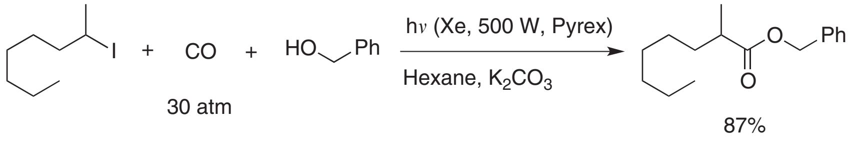
(1)

Lactones and lactams can be prepared by intramolecular Heck carbonylation, however, the application to medium to macrocyclic rings is scarce.[20] The intramolecular Heck carbonylation using palladium-complexed dendrimers immobilized on silica gel provides a powerful method for the synthesis of 12- to 18-membered ring macrocycles.[25] An example for preparation of a nitrogen and oxygen-containing 12-membered ring is shown in equation 2. The employed dendritic catalyst can be easily recovered by simple filtration in air and reused for eight cycles with only a slight loss of activity.



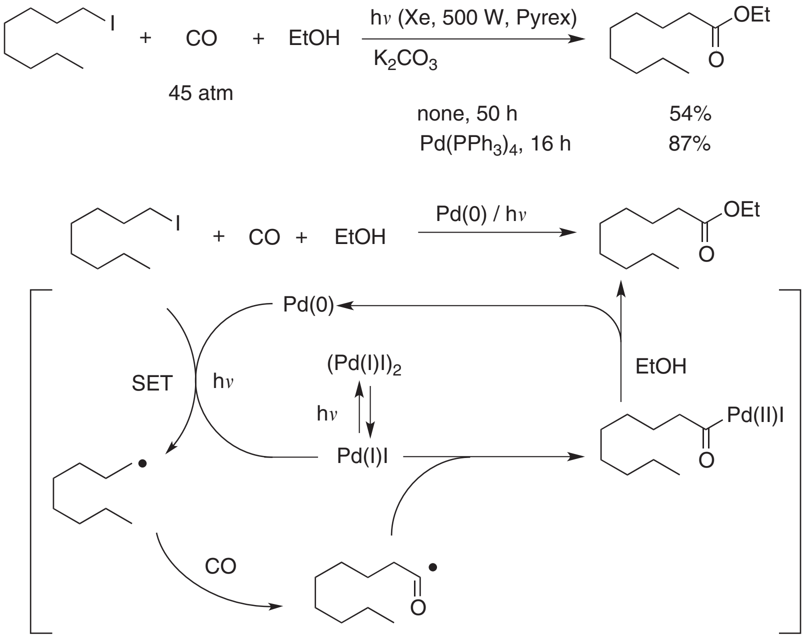
(2)

An important issue to be overcome surrounding Pd-catalyzed carbonylation chemistry is low reactivity of alkyl halides toward oxidative addition onto the metal center. Even in the case that alkylpalladiun species are formed, isomerization of the resulting alkyl Pd species takes place to give a mixture of isomeric alkyl Pd species. Conceptually different radical approach for carbonylation has circumvented the long-standing problem.[18] The carbonylation of alkyl iodides leading to aliphatic carboxylic acid derivatives is achieved based on the combination of radical carbonylation and the subsequent atom transfer reaction, which is called as atom transfer carbonylation (ATC).[18] Light irradiation is necessary for the radical initiation step (equation 3),[26] however, thermal initiation using a radical initiator such as (2,2′-azobisisobutyronitrile (AIBN) and allyltributyltin) can also be used.[27,28] Recent work applied the photo-induced ATC of alkyl iodides to positron emission tomography (PET) labeling chemistry using ^{11}CO.[29]



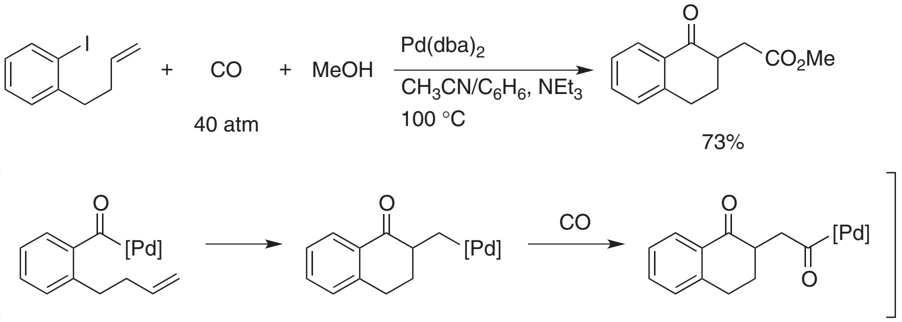
(3)

ATC reaction is sluggish when 'primary' alkyl iodides are used. Molecular orbital calculations predict that atom transfer step that converts stable acyl radicals to less stable primary alkyl radicals is considerably uphill.[30] It has been well acknowledged that transition metal-catalyzed carbonylation of alkyl iodides is accelerated by photo-irradiation.[31] Recent work has shown that the addition of Pd catalysts such as $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ to ATC conditions has accelerated the ATC reactions (equation 4).[32] Possible mechanism involves the generation of a pair of alkyl radicals and Pd(I)I radicals by the reaction of Pd(0) with RI. The resulting alkyl radicals add to CO to afford acyl radicals, which are ultimately trapped by Pd(I)I to form acylpalladium complexes. Pd dimer complex, such as $[Pd_2(CNMe)_6][PF_6]_2$,[33] also catalyzes the carbonylation of iodoalkanes under photo-irradiation conditions.[34]

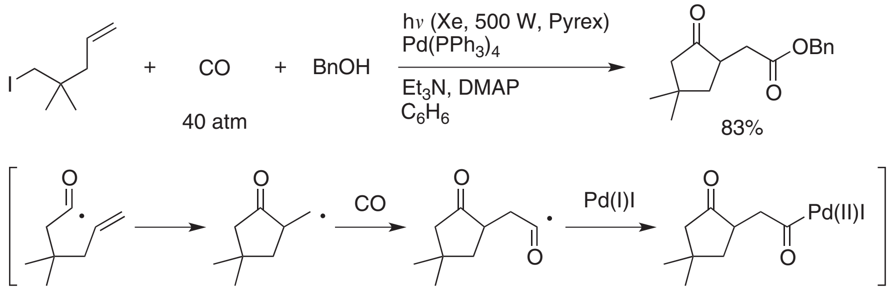


(4)

Cyclizative double carbonylation is a useful cascade reaction to obtain cycloalkanones having an alkoxycarbonylmethyl or aminocarbonylmethyl tether at α-position. In the Pd-catalyzed carbonylative cyclization of *ortho*-alkenyl iodobenzenes, two molecules of carbon monoxide are incorporated to give cyclic keto esters in good yields (equation 5).[35] An ATC system boosted by Pd/light system works well for a similar cascade carbonylation reaction of 4-alkenyl iodides. In an example shown in equation 6, carbonylative cyclization of 5-pentenyl iodide under Pd/light system takes place to give a cyclic keto ester in good yield.[36]

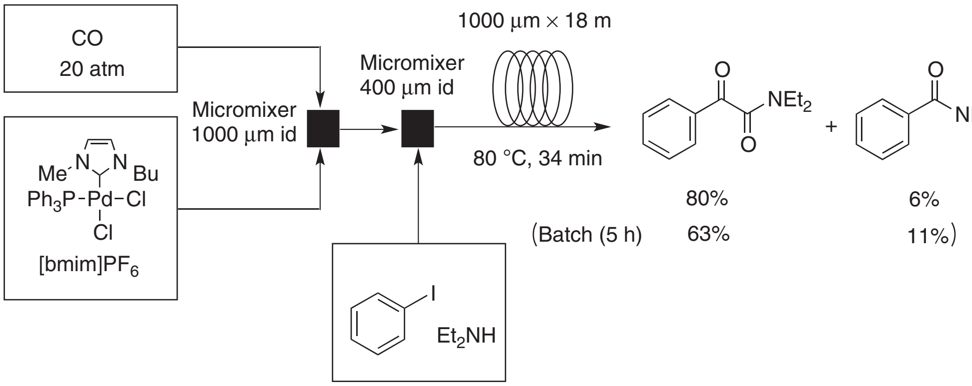


(5)



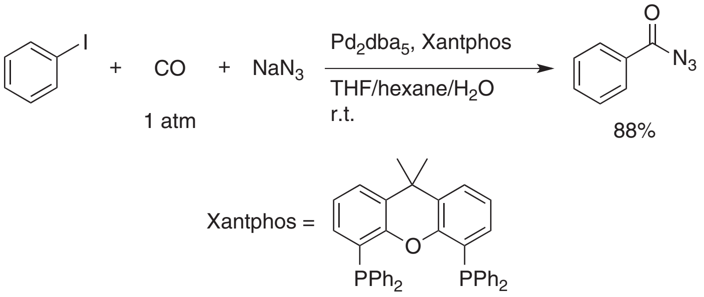
(6)

It is known that Pd-catalyzed carbonylation of aryl halides in the presence of primary and secondary amines affords α-keto amides, double carbonylation product.[37] This seemingly consecutive double carbonylation reaction is rationalized by the formation and the reductive elimination of (acyl)carbamoyl Pd complexes. Recent work has shown that $[PdCl(\eta^3\text{-}C_3H_5)]_2/PPh_3/$DABCO[38] and $Pd(^tBu_3P)_2$/DBU[39] system efficiently catalyze the double carbonylation at atmospheric pressure of CO. In a Pd/light system using amines as a trap, double carbonylation of alkyl iodides proceeds to give α-keto amides.[32] Recently, the double carbonylation reaction of aryl halides is investigated using a flow microreactor.[40–42] In an example shown in equation 7, Pd-catalyzed double carbonylation of iodobenzene in a flow system using an ionic liquid, $[bmim]PF_6$ as a reaction medium takes place to give a keto amide with good selectivity.[41] The superior efficiency of the microflow system to that of the batch reactor system may be attributed to a large interfacial area to volume ratio between the CO and liquid phase.



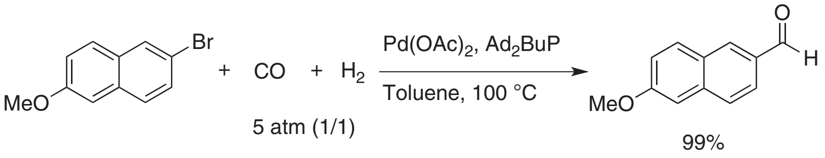
(7)

Since aroyl azides are thermally unstable and can undergo the Curtius rearrangement, to obtain aroyl azides by a carbonylation procedure has been thought to be difficult. However, the combination of Pd_2dba_5 with Xantphos (9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene) is found to be effective for the azidocarbonylation carried out at room temperature (equation 8).[43]



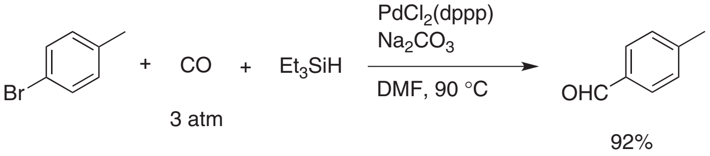
(8)

Dihydrogen is known to serve as a source of formyl hydrogen in carbonylation of aryl halides to give aldehydes.[44,45] In an example shown in equation 9, Pd catalyst having a quite bulky phosphine ligand, Ad_2BuP, affects such a transformation under low CO pressure conditions.[46]



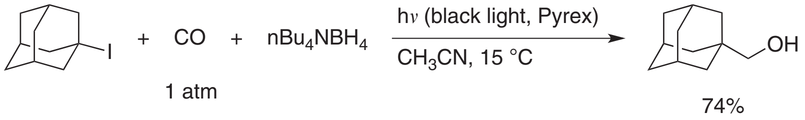
(9)

Stille formylation reaction attains the use of tin hydride as formyl hydrogen in the Pd-catalyzed carbonylation reaction of aryl and vinyl halides.[47] Recent progress involves the use of hydrosilanes[48,49] in conjunction with bidentate ligands, such as dppp, dppf, and BINAP (equation 10).[50]



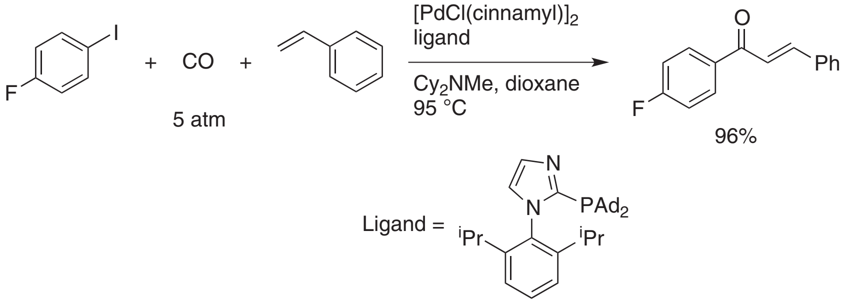
(10)

Although Stille formylation is not applicable to the synthesis of aliphatic aldehydes from alkyl halides, the methodology based on radical carbonylation using tributyltin hydride and AIBN fills the void.[51,52] In a further effort to find a process without using toxic tin reagents, recent work employs borohydride reagents as a radical mediator. The formylation and *in situ* reduction of 1-iodoadamantane takes place using tetrabutylammonium borohydride and CO under black light irradiation (wavelength: 352 nm), in which tetrabutylammonium borohydride acts as both a hydrogen source and a hydride anion source to reduce initially formed 1-adamantanecarboxaldehyde (equation 11).[53]



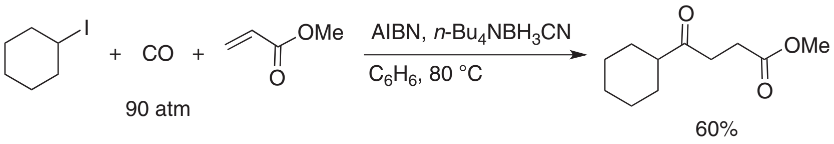
(11)

The combination of a bulky phosphine ligand and Cl-bridged Pd dimer complex is found to be a useful catalyst system available for carbonylative Heck type reaction. In an example given in equation 12, the reaction of an aryl iodide with CO and styrene proceeds to give a chalcone derivative in excellent yield.[54]



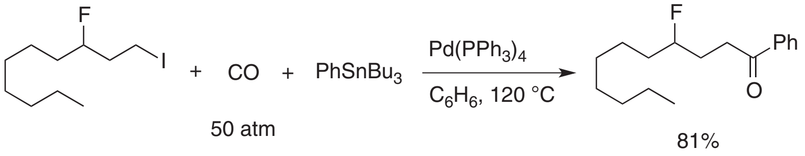
(12)

Whereas tributyltin hydride and tris(trimethylsilyl)silane (TTMSS) are used as a radical mediator to prepare unsymmetrical ketones from haloalkanes, CO, and electron-deficient alkenes,[55–57] the recent work attains the similar transformation by the use of tetrabutylammonium borohydride as a radical mediator (equation 13).[58]



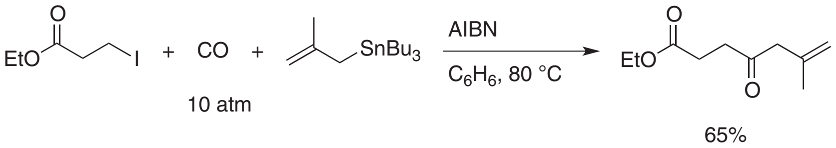
(13)

The Pd-catalyzed carbonylation of aryl halides, vinyl halides, and aryl triflates in the presence of vinyl or arylstannanes gives aryl vinyl or diaryl ketones.[59] Such Stille-type carbonylation with $PhSnBu_3$ can be extended to include alkyl iodides under pressurized CO conditions (equation 14).[60]



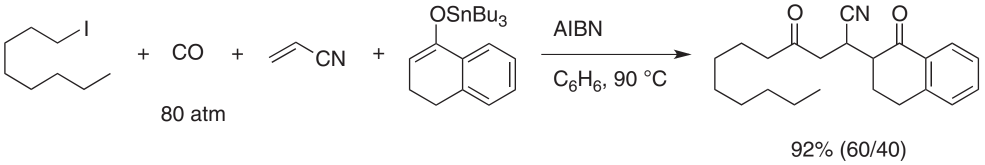
(14)

Both allyltributyltin and tributyltin enolates act as excellent unimolecular chain transfer (UMCT) reagent.[61] The combination of these reagents with radical carbonylation is particularly useful to obtain functionalized ketones. In the given example (equation 15), β,γ-unsaturated ketone is synthesized by a radical chain reaction.[62]



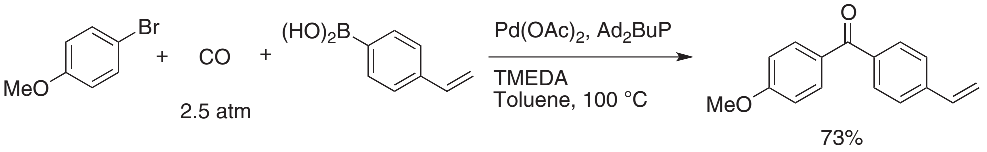
(15)

Four-component coupling reaction of alkyl halides, CO, electron-deficient alkenes, and allyltin gives β-functionalized δ,ε-unsaturated ketones in good yield.[63] β-Functionalized δ-diketones can be obtained when tin enolates are used (equation 16).[64]



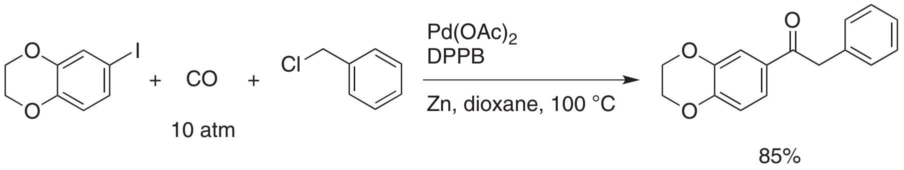
(16)

Unsymmetrical ketones can also be prepared by Pd-catalyzed carbonylation of aryl halides using arylboronic acids as a coupling partner.[65] In a given example in equation 17, p-MeO-phenyl bromide couples with CO and an arylboronic acid in the presence of $Pd(OAc)_2/Ad_2BuP$ catalyst.[66] The reaction of alkyl iodides with CO and alkyl 9-BBN takes place in the presence of $Pd(PPh_3)_4$ under photo-irradiation to give unsymmetrical dialkyl ketones.[67]



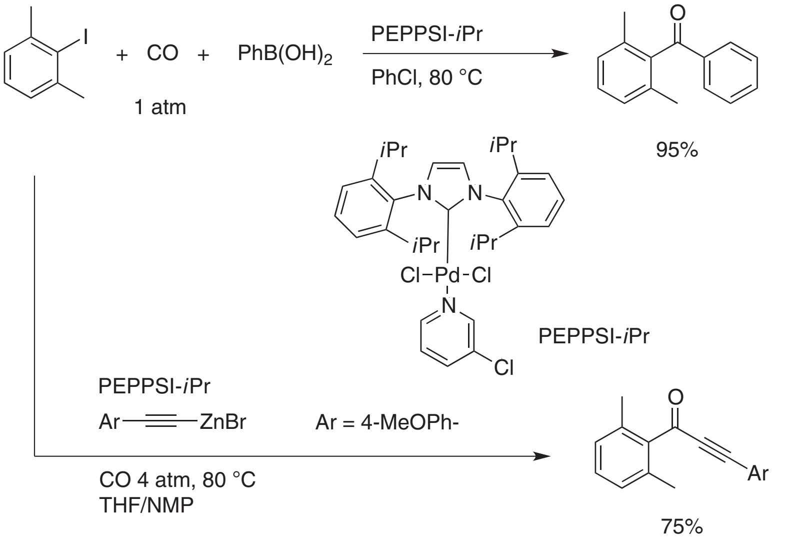
(17)

Oganozinc reagents also participate in Pd-catalyzed carbonylative coupling reactions.[68,69] A recent example for the synthesis of 1,2-diarylethanones uses a technique to prepare benzylzinc species *in situ* by adding Zn powder in the reaction system (equation 18).[70]



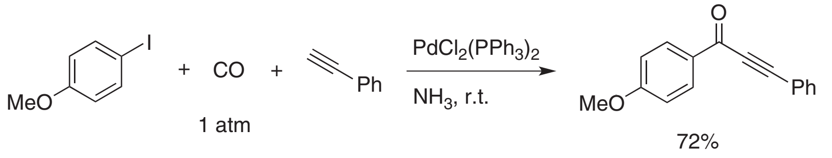
(18)

When PEPPSI–iPr Pd complex is used as a catalyst, sterically congested *ortho*-disubstituted iodoarenes can undergo carbonylative cross-coupling reactions with arylboronic acids and alkynylzinc bromides to give the corresponding aromatic ketones (equation 19).[71]



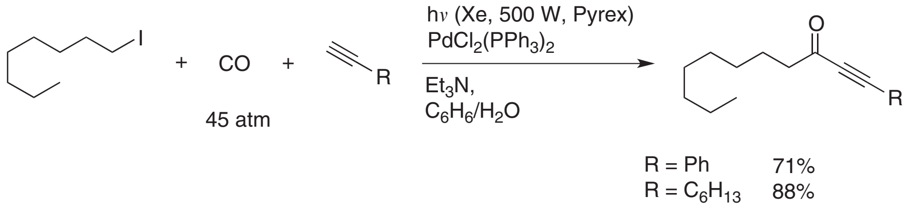
(19)

The Pd-catalyzed carbonylative coupling of aryl halides with terminal alkynes is known to give aryl acetylenic ketones.[72] In the presence of aqueous NH_3 as a base, the reaction proceeds under very mild conditions (atmospheric pressure of CO and room temperature) (equation 20).[73] Addition of CuI is necessary when aliphatic alkynes are employed.



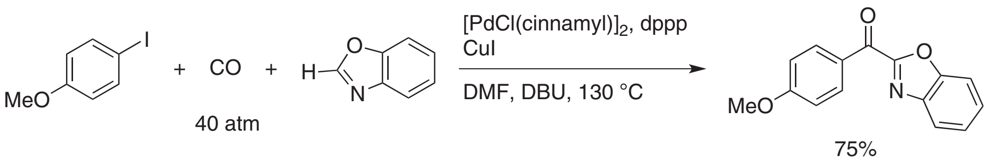
(20)

Alkyl alkynyl ketones can be prepared by Pd/light-induced carbonylation of alkyl iodides with CO in the presence of terminal alkynes (equation 21).[74]



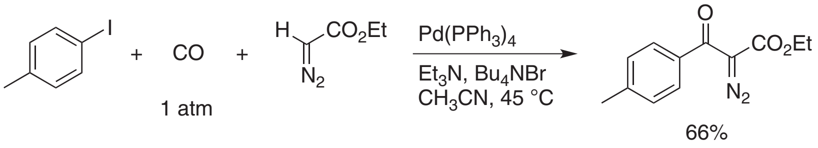
(21)

Heterocycles, such as oxazoles, thiazoles, and imidazoles, can be employed as a coupling partner of Pd-catalyzed carbonylation of iodoarenes, in which $[PdCl(cinnamyl)]_2$/DPPP/CuI is used as a catalyst (equation 22).[75]



(22)

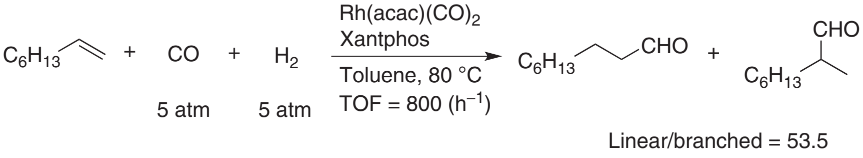
The coupling reaction of aryl iodides with CO and ethyl diazoacetate is catalyzed by $Pd(PPh_3)_4$ to afford β-keto α-diazo-carbonyl compounds, in which labile diazo moiety remains intact through the reaction (equation 23).[76]



(23)

3.22.3 Carbonylation of C–C Unsaturated Bonds

Hydroformylation reactions of alkenes give aldehydes with the incorporation of CO and molecular hydrogen, in which a variety of metal complexes, including Co, Rh, Ir, Ru, and Pt, act as the catalyst.[77] Control of the regiochemistry of the hydroformylation of terminal alkenes still remains a challenge of research and therefore a variety of designed ligands have been examined. A high linear selectivity can be achieved by using phosphine ligands, such as Xantphos and BISBI, which have a natural bite angle of 120° approximately.[78,79] For example, Rh/Xantphos (natural bite angle = 111.4°)[78] shows 53.5/1 selectivity in favor of linear aldehydes (equation 24). Rh/BISBI (2,2′-bis[(diphenylphosphino)methyl]-1,1′-biphenyl; natural bite angle = 113°) having CF_3-group on aryl group shows both very high linear selectivity and good catalytic activity (equation 25).[79]



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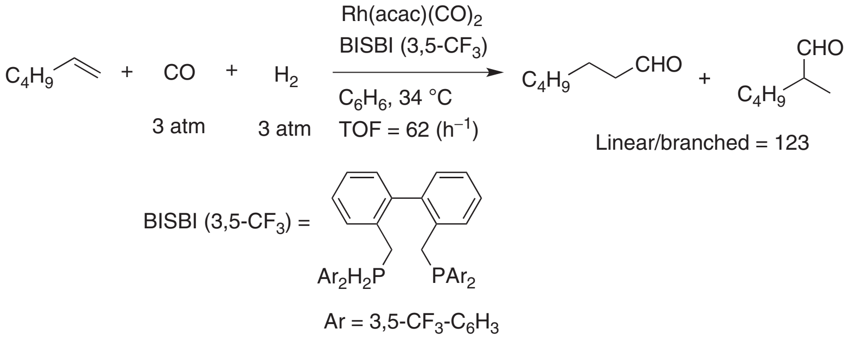
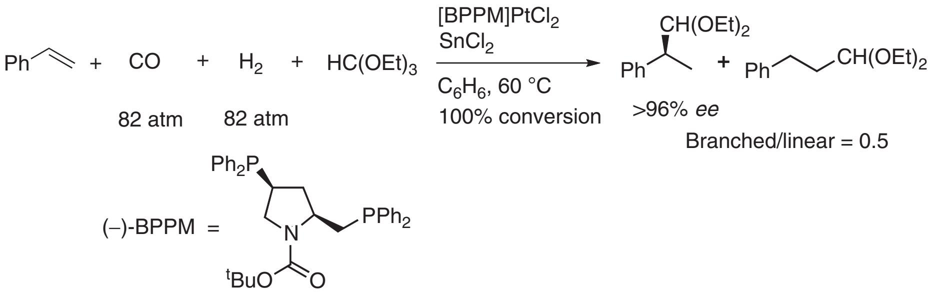


(25)

Selective hydroformylation to obtain branched aldehydes has also been studied actively using vinylarenes as a model substrate in the context of asymmetric induction. High level of *ee*s have been achieved in asymmetric hydroformylation of vinylarenes.[80] Hydroformylation/*in-situ* acatalization of styrene using $PtCl_2/SnCl_2$ and (2*S*, 4*S*)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine ((–)-BPPM) as a catalyst resulted in high *ee* values but with low selectivity for branched product (equation 26).[81] Both high enantioselectivity and a good branched/linear ratio are achieved with a Rh/BINAPHOS catalyst (equation 27). The branched aldehyde is obtained with 94% *ee* and 7.3/1 selectivity to the linear aldehyde.[82]



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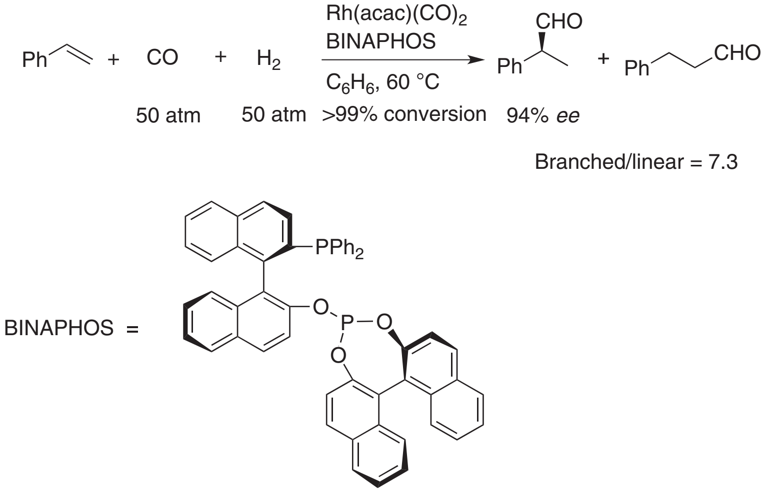
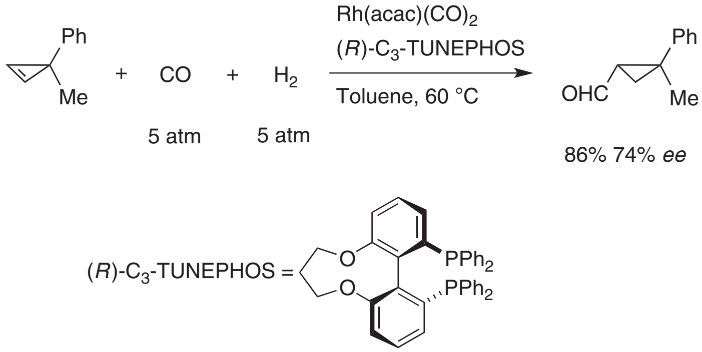


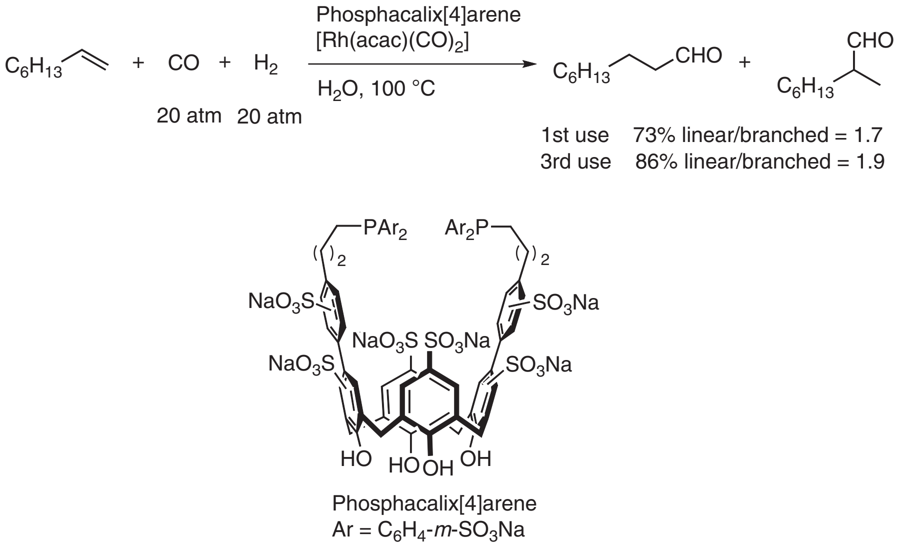
(27)

The asymmetric hydroformylation of cyclopropenes is carried out using Rh/(*R*)-C3-TUNEPHOS as the catalyst, giving enantiomerically enriched cyclopropylcarboxaldehydes (equation 28).[83]



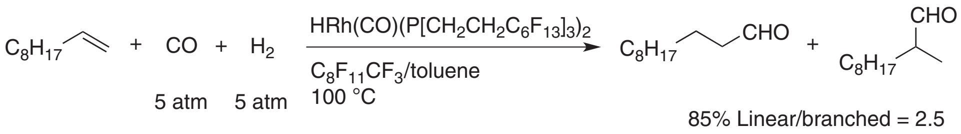
(28)

Biphasic solvent systems have been exploited to recover precious rhodium catalysts. Phosphacalix[4]arene–rhodium complex catalyzes hydroformylation of 1-octene in water (equation 29).[84] After extraction of the products, aqueous layer containing water soluble calixarene–rhodium complex can be used repeatedly.



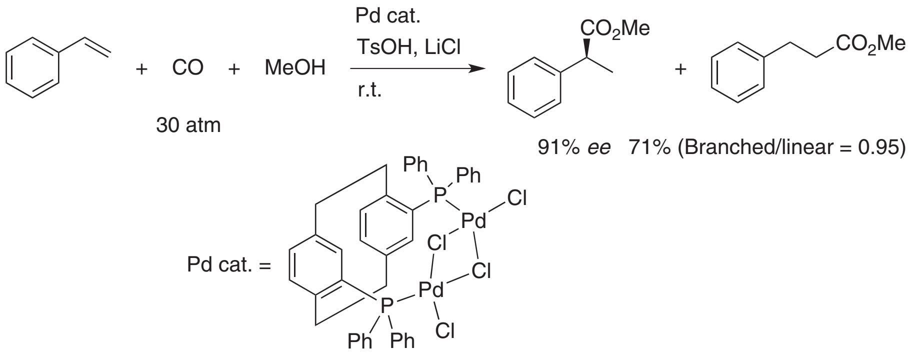
(29)

The thermomorphic behavior in a fluorous/organic mixed system was applied to hydroformylation reaction of alkenes catalyzed by a fluorous Rh complex (equation 30).[85] After the reaction, on cooling two solvents are separated out, enabling facile separation of Rh-catalyst having a fluorous phosphine ligand and products and reuse of the recovered catalyst.



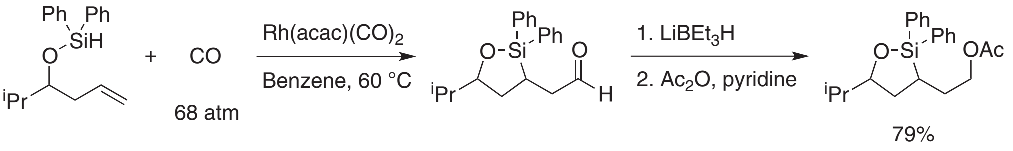
(30)

The asymmetric alkoxycarbonylation of vinylarenes catalyzed by palladium complexes bearing chiral phosphine ligands has attracted considerable attention, since the products of alkoxycarbonylation reactions are important intermediates in the syntheses of the nonsteroidal antiinflammatory drugs, such as 2-arylpropionic acids, ibuprofen, and naproxen.[86] Asymmetric methoxycarbonylation of styrene takes place in the presence of Pd complex having a cyclophane-bridged chiral bisphosphine ligand (PhanePhos) to give methyl 2-phenylpropionate in good enantioselectivity (equation 31).[87]



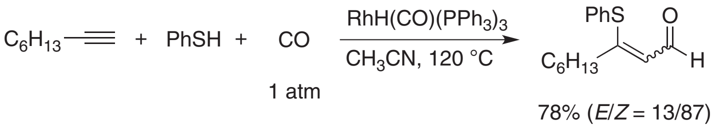
(31)

A combination of CO/hydrosilanes or CO/thiols has brought a variety of catalytic carbonylation reactions to alkenes and alkynes. The reaction of alkenes with hydrosilanes and CO in the presence of $Co_2(CO)_8$ does not take a course of silylformylation but a course to give enol silyl ethers.[88,89] Recent work has shown that intramolecular silylformylation of alkenes is possible, when butenoxysilanes are exposed to pressurized CO in the presence of $Rh(acac)(CO)_2$ as the catalyst (equation 32).[90]



(32)

In case of terminal alkynes, however, silylformylation does take place in the presence of Rh[91] and Rh/Co mixed catalyst.[92] The thioformylation of alkynes using thiols can be catalyzed by $RhH(CO)(PPh_3)_3$ to give *β*-thio-substituted *α*,*β*-unsaturated aldehydes (equation 33).[93] Radical-mediated thioformylation of alkynes also proceeds but with the opposite regioselectivity, since thiyl radical addition takes place at less hindered alkyne terminus.[94] However, the reaction of enynes with CO and thiols in the presence of Pd catalyst prefers a hydrothioesterification course, which gives *α*,*β*-unsaturated thioesters (equation 34).[95]



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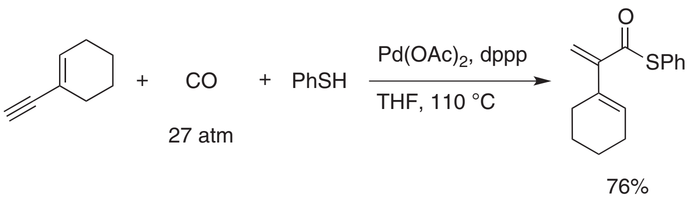
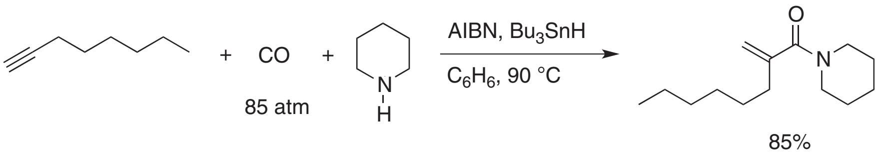


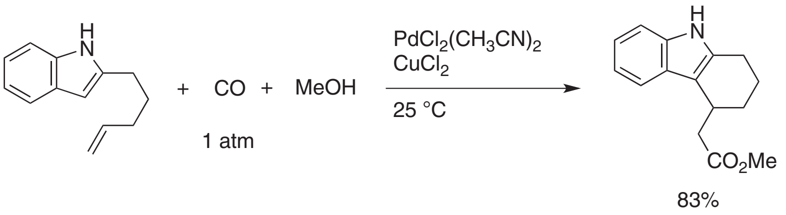
(34)

Pd-catalyzed reactions of terminal alkynes with CO and amines give *α*-substituted acrylic amides in good yields.[96] In these reactions, however, *β*-substituted acrylamides are also formed as minor product. In contrast, radical aminocarbonylation of terminal alkynes in the presence of AIBN and Bu_3SnH proceeds with a complete regioselectivity to give *α*-substituted acrylic amides (equation 35).[97]



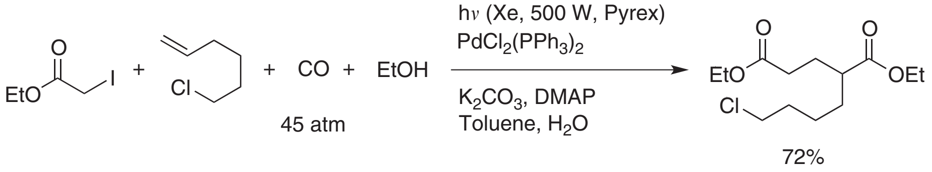
(35)

Oxidative carbonylation reactions of alkenes, such as alkoxycarbonylation and aminocarbonylation, by Wacker-type catalysts have been widely investigated.[98,99] In an example given in equation 36, indole having a 4-pentenyl tether reacts with CO and MeOH in the presence of $PdCl_2(CH_3CN)_2/CuCl_2$ to give cyclic ester in good yield.[100]



(36)

Consecutive radical carbonylation methods are available to synthesize selenol and thiol esters, in which transfer of RSe or RS group to acyl radicals serves as a key step.[101,102] Recent work using a Pd/light system enables to prepare esters via four-component coupling reaction of α-substituted iodoalkanes, alkenes, CO, and alcohols (equation 37).[103]

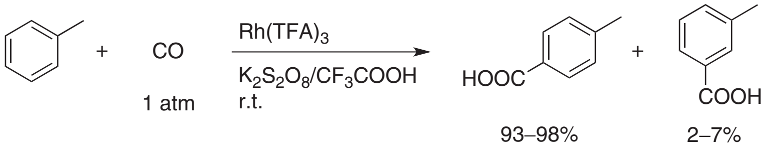


(37)

3.22.4 Carbonylation of C–H Bonds

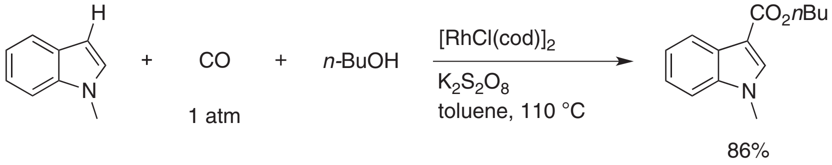
The transition metal-catalyzed functionalization of C–H bonds is a topic of considerable interest in modern organic chemistry.[104,105] The efficient direct C–H carbonylation of alkanes and arenes is an ongoing challenge.[106,107] The conversion of methane to acetic acid by carbonylation is achieved by several catalyst systems such as $RhCl_3/HI$[108] and $Pd(OCOEt)_2/CuSO_4$.[109] The catalytic C–H carbonylation of linear alkanes confronts regiochemical issues and in this regard high terminal preference of the formylation of sp^3 C–H bond of hexane using Rh/light/CO system is still a landmark.[110]

Low turnover numbers and *para*-selectivity of Pd-induced oxidative C–H carbonylation of arenes, known as the Fujiwara reaction, has been improved by the use of $Rh(TFA)_3$ (prepared from $Rh(CO)_2(CF_3CO_2)_n$ and 30% H_2O_2) as a catalyst and $K_2S_2O_8$ as an oxidant. Under 1 atm of CO, toluene is converted to a mixture of *para*- and *meta*-toluic acids with 93–98% para-selectivity and 40 times of TON (equation 38).[111]



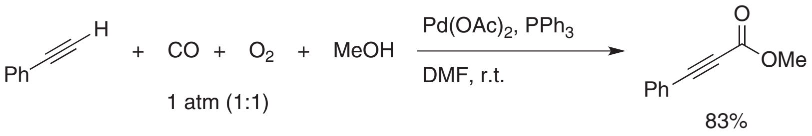
(38)

Rh-catalyzed C–H carbonylation of indoles takes place regioselectively to give indole-3-carboxylates (equation 39).[112]



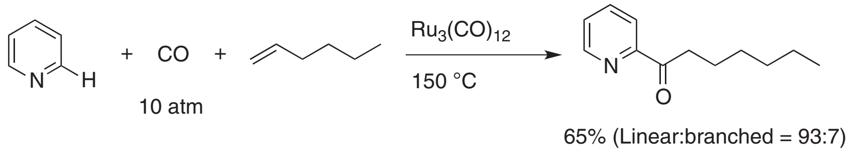
(39)

Carbonylation of sp C–H bond can be catalyzed by $Pd(OAc)_2/PPh_3$ under oxygen as an oxidant (equation 40).[113]



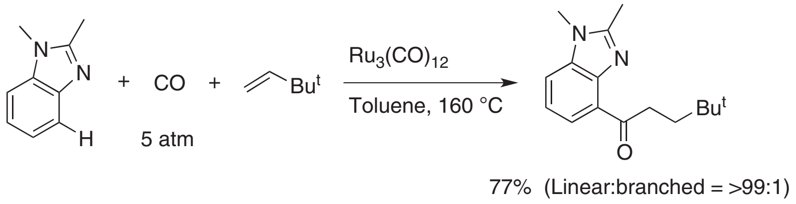
(40)

Transition metal-catalyzed C–H carbonylation, exploiting intramolecular coordination of metals, is frequently investigated. Many of successful examples focus on a variety of *N*-containing compounds, since *N*-heterocycles are readily available and coordination ability of nitrogen to metal center is excellent. The reaction of pyridine with CO and terminal alkenes in the presence of a catalytic amount of $Ru_3(CO)_{12}$ gives pyridyl ketones (equation 41).[114] Similarly, the C–H carbonylation of five-membered *N*-heterocyclic aromatics, such as imidazoles, thiazoles, oxazoles, and pyrazoles, with CO and olefins, takes place in aromatic C–H bonds adjacent to the nitrogen atom, giving the corresponding heteroaryl alkyl ketones in good yields.[115]



(41)

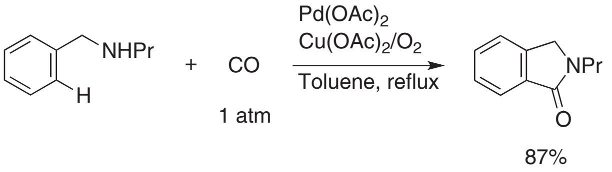
Nitrogen-directed C–H carbonylation also takes place at β-C–H bonds. Indeed, 1,2-dimethylbenzimidazole undergoes carbonylation at a C–H bond β to the nitrogen atom (equation 42).[116]



(42)

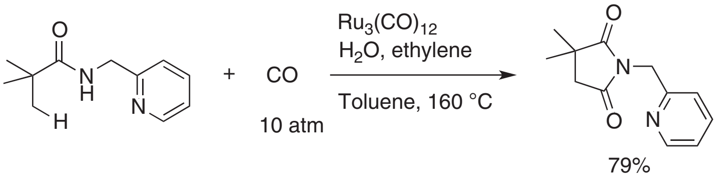
In the reaction of 2-*ortho*-tolylpyridine with CO and ethylene in the presence of $Ru_3(CO)_{12}$, carbonylation of the benzene ring at *ortho* C–H position takes place to give aryl ethyl ketone in good yield.[117]

In a Wacker-type system, palladium-catalyzed aromatic carbonylation of benzylamines takes place at *ortho* C–H position to give the corresponding benzolactams in good yields (equation 43).[118]



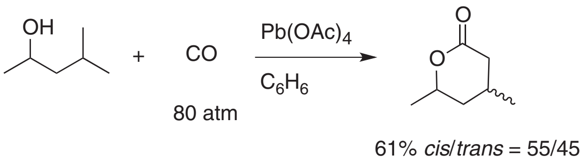
(43)

With the aid of two nitrogen atoms, $Ru_3(CO)_{12}$ complex catalyzes the regioselective carbonylation of an sp^3 C–H bond of methyl group (equation 44).[119]



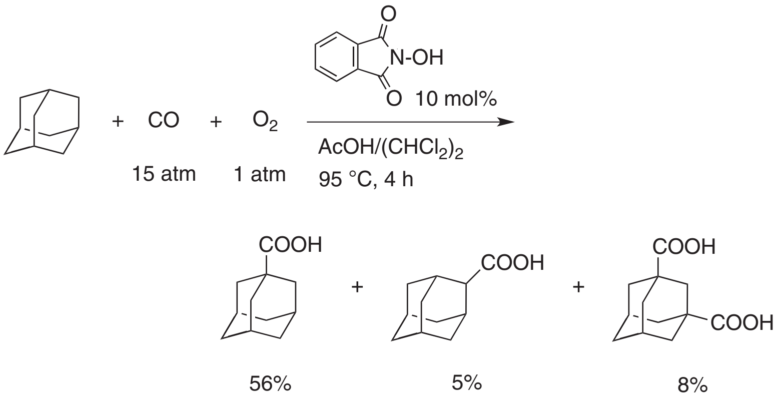
(44)

Radical reaction can also be used for C–H carbonylation. The Barton type 1,5-radical translocation reaction from O to C can be applied to carbonylation of δ-C–H bonds of saturated alcohols.[120] Thus, using a combination of lead tetraacetate and CO, γ-lactones are synthesized (equation 45).[121]



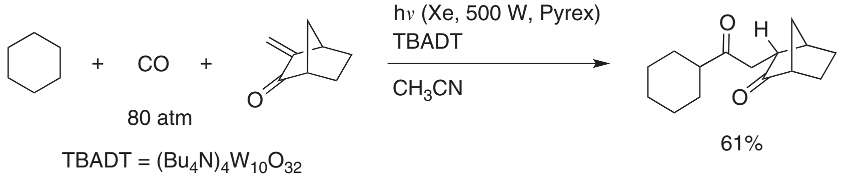
(45)

NHPI (*N*-hydroxyphtalimide) catalyzes the C–H carbonylation of adamantane under aerobic conditions, which leads to the production of adamantane carboxylic acids (equation 46).[122]



(46)

Ability of tetrakis(tetrabutylammonium) decatungstate (TBADT) to cause hydrogen abstraction from C–H bonds is exploited to develop C–H/carbonylation reactions. Although cyclohexane can be carbonylated to give cyclohexanecarboxaldehyde using TBADT as a photo catalyst,[123] the yield is quite low presumably due to a backward reaction triggered by abstraction of formyl hydrogen of the product. However, recent work demonstrates that photo-catalytic radical carbonylation of alkanes with electron-deficient alkenes using TBADT as a photo catalyst gives unsymmetrical ketones in good yields (equation 47).[124]

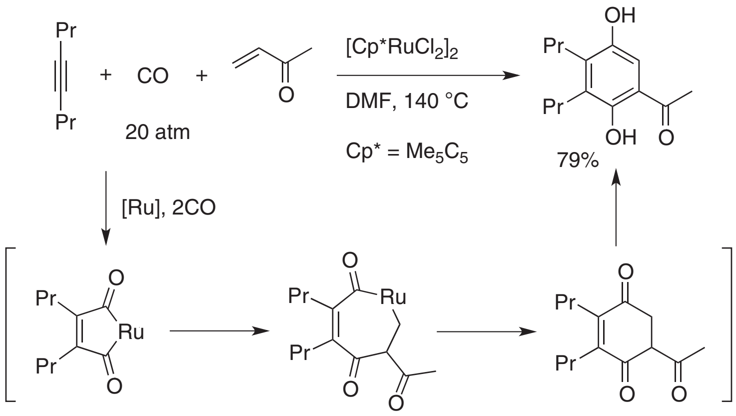


(47)

3.22.5 Carbonylative Cyclization

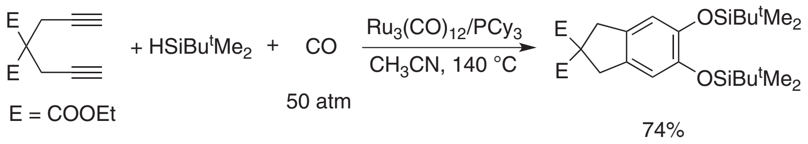
Carbonylative cyclization provides a straightforward tool for the synthesis of carbonyl-containing cyclic compounds.[125] The [2 + 2 + 1] cycloaddition of alkyne, alkene, and CO to give cyclopentenone, called as the Pauson–Khand reaction, has been most extensively studied.[126] As the original work mainly used stoichiometric amounts of haxacarbonyldicobalt(0) complexes of alkynes, nowadays a variety of transition metal complexes such as rhodium, iridium, ruthenium, and titanium, are shown to act as a catalyst for the Pauson–Khand reaction.[126] Since the Pauson–Khand reactions are well surveyed,[127] this section rather focused on different types of cycloaddition reactions with CO.

Substituted hydroquinone can be synthesized by the carbonylative cycloaddition of an alkyne, an alkene, and two molecules of CO, in which $[\mathrm{Cp{*}RuCl_2}]_2$ is used as a catalyst.[128] A variety of electron-deficient alkenes, such as α,β-unsaturated ketones, esters, and amides, participate in this reaction (equation 48). Formation of maleoylruthenium complex is proposed as a possible intermediate.



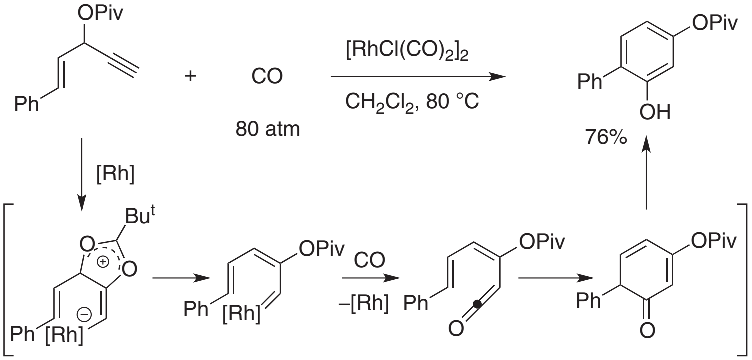
(48)

Bissilylated catechols are synthesized by $Ru_3(CO)_{12}$-catalyzed reaction of 1,6-diyenes with hydrosilane and two molecules of CO.[129] This represents a [2 + 2 + 1 + 1] cycloaddition (equation 49).



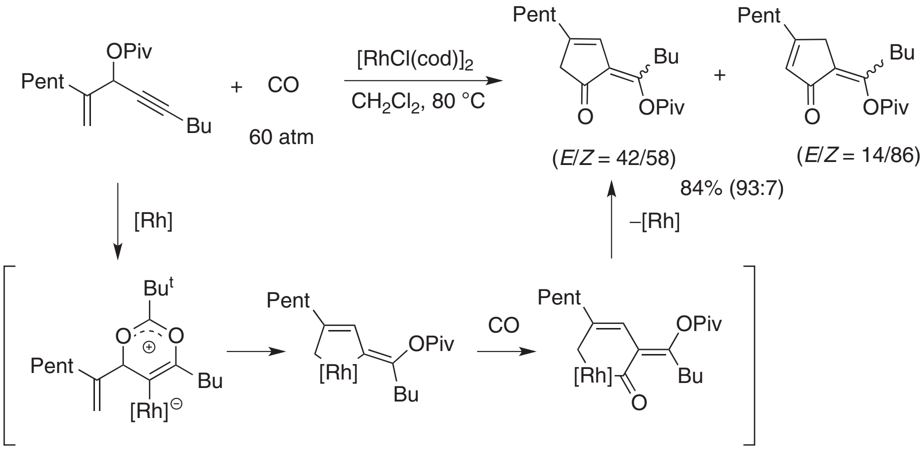
(49)

1,4-Enyne esters undergoes [5 + 1] cycloaddition with CO in the presence of rhodium catalyst. The reaction involves cationic 1,2-acyloxy migration to make a key species (equation 50).[130] A variety of functionalized resorcinols, including biaryl derivatives, can be synthesized from readily available 1,4-enyne esters and CO.



(50)

Interestingly, when 1,4-enyne esters having a substituent at an alkyne terminus is employed under similar conditions, cyclopentenones are obtained via cationic 1,3-acyloxy migration and the subsequent [4 + 1] cycloaddition (equation 51).[131,132] In a related study, propargyl esters having a cyclopropyl substituent at alkyne terminus undergoes 1,3-acyloxy migration and the subsequent [5 + 1] cycloaddition (equation 52).[133]



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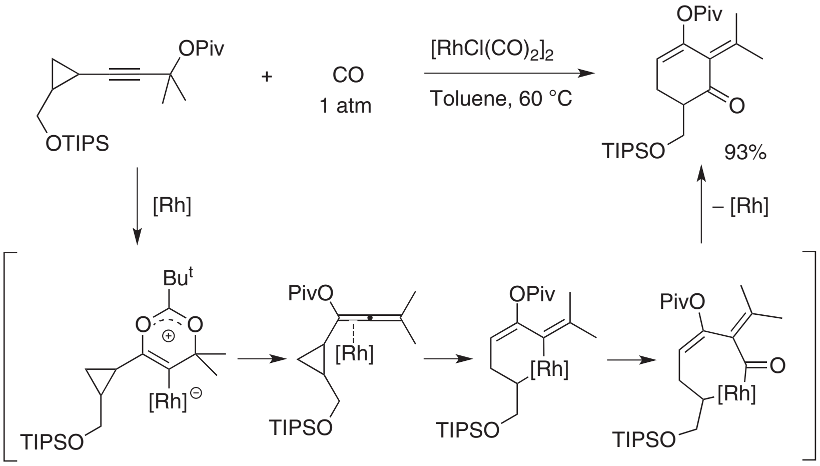
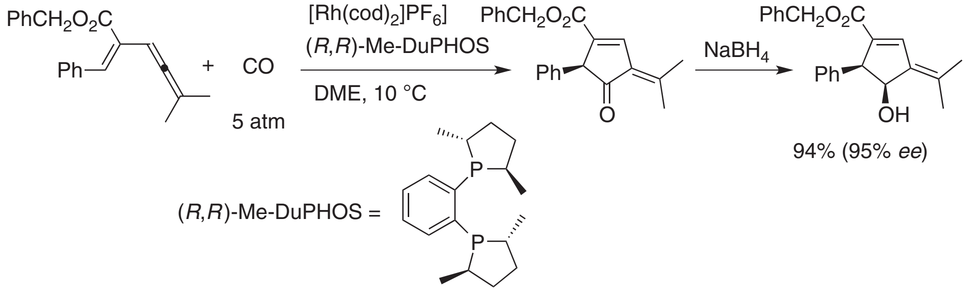


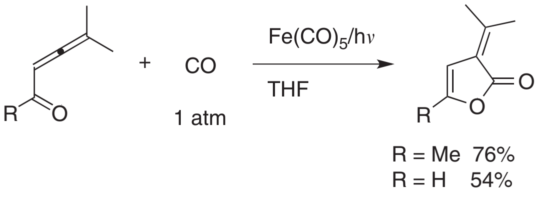
(52)

The asymmetric [4 + 1] cycloaddition of vinylallenes with CO is affected by rhodium or platinum/Me-DuPHOS catalyst (equation 53).[134] After reduction of the product with $NaBH_4$ the obtained cyclopentenol shows high *ee*.



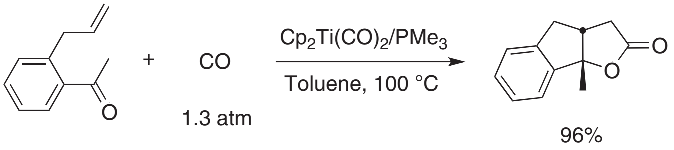
(53)

Under photo-irradiation conditions, allenyl aldehydes and ketones undergo iron-catalyzed [4 + 1] cycloaddition with CO to give α-methylene lactones (equation 54).[135]



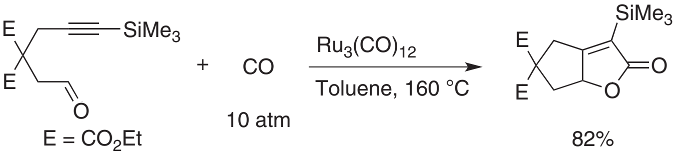
(54)

Intramolecular [2 + 2 + 1] cycloaddition of alkene, ketone, and CO is catalyzed by titanium complex, which gives γ-lactone in high yield (equation 55).[136]



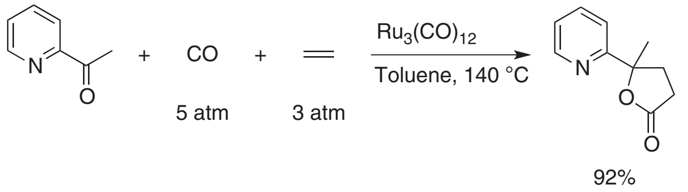
(55)

Lactones can be obtained by the carbonylative cyclization of unsaturated carbonyl compounds. $Ru_3(CO)_{12}$ catalyzes the [2 + 2 + 1] cycloaddition of yne-aldehyde with CO, giving good yield of unsaturated lactone (equation 56).[137] The transformation represents a hetero Pauson–Khand reaction.



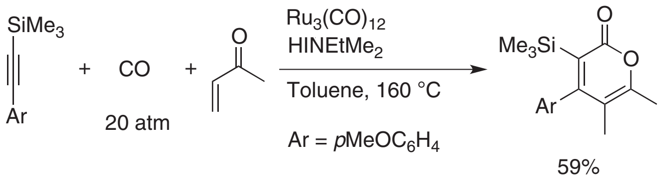
(56)

In the presence of $Ru_3(CO)_{12}$ as a catalyst, 2-acetylpyridine undergoes [2 + 2 + 1] cycloaddition with CO and ethylene to give γ-lactone in high yield (equation 57).[138]



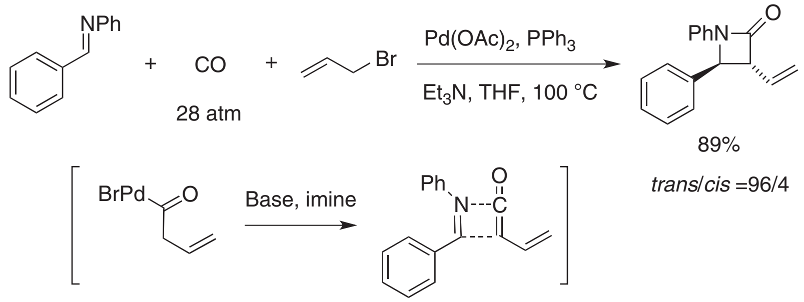
(57)

The reaction of silylalkynes with vinyl ketones and CO in the presence of $Ru_3(CO)_{12}$ and ethyldimethylamine gives tetra-substituted α-pyrones (equation 58).[139] In this [3 + 2 + 1] cycloaddition reaction, the carbonyl group and α-carbon of vinyl ketones are incorporated as a three-atom assembling unit.



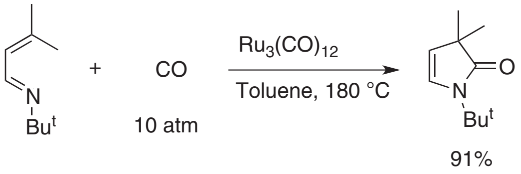
(58)

Pd-catalyzed [2 + 2] cycloaddition reaction is attained using aromatic imines, allylic halides, and CO in which vinyl ketene is proposed as the key intermediate (equation 59).[140]



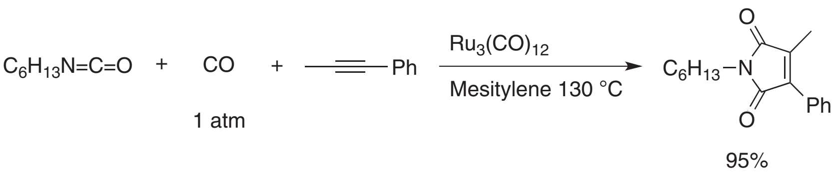
(59)

Under high temperature conditions, $Ru_3(CO)_{12}$ effectively catalyzes the [4 + 1] cycloaddition of α,β-unsaturated imines with CO (equation 60).[141]



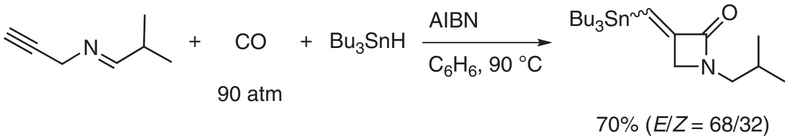
(60)

Maleimides are obtained by $Ru_3(CO)_{12}$-catalyzed [2 + 2 + 1] cycloaddition of alkynes, isocyanates, and CO (equation 61).[142]



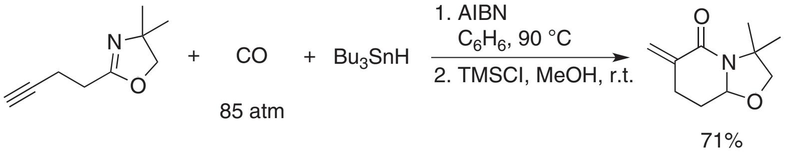
(61)

Combination of radical carbonylation with the subsequent cyclization onto N–C bonds gives a promising tool for the synthesis of a variety of lactams.[143–145] Stannylcarbonylation of aza-enynes using Bu_3SnH/CO in the presence of AIBN gives α-stannylmethylene lactams in good yields (equation 62).[144] In this reaction, four- to eight-membered lactams can be prepared. The subsequent treatment with TMSCl/MeOH gives α-methylene lactams quantitatively.



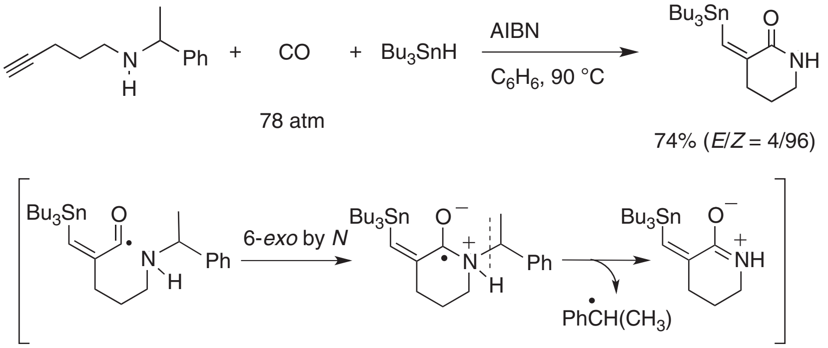
(62)

δ-Lactams are obtained by 6-*endo* cyclization of acyl radicals onto N–C double bonds of imines and oxazolines (equation 63).[145] Cyclization of acyl radicals always takes place onto N, which is rationalized by dual orbital effect between nitrogen lone pair and acyl radical $\pi*$ and acyl radical SOMO and imine $\pi*$.[146]



(63)

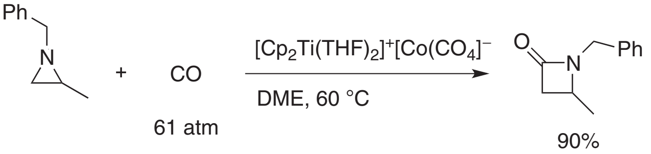
Alkynyl phenethyl amines give nitrogen-unsubstituted lactams via radical-mediated stannylcarbonylation followed by the elimination of a phenethyl radical (equation 64).[147]



(64)

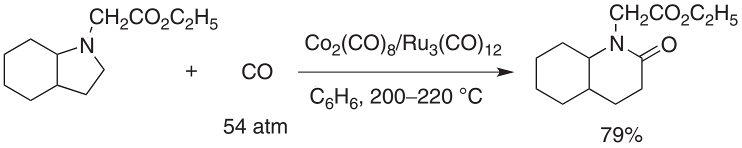
3.22.6 Carbonylative Ring-Expansion

The carbonylative ring-expansion of carbo- and heterocyclic compounds provides a straightforward method for producing carbonyl-containing carbo- and heterocycles.[148] For carbonylative ring-expansion of aziridines leading to *β*-lactams, the original work used $[RhCl(CO)_2]_2$ as the catalyst.[149] Recent work has shown that $[Cp_2Ti(THF)_2]^+[Co(CO)_4]^-$ prepared from $Cp_2Ti(CO)_2$ and $Co_2(CO)_8$ efficiently catalyzes the carbonylative ring-expansion of aziridines (equation 65).[150]



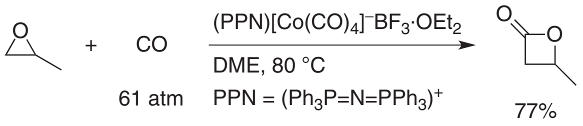
(65)

Pyrrolidinones[151] and piperidinones[152] are obtained from azetidines and pyrrolidines by carbonylative ring-expansion reaction. In the case of piperidinone synthesis, a dual catalyst system consisting of cobalt and ruthenium carbonyl is found to be effective to attain the transformation (equation 66).[152]



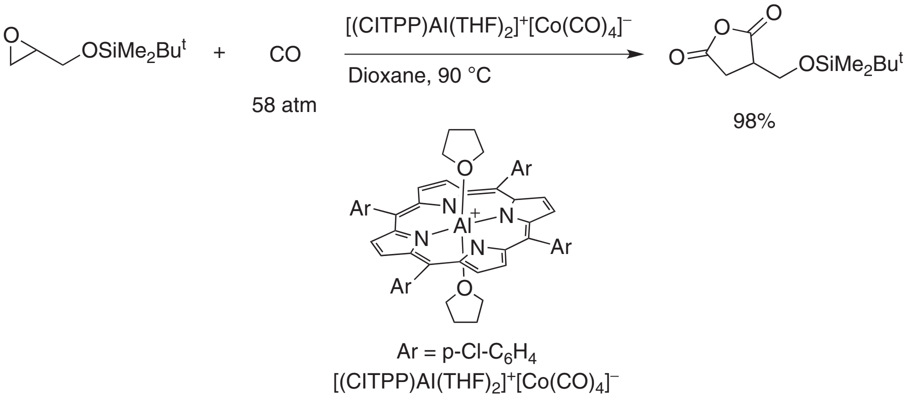
(66)

The carbonylative ring-expansion of epoxides to *β*-lactones is effectively catalyzed by a cobalt/Lewis acid combined system, $(PPN)[Co(CO)_4]^-/BF_3 \cdot OEt_2$ (equation 67).[153]



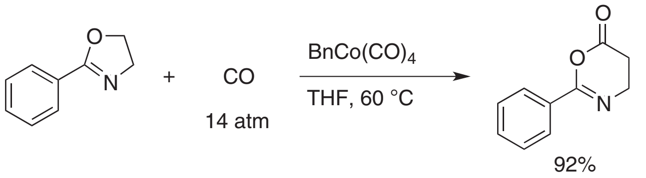
(67)

Recent work has demonstrated that double carbonylation of epoxides leading to succinic anhydrides can be catalyzed by $[(\mathrm{ClTPP})\mathrm{Al}(\mathrm{THF})_2]^+[\mathrm{Co(CO)_4}]^-$ (ClTPP, *meso*-tetra(4-chlorophenyl)porphyrinato) (equation 68).[154]



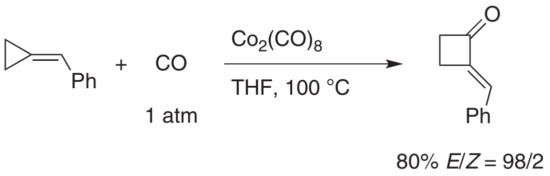
(68)

Benzyl cobalt carbonyl catalyzes the carbonylative ring-expansion of 2-aryl-2-oxazolines to give 4,5-dihydro-1,3-oxazin-6-one, in which carbonyl insertion into C–O bond takes place selectivity (equation 69).[155]



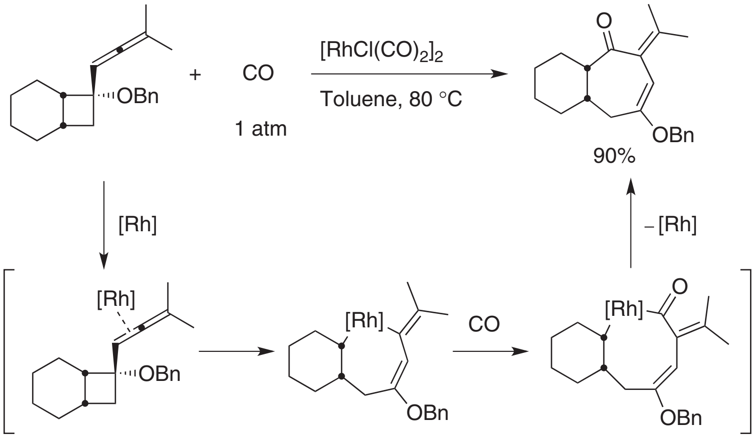
(69)

Carbonylative ring-expansion of methylenecyclopropanes to give methylenecyclobutanones is attained (equation 70), for which $\mathrm{Co_2(CO)_8}$ is used as the catalyst.[156]



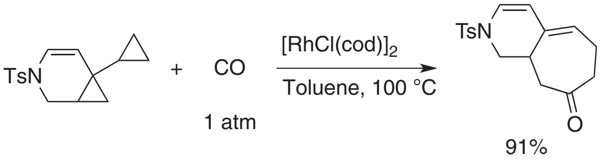
(70)

Allenyl substituted cyclobutane reacts with CO in the presence of $[\mathrm{RhCl(CO)_2}]_2$ to give ring-expanded cycloheptanone in good yield (equation 71).[157] In this reaction, rodacycles are proposed as key imtermediates.[157]



(71)

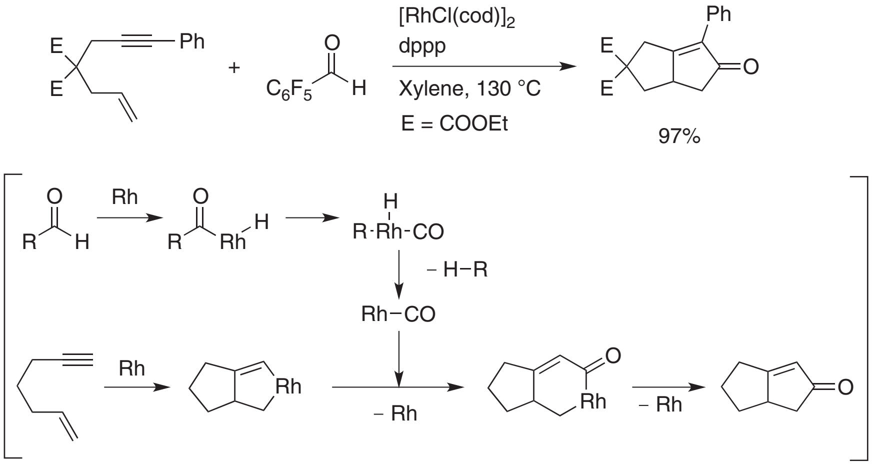
Rhodium-catalyzed carbonylation of biscyclopropanes with a vinyl substituent gives cycloheptenones in good yields, representing [3 + 3 + 1] cycloaddition (equation 72).[158]



(72)

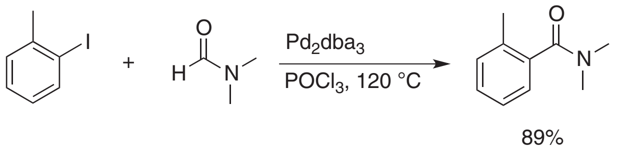
3.22.7 Carbonylation Without CO Gas

Although a wide variety of transition metal-catalyzed carbonylation reactions using CO gas have been extensively developed, the difficulty in handling toxic, gaseous carbon monoxide often limits its use in organic synthesis. Recently, new tools for the carbonylation reaction without the direct use of carbon monoxide have been developed.[159] Using pentafluorobenzaldehyde as a CO source, the rhodium-catalyzed Pauson–Khand reaction can be carried out without the use of CO gas (equation 73).[160] Reaction of enyne with *in situ*-generated CO from cinnamaldehyde is also possible.[161]



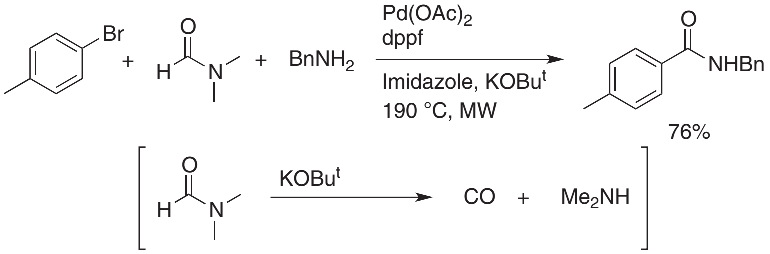
(73)

Pd-catalyzed aminocarbonylation of aryl and alkenyl iodides with *N*,*N*-dimethylformamide (DMF) proceeds in the presence of phosphoryl chloride to afford good yields of tertiary amides, in which imminium salt, formed from DMF and phospohoryl chloride, act as a carbamoyl source (equation 74).[162]



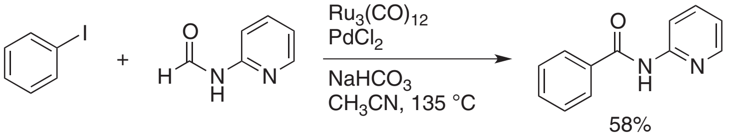
(74)

The amino carbonylation of aryl bromides proceeds under microwave irradiation conditions, in which DMF is employed as a CO source in conjunction with KOBu^t (equation 75).[163]



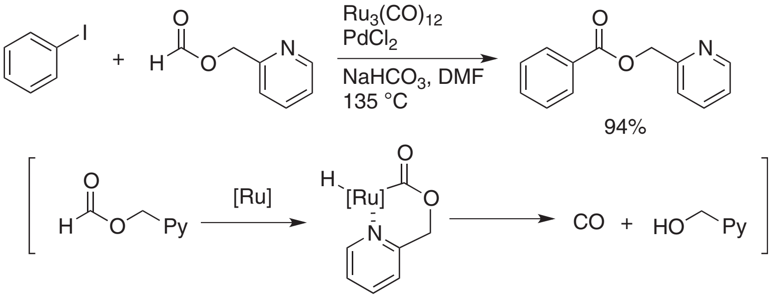
(75)

The reaction of aryl halides with formamide in the presence of ruthenium and palladium catalysts provides the aminocarbonylation product (equation 76).[164] In this reaction, ruthenium catalyzes the decarbonylation of formamide to yield CO and 2-aminopyridine, and palladium catalyzes the aminocarbonylation of aryl iodides with the formed CO and 2-aminopyridine.



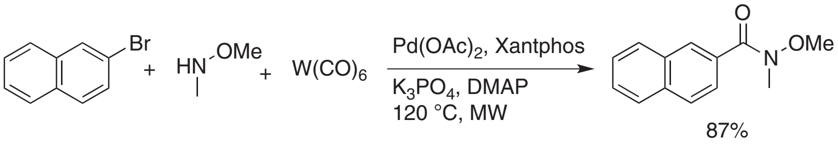
(76)

Formates can also serve as a CO source. The reaction of aryl iodides with formate gives benzoic esters in the Pd/Ru dual catalyst system, in which ruthenium-catalyzed decarbonylation of formate leads to *in situ* generation of CO which is subsequently used for palladium-catalyzed carbonylation (equation 77).[165]



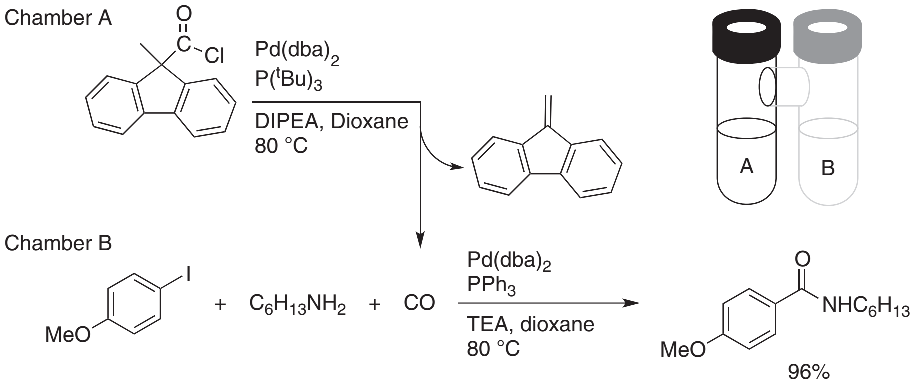
(77)

Metal carbonyl complexes, such as Cr(CO)$_6$, Mo(CO)$_6$, and W(CO)$_6$, can be used as the CO source in the palladium-catalyzed carbonylation.[166] Aminocarbonylation of aryl bromides with *O*,*N*-dimethylhydroxylamine in the presence of W(CO)$_6$ as a CO source furnishes good yields of the Weinreb amides (equation 78).[166]



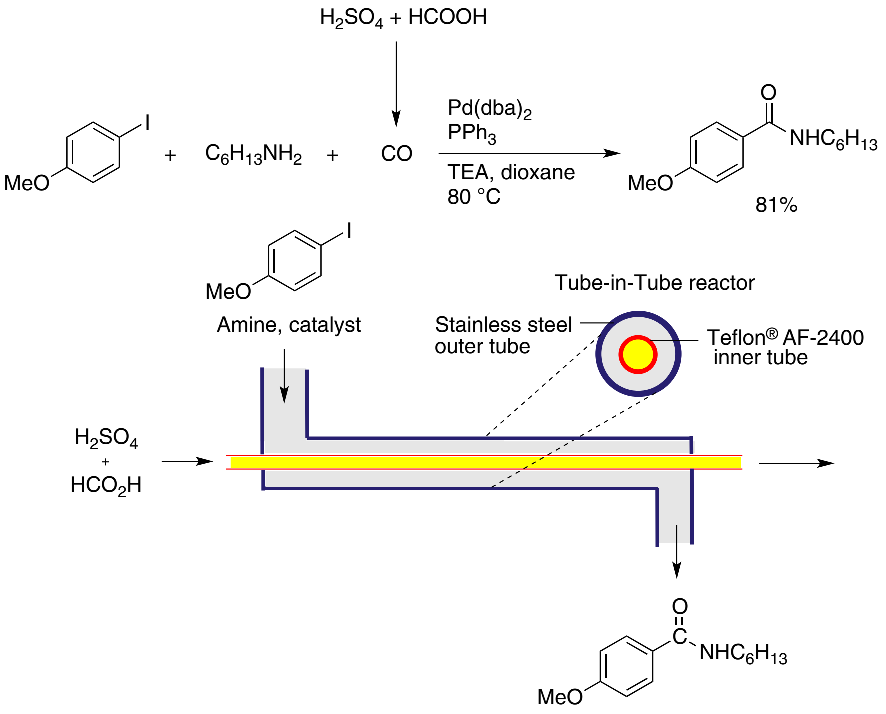
(78)

Although carbonylation reactions with *in situ*-generated CO represent an interesting protocol, it may be difficult to conduct the reaction in the same vessel in which all the reagents, catalysts, substrates, CO sources, and additives are mixed together. A practical protocol using a dual chamber flask as a CO generator has solved the problem. Aminocarbonylation of aryl iodides can be conducted applying this type of reactor (equation 79).[167] The Pd-catalyzed decarbonylation of acid chlorides generates CO in chamber A, which is consumed in a parallel aminocarbonylation in chamber B. This *ex situ* CO generation system allows the use of near stoichiometric amounts of CO. Isotope labeling experiment, incorporating ^{13}CO, can be easily conducted.



(79)

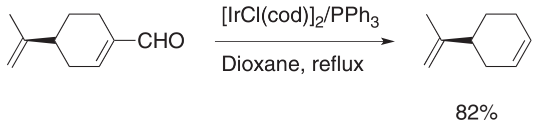
In a microflow system consisting of a gas-permeable tube (Teflon® AF-2400),[168] CO generated from H_2SO_4 and HCOOH can be used for the Pd-catalyzed aminocarbonylation of aryl iodides (equation 80).[169] The CO gas generated in the inner tube permeates through the tube to a solution of the Pd catalyst and substrates, and then reacts.



(80)

3.22.8 Decarbonylation

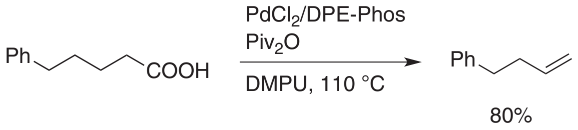
The catalytic decarbonylation of aliphatic and aromatic aldehydes by rhodium complexes are well investigated.[170] However, harsh reaction conditions (typically >160 °C) are required in order to realize the efficient decarbonylation of aldehydes. Iridium-catalyzed decarbonylation of aldehydes, using $[IrCl(cod)]_2$ with PPh_3, takes place under refluxing dioxane (102 °C) (equation 81).[171]



(81)

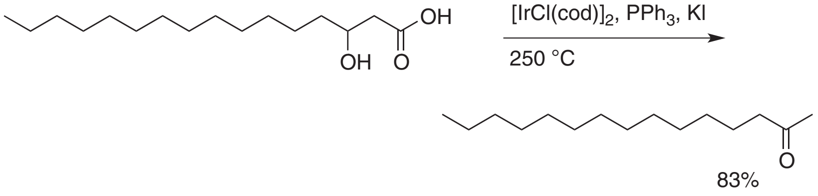
A variety of rhodium or palladium complexes are known to catalyze decarbonylation of aliphatic acid chlorides, in which alkenes are formed as products.[172] Decarbonylation of aliphatic carboxylic acids leading to alkenes are also investigated by using

Rh,[173] Pd,[174] Ir,[175] and Fe complexes as catalyst.[176] Generally high temperatures are necessary to affect the reaction, however, as shown in equation 82, addition of acid anhydride contributes to lower the reaction temperature dramatically.[174]



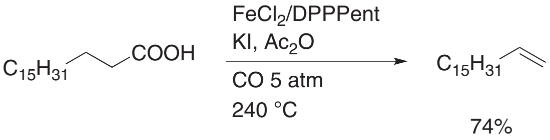
(82)

Vaska's complex in conjunction with KI works as a catalyst for the decarbonylation of aliphatic carboxylic acids.[175] In an example given in equation 83, ketone is formed via decarbonylative enol formation.



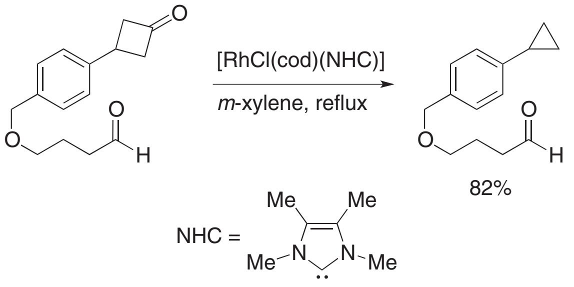
(83)

Recent work has revealed that $FeCl_2$/DPPPent (1,5-bis(diphenylphosphino)pentane) can replace expensive metal catalysts, in which the slightly pressurized CO conditions facilitate the reaction (equation 84).[176]



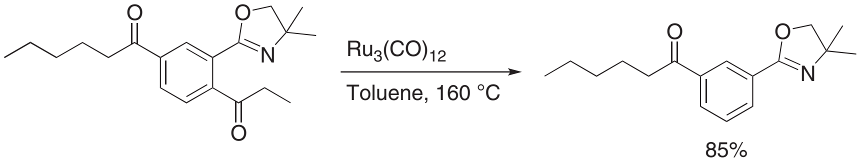
(84)

Decarbonylative ring contraction of cyclobutanone to give cyclopropane is achieved in the presence of rhodium–NHC catalyst (equation 85).[177] Interestingly, decarbonylation is chemoselective and a formyl group remains intact under the reaction conditions.



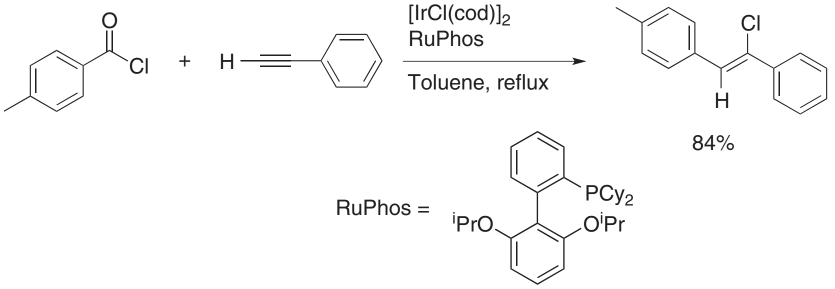
(85)

$Ru_3(CO)_{12}$-catalyzed decarbonylation of a bis-acylated phenyloxazoline takes place selectively at *ortho*-aryl group, which is accounted for the role of the directing group (equation 86).[178]



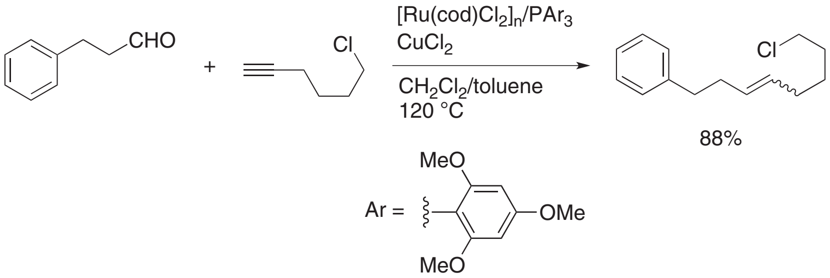
(86)

Cross-coupling reactions can be combined with catalytic decarbonylation. Decarbonylative addition of acid chlorides to terminal alkynes is catalyzed by rhodium[179] and iridium[180] complexes to give the corresponding vinyl chlorides having Z-geometry (equation 87).



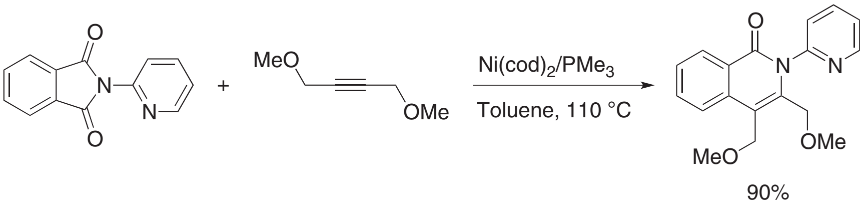
(87)

A catalyst system comprising $[Ru(cod)Cl_2]_2$ and $CuCl_2$ affects decarbonylative addition of aliphatic aldehydes to terminal alkynes (equation 88).[181]



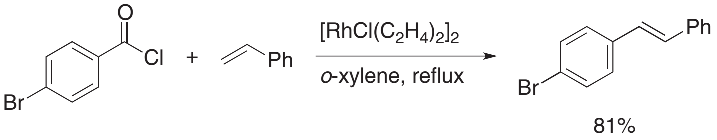
(88)

Decarbonylative cycloaddition of *N*-arylphthalimides with internal alkynes is effectively catalyzed by $Ni(cod)_2/PMe_3$. Isoquinolones are obtained in high yields (equation 89).[182]



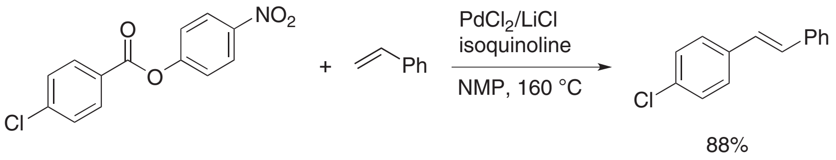
(89)

The decarbonylative Mizoroki–Heck-type arylation of alkenes with acid chlorides can be performed by a rhodium catalyst (equation 90).[183] This reaction requires neither any phosphine ligand nor base.



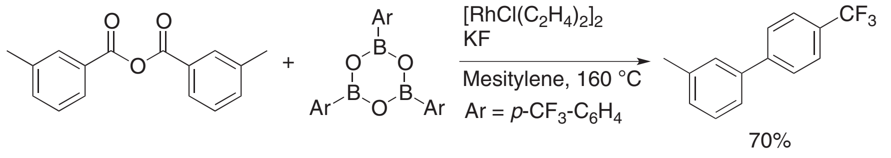
(90)

The decarbonylative Mizoroki–Heck-type reaction of *p*-nitrophenol esters proceeds using a catalytic amount of $PdCl_2/LiCl/$isoquinoline at 160 °C (equation 91).[184]



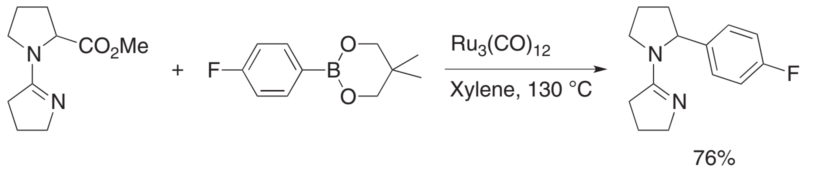
(91)

Rhodium-catalyzed decarbonylative Suzuki–Miyaura coupling of acid anhydrides with arylboroxines leads to the formation of biaryls (equation 92).[185]



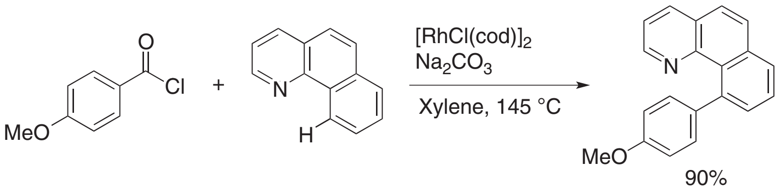
(92)

$Ru_3(CO)_{12}$-catalyzed carbonylative Suzuki–Miyaura coupling reaction of esters is achieved in a system having a nitrogen directing group. This reaction attains C(sp^2)–C(sp^3) bond formation (equation 93).[186]



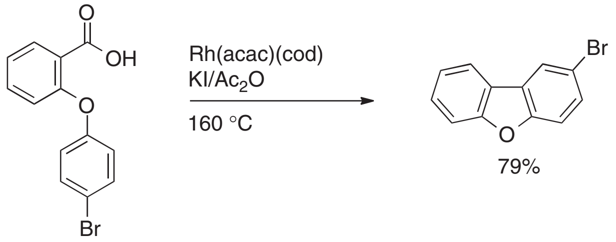
(93)

Decarbonylative coupling of acid halides with aromatic C–H bonds takes place using a rhodium catalyst, in which nitrogen in the aromatic substrate acts as a directing group (equation 94).[187]



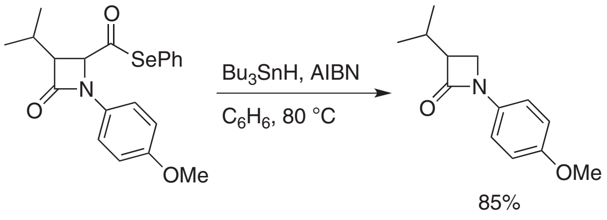
(94)

Decarbonylative intramolecular C-H arylation of 2-aryloxybenzoic acids leading to dibenzofuran derivatives is effectively catalyzed by Rh(acac)(cod) in the presence of KI and Ac_2O (equation 95).[188] The reaction is widely applicable to substrates bearing various functionalities, which involves halogen substituents.



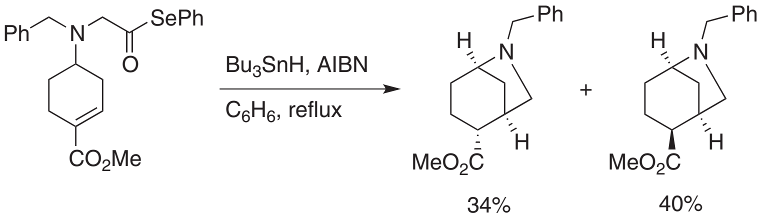
(95)

Radical-mediated decarbonylation of acyl chlorides or selenoesters using AIBN/tributyltin hydride, proceeds to give alkanes in good yields, in which decarbonylation of acyl radical to give stable amido alkyl radical takes place (equation 96).[189]



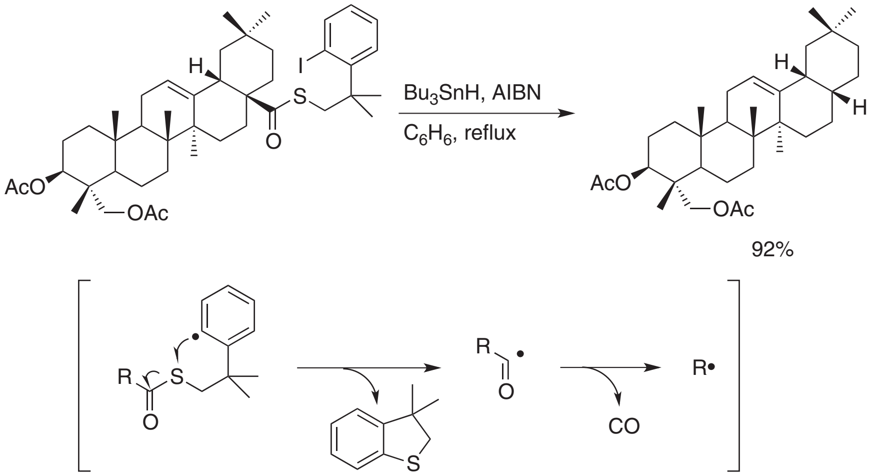
(96)

Radical-mediated decarbonylation of α-amino selenoesters is successfully sequenced by 5-*exo* cyclization to give *N*-heterocyclic compounds (equation 97).[190]



(97)

Thioesters are rarely used for radical decarbonylation reactions because of the relatively strong C–S bonds compared with C–Se bonds. However, intramolecular homolytic substitution at sulfur does proceed to lead to the formation of an acyl radical, which undergoes decarbonylation and hydrogen abstraction (equation 98).[191]



(98)

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3.23 Carbon–Carbon σ-Bond Formation via C–H Bond Functionalization

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3.23.1 **Introduction** 1102
3.23.2 **Reactions with C–C/C–X Multiple Bonds** 1103
3.23.2.1 Reactions with C–C Multiple Bonds 1103
3.23.2.1.1 Palladium-catalyzed reactions with C–C multiple bonds 1103
3.23.2.1.1.1 Palladium-catalyzed reactions of simple (hetero)arenes with alkenes 1103
3.23.2.1.1.2 Palladium-catalyzed directing group-assisted reactions with alkenes 1107
3.23.2.1.1.3 Palladium-catalyzed reactions of C–H bonds with alkynes 1111
3.23.2.1.2 Rhodium-catalyzed reactions with C–C multiple bonds 1112
3.23.2.1.2.1 Rh(I)-catalyzed C–H alkylation with alkenes 1112
3.23.2.1.2.2 Rh(III)-catalyzed C–H alkenylation with alkenes 1115
3.23.2.1.2.3 Rh-catalyzed reactions of C–H bonds with alkynes 1116
3.23.2.1.3 Ruthenium-catalyzed reactions with C–C multiple bonds 1119
3.23.2.1.4 Other transition-metal-catalyzed reactions with C–C multiple bonds 1123
3.23.2.1.4.1 Nickel-catalyzed reactions of C–H bonds with C–C multiple bonds 1123
3.23.2.1.4.2 Iridium, platinum, and rhenium-catalyzed reactions of C–H bonds with C–C multiple bonds 1125
3.23.2.2 Reactions with C=O and C=N Bonds 1127
3.23.2.2.1 Palladium-catalyzed reactions of C–H bonds with aldehydes and imines 1127
3.23.2.2.2 Other-transition-metal-catalyzed reactions of C–H bonds with C=O and C=N bonds 1129
3.23.2.2.3 Carboxylation of C–H bonds with CO_2 1131
3.23.2.2.4 Reactions of C–H bonds with nitriles 1132
3.23.2.3 Reactions with CO 1133
3.23.2.3.1 Palladium-catalyzed reactions of C–H bonds with CO 1133
3.23.2.3.2 Rhodium-catalyzed reactions of C–H bonds with CO 1135
3.23.2.3.3 Ruthenium-catalyzed reactions of C–H bonds with CO 1136
3.23.3 **Reactions with (Pseudo)halides** 1139
3.23.3.1 Pd-Catalyzed Reactions with (Pseudo)halides 1140
3.23.3.1.1 Pd-catalyzed nondirected reactions of (hetero)arenes with (pseudo)halides 1140
3.23.3.1.1.1 Pd-catalyzed nondirected reactions of (hetero)arenes with (pseudo)halides via Pd(0)/Pd(II) catalytic cycle 1141
3.23.3.1.1.2 Pd-catalyzed nondirected reactions of (hetero)arenes with (pseudo)halides via Pd(II)/Pd(IV) catalytic cycle 1148
3.23.3.1.2 Pd-catalyzed-directed reactions of (hetero)arenes with (pseudo)halides 1148
3.23.3.1.2.1 Pd-catalyzed-directed reactions of (hetero)arenes with (pseudo)halides via Pd(0)/Pd(II) catalytic cycle 1148
3.23.3.1.2.2 Pd-catalyzed-directed reactions of (hetero)arenes with (pseudo)halides via Pd(II)/Pd(IV) catalytic cycle 1150
3.23.3.1.3 Pd-catalyzed arylation of C(sp^3)-H bonds with aryl (pseudo)halides 1152
3.23.3.2 Rhodium-Catalyzed Reactions with (Pseudo)halides 1156
3.23.3.2.1 Rhodium-catalyzed nondirected reactions with (pseudo)halides 1156
3.23.3.2.2 Rhodium-catalyzed-directed reactions with (pseudo)halides 1158
3.23.3.3 Ruthenium-Catalyzed Reactions with (Pseudo)halides 1159
3.23.3.4 Other Transition-Metal-Catalyzed Reactions with (Pseudo)halides 1162
3.23.3.4.1 Copper-catalyzed reactions with (pseudo)halides 1162
3.23.3.4.2 Nickel-catalyzed reactions with (pseudo)halides 1163
3.23.3.4.3 Iron/cobalt/iridium-catalyzed reactions with (pseudo)halides 1166
3.23.4 **Reactions with Organometallic Reagents** 1168
3.23.4.1 Palladium-Catalyzed Reactions with Organometallic Reagents 1168
3.23.4.1.1 Palladium-catalyzed coupling of C(sp^2)-H bonds with organometallic reagents 1168
3.23.4.1.2 Palladium-catalyzed coupling of C(sp^3)-H bonds with organometallic reagents 1173
3.23.4.2 Rhodium-Catalyzed Reactions with Organometallic Reagents 1175
3.23.4.3 Ruthenium-Catalyzed Reactions with Organometallic Reagents 1176
3.23.4.4 Iron, Cobalt, and Nickel-Catalyzed Reactions with Organometallic Reagents 1178
3.23.5 **Reactions with C–H Bonds** 1181
3.23.5.1 Palladium-Catalyzed Reactions with C–H Bonds 1181
3.23.5.1.1 Palladium-catalyzed homocoupling of two C–H bonds 1181
3.23.5.1.2 Palladium-catalyzed coupling of two different C–H bonds 1182
3.23.5.1.3 Palladium-catalyzed intramolecular coupling of two C–H bonds 1186

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3.23.5.1.4 Palladium-catalyzed-directed coupling of two C—H bonds 1188
3.23.5.2 Other Transition-Metal-Catalyzed Reactions with C—H Bonds 1190
3.23.6 Miscellaneous C—H Functionalization Reactions 1192
3.23.6.1 C—H Alkynylation with Terminal Alkynes 1192
3.23.6.2 Decarboxylative C—H Arylation with Aromatic Acids 1195
3.23.6.3 C—H Trifluoromethylation 1197
3.23.6.4 C—H Alkylation with α C—H Bonds of Carbonyl Groups 1199
3.23.7 Summary and Outlook 1202
References 1203

3.23.1 Introduction

Organic synthesis relies mainly on the manipulation of functional groups, chemical moieties exhibiting relatively high reactivity. Owing to their inertness, carbon–hydrogen (C–H) bonds are not generally viewed as functional groups in this context.[1] Not only is the introduction of functional groups often laborious and time-consuming, but quite often, the synthetic sequences to manipulate these functional groups often generate unnecessary chemical waste. Direct functionalization of C–H bonds, which are ubiquitous in organic molecules, would allow unproductive functional groups manipulations to be avoided and would reduce chemical waste because theoretically, this technology would not produce any byproducts except molecular hydrogen. Moreover, since C–H functionalization can introduce new functionalities directly through the transformation of C–H bonds, this class of reactions also provides opportunities for markedly different synthetic strategies, offering distinct retrosynthetic approaches to the synthesis of complex molecules, while at the same time, increasing overall efficiency and reducing step-count.

Although it is challenging to activate C–H bonds because of their high bond strength and low polarity, a number of C–H functionalization reactions have nonetheless been developed.[2] Nature functionalizes C–H bonds using enzymes highly efficiently and selectively, and it has inspired chemists to successfully develop enzymatic C–H functionalization reactions.[3] Moreover, C–H functionalization via radicals was discovered a long time ago and has been extensively exploited.[4] It is important to note that although there are a number of other classic reactions involving C–H bond disconnection, such as electrophilic aromatic substitution, directed ortholithiation, and enolate chemistry, these reactions normally are not categorized as C–H functionalization reactions.

In recent decades, transition-metal catalysis has emerged as an effective means for effecting C–H insertion, and as a consequence, a number of new C–H bond transformations have been developed, and a variety of chemical bonds can be formed in an efficient manner, including carbon–carbon bond and carbon–heteroatom,[5] C–O,[6] C–N,[7] C–B,[8] C–Si, C–S, and C–X (X=F, Cl, Br, I) bond formation. Remarkably, although in its infancy, transition-metal-catalyzed C–H functionalization has proved applicable in the total synthesis of complex organic molecules.[9,10]

Because C–H bonds are ubiquitous in organic molecules, the desired C–H bonds must be activated selectively to develop synthetically useful reactions. Although regioselective C–H functionalization can be achieved by taking advantage of differentiated electronic properties or steric effects of different C–H bonds, it is usually a challenge to functionalize C–H bonds selectively. Currently, a directing group is often employed in a number of transition-metal-catalyzed C–H functionalization reactions. The directing groups are usually functional groups containing heteroatoms such as oxygen and nitrogen, which can coordinate with transition metals and force transition metals to cleave proximal C–H bonds selectively. Furthermore, the directing groups facilitate C–H activation by delivering transition metals to C–H bonds.[11]

A variety of carbon–heteroatom bond-forming reactions have been developed based on C–H activation. However, in light of the great advantages of transition metals in organic synthesis for constructing carbon–carbon bonds (primarily σ-bonds), transition-metal-catalyzed carbon–carbon bond-forming reactions via C–H activation are very attractive. A wide range of carbon–carbon σ-bonds, including C(sp^2)-C(sp^2), C(sp^2)-C(sp^3), C(sp^2)-C(sp), and C(sp^3)-C(sp^3), can be formed via C–H activation.[12–14] In addition, a wide range of transition metals have been found to be able to promote C–C bond formation via C–H activation. As their role in the regular transition-metal-catalyzed reactions, palladium,[15] rhodium,[16] and ruthenium[17] are the most-investigated transition metals in this research field. However, other transition metals have also been found to catalyze C–H functionalization reactions. The first-row transition metals are very attractive as catalysts because of their abundance and low cost, and have been extensively utilized to catalyze C–H functionalization reaction.[18] The reactions catalyzed by the third-row transition metals, such as Au, Pt, Ir, and Re, have also been reported.

This chapter aims to provide a comprehensive survey of transition-metal-catalyzed carbon–carbon σ-bond formation reactions via C–H activation. It is noted that the reactions involving radical pathways or transition-metal-carbenoids[19] are not covered here. However, some examples will be described in some sections. Au-catalyzed C–H functionalization[20] and Catellani reaction,[21] which involves norbornene-mediated C–H functionalization, have been reviewed, so these reactions are beyond the scope of this chapter. Furthermore, numerous C–H functionalization reactions have been developed, it is impossible to cover all of them. We apologize for not being able to include every reaction, although they are very important.

This chapter is organized based on the reaction partners of C–H bonds, and it consists of five sections: (1) multiple carbon–carbon/heteroatom bonds; (2) aryl/alkyl (pseudo)halides; (3) organometallic reagents; (4) C–H bonds; and (5) other miscellaneous reactions. Some sections are further divided into several subsections if more than one type of reaction partners is available in the sections. The reactions in each section are organized based on the transition-metal catalysts used in the reactions, normally starting from palladium, followed by rhodium and ruthenium, and ended with other transition metals. For each type of reactions, a general mechanism, if available, will be discussed.

3.23.2 Reactions with C–C/C–X Multiple Bonds

In the presence of transition-metal catalysts, C–H bonds can react with a variety of multibonds, including C–C multibonds (alkenes and alkynes) and polar C–X multibonds (aldehydes, carbonyls, imines, and carbon monoxide), providing an atom-economical strategy to form C–C bonds.[22] A wide range of transition metals have been developed as efficient catalysts to promote such reactions, and numerous examples are available. In addition, the reactions of C–H bonds with carbon dioxide and cyanides have also been reported.

3.23.2.1 Reactions with C–C Multiple Bonds

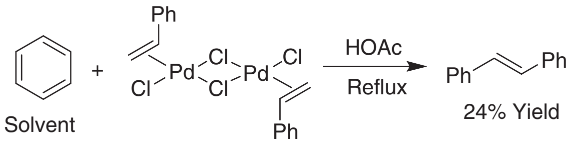
The addition of C–H bond to C–C multibonds is one of the most-investigated C–H activation reactions. The reactions with alkenes can form either alkenylated or alkylated products, depending on catalysts and reaction conditions. On the contrary, the addition to alkynes only leads to alkenylation products.

3.23.2.1.1 Palladium-catalyzed reactions with C–C multiple bonds

As one of the most widely used transition metals in organic synthesis, Pd is an attractive catalyst for C–H functionalization. Although Pd(0) is used as the primary catalyst in traditional cross-coupling reactions involving oxidative addition of aryl/alkyl (pseudo)halides, Pd(II) is active for C–H cleavage. As Pd has versatile reactivity in traditional Pd(0)-catalyzed cross-coupling reactions, a variety of Pd(II)-catalyzed C–H functionalization reactions have been developed that emulate this reactivity; and currently, most modes of bond construction that can be achieved with traditional Pd(0)-catalyzed cross-coupling reactions have been realized through C–H activation. The coupling partners for Pd-catalyzed C–H functionalization reactions mainly include C–C multiple bonds, CO, (pseudo) halides, organometallics, and other C–H bonds.

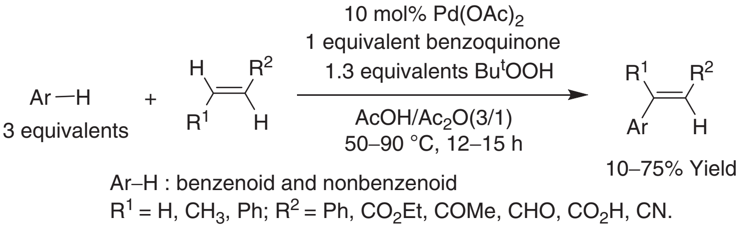
3.23.2.1.1.1 Palladium-catalyzed reactions of simple (hetero)arenes with alkenes

In 1967, Fujiwara and Moritani disclosed the first example of stoichiometric oxidative coupling of arenes with olefins (Scheme 1).[23] A styrene-palladium chloride dimer reacted with benzene to give *trans*-stilbene by refluxing in a mixture of benzene and acetic acid. The reactivities of different arenes and the regioselectivities found with substituted benzenes were similar to those of electrophilic aromatic substitution. Moreover, the use of acids was required. Hence, the authors proposed that the first step of the reaction involved electrophilic aromatic substitution to form an aromatic Pd σ complex, which was followed by its addition to the olefin and elimination of a Pd-H unit to give olefination products.[24]



Scheme 1 Pd-mediated stoichiometric olefination of benzene with styrene (Fujiwara et al., 1967).

Fujiwara's pioneering work was the starting point of direct arylation of olefins, and a number of reactions of this type have been developed.[25] Much effort was made to develop catalytic reactions, and a variety of oxidation systems were successfully developed. One of the efficient examples is the olefination of arenes using peroxide as the oxidant (Scheme 2).[26]



Scheme 2 Pd-catalyzed olefination of benzene with *tert*-butyl hydroperoxide as oxidant (Fujiwara et al., 1999).

A typical mechanism for Pd-catalyzed reactions of C–H bonds with alkenes is shown in Figure 1.[15] Therefore, Pd(II) catalysts cleave C–H bonds to form arylpalladium(II) species. The subsequent reaction steps are analogous to those in Heck reaction, which include migratory insertion and β-H elimination, affording alkenylation products and releasing Pd(0). The generated Pd(0) needs to reoxidize to Pd(II) catalyst to continue catalytic cycles.

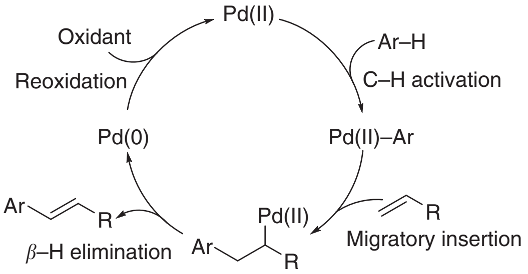
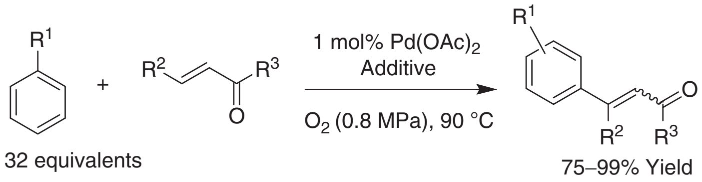


Figure 1 A general mechanism for Pd-catalyzed reactions of C–H bonds with alkenes.

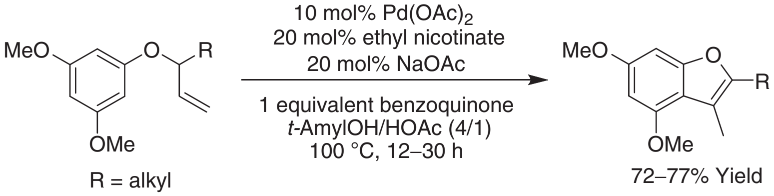
However, there are still two major drawbacks which hampered the application of the olefination of simple arenes. The first one was a lack of the control of regioselectivity when substituted benzene was used as the substrate, and the reaction often gave a mixture with *ortho-*, *para-*, *meta-*isomers, as shown in Scheme 3.[27] The second was that a large excess of arenes was required.



R^1 = H, Me, OMe; R^2 = H, Ph; R^3 = OBu, OEt, Me.
Additive: $Mn(acac)_2$, $Co(OAc)_2{\cdot}4H_2O$, $Mn(OAc)_3{\cdot}2H_2O$, PhCOOH.

Scheme 3 Pd-catalyzed direct olefination of monosubstituted benzenes (Jacobs et al., 2003).

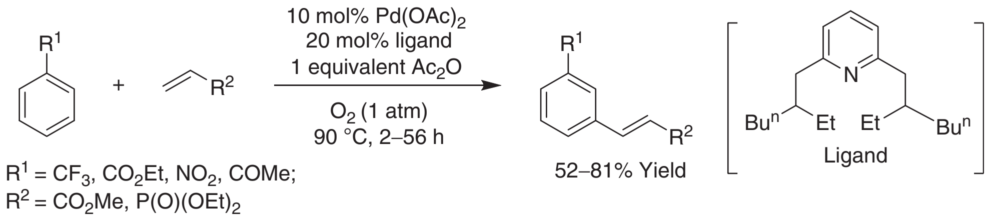
Intramolecular reactions have also been reported. In 2004, Stoltz and coworkers developed an intramolecular C–H olefination reaction using highly electron-rich arenes, which contained multiple methoxy substituents on the arene moiety (Scheme 4).[28] This protocol provides access to highly substituted benzofuran and dihydrobenzofuran derivatives. Notably, mechanistic studies in this work provided strong evidence that the reaction proceeded by C–H cleavage and the subsequent Heck-type olefination, instead of Pd-catalyzed nucleophilic attack of arenes.



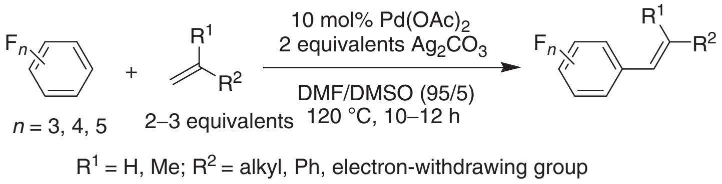
Scheme 4 Pd(II)-catalyzed intramolecular olefination of electron-rich arenes for the synthesis of benzofuran and dihydrobenzofuran (Stoltz et al., 2004).

Since the above C–H activation was an electrophilic process, electron-deficient arenes were unreactive in these reactions. An unprecedented olefination of electron-deficient arenes has been described by Yu and coworkers (Scheme 5).[29] A wide range of arenes possessing electron-withdrawing groups can react with olefins using 1 atm O_2 as the oxidant and 2,6-disubstituted pyridine as the ligand. Notably, the reactions gave *meta*-olefinated arenes as the major products because of the ligand, which is remarkable considering that the reactions of simple arenes gave a mixture of isomers and the use of directing groups leads to *ortho*-products.

Recently, an elegant example of direct C–H olefination of highly electron-deficient arenes has been reported by Zhang and coworkers (Scheme 6).[30] Thus, perfluoro arenes were olefinated with a variety of olefins including activated and nonactivated ones.

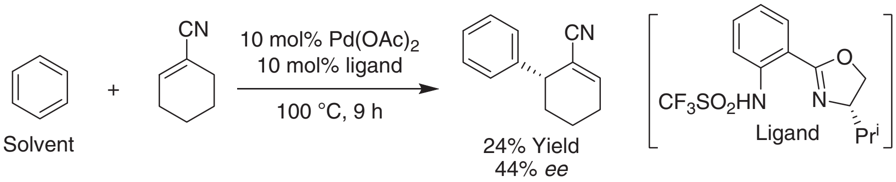


Scheme 5 Pd-catalyzed *meta*-selective olefination of electron-deficient arenes (Yu et al., 2009).



Scheme 6 Pd(II)-catalyzed direct olefination of perfluoroarenes (Zhang et al., 2010).

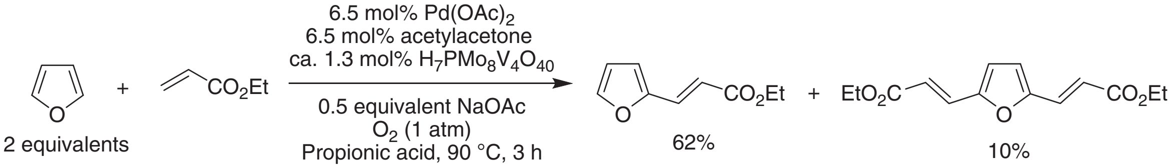
Interestingly, although with low enantiomeric excess, asymmetric C–H olefination of benzene has been demonstrated with a chiral sulfonylamino-oxazoline ligand (Scheme 7).[31] The creation of a chiral center was made possible by using cyclic alkenes as the substrate, which forced β-hydride elimination to occur from the opposite position to the entering phenyl group.



Scheme 7 Pd-catalyzed asymmetric olefination of benzene (Terada et al., 1999).

Not surprisingly, heteroarenes can undergo similar Pd(II)-catalyzed C–H olefination to simple arenes. The stoichiometric reactions were reported as early as 1972.[32,33] Since then, a number of catalytic C–H olefination reactions of heteroarenes have been developed, and a wide range of heteroarenes, mainly electron-rich heteroarenes including furan, benzofuran, benzothiophene, pyrrole, and indole, have been found to be reactive.[25] Although the olefination reactions of monosubstituted arenes usually gave a mixture of regioisomers, heteroarenes were often olefinated regioselectively by taking advantage of differentiated electronic properties of C–H bonds on heteroarenes.

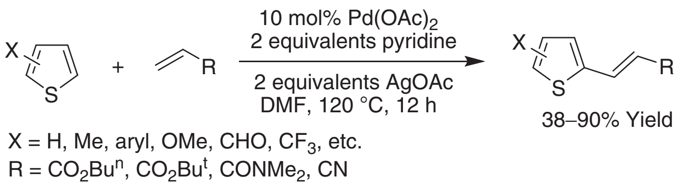
Pd-catalyzed C–H olefination of furans largely took place at the α-position, and 2,5-difuncationalized product was often formed. One of the elegant examples is shown in Scheme 8.[34]



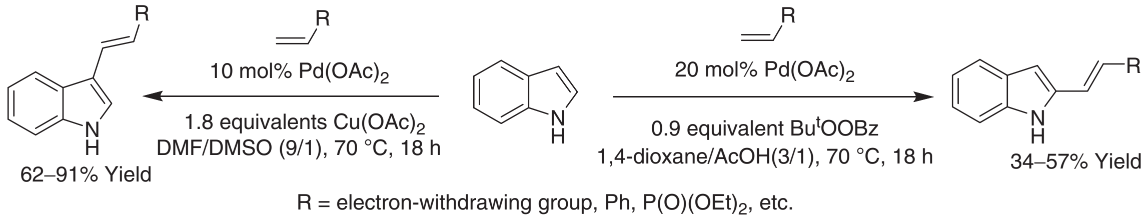
Scheme 8 Pd-catalyzed direct olefination of furan (Ishii et al., 2003).

Many of Pd(II)-catalyzed reaction protocols between furans and olefins have been applied to the C–H olefination of thiophenes. An example mainly devoted to thiophenes was recently reported by Zhang and coworkers (Scheme 9).[35] A variety of thiophenes reacted with a wide range of activated alkenes to give monoalkenylated products at the α-positions.

The first Pd-catalyzed C–H olefination of *N*-arenes was reported as early as in 1983. Thus, Itahara and coworkers disclosed the olefination of 1-(2,6-dichlorobenzoyl) indole with methyl acrylate to give the 3-substituted product.[36] Although most of the current C–H olefination reactions of indoles mainly led to the 3-substituted product when both 2- and 3-positions are available, 2-substituted products could also be formed. In 2005, Gaunt and coworkers described a general method for the regioselective functionalization of free indole. Either 2- or 3-olefinated indoles could be synthesized by using different solvents (Scheme 10).[37]

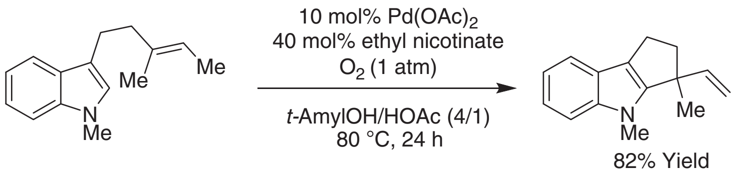


Scheme 9 Pd-catalyzed direct olefination of thiophenes (Zhang et al., 2009).

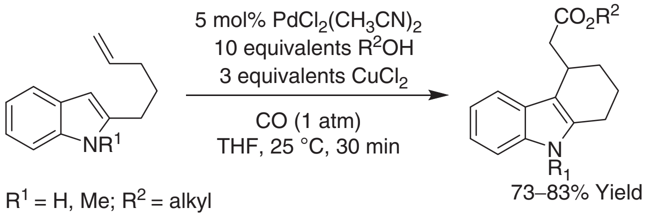


Scheme 10 Solvent-controlled regioselective Pd-catalyzed olefination of indoles (Gaunt et al., 2005).

Intramolecular C–H olefinations of indoles have also been reported. Both 2- and 3-positions of indoles could be readily functionalized, even with unactivated double bonds (Schemes 11 and 12).[38,39]

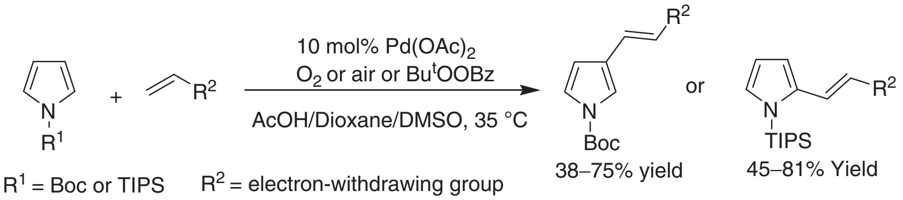


Scheme 11 Pd-catalyzed intramolecular olefination of indoles using O_2 as the oxidant (Stoltz et al., 2003).



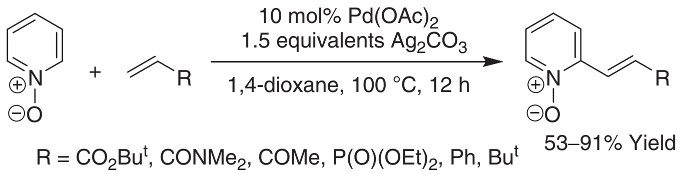
Scheme 12 Pd-catalyzed intramolecular olefination/carboalkoxylation of indoles (Widenhoefer et al., 2004).

Gaunt and coworkers also reported C–H olefination of pyrroles (Scheme 13).[40] Interestingly, depending on the *N*-substituents of pyrroles, either 2- or 3-olefinated products could be formed regioselectively.



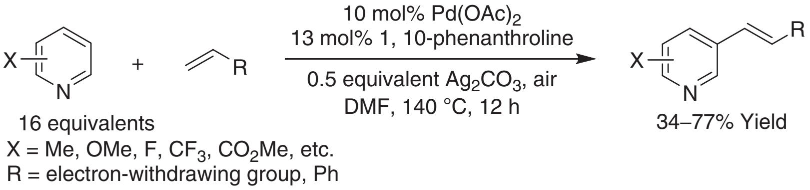
Scheme 13 Protecting group-controlled regioselective Pd-catalyzed olefination of pyrroles (Gaunt et al., 2006).

Pd-catalyzed C–H functionalization of pyridine has been a challenge because of the poor electron density of the pyridine ring. This problem has been solved by employing pyridine *N*-oxide as the reactant. In 2008, the C2-selective olefination of pyridine *N*-oxide was described by Chang and coworkers (Scheme 14).[41] Remarkably, the C–H olefination of simple pyridines has also



Scheme 14 Pd-catalyzed olefination of pyridine *N*-oxides (Chang et al., 2008).

been achieved using 1,10-phenanthroline as the ligand by Yu and coworkers. It is noted that the C-3-positions were selectively olefinated (**Scheme 15**).[42]

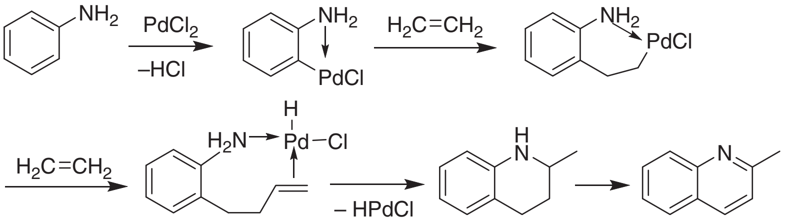


Scheme 15 Pd-catalyzed C-3 selective olefination of pyridines (Yu et al., 2011).

Pd-catalyzed C–H olefination of a variety of other heteroarenes has also been reported, such as thiazoles and oxazoles,[43] indolizines,[44] 1,2,3-triazoles.[45]

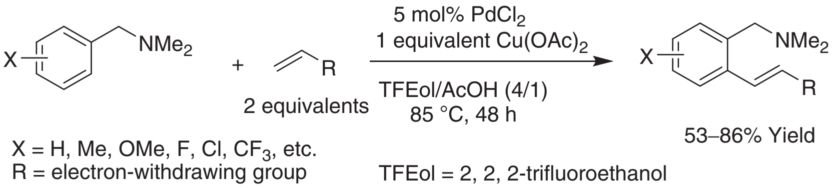
3.23.2.1.1.2 Palladium-catalyzed directing group-assisted reactions with alkenes

As mentioned in Section 3.23.1, a directing group leads to *ortho*-selectivity in transition-metal-involved C–H activation. A variety of directing groups have been employed in Pd-catalyzed C–H olefination reactions. The amino group is one of the earliest directing groups. In 1969, Tsuji and coworkers disclosed the reaction of the cyclopalladation complex of *N*,*N*-dimethylbenzylamine with styrene.[46] The Pd-catalyzed reaction of aniline with ethane was also reported in 1979 (**Scheme 16**).[47]



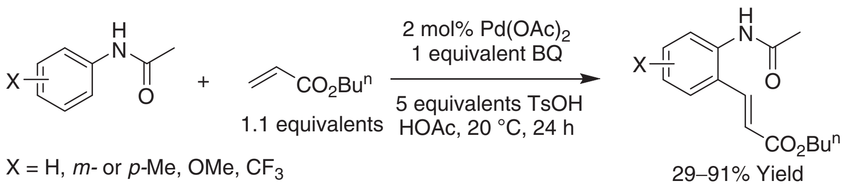
Scheme 16 Pd-catalyzed amino-directed olefination (Diamond et al., 1979).[25]

A catalytic C–H olefination of *N*,*N*-dimethylbenzylamines was described by Shi and coworkers in 2007 (**Scheme 17**). Therefore, a wide range of benzylamines were olefinated by reacting with activated alkenes. It is noted that the amino group could be removed to make this protocol more useful.[48]



Scheme 17 Pd-catalyzed amino-directed olefination of benzylamines (Shi et al., 2007).

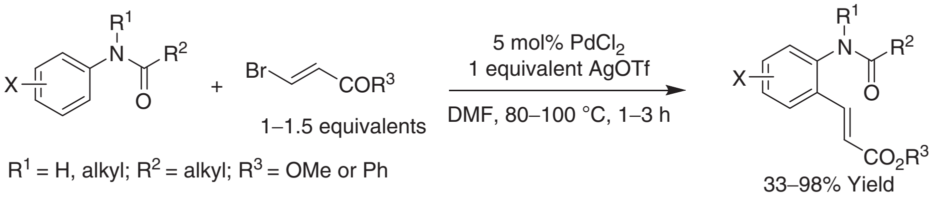
An early example involving the stoichiometric vinylation of acetanilides with alkenes in the presence of $Pd(OAc)_2$ was disclosed by Horino and Inoue in 1981.[49] After approximately 20 years, Leeuwen and coworkers described the catalytic C–H olefination of anilides (**Scheme 18**).[50] Remarkably, the reactions proceeded smoothly at room temperature.



Scheme 18 Pd-catalyzed amide-directed olefination of anilides (de Vries and van Leeuwen et al., 2002).

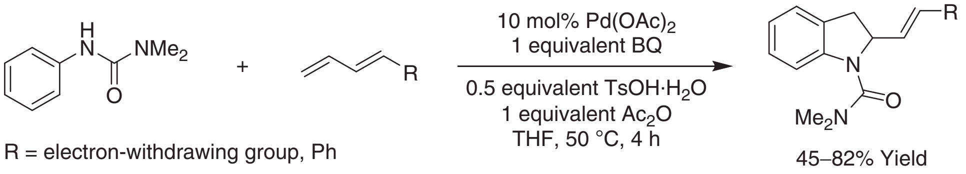
In 2010, an interesting work regarding C–H olefination of anilides was reported by Lipshutz and coworkers.[51] This reaction was carried out in water as the only medium. Furthermore, a highly active cationic Pd(II) catalyst, $[Pd(MeCN)_4](BF_4)_2$, was found to be able to activate aromatic C–H bonds efficiently.

Pd-catalyzed C–H olefination of anilides was also made possible by reacting with haloolefins instead of simple alkenes (Scheme 19).[52] In this reaction, the final β-halo elimination gave the same olefinated products as those in the reaction with simple alkenes.



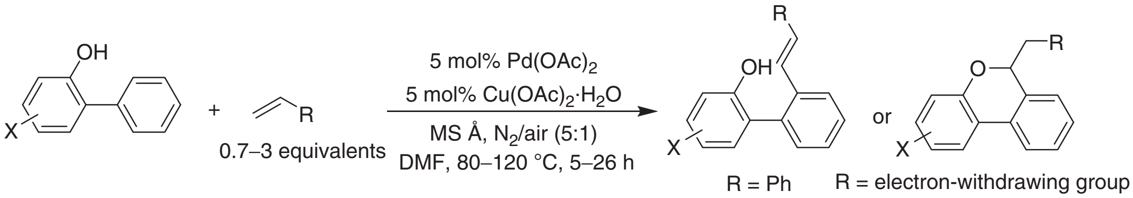
Scheme 19 Pd-catalyzed amide-directed olefination of anilides with haloolefins (Daugulis et al., 2005).

The urea group was also successfully employed to direct C–H activation by Booker-Milburn and coworkers (Scheme 20).[53] Thus, N-methyl-N′-phenyl ureas were found to react with a wide range of dienes, and subsequent cyclization formed indoline derivatives.



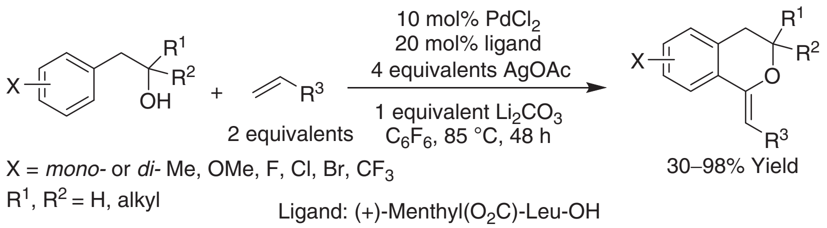
Scheme 20 Pd-catalyzed urea-directed 1,2-carboamination of arylureas with dienes (Booker-Milburn et al., 2008).

In 1997, Miura and coworkers reported Pd-catalyzed olefination of 2-phenylphenols (Scheme 21).[54] In this reaction, the hydroxyl of the phenol functions as the directing group by chelating with palladium. Employing a hydroxy group on a saturated carbon is challenging, because Pd(II) is known to oxidize primary and secondary alcohols and decompose tertiary alcohols.[55] This problem was addressed by Yu and coworkers in 2010 (Scheme 22).[55] Therefore, a wide range of phenylethyl alcohols were olefinated in the presence of a base. Although a tertiary hydroxy was employed as the directing group in most cases, a primary and secondary alcohol was also compatible albeit with a low yield. Notably, a mono-N-protected amino acid ligand was found to promote the reaction.

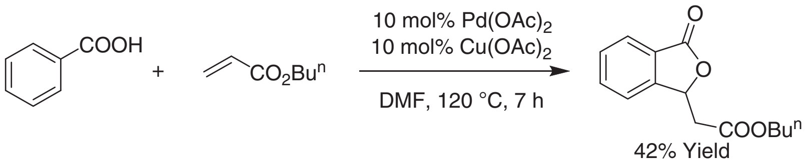


Scheme 21 Pd-catalyzed hydroxyl-directed olefination of 2-phenylphenols (Miura et al., 1997).

The carboxyl group is an ideal directing group because it occurs widely in natural organic molecules, and can be readily transformed to other desired functional groups. As early as 1998, Miura and coworkers reported the carboxyl-directed reactions of benzoic acids with alkenes via C–H activation (Scheme 23).[56] In this reaction, the immediate cyclization gave a lactonate.

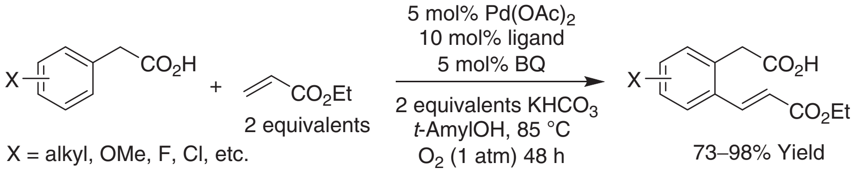


Scheme 22 Pd-catalyzed hydroxyl-directed olefination of arenes (Yu et al., 2010).



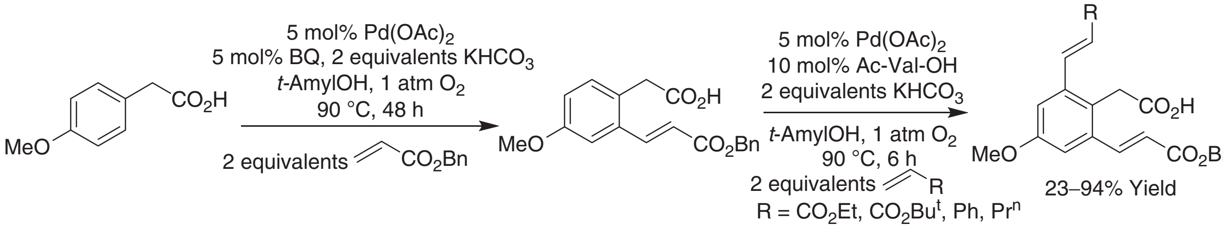
Scheme 23 Pd-catalyzed carboxyl-directed olefination of benzoic acid (Miura et al., 1998).

Pd-catalyzed C–H olefination of phenylacetic acids and 3-phenylpropionic acids has also been achieved by Yu and coworkers in 2010 (Scheme 24).[57] Remarkably, the two *ortho*-positions of the acids could be differentiated by introducing amino acid derivatives as the ligands, so the reactions gave high positional selectivities. The versatility and utility of the method were demonstrated through direct elaboration of commercial drug scaffolds and efficient syntheses of 2-tetralone and naphthoic acid natural product cores. This work has illustrated the importance of ligand development for enabling unique reactivity and selectivity in C–H activation.[57]



Scheme 24 Pd-catalyzed carboxyl-directed olefination of phenylacetic acids (Yu et al., 2010).

Inspired by this discovery, Yu and coworkers developed sequential C–H olefination of phenylacetic acids (Scheme 25).[58] Thus, different olefins were introduced to a desired position of phenyl group by tuning reactivity with amino acid-based ligands, which offered an efficient way to synthesize multiple-olefinated arenes.

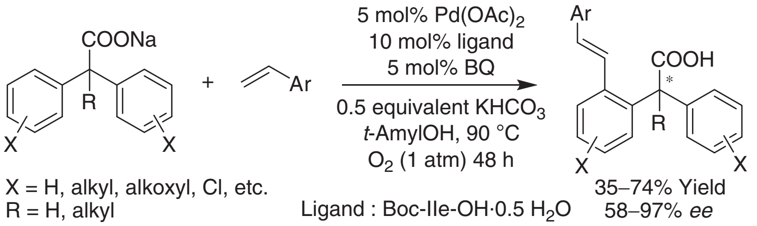


Scheme 25 Pd-catalyzed carboxyl-directed diolefination of phenylacetic acids (Yu et al., 2010).

To investigate the dramatic effects of the amino acid derivatives on the Pd-catalyzed C–H activation, Yu and coworkers has conducted extensive mechanistic studies.[59] The experimental results implied that the observed rate increases were a result of acceleration in the C–H cleavage step. Furthermore, the authors suggested that the origin of this phenomenon was a change in the mechanism of C–H cleavage from electrophilic palladation to proton abstraction.[59]

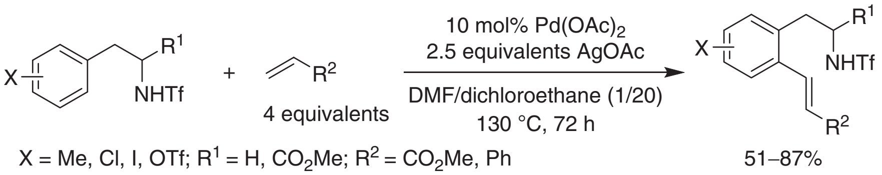
As direct C–H functionalization has emerged as promising synthetic tools, it is attractive to develop enantioselective C–H activation. However, enantioselectvie C–H activation has been a longstanding challenge. As far as Pd-catalyzed C–H activation is concerned, there are at least two problems imposing obstacles to achieve high enantioselectivities. First, the relatively high temperature required in C–H activation reactions make chiral recognition challenging; second, chiral ligands may outcompete the substrate for binding to the Pd center or deactivate Pd for cleavage of the desired C–H bond.[15]

In 2008, Yu and coworkers achieved enantioselective C–H arylation by successfully desymmetrizing prochiral C–H bonds on geminal groups, which will be discussed in Section 3.23.4.1.1. This protocol was successfully extended to enantioselective C–H olefination of diphenylacetic acids (Scheme 26).[60] Therefore, one of the arenes in diphenylacetic acids could be olefinated with excellent enantioselectivity using chiral amino acid derivatives as the ligands.



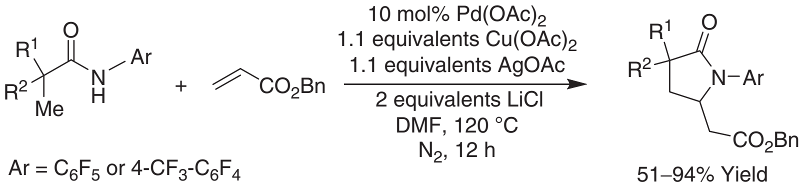
Scheme 26 Pd-catalyzed enantioselective olefination of diphenylacetic acids (Yu et al., 2010).

Triflamide-directed C–H olefination was reported by Yu and coworkers in 2008 (Scheme 27).[61] Thus, arenes substituted by a triflamidoethyl group were olefinated with alkenes. It is noted that the subsequent cyclization offered an efficient method to synthesize tetrahydroisoquinolines from arylethylamines.



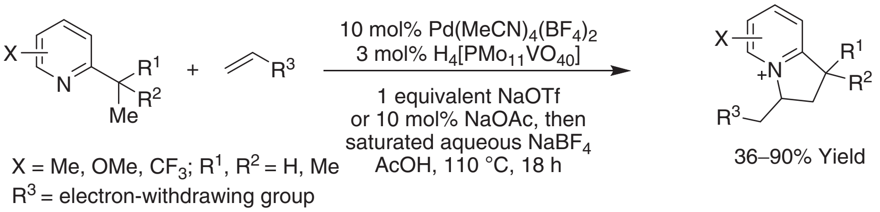
Scheme 27 Pd-catalyzed trifluoromethanesulfonamide-directed olefination of arenes (Yu et al., 2008).

The Pd-mediated functionalization of C(sp^3)-H bonds is much more challenging than that of C(sp^2)-H bonds because of not only competing β-hydride elimination, but also less facile cleavage of C(sp^3)-H bonds.[62] In 2010, the first C(sp^3)-H olefination was achieved by Yu and coworkers (Scheme 28).[63] In this landmark report, an acidic *N*-arylamido group containing an electron-deficient phenyl substituent was employed as the directing group. Therefore, a wide range of methylene C–H bonds including those in cyclopropanes were found to react with alkenes, and the resulting amide products underwent 1,4-conjugate addition to give the corresponding lactam compounds. Remarkably, the substrates containing β-hydrogen atoms were also compatible.



Scheme 28 Pd-catalyzed highly acidic amide-directed olefination of C(sp^3)-H bonds (Yu et al., 2010).

Another example of Pd-catalyzed unactivated C(sp^3)-H olefination was disclosed by the Sanford and coworkers (Scheme 29).[64] The β-C(sp^3)-H bond of pyridines underwent olefination reaction with a range of activated alkenes, and the subsequent intramolecular Michael addition to the olefin products formed cyclic pyridinium salts.

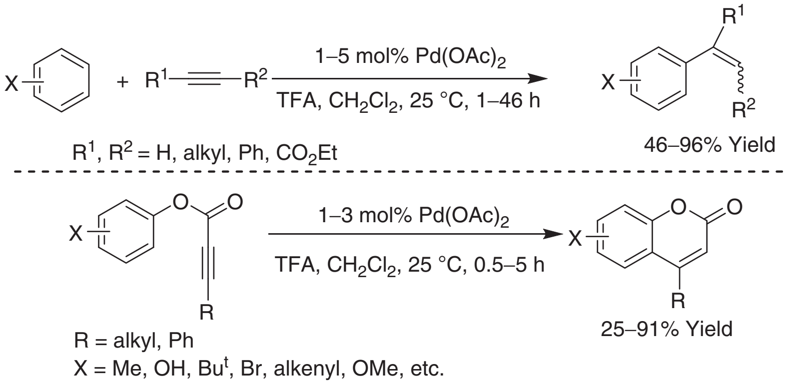


Scheme 29 Pd-catalyzed pyridine-directed olefination of C(sp^3)-H bonds (Sanford et al., 2011).

3.23.2.1.1.3 Palladium-catalyzed reactions of C–H bonds with alkynes

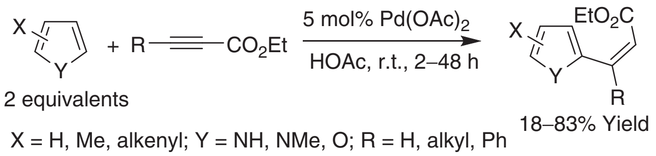
The reactions of C–H bonds and alkynes have been also extensively investigated, and a wide range of transition metal proved applicable in the hydroarylation of alkynes.[65,66] The reactions primarily yielded alkenylated products, which provided an alternative method to synthesize alkenyl arenes.

In 2000, Fujiwara and coworkers reported $Pd(OAc)_2$-catalyzed hydroarylation of alkynes (Scheme 30).[67,68] A variety of electron-rich arenes were reactive to give alkenylated products. In addition, various aryl alkynoates and alkynanilides underwent intramolecular hydroarylation to afford coumarins and quinolinones, respectively. The reactions proceeded in a mixed solvent containing trifluoroacetic acid (TFA) at room temperature. Both internal and terminal alkynes were compatible in this reaction. It is noted that the intermolecular reactions were *trans*-selective to give thermodynamically unfavorable *cis*-alkenes. The proposed mechanism suggested that the aryl C–H bond was cleaved via electrophilic metalation, which is analogous to that in the Pd(II)-catalyzed arylation of alkenes. However, another mechanism proposed that the cationic Pd(II) species attacked the alkynes to form an alkenyl carbocation intermediate in the first step, which then could cleave the C–H bonds of the arenes.



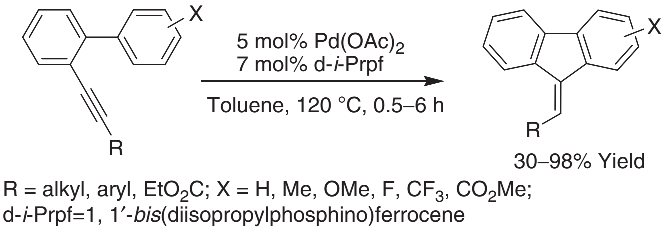
Scheme 30 Pd(II)-catalyzed alkenylation of arenes with alkynes (Fujiwara et al., 2000).

The analogous hydroarylation of alkynes with heteroarenes has also been realized by Fujiwara and coworkers (Scheme 31).[69] The arene scope was still limited to electron-rich heteroarenes, including pyrroles, furans, and indoles. The reactions occurred at the α-position for pyrroles and furans and the β-position for indoles regioselectively. However, the α-alkenylated product was produced for β-methylated indoles. The *cis*-heteroalkenes were obtained in most case as a result of *trans*-selectivity.



Scheme 31 Pd-catalyzed alkenylation of heteroarenes with alkynes (Fujiwara et al., 2000).

Gevorgyan and coworkers described the novel intramolecular 5-*exo-dig* hydroarylation of a variety of *o*-alkynyl biaryls (Scheme 32).[70] The biaryls possessing electron-neutral and electron-deficient aryl rings underwent cyclization to generate the geometrically pure fluorenes in a *cis*-selective fashion. On the basis of the high efficiency of the cyclization of substrates bearing electron-deficient aryl rings, the observed high values of kinetic isotope effects, as well as on the exclusive *cis*-selectivity of cyclization, the author excluded a Friedel–Crafts mechanism and the C–H activation was proposed to account for the transformation.[70]



Scheme 32 Pd-catalyzed intramolecular alkenylation (Gevorgyan et al., 2008).

3.23.2.1.2 Rhodium-catalyzed reactions with C–C multiple bonds

Over the course of the past decade, Rh-catalyzed C–H functionalization was also extensively investigated, and a wide range of reactions have been developed.[71] Rhodium can cleave C–H bonds mainly via two distinct pathways. In Rh(I)-catalyzed alkylation, C–H bonds are cleaved via an oxidative addition pathway to afford Ar-Rh(III)-H species. Subsequent migratory insertion and reductive elimination furnish the alkylation products and release Rh(I) catalyst (Figure 2).[71]

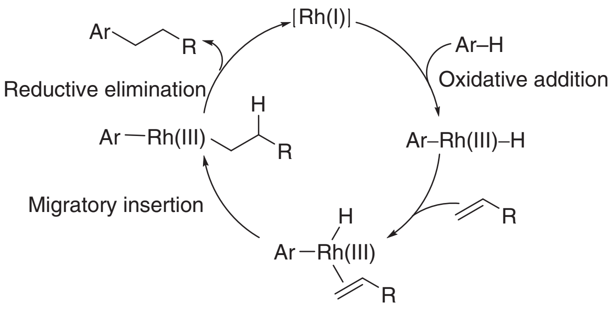


Figure 2 A general mechanism of Rh(I)-catalyzed C–H alkylation with alkenes.

A second mechanism involves a Rh(III)/Rh(I) catalytic cycle, which is analogous to the Pd(II)/Pd(0) pathway. In this mechanism, a Rh(III) species acts as the active catalyst to cleave C–H bonds, affording arylrhodium(III) intermediates. The subsequent alkene insertion and β-hydride elimination give the alkenylation products and Rh(I) species. Finally, the resulting Rh(I) species are oxidized to Rh(III) catalysts to close the catalytic cycle (Figure 3).[72]

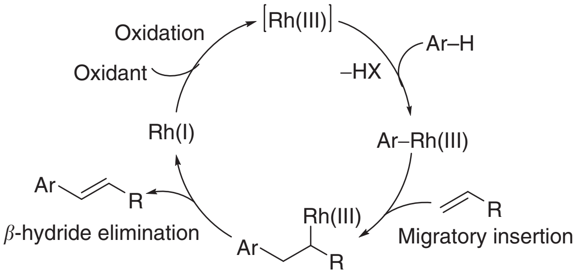
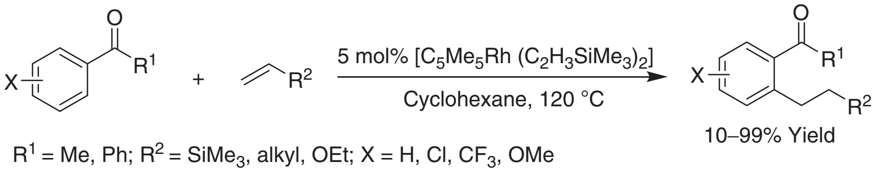


Figure 3 A general mechanism of Rh(III)-catalyzed C–H alkenylation.

Both Rh(III) and Rh(I) have been demonstrated to be able to catalyze the reaction of C–H bonds with alkenes.[71,72] Although the reactions catalyzed by Rh(III) species often form olefinated products, the alkylation generally takes place in the Rh(I)-catalyzed reactions.

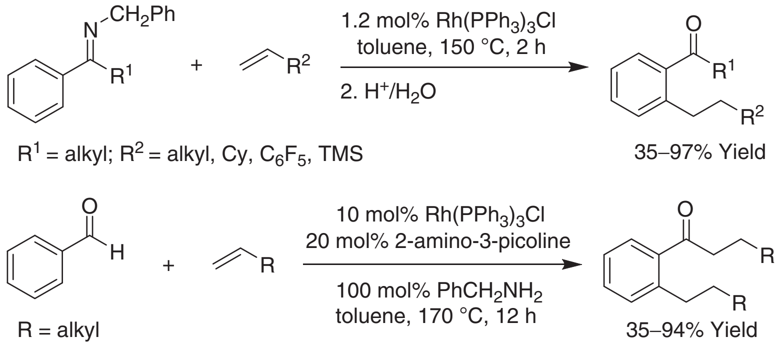
3.23.2.1.2.1 Rh(I)-catalyzed C–H alkylation with alkenes

Lim and Kang reported pioneering work in the field of Rh(I)-catalyzed reactions of C–H bonds with alkenes. A pyridine group was employed as the directing group to enable the alkylation of arenes. In addition to the pyridine group, a wide range of functionalities have been developed as the directing group in the Rh(I)-catalyzed C–H alkylation reactions. In 1999, Brookhart reported the alkylation of aromatic ketones by using the rhodium bis-olefin complex [$C_5Me_5Rh(C_2H_3SiMe_3)_2$] (Scheme 33).[73]



Scheme 33 Rh(I)-catalyzed carbonyl-directed alkylation (Brookhart et al., 1999).

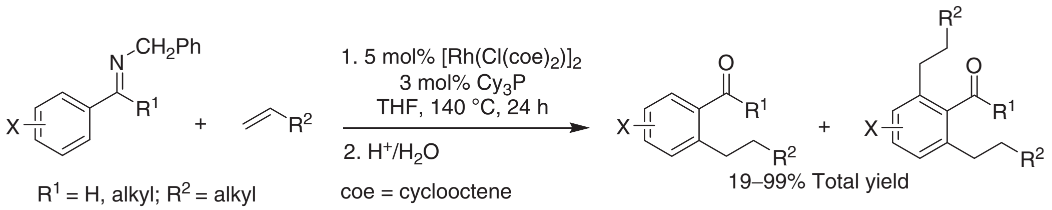
The imine functionality has also been utilized as the directing group in the Rh(I)-catalyzed C–H alkylation by Jun and coworkers (Scheme 34).[74] Therefore, in the presence of Wilkinson's catalyst, the ketimines reacted with a broad range of alkenes, including simple unactivated and even internal alkenes that isomerize to the terminal alkenes before coupling, to give the *ortho*-alkylated products. Aldimines were also reactive with the aid of 2-amino-3-picoline as a cocatalyst. In these reactions, the aldimines, which were generated *in situ* from aldehydes and benzylamine, underwent transimination with 2-amino-3-picoline to



Scheme 34 Rh(I)-catalyzed imino-directed alkylation (Jun et al., 2000).

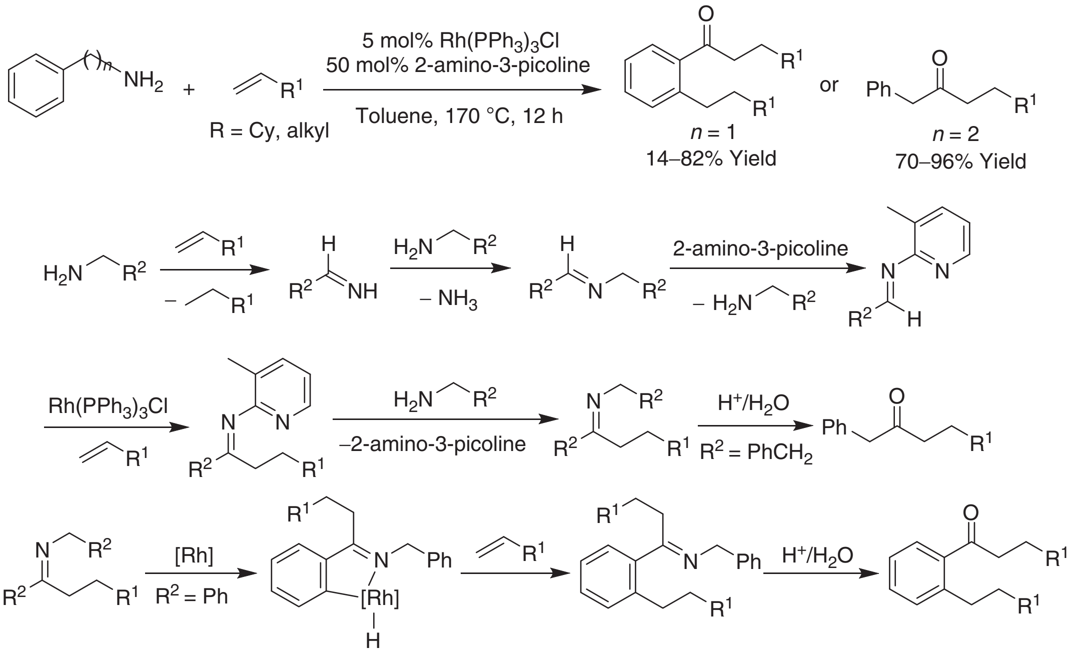
give *N*-pyridyl imines, which were the actual directing group. Interestingly, the reactions started with the hydroacylation of the imine to the alkenes, and the subsequent imino-directed alkylation provided the hydroacylated and alkylated products.

Rh(I)-catalyzed imino-directed alkylation of aldimines and ketimines was also enabled using Rh(Cl(coe)$_2$)]$_2$ and Cy$_3$P catalytic system by Lim and coworkers (Scheme 35).[75] Although the aldimines mainly gave the double *ortho*-alkylated products, the ketimines provided the mono-alkylated products predominantly.



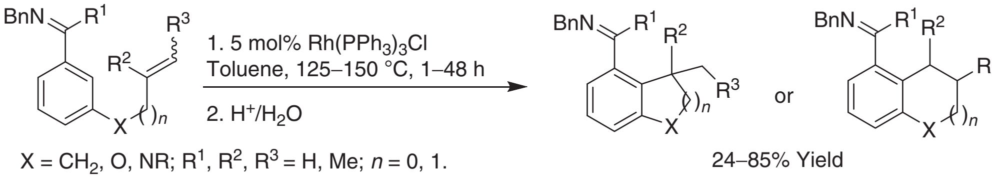
Scheme 35 Rh(I)-catalyzed imino-directed alkylation of aldimines and ketimines (Lim et al., 2001).

Interestingly, the imine-directing group can be introduced through the oxidation of primary amines (Scheme 36).[76] The benzylamines gave hydroacylated and alkylated products. However, the hydroacylation occurred exclusively for the phenylethylamines.



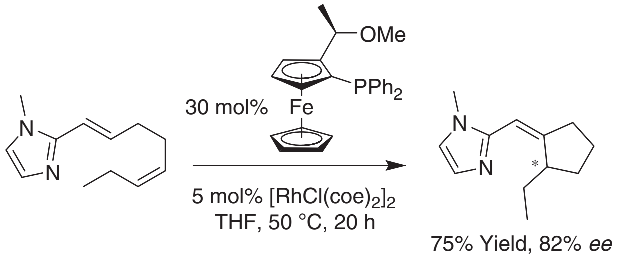
Scheme 36 Rh(I)-catalyzed alkylation assisted by *in situ* generated imines (Jun et al., 2001).

The intramolecular alkylation directed by an imino group was achieved by Bergman and Ellman (Scheme 37).[77] Using Wilkinson's catalyst, aryl ketimines could cyclize efficiently with a broad range of simple olefins tethered to the *meta*-position, which provided a novel method to synthesize indane, tetralane, dihydrobenzofuran, and dihydroindole derivatives.



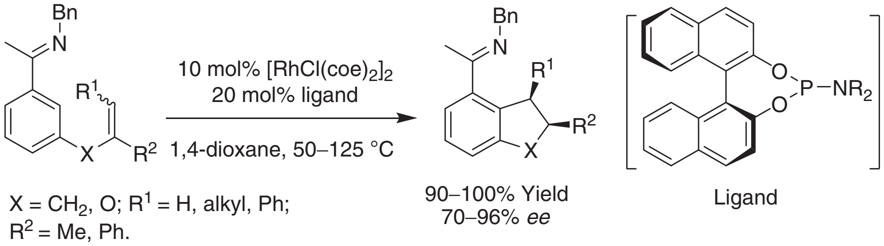
Scheme 37 Rh(I)-catalyzed imino-directed intramolecular alkylation (Bergman and Ellman et al., 2001).

The introduction of new chiral centers in the Rh(I)-catalyzed C–H alkylation opened the possibility of developing asymmetric version of the reactions. The first enantioselective C–H alkylation catalyzed by Rh(I) species was reported as early as 1997.[78] In the presence of ferrocenyl-based phosphine as the chiral ligand, the intramolecular alkylation of imidazoyl dienes was achieved to give moderate *ee*s (Scheme 38).



Scheme 38 Rh(I)-catalyzed enantioselective alkylation of olefins (Murai et al., 1997).

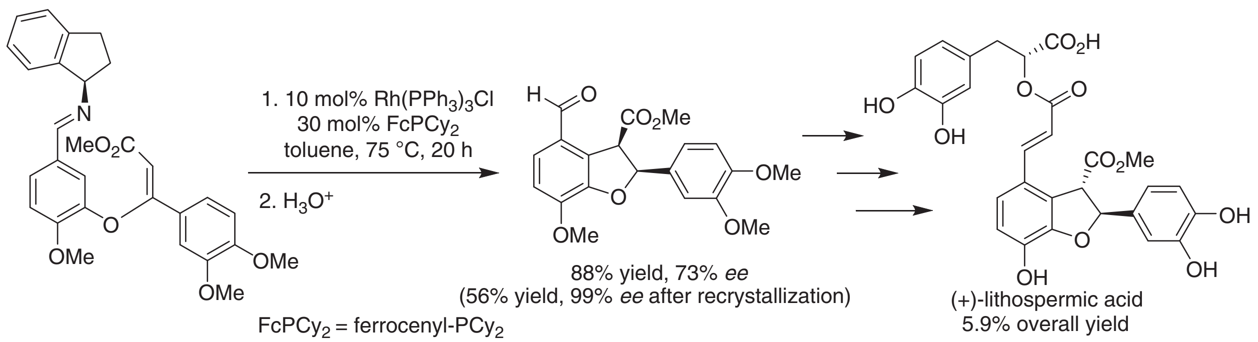
The highly enantioselective version of this reaction was achieved using monodentate chiral phosphoramidite ligands by Ellman and Bergman in 2004 (Scheme 39).[79] Therefore, the aryl ketimines underwent intramolecular cyclization with a broad range of olefins in a highly efficient and enantioselective manner. Notably, in the case of trisubstituted olefins, the reactions set two stereocenters with high enantioselectivities.



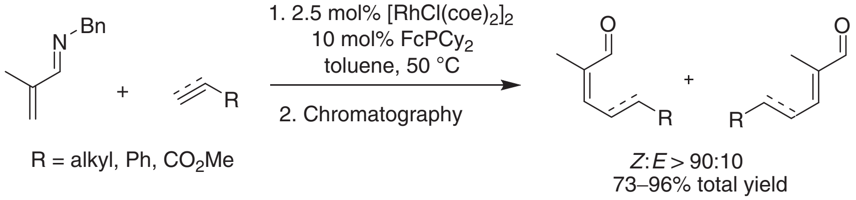
Scheme 39 Rh(I)-catalyzed imino-directed ligand-enabled enantioselective alkylation (Bergman and Ellman et al., 2004).

The Rh(I)-catalyzed intramolecular C–H alkylation has been successfully applied to the synthesis of some natural products.[71] One of the examples is synthesis of (+)-lithospermic acid, which is a key constituent of a popular traditional herbal medicine with a variety of biological activities (Scheme 40).[80] The key step in the exciting total synthesis is the Rh(I)-catalyzed asymmetric cyclization. It is worth noting that the chirality was incorporated into the cyclized product by using a chiral amine auxiliary, which represents an alternative method to achieve asymmetric Rh(I)-catalyzed C–H alkylation.

Rh(I)-catalyzed C–H alkylation reactions of olefins were also developed, although underdeveloped if compared to arenes. Early examples involve the use of heterocyclic directing groups such as pyridine, imidazole, and oxazoline to afford inter- and intramolecular alkylation.[71] The first Rh (I)-catalyzed alkylation of an α,β-unsaturated carbonyl derivative was disclosed by Jun and coworkers in 2002.[81] In 2006, Bergman and Ellman described the C–H alkylation of α,β-unsaturated imines (Scheme 41).[82] Remarkably, the reaction proceeded at mild temperature in the presence of the electron-donating (dicyclohexylphosphinyl)ferrocene ligand. Moreover, the *Z* isomers were produced predominantly, and the reactions had broad substrate scope. Alkynes were also compatible in this reaction.

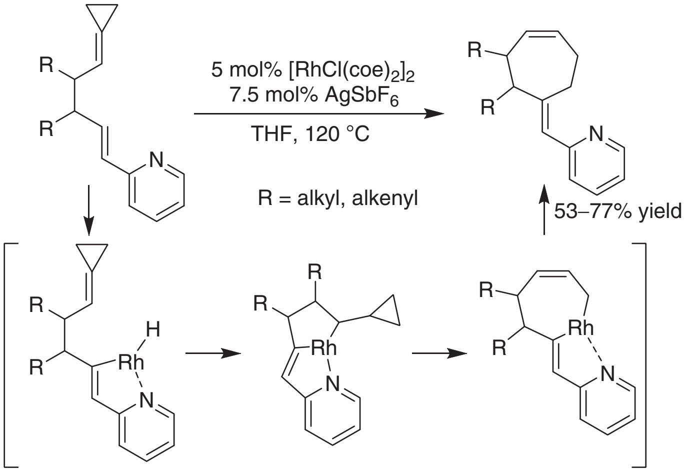


Scheme 40 Rh(I)-catalyzed imino-directed stereoselective alkylation using a chiral auxiliary in the total synthesis of (+)-lithospermic acid (Bergman and Ellman et al., 2005).



Scheme 41 Rh(I)-catalyzed imino-directed alkylation of olefins (Bergman and Ellman et al., 2006).

In 2007, Fürstner developed a very interesting protocol for the formation of seven-membered rings initiated by the pyridine-directed C–H activation of olefins (Scheme 42).[83] Therefore, following initial C–H activation, the resulting vinylmetal hydride species underwent hydrometalation of an alkylidenecyclopropane in vicinity to give a metallacycle, which cleaved the C–C bond of the adjacent cyclopropane to give the ring enlarged complex. The following reductive elimination formed the seven-membered ring.

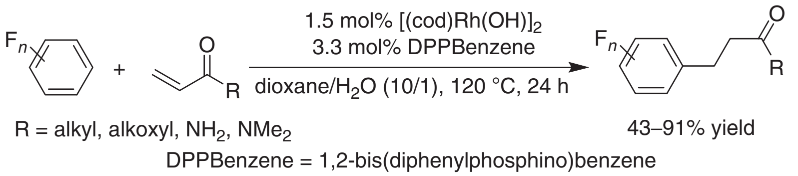


Scheme 42 Rh(I)-catalyzed pyridine-directed alkylation of olefins followed by cycloisomerization (Fürstner et al., 2007).

Rh(I)-catalyzed undirected C–H alkylation was reported by Zhao and coworkers (Scheme 43).[84] Thus, electron-deficient perfluoroarenes underwent hydroarylation reaction with a variety of α,β-unsaturated carbonyl derivatives by using [(cod)-Rh(OH)]$_2$ as the catalyst and DPP Benzene as the ligand. It is worth noting that olefination products were formed in the absence of water.

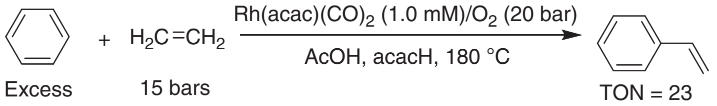
3.23.2.1.2.2 Rh(III)-catalyzed C–H alkenylation with alkenes

As discussed in Section 3.23.2.1.2, Rh(III) can catalyze the oxidative coupling reactions of C–H bonds with alkenes. The reaction proceeds in an analogous way to that involving Pd(II)/Pd(0) process, and generally gives the similar arylation products. However,



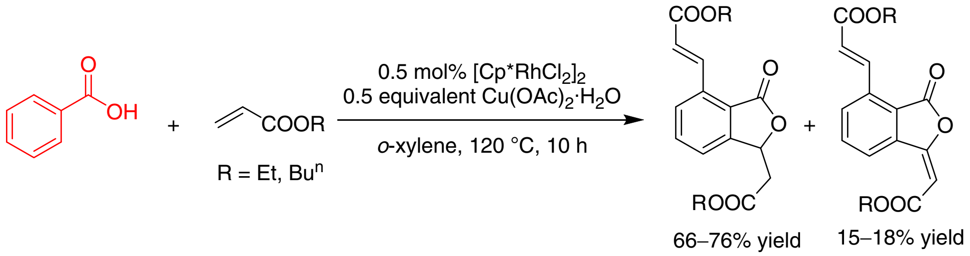
Scheme 43 Rh(I)-catalyzed alkylation of electron-deficient perfluoroarenes (Zhao et al., 2010).

the Rh(III)-catalyzed reactions were less explored than those with palladium. In 2000, Matsumoto and Yoshida reported the reaction of benzene and ethylene-catalyzed Rh(acac)(CO)$_2$ in the presence of acetylacetone and O$_2$ (**Scheme 44**). The actual catalyst was proposed to be an Rh(III) species, which was possibly formed by *in situ* oxidation.[85]



Scheme 44 Rh(III)-catalyzed alkenylation of benzene (Yoshida et al., 2000).

Over the past 5 years, Rh(III)-catalyzed coupling reactions of aryl C–H bonds with alkenes and alkynes have been extensively investigated, and most of them rely on the use of a directing group. Among the discovered reactions to date, [Cp*RhCl$_2$]$_2$ is the dominant catalyst. The carboxyl functionality is one of the early examples as the directing group in Rh(III)-catalyzed C–H arylation of olefins. In 2007, Miura and Satoh reported the reaction of benzoic acid with acrylate by the use of catalyst [Cp*RhCl$_2$]$_2$ (**Scheme 45**).[86] Both of the two *ortho*-positions were functionalized, and the subsequent cyclization gave a phthalide and a minor amount of its dehydrogenative derivative. The Rh(I) species occurring in the reaction was reoxidized in the presence of the copper catalyst under air to regenerate the active Rh(III) catalyst.



Scheme 45 Rh(III)-catalyzed carboxyl-directed alkylation/alkenylation (Miura and Satoh et al., 2007).

Miura and Satoh also utilized *N*-containing heteroaryl groups as the directing group in the Rh(III)-catalyzed arylation of alkenes (**Scheme 46**).[87] Under similar reaction conditions, 1-phenyl-1*H*-pyrazole were olefinated with alkenes. Notably, two different vinyl groups could be installed in a simple one-pot manner. 2-Phenylpyridine and 2-phenyl-1*H*-imidazole were also reactive.

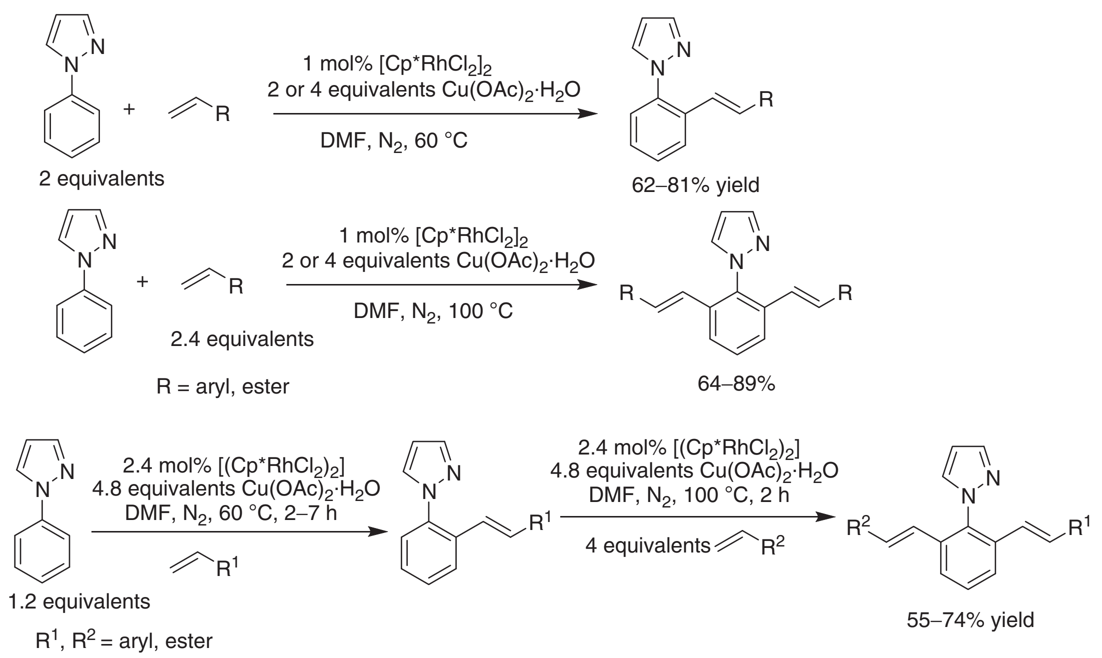
A wide range of carbonyl-containing functional groups have also been successfully developed as the directing group. The reactive substrates include acetophenones, benzamides (**Scheme 47**),[88] benzoates, and benzaldehydes (**Scheme 48**).[89]

Glorius and coworkers reported the C–H olefination of *N*-methoxybenzamides (**Scheme 49**).[90] Interestingly, the directing group CONH(OMe) functioned as the oxidant as well to oxidize Rh(I) species to regenerate Rh(III) catalyst, so the use of an external oxidant was avoided.

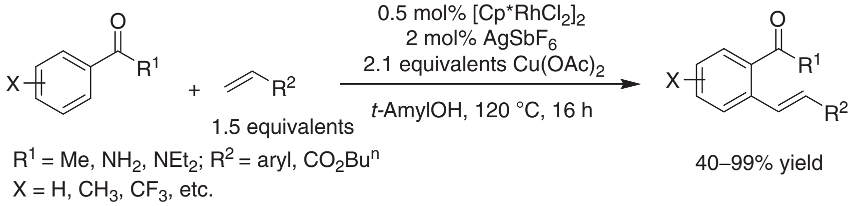
3.23.2.1.2.3 Rh-catalyzed reactions of C–H bonds with alkynes

Although the Rh(I)-catalyzed hydroarylation of olefins has seen broad success, the analogous reactions with alkynes were less exploited. Lim and Kang successfully extended the catalyst system in the alkylation reaction with alkenes to the hydroarylation of alkynes (**Scheme 50**).[91] Therefore, 2-phenylpyridines reacted primarily with internal, symmetrical alkynes in the presence of Wilkinson's catalyst to yield *ortho*-vinylated products.

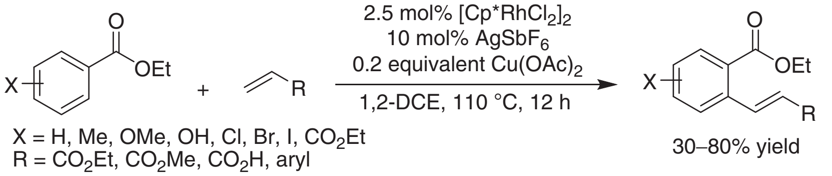
In addition to the pyridyl group, a range of directing groups could assist vinylation of arenes under similar reaction conditions when triisopropylacetylene was used as the coupling partner. The directing groups included imidazole, benzimidazole, ketimine, and ketoxime.[92] Notable, the alkenylation of aryl ketimines with terminal alkynes has been reported by Jun and coworkers.[93]



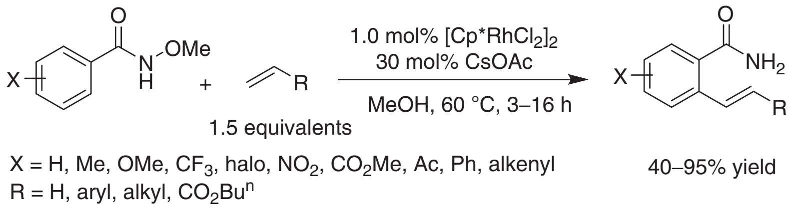
Scheme 46 Rh(III)-catalyzed heteroarene-directed alkenylation (Miura and Satoh et al., 2009).



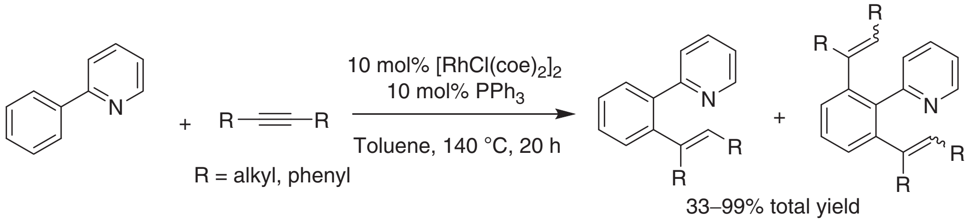
Scheme 47 Rh(III)-catalyzed carbonyl-directed alkenylation (Glorius et al., 2011).



Scheme 48 Rh(III)-catalyzed ester-directed alkenylation of benzoates (Chang et al., 2011).

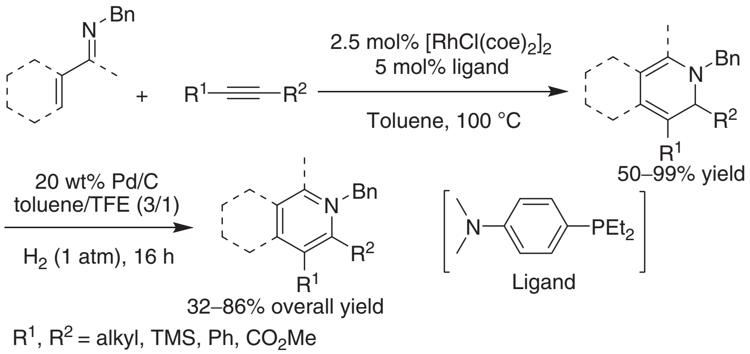


Scheme 49 Rh(III)-catalyzed CONH(OMe)-directed alkenylation (Glorius et al., 2011).



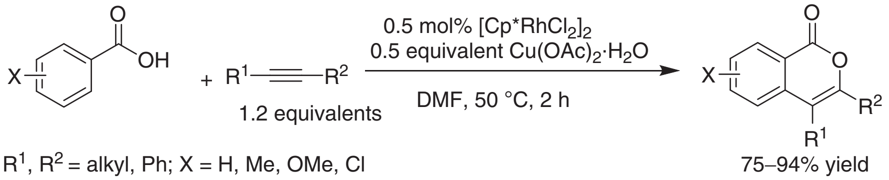
Scheme 50 Rh(I)-catalyzed pyridine-directed alkenylation with alkynes (Lim and Kang et al., 2001).

Interestingly, Bergman and Ellman reported a convenient one-pot procedure for the synthesis of highly substituted pyridines from α,β-unsaturated imines and alkynes (Scheme 51).[94] The synthesis was initiated by the imino-directed C–H alkenylation of the alkenes. The subsequent electrocyclization/aromatization formed highly substituted pyridines. It is notable that a new class of ligands was found to expand the scope the C–H alkenylation reaction greatly.



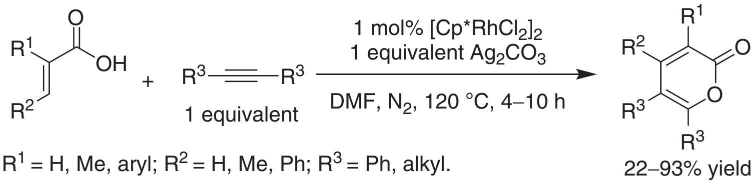
Scheme 51 Rh(I)-catalyzed imino-directed alkenylation of olefins in the synthesis of pyridines (Bergman and Ellman et al., 2008).

As mentioned in Section 3.23.2.1.2.2, Rh(III)-catalyzed C–H alkenylation with alkynes has been extensively investigated, and the majority of the reactions used $[Cp^*RhCl_2]_2$ as the catalyst. In the paper regarding Rh(III)-catalyzed olefination of benzoic acids with alkenes, which has been discussed in Section 3.23.2.1.2.2, Miura and Satoh also reported the alkenylation reactions of benzoic acids with alkynes under similar conditions (Scheme 52).[86] Therefore, a range of benzoic acids were *ortho*-alkenylated with internal alkynes, and the subsequent reductive elimination provided isocoumarins. Besides benzoic acids, heteroarene carboxylic acids also underwent analogous reactions with diphenylacetylene to form heteroaryl analogs of isocoumarins.[95] The employed heteroarenes included indole, pyrrole, benzothiophene, thiophene, and furan.



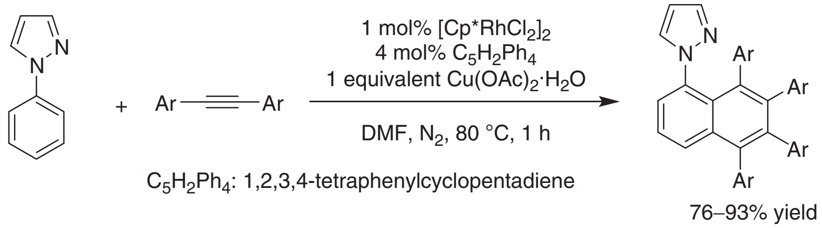
Scheme 52 Rh(III)-catalyzed carboxyl-directed alkenylation with alkynes (Miura and Satoh et al., 2009).

The C–H bonds of alkenes were also allowed to react with alkynes. A straightforward and efficient synthesis of α-pyrone derivatives has been achieved by the rhodium-catalyzed oxidative coupling reactions of substituted acrylic acids with alkynes (Scheme 53). Alkenes were also reactive to give butenolide derivatives.[96]



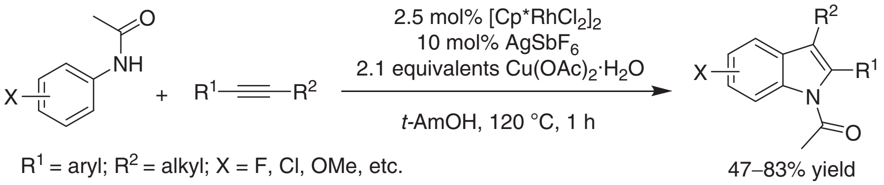
Scheme 53 Rh(III)-catalyzed carboxyl-directed alkenylation of alkenes (Miura and Satoh et al., 2009).

A range of directing groups have been applied to assist the Rh(III)-catalyzed alkenylation of arenes with alkynes. Miura and Satoh reported the direct coupling of phenylazoles with internal alkynes in the presence of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$ (Scheme 54).[97] Interestingly, the rhodacycle intermediate resulted from the C–H alkenylation of heteroarenes underwent a second C–H activation and alkyne insertion, which provided an efficient way to construct polyarylated naphthyl- and anthrylazole derivatives. Pyrazole, imidazole, and benzoxazole proved effective as the directing group in the reactions.



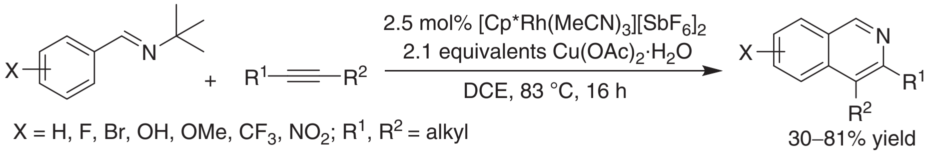
Scheme 54 Rh(III)-catalyzed heteroarene-directed alkenylation with alkynes (Miura and Satoh et al., 2008).

The Rh(III)-catalyzed oxidative coupling of *N*-acetyl anilines and alkynes was realized by Fagnou and coworkers (Scheme 55).[98] Following C–H alkenylation, the cyclization via reductive elimination occurred to form indole derivatives. Interestingly, nonsymmetrical anilines underwent indolization at the more sterically accessible *ortho*-position, and high regioselectivities were achieved for unsymmetrical alkynes.



Scheme 55 Rh(III)-catalyzed acetamido-directed alkenylation with alkynes (Fagnou et al., 2008).

A different Rh(III) catalyst was employed by Fagnou and coworkers to catalyze imino-directed alkenylation of arenes with alkynes (Scheme 56).[99] In the presence of $[Cp^*Rh(MeCN)_3][SbF_6]_2$, aryl aldimines underwent C–H alkenylation and $C(sp^2)$-$N(sp^2)$ bond reductive elimination to provide isoquinoline.



Scheme 56 Rh(III)-catalyzed imino-directed alkenylation (Fagnou et al., 2009).

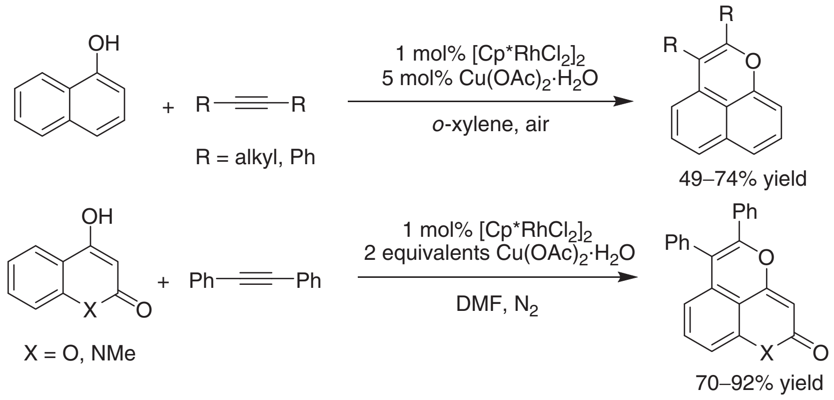
The hydroxyl group without α-hydrogen also proved viable in Rh(III)-involved C–H alkenylation with alkynes (Scheme 57). The *peri* C–H bond of 1-naphthols and analogs including 4-hydroxycoumarin and -quinolinone and 9-phenylxanthen-9-ol were cleaved, and the analogous reaction sequence produced fused pyran derivatives.[100]

Glorious and Chen disclosed the reactions of aryl ketones and alkynes almost at the same time.[101,102] The intramolecular insertion of the carbonyl group into the formed rhodium–alkenyl bond afforded substituted indenols. In the Glorious' work, electron-neutral and electron-rich phenones bearing protons in dehydrative positions (α or γ) generally led to the corresponding fulvene derivatives (Scheme 58).

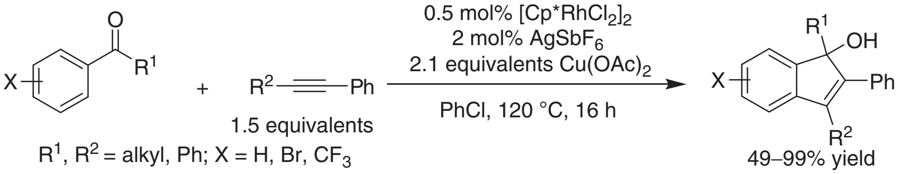
The coupling reaction of *N*-methoxybenzamides with alkynes was achieved by Guimond and coworkers to yield isoquinolines (Scheme 59).[103] As the reactions with alkenes discussed in Section 3.23.2.1.2.2, the CONH(OMe) oxidized Rh(I) species formed in the reaction to active Rh(III) catalyst.

3.23.2.1.3 Ruthenium-catalyzed reactions with C–C multiple bonds

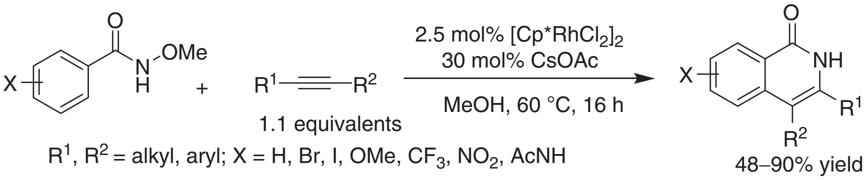
Ru-catalyzed C–H functionalization has also been extensively explored, and a range of C–C bond forming reactions has been discovered. The reaction partners include alkenes, alkynes, (pseudo)halides, and organometallic reagents. An initial work involved



Scheme 57 Rh(III)-catalyzed hydroxyl-directed alkenylation with alkynes (Miura and Satoh et al., 2010).

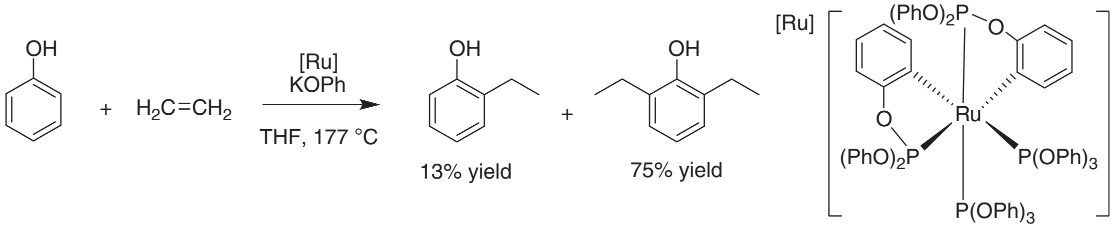


Scheme 58 Rh(III)-catalyzed keto-directed alkenylation with alkynes (Glorius et al., 2011).



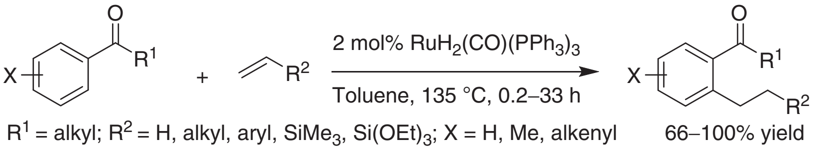
Scheme 59 Rh(III)-catalyzed CONH(OMe)-directed alkenylation with alkynes (Guimond et al., 2010).

the reaction of phenol with ethylene to give mono and double *ortho*-alkylation products by using a cyclometalated ruthenium phosphite complex (Scheme 60).[104]



Scheme 60 Ru-catalyzed ethylation of phenol with ethylene (Lewis et al., 1986).

A decisive breakthrough in Ru-catalyzed C–H functionalization was reported by Murai and coworkers in 1993 (Scheme 61).[105] Therefore, a range of aromatic and heteroaromatic ketones were alkylated by reacting with olefins in the presence of the complex



Scheme 61 Ru-catalyzed carbonyl-directed alkylation (Murai et al., 1993).

$RuH_2(CO)(PPh_3)_3$. The seminal reaction is a pioneering work in chelation-assisted C–H activation. It was proposed that the actual active catalyst was Ru(0) species, which was generated *in situ* through the reaction of the complex $RuH_2(CO)(PPh_3)_3$ with alkene.[106] The C–H cleavage occurs via an agostic interaction instead of the usual oxidative addition mechanism. The subsequent olefin insertion and reductive elimination formed the alkylated products (Figure 4).[22]

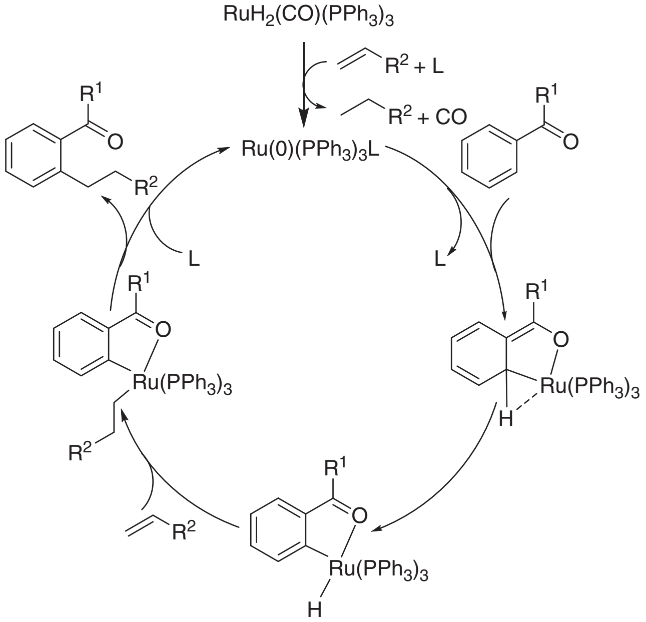
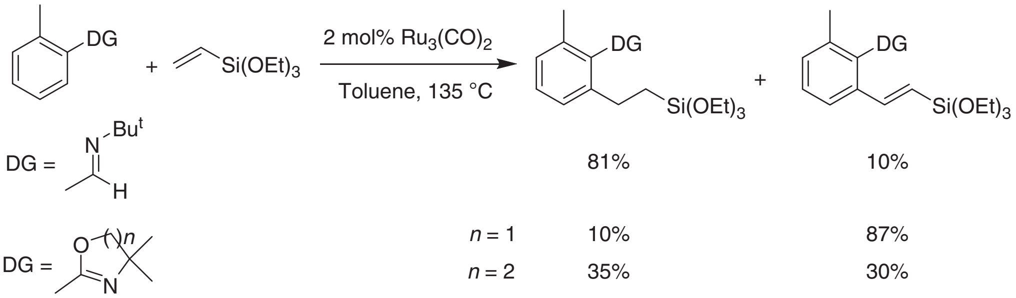


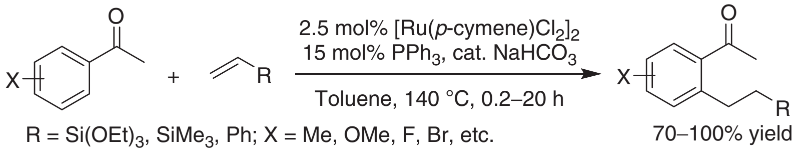
Figure 4 The mechanism of Ru(0)-catalyzed carbonyl-directed alkylation.

The related complex $Ru_3(CO)_2$-catalyzed reactions with imidates or imines as the directing group gave a mixture of alkylated and olefinated products (Scheme 62).[107,108] The olefination products were believed to be formed by β-hydride elimination from a carbometalation intermediate. The intermediate was produced through olefin insertion into the Ru–C bond, which was formed by the oxidative addition of C–H bond to the Ru catalyst.[22]



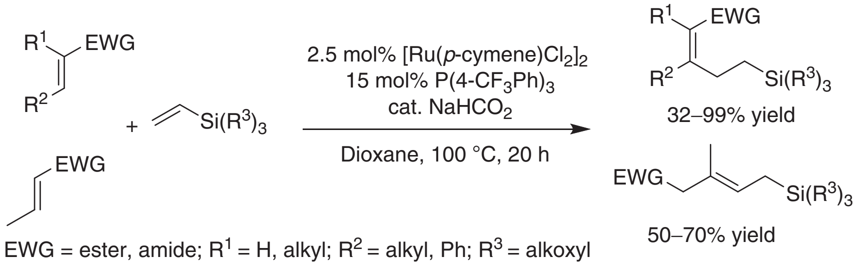
Scheme 62 Ru-catalyzed-directed alkylation/alkenylation (Murai et al., 1999).

A commercially available and stable complex $[Ru(p\text{-cymene})Cl_2]_2$ was elegantly exploited by Darses and Genet for the C–H alkylation of arenes (Scheme 63).[109] $[Ru(p\text{-cymene})Cl_2]_2$ generated an active catalyst species, likely to be $\{RuH_2\}$, in the presence of a formate salt and triphenylphosphine ligand. This *in situ*-generated catalyst had a similar or higher activity than the above Murai catalyst in the alkylation reaction of aromatic ketones.



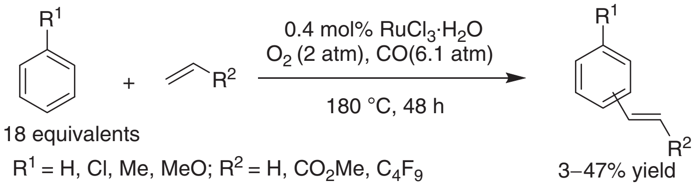
Scheme 63 Ru-catalyzed carbonyl-directed alkylation (Darses and Genet et al., 2006).

The above complex was also successfully extended to the functionalization of Michael acceptors (Scheme 64).[110] In the presence of electron-deficient $P(4\text{-}CF_3Ph)_3$ instead of PPh_3, a range of α,β-unsaturated amides and esters reacted with vinylsilanes to give alkylated products. Interestingly, on some particular substrates, mainly crotonic acid derivative, stereodefined trisubstituted allylsilanes were formed. The formation of such compounds was believed to be the result of β-hydride elimination followed by reductive elimination.



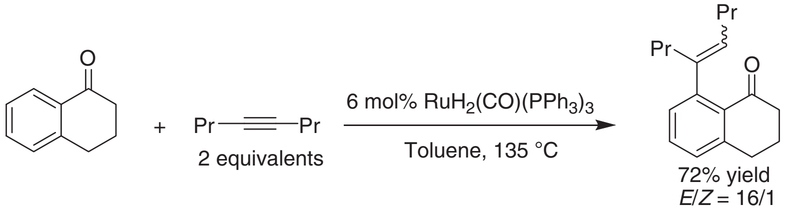
Scheme 64 Ru-catalyzed carbonyl-directed alkylation of alkenes (Darses et al., 2009).

Although the above Ru(0)-catalyzed reactions normally gave alkylated products, the $RuCl_3$-catalyzed C–H alkenylation of simple arenes was disclosed by Milstein and coworkers (Scheme 65).[111] The reactions required a CO atmosphere, and monosubstituted arenes formed a mixture of regioisomers. The proposed mechanism was similar to that involved in the Pd(II)-catalyzed C–H alkenylation of arenes. Therefore, the C–H bond cleavage resulted from electrophilic attack of the metal on a C–H bond. The resulting Ar-[Ru] species underwent olefin insertion and β-H elimination to yield the aromatic alkene and a ruthenium hydride, which was oxidized by olefins or oxygen to regenerate the electrophilic species.



Scheme 65 Ru-catalyzed direct alkenylation of simple arenes (Milstein et al., 2001).

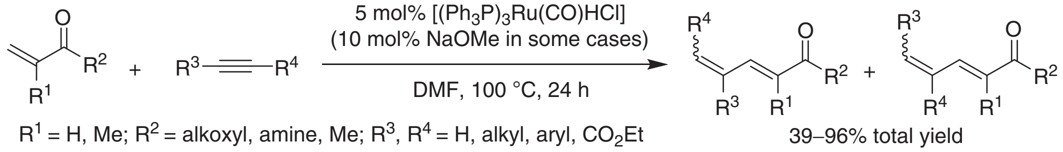
The catalytic system in the $RuH_2(CO)(PPh_3)_3$-catalyzed alkylation reaction with alkenes also proved applicable to the reaction of aromatic ketones with alkynes (Scheme 66).[112] Under similar conditions, aromatic ketones reacted with alkynes with two identical substitutions to provide alkenylated products as a mixture of two *E*/*Z* isomers.



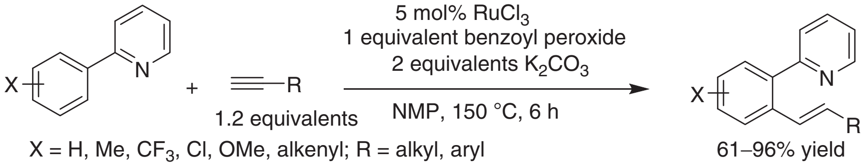
Scheme 66 Ru-catalyzed carbonyl-directed alkenylation with alkynes (Murai et al., 1995).

Plietker and coworkers reported hydrovinylation reaction of alkynes (Scheme 67).[113] The reactions were catalyzed by an air and moisture-stable ruthenium hydride complex that was prepared in one step starting from $RuCl_3$ and activated by addition of NaOMe before use. A broad range of terminal alkynes were hydrovinylated with electron-deficient olefins to give highly substituted 1,3-dienes.

$RuCl_3$-catalyzed C–H alkenylation of arylpyridines with alkynes was disclosed by Zhang and coworkers (Scheme 68).[114] Therefore, a variety of arylpyridines underwent regio- and/or stereoselective alkenylation reactions efficiently with terminal alkynes to give (*E*)-alkenylated products. Benzoyl peroxide or benzoic acid was required to achieve high yield.



Scheme 67 Ru-catalyzed carbonyl-directed alkenylation of alkenes with alkynes (Plietker et al., 2009).



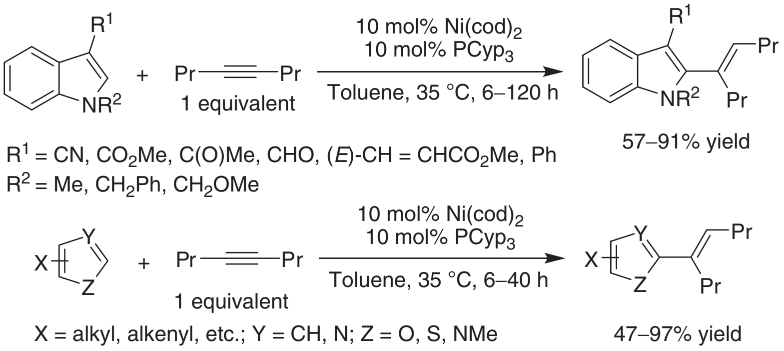
Scheme 68 Ru-catalyzed pyridine-directed alkenylation with alkynes (Zhang et al., 2008).

3.23.2.1.4 Other transition-metal-catalyzed reactions with C–C multiple bonds

Besides the Ru, Rh, Pd triad, a range of other transition metals also proved viable to catalyze the direct reaction of C–H bonds and alkenes or alkynes.

3.23.2.1.4.1 Nickel-catalyzed reactions of C–H bonds with C–C multiple bonds

In 2006, Nakao, Hiyama and coworkers reported Ni-catalyzed hydroheteroarylation of alkynes (Scheme 69).[115] Therefore, a wide range of heteroarenes were allowed to react with alkynes in the presence of the catalyst Ni(cod)$_2$ and the ligand PCyp$_3$ to afford alkenylated products under mild conditions. A variety of functionalities were tolerated and a range of internal alkynes were reactive in this reaction. The authors suggested the reaction started with alkyne-coordinating Ni(0) species, which then underwent oxidative addition of an Ar–H bond to give alkyne-coordinating Ar-Ni(II)-H intermediate. The subsequent hydronickelation and reductive elimination to afford a *cis*-hydroarylation product and regenerate Ni(0) species (Figure 5).[115]



Scheme 69 Ni-catalyzed alkenylation of heteroarenes with alkynes (Hiyama and Nakao et al., 2006).

Inspired by this elegant reaction, the authors investigated the Ni-catalyzed reactions of C–H bonds with C–C multiple bonds extensively, and discovered a series of novel reactions.[116] Under the almost same reaction conditions, a diverse range of pyridine-*N*-oxides reacted with internal alkynes to afford (*E*)-2-alkenylpyridine-*N*-oxides regioselectively and stereoselectively. In the case of asymmetrical alkynes, the reaction took place at the carbon with the smaller substituent selectively (Scheme 70).[117]

The alkenylation of simple pyridines was realized in the presence of a Lewis acid, which coordinated with the nitrogen on the pyridine ring and made the nitrogen electron-deficient that enhanced the acidity of the C(2)–H bond (Scheme 71).[118] By using diorganozincs such as ZnMe$_2$ and ZnPh$_2$ as the Lewis acid, a broad range of pyridines were alkenylated with internal alkynes. Interestingly, the use of AlMe$_3$ as the Lewis acid generated a C2-dienylated pyridine as a result of double insertion of alkynes.

Although the direct C–H functionalization of pyridine usually occurs at C-2 position, the selective C-3 or C-4 functionalization has been a challenge in the absence of a directing group. Remarkably, Hiyama and Nakao disclosed Ni(cod)$_2$-catalyzed efficient C-4 alkylation of simple pyridines with alkenes in the presence of *N*-heterocyclic carbene (NHC) and AlMe$_3$ as ligand and LA catalyst, respectively (Scheme 72).[119] In most cases, the reaction occurred at the terminal position of alkenes dominantly, and a very minor amount of internal product was observed. The reaction of pyridine with alkynes gave a mixture of C-3 and C-4

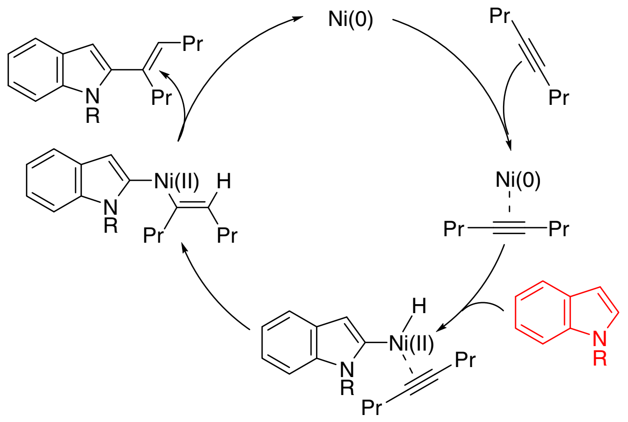
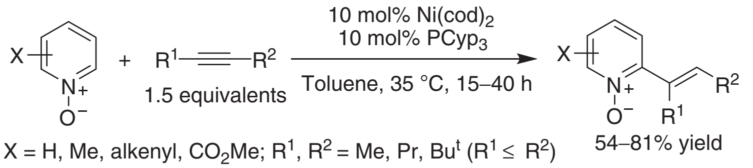
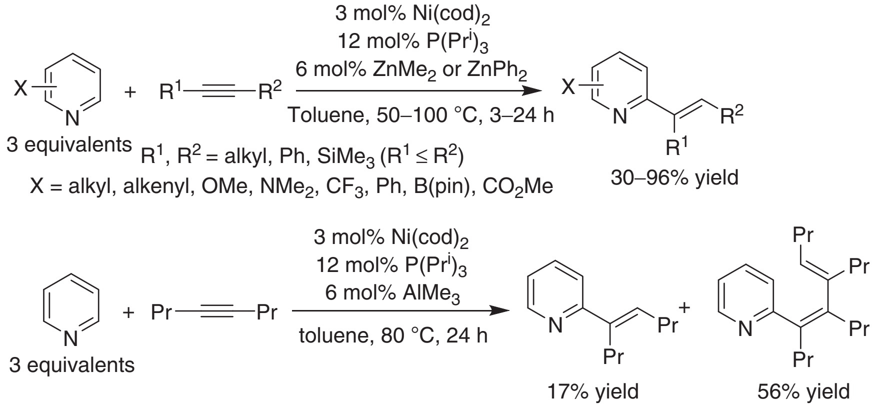


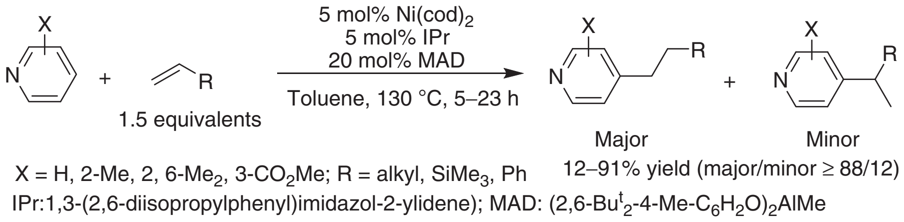
Figure 5 Mechanism of Ni-catalyzed alkenylation.



Scheme 70 Ni-catalyzed alkenylation of pyridine-*N*-oxides with alkynes (Hiyama and Nakao et al., 2007).



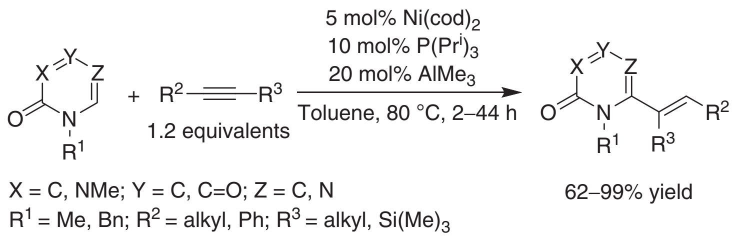
Scheme 71 Ni-catalyzed alkenylation of pyridine with alkynes (Hiyama and Nakao et al., 2008).



Scheme 72 Ni-catalyzed C-4 alkenylation of pyridine with alkenes (Hiyama and Nakao et al., 2010).

alkenylated products. The novel regioselectivity was attributed to the η^2-coordination of the C(3)–C(4) double bond of pyridine to the Ni(0)/NHC complex.

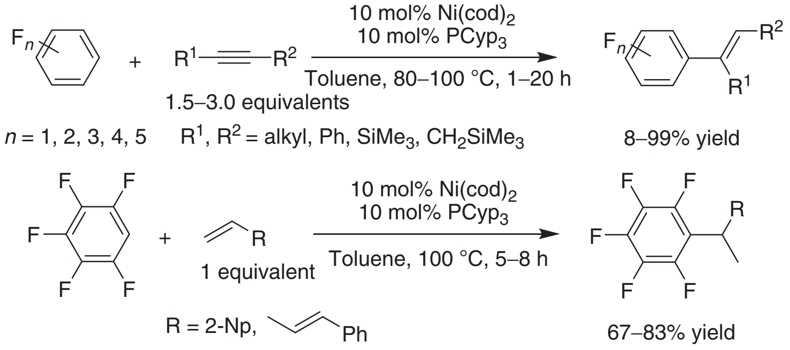
The idea of employing Lewis acids to increase the activity of pyridines was also successfully extended to the alkenylation/alkylation of 2-pyridone derivatives by Hiyama and Nakao (Scheme 73).[120] The Lewis acid coordinated with the carbonyl oxygen of 2-pyridones and the C(6)–H bond was selectively functionalized in a manner similar to that of pyridines. Therefore, a variety of



Scheme 73 Ni-catalyzed alkenylation/alkylation of pyridone with alkynes (Hiyama and Nakao et al., 2009).

substituted 2-pyridones reacted with 4-octyne to afford alkenylated products in the presence of the Ni(cod)$_2$, P(Pr^i)$_3$, and AlMe$_3$. As a representative, *N*,*N*-dimethyluracil was demonstrated to undergo reactions with a range of alkynes.

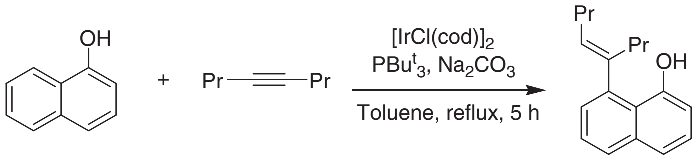
Ni-catalyzed alkenylation of electron-deficient fluoroarenes was also developed by Hiyama and Nakao (Scheme 74).[121] Thus, fluoroarenes containing different number of fluorines underwent alkenylation reactions with a range of internal alkynes to afford *cis*-adducts. It was observed that fluoroarenes with a lower number of fluorines gave a lower yield. In the case of the substrates with more than one possible reaction site, the reactions occurred at the position *ortho* to an F substituent selectively. The alkylation of perfluoroarenes with alkenes also proved viable under similar reaction conditions.



Scheme 74 Ni-catalyzed alkenylation/alkylation of fluoroarenes with alkynes/alkenes (Hiyama and Nakao et al., 2008).

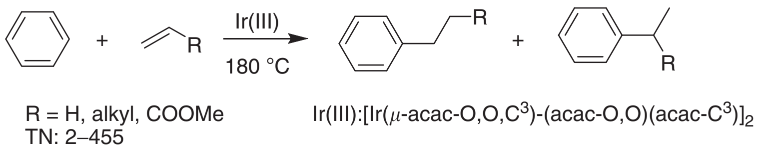
3.23.2.1.4.2 Iridium, platinum, and rhenium-catalyzed reactions of C–H bonds with C–C multiple bonds

In 1999, Ir-catalyzed C–H alkenylation with alkynes was disclosed (Scheme 75).[122] In the presence of catalyst [IrCl(cod)]$_2$ and ligand PBu$^t_3$, 1-hydroxynaphthalene was allowed to react with oct-4-yne to afford the *cis*-adduct.



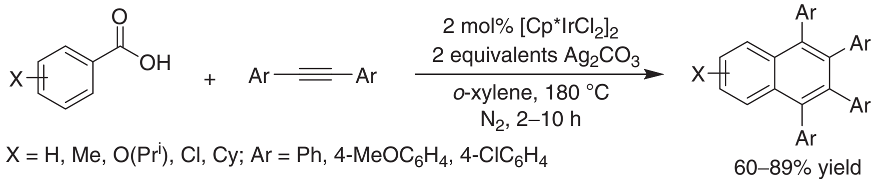
Scheme 75 Ir(I)-catalyzed hydroxyl-directed alkenylation with alkynes (Miura et al., 1999).

Periana and coworkers developed Ir(III) systems for the alkylation of benzene (Scheme 76).[123] The reactions formed linear alkyl arenes as the major products, which indicated a Friedel–Crafts mechanism was not operative. Detailed mechanistic studies suggested that the reaction involved phenyl C–H activation that occurred through a novel concerted oxidative hydrogen transfer mechanism.[124]



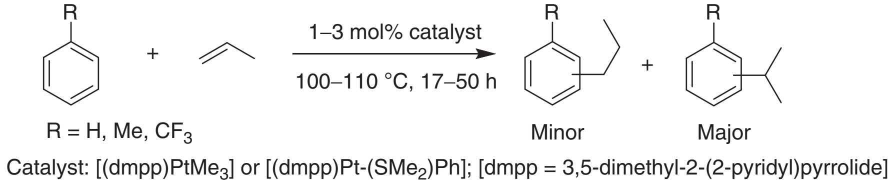
Scheme 76 Ir(III)-catalyzed alkylation of benzene with alkenes (Matsumoto and Periana et al., 2000).

Ir-catalyzed alkenylation of benzoic acids was described by Miura and Satoh (Scheme 77).[125] Interestingly, the iridocycle formed by the alkyne insertion underwent decarboxylation to give a five-membered iridocycle rather than reductive elimination. Subsequently, a second alkyne insertion and the intramolecular reductive elimination afforded naphthalene products. A range of benzoic acids were reactive with internal aryl alkynes in the presence of catalyst $[Cp^*IrCl_2]_2$. Ag_2CO_3 was required as the oxidant.



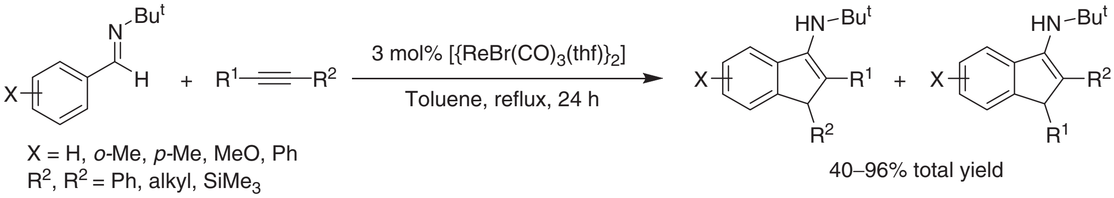
Scheme 77 Ir(III)-catalyzed carboxyl-directed alkenylation with alkynes (Miura and Satoh et al., 2007).

A few examples of Pt-catalyzed reactions of arenes with alkenes have been reported.[126] The reactions yielded alkylated arenes, and branched alkyl arenes were formed predominantly, however, linear products were also observed. Currently, the substrate scopes were primarily limited to simple arenes and alkenes. A representative example is the alkylation reaction of simple arenes reported by Goldberg and coworkers (Scheme 78).[127] In the presence of the catalyst $[(dmpp)PtMe_3]$ or $[(dmpp)Pt\text{-}(SMe_2)Ph]$, simple arenes were successfully alkylated with alkenes. In the case of propene, both branched and linear alkyl arenes were formed in a ratio of approximately 85:15. For the substituted arenes, the reactions yielded a mixture of *o*/*p*/*m* alkylated products with the isomeric distribution *meta* > *para* > *ortho*.



Scheme 78 Pt-catalyzed alkylation of simple arenes with alkenes (Goldberg et al., 2008).

Rhenium has also been found to be able to catalyze the reactions of C(sp^2)–H bonds with alkynes/alkenes. In 2005, Takai and Kuninobu reported the alkenylation of aromatic aldimines with acetylenes (Scheme 79).[128] In the presence of the catalyst $[\{ReBr(CO)_3(thf)\}_2]$, the aldimines with a diversity of substituents on the aromatic ring were allowed to react with internal alkynes to form various indene derivatives. The proposed mechanism involved Re(I)-catalyzed C–H bond activation, insertion of an acetylene to the resulting rhenium–carbon bond, intramolecular nucleophilic attack of the formed alkenyl–rhenium moiety to a carbon atom of the imine, reductive elimination and 1,3-rearrangement of hydrogen atoms (or vice versa) (Figure 6).[128]



Scheme 79 Re-catalyzed imino directed alkenylation with alkynes (Takai and Kuninobu et al., 2005).

The above catalyst system was extended to the reaction of aromatic ketones with alkenes (Scheme 80).[129] The ketones were *in situ* transformed into the imines, which then underwent analogous reactions with α, β-unsaturated esters and the final elimination of aniline to form indene derivatives.

Re-catalyzed reactions of olefinic C–H bonds with alkenes also proved viable (Scheme 81).[130] By using $Re_2(CO)_{10}$, a wide range of α,β-unsaturated ketimines reacted with diverse α,β-unsaturated carbonyl compounds to form cyclopentadiene via an analogous reaction pathway. Interestingly, the resulted cyclopentadienes formed Cp-Re complex with catalyst $Re_2(CO)_{10}$.

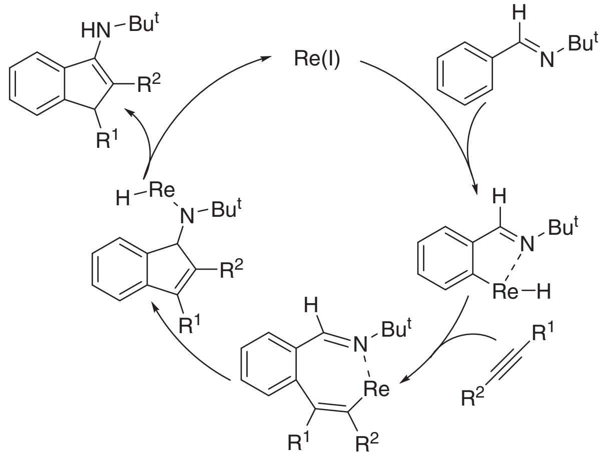
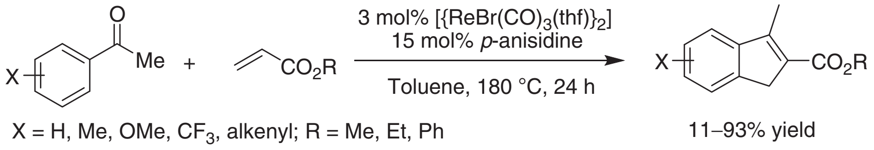
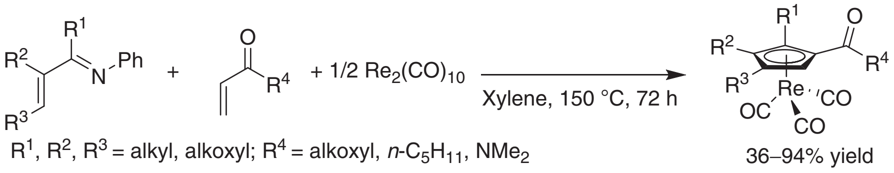


Figure 6 Mechanism of Re-catalyzed alkenylation of aldimines with alkynes.



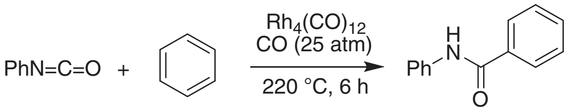
Scheme 80 Re-catalyzed imino-directed annulation via C–H alkenylation (Takai et al., 2006).



Scheme 81 Re-catalyzed imino-catalyzed olefinic C–H alkylation (Takai and Kuninobu et al., 2008).

3.23.2.2 Reactions with C=O and C=N Bonds

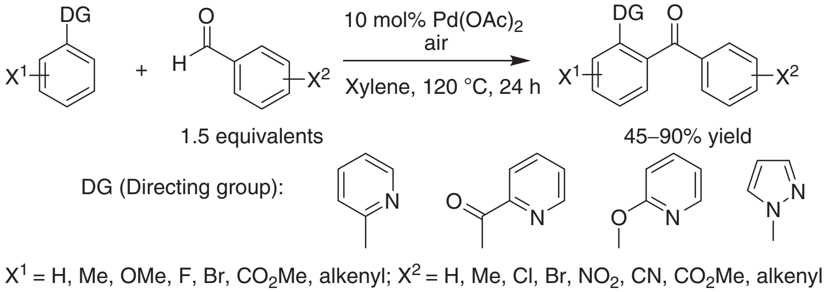
Recently, the reaction of C–H bonds with polar multibonds has attracted considerable attention, and quite a number of reactions have been developed. A range of transition metals were found to catalyze the addition of C–H bonds to C=O and C=N bonds effectively. Just as the reactions with C=C double bonds, the reactions with polar C=X bonds may also form arylation/alkylation or hydroarylation/alkylation products, depending on the transition metals used in the reactions. The first catalytic example of such an addition reaction was reported by Hong and coworkers in 1978 (Scheme 82).[131] Therefore, benzene was allowed to react with a range of aryl isocyanates in the presence of catalyst $Rh_4(CO)_{12}$ and CO, yielding the corresponding benzanilides.



Scheme 82 Rh-catalyzed C–H addition of benzene to isocyanates (Hong et al., 1978).

3.23.2.2.1 Palladium-catalyzed reactions of C–H bonds with aldehydes and imines

Pd has been successfully utilized to catalyze the addition of $C(sp^2)$–H bonds to carbonyl groups. The substrates are still limited to aldehydes, and the reactions give arylated products. An early example is the heteroarene-directed acylation of $C(sp^2)$–H bonds reported by Cheng and coworkers (Scheme 83).[132] Therefore, arenes with nitrogen-containing heteroarenes were acylated with aryl aldehydes to give diaryl ketones regioselectively. Air was utilized as the terminal oxidant. A wide range of functional groups were tolerated under the reactions conditions. The proposed mechanism was similar to that involved in the arylation of alkenes, including Pd-mediated C–H cleavage, the insertion of the carbonyl group into the formed carbopalladium bond, β-hydride elimination to release the ketones and Pd(II) species, the reductive elimination of the Pd(II) to produce Pd(0) species, which was reoxidized to Pd(II) to close the catalytic cycle (Figure 7).[132]



Scheme 83 Pd-catalyzed heteroarene-directed acylation with benzaldehydes (Cheng et al., 2009).

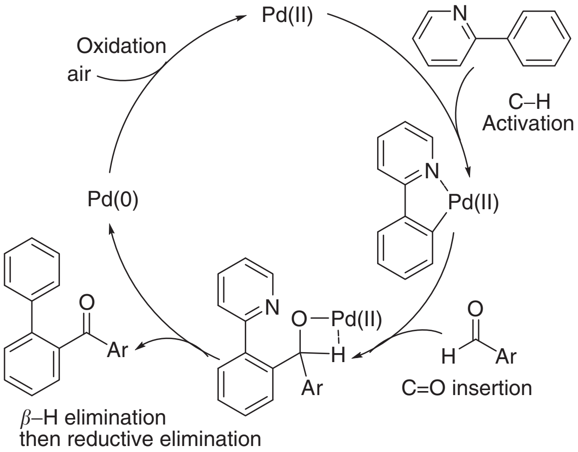
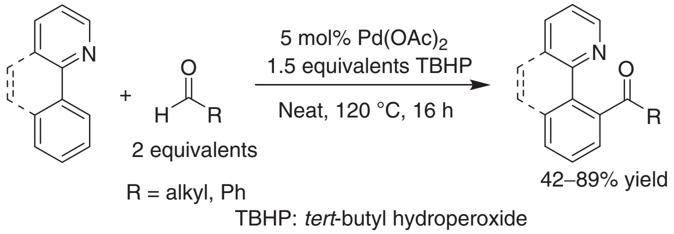


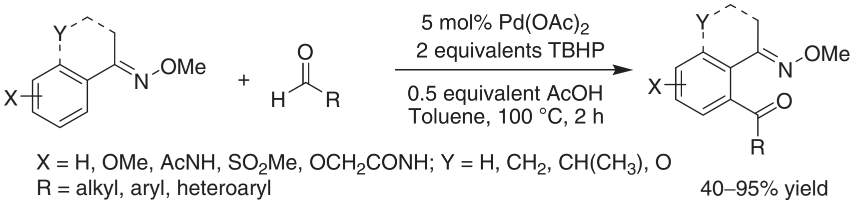
Figure 7 Proposed mechanism of Pd-catalyzed acylation with aldehydes.

Subsequently, Li and coworkers disclosed unprecedented acylation reactions with aliphatic aldehydes (Scheme 84).[133] Thus, in the absence of solvents, 2-phenylpyridine and benzo[*h*]quinoline underwent the solvent-free acylation with a variety of aliphatic aldehydes using *t*-butylhydroperoxide (TBHP) as the oxidant. The catalytic systems proved applicable to the acylation of aromatic aldehydes. Palladium (IV) complexes, which were formed through the oxidation of the aryl-Pd(II)-COR intermediates by TBHP, were proposed as key intermediates in this C–H acylation reaction. Therefore, the formed aryl-Pd(IV)-COR intermediates underwent reductive elimination to furnish the acylated products and regenerate Pd(II) catalyst.



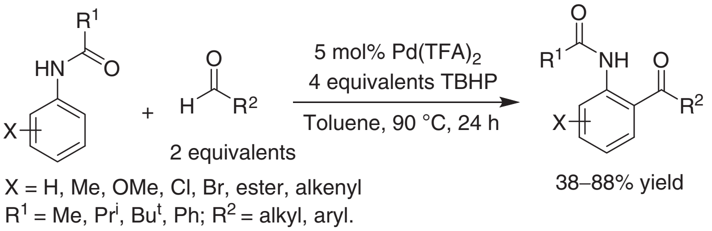
Scheme 84 Pd-catalyzed pyridine-directed acylation with alkyl aldehydes (Li et al., 2010).

The similar acylation were also enabled by using other directing groups. Yu and coworkers realized the oxime-directed coupling of aryl ketone oximes and aldehydes (Scheme 85).[134] The use of 0.5 equivalent acetic acid gave a slightly higher yield.



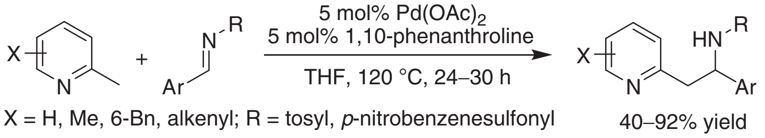
Scheme 85 Pd-catalyzed oxime-directed acylation with aldehydes (Yu et al., 2010).

Both aromatic and aliphalic aldehydes were compatible under the reaction conditions. Mechanistically, on the contrary to the direct reaction of palladacycles with aldehydes in the above reactions, the authors proposed that acyl radicals, which were generated *in situ* by hydrogen atom abstraction of the aldehydes, were the actual reaction partners. The acyl radicals reacted with the palladacycles to afford the product ketones via either reactive Pd(IV) or dimeric Pd(III) intermediates. Subsequently, such an acylation of acetanilides was demonstrated by Li and Kwong using $Pd(TFA)_2$ as the catalyst (Scheme 86). A mechanism involving radicals was also proposed.[135]



Scheme 86 Pd-catalyzed amide-directed acylation with aldehydes (Kwong and Li et al., 2011).

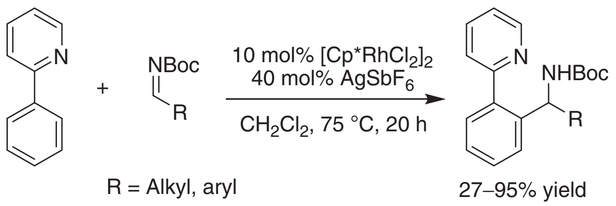
The carbopalladium bond formed via C–H cleavage has also been demonstrated to undergo the nucleophilc attack to imines in a similar manner to that to carbonyl groups. Remarkably, Xia and Huang discovered the addition reaction of benzylic C–H bonds to aldimines (Scheme 87).[136] Therefore, a range of 2-methyl azaarenes reacted with *N*-sulfonyl aldimines in the presence of catalyst $Pd(OAc)_2$ and ligand 1,10-phenanthroline. It is noted that protolysis took place instead of β-hydride elimination in the reaction, affording amines as the final product and release Pd(II) species. Hence, the formation of Pd(0) was avoided and no oxidants were required.



Scheme 87 Pd-catalyzed reactions of benzylic C–H bonds with *N*-sulfonyl aldimines (Xia and Huang et al., 2010).

3.23.2.2.2 Other-transition-metal-catalyzed reactions of C–H bonds with C=O and C=N bonds

Rh-enabled addition of organometallic reagents to carbonyls and imines has been extensively explored and provided chemists with attractive alternatives to the Grignard-type additions.[137] Such an addition reaction via C–H activation is intriguing and gained attention recently. The first Rh-catalyzed addition of C–H bonds to imines was reported by Bergamn and Ellman (Scheme 88).[138] Therefore, catalyst $[Cp^*RhCl_2]_2$ was found to catalyze the addition of 2-arylpyridines to *N*-Boc- and *N*-sulfonyl-aldimines via C–H bond functionalization to give branched amine products in the presence of oxidant $AgSbF_6$. A wide range of



Scheme 88 Rh-catalyzed pyridine-directed reactions of C–H bonds with Boc-imine (Bergman and Ellman et al., 2011).

functional groups were compatible with the reaction. Mechanistically, the C–H cleavage involved electrophilic deprotonation caused by the Rh(III) catalyst. The formed Ar-Rh(III) added to the imines, followed by protonolysis to afford the final products and regenerate the Rh(III) catalyst (Figure 8).[138]

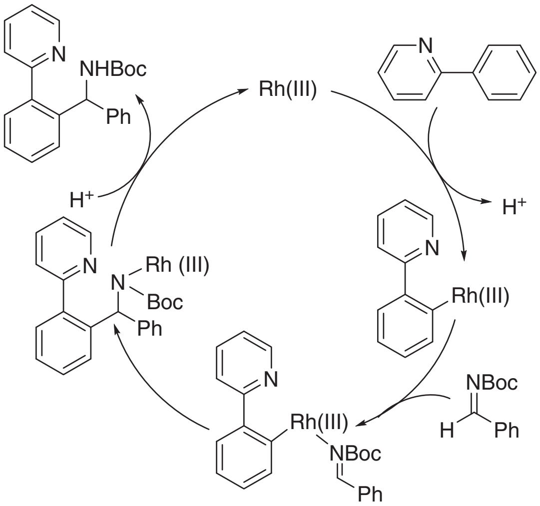
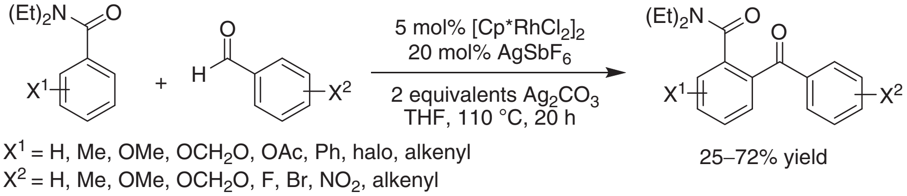


Figure 8 Proposed mechanism of Rh-catalyzed reaction of C–H bonds with imines.

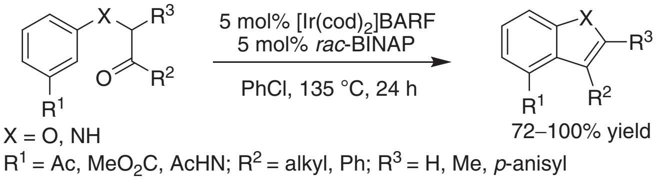
Concurrently, Shi and coworkers reported a similar addition reaction of 2-arylpyridines with *N*-sulfonyl aldimines using catalyst [Cp*Rh(CH_3CN)$_3$][SbF_6]$_2$.[139]

The Rh-catalyzed addition of C–H bonds to carbonyls also proved viable. In 2011, Jung and Kim reported that a wide range of benzamides underwent acylation reactions with (hetero)aryl aldehydes to form diaryl ketones in the presence of [Cp*RhCl_2]$_2$ and AgSbF_6, and Ag_2CO_3 as the oxidant (Scheme 89). It is noted that reductive elimination products were obtained instead of protonolysis products, which were produced in the above reactions with imines.[140]



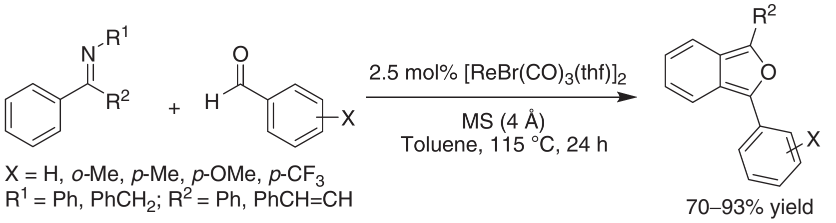
Scheme 89 Rh-catalyzed amide-directed acylation with benzaldehydes (Jung and Kim et al., 2011).

For all the above reactions, the substrate scopes were limited to aldehydes. By using catalyst [Ir(cod)$_2$]BARF/*rac*-BINAP, Shibata and coworkers realized the addition of C–H bonds to ketones with elegantly-designed substrates (Scheme 90).[141] The substrates were so designed that the reacting carbonyl group was attached to the arenes through a linker and a directing group was installed at the *meta*-position. As a result, a bidentate chelating group consisting of the directing group and the carbonyl group enabled C–H activation at the more congested *ortho*-position regioselectively. Subsequently, intramolecular 1,2-addition to the carbonyl moiety and dehydration formed benzoheteroles including indoles and benzofurans. A range of directing groups were found to be effective in the reaction.



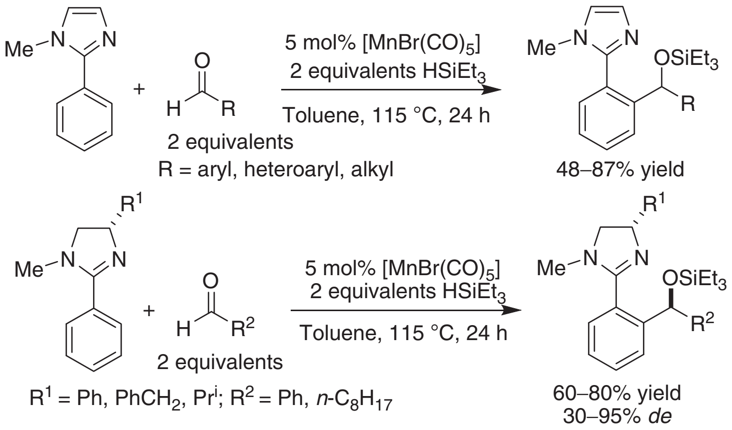
Scheme 90 Ir-catalyzed intramolecular reactions of C–H bonds with carbonyl groups (Shibata et al., 2009).

Rhenium has lower electronegativity than rhodium and ruthenium, so the carbon–rhenium bond is more polarized than the carbon–ruthenium and –rhodium bonds, and the organorhenium species will hopefully react with aldehydes such as Grignard reagents.[142] Inspired by this conjecture, Takai and Kuninobu disclosed the insertion of aldehydes into a C–H bond of aromatic ketimines by using a rhenium complex $[ReBr(CO)_3(thf)]_2$, as a catalyst. The reactions provided isobenzofuran derivatives via C–H bond activation, insertion of the aldehyde, intramolecular nucleophilic cyclization, reductive elimination, and elimination of aniline (Scheme 91).[142]



Scheme 91 Re-catalyzed imino-directed reactions of C–H bonds with benzaldehydes (Takai and Kuninobu et al., 2006).

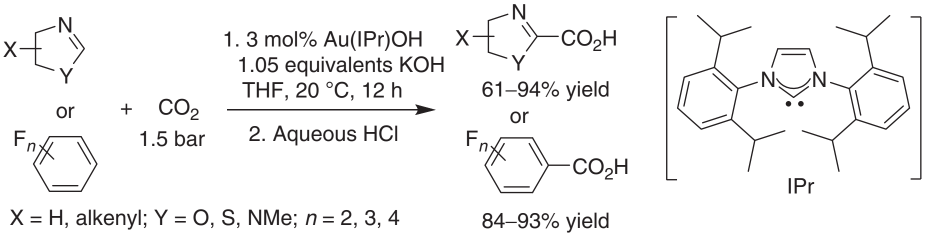
Subsequently, Takai and Kuninobu reported analogous insertion reaction catalyzed with manganese (Scheme 92).[143] In the presence of $[MnBr(CO)_5]$, 2-phenylimidazoles underwent a Grignard-type reaction with aromatic and aliphalic aldehydes via C–H activation. The mechanism was similar to that involved in Re-catalyzed insertion reaction, except that Mn-catalyzed reactions ended up with silyl protection with $HSiEt_3$, which provided silyl ethers as the final products and released dihydrogen. Notably, the use of chiral imidazoles led to asymmetric reactions with moderate diatereoselectivities.



Scheme 92 Mn-catalyzed imidazole-directed reactions of C–H bonds with aldehydes (Takai et al., 2007).

3.23.2.2.3 Carboxylation of C–H bonds with CO_2

The use of carbon dioxide for chemical synthesis has been intriguing, because it is an abundant, cheap, and nontoxic renewable source. Although the carboxylation with CO_2 has seen broad applications for a long time, the reactions via C–H activation are very rare. An elegant example is the gold-catalyzed carboxylation reported by Nolan and Boogaerts in 2010 (Scheme 93).[144] By using Au(IPr)OH as the catalyst, a variety of acidic (hetero)arenes were carboxylated with CO_2 in the presence of KOH. The reactions occurred selectively at the most acidic C–H bonds, which can be rationalized in terms of simple acid/base theory. Mechanistic



Scheme 93 Au-catalyzed carboxylation of acidic C–H bonds with CO_2 (Nolan et al., 2010).

studies, along with the necessary use of a strong base and basic Au(IPr)OH complex, supported that the reactions proceeded via a deprotonative reaction mechanism. Therefore, protonolysis of [IRr]AuOH] by the oxazole gave the gold(I) oxazole intermediate. The subsequent nucleophilic addition of the oxazole ligand to the carbon atom of CO_2 afforded Au(I)–carboxylate complex, which underwent metathesis with KOH furnished the carboxylation product and regenerate [IRr]AuOH] (**Figure 9**).[144]

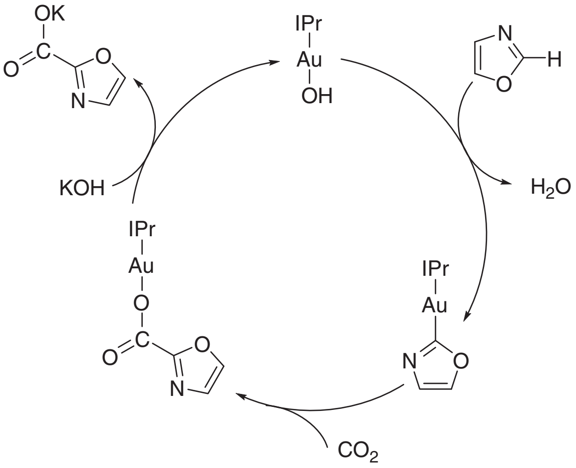
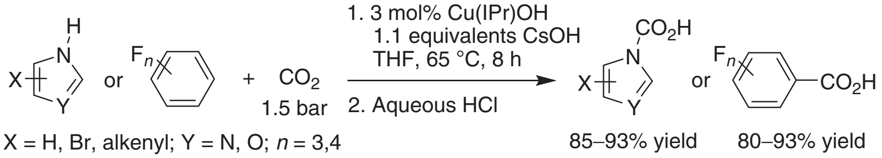


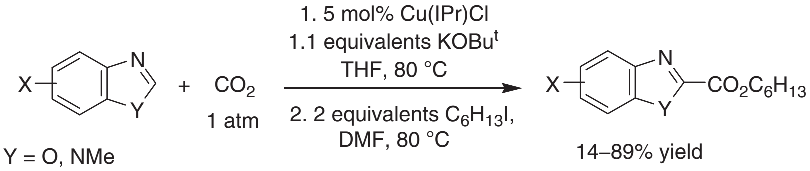
Figure 9 Proposed mechanism of Au-catalyzed carboxylation with CO_2.

Subsequently, Nolan and Cazin reported similar carboxylation reactions catalyzed by copper (**Scheme 94**).[145] Acidic heteroarenes and polyfluorinated arenes underwent similar carboxylation using catalyst Cu(IPr)OH and base CsOH. The proposed mechanism was similar to that proposed in the above gold-catalyzed carboxylation reaction.



Scheme 94 Cu-catalyzed carboxylation of electron-deficient arenes with CO_2 (Nolan and Cazin et al., 2010).

Independently, Hou and coworkers disclosed the Cu(IPr)Cl-catalyzed C–H carboxylation of acidic heteroarenes with CO_2 in the presence of $KOBu^t$ (**Scheme 95**). The formed carboxylic acids were transformed into esters because of the slow uncatalyzed decomposition.[146]

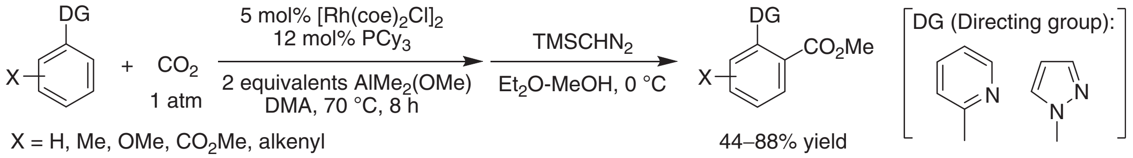


Scheme 95 Cu-catalyzed carboxylation of heterocycles with CO_2 (Hou et al., 2010).

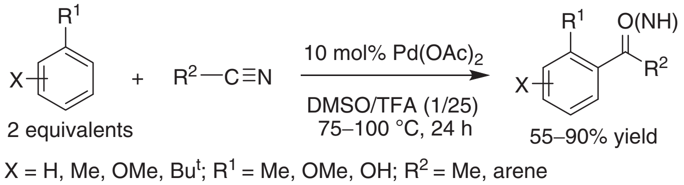
All of the above carboxylation reactions relied on the use of the substrates with acidic C–H bonds and proceeded via a deprotonation mechanism, which severely limited their application in chemical synthesis. In 2011, Iwasawa and coworkers successfully realized the C–H carboxylation of less acidic arenes (**Scheme 96**).[147] Therefore, arenes-containing directing groups, including pyridine and pyrazole, underwent carboxylation with CO_2 in the presence of $[Rh(coe)_2Cl]_2$ and PCy_3. Methylaluminum alkoxides were found to promote the carboxylation efficiently, mainly because they underwent transmetallation to regenerate active catalyst methylrhoduim(I) species. A wide range of functional groups were tolerated under the reaction conditions.

3.23.2.2.4 Reactions of C–H bonds with nitriles

Another intriguing polar multiple bond is nitrile. The first Pd-catalyzed C–H addition to nitriles was demonstrated by Larock and coworkers (**Scheme 97**).[148,149] In the presence of $Pd(OAc)_2$, a wide range of simple arenes with electron-donating substituents



Scheme 96 Rh-catalyzed heteroarene-directed carboxylation with CO_2 (Iwasawa et al., 2011).



Scheme 97 Pd-catalyzed acylation of simple arenes with nitriles (Larock et al., 2004).

reacted with benzonitriles to afford ketimines, which were converted into corresponding ketones very readily. The reactions were conducted in TFA, and the addition of a small amount of dimethyl sulfoxide (DMSO) increased the yields dramatically. In the case of substrates with one substituent, the mixtures of *o*/*p*/*m* isomers were formed, with *para*-isomer as the major product. The proposed mechanism involved Pd-catalyzed C–H activation, intermolecular carbopalladation of a nitrile, and the protonation to give ketimines.

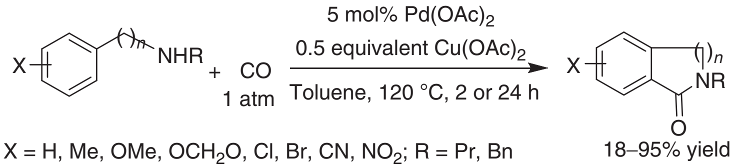
3.23.2.3 Reactions with CO

Transition-metal-catalyzed carbonylation of aryl (pseudo)halides with carbon monoxide provides an efficient method to access carboxylic acid derivatives. Direct carbonylation of C–H bonds are advantageous, and have been extensively exploited and a range of transition metals can catalyze such a carbonylation with carbon monoxide effectively.

3.23.2.3.1 Palladium-catalyzed reactions of C–H bonds with CO

The first Pd-mediated carboxylation of arenes with CO was reported by Fujiwara and coworkers in 1980 in the presence of stoichiometric amount of $Pd(OAc)_2$.[150] The catalytic reactions proved viable in the presence of oxidants such as O_2, Bu^tOOH, alkyl halides, or $K_2S_2O_8$. Both arenes and heteroarenes such as furan and thiophene were reactive to give the corresponding aryl carboxylic acids.[151]

Pd-catalyzed carbonylation with CO was achieved by Orito and coworkers in 2004 (Scheme 98).[152] Therefore, with the aid of a directing group, a range of benzylic amines and phenethyl amines were carbonylated in the presence of 1 atm CO and a catalytic amount of $Pd(OAc)_2$ to give five- or six-membered benzolactams, respectively. The oxidant $Cu(OAc)_2$ was required to regenerate Pd(II) to make the reaction catalytic. The authors proposed that the carbonylation involved *ortho*-palladation with $Pd(OAc)_2$, the insertion of CO, and the nucleophilic attack of the internal amino group on the carbonyl group to generate benzolactams and Pd(0) (Figure 10).[152] This mechanism represents a general pathway for palladium-catalyzed arene carbonylation with CO.



Scheme 98 Pd-catalyzed amino-directed carbonylation (Orito et al., 2004).

Yu and coworkers described the carboxyl-directed carboxylation with CO (Scheme 99).[153] Both benzoic acids and phenyl acetic acids were allowed to react with CO in the presence of an inorganic base to afford dicarboxylic acid derivatives. It is noted that β-vinyl C–H bond in α,β-unsaturated carboxylic acid was also carboxylated selectively to give *cis*-1,2-dicarboxylic acid.

The analogous carboxylation of anilides was also realized by Yu and coworkers (Scheme 100).[154] The formed *N*-acyl anthranilic acids in the reaction could be readily transformed into biologically and pharmaceutically significant molecules, such as benzoxazinones and quinazolinones, making the reaction synthetically useful. The use of $p\text{-TsOH} \cdot H_2O$ proved crucial to achieve high yields.

Concurrently, Lloyd-Jones and Booker-Milburn disclosed the urea-directed carbonylation (Scheme 101).[155] Remarkably, the precatalyst $[(MeCN)_2Pd(OTs)_2]$ proved highly effective and the reaction proceeded smoothly at room temperature.

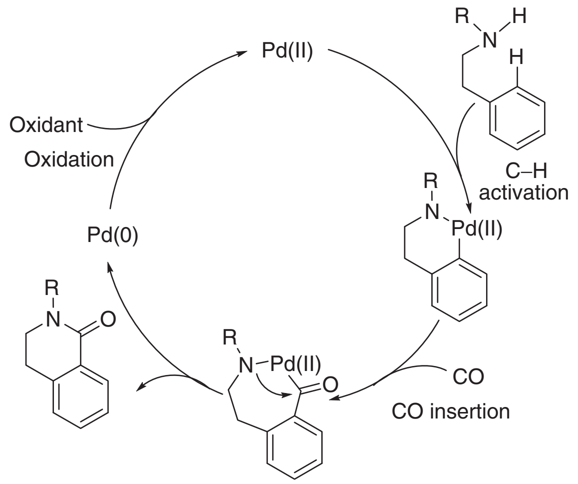
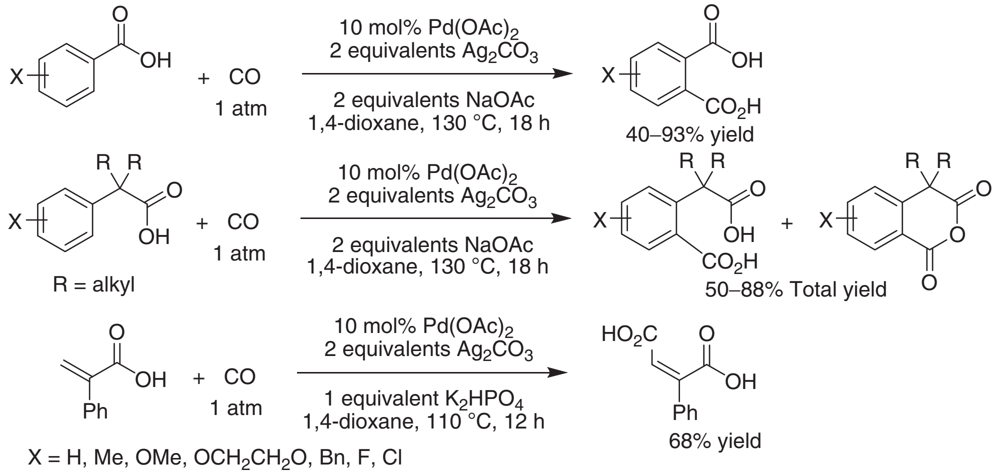
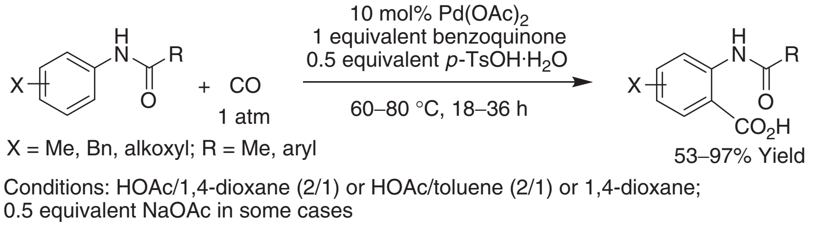


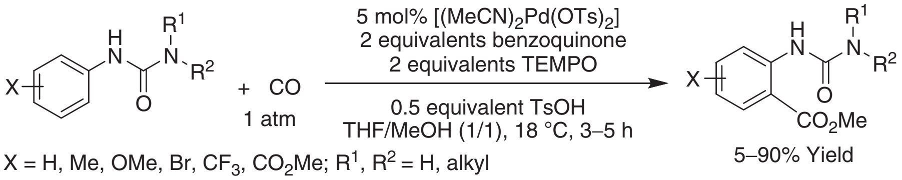
Figure 10 Proposed mechanism of Pd-catalyzed carbonylation with CO.



Scheme 99 Pd-catalyzed carboxyl-directed carbonylation (Yu et al., 2008).

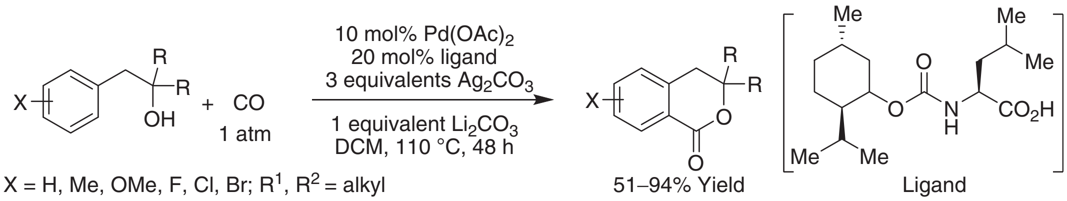


Scheme 100 Pd-catalyzed amide-directed carbonylation of acetylanilines (Yu et al., 2010).



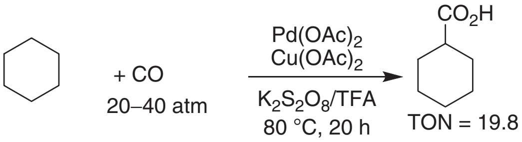
Scheme 101 Pd-catalyzed urea-directed carbonylation of phenylureas (Booker-Milburn and Lloyd-Jones et al., 2009).

Yu and coworkers also reported the alkyl hydroxyl-directed carbonylation with CO (Scheme 102).[156] Thus, phenylethanol was carbonylated to afford 1-isochromanones in the presence of a catalytic amount of $Pd(OAc)_2$ and one equivalent of Li_2CO_3. An amino acid ligand was beneficial to the reaction, and a wide range of functionalities were tolerated. However, the substrate scope was still limited to tertiary alcohols.



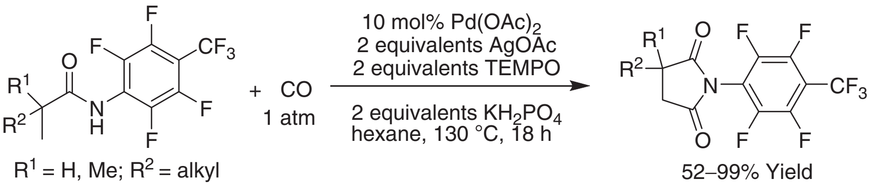
Scheme 102 Pd-catalyzed hydroxyl-directed carbonylation (Yu et al., 2011).

The reaction of C(sp^3)–H bonds with CO also proved viable. In 1989, Fujiwara and coworkers reported the carboxylation of cyclohexane with CO (20–40 atm) using Pd(II)/Cu(II) catalytic systems in TFA, which is the first example of transition metal-catalyzed alkane carboxylation (Scheme 103).[157] Other alkanes such as methane, ethane, and propane were also carboxylated to give the corresponding carboxylic acids.[158]



Scheme 103 Pd-catalyzed carboxylation of alkanes with CO (Fujiwara et al., 1989).

By using an acidic amide group as the directing group, the efficient carbonylation of C (sp^3)–H bonds was achieved by Yu and coworkers (Scheme 104).[159] The amide group was made acidic by introducing a highly electron-withdrawing perfluorophenyl group. The β-C(sp^3)–H bonds of *N*-arylamides were carbonylated with 1 atm CO to form succinimides in the presence of TEMPO and KH_2PO_4. It is noted that substrates with an α-H were compatible under the reaction conditions. The C–H bonds of cyclopropanes were also reactive. Interestingly, *n*-hexane, has rarely been an effective solvent in C–H functionalization reactions, was found to be the optimal solvent.

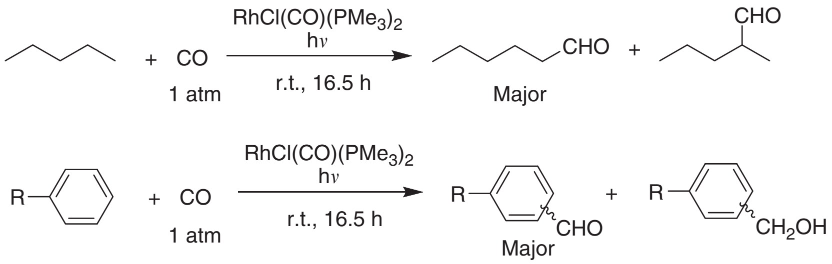


Scheme 104 Pd-catalyzed acidic amide-directed carbonylation of C(sp^3)-H bonds (Yu et al., 2010).

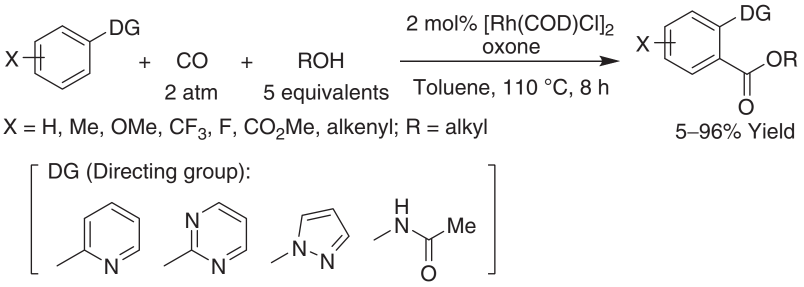
3.23.2.3.2 Rhodium-catalyzed reactions of C–H bonds with CO

In 1983, Eisenberg and coworkers described the first example of the carbonylation of benzene using $IrH_3(CO)(dppe)$ complex ($dppe{=}Ph_2PCH_2CH_2PPh_2$) in the presence of CO.[160] The reaction was conducted under photo-irradiation conditions and formed benzaldehyde as the major product. $RhCl(CO)(PPh_3)_2$ was also found to catalyze such a carbonylation.[161] Inspired by the pioneering works, Tanaka and coworkers investigated the $RhCl(CO)(PMe_3)_2$-catalyzed carbonylation of C–H bonds under irradiation extensively. They successfully realized carbonylation of simple arenes and alkanes in the presence of $RhCl(CO)(PMe_3)_2$ to afford the corresponding aldehydes (Scheme 105).[162] The reaction proceeded at an ambient temperature under an atmospheric pressure of CO. In the reactions of monosubstituted benzenes, *meta*-substituted benzaldehydes were formed as the major products. In the case of *n*-alkanes, the carbonylation took place preferentially at the terminal methyl group to give a linear aldehyde.

The analogous carbonylation with the aid of a directing group was also disclosed. Zhang and Liang reported the Rh-catalyzed oxidative carbonylation of arenes and heteroarenes with CO (Scheme 106).[163] A variety of *N*-containing heteroarenes or an amide group was the effective directing group. The reactions afforded esters as the final products because of the presence of an alcohol. Oxone was found to play an important role in the reactions.

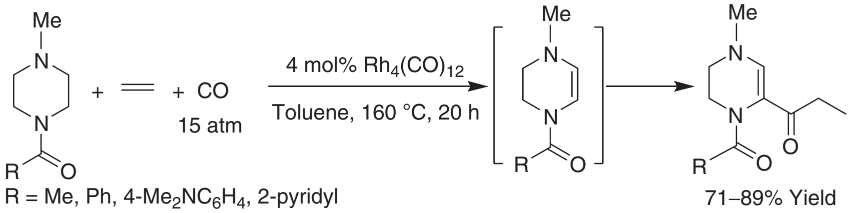


Scheme 105 Rh-catalyzed carbonylation of simple arenes and alkanes with CO (Tanaka et al., 1990).



Scheme 106 Rh-catalyzed heteroarene-directed carbonylation (Zhang and Liang et al., 2009).

Although the above Rh/Ir-catalyzed carbonylation involves the insertion of CO into C–H bonds leading to aldehydes, a three-component coupling acylation of C–H bonds, CO, and alkenes may take place to give ketones.[12] As early as 1979, Hong and coworkers observed $Rh_4(CO)_{12}$-catalyzed acylation of benzene with CO and ethylene.[164] Another example of such an acylation is the $Rh_4(CO)_{12}$-catalyzed reaction of *N*-acylpiperazines with CO and ethylene discovered by Murai and coworkers (Scheme 107).[165] The reactions started with the amide group-directed olefinic C–H activation of *N*-acyl-1,2,3,4-tetrahydropyrazines, which were generated through Rh-catalyzed hydrogen transfer from the piperazines to ethylene. The next reaction steps involved the insertion of ethylene into the Rh–H bond in the formed rhodocycle complex, the subsequent CO insertion to form acyl Rh complex, and the reductive elimination to afford the final acylated products (Figure 11).[165]



Scheme 107 Rh-catalyzed amide-directed three-component coupling acylation of *N*-acylpiperazines (Murai et al., 1997).

The direct Rh-catalyzed three-component coupling acylation of C(sp^3)–H bonds was realized by Murai and coworkers in 2000 (Scheme 108).[166] Therefore, the C(sp^3)–H bonds adjacent to a nitrogen atom in alkylamines were acylated by reaction with CO and ethylene in the presence of catalyst $[RhCl(cod)]_2$. The reactions relied on the use of pyridine or pyrimidine as the directing groups. The scope of substrates and alkenes was still quite limited.

3.23.2.3.3 Ruthenium-catalyzed reactions of C–H bonds with CO

Ruthenium was also successfully used to catalyze the reaction of C–H bonds with CO, and both carbonylation and acylation have been demonstrated. An elegant example is the carbonylation of aromatic amides reported by Chatani and coworkers (Scheme 109).[167] Remarkably, a *N*,*N*-bidentate directing group consisting of an amide and a pyridine group was designed. This novel directing group strongly coordinated to the Ru catalyst even under high-pressure CO. In the presence of catalyst $Ru_3(CO)_{12}$ and 10 atm CO, a range of aromatic amides bearing a pyridin-2-ylmethylamine moiety underwent *ortho*-carbonylation of C–H bonds and the nucleophilic attack of the nitrogen of the amide group to afford phthalimides. Interestingly, the acylation products were not observed even in the presence of 10 atm ethylene.

The bidentate directing group was successfully extended to the carbonylation of C(sp^3)–H bonds with CO (Scheme 110).[168] Thus, the C(sp^3)–H bonds of alkyl amides containing a 2-pyridinylmethylamino moiety were effectively carbonylated under the

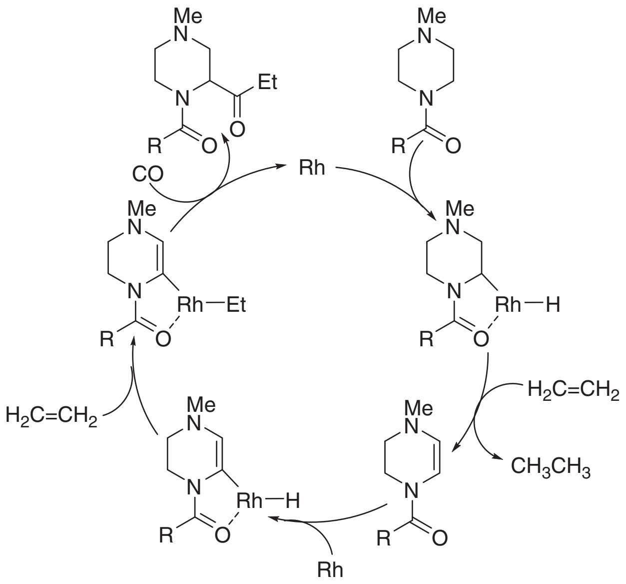
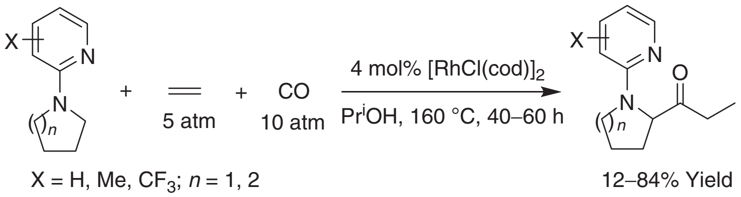
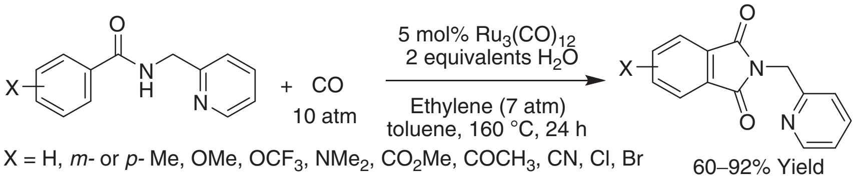


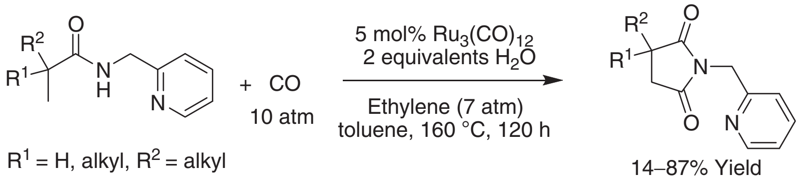
Figure 11 Proposed mechanism of Rh-catalyzed amide-directed acylation of *N*-acylpiperazines.



Scheme 108 Rh-catalyzed pyridine-directed three-component coupling acylation of C(sp^3)-H bonds (Murai et al., 2000).



Scheme 109 Ru-catalyzed *N*,*N*-bidentate directing group-assisted carbonylation (Chatani et al., 2009).



Scheme 110 Ru-catalyzed bidentate directing group-assisted carbonylation of C(sp^3)-H bonds (Chatani et al., 2011).

same reaction conditions to afford the corresponding succinimides. A variety of functional groups were tolerated and the reactions took place selectively at a methyl C–H bond over a methylene C–H bond. Although the substrates with an α-tertiary carbon showed the best reactivity, those with one α-H were also reactive. Mechanistically, the authors proposed that the reaction was initiated by the formation of a ruthenium hydride complex arising from N–H bond activation. The subsequent ethylene insertion followed by C–H bond activation gave the metallacycle with the concomitant generation of ethane. It is interesting that no direct C–H bond cleavage took place in the hydride complex. Finally, the insertion of CO and subsequent reductive elimination furnished the final product and regenerated the ruthemiun catalyst (Figure 12).[168]

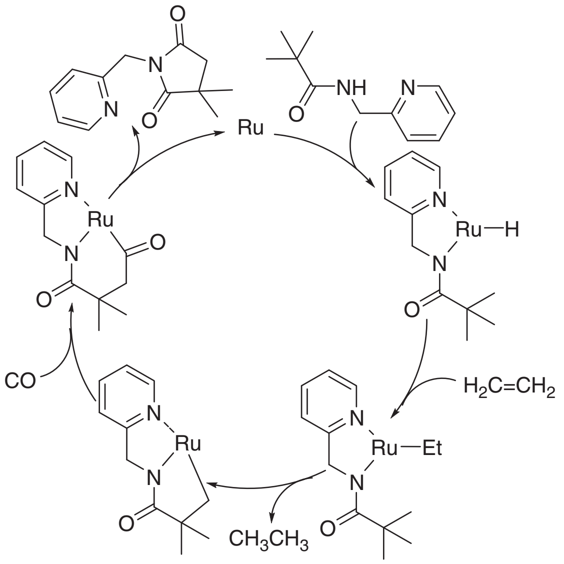
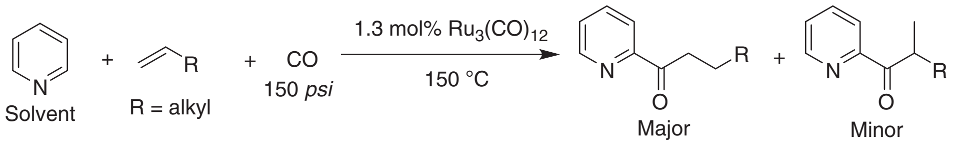


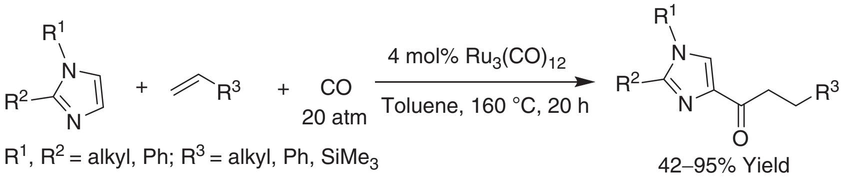
Figure 12 Proposed mechanism of Ru-catalyzed carbonylation of C(sp^3)-H bonds.

Ruthenium was also found to catalyze the three-component coupling acylation of C–H bonds effectively. In 1992, Moore and coworkers described the acylation reactions of pyridines with CO and olefins using catalyst $Ru_3(CO)_{12}$ (Scheme 111).[169] The reaction occurred at the α-position of the pyridine selectively. A range of terminal olefins underwent the acylation to give the linear pyridyl ketone as the major product. Remarkably, *cis*/*trans* internal olefins were also reactive and yielded the same linear/branched product ratio as the terminal olefins, indicating that a rapid olefin isomerization occurred in the reaction.



Scheme 111 Ru-catalyzed three-component coupling acylation of pyridine (Moore et al., 1992).

The $Ru_3(CO)_{12}$-catalyzed three-component coupling acylation of imidazoles was also reported (Scheme 112).[170] A range of imidazoles reacted with alkenes and CO to afford 5-acyl imidazoles selectively. The linear products were formed predominantly.

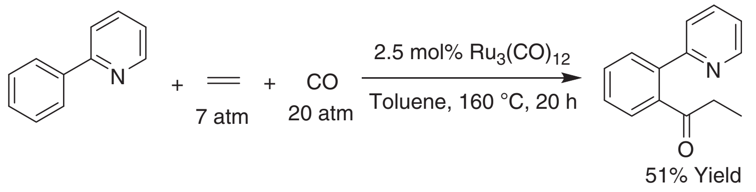


Scheme 112 Ru-catalyzed three-component coupling acylation of imidazoles (Murai et al., 1996).

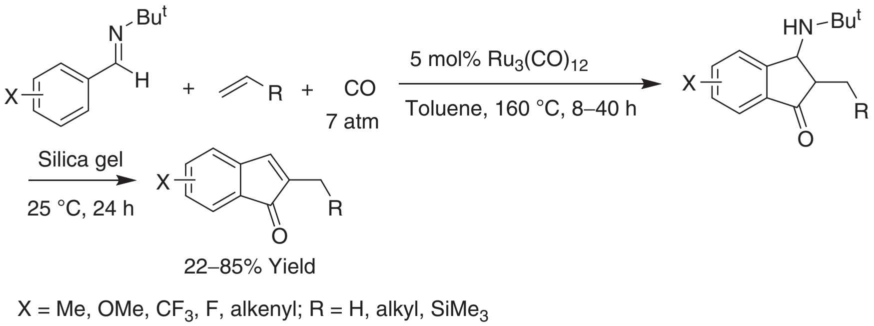
The above catalytic systems proved applicable to the acylation of arenes with the aid of pyridine directing groups. Therefore, pyridylbenzenes were allowed to react with CO and ethylene to yield propionylated products under similar conditions (Scheme 113).[171] In addition to pyridine, pyrimidine was also found to be an effective directing group. Moreover, some heteroarenes, such as thiophene derivatives, were also reactive.

Murai and coworkers developed a range of the sp^2 nitrogen-directed three-component coupling acylation using catalyst $Ru_3(CO)_{12}$. In 1997, they reported the analogous acylation of aromatic aldimines with the aid of imine directing groups (Scheme 114).[172] The formed acylated products were labile and underwent the rapid cyclization to form indenone derivatives via intramolecular aldol condensation.

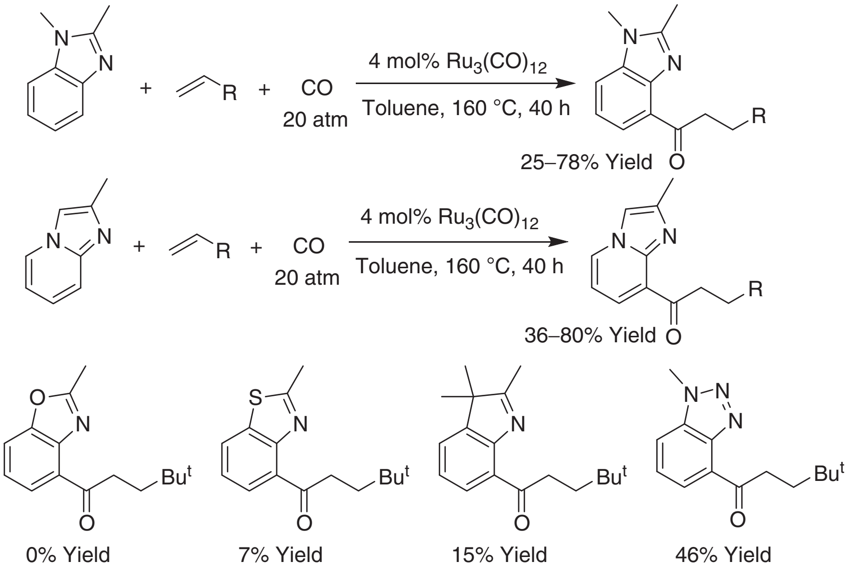
Notably, Murai and coworkers successfully achieved the similar acylation at the C–H bonds β to a directing nitrogen atom (Scheme 115).[173] A wide range of azo-heteroarenes underwent the acylation to afford aryl ketones under the similar conditions.



Scheme 113 Ru-catalyzed pyridine-directed three-component coupling acylation of pyridylbenzenes (Murai et al., 1997).



Scheme 114 Ru-catalyzed imino-directed three-component coupling acylation (Murai et al., 1997).



Scheme 115 Ru-catalyzed three-component coupling acylation of aza-heterocycles (Murai et al., 1998).

This reaction is remarkable, because the C–H activation relying on directing groups usually takes place at the position γ or δ to a chelating atom because of the facile formation of five or six-membered metalacycles. The unusual reactivity was attributed to the formation of a carboruthenium complex consisting of a trimetalic $Ru_3(CO)_{12}$ cluster. One of the Ru atoms was chelated by the directing nitrogen atom, and another Ru atom was bonded to the β carbon, which formed a stable five-membered ruthenocycle complex. For the substrates without 2-substituents, the acylation occurred at the 2-postion preferentially.

3.23.3 Reactions with (Pseudo)halides

Aryl (pseudo)halides play crucial roles in transition-metal-catalyzed reactions. Many classical reactions, such as Heck coupling and cross-coupling reactions, are initiated by an oxidative addition of aryl (pseudo)halides with transition metals. Aryl (pseudo)-halides have also been extensively exploited in the transition-metal-catalyzed direct arylation via C–H activation in the last three decades. A great number of reactions have been developed, and a diversity of transition metals have seen applications in the direct aryl–aryl bond formation reactions involving aryl (pseudo)halides.[13,14]

3.23.3.1 Pd-Catalyzed Reactions with (Pseudo)halides

In Pd-mediated C–H arylation reactions with aryl (pseudo)halides, there are two principal mechanistic manifolds. One involves Pd(II)/Pd(IV) catalysis, and the other one proceeds via a Pd(0)/Pd(II) catalytic cycle. In the Pd(II)/Pd(IV) mechanism, the reactions usually start with Pd(II)-mediated C–H cleavage. Next, the newly formed organopalladium species undergoes oxidative addition of the aryl (pseudo)halide (normally aryl iodides or aryl iodonium species, such as $[Ph_2I]BF_4$) to form a Pd(IV) species. Finally, reductive elimination from the Pd(IV) species generates the new aryl–aryl bond and releases the Pd(II) catalyst to continue the catalytic cycle. For reactions involving a Pd(0)/Pd(II) mechanism, however, the initial step is oxidative addition of the aryl (pseudo)halide to the Pd(0) catalyst to form a Pd(II) species. This arylpalladium species then cleaves a C–H bond and forms an aryl-Pd(II)-aryl complex. Finally, reductive elimination generates the arylated product and regenerates the Pd(0) catalyst (Figure 13).[15]

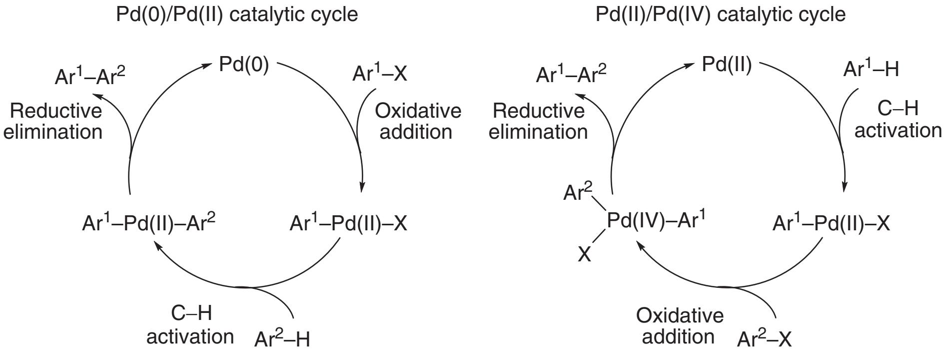


Figure 13 Two general mechanisms in Pd-catalyzed arylation of C–H bonds with (pseudo)halides.

3.23.3.1.1 Pd-catalyzed nondirected reactions of (hetero)arenes with (pseudo)halides

As discussed in Section 3.23.1, regioselectivity is one of the major issues in nondirected C–H functionalization of (hetero)arenes. The presence of multiple sites for C–H functionalization can lead to a mixture of isomeric products. However, unlike intermolecular direct arylation of carbocyclic arene systems, the inherent electronic bias of the heterocycle itself is often sufficient to control the regioselectivity of direct arylation reactions.[174] The body of literature on Pd-catalyzed C–H functionalization reactions of heteroarenes reveals a general tendency for preferential reactivity at the position α- to the heteroatom, as represented in Figure 14.[13,174] However, the nature of the catalyst, base, solvent, and additives can influence the regioselectivity to a great extent.

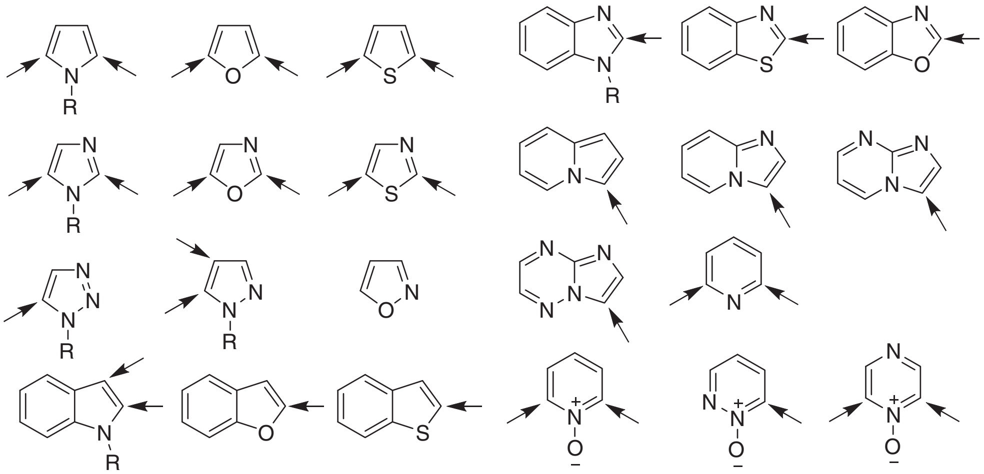
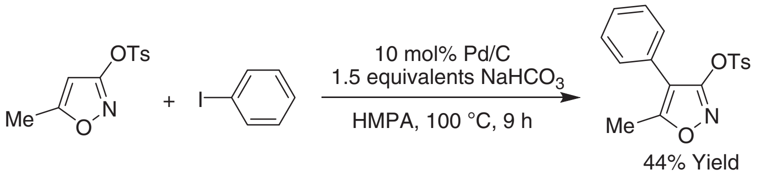


Figure 14 The preferred reaction sites for the C–H functionalization of heteroarenes.

Tuning of the reaction conditions has been used to alter the regioselectivity to achieve the desired product. Furthermore, C–H functionalization at other positions can be achieved if the favorable α-position is blocked.

3.23.3.1.1.1 Pd-catalyzed nondirected reactions of (hetero)arenes with (pseudo)halides via Pd(0)/Pd(II) catalytic cycle

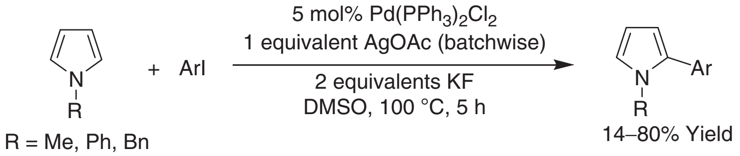
One of the first examples for Pd-catalyzed reactions of C–H bonds with aryl halides was the arylation of isoxazoles (**Scheme 116**).[175] Therefore, the 3,5-disubstituted isoxazoles were phenylated with iodobenzene at the 4-position using Pd/C as the catalyst.



Scheme 116 Pd-catalyzed arylation of isoxazole with aryl iodide (Nakamura et al., 1982).

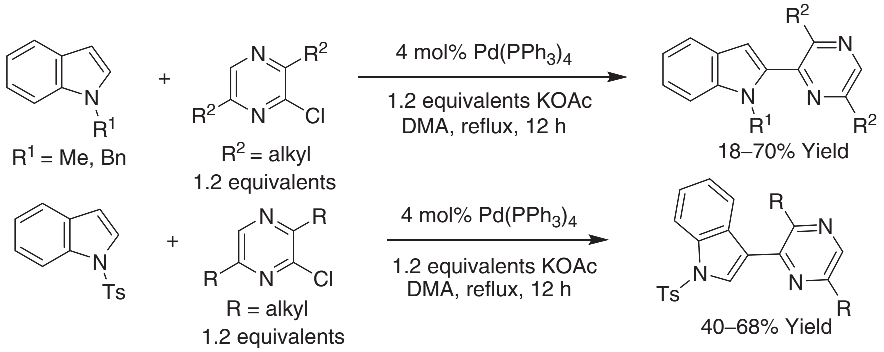
Currently, a variety of heteroarenes have been found to undergo Pd-catalyzed arylation with aryl halides, including aryl chloride, -bromides and -iodides.[176,177] A large number of reactions have been disclosed, making it impossible to cover all of them. This section presents representative reactions for each type of heteroarene.

An elegant example of arylation of pyrroles with aryl iodide was reported by Gryko and coworkers (**Scheme 117**).[178] By using $Pd(PPh_3)_2Cl_2$ as the catalyst, *N*-protected pyrroles were arylated with a wide range of aryl iodides in the presence of AgOAc and KF. The arylation occurred at the C-2 position selectively.



Scheme 117 Pd-catalyzed C2-arylation of pyrroles with aryl iodides (Gryko et al., 2009).

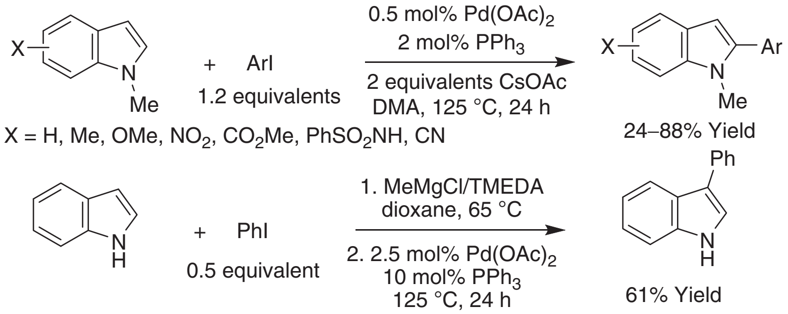
The arylation of indole was reported as early as 1989 by Ohta and coworkers (**Scheme 118**).[179] 1-Substituted indoles underwent coupling reaction with 2-chloro-3,6-dialkylpyrazines using $Pd(PPh_3)_3$ and KOAc. Interestingly, while 1-tosylindole formed 3-arylated indoles as the major products, the reactions occurred at the 2-position for 1-methyl or 1-benzylindole.



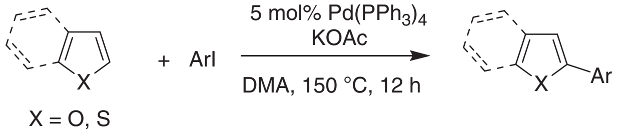
Scheme 118 Pd-catalyzed regioselective arylation of indoles with chloropyrazines (Ohta et al., 1989).

Regioselective arylation of indoles was described by Sames and coworkers. The authors first discovered the C2-arylation reactions of *N*-substituted indoles with a wide range of aryl iodides.[180] The mechanistic studies suggested that the reactions involved an electrophilic palladation of indole, accompanied by a 1,2-migration of an intermediate palladium species. Based on the mechanism, the authors designed new catalytic conditions for the C3-arylation of indole. Therefore, in case of free (NH)-indole, regioselectivity of the arylation reaction (C-2 vs. C-3) was achieved by the choice of magnesium base (**Scheme 119**).[181]

In 1990, Aoyagi described C2-arylation of furans and thiophenes (**Scheme 120**).[182] In the presence of $Pd(PPh_3)_4$ and KOAc, the arylation was enabled by treating with aryl iodides. Benzofuran and benzothiophene were also reactive under the chemical

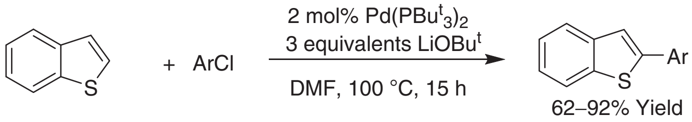


Scheme 119 Pd-catalyzed regioselective arylation of indoles with aryl iodides (Sames et al., 2005).



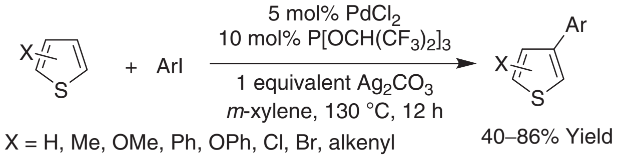
Scheme 120 Pd-catalyzed C2-arylation of furans and thiophenes with aryl iodides (Aoyagi et al., 1990).

conditions. Remarkably, aryl chlorides were also found to react with benzothiophene to yield 2-arylated products (Scheme 121).[183]



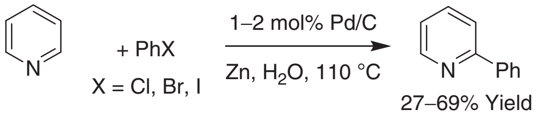
Scheme 121 Pd-catalyzed C2-arylation of benzothiophene with aryl chlorides (Mori et al., 2010).

Notably, C3-arylation of thiophenes was achieved by Itami and coworkers (Scheme 122).[184] The arylation occurred at the 3-position with >99% selectivity by using $PdCl_2/P(OCH(CF_3)_2)_3/Ag_2CO_3$ catalytic system. The electron-withdrawing ligand $P(OCH(CF_3)_2)_3$ was a necessity to achieve the high 3-selectivity. A wide range of functional groups on the benzene rings of aryl iodides were tolerated in the reactions.



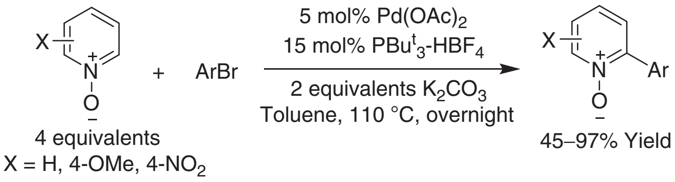
Scheme 122 Pd-catalyzed C3-arylation of thiophenes with aryl iodides (Itami et al., 2010).

Pyridine was found to undergo 2-phenylation on a heterogenous palladium catalyst on carbon in the presence of zinc and water (Scheme 123).[185] Besides phenyl bromide and iodide, phenyl chloride was also reactive.



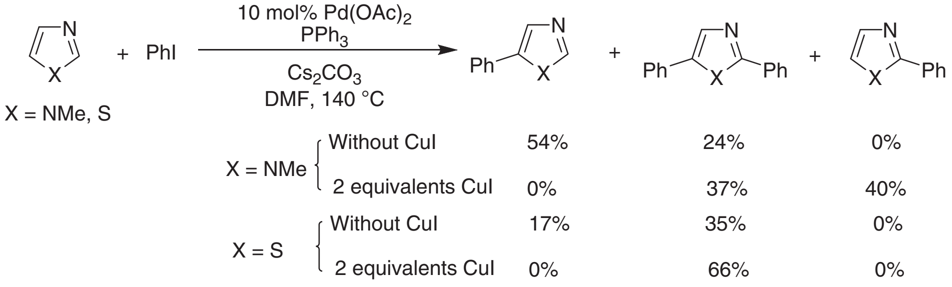
Scheme 123 Pd-catalyzed C2-phenylation of pyridine with phenyl halides (Sasson et al., 2000).

Fagnou and coworkers reported C2-arylation of pyridine *N*-oxides (Scheme 124).[186] The reactions occurred in high yields with a wide range of aryl bromides in the presence of $Pd(OAc)_2/(Bu^t)_3P\text{-}HBF_4$ and K_2CO_3.



Scheme 124 Pd-catalyzed C2-arylation of pyridine *N*-oxides with aryl bromides (Fagnou et al., 2005).

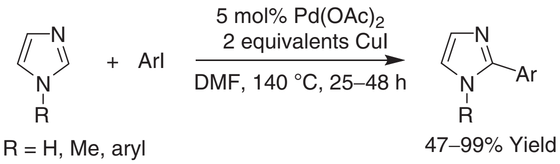
Miura and coworkers conducted extensive studies toward the palladium-catalyzed arylation of a variety of azoles.[187] The representative examples are the reactions of *N*-methylimidazole and thiozole with iodobenzene (**Scheme 125**). Interestingly, the arylation could be controlled depending on the catalyst used. In the absence of CuI, the arylations occurred preferentially at the C-5 position, followed by C2-arylation. On the contrary, in the presence of CuI, 2- and 2,5-diarylated imidazoles were the only products for *N*-methylimidazole, and only 2,5-diarylated thiozole was observed for thiazole. Notably, in the absence of palladium catalyst, CuI-catalyzed arylation occurred to give the C-2 products, albeit in low yields.



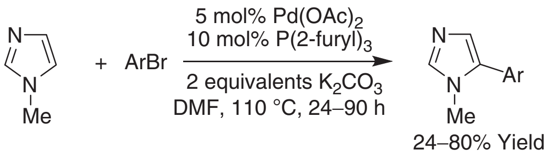
		Ph (C5)	Ph, Ph (C2,C5)	Ph (C2)
X = NMe	Without CuI	54%	24%	0%
	2 equivalents CuI	0%	37%	40%
X = S	Without CuI	17%	35%	0%
	2 equivalents CuI	0%	66%	0%

Scheme 125 Pd-catalyzed phenylation of azoles with iodobenzene (Miura et al., 1998).

Selective C-2 arylation of imidazoles was reported by Bellina and Rossi (**Scheme 126**).[188] A variety of azoles, including *N*-methylimidazole, *N*-arylimidazoles, free (NH)-imidazole, thiazole, and oxazole, underwent arylation with aryl iodides in the presence of $Pd(OAc)_2$ and CuI. Subsequently, the same authors disclosed C5-arylation of imidazoles (**Scheme 127**).[189] Therefore, 1-methyl-1*H*-imidazoles was arylated with a wide variety of aryl bromides using $Pd(OAc)_2/P(2\text{-furyl})_3$ catalyst system.

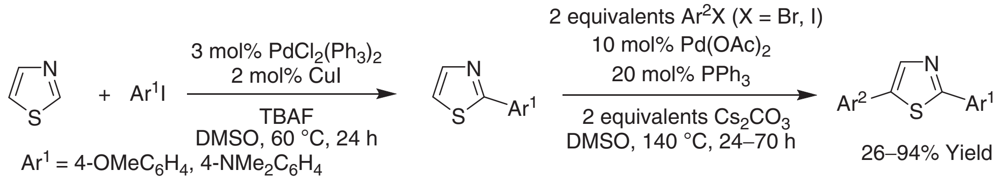


Scheme 126 Pd-catalyzed C2-arylation of imidazoles with aryl iodides (Bellina and Rossi et al., 2006).

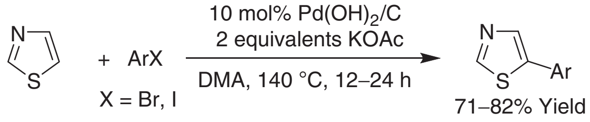


Scheme 127 Pd-catalyzed C5-arylation of imidazoles with aryl bromides (Bellina and Rossi et al., 2008).

Both C2 and C5-arylation of thiazoles have also been proved viable. Mori reported Pd/Cu-catalyzed C2-arylation of thiazole with a wide range of aryl iodides (**Scheme 128**).[190] In this reaction, tetra-*n*-butylammonium fluoride (TBAF) serves a novel and excellent activator. It is noted that the formed 2-arylated thiazoles may undergo a second Pd-catalyzed arylation at C-5 position with aryl iodide, which provided an efficient method to synthesize 2,5-diarylated thiazole. Subsequently, Fagnou and coworkers disclosed selective C5-arylation of simple thiazole by using Pearlman's catalyst (palladium hydroxide on carbon) (**Scheme 129**).[191] The catalyst system also proved applicable to the intramolecular arylation of a variety of arenes tethered with aryl iodide/bromides. Furthermore, regioselective arylation of imidazo[1,2-*a*] pyrimidines and furan was also enabled under the



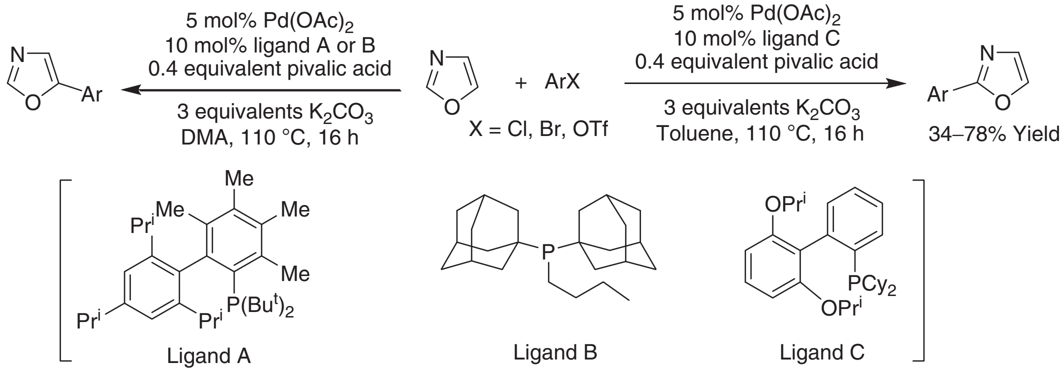
Scheme 128 Pd-catalyzed regioselective arylation of thiazole with aryl iodide (Mori et al., 2003).



Scheme 129 Pd-catalyzed C5-arylation of thiazole with aryl bromides/iodides (Fagnou et al., 2005).

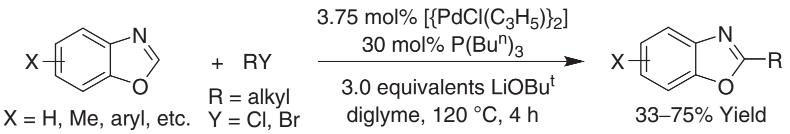
same reaction conditions. The reactions occurred at 3-position for imidazo[1,2-a]pyrimidines and at 2-position for furan, respectively.

Regioselective C2- or C5-arylation of oxazole can be controlled by employing different ligand (Scheme 130).[192] Therefore, in the presence of ligand C and nonpolar solvent such as toluene, oxazole was arylated predominantly at the C-2 position, whereas C5-arylation is preferred in polar solvent as *N,N*-dimethylacetamide (DMA) with ligand A or B, which represents the first general method for C5-arylation of oxazole. Remarkably, the methods were applicable to diverse (pseudo)halides, including chlorides, bromides, and tosylates. Based on the mechanistic studies, the author proposed that C5-arylation took place through concerted-metalation-deprotonation (CMD) pathways, whereas deprotonation mechanisms accounted for C2-arylation.



Scheme 130 Pd-catalyzed C2/C5-arylation of oxazole with aryl halides/triflates (Strotman and Chobanian et al., 2010).

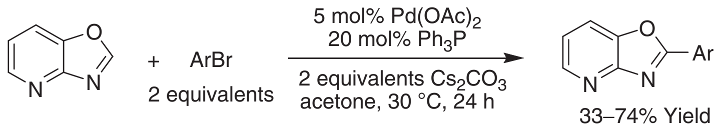
Compared to aryl (pseudo)halides, alkyl (pseudo)halides are much less explored in the transition-metal-catalyzed organic reactions. Recently, Hirano and Miura reported the direct alkylation of benzoxazoles with alkyl halides (Scheme 131).[193] Thus, in the presence of strong base LiO-Bu^t, benzoxazoles underwent C2-alkylation using catalyst [{PdCl(C_3H_5)}$_2$] and ligand P(Bu^n)$_3$. Both alkyl chlorides and bromides were compatible in the reactions.



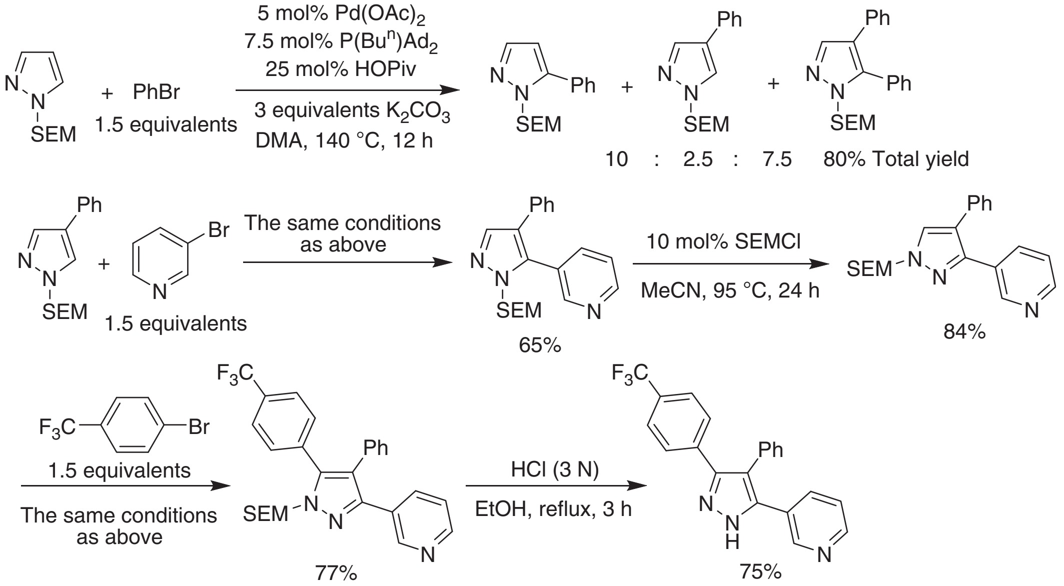
Scheme 131 Pd-catalyzed C2-alkylation of benzoxazole with alkyl halides (Hirano and Miura et al., 2010).

The Pd(OAc)$_2$/Ph$_3$P-catalyzed direct arylation of oxazole[1,2-b] pyridine occurred regioselectively at the C-2 position of the oxazole (Scheme 132).[194]

Sames and coworkers undertook systematic studies in an effort to achieve the C–H arylation of pyrazoles. They identified a palladium-pivalate catalytic system as the most effective protocol and mapped the reactivity of all three C–H bonds of the 2-trimethylsilylethoxymethoxy (SEM)-protected pyrazole (C-5 > C-4 ≫ C-3) (Scheme 133).[195] Interestingly, to circumvent the low reactivity of the C-3 position, the authors developed a smart method to transpose the SEM-protecting group from one nitrogen to the other in one step, which transformed the unreactive C-3 position to the reactive C-5 position. Therefore, the C-4 arylated



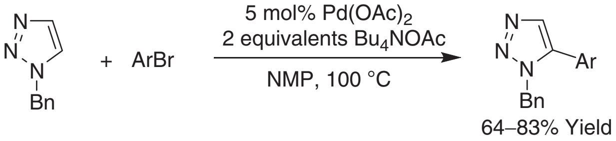
Scheme 132 Pd-catalyzed C2-arylation of oxazole [1,2-b] pyridine with aryl bromides (Zhuravlev, 2006).



Scheme 133 Pd-catalyzed arylation of pyrazole with aryl bromides (Sames et al., 2009).

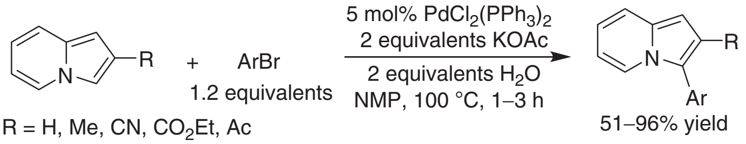
substrates were arylated at C-5 position regioselectively in the first step. Subsequently, the SEM-protecting group was transposed to the other nitrogen atom. As a result, the initial unreactive C-3 was switched to reactive C-5, which could be readily arylated under the same conditions. This protocol enabled sequential arylation of C-5 and C-3 position of pyrazole, providing rapid access to protected or free 3,4,5-triarylpyrazoles (the C-4 arene ring was readily introduced by bromination and Suzuki coupling).

In the Pd(OAc)$_2$-catalyzed arylation of Bn-protected 1,2,3-triazole reported by Gevorgyan, the reactions occurred at the C-5 position regioselectively (Scheme 134).[196] However, C-4 arylation may take place under similar conditions when the C-5 positions were blocked with substituents, albeit in moderate yields.



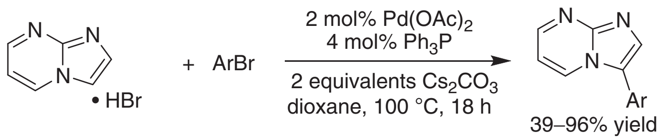
Scheme 134 Pd-catalyzed C5-arylation of 1,2,3-triazole with aryl bromides (Gevorgyan et al., 2007).

Gevorgyan and coworkers also developed a highly effective method for selective arylation and heteroarylation of indolizines at the C-3 position (Scheme 135).[197] A variety of aryl and heteroaryl bromides were compatible in the reactions. Mechanistic studies unambiguously supported an electrophilic substitution pathway for this transformation.



Scheme 135 Pd-catalyzed C3-arylation of indolizines with aryl bromides (Gevorgyan et al., 2004).

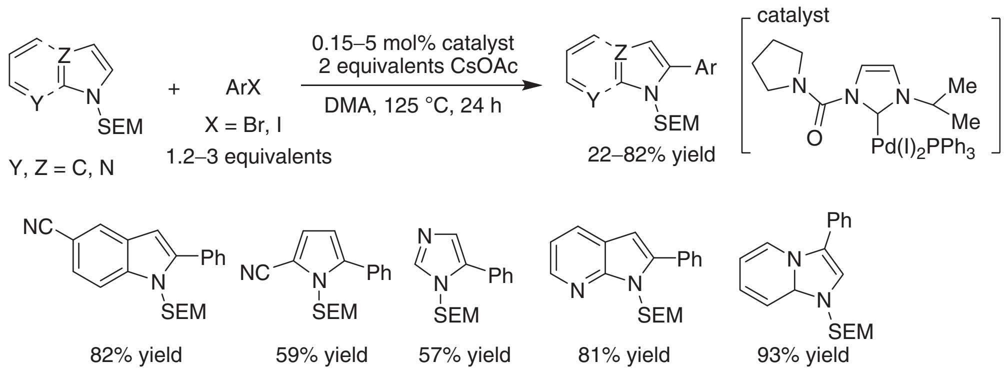
The direct arylation of imidazo[1,2-*a*]pyrimidine was also investigated by Li and coworkers (Scheme 136).[198] The authors found that imidazo[1,2-*a*]pyrimidine can be arylated at the 3-position with aryl bromides in the presence of Cs_2CO_3 and



Scheme 136 Pd-catalyzed C3-arylation of imidazo[1,2-*a*]pyrimidine with aryl bromides (Li et al., 2003).

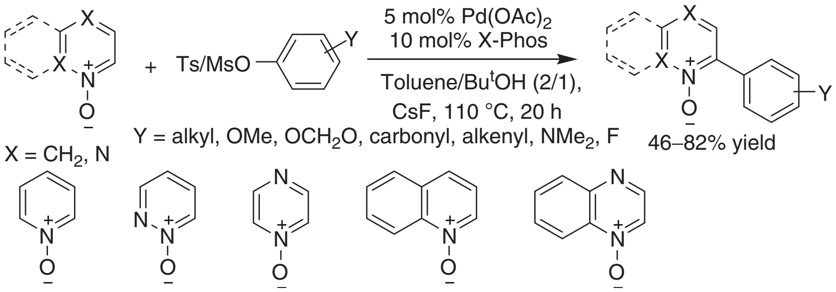
Pd(OAc)$_2$/Ph$_3$P. A variety of substituents on the aryl bromides were tolerated under the reaction conditions. The proposed mechanism involved an electrophilic metalation in the C–H activation step, consistent with the observed outcome that the arylation took place at the electron-rich imidazole ring instead of the electron-deficient pyrimidine ring.

Sames and coworkers described a general protocol for the arylation of azoles palladium complexes containing imidazolyl carbene ligand (Scheme 137).[199] Therefore, a wide range of SEM-protected azoles were arylated with aryl iodides or bromides using the palladium complex (shown in scheme) as the catalyst. The reactive azoles included pyrroles, indoles, imidazoles, and imidazo[1,2-a]pyridines. In most cases, the arylation occurred at the position α to SEM-protected nitrogen. However, a mixture of isomers or diarylated products was also observed for some substrates.



Scheme 137 Pd-catalyzed arylation of heteroarenes with aryl halides (Sames et al., 2006).

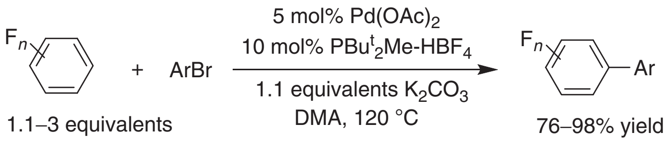
Another general catalytic system was developed for the arylation of heterorenes *N*-oxide by Ackermann and coworkers (Scheme 138).[200] In the presence of catalyst Pd(OAc)$_2$/X-Phos and base CsF, pyridine *N*-oxide and its analogs underwent α-arylation with aryl tosylates or mesylates. Alkenyl tosylates and electron-deficient fluorinated arenes were also reactive under the reaction conditions.



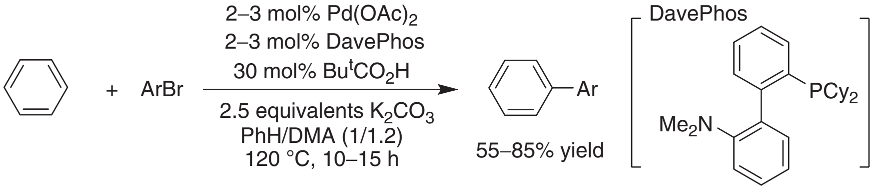
Scheme 138 Pd-catalyzed arylation of heteroarenes with aryl tosylates/mesylates (Ackermann et al., 2011).

The Pd-catalyzed direct arylation of arenes lacking directing groups was discovered much later than that of heteroarenes. In 2006, Fagnou and coworkers reported the first nondirected catalytic benzene arylation (Scheme 139).[201] Thus, electron-deficient polyfluorobenzenes underwent arylation reaction with a wide range of aryl bromide in the presence of catalyst Pd(OAc)$_2$/PBu$^t_2$Me–HBF$_4$ and K$_2$CO$_3$. Aryl chlorides and iodides can also be used. In the reactions, the more electron-deficient arenes showed higher reactivities, and the arylation occurred preferentially at the most acidic conditions for the substrates with two distinct C–H bonds.

Subsequently, Fagnou and coworkers also achieved the arylation of simple arenes (Scheme 140).[202] Notably, pivalate anion played a key role in this C–H bond cleavage. It acted as a catalytic proton shuttle from benzene to the stoichiometric carbonate base and lowered the energy of C–H bond cleavage. By using palladium-pivalic acid cocatalyst combination, benzene was arylated



Scheme 139 Pd-catalyzed arylation of perfluorobenzenes with aryl bromides (Fagnou et al., 2006).

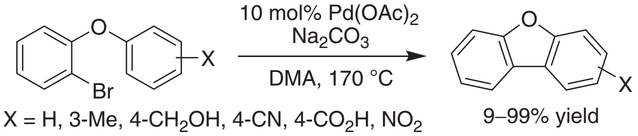


Scheme 140 Pd-catalyzed arylation of benzene with aryl bromides (Fagnou et al., 2006).

with aryl bromides in the presence of DavePhos and K_2CO_3. A variety of substituents of aryl bromides were compatible in the reaction, and the monosubstituted benzenes, including anisole and fluorobenzene, gave a mixture of *o*/*p*/*m* regioisomers.

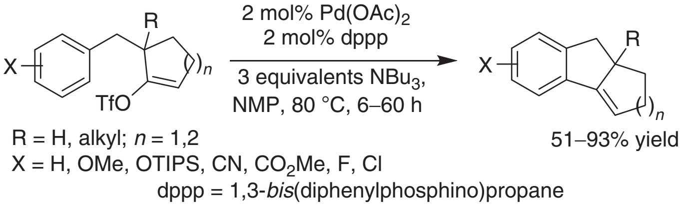
Pd-catalyzed intramolecular reactions of arenes with halides have also been developed. The reactions are remarkable, because they provide efficient methods to synthesize complex polycycles. In these reactions, the substrates contain an arene tethered with a halide, including aryl, alkenyl, and alkyl halides. As the intermolecular reactions, the intramolecular reactions were also initiated with the oxidative addition of the halides to Pd(0). The subsequent intramolecular Pd(II)-mediated C–H cleavage and reductive elimination formed new C–C bonds.

As early as 1983, Ames and coworkers disclosed intramolecular dehydrobromination of 2-bromophenyl phenyl ethers by using a catalytic amount of $Pd(OAc)_2$, which provided a convenient, general process for the synthesis of substituted dibenzofurans (Scheme 141).[203] The reactions tolerated electron-withdrawing and electron-releasing group.



Scheme 141 Pd-catalyzed intramolecular arylation of arenes (Ames et al., 1983).

The intramolecular alkenylation of arenes was described by Willis and coworkers (Scheme 142).[204] Therefore, a catalyst generated from $Pd(OAc)_2$ and dppp was found to effectively catalyze the direct intramolecular arylation of alkenyl triflates, yielding conjugated alkene-arene-containing carbocycles in good yield.

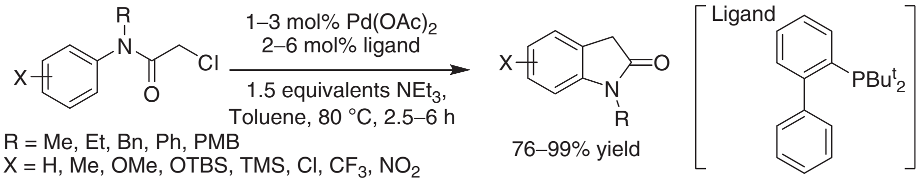


Scheme 142 Pd-catalyzed intramolecular alkenylation of arenes (Willis et al., 2007).

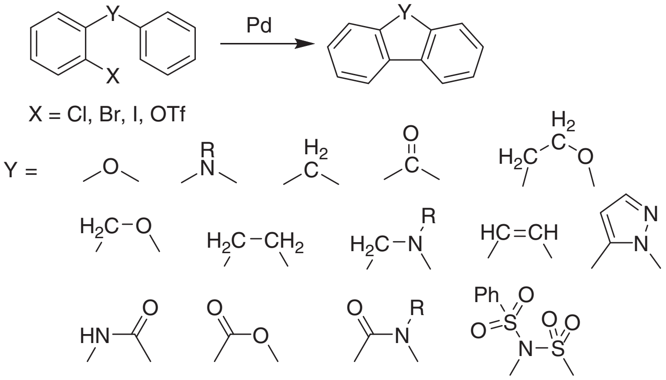
Buchwald and coworkers developed intramolecular alkylation of arenes with alkyl chlorides (Scheme 143).[205] In the presence of a bulky phosphine ligand, the reactions proceeded under quite mild conditions to form substituted oxindoles. A wide range of functional groups were tolerated under the reaction conditions.

Notably, a diverse variety of tethers have proved applicable to the intramolecular aryl–aryl bond formation by Pd-catalyzed direct arylation, and various (pseudo)halides, including Cl, Br, I, and OTf, were used to initiate the C–H activation (Scheme 144).[13]

Moreover, the intramolecular direct arylation of heteroaryl C–H bonds have been extensively investigated, and a great number of reactions have been reported. A wide range of heteroarenes may undergo C–H activation and subsequent arylation by reacting with carbopalladium, which are generated by the oxidative addition of aryl halides to Pd(0). The reactions formed aryl–heteroaryl bonds.[174]



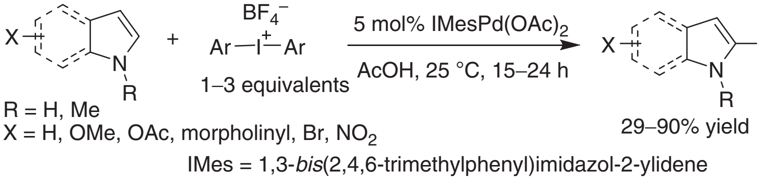
Scheme 143 Pd-catalyzed intramolecular alkylation of arenes (Buchwald et al., 2003).



Scheme 144 Pd-catalyzed intramolecular C–H arylation.

3.23.3.1.1.2 Pd-catalyzed nondirected reactions of (hetero)arenes with (pseudo)halides via Pd(II)/Pd(IV) catalytic cycle

Although all of the above Pd-catalyzed direct arylation reactions involve Pd(0)/Pd(II) mechanisms, the Pd(II)/Pd(IV) catalytic process has also been utilized to enable arylation of heteroarenes. In 2006, Sanford and coworkers reported such an arylation of indoles and pyrroles, using [Ph-I-Ph]BF_4 as the arylation reagent (Scheme 145).[206] The reactions proceeded under remarkably mild conditions (often at room temperature), and occurred at C-2 position regioselectively. However, appreciable amounts of phenylation at the C-3 position were also observed when C-2 was blocked. A diverse variety of substituents of indoles were well tolerated.



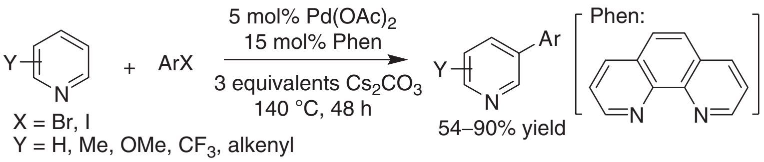
Scheme 145 Pd-catalyzed C2-arylation of indoles with [Ph-I-Ph]BF_4 (Sanford et al., 2006).

As discussed in Section 3.23.2.1.1.1, the direct C–H functionalization of pyridine has been a challenge. Among the rare reported examples, the reactions usually occurred at C-2 position. Recently, Yu and coworkers described the first example of Pd-catalyzed, C3-arylation of unprotected pyridines (Scheme 146).[207] Therefore, by employing a catalytic system consisting of $Pd(OAc)_2$ and 1,10-phenanthroline, pyridine and its derivatives were 3-arylated with a wide range of aryl bromides or iodides. The Pd(II)/(IV) mechanism was also proposed to be responsible for the novel procedure.

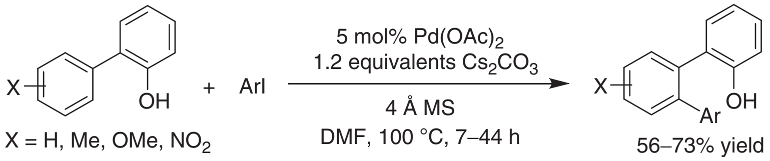
3.23.3.1.2 Pd-catalyzed-directed reactions of (hetero)arenes with (pseudo)halides

3.23.3.1.2.1 Pd-catalyzed-directed reactions of (hetero)arenes with (pseudo)halides via Pd(0)/Pd(II) catalytic cycle

A diversity of directing groups has been utilized to assist the direct arylation of arenes with aryl halides, forming *ortho*-arylated products regioselectively. In 1997, Miura and coworkers reported the hydroxyl-assisted arylation of 2-phenylphenols (Scheme 147).[208] Thus, 2-phenylphenols were *ortho*-arylated with aryl iodides in the presence of $Pd(OAc)_2$ with Cs_2CO_3 as base. Cs_2CO_3 was crucial to the success of the reaction because of its relatively high solubility in dimethylformamide (DMF), facilitating the deprotonation and the subsequent transmetalation. Furthermore, the mono- or diarylated product could be selectively obtained by controlling the amount of aryl iodide and Cs_2CO_3.

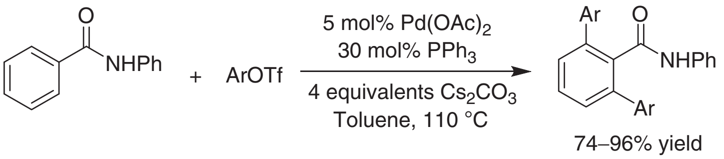


Scheme 146 Pd-catalyzed C3-arylation of pyridines with aryl bromides/iodides (Yu et al., 2011).



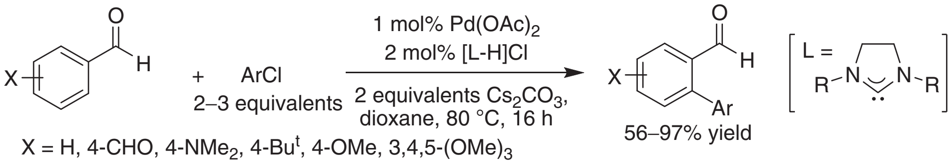
Scheme 147 Pd-catalyzed hydroxyl-directed arylation with aryl iodides (Miura et al., 1997).

The amide group was also found to be an efficient directing group in the C–H arylation reactions (**Scheme 148**).[209] Therefore, benzanilides underwent diarylation with aryl triflates using catalyst $Pd(OAc)_2/PPh_3$ and base Cs_2CO_3. Notably, the arylation occurred on the benzoyl moiety selectively, and neither the *N*-arylated product nor the arylated anilide was observed.



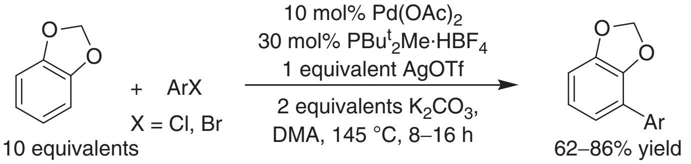
Scheme 148 Pd-catalyzed amide-directed arylation with aryl triflates (Miura et al., 2000).

The arylation of benzaldehydes was also reported (**Scheme 149**).[210] By using $Pd(OAc)_2$ and a bulky electron-rich *N*-heterocyclic carbene ligand, a variety of benzaldehydes were allowed to react with a wide range of aryl chlorides, forming the arylated products in good to excellent yields. The diarylated products were produced when aryl bromides were used.



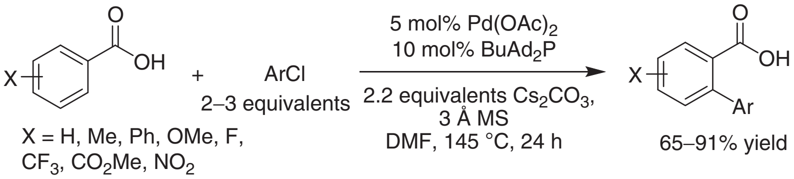
Scheme 149 Pd-catalyzed aldehyde-directed arylation with aryl chlorides (Çetinkaya et al., 2005).

Ethers have been seldom used as the directing group in the transition-metal-catalyzed C–H functionalization reactions because of their weak coordination with metals. Remarkably, Fagnou and coworkers achieved the first ether-directed arylation in 2006 (**Scheme 150**).[211] 1,3-benzodixole was arylated with a range of aryl bromides and chlorides in the presence of $Pd(OAc)_2$, $PBu^t_2Me \cdot HBF_4$, AgOTf, and K_2CO_3.



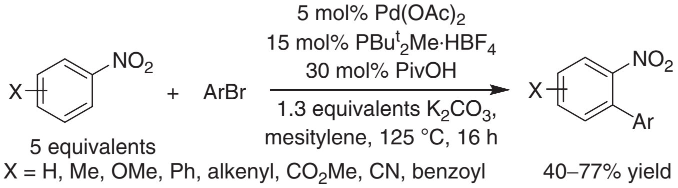
Scheme 150 Pd-catalyzed arylation of 1, 3-benzodioxles with aryl chlorides/bromides (Fagnou et al., 2006).

Daugulis and coworkers described the direct arylation of benzoic acids with aryl chlorides by using ligand $BuAd_2P$ (Scheme 151).[212] The reaction required the presence of molecular sieves. Benzoic acids of any properties were reactive. Isotope effect studies pointed to heterolytic C–H bond cleavage as the turnover-limiting step.



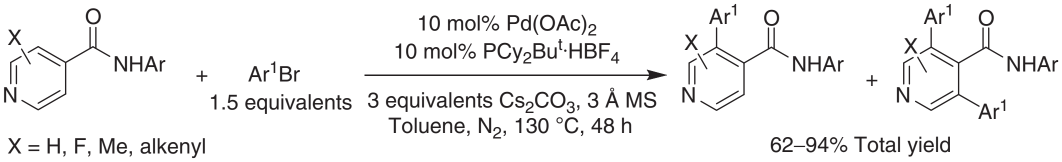
Scheme 151 Pd-catalyzed carboxyl-directed arylation with aryl chlorides (Daugulis et al., 2007).

The C–H arylation of electron-deficient arenes have been less extensively investigated, because they are less reactive. As such, the arylation with a electron-withdrawing directing group, such as nitro, should be more challenging. However, the reactions would benefit from electron-deficiency if they occurred through a concerted metalation-deprotonation (CMD) pathway. The arylation of electron-poor arenes have been reported, and the CMD mechanisms were proposed to be operative in these reactions. Inspired by the successes, Fagnou and coworkers reported the arylation of nitrobenzenes with a variety of aryl bromides (Scheme 152).[213] The reactions could be performed on gram scale. The competition experiments revealed that the arylation of nitrobenzene was highly favored over those of electron-richer arenes, including methylbenzoate and anisole.



Scheme 152 Pd-catalyzed nitro-directed arylation with aryl bromides (Fagnou et al., 2008).

It is not surprising that the C–H arylation of pyridines is a challenge. Recently, Yu and coworkers reported a $Pd(0)/PR_3$-catalyzed arylation procedure for *N*-phenylnicotinamides and *N*-phenylisonicotinamides with the acidic amides as directing groups (Scheme 153). This reaction constituted the first example of directed transition-metal-catalyzed C–H functionalization of a pyridine ring at the 3- or 4-positions. The reactions of *N*-phenylisonicotinamides formed a mixture of mono- and diarylated products when the two *meta*-C–H bonds were available. However, the use of 3,5-dimethylphenyl as the protecting group significantly improved the monoselectivity. For the substrate *N*-phenylisonicotinamides, *para*-arylation occurred preferentially.[214]

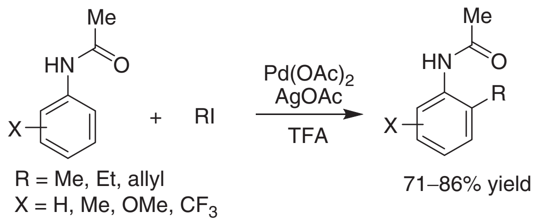


Scheme 153 Pd-catalyzed amide-directed arylation of nicotinic and isonicotinic acid derivatives with aryl bromides (Yu et al., 2010).

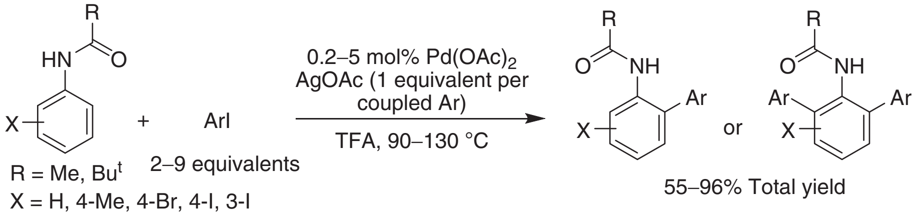
3.23.3.1.2.2 Pd-catalyzed-directed reactions of (hetero)arenes with (pseudo)halides via Pd(II)/Pd(IV) catalytic cycle

All of the above directed C–H arylation reactions were proposed to proceed through a Pd(0)/Pd(II) mechanism. Pd(II)/Pd(IV) catalysis have also been extensively exploited for the Pd-catalyzed reactions of C–H bonds with aryl halides with the assistance of directing groups. The pioneering work is the C–H methylation of anilides with MeI reported by Tremont and coworkers in 1984 (Scheme 154).[215] The use of AgOAc and TFA was required to make the reactions catalytic. The alkylation of the cyclopalladated intermediates was proposed to involve either an electrophilic attack of MeI on the Pd–carbon bond or a Pd(IV) intermediate. Ethyl and allyl iodide were also reactive to give the corresponding ethylated and allylated products.

Twenty years later, Daugulis and coworkers reported the arylation of anilides under similar conditions (Scheme 155).[216] Although the monoarylated products were formed for the *meta*- or *ortho*-substituted anilides, the reactions yielded diarylated anilides in the absence of *meta*- or *ortho*-substituents. The reactions were highly tolerant to functional groups including bromide and iodide. It is noted that up to 1000 turnovers were demonstrated for this method.

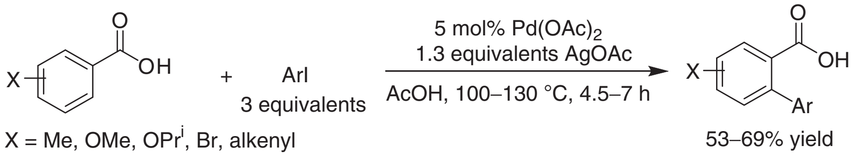


Scheme 154 Pd-catalyzed amide-directed alkylation with alkyl iodides (Tremont et al., 1984).



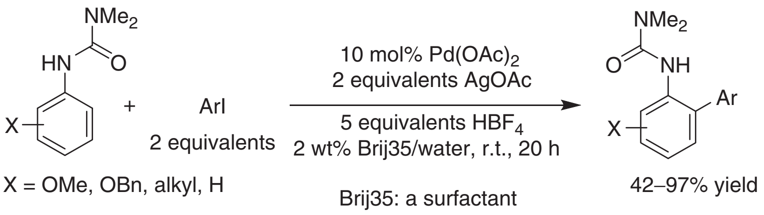
Scheme 155 Pd-catalyzed amide-directed arylation with aryl iodides (Daugulis et al., 2005).

The similar protocol was also successfully extended to the arylation of benzoic acids (Scheme 156).[212] A range of benzoic acids were *ortho*-arylated in the presence of $Pd(OAc)_2$ and AgOAc. Acetic acid was used as the solvent instead of TFA. Mechanistic studies supported that a Pd(II)/Pd(IV) mechanism was operative.



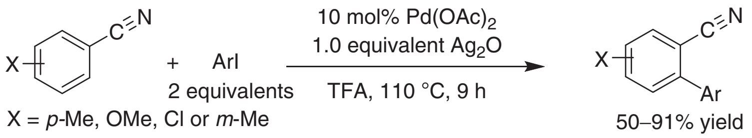
Scheme 156 Pd-catalyzed carboxyl-directed arylation with aryl iodides (Daugulis et al., 2007).

Remarkably, Lipshutz described the room temperature arylation of anilides with aryl iodides, using urea as the directing group (Scheme 157).[217] A range of aryl ureas were arylated with various aryl iodides. The reactions were conducted in water, and the use of HBF_4 and the surfactants was crucial for the novel reactivity. The surfactant Brij proved to give the best yield.



Scheme 157 Pd-catalyzed urea-directed arylation with aryl iodides (Lipshutz et al., 2010).

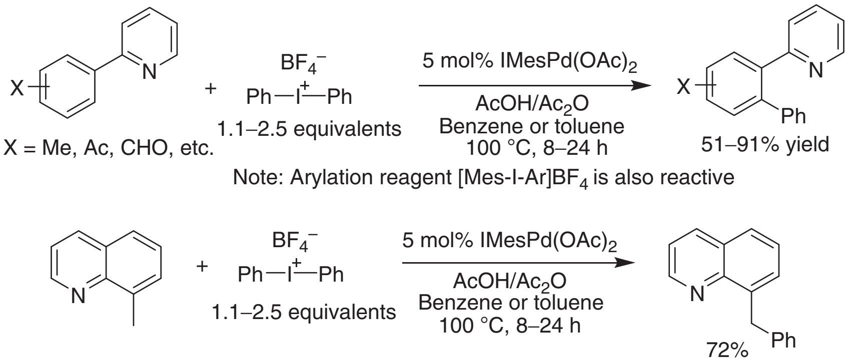
Interestingly, the cyano group also proved to be an effective directing group in the arylation of aryl nitriles (Scheme 158).[218] Ag_2O was found to give good yields, whereas a trace amount of products were formed in the presence of AgOAc, which was used in the other similar arylation reactions with aryl iodides.



Scheme 158 Pd-catalyzed cyano-directed arylation with aryl iodides (Sun et al., 2011).

The purine[219] and *N*-methoxyamide groups[220] were also successfully employed to assist the C–H arylation of the corresponding arenes with aryl iodides. The reactions were conducted under the conditions similar to those for the other arylation reactions.

Although aryl iodides were the most common arylation reagents in the Pd-catalyzed arylation of C–H bonds, Sanford and Daugulis independently developed a general approach using iodine(III) reagent $[Ph_2I]BF_4$ and $[Ph_2I]PF_6$ for C–H arylation (Scheme 159).[221] In Sanford's reactions, 2-phenylpyridines were arylated by using catalyst IMesPd$(OAc)_2$ in the presence of AcOH and Ac_2O. In addition to pyridine, diverse heterocycles, including quinolines, pyrrolidinones, and oxazolidinones, were effective directing groups, and a wide variety of functionalities were well tolerated. Intriguingly, the benzylic C–H bonds were also arylated under the reaction conditions. Preliminary mechanistic experiments provided evidence in support of a Pd(II)/(IV) catalytic cycle for this reaction. In Daugulis' method, *N*-*p*-tolylpivalamide underwent arylation reaction with $[Ph_2I]PF_6$ in the presence of catalyst $Pd(OAc)_2$ and solvent AcOH.



Scheme 159 Pd-catalyzed pyridine-directed arylation with $[Ph_2I]BF_4$ (Sanford et al., 2005).

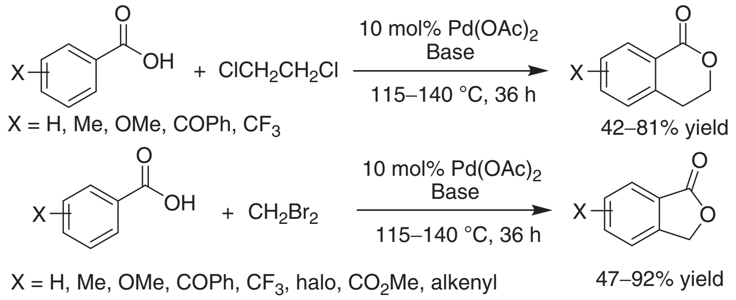
An analogous iodine(III) reagent $Ph_2I^+OTf^-$ was employed for the arylation of phenol esters by Liu and coworkers (Scheme 160).[222] The use of HOTf was required to achieve the high yields, and Ac_2O was added so that the reaction would not be sensitive to moisture. It is noted that the first cyclopalladation complex formed from a simple phenol ester was characterized by X-ray crystallography.

Scheme 160 Pd-catalyzed ester-directed arylation with $Ph_2I^+OTf^-$ (Liu et al., 2010).

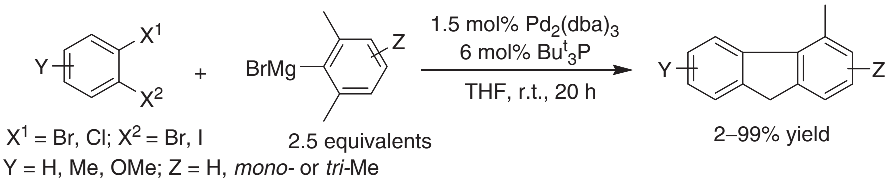
Intriguingly, Yu and coworkers reported a simple method for the alkylation of benzoic acids (Scheme 161).[223] A range of benzoic acids underwent *ortho*-C–H alkylation reaction with $ClCH_2CH_2Cl$ and CH_2Br_2 in the presence of $Pd(OAc)_2$ and bases. The subsequent cyclization afforded five- or six-membered benzolactones. Remarkably, the reactions avoided the use of expensive Ag^+ salt, which is required in the arylation reactions with aryl iodides. 2-Chloroethyl or bromomethyl benzoate did not form the corresponding benzolactones under the same conditions. This fact provided evidence that the reaction was initiated by C–H activation instead of Friedel–Crafts-type reactions. Either a Pd(II)/Pd(IV) mechanism or direct σ-bond metathesis between the aryl–Pd bond and the alkyl halide was proposed to account for the transformation.

3.23.3.1.3 Pd-catalyzed arylation of C(sp^3)-H bonds with aryl (pseudo)halides

In 2006, Hu and coworkers reported the intramolecular arylation of benzylic C–H bonds (Scheme 162).[224] In this work, the Pd(0)/Pd(II) chemistry was elegantly combined with a Kumada coupling reaction to enable the arylation of C(sp^3)-H bonds with aryl halides. Therefore, by using catalyst $Pd_2(dba)_3/Bu^t_3P$, 1,2-dihalobenzenes first reacted with 2,6-dimethylphenylmagenisium bromides to form the intermediate biaryls. The use of hindered Grignard reagents was crucial to suppress a second cross-coupling reaction. The oxidative addition of the remaining C–Cl bond to Pd(0) generated another Pd(II) species, which cleaved the benzylic C–H bonds to form a palladacycle complex. The subsequent reductive elimination yielded substituted fluorenes as the final products.

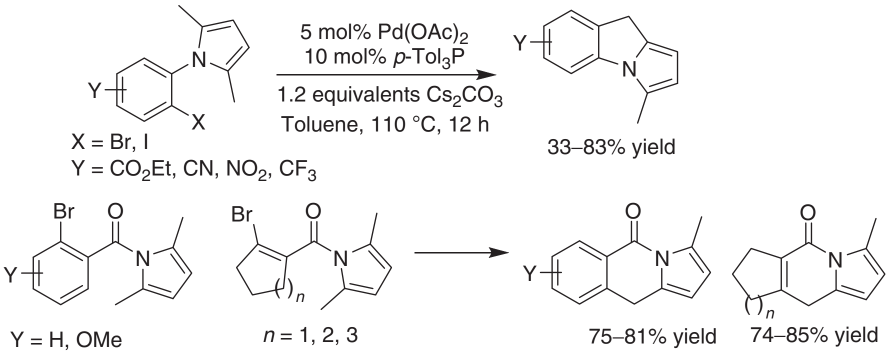


Scheme 161 Pd-catalyzed alkylation of benzoic acids with alkyl halides (Yu et al., 2009).



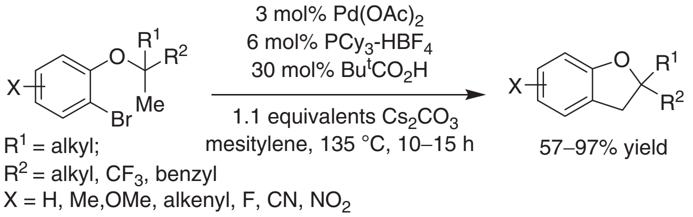
Scheme 162 Pd-catalyzed intramolecular arylation of benzylic C–H bonds (Hu et al., 2006).

Another intramolecular arylation of benzylic C–H bonds was described by Knochel and coworkers (Scheme 163).[225] The C–H bond of the methyl group at position 2 of a pyrrole ring was cleaved. This reaction provided an efficient route to construct tricyclic heterocycles. Alkenylbromides were also reactive under the reaction conditions.



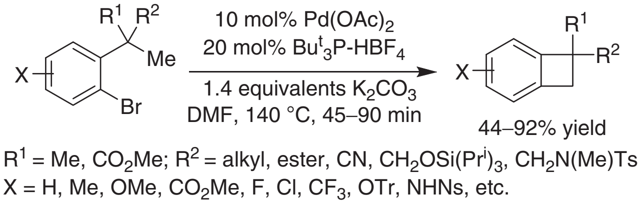
Scheme 163 Pd-catalyzed intramolecular arylation of benzylic C–H bonds (Knochel et al., 2006).

The intramolecular arylation of unactivated C(sp^3)-H bonds was also achieved by Fagnou and coworkers (Scheme 164).[226] Thus, in the presence of Pd(OAc)$_2$, PCy$_3$–HBF$_4$, Bu^{t}CO$_2$H and Cs$_2$CO$_3$, alkyl bromides and chlorides were alkylated via intramolecular C(sp^3)-H bond activation, leading to the formation of 2,2-dialkyldihydrobenzofurans. A variety of functional groups were well tolerated. However, the substrate scope was still limited to compounds without hydrogen atoms at the position α to the reactive methyl groups.

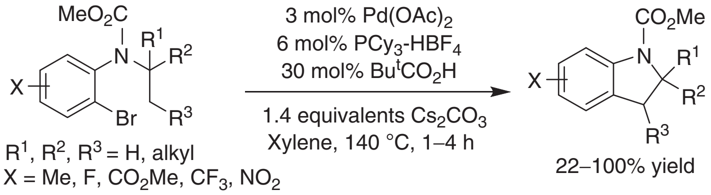


Scheme 164 Pd-catalyzed intramolecular arylation of C(sp^3)-H bonds (Fagnou et al., 2007).

Subsequently, Baudoin (Scheme 165)[227] and Ohno (Scheme 166)[228] reported the analogous intramolecular arylation under similar conditions. It is noted that a four-membered ring was formed in Baudoin's reactions.

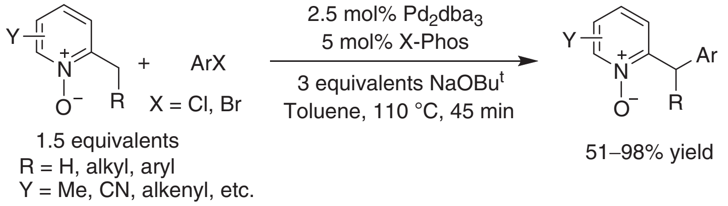


Scheme 165 Pd-catalyzed intramolecular arylation of C(sp^3)-H bonds (Baudoin et al., 2008).



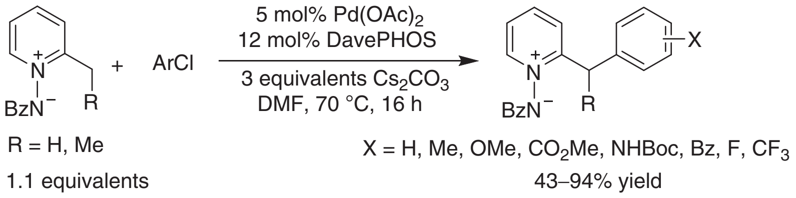
Scheme 166 Pd-catalyzed intramolecular arylation of C(sp^3)-H bonds (Ohno and Fujii et al., 2008).

Pd-catalyzed intermolecular arylation of C(sp^3)-H bonds have also been realized. In 2008, Fagnou reported benzylic C–H arylation with aryl chlorides and bromides (Scheme 167).[229] Therefore, the 2-methyl groups of pyridine *N*-oxides were arylated using catalyst Pd_2dba_3/X-Phos and base NaOBu^t. The azine and diazine *N*-oxides were also reactive under the reaction conditions. It is noted that the secondary C(sp^3)-H bonds were also compatible in the reactions, forming the corresponding arylated products, albeit in lower yields. Interestingly, the α-C(sp^2)-H bonds can be arylated site-selectively when the reactions were carried out under different conditions.



Scheme 167 Pd-catalyzed arylation of benzylic C–H bonds of pyridine *N*-oxides with aryl chlorides/bromides (Fagnou et al., 2008).

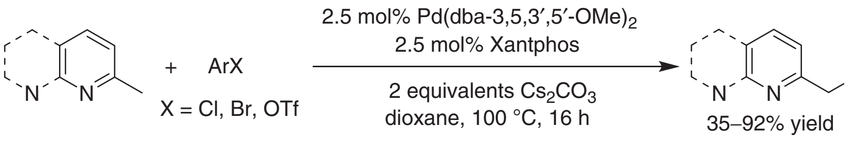
Charette and coworkers described an analogous benzylic C–H arylation of 2-alkyl substituted *N*-iminopyridinium ylides with various aryl chlorides (Scheme 168).[230] 2-ethyl pyridinium ylides were also reactive and underwent arylation at the benzylic position in good yields. Furthermore, the diarylated products may be obtained when 2.2 equivalents of chlorobenzene was added.



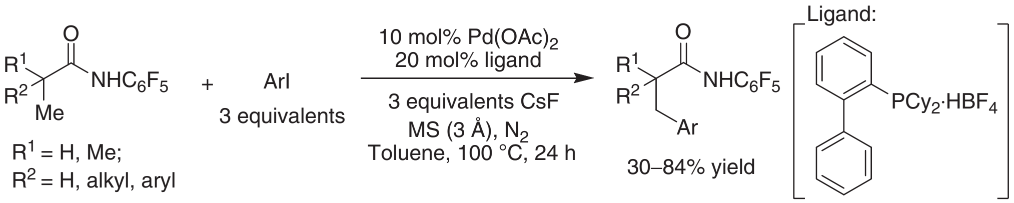
Scheme 168 Pd-catalyzed arylation of benzylic C–H bonds of 2-substituted *N*-iminopyridinium ylides with aryl chlorides (Charette et al., 2008).

The arylation of 2-methyl group of unprotected pyridines was disclosed by Morris and coworkers (Scheme 169).[231] A variety of (pseudo)halides, including iodides, bromides and triflates, were found to effectively arylate the methyl groups of pyridines and their analogs. However, chlorobenzene did not yield any desired product. A wide range of functional groups of aryl halides were well tolerated.

Remarkably, Yu and coworkers realized the intermolecular arylation of unactivated C(sp^3)-H bonds by employing a highly acidic amide group as the directing group (Scheme 170).[232] Thus, the α-methyl groups of *N*-pentafluorophenyl amides were arylated with aryl iodides in the presence of Pd(OAc)$_2$, Buchwald's cyclohexyl JohnPhos ligand, and CsF. It is noted that a wide range of substrates with one α-hydrogen were compatible in the reactions. The directing group can be removed readily and transformed into carboxylic acids. Therefore, this reaction provides a simple method for *β*-arylation of carboxylic acids.

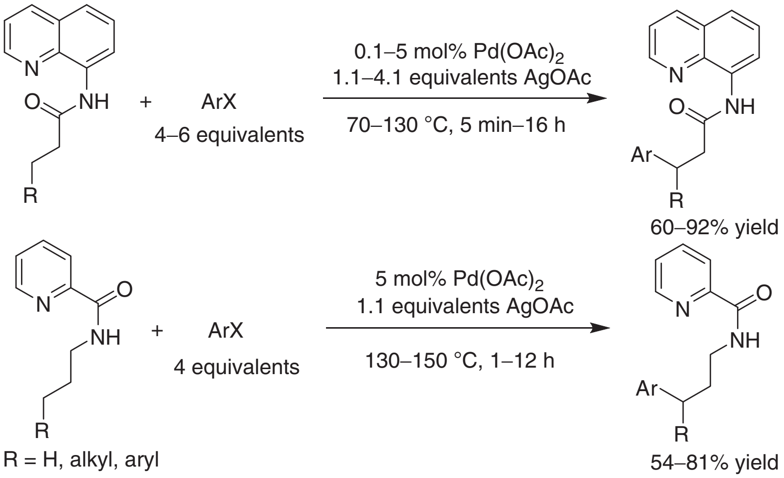


Scheme 169 Pd-catalyzed benzylic arylation of 2-methyl azaarenes (Morris et al., 2010).



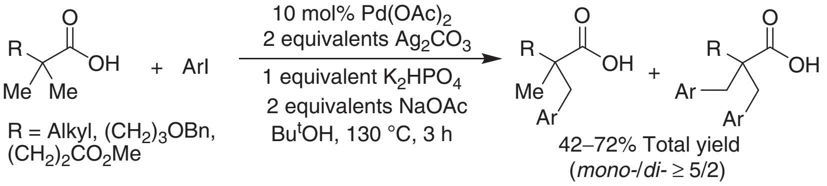
Scheme 170 Pd-catalyzed acidic amide-directed arylation of C(sp^3)-H bonds with aryl iodides (Yu et al., 2009).

All of the above arylation reactions of C(sp^3)-H bonds were proposed to proceed via Pd(0)/Pd(II) mechanisms. The Pd(II)/Pd(IV) catalysis also proved viable to arylate C(sp^3)-H bonds. By using a well-designed bidentate directing group, Daugulis and coworkers successfully achieved the arylation of simple alkanes (Scheme 171).[233] Thus, in the presence of Pd(OAc)$_2$ and AgOAc, carboxylic amides possessing a directing aminoquinoline group were β-arylated with aryl iodides regioselectively. The γ-arylation of amine derivatives with 2-picolinic acid as an auxiliary also took place effectively under the similar conditions. Subsequently, the protocol was successfully extended to the β-arylation of amino acids.[234]



Scheme 171 Pd-catalyzed bidentate directing group-assisted arylation of C(sp^3)-H bonds with aryl iodides (Daugulis et al., 2005).

Yu and coworkers described the β-arylation of simple aliphatic acids with aryl iodides, which was the first example of Pd-insertion into β C(sp^3)-H bonds in simple aliphatic acids (Scheme 172).[235] The reactions formed a mixture of mono- and diarylated products, and only the acids without α-hydrogens were compatible.



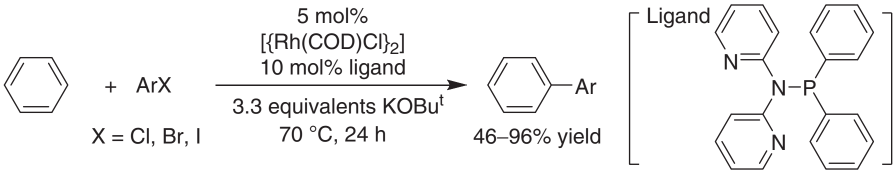
Scheme 172 Pd-catalyzed carboxyl-directed arylation of C(sp^3)-H bonds with aryl iodides (Yu et al., 2007).

3.23.3.2 Rhodium-Catalyzed Reactions with (Pseudo)halides

Rh-enabled reactions of C–H bonds with halides have also been exploited, and a variety of arylation reactions have been reported, albeit a fewer number of examples in comparison with those catalyzed by palladium.[16,71]

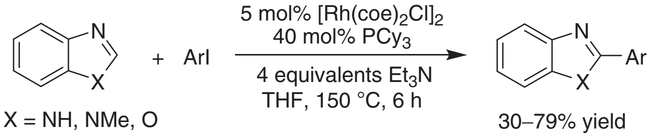
3.23.3.2.1 Rhodium-catalyzed nondirected reactions with (pseudo)halides

In 2007, Kempe and coworkers disclosed the Rh(I)-catalyzed direct arylation of benzene by employing a novel bimetallic rhodium complex derived from $[\{Rh(COD)Cl\}_2]$ and a P, N-ligand (**Scheme 173**).[236] The bimetallic complex was necessary for catalysis and was found to catalyze the arylation of benzene efficiently. In addition to aryl iodides, aryl bromides, and chlorides were found to be effective arylation reagents, and a diversity of functional groups of aryl halides was well tolerated. The mechanism involved in the reactions and superior catalytic activity of the bimetallic catalyst remained to be clarified.



Scheme 173 Rh-catalyzed arylation of benzene (Kempe et al., 2007).

A variety of heteroarenes have been found to undergo Rh-catalyzed arylation reactions with aryl halides. One of the representative examples is the arylation of azoles with aryl iodides described by Bergman and Ellman in 2004 (**Scheme 174**).[237] Therefore, a wide range of azoles and their analogs, including benzimidazole, benzoxazole, 3,4-dihydroquinazoline, and oxazolines, were arylated in the presence of $[Rh(coe)_2Cl]_2$, PCy_3, and Et_3N. The arylation occurred at the 2-positions of the azoles selectively. In addition to the desired arylated products, a large amount of benzene was formed because of the hydrodehalogenation of PhI. Based on the mechanistic studies, the reactions were believed to proceed via key rhodium-*N*-heterocyclic-carbene (NHC) intermediates. Therefore, the carbene complex was formed via a C–H activation/tautomerizaion process. The low-valent Rh complex underwent oxidative addition of aryl iodides to generate the (aryl)(carbene)rhodium complex. The subsequent HBr elimination from the complex and reductive elimination furnished the final arylated products and regenerated the Rh catalyst (**Figure 15**).[237]



Scheme 174 Rh-catalyzed C2-arylation of azoles with aryl iodides (Bergman and Ellman et al., 2004).

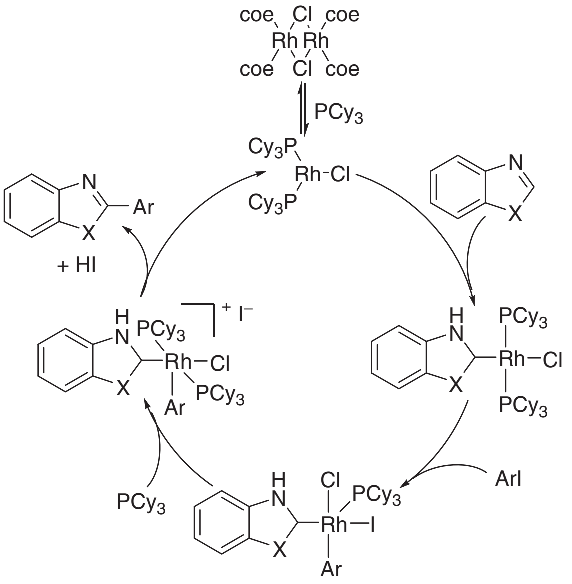
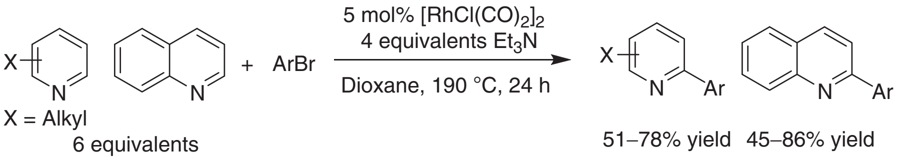


Figure 15 Proposed mechanism of Rh-catalyzed C2-arylation of azoles.

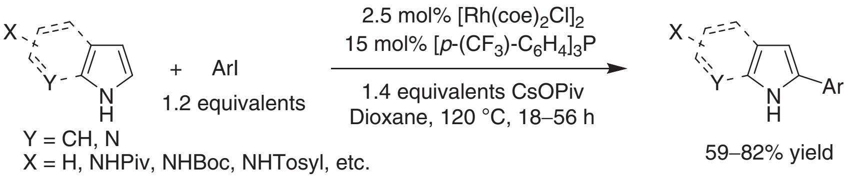
Inspired by this initial discovery, Bergman and Ellman continued their efforts to optimize the original procedure for the arylation of heterocycles with aryl halides. After gaining a deeper understanding of the reaction mechanism, the authors improved the procedure to successfully overcome the shortcomings of the initial methodology. By using a more hindered amine base, a bulky bicyclic trialkylphosphine ligand, and microwave irradiation, the substrate scope was expanded to include a broader range of heterocycles and aryl bromides.[238,239]

Subsequently, Bergman and Ellman disclosed Rh-catalyzed direct arylation of pyridines and quinolines (**Scheme 175**).[240] Thus, pyridines and quinolines underwent 2-arylation with a diversity of aryl bromides in the presence of $[RhCl(CO)_2]_2$ and Et_3N. Interestingly, a phosphine ligand, which was required in the arylation reactions of other heterocycles, was found to suppress the catalytic activity. Although no mechanism was provided for these arylation reactions, Itami and Bouffard proposed that the reactions were likely to share a common mechanism, which involves the formation of a Rh(I)-NHC complex, with the above heterocycle arylation processes.[16]



Scheme 175 Rh-catalyzed C2-arylation of pyridines and quinolines with aryl bromides (Bergman and Ellman et al., 2008).

Although the above Rh(I)-catalyzed arylation reactions proceeded through NHC mechanisms, the arylation of electron-rich heteroarenes were realized by using electron-deficient Rh(III) complexes. One of the representative examples is the 2-arylation of free (NH)-indoles and pyrroles with aryl iodides reported by Sames and coworkers (**Scheme 176**).[241] Notably, the C-arylation occurred selectively even in the presence of the acidic NH bonds. The proposed mechanism involved a Rh(I)/Rh(III) catalytic cycle, which is analogous to the Pd(0)/Pd(II) mechanism for Pd-catalyzed arylation of C–H bonds with (pseudo)halides. Therefore, the catalytically active Rh(III) was generated through the oxidative addition of aryl iodides to the Rh(I) precatalyst. The formed Rh(III) complex then participated in the electrophilic metalation to insert the C–H bonds. The subsequent reductive elimination generated the coupling products and released Rh(I) species (**Figure 16**).[241] The electrophilicity of Rh(III) was augmented by using a electron-deficient phosphine ligand. Furthermore, the pivalate ligand from CsOPiv was also crucial for the remarkable reactivity. The use of the phosphine and pivalate ligand accounted for the novel selective C-arylation.



Scheme 176 Rh-catalyzed arylation of indoles and pyrroles with aryl iodides (Sames et al., 2005).

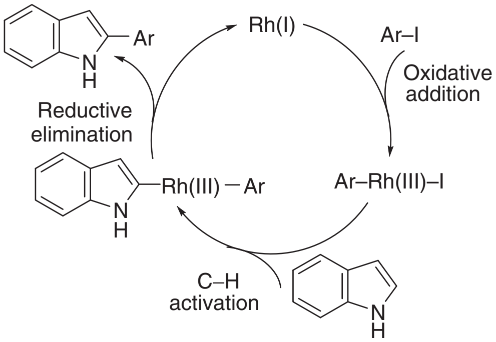
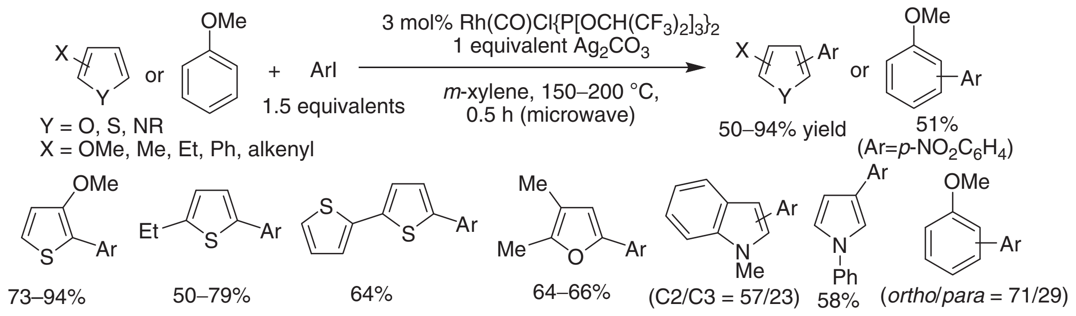


Figure 16 Proposed mechanism of Rh-catalyzed arylation of indoles and pyrroles with aryl iodides.

Itami and coworkers developed a general protocol for the arylation of a variety of heterocycles (**Scheme 177**).[242] In this reaction, a rhodium complex bearing a strongly π-accepting ligand, $P[OCH(CF_3)_2]_3$, was developed. Therefore, in the presence of $Rh(CO)Cl\{P[OCH(CF_3)_2]_3\}_2$ and Ag_2CO_3, a diverse variety of electron-rich heteocycles, including furans, thiophenes, pyrroles,

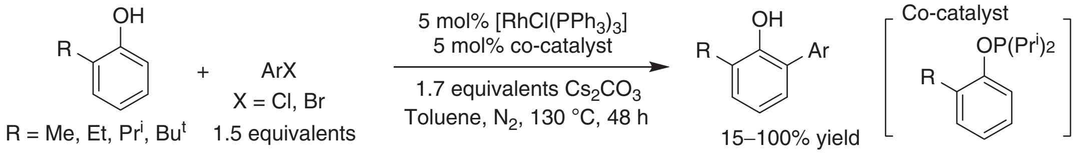


Scheme 177 Rh-catalyzed arylation of (hetero)arenes with aryl iodides (Itami et al., 2006).

and indoles, underwent arylation reaction with (hetero)aryl iodides. Although the reactions took place at 2-positions selectively for furans and thiophenes, the 3-arylated product was produced for 1-phenylpyrrole and the arylation of 1-methylindole resulted in a mixture of regioisomers. This protocol also proved applicable to the arylation of simple arenes. A mixture of *ortho*- and *para*-isomers was yielded for anisole in a ratio of 29:71, which was consistent with an electrophilic metalation manifold. A similar Rh(I)/Rh(III) mechanism was also proposed to be operative in the reaction.

3.23.3.2.2 Rhodium-catalyzed-directed reactions with (pseudo)halides

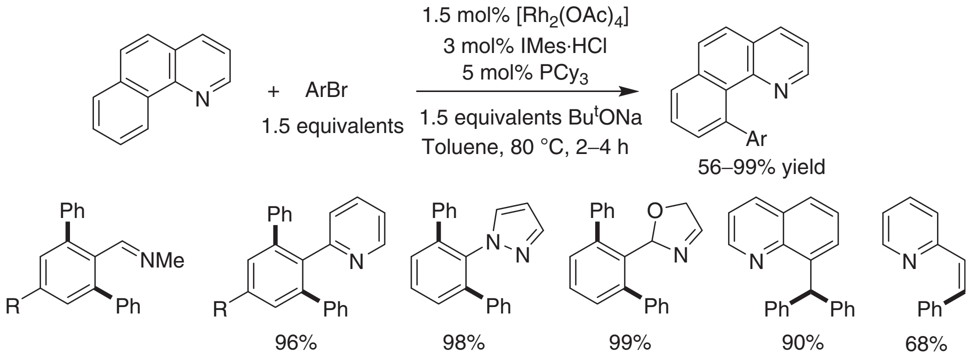
The Rh-catalyzed arylation relying on a directing group has also been reported. Earlier than the direct arylation of heteroarenes, Bedford and coworkers described that phenols were *ortho*-arylated with aryl halides in the presence of Wilkinson's catalyst ($RhCl(PPh_3)_3$) and a catalytic amount of an aryl dialkylphosphinite as cocatalyst (Scheme 178).[243] The phosphinite, which was transferred to the phenols by transesterification, functioned as the actual directing group. The presence of one *ortho*-substituent on the reactive phenols was required to enable the arylation reaction, and bulkier substituents gave higher yields. Bromoarenes with electron-withdrawing or donating groups were reactive, whereas chloroarenes gave much lower yields. The proposed mechanism was similar to those for the above Rh(III)-catalyzed arylation of electron-rich heterocycles.



Scheme 178 Rh-catalyzed *ortho*-arylation of phenols with aryl chlorides/bromides (Bedford et al., 2003).

A major drawback of the above catalytic system is that an aryl diisopropylphosphinite cocatalyst has to be prepared. To avoid the formation of by-products derived from the cocatalyst, the aryl group of the cocatalyst should match the phenolic substrates. To circumvent this drawback, Bedford and coworkers developed a new catalytic system chlorodialkylphosphines/$[Rh(cod)Cl]_2$, which gave the identical results to $RhCl(PPh_3)_3/ArOPPr^i_2$.[244] Furthermore, Oi and coworkers independently disclosed an analogous rhodium-catalyzed *ortho*-arylation of phenols with aryl bromides by using hexamethylphosphotriamide (HMPT) as the phosphinyl group transfer agent.[245]

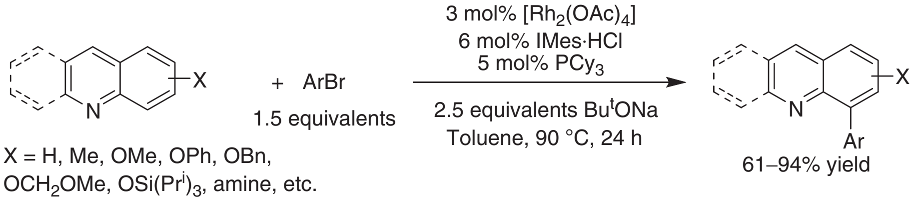
In 2009, Chang and coworkers reported basic nitrogen-directed arylation (Scheme 179).[246] In this procedure, a wide range of basic nitrogen-containing heteroarenes and imine were found to effectively direct the metalation of arenes in Rh-catalyzed C–H



Scheme 179 Rh-catalyzed-directed arylation of C(sp^2)/sp^3)-H bonds with aryl bromides (Chang et al., 2009).

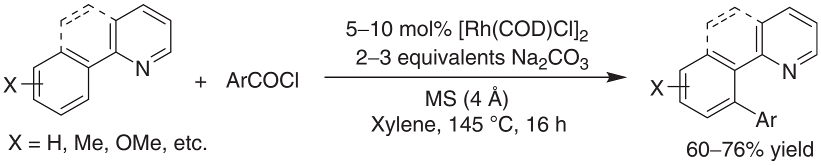
arylation. [$Rh_2(OAc)_4$] was used as the catalyst, and the simultaneous employment of electron-rich *N*-heterocyclic carbene and PCy_3 ligands dramatically increased the reactivity of the rhodium catalyst. Diarylated products were formed in the reactions. Mechanistic studies revealed that the C–H activation occurred by a proton abstraction pathway with the aid of Bu^tONa. The formed carborhodiums underwent oxidative addition to aryl bromides and reductive elimination, yielding the final arylated products. Notable, benzylic and vinylic C–H bonds were also arylated under the reaction conditions.

This protocol also proved applicable to the arylation of quinolines (Scheme 180).[247] By using the identical catalytic system, a wide range of quinolines were arylated with aryl bromides at 8-position regioselectively. The formation of a bimetallic Rh species bound to an NHC ligand was proposed to be the active catalyst species and be responsible for the regioselectivity.



Scheme 180 Rh-catalyzed C8-arylation of quinolines with aryl bromides (Chang et al., 2011).

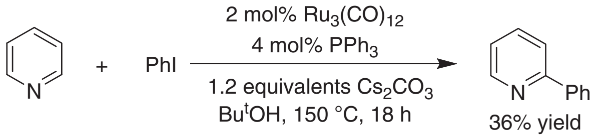
Interestingly, the similar arylation can be realized by using acid chlorides as coupling partners. In 2008, Yu and coworkers reported pyridine-directed C–H arylation with benzoic chlorides (Scheme 181).[248] Therefore, 2-phenylpyridines and their analogs were arylated in the presence of $[Rh(COD)Cl]_2$, Na_2CO_3, and molecular sieves. The proposed mechanism consisted of oxidative addition of benzoic chlorides to Rh(I), decarbonylation, cyclometalation, and subsequent reductive elimination to form the final arylated products. Anhydrides have also been used as the arylation reagents to achieve the similar results.[249]



Scheme 181 Rh-catalyzed pyridine-directed arylation with benzoic chlorides (Yu et al., 2008).

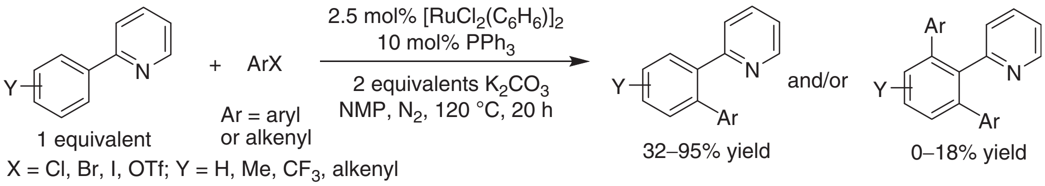
3.23.3.3 Ruthenium-Catalyzed Reactions with (Pseudo)halides

In 2005, Sames and coworkers disclosed $Ru_3(CO)_{12}$-catalyzed 2-phenylation of pyridine with iodobenzene. This novel protocol set the precedent for the development of new methodologies for direct arylation of π-deficient heteroarenes (Scheme 182).[250] Mechanistic studies demonstrated that a bimetallic complex was the catalytically active species.



Scheme 182 Ru-catalyzed C2-phenylation of pyridine with iodobenzene (Sames et al., 2005).

Directed C–H arylation with aryl halides was achieved by Oi, Inoue and coworkers in 2001 (Scheme 183).[251] In the presence of the catalyst $[RuCl_2(C_6H_6)]_2$ and the ligand PPh_3, 2-phenylpyridines were *ortho*-arylated with a broad range of aryl bromides with the aid of K_2CO_3. A mixture of mono- and diarylated products was produced for 2-phenylpyridine without any substituents, whereas the substrates with substituents on either phenyl or pyridyl group gave the sole monoarylated products. Alkenylation also proceeded effectively under the reaction conditions by using alkenyl bromides. In addition, other (pseudo)halides, including iodobenzene, chlorobenzene, and phenyltriflate, were also found to be reactive, albeit in lower efficiency. The proposed mechanism involved a Ru(II)/Ru(IV) catalytic cycle. A Ru(IV) species was suggested to be the key intermediate, which was generated by the oxidative addition of aryl bromides to the Ru(II) complex. The Ru(IV) complex cleaved the C–H bonds of 2-phenylpyridines electrophilically with the aid of the chelation of the pyridyl group, to form ruthenocycles. The subsequent reductive elimination afforded the final arylated products (Figure 17).[251]



Scheme 183 Ru-catalyzed pyridine-directed arylation/alkenylation of arenes (Oi and Inoue et al., 2001).

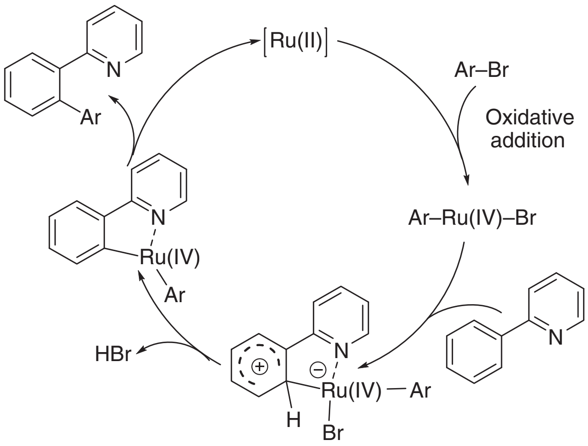
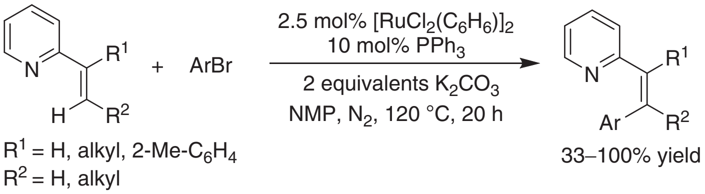


Figure 17 Proposed mechanism of Ru-catalyzed pyridine-directed arylation/alkenylation of arenes.

The Oi and Inoue also demonstrated that the protocol may be applicable to the directed arylation of a wide range of substituted arenes, which include aromatic imines,[252] imidazolines, oxazolines,[253,254] and azoles.[255] Interestingly, this protocol was also extended to purine- and deoxyribonucleoside-directed arylation by Lakshman and coworkers.[256]

Furthermore, the arylation of vinylic C–H bonds also proved viable under the identical reactions (Scheme 184).[257] Thus, 2-alkenylpyridines underwent arylation with aryl bromides, affording *β*-arylated (*Z*)-2-alkenylpyridines in a regio- and stereoselective manner. It is noteworthy that the aryl moiety was introduced *cis* to the pyridyl group. This geometrical selectivity is in sharp contrast to the Mizoroki–Heck reaction. Mechanistically, four possible pathways were proposed, and Ru(0), Ru(II) or Ru(IV) catalyst might be responsible for the C–H cleavage.

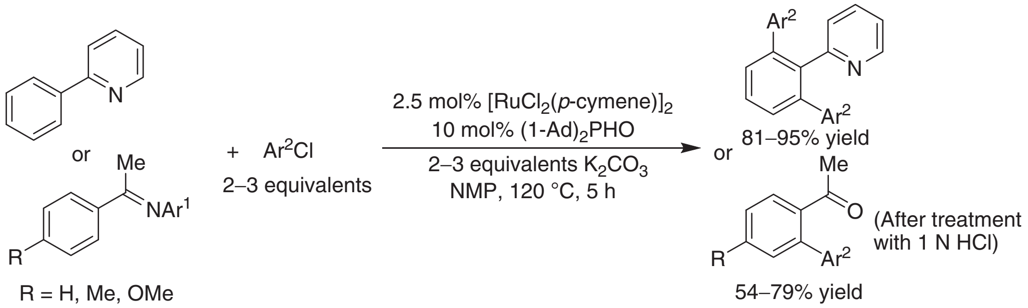


Scheme 184 Ru-catalyzed pyridine-directed arylation of alkenes with aryl bromides (Oi and Inoue et al., 2005).

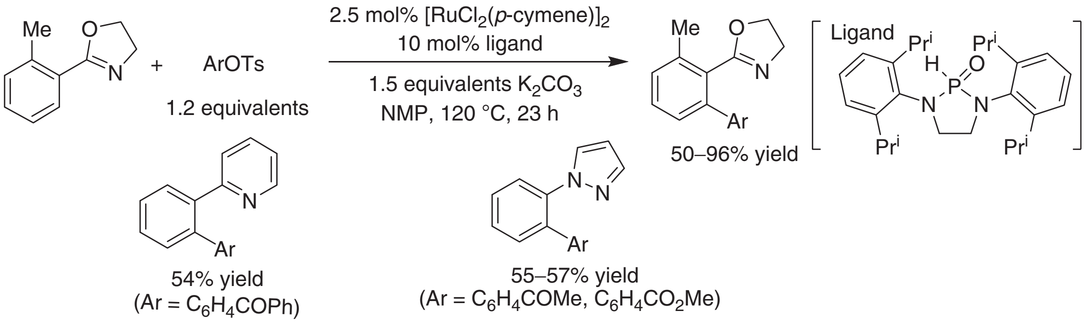
Ackermann developed another Ru-catalyzed arylation protocol (Scheme 185).[258] This protocol relied on the use of a sterically hindered adamantly-substituted phosphine oxide as the preligand, which allowed for diarylation of aryl pyridines and monoarylation of aryl imines with diversely substituted aryl chlorides. A wide range of functional groups were well tolerated.

By using an analogous bulky phosphine oxide preligand, Ackermann and coworkers successfully achieved Ru-catalyzed C–H arylation with aryl tosylates (Scheme 186).[259] Under the similar conditions, arenes with different directing groups, including oxazoline, pyridine, and pyrazole, underwent arylation reaction with a wide range of aryl tosylates to afford monoarylated products. It is noted that aryl chlorides were also reactive to give diarylated products predominantly. Hence, this protocol allowed for selective arylation through the judicious choice of arylation reagents. Interestingly, the catalytic system enabled direct arylation with phenols in the presence of sulfonyl chloride.[260]

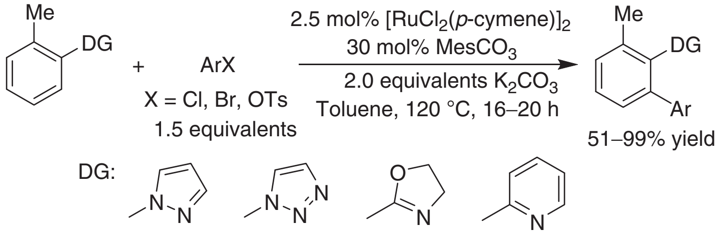
The high catalytic efficacy of phosphine oxide preligands inspired Ackermann and coworkers to conjecture that an assisted intramolecular proton abstraction mechanism might be operative in the above Ru-catalyzed arylation reactions (Scheme 187).[261] Based on this conjecture, the authors envisioned that the similar reactivities should be accessible through the use of sub-stoichiometric amounts of carboxylates, which may enable C–H activation via a concerted cyclometalation-deprotonation



Scheme 185 Ru-catalyzed-directed arylation of arenes with aryl chlorides (Ackermann, 2005).



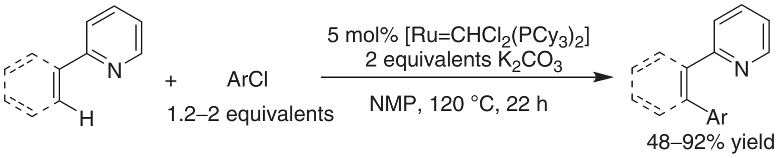
Scheme 186 Ru-catalyzed-directed arylation of arenes with aryl tosylates (Ackermann et al., 2006).



Scheme 187 Ru-catalyzed-directed arylation of arenes (Ackermann et al., 2008).

process. Gratingly, by replacing the phosphine oxide with $MesCO_2H$, the similar arylation proceeded effectively in toluene. This reaction displayed a broad substrate scope and allowed for efficient-directed arylations of 1,2,3-triazoles, pyridines, pyrazoles, or oxazolines. Aryl bromides, chlorides and tosylates were compatible under the reaction conditions.

Interestingly, ruthenium(IV) carbene complexes have also been found to enable direct arylation with aryl (pseudo)halides (Scheme 188).[262] Therefore, the use of precatalyst $[Ru{=}CHCl_2(PCy_3)_2]$ allowed for the pyridine-directed arylation of arenes and alkenes with a wide range of aryl chlorides in the presence of K_2CO_3. Pyrazole and oxazoline also functioned as directing groups effectively.



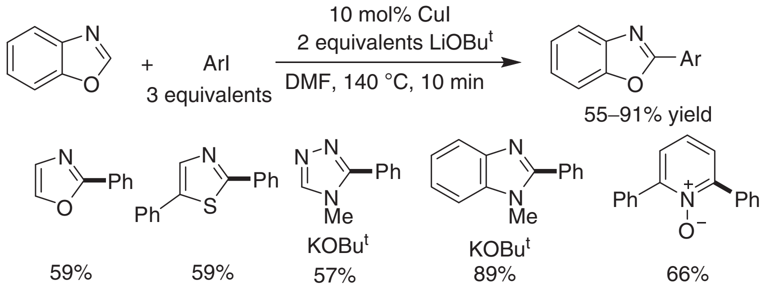
Scheme 188 Ru-catalyzed pyridine-directed arylation of arenes with aryl chlorides (Ackermann et al., 2007).

3.23.3.4 Other Transition-Metal-Catalyzed Reactions with (Pseudo)halides

3.23.3.4.1 Copper-catalyzed reactions with (pseudo)halides

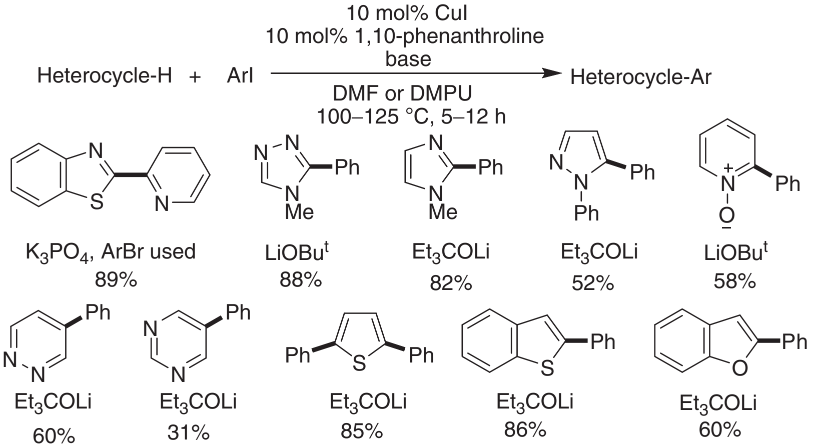
Copper was the first transition metal to promote C–H bond arylation. As early as 1941, substantial amounts of trithienyl was observed in the Ullmann reaction of 2-iodothiophene, which was generated via C–H bond arylation.[263] Although underexploited in comparison with those catalyzed by palladium, quite a number of copper-promoted C–H arylation reactions have been reported, especially in the past 5 years.

In 2007, Daugulis reported CuI-catalyzed arylation of heteroarenes with aryl iodides with the assistance of LiOBu^t (**Scheme 189**).[264] A variety of heteroarenes with acidic C–H bonds, including imidazole, thiazole, and pyridine *N*-oxide, were reactive. Mechanistic studies suggested that the heterocycles were first deprotonated by LiOBu^t, which may be assisted by copper precoordination to the heterocycle. The subsequent lithium–copper transmetalation formed the organocopper species, which reacted with aryl iodide to afford the final arylation products. For less acidic imidazole, 1,2,4-triazole, and caffeine derivatives, the use of a stronger base KOBu^t is required. It is noteworthy that a copper-assisted benzyne-type mechanism was believed to be operative for the strong base-promoted arylation.



Scheme 189 Cu-catalyzed arylation of heteroarenes with aryl iodides (Daugulis et al., 2007).

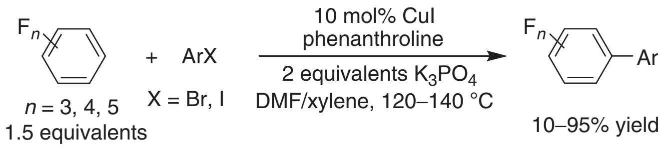
Daugulis and coworkers optimized the protocol by employing the ligand 1,10-phenanthroline. The optimized reaction conditions allowed for the arylation of a broader range of heteroarenes, including the less acidic ones that were not reactive under the initial conditions (**Scheme 190**).[265] For comparatively acidic heterocycles with DMSO p*K*as below 27, K_3PO_4 was basic enough to promote the arylation reactions. If the substrates were less acidic (p*Ka* 27–35), a stronger lithium alkoxide base Bu^{t}OLi or Et_3COLi may be employed. The unnecessity of Bu^{t}OK shut down the benzyne mechanism, ensuring arylation regioselectivity. Furthermore, the use of hindered base Et_3COLi may suppress the nucleophilic substitution of aryl iodide by alkoxide.



Scheme 190 Cu-catalyzed arylation of heteroarenes with aryl iodides with the aid of a ligand (Daugulis et al., 2008).

The similar arylation reactions of heteroarenes have also been reported by other groups independently.[266,267] The protocol also proved applicable to the arylation of 1,2,3-triazole[268] and benzotriazepines,[269] affording 5-arylated products in all cases.

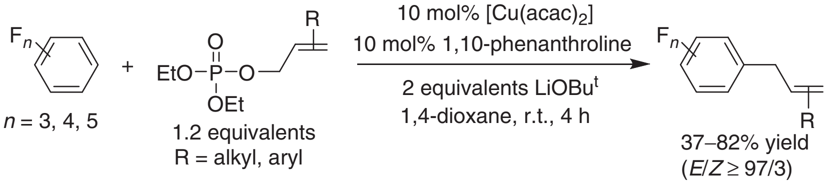
Since the above C–H bond cleavage involved a deprotonation mechanism, it was reasonable to assume that acidic polyfluorobenzenes may be arylated in a similar manner. Daugulis and coworkers demonstrated that pentafluorobenzene was arylated with a wide range of aryl bromides under the similar conditions, with K_3PO_4 as base (**Scheme 191**).[270] The arylation of other polyfluorobenzenes with various numbers of fluorines had also been exemplified by using 4-iodotoluene as the coupling partner. Other electron-deficient arenes with acidic C–H bonds were also arylated efficiently. The reactivity paralleled the acidity of C–H



Scheme 191 Cu-catalyzed arylation of polyfluoroarenes aryl iodides (Daugulis et al., 2008).

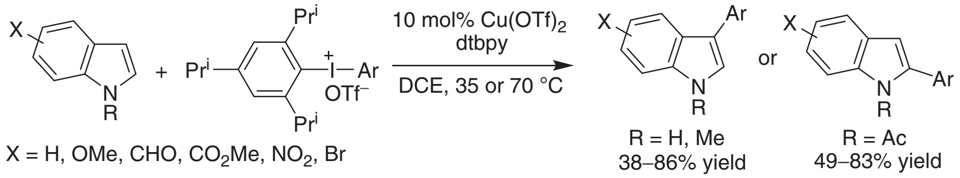
bonds, and the most acidic C–H bonds were arylated preferentially. The reactive arenes included polychlorobenzenes, 1, 3-dinitrobenzene, and 3-nitrobenzonitrile, and the reactions afforded the arylation products in moderate yields. For less acidic arenes possessing only one electron-withdrawing group, such as nitro-, chloro-, fluoro-, and cyanobenzene, <5% conversion to products was observed.[265]

Interestingly, Miuro, Hirano and coworkers reported the allylation of polyfluoroarenes with allyl phosphates following the similar catalytic system (Scheme 192).[271] It is noteworthy that the stereochemical information of the allyl phosphates was retained in the reaction. The *E*/*Z* olefin stereochemistry of the starting material was translated to the product in a highly stereospecific manner.



Scheme 192 Cu-catalyzed allylation of polyfluoroarenes with allyl phosphates (Hirano and Miura et al., 2011).

Although the above Cu(I)-catalyzed arylation protocol takes advantage of acidic C–H bonds to facilitate C–H cleavage, the Gaunt and coworkers put forward a second concept to realize Cu-promoted C–H arylation. Considering that electrophilic metalation is one of the major pathways in transition-metal-enabled C–H activation and that Cu(III) should be highly electrophilic, Gaunt reasoned that Cu(III) could cleave C–H bonds under mild conditions. This hypothesis proved viable in the arylation of electron-rich indoles (Scheme 193).[272] Therefore, both *NH*- and *N*-substituted indoles were arylated with diaryl-iodine(III) reagents in the presence of Cu(OTf)$_2$ and 2,6-di-*tert*-butylpyridine (dtbpy). It is noted that the regioselectivities were dependent on the substituents on the nitrogen of indoles. Although *N*-methyl and 1-*H* indoles afforded C3-arylated products, the arylation occurred at 2-position selectively for *N*-acylindoles.



Scheme 193 Cu-catalyzed site-selective arylation of indoles with diaryl-iodine(III) reagents (Gaunt et al., 2008).

The reaction was proposed to proceed via a Cu(III)-aryl species that underwent electrophilic addition at the C-3 position of the indole motif. The Cu(III)-aryl species were generated through the oxidation of Cu(I) by diaryl-iodine(III) reagents. The formation of the C2-arylated products arose through migration of the Cu(III)-aryl group from C3 to C2 (Figure 18).[272]

Interestingly, when a similar protocol was applied to the arylation of acetanilides, *meta*-arylated products were observed (Scheme 194).[273] This discovery is remarkable because transition-metal-catalyzed C–H functionalization usually occurs at *ortho*-position and classical electrophilic aromatic substitution reactions yield *para*- and *ortho*-products predominantly for electron-rich arenes. The unusual site selectivity was proposed to arise through antioxy-cupration of the carbonyl group of an acetamide across the 2,3-positions on the arene ring, which placed the Cu(III)-aryl species at the *meta* position (Figure 19).[273]

Subsequently, Gaunt and coworkers demonstrated that the protocol was applicable to the arylation of anilines and phenols (Scheme 195).[274] It is noted that the reactions occurred at *para*-position selectively, which represented the first highly *para*-selective arylation of aniline and phenol derivatives. For *para*-substituted anilines, *ortho*-arylated products were formed.

3.23.3.4.2 Nickel-catalyzed reactions with (pseudo)halides

In 2009, Itami and coworkers reported Ni-catalyzed arylation of acidic heteroarenes under conditions similar to those for the Cu-promoted arylation (Scheme 196).[275] A variety of heteroarenes with acidic C–H bonds, such as imidazoles, oxazoles, and

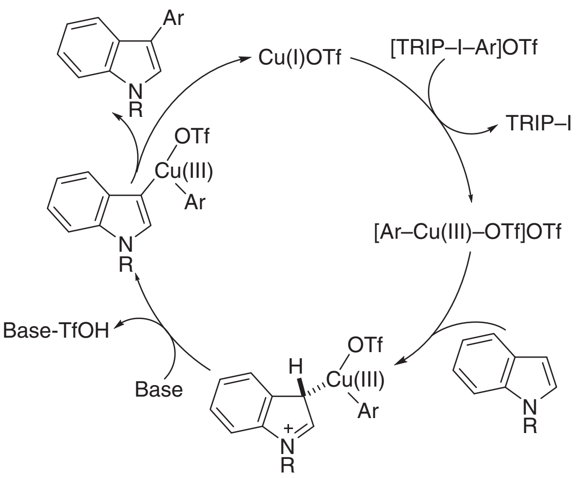
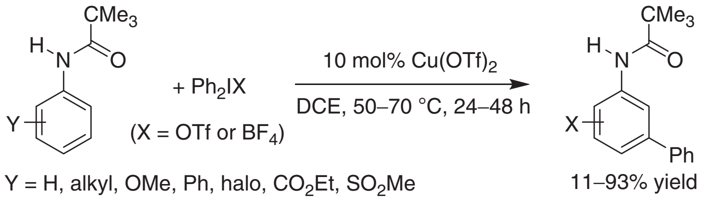


Figure 18 Proposed mechanism of Cu-catalyzed site-selective arylation of indoles.



Scheme 194 Cu-catalyzed *meta*-selective arylation of acetanilides with diaryl-iodine(III) reagents (Gaunt et al., 2009).

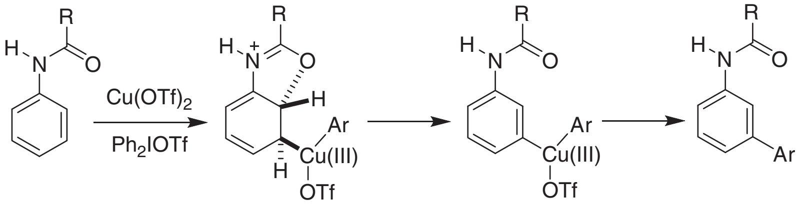
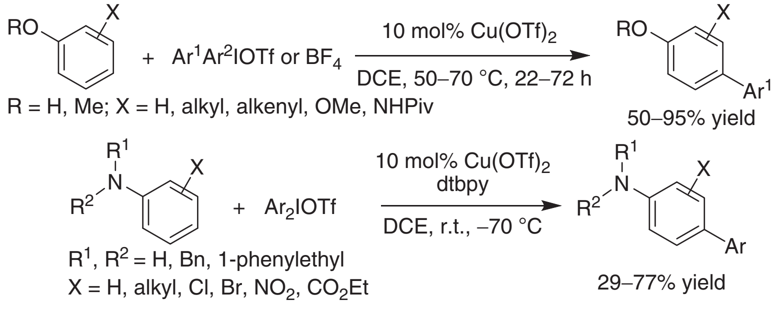
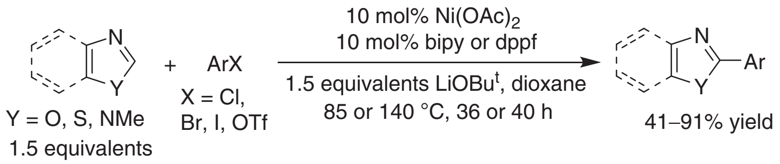


Figure 19 Proposed mechanism of Cu-catalyzed *meta*-selective arylation of arenes.



Scheme 195 Cu-catalyzed *para*-selective aryltion of aniline and phenol derivatives with diaryl-iodine(III) reagents (Gaunt et al., 2011).

thiazoles were arylated at the most acidic positions in the presence catalyst $Ni(OAc)_2$, ligand 2,2′-bipyridyl (bipy) or 4,4′-$(Bu^t)_2$bipy, and base $LiOBu^t$. Aryl iodide, bromide and chloride were shown to be effective coupling partners. Aryl triflate was also reactive, albeit in modest yields. A diverse variety of functional groups on the aryl halides were well tolerated. The proposed mechanism involved Ni(0)/Ni(II) redox catalysis, which included the oxidative addition of aryl (pseudo)halide to Ni(0) (*in situ*



Scheme 196 Ni-catalyzed arylation of heteroarenes (Itami et al., 2009).

generated), metalation of heteroarenes (Het-H) generating Ar-Ni(II)-Het, and reductive elimination affording the coupling products and regenerating Ni(0) species (**Figure 20**).[275]

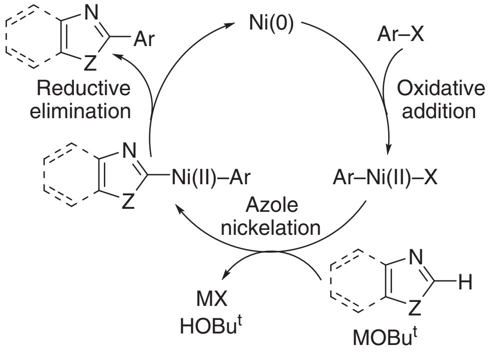
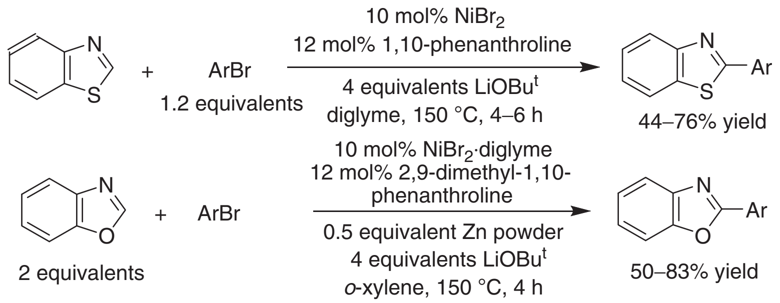


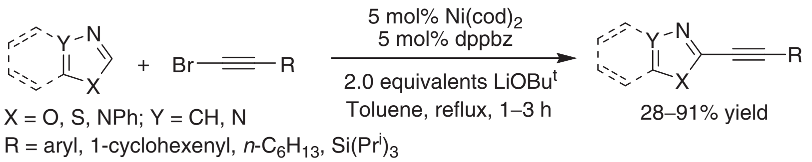
Figure 20 Proposed mechanism of Ni-catalyzed arylation of heteroarenes.

Concurrently, Miura and coworkers disclosed analogous arylation of heteroarenes independently (**Scheme 197**).[276] The catalytic system including $NiBr_2$, 1,10-phenanthroline and $LiOBu^t$ was found to be the most effective for the arylation of benzothiazoles. However, for benzoxazoles, the reactions gave the highest yields in the presence of $NiBr_2$•diglyme, 2,9-dimethyl-1,10-phenanthroline, $LiOBu^t$ and Zn powder.



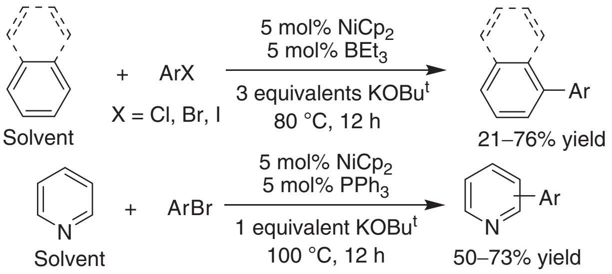
Scheme 197 Ni-catalyzed arylation of heteroarenes with aryl bromides (Miura et al., 2009).

Interestingly, a similar protocol was developed to enable the alkynylation of azoles with alkynyl bromides by using catalyst $Ni(cod)_2$ and ligand 1,2-bis(diphenylphosphino)benzene (dppbz) (**Scheme 198**).[277] In some cases, a catalytic amount of CuI was employed to enhance the reaction yields.



Scheme 198 Ni-catalyzed alkynylation of azoles with alkynyl bromides (Miura et al., 2009).

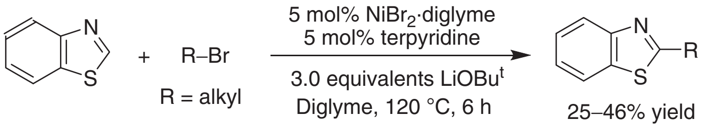
Ni-catalyzed direct C–H arylation of simple arenes using aryl halides was achieved by the Yamakawa and coworkers (**Scheme 199**).[278] For the first time, the arylation of benzene and naphthalene was successfully catalyzed by Cp_2Ni in the presence



Scheme 199 Ni-catalyzed arylation of benzene, naphthalene, and pyridine (Yamakawa et al., 2009).

of KOBu^t and BEt$_3$. A mixture of 1- and 2-arylated products was produced for naphthalenes. This Ni catalyst system was also successfully applied to direct C–H arylation of pyridine. PPh$_3$ was found to be superior to BEt$_3$, and a mixture of 2-, 3-, and 4-substituted arylated derivatives was formed.

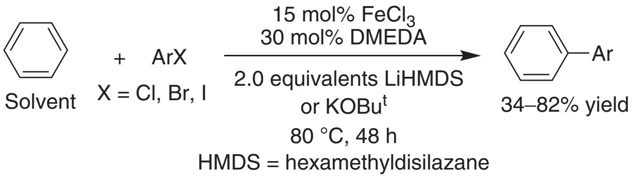
In 2010, Miura and coworkers described NiBr$_2$•diglyme-catalyzed alkylation of benzothiazole with alkyl bromides (Scheme 200).[193] The reactions were proposed to proceed by a radical mechanism.



Scheme 200 Ni-catalyzed alkylation of benzothiazole with alkyl bromides (Miura and Hirano et al., 2010).

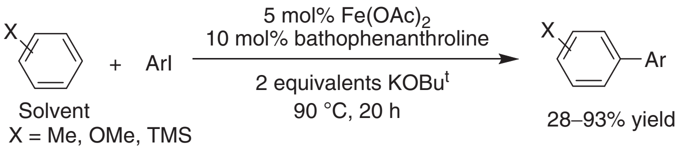
3.23.3.4.3 Iron/cobalt/iridium-catalyzed reactions with (pseudo)halides

In 2010, Lei and coworkers reported Fe-catalyzed direct arylation of benzene with aryl halides (Scheme 201).[279] A wide range of aryl iodides and bromides were effective coupling partners in the presence of FeCl$_3$, DMEDA (*N*^{1},*N*^{2}-dimethylethane-1,2-diamine), and LiHMDS or KOBu^t. Aryl chlorides were also reactive, albeit in lower yields.



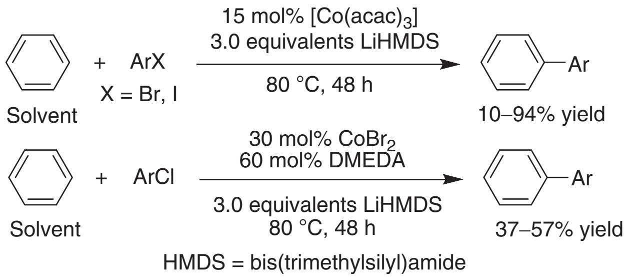
Scheme 201 Fe-catalyzed arylation of benzene (Lei et al., 2010).

Concurrently, an analogous arylation was disclosed by the Charette and coworkers (Scheme 202).[280] By using catalyst Fe(OAc)$_2$ and ligand bathophenanthroline, benzene was arylated with a variety of aryl iodides with the aid of KOBu^t. The arylation of substituted arenes also proceeded effectively under the reaction conditions, and a mixture of regioisomers were produced in the cases that more than one reactive position were available. Mechanistic evidence suggested that the transformation proceeded through a Fe-catalyzed radical process giving a metal-catalyzed radical living direct arylation.



Scheme 202 Fe-catalyzed arylation of simple arenes with aryl iodides (Charette et al., 2010).

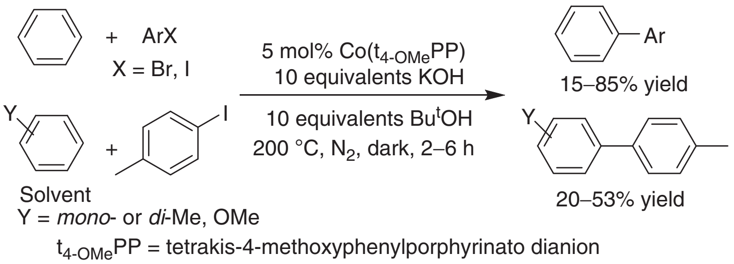
In a continuous effort to develop direct coupling reactions, Lei and coworkers demonstrated that Co can act as a similar catalyst to iron in the direct arylation of simple arenes (Scheme 203).[281] By using catalyst [Co(acac)$_3$], benzene was allowed to react with a wide range of aryl bromides and iodides in the presence of LiHMDS. Remarkably, the chloro substituent was well tolerated under the reaction conditions. However, the use of a different catalyst system consisting of CoBr$_2$ and DMEDA



Scheme 203 Cocatalyzed arylation of benzene (Lei et al., 2011).

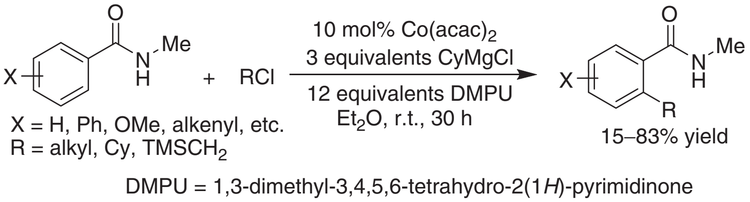
(N^1,N^2-dimethylethane-1,2-diamine) enabled aryl chlorides as reactive coupling partners, albeit in lower yields. Preliminary mechanistic studies suggested that the reactions operated by a radical mechanism.

Independently, Chan and coworkers reported an analogous arylation of simple arenes (Scheme 204).[282] Thus, benzene was effectively arylated with either aryl bromides or iodides in the presence of Co($t_{4\text{-OMe}}$PP), KOH and Bu^{t}OH. The arylation of substituted arenes were also examined with *para*-iodotoluene. Arenes with methyl or methoxy groups were found to be reactive under the identical reaction conditions, and a mixture of regioisomers was formed. A radical mechanism was also proposed.



Scheme 204 Cocatalyzed arylation of simple arenes (Chan et al., 2011).

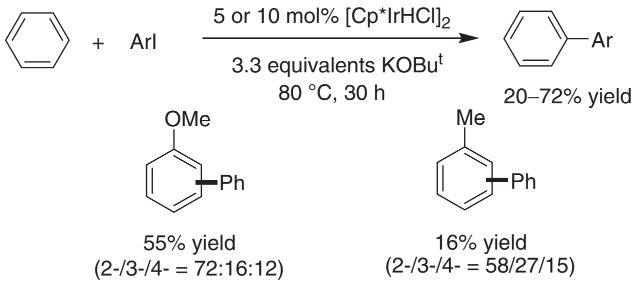
Concurrently, the Nakamura and coworkers disclosed cobalt-catalyzed *ortho*-alkylation of benzamide with alkyl chloride (Scheme 205).[283] Therefore, secondary benzamides underwent alkylation with a range of alkyl chloride including Bu^{t}Cl using Co(acac)$_2$, CyMgCl, and DMPU. The Grignard reagent formally acted to remove hydrogen atoms from the amide nitrogen and from the *ortho*-position and to generate the active cobalt species.



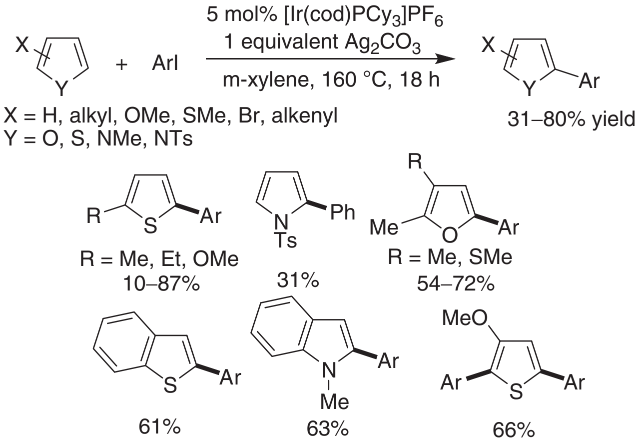
Scheme 205 Co-catalyzed amide-directed alkylation of benzamides with alkyl chlorides (Nakamura et al., 2011).

Iridium has also been utilized to enable the direct arylation of simple arenes. In 2004, the Fujita, Yamaguchi and coworkers reported [Cp*IrHCl]$_2$-catalyzed arylation of benzene with aryl iodides (Scheme 206).[284] The use of KOBu^t was required, and other bases were ineffective. The arylation of toluene and anisole with iodobenzene was also demonstrated, affording *ortho*-, *meta*- and *para*-arylated products. An aryl radical, which was formed via an electron transfer from Cp*Ir(II) species to aryl iodide, was proposed to react with benzene to give the biaryl products. The Cp*Ir(II) species were generated by the reduction of Cp*Ir(III) species with base.

The Ir-catalyzed direct arylation of heteroarenes has also been achieved by Itami and coworkers (Scheme 207).[285] Therefore, a variety of electron-rich heteroarenes were arylated with aryl iodides in the presence of [Ir(cod)PCy$_3$]PF$_6$ and Ag$_2$CO$_3$. The reactions occurred at the α-positions selectively for pyrroles, furans, and thiophenes, whereas 3-arylated products were formed for indoles. Furthermore, the diarylated thiophene was yielded when the reaction was treated with an excess amount of iodobenzene. A diversity of functionalities including bromo group were well tolerated. An electrophilic metalation mechanism was proposed to be responsible for the C–H cleavage.



Scheme 206 Ir-catalyzed arylation of simple arenes with aryl iodides (Fujita and Yamaguchi et al., 2004).



Scheme 207 Ir-catalyzed aryltion of heteroarene (Itami et al., 2009).

3.23.4 Reactions with Organometallic Reagents

Given that the cross-coupling of aryl (pseudo)halides and organometallic reagents serves as a powerful tool for C–C bond formation (primarily for aryl–aryl bond formation), the C–H activation version of this reaction, which substitutes a C–H bond for the C–X bond of the aryl halide, has received considerable interest, and a number of reactions of this type have been reported. Among the developed reactions, Pd has predominantly been the catalyst of choice. However, other metals, including Rh, Ru, Fe, Co, and Ni, have also found success in promoting the cross-coupling of C–H bonds with organometallic reagents. Moreover, while organoboron reagents are the reaction partners in most of the reported Pd-catalyzed reactions, reactions involving other organometallic reagents, such as organotin, organosilane, and organozinc reagents have also been developed.

3.23.4.1 Palladium-Catalyzed Reactions with Organometallic Reagents

Although Pd(0) species is used as the catalyst in cross-coupling reactions of aryl or alkyl (pseudo)halides with organometallic reagents, Pd(II) species in C–H activation would cause big troubles in coupling reactions of C–H bonds with organometallic reagents. Pd(II) tends to react preferentially with organometallic reagents rather than the more inert C–H bonds, which leads to the homocoupling of organometallic reagents and the precipitation of palladium black.

A typical Pd-catalyzed direct coupling of C–H bonds with organometallic reagents commences with Pd-mediated C–H activation. Transmetallation with organometallic reagents and subsequent reductive elimination gives coupling products and Pd(0). Pd(0) needs to be reoxidized to Pd(II) to complete the catalytic cycle (Figure 21).[15]

3.23.4.1.1 Palladium-catalyzed coupling of C(sp^2)-H bonds with organometallic reagents

In 2006, Yu and coworkers reported Pd-catalyzed coupling of C–H bonds with organometallic reagents (Scheme 208).[286] In this remarkable protocol, aromatic C–H bonds were alkylated with alkyltin reagents by using oxazoline as the directing group. To slow down the homocoupling of organotin reagents, the organotin reagent was added batchwise. It is noteworthy that benzoquinone plays crucial roles in these reactions. Benzoquinone may not only be involved in the reoxidation of Pd(0) to Pd(II), but also promote C–H activation.

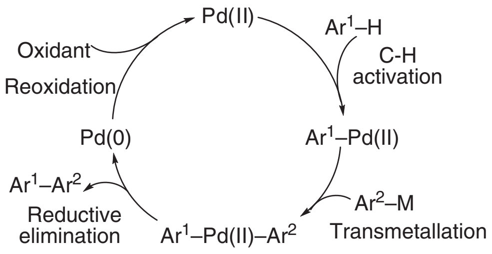
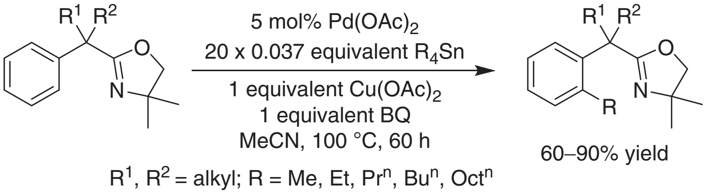
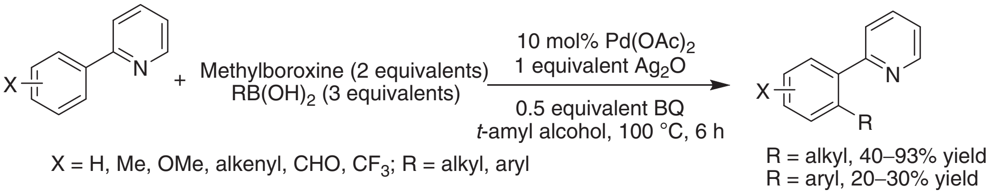


Figure 21 A general mechanism of Pd-catalyzed coupling of C–H bonds with organometallic reagents.



Scheme 208 Pd-catalyzed oxazoline-directed coupling reaction with organotin reagents (Yu et al., 2006).

Although Pd-catalyzed alkylation of C–H bonds with organotin reagents opened an avenue for Pd-catalyzed coupling of C–H bonds with organometallic reagents, the batchwise addition of organotin reagents and their toxicity diminishes this protocol practicality. Organoboron reagents are the most widely used coupling partners because of their ready availability, stability, and functional group tolerance,[287] so it is attractive to develop the coupling reactions of C–H bonds with organoboron reagents. Pd-catalyzed coupling reaction of C–H bonds was also developed by Yu and coworkers (**Scheme 209**).[288] A variety of aromatic rings can be alkylated with alkylboronic acids or methylboroxine in the presence of pyridine as the directing group, and arylboronic acids could also be used in spite of poor yields.

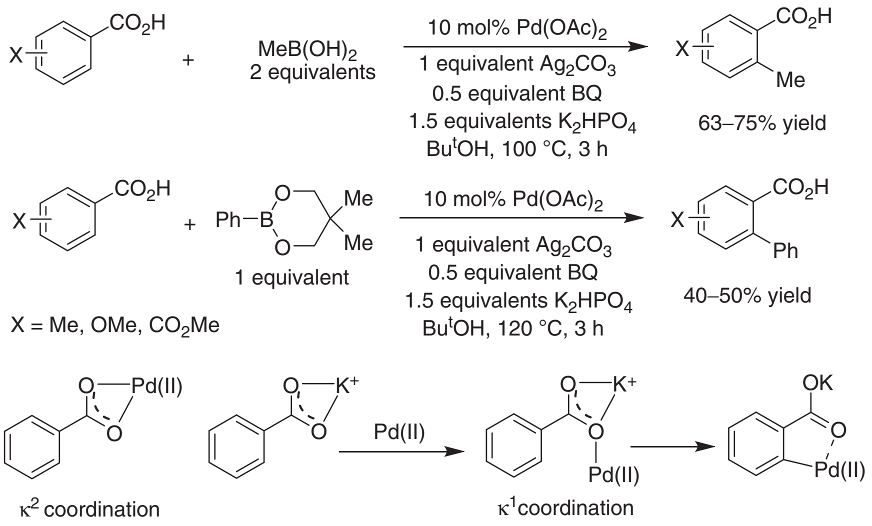


Scheme 209 Pd-catalyzed pyridine-directed coupling reaction of pyridylbenzenes with organoboron reagents (Yu et al., 2006).

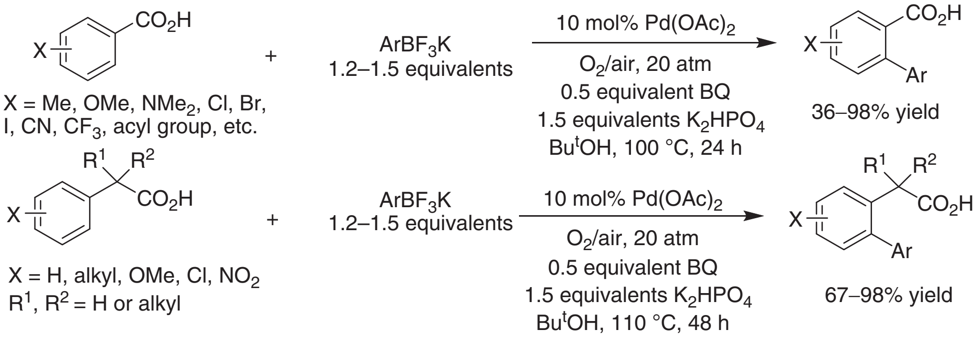
Pyridine and oxazoline are strong coordinating groups for palladium to insert C–H bonds. However, the substrates with such a group have limited applications because of the lack of versatility for further synthetic manipulations and the required pre-installation of oxazolines. Yu and coworkers continued their effort to develop more practical coupling reactions of C–H bonds with organometallic reagents. They achieved carboxyl-directed coupling reaction of C–H bonds with methylboronic acid or arylboronate in 2007 (**Scheme 210**).[235] It should be noted that the presence of a cationic counter ion-promoted Pd insertion into C–H bonds of carboxylic acid substrates because it can prevent Pd from coordinating with the carboxyl group in a κ^2 fashion, which keeps Pd far away from C–H bonds and makes C–H insertion impossible.

The versatility and practicality of the above coupling protocol, which suffered from narrow substrate scope and poor yields, was then substantially improved by using potassium aryltrifluoroborates as the coupling partners (**Scheme 211**).[289] Remarkably, inexpensive and environmentally benign air or O_2 was used as the oxidant instead of expensive Ag_2CO_3 in this new protocol. A wide range of benzoic acids including those containing electron-withdrawing groups were tolerated under these new conditions. This protocol was also applicable to the coupling of C–H bonds of phenylacetic acids, which is synthetically useful because the broadly useful lithiation/iodination/arylation sequence is incompatible with this type of substrates because of the presence of acidic α-hydrogen atom.

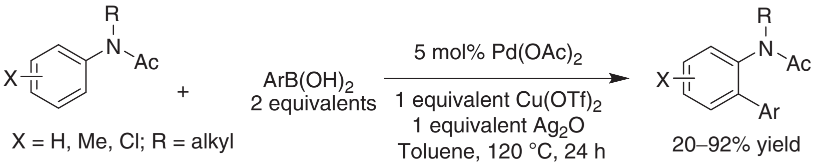
Shi and coworkers reported Pd-catalyzed arylation of C–H bonds of anilides with arylboronic acids by using *N*-alkyl acetamino group as the directing group (**Scheme 212**).[290] The coupling of C–H bonds of anilides with trialkyloxyarylsilanes has also been developed (**Scheme 213**).[291] The unprotected acetamino group had to be used as the directing group as compared *N*-alkylated acetamino group in the coupling with arylboronic acids. Electron-withdrawing groups on the phenyl ring of the anilides decreased the efficiency of the coupling reactions.



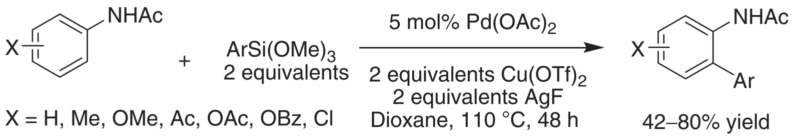
Scheme 210 Pd-catalyzed carboxyl-directed coupling reaction of benzoic acids with organoboron reagents (Yu et al., 2007).



Scheme 211 Pd-catalyzed carboxyl-directed coupling reaction with organoboron reagents (Yu et al., 2008).



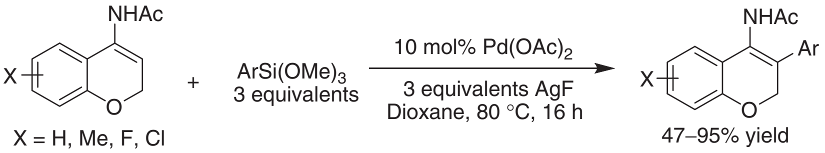
Scheme 212 Pd-catalyzed acetamide-directed coupling reaction of acetanilides with boronic acids (Shi et al., 2007).



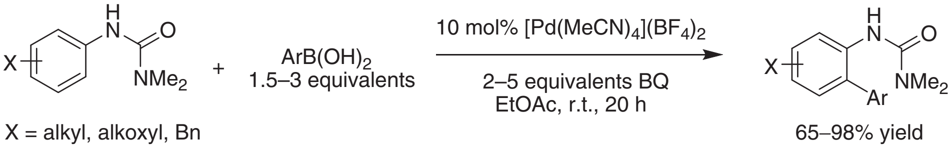
Scheme 213 Pd-catalyzed acetamide-directed coupling reaction of acetanilides with organosilyl reagents (Shi et al., 2007).

The Pd-catalyzed direct arylation of vinylic C–H bonds has also been reported by Loh and coworkers (Scheme 214).[292] Therefore, the vinylic C–H bonds of cyclic enamides were arylated by reacting with trialkyloxyarylsilanes. Various functional groups including chloro and bromo were tolerated to afford coupling products in moderate to excellent yields.

Most of Pd-catalyzed C–H coupling reactions have to rely on high temperatures, which severely limits their potential for synthetic applications. Intriguingly, Lipshutz and coworkers reported Pd-catalyzed coupling reactions of aryl C–H bonds with arylboronic acids at room temperature (Scheme 215).[293] This approach employed cationic palladium ($[Pd(MeCN)_4](BF_4)_2$) as



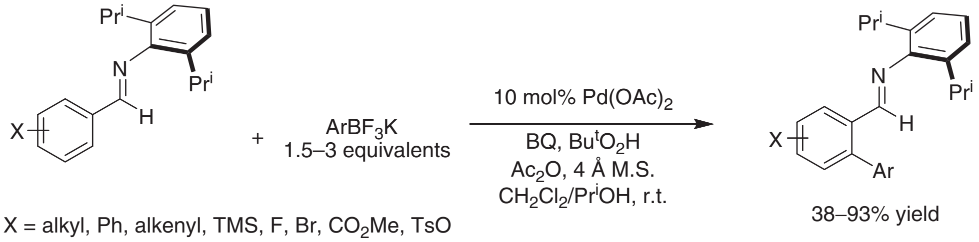
Scheme 214 Pd-catalyzed vinyl C–H coupling reaction of cyclic enamides with organosilicon reagents (Loh et al., 2009).



Scheme 215 Cationic Pd(II)–catalyzed urea-directed coupling reaction of arylureas with arylboronic acids at room temperature (Lipshutz et al., 2010).

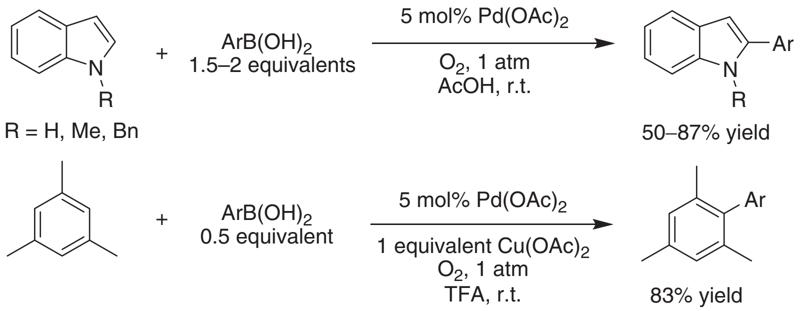
catalyst and dimethyl urea as directing group, which can be removed by hydrolysis to produce the corresponding amine quantitatively. A wide range of arylboronic acids were reactive under these mild conditions.

Another Pd-catalyzed coupling reaction of C–H bonds at room temperature was reported by Gaunt and coworkers (Scheme 216).[294] It is noteworthy that an electron-withdrawing imine directing group was used in this protocol, and the low temperature enabled arylation of benzaldimines containing sensitive functional groups.



Scheme 216 Pd-catalyzed imine-directed coupling reaction of electron-deficient arenes with organoboron reagents at room temperature (Gaunt et al., 2011).

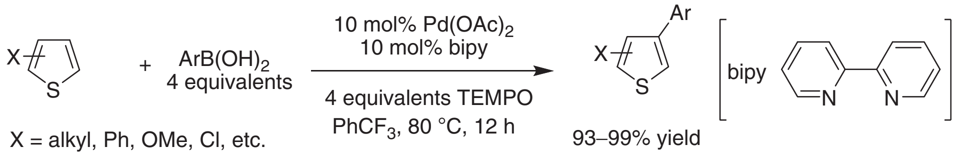
Although all the above C–H coupling reactions rely on the use of directing groups, nondirected coupling reactions of C–H bonds with organometallic reagents have also been achieved. Thus, electron-rich arenes and heteroarenes could be arylated via coupling of their C–H bonds with arylboronic acids (Scheme 217).[295] In the couplings of arenes, $Cu(OAc)_2$ and 1 atm O_2 were employed as the oxidants, and the sole O_2 was able to oxidize Pd(0) to Pd(II) in the coupling reactions of heteroarenes. In addition, the coupling of indoles selectively occurred at 2-position.



Scheme 217 Pd-catalyzed coupling reaction of electron–rich arenes with arylboronic acids (Shi et al. 2008).

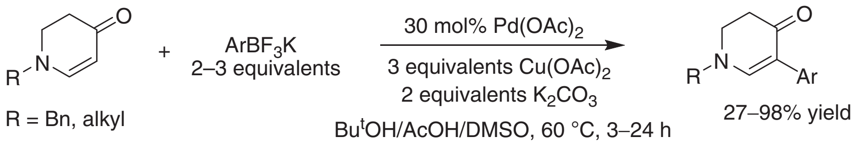
In Shi's approach, the coupling reactions of all of the heteroarenes, including indole, pyrrole, 2,3-benzofuran, and 2,3-benzothiophene, occurred at 2-position regioselectively. Conversely, Itami and Studer and coworkers described the Pd-catalyzed

C-4 selective C–H arylation of thiophenes and thiozoles with arylboronic acids (**Scheme 218**),[296] which was also contrary to the C–H arylation of thiophenes with haloarenes occurring preferentially at the positions α to the sulfur atom (Section 3.23.3.1.1). The use of 2,2′-bipyridine as the ligand was necessary for the reactions to occur. Mechanistic studies revealed that the presence of excess boronic acids was necessary for the C-4 selectivities. The authors proposed that the C-4 selectivities arose from aryl group migration to C-4-position after the initial C–H insertion at the C-5 position. Intriguingly, the authors also proposed that the transmetalation of [(bipy)Pd(OAc)$_2$] with ArB(OH)$_2$ occurred before the C–H insertion of palladium, which is different from the widely proposed mechanism involving the C–H activation of Pd(OAc)$_2$.



Scheme 218 Pd-catalyzed C4-coupling reaction of thiophenes/thiazoles with arylboronic acids (Itami et al., 2011).

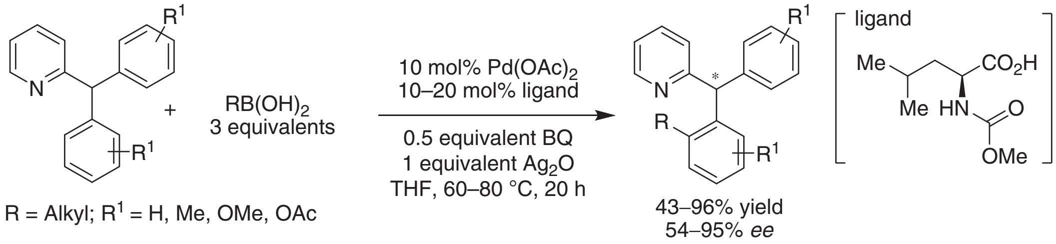
Interestingly, direct coupling reactions of enaminones have also been demonstrated by Georg and coworkers (**Scheme 219**).[297] *N*-protected enaminones with electron-pushing protecting groups could be arylated by the coupling reactions of their C–H bonds with aryltrifluoroborates, and a wide variety of aryltrifluoroborates were compatible in these coupling reactions. Notably, this approach provides a direct method for the construction of 3-arylpiperidine scaffolds, a privileged structure and prevalent motif in many natural products.



Scheme 219 Pd-catalyzed coupling reaction of enaminones with aryltrifluoroborates (Georg et al., 2008).

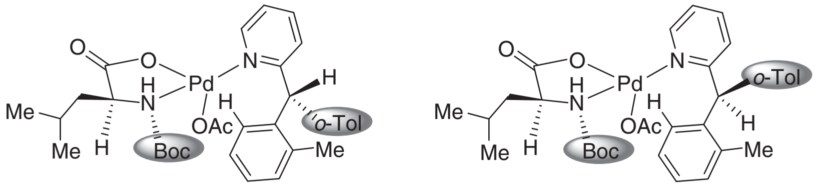
It should be mentioned that only electron-rich substrates have been demonstrated to undergo Pd-catalyzed C–H coupling reactions with organometallic reagents in the above approaches, which indicates that the C–H activation of these coupling reactions may involve an electrophilic process. Continued efforts are expected to study the direct coupling reactions of unactivated arenes, especially electron-deficient ones. Furthermore, as other C–H functionalizations of monosubstituted benzenes, the regioselective arylation with organometallic reagents remains to be a challenge.

As mentioned in Section 3.23.2.1.1.2, Yu and coworkers developed Pd-catalyzed C–H activation by successfully desymmetrizing prochiral C–H bonds on geminal groups (**Scheme 220**).[298] Therefore, one of the C–H bonds on the two geminal aryl groups was enantioselectively alkylated by coupling with alkylboronic acids in the presence of a pyridine as the directing group. Remarkably, cheap and readily prepared monoprotected amino acids were used as the chiral ligand, and a wide range of amino acids were effective for these enantioselective C–H coupling reaction.



Scheme 220 Enantioselective C(sp^2)–H coupling with alkylboronic acids (Yu et al., 2008).

Based on the mechanistic studies, Yu and coworkers proposed a stereomodel for the asymmetric C–H insertion (**Figure 22**).[298] The enantioselective C–H insertion is caused by the steric interaction between the protecting group on the chiral ligand and the aryl group of the substrate. It should be noted that the chirality on the α carbon of the ligand is relayed to the nitrogen atom attached to the palladium center, which is crucial for the chiral recognition.



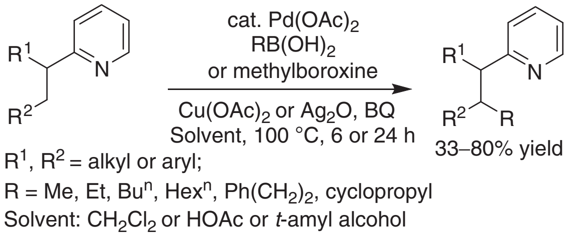
Disfavored

Favored

Figure 22 A simplified stereomodel for Yu's asymmetric C–H insertion.

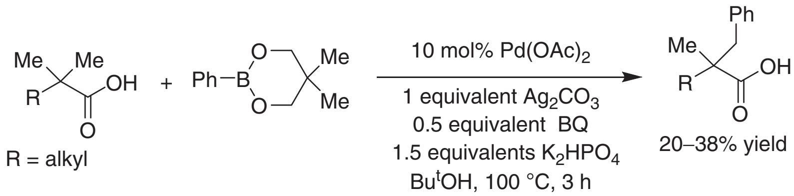
3.23.4.1.2 Palladium-catalyzed coupling of C(sp^3)-H bonds with organometallic reagents

Although impressive progress has been made in the coupling reaction of C(sp^3)-H bond with halides, efforts to couple C(sp^3)-H with organometallic reagents have met numerous problems. On the basis of the progress in the coupling reactions of C(sp^2)-H bond, Yu and coworkers have also achieved successes in the coupling reactions of C(sp^3)-H bond with organometallic reagents. Thus, they developed the first protocol for Pd-catalyzed alkylations of C(sp^3)-H bonds β to pyridine with either methylboroxine or alkylboronic acids (Scheme 221).[288]

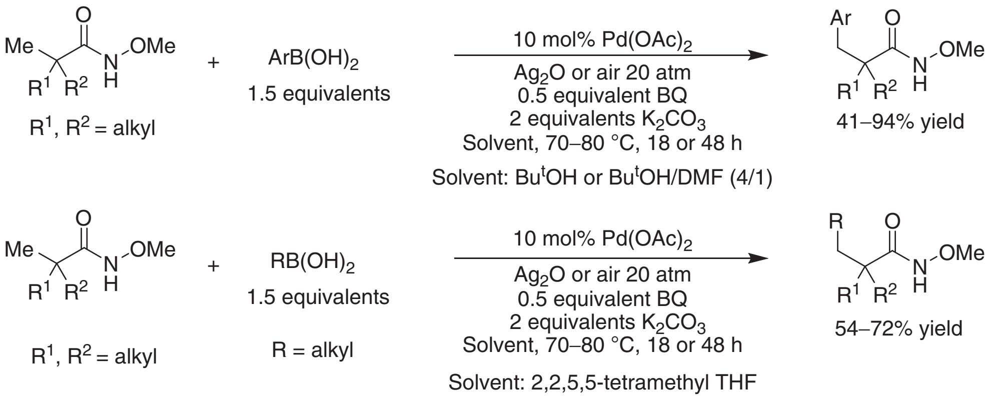


Scheme 221 Pd-catalyzed pyridine-directed coupling reaction of C(sp^3)–H bond with organoboron reagents (Yu et al., 2006).

The coupling of simple aliphatic carboxylic acids with organoboron reagents was also observed (Scheme 222).[235] However, this approach suffered from poor yields and limited substrate scope. Only arylboronic esters and methylboronic acid were reactive under the reaction conditions, likely because of undesired homocoupling or β-hydride elimination from the alkyl fragments of the sp^3 boronic acids. Yu and coworkers successfully solved these problems by substituting the CONHOMe group with the CO_2H group, because the CONHOMe group may exhibit similar but stronger binding to palladium (Scheme 223).[299] Thus, β-C(sp^3)-H



Scheme 222 Pd-catalyzed carboxyl-directed coupling reaction of C(sp^3)–H bond with organoboron reagents (Yu et al., 2007).



Scheme 223 Pd-catalyzed CONHOMe-directed coupling reaction of C(sp^3)–H bond with aryl/alkylboronic acids (Yu et al., 2008).

bonds of O-methyl hydroxamic acids can couple with a wide range of aryl/alkylboronic acids. Remarkably, in these coupling reactions, air could also be used as the oxidant instead of expensive silver reagents. Furthermore, the CONHOMe groups can be readily converted into esters and amides or reduced to alkane fragments, making this approach synthetically useful.

The utility of this coupling reaction was further demonstrated by the derivatization of dehydroabietic acid (Figure 23),[299] a natural product identified as an efficient BK channel opener. Typically, it is difficult to diversify such structures because of the absence of reactive chemical functional groups aside from the carboxylic acid moiety. The methyl C–H bond could be readily alkylated with a range of alkylboronic acids by converting the carboxylic acid into the hydroxamic acid as the directing group, affording a novel class of analogs that may display improved pharmacokinetic properties.

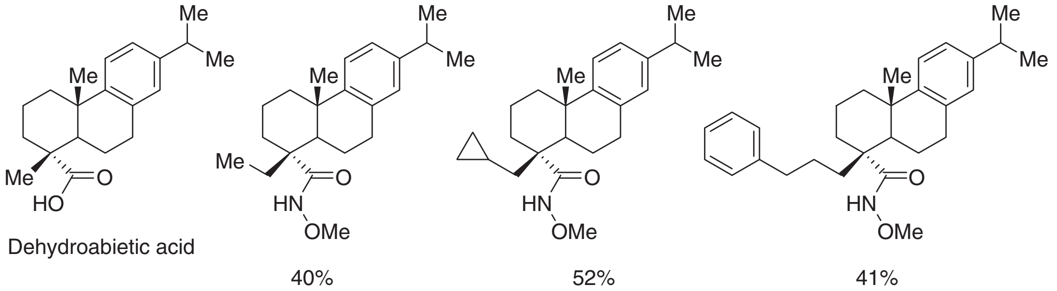
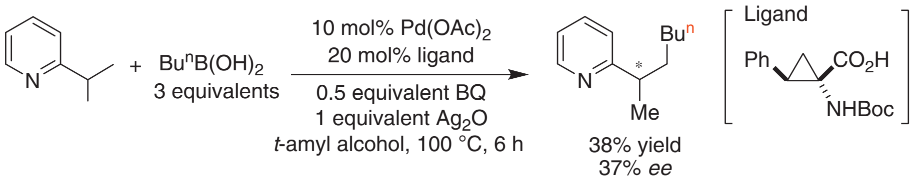


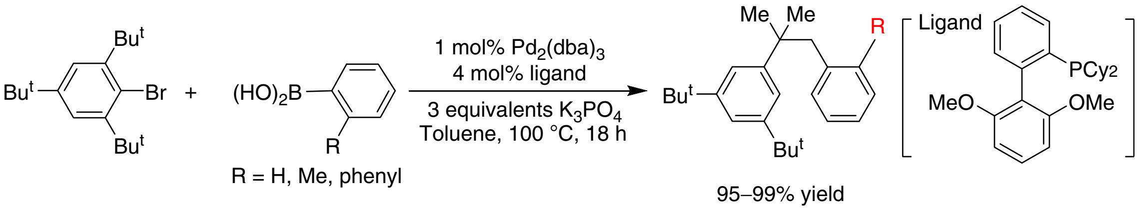
Figure 23 Functionalization of dehydroabietic acid via C(sp^3)–H activation.

Notably, Yu and coworker also extended the protocol of enantioselective C(sp^2)-H activation to the direct alkylation of C(sp^3)-H bond (Scheme 224).[298] Intriguingly, the use of a rigid ligand gave the highest enantioselectivity (37% *ee*), whereas other monoprotected amino acid ligands yielded poorer enantioselectivities. Although the enantioselectivities obtained so far are still poor, it opened an avenue for enantioselective C(sp^3)-H functionalization. Furthermore, the sensitive response of enantioselectivity to the ligand structures suggested that there were great potentials of improving enantioselectivity by tuning the existing ligand structures or designing entirely new ligands.



Scheme 224 Enantioselective C(sp^3)–H coupling reaction with alkylboronic acid (Yu et al., 2008).

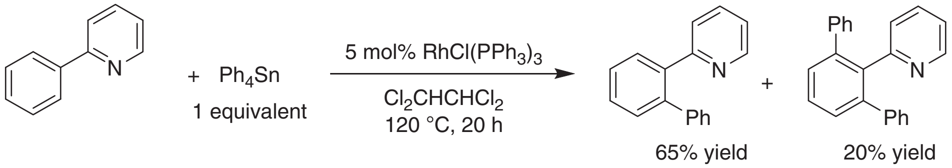
During the investigation of Suzuki–Miyaura coupling reaction of sterically hindered aryl bromides, Buchwald observed the products resulting from the arylation of C(sp^3)–H bonds with phenylboronic acids, instead of the desired biaryls (Scheme 225).[300] Therefore, in the presence of $Pd_2(dba)_3$ and the bulky ligand, the reaction of 2,4,6-tri-*tert*-butylbromobenzene with phenylboronic acid yielded the α,α-dimethyl-β-aryl hydrostyrene derivatives. The proposed mechanism involved: the oxidative addition of the aryl bromide to Pd(0), cyclometalation by the formed Pd(II) species via abstraction of one of the hydrogen atoms from the *tert*-butyl group, selective protonation of the C(sp^3)-Pd bond to afford the alkyl Pd(II) species, the subsequent transmetalation with the boronic acid, and the reductive elimination to form the C(sp^3)–C(sp^2) bond and release Pd(0).



Scheme 225 Pd-catalyzed arylation of C(sp^3)-H bonds (Buchwald et al., 2005).

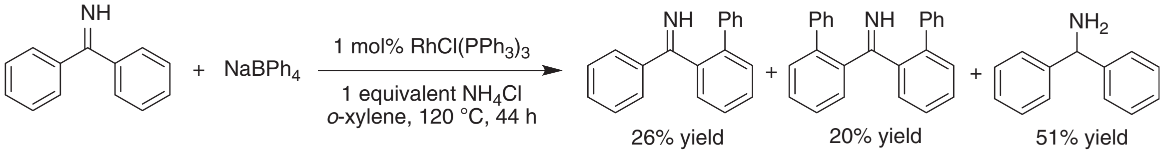
3.23.4.2 Rhodium-Catalyzed Reactions with Organometallic Reagents

Although in total more examples using palladium have been reported, rhodium was the metal employed in the first successful cross-coupling reaction between aromatic C–H bonds and organometallic reagents. In 1998, Oi and coworkers disclosed $RhCl(PPh_3)_3$-catalyzed arylation of 2-phenylpyridine with tetraphenylstannane in 1,1,2,2-tetrachloroethane (Scheme 226).[301] The reaction afforded mono- and diarylated products, whereas only monophenylated products were observed for the other pyridine-substituted arene substrates. The use of 1,1,2,2-tetrachloroethane as the solvent was crucial for the transformation. The possible mechanism involved the directed oxidative addition of the low-valent Rh complex to the *ortho*-C–H bond of the phenyl ring followed by phenylation with tetraphenylstannane.



Scheme 226 Rh-catalyzed pyridine-directed arylation of 2-phenylpyridine with tetraphenylstannane (Oi et al., 1998).

The use of less toxic organoboron reagents as the coupling partners was achieved by the Miura, Satoh and coworkers (Scheme 227).[302] By using the same catalyst, diphenylmethanimine underwent arylation with sodium tetraphenylborate in the presence of ammonium chloride. Unfortunately, the reaction gave a relatively low yield because of the formation of diphenylmethanamine. Mechanistically, the C–H bond was proposed to be cleaved by an *in situ* generated phenylrhodium(I) species, forming the rhodacycle intermediate. The subsequent reductive elimination afforded the arylated products and released rhodium hydride, which consumed another molecule of diphenylmethanimine to form diphenylmethanimine and to regenerate Rh(I)Cl (Figure 24).[302]



Scheme 227 Rh-catalyzed imine-directed arylation with tetraphenylborate (Miura and Satoh et al., 2005).

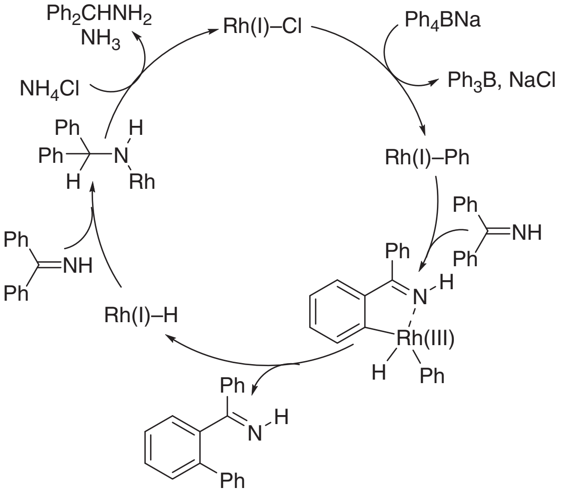
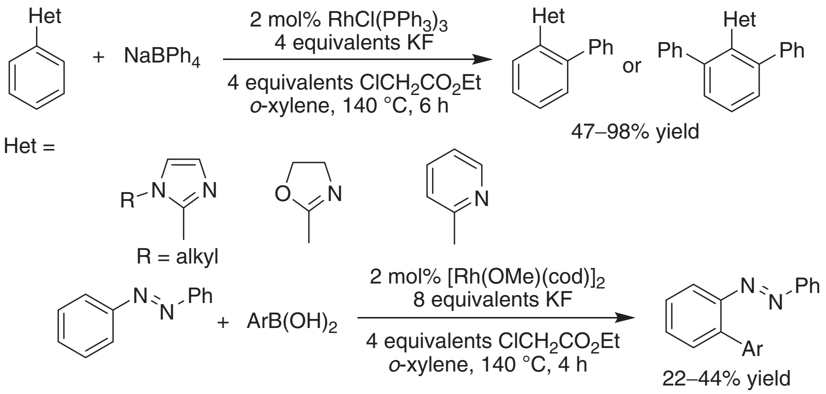


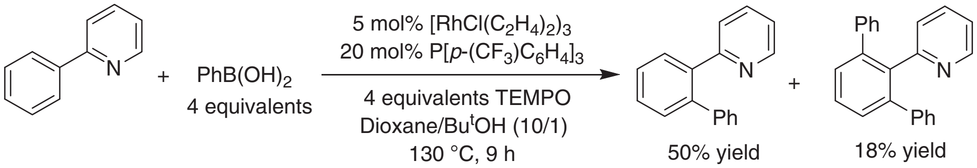
Figure 24 Proposed mechanism of Rh-catalyzed arylation with tetraphenylborate.

The yields were improved by the addition of ethyl chloroacetate and potassium fluoride as a hydrogen acceptor and a promoter, respectively (Scheme 228).[303] A wide range of heteroarenes, including imidazoles, oxazolines, and pyridines, were found to act as effective directing groups for the arylation. Notably, boronic acids were used as the arylating reagents in the arylation of azobenzene. The reactions were rendered catalytic by the oxidative addition of ethyl chloroacetate to the formed rhodium hydride in reaction and the subsequent reductive elimination.



Scheme 228 Rh-catalyzed-directed arylation with organoboron reagents (Miura and Satoh et al., 2008).

Studer and coworkers reported another efficient protocol for Rh-catalyzed C–H arylation with boronic acids (Scheme 229).[304] The catalytic system consisted of $[RhCl(C_2H_4)_2]_2$ and $P[p\text{-}(CF_3)C_6H_4]_3$, and TEMPO was used as the terminal oxidant. Various boronic acids were found to be effective arylating reagents. A 2-pyridyl group and an imine functional group served as *ortho*-directing groups. In addition, the direct arylation of thiophenes also proceeded effectively under the reaction conditions. A Rh(III)/Rh(I) catalysis was proposed to be operative for this transformation. Therefore, the transmetalation of aryl boronic acids with Rh(I) catalyst formed aryl rhodium(I) species. The subsequent oxidation with TEMPO gave rise to Rh(III) species, which cleaved C–H bonds to afford the key cyclometalated complex. The reductive elimination afforded the final arylated products and regenerated Rh(I) catalyst (Figure 25).[304]



Scheme 229 Rh-catalyzed pyridine-directed arylation of 2-phenylpyridine with boronic acids (Studer et al., 2008).

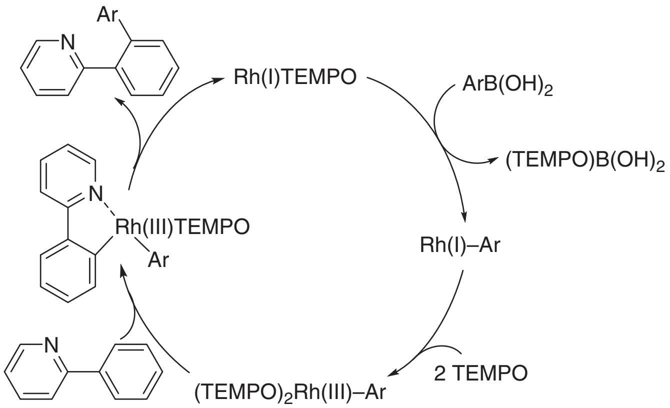
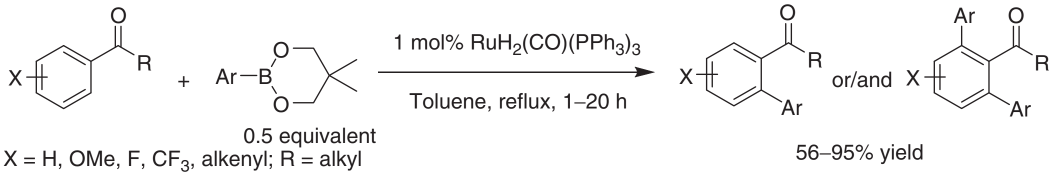


Figure 25 Proposed mechanism of Rh-catalyzed arylation with boronic acids.

3.23.4.3 Ruthenium-Catalyzed Reactions with Organometallic Reagents

The first Ru-catalyzed C–H arylation with organometallic compounds was achieved by Kakiuchi and coworkers in 2003 (Scheme 230).[305] In the presence of the catalyst $RuH_2(CO)(PPh_3)_3$, aromatic ketones were *ortho*-arylated with a variety of arylboronates. Diarylated products were formed preferentially for some of the starting ketones. The use of two equivalents of aryl ketones was required to achieve high yields, and a nearly equivalent amount of alcohol derived from the reduction of the starting



Scheme 230 Ru-catalyzed carbonyl-directed arylation with arylboronates (Kakiuchi et al., 2003).

ketone was obtained as a byproduct. The proposed mechanism suggested that the C–H bond was cleaved by Ru(0) complex to give the *ortho*-metalated intermediate. The formed Rh–H bond added to the ketone carbonyl group to produce an (alkoxy)-ruthenium intermediate, which accounted for the consumption of one equivalent of the aryl ketones. The subsequent transmetalation with phenylboronate and reductive elimination afforded the final arylation products and regenerate the active Ru(0) catalyst (**Figure 26**).[305]

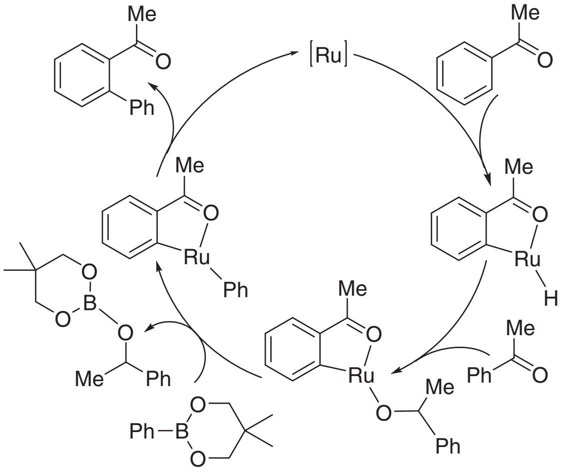
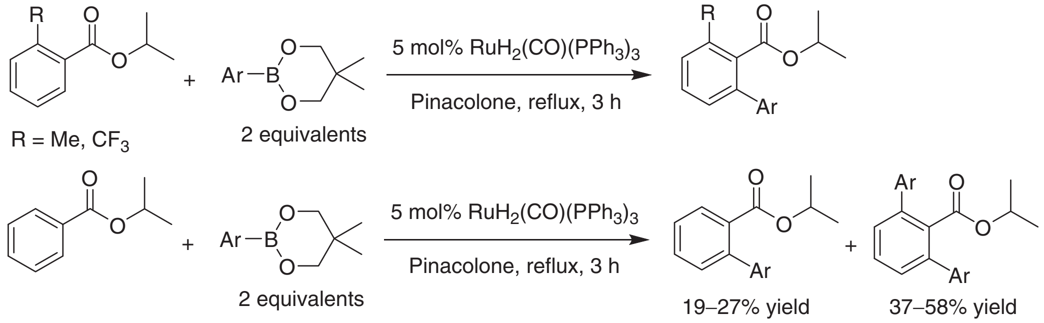


Figure 26 Proposed mechanism of Ru-catalyzed arylation with organoboron reagents.

A major drawback for the above novel arylation method is that one equivalent of starting ketones was consumed in the reaction. Remarkably, this problem was elegantly addressed by the addition of aliphatic ketones as a scavenger.[306] Therefore, the use of pinacolone as the solvent dramatically suppressed the reduction of the ketone starting material, and as a result, high yields were obtained. The arylation protocol has been further optimized. For instance, the authors found that the use of styrene as an additive led to selective formation of monoarylated product using acetophenone starting materials bearing two potentially reactive *ortho*-C–H bonds.[307]

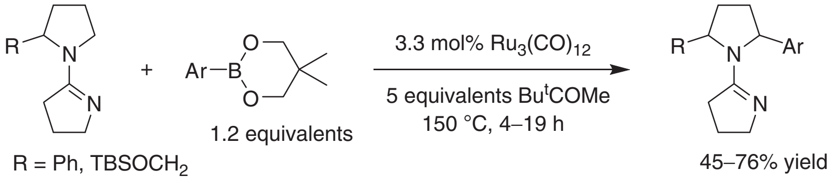
The method was successfully extended to the arylation of anthraquinone[308] and perylene bisimide (PBI).[309] Tetraarylated products were produced for both of the substrates, which set a stage for the efficient multiarylation of complex arenes.

The arylation protocol also proved applicable to the arylation of benzoates (**Scheme 231**).[310] Isopropyl esters were found to give particularly high yields, and the introduction of electron-withdrawing CF_3 group also increased the product yield.



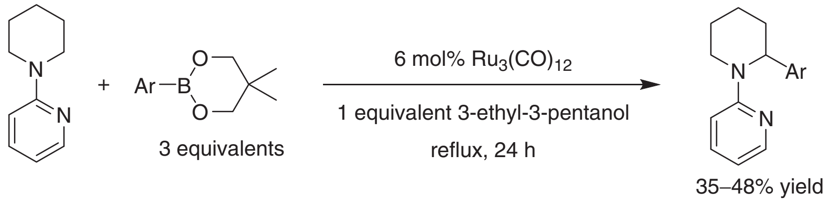
Scheme 231 Ru-catalyzed ester-directed arylation of benzoates with arylboronates (Kakiuchi et al., 2010).

Inspired by the above work, Sames and coworkers developed Ru-catalyzed C(sp^3)-H arylation with arylboronates (Scheme 232).[311] Thus, in the presence of $Ru_3(CO)_{12}$ and Bu^tCOMe, 2-substituted pyrrolidines bearing cyclic imine-directing groups were α-arylated with a wide range of arylboronates. The reactions gave mixtures of *trans*/*cis* diastereomers with ratios ranging from 3:1 to 6:1. The arylation of piperidines was also demonstrated, and pyridine and pyrimidine were also found to be effective directing groups. The mechanism was analogous to that proposed in the above $RuH_2(CO)(PPh_3)_3$-promoted C(sp^2)-H arylation, which involved the C(sp^3)-H cleavage by the oxidative addition to a Ru(0) species and pinacolone as a scavenger of α-hydrogens of the pyrrolidines.



Scheme 232 Ru-catalyzed imine-directed C(sp^3)-H arylation with arylboronates (Sames et al., 2006).

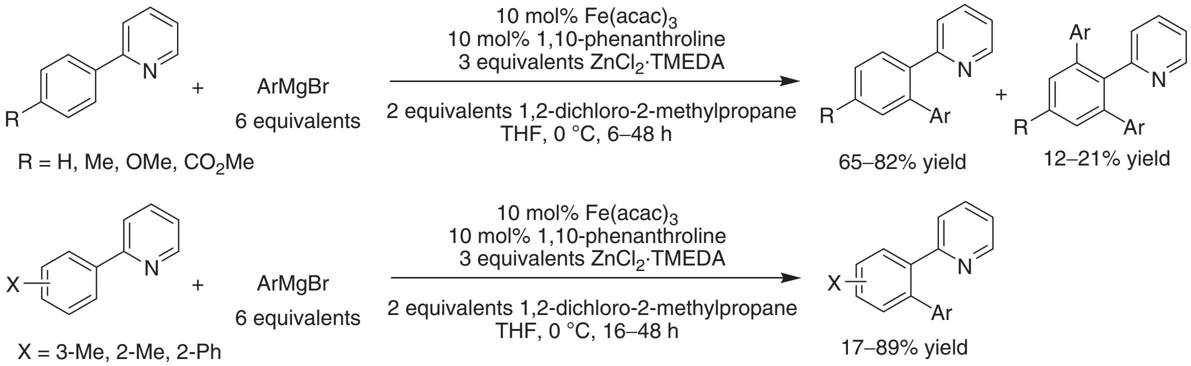
In Sames' work, the arylation of piperdines gave moderate yields because of their chair conformation. Maes and coworkers demonstrated that the yields could be improved by using 3-ethyl-3-pentanol in place of pinacolone as the scavenger (Scheme 233).[312] The idea of using 3-ethyl-3-pentanol was based on the assumption that pinacolborane, which is generated during transmetalation of the [Ru(II)-H] intermediate with the arylboronate, could poison the catalyst and needed to be sequestered to achieve high yields. As such, the role of 3-ethyl-3-pentanol was to scavenge the pinacolborane species, with formation of the corresponding 3-ethyl-3-pentylborate and H_2. The hypothesis was supported by the fact that the conversion could be further increased by carrying out the reaction in an open vial under reflux conditions.



Scheme 233 Ru-catalyzed pyridine-directed C(sp^3)-H arylation with arylboronates (Maes et al., 2010).

3.23.4.4 Iron, Cobalt, and Nickel-Catalyzed Reactions with Organometallic Reagents

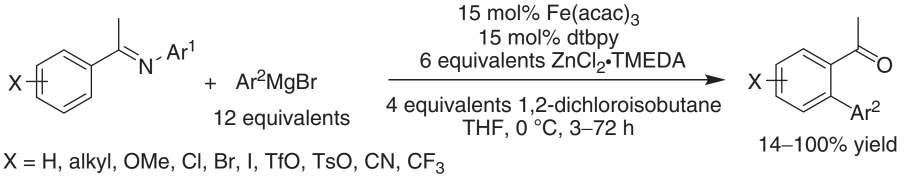
In 2008, the Nakamura and coworkers disclosed Fe-catalyzed C–H arylation with arylzinc reagents under the conditions shown in Scheme 234.[313] The combination of the employed reagents was important for the success of the reactions. The arylzinc reagents were generated *in situ* from the corresponding Grignard reagents and zinc chloride. The use of an excess amount of arylzinc reagents was required. Although 1st equivalent was required for the desired arylation reaction, a 2nd equivalent was required to remove the hydrogen. In addition, a certain amount of the phenylzinc reagent was also consumed because of the biphenyl



Scheme 234 Fe-catalyzed pyridine-directed arylation of pyridylarenes with arylzinc reagents (Nakamura et al., 2008).

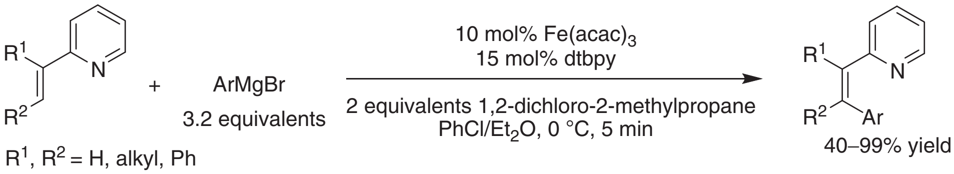
forming side reaction. The reaction might involve a redox cycle of iron with the dichloride acting as an electron acceptor. It is remarkable that the reactions proceeded smoothly at 0 °, whereas the majority of C–H functionalization reactions were run at high temperature. In addition to pyridine, pyrimidine, and pyrazole also acted as the effective directing groups for this transformation.

This method was also successfully extended to the arylation of aryl imines (**Scheme 235**).[314] 4,4′-Di-*tert*-butyl-2,2′-bipyridine (dtbpy) was found to be superior to 1,10-phenanthroline. Although the imines derived from acetophenones gave the sole monoarylated products, the aldehyde-derived imines delivered a mixture of mono- and diarylated products. The resulted arylated imines were converted into the corresponding ketones via *in situ* hydrolysis. Notably, this reaction showed an excellent tolerance for functional groups. A wide range of substituents of aryl imines, including iodide, bromide, chloride, sulfonate, and triflate, were well tolerated in the reaction.



Scheme 235 Fe-catalyzed imine-directed arylation with arylzinc reagents (Nakamura et al., 2009).

Subsequently, the Nakamura and coworkers discovered the C–H arylation with Grignard reagents (**Scheme 236**).[315] When the authors tried to apply the above method to the arylation of vinylic C–H bonds, no desired products were obtained under the identical conditions. However, the reactions occurred effectively after the removal of zinc chloride and a further condition optimization. Therefore, a variety of olefinic C–H bonds were arylated with Grignard reagents, with pyridine as the directing group. The arylation reaction took place only at the 2-position of the olefin, notably, in a *syn*-specific manner. The preliminary mechanistic studies suggested that a five-membered metallacycle was formed via pyridine-directed C–H activation. Subsequently, the intermediate underwent reductive elimination, perhaps after interaction with 1,2-dichloro-2-methylpropane, to afford the *syn*-substituted olefins (**Figure 27**).[315]



Scheme 236 Fe-catalyzed pyridine-directed arylation of vinylic C–H bonds with Grignard reagents (Nakamura et al., 2011).

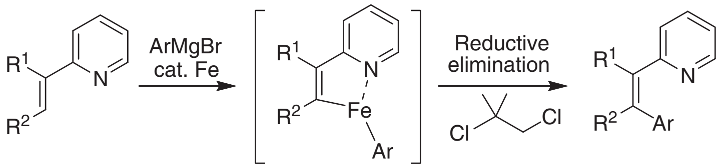
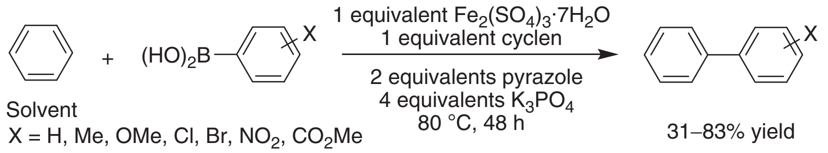


Figure 27 Proposed mechanism of Fe-catalyzed arylation of vinylic C–H bonds with Grignard reagents.

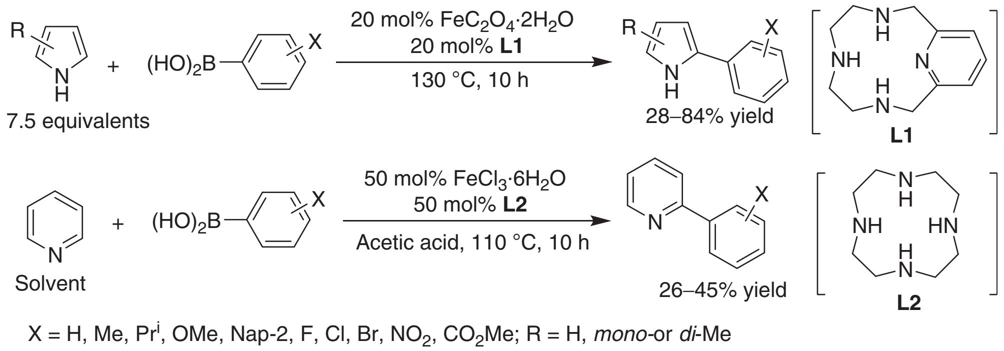
Notably, boronic acids were also successfully developed as the arylation reagents in the Fe-promoted C–H arylation. In 2008, the Yu and coworkers disclosed the $Fe_2(SO_4)_3$•7 H_2O/cyclen-mediated arylation of benzene with arylboronic acids in the presence of pyrazole and tripotassium phosphate (**Scheme 237**).[316] A wide range of substituents of arylboronic acids were compatible including chloro and bromo in the reaction. A diversity of substituted arenes such as bromobenzene and chlorobenzene were also found to be reactive, affording mixtures of regioisomers. In the cases of monosubstituted benzenes, *ortho*-, *meta*-, and *para*-arylated products were generated.

Subsequently, Yu and coworkers described analogous protocols for the C–H arylation of nitrogen-containing heteroarenes (**Scheme 238**).[317] The arylation of both electron-rich pyrroles and electron-deficient pyridine were demonstrated. In the arylation of pyrroles, the reactions occurred at the 2-positions selectively. For pyridine, 2-arylated product was also formed predominantly, but 3- and 4-arylation was also observed. Preliminary mechanistic studies suggested that an oxoiron species derived from oxygen was the catalytically active species, which cleaved C–H bonds via electrophilic metalation with the assistance of the heteroatoms.

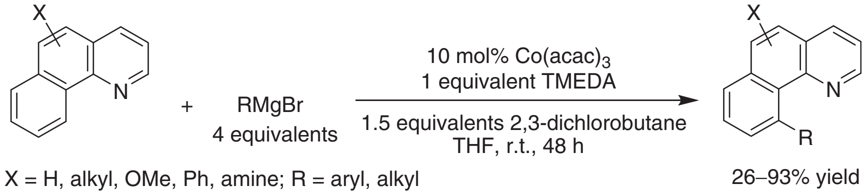
Shi and coworkers demonstrated that cobalt was able to enable C–H arylation/alkylation with Grignard reagents catalytically under the similar conditions to iron (**Scheme 239**).[318] Therefore, benzo[*h*]quinolines and 2-phenylpyridine reacted with a wide



Scheme 237 Fe-catalyzed arylation of benzene with boronic acids (Yu et al., 2008).



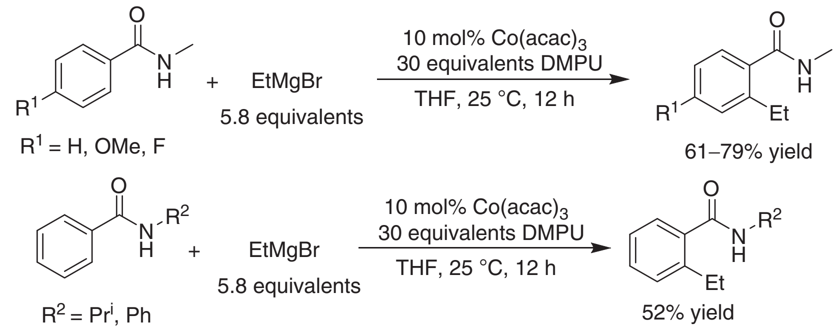
Scheme 238 Fe-catalyzed C2-arylation of pyrroles/pyridine with boronic acids (Yu et al., 2010).



Scheme 239 Co-catalyzed pyridine-directed arylation/alkylation with Grignard reagents (Shi et al., 2011).

range of aryl/alkyl Grignard reagents in the presence of Co(acac)$_3$, TMEDA, and 2,3-dichlorobutane, affording the corresponding arylated/alkylated products. Based on the mechanism experiments, the authors ruled out a radical mechanism, and proposed that the C–H bonds were cleaved via the oxidative addition of the aryl/alkylcobalt species to the C–H bonds. 2,3-dichlorobutane acted as an oxidant in a similar manner to the dichloroalkanes employed in the Fe-catalyzed C–H arylation reactions, and was reduced to 2-butene.

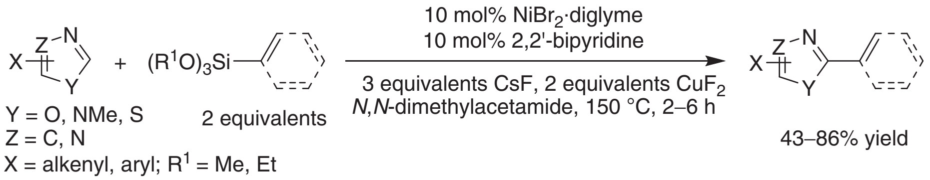
Subsequently, Nakamura and coworkers reported a different protocol for Co-catalyzed C–H alkylation of benzamides with Grignard reagents (Scheme 240).[319] The use of the ligand DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone) was crucial for the success of this new method. It is noted that dichloroalkanes were not used and air acted as the sole oxidant. For the alkylation of *N*-methylbenzamides, dialkylated products were produced preferentially. However, the dialkylation could be suppressed by the choice of a suitable organic substituent on the amide nitrogen atom, such as phenyl and isopropyl groups.



Scheme 240 Co-catalyzed amide-directed alkylation of benzamides with Grignard reagents (Nakamura et al., 2011).

Moreover, benzo[*h*]quinolines and 2-phenylpyridines were also ethylated under the similar conditions, largely affording monoethylated products.

Nickel also proved applicable to promote the C–H arylation with organometallic reagents. In 2010, Miura and coworkers disclosed nickel-catalyzed arylation of heteroarenes with organosilicon reagents in the presence of $NiBr_2$•diglyme, 2,2′-bipyridine, CsF, and CuF_2 (**Scheme 241**).[320] An array of heteroarenes such as 5-aryloxazole, benzothiazole, benzimidazole, and 1,3,4-oxadiazole underwent the arylation effectively. Alkenylation with alkenylsilane also occurred smoothly under the conditions, with the concomitant minor *E*/*Z* isomerization. The proposed mechanism involved the C–H cleavage by Ni(II) with the assistance of CsF, the transmetalation with organosilicon reagents, and the subsequent reductive elimination to afford the coupling products and Ni(0) species. The reoxidation of the formed Ni(0) species with CuF_2 regenerated the active Ni(II) catalyst to complete the catalytic cycle.



Scheme 241 Ni-catalyzed coupling reaction of heteroarenes with organosilicon reagents (Miura et al., 2010).

3.23.5 Reactions with C–H Bonds

Although the reactions of C–H bonds with (pseudo)halides and organometallic reagents have great advantages over traditional cross-coupling reactions, they are not ‘perfect’ considering that one of the reaction partners needs to be preactivated and unwanted byproducts are still generated in the reactions. As illustrated in many of the reactions in this chapter, [M–R] species, obtained from the oxidative addition of halides to transition metals or other sources, can react with C–H bonds. However, it has also been demonstrated that transition-metal-promoted C–H activation may form the C–M intermediates with the similar reactivity. As such, it is quite obvious to envision that the C–M intermediates produced via C–H activation could react with a second C–H bonds, providing dehydrogenative coupling products. Such a reaction involving the coupling of two C–H bonds provides a novel C–C bond forming strategy through double C–H activation. The coupling of two C–H bonds would obviate the need for any preactivation of substrates and produce a minimum of byproducts, so that it should count as ‘perfect reactions.’ However, this attractive reaction is very challenging, because a new problem regarding chemoselectivity arises, in addition to those existing in the C–H functionalization reactions with one preactivated substrate. The C–M intermediate generated in the first C–H activation may react with both of the coupling partners to gave a mixture homocoupling and heterocoupling products. Therefore, for a successful dehydrogenative coupling reaction, the desired coupling must occur selectively. For synthetically more useful reactions, the catalyst must react with one substrate selectively first and then invert its reactivity to react with the second C–H bond in the second step. In spite of the challenge, a number of coupling reactions involving double C–H bond activation have been developed,[321] and Pd is the dominant catalyst used in these reactions. To achieve desired heterocoupling, the coupling partners with distinct C–H bonds were often employed, and one of the partners was excessive, often as solvent. It should be mentioned because these reactions are categorized as double C–H activation reactions, both of the reacting C–H bonds are restricted to those with high p*K*a values.

3.23.5.1 Palladium-Catalyzed Reactions with C–H Bonds

Pd-promoted coupling of two C–H bonds have been extensively investigated, and a number of reactions have been developed, including homocoupling and heterocoupling reactions Among these reactions, the vast majority of them involve aryl–aryl bond formation, and a variety of arenes have been demonstrated to undergo the dehydrogenative coupling reaction, providing a novel method for the synthesis of biaryls.[322] To illustrate the mechanism involved in such a reaction, a representative catalytic cycle for Pd-catalyzed cross-coupling of two arenes illustrated shown in **Figure 28**.[15] Therefore, the reaction is initiated by Pd(II)-enabled C–H activation. The formed arylpalladium(II) species cleaves the C–H bond of a second arenes. The subsequent reductive elimination yield the desired biaryl product and generate Pd(0) species. Finally, the Pd(0) species is oxidized by an oxidant to Pd(II) complex, which then continues a second catalytic cycle.

3.23.5.1.1 Palladium-catalyzed homocoupling of two C–H bonds

The homocoupling of benzene is relative simple compared to the complicated coupling of two different arenes, because biphenyl is the sole possible coupling product. As early as 1965, Pd-mediated homocoupling of benzene to biphenyl was observed.[323] Subsequently, the similar coupling was reported.[324,325] Inspired by these early observations, this attractive reaction gained considerable interest, and a number of effective protocols have been developed and catalytic reactions have been enabled.

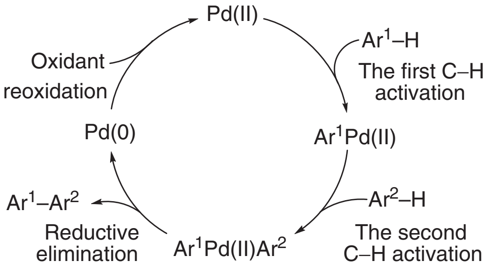
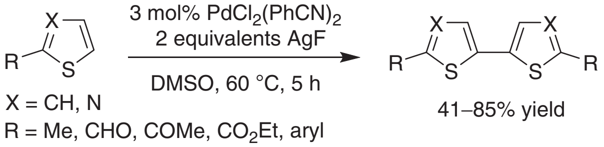


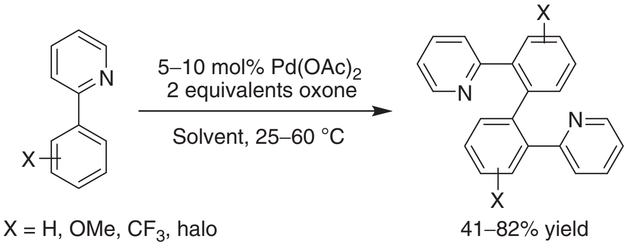
Figure 28 A general mechanism of Pd-catalyzed cross-coupling of two arenes.

The homocoupling of heteroarenes have also been extensive investigated, and a wide range of electron-rich heteroarenes were found to undergo homocoupling reaction to form dimerization products. One of the recent examples is the homocoupling of thiophene reported by the Mori and coworkers (Scheme 242).[326] Therefore, a variety of 2-substituted thiophenes underwent dimerization to afford homocoupling products in the presence of a catalytic amount of $PdCl_2(PhCN)_2$ and 2 equivalents of AgF. The reaction occurred selectively at the 5-positions. In addition, 2-(4-methoxyphenyl)thiazole was also found to undergo the similar homocoupling reaction.



Scheme 242 Pd-catalyzed coupling of thiophene and thiazole (Mori et al., 2004).

The homocoupling with the assistance of a directing group was also achieved. In 2006, Sanford and coworkers described the $Pd(OAc)_2$-promoted homocoupling of 2-arylpyridines using oxone as the oxidant (Scheme 243).[327] The β-selectivity of the reactions demonstrated that pyridine acted as a directing group. Detailed mechanistic studies suggested that the reactions involved two different C–H activation mechanism, one at Pd(II) center and one at Pd(IV) center.

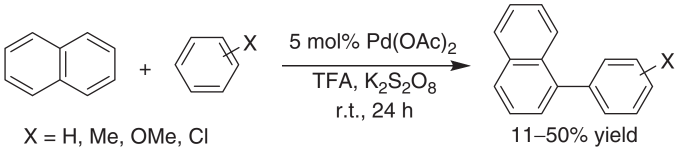


Scheme 243 Pd-catalyzed homocoupling of 2-arylpyridines (Sanford et al., 2006).

3.23.5.1.2 Palladium-catalyzed coupling of two different C–H bonds

The Pd-mediated cross-couplings of two different arenes were also observed quite early. In 1976, Kozhevnikov isolated the cross-coupling products of furan and thiophene during the study on the $Pd(OAc)_2$-mediated oxidative homocoupling of furan or thiophene.[328] Subsequently, Itahara observed 2-phenylation products of pyrroles and indoles along with their homocoupling products when pyrroles or indoles were stirred with a stoichiometric amount of $Pd(OAc)_2$ in a mixture of benzene and acetic acid.[329] Another example is the direct arylation of isoxazole reported by Nakamura and coworkers.[175]

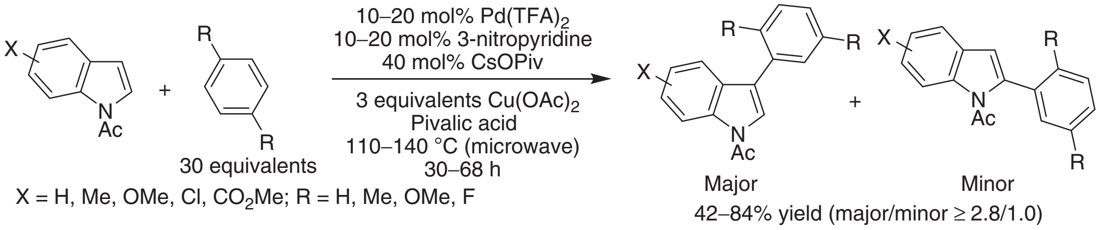
One of the earliest catalytic cross-coupling of two arenes was the contribution of the Lu and coworkers in 2006 (Scheme 244).[330] The authors found that unsymmetrical biaryls were formed preferentially over homocoupling products when a



Scheme 244 Pd-catalyzed cross-coupling of naphthalene and arenes (Lu et al., 2006).

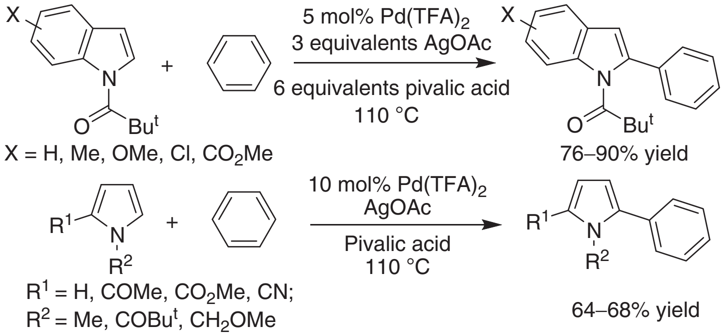
mixture of benzene and anisole/mesitylene was stirred with $Pd(OAc)_2$ in the presence of TFA and $K_2S_2O_8$ at room temperature. Under the similar conditions, naphthalene reacted with a wide range of simple arenes to afford arylated products with turnover up to 22. Preliminary mechanistic studies suggested that two aromatic C–H activation steps were involved in the tandem direct arylation.

Although the yields of the above reactions were quite low, these early works provided great inspiration for the development of efficient cross-coupling reactions via double C–H activation. A decisive breakthrough was made by Fagnou and coworkers in 2007, when the authors reported the arylation of *N*-acetylindoles with simple arenes in high yield and high regioselectivity under the conditions shown in Scheme 245.[331] The reaction occurred at the 3-position preferentially, and a range of functional groups of the indoles were compatible in the reactions. In addition to benzene, other substituted arenes such as *p*-xylene, 1,4-difluorobenzene, and 1,4-dimethoxybenzene were also reactive. Notably, no arene homocoupling products were detected in the reactions, indicating that a complete inversion in catalyst selectivity occurred at the crucial arene metalation steps of the catalytic cycle.[331]



Scheme 245 Pd-catalyzed coupling of indoles and simple arenes (Fagnou et al., 2007).

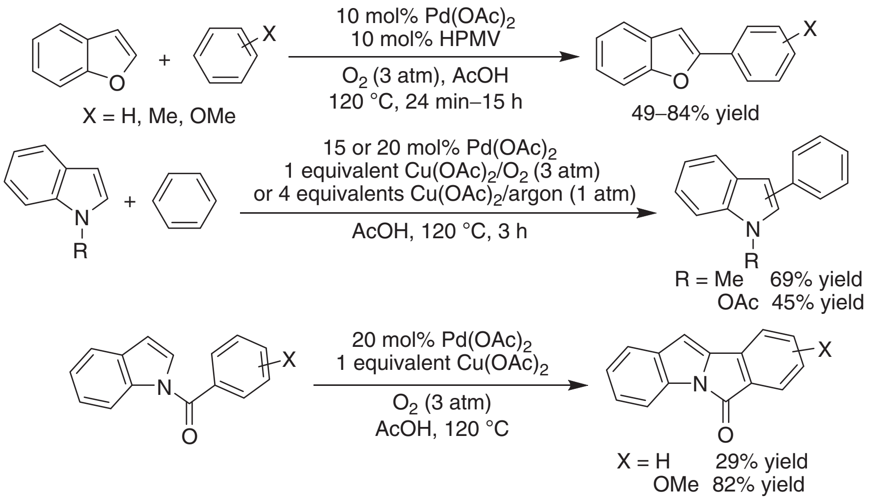
Interestingly, a reversal in regioselectivity was observed when *N*-pivaloyl indoles were employed and the reaction conditions were modified to employ $Pd(TFA)_2$, AgOAc, and pivalic acid (Scheme 246).[332] The use of the oxidant AgOAc was crucial for the C2 selectivity, whereas $Cu(OAc)_2$ favored C3-arylation. The new conditions tolerated a variety of substituents, and some symmetrically substituted benzenes were also found to be reactive. In addition, the protocol was extended to the arylation of indoles, and the reactions also gave C2-arylated indoles as the major products. Further experiments revealed that the C2/C3 selectivity was greatly influenced by Pd concentration and acetate additives. The acetate base, when added as a Ag(I) or Cs(I) salt, increased C2 selectivity. To explain these findings, the authors proposed that the formation of higher-order Pd and/or Pd-Cu clusters accounted for the favored C3-arylation, whereas acetates may cleave Pd clusters and thus promote cross-coupling at C2-position.



Scheme 246 Pd-catalyzed coupling of indoles/pyrroles and benzene (Fagnou et al., 2007).

Concurrently, DeBoef and coworkers reported the similar oxidative coupling of benzofurans and indoles with simple arenes (Scheme 247).[333] Although the use of the heteropolymolybdovanadic acid $H_4PMo_{11}VO_{40}$ (HPMV) as the cooxidant gave the optimal outcome for the arylation of benzofurans, both *N*-acetylindole and *N*-methylindole decomposed under the reaction conditions. However, the milder oxidant $Cu(OAc)_2$ proved effective to enable the arylation of *N*-acetylindole, and the more electron-rich *N*-methylindole could only be arylated in the absence of oxygen. The arylation took place at the 2-position preferentially, but the selectivity for *N*-methylindole was poor. Moreover, the method also proved viable in the intramolecular hetero-coupling of *N*-benzoylindoles via double C–H activation, affording cyclized products.

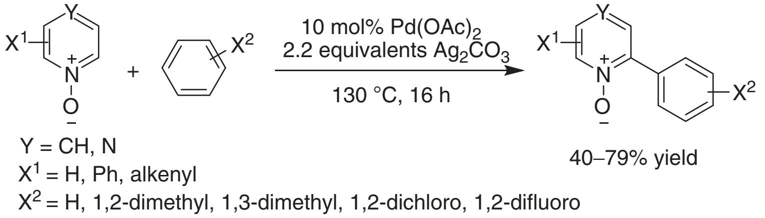
Subsequently, DeBoef and coworkers improved the arylation of electron-rich indoles primarily by tuning the acidity of the reaction medium.[334] The authors successfully achieved C2-arylation of indoles by using a new catalytic system consisting of $Pd(OAc)_2$, pivalic acid, and AgOAc. A wide range of electron-rich indoles were arylated with various simple arenes with high C2 selectivity. The reaction mechanism was investigated. Based on the experimental and computational data, the authors believed that both C–H palladation steps should involve a CMD mechanism.



Scheme 247 Pd-catalyzed coupling of indoles and simple arenes (DeBoef et al., 2007).

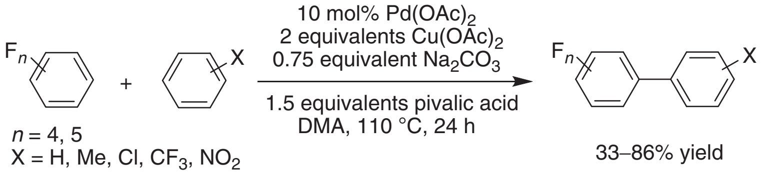
Interestingly, Stahl and coworkers found that the C2/C3 selectivity in the cross-couplings of indoles and benzene can be controlled by using different 4,5-diazafluorene ligands. It is noteworthy that the use of the ligands enabled the aerobic cross-coupling to proceed efficiently with oxygen as the sole oxidant, and other oxidant such as Ag(I) and Cu(II) salts were not needed.[335]

In 2008, the Chang and coworkers described the cross-coupling of pyridine *N*-oxides and simple arenes (Scheme 248).[41] During the course of the studies on the alkenylation of pyridine *N*-oxides, the authors isolated 2-phenylpyridine *N*-oxide when the reaction was carried out in benzene. After extensive condition optimization, it was found that a variety of pyridine *N*-oxides could be α-arylated with a range of simple arenes in the presence of $Pd(OAc)_2$ and Ag_2CO_3. *N*-Oxides of pyrazine and quinoxaline also underwent the arylation with benzene at the α-position.



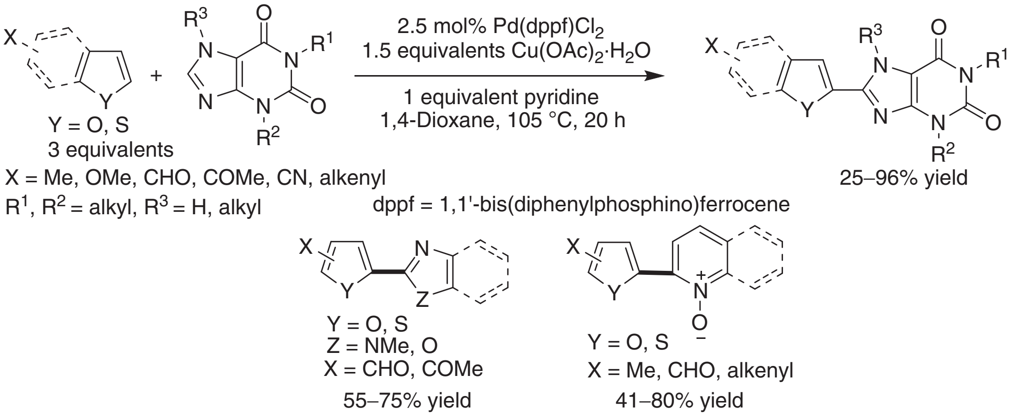
Scheme 248 Pd-catalyzed regioselective coupling of pyridine *N*-oxides and simple arenes (Chang et al., 2008).

The C–H bonds of polyfluorobenzenes are relatively acidic and can be cleaved via a different mechanism from those involved in the C–H activation of simple arenes. As such, it is reasonable to envision that polyfluorobenzenes could undergo dehydrogenative cross-coupling with other arenes. In 2010, Su and coworkers developed an efficient protocol for the arylation of polyfluoroarenes (Scheme 249).[336] A range of tetrafluoroarenes and pentafluorobenzene cross-coupled with simple arenes via double C–H activation. A diversity of simple arenes, including nitrobenzene, chlorobenzene, and trifluoromethylbenzene, were found to be effective coupling partners. Monosubstituted arenes gave a mixture of *para-* and *meta*-isomers with a ratio of approximately 1–2.5.



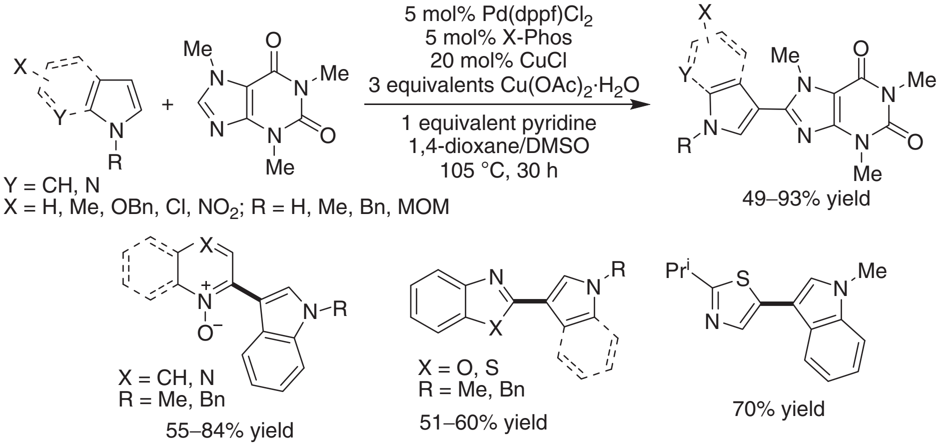
Scheme 249 Pd-catalyzed coupling of polyfluoroarenes and simple arenes (Su et al., 2010).

Different types of heteroarenes often have distinct electronic characteristics and their C–H bonds should be able to be differentiated and cleaved in a sequential way. In 2010, You and coworkers reported the oxidative cross-coupling of two heteroarenes (Scheme 250).[337] Therefore, in the presence of Pd(dppf)Cl_2, $Cu(OAc)_2 \cdot H_2O$, and pyridine, xanthines reacted with diversely substituted furans or thiophenes to afford biheteroaryl products. The reactions occurred at the 2-positions of furans or thiophenes selectively. It is noted that this new method had a very broad substrate-scope. A wide range of heteroarenes (xanthines, azoles, indolizines, and pyridine *N*-oxides) underwent effective heterocoupling with furans or thiophenes.



Scheme 250 Pd-catalyzed coupling of furans/thiophenes and heteroarenes (You et al., 2010).

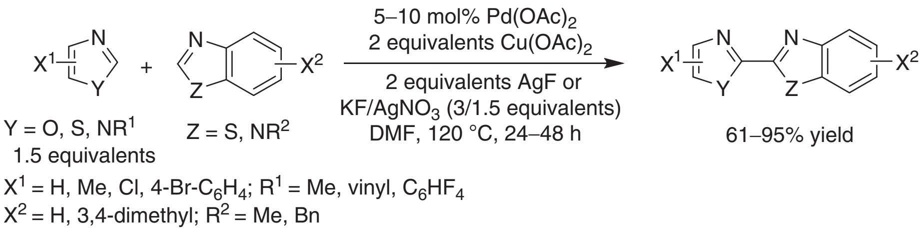
Subsequently, You and coworkers described an analogous hetero-coupling of indoles and pyrroles with heteroarenes-containing acidic C–H bonds (Scheme 251).[338] Similar to the above reactions, a wide range of heteroarenes reacted with indoles or pyrroles under a new catalytic system as shown in Scheme 251. In contrast to the C2 selectivities in the above reactions involving thiophenes and furans, this reaction occurred selectively at the 3-positions of pyrroles and indoles. For the other coupling partners, the most acidic C–H bonds were the reactive sites and cleaved selectively. Interestingly, 2-substituted thiazole gave 5-arylated product.



Scheme 251 Pd-catalyzed coupling of indoles/pyrroles and heteroarenes (You et al., 2011).

Concurrently, Zhang and Li reported Pd(II)-catalyzed oxidative coupling between pyridine *N*-oxides and *N*-substituted indoles with using Ag_2CO_3 as an oxidant and the additive tetrabutylammonium bromide (TBAB).[339] The reactions also took place at the 3-position of indoles selectively. In addition, the heterocoupling between xanthines and simple arenes has also been disclosed.[340]

Although the coupling partners in the above reactions have distinctly differentiated C–H bonds, Ofial and coworkers reported oxidative cross-coupling of two heteroarenes with similar electronic characteristics: azoles and benzazoles (Scheme 252).[341] A broad-scope of azoles, including imidazoles, oxazoles, and thiazoles, coupled with benzazoles selectively to afford 2,2′-bisheteroaryls in high yields. The use of Ag^+ was mandatory for the highly selective heterocoupling. The C–H bonds of more electron-rich azoles were believed to be cleaved as the initial step. The formed heteroarylpalladium(II) intermediate promoted a second C–H cleavage selectively with benzazoles.

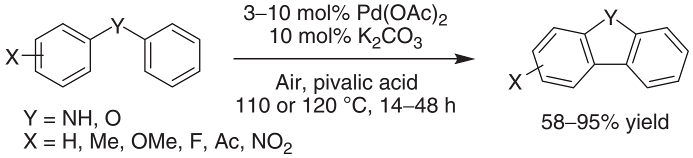


Scheme 252 Pd-catalyzed coupling of azoles and benzazoles (Ofial et al., 2011).

3.23.5.1.3 Palladium-catalyzed intramolecular coupling of two C–H bonds

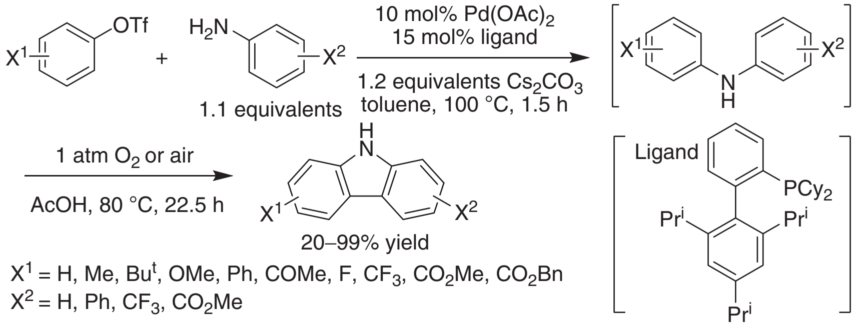
As far as selectivity is concerned, the intramolecular dehydrogenative coupling of two C–H bonds should be less challenging because of entropically favored intramolecular reaction. As intermolecular reaction, Pd-catalyzed intramolecular coupling of two arenes have attracted great attention[342,343] since the oxidative coupling of benzene to biphenyl reported by van Helden and Verberg in 1965.[323] One of the earliest examples is the $Pd(OAc)_2$-catalyzed coupling of diphenyl ether to dibenzofuran disclosed by Itanani and coworkers in 1973.[344,345] In this reaction, the yield of dibenzofuran was up to 10 400% based on the reacted $Pd(OAc)_2$. In 1975, Akermark and coworkers reported $Pd(OAc)_2$-mediated intramolecular dehydrogenative coupling of diphenyl ether, diphenylamine, benzophenone, and benzanilide.[346] Subsequently, the catalytic reactions were also achieved by the same authors.[347] Oxygen was the sole oxidant, and a variety of heterocyclic compounds were synthesized via double C–H activation. Furthermore, the palladium-mediated intramolecular coupling of *N*-arylindoles and *N*-arylpyrroles were also demonstrated by Itahara and coworkers.[348–351]

In 2008, Fagnou and coworkers developed new reaction conditions to improve intramolecular biaryl coupling (Scheme 253).[352] Under the new conditions, which employed pivalic acid as the solvent, diphenylethers or diphenylamines underwent intramolecular dehydrogenative coupling with greater reproducibility, higher yields, and broader scope.



Scheme 253 Pd-catalyzed intramolecular coupling of two arenes (Fagnou et al., 2008).

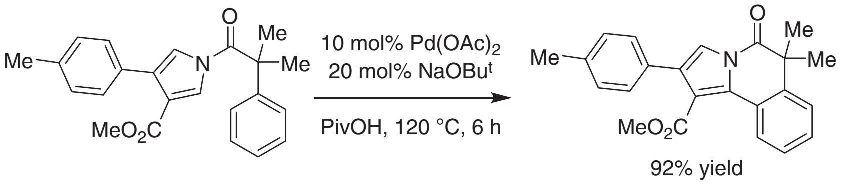
Interestingly, the Fujii, Ohno and coworkers developed an efficient method for construction of various functionalized carbazoles by one-pot *N*-arylation-oxidative biaryl coupling from readily available anilines and phenyl triflates (Scheme 254).[353] The reactions started with Pd(0)-promoted Buchwald–Hartwig amination. The subsequent intramolecular coupling afforded functionalized carbazoles.



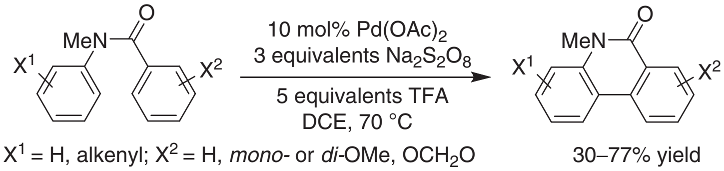
Scheme 254 Pd-catalyzed intramolecular coupling of two arenes in the one-pot synthesis of carbazoles (Fujii and Ohno et al., 2009).

Six-membered rings can also be constructed through Pd-catalyzed intramolecular dehydrogenative coupling. The first example is the oxidative cyclization shown in Scheme 255, which was reported by the Fagnou and coworkers.[354]

Subsequently, Dong and coworkers described the oxidative cyclization of *N*-phenylbenzamides (Scheme 256).[355] In the presence of $Na_2S_2O_8$ and TFA, a range of six-membered lactams could be synthesized efficiently.

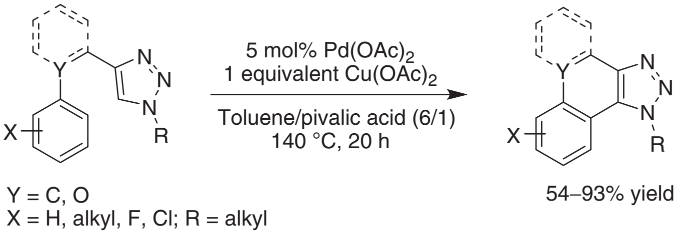


Scheme 255 Pd-catalyzed intramolecular coupling of pyrrole and benzene (Fagnou et al., 2008).



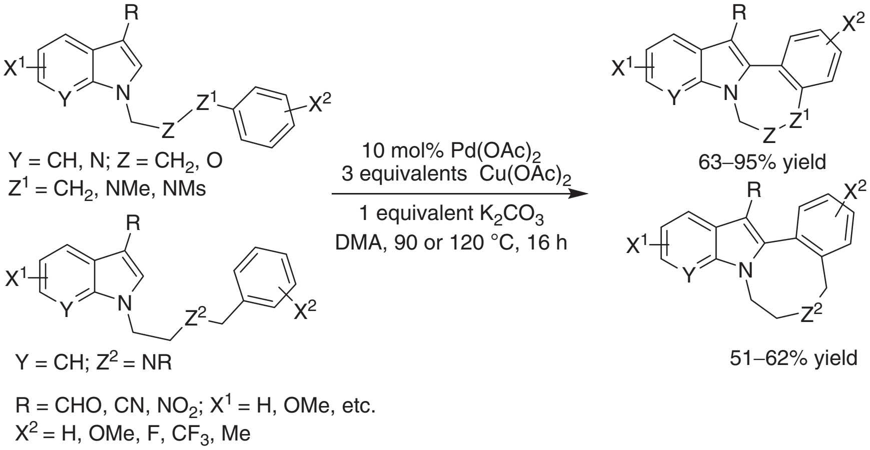
Scheme 256 Pd-catalyzed intramolecular coupling of *N*-phenylbenzamides (Dong et al., 2010).

The intramolecular coupling between 1,2,3-triazoles and phenyl groups were demonstrated by Ackermann and coworkers (Scheme 257).[356] The direct arylation of 1,2,3-triazoles provided a facile way for the synthesis of annulated phenanthrenes. A variety of tethers were compatible with the reaction.



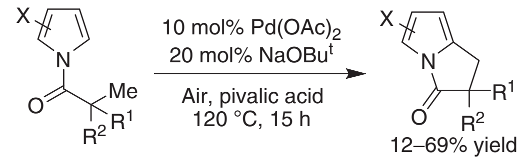
Scheme 257 Pd-catalyzed intramolecular coupling of 1,2,3-triazoles and simple arenes (Ackermann et al., 2010).

Remarkably, Greaney and Pintori disclosed an effective strategy for synthesizing medium-ring compounds via intramolecular C–H coupling for the first time (Scheme 258).[357] In the presence of Cu(OAc)$_2$ and K$_2$CO$_3$, tethered indoles and phenyl groups underwent dehydrogenative coupling, forming annulated heterocycles. Both seven- and eight-membered rings could be constructed efficiently, and a rich array of functional groups was well tolerated. In addition to phenyl groups, heteroarenes such as indoles, benzimidazoles, and pyrazoles, also underwent coupling reaction with indoles under the reaction conditions. Mechanistically, the indoles were proposed to be palladated first. The second C–H activation involved a CMD mechanism.



Scheme 258 Pd-catalyzed intramolecular coupling of indoles and arenes to construct medium-rings (Greaney et al., 2011).

Finally, intramolecular C(sp^2)-H/C(sp^3)-H coupling was reported by Fagnou and coworkers in 2008 (Scheme 259).[354] By using air as the terminal oxidant, the coupling of pyrroles and unactivated methyl groups proceeded smoothly in the presence of Pd(OAc)$_2$



X = Me, CO_2Me, aryl, Ac, COPh; R^1, R^2 = alkyl

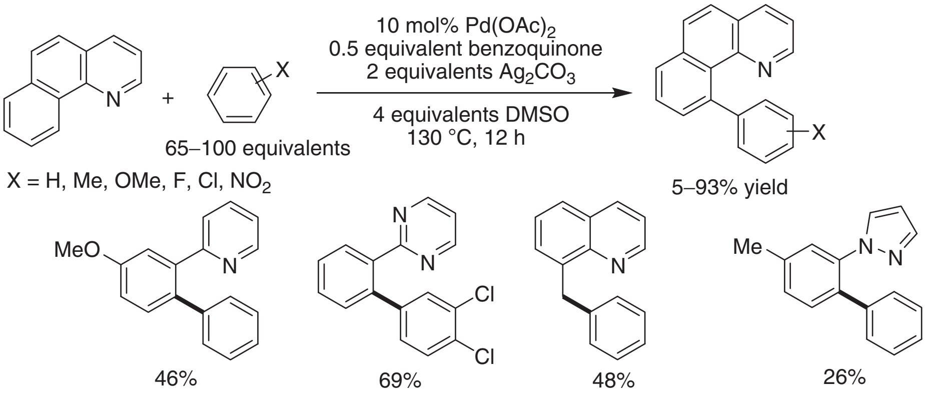
Scheme 259 Pd-catalyzed intramolecular coupling of arenes and unactivated alkane (Fagnou et al., 2008).

and NaOBu^t. The reactions exhibited high regioselectivity with respect to both the pyrrole and the methyl moieties. The proposed mechanism involved the palladation of pyrroles as the first step. The subsequent *sp*^{3} C–H activation was the rate-limiting step.

3.23.5.1.4 Palladium-catalyzed-directed coupling of two C–H bonds

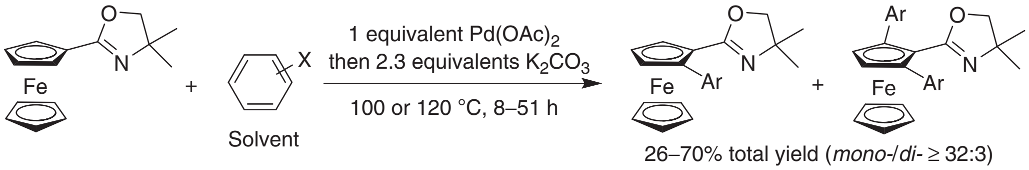
Although the intermolecular C–H coupling of two arenes involves regioselectivity for both of the two coupling partners, the introduction of directing groups can avoid this problem at least for one of the reactants. This strategy gained considerable interests recently, and a wide range of directing groups has been successfully employed to promote this type of dehydrogenative coupling.

In 2007, Sanford and Hull described oxidative cross-coupling of Benzo[*h*]quinolines and simple arenes (Scheme 260).[358] A diverse variety of simple arenes were found to be effective coupling partners. The reactions were highly chemoselective and homocoupling of either benzo[*h*]quinoline or arene partners was not observed. As usual, the C–H activation for benzo[*h*]quinoline was controlled by the directing group. For most of the reacting simple arenes, their C–H bonds were also cleaved with high regioselectivity, which was controlled by steric effects. Although 1, 2-disubstitued arenes gave 4-arylated products, the reactions occurred primarily at the less-hindered 5-positions for 1,3-disubstituted arenes. For monosubstituted arenes, the regioselectivities were still poor. Furthermore, pyridine, pyrimidine, and pyrazole were also found to be effective directing groups. It is remarkable that benzylic C(*sp*^{3})-H bond underwent the coupling with benzene under the reaction conditions. The mechanism experiments supported that directing group-assisted C–H activation took place first, followed by a second C–H cleavage of simple arenes via a dissociative σ-bond metathesis mechanism. The use of a substoichiometric quantity of a 1,4-benzoquinone (BQ) derivative was required to promote the oxidative coupling reaction and the regioselectivity was strongly influenced by the structure of the quinone for some simple arenes. Subsequently, the authors carried out the detailed mechanistic studies to elucidate the role of the quinone in this novel coupling reaction.[359] It was found that the rate-determining step in the reaction was dependent on the concentration of the quinone promoter. Therefore, at high concentration, the C–H activation of the simple arenes was the rate-limiting step. However, benzoquinone-promoted reductive elimination was rate-limiting at low concentration of benzoquinone.



Scheme 260 Pd-catalyzed heteroarene-directed coupling of two C–H bonds (Sanford et al., 2007).

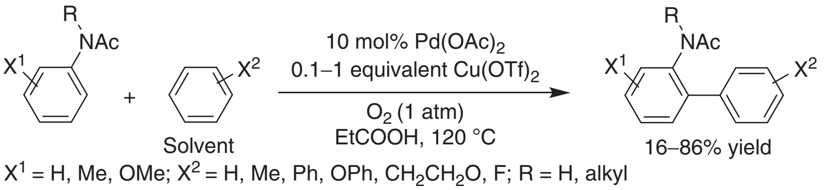
Concurrently, the You and coworkers reported a facile method for the arylation of ferrocene via dehydrogenative coupling of ferrocenes bearing oxazoline as the directing group (Scheme 261).[360] Although the catalytic reactions gave moderate yields, the



Scheme 261 Pd-catalyzed oxazoline-directed coupling of ferrocene and simple arenes (You et al., 2007).

use of a stoichiometric amount of $Pd(OAc)_2$ proved more successful. The reactions were tolerant of a wide range of arenes, including electron-neutral, -rich, and -deficient ones. It is noteworthy that diastereoselectively pure products were obtained when enantiopure ferrocenyl oxazolines were used.

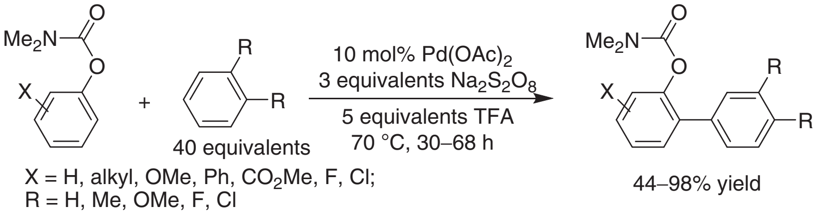
Another concurrent work was the cross-coupling of *N*-acetanilides and simple arenes disclosed by Shi and coworkers (Scheme 262).[361] In the reactions, oxygen was used as the oxidants along with a catalytic or stoichiometric amount of $Cu(OTf)_2$. The reactions displayed a broad substrate scope with respect to both coupling partners. Interestingly, the authors demonstrated that the formed 2-arylated acetanilides could underwent cyclization via an intramolecular C–H amination, providing an efficient method for the synthesis of carbazole structures. The practicability of this method was demonstrated by a short synthesis of 4-deoxycarbazomycin B.



Scheme 262 Pd-catalyzed acetamide-directed coupling of *N*-phenylacetamides and simple arenes (Shi et al., 2008).

Shortly thereafter, Buchwald and coworkers reported a similar arylation of acetanilides with simple arenes.[362] By using oxygen as the sole oxidant and TFA as the solvent, a wide range of *N*-acetanilides were allowed to couple with various arenes in the presence of 10 mol% $Pd(OAc)_2$ and 10–20 equivalents DMSO, affording 2-arylated acetanilide products.

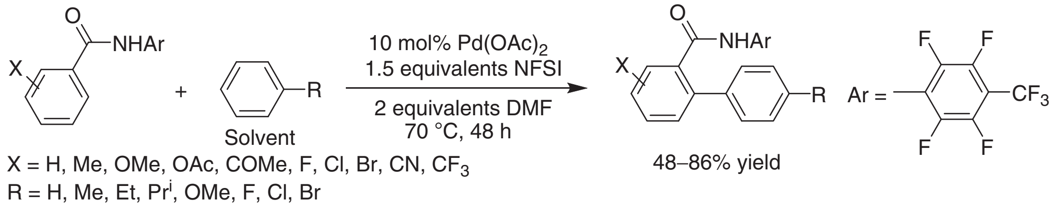
O-carbamates were also found to be effective directing groups to assist the coupling of *O*-phenylcarbamates and simple arenes (Scheme 263).[363] $Na_2S_2O_8$ was used as the oxidant and the addition TFA was critical for the successful cyclopalladation of *O*-phenylcarbamates. In addition to benzene, a variety of *ortho*-disubstituted benzenes were found to be reactive, and the reactions took place at the 4-positions selectively for these arenes. Diarylated *O*-phenylcarbamates were obtained when two *ortho*-C–H bonds were available and no *meta*-substituents were present. The authors carried out detailed mechanistic studies, and the experimental results supported a mechanism involving cyclopalladation of *O*-phenylcarbamates as the first C–H activation. The formed palladacycles underwent electrophilic metalation with simple arenes. However, the authors noted that a CMD could not be ruled out.



Scheme 263 Pd-catalyzed carbamate-directed coupling of *O*-phenylcarbamates and simple arenes (Dong et al., 2010).

The above coupling protocol proved to be versatile. A broad class of arenes, including phenylacetamides, benzamides, and anilides, underwent cross-coupling reaction efficiently with simple arenes in a similar manner to the reactions of *O*-phenylcarbamates.[355] The intramolecular dehydrogenative coupling of benzanilides also proved viable under the similar conditions, affording lactam products. It is noted that although the reactions with these substrates yielded the similar outcomes as the arylation of *O*-phenylcarbamates, the mechanisms may be different. It was evidenced by the observations that the bimetallic palladium complex derived from *O*-phenylcarbamates underwent the *ortho*-arylation with simple arenes in excellent yields in the absence of any external oxidant, the addition of $Na_2S_2O_8$ was required for the arylation of the palladacycles of *N*-(*m*-tolyl)pivalamide and *N*-phenylpyrrolidine.

Finally, Yu and coworkers reported the cross-coupling of benzamides and monosubstituted arenes (Scheme 264).[364] In the reactions, the acidic amide derived from 4-trifluoromethyl-2,3,5,6-tetrafluoroaniline was used as the directing group, and an F^+ reagent as the bystanding oxidant. A great breakthrough for this reaction was that excellent *para*-selectivity was achieved for the C–H functionalization of monosusbstituted arenes. As discussed in Sections 3.23.2.1.1.1 and 3.23.3.1.1.1, the reactions involving the C–H activation of monosubstituted simple arenes always gave a mixture of regiomers with poor selectivities, in the alkenylation or cross-coupling reactions. Remarkably, a wide range of monosubstituted arenes were *para*-arylated with high selectivities. Only a minor amount of *meta*-isomers was formed, and no *ortho*-products were observed. In some of the reactions, the *para*-isomers were the sole products. The use of F^+ oxidant was crucial for the *para*-selectivity, and other oxidants such as $Na_2S_2O_8$ gave

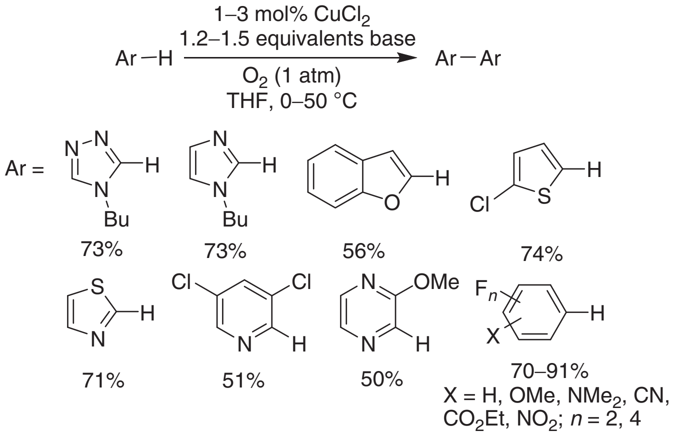


Scheme 264 Pd-catalyzed amide-directed coupling of benzamides and monosubstituted arenes with high regioselectivities (Yu et al., 2011).

a low selectivity. The [ArPd(IV)F] species, which was formed through the oxidation of the palladacycles derived from the benzamides by the F$^+$ oxidant, was proposed to be partially responsible for selective *para*-C–H cleavage of monosubstituted arenes.

3.23.5.2 Other Transition-Metal-Catalyzed Reactions with C–H Bonds

Contrary to the availability of a great number of examples for palladium-promoted dehydrogenative reactions, other transition-metal-catalyzed oxidative coupling of two C–H bonds are quite rare. In 2009, Daugulis and coworkers disclosed copper-catalyzed homocoupling of arenes with one atmosphere of oxygen as the terminal oxidant (Scheme 265).[365] Therefore, a variety of heteroarenes and polyfluoroarene underwent deprotonative dimerization in the presence of CuCl$_2$ and a strong base, affording symmetrical biaryl products. The strong base could be hindered magnesium or zinc amides, but the exact composition of the bases needed to be optimized for each substrate. For polyfluoroarenes, the method was tolerant to functionalities such as ester, amino, cyano, and nitro group.



Scheme 265 Cu-catalyzed homocoupling of (hetero)arenes (Daugulis et al., 2009).

Subsequently, the same authors developed a general method for a highly regioselective copper-catalyzed cross-coupling of two different aromatic compounds (Scheme 266).[366] In the reactions, one of the arenes was initially iodinated with iodine, and the formed iodides reacted with the most acidic C–H bond of the other coupling component, yielding cross-coupling products. Several coupling protocols were developed based on the operative iodination mechanisms. As a result, the method displayed excellent substrate scope, and cross-coupling of electron-rich arenes, electron-poor arenes, and five- and six-membered

$$\text{Ar—H} \quad + \quad \text{H—Ar}^1 \xrightarrow[\substack{\text{0–1.0 equivalent pyridine} \\ \text{1,2-dichlorobenzene or dioxane} \\ \text{base, 130 °C}}]{\substack{\text{10 mol\% CuI/phenanthroline} \\ \text{1.2–1.5 equivalents I}_2}} \text{Ar—Ar}^1$$

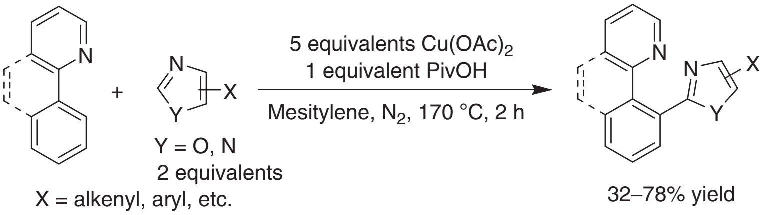
Compatible coupling partners:

Ar = Electron-rich arenes; Ar^1 = Heterocycles and electron-poor arenes;
Ar = Electron-deficient arenes; Ar^1 = Heterocycles and electron-poor arenes;
Ar = Five-membered heterocycles; Ar^1 = Heterocycles and electron-poor arenes;
Ar = Pyridines; Ar^1 = Heterocycles and electron-poor arenes.

Scheme 266 Cu-catalyzed coupling of two different (hetero)arenes (Daugulis et al., 2011).

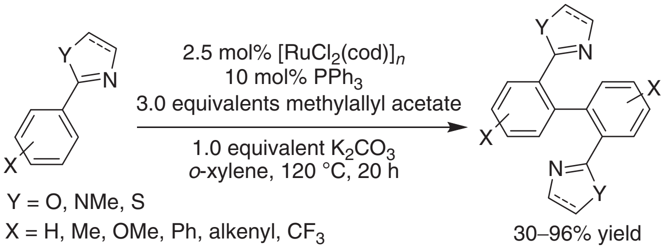
heterocycles proved viable in many combinations. Although most of the existing dehydrogenative arene cross-coupling reactions employed one of the arenes as the solvent, a 1/1.5–1/3 ratio of coupling components was used in this remarkable method.

The directing group-assisted dehydrogenative coupling has also been developed by the Hirano, Miura group in 2011 (**Scheme 267**).[367] Therefore, 2-phenylpyridines and benzoquinolines coupled with azoles in the presence of a stoichiometric amount of $Cu(OAc)_2$ and pivalic acid. The reactive azoles included benzoxazoles, 3-substituted oxazoles, and an imidazole derivative. Two equivalents of azoles were enough to ensure the heterocoupling reactions to take place efficiently. Based on the results of the mechanism experiments, the authors proposed the following reaction steps: (1) reversible C–H cupration of the azoles involving carboxyl-ligand-promoted proton abstraction, (2) C–H metalation of the arylazine, and (3) productive reductive elimination.[365]



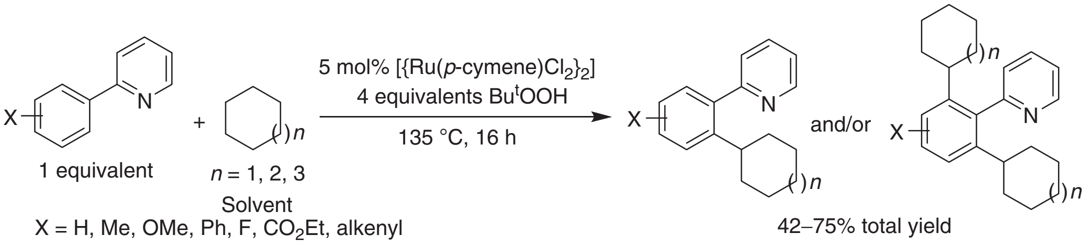
Scheme 267 Cu-mediated pyridine-directed coupling of arenes and oxazoles/imidazoles (Hirano and Miura et al., 2011).

Ru has also been utilized to promote the coupling of two C–H bonds. In 2008, the Oi and Inoue and coworkers reported directed homocoupling reaction of aromatic compounds catalyzed by a ruthenium complex (**Scheme 268**).[368] The catalytic system consisted of $[RuCl_2(cod)]_n$, PPh_3 and methyl allyl acetate as the hydrogen scavenger. Arenes bearing a variety of nitrogen-containing heteroaryl, including oxazole, imidazole, pyrazole, or thiazole, could be homocoupled regioselectively.



Scheme 268 Ru-catalyzed homocoupling of arylazoles (Oi and Inoue et al., 2008).

Remarkably, Li and coworkers reported Ru-catalyzed $C(sp^2)$-H/$C(sp^3)$-H coupling reactions (**Scheme 269**).[369] Therefore, in the presence of the catalyst $[\{Ru(p\text{-cymene})Cl_2\}_2]$ and oxidant Bu^{t}OOH, 2-phenylpyridines reacted with simple cycloalkanes to give alkylated products. Depending on the structures of 2-phenylpyridines, monoalkylated or a mixture of mono- and dialkylated products were obtained. The proposed mechanism involved the initial chelation-assisted C–H activation of 2-phenylpyridines, the reaction of the formed ruthenacycles with cycloalkanes and the peroxide, and the final reductive elimination to afford the final coupling products (**Figure 29**).[369]



Scheme 269 Ru-catalyzed pyridine-directed alkylation of arenes with cycloalkanes (Li et al., 2008).

Subsequently, the Li and coworkers described the *para*-selective coupling of substituted arenes and cycloalkanes catalyzed by $Ru_3(CO)_{12}$/dppb (bis(diphenylphosphino)butane) (**Scheme 270**).[370] The peroxide TBP (di-*tert*-butyl peroxide) was used as the oxidant. A wide range of benzenes bearing one substituent were found to undergo dehydrogenative coupling with cycloalkanes. The arenes with one electron-withdrawing substituent, such as COOMe, COOH, COMe, and CONHMe, were alkylated with high

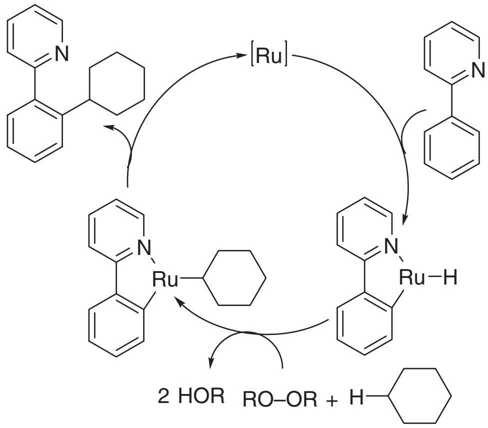
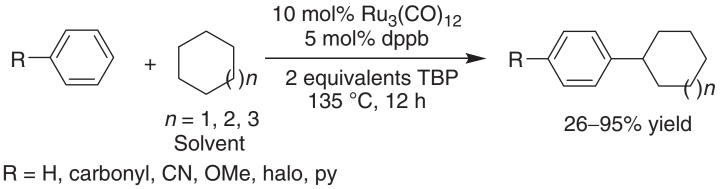


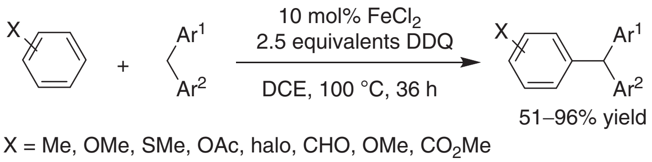
Figure 29 Proposed mechanism of Ru-catalyzed pyridine-directed alkylation of arenes.



Scheme 270 Ru-catalyzed alkylation of simple arenes with cycloalkanes (Li et al., 2011).

para-selectivity; the substituents F, Cl, Br, OMe, and CN mainly gave *para*-alkylated products. It is remarkable that *para*-functionalized products instead of *ortho*-ones were produced even in the presence of the widely employed directing group in transition-metal-catalyzed C–H functionalization. In addition, the 1, 2- and 1, 3-disubstituted arenes also gave high *para*-selectivity.

Finally, although the methylene C–H bond of diphenylmethane is quite acidic, we wish to illustrate the intriguing Fe-catalyzed cross-coupling of benzylic C–H bonds with arenes disclosed by Shi and coworkers (Scheme 271).[371] Thus, diphenylmethanes underwent 'cross-dehydrogenative arylation' (CDA) with a rich array of simple arenes in the presence of $FeCl_2$ and 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ). The reaction displayed excellent functional group compatibility and gave high regioselectivity for the arene-coupling partners. The *ortho*- and *para*-alkylated products were formed preferentially for the arenes bearing electron-donating groups. This proposed mechanism involved single-electron-transfer oxidation and Friedel–Crafts alkylation. The observed large primary kinetic isotope effect for diphenylmethane ($k_H/k_D=6.0$) indicated that benzylic C–H bond cleavage was the rate-limiting step.



Scheme 271 Fe-catalyzed coupling of benzylic C–H bonds and arenes (Shi et al., 2009).

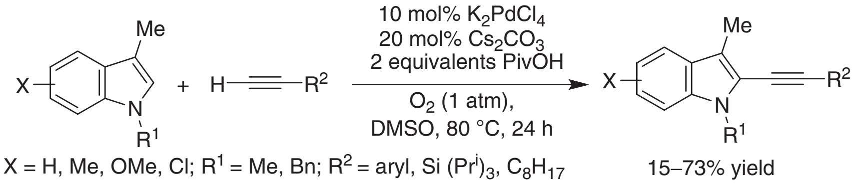
3.23.6 Miscellaneous C–H Functionalization Reactions

In addition to the four major categories of reactions presented in Sections 3.23.2, 3.23.3, 3.23.4, and 3.23.5, C–H bonds have also been demonstrated to be able to react with a variety of other reaction partners to form C–C σ-bonds. In this section, four types of reactions will be discussed, including alkynylation with terminal alkynes, decarboxylative coupling with aromatic acids, trifluoromethylation, and alkylation by reacting with α-C–H bonds of carbonyl groups.

3.23.6.1 C–H Alkynylation with Terminal Alkynes

In Sonogashira reaction, the cross-coupling between a hetero(aryl) halide and a terminal alkyne, serves as a powerful tool for the functionalization of terminal alkynyl carbons. Recently, an alternative strategy, an 'inverse Sonogashira coupling,' has gained considerable attraction.[372] The new strategy involves the direct alkynylation of unreactive C–H bonds with alkynyl halides. However, the more attractive methods are the direct coupling between C–H bonds and terminal alkynes. The development of such a reaction has been hampered mainly by the uncontrolled homocoupling of terminal alkynes.

In 2010, Li and coworker reported Pd-catalyzed coupling of indoles and terminal alkynes (Scheme 272).[373] Therefore, a variety of terminal alkynes reacted with 1, 3-dialkylindoles in the presence of a catalytic amount of K_2PdCl_4 and a buffer system consisting of Cs_2CO_3 and PivOH, affording 2-alkynylated indole products. Oxygen was used as the oxidant, and the use of the buffer system was crucial for high yields. To suppress its homocoupling, acetylene was added slowly using a syringe pump. The proposed mechanism included the following reaction sequences: (1) the alkynes were palladated by reacting with Pd(II) catalyst with the assistance of CsOPiv; (2) the key C–H cleavage involved the electrophilic attack of the formed alkynylpalladium species at the 2-position of the indoles and the subsequent deprotonation by CsOPiv; (3) the reductive elimination gave the final coupling products and Pd(0), which was reoxidized to Pd(II) in the presence of O_2 and PivOH (Figure 30).[373]



Scheme 272 Pd-catalyzed C2-alkynylation of indoles (Li et al., 2010).

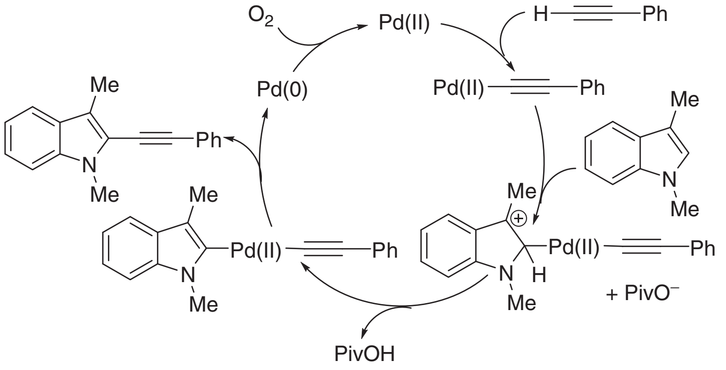
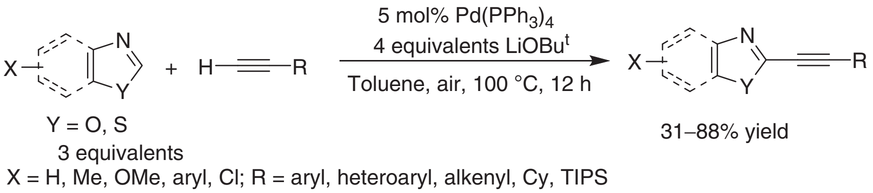


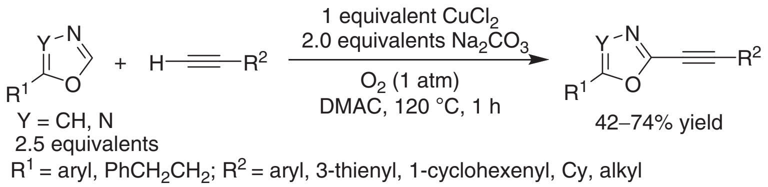
Figure 30 Proposed mechanism of Pd-catalyzed alkynylation of indoles.

Subsequently, the Chang and coworkers described the alkynylation of azoles using the conditions shown in Scheme 273.[374] A wide range of alkynes were found to be effective coupling partners, and the reactive azoles included benzoxazoles, oxazoles, and benzothiazoles. The reaction of a partially saturated oxazoline was also demonstrated, albeit in a poor yield. Contrary to the mechanism proposed in the Li's reactions, the C–H cleavage of azoles in this reaction was proposed to take place before the palladation of alkynes. The active Pd(II) species was generated *in situ* by the oxidation of Pd(0).



Scheme 273 Pd-catalyzed alkynylation of azoles (Chang et al., 2011).

Cu has also been found to enable the coupling of arenes and terminal alkynes. In 2010, Miura and coworkers disclosed copper-mediated alkynylation of 1,3,4-oxadiazoles and oxazoles in the presence of $CuCl_2$, Na_2CO_3, and one atmosphere of oxygen (Scheme 274).[375] The presence of oxygen was necessary for the reaction to occur, since the N_2 atmosphere did not lead to the product even in the presence of a stoichiometric amount of $CuCl_2$. A rich array of terminal alkynes bearing substituents such as aryl, alkenyl, and alkyl groups was compatible under the reaction conditions. The proposed mechanism involved the initial ligand exchange between Cu(II) species and the terminal alkyne, the subsequent cupration of an oxadiazole or oxazole, and the final



Scheme 274 Cu-catalyzed alkynylation of 1, 3, 4-oxadiazoles and oxazoles (Miura et al., 2010).

reductive elimination to yield the coupling products. Oxygen may act as a promoter in the productive reductive elimination by coordinating to the copper center (Figure 31).[375]

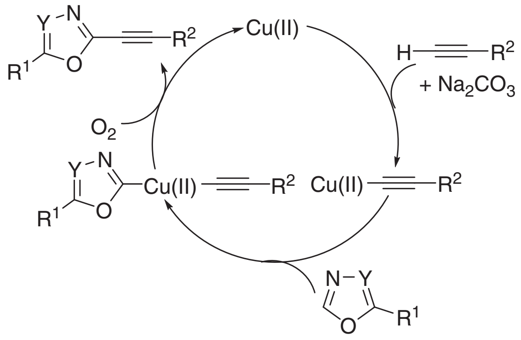
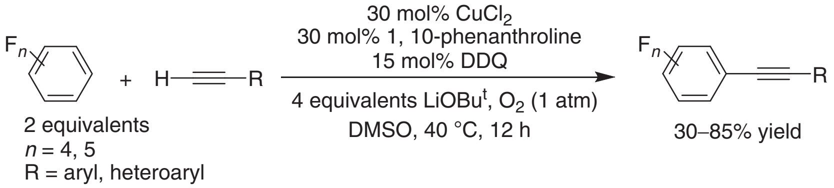


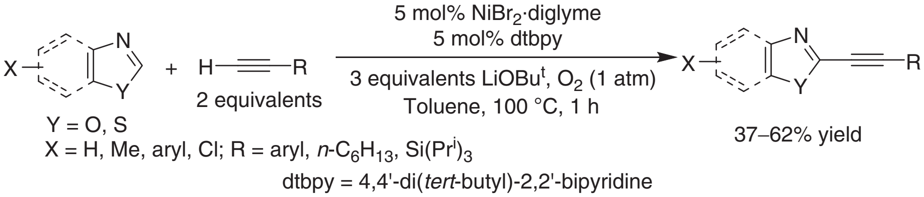
Figure 31 Proposed mechanism of Cu-catalyzed alkynylation of 1,3,4-oxadiazoles and oxazoles.

Concurrently, the Su and coworkers achieved Cu-catalyzed alkynylation of polyfluoroarenes by using a catalytic system consisting of $CuCl_2$, 1,10-phenanthroline and DDQ (Scheme 275).[376] The use of the strong base LiOBu^t was required and oxygen was used as the oxidant. The reactions exhibited a broad substrate scope with respect to alkynes. Although penta- and a range of tetrafluoroarenes were compatible under the reaction conditions, di- or trifluoroarenes did not yield the desired products, presumably because of the decreased acidity. The possible mechanism was similar to that proposed by Miura and coworkers.



Scheme 275 Cu-catalyzed alkynylation of polyfluoroarenes (Su et al., 2010).

Finally, Miura and coworkers reported Ni-catalyzed coupling of azoles and terminal alkynes under the conditions shown in Scheme 276.[377] The reactive azoles included benzoxazoles, oxazoles, and benzothiazoles, and both of aryl- and alkyl- terminal alkynes were compatible in the reaction. The mechanism was proposed to parallel that of Cu-promoted azole alkynylation. Moreover, the catalytic alkynylation of perfluoroarenes using $Cu(OTf)_2$ was also described.

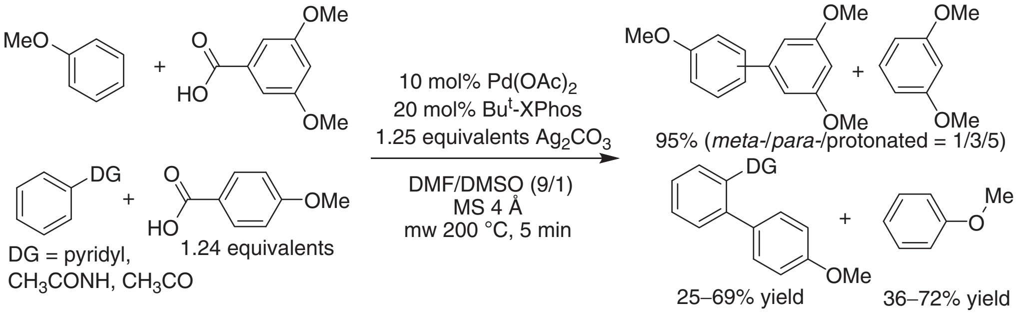


Scheme 276 Ni-catalyzed alkynylation of azoles (Miura et al., 2010).

3.23.6.2 Decarboxylative C–H Arylation with Aromatic Acids

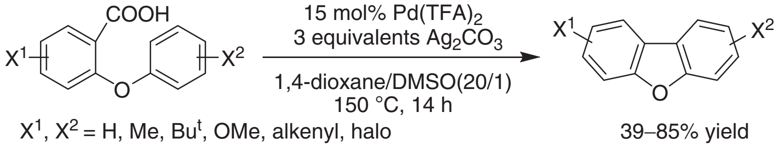
There is a developing interest in decarboxylative coupling reactions and numerous catalytic transformations have been discovered.[378] In these decarboxylative transformations, carboxylic acids can function as the synthetic equivalent of either aryl halides or organometallic reagents. In comparison to the traditional coupling partners, many aromatic acids are easily available, cheap, stable, and nontoxic.

Recently, combining decarboxylative coupling and C–H activation has gained much attention. One of the earliest examples was disclosed by Crabtree and coworkers.[379] Therefore, under the conditions as shown in Scheme 277, anisole was allowed to react with 3, 5-dimethoxylbenzoic acid to form the *meta-* and *para*-coupling products as well as the protonated byproduct 1,3-dimethoxybenzene. However, the arenes bearing directing groups were arylated with 4-methoxybenzoic acid at the *ortho*-positions selectively. In the reaction, microwave heating was crucial and greatly enhanced yields and shortened reaction time. In addition, the intramolecular coupling of 2-phenoxybenzoic acid also proved viable under the similar conditions, yielding the annulated product, dibenzofuran, in a moderate yield.



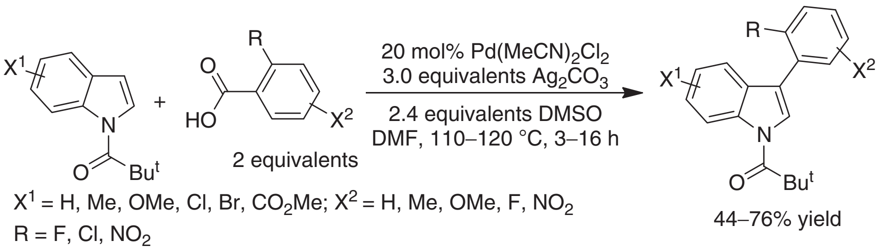
Scheme 277 Pd-catalyzed decarboxylative coupling reaction with arenes (Crabtree et al., 2008).

The highly efficient intramolecular decarboxylative coupling of 2-phenoxybenzoic acids was achieved using a new catalytic system consisting of Pd(TFA)$_2$ and Ag$_2$CO$_3$ by Glorius and coworkers (Scheme 278).[380] The Ag salt not only assisted the decarboxylation, but also acted as the oxidant for the C–H activation. The reaction accommodated a range of functionalities such as F, Cl, and Br. Dibenzofurans were formed in good yields and only a trace amount of protonation products were observed. The suggested mechanism involved Ag-mediated decarboxylation, transmetalation with Pd(II) catalyst to form arylpalladium species, and final reductive elimination to afford dibenzofurans as the final products.



Scheme 278 Pd-catalyzed intramolecular decarboxylative coupling reaction (Glorius et al., 2009).

Concurrently, Larrosa and coworkers reported Pd(MeCN)$_2$Cl$_2$-catalyzed coupling of *N*-pivaloylindole and benzoic acids (Scheme 279).[381] The reactive benzoic acids were limited to those bearing *ortho*-electron-withdrawing substituents, and the reaction took place at the 3-positions of the indoles selectively. Mechanistically, the authors proposed that the C–H activation involved electrophilic palladation of indoles by Pd(II) catalyst, affording arylpalladium species. The Ag(I)-mediated decarboxylation formed arylsilver, which underwent transmetalation to the arylpalladium species to yield aryl-Pd-aryl complex. The subsequent reductive elimination gave the final coupling products (Figure 32).[381]



Scheme 279 Pd-catalyzed decarboxylative coupling reaction with indoles (Larrosa et al., 2009).

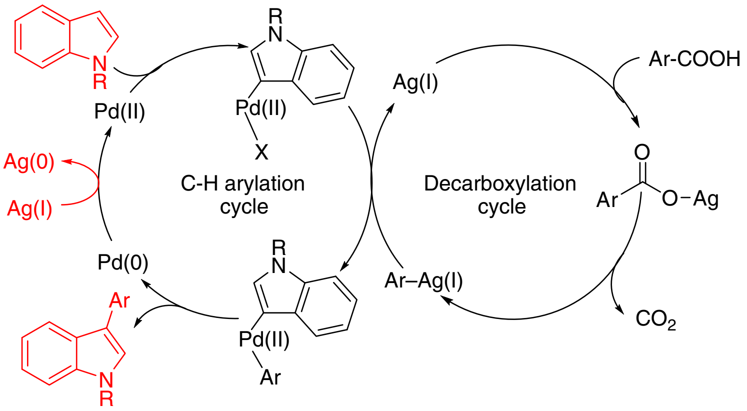
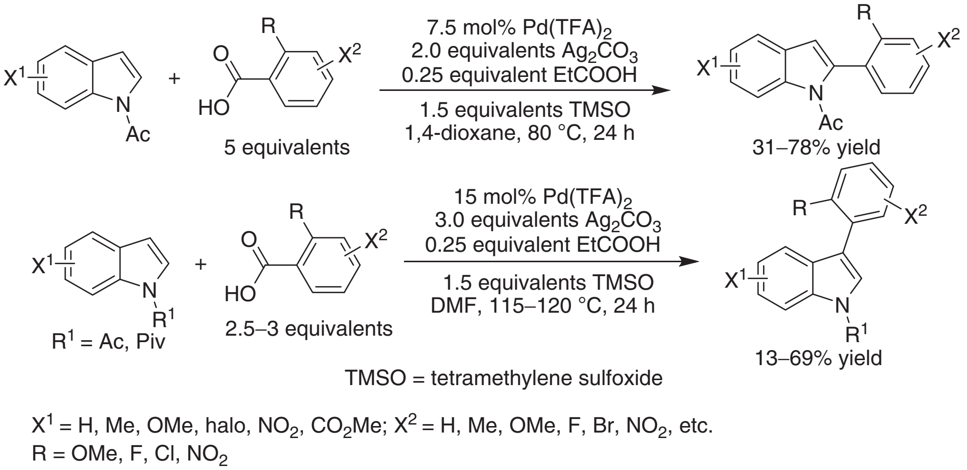


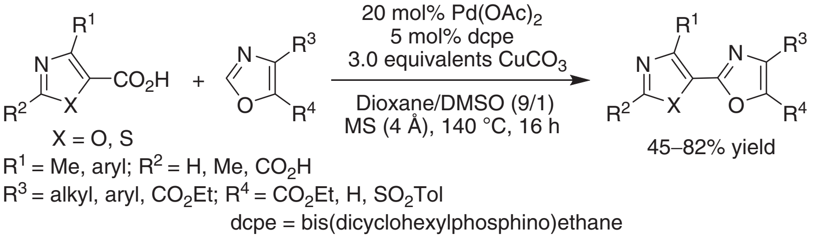
Figure 32 Proposed mechanism of Pd-catalyzed decarboxylative coupling reaction with indoles.

Subsequently, the Su and coworkers developed a versatile protocol for regioselective arylation of indoles with benzoic acids (Scheme 280).[382] Although the benzoic acids with *ortho*-electron-donating functionalities gave 2-arylated indole products, the arylation took place at the 3-positions of indoles selectively for the benzoic acids bearing *ortho*-electron-withdrawing groups under similar conditions. Mechanism experiments revealed that $Pd(TFA)_2$ alone could enable the decarboxylation of 2,4-dimethoxybenzoic acid and the arylation reaction. However, Ag_2CO_3 was required for the decarboxylation of electron-deficient benzoic acids. Based on these observations, the authors suggested that two different mechanisms were operative in this novel arylation reaction. In the cases of electron-rich benzoic acids, the decarboxylation was promoted by Pd(II), and the C2-selectivity resulted from the migration of aryl–Pd fragment from C3 to C2. As for electron-deficient benzoic acids, Ag(I) was still responsible for the decarboxylation.



Scheme 280 Pd-catalyzed decarboxylative coupling reaction with indoles (Su et al., 2010).

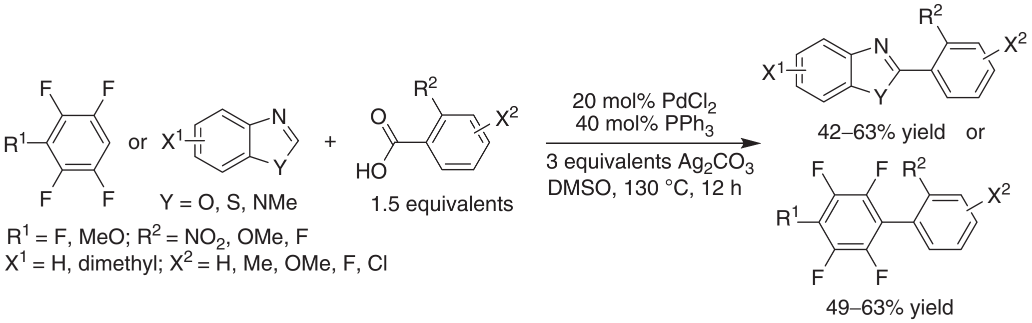
Greaney and coworkers reported decarboxylative C–H cross-coupling of azoles (Scheme 281).[383] A range of substituted oxazole/thiazole-5-carboxylic acids coupled with various 5-substituted oxazoles to afford 2,5′-biazole products. The absence of 5-substituents for the oxazoles without carboxylic acids led to the formation of mixtures of products because of the difficulty in



Scheme 281 Pd-catalyzed decarboxylative coupling reaction for biheteroaryl synthesis (Greaney et al., 2010).

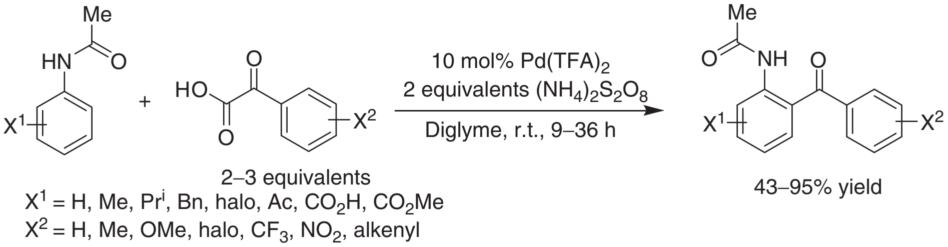
discriminating the 2- and 5-positions. Only the arylation of 2,4-disubstituted oxazole/thiazole-5-carboxylic acids were demonstrated. The isomeric oxazole-4-carboxylic acids without 5-substituents could give multiarylated products because of C–H/C–H cross-coupling.

Concurrently, the Tan and coworkers disclosed the arylation of benzoxazoles/benzothiazoles and polyfluoroarenes via decarboxylative C–H coupling (Scheme 282).[384] The reaction was compatible to a broad range of benzoic acids, including electron-rich and electron-poor ones. The arylation of 4,5-dimethylthiazole was also effective under the reaction conditions.



Scheme 282 Pd-catalyzed decarboxylative coupling reaction with benzoxazoles and polyfluorobenzenes (Tan et al., 2010).

Intriguingly, the Ge and coworkers reported a novel acylation method via decarboxylative C–H coupling with α-oxocarboxylic acids (Scheme 283).[385] Therefore, a broad range of acetanilides were *ortho*-acylated with various 2-oxo-2-phenylacetic acids using the catalyst $Pd(TFA)_2$ and the oxidant $(NH_4)_2S_2O_8$. It is noted that no silver salts were required to promote decarboxylation and the reaction proceeded smoothly at room temperature. The reactions exhibited an excellent substrate scope with respect to both of the substrates. A diversity of functionalities, including F, Cl, and Br, were well tolerated. In addition, the similar acylation of 2-phenylpyridines was also demonstrated by the same authors.[386] The catalytic system consisted of $Pd(PhCN)_2$, Ag_2CO_3, and $K_2S_2O_8$.



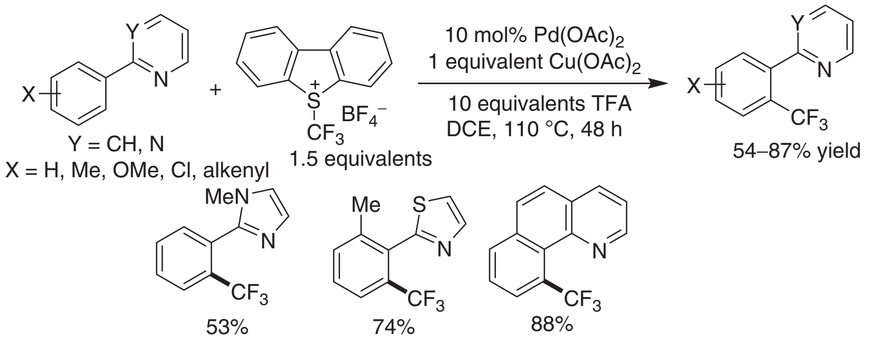
Scheme 283 Pd-catalyzed decarboxylative acylation of acetanilides with α-oxocarboxylic acids (Ge et al., 2010).

3.23.6.3 C–H Trifluoromethylation

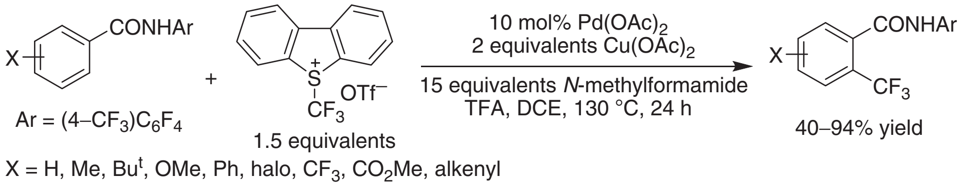
The introduction of trifluoromethyl groups into organic molecules can dramatically change their physical properties and biological activity, and trifluoromethylated aromatic compounds are widely found in pharmaceuticals, agrochemicals, and organic materials.[387] Therefore, the development of new methods for the introduction of trifluoromethyl groups has gained considerable attention, and a number of protocols for efficient trifluoromethylation have been reported. In particular, transition-metal-catalyzed cross-coupling has emerged as a powerful tool for the construction of $C(sp^2)$-CF_3 bond.[388]

Recently, direct C–H trifluoromethylation has been the subject of intense research, and a variety of transition metals have been demonstrated to be able to promote $C(sp^2)$-CF_3 bond formation via C–H activation. In 2010, Yu and coworkers reported Pd-catalyzed-directed trifluoromethylation of arenes using the CF_3^+ reagent 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate (Scheme 284).[389] In this reaction, a wide range of *N*-containing heteroarenes, including pyridine, pyrimidine, imidazole, and thiazole could be used as the directing group, and TFA was crucial for the success of this novel trifluoromethylation method. In addition, $Cu(OAc)_2$ was found to enhance the catalytic turnover effectively.

The above strategy has been successfully extended to the trifluoromethylation of *N*-arylbenzamides (Scheme 285).[390] Therefore, under similar conditions, a range of *N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)benzamides were *ortho*-trifluoromethylated with 5-(trifluoromethyl)dibenzothiophenium triflate. *N*-methylformamide was crucial for the effective C–CF_3 bond formation.



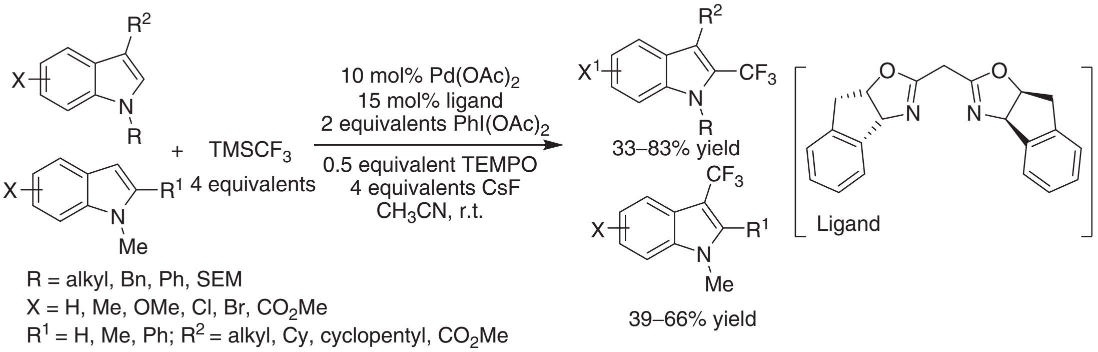
Scheme 284 Pd-catalyzed heteroarene-directed trifluoromethylation (Yu et al., 2010).



Scheme 285 Pd-catalyzed acidic amide-directed trifluoromethylation of *N*-arylbenzamides (Yu et al., 2012).

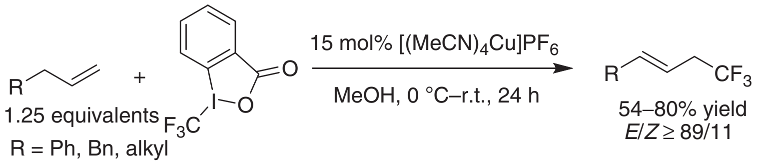
It is noted that Sanford and coworkers carried out the detailed mechanistic studies of the trifluoromethylation with CF_3^+ reagents.[391] The authors systematically investigated the formation of the monomeric Pd(IV) aquo complex (bzq)Pd(CF_3)-$(OAc)_2(OH_2)$ and its reductive elimination to form aryl C–CF_3 bond. The experimental data provided evidence that the formation of a Pd(IV) intermediate, which was produced through the oxidation of the arylpalladium(II) species by the CF_3^+ reagent, was responsible for the aryl C–CF_3 bond formation. The reductive elimination of the Pd(IV) species can afford the trifluoromethylated products effectively and generate Pd(II) catalyst. Actually, the major challenge in transition-metal-catalyzed aryl C–CF_3 bond forming reaction is that CF_3 ligands are typically inert toward C–C bond-forming reductive elimination. However, it has been shown that the formation of Pd(IV) species can accelerate reductive elimination which is difficult to occur on the other metal center.[392] As such, the trifluoromethylation protocol involving the formation of Pd(IV) intermediates with CF_3^+ reagents provides a novel strategy for the development of trifluoromethylation reactions.

Subsequently, the Liu and coworkers developed another trifluoromethylation method by using the CF_3^- reagent $TMSCF_3$.[393] Therefore, 3-substituted indoles underwent 2-trifluoromethylation smoothly under the conditions shown in Scheme 286. 3-Trifluoromethylation could be enabled by blocking the 2-position with a substituent, and the reaction for indoles without 2 or 3 substituents occurred at the 3-positions selectively, albeit in a low yield. The addition of TEMPO significantly improved the reaction yields, which was against a possible radical pathway. The reaction may also involve a Pd(II)/Pd(IV) catalytic cycle. However, the Pd(IV) species were formed through oxidation by $PhI(OAc)_2$ instead of CF_3^+ reagents.



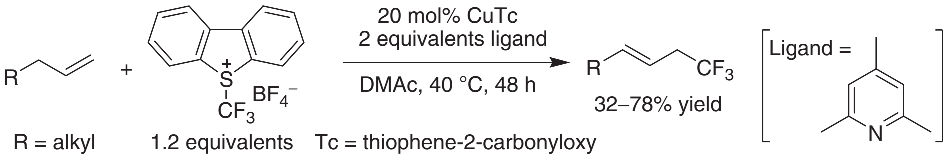
Scheme 286 Pd-catalyzed trifluoromethylation of indoles with $TMSCF_3$ (Liu et al., 2011).

Buchwald described the copper-catalyzed allylic trifluoromethylation of unactivated terminal olefins (Scheme 287).[394] In the presence of the catalyst $[(MeCN)_4Cu]PF_6$, terminal olefins reacted with the Togni electrophilic trifluoromethylating reagent to give linear allylic trifluoromethylation products in good yields. The reactions also displayed high *E*/*Z* selectivity with *E*/*Z* ratios ranging from 89:11 to 97:3.



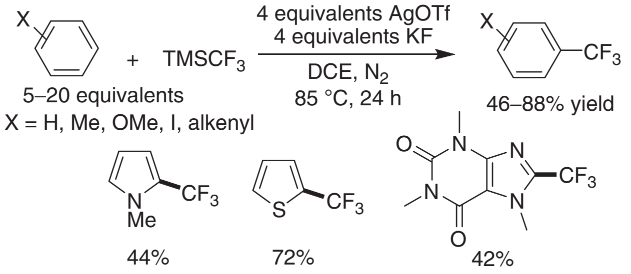
Scheme 287 Cu-catalyzed allylic trifluoromethylation of terminal alkenes (Buchwald et al., 2011).

Concurrently, the Liu and coworkers reported an analogous Cu-catalyzed allylic trifluoromethylation using 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate as the trifluoromethyl source (Scheme 288).[395] The Cu(I) salts (thiophene-2-carbonyloxy)copper (CuTc) and the ligand 2,4,6-trimethylpyridine gave the best yields, and the reaction showed good functional group tolerance. Mechanistically, both experimental and theoretical analyses indicated that the trifluoromethylation may occur via a Heck-like four-membered-ring transition state.[393]



Scheme 288 Cu-catalyzed allylic trifluoromethylation of terminal alkenes (Liu et al., 2011).

Sanford and coworkers disclosed Ag-mediated trifluoromethylaion of simple arenes with $TMSCF_3$ in the presence of KF (Scheme 289).[396] Various substituted arenes and benzene were trifluoromethylated effectively under the conditions as shown in the scheme. A mixture of regioisomers was obtained for substituted arenes. In addition, heteroarenes such as *N*-methylpyrrole, thiophene, and caffeine also underwent such a reaction. For *N*-methylpyrrole and thiophene, the reactions took place at the C2 positions preferentially. Although the detailed mechanism remains to be clarified, the authors proposed that the reactions proceeded via an $AgCF_3$ intermediate, and preliminary mechanistic studies suggested against a free CF_3• pathway.



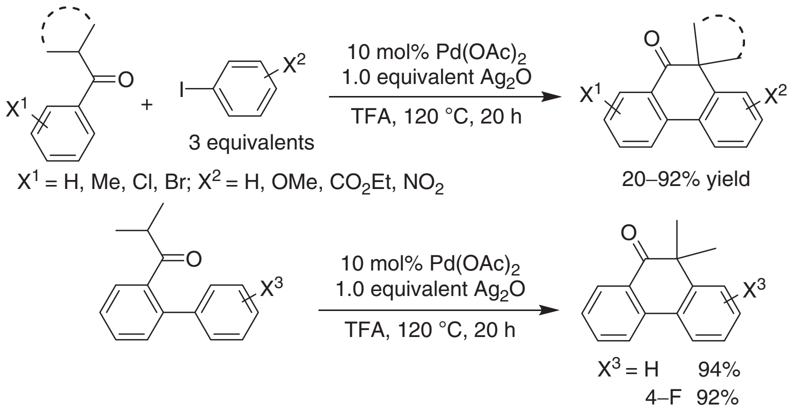
Scheme 289 Ag-mediated trifluoromethylation of (hetero)arenes with $TMSCF_3$ (Sanford et al., 2011).

3.23.6.4 C–H Alkylation with α C–H Bonds of Carbonyl Groups

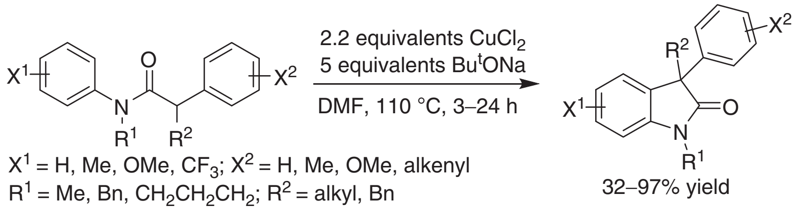
In 2010, during the course of the investigation of the direct coupling of acetophenones with aryl iodides, Cheng and coworkers obtained the cyclization product phenanthrones, which arose from the intramolecular reaction of aryl C–H bonds with the α-C–H bonds of the carbonyl groups following the coupling reaction of the acetophenones and the aryl iodides (Scheme 290).[397] The prepared coupling intermediate *ortho*-arylated acetophenones also underwent the cyclization reaction under the same conditions, affording phenanthrone products.

In 2009, Kündig and coworkers developed a novel and efficient method for the synthesis of oxindoles by the Cu-mediated oxidative coupling of aryl C–H bonds and α-C–H bonds of amides (Scheme 291).[398] Therefore, *N*,2-diphenylacetamide derivatives underwent intramolecular α-arylation reaction effectively in the presence of $CuCl_2$ and Bu^{t}ONa to yield the cyclization product oxindoles. The reactive substrates were limited to those with one α-hydrogen and *N*-protected amide groups. In addition, the presence of the α-aryl groups was crucial for the success of the α-arylation reaction. The proposed mechanism involved a radical pathway.

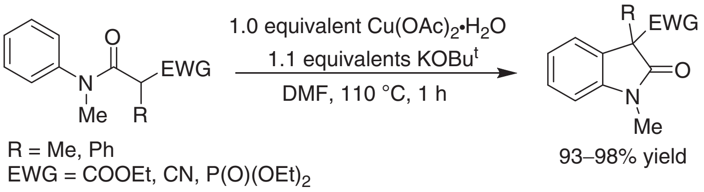
Taylor and coworkers reported an analogous Cu-mediated α-arylation via C–H activation for the synthesis of 3,3-disubstituted oxindoles (Scheme 292).[399] In the reactions, electron-withdrawing groups were introduced to activate the α-C–H bonds instead of phenyl groups that were used in the Kündig method. The author also preferred a radical mechanism, which



Scheme 290 Pd-catalyzed intramolecular C(sp^2)-H alkylation (Cheng et al., 2010).



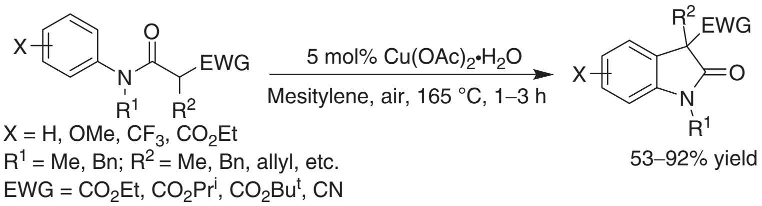
Scheme 291 Cu-mediated intramolecular C(sp^2)-H alkylation (Kündig et al., 2009).



Scheme 292 Cu-mediated intramolecular C(sp^2)-H alkylation (Taylor et al., 2009).

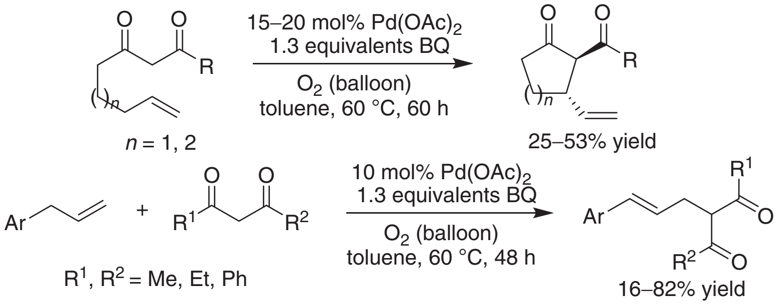
involved the generation of a β-dicarbonyl-flanked radical by Cu(II) and the subsequent intramolecular homolytic aromatic substitution.

Subsequently, the α-arylation reaction was rendered catalytic by using air as the oxidant (Scheme 293).[400] The reaction could be run in mesitylene or toluene. Interestingly, no additional base was required.



Scheme 293 Cu-catalyzed intramolecular C(sp^2)-H alkylation (Taylor et al., 2010).

Allylic alkylation provides a powerful tool for the construction of C–C bonds, and has found widespread use in modern organic synthesis. In such a reaction, a substrate containing a leaving group at the allyl position is generally employed. Just as other C–H functionalization reactions, allylic C–H alkylation is highly advantageous because it could allow for the direct functionalization of simple allylic compounds and avoid the prefunctionalization required in the traditional allylic alkylation. As early as 1978, Trost and coworkers reported two-step allylic C–H alkylation in the presence of stoichiometric amount of $Pd(OAc)_2$, mainly because the *in situ* reoxidation of Pd(0) to Pd(II) was difficult.[401] The catalytic version of such a reaction was not achieved until the Shi and coworkers reported the first Pd-catalyzed allylic C–H alkylation in 2008 (Scheme 294).[402] Therefore, inter/intramolecular coupling between allylic C–H bonds and α-C–H bonds of 1,3-diketones proceeded smoothly in the presence of BQ and an atmosphere of oxygen. For the intramolecular reactions, simple aliphatic allylic substrates were reactive and the internal allylic alkylation products were formed because of the preferential formation of five- or six-membered rings. In the case of prochiral substrates, two diastereoisomers were isolated in high diastereoselectivities. As for the intermolecular reactions, the substrates bearing allylic aryl groups were required, and the reactions yielded linear alkylation products. The proposed mechanism involved the formation of π-allylpalladium via an electrophilic allylic C–H bond cleavage by Pd(II) catalyst. The subsequent nucleophilic attack by 1,3-dicarbonyl compounds or their enolate forms afforded the final allylic alkylation product. BQ acted as the oxidant to reoxidize Pd(0) to Pd(II) to fulfill the catalytic cycle (Figure 33).[402]



Scheme 294 Pd-catalyzed allylic alkylation of C(sp^3)-H bonds (Shi et al., 2008).

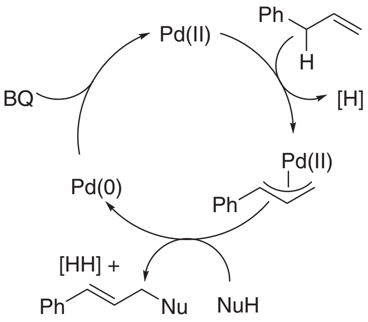
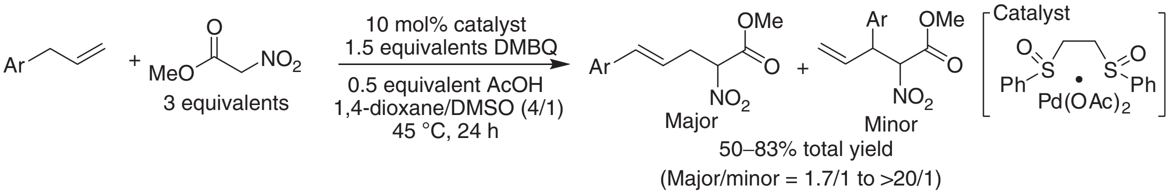


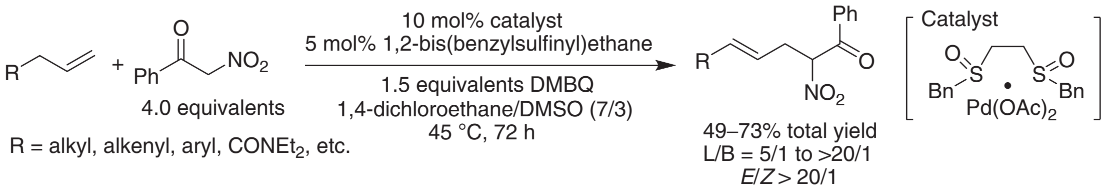
Figure 33 Proposed mechanism of Pd-catalyzed allylic alkylation of C(sp^3)-H bonds.

Simultaneously, the White and coworkers reported an analogous intermolecular allylic C–H alkylation under the conditions shown in Scheme 295.[403] The π-acceptor ligand DMSO was critical for the reactions to occur. Although the allylic aryl group was also required to achieve high yields, aliphatic allylic substrates were also reactive, albeit in a very poor yield. In addition to benzoylnitromethane, methyl nitroacetate and (phenylsulfonyl)nitromethane also afforded alkylated products in excellent yields. The reaction furnished excellent E/Z selectivity (>20:1) and good regioselectivity, with a linear: branched product ratio >3 in most of the cases.



Scheme 295 Pd-catalyzed allylic C–H alkylation (White et al., 2008).

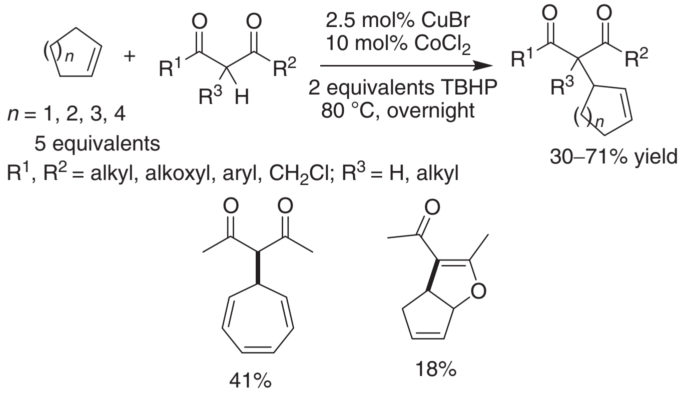
Remarkably, the White and coworkers successfully achieved the intermolecular allylic alkylation of unactivated α-olefins by using the ligand benzyl bis(sulfoxide) in place of benzyl bis(sulfoxide) (Scheme 296).[404] In the allylic C–H alkylation reaction developed by the White and coworkers, the ligand bis(sulfoxide) was crucial for the C–H activation and the addition of DMSO was required to promote the subsequent alkylation. However, DMSO also could inhibit the binding of bis(sulfoxide) to the



Scheme 296 Pd-catalyzed allylic C–H alkylation of unactivated α-olefins (White et al., 2011).

palladium center and consequently suppress the allylic C–H activation, so the substrate scope of the above alkylation protocol was limited to activated allylic substrates. The new ligand benzyl bis(sulfoxide) is a stronger σ-donor than benzyl bis(sulfoxide) and is better able to compete with DMSO for binding to the palladium center, which accounted for the success of this novel alkylation reaction. The reaction proceeded with high regioselectivity (L/B > 20:1 in most cases) and excellent E/Z selectivity (> 20:1) and a variety of functionality at the homoallylic positions were well tolerated. Furthermore, the reaction conditions were also amenable to allylbenzene substrates and other classes of activated substrates such as amides and enols.

In 2006, the Li and coworkers disclosed the Cu-catalyzed alkylation of cycloalkenes with 1, 3-dicarbonyl compounds, which is the first catalytic allylic C–H alkylation (Scheme 297).[405] Therefore, by using a combination of the catalysts CuBr and $CoCl_2$, a range of cycloalkenes reacted with 1,3-diketones and acetoacetate derivatives in the presence of the oxidant TBHP to afford allylic alkylation products. The alkylation of cycloheptatriene and cyclopentadiene also took place under the reaction conditions, albeit in low yields. Mechanistically, the authors proposed that the reaction started with the formation of a π-allyl copper or allyl cobalt complex via the allylic H-abstraction. Subsequently, standard allylic alkylation followed by oxidation furnished the alkylation product and regenerated the catalyst.



Scheme 297 Cu-catalyzed allylic C(sp^2)-H alkylation (Li et al., 2006).

3.23.7 Summary and Outlook

Transition-metal-catalyzed C–H functionalization has made explosive growth over the last two decades, and has emerged as a powerful tool for forming various chemical bonds, including C–C, C–X, C–N, C–O, and C–S. As classical transition-metal-promoted reactions, reactions via C–H activation have also proved most valuable in the construction of C–C bonds, especially C–C σ-bonds. It has been demonstrated that a variety of C–C σ-bonds can be formed through transition-metal-catalyzed C–H functionalization. Although the formation of aryl–aryl and aryl–alkenyl bonds has proved the most successful, other C–C σ-bonds such as aryl–alkyl, aryl–alkynyl, and alkyl–alkyl have also been constructed effectively. To form these C–C σ-bonds, a diverse variety of reactions via C–H activation have been developed. The major strategy is to substitute C–H bonds for one of the reaction partners in classical coupling reactions. Therefore, C–H bonds can react with (pseudo)halides, organometallic reagents to form C–C bonds. Heck-type C–H alkenylation involves the reactions of C–H bonds with alkenes, which also may provide alkylation products, depending on the catalyst and reaction conditions. The reaction of C–H bonds with carbonyl and imino groups have also been demonstrated, which afford expedient methods for the synthesis of ketones or amines, respectively. The more attractive dehydrogenative cross-coupling, wherein two reaction partners are replaced with C–H bonds, offer a waste-free and the most atom-economic method for C–C bond formation. In addition, many other types of C–H functionalization reactions have been reported, which include alkynylation with terminal alkynes, arylation with benzoic acids, trifluoromethylation with CF_3^+ or CF_3^- reagents, and alkylation with activated C(sp^3)-H bonds.

Pd is the most-extensively investigated transition metal in C–H activation. It has been successfully utilized to promote almost all the types of reactions discussed in this chapter. Rh and Ru also proved applicable in various C–H functionalization reactions.

The first-row transition metals, especially Fe, Cu, and Ni, also attract considerable interests because of their low cost and rich abundance in nature. These metals are also able to act as effective catalysts to enable C–C σ-bonds formation, mainly aryl–aryl bond formation.

It is noted that transition-metal-catalyzed C–H functionalization reactions has proved viable in the synthesis of complex natural products, and quite a few examples have been reported. However, many major challenges must still be overcome before the reactions find broad applicability.

1. Most of transition-metal-catalyzed C–H functionalization reactions are run under harsh conditions such as high temperature, which diminishes their practicality, especially in the synthesis of complex molecules. However, quite a few examples, which proceed effectively under mild conditions, have been reported. It indicates that C–H activation and the subsequent functionalization reaction can take place even under mild conditions. Developing new catalysts and ligands may be a solution to achieve this end.
2. Many C–H functionalization reactions, especially Pd-catalyzed reactions, require 5–10 mol% catalyst, or even higher. Considering the high cost of these transition metals, it is necessary to lower the catalyst loading and improve turnovers.
3. One of the greatest advantages for C–H activation is that it can reduce the production of chemical wastes. However, in many cases, the C–H functionalization reactions require the use of stoichiometric amounts of oxidants, which end up with chemical wastes. It not only increases the cost of the reactions, but also cancel the chemical waste-saving advantage of C–H activation. To solve this problem, developing reactions using cheap and safe oxidants such as air or avoiding the use of oxidant may be the long-term goal. Fortunately, many examples using oxygen or air as the oxidant are available, which laid a foundation for developing chemical-waste-saving C–H activation reactions.
4. Although the existence of ubiquitous C–H bonds in organic molecules offers great opportunities for the development of C–H activation reactions, it also causes troubles for selective functionalization. Although the use of directing groups can afford high regioselectivity, selective C–H activation in the absence of directing groups is still a challenge. The introduction and removal/conversion of directing groups not only cost additional synthetic steps, but also limits the substrate scope. Hence, developing regioselective C–H activation without the assistance of directing groups is paramount.
5. Although a few examples have been reported, enantioselective C–H functionalization is still a great challenge. The major hurdle is the lack of effective chiral ligands which can not only facilitate C–H activation, but also furnish high enantioselectivities. Furthermore, the use of harsh conditions, which are required in most of the current C–H activation reactions, also hamper high enantioselectivity.
6. Understanding the detailed reaction mechanisms underlying the C–H activation reactions will lay a foundation for developing new catalytic systems to solve the above problems. Many mechanism experiments have been carried out to decipher the mechanism responsible for the C–H activation, and many reasonable mechanism have been proposed. However, more strong experimental evidences are needed, and more detailed mechanisms have yet been elucidated.

In addition, there still exists a wide variety of C–C bond-forming reactions via C–H bond activation remain to be developed, and continuous efforts are needed to direct toward more practical methods for the construction of C–C σ-bonds.

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